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Prostate Cancer

Does Protocol Make a Difference? Comparison of Two Prostate Cancer Active Surveillance Cohorts: A Non-protocol-based Follow-up and a Protocol-based Contemporary Follow-up

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Abstract

Background: Active surveillance (AS) is the preferred option for initial management for low-risk prostate cancer (PC). Although many AS protocols exist, there is little evidence to support one over another.

Objective: To assess whether there is difference in overall (OS), prostate cancer-specific (CSS), metastasis-free (MFS), or treatment-free (TFS) survival between a strict (Prostate Cancer Research International: Active Surveillance [PRIAS]) and a loose (European Randomized study of Screening for Prostate Cancer [ERSPC]) AS protocol.

Design, setting, and participants: This study included two cohorts of men (n = 518) with low-risk, localized, Gleason score ≤ 7 PC. The ERSPC cohort included 241 men followed for 9.5 yr (median) with a non-protocol-based follow-up. The PRIAS cohort included 277 men followed for 5 yr (median) with a strict protocol.

Outcome measurements and statistical analysis: OS, CSS, MFS, and TFS were compared by the Kaplan-Meier method, competing risk analysis, and Cox proportional hazard regression.

Results and limitations: As expected, due to the difference in median follow-up time between the cohorts, a difference in the absolute number of events was seen. However, no difference in any of the survival outcomes was evident in the Kaplan-Meier or competing risks analysis. Furthermore, in Cox proportional hazard regression analysis, cohort (ERSPC vs PRIAS) was not associated with any of the outcomes. Results are limited by the retrospective study design, limited statistical power, and inability to match the cohorts for predictive factors.

Conclusions: There was no difference in survival outcomes between a non-protocol-based follow-up and a protocol-based contemporary AS follow-up of patients with low-risk PC. However, a longer follow-up is needed.

Patient summary: We compared survival outcomes of two cohorts of patients with low-risk prostate cancer: a strict and a loose follow-up protocol. We found no differences in survival measures between the cohorts.

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1. Introduction

Prostate cancer (PC) is the leading cause of cancer incidence in men, with one in 15 developing PC between birth and age 79 yr [1]. In the prostate-specific antigen (PSA) era, many of the diagnosed cancers are indolent and low risk, and have a low metastatic potential. These PCs have excellent prognosis, and rarely cause any symptoms or pose a threat to men in their lifetime [2]. Diagnosis of these small, localized, and well-differentiated cancers is often referred to as overdiagnosis, diagnosing “cancers” that would otherwise not go on to cause symptoms or death. Often these diagnoses, however, lead to treatments (representing overtreatment), which can be harmful due to treatment-related complications and other adverse effects. Further, radical treatments, such as radical prostatectomy (RP) and radiation therapy (RT), have very little, if any, potential to aid these men with low-risk disease due to the very low baseline risks of PC death [3].

Active surveillance (AS) has emerged as the preferred management option for low-risk PCs. The aim of AS is to avoid overtreatment, while also identifying men in need of curative treatment in a timely fashion [2,4]. Contemporary AS includes regular clinical checkups, PSA tests, repeat biopsies, and increasingly frequently prostate magnetic resonance imaging (MRI). Although a wide range of AS protocols exist [5], there is a paucity of evidence to support one AS protocol over another.

The European Randomized study of Screening for Prostate Cancer (ERSPC) trial was shown to reduce PC mortality by 25% [6]. However, PSA-based screening is asso-

ciated with significant harm in the form of overdiagnosis. It is estimated that 40–50% of PC cases diagnosed by screening represent overdiagnosis [7]. Another trial, Prostate cancer Research International: Active Surveillance (PRIAS), was based on the initial encouraging reports on AS and the realization of the significant problem of overdiagnosis within the ERSPC trial. In contrast to the loose monitoring used for men in the ERSPC trial, the PRIAS trial had a strict protocol for inclusion, follow-up, and triggers for treatment.

Here, we compare the outcomes of two cohorts of men with low-risk PC. The ERSPC cohort followed a non-protocol-based follow-up, while the PRIAS cohort adhered to a strict protocol for follow-up. We aim to assess whether a strict protocol makes a difference in patient-important (clinically relevant) outcomes.

2. Patients and methods

We compared two separate cohorts of patients with low-risk PC. First, we included men who underwent screening for PC in the Helsinki arm of the ERSPC trial and were diagnosed with low-risk PC. Most of these men had Gleason score (GS) ≤ 6 cancers and a few had GS 7 (3 + 4) cancers. Characteristics of the cohort are presented in Table 1. The detailed protocols for the ERSPC and its Finnish arm have been published elsewhere [8,9]. In ERSPC, men were diagnosed by transrectal six-core biopsy and expectantly managed without a fixed surveillance protocol, that is, no recommendation for follow-up or trigger for treatment. These men were followed according to the treating urologist's preference, and the follow-up was therefore variable. All patients underwent PSA tests, on average every 6 mo, but clinical examination including digital rectal examination (DRE) was not performed regu-

Table 1 – Characteristics of the two cohorts at diagnosis

	Main analysis		Sensitivity analysis	
	ERSPC cohort	PRIAS cohort	ERSPC cohort	PRIAS cohort
No. of cases	241	277	123	277
PSA (ng/ml), median (IQR)	5.1 (4.2–6.5)	5.6 (4.4–6.8)	4.7 (4.1–5.4)	5.6 (4.4–6.8)
Prostate volume (ml), median (IQR)	35 (28–45)	40 (33–50)	38 (30–46)	40 (33–50)
PSA density (ng/ml/ml) median (IQR)	0.14 (0.04–0.81)	0.14 (0.11–0.16)	0.13 (0.10–0.16)	0.14 (0.11–0.16)
Age at diagnosis median (IQR)	67 (63–68)	63 (59–68)	67 (63–68)	63 (59–68)
No. of biopsy cores median (IQR)	6 (6–12)	12 (12–12)	6 (6–12)	12 (12–12)
No. of cancer-positive biopsy cores, n (%)				
1	136 (56)	187 (68)	95 (77)	187 (68)
2	54 (22)	90 (32)	28 (23)	90 (32)
3	9 (4)	0 (0)	0 (0)	0 (0)
4	8 (3)	1 (0)	0 (0)	0 (0)
5	3 (1)	0 (0)	0 (0)	0 (0)
NA	31 (13)			
Gleason score, n (%)				
≤ 6	216 (90)	277 (100)	123 (100)	277 (100)
3 + 4	7 (3)	0 (0)	0 (0)	0 (0)
4 + 3	3 (1)	0 (0)	0 (0)	0 (0)
NA	15 (6)	0 (0)	0 (0)	0 (0)
Clinical T stage, n (%)				
T1	215 (89)	271 (98)	118 (96)	271 (98)
T2	15 (6)	6 (2)	5 (4)	6 (2)
NA	11 (5)	0 (0)	0 (0)	0 (0)

ERSPC = European Randomized study of Screening for Prostate Cancer; IQR = interquartile range; NA = not available; PRIAS = Prostate cancer Research International: Active Surveillance; PSA = prostate-specific antigen.

larly and biopsies were taken rarely. Most patients were not followed at the urological clinic. After diagnosis, they were encouraged to contact their health station, where a general physician continued the follow-up. After 6 yr, two-thirds still had a PSA test taken, and after 8 yr, less than half had any follow-up visits anymore. The follow-up was not systematical as in PRIAS, and follow-up visits were much rarer. Second, we included men with low-risk PC who were enrolled in the Finnish arm of the prospective PRIAS study [10]. The inclusion criteria for the PRIAS trial were a maximum of two cancer-positive biopsy cores, GS ≤ 6 (3 + 3), clinical T stage ≤ 2 , PSA level ≤ 10 ng/ml, and PSA density (PSA-D) < 0.2 ng/ml/cc. Characteristics of the cohort are presented in Table 1. Men were typically diagnosed by using transrectal 12-core biopsy and had to be fit for curative treatment when indicated. During AS, patients were monitored carefully. The protocol included PSA tests every 3 mo and a clinical examination with DRE every 6 mo during the first 2 yr. After 2 yr, PSA was measured every 6 mo and DRE was performed yearly. Repeat biopsies were taken 1, 4, and 7 yr after inclusion as well as for rapidly rising PSA (PSA doubling time [PSA-DT] between 3 and 10 yr) or whenever considered necessary. Criteria for discontinuation of AS and switching to active treatment were PSA-DT < 3 yr, clinical T stage > 2 , PC in more than two biopsy cores, and/or GS > 6 (3 + 3). Adherence to protocol was excellent. This was ensured by a urological nurse who personally contacted the patients for follow-ups.

The ERSPC study recruited between 1991 and 2005. The PRIAS study started recruitment in 2006 and recruitment is ongoing. This impacts the follow-up times for the cohorts in our study. To make the cohorts more comparable, the follow-up time for the ERSPC cohort was cut off at 9.5 yr for all the analyses.

Data were analyzed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). The cutoff level for statistical significance was set at $p < 0.05$ for all tests. Overall survival (OS), prostate cancer-specific survival (CSS), treatment-free survival (TFS), and metastasis-free survival (MFS) were analyzed by the Kaplan-Meier method. We performed a competing risk analysis of the same endpoints using the cumulative incidence function. We also conducted a sensitivity analysis where we included only those patients from the ERSPC cohort who fulfilled the PRIAS inclusion criteria. Furthermore, a Cox proportional hazard regression was conducted using PSA, PSA-D, age at diagnosis, year of diagnosis, and cohort (ERSPC or PRIAS) as covariates to investigate factors associated with survival.

Originally both ERSPC (55/2000) and PRIAS (HUS 276/E6/06) were approved by the local ethics committee, and written informed consent was obtained from all study participants at study entry. This retrospective analysis was approved by the hospital administrative body (HUS/333/2019).

3. Results

Data of 518 patients were available, 241 men from ERSPC and 277 men from PRIAS. In the sensitivity analysis, 123 men from ERSPC and 277 from PRIAS were included (Table 1).

The median follow-up after PC diagnosis in ERSPC was 9.5 yr (interquartile range [IQR]: 9.5–9.5), and in PRIAS it was 5.2 yr (IQR 3.7–7.1). In ERSPC, 50 (21%) men died during follow-up; five (2%) died of PC. In PRIAS, 21 (8%) men died during follow-up; one ($< 1\%$) died of PC. A total of 141 (59%) men in ERSPC switched to active treatment after a median of 2.8 yr, whereas 125 (45%) men in PRIAS switched to active treatment after a median of 1.2 yr. In ERSPC, 122 (51%) men received treatment with curative intent (RP [32%] or RT [68%]). In PRIAS, 125 (45%) men received treatment with curative intent (RP [76%] or RT [24%]). In ERSPC, 19 (8%) men received primary treatment with noncurative intent (hormonal therapy or orchiectomy). In PRIAS, no patients received treatment with noncurative intent as primary treatment. In ERSPC, eight (3%) men received treatment with noncurative intent as secondary treatment, after primary curative treatment had failed. In PRIAS, four (1%) men received treatment with noncurative intent as secondary treatment, after primary curative treatment had failed. In PRIAS, 27 (10%) men switched to watchful waiting (WW) during follow-up. These findings are presented in Table 2.

In Kaplan-Meier analysis for OS, we observed no evidence of a difference between cohorts (Fig. 1). Similarly, Kaplan-Meier analysis was performed for the other endpoints (CSS, TFS, and MFS), and no differences were observed (Supplementary Fig. 1). As other causes of death

Table 2 – Follow-up data

	Main analysis (n = 518)		Sensitivity analysis (n = 400)	
	ERSPC (n = 241)	PRIAS (n = 277)	ERSPC (n = 123)	PRIAS (n = 277)
Follow-up time (yr), median (IQR)	9.5 (9.5–9.5)	5.2 (3.7–7.1)	9.5 (9.5–9.5)	5.2 (3.7–7.1)
Time to active treatment (yr), median (IQR)	2.8 (1.2–5.3)	1.2 (1.0–2.1)	3.5 (1.5–5.5)	1.2 (1.0–2.1)
Died during follow-up, n (%)	50 (21)	21 (8)	23 (19)	21 (8)
Died of prostate cancer, n (%)	5 (2)	1 (0)	2 (2)	1 (0)
Active treatment, n (%)	141 (59)	125 (45)	69 (56)	125 (45)
Treatment with curative intent	122 (51)	125 (45)	62 (50)	125 (45)
Radical prostatectomy	39 (32)	95 (76)	17 (27)	95 (76)
Radiation therapy \pm hormonal therapy	83 (68)	30 (24)	45 (73)	30 (24)
Treatment with noncurative intent	19 (8)	0 (0)	7 (7)	0 (0)
Orchiectomy	2 (1)	0 (0)	2 (2)	0 (0)
Hormonal castration	10 (4)	0 (0)	4 (3)	0 (0)
Antiandrogen	7 (3)	0 (0)	1 (1)	0 (0)
Secondary noncurative treatment	8 (3)	4 (1)	3 (2)	4 (1)
Development of metastasis	2 (1)	4 (1)	0 (0)	4 (1)
Watchful waiting, n (%)	0 (0)	27 (10)	0 (0)	27 (10)
Moved to other town, n (%)	2 (1)	3 (1)	2 (2)	3 (1)

ERSPC = European Randomized study of Screening for Prostate Cancer; IQR = interquartile range; PRIAS = Prostate cancer Research International: Active Surveillance.

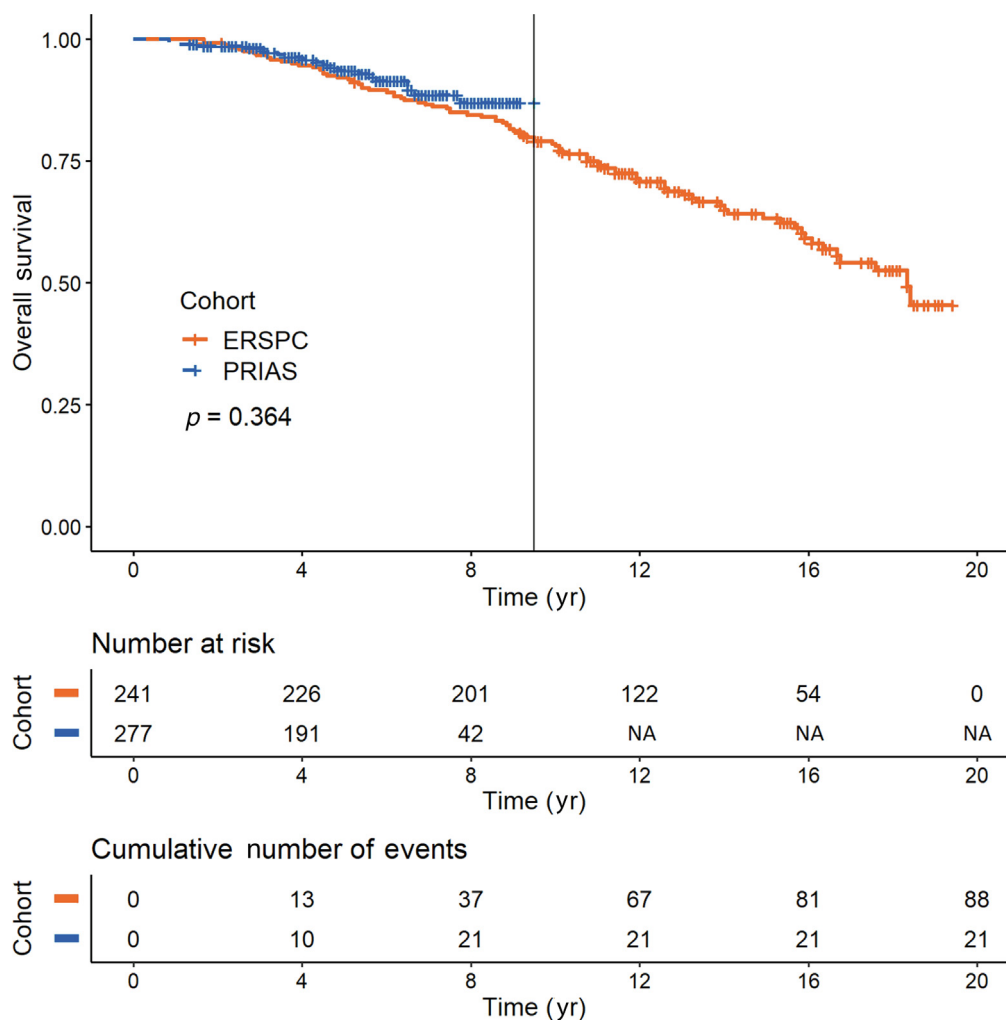


Fig. 1 – Kaplan-Meier curves for overall survival in the whole cohort with censoring for 9.5 yr at vertical line. The vertical line marks the cutoff point for statistical analyses, and data beyond this point were not used in survival analyses. ERSPC = European Randomized study of Screening for Prostate Cancer; NA = not available; PRIAS = Prostate cancer Research International: Active Surveillance.

are competing risks for CSS, TFS, and MFS, we next performed a competing risk analysis, and again no differences between cohorts were observed (Fig. 2). Results of the sensitivity analyses reflected the findings of the main analyses (Supplementary Fig. 2 and 3). During the follow-up, two (1%) men in the ERSPC cohort and four (1%) in the PRIAS cohort developed distant metastasis.

In the Cox proportional hazard regression analysis, PSA-D was associated with OS (hazard ratio [HR] 1.7 [95% confidence interval {CI} 1.3–2.3], $p < 0.001$) and with TFS (HR 1.3 [95% CI 1.1–1.6], $p = 0.003$). Age was associated with OS (HR 3.5 [95% CI 2.0–6.1], $p < 0.001$). None of the tested variables were associated with CSS or MFS. Cohort (PRIAS or ERSPC) was not associated with any of the survival outcomes (OS, CSS, MFS, or TFS). Findings are presented in Table 3.

4. Discussion

We aimed to assess whether a strict AS protocol is superior to a loose protocol regarding OS, CSS, MFS, and TFS in men diagnosed with low-risk PC, using the ERSPC (loose) and the

PRIAS (strict) cohorts. Our main finding is that patient important endpoints are rare, and there are no differences in any of the outcomes between cohorts during the first decade of follow-up. This questions the rationale of a strict AS protocol, at least during the initial follow-up period.

The follow-up was significantly longer in the ERSPC cohort, translating to more PC-related deaths and overall mortality, as expected. Thus, the absolute number of events between the cohorts should not be compared directly. Importantly, however, the absolute number of events is low even without a follow-up protocol. Furthermore, when survival was analyzed as a function of time (Kaplan-Meier method and competing risk analyses), there appear to be no differences between the cohorts. Further, in a Cox proportional hazard regression analysis, cohort (ERSPC or PRIAS) was not associated with any of the survival outcomes. In our study, strict surveillance did not provide benefit for patients for the studied outcomes. Questions have been raised before about the use of strict surveillance protocols, such as the PRIAS protocol [11,12]. In addition, data from the pre-PSA era suggest that men not followed accord-

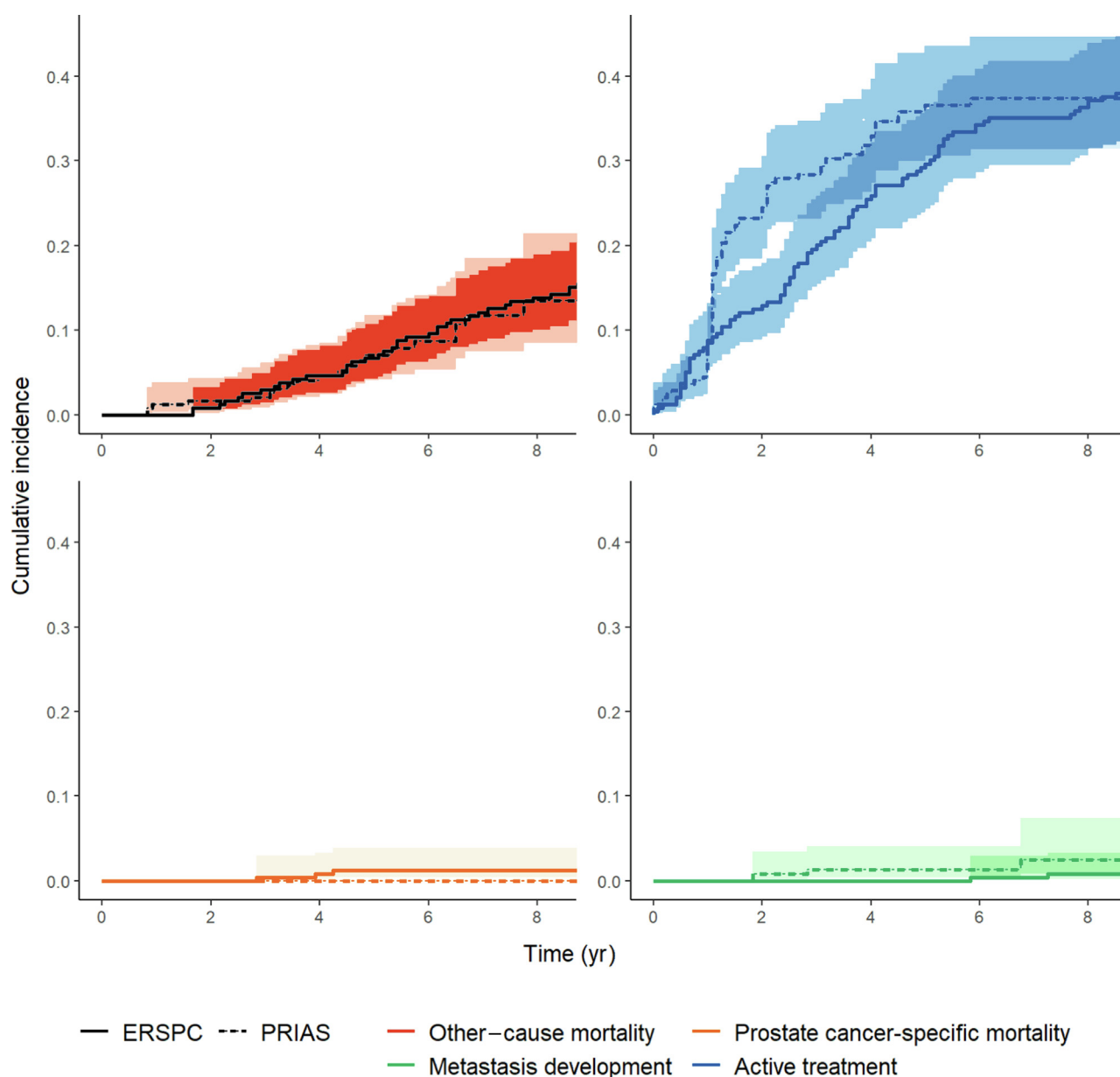


Fig. 2 – Competing risk analysis of other-cause mortality, prostate cancer-specific mortality, active treatment, and metastasis development with censoring for 9.5 yr (whole cohort). ERSPC = European Randomized study of Screening for Prostate Cancer; PRIAS = Prostate cancer Research International: Active Surveillance.

ing to a strict protocol still have excellent PC survival [13,14]. Interestingly, our results are also well in agreement with a recent study in which a simulation model was developed to study the impact of biopsy frequencies on mortality and development of metastasis in men on AS [15]. The authors concluded that a less frequent biopsy schedule might be the preferable option.

Active treatment was initiated in 141 (59%) of the ERSPC patients and 125 (45%) of the PRIAS patients, but there was no difference in TFS (Fig. 2). Similar active treatment rates have been reported in other AS studies [11,16]. One would expect active treatment to be initiated more often in the ERSPC cohort for several reasons. First, the cancers in the ERSPC cohort were more likely to be misclassified at diagnosis due to six versus 12 biopsy cores. Reclassification of

PC has been well established previously [17–20]. Second, some patients in the ERSPC cohort had more aggressive cancer at diagnosis, although this number was comparably small. Third, true biological progression of PC is more likely to have occurred in the ERSPC cohort as a consequence of the longer follow-up. An earlier surveillance study showed that progression can develop over a long period of time even in patients considered to be at low risk at diagnosis [13]. In that study, the authors detected a drop in CSS between 15 and 20 yr of follow-up. Whether this drop reflects true biological progression of the disease or, more likely, an artifact due a limited number of men at risk in that study at that time period remains to be elucidated. In our study, 27 (10%) patients in the PRIAS cohort discontinued AS and continued on WW. None of these patients died of

Table 3 – Multivariable Cox proportional hazard regression for overall, prostate cancer–specific, metastasis-free, and treatment-free survival^a

	HR	95% CI	p value
OS			
PSA	0.98	0.87–1.10	0.682
PSA density	1.72	1.28–2.31	<0.001
Age at diagnosis (10 yr)	3.50	1.99–6.14	<0.001
Year of diagnosis	1.05	0.94–1.16	0.406
Cohort (ERSPC or PRIAS)	0.88	0.36–2.15	0.772
CSS			
PSA	1.17	0.86–1.60	0.318
PSA density	0.75	0.21–2.73	0.663
Age at diagnosis (10 yr)	1.96	0.22–17.29	0.546
Year of diagnosis	0.86	0.60–1.23	0.410
Cohort (ERSPC or PRIAS)	1.24	0.03–47.93	0.908
MFS			
PSA	0.86	0.47–1.58	0.624
PSA density	10.95	0.41–289.59	0.152
Age at diagnosis (10 yr)	0.93	0.22–3.89	0.921
Year of diagnosis	1.04	0.58–1.83	0.906
Cohort (ERSPC or PRIAS)	NA	0.00–NA	0.998
TFS			
PSA	0.97	0.90–1.04	0.363
PSA density	1.30	1.09–1.55	0.003
Age at diagnosis (10 yr)	0.84	0.65–1.09	0.201
Year of diagnosis	0.95	0.90–1.00	0.073
Cohort (ERSPC or PRIAS)	1.45	0.86–2.44	0.159

CI = confidence interval; CSS = prostate cancer–specific survival; ERSPC = European Randomized study of Screening for Prostate Cancer; HR = hazard ratio; MFS = metastasis-free survival; NA = not available; OS = overall survival; PRIAS= Prostate cancer Research International: Active Surveillance; PSA = prostate-specific antigen; TFS = treatment-free survival.
^a Age was calculated in 10-yr units.

PC. This further underlines the benign nature of low-risk PC in relation to other comorbidities in these men. Furthermore, data from randomized trials in the PSA era show little benefit from immediate curative treatments over surveillance in terms of survival endpoints [21–23].

As expected, more men in the PRIAS cohort switched to active treatment at approximately 1 yr of AS (Fig. 2). The finding is probably an effect of the PRIAS protocol, since the first rebiopsy is taken at 1 yr of follow-up. PSA-DT is also evaluated for the first time at 1 yr and used as a trigger for active treatment. We have earlier shown in the PRIAS trial that although PSA-DT is a relatively sensitive trigger for active treatment, it is too unspecific. Approximately 50% of patients who undergo RP due to fast rising PSA (PSA-DT <3 yr) have clinically insignificant PC at final pathology [11]. This stresses the fact that triggers for active treatment in AS protocols need to be specific enough to alleviate the risk of overtreatment. Overtreatment still seems to pose a greater threat to the patient than progression of the disease itself.

Development of metastasis was very rare in both cohorts, and there was no difference in MFS between the cohorts (Fig. 2). Development of metastasis is a rare event in patients on AS, especially in the first years.

Primary treatment with noncurative intent was initiated in 19 (8%) patients in the ERSPC cohort, in contrast to none in the PRIAS cohort. Such a difference suggests an advantage for the PRIAS cohort, especially as both hormonal therapy and surgical castration are often associated with adverse effects and lower quality of life. It is tempting to speculate that this merely reflects differences of treatment approaches in different eras and that these men would

today be more likely to start WW instead of hormonal therapy. The past decades have witnessed a change in PC management owing to more effective and less burdensome radical treatments, and more precise and readily available imaging. Currently, hormonal therapy is rarely recommended solely based on rising PSA [24]. Another possible explanation why patients in the ERSPC cohort were assigned to noncurative treatment is their possible ineligibility for treatments such as RP or RT due to factors such as age and comorbidities.

The aim of AS is to postpone or even prevent active treatment of low-risk PC, thereby alleviating side effects inherent to all contemporary PC treatments. In order to achieve this, we need to know which criteria most precisely predict progression and a worse outcome. Our current results and previous research suggest that the current PRIAS criteria are too strict. This is especially important as adherence to AS protocols is poor, especially in respect to rebiopsies [25]. All contemporary AS protocols are highly dependent on routine rebiopsing. A possible explanation for nonadherence is the associated discomfort [26] and complications after biopsy [27–29]. Prostate MRI has emerged as a promising tool to diagnose clinically significant PCs more specifically [30,31]. MRI might also provide significant benefits in AS, comprising better risk stratification at diagnosis, less reclassification at follow-up, less biopsy-related discomfort [26,28], and thus better protocol adherence. However, contradictory results on MRI use in AS exist [30,32].

Finally, a recent study looked at the causes of anxiety in men with PC on AS [33]. They noted “PSA-related anxiety” in 31% of the patients. One could speculate that a more strict protocol may induce more distress regarding protocol-based follow-up activities (PSA measurement, imaging, DRE, and biopsies), while this needs to be balanced against fear and anxiety of cancer progression and can be studied properly only in a prospective randomized study.

While the strengths of our study are the prospectively collected cohorts, the analyses here are retrospective, ad hoc, and subject to bias. We tried to alleviate the inherent bias by conducting the sensitivity analysis. A longer follow-up, especially for the PRIAS cohort, is needed to verify the results. Another limitation is the low number of events for some of the studied endpoints. This limits the statistical power. The number of PC deaths and development of metastasis was very low in both cohorts, which is well documented for low-risk PC. However, besides being a limitation, the limited number of PC-specific endpoints is also an argument against a very strict protocol during the first years of surveillance—there is little room for improvement. Further strengths are the relatively large patient cohorts and long follow-up, especially for the ERSPC cohort, although we acknowledge the evident difference in follow-up times between the two cohorts. However, this is inherent to the study design and avoidable only in a prospective, comparative, and preferentially randomized trial.

5. Conclusions

Our results suggest that AS protocols that currently rely heavily on repeat biopsies and intensive PSA testing should

be revisited for the early follow-up period. We advocate a personalized and less strict follow-up for PC AS in the contemporary era, while we urge publication of long-term data.

Author contributions: Inari Kalalahti 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: Kalalahti, Vasarainen, Erickson, Rannikko.

Acquisition of data: Kalalahti, Vasarainen, Rannikko.

Analysis and interpretation of data: Kalalahti, Vasarainen, Erickson, Siipola, Tikkinen, Rannikko.

Drafting of the manuscript: Kalalahti, Vasarainen, Erickson, Siipola, Tikkinen, Rannikko.

Critical revision of the manuscript for important intellectual content: Kalalahti, Vasarainen, Erickson, Siipola, Tikkinen, Rannikko.

Statistical analysis: Kalalahti, Vasarainen, Erickson, Siipola, Rannikko.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euros.2021.09.016>.

References

- [1] Global Burden of Disease C Collaboration, Fitzmaurice C, Dicker D, et al. The global burden of cancer 2013. *JAMA. Oncol* 2015;1:505–27.
- [2] Klotz L. Active surveillance for low-risk prostate cancer. *Curr Opin Urol* 2017;27:225–30.
- [3] Kilpeläinen TP, Jarvinen P, Tikkinen KAO. Randomized trials show a consistent benefit of radical prostatectomy on mortality outcomes. *J Urol* 2019;202:1106–8.
- [4] Bul M, van den Bergh RC, Zhu X, et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. *BJU Int* 2012;110:1672–7.
- [5] Bruinsma SM, Bangma CH, Carroll PR, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. *Nat Rev Urol* 2016;13:151–67.
- [6] Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr follow-up of the European Randomized study of Screening for Prostate Cancer. *Eur Urol* 2019;76:43–51.
- [7] Srivastava S, Koay EJ, Borowsky AD, et al. Cancer overdiagnosis: a biological challenge and clinical dilemma. *Nat Rev Cancer* 2019;19:349–58.
- [8] Schroder FH, Denis LJ, Roobol M, et al. The story of the European Randomized study of Screening for Prostate Cancer. *BJU Int* 2003;92 (Suppl 2):1–13.
- [9] Finne P, Stenman UH, Maattanen L, et al. The Finnish trial of prostate cancer screening: where are we now? *BJU Int* 2003;92 (Suppl 2):22–6.
- [10] van den Bergh RC, Roemeling S, Roobol MJ, Roobol W, Schroder FH, Bangma CH. Prospective validation of active surveillance in prostate cancer: the PRIAS study. *Eur Urol* 2007;52:1560–3.
- [11] Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol* 2016;70:954–60.
- [12] van den Bergh RC, Vasarainen H, van der Poel HG, et al. Short-term outcomes of the prospective multicentre 'Prostate cancer research international: active surveillance' study. *BJU Int* 2010;105:956–62.
- [13] Albertsen PC, Hanley JA, Fine J. 20-Year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005;293:2095–101.
- [14] Popiolek M, Rider JR, Andren O, et al. Natural history of early, localized prostate cancer: a final report from three decades of follow-up. *Eur Urol* 2013;63:428–35.
- [15] Lange JM, Laviana AA, Penson DF, et al. Prostate cancer mortality and metastasis under different biopsy frequencies in North American active surveillance cohorts. *Cancer* 2020;126:583–92.
- [16] Marengi C, Alvisi MF, Palorini F, et al. Eleven-year management of prostate cancer patients on active surveillance: what have we learned? *Tumori* 2017;103:464–74.
- [17] 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.
- [18] Cary KC, Cowan JE, Sanford M, et al. Predictors of pathologic progression on biopsy among men on active surveillance for localized prostate cancer: the value of the pattern of surveillance biopsies. *Eur Urol* 2014;66:337–42.
- [19] Patel HD, Feng Z, Landis P, Trock BJ, Epstein JI, Carter HB. Prostate specific antigen velocity risk count predicts biopsy reclassification for men with very low risk prostate cancer. *J Urol* 2014;191:629–37.
- [20] Serkin FB, Soderdahl DW, Cullen J, Chen Y, Hernandez J. Patient risk stratification using Gleason score concordance and upgrading among men with prostate biopsy Gleason score 6 or 7. *Urol Oncol* 2010;28:302–7.
- [21] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375:1415–24.
- [22] Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203–13.
- [23] Wilt TJ, Vo TN, Langsetmo L, et al. Radical prostatectomy or observation for clinically localized prostate cancer: extended follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT). *Eur Urol* 2020;77:713–24.
- [24] Mottet N, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2011;59:572–83.
- [25] 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.
- [26] Eineluoto JT, Jarvinen P, Kilpeläinen T, et al. Patient experience of systematic versus fusion prostate biopsies. *Eur Urol Oncol* 2018;1:202–7.
- [27] Ehdäie B, Vertosick E, Spaliviero M, et al. The impact of repeat biopsies on infectious complications in men with prostate cancer on active surveillance. *J Urol* 2014;191:660–4.
- [28] Bokhorst LP, Lepistö I, Kakehi Y, et al. Complications after prostate biopsies in men on active surveillance and its effects on receiving further biopsies in the Prostate Cancer Research International: Active Surveillance (PRIAS) study. *BJU Int* 2016;118:366–71.
- [29] Kalalahti I, Huotari K, Lahdensuo K, et al. Rectal *E. coli* above ciprofloxacin ECOFF associate with infectious complications

- following prostate biopsy. *Eur J Clin Microbiol Infect Dis* 2018;37:1055–60.
- [30] Eineluoto JT, Jarvinen P, Kenttamies A, et al. Repeat multiparametric MRI in prostate cancer patients on active surveillance. *PLoS One* 2017;12:e0189272.
- [31] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate cancer diagnosis. *N Engl J Med* 2018;378:1767–77.
- [32] Tran GN, Leapman MS, Nguyen HG, et al. Magnetic resonance imaging-ultrasound fusion biopsy during prostate cancer active surveillance. *Eur Urol* 2017;72:275–81.
- [33] Alvisi MF, Dordoni P, Rancati T, et al. Supporting patients with untreated prostate cancer on active surveillance: what causes an increase in anxiety during the first 10 months? *Front Psychol* 2020;11:576459.