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Follow-up in Active Surveillance for Prostate Cancer: Strict Protocol Adherence Remains Important for PRIAS-ineligible Patients

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Abstract

Background: Active surveillance (AS) is a safe treatment strategy for men with low-risk prostate cancer (PC) when performed in a research setting using strict follow-up. However, less is known about the protocol adherence and outcomes for AS in real-world practice.

Objective: To evaluate Prostate Cancer Research International Active Surveillance (PRIAS) protocol adherence in a real-world cohort and to relate follow-up intensity to oncological safety.

Design, setting, and participants: Patients with biopsy-detected PC diagnosed from 2008 to 2014 treated with AS at six teaching hospitals in The Netherlands.

Intervention: AS included regular prostate-specific antigen (PSA) testing (every 3–6 mo) combined with a confirmatory biopsy 1 yr after diagnosis and every 3 yr thereafter.

Outcome measurements and statistical analysis: The proportions of patients complying with the PRIAS biopsy and PSA monitoring protocol were determined. We assessed if PRIAS-discordant follow-up was associated with a higher risk of metastasis compared with PRIAS-concordant follow-up using Cox regression analysis. Analysis was performed for separate risk groups (PRIAS-eligible and PRIAS-ineligible) on the basis of the PRIAS inclusion criteria.

Results and limitations: Of all patients on AS for >6 mo, 706/958 (74%) had PRIAS-concordant PSA monitoring. Overall concordant follow-up (PSA and repeat biopsy) was observed in 415/958 patients (43%). The percentage of patients with overall concordant follow-up varied between hospitals (range 34–60%; $p < 0.001$). Among PRIAS-ineligible patients, PRIAS-discordant PSA monitoring was associated with a higher risk of developing PC metastases during AS compared with patients with concordant follow-up (hazard ratio 5.25, 95% confidence interval 1.02–27.1). In the PRIAS-eligible population, we found no significant differences regarding rates of metastases between patients with discordant and concordant follow-up.

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Conclusions: We observed substantial variation in AS follow-up intensity between large urological practices in the Netherlands. Overall, 43% of patients on AS in daily clinical practice receive PRIAS-concordant follow-up. Noncompliance with the PRIAS follow-up protocol was associated with a higher rate of metastasis among PRIAS-ineligible patients, indicating that strict protocol adherence is important when these patients opt for AS.

Patient summary: Fewer than half of patients with prostate cancer on active surveillance are monitored according to the follow-up protocol of the largest ongoing active surveillance study. Lower-intensity monitoring may be less safe for patients who are not in the lowest risk group.

1. Introduction

The principle of active surveillance (AS) is to avoid overtreatment of clinically insignificant prostate cancer (PC) and to defer treatment until objective evidence of disease progression [1]. Favorable AS outcomes in a trial setting have led to its widespread acceptance [2–4]. However, the challenge remains to identify men with indolent disease among those with progressive PC at risk of missing the window of curability.

The protocols of published AS studies adhere to the same principles: repeat prostate biopsies (intensity varying per protocol, from yearly to every 3–4 yr) combined with regular prostate-specific antigen (PSA) testing every 3–6 mo [5]. However, these monitoring protocols are time-consuming and therefore expensive. Moreover, repeat biopsies are unpleasant for the patient and bear a risk of bleeding and infection. It is therefore conceivable that AS protocols are not followed as strictly in daily practice as is recommended by the prevailing guidelines. This hypothesis is supported by an inventory of real-world practice patterns in the USA, which revealed that <13% of PC patients undergo repeat biopsy beyond the first two years of AS [6]. Furthermore, a survey among European urologists indicated that 47% of those practicing AS do not use an official AS protocol or are not involved in a clinical AS trial [7]. A nationwide survey in Japan also showed that only 40.6% of the urologists surveyed performed a scheduled repeat biopsy at 1 yr after AS initiation [8]. The possible consequences of these AS protocol deviations with regard to oncological safety are for the most part unknown. This calls for research assessing the safety of lower-intensity AS monitoring.

In the present study, we evaluated AS follow-up strategies for PC in six large Dutch teaching hospitals covering up to 15% of PC patients in the Netherlands. We determined the proportions of patients who undergo follow-up testing according to the Dutch guidelines, which are based on the follow-up protocol of the Prostate Cancer International Active Surveillance (PRIAS) study [9]. Furthermore, we assessed if patients with low-intensity monitoring had a higher risk of missing the window of curability because of the development of metastatic PC during AS.

2. Patients and methods

2.1. Study setting and data collection

This study was conducted within the Santeon consortium, which consists of seven large nonacademic teaching hospitals in the Netherlands. During the study period, data for the AS cohorts from six of these seven hospitals were available. The study focuses on the same cohort of PC patients on AS diagnosed between January 1, 2008 and December 31, 2014 on which we reported previously [10].

Data collection and analysis included initial age and tumor characteristics at diagnosis, dates of follow-up serum PSA tests, repeat biopsies, magnetic resonance imaging (MRI) of the prostate, and metastasis rates [11].

2.2. Variation in follow-up strategy and compliance with PRIAS

The Dutch PC guidelines recommend that AS follow-up should be in accordance with the protocol as described in PRIAS [12]. This includes a PSA test every 3 mo in the first 2 yr, and every 6 mo thereafter. Scheduled repeat biopsies should be performed at 1, 4, 7, and 10 yr following diagnosis.

Definitions used for follow-up compliance with the PRIAS protocol were comparable to those published by the PRIAS study group [13]. PSA follow-up was regarded as concordant if a patient had undergone ≥75% of the recommended number of PSA tests for their follow-up duration. For example, a patient with an AS duration of 14 mo should have undergone three or more PSA tests to be regarded as compliant.

To assess compliance with repeat biopsy testing, we evaluated the percentage of patients who underwent the first (1 yr), second (4 yr), and third biopsy (7 yr) among men with follow-up of >1.5, >4.5, and >7.5 yr, respectively. We also determined the percentage of patients who received all scheduled biopsies according to the protocol, taking AS duration into account. Follow-up was scored as discordant if a patient should have undergone one or more biopsies according to the follow-up scheme, but missed one or more. A separate analysis was performed to determine in how many cases MRI of the prostate were performed instead of a prostate biopsy. Protocol adherent follow-up was assessed in patients with an AS duration of >6 mo.

We assessed whether discordant follow-up was associated with a higher rate of metastasis during AS follow-up using risk classification based on the PRIAS inclusion criteria: PSA ≤10 ng/ml, PSA density <0.2 ng/ml/ml, Gleason ≤6, fewer than three positive biopsy cores, and clinical stage ≤T2 [9]. Patients were classified as PRIAS-eligible if they met all these criteria at baseline, and PRIAS-ineligible if they did not.

2.3. Outcome measures

Our primary outcome measure was the total percentages of patients who received PSA monitoring, repeat biopsy testing, and overall follow-up (PSA and biopsies combined) concordant with the PRIAS follow-up protocol. Differences between hospitals in the proportion of patients with concordant follow-up were determined. A secondary outcome measure was the rate of metastasis (bone and/or lymph node) during AS monitoring. A patient was considered to have developed metastatic PC during AS follow-up (time between the date of diagnosis and discontinuation of AS) if metastases were detected via diagnostic imaging (MRI, choline or prostate-specific membrane antigen positron emission tomography/computed tomography for lymph node metastasis and/or visceral metastasis and a bone scan for bone metastasis) or lymph node metastasis found via lymph node dissection.

2.4. Statistical analysis

Possible significant differences in mean values between hospitals were assessed using one-way analysis of variance. We evaluated differences in the proportion of patients using Fisher's exact test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using univariable Cox regression. Analysis was performed using SPSS for Windows v.24.0 (IBM Corp, Armonk, NY, USA). A p value of <0.05 was considered significant.

3. Results

3.1. Study population

A total of 1181 patients were diagnosed with PC and enrolled in AS between January 1, 2008 and December 31, 2014 at six Santeon hospitals. This included an initial 181/1181 patients (15%) with incidental tumors (cT1a/b), who were later excluded. Baseline characteristics for the 1000 patients with screen-detected PC on AS are presented in Table 1. The table shows differences between hospitals with regard to baseline serum PSA, PSA density, number of positive biopsy cores, and proportions of PRIAS-eligible and PRIAS-ineligible patients.

3.2. PSA follow-up testing

A total of 958 patients had treatment-free follow-up of more than 6 mo. The percentages of patients receiving PRIAS-concordant and -discordant PSA testing are presented in Fig. 1. The variation between hospitals was considerable. Hospital 1 had the highest compliance, as 83% of patients had PRIAS-concordant PSA monitoring. The least strict monitoring occurred in hospital 4, where only 55% of the patients has PRIAS-concordant PSA monitoring. Overall, 706/958 patients (74%) had PRIAS-concordant PSA monitoring. The proportion of patients with a PSA doubling time (PSADT) of <3 yr did not differ significantly between the groups with discordant and concordant PSA follow-up (42% vs 48%; $p = 0.156$). The group of patients with discordant PSA testing was slightly younger (mean age 66.8 vs 68.7 yr; $p < 0.001$).

3.3. Repeat biopsies and overall PRIAS-concordant follow-up

Protocol adherence regarding scheduled prostate biopsies also differed between hospitals. As can be seen in Fig. 2, the highest percentage of patient compliance with the first

Table 1 – Baseline characteristics of the active surveillance patient population by hospital[a]

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	p value
Patients (n)	248	144	166	178	78	186	
Age (yr)	67.9 ± 6.4	67.3 ± 6.5	68.1 ± 6.6	67.4 ± 5.6	67.6 ± 5.7	65.3 ± 6.8	<0.001
PSA (ng/ml)	8.2 ± 5.4	7.4 ± 3.4	7.0 ± 3.3	9.2 ± 4.8	8.2 ± 4.1	8.6 ± 4.9	<0.001
PSAD (ng/ml/ml)	0.17 ± 0.14	0.18 ± 0.11	0.14 ± 0.07	0.21 ± 0.12	0.19 ± 0.11	0.18 ± 0.12	<0.001
cT stage, n (%)[b]							
T1c	200 (81)	110 (76)	104 (63)	144 (81)	74 (95)	156 (84)	
T2a	11 (4)	10 (7)	25 (15)	8 (5)	1 (1)	9 (5)	
T2b	2 (1)	1 (1)	4 (2)	7 (4)	0 (0)	0 (0)	
T2c	4 (2)	3 (2)	0 (0)	4 (2)	0 (0)	4 (2)	
T2	24 (10)	19 (12)	31 (19)	15 (8)	3 (3)	16 (9)	
T3/T4	7 (3)	1 (1)	2 (1)	0 (0)	0 (0)	1 (1)	
Total biopsy cores (n)	9.4 ± 2.1	9.5 ± 1.7	8.9 ± 2.2	8.7 ± 2.4	9.9 ± 0.7	8.1 ± 1.2	<0.001
Positive cores (n)	1.8 ± 1.1	1.6 ± 1.0	1.6 ± 0.9	1.8 ± 1.2	1.6 ± 1.1	1.4 ± 0.8	<0.001
GS, n (%)							
4	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	2 (1)	
5	0 (0)	5 (4)	0 (0)	0 (0)	2 (3)	3 (2)	
6	230 (93)	136 (83)	165 (99)	171 (96)	74 (95)	169 (91)	
3 + 4	15 (6)	10 (6)	1 (1)	6 (3)	2 (3)	12 (7)	
4 + 3	3 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	
Risk group, n (%)[c]							
PRIAS-eligible	123 (50)	85 (59)	104 (63)	60 (34)	36 (46)	102 (55)	
PRIAS-ineligible	125 (50)	59 (41)	62 (37)	118 (66)	42 (54)	84 (45)	

PSA = prostate-specific antigen; PSAD = PSA density (PSA/prostate volume measured via transrectal ultrasound or magnetic resonance imaging); GS = Gleason sum score at diagnosis

[a] Results for continuous variables are reported as mean ± standard deviation.

[b] Clinical T stage based on digital rectal examination and transrectal ultrasonography

[c] Risk classification based on PRIAS. PRIAS-eligible: PSA ≤10 ng/ml, PSAD <0.2 ng/ml/ml, GS ≤6, <3 positive biopsy cores, and cT stage ≤T2; PRIAS-ineligible: not complying with one or more of the PRIAS inclusion criteria listed for eligibility.

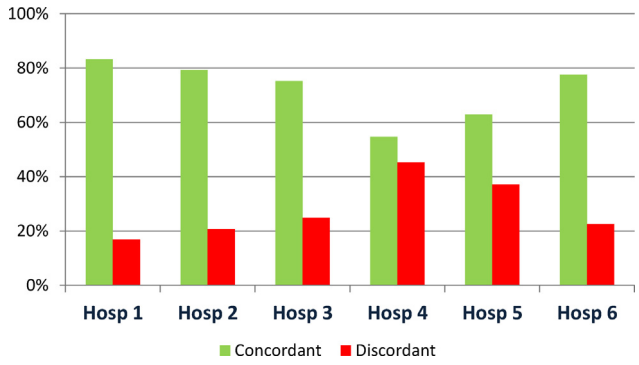

Fig. 1 – Percentage of patients with PRIAS concordant PSA testing. For PRIAS-concordant testing, patients underwent ≥75% of the recommended PSA tests, according to AS duration. For PRIAS-discordant testing, patients underwent <75% of the total PSA tests recommended by the PRIAS protocol.

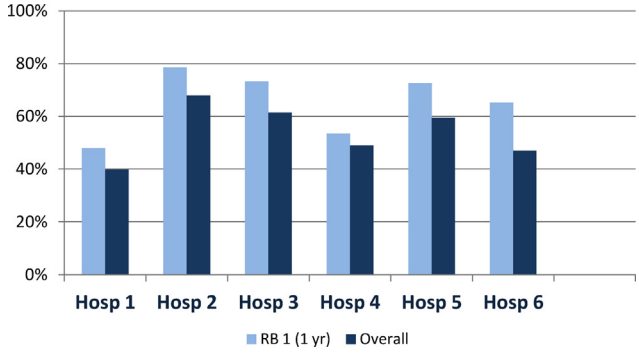

Fig. 2 – Percentage of patients with PRIAS-concordant follow-up biopsies. RB 1 = first repeat biopsy at 1 yr after diagnosis; Overall = compliant with all scheduled biopsies according to AS duration.

scheduled repeat biopsy was in hospital 2 (79%), while the lowest was in hospital 1 (48%). In the overall population, 473/912 patients (52%) were compliant with all scheduled repeat biopsies during their follow-up. At an institutional level, the highest percentage was found in hospital 2 (68%) and the lowest in hospital 1 (40%).

There was also great variation between hospitals in the percentage of patients with overall PRIAS-concordant follow-up; hospital 4 had the lowest proportion of patients with overall concordant follow-up (34%) and hospital 2 had the highest (60%; Fig. 3).

3.4. *MRI for follow-up*

MRI of the prostate was performed during follow-up in 449/1000 patients (45%). The proportion of patients undergoing prostate MRI during AS varied significantly among institutions. The highest percentage was observed in hospital 6 (104/186, 56%) and the lowest in hospital 5 (22/78, 28%; $p < 0.001$). In some cases, MRI was performed instead of repeat biopsy. In a total of 41 patients, MRI of the prostate was performed instead of the first repeat biopsy. If we consider patients as compliant if MRI was performed instead of the scheduled biopsy, the total number of patients with PRIAS-concordant repeat biopsy (or MRI) follow-up would increase from 473/912 (52%) to 537/912 (59%). Prostate MRI increasingly replaced prostate biopsies over time. Of all patients diagnosed in 2008, 2/90 (2%) underwent MRI instead of the first repeat biopsy. Among patients diagnosed in 2014, this was performed in 15/126 cases (12%).

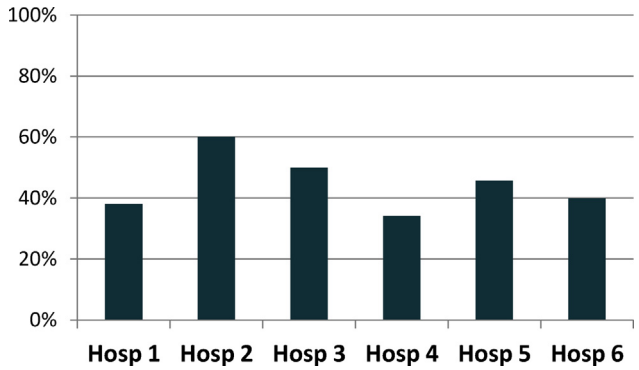

Fig. 3 – Percentages of patients with overall PRIAS-concordant follow-up (concordant PSA monitoring and biopsy testing).

3.5. *Follow-up intensity and oncological outcome*

A total of 13 patients developed metastatic PC (positive lymph nodes and/or bone metastasis) while on AS, and thus missed the window of curability during monitoring. The median duration of AS was 40.8 mo (interquartile range 16.8–59.1). The baseline characteristics for these patients are presented in Table 2.

To evaluate the potential association between follow-up intensity and unfavorable oncological outcomes, data for men who developed metastatic PC during AS follow-up were analyzed. The rate of metastasis was significantly higher among men who had low-intensity PSA monitoring (<75% of recommended; Table 3). In the PRIAS-ineligible risk group, the HR for developing metastasis during AS was significantly higher among patients with discordant PSA monitoring than the concordant PSA monitoring group (HR 5.3, 95% CI 1.02–27.10).

We found no significant correlation between discordant biopsy testing and the rate of metastasis for both the PRIAS-eligible and PRIAS-ineligible subgroups ($p = 0.6$). However, among all the patients with discordant biopsy testing, 35% had rapidly increasing PSA levels (defined as PSADT <3 yr), which is significantly lower than for the concordant biopsy group (54%; $p < 0.001$).

In the PRIAS-ineligible group, overall discordant follow-up (discordant PSA monitoring and/or discordant biopsy testing) was also associated with a higher rate of metastatic PC (2% vs 0%; $p = 0.047$).

4. Discussion

In this study, we observed significant variation in AS protocol adherence between six large teaching hospitals in

Table 2 – Patients who developed metastatic prostate cancer during AS FU

H	No	cT	PSA (ng/ml)	Pos. cores (*n*)	GG	Risk group[a]	PRIAS eligible	PSADT (yr)	Location[b]	AS FU (mo)	PRIAS-C	
											PSA	RB
1	626	T2	23.0	1	1	High	No	3.4	LN	26	No	No
	912	T2	11.4	7	2	Intm.	No	1.4	LN	19	Yes	No
2	1192	T2	7.4	2	1	Low	Yes	0.9	Bone	13	Yes	Yes
	1241	T1c	6.3	1	1	Low	Yes	9.3	LN	84	Yes	Yes
3	1881	T1c	9.0	1	1	Low	No	4.6	Bone	49	No	Yes
4	1497	T1c	16.0	1	1	Intm.	No	0.3	LN	25	No	Yes
	1508	T2b	5.9	2	1	Low	Yes	1.9	Bone, LN	39	No	No
	1577	T1c	17.0	1	1	Intm.	No	0.9	Bone, LN	11	No	Yes
5	2280	T1c	10.0	3	1	Low	No	1.3	LN	13	No	Yes
	2284	T1c	5.8	1	1	Low	Yes	1.2	LN	7	Yes	Yes
	2330	T1c	4.9	1	1	Low	Yes	1.1	LN	4	Yes	Yes
	2573	T1c	7.0	1	1	Low	No	7.5	Bone	73	Yes	No
6	2843	T2	7.0	1	1	Low	Yes	2.1	LN	24	No	No

AS = active surveillance; H = hospital; PSA = prostate-specific antigen; Pos. = positive; GG = grade group; Intm. = intermediate; PSADT = PSA doubling time; LN = lymph node; FU = follow-up; PRIAS-C = PRIAS-compliant; RB = repeat biopsy.
[a] Risk group classification (modified D'Amico) based on the following parameters. Low risk: PSA ≤10 ng/ml and Gleason ≤6 and cT stage ≤T2; intermediate risk: PSA 10–20 ng/ml and/or Gleason >6 and cT stage ≤T2; high risk: PSA >20 ng/ml and/or Gleason >7 and/or cT stage >T2.
[b] Location where metastatic prostate cancer was found (no distinction between distant and local LNs).

Table 3 – Risk of metastasis for low-intensity monitoring by risk group

	FU	Patients who developed mPC during AS, *n*/*N* (%)	*p* value[a]	HR (95% CI)
PSA				
PRIAS-eligible (*n* = 495)	Discordant PSA monitoring	2/104 (2)	0.611	2.39 (0.42–13.50)
	Concordant PSA monitoring[b]	4/391 (1)		
PRIAS-ineligible (*n* = 463)	Discordant PSA monitoring	5/148 (3)	0.037	5.25 (1.02–27.1)
	Concordant PSA monitoring	2/315 (1)		
Biopsy				
PRIAS-eligible (*n* = 481)	Discordant RB testing[c]	2/210 (1)		
	Concordant RB testen	4/271 (2)	0.701	0.36 (0.06–2.08)
PRIAS-ineligible (*n* = 431)	Discordant RB testing	3/229 (1)		
	Concordant RB testen	4/202 (2)	0.711	0.32 (0.07–1.51)
Overall				
PRIAS-eligible (*n* = 495)	Overall discordant FU	2/257 (1)	0.434	0.30 (0.05–1.69)
	Overall concordant FU[d]	4/238 (2)		
PRIAS-ineligible (*n* = 463)	Overall discordant FU	7/286 (2)	0.047	32.9 (0.02–51163.29)
	Overall concordant FU	0/177 (0)		

AS = active surveillance; mPC = metastatic prostate cancer; RB = repeat biopsy; FU = follow-up; HR = hazard ratio; CI = confidence interval.
[a] Fisher's exact test.
[b] Patients underwent ≥75% of recommended PSA tests according to the PRIAS protocol for their AS duration.
[c] Patients underwent all scheduled RBs for their AS duration.
[d] Patients underwent PRIAS-concordant PSA monitoring and RB testing.

the Netherlands. In the overall population, 43% of the patients on AS received follow-up concordant with PRIAS. These are important findings, as they confirm our hypothesis that AS follow-up is less strict in daily clinical practice.

Results from a large number of prospective AS cohorts have been published in the literature [12,14–21]. However, results for compliance rates with the respective follow-up protocols are limited. We identified two other study groups that performed comparable research. Our findings are in line with their results, as Luckenbaugh et al. [22] also observed limited protocol adherence in a real-world cohort treated with AS at collaborating urological practices in Michigan (MUSIC). The authors reported that 26.5% of the patients who remained on AS for a minimum of 2 yr had follow-up compliant with the National Comprehensive Cancer Network guidelines [22]. The PRIAS study group reported that 91% of patients complied with all PSA visits and 81% complied with the 1-yr prostate biopsy [16]. Overall percentages in our cohort were lower, as we observed that 74% of patients (706/958) had concordant PSA testing and 63% (570/912) complied with the first repeat biopsy. The differences between the PRIAS cohort and the real-world populations described in the present study and the MUSIC study indicate that there is a substantial gap regarding AS protocol adherence between the research setting and daily practice. The size of this gap may also differ at an institutional level, as significant differences between institutions were observed in both studies.

Noncompliance with AS protocols is understandable, as patients consider repeat biopsies painful [13]. Moreover, biopsies are associated with several complications such as pain, hematuria, urinary tract infections, and even urosepsis [23]. Given the significant burden, costs, and time associated with frequent monitoring, we have to deliberate on the intensity of AS follow-up schedules. However, it remains challenging to determine for whom and to what extent the intensity of AS follow-up schedules can be reduced. Given the higher risk of missing the window of curability, low-intensity monitoring may not be a safe option for PRIAS-ineligible patients. However, we found no significant difference in the rate of metastasis between discordant and concordant monitoring in the PRIAS-eligible group. This suggests that patients who can be classified with the lowest risk at diagnosis might be candidates for a less intensive follow-up schedule without being at risk of worsening of their prognosis.

We did not observe a higher rate of metastasis among patients noncompliant with the PRIAS repeat biopsy schedule in comparison to compliant patients. The lack of association between biopsy noncompliance and prognosis can be partly explained by the fact that most of these men did not have rapidly increasing PSA (65% had a PSADT of $>$3 yr). Of the patients who were compliant, 54% had a PSADT of $<$3 yr, indicating that repeat biopsies were performed more frequently in cases with faster rising PSA. This indicates that the decision to repeat prostate biopsy was partly based on serial serum PSA results instead of the protocol advised. This can be further explained by taking hospital 1 as an example. Hospital 1 had the lowest percentage of patients complying with 1-yr repeat biopsy (48%) but the highest percentage of patients with concordant PSA monitoring (83%). The rate of metastasis was relatively low in this hospital (2/248, 1%) in comparison to the other clinics. These findings suggest that deviating from the repeat biopsy protocol may be safe as long as PSA kinetics are monitored closely.

The strengths of our study include the large sample size, a study population representing the real-world clinical situation, and evaluation of AS management strategies including a wide range of follow-up tests. Besides the strengths of the study, some limitations should be acknowledged. First, the retrospective nature of the study is a limitation and carries a risk of bias due to confounding by indication, especially concerning allocation of patients to a low- or high-intensity monitoring strategy. However, given the fact that it is possible that patients with more aggressive tumors received closer monitoring than patients with less aggressive tumors, we still found significant differences regarding rates of metastasis. Thus, this form of bias has not altered our conclusions. Second, we only evaluated whether AS follow-up was concordant with the PRIAS follow-up guidelines. We did not evaluate deviations from the PRIAS protocol regarding recommendations for discontinuation of AS (ie, Gleason sum score $\geq$7 on repeat biopsy or $>$2 cores positive). Therefore, we cannot assess the potential impact of this on our observed outcomes, as we do not know which patients remained on AS despite Gleason upgrading or a substantial increase in tumor volume. However, we did collect data for an individual's PSA course, which also provides important information on tumor aggressiveness.

5. Conclusions

Compliance with an AS protocol in a real-world cohort is low: 43% of patients on AS in daily clinical practice receive PRIAS-concordant follow-up (52% comply with the biopsy schedule and 74% with the PSA schedule). Compliance rates vary substantially between hospitals, indicating a need for a better understanding of outcomes among patients receiving PRIAS-concordant and PRIAS-discordant follow-up. Noncompliance with the PRIAS follow-up protocol was associated with a higher rate of metastasis among PRIAS-ineligible patients. Higher rates of metastasis were found for discordant PSA monitoring, but not among patients not complying with the biopsy schedule, suggesting that PSA compliance is more important, since low biopsy compliance seemed to be "compensated" by high PSA compliance. The fact that discordant follow-up was not associated with a higher rate of metastasis among PRIAS-eligible patients suggests that less strict monitoring may be safe in this subgroup. This information is vital in our journey towards a more individualized approach for AS follow-up intensity depending on the patient's preferences and baseline tumor characteristics.

Author contributions: Timo F.W. Soeterik 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: Soeterik, Dijksman, van Melick, van Basten.
Acquisition of data: Soeterik.
Analysis and interpretation of data: Soeterik, Dijksman, van Melick, van Basten.
Drafting of the manuscript: Soeterik, Dijksman, van Melick, van Basten, Witjes, Biesma.
Critical revision of the manuscript for important intellectual content: Soeterik, Dijksman, van Melick, van Basten, Witjes, Biesma.
Statistical analysis: Soeterik.
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Supervision: Dijksman, van Melick, van Basten, Witjes, Biesma.
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References

[1] Bruinsma SM, Bokhorst LP, Roobol MJ, Bangma CH. How often is biopsy necessary in patients with prostate cancer on active surveillance? J Urol 2016;195:11–2.

[2] Loeb S, Berglund A, Stattin P. Population based study of use and determinants of active surveillance and watchful waiting for low and intermediate risk prostate cancer. J Urol 2013;190:1742–9.

[3] Weerakoon M, Papa N, Lawrentschuk N, et al. The current use of active surveillance in an Australian cohort of men: a pattern of care analysis from the Victorian Prostate Cancer Registry. BJU Int 2015;115(Suppl 5):50–6.

[4] Loeb S, Folkvaljon Y, Curnyn C, Robinson D, Bratt O, Stattin P. Uptake of active surveillance for very-low-risk prostate cancer in Sweden. JAMA Oncol 2017;3:1393–8.

[5] Tosoian JJ, Carter HB, Lepor A, Loeb S. Active surveillance for prostate cancer: current evidence and contemporary state of practice. Nat Rev Urol 2016;13:205–15.

[6] Loeb S, Walter D, Curnyn C, Gold HT, Lepor H, Makarov DV. How active is active surveillance? Intensity of followup during active surveillance for prostate cancer in the United States. J Urol 2016;196:721–6.

[7] Azmi A, Dillon RA, Borghesi S, et al. Active surveillance for low-risk prostate cancer: diversity of practice across Europe. Ir J Med Sci 2015;184:305–11.

[8] Mitsuzuka K, Koga H, Sugimoto M, et al. Current use of active surveillance for localized prostate cancer: a nationwide survey in Japan. Int J Urol 2015;22:754–9.

[9] 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.

[10] Soeterik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, van Basten JA. Active surveillance for prostate cancer in a real-life cohort: comparing outcomes for PRIAS-eligible and PRIAS-ineligible patients. Eur Urol Oncol 2018;1:231–7.

[11] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.

[12] 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.

[13] 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.

[14] Barnett CL, Auffenberg GB, Cheng Z, et al. Optimizing active surveillance strategies to balance the competing goals of early detection of grade progression and minimizing harm from biopsies. Cancer 2018;124:698–705.

[15] Kearns JT, Faino AV, Newcomb LF, et al. Role of surveillance biopsy with no cancer as a prognostic marker for reclassification: results from the Canary prostate active surveillance study. Eur Urol 2018;73:706–12.

[16] Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272–7.

[17] Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J. Long-term results of active surveillance in the Göteborg randomized, population-based prostate cancer screening trial. Eur Urol 2016;70:760–6.

[18] Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. Eur Urol 2013;64:981–7.

[19] Thompson JE, Hayen A, Landau A, et al. Medium-term oncological outcomes for extended vs saturation biopsy and transrectal vs transperineal biopsy in active surveillance for prostate cancer. BJU Int 2015;115:884–91.

[20] Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33:3379–85.

[21] Eggener SE, Mueller A, Berglund RK, et al. A multi-institutional evaluation of active surveillance for low risk prostate cancer. J Urol 2013;189:S19–25.

[22] Luckenbaugh AN, Auffenberg GB, Hawken SR, et al. Variation in guideline concordant active surveillance followup in diverse urology practices. J Urol 2017;197:621–6.

[23] Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64:876–92.