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Active Surveillance for Incidental (cT1a/b) Prostate Cancer: Long-Term Outcomes of the Prospective Noninterventional HAROW Study

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Keywords
HAROW study · Active surveillance · Incidental prostate cancer · Health-service research · T1a prostate cancer · T1b prostate cancer

Abstract
Introduction: Optimal treatment for incidental prostate cancer (IPC) after surgical treatment for benign prostate obstruction is still debatable. We report on long-term outcomes of IPC patients managed with active surveillance (AS) in a German multicenter study. ***Methods:*** HAROW (2008–2013) was designed as a noninterventional, prospective, health-service research study for patients with localized prostate cancer (≤cT2), including patients with IPC (cT1a/b). A follow-up examination of all patients treated with AS was carried out. Overall, cancer-specific, and metastasis-free survival and discontinuation rates were determined. ***Results:*** Of 210 IPC patients, 68 opted for AS and were available for evaluation. Fifty-four patients had cT1a category and 14 cT1b category. Median follow-up was 7.7 years (IQR: 5.7–9.1). Eight patients died of which 6 were still under AS or watchful waiting (WW). No PCa-specific death could be observed. One patient developed metastasis. Twenty-three patients (33.8%) discontinued AS changing to invasive treatment: 12 chose radical prostatectomy, 7 radiotherapy, and 4 hormonal treatment. Another 19 patients switched to WW. The Kaplan-Meier estimated 10-year overall, cancer-specific, metastasis-free, and intervention-free survival was 83.8% (95% CI: 72.2–95.3), 100%, 98.4% (95% CI: 95.3–99.9), and 61.0% (95% CI: 47.7–74.3), respectively. In multivariable analysis, age (RR: 0.97; $p < 0.001$), PSA density ≥0.2 ng/mL^2 (RR: 13.23; $p < 0.001$), and PSA ≥1.0 ng/mL after surgery (RR: 5.19; $p = 0.016$) were significantly predictive for receiving an invasive treatment. ***Conclusion:*** In comparison with other AS series with a general low-risk prostate cancer population, our study confirmed the promising survival outcomes for IPC patients, whereas discontinuation rates seem to be lower for IPC. Thus, IPC patients at low risk of progression may be good candidates for AS.

Introduction

Incidental prostate cancer (IPC) is a tumor diagnosed after surgical treatment for benign prostate obstruction (BPO). According to the current tumor-node-metastasis

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(TNM) classification, IPC is subdivided into stage T1a (≤5%) and stage T1b (>5% of the resected tissue) [1, 2]. Treatment modalities for these tumors include active surveillance (AS), radical prostatectomy (RP), radiation therapy (RT), hormone therapy (HT), or watchful waiting (WW). Since many IPCs have a low progression rate [3] and up to 30% of specimens after subsequent RP do not exhibit residual tumor (pT0) [4], it remains unclear which patients benefit from invasive treatment (RP, RT, and HT) and which benefit from noninvasive management (AS and WW). In recent years, AS has been increasingly used in patients with low-risk prostate cancer [5, 6] and is therefore also suitable for patients with IPC and a favorable risk profile. In contrast to the palliative WW, AS implies curative intention. Prostate-specific antigen (PSA) assessment, digital-rectal examination (DRE), and rebiopsies are performed frequently in order to switch to an invasive treatment when signs of progression appear [7, 8]. However, due to the low detection rate of 4–9% of prostate cancer after surgical BPO treatment [9–13], data on oncological outcomes of IPC patients are scarce, especially of those managed with AS.

HAROW (2008–2013) was designed as a prospective, multicenter, health-service research study with the aim of investigating the treatment of localized prostate cancer, including IPC, in the community setting in Germany [14]. We herein report on the subgroup of IPC patients who opted for AS as primary treatment. Our results include long-term outcomes with up to 11 years of follow-up, including overall, cancer-specific, and metastasis-free survival, as well as discontinuation rates and risk factors for deferred invasive treatment.

Materials and Methods

HAROW Study

From July 2008 to July 2013, patients with newly diagnosed localized prostate cancer (≤T2c) were prospectively enrolled by 259 study centers, of whom 86% were office-based urologists. Half of them (n = 131) recruited patients in AS. Although AS was mentioned in the guidelines of the European Association of Urology (EAU) at that time [15], it was still largely unknown, or reluctantly accepted, among German urologists. Because of the noninterventional character of the study, participants received recommendations only regarding inclusion, follow-up, and discontinuation of AS, all of them corresponding to those available in the literature at that time [16] and the European PRIAS study (Prostate Cancer Research International Active Surveillance), the then largest published prospective trial of AS [17]. Inclusion criteria for AS were T category ≤cT2c, PSA ≤10 ng/mL, Gleason grade group 1, PSA density ≤0.2 ng/mL^2, and ≤2 positive biopsies. Based on these recommendations, it was possible to also include patients with IPC.

The recommended follow-up procedure included DRE, PSA, and PSA doubling time (PSA-DT) every 3 months during the first 2 years and every 6 months thereafter. Rebiopsy was recommended after 1 year and then every 3 years. Discontinuation of AS was recommended in case of histological evidence of progressive disease, increasing PSA levels with PSA-DT <3 years, or clinical signs of progression on DRE, alternatively on patient's request. Data of recruitment, diagnostics, and course of disease in the total cohort and the IPC cohort with a median observation period of 26.5 months have been published elsewhere [18, 19].

Follow-Up of the AS Group

A follow-up survey of all AS patients including patients who had switched to another treatment was carried out until August 2019. Questionnaires were sent to the patients by mail. All nonresponders were contacted again and interviewed by telephone. In case of missing response or lacking information on course of the disease including cause of death, treating study physicians were contacted. The following parameters were collected: overall, cancer-specific, metastasis-free, and intervention-free survival; reasons for discontinuation of AS; and type of deferred treatment. We herein present a subgroup analysis of the IPC patients.

Statistical Analysis

Data were analyzed using IBM's statistical program SPSS, version 22. The metric variables were evaluated by means of univariate ANOVA. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. Kaplan-Meier method and log-rank test were used to analyze overall, metastasis-free, and invasive-treatment-free survival. We have used logistic regression as a multivariate analysis to determine independent factors influencing the target variable "receiving interventional treatment." The significance level was set at 5% for all calculations.

Results

Of 2,957 patients enrolled in HAROW, 210 (7.1%) had IPC (cT1a/b), of which 99 (47.1%) opted for AS as treatment modality. Reasons for drop-out during the study and follow-up included consent withdrawn (n = 7), lost to follow-up (n = 19), and other reasons, for example, change of residence and physician abandoned practice (n = 5). Finally, data from 68 patients were available for evaluation (Fig. 1).

Patient characteristics at baseline are presented in Table 1. Median age was 69.9 years (interquartile range [IQR] = 63.6–72.5). Fifty-four (79.4%) patients presented with a tumor of cT1a category and 14 (20.6%) with cT1b category. The majority had Gleason grade group = 1 (94.1%), PSA <4 ng/mL (57.4%), and PSA density <0.2 ng/mL^2 (76.5%).

Median follow-up was 7.7 years (IQR: 5.7–9.1, min-max: 0.1–10.7). In this period, 8/68 patients (11.8%) died, 6 of whom under AS or WW, at the median age of 72 years

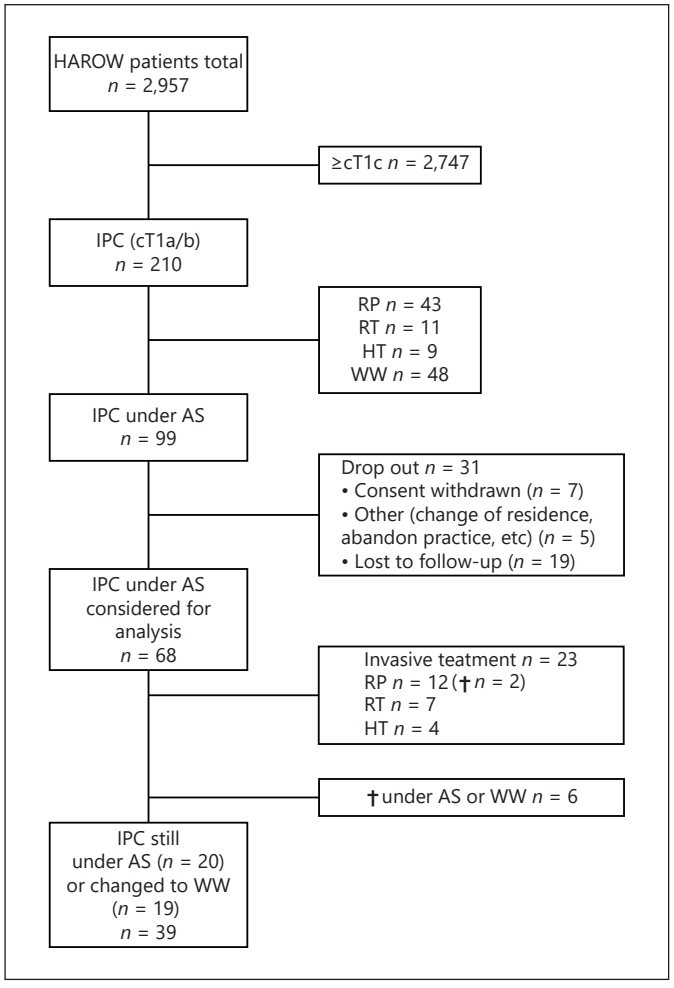
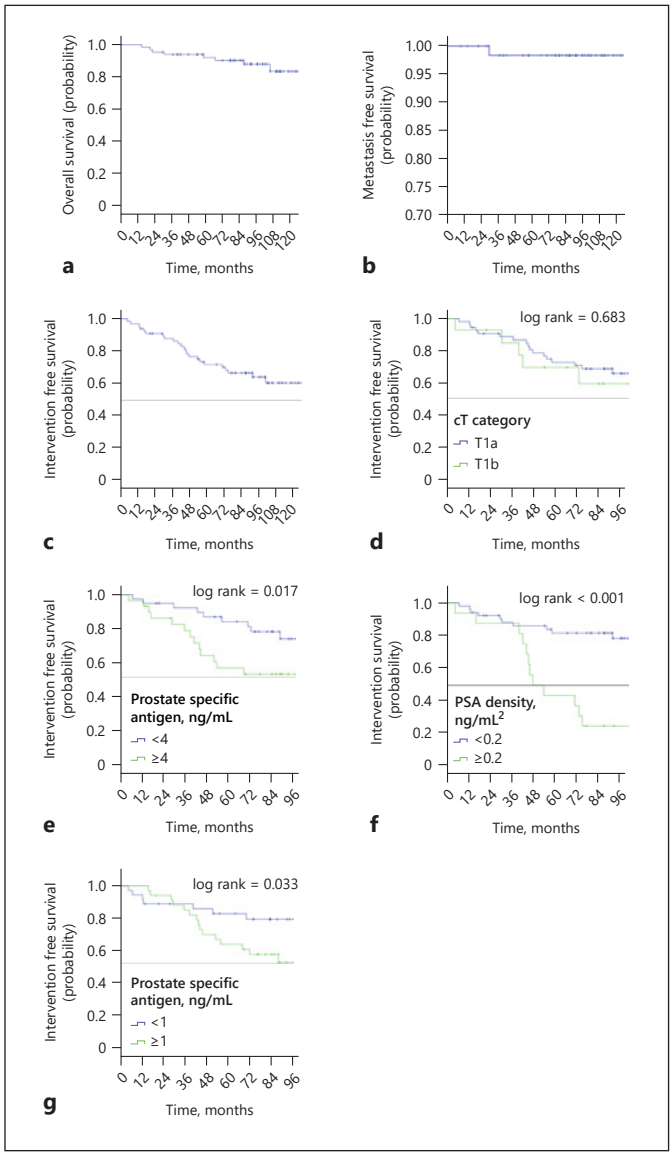


Fig. 1. Flowchart of the HAROW study and outcome of patients with IPC treated with AS. IPC, incidental prostate cancer; AS, active surveillance; RP, radical prostatectomy; RT, radiotherapy; HT, hormone treatment; WW, watchful waiting; †, death.



Color version available online

Fig. 2. Kaplan-Meier curves illustrating **a** overall survival, **b** metastasis-free survival, and **c** intervention-free survival for all 68 patients with IPC treated with AS and stratified to cT1a versus cT1b (**d**), initial PSA <4.0 versus ≥4.0 ng/mL (**e**), initial PSA density <0.2 versus ≥0.2 ng/mL^2 (**f**), and PSA decline after surgical treatment of BPO <1.0 versus ≥1.0 ng/mL (**g**). IPC, incidental prostate cancer; AS, active surveillance; PSA, prostate-specific antigen; BPO, benign prostate obstruction.

(IQR: 72–78) and median follow-up of 3.6 years (IQR: 1.65–5.7). Four patients had cT1a and 4 had a cT1b category. Case histories of these patients are shown in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000512893). No PCa-specific cause of death could be detected. One patient (1.5%) developed metastasis after 3.9 years and received HT. This patient was 71 years old when diagnosed with PCa and had an initial PSA of 2.4 ng/mL, Gleason grade group 1, and cT category 1a.

A total of 23/68 patients (33.8%) discontinued AS in favor of invasive treatment: 12 chose RP, 7 RT, and 4 HT (Fig. 1). In addition, 19 patients switched from AS to WW and maintained a noninvasive approach. Main reasons for discontinuation of patients opting for RP were biopsy upgrade (41.7%) and PSA elevation for those changing to RT (42.9%). Time to change to RP and RT was significantly earlier (33.9 and 44.4 months, respectively) than for HT and WW (73.5 and 75.8 months, respectively, $p < 0.001$).

The Kaplan-Meier estimated 10-year overall, metastasis-free, and intervention-free survival was 83.8% (95%

Table 1. Patient characteristics at baseline

	Total (n = 68)		Patients remained on AS/WW (n = 45)		Patients with deferred treatment (n = 23)		p value
	median	(IQR)	median	(IQR)	median	(IQR)	
Age, years	69.9	(63.6–72.5)	69.9	(64.7–72.5)	70.1	(60.5–72.6)	0.727
PSA, ng/mL	3.7	(2.0–5.9)	2.9	(1.4–5.0)	4.5	(2.4–8.0)	0.023
Prostate volume, mL	35.0	(27–47)	37.5	(29–51)	30.0	(24–45)	0.315
PSA density, ng/mL/mL	0.1	(0.04–0.16)	0.08	(0.04–0.13)	0.15	(0.08–0.23)	0.010
Follow-up, years	7.7	(5.7–9.1)	8.0	(6.6–9.0)	6.8	(3.5–9.2)	0.131
	n	(%)	*n*	(%)	*n*	(%)	
Tumor category							
cT1a	54	(79.4)	36	(80.0)	18	(78.3)	1.000
cT1b	14	(20.6)	9	(20.0)	5	(21.7)	
Gleason grade group							
1	64	(94.1)	44	(97.8)	20	(87.0)	0.113
2	4	(5.9)	1	(2.2)	3	(13.0)	
PSA, ng/mL							
<4	39	(57.4)	30	(66.7)	9	(39.1)	0.780
4–10	24	(35.3)	13	(28.9)	11	(47.8)	
>10	5	(7.4)	2	(4.4)	3	(13.0)	
PSA density, ng/mL/mL							
<0.2	52	(76.5)	41	(91.1)	11	(47.8)	<0.001
≥0.2	16	(23.8)	4	(8.9)	12	(52.2)	
PSA decline after surgical treatment							
<1.0 ng/mL	35	(51.5)	28	(62.2)	7	(30.4)	0.020
≥1.0 ng/mL	33	(48.5)	17	(37.8)	16	(69.6)	
CCI							
0	54	(79.4)	38	(84.4)	16	(69.6)	0.300
1	9	(13.2)	5	(11.1)	4	(17.4)	
≥2	5	(7.4)	2	(4.4)	3	(13.0)	

IQR, interquartile range; AS, active surveillance; WW, watchful waiting; PSA, prostate-specific antigen; CCI, Charlson Comorbidity Index.

CI: 72.2–95.3), 98.4% (95% CI: 95.3–99.9), and 61.0% (95% CI: 47.7–74.3), respectively (Fig. 2a–c). Cancer-specific survival was 100%.

Intervention-free survival was comparable for patients with cT1a and cT1b tumors (66.7 vs. 64.3%; $p = 0.683$) but differed significantly between patients with an initial PSA <4 and ≥4 ng/mL (76.9 vs. 51.7%; $p = 0.017$), patients with an initial PSA density <0.2 and ≥2 ng/mL^2 (78.8 vs. 25.0%; $p < 0.001$), and patients with a PSA decline <1 and ≥1 ng/mL within 12 months after surgical treatment of BPO (80.0 vs. 51.5%; $p = 0.033$) (Fig. 2d–g).

In multivariable analysis, age (RR: 0.97; $p < 0.001$), PSA density ≥0.2 ng/mL^2 (RR: 13.23; $p < 0.001$), and PSA ≥1.0 ng/mL after surgical treatment (RR: 5.19; $p = 0.016$) were significantly predictive for receiving an invasive treatment (Table 2).

Discussion/Conclusion

Therapy for IPC is still debatable. It remains unclear under which circumstances noninvasive (AS and WW) or invasive measures (RP, RT, and HT) should be the treatment of choice. The incidence of IPC is low and seems to be similar between conventional surgical techniques such as transurethral resection of the prostate or

Table 2. Multivariate analysis for association between patient characteristics and deferred invasive treatment

Variable	Category	Adjusted RR	(95% CI)	*p* value
Age	Continuous	0.97	(0.95–0.98)	<0.001
Prostate volume	Continuous	0.99	(0.93–1.03)	0.614
Charlson Comorbidity Index	0	1	Reference	
	1	4.16	(0.63–27.39)	0.138
	≥2	3.84	(0.29–49.77)	0.303
PSA initial	<4 ng/mL	1	Reference	
	≥4 ng/mL	2.26	(0.55–9.19)	0.256
PSA density	<0.2 ng/mL^2	1	Reference	
	≥0.2 ng/mL^2	13.23	(3.12–26.16)	<0.001
PSA decline after surgical treatment	<1.0 ng/mL	1	Reference	
	≥1.0 ng/mL	5.19	(1.36–19.74)	0.016
Gleason grade group	1	1	Reference	
	2	5.38	(0.2–145.08)	0.317
cT category	cT1a	1	Reference	
	cT1b	0.64	(0.1–4.09)	0.638

RR, relative risk, 95% CI, 95% confidence interval, PSA, prostate-specific antigen.

open prostatectomy and newer laser techniques such as holmium laser enucleation of the prostate [13].

Recently, several diagnostic procedures, such as multiparametric magnetic resonance imaging (mpMRI) or prostate health index, have become available to increase the prediction of IPC [20, 21]. On the other hand, it has so far been difficult to anticipate the occurrence of IPC after surgical treatment of BPO. Therefore, only a few retrospective studies report on IPC patients under AS, in which treatment protocols are not uniformly defined. In 2008, Descazeaud et al. [22] reported on 144 patients with cT1a tumors, who were initially monitored and in case of increasing PSA subjected to a transrectal core needle biopsy of the prostate and/or a diagnostic workup based on imaging studies. Of these patients, 21% had disease progression after a mean follow-up of 5.1 years, and half of them received HT. In 2014, Lee et al. [23] reported on a cohort of 46 Korean IPC patients under AS. No repeat biopsies were performed, and PSA progression was defined as doubling of the PSA value after surgery for BPO. After a mean follow-up of 40.0 months, 30% received interventional treatment, mainly HT.

Most of the prospective AS series so far include patients with cT categories ≤2a–c but did not specify the proportion of their cT1a/b patients [24–26]. Only the Sunnybrook Toronto series report of a share of 4.8% cT1a/b tumors [27]. However, a subgroup analysis of these patients has not yet been reported.

Therefore, our study represents the first prospective cohort of IPC patients managed with AS. Short-term outcomes of this cohort within the study period of HAROW (2008–2013, mFU 26.5 months) have already been published [19]. Although AS was a fairly new approach at the start of HAROW, German urologists seemed very inclined to introduce it as a therapeutic option in IPC, and the specified enrollment criteria for AS have been met in most cases. Only a minority of patients (16%) experienced disease progression within the period of recruitment, and most of them received a deferred invasive treatment.

Especially for tumors with low malignant potential, only long-term data can provide information of survival data with specific treatments and their applicability in routine care. In this context, we present the outcomes of the IPC subgroup with a median follow-up of 7.7 years, which yield to important findings.

First, as no cancer-specific death was observed and only 1 patient (1.5%) developed metastasis, our results support the safety of AS even, and in particular, for IPC patients with a favorable risk profile. These results are in line with the encouraging outcomes from other prospective AS cohorts. Klotz et al. [27] reported on 10- and 15-

year cancer-specific survival rates of 98 and 94%. The more conservative Johns Hopkins AS program revealed a 15-year cancer-specific and metastasis-free survival of 99.9 and 99.4%, respectively [24].

However, the cancer-specific survival in our study is 100% and therefore slightly higher compared to most other AS series with medium to long-term follow-up. Thus, it could be assumed that some PCa-specific deaths may not have been identified. In order to scrutinize this point, all treating urologists of the deceased patients were contacted. In four out of 8 patients, causes of death could be determined, revealing no PCa-specific deaths. Furthermore, in none of the remaining four patients an event of metastasis has been reported, so that even in these patients, death of PCa seems to be unlikely (online suppl. Table 1).

Second, the rate of patients in HAROW who discontinued AS in favor of an invasive treatment was 33.8%, amounting to an estimated 10-year intervention-free survival of 61.0%. Although the Toronto cohort reported a similar 10-year intervention-free survival of 63% [27], our rate is higher than results from most other general AS series ranging from 27 to 51% [24, 25, 28]. An explanation could be a less aggressive growth pattern of IPC in contrast to ≥cT1c prostate cancer and a rate of up to 30% of patients who do not harbor residual cancer after surgical treatment for BPO [4]. Another explanation could be the more intense follow-up examinations of clinical controlled AS trials, which might lead to higher discontinuation rates compared with our noninterventional study. Although rebiopsies and PSA measures were only determined within the time of recruitment (2008–2013), it could be shown that follow-up examinations in our cohort were lower than it could be expected: only 29.4% received at least 1 rebiopsy and 70.5% received ≥4 PSA measures within this period of median 26.5 months. Similar observations of less intense follow-up outside controlled clinical trials were demonstrated by Loeb et al. [29] on the basis of a SEER-Medicare database analysis. Among 5192 AS patients, >80% had >1 PSA test per year but <13% received biopsy beyond the first 2 years.

Third, we could demonstrate that younger age, PSA density ≥0.2 ng/mL^2, and PSA ≥1.0 ng/mL after surgery were significantly predictive for receiving an invasive treatment. In addition, the preoperative PSA value was associated with intervention-free survival in the univariate analysis but failed to do so in the multivariate analysis. Similar findings were made by Descazeaud et al. [22]. They reported that pre- and postoperative PSA, Gleason grade group, resection weight, and preoperative prostate volume were positively associated with an increased risk of disease progression. Since prostate volume enters into the calculation of PSA density, the predictive power of the latter may be assumed.

Fourth, because only a small percentage of our patients had Gleason grade group 2 (5.9%), our study cannot recommend AS for IPC patients with intermediate risk profile. Particularly, since Gleason grade group 2 has been identified as a leading risk factor for adverse pathological features after RP [30].

Finally, our data did not reveal any association of category cT1a or cT1b with intervention-free survival demonstrating that this differentiation is not adequate to correctly reflect the levels of risk. This is most likely due to the fact that the TNM classification for prostate cancer dates from the early 1990s [1, 2]. At that time, prior to the introduction of PSA, extent of tumor infiltration (<5 vs. >5%) offered the most precise prognosis regarding cancer-specific and metastasis-free survival [31]. Accordingly, Capitanio et al. [32] and Magheli et al. [33] were unable to conclusively estimate the prognosis for the TNM category regarding biochemical recurrence-free survival or organ-confined disease of IPC patients after RP. Today, improved diagnostic tools, such as PSA value and mpMRI of the prostate, lead to the preoperative selection of most aggressive tumors. For this reason, the current prognostic assessment of tumor infiltration <5 versus >5% is increasingly doubted.

The strength of our study includes its prospective nature, its noninterventional design, the long follow-up period, and the high number of study centers, consisting mainly of office-based urologists, thus reflecting a "real life scenario" better than AS studies from single tertiary care centers. A limitation of our study is the low number of patients, which is characteristic for studies on IPC patients due to the abovementioned reasons. Further limitations include the drop-out rate of 31%. Considering this rate more closely, it becomes evident that in 12% of these cases, reasons for drop-out were stated and only 19% were lost to follow-up, which is in line with other health-service research studies. Furthermore, information about histologic results after RP or rebiopsy is lacking, as well as frequency of follow-up examinations beyond the study period of 2008–2013. It should also be noted that our study was conducted in the era before mpMRI and biomarkers became available as diagnostic tools which since have shown promising results in better patient selection and monitoring for men who undergo AS [34].

In conclusion, this is the first report of a prospectively evaluated group of IPC patients treated with AS. It confirms the promising outcomes of this treatment approach for this specific subgroup of cT1a/b prostate cancer patients, providing a low Gleason grade group. Discontinuation rates were lower than those reported from most AS trials with a general low-risk prostate cancer population. Furthermore, we could identify age, PSA density, and PSA after surgery as predictors for AS discontinuation, whereas TNM category was not predictive, and therefore in its present form seems to be unsuitable for the classification of IPC.

Statement of Ethics

The HAROW study was approved by the ethics committee of the Bavarian State Board of Physicians (No. 08012). It was registered under study ID 479 at the DKSR (German Cancer Study Registry; February 2008). All procedures performed in the trial involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

Jan Herden, Andreas Schwarte, and Edith A. Boedefeld have no conflicts of interest to declare. Lothar Weissbach has acted as a paid consultant for the Scientific Institute (WIdO) of the statutory AOK health insurance provider. He has received study support (third-party funding) from Gazprom Germania, which sponsored the Foundation of Men's Health by providing an unconditional grant for data collection and data management.

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Author Contributions

Conception or design of the work: Jan Herden and Lothar Weissbach. Acquisition of data: Andreas Schwarte and Lothar Weissbach. Interpretation of data for the work: Jan Herden, Andreas Schwarte, and Lothar Weissbach. Drafting the paper: Jan Herden. Critically revising the paper: Edith A. Boedefeld and Lothar Weissbach.

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