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Treatment of intermediate-risk prostate cancer with active surveillance in the routine care—Long-term outcomes of a prospective noninterventional study (HAROW)

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Abstract

Background: We report here the long-term outcomes of patients with intermediate-risk prostate cancer (PCa) treated with active surveillance (AS) in a daily routine setting.

Material and methods: HAROW (2008–2013) was a noninterventional, health service research study investigating the management of localized PCa in a community setting. A substantial proportion of the study centers were office-based urologists. A follow-up examination of all intermediate-risk patients with AS was conducted. Overall, cancer-specific, metastasis-free, and treatment-free survival rates, as well as reasons for discontinuation, were determined and discussed.

Results: Of the 2957 patients enrolled, 52 with intermediate-risk PCa were managed with AS and were available for evaluation. The median follow-up was 6.8 years (interquartile range, 3.4–8.6 years). Seven patients (13.5%) died of causes unrelated to PCa, of whom 4 were under AS or under watchful waiting. Two patients (3.8%) developed metastasis. The estimated 8-year overall, cancer-specific, metastasis-free, and treatment-free survival rates were 85% (95% confidence interval [CI], 72%–96%), 100%, 93% (95% CI, 82%–100%), and 31% (95% CI, 17%–45%), respectively. On multivariable analysis, prostate-specific antigen density of ≥0.2 ng/mL^2 was significantly predictive of receiving invasive treatment (hazard ratio, 3.29; $p = 0.006$). Reasons for discontinuation were more often due to patient's or physician's concerns (36%) than due to observed clinical progression.

Conclusions: Although survival outcome data for intermediate-risk patients managed with AS in real-life health care conditions were promising, rates of discontinuation were high, and discontinuation was often a patient's decision, even when the signs of disease progression were absent. This might be an indication of higher levels of mental burden and anxiety in this specific subgroup of patients, which should be considered when making treatment decisions. From a psychological perspective, not all intermediate-risk patients are optimal candidates for AS.

Keywords: Active surveillance; Intermediate-risk prostate cancer; HAROW study; Conservative management; Outcomes research

1. Introduction

Approximately 20 years ago, active surveillance (AS) was developed as a noninvasive treatment option for patients with localized low-risk prostate cancer (PCa) to counteract the dangers of overtreatment and possible adverse effects of invasive types of treatment such as radical prostatectomy or radiotherapy. Since then, AS has found its way into the official guidelines[1–3] and has become a well-established modality in the therapeutic practice in many countries.[4,5] Prospective long-term clinical studies have confirmed a 10-year cancer-specific survival of greater than 98% with AS, which is comparable to that of immediate invasive treatment.[6–9]

Although AS is recommended for patients with very low- or low-risk PCa, some guidelines allow AS even for selected patients with intermediate risk, despite limited evidence supporting this approach.[1–3]

Some studies on intermediate-risk patients achieved promising results similar to those of low-risk patients.[10–13] Most of these studies were clinical trials from large academic or tertiary care centers, whereas in daily routine care, AS is predominantly managed by office-based urologists. Hence, the question arises if the results of studies on intermediate-risk patients are reproducible in a real-life setting.

In this context, the aim of the HAROW study is to report on survival outcomes as well as dropout rates and risk factors associated with deferral of invasive treatment in a subgroup of intermediate-risk patients who opted for AS as primary treatment in a community-based setting within the German health system.[14] As it was a noninterventional study approach with no restrictions on the choice of treatment, it was also possible to initially manage intermediate-risk patients with AS.

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2. Materials and methods

HAROW is a prospective, observational, multicenter study on patients with newly diagnosed localized PCa, with no restrictions on the choice of treatment. From July 2008 to July 2013, patients with newly diagnosed localized (≤T2c) PCa were prospectively enrolled by 259 study centers, 86% of which were office-based urologists. Although AS was mentioned in the guidelines of the European Association of Urology at that time,[15] it was still a largely unaccepted treatment strategy. Because of the noninterventional nature of the study, only recommendations regarding inclusion, follow-up, and discontinuation of AS were provided, which corresponded to those available in the literature[16,17] and listed in the European PRIAS study (Prostate Cancer Research International Active Surveillance)—the largest published prospective trial of AS at that time.[18] Inclusion criteria for AS included T-category ≤cT2c, prostate-specific antigen (PSA) ≤10 ng/mL, Gleason grade group (GG) 1, PSA density of ≤0.2 ng/mL^2, and ≤2 positive biopsies. However, because these recommendations were not considered fixed inclusion criteria, it was also possible to include patients with higher-risk features in the AS group.

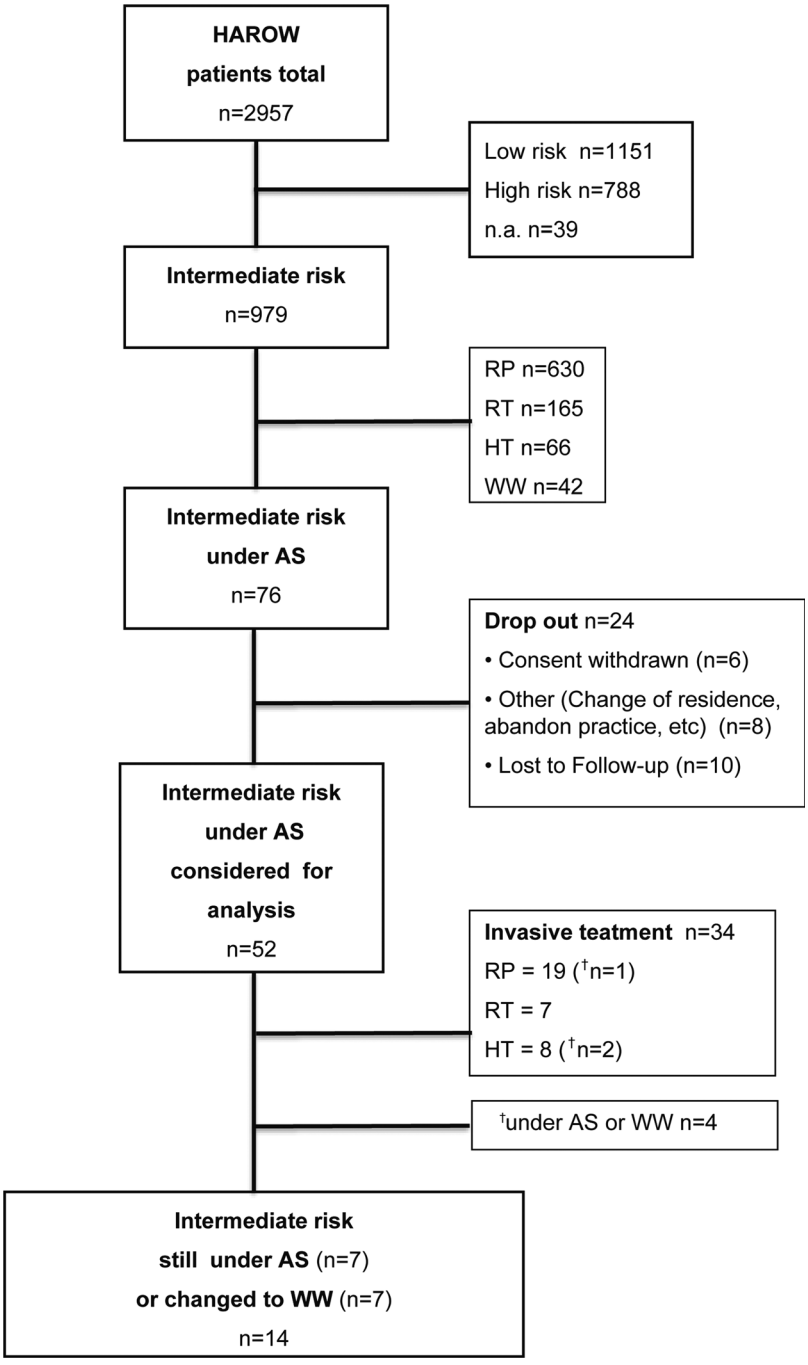

Figure 1. Flowchart of the HAROW study and its outcomes in patients with intermediate-risk prostate cancer treated with active surveillance. †death; AS = active surveillance; HT = hormone treatment; n.a. = not assigned; RP = radical prostatectomy; RT = radiotherapy; WW = watchful waiting.

At the time of the study, sonography-guided transrectal prostate biopsy was the diagnostic standard. Magnetic resonance imaging (MRI) fusion biopsy was not available yet. Accordingly, a transrectal biopsy was performed in all patients. In total, more than 10 biopsy cylinders were obtained in 74.5% of patients according to the recommendations of the guidelines at that time,[15] including 51% of patients who had at least 12 biopsies.[14]

The recommended follow-up procedure included digital rectal examination, PSA, and PSA doubling time every 3 months in the first 2 years and every 6 months thereafter. Rebiopsy was recommended after 1 year and every 3 years thereafter. In case of histological evidence of progressive disease, increasing PSA levels with PSA doubling time <3 years, or clinical signs of progression on digital rectal examination, discontinuation of AS was recommended. Alternatively, AS was withheld at the patient's request.

Data related to patient recruitment, diagnostics, and disease course in the total cohort for the study period with a median observation period of 28.4 months have been published elsewhere.[19]

2.1. Follow-up of the AS group

A follow-up survey of all patients with AS, including those who have switched to another treatment, was carried out until August 2019. Questionnaires were mailed to all the patients. All nonresponders were contacted again and interviewed via telephone. In case of missing responses or lack of information on the course of the disease, including the cause of death, treating study physicians were contacted. The following data were collected: overall survival, cancer-specific survival, metastasis-free survival, treatment-free survival, reasons for discontinuation of AS, and type of deferred treatment. This report presents a subgroup analysis of patients with intermediate-risk PCa. Risk stratification was performed using the European Association of Urology risk groups for biochemical recurrence of localized PCa, in which "intermediate-risk" was defined as cT2b, GG 2/3, or PSA of 10 to 20 ng/mL.

2.2. Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows software, version 22 (IBM Corp, Armonk, NY). The Kaplan-Meier method and log-rank test were applied to analyze overall, metastasis-free, and invasive treatment–free survival. Logistic regression as a multivariate analysis was used to determine independent factors influencing the target variable "receiving interventional treatment" including age, prostate volume, PSA, PSA density, GG, and cT category. The significance level was set at 5% for all calculations.

2.3. Ethics

This 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 German Cancer Study Registry (DKSR; February 2008). All procedures performed in the trial involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all the participants included in the study.

3. Results

Of 2957 patients enrolled in the HAROW study, 979 (33%) had intermediate-risk PCa according to the National Comprehensive Cancer Network guidelines,[2] and 76 (8%) chose AS. Reasons for dropout during follow-up included consent withdrawal (n = 6 [8%]), loss to follow-up (n = 10 [13%]), and other reasons such as change of residence or practice termination by a responsible physician (n = 8 [11%]). Finally, data from 52 patients (68%) were available for the evaluation (Fig. 1).

Patient characteristics at baseline are presented in Table 1. The median age was 70.0 years (interquartile range [IQR], 65.6–74.2 years), and the median PSA was 7.2 ng/mL (IQR, 5.1–12.5 ng/mL). Seven patients (13.5%) had ≥3 positive biopsy cores, 31 (59.6%) had GG 1, and 21 (40.4%) had GG 2. None of the patients with a GG ≥3 was selected for AS.

The median follow-up was 6.8 years (IQR, 3.4–8.6; min–max years, 0.1–10.8 years). In this period, 7 patients (13.5%) died at a median age of 78 years (IQR, 74.5–79.5 years) after a median of 4.7 years (IQR, 2.4–5.6 years), of which 4 were still under AS or watchful waiting (WW). The case histories are shown in Table 2. No PCa-specific causes of death were reported. Two patients (3.8%) developed metastases and received hormone deprivation therapy. At the time of PCa diagnosis, 1 patient had GG 1 with PSA of 12.9 ng/mL, and 1 had GG 2 with PSA of 8.8 ng/mL, whereas both patients had a Charlson comorbidity index of 0, cT category 2a, and 1 positive biopsy core.

A total of 34 patients (65%) switched from AS to invasive treatment: 19 chose radical prostatectomy, 7 radiotherapy, and 8 hormone deprivation therapy. The main reasons for discontinuation

Table 1

Baseline characteristics of the patients (n = 52).

Characteristics	Median (IQR) or n (%)*
Age, yr	70.0 (65.6–74.2)
PSA, ng/mL	7.2 (5.1–12.5)
Prostate volume, mL	35 (28–55)
PSA density, ng/mL^2	0.20 (0.14–0.31)
Follow-up, yr	6.8 (3.4–8.6)
Tumor category	
cT1a/b	9 (17.3)
cT1c	19 (36.5)
cT2a	8 (15.4)
cT2b	16 (30.8)
Gleason grade group	
1	31 (59.6)
2	21 (40.4)
No. positive cores per biopsy	
0†	6 (11.5)
1	23 (44.2)
2	15 (28.9)
≥3	7 (13.5)
n.a.	1 (1.9)
PSA, ng/mL	
≤10	31 (59.6)
>10	21 (40.4)
PSA density, ng/mL^2	
<0.2	22 (42.3)
>0.2	22 (42.3)
n.a.	8 (15.3)
CCI	
0	38 (73.0)
1	7 (13.5)
≥2	5 (9.6)
n.a.	6 (1.8)

CCI = Charlson Comorbidity Index; IQR = interquartile range; n.a. = not assigned; PSA = prostate-specific antigen.

*n(%) express the quantitative data.

†Patients with no positive biopsies were diagnosed with incidental prostate cancer by transurethral resection of the prostate.

Table 2

Case histories of 7 patients who died during the course of the follow-up.

Patient number	Year of death	Age upon death, yr	Time from PCa diagnosis to death, yr	CCI (study entry)	Cause of death	Metastasis due to PCa?	Last PCa treatment
1	2015	80	6.3	0	Unknown*	No	AS
2	2012	78	2.4	0	Unknown*	No	HT
3	2015	79	4.8	3	Bladder cancer	No	AS
4	2016	77	4.7	3	Cardiac insufficiency	No	WW
5	2013	72	0.7	2	Myocardial infarction	No	AS
6	2015	72	2.4	1	Unknown*	No	RP
7	2019	85	10.0	0	Renal failure	No	HT

AS = active surveillance; CCI = Charlson Comorbidity Index; HT = hormone treatment; PCa = prostate cancer; RP = radical prostatectomy; WW = watchful waiting.
*In patients whose cause of death was unknown, mortality due to PCa was excluded.

included patient's decision with no disease progression (27%), biopsy upgrade and PSA elevation (24% each), and physician's advice without signs of progression (9%); 17% of patients discontinued AS for unclear reasons (Table 3). In addition, 8 patients switched from AS to WW and maintained a noninvasive approach.

The Kaplan-Meier estimated 8-year overall, cancer-specific, metastasis-free, and treatment-free survival rates were 85% (95% confidence interval [CI], 72%–96%), 100%, 93% (95% CI, 82%–100%), and 31% (95% CI, 17%–45%), respectively (Figs. 2A–C). Treatment-free survival was the same for patients with GG 1 and GG 2 (31% [95% CI, 14%–45%] vs. 33% [95% CI, 12%–55%]; $p = 0.859$) (Fig. 2D).

In multivariable analysis, only PSA density ≥0.2 ng/mL^2 was significantly predictive of receiving an invasive treatment (hazard ratio, 3.29; $p = 0.006$) (Table 4).

4. Discussion

Intermediate-risk PCa is a heterogeneous disease. Whereas some intermediate-risk patients have indolent disease and may benefit from AS, others may suffer from a more aggressive type of cancer that requires a definitive therapy at an early stage. Therefore, some guidelines further subdivide intermediate-risk tumors into "favorable" and "unfavorable," based mainly on the presence of GG 3.[2,3]

Only scanty evidence supports guidelines that allow AS in selected intermediate-risk patients. Recommendations for inclusion are inconsistent, and standardized follow-up protocols or distinct criteria for discontinuation in favor of invasive treatment are lacking.[1–3] The controversy surrounding AS in intermediate-risk PCa is mainly due to differences in definitions and guideline recommendations related to this disease and has recently been reviewed in detail by Nayan et al.[20]

Table 3

Main reasons for initiation of invasive treatment in 34 patients who had discontinued active surveillance (8 patients who switched from active surveillance to watchful waiting were not included).

	n (%)
Patient's decision (without disease progression)	9 (26.5)
Biopsy upgrade	8 (23.5)
PSA elevation	8 (23.5)
Physician's advice (without progression)	3 (8.8)
n.a.	6 (17.6)

n.a. = not assigned; PSA = prostate-specific antigen.

In a meta-analysis, Enikeev et al.[13] evaluated 17 articles with long-term follow-ups. In their analysis, the proportion of patients who remained under AS was comparable between the low- and intermediate-risk groups after 10 and 15 years of follow-up. Cancer-specific and metastasis-free survival rates did not differ after 5 years but were significantly worse for intermediate-risk patients after 10 years.[13] However, interpretation of these studies and comparison with low-risk disease are often difficult because of the aforementioned heterogeneity of prostate tumors.

The present article focuses on intermediate-risk patients under AS and demonstrates promising results in terms of oncologic safety in the daily routine setting. After nearly 7 years of follow-up, no cancer-specific deaths have been noted, and the metastasis rate has been low (3.8%). However, a large proportion of patients discontinued AS and opted for invasive treatment. At the end of the observation period, only 13% of patients adhered to AS, whereas 13% switched from AS to WW, remaining under noninvasive care. The reasons for discontinuing treatment were more often patient concerns than confirmed disease progression.

Data were collected as part of an observational, noninvasive study with the aim of examining the use of AS in routine care. Contrary to clinical AS studies from academic or tertiary care centers with a fixed treatment protocol, HAROW aims to represent the "real-world" setting. The multicenter setup and participation of mainly office-based urologists were intended to increase the generalizability of our results. Outcome data for the total AS cohort, mainly consisting of very low- and low-risk patients, have already been published and revealed an estimated 10-year overall, cancer-specific, and metastasis-free survival rates of 86%, 100%, and 97%, respectively.[21]

With regard to patient selection, the present study demonstrated a strong adherence to the existing recommendations, where AS is primarily reserved for patients with GG 1 and GG 2 ("favorable" intermediate-risk), because no patient with GG 3 was selected for AS.

The reported cancer-specific survival of 100% is in line with the results of the AS series from Canada (Vancouver),[10] Denmark,[11] and the United States.[22] None of the studies recorded PCa-specific deaths in intermediate-risk patients within the period of 10 years. On the other hand, in another study from Canada (Toronto)[23] and a study from Sweden (Göteborg),[24] PCa-specific deaths were recorded for intermediate-risk patients, resulting in 10-year cancer-specific survival rates of 97% and 98%, respectively. This could be explained

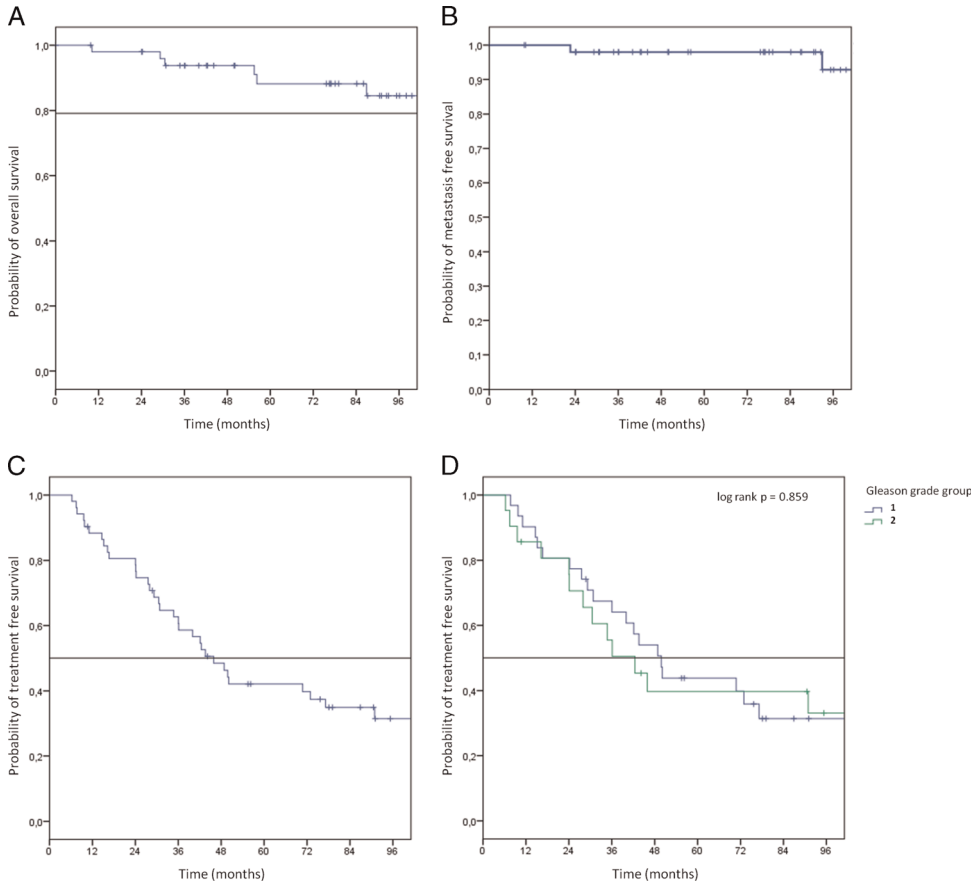

Figure 2. Kaplan-Meier curves illustrating the probability of (A) overall, (B) metastasis-free, and (C) treatment-free survival for the total cohort (n = 52) and (D) treatment free-survival stratified into patients with Gleason grade group 1 (n = 31) and Gleason grade group 2 (n = 21).

by more liberal inclusion criteria for AS in these studies. The Toronto cohort allowed AS even for patients with "unfavorable" intermediate-risk PCa during the first years of recruitment. Unsurprisingly, the presence of GG 3 (formerly Gleason score 4 + 3) was the main driver of the metastasis rate.

Two intermediate-risk patients (3.8%) developed metastases. Even though this represents a low rate, it was higher than that in very low- and low-risk patients in our cohort (1.8%).[21] Similarly, in other studies, the risk of metastasis tended to be higher for intermediate-risk patients than for very low- and low-risk patients.[13] Three prospective cohorts provided data on the frequency of developing metastases, whereas AS was used for intermediate-risk patients. In the Vancouver cohort, 1 patient (0.7%) developed metastasis during the 4.5 years of follow-up.[10] The US study reported an approximate metastasis rate of 2% after 5 years,[22] and the Toronto cohort reported a 9% metastasis rate, resulting in a 10-year metastasis-free survival of 91%.[23] The later resembles our results, that is, a calculated 8-year metastasis-free survival of 93%.

Thirty-four of 52 patients (65.4%) discontinued AS and switched to invasive treatment, resulting in an estimated 8-year treatment-free survival of 31% without significant differences between patients with GG 1 and GG 2. Treatment-free survival in our cohort was lower than that for intermediate-risk patients in other prospective AS series, ranging from 41% to 69% after 10 years.[11,12,24] This observation may indicate that switching to invasive therapy is more common in routine care settings than in clinical studies from academic centers. One reason for this could be that patients and physicians outside of the academic setting feel less confident in dealing with AS. This becomes evident when examining the reasons for discontinuation: 36% of patients switched to invasive treatment upon their own decision or physician's advice in the absence of any signs of progression. Although most studies and meta-analyses support the assumption that AS is not a threat to the psychological well-being of PCa patients,[25] some patients report having the perception of risking their life by submitting to AS alone.[26,27] In addition, patients significantly overestimate the risk of PCa mortality, regardless of the treatment option chosen. In a

Table 4

Multivariate analysis predicting the correlation between patient and tumor characteristics and the probability of receiving a deferred invasive treatment (n = 52).

Variable	Category	Adjusted RR	95% CI	*p*
Age	Continuous	1.00	0.97–1.04	0.980
Prostate volume	Continuous	0.99	0.95–1.03	0.496
PSA (initial)	<10 ng/mL	1	Reference	
	≥10 ng/mL	1.29	0.19–8.87	0.799
PSA density	<0.2 ng/mL^2	1	Reference	
	≥0.2 ng/mL^2	3.29	1.41–7.66	0.006
Gleason grade group	1	1	Reference	
	2	1.19	0.23–6.05	0.837
cT category	cT1	1	Reference	
	cT2	2.12	0.48–9.43	0.325

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

study by Kendel et al.,[28] the patient-estimated mortality risk of AS was 3 times higher than that of surgery. Our observations could indicate a higher level of psychological distress and anxiety in a specific subgroup of intermediate-risk patients in a real-life setting. Therefore, from a psychological perspective, not all intermediate-risk patients are optimal candidates for AS.

On multivariable analysis, we could identify PSA density of ≥0.2 ng/mL^2 as a predictor for receiving invasive treatment. This confirms the results of other AS series, in which PSA density was positively associated with the risk of biopsy reclassification.[7,29] Recently, Maggi et al.[30] examined the combination of GG and PSA density in AS patients. In their study, patients were subdivided into 3 groups: GG 1 with PSA density of <0.15 ng/mL^2, GG 1 with PSA density of ≥0.15 ng/mL^2, and GG 2 with any PSA density. After 7 years, patients with GG 2 and any-PSA density had a nearly favorable metastasis-free survival (96%) compared with GG 1 and PSA density ≤0.15 ng/mL^2 (99%) or ≥0.15 ng/mL^2 (100%). These data support the assumption that AS may also be a suitable treatment option for some men with intermediate-risk profiles. The importance of PSA density also becomes evident from the results of that recent study: AS discontinuation rates in patients with GG 2 and any PSA density were similar to those in patients with GG 1 + PSA density of ≥0.15 ng/mL^2 (58% and 54%, respectively) and therefore significantly higher than those in patients with GG 1 + PSA density of <0.15 ng/mL^2 (31%). In daily clinical practice, this easily calculable parameter could be taken into account when deciding whether a patient should be put on AS.

The strengths of our study include its prospective nature, noninterventional design, long follow-up period, and high number of participating study centers, including mainly office-based urologists, thus reflecting reality better than single tertiary care center–based studies.

One limitation of our study was the relatively high dropout rate (31.5%). However, the reasons for dropout in the majority of these cases were known, and only 13% of the patients were lost to follow-up. Further limitations include the lack of information about the quantity of the Gleason 4 pattern in the histologic results of the biopsies. The clinical utility of the quantitative Gleason score was reported by Sauter et al.[31] In their study, biochemical recurrence was more frequent after 6 years, with a higher percentage of Gleason 4 pattern.

It is also important to note that our study was conducted at a time when MRI and biomarkers were not yet available as diagnostic tools. Particularly, MRI has since shown great utility in the selection and monitoring of patients with AS.[32,33]

5. Conclusions

Although the survival data reported here for intermediate-risk patients receiving AS in a real-world care setting are promising, discontinuation rates were higher than expected, with as many as two-thirds of patients halting AS in favor of invasive treatment. Decisions to discontinue treatment were most often made by patients without reclassification based on biopsy or PSA increase, which may indicate a higher level of burden and anxiety in this specific subgroup of patients. This should be taken into account in treatment decisions, as not all patients seem to be suitable candidates for AS in this context.

Acknowledgments

None.

Statement of ethics

This 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 German Cancer Study Registry (DKSR; February 2008). Informed consent was obtained from all the participants included in the study. All procedures performed in the trial involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest statement

JH, AS, and EAB declare that they have no conflict of interest. LW 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.

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Author contributions

JH: Project development, data analysis, manuscript writing;
AS: Data collection, management, and analysis;
EAB: Manuscript editing;
LW: Project development, data analysis, manuscript editing.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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