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Prognostic and Predictive Factors for Anti-androgen Withdrawal in Castration-resistant Prostate Cancer

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Abstract. *Background/Aim: We aimed to identify prognostic and predictive factors for anti-androgen withdrawal syndrome (AWS) to help guide decisions on anti-androgen withdrawal in castration-resistant prostate cancer (CRPC). Patients and Methods: This study included 95 patients with prostate cancer which progressed to CRPC despite primary androgen-deprivation therapy (ADT). AWS was defined as >50% prostate-specific antigen decline after anti-androgen withdrawal. Associations between AWS, and clinico-pathological factors and prognosis were investigated. Results: Among the 95 patients, 84 (88.4%) underwent anti-androgen withdrawal, among whom AWS was recognized in nine (10.8%). Gleason score and response duration to primary ADT were predictors of AWS. Long duration of response to primary ADT was also associated with better progression-free survival [hazard ratio (HR)=0.021, 95% confidence interval (CI)=0.0025-0.14, p<0.0001] and overall survival (HR=0.0042, 95% CI=0.0001-0.089, p<0.0001). Age (HR=7.19, 95% CI=1.08-54.27, p=0.041) and radiological/clinical progression (HR=3.14, 95% CI=1.35-6.43, p=0.010) were associated with worse overall survival. Intriguingly, radiological/clinical progression was associated with the differential effect of anti-androgen withdrawal on overall survival (interaction p=0.031). Conclusion: Patients who suffer radiological/clinical progression are unsuitable candidates for anti-androgen withdrawal.*

Although the incidence of advanced prostate cancer has decreased in Western countries, probably due to widespread prostate-specific antigen (PSA) screening, in the United States, 5% of prostate cancers are diagnosed at advanced stage with nodal or distant metastatic disease (1). However, a recent decreasing trend in PSA testing based on US Preventive Services Task Force recommendation (2) has purportedly led to an increased incidence trend of metastatic prostate cancer, especially in the elderly (3). In Japan, 10-20% of men with prostate cancer are diagnosed with metastatic disease, probably due to inadequate PSA screening (4, 5).

Androgen-deprivation therapy (ADT) reduces androgen production and inhibits androgen action in prostate cancer cells, and has been the standard treatment for recurrent or advanced prostate cancer since 1941 (6). ADT is also used to treat localized prostate cancer in certain cases, although established evidence of its life-prolonging effect is lacking (6). Although most men with prostate cancer initially respond well to ADT, many of their cancers eventually recur as castration-resistant prostate cancer (CRPC) and eventually become lethal (7). Previously, no life-prolonging treatment for CRPC was available. Therefore, so-called vintage hormone therapies such as alternative anti-androgen therapy, estrogenic agents and steroid agents have been empirically utilized for many years (8). Anti-androgen withdrawal has also been used for cancer that progresses to CRPC during treatment with anti-androgen agents such as bicalutamide and flutamide.

Reportedly, 15-30% of patients experienced paradoxical PSA decline by more than 50% after stopping anti-androgen agents, a condition called anti-androgen withdrawal syndrome (AWS) (9), which is thought to result mainly from androgen receptor (AR) mutations that confer agonistic effects on receptors (10, 11). Intriguingly, the reported frequency of AR mutation in CRPC is similar to that of AWS: 10-30% (12).

Previously, anti-androgen withdrawal had been recommended as a preliminary to subsequent therapy, in order to avoid effects of AWS on prognosis and efficacy of later therapies. However, several novel agents such as the cytochrome P450 family 17 (CYP17) inhibitor abiraterone acetate, second-generation anti-androgen enzalutamide, taxanes and radiotherapeutic Ra-223 have shown overall

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survival (OS) benefits in such patients (8, 13), which has changed the clinical view and use of anti-androgen withdrawal. Furthermore, in 2014, the European Association of Urology guideline discontinued their discussion of anti-androgen withdrawal as a therapeutic option for CRPC (14). However, anti-androgen withdrawal is still used for some patients with CRPC. This study investigated prognostic and predictive factors for AWS in order to help guide clinical decisions on use of anti-androgen withdrawal in patients with CRPC.

Patients and Methods

Patients. This study retrospectively enrolled 95 men who were treated at the Kyushu University Hospital (Fukuoka, Japan) from 2000 to 2013, for prostate cancer that had progressed to CRPC after first-line ADT treatment. Patients who had received local treatment before or concurrently with ADT, or who received other treatments, such as chemotherapy, before disease progression were excluded. This study was approved by Kyushu University Hospital's Institutional Review Board. All patients were histopathologically diagnosed with adenocarcinoma of the prostate, including 80 men who were biopsied at Kyushu University Hospital and 15 who were biopsied at another institution (from whom five of the biopsy specimens were reviewed at our Institution). Clinical staging was determined by the unified TNM criteria (15), based on results of digital rectal examinations, transrectal ultrasound, magnetic resonance imaging, computed tomography, and bone scans. All patients were primarily treated by ADT with surgical castration, or medical castration using a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprorelin acetate) with/without an anti-androgen (bicalutamide or flutamide); 92 men were primarily treated with combined androgen blockade, and three men were treated with castration alone. Continuous ADT was employed in 91 patients, and intermittent ADT was performed in four patients. Prior anti-androgens were bicalutamide and flutamide in 91 men and four men, respectively. Progression on anti-androgen-based ADT was judged by each patient's physician, and was defined as three consecutive increases in PSA, or two consecutive increases in PSA of >2 ng/ml and 25% increase over the nadir. Radiographic progression was defined as the appearance of two new lesions or progression of one or more known lesions, as classified by the Response Evaluation Criteria in Solid Tumours (RECIST) (15). Clinical progression was defined as the appearance or exacerbation of symptoms related to prostate cancer progression, such as pain, fatigue, and lower urinary tract symptoms. Progressive disease during anti-androgen withdrawal was determined by PSA progression, defined as an increase in PSA of >2 ng/ml and 50% increase over the nadir, radiological progression, or initiation of new therapeutics for CRPC (except for bone-modifying agents such as zoledronic acid and denosumab). Progression-free survival (PFS) and OS were defined as the duration from the initiation of anti-androgen withdrawal to progression and death from any cause, respectively.

Statistical analysis. All statistical analyses were performed using JMP11 software (SAS Institute, Cary, NC, USA). Continuous and categorical data were analyzed by Wilcoxon rank-sum and Pearson's chi-square tests, respectively. Survival analyses were conducted by the Kaplan–Meier method and log-rank test. The Cox proportional hazards model was used to estimate hazard ratios (HRs). The predictive role of subgroups for anti-androgen withdrawal prognosis were investigated through interaction tests. All *p*-values were two-sided; $p<0.05$ was considered significant.

Results

Among the 95 patients, 84 men (88.4%) underwent anti-androgen withdrawal and 11 men (11.6%) did not, depending on their physicians' judgement. Interestingly, in the no-anti-androgen withdrawal group, PSA level at progression was higher, and radiological/clinical progression was recognized more frequently, whereas other characteristics, such as PSA level at diagnosis, Gleason score and TNM-stage at initial diagnosis were comparable (Table I).

Next, patient characteristics were compared by their PSA responses after anti-androgen withdrawal. Among the 84 patients who underwent anti-androgen withdrawal, 22 men (26.2%) experienced some PSA decline after anti-androgen withdrawal, as shown by PSA waterfall plot (Figure 1A). PSA decline by >30% was recognized in 14 men (16.9%), and decline by >50% decline was seen in nine men (10.8%). AWS was defined as >50% PSA decline after anti-androgen withdrawal. The AWS group had lower Gleason scores and longer response duration to primary ADT than did the non-AWS group (Table II).

Among men who underwent anti-androgen withdrawal, median PFS was 1.9 months [95% confidence interval (CI)=1.6-2.6 months], and median OS was 37 months (95% CI=32-53 months). The prognosis was significantly worse in the no-AWS group, as shown by Kaplan–Meier curves for PFS ($p<0.0001$) and OS ($p=0.0028$; Figure 1B). Only long response to primary ADT was associated with lower risk of PFS (HR=0.021, 95% CI=0.0025-0.14, $p<0.0001$; Table III). We found OS after anti-androgen withdrawal (*i.e.* risk of death from any cause) to be significantly associated with older age (HR=7.19, 95% CI=1.08-54.27, $p=0.041$), long response to primary ADT (HR=0.0042, 95% CI=0.0001-0.089, $p<0.0001$), and radiological/clinical progression (HR=3.14, 95% CI=1.35-6.43, $p=0.010$; Table III).

Although we found that anti-androgen withdrawal was not a risk factor of any-cause-death in the cohort as a whole (HR=0.61, 95% CI=0.30-1.39, $p=0.22$, Table IV), subgroup analysis associated radiological/clinical progression with the differential effect of anti-androgen withdrawal on OS (interaction $p=0.031$; Table IV).

Discussion

In 1993, for the first time, a case report that showed PSA decline after withdrawal of the anti-androgen flutamide in patients whose disease had progressed on combined androgen blockade (17). This paradoxical phenomenon was

Table I. *Characteristics of patients with and without anti-androgen withdrawal (AWD).*

Variable		AWD		*p*-Value
		With (n=84)	Without (n=11)	
Age at diagnosis, years	Median (IQR)	74 (68-77)	72 (64-77)	0.69
PSA at diagnosis, ng/ml	Median (IQR)	223.4 (73.8-714.2)	164 (75.9-483.0)	0.79
Biopsy Gleason score, n (%)	≤8	28 (35.4%)	1 (9.1%)	
	>8	51 (64.6%)	10 (90.9%)	0.080
	NA	5	0	
Clinical T-stage, n (%)	cT1/2/3a	34 (41.5%)	4 (36.4%)	
	cT3b/4	48 (58.5%)	7 (63.6%)	0.75
	NA	2	0	
Clinical N-stage, n (%)	N0	31 (37.3%)	2 (18.2%)	
	N1	52 (62.7%)	9 (81.8%)	0.21
	NA	1	0	
Clinical M-stage, n (%)	M0	8 (9.6%)	1 (9.1%)	
	M1a	3 (3.6%)	1 (9.1%)	
	M1b	69 (83.1%)	9 (81.8%)	
	M1c	3 (3.6%)	0 (0.0%)	0.78
	NA	1	0	
Response duration to primary ADT, months	Median (IQR)	14.3 (11.0-25.3)	8.7 (6.0-18.7)	0.13
PSA at AWD, ng/ml	Median (IQR)	3.8 (1.1-12.3)	22.9 (2.0-73.5)	**0.041**
Radiographic/clinical progression at AWD, n (%)	Absence		3 (27.3%)	
	Presence		8 (72.7%)	**<0.0001**

ADT: Androgen-deprivation therapy; IQR: interquartile range; PSA: prostate-specific antigen; NA, not available. Statistically significant *p*-values are shown in bold.

Table II. *Patient characteristics by presence or absence of anti-androgen withdrawal syndrome [AWS: >50% prostate-specific antigen (PSA) decline].*

Variable		AWS		*p*-Value
		Present (n=9)	Absent (n=75)	
Age at diagnosis, years	Median (IQR)	68 (59-80)	73 (68-77)	0.52
PSA at diagnosis, ng/ml	Median (IQR)	99.9 (40.8-1144.3)	271.3 (74.5-720.2)	0.31
Biopsy Gleason score, n (%)	≤8	6 (75.0%)	22 (31.0%)	
	>8	2 (25.0%)	49 (69.0%)	**0.014**
	NA	1	4	
Clinical T-stage, n (%)	cT1/2/3a	3 (33.3%)	31 (42.5%)	
	cT3b/4	6 (66.7%)	42 (57.6%)	0.60
	NA	0	2	
Clinical N-stage, n (%)	N0	3 (33.3%)	28 (37.8%)	
	N1	6 (66.7%)	46 (62.2%)	0.79
	NA	0	1	
Clinical M-stage, n (%)	M0	1 (11.1%)	7 (9.5%)	
	M1a	0 (0.0%)	3 (4.1%)	
	M1b	7 (77.8%)	62 (83.8%)	
	M1c	1 (11.1%)	2 (2.7%)	0.57
	NA	0	1	
Response duration to primary ADT, months	Median (IQR)	36.8 (14.8-77.9)	13.8 (11.0-24.0)	**0.026**
PSA at AWD, ng/ml	Median (IQR)	1.6 (0.5-18.3)	4.1 (1.1-12.7)	0.19
Radiographic/clinical progression at AWD, n (%)	No	9 (100%)	65 (86.7%)	
	Yes	0 (0%)	10 (13.3%)	0.24

ADT: Androgen-deprivation therapy; AWD: anti-androgen withdrawal; IQR: interquartile range. Statistically significant differences are shown in bold.

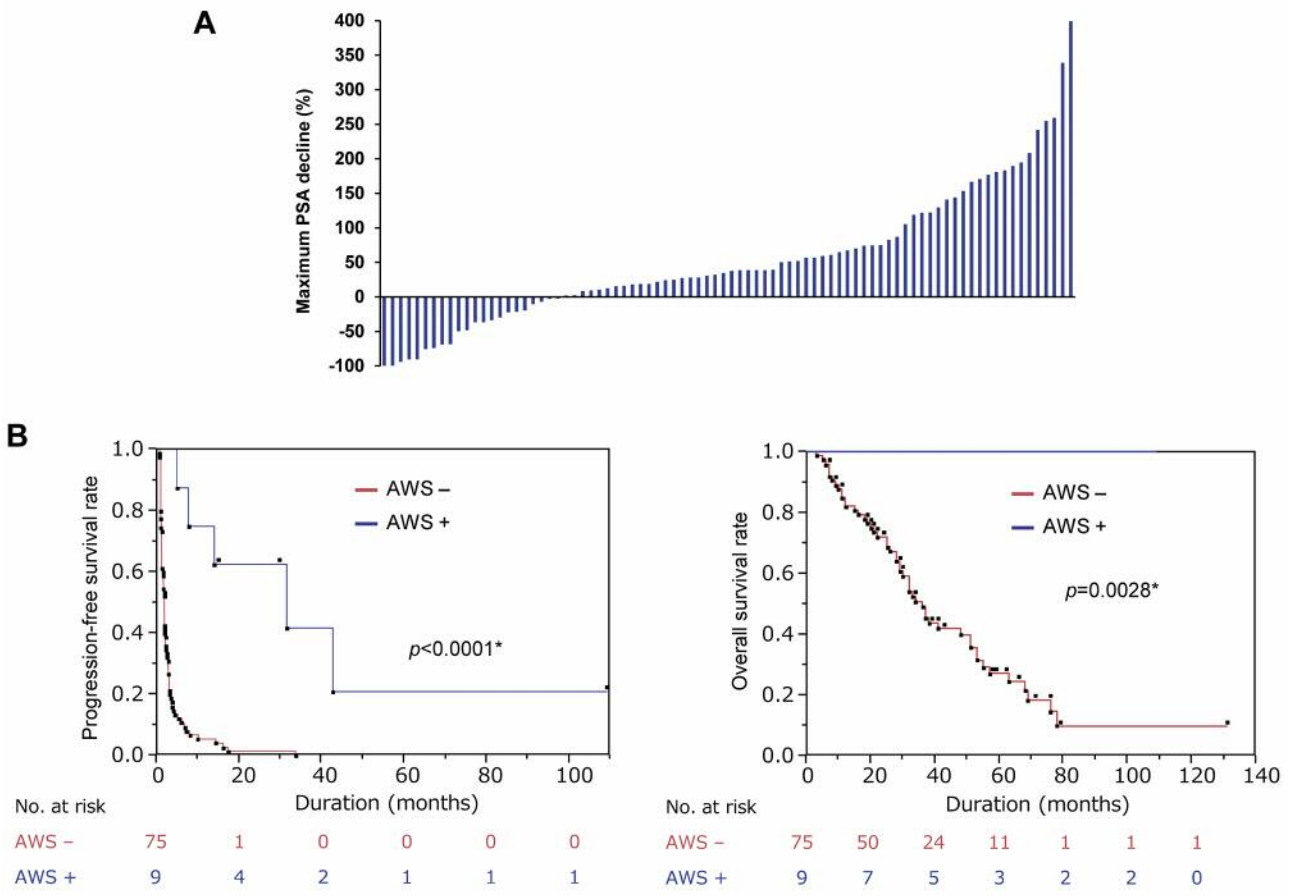

Figure 1. *Androgen withdrawal syndrome (AWS) in 84 patients who underwent anti-androgen withdrawal. A: Waterfall plot showing greatest decline in prostate-specific antigen (PSA) values from baseline in 84 patients with castration-resistant prostate cancer who underwent anti-androgen withdrawal. B: Progression-free survival (upper panel) and overall survival (lower panel) in 84 patients with castration-resistant prostate cancer who underwent anti-androgen withdrawal according to PSA response after anti-androgen withdrawal. AWS was defined as >50% PSA decline after anti-androgen withdrawal.*

confirmed in 35 patients, among whom 29% had experienced >50% PSA decline after flutamide withdrawal (18). Similar phenomena have been reported after withdrawal of other anti-androgens, bicalutamide (19) and enzalutamide (20), and abiraterone acetate (21, 22).

Previously, the rate of AWS (defined as >50% decline of PSA after anti-androgen withdrawal) was reportedly 15-30% (9), which is higher than the AWS rate in this study. The reason for this possible difference in AWS rate is unclear, but our inclusion of cases only treated with primary ADT (*i.e.* excluding salvage ADT cases), high rate of anti-androgen withdrawal (88.4%), and common use of bicalutamide as first-line anti-androgen for most patients may have affected the rate.

This study found both Gleason score at initial diagnosis and response duration to primary ADT to be predictors of AWS. The results of our study correspond with the finding that anti-androgen therapy duration of 32 months or more correlated with AWS in the SWOG 9426 study (23), which was supported by retrospective studies (24, 25). The association of Gleason score at initial diagnosis with better cancer-specific survival has been reported (26). Intriguingly, prostate cancer tumors with low Gleason scores reportedly have a higher *AR* mutation rate (27), which supports our finding that patients with low Gleason scores at initial diagnosis experienced AWS more frequently, possibly due to *AR* mutation.

This study also showed AWS to be closely associated with prognosis, which is consistent with previous studies (25, 28). In addition, several studies have reported on prognostic significance of some clinicopathological factors with regard to anti-androgen withdrawal. Previously, PSA-only progression, low PSA level at anti-androgen withdrawal, and long anti-androgen therapy duration before anti-androgen withdrawal were reported to be possible predictors of longer

Table III. *Associations between clinicopathological parameters and prognosis among men with anti-androgen withdrawal (AWD).*

		Progression-free survival			Overall survival		
Variable		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Median age at diagnosis	per range	1.07	0.35-3.33	0.91	7.19	1.08-54.27	**0.041**
Median PSA at diagnosis	per range	2.05	0.61-5.43	0.22	1.98	0.40-6.77	0.37
Biopsy Gleason score	≤8	1			1		
	>8	1.25	0.78-2.05	0.35	1.80	0.98-3.48	0.060
	cT1/2/3a	1			1		
Clinical T-stage	cT3b/4	1.14	0.73-1.81	0.57	0.86	0.49-1.55	0.60
	N0	1			1		
	N1	1.53	0.97-2.47	0.069	0.71	0.38-1.35	0.29
Clinical N-stage	M0	1			1		
	M1a	1.49	0.32-5.23	0.57	1.45	0.30-5.55	0.61
	M1b	1.46	0.74-3.33	0.29	0.91	0.42-2.40	0.84
Clinical M-stage	M1c	1.63	0.35-5.71	0.49	1.21	0.18-5.32	0.82
Median response duration to primary ADT	per range	0.021	0.0025-0.14	**<0.0001**	0.0042	0.0001-0.089	**<0.0001**
Median PSA at AWD	per range	1.40	0.30-4.27	0.62	1.19	0.19-5.30	0.86
Radiological/clinical progression at AWD	Absence	1			1		
	Presence	1.45	0.69-2.71	0.30	3.14	1.35-6.43	**0.010**

ADT: Androgen-deprivation therapy; IQR: interquartile range; PSA: prostate-specific antigen. Significant *p*-values are shown in bold.

Table IV. *Overall survival among men treated with and without antiandrogen withdrawal (AWD) according to clinicopathological parameters.*

		Without/with AWD			
Variable		No. of patients	Median OS (months)	*p*-Value	Interaction *p*-Value
All patients		11/84	28/37	0.22	
Age, years	≤75	8/55	34/51	0.43	0.29
	>75	3/29	12/32	0.14	
PSA at diagnosis, ng/ml	≤100	3/29	16/37	0.093	0.34
	100-500	6/29	28/53	0.40	
	>500	2/26	40/32	0.96	
Biopsy Gleason score	≤8	2/28	10/63	**0.0047**	0.19
	>8	9/51	31/37	0.63	
Clinical T-stage	cT1/2/3a	4/34	NYR/32	0.42	0.091
	cT3b/4	7/48	28/37	**0.042**	
Response duration to primary ADT, months	≤12	6/27	20/25	0.86	0.14
	>12	5/57	33/48	0.21	
PSA at AWD, ng/ml	≤10	4/61	28/51	0.097	0.26
	>10	7/23	23/25	0.69	
Radiological/clinical progression at AWD	Absence	3/75	39/48	0.23	**0.031**
	Presence	8/8	24/11	0.14	

ADT: Androgen-deprivation therapy; IQR: interquartile range; PSA: prostate-specific antigen. Statistically significant differences are shown in bold.

PFS (23). Our findings that response duration to primary ADT was a significant prognostic factor for PFS and OS, and that radiological/clinical progression and age were predictors of OS are consistent with these results.

As yet, the survival benefit of anti-androgen withdrawal has never been well demonstrated. This study showed anti-androgen withdrawal was not a significant risk factor of OS as a whole. However, notably, undergoing anti-androgen withdrawal in men with radiological/clinical progression was associated with worse prognosis, which implies that anti-androgen withdrawal has an adverse effect on prognosis in some patients with CRPC, where approximately 10% of

patients experienced clinical progression during anti-androgen withdrawal. Approximately disease in one-third of patients with CRPC radiographically progresses within 2 months, as shown by the placebo group in the PREVAIL trial (29). Thus, these results suggest that significant progression during anti-androgen withdrawal adversely affects prognosis. Therefore, men with aggressively progressive disease should not undergo anti-androgen withdrawal because delaying effective treatment for CRPC is likely to shorten their survival. Actually, in the present cohort, eight out of the 15 men with progressive disease did not undergo anti-androgen withdrawal. Intriguingly, Gleason score, response duration to primary ADT and radiological/clinical progression, which were identified as predictors of AWS and prognostic factors in anti-androgen withdrawal, were also suggested as clinical criteria for taxane chemotherapy among patients with CRPC, in addition to visceral metastasis, extensive disease and high tumor burden, despite a low PSA level (30), in consideration of their expected lower response to hormonal manipulation.

In addition to its therapeutic significance, anti-androgen withdrawal has diagnostic significance. If AWS is overlooked, patients could be treated with other agents, such as taxanes, or the novel AR-targeting agents, abiraterone and enzalutamide. Although these therapies exert excellent anticancer effects, patients with AWS plus non-progressive disease would benefit from them less, and could be exposed to physiological, mental and economic stress. Thus, as anti-androgen withdrawal is diagnostically significant, patients who are expected to have better prognoses – as indicated by their long responses to primary ADT, low Gleason scores and lack of radiological/clinical progression – may be good candidates for anti-androgen withdrawal.

The present study had several limitations. Its design was retrospective, and our sample size was small. In addition, approximately half the patients did not undergo radiological evaluations before anti-androgen withdrawal. However, despite these limitations, our results indicate that anti-androgen withdrawal carries adverse prognostic significance for some patients with CRPC, although these findings should be verified by further study.

Conclusion

This study found that Gleason score and response to primary ADT were associated with AWS; whereas response to primary ADT and radiological/clinical progression during anti-androgen withdrawal were associated with survival. Among patients for whom good prognoses are expected with anti-androgen withdrawal, anti-androgen withdrawal might help avoid unnecessary additional therapies. However, patients with radiological/clinical progression are apparently not good candidates for anti-androgen withdrawal.

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