ANTICANCER RESEARCH *37*: 5631-5637 (2017)
doi:10.21873/anticanres.11998

Differential Risk of Castration Resistance After Initial Radical Prostatectomy or Radiotherapy for Prostate Cancer

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Abstract. *Background/Aim: Salvage androgen-deprivation therapy (ADT) is standard treatment for recurrent prostate cancer after curative therapy. However, the prognostic impact of different treatment modalities on the time to castration resistance remains unclear. In this study, we investigated the prognosis of men treated with salvage ADT after initial radical prostatectomy or radiotherapy for prostate cancer. Patients and Methods: Between 2000 and 2013, 149 Japanese men with recurrent prostate cancer who were initially treated with radical prostatectomy (n=95) or radiotherapy (n=54) and were subsequently treated with salvage ADT after disease recurrence were enrolled in this study. The prognostic significance of the curative treatment modality and clinicopathological findings were analyzed. Results: During a median follow-up period of 4.7 years after recurrence, castration-resistant progression was observed in 22 men. The 5-year progression-free survival, metastasis-free survival, cause-specific survival, and overall survival rates for all patients were 86.3%, 81.4%, 95.7%, and 94.5%, respectively. Multivariate analysis identified the biopsy Gleason score at initial diagnosis and the initial curative treatment modality as significant predictors of castration resistance. Conclusion: This study showed that low biopsy Gleason score (≤7) at diagnosis and radical prostatectomy as the curative treatment may be favorable prognostic factors for treatment with salvage ADT.*

Prostate cancer is one of the most common cancers in men in developed countries. Androgen-deprivation therapy (ADT), which reduces the production and action of androgens, has been a standard therapy for metastatic prostate cancer since the 1940s (1). More recently, chemohormonal therapy using ADT with docetaxel has emerged as a novel standard therapy for metastatic castration-sensitive prostate cancer (2, 3). Additionally, ADT is used to treat localized prostate cancer without established evidence of survival benefit. Following curative treatment for prostate cancer by surgery (radical prostatectomy) or radiotherapy, approximately 20-30% of patients experience biochemical recurrence presenting as elevated prostate-specific antigen (PSA) levels (4), for which salvage prostatic bed-only radiotherapy or salvage ADT are common therapeutic options. Retrospective studies have demonstrated a possible survival benefit of salvage ADT for disease recurrence after radical prostatectomy (5). In addition, treatment of metastatic regional lymph node-positive prostate cancer with adjuvant ADT after radical prostatectomy conferred a survival benefit compared to salvage ADT, delayed until detection of distant metastases or symptom recurrence (6, 7). Furthermore, a recent randomized trial of men with recurrent prostate cancer after curative treatment reported marginally superior survival when salvage ADT was administered immediately rather than later (8). However, there is little evidence for a survival advantage of salvage ADT after curative radiotherapy.

To date, several factors have been identified to have prognostic value for the efficacy of salvage ADT after curative therapy. For patients receiving curative radical prostatectomy, seminal vesicle invasion at radical prostatectomy (9) and a rapid increase in PSA levels at recurrence (5) were reported to be unfavorable prognostic factors for the efficacy of salvage ADT. For patients receiving initial radiotherapy, a high biopsy Gleason score, cT3/4 stage, a rapid increase in PSA levels at recurrence, and shorter time to recurrence were reported to be unfavorable prognostic factors after salvage ADT (10). However, the impact of previous local treatment on overall survival among men with metastatic disease was reported in a subgroup analysis of the SWOG 8894 trial, which compared prognosis after orchiectomy plus either placebo or antiandrogen flutamide (11). That study showed a tendency toward superior survival for men who received previous

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Key Words: Androgen-deprivation therapy, castration-resistant prostate cancer, prostate cancer, radical prostatectomy, radiotherapy.

Table I. *Clinicopathological characteristics of patients treated with radical prostatectomy or radiotherapy.*

Variable	Radical prostatectomy (n=95)	Radiotherapy (n=54)	*p*-Value
Median age at recurrence, years (IQR)	70 (63-74)	74 (68-79)	0.0005*
Median PSA at diagnosis, ng/ml (IQR)	11.6 (6.6-16.4)	12.5 (8.3-27.8)	0.067
NA	1	0	
Biopsy Gleason score at diagnosis, n (%)			
≤7	58 (65.9%)	328 (70.4%)	
>7	30 (34.1%)	16 (29.6%)	0.58
NA	7	0	
Clinical T-stage at diagnosis, n (%)			
cT1/2a	53 (59.6%)	20 (37.7%)	
cT2b	10 (11.2%)	3 (5.7%)	
cT2c	18 (20.2%)	4 (7.5%)	
cT3/4	8 (9.0%)	26 (49.1%)	<0.0001*
NA	6	1	
Median duration to recurrence, years (IQR)	1.0 (0.4-2.1)	3.6 (1.8-5.7)	<0.0001*
Median PSA at ADT initiation, ng/ml (IQR)	0.6 (0.4-1.0)	3.7 (2.9-4.8)	<0.0001*
Median PSA velocity at ADT initiation, ng/ml/year (IQR)	0.87 (0.39-2.29)	3.40 (1.90-6.94)	<0.0001*
Metastatic disease at ADT initiation, n (%)			
Absence	84 (88.4%)	46 (85.2%)	
Presence	11 (11.6%)	8 (14.8%)	0.57
Regional lymph node	2 (2.1%)	0 (0.0%)	
Bone	7 (7.4%)	7 (13.0%)	
Lung	2 (2.1%)	1 (1.9%)	

*Statistically significant. ADT: Androgen-deprivation therapy; IQR: interquartile range; NA: not available; PSA: prostate specific antigen.

radical prostatectomy compared with previous radiotherapy, and for men who received either treatment compared with no previous curative treatment. However, the prognostic impact of the initial treatment modality on the time to castration resistance remains unclear for men without metastatic disease. Therefore, in this study, we investigated the prognosis of a cohort of men treated at a single institution with salvage ADT for non-metastatic or metastatic prostate cancer after either curative radical prostatectomy or radiotherapy.

Patients and Methods

Between 2000 and 2013, we enrolled 149 patients with recurrent prostate cancer after curative treatment (radical prostatectomy, n=95; radiotherapy n=54) who were treated with salvage ADT at Kyushu University Hospital (Fukuoka, Japan). This study was approved by the Institutional Review Board of the hospital. All patients were histopathologically diagnosed with adenocarcinoma of the prostate. Of the 149 men, 60 were biopsied at Kyushu University Hospital and 89 were biopsied at another institution; 57 of these 89 biopsies were reviewed at our institution. Clinical staging was determined in accordance with the unified TNM criteria based on the results of digital rectal examination, transrectal ultrasound, computed tomography, magnetic resonance imaging, and bone scan (12). Recurrence after radical prostatectomy and radiotherapy was defined as serum PSA levels of >0.2 ng/ml and an incremental increase of >2.0 ng/ml above the nadir PSA level, respectively. The case of 41 men who experienced recurrence after radical prostatectomy were treated with prostate bed-only salvage radiotherapy.

All patients were treated by salvage ADT with surgical castration or medical castration using a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprorelin acetate)/antagonist (degarelix acetate) and/or an antiandrogen agent (bicalutamide, flutamide, or chlormadinone acetate). Of these patients, 50, 68, and 31 men were initially treated with combined androgen blockade by castration with antiandrogen agent, castration alone, and antiandrogen agent alone, respectively. Among the men treated with antiandrogen agent alone, 10 were additionally treated with castration because of increased PSA or adverse effects of the antiandrogen agent. Imaging examinations, including computed tomography and bone scans, were performed at ADT initiation. Progressive disease during ADT was defined as at least one of the following: (i) increased serum PSA of >2 ng/ml and ≥25% increase over the nadir, (ii) the appearance of a new lesion, (iii) progression of one or more known lesions (classified according to the Response Evaluation Criteria in Solid Tumors [RECIST]) despite surgical or medical castration (13). Radiographic progression was defined as the progression of measurable disease on computed tomography or bone scan. Time to progression during ADT was defined as the date of recurrence after initial curative treatment to the date of progression during ADT. Continuous or intermittent ADT was employed based on discussions between the physician and patient because both ADT modalities show equivalent oncological outcomes for recurrent disease after curative therapy (14).

All statistical analyses were performed using JMP11 software (SAS Institute; Cary, NC, USA). Categorical and continuous data

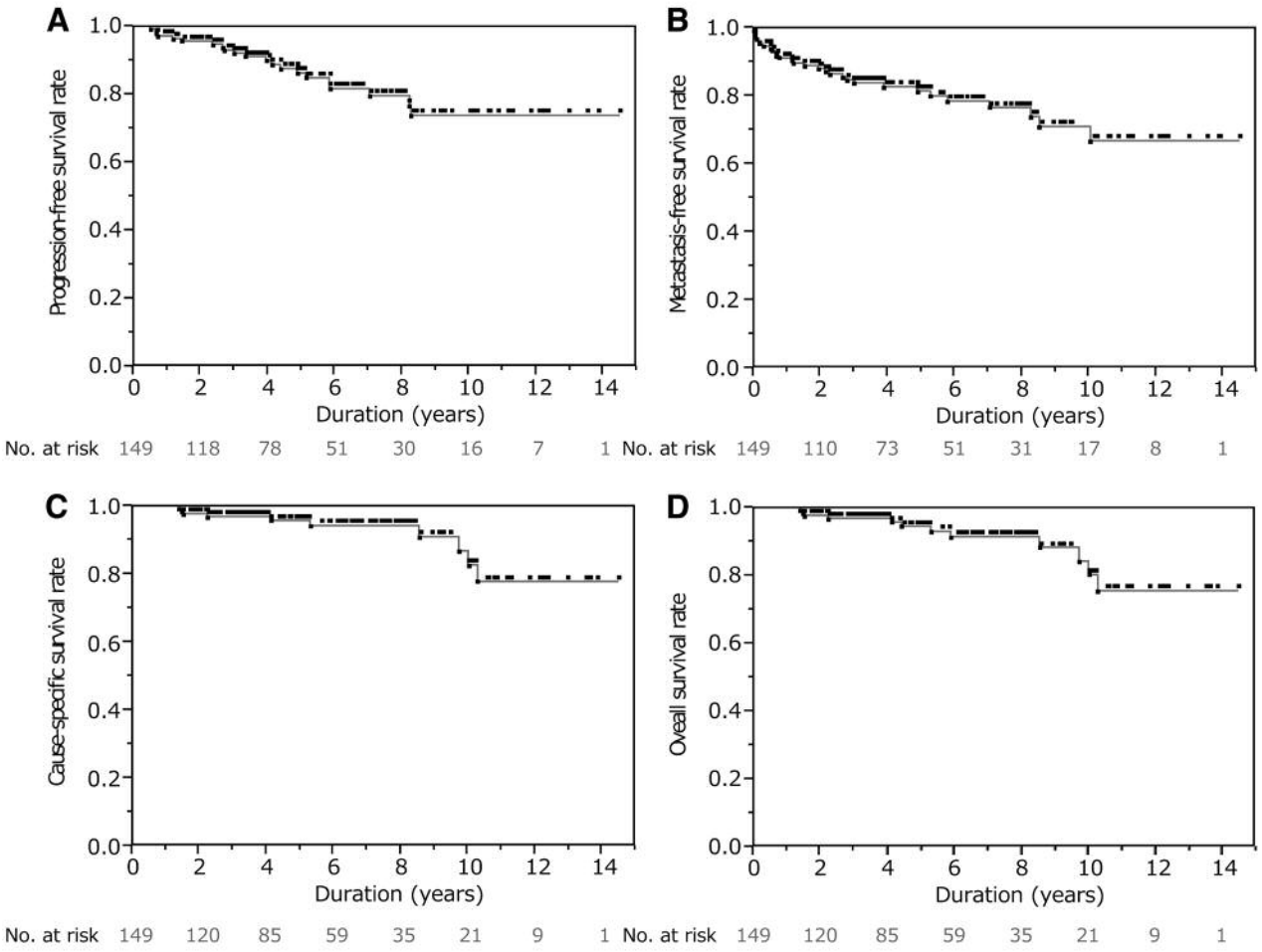

Figure 1. *Survival outcomes for patients with prostate cancer treated with salvage ADT. (A)–(D) Kaplan–Meier curves showing (A) progression-free survival, (B) metastasis-free survival, (C) cause-specific survival, and (D) overall survival of 149 patients with prostate cancer treated with salvage ADT.*

were analyzed by Pearson's chi square and Wilcoxon rank sum tests, respectively. The Kaplan–Meier method and log-rank statistics were employed to compare survival duration across groups. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. All *p*-values were two-sided, and $p<0.05$ was considered significant.

Results

The clinicopathological characteristics of the 149 Japanese patients enrolled in this study are shown in Table I. The initial curative therapy was radical prostatectomy for 95 men and radiotherapy for 54 men. At disease recurrence, the patients treated with radical prostatectomy (median age 70 years, interquartile range [IQR] 63-74) were younger than the men treated with radiotherapy (median 74 years, IQR=68-79; $p=0.0005$). Although the median PSA level ($p=0.067$) and biopsy Gleason score ($p=0.58$) at initial diagnosis were similar for the men treated with curative radical prostatectomy and radiotherapy, advanced clinical stage (cT3/4) at initial diagnosis was less frequent in the radical-prostatectomy group than in the radiotherapy group ($p<0.0001$). Men in the radical prostatectomy group also had a shorter time to recurrence ($p<0.0001$), lower PSA level at ADT initiation ($p<0.0001$), and lower PSA velocity at ADT initiation ($p<0.0001$) than men treated with radiotherapy. The metastatic disease rate at ADT initiation was similar between the two groups ($p=0.57$).

Figure 1 shows the progression-free survival (PFS, Figure 1A), metastasis-free survival (Figure 1B), cause-specific survival (Figure 1C), and overall survival (OS, Figure 1D) of the 149 patients. During the median follow-up period of 4.7 years, disease progression, cancer-specific death, and

Table II. *Associations between clinicopathological parameters, disease progression, and initial treatment modality.*

	Radical prostatectomy (n=95)			Radiotherapy (n=54)		
Variable	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age at recurrence (per range)	0.10	0.0086-1.12	0.062	3.08	0.18-73.57	0.45
PSA at diagnosis (per range)	2.69	0.096-26.87	0.50	10.73	0.43-133.23	0.13
Biopsy Gleason score at diagnosis						
≤7	1	-	-	1	-	-
>7	3.32	1.00-12.70	0.0496*	2.04	0.50-7.74	0.30
Clinical T-stage at diagnosis						
cT1/2a	1	-	-	1	-	-
cT2b	1.96	0.28-9.12	0.45	0.00	0.00-2.01	0.13
cT2c	1.84	0.37-7.68	0.37	0.92	0.043-7.77	0.94
cT3/4	1.07	0.055-6.71	0.95	0.56	0.12-2.98	0.48
Duration to recurrence (per range)	0.0074	0.00-1.54	0.078	0.50	0.026-6.70	0.61
PSA at ADT initiation (per range)	0.050	0.00-8.54	0.52	49.06	1.93-1263.12	0.024*
PSA velocity at ADT initiation (per range)	0.90	0.000082-12.68	0.96	854.60	10.12-59730.7	0.0051*
Metastatic disease at ADT initiation						
Absence	1	-	-	1	-	-
Presence	2.32	0.11-2.82	0.33	3.27	0.69-12.44	0.12

*Statistically significant. ADT: Androgen-deprivation therapy; CI: confidence interval; HR: hazard ratio; PSA: prostate specific antigen.

Table III. *Univariate and multivariate analysis of associations between clinicopathological parameters and risk of disease progression*

	Univariate analysis			Multivariate analysis		
Variable	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age at recurrence (per range)	0.54	0.067-4.86	0.57			
PSA at diagnosis (per range)	10.00	0.93-68.34	0.057			
Biopsy Gleason score at diagnosis						
≤7	1	-	-	1	-	-
>7	2.53	1.04-6.28	0.040*	2.66	1.10-6.62	0.031*
Clinical T-stage at diagnosis						
cT1/2a	1	-	-			
cT2b	1.09	0.16-4.37	0.91			
cT2c	1.50	0.40-4.81	0.52			
cT3/4	1.61	0.53-4.62	0.39			
Duration to recurrence (per range)	0.66	0.042-6.09	0.73			
PSA at ADT initiation (per range)	0.53	0.00-9.00	0.78			
PSA velocity at ADT initiation (per range)	1.54	0.0083-12.59	0.79			
Metastatic disease at ADT initiation						
Absence	1	-	-			
Presence	2.97	0.97-7.65	0.057			
Therapeutic modalitis						
Radical prostatectomy	1	-	-	1	-	-
Radiotherapy	2.55	1.02-6.17	0.045*	2.71	1.06-6.88	0.038*

*Statistically significant. ADT: Androgen-deprivation therapy; CI: confidence interval; HR: hazard ratio; PSA: prostate specific antigen.

death from any cause was observed for 21 (14.1%), 10 (6.7%), and 12 (8.1%) patients, respectively. Metastases were detected in 19 men at ADT initiation (n=11 and 8 previous radical prostatectomy and radiotherapy, respectively). Of the 21 men with progressive disease during ADT, 11 and 10 progressed to metastatic and non-metastatic castration-resistant disease, respectively. The 5-year PFS, metastasis-free survival, cause-specific survival, and OS rates for all 149 patients were 86.3%, 81.4%, 95.7%, and 94.5%, respectively.

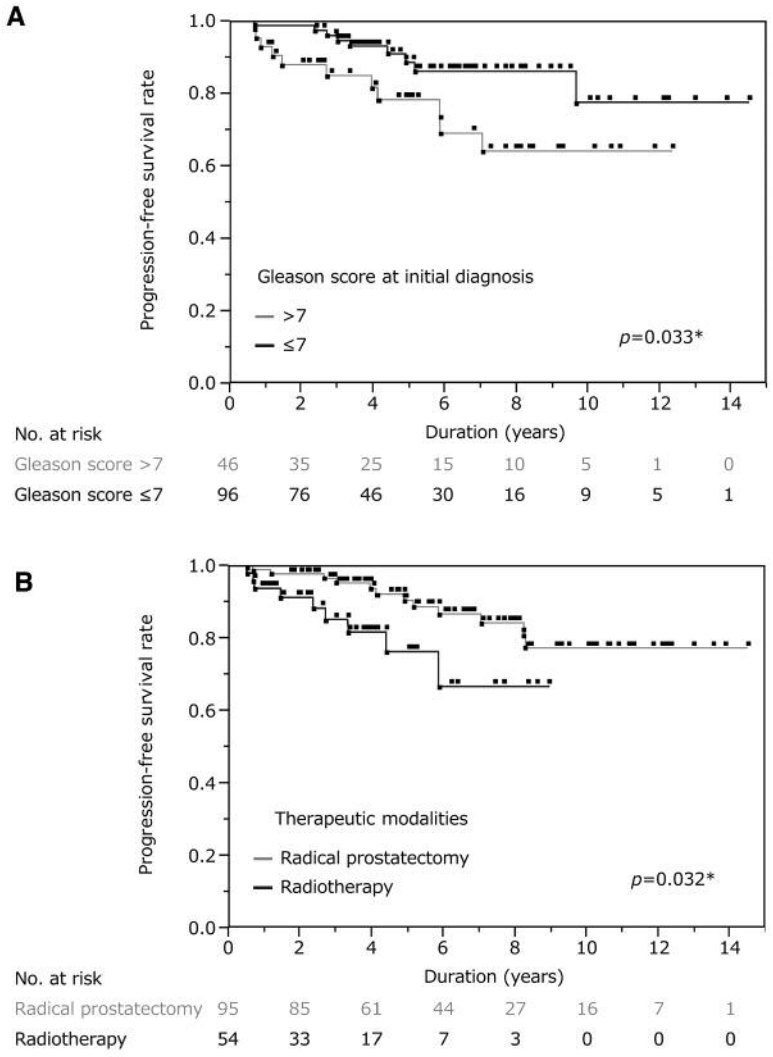

Figure 2. *Progression-free survival of patients with prostate cancer treated with salvage ADT. (A) and (B) Kaplan–Meier curves showing progression-free survival of 149 patients with prostate cancer treated with salvage ADT. Data are stratified according to (A) the biopsy Gleason score at initial diagnosis and (B) initial therapeutic modality. p-Values were calculated with the log-rank test.*

We performed univariate analyses on the prognostic factors for castration-resistant progression according to the curative treatment modality. As shown in Table II, a biopsy Gleason score >7 was significantly associated with castration resistance for men treated with radical prostatectomy as initial therapy. In contrast, the PSA level at ADT initiation and the PSA velocity at ADT initiation, but not the initial biopsy Gleason score, were prognostic factors for castration resistance for men treated with radiotherapy as initial treatment (Table II).

To identify prognostic indicators of PFS after salvage ADT, we performed univariate and multivariate analyses of factors at initial diagnosis (PSA level, biopsy Gleason score, and clinical T stage), factors at ADT initiation (age, time to recurrence, PSA level, PSA velocity, and metastatic status), and previous therapeutic modality (Table III). On univariate analysis, the biopsy Gleason score at initial diagnosis (hazard ratio [HR] 2.53, 95% confidence interval [CI]=1.04-6.28; p=0.0040) and radiotherapy as initial curative treatment (HR 2.55, 95%CI=1.02-6.17; p=0.045) were identified as significant predictors of PFS, while PSA level at diagnosis and metastatic status at ADT initiation showed a tendency toward association with PFS but did not reach the level of statistical significance (Table III). The Kaplan–Meier curves shown in Figure 2 indicate the association between the Gleason score at initial diagnosis (Figure 2A)

and curative treatment modality (Figure 2B) and the time to castration resistance. In multivariate analysis, the biopsy Gleason score at initial diagnosis (HR 2.66, 95%CI=1.10-6.62; p=0.031) and the curative treatment modality (HR 2.71, 95%CI=1.06-6.88; p=0.038) were identified as independent risk factors for disease progression during salvage ADT (Table III). However, there were no significant differences between radical prostatectomy and radiotherapy as the initial treatment and the risk of metastasis-free survival (HR 1.66, 95%CI=0.75–3.52; p=0.20), disease-specific survival (HR 2.62, 95%CI=0.49-12.65; p=0.24), or overall survival (HR 1.83, 95%CI=0.37-7.23; p=0.42). Finally, high biopsy Gleason score at initial diagnosis (>7) correlated with an increased risk of cancer-specific survival (HR 6.77, 95%CI=1.63-45.52; p=0.0075) and overall survival (HR 3.34, 95%CI=1.01-12.78; p=0.049) but not with metastasis-free survival (HR 1.65, 95%CI=0.78–3.43; p=0.19).

Discussion

In this study cohort, the median time to metastasis and death were longer than in several previous reports (10, 15, 16) but comparable to those in a recent report (17). The better prognosis observed in the present study may derive from immediate or earlier initiation of salvage ADT compared with the previous studies (10, 15-17), the differential sensitivity to ADT among races (18, 19), and/or the emergence of novel agents for castration-resistant prostate cancer (20).

This study identified the biopsy Gleason score at initial diagnosis as a prognostic factor for castration resistance, especially for patients treated with radical prostatectomy. This finding is consistent with a previous report that the biopsy Gleason score at initial diagnosis before radiotherapy (10) and the pathological Gleason score at radical prostatectomy (15-17) are prognostic factors for disease recurrence. Moreover, we found that PSA level and PSA velocity at ADT initiation were prognostic factors for men treated with radiotherapy. A rapid PSA increase at recurrence has also previously been reported to be a prognostic factor after treatment with radical prostatectomy (5, 15-17) and radiotherapy (10). In addition, our finding that prognosis is better for men with low PSA levels at ADT suggests that earlier initiation of ADT may lead to a more favorable outcome for recurrence after radiotherapy. Indeed, this is supported by reports showing improved survival when ADT is initiated early after curative therapy (8) and by the recommendation of the European Association of Urology that PSA recurrence indicative of systemic relapse is best treated early with ADT if poor prognostic risk factors, such as PSA-doubling time <12 months or Gleason score 8-10, are present (21). Furthermore, early initiation of ADT is supported by reports of improved survival with adjuvant ADT in node-positive prostate cancer after radical prostatectomy (6, 7) and of the possible merit of early ADT in patients with aggressive non-metastatic cancer (22).

In addition to the prognostic factors described above, we identified the curative therapeutic modality to be prognostic. The exact reason why salvage ADT had superior effects after radical prostatectomy than radiotherapy is unclear. In the case of radical prostatectomy, removal of the prostate, which is involved in *de novo* androgen synthesis, may have been beneficial (23), whereas the possible development of cross-resistance to ADT may have had a negative effect on the development of castration resistance after radiotherapy (24). However, the differential prognosis may also have been influenced by the time to disease recurrence, which was significantly different after initial treatment with radical prostatectomy compared with radiotherapy.

The present study had several limitations. The study design was retrospective, and the sample size was relatively small. Additionally, the methods of surgery and radiotherapy varied depending on the year, and the modalities of ADT differed among the cases. However, despite these limitations, the results of this study showed a significant difference in prognosis after radical prostatectomy and radiotherapy among Japanese men treated with salvage ADT at a single institution.

Conclusion

In conclusion, this single-institution study showed that biopsy Gleason score at initial diagnosis and the curative therapeutic modality were independent risk factors for the progression of prostate cancer to castration resistance. For Japanese men, low Gleason score (≤7) and radical prostatectomy may predict a favorable outcome of salvage ADT for recurrent disease.

Acknowledgements

This work was supported by Kakenhi grants (17K11145) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), Medical Research Promotion Grant from Takeda Science Foundation, and Research Promotion Grant from Shin-Nihon Advanced Medical Research Foundation. The Authors would like to thank Edanz Group Japan for editorial assistance.

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Received August 28, 2017
Revised September 18, 2017
Accepted September 19, 2017