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Optimal PSA Threshold for Androgen-Deprivation Therapy in Patients with Prostate Cancer following Radical Prostatectomy and Adjuvant Radiation Therapy

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Purpose: The benefits of early administration of androgen-deprivation therapy (ADT) in patients with prostate-specific antigen (PSA)-only recurrent prostate cancer (PCa) following radical prostatectomy (RP) are controversial. We investigated the impact of early versus delayed ADT on survival outcomes in patients with non-metastatic, localized or locally advanced PCa who received radiation therapy (RT) following RP and later developed distant metastasis.

Materials and Methods: A retrospective analysis was performed on 69 patients with non-metastatic, localized or locally advanced PCa who received RT following RP and later developed distant metastasis between January 2006 and December 2012. Patients were stratified according to the level of PSA at which ADT was administered (<2 ng/mL vs. ≥2 ng/mL). Study endpoints were progression to castration-resistant prostate cancer (CRPC)-free survival and cancer-specific survival (CSS).

Results: Patients were stratified according to the criteria of 2 ng/mL of PSA at which ADT was administered, based on the Youden sensitivity analysis. Delayed ADT at PSA ≥2 ng/mL was an independent prognosticator of cancer-specific mortality (p=0.047), and a marginally significant prognosticator of progression to CRPC (p=0.051). During the median follow-up of 81.0 (interquartile range 54.2–115.7) months, patients who received early ADT at PSA <2 ng/mL had significantly higher CSS rates compared to patients who received delayed ADT at PSA ≥2 ng/mL (p=0.002). Progression to CRPC-free survival was comparable between the two groups (p=0.331).

Conclusion: Early ADT at the PSA level of less than 2 ng/mL confers CSS benefits in patients with localized or locally advanced PCa who were previously treated with RP.

Key Words: Androgens, neoplasm metastasis, prostatic neoplasm, survival

INTRODUCTION

Radical prostatectomy (RP) is used as a curative therapy for patients with prostate cancer (PCa). RP has been shown to confer excellent oncological control and long-term survival for localized PCa by reducing the risk of local tumor progression and metastasis.[1] RP can be used as an option for various stages of PCa, from localized to high-risk disease.[2] Furthermore, evidence suggests a survival benefit when RP is included as part of multimodal therapy in patients with oligometastatic PCa.[3]

Androgen-deprivation therapy (ADT) is the standard therapy for patients with metastatic PCa and it can also be employed as part of multimodal therapy following RP. For patients exhibiting adverse pathological features, ADT can be used with radiation therapy (RT) to improve cancer-specific survival (CSS) and overall survival (OS).[4-8] ADT can also be administered after prostate-specific antigen (PSA) recurrence with RT,

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depending on the presence of metastasis, as a salvage treatment.[9,10] However, the optimal value of PSA and the disease landscape in which ADT should be administered are still a matter of debate.

Early initiation of ADT may be superior to delayed ADT in terms of short-term oncological outcomes; however, the benefit of early ADT is unclear in terms of CSS or OS outcomes.[2] Adverse effects of ADT cannot be overlooked. Moreover, the advent of non-metastatic castration-resistant disease may be attributed to early administration of ADT.[11] On the other hand, 12% of patients receiving RP for localized or locally advanced PCa are destined to develop metastasis during the median follow-up of 2.2 years, and early ADT may be a feasible option to delay metastatic progression.[12,13]

Contemporary guidelines do not indicate the optimal timing for administering ADT following RP, and state that treatment should be individualized depending on PSA kinetic parameters such as PSA doubling time (PSADT), PSA velocity (PSAV), patient anxiety, underlying comorbidities, and life expectancy.[2] Indeed, this disease spectrum poses uncertainty for both patients and physicians and warrants investigation. The primary endpoint of our study was the impact of early versus delayed ADT on survival outcomes in patients with localized or locally advanced PCa who received RP and later developed metastasis. The secondary study endpoint was the definition of a specific level of PSA-related parameters that can be utilized to select candidates for early initiation of ADT.

MATERIALS AND METHODS

Patient selection

This multicenter study evaluated data from 923 consecutive patients with non-metastatic, localized or locally advanced PCa who received adjuvant or salvage RT for PSA-only recurrence following RP between January 2006 and December 2012. Among these patients, 69 (7.5%) patients who later developed distant metastasis were selected for analysis (Fig. 1). The study's protocol was approved by the Institutional Ethics Committee (2017-0186-001).

Data collection

The patients' clinicopathological characteristics were retrieved from the institutional electronic medical records database. The variables included age, body mass index, Eastern Cooperative Oncology Group Performance Status Scale, National Comprehensive Cancer Network (NCCN) risk category, time to PSA recurrence, time from PSA recurrence to ADT initiation, pathological Gleason score and stage, preoperative PSA level, PSA nadir at RP, PSA level at ADT initiation, PSAV and PSADT before ADT, PSA nadir after ADT, and time to PSA nadir.

PCa staging was determined according to the 7th version of the American Joint Committee on Cancer TNM system. Castration-resistant prostate cancer (CRPC) was defined as the progression of disease or an increase in serum PSA using the Prostate Cancer Working Group 2 criteria.[14] The progression of disease was diagnosed based on a continuous increase in serum PSA levels, new symptom development, or a metastatic lesion detected during ADT using radiographic imaging.

For all patients, the status of survival and cause of death were investigated using institutional electronic medical records, the National Cancer Registry Database, or the Social Security Death Index. Death was attributed to PCa if evidence of progressive metastatic CRPC was present, PCa was listed on the death certificate as the cause of death, or if the patient died of complications of PCa treatment.

Treatments

Robot-assisted laparoscopic RP was recommended for patients who were determined to be reasonable surgical candidates and desired surgical treatment. Surgery was performed with the extent of pelvic lymph node dissection being based

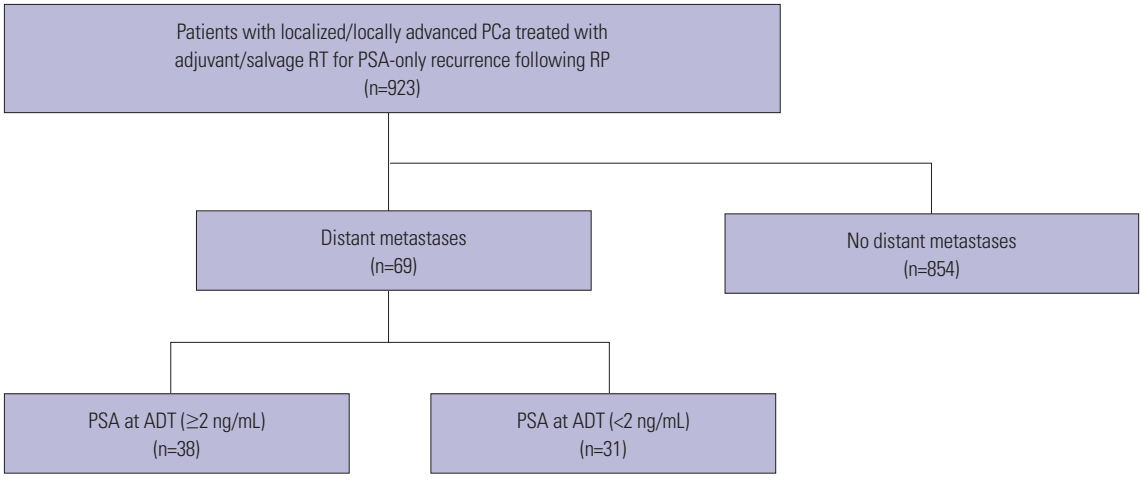

Fig. 1. Flowchart of patient selection. ADT, androgen-deprivation therapy; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.

upon the risk category of the patient.

RT was delivered to the prostatic fossa with defined margins according to the guidelines of the European Organization for Research and Treatment of Cancer.[15] At both institutions, RT consisted of 3D conformal RT from 2000 to 2007 and intensity-modulated external beam RT from 2007 to 2016. The median RT dose delivered was 6300 cGy [interquartile range (IQR) 6300–6300 cGy].

ADT included luteinizing hormone-releasing hormone agonists only or combined androgen blockade. In the subset of patients who received concurrent ADT with RT, ADT was administered for 6 to 24 months according to the physician's discretion. In the subset of patients who received ADT as an adjuvant setting, ADT was administered to patients with a PSA persistence or an increasing PSA following RT. All patients included in our study cohort received continuous ADT, and no patient received intermittent ADT. For patients who progressed to CRPC, lifelong ADT was performed until death or last follow-up. All patients received the standard-of-care according to contemporary guidelines until death or the last follow-up.

Study endpoints

The primary endpoint was progression to CRPC-free survival and CSS. The secondary endpoint was specific levels of PSA-related parameters that can be utilized to select candidates for the initiation of ADT.

Statistical analysis

Chi-square test and ANOVA were used to compare two or more variables, and Mann-Whitney U test was used for the analysis of continuous variables. Survival analysis was evaluated and compared using the Kaplan-Meier method and compared with the log-rank test.

The prognostic significances of PSAV and PSADT before ADT, PSA at ADT, and PSA nadir after ADT were dichotomized at 2 ng/mL/year, 12 months, 2 ng/mL, and 1 ng/mL, respectively. These optimal cut-off values were based on predefined values and according to sensitivity analysis using Youden's Index. Multivariate analyses were performed with Cox-proportional hazards regression models to adjust for potential confounders. The following covariates were included: age, body mass index, Eastern Cooperative Oncology Group Performance Status Scale, pathological Gleason score and stage, time to PSA recurrence, time from PSA recurrence to ADT initiation, preoperative PSA level, PSA nadir at RP, PSAV and PSADT before ADT, PSA level at ADT initiation, PSA nadir following ADT, and time to PSA nadir. All statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corporation, Armonk, NY, USA). Differences with a p-value of <0.05 were considered statistically significant.

RESULTS

Patient characteristics

Patient demographics and clinicopathological features of groups stratified by the PSA level at ADT of 2 ng/mL are presented in Table 1. There were no significant differences between the two groups regarding the patients' age, body mass index, performance status, preoperative PSA level, NCCN risk category, pathological Gleason score and stage, type of RT, and PSAV and PSADT before ADT. There were no differences in patient distributions according to the type of RT or timing of ADT administration.

Prognosticators of survival

Cox proportional hazards regression analyses of predictors for progression to CRPC are presented in Table 2. On univariate analyses, PSA at ADT initiation ≥2 ng/mL (p=0.032) and PSA nadir following ADT ≥1 ng/mL (p=0.016) were significantly associated with an increased risk of progression to CRPC. On multivariate analyses, PSA at ADT initiation ≥2 ng/mL was a marginally significant prognosticator (p=0.051).

Cox proportional hazards regression analyses of predictors for cancer-specific mortality are presented in Table 3. On univariate analyses, Gleason score ≥8 (p=0.024), PSA at ADT initiation ≥2 ng/mL (p=0.015), and PSA nadir following ADT ≥1 ng/mL (p=0.019) were significantly associated with an increased risk of cancer-specific mortality. On multivariate analyses, PSA at ADT initiation ≥2 ng/mL was an independent predictor of cancer-specific mortality (p=0.047).

Patients' age, body mass index, grade and stage, preoperative PSA, PSA nadir at RP, PSAV and PSADT prior to ADT, and time to PSA nadir following ADT were not independently associated with progression to CRPC and cancer-specific mortality.

Survival outcome

Survival outcomes were compared according to the PSA level at ADT, which was stratified at 2 ng/mL (Table 4). During the median follow-up of 81.0 (IQR 54.2–115.7) months, patients who received ADT at PSA <2 ng/mL had significantly higher CSS rates than men who received ADT at PSA ≥2 ng/mL (p=0.002) (Fig. 2). Progression to CRPC-free survival was comparable between the two groups (p=0.331) (Fig. 3).

DISCUSSION

ADT is a treatment option for all stages of PCa, from localized disease with a high risk of recurrence to castration-resistant disease.[16] Following RP, ADT can be used as an adjuvant therapy combined with RT to maximize survival outcomes in patients exhibiting adverse pathological features. Previous reports have suggested that the use of ADT in this clinical

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Table 1. Clinicopathological Characteristics of Patients with Localized Prostate Cancer Who Underwent Radical Prostatectomy and Later Developed Metastasis

	Overall	PSA level at ADT initiation		*p* value
		<2 ng/mL	≥2 ng/mL	
N	69	31 (45.0)	38 (55.0)	NS
Age (yr)	69.0 (67.0–72.5)	68.5 (61.5–75.8)	71.0 (69.0–70.5)	0.861
BMI (kg/m^2)	22.9 (21.9–26.8)	21.9 (20.6–26.1)	23.1 (21.7–27.3)	0.765
ECOG PS				0.644
≤1	60 (86.9)	27 (87.1)	33 (86.8)	
≥2	9 (13.1)	4 (12.9)	5 (13.2)	
Preoperative PSA (ng/mL)	17.4 (7.4–50.0)	20.0 (9.3–43.0)	14.8 (8.6–75.5)	0.256
PSA velocity				0.191
≥2 ng/mL/year	38 (55.1)	16 (51.6)	22 (57.9)	
<2 ng/mL/year	31 (44.9)	15 (48.4)	16 (42.1)	
PSA doubling time				0.246
≥12 months	33 (47.8)	14 (45.2)	19 (50.0)	
<12 months	36 (52.2)	17 (54.8)	19 (50.0)	
Time from PSA recurrence to ADT initiation (months)	4.0 (2.0–9.0)	3.0 (1.0–16.5)	4.5 (2.8–6.8)	0.804
NCCN risk category				0.197
Low	7 (10.1)	5 (16.2)	2 (5.3)	
Intermediate	18 (26.1)	9 (29.0)	9 (23.7)	
High	44 (63.8)	17 (54.8)	27 (71.0)	
Gleason score				0.582
≤6	13 (18.8)	7 (22.6)	6 (15.8)	
7	15 (21.7)	8 (25.8)	7 (18.4)	
≥8	41 (59.5)	16 (51.6)	25 (65.8)	
Pathological stage				0.541
T2	12 (17.4)	7 (22.6)	5 (13.1)	
T3	47 (68.1)	20 (64.5)	27 (71.1)	
T4	10 (14.5)	4 (12.9)	6 (15.8)	
Type of radiation therapy				0.158
Adjuvant	11 (15.9)	5 (16.1)	6 (15.8)	
Salvage	58 (84.1)	26 (83.9)	32 (84.2)	
Timing of ADT administration				0.835
Concurrent with radiation therapy	37 (53.6)	17 (54.8)	20 (52.6)	
Adjuvant	32 (46.4)	14 (45.2)	18 (47.4)	

ADT, androgen-deprivation therapy; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.
Data are expressed as median (interquartile range) and number (%).

scenario may improve CSS and OS.[4-9] ADT can also be administered with RT at PSA recurrence, depending on the presence of metastasis, as a salvage treatment option, which may result in clinical benefit.[9] However, the optimal level of PSA at which ADT should be administered remains controversial. In this study, we observed that delaying ADT following PSA elevation beyond 2 ng/mL was associated with an increased risk of progression to CRPC and cancer-specific mortality.

In our study, a PSA cut-off value of 2 ng/mL based on Youden sensitivity analysis was revealed to be a prognosticator for CSS in patients with PSA-only recurrent PCa following RP. Previous studies report varying indications for initiating ADT following RP. Amling, et al.[17] suggested that a PSA value of greater than 0.4 ng/mL should be used to define PSA recurrence, since this cut-off point is associated with an increased risk of biochemical and/or clinical progression. Freedland, et al.[18] reported that the risk of the need for secondary treatment following PSA recurrence depends on the cut-off value of PSA. Based on the finding that patients with a postoperative PSA greater than 0.2 ng/mL had a 100% 3-year risk of PSA progression, this cut-off point was suggested to be an indicator to initiate treatment. Siddiqui, et al.[19] suggested that adjuvant ADT within 90 days after RP improves CSS and systemic progression-free survival in node-negative patients. However, there were no differences in systemic progression-free survival or CSS between patients who began ADT at PSA values of 0.4, 1.0, and 2.0 ng/mL. A ran-

Table 2. Cox-Regression Models for the Association of Risk Factors with Progression to Castration-Resistance

	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	0.951	0.884–1.023	0.173			
BMI	1.085	0.928–1.269	0.306			
ECOG PS						
≤1	1	Reference				
≥2	0.504	0.139–1.829	0.298			
Gleason score						
≤7	1	Reference				
≥8	2.202	0.894–5.424	0.086			
Pathological stage						
≤T2	1	Reference				
≥T3	0.779	0.168–3.607	0.749			
Time to PSA recurrence	0.938	0.870–1.011	0.092			
Time from PSA recurrence to ADT initiation	1.033	0.741–1.442	0.847			
Preoperative PSA	1.004	0.994–1.015	0.408			
PSA nadir at RP	2.113	0.847–5.270	0.109			
PSAV before ADT						
<2 ng/mL/year	1	Reference				
≥2 ng/mL/year	1.487	0.604–3.657	0.388			
PSADT before ADT						
<12 months	1	Reference				
≥12 months	0.983	0.961–1.005	0.134			
PSA at ADT initiation						
<2 ng/mL	1	Reference				
≥2 ng/mL	3.184	1.104–9.179	0.032	3.934	0.994–15.57	0.051
PSA nadir following ADT						
<1 ng/mL	1	Reference				
≥1 ng/mL	3.792	1.286–11.19	0.016	1.301	0.669–4.382	0.511
Time to PSA nadir	0.955	0.872–1.046	0.324			

ADT, androgen-deprivation therapy; BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazards ratio; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSAV, prostate-specific antigen velocity; RP, radical prostatectomy.

domized trial investigated the efficacy of immediate ADT versus delayed ADT after randomization among patients with PSA recurrence who were considered ineligible for curative treatment.[20] In the overall group, immediate ADT was associated with improvements in OS and time to clinical progression. However, no improvement of OS was observed in patients with PSA recurrence following curative therapy. A common limitation of these studies was that not all patients had received RT as multimodal therapy, as suggested by contemporary guidelines. In our study, all of the patients were treated with RT in an adjuvant or salvage setting according to the guidelines, which implies the generalizability of our data.

In our study, PSAV, PSADT, and Gleason score were not independently associated with survival endpoints. Contrarily, studies have recommended that these parameters be utilized to decide on the timing of ADT at PSA-recurrence following RP.[20-30] Van den Bergh, et al.[22] reported in a systematic review that early ADT cannot be recommended as the standard-of-care for PSA recurrence or local recurrence, and that ADT should be reserved for patients with the highest risk of disease progression, defined as short PSADT of less than 6–12 months or Gleason score of greater than 8. Algarra, et al.[23] reported seminal vesical involvement, PSAV of greater than 0.84 ng/mL/year, and PSADT to be considered as adverse features associated with disease progression in patients who received ADT at PSA recurrence. In a cohort of patients with mainly high-risk disease, faster PSADT, higher Gleason score, and early intervention were associated with a lower risk of CSS.[26] The significance of PSADT was consistent in patients receiving intermittent ADT, in which a PSADT and PSA nadir of less than 1 ng/mL during the first cycle was associated with improvement in CRPC-free survival.[25] On the other hand, studies have reported higher PSA and PSA nadir after starting ADT, rather than PSADT or PSAV, to be significant indicators for CSS.[29,30] As seen in these studies, the parameters utilized for clinical endpoints were inconsistent, which defers a definite conclusion. Moreover, vari-

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Table 3. Cox-Regression Models for the Association of Risk Factors with Progression to Cancer-Specific Mortality

	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.036	0.922–1.165	0.552			
BMI	0.994	0.767–1.288	0.963			
ECOG PS						
≤1	1	Reference				
≥2	3.063	0.651–14.42	0.157			
Gleason score						
≤7	1	Reference				
≥8	5.743	1.264–26.09	0.024	3.844	0.834–17.72	0.084
Pathological stage						
≤T2	1	Reference				
≥T3	2.939	0.896–9.631	0.075			
Time to PSA recurrence	0.864	0.691–1.081	0.201			
Time from PSA recurrence to ADT initiation	0.955	0.737–1.226	0.688			
Preoperative PSA	0.994	0.981–1.008	0.376			
PSA nadir at RP	1.802	0.619–5.240	0.281			
PSAV before ADT						
<2 ng/mL/year	1	Reference				
≥2 ng/mL/year	0.940	0.268–3.298	0.923			
PSADT before ADT						
<12 months	1	Reference				
≥12 months	0.996	0.971–1.021	0.737			
PSA at ADT initiation						
<2 ng/mL	1	Reference				
≥2 ng/mL	6.495	1.432–29.47	0.015	5.211	1.076–25.23	0.047
PSA nadir following ADT						
<1 ng/mL	1	Reference				
≥1 ng/mL	4.353	1.276–14.86	0.019	2.234	0.624–8.003	0.217
Time to PSA nadir	0.972	0.864–1.092	0.631			

ADT, androgen-deprivation therapy; BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazards ratio; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSAV, prostate-specific antigen velocity; RP, radical prostatectomy.

Table 4. Oncological Outcomes of Patients with Localized Prostate Cancer who Underwent Radical Prostatectomy and Later Developed Metastasis

	PSA at ADT		*p* value
	<2 ng/mL	≥2 ng/mL	
Time to metastasis (months)	33.5 (14.0–42.3)	31.2 (12.3–41.1)	0.971
Metastatic site			
Bone	27 (87.1)	33 (86.8)	0.468
Lymph nodes	3 (10.0)	5 (13.2)	0.621
Viscera	2 (6.5)	3 (7.9)	0.133
CRPC (%)	17 (53.1)	30 (51.7)	0.548
Time to CRPC (months)	55.5 (35.2–97.8)	42.5 (32.3–73.8)	0.051
CRPC-free progression, 5 yr (%)	70.8	64.7	0.311
Death	7 (21.9)	22 (37.9)	0.001
Time to CSM (months)	72.0 (45.0–108.9)	65.0 (52.5–90.0)	0.045
CSS, 5 yr (%)	86.1	68.7	0.002
Follow-up (months)	83.5 (70.5–118.5)	78 (52.4–94.0)	0.074

ADT, androgen-deprivation therapy; CRPC, castration-resistant prostate cancer; CSM, cancer-specific mortality; CSS, cancer-specific survival; PSA, prostate-specific antigen.
Data are expressed as median (interquartile range) and number (%).

ous cut-off points were used for stratification of PSADT or PSAV, if they were not evaluated as continuous variables. To our knowledge, the present study is the first to suggest an optimal cut-off point of PSA to initiate ADT to confer CSS benefit in patients who underwent RT after PSA-only recurrence. Our results are meaningful since the patients included in our study were a homogeneous group who were treated with RT and standard care according to contemporary guidelines until death or last follow-up.

Based on accumulating evidence, there has been a paradigm shift in considering aggressive treatments targeted at both the primary tumor and metastatic lesions of PCa to avoid or delay the need for palliative treatments and to achieve maximal survival benefit.[3] PSA recurrence is the most common pattern of disease relapse following RP, observed in up to 35% of patients.[31] In an era of aggressive treatments for oligometastatic PCa, it is certain that more patients will experience postoperative PSA recurrence and would be candidates for ADT. We believe that our findings provide relevant evidence for the decision-making and patient stratification in future clinical trials.

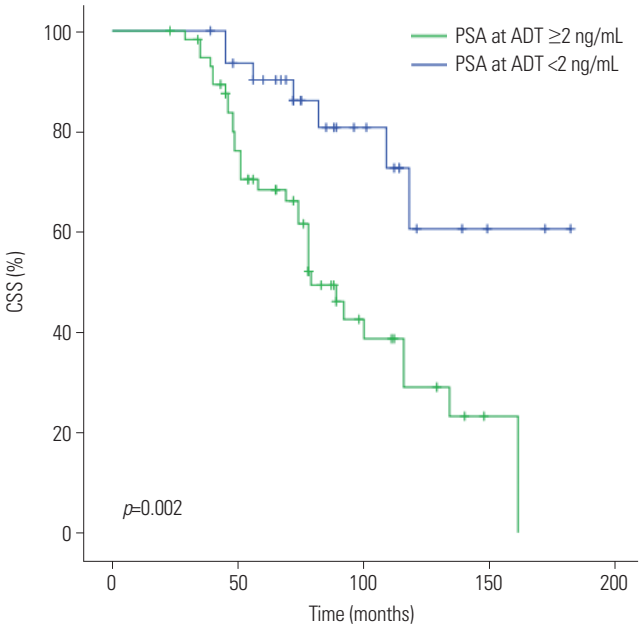

Fig. 2. Kaplan-Meier curves showing CSS, stratified by the PSA level at ADT of 2 ng/mL. ADT, androgen-deprivation therapy; CSS, cancer-specific survival; PSA, prostate-specific antigen.

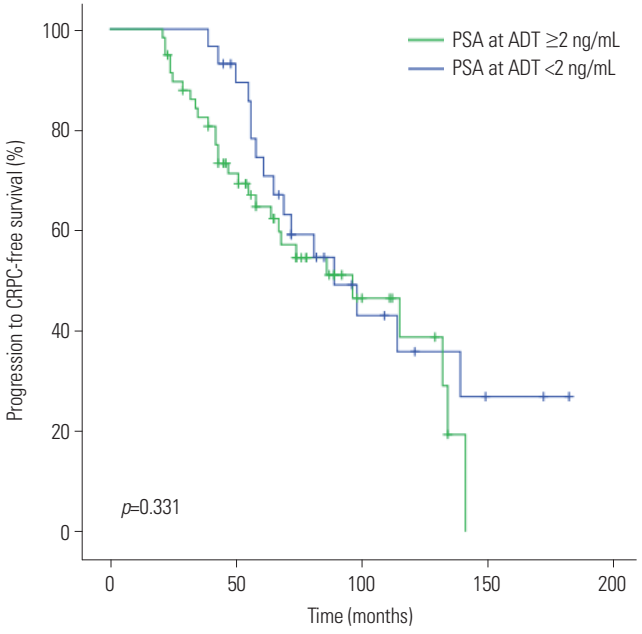

Fig. 3. Kaplan-Meier curves showing progression to CRPC-free survival, stratified by the PSA level at ADT of 2 ng/mL. ADT, androgen-deprivation therapy; CRPC, castration-resistance prostate cancer; PSA, prostate-specific antigen.

The strengths of our study were the inclusion of detailed PSA kinetic data, comorbidities, performance status, and clinicopathological data that were available for all patients. At the same time, we acknowledge several limitations: first, our study was limited by its retrospective design and the sampling intervals used to estimate PSA kinetics were not standardized. Moreover, the administration of ADT may not have been well-structured among physicians. Second, the potential existence of bias regarding subgroup differences may have confounded the results, although there were no statistically significant differences between the two groups stratified by the level of PSA at ADT. Third, patient and physician preferences affected the implementation of specific treatments, including the timing of ADT and RT. Finally, the OS may serve as a proxy for survival outcomes. However, we chose to use CSS as the endpoint, as our study population included patients who were relatively older and of lower performance status compared to the general population. Since OS may be affected by competing risks, we considered that this survival endpoint might not reliably reflect prostate CSS benefits conferred by early ADT.

Early ADT at the PSA level of less than 2 ng/mL confers a CSS benefit in patients with localized or locally advanced PCa who were previously treated with RP. Future larger-scale analyses are warranted to validate our results.

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AUTHOR CONTRIBUTIONS

Conceptualization: Kyo Chul Koo. Data curation: Kwang Suk Lee and Daeho Kim. Formal analysis: Hyun Kyu Ahn. Funding acquisition: Kyo Chul Koo. Investigation: Hyun Kyu Ahn and Kyo Chul Koo. Methodology: Hyun Kyu Ahn and Kwang Suk Lee. Project administration: Koon Ho Rha, Sung Joon Hong, and Byung Ha Chung. Resources: Koon Ho Rha and Sung Joon Hong. Supervision: Kyo Chul Koo. Writing—original draft: Hyun Kyu Ahn. Writing—review & editing: Kyo Chul Koo. Approval of final manuscript: all authors.

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