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Research Article

Prostate-specific antigen doubling time predicts the efficacy of site-directed therapy for oligoprogressive castration-resistant prostate cancer

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ABSTRACT

Background: In recent years, site-directed therapies (SDTs) targeting progressive lesions in patients with oligometastatic prostate cancer have attracted attention. However, whether they effectively treat oligoprogressive castration-resistant prostate cancer (CRPC) remains unclear. Here, we investigated the efficacy of SDT in patients with oligoprogressive CRPC and identified prognostic factors.

Methods: We reviewed 59 patients with oligoprogressive CRPC who underwent SDT targeting prostate or metastatic lesions between April 2014 and March 2022. We evaluated the associations between several pretreatment clinical variables and treatment procedures and a >50% prostate-specific antigen (PSA) response, progression-free survival (PFS), and time to next treatment (TTNT).

Results: A PSA response of >50% was observed in 66% of patients. The median PFS and TTNT were 8.3 months and 9.9 months, respectively. Patients with PSA doubling time ≥6 months showed a higher >50% PSA response rate (87% vs. 45%; $P < 0.001$), longer PFS (median, 15.0 vs. 5.0 months; $P < 0.001$), and longer TTNT (median, 16.3 vs. 5.9 months; $P < 0.001$) than patients with PSA doubling time <6 months. In multivariate analyses, a PSA doubling time of ≥6 months independently predicted a >50% PSA response, favorable PFS, and TTNT ($P = 0.037$, 0.025, and 0.017, respectively).

Conclusion: PSA doubling time of ≥6 months may be a key indicator of the favorable efficacy of SDT for oligoprogressive CRPC.

1. Introduction

Previously, the conventional treatment of prostate cancer with distant metastases exclusively involved systemic androgen-deprivation therapy (ADT). Local treatment of metastases mainly included palliative radiotherapy to alleviate pain and prevent paralysis due to bone metastases and was rarely used for systemic cancer control. However, recently, next-generation imaging tests including choline positron emission tomography (PET) [1-3], whole-body magnetic resonance diffusion-weighted imaging with background suppression (DWIBS) [3-5], fluorocholine PET [5-7], and prostate-specific membrane antigen (PSMA)-PET [8-10], have made it possible to identify micrometastasis that could not be identified by conventional imaging techniques such as computed

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Abbreviations

ADT	androgen-deprivation therapy
ARAT	androgen receptor-axis targeted
CRPC	castration-resistant prostate cancer
DWIBS	diffusion-weighted whole-body imaging with background suppression
EBRT	external beam radiotherapy
Fr	fractions
HSPC	hormone-sensitive prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSMA	prostate-specific membrane antigen
RCT	randomized controlled trial
SDT	site-directed therapy
SRT	stereotactic radiotherapy
TTNT	time to next treatment

tomography and bone scintigraphy. Hence, the concept of oligometastasis has been proposed [11,12]. Local treatment of prostate cancer with oligometastases is now attracting attention.

Much of the evidence for local treatment of prostate cancer with oligometastases has come from studies of hormone-sensitive prostate cancer (HSPC). The STAMPEDE trial, a phase III randomized controlled trial (RCT), demonstrated an additive effect of prostate-targeted radiotherapy and ADT in de novo and low-volume metastatic HSPC [13]. Two phase II RCTs, the STOMP and ORIOLE trials, documented the efficacy of metastasis-directed therapy in HSPC cases with oligo-recurrence after radical therapy [14-16]. On the other hand, information regarding the local treatment of oligoprogressive castration-resistant prostate cancer (CRPC) is still scarce, although several retrospective studies have reported the high efficacy of site-directed therapy (SDT) [17-23]. Here, we aimed to identify the clinical factors predicting the efficacy of SDT for oligoprogressive CRPC.

2. Materials and Methods

2.1. Patients

Patients with oligoprogressive CRPC who underwent SDT targeting prostate or metastatic lesions at the University of Tokyo Hospital and the Center Hospital of the National Center for Global Health and Medicine between April 2014 and March 2022 were included in this study. The inclusion criteria were as follows: (1) a diagnosis of CRPC, as defined by an increase in prostate-specific antigen (PSA) levels of $\geq$25% and $\geq$2 ng/mL above the nadir level or radiographic progression under <50 ng/dL serum total testosterone [24]; (2) four or fewer progressive lesions on imaging tests; and (3) receipt of SDT targeting all identified progressive lesions. The clinical characteristics of the patients at the start of SDT were obtained via retrospective review of medical records and included age, PSA level, imaging tests used to detect CRPC oligoprogression, site and number of oligoprogressive lesions, history of multiple metastases, prior radical treatments, prior systemic treatments, type of SDT, and post-treatment courses. PSA doubling time (PSADT) was calculated by log (2) divided by the slope of the linear regression of log (PSA) over time in months [25].

This retrospective multicenter study was approved by the Institutional Review Board of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (approval number: 11279), and that of the National Center for Global Health and Medicine. Given the retrospective nature of this study, the requirement for written informed consent was waived.

2.2. Outcomes

The primary outcome measures in the present study were PSA response, progression-free survival (PFS), and time to the next

Table 1
Clinical characteristics of patients at the start of site-directed therapy (n = 59)

Parameter	Value
Age, years; median [IQR]	75 [69–81]
PSA, ng/mL; median [IQR]	8.1 [3.9–17.8]
PSA doubling time, months; median [IQR]	6.1 [3.7–13.7]
Imaging tests (including duplicates); no. (%)	
Choline PET	24 (41)
Fluorodeoxyglucose PET	20 (34)
DWIBS	13 (22)
Only conventional tests (CT and/or bone scintigraphy)	12 (20)
Number of targeted lesions; no. (%)	
1	42 (71)
2	12 (20)
3	3 (5)
4	2 (3)
Site of targeted lesions; no. (%)	
Prostate	21 (36)
Bone metastasis	23 (39)
Lymph node metastasis	18 (31)
Others	4 (7)
Target lesion in only the prostate; no. (%)	
Yes	15 (25)
No	44 (75)
History of multiple metastases; no. (%)	
No	32 (54)
Yes	27 (46)
Prior radical treatment; no. (%)	
Radiation therapy	25 (42)
Radical prostatectomy	11 (19)
No	23 (39)
Time from radical treatment, years; median [IQR]	7.8 [4.8–10.6]
Number of prior systematic treatments; no. (%)	
1	15 (25)
2–3	13 (22)
4–8	31 (53)
Prior ARAT for CRPC; no. (%)	
Yes	33 (56)
No	26 (44)
Prior docetaxel for CRPC; no. (%)	
Yes	25 (42)
No	34 (58)
Time from start of ADT, years; median [IQR]	6.1 [2.6–9.2]
Time from diagnosis with CRPC, years; median [IQR]	2.3 [0.7–4.4]
Type of SDT; no. (%)	
Radiotherapy	50 (85)
Prostatectomy	6 (10)
Lymph node dissection	2 (3)
TUR	1 (2)

ADT, androgen-deprivation therapy; ARAT, androgen receptor-axis targeted agent; CT, computed tomography; CRPC, castration-resistant prostate cancer; DWIBS, diffusion-weighted whole-body imaging with background suppression; IQR, interquartile range; PSA, prostate-specific antigen; PET, positron emission tomography; SDT, site-directed therapy; TUR, transurethral resection.

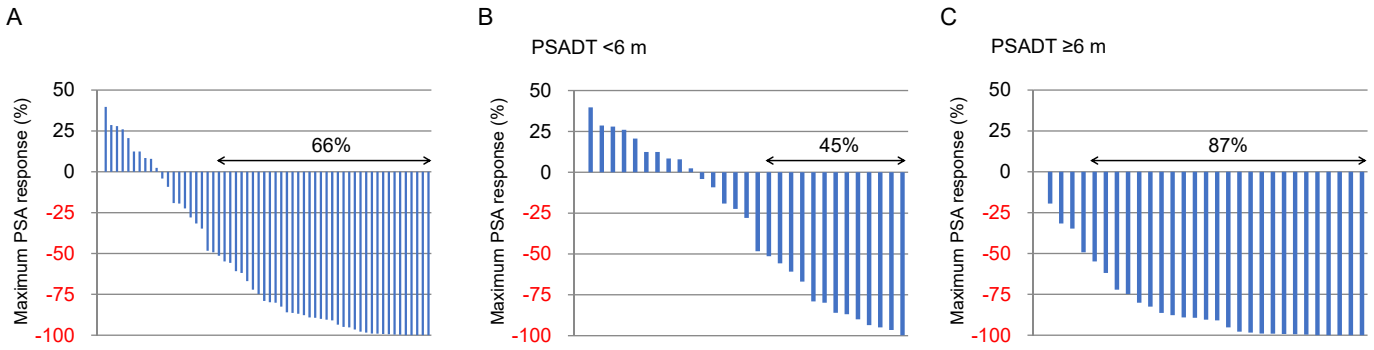

Figure 1. Maximum prostate-specific antigen (PSA) responses to site-directed therapy (SDT) in all patients (A), patients with a PSA doubling time (PSADT) <6 months (B), and patients with a PSADT ≥6 months (C). m, months; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; SDT, site-directed therapy.

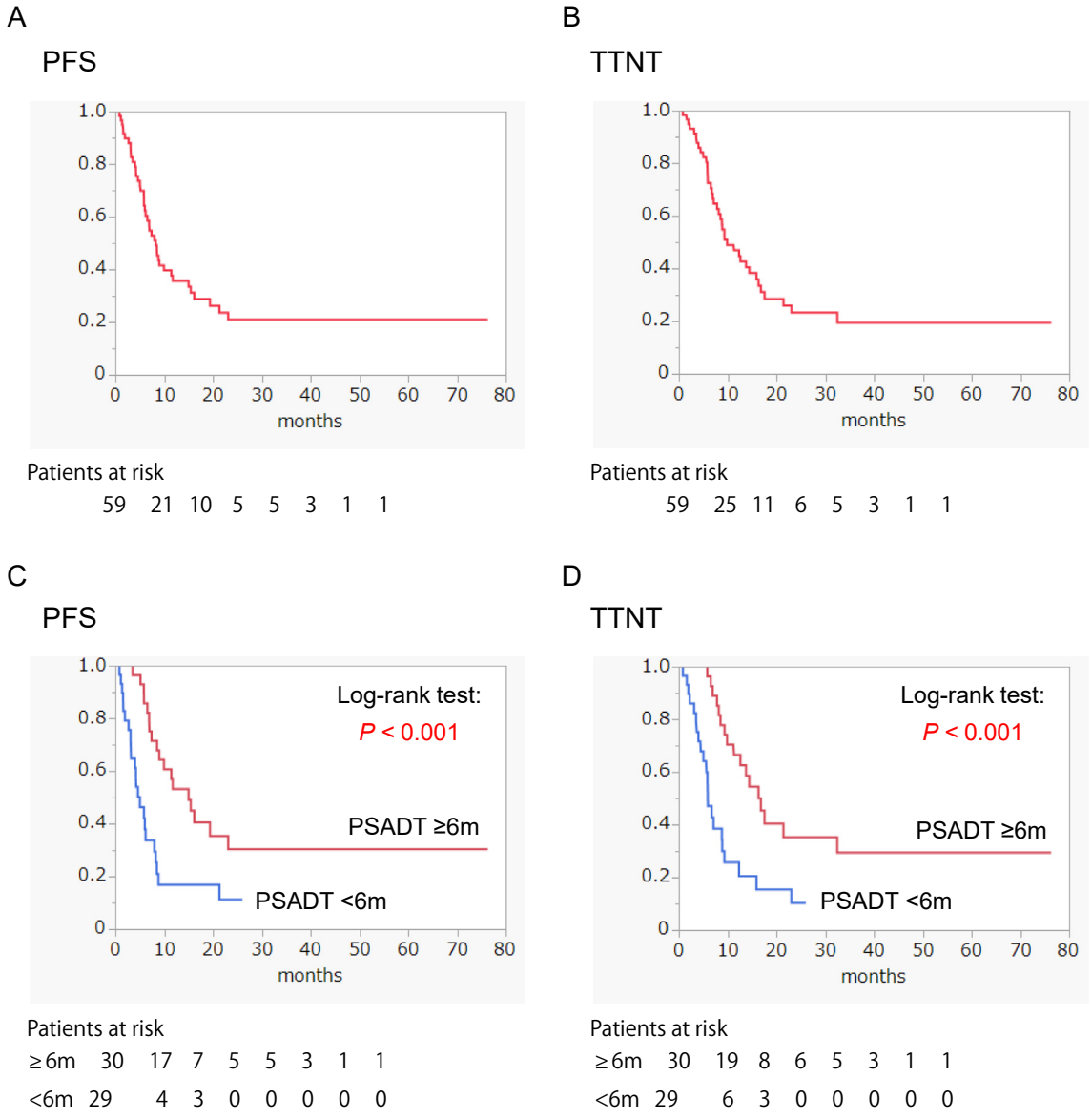

Figure 2. Progression-free survival (PFS) (A) and time to next treatment (TTNT) (B) in patients who underwent site-directed therapy (SDT). Comparisons of PFS (C) and TTNT (D) between patients with a PSA doubling time (PSADT) ≥6 months and <6 months. m, months; PFS, progression-free survival; PSADT, prostate-specific antigen doubling time; SDT, site-directed therapy; TTNT, time to next treatment.

treatment (TTNT). A PSA response was defined as a reduction in PSA level from the start of treatment; a reduction of >50% was considered to be a favorable response. Progression was defined as a PSA level ≥25% and ≥2 ng/mL above the nadir level or radiographic progression.

2.3. Statistical analyses

Spider and waterfall plots were used to show changes in PSA responses during the first year after SDT initiation and maximum PSA responses to SDT, respectively. PFS and TTNT were determined via Kaplan–Meier analysis and compared using the long-rank test. Factors resulting in a PSA response of >50% were evaluated via univariate and multivariate logistic regression analysis. Factors affecting PFS and TTNT were evaluated using the Cox proportional hazard model. Multivariate analyses included factors with univariate *P* values <0.05.

All statistical analyses were performed using JMP Pro version 16.0.0 software (SAS Institute, Cary, NC, USA). *P* values <0.05 were considered statistically significant.

3. Results

3.1. Patients

Our study included 59 patients; their characteristics are shown in Table 1. The median age was 75 years (interquartile range, 69–81 years). The median PSA level at the start of SDT was 8.1 ng/mL (interquartile range, 3.9–17.8 ng/mL), and the median PSADT was 6.1 months (interquartile range, 3.7–13.7 months). The type of imaging test used to identify the target lesion was selected at the discretion of the physician in charge. Choline PET, fluorodeoxyglucose PET, and DWIBS were used to identify target lesions in 41%, 34%, and 22% of cases, respectively (including duplicates). In 20% of cases, only conventional imaging tests of computer tomography (CT) and/or bone scintigraphy were used. Most patients had one (71%) or two (20%) SDT-targeted lesions. The lesions targeted by SDT were in the prostate, bone, lymph nodes, and other locations in 36%, 39%, 31%, and 7% of the patients, respectively (some patients had lesions at more than one site). In 25% of cases, the prostate was the only lesion targeted by SDT.

Table 2
Univariate and multivariate analyses of factors associated with a >50% prostate-specific antigen response

Parameters	Univariate		Multivariate	
	OR [95% CI]	*P*	OR [95% CI]	*P*
Age, years				
Continuous	0.65 [0.06–7.14] per score	0.72		
PSA, ng/mL				
≥8	Ref	0.41		
<8	1.58 [0.53–4.71]			
PSA doubling time, months				
<6	Ref	<0.001*	Ref	0.037*
≥6	8.00 [2.22–28.8]		4.49 [1.09–18.4]	
Imaging tests				
Conventional	Ref	0.46		
PET or DWIBS	0.59 [0.14–2.47]			
Number of targeted lesions				
2–4	Ref	0.053		
1	3.17 [0.98–10.3]			
Targeted lesions in only the prostate				
No	Ref	0.028*	Ref	0.45
Yes	10.6 [1.28–88.2]		2.62 [0.22–30.9]	
History of multiple metastases				
Yes	Ref	0.12		
No	2.40 [0.80–7.23]			
Prior radical treatment				
Yes	Ref	0.005*	Ref	0.29
No	5.96 [1.50–23.7]		2.43 [0.48–12.5]	
Number of prior systematic treatments				
≥4	Ref	0.17		
≤3	2.17 [0.71–6.60]			
Prior ARAT				
Yes	Ref	0.12		
No	2.46 [0.78–7.71]			
Prior docetaxel				
Yes	Ref	0.16		
No	2.18 [0.73–6.54]			
Time from start of ADT, years				
≥6	Ref	0.31		
<6	1.75 [0.59–5.23]			
Time from diagnosis with CRPC, years				
≥2	Ref	0.79		
<2	1.16 [0.39–3.43]			
Type of SDT				
Radiotherapy	Ref	0.15		
Surgery	4.90 [0.57–42.3]			

ADT, androgen-deprivation therapy; ARAT, androgen receptor-axis targeted agent; CI, confidence interval; CRPC, castration-resistant prostate cancer; DWIBS, diffusion-weighted whole-body imaging with background suppression; OR, odds ratio; PET, positron emission tomography; PSA, prostate-specific antigen; Ref, reference; SDT, site-directed therapy.

* Statistically significant.

3.2. Execution of SDT

The types of SDT performed were radiotherapy, prostatectomy, lymph node dissection, and transurethral resection in 85%, 10%, 3%, and 2% of the patients, respectively (Table 1). Irradiation of the prostate was performed using intensity modulated radiotherapy with a median total dose of 63 Gy given in 26 fractions (Fr.) (range, 54–78 Gy/18–39 Fr.) or stereotactic radiotherapy (SRT) with a median total dose of 40 Gy given in 5 Fr. (range, 36–40 Gy/5 Fr.). Irradiation of the lymph node metastases was performed using external beam radiotherapy (EBRT) with a median total dose of 50 Gy given in 25 Fr. (range, 30–54 Gy/10–28 Fr.) or SRT with a median total dose of 35 Gy given in 5 Fr. (range, 35–60 Gy/5–10 Fr.). Irradiation of the bone metastases was performed using EBRT with a median total dose of 40 Gy given in 20 Fr. (range, 30–54 Gy/15–20 Fr.) or SRT with a median total dose of 35 Gy given in 5 Fr. (range, 35–40 Gy/5 Fr.). Prostatectomy, lymph node dissection, and transurethral bladder tumor resection were performed in patients whose target lesions were prostate only, lymph node only, and bladder only, respectively. All prostatectomies were performed using robot-assisted laparoscopy. After the start of SDT, 35 patients (59%) continued the systemic therapy that had been administered before SDT, 14 patients (24%) switched from systemic therapy other than ADT monotherapy to ADT monotherapy, and 10 patients (17%) discontinued systemic therapy including ADT monotherapy. The median follow-up period after the start of SDT was 23.9 months (interquartile range, 10.6–43.0 months).

3.3. Effects of SDT

A maximum PSA response of >50% was observed in 66% of the patients (Fig. 1A). The median PFS and TTNT were 8.3 and 9.9 months, respectively (Fig. 2A and B).

3.4. Factors associated with a >50% PSA response

Fig. 1B and C show the maximum PSA response in patients with a PSADT of <6 months and ≥6 months, respectively. A >50% PSA response rate was significantly higher in patients with PSADT ≥6 months than in patients with PSADT <6 months (87% vs. 45%;

Table 3
Univariate and multivariate analyses of factors associated with progression-free survival

Parameters	Univariate		Multivariate	
	HR [95% CI]	*P*	HR [95% CI]	*P*
Age, years				
Continuous	0.93 [0.26–3.78] per score	0.92		
PSA, ng/mL				
≥8	Ref	0.033*	Ref	0.64
<8	0.49 [0.25–0.93]		0.82 [0.35–1.87]	
PSA doubling time, months				
<6	Ref	<0.001*	Ref	0.025*
≥6	0.34 [0.18–0.64]		0.45 [0.22–0.90]	
Imaging tests				
Conventional	Ref	0.44		
PET or DWIBS	1.35 [0.66–3.16]			
Number of targeted lesions				
2–4	Ref	0.17		
1	0.63 [0.33–1.25]			
Targeted lesions in only the prostate				
No	Ref	0.023*	Ref	0.61
Yes	0.42 [0.18–0.87]		0.78 [0.28–2.06]	
History of multiple metastases				
Yes	Ref	0.31		
No	0.72 [0.39–1.36]			
Prior radical treatment				
Yes	Ref	0.013*	Ref	0.75
No	0.45 [0.23–0.85]		0.86 [0.35–2.09]	
Number of prior systematic treatments				
≥4	Ref	0.002*	Ref	0.22
≤3	0.37 [0.18–0.70]		0.53 [0.18–1.45]	
Prior ARAT				
Yes	Ref	0.061		
No	0.56 [0.29–1.06]			
Prior docetaxel				
Yes	Ref	0.006*	Ref	0.96
No	0.42 [0.22–0.79]		0.98 [0.40–2.26]	
Time from start of ADT, years				
≥6	Ref	0.40		
<6	0.76 [0.41–1.41]			
Time from diagnosis with CRPC, years				
≥2	Ref	0.23		
<2	0.67 [0.35–1.25]			
Type of SDT				
Radiotherapy	Ref	0.94		
Surgery	0.98 [0.40–2.09]			

ARAT, androgen receptor-axis targeted agent; ADT, androgen-deprivation therapy; CI, confidence interval; CRPC, castration-resistant prostate cancer; DWIBS, diffusion-weighted whole-body imaging with background suppression; HR, hazard ratio; PET, positron emission tomography; PFS, progression-free survival; PSA, prostate-specific antigen; Ref, reference.

* Statistically significant.

$P < 0.001$). In the univariate analysis, a >50% PSA response correlated with a PSADT of ≥6 months (odds ratio, 8.00; $P < 0.001$), targeted lesion in only the prostate ($P = 0.028$), and no prior radical treatment ($P = 0.005$) (Table 2). In the multivariate analysis, only PSADT ≥6 months predicts a >50% PSA response (odds ratio, 4.49; $P = 0.037$) (Table 2).

3.5. Factors associated with PFS

PFS was significantly longer in patients with PSADT ≥6 months than in patients with PSADT <6 months (median PFS, 15.0 vs. 5.0 months; $P < 0.001$) (Fig. 2C). In the univariate analysis, favorable PFS correlated with PSADT ≥6 months (hazard ratio, 0.34; $P < 0.001$), PSA <8 ng/mL ($P = 0.033$), targeted lesion in only the prostate ($P = 0.023$), no prior radical treatment ($P = 0.013$), prior systematic treatments of ≤3 lines ($P = 0.002$), and no prior docetaxel treatment ($P = 0.006$) (Table 3). In the multivariate analysis, only PSADT ≥6 months predicted favorable PFS (hazard ratio, 0.45; $P = 0.025$) (Table 3).

3.6. Factors associated with TTNT

TTNT was significantly longer in patients with PSADT ≥6 months than in patients with PSADT <6 months (median TTNT, 16.3 vs. 5.9 months; $P < 0.001$) (Fig. 2D). In the univariate analysis, favorable TTNT correlated with PSADT ≥6 months (hazard ratio, 0.32; $P < 0.001$), targeted lesion in only the prostate ($P = 0.033$), no prior radical treatment ($P = 0.027$), prior systematic treatments of ≤3 lines ($P = 0.007$), and no prior docetaxel treatment ($P = 0.011$) (Table 4). In the multivariate analysis, only PSADT ≥6 months predicted favorable TTNT (hazard ratio, 0.41; $P = 0.017$) (Table 4).

4. Discussion

The present study showed that 66% of patients with oligo-progressive CRPC achieved a PSA response of >50% after undergoing SDT. The median PFS and TTNT were 8.3 months and 9.9 months, respectively. Furthermore, a PSADT of ≥6 months significantly correlated with a >50% PSA response and favorable PFS and TTNT.

Table 4
Univariate and multivariate analyses of factors associated with time to next treatment

Parameters	Univariate		Multivariate	
	HR [95% CI]	*P*	HR [95% CI]	*P*
Age, years				
Continuous	0.93 [0.25–3.98] per score	0.92		
PSA, ng/mL				
≥8	Ref	0.073		
<8	0.55 [0.28–1.06]			
PSA doubling time, months				
<6	Ref	<0.001*	Ref	0.017*
≥6	0.32 [0.17–0.62]		0.41 [0.19–0.86]	
Imaging tests				
Conventional	Ref	0.41		
PET or DWIBS	1.39 [0.67–3.25]			
Number of targeted lesions				
2–4	Ref	0.11		
1	0.58 [0.30–1.17]			
Targeted lesions in only the prostate				
No	Ref	0.033*	Ref	0.61
Yes	0.44 [0.19–0.91]		0.78 [0.29–2.05]	
History of multiple metastases				
Yes	Ref	0.14		
No	0.62 [0.33–1.18]			
Prior radical treatment				
Yes	Ref	0.027*	Ref	0.99
No	0.48 [0.24–0.92]		0.99 [0.41–2.41]	
Number of prior systematic treatments				
≥4	Ref	0.007*	Ref	0.15
≤3	0.41 [0.20–0.78]		0.53 [0.22–1.27]	
Prior ARAT				
Yes	Ref	0.10		
No	0.58 [0.30–1.11]			
Prior docetaxel				
Yes	Ref	0.011*	Ref	0.82
No	0.44 [0.23–0.85]		0.90 [0.36–2.11]	
Time from start of ADT, years				
≥6	Ref	0.57		
<6	0.83 [0.44–1.58]			
Time from diagnosis with CRPC, years				
≥2	Ref	0.22		
<2	0.67 [0.35–1.26]			
Type of SDT				
Radiotherapy	Ref	0.96		
Surgery	1.02 [0.41–2.19]			

ARAT, androgen receptor-axis targeted agent; ADT, androgen-deprivation therapy; CI, confidence interval; CRPC, castration-resistant prostate cancer; DWIBS, diffusion-weighted whole-body imaging with background suppression; HR, hazard ratio; PSA, prostate-specific antigen; PET, positron emission tomography; Ref, reference; TTNT, time to next treatment.

* Statistically significant.

Previous retrospective studies of SDT for oligoprogressive CRPC reported a >50% PSA response rate of 70–73% [18,20,23], PFS of 8.7–17.9 months [18-23], and TTNT of 9.3–21.8 months [19,21-23]. These results and ours are largely consistent and suggest that SDT may be a promising treatment strategy for oligoprogressive CRPC. SDT has also been shown to improve the efficacy of androgen receptor-axis-targeted (ARAT) agents [26]. In the study by Yoshida et al. the factors associated with a good response to SDT were localization of the progressive lesion in the pelvis and no history of multiple metastases [18,27,28].

The present study identified PSADT as a novel predictor of SDT outcome. PSADT reflects the speed of prostate cancer progression and is an established predictive marker for the development of metastases in nonmetastatic CRPC [29]. RCTs of ARAT agents (apalutamide, enzalutamide, and darolutamide) for nonmetastatic CRPC all included a PSADT of 10 months or less as an inclusion criterion [30-32]. Unlike conventional imaging tests, next-generation imaging tests (e.g. choline PET, fluorodeoxyglucose PET, DWIBS, and PSMA-PET) can identify oligoprogressive sites. It is reasonable to assume that a short PSADT indicates the presence of lesions not detectable via conventional imaging. In our study, we used the above next-generation imaging tests to identify oligoprogressive lesions, excepting PSMA-PET, which has superior diagnostic capability but is not yet available in Japan. A study of 67 patients with oligoprogressive CRPC identified via 68Ga-PSMA-PET reported a >50% PSA response rate of 73.1%, PFS of 11.0 months, and TTNT of 16.4 months following SDT with radiotherapy [23]. Our results are comparable: a PSA response rate of 87%, PFS of 15.0 months, and TTNT of 16.3 months in patients with a PSADT $\geq$6 months. Collectively, these findings suggest that consideration of PSADT plus the performance of imaging tests other than PSMA-PET can identify true “oligoprogressive” CRPC as efficiently as does PSMA-PET. This is a useful finding for regions such as Japan where PSMA-PET is unavailable.

The present study had several limitations. First, it was a retrospective study with a relatively small number of patients. Second, the assessment of SDT efficacy was complicated by concurrent systemic therapy. If the efficacy of SDT is to be evaluated purely, it would be appropriate to continue the systemic treatment that had been provided before SDT. However, there were several cases in which patients who were receiving invasive systemic treatment such as docetaxel were switched to ADT monotherapy at the discretion of their attending physicians when SDT was started. In addition, some patients were challenged to turn off ADT due to the possibility of SDT. There is a possibility that these patients had a shortened PFS even if SDT was effective temporarily. Third, our patient cohort was quite heterogeneous. In particular, our study included 25% of patients with progressive lesions in only the prostate gland. However, because systemic treatment is the standard treatment for patients with CRPC, we treated the progressive sites in the prostate with radiotherapy and prostatectomy as SDT. In fact, a targeted lesion in only the prostate significantly correlated with a >50% PSA response, PFS, and TTNT in the univariate analysis; it did not, however, correlate with all three factors in the multivariate analysis.

In conclusion, this is the first study to associate PSADT with PSA response, PFS, and TTNT in patients undergoing SDT for oligoprogressive CRPC. PSADT may be a key predictor of the efficacy of SDT for oligoprogressive CRPC. SDT should be considered for patients with oligoprogressive CRPC with PSADT $\geq$6 months, whereas patients with PSADT <6 months may be better off avoiding SDT and considering a change in systemic therapy.

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Statistical analysis: Taketo Kawai.

Administrative, technical, or material support: None.

Supervision: Tohru Nakagawa, Haruki Kume.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflict of interest.

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