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Predictive Value of the Prostate-specific Antigen Doubling Time for the Effectiveness of Metastasis-directed Radiotherapy in Patients With Oligometastases After Radical Treatment for Non-metastatic Prostate Cancer

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Abstract. *Background/Aim: Data on metastasis-directed radiotherapy (MDRT) are limited, particularly regarding its association with the prostate-specific antigen (PSA) doubling time (PSADT). The present study evaluated the oncological outcomes of MDRT on the basis of the PSADT in oligo-recurrent prostate cancer patients. Patients and Methods: We retrospectively reviewed clinical data of 35 MDRTs for 29 patients at the Kitasato University Hospital, targeting oligometastatic prostate cancer developed after radical treatment for non-metastatic prostate cancer. Thirty-five MDRTs were classified into the PSADT >3 months (n=25) or PSADT ≤3 months group (n=10). Statistical analyses were performed to compare associations between the two PSADT groups and oncological outcomes such as progression-free survival (PFS) and PSA response after MDRT. Results: There were no significant differences between the two groups in terms of the clinicopathological features. Kaplan-Meier analysis showed that PFS was significantly better in the PSADT >3 months group than in the PSADT ≤3 months group [median: 13.3 versus (vs.) 2.6 months, p=0.046]. Regarding castration sensitivity, the predictive role of PSADT >3 months was maintained in 21 patients who received MDRT without prior salvage hormone therapy (median PFS: 12.7 vs. 2.6 months, p=0.024). In the castration-resistant setting (n=14), the frequency of a decrease in serum PSA levels after MDRT by 90% was 54.5% (median PFS: 23.1 months). Conclusion: MDRT can provide benefit especially for patients with PSADT ≥3 months who had oligo-recurrence after the radical treatment for non-metastatic prostate cancer.*

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Key Words: Metastasis-directed therapy, radiotherapy, prostate-specific antigen doubling time, prostate cancer, oligometastases, oligo-recurrence.

Metastatic prostate cancer (PCa) has remarkable diversity in its biological aggressiveness (1). The type with no more than five metastatic sites, according to clinical trials, is known as oligometastatic PCa (OMPCa) (2-4). The oligometastatic status is defined on the basis of theories that the development of malignancy depends on its multistep nature, and the increased number of metastases subsequently reflects greater aggressiveness of the disease (5). In other words, the oligometastatic status is considered an intermediate stage between non-metastatic disease and widespread metastases. Therefore, Hellman and Weichselbaum, who initially presented with an oligometastatic status in 1995, hypothesized that metastasis-directed therapy (MDT) could offer survival benefit even in the metastatic setting when the number of metastases is limited (5).

In several cancers, oligo-recurrence leads to development of MDT with radiotherapy (MDRT) (6, 7). In 2006, Niibe *et al.* proposed oligo-recurrence as a controlled primary site with one to several metastases, distinguishing it from oligometastases for which MDT is unlikely to have a prognostic impact due to an uncontrolled primary site (6). In fact, high-level evidence of MDRT currently comes from metachronous oligo-recurrent PCa (2, 3). In a phase 2, multicenter, randomized STOMP trial with a median follow-up of 36 months, patients with MDT

consisting of the majority (80.6%) with MDRT had longer androgen deprivation therapy-free survival than those without MDT (median: 21 *vs*. 13 months, p=0.11) (2). The phase 2 randomized ORIOLE trial with a median follow-up of 18.8 months demonstrated a significantly longer progression-free survival (PFS) in patients receiving MDRT than in those not receiving MDRT (median: not reached *vs*. 5.8 months, p=0.002) (3). Additionally, although real-world data on MDT for OMPCa are scarce, MDRT is also prevalent in oligo-progressive castration-resistant PCa (CRPC) and has demonstrated favorable survival benefits in retrospective studies (8-10). Given that metastasis of PCa frequently occurs in anatomically sensitive sites, such as the bone, it is reasonable to assume that much attention has been paid to MDRT rather than to MDT with surgery because of less invasiveness.

Yet, major concerns have been raised regarding the identification of optimal candidates for MDRT. A recent systematic review and meta-analysis reported that the sensitivities of modern modalities for nodal and bone metastasis of PCa were lower than their specificities. In other words, false-negatives were indicated to be higher than false-positives in the diagnosis, even *via* radiographic and nuclear medicine imaging such as prostate-specific membrane antigen positron emission tomography (PSMA-PET) (11). Therefore, some patients are unlikely to benefit from MDRT based only on radiographic imaging; thus, another approach that is easily available in clinical practice and that can actively reflect the metastatic aggressiveness of PCa, including micrometastasis, is needed.

It is beyond doubt that prostate-specific antigen (PSA) is the widespread marker in the management of PCa even including CRPC (12), and PSA-doubling time (PSADT) in particular may be an effective surrogate of the aggressiveness of PCa. Robust evidence of the predictive value of PSADT for the metastasis has been already established in patients with biochemical recurrence (BCR) after radical prostatectomy (RP) and radiotherapy (RT) for non-metastatic PCa (nmPCa) (13-16). Currently, data on the association between the treatment effect of MDRT and PSADT are very scarce. Therefore, the present study aimed to retrospectively evaluate the survival benefit of MDRT on the basis of PSADT in patients who developed OMPCa after radical treatment for nmPCa.

Patients and Methods

Ethics statements. This study was approved by the Institutional Review Boards of the Kitasato University School of Medicine and the Kitasato University Hospital (Kanagawa, Japan; approval numbers: B22-114, B22-013, and B23-106) and was conducted in accordance with the Declaration of Helsinki. Potential participants received information regarding the opportunity to opt out of the study *via* our website and posters.

Study design and population. We retrospectively reviewed clinical data of 35 MDRTs for 29 patients targeting OMPCa after RP or RT for nmPCa performed between 2015 and 2023 at Kitasato University Hospital. All 35 MDRTs targeted bone or lymph node metastases without visceral metastasis. The initial diagnosis of nmPCa was histologically confirmed through an eight-core transrectal ultrasound prostate biopsy, and initial staging was assessed *via* conventional imaging (CI) using computed tomography (CT), a bone scan (BS), and magnetic resonance imaging. PSMA-PET was not covered by health insurance in Japan at the time of this writing. OMPCa was defined as five or fewer metastases without visceral organ metastases and was evaluated *via* CI or diffusion-weighted whole-body imaging with background body signal suppression (DWIBS). All the radiographic stagings were confirmed with consideration of radiology reports of the modalities from experienced radiologists at Kitasato University Hospital.

Definition of OMPCa and disease progression. Metachronous i) oligo-recurrent PCa and ii) oligo-progressive CRPC were defined as OMPCa with a history of radical treatment for nmPCa that occurred i) not under active systemic therapy and ii) under active systemic therapy, respectively (17-19). Disease progression after MDRT was assessed using the serum PSA level and radiographic tests, and was defined as follows: i) when the disease is hormone-sensitive: PSA of ≥0.2 ng/ml in two consecutive measurements in patients with prior RP or PSA nadir of 2 ng/ml in patients with prior RP; ii) when the disease is castration-resistant: three consecutive increases in the serum PSA level with two of the three increases of PSA by 50% and 2.0 ng/ml from the nadir under a serum testosterone level of <50 ng/dl; iii) irrespective of the type of prior radical treatment and castration-sensitivity, a new radiographic lesion or radiographic progression of a known lesion based on Response Evaluation Criteria in Solid Tumors was classified as progression (20).

Data collection. The following data on patient characteristics were collected from the patients' medical charts: age; serum PSA level; Gleason score (GS) obtained through prostate biopsy or RP; stage at the initial diagnosis of nmPCa with consideration of pathological T and N stages obtained through RP; type of prior radical treatment; type of prior salvage treatment; site of OMPCa; PFS; dose and fraction of MDRT; post-MDRT courses; and mortality.

Statistical analysis. Patients were divided into either the PSADT >3 months (L-PSADT) or PSADT ≤3 months (S-PSADT) group, and statistical analysis was performed to evaluate clinical outcomes in these two groups. Comparisons of patient background characteristics were performed using the chi-square test (or Fisher exact test, if appropriate) for categorical variables and the Mann-Whitney U-test for continuous variables. PFS was estimated using the Kaplan-Meier method with the log-rank test. Hazard ratios (HR) were estimated using the Cox model. The area under the curve (AUC) and best cutoff point were calculated using receiver operating characteristic analyses. All statistical analyses were performed using Stata (version 14 for Windows; StataCorp, Chicago, IL, USA). All p-values were two-sided, and p<0.05 was considered statistically significant. A median follow-up after the introduction of MDRT was 46.0 months (interquartile range=27.1-57.0 months).

Results

The characteristics of patients with 35 MDRTs are shown in Table I. Patients with S-PSADT and L-PSADT were 10 (28.6%) and 25 (71.4%), respectively. The number of

Table I. *Characteristics of patients with MDRT in terms of PSADT.*

Variable	L-PSADT (n=25)	S-PSADT (n=10)	*p*-Value
Second MDRT	3 (12.0)	3 (30.0)	0.33
PSADT, months, median (range)	7.2 (3.4-33.0)	2.7 (0.9-3.0)	0.005
Age at MDRT, years, median (range)	70.0 (56-78)	70.5 (64-79)	0.77
PSA, ng/ml, median (range)	8.8 (5.7-273.0)	16.5 (6.1-55.2)	0.34
Gleason score ≥9	14 (56.0)	4 (40.0)	0.47
T stage ≥3b	8 (32.0)	1 (10.0)	0.23
N stage	1 (4)	0	
M stage	0	0	
Radical treatment			
IMRT	0	1 (10.0)	0.005
LDR-B	0	2 (20.0)	
HDR-B	9 (36.0)	3 (30.0)	
Prostatectomy	16 (64.0)	4 (40.0)	
Salvage pelvic radiation	13 (52.0)	4 (40.0)	0.71

MDRT, Metastasis-directed radiotherapy; PSADT, prostate-specific antigen doubling time; PSA, prostate-specific antigen; IMRT, intensity-modulated radiotherapy; LDR-B, low-dose rate brachytherapy; HDR-B, high-dose rate brachytherapy; L-PSADT, PSADT >3 months; S -PSADT, PSADT ≤3 months.

Table II. *Details of MDRT in terms of PSADT.*

Variable	L-PSADT (n=25)	S-PSADT (n=10)	*p*-Value
Time from radical treatment to MDRT, months, median (range)	73 (25-169)	66.5 (18-122)	0.55
Timing of MDRT in terms of systemic therapy, N (%)			
Oligo-recurrent prostate cancer	13 (52.0)	8 (80.0)	0.26
Oligo-progressive CRPC	12 (48.0)	2 (20.0)	
Metastatic sites, N (%)			
Bone alone	20 (80.0)	9 (90.0)	0.31
Lymph node alone	5 (20.0)	1 (10.0)	
Bone and lymph node	0	0	
Number of metastatic sites, median (range)	1 (1-4)	1 (1-5)	0.87
Type of radiotherapy, N (%)			
EBRT	19 (76.0)	6 (60.0)	0.42
SRT	6 (24.0)	4 (40.0)	

MDRT, Metastasis-directed radiotherapy; PSADT, prostate-specific antigen doubling time; CRPC, castration-resistant prostate cancer; EBRT, external beam radiotherapy; SRT, Stereotactic radiotherapy; L-PSADT, PSADT >3 months; S -PSADT, PSADT ≤3 months.

patients who received a second MDRT for different targets from the first one was three each in the two groups (L-PSADT: 12.0% *vs*. S-PSADT: 30.0%, p=0.33).

The data of one of the six patients who underwent the first MDRT were excluded from the present analysis because of the concomitant use of hormone therapy. The clinicopathological factors at radical treatment, including age, PSA level, GS, and TNM stage, did not differ significantly between the two groups. Regarding the type of radical treatment, RP was dominant, followed by high-dose brachytherapy in the two groups (L-PSADT: 64.0%, n=16 and 36.0%, n=9, respectively; S-PSADT: 40.0%, n=4 and 30.0%, n=3, respectively). The GS obtained by the prostate biopsy was underestimated in seven (35%) of the 20 patients with RP.

Table II shows the details of the 35 MDRTs, at most times there was one MDRT targets (88.6%, n=31), and bone alone was the main target (S-PSADT: 90.0%, n=9; L-PSADT: 80.0%, n=20). The patients who received MDRT for the metachronous oligo-recurrent PCa comprised the majority of the cohort (S-PSADT: 80.0%, n=8; L-PSADT: 52.0%, n=13), and the remaining 14 patients underwent MDRT for the metachronous oligo-progressive CRPC (S-PSADT: 14.3 %, n=2 and L-PSADT: 85.7 %, n=12).

Regarding the modality and dose of MDRT, irradiation of lymph node metastases was performed using external beam

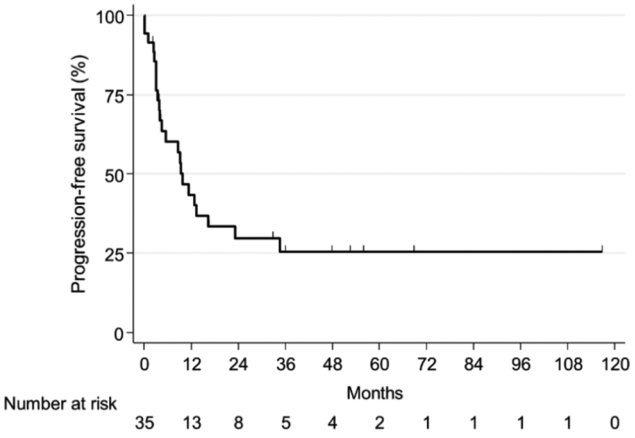


Figure 1. *Kaplan-Meier estimates of progression-free survival after metastasis-directed radiotherapy for 35 cases.*

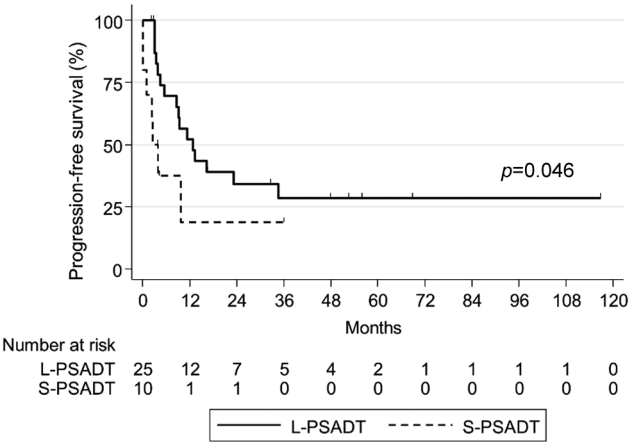


Figure 2. *Kaplan-Meier estimates of progression-free survival after metastasis-directed radiotherapy for 35 cases by prostate-specific antigen doubling time (PSADT) ≤3 months (S-PSADT) and >3 months (L-PSADT).*

RT with a median total dose of 47 Gy (range=40-54 Gy/18-20 Fr.) or stereotactic RT with a median total dose of 28.5 Gy (range=27-20 Gy/ 3-5 Fr.). Irradiation of the bone metastases was performed using external beam RT with a median total dose of 40 Gy (range=30-50 Gy/10-25 Fr.) or stereotactic RT with a median total dose of 27 Gy (range=27-30 Gy/3-5 Fr.).

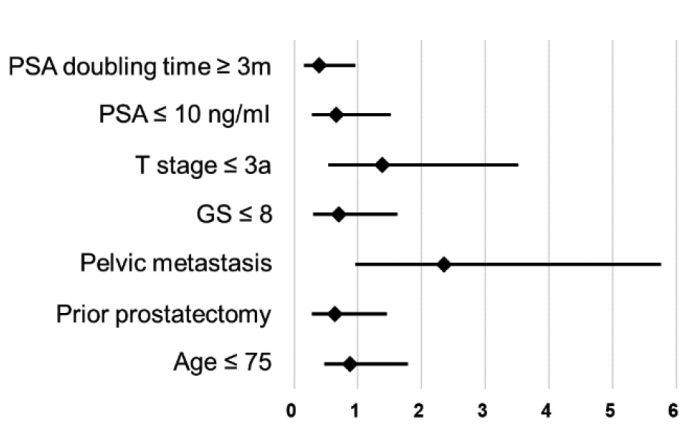
Survival analyses were performed and Kaplan-Meier analysis showed that the median PFS was 11.6 months (range=1.9-116.6 months), and L-PSADT showed significantly longer PFS than S-PSADT (median PFS: 13.3 *vs*. 2.6 months, p=0.046) (Figure 1 and Figure 2). Among 13 patients who had no progression at >12 months, 12 (92.3%) were classified into the L-PSADT group (median: 34.6 months, range=12.-116.6 months). Figure 3 shows a forest plot of HRs to explore the optimal candidate for MDRT; L-PSADT had an HR of 0.39 (95%CI=0.15-0.96) in a comparison with S- PSADT. There were no significant differences in PSA levels, T stage, GS, site of metastasis, history of radical treatment, or age between groups.

Concerning the history of salvage hormone therapy, Kaplan-Meier analysis demonstrated a significant difference in PFS between L-PSADT and S-PSADT in 21 patients who received MDRT for metachronous oligo-recurrent PCa (median PFS: 12.7 in the L-PSADT group *vs*. 2.6 months in the S-PSADT group, p=0.024) (Figure 4). Of the 21 patients, seven who undertook RT with adjuvant hormone therapy had serum testosterone level within the normal limit at the time of MDRT. For metachronous oligo-progressive CRPC, the median PFS was 23.1 months in the L-PSADT group (n=12), ranging from 2.8 to 116.6 months.

The PSA response was compared between the two PSADT groups, with the exclusion of two CRPC patients in L-PSADT with undetectable levels of serum PSA at the identification of OMPCa. Decreases in PSA levels from the initiation of MDRT of 50% and 90% were categorized as PSA50 and PSA90, respectively, and the L-PSADT group tended to have greater proportions of PSA50 and PSA90 than the S-PSADT group (52.2%, n=12 *vs*. 40%, n=4, p=0.71 and 43.5%, n=10 *vs*. 30.0%, n=3, p=0.70, respectively). In 12 patients who received MDRT for metachronous oligo-progressive CRPC (short PSADT, n=1; long PSADT, n=11), PSA50 and PSA90 occurred in seven (63.6%) and six patients (54.5%) in the L-PSADT group.

Over a median follow-up of 46.0 months after the introduction of MDRT, 21 (60.0%) patients received any subsequent treatment after MDRT, including seven (70.0%) in the S-PSADT group and 14 (56%) in the L-PSADT group, as follows: hormone therapy (S-PSADT: 60%, n=6 and L-PSADT: 32.0%, n=8), MDRT (S-PSADT: n=1: 10.0% and L-PSADT: n=4, 16.0%) and RT for prostate fossa (L-PSADT: n=2.8%). Two (4.0%) patients in the L-PSADT group discontinued hormone therapy after the introduction of MDRT; one patient had PFS of 32.6 months with serum testosterone level recovery and the other had 55.6 months under serum testosterone levels <50 ng/dl without disease progression through radiographic tests. Regarding mortality, no patient died due to either PCa or other causes during the follow-up periods.

In the evaluation of the 35 targets for which MDRT was performed, DWIBS and CI were performed 18 (51.4%) and 34 times (97.1%), respectively. On the 18 DWIBSs, all the lesions were bone, and the numbers of lesions detectable *via* both DWIBS and CI, only CI, and only DWIBS were 4 (22.2%), 4 (22.2%), and 10 (55.6%), respectively. To assess the diagnostic performance of radiographic tests in relation to serum PSA levels, data from 35 radiographic tests performed in patients without prior salvage hormone therapy were analyzed (Table III). OMPCa was found in 24 (68.6%) patients, including three who were introduced salvage hormone therapy after the identification of OMPCa, and distant metastasis was undetectable in the remaining 11 (31.4%). CI and DWIBS were performed in 34 (97.1%) and 16 patients (45.7%), respectively.



	HR	95% CI	*P*-value	N (%)
PSA doubling time ≥ 3m	0.39	0.15-0.96	0.041	25 (71.4)
PSA ≤ 10 ng/ml	0.66	0.28-1.52	0.33	18 (51.4)
T stage ≤ 3a	1.38	0.54-3.52	0.51	17 (48.6)
GS ≤ 8	0.70	0.30-1.62	0.51	18 (51.4)
Pelvic metastasis	2.34	0.96-5.76	0.062	15 (42.9)
Prior prostatectomy	0.29	0.28-1.46	0.64	21 (60.0)
Age ≤ 75	0.56	0.47-1.79	0.88	8 (22.9)

Figure 3. *Forest plot of hazard ratios for the treatment effect of metastasis-directed radiotherapy for 35 cases.*

Of the 24 lesions, nine (37.5%) were identified *via* DWIBS, but not *via* CI. A median PSA at the time of the tests was 1.17 ng/ml (range=0.3-30.8 ng/ml), and the receiver operating characteristic AUC for PSA in the radiographic tests was 0.80 (95% confidence interval=0.64-0.96). Using a PSA cutoff value of 1.00 ng/ml, the sensitivity and specificity for predicting OMPCa were 82.6% and 73.3%, respectively. Regarding PSADT, the median period was 5.3 months, and the proportion of doubling time from ≤3 to ≤9 months ranged from 36.1% (n=13) to 77.8% (n=28). A median PSA level at the diagnosis of the lesions detectable only *via* DWIBS was 1.5 ng/ml (range=0.3-3.3 ng/ml), whereas that *via* CI was 1.8 ng/ml (range=0.5-30.8 ng/ml, p=0.19).

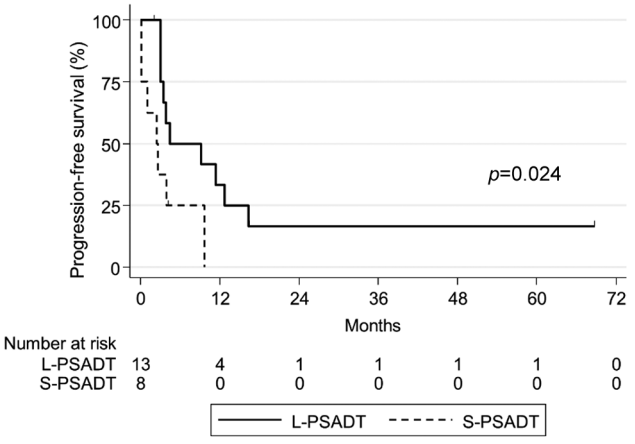


Figure 4. *Kaplan-Meier estimates of progression-free survival after metastasis-directed radiotherapy by prostate-specific antigen doubling time (PSADT) ≤3 months (S-PSADT) and >3 months (L-PSADT) in 21 patients with oligo-recurrent prostate cancer.*

Discussion

The present study focused on patients who developed OMPCa after radical treatment for nmPCa and evaluated the oncological outcomes of MDRT on the basis of PSADT. Although real-world data on MDRT for the same cohort as those in the present study are very limited, our overall result of a median PFS of nearly 12 months was in line with that of the largest retrospective study including 67 patients (21). Notably, the present study uniquely showed significantly better PFS in the L-PSADT group than in the S-PSADT group, with a median difference of approximately 10 months. This predictive value of PSADT should be particularly highlighted because the treatment effectiveness of MDRT in the L-PSADT group was found in the oligo-recurrent cohort in which serum PSA levels were not influenced by hormone therapy. Moreover, the L-PSADT group showed a favorable PSA response even in the patients who had metachronous oligo-progressive CRPC. Additionally, a combination evaluation of CI and DWIBS showed acceptable diagnostic potential for the metastasis when using a PSA cutoff value of 1.00 ng/ml in patients who received MDRT without prior salvage hormone therapy.

An ideal prerequisite for favorable outcomes following MDRT is the absence of metastases other than those identified *via* radiographic imaging. A key indicator of MDRT in combination with radiographic testing is required as a potential surrogate for metastatic progression of PCa. PSADT has been historically shown to be a strong predictive factor for metastasis and a potential reflection of the existence of micrometastases in patients who have undergone RP and RT for nmPCa (13-16). For example, in a large retrospective study based on data from the Center for Prostate Disease Research and Johns Hopkins University involving 656 men with BCR following RP, multivariate analysis showed a significant uptrend in HR for developing metastasis as patients had showed shorter PSADT (6.01-7.50 months, HR=2.42; 3.01-4.51 months, HR=4.24; ≤3 months, HR=5.24) (13, 14). Therefore, the statistical association between better PFS and L-

Table III. *Characteristics of 35 radiographic tests in patients without prior salvage hormone therapy.*

Variable	N (%)
Imaging modality, N (%)	
CT	34 (97.1)
DWIBS	16 (45.7)
Combination of CT and DWIBS	15 (93.8)
DWIBS only	1 (6.2)
Detectable lesion, N (%)	
Yes	24 (68.6)
Detectable only *via* DWIBS	9 (37.5)
Detectable only *via* CT	3 (12.5)
Serum PSA level, ng/ml, median (range)	
At the radiographic tests	1.17 (0.23-30.8)
At the diagnosis of the lesions detectable only *via* DWIBS	1.5 (0.3-3.3)
At the diagnosis of the lesions detectable *via* CT	1.8 (0.5-30.8)
PSADT, median (range)	5.3 (0.9-17.3)
PSADT, N (%)	
≤3 months	13 (36.1)
≤6 months	23 (63.9)
≤9 months	28 (77.8)

CT, Computed tomography; DWIBS, diffusion weighted whole body imaging with background body signal suppression; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

PSADT in the present study could be theoretically explained, especially given that the predictive role of PSADT for MDRT was also found in the present study, with no influence of salvage hormone therapy. However, data on PSADT in the treatment with MDRT for OMPCa is exceedingly scarce when conference reports are excluded; thus, further studies are required to validate our proposed rationale (22).

In the treatment of metastatic CRPC, some studies have demonstrated better oncological outcomes following MDRT for oligo-progressive metastasis in patients with long PSADT (22). This may be explained as follows: first, as such lesions identified under castration resistance are deemed refractory to current systemic therapy, one of the subsequent treatment options can be radiotherapy; second, accumulating evidence of PSADT as an alternative marker for the progression of PCa was also established in non-metastatic CRPC, with an example of an association between PSADT <8 months and a rapid increase in the risk of bone metastasis (23). This hypothesis supports the favorable outcomes observed in the present CRPC setting with respect to the median PFS and achievement rates of PSA50 and PSA90 in L-PSADT. The predictive role of PSADT was also demonstrated in real-world data from Japan, including 59 patients with CRPC who received MDRT for oligo-progressive sites of the prostate or metastatic lesions. The majority of patient (61%) had received prior radical treatment for nmPCa, and a significantly longer PFS was shown in patients with PSADT <6 months than that in those without (median: 15.0 *vs*. 5.0 months; $p<0.001$) (22). Here, one might argue for the clinical importance of such a difference of 10 months in PFS between the two PSADT groups shown in both the present and Japanese studies. However, given the reported median overall survival of approximately 8 years in metachronous low-volume PCa defined by the CHARRTED criteria (24, 25), we believe that the nearly one-year benefit potentially provided by MDRT for metachronous OMPCa should be considered even in CRPC patients with L-PSADT.

Another clue for identifying the optimal patients for MDRT may be associated with the diagnostic accuracy of radiographic imaging for metastasis. The diagnostic power shown in the present study seemed acceptable in comparison to that previously reported *via* CI under a low PSA level; only 14-30% of patients with BCR after RP had some positive lesions on CT, and a lower rate was reported *via* the BS (<5%) when the PSA level was <7 ng/ml (26-28). The high diagnostic power for metastases demonstrated in this study may be attributed to DWIBS and the short PSADT. Compared with CI, DWIBS has favorable sensitivity, especially for bone metastasis (29). Indeed, the present study showed that all the lesions undetectable *via* CI but identified *via* DWIBS were bone metastases, and the PSA level at the diagnosis of the lesions *via* DWIBS was lower than that *via* CI. Regarding PSDT, its predictive value for metastasis is worth validating *via* PSMA-PET because it seems to have the highest diagnostic performance for detecting disease progression among all next-generation imaging modalities (30-32). A prospective multicenter study of 1004 men with BCR after radical therapy (RP and RT) for nmPCa showed short PSADT, *e.g.*, ≤10 months, as an independent risk factor for distant metastasis *via* PSMA-PET (30). Concerning our cohort without prior salvage hormone therapy, most of the patients (78.8%, n=28) had PSADT ≤9 months with a median of 5.3 months. Therefore, in clinical practice, where PSMA-PET is unavailable, DWIBS with a combination of CI should be considered even in patients with low PSA levels, especially when the PSADT is short.

Our study had some limitations. First, the retrospective study design may have introduced bias into the patient selection process. Second, PSADT might not be associated with a predictive value for the effect of MDRT because there was a possibility that L-PSADT had a better prognosis than S-PSADT, irrespective of MDRT. However, as PFS after MDRT was objectively assessed using PSA and radiographic tests, the predictive role of PSADT should be reasonable, as long as the endpoint of the present study was limited to PFS after MDRT and not overall survival. Third, the small sample size of the current study did not statistically allow us to consider potential confounding factors on multivariate analysis for the evaluation of the predictive role of PSADT. However, the clinicopathological features of the present

cohort were matched between the two PSADT groups. Fourth, the small sample size consisting of only two patients with CRPC in the S-PSADT group did not allow us to perform Kaplan-Meier analysis for the comparison of PFS in the two PSADT groups under castration resistance. Fifth, more experience is needed to identify OMPCa, especially when using DWIBS, and there is a possibility of false positives and false negatives due to the interruption of radiographic images. Lastly, as the GS obtained by prostate biopsy was underestimated in approximately one-third of the patients with RP, the transrectal ultrasound prostate biopsy routinely performed in our institution should be modified with more than eight cores for a precise diagnosis.

Conclusion

The present study using a small patient cohort showed that PFS was significantly better with L-PSADT than with S-PSADT, with a median difference of approximately 10 months. Moreover, the predictive role of PSADT in MDRT was maintained regardless of castration sensitivity in the subgroup analysis. Hence, we believe that MDRT can provide benefit especially for patients with PSADT ≥3 months who have oligo-recurrent PCa after the radical treatment for nmPCa. Further large study is encouraged to validate such predictive value of PSADT and the appropriate PSA cutoff value for detecting OMPCa by using PSMA-PET.

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Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

D.K., K.T. and Y.N.: conceptualization; K.T. and Y.N.: methodology; D.K.: formal analysis; D.K., K.T., M.K., S.S., S.H., T.S., and M.Ik., and K.M: investigation; D.K. and K.T.: writing—original draft preparation; M.Iw: supervision. All Authors have read and agreed to the published version of the manuscript.

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