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Clinical Outcomes of Metastasis-directed Therapy for Oligo-metastatic Prostate Cancer Diagnosed Using PSMA-PET/CT or Whole-body MRI

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Abstract

Background/Aim: Data on clinical outcomes in Japanese patients following metastasis-directed therapy (MDT) for oligo-metastatic prostate cancer (PCa) diagnosed using next-generation imaging modalities [prostate-specific membrane antigen-targeted positron emission tomography/computed tomography (PSMA-PET/CT) or whole-body diffusion-weighted magnetic-resonance imaging (WB-MRI)] are limited.

Patients and Methods: We retrospectively evaluated clinical outcomes in patients with oligo-metastatic PCa diagnosed using PSMA-PET/CT or WB-MRI and subsequently treated with MDT between February 2018 and June 2023 at our institution.

Results: In total, 26 patients were analyzed: 14 with hormone-sensitive PCa (oligo-recurrence) and 12 with castration-resistant PCa (oligo-progression). The median patient age was 74 years at the time of diagnosing oligo-metastasis. A total of 30 sites were irradiated. The median prescribed dose was 62.4 Gy in 31 fractions for sites treated with conventional fractionated or moderately hypo-fractionated external-beam radiation therapy (EBRT), and 35 Gy in five fractions for those treated with stereotactic body radiation therapy (SBRT). Systemic therapies were administered in 88.5%. The median follow-up period after the diagnosis of oligo-metastasis was 34.2 months. The overall survival, biochemical failure-free survival, and clinical failure-free survival rates were 94.1, 48.7, and 55.4% at three years, respectively. The local control rate of MDT sites was 96.7%. Grade 2 MDT-related toxicities were observed in 7.6%, whereas no ≥ grade 3 toxicities were reported.

Conclusion: MDT for oligo-metastatic PCa diagnosed using next-generation imaging modalities in a Japanese population can result in favorable disease-free and survival outcomes with acceptable morbidities.

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Introduction

Oligo-metastasis is considered an intermediate oncological state between localized and widely disseminated disease (1, 2). In 2015, integrated analyses of subclonal architecture regarding patterns of metastatic spread of prostate cancer (PCa) using whole-genome sequencing by Gundem *et al.* revealed that the "metastasis-to-metastasis spread" pattern was common in patients with metastatic PCa (3). This finding formed the basis for the rationale of metastasis-directed therapy (MDT), which is currently regarded as one of the promising treatment options for this patient population in several treatment guidelines or consensus conferences (4, 5).

The success of MDT is highly dependent on the accuracy of diagnosing oligo-metastasis. As prostate-specific membrane antigen-targeted (PSMA) positron emission tomography/computed tomography (PET/CT) has shown excellent diagnostic accuracy regarding the detection of metastatic sites (6), and the use of PSMA-PET/CT is recommended when applying MDT to treat patients with oligo-metastatic PCa (7). Whole-body diffusion-weighted magnetic-resonance imaging (WB-MRI) is also effective for detecting metastatic disease (8). Although clinical outcomes of MDT for patients with oligo-metastatic PCa would be markedly improved with the use of such next-generation imaging modalities, to our knowledge, data on MDT for patients with oligo-metastatic PCa diagnosed with next-generation imaging modalities are limited in Japanese populations (9, 10).

Therefore, the aim of the current study was to evaluate clinical outcomes of MDT for patients with oligo-metastatic PCa diagnosed using PSMA-PET/CT or WB-MRI.

Patients and Methods

This study followed the tenets of the Helsinki Declaration, with approval from the institutional ethical review board (approval number: R1048-3). Written informed consent to the current study was not obtained due to the retrospective nature of the study. Instead, that was obtained in the form of opt-out on our website, and those who rejected were excluded.

Patients. We retrospectively reviewed an institutional database and searched for eligible patients. The eligibility criteria were as follows: 1) no distant metastasis at initial diagnosis; 2) primarily received definitive treatment; 3) oligo-metastatic recurrence diagnosed using PSMA-PET/CT or WB-MRI between February 2018 and June 2023; oligo-metastasis was defined as three or fewer nodal or distant metastatic lesions, in which lymph nodes were located in the same nodal region [*e.g.*, para-aortic lymph nodes (PAN)] were counted as a single metastatic lesion; 4) MDT was performed for all recurrent lesions detected using PSMA-PET/CT or WB-MRI.

PSMA-PET/CT and WB-MRI. In our institution, we performed phase 1 and 2 studies using PSMA-PET/CT (11, 12). After completing those clinical studies, we applied WB-MRI to detect sites of recurrent PCa mainly after primary definitive therapy.

For PSMA-PET/CT, PET/CT with a novel PSMA-targeted probe, ^{18}F-FSU-880, was used. ^{18}F-FSU-880 was synthesized using a COSMiC-Compact 24XX automated module (NMP Business Support Co., Ltd., Hyogo, Japan), following the procedures outlined in previous studies (13), and subsequently sterilized *via* filtration. PET/CT scans were performed using an integrated system (Discovery IQ; GE Healthcare, Waukesha, WI, USA) and a 16-slice CT scanner. Low-dose CT was employed for attenuation correction and anatomical alignment. Whole-body PET images were acquired from the mid-thigh to the skull vertex at 1 and 3 h after intravenous administration of ^{18}F-FSU-880 (101.8-380.0 MBq) (12).

For WB-MRI, diffusion-weighted whole-body imaging with background suppression (DWIBS) was acquired in the axial plane using the following parameters: diffusion gradient encoding in three orthogonal directions; b-values of 0 and 1,000 s/mm^2; repetition time (TR)/echo time (TE)/flip angle, 5,640 ms/73 ms/90˚; field of view, 365×450 mm; matrix size, 207×256; voxel size, 1.76×1.76×5 mm; slice thickness, 5 mm; 200 slices; and an acquisition time of 1 min 25 s per bed position. In addition to DWIBS, T1-weighted imaging (T1WI) and Short-TI Inversion Recovery (STIR) were also acquired. For DWIBS, 5 bed positions were required for each patient to achieve whole-body coverage. T1WI anatomical images were acquired separately for image fusion, requiring 22 s per bed position. The total scan time was approximately 25 min.

Metastasis-directed therapy. MDT consisted of high-dose EBRT, stereotactic body radiation therapy (SBRT), or surgical resection. Bone metastasis was basically treated with SBRT or hypo-fractionated EBRT. Pelvic lymph node metastasis was basically treated with conventional fractionated EBRT in combination with pelvic regional irradiation. The treatment details of salvage pelvic EBRT were described previously (14). In brief, salvage pelvic EBRT consisted of prophylactic pelvic regional irradiation of the upper pelvis (50.4-54 Gy; 1.8 Gy per fraction), followed by boost irradiation of recurrent nodes (60-64 Gy).

Systemic therapy. For hormone-sensitive PCa (HSPC) (oligo-recurrence), androgen-deprivation therapy (ADT) was basically added to MDT. For HSPC with pelvic lymph node and/or PAN metastasis, long-term ADT, consisting of 6-month neo-adjuvant combined androgen blockade and 2-year concurrent and adjuvant ADT, was basically applied. For HSPC with bone or other-organ metastasis, the duration of ADT was determined at the physician's discretion in accordance with the clinical course. For castration-resistant PCa (CRPC) (oligo-progression), the same regimen of ADT or androgen receptor signaling inhibitor (ARSI) was basically continued during and after MDT.

Statistical analysis. The timing of occurrence of each event was calculated from the date of diagnosis of oligo-metastasis using PSMA-PET/CT or WB-MRI. The Kaplan–Meier method was used to estimate overall survival (OS), biochemical failure (BF)-free survival (BFFS), and clinical failure (CF)-free survival (CFFS) rates. BF was defined as follows: 1) PSA elevation >2.0 ng/ml above the nadir for patients with HSPC after definitive EBRT, >0.2 ng/ml for patients with HSPC after radical prostatectomy (RP), or >1.0 ng/ml above the nadir for patients with CRPC after EBRT or RP; 2) a change in treatment due to disease progression. CF was defined as clinical progression on radiographic examinations. CRPC progression among patients with oligo-metastatic HSPC was defined as follows: 1) prostate-specific antigen (PSA) elevation >1.0 ng/ml above the nadir during ADT (15); 2) CF during ADT; 3) a change in treatment due to disease progression during ADT. PSA elevation during off-periods of intermittent ADT was not counted as CRPC. The Cox proportional hazard model was used to estimate the hazard ratio (HR) in univariate analysis (UVA) to evaluate the impact of hormone sensitivity (HSPC *vs.* CRPC) at MDT on BFFS and CFFS. For CRPC cases at MDT, we analyzed the PSA response to MDT. PSA reduction rate at 3 and 6 months after MDT were evaluated; for this, PSA levels at 3 and 6 months post MDT were compared with those at PSMA-PET/CT or WB-MRI. MDT-related late toxicities (≥ grade 2) were assessed using Common Terminology Criteria for Adverse Events, version 5.

All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A value of $p<0.05$ denoted significance.

Results

Patient characteristics. Twenty-six consecutive patients met the eligibility criteria, and all patients were included in the analysis. The diagnosis of oligo-metastatic disease was according to: PSMA-PET/CT in 53.8% (N=14), WB-MRI in 38.5% (N=10), and both PSMA-PET/CT and WB-MRI in 7.7% (N=2). The median patient age was 74 (range=64-80

years) at PSMA-PET/CT or WB-MRI. The median PSA level at PSMA-PET/CT or WB-MRI was 2.71 ng/ml (range=0.79-59.5 ng/ml). Among the 26 patients, 53.8% (N=14) and 46.2% (N=12) had HSPC (oligo-recurrence) and CRPC (oligo-progression), respectively, and 7.7% (N=2) had a history of MDT for oligo-metastatic lesions diagnosed using conventional imaging modalities. The median number of metastatic lesions per patient was one (range=1-3). Patient characteristics are summarized in Table I.

Table I. *Patient characteristics.*

Characteristics	
Age at PSMA-PET/CT or WB-MRI (years)	
Median (range)	74 (64-81)
PSA at PSMA-PET/CT or WB-MRI (ng/ml)	
Median (range)	2.71 (0.79-59.5)
Diagnostic modality, N(%)	
PSMA-PET/CT	14 (53.8)
WB-MRI	10 (38.5)
Both	2 (7.7)
Number of metastases	
Median (range)	1 (1-3)
Location of metastasis (per patients), N(%)	
Nodal metastasis	
Pelvic nodes	9 (34.6)
Extra-pelvic nodes	1 (3.8)
Pelvic and para-aortic nodes	1 (3.8)
Non-nodal metastasis	
Bone	11 (42.3)
Lung	1 (3.8)
Lung and bone	1 (3.8)
Combination of nodal and non-nodal	
Bone and nodes	2 (7.7)
Hormone status at PSMA-PET/CT or WB-MRI, N(%)	
HSPC (oligo-recurrence)	14 (53.8)
CRPC (oligo-progression)	12 (46.2)
Previous MDT (based on conventional imaging), N(%)	
No	24 (92.3)
Yes	2 (7.7)
Primary stage (NCCN risk classification), N(%)	
Intermediate	3 (11.5)
High	5 (19.2)
Very high	13 (50.0)
Regional (N1 disease)	4 (15.4)
Not available (without distant metastasis)	1 (3.9)
Primary treatment modality, N(%)	
Radiation therapy	18 (69.2)
Radical prostatectomy	8 (30.8)

PSMA-PET/CT: Prostate-specific membrane antigen-targeted positron emission tomography/computed tomography; WB-MRI: Whole-body diffusion-weighted magnetic-resonance imaging; PSA: prostate-specific antigen: HSPC: hormone-sensitive prostate cancer; CRPC: castration-resistant prostate cancer; MDT: metastasis-directed therapy; NCCN: National Comprehensive Cancer Network.

Metastasis-directed therapy and systemic therapies. A total of 30 sites were irradiated: lymph node metastasis, 13 sites (including 10 pelvic lymph node metastases alone); bone metastasis, 15 sites: lung metastasis, two sites. For lymph node metastasis, conventional fractionated EBRT in combination with the nodal area was mainly applied (84.6%, N=11/13). For bone (N=15) or lung (N=2) metastasis, SBRT was used in all patients. Of the 13 sites treated with conventional fractionated or moderately hypo-fractionated EBRT, the median prescribed dose was 62.4 (range=48-75 Gy) in 31 (range=15-35) fractions. The median dose prescribed to the prophylactic nodal area was 50.4 (range=42-55.8) Gy in 28 (range=15-31) fractions. For the remaining 17 sites, SBRT was used. The median prescribed dose was 35 (range=24-50) Gy in five (range=2-10) fractions.

Among patients with HSPC, 78.6% (N=11/14) received ADT with a median duration of 19.2 months (range=4.2-69.3 months). ARSI was not used in combination with MDT for any patients with HSPC. Among patients with CRPC, 91.7% (N=11/12) received systemic therapy. Of them, the same agents used before MDT were continuously administered in 90.9% of cases (N=10) including one patient whose docetaxel use was discontinued before MDT, and ARSI was added in 9.1% (N=1). Details of MDT and systemic therapies are summarized in Table II.

Oncological outcomes and MDT-related toxicities. The median follow-up period after the diagnosis of oligo-metastasis using PSMA-PET/CT or WB-MRI was 34.2 (range=6.7-71.8 months). During the follow-up, one patient (3.4%) died due to another cause; however, no patient died due to PCa. OS rates were 100% at 2 years and 94.1% [95% confidence interval (CI)=65.0-99.1] at three years, respectively.

Also, during the follow-up, 11 patients (42.3%) developed BF at a median of 13.3 (range=1.2-54.4

months) months after PSMA-PET/CT or WB-MRI. BFFS rates were 64.9% (95%CI=41.6-80.8) at two years and 48.7% (95%CI=26.2-67.9) at 3 years (Figure 1A). These rates among patients with HSPC and CRPC were 83.6% (95%CI=48.0-95.7) and 46.9% (95%CI=17.6-71.8) at 2 years, and 62.7% (95%CI=27.6-84.4) and not available at 3 years, respectively (HR=0.363, 95%CI=0.104-1.27, p=0.1117) (Figure 1B).

A total of 10 patients (38.5%) developed CF at a median of 21.7 (range=7.1-59.6) months after PSMA-PET/CT or WB-MRI. CFFS rates were 72.0% (95%CI=47.7-86.5) at 2 years and 55.4% (95%CI=31.3-74.1) at 3 years (Figure 2A). These rates among patients with HSPC and CRPC were 90.9% (95%CI=50.8-98.7) and 50.0% (95%CI=17.2-76.1) at two years, and 70.7% (95%CI=33.7-89.5) and not available at 3 years, respectively (HR=0.283, 95%CI=0.070-1.15, p=0.077) (Figure 2B). Among the 10 patients with CF, the majority of the initial sites of CF were other than MDT sites (90%, N=9/10). The local control rate during follow-up was estimated as 96.7% (N=1/30).

Among the 14 patients with HSPC, one developed CRPC progression 41.6 months after PSMA-PET/CT. CRPC-free survival rates were 100% (95%CI= not available) at both 2 and 3 years.

Among the 12 patients with CRPC, a PSA decrease was observed in all cases, in which a decrease in PSA levels of more than 50% (50% PSA decrease) was observed in 50% (N=6) at 3 months and 66.7% (N=8) at 6 months after MDT (Figure 3A and B).

Regarding MDT-related toxicities, 3.8% (N=1) and 3.8% (N=1) of patients developed grade 2 bone fracture (sacrum) and urinary incontinence, respectively. No patients developed grade 3 or higher toxicities.

Table II. *Details of metastasis-directed therapy (MDT) and systemic therapy.*

Characteristic	
Metastasis-directed therapy (site)	30
Conventional or moderate-hypofraction, N(%)	13 (43.3)
Median dose, Gy (range)	62.4 (48-75)
Fraction, (range)	31 (15-35)
Stereotactic body radiation therapy, N(%)	17 (56.7)
Median dose, Gy (range)	35 (24-50)
Fraction, (range)	5 (2-10)
Use of prophylactic irradiation, N(%)	11 (36.7)
Median dose, Gy (range)	50.4 (42-55.8)
Fraction, (range)	28 (15-31)
Androgen-deprivation therapy for HSPC, N(% among HSPC)	11 (78.6)
Median duration, months (range)	19.2 (4.2-69.3)
Use of ARSI	0 (0)
Systemic therapy for CRPC, N(% among CRPC)	11 (91.7)
Same agents used before MDT, N(% among CRPC)	10 (83.4)
Addition or change to new agents, N(% among CRPC)	1 (8.3)
None	1 (8.3)

HSPC: Hormone-sensitive prostate cancer; CRPC: castration-resistant prostate cancer.

Discussion

In the current study, we retrospectively evaluated the clinical outcomes of MDT for oligo-metastatic PCa diagnosed using PSMA-PET/CT or WB-MRI. As a result, BFFS and CFFS rates were 48.7 and 55.4% at 3 years, respectively, and the incidence of grade 2 or higher MDT-related toxicities was relatively low. Therefore, MDT for this population was considered effective and safe. To our best knowledge, this is the first investigation of MDT with a definitive dose for patients with oligo-metastatic PCa diagnosed using next-generation imaging modalities among a Japanese population.

In most investigations on MDT, oligo-recurrent distant and regional lymph node metastases were both included in the study populations (16-21), although these disease states are considered different regarding tumor spread. For example, the STOMP randomized phase 2 trial, which compared MDT with surveillance among 62 patients with oligo-recurrent HSPC, demonstrated improved ADT-free survival in the MDT arm (median ADT-free survival: 21 *vs.* 13 months, HR=0.6, 80%CI=0.4-0.9, p=0.11) (17). In this study, one third of patients exhibited oligo-recurrent regional lymph node metastasis (recurrent N1 case). Similarly, in the ORIOLE randomized phase 2 trial, investigating the benefit of MDT compared with observation among patients with oligo-recurrent HSPC, approximately 60% of the patients had node-only disease

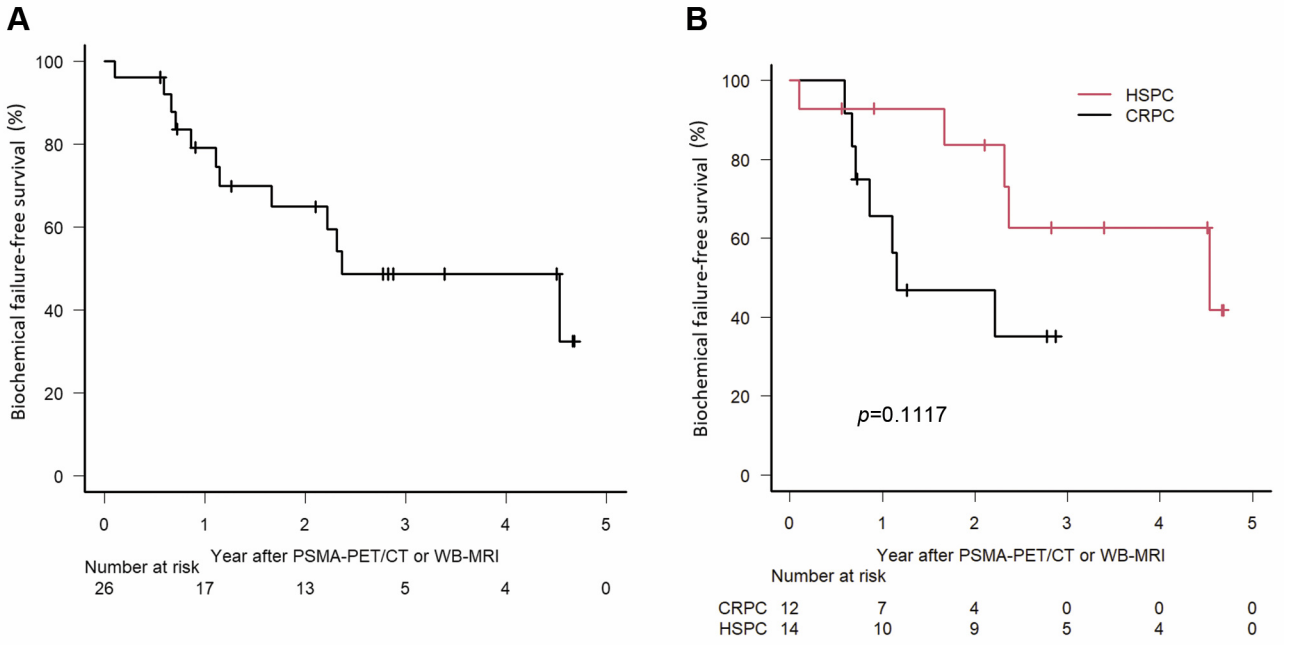

Figure 1. *Kaplan–Meier curves of biochemical failure-free survival rate after diagnosis of oligo-metastasis using prostate-specific membrane antigen-targeted positron emission tomography/computed tomography (PSMA-PET/CT) or whole-body diffusion-weighted magnetic-resonance imaging (WB-MRI) among (A) all patients and (B) those with hormone-sensitive prostate cancer (HSPC) versus castration-resistant prostate cancer (CRPC).*

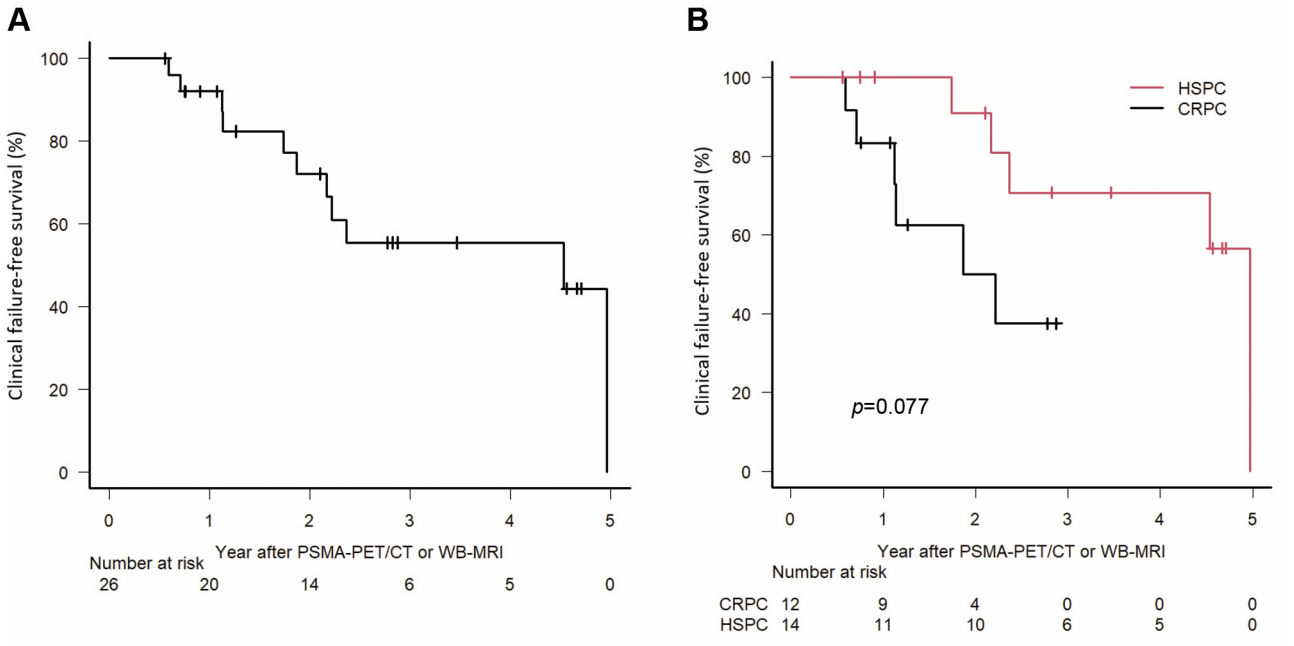

Figure 2. *Kaplan–Meier curves of clinical failure-free survival rate after diagnosis of oligo-metastasis using prostate-specific membrane antigen-targeted positron emission tomography/computed tomography (PSMA-PET/CT) or whole-body diffusion-weighted magnetic-resonance imaging (WB-MRI) in (A) all patients and (B) those with hormone-sensitive prostate cancer (HSPC) versus castration-resistant prostate cancer (CRPC).*

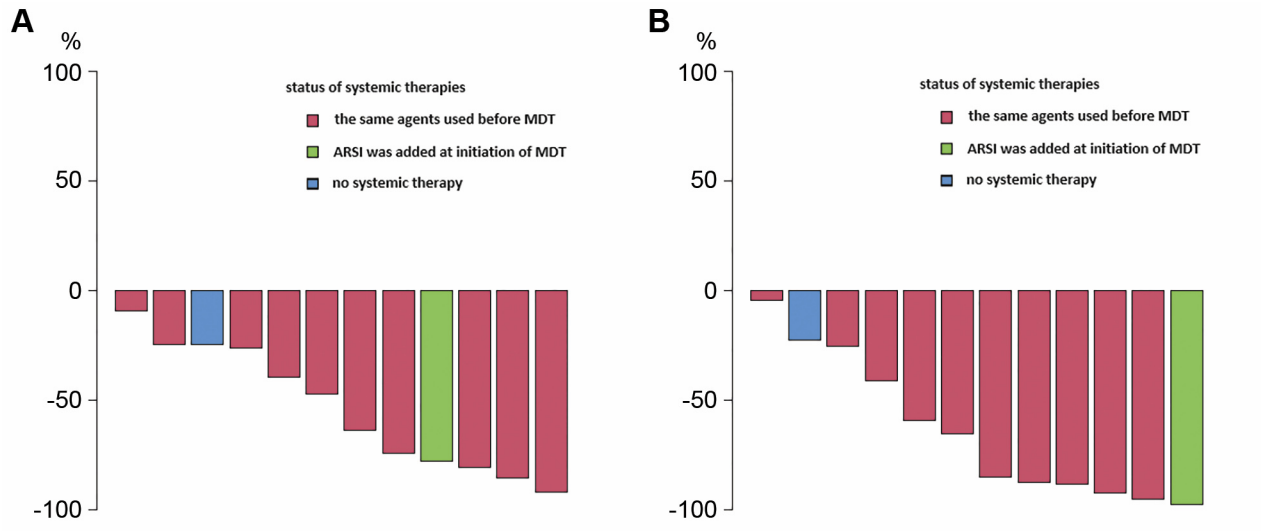

Figure 3. *Waterfall plot of change in prostate-specific antigen from baseline to (A) three months and (B) six months after the start of metastasis-directed therapy.*

(18). In those studies, only recurrent sites were treated with MDT both in distant and regional lymph node metastases. On the contrary, in the current study, we basically applied prophylactic regional irradiation for patients with oligo-recurrent regional lymph node metastasis. According to a retrospective analysis investigating the failure pattern following MDT for oligo-metastatic PCa (22), among patients who received MDT, 41% maintained long-term control and 23% developed poly-progression, whereas 36% of the patients developed oligo-recurrence again and they are considered candidates for repeated MDT in clinical practice. Another investigation regarding the pattern of recurrence after MDT revealed that nearly 40% of recurrence sites following SBRT for pelvic lymph nodes were limited to the pelvic nodal region (23). This observation suggests the merit of adding prophylactic irradiation from the perspective of curability. In addition, repeating MDT for these patients, whose recurrence sites are located near previous MDT sites, is generally difficult due to the overlapping of irradiation fields. The OLIGOPELVIS (GETUG P07) phase 2 trial investigated the role of prophylactic pelvic nodal irradiation among oligo-recurrent regional lymph node metastases following definitive treatment (EBRT or radical prostatectomy) in combination with six months of ADT (24). In that trial, being similar to the current study, prophylactic pelvic regional irradiation field in cases with prior definitive RT was limited to the upper pelvis to avoid overlapping with the previously irradiated field. The progression-free, BF-free, and ADT-free survival rates were reported as 39, 31, and 64% at five years, respectively. These results support our treatment strategy for oligo-recurrent regional lymph node metastasis.

Initial studies on MDT focused on prolonging ADT-free periods principally among patients with oligo-recurrent HSPC (17, 18). Two randomized phase 2 trials, STOMP and ORIOLE trials, both investigated the effect of MDT under the condition of no-ADT use (17, 18). Current investigations focus on increasing intensity by combining ADT or ARSI (25, 26). The EXTEND randomized phase 2 trial investigated the additional benefit of MDT on ADT with or without ARSI among patients with oligo-metastatic PCa (25). After a median follow-up of 22 months, progression-free survival was significantly more favorable in the MDT plus ADT group (HR=0.25, 95%CI=0.12-0.55,

p<0.001). In the current study, ADT was added to MDT for the majority of patients with HSPC (78.6%). At present, our institution adds 2-year ADT and ARSI to MDT for patients with oligo-recurrent distant metastatic HSPC to increase the treatment intensity. To determine the optimal combination of systemic agents and its duration, further investigations are warranted.

Our study cohort included 46.2% CRPC. Although reports on MDT for patients with oligo-progressive CRPC are relatively rare compared with those for patients with HSPC, the effectiveness of MDT for patients with oligo-progressive CRPC has been reported (10, 27-30). Yoshida *et al.* investigated the efficacy of progressive site-directed therapy (PSDT) for oligo-progressive CRPC (10). In their investigation, WB-MRI was used to diagnose oligo-metastasis, and EBRT using 60-78 Gy (2 Gy per fraction) for prostate or lymph node metastasis and 30-39 Gy (2-3 Gy per fraction) for bone metastasis was administered as PSDT. Among the 23 patients who received PSDT for oligo-progressive CRPC, a PSA decrease was observed in 91% (N=21), which included 70% (N=16) achieving a PSA decrease of at least 50%. The ARTO randomized phase 2 trial investigated the benefit of MDT using SBRT in addition to abiraterone acetate plus prednisone (AAP) as first-line treatment for oligo-metastatic CRPC (27). A biochemical response (defined as PSA decrease ≥50% from baseline to 6-month point of treatment) was more frequently observed in the MDT plus AAP arm compared with the AAP-alone arm (92 *vs.* 68.3%, respectively, odds ratio: 5.34, 95%CI=2.05-13.88, p=0.001), and progression free-survival was significantly better in the MDT plus AAP arm (HR=0.35, 95%CI=0.21-0.57, p<0.001). In the current study, among the 12 patients with CRPC, a PSA decrease of at least 50% was achieved in 50% at 3 months and 66.7% at 6 months after MDT (Figure 3A and B). Although disease control outcomes tended to be poorer compared with patients with HSPC (p=0.11 for BFFS and p=0.077 for CFFS), MDT for patients with oligo-metastatic CRPC diagnosed with PSMA-PET/CT or WB-MRI was considered effective, especially regarding prolonging the effective duration of systemic therapies and delaying the start of the next treatment line.

Our study has several limitations, including the retrospective nature of the analysis. The size of our cohort was small, precluding us from performing multivariable analysis. In addition, our cohorts consisted of heterogeneous populations, especially regarding the previous treatment history including systemic therapies and MDT. Furthermore, as institutional treatment protocols were not established in the current study, the RT dose, use of systemic therapy, and duration were not uniform, and they were basically determined by the physician's judgement in consideration of the disease aggressiveness in each case. Due to these limitations, the present findings are not conclusive, but merely hypothesis-generating. Nevertheless, given the lack of clinical results of MDT for oligo-metastasis diagnosed exclusively using next-generation imaging modalities in Japanese populations, we believe that our results may serve as baseline data on MDT for such populations.

In conclusion, MDT for patients with oligo-metastatic PCa diagnosed using PSMA-PET/CT or WB-MRI can result in favorable disease-free and survival outcomes with acceptable morbidities. To determine the optimal combination of systemic agents added to MDT and its duration, further investigations are needed.

Conflicts of Interest

The Authors report no conflicts of interest related to the subject of this study.

Authors' Contributions

Rihito Aizawa: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft; Takashi Ogata: Investigation, Writing – review & editing; Takayuki Goto: Investigation, Writing – review & editing; Tomoaki Otani: Investigation, Writing – review & editing; Kiyonao Nakamura: Investigation, Writing – review & editing; Yuki Kita: Investigation, Writing – review & editing; Ryusuke Nakamoto: Investigation, Writing – review & editing; Yoichi Shimizu: Investigation, Writing – review & editing; Takayuki Sumiyoshi: Investigation, Writing – review

& editing; Kaoru Murakami: Investigation, Writing – review & editing; Kei Mizuno: Investigation, Writing – review & editing; Takashi Kobayashi: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing; Yuji Nakamoto: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing; Takashi Mizowaki: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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