Prostate-Specific Membrane Antigen PET/CT–Guided, Metastasis-Directed Radiotherapy for Oligometastatic Castration-Resistant Prostate Cancer

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Systemic treatments for metastatic castration-resistant prostate cancer (mCRPC) include androgen deprivation therapy, androgen receptor pathway inhibitors, chemotherapy, and radiopharmaceuticals, all of which have associated toxicity. Prostate-specific membrane antigen (PSMA) PET/CT allows for higher sensitivity in detecting metastatic disease than is possible with conventional imaging. We hypothesized that PSMA PET/CT–guided, metastasis-directed radiotherapy may offer durable disease control with low toxicity rates in patients with mCRPC who have a limited number of metastases. **Methods:** We retrospectively screened 5 prospective PSMA PET/CT studies for patients with mCRPC who had up to 5 sites of oligorecurrent or oligoprogressive disease on PSMA PET/CT and subsequently received definitive-intent, metastasis-directed radiotherapy to all new or progressing sites with concurrent androgen deprivation therapy. Progression-free survival, freedom from new lines of systemic therapy, and overall survival (OS) were calculated from the start of metastasis-directed radiotherapy using Kaplan–Meier analysis. Biochemical response was defined as at least a 50% decrease in prostate-specific antigen 6 mo after the start of treatment. Toxicity was graded using the Common Terminology Criteria for Adverse Events, version 5. **Results:** Twenty-four patients met the inclusion criteria with a median follow-up of 33.8 mo (interquartile range, 27.6–45.1 mo). Between October 2017 and April 2023, 11 patients (45.8%) had 1 treated site, 10 patients (41.7%) had 2, and 3 patients (12.5%) had 3. Five sites were prostate or prostate bed, 15 were nodal, 19 were osseous, and 1 was visceral. Seventeen patients (70.8%) continued their preexisting systemic therapy, whereas 7 (29.2%) started a new systemic therapy. Median progression-free survival was 16.4 mo (95% CI, 9.8–23.0 mo). The biochemical response rate was 66.7%. Median freedom from a new line of systemic therapy was 29.0 mo (95% CI, 7.6–50.4 mo). Median OS was not reached. The 2- and 4-y OS rates were 91.1% (95% CI, 79.3%–100%) and 68.8% (95% CI, 45.1%–92.5%), respectively. Grade 2 and grade 3 or higher toxicity rates were 4.2% and 0%, respectively. **Conclusion:** PSMA PET/CT–guided, metastasis-directed radiotherapy appears to offer durable disease control with low toxicity rates for oligometastatic castration-resistant prostate cancer. Further prospective studies are needed to compare metastasis-directed radiotherapy with systemic therapy versus systemic therapy alone and PSMA PET/CT–guided versus conventional imaging–guided radiotherapy.

Key Words: castration resistance; metastasis-directed therapy; prostate cancer; prostate-specific membrane antigen PET; radiation therapy

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Systemic therapies for metastatic castration-resistant prostate cancer (mCRPC) include androgen deprivation therapy (ADT) (*1*), androgen receptor pathway inhibitors (ARPIs) (*2–5*), chemotherapy (*6,7*), and radiopharmaceutical therapy (*8,9*). These have associated toxicities, including hot flashes, nausea, diarrhea, hypertension, rashes, metabolic changes, neutropenia, and anemia.

For patients with mCRPC who have 5 or fewer oligoprogressive sites, metastasis-directed radiotherapy may be able to control disease and delay initiation of new lines of systemic therapy. Metastasis-directed radiotherapy has been studied predominantly in the setting of metastatic hormone-sensitive prostate cancer with encouraging results (*10–15*).

In parallel, the development of prostate-specific membrane antigen (PSMA) PET/CT allows for higher sensitivity in detecting metastatic disease than do conventional imaging modalities such as CT, MRI, and bone scanning (*16,17*). Accordingly, PSMA PET/CT may allow for earlier and more accurate patient selection for metastasis-directed radiotherapy with fewer sites of untreated disease (*13*).

We hypothesized that PSMA PET/CT–guided, metastasis-directed radiotherapy may offer durable disease control with low toxicity rates in patients with mCRPC who have a limited number of new or progressing metastases.

MATERIALS AND METHODS

Study Population

This was a retrospective analysis of 5 institutional review board–approved, prospective studies of patients with prostate cancer who underwent PSMA PET/CT at UCLA between January 2016 and February 2023

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(NCT02940262, NCT04050215, NCT04282824, NCT04348682, and NCT04279561). All patients provided written informed consent before inclusion in the databases. The databases were queried for patients with mCRPC who had up to 5 sites of oligorecurrent or oligoprogressive disease on PSMA PET/CT; who received definitive-intent, metastasis-directed radiotherapy to all new or progressing sites of disease with concurrent ADT; and who had at least 6 mo of postradiotherapy follow-up. Progressing sites were defined by increasing size or PSMA uptake on PET/CT. Stable or responding sites did not have to be treated. Lymph nodes in a contiguous radiation field were counted as a single treated site. Castration resistance was defined as biochemical progression (2 consecutive prostate-specific antigen [PSA] increases ≥ 3 wk apart) or radiographic progression on conventional imaging or PSMA PET/CT while on ADT with testosterone less than 50 ng/dL. Patient data were collected retrospectively by the investigators from the electronic medical record. Consent for data collection was waived because of the retrospective design of the study (institutional review board approval 23-000611).

PSMA PET/CT Imaging

PSMA PET/CT findings were obtained from the written reports. All scans were performed using ^{68}Ga-PSMA-11. The median injected activity was 185 MBq (range, 181.3–292.3 MBq) with a median uptake time of 60 min (range, 35–75 min). Scans were obtained with diagnostic CT and intravenous contrast medium for 23 patients and with low-dose CT without intravenous contrast medium for 1 patient. Images were interpreted by board-certified radiologists and nuclear medicine physicians. Results were reported according to Prostate Cancer Molecular Imaging Standardized Evaluation criteria for whole-body staging using molecular imaging TNM, version 1.0. Reports and images were accessible to the treating radiation oncologist before metastasis-directed radiotherapy.

Radiotherapy Planning and Delivery

All patients were treated with definitive-intent, metastasis-directed radiotherapy to all new or progressing sites of disease identified on PSMA PET/CT. Radiation dose, fractionation, target volumes, and delivery technique were decided by the treating radiation oncologist. Intensity-modulated radiotherapy, stereotactic body radiotherapy (SBRT), and brachytherapy techniques were included. Concurrent systemic therapy was given per treating physician discretion and included ADT for all patients.

Study Endpoints

Progression-free survival (PFS) was defined as the duration until biochemical progression (PSA increase > 25% and 2 ng/mL above nadir, confirmed by repeat measurement ≥ 3 wk later), radiographic

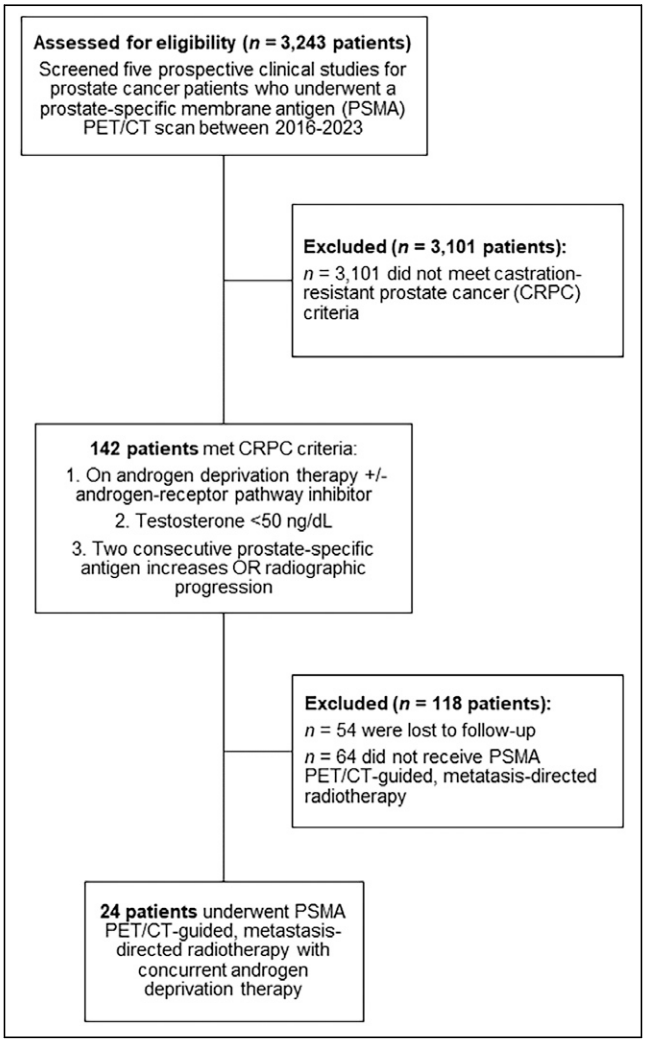

FIGURE 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.

TABLE 1
Patient Characteristics at Time of PSMA PET/CT (*n* = 24 Patients)

Characteristic	Data
Median age (y)	68.8 (IQR, 65.7–71.7)
Median time since initial diagnosis (y)	6.1 (IQR, 3.6–12.0)
Median time since castration resistance (y)	1.6 (IQR, 0.3–3.7)
Median PSA (ng/mL)	1.2 (IQR, 0.4–3.2)
Initial NCCN risk group (*n*)	
Localized favorable intermediate risk	3 (12.5%)
Localized unfavorable intermediate risk	2 (8.3%)
Localized high risk	9 (37.5%)
Localized very high risk	3 (12.5%)
Metastatic	6 (25.0%)
Unknown	1 (4.2%)
Prior therapies (*n*)	
RP + ADT + ARPI	5 (20.8%)
RP + RT + ADT	5 (20.8%)
RP + RT + ADT + ARPI +/− sipuleucel-T	7 (29.2%)
RP + RT + ADT + ARPI + chemotherapy	2 (8.3%)
RT + ADT + ARPI	1 (4.2%)
ADT + ARPI +/− sipuleucel-T	3 (12.5%)
ADT + chemotherapy + ^{177}Lu-PSMA-617	1 (4.2%)

NCCN = National Comprehensive Cancer Network; RP = radical prostatectomy; RT = radiotherapy.

TABLE 2
PSMA PET/CT Findings (n = 24 Patients)

Finding	Data
On systemic therapy at time of PSMA PET/CT	23 (95.8%)
Indication for PSMA PET/CT	
Biochemical recurrence	15 (62.5%)
Evaluation of treatment response	9 (37.5%)
T+ disease	5 (20.8%)
N1 disease	13 (54.2%)
M1 disease	20 (83.3%)
M1a only	6 (25.0%)
M1b only	12 (50.0%)
M1a + M1b	1 (4.2%)
M1c only	1 (4.2%)
Staging	
miT0N1M0	3 (12.5%)
miT+N1M0	1 (4.2%)
miT0N0M1a	1 (4.2%)
miT+N0M1a	1 (4.2%)
miT0N1M1a	4 (16.7%)
miT0N0M1b	6 (25.0%)
miT+N0M1b	2 (8.3%)
miT0N1M1b	4 (16.7%)
miT+N1M1b	1 (4.2%)
miT0N0M1c	1 (4.2%)

Data are number.

progression on conventional imaging or PSMA PET/CT, initiation of a new line of systemic or local therapy, or death. Biochemical response was defined as a PSA decrease of at least 50% 6 mo after the start of treatment. Complete biochemical response was defined as a PSA decrease to no more than 0.2 ng/mL 6 mo after the start of treatment. Biochemical recurrence-free survival was defined as the duration until biochemical progression, initiation of a new line of systemic or local therapy, or death. In-field local failure was defined as disease recurrence within the original radiotherapy treatment volume. Toxicity from metastasis-directed radiotherapy was graded using the Common Terminology Criteria for Adverse Events, version 5.

Statistical Analysis

Patient and treatment characteristics were reported using descriptive statistics. PFS, biochemical recurrence-free survival, freedom from local progression, freedom from distant progression, freedom from new lines of systemic therapy, and overall survival (OS) were calculated from the start of metastasis-directed radiotherapy using Kaplan–Meier analysis and reported with 95% CIs. If no event occurred, patients were censored at the time of the last follow-up. Rates of in-field local failure, biochemical response, complete biochemical response, and toxicity were reported using descriptive statistics. PFS and OS were compared using log rank tests between patients who had a change in systemic therapy within 60 d of starting metastasis-directed radiotherapy versus patients who continued preexisting systemic therapy, patients who had bone or visceral metastasis versus nodal metastasis, and patients who had a single versus multiple treated metastases. P values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics, version 28 (IBM Corp.).

RESULTS

Study Population

Twenty-four patients met the inclusion criteria for this study (Fig. 1). At the time of PSMA PET/CT, median age was 68.8 y (interquartile range [IQR], 65.7–71.7 y) (Table 1). Median PSA was 1.2 ng/mL (IQR, 0.4–3.2 ng/mL). Nineteen patients (79.2%) had a prior radical prostatectomy, 1 (4.2%) had prior definitive radiotherapy, 14 (58.3%) had prior salvage or adjuvant radiation therapy, all had received ADT, 18 (75.0%) had received an ARPI, and 3 (12.5%) had received chemotherapy. Median time from initial diagnosis was 6.1 y (IQR, 3.6–12.0 y). Median time from castration resistance was 1.6 y (IQR, 0.3–3.7 y).

Twenty-three patients (95.8%) were on systemic therapy at the time of PSMA PET/CT.

PSMA PET/CT Findings

Fifteen patients (62.5%) underwent PSMA PET/CT for biochemical recurrence, and 9 (37.5%), for treatment response evaluation (Table 2). Four patients (16.7%) had intrapelvic disease only (M0), 6 (25.0%) had extrapelvic nodal metastasis, 12 (50.0%) had

TABLE 3
PSMA PET/CT Lesions (n = 24 Patients)

Visible lesions	n	New or progressing lesions	Stable lesions	Treated lesions	Nontreated lesions
1	6 (25.0%)	1	0	1	0
2	4 (16.7%)	2	0	2	0
	1 (4.2%)	1	1	1	1
3	3 (12.5%)	3	0	3	0
	3 (12.5%)	2	1	2	1
	4 (16.7%)	1	2	1	2
5	1 (4.2%)	2	3	2	3
6	1 (4.2%)	2	4	2	4
>10	1 (4.2%)	2	>10	2	>10

TABLE 4
Patient Treatment Characteristics (n = 24 Patients)

Characteristic	Data
Median time from PSMA PET/CT to metastasis-directed radiotherapy (mo)	1.4 (IQR, 0.9–2.8)
Treated sites (n)	
1	11 (45.8%)
2	10 (41.7%)
3	3 (12.5%)
Concurrent systemic therapy (n)	
ADT	4 (16.7%)
ADT + sipuleucel-T	3 (12.5%)
ADT + ARPI	16 (66.7%)
ADT + ARPI + sipuleucel-T	1 (4.2%)
Change in systemic therapy (n)	
Continued preexisting systemic therapy	17 (70.8%)
Started new systemic therapy	7 (29.2%)

TABLE 5
Treated Site Characteristics (n = 40 Sites)

Characteristic	Prostate/prostate bed (n = 5)	Lymph nodes (n = 15)	Bones (n = 19)	Viscera (n = 1)
Median size (cm)	3.8 (IQR: 2.9–4.0)	1.1 (IQR: 0.6–1.1)	1.6 (IQR: 1.2–2.2)	2.0
Median SUV_{max}	10.4 (IQR: 4.2–30.2)	12.6 (IQR: 6.7–28.7)	7.8 (IQR: 3.7–14.5)	17.8
Location				
Prostate	3 (60.0%)			
Prostate bed	1 (20.0%)			
Bladder base	1 (20.0%)			
Pelvic lymph nodes		9 (60.0%)		
Retroperitoneal lymph nodes		6 (40.0%)		
Pelvic bone			8 (42.1%)	
Spine			6 (31.6%)	
Ribs/sternum			4 (21.1%)	
Skull			1 (5.3%)	
Corpus cavernosum				1 (100%)
Treatment modality				
SBRT	3 (60.0%)	8 (53.3%)	19 (100%)	0 (0.0%)
Intensity-modulated radiotherapy	2 (40.0%)	7 (46.7%)	0 (0.0%)	0 (0.0%)
High-dose-rate brachytherapy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Dose and fractionation				
35–40 Gy in 5 fractions	3 (60.0%)			
66–74 Gy in 37 fractions	2 (40.0%)			
32 Gy in 4 fractions		1 (6.7%)		
30–40 Gy in 5 fractions		7 (46.7%)		
55–60 Gy in 23–33 fractions		4 (26.7%)		
Unknown		3 (20%)		
18 Gy in 1 fraction			2 (10.5%)	
18–27 Gy in 3 fractions			10 (52.6%)	
25 Gy in 5 fractions			1 (5.3%)	
35–50 Gy in 5 fractions			6 (31.6%)	
35 Gy in 8 fractions				1 (100%)

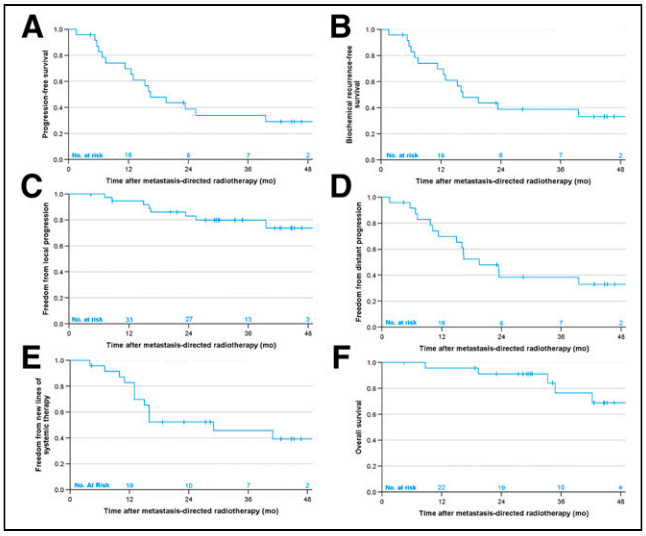

FIGURE 2. (A) PFS. (B) Biochemical recurrence-free survival. (C) Freedom from local progression (40 sites). (D) Freedom from distant progression. (E) Freedom from new lines of systemic therapy. (F) OS.

osseous metastasis, 1 (4.2%) had extrapelvic and osseous metastasis, and 1 (4.2%) had visceral metastasis (corpus cavernosum). Six patients (25.0%) had 1 visible lesion, 5 (20.8%) had 2, 10 (41.7%) had 3, 1 (4.2%) had 5, 1 (4.2%) had 6, and 1 (4.2%) had more than 10 (Table 3). Among these visible lesions, 40 represented new or progressing disease and were recommended for treatment (Tables 4 and 5). Five were prostate or prostate bed (median size, 3.8 cm; median SUV_{max}, 10.4), 15 were nodal (median size, 1.1 cm; median SUV_{max}, 12.6), 19 were osseous (median size, 1.6 cm; median SUV_{max}, 7.8), and 1 was visceral (size, 2.0 cm; SUV_{max}, 17.8).

Treatment Characteristics

Between October 2017 and April 2023, 11 patients (45.8%) had 1 site treated, 10 (41.7%) had 2, and 3 (12.5%) had 3 (Tables 4 and 5). Median time from PSMA PET/CT to metastasis-directed radiotherapy was 1.4 mo (IQR, 0.9–2.8 mo). In total, 40 sites were treated. Thirty (75%) were treated using SBRT, 9 (22.5%) were treated using intensity-modulated radiotherapy, and 1 (2.5%) was treated using high-dose-rate brachytherapy. All patients received concurrent systemic therapy: 4 (16.7%) received ADT, 3 (12.5%) received ADT plus sipuleucel-T, 16 (66.7%) received ADT plus an ARPI, and 1 (4.2%) received ADT plus an ARPI and sipuleucel-T. Seventeen patients (70.8%) continued their existing systemic therapy, whereas 7 (29.2%) started a new systemic therapy.

Clinical Outcomes

Median follow-up was 33.8 mo (IQR, 27.6–45.1 mo). All patients underwent PSA testing, and 18 patients (75.0%) underwent PSMA PET/CT after treatment. Median PFS was 16.4 mo (95% CI, 9.8–23.0 mo) (Fig. 2A; Table 6). The 2- and 4-y PFS rates were 38.7% (95% CI, 18.5%–58.9%) and 29.0% (95% CI, 10.0%–48.0%), respectively. One patient (4.2%) had biochemical progression with negative PSMA PET/CT findings, 5 (20.8%) had progression on PSMA PET/CT and were retreated before biochemical progression, and 10 (41.7%) had biochemical and radiographic progression.

Sixteen patients (66.7%) had a biochemical response (Fig. 3). Twelve (50%) had a complete biochemical response. Seven of the 12 patients (58.3%) with a complete biochemical response initially had a single progressing site, versus 2 of 12 patients (16.7%) without a complete biochemical response ($P = 0.035$, χ^2 test). Median biochemical recurrence-free survival was 16.4 mo (95% CI, 9.8–23.0 mo; Fig. 2B). The 2- and 4-y biochemical recurrence-free survival rates were 38.7% (95% CI, 18.5%–58.9%) and 33.2% (95% CI, 13.2%–53.2%), respectively.

Median freedom from local progression was not reached (Fig. 2C). The 2- and 4-y rates of freedom from local progression were 82.9% (95% CI, 70.4%–95.4%) and 73.7% (95% CI, 56.8%–90.6%), respectively. There was one instance (2.5%) of true in-field local failure at an osseous site. Median freedom from distant progression was 19.5 mo (95% CI, 8.8–30.3 mo; Fig. 2D). The 2- and 4-y rates of freedom from distant progression were 38.3% (95% CI, 18.1%–58.5%) and 32.9% (95% CI, 12.9%–52.9%), respectively. All sites of local or distant progression were detected by PSMA PET/CT.

TABLE 6
Long-Term Clinical Outcomes ($n = 24$ Patients)

	Median (mo)		1 y (%)		2 y (%)		4 y (%)	
Outcome	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
PFS	16.4	9.8–23.0	69.7	50.9–88.5	38.7	18.5–58.9	29.0	10.0–48.0
Biochemical recurrence-free survival	16.4	9.8–23.0	69.7	50.9–88.5	38.7	18.5–58.9	33.2	13.2–53.2
Freedom from local progression	NR		94.6	87.3–100	82.9	70.4–95.4	73.7	56.8–90.6
Freedom from distant progression	19.5	8.8–30.3	69.7	50.9–88.5	38.3	18.1–58.5	32.9	12.9–52.9
Freedom from new lines of systemic therapy	29.0	7.6–50.4	82.8	67.5–98.1	52.3	31.9–72.7	39.2	17.2–61.2
OS	NR		95.7	87.3–100	91.1	79.3–100	68.8	45.1–92.5

NR = not reached.

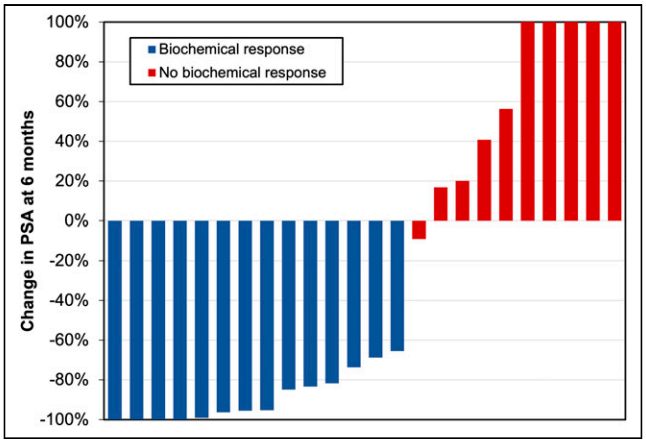

FIGURE 3. Change in PSA level from baseline at 6 mo. Biochemical response was defined as PSA decrease ≥ 50% from baseline. *>100% increase.

Median freedom from new lines of systemic therapy was 29.0 mo (95% CI, 7.6–50.4 mo; Fig. 2E). The 2- and 4-y rates of freedom from new lines of systemic therapy were 52.3% (95% CI, 31.9%–72.7%) and 39.2% (95% CI, 17.2%–61.2%), respectively.

Median OS was not reached (Fig. 2F). The 2- and 4-y OS rates were 91.1% (95% CI, 79.3%–100%) and 68.8% (95% CI, 45.1%–92.5%), respectively.

Patients who changed systemic therapy with the start of metastasis-directed radiotherapy had longer PFS (median, 49.3 vs. 12.9 mo; $P = 0.001$) and higher OS (2-y rate, 100% vs. 87.1%; $P = 0.059$) than patients who did not change systemic therapy (Fig. 4A). Patients treated for nodal metastasis had longer PFS (median, 39.6 vs. 12.5 mo; $P = 0.056$) and higher OS (2-y rates, 100% vs. 85.1%; $P = 0.023$) than patients treated for bone or visceral metastasis (Fig. 4B). There was no significant difference between patients with multiple versus single treated metastases for PFS (median, 15.3 vs. 19.5 mo; $P = 0.5$) or OS (2-y rates, 91.7% vs. 90.0%; $P = 0.6$; Fig. 4C).

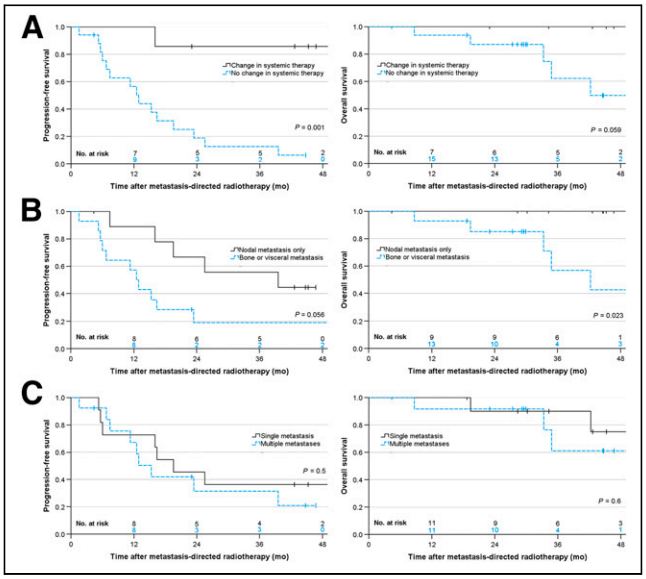

FIGURE 4. (A) Comparison of patients who changed systemic therapy vs. patients who did not. (B) Comparison of patients who had nodal metastasis vs. bone or visceral metastasis. (C) Comparison of patients who had single vs. multiple treated metastases.

Figures 5 and 6 show the PSMA PET/CT imaging and radiotherapy dose plans for 2 patients in this cohort.

Toxicity

There was one case (4.2%) of grade 2 toxicity and no cases of grade 3 or higher toxicity related to metastasis-directed radiotherapy. The case of grade 2 toxicity was worsening urinary incontinence after brachytherapy to the corpus cavernosum.

DISCUSSION

In this retrospective cohort of patients with oligometastatic castration-resistant prostate cancer, PSMA PET/CT–guided, metastasis-directed radiotherapy achieved durable disease control without significant toxicity. Median PFS was 16.4 mo, median time to a new line of systemic therapy was 29.0 mo, and median OS was not reached. In-field local failure was rare and occurred in only one case. Metastasis-directed radiotherapy was associated with 1 grade 2 toxicity event and no toxicity events of grade3 or higher. Finally, even with metastasis-directed radiotherapy, bone or visceral metastasis is associated with worse OS and may require further treatment intensification.

A limited number of retrospective series have reported their experience with PSMA PET/CT–guided, metastasis-directed radiotherapy for patients with mCRPC. Onal et al. examined a cohort of 67 patients with mCRPC (≤5 lymph node or bone metastases) and reported clinical outcomes similar to those in our study (*18*). Their 2-y OS rate was 86.9% (vs. 91.1% in our study), and their 2-y PFS rate was 34.4% (vs. 38.7% in our study). Henkenberens et al. examined a cohort of 42 patients with mCRPC (≤5 bone or visceral metastases) (*19*). They reported lower median biochemical failure-free survival (12.0 vs. 16.4 mo in our study) and median time to a new line of systemic therapy (15.0 vs. 29.0 mo in our study). These differences may be due to the inclusion of multiple patients with visceral metastases and the fact that no patients in their cohort received an ARPI.

Metastasis-directed radiotherapy for mCRPC using a mix of PSMA PET/CT and conventional imaging has been more extensively reported. ARTO was a phase II randomized trial that enrolled 157 patients with mCRPC (≤3 nodal or osseous metastatic sites according to either conventional imaging or advanced molecular imaging) (*20*). Patients were randomized to receive ADT and abiraterone acetate with versus without metastasis-directed SBRT. The investigators reported rates of biochemical response (PSA decrease ≥ 50% compared with baseline) and complete biochemical response (PSA ≤ 0.2 ng/mL) at 6 mo. The arm receiving metastasis-directed SBRT had a higher biochemical response (92% vs. 68%, $P = 0.001$) and complete biochemical response (56% vs. 23%, $P < 0.001$) than the arm receiving systemic therapy alone. Pretreatment staging with PSMA or fluciclovine PET/CT was associated with a higher odds of a complete biochemical response (odds ratio, 2.1; $P = 0.042$). Overall, this study was consistent with our findings and supported both metastasis-directed radiotherapy for mCRPC and advanced molecular imaging such as PSMA PET/CT.

The MEDCARE trial was a single-arm, phase II clinical trial that enrolled patients with mCRPC (≤3 sites) to receive conventional imaging-guided, metastasis-directed radiotherapy (*21*,*22*).

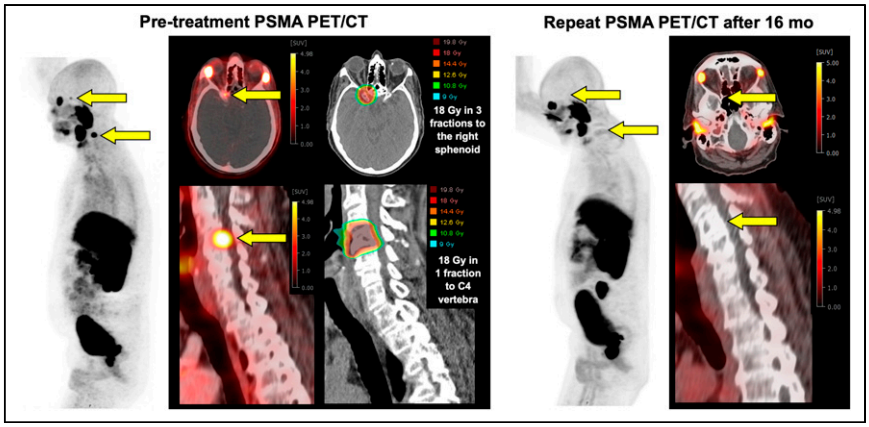

FIGURE 5. PSMA PET/CT showed new metastases (arrows) in C4 vertebra and right sphenoid bone. Patient underwent metastasis-directed radiotherapy to both sites. Repeat PSMA PET/CT showed resolution of PSMA avidity (arrows) in both treated sites. It also showed multifocal distant disease progression, and patient subsequently started ^{177}Lu-PSMA therapy.

A preliminary analysis was performed after 20 patients were enrolled in the study with a median follow-up of 6 mo. Eight patients (40%) experienced clinical progression (vs. 30.3% at 1 y in our study). Median time to a new line of systemic therapy was 12 mo (vs. 29.0 mo in our study). Deek et al. examined a cohort of 68 patients with mCRPC (≤5 sites) who received predominantly conventional imaging–guided, metastasis-directed SBRT (*23*). Median time to biochemical recurrence was 9.7 mo (vs. 16.4 mo in our study), and median time to distant metastasis was 10.8 mo (vs. 19.5 mo in our study). Valeriani et al. examined a cohort of 29 patients with mCRPC (≤3 sites on ^{18}F-choline PET/CT) who received metastasis-directed radiotherapy (*24*). The 2-y OS rate was 82.2% (vs. 91.1% in our study). Overall, these cohorts reported worse oncologic outcomes than were found in our study, suggesting that PSMA PET/CT guidance is associated with improved oncologic outcomes compared with conventional imaging guidance, though more prospective data are needed.

Finally, we await the results of several ongoing randomized trials for mCRPC. The FORCE trial (NCT03556904) is examining standard-of-care systemic therapy with or without metastasis-directed radiotherapy (*25*). Three other randomized trials are examining specific systemic therapy agents with or without metastasis-directed radiotherapy: the DECREASE trial (NCT04319783) is studying darolutamide, the PCS IX trial (NCT02685397) is studying enzalutamide, and the PILLAR trial (NCT03503344) is studying apalutamide.

Our study had several limitations. First, it was retrospective. Prospective studies with larger sample sizes will be needed to confirm these findings. Second, the patient population was heterogeneous, with significant variation in time from diagnosis, number of metastatic sites, and prior systemic and local therapies. We have yet to identify the ideal patient population for metastasis-directed radiotherapy in the setting of mCRPC. Third, there was significant variation in the systemic therapy and metastasis-directed radiotherapy that patients received. These management decisions were individualized for each patient and considered their disease course, prior treatment history, metastatic target location, and provider preference.

CONCLUSION

For patients with oligometastatic castration-resistant prostate cancer, metastasis-directed radiotherapy appears to offer durable disease control with low toxicity rates. Further prospective studies are needed to compare metastasis-directed radiotherapy with systemic therapy versus systemic therapy alone and PSMA PET/CT–guided versus conventional imaging–guided radiotherapy.

DISCLOSURE

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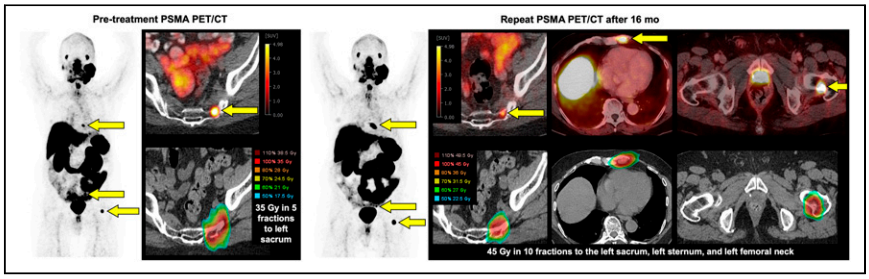

FIGURE 6. PSMA PET/CT showed new left sacral metastasis with stable disease in left femur and sternum (arrows). Patient underwent metastasis-directed radiotherapy to sacrum. Repeat PSMA PET/CT showed in-field local failure in sacrum and new progression in left femur and sternum (arrows). Patient underwent reirradiation to sacrum and metastasis-directed radiotherapy to left femur and sternum.

KEY POINTS

QUESTION: What is the role of PSMA PET/CT–guided, metastasis-directed radiotherapy for patients with oligometastatic castration-resistant prostate cancer involving 5 or fewer progressing sites?

PERTINENT FINDINGS: Patients treated with PSMA PET/CT–guided, metastasis-directed radiotherapy had a median PFS of 16.4 mo and a median time to a new line of systemic therapy of 29.0 mo. Most patients were alive after 4 y. There was no grade 3 or higher radiation-related toxicity.

IMPLICATIONS FOR PATIENT CARE: For patients with oligometastatic castration-resistant prostate cancer, PSMA PET–guided, metastasis-directed radiotherapy achieved durable disease control with no significant toxicity, though further prospective studies are needed to confirm these findings.

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