Advances in Radiation Oncology (2022) 7, 100808

advances in radiation oncology

www.advancesradonc.org

Research Letter

Evaluating the Role of Stereotactic Body Radiation Therapy With Respect to Androgen Receptor Signaling Inhibitors for Oligometastatic Prostate Cancer

Victoria Brennan, MB, BCh, BAO,[a] Alexander Spektor, MD, PhD,[a] Christopher Sweeney, MBBS,[b] Atish Choudhury, MD, PhD,[b] Dana Rathkopf, MD,[c] Mark Pomerantz, MD,[b] Lauren Hertan, MD,[d] Paul Nguyen, MD,[a] Neil Martin, MD, MPH,[a] Tracy Balboni, MD, MPH,[a] Mai Anh Huynh, MD, PhD,[a,1,*] and Martin King, MD, PhD[a,*,1]

[a]Dana-Farber/Brigham and Women's Cancer Center, Boston, Massachusetts; [b]Dana-Farber Cancer Institute, Boston, Massachusetts; [c]Memorial Sloan Kettering Cancer Center, New York, New York; [d]Beth-Israel Deaconess Medical Center, Boston, Massachusetts

Received February 23, 2021; accepted September 8, 2021

Abstract

Purpose: Outcomes of stereotactic body radiation therapy (SBRT) with respect to androgen receptor signaling inhibitors (ARSI) have not been characterized for oligometastatic prostate cancer. We sought to characterize prostate specific antigen (PSA) response and progression-free survival (PFS) after SBRT among men who have progressed on ARSI therapy in the oligometastatic castration-resistant setting.

Methods and Materials: A single-institution retrospective analysis was performed for men with ARSI-resistant, oligometastatic, castrate-resistant prostate cancer (omCRPC). Intervention consisted of SBRT. PSA reduction greater than 50% and median PFS (PSA or radiographic progression) as determined by routine care comprised outcome measurements. Cox regression analysis was used to determine factors influencing PFS.

Results: Thirty-five men with ARSI-resistant omCRPC and 65 lesions treated with SBRT were followed for a median of 17.2 months. In 63% of men PSA reduction greater than 50% was achieved. Median PFS was 9.0 months. Incomplete ablation (defined as the presence of untreated lesions after SBRT or receipt of prior palliative radiation therapy doses) was associated with worse PFS (hazard ratio 4.21 [1.74-10.19]; $P < .01$). For a subgroup of 22 men with complete ablation of metastatic sites with SBRT, the median PFS was 13.1 months. One-year overall survival was 93.1% (95% confidence interval, 84.4-100).

Conclusions: SBRT may augment the efficacy of ARSI in omCRPC, provided that all lesions receive ablative radiation doses. Future prospective study of SBRT for men receiving ARSI is warranted.

Sources of support: M.A.H. was supported by the Dana Farber Cancer Institute Early Career Innovation Fund.
Disclosures: none.
Research data are not available at this time.
*Corresponding author: Mai Anh Huynh, MD, PhD; E-mail: mhuynh@bwh.harvard.edu
[1] M.A.H. and M.K. are co-senior authors.

https://doi.org/10.1016/j.adro.2021.100808

Introduction

Androgen receptor signaling inhibitors (ARSI) have revolutionized the treatment of prostate cancer and have been shown to improve overall survival (OS) for men with metastatic castration-resistant prostate cancer (CRPC), metastatic castration-sensitive prostate cancer (CSPC), and nonmetastatic CRPC.[1-4] Because these oral agents have also been associated with better quality of life than docetaxel,[5] ARSI may be increasingly used as first-line therapy for men with oligometastatic CSPC and CRPC (omCRPC).

The phase 2 STOMP (Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence) and ORIOLE (Stereotactic Body Radiation for Prostate Oligometastases) trials reported that stereotactic body radiation therapy (SBRT) prolongs progression-free survival (PFS) compared with observation for men with oligorecurrent CSPC.[6,7] However, no randomized controlled trials have reported whether adding SBRT after progression on ARSI improves outcomes for omCRPC. Furthermore, retrospective studies have not specifically evaluated SBRT with respect to progression on ARSI.[8-13] Given the lack of durable treatment options after progression on ARSI, SBRT may be an effective option to address this unmet clinical need.

The purpose of this study is to characterize prostate-specific antigen (PSA) response and PFS for men receiving SBRT after progression on ARSI. We hypothesize that SBRT may provide durable oncologic outcomes for men with oligometastatic disease, even after the development of ARSI resistance.

Patients and Methods

Patient population

With institutional review board approval, we performed a retrospective review of men who received SBRT for ARSI-resistant (ARSI-r) omCRPC. Metastatic burden was quantified based on the number of active sites on pre-SBRT bone scans, enlarged lymph node or visceral metastasis on computed tomography (CT; ≥1.5 cm in short axis), or avid lesions on positron emission tomography (PET; fluciclovine or prostate specific membrane antigen). Castration resistance was defined as a rising PSA despite a testosterone level <50 ng/mL. We defined ARSI-r as PSA progression (PSA rise ≥0.1 ng/mL above nadir) or radiographic progression that prompted subsequent SBRT. SBRT regimens included 16 to 20 Gy in 1 fraction, 27 to 30 Gy in 3 fractions, and 30 to 40 Gy in 5 fractions.

For follow-up, most patients were seen every 3 to 6 months with a PSA, CT/bone scan, or magnetic resonance imaging if indicated, and toxicity assessment. Toxicity was graded per Common Terminology Criteria for Adverse Events version 4.0 criteria.

Statistical analysis

We calculated PSA reduction greater than 50% (PSA50) and PSA reduction greater than 30% (PSA30) as PSA decline ≥50% and ≥30%, respectively. Survival endpoints were defined from the SBRT completion date. We performed Kaplan-Meier analysis to estimate PFS, which included endpoints of PSA progression per Prostate Cancer Working Group 3 (PCWG3) criteria (PSA rise ≥2 ng/mL and ≥25% above nadir),[14] radiographic progression, or death, whichever came first. We performed univariable Cox regression analysis to evaluate factors associated with PFS. All statistical analyses were conducted with R version 3.6.2; P values ≤.05 were classified as statistically significant.

Results

We identified 35 men treated with SBRT between February 2015 and June 2019. A total of 65 lesions were treated using 56 treatment isocenters. Patients with lesions in close proximity (eg, contiguous vertebral lesions) were treated using the same radiation isocenter and plan, with no more than 3 SBRT isocenters used per patient. Median follow-up was 17.2 months (range 10.4, 28.6). Baseline characteristics and SBRT fractionation regimens are summarized in Table 1 and 2, respectively.

Median times to SBRT since initial metastasis and ARSI initiation were 46.7 and 26.4 months, respectively. The median pre-SBRT PSA was 2.9 ng/mL. The numbers of men who received 2+ ARSI courses, docetaxel, and radium-223 were 9, 6, and 4, respectively. Ten men received prior palliative external beam radiation therapy (EBRT) to bony lesions, of whom 3 had SBRT fields overlapping with prior EBRT fields. Four men had an untreated disease site after SBRT, which was considered nonprogressive at the time of SBRT. This included an untreated spine lesion, stable pathological (≥1.5 cm) lymph node, stable active spine disease previously treated with palliative EBRT, and a liver lesion initially interpreted as benign on the pre-SBRT CT scan, but with subsequent biopsy-proven progression after SBRT (Table 1). Twenty-eight men received an ARSI concurrently with SBRT. Twenty-nine men received a post-SBRT intervention, including 23 who initiated non-ARSI therapy (6 docetaxel, 2 EBRT, 6 radium-223, 5 SBRT, and 4 other treatments). The percentage of men achieving PSA50 was 62.9% and PSA30 was 74.8% (Table 3). One-year OS was 93.1%. The median PFS was 9.0 months. Two men

Table 1 Clinical characteristics

Clinical characteristic	N = 35
Initial Gleason score	
6-7	14
8	8
9-10	12
Not applicable	0
Initial local treatment	
Radical prostatectomy	20
Radiation therapy	11
None	4
Time since initial metastasis (mo)	46.7 (21.9-91.5)
Number of initial metastases	
1-2	24
3-5	5
>5	6
Time since ARSI initiation (mo)	26.4 (12.8-32.7)
Prior ARSI	
0 (started <90 days after SBRT)	0
1	26
2+	9
Prior non-ARSI systemic therapy	
Docetaxel	6
Radium-223	4
Sipuleucel-T	12
Prior radiation therapy	
Prostate or prostate bed	32
Palliative external beam radiation therapy	10
SBRT	4
Pre-SBRT PSA (ng/mL)	2.9 (1.3-9.5)
Pre-SBRT PSA above nadir (ng/mL)	2.0 (0.8-5.3)
Pre-SBRT PSA doubling time (mo)	5.0 (3.0-8.7)
Pre-SBRT progression	
De novo oligometastasis	0
PSA progression <2 ng/mL only	9
PSA progression ≥2 ng/mL only	8
Radiographic oligoprogression (≤5 new metastases)	18
Radiographic polyprogression (>5 new metastases)	0
Pre-SBRT baseline pain ≥3	7
Pre-SBRT prostate positron emission tomography	4
Pre-SBRT number of active metastases	
1-2	22
3-5	13
>5	0
Pre-SBRT metastasis locations	
Bone only	31
Nodal only	2
Bone and nodal	1
Bone and viscera	1
Pre-SBRT known uncontrolled primary	0
SBRT number of treated metastases	
1-2	24
3-5	11
SBRT number of treatment isocenters	
1	21
2	7
3	7
SBRT number of untreated metastases	

(*continued on next page*)

Table 1 (*Continued*)

Clinical characteristic	N = 35
0	31
1-5	4
>5	0
SBRT gross tumor volume (mL)	27.0 (6.0-54.2)
SBRT equivalent dose in 2 Gy fractions (alpha/beta ratio = 1.5)	85.0 (64.3-104.5)
SBRT overlap with prior palliative radiation therapy fields	3
Postoperative SBRT after spine surgery	2
Concurrent therapy with SBRT	
Androgen deprivation therapy alone	3
ARSI	28
Radium-223	3
Other systemic	1
Post-SBRT intervention	
None	6
New ARSI	6
Radium-223	6
Docetaxel	6
Other systemic	4
External beam radiation therapy	2
SBRT	5

Abbreviations: ARSI = androgen receptor signaling inhibitor; PSA = prostate specific antigen; SBRT = stereotactic body radiation therapy.

Table 2 Stereotactic body radiation therapy dose and fractionation by treatment site

N	Dose prescribed	Fraction	Equivalent dose in 2 Gy fractions (alpha/beta ratio = 1.5)	Bone	Bone and lymph node	Bone and viscera	Lymph node	Prior radiation therapy
13	30	5	64.3	11	0	1	1	4
2	27	3	81	2	0	0	0	2
3	35	5	85	3	0	0	0	0
5	30	3	98.6	5	0	0	0	1
3	18	1	100.3	3	0	0	0	1
1	40	5	108.6	0	0	0	1	0
8	20	1	122.9	7	1	0	0	2

Table 3 Tabulation of clinical outcomes after treatment with stereotactic body radiation therapy

Variable	N = 35
Median follow-up (mo)	17.2 (10.4-28.6)
PSA decline	
≥50% or <0.05 ng/mL	22
0%-49%	7
<0% (rising PSA)	6
PSA decline ≥50%	62.9
PSA decline ≥30%	74.8
Progression (PSA or radiographic)	28
PSA progression (Prostate Cancer Working Group 3 criteria[14]) only	23
Radiographic progression only	25
Death	5

Abbreviation: PSA = prostate specific antigen.

remained on androgen deprivation therapy alone for at least 5 months after SBRT.

Cox regression analysis for oligometastatic ARSI-r CRPC

In total, 28 men experienced progression. Table 4 shows results of the Cox regression analysis evaluating the association of factors with PFS for ARSI-r omCRPC. On univariate analysis, prior radium-223 (hazard ratio [HR] 4.56; 95% confidence interval [CI] 1.50-13.92; $P = .008$), prior palliative EBRT (HR 2.63; 95% CI 1.10-6.30; $P = .03$), and the presence of untreated lesions after SBRT (HR 6.54; 95% CI 1.90-22.55; $P = .003$) were associated with worse PFS. The type of progression before SBRT (PSA progression meeting PCWG3 criteria or

Table 4 Cox regression analysis of outcomes for oligometastatic ARSI-resistant castration-resistant prostate cancer

Clinical factor	Progression-free survival Univariable analysis HR (95% CI)	*P* value
Initial Gleason score		
6-7	Baseline	
8	0.83 (0.30-2.27)	0.72
9-10	1.06 (0.44-2.56)	0.89
Initial local treatment		
Radical prostatectomy	Baseline	
Radiation therapy	0.97 (0.26-3.53)	0.96
None	0.87 (0.38-1.98)	0.74
Number of initial metastases		
1-2	Baseline	
3-5	1.62 (0.60-4.42)	0.34
>5	0.98 (0.34-2.84)	0.98
Prior ARSI (2+ prior courses)	1.08 (0.45-2.57)	0.86
Prior non-ARSI systemic therapy		
Prior docetaxel	1.75 (0.64-4.73)	0.27
Prior radium-223	4.56 (1.50-13.92)	0.008
Prior sipuleucel-T	1.64 (0.77-3.49)	0.2
Prior radiation therapy		
Prostate or prostate bed	1.53 (0.34-6.92)	0.58
Palliative external beam radiation therapy	2.63 (1.10-6.30)	0.03
SBRT	2.25 (0.63-8.00)	0.21
Pre-SBRT PSA (ng/mL) ≥median	1.01 (0.98-1.04)	0.47
Pre-SBRT PSA above nadir (ng/mL)	1.03 (0.99-1.07)	0.21
PSA doubling time (mo)	0.61 (0.25-1.47)	0.27
Pre-SBRT progression		
PSA rise (not meeting Prostate Cancer Working Group 3 criteria[14])	Baseline	
PSA progression per Prostate Cancer Working Group 3 criteria[14]	1.08 (0.38-3.10)	0.88
Radiographic oligoprogression without PSA progression	1.34 (0.53-3.38)	0.53
Pre-SBRT prostate positron emission tomography	1.72 (0.58-5.08)	0.32
Pre-SBRT number of active metastases		
1-2	Baseline	
3-5	1.65 (0.74-3.65)	0.22
Pre-SBRT metastasis locations		
Bone only	Baseline	
Other	0.77 (0.22-2.66)	0.68
SBRT number of treated metastases		
1-2	Baseline	
3-5	1.29 (0.57-2.92)	0.55
SBRT number of treatment isocenters	1.00 (0.62-1.62)	1
Presence of untreated metastases after SBRT	6.54 (1.90-22.55)	0.003
SBRT gross tumor volume (mL)	1.01 (1.00-1.02)	0.26
SBRT equivalent dose in 2 Gy fractions ($\alpha/\beta = 1.5$)	1.00 (0.98-1.01)	0.61
SBRT overlap with prior palliative radiation therapy fields	2.67 (0.77-9.27)	0.12
Postoperative SBRT after spine surgery	2.65 (0.60-11.62)	0.2

Abbreviations: ARSI = androgen receptor signaling inhibitor; PSA = prostate specific antigen; SBRT = stereotactic body radiation therapy.

radiographic oligoprogression vs PSA progression not meeting PCWG3 criteria [<2 ng/mL above nadir]) had no significant impact on PFS.

We defined incomplete ablation as either the presence of untreated lesions after SBRT or prior palliative EBRT, given the higher likelihood of residual disease with nonablative EBRT doses. Incomplete ablation was associated with worse PFS (HR 4.21 [1.74-10.19]; $P < .01$).

Figure 1 shows the associated Kaplan-Meier curves for PFS among ARSI-r omCRPC patients based on complete versus incomplete ablation. Of the 22 men with complete ablation, the median PFS was 13.1 months.

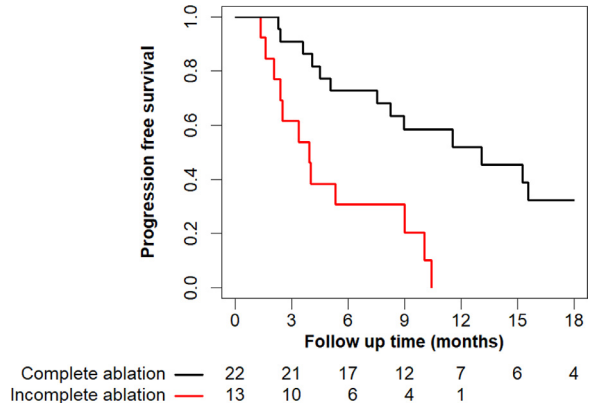

Figure 1 Clinical outcomes for oligometastatic ARSI-r CRPC by degree of ablation with SBRT. Progression-free survival among men with oligometastatic ARSI-resistant CRPC by complete or incomplete ablation of oligometastatic sites of disease. Complete ablation included patients treated with stereotactic body radiation therapy (SBRT) to all known active sites of disease at time of SBRT. Incomplete ablation was defined as the presence of untreated lesions at the time of SBRT or receipt of prior palliative radiation.

There were no acute grade 3+ toxicities. One patient with prior mantle field irradiation for lymphoma developed grade 4 pneumonitis after SBRT to a T2 lesion.

Discussion

To our knowledge, this is the largest single-institution experience of SBRT for the treatment of ARSI-resistant oligometastatic prostate cancer, with 1-year OS of 93.1% and a median PFS of 9 months. Complete ablation of metastatic disease with SBRT was associated with improved PFS.

Our results are consistent with an oligometastatic paradigm and the hypothesis that maximal benefit of SBRT is associated with the ability to address all known sites of active disease with ablative intent. The ORIOLE trial showed that omCSPC patients who had untreated occult metastases on conventional imaging fared worse than patients in whom all sites of disease were treated based on prostate specific membrane antigen-PET imaging.[7] In our study, the subgroup of 22 men with ARSI-r omCRPC and complete ablation had durable cancer control outcomes

Table 5 Comparison of oncologic outcomes of stereotactic body radiation therapy against systemic therapies for ARSI-sensitive and ARSI-resistant disease

Trial	Intervention	ARSI sensitive/ resistant	% Prior chemotherapy	PSA response	Progression-free survival (including PSA endpoint)
PLATO, *J Clin Oncol* 2018[27]	Enzalutamide	ARSI sensitive	0	PSA50 67%	
	Enzalutamide followed by abiraterone	ARSI resistant	0	PSA50 1%	2.8 mo
	Enzalutamide followed by abiraterone + enzalutamide	ARSI resistant	0	PSA50 2%	2.8 mo
Khalaf, *Lancet Oncol* 2019[16]	Enzalutamide	ARSI sensitive	5%	PSA30 83%	7.3 mo
	Enzalutamide followed by abiraterone	ARSI resistant	5%	PSA30 4%	1.7 mo
	Abiraterone	ARSI sensitive	6%	PSA30 68%	7.9 mo
	Abiraterone followed by enzalutamide	ARSI resistant	6%	PSA30 36%	2.7 mo
COU-AA302					
Eur Urol, 2014[26]	Abiraterone	ARSI sensitive	0%	PSA50 68%	
Eur Urol, 2017[14]	Followed by docetaxel	ARSI resistant	0%	PSA50 40%	7.6 mo
de Bono, *Eur Urol*, 2018[21]	Abiraterone followed by enzalutamide	ARSI resistant	32%	PSA50 27%	5.7 mo
de Bono, *N Engl J Med*, 2020 (combined cohort)[19]	Abiraterone or enzalutamide	ARSI resistant	64%	PSA50 10%	
	Olaparib	ARSI resistant	66%	PSA50 30%	
This study (retrospective)	Total cohort N = 35	ARSI resistant	19%	PSA50 63% PSA30 74.8%	9.0 mo
	Complete ablation subgroup	ARSI resistant	14%	PSA50 68%	13.1 mo

Abbreviations: ARSI = androgen receptor signaling inhibitor; PSA = prostate specific antigen; PSA50 = PSA reduction greater than 50%; PSA30 = PSA reduction greater than 30%. PLATO trial: Safety Study of Continued Enzalutamide Treatment In Prostate Cancer Patients. COU-AA302: Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer.

compared with men with untreated metastases or lesions addressed with a lower dose of conventional palliative radiation. The median PFS for this population was 13.1 months. Such men may be able to continue ARSI and avoid cytotoxic systemic therapy for over a year after SBRT. Prior EBRT and radium-223 were associated with higher rates of progression and may reflect a higher burden of disease among patients with oligoprogressive or pretreated disease, including those with subclinical disease not detectable on conventional imaging. In patients with prior EBRT, re-irradiation also resulted in the use of lower doses of SBRT (Table 1).

The oligometastatic ARSI-resistant CRPC space is intriguing for several reasons. First, the incidence of ARSI-r oligometastatic disease will rise as more men receive ARSI for nonmetastatic CRPC based on recent US Food and Drug Administration approvals.[15-17] Second, the improved sensitivity of next-generation prostate cancer PET imaging[18] may detect oligometastatic disease at lower PSA values for ARSI-r disease. Finally, current systemic treatment options for men with oligometastatic ARSI-resistant CRPC do not provide adequate PSA response rates. PSA response rates for enzalutamide after abiraterone progression (PSA30 36%), abiraterone after enzalutamide progression (PSA30 4%), docetaxel after abiraterone (PSA50 40%), or olaparib (PSA50 30%)[19, 20] are low (Table 5).[21] SBRT may demonstrate favorable PSA response rates for men receiving complete ablation (PSA50 62.9%/PSA30 74.3% in this study), by ablating ARSI-r clones that congregate within macroscopic lesions, thereby extending the efficacy of ARSI for micrometastatic disease. The existence of such clones was recently reported in a prospective study using sodium-fluoride PET to selectively identify oligoprogressive ARSI-resistant lesions.[22]

Two recent studies have evaluated the role of SBRT in omCRPC; however, neither of these studies specifically evaluated outcomes of SBRT with respect to ARSI-r disease. Triggiani et al reported 1-year and 2-year distant PFS of 52.3% and 33.7%, respectively, among men with bone or nodal recurrences on androgen deprivation therapy, excluding those who had prior docetaxel or ARSI.[23] Deek et al included omCRPC patients with prior use of systemic therapy or ARSI in their multi-institutional retrospective review of SBRT.[9] A supracastrating agent was used in 55.9% of cases, and chemotherapy in 38.2% of cases. Median distant metastasis-free survival was 10.83 months, and 73.5% of patients demonstrated stability or a decline in their PSA. Consistent with our study, patients who had consolidative SBRT to both progressive and stable lesions had better outcomes overall in time to PSA failure, distant metastasis, or next intervention.

For oligometastatic ARSI-resistant CRPC, there has been rapid proliferation of randomized controlled trials evaluating novel systemic agents versus ARSI.[19, 24-26] Given the toxicities of the novel systemic agents, SBRT may be an attractive alternative for improving quality of life.

Conclusions

SBRT for oligometastatic CRPC may improve outcomes after progression on ARSI, provided all lesions have been addressed with an ablative dose of radiation. Future prospective study is needed to determine whether integrating SBRT with ARSI improves long-term oncologic outcomes.

References

1. Hoyle AP, Ali A, James ND, et al. Abiraterone in "high-" and "low-risk" metastatic hormone-sensitive prostate cancer. *Eur Urol*. 2019;76:719–728.
2. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377:338–351.
3. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187–1197.
4. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: Final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*. 2021;39:2294–2303.
5. Rush HL, Cook AD, Brawley CD, et al. Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial. *J Clin Oncol*. 2020;38(suppl):14.
6. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36:446–453.
7. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6:650–659.
8. Berghen C, Joniau S, Ost P, et al. Progression-directed therapy for oligoprogression in castration-refractory prostate cancer. *Eur Urol Oncol*. 2021;4:305–309.
9. Deek MP, Taparra K, Phillips R, et al. Metastasis-directed therapy prolongs efficacy of systemic therapy and improves clinical outcomes in oligoprogressive castration-resistant prostate cancer. *Eur Urol Oncol*. 2021;4:447–455.
10. Deek MP, Yu C, Phillips R, et al. Radiation therapy in the definitive management of oligometastatic prostate cancer: The Johns Hopkins experience. *Int J Radiat Oncol Biol Phys*. 2019;105:948–956.
11. Ingrosso G, Trippa F, Maranzano E, et al. Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: A two-institution experience. *World J Urol*. 2017;35:45–49.
12. Yoshida S, Takahara T, Arita Y, et al. Progressive site-directed therapy for castration-resistant prostate cancer: Localization of the progressive site as a prognostic factor. *Int J Radiat Oncol Biol Phys*. 2019;105:376–381.
13. Valeriani M, Marinelli L, Macrini S, et al. Radiotherapy in metastatic castration resistant prostate cancer patients with oligo-progression during abiraterone-enzalutamide treatment: A mono-institutional experience. *Radiat Oncol*. 2019;14:205.

14. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016;34:1402–1418.
15. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378:2465–2474.
16. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380:1235–1246.
17. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378:1408–1418.
18. Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer?updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: A systematic review and meta-analysis. *Eur Urol*. 2020;77:403–417.
19. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091–2102.
20. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: A multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol*. 2019;20:1730–1739.
21. de Bono JS, Smith MR, Saad F, et al. Subsequent chemotherapy and treatment patterns after abiraterone acetate in patients with metastatic castration-resistant prostate cancer: Post hoc analysis of COU-AA-302. *Eur Urol*. 2017;71:656–664.
22. Kyriakopoulos CE, Heath EI, Ferrari A, et al. Exploring spatial-temporal changes in (18)F-sodium fluoride PET/CT and circulating tumor cells in metastatic castration-resistant prostate cancer treated with enzalutamide. *J Clin Oncol*. 2020;38:3662–3671.
23. Triggiani L, Mazzola R, Magrini SM, et al. Metastasis-directed stereotactic radiotherapy for oligoprogressive castration-resistant prostate cancer: A multicenter study. *World J Urol*. 2019;37:2631–2637.
24. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381:2506–2518.
25. Ryan CJ, Abida W, Bryce AH, et al. TRITON3: An international, randomized, open-label, phase III study of the PARP inhibitor rucaparib vs. physician's choice of therapy for patients with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD). *J Clin Oncol*. 2018;36(suppl):TPS389.
26. Sartor AO, Morris MJ, Messman R, Krause BJ. VISION: An international, prospective, open-label, multicenter, randomized phase III study of 177Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol*. 2020;38(suppl):TPS259.
27. Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. *J Clin Oncol*. 2018;36:2639–2646.