ISTANBUL UNIVERSITY PRESS

RESEARCH / ARAŞTIRMA
DOI: 10.26650/IUITFD.1211556
İst Tıp Fak Derg 2023 / J Ist Faculty Med 2023

SURVIVAL EFFECT OF PALLIATIVE RADIOTHERAPY IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER DEVELOPING OLIGO-PROGRESSION UNDER ANTIANDROGEN TREATMENT

ANTİANDROJEN TEDAVİSİ ALTINDA OLİGO-PROGRESYON GELİŞEN METASTATİK KASTRASYONA DİRENÇLİ PROSTAT KANSERLİ HASTALARDA METASTAZA YÖNELİK VÜCUT RADYOTERAPİSİNİN SAĞKALIM ETKİSİ

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Cite this article as: Goktas Aydin S, Kutlu Y, Muglu H, Acikgoz O, Aydin A, Bilici A, et al. Survival effect of palliative radiotherapy in patients with metastatic castration-resistant prostate cancer developing oligo-progression under antiandrogen treatment. J Ist Faculty Med 2023;86(2):117-122. doi: 10.26650/IUITFD.1211556

ABSTRACT

Objective: Androgen pathway inhibitors have a significant impact on the treatment of prostate cancer. The treatment approach is controversial in patients who develop oligo-progression under anti-androgen therapy. This study aimed to investigate the effects of metastasis-directed stereotactic body radiotherapy (SBRT) on survival in the first-line setting of patients with metastatic castration-resistant prostate cancer who continued the antiandrogen therapy after oligo-progression.

Materials and Methods: Fifty-seven metastatic castration-resistant (serum testosterone <50 ng/dl) prostate cancer patients treated with abiraterone or enzalutamide in the first-line setting were analysed retrospectively. Thirty-nine of the patients with the oligo-progressive disease, which was defined as ≤3 lesions on imaging, received SBRT by continuing the same antiandrogen therapy.

Results: The median age was 70 (range 40-85). In the castration-sensitive setting, 27 (47.4%) patients received docetaxel. The oligo-progressive metastatic sites were as follows: bone in 21 (52.3%), lymph node in 6 (15.3%) and visceral metastasis in 12

ÖZET

Amaç: Androjen yolağı inhibitörleri prostat kanserinin tedavisinde önemli etkiye sahiptir. Anti-androjen tedavisi altında oligo-progresyon gelişen hastalarda tedavi yaklaşımı tartışmalıdır. Bu çalışma, metastaza yönelik stereotaktik vücut radyoterapisinin (SBRT) oligo-ilerlemeden sonra antiandrojen tedavisine devam eden metastatik kastrasyona dirençli prostat kanserli hastalarda birinci basamakta sağkalım üzerindeki etkilerini araştırmayı amaçladı.

Gereç ve yöntem: Birinci basamakta abirateron veya enzalutamid ile tedavi edilen 57 metastatik kastrasyon dirençli (serum testosteron <50 ng/dl) prostat kanseri hastası retrospektif olarak analiz edildi. Görüntülemede ≤3 lezyon olarak tanımlanan oligo-progresif hastalığı olan 39 hasta aynı antiandrojen tedavisine devam edilerek SBRT aldı.

Bulgular: Medyan yaş 70 (dağılım 40-85) idi. Kastrasyona duyarlı ortamda, hastaların 27'si (%47,4) dosetaksel almıştır. Oligo-progresif metastatik bölgeler 21 (%52,3) hastada kemik, 6 (%15,3) hastada lenf nodu ve 12 (%30,9) hastada visseral metastaz olarak saptandı. Abirateron ve enzalutamid sırasıyla %47,4, %52,6

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Submitted/Başvuru: 29.11.2022 • **Revision Requested/Revizyon Talebi:** 28.02.2023 •
Last Revision Received/Son Revizyon: 28.02.2023 • **Accepted/Kabul:** 06.03.2023 • **Published Online/Online Yayın:** 30.03.2023

(30.9%) patients. Abiraterone and enzalutamide were preferred in 47.4% and 52.6% of patients, respectively. The 12-month progression-free survival (PFS) was 79.0% and 88.9% in patients who received or did not receive SBRT (p<0.001). SBRT-related grade 1-2 toxicity was observed in 35 (61.4%) patients. SBRT was also an independent risk factor for PFS (p=0.007, HR:15.7; 95% CI 2.05-118.7). The presence of visceral metastases, isolated bone metastases, the choice of anti-androgen therapy, and Eastern Cooperative Oncology Group Scale Performance Status (ECOG PS) were not significantly associated with PFS. SBRT had no impact on overall survival.

Conclusion: Patients treated with metastasis-directed SBRT without changing treatment in the oligo-progression setting had worse survival outcomes. Thus, metastasis-directed SBRT with continuation of the same antiandrogen therapy should be prioritised only in selected cases.

Keywords: Stereotactic body radiotherapy, abiraterone, enzalutamide, castration-resistant prostate cancer

hastada tercih edildi. SBRT alan ve almayan hastalarda 12 aylık progresyonsuz sağkalım (PFS) %79,0 ve %88,9 idi (p<0,001). Otuz beş (%61,4) hastada SBRT ile ilişkili derece 1-2 toksisite gözlendi. SBRT ayrıca PFS için bağımsız bir risk faktörüydü (p=0,007, HR:15,7; %95 GA 2,05-118,7). Visseral metastazlar, izole kemik metastazları, anti-androjen tedavi seçimi ve Eastern Cooperative Oncology Group (ECOG) performans skalası varlığı, PFS ile istatistiksel olarak anlamlı değildi. SBRT'nin genel sağkalım üzerinde hiçbir etkisi olmamıştır.

Sonuç: Oligo-progresyon durumunda tedaviyi değiştirmeden metastaza yönelik SBRT ile tedavi edilen hastalarda sağkalım sonuçları daha kötüydü. Bu nedenle, aynı antiandrojen tedavisine devam edilerek metastaza yönelik SBRT'ye sadece seçilmiş vakalarda öncelik verilmelidir.

Anahtar Kelimeler: Stereotaktik vücut radyoterapisi, abiraterone, enzalutamide, kastrasyona dirençli prostat kanseri

INTRODUCTION

Prostate cancer is the most common cancer in men worldwide, and up to 60% of cases are diagnosed in metastatic settings (1). Castration-resistant prostate cancer (CRPC) is defined as having evidence of disease progression (an increase in serum prostate-specific antigen (PSA), new metastases, or progression of existing metastases), under castrate levels of serum testosterone (<50 ng/dL) (2).

The androgen pathway inhibitors such as enzalutamide, abiraterone etc. have less toxicity than chemotherapy, and are additionally related to a better quality of life (3,4). However, CRPC is still a life-limiting illness, and the median progression-free survival (PFS) under enzalutamide or abiraterone is 15-17 months (5,6). A subgroup of these patients shows oligo-progression, which was defined as the progression of only a limited number of metastatic lesions (≤3 metastasis). Meanwhile, all other lesions remain controlled by systemic therapy. Several trials showed the efficacy and safety of metastasis-directed therapy as surgery or stereotactic body radiotherapy (SBRT) in prostate cancer and many cancer types (7-10). Eliminating these oligo-progressed lesions with SBRT, which is thought to be the resistant clone to ongoing therapy, may allow continuing the same systemic therapy and may delay the following progression time. The benefit of SBRT with systemic treatment prolonged survival and was related to favourable outcomes in patients with metastatic CRPC (11-13). The phase II trial showed the benefit of SBRT by delaying the androgen deprivation therapy-free survival (14). In the CRPC setting, few studies with small sample sizes have shown the benefit of metastasis-directed SBRT (15,16). In the literature, the use of single or multiple fractions (3–4–5–8) has been described, with no current standardisation of the dose fractionation (17-19).

This study aimed to enhance the data in current literature on the benefit of metastasis-directed SBRT by continuing the same antiandrogen therapy in the oligo-progression setting of the metastatic CRPC.

MATERIAL and METHODS

Fifty-seven men diagnosed with oligo-progressive metastatic castration-resistant (serum testosterone <50 ng/dl) prostate cancer (CRPC) between 2015-2021 were included in this study. Oligo-progressive disease was defined as ≤3 lesions on conventional imaging. Androgen deprivation therapy was continued in all patients. Thirty-nine of the patients received metastasis-directed therapy continued by the same antiandrogen therapy; the remaining patients were treated with the subsequent line of treatment. The physician's choice antiandrogen therapy was enzalutamide 160 mg once daily or abiraterone 1,000 mg once daily (in combination with prednisone 5 mg twice daily). Leuprolide acetate 22.5 mg every three months was continued in all patients. Patients' data were retrospectively obtained from patients' charts. Patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 3 and 4, who could not continue to active follow-up, were excluded from data analysis.

SBRT was performed to all oligo-progressive lesions (≤3). SBRT was linac-based in all cases, and daily image-guided radiotherapy was performed for each patient. The planning target volume was defined as the gross tumour volume plus a 5–8 mm isotropic margin, depending on tumour location. 48 Gy per five fractions and 60 Gy per three fractions were used for lung metastasis. SBRT of lymph node metastasis was performed in a single fraction. For bone lesions the fraction of SBRT was 35 Gy in five fractions or 30 Gy in three fractions.

The treatment response, including partial response (PR), complete response (CR), stable disease (SD) and progressive disease (PD), as well as objective response rates (PR and CR), were evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 by conventional thorax and abdomen computerized tomography (CT) scan and prostate-specific membrane antigen/positron emission tomography (PSMA/PET) CT. However, biochemical response to treatment was not assessed.

Written informed consent was obtained from patients, and the Local Ethics Committee of Istanbul Medipol University approved the study (Date: 26.10.2022, No: 904).

Statistical analysis

SPSS 24.0 (SPSS Inc., IBM Corp, ARMONK, NY, USA) software was used for all statistical analyses. Parameters were described with their median values, and due to non-normal distribution, nonparametric tests were used. PFS was defined as the allocation date of enzalutamide or abiraterone to the radiological progression date. Overall survival (OS) was defined as the time from CRPC diagnosis to the death or last seen date or loss to follow-up. Survival analysis and curves were performed using the Kaplan-Meier method and compared with the log-rank test. The multivariate COX regression analysis was performed to evaluate independent prognostic factors. Toxicity was defined according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests, and p values less than or equal to 0.05 were considered statistically significant.

RESULTS

The median age was 70 (range 40-85). The number of patients with ECOG PS of 0.1 and 2 was 29 (50.9%), 23 (40.4%) and 5 (8.8%), respectively. Most of the patients were Gleason grade 4 and 5 (25.5% and 56%). The number of patients who received docetaxel chemotherapy in the castration-sensitive setting was 27 (47.4%). Eight (14.0%) patients had visceral metastases, and 23 (40.4%) patients had isolated bone metastases. Abiraterone was preferred in 47.4% and enzalutamide in 52.6% of patients. Thirty-nine patients (68.4%) had oligo-progression and were treated with palliative radiotherapy, continued by the same antiandrogen therapy. The oligo-progressive metastatic sites were as follows: bone in 21 (52.3%), lymph node in 6 (15.3%) and visceral metastasis in 12 (30.9%) patients. SBRT-related grade 1-2 toxicity was observed in 35 (61.4%) patients. The most seen grade1/2 side effects were fatigue (21.0%), nausea (14.0%), skin irritation (7.0%) and thrombocytopenia (8.7%). Only one patient had grade 3 cytopenia after SBRT. Of the 57 patients, 32 had CR or PR (56.1%), 13 (22.8%) had SD, 12 had (20.1%) PD, and death occurred in 29 (50.9%) patients (Table 1). The rate of local control in irradiated sites were 85.9% (n=49).

Table 1: Patients and tumour characteristics

Characteristics	Number of patients
	n (%)
Median age (range)	70 (40-85)
Median PSA (before treatment)	7 (0.50-90.2)
Gleason grade grup	
2	3 (5.5)
3	7 (12.7)
4	14 (24.5)
5	31 (54.3)
Unknown	2 (3.0)
ECOG PS	
0	29 (50.9)
1	23 (40.4)
2	5 (8.8)
Pre-docetaxel treatment	27 (47.4)
Metastatic sites	
Visceral metastasis	8 (14.0)
Only bone metastatic disease	23 (40.4)
Multiple metastases	26 (45.6)
Choice of antiandrogen therapy	
Abiraterone	27 (47.4)
Enzalutamide	30 (52.6)
Metastasis-directed SBRT	
Present	39 (68.4)
Absent	21 (31.6)
Oligo-progressive metastatic site	
Bone	21 (53.8)
Lymph-node	6 (15.3)
Visceral	12 (30.9)
Toxicity related to SBRT	
Grade 1-2	35 (61.4)
Grade 3-4	1 (1.7)
Treatment response	
Complete/partial response	32 (56.1)
Stable disease	13 (22.8)
Progressive disease	12 (20.1)

PSA: Prostate-specific antigen, ECOG PS: Eastern Cooperative Oncology Group Performance status, SBRT: Stereotactic body radiotherapy

At a median follow-up of 19.2 months (range: 1.7-55.2 months), the median PFS was 12.8 months, and the median OS was 25.6 months in the total cohort. The median PFS in patients who received SBRT was 11.1 months, and the median OS was 25.7 months.

Twelve month PFS was 79.0% in the group that received SBRT, while it was 88.9% in the group that did not ($p<0.001$) (Figure 1). The oligometastatic site, Gleason

grade group (p=0.4), pre-docetaxel treatment (p=0.2), the choice of antiandrogen therapy (p=0.8), and ECOG PS (p=0.08) were not significantly associated with PFS. SBRT was also a significant independent risk factor for PFS (p=0.007, HR: 15.7; 95% CI 2.05-118.7) in multivariate analysis. Changing systemic treatment in the oligo-progression setting was significantly correlated with better PFS rates (Table 2).

The 24-month OS rate in patients treated with metastasis-directed SBRT was 85.9%, while the 24-month OS rate in patients whose systemic treatment changed without SBRT was 73.4% (Figure 2). Thus, metastasis-directed SBRT did not significantly affect OS in this study (p=0.2). The univariate analysis revealed that there was no significant correlation between OS and Gleason grade group (p=0.6), pre-docetaxel treatment (p=0.3), oligo-progression in bone, lymph node and visceral metastatic sites

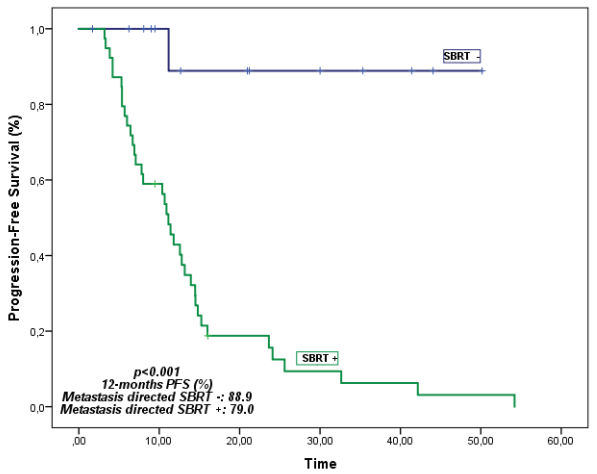

Figure 1: Progression-free survival in patients treated with metastasis-directed Stereotactic body radiotherapy

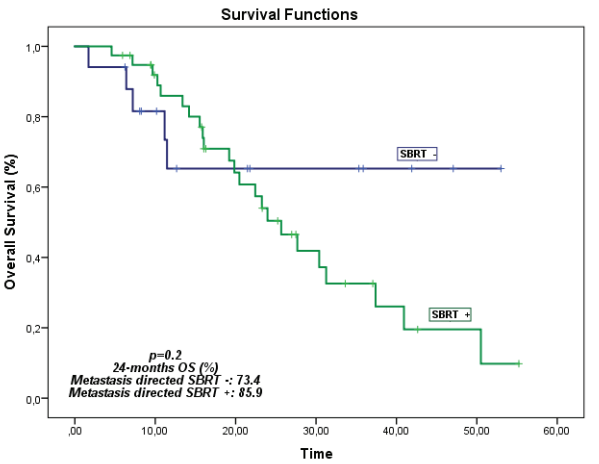

Figure 2: Overall survival in patients treated with metastasis-directed Stereotactic body radiotherapy

Table 2: The prognostic factors for PFS and OS

Factors	Progression-free survival		Overall survival	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	p	P (HR 95% CI)	P	P (HR 95% CI)
Gleason score (Risk group*) High/very high risk versus intermediate/low risk	0.4		0.6	
ECOG PS	0.08	0.6 (1.1; 0.70-1.77)	**0.04**	**0.03 (1.7; 1.05-2.75)**
Pre-docetaxel treatment	0.2	0.2 (0.6; 0.28-1.36)	0.3	
Site of oligo-progression				
Bone	0.2	0.3 (1.7; 0.55-5.18)	0.5	0.4 (0.6; 0.29-1.59)
Lymph-node	0.6		0.06	
Visceral	0.09		0.4	
Choice of enzalutamide or abiraterone	0.8		0.9	
Metastasis-Directed SBRT	**<0.001**	**0.007 (15.7; 2.05-118.7)**	0.2	0.6 (1.2; 0.41-3.93)

*Risk Groups are defined by the Grade Group of the cancer and other measures, including PSA, clinical tumour stage (T stage), PSA density, and number of positive biopsy cores,*CI: Confidence interval, *SBRT: Stereotactic body radiotherapy,* ECOG PS: Eastern Cooperative Oncology Group Performance Status

(p=0.5, p=0.06, p=0.4 respectively) and the choice of antiandrogen therapy (p=0.9). In multivariate analysis, ECOG PS was the only statistically significant factor on OS (p=0.03, HR:1.7; 95%CI 1.05-2.75).

DISCUSSION

Oligometastatic disease in CRPC is common, and the metastasis-directed SBRT ought to eradicate resistant clones and delay progression. There is no optimal consensus on the oligometastatic setting, and each decision has several risks and benefits. Several retrospective studies have shown the benefit of SBRT in oligometastatic settings in small cohorts. Thus, we aimed to contribute to the literature with our single-centre experience with SBRT in patients treated with abiraterone or enzalutamide in the first line of CRPC.

Berghen et al. examined 30 metastatic CRPC patients who experienced oligo-progression under any systemic treatment, including antiandrogen therapies. All patients received SBRT to the oligo-progressive lesions while ongoing systemic treatment was continued. The median time for next-line systemic treatment (NEST) was 16 months (95% CI: 10–22), and the median progression-free survival was ten months (95% CI 6–15) (15). Similarly, SBRT to all oligo-progressive lesions in 34 CRPC patients led to a median NEST-free survival of 16.9 months and a median PFS of 13.47 months in a retrospective study by Ingrosso et al. (16). Another study compared SBRT with a cohort of patients treated with a change in systemic treatment alone. SBRT was associated with favourable outcomes and improved cancer control (13). Despite these retrospective trials in our study, we could not demonstrate a significant benefit of SBRT. Moreover, SBRT was significantly related to worse PFS rates. A possible reason might be the inclusion of patients (47.4%) treated with docetaxel chemotherapy in metastatic castration-sensitive settings.

Sixty-two prostate cancer patients had a biochemical recurrence after primary curative intent treatment, had oligo-progression and had serum testosterone levels > 50 ng/mL. We were enrolled in a phase II trial. They compared active surveillance and metastasis-directed SBRT, which showed the survival benefit of SBRT (13 months (80% CI, 12 to 17 months) vs 21 months (80% CI, 14 to 29 months) respectively) (14). We found that 12-month PFS was 79.0% in the group that received SBRT, while it was 88.9% in the group that did not (p<0.001). These controversial results are related to the design of our study. We enrolled patients who had oligo-progression under first-line CRPC treatment; 12 of the patients (30.9%) had progression on visceral sites, and the majority of the patients were in Gleason grade groups 4 and 5 (25.5% and 56%).

Another study demonstrated the survival benefit of SBRT compared to treatment change in 30 patients with oligo-progression, mostly in bone (17). A multicentre retrospective study by Detti et al. demonstrated a median PFS of 9.6 months in an oligo-progression setting of metastatic CRPC patients treated with abiraterone (20). Another multicentre study by Triggiani et al. included 86 patients with bone or lymph node oligo-progressive lesions treated with SBRT and revealed that the median new metastasis-free survival was 12.3 months, with a majority of the patients receiving further SBRT (10). In our study, the median PFS in the SBRT group was 11.1 months, and the median OS was 25.6 months. The median PFS of our study was similar to these previous studies (10,17,19).

We acknowledge that the limitation of our study was the retrospective design and enrolling the high-risk featured patients, which may affect the results. And we should have analysed the progression after SBRT. Thus, we cannot comment on the additional benefit of SBRT over changing the systemic treatment. However, this study reflects real-world practice and highlights characteristics within a cohort of patients who oligo-progressed on antiandrogen therapy. We contribute to the literature by demonstrating that the high-risk featured metastatic CRPC patients who had oligo-progressed under antiandrogen therapy may not be eligible for metastasis-directed SBRT. Progression under enzalutamide or abiraterone may relate to systemic resistance; thus, next-line treatment would be the best option in these patients.

CONCLUSION

In our single-centre study, we could not demonstrate any survival benefit with metastasis-directed SBRT. Additionally, the PFS was poorer in the metastasis-directed SBRT group than in patients who received next-line systemic treatment. However, it is difficult to draw any conclusions due to this study's small number of patients. Metastasis-directed SBRT with continuing the same antiandrogen therapy should be prioritised only in selected cases.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Istanbul Medipol University (Date: 26.10.2022, No: 904).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.G.A., A.B.; Data Acquisition- A.A., E.K., Y.K., H.M.; Data Analysis/Interpretation- A.B., S.G.A.; Drafting Manuscript- S.G.A., Ö.A., D.Ü.; Critical Revision of Manuscript- A.B., Ö.F.Ö., Ö.Y.; Final Approval and Accountability- S.G.A., E.K., A.B., A.A., Ö.Y., H.M., Y.K., Ö.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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