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RADIOTHERAPY

Radiotherapy at oligoprogression for metastatic castration-resistant prostate cancer patients: a multi-institutional analysis

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Abstract

Purpose To retrospectively estimate the impact of radiotherapy as a progression-directed therapy (PDT) in oligoprogressive metastatic castration-resistant prostate cancer (mCRPC) patients under androgen receptor-target therapy (ARTT).

Materials and methods mCRPC patients are treated with PDT. End-points were time to next-line systemic treatment (NEST), radiological progression-free survival (r-PFS) and overall survival (OS). Toxicity was registered according to Common Terminology Criteria for Adverse Events v4.0. Survival analysis was performed using the Kaplan–Meier method; univariate and multivariate analyses were performed.

Results Fifty-seven patients were analyzed. The median follow-up after PDT was 25.2 months (interquartile, 17.1–44.5). One-year NEST-free survival, r-PFS and OS were 49.8%, 50.4% and 82.1%, respectively. At multivariate analysis, polymetastatic condition at diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC) (HR 2.82, $p = 0.004$) and PSA doubling time at diagnosis of mCRPC (HR 2.76, $p = 0.006$) were associated with NEST-free survival. The same variables were associated with r-PFS (HR 2.32, $p = 0.021$; HR 2.24, $p = 0.021$). One patient developed late grade ≥ 2 toxicity.

Conclusion Our study shows that radiotherapy in oligoprogressive mCRPC is safe, is effective and seems to prolong the efficacy of ARTT in patients who otherwise would have gone systemic treatment switch, positively affecting disease progression. Prospective trials are needed.

Keywords Metastatic castration-resistant prostate cancer · Oligoprogression · Androgen receptor-targeted therapy · Progression-directed therapy · Radiotherapy

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Introduction

Metastatic castration-resistant prostate cancer (mCRPC) represents a clinical scenario with disease progression below castrate threshold (serum testosterone < 50 ng/ml), due to the ADT-induced selection of castration-refractory clones. At this stage of disease, which is characterized by a median survival of approximately 35 months [1], patients often experience impaired quality of life mainly related to the occurrence of ingravescent pain and carry the burden of several lines of systemic therapy. Androgen receptor-targeted therapy (ARTT) is frequently used as first-line treatment in mCRPC; it has shown to be effective and generally well-tolerated [2] allowing its use in elderly patients, who are often unfit for chemotherapy. Many patients receiving ARTT undergo oligoprogression, consisting in the onset of new lesions in a limited number (generally less than 5) or in the volume increase of few existing lesions. In oligoprogressive mCRPC patients, some studies demonstrated that it can be clinically useful to adopt progression-directed therapeutic strategies, such as surgery or radiotherapy, in order to avoid the switch to a next-line systemic treatment (NEST) [3–5]. The aim of the present study is to estimate the impact of radiotherapy as a progression-directed therapy (PDT) in oligoprogressive mCRPC patients under ARTT.

Materials and methods

We retrospectively collected data from 57 patients affected by mCRPC. Inclusion criteria were: oligoprogression during treatment with androgen deprivation therapy (ADT) in combination with androgen receptor-targeted therapy (ARTT); testosterone level below 50 ng/ml; radiotherapy to all oligoprogressive lesions (SBRT as well as fractionated radiotherapy); Eastern Oncology Cooperative Group (ECOG) 0–1. Oligoprogression was defined as the onset of up to five metastases, including the radiological progression of existing lesions, in mCRPC patients receiving ADT in combination with ARTT. Radiotherapy intent was considered ablative when a dose ≥ 5 Gy per fraction to a biologically effective dose ≥ 80 Gy using a α/β ratio of 3 was delivered [6], otherwise the treatment was defined as palliative. All patients provided informed consent for this retrospective multi-institutional analysis, which includes mCRPC oligoprogressive patients treated with radiotherapy from December 2013 to March 2020.

Table 1 Patient (no. 57) and treatment features

Parameter	Result
At initial PCa diagnosis	
Median age, year (IQR)	66 (63–72)
Median PSA, ng/ml (IQR)	28 (13.2–48.3)
Risk class, n (%)	
Intermediate	9 (16)
High	38 (66.5)
Metastatic	8 (14)
Unknown	2 (3.5)
Local treatment* of the primary tumor, *n* (%)	47 (82.5)
ADT only, *n* (%)	10 (17.5)
Median time to mHSPC for patients with initial nmPC, months (IQR)	32 (15–74)
At mHSPC diagnosis	
Median age at diagnosis of mHSPC, year (IQR)	71 (66–76)
Imaging modality at diagnosis of mHSPC	
Choline-PET	49 (86)
PSMA-PET	2 (3.5)
Bone scan	2 (3.5)
CT + bone scan	3 (5.2)
CT	1 (1.8)
Median PSA at diagnosis of mHSPC, ng/ml (IQR)	3.1 (2.2–10.1)
Metastatic burden, n (%)	
Low	40 (70)
High	17 (30)
Therapy at mHSPC, n (%)	
ADT	53 (93)
Surgery	0 (0)
Ablative radiotherapy	26 (45.5)
Palliative radiotherapy	6 (10.5)
At mCRPC diagnosis	
Median time from mHSPC to mCRPC, months (IQR)	12 (1–29)
Median age, year (IQR)	72 (67–79)
Median PSA, ng/ml (IQR)	7 (3.5–11)
Median PSADT, months (IQR)	3 (2–5)
Imaging modality at diagnosis of mCRPC, n (%)	
Choline-PET	42 (73.5)
PSMA-PET	2 (3.5)
Bone scan	5 (9)
CT + bone scan	3 (5.2)
CT	4 (7)
MRI	1 (1.8)
Number of metastases, n (%)	
1–3	27 (52)
4–5	13 (23)
> 5	17 (30)
First-line systemic treatment, n (%)	
Abiraterone	49 (86)
Enzalutamide	8 (14)

*Local treatment: surgery, radiotherapy, ADT + radiotherapy. PCa: prostate cancer; IQR: interquartile; ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer

Hormone-sensitive disease

Patients' baseline clinical characteristics are summarized in Table 1. At the initial diagnosis, 38 (67%) patients were affected by high-risk localized prostate cancer, while 8 (14%) were metastatic. Forty-seven (82%) patients underwent local treatment for their primary tumor. At the diagnosis of metastatic hormone-sensitive prostate cancer (mHSPC), the median PSA was 3.1 ng/ml (interquartile [IQR], 2.2–10.1). Forty-nine (86%) patients were staged with choline-PET, and 2 (3.5%) with PSMA-PET. Forty (70%) had a diagnosis of oligometastatic disease (defined as ≤ 5 sites), whereas 17 (30%) were polymetastatic (> 5 sites and/or bone involvement beyond the vertebral bodies and pelvis). Fifty-three patients received ADT as treatment of choice, whereas four patients underwent exclusive SBRT.

Metastatic-CRPC disease

The median time from mHSPC to mCRPC was 12 months (IQR, 1–29). The median PSA doubling-time (PSADT) at the time of diagnosis of mCRPC was 3 months (IQR, 2–5). Choline-PET was used in 42 patients to define the mCRPC state. Regarding systemic therapy, 49 (86%) patients received treatment with abiraterone and 8 (14%) patients with enzalutamide. Metastatic CRPC oligoprogression during ARTT was detected with choline-PET in 41 (72%)

Table 2 Patient (no 57) and treatment features at mCRPC oligoprogression

Parameter	Result
Median time to mCRPC oligoprogression, months (IQR)	10.5 (6–17)
Imaging modality at mCRPC oligoprogression (%)	
Choline-PET	41 (71.8)
PSMA-PET	8 (14)
CT	5 (9)
CT + bone scan	3 (5.2)
Metastatic sites, n (%)	
Lymph node	8 (14)
Bone	40 (70)
Lymph node + bone	6 (10.5)
Lung	2 (3.5)
Lung + bone	1 (1.8)
Number of metastases, n (%)	
1–2	44 (77)
3–4	9 (16)
5–6	4 (7)
Radiotherapy intent at oligoprogression, n (%)	
Ablative	34 (60)
Palliative	23 (40)
Fractionation scheme, total dose in Gy (IQR); no of fractions (IQR)	
Ablative	30 (27–36); 3 (3–5)
Palliative	30 (20–30); 5 (5–10)
At the end of follow-up	
Median follow-up, mo (IQR)	25.2 (17.1–44.5)
Patients still in first-line systemic treatment, *n* (%)	20 (35)
Patients in second-line systemic treatment, *n* (%)	12 (21)
Patients dead of the disease	25 (44)
Median NEST-free survival, months (95% CI)	11.1 (5.2–27.9)
Median PFS, months (95% CI)	12.3 (5.2–23.5)
Median OS, months (95% CI)	30.4 (15.1–42)
Late toxicity related to radiotherapy, no (%)	
Grade < 2	56 (98.2)
Grade ≥ 2	1 (1.8)

mCRPC: metastatic castration-resistant prostate cancer; IQR: interquartile; NEST: Next Systemic Treatment; PFS: Progression-Free Survival; OS: overall survival

patients (Table 2) and involved mainly bones. After radiotherapy for mCRPC oligoprogressive disease, patients were scheduled for serial follow-up with PSA, testosterone and imaging every 3–6 months or at change in PSA dynamics. Biochemical progression after radiotherapy on oligoprogressive lesions was defined according to Prostate Cancer Working Group 3 (PCWG3) criteria [7].

Statistical analysis

Clinical end-points of this retrospective study were time to next-line systemic treatment (NEST), radiological progression-free survival (r-PFS) defined as any radiological progression (in-field and/or out-field) after radiotherapy to oligoprogressive lesions, and overall survival (OS). All end-points were calculated from the start date of radiotherapy. Toxicity was registered according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. We applied the Fisher's exact test to compare the distribution of categorical variables according to patients' outcomes. The Kaplan–Meier method and log-rank test were used for univariate survival analysis, and the Cox proportional hazards model, with time since start of the radiation treatment as the time variable, and backward elimination for the selection of the final model, for multivariable analysis. In some cases, the final regression model consisted of a model with a single variable included, whose HR and 95% CI therefore coincided with that of the univariate model (see "Results").

Results

Median time from the start of the first-line ARTT to oligoprogression was 10.5 months (IQR, 6–17). Most of the patients had ≤ 2 sites of oligoprogression. Radiotherapy was delivered to all progressive lesions; treatment intent was ablative in 34 patients, while it was palliative in 23. Regarding SBRT, the median total dose was 30 Gy (IQR, 27–36) in 3–5 fraction. For palliative intent, a median total dose of 30 Gy (IQR, 20–30) in 5–10 fractions was delivered to the target volume. Patient and treatment features are reported in Table 2. The median follow-up was 25.2 months (IQR 17.1–44.5). At the time of analysis, 20 patients were still in first-line ARTT, whereas 12 patients experienced a switch to a second-line systemic treatment; 25 patients were dead of disease. Median NEST-free survival, r-PFS and OS were 11.1 months (95% CI 5.2–27.9), 12.3 months (95% CI 5.2–23.5) and 30.4 months (95% CI 15.2–42), respectively (Fig. 1).

One- and 2-year NEST-free survival were 49.8% (95% CI 35.8–62.4) and 30.3% (95% CI 17.7–44), respectively (Fig. 1a). At univariate analysis (Table 3), the metastatic burden (oligo vs. polymetastatic) at diagnosis of mHSPC (HR 2.49, 95% CI 1.26–4.90, $p = 0.009$) and PSADT (≤ 3 vs. > 3 months) at diagnosis of mCRPC (HR 1.91, 95% CI 0.99–3.71, $p = 0.05$) affected NEST-free survival. Time interval from mHSPC to mCRPC longer than 12 months was also positively correlated with NEST-free survival (HR 1.97, 95% CI 1.02–3.80, $p = 0.042$). At multivariate analysis, the metastatic burden at mHSPC (HR 2.82, 95% CI 1.39–5.70, $p = 0.004$) and PSADT calculated at diagnosis of mCRPC (HR 2.76, 95% CI 1.34–5.66, $p = 0.006$) was independent variables correlated with NEST-free survival (Table 3).

Radiological-PFS at 1 and 2 years was 50.4% and 22.7% (Fig. 1b). Regarding the correlation of this end-point with all analyzed variables, the polymetastatic condition at diagnosis of mHSPC and PSADT ≤ 3 months at diagnosis of mCRPC was associated with worse r-PFS (Table 3).

One- and 2-year OS were 82.1% (95% CI 68.4–90.3) and 66.4% (95% CI 50.9–78.1), respectively (Fig. 1c). At univariate analysis, no variable affected OS (Table 3).

Eventually, patients treated with palliative RT or SBRT did not differ in terms of median NEST-free survival (p value 0.435), r-PFS (p value 0.689) and OS (p value 0.724).

Regarding late toxicity, only one patient developed a grade 2 late upper gastro-intestinal toxicity due to the irradiation of the cervical spine with Tomotherapy to a total dose of 20 Gy (5 × 4 Gy).

Discussion

In the present study, after high-dose radiotherapy to all oligoprogressive lesions, we obtained a median NEST-free survival of 11.1 months, significantly prolonging the effect of ARTT in patients who otherwise would have gone systemic treatment switch. At a median follow-up of 25.2 months, only one (1.7%) patient developed grade 2 toxicity after radiotherapy on oligoprogressive lesion on the cervical spine. Limited studies have evaluated the toxicity of radiotherapy in combination with ARTT [5, 8] reporting no adverse events leading to treatment suspension or discontinuation, and no grade ≥ 2 toxicity related to the combination of RT and drug. To date, few experiences have investigated the role of radiotherapy in the oligoprogressive mCRPC setting, reporting NEST-free survival values ranging from 4.8 to 16 months [3, 8]. Despite this wide interval reported, we can hypothesize that high-dose radiotherapy targeting oligoprogressive lesions might have a role in the management of these patients, destroying the tumor clones not sensitive to ARTT and allowing the continuation of the ongoing systemic therapy. Moreover, local treatment can not only reduce the metastatic load but can also disrupt the metastatic crosstalk, preventing further seeding [9, 10]. With high-dose radiotherapy, we obtained a median r-PFS of 12.3 months, which might be, from the clinical point of view, the direct

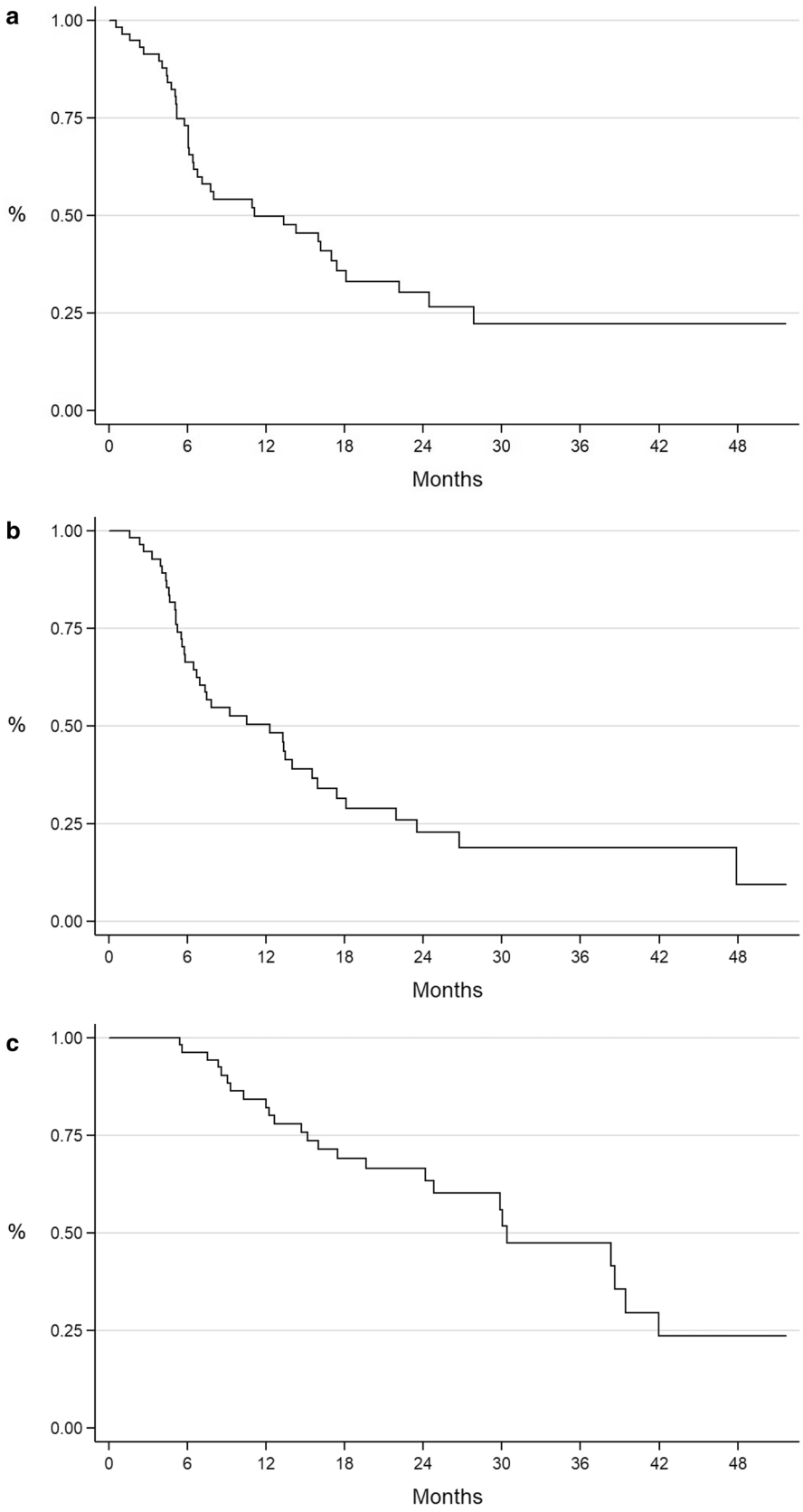

Fig. 1 **a** Next systemic treatment-free survival. **b** Radiological progression-free survival. **c** Overall survival

Table 3 Univariate and multivariate logistic regression analysis (57 pts)

Variable	NEST-free survival					r-PFS					OS				
	Log-rank test	Univariate Cox regression		Multivariate Cox regression		Log-rank test	Univariate Cox regression		Multivariate Cox regression		Log-rank test	Univariate Cox regression		Multivariate Cox regression	
	p value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Metastatic burden at mHSPC diagnosis (poly vs oligomet.)	0.007*	2.49 (1.26–4.90)	0.009*	2.82 (1.39–5.70)	0.004*	0.021*	2.23 (1.11–4.48)	0.024*	2.32 (1.13–4.74)	0.021*	0.222	1.66 (0.73–3.80)	0.226		
No of metastases at mHSPC diagnosis (> 3 vs. ≤ 3)	0.488	1.26 (0.65–2.44)	0.49			0.616	1.18 (0.62–2.26)	0.617			0.786	0.89 (0.39–2.03)	0.786		
No of metastases at mCRPC diagnosis (> 3 vs. ≤ 3)	0.103	1.74 (0.89–3.40)	0.107			0.427	1.30 (0.68–2.47)	0.429			0.535	1.29 (0.58–2.87)	0.536		
PSA [ng/ml] at mCRPC diagnosis (> 7 vs. ≤ 7)	0.293	0.70 (0.36–1.37)	0.297	0.5 (0.24–1.02)	0.056	0.319	0.72 (0.37–1.38)	0.322	0.55 (0.28–1.11)	0.096	0.764	1.13 (0.51–2.53)	0.764		
PSADT [months] at mCRPC diagnosis (≤ 3 vs. > 3)	0.050*	1.91 (0.99–3.71)	0.050*	2.76 (1.34–5.66)	0.006*	0.081	1.77 (0.92–3.40)	0.085	2.24 (1.13–4.44)	0.021*	0.705	1.17 (0.53–2.58)	0.705		

Table 3 (continued)

Variable	NEST-free survival					r-PFS					OS				
	Log-rank test	Univariate Cox regression		Multivariate Cox regression		Log-rank test	Univariate Cox regression		Multivariate Cox regression		Log-rank test	Univariate Cox regression		Multivariate Cox regression	
	p value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
No of sites at mCRPC oligoprogression (≥ 3 vs. < 3)	0.836	1.08 (0.52–2.25)	0.836			0.178	1.60 (0.80–3.18)	0.182			0.168	1.80 (0.77–4.18)	0.174		
Time [months] from localized to mHSPC (< 45 vs. ≥ 45)	0.548	1.22 (0.63–2.35)	0.549			0.247	1.46 (0.77–2.77)	0.250			0.839	1.09 (0.49–2.38)	0.839		
Time [months] from mHSPC to mCRPC (< 12 vs. ≥ 12)	0.038*	1.97 (1.02–3.80)	0.042*			0.105	1.68 (0.89–3.18)	0.108			0.075	2.08 (0.91–4.72)	0.081	2.08 (0.91–4.72)	0.081
Time [months] from mCRPC to oligoprogression (< 10 vs. ≥ 10)	0.555	1.21 (0.64–2.32)	0.556			0.947	0.99 (0.52–1.85)	0.947			0.568	0.79 (0.34–1.80)	0.569		

HR: Hazard Ratio; CI: Confidence Interval; NEST: Next Systemic Treatment; r-PFS: radiological Progression-Free Survival; OS: overall survival

*Significant value

consequence of the progression-directed therapy to ARTT-resistant clones. Data on PDT in this setting are emerging because, based on the results of many studies [11–14], there is great interest in integrating local therapies in the management of metastatic disease. For instance, in the setting of oligometastatic CRPC the ongoing phase II ARTO trial (NCT03449719) randomizes patients to upfront SBRT combined with first-line ARTT versus ARTT alone. Recently, long-term results of the SABR-COMET trial showed that adding ablative radiotherapy to standard-of-care systemic therapy in oligometastatic patients from different histologies has a significant impact not only on PFS but also on overall survival [13]. Regarding mCPRC patients, the few reports available in the literature on PDT during first-line treatment ARTT obtained a PFS of about 1 year [3, 4, 8]. In the study by Berghen et al. [3], 30 patients undergoing PDT (either SBRT or metastasectomy as well as fractionated radiotherapy) experienced a median PFS of 10 months (95% CI 6–15). Similar results were obtained by Deek et al. [4], who treated 68 mCRPC oligoprogressive patients with SBRT as a PDT, and the median PFS was 10.8 months (95% CI 7.5–13.6).

In our series, median OS after PDT was 30.4 months. At statistical analysis, none of the variables was associated with this end-point, whereas better NEST-free survival and r-PFS were associated with low metastatic burden at mHSPC and with PSADT > 3 months calculated at diagnosis of mCRPC. These results might suggest that patients affected by a more aggressive disease might not benefit from PDT continuing the current systemic therapy, and we could hypothesize that the combination of PDT and systemic treatment switch may be indicated.

Although our study has several limitations (retrospective design, low number of analyzed data) with only hypothesis generating results, it adds some interesting findings to the currently scarce available literature about oligoprogressive mCRPC.

Conclusions

Radiotherapy as a PDT seems to prolong the efficacy of current systemic therapy at oligoprogression. Patients affected by a more aggressive disease (i.e., polymetastatic state, PSADT < 3 months) should not continue the ongoing systemic therapy, and they could possibly benefit from the combination of PDT and a new systemic treatment. Prospective trials are needed.

Authors' contribution Valeriani, Detti, Lancia, Ingrosso, Francolini performed study concept and design. All authors done acquisition of data. Caini, Detti, Ingrosso, Lancia were involved in analysis and interpretation of data. Ingrosso, Detti, Caini, Francolini, Lancia, Valeriani drafted the manuscript. All authors done critical revision of the manuscript for important intellectual content. Caini, Ingrosso, Detti, Valeriani done statistical analysis. Fodor, Magrini, Livi, Musio, Osti, Filippi, Maranzano, Di Muzio, Aristei supervised the study. All authors have made a substantial contribution to research design, or the acquisition, analysis or interpretation of data. All authors have drafted the paper and revised it critically and have approved the submitted final version.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Ethical approval was waived by the local Ethics Committee of University of Perugia in view of the retrospective nature of the study and all the procedures being performed were part of routine care. The study was performed according to the Declaration of Helsinki, and written informed consent was obtained for all patients. Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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