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ORIGINAL ARTICLE

Metastasis-directed stereotactic radiotherapy for oligoprogressive castration-resistant prostate cancer: a multicenter study

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Abstract

Purpose Herein, we report the clinical outcomes of a multicenter study evaluating the role of SBRT in a cohort of patients affected by oligoprogressive castration-resistant prostate cancer (CRPC).

Materials and methods This is a retrospective multicenter observational study including eleven centers. Inclusion criteria of the current study were: (a) Karnofsky performance status > 80, (b) histologically proven diagnosis of PC, (c) 1–5 oligoprogressive metastases, defined as progressive disease at bone or nodes levels (detected by means of choline PET/CT or CT plus bone scan) during ADT, (d) serum testosterone level under 50 ng/ml during ADT, (e) controlled primary tumor, (f) patients treated with SBRT with a dose of at least 5 Gy per fraction to a biologically effective dose (BED) of at least 80 Gy using an alpha-to-beta ratio of 3 Gy, (g) at least 6 months of follow-up post-SBRT.

Results Eighty-six patients for a total of 117 lesions were treated with SBRT. The median follow-up was 30.7 months (range 4–91 months). The median new metastasis-free survival after SBRT was 12.3 months (95% CI 5.5–19.1 months). One- and two-year distant progression-free survival was 52.3% and 33.7%, respectively. Twenty-six out of 86 patients underwent a second course of SBRT due to further oligoprogressive disease: This resulted in a median systemic treatment-free survival of 21.8 months (95% CI 17.8–25.8 months). One-year systemic treatment-free survival was 72.1%.

Conclusion SBRT appears to be a promising approach in oligoprogressive castration-resistant prostate cancer. Further investigations are warranted.

Keywords Prostate cancer · SBRT · CRPC · Metastasis-directed therapy · Radiotherapy

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Introduction

The landscape of the therapeutic armamentarium in metastatic prostate cancer (PC) is rapidly evolving. Historically, androgen deprivation therapy (ADT) represented the first choice therapy in case of castration-naive PC, whereas docetaxel was administered for a long time as exclusive treatment option in case of metastatic castration-resistant PC (mCRPC) [1, 2]. Unfortunately, long-term effectiveness of the above-mentioned strategies remained unsatisfactory, influencing the natural history of the metastatic PC only with a palliative effect. Due to the disappointing results, the uro-oncologic community has made remarkable efforts to improve the oncologic outcomes in metastatic PC. In particular, the adoption of new molecules such as abiraterone, enzalutamide, cabazitaxel and radium-223 has further optimized the therapeutic algorithm, most of all in mCRPC [3–9]. Furthermore, several studies have explored the potential role of metastasis-directed therapy (MDT) by means of stereotactic body radiation therapy (SBRT) in case of limited tumor burden or oligometastatic disease [10–16]. PC patients with a limited number of metastatic foci have more favorable outcome comparing to PC patients affected by widespread dissemination of disease [17]. The rationale of MDT would be to destroy lethal cancer clones or to activate the immune system against resistant colones with the aim of modifying the natural history of oligometastatic PC, synergistically with the adoption of systemic therapies [16]. To date, the majority of the available studies have reported interesting data regarding MDT in oligorecurrent castration-sensitive PC. In this last clinical scenario, the potential usefulness of MTD is mainly related to the potential impact on: (1) delaying the administration of palliative hormonal therapies in case of oligorecurrent PC and (2) improving the new metastasis-free survival [10, 11]. In contrast, data are lacking regarding the influence of MDT in case of oligoprogressive CRPC.

The main aim of the study is to estimate the impact of SBRT on oligoprogressive CRPC in terms of distant progression-free survival and new systemic therapy-free survival after SBRT.

Materials and methods

Study design

This is a retrospective multicenter observational study including eleven centers. All patients signed a center-specific informed consent before undergoing SBRT. CRPC was defined according to the European Association of Urology guidelines [1].

Inclusion criteria of the current study were: (a) Karnofsky performance status ≥ 80, (b) histologically proven diagnosis of PC, (c) 1–5 oligoprogressive metastases, defined as progressive disease at bone (vertebral body or pelvis) or nodes levels (detected by means of choline PET/CT or CT plus bone scan) during ADT, (d) serum testosterone level under 50 ng/ml during ADT, (e) controlled primary tumor, (f) patients treated with SBRT with a dose of at least 5 Gy per fraction to a biologically effective dose (BED) of at least 80 Gy using an alpha-to-beta ratio of 3 Gy, (g) at least 6 months of follow-up post-SBRT.

Exclusion criteria were: use of new androgen receptor-targeted agents (such as abiraterone or enzalutamide) or chemotherapy before or during the SBRT course and visceral metastasis.

SBRT was delivered to each site of oligoprogressive metastatic disease.

The updated information of some patients included in the previous study [10] was analyzed in the current series.

SBRT procedures and follow-up

Patients underwent a CT-based SBRT planning with a 2–3 mm slice thickness in supine position. Gross tumor volume (GTV), defined by means of morphologic and/or metabolic diagnostic instruments, was equivalent to the clinical target volume (CTV). The planning target volume (PTV) was defined by CTV adding an isotropic 3–5 mm margin. Organs at risk were delineated depending on the tumor location. The prescribed total dose and RT techniques varied according to the policy of each center. Before each fraction, image-guided radiotherapy by means of cone-beam or megavolt CT was performed depending on the use of linear accelerator or tomotherapy.

After SBRT all patients were followed every 4 months with clinical evaluation and PSA. Choline PET/CT or CT scan plus bone scan was performed in case of symptomatic progression or new PSA rising after SBRT.

If further oligoprogression occurs after MTD, a second course of SBRT was generally proposed if less than of ≤ 3 new lesions were diagnosed, outside the previous irradiated field. In the remaining cases, a new systemic therapy was proposed.

Toxicity evaluation

All adverse events SBRT-related were scored according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) scale. Toxicities were prospectively registered by each center and retrospectively analyzed in the present study.

Statistical analysis

The primary endpoint was the distant progression-free survival after SBRT, defined as the interval between the first fraction of SBRT and the detection of a new metastasis outside the field of irradiation. Secondary endpoints were: (a) systemic therapy-free survival (STFS) was defined as the interval between the first fraction of SBRT and the administration of a systemic therapy or the last follow-up visit, if no systemic therapy was started after SBRT. Systemic therapy was administered in case of disease progression, according to the RECIST/PERCIST criteria, not amenable of a second course of SBRT; (b) local control (LC), defined as the absence of in-field recurrence; (c) SBRT-related toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) scale. Local progression or in-field progression was defined according to the RECIST and PERCIST criteria [18]. Systemic treatment-free survival was defined as the interval between the last SBRT fraction and the date of initiation of new systemic therapy or the last follow-up visit, if no systemic therapy was started after SBRT. Systemic therapy was administered in case of disease progression, according to the RECIST/PERCIST criteria, not amenable of a second course of SBRT.

Univariate analysis was performed to evaluate factors influencing outcome. Kaplan–Meier analysis was carried out for survival functions. The following variables were analyzed: Gleason Score at PC diagnosis (≥ 7 or < 7), PSA value at the time of oligoprogression, number of lesions (< 1 or ≥ 1), BED, site of metastasis (N or M1a/M1b), time to castrate resistance. The following variables were dichotomized at the median value: the PSA value at the time of oligoprogression, BED, time interval to castration resistance onset.

Statistical analysis was carried out by means of SPSS software (version 20.0, USA). A p value < 0.05 was considered statistically significant.

Results

Patients

According to the inclusion criteria of the current study, the clinical outcomes of 86 patients for 117 lesions underwent SBRT were here analyzed. At the time of the analysis, the median follow-up was 30.7 months (range 4–91 months). The median age of patients was 65 years (range 49–82 years). Median BED of SBRT schedule was 116 Gy (range 80–216 Gy). In case of nodal oligometastases the most adopted schedules were 7.5 Gy in six fractions and 6 Gy in six fractions. In case of bone metastases the schedule adopted was 8 Gy in three fractions. Baseline patient's characteristics are detailed in Table 1.

Before SBRT, new metastases were detected by means of choline PET/CT in 77 patients (89.5%), whereas CT scan plus bone scan was used in the remaining patients. Fifty-eight patients (67%) underwent SBRT for nodal relapses, while 28 patients (33%) for bone lesions. For patients with lymph nodes, 38 patients of them (65%) were treated with SBRT on a single lymph node, 13 patients (22%) on two lymph nodes and 6 patients on three nodes (10%). More than three lymph nodes were simultaneously treated with SBRT only on a single case (3%). In case of bone metastases, 23 patients (82%) were treated with SBRT on a single bone lesion, 2 patients (7%) on two bone metastases, 2 patients (7%) on three bone metastases. More than three bone lesions

Table 1 Baseline patient's characteristics

Clinical characteristics: oligoprogressive mCRCP	Value
Number of patients	86
Age, median	65 (43–81)
GS at diagnosis	
6	8 (10%)
7	32 (37%)
8	20 (23%)
9	25 (29%)
10	1 (1%)
Risk class	
Very low and low	8 (9%)
Intermediate favorable and unfavorable	7 (8%)
High, very high and node positive	71 (83%)
Treatments at diagnosis	
Surgery	17 (20%)
Radiotherapy ± hormone therapy	17 (20%)
Brachytherapy	2 (2%)
Surgery plus adjuvant radiotherapy	16 (19%)
Surgery plus salvage radiotherapy	27 (31%)
Hormonal therapy	7 (8%)
PSA at oligoprogression (pre-SBRT) median	3.5 ng/ml (2.4–9.77)
Restaging	
Choline PET/CT	77 (90%)
CT/bone scan	9 (10%)
Number of lesions treated (for first SBRT course)	
1	60 (70%)
≥ 2	26 (30%)
BED ($\alpha/\beta = 3$ Gy)	
≤ 100	24 (28%)
> 100	62 (72%)
TNM classification of lesions treated	
N (regional metastasis)	36 (42%)
Distant metastasis node or bone (M1a M1b)	50 (58%)

were simultaneously treated with SBRT only in a single case (3%). In 26 patients (30%), a second course of SBRT was adopted for further oligoprogressive disease after SBRT.

Clinical outcomes

At the time of the analysis, the median new metastasis-free survival after SBRT was 12.3 months (95% CI 5.5–19.1 months). One- and two-year distant progression-free survival was 52.3% and 33.7%, respectively. Twenty-six out of 86 patients (11 treated on bone lesions and 15 treated on nodal disease) underwent a second course of SBRT due to further oligoprogressive disease (for a total of 33 lesions in 26 patients, 20 nodal lesions and 13 bone metastasis): This resulted in a median systemic treatment-free survival of 21.8 months (95% CI 17.8–25.8 months). One-year systemic treatment-free survival was 72.1%. At the time of the analysis, the LC was equal 80%.

At statistical analysis, the value of PSA at diagnosis and the initial T-stage did not influence outcomes. In the current population of study, PSA value at the oligoprogression is not available for all the patients, whereas the site of metastases did not influence the efficacy of SBRT (i.e., in-field response). Kaplan–Meier curves concerning the distant progression-free survival (a) and systemic treatment-free survival (b) are shown in Fig. 1.

Acute toxicity was registered as follows: Two patients reported G1 intestinal toxicity and one patient suffered from G2 genitourinary toxicity. Late toxicity resulted as follows: One patient experienced G1 intestinal toxicity and one patient G2 genitourinary toxicity. At the time of the analysis, no cases of fracture or chronic pain were recorded.

At the univariate statistical analysis, the total radiation dose delivered (estimated by means of BED) were significantly related to a higher systemic treatment-free survival. In Table 2, the results by the univariate analysis are detailed.

In case of multi-sites disease progression post-SBRT, the following systemic therapies were adopted: androgen receptor-targeted agents (ARTA) for 33 patients (38.4%), chemotherapy for 11 patients (12.8%) and hormonal manipulation for 19 patients (22.1%).

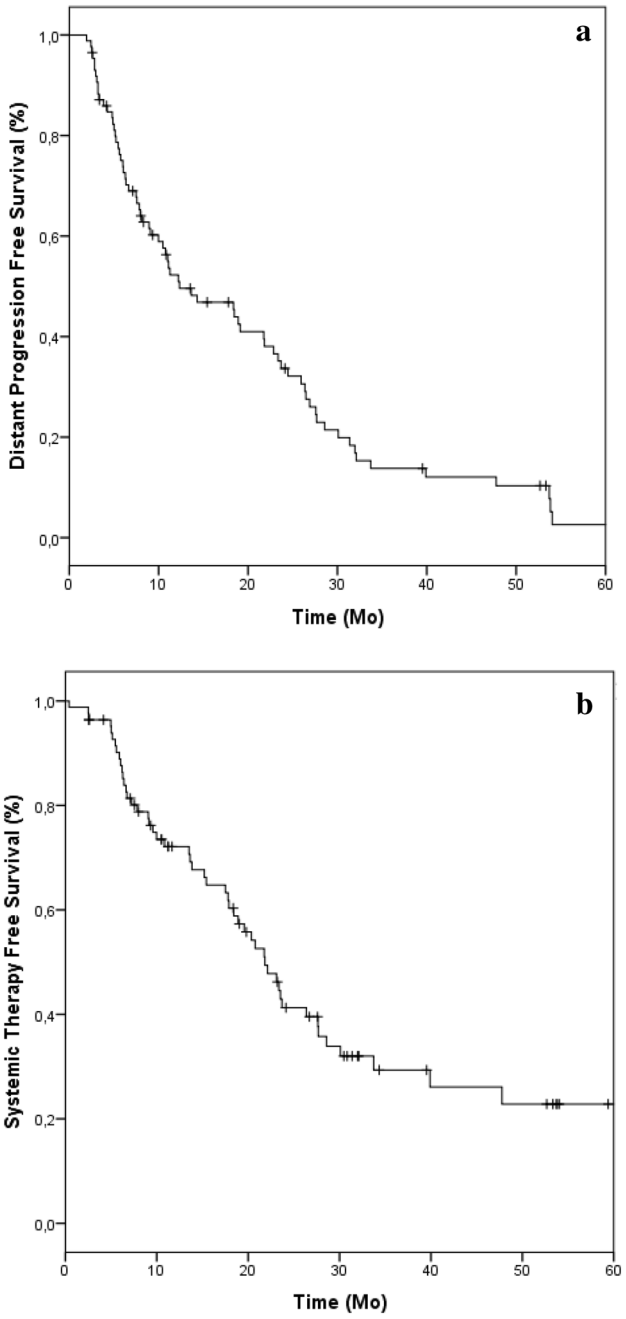

Fig. 1 Distant progression-free survival (**a**) and systemic treatment-free survival (**b**) curves

Discussion

The natural history of metastatic PC is well known: The clinical benefit of systemic therapy is generally limited to 2–3 years starting from the diagnosis of the castration-sensitive phase. Subsequently, the selective pressure of castration-resistant cellular clones does establish the so-called CRPC status that is no more responsive to ADT alone [19]. In some cases, the evolution of metastatic PC seems to be more indolent with time. Indeed, it is well established that patients with a low-volume metastatic disease or oligometastatic PC have a better prognosis [17]. As a rule, clinicians are used to recognize at least two different patterns of oligometastatic PC patients: (i) the oligorecurrent disease, defined as the appearance of metastases following biochemical relapse in castration-naive PC, and (ii) the oligoprogressive disease, defined as a metastatic progression detected after a PSA rise during ADT in which PC cells became castration-resistant [11–13]. Recently,

Table 2 Findings by the univariate analysis

	Median DPFS (months)	1-year DPFS	2-year DPFS	3-year DPFS	Median STFS (months)	1-year STFS	2-year STFS	3-year STFS
Whole population	12.3	53.3%	33.7%	13.8%	21.8	72.1%	38.5%	21.1%
Initial GS	$p=0.53$				$p=0.065$			
≤7	19	36%	25.2%	18%	15.2	59.2%	32.1%	26.7%
>7	21	63.3%	39.4%	8.5%	28	84.1%	54.0%	39.0%
PSA at SBRT	$p=0.6$				$p=0.7$			
≤3.5	13.6	43,8%	29.2%	7.3%	23.1	73%	48.8%	27.4%
>3.5	12	52.7%	34.2%	14.4%	19.9	67.6%	35.3%	26.5%
Time to castrate resistance (months)	$p=0.8$				$p=0.39$			
≤42	21.7	60.8%	35,9%	7.2%	20.7	74.2%	33.1%	11.0%
>42	11	44.2%	31.1%	15.1%	28.5	70.2%	32.7%	32%
Site of metastasis (TNM)	$p=0.5$				$p=0.2$			
N	14.3	51.3%	31.7%	7.7%	23.7	75.6%	54%	32.4%
M	12.3	50.7%	34.7%	9.9%	18.9	66.8%	36%	21.7%
Number of lesions	$p=0.55$				$p=0.098$			
1	12	51.5%	36.7%	13.8%	23.1	75.8%	43.3%	32.8%
≥2	13.6	57.4%	24.3%	9.7%	15.3	67%	37.7%	17.9%
BED	$p=0.41$				$p=0.004$			
≤100	10.5	39.5%	35.1%	10%	11.7	44%	17.6%	8.8%
>100	18.3	55.8%	33.2%	15.5%	23.7	77.3%	49.5%	43.3%

there have been several landmark studies on the use of SBRT for oligometastatic castration-sensitive prostate cancer, including the STAMPEDE trial, HORRAD trial and the SABR COMET trial that will be changing practice, in the next future, concerning the use of radiotherapy for prostate cancer patients [20–22].

In many cases, clinicians are frequently motivated to adopt a local approach in the so-called oligometastatic PC patients, for a better management of the available drug administration in metastatic PC setting. Of note, MDT lacks to demonstrate a potential advantage in terms of overall survival, whereas it seems likely a potential impact regarding the metastasis-free survival and systemic treatment-free survival [10, 11]. Thus, speculatively, MDT could be considered equivalent to a metastasis-directed molecule to add in the therapeutic algorithm of metastatic PC patients.

In a meta-analysis focused on the role of SBRT in ADT-naive PC [11], approximately half of the patients were metastasis-free 1–3 years after MDT. Conversely, in the specific setting of CRPC, the available published experiences are more limited. In a previous study by Triggiani and colleagues [10], 41 CRPC patients affected by oligometastases were treated with SBRT instead of a "standard" second-line therapy for CRPC phase (such as docetaxel, abiraterone enzalutamide or radium-223). The median distant progression-free survival (DPFS) was 11 months after SBRT with 1- and 2-year DPFS of 43.2% and 21.6%, respectively. Interestingly, during that interval it was not necessary to start a second-line systemic therapy.

Based on that background, we conducted a large-scale retrospective multicenter trial with the aim of investigating the impact of SBRT on the oligoprogressive CRPC setting. So far, to the best of our knowledge, the present study reports the largest mCRPC population witch underwent SBRT.

The median distant progression-free survival after SBRT was 12.3 months (95% CI 5.5–19.1 months). Interestingly, 26 out of 86 patients (30%) were found to be again oligoprogressive after SBRT and, thus, amenable of a new course of SBRT. This strategy allowed delaying considerably the systemic treatment. Specifically, the median systemic treatment-free survival after SBRT was 21.8 months (95% CI 17.8–25.8 months). In the present study, an association between BED and systemic treatment-free survival was found. To date, BED is considered a predictive parameter of SBRT effectiveness in several settings. In the last years, the role of SBRT in case of oligometastases was upgraded as able to modify the natural history of the diseases [23]. Metastasis evolution and the propensity to spawn metastatic cascades are subject to variability between patients, disease histology and intrinsic tumor biology. Concerning the therapeutic impact of SBRT, it is known that the ablation of metastases progenitors could potentially halt the emergence of polymetastatic disease. Probably, in case of castration-resistant prostate

cancer, MDT might prevent the development of new metastatic lesions due to the ablation of resistant clones. Obviously, the ablation of all metastatic deposits depends on BED delivery [24].

Biochemical control was not evaluated in the present analysis. The significance of biochemical control has not been well elucidated in metastatic CRPC patients, and furthermore, there is no general definition of biochemical control in this last setting of disease. For these reasons, distant progression-free survival seems to be a more useful endpoint which is easier to define, e.g., appearance of new metastatic lesions on imaging. In a panel of expert, it was stressed that such treatments should not be stopped or evaluate for PSA progression/control alone in CRPC [1].

In a previous experience by Ost and colleagues [25], it was documented that, in some cases, the pattern of failure after SBRT for nodal oligometastatic castration-naive PC was again in an oligometastatic manner, potentially amenable to a new course of local therapy. This last behavior was here observed even in the setting of CRPC, in around 30% of the study population. This finding confirms that oligometastatic PC patients represent a heterogeneous cancer population in which unknown biological factors could play a relevant role in the distant spread of disease. Likely, some patients with an aggressive phenotype could benefit of drug treatment only, while other patients with indolent distant progression could receive SBRT alone with mild-term satisfactory results and some other patients could optimize long-term disease control by means of upfront SBRT plus drugs. Much research source has to be made to identify each group of patients and, thus, to optimize the application of *precision medicine* to this clinical scenario.

Obviously, the present study has some methodological limitations, such as: (1) the retrospective nature; (2) the possible heterogeneities of the population analyzed, due to the multicenter retrospective design; (3) the inherent selection bias and (4) the lack of a control arm. Moreover, the absence of a treatment and dose standard protocol could probably affect the quality of results. Anyway, among the inclusion criteria there were patients treated with SBRT with a dose of at least 5 Gy per fraction to a BED of at least 80 Gy using an alpha-to-beta ratio of 3 Gy.

In the present study, new metastases were detected by means of choline PET/CT in 77 patients (89.5%), whereas CT scan plus bone scan was used in the remaining patients. These last diagnostic imaging techniques have different sensibilities and specificities that could affect the results because of misdetection [26, 27]. However, the results here reported suggest that further studies with a more robust methodological design are strongly advocated.

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Compliance with ethical standards

Conflict of interest No potential conflict of interest relevant to this article was reported.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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