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Stereotactic ablative radiotherapy for oligometastatic prostate cancer

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ABSTRACT

Background: The present study assessed clinical outcomes of stereotactic body radiotherapy (SBRT) in oligometastatic prostate cancer patients.

Materials and methods: Between 2017 and 2020, 37 lesions (12 osseous and 25 nodal targets) detected with conventional and/or functional imaging, were treated in 29 patients (pts), in different clinical settings: de novo oligometastatic (2 pts), oligorecurrent castration-sensitive (19 pts), castration-resistant (6 pts) prostate cancers and oligoprogressive disease during systemic therapy (2 pts). SBRT was delivered with volumetric modulated arc therapy up to a total dose of 21 Gy given in 3 fractions for bone and 30 Gy in 5 fractions for nodal metastases. A total of 34% of pts received hormonal therapy. We evaluated biochemical control [prostate serum antigen (PSA) increase < 10%)], progression free-survival (PFS) (time from SBRT to biochemical progression), local control (LC) (time from SBRT to in-field radiologic progression), hormone/systemic therapy-free survival, acute and late toxicities.

Results: At 3 months, biochemical response was observed in 20/29 pts (69%). At a median follow-up of 17 months (range 6-33), 8/20 (40%) of the 3-month responders remained free from progression. Two-year PFS and LC were 37% and 70%, respectively. In-field progression occurred in 3/37 (8%) lesions. Hormone/systemic therapy was delayed by an average of 11.6 months (range 3–28). No significant difference in PFS based on the type of lesion or concomitant endocrine therapy was observed and no toxicity > grade 2 was reported.

Conclusions: SBRT for oligometastatic prostate cancer offers a good biochemical/local control and tangible delay of hormone/systemic therapy without major toxicities.

Key words: prostate cancer; stereotactic radiotherapy; oligometastasis; lymph node metastases; bone metastases

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Introduction

Around 20% of prostate cancer patients bears metastasis at diagnosis [1]. Oligometastatic cancer was originally proposed by Hellman and Weichselbaum as an intermediate state between localized and disseminated disease and represents a current topic of research [2]. In 2015, the Advanced Prostate Cancer Consensus Conference of St. Gallen (APCCC) suggested ≤ 3 synchronous metastases involving bone and /or lymph nodes as a definition for oligometastatic prostate cancer [3]. In 2017, the same

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APCCC introduced further parameters to better define the concept of oligometastatic disease: number and location of lesions, presence of sensitive or castration-resistant disease, synchronous or metachronous metastases, imaging modalities used for assessment [4]. Indeed, a broad spectrum of conditions may converge into oligometastatic prostate cancer, including situations that may differ in terms of biology, treatment implications and prognosis [5]. The number of oligometastatic prostate cancers recently increased due to the use of new PET tracers, and longer patient survival thanks to refined treatment strategies [6]. Treatment options for metastatic prostate cancer have changed significantly, with the optimization of chemo-hormonal therapy and the introduction of metastasis-directed approaches. A survival advantage by combining ADT with docetaxel in patients with high burden of disease has been shown [7–9]. The use of abiraterone in combination with ADT leads to an advantage over ADT alone even in patients with low disease burden [10, 11]. The adoption of metastasis-directed stereotactic body radiation therapy (SBRT) provides local disease control and takes advantage of radiobiological considerations [12, 13]. Several studies evaluated the clinical results of targeted radiotherapy in the treatment of lymph node and bone metastases, but long-term outcomes are still pending [14–20]. The purpose of the study was to assess biochemical progression-free survival (PFS), local control (LC), hormone/systemic therapy-free survival and toxicity in a prospective cohort of oligometastatic prostate cancer patients to the bone and lymph nodes, treated with SBRT at a tertiary university hospital.

Materials and methods

Patients' population

Clinical records of oligometastatic prostate cancer patients with lymph node or bone metastases treated with SBRT at the Department of Radiation Oncology of the University Hospital "Maggiore della Carità" in Novara, Italy, were retrieved and analysed.

Patients included refer to four clinical scenarios:

- de novo oligometastatic cancer;
- oligorecurrent castration-sensitive;
- castration-resistant after primary treatment diseases;
- oligoprogressive disease under systemic therapy.

Oligometastatic state was assessed with morphological and functional imaging: computed tomography (CT), magnetic resonance (MRI), positron emission tomography (PET) with either ^{11}C-choline or ^{68}Ga-prostate specific membrane antigen (PSMA) as tracers. Patients receiving hormonal therapy at the time of SBRT we also included. For each patient, age, Karnofsky performance status (KPS), Gleason Score (GS), prostate specific antigen (PSA) baseline level, risk class according to National Comprehensive Cancer Network (NCCN), classification and type of primary treatment were recorded. All patients were discussed within a multidisciplinary tumor board. The institutional review board approved the study and a written patients' informed consent was obtained in all cases.

Treatment

All patients were imaged with a 1-mm slice thickness CT-simulation, taken in supine position. Gross tumour volume (GTV) and clinical target volume (CTV) were defined co-registering the simulation CT with pre-treatment images (PET or MRI). A 3-mm isotropic margin was then generated to create the corresponding planning target volume (PTV). Different organs at risk (OARs) were outlined depending on the treated site. The dose volume constraints of Benedict et al. were used [21]. Treatment plans were computed on Raystation (RaySearch Laboratories, Stockholm, Sweden). SBRT was delivered with a flattening filter free, 6 MV photon volumetric modulated arc therapy (VMAT). Dose prescription was 21 Gy in 3 fractions for bone and of 30 Gy in 5 fractions for lymph node metastases. The accuracy of target localization was assessed on a daily basis with Cone-Beam CT. Real time monitoring of the patient surface position with the AlignRT system (VisionRT, London, United Kingdom) was performed.

Data collection and response assessment

After SBRT, PSA was evaluated every 3 months. Biochemical complete response was defined as a reduction of pre-SBRT PSA > 50%; partial response as a reduction ranging between 10-50%; progression disease as an increase > 10%. Stable disease was defined as PSA differences between ± 10% compared to baseline values. In case of biochemical progression, a radiological assessment was performed. Le-

sions were therefore classified according to the European Organization for Research and Treatment of Cancer Response Evaluation Criteria in Solid Tumors (EORTC-RECIST version 1.1). Metabolic response was defined according to PET Response Criteria in Solid Tumors (PERCIST) [22].

The study end points were:

- progression free survival (PFS), defined as the time from SBRT to the onset of biochemical progression;
- local control (LC), defined as the time from SBRT to the onset of detectable relapse in the treated volume;
- hormone/systemic therapy-free survival, calculated as the time from SBRT treatment to the start of androgen deprivation therapy (ADT) or systemic therapy;
- acute and late toxicity, assessed according to the Radiation Therapy Oncology Group (RTOG) scale [21].

Statistical analysis

Numerical data were presented with median values ± standard deviation (SD), while qualitative variables with percentage values. Frequency distribution was used to evaluate changes in PSA values during time. Wilcoxon's non-parametric method was used to compare paired data. The significance level was set at 5% ($p < 0.05$). Kaplan-Meier methods were used to determine PFS and actuarial LC. Log-rank test was used to compare survival distributions.

Results

The study cohort consists of a series of 37 metastases in 29 patients with oligometastatic prostate cancer with ≤ 3 bone (12 lesions) and/or pelvic or abdominal lymph node (25 lesion) metastases, treated with SBRT. Overall, 2 patients (7%) had de novo oligometastatic prostate cancer with bone lesions; 19 (65%) oligorecurrent castration-sensitive disease; 6 (21%) oligorecurrent castration-resistant cancer; 2 (7%) oligoprogressive disease during systemic therapy. Twenty-eight (96%) patients were treated on the primary tumour with radical surgery and one patient was treated with radical radiotherapy associated with ADT. Six patients (21%) received adjuvant or salvage radiotherapy to the tumour bed and pelvic lymph nodes after primary treatment. At the time of diagnosis, median age was 70.2 years (± 7.1) and median PSA level was 23.2 ng/mL (± 26.6). Excluding the two oligometastatic patients at diagnosis, the mean time between primary treatment and the onset of metastasis was 111.5 months (± 3.9). Median pre-SBRT PSA was 6.8 ng/mL (± 15.9). Patient characteristics are listed in Table 1.

Most of patients (62%) underwent PSMA-PET before SBRT. Nineteen patients (66%) were treated for pelvic or abdominal lymph node metastases, while 10 (34%) for bone metastases. In five patients (17%), two metastases were treated synchronously with SBRT; 3 patients (10%) developed additional metastases during the follow-up period and were treated metachronously on the new lesions with SBRT. In 10/29 (35%) patients, SBRT was delivered concurrent to hormonal therapy. Lesions and treatments characteristics are listed in Table 2.

Table 1. Patients characteristics

Characteristics	N	%/SD
Median age (years)	70.2	7.1
KPS		
80	1	3
90	19	66
100	9	31
GS		
< 8	13	45
≥ 8	16	55
Median PSA at diagnosis	23.2	26.6
Risk class		
Intermediate	5	17
High	24	83
Primary treatment		
Surgery	1	3
RT ± HT	28	97
Clinical scenario		
Oligometastatic at diagnosis	2	7
Oligometastatic HT-sensitive	19	65
Oligometastatic HT-resistant	6	21
Oligorecurrent during CT	2	7
Concomitant HT		
No	19	65
Yes	10	35
Median pre-SBRT PSA	6.8	15.9
Median time of onset of metastases	115.5	3.9

N — number; SD — standard deviation; KPS — Karnofsky performance status; GS — Gleason score; RT — radiotherapy; HT — hormone therapy; SBRT — stereotactic body radiotherapy; PSA — prostate specific antigen

Table 2. Lesions and treatments characteristics

Characteristics	N	%
Type of lesion		
Bone	12	32
Lymph node	25	68
Number of metastases		
Single	30	81
Multiple	7	19
Timing of onset		
Synchronous	4	11
Metachronous	3	8
Single lesion	30	81
Imaging		
CT	1	3
MRI	3	8
PET-choline	10	27
PET-PSMA	23	62
RT dose		
30 Gy 6 Gy/fr (lymph node)	12	32
21 Gy 7 Gy/fr (bone)	25	68

N — number; CT — computed tomography; MRI — magnetic resonance; PET — positron emission tomography; RT — radiotherapy

Median follow-up of the whole series was 21 months (range 3–33 months). At 3 months after SBRT, complete biochemical response was observed in 12/29 patients (41%), partial response in 8 (28%), and progressive disease in 9 patients (31%). The difference between median PSA level before SBRT and at first assessment after treatment was statistically significant ($p < 0.05$) (Supplementary File — Fig. S1). At a median follow-up of 17 months (range 6–33), 8/20 (40%) of the patients who had a biochemical response at 3 months (either partial or complete) remained free from progression. Six of these patients (1 castration resistant and 5 castration sensitive disease) had persistent remission without the need for hormone or systemic therapy. Patients in partial biochemical response at 3 months developed biochemical progression after a median time of 11.0 months (± 3.9). The PSA trend in the first year of follow-up is shown in Supplementary File — Figure S2. Progression free survival (PFS) at 6, 12, and 24 months were 60%, 40%, and 38%, respectively (Supplementary File — Fig. S3).

The difference in PFS between patients with pre-SBRT PSA above or below 1 ng/mL was statistically significant (Fig. 1). No significant difference in PFS depending on the type of lesion (bone versus lymph nodes), number of lesions (single versus multiple) or administration of concomitant hormone therapy was observed (Supplementary File — Fig. S4).

In 25 (68%) cases of biochemical progression, radiological re-evaluation was performed: complete or partial responses, disease stability or progression of the treated lesion was respectively recorded in 9 (36%), 10 (40%), 3 (12%), 3 (12%) cases. In 15 patients with biochemical progression, imaging revealed stability or partial response of the treated lesions, but disease progression outside the treated volumes. Three (20%) of these lesions were suitable to further SBRT.

Overall, in-field progression occurred in 3/37 (8%) lesions after a median time of 7.3 months (± 3.8). Out-of-field progression was recorded in 13 (35%) lesions after a median time of 8.8 months (± 5.4). None of the lymph node metastasis developed in field progression.

Local control (LC) at 6, 12 and 24 months was 85%, 73% and 70%, respectively (Fig. 2).

Four out of six oligo-recurrent castration-resistant patients started systemic therapy after a median time of 6.6 months (± 3.0), while 8/19 oligo-recurrent castration-sensitive patients started hormonal therapy after a median time of 9.4 months (± 6.7). Globally, androgen deprivation therapy or systemic therapy in oligo-recurrent patients was delayed by an average of 11.6 months (range 3.0-28.0) after SBRT.

No patient developed genitourinary, gastrointestinal, hematological or bone acute or late toxicity ≥ grade 2.

Discussion

Oligometastatic prostate cancer represents a challenging clinical scenario, due to its heterogeneity in terms of disease definition, radiological assessment, treatment options and clinical endpoints. Given the lack of prospective studies comparing different treatment approaches, the proper management remains uncertain. We analyzed the clinical impact of SBRT in patients affected with oligometastatic prostate cancer. Two-year PFS rate was 38%, in agreement with previous reports [24]. In our study, 6/19 patients treated with exclusive SBRT achieved persistent disease control with no need for systemic therapies. This is in line

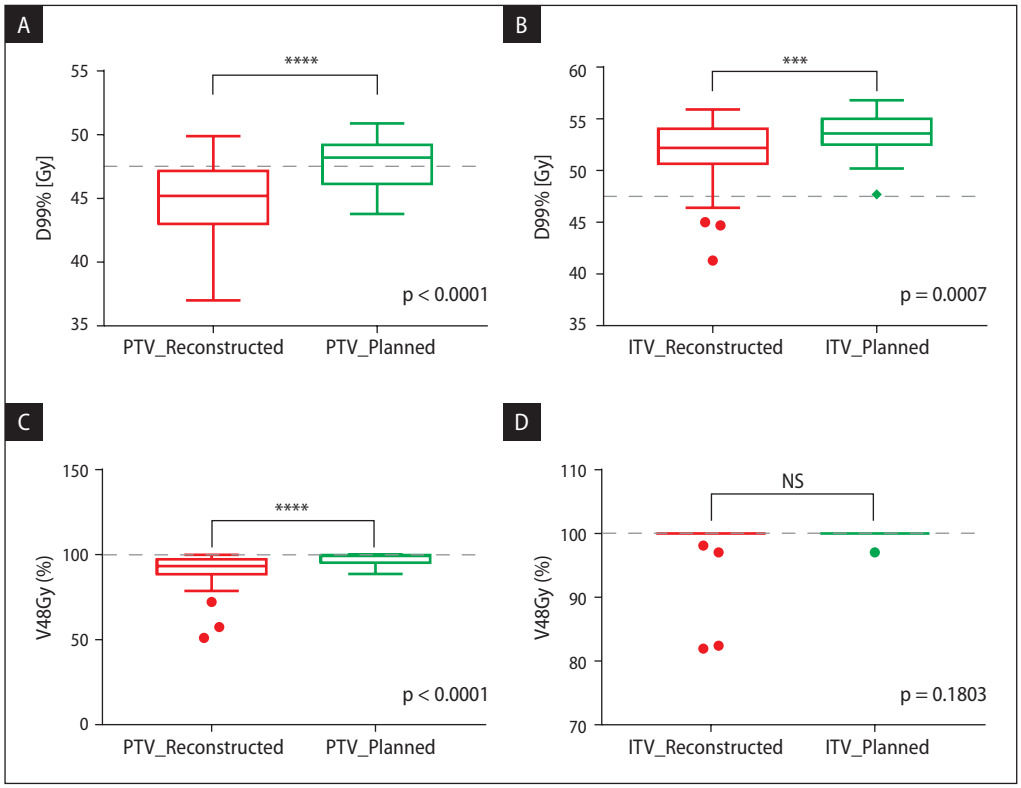

Figure 1. Difference in progression free survival profression free survival (PFS) between patients with prostate-specific antigen (PSA) before stereotactic body radiotherapy (pre-SBRT) > or < of 1 ng/mL ($p < 0.05$). PTV — planning target volume; ITV — internal target volume

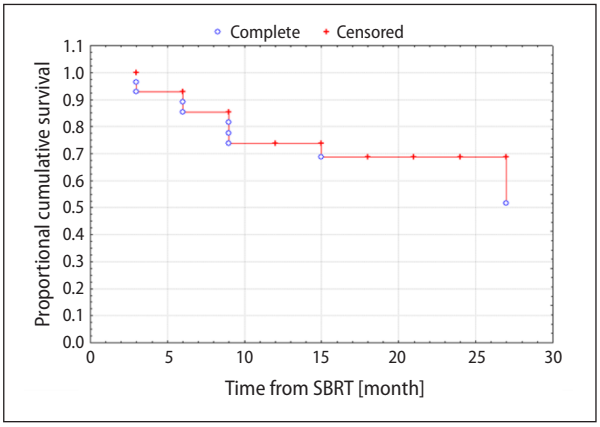

Figure 2. Local control (LC) of the treated lesions

with available literature data on metastasis-directed therapy with SBRT, showing high local control rate and a detectable proportion of patients having no progressive disease after 2 years [25]. However, the role of ADT in association with SBRT in this setting is still debated, since Authors showed no impact on PFS, nor on delay of systemic therapies [6, 24]. Accordingly, no significant difference in PFS was observed in our study, with the administration of concomitant hormone therapy. However, this finding should be carefully evaluated considering the current knowledge on metastatic castration-responsive prostate cancer, where the addition of ADT to other systemic strategies provided an improvement in OS [7, 8, 10, 26].

Half of the patients enrolled in our study experienced biochemical progression of disease [27]. At restaging, metastatic lesions amenable to further SBRT were found in 3 patients. Average time to appearance of new metastatic lesions resulted in around 9 months, similarly to other reports [6].

Local control rate at 1 year was 73%, in agreement with other studies [28-30]. We observed 3 cases (8%) of in field progression, as in Jereczek-Fossa et al [24]. These patients had castration-resistant disease with bone metastases. This may suggest an unfavorable prognostic feature for prostate cancer with bone metastasis compared to nodal lesions, as pointed out in the most recent APCCC reports, where most experts voted in favor of separating these two categories [26]. As a confirmatory finding, none of the patients

with lymph node metastases developed in field progression in our study. In 2 studies, castration-resistant disease was found as an independent risk factor for inferior PFS compared to hormone-sensitive disease, probably due to a more aggressive tumor biology and/or a poorer response to metastasis-directed therapies [6, 25, 31].

Some authors considered survival time without hormonal therapy as a parameter to evaluate the efficacy of SBRT, reporting an average 38 month time delay for ADT [32]. Palacios et al. reported a range of survival free from ADT of 16–40 months [27]. In our study, the average time of delay to ADT was around 10 months, similarly to Jereczek-Fossa et al [24]. The STOMP study showed a prolonged ADT-free survival with metastasis-directed therapy compared to observation after a median follow-up of 3 years (21 *vs*. 13 months) [15].

With respect to toxicity profile, in our cohort, no patient developed major acute or late toxicity after treatment, highlighting the general tolerability of this treatment approach [17, 24].

SBRT is an effective therapeutic option even if most of the studies include heterogeneous patient populations, different patterns of metastatic spread and clinical presentations. Authors evaluated the response to SBRT in different scenarios to find out which group of patients could benefit the most. Franzese et al. reported PFS rates at 6, 12 and 18 months of 76%, 46% and 32% in castration-sensitive patients versus 56%, 16% and 8% in castration-resistant patients, respectively [6].

Other reports, however, support the use of SBRT also for castration-resistant patients. The POP-START trial reported a 1- and 2- year PFS of 58% and 39% [17]. A multicentric study [12] observed a PFS of 22%, while a phase II trial reported a free-from-ARTA survival of 66% after almost 10 months from SBRT [12, 33]. In our study, we observed an average delay time of around 7 months, before starting systemic therapy.

To select patients more likely to respond to SBRT, some authors also analyzed the differences between patients receiving metastasis-directed therapy to bone lesions or nodal metastases. No significant differences were found with respect to PFS in our study. A retrospective study reported a 1- 2- and 3-year OS rate of 90%, 76% and 70%, respectively, in 71 patients treated with CyberKnife for bone metastases [34]. Priyanka et al. observed a similar 24-month PFS after SBRT in 64 patients treated for bone and lymph-node metastases [35]. A multicentric study reported an almost 18-month average PFS after SBRT, comparably for patient with bone and nodal metastases [12]. A recent systematic review, which considers studies with patients exclusively presenting with bone metastases, reported 2-year LC and PFS rates of 76-100% and 27–38%, respectively [36].

Our study revealed no significant difference in terms of PFS based on the number (single versus multiple) or the type of lesion (bones versus lymph nodes).

Several studies are currently testing the benefit of treating the primary tumor, with SBRT to all metastatic lesions, focusing on hormone-sensitive and resistant oligo-recurrent prostate patients. All these studies include patients with 1 to 5 nodal and/or bone metastases, with PFS as the primary endpoint. The ORIOLE study is the first randomized study assessing the efficacy of SBRT as a measure of the amount of circulating tumor cells in oligometastatic hormone-sensitive patients [37]. The CORE study compares the best standard treatment available with or without SBRT [38]. The STORM study randomizes patients suitable for targeted treatment to lymph node metastases [39]. Finally, the PCS IX study analyzes the role of enzalutamide associated to SBRT [40].

Available data suggest that patients with a limited number of metastases may achieve long-term disease control, provided that all sites of disease are ablated. However, long-term data are lacking, apart from the recently reported long-term results of the SABR-COMET trial which showed a benefit in terms of PFS and OS for patients undergoing metastasis-directed therapy in oligometastatic cancer patients with different tumor types [41].

Different dose and fractionation schedules are reported in literature, depending on lesion site and size, organs at risk proximity, previous treatments and the biological effective dose.

For bone metastases, authors used single fractions, with doses ranging from 12 to 24 Gy, or fractionated schedules with total doses of 21–27 Gy given in 3 fractions or 20–35 Gy in 5 fractions [20]. A prospective randomized trial showed that a single high-dose of 24 Gy compared to hypofractionated fractionated SBRT (9 Gy x 3) can be more effective in ablating bone metastases and may lead

to a longer time to distant metastatic progression [42]. Clinical trials and consensus guidelines are needed to better identify proper total dose and fractionation [20]. Nevertheless, different studies showed the efficacy of a biological effective dose (BED) > 100 Gy in achieving a prolonged systemic treatment-free survival [36].

Total doses ranged from 30 to 45 Gy, with daily fractions of 7–12 Gy for abdominal lymph nodes, with dose limiting organs at risk (OARs) (liver, kidneys, bowel, and bladder) [19]. Recommended doses in oligometastatic disease according to SABR-COMET-10 phase III trial are 20 Gy in 1 fraction, 30 Gy in 3 fractions, or 35 Gy in 5 fractions [41].

Plan quality is assessed also based on other parameters: target dose distribution, dose homogeneity, healthy tissue tolerance, dose limits for OAR and dose outside the target [43]. The Report AAPM 101 used in our study, indicated the maximum dose and threshold limits for different OAR in a single or multiple fraction (3 or 5) SBRT, were most adopted [21, 43]. However, several publications reported different constraints for OAR. This critical issue was recently explored in a review article [44] about OAR dose constraints adopted in 53 ongoing clinical trials of SBRT in different body areas. A variability in OAR dose constraints was found, which suggested future research to reach standardization.

Our study has some limitations consisting in the retrospective design, the relatively small sample size and the length of follow-up. However, it confirms the feasibility, with a very low toxicity profile, of a potentially curative treatment such as SBRT in a daily practice.

Conclusions

Stereotactic body radiation therapy is a viable and safe treatment option for oligometastatic prostate cancer. Our results confirm that SBRT offers a good biochemical and local control: one-third of the patients was progression-free after one year and two-third maintained in field disease control after two years. In field progression occurred in only 8% of cases. Almost one-third of the patients treated with SBRT without association of hormone therapy had disease remission after one year. In patients with progressive disease, androgen deprivation therapy or systemic therapy was delayed by almost one year. More studies are needed to investigate the effect of combined hormonal therapy, the impact of different clinical scenarios, as well as the optimal radiotherapy doses and volumes to identify which patients would most benefit from a radiotherapy treatment with ablative intent.

Conflict of interest

None declared.

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