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RESEARCH PAPER

Stereotactic body radiotherapy to lymph nodes in oligoprogressive castration-resistant prostate cancer patients: a post hoc analysis from two phase I clinical trials

D. Pezzulla[1] · G. Macchia[1] · S. Cilla[2] · M. Buwenge[3,4] · M. Ferro[1] · P. Bonome[1] · C. Romano[2] · A. Zamagni[3,4] · V. Valentini[5,6] · A. G. Morganti[3,4] · F. Deodato[1,6]

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Abstract

The prognosis of prostate cancer (PC) is generally favorable but the incidence of metastases is relatively high after the treatment of the primary tumor, especially in high-risk patients. Fractionated stereotactic body radiotherapy (SBRT) or single fraction stereotactic body radiosurgery (SRS) are emerging treatment options in this setting. However, data on SBRT/SRS in patients with metastatic castration-resistant PC (mCRPC) are largely lacking, particularly in subjects with nodal lesions. Therefore, we evaluated outcomes and toxicity recorded in mCRPC patients with nodal oligoprogression. Patients included in this analysis had ≤ 5 metastatic sites without visceral lesions and underwent SBRT/SRS on nodal metastases. Thirty-eight patients carrying out 61 nodal metastases were analyzed. The median SRS dose was 20 Gy (range 12–24 Gy) and the most common schedule was 20 Gy (44.8%). The median SBRT dose was 45 Gy (range 20–50 Gy) and the most common regimen was 45 Gy in 5 fractions (37.9%). Thirty-seven patients (97.4%) showed only grade 0–1 acute toxicity while one patient reported grade 2 dysphagia. In terms of late toxicity, one grade 2 laryngeal, one grade 1 skin and one grade 1 gastrointestinal toxicities were recorded. Two-year actuarial local control (LC), distant progression-free survival, progression-free survival (PFS) and overall survival were 94.0, 47.2, 47.2, and 90.2%, respectively. Two-year next line systemic therapy-free survival (NEST-FS) was 67.7%. In conclusion, the efficacy in terms of LC of SBRT/SRS in patients with nodal metastases from PC was confirmed. Moreover, this analysis suggests the efficacy in terms of PFS and NEST-FS also in the setting of oligoprogressive PC. In fact, about one-third of patients were free from progressive disease and two-third of subjects did not require hormonal therapy switch or discontinuation three years after treatment.

Keywords Prostate cancer · Stereotactic body radiotherapy · SBRT · Radiosurgery · SRS · mCRPC · NEST

Abbreviations

PC	Prostate cancer
ADT	Androgen deprivation therapy
MDT	Metastases directed therapies
SBRT	Stereotactic body radiotherapy
SRS	Single fraction stereotactic body radiosurgery
LC	Local control
PFS	Progression free survival
NEST-FS	Time to next-line systemic treatment free survival
VMAT	Volumetric modulated arc therapy

D. Pezzulla and G. Macchia have contributed equally to this paper.

A. G. Morganti and F. Deodato share the last authorship.

✉ G. Macchia
macchiagabriella@gmail.com

[1] Radiation Oncology Unit, Gemelli Molise Hospital, Università Cattolica del Sacro Cuore, Campobasso, Italy

[2] Medical Physics Unit, Gemelli Molise Hospital, Università Cattolica del Sacro Cuore, Campobasso, Italy

[3] Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[4] Department of Experimental, Diagnostic, and Specialty Medicine - DIMES, Alma Mater Studiorum Bologna University, Bologna, Italy

[5] Dipartimento di Scienze Radiologiche, Radioterapiche ed Ematologiche, IRCCS, UOC di Radioterapia, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

[6] Istituto di Radiologia, Università Cattolica del Sacro Cuore, Rome, Italy

GTV	Gross tumor volume
CT	Computed tomography
PET	CT- positron emission tomography
MRI	Magnetic resonance imaging
PTV	Planning target volume
ECOG-PS	Eastern cooperative oncology group performance status
PSA	Prostate serum antigen
DPFS	Distant progression-free survival
OS	Overall survival
BED	Biologically effective dose

Introduction

Prostate cancer (PC) is very common, being the fifth leading cause of cancer death in males [1]. The prognosis is generally favourable even if the rate of metastasis after the treatment of the primary tumor is relatively high, especially in patients with high-risk cancer. [2]. In patients with metastatic PC, international guidelines recommend androgen deprivation therapy (ADT) alone or in combination with other drugs based on the castration status [3, 4].

In patients with nodal metastases from PC, stereotactic body radiotherapy (SBRT) or single fraction stereotactic body radiosurgery (SRS) were tested with the aim to improve clinical outcomes and to delay next-line systemic treatments (NEST), based on their tolerability and efficacy in achieving prolonged local control [5–19].

However, in this setting the evidence is sparse and inhomogeneous. Moreover, although most studies reported data on local control (LC) and/or progression free survival (PFS), specific information on biochemical [8, 9, 11, 15, 18, 19] and clinical response [8, 14], ADT- [7, 11, 18] or NEST-free survival [20] and overall survival are frequently lacking [7, 9, 14].

Furthermore, most available studies included patients with nodal oligorecurrent castration-sensitive PC while only one retrospective study reported on a small series (15 patients) of oligoprogressive castration-resistant nodal PC [21]. Therefore, there is a lack of clear evidence in this setting and in particular in the subgroup of patients with oligoprogressive CP.

Based on this background, the aim of this report is to analyze outcomes and toxicity of patients with nodal oligoprogressive PC enrolled in two dose-escalation phase I trials.

Materials and methods

Study design

This is a post hoc analysis of data from the DESTROY trials [22, 23], two multi-arm phase I studies exploring SBRT and SRS in several cancer settings. In details, the DESTROY-1 trial was a dose escalation study on SBRT delivered with fixed non-coplanar conformal fields or Volumetric Modulated Arc Therapy (VMAT) in patients with primary, oligorecurrent or oligometastatic cancers [22]. The DESTROY-2 trial was based on dose-escalated SRS delivered with VMAT in the same clinical settings [23]. Both trials were approved by the local Ethics Committee and by the Institutional Review Board. All patients signed a written informed consent before treatment. Details on endpoints, inclusion–exclusion criteria, treatment planning and delivery, and results of these two trials have been previously reported [22, 23].

Inclusion criteria

In this analysis, we included oligoprogressive castration-resistant PC (mCRPC) patients with a small number (≤ 5) of metastatic sites who underwent SBRT/SRS on nodal metastases. Patients with visceral metastases were excluded. The definition of castration-resistance was based on the European Association of Urology guidelines [24]. Ongoing ADT and type of lesions (synchronous versus metachronous) did not represent exclusion criteria. The gross tumor volume (GTV) was identified by computed tomography (CT) and/or CT-positron emission tomography (PET) and/or magnetic resonance imaging (MRI) and the Clinical Target Volume was defined as the GTV. Organ motion and setup inaccuracies were analyzed to define the planning target volume (PTV) as previously described [22, 23]. Data on age, Eastern Cooperative Oncology Group performance status (ECOG-PS), comorbidities, pre- and post-radiotherapy prostate serum antigen (PSA) levels, systemic therapies, lesions site, fractionation, total prescribed dose, toxicity and outcome were collected.

Toxicity and response evaluation

Acute and late toxicities were evaluated by RTOG and CTCAE 4.03 scales, respectively [22, 23, 25]. The evaluation of biochemical response was carried out four-months after treatment following the Jereczek Fossa et al. proposal: a reduction of the PSA value $> 10\%$ compared to the pre-SBRT PSA levels was considered as a response (complete response if $> 50\%$). A stable disease was defined as PSA levels ≤ 10 to $\geq 10\%$ compared to the pre-SBRT value, while a PSA increase $> 10\%$ was classified as a biochemical progression [22, 26]. Moreover, in patients with PSA levels > 1 ng/ml, a 11C-choline PET-CT scan was performed and the SBRT/SRS response was classified also according to the PERCIST criteria [27].

Statistical analysis

Patients' characteristics were reported as frequencies and percentages for categorical variables and as medians and ranges for continuous variables. The Kaplan–Meier method was used to calculate the actuarial outcomes. LC and response were defined on a "per lesion" basis. Moreover, LC was calculated from the date of SBRT/SRS to the date of in-field relapse/progression or to the date of the last follow-up. The NEST-free survival was defined as the time between SBRT/SRS and NEST (second-generation anti-androgens or chemotherapy). Distant progression free survival (DPFS) was calculated from the date of SBRT/SRS to the date of relapse/progression outside SBRT/SRS field or the last seen date. PFS was defined as the time between the date of SBRT/SRS and the date of first progression event (local or distant) or the last follow-up visit for censored patients. Overall survival (OS) was defined as the time from SBRT/SRS to the date of the last follow-up or death. NEST-free survival, DPFS, PFS, and OS were calculated on a "per patient" basis. Univariate and multivariate analysis of factors predicting outcomes was carried out by logistic regression. Differences between subgroups were evaluated by log-rank tests and Cox's regression model for univariate and multivariate analyses, respectively. Statistical analysis was performed using XLSTAT statistical software (Addinsoft, Paris, France).

Table 1 Patients' characteristics

	n (%)	
Patients	38	
Lesions	61	
Median age, range, years	73.5	62.0–85.0
Primary PCa gleason score		
4	4 (10.5)	
5	5 (13.1)	
6	3 (7.9)	
7	11 (28.9)	
8	7 (18.4)	
9	7 (18.4)	
10	1 (3.3)	
Median BMI, range	28.0	21.8–38.0
Median pre-SBRT PSA, range	5.3 ng/ml	0.03–382 ng/ml
Median post-SBRT PSA, range	2.41 ng/ml	0.001–346 ng/ml
ECOG		
0	32 (84.2)	
1	6 (15.8)	
Comorbidities		
Hypertension	18 (47.8)	
Coronary artery disease	4 (13.5)	
Diabetes	5 (10.2)	
Lung disease	5 (10.2)	
Hepatopathy	1 (2.6)	

PC prostate cancer, *BMI* body mass index, *PSA* prostatic specific antigen, *SBRT* stereotactic body radiotherapy, *ECOG* eastern cooperative oncology group performance status

Results

Patients' characteristics

Thirty-eight mCRPC patients with 61 nodal metastases were treated between May 2005 and June 2020 and included in this analysis. All patients had ECOG 0–1 performance status and median age was 73.5 years (range, 62–85). As shown in Table 1, 24 patients (63.2%) had at least one comorbidity, mainly represented by hypertension (47.8%), coronary artery disease (13.5%), diabetes (10.2%), lung disease (10.2%), and hepatopathy (2.6%). All patients were on ADT at the time of SBRT/SRS and were considered as "low burden" patient based on the definition used in the CHAARTED trial [28]. In terms of radiotherapy delivered before SBRT/SRS, 18 patients were previously treated with prophylactic pelvic nodal irradiation, of whom 12 with pelvic nodal relapse occurring after a median interval of 22 months (2–76 months) from the first irradiation. No lesions was previously treated with metastasis-directed therapies.

Lesions and treatment details are reported in Table 2. Nodal metastases sites were mainly pelvis (67.2%) and abdomen (24.6%), followed by the thorax (8.2%). Twenty-six patients had one single lesion (68.4%) and received only one SBRT/SRS treatment while concurrent or sequential treatments were performed in 12 patients bearing more than one lesion (total: 35, 9 metachronous and 26 synchronous). Moreover, five patients (13.2%) had been previously irradiated on bone metastases with curative aim. Among these, 2 patients were treated on spine metastases and one on a rib lesion. Another patient treated on 2 metachronous nodal metastases was previously irradiated on 2 bone metastases with SRS in between nodal irradiations. Finally, one patient was previously irradiated on 5 metachronous bone metastases.

Treatment details

The median PTV was 16 cm^3 (range: 1.2–137.0). Thirty-two lesions (52.5%) were treated with SBRT and 29 (47.5%) lesions were treated with SRS. The biologically effective dose $(BED)_{\alpha/\beta 1.5}$ was calculated as shown in Table 2. The median dose delivered with SRS was 20 Gy (range: 12–24 Gy), with 286 Gy (range: 108–408) median $BED_{\alpha/\beta 1.5}$. The most frequent SRS schedule was 20 Gy in single fraction (44.8%). The median SBRT dose was 45 Gy (range: 20–50 Gy) with 315 Gy median $BED_{\alpha/\beta 1.5}$

Table 2 Characteristics of lesions (N = 61) and treatment's detail

Anatomical site	*n* (%)
Pelvis	41 (67.2)
Upper abdomen	15 (24.6)
Thorax	5 (8.2)
Stereotactic radiosurgery (SRS)	
Technique	
SRS, 1 fraction	29 (47.5)
Median total dose, range, Gy	20 (12.0–24-0)
Median $BED_{\alpha/\beta 1.5}$, range, Gy	236 (108.0–408.0)
Schedules (Total dose, Gy)	
12	8 (27.5)
16	1 (3.4)
18	1 (3.4)
20	13 (44.8)
24	6 (20.6)
Stereotactic body radiotherapy (SBRT)	
Technique	
SBRT, 5 fractions	32 (52.5)
Median total dose, range, Gy	45 (20.0–50.0)
Median $BED_{\alpha/\beta 1.5}$, range, Gy	315 (73.0–383.0)
Schedules (Total dose, Gy)	
20	2 (6.3)
25	1 (3.1)
30	3 (9.3)
35	5 (15.5)
40	4 (12.4)
45	12 (37.9)
50	5 (15.5)

SRS stereotactic radiosurgery, *SBRT* stereotactic body radiotherapy, *BED* biologic effective dose

(range: 73–383 Gy). The most frequent SBRT fractionation regimen was 45 Gy in 5 fractions (37.9%) as reported in Table 2.

Response evaluation

In terms of biochemical response, the median PSA before SBRT/SRS was 5.3 ng/ml (0.03–382 ng/ml), while the median PSA at the first evaluation after treatment (4 months) was 2.4 ng/ml (0.001–346 ng/ml). In particular, we recorded 20 (33.0%) complete and 12 (19.0%) partial biochemical responses, 5 (8.0%) stable PSA levels and 19 (32.0%) biochemical progressions, while the PSA level was not available in five cases (8.0%). Moreover, the functional evaluation was performed in 35 lesions whose patient had a detectable PSA (> 1 ng/ml) after SBRT/SRS. We recorded 30 complete responses, 3 partial responses and 2 stable diseases.

Toxicity

Thirty-seven patients (97.4%) experienced none or mild (Grade 0–2) acute toxicity. In details, six grade 1 skin, five grade 1 genitourinary, eight grade 1 gastrointestinal toxicities and one case of grade 2 dysphagia were recorded. In terms of late toxicity, one G2 laryngeal toxicity was recorded 12 months after SRS (24 Gy) in one patient with a nodal lesion in the subclavicular region. He developed a laryngeal stenosis with recurrent laryngeal nerve paralysis due to which he underwent a temporary tracheostomy with subsequent decannulation after two months. Furthermore, one grade 1 skin and one grade 1 gastrointestinal late toxicities were recorded.

Outcome

Median follow-up was 27 months (range: 1–133 months). At last observation (December 2020), seven patients (18.5%) were dead of disease and 31 (81.5%) were alive. Of the latter, 15 patients (39.0%) had out-of-field recurrences while one patient (2.0%) was alive with both in-field and out-of-field relapses. Two-year actuarial LC, NEST-FS, DPFS, PFS, and OS were 94.0, 67.7, 47.2, 47.2, and 90.2%, respectively (Fig. 1, Table 3). Regarding the above mentioned outcomes, no significant differences were found based on age, body mass index, PTV, irradiation technique, $BED_{\alpha/\beta 1.5}$, and clinical response (data not shown).

Discussion

mCRPC patients with nodal oligoprogression during ADT are a highly selected population in which effective local treatments could improve prognosis. Furthermore, sterilizing castration-resistant tumor clones by treating oligoprogressive lesions with SBRT/SRS could delay the systemic treatment shift [29]. The most important result of our study is the prolongation of ADT alone achieved with SBRT/SRS, with approximately two thirds of patients without changes or interruptions of this systemic therapy for at least 3 years. Furthermore, since LC is a necessary condition to achieve this goal, this study confirms the efficacy of SBRT/SRS in patients with mCRPC, the recorded LC rate being close to 90%.

Interestingly, the recorded NEST-free survival (3-year: 67.7%) was comparable to the ADT-free survival in castration-sensitive patients (median: 44 months, Table 3) [30], suggesting that SBRT/SRS could hinder tumor progression also in patients with nodal oligometastases from mCRPC.

In our analysis, based on patients treated with a wide range of BEDs, no significant impact of the delivered dose on LC rates was recorded. This lack of dose–effect may arise

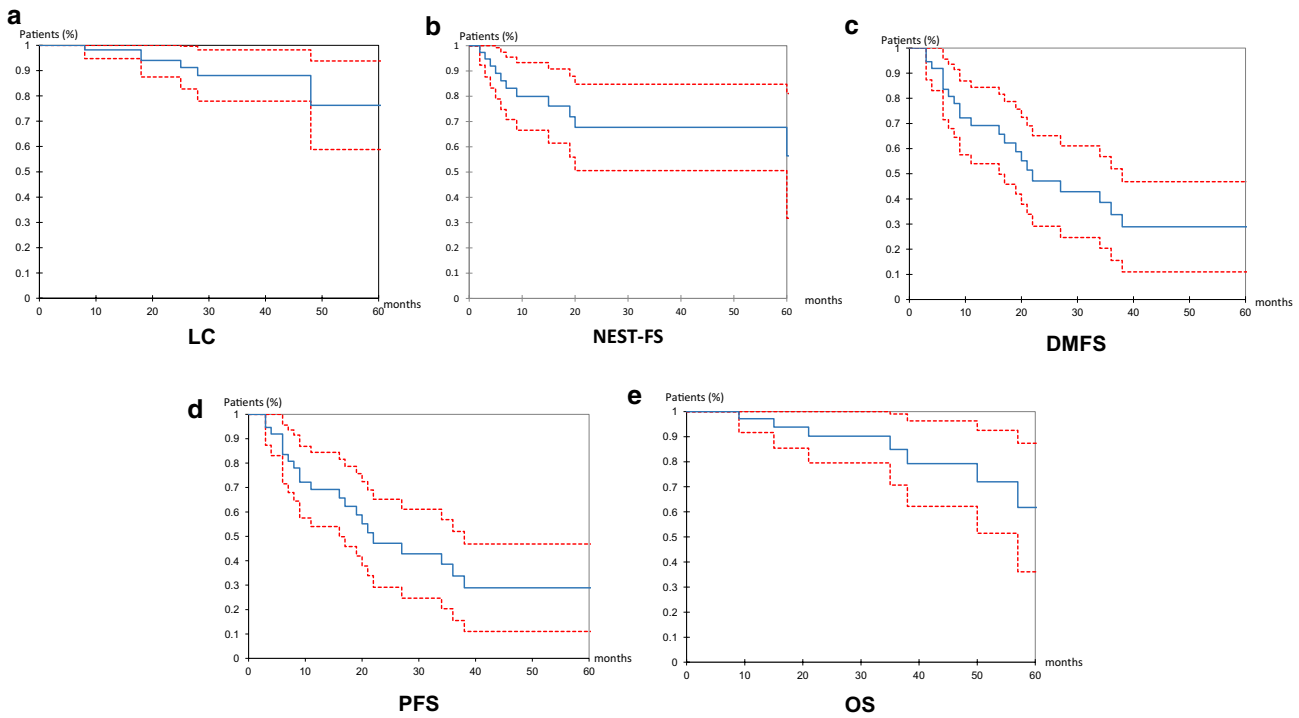

Fig. 1 Actuarial clinical outcomes: **a** local control (LC); **b** next line sistemic therapy free survival (NEST-FS); **c** distant progression free survival (DPFS); **d** progression free survival (PFS); **e** overall survival (OS)

from the small sample size or from the relatively high BED (≥ 315 Gy) delivered in most patients. However, this data confirms the lack of clear evidence on the impact of radiation dose in the treatment of lymph node oligometastases [20]. Interestingly, the LC rates recorded in our series seem similar to those recorded in studies [5, 7, 8, 14, 15, 18, 21, 30] on castration-sensitive patients (Table 3). Furthermore, the LC rates registered in the latter analyses were uniformly high, regardless of the percentage of patients undergoing ADT (Table 3). These data suggest that the local effect of SBRT/SRT in PC nodal oligometastases could be independent of the possible impact of concomitant or adjuvant ADT.

Equally noteworthy is the similarity of our results, in terms of PFS, to series including oligorecurrent patients [5, 7, 8, 14, 15, 18, 21, 31, 32] undergoing concomitant or adjuvant ADT (Table 3). This data suggests, also in the setting of mCRPC, the efficacy of metastasis directed therapies in improving tumor control despite the theoretical higher aggressiveness of ADT-refractory patients. Furthermore, the 2-year PFS recorded in our study (47.2%) is similar to that reported by Onal et al. (36.7%) in mCRPC patients with nodal oligoprogression [21]. These figures seem higher than the results recorded in series of oligoprogressive PC bone metastases (median: 10–13.5 months) [31, 32].

Surprisingly enough, the recorded OS rates in nodal oligoprogression from mCRPC, in both the present study and that of Onal et al. [21] (2-year: 90.2–91%), are similar to the figures recorded in castration-sensitive patients (2-year: 67–92%) [7, 14]. This similarity, beyond the intrinsic limits due to the small number and small sample size of the analyzed series, seems to suggest that lymph node oligometastases might have a favourable prognosis regardless of the castration status when treated with SBRT/SRS.

The low recorded incidence and severity of side effects confirm the tolerability of SBRT/SRS in the treatment of lymph node oligometastases [20]. Actually, only one patient required hospitalization due to a temporary laryngeal stenosis resulting from recurrent laryngeal nerve paralysis recorded 12 months after SRS (24 Gy). Peripheral nerve damages were previously reported in patients with lung cancer treated with SBRT. For example, Shultz et al. reported two cases of neuropathy (either vagal or recurrent laryngeal nerves) in a series of 67 non-small cell lung cancers of the upper lobe treated with SBRT. The two subjects had received a moderately higher cumulative dose on the nerves compared to patients not developing vocal fold paresis [33]. Therefore, it should be emphasized that, even if rarely, cases of relevant toxicity are possible especially in the thoracic sites, as reported in a systematic literature review [20].

Our study has inherent limitations related to the sample size and trial design. The relatively small sample size (38 patients), although larger compared to the only study reporting results on SBRT in nodal oligoprogressive PC (15 patients) [21], hampered the identification of significant

Table 3 Comparison between our series and other studies

Authors, year	Study design	Pts	Setting	Dose (Gy)/fractions	Concurrent/adjuvant ADT	Local progression-free survival	Progression-free survival	Clinical response	Systemic therapy-free survival	Overall Survival
Casamassima et al. [14]	Retrospective	25	Oligorecurrences	30/3	NR	1y: 95% 2y: 90% 3y: 90%	1y: 80% 2y: 50% 3y: 17%	PET: CR: 56.5%	NR	1y: 92%, 2y: 92%, 3y: 92%
Jereczek-Fossa et al. [15]	Retrospective	16	Oligorecurrences	33/3	75%	NR	2.5y: 63.5%	NR	NR	NR
Napieralska et al. [7]	Retrospective	18	Oligorecurrences	24–45/1–3	100%	1y: 93%, 2y: 70%	NR	NR	NR	1y: 100%, 2y: 67%
Ost et al. [30]	Retrospective	72	Oligorecurrences	Biological effective dose ≥ 80 (α/β: 3)	57%	3y: 94%, 5y: 94%	Distant-metastasis-free survival: 3y: 34% 5y: 13%	NR	Median ADT-free survival: 44 months	3y: 96% 5y: 96%
Franzese et al. [8]	Retrospective	26	Oligorecurrences	25–45/4–6	68.2%	1y: 80% 2y: 75% 3y: 75%	1y: 55.2% 2y: 35.1%	PET: CR: 44.7%, PR: 38%, SD: 7.9%, PD: 7.9%	NR	NR
Jereczek-Fossa et al. [18]	Retrospective	94	Oligorecurrences: 98.9% Oligoprogressions: 1.1%	15–36/3–6	36.2%	2y: 84%	2y: 30%	NR	Median ADT-free survival: 7.2 months	NR
Siva et al. [5]	Phase II trial	13	NRS (in the whole cohort including bone lesions, oligorecurrences: 67%)	20/1	NRS (in the whole cohort including bone lesions: 33%)	2y: 100%	NRS (in pelvic nodal lesions, 2y distant progression-free survival: 42%)	NR	NRS (2y ADT-free survival in the whole cohort including bone lesions: 48%)	NR
Onal et al. [21]	Retrospective	15	Oligoprogressions	Most adopted prescription: 30–35/5	NRS	2y: NR	2y: 36.7%	NRS	NEST: 2y: 44.8	2y: 91%
Present series	Pooled analysis from two phase I trials	38	Oligoprogressions	12–500/1–5	100%	1y: 98.2% 2y: 94.0% 3y: 88.0% 5y: 76.3%	1y: 69.2% 2y: 47.2% 3y: 33.8% 5y: 28.9%	PET: CR: 49.1% PR: 4.9% SD: 3.4% NA: 42.6%	NEST: 1y: 79.9% 2y: 67.7% 3y: 67.7% 5y: 56.4%	1y: 97.1% 2y: 90.2% 3y: 84.9% 5y: 61.7%

ADT androgen deprivation therapy, *NEST* next-line systemic treatment-free survival, *NR* not reported, *NRS* not reported separately for nodal oligometastases, *y* year

correlations between analyzed variables and outcomes. Furthermore, our study being a pooled analysis from two dose-escalation trials, total dose and dose/fraction were highly variable. Therefore, an evaluation of the efficacy of a single treatment regimen was not possible. Obviously, studies able to provide clear indications on effective dose/fractionation SBRT/SRS regimens in this setting would be very useful. Finally, the assessment of response was hindered by the exclusion from restaging of patients with PSA < 1 ng/mL after treatment, with a clear bias in the analysis of this outcome.

On the other hand, we analyzed a highly selected subset of metastatic PC patients, with a homogeneous population in terms of disease spread and hormonal status. Hence, a strong point of this study is that it can be considered a very effective model for describing the role of SBRT in mCRPC with few nodal lesions.

In conclusion, our analysis confirms the efficacy and safety of SBRT/SRT in the treatment of mCRPC patients. Despite the use of relatively low doses, the efficacy of this treatment in terms of LC in lymph node metastases is confirmed. Moreover, the analysis suggests the efficacy of metastasis directed therapies in prolonging PFS and NEST-free survival even in castration-resistant patients, with about one third of patients free from disease progression and two third of patients not requiring hormonal switch or discontinuation three years after the treatment. These results justify the design of prospective trials aimed at confirming these preliminary data.

Data availability Data will be made available on reasonable request.

References

1. Sung H, Ferlay J, Siegel RL et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209
2. Hansen EK, Roach M (2018) Handbook of evidence-based radiation oncology. Springer, Cham
3. NCCN Guidelines Version 2.2021 Prostate Cancer. https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf. Accessed 19 Mar 2021
4. EAU. Guidelines: prostate cancer uroweb. https://uroweb.org/guideline/prostate-cancer/. Accessed 19 Mar 2021
5. Siva S, Bressel M, Murphy DG et al (2018) Stereotactic abative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. Eur Urol 74:455–462
6. Kneebone A, Hruby G, Ainsworth H et al (2018) Stereotactic body radiotherapy for oligometastatic prostate cancer detected via prostate-specific membrane antigen positron emission tomography. Eur Urol Oncol 1:531–537
7. Napieralska A, Miszczyk L, Stąpór-Fudzińska M (2016) CyberKnife stereotactic ablative radiotherapy as an option of treatment for patients with prostate cancer having oligometastatic lymph nodes: single-center study outcome evaluation. Technol Cancer Res Treat 15:661–673
8. Franzese C, Lopci E, Di Brina L et al (2017) 11C-choline-pet guided stereotactic body radiation therapy for lymph node metastases in oligometastatic prostate cancer. Cancer Invest 35:586–593
9. Ingrosso G, Trippa F, Maranzano E et al (2017) Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: a two-institution experience. World J Urol 35:45–49
10. Bouman-Wammes EW, van Dodewaard-De Jong JM, Dahele M et al (2017) Benefits of using stereotactic body radiotherapy in patients with metachronous oligometastases of hormone-sensitive prostate cancer detected by [18F]fluoromethylcholine PET/CT. Clin Genitourin Cancer 15:e773–e782
11. Oehler C, Zimmermann M, Adam L et al (2019) Predictive factors for response to salvage stereotactic body radiotherapy in oligorecurrent prostate cancer limited to lymph nodes: a single institution experience. BMC Urol 19:84
12. Pasqualetti F, Panichi M, Sainato A et al (2016) [18F]Choline PET/CT and stereotactic body radiotherapy on treatment decision making of oligometastatic prostate cancer patients: preliminary results. Radiat Oncol 11:1–8
13. Decaestecker K, De Meerleer G, Lambert B et al (2014) Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 9:1–10
14. Casamassima F, Masi L, Menichelli C et al (2011) Efficacy of eradicative radiotherapy for limited nodal metastases detected with choline PET scan in prostate cancer patients. Tumori 97:49–55
15. Jereczek-Fossa BA, Beltramo G, Fariselli L et al (2012) Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys 82:889–897
16. Ong WL, Koh TL, Lim Joon D et al (2019) Prostate-specific membrane antigen-positron emission tomography/computed tomography (PSMA-PET/CT)-guided stereotactic ablative body radiotherapy for oligometastatic prostate cancer: a single-institution experience and review of the published literature. BJU Int 124:19–30
17. Jereczek-Fossa BA, Fariselli L, Beltramo G et al (2009) Linac-based or robotic image-guided stereotactic radiotherapy for isolated lymph node recurrent prostate cancer. Radiother Oncol 93:14–17
18. Jereczek-Fossa BA, Fanetti G, Fodor C et al (2017) Salvage Stereotactic body radiotherapy for isolated lymph node recurrent prostate cancer: single institution series of 94 consecutive patients and 124 lymph nodes. Clin Genitourin Cancer 15:e623–e632
19. Detti B, Bonomo P, Masi L et al (2015) Stereotactic radiotherapy for isolated nodal recurrence of prostate cancer. World J Urol 33:1197–1203
20. Deodato F, Macchia G, Buwenge M et al (2021) Systematic review of stereotactic body radiotherapy for nodal metastases. Clin Exp Metastasis 38(1):11–29
21. Onal C, Ozyigit G, Oymak E et al (2021) Stereotactic radiotherapy to oligoprogressive lesions detected with 68Ga-PSMA-PET/CT in castration-resistant prostate cancer patients. Eur J Nucl Med Mol Imaging 48:3683
22. Deodato F, Macchia G, Cilla S et al (2019) Dose escalation in extracranial stereotactic ablative radiotherapy (DESTROY-1): a multiarm phase I trial. Br J Radiol 92(1094):20180422
23. Deodato F, Cilla S, Macchia G et al (2014) Stereotactic radiosurgery (SRS) with volumetric modulated arc therapy (VMAT): interim results of a multi-arm phase I trial (DESTROY-2). Clin Oncol 26(12):748–756
24. Cornford P, Bellmunt J, Bolla M et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing,

metastatic, and castration-resistant prostate cancer. Eur Urol 71:630–642
25. National Cancer Institute (2010) Common terminology criteria for adverse events v.4.03 (CTCAE v.4.03). Accessed http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
26. Jereczek-Fossa BA, Beltramo G, Fariselli L et al (2012) Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostatecancer. Int J Radiat Oncol Biol Phys 82:889–897
27 Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA et al (1999) Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET study group. Eur J Cancer. 35(13):1773–1782
28. Sweeney CJ, Chen YH, Carducci M et al (2015) Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373(8):737–746
29. Onal C, Kose F, Ozyigit G et al (2021) Stereotactic body radiotherapy for oligoprogressive lesions in metastatic castration-resistant prostate cancer patients during abiraterone/enzalutamide treatment. Prostate 81(9):543–552
30. Ost P, Jereczek-Fossa BA, As NV et al (2016) Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 69(1):9–12
31. Ingrosso G, Detti B, Fodor A et al (2021) Stereotactic ablative radiotherapy in castration-resistant prostate cancer patients with oligoprogression during androgen receptor-targeted therapy. Clin Transl Oncol 23(8):1577–1584
32. Berghen C, Joniau S, Ost P et al (2021) Progression-directed therapy for oligoprogression in castration-refractory prostate cancer. Eur Urol Oncol 4:305–309
33. Shultz DB, Trakul N, Maxim PG et al (2014) Vagal and recurrent laryngeal neuropathy following stereotactic ablative radiation therapy in the chest. Pract Radiat Oncol 4(4):272–278