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Posted Date: 29 February 2024

doi: 10.20944/preprints202402.1720.v1

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Lymph-Nodal Oligometastases from Prostate Cancer: Different Outcomes and Pattern of Relapse between Pelvic and Para-Aortic Disease

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Abstract: Introduction: Lymph-nodal prostate cancer oligometastases are differently treated according to their site: pelvic are locoregional lymph-nodes, instead para-aortic lymph-nodes are considered as distant metastases. Aim of the study was a comparison between para-aortic and pelvic oligometastases treated with stereotactic body radiation therapy (SBRT). Material/methods: This is a retrospective analysis. De-novo metastatic or extra-nodal disease were excluded. Univariate and multivariate analyses were performed; pattern of recurrence was evaluated too. A propensity score matching (PSM) was applied to create comparable cohorts. Primary end-point was the progression-free survival (PFS). Secondary end-points were biochemical relapse-free survival (BRFS), ADT-free survival (ADTFS), polymetastases-free survival (PMFS), local progression-free survival (LPFS) and pattern of relapse. Results: 240 lymph-nodal oligometastases in 164 patients (127 pelvic and 37 para-aortic) were treated. Median PFS was 20 and 11 months in pelvic and para-aortic patients respectively (p=0.042). The difference was not confirmed at the multivariate analysis (p=0.06). Median BRFS was 16 and 9 months respectively in pelvic and para-aortic group (p=0.07). No statistically significant differences for ADTFS or PMFS were detected. The cumulative 5-years LPFS was 90.5%. At PSM no statistically significant differences for all the study end-points were detected. Conclusions: Patients affected by para-aortic disease might have PFS comparable to pelvic disease; local control is high in both cohorts. Our results support the use of SBRT also to para-aortic metastases.

Keywords: SBRT; oligometastases; prostate cancer; SABR

Introduction

Oligometastatic disease (OMD) is an intermediate state between localized and polimetastatic disease, characterized by a limited number of distant metastases [1,2]. Several factors have been analyzed to identify patients who can benefit more from local treatment, such as number and size of metastases, disease-free interval (DFI), and the rate of distant metastases [3–5]. Several OMD subgroups have been identified [6], even though the biologic mechanism behind their generally slower clinical behavior has not been completely elucidated [7]. Therefore, oligometastatic patients are eligible for Metastases Directed Therapy (MDT), with the aim of improving disease progression, prolonging the use of systemic therapies or even delaying their start.

Stereotactic body radiation therapy (SBRT) as MDT is supported by several trials across different tumor histologies, demonstrating improvement in progression-free survival (PFS) [8–10]. The

 doi:10.20944/preprints202402.1720.v1

STOMP and ORIOLE trials specifically showed the benefit of SBRT compared to observation in nodal oligometastatic prostate cancer (PC) patients [11,12]. More recently, the EXTEND trial demonstrated that the addition of SBRT to 6-months androgen deprivation therapy (ADT) significantly improves PFS, compared to 6-months ADT alone. [13]

The growing use of PSMA-PET in clinical practice, thanks to its high accuracy in detecting metastases at low PSA levels, has increased the possibility of early oligometastases identification [14,15]. At the same time, advancements in radiation therapy technology and its increased accuracy empower clinicians to confidently delivered high-dose treatments [16,17].

Lymph-nodes are a common site of metastatic spread in PC, exhibiting a characteristic progression along a single caudocranial pathway. The spread shows an upward trend, and these nodes are treated differently based on their location: pelvic nodes are classified as locoregional lymph nodes (cN1), while nodes above the aortic bifurcation are considered distant metastases (cM1a). Patients with nodal metastases in PC generally have a better prognosis than those with bone or visceral metastases [18]. The use of SBRT is well-established in clinical practice for oligometastatic pelvic lymph nodes due to its excellent local control [19]. However, only a few studies have evaluated the use of MDT on para-aortic lymph nodes. We reported the retrospective data of a multi-centric cohort of PC patients who received SBRT for pelvic or para-aortic nodal oligometastases with the aim to compare the clinical outcome.

Material and Methods

Between 2012 to 2022, a series of oligometastatic PC patients with pelvic or para-aortic lymph-node oligometastases treated with SBRT in 3 different Departments (IRCCS Sacro Cuore Don Calabria - Negrar, Brescia University Spedali Civili di Brescia and Borgo Trento Hospital – Verona) were retrospectively reviewed. This study was approved by the Institutional Review Board. Patients were included according to the following characteristics: (a) performance status—Eastern Cooperative Oncology Group (PS (ECOG)) ≤ 2; (b) PC with evidence of pelvic or para-aortic lymph-nodal metastases diagnosed by PSMA or choline PET/CT and treated with SBRT [20]. Patients with *de novo* synchronous metastatic PC, history of metastatic disease, or affected by castration-resistant PC were excluded.

The primary end-point was the PFS. The secondary end-points were biochemical relapse-free survival (BRFS), local progression-free survival (LPFS), ADT-free survival (ADTFS), and polymetastases-free survival (PMFS). Pattern of recurrence and toxicity were also evaluated. The PFS was defined as the time between SBRT and the radiologic evidence of disease progression (both local or distant). The DPFS was defined as the time between SBRT and the radiological diagnosis of distant progression to new metastatic sites. The BRFS was defined as the time between SBRT and the biochemical relapse, defined as any PSA increase after SBRT. The LPFS was defined as the time between the end of SBRT and the radiological diagnosis of local in-field relapse. The ADTFS was defined as the time between SBRT and the start of ADT. The PMFS was defined as the interval between the SBRT and the onset of more than 3 new metastases. PSA doubling-time (PSADT) was calculated using MSKCC algorithm [21]. The DFI was defined as the time between the diagnosis and the occurrence of oligometastatic disease. Toxicity was recorded according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0) as acute (within 60 days from SBRT end) and late (more than 60 days after SRT end). PSA monitoring was conducted every 3 months, and in the event of an increase in PSA levels following SBRT, 18F-PSMA PET-TC imaging was conducted.

Statistical analysis

Survival analysis was performed using the Kaplan-Meier method. The univariate analysis was performed using the log-rank test and the multivariate analysis was performed with Cox proportional hazard regression including all the relevant covariates at the univariate analysis ($p \leq 0.10$). The Chi-squared test in 2x2 contingency tables was used to evaluate the pattern of relapse. A propensity score matched (PSM) analysis was performed by matching patients with pelvic or para

 doi:10.20944/preprints202402.1720.v1

aortic lymph-nodes in a 1:1 ratio, based on the following four covariates: PSA before SBRT (allowed variation +/-0.5 ng/ml); DFI (under or over 72.5months); number of treated lymph-nodes (one versus more than one); risk-class at diagnosis (low, intermediate or high risk).

Treatment procedure

For patients treated with VMAT technique, a simulation CT was acquired with a slice thickness of 3 mm. Set-up error was corrected by cone-beam CT before each treatment fraction. For metastases treated with 1.5T MR-linac, the simulation consisted of a planning CT with a slice thickness of 3 mm, and a 3D T2 weighted MRI with a slice thickness of 1 mm. The same MR scan was performed daily for the treatment procedures. MR-guided treatments were delivered using Intensity-modulated radiation therapy (IMRT) and most patients were treated through adapt to position (ATP) technique which consist of an online replanning after updating treatment isocenter, matching the current position of target and organs at risk, without recontouring. ATP workflow and characteristics was detailed elsewhere [17,22,23]. All scans were acquired with patients in the supine position, with support for the knees and arms on the chest.

When necessary, the diagnostic PET-CT was co-registrered to simulation images to better identify the target. The gross tumor volume (GTV) was defined as the pathological lymph-node and the corresponding PTV was obtained by adding 3 to 5 mm to the GTV.

Treatments were prescribed to ensure that at least 95% of the PTV received at least 95% of the prescribed dose, without exceeding 107% at the maximum dose. The median prescription dose was 36 Gy (range 21-45 Gy) in 5 fractions (range 1-6). Bowel constraints for the bowel were V15Gy, V30 Gy, and V32 Gy <1 cc in 1, 5 and 6 fractions schedule, respectively.

Results

From 2012 to 2022, 164 PC patients were treated with SBRT to oligometastatic pelvic or para-aortic lymph-nodes. Disease dissemination was pelvic in 127 and para-aortic in 37.. Patients characteristics are summarized in Table 1. The median follow-up was 37 months.

Table 1. Patients' characteristics.

	Pelvic (127)	Para-aortic (37)	p
Age (median)	71 (range 56-89)	71 (59-86)	0.65
Initial PSA	8.4 (1.3-86)	10.9 (3.5-50)	0.76
Class risk at diagnosis	Low: 12 (9.4%) Intermediateo: 30 (23.6%) High. 85 (66.9%)	Low: 2 (5.4%) Intermediate: 6 (16.2%) High: 29 (78.4%)	0.4
First treatment on primitive site	Surgery: 109 (85.8%) RT: 18 (14.2%)	Surgery: 30 (81,1%) RT: 7 (18.9%)	0.48
Salvage RT	80 (73.4%)	25 (83.3%)	0.61
Previous pelvic treatments (LAD or pelvic RT)	60 (47.2%)	22 (59.4%)	0.19
Previous ADT	43 (39.4%)	20 (54%)	0.026

 doi:10.20944/preprints202402.1720.v1

PSA at SBRT	1.16 (0.1-16.4)	1.33 (0.23-5.25)	0.48
PSA DT	4.7 (1-17)	5.25 (1-17)	0.84
DFI	69 (3-246)	78 (6-223)	0.98
PET	choline 62 (48.8%) PSMA 65 (51.2%)	choline 15 (40,5%) PSMA 22 (59,5%)	0,37
Number of treated lymph-nodes(median)	1 (1-3)	1 (1-3)	/
More than 1 lymph nodes treated	35 (27,6%)	18 (48,6%)	0.016
Median RT dose	36 (21-45)	36 (21-45)	0.40
Number of fractions	5 (1-6)	5 (1-6)	0.21
RT technique	VMAT 112 (88.2%) MR Linac 15 (11.8%)	VMAT 33 (89.2%) MR Linac 4 (10.8%)	0.86
Cuncurrent ADT	13 (10.2%)	5 (13.5%)	0.57
RT: radiotherapy; LAD: lymphadenectomy; ADT: androgen deprivation therapy; SBRT: stereotactic body radiotherapy; DT: doubling time; DFI: disease-free interval; VMAT: volumetric modulated arc therapy			

Progression-free survival

Pelvic patients had 1-, 3- and 5-years PFS of 66.3%, 35.2% and 30.2% respectively, with a median PFS of 20 months (range 2-80). Para-aortic group had a 1-, 3- and 5-years PFS of 45.9%, 22.4% e 14.9% respectively, with a median PFS of 11 months (range 2-73 (p= 0.042) (Figure 1). The difference was not confirmed at the multivariate analysis, but a trend was mantained (p=0.06; HR 1.49; IC: 0.98-2.28). At the multivariate analysis, association of ADT correlated with longer PFS (p=0.04; HR 0.49; IC:0.25-0.98). At the uni and multivariate analysis, lower PSA value at SBRT correlated with longer PFS (p=0.03 and p=0.04; HR: 1.47: IC: 1.01-2.28) (Table 2).

 doi:10.20944/preprints202402.1720.v1

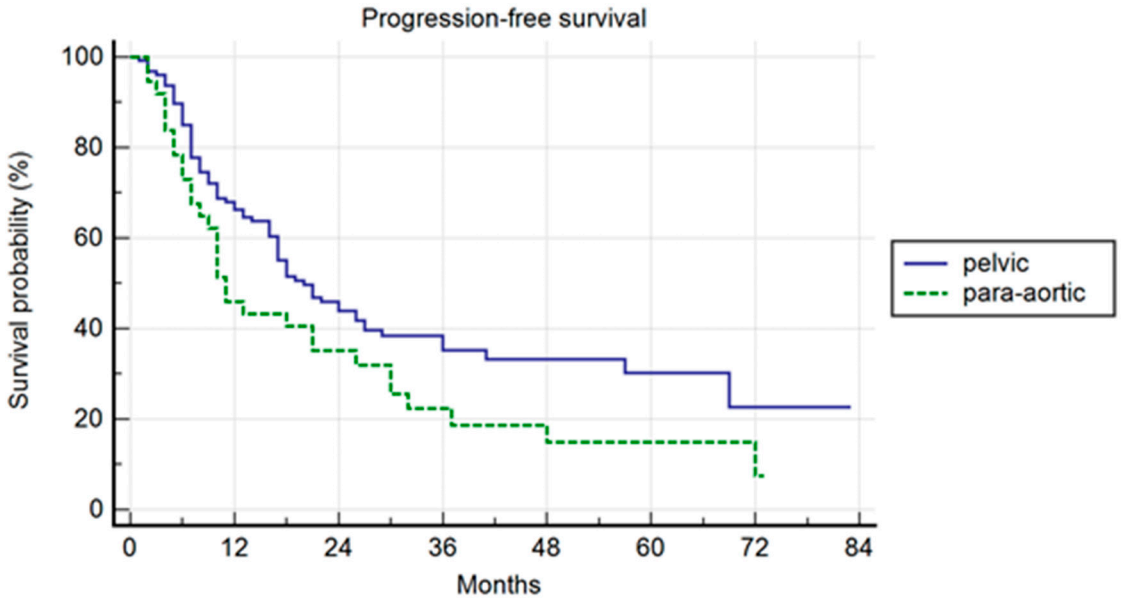

Figure 1. Kaplan-Meier of PFS: pelvic versus para-aortic metastases.

Table 2. PFS at univariate and multivariate analysis.

	Univariate	Multivariate
PSA at SBRT	p= 0.036	p=0.04 (HR:1.47; IC: 1.01-2.28)
PSA DT	p=0.31	/
DFI	p=0.79	/
PET choline vs PSMA	p=0.25	/
Number of lymph-nodes treated (1 vs > 1)	p=0.14	/
Previous pelvic treatments	p=0.67	/
Previous ADT	p=0.17	/
Cuncurrent ADT	p=0.058	p=0.04 (HR 0.49; IC: 0.25-0.98)
Treatment on primitive site (surgery vs RT)	p=0.26	/

 doi:10.20944/preprints202402.1720.v1

Pelvic vs para-aortic	P=0.042	p=0.06 (HR:1.49; IC: 0.98-2.28)
SBRT: stereotactic body radiotherapy; DT: doubling time; DFI: disease-free interval; ADT: androgen deprivation therapy; RT: radiotherapy		

Biochemical relapse-free survival

Pelvic patients had a 1, 3 and 5 years BRFS of 59.4%, 22.8% and 15.9%, with a median BRFS of 16 months (range 1-78); para-aortic group had a 1, 3 and 5 years BRFS of 35.1%, 14.4% and 7.2%, with a median BRFS of 9 months (range 2-73) (p= 0.007). At the univariate and multivariate analysis, association of ADT to SBRT correlated with longer BRFS (p=0.01; HR: 0.47; IC: 0.25-0.87)

ADT-free survival

The subgroup of patients with pelvic lymph-node involvement had a 1-, 3- and 5-years ADTFS of 73.2%, 38.3% and 25.4% respectively, with a median ADTFS of 28 months (range 2-84); whilst the para-aortic group had a 1-, 3- and 5-years ADTFS of 64.9%, 39.2% and 19.6% respectively with a median ADTFS of 19 months (3-78) (p= 0.43). At the univariate and multivariate analysis, the number of treated lymph-nodes was associated with ADTFS: patients treated to one lymph-node had better ADTFS than patients treated on more than one lymph-node (p= 0.001; HR 1.68; IC: 1.08-2.59).

Polymetastatic-free survival

Pelvic patients had a 1-, 3- and 5-years PMFS of 94.3%, 82.9% and 75.4%; para-aortic patients had 1, 3 and 5 years PMFS respectively of 94.3%, 82.9% and 62.4% (p=0.10). Both at univariate and multivariate analysis, the number of treated nodes was associated with PMFS (p= 0.03; HR 2.01; IC: 1.06-3.78). The 5-years overall local control was 90.5%

Pattern of relapse

The pattern of relapse was also evaluated. Forty (40) pelvic patients recurred into the pelvis again (51.8%) while only 4 para-aortic patients (12.9%) had a pelvic relapse (p=0.001). Para-aortic patients relapsed more on para-aortic lymph-nodes (Table 3). At first progression, 77% pelvic and 71% para-aortic patients maintained an oligometastatic disease (p= 0.50). No toxicity events of grade 2 or higher were recorded.

Table 3. Pattern of relapse.

Site of relapse	total	pelvic	Para-aortic	P
Prostate bed	1	1 (1,3%)	0	/
Pelvis	44	40 (51,9%)	4 (12,9%)	0.001
Para-aortic nodes	25	13 (16,9%)	12 (38,7%)	0.16
Other lymph-nodes	6	3 (3,9%)	3 (9,6%)	0.24
Metastases	32	20 (26%)	12 (38,7%)	0.2

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Total	108	77	31	

Propensity score analysis

At the PSM analysis, randomization was 1:1 and 30 patients for each cohort were compared. Patients characteristics are summarized in Table 4. The median PFS was 26 months and 10 months respectively in pelvic and para-aortic group (p=0.20). One, 3 and 5 years PFS were 72.1%, 26%.5 and 26.5% in pelvic patients and 40%, 25% and 16.7% in para-aortic patients. Median BRFS was 12 months and 8 months respectively for pelvic and para-aortic patients (p=0.14) (Figure 2). No statistical differences were recorded between the 2 groups in ADTFS, BRFS, CRFS, PMFS and LPFS

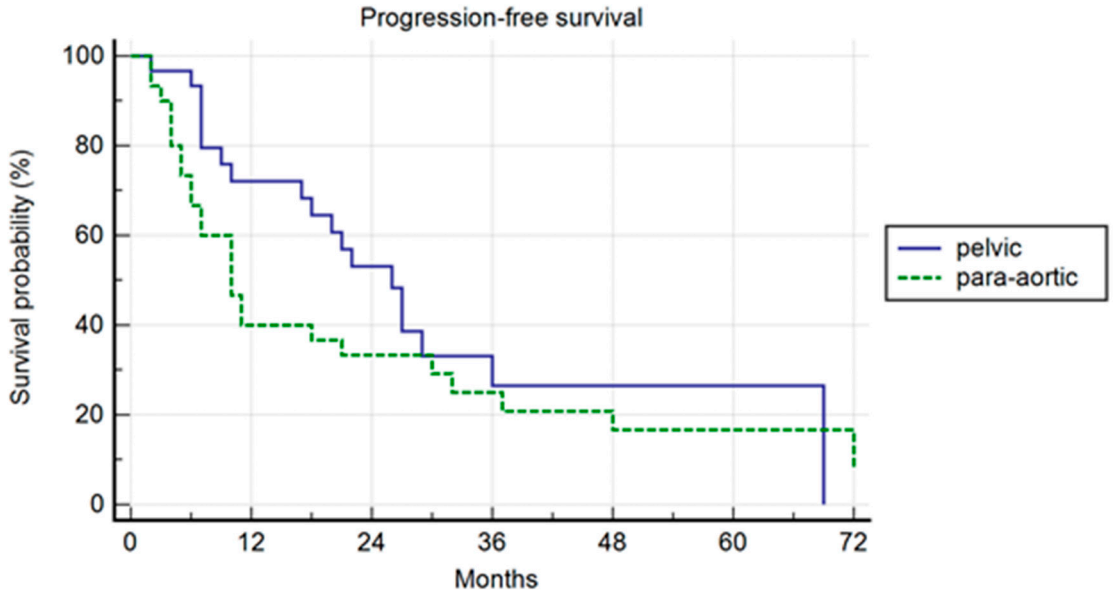

Figure 2. Kaplan-Meier of PFS at PSM.

Table 4. PSM: patients' characteristics.

	Pelvic (30)	Para-aortic (30)	p
High risk PC	26	26	1
PSA at SBRT	1.09 ng/ml (0.17-4.77)	1,1 ng/ml (0.23-4,67)	0.6
Median DFI	78.5 (11-155)	79 mesi (11-223)	1
SBRT on 1 node	17	17	1
Surgery as first treatment	26	26	1

 doi:10.20944/preprints202402.1720.v1

Previous ADT	15	17	0.53
PSA DT months	3,5 (2-8)	4,5 (1,5-17)	0.24
Cuncurrent ADT	4	3	0.69
PC: prostate cancer; SBRT: stereotactic body radiotherapy; DFI: disease-free interval; ADT: androgen deprivation therapy; DT: doubling time			

Discussion

Modern radiotherapy enables the precise delivery of high-dose treatments with minimal toxicity. . SBRT for oligometastases is widely accepted as a treatment strategy and PC patients may benefit from MDT in both in hormone-sensitive and in castration-resistant settings. This approach can help delay the initiation of systemic therapy, extend its duration, or facilitate a transition to a subsequent treatment line [19,23–25]."

In our study, we compared the efficacy of SBRT in treating pelvic and para-aortic oligometastatic lymph-nodes from PC. Para-aortic patients showed similar outcomes to pelvic patients. Specifically, neither the multivariate nor the PSM analysis showed any statistically significant difference in PFS or BRFS. Patients with para-aortic disease at presentation had a higher percentage of more than one pathological lymph-nodes compared to pelvic patients. The number of lymph-nodes treated was a predictive factor: patients with just one pathological lymph-node showed better outcomes than those with more than one lymph-node, suggesting a possibly higher burden of microscopical disease in patients with more extensive macroscopic disease. Despite the higher proportion of patients with unfavourable clinical variables in the para-aortic group, no statistically significant differences in outcomes were demonstrated, thus suggesting that SBRT is still a valid option in this group of patients.

Pelvic patients tend to experience recurrent in the pelvis in over half of the cases, whereas only one-third of para-aortic patients relapsed in the same site. [26]. Data from a study by Ost et al. documented that patients with nodal oligometastases typically continue to experience recurrences in the lymph nodes

Recently, Francolini et al. evaluated the pattern of relapse after SBRT in nodal para-aortic oligometastatic PC patients. The PFS was 10 months and 43% of recurrences were in para-aortic levels again [27]. Those data are comparable to our cohort, although in the abovementioned study both hormone-sensitive and castration-resistant PC patients were included.

Rich et al. described a different approach for treating para-aortic oligometastases by including the entire para-aortic nodal station with a dose of 45-50 Gy and a simultaneous integrated boost up to 60-65 Gy to PET-positive nodes in a series of 34 PC patients [28]. In this study, the 2-years PFS was 83.4%, but 2 events G3 (gastrointestinal and urinary) were recorded. Interestingly, The PFS was higher compared to our study. As previously described, in our population, 38.7% of para-aortic patients had a new oligorecurrence cranially to the same nodal station, suggesting the presence of a microscopic disease at the time of SBRT in a relevant proportion of patients. Considering this, the inclusion of a larger prophylactic volume might improve disease control. However, on one hand, this approach might lead to higher toxicity [28], on the other hand focal SBRT in PC oligometastases is virtually free of severe side effects and can be safely administered in metachronous oligometastases [11–13]. In fact, in this cohort more than half of the relapse occurred in other sites. For these patients with multiple microscopic metastases, a larger treatment volume would not have improved their prognosis. In addition, in our study more than 70% of patients had a sequential oligoprogression

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potentially amenable of SBRT rechallenge, suggesting that PFS may not the best endpoint to compare different radiotherapy approaches.

No differences in the rate of metastatic progression between pelvic and para-aortic nodes were found in our study. Considering Given the relatively indolent clinical behavior of para-aortic lymph-node and the possibility to effectively treat those lesions with SBRT, in the OMD disease spectrum, this localization could be considered closer to the pelvic lymph-node spread than purely distant metastasic disease. Therefore, a focused approach with a combination of SBRT with or without systemic treatment might be considered in selected cases.

This study however is not free from limitations: its retrospective nature exposes it to potential bias, though partly mitigated by the PSM analysis, and the limited number of para-aortic patients, that may have reduced the statistical power. Lastly, the different use of ADT between groups might have impacted on survival end-points. The definition of a specific setting of metastatic PC and diagnosis through PSMA or choline PET for all metastases represents instead a potential strength. Currently, there is ongoing research to identify patients with pure oligometastatic disease and determine relevant characteristics that can predict their response to MDT. Emerging evidence seems to show that PC with exclusive lymph-node metastases, can be considered a subset of metastatic PC with a typical indolent course and amenable of MDT. Definitely, in the future, also genomic profiling will help us identify patients that can benefit most from SBRT in the treatment of oligometastases.

Conclusion

Oligometastatic para-aortic disease seems to have similar outcomes compared to pelvic disease. Both groups have shown good local control with no relevant toxicity. Our data support the use of SBRT for para-aortic oligometastases. Further randomized prospective trials are warranted, to provide supporting evidence for SBRT commissioning in this setting and to elucidate which patients could benefit the most from this approach.

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