Salvage Stereotactic Body Radiotherapy for Isolated Lymph Node Recurrent Prostate Cancer: Single Institution Series of 94 Consecutive Patients and 124 Lymph Nodes

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Abstract

Stereotactic body radiotherapy is being investigated in nodal oligometastatic prostate cancer recurrences as an alternative to systemic treatment. This approach yields excellent in-field control and a low toxicity profile. In selected cases, this approach might also defer palliative androgen deprivation therapy.

Background: The purpose of the study was to evaluate the prostate serum antigen (PSA) response, local control, progression-free survival (PFS), and toxicity of stereotactic body radiotherapy (SBRT) for lymph node (LN) oligorecurrent prostate cancer. **Patients and Methods:** Between May 2012 and October 2015, 124 lesions were treated in 94 patients with a median dose of 24 Gy in 3 fractions. Seventy patients were treated for a single lesion and 25 for >1 lesion. In 34 patients androgen deprivation (AD) was combined with SBRT. We evaluated biochemical response according to PSA level every 3 months after SBRT: a 3-month PSA decrease from pre-SBRT PSA of more than 10% identified responder patients. In case of PSA level increase, imaging was performed to evaluate clinical progression. Toxicity was assessed every 6 to 9 months after SBRT. **Results:** Median follow-up was 18.5 months. In 13 patients (14%) Grade 1 to 2 toxicity was reported without any Grade 3 to 4 toxicity. Biochemical response, stabilization, and progression were observed in 64 (68%), 10 (11%), and 20 (21%) of 94 evaluable patients. Clinical progression was observed in 31 patients (33%) after a median time of 8.1 months. In-field progression occurred in 12 lesions (9.7%). Two-year local control and PFS rates were 84% and 30%, respectively. Age older than 75 years correlated with better biochemical response rate. Age older than 75 years, concomitant AD administered up to 12 months, and pelvic LN involvement correlated with longer PFS. **Conclusion:** SBRT is safe and offers good in-field control. At 2 years after SBRT, 1 of 3 patients is progression-free. Further investigation is warranted to identify patients who benefit most from SBRT and to define the optimal combination with AD.

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Keywords: Lymph node recurrence, Oligometastases, Recurrent prostate cancer, Robotic stereotactic radiotherapy, Salvage radioablation

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Introduction

For years, androgen deprivation (AD) has been considered a first-choice approach to recurrent prostate cancer (PC)[1] with significant side effects and a deterioration in the quality of life.[2] Evolution of imaging and radiotherapy (RT) modalities has allowed the diagnosis of low-burden recurrent cancer and enabled precise tumor-targeting using high doses per fraction (stereotactic ablative body RT [SBRT]). Interestingly, whole-body magnetic resonance imaging with diffusion-weighted noninvasive imaging of metastatic landing sites shows that 28% of the metastatic hormone-naive PC and 52% of the metastatic castration-resistant PC might be labeled as oligometastatic PC.[3] The treatment armamentarium for metastatic PC has changed significantly in the past decade, ranging from chemohormonal therapy to a metastasis-directed approach.[4,5] The potential elimination of all macroscopic cancer foci can reduce the burden of systemic therapies for recurrent/metastatic PC.[5-8] Indeed 51% of oligometastatic PC patients were progression-free 1 to 3 years after salvage metastasis-directed therapy.[5] PC is a radiosensitive disease and RT commonly plays a curative role in localized PC.[1,6] Theoretically, small-volume high-dose SBRT to limit recurrences from PC might reduce the tumor load prolonging the progression-free interval.

Stereotactic ablative body RT can be performed using linear accelerators (linacs) or dedicated machines such as GammaKnife or CyberKnife (Accuray Inc, Sunnyvale, CA).[9] Despite numerous reports on SBRT for various metastatic tumors, the experience of SBRT for metastatic PC is limited.[8,10-16] Most of PC SBRT reports include nonmetastatic organ-confined patient series.[17-20]

Initially, we used linac-based SBRT to treat oligometastases from PC. In 2007 a collaboration between the European Institute of Oncology, Milan, Italy and the CyberKnife Center Centro Diagnostico Italiano, Milan, included a prospective evaluation of the outcome. Our previous reports on SBRT for recurrent PC involving isolated lymph node (LN) metastases, showed excellent in-field control and a low toxicity profile.[11,20,21] These findings were confirmed in our subsequent larger series.[12,13] In this report we present a cohort of 94 patients (124 LNs) treated at the European Institute of Oncology with the Vero system (Mitsubishi Heavy Industries, Ltd., Tokyo, Japan and Brainlab AG, Feldkirchen, Germany) or CyberKnife-based SBRT for LN oligorecurrent PC. The patients from our previous reports are not included in this study (the patients from our previous series were treated using linac-based SBRT or CyberKnife-based SBRT at the Centro Diagnostico Italiano). The data of 41 patients from the current series have been used for the multi-institutional analysis accepted for the eighth European Multidisciplinary Meeting on Urological Cancers 2016 presentation.[14]

Patients and Methods

Inclusion Criteria

The criteria for inclusion in the study were: (1) isolated oligometastatic ($\leq$ 5) PC LN recurrence; (2) treatment with SBRT between May 2012 and October 2015; (3) all cases were approved by the multidisciplinary uro-oncology board; (4) written informed consent (wIC) for the SBRT; and (5) wIC for the use of the anonymized data for research or educational purpose. The study was a part of general SBRT and image-guided RT research notified to the Ethical Committee of the European Institute of Oncology, Milan, Italy (notifications 79/10, 86/11, 87/11, and 93/11).

The diagnosis of a clinically evident LN recurrent PC was on the basis of biochemical progression and imaging studies. Total body staging was required to exclude other disease sites using [^{11}C] choline positron emission tomography (PET)/computed tomography (CT), a CT scan of the thorax and abdomen and/or magnetic resonance imaging (MRI). LNs were classified as "pelvic" or regional (pLN) and "extrapelvic" or metastatic (eLN).

Any kind of previous PC therapy was permissible. Those who had begun systemic treatment when diagnosed with recurrent PC (which was given concomitantly with the SBRT) were admitted. No other local therapy for recurrent lesions was permitted.

Treatment Protocol

The SBRT dose prescribed was dependent on the volume of the LN and its location. In case of unfavorable location or reirradiation, lower dose per fraction or lower total dose was administered.

For CyberKnife SBRT, the Multiplan treatment planning system (version 2.0.5 Accuray) was used. Photon energy of 6 MV was used. Fiducials were not used. Xsight Spine detecting system (Accuray) was applied. All patients were immobilized during CT simulation and treatment, using a customized external vacuum-type cast. The gross tumor volume (GTV) was contoured on the CT scan and a 2-mm margin was added to the GTV to obtain the planning target volume (PTV). During the irradiation the patient position is controlled by the spine tracking system imaging (on average every 50 seconds). The dose was prescribed to the mean 77.5% isodose using a non-isocentric and noncoplanar CyberKnife treatment technique.

For Vero system SBRT, Iplannet (version 4.5.3; BrainLab) was used. All patients were immobilized during CT simulation and treatment using the Combifix (CIVCO Medical Solutions) device. Seven infrared markers were put on the chest wall for CT simulation and treatment session to correct the setup errors and the shifts during the treatment. The GTV was contoured on the CT scan and a 3-mm margin was added to the GTV to compensate for the geometrical penumbra of the system. These relatively narrow margins were feasible because of the high precision of CyberKnife and BrainLab Vero treatment delivery.[22,23] Several coplanar and no coplanar dynamic arcs were used for treatment planning. During Vero system beam delivery, the ExacTrac (BrainLab) system on the basis of the infrared markers, was used to monitor the position of the target.[11] Cone-beam CT (CBCT) was performed before every Vero system session. Daily treatment times were kept at less than 15 to 20 minutes.

Organs at risk depended on the localization of the LN. For pLN, the rectum (external contour), urinary bladder (external contour), urethra, femoral heads, and small bowel were contoured. The dose volume constraints of Timmerman et al were applied.[24] Particular attention was paid to patients who had already been irradiated and SBRT was used for in-field LN recurrence: for all those patients the original treatment plans were reviewed.

After SBRT, a prostate serum antigen (PSA) test was performed every 3 months (first evaluation after SBRT was performed at 3 months) and clinical examination every 6 months. Biochemical response was defined a reduction of PSA value $>$ 10% (complete if $>$ 50%) with respect to pre-SBRT PSA value. Stabilization referred

to 3-month PSA between 10% and −10% of the pre-SBRT value.[13] A PSA increase > 10% was classified as biochemical progression. In case of biochemical failure, radiological (CT or MRI) or [^{11}C]choline PET/CT re-evaluation was requested.

Statistical Analysis

Continuous data were expressed as mean ± SD if normally distributed, as median and range or interquartile range otherwise; categorical variables were expressed as percentages. Progression-free survival (PFS) and local progression were calculated from date of the end of SBRT treatment to the date of biochemical or clinical progression, respectively, or latest follow-up. In the analysis of local progression reported in the treatment field, any other clinical or biochemical out-of-field (ie, planning treatment volume or PTV) event, as well as any deaths, were considered as competing events.[25] Because of the very small number of deaths, no overall survival rate was calculated. Survival data were represented using the Kaplan−Meier approach[26] with differences between groups evaluated using the log rank test. Prognostic factors were evaluated using a multivariate proportional hazard Cox model.[27] Factors were included in the multivariable models if its univariate P value was ≤ .20. Covariates included in the models were selected among the following: primary treatment (surgery vs. surgery with RT vs. RT), initial Gleason score, initial T status (T1, T2, T3/4), SBRT treatment machine (Vero system vs. CyberKnife), age at the time of SBRT, concomitant AD (no vs. ≤ 12 months vs. ≥ 12 months), Karnofsky score, SBRT as first treatment or no, number of lesions per patient, and pLN versus eLN. Results from Cox multivariable models were presented in terms of hazard ratio and 95% confidence interval along with the Wald test P value. The Gray model,[28] which takes competing events into account, was performed for the analysis of local events. The significance of differences was assessed using Pearson χ^2 for categorical variables. Factors associated with response to treatment were evaluated using logistic regression. The analyses were performed with the SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC). The plot and estimates of the cumulative incidence for local control were performed using the R software (http://cran.r-project.org) with the cmprsk library developed by Gray (https://cran.r-project.org/web/packages/cmprsk/cmprsk.pdf). All reported P values were 2-sided.

Results

Patients

Ninety-four patients with LN oligorecurrent PC (124 LNs) were included in the study between May 2012 and October 2015. The median age at the time of the SBRT was 70.7 years. All baseline characteristics are shown in Table 1. The median interval between the diagnosis of PC and the first day of SBRT treatment was 49.6 months (range, 27.2-122.4 months).

Total body staging was performed to exclude other sites of disease: 90, 3, and 1 patient underwent [^{11}C]choline PET/CT, MRI, and CT examination, respectively.

Treatment

CyberKnife-SBRT or Vero system-SBRT was applied in 10 (10.6%) and 84 (89.4%) patients, respectively. Seventy patients (74.5%) had single LN and in 24 (25.5%) more than 1 (2−4) LNs were treated concomitantly (synchronous SBRT). Only 1 patient had 4 LNs involved. Five and 1 patient were treated with 2 and 3 SBRT treatments (metachronous SBRT) for different LN recurrences, respectively. In 2 cases SBRT was repeated to the same LN because of in-field relapse.

Median PSA pre-SBRT was 3.5 ng/mL. In 9 patients (9.6%) SBRT was performed as a reirradiation (the recurrent lesion was situated in the previously irradiated volume) and for 86 patients (90.4%) SBRT was a first radiation treatment.

For 34 patients (36.2%), some form of neoadjuvant and concomitant AD was combined with SBRT treatment (median duration, 14.5 months). One patient was castration-resistant and received a taxane-based chemotherapy regimen before SBRT.

Table 1 Patient and Tumor Characteristics (N = 94 Patients)

Characteristic	Value
Initial Treatment	
RRP with or without AD	39 (41.5%)
RRP with RT with or without AD	34 (36.2%)
RT with or without AD	19 (20.2%)
Brachytherapy	2 (2.1%)
Initial PSA (ng/mL)[a]	
n	88 (6 missing data)
Median (IQR)	9.8 (6.1-18.0)
Initial Gleason Score[b]	
n	89 (5 missing data)
Median (IQR)	7 (7-8)
Initial T[c]	
T1	10 (10.6%)
T2	29 (30.9%)
T3	50 (53.2%)
T4	2 (2.1%)
T unknown	3 (3.2%)
SBRT Treatment	
Vero system (Mitsubishi-Brainlab)	84 (89.4%)
CyberKnife (Accuray)	10 (10.6%)
Age at the SBRT, Years	
n	94
Mean ± SD	69.7 (8.0)
Median (IQR)	70 (65-76)
KPS at the SBRT	
80	2 (2.1%)
90	26 (27.7%)
100	66 (70.2%)
Interval Between Diagnosis of Prostate Cancer and SBRT, Months	
N	94
Mean ± SD	74.8 (47.6)
Median (IQR)	61 (41-109)

Abbreviations: AD = androgen deprivation; IQR = interquartile range; KPS = Karnofsky performance status; PSA = prostate serum antigen; RRP = radical retropubic prostatectomy; RT = radiotherapy; SBRT = stereotactic body radiotherapy.
[a]Initial PSA available in 88 patients.
[b]Initial Gleason Score available in 90 patients (%).
[c]Clinical/pathological T.

All patients completed the SBRT. No protocol violation was recorded. The median dose was 24 Gy (range, 15−36 Gy) in 3 fractions. The median biological effective dose was 152 (range, 65−324) calculated on the basis of $\alpha/\beta = 1.5$ Gy. The median duration of the SBRT course was 3 days (the treatment was given on consecutive days in most patients; Table 2).

Follow-up

No patient was lost to follow-up. The median follow-up period was 18.5 months (range, 3−42 months). At the time of the analysis, 32 (34%) patients were alive with no evidence of disease, 60 (63.8%) were alive with clinically evident disease, and 2 (2.2%) patients died (Table 3).

Table 2 Patient and SBRT Treatment Characteristics (N = 94 patients,124 Lesions)

Characteristic	Value
Pre-SBRT PSA, ng/mL	
N	94
Median (IQR)	3.5 (1.6-6.1)
Number of Lymph Nodes at SBRT	
1	70 (74.5%)
2	19 (20.2%)
3	4 (4.3%)
4	1 (1.0%)
Total Lymph Nodes (Per Lesion)	124
Pelvic	75 (60.5%)
Extrapelvic	49 (39.5%)
SBRT as	
1st Treatment	85 (90.4%)
Reirradiation	9 (9.6%)
Concomitant Systemic Treatment	
Yes (ADT)	34 (36.2%)
Yes (Other)	3 (3.2%)
No	57 (60.6%)
SBRT Data (Per Lesion)	
Total median dose (range), Gy	24 (15-36)
Median dose per fraction (range)	8 (5-12)
Median number of fractions (range)	3 (3-6)
SBRT Regimen (Per Lesion), n	
5 Gy per 3 fractions	2
5 Gy per 5 fractions	8
6 Gy per 3 fractions	3
6 Gy per 4 fractions	2
6 Gy per 5 fractions	7
8 Gy per 3 fractions	65
8 Gy per 4 fractions	3
10 Gy per 3 fractions	23
12 Gy per 3 fractions	2
Other	9

Abbreviations: ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate serum antigen; SBRT = stereotactic body radiotherapy.

Tumor Outcome

Response. At 3 months PSA evaluation was performed: biochemical response (BR) was defined as a PSA level reduction > 10% of pre-SBRT value (complete if > 50%), stabilization referred to pre-SBRT PSA level ± 10%, and progression if PSA was 10% greater than pre-SBRT PSA value. BR or stable disease was observed in 74 of 94 patients (78.7%). In 20 patients (21.3%) progressive disease was observed. During follow-up, clinical progression was observed in 31 patients (33%) after a median time of 8.1 months (range, 2.3−31.8 months) from SBRT. Considering all progressive disease events (61 patients, ie, 20 and 41 patients with progression at first evaluation and during follow-up, respectively), 30 (32%) patients showed only biochemical progression, and 31 (33%) biochemical and clinical progression. Eleven patients (12%) had locoregional recurrence and 20 patients (21%) had distant metastases of whom 10 showed only LN progression. In-field progression was observed in 12 of 124 irradiated LNs (9.7%) after a median time of 7 months (range, 4-22 months). In-field progressions were 4 (3.2%) in the subgroup of patients who received concomitant AD. Two-year local control and PFS probability were 84% and 30%, respectively (Figures 1 and 2). In patients treated with concomitant AD, 2-year PFS and local control probability were 49.4% and 27.2%, respectively. In patients treated with SBRT alone, 2-year PFS and local control probability were 22.6% and 25.1%, respectively.

In multivariate analysis age older than 75 years was correlated with a better biochemical response rate ($P = .047$). RT as primary treatment was correlated with lower response rate ($P = .04$). Also pre-SBRT PSA level had a negative effect on response rate if between 4 and 10 ng/mL or > 10 ng/mL ($P = .04$ and .05, respectively; Table 4). Age older than 75 years, AD administered up to 12 months, and pLN involvement were correlated with longer PFS ($P < .01$, $P = .03$, and $P = .01$ if 1 pLN was involved and $P = .02$ if 2 pLNs were involved; Table 5). RT as primary treatment and pre-SBRT PSA level between 4 and 10 ng/mL were correlated with a lower PFS rate ($P = .03$ and $P = .01$, respectively).

In the 57 patients treated with salvage SBRT alone with no concomitant therapy, PSA response, stabilization, and progression were observed in 38 (66.6%), 9 (16%), and 10 (17.5%) cases, respectively. In 17 patients (36%) with progressive disease after SBRT, AD was started in a median time of 7.2 months (range, 2.4−32.1 months). In 38% of patients AD was deferred by at least 1 year. AD was administered to those patients when not only PSA value increased more than 10% over pre-SBRT values but a trend in increasing was confirmed in a second PSA value 30 to 45 days later. PFS was longer when AD was combined with SBRT for a period of less than 12 months (median PFS in these patients: 28 months vs. 11 months; $P = .03$ vs. $P = .24$, in the patients with AD for > 12 months).

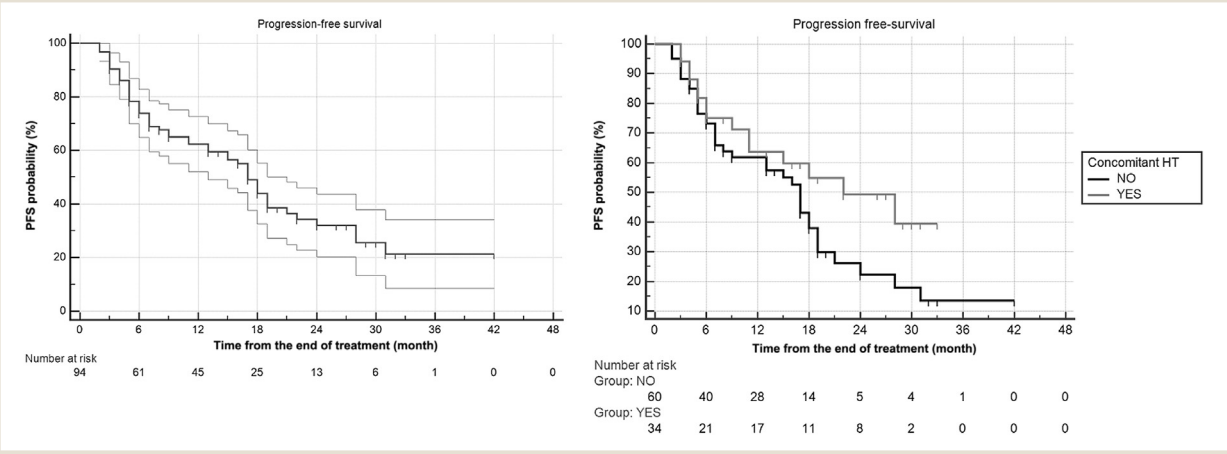
In the subgroup of patients who received concomitant AD PSA response, stabilization, and progression were observed in 25 (73.5%), 1 (2.9%), and 8 (23.5%), respectively. Biochemical complete response was found in 20 (58.8%) of those patients. Furthermore, clinical progression was reported in 5 patients (14.7%) who received concomitant AD after a median of 9.1 months (range, 3.9−28.3 months; Table 3).

Table 3 Treatment Response and Disease Progression (94 Patients With Follow-Up)

Characteristic	All Patients	Only Extrapelvic	1 Pelvic LN	2 Pelvic LNs
Patients With Follow-Up Data	N = 94	n = 27	n = 59	n = 8
Biochemical Response to SBRT at First Follow-Up				
All patients				
CR	40 (42.6)	7 (25.9)	28 (47.5)	5 (62.5)
PR	24 (25.5)	7 (25.9)	16 (27.1)	1 (12.5)
SD	10 (10.6)	4 (14.8)	5 (8.5)	1 (12.5)
PD	20 (21.3)	9 (33.3)	10 (16.9)	1 (12.5)
Biochemical Response in Patients With No Neoadjuvant and/or Concomitant Systemic Therapy (CHT/AD)	N = 57	n = 14	n = 39	n = 4
CR	19 (33.3)	2 (14.3)	16 (41.0)	1 (25.0)
PR	19 (33.3)	5 (35.7)	13 (33.3)	1 (25.0)
SD	9 (15.8)	4 (28.6)	4 (10.3)	1 (25.0)
PD	10 (17.5)	3 (21.4)	6 (15.4)	1 (25.0)
Biochemical Response in Patients With Neoadjuvant and/or Concomitant AD	N = 34	n = 12	n = 18	n = 4
CR	20 (58.8)	5 (41.7)	11 (61.1)	4 (100)
PR	5 (14.7)	2 (16.6)	3 (16.7)	0
SD	1 (2.9)	0	1 (5.6)	0
PD	8 (23.5)	5 (41.7)	3 (16.7)	0
Disease Progression During Follow-Up	n = 94	n = 27	n = 59	n = 8
No	33 (35.1)	6 (22.2)	24 (40.7)	3 (37.5)
Biochemical	30 (31.9)	12 (44.4)	17 (28.8)	1 (12.5)
Clinical (locoregional lymph nodes)	11 (11.7)	3 (11.1)	6 (10.2)	2 (25.0)
Clinical with metastasis	20 (21.3)	6 (22.2)	12 (20.3)	2 (25.0)
Disease Progression During Follow-Up in Patients With No Neoadjuvant and/or Concomitant Systemic Therapy (CHT/AD)	N = 57	n = 14	n = 39	n = 4
No	17 (29.8)	3 (21.4)	14 (35.9)	0
Biochemical	15 (26.3)	4 (28.6)	10 (25.6)	1 (25)
Clinical (locoregional lymph nodes)	10 (17.6)	3 (21.4)	6 (15.4)	1 (25)
Clinical with metastasis	15 (26.3)	4 (28.6)	9 (23.1)	2 (50)
Disease Progression During Follow-Up in Patients With Neoadjuvant and/or Concomitant AD	N = 34	n = 12	n = 18	n = 4
No	16 (47.1)	3 (25)	10 (55.6)	3 (75)
Biochemical	13 (38.2)	7 (58.3)	6 (33.3)	0
Clinical (locoregional lymph nodes)	1 (2.9)	0	0	1 (25)
Clinical with metastasis	4 (11.8)	2 (16.7)	2 (11.1)	0
Site of Metastasis After Lymph Node SBRT, n				
Lymph nodes	10	3	5	2
Bones	5	1	4	0
Lymph nodes and bones	2	1	1	0
Muscles	1	0	1	0
Bones and lung	1	0	1	0
Bones and muscles	1	1	0	0
Status at Last Contact				
Alive without disease	32 (34.0)	6 (22.2)	23 (39.0)	3 (37.5)
Alive with disease	60 (63.8)	20 (74.1)	35 (59.3)	5 (62.5)
Died of disease	1 (1.1)	1 (3.7)	0	0
Died	1 (1.1)	0	1 (1.7)	0
Follow-Up Duration, Months				
Median (range)	18.5 (3-42)	17 (3-42)	19 (4-35)	21 (3-33)

Data are presented as n (%) except where otherwise noted.
Abbreviations: AD = androgen deprivation; CHT = chemotherapy; LN = lymph node; SBRT = stereotactic body radiotherapy.

Figure 1 Progression-Free Survival (PFS) Curve, Including Biochemical and Clinical Progression



All events of clinical failure were preceded by biochemical progression. Median PFS rates in patients treated for the single versus multiple LNs were 16 and 11 months, respectively. Median PFS rates in patients treated for eLN was 6 months, whereas for patients treated for 1 or 2 pLNs median PFS was 18 and 15.5 months ($P = .01$ vs. $P = .02$), respectively.

Toxicity

Follow-up examinations were performed every 6 to 9 months after SBRT. In 88 patients (92.6%) no acute or late toxicity was observed. Acute toxicity included urinary (6 and 1 Grade 1 and Grade 2 events, respectively) and rectal events (1 Grade 1). Late toxicity included urinary (2 and 3 Grade 1 and Grade 2 events, respectively). No toxicity was registered in the patients treated for eLN.

Discussion

To the best of our knowledge this is the largest series on isolated LN recurrent PC treated with salvage SBRT. Our study showed that salvage SBRT is a safe approach in this scenario; it offers a high in-field tumor control rate and a low toxicity profile. More than 50% of patients were free of progression at 1 year after the SBRT and one-third remained progression-free at 2 years. In patients who received concomitant AD, PFS rates were 64.2% and 49.4% at 12 and 24 months, respectively, whereas in patients treated with SBRT alone were 62.2% and 22.6%, respectively. Only 12 cases of in-field progression (9.7%) were observed. A complete biochemical response was observed in almost 33% of the lesions treated with exclusive SBRT alone (no concomitant AD). The side effects observed were mild and almost 93% of all patients did not experience any toxicity at all. Indeed, our series included unselected real-world patients referred for low-burden metastasis-directed SBRT (worse-prognosis patients like eLN, reirradiation, presence of more than 1 LN, long pre-SBRT AD, castration-resistant disease etc, were included). Such good results despite inclusion of numerous unfavorable-prognosis patients makes SBRT a valuable salvage treatment option for LN oligometastatic PC that should be

Figure 2 Local Recurrence Cumulative Incidence (LRci)

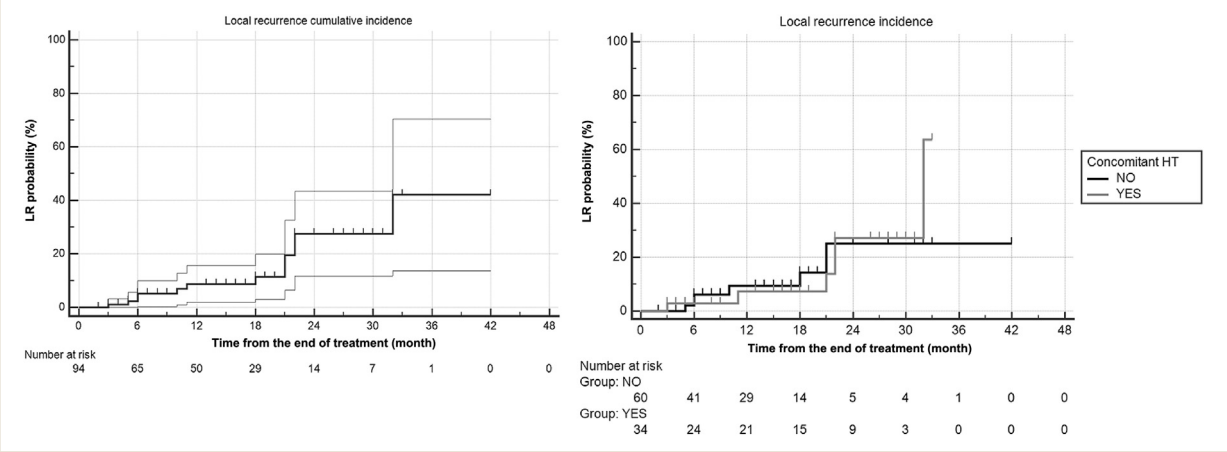


Table 4 Uni- and Multivariate Analysis of Factors Correlated With Better Biochemical Response to SBRT at First Follow-Up (N = 94)

		Univariate		Multivariate[a]	
Variable	**n**	**Positive Response (CR + PR + SD), %**	***P*[b]**	**OR (95% CI)[c]**	***P* (Wald χ^2)**
All Patients	94	74 (78.7)			
Primary Treatment			.07		
RRP	39	34 (87.2)		1	
RRP with RT with or without AD	34	27 (79.4)		0.47 (0.11-2.02)	.31
RT (BT) with or without AD	21	13 (61.9)		0.14 (0.02-0.87)	**.04**
Initial GS (Total)			.60[d]		
≤6	15	10 (66.7)			
7	48	40 (83.3)			
≥8	26	20 (76.9)			
Initial T			.18[d]		
1	10	6 (60)			
2	29	24 (82.8)			
3	50	41 (82.0)			
4	2	2 (100.0)			
Unknown	3	1			
Treatment			.92		
Vero system (Mitsubishi-Brainlab)	84	66 (78.6)			
CyberKnife (Accuray)	10	8 (80.0)			
Age at SBRT, n			.09		
≤65	23	18 (78.3)		1	
66-70	25	19 (76.0)		0.73 (0.44-1.81)	.70
71-75	23	15 (65.2)		0.44 (0.28-1.42)	.31
>75	23	22 (95.6)		14.3 (1.04-195)	**.047**
AD			.92		
No	60	48 (80.0)			
≤12 months	13	10 (76.9)			
>12 months	21	16 (76.2)			
KPS at SBRT			.32		
80-90	29	21 (72.4)			
100	65	53 (81.5)			
Pre-SBRT PSA (ng/mL)			.01		
<4	52	47 (90.4)		1	
4-10	29	20 (69.0)		0.23 (0.06-0.90)	**.04**
>10	12	7 (58.3)		0.18 (0.03-1.02)	**.05**
SBRT as			.94		
1st Radiotherapy	85	67 (78.8)			
Reirradiation	9	7 (77.8)			
Lesions, n			.27		
1	70	57 (81.4)			
≥2	24	17 (70.8)			
Ln Pelvic Site			.08[d]		
0 (Extrapelvic)	27	18 (66.7)		1	
1	59	49 (83.0)		1.47 (0.41-5.30)	.56
2	8	7 (87.5)		11.9 (0.64-222.5)	.1

Statistically significant *P* values are shown in bold.
Abbreviation: AD = androgen deprivation therapy; BT = brachytherapy; GS = Gleason score; KPS = Karnofsky performance status; Ln = lymph node; PSA = prostate serum antigen; RRP = radical retropubic prostatectomy; SBRT = stereotactic body radiotherapy.
[a]Includes the variables statistically significant after univariate analysis ($P < .1$).
[b]Pearson χ^2.
[c]OR > 1 means higher probability of positive response to treatment.
[d]Mantel-Haenszel test per trend.

Table 5 Uni- and Multivariate Analysis of Factors Correlated With Longer Progression-Free Survival (94 Patients With Follow-Up)

Variable	N	Univariate			Multivariate[a]	
		Events, n[b]	Median Survival (95% CI), Months	*P*[c]	HR (95% CI)	*P* (Wald χ^2)
All Patients	94	61	15 (9-18)			
Primary Treatment				.19		
RRP	39	22	17 (8-30)		1	
RRP with RT	34	22	17 (8-19)		0.91 (0.46-1.82)	.79
RT (BT)	21	17	7 (5-18)		2.44 (1.10-5.40)	**.03**
Initial GS (Total)				.25		
≤6	15	11	17 (3-21)			
7	48	35	13 (7-17)			
≥8	26	13	18 (5-inf)			
Initial T[d]				.84		
1	10	7	9.5 (3-inf)			
2	29	20	17 (8-21)			
3	50	31	13 (6-18)			
4	2	1	—			
Treatment				.63		
Vero system (Mitsubishi-Brainlab)	84	54	15 (9-19)		1	
CyberKnife (Accuray)	10	7	17 (3-18)		0.56 (0.21-1.52)	.26
Age at SBRT, n				.15		
≤65	23	18	9 (5-19)		1	
66-70	25	17	13 (5-17)		0.89 (0.44-1.81)	.88
71-75	23	14	14 (5-21)		0.63 (0.28-1.42)	.27
>75	23	12	28 (10-31)		0.30 (0.13-0.72)	**<.01**
AD				.13		
No	60	43	15 (7-18)		1	
≤12 Months	13	6	28 (5-inf)		0.35 (0.14-0.88)	**.03**
>12 Months	21	12	11 (5-inf)		0.62 (0.28-1.37)	.24
KPS at SBRT				.43		
80-90	29	19	11 (5-18)			
100	65	42	17 (9-19)			
Pre-SBRT PSA (ng/mL)				.22 (.01)[b]		
<4	52	29	17 (13-21)		1	
4-10	29	21	7 (4-18)		2.27 (1.18-4.35)	**.01**
>10	12	10	8.5 (4-18)		1.15 (0.49-2.70)	.75
SBRT as				.64		
1st Radiotherapy	85	57	15 (9-18)			
Re-irradiation	9	4	Nonestimable			
Lesions, n				.89		
1	70	45	16 (9-19)			
≥2	24	16	11 (5-21)			
Ln Pelvic Site				.04		
0 (Extrapelvic)	27	21	6 (4-17)		1	
1	59	35	18 (10-24)		0.41 (0.21-0.81)	**.01**
2	8	5	15.5 (5- inf)		0.23 (0.07-0.76)	**.02**

Statistically significant *P* values are shown in bold.
Abbreviations: AD = androgen deprivation therapy; BT = brachytherapy; GS = Gleason score; HR = hazard ratio; inf = infinite; KPS = Karnofsky performance status; Ln = lymph node; PSA = prostate serum antigen; RRP = radical retropubic prostatectomy; RT = radiotherapy; SBRT = stereotactic body radiotherapy.
[a]Includes the variables statistically significant after univariate analysis ($P < .2$).
[b]Wilcoxon test.
[c]Log-rank test.
[d]Wald χ^2.

compared with the standard salvage systemic therapy. Ongoing studies will hopefully help to define the best treatment strategy for oligometastatic and oligorecurrent PC.[29]

Stereotactic ablative body RT allows delivery of higher dose per fraction with more significant cytotoxic efficacy and less dose to normal tissues and organs at risk.[30] This advanced technique allowed us to implement the hypofractionation. Recently, interest in SBRT has increased because of its potential in curative finality in the oligometastatic setting. Hellmann and Weichselbaum[31] first defined the concept of oligometastatic that since has been considered as a limited disease extension of up to 3 or 5 detectable metastases.[32,33] Afterward, various studies evaluated the possible curative aim of local treatments (ie, surgery, SBRT, high-intensity focused ultrasound etc) in this particular metastatic scenario. Importantly, tumor-directed irradiation can produce a systemic antitumor activity called the abscopal effect and this phenomenon could at least partially explain the benefit of metastases-directed therapy on the malignant disease course in general.[34]

In our institution 2 technologies are available for SBRT: CyberKnife and Vero system. These 2 systems differ in image guidance: Vero system is pretreatment CBCT-based but CyberKnife is on the basis of infratreatment x-ray. Thus, CyberKnife needs fiducials or spine tracking. CyberKnife is preferred when particular attention to critical structures is required and spine tracking is possible. If considering LN recurrence, the length of treatment delivery with CyberKnife is higher than with the Vero system. For all of these considerations we reserved selected cases for CyberKnife. This choice showed no effect on treatment response, however, the low number of patients treated with CyberKnife makes the definitive comparison of these 2 SBRT approaches unfeasible (Table 4).

Concerning PC, AD remains the gold standard treatment in the metastatic setting. In higher-volume metastatic disease added use of chemotherapy might increase tumor control, whereas the effect of chemohormonal therapy in low-volume metastatic PC remains unclear.[4] AD can negatively affect the quality of life as well as the metabolism, and increase occurrence of cardiovascular events and metabolic syndrome.[35,36] Therefore, local therapies are investigated to delay the AD administration. Some authors have introduced the concept of AD therapy-free survival, showing median time of AD deferral of 38 months and AD-free survival of 82% at 1 year.[15] In our series, the response rates were similar in patients treated with SBRT alone or with concomitant AD. On the contrary, AD had a great effect on PFS: if AD was administered for a period of a maximum of 12 months median PFS was 28 months versus 15 months of AD-free patients. This is in accordance with the review of metastasis-directed therapy by Ost et al.[5] The group with AD longer than 12 months had a poor PFS (11 months). This finding might be explained by the inclusion in the long-AD group the patients with long history of PC (initial phase of castration-resistance?). SBRT performed after a long period of AD might be less effective because of radioresistance of heavily AD pretreated PC cells.[36] Our patients who were treated with SBRT alone, showed a median AD-free survival of 7 months with the longest AD-free survival was 32 months. Importantly, in almost 40% of patients AD was deferred by at least 1 year. However, patients treated with SBRT and concomitant AD showed a higher rate of biochemical responses (73.5% vs. 66.6% of patients treated with SBRT alone) and lower rate of progression (52.9% vs. 70.2% of patients treated with SBRT alone). These differences need to be further investigated to define the effect of the combined approach (SBRT with AD vs. SBRT or AD alone) on primary (overall survival) and secondary (biochemical control, etc) end points. Our series showed better outcome in pLN recurrence. Patients with single-pLN recurrence experienced progression of disease later than the ones with 2-pLN recurrence (median PFS of 18 vs. 15.5 months). eLN involvement was associated with poor median PFS (6 months).

Regarding the management of progressive disease, in almost 50% of our patients AD was started but in 20% of patients a new course of SBRT was performed underlining that repeated SBRT is safe without relevant events.

The local control rate we obtained with SBRT represents a milestone: only 12 in-field progression events of 124 treated lesions. This finding suggests relevant clinical implications such as preventing the local compression and invasion of closer organs that is considerable especially for PC long life expectancy. Moreover, most of the in-field progressions occurred after 12 months from SBRT: that implies a possible palliative reirradiation. The dose used in our study was relatively low and atoxic, suggesting there is room for dose escalation in future SBRT for isolated LN recurrence. Several investigators discuss the necessity of single LN versus whole pelvis salvage irradiation[5,37,38]: prospective comparison is warranted to define the best treatment option. We remark on the favorable toxicity profile in our series with no Grade $>$ 2 acute or late events. Our longest follow-up was 42 months so other updates of this cohort of patients are required to evaluate possible late toxicities. To our knowledge no studies with longer follow-up have been so far published.

Conclusion

Stereotactic ablative body RT is a feasible approach to LN oligorecurrent PC, offering excellent in-field tumor control and an extremely low toxicity profile. At least half of the patients were progression-free at 1 year after SBRT, one-third was progression-free at 2 years. Among patients treated with SBRT alone, almost 40% of patients were AD-free at 1 year. Further investigations are needed to identify the patients who would most benefit from this treatment modality delivered alone or in combination with AD or chemohormonal therapy.

Clinical Practice Points

- SBRT is feasible in prostate cancer lymph nodal oligorecurrences.
- Local control is very high with in field recurrences in less than 10% of cases.
- Toxicity profile is favorable with only G1-G2 toxicity in low percentage of patients.
- This approach can delay androgen deprivation therapy administration: in our cohort only 36% of patients showed progressive after SBRT alone and started ADT after 7 months.

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"Short-term high precision RT for early PC with concomitant boost to the dominant lesion," registered at ClinicalTrials.gov (NCT01913717), approved by the Instituto Europeo di Oncologia (IEO) S768/113 and IG-14300 "Carbon ions boost followed by pelvic photon RT for high risk prostate cancer," registered at ClinicalTrials.gov (NCT02672449), approved by IEO R86/14-IEO 98 and by research grants from Fondazione IEO.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. National Comprehensive Cancer Network. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, version 2.2016. Prostate cancer, Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#prostate. Accessed: October 4, 2016.
2. Smith DP, King MT, Egger S, et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *BMJ* 2009; 339: b4817.
3. Graziani T, Ceci F, Castellucci P, et al. (11)C-choline PET/CT for restaging prostate cancer. Results from 4,426 scans in a single-centre patient series. *Eur J Nucl Med Mol Imaging* 2016; 43:1971-9.
4. Saluja R, Cheung P, Zukotynski K, et al. Disease volume and distribution as drivers of treatment decisions in metastatic prostate cancer: from chemohormonal therapy to stereotactic ablative radiotherapy of oligometastases. *Urol Oncol* 2016; 34:225-32.
5. Ost P, Bossi A, Decaestecker K, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol* 2015; 67:852-63.
6. Jereczek-Fossa BA, Orecchia R. Evidence-based radiation oncology: definitive, adjuvant and salvage radiotherapy for non-metastatic prostate cancer. *Radiother Oncol* 2007; 84:197-215.
7. Ploussard G, Almeras C, Briganti A, et al. Management of node only recurrence after primary local treatment for prostate cancer: a systematic review of the literature. *J Urol* 2015; 194:983-8.
8. Ingrosso G, Trippa F, Maranzano E, et al. Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: a two-institution experience. *World J Urol* 2017; 35:45-9.
9. Chang BK, Timmerman RD. Stereotactic body radiation therapy: a comprehensive review. *Am J Clin Oncol* 2007; 30:637-44.
10. Ost P, Jereczek-Fossa BA, Van As N, et al. Pattern of progression after stereotactic body radiotherapy for oligometastatic prostate cancer nodal recurrences. *Clin Oncol (R Coll Radiol)* 2016:e115-20.
11. Jereczek-Fossa BA, Fariselli L, Beltramo G, et al. Linac-based or robotic image-guided stereotactic radiotherapy for isolated lymph node recurrent prostate cancer. *Radiother Oncol* 2009; 93:14-7.
12. Ost P, Jereczek-Fossa BA, As NV, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. *Eur Urol* 2016; 69:9-12.
13. Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; 82:889-97.
14. Ost P, Van As N, Pasquier D, et al. Stereotactic body radiotherapy for nodal oligorecurrent prostate cancer: a multi-institutional analysis. *Eur Urol Suppl* 2016; 15:e1642-3.
15. Berkovic P, De Meerleer G, Delrue L, et al. Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. *Clin Genitourin Cancer* 2013; 11:27-32.
16. Friedland JL, Freeman DE, Masterson-McGary ME, et al. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat* 2009; 8:387-92.
17. Buyyounouski MK, Price RA Jr, Harris EE, et al. Stereotactic body radiotherapy for primary management of early-stage, low- to intermediate-risk prostate cancer: report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee. *Int J Radiat Oncol Biol Phys* 2010; 76:1297-304.
18. Henderson DR, Tree AC, van As NJ. Stereotactic body radiotherapy for prostate cancer. *Clin Oncol (R Coll Radiol)* 2015; 27:270-9.
19. Baker BR, Basak R, Mohiuddin JJ, et al. Use of stereotactic body radiotherapy for prostate cancer in the United States from 2004 through 2012. *Cancer* 2016; 122: 2234-41.
20. Vavassori A, Jereczek-Fossa BA, Beltramo G, et al. Image-guided robotic radiosurgery as salvage therapy for locally recurrent prostate cancer after external beam irradiation: retrospective feasibility study on six cases. *Tumori* 2010; 96:71-5.
21. Zerini D, Jereczek-Fossa BA, Fodor C, et al. Salvage image-guided intensity modulated or stereotactic body reirradiation of local recurrence of prostate cancer. *Br J Radiol* 2015; 88:20150197.
22. Garibaldi C, Piperno G, Ferrari A, et al. Translational and rotational localization errors in cone-beam CT based image-guided lung stereotactic radiotherapy. *Phys Med* 2016; 32:859-65.
23. Mastella E, Vigorito S, Rondi E, et al. Validation of a pretreatment delivery quality assurance method for the CyberKnife Synchrony system. *Med Phys* 2016; 43:4565.
24. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008; 18:215-22.
25. Marubini E, Valsecchi MG. *Analysing Survival Data From Clinical Trials and Observational Studies*. Chichester: John Wiley & Sons; 1995.
26. Kaplan E, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-81.
27. Cox DR. Regression models and life-tables (with discussion). *J R Stat So Ser B* 1972; 34:187-220.
28. Gray RJ. A class of K-sample tests form comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; 16:1141-54.
29. Decaestecker K, De Meerleer G, Ameye F, et al. Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial. *BMC Cancer* 2014; 14:671.
30. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303:1070-6.
31. Hellmann S, Weichselbaum R. Oligometastases. *J Clin Oncol* 1995; 13:8-10.
32. Alongi F, Arcangeli S, Filippi AR, et al. Review and uses of stereotactic body radiation therapy for oligometastases. *Oncologist* 2012; 17:1100-7.
33. Golden EB, Chhabra A, Chachoua A, et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. *Lancet Oncol* 2015; 16: 795-803.
34. Lilleby W, Stensvold A, Dahl AA. Fatigue and other adverse effects in men treated by pelvic radiation and long-term androgen deprivation for locally advanced prostate cancer. *Acta Oncol* 2016; 9:1-7.
35. Zareba P, Duivenvoorden W, Leong DP, et al. Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? *Ther Adv Urol* 2016; 8:118-29.
36. Bhattasali O, Chen LN, Tong M, et al. Rationale for stereotactic body radiation therapy in treating patients with oligometastatic hormone-naïve prostate cancer. *Front Oncol* 2013; 3:293.
37. Jereczek-Fossa BA, Ronchi S, Orecchia R. Is stereotactic body radiotherapy (SBRT) in lymph node oligometastatic patients feasible and effective? *Rep Pract Oncol Radiother* 2015; 20:472-83.
38. Incerti E, Fodor A, Mapelli P, et al. Radiation treatment of lymph node recurrence from prostate cancer: is 11C-choline PET/CT predictive of survival outcomes? *J Nucl Med* 2015; 56:1836-42.