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*Article*

# 1.5T MR-Guided Daily-Adapted SBRT on Lymphnode Oligometastases from Prostate Cancer

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**Abstract: Introduction:** The aim of our study was to evaluate the efficacy and toxicity of a daily-adaptive MR-guided SBRT on 1.5 T MR-linac in patients affected by lymphnode oligometastases from PCa. **Materials and Methods:** The present study is a prospective observational study conducted in a single institution (protocol n°: MRI / LINAC n. 23748). Patients with oligometastatic lymphnodes from PCa treated with daily-adaptive MR-guided SBRT on 1.5T MR-linac were included in the study. Minimum required follow-up of 3 months after SBRT. Primary end-point was local progression-free survival (LPFS). Secondary end-points were: nodal progression-free survival (NPFS), and progression-free survival (PFS), and toxicity. **Results:** 118 lymphnode oligometastases from PCa were treated with daily-adaptive 1.5T MR-guided SBRT in 63 oligometastatic patients. 63.5% patients were oligoprogressive and 36.5% oligoprogressive. Two-year LPFS was 94.5%. Median NPFS was 22.3 months, and the 2-year NPFS was 46.5%. Having received hormone therapy before SBRT was correlated with lower NPFS at the multivariate analysis (1-y NPFS 87.1% versus 42.8%; p= 0.002 - HR 0.199, 95% CI 0.073-0.549). Furthermore, the oligorecurrent state during ADT was correlated with a lower NPFS than the oligoprogressive state. Median PFS was 10.3 months, the 2-year PFS was 32.4%. Patients treated with hormone therapy before SBRT had a significantly lower 1-year PFS the others (28% versus 70.4%; p= 0.01 - HR 0.259, 95% CI 0.117-0.574). No acute and late toxicities occurred during treatment. **Conclusion:** the present is the largest prospective study of 1.5T lymphnode SBRT on MR-linac in patients with PCa. Lymphnode SBRT by 1.5T MR-linac provides high local control rates with an excellent toxicity profile.

***Keywords:*** Adaptive radiotherapy; Lymph node; MR-linac; MRgRT; Oligometastases; SBRT; prostate cancer

## Introduction

Prostate cancer (PCa) is the second most frequent cancer and the fifth leading cause of cancer death in men worldwide (1). PCa incidence and mortality rates are closely related to the widespread use of PSA screening, as this allows for early cancer detection but also increases the identification of latent prostate cancer. Furthermore, advances in imaging techniques in recent years have led to an increase in the detection of metastatic and oligometastatic disease and thus to a growing interest in metastasis-directed therapies (MDT) (2). Several prospective studies confirmed a disease-progression and survival improvement in oligometastatic patients when MDT in implemented in the therapeutic workflow (3-5). Based on international guidelines, the current standard of treatment for metastatic PCa is still androgen deprivation therapy (ADT) eventually associated to other

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systemic therapies, with no specific indications for the subgroup of oligometastatic patients. (6). The ideal time to initiate ADT (immediate or delayed until symptoms occurrence) remains controversial. (7). In recent years, growing evidence suggests that local treatment of the oligometastatic PCa could be a therapeutic option due to the high local control level, good tolerability, aiming to delay initiation of systemic treatments (4). Recently, the Advanced Prostate Cancer Consensus Conference recommended the association of ADT with local treatment to all oligorecurrent lesions, also thanks to a better toxicity profile of the MDT versus chemotherapy or ADT (7,8). Lymphnode metastases are a particular site of PCa oligometastatic disease amenable of MDT and might identify a less severe degree of metastatic PCa (9). Several evidence, both prospective and retrospective, evaluated the role of stereotactic body radiotherapy (SBRT) in the management of lymphnode oligometastases, reporting few side effects and adequate local control level (10-12). The widespread use of metabolic imaging in the very early phase of the PCa metastatic disease have permitted the early identification of metastatic lesions, also infracentimetrical (13). Despite image-guided radiotherapy significantly increased treatment accuracy, there might be some dosimetrical and imaging limitations when lesions are small or close organs at risk or vessels (14,15). Moreover, standard radiotherapy on conventional linac don't allow clinicians to modify treatment plans in case of lesions displacement of when OARs (i.e. bowel loops) fall within the treatment field, as it may occur for abdominal targets. The recent introduction of MR-linac might overcome this problem by allowing for daily treatment adaptation and exploiting the high tissue contrast provided by MR images (16). Recent evidence showed dosimetrical improvement to bowel loops in lymphnode metastases treated with SBRT on a 1.5T MR-linac (14). However, to date clinical data are limited by small retrospective series and short follow-up (17,18), therefore little is known regarding the clinical impact of MR-guided radiotherapy (MRgRT). The aim of the present prospective study is to evaluated efficacy and safety of MR-guided SBRT to lymphnode oligometastases in patients affected by PCa.

## Material and methods

The present study is a prospective observational study conducted at the IRCSS Sacro Cuore Don Calabria (Negrar di Valpolicella, Verona), approved in April 2019 by the local Ethics Committee (MRI / LINAC n. 23748). Patients with metastatic lymphnodes from PCa treated with daily-adaptive MR-guided SBRT on 1.5T MR-linac were included in the study. The inclusion criteria were:

- age ≥ 18 years.
- histological diagnosis of PCa
- performance status ECOG (Eastern Cooperative Oncology Group Criteria) <= 2
- Oligometastatic or oligoprogressive disease (≤ 5 disease sites) from PCa diagnosed with PET-choline or PET-PSMA
- minimum follow-up of 3 months after SBRT.

The exclusion criteria are:

- general contraindications for 1.5 T MR
- claustrophobia

Patients could have received ADT before or during SBRT. Initial treatment included radical surgery, radical radiotherapy, HIFU or hormone therapy (the latter in the case of *de novo* metastatic disease).

### *Treatment procedure*

The pre-treatment imaging consisted of a planning CT (Somatom AS, Siemens, Germany), with a slice thickness of 3 mm, and a 3D T2-weighted MRI (T2w) (1.5 T Philips Ingenia) (1mm slice thickness). The same MR scans were performed daily for treatment procedures. All scans were acquired in the supine position with head-first orientation with support for the knees and arms on the chest in case of pelvic or lower abdominal

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targets. The anterior coil was placed on the patient's body to maximize the signal-to-noise ratio. The same patient and coil position was reproduced for each treatment fraction.

Planning CT and MR images were rigidly co-registered based on bone anatomy, primarily to obtain bulk densities for each tissue. Target lymph node volume (GTV) and OARs were contoured on MRI with the aid of co-registered CT and staging diagnostic exams (i.e.: PET). Therefore, GTV was delineated on MR as the entire visible tumor and was considered equal to the clinical target volume (CTV). The OARs were configured as avoidance structures depending on the proximity to the target. All volumes, including OARs, were delineated by a Radiation Oncologist experienced in MR imaging in accordance with the guidelines, specifically contouring the portion of bowel close to the target with a cranio-caudal extension up to 1 cm above. and below.

The GTV to Planning Target Volume (PTV) margin was created by adding 2 to 4 mm, based on the distance and movement between the target and OARs. More specifically, the strategy for defining the PTV comprised a progressive margin reduction from 4 to 2 mm within the protocol.

The pretreatment plan was generated using the Monaco planning system 5.40.01 (Elekta AB, Stockholm, Sweden). Offline intensity modulated radiotherapy (IMRT) plans have been optimized on MR scanning, typically with 10-11 fixed beam angles. An flattening filter-free (FFF) photon beam was employed.

Treatment was usually prescribed to ensure that at least 95% of the PTV received at least 95% of the prescribed dose. The maximum dose in the PTV was not to exceed 107%. Lower PTV coverage was only accepted to comply with maximum dose constraints for surrounding OARs. All pretreatment plans passed the standard quality control procedure prior to the first treatment session.

The daily workflow consisted of an initial T2w 3D MR scan, rigidly fused with the pretreatment MR scan. The contours of the target and the OARs were automatically propagated to the scan of the day from a deformable registration and used for the optimization of the plan. In all sessions, the treatment was delivered using the Adaptive workflow, choosing between two possibilities: Adapt To Position (ATP) or Adapt To Shape (ATS) (18,19). The ATS approach is the most robust because it allows a complete adaptation of the contours (manually or by deformable registration) and a full re-planning, considering any movement or change in the shape or volume of the OARs. A possible limitation of ATP, in which only the isocenter is modified, is that the exact dose received by the OARs in each fraction is unknown, as the same contours are used as an avoidance framework for re-planning, and the outlined OARs do not represent the OARs acquired during the MRI performed daily. Consequently, although the ATS approach might requires more time it allows for a better assessment of the real dose received by the organs close to the target. Therefore, the choice of the ATP approach was usually adopted to speed up this procedure only in the case of no substantial differences in the daily anatomy compared to the reference imaging. In the meantime, a complete re-optimization of the plan was performed, a verification MR before treatment administration was acquired to evaluate any target and OARs movement (19). Afterwards, the Radiation Oncologist and the Physicist evaluated the new treatment plan and verified the absence of important movements through the visual comparison (iso-iso) of the images and contours. In the event that a major change in the anatomy of the OARs or the target was found, a new ATP or ATS was started, otherwise the radiation treatment was administered. Before and during RT administration, intra-fraction motion was monitored with a real-time 2D cine-MRI (T2 / T1-weighted balanced free precession at steady state) acquired in the coronal and sagittal views. Finally, another MR scan was acquired after treatment for offline recalculation purposes, such as the assessment of intrafractional target coverage. The entire session time, defined as the time between patient entry and exit from the treatment room, was measured by a radiotherapy technician (RTT). Treatment duration for lymphnode SBRT on a MR-linac was between 22 and 31 minutes (average 25 minutes).

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*End-points and statistics*

The primary end point was local progression-free survival (LPFS). Secondary end-points were acute and late toxicity, nodal progression-free survival (NPFS) and disease progression-free survival (PFS). LPFS was defined as the time between the onset of SBRT and the radiological diagnosis of local recurrence. NPFS was defined as the time between SBRT and the radiological diagnosis of nodal progression. PFS was defined as the time between SBRT and disease progression (both biochemical and radiological). Acute and late toxicity were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 scale (ref). Toxicity was prospectively recorded in a specific form by the treating physician or nurse before treatment and during follow (3 and 6 months after SBRT administration and each 6 months for two years, afterwards).

Univariate analyzes were performed with the Kaplain-Meyer method. The log-rank test was used to determine a difference between the corresponding curves. The following independent variables were evaluated for LPFS, NPFS and PFS: Biological Effective Dose (BED) Gy1.5, mm of PTV expansion, median PSA value before SBRT, Gleason Score at diagnosis, ADT administration before or during SBRT, oligometastatic state (oligorecurrent versus oligoprogressive), lymph node site (pelvis versus extrapelvic). The multivariate analysis was performed with the Cox regression model; all the clinically relevant variables in the univariate analysis ($p < 0.2$) were included in the analysis. The BED was calculated using an alpha\beta ratio of 1.5 Gy. The statistical analysis was performed using the SPSS v.20.0 software. (IBM software, USA). A p value $<0.05$ indicated a significant correlation.

## Results

Between November 2019 and March 2022, a total of 118 metastatic lymph nodes from PCa were treated with daily-adaptive 1.5T MR-guided SBRT in 63 oligometastatic patients. The median age was 71 years (range 54-87). Treatment of primary tumor was: surgery was (81%), RT (9.5%), HIFU (0.5%), and ADT (9%). The median PSA before SBRT was 2.23 ng/ml. Regarding the oligometastatic state, 63.5% patients were oligoprogressive and 36.5% oligoprogressive. Patients' characteristics are summarized in table 1. The median diameter of lymphnode metastases was 6 mm (range 2-26). 74.6% of the treated lymph nodes were located in the pelvis, and 25.4% were extrapelvic. The median BED was 198.33 Gy1.5 (range 65-315). Lesion and treatment characteristics are summarized in Table 2.

**Table 1.** Patients' characteristics (n=63).

| | |
|---|---|
| **Mean age (years) (range)** | 71 (54-87) |
| **ECOG PS** | |
| • 0 | 62 |
| • 1 | 1 |
| **Initial treatment** | |
| • RP +/- ADT | 51 (81) |
| • RT +/- ADT | 6 (9.5) |
| • HIFU/altro | 2 (0.5) |
| • ADT | 4 (9) |
| **Initial Stage** | |
| • T2 | 17 |
| • T3 | 32 |
| • T4 | 1 |
| • Unknown | 13 |
| **Initial PSA (ng/ml) (range)** | 19.1 (3.5-140) |
| **Initial Gleason** | |
| • 6 | 9 |
| • 7 | 22 |

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| | |
|---|---|
| • >8 | 28 |
| • Unknow | 4 |
| **PSA before SBRT (ng/ml) (range)** | 2.23 (0.22-36.84) |
| **Oligometastatic status** | |
| • Oligoreccurent | 40 |
| • Oligoprogressive | 23 |
| **Imaging pre-SBRT** | |
| • Choline-PET | 12 |
| • PSMA-PET | 51 |
| **N° of treated lesions (per patients)** | |
| • 1 | 41 |
| • 2 | 24 |
| • 3 | 7 |
| • 4 | 2 |
| **Total SBRT course** | |
| • 1 | 58 |
| • 2 | 7 |
| • 3 | 1 |

ECOG PS: Eastern Cooperative Oncology Group – Performance Status; RP: radical prostatectomy; ADT: androgen deprivation therapy; HIFU: High intensity Focused Ultrasound; SBRT: stereotactic Body Radiotherapy.

**Table 2.** Lesions and treatment characteristics (n=118).

| | |
|---|---|
| Lesion diameter (mm) tot 118 | 6 |
| Range (mm) | 2-26 |
| Lymphnode site | |
| Pelvic | 88 |
| Extrapelvic | 30 |
| SBRT regimen | |
| Median dose (range) | 35 (15-40) |
| Median dose/fractions (range) | 7 (5-21) |
| Median BED ($\alpha/\beta = 1.5$) | 198.33 (65-315) |

*Local control, survivals, and toxicity*

The median follow-up was 17 months (range 3-34). At the last follow-up only one patient died from disease progression. The 1- and 2-year LPFS was 94.5% (figure 1). In univariate analysis, only concomitant hormone therapy and pelvic location of the lymph nodes were correlated with improved LPFS. However, no factor remained significantly associated in the multivariate analysis. The following isotropic PTV expansions were used for MR-guided lymphnode SBRT: 36 lesions (30.5%) 4 mm, 46 lesions (39%) with 3 mm and 36 (30.5%) lesions 2 mm, however there was no statistically significant difference in LPFS between the 3 groups (p= 0.42).

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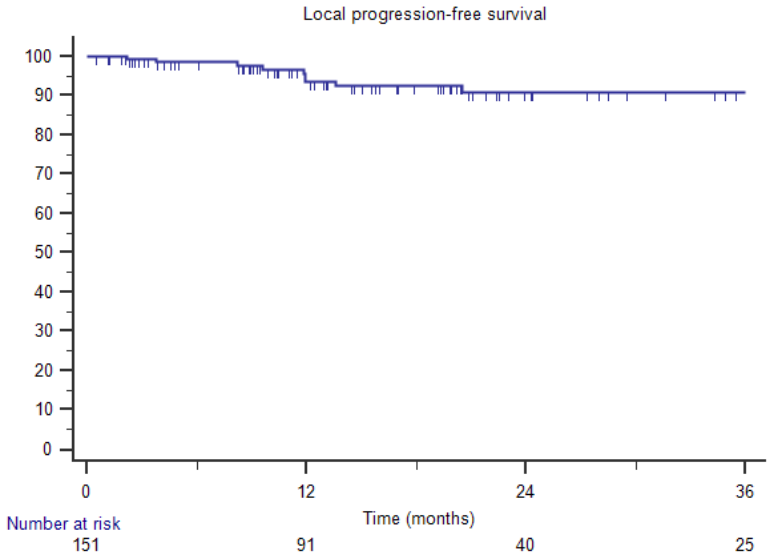


**Figure 1.** Kaplan-Meier curve showing local progression-free survival.

The median NPFS was 22.3 months (range 16-28 months) and the 1- and 2-year NPFS were 65.4% and 46.5%, respectively. In the univariate analysis, having received hormone therapy before SBRT was correlated with lower NPFS (p=0.014) (table 3). The factor remained significantly correlated in the multivariate analysis. In particular, the 1-year NPFS was 87.1% for patients not previously treated with ADT and 42.8% for those previously treated with ADT (P= 0.002 - HR 0.199, 95% CI 0.073-0.549; figure 2). Furthermore, the oligorecurrent state during ADT was correlated with a lower NPFS than the oligoprogressive state. More specifically, the 1-year NPFS was 79.4% and 54.7% for the oligoprogressive and oligoprogressive state, respectively (P= 0.018 - HR 3.679, 95% CI 1.247-10.851; see figure 3). See multivariate analysis in table 4.

**Table 3.** Univariate analysis.

| Covariates | LPFS | NPFS | PFS |
|---|---|---|---|
| | | p | |
| BED 198.33 | 0.344 | 0.968 | 0.08 |
| Mm exp | 0.427 | 0.496 | 0.674 |
| PSA 0.82 | 0.573 | 0.604 | 0.494 |
| PSA 0.7 | 0.17 | 0.783 | 0.379 |
| PSA 0.9 | 0.573 | 0.604 | 0.494 |
| Gleason | 0.267 | 0.608 | 0.795 |
| ADT concomitant | 0.07 | - | - |
| ADT before SBRT | 0.171 | *0.014* | *0.002* |
| Oligorecurrent versus oligoprogressive | - | 0.068 | 0.158 |
| Pelvic versus extrapelvic | *0.004* | 0.076 | 0.233 |

LPFS: local progression-free survival; NPFS: nodal progression-free survival; PFS: progression-free survival; BED: biological effective dose; ADT: androgen deprivation therapy; SBRT: sterotactic body Radiotherapy.
Italiac values indicate a significant correlation.

**Table 4.** Multivariate analysis

| Covariates | LPFS | NPFS | PFS |
|---|---|---|---|
| PSA before SBRT <0.7 | P= 0.149 (HR 0.134, 95%CI 0.009-2.060) | - | - |
| Concomitant ADT | P= 0.872 (HR 805, 95%CI 0-1.705) | - | - |
| ADT before SBRT | P=0.503 (HR 2.665, 95%CI 0.151-46.966) | P= 0.002 (HR 0.199, 95%CI 0.073-0.549) | P=0.01 (HR 0.259, 95%CI 0.117-0.574) |

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| | | | |
|---|---|---|---|
| Pelvic versus extrapelvic lymphnode | P= 0.923 (HR 0, 95%CI 0-8.826) | P=0.51 (HR 1.492, 95%CI 0.454-4.895) | |
| Oligorecurrent versus oligoprogressive | - | P=0.018 (HR 3.679, 95%CI 1.247-10.851) | P=0.106 (HR 1.975, 95%CI 0.865-4.511) |
| BED | - | - | P=0.442 (HR 1.784, 95%CI 0.408-7.811) |

LPFS: local progression-free survival; NPFS: nodal progression-free survival; PFS: progression-free survival; SBRT: Stereotactic Body Radiotherapy; ADT: androgen deprivation therapy; BED: biological effective dose.

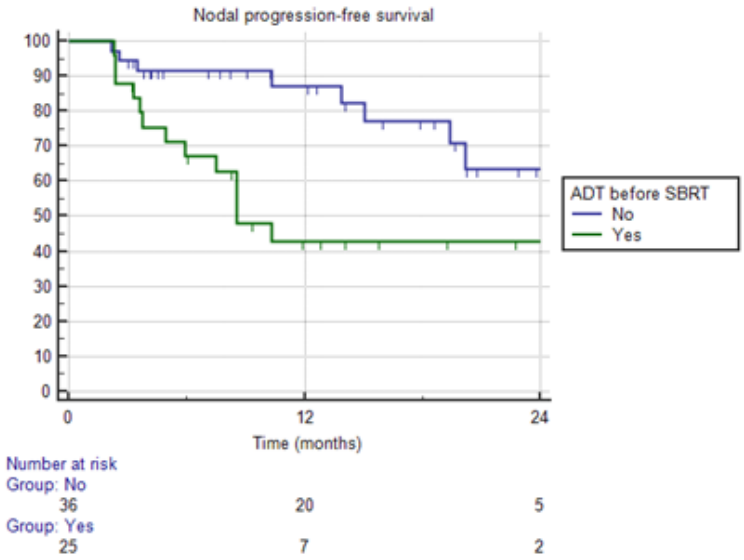


**Figure 2.** Kaplan-Meier curve showing nodal progression-free survival stratified by androgen deprivation therapy (ADT) before SBRT administration.

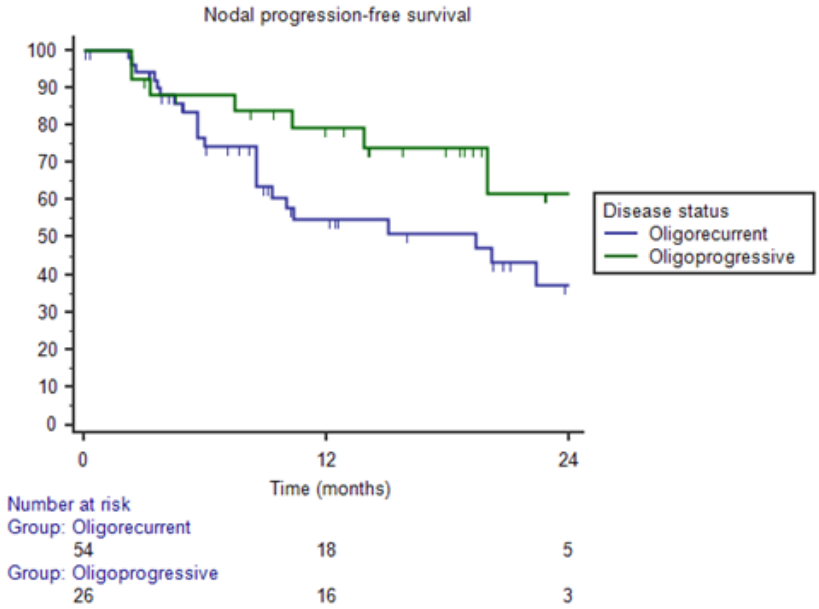


**Figure 3.** Kaplan-Meier curve showing nodal progression-free survival stratified by oligometastatic state (oligorecurrent versus oligoprogressive).

The median PFS was 10.3 months (range 5-20.5); the 1 and 2-year PFS were 49.8% and 32.4%, respectively. In the univariate analysis, hormone therapy before SBRT was associ-

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ated with a worse PFS (p= 0.002). In multivariate analysis, the covariate remained significantly associated with PFS. In particular, patients treated with hormone therapy before SBRT had a significantly lower 1-year PFS than patients not treated with hormone therapy (28% versus 70.4%, respectively) (P= 0.01 - HR 0.259, 95% CI 0.117-0.574; see figure 4). No acute and late toxicities occurred during treatment; all patients completed the treatment.

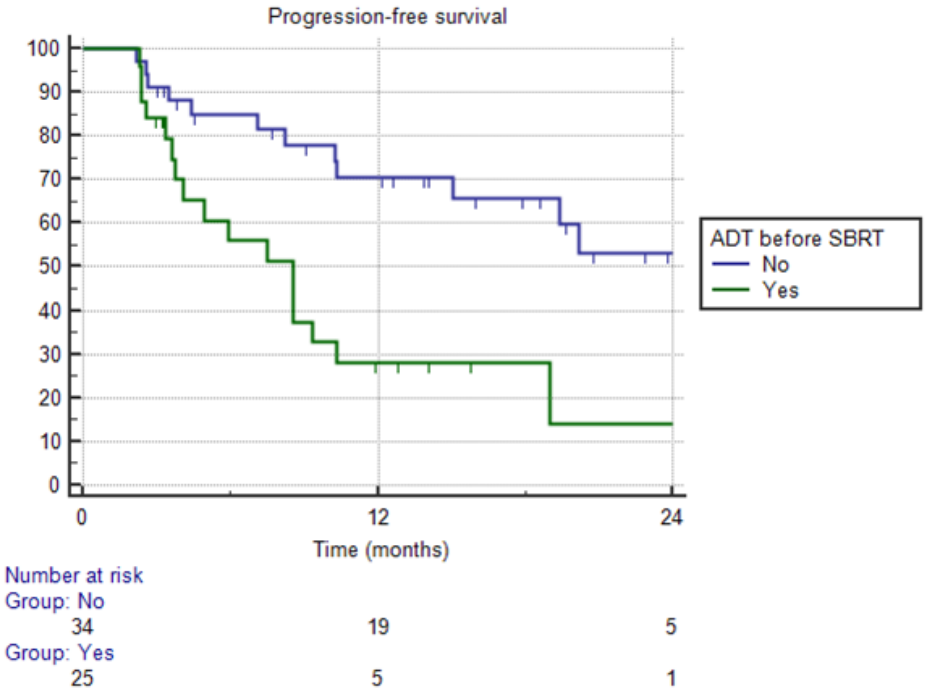


**Figure 4.** Kaplan-Meier curve showing progression-free survival stratified by androgen deprivation therapy (ADT) before SBRT administration.

*Pattern of recurrence*

After SBRT, 19 lymphnode recurrences occurred of which 3 (15.8%) in the same lymphnode station, 14 (73.7%) in a different lymphnode site and 2 (10.5%) in both. Disease recurrence globally occurred in 47.6% of patients. Pattern of recurrence was: 50% lymph node only, 23.4% bone only, 13.3% both lymphnode and bone, 6.7% biochemical only, 3.3% visceral, and 3.3% in prostate bed. (See table 5).

**Table 5.** Pattern of recurrence.

| | |
|---|---|
| *Nodal recurrence* | |
| Some nodal level | 6 (31.5) |
| Different nodal level | 11 (58) |
| Both | 2 (10.5) |
| | |
| *Global disease recurrence* | |
| Nodal | 15 (50) |
| Bone | 7 (23.4) |
| Node + Bone | 4 (13.3) |
| Visceral | 1 (3.3) |
| Prostate bed | 1 (3.3) |
| Biochemical | 2 (6.7) |

## Discussion

In recent years, several studies have been published on the role of SBRT in the treatment of lymphnode oligometastases from PCs. In fact, lymphnode oligometastases seem

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to identify an initial phase in the PCa disease progression characterized by a better prognosis than that to bone or visceral lesions. (9).

In the context of oligometastatic lymphnode disease, MDT use resulted in an excellent rate of local control and PFS, without unexpected side effects (4,20,21). In particular, SBRT is based on the possibility of delivering high radiation dose to small volumes with high precision, generally using cone-beam CT-based for image-guidance. The consequent greater precision in treatment administration has led to a significant reduction in the interfraction variability due to set-up errors and physiological changes in the healthy structure position and volume. However, especially in the abdominal-pelvic area, target identification may not be always optimal with cbCT IGRT methods due to lower resolution than conventional CT and low soft tissue contrast. (14,15).

In this scenario, the recent introduction of MR-linac technology into clinical practice represents a potential paradigm shift in the implementation of SBRT. Based on a higher anatomical visualization, MR-linac could improve not only the definition of target volumes and OARs thanks to the image quality of MR, but also improve treatment safety and accuracy due to the daily-adaptive modality (16). This latter is a crucial issue especially in the case of targets close to healthy structures, which are more influenced by daily anatomical variations, such as bowel loops. (14,18,22). The aim of our study was to evaluate the efficacy and toxicity of a daily-adaptive MR-guided SBRT on 1.5 T MR-linac in patients affected by lymphnode oligometastases from PCa.

To our knowledge, the present is the largest prospective study of 1.5T lymphnode SBRT on MR-linac in patients with PCa. Previous evidence, mainly retrospective on the use of SBRT in the PCa lymphnode oligometastases with conventional linacs reported local control rates around 93% at two years (10-12). In our experience, in line with these previous experiences, the 2-year local control rate was 94.5%. Specifically, patients were treated with a median total dose of 35 Gy with a median BED of 198.33 Gy1.5. Most of our patients were treated using the ATS modality (87%) which allows for a more robust calculation of the treatment plan than ATP with a variation in planning time between the two modalities of approximately 2-3 minutes. In our clinical experience, the increase in planning time should not have reduce the accuracy of the treatment, which is guaranteed by the pre-treatment MR and online verification with the cine-MRI. In a previous experience on PCa patients treated with prostate SBRT on MR-linac it was shown that the longer pre-treatment time (imaging acquisition, contouring, planning and pre-administration MR verification) did not affect treatment accuracy, and dose constraints to OARs were respected when compared with conventional linac (19,22). The accuracy of the MR-linac allowed us to test the effect of the reduction of the PTV margins on local control compared to the standard of 5 mm on conventional linac. Specifically, we have progressively reduced the margins from 4 to 2 mm, reporting no difference in terms of local control. In a previous study by Jereczek-Fossa et al., patients with metastases from solid tumor (16 of which lymphnodes), were treated on Cyberknife with SBRT by applying a margin of 1-2 mm through the implantation of fiducial markers (23). At a median follow-up of 16 months, there were no local recurrences in the subgroup of lymph node metastases. Although encouraging, but limited to a small population, these results required an invasive procedure. On the contrary, a treatment on MR-linac could guarantee comparable results in terms of local control, without invasive procedures. The reduction of the treatment margin can have important clinical consequences. The main and most direct consequence is the reduction of the dose to the OARs, further consequences could be the possibility of safely escalate treatment dose. This approach could be especially useful in patients with cancers different from prostate, with an alpha/beta ratio greater than 1.5 Gy, in which the advantages of hypofractionation are minor and a higher radiation dose is required to obtain a higher BED (24,25). The use of smaller treatment volumes could also facilitate a re-challenge with SBRT in patients with recurrence of the disease in the cranial or caudal area to the previous treatment field, limiting possible overlaps with previous treatment fields. This pattern of relapse is, for example, relatively common in PCa, in which up to

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50% of patients with lymphnode disease may have cranial recurrence in the same lymphnode station previously treated with SBRT (9,10).

The standard of treatment in case of metastatic prostatic disease is ADT, possibly associated with chemotherapy or second-generation antiandrogens (26-28). However, in the oligometastatic setting, the SABR-COMET study demonstrated that the addition of SBRT to the standard of treatment can increase the overall survival (3). In particular, this phase II study, closed early due to the superiority of the experimental arm, included 99 patients affected by different histologies, including the prostate. The latest update confirmed a median survival advantage of the experimental arm (42.3 versus 17.7 months). In recent years however, some studies have shown that oligometastatic PCa patients treated with SBRT alone could have relatively long disease-free interval, thus underlining the need to identify patients who can really benefit from an early onset of ADT or not (11).

For example, in an Italian multicenter study (11), 141 patients treated with SBRT to 209 lesions reported a 2-year ADT-free survival of 47.3%. In a phase II study by Ost et al. (4) patients with oligometastatic prostate cancer underwent SBRT on active disease sites or observation. The results reported increased ADT-free survival of 21 versus 14 months in the experimental and observational arm, respectively. In our study, the 1-year PFS was 49.8%, in line with these previous experiences. There is currently no robust evidence on the timing of onset and duration of ADT concomitant with SBRT, as highlighted by a recent review (12) which analyzed 15 studies of SBRT in oligometastatic PCa patients. The authors reported a high heterogeneity in ADT administration concomitant with SBRT in a range between 33% and 100%, and a duration between 14.5 and 17.5 months. The study confirmed the high rate of local control and PFS at 2 years after lymphnode SBRT of 84% and 38.6%, respectively.

The review also reported generally low rates of acute toxicity after SBRT. Specifically, acute and late G1-G2 toxicity rates were about 1.9% and on average severe acute and late toxicities ≥G3 occurred in about 0.6% of cases (12). This date is in line with our prospective series in which no acute and late toxicity episodes occurred.

Considering the peculiar pattern of PCa lymphnode recurrence after SBRT (9,10), some studies investigated the role of pelvic irradiation. Lepinoy et al. evaluated the use of whole-pelvis radiotherapy (WPRT) compared to the MDT approach, reporting a 3-year PFS of 88% and 55% for WPRT and MDT, respectively (29). A recent DEGRO expert group report on PCa (30) recommended treating pelvic-only oligorecurrent lymphnode metastases from PCa with WPRT plus a boost to the involved lymphnodes and to consider SBRT alone in nodal extra-pelvic oligorecurrent cases. However, they pointed out that in some situations with low-risk characteristics, such as PSA doubling time >10 months and relapse-free interval from primary curative treatment >2 years, focal treatment might be considered.

The present study is not without limitations: the use of different fractionation schemes, although 68.7% of patients were treated with a homogeneous schedule (35Gy in 5 fractions); the use of 2 different PET tracers (choline and PSMA) in the staging phase which, although it has no impact on local control, primary end-point of the study, could limit the analysis of PFS; the lack of a comparison group treated on conventional linac. A comparison analysis in this regard is currently underway at our Center. Strengths of the study included the prospective nature and the sample size that to our knowledge represents the largest study of lymphnode SBRT from PCa treated with 1.5T MR-linac.

## Conclusion

Lymphnode SBRT by 1.5T MR-linac provides high local control rates with an excellent toxicity profile. This method would appear not inferior than the standard of treatment on conventional linac, although a direct comparison study will be required to confirm this hypothesis. SBRT is also confirmed as a valid therapeutic tool for postponing the initiation of systemic treatment in selected patients. The ability to administer SBRT with the same

accuracy reducing treatment margins, could allow for radiation dose-escalation in order to maximize local control while controlling toxicity.

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