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Stereotactic ablative radiotherapy (SABR) for pelvic nodal oligorecurrence in prostate cancer

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ABSTRACT

Background: This study evaluated the clinical outcomes of stereotactic ablative radiotherapy (SABR) in the treatment of oligometastatic pelvic node prostate cancer to delay androgen deprivation therapy (ADT).

Materials and methods: Pelvic lymph node metastases were identified by ^{11}C-choline positron emission tomography (PET)-computed tomography (CT), and patients were not receiving ADT. SABR was administered using linear accelerators with intensity-modulated and image-guided radiotherapy, at a prescribed dose of 35 Gy in 5 fractions over 2 weeks. Response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, and prostate-specific antigen (PSA) levels were monitored post-SABR. Toxicity and quality of life were assessed by the Common Terminology Criteria for Adverse Events Toxicity (CTCAE) v.5.0 and European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires QLQ-C30/QLQ-PR25, respectively. Kaplan-Meier and T-test were used for statistical analysis.

Results: Between June 2015 and November 2023, 56 patients with 85 lesions were treated at our institution. Median follow-up was 30 months [95% confidence interval (CI): 24–33.6]. Prostatectomy was the radical treatment in 85.7% of patients, and radiotherapy in 14.3%. Response rates were 67.1% for complete response, 27.4% for partial response, and 1.4% for stable disease. In-field progression was observed in only 3 lesions (3.5%). The median time to biochemical relapse post-SABR was 15 months (95% CI: 11.4–18.6). Three-year pelvic nodal and distant progression-free survival were 62.5% and 80%, respectively. There was a significant decrease in PSA levels after SABR compared to pretreatment levels (0.77 *vs.* 2.16 ng/mL respectively, $p = 0.001$). No grade ≥ 2 genitourinary or gastrointestinal toxicities. The median global health status score was 83.33 points at both time points analysed.

Conclusion: SABR can delay the ADT and provide excellent local control while preserving quality of life.

Key words: stereotactic ablative radiotherapy; oligorecurrence; prostate cancer; oligometastases; pelvic lymph nodes

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Introduction

Prostate cancer is the second most common cancer in men, after lung cancer [1]. Following curative treatment of the primary tumour, such as radical prostatectomy and/or radiotherapy, 20–30% of patients experience biochemical recurrence (BCR) within 10 years of initial definitive therapy. The Phoenix criteria are used to define BCR following radiotherapy, which requires a prostate-specific antigen (PSA) increase of at least 2 ng/mL above the post-radiation PSA nadir, whereas BCR after prostatectomy is defined as at least two PSA levels of 0.2 ng/mL or higher [2]. In addition to local recurrence, lymph nodes and bone are the most common sites of metastatic spread [3].

In 1995, Hellman and Weichselbaum described an intermediate stage of spread characterised by limited metastases (up to five) confined to nodal and bone sites. This suggested that eradication by ablative therapy could improve survival [4].

Three scenarios of oligometastatic prostate cancer have been identified:

- *de novo* oligometastatic disease (synchronous metastases) is defined as the occurrence of metastases at the initial diagnosis of prostate cancer;
- oligorecurrent disease (metachronous metastases) is defined as the occurrence of metastases after the initial tumour being diagnosed;
- oligoprogressive disease is defined as the progression of oligometastatic disease. This occurs when metastases develop and progress despite ongoing systemic treatment.

The European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) have proposed a classification of nine oligometastatic subtypes, reflecting different clinical conditions and underlying biological processes [5]:

- de novo oligometastatic disease (no previous history of oligometastasis) is subdivided into three categories: synchronous oligometastatic cancer, metachronous oligorecurrence and metachronous oligoprogression;
- repeat oligometastatic disease (previously diagnosed oligometastatic disease) is subdivided into three categories: repeat oligorecurrence, repeat oligoprogression and repeat oligopersistence;
- induced oligometastatic disease (previously diagnosed with polymetastatic disease) is subdivided into three categories: induced oligorecurrence, induced oligoprogression and induced oligopersistence.

In repeat and induced oligometastatic disease the primary tumour is assumed to be controlled by ongoing or previous treatment.

Oligorecurrent disease is the clinical scenario associated with more favourable outcomes compared to synchronous disease due to a more indolent biology [6]. Following nodal ablative treatment, up to 50% of patients experience new oligometastatic relapse in adjacent nodal areas [7].

The identification of cell clones in biopsies of metastatic tissue has shown that oligometastasis is a common phenomenon and is not always derived from the primary tumour [8]. In a study employing whole genome sequencing, Gundem et al. [8] examined metastases in ten patients with metastatic prostate cancer. Their findings revealed that metastasis-to-metastasis spread is a prevalent phenomenon, occurring through de novo monoclonal seeding or, less frequently, through the transfer of tumour clones between the respective metastatic sites. This has led to the hypothesis that the removal of metastases at an early stage may prevent further dissemination.

Advances in imaging modalities, such as positron emission tomography (PET) and the development of new radiotracers, such as choline, prostate-specific membrane antigen (PSMA), gallium-68 (^{68}Ga)/fluorine-18 (^{18}F), and ^{18}F-fluciclovine (leucine analogue), have greatly improved the detection of oligometastases [9].

Although the current standard of care for nodal oligorecurrence typically involves the use of androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs), prospective trials published to date have mostly evaluated metastasis-directed therapy (MDT) without ADT. The aim of these trials was to delay the onset of oligorecurrence and improve patients' quality of life [10–12].

Stereotactic ablative radiotherapy (SABR) is an external beam radiotherapy technique that delivers high doses of radiation (biological dose equivalent > 100 Gy) in a few fractions (1–8 fractions). It requires high precision with modern, state-of-the-art radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), in

order to reduce normal tissue toxicity and facilitate outpatient administration [13]. It is important to note that appropriate patient selection remains a critical factor in the optimal management of oligometastatic disease.

This study aimed to evaluate the efficacy and safety of SABR for the treatment of pelvic lymph node metastases in patients with oligorecurrent hormone-sensitive prostate cancer. The hypothesis was that SABR could delay ADT and be beneficial in patients who are not candidates for or refuse ADT.

Materials and methods

A retrospective analysis was performed using a prospective database of patients with pelvic lymph node oligorecurrence treated with SABR at our institution. The study included patients with hormone-sensitive prostate cancer with up to three pelvic lymph node metastases diagnosed by computed tomography (CT)-positron emission tomography (PET) using choline or PSMA as radiotracer and who had not started ADT within six months prior to SABR. All patients had previously undergone radical treatment, including prostatectomy or radiotherapy.

SABR treatment planning was performed using intravenous contrast-enhanced CT simulation with a 2 mm slice thickness, acquired in the supine position, and CT-PET fusion. The gross tumour volume (GTV) was defined by the involved lymph node, with a 5 mm margin to determine the planning target volume (PTV). The organs at risk were defined as follows: rectum, sigma, small bowel, large bowel, sacral plexus, bladder and femoral heads. The prescribed dose was 35 Gy in five fractions over two weeks. The treatment was prescribed to achieve 95% coverage of the median PTV dose. The dose constraints to organs at risk were in accordance with the recommendations of the American Association of Physicists in Medicine Task Group 101 (AAPM TG101) [14]. The treatment was delivered using linear accelerators with IMRT and IGRT, with cone beam CT being employed prior to each daily session.

Treatment plans were calculated on Raystation (RaySearch Laboratories, Stockholm, Sweden) or TomoTherapy (Accuray, Sunnyvale, CA). SABR was delivered with a flattening filter-free, 6 MV photon volumetric arc therapy (VMAT) or TomoTherapy.

Data were collected on the clinicopathological characteristics at presentation (including age, PSA levels, cTNM staging, D'Amico risk classification and treatment received), as well as the clinical scenario at diagnosis of oligorecurrence (PSA levels, PSA doubling time (DT-PSA), number and location of pelvic lymph node metastases).

Follow-up included PSA analytical controls at three-month intervals during the first year, at six-month intervals after the second year, or earlier if PSA increased based on DT-PSA, and a CT scan six months after SABR. PET-CT was repeated in the event of biochemical recurrence, using choline as the radiotracer if PSA levels were ≥ 2 ng/mL, and PSMA if < 2 ng/mL.

The primary endpoints were in field radiation relapse-free survival (IFRFS), pelvic lymph node relapse-free survival (PLNRFS), distant relapse-free survival (DRFS), overall survival (OS) and new treatment-free survival, calculated as the interval between the event occurrence and the initiation of SABR. Subsequent treatments included re-SABR, salvage pelvic radiotherapy and ADT, ADT, and new antiandrogens (enzalutamide, apalutamide, abiraterone).

Biochemical progression following SABR was defined as an increase in PSA to a nadir value plus 2 ng/mL in the case of radiotherapy as the primary treatment, and as two consecutive 50% increases above the nadir value, but a PSA level below 2 ng/mL in the event that the treatment was radical prostatectomy.

Local progression of the irradiated nodal metastatic lesion was defined according to the Response Evaluation Criteria in Solid Tumours (RECIST v. 1.1) as an increase of ≥ 20% in the major axis, with a minimum absolute increase of 5 mm.

Secondary endpoints included the assessment of toxicity of SABR treatment using the Common Terminology Criteria for Adverse Events Toxicity (CTCAE) version 5.0 scale and the assessment of health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires, specifically the Quality-of-Life Questionnaire (QLQ)-C30 and the QLQ-PR25, both at baseline and six months' post-SABR.

The study was approved by the institutional review board and written informed consent was obtained from all patients.

Continuous variables were described using measures of dispersion and central tendency, while the distribution of categorical variables was analysed using frequency tables. Pearson's chi-squared test was used to compare categorical variables, and Student's t-test was used to compare continuous variables where normality could be assumed. Kaplan-Meier curves were used to estimate survival times. A p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 19 software.

Results

A total of 85 pelvic lymph node metastases were treated in 56 patients between June 2015 and November 2023. Of the patients, 76% exhibited a single lesion, while 24% had up to three lesions. A total of 69% of lesions were diagnosed using choline CT-PET, while 31% were diagnosed using PSMA CT-PET. At the time of oligorecurrence, the median age was 70 years (range 52–84). The primary radical treatment for 85.7% of patients was prostatectomy, while 14.3% received radiotherapy. Table 1 presents a detailed overview of the patient characteristics, and Figure 1 depicts the distribution of oligometastases.

The median follow-up was 30 months (95% CI: 24–33.6). The median pre-SABR PSA level was 1.58 ng/mL (interquartile range: 1–2.87) and the PSA doubling time (DT-PSA) was 6.1 months (interquartile range: 4.12–11.9). A PSA doubling time of ≤ 6 months was observed in 46.4% of patients.

SABR resulted in a statistically significant reduction in mean pretreatment PSA levels, with a decrease from 2.07 to 0.77 (p = 0.000). This reduction was consistent regardless of whether patients had a PSA doubling time greater than or less than six months.

Of the 85 lesions treated, only three exhibited local progression within the radiation field. According to the RECIST v.1.1 criteria, 67.1% (49 lesions) achieved a complete response (CR), 27.4% (20 lesions) exhibited a partial response (PR), 1.4% (1 lesion) maintained stable disease (SD) and 4.1% (3 lesions) experienced disease progression (PD). The three-year local relapse-free survival rate within the field was 94% (Fig. 2).

The median biochemical progression-free survival was 15 months (95% CI: 11.4–18.6). At the end of the follow-up, the biochemical recurrence rate was 73.2%. The median PSA at recurrence in patients who had relapsed was 1.92 ng/mL (interquartile range: 1–2.97). In patients with biochemical recurrence, 70.7% (29 patients) underwent choline CT-PET and 29.3% (12 patients) underwent PSMA to detect recurrence.

Table 1. Patient characteristics

Characteristic	N	%/range
Median age [years]	70	52–84
Gleason score		
≤ 6	13	23.2%
3 + 4	19	33.9%
4 + 3	9	16.1%
≥ 8	15	26.8%
Stage T		
p/c T1	5	9%
p/c T2	26	46.4%
p/c T3 o T4	25	44.6%
Stage N		
p/cNx	27	48.2%
p/cN0	25	44.6%
p/cN1	4	7.2%
D'Amico risk		
Low risk	9	16.1%
Intermediate risk	25	44.6%
High risk	22	39.3%
Primary treatment		
Prostatectomy	48	85.7%
Radiotherapy	8	14.3%
Margin status		
R0	33	68.8%
R1	15	31.2%
ADT at PCa diagnosis		
No ADT	49	87.5%
Large ADT	6	10.7%
Short ADT	1	1.8%
Radiotherapy		
Radical	8	14.3%
Adjuvant	6	10.7%
Salvage	35	62.5%
No RT	7	12.5%
CT-PET oligometastases (n = 85)		
Choline	59	69.4%
PSMA	26	30.6%
PSA-DT		
≤ 6 months	26	46.4%
> 6 months	30	53.6%

ADT — androgen deprivation therapy; CT-PET — computed tomography-positron emission tomography; PCa — prostate cancer; PSA-DT — prostate-specific antigen doubling time; PSMA — prostate-specific membrane antigen; RT — radiotherapy

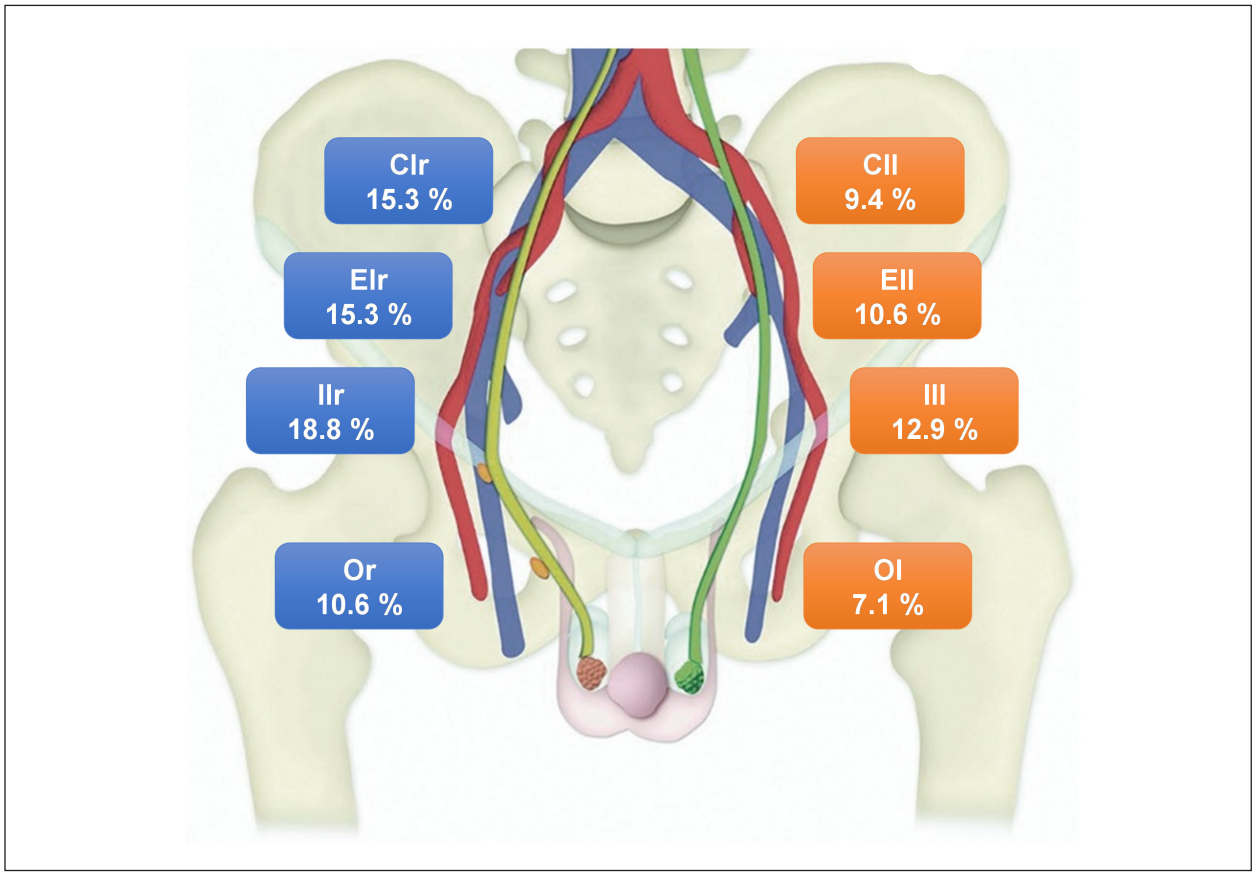


Figure 1. Distribution pelvic lymph nodes oligometastases. CI — common iliac; EI — external iiac; II — internal iliac; O — obturator, l — left; r — right

At the three-year follow-up, pelvic lymph node progression-free survival was 62.5%, while distant progression-free survival was 80%. The most common metastatic sites were classified as M1a in 70% and M1b in 30% of cases.

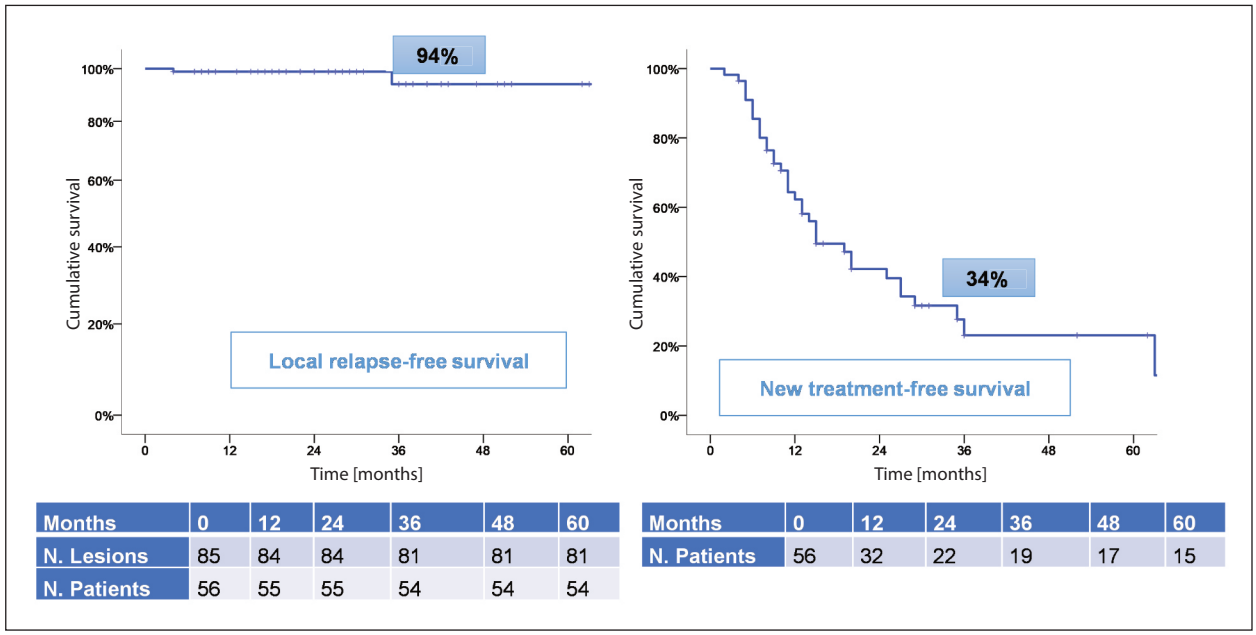
The median time to a new treatment regimen involving radiotherapy and/or ADT ± ARPIs was 15 months (95% CI: 9–21 months). At the three-year follow-up, 34 % of patients had not received a new treatment following SABR (Fig. 2). A total of 37 patients (66%) underwent retreatment after SABR.

The types of new treatments administered after SABR were as follows: SABR was administered to seven patients (19%) with 12 oligoprogressive lesions. Radiotherapy combined with ADT was employed for eight patients (21.6%), while ARPIs were administered to ten patients (27%), with apalutamide and enzalutamide being employed in equal proportions. ADT alone was employed for twelve patients (32.4%). The median biochemical relapse-free survival following additional SABR was 11 months (95% CI: 9–21).

In the analysis of prognostic factors, neither pathological factors (perineural infiltration (IPN), margin status (MS), lymphovascular infiltration (ILV) and D'Amico risk classification) nor analytical factors (PSA-DT) were found to influence biochemical recurrence-free survival (BRFS), the FRFS, the PLNRFS, the distant progression free survival (DPFS) or the overall survival (OS).

Of the 56 patients treated, only one died during follow-up from a cause unrelated to the disease. No grade 2 or higher genitourinary or gastrointestinal toxicities were reported according to CTCAE v5.0.

A total of 37 patients completed the QLQ-C30 and the QLQ-PR25 questionnaires at both baseline and six months. The median global health status score remained constant at 83.33 points (interquartile range: 75–100) at the two time points analysed. No significant differences were observed in sexual activity, urinary function, or digestive function.



Months	0	12	24	36	48	60
N. Lesions	85	84	84	81	81	81
N. Patients	56	55	55	54	54	54

Months	0	12	24	36	48	60
N. Patients	56	32	22	19	17	15

Figure 2. Local relapse progression-free survival and new treatment-free survival Kaplan Meier curves

Discussion

The use of SABR in the management of oligometastatic disease remains controversial due to the limited data available, which is primarily derived from retrospective studies and the absence of phase II clinical trials.

However, modern imaging modalities, such as choline radiotracer PET and PSMA-PET, have emerged as essential tools in the diagnosis of oligometastatic disease. These developments are supported by data from phase I–II clinical trials, including PSMA MRgRT [15], OLI-P [16], and POPSTAR [17]. Furthermore, a post-hoc analysis of the ORIOLE [18] study demonstrated significant improvements in progression-free survival (PFS) ($p = 0.006$) and metastasis-free survival (MFS) ($p < 0.001$) when all metastatic lesions were identified using PSMA-PET.

In our series, PET scans with choline and PSMA were performed on all patients at the start of SABR treatment and during recurrence. The findings of this study align with previous research, demonstrating the potential of SABR to delay the onset of systemic treatment in patients with oligometastatic disease. The ADT-free survival (ADT-FS) rate with SABR is estimated to be between 40–49% at two years [15–17], which is consistent with our own observation of a 42% rate at the same time point. Additionally, it is noteworthy that 30.3% of the patients did not require retreatment after three years, and the median biochemical PFS was 15 months.

A pooled analysis of the ORIOLE and STOMP trials [10], with a median follow-up of 52.2 months, demonstrated a median PFS of 12 months with metastasis-directed therapy. Our analysis revealed that 26.7% of patients remained alive and progression-free or without the need for ADT for more than four years. This suggests a potential for a long-lasting response with SABR.

The feasibility of using SABR after a new relapse was also confirmed in our study, with a median biochemical relapse-free survival of 11 months. SABR can delay the onset of ADT and prevent its side effects in appropriately selected and informed patients. This is particularly beneficial for elderly patients, those with cardiac comorbidities or those who refuse ADT. The ADT-free interval could preserve quality of life and reduce the financial burden on healthcare systems [19, 20].

In order to determine the most effective treatment for patients, predictive factors such as elevated pre-SABR PSA levels or the number of treated metastases could be considered [21]. Previous studies have demonstrated that a short PSA doubling time (≤ 6 months) is associated to worse PFS and ADT-FS [22, 23]. Our study found that SABR significantly delayed the initiation of ADT, regard-

less of PSA doubling time, which is consistent with the results of the STOMP study [24]. No significant predictive factors were identified in our series. The literature indicates that nodal oligorecurrence may occur in up to 50–60% of patients within two years after SABR [7, 22, 25, 26]. This suggests the potential benefit of combining elective nodal irradiation with ADT to delay or prevent recurrence in micrometastatic disease. In our series, only 23% of patients experienced nodal oligorecurrence at two years. The OLIGOPELVIS-GETUG-P07 [27] study demonstrated that combination therapy resulted in complete remission in 46% of patients after three years, with less than 10% experiencing grade > 2 toxicity. In our study, 3-year biochemical relapse-free survival was 17%, and nodal relapse-free survival was 62.5%, with no reports of grade ≥ 2 toxicity.

The PEACE-V (STORM) trial aimed to determine whether SABR + ADT (for six months) could extend oligorecurrent metastasis-directed survival compared to pelvic irradiation + SABR + ADT (for six months). There were no significant differences in gastrointestinal ($p = 0.13$) and genitourinary ($p = 0.54$) toxicity between the two groups. It is important to note that irradiation is more extensive when the pelvis is included [28]. Results from SLM are pending presentation.

Regarding the addition of ADT, the findings from the SBRT-SG-05 trial [29] suggest that it is a safe treatment option with favourable clinical outcomes, with a median follow-up time of 54.2 months. Furthermore, Deek et al. reported that the use of ADT did not significantly decrease metastatic progression [30], but was associated with a higher rate of freedom from biochemical progression at 5 years ($p < 0.0001$) [31]. Our series showed an 80% distant metastasis-free survival rate at 5 years. The EXTEND trial demonstrated that combining SABR with six months of intermittent ADT improved PFS compared to ADT alone ($p < 0.001$). Additionally, eugonadal PFS was also improved with SABR (6.1 months *vs.* 3.7 months, $p = 0.03$) [32].

Several ongoing trials are currently investigating these questions. For instance, the RADIOSA [33] (phase II) trial compares SABR with SABR combined with six months of ADT. The SPARKLE [34] (phase III) trial compares MDT with MDT plus ADT for one month with MDT plus ADT plus six months of enzalutamide. The PROMETHEAN [35] (phase II) trial compares SABR with SABR plus six months of Relugolix. The DART (phase II) trial compares SABR with SABR plus darolutamide for six months.

The results of our quality-of-life study, which employed the QLQ-30 and PR25 questionnaires, demonstrate that treatment with SABR does not affect the quality of life. There was no change in results, with an 83.33-point score before and after SABR. This treatment option represents a safe and viable alternative for frail patients with significant comorbidities, for whom treatment with ADT or new antiandrogens can potentially exacerbate their baseline situation. Furthermore, in routine clinical practice, some patients decline systemic treatment due to deterioration of their sexual function.

Some authors express doubt about the effectiveness of metastasis-directed therapy in delaying the onset of ADT or the need for new lines of treatment. The authors argue that these endpoints are less robust than PFS and MFS. Consequently, there is a need for randomised clinical trials with homogeneous patient populations to determine the optimal therapeutic approach for oligometastatic patients.

This study is limited by its small sample size and retrospective design. Further research, including randomised clinical trials, is essential to confirm these findings and establish more definitive guidelines for the management of oligometastatic disease with SABR. Despite these limitations, our results contribute to the growing body of evidence suggesting that SABR is a promising treatment option for delaying systemic therapy and improving outcomes in patients with oligometastatic disease.

Conclusion

SABR is a safe and effective treatment for metachronous pelvic lymph node recurrence, with the potential to delay the need for ADT. This treatment offers an optimal balance between local control and overall survival, as well as quality of life. Therefore, it is an appropriate choice for patients who are ineligible for ADT due to severe cardiovascular disease, cognitive impairment, or other comorbidities, as well as for those who refuse ADT. These findings provide support for the incorpora-

tion of SABR into standard treatment protocols. Nevertheless, further research is necessary to better define the patient subgroups that would benefit most from this approach and to optimise treatment protocols. The identification of predictive factors for response to SABR will be of significant importance in the personalisation of treatment and the improvement of outcomes for patients with oligometastatic disease.

Conflict of interest

None declared.

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