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Original Article

The role of stereotactic body radiotherapy in oligoprogressive prostate cancer: A site-specific analysis of the prospective, phase II RADIANT trial

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ABSTRACT

Background and Purpose: Changing to next-line systemic therapy is the standard-of-care for patients with progressive metastatic castrate-resistant prostate cancer. However, to preserve systemic therapy options and minimize toxicity, stereotactic body radiation therapy (SBRT) is being increasingly considered for patients with limited disease progression ('oligoprogression'). Herein, we report clinical, toxicity and quality of life (QOL) outcomes for an oligoprogressive prostate cancer cohort from a prospective trial.

Materials and methods: RADIANT (NCT04122469) was a single-arm, phase-II basket trial which included patients with metastatic prostate cancer on any systemic therapy $\geq$ 3 months, with radiographic evidence of oligoprogression in $\leq$ 5 sites. Analysis by disease site was planned *a priori*. Patients received SBRT in 1–5 fractions to all progressive sites and were maintained on their current systemic therapy. The primary endpoint was cumulative incidence of change in systemic therapy. Key secondary endpoints included local control, toxicity and health-related (HR) QOL.

Results: Thirty-two patients were analyzed; median age was 74.0 years, median PSA 6.7 μg/L, 25% with visceral metastases and a median of 2 prior systemic therapy lines. Median follow-up was 14.1 months (range 4.8–51.9 months). At 1-year, 55.1% of patients remained on the same systemic line and local control was 84.0%. The cumulative incidence of grade 2 toxicity was 25.0% at 1 year, with no grade 3+ toxicities. HRQOL was maintained, with no detriment following SBRT delivery.

Conclusion: Among patients with oligoprogressive prostate cancer, SBRT is an effective and safe intervention, including in patients with aggressive clinicopathologic features. Larger, randomized trials are needed to validate these findings.

Introduction

The standard-of-care treatment for metastatic hormone-sensitive prostate cancer (mHSPC) is systemic therapy, possibly with prostate radiotherapy if low-volume disease [1–6]. Ultimately, most patients with mHSPC progress to metastatic castrate-resistant prostate cancer

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(mCRPC), due to androgen-receptor dependent and independent mechanisms [7]. Systemic therapy is also the mainstay for management of mCRPC, with multiple therapeutic options, depending on prior systemic therapies received, patient and tumor factors [8,9]. In the setting of progressive metastatic disease, regardless of castration status, standard-of-care is changing systemic therapy [8,10]. However, this may not be the optimal strategy in all cases, particularly when there are limited subsequent systemic options, toxicity concerns or in the case of 'oligoprogressive' disease (OPD)—defined by limited sites of disease progression, on a background of metastatic disease that is stable on the current systemic therapy [11,12]. In an effort to preserve systemic options, patients with OPD are increasingly considered for local ablative therapies, such as stereotactic body radiation therapy (SBRT) to address the progressing site(s), with the goal of maintaining the patient on their current therapy and delaying the start of next-line systemic therapy [10].

To date the benefit of SBRT for OPD has been more strongly demonstrated for some cancer types than others, and it is increasingly clear that the benefits are disease site and context specific [10,13–16]. There is currently limited prospective evidence to definitively support the use of SBRT in patients with oligoprogressive prostate cancer [17]. Herein, we present the clinical, toxicity and quality of life (QOL) results of an oligoprogressive prostate cancer cohort from a prospective, phase-II clinical trial of patients with OPD.

Materials and methods

Trial design

The Role of SBRT in Oligoprogressive Malignant Disease (RADIANT) trial was an investigator-initiated, single-institution, single-arm, open-label, phase-II basket trial (NCT04122469), approved by the University Health Network Research Ethics Board (REB; UHN18-6047). All patients provided informed written consent. The details of the study design have been previously described [18]. Briefly, patients with a primary diagnosis of genitourinary, breast or gastrointestinal cancer, who were on systemic therapy for $\geq$ 3 months, and had radiographic evidence of oligoprogression in $\leq$ 5 lesions (on conventional or molecular imaging), were enrolled [18]. After completing initial study accrual, with sample size of 70 across the cancer subtypes, a decision was made to continue accrual only for the genitourinary and breast cohorts, and subsequently only the genitourinary cohort given maintained physician and patient interest in OPD for these cancers. The present study analyzed enrolled patients with a primary histological diagnosis of prostate cancer. Analysis by disease site was planned *a priori*. SBRT was delivered to all sites of OPD. Radiation treatments were based on established institutional policies for the applicable body sites. Androgen deprivation therapy (ADT) was counted a systemic therapy line. Patients were assessed during SBRT, at 6-weeks, 3 and 6-months post-treatment, and then routinely every 6 months for clinical outcomes (including radiographic outcomes), toxicity and QOL data.

The primary study endpoint was change in systemic therapy to next-line therapy (which could also include best supportive care) [18]. Secondary endpoints included radiographic local failure (LF), radiographic distant failure (DF), radiographic progression-free survival (PFS) (defined as a composite of local and/or distant failure), overall survival (OS), toxicity related to radiation (using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0), and health-related QOL (HRQOL; European Organization for Research and Treatment of Cancer (EORTC) Core QOL (QLQ-C30) questionnaire) [18]. Maximal biochemical response after SBRT was defined as the maximum change in prostate-specific antigen (PSA) and PSA50 was defined as decrease $>$ 50%; both measured from the time of trial enrollment and captured only until the patient changed to next systemic therapy line, in order to avoid bias. An alpha/beta ratio of 1.5 Gy was used for prostate cancer when calculating biologically effective dose (BED) [19].

Statistical analysis

Demographic and tumour characteristics were summarized using medians and ranges for continuous variables and proportions for categorical variables. Time-to-event was calculated as the time from SBRT start date to first event, death or last follow-up, whichever was earliest. The cumulative incidences of change in systemic therapy, LF and DF were estimated using the Aalen-Johansen method, where death without the event of interest was treated as a competing risk event, while alive without the event of interest was censored. PFS and OS were estimated using the Kaplan-Meier method. The univariate Fine and Gray competing risk models and Cox proportional hazard models (for PFS and OS) were applied to examine the association between time to change in systemic therapy, LF, DF, PFS and OS with patient characteristics. Variables assessed in the model included age, number of metastases at trial enrollment, number of prior systemic lines, number of lesions treated with SBRT, maximal biochemical response and BED. Multivariable analyses were further conducted, if applicable, using variables identified to be associated with the outcomes in the univariate analyses, or based on clinical relevance. Cumulative incidences of acute toxicity (defined as occurring $\leq$ 3 months from the time of SBRT) and late toxicity (defined as occurring $>$ 3 months from SBRT) were estimated using the Aalen-Johansen method. The change in global HRQOL at 6 months from baseline was described, and the change in HRQOL over time was also analyzed using mixed-effect linear models for longitudinal data, with covariance structure of autoregressive of order 1. The minimal clinically important difference, defined as a change of $>$ 10 points compared with baseline on a 100-point scale, was examined [18]. A higher score represents better HRQOL. The data management and all statistical analyses were performed using SAS 9.4 (SAS institute, Cary, NC). A 2-sided p-value of $<$ 0.05 was considered statistically significant.

Results

Between October 2019 and December 2023, 32 eligible patients with a diagnosis of metastatic prostate cancer were enrolled and analyzed (Fig. 1). Baseline patient characteristics are outlined in Table 1. Median

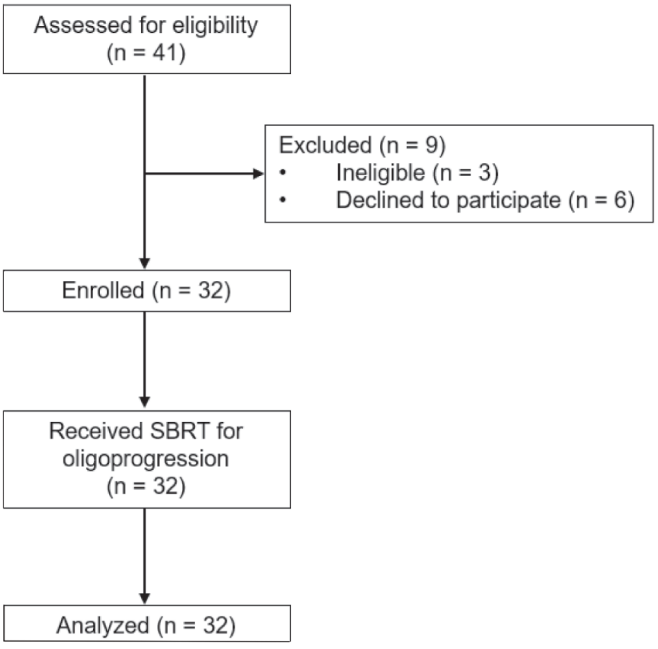


Fig. 1. Trial consort diagram. *Abbreviation:* SBRT = stereotactic body radiation therapy.

Table 1
Baseline patient characteristics.

Characteristic	All patients (n = 32)
Age (years)	
Median (range)	74.0 (61.0–82.0)
ECOG, n (%)	
0	13 (44.8)
1	13 (44.8)
2	3 (10.3)
Missing	3 (10.3)
PSA (μg/L)	
Median (range)	6.7 (0.03–86.6)
Castrate status, n (%)	
Castrate resistant	32 (100.0)
BRCA mutation	
Yes	1 (3.1)
Variant of unknown significance	3 (9.4)
No	28 (87.5)
Prior prostate-directed therapy	
Radical prostatectomy, +/- post-operative radiotherapy	12 (37.5)
Radical radiotherapy	12 (27.5)
None	8 (25.0)
Number of systemic therapy lines, n (%)	
1	5 (15.6)
2	12 (37.5)
3	8 (25.0)
4	6 (18.8)
5	1 (3.1)
Prior systemic therapy type(s), n (%)	
ARPI	25 (78.1)
Chemotherapy	8 (25.0)
Radioligand therapy	3 (9.4)
Number of total metastases	
Median (range)	2 (1–7)
Number of oligoprogressive metastases	
Median (range)	1 (1—5)
Site(s) of metastases, n (%)	
Lymph node only	10 (31.3)
Lymph node and bone	14 (43.8)
Visceral	8 (25.0)
Staging type to diagnose oligoprogressive metastases	
Conventional imaging	26 (81.3)
PSMA-PET	6 (18.7)

Abbreviations: ECOG = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; ARPI = androgen receptor pathway inhibitor.

Table 2
SBRT characteristics.

Characteristic	All patients (n = 32)
Number of lesions treated, n (%)	
1	16 (50.0)
2	6 (18.8)
3	4 (12.5)
4	5 (15.6)
5	1 (3.1)
Sites of SBRT, n (%)	
Lymph node only	10 (31.3)
Lymph node and bone	14 (43.8)
Visceral	8 (25.0)
Total GTV volume(s) (cc)	
Median (range)	13.6 (0.1–78.1)
SBRT total dose (Gy)	
Median (range)	35 (24–50)
SBRT dose fractionations (Gy/number of fractions), n (%)	
24/2	4 (12.5)
30/5	6 (18.8)
35/5	18 (56.3)
40/5	3 (9.4)
50/5	1 (3.1)
BED (Gy)	
Median (range)	198.3 (150.0–383.3)
Follow-up (months)	
Median (range)	14.1 (4.83–51.88)

Abbreviations: GTV = gross tumour volume; BED = biologically effective dose.

patient age was 74.0 years, mostly ECOG 0–1, median PSA 6.7 μg/L. All patients met criteria for mCRPC. Most patients had undergone prior local therapy (75.0%, n = 24) and were on second line (37.5%, n = 12) or third line (25.0%, n = 8) systemic therapy. Most patients had received an ARPI (78.1%, n = 25) and 25% (n = 8) of patients had received cytotoxic chemotherapy (not mutually exclusive). Most patients had both lymph node and bone metastases (43.8%, n = 14), while 31.3% (n = 10) of patients had only lymph node metastases and 25.0% (n = 8) of patients had visceral metastases. Most oligoprogressive disease was diagnosed on conventional imaging, as compared to prostate-specific membrane antigen (PSMA) positron emission tomography (PET). The median number of oligoprogressive metastases at enrollment was 1.

SBRT details are outlined in Table 2. Dose fractionation schema and dose constraint details are provided in Supplemental Tables 1 and 2. Most patients had a single lesion treated (50.0%, n = 16), while 18.8% (n = 6) had two lesions treated. Lymph node and bone targets were most commonly treated (43.8%, n = 14). The median gross tumour volume (GTV) (considering all targets, if multiple targets were treated) was 13.6 cc. The most common dose-fractionation was 35 Gy in 5 fractions. Median BED was 198.3 Gy. Median follow-up time was 14.1 months (range 4.8–51.9 months) (Table 2).

The cumulative incidence of change in systemic therapy at 6-months was 25.3% (95% confidence interval (CI), 13.7–46.5%) (Fig. 2a), and at 1-year was 44.9% (95% CI, 30.1–67.0%) (Fig. 2a). The median time from SBRT delivery to change in systemic therapy was 13.4 months (Fig. 2a). No patients died without a change in systemic therapy. All patients who changed systemic therapy (n = 18) did so due to disease progression. On univariate analysis, being on the second or greater line of systemic therapy was associated with a statistically significantly lower hazard of change in systemic therapy (HR 0.34, 95% CI 0.12–0.98, $p = 0.047$) (Supplemental Table 3). Patients who changed systemic therapy after SBRT most often commenced chemotherapy (55.6%, n = 10), followed by ARPI (22.2%, n = 4), radium-223 (16.7%, n = 3) and best supportive care (5.6%, n = 1).

The cumulative incidence of local failure (95% CI) at 6-months was 12.6% (5.0–32.0%), and at 1-year was 16.0% (7.0–36.2%) (Fig. 2b). The cumulative incidence of distant failure (95% CI) at 6-months was 28.1% (16.0–49.5%) and at 1-year was 60.3% (45.0–80.9%) (Fig. 2c). The median time to distant failure was 10.3 months (95% CI, 6.6–13.0 months) (Fig. 2c).

The median PFS was 10.2 months (95% CI, 6.7–18.4) (Fig. 3a). At 6-months and 1-year, PFS was 68.8% (95% CI, 54.4–86.8%) and 39.8% (95% CI, 25.9–61.3%), respectively (Fig. 3a). OS at 6-months was 100.0% and at 1-year was 92.6% (95% CI, 83.3–100.0%) (Fig. 3b). Four patients died during study data collection, all due to prostate cancer. Of the 78.1% (n = 25) patients who had distant disease progression, 52.0% (n = 13) developed new metastatic lesions, while 48.0% (n = 12) had progression of pre-existing, non-irradiated lesions. Fourteen (43.8%) patients went on to have further radiotherapy; 85.7% (n = 12) for further OPD, and 14.3% (n = 2) for symptom palliation. On univariate analysis, there were no significant findings associated with PFS (Supplemental Table 3). Univariate analysis could not be performed for OS due to too few events. No multivariable analyses were further performed for any outcome variable, given the lack of significant findings on univariate analyses.

A waterfall plot of the maximal biochemical response after SBRT (compared to trial enrollment), prior to changing systemic lines, is shown in Fig. 4. Most patients (62.5%, n = 20) experienced a decrease in PSA after SBRT, prior to any change in systemic therapy. One patient had no change in PSA and 11 patients (34.4%) had an increase in PSA after SBRT. PSA50 response rate was 43.8% (Fig. 4). On univariate analysis, biochemical response was not found to be associated with any outcome variables (Supplemental Table 3).

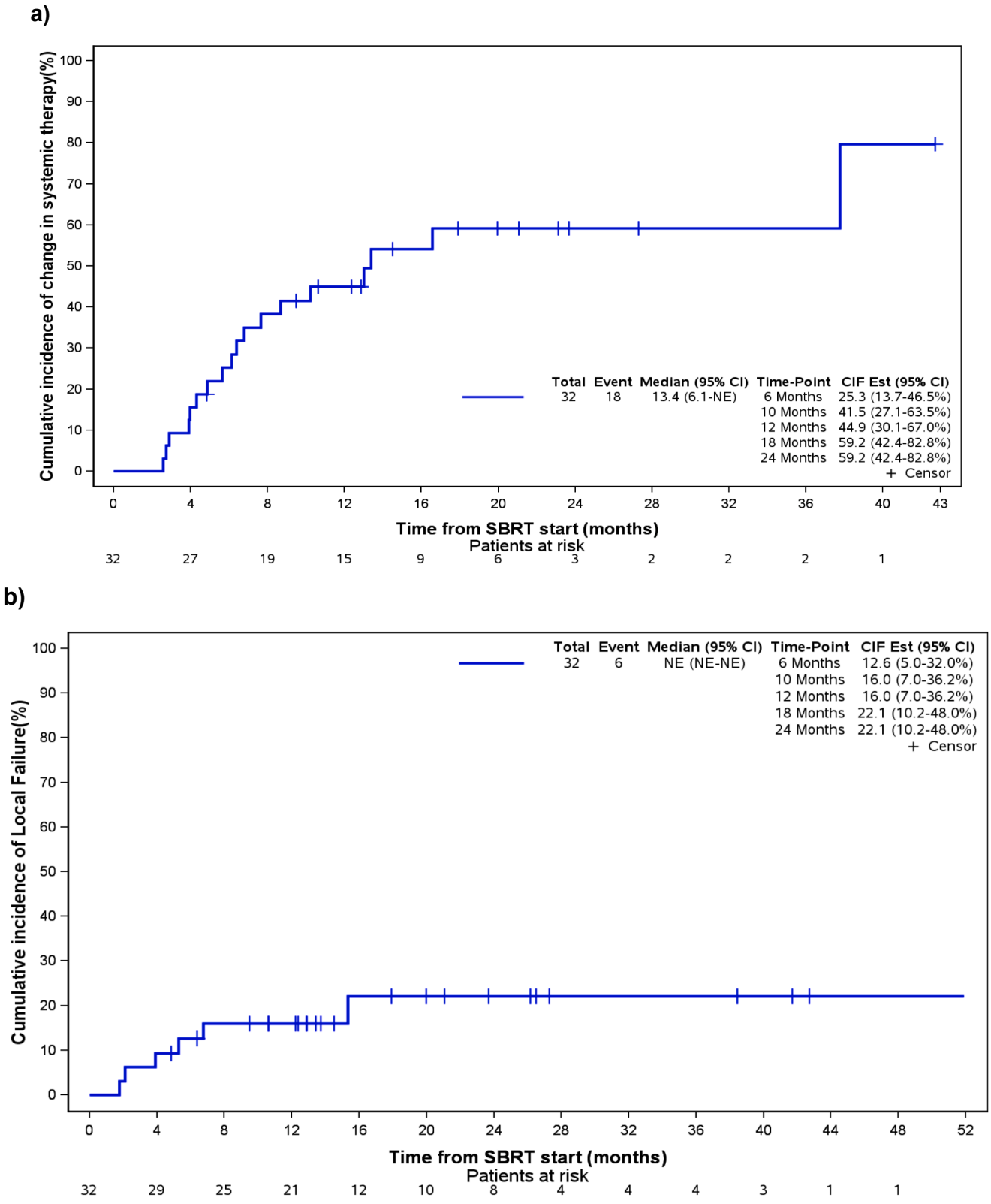


Fig. 2. Cumulative incidence of **(a)** change in systemic therapy, **(b)** local failure, and **(c)** distant failure. Death without event of interest was treated as a competing risk event.

Fifteen patients (46.9%) experienced at least one acute adverse event of any grade (Supplemental Fig. 1a). Eight patients (25.0%) experienced a grade 2 adverse event (Supplemental Fig. 1b). No patients experienced grade $\geq$ 3 adverse event. The median time from SBRT delivery to development of any grade toxicity was estimated as 7.9 months (range 0–41.7 months), and to grade 2 toxicity was 12.6 months (range

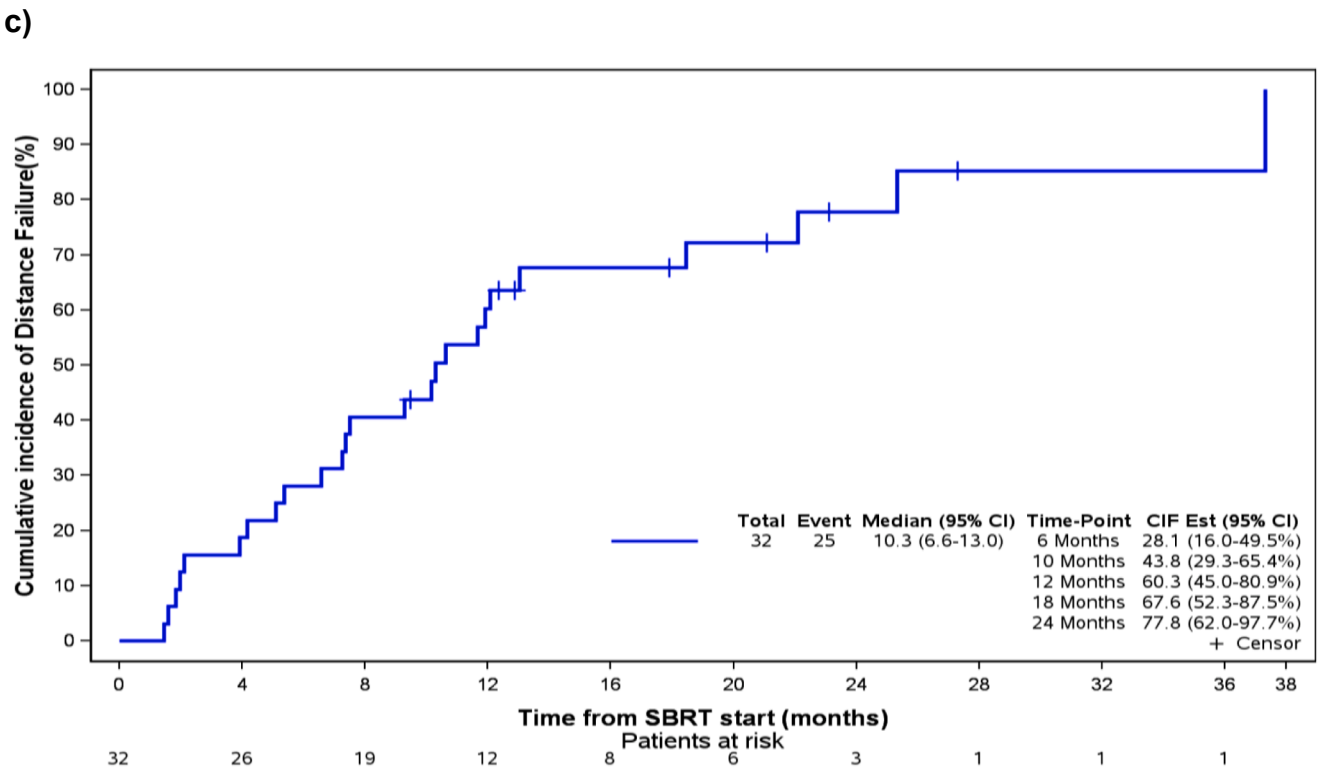


Fig. 2. (*continued*).

0.1–51.9 months), without accounting for the censor or competing risk. The most common toxicity of any grade was fatigue. Given the small number of toxicity events, regression analyses were not performed. Adverse events and their association with SBRT (scored according to adverse event details and timing around SBRT delivery) are included in Supplemental Table 4.

The mean (SD) global HRQOL was 58.3 (22.5) at baseline, compared to 59.9 (21.1) and 58.7 (24.4) at 6-months and 1-year following SBRT, respectively. The global HRQOL status score was statistically and clinically significantly higher than baseline at 6 weeks post-SBRT (10.0-point change from baseline, 95% CI, 4.2–15.8). The mean (SD) QLQ-C30 summary score was 80.2 (12.1) at baseline, compared to 80.7 (17.6) at 6-months post-SBRT and 78.3 (16.8) at 1-year after SBRT. Overall, there was no difference in the change in QLQ-C30 summary score from baseline with delivery of SBRT. The mean (SD) pain score for patients remained stable throughout follow-up (28.57 (29.70) at 6-months post-SBRT and 32.54 (30.95) at 1-year post-SBRT delivery).

Discussion

The role of radiation in the management of mCRPC has historically been limited to palliative treatments to alleviate symptoms. However, with continued advancements in systemic therapies, patients with mCRPC may increasingly present with OPD. By utilizing ablative radiation to address progressive disease sites, patients can continue their current systemic treatment and preserve future treatment lines [10,17,20–22]. Our results provide data supporting this concept, as the use of SBRT for OPD allowed over half of patients to remain on their current systemic therapy at 1-year, conferred a 1-year local control rate of 84.0% and low toxicity. These results support further randomized studies to evaluate the role of ablative therapy with SBRT in prostate cancer patients with OPD.

While SBRT for oligometastatic prostate cancer has been more widely studied (for example, STOMP, ORIOLE, EXTEND, SABR-COMET), these studies largely focused on new oligometastases in mHSPC [16,23–25]. However, our results align with the early results of the TRAP (targeted radiotherapy in androgen-suppressed prostate cancer patients; NCT03644303) and MEDCARE (metastasis-directed therapy in CRPC; NCT04222634) trials, both single-arm phase-II studies, which showed safety of SBRT and a delay to start next-line therapy in patients with oligoprogressive prostate cancer [26,27]. In MEDCARE, 2-year local control was 95%, which is higher than our 1-year data (local control 84.0% at 1-year), likely owing to the sites of disease being treated (MEDCARE treated 2/20 patients with visceral metastases, whereas RADIANT treated 8/32 patients with visceral metastases) and advanced state of disease (MEDCARE patients were mostly on first or second-line therapy, versus 46.9% of RADIANT patients were on third-line or greater [27]. In our cohort, being on second line or greater systemic therapy was, interestingly, significantly associated with a lower hazard of change in systemic therapy, which we speculate reflects the limited subsequent systemic therapy options as patients progress through the disease, and the subsequent desire to remain on the same systemic therapy for as long as possible. Acknowledging the heterogeneity within our cohort, including the patients with classically high-risk features (visceral disease, late line systemic therapy), our findings are promising, showing a majority of patients maintained on their current therapy. Finally, it is worth comparing our findings to those of the phase-II ARTO and GROUQ-PCS 9 trials, which to date contain the only randomized data to support the upfront combination of SBRT with ARPI therapy for patients newly progressed to mCRPC [28,29]. The TROG 19.06 DECREASE study similarly is investigating ARPI therapy in combination with SBRT, with results pending, while the SBRT-SG05 study recently reported favourable PFS outcomes when combining ADT and SBRT, including for subset of mCRPC patients [30]. In the ARTO and GROUQ-PCS 9 studies, the addition of SBRT improved biochemical response, as well as PFS and radiographic PFS, warranting further investigation in a Phase-III design [28,29]. In contrast to our cohort, ARTO and GROUQ-PCS 9 included a more homogenous patient cohort, earlier in the mCRPC disease trajectory, all ARPI-naïve, without or with few patients with visceral involvement, and received upfront

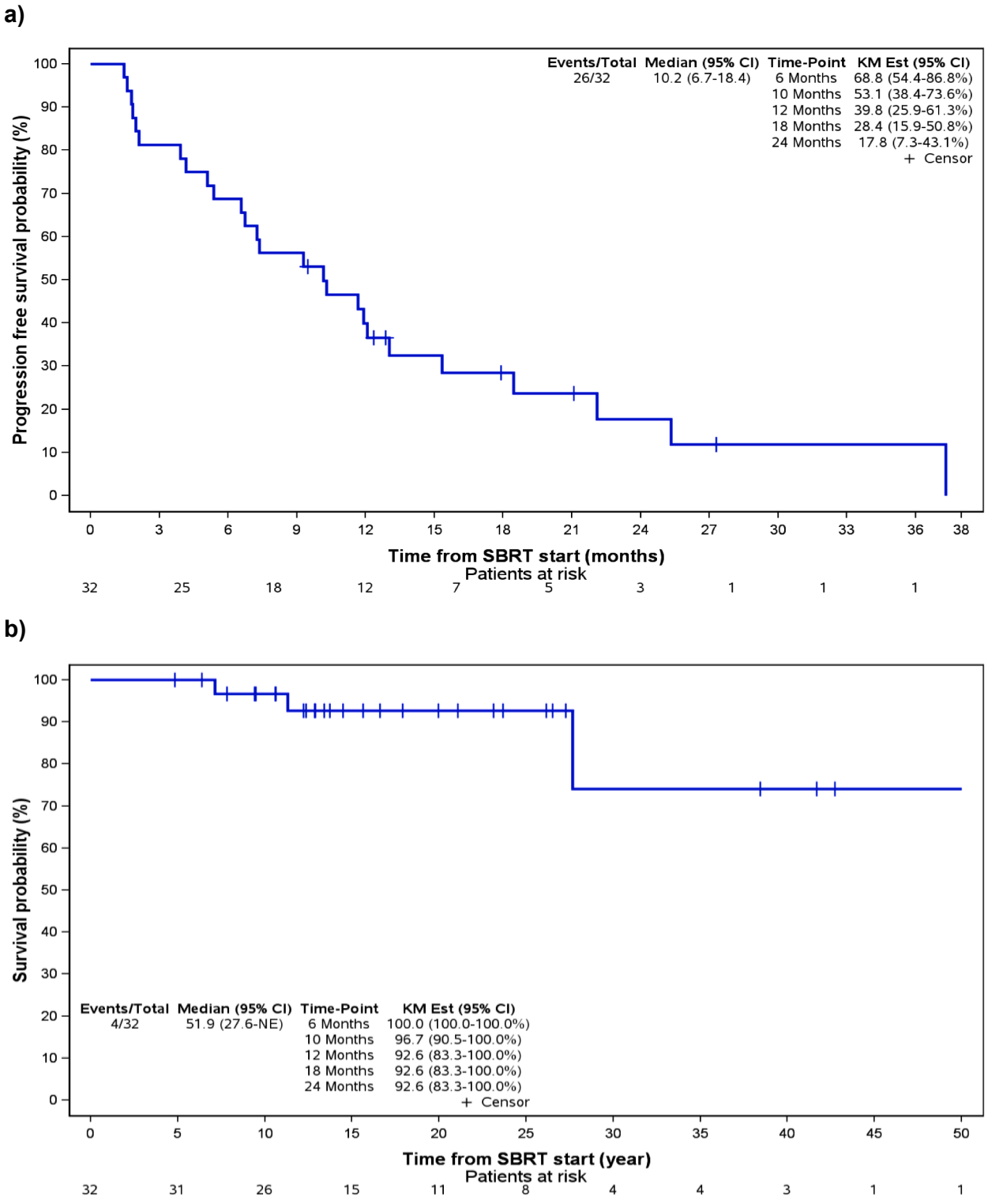


Fig. 3. Kaplan-Meier estimates of **(a)** progression-free survival, and **(b)** overall survival.

SBRT to all metastatic sites upon designation as mCRPC [28,29]. It appears that SBRT may afford a larger benefit in disease outcomes when delivered earlier in the disease trajectory. Considering the clinicopathologic features of much of our cohort, our findings nonetheless highlight the utility of SBRT for oligoprogressive prostate cancer in more advanced disease stages, at least for a subset of patients; this is particularly relevant for patients who did not or cannot receive SBRT to oligometastatic sites earlier in their disease course.

Accumulating data across disease sites suggests that the benefits of SBRT for OPD are site and context specific, warranting devoted prospective studies [10]. The CURB trial—the only randomized trial of OPD published to date—demonstrated differential benefit to SBRT between disease sites [14]. CURB highlighted that differences in metastatic patterns (whether patients develop new metastatic lesions versus progress from pre-existing, non-irradiated lesions) may be important when considering the utility of SBRT; it can be hypothesized that SBRT may be

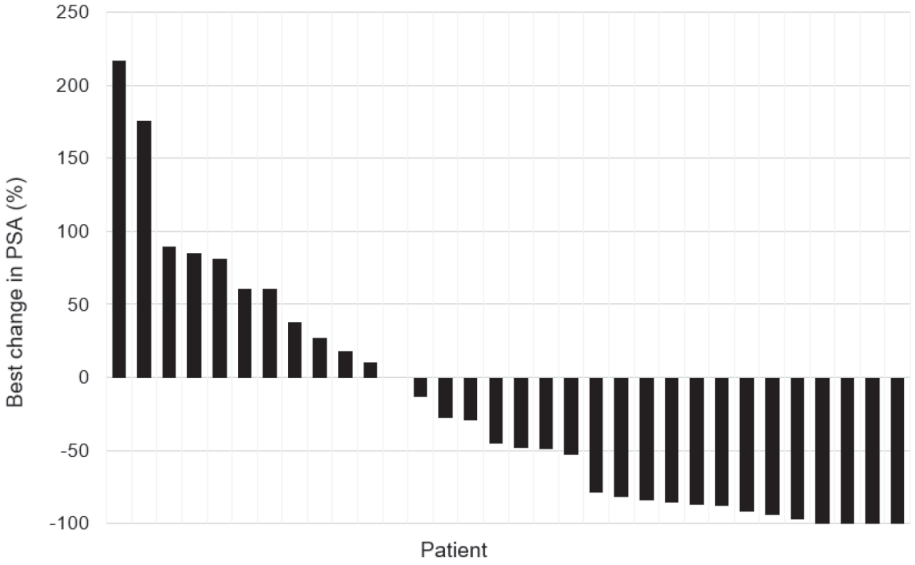


Fig. 4. Maximal biochemical response after SBRT.

most beneficial in the latter group [14]. In our cohort, of the patients who failed distantly, there was a near even divide between those who progressed due to the development of new metastatic lesions, versus due to progression of pre-existing, non-irradiated lesions. This raises the possibility that prostate cancer represents a more heterogeneous metastatic disease spectrum. Future work is needed to better identify the patients with oligoprogressive prostate cancer who are most likely to derive benefit from locally ablative treatments, including with further assessments of tumor biology and using PSMA PET, as this was not mandated in the present study, and only a minority of patients in RADIANT underwent PSMA PET. As PSMA PET is a more sensitive imaging modality compared to conventional imaging, it may identify areas of occult disease, thereby allowing for total consolidative therapy of all progressive sites. This may have been particularly important for at least the cohort of patients (48.0%) who developed disease progression on the basis of progression of pre-existing, non-irradiated lesions. Further research examining 'total consolidative therapy' for oligoprogressive prostate cancer is needed. The ORIOLE study provided support that treating all lesions (as identified on PSMA PET) leads to improved outcomes compared to sub-total treatment (treating only lesions identified on conventional imaging), although this study notably focused on a hormone-sensitive oligorecurrent patient population [23]. The role for improved patient selection is further highlighted by the fact that over a third of patients in our cohort did not have any biochemical response following SBRT, but rather had continued biochemical progression. Despite this, and although the present study did not examine total consolidative therapy (given the non-mandatory use of PSMA PET), the overall findings, including both the maintenance of over half the cohort on their current systemic therapy at 1-year, and high local control rates following SBRT delivery, nonetheless provide a favourable foundation to continue investigating the optimal use of metastasis-directed therapy with SBRT in this disease space.

Our study has limitations that should be considered. First, RADIANT was a single-institution, non-randomized, open-label study, which could introduce bias. It is not possible to draw definitive conclusions regarding SBRT without a standard-of-care control arm. Second, although this analysis is a single histology cohort and is meant to enhance the findings of the prior basket cohort analysis, there remains inherent heterogeneity in terms of overall disease burden and prior management of these patients [18]. However, this variability mirrors real-world clinical practice and can be considered a strength. Our sample size is relatively small, although it is comparable to other similar phase-II studies of SBRT for OPD [14,18,26,27,31]. Together however, the cohort heterogeneity, coupled with a small sample size, limits the extent of regression and subgroup analyses that can be conducted. As a result, there remains opportunity for a larger trial to identify a specific subgroup of oligoprogressive prostate cancer patients that derive clear benefit from metastasis-directed therapy. Lastly, the primary endpoint of RADIANT was change in systemic therapy; these decisions were at the discretion of the treating physician and were not mandated by the study protocol (given the basket design of the study and heterogeneity of included cancer types and pragmatic study design). However, all patients in our prostate cohort changed systemic therapy due to disease progression.

Conclusions

In summary, this site-specific analysis of oligoprogressive prostate cancer patients enrolled on the RADIANT trial demonstrates SBRT to be an effective treatment. Our cohort included a heterogenous cohort of mCRPC patients on median third line systemic therapy with aggressive clinicopathologic features. Despite this, the primary endpoint of delaying change in systemic therapy was seen in over half of patients at 1-year. Future research should focus on predictors of response to SBRT to help optimize patient selection for this treatment strategy, and larger, randomized prospective phase-III studies are necessary to definitively validate the efficacy of SBRT in patients with oligoprogressive prostate cancer.

Author contributions

All authors all contributed to study conception and design. KMR and RMG acquired the study data. KMR, XYY and RMG analyzed and interpreted the data. XYY performed the statistical analyses. KMR and RMG drafted the manuscript. All authors reviewed, edited and approved the manuscript. AB and JH obtained funding.

CRediT authorship contribution statement

Kara M. Ruicci: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aisling Barry:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization. **Xiang Y. Ye:** Writing – review & editing, Visualization, Software, Project administration, Methodology, Formal analysis, Conceptualization. **Peter W. Chung:** Writing – review & editing, Resources, Project administration, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111041.

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