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Phase II evaluation of Stereotactic Ablative Radiotherapy (SABR) and immunity in ^{11}C-Choline-PET/CT-identified oligometastatic castration-resistant prostate cancer

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Abstract

Purpose: Outcomes for resistant metastatic castration-resistant prostate cancer (CRPC) are poor. Stereotactic ablative radiotherapy (SABR) induces anti-tumor immunity in clinical and preclinical studies, but immunological biomarkers are lacking.

Experimental Design: 89 patients with oligometastatic CRPC were identified by ^{11}C-Choline-PET (Choline-PET) from August 2016-December 2019 and treated with SABR. Pre-specified co-primary endpoints were 2-year overall survival (OS) and PSA progression. Secondary endpoints included 2-year SABR-treated local failure and 6-month adverse events. Correlative studies included peripheral blood T cell subpopulations before and after SABR.

Results: 128 lesions in 89 patients were included in this analysis. Median OS was 29.3 months, and 1- and 2-year OS were 96% and 80%, respectively. PSA PFS was 40% at one year and 21% at two years. Local PFS was 84.4% and 75.3% at 1 and 2 years, respectively, and no Grade

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SSP, HD, EDK, TMP, KRO, MAN, and GBJ conceived the project and obtained approvals, funding, and recruitment to the trial. Review of Choline-PET, MRI, and CT as indicated was performed by BJS, VJL, EJT, MSB, CRC, DHB, MJI, BJD, GBJ, MAN, KRO, TMP, and SSP. Additional trial recruitment and follow-up clinical data were provided by JJO, FA, BJS, VJL, EJK, MSB, LCP, CRC, DHB, MJI, BJD, JFQ, BAC, and SSP. HZ, JJO, VLJ, FL, and JJO performed laboratory studies. FA and WSH provided statistical design and support. HZ, JJO, and SSP wrote the manuscript and performed additional analyses.

Prior presentations

Preliminary data were presented at the 2020 ASTRO annual meeting

Conflicts of Interest

The authors report no other relevant conflicts of interest.

≥ 3 AEs were observed. Baseline high levels of tumor reactive T cells (T_{TR}; $CD8^+CD11a^{high}$) predicted superior local, PSA, and distant PFS. Baseline high levels of effector memory T cells (T_{EM}; $CCR7^-CD45RA^-$) was associated with improved PSA PFS. An increase in T_{TR} at day 14 from baseline was associated with superior OS.

Conclusions: This is the first comprehensive effector T cell immunophenotype analysis in a phase II trial before and after SABR in CRPC. Results are favorable and support the incorporation of immune-based markers in the design of future randomized trials in oligometastatic CRPC patients treated with SABR.

Trial Registration: ClinicalTrials.gov Identifier: NCT02816983. Oligometastatic Prostate cancer Radiotherapy Augmenting T Immune Cells (OPeRATIC).

Introduction

Clinical outcomes for patients with metastatic castration-resistant prostate cancer (CRPC) whose disease is refractory to second-generation antiandrogens and chemotherapy are poor with median overall survival of 11 to 13.6 months.[1] This highlights an urgent need for improved therapeutic strategies. In refractory CRPC, systemic agents are offered with non-curative intent. Similarly, clinicians may also offer localized therapies like radiotherapy (RT); however, most reserve these as purely palliative measures for symptomatic metastases. The extent to which patients with metastatic disease benefit from these localized therapies is an area of active inquiry.

The term “oligometastasis” was coined by Hellman and Weichselbaum,[2] and the rationale for aggressive metastasis-directed therapy in this patient population stems from surgical experience; metastasectomies for various solid tumors have demonstrated a 5-year survival rate of 25–45%.[3–5] Although differing theories explain the oligometastatic state, the main premise is that the removal of tumor clones that give rise to metastases will reduce the risk of secondary metastases and thus improve survival. The clinical benefit of stereotactic ablative radiotherapy (SABR) in oligometastatic castration-sensitive prostate cancer (CSPC) is supported by results of recent phase II randomized trials STOMP and ORIOLE.[5,6]

A major obstacle in obtaining favorable outcomes in patients with oligometastatic disease is the identification and selection of patients with a truly limited number of metastases. ^{11}C-Choline-PET (Choline-PET) is more sensitive in detecting pelvic lymph node and distant metastases than traditional imaging modalities with validated sensitivity, specificity, positive predictive value, and negative predictive value at 85–100%, 76–96%, 76–91%, and 81–100%, respectively.[7–12] These appear to be similar to other advanced imaging techniques.[13] Therefore, we hypothesized that SABR in choline-PET-identified oligometastatic CRPC may improve outcomes. A goal of the present study is to identify blood-based biomarkers that will select patients who benefit from SABR in this setting.

A second major obstacle is the subclinical microscopic disease burden that resists systemic therapy and drives distant failures following SABR. While immune checkpoint inhibition has revolutionized treatment of many cancers, the utility of PD-1/PD-L1 axis inhibition in prostate cancer has been limited.[14] Research in engaging anti-tumor immunity against

CRPC is ongoing. A highly promising lead in this area has been the use of tumor-directed radiotherapy to boost immune response.[15,16] Metastasis-directed SABR offers excellent local control and can elicit immune responses in advanced prostate cancer.[6,7,17,18] We previously demonstrated that SABR and anti-PD-1 therapy induced antigen-specific abscopal responses in a preclinical oligometastatic cancer model, suggesting that such anti-cancer immune responses may not be limited to certain tumor histologies or host genetic factors.[19] These antigen-specific responses are reflected in CD11a-high CD8+ T cells.[20] We further demonstrated that tumor-reactive effector T cells predict superior survival in melanoma patients and are important in driving the abscopal response in preclinical models.[19–21] However, clinical data supporting SABR-induced anti-prostate cancer immunity is lacking.

Herein, we report outcomes of our prospective clinical trial that evaluated SABR in Choline-PET-identified oligometastatic CRPC and the induction of anti-prostate cancer immunity based on our prior translational studies.[20–22]

Methods and Materials

Patient Population

This study was performed in accordance with the Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board (IRB). The study was registered with ClinicalTrials.gov (NCT02816983). Informed written consent was obtained from each subject. From August 2016 to December 2019, eighty-nine patients with oligometastatic CRPC were prospectively enrolled on this single arm, single institution, IRB-approved phase II trial (NCT02816983). Eligibility criteria included histologically confirmed prostate cancer, ≤ 3 lesions identified on Choline-PET/CT performed as described previously,[23,24] castrate levels of testosterone (< 50 ng/dL) on androgen deprivation therapy (ADT), ECOG performance status score of 0–2, > 6 months of life expectancy, and consent for blood draws. Co-primary endpoints were 2-year overall survival (OS) and PSA progression (Prostate Cancer Working Group criteria).[25] Secondary endpoints included 2-year SABR-treated local failure (LF, defined radiographically) and 6-month rates of adverse events (AEs) per Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Peripheral blood samples were collected for immunologic biomarker correlative analyses as previously described.[22,26]

Statistical Analysis

Co-primary endpoints were overall survival (OS) and PSA progression while the secondary endpoints included local failure (LF) of SABR-treated lesion(s) and distant failure (DF). Hussain *et al* demonstrated that PSA progression in metastatic CRPC predicts OS, and the median PSA PFS was 8.1 months for the SWOG 99–16 cohort using the PCWG 2008 PSA progression definition.[27]Overall survival was 17 months. This translates to a one-year PSA PFS of 35.8% assuming an exponential distribution. Assuming alpha 0.05, our cohort of 89 patients was powered at 80% to detect a statistically significant difference in survival. Of these, 9 were treated with conventional RT due to insurance denial of SABR while the remaining 80 received SABR treatment. Descriptive statistics are reported as median and inter-quartile range (IQR) for continuous values and reporting of median follow-up and

median survival. For discrete variables, the number and percentage are reported.Follow-up visits were routinely performed every 3–4 months in person (or telephone with mail-in PSA) at physician's discretion. The minimum time from SABR to follow-up imaging was at least 3 months and any increase in PSA triggered imaging with choline PET. LF and DF were respectively defined as choline uptake at the site of prior SABR-treated or elsewhere. A positive ^{11}C-choline PET/CT was defined as a PET/CT study that identified a tracer-avid lesion (focal tracer uptake greater than the surrounding blood pool). For LF, an increase in max SUV value after SABR, and when available, expansion of bony metastasis on CT or MRI was used. For new spine or pelvic metastases, MR was performed to verify Choline findings. For extremity bone, PET finding was confirmed on planning CT. PSA progression was defined per Prostate Cancer Working Group criteria (25% increase between PSA measured at any of the 6 follow-up time points and nadir of 2 ng/mL or greater).[25]

We verified patient survival from the third-party agent Accurint in addition to the medical record. For all other outcomes, data were collected up to and censored at the most recent follow up visit. Kaplan-Meier estimates were used to estimate survival curves and a univariate Cox model was used to determine the association of patient and disease variables with the risk of each outcome of interest. Expected 2-year overall survival was estimated at 30–35% for the powering of this study. The alpha-level for statistical significance was prespecified at 0.05. OS and recurrence-free survival (biochemical, local, and distant) estimates are reported with 95% confidence intervals. The alpha-level for statistical significance was prespecified at 0.05.

Immunological biomarkers were measured as continuous variables for correlative studies and converted to a categorical variable to classify patients as high versus low risk. We used the Contal and O'Quigley method[28] based on the log rank test statistic to estimate the cutoff value needed to categorize each immune cell quantity. The best cutoff value for each survival outcome was calculated based on baseline values. These cutoff values were then used at all other time points. Cutoffs were 7% for T_{TR}, 44% for PD-1-positive T_{TR}, and 24% for T_{EM}.

Imaging Technique

^{11}C-choline PET/CT was performed on an integrated PET/CT scanner (Discovery LS, RX, 690, or 710, GE Healthcare) with the use of 11C-choline produced at our on-site cyclotron facility as previously described.[19,21] A CT scout scan was performed to define the body axial range to be imaged. Next, each patient received a single-dose, intravenous bolus injection of 555 to 740 MBq 11C-choline (half-life 20.4 minutes). Low-dose helical CT images were then obtained with the patient doing shallow breathing for attenuation correction and anatomic localization (detector row configuration, 16 × 0.625 mm; pitch, 1.75; gantry rotation time, 0.5 sec; slice thickness, 3.75 mm; 140 kVp; and range 60–120 mA with the use of automatic current modulation) followed by PET acquisition initiated at approximately 5 minutes after injection. PET images were acquired from mid-thigh to the orbits (in three dimensions, with a 128 x 128 matrix and at a rate of 3-to 4 minutes per bed position depending on body mass index). PET images were reconstructed with a three-dimensional ordered-subsets expectation maximization algorithm (28 subsets, two iterations).

SABR Technique

Patient immobilization, SABR planning, and delivery were performed as previously described.[2,29] In brief, SABR was delivered in 1 to 5 fractions (RANGE 20–50 Gy total) in accordance with AAPM Task Group 101 recommendations.[30] Modal dose and fractionation were 20 Gy and 1 fraction, respectively.

We highlight that our SABR planning process incorporates diagnostic Choline-PET image fusion with planning CT to delineate target volumes. MRI acquired in the RT treatment position was obtained for spine metastases, which confirmed target volumes and helped to define the spinal cord and cauda equina. For spine lesions, clinical target volume (CTV) was defined per RTOG 0631.[31] Five mm planning target volume (PTV) expansion was used where appropriate. In cases of spine lesions, 2–3 mm was used.

Immunological Studies

We collected peripheral blood mononuclear cells (PBMCs) at four time points: at baseline and on days 1, 7, and 14 post-SABR. We performed two-color staining for CD11a and CD8 to monitor the frequency of tumor-reactive T cells (T_{TR}; $CD8^+CD11a^{high}$).[20,22,26] Markers CCR7 and CD45RA defined pre-determined subsets of $CD8^+$ T cells assigned to one of four subgroups based upon the intensity of biomarker staining: naïve ($CCR7^+CD45RA^+$), central memory (T_{CM}; $CCR7^+CD45RA^-$), effector/effector memory (T_{EM}; $CCR7^-CD45RA^-$), and terminally differentiated ($CCR7^-CD45RA^+$). We analyzed PBMCs both at baseline and at defined time points after SABR as described above using flow cytometry. We analyzed between 10,000 and 100,000 peripheral blood T cells per patient according to cell recovery.

Flow analysis of human T-cells isolated from peripheral blood

We identified PBMC subpopulations with the following antibody panel: CD8-PE-Cy7 (BD Pharmingen, clone RPA-T8, catalog 304006), CD11a-APC (BioLegend, clone HI111, catalog 301212), PD-1 FITC (BioLegend, clone EH12.2H7, catalog 32990), Ki-67-BV421(BD Biosciences, clone B56, catalog 562899), CCR7-BV650 (BD Biosciences, clone 2-L1-A, catalog 566756), and CD45RA (BD Biosciences, clone HI100, catalog 563031). We stained surface markers prior to intracellular markers. Flow cytometry was performed at the institutional flow cytometry core facility on a FACS Canto II (BD Biosciences, San Jose, CA) and data were collected on a CytoFLEX LX (Beckman Coulter, Atlanta, Georgia). We analyzed flow cytometry data with FlowJo 10.4 (Tree Star, Palo Alto, California).

Results

Patient and treatment characteristics

Baseline patient characteristics are presented in Table 1. Median follow-up was 23 months (IQR 11–25), and median age was 71 years (range 51–84; IQR 64–75). Eighty-nine patients with 128 total metastatic lesions treated were included in the analysis. Fifty-eight patients (65%) had one lesion, 23 (26%) had two lesions, and eight (9%) had three lesions. Nine of the 89 subjects received conventional RT as noted in the methods (8 Gy in 1 fraction). Median PSA before SABR was 0.7 ng/mL (IQR 0.25, 3.1), and 64% had PSA < 2 ng/mL. Prior to SABR (n=80), 61%, 44%, and 19% had disease progression while receiving

chemotherapy, abiraterone, or enzalutamide, respectively. Significantly, 38% of the cohort had progressed on both chemotherapy and at least one second-generation antiandrogens. Seventy-one percent of patients had received prior SABR to the prostate or prostate fossa. Patients were maintained on the same systemic therapy before and after SABR until clinical failure.

Disease outcomes

Overall Survival (OS)—18 deaths were observed with median OS of 29.3 months. OS at one and two years was 95.9% (95% CI 91.5–100.0%) and 80.2% (95% CI 69.9–91.9%), respectively (Figure 1A). No significant difference in OS was noted between patients with one or more than one metastasis (HR 0.55 [95% CI = 0.16–1.9], p = 0.33). In multivariate analyses, number of metastases did not significantly change outcomes.

PSA Progression-Free Survival—Sixty-three patients experienced PSA progression within 2 years of treatment. Median time to PSA progression for these patients was 9.2 months (95% CI 7.0–12.4 months). PSA progression free survival (PFS) was 39.5% at one year (95% CI 30.1–51.8%) and 20.8% at two years (95% CI = 13.1–33%) (Figure 1B). Median time to PSA progression was 9.5 months for patients treated with SABR and 7.7 months for patients treated with conventional RT. Seven of the nine patients in the conventional RT group experienced PSA progression within the first year. One patient was lost to follow-up at 15 months and the remaining patient progressed at approximately 23 months. PSA PFS at one year was 40.9% (95% CI = 31–54%) for patients treated with SABR compared to 27.8% (95% CI 8.9–86.9%) for patients treated with conventional RT. At two years, the PSA PFS for patients treated with SABR was estimated at 22.5% (95% CI = 14.3–35.4%). Conversely, all patients with conventional RT experienced disease progression.

The number of metastatic sites correlated with PSA progression-free survival (Supplementary Figure 1A, Supplementary Table 1). Patients with three treated metastatic sites experienced significantly inferior PSA progression-free survival (median 5 months) relative to patients with two metastases (median 10.9 months, HR 0.33 [95% 0.13–0.83], p=0.018) or one metastasis (9.7 months, HR 0.33 [0.14–0.76], p=0.019).

Local progression of SABR-treated metastases and distant progression—Twenty-one patients experienced LF after radiotherapy. Median time to LF was not reached. Local PFS was 84.4% and 75.3% at 1 and 2 years, respectively (Figure 1C).

A total of 66 patients experienced DF with a median time to DF of 5.1 months (95% CI 3.6–6.9). Distant PFS for all patients was 17.6% (95% CI = 10.6–29.5%) and 5.0% (95% CI = 1.7–14.8%) at one and two years, respectively. All conventional RT patients had distant recurrences by nine months. The one- and two-year distant PFS for patients receiving SABR was 19.4% (95% CI = 11.6–32.2%) and 5.5% (95% CI = 1.9–16.2%), respectively (Figure 1D). Distant PFS was not significantly related to the number of metastases detected at baseline (Supplementary Figure 1B, Supplementary Table 2).

Adverse Events—Adverse events at six months were not evaluable in 17 patients (20%). Among 72 evaluable patients, no Grade ≥ 3 AEs were observed. Grade 2 AEs included pain flare (8.5%), fracture (2.9%), and fatigue (1.4%).

Immunological parameters and outcomes—We previously validated $CD8^+$ $CD11a^{high}$ tumor reactive (T_{TR}) T cell populations as significant in anti-tumor immunity.[20,22,26] To determine whether these cells or other known anti-tumor T cell populations predict patient outcomes, we measured these cells in systemic circulation before and after radiotherapy (see Supplementary Figure 2).

Baseline T_{TR} levels predicted significantly improved PSA PFS, local PFS, and distant PFS (Figure 2A-C, Supplementary Table 3). Patients with baseline T_{TR} levels above the cutoff experienced prolonged median time to PSA progression compared to patients with levels below the cutoff (9.7 vs. 5.6 months; HR 0.57, 95% CI [0.3 –0.99]; p= 0.04). Similarly, patients with baseline T_{TR} above the cutoff did not reach median time to LF while their counterparts achieved a median 23 months local PFS (HR 0.27 [95% CI 0.09 – 0.80]; p=0.01). Interestingly, patients with PD-1^+ T_{TR} at baseline above the cutoff experienced shorter median time to LF (9.1 vs. not reached; HR 6.45, 95% CI 1.68 –24.79; p=0.002).

Median time to DF was also improved in patients with T_{TR} above the cutoff compared to their counterparts with T_{TR} below the cutoff (6.4 vs. 3.5 months; HR 0.44, 95% CI 0.24 – 0.83; p=0.009).

Next, we correlated clinical outcomes with baseline T cell subgroups: naïve (T_N, $CCR7^+CD45RA^+$), central memory (T_{CM}, $CCR7^+CD45RA^-$), effector memory (T_{EM}, $CCR7^-CD45RA^-$), and terminally differentiated (T_{TD}, $CCR7^-CD45RA^+$). Patients with T_{EM} at baseline above the cutoff achieved prolonged median time to PSA progression (10.5 vs 6.2 months; HR 0.46, 95% CI [0.22 – 0.96]; p=0.03).

We next assessed whether $CD8^+$ T cell population changes after SABR predict clinical outcomes by assessing the percent change of various effector T cell levels pre- and post-SABR (Figure 3, Supplementary Figure 3). Patients with increased T_{TR} at day 14 experienced improved OS compared to those with decreased T_{TR} at day 14 (median OS 33.3 months vs 28.2 months; HR 6.21, p=0.04). Conversely, there was a trend for worse survival with an increase in T_{CM} on day 1 (median OS 32.7 vs. 29.3 months; HR 0.18; p=0.08). Increasing T_{CM} consistently predicted inferior local control (median time to LF not reached vs. 15.8 months; p= 0.053). Increasing Ki67 in T_{TR} (p=0.042) and T_{EM} (p=0.049) populations at Day 1 and 7, respectively, predicted improved local control.

Patients with increasing T_{TR} at day 1 achieved superior median time to DF (6.7 vs. 3.6 months; HR 0.49, 95% CI 0.2 –0.84; p=0.008). In addition, patients with increasing T_{EM} at day 14 achieved superior median time to PSA progression (median not reached vs. 7.9 months; HR 2.69, 95% CI 1.03–7.06; p=0.04).

Discussion

To our knowledge, this study is both the first prospective PET-informed metastasis-directed SABR trial in oligoprogressive CRPC and the first to correlate response to SABR therapy with immune cell populations. 2-year OS and PSA PFS were 80% and 21%, respectively. SABR was well tolerated with no grade ≥ 3 AEs. Baseline levels of tumor reactive (T_{TR}, $CD8^{+}CD11a^{high}$) effector T cells and T effector memory cells (T_{EM}; $CCR7^{-}CD45RA^{-}$) predicted improved PSA and local PFS. Post-SABR increases in T_{TR} and T_{EM} were associated with improved distant and PSA PFS, respectively, and an increase in Ki67 T_{TR} and T_{EM} was associated with improved local control. Conversely, T_{CM} correlated with inferior OS and local control.

Emerging randomized trials have determined a clinical benefit of SABR in patients with oligometastatic disease.[5,6,32,33] In CSPC, SABR improved 5-year ADT-free survival in STOMP[34] and median PFS in ORIOLE.[5] Oligometastasis-directed SABR is safe and locally effective treatment of metastatic prostate cancer. SABR may delay more toxic systemic therapies as demonstrated in the recent NRG-BR001 phase 1 trial in a spectrum of solid tumor types.[35]

In this study, we selected OS and PSA PFS as co-primary endpoints. Our cohort comprised advanced, CRPC with resistance to multi-systemic therapy. The single-arm design of the trial reflected clinician concern that equipoise between observation and SABR in patients with advanced CRPC was not possible. Despite resistance to or intolerance of prior chemotherapy (61%), abiraterone or enzalutamide (44%), or both chemotherapy and a next generation antiandrogen (38%) prior to SABR, our patients with oligometastatic CRPC experienced median OS and PSA PFS of 29.3 and 9.2 months, respectively. In the CARD trial, OS was 13.6 months and PFS was 4.4 months.[36] The CARD trial included patients with similar characteristics, although different imaging modalities were used to define metastatic disease and some non-metastatic disease was included in the CARD trial. Choline-PET-directed SABR with or without novel systemic therapy warrants further investigation.

The precise imaging afforded by Choline-PET offers several advantages. First, highly specific modalities identify patients with metastatic disease in whom additional treatment is effective. Second, highly sensitive modalities select patients with truly oligometastatic disease. Although this selection may inflate survival by excluding patients with more advanced disease previously included in such studies,[37] it crucially also rules out patients for whom such interventions are not effective. In this study, the presence of a third metastasis predicted inferior outcomes despite localized therapy. We can infer that Choline-PET successfully selected oligometastatic disease from a cohort whose disease is highly resistant to systemic therapy for a highly promising local treatment modality. Equipoise was not present in our population to ethically conduct a randomized controlled trial with an observational arm.

Regarding SABR-treated metastasis, local PFS of 84.4% and 75.3% at 1 and 2 years were lower than seen in some prior studies. In our previous report of patients with CSPC, local

PFS at 2 years was 95% with single SABR fraction dose ≥ 18Gy.[2] In our follow up study of 201 patients, 1 and 3-year local PFS were 95.5% and 87.1%, respectively.[38] In addition, castration resistance in prostate cancer is commonly associated with altered AR expression and signaling, which is associated with broad chemo- and radioresistance as previously demonstrated.[39] These results are not unexpected, as resistance mechanisms in prostate cancers are commonly distal to DNA-damaging small molecules, radiation, and biologics.[40]

We examined the impact of SABR and its ability to induce anti-prostate cancer immunity in our CRPC cohort. We have previously identified specific T cell 'states' (T_{TR} and T_{AC}) that have important tumoricidal function following photon radiation. Consistent with the importance of PD-1, we showed that effector $CD8^+$ T cells positive for PD-1 and $CD11a^{high}$ are induced after tumor irradiation and are tumor-reactive.[26] Using this biomarker, we monitored the frequency of prostate cancer reactive $CD8^+$ T cells in the peripheral blood. Cutoffs were retrospective and these observations will require confirmation.

We previously reported that SABR can induce systemic antitumor immune response by promoting peripheral expansion of T_{TR} with an effector phenotype.[22,26] Expansion of these specific T_{TR} is a prerequisite for an active local and systemic antitumor immune response (abscopal effect). Herein, we further underscore the role of SABR in antitumor immunity where expansion of T_{TR} and T_{EM} was associated with improved clinical outcomes. However, high rates of distant failure suggest that other determinants impair SABR-induced antitumor immunity. Radiotherapy upregulates expression of PD-1 on T_{TR} which induce T cell apoptosis upon engagement with PD-L1. In our study, patients with PD-1^+ T_{TR} at baseline above the cutoff experienced shorter median time to LF (9.1 vs. not reached; p=0.002). We can speculate whether the PD-1/PD-L1 axis blockade along with SABR may rescue the exhausted T_{TR} and change the clinical course. As demonstrated previously, the combination of SABR with PD-1 blockade may prevent T-cell death and facilitate an effective and sustained antitumor immune response.[41] In patients with melanoma, circulating tumor-reactive PD-1^+ T_{TR} with elevated expression of Bim, a promoter of apoptosis downstream from PD-1, was a predictor of poor survival in patients who did not receive anti-PD-1 therapy; further, an anti-PD-1 therapy-induced reduction of Bim in T_{TR} cells was associated with improved survival.[22,26] There is a striking report of a patient with immunotherapy-resistant melanoma who was treated with local radiation and anti-PD-1 therapy experienced a dramatic response to therapy coupled with decreased Bim in T_{TR} cells (manuscript under review), which highlights the potential interaction between radiation and anti-melanoma immunity.

We report a similar dependence on T_{TR} cells for systemic immunity induction following SBRT in oligometastatic prostate cancer. We also have identified actively cytotoxic $CD8^+$ effector T (T_{AC}) cells associated with the abscopal effect that can migrate into tumors and execute tumoricidal functions.[22] These data highlight the interplay between radiation and anti-tumor immunity and support our hypothesis that specific T cell subsets (T_{TR} and T_{AC}) are key mediators of anti-tumor immunity associated with the abscopal effect. LET optimized proton and carbon ion therapy create more complex DNA damage and greater cell kill than conventional high energy photons. Based on these physical properties,

investigations are ongoing whether higher LET radiations may differentially affect local and systemic anti-tumor immunity.

Beyond quantitating differences in T_{TR} and T_{AC} subsets and their functionality, we examined T effector differentiation states and their proportions following SABR. An increase in central and effector memory cells, which should be seen within one to two weeks, would suggest that RT was effective in inducing anti-tumor responses, irrespective of prostate tumor antigen reactivity. Our study suggests that these cells may help determine prognosis as well as direct future treatment modalities to overcome resistance. This may simply reflect the concomitant decrease in T_{EM} in these same patients. The baseline presence of T_{TR} and T_{EM} suggest there are pre-existing tumor antigen primed T-cells, and these T-cells can be further induced into expansion upon re-activation by tumor antigens that are released during SBRT. While the natural anti-tumor immune response does lead to some local control benefit, this also shows potential synergy with immune check-point blockade therapy.

Conclusion

In this study, we treated 89 patients with oligometastatic CRPC identified by Choline-PET. We observed an estimated 2-year OS of 80% in this heavily-treated population after metastasis-directed therapy with no grade ≥ 3 AEs. High levels of tumor reactive (T_{TR}, $CD8^{+}CD11a^{high}$) effector T cells at baseline were associated with improved PSA, local, and distant PFS. Radiotherapy may also indirectly induce T cell changes through either antigen release or pro-inflammatory cytokine production. These results are favorable compared to other treatment modalities and support the incorporation of immune-based markers in the design of future clinical trials in oligometastatic CRPC patients treated with SABR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

Although metastasis-directed stereotactic ablative radiotherapy (SABR) benefits 10–20% of oligometastatic patients, biomarkers that identify which patients will benefit from SABR is lacking. In this prospective trial, patients with oligometastatic CRPC identified by 11^{C}-Choline-PET (Choline-PET) were treated with SABR and anti-tumor immune parameters were measured before and after radiotherapy from peripheral blood. Significantly, high levels of tumor-reactive effector T cells (T_{TR}) at baseline were associated with improved PSA, local, and distant progression-free survival and an increase in T_{TR} after SABR was associated with improved overall survival. Baseline T_{TR} can be an immunological biomarker endpoint in future randomized trial design to identify oligometastatic prostate cancer patients who will benefit from SABR and help unlock the abscopal potential of radiotherapy in treatment-refractory prostate cancer.

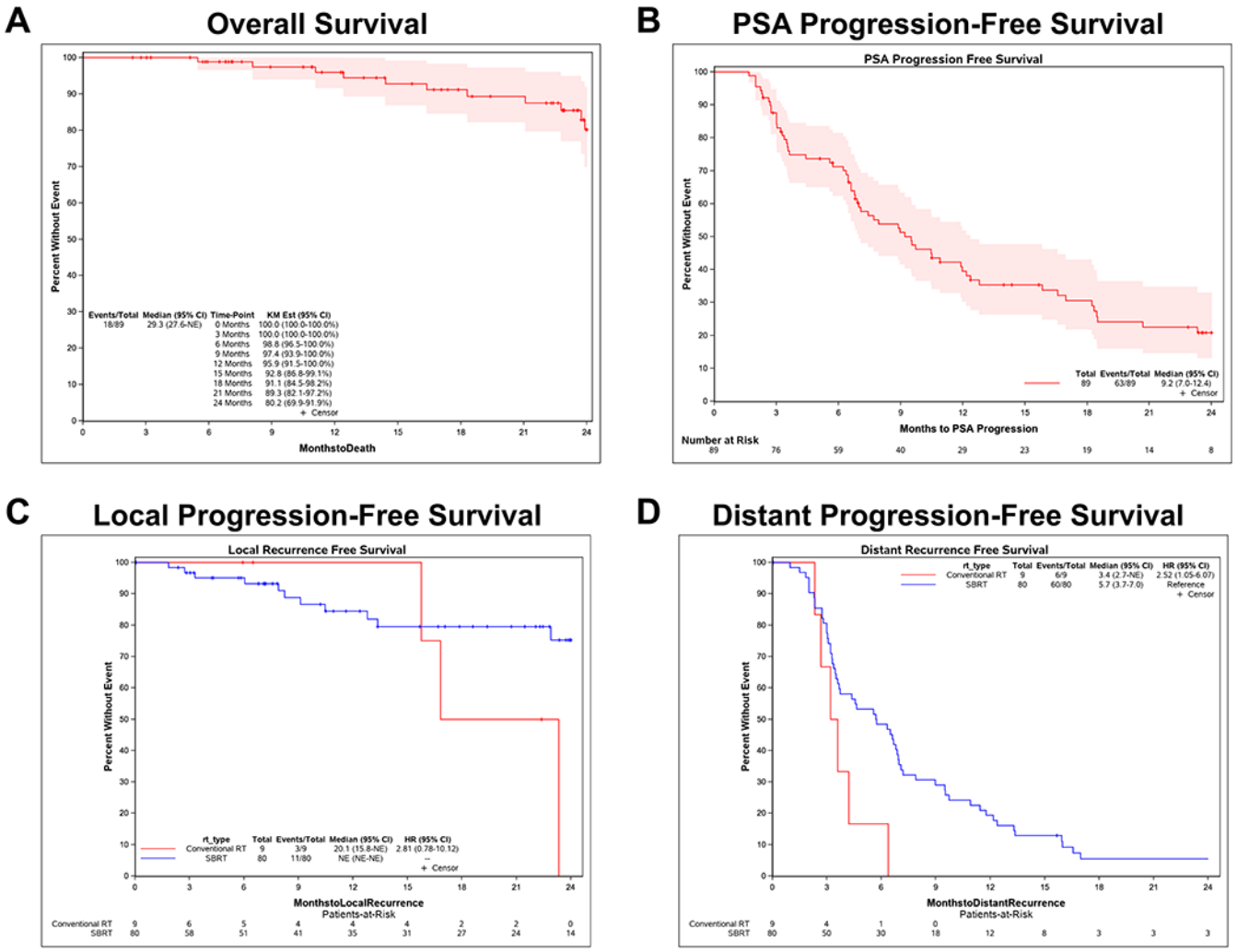

Fig 1. Patient outcomes.

(A) Overall survival of all patients in the study. **(B)** PSA progression-free survival of all patients in the study. **(C-D)** Local and distant progression-free survival by modality (conventional versus stereotactic RT).

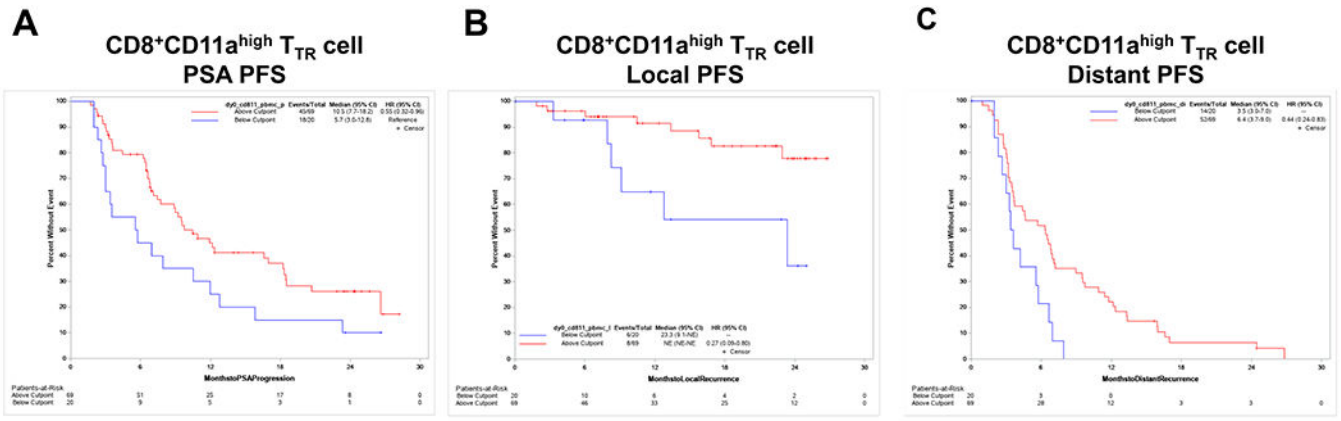

Fig 2. High baseline T_{TR} levels predict superior PSA, local, and distant PFS.

(A) Biochemical progression-free survival. **(B)** Local progression-free survival. **(C)** Distant progression-free survival.

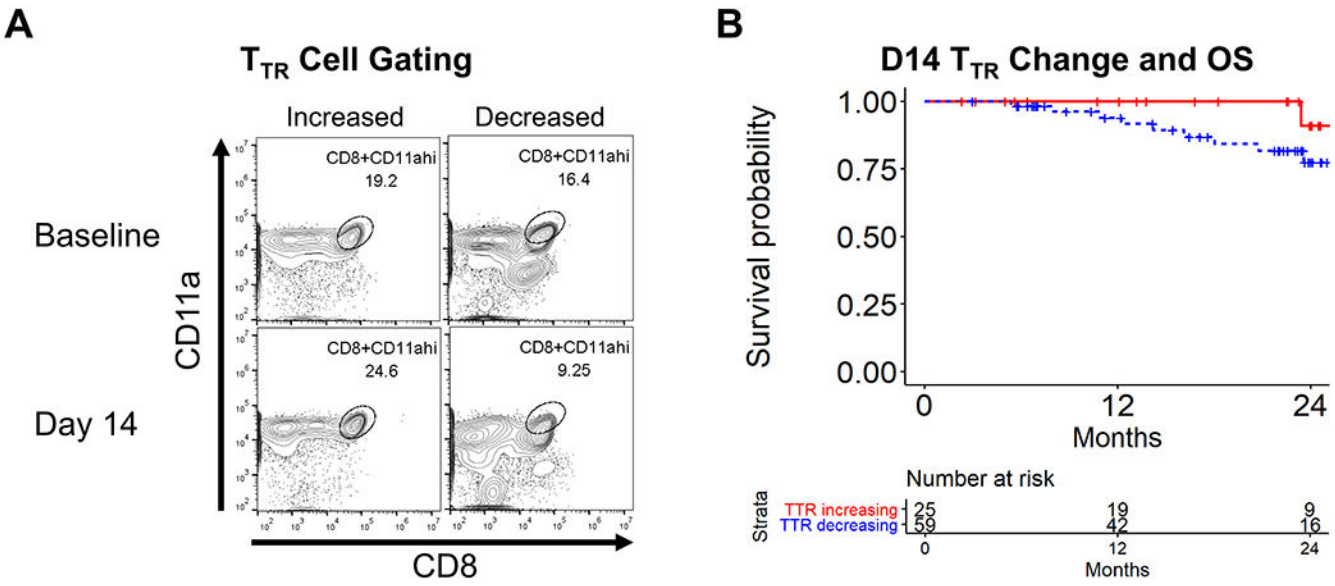

Fig 3. T_{TR} cell changes after radiotherapy predict OS in oligometastatic CRPC.

(A) T_{TR} cells are defined by expression of both CD8 and CD11a. **(B)** Patients with increasing T_{TR} levels at day 14 after radiotherapy to oligometastases experience superior OS in CRPC.

Table 1

Patient and Treatment Characteristics.

'Table of baseline Demographic and Treatment variables'	Total (N=89)
Age	
Mean (SD)	69.7 (7.0)
Median	70.8
Q1, Q3	63.8, 74.7
Range	(51.0-83.9)
Race/Ethnicity	
White	83 (93.3%)
Asian	1 (1.1%)
Unknown or Not reported	4 (4.5%)
Other	1 (1.1%)
T score at initial diagnosis	
Missing	6
T1c	3 (3.6%)
T2a	7 (8.4%)
T2b	3 (3.6%)
T2c	15 (18.1%)
T3a	18 (21.7%)
T3b	34 (41.0%)
T4	3 (3.6%)
N score at time of diagnosis	
Missing	2
NX	7 (8.0%)
N0	56 (64.4%)
N1	23 (26.4%)
N2	1 (1.1%)
M score at time of diagnosis	
Missing	8
MX	21 (25.9%)
M0	54 (66.7%)
M1	6 (7.3%)
SABR Dose (Gy) (all 128 sites treated)	
N	128
Mean (SD)	27.45 (11.3)
Median	23.0
Q1, Q3	20.0, 39.0
Range	(8.0-50.0)

'Table of baseline Demographic and Treatment variables'	**Total (N=89)**
Number of Fractions (all 128 sites treated)	
N	128
Mean (SD)	2.1 (1.3)
Median	1.0
Q1, Q3	1.0, 3.0
Range	(1.0-5.0)
Number of sites treated	
1	58 (65.2%)
2	23 (25.8%)
3	8 (9.0%)
Sites treated	
Bone only: Spine	41 (46.1%)
Bone only: Non-Spine	30 (33.7%)
Lymph Nodes only	5 (5.6%)
Bone & Lymph Nodes	12 (13.5%)
Other	1 (1.1%)
ECOG Performance Score	
0	74 (83.1%)
1	15 (16.9%)
Prior radiation	77 (85%)
Primary Prostate	23 (25.8%)
Prostate Bed/pelvic lymph nodes	22 (24.7%)
Metastatic Disease	17 (19.1%)
Primary Prostate & Metastatic Disease	10 (11.2%)
Prostate bed & Metastatic Disease	8 (9.0%)
Prior Therapy	
Chemotherapy/Docetaxel	54 (60.7%)
Abiraterone	39 (43.8%)
Enzalutamide	17 (19.1%)
Both Chemotherapy + Abiraterone	30 (33.7%)
Both Chemotherapy + Enzalutamide	10 (11.2%)
Androgen Deprivation Method	
Leuprolide	87 (97.8%)
Goserelin	2 (2.2%)
Orchiectomy	2 (2.2%)
Prostatectomy (including salvage)	
No	13 (14.9%)
Yes	74 (85.1%)

'Table of baseline Demographic and Treatment variables'	Total (N=89)
Missing	2