



Stereotactic ablative radiation therapy for oligometastatic prostate cancer delays time-to-next systemic treatment

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Abstract

Purpose Local ablative treatment to oligometastatic patients can result in long-term disease-free survival in some cancer patients. The importance of this treatment paradigm in prostate cancer is a rapidly evolving field. Herein, we report on the safety and preliminary clinical outcomes of a modern cohort of oligometastatic prostate cancer (OPC) patients treated with consolidative stereotactic ablative radiation (SABR).

Methods Records of men with OPC who underwent consolidative SABR at our institution were reviewed. SABR was delivered in 1–5 fractions of 5–18 Gray. Kaplan–Meier estimates of local progression-free survival (LPFS), biochemical progression-free survival (bPFS; PSA nadir + 2), distant progression-free survival (DPFS), and time-to-next intervention (TTNI) were calculated.

Results In total, 66 OPC patients were identified with consolidative SABR delivered to 134 metastases: 89 bone, 40 nodal, and 5 viscera. The majority of men (49/66) had hormone-sensitive prostate cancer (HSPC). Crude grade 1 and 2 acute toxicities were 36% and 11%, respectively, with no \geq grade 3 toxicity. At 1 year, LPFS was 92% and bPFS and DPFS were 69%. Of the 18 men with HSPC who had deferred hormone therapy, 11 (56%) remain disease free following SABR (1-year ADT-FS was 78%). In 17 castration-resistant men, 11 had > 50% prostate-specific antigen (PSA) declines with 1-year TTNI of 30%.

Conclusions Consolidative SABR in OPC is feasible and well tolerated. The heterogeneity and small size of our series limit extrapolation of clinically meaningful outcomes following consolidative SABR in OPC, but our preliminary data suggest that this approach warrants continued prospective study.

Keywords Oligometastatic prostate cancer · Stereotactic ablative radiation therapy · Androgen-deprivation therapy

Introduction

Originally proposed by Hellman and Weichselbaum [1], the oligometastatic or low-volume metastatic state is currently defined as having fewer than three-to-five metastatic lesions [2]. As the collective understanding of this state evolves, biological parameters may someday inform or supplant this descriptive clinical definition [3–5]. Improvements in imaging and metastasis-directed therapies (MDT) have placed new emphasis on the oligometastatic state [6]. Local ablative treatment for limited metastatic disease has been correlated retrospectively with improvements in long-term disease-free survival in lung, breast, colorectal, and sarcoma patients [6] and mounting prospective evidence suggests improvements in progression-free survival for oligometastatic lung

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cancers and hormone-sensitive oligorecurrent prostate cancer [7–10].

Traditionally, metastatic prostate cancer has been, regardless of tumor burden, treated systemically with androgen-deprivation therapy (ADT) and/or chemotherapy [11]. The importance of consolidating all macroscopic tumor deposits in men with oligometastatic prostate cancer is an area of active investigation [9, 12, 13], but the observation that men with lower numbers of metastases have better outcomes [14–16] supports a fundamental difference between oligometastatic prostate cancer (OPC) and higher volume disease. By this logic, recent studies have explored MDT of OPC by ablative and surgical treatments [17–20], as well as stereotactic ablative radiation (SABR) [21], also known as stereotactic body radiation therapy (SBRT) [22]. This highly targeted, high-dose approach provides millimeter-scale precision while minimizing collateral tissue damage and has shown efficacy in the management of OPC [17–19, 21, 23, 24].

Studies to date have been conducted predominately in patients with a single metastasis [9, 17–19, 23, 24]. Herein, we review our early institutional outcomes with SABR for OPC in 66 consecutively treated patients with the majority having ≥ 2 metastases. We demonstrate that SABR is well tolerated and can significantly delay time to subsequent intervention.

Methods

Criteria

With approval from our institutional review board, we reviewed our retrospectively collected Johns Hopkins prostate cancer (PCa) radiation oncology database for consecutively SABR-treated patients from 02/07/2011 to 1/15/2017. Inclusion criteria were: biopsy-proven PCa, diagnostic imaging consistent with ≤ 5 metastases, and follow-up with post-SABR prostate-specific antigen (PSA) testing. Three patients with ≤ 5 initially observed metastases who were found during treatment planning to have six metastases were included. Of the 84 total men during this period with OPC treated with SABR, we only examined the first 66 men to allow for a minimum of 4.5 months of follow-up.

SABR technique

During CT simulation, patients were immobilized using an Alpha Cradle (Smithers Medical Products, Inc, North Canton, Ohio) or equivalent device. Magnetic resonance imaging (MRI), bone scan, NaF, or DCFPyL positron emission tomography [25]/CT images were used to delineate the gross tumor volume (GTV) and when possible fused with the

planning CT. As per our institutional policy, if patients had ≥ 3 mm breathing motion on four-dimensional CT, active breathing control (ABC) was used for motion management. If breathing was < 3 mm, patients were treated free breathing (FB) with an internal target volume based on the 0% and 60% phases of the breathing cycle. GTV was defined as the sum of the abnormalities noted on PET, MRI T1 post-gadolinium sequences, bone scan, and/or CT. In general, the clinical tumor volume (CTV) was equal to the GTV. Most commonly, the planning target volumes (PTV) were the GTV with the addition of 3–5 mm used as the volume to which the prescription was assigned [17]. If men were treated with CyberKnife, then image guidance was as per that device. During non-CyberKnife SABR delivery, a cone-beam CT scan was co-registered (spine) with the FB or ABC simulation scan. To verify tumor positioning before SABR, patients were shifted to align with the GTV for each beam based on fluoroscopy, cone-beam CT, or kV images.

Follow-up

Patients were scheduled for serial follow-up exams every 3–6 months with history and physical, PSA, testosterone, and imaging every 6–12 months unless a shorter interval was clinically indicated. Repeat imaging with NaF or DCFPyL PET/CT, MRI, or bone scans was conducted at 3–6-month intervals after SABR. The majority of patients were treated by a limited number of Johns Hopkins medical oncologists with similar practice patterns. Therefore, broadly, the indication for the next intervention was determined by disease-objective evidence of disease progression by PSA and/or radiographic testing or symptomatic progression.

Statistical analysis

Clinical endpoints reported include biochemical progression-free survival (bPFS), local progression-free survival (LPFS), distant progression-free survival (DPFS), overall survival (OS) [25], ADT-free survival (ADT-FS), and time-to-next intervention (TTNI); all were calculated from the date of SABR. Biochemical failure was defined as: (1) PSA rise ≥ 2 above nadir following SABR or (2) an increase of PSA following SABR with failure to decline initially. LPFS was defined as the lack of tumor progression within the treated planning tumor volume (PTV) margin on follow-up imaging. DPFS was defined as the lack of new metastases on follow-up imaging. For both local and distant progression-free survival, clinically significant events (e.g., bone fractures) in a previously stable lesion were considered as clinical progression. TTNI was defined as the interval to the next local or systemic intervention due to progression. The Kaplan–Meier method was used to estimate the rates of bPFS, LPFS, DPFS, OS, ADT-FS, and TTNI. Analysis

of LPFS was performed with each treated lesion considered individually ($n = 134$), while all the other endpoints were analyzed with each patient considered individually.

Results

Patient and disease characteristics

Sixty-six men with 134 metastatic PCa lesions were identified and analyzed. Prior treatment of metastatic tumors (including radiation and surgery) did not exclude patients from this review. Patients were generally asymptomatic or had minimal pain associated with their metastatic burden. Thirty-eight percent of men presented with synchronous or de novo oligometastases, while 62% developed metachronous oligometastases between the conclusion of definitive treatment for their prostate cancer and consultation for SABR treatment. Prior chemotherapy was allowed with 55% ($n = 36$) of patients receiving chemotherapy prior to or concurrently with treatment. Forty-nine (or 74%) men had hormone-sensitive prostate cancer (HSPC) at the time of SABR and 17 (or 26%) had castration-resistant prostate cancer (CRPC). Initial Gleason scores (GS) were as follows: GS 6 ($n = 7$), GS 7 ($n = 16$), GS 8 ($n = 18$), GS 9 ($n = 22$), and GS 10 ($n = 3$). Additional patient and disease characteristics are shown in Table 1.

The median and mean PSA reported prior to SABR were 1.2 ng/mL and 9.0 ng/mL, respectively. The majority of patients, 68% ($n = 45$), underwent SABR with a PSA ≤ 5 . Fifty-three percent of men ($n = 35$) had ≥ 2 metastases. Consolidative SABR was delivered to a total of 134 metastases, with 89 osseous (66%), 40 nodal (30%) and 5 visceral (4%) lesions. The mean GTV was 9.1 cm³ (range 0.1–152.3 cm³). Additional patient characteristics at the time of SABR are shown in Table 2. SABR was delivered to all lesions with a total dose in the range of 15–55 Gy. The majority of lesions (72%) were treated with total doses > 15 Gy with varied fractionation, while 28% of lesions were treated with 15 Gy as a single fraction (Supplemental Table 1).

Clinical outcomes

Median and mean follow-up were 61 and 66 weeks, respectively. Acute toxicities were noted in 46% ($n = 30$) of patients, whereas late toxicities were noted in 27% ($n = 18$) of patients with the most common toxicities being fatigue and hot flashes (Supplemental Table 2). In total, grade 1 toxicities were noted in 24 patients and grade 2 toxicities were noted in 7. There were no grade 3 or higher toxicities observed.

The average time to any failure was 35 weeks. Overall, LPFS at 1 year was 92% (Fig. 1a) with LPFS of 100% for

Table 1 Patient and disease characteristics at diagnosis ($n=66$)

Characteristic	Value
Age at diagnosis (years), median (range)	65 (47–84)
Gleason score, n (%)	
6	7 (10.6)
7	16 (24.2)
8	18 (27.3)
9	22 (33.3)
10	3 (4.5)
PSA	
Initial value (ng/mL), median (range)	8.7(1.9–2155)
PSA value (ng/mL), n (%)	
0–5	9 (13.6)
> 5–10	24 (36.4)
> 10–20	9 (13.6)
> 20	14 (21.2)
Unknown	10 (15.2)
pT stage, n (%)	
pT1	0 (0.0)
pT2	15 (22.7)
cT3	31 (47.0)
pT4	0 (0.0)
Unknown	3 (4.5)
cT stage, n (%)	
cT1	5 (7.6)
cT2	6 (9.1)
cT3	5 (7.6)
cT4	1 (1.5)
N stage, n (%)	
N0	50 (75.8)
Synchronous N1	16 (24.2)
M stage, n (%)	
M0, Metachronous	41 (62.1)
Synchronous M1	25 (37.9)
Primary treatment, n (%)	
RP	48 (72.7)
RT	17 (25.8)
Post-RP XRT	30 (45.5)
RT and salvage RP	0 (0.0)
Chemotherapy, n (%)	
Prior or concurrent	36 (54.5)
Adjuvant androgen-deprivation therapy, n (%)	
Neoadjuvant	53 (80.3)
Concurrent	53 (80.3)
Adjuvant	48 (72.7)
Sensitivity to hormone therapy n (%)	
HSPC	49 (74.2)
CRPC	17 (25.8)

PSA prostate-specific antigen, RP radical prostatectomy, RT radiation therapy, XRT external beam radiation therapy, HSPC hormone-sensitive prostate cancer, CRPC castration-resistant prostate cancer

Table 2 Patient and disease characteristics at the time of stereotactic ablative radiotherapy

Characteristic	Patient (<i>n</i> = 66)	Lesion (<i>n</i> = 134)
Pre-SABR PSA (ng/mL)	1.2 (0.01–95.8)	
Median (range) and mean	9.0	
PSA (ng/mL), <i>n</i> (%)		
0–5	45 (68.2)	
> 5–10	5 (7.6)	
> 10–20	7 (10.6)	
> 20	9 (13.6)	
Total no. of metastases, no. of patients (%)		
1	31 (47.0)	
2	19 (28.8)	
3	7 (10.6)	
4	4 (6.1)	
5	2 (3.0)	
6	3 (4.5)	
Regions treated, <i>n</i> (%)		
Bone	41 (62.1)	89 (66.4)
Node	24 (36.4)	40 (29.9)
Other	3 (4.5)	5 (3.7)
Lesion gross tumor volume, cm ³ (<i>n</i> = 134)		
Mean (range)		9.09 (0.1–152.3)
Median		2.45

SABR stereotactic ablative radiotherapy, PSA prostate-specific antigen

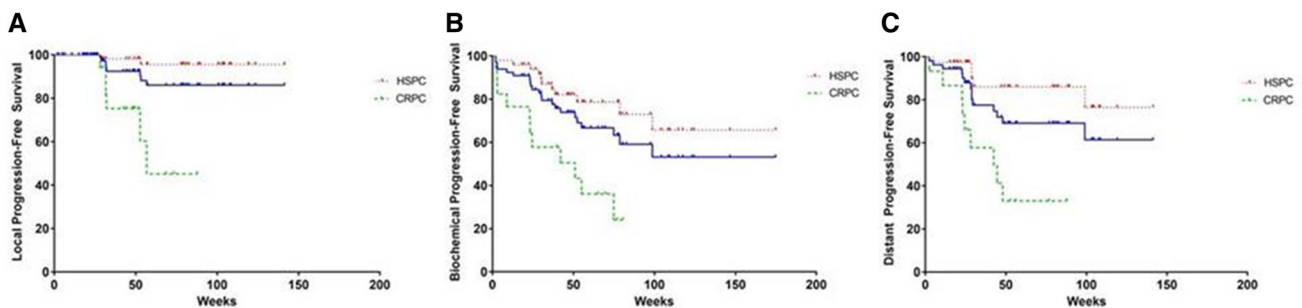


Fig. 1 Effect of stereotactic ablative radiotherapy on clinical progression in men with oligometastatic prostate cancer. **a** Local progression-free survival of the entire cohort (blue), HSPC [34] and CRPC

(green). **b** Biochemical progression-free survival of the entire cohort (blue), HSPC [34] and CRPC (green). **c** Distant progression-free survival of the entire cohort (blue), HSPC [34] and CRPC (green)

SABR biologically equivalent doses (BED with $\alpha/\beta = 10$) of > 50. The bPFS and DPFS for the entire cohort at 1 year were each 69% (Fig. 1b, c). For all types of failure, men with oligometastatic HSPC had better outcomes than those with CRPC (Fig. 1a–c). Twenty-two men had a new intervention secondary to progression of their disease post-SABR, with median TTNI not reached overall with our current follow-up of 15 months (Fig. 2a). Of the 18 men with HSPC who were not treated with adjuvant hormone therapy, 11 (61%) remain free of disease following SABR

corresponding to a 1-year ADT-FS of 78% (Fig. 2b) and a median ADT-FS that was not reached. Of the 17 men with oligometastatic CRPC treated with SABR, 11 had > 50% PSA that declines with a 1-year TTNI of 38% (Fig. 2a) and a median TTNI of 45 weeks. This was congruent with a 1-year bPFS and DPFS of 43% and 33%, respectively (Fig. 1b, c), in men with CRPC. During the study period, two patients died: one of the complications related to their metastatic CRPC and the other from unconfirmed causes not likely related to prostate cancer.

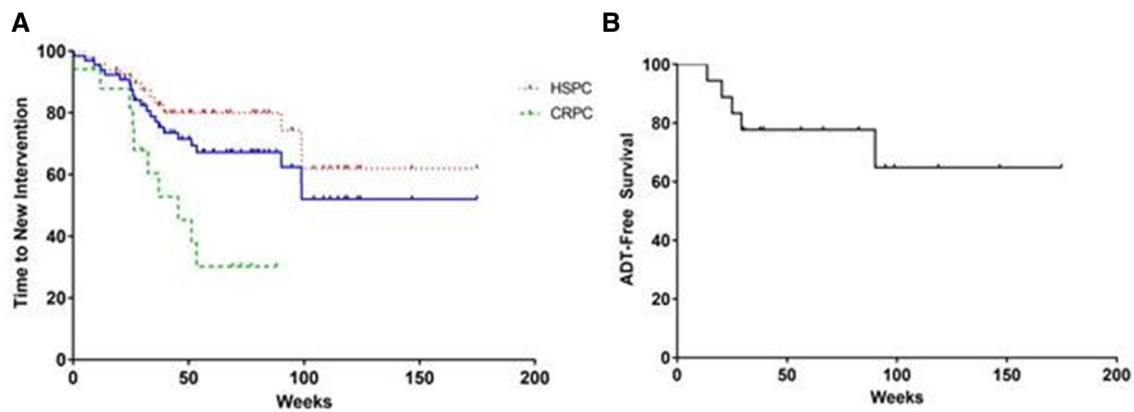


Fig. 2 Effect of stereotactic ablative radiotherapy on delaying subsequent therapy in men with oligometastatic prostate cancer. **a** Time-to-next therapy of the entire cohort (blue), HSPC [34] and CRPC (green). **b** Time to ADT initiation in men with oligometastatic HSPC

Discussion

This study demonstrates that consolidative SABR in men with OPC is well tolerated and appears to have a clinical signal adding to a growing literature of evidence, validating its use. We report 1-year LPFS of 92% and bPFS and DPFS of 69%, and in those with HSPC not treated with hormone therapy, 61% remain free of disease following SABR. Furthermore, treatment was very well tolerated with 24 patients experiencing grade 1 toxicity, 7 with grade 2 toxicities, and no grade 3 or higher toxicities observed.

Perhaps, the most notable contributor to the subjective well-being of a man with metastatic HSPC is the delaying or deferring of ADT, the side effects of which can significantly hamper a patient's lifestyle and systemic health [11]. With ADT, in addition to decrease in subjective feelings of wellness associated with androgen loss, there has been reported increased risk of osteoporosis, cardiovascular-related mortality, and diabetes [26]. Consistent with prior retrospective reports [12, 27] and the recently reported randomized phase II STOMP trial [9], our study also suggests that SABR can substantially delay initiation of ADT in men with oligometastatic HSPC for up to a year. In addition, unlike ADT, SABR is associated with mild side effects without an associated decrement in quality of life measured in both acute and long-term follow-ups [9].

STOMP represents the first published prospective randomized trial of MDT in OPC and validated the efficacy of SABR for MDT by demonstrating a superior ADT-FS (21 months vs 13 months) compared to observation [9, 13]. Justification for its advent was supported by an accumulation of retrospective and observational studies reporting durable LPFS, DPFS, and ADT-FS with the use of MDT [17–19, 23, 24]. The results of our institutional experience are concordant with these reports and in addition add novel information to the already established body of the literature. Specifically,

the majority of men in this report (53%) had ≥ 2 metastases, and thus, our study examines a population of OPC with a heavier disease burden than has been explored in the current literature [9, 17, 19, 28]. Rates of 2-year distant and progression-free survival reported in the literature following SABR range from 30 to 40%, and in a subset of those with oligometastatic progression retreated with SABR, the proportion of individuals remaining progression-free is as high as 50% at last follow-up [28]. Herein, we report a 1-year DPFS rate of 69%, which compares favorably to the aforementioned studies and, therefore, may justify the more aggressive use of MDT in men with several oligometastatic foci.

Thus far, the outcomes of interest and treatment intent of SABR in OPC have, for the most part, been aimed at delaying the start of palliative ADT. With growing support for its efficacy in this realm, the aims and goals of MDT may shift from a palliative nature to a definitive one by offering these men a second (and in the context of salvage radiation, a third) chance for cure. In alignment with the Hellman–Weichselbaum spectrum theory of metastasis, the validation and subsequent adoption of more sensitive imaging modalities such as NaF, Choline C-11, and DCFPyL PET/CT scan can allow for earlier detection of low-volume metastatic disease that subsequently can be treated with local therapy, possibly with definitive intent. Justification for such a paradigm is also supported by retrospective evidence that MDT improves prostate cancer cause specific survival in a propensity-matched cohort [29]. Therefore, treatment intensification aimed at simultaneously eradicating other sites of microscopic metastatic disease through the use of concurrent ADT, which is retrospectively associated with improved DPFS when combined with SABR [17], non-castrating antiandrogens such as enzalutamide, and chemotherapies such as docetaxel and radiopharmaceuticals may be justified.

In addition to prevent the site-specific complications associated with local progression of metastases, SABR is

a complimentary local treatment to maximize durability of systemic approaches. SABR has already been shown to improve disease control in lung cancer patients treated with systemic oncogene-directed therapies through ablation of resistant clones [7, 30, 31]. The ability to maintain men with CRPC on second-line hormonal agents that are oligoprogressing and delay chemotherapy adds significantly to the clinical options for these patients. Our data showing that SABR can delay distant progression and time-to-initiation of the next line of therapy (median 42–45 weeks) compares very favorably to any of the approved systemic agents in the CRPC space [32, 35]. Finally, the highly conformal nature of SABR limits radiation-associated immunosuppression [33] and may be well suited for concurrent use with immune therapies.

Our study has all the intrinsic limitations of a small retrospective series, heterogeneity, and inclusion of shorter follow-up timeframes in our series limits definitive conclusions following consolidative SABR in OPC. In addition, a compelling weakness is that attempts to define the oligometastatic state by radiographic enumeration of lesions will always be limited by the sensitivity and specificity of the imaging modality and other patient–disease factors that are not well understood. As molecular imaging modalities such as prostate-specific membrane antigen (PSMA)-targeted imaging mature, the value of MDT in the oligometastatic state may increase further as patients previously defined as oligometastatic based on conventional imaging may have additional detectable tumor deposits and require reclassification as polymetastatic [36]. Regardless, our preliminary data suggest that SABR in OPC men warrants continued prospective study. In addition to the recent reporting of the Belgian STOMP trial, more definitive conclusions await the completion and reporting of other prospective randomized studies such as our Baltimore ORIOLE trial (NCT02680587).

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development and data collection or management. EMS protocol/project development and data collection or management. KJP protocol/project development, data collection or management, and manuscript writing/editing. ME protocol/project development, data collection or management, data analysis, and manuscript writing/editing. PTT protocol/project development, data collection or management, data analysis, and manuscript writing/editing

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals For this type of study, formal consent is not required.

Informed consent For this type of study, formal consent is not required.

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