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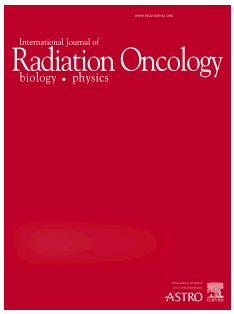

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Stereotactic Body Radiotherapy for High-Risk Localized CARcinoma of the Prostate (SHARP) Consortium: Analysis of 344 Prospectively Treated Patients

SBRT for HRPCa: Analysis of 344 Patients

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ABSTRACT

PURPOSE: To explore the efficacy and toxicity of stereotactic body radiotherapy (SBRT) in high risk prostate cancer (HRPCa) in a consortium of seven institutional phase II trials and prospective registries.

METHODS AND MATERIALS: Individual patient data were pooled for 344 patients with a minimum follow-up of 24 months. Biochemical recurrence-free survival (BCRFS) and distant metastasis-free survival (DMFS) were estimated using a Kaplan-Meier framework. Fine and Gray competing risk and Cox proportional hazards regression models were developed to assess the association between time to BCR and time to distant metastasis and pre-specified variables of interest. Logistic regression models were developed to evaluate associations between acute and late grade ≥2 genitourinary (GU) and gastrointestinal (GI) and the following *a priori* specified variables: age, dose per fraction, ADT use, and nodal radiotherapy.

RESULTS: Median follow-up was 49.5 months. Seventy-two percent of patients received ADT, with a median duration of 9 months, and 19% received elective nodal radiotherapy. Estimated four-year BCRFS and DMFS rates were 81.7% (95% CI, 77.2-86.5%) and 89.1% (95% CI, 85.3%-93.1%). The crude incidences of late grade ≥3 genitourinary and gastrointestinal toxicity were 2.3% and 0.9%.

CONCLUSIONS: These data support a favorable toxicity and efficacy profile for SBRT for HRPCa. Further prospective studies are needed to evaluate the optimal dose and target volume in the context of SBRT for HRPCa.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a form of ultra-hypofractionated radiotherapy in which advanced treatment delivery techniques are utilized to deliver high doses of radiation over the course of five or fewer treatments. The 2020 National Comprehensive Cancer Network (NCCN) guidelines suggest that SBRT can be considered for patients with high-risk prostate cancer (HRPCa) provided they have social or medical hardships that preclude longer courses of radiation.[1] The 2020 European Association of Urology guidelines are less supportive of this and note that the major evidence to support ultra-hypofractionation for HRPCa comes from a subset of 126 patients enrolled on the randomized HYPO-RT-PC trial.[2,3] These patients did not receive concurrent androgen deprivation therapy (ADT), which is now considered a standard of care for patients with HRPCa receiving definitive radiotherapy, and the authors conclude that their general conclusions of oncologic equivalency may not be applicable for patients with HRPCa. Other published prospective data supporting SBRT for HRPCa are limited to medium-term results from two small phase II trials and a small prospective database with short-term data.[4–6]

MATERIALS AND METHODS

To evaluate efficacy and toxicity outcomes among men receiving SBRT for HRPCa in a larger cohort, we established a consortium and obtained patient-level data from seven institutions with phase II studies and prospective databases. The site-specific distribution of patients and their treatment characteristics are shown in Table 1. Each institutional review board approved contribution of its data to the coordinating data center (XXXX). Analyses were limited to patients with ≥24 months of follow-up. Biochemical recurrence (BCR) was defined as a PSA rise >2 ng/mL above the lowest value after SBRT, per the Phoenix definition.[7] Gastrointestinal (GI) and genitourinary (GU) toxicity were scored by the common terminology criteria for adverse

events (CTCAE) version 3.0 or version 4.0. Kaplan-Meier methods were used to obtain 4-year survival estimates of BCR-free survival (BCRFS) and distant metastasis-free survival (DMFS) with time to event measured from the final day of SBRT. Univariate and multivariable Fine and Gray competing risk and Cox proportional hazards regression models were developed to assess the association between time to BCR and time to distant metastasis. Multivariable models were adjusted for dose per fraction (categorical, with 8 Gy as the reference dose), age at treatment, clinical T stage (T3-4 vs. T1-2), ln(initial prostate-specific antigen), and Gleason grade group (1-3 vs 4-5). Due to the non-uniform use of ADT and nodal radiotherapy, and the consideration that important other variables that might confound potential associations, such as socioeconomic status, were not available, these variables were not included in the multivariable analyses. Multivariable logistic regression models were developed to evaluate associations between acute and late grade ≥2 GU and GI and the following *a priori* specified variables: age at treatment, dose per fraction (categorical, with 8 Gy per fraction as the reference dose), ADT use, and nodal radiotherapy. In this case, ADT use and nodal radiotherapy were included in the model as the impact of selection biases related to their use and the absence of information about important confounding variables was thought to be less important in investigating relationships with toxicity versus measures of efficacy. Due to the low event rate, Firth's penalized likelihood method was used to estimate the relevant odds ratios (ORs) and hazard ratios (HRs). Cumulative incidence curves were developed using Allen estimator and Gray's test was used to compare the equality of cumulative incidence functions across strata.[8] Analyses were completed using SAS (9.4 SAS Institute Inc., Cary, NC, USA) and R, version 3.3.2. All *P* values were from 2-tailed tests, and results were deemed statistically significant at $P < .05$.

RESULTS

Overall, 344 patients were included in this analysis, with a median follow-up of 49.5 months (interquartile range, 35.8-61.9 months) (Table 2). Two-hundred-forty-eight patients (72%) received ADT, with a median duration of 9 months (IQR, 9-18 months). Estimated four-year BCRFS and DMFS rates were 81.7% (95% CI, 77.2-86.5%) and 89.1% (95% CI, 85.3%-93.1%). Overall, 59 patients (17%) experienced a BCR and 26 patients (8%) experienced a DM. On multivariable competing risk analyses, 7 Gy vs. 8 Gy per fraction was significantly associated with increased risk of BCR (subdistribution hazard ratio [sHR] 2.15; 95% CI 1.07-4.32; p=0.03), as was ln-iPSA (sHR 1.42; 95% CI 1.0-1.08; p=0.02) (Table 3). No statistically significant predictors of time to DM were identified (Table 3). Cause-specific models had similar results for BCR and DM, additionally, 1 year increase in age at treatment was significantly associated with increased risk of BCR (hazard ratio [HR] 1.04; 95% CI 1-1.07; p=0.035) (Supplemental Tables 1 and 2). Kaplan-Meier curves of BCRFS and DMFS stratified by ADT use are shown in Figure 1. BCRFS was significantly greater among patients receiving ADT (p-value 0.009 by log-rank), but DMFS was not significantly different (p-value 0.097 by log-rank). Similar curves stratified by nodal RT and iPSA are shown in Supplemental Figures 1 and 2, respectively. Cumulative incidences of BCR and DM, stratified by ADT use, are shown in Supplementary Figure 3. The cumulative incidence of BCR was significantly lower among patients receiving ADT (p-value 0.017 by Gray's test), while the cumulative incidence of DM was no different (p-value 0.36 by Gray's test). Meaningful analysis of ADT duration was precluded by the low event rate within any given ADT duration (none vs. ≤9 vs. 9-18 vs. >18 months) as well as selection biases inherent to the duration of ADT provided, given the heterogeneity in practice patterns.

Acute grade ≥2 GU and GI toxicity were seen in 18% and 5% of patients, respectively; no acute grade ≥3 GU or GI toxicities were seen. Results of multivariable logistic regression models for acute grade ≥2 GU or GI toxicities are shown in Supplemental Table 3. A dose per fraction of 7 Gy vs 8 Gy and ADT use were associated with lower and higher odds of acute grade ≥2 GU toxicity, respectively (ORs 0.09 [95% CI 0.02-0.48], p=0.005 for dose per fraction 7 Gy vs 8 Gy and 4.1 [95% CI 1.3-13.4], p=0.02 for ADT use). No significant predictors of acute GI toxicity were identified. Cumulative incidence curves late grade ≥2 GU and GI toxicity are shown in Figure 2. The 4-year cumulative incidence estimates for late grade ≥2 GU and GI toxicity were 17.6% (95%CI, 13.6-21.9%) and 6.4% (95% CI, 3.7-10.1%), respectively. The crude incidence of late grade 3 GU toxicity was 2.3% (median time to onset 21 months) and the crude incidence for late grade 3 GI toxicity was 0.9% (median time to onset 22 months). Results of multivariable logistic regression models for late grade ≥2 GU or GI toxicities are shown in Table 4. Dose per fraction of 7.25 vs 8 Gy and ADT use were associated with lower and higher odds of late grade ≥2 GU toxicity, respectively (OR 0.09 [95% CI, 0.02-0.48], p=0.05 for 7.25 Gy vs 8 Gy and 4.09 [95% CI 1.25-13.4], p=0.02 for ADT use) (Table 4).The same variables were also associated with lower and higher odds of late grade ≥2 GI toxicity, respectively (OR 0.18 [95% CI, 0.06-0.54], p=0.002 and 0.28 [95% CI, 0.11-0.56], p=0.001 for dose per fraction 7 Gy and 7.25 vs 8 Gy and OR 4.34 [95% CI 1.68-11.2], p=0.002 for ADT use) (Table 5).

DISCUSSION

The results of this consortium analysis highlight several important points. First, these prospective data underscore the efficacy of this approach. The estimated 4-year BCRFS rate of 81.7% for patients receiving SBRT in this consortium is similar to the 5-year BCRFS rates for HRPCa patients enrolled on ASCENDE-RT who received a brachytherapy boost (85.5%) or

dose-escalated conventionally fractionated radiotherapy alone cohort (83.6%) along with 12 months of ADT, despite the inclusion of patients in the present consortium who either received no ADT or received shorter durations of ADT.[9] Second, overall toxicity rates were low and consistent with prior SBRT reports in low- and intermediate-risk disease.[10] The estimated four-year cumulative incidence of late grade ≥2 GU toxicity was 17.6% in this study, versus 5-year cumulative incidences of late grade ≥2 GU toxicity of 53.3% with a brachytherapy boost and 26.4% with dose-escalated conventionally fractionated radiotherapy alone in ASCENDE-RT (though that trial did not utilize intensity modulated radiotherapy). Similarly, the estimated four-year cumulative incidence of late grade ≥2 GI was 6.4% in this study, versus 5-year cumulative incidences of late grade ≥2 GI toxicity of 40.4% with a brachytherapy boost and 23.4% with dose-escalated conventionally fractionated radiotherapy alone in ASCENDE-RT. These rates of late grade ≥2 GU and GI toxicity are also comparable to the 5-year cumulative incidences of toxicity seen in prospective randomized trials evaluating moderate hypofractionation, including CHHiP, which identified a 11.7% and 11.9% rate of late grade ≥2 GU and GI toxicity in the 60 Gy arm, respectively.[11] Caution must be exercised when comparing these toxicity rates, as ASCENDE-RT and CHHiP utilized single-protocol prospective data collection methods while our pooled cohort may underreport due to the disparate nature of data collection. Nevertheless, the low incidence of grade 3 GI and GU toxicity in this cohort remains encouraging. We did find that dose per fraction and ADT were associated with increased toxicity, consistent with prior studies.[12,13] The etiology of the relationship between ADT use and toxicity is not clear, but increased frequencies of both late GI and GU toxicity have been reported in the setting of ADT, and the phase III NRG-GU003 trial investigating GI and GU outcomes in the setting of post-prostatectomy radiation includes ADT as a prespecified stratification factor.[14–17] Third, nodal

radiotherapy was associated with neither improved outcomes nor increased toxicity. A significantly smaller analysis of two trials included in the present study did identify a difference in cumulative incidence of BCR favoring nodal radiotherapy, but this finding may have been biased by the small sample size.[5]

This study has several limitations. First, this is a consortium analysis of multiple single-arm phase II studies and prospective registries, and therefore cannot provide level I evidence to support SBRT for HRPCa due to the non-randomized nature. Second questions regarding the association of ADT or nodal radiotherapy cannot be answered by the current multivariable analyses as, in addition to the selection biases associated with ADT use and duration (as well as nodal radiotherapy use), important variables, including details of socioeconomic status, gland size, and geographic considerations, were not available. These limitations also impact the multivariable analyses that were performed regarding factors associated with toxicity. Third, heterogeneity in contouring, planning, and treatment delivery introduce additional uncertainty when attempting to pool results from disparate studies and institutions. Fourth, additional patient- and treatment-specific covariates that may have affected toxicity, such as prostate size or rectal dose, were unavailable for analysis. Fifth, patient-reported quality of life indices were not available for analysis, and neither were doses received by normal tissues – both would help inform our understanding of toxicity. Finally, the median follow-up of 48 months must be taken in context of the long natural history of prostate cancer, and as such, these should be considered medium-term rather than long-term results.

In summary, SBRT has shown promising efficacy in patients with HRPCa in a multi-institutional, international setting. Further prospective studies are needed to verify these results and investigate the optimal dose and target volume in the context of SBRT. The ongoing

randomized PACE-C trial is expected to provide additional level 1 evidence concerning the efficacy of SBRT vs conventional radiotherapy among patients with HRPCa.[18]

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FIGURE CAPTIONS

Figure 1. Biochemical Recurrence-Free Survival and Distant Metastasis-Free Survival Among Patients receiving stereotactic body radiotherapy (SBRT) with or without androgen deprivation therapy (ADT).

Figure 2. Cumulative Incidence of late grade ≥2 GU toxicity (left) late grade ≥2 GI toxicity (right) in patients receiving stereotactic body radiotherapy (SBRT).

Table 1. Individual prospective study characteristics.

NCT/IRB	Institution or trial	No. of patients	Dose / fraction	Seminal Vesicle Coverage*	Margins**	Prescription	Intrafraction motion monitoring?	Image guidance	Fractionation	Original toxicity scoring
XXXX	XXXX	71	8 Gy x 5	Proximal 1 cm	5 mm/3 mm posterior	100% of Rx to cover 95% of PTV Max: 105%	Yes	Cone beam CT before treatment; planar imaging during treatment, fiducials in place	Every other day	CTCAE v4.0
XXXX	XXXX	104	7-7.5 Gy x 5	Proximal 1 cm	5 mm/3 mm posterior	100% of Rx to cover 95% of PTV Max:120-128%	Yes	Cyberknife fiducial-based tracking	Every other day	CTCAE v4.0
XXXX	XXXX	16	8 Gy x 5	Proximal 1 cm	5 mm/4 mm anterior and posterior	100% of Rx to cover 95% of PTV Max: 200%	Yes	Cyberknife fiducial-based tracking	Daily	CTCAE v3.0
XXXX	XXXX	45	7-7.25 Gy x 5	Proximal 1 cm	5 mm/3 mm posterior Max: 117-121%	100% of Rx to cover 95% of PTV	Yes	Cyberknife fiducial-based tracking	Daily	RTOG
XXXX	XXXX	28	7-7.5 Gy x 5	Proximal 2.4 cm	5 mm/3 mm posterior Max 107%	95% of Rx to cover 98% of PTV	No	Cone beam CT before treatment, no fiducials	Every other day	RTOG
XXXX***	XXXX	29	8 Gy x 5	Proximal 1 cm	5 mm Max: 107%	100% of Rx to cover 99% of CTV; 95% of Rx to cover 99% of PTV	No	Cone beam CT before treatment. fiducials in place	Weekly	CTCAE v3.0
XXXX***	XXXX	30	8 Gy x 5	Proximal 1 cm	3 mm Max: 107%	100% of Rx to cover 99% of CTV; 83% of Rx to cover 99% of PTV	No	Cone beam CT before treatment, fiducials in place	Weekly	CTCAE v3.0
XXXX	XXXX	21	7.25 Gy x 5	Proximal 2 cm	3 mm/0 mm posteriorly Max: Unlimited	100% of Rx to cover 95% of PTV	Yes	Triggered imaging every 30° with a 2 mm threshold, fiducials in place	Every other day	CTCAE v3.0

***Full seminal vesicle coverage was pursued if cT3b disease**

****No patients had rectal spacers used**

*****No MRI fusion used to guide contour delineation**

CTCAE, common terminology criteria for adverse events; CT, computed tomography; CTV, clinical treatment volume; PTV, planning treatment volume; Rx, prescription

Table 2. Clinical, Demographic, and Treatment Characteristics

Parameter	Distribution
Age (median, IQR)	72.3 (67-78.5)
Initial prostate specific antigen	
Median, IQR	11 (7-21.3)
Mean (SD)	18.8 (25.9)
<10	146 (42%)
10-20	94 (27%)
>20	103 (30%)
T stage	
T1	151 (45%)
T2	144 (43%)
T3a	25 (7%)
T3b	15 (4%)
T4	3 (1%)
Gleason grade group	
1	25 (7%)
2	43 (12%)
3	38 (11%)
4	156 (45%)
5	82 (24%)
Androgen deprivation therapy	
Use	248 (72%)
Duration (median, IQR)	9 (9-18)
Nodal radiotherapy	66 (19%)
Dose per fraction	
7	67 (19%)
7.5	124 (36%)
8	153 (44%)
Acute GU Grade>=2	
Yes	44 (18%)
no	196 (82%)
Acute GI Grade>=2	
Yes	12 (5%)

no	228 (95%)
Late GU Grade>=2	
Yes	64 (19%)
no	279 (81%)
Late GI Grade>=2	
Yes	32 (9%)
no	311 (91%)

IQR, interquartile range

Table 3. Competing Risk Regression Analysis for Predictors of Biochemical Recurrence and Distant Metastasis

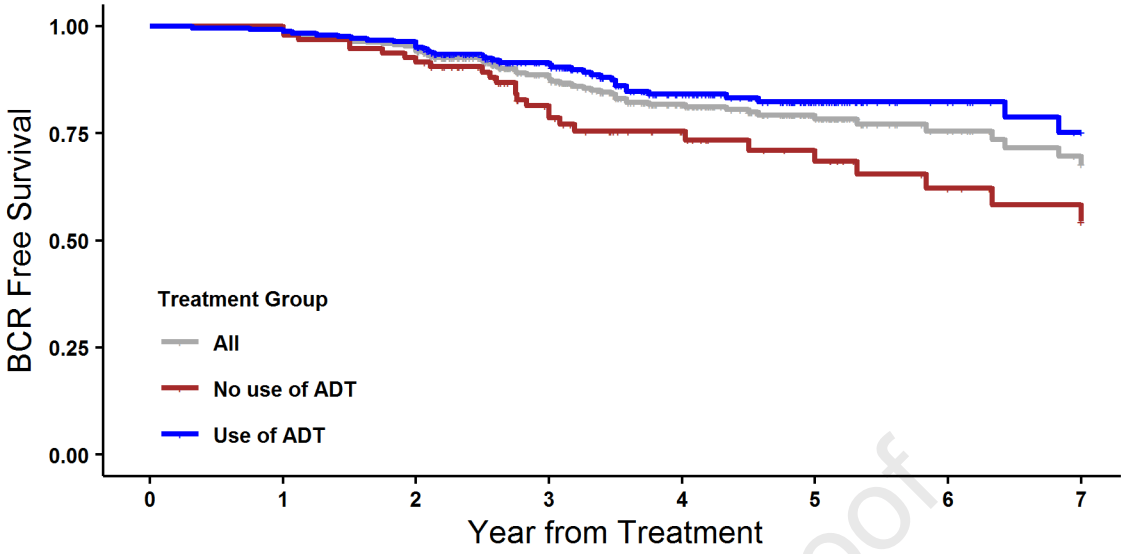
Variable	sHR (95% CI)	p-value
Biochemical Recurrence		
Age at Treatment (1-yr increase)	1.04 (1-1.08)	0.067
Natural Log iPSA	1.42 (1.06-1.9)	0.021
Gleason Grade Group 4-5 vs 1-3	1.06 (0.57-1.97)	0.845
T3/4 (yes vs no)	0.5 (0.15-1.62)	0.245
Dose/Fraction (ref=8 Gy)		
7 vs 8 Gy	2.15 (1.07-4.32)	0.033
7.25 vs 8 GY	1.29 (0.64-2.6)	0.473
Distant Metastasis		
Age at Treatment	1.02 (0.97-1.08)	0.344
Natural Log iPSA	1.2 (0.79-1.84)	0.39
Gleason Grade Group 4-5 vs 1-3	2.31 (0.81-6.59)	0.118
T3/4 no vs yes	1.97 (0.6-6.4)	0.262
Dose/Fraction (ref=8 GY)		
7 vs 8 Gy	1.37 (0.46-4.06)	0.566
7.25 vs 8 GY	0.72 (0.27-1.97)	0.526

CI, confidence interval; HR, hazard ratio; iPSA, initial prostate specific antigen

Table 4. Multivariable Logistic Regression for Late Grade ≥2 Toxicity

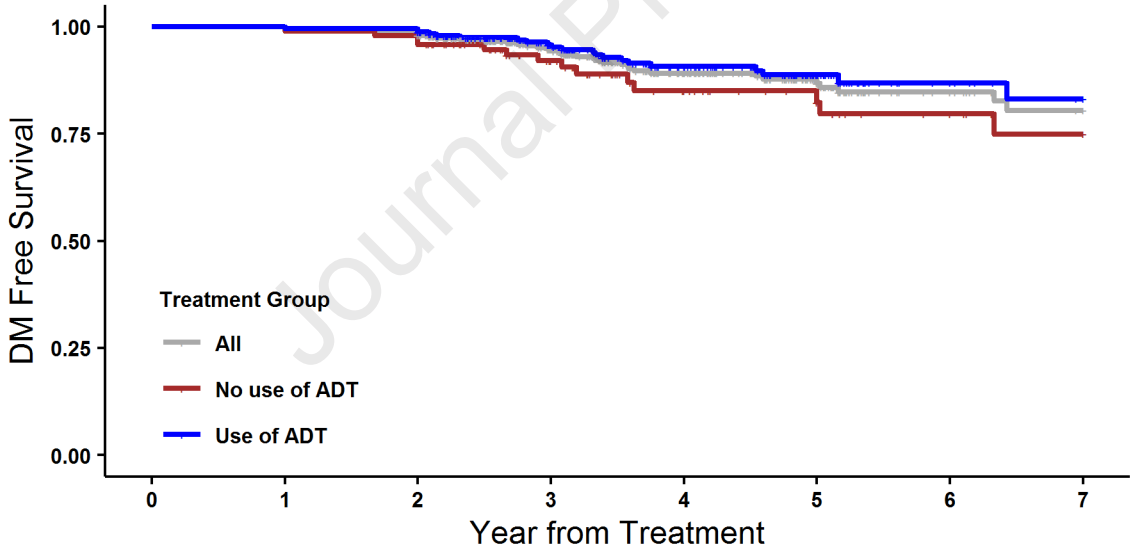
Variable	OR (95% CI)	p-value
Genitourinary Toxicity		
Age at Treatment (1-yr increase)	1.02 (0.98-1.06)	0.343
Dose/Fraction (ref=8 Gy)		
7 vs 8 Gy	0.18 (0.06-0.54)	0.002
7.25 vs 8 Gy	0.25 (0.11-0.56)	0.001
ADT Use (yes vs no)	4.34 (1.68-11.2)	0.002
Nodal Radiotherapy (yes vs no)	1.53 (0.75-3.13)	0.243
Gastrointestinal Toxicity		
Age at Treatment (1-yr increase)	0.98 (0.93-1.03)	0.475
Dose/Fraction (ref=8 Gy)		
7 vs 8 Gy	0.1 (0.02-0.54)	0.008
7.25 vs 8 Gy	0.2 (0.07-0.57)	0.002
ADT Use (yes vs no)	0.11 (0.02-0.58)	0.009
Nodal Radiotherapy (yes vs no)	0.66 (0.28-1.59)	0.358

ADT, androgen deprivation therapy; CI, confidence interval; OR, odds ratio



Number at risk

All	340	338	324	226	154	91	48	35
No use of ADT	95	95	88	57	38	28	19	15
Use of ADT	245	243	236	169	116	63	29	20
	0	1	2	3	4	5	6	7



Number at risk

All	335	335	332	236	161	96	51	37
No use of ADT	96	96	94	66	41	32	23	16
Use of ADT	239	239	238	170	120	64	28	21
	0	1	2	3	4	5	6	7