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Clinical Investigation

Stereotactic Body Radiation Therapy and High-Dose-Rate Brachytherapy Boost in Combination With Intensity Modulated Radiation Therapy for Localized Prostate Cancer: A Single-Institution Propensity Score Matched Analysis

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Purpose: To perform a propensity-score matched analysis comparing stereotactic body radiation therapy (SBRT) boost and high-dose-rate (HDR) boost for localized prostate cancer.

Methods and Materials: A single-institution retrospective chart review was conducted of men treated with pelvic external beam radiation therapy (EBRT) and SBRT boost (21 Gy and 19 Gy in 2 fractions) to the prostate for prostate cancer. A cohort treated at the same institution with HDR brachytherapy boost (19 Gy in 2 fractions) was compared. Propensity-score (PS) matching and multivariable Cox regression were used for analysis. Outcomes were biochemical recurrence freedom (BCRF) and metastasis freedom (MF).

Results: One hundred thirty-one men were treated with SBRT boost and 101 with HDR boost with median follow-up of 73.4 and 186.0 months, respectively. In addition, 68.8% of men had high-risk and 26.0% had unfavorable-intermediate disease,

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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and 94.3% received androgen deprivation therapy. Five- and 10-year unadjusted BCRF was 88.8% and 85.3% for SBRT and 91.8% and 74.6% for HDR boost (log-rank $P = .3$), and 5- and 10-year unadjusted MF was 91.7% and 84.3% for SBRT and 95.8% and 82.0% for HDR (log-rank $P = .8$). After adjusting for covariates, there was no statistically significant difference in BCRF (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.37-1.79; $P = .6$) or MF (HR 1.07; 95% CI, 0.44-2.57; $P = .9$) between SBRT and HDR boost. Similarly, after PS matching, there was no statistically significant difference between SBRT and HDR (BCRF: HR 0.66, 0.27-1.62, $P = .4$; MF: HR 0.84, 0.31-2.26, $P = .7$). Grade 3+ genitourinary and gastrointestinal toxicity in the SBRT cohort were 4.6% and 1.5%, and 3.0% and 0.0% in the HDR cohorts ($P = .4$, Fisher exact test).

Conclusions: SBRT boost plus pelvic EBRT for prostate cancer resulted in similar BCRF and MF to HDR boost in this single institution, PS matched retrospective analysis. Toxicity was modest. Prospective evaluation of SBRT boost for the treatment of unfavorable-intermediate and high-risk prostate cancer is warranted. © 2020 Elsevier Inc. All rights reserved.

Introduction

The use of dose-escalated external beam radiation therapy or combination external beam radiation therapy with a brachytherapy boost (EBRT + BT) in combination with androgen deprivation therapy (ADT) as definitive therapy for intermediate to high-risk prostate cancer is well established.[1-6] Randomized trials have shown superior biochemical control with the use of EBRT + BT over dose escalated EBRT,[1,2,4,7] and a recent large retrospective multi-institutional cohort study has suggested a significant benefit to clinical outcomes including survival.[5] Traditionally, brachytherapy boost treatment has been delivered using low-dose-rate brachytherapy and, more recently, using high-dose-rate techniques.[6] Although toxicity in the seminal Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial was significantly worse in the EBRT + BT arm,[8] more recent prospective data suggest that low rates of acute and late toxicities can be achieved with HDR brachytherapy. For example, the rate of grade 3 toxicities in Radiation Therapy Oncology Group (RTOG) 0321 was 5%, with no grade 4 or 5 toxicities reported.[6,9]

Recently, stereotactic body radiation therapy (SBRT) has become increasingly well established as a form of monotherapy for low- and favorable intermediate-risk prostate cancer and has been shown to be safe and to provide excellent outcomes.[10-13] The efficacy and safety of SBRT as a boost in combination with pelvic EBRT, however, is less well studied[14,15] and is the subject of an ongoing prospective trial (PROMETHEUS, ACTRN12615000223538).

The aim of this study was to report the biochemical and toxicity outcomes of a single institution cohort of patients receiving pelvic EBRT and SBRT boost (EBRT + SBRT) as definitive therapy for intermediate to high-risk localized prostate cancer. In the absence of randomized prospective data, we sought to compare EBRT + SBRT with a matched cohort of patients from the same institution receiving HDR boost (EBRT + HDR).

Methods and Materials

Study design

A retrospective chart review was performed of consecutive men treated for localized prostate cancer (cTXN0) using combination pelvic EBRT and an SBRT boost to the prostate and proximal seminal vesicles at the University of California, San Francisco between June 2006 and January 2018. Clinical characteristics including age, pretreatment prostate-specific antigen (PSA), Gleason score, T-stage, and ADT duration were collected. With the exception of ADT duration in 2 HDR boost patients, complete treatment data were available for patients. Patients were categorized by National Comprehensive Cancer Network risk groups. Biochemical recurrence was defined using the Phoenix criteria as nadir plus 2. Metastasis was defined at the time of imaging study or biopsy confirming metastatic disease. Time to event was defined from the end of radiation therapy. The primary outcomes were biochemical recurrence freedom (BCRF) and metastasis freedom (MF), and death was treated as a censored event. A previously published cohort of patients who underwent combination pelvic EBRT and a 2-fraction HDR brachytherapy boost at the same institution was used as a comparison.[16] Data were collected from the institutional electronic medical record, which is also linked electronically to other institutions using the same or similar electronic health record systems. This study was approved by the institutional review board (number 10-03010).

Radiation and treatment characteristics

The institutional practice for SBRT boost was to irradiate the elective pelvic nodal volume (superior border L5-S1 or L4-L5), prostate, and at least the proximal seminal vesicles to a dose of 45 Gy in 25 daily fractions using intensity modulated radiation therapy (IMRT) and daily cone beam computed tomography, in combination with a 2-fraction

SBRT boost to the prostate and 1 to 2 cm of proximal seminal vesicles, delivered within 2 weeks of pelvic EBRT, on consecutive days using CyberKnife and 3-fiducial tracking. A magnetic resonance imaging or urethrogram was used to delineate the urethra volume. For the SBRT boost, dose constraints were generally rectum/bladder Dmax <100%, rectum V75% <1 cm^3 and bladder V75% <2 cm^3, and urethra Dmax <120%.[17] Rectal spacers were not routinely used. The clinical target volume to planning target volume expansion was 2 mm and 0 mm posteriorly.

As previously described, HDR patients received HDR boost treatment approximately 1 week after completing EBRT, with 16 interstitial catheters placed transperineally and periurethrally using a template-free, free-hand technique under transrectal ultrasound guidance.[16] Catheter placement was customized to cover any areas of extracapsular extension or seminal vesicle invasion to the extent possible. If not already present, gold markers were placed at the apex and base of the prostate to aid in target delineation. Intraoperative cystoscopy was used to confirm urethral integrity and identify catheters violating the bladder wall, which were retracted. CT based planning using the inverse planning simulated annealing algorithm was used.[18] No margins were applied to the target volume. At our institution, dose constraints for SBRT were based on our experience with HDR boost and thus were generally identical to that described for SBRT boost. The first fraction was given on the day of implantation, and the second fraction was given the following morning, without rescan or replanning, as previously described.

ADT was administered using leuprolide injections overlapping with bicalutamide (50 mg daily until the end of radiation therapy). Short-term ADT was defined as any duration of ADT less than or equal to 6 months and was most commonly a 4-month duration. Long-term ADT was defined as any duration of ADT greater than or equal to 18 months and was generally 18 to 24 months. The start of ADT was planned to precede radiation by 2 months.

Statistical analysis

Statistical analyses were performed in *R* (version 3.6.2). Multivariable Cox regression of relevant clinical variables determined a priori was performed. The proportional hazards (PH) assumption was assessed via visual inspection of Schoenfeld residuals and via an interaction term between time and each covariate, and a 2-sided P value <.05 was considered evidence for non-PH. We found that the PH assumption was met for all variables.

Survival curves were compared via the log-rank test. As a sensitivity analysis to ensure that competing risks did not alter findings, cumulative incidences were calculated treating death from any cause as a competing risk. Gray's test was used to compare cumulative incidence curves. The Fine-Gray subdistribution regression model[19] was used for multivariable competing risks analysis via the *cmprsk* package (version 2.2-10).

Propensity-score (PS) matching of HDR boost and SBRT boost was performed using the *MatchIt* package in *R* (version 3.0.2), using the greedy "nearest neighbor" method with default settings, logit distance, without replacement, ratio equal to 1, and caliper value equal to 0.25 standard deviations, along with other default settings.[20] Guidelines for reporting of propensity matching analyses were followed.[21] Variables used for matching included age, Gleason score, PSA, ADT duration, and T-stage.

Patients with missing data (n = 2, ADT duration) were excluded for multivariable analysis and propensity matching. Median follow-up time and ranges were estimated via the reverse Kaplan-Meier method.[22] Two-sided P values <.05 were considered statistically significant.

Results

One hundred and thirty-one consecutive men treated with combination pelvic external beam radiation (EBRT) and a 2-fraction SBRT boost between August 2006 and January 2018, and 101 men treated with combination pelvic EBRT and a 2-fraction HDR brachytherapy boost between June 2000 and November 2005 were included. Median follow-up for the SBRT boost cohort was 73.4 (interquartile range [IQR], 41.8-111.8 months), with186.0 months for the HDR cohort (IQR, 82.4-211.6 months), respectively. Clinical characteristics are reported in Table 1. Most patients had high- or very high-risk disease (77%), whereas only 5.6% had favorable intermediate-risk disease, and none had low-risk disease. The use of ADT was common, with 94.3% of patients receiving ADT and approximately one-third receiving long-term ADT (at least 18 months). Patients receiving SBRT boost tended to be older (median 70.6 vs 64.4 years, $P < .0001$) and were more likely to receive long-term ADT (42.0% vs 24.8%, $P = .006$, Fisher exact test), although the overall duration of ADT was similar (median 6 [IQR, 4-24] vs 5 [IQR, 4-20] months, $P = .11$). In addition, patients receiving HDR boost had a greater proportion of T3a disease (43.6% vs 19.1%). All high-risk SBRT boost patients received ADT (n = 81 of 81). Similarly, nearly all high-risk HDR boost patients received ADT (n = 77 of 78) but were less likely to receive long-term ADT than SBRT patients (35.1% vs 60.5%, $P = .0015$).

Overall, the 5-year BCRF was 88.8% (95% CI, 82.5%-95.5%) for SBRT boost and 91.8% (95% CI, 86.5%-97.4%) for HDR boost (Fig. 1A, $P = .3$, log-rank test), and 10-year BCRF was 85.3% (95% CI, 77.9%-93.5%) for SBRT and 74.6% (95% CI, 65.3%-85.2%) for HDR boost. There was no statistically significant difference in BCRF between the 2 SBRT doses used (19 Gy vs 21 Gy, $P = .51$, log-rank test). Five-year MF was 91.7% (95% CI, 86.2%-97.6%) for SBRT and 95.8% (91.9%-99.9%) for HDR boost ($P = .8$, log-rank), and 10-year MF was 84.3% (95% CI, 74.8%-

Table 1 Patient characteristics

	SBRT (N = 131)	HDR (N = 101)	*P* value
Median age (IQR), Y	70.6 (65.7-75.8)	64.4 (59.2-73.2)	<.0001 (MW)
Boost dose			
21 Gy in 2 fx	35 (26.7%)	0 (0%)	
19 Gy in 2 fx	96 (73.3%)	101 (100%)	
ADT duration			.006
Long term (18 mo or more)	55 (42%)	27 (24.8%)	
Intermediate term (6-18 mo)	9 (6.9%)	18 (17.8%)	
Short term (6 mo or less)	62 (47.3%)	46 (43.6%)	
No ADT	5 (3.8%)	8 (7.9%)	
Median ADT duration (IQR), mo	6 (4-24)	5 (4-20)	.11 (MW)
Mean [SD]/median (IQR) PSA	12.5 [9.5]/9.7 (6.3-18.0)	11.2 [11.9]/9.5 (6.1-18.4)	.96 (MW)
Gleason score			.003
6	2 (1.5%)	14 (13.9%)	
7	74 (56.5%)	49 (48.5%)	
8	26 (19.8%)	23 (22.8%)	
9-10	29 (22.1%)	15 (14.9%)	
T-stage			<.0001
T1c-2a	62 (47.3%)	29 (28.7%)	
T2b-c	21 (16%)	9 (8.9%)	
T3a	25 (19.1%)	44 (43.6%)	
T3b-4	23 (17.6%)	7 (6.9%)	
NCCN risk group			.003
Favorable intermediate	6 (4.6%)	7 (6.9%)	
Unfavorable intermediate	44 (33.6%)	16 (15.8%)	
High	38 (29%)	50 (49.5%)	
Very high	43 (32.8%)	28 (27.7%)	
Median follow-up (IQR), mo	73.4 (41.8-111.8)	186 (82.4-211.6)	

Abbreviations: ADT = androgen deprivation therapy; fx = fractions; HDR = high dose rate; IQR = interquartile range; MW = Mann-Whitney test; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; SBRT = stereotactic body radiation therapy; SD = standard deviation.

95.1%) for SBRT and 82.0% (95% CI, 73.8%-91.2%) for HDR. Outcomes stratified by National Comprehensive Cancer Network (NCCN) risk group are shown in the supplement (Fig. E1). Among nonrecurrent and alive SBRT patients, the median latest PSA after testosterone recovery was 0.088 (IQR, 0.03-0.10).

Cumulative incidence accounting for competing risk of death showed similar findings (Fig. E2). Subgroup analysis of patients with Gleason 8 to 10, T3-T4, and very-high-risk disease (multiple high-risk factors) revealed similar BCRF and MF between the SBRT and HDR boost cohorts (Fig. 1C-F, Fig. E3).

Stratification by ADT duration into short-, intermediate-, and long-term durations did not reveal statistically significant differences in BCRF ($P = .4$, stratified log-rank test) or MF ($P = .8$, stratified log-rank test) between treatment groups. Similarly, an interaction term between ADT duration and treatment group on Cox regression was not statistically significant for BCRF ($P = .10$) or MF ($P = .11$). Finally, among high-risk patients who received long-term ADT (n = 76, 27 in HDR and 49 in SBRT groups), there was likewise no statistically significant difference in BCRF ($P = .6$, log-rank), or MF ($P = .2$, log-rank).

On multivariable Cox analysis, after adjusting for age, pretreatment PSA, ADT duration, Gleason score, and T-stage, there was no statistically significant difference in BCRF (Table 2; HR 0.81; 95% CI, 0.37-1.79; $P = .61$) or MF (HR 1.07; 95% CI, 0.44-2.57; $P = .88$) between SBRT and HDR boost. Similarly, multivariable competing risks analysis did not reveal statistically significant differences in BCRF or MF (Table 2) between SBRT and HDR boost. On both Cox and Fine-Gray regression, T3-4 disease was associated with worse BCRF (Table 2, Cox: HR 4.08; 95% CI, 1.61-10.33; $P = .003$) and MF (Cox: HR 4.02; 95% CI, 1.44-11.25; $P = .007$).

To better account for differences in patient characteristics, HDR boost patients were propensity-matched using a nearest neighbor matching algorithm to the SBRT boost cohort, resulting in a subset of 67 patients from each treatment group better matched for age, Gleason score, PSA, ADT duration, and T-stage (Tables E1 and E2). There was no statistically significant difference in BCRF or MF between the 2 matched cohorts (Fig. 2; BCRF: propensity score HR 0.66, 0.27-1.62, $P = .4$; MF: propensity score HR 0.84, 0.31-2.26, $P = .7$).

The patterns of initial relapse are reported in Table E3. The most common pattern of relapse was bone metastasis

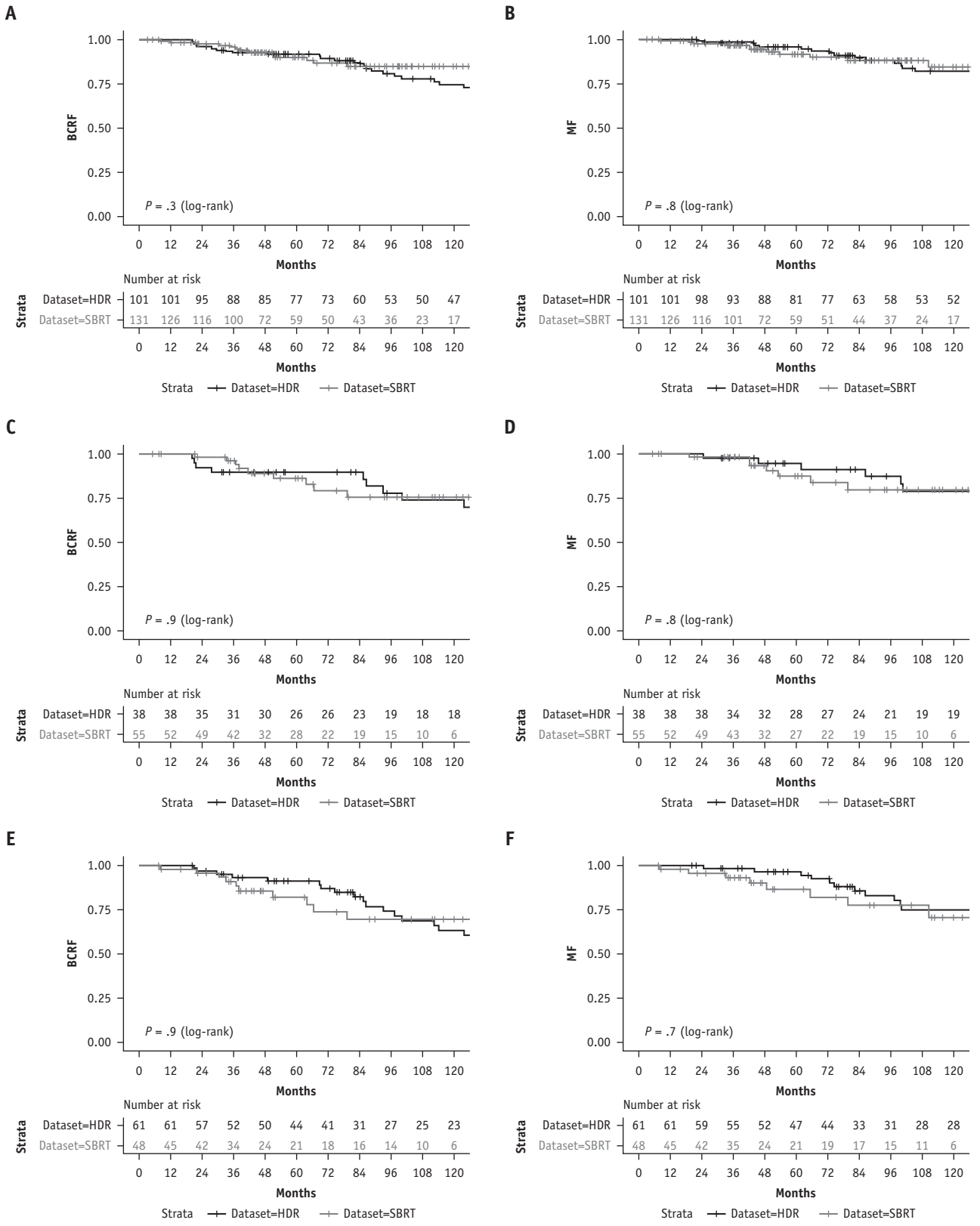


Fig. 1. Kaplan-Meier curves for biochemical recurrence freedom (BCRF) and metastasis freedom (MF) in the whole cohort. Kaplan-Meier curves are shown for BCRF and MF for the whole cohort in (A and B), for patients with Gleason 8 or higher disease (C and D), and in patients with T3 or greater disease (E and F). *P* values for the log-rank test are shown.

Table 2 Multivariable analysis of biochemical recurrence freedom and metastasis freedom

Cox regression	BCRF, HR (95% CI)	*P* value	MF, HR (95% CI)	*P* value
Age	1.02 per year (0.98-1.07)	.29	1.04 per year (0.99-1.10)	.12
ADT duration	1.02 per month (0.99-1.06)	.12	1.02 per month (0.98-1.06)	.42
Pretreatment PSA	1.007 per ng/mL (0.995-1.02)	.26	1.005 per ng/mL (0.99-1.02)	.53
Gleason score	1.13 (0.76-1.69)	.55	1.07 (0.66-1.74)	.77
T3-4 vs T1-2	4.08 (1.61-10.33)	.003	4.02 (1.44-11.25)	.007
SBRT vs HDR boost	0.81 (0.37-1.79)	.61	1.07 (0.44-2.57)	.88
Fine-Gray regression	**BCRF, S-HR (95% CI)**		**MF, S-HR (95% CI)**	
Age	1.02 per year (0.97-1.07)	.44	1.07 per year (1.00-1.13)	.05
ADT duration	1.01 per month (0.98-1.04)	.36	1.01 per month (0.97-1.06)	.50
Pretreatment PSA	1.004 per ng/mL (0.99-1.02)	.58	1.00 per ng/mL (0.97-1.02)	.89
Gleason score	1.18 (0.80-1.74)	.40	1.03 (0.66-1.62)	.89
T3-4 vs T1-2	3.46 (1.27-9.46)	.015	5.73 (1.81-18.16)	.003
SBRT vs HDR boost	0.78 (0.32-1.88)	.58	0.61 (0.21-1.80)	.37

Abbreviations: ADT = androgen deprivation therapy; BCRF = biochemical recurrence freedom; CI = confidence interval; HDR = high-dose-rate; HR = hazard ratio; MF = metastasis freedom; PSA = prostate-specific antigen; SBRT = stereotactic body radiation therapy; S-HR = subdistribution hazard ratio.

alone (n = 14 of 38, 36.8%), without imaging evidence of nodal involvement, followed by isolated nonregional node relapse (n = 5, 13.2%) or relapse in multiple sites including bone, nodes, and organs (n = 5, 13.2%). Pelvic nodal relapse alone was rare (n = 2 of 38, 5.3%), and local recurrence was uncommon (n = 4 of 38 recurrences, 10.5%; n = 4 of 231, 1.7%). One local recurrence was seen after SBRT boost and 3 after HDR boost. Thirteen patients total received prostate biopsy after biochemical relapse, and 4 of 13 biopsies (30.7%) were positive for recurrent disease (1 SBRT, 3 HDR patients). After local recurrence, 1 patient each received salvage cryoablation and salvage HDR brachytherapy (36 Gy in 6 fractions) with brief periods of PSA response followed by development of metastases (lung in one and bone in the other). When present, nonregional nodal relapse most commonly included the paraortic nodes (n = 4), perirectal nodes (n = 3), and 1 case of inguinal nodal relapse. Remarkably, isolated nodal relapse was seen up to 180.2 months after end of radiation.

SBRT boost was well tolerated. The rate of grade 3 genitourinary toxicity was 4.6% (6 of 131 patients). These consisted of 1 case each of hemorrhagic cystitis, urethritis responding to hyperbaric oxygen, retention requiring transurethral resection of the prostate, encapsulated bladder stone requiring cystoscopic resection, bilateral ureteral stenosis requiring stents, and urethral necrosis, which later resolved. There were no grade 4 or 5 genitourinary toxicities. The rate of grade 3+ gastrointestinal toxicity was 1.5% (2 of 131 patients), including 1 grade 3 (proctitis responding to steroid enema) and 1 grade 4 toxicity (colitis and ileitis leading to colovesicular fistula requiring colectomy). Symptomatically, the median International Prostate Symptom Score (IPSS) preradiation was 9 (IQR, 4-15). The majority of patients had improved or stable urinary symptoms (delta-IPSS $\leq$+5 points) at early (71.4%, 75 of 105 patients, median 3.3 months postradiation) and late timepoints (74.3%, 55 of 74 patients, median 18.7 months postradiation). The median IPSS at early and late time points were 11 (IQR, 6-17) and 11 (IQR, 6-16), respectively. The rate of long-term urinary incontinence requiring a pad after SBRT boost was 1.5% (2 of 131 patients).

HDR boost was similarly well tolerated. The rate of grade 3 genitourinary toxicity was 3.0% (n = 3 of 101 patients), consisting of 1 case each of urethral stricture requiring direct vision internal urethrotomy 8 years after radiation, lower urinary tract symptoms, and obstructive symptoms requiring a transurethral resection of the prostate, and radiation urethritis and cystitis causing recurrent macroscopic hematuria. There were no grade 4 or 5 genitourinary toxicities, and no grade 3 or higher gastrointestinal toxicities. There was no significant difference in combined rate of grade 3+ toxicities between SBRT and HDR boost (Fisher exact test, P = .4).

Discussion

Key findings

Pelvic EBRT in combination with SBRT boost provided good biochemical control and metastasis freedom with acceptable toxicity in this retrospective cohort of men with intermediate- to high-risk prostate cancer and similar outcomes compared with a matched cohort of patients receiving HDR boost. To our knowledge, this is the largest reported cohort of patients undergoing SBRT boost and pelvic EBRT for prostate cancer.

The cohort of patients we report for both SBRT and HDR boost are similar in characteristics to those reported in ASCENDE-RT.[4] Mean preradiation PSA was 13.3 in ASCENDE-RT and 17.0 or 13.9 in the SBRT or HDR cohorts. In addition, 53.8% of patients had Gleason 7 disease in ASCENDE-RT compared with 56.5% and 48.5% (SBRT and HDR, respectively), and 40.7% of patients had Gleason

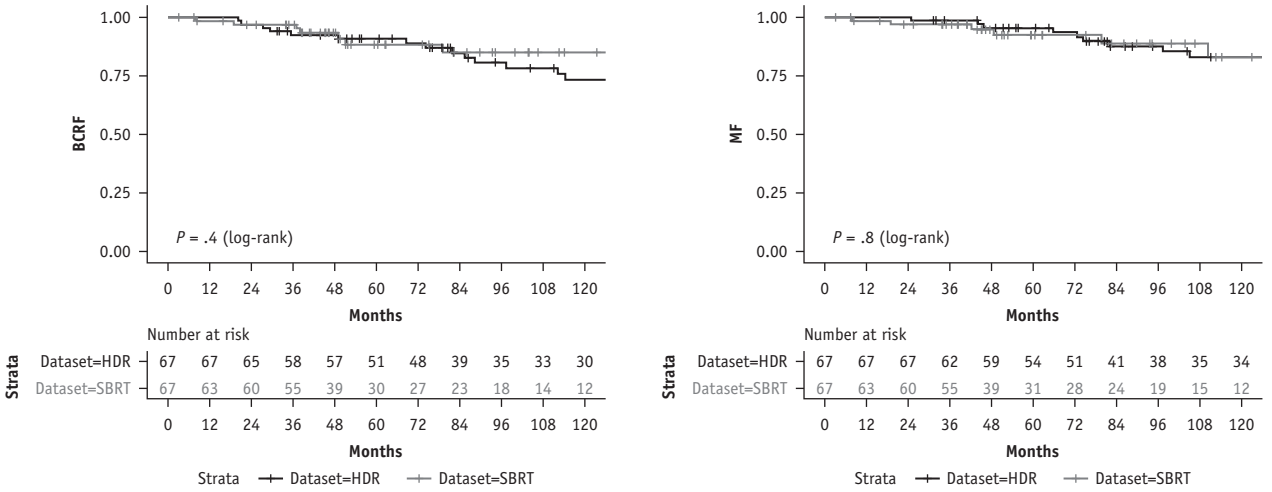


Fig. 2. Kaplan-Meier curves for biochemical recurrence freedom (BCRF) and metastasis freedom (MF) in the propensity-score matched cohort. Kaplan-Meier curves are shown for BCRF and MF for the propensity-score matched cohort. *P* values for the log-rank test are shown.

8 disease in ASCENDE-RT compared with 41.9% and 37.7% (SBRT and HDR, respectively). Consistently, the HDR boost patients in our cohort experienced a favorable BCRF at 5 years (91.8%), comparable with ASCENDE-RT, which reported a 7-year biochemical control of 86%. SBRT boost appeared to yield very similar BCRF to HDR boost in our cohort, even after propensity matching and adjusting for clinical characteristics using multivariate analysis. SBRT boost led to low late PSA levels among living patients without recurrence (median 0.088), comparable with the low nadirs reported in the boost arm of ASCENDE-RT (mean 0.08). Furthermore, there was significant variation in the minimum detection level of the PSA assays used in our retrospective cohort, ranging from 0.015 to 0.2, and therefore the true late PSA level and nadir was likely lower than the median 0.088 we report.

The toxicity rate with SBRT boost was modest, and comparable with rates reported with HDR boost in RTOG 0321.[6] Notably, both our cohort and RTOG 0321 reported substantially lower rates of urethral stricture compared with ASCENDE-RT. Urethral toxicity has previously been shown by our group, RTOG 0321, and others to be related to maximal urethral dose, and the low rates of genitourinary tract toxicity reported in our cohort and RTOG 0321 lend support to the dose constraints used.[9,17,23] Other institutional practices for HDR implantation such as systematic placement of a fiducial marker to delineate the prostatic apex as well as intraoperative cystoscopy to confirm the integrity of the urethra and identify any catheters puncturing the bladder neck, may also contribute to lower genitourinary toxicity.

Our reported patterns of initial relapse are informative, although many relapses occurred before the era of molecular imaging. It is possible that many patients with bone-only relapse identified by conventional imaging alone may have harbored nodal, local, or other disease that would have been identified by fluciclovine or prostate-specific membrane antigen positron emission tomography imaging. Thus, although local and pelvic nodal relapses appeared rare in our cohort, and the majority of patients appeared to fail at distant sites, this conclusion must be taken with a grain of salt. Nevertheless, this pattern of failure appears to be similar to the pattern also noted in the most recent NRG consensus atlas for pelvic lymph node delineation based on modern molecular imaging.[24] The low local and pelvic recurrence rate we find lends support to ongoing efforts to study other avenues of treatment escalation such as addition of chemotherapy (RTOG 0521) or next-generation antiandrogens for the highest risk patients who, despite combined "ultra" dose-escalated combination radiation and hormone therapy leading to excellent local and regional control, are still at substantial risk for metastasis and prostate cancer mortality.[25] Based on our data, this may include high-risk patients with locally advanced, T3-4 disease. In addition, further study of the true prostate biopsy negative rate after combined "ultra" dose escalation with SBRT or brachytherapy boost to the prostate is also needed to ascertain to what extent occult residual or locally recurrent disease precedes metastatic disease. Finally, the growing use of molecular imaging for staging may better identify patients with microscopic nodal or occult metastatic disease before treatment.

The clinical use of SBRT boost as part of combination radiation may be greatest realized in patients unable to undergo a brachytherapy procedure, either due to medical comorbidities, age, lack of access to brachytherapy providers,[26,27] health care resource reallocation (as in the current COVID-19 pandemic), or personal preference. The existence of a safe, effective alternative to provide "ultra" dose escalation may enable definitive therapy for these high-risk patients comparable with the current gold standard of ERBT + BT, which has been suggested to afford

improved recurrence free survival compared with conventional dose escalated EBRT.[1,5,28] Our study adds to prior reports of SBRT boost for intermediate and high-risk prostate cancer,[29] and is the largest such cohort reported thus far. To the best of our knowledge, it is also the first such study to report metastasis-freedom in addition to biochemical control.

Limitations

The present study has several limitations. First, as a retrospective chart review, it is subject to the biases and limitations inherent to retrospective studies, including selection bias, reviewer bias and missing data. Toxicity data collected retrospectively based on chart review may be undersensitive and lead to underreporting of toxicities. Although we attempted to mitigate this limitation by multivariable analysis as well as propensity matching, these methods are imperfect and cannot account for all sources of bias or for imbalances in the 2 treatment groups. Because biochemical recurrence or metastasis during castration induced by ADT is considered rare, immortal time bias due to varying ADT duration was of concern, although neither stratification by ADT duration nor adjusting for ADT duration or treatment interaction with ADT duration altered our findings. Second, follow-up in the SBRT cohort was midterm (approximately 6.1 years), although it was comparable with early results of ASCENDE-RT (6.5 years). This is of some concern as the difference between the EBRT + BT and EBRT arms of ASCENDE-RT only began to manifest at year 4 to 5 and was most prominent at late timepoints. Nevertheless, the follow-up of the SBRT cohort was comparable with that of ASCENDE-RT (6.5 years), and the long-term BCRF in the SBRT cohort, 85.3% at 10 years, is comparable with that reported in the EBRT + BT arm of ASCENDE-RT (83% at 9 years), and higher than that of the EBRT arm of that study (62% at 9 years). Furthermore, there was no evidence of a sharp drop-off in biochemical control at late timepoints in either the SBRT or HDR cohorts. Third, another limitation of our study is that patients in the SBRT and HDR cohorts were treated during 2 eras; SBRT boost patients were treated during an era when IMRT was routinely used at our institution for pelvic radiation. Some HDR patients were treated during a transition period during which time some patients would have been treated with 3-dimensional conformal radiation therapy, although by the period in question our institution was mainly using IMRT and fiducial based image guidance for pelvic radiation. Nevertheless, although some studies have associated IMRT with lower rates of toxicity, its use in pelvic radiation in the context of combination radiation is not commonly thought to be correlated with improved disease control.

Our study should be interpreted in the context of the limitations listed. Ultimately, prospective validation with longer term follow-up in a randomized trial is needed to validate the findings of the present study.

Conclusion

Combination pelvic EBRT and SBRT boost appears to provide excellent biochemical control and acceptable toxicity in this retrospective cohort of men with intermediate to high-risk prostate cancer. Biochemical control and metastasis freedom were similar compared with a propensity-matched cohort of patients receiving HDR boost and after adjusting for clinical variables.

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