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Original Article

Dose–response with stereotactic body radiotherapy for prostate cancer: A multi-institutional analysis of prostate-specific antigen kinetics and biochemical control

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ABSTRACT

Background and purpose: The optimal dose for prostate stereotactic body radiotherapy (SBRT) is still unknown. This study evaluated the dose–response relationships for prostate-specific antigen (PSA) decay and biochemical recurrence (BCR) among 4 SBRT dose regimens.

Materials and methods: In 1908 men with low-risk (50.0%), favorable intermediate-risk (30.9%), and unfavorable intermediate-risk (19.1%) prostate cancer treated with prostate SBRT across 8 institutions from 2003 to 2018, we examined 4 regimens (35 Gy/5 fractions [35/5, n = 265, 13.4%], 36.25 Gy/5 fractions [36.25/5, n = 711, 37.3%], 40 Gy/5 fractions [40/5, n = 684, 35.8%], and 38 Gy/4 fractions [38/4, n = 257, 13.5%]). Between dose groups, we compared PSA decay slope, nadir PSA (nPSA), achievement of nPSA $\leq$0.2 and $\leq$0.5 ng/mL, and BCR-free survival (BCRFS).

Results: Median follow-up was 72.3 months. Median nPSA was 0.01 ng/mL for 38/4, and 0.17–0.20 ng/mL for 5-fraction regimens ($p < 0.0001$). The 38/4 cohort demonstrated the steepest PSA decay slope and greater odds of nPSA $\leq$0.2 ng/mL (both $p < 0.0001$ vs. all other regimens). BCR occurred in 6.25%, 6.75%, 3.95%, and 8.95% of men treated with 35/5, 36.25/5, 40/5, and 38/4, respectively ($p = 0.12$), with the highest BCRFS after 40/5 (vs. 35/5 hazard ratio [HR] 0.49, $p = 0.026$; vs. 36.25/5 HR 0.42, $p = 0.0005$; vs. 38/4 HR 0.55, $p = 0.037$) including the entirety of follow-up, but not for 5-year BCRFS ($\geq$93% for all regimens, $p \geq 0.21$).

Conclusion: Dose-escalation was associated with greater prostate ablation and PSA decay. Dose-escalation to 40/5, but not beyond, was associated with improved BCRFS. Biochemical control remains excellent, and prospective studies will provide clarity on the benefit of dose-escalation.

Stereotactic body radiation therapy (SBRT) is an effective, convenient, and cost-effective definitive radiotherapy option for localized prostate cancer and is supported by the National Comprehensive Cancer Network (NCCN) for low-, intermediate-, and high-risk disease [1–3]. This technique exploits the estimated low α/β ratio for prostate cancer of approximately 1.5–3.0 Gy, which denotes a greater sensitivity to hypofractionation [4–7]. The use of SBRT for definitive treatment of prostate cancer is

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increasing rapidly [8,9], yet the dose–response and optimal dose are still uncertain [10].

A consistent association between higher doses and improved biochemical- and progression-free survival has been shown with conventionally fractionated external beam radiotherapy (EBRT) [11–15]. However, this might not readily translate to ultrahypofractionated regimens, as the radiobiology of treatment response might be different [7]. Indeed, the optimal dose or range of dose-fractionation regimens for prostate SBRT is still unknown [16–23]. The combined ASTRO/ASCO/AUA recommendations for ultrahypofractionation recommended doses of 35–36.25 Gy in 5 fractions, but this was based on the large number of published series using this dose and the comparative dearth of studies that have investigated the dose–response for doses below 40 Gy in 5 fractions [16,19,24]. Currently, NCCN-preferred ultrahypofractionated regimens for SBRT fall within 36.25–40 Gy in 5 fractions [1]. Further dose-intensification with high-dose rate-like dosing for SBRT using 38 Gy in 4 fractions has also demonstrated similar biochemical control outcomes [22], but has not been directly compared to other regimens.

Several prostate-specific antigen (PSA) kinetic parameters may act as surrogate earlier predictors of biochemical control, such as rate of PSA decay, nadir PSA (nPSA), and achievement of PSA levels below certain threshold values including an ablative effect on the prostate [19,25–29]. As the prostate SBRT dose–response is not well established, how PSA kinetics and the extent of prostate ablation differ within the range of commonly used dose regimens, and whether these differences translate to differences in disease control outcomes, remain unknown. In favorable risk populations with a long time-to-failure natural history, understanding these kinetics may aid in predicting outcomes.

We evaluated the impact of prostate SBRT dose on PSA response kinetics and biochemical control in a multi-institutional cohort of 1908 men treated with one of four SBRT dose-fractionation regimens: 35 Gy in 5 fractions, 36.25 Gy in 5 fractions, 40 Gy in 5 fractions, and 38 Gy in 4 fractions. This study aimed to identify associations between dose and both post-treatment PSA response patterns and biochemical recurrence-free survival (BCRFS) by exploring outcomes in a large pooled consortium of patients receiving prostate SBRT.

Methods and materials

Patient population

Eight institutions were included in this multi-institutional analysis of 1908 men with NCCN low- and intermediate-risk prostate cancer treated with SBRT from 2003 to 2018. Patients with less than 12 months of PSA follow-up or who received upfront androgen deprivation therapy (ADT) were excluded. Patient selection for SBRT was determined per institutional standards. Patients had PSAs measured per institutional protocol, generally at least every 6–12 months in accordance with NCCN guidelines.

SBRT regimens

Four SBRT dose-fractionation regimens were included in this analysis. Equivalent dose in 2-Gy fractions (EQD2) using an α/β for prostate cancer of 3 ($EQD2_3$) was calculated for each regimen to facilitate comparison between dose groups using the equation: $EQD2 = D * ([d + (\alpha/\beta)]/[2\ Gy + (\alpha/\beta)])$ [30]. Using $EQD2_3$, the SBRT regimens were: 35 Gy in 5 fractions (35/5, $EQD2_3$ = 70 Gy), 36.25 Gy in 5 fractions (36.25/5, $EQD2_3$ = 74.3 Gy), 40 Gy in 5 fractions (40/5, $EQD2_3$ = 88 Gy), and 38 Gy in 4 fractions (38/4, $EQD2_3$ = 95 Gy; virtual high-dose-rate treatment planning [22]). Patients were treated either on a daily or every-other-day schedule until 2011, after which time nearly all patients were treated with an every-other-day schedule (effectively, 2–3 times per week).

PSA decay kinetics and nPSA

PSA decay was first analyzed by examining the slope of decay. Each patient's PSA values were plotted over time as ln(PSA) vs. ln (time), and the slope of PSA decline for each patient was obtained. The slope of PSA decay was then calculated for each dose group and for each risk group. Subsequent multivariate analyses were then conducted to further evaluate specific kinetic parameters for nPSA and achievement of pre-determined PSA threshold values.

The nPSA was defined as the lowest measured post-treatment PSA, in the absence of salvage therapy for a biochemical recurrence (BCR). Time to the nPSA was defined as the elapsed time between the date of SBRT completion and the date on which the nPSA was measured. The initial PSA (iPSA) was taken as the most recent pre-treatment PSA.

Achievement of nPSA $\leq$0.2 ng/mL and nPSA $\leq$0.5 ng/mL ("threshold values"), which may be early predictors of biochemical control [26,29,31,32], were assessed. We defined achievement of nPSA $\leq$0.2 and $\leq$0.5 ng/mL as attaining a PSA value below these threshold values at any time, in the absence of salvage therapy for BCR. Achievement of PSA threshold values, nPSA, and time to nPSA were reported for the overall population, for each dose group, and compared between dose groups.

Biochemical recurrence

BCR was defined by the Phoenix criteria as a PSA rise $\geq$2.0 ng/mL from the nPSA [33].

Statistical analysis

Descriptive statistics for patient characteristics were presented overall and by dose groups (Table 1). Differences between dose groups were analyzed using the Kruskall–Wallis test and Chi-square test.

For PSA decay slope analyses, analysis of variance that employed mixed-effects modeling was used to compare differences in slope of decay between dose groups, risk groups, and between dose groups within each risk group given a significant dose-risk group interaction. For each patient's values for log-transformed PSA vs. log-transformed time, the slope equation and r^2 were calculated. Median and interquartile range (IQR) r^2 values for the entire population were then obtained.

For each regimen, the mean and median frequencies of PSA testing per year were calculated. The incidence rate ratio (IRR) was calculated to evaluate for differences in PSA testing frequency between dose groups. An adjusted IRR was also calculated, adjusting for risk group, age, ln(iPSA), T stage, and Gleason grade.

For PSA kinetics analyses, multivariate regression was performed to evaluate between-regimen differences in ln(nPSA) and time to nPSA. Logistic regression analyses were used for achievement of nPSA $\leq$0.2 and $\leq$0.5 ng/mL. All analyses were adjusted for risk group, age, ln(iPSA), T stage, and grade group. The dose group-risk group interaction was calculated and further risk-group stratified results are presented where significant. Due to the variation in laboratory standards and PSAs below the limit of detection for ultra-low PSA values, we imputed a standard value of 0.01 for PSA values that were reported as below the limit of detection (e.g. <0.04) or 0.

Crude rates of BCR were calculated for the overall population, for each dose group, and by risk group. Logistic regression was used to model the crude BCR rate. BCRFS was calculated from completion of SBRT to BCR or death, or in the absence of these out-

Table 1
Patient characteristics.

	All patients	35 Gy/5 fx	36.25 Gy/5 fx	40 Gy/5 fx	38 Gy/4 fx	*p*-value
n (%)	1908	265 (13.4)	711 (37.3)	684 (35.8)	257 (13.5)	
Follow-up time, median (IQR), in months	72.3 (39.1–96.0)	66.2 (37.6–84.0)	62.3 (31.0–96.0)	78.0 (56.0–96.0)	72.4 (48.1–96.3)	<0.001
Age, median (IQR), in years	68 (63–73)	70 (64–74)	68 (63–73)	68 (62–73)	69 (65–74)	0.02
iPSA, median (IQR), [range], ng/mL	5.9 (4.6–8.1) [0.3–19.9]	5.7 (4.5–7.7) [0.6–19.9]	6.0 (4.7–8.1) [0.8–19.0]	5.8 (4.6–8.1) [0.3–19.5]	6.2 (4.5–8.5) [0.8–19.3]	0.28
Grade group, *n* (%)						<0.001
GG 1	1104 (57.9)	156 (60.9)	431 (60.6)	397 (58.0)	120 (46.7)	
GG 2	606 (31.8)	79 (30.9)	196 (27.6)	229 (33.5)	102 (39.7)	
GG 3	198 (10.4)	21 (8.2)	84 (11.8)	58 (8.5)	35 (13.6)	
cT stage, *n* (%)						<0.001
cT1	1449 (75.9)	208 (81.3)	536 (75.4)	560 (81.9)	145 (56.4)	
cT2a	340 (17.8)	32 (12.5)	112 (15.8)	111 (16.2)	85 (33.1)	
cT2b	97 (5.1)	11 (4.3)	46 (6.5)	13 (1.9)	27 (10.5)	
cT2c	22 (1.2)	5 (1.9)	17 (2.4)	0 (0)	0 (0)	
Risk group, n (%)						0.01
Low	954 (50.0)	136 (53.1)	365 (51.3)	353 (51.6)	100 (38.9)	
Favorable intermediate	589 (30.9)	78 (30.5)	221 (31.1)	198 (28.9)	93 (36.2)	
Unfavorable intermediate	363 (19.1)	42 (16.4)	125 (17.6)	133 (19.4)	64 (24.9)	

Fx: fractions; IQR: interquartile range; SBRT: stereotactic body radiation therapy; GG: grade group; cT stage: clinical T stage.

comes, patients were censored at last follow-up. Cox proportional hazards models were constructed to compare BCRFS differences between dose groups. BCR and BCRFS analyses were adjusted for risk group, age, ln(iPSA), T stage, grade group, and treatment year. Evaluation of the effect of these covariates, in addition to the dose group-risk group interaction, was performed by fitting multivariate Cox proportional hazards models. Kaplan–Meier estimates for BCRFS for each dose group were obtained and presented in figures for the overall population as well as stratified by risk group. Between-group differences in BCRFS rates at 5 years were also reported.

For all statistical investigations, tests for significance were 2-tailed unless otherwise specified. A *p*-value less than the 0.05 significance level was considered to be statistically significant. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, 2012).

Results:

Median PSA follow-up was 72.3 months (IQR 39.1–96.0 months). Characteristics for the entire population of 1908 men and separately for each dose group are displayed in Table 1. Men received 35/5 (n = 265, 13.4%), 36.5/5 (n = 711, 37.3%), 40/5 (n = 684, 35.8%), or 38/4 (n = 257, 13.5%). The majority (81%) of patients had low- or favorable intermediate-risk disease. Median iPSA was 5.9 ng/mL and did not significantly differ between dose cohorts (p = 0.28) (Table 1).

Data contributions and SBRT treatment regimens for each of the eight institutions are presented in Supplementary Table 1. Dose constraints and prescription goals – including planning target volume normalization and homogeneity practices – for the contributing institutions are available in Supplementary Table 2.

Fig. 1 shows sample natural log-transformed PSA decay curves for patients in each dose group. Overall, these curves had high r^2 values, with median values of 0.81, 0.82, 0.82, and 0.78 for men treated with 35/5, 36.25/5, 40/5, and 38/4, respectively. The steepest slope of PSA decay was seen with the 38/4 dose group, which had a faster rate of PSA decay compared to all other dose groups ($p < 0.0001$ for all). Men treated with 40/5 also exhibited a significantly steeper PSA decay slope compared to 36.25/5 ($p < 0.0001$) though not 35/5 (p = 0.15). The slope of PSA decay did not significantly differ for men treated with 35/5 versus 36.25/5 (p = 0.56). An interaction between dose-group and risk-group was detected ($p < 0.0001$). By risk group, low-risk disease exhibited the steepest slope of decay, followed by favorable intermediate-risk, with the shallowest slope observed for unfavorable intermediate-risk disease. Stratified by risk group, the significantly steeper slope seen after 38/4 compared to all other regimens persisted for both low-risk ($p < 0.0001$) and favorable intermediate-risk disease ($p \leq 0.002$), though in unfavorable intermediate-risk disease, the only significant between-regimen difference was steeper decay after 40/5 compared to 36.25/5 ($p < 0.0001$).

The median PSA testing frequency per year ranged from 1.7 to 2.4, with a significantly lower PSA testing frequency per year in the 40/5 dose group ($p < 0.001$), and a significantly higher PSA testing frequency per year in the 38/4 dose group ($p \leq 0.01$) (Supplementary Table 3).

The median nPSA achieved for the entire population was 0.18 ng/mL (IQR 0.10–0.33, range 0.01–15.30), and was 0.17, 0.20, 0.19, and 0.01 ng/mL for dose groups 35/5, 36.25/5, 40/5 and 38/4, respectively (Table 2). Men treated with 38/4 achieved a significantly lower nPSA compared to each of the other dose groups ($p < 0.0001$ for each). nPSA was not significantly different for comparisons among 35/5, 36.25/5 and 40/5 (p = 0.08–0.67). On multivariate analysis incorporating the dose group-risk group interaction ($p < 0.0001$), men treated with 38/4 still achieved a significantly lower nPSA compared to each risk strata in each of the other dose groups ($p \leq 0.002$ for all comparisons). Among unfavorable intermediate-risk patients, 40/5 achieved a significantly lower nPSA compared to 35/5 (p = 0.006), though for low-risk patients, both 35/5 and 36.25/5 achieved lower nPSAs compared to 40/5 (p = 0.009 and p = 0.03, respectively).

Median time to nPSA was 47.7 months (IQR 24.0–72.0) overall, and 44.8, 36.2, 51.8, and 38.9 months for the 35/5, 36.25/5, 40/5, and 38/4 dose groups, respectively (Table 2). Covariate-adjusted comparisons between dose groups revealed a significantly longer time to nPSA for the 40/5 cohort compared to all other dose groups ($p \leq 0.024$) and for 38/4 compared to 36.25/5 (p = 0.02).

Most patients (81.7%) achieved nPSA ≤0.5 ng/mL (Table 2). Men treated with 40/5 and 38/4 had significantly greater odds of achieving nPSA ≤0.5 ng/mL compared to treatment with 36.25/5 (odds ratio [OR] 1.95, [95% confidence interval [CI] 1.46–2.62], $p < 0.0001$; OR 2.19 [95% CI 1.46–3.31], p = 0.0002, respectively) (Supplementary Table 4).

nPSA ≤0.2 ng/mL was achieved by 52.5% of men (Table 2). The odds of achieving nPSA ≤0.2 ng/mL were significantly higher for men treated with 38/4 compared to all other dose groups (vs. 35/5: OR 2.83 [95% CI 1.93–4.13]; vs. 36.25/5: OR 2.93 [95% CI

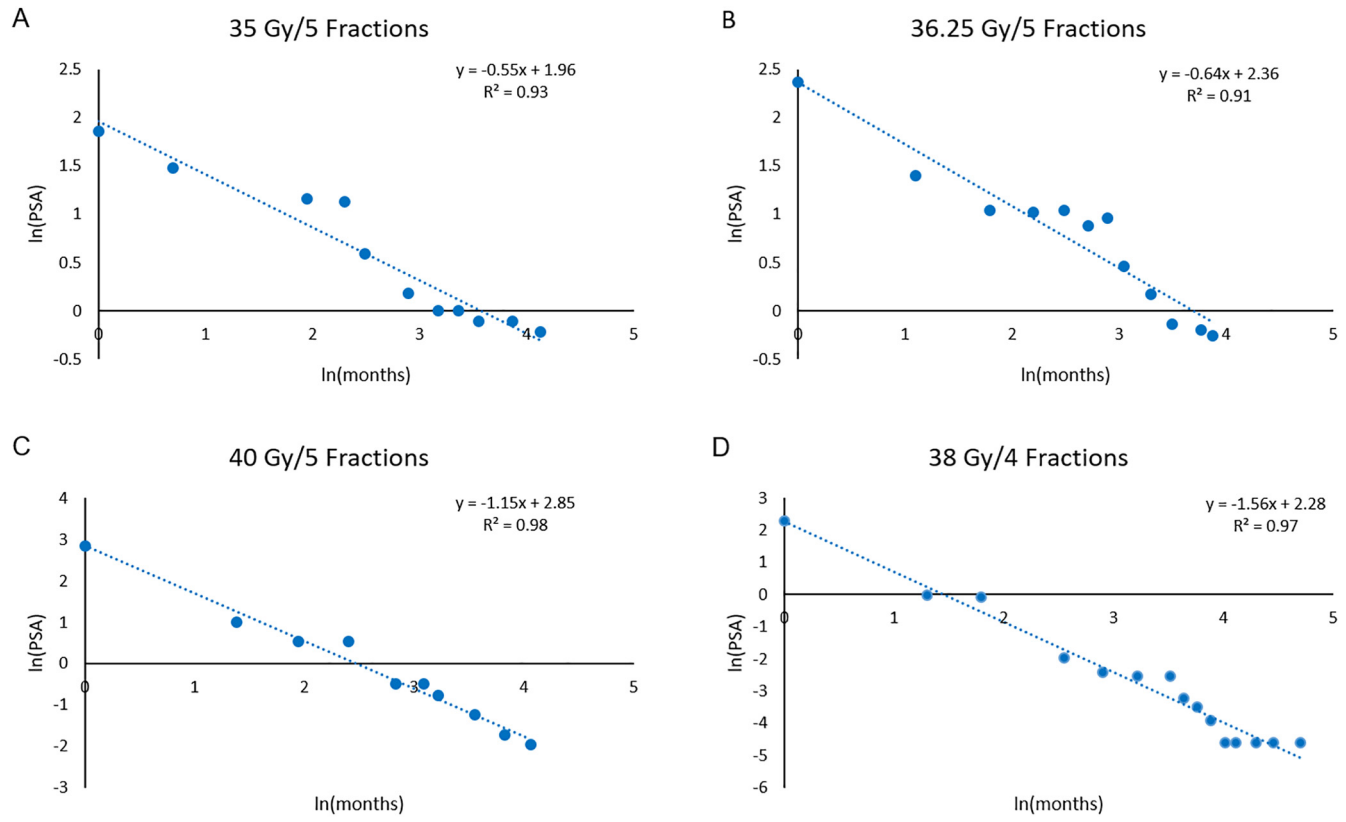

Fig. 1. Representative log-transformed PSA decay slopes for each dose group.

Table 2
PSA kinetics.

	All patients	35 Gy/5 fx	36.25 Gy/5 fx	40 Gy/5 fx	38 Gy/4 fx	*p*-value*
nPSA, median (IQR), mean, ng/mL	0.18 (0.10–0.33), 0.34	0.17 (0.10–0.32), 0.31	0.20 (0.09–0.47), 0.39	0.19 (0.12–0.30), 0.33	0.01 (0.01–0.20), 0.30	<0.0001
Time to nPSA, months, median (IQR)	47.7 (24.0–72.0)	44.8 (24.8–62.4)	36.2 (21.2–61.2)	51.8 (28.0–78.0)	38.9 (24.3–60.2)	<0.0001
Achievement of nPSA ≤0.5 ng/mL, *n* (%)	1559 (81.7)	211 (82.4)	541 (76.1)	586 (85.7)	221 (86.0)	<0.0001
Achievement of nPSA ≤0.2 ng/mL, *n* (%)	1001 (52.5)	130 (50.8)	343 (48.2)	347 (50.7)	181 (70.4)	<0.0001

Fx: fractions; nPSA: nadir prostate-specific antigen; IQR: interquartile range.
*p-value derived from multivariate/logistic regression, adjusting for risk group, age, ln(iPSA), T stage, and grade group. Detailed between-group comparisons for threshold values are available in Supplementary Table 4.

2.13–4.03]; vs. 40/5: OR 2.79 [95% CI 2.02–3.85]; $p < 0.001$ for all). There were no other significant differences for achievement of nPSA ≤0.2 ng/mL between other dose groups (Supplementary Table 4).

There were 114 reported BCRs (crude event rate 5.98%). BCR occurred in 6.25%, 6.75%, 3.95%, and 8.95% of men treated with 35/5, 36.25/5, 40/5, and 38/4, respectively, with no significant differences in these crude event rates between dose groups ($p = 0.12$) (Supplementary Table 5).

With respect to BCRFS, significant differences between dose groups emerged. Fig. 2 displays BCRFS curves stratified by dose group for the entire population (Fig. 2A), and for low-risk (Fig. 2B), favorable intermediate-risk (Fig. 2C), and unfavorable intermediate-risk (Fig. 2D) cohorts. Comparing BCRFS between regimens, treatment with 40/5 was associated with a lower probability of BCR compared to all other dose groups (vs. 35/5: HR 0.49 [95% CI 0.26–0.92], $p = 0.026$; vs. 36.25/5: HR 0.42 [95% CI 0.26–0.69], $p = 0.0005$; vs. 38/4: HR 0.55 [95% CI 0.31–0.97], $p = 0.037$) (Table 3). Risk group had a significant effect on BCRFS ($p = 0.003$); the dose group-risk group interaction was not significant ($p = 0.12$).

When restricting to the 5-year post-treatment period, 5-year BCRFS rates were 95.65% overall, and not significantly different between dose groups, ranging from 93.00 to 96.49% ($p \geq 0.21$ for all between-dose group comparisons).

Discussion

In this multi-institutional analysis of 1908 men with NCCN low-, favorable intermediate-, and unfavorable intermediate-risk prostate cancer treated with SBRT, treatment with 40/5 demonstrated superior BCRFS compared to 35/5, 36.25/5, and 38/4. BCRFS followed a dose–response among 5-fraction regimens, though this was not seen with the most dose-escalated regimen (38/4). Importantly, rates of BCR were low across all dose groups, with 5-year BCRFS estimates of at least 93%. The observed between-regimen

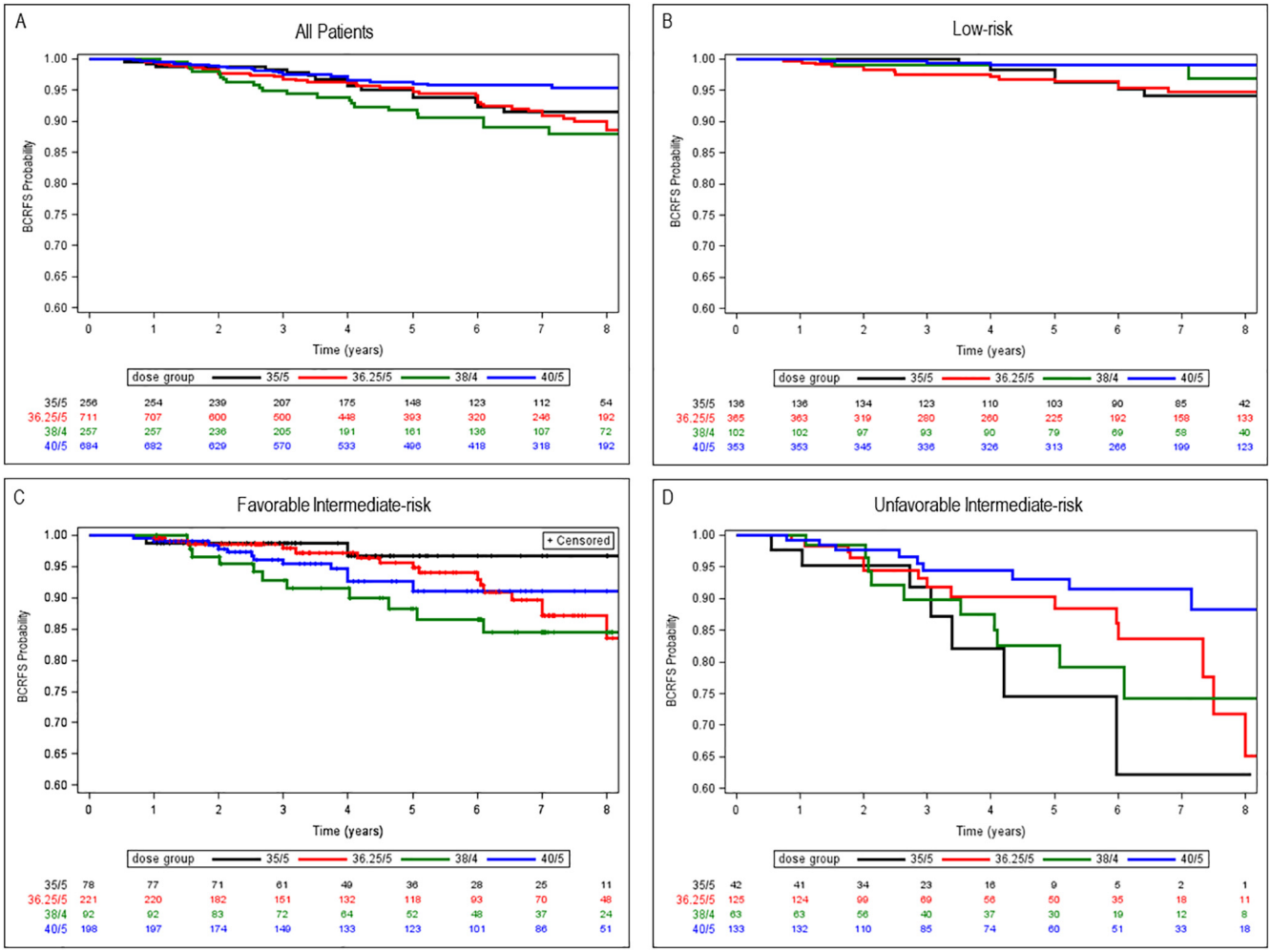

Fig. 2. Kaplan–Meier curves for biochemical recurrence-free survival (BCRFS) for (A) all patients, (B) low-risk disease, (C) favorable intermediate-risk disease, and (D) unfavorable intermediate-risk disease, treated with one of four SBRT dose regimens without neoadjuvant/concurrent androgen deprivation therapy.

Table 3
Between-regimen comparisons for biochemical recurrence-free survival.

Dose group comparison	Hazard ratio (95% CI)	*p*-value
36.25/5 vs. 35/5	1.16 (0.66–2.05)	0.60
40/5 vs. 35/5	**0.49 (0.26–0.92)**	**0.026**
40/5 vs. 36.25/5	**0.42 (0.26–0.69)**	**0.0005**
40/5 vs. 38/4	**0.55 (0.31–0.97)**	**0.037**
38/4 vs. 35/5	0.90 (0.47–1.72)	0.75
38/4 vs. 36.25/5	0.77 (0.46–1.30)	0.33

CI: confidence interval; 36.25/5: "36.25 Gy in 5 fractions".

differences in BCRFS manifested with longer follow-up and were not seen when restricting examination to the 5-year post-treatment time period, consistent with the slower natural history and overall low event rate in this patient population. All dose groups in our study achieved median nPSAs of 0.2 ng/mL or lower. Post-treatment PSA kinetics showed a more apparent dose–response relationship than BCRFS. Indeed, treatment with 38/4 was associated with the fastest rate of decay as well as a more frequent achievement of nPSA $\leq$0.2 and a lower nPSA than lower dose regimens.

A dose–response association between increasing prostate SBRT dose and BCRFS is supported by a large meta-analysis incorporating 33 prospective studies that reported on biochemical control after prostate SBRT.[2] Among included regimens, which ranged from 5-10 Gy per fraction delivered in 4–9 fractions, increasing dose (in $BED_{2.5\ Gy}$) was significantly associated with improved BCRFS. A significant distinction in the present analysis is access to individual patient data, allowing an exploration of individual patient outcomes as well as an ability to adjust for patient-specific clinicopathologic features that might be of importance, as well as potential dose-risk group interactions.

A potential explanation for our finding that escalation to a dose above 40 Gy/5 fractions was not associated with improved biochemical outcomes despite improved prostate ablation is that, beyond a certain threshold, prostate ablation may simply become decoupled from biochemical control as the extraprostatic failures may begin to drive the pattern of relapse. Given that this analysis only included patients who did not receive ADT, the results suggest that dose-escalation alone may not be sufficient to clearly improve outcomes in patients already receiving relative high-dose radiation. This concept is supported by studies of dose-escalation with conventionally fractionated EBRT, which suggest that dose escalation alone does not permit the omission of ADT [15,34–36]. Although the dose-risk group interaction for BCR was not significant (and thus analyses were only adjusted for risk group and associated covariates but not for the dose-risk group interaction), it is possible that the presence of more unfavorable risk disease factors in the 38/4 cohort may still have influenced results. Additionally,

we identified a higher PSA testing frequency in the 38/4 group, which could lead to earlier detection of BCR. Conversely, the 40/5 group had the lowest PSA testing frequency, which could have influenced the data to demonstrate a longer time to BCR.

Length of follow-up may also play a role in the observed outcomes. Given the long time-to-event in this population, our median follow-up of 6 years, while long for most published SBRT series, does not address potential longer-term differences in biochemical control, which have been associated with lower nPSAs [25,29]. Randomized trial data of dose-escalation in conventional fractionation for favorable risk populations indicate that while dose-escalation affords disease control benefits for local and distant control, these differences are numerically small and emerge relatively late [15]. Recent data in low dose rate brachytherapy identified the threshold of nPSA $\leq$0.2 ng/mL at 4 years as a predictor of long-term freedom from recurrence at $\geq$10 years post-treatment [29]. Given the greater odds of achieving nPSA below this threshold in the most dose-escalated group, it is unknown whether biochemical control differences beyond the length of follow-up presented here may still appear. Of note, differences in follow-up would be expected to favor newer regimens. We did perform a sensitivity analysis including year of treatment in a multivariable analysis, and found that even accounting for year of treatment, BCRFS remained highest in patients receiving 40 Gy/5 fractions. Thus, the observed dose–response cannot be explained by differential follow-up.

There have been few, relatively small prospective studies of dose-escalation in prostate SBRT. These have demonstrated a clear dose–response for prostate ablation (i.e., nPSA) but mixed results regarding a disease control benefit. A comparison of two prospective trials using 35/5 versus 40/5 found no significant differences in the probability of BCR between the two regimens [19]. In contrast, a phase I dose-escalation study identified a significantly lower 2-year positive post-treatment biopsy rate of 7.7% and a 0% cumulative BCR incidence after 40/5 compared to 16.7% and 0% after 37.5/5 and 19.2% and 6% after 35/5, respectively [16]. A small study of further dose-escalation among 26 low- and intermediate-risk patients who received 40, 45, or 50 Gy in 5 fractions found no biochemical control benefit to further dose-escalation above 40 Gy [21], which is consistent with our results. Across these studies, nPSA decreased with dose-escalation, which was clearly seen after 38/4 but not as distinct between our 5-fraction regimen cohorts, though nPSAs overall in the above studies tended to be higher than those in our population [16,19,21].

A limitation of the present study is the absence of toxicity data available for comparison between dose cohorts, though published toxicity data for each of the studied prostate SBRT regimens are available in the literature [18,20,37,38]. Heterogeneity in treatment planning and dosimetry between CyberKnife and linear accelerator-based prostate SBRT is also a limitation. Patients treated with CyberKnife included in this series were treated with plans that were normalized to the 90% isodose line to achieve 95% prescription coverage of the planning target volume through at least 2011 [39]. The treatment plans in subsequent years were in some cases normalized to lower isodose lines, and therefore certain regions of the prostate may have in fact received doses of over 110% of the prescription. Thus, the reported prescription dose might not entirely match, for any given dose, the maximum doses delivered to portions of the prostate. Greater detail regarding normalization and prescribing practices for the planning target volume are available for review in Supplementary Table 2. Because of the low BCR rate in this study (approximately 6%), the impact of small differences in outcomes between cohorts might be amplified even though these differences might not be actually clinically meaningful. Due to their event rarity, we did not evaluate metastasis-free or cancer specific survival, which are more clinically meaningful endpoints [40]. Individual data about patterns of failure were not available, and thus conclusions about local control cannot be drawn. Finally, though we statistically accounted for multiple covariates, a prospective randomized evaluation of the optimal dose for prostate SBRT would be the gold-standard for evaluating different dose-fractionation schemes.

In summary, all dose groups demonstrated excellent biochemical control rates. PSA kinetics followed a dose–response pattern, with faster rates of PSA decay, lower nPSA, and a greater likelihood of achieving an ablative PSA $\leq$0.2 ng/mL with the greatest dose-escalation (38 Gy in 4 fractions). However, these PSA kinetics were not uniformly associated with biochemical control. Dose-intensification with 40 Gy in 5 fractions was associated with superior BCRFS compared to lower BED regimens (35–36.25 Gy in 5 fractions); however, further dose-escalation was not. Thus, in the setting of low nPSAs achieved across all groups, further decreases in nPSA may reflect ablation of normal prostate tissue rather than incremental ablation of cancer cells. Corresponding toxicity data and even longer follow-up may bolster further analyses, but prospective trials are needed to determine the optimal dose for prostate SBRT.

Conflicts of Interest

R Levin-Epstein, NY Jiang, X Wang, S Upadhyaya S, Suy, N Aghdam, C Mantz, AJ Katz, A Napieralska, A Namysl-Kaletka, N Prionas, H Bagshaw, MK Buyyounouski, A Dang, Y Yuan, PA Kupelian, NG Zaorsky, O Mohamad, J Juarez, D Shabsovich, T Jiang, S Kahlon, A Patel and J Patel report no conflicts of interest.

SP Collins: Clinical consultant for Accuray.

L Miszczyk: Speaking and travel honoraria from Accuray.

M Cao: Personal fees from Varian and Guidepoint LLC.

DE Spratt: Advisory board for Blue Earth Diagnostics, Janssen, and AstraZeneca

F Feng: Personal fees from Dendreon, EMD Serono, Janssen Oncology, Ferring, Sanofi, Bayer, Blue Earth Diagnostics, Celgene, Medivation/Astellas, and Clovis Oncology, and ownership interests in PFS Genomics outside the submitted work; in addition, F Feng has a patent issued (EP3047037 A4)

NG Nickols: Grants from Veterans Affairs, Prostate Cancer Foundation, STOP Cancer Foundation, Janssen, Bayer, Progenics, and Varian; Personal fees from Gene Sciences, Inc.

ML Steinberg: Honoraria from ViewRay, Consulting role for VisionRT and Boston Scientific.

DB Fuller: Consultant for Accuray. Stock interests for Accuray, Viewray, and Varian.

AU Kishan: Advisory role for Janssen; Consulting role for mPROS; Grants from Prostate Cancer Foundation; Honoraria from Varian and ViewRay.

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Appendix A. Supplementary data

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