



## Optimal timing of radiotherapy in high risk prostate cancer: Do missed days matter?



Shaakir Hasan<sup>a,\*</sup>, Daniel Gorovets<sup>b</sup>, Eric Lehrer<sup>c</sup>, Stanislav Lazarev<sup>c</sup>, Robert H. Press<sup>a</sup>, Madhur Garg<sup>d</sup>, Keyur J. Mehta<sup>d</sup>, Arpit M. Chhabra<sup>a</sup>, J. Isabelle Choi<sup>a</sup>, Charles B. Simone II<sup>a</sup>

<sup>a</sup> New York Proton Center, New York, NY, USA

<sup>b</sup> Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

<sup>c</sup> Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>d</sup> Department of Radiation Oncology, Montefiore Medical Center, Bronx, NY, USA

### ARTICLE INFO

#### Article history:

Received 4 August 2020

Revised 10 November 2020

Accepted 12 November 2020

Available online 25 November 2020

#### Keywords:

Radiation oncology

Urology

Prostate cancer

External beam radiation therapy

Androgen deprivation therapy

Survival

### ABSTRACT

**Introduction:** High-risk prostate cancer is associated with poorer overall survival (OS) and biochemical control compared to more favorable risk groups. External beam radiation therapy (EBRT) is widely used; however, outcomes data are limited with respect to time elapsed between diagnosis and initiation of EBRT.

**Methods:** The National Cancer Database was queried from 2004 to 2015 for patients diagnosed with high-risk adenocarcinoma of the prostate who received androgen deprivation therapy (ADT) and definitive EBRT. Logistic regression was utilized to determine covariates associated with missing EBRT treatments. OS was analyzed using multivariate cox proportional hazards models and propensity score matching.

**Results:** 9,610 patients met inclusion criteria with median follow-up of 40.6 months and median age of 72 years. Median PSA was 8.7 and median EBRT dose was 78 Gy. ADT was initiated at a median of 36 days and EBRT at a median of 63 days post-diagnosis. Median number of prolonged treatment days was 2.2. Black race (OR: 1.40;  $p < 0.01$ ), treatment at a community clinic (OR: 1.32;  $p < 0.01$ ), and living in an urban/densely populated area were associated with prolonged treatment. Time elapsed between ADT and EBRT > 74 days (HR: 1.20;  $p = 0.01$ ) and prolonged treatment > 3 days of EBRT (HR: 1.26;  $p = 0.005$ ) were associated with an increased hazard of death. The 5-year OS was 79.6% and 82.9% for patients with prolonged treatment of 3 days or more of EBRT and those missing 3 days or less, respectively ( $p = 0.0006$ ). **Conclusion:** In this hypothesis-generating study, prolonged treatment delays and missing three or more EBRT treatments was associated with poorer OS in patients with high-risk adenocarcinoma of the prostate.

© 2020 Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### 1. Introduction

Although prostate cancer in general is largely curable with a low mortality rate, the long term biochemical control and overall survival for high risk disease is only 62% and 73%, respectively, per recent 9-year randomized data [1]. Currently the standard of care for high risk disease includes prostatectomy or a combination of androgen deprivation therapy (ADT) and radiotherapy [2]. To date, no study has evaluated the role of external beam radiotherapy (EBRT) timing, including time from diagnosis to treatment

and total days elapsed during radiation, in this specific patient population.

Previous data regarding the impact of overall treatment time in prostate EBRT are limited, mixed, and largely predate the dose-escalation and PSA era. For instance, a 1991 pooled analysis of Radiation Therapy Oncology Group trials 75–06 and 77–06 found no correlation between treatment time and local control or overall survival in a heterogeneous patient population treated to 65 Gy, and similar findings were reported in a more recent study for patients treated to at least 74 Gy [3,4]. Conversely, Amdur et al. noted that prolonged treatment times over 8 weeks for prostate cancer treated to 65–70 Gy had inferior local control, as did another analysis by Liauw and colleagues (although no difference was noted above 74 Gy) [5,6]. Notably, most of these studies were not conducted with patients treated with dose-escalated radiotherapy and ADT.

\* Corresponding author at: New York Proton Center, 225 East 126<sup>th</sup> Street, New York, NY 10035, USA.

E-mail address: [shasan@nyproton.com](mailto:shasan@nyproton.com) (S. Hasan).

Furthermore, to our knowledge there has been no specific analysis of high risk disease, which is notably more aggressive and may therefore be more susceptible to missed treatment days, as has proven to be the case in other disease sites [7–11].

The prevailing consensus appears to be that the low alpha–beta ratio implies that prostate cancer is highly sensitive to changes in fraction dose but rather insensitive to total treatment time. [3,12,13] However, recent studies demonstrate that high Gleason scores and certain molecular subtypes have a substantially worse prognosis, highlighting the heterogeneity in adenocarcinoma of the prostate, and possibly a non-uniform sensitivity to treatment timing.[2,14] Herein, we isolated the Gleason grade group 4 and 5 populations to analyze the impact of EBRT completion time on outcome and correlates thereof.

## 2. Methods

### 2.1. Patient selection

We queried the National Cancer Database, which details approximately 70% of cancers diagnosed in the United States, to identify patients with localized, high-risk adenocarcinoma of prostate treated definitively with ADT and conventionally fractionated dose-escalated EBRT with daily fractionation between the years 2004–2015 (only patients treated from 2010 to 2014 remained after exclusion) in this IRB-exempt study. High risk was defined as either clinical stage T3, a PSA above 20, or a Gleason grade 8–10 with node negative disease. Starting from 282,220 patients with T1–T3N0M0 prostate cancer treated with radiotherapy, cases were excluded for unknown or Gleason grade groups 1–3 ( $n = 247,763$ ), if ADT use was not reported or not used ( $n = 7,135$ ), for follow-up <12 months to account for immortal time bias ( $n = 6,079$ ), for prior surgery ( $n = 2,566$ ), if brachytherapy was given ( $n = 3,570$ ), if PSA was >40 (as done in recent clinical trials involving high risk disease [1]) ( $n = 1,442$ ), if ADT/EBRT timing details were unknown ( $n = 1,628$ ), if dose was unknown or not between 74 and 81 Gy at 1.8–2 Gy per fraction ( $n = 1,344$ ), if ADT was initiated beyond 6 months from diagnosis, if EBRT started over 6 months from ADT initiation, if elapsed time of EBRT exceeded 75 days ( $n = 840$ ), and if patients were older than 85 or had a Charlson/Deyo combined comorbidity score over 2 ( $n = 243$ ). Ultimately, 9,610 patients were eligible for analysis. [Fig. 1]

### 2.2. Statistics

Our methodology for determining appropriate timing parameters has been previously reported [15]. Receiver operating characteristic (ROC) analyses independently determined a priori (optimal cutoff) values for time to initiation (from diagnosis to either ADT or EBRT, whichever came first), duration of EBRT, and missed days of EBRT that were predictive of the greatest survival discrepancy. Since previous conventionally fractionated dose escalation studies proved a biochemical failure control benefit between 74 and 81 Gy, but they have not reported a particular dose within that dose range to be superior, all doses between 74 and 81 Gy at 1.8–2 Gy per fraction were included in this study. Consequently, there is an inherent variability in “duration” of EBRT, making it a difficult variable to control for with multivariable regression analyses. Instead, we elected to consider “prolonged treatment” days the primary timing parameter analyzed in this study, as has been previously performed for similar analysis in other disease sites. Prolonged treatment days are defined as the [number of elapsed days during EBRT minus (number of fractions divided by 5 fractions per week, multiplied by 7 days per week)], rounding to the higher whole number. For instance, a 78 Gy in 39 fraction course is expected to be com-

pleted in 55 days (39 divided by 5, multiplied by 7 and rounded up), and if a patient finishes in 58 days, we counted that as 3 missed days.

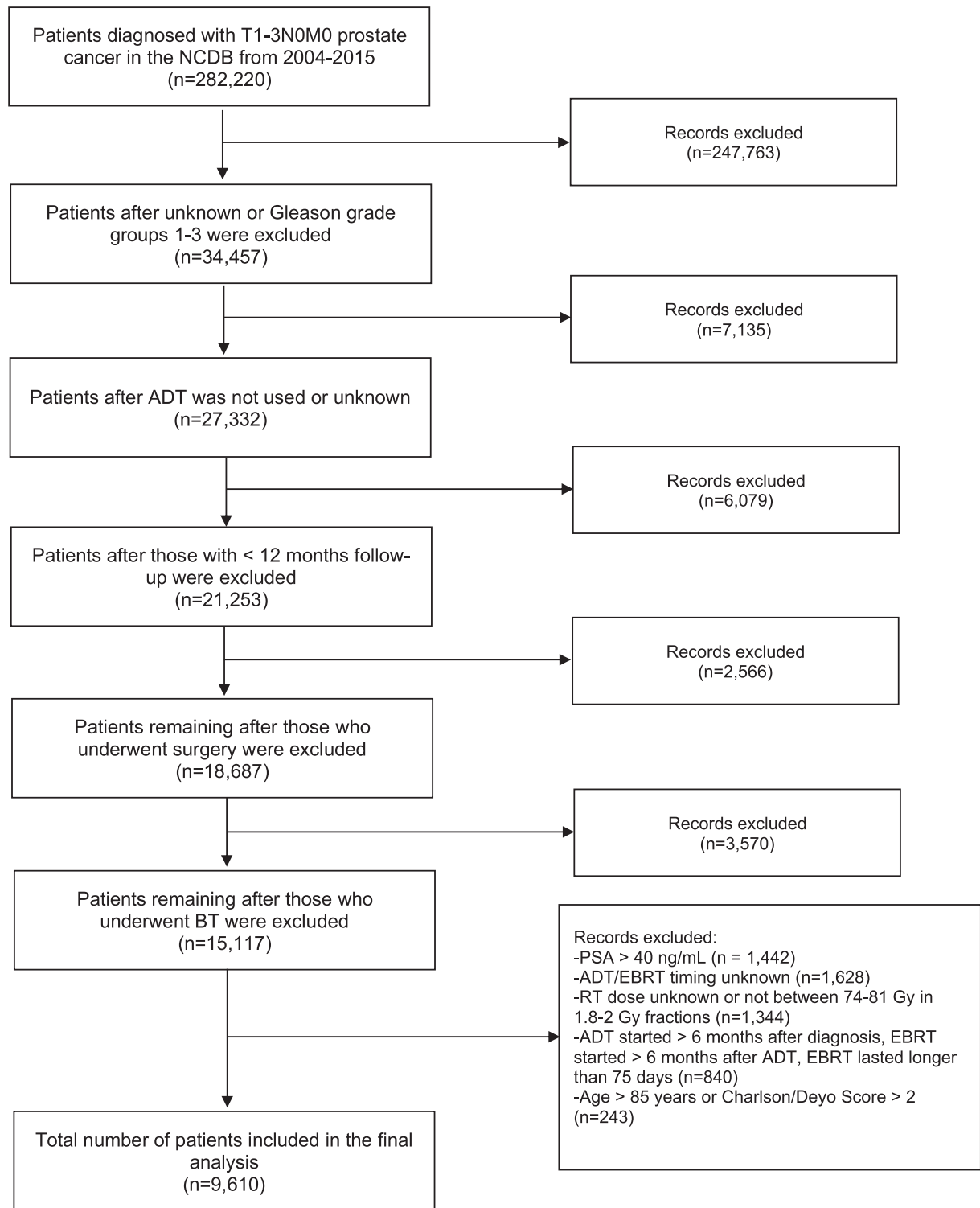
Time to treatment initiation and prolonged treatment days were then analyzed in separate propensity score-matched multivariable Cox regression analyses for survival. Proportional hazards assumptions for the Cox analyses were fulfilled. Adjusted hazard ratios (HR) and 95% confidence interval (CI) are reported, with  $\alpha = 0.05$  used to indicate statistical significance. Bivariate logistic regression models evaluated the association between independent variables of interest and particular timing group. Overall survival was calculated from the date of diagnosis to the date of last contact or death using Kaplan Meier methodology to present the cumulative probability of survival, and log-rank statistics to assess statistical significance between groups.

Propensity score analysis was used to account for indication bias caused by lack of randomization [16]. Propensity scores were calculated by multivariable logistic regression to provide a score reflecting the conditional probability of receiving EBRT within or beyond the particular time frame of interest. The propensity model included observable variables significantly associated with time-frame selection on multivariable logistic regression. Subsequently we constructed a Cox proportional hazards model adjusting for propensity score. To strengthen the assumption of balance between groups, the propensity-adjusted score was validated by stratification into propensity score-based quintiles, which demonstrated that standardized difference between the treatment groups was <0.10. Further validation was executed by creating a pseudopopulation ( $n = 2,416$ ) matched to within a value of 0.05 of the propensity score for each timing parameter assessed, with t-tests confirming no statistical difference in observable variables between the two groups in the particular timing parameter being compared (missed treatment days or time from diagnosis to intervention). Statistical analysis was performed via MedCalc version 22 (New York, NY).

## 3. Results

After exclusion, 9,610 high-risk prostate cases treated with ADT and dose-escalated EBRT were included in this study with a median follow-up of 40.6 months, interquartile range (IQR) 28–56.5 months). Their median age was 72 years (IQR 66–76), with a racial breakdown of 82.5% white, 14.1% black, and 3.5% other (mostly Asian). The plurality of cases were cT1 (48.6%), followed by cT2 (40.6%) and T3 (10.8%). Gleason grade group 4 (Gleason 4 + 4 = 8) was diagnosed in 52.5%, and the remaining cases were Gleason grade group 5 (Gleason 9 or 10). The median PSA was 8.7 ng/mL (IQR 5.8–14.4 ng/mL), with 57.3%, 28.4%, and 14.3% of cases were under 10 ng/mL, between 10 and 20 mg/dL, and 20–40 ng/mL, respectively. The median dose delivered was 78 Gy (IQR 77.4–79.2 Gy) in 43 fractions (IQR 42–44). Patients initiated ADT a median 36 days (IQR 22–57) from the date of diagnosis, and EBRT a median of 63 days (IQR 46–84) after ADT. The median number of prolonged treatment days was 2.2 (range 0–10; IQR 0–4).

Per receiver operating characteristic analysis, the *a priori* values that conferred the greatest survival difference for time from diagnosis to ADT, time from ADT to EBRT, and prolonged treatment days were 43, 74, and 3 days, respectively. As depicted on Table 1, per binomial logistic regression analysis, variables associated with an increased probability of missing over three treatment days included black race (OR = 1.40, 95% CI 1.22–1.61), treatment at community clinics (OR = 1.32, 95% CI 1.19–1.62), an urban environment/areas with population over 250,000 people (OR = 1.33, 95% CI 1.14–1.59), a Charlson/Deyo combined comorbidity score over 1



Abbreviations: ADT: androgen deprivation therapy; BT: brachytherapy; EBRT: external beam radiation therapy; Gy: gray; NCDB: National Cancer Database; PSA: prostate specific antigen; RT: radiation therapy

**Fig. 1.** CONSORT diagram of patient selection. CONSORT diagram depicting our stepwise implementation of exclusion criteria. A total of 282,220 patients from 2004 to 2015 were recorded in the NCDB with T1-3N0M0 adenocarcinoma of the prostate in the NCDB. Ultimately, 9,610 patients met inclusion criteria and were included in this analysis.

(OR = 1.23, 95% CI 1.08–1.40), dose < 78 Gy (OR = 1.17, 95% CI 1.06–1.30), and PSA over 20 (OR = 1.16, 95% CI 1.01–1.33). There was no correlation with time to starting ADT or time from ADT to starting EBRT with the number of prolonged treatment days while on treatment.

The Kaplan Meier 5-year survival was 82% for the entire cohort and the median survival was not reached. Among all the timing parameters tested, the largest discrepancy in 5-year survival with Kaplan Meier univariable analysis were for those with over 3 days of prolonged treatment EBRT (79.6%) compared to those missed

**Table 1**  
Baseline Characteristics for patients categorized by number of missed treatment days.

Table 1. Baseline Characteristics for patients completing EBRT with up to or >3 missed treatment days					
Characteristics	≤ 3 days N = 7185(%)	> 3 days N = 2425(%)	OR	95% CI	P value
Age in years (Median)	72	72	0.99*	0.991–1.006	0.72
Race					
White	6046 (76.3)	1880(77.5)	1	Reference	
Black	900 (12.5)	452(18.6)	1.40	1.22–1.61	<b>&lt;0.01</b>
Other	239 (3.3)	93(3)	1.12	0.87–1.45	0.38
Insurance					
Uninsured	81 (1.1)	39 (1.6)	1	Reference	
Private	1647 (22.9)	526 (21.7)	0.74	0.49–1.11	0.14
Medicaid	141 (2.0)	93 (3.8)	1.31	0.81–2.09	0.26
Medicare	5010 (69.7)	1658 (68.4)	0.81	0.54–1.21	0.31
Median Income zip code					
< \$48,000	2897 (40.4)	1015 (42.0)	1	Reference	
\$48,000 or more	4273 (59.6)	1401 (58.0)	0.92	0.77–2.174	0.36
Facility					
Community	765(10.6)	309(12.7)	1	Reference	
Comprehensive Community	3623(50.4)	1109(45.7)	0.72	0.615–0.84	<b>&lt;0.01</b>
Academic	2101(29.2)	753(31.1)	0.76	0.64–0.91	<b>0.01</b>
Integrated network cancer program	696(9.7)	254(10.5)	0.76	0.61–0.93	<b>0.01</b>
Population					
Metro (over 1 million)	2900 (41.5)	1094 (46.4)	1	Reference	
Urban (250 k–1 million)	1678 (24.0)	585 (24.8)	0.9825	0.86–1.11	0.10
Suburban (20,000–250,000)	995 (14.2)	263 (11.2)	0.7505	0.63–0.88	<b>0.01</b>
Rural (<20,000)	1332 (19.2)	254 (16.8)	0.8025	0.64–0.99	<b>0.04</b>
Distance to facility in miles (median)	9.2	9	1.00*	0.99–1.01	0.99
Comorbid (Charlson-Deyo)					
0	5977 (83.2)	1966 (81.1)	1	Reference	
1	987 (13.7)	396 (16.3)	1.23	1.08–1.40	<b>0.01</b>
2	221 (3.1)	63 (2.6)	0.87	0.65–1.16	0.34
Years					
2010–2012	4168 (57.9)	1375 (56.7)	1	Reference	
2013–2014	3017 (42.1)	1050 (43.3)	1.05	0.90–1.22	0.50
Days from diagnosis to ADT (median)	36	36	1.00*	0.99–1.01	0.58
Days from ADT to EBRT (median)	63	63	0.99	0.99–1.00	0.12
Radiation Dose					
<78 Gy	2897 (40.3)	1046 (43.1)	1	Reference	
Greater than or equal to 78 Gy	4288 (59.7)	1379 (56.9)	0.85	0.77–0.94	<b>0.01</b>
Clinical T Stage					
T1	3464 (48.2)	1205 (49.7)	1	Reference	
T2	2937 (40.9)	964 (39.8)	1.00	0.91–1.11	0.85
T3	784 (10.9)	256 (10.6)	0.99	0.84–1.16	0.91
Gleason grade group					
4	3780 (52.6)	1269 (52.3)	1	Reference	
5	3405 (47.4)	1156 (47.7)	1.01	0.91–1.10	0.85
PSA					
<10	4162 (57.9)	1349 (55.6)	1	Reference	
10–19.9	2034 (28.3)	692 (28.5)	1.03	0.92–1.14	0.57
20–40	989 (13.8)	384 (15.8)	1.16	1.01–1.33	<b>0.02</b>

EBRT, external beam radiotherapy; OR, odds ratio; CI, confidence interval; PSA, prostate specific antigen; \*as continuous variable.

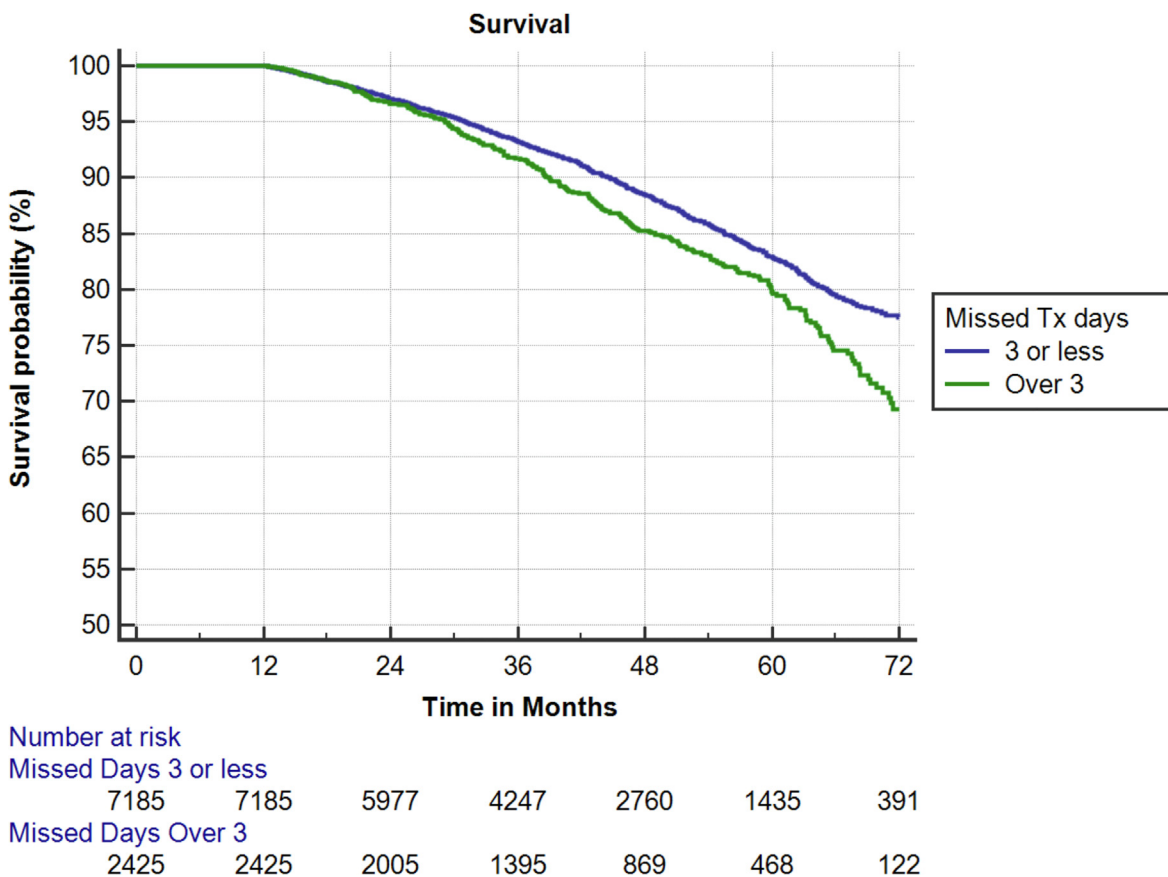
less than that (82.9%). The 6-year survival difference was 79.5% vs 72.5% ( $P = 0.0006$ ) [Fig. 2]. This discrepancy remained statistically significant with multivariable Cox regression analysis (both propensity match adjusted and non-propensity-match adjusted), with a hazard ratio of 1.26 (95% CI 1.07–1.48). Time from ADT to start to EBRT beyond 74 days was also an independent predictor of worse survival in the multivariable model (HR = 1.20,  $P = 0.01$ ), but time from diagnosis to ADT start beyond 43 days was not (HR = 0.87,  $P = 0.10$ ). When analyzed as continuous variables, prolonged treatment days was the only timing parameter predictive of worse survival (HR = 1.027,  $P < 0.001$ ) [Table 2].

In addition to limiting prolonged treatment days to 3, other statistically significant independent predictors of better survival are detailed on Table 3. They include younger age (HR = 0.96 as a continuous variable), lower comorbidity score (HR = 0.81), “other” (mostly Asian) race (HR = 0.51), higher income (HR = 0.81), PSA under 10 (HR = 0.76), Gleason grade group 4 instead of 5

(HR = 0.77), and EBRT dose 78 Gy or higher (HR = 0.87). The same parameters remained statistically significant on the propensity-score matched multivariable analysis with the exception of income [Supplementary Fig. 1].

#### 4. Discussion

In the largest study of its kind, our analysis demonstrates that prolonging scheduled treatment days during a course of EBRT in localized Gleason 8 and higher prostate cancer may be an independent predictor of worse survival. It is important to note that this is a highly selected group of patients and, therefore, these conclusions cannot be applied broadly to all prostate cancers, especially lower risk prostate cancers. We specifically focused on Gleason groups 4 and 5 tumors, as this is the strongest indicator of intrinsic biological aggressiveness among the components considered in traditional “risk groups” [17]. There may be a biologic explanation



**Fig. 2.** Kaplan Meier survival curve for all patients completing EBRT within and beyond 3 missed treatment days. Kaplan Meier curves for overall survival among patients who missed 3 days or less of EBRT (blue) and over 3 days of EBRT (green), where the x-axis represents the time in months and the y-axis represents the survival probability. At 6-years, the OS was 79.5% for the former and 72.5% for the latter ( $p = 0.0006$ ). Abbreviations: EBRT: external beam radiation therapy, OS: overall survival. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 2**  
Summary of timing parameters.

Timing Parameter	Median days (range)	ROC value	HR for death beyond ROC value*	Difference in 6-year survival^	HR for death (continuous variable)
Missed Days	0 (0–10)	3	<b>1.26 (P = 0.005)</b>	8.0%	<b>1.027 (P &lt; 0.001)</b>
Time from ADT to EBRT	63 (0–180)	74	<b>1.20 (P = 0.01)</b>	1.9%	1.00 (P = 0.62)
Time from Dx to ADT	36 (0–180)	43	0.87 (P = 0.10)	–5.8%	0.99 (P = 0.12)

Abbreviations: ROC, receiver operating characteristic; HR, hazard ratio; Dx, diagnosis; Tx, treatment (either androgen deprivation therapy or radiotherapy); \*With propensity matching; ^Based on Kaplan Meier analysis on propensity-matched pseudopopulation.

for this, as some studies indicate that high Gleason tumors have a higher alpha–beta ratio than the 1.5 value that is typically ascribed to adenocarcinoma of the prostate [12,13]. Per various radiobiologic models, this not only suggests that high grade prostate tumors may be less sensitive to changes in dose per fraction than their indolent counterparts, but they are also sensitive to completion time, perhaps because they take less time to undergo accelerated repopulation [18,19]. Such phenomena has been well established in malignancies with alpha beta ratios closer to 10, such as in cancers of the cervix, head and neck, and lung, where local control rates are reduced by 0.5–1% for every missed treatment day [7,9].

Although the *a priori* number of 3 prolonged treatment days was used in this study for the purposes of propensity matching, the more statistically robust evaluation lies with the multivariable regression analysis using “prolonged treatment” as a continuous variable, which indicate that for every day beyond the minimum

required to complete EBRT, the hazard ratio for death increased by 2.7%. That number may be exaggerated relative to a real-life setting, but it should be noted that the correlation between treatment duration and outcome exists as a continuous spectrum, rather than just those who extended treatment over 3 days (which makes no distinction between those who missed 4 or 10 days). Equally noteworthy, time from diagnosis to ADT and time from ADT to EBRT (each up to 6 months) had no correlation with survival as continuous variables with any of the multivariable analyses. Although not tested in high risk disease, the latter has been corroborated with a phase III randomized trial by Malone et al., where there was no statistical difference in biochemical failure free survival between those who initiated ADT at the same time as EBRT or 6 months prior to it [20].

Other independent correlates of improved survival were not particularly surprising, such as younger age, lower comorbidity score, lower PSA, and lower Gleason grade group. Although Asian

**Table 3**  
Multivariable analysis for survival.

Table 2. Multivariable Cox Proportional Hazards Models for Survival				
Characteristics	Without Propensity Score		Propensity Score-Adjusted	
	Hazard of Death(95% CI)	P Value	Hazard of Death(95% CI)	P Value
Missed days				
≤ 3 days	Reference		Reference	
> 3 days	1.26 (1.10–1.44)	<b>&lt;0.001</b>	1.26 (1.07–1.48)	<b>0.005</b>
Age (continuous variable)				
	1.04 (1.03–1.05)	<b>&lt;0.001</b>	1.03 (1.02–1.04)	<b>&lt;0.001</b>
Comorbidity score (Charlson-Deyo)				
0	Reference		Reference	
1	1.24 (1.06–1.45)	<b>0.001</b>	1.08 (0.87–1.35)	0.46
2 or higher	1.62 (1.19–2.19)	<b>&lt;0.001</b>	1.54 (1.00– 2.37)	<b>0.05</b>
Race				
White	Reference		Reference	
Black	0.89 (0.74–1.09)	0.26	0.83 (0.65–1.09)	0.18
Other (mostly Asian)	0.51 (0.32–0.78)	<b>0.002</b>	0.47 (0.26–0.87)	<b>0.02</b>
Income (dollars)				
>48,000	Reference			
< 48,000	1.23 (1.01–1.49)	<b>0.04</b>	–	–
PSA				
<10	Reference		Reference	
10–19.9	1.31 (1.15–1.50)	<b>&lt;0.01</b>	1.36 (1.13–1.64)	<b>0.001</b>
20–40	1.54 (1.31–1.81)	<b>&lt;0.01</b>	1.69 (1.36–2.11)	<b>&lt;0.001</b>
Gleason grade group				
4	Reference		Reference	
5	1.29 (1.15–1.45)	<b>&lt;0.001</b>	1.32 (1.12–1.55)	<b>&lt;0.001</b>
Radiation dose				
< 78 Gy	Reference		–	–
≥ 78 Gy	0.87 (0.77–0.98)	<b>0.03</b>	0.82 (0.69–0.97)	<b>0.02</b>

Abbreviations: CI, confidence interval; bold indicates statistical significance.

patients were associated with improved survival, as has been previously demonstrated [21,22], interestingly there was no such correlation with outcome for white relative to black patients. This is incongruent with other published studies including other prostate cancer analyses using the NCD [23,24], and the reasons are unclear. However, perhaps the baseline aggressiveness of Gleason 8–10 disease supersedes any potential biologic difference attributed to race (which is also a controversial and widely debated concept) [25,26]. Given that the current study demonstrates missed treatment days to be independently associated with survival detriment in conjunction with a greater likelihood of prolonged treatment days for African American patients, these data appear to support the hypothesis that other factors, such as health disparities, may contribute more to disparate outcomes than tumor biology alone. Regardless, if missed treatment days truly do correlate with outcome, then the substantial correlation between African American patients and missed days should be added to the growing list of healthcare disparities that clinicians and epidemiologists need to address.[27]

Another notable independent predictor of improved survival is a dose of 78 Gy or higher. The lower limit dose included on this study was 74 Gy, which is considered to be an “escalated” dose relative to prior historical doses in dose escalation studies;[28] however, more recent non-randomized evidence suggests that doses above 80 Gy lead to improved biochemical control [29]. Additionally, brachytherapy boosts, which delivers a considerably higher equivalent dose to the prostate, have demonstrated better control rates in a randomized trial,[1] and improved survival in non-randomized but prospective meta-analyses [17]. A reasonable argument can be made that a brachytherapy boost mitigates any outcome discrepancies due to prolonged treatment days with EBRT. However, studies show a higher rate of long-term grade 3 toxicities with brachytherapy,[1] and the utility rate of brachytherapy has constantly diminished over time, leaving the combination of EBRT and ADT as the most commonly employed non-surgical treatment modality for high risk prostate cancer [30].

In the absence of brachytherapy, another strategy to mitigate prolonged treatment duration is with hypofractionation, which is rapidly replacing conventional fractionation in low and intermediate risk disease following the publication of multiple phase III trials and new guidelines.[31–35] Patients have considerably more opportunity to miss treatment days during a 44-fraction course compared to a 28-fraction course, and it is also possible that the higher dose per fraction more effectively mitigates the negative impact of missed treatments with conventional fractionation. However, currently, the hypofractionation data are very limited and not yet mature in high risk disease, which is why it has not yet reached consensus recommendation per the ASTRO/AUA, and is still not broadly utilized nationwide [31,36]. Until such data are published, conventionally fractionated radiotherapy will likely remain a standard of care in high risk disease.

No large, retrospective analysis is immune to inherent selection bias, and our study is no different. However, the highly selected patient population also allowed us to analyze a relatively homogeneous cohort, the lack of which often limits NCD analyses. Such homogeneity is demonstrated by the fact that the propensity-matched multivariable Cox regression analysis closely approximates the non-propensity matched model. That is not to suggest that this study is devoid of selection bias—as patients who prolonged treatment over 3 days were also more likely to be of lack race, treated in a community setting, have higher comorbidity scores and PSA, and be treated to <78 Gy. The latter three variables were all independent predictors of survival, although the magnitude of disproportionality was small, which is likely why the asymmetry between cohorts did not appear to impact the influence of missed treatment days on survival with multivariable analysis. Furthermore, the two strongest predictors of survival - age and Gleason group - were nearly identical between groups. Since prostate cancer patients often do not die from their disease, a more pertinent endpoint would have been cancer specific mortality, which unfortunately the NCD does not collect. However, we intentionally only selected high risk patients partly because this particular

selection of patients are for more likely to have their mortality affected by prostate cancer compared with other risk groups. Another potential criticism of this study is that prolonged treatment could serve as a surrogate for overall noncompliance, which might include a discontinuation of ADT before the recommended duration, missed follow-ups, and/or non-adherence to recommended salvage therapies. While we cannot control for such factors using this database, we did limit the maximum number of prolonged treatment days to 10, and 90% of those who prolonged any treatments missed only between 1 and 7 days. Furthermore, in order to be a surrogate for noncompliance, one would expect that those with multiple missed treatment days would also correlate with a delay to the initiation of ADT or EBRT, and no such correlation exists, as demonstrated on Table 1.

## 5. Conclusion

This novel study suggests that prolonging the duration of radiotherapy for Gleason group 4 and 5 prostate cancers treated definitively with ADT and conventionally fractionated EBRT can result in poorer outcomes. Ideally, this would be evaluated in a prospective fashion; however, such an unethical study design prohibits such trials from being conducted. The conclusions here are hypothesis generating, and do challenge the conventionally held notion that the typically indolent nature of prostate cancer necessarily makes it insensitive to treatment duration of EBRT. Rather, there may be a certain prostate cancer population with aggressive disease who benefit from adhering to a strict radiation schedule, further highlighting the importance of appropriate patient selection.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

None.

## Appendix A. Supplementary Fig. 1

Supplementary Fig. 1 Forest plot of variables significantly correlated with survival on multivariable analysis to this article can be found online at <https://doi.org/10.1016/j.ctro.2020.11.006>.

## References

- [1] Morris WJ, Tyldesley S, Rodda S, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2017;98(2):275–85. <https://doi.org/10.1016/j.ijrobp.2016.11.026>
- [2] Wang Z, Ni Y, Chen J, et al. The efficacy and safety of radical prostatectomy and radiotherapy in high-risk prostate cancer: A systematic review and meta-analysis. *World J Surg Oncol* 2020;18(1):42. <https://doi.org/10.1186/s12957-020-01824-9>
- [3] Lai PP, Pilepich Mv, Krall JM, et al. The effect of overall treatment time on the outcome of definitive radiotherapy for localized prostate carcinoma: The radiation therapy oncology group 75–06 and 77–06 experience. *Int J Radiat Oncol Biol Phys* 1991;21(4):925–33. [https://doi.org/10.1016/0360-3016\(91\)90731-J](https://doi.org/10.1016/0360-3016(91)90731-J)
- [4] Dong Y, Zaorsky NG, Li T, et al. Effects of interruptions of external beam radiation therapy on outcomes in patients with prostate cancer. *J Med Imag Radiat Oncol* 2018;62(1):116–21. <https://doi.org/10.1111/1754-9485.12675>
- [5] Amdur RJ, Parsons JT, Fitzgerald LT, Million RR. Adenocarcinoma of the prostate treated with external-beam radiation therapy: 5-year minimum follow-up. *Radiation Oncol* 1990;18(3):235–46. [https://doi.org/10.1016/0167-8140\(90\)90059-6](https://doi.org/10.1016/0167-8140(90)90059-6)
- [6] Liauw SL, Liauw SH. Prolongation of total treatment time because of infrequently missed days of treatment is not associated with inferior biochemical outcome after dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;81(3):751–7. <https://doi.org/10.1016/j.ijrobp.2010.06.054>
- [7] Murphy CT, Galloway TJ, Handorf EA, et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. *J Clin Oncol* 2016;34(2):169–78. <https://doi.org/10.1200/JCO.2015.61.5906>
- [8] Chen M, Jiang GL, Fu XL, et al. The impact of overall treatment time on outcomes in radiation therapy for non-small cell lung cancer. *Lung Cancer* 2000;28(1):11–9. [https://doi.org/10.1016/S0169-5002\(99\)00113-0](https://doi.org/10.1016/S0169-5002(99)00113-0)
- [9] Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;32(5):1275–88. [https://doi.org/10.1016/0360-3016\(95\)00220-5](https://doi.org/10.1016/0360-3016(95)00220-5)
- [10] Graf R, Wust P, Hildebrandt B, et al. Impact of overall treatment time on local control of anal cancer treated with radiochemotherapy. *Oncology* 2003;65(1):14–22. <https://doi.org/10.1159/000071200>
- [11] McMillan MT, Ojerholm E, Verma V, et al. Radiation Treatment Time and Overall Survival in Locally Advanced Non-small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2017;98(5):1142–52. <https://doi.org/10.1016/j.ijrobp.2017.04.004>
- [12] Vogelius IR, Bentzen SM. Meta-analysis of the alpha/beta ratio for prostate cancer in the presence of an overall time factor: Bad news, good news, or no news? *Int J Radiat Oncol Biol Phys* 2013;85(1):89–94. <https://doi.org/10.1016/j.ijrobp.2012.03.004>
- [13] Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-Fractionation Sensitivity of Prostate Cancer Deduced from Radiotherapy Outcomes of 5,969 Patients in Seven International Institutional Datasets:  $\alpha/\beta = 1.4$  (0.9–2.2) Gy; 2012. doi:10.1016/j.ijrobp.2010.10.075.
- [14] Spratt DE, Zhao SG, Chang SL, et al. Identification and Validation of Intrinsic Subtypes of Prostate Cancer. *Int J Radiat Oncol • Biol • Phys* 2016;96(2):S3–4. <https://doi.org/10.1016/j.ijrobp.2016.06.025>
- [15] Hasan S, White R, Renz P, et al. Optimal timing of thoracic radiotherapy in limited stage small cell lung cancer (SCLC) with daily fractionation: A brief report. *Radiation Oncol* 2019;132:23–6. <https://doi.org/10.1016/j.radonc.2018.11.005>
- [16] Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivar Behav Res* 2011;46(3):399–424. <https://doi.org/10.1080/00273171.2011.568786>
- [17] Kishan AU, Cook RR, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with gleason score 9–10 prostate cancer. *JAMA - J Am Med Assoc* 2018;319(9):896–905. <https://doi.org/10.1001/jama.2018.0587>
- [18] Alpha-Beta Ratio - an overview | ScienceDirect Topics. <https://www.sciencedirect.com/topics/medicine-and-dentistry/alpha-beta-ratio>. Accessed May 7, 2020.
- [19] Cosset JM, Chargari C, Créange G. Which alpha/beta ratio for prostate cancer in 2019? *Cancer/Radiation Oncol* 2019. <https://doi.org/10.1016/j.canrad.2019.01.004>
- [20] Malone S, Roy S, Eapen L, et al. Sequencing of androgen-deprivation therapy with external-beam radiotherapy in localized prostate cancer: A Phase III randomized controlled trial. *J Clin Oncol* 2020;38(6):593–601. <https://doi.org/10.1200/JCO.19.01904>
- [21] Robbins AS, Koppie TM, Gomez SL, Parikh-Patel A, Mills PK. Differences in prognostic factors and survival among white and Asian men with prostate cancer, California, 1995–2004. *Cancer* 2007;110(6):1255–63. <https://doi.org/10.1002/cncr.22872>
- [22] Man A, Pickles T, Chi KN, et al. Asian race and impact on outcomes after radical radiotherapy for localized prostate cancer. *J Urol* 2003;170(3):901–4. <https://doi.org/10.1097/01.ju.0000081423.37043.b4>
- [23] Mahal BA, Chen YW, Efstathiou JA, et al. National trends and determinants of proton therapy use for prostate cancer: A National Cancer Data Base study. *Cancer* 2016;122(10):1505–12. <https://doi.org/10.1002/cncr.29960>
- [24] Roach M, Krall J, Keller JW, et al. The prognostic significance of race and survival from prostate cancer based on patients irradiated on radiation therapy oncology group protocols (1976–1985). *Int J Radiat Oncol Biol Phys* 1992;24(3):441–9. [https://doi.org/10.1016/0360-3016\(92\)91058-U](https://doi.org/10.1016/0360-3016(92)91058-U)
- [25] Dess RT, Hartman HE, Mahal BA, et al. Association of Black Race with Prostate Cancer-Specific and Other-Cause Mortality. *JAMA Oncol* 2019;5(7):975–83. <https://doi.org/10.1001/jamaoncol.2019.0826>
- [26] Radiation therapy outcomes better for African-American prostate cancer patients than Caucasian patients - American Society for Radiation Oncology (ASTRO) - American Society for Radiation Oncology (ASTRO). <https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2018/Radiation-therapy-outcomes-better-for-African-Amer>. Accessed May 7, 2020.
- [27] Polite BN, Adams-Campbell LL, Brawley OW, et al. Charting the future of cancer health disparities research: A position statement from the American association for cancer research, the American cancer society, the American society of clinical oncology, & the national cancer institute. *J Clin Oncol* 2017;35(26):3075–82. <https://doi.org/10.1200/JCO.2017.73.6546>
- [28] Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: Long-term results from the MRC

- RT01 randomised controlled trial. *LancetOncol* 2014;15(4):464–73. [https://doi.org/10.1016/S1470-2045\(14\)70040-3](https://doi.org/10.1016/S1470-2045(14)70040-3).
- [29] Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H. Long-Term Outcome of High Dose Intensity Modulated Radiation Therapy for Patients With Clinically Localized Prostate Cancer. *J Urol* 2006;176(4):1415–9. <https://doi.org/10.1016/j.juro.2006.06.002>.
- [30] Eisenstein M. The declining art of brachytherapy. *Nature* 2019;574(7780):S81. <https://doi.org/10.1038/d41586-019-03275-z>.
- [31] Morgan SC, Hoffman K, Andrew Loblaw D, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline Conflict of Interest Disclosure Statement.; 2018.
- [32] Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *LancetOncol* 2016;17(8):1061–9. [https://doi.org/10.1016/S1470-2045\(16\)30070-5](https://doi.org/10.1016/S1470-2045(16)30070-5).
- [33] Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017;35(17):1884–90. <https://doi.org/10.1200/JCO.2016.71.7397>.
- [34] Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *LancetOncol* 2016;17(8):1047–60. [https://doi.org/10.1016/S1470-2045\(16\)30102-4](https://doi.org/10.1016/S1470-2045(16)30102-4).
- [35] Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol* 2016;34(20):2325–32. <https://doi.org/10.1200/JCO.2016.67.0448>.
- [36] Stokes WA, Kavanagh BD, Raben D, Pugh TJ. Implementation of hypofractionated prostate radiation therapy in the United States: A National Cancer Database analysis. *Pract Radiat Oncol* 2017;7(4):270–8. <https://doi.org/10.1016/j.prro.2017.03.011>.