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Original Research Article

Treatment interruptions affect biochemical failure rates in prostate cancer patients treated with proton beam therapy: Report from the multi-institutional proton collaborative group registry

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ABSTRACT

Introduction: To date, no studies examining the effect of treatment interruptions (TI) with proton beam therapy (PBT) have been published. The goal of our study was to determine the predictors of TI amongst patients with prostate cancer (PCa) treated with PBT and to determine whether TI are associated with biochemical failure (BF). We hypothesized that any correlation between TI and biochemical control would be more pronounced in high risk groups.

Methods: Data for 4278 patients with PCa was obtained from the prospectively collected Proton Collaborative Group (PCG) data registry. Univariate and multivariate logistic regression analysis (MVA) was used to model possible predictors of BF. A subset analysis was performed for high risk patients treated with ADT and PBT. Finally, propensity score (PS) analysis was performed to account for any indication bias caused by lack of randomization.

Results: Total treatment duration (OR, 1.05 [1.04–1.06]; $p < 0.001$) increased the likelihood of TI on MVA. TI did not have a statistically significant correlation with BF (OR, 1.44 [0.86–2.39]; $p = 0.162$) amongst PS matched patients. However, on subset analyses of high risk group patients with PS matching, there was a trend towards worse BF in patients with TI (OR 3.85; 95%CI (0.96–15.44); $p = 0.057$).

Conclusion: In the first analysis of its kind, the results suggest that TI in high risk PCa patients treated with PBT and ADT have worse BF rates. Interventions such as increased patient education, proper maintenance of proton facilities, and decreasing total treatment duration with alternative fractionation schedules may help avoid the unintended negative effects on tumor control due to TI. However, future analyses on a larger patient population is needed.

1. Introduction

Annually in the United States, prostate cancer (PCa) accounts for 21% (191,930) of incident cancer cases in men [1]. Until recently, standard definitive external beam radiation treatment (EBRT) lasted for eight weeks. Although this remains a frequently implemented fractionation regimen, the adoption of hypofractionation continues to increase, decreasing total treatment duration in half. Regardless of treatment length, many patients have unintentional treatment interruptions (TI), which may increase tumor repopulation and affect tumor control rates.

Generally, we prescribe the total radiation dose within a specific time frame based on the theory that any treatment prolongation results in worse tumor control rates [2]. Historically, TI in anal[3],

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cervical[4], lung[5,6], and head and neck[7] cancers result in inferior outcomes as a result of their rapid proliferation and repopulation. In contrast to these malignancies, PCa has a more indolent natural course, and >80% of men survive ten[1] years after their initial diagnosis[8,9]. Furthermore, >60% of those deceased die from non-cancer related causes[10].

Several retrospective analyses examined the effect of TI in PCa patients treated with definitive EBRT with varying and conflicting results[11–17]. D'ambrosio et al found TI to be an adverse factor for biochemical failure (BF) in low risk patients, whereas Thames et al found inferior BF rates in low and intermediate risk patients. Amdur et al found worse local control (LC) in patients with radiation treatment (RT) time >8 weeks. Although the analyses by Amdur predated the PSA era, they included patients who would currently be staged as T3b. The remaining analyses[12,13,15,17] found no difference in patients with or without TI. In addition, all previous studies used EBRT treatments with photons.

To date, no studies examining the effect of TI with proton beam therapy (PBT) exist. The goal of our study was to identify predictors of TI amongst PCa patients treated with PBT and determine whether TI are associated with biochemical failure (BF), partitioned by risk groups. Specifically, we hypothesized that any correlation between TI and biochemical control would be more pronounced in high risk groups due to their more aggressive nature.

2. Methods

2.1. Database and patient population

We obtained data for this study from the prospectively collected Proton Collaborative Group (PCG) data registry. This study is an institutional review board–approved analysis of the multi-institutional PCG data registry of 4278 consecutive PCa patients treated with definitive PBT between 1995 and 2019.

2.2. Cohort definition

4278 patients with newly diagnosed and biopsy confirmed PCa were identified. Patient treatment reflected clinical decision making at the time of diagnosis and RT dates were required. Selected patients were required to have definitive PBT. In addition, patients with missing diagnosis, unknown risk group, or unavailable follow up information were excluded. Our study cohort comprised 2794 patients (Fig. 1).

2.3. Statistical analysis

TI are reported within the PCG registry as a treatment course completed beyond the initially scheduled end date. Treatment initiation and termination dates were also reported but too many were absent for inclusion as a variable. Therefore, TI were analyzed as a binary variable. Comparison of continuous and categorical variables were assessed by ANOVA and Pearson chi-square, respectively. Univariate and multivariate logistic regression analyses (MVA) were used to model possible predictors of BF including age, gender, race, radiation fractionation schedule, EQD2, ADT use, and tumor characteristics. A similar subset analysis was performed for high risk patients treated with ADT and PBT. We defined statistical significance as $p < 0.05$.

2.4. Survival and biochemical control data analysis

Kaplan–Meier product-limit estimates with time-to-event curves were generated. Outcomes were compared by demographic, clinical, and treatment variables using the log-rank test. Outcome was BF, with follow-up time and time to event from date of diagnosis until PSA increased by >2 from nadir. The median interquartile range (IQR) follow-up time was 24.5 months (12–44.8). Additional calculations of hazard ratio (HR) with Wald 95% confidence interval (CI) and reference groups were performed. MVA to identify predictors of TI was adjusted for age, race, radiation fractionation schedule, EQD2, and ADT use. In order to avoid multiparameter testing, factors significant on univariate analysis were entered in hierarchical fashion using forward selection of the covariates likelihood ratios, and for confirmation, the same results were obtained using stepwise backward elimination procedure. Additional univariate and MVA were performed for the subset of high risk PCa patients. All statistical tests are two-sided, and analyses were performed using Medcalc version 22.

2.5. Propensity score matching

Propensity score (PS) analysis was derived by a MVA model reflecting the conditional probability of having TI or not having TI. The propensity model contained observable variables including age, race, EQD2, hypofractionation, ADT usage, and risk group [18,19]. Patients were propensity matched 1:1 into TI and no TI groups. Construction of a pseudopopulation using case control functions with exact matches yielded a matched population of 184 patients per group. Balance in baseline covariates before and after matching was examined by evaluating standardized mean differences with mirror histograms[20]. Standardized differences <10% were considered to be sufficiently matched. BF was compared between TI and no TI groups using Kaplan-Meier method by log-rank test.

3. Results

3.1. Baseline Characteristics, by treatment group

The baseline characteristics of all patients are presented in Table 1. Of the 4,278 patients with PCa prospectively enrolled between 1995 and 2019, there were a total of 2,794 in our cohort who underwent definitive PBT. The majority were white (89.7%) with a median age of 68 years (range 40–92). Among all patients, 693 (24.8%) were low, 869 (31.1%) favorable intermediate, 627 (22.4%) unfavorable intermediate, and 605 (21.7%) high risk. Only 676 patients (24.2%) were treated with ADT, and 312 (11.2%) of patients were treated with hypofractionation (dose range 57.5–120.7 Gy at 2.4–7.0 Gy per fraction). The median EQD2 for total dose was 75 Gy (74–89). A total of 901 (32.2%) patients had TI of at least one day. The median pre-treatment IPSS score for all patients was 6 (IQR 7). Significant differences did not exist between the baseline characteristics of patients with or without TI (see Table 2).

3.2. Predictors of treatment interruptions

The predictors of BF are presented in Table 2. Patients with high risk disease were less likely to have TI (OR, 0.72 [0.54–0.97]; $p = 0.03$) whereas total treatment duration (OR, 1.05 [1.04–1.06]; $p < 0.001$) increased the likelihood of TI on MVA. We found no correlation between TI and other variables such as age, ethnicity, treatment with ADT, and hypofractionation.

3.3. Factors associated with biochemical failure

The median follow up time for the no TI and TI groups were 24.5 and 24.7 months respectively. At last follow up, 99.2% of patients

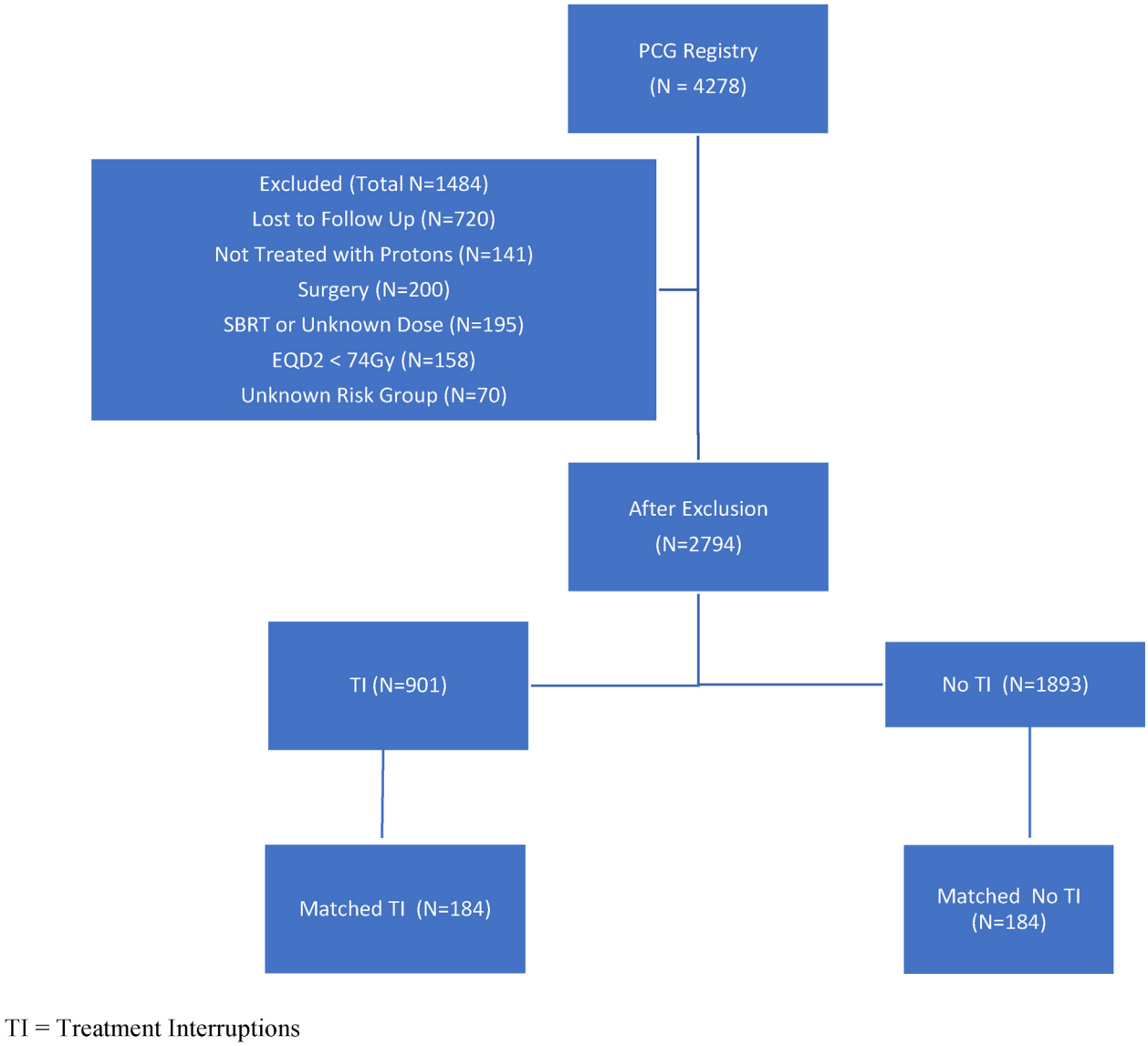

Fig. 1. CONSORT Diagram of Patient Cohort. TI = Treatment Interruptions.

were alive. The median survival was not reached because overall survival (OS) rates were so high.

The MVA of variables associated with BF among all patients are presented in Table 3. In general, patients with higher risk group disease tended to have statistically significant correlations with increasing BF rates among all patients. Patients treated with ADT (OR, 1.80[1.09–2.97]; p = 0.021) and disease categorized as favorable intermediate (OR, 2.66[1.05–6.75]; p < 0.004), unfavorable intermediate (OR, 5.31[2.12–13.33]; p < 0.001), and high risk (OR, 6.24[2.39–16.30]; p < 0.001) tended to have worse BF with statistical significance on binomial regression MVA. However, on Cox regression MVA, treatment with ADT did not have a statistically significant association with BF (OR, 1.33[0.80–2.19]; $p \leq 0.270$). No correlation exists between radiation dose fractionation or EQD2 and BF rates. Each of the disease specific risk groups, favorable intermediate (OR, 3.14[1.25–7.90]; p < 0.015), unfavorable intermediate (OR, 6.07[2.45–15.08]; p < 0.001), and high risk (OR, 9.56[3.65–25.03]; p < 0.001) maintained their statistically significant correlation with BF on Cox regression MVA.

Neither the TI nor no TI groups met the median overall BF free time point. The overall failure rates did not differ between the no TI and TI groups (3.01% vs 3.89%; p = 0.24). At five years, the BF rates in the no TI and TI groups were 93.1% and 92.7% respectively. The overall BF rates for all patients including hypofractionation versus those treated specifically with conventional fractionation were 4.17% vs 3.24% (p = 0.22). TI did not have a statistically significant correlation with overall BF (HR 1.30 [0.85–2.0]; p = 0.24) on MVA.

Within the high risk group of 385 patients treated with ADT, 100 had TI. The median biochemical free survival was not reached for either TI or no TI groups. The BF rate for the TI group trended higher than for the no TI group (13% vs 6%, HR = 2.10 [0.95–4.67]; p = 0.066 with Kaplan Meier method) (HR 1.94 [0.94–4.01]; p = 0.078 with Cox proportional hazards regression analysis). TI were associated with a statistically significant increase in BF rate on binomial MVA at a median follow up of 79 months (HR 2.32[1.06 – 5.10]; p = 0.035) (Table 4). This did not remain statistically significant on Cox regression MVA, although it did trend towards significance (HR, 2.00 [0.94–4.24]; p = 0.068).

3.4. Propensity score analysis

PS matched analysis 1:1 of TI (N = 184) to no TI (N = 184) was performed and patient characteristics were well balanced amongst both groups. Among matched patients, those with higher risk

Table 1
Baseline patient, tumor and treatment characteristics.

Characteristic	No. (%) N = 2794
Age	
Median	68
Range	40–92
Ethnicity	
White	2505(89.7)
Black	222(7.9)
Other	67(2.4)
Risk Group	
Low	693(24.8)
Favorable Intermediate	869(31.1)
Unfavorable Intermediate	627(22.4)
High	605(21.7)
Treatment with ADT	
No	2118(75.8)
Yes	676(24.2)
Treatment with hypofractionation	
No	2482(88.8)
Yes	312(11.2)
Treatment Interruption	
No	1893(67.8)
Yes	901(32.2)

group disease tended to have higher BF rates: favorable intermediate (OR 6.08[1.35–27.30]; p = 0.019), unfavorable intermediate (OR 11.89[2.68–52.75]; p = 0.001), and high risk (OR 21.94[4.81–100.10]; p < 0.001) (Table 5). TI did not have a statistically significant correlation with BF (OR 1.44[0.86–2.39]; p = 0.162). However, there was a trend towards worse BF in patients with TI (OR 3.85 [0.96–15.44]; p = 0.057) (Fig. 2 and Table 6), on subset analyses of high risk group patients.

4. Discussion

During RT, the goal is to provide continuous treatment daily Monday to Friday. However, unintended toxicities, obligations, or other medical illness may lead to TI. Several retrospective analyses examined the effect of TI in PCa patients treated with definitive EBRT.

The previous analyses conclude that TI for PCa patients generally do not have significant effects on treatment outcomes. However, none specifically examined the effect of TI on PCa patients treated with PBT. Lai et al[12] found that total duration of RT had no effect on survival, local control, or complications in all groups of PCa patients treated with a median dose of 63 Gy. A pooled analysis from Radiation Therapy Oncology Group (RTOG) trials 75–06 and 77–06[17] also found no differences in LC, disease-free survival, or OS. Amdur et al[11] reported worse LC in patients treated with 65–70 Gy in patients who had a total treatment time >8 weeks. However, the criticisms of these earlier studies emphasize the insufficient total dose and analyses during a pre-PSA era, which is now used to group patients into risk categories.

Several additional retrospective analyses regarding TI in PCa have been published in the modern era of dose escalation. Liauw et al[13] analyzed 596 patients (30% high risk) treated to a median dose of 72 Gy and found that those not receiving ADT had a lower freedom from BF rate with more missed days of treatment. However, this association was not seen in patients treated with doses $\geq$ 74 Gy.

Dong et al[15] reported outcomes on PCa patients treated with a dose $\geq$ 74 Gy, excluding those on ADT, and found no differences with outcomes in disease risk group using a 4 fraction threshold to define a lengthy treatment break. D'ambrosio et al[16] identified an increased non-treatment day ratio (NTDR, number of non-treatment days divided by the total elapsed days of RT) as an adverse factor in PCa patients treated with a median dose of 76 Gy, specifically in low-risk patients, but not intermediate, high, or all groups combined. Thames et al confirmed the significance of NTDR for low risk groups but not in other groups. None of these analyses found a specific association with treatment outcomes with TI in high risk groups.

We found a statistically significant association with TI and BF for high risk PCa on MVA (HR 2.32 [1.06 – 5.10]; p = 0.035). This did not remain significant on Cox regression MVA, although it trended towards significance (HR 2.00[0.95–4.24]; p = 0.068). These results indicate that TI in high risk PCa patients treated with ADT may lead to worse BF rates. However, longer follow up time is required to detect any change in OS, even in high risk disease which has a 9-year survival>75% [21].

Generally, operation of a proton center requires methodical weekly preventive maintenance plans supported by highly trained service personnel with a comprehensive supply of spare parts. No proton centers in the United States have a co-located backup pro-

Table 2
Univariate and Multivariate Predictors of Treatment Interruptions.

	Treatment Group		Association with Treatment Interruptions Multivariate Analysis	
Characteristic	No TI	TI	OR (95% CI)	P
Age				
Median	67	67	0.99(0.98–1.01)	0.09
Ethnicity				
White	1579(83.4)	773(85.8)	Reference	
Black	148(7.8)	74(8.2)	1.0(0.74–1.35)	0.99
Other	166(8.8)	54(6.0)	1.33(0.81–2.18)	0.27
Risk Group				
Low	439(23.2)	254(28. 2)	Reference	
Favorable Intermediate	567(29.9)	302(33.5)	0.98(0.79–1.22)	0.85
Unfavorable Intermediate	444(23.5)	183(20.3)	0.81(0.63–1.03)	0.09
High	443(23.4)	162(18.0)	0.72(0.54–0.97)	**0.03**
Treatment with ADT				
No	1406(74.3)	712(79.0)	Reference	
Yes	487(25.7)	189(21.0)	0.94(0.74–1.17)	0.56
Treatment with Hypofractionation				
No	1665(88.0)	817(90.7)	Reference	
Yes	228(12.0)	84(9.3)	0.76(0.59–1.00)	0.058
Total Treatment Days			1.05(10.4–1.06)	**<0.001**

TI = treatment interruptions.

Table 3
Multivariate Analysis of Variables Associated with Biochemical Failure Among All Patients.

	Binomial Regression		Cox Regression	
Characteristic	OR (95% CI)	P	OR (95% CI)	P
Age	0.99(0.96–1.01)	0.326	1.00(0.97–1.03)	0.935
TI				
No	Reference		Reference	
Yes	1.27(0.81–2.01)	<0.30	1.43(0.94–2.19)	0.097
ADT				
No	Reference		Reference	
Yes	1.80(1.09–2.97)	**0.021**	1.33(0.80–2.19)	0.270
Risk Group				
Low	Reference		Reference	
Favorable Intermediate	2.66(1.05–6.75)	**0.004**	3.14(1.25–7.90)	**0.015**
Unfavorable Intermediate	5.31(2.12–13.33)	**<0.001**	6.07(2.45–15.08)	**<0.001**
High	6.24(2.39–16.30)	**<0.001**	9.56(3.65–25.03)	**<0.001**
Ethnicity				
White	Reference		Reference	
Black	0.52(0.20–1.31)	0.164	0.67(0.27–1.66)	0.384
Other	0.84(0.20–3.55)	0.812	1.20 (0.29–4.91)	1.20
Hypofractionation				
No	Reference		Reference	
Yes	0.60(0.12–3.03)	0.054	0.72(0.22–2.34)	0.59
EQD2 > 74	0.90(0.69–1.17)	**0.044**	0.99 (0.90–1.09)	0.908

Table 4
Multivariate Analysis of Variables Associated with Biochemical Failure Among High Risk Patients Treated with ADT.

	Binomial Regression		Cox Regression	
Characteristic	OR (95% CI)	P	OR (95% CI)	P
Age	0.95(0.90–1.00)	0.058	0.97(0.92–1.01)	0.163
TI				
No	Reference		Reference	
Yes	2.32(1.06–5.10)	**0.035**	2.00(0.95–4.24)	0.068
Ethnicity				
White	Reference		Reference	
Black	0.88(0.24–3.22)	0.848	1.30(0.38–4.48)	0.673
Other	1.54(0.18–12.96)	0.692	3.01(0.39–23.07)	0.289
Hypofractionation				
No	Reference		Reference	
Yes	4.32(0.22–83.7)	0.334	6.85(0.58–81.06)	0.127
EQD2 > 74	0.79(0.48–1.30)	0.353	0.90(0.64–1.27)	0.535

Table 5
Propensity Score Matched Analysis of Biochemical Failure Among All Patients.

Characteristic	OR (95% CI)	P
Age	1.00(0.97–1.04)	0.943
TI		
No	Reference	
Yes	1.44(0.86–2.39)	0.162
ADT		
No	Reference	
Yes	1.25(0.68–2.29)	0.469
Risk Group		
Low	Reference	
Favorable Intermediate	6.08(1.35–27.30)	**0.019**
Unfavorable Intermediate	11.89(2.68–52.75)	**<0.001**
High	21.94(4.81–100.10)	**<0.001**
Ethnicity		
White	Reference	
Black	1.05(0.41–2.66)	0.925
EQD2 > 74	0.98(0.85–1.14)	0.814

ton source in case the primary source fails. Recent analyses have found that most maintenance and accelerator shutdowns occur on weekends when major pieces of equipment are turned off and/or being serviced, from power failures, and from inclement weather. Since most radiation treatment centers have multiple linear accelerators, patients can often easily be moved to other units when one becomes non-functional[22]. Conversely, all proton treatment rooms rely on a single cyclotron or synchroton for treatment, so patients cannot be moved from one machine to another. Even when the proton source is not the cause of missed treatments, few multi-center proton facilities currently have all matched rooms to allow immediate treatment resumption in a different room when one is down, and this is not an option in single-room facilities. Our results highlight the necessity to continuously strive for improved performance metrics related to the maintenance and operating procedures of a proton facility to minimize the chance of TI for high risk patients treated with ADT.

As expected, we found that total treatment duration (OR 1.05 [1.04–1.06]; $p < 0.001$) increased the likelihood of TI on MVA. Hypofractionation for PCa decreases the total duration of treatment from 8 weeks to 4–5 weeks. RTOG 0415 trial[23], CHHiP trial[24], PROFIT [25], the HYPRO[26], and an Italian trial by Arcangeli et al[27] found no differences in tumor control rates between hypofractionation and conventional fractionation. Therefore, the task force from ASTRO-ASCO-AUA[28] reached a strong agreement that providers should offer hypofractionation to PCa patients amongst all risk groups.

Despite the findings of total treatment duration correlating with TI, we found no differences in TI between patients treated with hypofractionation versus conventional treatment. However, only 11.2% of patients received hypofractionated treatment in this study, with<10 patients per each risk group. Therefore, further investigation on a larger data set can provide additional clarity as to whether a shorter total treatment duration with hypofractionation can help reduce TI. A currently open randomized phase III

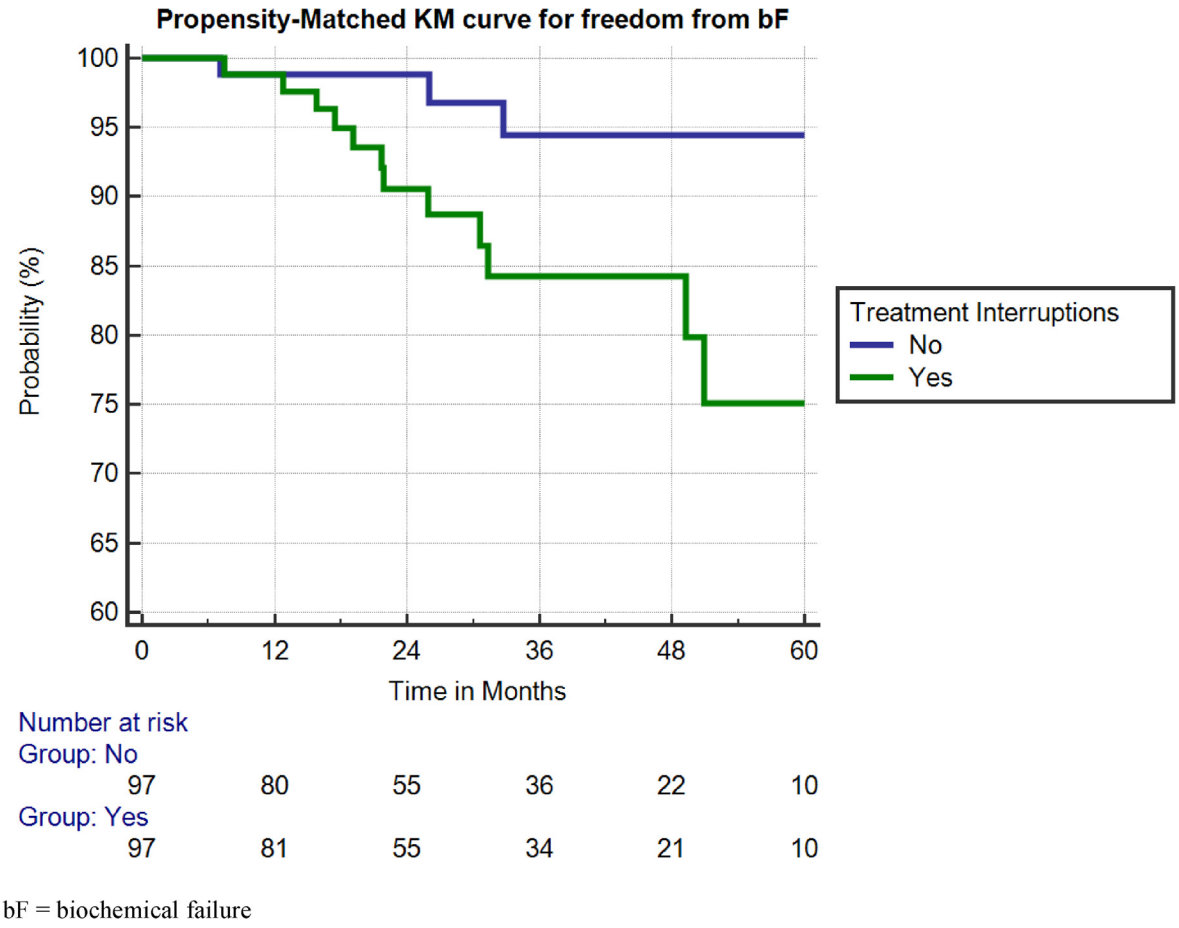

Fig. 2. Biochemical Failure For Subset of Propensity Score Matched High Risk Group Patients With and Without Treatment Interruptions. bF = biochemical failure.

Table 6
Propensity Score Matched Analysis of Biochemical Failure Among High Risk Patients Treated with ADT.

Characteristic	OR (95% CI)	P
Age	0.98(0.91–1.05)	0.532
TI		
No	Reference	
Yes	3.85(0.96–15.44)	0.057
Ethnicity		
White	Reference	
Black	1.60(0.33–7.68)	0.560
Hypofractionation		
No	Reference	
Yes	5.97(0.26–135.68)	0.262
EQD2 > 74	0.93(0.69–1.25)	0.639
IPSS	1.05(0.99–1.12)	0.102

clinical trial, COMPPARE, is comparing standard fractionation versus moderate hypofractionation between parallel cohorts of men with PCa treated simultaneously at proton therapy facilities and at geographically similar photon-based radiation facilities using intensity-modulated radiation therapy (IMRT). Future analyses of TI on the effect of BF within all risk groups, fractionation schedules, and treatment modalities between PBT and IMRT may provide additional clarification to this question.

Several investigators have found increased proliferation of epithelial and tumor cells after the initiation of RT[29,30]. Fowler et al hypothesized that RT quickly eradicates well oxygenated cells, resulting in decreased spontaneous death of remaining tumor cells, leading to accelerated repopulation with magnified effects over the course of treatment. Therefore, the inherent biology of higher risk disease probably plays a significant role in determining BF rates in this patient population. Specifically, the rapid proliferation of more aggressive and radioresistant clonogenic cells in high risk groups may be the etiology of increased BF rates with TI in these patients. In addition, high risk groups are typically treated with conventional fractionation for a duration of 8 weeks, so any TI in this patient population may be of more significance compared to others. This is also consistent with our findings that total treatment duration increased the likelihood of TI on MVA. Lengthening treatment time in general may increase the chance of both avoidable and unavoidable TI. Broader application of hypofractionation, which decreases total treatment duration by 50%, may help avoid TI from any cause. Ultimately, patients with high risk disease tend to have worse BF and OS rates. Therefore, patient self-awareness, and cognizance of their poorer prognosis may play a psychological role that contributes to a patient's adherence to their daily treatments, highlighting the importance of patient counseling and education.

Finally, data from in vitro experiments with non-small cell lung cancer[31] and glioma[32] cancer stem cells treated with PBT suggests greater cytotoxic DNA damage with inhibited repair mechanisms compared to photon treatment. Although these results are not specific to PCa, this suggests that any treatment effect related to TI may be less detrimental with PBT than with photons.

This analysis is subject to inherent limitations of a retrospective study, including the lack of clinically relevant data such as ADT duration and size of radiation field, specifically whole pelvis versus

prostate plus seminal vesicles. However, all data in this study were prospectively collected. Additionally, unlike other large aggregate datasets, the PCG data undergoes rigorous quality review by the institutions who submit the cases. As such, we were able to use an objective endpoint in BF, as opposed to local failure, or death. In addition, we did not perform subgroup analyses on the low and intermediate risk groups. However, we found that TI do not statistically correlate with BF amongst the entire patient population which suggests that these groups are driving the negative results. Unfortunately, we do not have data regarding the causes of TI which could be both from avoidable and unavoidable causes. However, there is a well established history of TI with proton centers and treatment breaks from acute toxicities are rare for PCa patients. Therefore, we can infer that the majority of TI were due to technical issues and mechanical disruptions with proton units or other logistical reasons.

Other common sources of TI are holidays, urinary or other toxicities, social and logistical issues, critical obligations, intercurrent medical illness, or machine issues. Although the various analyses presented in this study contain some degree of selection bias due to the presence of unobservable variables, we did employ several methods such as MVA and PS matching to account for as many observable variables as possible.

In the first analysis of its kind, the results suggest that TI in high risk PCa patients treated with PBT and ADT have worse BF rates. Therefore, several interventions such as increased patient education, proper maintenance of proton facilities, and decreasing total treatment duration with alternative fractionation schedules may help avoid the unintended negative effects on tumor control due to TI. However, future analyses on a larger patient population is needed.

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.

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none.

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MM reports receiving an honorarium from Varian, outside of the scope of the current work. CBS reports a Varian Medical Systems honorarium outside of the submitted work. LR reports being a simple stock holder of IBA, Gilead, and Accuray. He is also part of the speakers bureau and receives honorariums for IBA (ion beam applications).

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