Optimizing Time-to-Treatment to achieve durable biochemical disease control after surgery in prostate cancer - A multi-institutional cohort study

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Abstract

Background

The impact of treatment delays on Prostate Cancer (PCa) specific outcomes remains ill-defined. This study investigates the effect of time to treatment on biochemical disease control after prostatectomy.

Methods

This retrospective study includes 1,807 patients who received a prostatectomy as a primary treatment *at two large tertiary referral centers* from 1987 – 2015. Multivariate cox model with restricted cubic spline were used to identify optimal time to receive treatment and estimate the risk of Biochemical recurrence.

Results

Median follow up time of the study was 46 (IQR 18 – 86) months. Time to treatment was subcategorized based on multivariate cubic spline cox model. In multivariate spline model, adjusted for all the pertinent pretreatment variables, inflection point in the risk of biochemical recurrence was observed around 3 month which further increased after 6 months. Based on spline model, time to treatment was then divided into 0-3 months (61.5%), >3-6 months (31.1%) and 6 months (7.4%). In the adjusted cox model, initial delays up to 6 months did not adversely affect the outcome, however, time to treatment >6 month had significantly higher risk of biochemical recurrence, Hazard Ratio = 1.84, 95% CI, 1.30 – 2.60, $p < 0.01$.

Conclusions

The initial delays up to 6 months in prostate cancer primary treatment may be sustainable without adversely affecting the outcome. However, significant delays beyond 6 months can unfavorably impact biochemical disease control.

Impact: Time to treatment can aide clinicians in the decision making of PCa treatment recommendation and educate patients against unintentional treatment delays.

Introduction

Time to receive treatment or treatment delays is a an important quality metric in patient-centered care that has been shown to impact outcome among various cancers (1), including breast, head and neck, colorectal, and melanoma (2-6) - with patients receiving treatment sooner after initial diagnosis being more likely to experience favorable treatment outcomes. However, the implications of treatment delays on PCa prognosis remain unclear in contemporary literature. Unlike other cancers, PCa usually has slow progression and does not present immediate risk to patient survival (7); rendering both clinicians and patients ample time to make decisions on the appropriate treatment choice. In addition, concerns related with overtreatment of PCa has prompted clinicians to adapt more pragmatic approaches towards treatment delivery which may increase the response time to treatment initiation, leading to increased time to treatment (8).

Few studies have demonstrated the possibility of adverse outcomes related with increasing time to treatment in PCa (9-11); however, the length of delays prior to the initiation of treatment which is sustainable to achieve durable PCa outcomes, without losing window of cure, remains debatable (12, 13). Additionally, studies have argued against the use of early intervention in PCa (14) and have shown that delays up to several years does not adversely affect PCa outcomes (15-17). Consequently, a lack of consensus among previously published studies have resulted in significant ambiguity in the association between time to treatment and PCa outcomes (14, 15, 18-21), which warrants further investigation. This study leverages the availability of 25 years' worth of data from two large tertiary referral centers, with detailed clinico-pathologic information, on PCa patients who received prostatectomy as part of their primary treatment. This study seeks to determine the optimal time to start treatment that maximizes favorable PCa outcomes and the clinical implications of treatment delays on biochemical disease control after prostatectomy.

Methods

Patient Population

This retrospective analysis includes a total of 1,891 patients with histologically confirmed localized non-active surveillance PCa who received prostatectomy as a primary treatment at two-large tertiary referral centers - H Lee Moffitt Cancer Center & Research Institute (MCC; Tampa, FL) and the University of Pennsylvania Health System (UPHS; Philadelphia, PA) - from 1987 to 2015 (Table 1). Patients who received prostatectomy at MCC were identified from the Health Research & Informatics platform, an enterprise wide data warehouse. Patients from UPHS were those recruited to the *Study of Clinical Outcomes, Risk and Ethnicity (SCORE)* between 1990 and 2012. In addition, patients who received neoadjuvant treatment prior to their surgery were excluded from the analysis (n = 84). Therefore a total 1,807 patients were used in the final analysis. Institutional Review Board (IRB) approval was obtained before the commencement of the study.

Baseline Covariates

All the patients included in the study received prostatectomy as definite primary treatment for their localized PCa. Detailed clinico-pathologic and demographic information including pretreatment variables such as clinical gleason score, prostate specific antigen (PSA), NCCN risk grouping on patients from both institutes were recorded (Table 1 and 2). Gleason score (GS) for the cohort was categorized using International society of urological Pathology and was divided in group 1 (GS 3+3), Group 2 & 3 (GS 7), group 4 (GS 8) and group 5 (GS 9 & 10) (22). Patients pretreatment risk status was determined by National Comprehensive Cancer Network and was categorized as low (PSA ≤ 10ng/ml and GS 3+3 and clinical T stage ≤ 2A), intermediate (PSA >10 – 20 ng/ml or GS 7, or clinical T stage 2b – 2c) and high risk (PSA > 20 ng/ml or GS ≥ 8 or clinical T stage > 3b) (23). In addition, MCC cohort had additional information

on patients marital, insurance and history tobacco exposure status. Date of diagnosis was used as an index date to determine time to treatment (delays between diagnosis and prostatectomy), and was calculated as months elapsed since the date of diagnosis to the date of prostatectomy.

Follow Up and Outcome

Biochemical disease control was used as the primary outcome of the study and was defined as Biochemical recurrence (BCR) after prostatectomy. To capture BCR, patients were followed after their prostatectomy for post-surgical PSA. BCR was determined by calculating the time between prostatectomy and PSA failure. PSA failure was determined by clinician documented single PSA ≥ 0.2 ng/ml or two consecutive PSA values of 0.2 ng/ml after prostatectomy (23, 24).

Statistical Analysis

In order to identify the optimal cutoff; time to treatment from the date of diagnosis and prostatectomy was introduced as a continuous variable in a multivariate cox regression model. Restricted cubic spline (RCS) function with 4 knots was used in cox model to allow nonlinear association between Hazard Ratio and time to treatment (2, 25). RCS based cox model was adjusted using all the pertinent pretreatment clinico-demographic variables including clinical GS, PSA, clinical T stage, race, age and year of prostatectomy. RCS in cox regression allowed us to not only identify the time point at which the risk of BCR increased (Figure 1) but also the precise subcategorization of the different time interval for the treatment start time for further comparison. Differences between final subcategories of time to treatment and clinico-pathologic/demographic characteristics were analyzed using Chi-square test. Methods of survival analysis including Kaplan Meier (KM) analysis and cox proportional hazard model (CPH), were used to analyze the association between time to treatment subcategories and biochemical disease control. Both univariate and multivariate CPH models were used to

estimate the risk of BCR. In the models, cGS, PSA, Time to treatment, and race category was used as a categorical, while as age at diagnosis and year of prostatectomy was used as numeric variables. A p value of ≤ 0.05 was considered as statistically significant to make clinically meaningful inference from the analysis. Analysis was completed using SAS 9.4 (26).

Results

Comparison of baseline characteristics from the two institutions is provided in table 1. Median follow up time of the study cohort was 46 (IQR 18 - 86) months, with an overall median time to treatment of 3 months. In multivariate cox regression model with RCS function, adjusted for all the pretreatment variables (Figure 1), provided optimal cutoffs for the time to treatment subcategories. Based on RCS model (Figure 1), around 3 – 4 months after the date of diagnosis, inflection in the risk of BCR was observed (HR started to increase) which further crossed the reference line (HR = 1) near 6 months. Using this model based approach, time to treatment was divided as 0 – 3, >3 – 6 and >6 months for further comparisons. A large proportion (61.5 %) of the patients received prostatectomy in 0 - 3 Months, followed by 31.1% in >3 - 6 Months and 7.4% after 6 months. Higher proportions of African American men (AAM) were likely to treatment after >6 months (Table 2). Delays beyond 6 months were also more prominent among patients with low risk NCCN group. There was no apparent association among time to treatment categories and other clinico-pathologic characteristics (Table 2).

Overall five year FFbF rate were 78% (95% CI 75% – 81%), 82% (95% CI 78% – 85%) and 69% (95% CI 59 – 77%) for time to treatment of 0 – 3, >3 – 6 and >6 months respectively, p < 0.001 (Figure 2A). Similarly, the trends in unfavorable BCR rate within the strata of time to treatment categories were also preserved when KM curves were stratified by NCCN especially among intermediate risk (Figure 2B, 2C, and 2D). In adjusted cox model, treatment delays after 6 months was significantly associated with an increased risk of BCR compared to those with 0 –

3 months, HR = 1.84, 95% CI, 1.30 – 2.60, p = < 0.001. Conversely, time to treatment >3 – 6 months did not show a significant effect on BCR. Both unadjusted and adjusted estimates for the risk of BCR are provided in the Table 3. To explain the possible heterogeneity within the strata of GS, PSA, race and NCCN risk groupings, the cross product interaction between these covariates and time to treatment subcategories were analyzed separately. There was no interaction (likelihood ratio p > 0.05) observed between these covariates and time to treatment (result not presented). we also ran a sensitivity analysis in MCC cohort for the multivariate cox model (Supplemental Table 1) to test whether inclusion of sociodemographic variables such as marital status, health insurance status, and history of tobacco exposure can impact the association between risk of BCR and time to treatment. Inclusion of these variable to the multivariate model adjusted for pretreatment clinical variables does not impact the hazard estimates as treatment delays beyond 6 month continue to negatively affect BCR (HR 2.41, 95% CI, 1.39 – 4.17, p = 0.001).

Discussion

Time to Treatment and Biochemical Disease Control

This study optimizes the ideal time to treatment by applying model based approach and assesses the implications of treatment delays on PCa outcome. In our analysis, we carefully included all the pretreatment or clinical variables in multivariate RCS cox model, that are available to clinicians in order to make treatment decision, to identify the time point beyond which the risk of biochemical recurrence was higher. Based on our results delays in treatment after diagnosis for up to 6 months may not adversely affect PCa outcome; however, significant delays beyond 6 months may lead to poor biochemical disease control. These results were consistent with another retrospective study by O'Brien and colleagues who reported a significantly higher risk of BCR among patients with surgical delays beyond 6 month. It is

important to note that in our RCS based model, risk of BCR increased around the same time point as of O'Brien et el reported (9). Interestingly, when stratified by NCCN risk groups, rate of BCR was significantly higher among intermediate risk patients, while as there was no statistical difference observed among low risk patients. Our finding aligns perfectly with a large retrospective study by Abern and colleagues, who reported a high risk of BCR among intermediate risk patients with delayed prostatectomy while no apparent risk of poor outcomes among low risk patients (10). Given that higher proportion of low risk patients were likely to wait for surgery beyond 6 months; observed nonsignificant effect of treatment delays on BCR can be reassuring. However, attempts to perform restaging after 6 months may be necessary to avoid any disease upgrade as delays negatively affect BCR.

Contrary to our findings, there are studies which argue against the association of treatment delays and its implications on PCa outcomes. In a study by Korest *et al*(14), the authors reported negligible effect of treatment delays on BCR-free survival and PCa pathology. Additionally, a review by Van Den Bergh and colleagues reported non-significant effect of treatment delays on PCa outcomes and reported that delays up to several years may not inferiorly impact PCa outcome (15). In another study by Morini et al on 908 PCa patients, authors reported non-significant association of treatment delays and BCR among low/intermediate risk patients (16). However, the study design used in most of these contemporary studies utilized arbitrary or a priori determined cutoff points to categorize time to treatment and then used these categories to predict PCa outcome (14, 15, 18-21). This approach is susceptible to misclassification bias as it ignores the important factors such as clinical characteristics which have a direct association with treatment planning and may impact time to treatment (2, 10, 27). Furthermore, most studies often fail to acknowledge that PCa progression is not fixed and alterations in the tumor characteristics as a result of biological changes are inevitable due to lack of definite treatment. Vickers et el draws attention to this

issue and points out to the frequent use of null hypothesis base approach in reporting that delayed treatment does not lead to any change in PCa pathology (28), which can be misleading since it does not render any clinical utility towards treatment recommendation. While analyzing our data we addressed this issue differently and applied model based approach to optimize time to treatment and provided an optimal time point beyond which risk of BCR starts to increase. In addition, with the inclusion of all the key clinical variables that are used in PCa treatment decision making we further increased the clinical relevance of our estimates to better guide PCa treatment planning. Additionally we included a pooled data from two large Cancer institutes and had significantly large sample size with higher statistical power to assess the association treatment delays and PCa.

Clinical Implications of Time to Treatment

Our results will aide in the shared decision making process of PCa treatment for both clinicians and patients. Although the cohort we used in analysis was consisted of non-active surveillance patients, our results may still have implications on the existing practices related to repeat biopsy especially among those who are likely to experience treatment delays. Currently, NCCN guidelines identifies active surveillance as viable strategy for very low, low risk and a small subset of favorable intermediate risk patients and recommends repeat biopsy in 12 months (23, 29). However, observed outcome defecits with increasing time to treatment may necessitates the restaging before 12 months especially among intermediate risk patients. While absence of any statistical association of treatment delays and BCR among low risk patients can be reassuring, attempts to avoid undue delays must be ensure to obviate any possibility of losing window of cure and prevent inferior outcomes. Our results underscore the clinical utility of time to treatment in targeting the subset of patients who are likely to benefit from initiation of treatment soon after diagnosis. This result necessitates the inclusion of time to treatment in the decision making of PCa treatment recommendation. Although, this study does not corroborate

whether Gleason progression or pathologic upstaging could have resulted in poor outcome among those with treatment delays beyond 6 months, future studies should focus on understanding the interaction between PCa pathology and treatment delays to explain outcomes heterogeneity with increasing time to treatment.

Presence of detailed clinico-pathologic information along with longer follow up from two large tertiary care referral centers adds significant value to the generalizability of our results. Additionally, patients across the different surgical era (1987 – 2015) were included in the analysis; therefore, allowing us to capture data spanning over 25 years. Compared to other studies evaluating similar associations (14, 15, 18-21), our study consisted of a higher percentage of a traditionally underrepresented population of AAM (~16% of the study population), thus, making our results more generalizable to AAM who are at risk of experiencing inferior outcomes. In our analysis application of the model based approach over arbitrary cut point selection methods, to select optimal time point for time to treatment, reduced the likelihood of selection biases among those with delayed treatment. This study also has few limitations. First, our cohort only consisted of prostatectomy patients, thus lacking the information on those who received or contemplated receiving radiation as a primary treatment. Therefore, our results may lack the generalizability across the treatment spectrum of PCa and further investigation may be warranted to confirm our finding in patients that received radiation as their primary treatment. Secondly, in order to significantly increases our sample size and provide generalizability of our findings, the analysis for this study was conducted using combined data from two different tertiary referral centers. Although we controlled for the health centers effects in multivariate analysis, unmeasured confounding resulting from the differential treatment practices and diagnostic ascertainment (lack of standardization in pathologist review across the patient population) remains a potential limitation. It is also important to note that UPHS was relatively older institution and contributed a large proportion of older cases in our cohort

(diagnosed before 2000). Since PSA screening was also begningng around the same time, treatment delays in the older cases were more prominent among patients from UPHS than MCC. This variation can explain the higher proportion of pT3b-pT4 disease (advance stage) in UPHS cohort (Table 1). Furthermore, loss to follow up was another limitation this study. Likelihood that many patients after receiving their primary treatment at one of the two tertiary centers (MCC and UPHS) would have moved on to seek care in their local facility remains higher and can result in inadequate follow up. Compared to other categories there were fewer patients with treatment delays beyond 6 months. Smaller number in this categorsy may reduce the precision in the observed risk estimate and their corresponding confidence interval. Lastly, BCR was the only surrogate used in the analysis compared to metastasis and PCa specific mortality. Use of BCR as a surrogate may potentially limit our ability to associate our finding with long term survival endpoints. As highlighted by McLaughlin et al. (3); ethical issues remain one of the major limitations in understanding the optimal time to initiate treatment, resulting in a lack of interventional prospective studies to determine optimal time to treatment. Continuing research will be required to advance existing guidelines on the delivery of PCa treatment.

Conclusions

Time to treatment > 6 months have detrimental effects on biochemical disease control after surgery. In order to achieve sustainable outcomes, definitive treatment for PCa must be delivered within 6 months. This study identifies time to treatment as an independent predictor of PCa outcome and therefore careful planning may be warranted while considering treatment delays.

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Table 1: Baseline characteristics of MCC and UPHS cohort

Clinico-Pathological/Demographic Characteristics	MCC (n = 648)	UPHS (n = 1,159)
Time to treatment (Months)		
Median (IQR)	3 (2 - 4)	3 (2 - 4)
Time to Treatment (Months)		
0 - 3	435 (67.1)	676 (58.3)
> 3 - 6	169 (26.1)	393 (33.9)
> 6	44 (6.8)	90 (7.8)
Age category		
≤ 50	91 (14.0)	105 (9.1)
> 50 - 60	282 (43.5)	519 (44.8)
> 60 - 70	252 (38.9)	507 (43.7)
≥ 70	23 (3.5)	28 (2.4)
Age		
Median (IQR)	59 (53 - 64)	60 (55 - 64)
Race		
AAM	147 (22.7)	147 (12.7)
EAM	501 (77.3)	1,012 (87.3)
NCCN Risk Group		
Low Risk	277 (42.7)	637 (55.0)
Intermediate Risk	285 (44.0)	315 (27.2)
High Risk	69 (10.6)	84 (7.2)
Unknown	17 (2.6)	123 (10.6)
iPSA Category		
0 - 6	374 (57.7)	650 (56.1)
> 6 - 10	177 (27.3)	317 (27.3)
> 10 - 20	77 (11.9)	151 (13.0)
> 20	20 (3.1)	41 (3.5)
Clinical Gleason Score		
Group 1	335 (51.7)	780 (67.3)
Group 2/3	235 (36.3)	183 (15.8)
Group 4	41 (6.3)	43 (3.7)
Group 5	5 (0.8)	12 (1.0)
Unknown	32 (4.9)	141 (12.2)
Clinical T Stage		
T1	493 (76.1)	649 (56.0)
T2	127 (19.6)	265 (22.9)
T3	11 (1.7)	9 (0.8)
Unknown	17 (2.6)	236 (20.4)
Pathology Gleason		

Group 1	240 (37.0)	598 (51.6)
Group 2/3	370 (57.1)	479 (41.3)
Group 4	21 (3.2)	51 (4.4)
Group 5	17 (2.6)	31 (2.7)
AJCC Pathological Stage		
pT2A - pT2B	517 (79.8)	814 (70.2)
pT3A	104 (16.0)	281 (24.2)
pT3B - pT4	6 (0.9)	63 (5.4)
PX	21 (3.2)	1 (0.1)
Marrital Status		
Married	569 (85.0)	-
Single	100 (15.0)	-
Insurance Status		
Private Insurance	423 (63.2)	-
Public Insurance	182 (27.2)	-
Uninsured	64 (9.6)	-
History Tobacco Status		
Present	310 (46.3)	-
Absent	325 (48.6)	-
Unknown	34 (5.1)	-

Abbreviations: IQR, Inter quartile range; AAM, African American; NCCN, National Comprehensive Cancer Network; iPSA, preoperative Prostate Specific Antigen; AJCC, American Joint Committee on Cancer

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Table 2: Clinico-Pathologic and Demographic characteristics among patients receiving prostatectomy at different time intervals

Variables	Time to Treatment in Months			p value
	0 - 3 (N = 1,111)	> 3 - 6 (N = 562)	> 6 (N = 134)	
Age category				
≤ 50	126 (11.3)	56 (10.0)	14 (10.4)	0.6
> 50 - 60	505 (45.4)	243 (43.2)	53 (39.5)	
> 60 - 70	450 (40.5)	245 (43.6)	64 (47.8)	
≥ 70	30 (2.7)	18 (3.2)	3 (2.2)	
Age				
Median	59	60	60	0.09
IQR	54 - 64	55 - 65	55 - 65	
Race				
AAM	149 (13.4)	111 (19.7)	34 (25.4)	< 0.001
White	962 (86.6)	451 (80.2)	100 (74.6)	
NCCN Risk Group				
Low Risk	529 (47.6)	312 (55.5)	73 (54.5)	0.03
Intermediate Risk	385 (34.6)	173 (30.8)	42 (31.3)	
High Risk	108 (9.7)	34 (6.0)	11 (8.2)	
Unknown	89 (8.0)	43 (7.6)	8 (6.0)	
iPSA Category				
0 - 6	639 (57.5)	315 (56.0)	70 (52.2)	0.4
> 6 - 10	288 (25.9)	166 (29.5)	40 (29.8)	
> 10 - 20	145 (13.0)	66 (11.7)	17 (12.7)	
> 20	39 (3.5)	15 (2.7)	7 (5.2)	
Clinical Gleason Score				
Group 1	661 (59.5)	371 (66.0)	83 (61.9)	0.2
Group 2/3	269 (24.2)	119 (21.2)	30 (22.4)	
Group 4	59 (5.3)	17 (3.0)	8 (6.0)	
Group 5	13 (1.2)	3 (0.5)	1 (0.7)	
Unknown	109 (9.8)	52 (9.2)	12 (8.9)	
Clinical T Stage				
T1	699 (62.9)	362 (64.4)	81 (60.4)	0.5
T2	238 (21.4)	120 (21.3)	34 (25.4)	
T3	16 (1.4)	4 (0.7)	0 (0)	
Unknown	158 (14.2)	76 (13.5)	19 (14.2)	
Pathology Gleason				
Group 1	498 (44.8)	278 (49.5)	62 (46.3)	0.4
Group 2/3	535 (48.1)	253 (45.0)	61 (45.5)	
Group 4	46 (4.1)	18 (3.2)	8 (6.0)	
Group 5	32 (2.9)	13 (2.3)	13 (2.2)	

Extracapsular extension				
Present	290 (26.1)	134 (23.8)	35 (26.1)	0.5
Absent	821 (73.9)	428 (76.2)	99 (73.9)	
Surgical Margins				
Present	257 (23.1)	115 (20.5)	34 (25.4)	0.3
Absent	854 (76.9)	447 (79.5)	100 (74.6)	
Seminal Vesicle Invasion				
Yes	63 (5.7)	27 (4.8)	9 (6.7)	0.6
No	1048 (94.3)	535 (95.2)	125 (93.3)	
AJCC Pathological Stage				
pT2A - pT2B	810 (72.9)	424 (75.4)	97 (72.4)	0.3
pT3A	250 (22.5)	108 (19.2)	27 (20.1)	
pT3B - pT4	39 (3.5)	24 (4.3)	6 (4.5)	
PX	12 (1.1)	6 (1.1)	4 (3.0)	
Gleason Upgrade				
Upgraded	292 (26.3)	157 (27.9)	36 (26.9)	0.8
No Upgrade	711 (64.0)	357 (63.5)	88 (65.7)	
Not Determined	108 (9.7)	48 (8.5)	10 (7.5)	

Abbreviations: IQR, Inter quartile range; AAM, African American; NCCN, National Comprehensive Cancer Network; iPSA, preoperative Prostate Specific Antigen; AJCC, American Joint Committee on Cancer

Table 3: Univariate and Multivariate cox proportional hazard model estimating the risk of biochemical recurrence after prostatectomy

Variables	No of Patients	No of Events	Univariate Model HR (95% CI)	p value	Multivariate Model* HR (95% CI)	p value
Time to Treatment (In Months)						
0 - 3	1111	242	*1 (Ref)*		*1 (Ref)*	
> 3 - 6	562	99	0.83 (0.66 - 1.05)	0.1	0.90 (0.71 - 1.14)	0.4
> 6	134	39	1.70 (1.21 - 2.38)	0.002	1.84 (1.30 - 2.60)	< 0.001
Race						
White	1513	311	*1 (Ref)*		*1 (Ref)*	
AAM	294	69	1.10 (0.84 - 1.43)	0.4	1.04 (0.79 - 1.38)	0.7
Clinical Gleason Score						
Group 1	1115	164	*1 (Ref)*		*1 (Ref)*	
Group 2/3	418	117	2.14 (1.68 - 2.71)	< 0.001	2.19 (1.71 - 2.82)	< 0.001
Group 4	84	42	4.41 (3.13 - 6.19)	< 0.001	3.58 (2.50 - 5.11)	< 0.001
Group 5	17	10	4.67 (2.46 - 8.85)	< 0.001	3.57 (1.84 - 6.90)	< 0.001
iPSA Category						
0 - 6	1,024	146	*1 (Ref)*		*1 (Ref)*	
> 6 - 10	494	121	1.76 (1.38 - 2.24)	< 0.001	1.61 (1.25 - 2.06)	< 0.001
> 10 - 20	228	82	3.10 (2.36 - 4.07)	< 0.001	2.91 (2.19 - 3.84)	< 0.001
> 20	61	31	3.89 (2.64 - 5.74)	< 0.001	2.56 (1.67 - 3.91)	< 0.001
Clinical T Stage						
T1	1142	204	*1 (Ref)*		*1 (Ref)*	
T2	392	112	1.49 (1.18 - 1.87)	< 0.001	1.28 (1.0 - 1.64)	0.04
T3	20	13	5.31 (3.19 - 8.84)	< 0.001	3.20 (1.83 - 5.57)	< 0.001
Age	1807	48	1.0 (0.99 - 1.02)	0.2	0.99 (0.97 - 1.0)	0.2
RP Year	1807	48	0.96 (0.94 - 0.98)	< 0.001	0.97 (0.95 - 1.0)	0.1

Abbreviations: AAM, African American; iPSA, preoperative Prostate Specific Antigen; HR, Hazard Ratio; CI, Confidence Interval

*Multivariate Model was also adjusted for the institutions used in the study (UPHS and MCC) to account for the institution specific effects

Figure Legends:

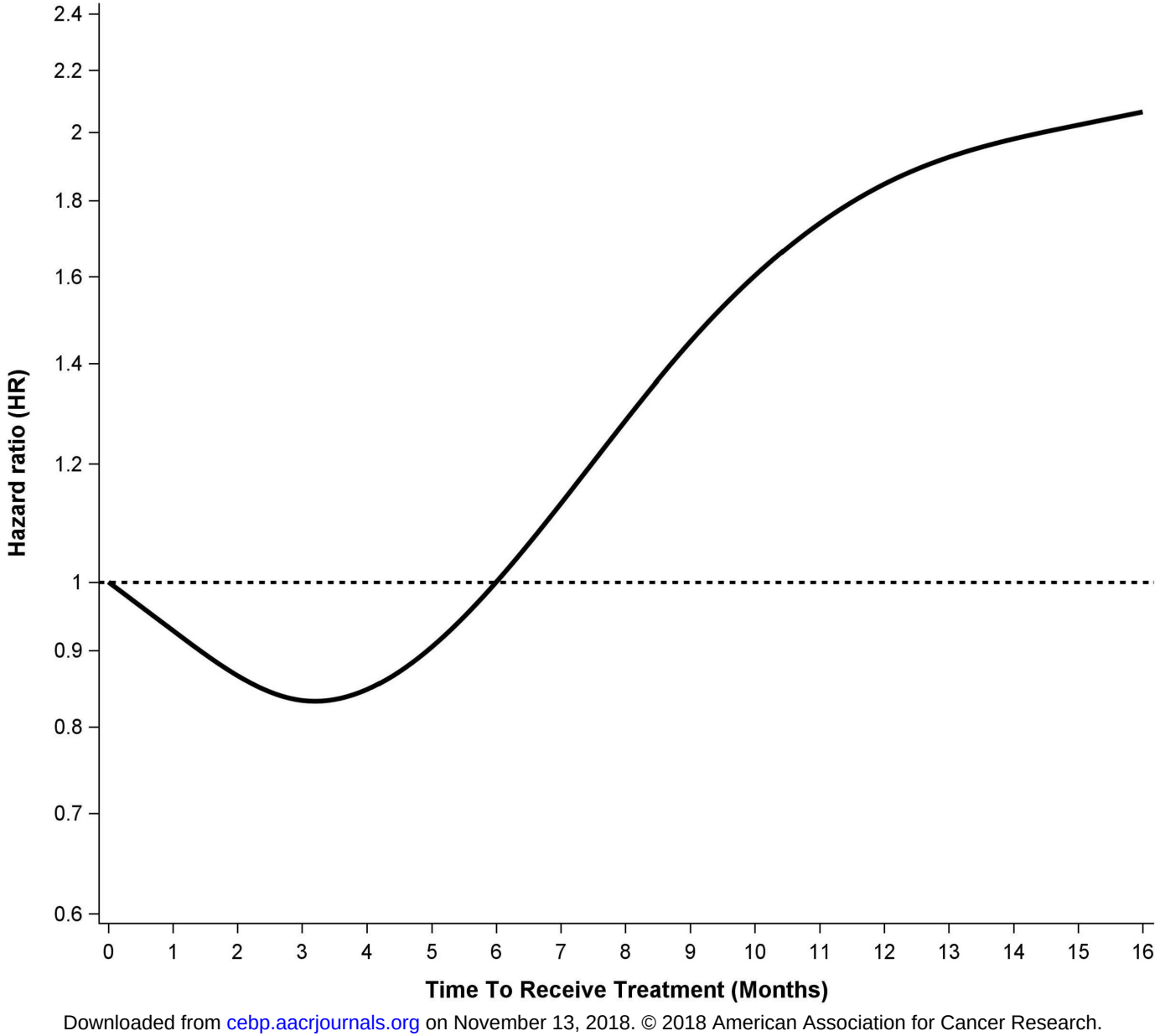
Figure 1: Adjusted Hazard ratio (HR) using time to receive treatment as continuous variable in the cox model with restricted cubic spline using 4 knots allowing non-linear association between HR of biochemical recurrence and time to treatment*

*RCS multivariate model was adjusted for clinical Gleason score, preoperative prostate specific antigen, clinical T Stage, race, age, data source institution, and year of surgery.

Figure 2: Kaplan Meier Graph estimating the rate of biochemical recurrence within the strata of time to treatment –

2A: Overall cohort
2B: NCCN low risk
2C: NCCN intermediate risk
2D: NCCN high risk

Figure 1



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Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Figure 2A

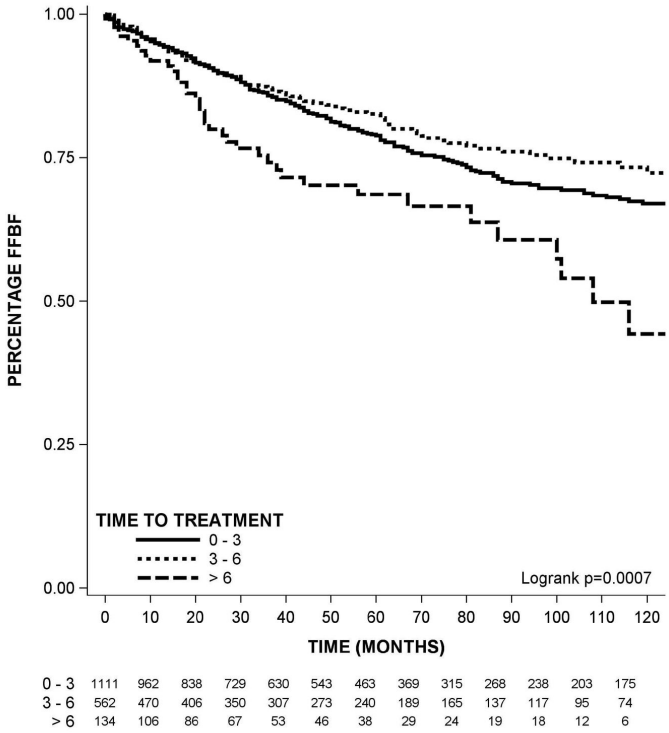


Figure 2B

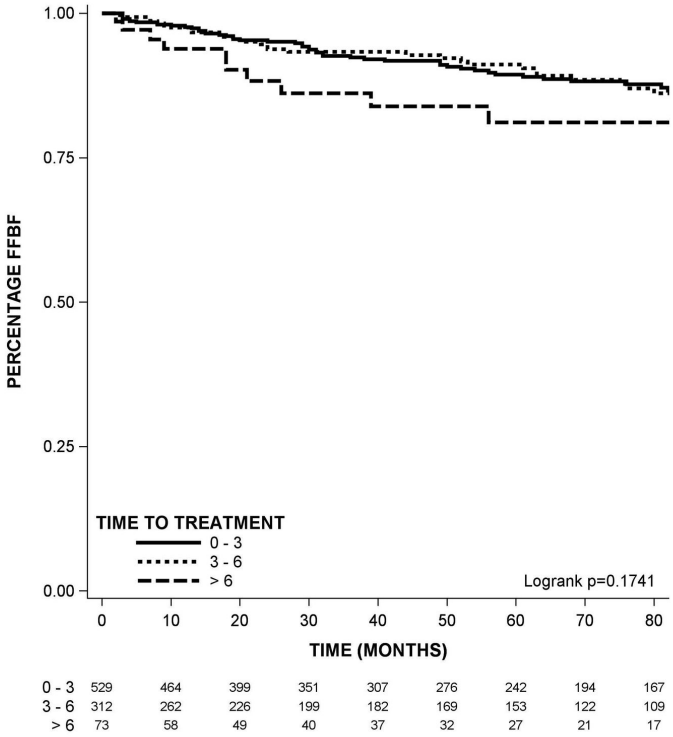


Figure 2C

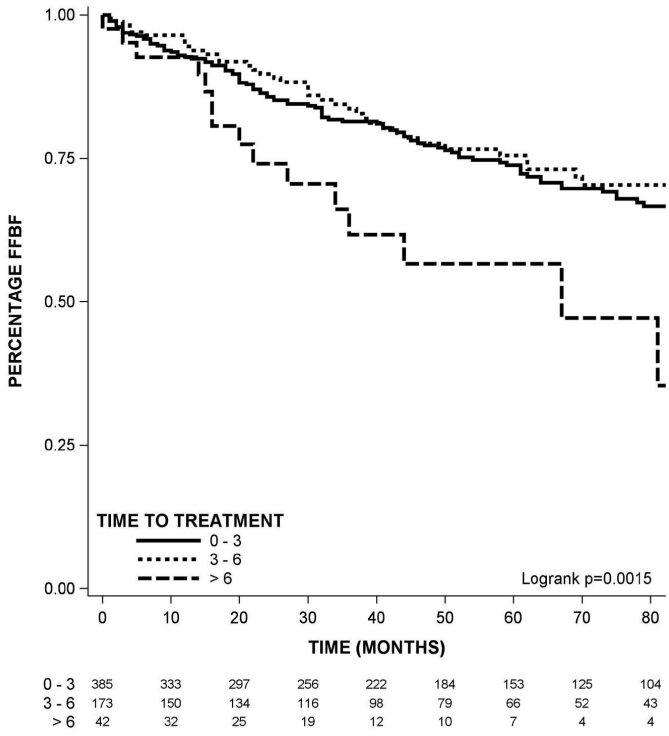
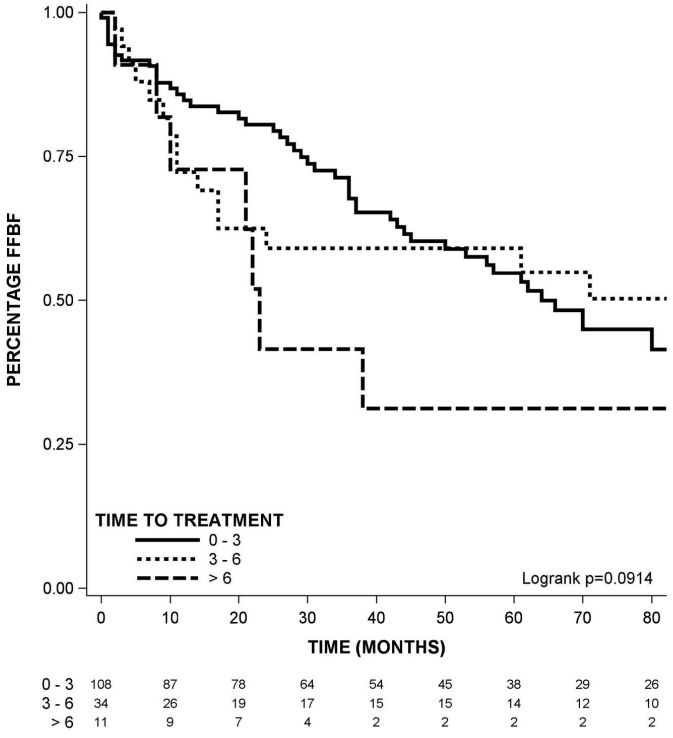


Figure 2D



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