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The Impact of Hormone Therapy on Overall Survival for Prostate Cancer Patients under Prostatectomy and Salvage Radiation Therapy

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Shanghai Jiao Tong University

2018

Thesis Committee Chair: Yuan Liu, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

The Impact of Hormone Therapy on Overall Survival for Prostate Cancer Patients under Prostatectomy and Salvage Radiation Therapy

By Xueying Lyu

Background:

Salvage radiotherapy (SRT) is one of common treatments to control biochemical recurrence after radical prostatectomy for prostate cancer patients. According to previous study, Salvage radiation therapy (SRT) with short-term hormone therapy is an efficient way to improve overall survival of prostate patients after radical prostatectomy but not equal benefit for all men. It is still unknown who benefits most from hormone therapy.

Method:

Patients with demographics, tumor and treatment characteristics information from the National Cancer Data Base (2004-2015) were divided into Radiation therapy only group and Radiation Therapy with Hormone therapy group. Univariate analyses, multivariate analyses (MVAs) and Propensity score (PS) weighting were implemented. The Kaplan-Meier method was used to describe overall survival for study groups.

Results:

There are 1931 patients included in cohort, 1529 (79.2%) took radiation therapy only after surgery whiles 402 (20.8%) took radiation therapy combined with hormone therapy. Compared to patients taking radiation therapy only, patients with radiation therapy and hormone therapy had a larger proportion of white people, with lower income, located in Midwest, more poorly or undifferentiated tumors, a higher proportion of pathologic T3 and in a high risk-group. Radiation with Hormone Therapy was associated with worse overall survival (HR=1.74, 95% CI 1.32-2.29, $P < 0.001$). The effect of the treatment group was then further estimated in the weighted sample with a Cox model, which yielded an HR of 1.20 (95% CI, 0.99 - 1.46; $P = 0.061$) for Radiation Therapy with Hormone Therapy versus Radiation Therapy only.

Conclusion:

Radiation with Hormone Therapy was associated with worse overall survival in a long-term compared with radiation therapy only. The greatest overall survival benefit from radiation therapy treatment was seen in subgroups of patients with more aggressive prostate cancer, such as those with a higher gleason score (Gleason Score from 8 to 10) and pathologic T-stage of T3.

Keywords: Prostate Cancer, Salvage Radiation Therapy, Hormone Therapy, Subgroups

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Introduction:

1. Background of Prostate Cancer:

Prostate cancer is the most common non-skin cancer in men. In 2019, 174,650 men in the United States are estimated to be diagnosed with prostate cancer.[1] Prostate Specific Antigen (PSA) Test and Digital Rectal Examination (DRE) are commonly used to screen for prostate cancer. [2] Even though the screening of prostate cancer is increased, and its mortality rate is declining, prostate cancer is still the second leading cause of cancer deaths among American men. 90% of prostate cancer cases are found at the local or regional stage with a 5-year survival rate of nearly 100%. Although it generally grows slowly[3] , proper and efficient treatments are still required to improve the quality and length of patients' life.

2.Current Treatments and Previous Clinical Trails:

Localized prostate cancer is the most common type of prostate cancer, which has not spread outside the prostate and generally without any symptoms. Active surveillance (AS) or watchful waiting (WW) until a later date is the preferred treatment option for old patients because surgery or radiation has not been shown to help them live longer. [4] For younger patients with qualifying health conditions, one of the preferred options for treating their organ-confined prostate cancer is radical prostatectomy (RP). The goal of RP is the eradication of prostate cancer while preserving continence and potency. It is the only treatment for localized prostate cancer to show benefit for overall survival (OS) and cancer-specific survival (CSS) compared with WW.[5] After radical prostatectomy, more than thirty percent of patients without salvage treatment relapse with a rise in PSA concentration. It is the signal of biochemical recurrence or radiographic disease developing distant metastases.[6] Salvage radiotherapy (SRT) is one of the common treatments for most patients with biochemical recurrence after radical prostatectomy.[7] Boorjian's study claims that the risk of distant metastasis reduces by 75% for patients with salvage therapy[8], but there are

still more than half of these patients suffering from biochemical relapse 5 years after salvage radiotherapy alone. [9, 10] Carrie and Shipley reported that adding short-term or long-term androgen suppression to salvage radiotherapy benefits those PSA rises after radical prostatectomy.[11, 12]

3. Study Hypothesis and Motivations:

According to the previous randomized trials, the addition of hormone therapy with SRT doesn't equally benefit all men. The added hormone therapy cannot significantly reduce the development of metastatic disease or death for patients with early SRT, and the side effects can decrease the quality or quantity of patients' life. PSA is one of the biomarkers found in previous researches. The benefits of hormone therapy with SRT seemed to be higher for patients with a PSA concentration of greater than 1.5 μg/L than for those with the PSA concentration lower than 1.5 μg/L. [11, 13] The sample sizes of previous randomized trials are not scientifically large enough. So, more studies are required to determine who benefits most from hormone therapy with SRT biologically. We did a retrospective study based on more data records, which is closer to real life, to figure out whether hormone therapy with SRT benefits men wildly in a larger population and determine more specific subgroups of patients who significantly benefit from this therapy. We use the data from the National Cancer Database (NCDB), a hospital-based registry with data sources from more than 1500 Commission on Cancer-accredited hospitals[14], and divided them into 2 study groups to compare the OS of patients with SRT added hormone therapy and those with only SRT. With the analysis of subgroups, we determined more biomarkers for selecting the use of Hormone therapy to improve the quality and length of patients' life.

Materials and Methods:

1. Source of data:

The data for analysis is from the National Cancer Database (NCDB). NCDB is a clinical oncology database sourced from hospital registry data that are collected in more than 1,500 Commission on Cancer (CoC)-accredited facilities, jointly sponsored by the American College of Surgeons and the American Cancer Society. Data contains more than 34 million historical records and the data of prostate patients is also included.[13]

2. Study population and patient characteristics

In this observational study, the chosen dataset includes 1931 male patients who diagnosed as prostate cancer aged at 40 years or older (mean age of diagnosis is 61.00) in stage of pT2-3B and pN0 or pNx (no extent of the regional lymph node) without extension enrolled from 2004 to 2015. Patients were excluded if they had other previous cancer or had undergone palliative care after diagnosis. Patients were excluded in the case of missing data concerning at least 1 of the variables of interest. The eligible cases had received radical prostatectomy before Salvage Radiation Therapy (radiation total dose >=59) with or without Hormone Therapy. Patients were also excluded if radiation therapy started more than 90 days after surgery or Hormone Therapy was started more than 2 weeks after Radiation Therapy.

Demographic and social economics characteristics (age, race, income, education level and location), medical and treatment history (year of diagnosis, Charlson-Deyo Score (CDCC_TOTAL_BEST), AJCC Clinical T (the clinically-determined size and/or extension of the primary tumor (cT) defined by the American Joint Committee on Cancer (AJCC)), PSA, Gleason Score, Regional and Boost Radiation Dose, days from diagnosis to treatment) were all recorded in the dataset for control of covariates in the analysis of outcomes. The risk group was defined by clinic_t (the pathologically determined tumor size and/or extension (pT) defined by AJCC),

Gleason Score and PSA. (Low: clinic_t < T2a and gleason score <=6 and PSA < 10; Intermediate: T2a-T2c or gleason score =7 or PSA 10-20; High: T3b-T4 OR gleason score 8-10 OR PSA >20.)[15]

3. Definition of cohort and outcome

In order to compare the efficiency of these two treatments, included cases were divided into two groups according to treatment, Radiation Therapy Only vs. Radiation with Hormone Therapy, with observations of 1529 and 402 respectively.

The primary endpoint was the rate of overall survival (OS), which included disease-specific death and non-disease-specific death. Disease-specific death included all deaths from prostate cancer or treatment complications as well as death from an unknown process in patients with active prostate cancer on the base of the centrally reviewed cause of death. Non-disease-specific death was defined as death from any other causes. The NCDB does not specify how institutions obtain follow-up information but expect institutions to provide a 90% rate of follow-up during a 5-year period. The NCDB does not capture the cause of the death so that cancer-specific survival cannot be calculated. Besides, other cancer outcomes, such as patterns of recurrence and time to first recurrence (progression-free survival), are also not available.[16]

4. Statistical Methods

4.1 Descriptive Analysis

The descriptive table was a summary for variables of interest including continuous variables and categorical variables. We summarized the mean, median, and standard deviation for continuous variables and presented the frequencies with percentages for categorical variables.

4.2 Univariate association with Cohorts Analysis

For the variables of interest in this database, we divided them into several levels according to their distribution and previous related researches, which makes it more convenient for data

analysis and outcome explanation. We used SAS macro created by Dr. Yuan Liu[17] to conduct a univariate analysis for cohorts with covariates individually. The Chi-Square test was used for comparison of categorical covariates. And for numerical covariates, the sample size, mean and median along with ANOVA test (parametric p-value) can be produced. The analysis of variance test was used for comparison of continuous variables between two cohorts. We also conducted backward selection with an alpha level of removal of 0.05 with SAS 9.4 (SAS, Cary, North Carolina) on a multivariate logistic regression model using the maximum possible sample size at each stage of the selection process. And all the covariates considered in the analysis are Age at Diagnosis, Charlson/Deyo Score, Facility Type, Primary Payor, Median Income Quartiles 2008-2012, Percent No High School Degree 2008-2012, PSA, Sequence Number, Regional+Boost Radiation Dose (GY), Year of Diagnosis, Race-Ethnic Groups, and Days from diagnosis to surgery, Facility Location, AJCC Pathologic T, Gleason Score and grade.

4.3 Survival Analysis

Overall survival is defined as months from the date of radiation started to death or last follow-up. Overall survival was described by the Kaplan-Meier method with log-rank test. The Cox' proportional-hazard model is used to estimated hazard ratio with 95% confidence interval to compare the treatment groups. To further investigate the joint effect by treatment and other characteristics in relation to outcomes, we conducted backward variable selection on a Cox proportional hazard model. The process was done in SAS macro %PHREG_SEL, in which the maximum possible sample size at each stage of the selection process was used instead of restricting to the sample size from the first step as in SAS automatic selection does.

Nine subgroup analyses of treatment efficiency were conducted within classes to better understand differential treatment effects on overall survival in subgroups. These analyses were performed within the following categories: Median Income Quartiles (< $38,000 vs. $38,000-

$47,999 vs. $48,000-$62,999 vs. >=$63,000), Primary Payor (Other Government/Not Insured/Unknown vs. Private vs. Medicare), Facility Type (Non-Academic /Research Program vs. Academic /Research Program), Years of Diagnosis (2004 to 2006 vs. 2007 to 2009 vs. 2010 to 2012 vs. 2013 to 2015), Charlson-Deyo Score (0 vs. 1 vs. >=2), AJCC Pathologic T (T2 vs. T3), Gleason score (2 to 6 vs. 7 vs. 8 to 10, on a scale from 2 to 10, with higher scores indicating a worse prognosis) and group of age (>=65 vs. >65). In addition, interaction effects between each factor and treatment were formally tested (α=0.05).

4.4 Propensity Score Matching

In non-randomized studies, the effect of treatment cannot be estimated by simply comparing outcomes between treatment groups. We used propensity score methods to estimate treatment effects in this observational study. The propensity score is defined as the probability of treatment assignment conditional on measured baseline covariates. The logistic regression model for Radiation Therapy versus Radiation Therapy added Hormone Therapy was used to estimate the propensity score for all covariates that predicted for OS. We use ATE (Averaged Treatment Effect) method to create weighted sample and conduct the weighted analyses by inversing the propensity score, through which we reshape sample distribution and achieve the covariate balance, which was evaluated with the standardized differences and a value < 0.1 was considered a negligible imbalance.[18] Let Z denote treatment assignment (Z = 1 denoting treatment; Z = 0 denoting absence of treatment), and let X denote a vector of observed baseline covariates. The propensity score is defined as e = P(Z = 1|**X**): the probability of a subject receiving the treatment of interest conditional on their observed baseline covariates. PS weighting for ATE is defined as $w=\frac{Z}{e}+\frac{1-Z}{1-e}$. The covariate balance was evaluated with the standardized differences, and a value < 0.1 was considered a negligible imbalance. [19]

Results：

1. Study samples characteristics

Demographic and histopathologic data are listed in Table 1. According to the table, the mean age at diagnosis of the patients was 61.00 and most of them are no more than 65 years old (n=1390, 72.0%). Over 80% of the patients were white people (n=1554, 80.5%) and more than half of the patients were from South (n=617,32.0%) and Midwest (n=620, 32.1%). Charlson-Deyo Score of the major of patients was zero with the meaning of no comorbid conditions recorded. 94.6% (n=1826) of them had a single malignant primary with the sequence number equal to 00. Majority of the patients had Poorly/Undifferentiated tumors (n=1478, 78.5%) and pathologic T3 stage tumors (n=1559, 80.7%). PSA was less than 10 for 64.9% patients (n=1186) and Gleason score for more than nine tenth of them was 7 or more (7: n=846, 47.6%; 8 to 10: n=888, 47.6%).

2. Difference between two treatment groups

Among the entire cohort, for the 1931 patients, 1529 (79.2%) took radiation therapy only after surgery whiles 402 (20.8%) took radiation therapy combined with hormone therapy. There were no significant differences between patients with radiation therapy only and those with radiation therapy and hormone therapy when comparing patient characteristics including age at diagnosis, education level, primary payor, facility type, year of diagnosis, sequence number, PSA, regional+boost radiation dose (GY) and Charlson-Deyo score (all $P > 0.05$, $\alpha=0.05$, Table 1). Compared to patients taking radiation therapy only, patients with radiation therapy and hormone therapy had a larger proportion of white people (white vs. black vs. other: 1554 vs. 277 vs. 100), with lower income (< $38,000 vs. $38,000-$47,999 vs. $48,000-$62,999 vs. >=63,000 : 344 vs. 415 vs. 514 vs. 659), located in Midwest (Midwest vs. South vs. Northwest vs. West : 620 vs. 617 vs. 393 vs. 301), more poorly or undifferentiated tumors (Well/Moderately Differentiated vs. Poorly/Undifferentiated: 405 vs. 1478), a higher proportion of pathologic T3 (T3 vs. T2: 1559 vs. 372) and in a high riskgroup (Low/Intermediate vs. High: 241 vs. 1682).

Table 1 also showed the outcome of multivariate logistic regression model and relative p-values. Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: Age at Diagnosis, Charlson-Deyo Score, Facility Type, Primary Payor, Median Income Quartiles 2008-2012, Percent No High School Degree 2008-2012, PSA, Sequence Number, Regional + Boost Radiation Dose (GY), Year of Diagnosis, Race-Ethnic Groups, and days from diagnosis to surgery.

3. Results of survival analysis and propensity score matching

On Cox regression for overall survival, Radiation with Hormone Therapy was associated with worse overall survival (HR=1.74, 95% CI 1.32-2.29, P < 0.001). Clinicopathologic and population factors associated with OS are listed in Table 2-1 and include medicare of primary payor, facility type, facility location, Charlson-Deyo Score, Sequence number, poor or undifferentiated tumor grade, pathologic T-stage, Gleason score and age at diagnosis. On multivariable Cox proportional Hazard model (Table 2-2), two factors persisted as being associated with treatment and include facility location of west (HR 0.54, 95% CI 0.33-0.88, P=0.014), Charlson-Deyo Score of 0 (HR=0.43, 95% CI 0.25-0.74, P=0.014), Sequence number (HR=0.32, 95% CI 0.23-0.45, P<0.001), poor or undifferentiated tumor grade (HR=2.07, 95% CI 1.02-4.26, P=0.047), gleason score (7:HR=0.57, 95% CI 0.43-0.76, P<0.001) and age at diagnosis (HR=1.04, 95% CI 1.02-1.06, P<0.001).

The Kaplan-Meier survival curves stratified by treatment groups are shown in Figure 1. The 5-year OS rates for Radiation Therapy with Hormone Therapy treatment group(86.0%; 95% CI, 81.5%-89.5%) was significant worse than Radiation Therapy only treatment group (94.0%; 95% CI, 92.4%-95.2%) and the 10-year OS rates for Radiation Therapy with Hormone Therapy treatment group (69.8%; 95% CI, 62.2%-76.2%) was significant worse than Radiation Therapy only treatment group (77.0%; 95% CI, 73.0%-80.4%) (p-value < 0.001).

Table 3 are results of subgroup analyses. The greatest overall survival benefits from Radiation therapy treatment was seen in subgroups of patients with more aggressive prostate cancer, such as those with a higher gleason score (Gleason Score from 8 to 10) and pathologic T-stage of T3. Some patients in the database had a gleason score less than 8 and the difference in OS within this subgroup did not reach the statistical significance. Patients with a single malignant primary also appear to have a larger benefit for OS with radiation therapy only treatment.

The weighted baseline patient demographics and treatment characteristics were similar (Table 4, Figure 2; ASD < 0.10). The Kaplan-Meier survival curves of weighted samples stratified by treatment groups are shown in Figure 3. The 5-year OS rates for Radiation Therapy with Hormone Therapy treatment group(90.1%; 95% CI, 85.1%-93.5%) and Radiation Therapy only treatment group (94.7%; 95% CI, 91.9%-95.1%) and the 10-year OS rates for Radiation Therapy with Hormone Therapy treatment group (77.4%; 95% CI, 68.6%-84.0%) and Radiation Therapy only treatment group (75.2%; 95% CI, 70.7%-79.1%) were not statistically different (P =0.061). The effect of the treatment group was then further estimated in the weighted sample with a Cox model, which yielded an HR of 1.20 (95% CI, 0.99-1.46; P = 0.061) for Radiation Therapy with Hormone Therapy versus Radiation Therapy only.

Discussion：

On average, hormone therapy adds no benefit to overall survival comparing to radiation alone. In some subgroups of patients with more aggressive prostate cancer, such as those with a higher gleason score (Gleason Score from 8 to 10) and pathologic T-stage of T3, a beneficial trend by adding hormone therapy showed with HR < 1. However, their statistical significance may be hampered by the small sample size in the subgroups with a not-significant p-value for the interaction term in the model. Our conclusion is a little different from the previous related clinical trials which hold the ideas that SRT with short-term hormone therapy can help to rise overall survival of prostate patients after radical prostatectomy. The main reason for the difference may be due to the flaw of retrospective study design. Generally, the treatment of SRT with short-term hormone therapy is more likely to be used for patients who are in worse physical conditions while patients with better physical conditions prefer to take the normal treatment, hormone therapy only treatment. The patients cannot be divided into treatment groups randomly and the reason for patients to choose SRT with short-term hormone therapy treatment may partially lead to a worse overall survival.

Compared with clinical trials with the sample size of 760 patients in total[12], our study was based on a larger population. Because the NCDB captures 70% of all diagnosed cancer cases in the United States and follows patients for about 10 years in a multi-institutional setting, it offers a unique, potentially well-suited opportunity for investigating questions about prostate cancer.[18] As we know, this is the largest series of prostate cancer patients with SRT and hormone therapy ever reported, which makes this study a breakthrough on this topic. Moreover, the data collection of NCDB makes the conclusion much closer to the real life than that from clinical trials.

Although an extensive array of statistical tools were applied in our study, there are still a few limitations. The time points of some histopathologic information, such as the time information of

PSA, are not clear. As a result, in this study, PSA is not a biomarker for selecting the use of Hormone therapy as concluded by previous study. Because of the limited number of patients with codeleted tumors and specific period of treatment without any missing data enrolled, the sample size is still not large enough. Observation studies with a large-scale retrospective database comparing these treatment paradigms are warranted. A future prospective design should be appropriate to detect additional benefit of using hormone therapy after proctectomy and radiation therapy for prostate cancer patients.

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Table 1 Baseline characteristics for the entire study population and by the study cohorts and the factors predict the utilization of Hormone therapy

Variable	Level	Total N (%) = 1931	Univariate Association with Radiation Modalities			Logistic Regression Model for the Probability of Hormone Usage Odds Ratio (95% CI)	
			Radiation N=1529	R+Hormone N=402	Parametric P-value*	Odds Ratio (95% CI)	Type3 P-value
Age at Diagnosis	<=65	1390 (72.0)	1113 (72.79)	277 (68.91)	0.123	NS	
	>65	541 (28.0)	416 (27.21)	125 (31.09)			
Race-Ethnic Groups	White	1554 (80.5)	1210 (79.14)	344 (85.57)	**0.004**	NS	
	Black	277 (14.3)	240 (15.7)	37 (9.2)			
	Other	100 (5.2)	79 (5.17)	21 (5.22)			
Median Income Quartiles 2008-2012	< $38,000	334 (17.4)	284 (18.66)	50 (12.5)	**0.037**	NS	
	$38,000-$47,999	415 (21.6)	326 (21.42)	89 (22.25)			
	$48,000-$62,999	514 (26.7)	400 (26.28)	114 (28.5)			
	>=$63,000	659 (34.3)	512 (33.64)	147 (36.75)			
	Missing	9	258 (16.92)	48 (12)			
Percent No High School Degree 2008-2012	>=21.0%	306 (15.9)	369 (24.2)	103 (25.75)	0.101	NS	
	13.0-20.9%	472 (24.5)	516 (33.84)	137 (34.25)			
	7.0-12.9%	653 (33.9)	382 (25.05)	112 (28)			
	<7.0%	494 (25.7)	141 (9.22)	33 (8.21)			
	Missing	6	917 (59.97)	244 (60.7)			
Primary Payor	Other Government/Not Insured/Unknown	174 (9.0)	471 (30.8)	125 (31.09)	0.819	NS	
	Private	1161 (60.1)	1051 (68.74)	276 (68.66)			
	Medicare	596 (30.9)	478 (31.26)	126 (31.34)			
Facility Type	Non-Academic/ Research Program	1327 (68.7)	306 (20.01)	87 (21.64)	0.975	NS	
	Academic/ Research Program	604 (31.3)	512 (33.49)	105 (26.12)			
Facility Location	Northeast	393 (20.4)	469 (30.67)	151 (37.56)	**0.013**	0.74 (0.53-1.03)	**0.041**
	South	617 (32.0)	242 (15.83)	59 (14.68)		1.08 (0.79-1.49)	
	Midwest	620 (32.1)	362 (23.68)	103 (25.62)		0.78 (0.53-1.15)	
	West	301 (15.6)	302 (19.75)	77 (19.15)		-	

Variable	Level	Total N (%) = 1931	Univariate Association with Radiation Modalities			Logistic Regression Model for the Probability of Hormone Usage Odds Ratio (95% CI)	
			Radiation N=1529	R+Hormone N=402	Parametric P-value*	Odds Ratio (95% CI)	Type3 P-value
Year of Diagnosis	2004-2006	465 (24.1)	461 (30.15)	120 (29.85)	0.873	NS	
	2007-2009	379 (19.6)	404 (26.42)	102 (25.37)			
	2010-2012	581 (30.1)	1249 (81.69)	329 (81.84)			
	2013-2015	506 (26.2)	236 (15.43)	56 (13.93)			
Charlson-Deyo Score	0	1578 (81.7)	44 (2.88)	17 (4.23)	0.314	NS	
	1	292 (15.1)	1452 (94.96)	374 (93.03)			
	>=2	61 (3.2)	77 (5.04)	28 (6.97)			
Sequence Number	0	1826 (94.6)	370 (24.88)	35 (8.84)	**0.129**	NS	
	1	105 (5.4)	1117 (75.12)	361 (91.16)			
Grade	Well/Moderately Differentiated	405 (21.5)	329 (21.52)	43 (10.7)	**<.001**	1.92 (1.21-3.04)	**0.005**
	Poorly/Undifferentiated	1478 (78.5)	1200 (78.48)	359 (89.3)		-	
	Missing	48	941 (65.3)	245 (63.31)			
AJCC Pathologic T	T2	372 (19.3)	282 (19.57)	84 (21.71)	**<.001**	0.57 (0.40-0.81)	**0.002**
	T3	1559 (80.7)	218 (15.13)	58 (14.99)		-	
PSA	<10	1186 (64.9)	120 (8.16)	12 (3.03)	0.642	NS	
	10-20	366 (20.0)	736 (50.07)	110 (27.78)			
	>20	276 (15.1)	614 (41.77)	274 (69.19)			
	Missing	103	423 (27.67)	131 (32.59)			
Gleason	2-6	132 (7.1)	397 (25.96)	122 (30.35)	**<.001**	0.45 (0.21-0.97)	**<.001**
	7	846 (45.3)	372 (24.33)	88 (21.89)		0.42 (0.32-0.55)	
	8-10	888 (47.6)	337 (22.04)	61 (15.17)		-	
	Missing	65	220 (14.46)	21 (5.22)			

Variable	Level	Total N (%) = 1931	Univariate Association with Radiation Modalities			Logistic Regression Model for the Probability of Hormone Usage Odds Ratio (95% CI)	
			Radiation N=1529	R+Hormone N=402	Parametric P-value*	Odds Ratio (95% CI)	Type3 P-value
Days from diagnosis to surgery	Days from diagnosis to surgery<=42	554 (28.7)	1301 (85.54)	381 (94.78)	**0.005**	NS	
	42<=Days from diagnosis to surgery<60	519 (26.9)	1529	402			
	60<=Days from diagnosis to surgery<82	460 (23.8)	69.9	68.8			
	Days from diagnosis to surgery>=82	398 (20.6)	68	68.4			
RiskGroup	Low/Intermediate	241 (12.5)	59	59.4	**<.001**	NS	
	High	1682 (87.5)	702	161			
	Missing	8	34.21	7.22			
Regional+Boost Radiation Dose (GY)	Mean	69.67	1529	402	0.552	NS	
	Median	68.4	60.9	61.38			
	Minimum	59	61	62			
	Maximum	702	41	41			
	Std Dev	30.62	89	78			
	Missing	0	7	7.04			
Age at Diagnosis	Mean	61	1529	402	0.223	NS	
	Median	61	60.9	61.38			
	Minimum	41	61	62			
	Maximum	89	41	41			
	Std Dev	7.01	89	78			
	Missing	0	7	7.04			

* The parametric p-value is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.

* Number of observations in the original data set = 1931. Number of observations used = 1819.

*NS: not selected by the variable backward elimination at a significance level of 0.05.

Table 2-1 Univariate association with overall survival

			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Radiation Cohorts	R+Hormone	402	1.74 (1.32-2.29)	**<.001**	**<.001**
	Radiation	1529	-	-	
Race-Ethnic Groups	Black	277	0.88 (0.61-1.28)	0.513	0.409
	Other	100	0.65 (0.32-1.31)	0.226	
	White	1554	-	-	
Median Income Quartiles 2008-2012	< $38,000	334	0.77 (0.54-1.11)	0.157	0.321
	$38,000-$47,999	415	0.90 (0.64-1.27)	0.554	
	$48,000-$62,999	514	0.76 (0.54-1.06)	0.108	
	>=$63,000	659	-	-	
Percent No High School Degree 2008-2012	>=21.0%	306	0.92 (0.63-1.34)	0.667	0.582
	13.0-20.9%	472	0.82 (0.57-1.16)	0.259	
	7.0-12.9%	653	0.82 (0.59-1.13)	0.228	
	<7.0%	494	-	-	
Primary Payor	Other Government/Not Insured/Unknown	174	1.43 (0.89-2.30)	0.137	**<.001**
	Medicare	596	1.94 (1.48-2.52)	**<.001**	
	Private	1161	-	-	
Facility Type	Non-Academic/Research Program	1327	1.39 (1.03-1.86)	**0.029**	**0.029**
	Academic/Research Program	604	-	-	
Facility Location	South	617	0.85 (0.60-1.22)	0.378	**0.035**
	Midwest	620	1.06 (0.75-1.49)	0.737	
	West	301	0.56 (0.35-0.91)	**0.019**	
	Northeast	393	-	-	
Year of Diagnosis	2013-2015	506	1.12 (0.60-2.07)	0.725	0.351
	2010-2012	581	1.20 (0.83-1.75)	0.337	
	2007-2009	379	1.34 (0.97-1.85)	0.074	
	2004-2006	465	-	-	
Charlson-Deyo Score	0	1578	0.29 (0.17-0.48)	**<.001**	**<.001**
	1	292	0.40 (0.22-0.71)	**0.002**	
	>=2	61	-	-	
Sequence Number	00	1826	0.28 (0.20-0.39)	**<.001**	**<.001**
	01	105	-	-	

			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Grade	Poorly/Undifferentiated	1478	2.62 (1.66-4.15)	**<.001**	**<.001**
	Well/Moderately Differentiated	405	-	-	
AJCC Pathologic T	T2	372	0.70 (0.50-0.99)	**0.043**	**0.043**
	T3	1559	-	-	
PSA	<10	1186	0.87 (0.60-1.25)	0.448	0.545
	10-20	366	1.02 (0.66-1.57)	0.941	
	>20	276	-	-	
Gleason	2-6	132	0.35 (0.20-0.61)	**<.001**	**<.001**
	7	846	0.48 (0.36-0.63)	**<.001**	
	8-10	888	-	-	
Days from diagnosis to surgery	Days from diagnosis to surgery>=82	398	1.09 (0.74-1.60)	0.662	0.297
	60<=Days from diagnosis to surgery<82	460	1.33 (0.94-1.88)	0.113	
	42<=Days from diagnosis to surgery<60	519	1.31 (0.94-1.83)	0.111	
	Days from diagnosis to surgery<=42	554	-	-	
RiskGroup	Low/Intermediate	241	0.55 (0.35-0.85)	**0.007**	**0.007**
	High	1682	-	-	
Regional+Boost Radiation Dose (GY)		1931	1.00 (1.00-1.00)	0.969	0.969
Age at Diagnosis		1931	1.06 (1.04-1.08)	**<.001**	**<.001**

Table 2-2 Multivariable Cox proportional hazard model for Overall Survival

			Overall Survival		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Radiation Cohorts	R+Hormone	390	1.30 (0.97-1.73)	0.078	0.078
	Radiation	1429	-	-	
Facility Location	South	581	0.94 (0.65-1.36)	0.748	**0.038**
	Midwest	587	1.04 (0.73-1.48)	0.815	
	West	290	0.54 (0.33-0.88)	**0.014**	
	Northeast	361	-	-	
Charlson-Deyo Score	0	1487	0.43 (0.25-0.74)	**0.002**	**0.003**
	1	273	0.59 (0.33-1.07)	0.083	
	>=2	59	-	-	
Sequence Number	00	1718	0.32 (0.23-0.45)	**<.001**	**<.001**
	01	101	-	-	
Grade	Poorly/Undifferentiated	1433	2.07 (1.01-4.26)	**0.047**	**0.047**
	Well/Moderately Differentiated	386	-	-	
Gleason	2-6	131	0.83 (0.36-1.94)	0.674	**<.001**
	7	826	0.57 (0.43-0.76)	**<.001**	
	8-10	862	-	-	
Age at Diagnosis		1819	1.04 (1.02-1.06)	**<.001**	**<.001**

* Number of observations in the original data set = 1931. Number of observations used = 1819.
** Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Facility Type, Primary Payor, Median Income Quartiles 2008-2012, Percent No High School Degree 2008-2012, PSA, AJCC Pathologic T, Regional+Boost Radiation Dose (GY), Year of Diagnosis, Race-Ethnic Groups, and Days from diagnosis to surgery.

Table 3 Multivariable Analysis for Subgroups

Covariate	Level	N (R+Hormone vs. Radiation)	Overall Survival		
			Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Median Income Quartiles 2008-2012 :			-	-	0.143
	< $38,000	50 vs. 255	0.71 (0.33-1.54)	0.390	-
	$38,000-$47,999	88 vs. 308	0.98 (0.51-1.91)	0.964	-
	$48,000-$62,999	107 vs. 384	1.60 (0.90-2.86)	0.111	-
	>=$63,000	143 vs. 475	1.79 (1.15-2.77)	0.010	-
Comparisons Stratified by Primary Payor :			-	-	0.730
	Other Government/Not Insured/Unknown	32 vs. 131	0.91 (0.30-2.76)	0.863	-
	Private	241 vs. 882	1.40 (0.94-2.08)	0.098	-
	Medicare	123 vs. 457	1.47 (0.95-2.28)	0.085	-
Comparisons Stratified by Facility Type :			-	-	0.723
	Non-Academic/Research Program	272 vs. 1008	1.34 (0.97-1.86)	0.080	-
	Academic/Research Program	124 vs. 462	1.51 (0.86-2.65)	0.153	-

Covariate	Level	N (R+Hormone vs. Radiation)	Overall Survival		
			Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Year of Diagnosis :			-	-	0.789
	2004-2006	101 vs. 334	1.35 (0.88-2.07)	0.174	-
	2007-2009	73 vs. 273	1.51 (0.89-2.55)	0.126	-
	2010-2012	120 vs. 459	1.19 (0.64-2.22)	0.573	-
	2013-2015	102 vs. 404	2.22 (0.74-6.66)	0.153	-
Comparisons Stratified by Charlson-Deyo Score :			-	-	0.554
	0	323 vs. 1199	1.29 (0.92-1.80)	0.140	-
	1	56 vs. 228	1.93 (1.00-3.71)	**0.049**	-
	>=2	17 vs. 43	1.31 (0.48-3.56)	0.594	-
Comparisons Stratified by Sequence Number :			-	-	**0.007**
	00	362 vs. 1356	1.62 (1.18-2.21)	0.003	
	01	28 vs. 73	0.54 (0.26-1.13)	0.102	
Comparisons Stratified by AJCC Pathologic T :			-	-	0.114
	T2	42 vs. 309	0.54 (0.16-1.75)	0.303	-
	T3	348 vs. 1120	1.44 (1.06-1.95)	**0.019**	-

Covariate	Level	N (R+Hormone vs. Radiation)	Overall Survival Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Gleason :			-	-	**0.047**
	2-6	11 vs. 120	2.16 (0.48-9.75)	0.315	-
	7	110 vs. 716	0.69 (0.37-1.29)	0.242	-
	8-10	269 vs. 593	1.65 (1.17-2.34)	**0.004**	-
Comparisons Stratified by Age at Diagnosis :			-	-	0.930
	<=65	273 vs. 1066	1.36 (0.94-1.97)	0.100	-
	>65	123 vs. 404	1.40 (0.89-2.20)	0.146	-

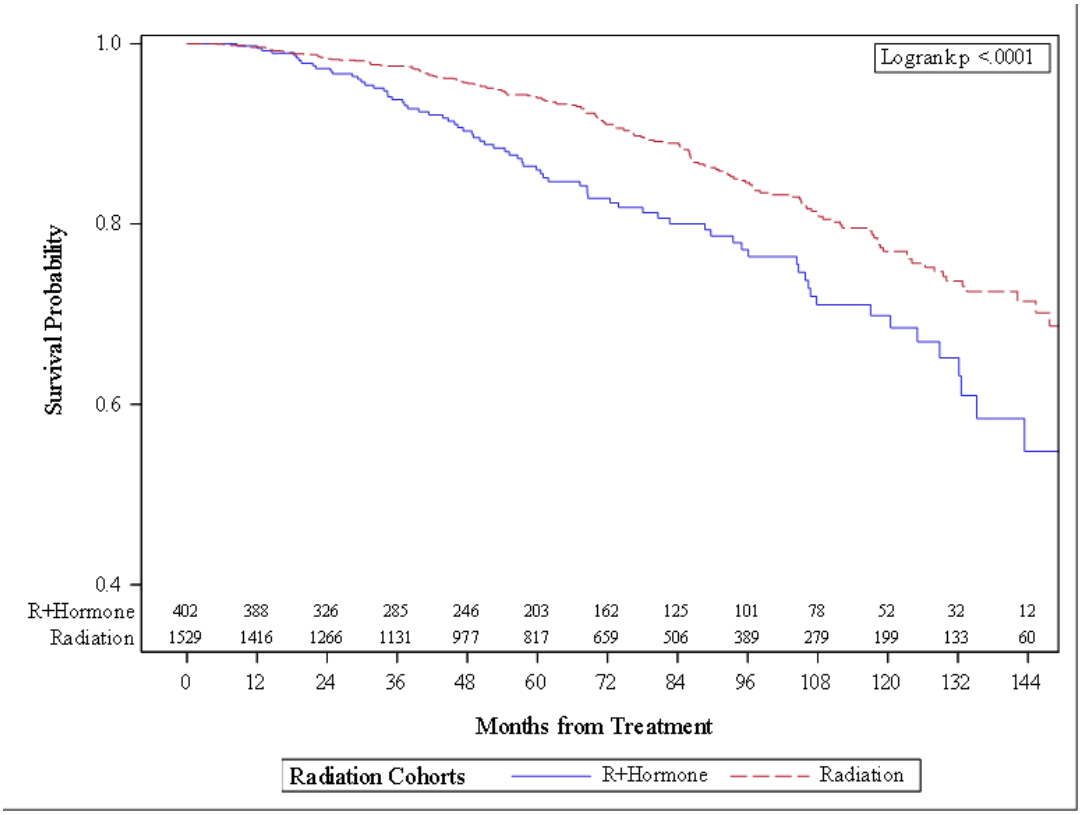
Table 4 Overall Sample Distribution and Balance Check for Before and After PS Average Treatment Effect Weighted Adjustment

		Study Sample Distribution		Absolute Standardized Difference(ASD)	
Covariate	**Level**	**Before**	**After**	**Before**	**After**
Radiation Cohorts	Overall	1715 (100.0)	3397 (100.0)	-	-
	Radiation	1340 (78.1)	1716 (50.5)	-	-
	R_Hormone	375 (21.9)	1681 (49.5)	-	-
Regional+Boost Radiation Dose (GY)	Mean(SD)	69.5 (28.6)	69 (30.5)	0.026	0.023
Age at Diagnosis	Mean(SD)	61 (7)	61.1 (9.7)	0.018	0.013
Race-Ethnic Groups	White	1390 (81)	2802 (82.5)	**0.164**	0.073
	Black	237 (13.8)	441 (13)	**0.176**	0.049
	Other	88 (5.1)	154 (4.5)	0.019	0.054
Median Income Quartiles 2008-2012	< $38,000	287 (16.7)	551 (16.2)	**0.17**	0.03
	$38,000-$47,999	384 (22.4)	760 (22.4)	0.033	0.004
	$48,000-$62,999	467 (27.2)	922 (27.1)	0.009	0.002
	>=$63,000	577 (33.6)	1163 (34.2)	**0.106**	0.021
Percent No High School Degree 2008-2012	>=21.0%	264 (15.4)	505 (14.9)	**0.135**	0.029
	13.0-20.9%	426 (24.8)	840 (24.7)	0.03	0.004
	7.0-12.9%	577 (33.6)	1207 (35.5)	0.02	0.069
	<7.0%	448 (26.1)	845 (24.9)	0.054	0.049
Primary Payor	Other Government/Not Insured/Unk	146 (8.5)	284 (8.4)	0.024	0.013
	Private	1046 (61)	2119 (62.4)	0.051	0.055
	Medicare	523 (30.5)	994 (29.3)	0.04	0.05
Facility Type	Non-Academic/Research Program	1177 (68.6)	2356 (69.4)	0.019	0.032
	Academic/Research Program	538 (31.4)	1040 (30.6)	0.019	0.032
Facility Location	Northeast	338 (19.7)	651 (19.2)	0.035	0.026
	South	539 (31.4)	1067 (31.4)	**0.126**	0.002
	Midwest	563 (32.8)	1128 (33.2)	**0.129**	0.021
	West	275 (16)	550 (16.2)	0.048	0.004
Year of Diagnosis	2004-2006	396 (23.1)	801 (23.6)	0.052	0.022
	2007-2009	326 (19)	613 (18.1)	0.003	0.044
	2010-2012	526 (30.7)	1029 (30.3)	0.008	0.014
	2013-2015	467 (27.2)	953 (28)	0.039	0.032
CDCC_TOTAL_BEST	0	1396 (81.4)	2728 (80.3)	0.024	0.046
	1	263 (15.3)	555 (16.3)	0.053	0.045
	2	56 (3.3)	114 (3.4)	0.051	0.01

Sequence Number	00	1617 (94.3)	3190 (93.9)	0.092	0.028
	01	98 (5.7)	207 (6.1)	0.092	0.028
Grade	Well/Moderately Differentiated	354 (20.6)	674 (19.9)	**0.407**	0.039
	Poorly/Undifferentiated	1361 (79.4)	2722 (80.1)	**0.407**	0.039
AJCC Pathologic T	T2	320 (18.7)	622 (18.3)	**0.283**	0.019
	T3	1395 (81.3)	2775 (81.7)	**0.283**	0.019
PSA	<10	1111 (64.8)	2201 (64.8)	0.035	0
	10-20	343 (20)	690 (20.3)	0.051	0.014
	>20	261 (15.2)	506 (14.9)	0.01	0.015
Gleason	2-6	114 (6.6)	211 (6.2)	**0.213**	0.036
	7	779 (45.4)	1526 (44.9)	**0.469**	0.019
	8-10	822 (47.9)	1659 (48.8)	**0.566**	0.036
Days from diagnosis to surgery	Days from diagnosis to surgery<=42	490 (28.6)	972 (28.6)	**0.111**	0.004
	42<=Days from diagnosis to surgery<60	474 (27.6)	969 (28.5)	0.093	0.034
	60<=Days from diagnosis to surgery<82	402 (23.4)	801 (23.6)	0.065	0.008
	Days from diagnosis to surgery>=82	349 (20.3)	655 (19.3)	**0.17**	0.052
RiskGroup	Low/Intermediate	207 (12.1)	395 (11.6)	**0.282**	0.028
	High	1508 (87.9)	3002 (88.4)	**0.282**	0.028

* The absolute standardized Difference (ASD) >= 0.1 is bold and indicates insufficient balance.

Figure 1. K-M plot for Overall Survival for original samples



Radiation Cohorts	No. of Subject	Event	Censored	Median Survival (95% CI)	60 Mo Survival	120 Mo Survival
R+Hormone	402	74 (18%)	328 (82%)	156.6 (135.2, NA)	86.0% (81.5%, 89.5%)	69.8% (62.2%, 76.2%)
Radiation	1529	170 (11%)	1359 (89%)	165.4 (165.4, NA)	94.0% (92.4%, 95.2%)	77.0% (73.0%, 80.4%)

Figure 2. Balance Check by ATE

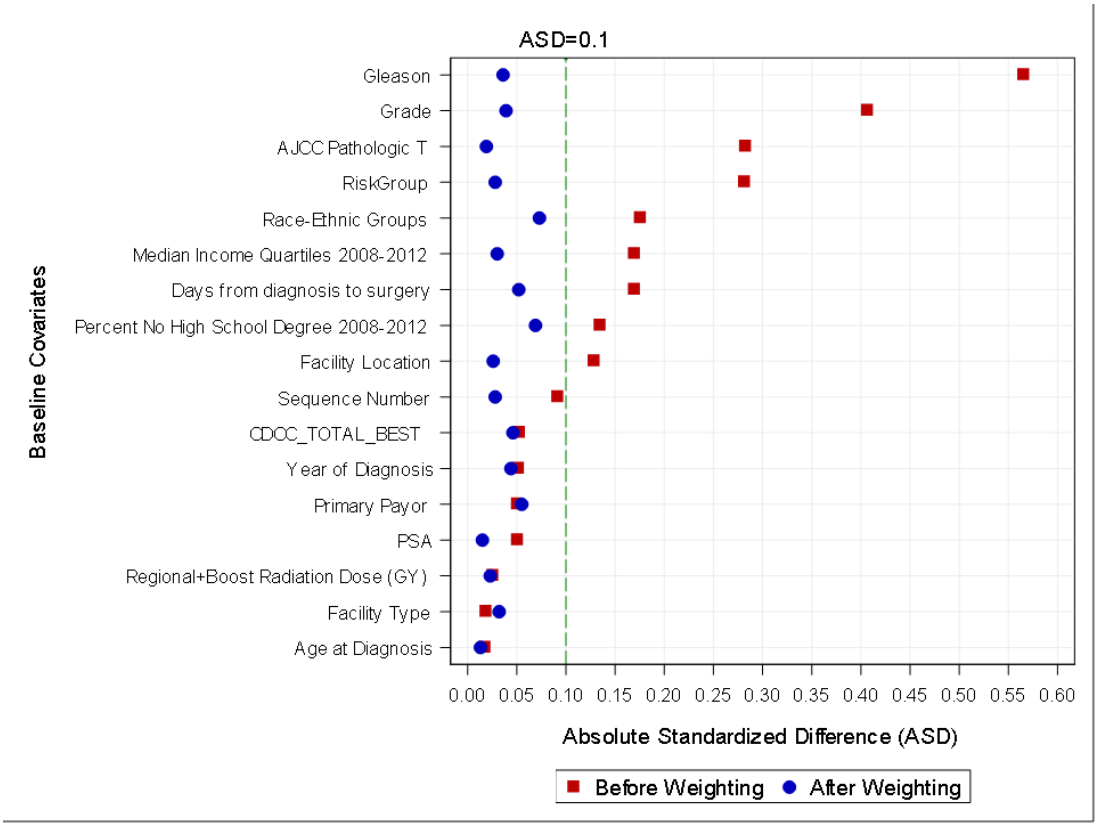
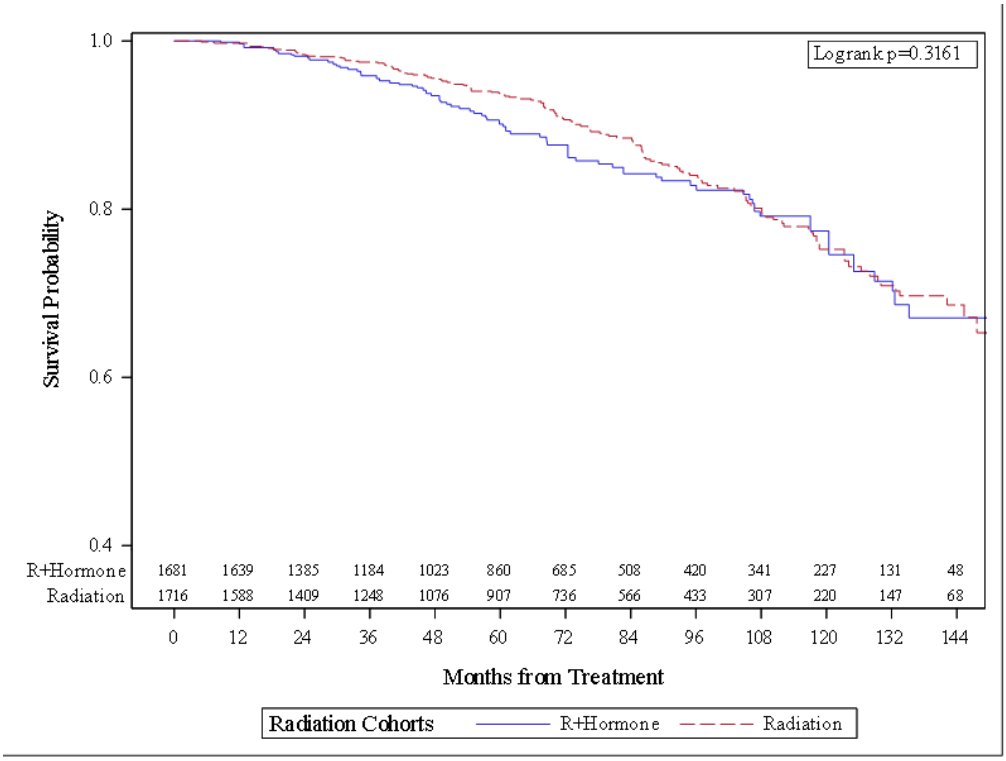


Figure 3. K-M plot for Overall Survival for weighted samples



Radiation Cohorts	No. of Subject	Event	Censored	Median Survival (95% CI)	60 Mo Survival	120 Mo Survival
R+Hormone	375	67 (18%)	308 (82%)	156.6 (156.6, NA)	90.1% (85.1%, 93.5%)	77.4% (68.6%, 84.0%)
Radiation	1340	151 (11%)	1189 (89%)	165.4 (165.4, 166.5)	93.7% (91.9%, 95.1%)	75.2% (70.7%, 79.1%)