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Radiation Therapy and Survival in Prostate Cancer Patients – A Population-based Study

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Abstract

Purpose—To investigate the association of overall and disease specific survival with the 5 standard treatment modalities for prostate cancer (CaP): radical prostatectomy (RP), brachytherapy (BT), external beam radiation therapy (EBRT), androgen deprivation therapy (ADT), and no treatment (NT) within 6 months after CaP diagnosis.

Methods and Materials—The study population included 10,179 men 65 years and older with incident CaP diagnosed between 1999 and 2001. Using the linked Ohio Cancer Incidence Surveillance System, Medicare, and death certificate files, we analyzed overall and disease specific survival through 2005 among the five clinically accepted therapies.

Results—Disease specific survival rates were 92.3% and 23.9% for patients with localized versus those with distant disease at 7 years, respectively. Controlling for age, race, comorbidities, stage, and

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Conflict of interest: None.

Disclaimer Cancer incidence data were obtained from the Ohio Cancer Incidence Surveillance System (OCISS), Ohio Department of Health. Use of these data does not imply that the Ohio Department of Health either agrees or disagrees with any presentation, analyses, interpretations, or conclusions. Information about the OCISS may be obtained at odh.state.oh.us/ODHPrograms/CI_SURV/ci_surv1.htm.

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Gleason score, results from the Cox multiple regression models indicated that the risk of CaP specific death was significantly reduced in patients receiving RP or BT, compared with NT. For localized disease, compared with NT, in mono-therapy cohort, RP and BT were associated with reduced hazard ratios (HR) =0.25 and 0.45 (95% confidence interval [0.13-0.48] and [0.23-0.87], respectively); while in the combination therapy cohort, HR were 0.40 [0.17-0.94] and 0.46 [0.27-0.80], respectively.

Conclusions—The present population-based study indicates that RP and BT are associated with improved survival outcomes. Further studies are warranted to improve clinical determinates in the selection of appropriate management of CaP, and to improve predictive modeling for which patient subsets may benefit most from definitive therapy, versus conservative management and/or observation.

Keywords

Prostate cancer; survival; treatment modalities; population-based study

Introduction

Prostate cancer (CaP) is one of the most common cancer diagnoses in men, and a leading cause of cancer death in the United States with 219,000 estimated new cases and 27,000 deaths each year. One-fifth of American men will be diagnosed with CaP in their lifetimes. The incidence increases with age, more than 65% cases are diagnosed in men 65 years and older (1).

There are several treatment options available for localized CaP, including radical prostatectomy (RP), brachytherapy (BT), external beam radiation therapy (EBRT), androgen deprivation therapy (ADT) and active surveillance (2-4). The choice of treatment is dependent upon several factors, including the likelihood that the CaP is confined to the prostate gland; the degree of aggressiveness or histological grade; a man's age and overall health, including comorbidities; as well as the expected outcomes and potential side effects associated with the different forms of treatment (5-7).

The optimal treatment for men with CaP remains controversial for several reasons. First, understaging is a possibility, as diagnostic imaging cannot always identify metastatic CaP. Second, the Gleason score, which is one of the most important factors in predicting disease progression, is subjective and dependent on a pathologist's interpretation of the submitted biopsy material (8). Third, Prostate Specific Antigen (PSA) screening may over-detect some clinically insignificant CaP. Fourth, important consideration is given to quality of life in choosing treatment modalities (9,10). Finally, given that the majority of CaP patients are older men, the aging of the population makes it even more important to thoroughly investigate treatment outcomes, as they may have a very significant public health impact.

Population-based cancer studies utilizing large databases are extremely valuable and powerful for conducting epidemiological studies, as the population will be more heterogeneous compared to hospital-based or center-based observational studies. Previous studies have used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 5-19 SEER geographic areas to evaluate CaP treatment patterns (11,12). There has been a dearth of studies comparing outcomes between patients receiving definitive treatment and those with NT. A recent study compared overall survival in patients with low and intermediate risk localized CaP between these two groups (13); another analyzed the effect of ADT relative to survival in patients with metastatic CaP (14). There is an urgent need for more studies confirming these results, both in patients residing in the SEER geographical areas and patients residing in other parts of the United States. In addition, studies comparing the entire standard treatment regimens (RP, BT, EBRT, ADT and NT) for the overall survival and disease specific survival using the SEER-Medicare data set are currently inadequate, BT or EBRT have not

been compared with NT. BT, alone or in combination with EBRT, has become widely accepted as first-line treatments for patients with localized CaP, and relevant outcomes studies have been conducted in smaller, center-based group of patients, but not in population-based data (15-17). We aimed to investigate survival outcomes in the State of Ohio, using the Cancer-Aging Linked Database (CALD), which mirrors the structure of the SEER-Medicare files, and combines data from the Ohio Cancer Incidence Surveillance System (OCISS) and Medicare enrollment and claims files.

Methods and Materials

Overview and data linkage procedures

The present large population-based retrospective cohort study used the Ohio CALD data, which was developed by linking records from the OCISS with Medicare enrollment and claims files, and the Ohio death certificate files. OCISS and Medicare data were linked by the Center for Medicare & Medicaid Services using the patient social security number. Approximately 97% of patients in the OCISS were identified successfully as Medicare beneficiaries. In parallel, OCISS and death certificate records were linked using patient social security number, name, and date of birth. Once Medicare and death certificate records were successfully identified for OCISS patients, a unique patient identifier variable “PATID”, originating from the OCISS, became the variable linking across all relevant data files. All sensitive patient identifiers were dropped from all the records. The institutional review boards of the Ohio Department of Health, and the University Hospitals of Cleveland approved this study.

In addition to patient identifiers and demographics, the OCISS contains cancer-specific characteristics, including date of diagnosis, anatomical site, stage at diagnosis, and tumor grade. Medicare claims files include the Medicare Provider Analysis and Review for inpatient admissions, the Standard Analytic Files cover all outpatient and ambulatory surgeries, the Physician Supplier files include services received in non-hospital and non-institutional providers. These data include up to 10 diagnosis and 10 procedures coded by the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) (18), the Current Procedure Terminology and/or Healthcare Common Procedure coding System.

Study population

Eligible men were aged 65 years or older residing in OH, diagnosed with incident CaP in years January 1, 1999 through December 31, 2001 with continuous Medicare coverage for at least 6 months prior to diagnosis. Death certificates for deaths occurred on or prior to December 31, 2005 were appended to the OCISS records. We excluded men who were enrolled in Medicare managed care programs in the 6 months prior to or 1 months following initial cancer diagnosis. We identified a total of 10,632 patients meeting our inclusion criteria. 453 men were excluded because they were diagnosed with CaP on the same day or after they were dead, leaving our study population to 10,179 men, of whom 8,255 were diagnosed with local-regional disease, 466 presented with distant metastases, and 1,458 men with unknown-stage.

Variables of interest

Outcome Variables—The main outcome is the overall survival and disease specific survival. Overall survival was defined from the date of diagnosis to the date of death from any reason; while disease specific survival was to the date of CaP specific death, including death codes as malignant neoplasm of prostate, malignant neoplasm without specification of site and/or multiple sites, and/or metastatic disease.

Independent Variables

Treatment modalities: The 5 common treatment modalities include curative intent therapies such as BT, EBRT, and RP; or ADT alone used for conservative management to delay disease progression; or NT, during the period of 1 month prior and 6 months after the CaP diagnosis (procedure codes are available upon request). Mono-therapy is defined as only receiving one treatment modality. Combination therapy for RP or BT is defined as receiving additional EBRT and/or ADT; EBRT is defined as receiving EBRT and ADT; ADT and NT are the same as in mono-therapy.

Demographics: Age is defined in 5-year increments and categorized into 4 ordinal levels for all patients 65 years of age or older: $65 \leq \text{age} < 70$, $70 \leq \text{age} < 75$, $75 \leq \text{age} < 80$, $\text{age} \geq 80$. Given the small representation of ethnic minorities in the Ohio population, race was categorized into African Americans and “All Other” – including Caucasians, Hispanics, and Asians, with limited number of Hispanics, and Asians.

Tumor characteristics: We used the SEER summary stage reported in the OCIS, as follows: in situ (excluded if unknown Gleason score), local, regional, distant disease, and unknown. We defined localized disease as local and regional disease. We excluded men with in situ disease from the study population. Gleason score was categorized as low (2-4), intermediate (5-6), high (7-10), and unknown.

Comorbidity: We first identified patients with in-hospital admission or out-patient visit 1-12 months prior to the CaP diagnosis. Comorbidity, based on inpatient and outpatient data, was defined using non-cancer diagnostic categories listed in the Charlson Index (19). The 4 levels were defined as: no in-hospital admission or out-patient visit history in the look-back period (level=-1); with hospital admission or out-patient visit but without any non-cancer conditions listed in the Charlson Index (level=0, used as reference group in the Cox regression analyses); a Charlson score of 1 (level=1); and a Charlson score of 2 and above (level=2+).

Statistical Analysis

Descriptive analysis was used to provide summaries about the patient and tumor characteristics. Overall and disease specific survival were estimated using univariate analysis, and stratified by treatment method used. Survival curves were calculated using the Kaplan-Meier methods and survival differences between groups were examined using the log-rank test. Cox regression model was used to evaluate the overall survival and disease specific survival in control of age, race, tumor stage, Gleason score, pre-treatment co-morbidity, and treatment modalities, for the entire cohort, localized disease group, or distant disease group. There was no violation of the proportional hazard assumption in all our final models. All tests were two-sided and p -values < 0.05 were considered to be statistically significant. All statistical analysis was performed with SAS 9.0 (Cary, NC).

Results

Table 1 details the distribution of each treatment option stratified by patient and tumor characteristics. A cohort of 10,179 men was included with CaP in the linked dataset. The 7-year overall and disease specific survival rates for the entire study cohort were 61.1% and 87.6%, respectively. The disease specific survival rates for the localized and distant disease group were 92.3% and 23.9% at 7 years. Figure 1 shows for both mono-therapy (A, B) and combination therapy (C, D), RP yield the highest overall and disease specific survival; followed by BT, then EBRT. Figure 2 illustrates survival outcomes in men with distant disease when receiving EBRT, ADT, or NT. Of note is the limited number of patients with distant disease to have received RP or BT (data not shown).

Cox multiple regression analysis for overall and disease specific survival in the entire cohort, localized disease group, and distant disease group are shown in Tables 2 (mono-therapy) and 3 (combination therapy). For the entire cohort and localized disease group, using either RP or BT as mono-therapy or combination therapy was significantly associated with better overall and disease specific survival comparing with NT, after controlling for age, race, comorbidities, tumor stage, and Gleason score. For distant disease group, there was no significant benefit using mono-therapy EBRT, while the risk for both overall and disease specific death decreased 50% by using EBRT in conjunction with ADT or ADT alone, comparing with NT, after adjusting for covariates.

Findings in Tables 2 and 3 also indicated that both tumor stage and Gleason score were positively and significantly associated with overall survival; and even more strongly associated with disease specific survival. The effect of Gleason score was consistently significant for the entire cohort, localized group, and distant disease group, for both mono-therapy and combination therapy, after controlling for covariates. Age and comorbidity, but not race, were significant in predicting both overall and disease specific survival adjusting for tumor and treatment effect.

Discussion

The present study is the first CaP survival analysis using the Ohio CALD, which mirrors in structure the SEER-Medicare files. We evaluated CaP incidence data linked with Medicare and Death Certificate files, and concluded that the definitive treatment modalities, RP and BT, were associated with significantly better overall and disease specific survival compared to NT. The present results provided demonstrate that the risk of CaP specific deaths decreased more than 50% when receiving BT alone or in conjunction with EBRT or ADT compared to NT, after controlling for age, race, comorbidities, tumor stage, and Gleason score. There are limited data available through randomized clinical trials providing information that directly compares all the treatment modalities: RP, BT, EBRT, and ADT versus NT (3). The overall survival rates and the definitive treatment effects of the present study are in agreement with the previously published studies using SEER-Medicare data analyzing aggressive treatment versus non-aggressive treatment for localized disease (13), and distant disease (14) – findings that attest to the validity of the data represented in the Ohio CALD.

Studies investigating the effect of RP versus NT in predicting overall and disease specific survival have not yielded consistent results. Findings from a randomized clinical trial (n=695 men with localized disease) indicated that RP predicted a significant overall survival benefit, in addition to a very significant reduction in the risks of disease specific death, metastasis, and local tumor progression comparing to watchful waiting (20). There were two other randomized clinical trials comparing RP versus NT or RP versus EBRT. With small sample size, neither trial was able to convincingly demonstrate an advantage of RP over NT or RP over EBRT (21). A retrospective population-based cohort study using data from the Connecticut Tumor Registry (n=767 men) showed that the annual mortality rate from CaP remained stable 15 years post diagnosis, a finding that does not support aggressive treatment for localized low-grade CaP (22). The present study provides evidence supporting RP for localized cohort in a more heterogeneous population.

In this study, we compared BT versus NT and showed that BT was significantly associated with better overall and disease specific survival. The risk of CaP specific death decreased more than 50% when receiving BT alone or in conjunction with EBRT or ADT compared to NT. No randomized clinical trials or large cohort studies comparing BT versus NT were found when performing Medline search. BT and NT are usually being offered to men with localized disease especially with low Gleason score. However, as we mentioned before, these men may

carry undetected high-grade disease (23). Men with shorter life expectancy tended to be observed instead of being treated. However, even after adjusting for age, race, comorbidities, tumor stage, and Gleason score, we still conclude that BT yields significantly better survival outcomes than NT. Baseline PSA and its velocity have a critical role in determining treatment, unfortunately PSA values cannot be obtained from the currently available databases. However, this is essential when comparing NT with other definitive treatment regimens because NT is usually assigned to those with low PSA, low Gleason score, and surrogates for clinically insignificant CaP (24,25). We would expect even more significant effects comparing both RP and BT versus NT when controlling for pretreatment PSA. This is especially true when comparing EBRT versus NT. Recent hospital-based or multi-center studies showed that 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT) could provide better disease specific survival, compared to the conventional radiation therapy; and that the outcome of EBRT and BT was similar to those of surgery patients with low risk disease (26). The present study showed significant decreased risk for patients treated with EBRT either alone or in conjunction with ADT compared with NT for the entire cohort. A more than 40% decreased CaP specific risk for the entire cohort indicated using EBRT could significantly improve survival in a large heterogeneous population. It failed to conclude whether EBRT with or without ADT, could provide significant benefit for disease specific survival for localized disease without adjusting for pretreatment PSA. One reason may be that the follow-up period is not long enough. With a small number of disease-specific deaths in localized disease, it is more difficult to show significant differences in survival. Another reason is that men who received EBRT usually have more aggressive disease than those who do not initiate definitive treatment within 6 months. In addition, even though we were able to control for the most important tumor and patients' characteristics, the results may be confounded by variables that we could not account for in our analyses. These include preoperative PSA and patients' performance status. For localized disease, it would be expected that those who had NT or received BT or RP as mono-therapy, would have a lower PSA than those receiving EBRT. EBRT in conjunction with ADT or ADT alone provides better survival than NT in distant disease group, which is in agreement with the previous SEER-Medicare study by Lu-Yao, et al (14).

The majority of patients who show progression are often patients in whom occult metastatic disease may have been present prior to definitive therapy, and thus they were under-staged, and technically not curable. Recent introduction of advanced imaging techniques (27) may hold promise for selecting patients for local therapies, or help to determine which patients would benefit from the addition of systemic treatment with either adjuvant hormonal therapies or other forms of adjuvant chemotherapy, along with improved local therapies like cryotherapy, cyberknife, and other new EBRT techniques such as IMRT and 3D conformal radiotherapy, etc. might be helpful in increasing the disease free survival of CaP patients (28).

Despite our attempts to adjust for all available confounding factors in the regression model, without proper randomization, the treatment effect may be biased with known and unknown confounding factors. Pretreatment PSA >10 or >20 ng/mL, is one of the most important factors when deciding the treatment modality, though not specific for CaP, it is usually considered a risk factor associated with disease specific survival (2). Recent studies show that PSA velocity not only predicts the presence of CaP but also is highly associated with disease specific death (29). Percent positive biopsies and proportion of higher Gleason grades are some other factors (30,31). Many other factors like smoking, certain food consumption, and other life style may significantly impact treatment selection and survival, which could not be adjusted for (32-34).

Additionally, although we controlled for comorbid conditions, there could well be other conditions such as performance status, functional dependence and presence of geriatric

conditions, which may characterize a patient as unfit to undergo more aggressive treatment. Future studies that link large population based data with multi-center clinical data are a potential direction when more, higher quality electronic clinical data may be routinely available. Like SEER data, the OCISS updates the stage information after a surgery. For CaP, RP is the only procedure that may have an up-graded stage. Compared to other treatment methods, RP may potentially have higher survival controlling for stage. However, we expect this proportion to be low and some even report the down grade of Gleason score (35). In the case that this happens and there is some degree of differential bias, we could expect better survival after BT than RP after controlling for this effect. For the finding that RP is better than NT, the hazard ratio will migrate towards the null when considering the up-grade effect.

As expected, age, tumor stage, Gleason score, and patient comorbidities are all very important factors in predicting overall and disease specific survival. We conclude that in the CaP survival analysis, without proper adjustment for age and the patient's health condition, the treatment effect cannot be evaluated conclusively.

In summary, the findings of this study suggest RP and BT significantly improve both overall and disease specific survival compared with NT, especially when used in conjunction with EBRT and ADT. This study provides more evidence supporting that earlier initiation of definitive treatments like BT or RP is better than NT in a more heterogeneous population. Despite our current inability to determine pre-treatment PSA data from our dataset, it should provide a sense of caution in not recommending treatment to patients who appear to have some higher degree of risk from the clinical staging, including not only PSA level, but PSA doubling times, Gleason scores of 7 or greater, and perhaps disease volume based on % positive core biopsies and % positive of each core. These results are very important for clinicians, patients, and their families in deciding the next step when facing the new diagnosis. Further research on CaP treatment related urinary and bowel function and erectile dysfunction are needed to better evaluate and interpret treatment outcomes.

Conclusions

After controlling for patient age, race, comorbidities, cancer stage and Gleason score, patients managed with curative intent therapy BT or RP either alone or in conjunction with EBRT or ADT, demonstrate improved overall and disease specific survival compared to those without curative therapy initiated within 6 months of diagnosis. With the inclusion of additional years of data, we expect to provide longer follow-up and obtain a larger, more homogenous population with further stratification, which may detect more important treatment effects. Further investigation on treatment side effects is needed in this Ohio population; to improve clinical determinates in the selection of appropriate management.

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Figure 1.

Kaplan-Meier overall (A, C) and disease specific survival (B, D) curves for the localized CaP, stratified by mono-therapy (M-) (A, B) and combination therapy (C-) (C, D), black: radical prostatectomy (RP), red: brachytherapy (BT), green: external beam radiation therapy (EBRT), light blue: androgen deprivation therapy (ADT), and blue: no treatment (NT) within 6 months after prostate cancer diagnosis.

Figure 2.

Kaplan-Meier overall (A, C) and disease specific survival (B, D) curves for the distant disease, stratified by mono-therapy (M-) (A, B) and combination therapy (C-) (C, D), green: androgen deprivation therapy (ADT), black: external beam radiation therapy (EBRT), and red: no treatment (NT) within 6 months after prostate cancer diagnosis.

Table 1

Patient characteristics among 10,179 men with prostate cancer underwent standard treatment or no treatment between January 1999 and December 2001 in Ohio (To protect patient information, we combined cells contain less than 11 men in the group).

Variables	Category	Mono-therapy*				Combination Therapy [†]				Sub-total Patients
		RP	BT	EBRT	ADT	RP	BT	EBRT	NT [‡]	
Age	65-69	562	189	178	348	109	234	287	279	2186
	70-74	318	312	378	684	71	366	553	581	3263
	75+	56	143	320	1915	15	223	612	1446	4730
Race	AA	70	35	86	297	12	64	104	246	914
	Non-AA	866	609	790	2650	183	759	1348	2060	9265
SEER-Stage	Local/Regional	889	595	783	2049	181	756	1286	1716	8255
	Distant/unknown	47	49	93	898	14	67	166	590	1924
Gleason Score	<7	714	531	674	1654	117	614	840	1617	6761
	7-10	177	53	135	991	65	156	505	336	2418
	Unknown	45	60	67	302	13	53	107	353	1000
Comorbidity	Level =-1	76	60	80	239	18	49	100	197	819
	Level =0	714	442	555	1762	145	571	956	1322	6467
	Level =1+	146	142	241	946	32	203	396	787	2893
Year at Diagnosis	1999	349	194	329	900	79	253	478	789	3371
	2000	306	208	305	984	50	257	503	766	3379
	2001	281	242	242	1063	66	313	471	751	3429
Sub-total Patients		936	644	876	2947	195	823	1452	2306	10179

Abbreviations: AA=African American, RP=radical prostatectomy, BT=brachytherapy, EBRT=external beam radiation therapy, ADT=androgen deprivation therapy, NT=no treatment.

* Mono-therapy was defined as receiving only one therapy during the first 6 months after the prostate cancer diagnosis: RP, BT, EBRT, or ADT.

[†]Combination therapy was defined as: RP with additional EBRT, or ADT, or both; BT with additional EBRT or ADT, or both; EBRT with additional ADT.

^{††}NT was defined as no definitive therapy within 6 months after prostate cancer diagnosis.

Table 2
Cox Regression models on overall and disease specific survival for the entire cohort, localized disease, and distant disease group, when receiving mono-therapy.

Variables	Category	Overall Survival				Disease Specific Survival			
		Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value
			lower	upper			lower	upper	
Age	5-year increments	1.50	1.44	1.56	<.0001	1.35	1.25	1.45	<.0001
Race	Non-AA								
	AA	1.06	0.94	1.20	0.3391	0.96	0.78	1.18	0.6870
Stage	Local								
	Regional	1.92	1.62	2.28	<.0001	4.54	3.42	6.04	<.0001
	Distant	4.75	4.19	5.38	<.0001	13.30	10.92	16.21	<.0001
	Unknown	1.47	1.34	1.61	<.0001	3.04	2.54	3.65	<.0001
	2-4								
Gleason Score	5-6	1.12	0.95	1.31	0.1732	1.93	1.10	3.39	0.0221
	7-10	1.65	1.39	1.96	<.0001	5.92	3.38	10.38	<.0001
	Unknown	1.98	1.65	2.38	<.0001	9.14	5.20	16.05	<.0001
	NT								
	RP	0.28	0.23	0.36	<.0001	0.16	0.09	0.28	<.0001
Mono-therapy	BT	0.34	0.27	0.42	<.0001	0.20	0.11	0.38	<.0001
	EBRT	0.60	0.52	0.70	<.0001	0.54	0.39	0.76	0.0003
	ADT	0.75	0.69	0.82	<.0001	0.71	0.61	0.83	<.0001
	Level =0								
Comorbidity	Level =-1	0.64	0.56	0.73	<.0001	0.61	0.49	0.75	<.0001
	Level =1	1.05	0.91	1.21	0.5052	0.56	0.43	0.72	<.0001
	Level =2+	1.54	1.33	1.78	<.0001	0.80	0.62	1.05	0.1049

Age	5-year increments	1.53	1.45	1.61	<.0001	1.49	1.32	1.68	<.0001
Race	Non-AA								
	AA	1.22	1.04	1.42	0.0141	1.18	0.81	1.72	0.3846
Stage	Local								
	Regional	1.88	1.58	2.24	<.0001	4.06	3.04	5.43	<.0001

Variables	Category	Overall Survival				Disease Specific Survival			
		Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value
			lower	upper			lower	upper	
Gleason Score	2-4								
	5-6	1.07	0.90	1.27	0.4434	1.53	0.83	2.85	0.1757
	7-10	1.48	1.22	1.79	<.0001	4.18	2.23	7.81	<.0001
	Unknown	1.35	1.06	1.71	0.0138	3.41	1.69	6.88	0.0006
Mono-therapy	NT								
	RP	0.32	0.25	0.41	<.0001	0.25	0.13	0.48	<.0001
	BT	0.40	0.32	0.52	<.0001	0.45	0.23	0.87	0.0181
	EBRT	0.63	0.53	0.75	<.0001	0.66	0.41	1.04	0.0731
	ADT	0.89	0.80	0.98	0.0243	1.32	1.01	1.73	0.0445
Comorbidity	Level =0								
	Level =-1	0.64	0.54	0.76	<.0001	0.82	0.56	1.20	0.2976
	Level =1	1.16	0.97	1.38	0.1101	0.68	0.43	1.06	0.0895
	Level =2+	1.83	1.52	2.20	<.0001	1.18	0.73	1.89	0.4977
Distant Diseases Only	Age								
	5-year increments	1.33	1.19	1.48	<.0001	1.19	1.05	1.35	0.0076
	Race								
	Non-AA								
	AA	1.01	0.75	1.34	0.9727	1.10	0.79	1.53	0.5830
	Gleason Score								
	2-4								
	5-6	2.44	0.76	7.86	0.1345	2.11	0.50	8.88	0.3103
	7-10	3.92	1.24	12.40	0.0201	4.34	1.06	17.75	0.0413
	Unknown	3.67	1.15	11.74	0.0281	4.10	0.99	16.99	0.0517
	NT								
	mono-therapy								
	EBRT	1.02	0.58	1.79	0.9488	1.12	0.56	2.25	0.7486
	ADT	0.40	0.32	0.51	<.0001	0.44	0.33	0.59	<.0001
	Comorbidity								
	Level =0								
	Level =-1	0.62	0.43	0.90	0.0118	0.57	0.38	0.87	0.0096
	Level =1	0.65	0.42	1.01	0.0539	0.48	0.28	0.82	0.0068
	Level =2+	0.75	0.48	1.17	0.1985	0.60	0.36	1.02	0.0569

Abbreviations: AA=African American, RP=radical prostatectomy, BT=brachytherapy, EBRT=external beam radiation therapy, ADT=androgen deprivation therapy, NT=no treatment.

Table 3

Cox Regression models on overall and disease specific survival for the entire cohort, localized disease, and distant disease group, when receiving combination therapy.

Variables	Category	Overall Survival				Disease Specific Survival			
		Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value
			lower	upper			lower	upper	
Age	5-year increments	1.45	1.39	1.51	<.0001	1.32	1.23	1.42	<.0001
Race	Non-AA								
	AA	1.00	0.89	1.13	0.9932	0.99	0.81	1.21	0.8892
Stage	Local								
	Regional	1.82	1.54	2.16	<.0001	3.75	2.87	4.91	<.0001
	Distant	4.93	4.38	5.56	<.0001	13.31	11.09	15.98	<.0001
	Unknown	1.48	1.35	1.62	<.0001	2.84	2.39	3.38	<.0001
	2-4								
Gleason Score	5-6	1.13	0.96	1.33	0.1406	1.94	1.13	3.33	0.0170
	7-10	1.70	1.44	2.02	<.0001	5.88	3.43	10.08	<.0001
	Unknown	2.01	1.68	2.41	<.0001	8.65	5.03	14.89	<.0001
	NT								
	RP	0.23	0.15	0.37	<.0001	0.26	0.12	0.53	0.0002
Combination Therapy	BT	0.29	0.23	0.36	<.0001	0.25	0.15	0.40	<.0001
	EBRT	0.53	0.47	0.60	<.0001	0.60	0.49	0.75	<.0001
	ADT	0.75	0.69	0.81	<.0001	0.71	0.61	0.83	<.0001
	Level =0								
Comorbidity	Level =-1	0.65	0.57	0.74	<.0001	0.60	0.49	0.73	<.0001
	Level =1	1.04	0.91	1.20	0.5602	0.57	0.45	0.73	<.0001
	Level =2+	1.58	1.36	1.83	<.0001	0.84	0.65	1.08	0.1741

Age	5-year increments	1.47	1.40	1.54	<.0001	1.44	1.29	1.61	<.0001
Race	Non-AA								
	AA	1.12	0.96	1.31	0.1643	1.29	0.92	1.81	0.1450
Stage	Local								
	Regional	1.79	1.51	2.12	<.0001	3.42	2.61	4.49	<.0001

Variables	Category	Overall Survival				Disease Specific Survival			
		Hazard Ratio	95% CI		<i>p</i> -value	Hazard Ratio	95% CI		<i>p</i> -value
			lower	upper			lower	upper	
Gleason Score	2-4								
	5-6	1.09	0.91	1.30	0.3596	1.54	0.83	2.85	0.1733
	7-10	1.58	1.30	1.90	<.0001	4.53	2.44	8.42	<.0001
	Unknown	1.42	1.12	1.80	0.0040	3.94	1.99	7.80	<.0001
	NT								
Combination Therapy	RP	0.27	0.17	0.44	<.0001	0.40	0.17	0.94	0.0361
	BT	0.32	0.26	0.41	<.0001	0.46	0.27	0.80	0.0055
	EBRT	0.57	0.49	0.66	<.0001	0.97	0.70	1.33	0.8423
	ADT	0.89	0.80	0.98	0.0233	1.36	1.04	1.77	0.0273
	Level =0								
Comorbidity	Level =-1	0.66	0.56	0.78	<.0001	0.80	0.55	1.15	0.2306
	Level =1	1.13	0.95	1.35	0.1775	0.72	0.47	1.10	0.1332
	Level =2+	1.91	1.58	2.30	<.0001	1.40	0.90	2.18	0.1342
Age	5-year increments	1.29	1.17	1.43	<.0001	1.16	1.03	1.30	0.0147
Race	Non-AA								
	AA	0.99	0.75	1.30	0.9233	1.04	0.76	1.43	0.8029
	2-4								
	5-6	2.54	0.79	8.15	0.1176	2.49	0.60	10.40	0.2121
	7-10	3.97	1.26	12.56	0.0189	4.47	1.09	18.26	0.0372
Gleason Score	Unknown	3.87	1.22	12.35	0.0220	4.24	1.03	17.51	0.0459
	NT								
	EBRT	0.47	0.33	0.66	<.0001	0.55	0.37	0.82	0.0031
	ADT	0.40	0.32	0.51	<.0001	0.43	0.33	0.58	<.0001
	Level =0								
Combination Therapy	Level =-1	0.57	0.39	0.81	0.0021	0.49	0.33	0.74	0.0006
	Level =1	0.69	0.45	1.05	0.0810	0.49	0.30	0.80	0.0046
	Level =2+	0.66	0.42	1.02	0.0583	0.51	0.30	0.84	0.0082

Distant Diseases Only

Abbreviations: AA=African American, RP=radical prostatectomy, BT=brachytherapy, EBRT=external beam radiation therapy, ADT=androgen deprivation therapy, NT=no treatment.