Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Jingning Ao Date

A Propensity Score Analysis: Exploring the Effect of Adjuvant Chemotherapeutic Agent with Radiation Therapy and Androgen Deprivation Therapy in Patients with High Risk Prostate Cancer

By

Jingning Ao
Master of Public Health

Biostatistics and Bioinformatics

Yuan Liu, PhD
Thesis Advisor

Amita Manatunga, PhD
Reader

A Propensity Score Analysis: Exploring the Effect of Adjuvant Chemotherapeutic Agent with Radiation Therapy and Androgen Deprivation Therapy in Patients with High Risk Prostate Cancer

By

Jingning Ao

B.S.
Case Western Reserve University
2013

Thesis Committee Chair: Yuan Liu, PhD
Reader: Amita Manatunga, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Biostatistics
2017

Abstract

A Propensity Score Analysis: Exploring the Effect of Adjuvant Chemotherapeutic Agent with Radiation Therapy and Androgen Deprivation Therapy in Patients with High Risk Prostate Cancer

By Jingning Ao

Introduction: Prostate cancer is still among the most prevalent cancers in men. Despite falling rates of mortality, it is still one of the leading causes of death. Accounting for the most important predictors in prostate cancer, patients are classified into three different prognostic categories, consisting of low, intermediate, and high risk groups. We define high risk prostate cancer as patients one of the following criteria - Gleason score ≥ 8, PSA ≥ 20, clinical T stage ≥ 2c, or pathological T stage ≥2c. The rates of mortality are significantly higher for those patients in the "high-risk" subset. For localized high risk patients, the most common treatment is the use of radiation therapy and long-term hormone therapy. More recent studies however have begun exploring the use of adjuvant chemotherapy. The objective of this study was to conduct a NCDB outcomes analysis of patients with localized high risk prostate cancer in order to examine the effect chemotherapy on overall survival.

Methods: A retrospective outcomes study was conducted using data from the National Cancer Database (NCDB). Patients must additionally be treated with radiation therapy, hormone therapy, or chemotherapy. Unadjusted overall survival was first estimated with univariate and multivariate Cox proportional hazards model. An adjusted overall survival was recalculated after accounting for baseline covariates using propensity score methods such as matching, weighting, and propensity score covariate adjustment.

Results: The final cohort contained 29,659 subjects of which only 177 patients received chemotherapy adjuvant. Unadjusted Univariate (HR=1.05[0.79, 1.4], p=0.723) and multivariate (HR= 0.89[0.67 -1.19], p=0.43) analysis concluded no survival benefits for the adjuvant chemotherapy. Use of propensity score analysis found that only matching was able to successfully balance the covariates between the treatment and control cohort, ultimately finding that there was still no benefit to the use of adjuvant chemotherapy (0.87[0.65-1.16], p=0.377).

Conclusion: Results from this analysis suggests that there were no clinical benefits to use of chemotherapeutic agent in addition to radiation therapy and hormone treatment such the additional treatment provided no survival benefits. For future analysis, a larger treatment cohort defined by use of docetaxel and higher radiation dose may provide reliable results.

A Propensity Score Analysis: Exploring the Effect of Adjuvant Chemotherapeutic Agent with Radiation Therapy and Androgen Deprivation Therapy in Patients with High Risk Prostate Cancer

By

Jingning Ao

B.S.
Case Western Reserve University
2013

Thesis Committee Chair: Yuan Liu, PhD
Reader: Amita Manatunga, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Biostatistics
2017

Contents

1. Introduction

Prostate Cancer is the second leading cause of death in the US. In 2016, there was approximately 1.6 million new cancer cases in the US, 10% of which comprised of prostate cancer. The American Cancer society estimates that, of the 180,890 estimated new cases, 26,120 (9%) will result in death. With increasing knowledge, of prostate cancer, prevalence of mortality has decreased since years past (Siegel, Miller, and Jemal 2016). As of 2007, prostate cancer consisted of 33% of all prostate cancers and 9% of cancer deaths in men (Jemal et al. 2007). None the less, prostate cancer is still one of the most prevalent cancers in men, and remains one of the most common causes of cancer death in men (Siegel, Miller, and Jemal 2016). High risk prostate cancer accounts for 15% prostate cancer. "High risk" describes a state of cancer in which the disease has the potential to be fatal and requires active treatment. In comparison, low risk prostate cancer can be monitored with active surveillance for years.

Treatment for high risk prostate cancer varies greatly due to high heterogeneity of the disease (Chang et al. 2015). Patients with high-risk prostate cancer have commonly been treated with radiation therapy and long-term hormone therapy. Chemotherapy on the other hand is more commonly used to treat patients with metastatic prostate cancer. More recently however, researchers have begun to explore the use of chemotherapy as an adjuvant treatment. Adjuvant chemotherapy for high risk patients was first introduced in RTOG 9902 trial. Analysis showed that the overall survival in the experimental arm did not differ significantly for that of the control arm. A more recent updated trial however (RTOC 0521) has shown clinical benefits associated with chemotherapy use in a similar scenario.

The purpose of this analysis is to assess the efficacy of adjuvant chemotherapy for patients with localized high risk prostate cancer treated with radiation therapy and hormone therapy using the National Cancer Database. Because there is a risk that the patient population between the chemotherapy group and non-chemotherapy group are systematically different, we propose using propensity score methods to adjust for these baseline covariates. While there are many different propensity score methods, we chose to use matching, weighting, and propensity score as a covariate because those are most commonly use propensity score methods and their performance have been frequently been compared in literature. Therefore we want to compare unadjusted and adjusted overall survival with three propensity score methods - matching, weighting, and propensity score as a covariate. Should evidence show that chemotherapy is indeed beneficial to our subset of patients, a more frequent use chemotherapy could help extend the lives of

non-metastatic high risk patients.

2. Background

Prostate cancer is the result of cellular mutation, resulting in uncontrollable cell grow in prostate cancer cells and occurs in approximately 1 in 7 men. This disease is most common in men above 50, and those of African-American decent have twice the risk of death compared to white men. Although the incidence of prostate cancer is high, it is not always a lethal disease. If detected in the early stages, it can almost always be treated, such that those men can be disease free after 5 years (Prostate Cancer Foundation 2017b).

2.1 Diagnosis

Prostate Cancer is most typically detected by monitoring PSA levels or through a digital rectal exams (DRE). Abnormal results from either of the two screening methods will lead to more definitive diagnostic tools such as an ultrasound and/or biopsy, which would allow for a histological confirmation of the disease (Mayo Clinic 2017). Prostate-specific Antigen (PSA) is a protein produced by prostate cells. Biologically, it liquefies semen during ejaculation, therefore, most of the PSA produced, is ejected from the body, while a small remainder is absorbed in the blood stream. Normally, serum PSA is very low, and a presence of high levels of PSA may indicate the presence of Prostate cancer, (although this is not necessarily always the case). A typical PSA threshold level for biopsy is 4.0 ng/mL although it is also recommended to take into account the patient's age, ethnicity, and other demographic characteristics (Prostate Cancer Foundation 2017b). Digital rectal exam on the other hand involve a physical inspection of the prostate for any irregularities in shape, size, or texture (Prostate Cancer Foundation 2017a).

2.2 Classification

Prostate Cancer is classified by stage and grade. The stage, which is specified further by Clinical or Pathological Staging, indicates the size, extent, and whether or not the tumor has spread. Clinical staging derives information from exams done prior to surgery such as physical exams, imaging tests, and biopsies. Pathological staging on the other hand is based on microscopic examination of cells removed during surgery or biopsies is the result of tests based on surgical (National Cancer Institute 2017). Although

clinical and pathological staging results are typically the same, pathological staging results can sometimes differ. As it is more precise, it can reveal that the cancer has spread further than previously indicated through clinical staging results. The staging system utilizes the TNM Classification where T stands for tumor, describes the primary tumor site; N stands for nodes - indicating whether the cancer spread to the nearby nodes; and M equals metastasis, illustrating whether or not the cancer has spread to other organs in the body. Each classification is additionally broken down through a numerical system, further indicating, spread and location of the cancer growth. Ultimately, all three can be combined for an overall stage I through IV where increasing value indicating increasing advancement of cancer (American Cancer Society 2017a).

Tumor grade on the other hand represents how quickly the tumor can grow and spread. This is done using a Gleason score, which represents a numerical value from 1 to 5 in which a lower score means that under the microscope, the cancerous tissue looks like healthy cells, while for higher scores the cancerous tissues looks dissimilar to normal tissue. However, since prostate cancer growth often occurs in different areas, at different grades, the grades at each location is summed up, with the highest Gleason score being a 10. Clinically a Gleason scores of 8 or greater indicate that the cells are poorly differentiated and do not look like healthy cell tissue (National Cancer Institute 2017; American Cancer Society 2017b).

Another method of classification that collectively utilizes PSA level, stage, biopsy results, and stage of cancer is risk stratification. Patients are categorized as very low risk, intermediate risk, and high risk. The lower the risk, the less of a chance that the cancer will grow or spread. Those in the low risk group meet the criteria of having a tumor classified as T1a, T1b, T1c or T2a, a PSA level of less than 10 ng/ml, and Gleason score of 6 or less. In the next levels of classification, the patients must meet at least 2 of follow characteristics. To be of intermediate risk, the patient's tumor must be classified as T2b or T2c, have a PSA level between 10 and 20ng/mL, or a Gleason score of 7. Finally, to be considered High Risk, the tumor must be classified as T3a or above, have a PSA level greater than 20 ng/mL, or a Gleason score greater than 8 (ASCO 2017).

This analysis in particular is focused on High Risk Patients who account for approximately 15% of all prostate cancer patients. For a prostate cancer patient to be classified as locally high risk they must at least one of the follow - a Gleason score between 8 - 10, meaning that the tumor is not only poorly differentiated, but their disease is considered aggressive and has a quick rate of growth and spread (American Cancer Society 2017b).

2.3 Treatment

Treatment for prostate cancer varies greatly from patient to patient and is dependent on cancer stage, rate of growth, and other risks. For some patients, there is no immediate need for treatment and as such those patients undergo active surveillance where in the patient is monitored for any change in the disease progression. For patients that do need immediate treatment, they often undergo surgery, radiation, hormone therapy, chemotherapy, or a combination of multiple treatments. Patients whose cancer is localized to the prostate gland can undergo surgical removal the tumor. Another standard treatment is radiation therapy, which is a localized treatment utilizing high energy radiation to kill cancer cells and shrink tumor growth. Hormone Therapy, also known as androgen deprivation therapy utilizes surgery, drugs, or other hormones in order to reduce androgen levels (male hormones) in the body or stop the androgen's effect on the prostate gland. Chemotherapy is the use of a chemical drug agent used to hinder carcinogenic cell growth or division, taken either intravenously or orally as a pill. Other standard treatments include biological therapy and freezing the prostate tissue (Brookhart, Wang, and Solomon 2006). However, in this study, we focus primarily on the use of radiation therapy, with concurrent use of hormone therapy, surgery, and chemotherapy.

2.4 Literature Review

Radiation therapy along with radical prostatectomy are considered definitive treatments in prostate cancer treatment. Radiation therapy in particular has been used since the early 1900's. However it wasn't until the mid to late 1900 that through advancement of more accurate and higher energy radiation beams that radiation therapy became a more standardized treatment for prostate cancer patients (Denmeade et al. 2014). It was also during this period that androgen deprivation therapy (aka hormone therapy) was first used in combination with radiation therapy in order to better improve the survival outcome of prostate cancer patients. Since then, it has long been established that the therapeutic effect of radiation therapy and hormone treatment themselves alone are inferior to radiation therapy combined with hormone blockage (Chang et al. 2015). The RTOC 8610 was one of the first phase III clinical trials to utilize neo-adjuvant hormone therapy before and concurrently with radiation therapy on locally advanced carcinoma. Conducted in 1987, the study enrolled around 900 patients with bulky primary tumors ($\geq 25cm$), clinical stage T2-T4 receiving external beam radiotherapy (EBRT) at a dose of 70 Gy

while the therapeutic group was also administered hormone therapy two months prior to and concurrently to radiation treatment. Trial results showed significant improvement in multiple clinical end points including local control, reduction in disease progression, overall survival for patients treated with adjuvant radiotherapy. This improvement was however more pronounced in patients with lower Gleason scores (2-6) (Ilepich et al. 2001).The use of hormone therapy prior to radiotherapy is thought to reduce tumor volume prior to radiotherapy, and when used during radiotherapy, interacts with the radiatiotherapy to affect cell kinetics. Similar results were found in a Scandinavian trial looking at the addition of radiation therapy for patients with locally advanced and aggressive, node-negative, and non-metastatic patients treated with hormone therapy (Widmark, 2008).

Further solidifying the benefits of radiation therapy in conjunction with hormone therapy, a parallel study to RTOG 8610, the Radiation Therapy Oncology Group (RTOG) conducted a second study exploring androgen therapy in conjunction with radiation therapy. In RTOG 8531, patients with histologically confirmed adenocarcinoma of the prostate cancer with CT3 disease or lymph node positive disease received long-term (indefinite) hormone therapy following radiation treatment (65-70 Gy) saw increased survival in patients with higher Gleason scores (7-10), although with additional follow up, this advantage was seen in the entire population (Pilepich et al. 2005). A study conducted by the European Organization for Research and Treatment of Cancer (EORTC) also looked at long term effects of androgen suppression, giving patients with T1-2 prostatic adenocarcinoma of histological grade 3, or T3-4 prostatic adenocarcinoma of any histological grade and goserelin immediately after irradiation (70 Gy) for 3 years. Like other long-term androgen therapy and radiation therapy combination trials, this protocol also showed improvement in disease-free and overall survival for locally advanced prostate cancer patients (Bolla et al. 2002). Even a shorter duration of long-term androgen therapy such as the 24 months of post radiation androgen therapy given to patients in RTOG 9202 showed significant improvement in all efficacy end points aside from overall survival (Hanks et al. 2003). Following these studies, the use of radiation therapy and long-term androgen deprivation therapy became the standard treatment for patients with high risk prostate cancer (Albers 2015)

Chemotherapy in itself is not a unique treatment. In prostate cancer treatment however, it has traditionally been used for patients with metastatic prostate cancer. More recently studies however are looking to move the use of chemotherapy earlier in the course of treatment in order to help improve survival for patients with high risk prostate cancer (Carlson 2015). RTOG 9902 was one of the first phase

III, multicenter trials looking to integrate chemotherapy treatment for patients with non-localized prostate cancer. They recruited 397 patients, testing the use of chemotherapy with radiation therapy and long-term androgen deprivation therapy. The chemical therapeutic agents used for this study was a combination of paclitaxel, estramustine, and oral etoposide and thee study ended prematurely due to patients in the experimental arm experiencing high incidents of thromboembolic events. While early results from the trial showed a slight improvement in survival for the treatment arm, long term results demonstrated no significant differences in overall survival and other study end points (Rosenthal et al. 2009). Preliminary results from a more recent study has shown evidence that adjuvant chemotherapy may benefit the high risk patients treated with radiation therapy and hormone therapy. This study was RTOC 0521, 'Phase III protocol of Androgen Suppression and 3DCRT/IMRT verses AS and 3DCRT/IMRT followed by chemotherapy with docetaxel and prednistone for localized, high risk prostate cancer'. Also conducted by the Radiation Therapy Oncology Group, this study was a phase III protocol looking at chemotherapy use in high risk patients with localized prostate cancer, who had received a combination of androgen suppressant and radiation therapy, followed by androgen suppressants looking at the comparative effect in overall survival. Ultimately, this trial was the first large randomized trial to show that the addition of adjuvant chemotherapy to androgen suppression and radiation therapy can improve survival. This trial began in 2005, and enrolled 563 patients over the course of 5 year. Differentiating from RTOG 9902, patients in RTOG 0521 were now receiving docetaxel as the chemotherapeutic agent rather than the combination of drugs previously used and additionally received higher doses of radiation (78Gy vs. 70.2Gy). Currently 4 -year overall survival rates show improved survival for those treated with chemotherapy (89% vs. 93%, HR = 0.68, p=0.03). This is the first study of its kind of show improved overall survival rates with the addition of adjuvant chemotherapy.

2.5 Study Population

The analysis conducted in this study was a retrospective observational study using the National Cancer Database. In order to separate out the study population, a set of clinical inclusion and exclusion criterial was applied to the National Cancer Database. The 2014 NCDB Prostate Participant User File (PUF) initially contained 1,294,126 prostate cancer cases. Patients were restricted to those that had been diagnosed with histologically confirmed prostate cancer between 2004 and 2014, of whom were categorized as "high risk" as defined by the D'Amico criteria. Under this the patient's tumor had to be invasive, and

was (stage) T2c, T3a, T3b, or T4, had a Gleason score of 8 or greater, or a PSA value of greater than 20. In addition, patients must have received definitive therapy which was defined as patients that had received chemo therapy and/or radiation without surgery. Subjects were excluded if they were metastatic, their chemotherapy status was unconfirmed, or was missing outcome data. Additionally, cases in which chemotherapy was received outside of an 8-month window from the start of definitive local therapy were also excluded. The final analytical dataset contained 29,659 cases of which 177 patients received chemotherapy in the definitive setting.

3. Statistical Methods

3.1 Data Source and Study Design

While clinical trials are considered the industry gold standard, they are expensive and difficult to conduct, involving considerable regulations and oversight. Observational database studies are being used more frequently as an alternative means of generating insight into different diseases using available data resources. This analysis used data from the National Cancer Database (NCDB). This clinical oncology database is a joint collaboration between the American Cancer Society and the American College of Surgeons and is a collection of HIPPA compliant patient data sourced from over 1500 hospital registries. It captures cancer related data from 70 percent of all newly diagnosed oncology cases in the United States and Puerto Rico. Data elements in the database are nationally standardized and validated before being accepted into the registry (American College of Surgeons 2017).

3.2 Variables and Measurements

The study variables were defined by the NCDB PUF Prostate 2014 Data Dictionary (NCDB, 2014) (http://ncdbpuf.facs.org/node/259). The outcome of interest is overall survival, which is defined as months from start of local therapy, i.e. whichever chemotherapy or radiation occurred first, to death or last followup. The treatment variable is binary, such that it is defined as those that have received or not received chemotherapy in addition to local therapy. For the purpose of this study, Local therapy is delineated by two types of radiation treatment - (1) beam radiation or (2) a combination of beam radiation with radioactive implants or radio isotopes. The covariate of interest in this study can be

organized into two categories - Clinical and Socio-economic characteristics.

For socio-economic factors, this analysis takes into account the patients Treatment Facility, Facility Location, Age at diagnosis, Race, Great Circle Distance, and the Year of Diagnosis. The treatment facility is sorted into three facility types - academic or research programs, non-academic/research programs, comprising of community cancer programs, comprehensive community cancer programs, or integrated network cancer programs, or unknown In addition, the facility location is divided into four commonly split US regions - Northeast, South, Midwest, and West. Race is distinguished as Black, White, or Other. Great Circle distance represents the distance from resident's zipcode to the treatment facility in miles.

Within the clinical variables, we focus on Charlson-Deyo Score, Gleason score, PSA, Regional Dose, Total Radiation Dose, Clinical and Pathological T and N, Clinical Stage Group, the Number of Treatments to the Radiation Therapy, Regional Treatment Modality, Radiation Treatment Volume, Time from Diagnosis to Hormone Therapy, Time from Diagnosis to Death or last contact, Time to Radiation, Length of Radiation Treatment, Time to Systemic Therapy, Time to cChemotherapy, and Time to Local therapy. All time related variables are measured in months. The Charlson-Deyo Score is collapsed into an indicator variable, signifying whether the patient experienced comorbidities. The Number of Treatments to this Volume indicates the total number of radiation sessions administered during the first course of treatment (National Cancer Institute 2017). Regional treatment modality indicates what was the dominant method in delivering the radiation treatment and is grouped into (1) Intensity-modulated radiation therapy (IMRT),(2) Conformal or 3-D therapy, or (3) all other modes. The Radiation Treatment Volume identifies the anatomical target while Regional Dose indicate the dominant total dose of regional radiation therapy for the first course of treatment and is measured in centiGray (NationalCancerInstitute2017). Due to small sample size within some categorical variables, some levels are collapsed in order to increase robustness of samples. Additionally, for continuous variables such as age, great circle distance, year of diagnosis, regional dose, total radiation dose, number of treatments in a volume, their quartile values are used to create categorical counterparts.

3.3 Statistical Analysis

Descriptive Statistics were calculated for all variables of interest for the overall patient population and within each treatment subgroup. This consists of means and standard deviations for continuous variables and then frequencies and percentages with regards to the categorical variables. Univariate analysis

was conducted to look at the association between patient clinical and socio-economical covariates with chemotherapy and overall survival using chi-squared test of independence for categorical variables and independent t-test and Analysis of Variance (ANOVA) for continuous covariates. Univariate association between the study covariates and overall survival was calculated using Cox proportional hazards models. Each covariate was regressed against overall survival while log-rank tests were used to compare the survival curves between treatment groups.

In addition to estimating overall survival, we used a multivariate logistic regression model to look at the association with chemotherapy in order to determine which patient covariates were associated with chemotherapy use. A backwards elimination procedure is applied to determine the final predictive model. Here significance is determined at a type I error rate of 10%. Starting with a full least squares model containing all the predictors in the model, the predictor with the highest p-value greater than an α of 0.10 is removed from the model. The model is re-fit, and each time, a similar removal procedure is applied until the all predictors in the model have a p-value less than 0.10.

In order to measure the effect of multiple explanatory variables on overall survival, a multivariate Cox proportional hazards model is employed to measure the effect of chemotherapy adjusting for other clinical and socio-economical characteristics. Based on results from the univariate analysis, variables that were significantly associated with chemotherapy were used in the cox proportional hazards model as possible confounders. The included variables were Local Therapy, Facility Type, Facility Location, Age, Race, Great Circle Distance, Charlson-Deyo Score, Gleason Score, PSA, Regional Dose, Total Radiation Dose, Clinical Stage T, Clinical Stage N, Number of Treatments to this volume, Regional Treatment Modality, Time from Diagnosis to Radiation, and Time from Diagnosis to local Therapy. The final model was constructed using a backwards elimination process and a threshold value of $\alpha = 0.10$. Since the main variable of interest was the treatment group, that variable was forced into the final model. Kaplan- Meier plots were created in order to compare survival curves by cohort in the overall population.

In addition to a main effects model, we also explored possible interactions between treatment and clinical N and T, Facility Type, Gleason Score, Great Circle Distance, Local Therapy, PSA, Race, Regional Treatment modality, and quantile Age. This was done using stratified Cox proportional hazard models. Effect variables used in model coincided with those used in the main effects model.

3.4 Propensity Score Methodology

The choice of utilizing propensity score based methods was to achieve an unbiased estimation of the treatment effects in order to minimize selection bias from other covariates. This allows us to make a direct comparison between treatment groups, as one would in a randomized clinical trial.

The propensity score method is utilized in causal inference as a means of estimating the causal effect of treatment in observational studies (Frangakis and Rubin 2002). This method engages the potential outcomes framework and the use of counterfactuals in order to compare two outcomes (survival or death) which would occur under the same condition, except for the treatment assignment. Thus, we assign the treatment to an indicator variable, Z, which is capable of taking on the value 1, given chemotherapy treatment, or 0, given the standard treatment. In this, we assume two potential outcomes, the patient's survival while receiving the standard treatment($Y_i(0)$) and the patient's survival receiving the experimental treatment ($Y_i(1)$). However, since only one out come can actually be observed, Y_i the observed outcome can be defined as $Y_i = Z_i Y_i(1) + (1 - Z_i)Y_i(0)$. The individual effect is therefore defiend as $Y_i(1) - Y_i(0)$. By taking the expectation, we can extend this to population level and determine the average treatment effect, $E[Y_i(1) - Y_i(0)]$. However, more often, what is actually of interest is the average effect of the treatment on the treated (ATT), which is defined as $E[Y(1) - Y(0)|Z = 1]$ (Holland 1986; Rubin 2005). Unlike clinical trials which randomizes treatment selection, data from the NCDB database is compiled from hospital cancer registries, therefore treatment regime is conditional on the patient's characteristics. This could result in systematically different baseline characteristics between the chemotherapy group and non-chemotherapy group . The choice of utilizing propensity score based analysis was to achieve an unbiased estimation of the treatment effects in order to minimize selection bias from other covariates. This allows us to make a direct comparison between treatment groups, as one would in a randomized clinical trial.

3.4.1 Propensity Score Estimation

The propensity score, which is defined as the probability of being assigned the treatment given a set of covariates such that $e(X_i) = Pr(Z_i = 1|X_i)$, where X is the set of observed covariates and $[X \perp Z|b(X)]$ (Rosenbaum and Rubin 1983). The propensity score therefore summarizes the set of covariates in to a single value between 0 and 1. "Conditional on the propensity score, the distribution of measured

baseline covariates is similar between treated and untreated subjects" (Austin 2011b). Ultimately the purpose of the propensity score is to allows us to achieve balance between the various covariates by removing the effects of confounding so that we may directly compare the treatment and control group and calculate an unbiased estimate of the treatment effect. This is achieved due to key properties of the propensity score such that, "Conditional on the true propensity score, the distribution of measured baseline covariates is independent of treatment assignment"(Austin 2011b) meaning that for patients with similar propensity score values, the treatment is unrelated to the confounders (Rosenbaum, P R, Rubin 1983). The propensity score is created using a regression model. Since we are working with a binary treatment, the propensity score is modeled using logistic regression. There has been some contention as to variable selection for the PS model (Brookhart, Wang, and Solomon 2006). Given the definition of the propensity score, it makes sense to include variales that influence the treatment selection. That can however be a long list of variables. Some literature even suggests that the variables used for the propensity score model should consists of prognostically important covariates related to outcome or confounding covariates related to treatment and outcome (Austin 2009). In practice however, most use predictor variables that consists of baseline covariates unrelated to the outcome (Brookhart, Wang, and Solomon 2006).

In this analysis, we looked at the effect of chemotherapy on advanced prostate cancer patients undergoing radiation and hormone therapy using propensity score methods such as matching, inverse weighting, and covariate adjustment of the propensity score to compare those results against an unadjusted treatment effect.

3.4.2 Matching

As the name implies, propensity score matching pairs up treated and control subjects based on similar propensity score values. In forming matched pairs, we must first consider whether this will occur with or without replacement. Then various matching algorithms can be used such as greedy, optimal, or nearest neighbor matching. In greedy matching, the first randomly selected treated subject is matched to the closest control subject, without consideration that this control might be better matched with another treated subject, with the process repeating until all treated subjects have been matched to a control. In comparison, optimal matching attempts to minimize the total within-pair difference (Rosenbaum 2002). Finally in nearest neighbor matching, for a given treated subject, it is paired with the closest control and

if there are multiple controls nearby that would match the treated subject, a control subject is selected at random (Austin 2011b). In addition to 1 to 1 matching, several controls can be matched to one treated subject. This is called 1:k matching. A critique or propensity score matching is that depending on the specific matching technique, it discards some of the data. Additionally, in matching with replacement, the use of the same subject for matching must be accounted for in the variance estimate.

3.4.3 Weighting

Similary well named, in Inverse Probability of Treatment weighting (IPTW), each subjects weight is equal to the inverse probability of receiving the treatment. This works by using the propensity score as weights, up-weighting subjects that are underrepresented, and down-weighting subjects that are over represented (Lanza, Stephanie; Moore, Julia E.; Butera 2013). The inverse probability of treatment weight is defined as $w_i = \frac{Z_i}{e(X_i)} + \frac{1-Z_i}{1-e(X_i)}$ which can be used to calculate the ATE while $w_{ATT} = Z_i + \frac{e(X_i)(1-Z_i)}{1-e(X_i)}$ are the weights used to estimate the average treatment effect in the treated (ATT). This creates a synthetic sample in which the treatment assignment is independent of potential outcomes given the covariates. If we denote Y as the outcome variable, then the average treatment effect (ATE) can now be estimated with $\frac{1}{n}\sum_{i=1}^{n}\frac{Z_iY_i}{e(X_i)} - \frac{1}{n}\sum_{i=1}^{n}\frac{(1-Z_i)Y_i}{1-e(X_i)}$ or alternatively, $\left(\sum_{n}^{i=1}\frac{Z_i}{e_i}\right)\sum_{i=1}^{n}\frac{Z_iY_i}{e(X_i)} - \left(\sum_{n}^{i=1}\frac{1-Z_i}{1-e_i}\right)\sum_{i=1}^{n}\frac{(1-Z_i)Y_i}{1-e(X_i)}$. Some downfalls to IPTW is that with extreme propensity score values can result in extremely large weights such that treated subjects with a propensity score close to 0 or a control subject with a propensity score value close to 1. These weights would increase the variability of the treatment effect and ultimately bias the treatment estimate. A solution to this is the use of stabilizing weights where $w_i = \frac{Z_iPr(Z=1)}{e(X_i)} + \frac{(1-Z_i)Pr(Z=0)}{1-e(X_i)}$ [Austin2010a].

3.4.4 Propensity Score as a Covariate

In practice, using the propensity score as a regression coefficient is a popular method. Of the three methods described, this is the most simplistic method, however it assumes that the relationship between the propensity score and the outcome has been modeled correctly and that there is a substantial overlap between the treatment and control group (Austin 2011b). It is applied by inserting the propensity score into a regression model, or in our case, a Cox proportional hazard model along with an indicator variable denoting treatment selection. Since the propensity score is a single value that represents the covariates, it can be accompanied with or without other covariates in the regression model. Both methods however

have proven to yield the same results (Rubin (1979)). While propensity score covariate adjustment is frequently used, there is however no agreed upon diagnostic method.

3.4.5 Subclassification

In propensity score subclassification, the patient population is divided into subgroups based on the creation of strata. Then within each strata, the treatment effect is calculated. These strata are common based on a distribution's quantile values. This method can generally remove approximately 90% of the biased. Creation of a greater number of strata can remove even more of the bias. A caveat is that with the strata, you need to have an even distribution of patients in both treatment groups and across strata.

3.4.6 Diagnostics

As mentioned earlier, the propensity score is a regression derived probability value for predicting treatment. It works by acting as a balance score. Not in the individual sense that, having the same propensity score means that two subject have the same baseline characteristics, but rather that between the treated and untreated subject populations, the distribution of baseline values should be the same after conditioning on the propensity score. If however, they are not, then this could indicate a miss-specified propensity model or possibly that the two populations are incompatible. In order to know that the propensity score model has been correctly specified, it is a matter of comparing the covariates between treated and untreated subjects. This is conducted after applying the propensity score method. For continuous variables the standardized difference is calculated by:

$$d = \frac{\bar{x}_{treatment} - \bar{x}_{control}}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}}$$

where $\bar{x}_{treatment}$ and $\bar{x}_{control}$ are the sample mean of the covariate of interest for the treatment and control and in our case, the chemotherapy and non-chemotherapy patients. $s^2_{treatment}$ and $s^2_{control}$ are the sample variances of the chemotherapy and non-chemotherapy subjects.For binary variables, the standardized difference is calculated by:

$$d = \frac{\hat{p}_{treatment} - \hat{p}_{control}}{\sqrt{\frac{\hat{p}_{treatment}(1-\hat{p}_{treatment}) + \hat{p}_{control}(1-\hat{p}_{control})}{2}}}$$

where $\hat{p}_{treatment}$ and $\hat{p}_{control}$ are the prevalence or mean of the binary variable of interest (Austin 2011b). Typically a standarized difference cut off value of 0.10 would indicate insignificant difference between the covariates in a treatment and control group. This value has not been agreed upon, with others suggesting that 0.2 is sufficient in achieving balance as well.

3.5 Propensity Score Analysis

The propensity score analysis was conducted by first estimating the propensity score. Since the treatment in this analysis is a binary variable, the propensity score is estimated by means of a logistic regression model. The covariate included in the propensity score model were Local Therapy, Facility Type, Facility Location, Race, Great Circle Distance, Charles-Deyo Score, Year of diagnosis, Gleason Score, Clinical Stage T, Clinical Stage N, Regional Treatment Modality, Age at Diagnosis, and Time from diagnosis to Local Therapy. These were based on the final multivariate Cox proportional hazards model where variables selected were based on a backwards elimination process. The propensity score values predicted from this model were utilized in three propensity score methods - matching, inverse probability of treatment weighting, and propensity score as a covariate. We briefly considered applying a propensity score subclassification method as well, however this method was unusable given the highly unproportional distribution of subjects between 5 strata. A balance check was employed for the matching and weighting methods by assessing the standardized difference for each covariate. If the standardized difference was below 0.1 then we considered the difference in that variable between the chemotherapy and non-chemotherapy patients negligible. Since the methods discussed above were used to eliminate systematic difference between the two populations, the subsequent Cox proportional hazards model for the three methods could be simplified. The adjusted treatment effect was calculated based on a univariate Cox proportional hazard model including the only the treatment variable for matching, the use of weights for iptw, and the addition of the logit of the propensity score in regressing the propensity score as a covariate. The propensity score matching method employed a 1:5 greedy matching algorithm. Kaplan Meier curves were also produced in order to directly compare the survival curves of the chemotherapy and non-chemotherapy populations for methods that resulted in a balanced cohort.

Statistical analysis was conducted using SAS Version 9.4 and R Version 0.99 , and SAS macros or software developed at the Biostatistics and Bioinformatics at Winship Cancer Institute.

4. Results

4.1 Descriptive Statistics

Application of the inclusion and exclusion criteria revealed a final analytical data set which contained 29,659 cases of which 177 patients received chemotherapy in the definitive setting (Table 0). Table 1 shows results of descriptive statistics. In terms of clinical distinctions, on average, patients had a Gleason score of 7.87 ± 1.0 , a PSA level of 20.13 ± 21.74 ng/mL, received a regional dose of 7341.42 ± 4728.00 Gy, and a total radiation dose of 7427.48 ± 61.40.81 Gy. Measuring from time of cancer diagnosis, the average time to radiation treatment was 4.26 ± 2.58 months, with treatment lasted 61.38 ± 19.57 days, with 37.87 ± 18.74 treatment sessions administered during the course of treatment. Patients who received chemotherapy, normally received it within 105.32 ± 74.30 days from diagnosis. Hormone therapy was generally started 49.25 ± 59.10 days from time of diagnosis. Overall the average time from diagnosis to systematic treatment was 49.26 ± 58.80 days, while time to local therapy was approximately 129.62 ± 78.44 days. The average time to last contact or death was 61.93 ± 32.84 months. Most of the patients only received beam radiation (72.1%) as a opposed to in combination with radioactive implants or isotopes (27.9%). A large majority of patients received a Charlson-Deyo score of 0 (86.4%) compared to a score of one or greater (13.6%). Tumor characteristics for patients were as such - 38.6% of patients of patients were of stage 0 or 1 such that there was no evidence of the tumor in the prostate or it could not be felt during a DRE or imaging test; 44.7% were classified as stage 2, in which the tumor is only located in the prostate and can be felt during a DRE; 14.8% of patients were stage 3 or 4, therefore, the tumor can be found outside the prostate tissue or extend to tissues other than the seminal vesicles. In almost all patients, the cancer did not spread to the regional lymph nodes (90.0% vs. 2.4%), while this was unknown for 7.6% of patients. Pathological stage T was unknown for almost all patients (95.8), with little to none patients in stage 0-1 (<0.1%), 2 (3.4%), 3-4 (0.7%). A similar pattern was seen for pathological stage N, again, as most patients were of unknown status (96.4%), 3.2% were found negative, and only 0.4% indicated positive. A combination of the clinical T and N classification makes up the overall clinical stage group in which 80.6% of patients were identified as stage 1-2, 15.6% identified as stage 3-4, and 3.8% were of unknown status.

With regards to patient characteristics, the mean age at diagnosis was 69.42 ± 8.16 years. A majority of subjects received treatment in non-academic research programs (68.6% vs. 31.4%), with most traveling

less than 50 miles to the treatment location. Distribution of patients over the country was even between the four coordinates (NE - 24.6%, S - 32.4%, MW - 25.0%, W - 18.0%). Most patients were white (78.7%), while 16.6% were black, and 4.7% were of another race.

4.2 Univariate Association with Chemotherapy

Table 2 shows the results of univariate analysis between chemotherapy use and our covariates of interest. Comparing subjects between those that received Chemotherapy and no chemotherapy, those that received chemotherapy were significantly younger (63.75 vs. 69.45, P<0.001), had higher Gleason scores (8.2 vs. 7.87, P<0.001), higher PSA values (23.88 vs. 20.11, p=0.023), received lower regional dose, and had shorter length of radiation treatment (56.88 vs. 61.4, p=0.002) compared to patients that did not receive radiation. Comparatively, on the average, they had similar distances to the treatment center, total radiation dose, and with regards to time from diagnosis, had similar time to hormone therapy, radiation treatment, total number of treatment session administered during the first course of treatment, as well as similar time from diagnosis to local therapy. Additionally, patients that were treated in academic research programs (p<0.001), had Charlson-Deyo scores of 0 (P=0.046), were of clinical T stage 3 and 4 (p<0.001), positive clinical N stage (p<0.001), and where the Pelvis (NOS) was the most significantly anatomic targets (p=0.002) were more likely to receive chemotherapy. In comparison, radiation method, facility location, race, and regional treatment modality for this cohort of patients was not significantly associated with chemotherapy treatment.

4.3 Multivariate Association with Chemotherapy

The results of the multivariate analysis between chemotherapy and the variables of interest are displayed in Table 3. Adjusting for the effects of multiple covariates, the predictor variables that have a significant effect on chemotherapy are facility type, facility location, race, Gleason score, PSA, clinical stage T and N, and age at diagnosis. The odds of chemotherapy use are greater for those treated in academic/research programs compared to those treated in non-academic programs (OR = 6.43, p<0.001), as were patients from the south compared to Northeast patients (OR = 1.79, p=0.004. In opposition, the odds of receiving chemotherapy were less for black patients compared to white patients (OR = 0.56, p=0.13). Patients with a Gleason score between 8-10 were more than twice as likely to undergo chemotherapy compared

those with a Gleason score between 2 and 7 (OR = 2.24, p<0.00), similarly for patients with a PSA value greater or equal to 20 verses those with a Gleason score of 10 to 20 (OR = 1.92, p=0.007). Those with tumor of stage 3 and 4 (OR = 2.34, p <0.001), as well as those with whose tumor had spread to the regional nodes (OR=1.84,p=0.031), were also twice as likely to receive chemotherapy compared to patients with stage 0-1 tumor and negative nodal spread. And finally, for each unit of increasing age, the odds of undergoing chemotherapy decreased (OR = 0.93, p<0.001).

4.4 Univariate Association with Overall Survival

Table 4 display the results of univariate association with overall survival while Figure 1 showes the Kaplan Meier plot of overall survival. Based on univariate results, treatment with chemotherapy was not associated with increased survival (HR=1.05[0.79, 1.4], p=0.723). However, looking at the other covariates individually most however were associated with increased survival. Using a combination of beam radiation, northeast facility location, Charlson-Deyo score of 0, Gleason score of 2-7, Clinical T stage of 0-1, negative Clinical N stage , and other treatment modality as the reference group, beam radiation (HR=1.67 [1.58-1.77], p<0.001), Midwest (HR=1.11 [1.04-1.19], p=0.003) and southern (HR=1.10 [1.03-1.18], p=0.004) facility location, Charlson-Deyo score of 1+ (HR=1.49 [1.40-1.60], p<0.001), Gleason score of 8-10 (HR=1.39 [1.31-1.59], p<0.001), Clinical T stage 3-4 (HR=1.16 [1.07-1.24], p<0.001), positive clinical N stage (HR=1.43 [1.23-1.67], p<0.001), and IMRT treatment modality (HR=1.17 [1.11-1.23], p<0.001) option were all associated with increased risk of death. patient's whose regional dose and total dose were greater than the smallest quartile value had increased risk of death compared to the reference group (all p<0.001).

In contrast to that those in Academic research programs (HR=0.88 [1.58-1.77],p<0.001), western facility locations(HR=0.88 [0.83-0.93],p<0.001), Black (HR=0.93 [0.86-0.99],p=0.029) and other Race (HR=0.70 [0.61-0.79],p<0.001), less than 10 (HR=0.77 [0.72-0.82],p<0.001) and greater or equal to 20 PSA (HR=0.86 [0.80-0.92],p<0.001), and had primary radiation directed at the prostate (HR=0.88 [0.80-0.97],p=0.009) had decreased risk of death compared to the reference groups indicated above. Additionally, all quartile age groups had less death events in proportion to those of 76-90 years of age, as did categorical great circle distance, such that those that lived farther had less deaths proportional to the those that lived within 50 miles of the treatment facility. For patients undergoing radiation, delaying radiation treatment by 1 month increased risk of mortality by 10%. A similar pattern is seen for those

who delayed local therapy.

4.5 Multivariate Association with Overall Survival

Main Effects Table 5 exhibits multivariate analysis of overall survival. Variables such as Pathological Stage T and N were not considered in the multivariate model due to a large amount of missing values. Additionally, due to issues of multicollinearity, Urban/Rural and clinical stage group was not considered for the model. The treatment variable was forced into the model while all other variables were selected utilizing a backwards elimination process. Adjusting for the In this process, regional dose (quartile), total radiation dose, number of treatments to this volume, radiation treatment volume, days from diagnosis to hormone therapy, months from diagnosis to radiation, length of radiation treatment were all removed from the model. Adjusting for the effects of the other covariates, we see that the hazard ratio flips from 1.05 to 0.89 (95%CI [0.67 -1.19], p=0.43), indicating that for those that did not use chemotherapy experienced less death events proportional to comparison group. This effect however is not statistically significant. For the most part, the hazard ratios from the multivariate analysis are similar to those found using univariate analysis, although the hazard ratio indicated non-significant but opposite risk for some variables. Univariate cox proportional hazard with overall survival indicated that survival was more favorable for patients that were black and PSA values >= 20, however, after control for other confounders, black patients(HR=1.04[0.97-1.12],p=0.302) and patients with the highest PSA values (HR=1.04[0.97-1.11],p=0.311) were found to have proportional death events compared to their reference groups. IMRT (HR=0.97[0.92-1.02],p=0.277) treatment modality patients were found to previously experience increased risk, are now also comparable to its reference group.

Interaction Effects Although we explored the interaction effects of chemotherapy and Clinical Stage T and N, facility type, Gleason score, great circle distance, time to local therapy, PSA, Race, Regional Treatment Modality, and Age, there were no signs of a significant difference in hazard between chemotherapy and non-chemotherapy patients taking into account effect modification by these variables. Detailed results can be found in Tables 6a-j. Kaplan Meier plots can be found in Figures 2a-d.

4.6 Propensity Score Results

Propensity Score Estimation In this analysis, we define the propensity score as the probability of chemotherapy treatment. It was estimated using logistic regression due to the binary outcome - Yes or No Chemotherapy treatment. Covariates utilizes in the propensity score model were based on the final model selected for the multivariate Cox proportional hazards model, consisting of the following variables - Local Therapy, Facility Type, Facility Location, Race, Great Circle Distance, Charles-Deyo Score, Year of diagnosis, Gleason Score, Clinical Stage T, Clinical Stage N, Regional Treatment Modality, Age at Diagnosis, and Time from diagnosis to Local Therapy. Distributions of the propensity score can be found in Figure 6 in the Appendix. The range of propensity score values ran from 1.71E-9 to 0.214, with an average of 0.00582 $\pm$ 0.012 for non-chemotherapy patients and for chemo patients, the PS score ranged from 0.000554 to 0.303 with an average of 0.0297 $\pm$ 0.039.

Matching The histogram of the propensity score between the two cohorts indicated a good overlap between the two populations. This allowed for a 1:5 matching, resulting in 885 non-chemotherapy treated patients matched to the 177 chemotherapy treated patients. This analysis utilized a greedy matching algorithm. The range of PS values for the matched samples ran from 0.000553 to 0.314, with an average of 0.029 $\pm$ 0.037 for non-chemotherapy patients and for chemo patients, the PS score ranged from 0.000554 to 0.303 with an average of 0.029 $\pm$ 0.039. Balance diagnostics was conducted by monitoring the standardized differences for each covariate between the treatment and control group. All patients in the chemotherapy group was successfully matched to 5 non-chemotherapy treated patient. A balance assessment of our cohorts after matching indicate that the standardized difference between chemotherapy and non-chemotherapy treated patients were below 0.10 for all covariates with a range of 0.002 to 0.075 across all 14 covariates. A table of complete values can be found in Table 7. This allowed us to proceed with an analysis of the overall survival between the matched samples. The probability of death after local therapy for chemotherapy and non-chemotherapy patients were 0.271 (48/177) and 0.213 (189/885) respectively. The median survival for those in the non-chemotherapy group was 130.6 [124.9, NA] while the 1 year, 5 year, and 10 year survival rate was 97.7% [96.4%-98.5%], 85.1%[82.3%-87.5%)], 61.9%[55.5%-67.6%)] respectively. In comparison, chemotherapy patients had a median survival of 127.1 [105.4, NA] with 1, 5, and 10 year rates of 98.9% [95.5%-99.7%], 82.4% [75.3%-87.6%], 59.3% [47.9%-69.1%]. The result is that the two curves were not statistically different from each other (p=0.3774) . This resulted

in a hazard ratio of 0.87[0.65-1.16] (Table 8). This result is comparable to the naive result calculated from a non-matched cohort. Figure 7 depicts the Kaplan-Meier plots comparing survival curves between chemotherapy and non-chemotherapy patients in the propensity matched sample.

Inverse Probability of Treatment Weighting (IPTW) Overall inverse propensity score weights ranged from a value of 0.0196 to 10.77. However, sub-grouped by treatment, weight value began smaller (0.994 - 1.45), the range of weights remained small, especially in comparison to non-chemotherapy patients whose weights ranged from 0.0196-10.77. the absolute standardized differences ranged broader, extending from 0.006 to 0.341. Even after inversely weighting patients by their propensity score, we were unable to achieve a complete balance as there was still significant differences between 5 of the 13 covariates. A table of the complete standardized differences can be found in Table 9. The risk of mortality was 5% greater for patients that had not received chemotherapy (HR=0.80 [0.50-1.30], P=0.372). This was however, not statistically significant. This result aligns with that of the unadjusted univariate association such that the treatment effect with weighting found no difference in survival rates between the two populations. This result however should be accepted with caution given that with this particular propensity model specification, we were unable to achieve balance between the treated and untreated subjects and as such is a biased result.

Propensity Score as a Covariate Covariate adjustment of the propensity was conducted using the logit of the propensity score. This was because transformation of the propensity score allowed for use of a greater range of values. The logit propensity score was included in a Cox proportional hazards model as the only other variable along side the chemotherapy index variable. Results were consistant with those found by matching and weighting. Again, the survival curves between the two cohorts were not statistically different. This resulted in a hazard ratio of 0.86 [95%CI (0.65-1.15), p=0.318] (Table 11).

Subclassification. In order to carry out subclassfication, the logit propensity score was divided in to 5 stratum based on the quartile values of the distribution. Distribution of chemotherapy patients between strata was not evenly distributed, with 75% of the chemotherapy treated patients scattered within in the first strata. Within the first quartile which consisted of of PS logit values [0, $\leq$ 5], while the second , third, fourth, and fifth quartile consisted of logit PS values of [$\geq$ 5, $\leq$ 6], [$\geq$ 6, $\leq$ 7],[$\geq$ 7, $\leq$ 8], and [$>$ 80, $\leq$ 21] respectively. Within the first quartile, cohort consisted of 5799 non chemotherapy patients and 133 chemotherapy patients. The second cohort had 5906 non-chemotherapy patients to 24 chemotherapy patients, with 5921 and 11 split between the third cohort, 5924 and 7 distributions in the fourth, and 5930

verses 2 in the fifth subset. Due to the disproportionate distribution of chemotherapy patients within each strata, we did not proceed further with this method

5. Discussion

In this analysis, the aim was to look at the efficacy of adjuvant chemotherapy treatment for high risk prostate cancer patients that have undergone radiation therapy and hormone therapy. This study design was based the RTOC 0521 study titled, "A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521)". Preliminary results from RTOC 0521 study indicate that 4-year overall survival rates were 89% for patients receiving ADT and RT verses 93% for patients treated additionally with docetaxel (HR = 0.70 [0.51-0.98], p= .04). Our study design is a retrospective cohort design using the 2014 NCDB Prostate Participant User File with 29,659 patients receiving standard treatment and 177 patients receiving chemotherapy on top of ADT and radiation therapy.

Results of the unadjusted multivariate cox proportional hazard analysis showed that the rate of overall survival was similar for both the chemo and non-chemotherapy group. However, because we are working with a retrospective database, we run into the issue that there are potentially underlying systematic differences between the two cohorts that might contribute to a biased effect through an unadjusted analysis. We employed propensity score methods in order to counteract that issue. Propensity score analysis utilizes various methods as a means to balance out the treatment and control population. Three methods that were utilized in this analysis were matching, weighting, and propensity score as a covariate. Although their hazard ratios varied slightly, the matching, weighting,and PS covariate adjustment methods consistantly showed slightly lower risk for non-chemotherapy patients, while the opposite was found for the unadjusted method. Overall however, we found that the results were similar between the calculated overall survival found using unadjusted methods and results found through the three propensity score methods.

There are several different factors to consider as a possible rational for the results, those dealing with the propensity score methods and those associated with the study design. With the propensity score methods, it should be acknowledged that the same propensity score model is used for all three PS methods

because this allowed us to compare the results of the three PS methods against each other. However, the only method that fully achieved balance was propensity score matching. A look at the standardized differences between chemotherapy treated and untreated populations with IPTW and subclassification showed that the difference in mean and prevalence for several covariates was greater than 10%. Since systematic difference between the two treatment populations remained even after conditioning on the propensity score, this an indication that the propensity score has been miss-specified. Typically, a method to address that issue would be to re-evaluate the variables in the PS model and repeat the diagnostic process until balance is achieve. Since that process was not done here, it is important to note the effect measured after IPTW is biased since we were unable to full balance the covariate effect between the two cohorts.

An overarching concern with propensity score analysis is that there is a lack of consensus on how the propensity score model should be specified. Although in practice, most use baseline covariates associated with the treatment are typically use, there are several other suggested methods in literature. Another is that, a component of the propensity score model is that by conditioning on the propensity score, what is being balanced are the measured baseline covariates. Therefore, there is a possibility that our results are still confounded by unmeasured covariates, there were either not included in the propensity score model, or was not available through the NCDB database (Winkelmayer and Kurth, 2014).

In regards to the study design. One major benefit of this analysis is that it makes use of a large nationally representative database. While clinical trials are considered the gold standard, they are sometimes prohibitively expensive, and the inclusion and exclusion criteria for patients are extremely stringent. A major advantage of the retrospective analysis utilizing nationally scaled database is that it allows a practical perceptive, allowing in sight on treatments using real world data. This method also leverages existing data to support research and can often be used for hypothesis generating studies. There are however drawbacks to this. While the NCDB database is abundant in content, it is perhaps unable to fully capture the intricacies of patient treatment.

In our scenario specifically, the drawback of analyzing a novel treatment is the lack of sample size consistent with that specific patient population. I noted above that in two most prominent studies utilizing adjuvant chemotherapy with radiation therapy and chemotherapy, the results of RTOG 9902 found no survival benefits and while the results of RTOG 0521 had successfully seen improved 4 year survival rates for chemotherapy patients. Major differences between the two studies were the use of docetaxel and

higher radiation dose of up to 78 Gy. It wasn't even until 2004 that docetaxel had been approved for use in metastatic prostate cancer patients. In order to achieve sufficient sample size, it was necessary to broaden the range of several variables, and those such as specificity of chemotherapy drugs was not considered. Additionally, we looked at a greater range of radiation dosage. Ultimately, more research is necessary to provide a more clear image of chemotherapy's role in the treatment of high risk prostate cancer patients. With the initial results of RTOG 0521 seeing clinical benefits to chemotherapy in this subgroup of prostate cancer patients, perhaps over time, the NCDB database will be more populated with that subset of patients. This would allow for better differentiation of the patient population and for future analysis would also provide a larger treatment cohort defined by use of docetaxel and higher radiation dose.

5.1 Conclusion

Through the use of various propensity score methods, we were unable to distinguish any clinical benefits to the use of chemotherapy in localized high risk prostate cancer patients. Given that chemotherapy use for high risk patients is a more recent addition to the prostate cancer treatment repertoire, we suspect that a large limiting reagent was the lack of sample size which in turn prohibited the exploration of a more specific subset of patients that might benefit from this treatment.

6. References

Albers, Peter. 2015. "Prostate cancer: No evidence for adjuvant chemotherapy in high-risk disease." *Nature Reviews. Urology* 12 (11). Nature Publishing Group: 602–3. doi:10.1038/nrurol.2015.219.

American Cancer Society. 2017a. "Cancer Staging." https://www.cancer.org/treatment/understanding-your-diagnosis/staging.html.

———. 2017b. "Understanding Your Pathology Report: Prostate Cancer." https://www.cancer.org/treatment/understanding-your-diagnosis/tests/understanding-your-pathology-report/prostate-pathology/prostate-cancer-pathology.html.

American College of Surgeons. 2017. "National Cancer Database." https://www.facs.org/quality-programs/cancer/ncdb.

ASCO. 2017. "Prostate Cancer - Stages and Grades." http://www.cancer.net/cancer-types/prostate-cancer/stages-and-grades.

Austin, Peter C. 2009. "Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples." *Statistics in Medicine* 28: 3083–3107. doi:10.1002/sim.

———. 2010. "The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies." *Statistics in Medicine* 29: 2137–48. doi:10.1002/sim.3854.

———. 2011a. "A Tutorial and Case Study in Propensity Score Analysis: An Application to Estimating the Effect of In-Hospital Smoking Cessation Counseling on Mortality." *Multivariate Behavioral Research* 46 (1): 119–51. doi:10.1080/00273171.2011.540480.

———. 2011b. "An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies." *Multivariate Behavioral Research* 46 (3): 399–424. doi:10.1080/00273171.2011.568786.

Austin, Peter C, and Elizabeth A Stuart. 2010. "Moving towards best practice when using inverse

probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies." *Statistics in Medicine*, no. 29: 2137–48. doi:10.1002/sim.6607.

Bolla, Michel, Laurence Collette, Léo Blank, Padraig Warde, Jean Bernard Dubois, René-olivier Mirimanoff, Guy Storme, et al. 2002. "Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial." *The Lancet* 360: 103–8.

Brookhart, M Alan, Philip Wang, and Daniel H Solomon. 2006. "NIH Public Access." *Epidemiology* 17 (3): 268–75. doi:10.1097/01.ede.0000193606.58671.c5.Evaluating.

Carlson, Robert H. 2015. "First Indication Chemotherapy Has Role in Adjuvant Therapy of Localized Prostate Cancer." *Oncology Times*, 30–31.

Chang, Albert J, Karen A Autio, I Howard, San Francisco, San Francisco, Oncology Service, and Memorial Sloan-kettering Cancer. 2015. "' High-Risk ' Prostate Cancer : Classification and Therapy." *Nature Reviews Clinical Oncology* 11 (6): 308–23. doi:10.1038/nrclinonc.2014.68.

Denmeade, Samuel R, John T Isaacs, Samuel R Denmeade, John T Isaacs, and Kimmel Comprehensive. 2014. "A history of prostate cancer treatment." *Nature Reviews Cancer* 2 (5): 389–96. doi:10.1038/nrc801.A.

Frangakis, Constantine E, and Donald B Rubin. 2002. "Principal Stratification in Causal Inference." *Biometrics* 58 (March): 21–29.

Greenland, Sanders, and James M Robins. 1988. "Identifiability, Exchangeability, and Epidemiological Confounding." *International Journal of Epidemiology* 15 (3): 413–19.

Hanks, Gerald E, Thomas F Pajak, Arthur Porter, David Grignon, Harmart Brereton, Varagur Venkatesan, Eric M Horwitz, et al. 2003. "Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02." *Journal of Clinical Oncology : Official*

Journal of the American Society of Clinical Oncology 21 (21): 3972–8. doi:10.1200/JCO.2003.11.023.

Holland, Paul W. 1986. "Statistics and Causal Inference." *Journal O* 81 (396): 945–60.

Horti, Jozsef, Anna Pluzanska, Kim N Chi, Stephane Oudard, Christine Théodore, Mark A Rosenthal, D Ph, and Mario A Eisenberger. 2004. "Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer." *The New England Journal of Medicine* 351 (15): 1502–12.

Ilepich, M Iljenko V P, K Athryn W Inter, M Adhu J J Ohn, B M Esic, W Illiam S Ause, P Hillip R Ubin, C Olleen L Awton, M Itchell M Achtay, and D Avid G Rignon. 2001. "Phase III Radiation Therapy Oncology Group (RTOG) Trial 86-10 of Androgen Deprivation Adjuvant to Definitive Radiotherapy in Locally Advanced Carcinoma of the Prostate." *International Journal of Radiation Oncology Biology Physics* 50 (5): 1243–52.

Imbens, Guido; Rubin, Don. 2015. "Chapter 17 Subclassification on the Propensity Score." In *Causal Inference in Statistics*, 1st ed., 1–29. Cambridge Univesrity press.

Jemal, Ahmedin, Rebecca Siegel, Elizabeth Ward, and Taylor Murray. 2007. "Cancer Statistics , 2007." *Cancer Statistics* 57 (1): 43–66.

Lanza, Stephanie; Moore, Julia E.; Butera, Nicole M. 2013. "Drawing Causal Inferences Using Propensity Scores: A Practical Guide for Community Psychologists." *American Journal of Community Psychology* 52 (0): 380–92. doi:10.1007/s10464-013-9604-4.Drawing.

Mayo Clinic. 2017. "Prostate cancer: Tests and Diagnosis." http://www.mayoclinic.org/diseases-conditions/prostate-cancer/basics/tests-diagnosis/con-20029597.

National Cancer Institute. 2017. "NCI Dictionary of Cancer Terms." https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=257214.

Pilepich, Miljenko V, Kathryn Winter, Colleen a Lawton, Robert E Krisch, Harvey B Wolkov, Benjamin Movsas, Eugen B Hug, Sucha O Asbell, and David Grignon. 2005. "Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma–long-term results of phase III RTOG 85-31." *International*

Journal of Radiation Oncology, Biology, Physics 61 (5): 1285–90. doi:10.1016/j.ijrobp.2004.08.047.

Prostate Cancer Foundation. 2017a. "PSA & DRE Screenings." https://www.pcf.org/c/psa-dre-screening/.

———. 2017b. "What is Prostate Cancer?" https://www.pcf.org/c/what-is-prostate-cancer/.

Roach, M, M DeSilvio, C Lawton, V Uhl, M Machtay, M J Seider, M Rotman, et al. 2003. "Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 21 (10): 1904–11. doi:10.1200/JCO.2003.05.004.

Rosenbaum, Paul R, and Donald B Rubin. 1983. "The Central Role of the Propensity Score in Observational Studies for Causal Effects." *Biometrika* 70 (1): 41–55.

Rosenbaum, Paul R. 2002. *Observational Studies*. 1st ed. New York: Springer-Verlag New York.

Rosenbaum, P R, Rubin, D B. 1983. "Assessing Sensitivity to an Unobserved Binary Covariate in an Observational Study with Binary Outcome." *Journal of the Royal Statistical Society. Series B (Methological)* 45 (2): 212–18.

Rosenthal, Seth a, Kyoungwha Bae, Kenneth J Pienta, Mark L Sobczak, Sucha O Asbell, Raghu Rajan, Kevin J Kerlin, Jeff M Michalski, and Howard M Sandler. 2009. "Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02." *International Journal of Radiation Oncology, Biology, Physics* 73 (3): 672–8. doi:10.1016/j.ijrobp.2008.05.020.

Rosenthal, Seth a, Daniel Hunt, a Oliver Sartor, Kenneth J Pienta, Leonard Gomella, David Grignon, Raghu Rajan, et al. 2015. "A Phase 3 Trial of 2 Years of Androgen Suppression and Radiation Therapy With or Without Adjuvant Chemotherapy for High-Risk Prostate Cancer: Final Results of Radiation Therapy Oncology Group Phase 3 Randomized Trial NRG Oncology RTOG 9902." *International Journal of Radiation Oncology, Biology, Physics* 93 (2). Elsevier Inc.: 294–302.

doi:10.1016/j.ijrobp.2015.05.024.

Rubin, Donald B. 1979. "Using Multivariate Matched Sampling and Regression Adjustment to Control Observational Studies." *Journal of American Statistical Association* 1978 (2): i–33.

———. 2005. "Causal Inference Using Potential Outcomes." *Journal of the American Statistical Association* 100 (469): 322–31. doi:10.1198/016214504000001880.

Sandler, Howard M, Chen Hu, Seth Rosenthal, Oliver Sartor, Leonard Gomella, Mahul Amin, James Purdy, et al. 2015. "A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521)." *2015 ASCO Annual Meeting*.

Siegel, Rebecca L, Kimberly D Miller, and Ahmedin Jemal. 2016. "Cancer Statistics , 2016." *Cancer Statistics* 66 (1): 7–30. doi:10.3322/caac.21332.

Symon, Zvi, Kent a Griffith, P.William McLaughlin, Molly Sullivan, and Howard M Sandler. 2003. "Dose escalation for localized prostate cancer: substantial benefit observed with 3D conformal therapy." *International Journal of Radiation Oncology*Biology*Physics* 57 (2): 384–90. doi:10.1016/S0360-3016(03)00569-8.

Thavaneswaran, Arane, and Lisa Lix. 2008. "Propensity Score Matching in Observational Studies." Manitoba Centre for Health Policy.

7. Appendix

Table 0: Inclusion/ Exclusion Criteria Diagram

Selection and Exclusion Criteria	Sample Size	Excluded
NCDB Prostate PUF Cancer Cases	1294126	-
Include Behavior = 3, Sequence Number in 0&1, Diagnostic Confirmation = 1	1176991	117135
Include Histology in 800,801,802,814	1155850	21141
Exclude Metastasis cases	1112459	43391
Include High Risk Population: Glean Socre 8-10 OR PSA >=20 Or T stage 2C,3, 3A, 3B, or 4	595131	517328
Include Patients who have received Definitive Local Therapy as Chemo and/or Radiation without Surgery	50035	545096
Exclude Unknown status of Chemotherapy	48722	1313
Exclude cases that had chemo outside 8-month window from the start of definitive local therapy	47817	905
Exclude cases with missing outcome	44467	3350
Include cases that received hormone therapy	29659	14808

Table 1: Patient Demographic and Clinical Characteristics

Variable	Level	N (%) = 29659
Chemotherapy	no	29482 (99.4)
	yes	177 (0.6)
Local Therapy	Beam radiation	21370 (72.1)
	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	8289 (27.9)
Facility Type	Unknown	2
	Non-Academic/Research Program	20351 (68.6)
	Academic/Research Program	9306 (31.4)
Facility Location	Northeast	7304 (24.6)
	South	9598 (32.4)
	Midwest	7411 (25.0)
	West	5344 (18.0)
	Missing	2
Age at diagnosis (quartile)	>=38, <=64	7934 (26.8)
	>64, <=70	7306 (24.6)
	>70, <=75	7009 (23.6)
	>75, <=90	7410 (25.0)
Race	White	23347 (78.7)
	Black	4917 (16.6)
	Others/Unknown	1395 (4.7)
Great Circle Distance (per 50 mi)(quartile)	>=0, <=1	7367 (24.8)
	>1, <=1	14684 (49.5)
	>1, <=78	7332 (24.7)
	Unknown	276 (0.9)
Charlson-Deyo Score	0	25624 (86.4)
	1+	4035 (13.6)

Variable	Level	N (%) = 29659
Year of Diagnosis (quartile)	>=2004, <=2006	9187 (31.0)
	>2006, <=2008	6439 (21.7)
	>2008, <=2011	8683 (29.3)
	>2011, <=2013	5350 (18.0)
Gleason Score (categorical)	2-7	10071 (34.0)
	8-10	19122 (64.5)
	unknown	466 (1.6)
PSA (categorical)	10-20	5746 (19.4)
	<10	13539 (45.6)
	>= 20	9687 (32.7)
	Unknown	687 (2.3)
Regional Dose(quartile)	>=45, <=7000	7238 (24.4)
	>7000, <=7560	7475 (25.2)
	>7560, <=7800	6572 (22.2)
	>7800, <=86409	6746 (22.7)
	Unknown	1628 (5.5)
Total Radiation Dose(quartile)	>=18, <=5040	7471 (25.2)
	>5040, <=7560	8030 (27.1)
	>7560, <=7800	6426 (21.7)
	>7800, <=136000	7271 (24.5)
	Unknown	461 (1.6)
AJCC Clinical T	0-1	11448 (38.6)
	2	13271 (44.7)
	3-4	4402 (14.8)
	Unknown	538 (1.8)
AJCC Clinical N	Negative	26688 (90.0)
	Positive	715 (2.4)
	Unknown	2256 (7.6)
AJCC Pathologic T	0-1	11 (0.0)
	2	1006 (3.4)
	3-4	216 (0.7)
	Unknown	28426 (95.8)

Variable	Level	N (%) = 29659
AJCC Pathologic N	Negative	961 (3.2)
	Positive	119 (0.4)
	Unknown	28579 (96.4)
AJCC Clinical Stage Group	1-2	23911 (80.6)
	3-4	4613 (15.6)
	unknown	1135 (3.8)
Number of Treatments to this volume(quartile)	>=1, <=29	7981 (26.9)
	>29, <=41	6905 (23.3)
	>41, <=43	8026 (27.1)
	>43, <=892	5331 (18.0)
	Unknown	1416 (4.8)
Regional Treatment Modality	Other	10554 (35.6)
	IMRT	17953 (60.5)
	Conformal or 3-D therapy	1152 (3.9)
Radiation Treatment Volume	Pelvis (NOS)	1884 (6.4)
	Prostate and pelvis	11576 (39.0)
	Prostate	16138 (54.4)
	Unknown	61 (0.2)
Age at Diagnosis	Mean	69.42
	Median	70.00
	Minimum	38.00
	Maximum	90.00
	Std Dev	8.16
	Missing	0.00
Great Circle Distance (per 50 mi)	Mean	0.66
	Median	0.17
	Minimum	0.00
	Maximum	77.97
	Std Dev	3.09
	Missing	276.00

Variable	Level	N (%) = 29659
Year of Diagnosis	Mean	2008.37
	Median	2008.00
	Minimum	2004.00
	Maximum	2013.00
	Std Dev	2.82
	Missing	0.00
Gleason Score	Mean	7.87
	Median	8.00
	Minimum	2.00
	Maximum	10.00
	Std Dev	1.00
	Missing	466.00
PSA	Mean	20.13
	Median	10.80
	Minimum	0.00
	Maximum	99.00
	Std Dev	21.74
	Missing	687.00
Regional Dose	Mean	7341.42
	Median	7560.00
	Minimum	45.00
	Maximum	86409.00
	Std Dev	4728.35
	Missing	1628.00
Total radiation dose	Mean	7427.48
	Median	7560.00
	Minimum	18.00
	Maximum	136000.0
	Std Dev	6140.81
	Missing	461.00

Variable	Level	N (%) = 29659
Hormone Therapy, Days from Dx	Mean	49.25
	Median	35.00
	Minimum	0.00
	Maximum	2311.00
	Std Dev	59.10
	Missing	2927.00
Last Contact or Death, Months from Dx	Mean	61.93
	Median	58.81
	Minimum	0.20
	Maximum	142.59
	Std Dev	32.84
	Missing	0.00
Radiation, Months from Dx	Mean	4.26
	Median	3.75
	Minimum	0.03
	Maximum	58.67
	Std Dev	2.58
	Missing	17.00
Number of Treatments to this Volume	Mean	37.87
	Median	41.00
	Minimum	1.00
	Maximum	892.00
	Std Dev	18.74
	Missing	1416.00
Radiation Ended, Days from Start of Radiation	Mean	61.38
	Median	61.00
	Minimum	1.00
	Maximum	577.00
	Std Dev	19.57
	Missing	696.00

Variable	Level	N (%) = 29659
Systemic, Days from Dx	Mean	49.26
	Median	35.00
	Minimum	0.00
	Maximum	2311.00
	Std Dev	58.80
	Missing	2708.00
Chemotherapy, Days from Dx	Mean	105.32
	Median	86.00
	Minimum	0.00
	Maximum	559.00
	Std Dev	74.30
	Missing	29482.00
Time from Dx to Local Therapy	Mean	129.62
	Median	114.00
	Minimum	0.00
	Maximum	1786.00
	Std Dev	78.44
	Missing	0.00

Table 2: Univariate Association with Chemotherapy

			Chemotherapy		
Covariate	**Statistics**	**Level**	**no N=29482**	**yes N=177**	**P-value***
Local Therapy	N (Row %)	Beam radiation	21234 (99.36)	136 (0.64)	0.155
	N (Row %)	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	8248 (99.51)	41 (0.49)	
Facility Type	N (Row %)	Non-Academic/Research Program	20306 (99.78)	45 (0.22)	**<.001**
	N (Row %)	Academic/Research Program	9174 (98.58)	132 (1.42)	
Facility Location	N (Row %)	Northeast	7258 (99.37)	46 (0.63)	0.522
	N (Row %)	South	9535 (99.34)	63 (0.66)	
	N (Row %)	Midwest	7375 (99.51)	36 (0.49)	
	N (Row %)	West	5312 (99.4)	32 (0.6)	
Age at diagnosis (quartile)	N (Row %)	>=38, <=64	7841 (98.83)	93 (1.17)	**<.001**
	N (Row %)	>64, <=70	7268 (99.48)	38 (0.52)	
	N (Row %)	>70, <=75	6975 (99.51)	34 (0.49)	
	N (Row %)	>75, <=90	7398 (99.84)	12 (0.16)	
Race	N (Row %)	White	23206 (99.4)	141 (0.6)	0.268
	N (Row %)	Black	4893 (99.51)	24 (0.49)	
	N (Row %)	Others/Unknown	1383 (99.14)	12 (0.86)	
Great Circle Distance (per 50 mi)(quartile)	N (Row %)	>=0, <=1	7338 (99.61)	29 (0.39)	**<.001**
	N (Row %)	>1, <=1	14601 (99.43)	83 (0.57)	
	N (Row %)	>1, <=78	7267 (99.11)	65 (0.89)	
	N (Row %)	Unknown	276 (100)	0 (0)	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Charlson-Deyo Score	N (Row %)	0	25462 (99.37)	162 (0.63)	**0.046**
	N (Row %)	1+	4020 (99.63)	15 (0.37)	
Year of Diagnosis (quartile)	N (Row %)	>=2004, <=2006	9108 (99.14)	79 (0.86)	**<.001**
	N (Row %)	>2006, <=2008	6398 (99.36)	41 (0.64)	
	N (Row %)	>2008, <=2011	8638 (99.48)	45 (0.52)	
	N (Row %)	>2011, <=2013	5338 (99.78)	12 (0.22)	
Gleason Score (categorical)	N (Row %)	2-7	10031 (99.6)	40 (0.4)	**0.005**
	N (Row %)	8-10	18989 (99.3)	133 (0.7)	
	N (Row %)	unknown	462 (99.14)	4 (0.86)	
PSA (categorical)	N (Row %)	10-20	5722 (99.58)	24 (0.42)	**0.004**
	N (Row %)	<10	13467 (99.47)	72 (0.53)	
	N (Row %)	>= 20	9615 (99.26)	72 (0.74)	
	N (Row %)	Unknown	678 (98.69)	9 (1.31)	
Regional Dose(quartile)	N (Row %)	>=45, <=7000	7199 (99.46)	39 (0.54)	**0.004**
	N (Row %)	>7000, <=7560	7410 (99.13)	65 (0.87)	
	N (Row %)	>7560, <=7800	6533 (99.41)	39 (0.59)	
	N (Row %)	>7800, <=86409	6717 (99.57)	29 (0.43)	
	N (Row %)	Unknown	1623 (99.69)	5 (0.31)	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Total Radiation Dose(quartile)	N (Row %)	>=18, <=5040	7432 (99.48)	39 (0.52)	0.054
	N (Row %)	>5040, <=7560	7966 (99.2)	64 (0.8)	
	N (Row %)	>7560, <=7800	6387 (99.39)	39 (0.61)	
	N (Row %)	>7800, <=136000	7237 (99.53)	34 (0.47)	
	N (Row %)	Unknown	460 (99.78)	1 (0.22)	
AJCC Clinical T	N (Row %)	0-1	11402 (99.6)	46 (0.4)	**<.001**
	N (Row %)	2	13201 (99.47)	70 (0.53)	
	N (Row %)	3-4	4344 (98.68)	58 (1.32)	
	N (Row %)	Unknown	535 (99.44)	3 (0.56)	
AJCC Clinical N	N (Row %)	Negative	26550 (99.48)	138 (0.52)	**<.001**
	N (Row %)	Positive	698 (97.62)	17 (2.38)	
	N (Row %)	Unknown	2234 (99.02)	22 (0.98)	
AJCC Clinical Stage Group	N (Row %)	1-2	23805 (99.56)	106 (0.44)	**<.001**
	N (Row %)	3-4	4551 (98.66)	62 (1.34)	
	N (Row %)	unknown	1126 (99.21)	9 (0.79)	
Number of Treatments to this volume(quartile)	N (Row %)	>=1, <=29	7935 (99.42)	46 (0.58)	**0.011**
	N (Row %)	>29, <=41	6851 (99.22)	54 (0.78)	
	N (Row %)	>41, <=43	7989 (99.54)	37 (0.46)	
	N (Row %)	>43, <=892	5306 (99.53)	25 (0.47)	
	N (Row %)	Unknown	1401 (98.94)	15 (1.06)	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Regional Treatment Modality	N (Row %)	Other	10480 (99.3)	74 (0.7)	0.121
	N (Row %)	IMRT	17859 (99.48)	94 (0.52)	
	N (Row %)	Conformal or 3-D therapy	1143 (99.22)	9 (0.78)	
Radiation Treatment Volume	N (Row %)	Pelvis (NOS)	1864 (98.94)	20 (1.06)	**0.002**
	N (Row %)	Prostate and pelvis	11493 (99.28)	83 (0.72)	
	N (Row %)	Prostate	16064 (99.54)	74 (0.46)	
	N (Row %)	Unknown	61 (100)	0 (0)	
Age at Diagnosis	N		29482	177	**<.001**
	Mean		69.45	63.75	
	Median		70	64	
	Min		38	41	
	Max		90	86	
	Std Dev		8.15	8.56	
Great Circle Distance (per 50 mi)	N		29206	177	0.578
	Mean		0.66	0.79	
	Median		0.17	0.29	
	Min		0	0	
	Max		77.97	20.99	
	Std Dev		3.09	1.99	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Year of Diagnosis	N		29482	177	**<.001**
	Mean		2008.37	2007.48	
	Median		2008	2007	
	Min		2004	2004	
	Max		2013	2013	
	Std Dev		2.82	2.5	
Gleason Score	N		29020	173	**<.001**
	Mean		7.87	8.2	
	Median		8	8	
	Min		2	2	
	Max		10	10	
	Std Dev		1	1.09	
PSA	N		28804	168	**0.025**
	Mean		20.11	23.88	
	Median		10.8	13.25	
	Min		0	0.2	
	Max		99	98	
	Std Dev		21.72	24.68	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Regional Dose(quartile)	N		29482	177	**0.035**
	Mean		2.82	2.53	
	Median		3	2	
	Min		1	1	
	Max		9	9	
	Std Dev		1.85	1.49	
Total radiation dose	N		29022	176	0.643
	Mean		7428.78	7213.47	
	Median		7560	7560	
	Min		18	2880	
	Max		136000	45000	
	Std Dev		6154.27	3228.09	
Hormone Therapy, Days from Dx	N		26562	170	0.674
	Mean		49.24	51.15	
	Median		35	41	
	Min		0	0	
	Max		2311	212	
	Std Dev		59.2	40.98	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Radiation, Months from Dx	N		29465	177	0.247
	Mean		4.26	4.04	
	Median		3.75	3.68	
	Min		0.03	0.69	
	Max		58.67	14.88	
	Std Dev		2.58	1.74	
Number of Treatments to this Volume	N		28081	162	0.965
	Mean		37.87	37.8	
	Median		41	39	
	Min		1	1	
	Max		892	200	
	Std Dev		18.74	18.64	
Radiation Ended, Days from Start of Radiation	N		28789	174	**0.002**
	Mean		61.4	56.88	
	Median		61	58.5	
	Min		1	1	
	Max		577	101	
	Std Dev		19.6	13.37	

Covariate	Statistics	Level	Chemotherapy		P-value*
			no N=29482	yes N=177	
Time from Dx to Local Therapy	N		29482	177	0.253
	Mean		129.66	122.9	
	Median		114	112	
	Min		0	21	
	Max		1786	453	
	Std Dev		78.57	52.93	

* The p-value is calculated by ANOVA for numerical covariates; and chi-square test or Fisher's exact for categorical covariates, where appropriate.

Table 3: Multivariate Association with Chemotherapy

		Chemotherapy=Yes		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Local Therapy	Beam radiation	1.36 (0.95-1.96)	0.095	0.095
	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	-	-	
Facility Type	Academic/Research Program	6.43 (4.51-9.15)	**<.001**	**<.001**
	Non-Academic/Research Program	-	-	
Facility Location	West	1.09 (0.68-1.75)	0.709	**0.005**
	Midwest	0.93 (0.60-1.45)	0.757	
	South	1.79 (1.20-2.67)	**0.004**	
	Northeast	-	-	
Race	Others/Unknown	1.02 (0.55-1.89)	0.943	**0.045**
	Black	0.56 (0.36-0.89)	**0.013**	
	White	-	-	
Year of Diagnosis (quartile)	>2011, <=2013	0.22 (0.12-0.41)	**<.001**	**<.001**
	>2008, <=2011	0.57 (0.39-0.84)	**0.004**	
	>2006, <=2008	0.73 (0.49-1.07)	0.104	
	>=2004, <=2006	-	-	
Gleason Score (categorical)	unknown	1.98 (0.69-5.67)	0.205	**<.001**
	8-10	2.24 (1.55-3.25)	**<.001**	
	2-7	-	-	
PSA (categorical)	Unknown	2.76 (1.25-6.09)	**0.012**	**0.011**
	>= 20	1.92 (1.19-3.08)	**0.007**	
	<10	1.35 (0.85-2.17)	0.205	
	10-20	-	-	

		Chemotherapy=Yes		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
AJCC Clinical T	Unknown	0.70 (0.20-2.42)	0.573	**<.001**
	3-4	2.34 (1.55-3.52)	**<.001**	
	2	1.34 (0.91-1.95)	0.134	
	0-1	-	-	
AJCC Clinical N	Unknown	1.56 (0.96-2.54)	0.075	**0.029**
	Positive	1.84 (1.06-3.21)	**0.031**	
	Negative	-	-	
Age at Diagnosis		0.93 (0.91-0.95)	**<.001**	**<.001**
Time from Dx to Local Therapy		1.00 (1.00-1.00)	0.055	0.055

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .1 was used. The following variables were removed from the model: Charlson-Deyo Score, Regional Dose, Regional Treatment Modality, and Great Circle Distance (per 50 mi)(quartile).

Table 4: Univariate Association with Overall Survival

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Chemotherapy	no	29482	1.05 (0.79-1.40)	0.723	0.717
	yes	177	-	-	
Local Therapy	Beam radiation	21370	1.67 (1.58-1.77)	**<.001**	**<.001**
	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	8289	-	-	
Facility Type	Academic/Research Program	9306	0.88 (0.83-0.93)	**<.001**	**<.001**
	Non-Academic/Research Program	20351	-	-	
Facility Location	West	5344	0.83 (0.77-0.90)	**<.001**	**<.001**
	Midwest	7411	1.11 (1.04-1.19)	**0.003**	
	South	9598	1.10 (1.03-1.18)	**0.004**	
	Northeast	7304	-	-	
Age at diagnosis (quartile)	>=38, <=64	7934	0.42 (0.39-0.45)	**<.001**	**<.001**
	>64, <=70	7306	0.52 (0.49-0.56)	**<.001**	
	>70, <=75	7009	0.67 (0.63-0.71)	**<.001**	
	>75, <=90	7410	-	-	
Race	Others/Unknown	1395	0.70 (0.61-0.79)	**<.001**	**<.001**
	Black	4917	0.93 (0.86-0.99)	**0.029**	
	White	23347	-	-	
Great Circle Distance (per 50 mi)(quartile)	Unknown	276	2.74 (2.26-3.31)	**<.001**	**<.001**
	>1, <=78	7332	0.89 (0.83-0.96)	**0.001**	
	>1, <=1	14684	0.92 (0.87-0.97)	**0.005**	
	>=0, <=1	7367	-	-	
Charlson-Deyo Score	1+	4035	1.49 (1.40-1.60)	**<.001**	**<.001**
	0	25624	-	-	

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Year of Diagnosis (quartile)	>2011, <=2013	5350	1.33 (1.17-1.51)	**<.001**	**<.001**
	>2008, <=2011	8683	1.18 (1.10-1.27)	**<.001**	
	>2006, <=2008	6439	1.11 (1.04-1.18)	**0.002**	
	>=2004, <=2006	9187	-	-	
Gleason Score (categorical)	unknown	466	1.34 (1.13-1.59)	**<.001**	**<.001**
	8-10	19122	1.39 (1.31-1.46)	**<.001**	
	2-7	10071	-	-	
PSA (categorical)	Unknown	687	1.20 (1.04-1.38)	**0.014**	**<.001**
	>= 20	9687	0.86 (0.80-0.92)	**<.001**	
	<10	13539	0.77 (0.72-0.82)	**<.001**	
	10-20	5746	-	-	
Regional Dose(quartile)	Unknown	1628	0.96 (0.85-1.09)	0.553	**<.001**
	>7800, <=86409	6746	1.40 (1.29-1.51)	**<.001**	
	>7560, <=7800	6572	1.59 (1.47-1.71)	**<.001**	
	>7000, <=7560	7475	1.78 (1.66-1.90)	**<.001**	
	>=45, <=7000	7238	-	-	
Total Radiation Dose(quartile)	Unknown	461	0.99 (0.78-1.25)	0.906	**<.001**
	>7800, <=136000	7271	1.48 (1.37-1.60)	**<.001**	
	>7560, <=7800	6426	1.65 (1.53-1.78)	**<.001**	
	>5040, <=7560	8030	1.80 (1.68-1.92)	**<.001**	
	>=18, <=5040	7471	-	-	
AJCC Clinical T	Unknown	538	1.24 (1.06-1.45)	**0.006**	**<.001**
	3-4	4402	1.16 (1.07-1.24)	**<.001**	
	2	13271	1.01 (0.96-1.07)	0.738	
	0-1	11448	-	-	
AJCC Clinical N	Unknown	2256	1.00 (0.93-1.09)	0.921	**<.001**
	Positive	715	1.43 (1.23-1.67)	**<.001**	
	Negative	26688	-	-	

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
AJCC Clinical Stage Group	unknown	1135	1.09 (0.98-1.22)	0.099	**<.001**
	3-4	4613	1.15 (1.08-1.23)	**<.001**	
	1-2	23911	-	-	
Number of Treatments to this volume(quartile)	Unknown	1416	1.31 (1.17-1.48)	**<.001**	**<.001**
	>43, <=892	5331	1.42 (1.31-1.55)	**<.001**	
	>41, <=43	8026	1.66 (1.55-1.78)	**<.001**	
	>29, <=41	6905	1.64 (1.53-1.76)	**<.001**	
	>=1, <=29	7981	-	-	
Regional Treatment Modality	Conformal or 3-D therapy	1152	1.10 (0.99-1.23)	0.083	**<.001**
	IMRT	17953	1.17 (1.11-1.23)	**<.001**	
	Other	10554	-	-	
Radiation Treatment Volume	Unknown	61	0.77 (0.48-1.24)	0.281	**<.001**
	Prostate	16138	0.88 (0.80-0.97)	**0.009**	
	Prostate and pelvis	11576	0.98 (0.89-1.08)	0.645	
	Pelvis (NOS)	1884	-	-	
Age at Diagnosis		29659	1.05 (1.04-1.05)	**<.001**	-
Great Circle Distance (per 50 mi)		29383	0.97 (0.95-0.98)	**<.001**	-
Year of Diagnosis		29659	1.04 (1.03-1.05)	**<.001**	-
Gleason Score		29193	1.24 (1.21-1.27)	**<.001**	-
PSA		28972	1.00 (1.00-1.00)	**<.001**	-
Regional Dose(quartile)		29659	0.99 (0.98-1.00)	**0.048**	-
Total radiation dose		29198	1.00 (1.00-1.00)	**0.001**	-
Hormone Therapy, Days from Dx		26732	1.00 (1.00-1.00)	0.906	-

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Radiation, Months from Dx		29642	1.01 (1.00-1.02)	**0.019**	-
Number of Treatments to this Volume		28243	1.00 (1.00-1.00)	**<.001**	-
Radiation Ended, Days from Start of Radiation		28963	1.00 (1.00-1.00)	0.856	-
Time from Dx to Local Therapy		29659	1.00 (1.00-1.00)	**0.017**	-

Table 5: Multivariate Association with Overall Survival

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy	no	29480	0.89 (0.67-1.19)	0.430	0.430
	yes	177	-	-	
Local Therapy	Beam radiation	21369	1.46 (1.37-1.55)	**<.001**	**<.001**
	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	8288	-	-	
Facility Type	Academic/Research Program	9306	0.89 (0.84-0.95)	**<.001**	**<.001**
	Non-Academic/Research Program	20351	-	-	
Facility Location	West	5344	0.85 (0.78-0.92)	**<.001**	**<.001**
	Midwest	7411	1.09 (1.02-1.17)	**0.012**	
	South	9598	1.14 (1.07-1.23)	**<.001**	
	Northeast	7304	-	-	
Race	Others/Unknown	1395	0.80 (0.70-0.91)	**0.001**	**0.002**
	Black	4916	1.04 (0.97-1.12)	0.302	
	White	23346	-	-	
Great Circle Distance (per 50 mi)(quartile)	Unknown	276	2.87 (2.37-3.47)	**<.001**	**<.001**
	>1, <=78	7330	0.95 (0.88-1.02)	0.129	
	>1, <=1	14684	0.95 (0.89-1.01)	0.075	
	>=0, <=1	7367	-	-	
Charlson-Deyo Score	1+	4035	1.49 (1.39-1.59)	**<.001**	**<.001**
	0	25622	-	-	
Year of Diagnosis (quartile)	>2011, <=2013	5350	1.21 (1.06-1.38)	**0.004**	**0.004**
	>2008, <=2011	8683	1.12 (1.04-1.20)	**0.004**	
	>2006, <=2008	6438	1.06 (1.00-1.13)	0.057	
	>=2004, <=2006	9186	-	-	

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Gleason Score (categorical)	unknown	466	1.17 (0.98-1.39)	0.078	**<.001**
	8-10	19121	1.39 (1.31-1.47)	**<.001**	
	2-7	10070	-	-	
PSA (categorical)	Unknown	687	1.15 (1.00-1.33)	**0.050**	**<.001**
	>= 20	9685	1.04 (0.97-1.11)	0.311	
	<10	13539	0.80 (0.75-0.85)	**<.001**	
	10-20	5746	-	-	
AJCC Clinical T	Unknown	538	1.30 (1.09-1.54)	**0.003**	**<.001**
	3-4	4402	1.34 (1.24-1.44)	**<.001**	
	2	13269	1.09 (1.04-1.16)	**0.001**	
	0-1	11448	-	-	
AJCC Clinical N	Unknown	2256	0.99 (0.90-1.08)	0.750	**<.001**
	Positive	715	1.47 (1.26-1.72)	**<.001**	
	Negative	26686	-	-	
Regional Treatment Modality	Conformal or 3-D therapy	1152	1.12 (1.00-1.25)	**0.044**	**0.034**
	IMRT	17952	0.97 (0.92-1.02)	0.277	
	Other	10553	-	-	
Age at Diagnosis		29657	1.04 (1.04-1.05)	**<.001**	**<.001**
Time from Dx to Local Therapy		29657	1.00 (1.00-1.00)	**<.001**	**<.001**

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.

Table 6a: Multivariable Survival Analysis of OS - interaction with AJCC Clinical N

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by AJCC Clinical N :	**Chemotherapy :**		-	-	0.296
Unknown	yes vs. no	22 vs. 2234	1.00 (0.42-2.43)	0.992	-
Positive	yes vs. no	17 vs. 698	1.81 (0.95-3.43)	0.070	-
Negative	yes vs. no	138 vs. 26548	1.03 (0.73-1.45)	0.885	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6b: Multivariable Survival Analysis of OS - interaction with AJCC Clinical T

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by AJCC Clinical T :	**Chemotherapy :**		-	-	0.986
Unknown	yes vs. no	3 vs. 535	1.04 (0.15-7.47)	0.965	-
3-4	yes vs. no	58 vs. 4344	1.10 (0.69-1.76)	0.684	-
2	yes vs. no	70 vs. 13199	1.09 (0.70-1.70)	0.701	-
0-1	yes vs. no	46 vs. 11402	1.26 (0.65-2.42)	0.492	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6c: Multivariable Survival Analysis of OS - interaction with Facility Type

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by Facility Type :	**Chemotherapy :**		-	-	0.424
Academic/Research Program	yes vs. no	132 vs. 9174	1.05 (0.74-1.47)	0.790	-
Non-Academic/Research Program	yes vs. no	45 vs. 20306	1.35 (0.80-2.29)	0.261	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6d Multivariable Survival Analysis of OS - interaction with Gleason Score

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by Gleason Score (categorical) :	**Chemotherapy :**		-	-	0.057
unknown	yes vs. no	4 vs. 462	4.12 (1.31-12.93)	**0.015**	-
8-10	yes vs. no	133 vs. 18988	1.00 (0.72-1.40)	0.977	-
2-7	yes vs. no	40 vs. 10030	1.39 (0.74-2.59)	0.303	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6e: Multivariable Survival Analysis of OS - interaction with Great Circle Distance (per 50 mi)

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by Great Circle Distance (per 50 mi)(quartile) :	**Chemotherapy :**		-	-	0.870
>1, <=78	yes vs. no	65 vs. 7265	1.07 (0.66-1.74)	0.771	-
>1, <=1	yes vs. no	83 vs. 14601	1.22 (0.80-1.86)	0.356	-
>=0, <=1	yes vs. no	29 vs. 7338	1.01 (0.52-1.95)	0.974	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Local Therapy, PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6f: Multivariable Survival Analysis of OS - interaction with Local Therapy

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by Local Therapy :	**Chemotherapy :**		-	-	0.772
Beam radiation	yes vs. no	136 vs. 21233	1.14 (0.84-1.56)	0.398	-
Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	yes vs. no	41 vs. 8247	1.01 (0.48-2.13)	0.969	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6g: Multivariable Survival Analysis of OS - interaction with PSA

			Survived Months from date of Local Therapy (Chemo or Radiation)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by PSA (categorical) :	**Chemotherapy :**		-	-	0.251
Unknown	yes vs. no	9 vs. 678	2.18 (0.90-5.31)	0.085	-
>= 20	yes vs. no	72 vs. 9613	1.19 (0.76-1.88)	0.447	-
<10	yes vs. no	72 vs. 13467	0.81 (0.48-1.37)	0.427	-
10-20	yes vs. no	24 vs. 5722	1.39 (0.74-2.59)	0.303	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6h: Multivariable Survival Analysis of OS - interaction with Race

Covariate	Level	N	Survived Months from date of Local Therapy (Chemo or Radiation)		
			Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Race :	**Chemotherapy :**		-	-	0.226
Others/Unknown	yes vs. no	12 vs. 1383	0.51 (0.13-2.05)	0.341	-
Black	yes vs. no	24 vs. 4892	1.75 (0.91-3.38)	0.095	-
White	yes vs. no	141 vs. 23205	1.10 (0.79-1.52)	0.577	-

* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6i: Multivariable Survival Analysis of OS - interaction with Regional Treatment Modality

Covariate	Level	N	Survived Months from date of Local Therapy (Chemo or Radiation) ---------- Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Regional Treatment Modality :	**Chemotherapy :**		-	-	0.716
Conformal or 3-D therapy	yes vs. no	9 vs. 1143	0.91 (0.29-2.83)	0.864	-
IMRT	yes vs. no	94 vs. 17858	1.03 (0.67-1.57)	0.898	-
Other	yes vs. no	74 vs. 10479	1.27 (0.84-1.93)	0.250	-

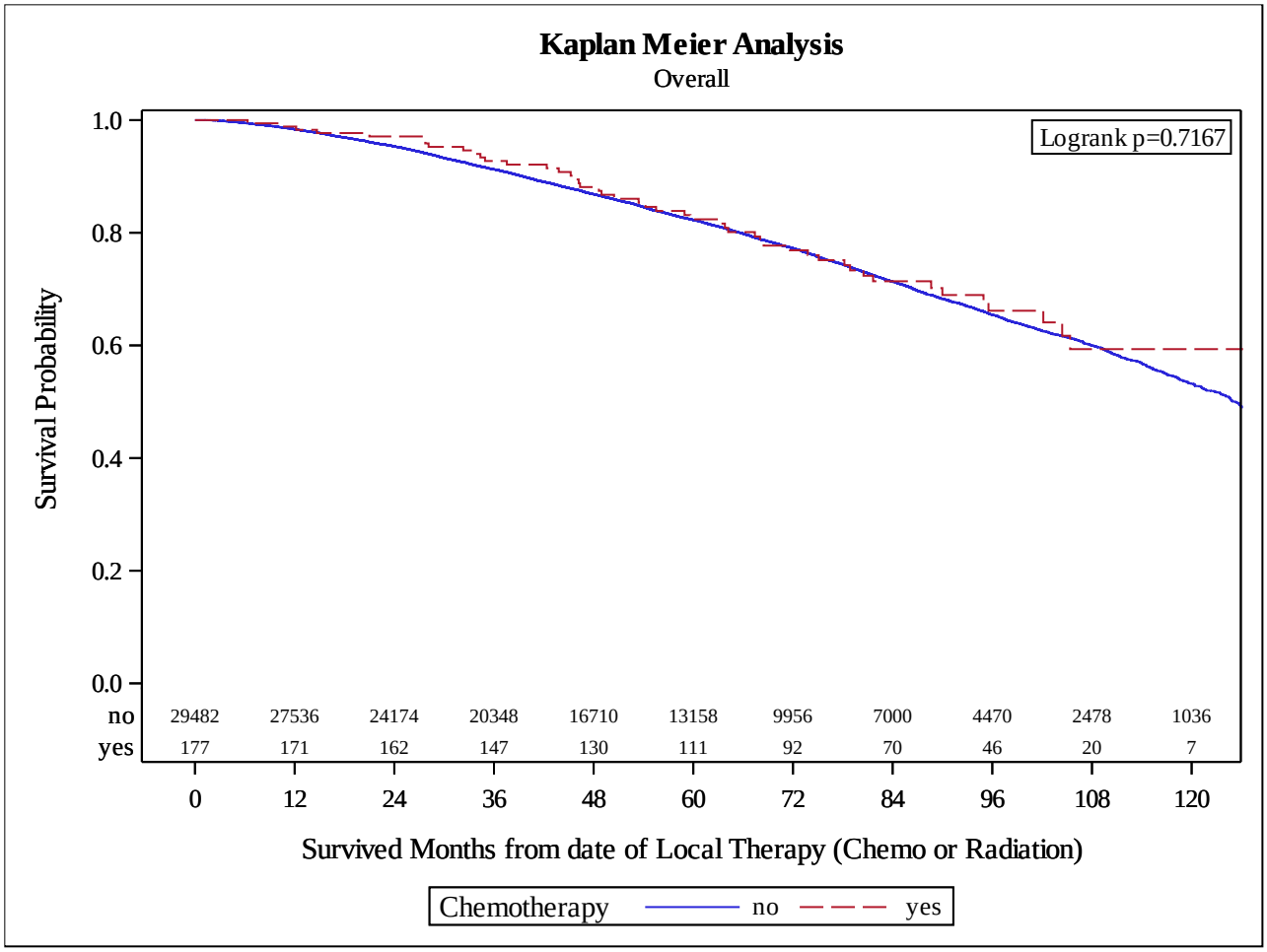
* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Age at Diagnosis, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Race, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Table 6j: Multivariable Survival Analysis of OS - interaction with Age-cut at median

Covariate	Level	N	Survived Months from date of Local Therapy (Chemo or Radiation) ---------- Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by age_cut :	**Chemotherapy :**		-	-	0.555
under 70	yes vs. no	131 vs. 15107	1.09 (0.76-1.55)	0.648	-
above 70	yes vs. no	46 vs. 14373	0.91 (0.56-1.47)	0.694	-

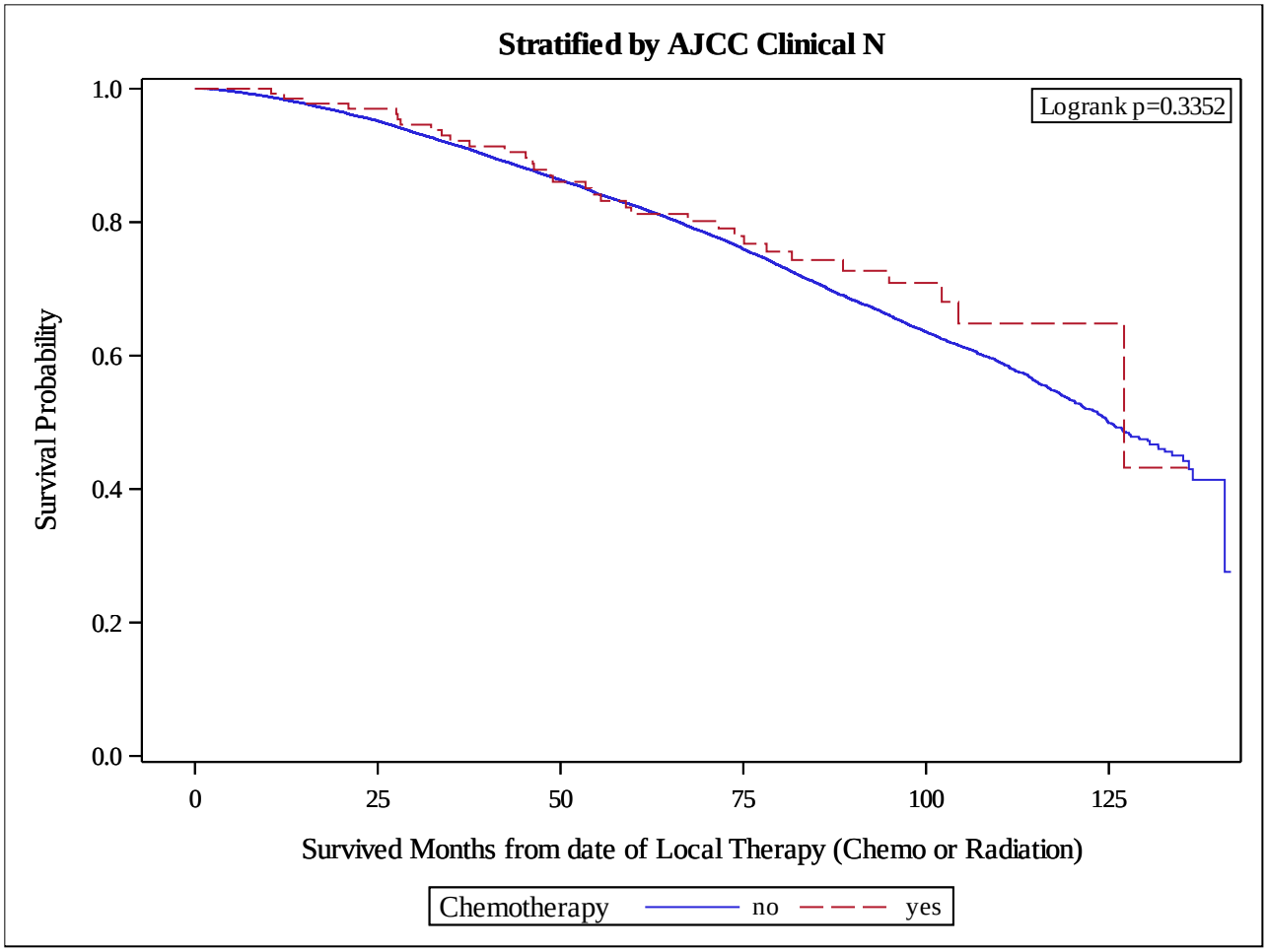
* Number of observations in the original data set = 29659. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Radiation Ended, Days from Start of Radiation, and Regional Dose.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical N, AJCC Clinical T, Charlson-Deyo Score, Facility Location, Facility Type, Gleason Score (categorical), Great Circle Distance (per 50 mi)(quartile), Local Therapy, PSA (categorical), Race, Regional Treatment Modality, Time from Dx to Local Therapy, Year of Diagnosis (quartile)

Figure 1: Kaplan Meier Curves of Overall Survival



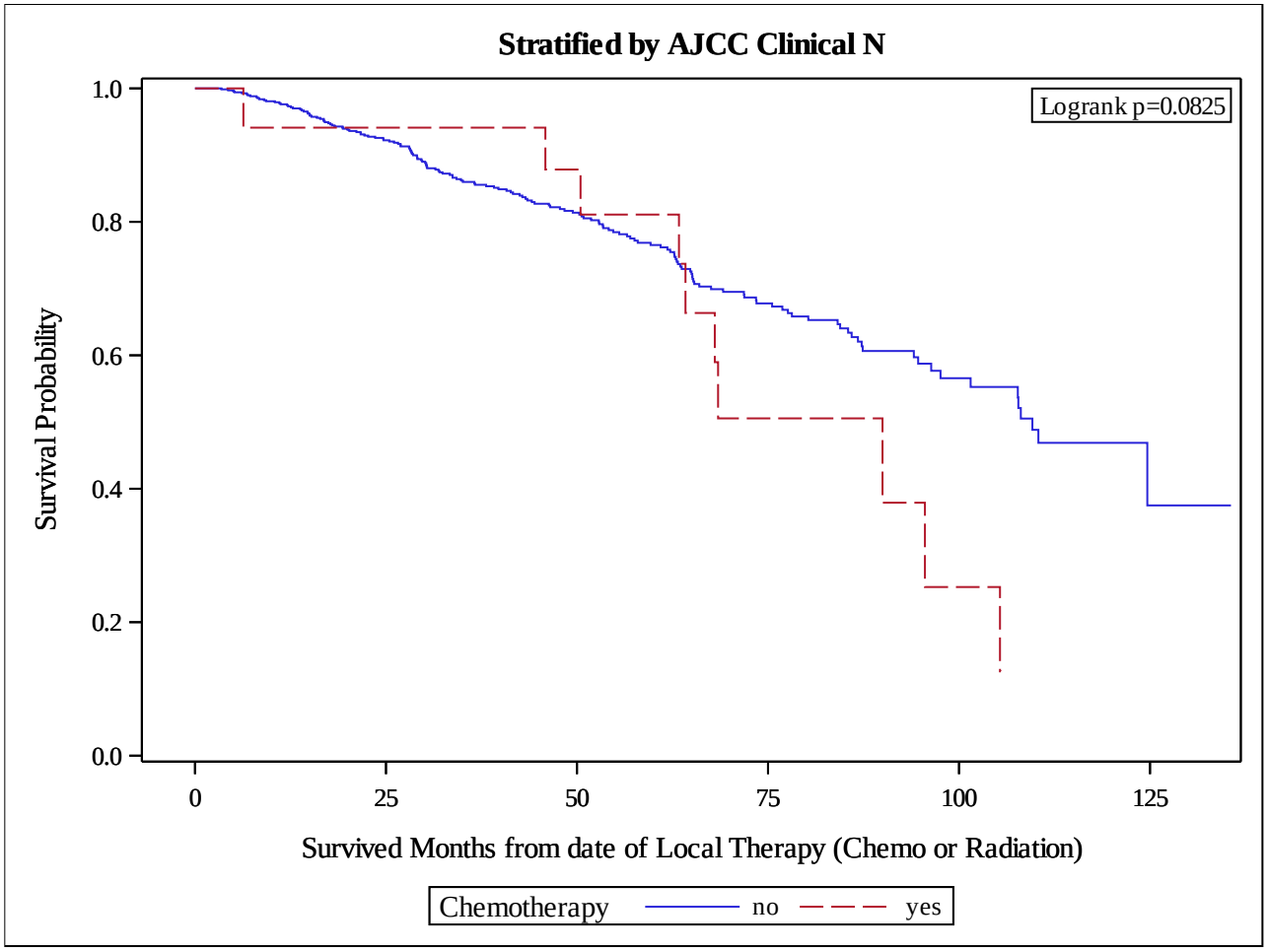
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival	84 Mo Survival	120 Mo Survival
no	29482	6438 (22%)	23044 (78%)	125.3 (123.5, 127.3)	98.4% (98.2%, 98.5%)	82.3% (81.7%, 82.8%)	71.3% (70.6%, 72.0%)	53.2% (51.9%, 54.4%)
yes	177	48 (27%)	129 (73%)	127.1 (105.4, NA)	98.9% (95.5%, 99.7%)	82.4% (75.3%, 87.6%)	71.4% (62.9%, 78.3%)	59.3% (47.9%, 69.1%)

Figure 2a: KM Plots - Stratified by AJCC Clinical N – Negative Cohort



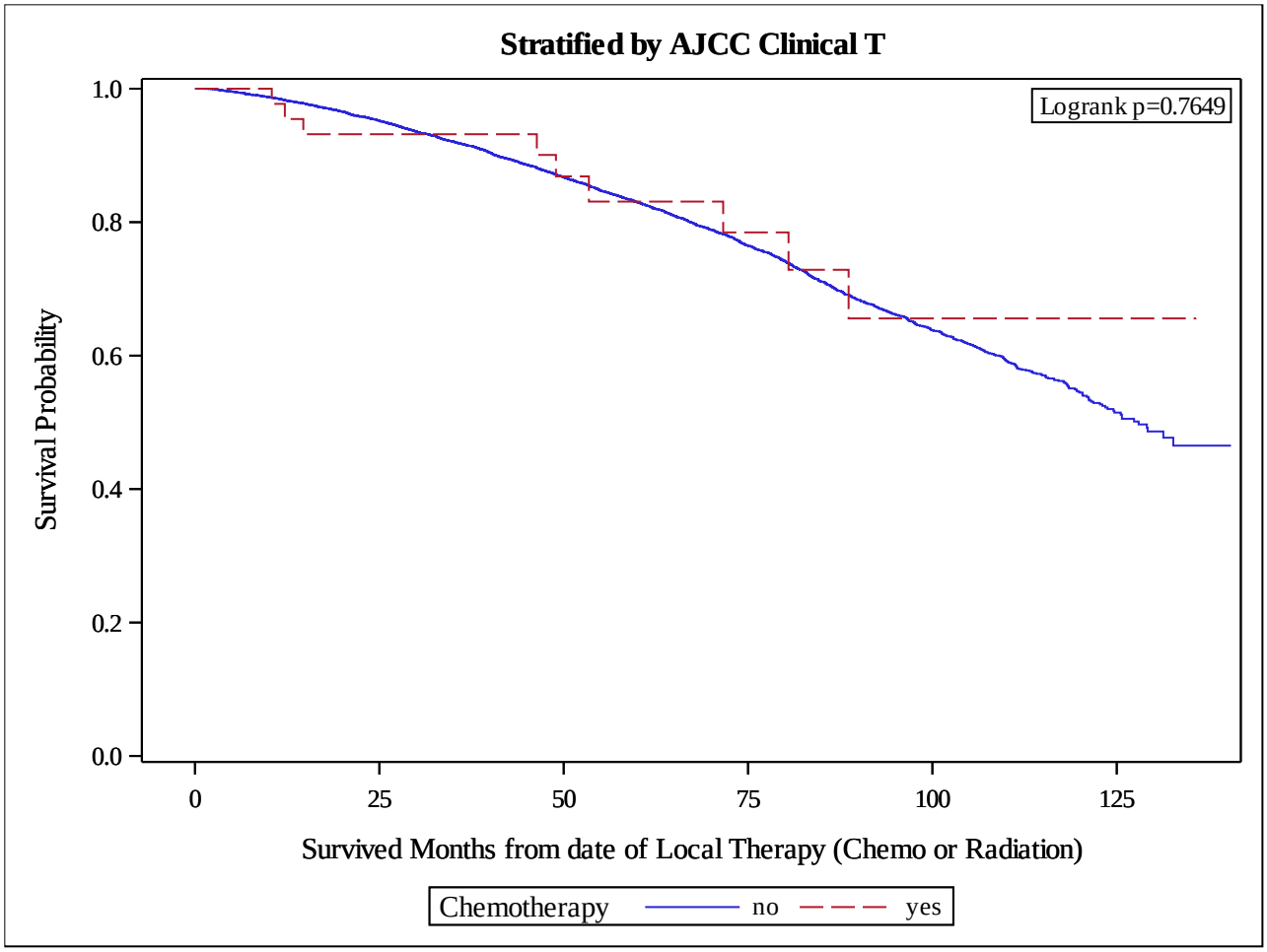
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	26550	5623 (21%)	20927 (79%)	124.9 (123.4, 127.8)	98.4% (98.2%, 98.5%)	82.5% (82.0%, 83.0%)
yes	138	33 (24%)	105 (76%)	127.1 (127.1, NA)	99.3% (94.9%, 99.9%)	81.2% (72.8%, 87.3%)

Figure 2b: KM Plots - Stratified by AJCC Clinical N – Positive



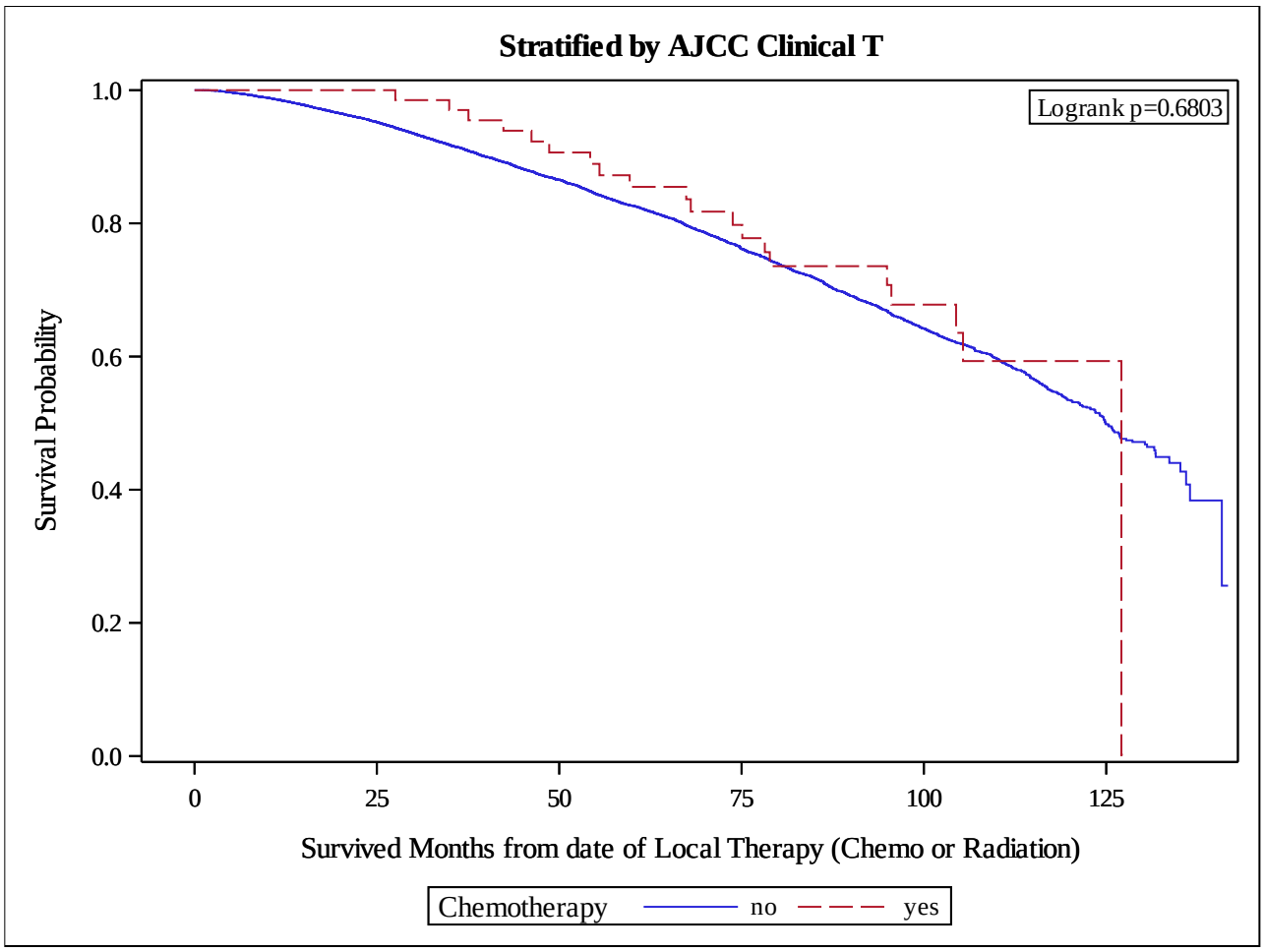
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	698	162 (23%)	536 (77%)	109.6 (97.6, NA)	97.6% (96.1%, 98.5%)	76.5% (72.3%, 80.2%)
yes	17	10 (59%)	7 (41%)	90 (63.3, 105.4)	94.1% (65.0%, 99.1%)	81.1% (51.9%, 93.5%)

Figure 3a: KM Plots - Stratified by AJCC Clinical T (0 - 1)



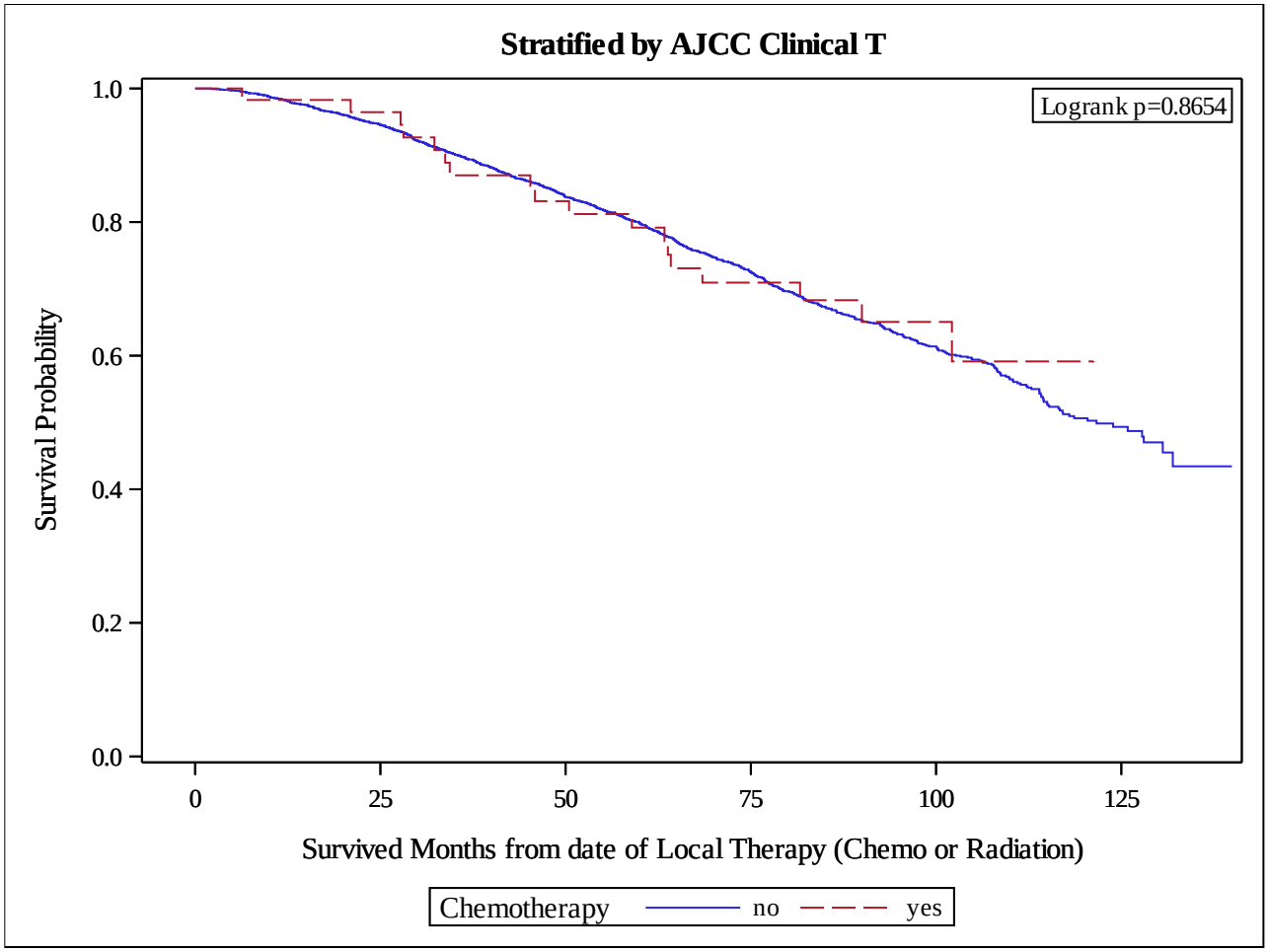
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	11402	2273 (20%)	9129 (80%)	128 (123.4, NA)	98.3% (98.1%, 98.6%)	83.0% (82.1%, 83.8%)
yes	46	9 (20%)	37 (80%)	NA (88.6, NA)	97.7% (84.9%, 99.7%)	83.1% (65.5%, 92.2%)

Figure 3b: KM Plots - Stratified by AJCC Clinical T (2)



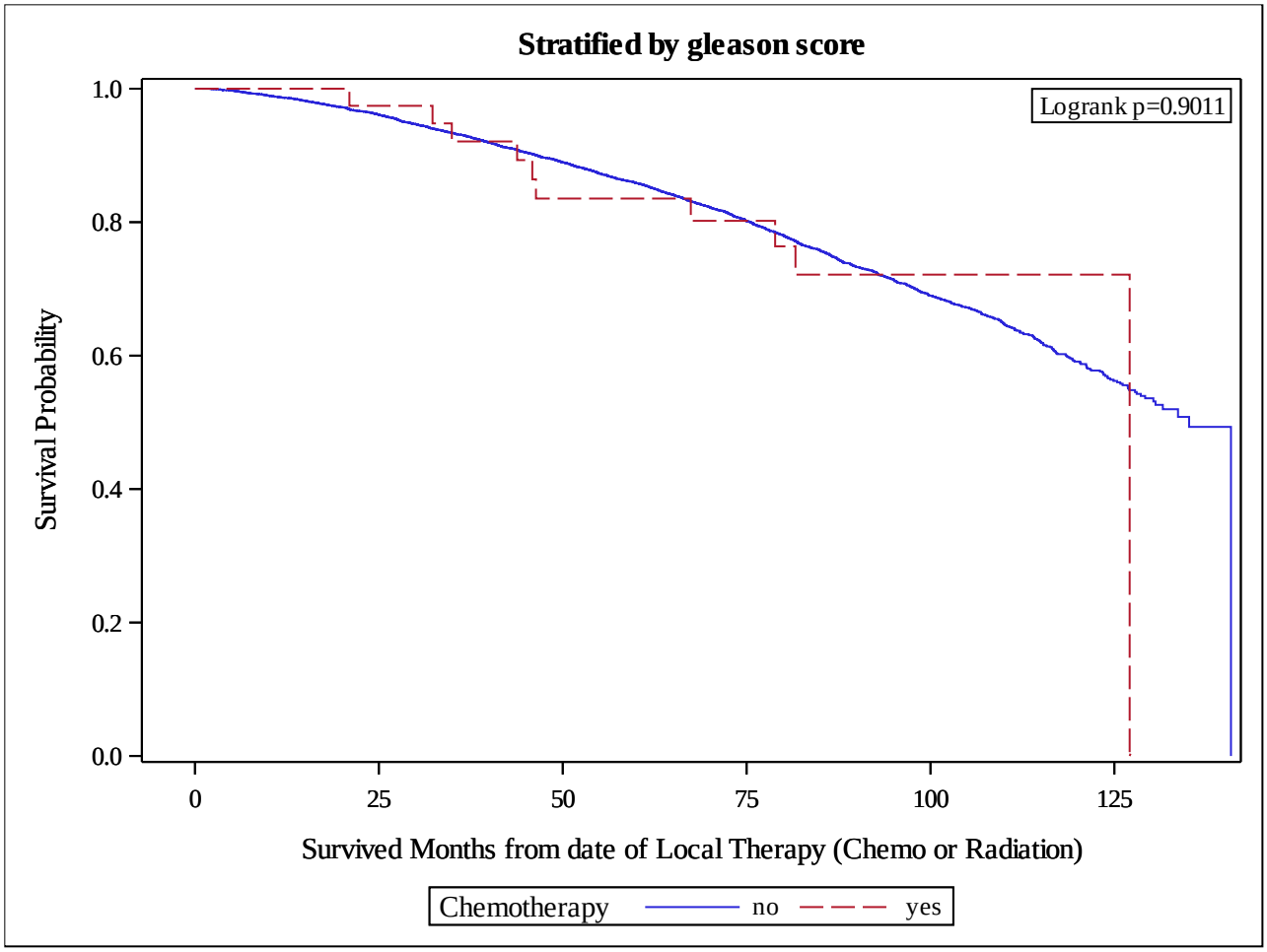
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	13201	2986 (23%)	10215 (77%)	124.9 (123.4, 127.7)	98.4% (98.2%, 98.6%)	82.7% (81.9%, 83.4%)
yes	70	20 (29%)	50 (71%)	127.1 (104.4, 127.1)	100.0% (NA, NA)	85.5% (73.9%, 92.2%)

Figure 3c: KM Plots - Stratified by AJCC Clinical T (3-4)



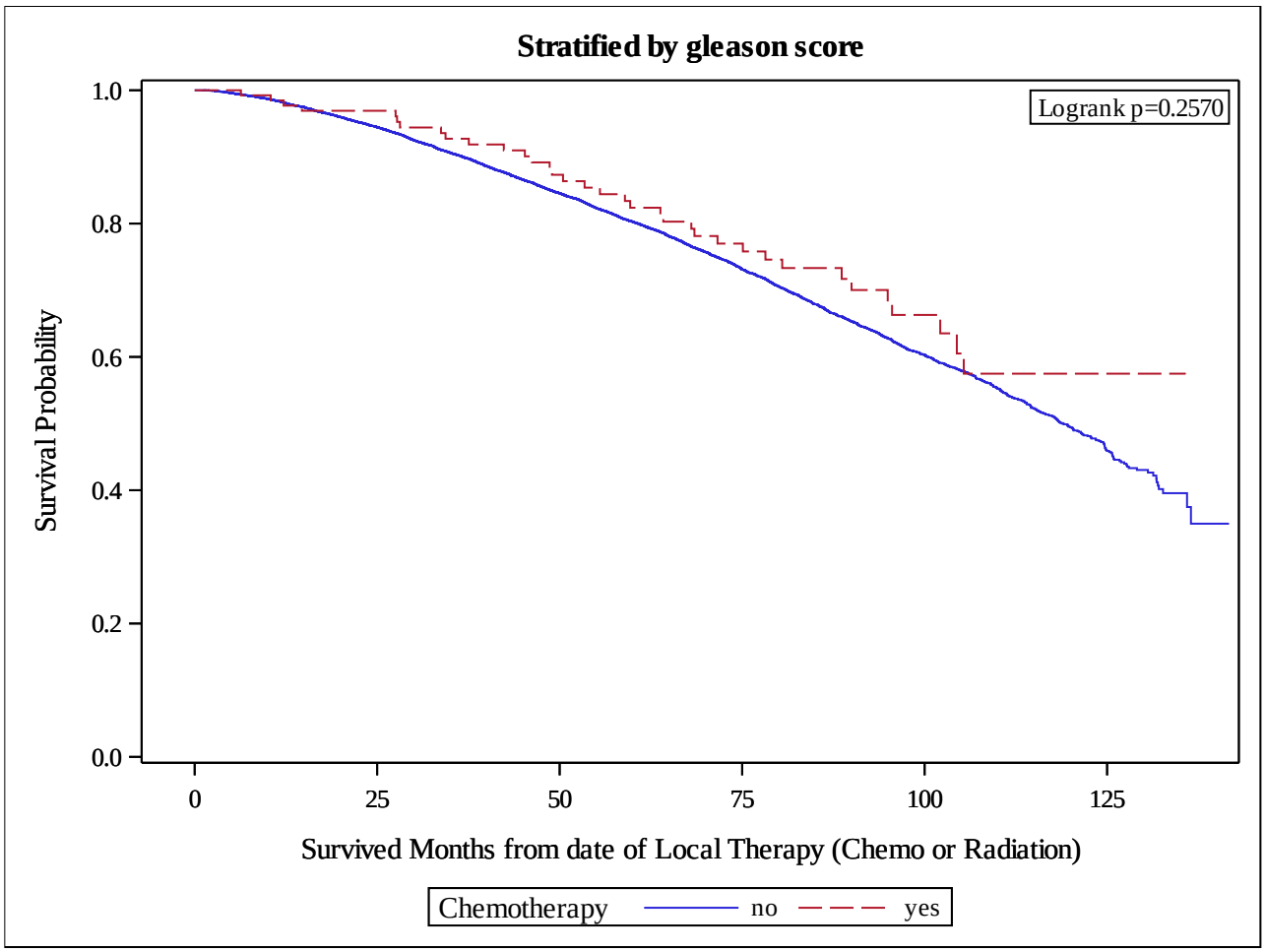
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	4344	1008 (23%)	3336 (77%)	121.7 (115, 131.9)	98.3% (97.9%, 98.7%)	79.8% (78.4%, 81.2%)
yes	58	18 (31%)	40 (69%)	NA (90, NA)	98.3% (88.4%, 99.8%)	79.2% (65.5%, 87.9%)

Figure 4a: KM Plots - Stratified by Gleason Score 2-7



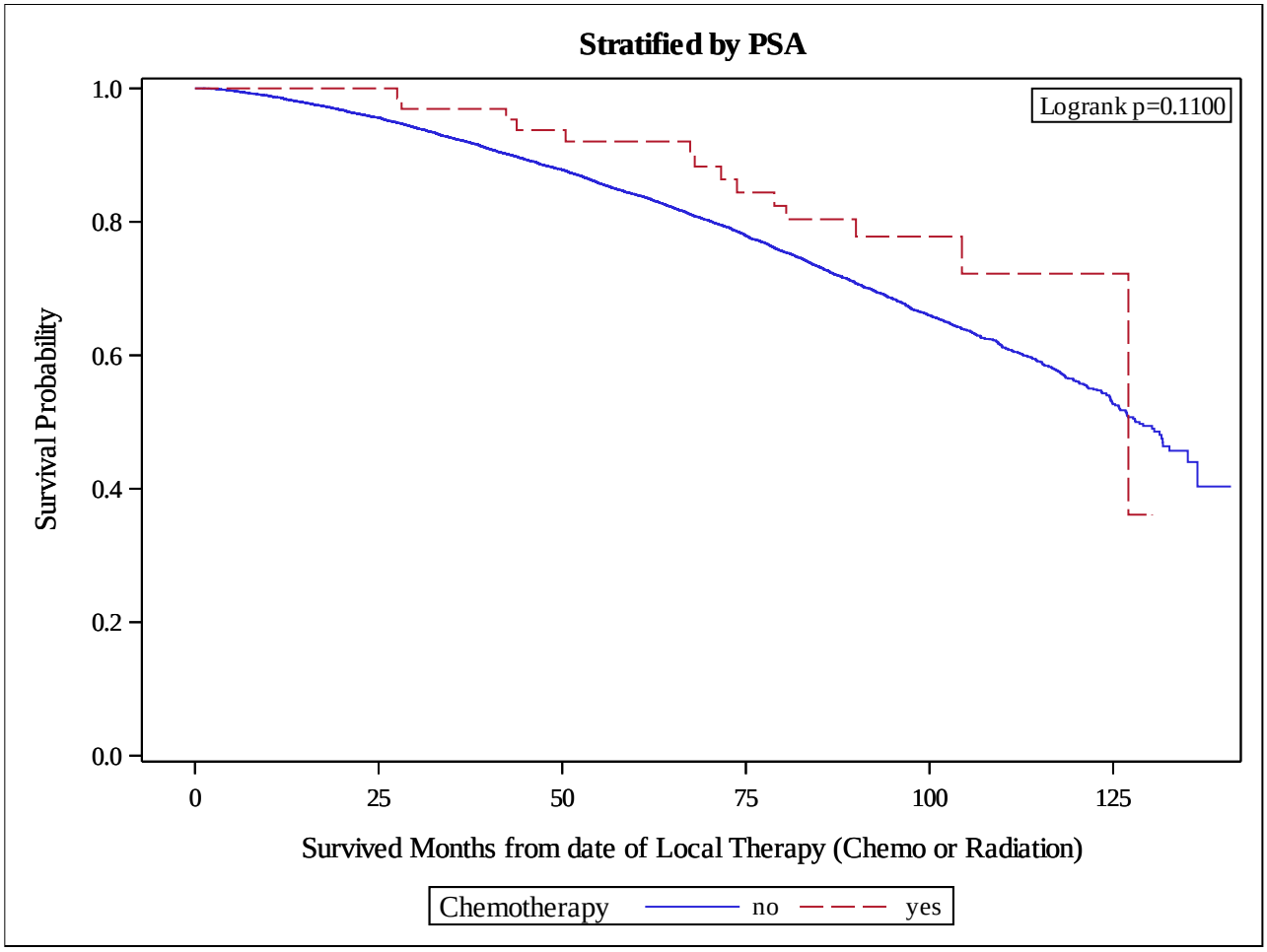
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	10031	2002 (20%)	8029 (80%)	135.2 (130.6, 140.9)	98.7% (98.4%, 98.9%)	85.8% (85.0%, 86.6%)
yes	40	10 (25%)	30 (75%)	127.1 (NA, NA)	100.0% (NA, NA)	83.5% (66.9%, 92.3%)

Figure 4b: KM Plots - Stratified by Gleason Score 8-10



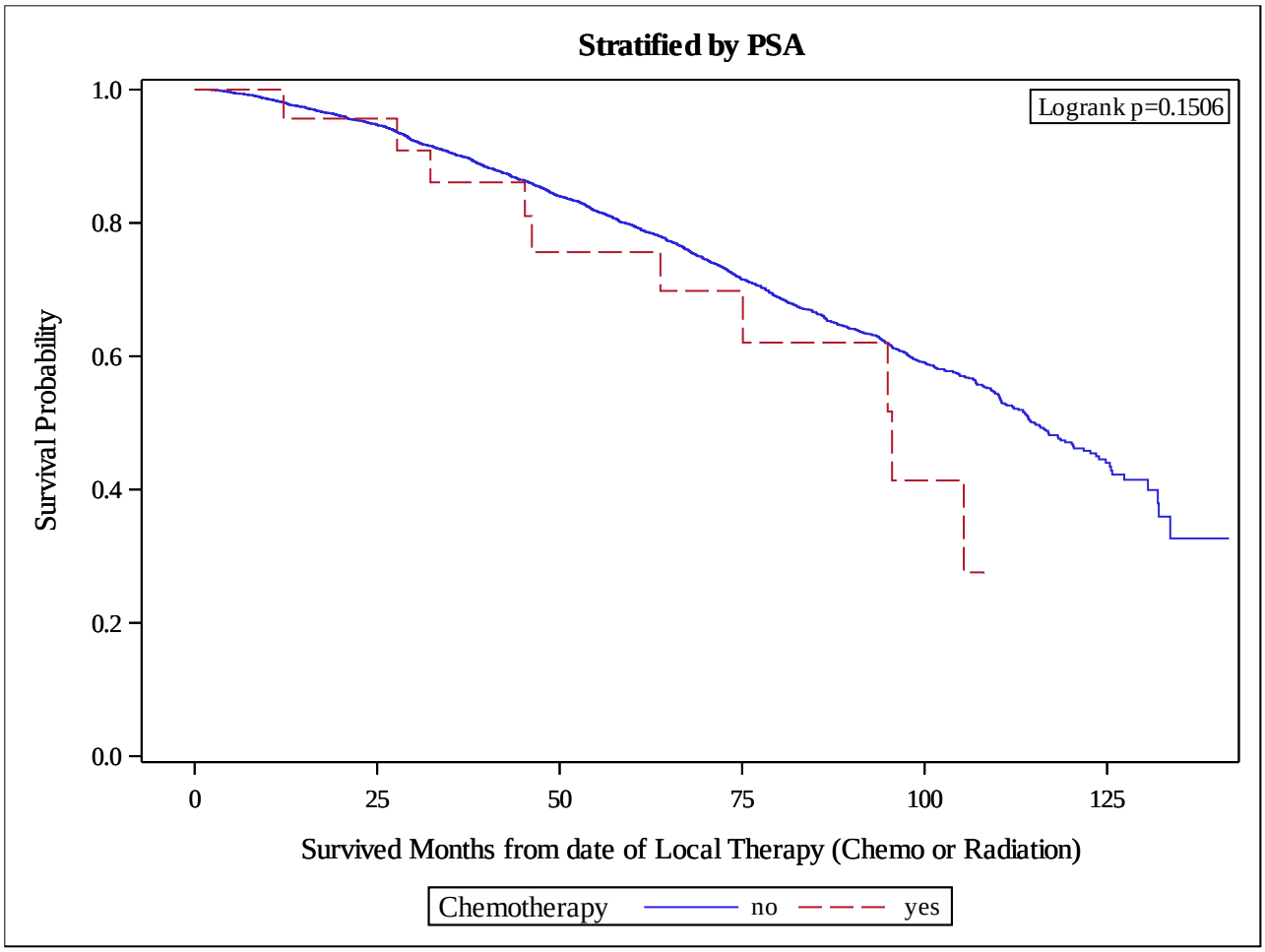
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	18989	4301 (23%)	14688 (77%)	118.9 (116.3, 121.8)	98.2% (98.0%, 98.4%)	80.3% (79.6%, 80.9%)
yes	133	35 (26%)	98 (74%)	NA (104.4, NA)	98.5% (94.0%, 99.6%)	82.4% (73.9%, 88.3%)

Figure 5a: KM Plots - Stratified by PSA < 10



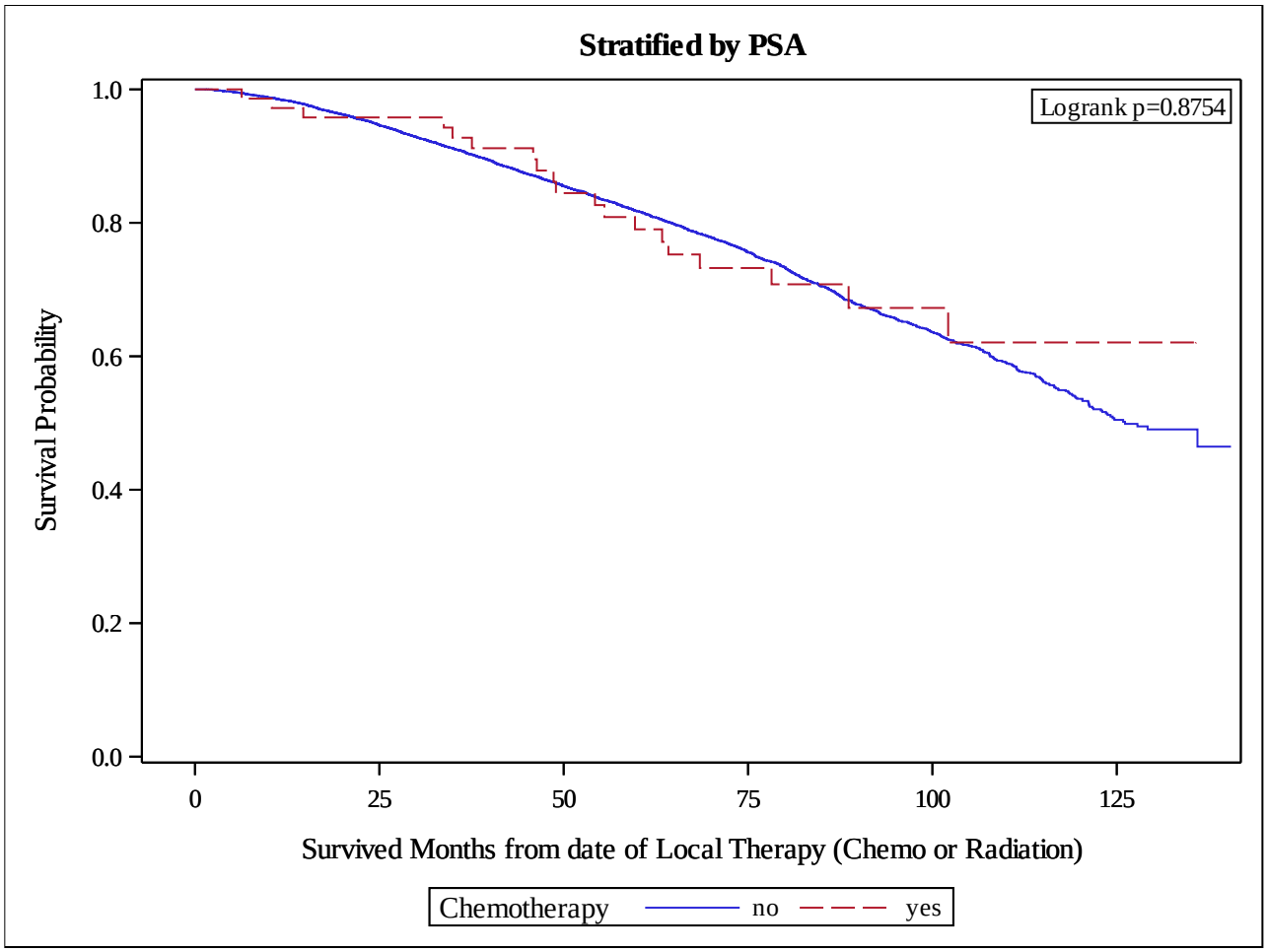
Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	13467	2742 (20%)	10725 (80%)	128 (125.8, 131.8)	98.5% (98.3%, 98.7%)	84.1% (83.3%, 84.8%)
yes	72	14 (19%)	58 (81%)	127.1 (127.1, NA)	100.0% (NA, NA)	92.0% (81.9%, 96.6%)

Figure 5b: KM Plots - Stratified by 10 ≤ PSA < 20



Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	5722	1408 (25%)	4314 (75%)	115 (112, 120.1)	98.1% (97.7%, 98.4%)	79.6% (78.3%, 80.8%)
yes	24	10 (42%)	14 (58%)	95.5 (63.8, NA)	100.0% (NA, NA)	75.6% (50.8%, 89.1%)

Figure 5c: KM Plots - Stratified by PSA ≥ 20



Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
no	9615	2076 (22%)	7539 (78%)	126.1 (121.7, NA)	98.4% (98.1%, 98.6%)	81.7% (80.8%, 82.6%)
yes	72	19 (26%)	53 (74%)	NA (102.1, NA)	97.2% (89.3%, 99.3%)	79.0% (66.5%, 87.3%)

Figure 6: Propensity Score distribution between Chemotherapy and Non-chemotherapy subjects

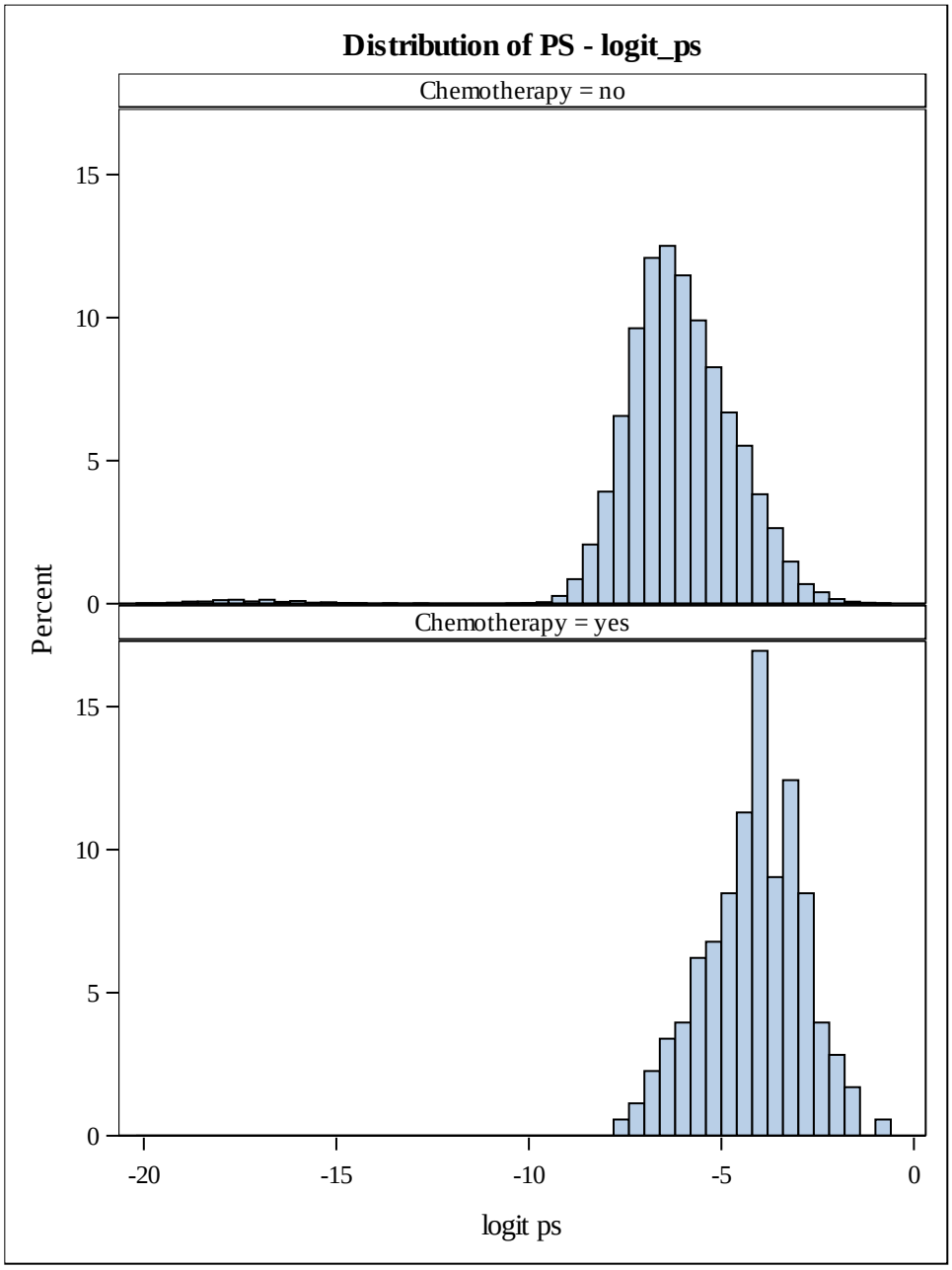
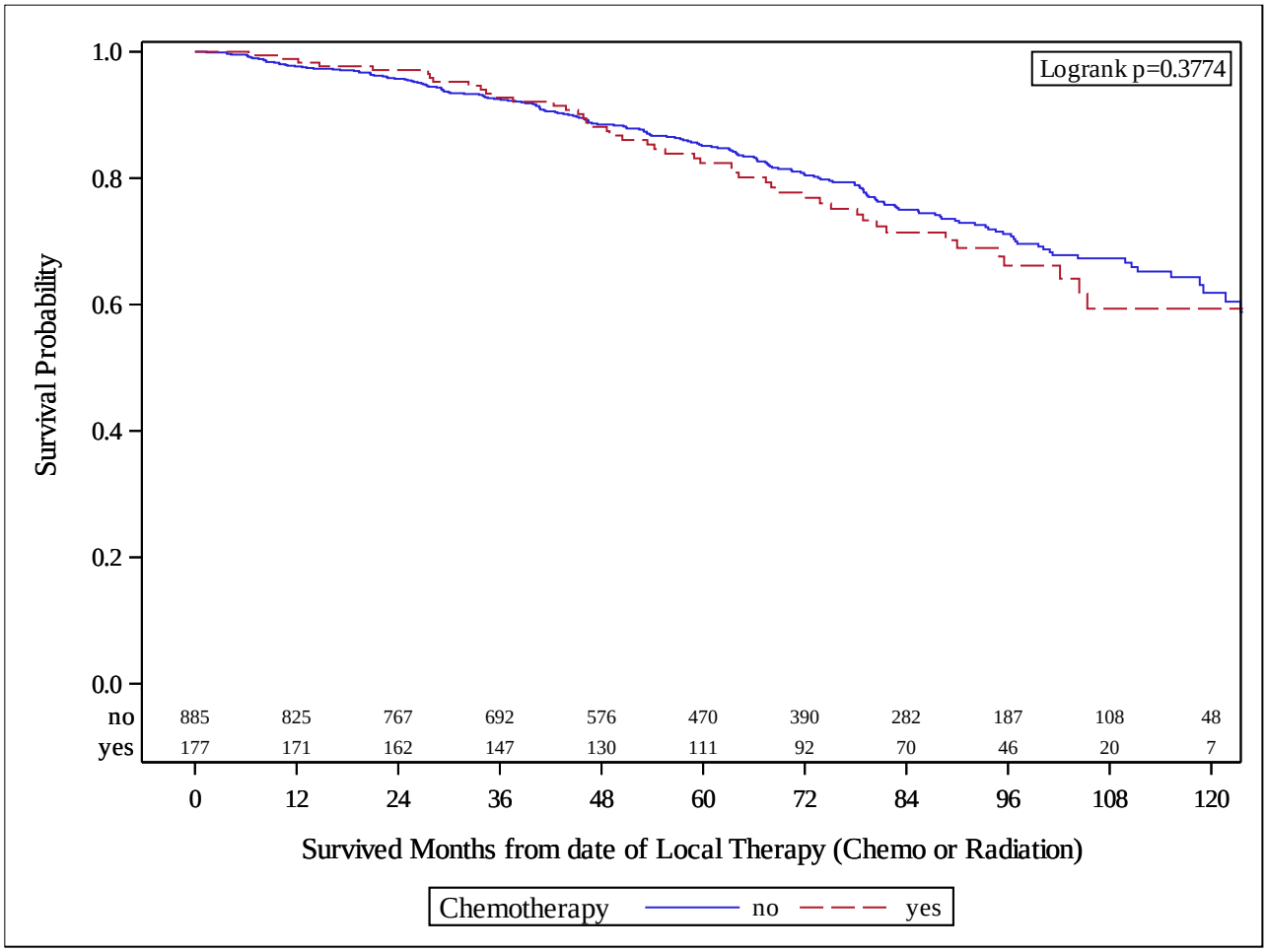


Figure 7: KM Plot - Overall Propensity Score for Matched Sample



Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival	84 Mo Survival	120 Mo Survival
no	885	189 (21%)	696 (79%)	130.6 (124.9, NA)	97.7% (96.4%, 98.5%)	85.1% (82.3%, 87.5%)	75.0% (71.2%, 78.4%)	61.9% (55.5%, 67.6%)
yes	177	48 (27%)	129 (73%)	127.1 (105.4, NA)	98.9% (95.5%, 99.7%)	82.4% (75.3%, 87.6%)	71.4% (62.9%, 78.3%)	59.3% (47.9%, 69.1%)

Table 7: Covariate Balance Check after Matching

Covariate	Level	Statistics	Chemotherapy		Parametric P-value*	Standardized Difference
			no N=885	yes N=177		
Local Therapy	Beam radiation	N (Col%)	697 (78.76)	136 (76.84)	0.571	0.046
	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	N (Col%)	188 (21.24)	41 (23.16)		0.046
Facility Type	Non-Academic/Research Program	N (Col%)	208 (23.5)	45 (25.42)	0.584	0.045
	Academic/Research Program	N (Col%)	677 (76.5)	132 (74.58)		0.045
Facility Location	Northeast	N (Col%)	241 (27.23)	46 (25.99)	0.927	0.028
	South	N (Col%)	306 (34.58)	63 (35.59)		0.021
	Midwest	N (Col%)	166 (18.76)	36 (20.34)		0.040
	West	N (Col%)	172 (19.44)	32 (18.08)		0.035
Race	White	N (Col%)	710 (80.23)	141 (79.66)	0.595	0.014
	Black	N (Col%)	101 (11.41)	24 (13.56)		0.065
	Others/Unknown	N (Col%)	74 (8.36)	12 (6.78)		0.060
Great Circle Distance (per 50 mi)(quartile)	>=0, <=1	N (Col%)	124 (14.01)	29 (16.38)	0.588	0.066
	>1, <=1	N (Col%)	448 (50.62)	83 (46.89)		0.075
	>1, <=78	N (Col%)	313 (35.37)	65 (36.72)		0.028
Charlson-Deyo Score	0	N (Col%)	812 (91.75)	162 (91.53)	0.921	0.008
	1+	N (Col%)	73 (8.25)	15 (8.47)		0.008

Covariate	Level	Statistics	Chemotherapy		Parametric P-value*	Standardized Difference
			no N=885	yes N=177		
Year of Diagnosis (quartile)	>=2004, <=2006	N (Col%)	396 (44.75)	79 (44.63)	0.980	0.002
	>2006, <=2008	N (Col%)	197 (22.26)	41 (23.16)		0.022
	>2008, <=2011	N (Col%)	236 (26.67)	45 (25.42)		0.028
	>2011, <=2013	N (Col%)	56 (6.33)	12 (6.78)		0.018
Gleason Score (categorical)	2-7	N (Col%)	212 (23.95)	40 (22.6)	0.804	0.032
	8-10	N (Col%)	647 (73.11)	133 (75.14)		0.046
	unknown	N (Col%)	26 (2.94)	4 (2.26)		0.043
PSA (categorical)	10-20	N (Col%)	112 (12.66)	24 (13.56)	0.951	0.027
	<10	N (Col%)	380 (42.94)	72 (40.68)		0.046
	>= 20	N (Col%)	351 (39.66)	72 (40.68)		0.021
	Unknown	N (Col%)	42 (4.75)	9 (5.08)		0.016
AJCC Clinical T	0-1	N (Col%)	232 (26.21)	46 (25.99)	0.997	0.005
	2	N (Col%)	347 (39.21)	70 (39.55)		0.007
	3-4	N (Col%)	289 (32.66)	58 (32.77)		0.002
	Unknown	N (Col%)	17 (1.92)	3 (1.69)		0.017
AJCC Clinical N	Negative	N (Col%)	705 (79.66)	138 (77.97)	0.867	0.041
	Positive	N (Col%)	81 (9.15)	17 (9.6)		0.016
	Unknown	N (Col%)	99 (11.19)	22 (12.43)		0.039
Regional Treatment Modality	Other	N (Col%)	354 (40)	74 (41.81)	0.669	0.037
	IMRT	N (Col%)	496 (56.05)	94 (53.11)		0.059
	Conformal or 3-D therapy	N (Col%)	35 (3.95)	9 (5.08)		0.054

Covariate	Level	Statistics	Chemotherapy		Parametric P-value*	Standardized Difference
			no N=885	yes N=177		
Age at Diagnosis		Mean (Std)	64.15 (8.49)	63.75 (8.56)	0.572	0.046
Time from Dx to Local Therapy		Mean (Std)	121.97 (64.84)	122.9 (52.93)	0.858	0.015

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

Table 8: Association with Overall Survival - Matched Sample

			Survived Months from date of Local Therapy (Chemo or Radiation) ---------- -	
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Chemotherapy	no	885	0.87 (0.65-1.16)	0.339
	yes	177	-	-

Analysis was taken the clustering effect within match_id into account, and N represented number of match_id-times.

Table 9: Covariate Balance Check Balance Check after IPTW

Covariate	Level	Statistics	Chemotherapy		Parametric P-value*	Standardized Difference
			no N=29499	yes N=158		
Local Therapy	Beam radiation	N (Col%)	21254 (72.05)	127 (80.56)	**0.017**	**0.201**
	Combination of beam radiation with Radioactive Implants or Radioactive implants or radioisotopes	N (Col%)	8243 (27.95)	30 (19.44)		**0.201**
Facility Type	Non-Academic/Research Program	N (Col%)	20241 (68.62)	106 (67.47)	0.756	0.025
	Academic/Research Program	N (Col%)	9256 (31.38)	51 (32.53)		0.025
Facility Location	Northeast	N (Col%)	7265 (24.63)	63 (40.39)	**<.001**	**0.341**
	South	N (Col%)	9546 (32.36)	31 (20.17)		**0.280**
	Midwest	N (Col%)	7370 (24.99)	25 (16.09)		**0.222**
	West	N (Col%)	5315 (18.02)	36 (23.36)		**0.132**
Race	White	N (Col%)	23221 (78.72)	128 (81.3)	0.731	0.065
	Black	N (Col%)	4889 (16.58)	23 (14.53)		0.057
	Others/Unknown	N (Col%)	1387 (4.7)	6 (4.17)		0.026
Great Circle Distance (per 50 mi)(quartile)	>=0, <=1	N (Col%)	7327 (24.84)	40 (25.38)	0.606	0.012
	>1, <=1	N (Col%)	14605 (49.51)	81 (51.67)		0.043
	>1, <=78	N (Col%)	7291 (24.72)	36 (22.95)		0.042
	Unknown	N (Col%)	274 (0.93)	0 (0)		**0.137**
Charlson-Deyo Score	0	N (Col%)	25485 (86.4)	138 (87.49)	0.688	0.033
	1+	N (Col%)	4013 (13.6)	19 (12.51)		0.033

Covariate	Level	Statistics	Chemotherapy		Parametric P-value*	Standardized Difference
			no N=29499	yes N=158		
Year of Diagnosis (quartile)	>=2004, <=2006	N (Col%)	9136 (30.97)	68 (43.08)	**0.001**	**0.253**
	>2006, <=2008	N (Col%)	6403 (21.71)	18 (11.41)		**0.280**
	>2008, <=2011	N (Col%)	8636 (29.28)	48 (30.8)		0.033
	>2011, <=2013	N (Col%)	5321 (18.04)	23 (14.72)		0.090
Gleason Score (categorical)	2-7	N (Col%)	10015 (33.95)	39 (25.08)	**0.033**	**0.196**
	8-10	N (Col%)	19019 (64.48)	117 (74.26)		**0.213**
	unknown	N (Col%)	463 (1.57)	1 (0.66)		0.086
PSA (categorical)	10-20	N (Col%)	5715 (19.37)	28 (17.69)	0.109	0.043
	<10	N (Col%)	13466 (45.65)	70 (44.7)		0.019
	>= 20	N (Col%)	9633 (32.66)	51 (32.36)		0.006
	Unknown	N (Col%)	683 (2.32)	8 (5.25)		**0.154**
AJCC Clinical T	0-1	N (Col%)	11386 (38.6)	68 (43.33)	**0.007**	0.096
	2	N (Col%)	13197 (44.74)	51 (32.33)		**0.257**
	3-4	N (Col%)	4379 (14.85)	33 (21.33)		**0.169**
	Unknown	N (Col%)	535 (1.81)	4 (3.01)		0.078
AJCC Clinical N	Negative	N (Col%)	26543 (89.98)	140 (88.72)	0.779	0.041
	Positive	N (Col%)	711 (2.41)	5 (3.22)		0.049
	Unknown	N (Col%)	2244 (7.61)	12 (8.06)		0.017
Regional Treatment Modality	Other	N (Col%)	10496 (35.58)	49 (31.15)	0.310	0.094
	IMRT	N (Col%)	17856 (60.53)	104 (66.21)		**0.118**
	Conformal or 3-D therapy	N (Col%)	1145 (3.88)	4 (2.63)		0.070

Covariate	Level	Statistics	Chemotherapy		Parametric P-value*	Standardized Difference
			no N=29499	yes N=158		
Age at Diagnosis		Mean (Std)	69.42 (8.16)	69.26 (7.82)	0.798	0.021
Time from Dx to Local Therapy		Mean (Std)	129.62 (78.51)	127.4 (46.28)	0.722	0.031

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

Table 10: Association with Overall Survival - Weighted Sample

Covariate	Level	N	Survived Months from date of Local Therapy (Chemo or Radiation) ---------- - Hazard Ratio (95% CI)	HR P-value
Chemotherapy	no	29480	0.80 (0.50-1.30)	0.372
	yes	177	-	-

Analysis was weighted by variable: adj_sipw
Analysis was taken the clustering effect within PUF_CASE_ID into account, and N represented number of PUF_CASE_ID-times.

Table 11: Association with Overall Survival – using PS as a Covariate

Covariate	Level	N	Survived Months from date of Local Therapy (Chemo or Radiation) ---------- Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Chemotherapy	no	29480	0.86 (0.65-1.15)	0.318	0.318
	yes	177	-	-	
logit ps		29657	0.90 (0.89-0.91)	**<.001**	**<.001**

* Number of observations in the original data set = 29657. Number of observations used = 29657.
** Backward selection with an alpha level of removal of .2 was used. No variables were removed from the model.