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The Application of Generalized Propensity Score Approaches on Dichotomous, Continuous, and Ordinal Treatment to Analyze the Effect of Total Radiation Dose on Cervical Esophageal Cancer Survival

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Abstract

The Application of Generalized Propensity Score Approaches on Dichotomous, Continuous, and Ordinal Treatment to Analyze the Effect of Total Radiation Dose on Cervical Esophageal Cancer Survival

By Alexandra Aiello

Introduction: The purpose of this paper is to investigate the impact of total radiation dose level on overall survival for cervical esophageal cancer (CEC) patients receiving chemoradiotherapy. As CEC is rare, there is little data currently available on the optimal radiation dosage for prolonging survival.

Methods: A retrospective cohort survival analysis was conducted using 2014 data from the National Cancer Database. Univariate, multivariable, and stratified Cox proportional hazards models are used to evaluate the impact of total radiation dose on overall survival. Cox-PH models using propensity score weighting and covariate adjustment are also used. For covariate adjustment, we evaluate two cases of the generalized propensity score: treating dose as a continuous variable and as an ordinal variable with four treatment groups: >4500-5040 cGy, >5040-5940 cGy, >5940-6400 cGy, and >6400-7020 cGy. We further use univariate and multivariable logistic regression models to investigate characteristics associated with a patient receiving a total radiation dose in the highest dose group.

Results: The multivariable and ordinal generalized propensity score Cox-PH models both show improved survival for patients in the highest total radiation dose group compared to patients in the lowest dose group (Hazard Ratios: 0.68 [0.50-0.90] and 0.732 [0.550, 0.973], respectively). The weighted propensity score model reveals patients in the highest dose groups have superior survival compared to patients in the three lower dose groups combined (HR: 0.71 [0.56-0.92]). The continuous generalized propensity score model shows that a general increase in total radiation dose is associated with improved survival (HR: 0.983 [0.969, 0.998]). Further, logistic regression shows that facility location, urban/rural residence, and regional treatment modality are associated with receiving a total radiation dose in the highest dose group. Stratified analysis showed that higher dose may be more beneficial to patients receiving IMRT radiation modality or patients with an AJCC clinical stage group of 3 or 4.

Conclusion: Total radiation dose above 6400 cGy appears to improve overall survival in CEC patients receiving chemoradiotherapy. Generalized propensity score methods are useful extensions of the traditional propensity score for evaluating treatment as a continuous or ordinal variable, but more research in proper assessment covariate balance is needed.

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INTRODUCTION

Cervical esophageal cancer is a rare form of esophageal cancer that is challenging to treat in part due to widespread treatment differences. The rarity and treatment diversity pose a challenge to determining the optimal protocol. In this thesis, we aim to address the question of best treatment for this unique type of cancer using data from the National Cancer Database, focusing on cervical esophageal cancer squamous cell carcinoma and adenocarcinoma cases. We investigate the impact of radiation treatment dose on overall survival for patients receiving chemoradiotherapy, simultaneous radiation therapy and chemotherapy also known as chemoradiation. We use traditional logistic regression, Cox proportional hazards, and stratified Cox proportional hazards models to evaluate this association using radiation dose as both a continuous and categorical variable.

We further consider various propensity score methods. Treating dose as a dichotomous variable, we attempt traditional propensity score methods in the form of matching and inverse probability of treatment weighting. We also try a generalized propensity score approach with covariate adjustment using treatment as both a continuous variable and as an ordinal categorical variable. For the generalized propensity score models, we investigate potential methods for evaluating covariate balance, as there is currently no standard practice.

BACKGROUND

Cervical esophageal cancer (CEC) is cancer of the upper third of the esophagus. It is the rarest type of esophageal cancer, representing less than 5% of all esophageal cancer cases (Cao et al., 2016; Yamada et al., 2006). The incidence rate is less than one case per 100,000 (Peng et al., 2015). Patients often have delayed diagnoses and poor prognosis (Peng et al., 2015). Due to its location in close proximity to the spinal cord and other organs, CEC is very difficult to treat

(Yamada et al., 2006). The cervical region of the esophagus is positioned "between the lower border of the cricoid cartilage and the thoracic esophagus inlet" and cancer of this area "frequently invades upward to the hypopharynx and downwards to the thoracic esophagus inlet" (Peng et al., 2015). There is copious lymphatic drainage through this area (Peng et al., 2015). Thus, treatment methods and outcomes of cervical esophagus cancer are often much different from those of other portions of the esophagus (Yamada et al., 2006).

Surgery poses a high risk to the patient due to the position of the cervical esophagus. Complete tumor resection is difficult to attain because of the closeness to the trachea (Stuschke et al., 2000), and surgery may leave the patient with a permanent tracheostomy (Yamada et al., 2006; Burmeister et al., 2000). Five-year survival after surgery is very low (Stuschke et al., 2000), and the impact on quality of life may be very destructive with surgery disrupting speech and swallowing (Cao et al., 2016). Further, Radiation may put many other important organs at risk including the spinal cord, parotid glands, thyroid gland, lungs, heart, larynx, trachea, and temporomandibular joints (Cao et al., 2016).

Chemoradiation, the combination of chemotherapy and radiation therapy, attempts to preserve organs and improve quality of life. (Yamada et al., 2006). While the studies of CEC patients by Yamada et al. (2006) and Stuschke et al. (2000) both found chemoradiation to be superior to radiation alone, little data are available as to what dose range and type of radiation are optimal for chemoradiotherapy. Cao et al. (2016) investigated the benefit of Intensity-modulated radiotherapy (IMRT) in 64 cases of cervical esophageal squamous cell carcinoma between May 2004 and March 2012. IMRT is an advanced form of radiotherapy which manipulates radiation beams to conform to the shape of the tumor (Mayo Clinic, 2015). It has the advantages of good coverage, organ sparing, and dose escalation ability (Cao et al., 2016). Cao et al. (2016) found

that IMRT was superior to other forms of radiation in patients undergoing chemoradiotherapy; however, they did not see a difference in survival with increases in dose level.

On the other hand, Stuschke et al. (2000) suggests increased total radiation dose as a strategy for improvement of the effectiveness of chemoradiotherapy. When investigating patients with all esophageal cancers treated with either radiotherapy or chemoradiotherapy, Zhang et al. (2015) did see a positive association between radiation dose and survival where patients receiving 54-64.8 cGy had superior outcomes to those receiving 30-51 cGy. However, Zhang et al. (2015) speculate that there may be a threshold of tumor response to radiation dose; i.e. there may be a level at which increasing radiation dose level further does not result in any added benefit. Another investigation of cancers of the full esophagus by De-Ren (1989) — including 115 upper, 541 middle, and 49 lower esophageal cancer cases — also found higher radiation dose to be superior. Patients receiving 60-69cGy had the best 5-year survival, and patients receiving 70-79 cGy had the best 10-year survival.

Dinshaw et al. (2006) also found higher radiation dose to be superior in the case of head and neck cancers, noting that of the 568 patients studied, those receiving over 66cGy had the best outcomes. Mendenhall et al. (1988) found that in CEC patients receiving radiation only, T2 lesions doses of 7000 cGy resulted in more local control, and that no T3 lesion was locally controlled at less than 6800 cGy. Thus, prior research indicates that higher radiation dose levels are superior for CEC radiotherapy patients, head, neck, and esophageal cancer radiotherapy patients and some cases of chemoradiotherapy patients. Therefore, we suspect that there may be a positive association between dose and survival in chemoradiotherapy treated CEC patients as well. In this study, we investigate this notion in hopes of determining the optimal total radiation dose level for CEC patients undergoing chemoratiotherapy. By determining the optimal

treatment regimen, we will be able to minimize unnecessary side-effects of ineffective treatments and/or maximize the benefit of effective treatments, increasing both the quality and length of life for CEC patients.

METHODS

Inclusion and Exclusion Criteria

Data for these analyses was obtained from the National Cancer Database (NCDB), a clinical oncology database of hospital registry data jointly commissioned by the American College of Surgeons and the American Cancer Society (American College of Surgeons, 2017). We used the NCDB Esophagus Participant User File (PUF) 2014, which includes 129,296 esophagus tumor cases. In this analysis, we include only patients with cervical esophageal Cancer. We further narrowed our selection to patients with invasive tumor behavior and squamous cell carcinoma or adenocarcinoma histology. We excluded patients with metastasis and surgery cases. We included only those who undergo concurrent chemoradiation with a lag time between radiation and chemotherapy start time of no more than two weeks. We included only those with a total radiation dose between 45 and 70.2 Gray (Gy), radiation volume of esophagus or unknown, and radiation regional treatment modality of one of the following: External Beam Not Otherwise Specified (NOS), Other NOS, Photons (2-5 MV, 6-10 MV, 11-19 MV, >19 MV, and mixed energies), Protons, IMRT, Conformal, 3-D Therapy, or unknown. Patients were excluded from the analyses if outcomes for their overall survival were missing. The final analytical data contains 586 patient records.

Outcome, Cohorts and Variables of Interest

The primary outcome of this study is overall survival (OS) defined in months from date of first chemotherapy or radiation treatment started to death or last follow up. Vital status for the year 2014 diagnosis year is not available, so related analysis for OS are limited to year 2013.

The treatment of interest for this analysis was total radiation dose, the sum of regional radiation dose and the boost radiation dose. Regional radiation is the radiation applied to the tumor and a buffer area surrounding the tumor, while boost radiation is applied only to the tumor itself. Data were divided into four cohorts based on total radiation dose quartiles. The cohorts are: total radiation dose 4500-5040, >5040-5940, >5940-6400, and >6400-7020 centiGray (cGy). We considered total radiation dose as a continuous variable as well.

In total, 21 variables of interest were considered: 9 demographic and 12 disease-specific. Demographic variables included are: sex (male or female), race (white, black or other), facility type (academic or non-academic), facility location (Northeast, South, Midwest, or West), urban/rural 2003 (Metro, Urban or Rural residence based on 2003 information), primary payor (Not Insured, Private, Medicaid, or Medicare/Other Government), median income based on zip code 2000 (quartiles), median income based on zip code 2008-2012 (quartiles), age at diagnosis, and great circle distance (the distance from the center of the zip code of the patient's address to the facility address in miles).

Disease-specific variables included are: histology (squamous cell carcinoma or adenocarcinoma), grade (well to moderately differentiated, poorly differentiated/undifferentiated or cell type not determined), Charlson-Deyo Score (0 or 1+), sequence number (00, 01, or 02-05), American Joint Commission on Cancer (AJCC) clinical T (1, 2, 3, or 4), AJCC clinical N (0-1 or 2-3), AJCC clinical stage group (0-2 or 3-4), regional treatment modality (external beam

NOS, Other NOS, photons(All), protons; IMRT; or conformal, 3-D therapy), chemotherapy (single-agent, multiagent, or number of agents unknown), year of diagnosis (quartiles), tumor size, and time lag (in weeks between diagnosis and radiation or chemotherapy treatment. The continuous variables age at diagnosis, great circle distance, and tumor size were considered in the discretized forms of quantiles and halves split at the median.

Statistical Analysis

Statistical analyses were performed using SAS Version 9.4, and SAS macros developed at the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute (Nickleach et al., 2013). The significant level was set at 0.05, and confidence intervals were set at the 95% confidence level.

Descriptive Statistics

Descriptive statistics were given for all levels of each variable of interest. Frequency and percent were provided for categorical variables, and mean and standard deviation were reported for continuous variables. The overall survival was plotted using a Kaplan-Meier curve. Median survival and median follow-up were also reported.

Univariate Analysis

The univariate associations between each variable of interest and radiation dose groups (4500-5040, >5040 -5940, >5940-6400, and >6400-7020 cGy), were assessed. The Chi-square test for independence was used for categorical covariates to determine if there was a significant association between the covariate and dose group assignment. The ANOVA test for independence was used for numerical covariates to determine if there was a significant difference in the mean of the covariate across cohort groups.

Univariate analysis was performed using the continuous form of the total radiation dose variable. The ANOVA test was used for continuous covariates to determine if there was a significant difference in the mean total radiation dose level across levels of the given covariate. Pearson's correlation coefficient was used for numeric covariates to determine if there was a significant association between the covariate and total radiation dose level.

The univariate association between overall survival and radiation dose group, between overall survival and continuous total radiation dose, and between overall survival and all of the covariates were assessed using Cox proportional hazards (Cox-PH) models. For interpretation purposes, the continuous dose variable was transformed from cGy to Gy. Log-rank tests were used to determine the presence of a univariate association for both categorical and continuous variables. A Kaplan-Meier plot was produced to compare the overall survival across the four total radiation dose groups.

Univariate logistic regression was conducted to evaluate to evaluate potential predictors of patients receiving a higher total radiation dose. The categorical treatment variable was collapsed into a dichotomous variable in which the three lower dose groups were combined into one group (>=4500-6400 cGy) for comparison to the highest dose group (>6400-7020 cGy). The odds ratio of being in the highest dose group versus being in one of the three lower dose groups collectively was reported for each covariate. Type-three p-values were also reported.

Multivariable Analysis

For both the categorical cohort treatment variable and the continuous treatment variable, multivariable Cox proportional hazards models were fit to determine if a relationship between total radiation dose and overall survival is present after accounting for confounding factors. All variables of interest are evaluated for selection into the multivariable analysis, with the exception

of only the most significant form of age at diagnosis (continuous), great circle distance (halves), and tumor size (quartiles) being included. Cox proportional hazards models were fit by a backward variable selection method applying an alpha level =.20 removal criteria, with treatment being forced into the model.

A multivariable logistic regression model was used to further analyze potential predictors of receiving higher radiation doses. The dichotomous form of total radiation dose (4500-6400 versus >6400-7020 cGy) was used again. The same variables of interest used in the multivariable Cox-PH model were considered for selection here. A backward variable selection method applying an alpha =0.20 removal criteria was used with no terms being forced into the model.

Stratified Analysis

Interactions between certain covariates and dose level group were assessed using stratified multivariable Cox proportional hazards models. Backwards variable selection with an alpha =0.20 removal criteria and the same variables of interest were considered for selection as in the multivariable models. The dose group variable, the stratification variable, and an interaction term between the two were all forced into the stratified models. Radiation regional modality, facility type, AJCC clinical N, tumor size (divided at the median), age at diagnosis (divided at the median), and AJCC clinical stage group were considered for potential strata. The variables regional modality, AJCC clinical N, and AJCC clinical T were collapsed into two levels for the stratification analysis. Kaplan-Meier plots were also produced to compare the survival curves by cohort for each stratum separately. The log-rank p-value for the univariate association between dose group and overall survival is reported for each stratum on the Kaplan-Meier plots.

Traditional Propensity Score Analysis

Overview

The randomized clinical trial (RCT) is the gold standard for scientific research. Confounding variables do not have to be included in the analysis for a RCT due to the design and randomization of the study. This allows the treatment effect to be tested independently of all other factors. Due to the observational nature of the data here, we must take into account the effect of the covariates. This is because treatment allocation may differ systematically for certain variables. However, using the propensity score, we are able to decrease the effects of confounding and analyze data similarly to as if it were from a RCT (Austin, 2011a).

The propensity score is "the probability of treatment assignment conditional on the observed baseline covariates" (Austin, 2011a; Rosenbaum and Rubin, 1983a) and is given by:

$$e_i = Pr\,(Z_i = 1 \,|\mathbf{X}_i)$$

where e_i denotes propensity score, Z_i is the treatment assignment, and $\mathbf{X}_i$ is a vector of covariates. When conditioned on the propensity score, the distribution of baseline covariates becomes similar across treatment groups, making the data resemble that of a RCT (Austin, 2011a; Rosenbaum and Rubin, 1983a), thus the propensity score is also viewed as a balance score. Two assumptions are necessary when using the propensity score to estimate a treatment effect. The first is that treatment assignment given the baseline covariates is independent of the potential outcomes such that $Y(1), Y(0) \perp T|X$, and the second is that every subject has a nonzero probability to receive either treatment (Austin, 2011; Rosenbaum and Rubin, 1983). There are four ways to use the propensity score to estimate treatment effect: matching, inverse probability of treatment weighting, stratification (sub-classification), and covariate adjustment. (Austin, 2011). In this section, we attempt matching and inverse probability of treatment

weighting for dichotomized treatment groups. We investigate covariate adjustment in the next section under the generalized extensions of the propensity score, which allow the treatment variable to be evaluated in continuous and ordinal form (Hirano and Imbens, 2004; Imai and van Dyk, 2004). This is useful to us as our treatment variable is continuous and we are primarily interested in differences in survival across four dose groups. We do not attempt stratification due to the small size of our sample.

Matching

In the matching process, we first estimate the propensity score using logistic regression of treatment group assignment on the covariates. The dichotomous form of total radiation dose (4500-6400 cGy versus 6400-7020 cGy) must be used for this process. Austin, Grootendorst, and Anderson (2007) suggest including only potential confounders or true confounders in the propensity score model. Further, Brookhart et al. (2006) suggests that variables that affect outcome but not exposure should always be included in the model, while variables that affect exposure but not outcome have no benefit. Therefore, we use the list of variables selected into the multivariable Cox proportional hazards model as the covariates for estimating propensity score. They include: age at diagnosis, time lag between chemotherapy and radiation treatment start, sex, Charlson-Deyo score, sequence number, median income quartiles 2008-2012, AJCC clinical stage group, and chemotherapy.

Next, subjects in the high dose group are matched to subjects in the low dose group based on the similarity of thier propensity scores on a one-to-one basis. A greedy matching algorithm is used which randomly selects a high dose subject then chooses the low-dose subject with the closest matching propensity score to be its pair, even if the low-dose subject is a closer match to a subsequent high-dose subject. It then randomly selects another high-dose subject and finds its

best match. This process repeats this process until no more pairs can be made. If there is a tie between multiple low-dose subjects for best match to the current high-dose subject, then one of the tied subjects is randomly selected to be the pair (Austin, 2011a; Parsons, 2001). The matched sample results in an equal number of subjects in the high and low dose groups.

In order to use the matched data for analysis, we must verify that the sample is balanced, i.e. that the distributions of the baseline covariates are not different across treatment groups. We do this using standardized difference, a statistic that compares distributions of variables. For continuous covariates, standardized difference is computed using the formula:

$$d = \frac{(\bar{x}_{high\ dose} - \bar{x}_{low\ dose})}{\sqrt{\frac{(s^2_{high\ dose} + s^2_{low\ dose})}{2}}}$$

where $\bar{x}_{high\ dose}$ and $\bar{x}_{high\ dose}$ are the sample means of the given covariate within the high and low dose groups, respectively, and $s^2_{high\ dose}$ and $s^2_{low\ dose}$ are the sample standard deviation of the given covariate within the high and low dose groups, respectively (Austin, 2011a). Similarly, for categorical covariates, the following formula is used:

$$d = \frac{(\hat{p}_{high\ dose} - \hat{p}_{low\ dose})}{\sqrt{\frac{[\,\hat{p}_{high\ dose}\left(1 - \hat{p}_{high\ dose}\right) + \hat{p}_{low\ dose}\left(1 - \hat{p}_{low\ dose}\right)\,]}{2}}}$$

where $\hat{p}_{high\ dose}$ is the proportion of patients with the specified value of the given covariate within the high dose group and $\hat{p}_{low\ dose}$ is the proportion of patients with the specified value of the given covariate within the low dose group (Austin, 2011a). We expect the distribution of each of the baseline covariates to be the same for both treatment groups because the matched sample was based on the propensity scores. Standardized difference values of less than 0.1 are deemed as acceptable (Austin, 2011a). If balance is achieved, we are able to directly estimate the treatment

effect from the matched sample without having to adjust for other factors. A Cox-PH model and Kaplan-Meier curves will be fit to determine the treatment effect directly from the matched sample.

Inverse Probability of Treatment Weighting

Rather than using the propensity score to find the nearest match, the inverse probability of treatment weighting (IPTW) approach uses the propensity as a weight for each subject. Each subject receives a weight equal to the inverse of the probability of receiving the treatment that the subject actually received (Rosenbaum, 1987a; Austin and Stuart, 2015; Austin, 2011). The weight for each subject is calculated using the formula:

$$w_i = \frac{Z_i}{e_i} + \frac{(1 - Z_i)}{(1 - e_i)}$$

This creates a "synthetic sample in which the distribution of measured baseline covariates is independent of treatment assignment" (Austin, 2011a), eliminating confounding by the baseline covariates. From this artificial sample, regression models, weighted by the inverse probability of treatment, estimate the treatment effect (Joffe et al., 2004; Austin and Stuart, 2015).

Balance for the weighted sample is again checked using standardized difference; however, the parameters are weighted by the inverse probability of treatment (w_i) such that:

$$\bar{x}_w = \frac{\Sigma w_i x_i}{w_i}, \text{ and}$$

$$s_w^2 = \frac{\Sigma w_i}{(\Sigma w_i)^2 - \Sigma w_i^2}\{\Sigma w_i (x_i - \bar{x}_w)\}$$

which are used in place of $\bar{x}$ and s^2 in the standard difference formula (Austin and Stuart, 2015). If balance is achieved, overall survival is modeled using weighted Kaplan-Meier plots and a

weighted Cox-PH model regressed on the binary dose group variable to evaluate the treatment effect (Austin, 2016).

Generalized Propensity Score Analysis

Overview

Generalized propensity score methods all use covariate adjustment by the propensity score to estimate treatment effect. The covariate adjustment approach uses the propensity score as a covariate in the outcome model alongside the treatment variable. No other variable is included. In this case, our outcome is overall survival; so, we use the propensity score as a covariate in a Cox proportional hazards model of dose group such that:

$$h(t) = h_0(t)\exp\{\beta_0 + \beta_1 Treatment + \beta_2 Propensity\ Score\}$$

The treatment effect is calculated from the coefficient of treatment (Austin et al., 2006), which we use to obtain the hazard ratio. We investigate two extensions of covariate adjustment under the generalized propensity score: total radiation dose as a continues variable and total radiation dose as an ordinal variable with multiple dose levels. The generalized propensity score is advantageous in removing the need to discretize the continuous treatment variable (Kluve et al., 2012), or allowing us to evaluate treatment in our original four dose group setting.

Continuous Treatment Variable

Similar to the traditional propensity score assignment, the generalized propensity score is assigned by regressing the covariates of interest on the treatment value. However, because we are using treatment as a continuous variable, linear regression is used instead of logistic regression. Hirano and Imbens (2004) define the generalized propensity score as:

$$R = r\,(T, X),$$

where $r\,(t, x) = f_{T|X}(t|x)$, *the conditional density of the treatment given the covariates.*

In our analysis, we assume the treatment, total radiation dose, to be normally distributed such that:

$$T_i|X_i \sim N(\beta_0 + \beta_1' X_i\,,\, \sigma^2)$$

Therefore, the generalized propensity score, R, is equal to the predicted value of the linear regression of treatment on the baseline covariates for each subject.

Within strata of the same R, covariates will be balanced and thus, conditional on the generalized propensity score, treatment assignment will not be confounded (Hirano and Imbens, 2004). In doing this, we assume that a linear association exist between total radiation dose and the covariates. The generalized propensity score also assumes of weak unconfoundedness such that:

$$Y(t) \perp T|X \; for \; all \; t \; \in T$$

i.e., the distribution of the actual treatment given the observed baseline covariates does not depend on the outcome, for each possible level of treatment individually (Hirano and Imbens, 2004, Imai and van Dyk, 2004). After R is assigned, it is used as a covariate alongside the continuous form of total radiation dose in the Cox-PH model to determine treatment effect:

$$h(t) = h_0(t)\exp\{\beta_0 + \beta_1 Total\ Radiation\ Dose + \beta_2 Generalized\ Propensity\ Score\}$$

shown above. For this model, total radiation dose is again converted from cGy to Gy for interpretation purposes.

Ordinal Treatment Variable

For this method, propensity score is modeled using total radiation dose as an ordinal variable based on our four total radiation dose groups. Rather than having one propensity score per subject, each subject receives four propensity scores: one for each treatment option

(Spreeuwenberg et al., 2010). This is done using the ordinal logistic model proposed by McCullagh (1980) to regress treatment assignment on the baseline covariates such that:

$$\log\left\{\frac{\Pr(Z_k \geq d)}{\Pr(Z_k < d)}\right\} = \theta_d + \beta^T \boldsymbol{X}_k, for\ d = 1,2,3,4$$

where Z_k is the dose group assignment for subject k, d is the dose group, and θ_k is the log of the dose group. (McCullagh and Nelder, 1989; Lu et al., 2001; Imai and van Dyk, 2004). The variable *d* is dose group assignment (1= 4500-5040 cGy, 2= >5040-5940 cGy, 3= >5940-6400 cGy, 4= >6400-7020 cGy). This model yields the cumulative probability of each treatment from which the individual probabilities can be calculated.

The propensity scores are the individual predicted probabilities of assignment to each treatment (Spreeuwenberg et al., 2010). Because the four assigned propensity scores add up to one within each subject and are complimentary, we are able to use one treatment group as a reference (Spreeuwenberg et al, 2010; Wang et al., 2001). To estimate treatment effect, we create a Cox-PH model for overall survival including a dummy variable for each dose group and three of the four propensity scores. We choose to use the lowest total radiation dose group (d=1; >4500-5040cGy) as the reference group, therefore we exclude the propensity score for dose 1 from the model (Spreeuwenberg et al., 2010) such that:

$$h(t) = h_0(t)\exp\{\beta_0 + \beta_1 I(d = 2) + \beta_2 I(d = 3)$$

$$+\beta_3 I(d = 4) + \beta_4 PS2 + \beta_5 PS3 + \beta_6 PS4\}$$

where *I(d=2), I(d=3), I(d=4)* are dummy variables for belonging to dose groups 2, 3, and 4. Since ordinal regression is used for propensity score assignment, this method relies on the assumption of proportional odds, also known as parallel regression. This means that we must assume that the slope (β) is constant across all dose levels; moreover, the coefficients are the same for each iteration of the function (UCLA: Statistical Consulting Group). We also assume

that the distribution of doses depends on the covariates only through the given function (Joffe and Rosenbaum, 1999) and that each subject has a nonzero probability of receiving each treatment.

Balance Checking

Because the generalized propensity score methods utilize covariate adjustment, checking the balance of covariates across treatment groups becomes challenging as standardized difference can no longer be used in its traditional form. For covariate adjustment with the traditional propensity score, the Receiver Operating Characteristic (ROC) curve and C-Statistic are often used to measure model discrimination between treated and untreated subjects instead; however, this method does not adequately assess covariate balance (Stürmer et al., 2006; Austin, 2008; Austin, 2011).

Austin (2008) proposes two alternative methods for assessing goodness of fit: weighted conditional standardized difference and quantile regression. Weighted conditional standardized difference is determined by regressing the covariate against the treatment, propensity score, and interaction of treatment and propensity score. Linear regression is used for continuous covariates and logistic regression is used for categorical covariates. Using these regression models, the predicted value is determined for each covariate then integrated over all values of the propensity score to obtain the conditional weighted standardized difference.

Austin's quantile regression method uses quantile regression between treated and untreated subjects with similar propensity scores to compare the distribution of continuous covariates. The 5^{th},25^{th}, 50^{th},75^{th}, and 95^{th} estimated regression quantiles are plotted against the estimated propensity score for treated and untreated subjects, allowing the distribution of the

given covariate to be evaluated at different levels of the propensity score in treated and untreated subjects (Austin, 2008).

Alternatively, many researchers divide the sample into quantiles based on the propensity score and assess balance, for the distribution of covariates should be similar amongst subjects with similar propensity scores. This can be evaluated using side-by-side boxplots, quantile-quantile plots, or standardized difference within each quantile (Austin et al., 2005; Austin and Mamdani, 2006; Austin, Grootendorst, and Anderson, 2007; Austin, 2008).

In the case of covariate adjustment by the generalized propensity score, Hirano and Imbens (2004) suggests dividing the data into 3 intervals based on treatment level. Within these intervals, they suggest using t-tests for each covariate to determine if the mean in one of the three treatment groups is different than the other two combined, first without adjusting for the propensity score then with adjustment. To adjust for the propensity score, each interval is "blocked" into 5 quintiles based on the propensity score evaluated at the midpoint of the treatment group. Subjects are assigned to the block in which their treatment level and propensity score fall, then the mean difference and standard error is calculated for each quintile between the three intervals. The five mean differences are then combined and weighted by the number of subjects in their respective quintile. This weighted mean difference value and its standard deviation are then used to determine the t-statistic.

Additionally, Imai and van Dyk (2004) proposed regressing each covariate on the treatment variable to assess balance. Logistic regression is used for categorical covariates and linear regression with a log transformation of the treatment variable is used for continuous covariates. The log transformation is necessary because the covariates are necessarily uncorrelated with treatment given the generalized propensity score (Iami and van Dyk, 2004).

The t-statistics of the coefficient of the treatment variables are evaluated before and after conditioning on the generalized propensity score. Ideally, the t-statistics will be smaller after conditioning on the propensity score, indicating improvement in covariate balance. Kluve et al. (2011) suggest using Imai and van Dyk's method but with conditioning on the distribution of the generalized propensity score evaluated at the 25^{th}, 50^{th} and 75^{th} percentile of the treatment variable.

For the case of multiple treatments, Spreeuwenberg et al. (2010) suggests significance testing to evaluate whether or not the distributions of the covariates are the same across all treatment groups. They use ANCOVA for continuous covariates, logistic regression for dichotomous covariates, and multinomial logistic regression for nominal covariates. This is done before and after covariate adjustment in hopes of seeing improvement in balance conditioned on the propensity score. When using significance testing to evaluate covariate balance, it is important to note that sample size will impact the test.

For this analysis, we attempt to apply the idea of standardized difference within quantiles to the generalized propensity score continuous case. Because our dataset is small, we use halves for our quantiles, split at the median propensity score. Within each half, we assess the standardized difference for all included covariates using the four total radiation dose groups as the treatment variable. Although we use the continuous form of total radiation dose in the generalized propensity score model, this discretization is necessary for us to be able to assess balance. Through this process, we are verifying that the distributions of covariates are relatively similar across treatment levels after adjusting for the propensity score. For the ordinal case, we cannot use standardized difference in this way because three propensity scores are used for covariate adjustment. We instead evaluate significance of the association between each

covariate and total radiation dose group before and after propensity score adjustment, as done by Spreeuwenberg et al. (2010), even though sample size may affect the results.

RESULTS

Statistical Analysis

Descriptive Statistics

The final study cohort included a total of 586 patients. The median survival was 24.5 months (Figure 1), and the median follow-up was 63.6 months (Table 1b). The descriptive statistics for the sample are summarized in Table 1a. The average total radiation dose level was 5785.6 cGy with a standard deviation of 722.3 cGy. Patients are somewhat evenly distributed across our four dose groups with 196 (33.4%) in the >=4500-5040 cGy group, 136 (23%) in the >5040-5949 cGy group, 111 (18.9%) in the >5940-6400 cGy group, and 143 (24.4%) in the >6400-7020 cGy group. The four dose groups were determined by quartiles; however, since there are a large number of cases at the Q1, Q2, and Q3 levels, the groups are not equal.

56.8% of patients attend non-academic facilities while 43.2% of patients attend academic facilities. Facilities are located in all portions of the country; however, the West has the smallest representation (15.6%). The majority (84.9%) of patients live in metro areas and the median great circle distance is 7.5. Medicare or other government insurance is the most popular primary payor (54.8%). The median year of diagnosis was 2009, and the diagnoses range from 2004-2013. The median age at diagnosis was 67 years. 63% of patients are male and 37% female; 80% of patients identified their race as white, 14.4% black, and 5.6% other. The median of median income level for patients' area of residence was $36,000 for the year 2000 and $48,000 for the 2008-2012 period.

Most patients were squamous cell carcinoma cases (95.2%) rather than adenocarcinoma cases (4.8%). Only 21.8% of patients had a Charlson-Deyo score greater than zero, and 32.8% of patients had a sequence number greater than zero. An AJCC clinical T stage of 3 was most common (32.4%), while most patients had an AJCC Clinical N of 0 or 1 (84.3%). 42.7% of patients were in AJCC clinical stage groups 0, 1, or 2; 39.9% of patients were in AJCC clinical stage groups 3 or 4, and 17.4% were missing. 43.3% of patients received IMRT radiation, 8.5% received conformal or 3-D therapy, and 48.1% received either external beam NOS, other NOS, photons, or protons.

77.6% of patients received multiagent chemotherapy, 15.9% received single-agent chemotherapy, and the remaining 6.5% received an unspecified mode of chemotherapy. The median tumor size was 4 centimeters, and the average number of treatments to the volume was 31.7. The average time lag between start of radiation and chemotherapy was 5.3 weeks, and the average time from start to end of radiation treatment was 6.9 weeks.

Univariate Analysis

For the four-group categorical dose variable; facility type, facility location, primary payor, histology, AJCC clinical stage group, regional treatment modality, and chemotherapy were significantly associated with total radiation dose (p-values < 0.05; Table 2a). For the continuous dose variable; primary payor, histology, AJCC clinical N, AJCC clinical stage group, regional treatment modality, and chemotherapy were significantly associated with total radiation dose (p-values < 0.05; Table 2b).

The log-rank test given in the Kaplan-Meier plot of overall survival by total radiation dose group (Figure 2) suggests there is a marginal difference in overall survival across the four groups (p-value: 0.0923). The univariate analysis between overall survival and treatment

variables and all other variables of interest (Table 3a) further suggests that there is improved survival for patients in the highest dose group compared to patients in the lowest dose group (Hazard Ratio (HR): 0.75, 95% Confidence Interval: [0.57-0.99]). The continuous form of total radiation dose, in Gy, suggests there is marginal significance between dose and overall survival with a p-value of 0.082 with a hazard ratio of 0.99 [0.97-1.00]. Other variables that appear to have a significant impact on overall survival are: Charlson-Deyo score, median income quartile 2008-2012, AJCC Clinical Stage Group, and great circle distance (p-values <0.05). Grade and AJCC clinical T are marginally significant (p-value < 0.1).

The univariate logistic regression of the dichotomous total radiation dose variable (highest dose group versus all others; Table 3b) suggests that facility location, urban/rural, and regional treatment modality are associated with a patient receiving a total radiation dose within the range of the highest dost group (type 3 p-values: 0.013, 0.028, <0.001; respectively). However, there is no change in the odds of being in the highest dose group between urban, rural, and metro facility location. An increase in odds is seen in patients who attend facilities in the South compared to the West (Odds Ratio (OR): 2.22 [1.19-4.14]), and a decrease in odds is seen for patients receiving regional treatment modality other than IMRT. Those receiving external beam NOS, other NOS, photons, or protons had nearly half the odds of high dose compared to IMRT (OR: 0.54 [0.37-0.80]), and those receiving conformal, 3-D therapy had roughly one-quarter of the odds of high dose compared to IMRT (OR: 0.24 [0.09-0.62]).

Multivariable Analysis

For the multivariable Cox-PH model with total radiation dose group (Table 4a-1); sex, median income quartiles 2008-2012, Charlson-Deyo score, sequence number, AJCC clinical stage group, chemotherapy, age at diagnosis, and time lag between chemotherapy and radiation

treatment start, were selected into the model. Total radiation dose group was significant at all levels. Each of the three lower does groups; 4500-5040 cGy, >5040-5940 cGy, >5940-6400 cGy; had worse survival than the highest total radiation dose group (HR: 1.48 [1.11-1.98], 1.46 [1.08-1.99], and 1.47 [1.06-2.02]; respectively). The hazard ratio of the highest dose group compared to the lowest dose group was 0.68 [0.50-0.90] (Table 4a-2).

Variables in this model that were significant confounders are median income quartiles 2008-2012, Charlson-Deyo score, AJCC clinical stage group, and age at diagnosis. Patients whose zip code areas have a median income of <$38,000 or $48,000-$62,999 were associated with worse survival compared to median incomes of $63,000+ (HR: 1.34 [1.01-1.80] and 1.58 [1.19-2.10], respectively). A Charlson-Deyo score of zero was associated with improved survival compared to a score greater than or equal to 1 (HR: 0.70 [0.55-0.90]). A higher AJCC clinical stage group — 3 or 4 versus 0, 1, or 2 — was associated with worse survival (HR: 1.55 [1.23-1.97]), as was increase in age (HR: 1.01 [1.00-1.02]).

Sequence number and chemotherapy were marginally significant. Patients with a sequence number of 01 had superior survival compared to those with a sequence number of 02, 03, 04, or 05 (HR: 0.58 [0.37-0.91]). Patients receiving single-agent chemotherapy fared worse than those receiving multiagent chemotherapy (HR: 1.34 [1.01-1.76]).

For the multivariate logistic regression model evaluating patient receipt of treatment in the highest total radiation dose group (Table 4b), variables selected into the model include: sex, facility type, facility location, urban/rural 2003, primary payor, median income quartiles 2000, and regional treatment modality. Facility location, urban/rural 2003, and regional treatment modality are significant terms in the model, thus likely predictors for receiving a high total radiation after controlling for other factors (p-values: 0.005, 0,027, and 0.009; respectively).

Patients attending facilities in the South had over two times the odds of receiving a high total radiation dose compared to patients in the West (OR: 2.52 [1.26-5.06]). IMRT was associated with an increase in the odds of receiving a high dose level compared to the external beam NOS, other NOS, photons, or protons group (OR: 1.71, [1.10-2.66]). The odds of receiving a high total radiation dose did not vary significantly for metro patients compared to rural patients or urban patients compared to rural patients.

Facility type and median income quartiles 2000 are marginally significant (p-values: 0.063 and 0.061, respectively). Academic facilities may be slightly less likely to administer high dosage compared to non-academic facilities (OR: 0.66 [0.43-1.02]), and patients residing in a zip-code area with a median income of less than $30,000 in 2000 may be slightly less likely to receive a high dose compared to those in an area with a median income of over $46,000 (OR: 0.48 [0.22-1.05]).

Stratified Analysis

In the stratified multivariable analyses of overall survival, we see that within the IMRT regional treatment modality stratum, the log-rank p-value is 0.0482; thus, there is a significant difference in survival based on dose groups especially for patients receiving IMRT (Figure 3a). Further, we see that the estimated stratified treatment effect of the highest dose group compared to the lowest dose group for patients receiving IMRT is the hazard ratio of 0.56 [0.36-0.89], indicating superior survival for the highest dose group (Table 5a).

In the case of tumor size, the stratum of tumor greater than or equal to four centimeters shows that the superior survival for the 5940-6400 cGy group compared to the 4500-5040 cGy group (HR: 1.84 [1.03-3.29]; Figure 3d). We also see that for the AJCC clinical stage group 3-4 strata, the highest dose group again outperforms the lowest in overall survival (HR: 0.59 [0.35-

0.99], Table 5f). All other interactions evaluated are not significant (Tables 5b-e, Figures 3b-c, Figures 3e-f).

Traditional Propensity Score Analysis

Matching

The propensity score assigned using logistic regression appears to be normally distributed overall and for each individual dose group. After matching, several variables displayed standardized difference values above the 0.1 level of acceptability (Table 6); therefore, the data is not fit for further matched analysis. This is likely due to the small sample size limiting the number of possible matched pairs in the dataset.

Inverse Probability of Treatment Weighting

After weighting, all included covariates had standardized difference values within the acceptable range (Table 7a). The Kaplan-Meier plot using the weighted sample (Figure 4) showed a significant improvement in overall survival for the 6400-7020 cGy group compared to the 4500-6400 cGy group (p-value: 0.0099). The weighted univariate Cox-PH model (Table 7b) also showed improved survival for those in the highest dose group compared to all other subjects (HR: 0.71 [0.56-0.92]).

Generalized Propensity Score Analysis

Continuous Treatment Variable

In the continuous generalized propensity score model (Table 8b), we see that survival tends to improve as total radiation dose increases. For every one Gy increase in total radiation dose, the hazard of death is 0.983 [0.969, 0.998] times lower.

Ordinal Treatment Variable

In the ordinal generalized propensity score model (Table 9b), we see that the highest total radiation dose group has significantly better survival than the lowest total radiation dose group (HR: 0.732 [0.550, 0.973]). The mid-range total radiation dose groups show no significant improvement in survival compared to the lowest does group.

Balance Checking

Both the generalized propensity score covariate adjustment methods yield similar results to that of the IPTW method; however, the results of these two methods may not be reliable as our balance checks revealed that covariate balance my not have been achieved for either case (Tables 8a-1, 8a-2, and 9a). There were standardized differences greater than 0.1 after adjusting for the continuous generalize propensity score, and adjusting for the ordinal generalized propensity scores did not show decrease in significance for all covariates' relationship with dose group. However, our standards for covariate balance for generalized propensity score covariate adjustment may be harder to achieve as the data is parsed down into multiple subgroups for the continuous case, and the statistical significance depends on sample size for the ordinal case.

DISCUSSION

Throughout our various analyses, it repeatedly appears that higher total radiation dose is associated with improved survival in CEC patients receiving chemoradiotherapy, especially those with a total radiation dose in the >6400-7020 cGy range. All three lower dose groups had significantly worse survival than the highest dose group in the multivariable Cox-PH model, and the highest dose group compared to the lowest dose group resulted in a hazard ratio of 0.68 [0.50-0.90]. The weighted propensity score analyses showed similar results with the highest dose group having superior survival compared to the other three dose groups combined (HR:

0.71 [0.56-0.92]). Both generalized propensity score models were also in agreement with this result. The continuous generalized propensity score models showed a hazard ratio of 0.983 [0.969, 0.998]. For the ordinal generalized propensity score model, the highest total radiation dose group was shown to be superior to the lowest group (HR: 0.732 [0.550, 0.973]).

While the ordinal generalized propensity score model does provide more information by including multiple treatment groups, it yields a slightly weaker estimate (p-value: 0.032) compared to the multivariable analysis (p-value: 0.008). The IPTW approach has similar strength to that of the multivariable analysis (p-value: 0.008), but it has added power due to the larger sample from combining the lower three dose groups. Still, the estimates for the hazard ratios are rather similar for all three models. Thus, it is likely that the benefits of higher total radiation dose are seen around 6400 cGy. The continuous generalized propensity score model also provides useful information in showing that any increase in total radiation dose appears to have some benefit in overall survival. Further research may be beneficial in evaluating total radiation dose response using a larger sample size to achieve more power.

Stratification shows that patients receiving IMRT or patients with an AJCC clinical stage group of 3 or 4 may have additional benefit of high total radiation dose. Based on the univariate and multivariable logistic regression models of the dichotomous total radiation dose group, variables that are associated with receiving a total radiation dose of >6400-7020 cGy are facility location, urban/rural 2003, and regional treatment modality. This suggests that certain groups of people are more likely to receive higher total radiation dose than others, and that certain patient types may benefit more from higher total radiation dose than others.

There are some limitations of using the NCDB data, such as lack of specificity with some variables. The median income and great circle distance variables are determined by the patients'

zip code thus may not accurately represent a given subject. The specific facility is not included to preserve confidentiality; however, this prevents us from accounting for potential practice variation by facility. We also do not know the specific drugs administered for chemotherapy or the dosage of chemotherapy. Furthermore, overall survival can only be modeled through the year 2013. There may be other unknown important variables that are excluded from the dataset as well. Lastly, the NCDB data includes about 70% of newly diagnosed cases. While this is a reasonably large amount, there are still 30% missing from the data, which could lead to bias if the missing cases are systematically different from those included.

There are some limitations to our analysis as well. First, we cannot be certain that all the important variables in the dataset are included in our analyses. We also only tested select variables for interaction and stratification, so it is possible that other interactions exist. In the weighted propensity score analyses, while we did achieve sufficient covariate balance, it is possible that a different set of covariates could have resulted in superior balance. Since we were unable to evaluate unmeasured covariates, there may be some unmeasured covariates for which our weighted sample is not balanced. Randomized controlled trials are able to account for these such unmeasured covariates in the randomization process, but retrospectively we must assume that only the variables included are important to the analysis. Propensity score analysis still provides a reasonably good alternative to a RCT for cervical esophageal cancer. The rarity of CEC makes clinical trials difficult to adequately power since it is hard to achieve a sufficient sample size.

However, the covariate adjustment by the propensity score method has several limitations. For instance, the validity of covariate adjustment depends on the assumption that relationship between the propensity score and outcome has been correctly modeled (Austin,

2011). When covariate adjusting, many researchers include interaction and higher-order terms of the treatment variable and propensity score in the model (Hirano and Imbens, 2004; Spreeuwenberg et al., 2010). We did not include these terms in our analysis, although they may improve model fit in future analyses. However, model manipulation with covariate adjustment in this manner should be done with caution as researchers have the temptation of creating the model that yields the result they want to see (Rubin, 2001; Austin, 2011). The lack of consistency in methods for assessing covariate balance is also a major limitation of covariate adjustment by the propensity score.

Moreover, there are also various ways to assess multiple treatments using the propensity score. While we used an ordinal logistic proportional odds model to evaluate treatment group as an ordinal variable, some researchers choose to evaluate treatment as a nominal variable. This can be done by using a multinomial logit model to assign propensity scores (Imbens, 2000; Spreeuwenberg et al., 2010; Feng et al., 2012; McCaffrey et al., 2013). McCaffrey et al. (2013) also suggest using a generalized boosted model (GBM). After propensity score assignment, the methodology for multiple treatments may vary further. Imbens (2000) suggests weighting by the inverse of the generalized propensity score for ordinal treatment variables. He also suggests using a smooth term for the treatment variable in the model if levels are ordered. Lu et al. (2001) proposed a method for matching with multiple ordinal treatments. They use the maximum likelihood estimate ($\beta\mathbf{X}$) from the proportional odds model for the matching process in which any individual can be matched to any other individual, regardless of treatment group. There are many methods and combinations of methods that may be used in attempt to strengthen the propensity score analysis.

CONCLUSION

In our analysis, we found inverse probability of treatment weighting to be a good alternative to propensity score matching with a small sample size. While covariate adjustment by the propensity score allows more room for error, we found that it still is a beneficial method, especially when used with forms of the generalized propensity score. In these cases, the decrease in precision is a trade off with increased knowledge from evaluating treatment as a non-binary term. More research is needed to identify the optimal method for assessing covariate balance when using covariate adjustment by the propensity score, especially for the continuous and multiple treatment cases. Still, all methods yield similar results indicating that higher total radiation dose improves survival for cervical esophageal cancer patients receiving chemoradiotherapy.

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APPENDIX: Tables and Figures
Descriptive Statistics:

Table 1a: Descriptive Statistics for all Variables of Interest

Variable	Level	N (%) = 586
Total Radiation Dose	4500-5040 cGy	196 (33.4)
	>5040-5940 cGy	136 (23.2)
	>5940-6400 cGy	111 (18.9)
	>6400-7020 cGy	143 (24.4)
Total Radiation Dose	4500-6400 cGy (lower three dose groups)	443 (75.6)
	>6400-7020 cGy (highest dose group)	143 (24.4)
Sex	Male	369 (63.0)
	Female	217 (37.0)
Race	White	469 (80.0)
	Black	84 (14.3)
	Others/Unknown	33 (5.6)
Facility Type	Non-Academic	327 (56.8)
	Academic	249 (43.2)
	Missing	10
Facility Location	Northeast	139 (24.1)
	South	179 (31.1)
	Midwest	168 (29.2)
	West	90 (15.6)
	Missing	10
Urban/Rural 2003	Metro	467 (84.9)
	Urban	72 (13.1)
	Rural	11 (2.0)
	Missing	36

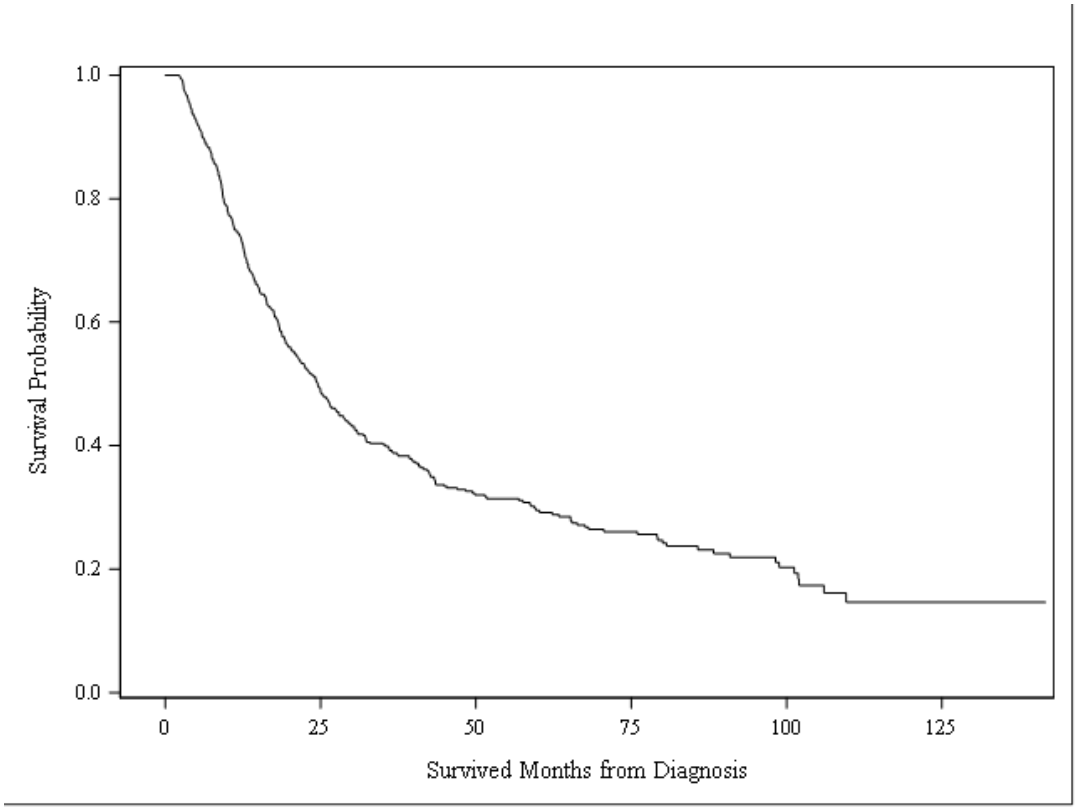
Variable	Level	N (%) = 586
Primary Payor	Not Insured/Unknown	24 (4.1)
	Private	173 (29.5)
	Medicaid	68 (11.6)
	Medicare/Other Government	321 (54.8)
Median Income Quartiles 2000	Not Available	32
	< $30,000	82 (14.8)
	$30,000 - $35,999	119 (21.5)
	$36,000 - $45,999	139 (25.1)
	$46,000 +	214 (38.6)
Median Income Quartiles 2008-2012	Not Available	18
	<$38,000	124 (21.8)
	$38,000-$47,999	138 (24.3)
	$48,000-$62,999	135 (23.8)
	$63,000 +	171 (30.1)
Histology	8070-8079	558 (95.2)
	8140-8149	28 (4.8)
Grade	Well to Moderately Differeentiated	272 (46.4)
	Poorly Differentiated/Undifferentiated	156 (26.6)
	Cell Type Not Determined	158 (27.0)
Charlson-Deyo Score	0	458 (78.2)
	1+	128 (21.8)
Sequence Number	00	394 (67.2)
	01	39 (6.7)
	02,03,04,05	153 (26.1)

Variable	Level	N (%) = 586
AJCC Clinical T	1	72 (12.3)
	2	93 (15.9)
	3	190 (32.4)
	4	121 (20.6)
	X	110 (18.8)
AJCC Clinical N	0,1	494 (84.3)
	2,3	33 (5.6)
	X	59 (10.1)
AJCC Clinical Stage Group	0,1,2	250 (42.7)
	3,4	234 (39.9)
	Missing	102 (17.4)
Regional Treatment Modality	External beam,NOS; Other,NOS; Photons(All); Protons;	282 (48.1)
	IMRT	254 (43.3)
	Conformal or 3-D Therapy	50 (8.5)
Chemotherapy	Chemo Administered, type and numbers of agents unknown	38 (6.5)
	Single-Agent	93 (15.9)
	Multiagent	455 (77.6)
Year of Diagnosis (quartile)	>=2004, <=2007	194 (33.1)
	>2007, <=2009	124 (21.2)
	>2009, <=2011	136 (23.2)
	>2011, <=2013	132 (22.5)
Tumor Size (cm) (grouped)	<4.00	160 (27.3)
	>=4.00	181 (30.9)
	Missing	245 (41.8)

Variable	Level	N (%) = 586
Great Circle Distance (grouped)	<7.50	283 (48.3)
	>=7.50	285 (48.6)
	Missing	18 (3.1)
Age at Diagnosis (grouped)	<67.00	283 (48.3)
	>=67.00	303 (51.7)
Tumor Size (cm) (quartile)	>=0, <=3	87 (14.8)
	>3, <=4	103 (17.6)
	>4, <=5	68 (11.6)
	>5, <=99	83 (14.2)
	Unknown	245 (41.8)
Great Circle Distance (quartile)	>=0, <=4	144 (24.6)
	>4, <=8	141 (24.1)
	>8, <=20	141 (24.1)
	>20, <=1375	142 (24.2)
	Unknown	18 (3.1)
Total Radiation Dose (Gy)	Mean	57.9
	Median	59.4
	Minimum	45.0
	Maximum	70.2
	Std Dev	7.2
	Missing	0.0
Age at Diagnosis	Mean	66.4
	Median	67.0
	Minimum	30.0
	Maximum	90.0
	Std Dev	11.3
	Missing	0.0

Variable	Level	N (%) = 586
Great Circle Distance	Mean	23.2
	Median	7.5
	Minimum	0.1
	Maximum	1374.6
	Std Dev	88.9
	Missing	18.0
Tumor Size (cm)	Mean	4.5
	Median	4.0
	Minimum	0.5
	Maximum	98.8
	Std Dev	5.6
	Missing	245.0
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment	Mean	5.3
	Median	4.5
	Minimum	0.3
	Maximum	33.0
	Std Dev	3.6
	Missing	0.0

Figure 1: Kaplan-Meier Plot of Overall Survival



No. of Subjects	Events	Censored	Median Survival, in months (95% CI)	12 Mo Survival (95% CI)	60 Mo Survival (95% CI)
586	392 (67%)	194 (33%)	24.5 (21.3, 27.3)	74.0% (70.1%, 77.4%)	29.5% (25.4%, 33.7%)

Table 1b: Median Follow-Up

Quartile Estimates				
Percent	Point Estimate (Months)	95% Confidence Interval		
		Transform	[Lower	Upper)
75	93.702	LOGLOG	82.826	99.680
50	63.570	LOGLOG	53.647	72.082
25	34.920	LOGLOG	28.882	40.116

Univariate Analysis:

Table 2a: Univariate Association with Total Radiation Dose – Four Dose Groups

Covariate	Statistics	Level	Total Radiation Dose				Parametric P-value*
			4500-5040 cGy N=196	>5040-5940 cGy N=136	>5940-6400 cGy N=111	>6400-7020 cGy N=143	
Sex	N (Col %)	Male	113 (57.65)	93 (68.38)	78 (70.27)	85 (59.44)	0.061
	N (Col %)	Female	83 (42.35)	43 (31.62)	33 (29.73)	58 (40.56)	
Race	N (Col %)	White	151 (77.04)	112 (82.35)	92 (82.88)	114 (79.72)	0.690
	N (Col %)	Black	30 (15.31)	19 (13.97)	15 (13.51)	20 (13.99)	
	N (Col %)	Others/Unknown	15 (7.65)	5 (3.68)	4 (3.6)	9 (6.29)	
Facility Type	N (Col %)	Non-Academic	117 (60.94)	56 (41.79)	66 (59.46)	88 (63.31)	**<.001**
	N (Col %)	Academic	75 (39.06)	78 (58.21)	45 (40.54)	51 (36.69)	
Facility Location	N (Col %)	Northeast	47 (24.48)	37 (27.61)	22 (19.82)	33 (23.74)	**0.041**
	N (Col %)	South	55 (28.65)	39 (29.1)	27 (24.32)	58 (41.73)	
	N (Col %)	Midwest	61 (31.77)	33 (24.63)	42 (37.84)	32 (23.02)	
	N (Col %)	West	29 (15.1)	25 (18.66)	20 (18.02)	16 (11.51)	
Urban/Rural 2003	N (Col %)	Metro	151 (84.36)	116 (89.92)	94 (88.68)	106 (77.94)	0.061
	N (Col %)	Urban	26 (14.53)	10 (7.75)	9 (8.49)	27 (19.85)	
	N (Col %)	Rural	2 (1.12)	3 (2.33)	3 (2.83)	3 (2.21)	
Primary Payor	N (Col %)	Not Insured/Unknown	10 (5.1)	8 (5.88)	4 (3.6)	2 (1.4)	**0.021**
	N (Col %)	Private	42 (21.43)	50 (36.76)	30 (27.03)	51 (35.66)	
	N (Col %)	Medicaid	29 (14.8)	11 (8.09)	16 (14.41)	12 (8.39)	
	N (Col %)	Medicare/Other Government	115 (58.67)	67 (49.26)	61 (54.95)	78 (54.55)	

Covariate	Statistics	Level	Total Radiation Dose 4500-5040 cGy N=196	>5040-5940 cGy N=136	>5940-6400 cGy N=111	>6400-7020 cGy N=143	Parametric P-value*
Median Income Quartiles 2000	N (Col %)	< $30,000	30 (16.57)	20 (15.04)	17 (16.5)	15 (10.95)	0.566
	N (Col %)	$30,000 - $35,999	35 (19.34)	26 (19.55)	19 (18.45)	39 (28.47)	
	N (Col %)	$36,000 - $45,999	47 (25.97)	30 (22.56)	27 (26.21)	35 (25.55)	
	N (Col %)	$46,000 +	69 (38.12)	57 (42.86)	40 (38.83)	48 (35.04)	
Median Income Quartiles 2008-2012	N (Col %)	<$38,000	45 (24.19)	26 (19.26)	27 (24.77)	26 (18.84)	0.714
	N (Col %)	$38,000-$47,999	45 (24.19)	34 (25.19)	22 (20.18)	37 (26.81)	
	N (Col %)	$48,000-$62,999	41 (22.04)	29 (21.48)	26 (23.85)	39 (28.26)	
	N (Col %)	$63,000 +	55 (29.57)	46 (34.07)	34 (31.19)	36 (26.09)	
Histology	N (Col %)	8070-8079	182 (92.86)	127 (93.38)	106 (95.5)	143 (100)	**0.014**
	N (Col %)	8140-8149	14 (7.14)	9 (6.62)	5 (4.5)	0 (0)	
Grade	N (Col %)	Well to Moderately Differeentiated	92 (46.94)	69 (50.74)	46 (41.44)	65 (45.45)	0.586
	N (Col %)	Poorly Differentiated/Undifferentiated	46 (23.47)	38 (27.94)	33 (29.73)	39 (27.27)	
	N (Col %)	Cell Type Not Determined	58 (29.59)	29 (21.32)	32 (28.83)	39 (27.27)	
Charlson-Deyo Score	N (Col %)	0	152 (77.55)	107 (78.68)	88 (79.28)	111 (77.62)	0.982
	N (Col %)	1+	44 (22.45)	29 (21.32)	23 (20.72)	32 (22.38)	
AJCC Clinical T	N (Col %)	1	26 (13.27)	16 (11.76)	11 (9.91)	19 (13.29)	0.186
	N (Col %)	2	34 (17.35)	24 (17.65)	13 (11.71)	22 (15.38)	
	N (Col %)	3	61 (31.12)	48 (35.29)	32 (28.83)	49 (34.27)	
	N (Col %)	4	31 (15.82)	24 (17.65)	36 (32.43)	30 (20.98)	
	N (Col %)	X	44 (22.45)	24 (17.65)	19 (17.12)	23 (16.08)	

Covariate	Statistics	Level	Total Radiation Dose				Parametric P-value*
			4500-5040 cGy N=196	>5040-5940 cGy N=136	>5940-6400 cGy N=111	>6400-7020 cGy N=143	
AJCC Clinical N	N (Col %)	0,1	161 (82.14)	117 (86.03)	94 (84.68)	122 (85.31)	0.138
	N (Col %)	2,3	8 (4.08)	5 (3.68)	10 (9.01)	10 (6.99)	
	N (Col %)	X	27 (13.78)	14 (10.29)	7 (6.31)	11 (7.69)	
AJCC Clinical Stage Group	N (Col %)	0,1,2	94 (47.96)	62 (45.59)	30 (27.03)	64 (44.76)	**<.001**
	N (Col %)	3,4	60 (30.61)	49 (36.03)	65 (58.56)	60 (41.96)	
	N (Col %)	Missing	42 (21.43)	25 (18.38)	16 (14.41)	19 (13.29)	
Regional Treatment Modality	N (Col %)	External beam,NOS; Other,NOS; Photons(All); Protons;	102 (52.04)	74 (54.41)	49 (44.14)	57 (39.86)	**0.003**
	N (Col %)	IMRT	73 (37.24)	48 (35.29)	52 (46.85)	81 (56.64)	
	N (Col %)	Conformal or 3-D Therapy	21 (10.71)	14 (10.29)	10 (9.01)	5 (3.5)	
Chemotherapy	N (Col %)	Chemo Administered, type and numbers of agents unknown	13 (6.63)	7 (5.15)	9 (8.11)	9 (6.29)	**0.050**
	N (Col %)	Single-Agent	17 (8.67)	28 (20.59)	20 (18.02)	28 (19.58)	
	N (Col %)	Multiagent	166 (84.69)	101 (74.26)	82 (73.87)	106 (74.13)	
Year of Diagnosis (quartile)	N (Col %)	>=2004, <=2007	64 (32.65)	45 (33.09)	35 (31.53)	50 (34.97)	0.949
	N (Col %)	>2007, <=2009	40 (20.41)	34 (25)	25 (22.52)	25 (17.48)	
	N (Col %)	>2009, <=2011	45 (22.96)	31 (22.79)	25 (22.52)	35 (24.48)	
	N (Col %)	>2011, <=2013	47 (23.98)	26 (19.12)	26 (23.42)	33 (23.08)	
	N (Col %)	<4.00	50 (25.51)	45 (33.09)	24 (21.62)	41 (28.67)	0.185
	N (Col %)	>=4.00	54 (27.55)	42 (30.88)	35 (31.53)	50 (34.97)	

Covariate	Statistics	Level	Total Radiation Dose				Parametric P-value*
			4500-5040 cGy N=196	>5040-5940 cGy N=136	>5940-6400 cGy N=111	>6400-7020 cGy N=143	
Tumor Size (cm) (grouped)	N (Col %)	Missing	92 (46.94)	49 (36.03)	52 (46.85)	52 (36.36)	
Great Circle Distance (grouped)	N (Col %)	<7.50	99 (50.51)	72 (52.94)	49 (44.14)	63 (44.06)	0.151
	N (Col %)	>=7.50	87 (44.39)	63 (46.32)	60 (54.05)	75 (52.45)	
	N (Col %)	Missing	10 (5.1)	1 (0.74)	2 (1.8)	5 (3.5)	
Age at Diagnosis (grouped)	N (Col %)	<67.00	90 (45.92)	70 (51.47)	50 (45.05)	73 (51.05)	0.594
	N (Col %)	>=67.00	106 (54.08)	66 (48.53)	61 (54.95)	70 (48.95)	
Tumor Size (cm) (quartile)	N (Col %)	>=0, <=3	29 (14.8)	26 (19.12)	12 (10.81)	20 (13.99)	0.284
	N (Col %)	>3, <=4	30 (15.31)	24 (17.65)	17 (15.32)	32 (22.38)	
	N (Col %)	>4, <=5	19 (9.69)	13 (9.56)	17 (15.32)	19 (13.29)	
	N (Col %)	>5, <=99	26 (13.27)	24 (17.65)	13 (11.71)	20 (13.99)	
	N (Col %)	Unknown	92 (46.94)	49 (36.03)	52 (46.85)	52 (36.36)	
Great Circle Distance (quartile)	N (Col %)	>=0, <=4	51 (26.02)	35 (25.74)	25 (22.52)	33 (23.08)	0.379
	N (Col %)	>4, <=8	48 (24.49)	37 (27.21)	25 (22.52)	31 (21.68)	
	N (Col %)	>8, <=20	48 (24.49)	35 (25.74)	26 (23.42)	32 (22.38)	
	N (Col %)	>20, <=1375	39 (19.9)	28 (20.59)	33 (29.73)	42 (29.37)	
	N (Col %)	Unknown	10 (5.1)	1 (0.74)	2 (1.8)	5 (3.5)	
Age at Diagnosis	N		196	136	111	143	0.892
	Mean		66.61	66.04	66.89	65.96	
	Median		68	65.5	69	66	
	Min		30	32	41	35	
	Max		90	86	89	87	
	Std Dev		11.55	11.29	11.14	11.31	

Covariate	Statistics	Level	Total Radiation Dose 4500-5040 cGy N=196	>5040-5940 cGy N=136	>5940-6400 cGy N=111	>6400-7020 cGy N=143	Parametric P-value*
Great Circle Distance	N		186	135	109	138	0.691
	Mean		19.81	23.58	31.96	20.39	
	Median		7.1	6.9	8.8	8.3	
	Min		0.1	0.1	0.2	0.3	
	Max		683.3	1336.2	1374.6	306.4	
	Std Dev		55.47	116.02	133.43	35.21	
Tumor Size (cm)	N		104	87	59	91	0.574
	Mean		4.25	5.22	4.36	4.2	
	Median		4	3.9	4.2	4	
	Min		1.3	1	0.5	1	
	Max		20	98.8	12.6	11	
	Std Dev		2.37	10.37	2.16	1.94	
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment	N		196	136	111	143	0.361
	Mean		5.45	4.83	5.49	5.45	
	Median		4.79	4	4.43	4.57	
	Min		0.43	0.57	0.57	0.29	
	Max		21.71	14.29	20.71	33	
	Std Dev		3.59	2.62	3.83	4.25	

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

Table 2b: Univariate Association with Total Radiation Dose – Continuous

Covariate	Statistics	Level	Total Radiation Dose: 4500-6400 cGy (lower three dose groups) N=443	Total Radiation Dose: >6400-7020 cGy (highest dose group) N=143	Parametric P-value*
Sex	N (Col %)	Male	284 (64.11)	85 (59.44)	0.315
	N (Col %)	Female	159 (35.89)	58 (40.56)	
Race	N (Col %)	White	355 (80.14)	114 (79.72)	0.920
	N (Col %)	Black	64 (14.45)	20 (13.99)	
	N (Col %)	Others/Unknown	24 (5.42)	9 (6.29)	
Facility Type	N (Col %)	Non-Academic	239 (54.69)	88 (63.31)	0.074
	N (Col %)	Academic	198 (45.31)	51 (36.69)	
Facility Location	N (Col %)	Northeast	106 (24.26)	33 (23.74)	**0.011**
	N (Col %)	South	121 (27.69)	58 (41.73)	
	N (Col %)	Midwest	136 (31.12)	32 (23.02)	
	N (Col %)	West	74 (16.93)	16 (11.51)	
Urban/Rural 2003	N (Col %)	Metro	361 (87.2)	106 (77.94)	**0.025**
	N (Col %)	Urban	45 (10.87)	27 (19.85)	
	N (Col %)	Rural	8 (1.93)	3 (2.21)	
Primary Payor	N (Col %)	Not Insured/Unknown	22 (4.97)	2 (1.4)	0.059
	N (Col %)	Private	122 (27.54)	51 (35.66)	
	N (Col %)	Medicaid	56 (12.64)	12 (8.39)	
	N (Col %)	Medicare/Other Government	243 (54.85)	78 (54.55)	
Median Income Quartiles 2000	N (Col %)	< $30,000	67 (16.07)	15 (10.95)	0.086
	N (Col %)	$30,000 - $35,999	80 (19.18)	39 (28.47)	
	N (Col %)	$36,000 - $45,999	104 (24.94)	35 (25.55)	
	N (Col %)	$46,000 +	166 (39.81)	48 (35.04)	
Median Income Quartiles 2008-2012	N (Col %)	<$38,000	98 (22.79)	26 (18.84)	0.290
	N (Col %)	$38,000-$47,999	101 (23.49)	37 (26.81)	
	N (Col %)	$48,000-$62,999	96 (22.33)	39 (28.26)	
	N (Col %)	$63,000 +	135 (31.4)	36 (26.09)	

Covariate	Statistics	Level	Total Radiation Dose: 4500-6400 cGy (lower three dose groups) N=443	Total Radiation Dose: >6400-7020 cGy (highest dose group) N=143	Parametric P-value*
Histology	N (Col %)	8070-8079	415 (93.68)	143 (100)	**0.002**
	N (Col %)	8140-8149	28 (6.32)	0 (0)	
Grade	N (Col %)	Well to Moderately Differeentiated	207 (46.73)	65 (45.45)	0.963
	N (Col %)	Poorly Differentiated/Undifferentiated	117 (26.41)	39 (27.27)	
	N (Col %)	Cell Type Not Determined	119 (26.86)	39 (27.27)	
Charlson-Deyo Score	N (Col %)	0	347 (78.33)	111 (77.62)	0.859
	N (Col %)	1+	96 (21.67)	32 (22.38)	
Sequence Number	N (Col %)	00	295 (66.59)	99 (69.23)	0.582
	N (Col %)	01	28 (6.32)	11 (7.69)	
	N (Col %)	02,03,04,05	120 (27.09)	33 (23.08)	
AJCC Clinical T	N (Col %)	1	53 (11.96)	19 (13.29)	0.891
	N (Col %)	2	71 (16.03)	22 (15.38)	
	N (Col %)	3	141 (31.83)	49 (34.27)	
	N (Col %)	4	91 (20.54)	30 (20.98)	
	N (Col %)	X	87 (19.64)	23 (16.08)	
AJCC Clinical N	N (Col %)	0,1	372 (83.97)	122 (85.31)	0.426
	N (Col %)	2,3	23 (5.19)	10 (6.99)	
	N (Col %)	X	48 (10.84)	11 (7.69)	
AJCC Clinical Stage Group	N (Col %)	0,1,2	186 (41.99)	64 (44.76)	0.327
	N (Col %)	3,4	174 (39.28)	60 (41.96)	
	N (Col %)	Missing	83 (18.74)	19 (13.29)	
Regional Treatment Modality	N (Col %)	External beam,NOS; Other,NOS; Photons(All); Protons;	225 (50.79)	57 (39.86)	0.327
	N (Col %)	IMRT	173 (39.05)	81 (56.64)	
	N (Col %)	Conformal or 3-D Therapy	45 (10.16)	5 (3.5)	
Year of Diagnosis (quartile)	N (Col %)	>=2004, <=2007	144 (32.51)	50 (34.97)	0.668
	N (Col %)	>2007, <=2009	99 (22.35)	25 (17.48)	
	N (Col %)	>2009, <=2011	101 (22.8)	35 (24.48)	

Covariate	Statistics	Level	Total Radiation Dose: 4500-6400 cGy (lower three dose groups) N=443	Total Radiation Dose: >6400-7020 cGy (highest dose group) N=143	Parametric P-value*
	N (Col %)	>2011, <=2013	99 (22.35)	33 (23.08)	
Tumor Size (cm) (grouped)	N (Col %)	<4.00	119 (26.86)	41 (28.67)	0.288
	N (Col %)	>=4.00	131 (29.57)	50 (34.97)	
	N (Col %)	Missing	193 (43.57)	52 (36.36)	
Great Circle Distance (grouped)	N (Col %)	<7.50	220 (49.66)	63 (44.06)	0.502
	N (Col %)	>=7.50	210 (47.4)	75 (52.45)	
	N (Col %)	Missing	13 (2.93)	5 (3.5)	
Age at Diagnosis (grouped)	N (Col %)	<67.00	210 (47.4)	73 (51.05)	0.448
	N (Col %)	>=67.00	233 (52.6)	70 (48.95)	
Tumor Size (cm) (quartile)	N (Col %)	>=0, <=3	67 (15.12)	20 (13.99)	0.357
	N (Col %)	>3, <=4	71 (16.03)	32 (22.38)	
	N (Col %)	>4, <=5	49 (11.06)	19 (13.29)	
	N (Col %)	>5, <=99	63 (14.22)	20 (13.99)	
	N (Col %)	Unknown	193 (43.57)	52 (36.36)	
Great Circle Distance (quartile)	N (Col %)	>=0, <=4	111 (25.06)	33 (23.08)	0.555
	N (Col %)	>4, <=8	110 (24.83)	31 (21.68)	
	N (Col %)	>8, <=20	109 (24.6)	32 (22.38)	
	N (Col %)	>20, <=1375	100 (22.57)	42 (29.37)	
	N (Col %)	Unknown	13 (2.93)	5 (3.5)	
Age at Diagnosis	N		443	143	0.616
	Mean		66.51	65.96	
	Median		67	66	
	Min		30	35	
	Max		90	87	
	Std Dev		11.35	11.31	
Great Circle Distance	N		430	138	0.673
	Mean		24.07	20.39	
	Median		7.2	8.3	
	Min		0.1	0.3	

Covariate	Statistics	Level	Total Radiation Dose: 4500-6400 cGy (lower three dose groups) N=443	Total Radiation Dose: >6400-7020 cGy (highest dose group) N=143	Parametric P-value*
	Max		1374.6	306.4	
	Std Dev		100.18	35.21	
Tumor Size (cm)	N		250	91	0.542
	Mean		4.61	4.2	
	Median		4	4	
	Min		0.5	1	
	Max		98.8	11	
	Std Dev		6.38	1.94	
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment	N		443	143	0.594
	Mean		5.27	5.45	
	Median		4.43	4.57	
	Min		0.43	0.29	
	Max		21.71	33	
	Std Dev		3.39	4.25	

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

Table 3a: Univariate Association with Overall Survival

			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Total Radiation Dose	>6400-7020 cGy	143	0.75 (0.57-0.99)	**0.043**	0.092
	>5940-6400 cGy	111	1.09 (0.83-1.44)	0.538	
	>5040-5940 cGy	136	0.96 (0.74-1.25)	0.773	
	4500-5040 cGy	196	-	-	
Total Radiation Dose	>6400-7020 cGy (highest dose group)	143	0.75 (0.59-0.95)	**0.018**	**0.017**
	4500-6400 cGy (lower three dose groups)	443	-	-	
Sex	Female	217	0.82 (0.67-1.01)	0.068	0.067
	Male	369	-	-	
Race	Black	84	0.90 (0.68-1.20)	0.486	0.206
	Others/Unknown	33	0.64 (0.38-1.08)	0.094	
	White	469	-	-	
Facility Type	Academic	249	1.08 (0.88-1.32)	0.452	0.453
	Non-Academic	327	-	-	
Facility Location	Northeast	139	0.88 (0.64-1.22)	0.437	0.304
	South	179	0.82 (0.61-1.12)	0.221	
	Midwest	168	1.03 (0.76-1.41)	0.828	
	West	90	-	-	
Urban/Rural 2003	Metro	467	1.24 (0.64-2.42)	0.518	0.322
	Urban	72	1.52 (0.75-3.10)	0.248	
	Rural	11	-	-	
Primary Payor	Private	173	0.71 (0.42-1.20)	0.202	0.082
	Medicaid	68	0.86 (0.49-1.53)	0.614	
	Medicare/Other Government	321	0.96 (0.58-1.59)	0.872	
	Not Insured/Unknown	24	-	-	
Median Income Quartiles 2000	< $30,000	82	1.12 (0.82-1.54)	0.486	0.496
	$30,000 - $35,999	119	1.24 (0.94-1.62)	0.128	

			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
	$36,000 - $45,999	139	1.07 (0.82-1.40)	0.618	
	$46,000 +	214	-	-	
Median Income Quartiles 2008-2012	<$38,000	124	1.37 (1.03-1.82)	**0.033**	**0.049**
	$38,000-$47,999	138	1.29 (0.97-1.72)	0.082	
	$48,000-$62,999	135	1.45 (1.10-1.92)	**0.009**	
	$63,000 +	171	-	-	
Histology	8070-8079	558	1.11 (0.70-1.77)	0.647	0.646
	8140-8149	28	-	-	
Grade	Well to Moderately Differeentiated	272	1.31 (1.03-1.68)	**0.030**	0.072
	Poorly Differentiated/Undifferentiated	156	1.30 (0.99-1.71)	0.062	
	Cell Type Not Determined	158	-	-	
Sequence Number	00	394	0.95 (0.76-1.19)	0.669	0.290
	01	39	0.72 (0.47-1.09)	0.120	
	02,03,04,05	153	-	-	
Charlson-Deyo Score	0	458	0.69 (0.55-0.87)	**0.002**	**0.002**
	1+	128	-	-	
AJCC Clinical T	X	110	1.68 (1.14-2.46)	**0.008**	0.065
	4	121	1.55 (1.06-2.27)	**0.024**	
	3	190	1.47 (1.03-2.10)	**0.034**	
	2	93	1.25 (0.83-1.87)	0.286	
	1	72	-	-	
AJCC Clinical N	X	59	1.30 (0.96-1.76)	0.093	0.105
	2,3	33	1.37 (0.89-2.12)	0.151	
	0,1	494	-	-	
AJCC Clinical Stage Group	Missing	102	1.39 (1.05-1.84)	**0.020**	**0.005**
	3,4	234	1.41 (1.13-1.76)	**0.002**	
	0,1,2	250	-	-	

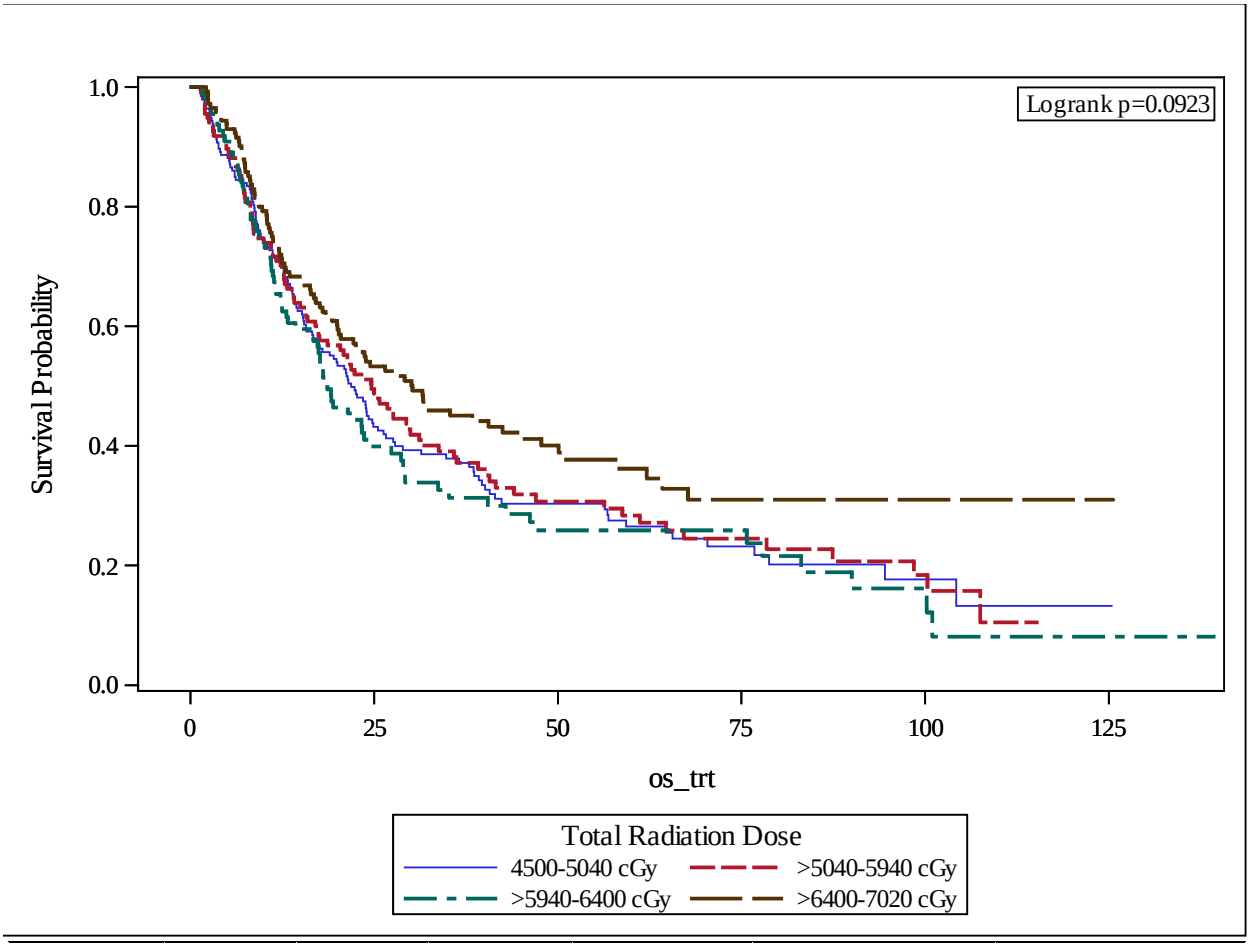
			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Regional Treatment Modality	External beam,NOS; Other,NOS; Photons(All); Protons;	282	1.11 (0.90-1.36)	0.339	0.474
	Conformal or 3-D Therapy	50	0.92 (0.63-1.34)	0.670	
	IMRT	254	-	-	
Chemotherapy	Chemo Administered, type and numbers of agents unknown	38	1.14 (0.76-1.71)	0.533	0.222
	Single-Agent	93	1.25 (0.96-1.61)	0.093	
	Multiagent	455	-	-	
Year of Diagnosis (quartile)	>=2004, <=2007	194	0.88 (0.66-1.19)	0.417	0.798
	>2007, <=2009	124	0.99 (0.72-1.36)	0.960	
	>2009, <=2011	136	0.97 (0.71-1.32)	0.839	
	>2011, <=2013	132	-	-	
Tumor Size (cm) (grouped)	Missing	245	1.15 (0.91-1.47)	0.249	0.429
	>=4.00	181	1.02 (0.78-1.33)	0.877	
	<4.00	160	-	-	
Great Circle Distance (grouped)	Missing	18	2.28 (1.38-3.75)	**0.001**	**0.004**
	>=7.50	285	1.03 (0.84-1.26)	0.764	
	<7.50	283	-	-	
Age at Diagnosis (grouped)	>=67.00	303	1.10 (0.90-1.35)	0.331	0.330
	<67.00	283	-	-	
Tumor Size (cm) (quartile)	Unknown	245	1.36 (1.00-1.86)	**0.050**	0.414
	>5, <=99	83	1.31 (0.89-1.92)	0.175	
	>4, <=5	68	1.24 (0.83-1.86)	0.287	
	>3, <=4	103	1.27 (0.89-1.81)	0.187	
	>=0, <=3	87	-	-	
Great Circle Distance (quartile)	Unknown	18	2.07 (1.23-3.47)	**0.006**	**0.012**
	>20, <=1375	142	0.92 (0.69-1.23)	0.590	
	>8, <=20	141	0.95 (0.72-1.26)	0.738	
	>4, <=8	141	0.83 (0.62-1.10)	0.194	

			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
	>=0, <=4	144	-	-	
Total Radiation Dose (Gy)		586	0.99 (0.97-1.00)	0.082	-
Age at Diagnosis		586	1.01 (1.00-1.02)	**0.048**	-
Great Circle Distance		568	1.00 (1.00-1.00)	0.170	-
Tumor Size (cm)		341	1.00 (0.98-1.02)	0.853	-
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		586	0.97 (0.94-1.00)	0.052	-

Figure 2: Kaplan-Meier Plot of Overall Survival by Total Radiation Dose Group



Total Radiation Dose	No. of Subjects	Events	Censored	Median Survival, in months (95% CI)	12 Mo Survival (95% CI)	60 Mo Survival (95% CI)
4500-5040 cGy	196	132 (67%)	64 (33%)	21.8 (17.3, 25.5)	71.6% (64.6%, 77.5%)	26.5% (19.6%, 33.9%)
>5040-5940 cGy	136	96 (71%)	40 (29%)	24.6 (17.4, 31.1)	70.9% (62.4%, 77.8%)	28.3% (20.2%, 37.0%)
>5940-6400 cGy	111	79 (71%)	32 (29%)	18.6 (14.3, 24.1)	65.4% (55.6%, 73.6%)	25.9% (17.3%, 35.3%)
>6400-7020 cGy	143	85 (59%)	58 (41%)	30.2 (20.2, 45.1)	73.4% (65.3%, 80.0%)	36.2% (27.4%, 45.0%)

Table 3b: Univariate Logistic Regression of Total Radiation Dose Group (Highest vs Rest)

			Total Radiation Dose=>6400-7020 cGy (highest dose group)		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Sex	Female	217	1.22 (0.83-1.79)	0.315	0.315
	Male	369	-	-	
Race	Black	84	0.97 (0.56-1.68)	0.922	0.921
	Others/Unknown	33	1.17 (0.53-2.58)	0.702	
	White	469	-	-	
Facility Type	Academic	249	0.70 (0.47-1.04)	0.075	0.075
	Non-Academic	327	-	-	
Facility Location	Northeast	139	1.44 (0.74-2.80)	0.284	**0.013**
	South	179	2.22 (1.19-4.14)	**0.012**	
	Midwest	168	1.09 (0.56-2.11)	0.803	
	West	90	-	-	
Urban/Rural 2003	Metro	467	0.78 (0.20-3.00)	0.721	**0.028**
	Urban	72	1.60 (0.39-6.55)	0.514	
	Rural	11	-	-	
Primary Payor	Private	173	4.59 (1.04-20.24)	**0.044**	0.074
	Medicaid	68	2.35 (0.49-11.38)	0.287	
	Medicare/Other Government	321	3.53 (0.81-15.32)	0.093	
	Not Insured/Unknown	24	-	-	
Median Income Quartiles 2000	< $30,000	82	0.77 (0.41-1.48)	0.437	0.090
	$30,000 - $35,999	119	1.69 (1.02-2.78)	**0.040**	
	$36,000 - $45,999	139	1.16 (0.71-1.92)	0.552	
	$46,000 +	214	-	-	
Median Income Quartiles 2008-2012	<$38,000	124	0.99 (0.56-1.75)	0.986	0.293
	$38,000-$47,999	138	1.37 (0.81-2.33)	0.237	
	$48,000-$62,999	135	1.52 (0.90-2.57)	0.115	
	$63,000 +	171	-	-	

Covariate	Level	N	Total Radiation Dose=>6400-7020 cGy (highest dose group) Odds Ratio (95% CI)	OR P-value	Type3 P-value
Histology	8070-8079	558	2021693 (0.00-I)	0.975	0.975
	8140-8149	28	-	-	
Grade	Well to Moderately Differeentiated	272	0.96 (0.61-1.51)	0.854	0.963
	Poorly Differentiated/Undifferentiated	156	1.02 (0.61-1.70)	0.948	
	Cell Type Not Determined	158	-	-	
Sequence Number	00	394	1.22 (0.78-1.91)	0.383	0.583
	01	39	1.43 (0.64-3.17)	0.380	
	02,03,04,05	153	-	-	
Charlson-Deyo Score	0	458	0.96 (0.61-1.51)	0.858	0.858
	1+	128	-	-	
AJCC Clinical T	X	110	0.74 (0.37-1.48)	0.392	0.892
	4	121	0.92 (0.47-1.79)	0.805	
	3	190	0.97 (0.52-1.80)	0.921	
	2	93	0.86 (0.43-1.76)	0.687	
	1	72	-	-	
AJCC Clinical N	X	59	0.70 (0.35-1.39)	0.306	0.430
	2,3	33	1.33 (0.61-2.86)	0.473	
	0,1	494	-	-	
AJCC Clinical Stage Group	Missing	102	0.67 (0.37-1.18)	0.164	0.332
	3,4	234	1.00 (0.67-1.51)	0.992	
	0,1,2	250	-	-	
Regional Treatment Modality	External beam,NOS; Other,NOS; Photons(All); Protons;	282	0.54 (0.37-0.80)	**0.002**	**<.001**
	Conformal or 3-D Therapy	50	0.24 (0.09-0.62)	**0.003**	
	IMRT	254	-	-	
Chemotherapy	Chemo Administered, type and numbers of agents unknown	38	1.02 (0.47-2.23)	0.957	0.379
	Single-Agent	93	1.42 (0.87-2.32)	0.165	

Covariate	Level	N	Total Radiation Dose=>6400-7020 cGy (highest dose group) Odds Ratio (95% CI)	OR P-value	Type3 P-value
	Multiagent	455	-	-	
Year of Diagnosis (quartile)	>=2004, <=2007	194	1.04 (0.63-1.73)	0.875	0.670
	>2007, <=2009	124	0.76 (0.42-1.37)	0.356	
	>2009, <=2011	136	1.04 (0.60-1.80)	0.890	
	>2011, <=2013	132	-	-	
Tumor Size (cm) (grouped)	Missing	245	0.78 (0.49-1.25)	0.304	0.289
	>=4.00	181	1.11 (0.68-1.79)	0.677	
	<4.00	160	-	-	
Great Circle Distance (grouped)	Missing	18	1.34 (0.46-3.91)	0.589	0.502
	>=7.50	285	1.25 (0.85-1.83)	0.260	
	<7.50	283	-	-	
Age at Diagnosis (grouped)	>=67.00	303	0.86 (0.59-1.26)	0.448	0.448
	<67.00	283	-	-	
Tumor Size (cm) (quartile)	Unknown	245	0.90 (0.50-1.62)	0.732	0.361
	>5, <=99	83	1.06 (0.52-2.16)	0.865	
	>4, <=5	68	1.30 (0.63-2.69)	0.481	
	>3, <=4	103	1.51 (0.79-2.89)	0.215	
	>=0, <=3	87	-	-	
Great Circle Distance (quartile)	Unknown	18	1.29 (0.43-3.90)	0.647	0.558
	>20, <=1375	142	1.41 (0.83-2.40)	0.201	
	>8, <=20	141	0.99 (0.57-1.72)	0.964	
	>4, <=8	141	0.95 (0.54-1.65)	0.851	
	>=0, <=4	144	-	-	
Age at Diagnosis		586	1.00 (0.98-1.01)	0.615	0.615
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		586	1.01 (0.96-1.07)	0.594	0.594

Multivariable Analysis

Table 4a-1: Multivariable Survival Analysis (Ascending Dose Groups)

			Overall Survival		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Total Radiation Dose	4500-5040 cGy	186	1.48 (1.11-1.98)	**0.008**	**0.029**
	>5040-5940 cGy	135	1.46 (1.08-1.99)	**0.015**	
	>5940-6400 cGy	109	1.47 (1.06-2.02)	**0.019**	
	>6400-7020 cGy	138	-	-	
Sex	Female	208	0.82 (0.66-1.03)	0.082	0.082
	Male	360	-	-	
Median Income Quartiles 2008-2012	<$38,000	124	1.34 (1.01-1.80)	**0.046**	**0.017**
	$38,000-$47,999	138	1.28 (0.96-1.71)	0.095	
	$48,000-$62,999	135	1.58 (1.19-2.10)	**0.002**	
	$63,000 +	171	-	-	
Charlson-Deyo Score	0	447	0.70 (0.55-0.90)	**0.004**	**0.004**
	1+	121	-	-	
Sequence Number	00	382	0.89 (0.70-1.13)	0.330	0.060
	01	38	0.58 (0.37-0.91)	**0.018**	
	02,03,04,05	148	-	-	
AJCC Clinical Stage Group	Missing	95	1.27 (0.94-1.72)	0.122	**0.001**
	3,4	229	1.55 (1.23-1.97)	**<.001**	
	0,1,2	244	-	-	
Chemotherapy	Chemo Administered, type and numbers of agents unknown	36	1.14 (0.74-1.77)	0.545	0.113
	Single-Agent	90	1.34 (1.01-1.76)	**0.039**	
	Multiagent	442	-	-	

Covariate	Level	N	Overall Survival Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Age at Diagnosis		568	1.01 (1.00-1.02)	**0.029**	**0.029**
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		568	0.97 (0.94-1.00)	0.051	0.051

* Number of observations in the original data set = 586. Number of observations used = 568.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Great Circle Distance (grouped), Facility Location, Facility Type, Grade, Histology, Primary Payor, Median Income Quartiles 2000, Race, Regional Treatment Modality, AJCC Clinical N, AJCC Clinical T, Tumor Size (cm) (quartile), Urban/Rural 2003, and Year of Diagnosis (quartile).

Table 4a-2: Multivariable Survival Analysis (Descending Dose Groups)

			Overall Survival		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Total Radiation Dose	>6400-7020 cGy	138	0.68 (0.50-0.90)	**0.008**	**0.029**
	>5940-6400 cGy	109	0.99 (0.73-1.34)	0.951	
	>5040-5940 cGy	135	0.99 (0.74-1.31)	0.931	
	4500-5040 cGy	186	-	-	
Sex	Female	208	0.82 (0.66-1.03)	0.082	0.082
	Male	360	-	-	
Median Income Quartiles 2008-2012	<$38,000	124	1.34 (1.01-1.80)	**0.046**	**0.017**
	$38,000-$47,999	138	1.28 (0.96-1.71)	0.095	
	$48,000-$62,999	135	1.58 (1.19-2.10)	**0.002**	
	$63,000 +	171	-	-	
Charlson-Deyo Score	0	447	0.70 (0.55-0.90)	**0.004**	**0.004**
	1+	121	-	-	
Sequence Number	00	382	0.89 (0.70-1.13)	0.330	0.060
	01	38	0.58 (0.37-0.91)	**0.018**	
	02,03,04,05	148	-	-	
AJCC Clinical Stage Group	Missing	95	1.27 (0.94-1.72)	0.122	**0.001**
	3,4	229	1.55 (1.23-1.97)	**<.001**	
	0,1,2	244	-	-	
Chemotherapy	Chemo Administered, type and numbers of agents unknown	36	1.14 (0.74-1.77)	0.545	0.113
	Single-Agent	90	1.34 (1.01-1.76)	**0.039**	

Covariate	Level	N	Overall Survival		
			Hazard Ratio (95% CI)	HR P-value	Type3 P-value
	Multiagent	442	-	-	
Age at Diagnosis		568	1.01 (1.00-1.02)	**0.029**	**0.029**
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		568	0.97 (0.94-1.00)	0.051	0.051

* Number of observations in the original data set = 586. Number of observations used = 568.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Great Circle Distance (grouped), Facility Location, Facility Type, Grade, Histology, Primary Payor, Median Income Quartiles 2000, Race, Regional Treatment Modality, AJCC Clinical N, AJCC Clinical T, Tumor Size (cm) (quartile), Urban/Rural 2003, and Year of Diagnosis (quartile).

Table 4b: Multivariable Logistic Regression of Total Radiation Dose Group (Highest vs Rest)

			Total Radiation Dose=>6400-7020 cGy (highest dose group)		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Sex	Female	190	1.40 (0.91-2.16)	0.130	0.130
	Male	337	-	-	
Facility Type	Academic	236	0.66 (0.43-1.02)	0.063	0.063
	Non-Academic	291	-	-	
Facility Location	Northeast	122	1.59 (0.77-3.29)	0.214	**0.005**
	South	162	2.52 (1.26-5.06)	0.009	
	Midwest	159	1.02 (0.50-2.10)	0.956	
	West	84	-	-	
Urban/Rural 2003	Metro	447	0.62 (0.15-2.63)	0.517	**0.027**
	Urban	69	1.41 (0.32-6.25)	0.652	
	Rural	11	-	-	
Primary Payor	Private	153	4.15 (0.89-19.33)	0.070	0.116
	Medicaid	64	2.01 (0.39-10.52)	0.407	
	Medicare/Other Government	289	3.31 (0.72-15.22)	0.124	
	Not Insured/Unknown	21	-	-	
Median Income Quartiles 2000	< $30,000	75	0.48 (0.22-1.05)	0.065	0.061
	$30,000 - $35,999	115	1.41 (0.79-2.49)	0.245	
	$36,000 - $45,999	134	1.01 (0.58-1.76)	0.972	
	$46,000 +	203	-	-	

Covariate	Level	N	Total Radiation Dose=>6400-7020 cGy (highest dose group) Odds Ratio (95% CI)	OR P-value	Type3 P-value
Regional Treatment Modality	External beam,NOS; Other,NOS; Photons(All); Protons;	247	0.58 (0.38-0.91)	0.017	**0.009**
	Conformal or 3-D Therapy	48	0.30 (0.11-0.81)	0.018	
	IMRT	232	-	-	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Age at Diagnosis, Charlson-Deyo Score, Great Circle Distance (grouped), Grade, Histology, Median Income Quartiles 2008-2012, Race, Chemotherapy, Sequence Number, AJCC Clinical N, AJCC Clinical Stage Group, AJCC Clinical T, Tumor Size (cm) (quartile),
Year of Diagnosis (quartile), and Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment.

Stratified Analysis

Table 5a: Multivariable Survival Analysis Stratified by Radiation Modality

Covariate	Level	N	Overall Survival: Hazard Ratio (95% CI)	Overall Survival: HR P-value	Overall Survival: Type3 P-value
Comparisons Stratified by Regional Treatment Modality :	**Total Radiation Dose :**		-	-	0.221
Conformal or 3-D Therapy;External beam,NOS; Other,NOS; Photons(All); Protons;	>5040-5940 cGy vs. 4500-5040 cGy	80 vs. 105	1.28 (0.87-1.88)	0.218	-
	>5940-6400 cGy vs. 4500-5040 cGy	53 vs. 105	1.43 (0.93-2.19)	0.099	
	>6400-7020 cGy vs. 4500-5040 cGy	57 vs. 105	0.83 (0.53-1.30)	0.417	
IMRT	>5040-5940 cGy vs. 4500-5040 cGy	45 vs. 65	0.76 (0.46-1.27)	0.298	-
	>5940-6400 cGy vs. 4500-5040 cGy	48 vs. 65	0.77 (0.47-1.24)	0.283	
	>6400-7020 cGy vs. 4500-5040 cGy	74 vs. 65	0.56 (0.36-0.89)	**0.015**	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical Stage Group, Age at Diagnosis, Charlson-Deyo Score, Chemotherapy, Facility Location, Facility Type, Great Circle Distance (grouped), Histology, Median Income Quartiles 2000, Median Income Quartiles 2008-2012, Primary Payor, Race, Radiation, Weeks from Dx, Sequence Number, Sex, Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment, Tumor Size (cm) (quartile), Urban/Rural 2003, Year of Diagnosis (quartile)

Figure 3a: Stratified Kaplan-Meier Plot by Radiation Modality

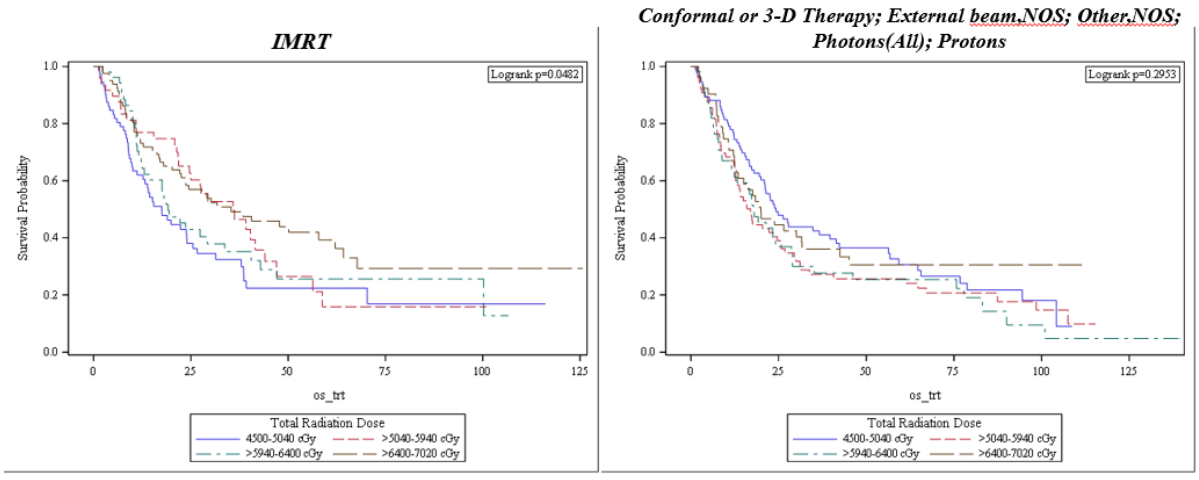


Table 5b: Multivariable Survival Analysis Stratified by Facility Type

Covariate	Level	N	Overall Survival Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Facility Type :	**Total Radiation Dose :**		-	-	0.912
Non-Academic	>5040-5940 cGy vs. 4500-5040 cGy	51 vs. 101	1.13 (0.72-1.77)	0.583	-
	>5940-6400 cGy vs. 4500-5040 cGy	57 vs. 101	1.20 (0.78-1.84)	0.408	
	>6400-7020 cGy vs. 4500-5040 cGy	82 vs. 101	0.79 (0.52-1.21)	0.277	
Academic	>5040-5940 cGy vs. 4500-5040 cGy	74 vs. 69	0.98 (0.64-1.49)	0.910	-
	>5940-6400 cGy vs. 4500-5040 cGy	44 vs. 69	0.99 (0.61-1.60)	0.969	
	>6400-7020 cGy vs. 4500-5040 cGy	49 vs. 69	0.65 (0.40-1.06)	0.083	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical Stage Group, Age at Diagnosis, Charlson-Deyo Score, Chemotherapy, Facility Location, Great Circle Distance (grouped), Histology, Median Income Quartiles 2000, Median Income Quartiles 2008-2012, Primary Payor, Race, Radiation, Weeks from Dx, Regional Treatment Modality, Sequence Number, Sex, Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment, Tumor Size (cm) (quartile), Urban/Rural 2003, Year of Diagnosis (quartile)

Figure 3b: Stratified Kaplan-Meier Plot by Facility Type

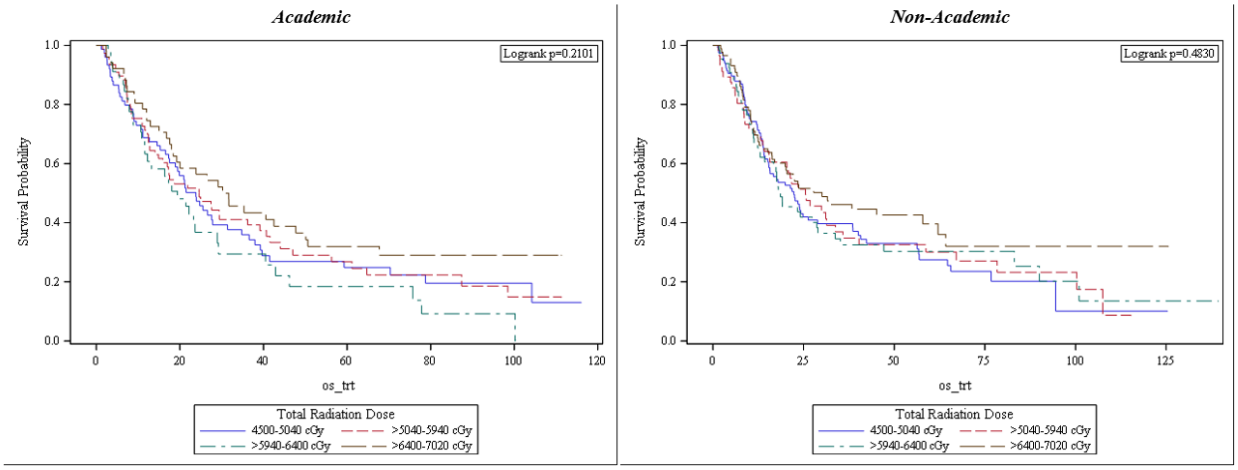


Table 5c: Multivariable Survival Analysis Stratified by AJCC Clinical N

			Overall Survival		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by AJCC Clinical N :	**Total Radiation Dose :**		-	-	0.147
AJCC Clinical N 0-1	>5040-5940 cGy vs. 4500-5040 cGy	106 vs. 140	1.00 (0.71-1.40)	0.981	-
	>5940-6400 cGy vs. 4500-5040 cGy	86 vs. 140	0.95 (0.66-1.37)	0.786	
	>6400-7020 cGy vs. 4500-5040 cGy	112 vs. 140	0.64 (0.45-0.92)	**0.015**	
AJCC Clinical N 2-3	>5040-5940 cGy vs. 4500-5040 cGy	5 vs. 7	2.93 (0.61-14.03)	0.179	-
	>5940-6400 cGy vs. 4500-5040 cGy	9 vs. 7	3.16 (0.80-12.48)	0.100	
	>6400-7020 cGy vs. 4500-5040 cGy	9 vs. 7	1.00 (0.23-4.34)	0.999	
Missing	>5040-5940 cGy vs. 4500-5040 cGy	14 vs. 23	1.05 (0.46-2.41)	0.909	-
	>5940-6400 cGy vs. 4500-5040 cGy	6 vs. 23	2.39 (0.86-6.66)	0.095	
	>6400-7020 cGy vs. 4500-5040 cGy	10 vs. 23	1.77 (0.72-4.34)	0.213	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical Stage Group, Age at Diagnosis, Charlson-Deyo Score, Chemotherapy, Facility Location, Facility Type, Great Circle Distance (grouped), Histology, Median Income Quartiles 2000, Median Income Quartiles 2008-2012, Primary Payor, Race, Radiation, Weeks from Dx, Regional Treatment Modality, Sequence Number, Sex, Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment, Tumor Size (cm) (quartile), Urban/Rural 2003, Year of Diagnosis (quartile)

Figure 3c: Stratified Kaplan-Meier Plot by AJCC Clinical N

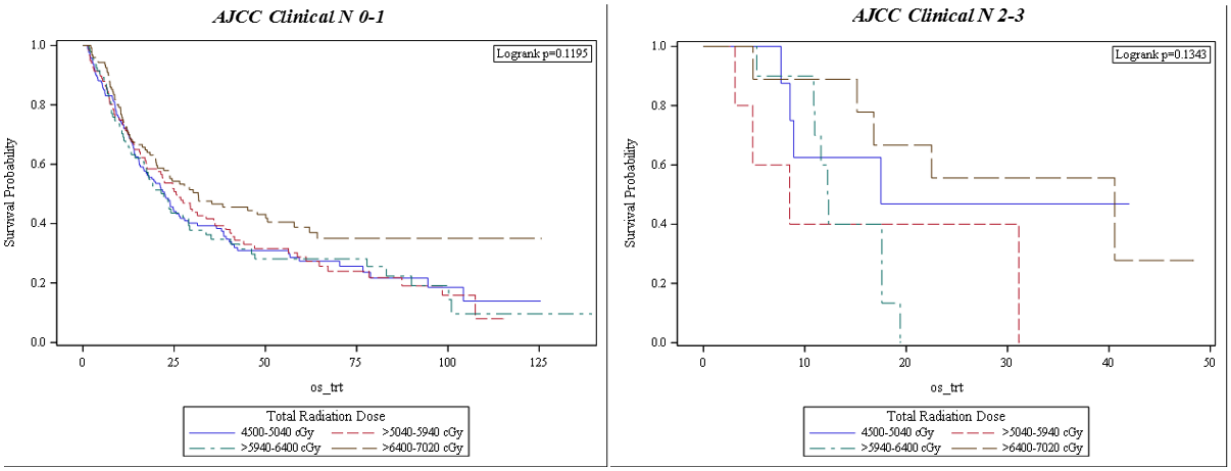


Table 5d: Multivariable Survival Analysis Stratified by Tumor Size

Covariate	Level	N	Overall Survival		
			Hazard Ratio (95% CI)	HR P-value	Type3 P-value
Comparisons Stratified by Tumor Size (cm) (grouped) :	**Total Radiation Dose :**		-	-	0.068
<4.00	>5040-5940 cGy vs. 4500-5040 cGy	39 vs. 43	1.36 (0.77-2.39)	0.285	-
	>5940-6400 cGy vs. 4500-5040 cGy	21 vs. 43	1.09 (0.56-2.10)	0.806	
	>6400-7020 cGy vs. 4500-5040 cGy	38 vs. 43	1.12 (0.62-2.02)	0.705	
>=4.00	>5040-5940 cGy vs. 4500-5040 cGy	41 vs. 50	1.61 (0.92-2.81)	0.095	-
	>5940-6400 cGy vs. 4500-5040 cGy	33 vs. 50	1.84 (1.03-3.29)	**0.041**	
	>6400-7020 cGy vs. 4500-5040 cGy	46 vs. 50	0.76 (0.43-1.35)	0.353	
Missing	>5040-5940 cGy vs. 4500-5040 cGy	45 vs. 77	0.67 (0.42-1.07)	0.094	-
	>5940-6400 cGy vs. 4500-5040 cGy	47 vs. 77	0.80 (0.51-1.26)	0.337	
	>6400-7020 cGy vs. 4500-5040 cGy	47 vs. 77	0.56 (0.34-0.92)	**0.021**	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical Stage Group, Age at Diagnosis, Charlson-Deyo Score, Chemotherapy, Facility Location, Facility Type, Great Circle Distance (grouped), Histology, Median Income Quartiles 2000, Median Income Quartiles 2008-2012, Primary Payor, Race, Radiation, Weeks from Dx, Regional Treatment Modality, Sequence Number, Sex, Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment, Urban/Rural 2003, Year of Diagnosis (quartile)

Figure 3d: Stratified Kaplan-Meier Plot by Tumor Size

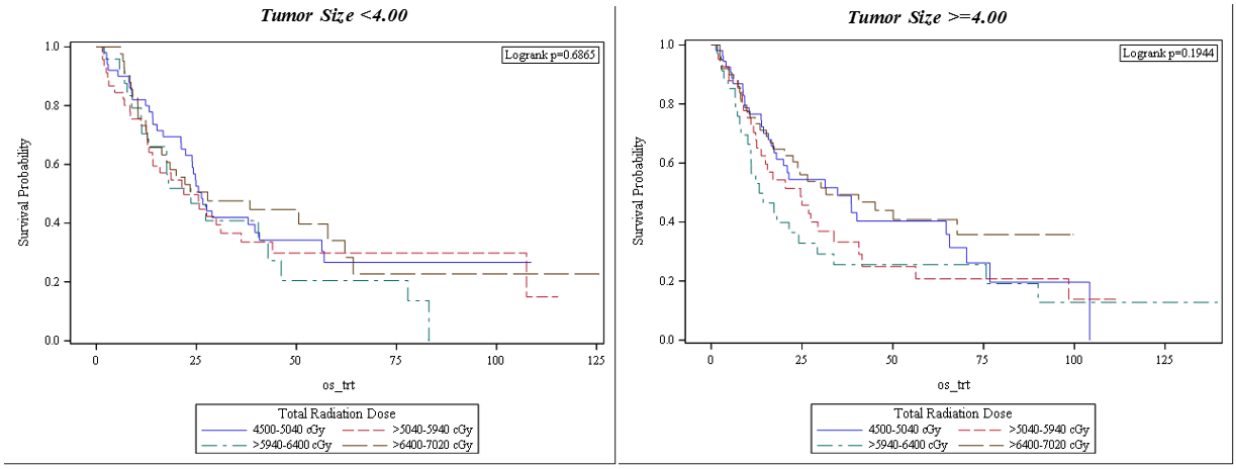


Table 5e: Multivariable Survival Analysis Stratified by Age (Median)

			Overall Survival		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Comparisons Stratified by Age at Diagnosis (grouped) :	**Total Radiation Dose :**		-	-	0.886
<67.00	>5040-5940 cGy vs. 4500-5040 cGy	61 vs. 79	1.03 (0.66-1.61)	0.886	-
	>5940-6400 cGy vs. 4500-5040 cGy	48 vs. 79	1.03 (0.64-1.65)	0.904	
	>6400-7020 cGy vs. 4500-5040 cGy	65 vs. 79	0.65 (0.41-1.04)	0.071	
>=67.00	>5040-5940 cGy vs. 4500-5040 cGy	64 vs. 91	1.10 (0.73-1.65)	0.646	-
	>5940-6400 cGy vs. 4500-5040 cGy	53 vs. 91	1.21 (0.78-1.87)	0.393	
	>6400-7020 cGy vs. 4500-5040 cGy	66 vs. 91	0.83 (0.54-1.29)	0.415	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.
*** The estimated stratified treatement effect was controlled by: AJCC Clinical Stage Group, Charlson-Deyo Score, Chemotherapy, Facility Location, Facility Type, Great Circle Distance (grouped), Histology, Median Income Quartiles 2000, Median Income Quartiles 2008-2012, Primary Payor, Race, Radiation, Weeks from Dx, Regional Treatment Modality, Sequence Number, Sex, Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment, Tumor Size (cm) (quartile), Urban/Rural 2003, Year of Diagnosis (quartile)

Figure 3e: Stratified Kaplan-Meier Plot by Age (Median)

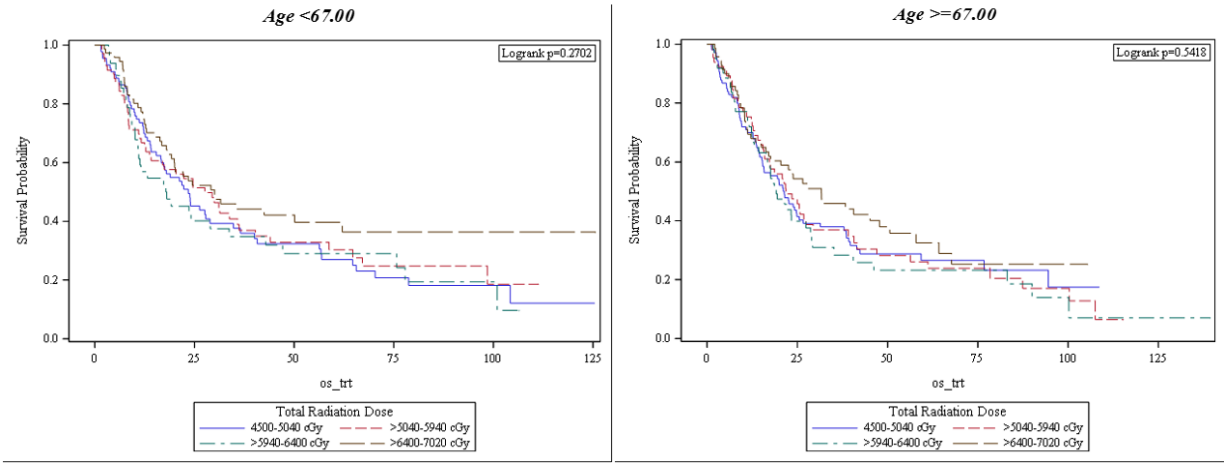
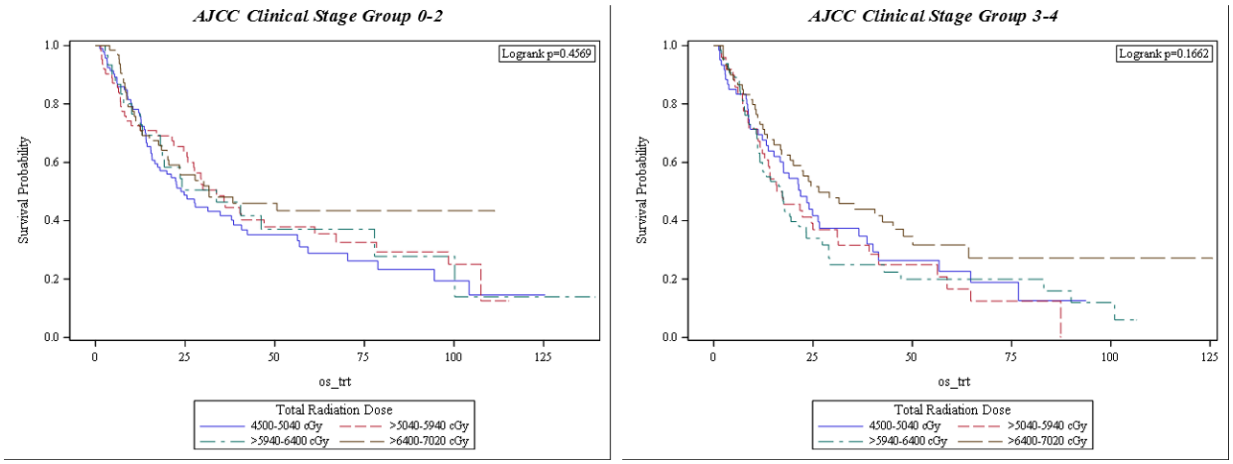


Table 5f: Multivariable Survival Analysis Stratified by AJCC Clinical Stage Group

Covariate	Level	N	Overall Survival: Hazard Ratio (95% CI)	Overall Survival: HR P-value	Overall Survival: Type3 P-value
Comparisons Stratified by AJCC Clinical Stage Group :	**Total Radiation Dose :**		-	-	0.654
AJCC Clinical Stage Group 0-2	>5040-5940 cGy vs. 4500-5040 cGy	60 vs. 84	1.00 (0.65-1.56)	0.983	-
	>5940-6400 cGy vs. 4500-5040 cGy	27 vs. 84	0.90 (0.51-1.57)	0.702	
	>6400-7020 cGy vs. 4500-5040 cGy	58 vs. 84	0.69 (0.43-1.12)	0.134	
AJCC Clinical Stage Group 3-4	>5040-5940 cGy vs. 4500-5040 cGy	43 vs. 52	1.00 (0.58-1.70)	0.988	-
	>5940-6400 cGy vs. 4500-5040 cGy	62 vs. 52	1.06 (0.65-1.73)	0.828	
	>6400-7020 cGy vs. 4500-5040 cGy	55 vs. 52	0.59 (0.35-0.99)	**0.047**	
Missing	>5040-5940 cGy vs. 4500-5040 cGy	22 vs. 34	1.18 (0.60-2.31)	0.628	-
	>5940-6400 cGy vs. 4500-5040 cGy	12 vs. 34	1.56 (0.68-3.55)	0.291	
	>6400-7020 cGy vs. 4500-5040 cGy	18 vs. 34	1.36 (0.65-2.87)	0.416	

* Number of observations in the original data set = 586. Number of observations used = 527.
** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.
*** The estimated stratified treatement effect was controlled by: Age at Diagnosis, Charlson-Deyo Score, Chemotherapy, Facility Location, Facility Type, Great Circle Distance (grouped), Histology, Median Income Quartiles 2000, Median Income Quartiles 2008-2012, Primary Payor, Race, Radiation, Weeks from Dx, Regional Treatment Modality, Sequence Number, Sex, Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment, Tumor Size (cm) (quartile), Urban/Rural 2003, Year of Diagnosis (quartile)

Figure 3f: Stratified Kaplan-Meier Plot by AJCC Clinical Stage Group



Propensity Score Analysis

Table 6: Balance Check after Propensity Score Matching

Covariate	Level	Statistics	Total Radiation Dose		Parametric P-value*	Standardized Difference
			4500-6400 cGy (lower three dose groups) N=136	>6400-7020 cGy (highest dose group) N=136		
Sex	Male	N (Col%)	71 (52.21)	80 (58.82)	0.272	**0.133**
	Female	N (Col%)	65 (47.79)	56 (41.18)		**0.133**
Median Income Quartiles 2008-2012	<$38,000	N (Col%)	26 (19.12)	26 (19.12)	0.851	0.000
	$38,000-$47,999	N (Col%)	31 (22.79)	37 (27.21)		**0.102**
	$48,000-$62,999	N (Col%)	39 (28.68)	37 (27.21)		0.033
	$63,000 +	N (Col%)	40 (29.41)	36 (26.47)		0.066
Charlson-Deyo Score	0	N (Col%)	111 (81.62)	106 (77.94)	0.450	0.092
	1+	N (Col%)	25 (18.38)	30 (22.06)		0.092
Sequence Number	00	N (Col%)	90 (66.18)	94 (69.12)	0.851	0.063
	01	N (Col%)	10 (7.35)	10 (7.35)		0.000
	02,03,04,05	N (Col%)	36 (26.47)	32 (23.53)		0.068
AJCC Clinical Stage Group	0,1,2	N (Col%)	60 (44.12)	61 (44.85)	0.904	0.015
	3,4	N (Col%)	60 (44.12)	57 (41.91)		0.045
	Missing	N (Col%)	16 (11.76)	18 (13.24)		0.044
Chemotherapy	Chemo Administered, type and numbers of agents unknown	N (Col%)	7 (5.15)	8 (5.88)	0.908	0.032
	Single-Agent	N (Col%)	23 (16.91)	25 (18.38)		0.039
	Multiagent	N (Col%)	106 (77.94)	103 (75.74)		0.052
Age at Diagnosis		Mean (Std)	65.7 (10.61)	65.92 (11.42)	0.869	0.020
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		Mean (Std)	5.5 (3.52)	5.29 (3.64)	0.625	0.059

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

Table 7a: Balance check after Inverse Probability of Treatment Weighting

Covariate	Level	Statistics	Total Radiation Dose		Parametric P-value*	Standardized Difference
			4500-6400 cGy (lower three dose groups) N=430	>6400-7020 cGy (highest dose group) N=138		
Sex	Male	N (Col%)	271 (63.23)	86 (62.27)	0.839	0.020
	Female	N (Col%)	158 (36.77)	52 (37.73)		0.020
Median Income Quartiles 2008-2012	<$38,000	N (Col%)	93 (21.83)	29 (21.69)	0.995	0.003
	$38,000-$47,999	N (Col%)	104 (24.43)	34 (25.14)		0.017
	$48,000-$62,999	N (Col%)	101 (23.58)	31 (22.58)		0.024
	$63,000 +	N (Col%)	129 (30.17)	42 (30.58)		0.009
Charlson-Deyo Score	0	N (Col%)	338 (78.71)	109 (78.95)	0.950	0.006
	1+	N (Col%)	91 (21.29)	29 (21.05)		0.006
Sequence Number	00	N (Col%)	288 (67.09)	90 (65.24)	0.919	0.039
	01	N (Col%)	28 (6.69)	9 (6.85)		0.006
	02,03,04,05	N (Col%)	112 (26.22)	38 (27.91)		0.038
AJCC Clinical Stage Group	0,1,2	N (Col%)	184 (43.02)	60 (43.59)	0.982	0.011
	3,4	N (Col%)	172 (40.21)	54 (39.31)		0.018
	Missing	N (Col%)	72 (16.77)	23 (17.11)		0.009
Chemotherapy	Chemo Administered, type and numbers of agents unknown	N (Col%)	27 (6.37)	9 (6.78)	0.984	0.017
	Single-Agent	N (Col%)	67 (15.8)	21 (15.54)		0.007
	Multiagent	N (Col%)	334 (77.83)	107 (77.68)		0.004
Age at Diagnosis		Mean (Std)	66.3 (11.32)	66.33 (11.42)	0.982	0.002
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		Mean (Std)	5.31 (3.43)	5.34 (4.13)	0.912	0.011

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

Figure 4: Kaplan-Meier Plot for Overall Survival with IPTW

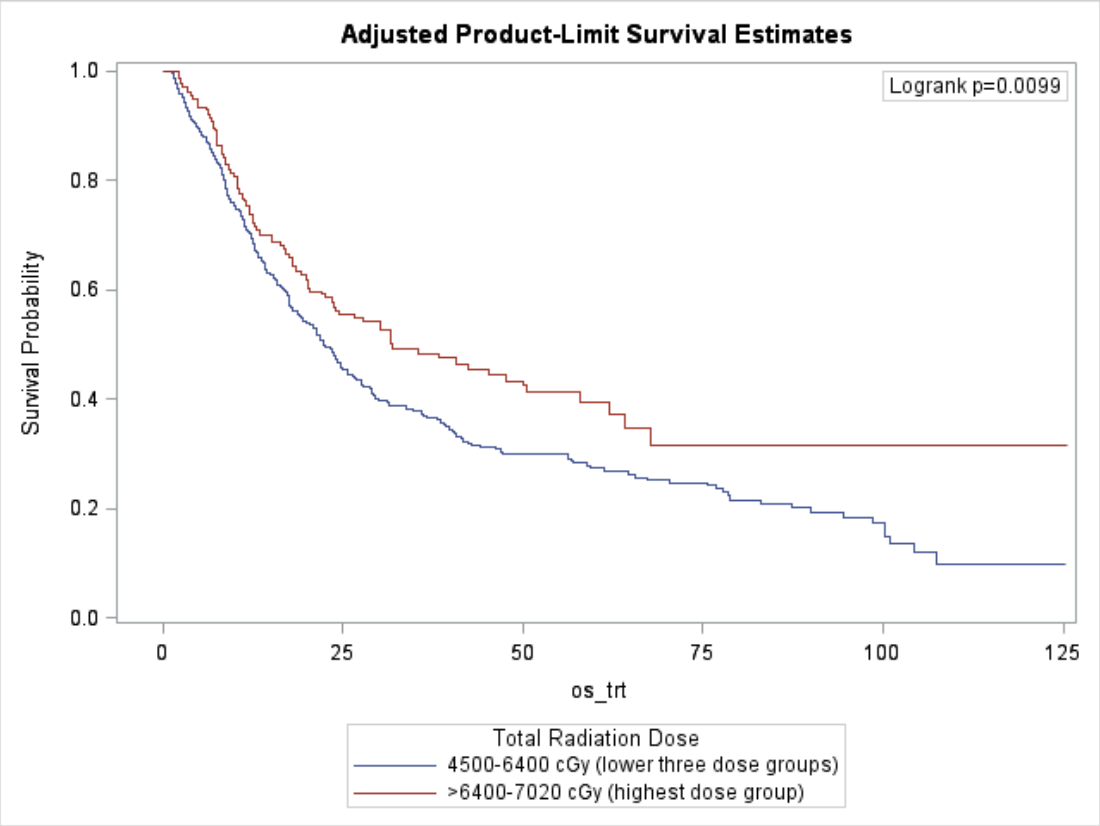


Table 7b: Cox-PH Model for Overall Survival with IPTW

			Overall Survival	
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Total Radiation Dose	>6400-7020 cGy (highest dose group)	138	0.71 (0.56-0.92)	**0.008**
	4500-6400 cGy (lower three dose groups)	430	-	-

Analysis was weighted by variable: adj_sipw

Table 8a-1: Balance Check for the Continuous Generalized Propensity Score – Half 1

Covariate	Level	Statistics	Total Radiation Dose 4500-5040 cGy N=121	>5040-5940 cGy N=63	>5940-6400 cGy N=36	>6400-7020 cGy N=64	Parametric P-value*	Standardized Difference
Sex	Male	N (Col%)	68 (56.2)	44 (69.84)	23 (63.89)	35 (54.69)	0.236	**0.317**
	Female	N (Col%)	53 (43.8)	19 (30.16)	13 (36.11)	29 (45.31)		**0.317**
Charlson-Deyo Score	0	N (Col%)	94 (77.69)	53 (84.13)	28 (77.78)	50 (78.13)	0.756	**0.164**
	1+	N (Col%)	27 (22.31)	10 (15.87)	8 (22.22)	14 (21.88)		**0.164**
Sequence Number	00	N (Col%)	77 (63.64)	42 (66.67)	23 (63.89)	36 (56.25)	0.875	**0.215**
	01	N (Col%)	6 (4.96)	4 (6.35)	1 (2.78)	4 (6.25)		**0.172**
	02,03,04,05	N (Col%)	38 (31.4)	17 (26.98)	12 (33.33)	24 (37.5)		**0.226**
Median Income Quartiles 2008-2012	<$38,000	N (Col%)	25 (20.66)	16 (25.4)	10 (27.78)	14 (21.88)	0.380	**0.167**
	$38,000-$47,999	N (Col%)	30 (24.79)	13 (20.63)	7 (19.44)	23 (35.94)		**0.375**
	$48,000-$62,999	N (Col%)	33 (27.27)	15 (23.81)	5 (13.89)	11 (17.19)		**0.336**
	$63,000 +	N (Col%)	33 (27.27)	19 (30.16)	14 (38.89)	16 (25)		**0.301**
AJCC Clinical Stage Group	0,1,2	N (Col%)	84 (69.42)	45 (71.43)	23 (63.89)	46 (71.88)	0.856	**0.172**
	3,4	N (Col%)	3 (2.48)	0 (0)	1 (2.78)	2 (3.13)		**0.254**
	Missing	N (Col%)	34 (28.1)	18 (28.57)	12 (33.33)	16 (25)		**0.184**
Chemotherapy	Chemo Administered, type and numbers of agents unknown	N (Col%)	10 (8.26)	5 (7.94)	2 (5.56)	3 (4.69)	0.246	**0.146**
	Single-Agent	N (Col%)	0 (0)	0 (0)	1 (2.78)	0 (0)		**0.239**
	Multiagent	N (Col%)	111 (91.74)	58 (92.06)	33 (91.67)	61 (95.31)		**0.148**
Age at Diagnosis		Mean (Std)	68.33 (11.03)	66.62 (10.67)	68.61 (11.29)	65.3 (11.9)	0.285	**0.291**
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		Mean (Std)	5.34 (3.58)	5.01 (2.66)	5.03 (3.69)	5.4 (3.78)	0.888	**0.114**

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

Table 8a-2: Balance Check for the Continuous Generalized Propensity Score – Half 2

			Total Radiation Dose					
Covariate	**Level**	**Statistics**	**4500-5040 cGy N=65**	**>5040-5940 cGy N=72**	**>5940-6400 cGy N=73**	**>6400-7020 cGy N=74**	**Parametric P-value***	**Standardized Difference**
Sex	Male	N (Col%)	40 (61.54)	49 (68.06)	55 (75.34)	46 (62.16)	0.263	**0.300**
	Female	N (Col%)	25 (38.46)	23 (31.94)	18 (24.66)	28 (37.84)		**0.300**
Charlson-Deyo Score	0	N (Col%)	51 (78.46)	54 (75)	59 (80.82)	58 (78.38)	0.866	**0.141**
	1+	N (Col%)	14 (21.54)	18 (25)	14 (19.18)	16 (21.62)		**0.141**
Sequence Number	00	N (Col%)	50 (76.92)	46 (63.89)	48 (65.75)	60 (81.08)	**0.004**	**0.392**
	01	N (Col%)	2 (3.08)	12 (16.67)	3 (4.11)	6 (8.11)		**0.468**
	02,03,04,05	N (Col%)	13 (20)	14 (19.44)	22 (30.14)	8 (10.81)		**0.493**
Median Income Quartiles 2008-2012	<$38,000	N (Col%)	20 (30.77)	10 (13.89)	17 (23.29)	12 (16.22)	**0.019**	**0.414**
	$38,000-$47,999	N (Col%)	15 (23.08)	21 (29.17)	15 (20.55)	14 (18.92)		**0.242**
	$48,000-$62,999	N (Col%)	8 (12.31)	14 (19.44)	21 (28.77)	28 (37.84)		**0.616**
	$63,000 +	N (Col%)	22 (33.85)	27 (37.5)	20 (27.4)	20 (27.03)		**0.225**
AJCC Clinical Stage Group	0,1,2	N (Col%)	7 (10.77)	17 (23.61)	6 (8.22)	16 (21.62)	0.055	**0.430**
	3,4	N (Col%)	54 (83.08)	49 (68.06)	64 (87.67)	56 (75.68)		**0.486**
	Missing	N (Col%)	4 (6.15)	6 (8.33)	3 (4.11)	2 (2.7)		**0.248**
Chemotherapy	Chemo Administered, type and numbers of agents unknown	N (Col%)	2 (3.08)	2 (2.78)	7 (9.59)	5 (6.76)	0.127	**0.286**
	Single-Agent	N (Col%)	15 (23.08)	28 (38.89)	19 (26.03)	27 (36.49)		**0.347**
	Multiagent	N (Col%)	48 (73.85)	42 (58.33)	47 (64.38)	42 (56.76)		**0.365**
Age at Diagnosis		Mean (Std)	63.18 (11.64)	65.58 (11.93)	65.79 (11.04)	66.34 (10.93)	0.387	**0.278**
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment		Mean (Std)	5.69 (3.68)	4.68 (2.6)	5.64 (3.91)	5.53 (4.76)	0.354	**0.286**

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

Table 8b: Overall Survival with Covariate Adjustment by the Continuous Generalized Propensity Score

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	
GPS	1	0.00115	0.0003620	10.1755	0.0014	1.001	1.000	1.002
Total Radiation Dose (Gy)	1	-0.01697	0.00754	5.0647	0.0244	0.983	0.969	0.998

Table 9a: Balance Check for the Ordinal Generalized Propensity Score

Covariate	Statistic	Association with Total Radiation Dose Group	
		Before PS Adjustment	**After PS Adjustment**
Sex	P-Value	0.5396	0.1415
Charlson-Deyo Score	P-Value	0.9387	0.9137
Sequence Number	P-Value	0.8577	0.6939
Median Income Quartiles 2008-2012	P-Value	0.3001	0.2665
AJCC Clinical Stage Group	P-Value	0.7504	0.9651
Chemotherapy	P-Value	0.0412	0.3417
Age at Diagnosis	P-Value	0.7409	0.9445
Time Lag, Weeks from Dx to Radiation or Chemotherapy Treatment	P-Value	0.7507	0.2375

Table 9b: Overall Survival with Covariate Adjustment by the Ordinal Generalized Propensity Score

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Total Radiation Dose >6400-7020 cGy	1	-0.31255	0.14572	4.6001	0.0320	0.732	0.550	0.973
Total Radiation Dose >5940-6400 cGy	1	0.08893	0.14974	0.3527	0.5526	1.093	0.815	1.466
Total Radiation Dose >5040-5940 cGy	1	-0.04347	0.14114	0.0948	0.7581	0.957	0.726	1.263
Independent Probability of >6400-7020 cGy	1	-5.89700	14.06193	0.1759	0.6750	0.003	0.000	2.5615E9
Independent Probability of >5940-6400 cGy	1	8.58282	11.23935	0.5831	0.4451	5339.128	0.000	1.97E13
Independent Probability of >5040-5940 cGy	1	-2.53612	5.65095	0.2014	0.6536	0.079	0.000	5113.008