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Kelli O'Connell Date

Propensity Score Matched Analysis to Compare the Effectiveness of Proton Therapy Versus Photon-Based Radiation for Non-Small Cell Lung Cancer Patients Based on National Cancer Database

By

Kelli O'Connell
Master of Science in Public Health
Biostatistics

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Yuan Liu, PhD
Thesis Advisor

_____

Kristin Higgins, MD
Reader

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By

Kelli O'Connell
B.A.
Wesleyan University
2011

Thesis Committee Chair: Yuan Liu, PhD

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Abstract

Propensity Score Matched Analysis to Compare the Effectiveness of Proton Therapy Versus Photon-Based Radiation for Non-Small Cell Lung Cancer Patients Based on National Cancer Database

By Kelli O'Connell

Introduction: Lung cancer is the leading cause of cancer death among adults in the United States. Theory suggests that proton beam therapy may provide benefits over conventional photon-based radiotherapies (external beam radiation, 3D Conformal radiotherapy, intensity-modulated radiation therapy, etc.) due to the lower dose of radiation delivered to healthy tissue. It is not known whether these dosimetric benefits translate into clinical benefits.

Methods: Cases with Stage I-IV non-small cell lung cancer (NSCLC) who received some form of external beam radiation directed to the lung or chest and who were not missing data on primary outcomes were extracted from the National Cancer Database (NCDB). Descriptive and univariate statistics were calculated for all variables. A multivariable Cox proportional hazards model was used to compare overall survival in two cohorts—one receiving proton therapy and one receiving photon-based radiation therapy—after controlling for socio-demographic, facility-level, and disease characteristics. Propensity score matching was performed to reduce confounding. A univariate Cox proportional hazards model was used to compare overall survival in the two matched cohorts. Stratified analyses were performed to investigate possible interaction between covariates and treatment group.

Results: There were 243,822 NSCLC (348 proton and 243,474 non-proton) cases included in the analysis. Patients who were treated at academic centers, in the west, on government insurance, and were wealthier were more likely to receive proton therapy (all $p < 0.001$). The multivariate Cox proportional hazards model suggested that non-proton patients were at a significantly higher risk of death compared to proton patients (HR = 1.21, $p = 0.005$). Propensity score matching yielded two cohorts of 308 patients each. A univariate Cox proportional hazards model comparing the two matched cohorts indicated to no significant differences in risk of death (HR = 1.16, $p = 0.12$). Stratified analyses suggested that proton therapy may be more beneficial for those who had more comorbidities, had adenocarcinoma histology, received chemotherapy, and were treated at academic centers.

Conclusion: Results suggest that there may be some clinical benefit to receiving proton therapy compared to conventional forms of radiation therapy. Randomized, controlled clinical trials are still needed to further confirm the advantages of proton therapy.

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Introduction

Lung cancer is the most common cause of cancer death in the United States. It accounts for about 27% of all cancer deaths and there were an estimated 221,200 new cases and 158,040 deaths due to lung cancer in 2015 alone (American Cancer Society, 2015a). Lung cancer occurs when normal cells in the bronchi or in other parts of the lung such as the bronchioles or alveoli acquire genetic mutations that cause them to grow abnormally fast. Eventually, a malignant tumor forms from the uncontrolled cell growth. There are two main types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), named for their relative sizes as seen under a microscope. NSCLC comprises about 85% to 90% of lung cancer cases and is the focus of this research (American Cancer Society, 2015b). NSCLC is divided into three main subtypes: squamous cell (epidermoid) carcinoma, adenocarcinoma, and large cell (undifferentiated) carcinoma. Squamous cell carcinomas make up 25% to 30% of all lung cancers and typically start in the squamous cells, which are flat cells inside the airways of the lungs (American Cancer Society, 2015b). These cancers are typically found in the middle of the lungs near a bronchus. Adenocarcinomas are the most common form of lung cancer, comprising about 40% of all lung cancer cases. They normally start in mucus-secreting cells on the outer parts of the lung and tend to have slower growth rates than other lung cancer types. Large cell carcinoma accounts for about 10% to 15% of lung cancers and can appear in any part of the lung (American Cancer Society, 2015b). It typically grows and spreads faster than other types of lung cancer. There are a few other subtypes of NSCLC, but they are much less common.

Treatment of NSCLC mainly depends on the stage of the cancer, but can also be influenced by the patient's overall health and traits of the cancer itself. Stage is determined either

clinically, based on physical exams, biopsies, and imaging tests or pathologically, which combines clinical staging information with results from surgery (American Cancer Society, 2015b). Although the pathological stage is generally more accurate, clinical staging is often used because many NSCLC patients do not have surgery. Treatment of patients with Stage 0 or Stage I cancer usually consists of surgery with occasional adjuvant chemotherapy or radiation therapy for Stage I patients whose cancer has a higher risk of recurrence. Stage II patients are also frequently treated with a combination of surgery and adjuvant chemotherapy and/or radiation therapy. However, due to the large size of lungs and symptoms that overlap with other illnesses, early stage lung cancer is difficult to detect. As a result, most lung cancer cases are diagnosed at Stage III or IV. With Stage III and Stage IV, the cancer has often advanced enough that it generally cannot be cured with surgery. Moreover, centrally located tumors may be too close to critical organs including the heart and great vessels to operate safely. It is estimated that among patients with locally advanced NSCLC, only 15% are candidates for surgery (Méry et al., 2015). Consequently, radiation therapy and chemotherapy are important components of treatment for these patients with locally advanced NSCLC not amenable to surgical resection. Typical long-term survival rates are modest, at approximately 20%, due to high rates of cancer recurrence.

Although some combination chemotherapy and radiation therapy is standard of care for most patients, this study focuses specifically on radiation therapy. Radiation therapy involves the use of high-energy particles or waves to damage the DNA in cancer cells, which causes the cells to die or stop dividing (American Cancer Society, 2015c). Traditional forms of radiation typically use photons or electrons, while a newly emerging form of radiation uses proton beams. There are several different modalities typically associated with conventional radiation therapy methods. External-beam radiation therapy (EBRT) is the most common form of radiation therapy

and is a broad category of treatment that usually involves radiation delivery in the form of photon beams (National Cancer Institute, 2010). One of the most common types of EBRT is 3-D conformal radiation therapy (3D CRT), which uses more sophisticated software and treatment machines to deliver radiation to targeted areas. Modern 3-D conformal therapy has achieved local control rates of 40-60% for locally advanced disease (Chang et al., 2006).Another type of EBRT is intensity-modulated radiation therapy (IMRT), an advanced form of 3-D therapy wherein the shape and intensity of radiation beams can be adjusted to limit the dose reaching healthy tissue (Change et al., 2006). American Cancer Society, 2015b). There is some concern that IMRT "may deliver low yet damaging doses to a larger volume of normal lung tissue" though (Chang et al., 2006). Proton therapy is a newer form of EBRT. Proton therapy differ from other forms of EBRT because protons—unlike the more common photons, x-rays, or electron beams-- deposit most of their energy at the end of their travel path to the treatment target rather than along the way to their target (National Cancer Institute, 2010).

Although radiation therapy has documented therapeutic properties (Perez et al., 1980), there are downsides to traditional radiation therapy as well, particularly in NSCLC. Radiation has many potential side effects such as radiation pneumonitis, pulmonary fibrosis, esophagitis, cardiac toxicity, and secondary malignancies. Patients with NSCLC often have other pulmonary diseases such as Chronic Obstructive Pulmonary Disease, which can mean that they do not have the pulmonary reserve needed to withstand radiation-induced pneumonitis or fibrosis. Radiation therapy can be especially problematic in NSCLC patients because radiation beams are directed to the lungs, which are near other vital organs including the heart. This can lead to cardiac toxicities that decrease survival. In one trial comparing standard dose versus high dose radiotherapy, the high dose arm had shorter survival that was linked to probable cardiopulmonary toxicities

associated with the higher dose (Bradley et al., 2015). Multivariate analyses of the factors associated with overall survival between standard-dose and high-dose radiation have demonstrated that lower heart V5 (the volume of the heart receiving a radiation dose of 5 Grays (Gy) or more) is associated with improved overall survival (Verma et al., 2015). Radiation can also cause secondary malignancies, or occurrence of a second cancer due to the carcinogenic properties of radiation. One study estimated that NSCLC survivors "treated with curative intent develop second primary pulmonary neoplasms at a rate of 1% to 2% per patient-year" (Johnson, 1998). Second primary tumors occurring outside of the lungs are estimated to occur in NSCKC patients at a incidence of 1.8% per patient-year of follow-up (Keller et al., 2003). As a result of these various factors, the highest dose levels of radiation do not result in increased survival, likely because "significant morbidity supervenes after damage to surrounding tissues and offsets any possible benefit of increased local tumor control" (Bonnet et al., 2001).

The emergence of proton therapy has generated a lot of excitement in the field of radiation oncology, as it has the potential to spare healthy tissue better than other radiation modalities. Although scientists have been hypothesizing that proton therapy could provide clinical benefits over traditional radiation since the 1940s, commercial development of proton therapy equipment for clinical purposes did not begin in earnest until the 1990s (Olsen, 2007; Wang, 2015). Since then, the clinical application of proton therapy for the treatment of cancers has grown rapidly: there were only 4 operational proton therapy facilities in the United States in 2005, but it is estimated that there will be 91 operational facilities worldwide by 2020 (Verma, 2015). Proton therapy is distinct from traditional radiation modalities in that its energy beam can be adjusted so that its peak amount of energy can be directed to the tumor being treated, which results in minimal radiation dose delivered to healthy tissue around the tumor. In contrast, photon

and electron radiation cannot be adjusted in this way and therefore will deliver radiation to healthy tissue in front of a tumor (Wang, 2015). Scientists hypothesize that this difference in dose distribution will lead to better tumor conformality and reduced radiation dose to the patient's healthy tissue. In turn, this could reduce radiation-induced secondary malignancies (Wang, 2015).

Thus far, clinical studies seem to support the hypothesis that proton therapy has dosimetric benefits—that the overall radiation dose to a patient is lower than that of traditional radiation (Oshiro et al., 2014; Makita et al., 2015). A study of Stage I and Stage III NSCLC patients showed that proton therapy reduced the radiation dose to normal tissue compared to 3D-Conformal therapy and IMRT (Chang et al., 2006). Another study at the University of Florida Proton Therapy Center showed acceptable toxicity in Stage III NSCLC patients treated with proton therapy and concomitant chemotherapy (Hoppe et al., 2012). A prospective Phase I/II study indicated that it was possible to deliver higher-than-conventional doses of radiation without excess pulmonary toxicity when proton therapy was used (Bonnet et al., 2001). Another study on 51 patients with NSCLC of varying stages showed little late toxicity (Shioyama et al., 2003).

However, there is less clinical data available on whether these dosimetric benefits translate to clinical benefits. One Phase II study of high-dose proton therapy and concurrent chemotherapy showed that this particular treatment regimen was well-tolerated in Stage III NSCLC patients and that the median survival time of 29.4 months was encouraging for inoperable stage III NSCLC (Chang et al., 2011). A retrospective cohort study suggests that proton therapy is not associated with a significantly increased risk of secondary malignancies compared to photon therapy (Chung et al., 2013). Another small cohort study of 27 patients with

Stage III NSCLC yielded 1-year and 2-year rates of local control at 68.1% and 36.4%, respectively, suggesting that proton therapy could be an effective treatment option for this particular patient population (Hatayama et al., 2015). A study with long-term follow-up on 134 Stage II-III inoperable NSCLC patients showed "excellent [overall survival] with tolerable toxicity" (Nguyen et al., 2015). Although most of these studies have promising results regarding the efficacy of proton therapy, many have relatively short follow-up times and lack a randomized, controlled study design. Therefore, it is hard to make definitive conclusions about whether the dosimetric advantages of proton therapy result in better overall survival than more conventional photon-based therapies.

The ambiguity surrounding the therapeutic benefit of proton therapy is concerning because it is quite expensive compared to traditional radiation methods. There are several factors driving the higher costs of proton therapy. First, proton therapy delivery systems are larger compared to traditional radiation therapy delivery systems and also require thick concrete walls surrounding treatment rooms and equipment; as a result, proton therapy centers have to be "designed and built to specifically house the proton therapy equipment" and come with high building expenses (Wang, 2015). The computer software necessary to deliver proton therapy can also be expensive to purchase and maintain, costing several million dollars to install (Wang, 2015). Due to the high building and maintenance costs, there is a higher cost to the patient and their payers as well. It is estimated that Medicare would have to pay about twice as much to treat a prostate cancer patient with proton therapy than with traditional radiation therapy (Emanuel and Pearson, 2012).

With such high costs associated with building and maintaining proton therapy centers, it is important to know whether proton therapy is actually providing a significant clinical benefit to

lung cancer patients. However, there is a lack of high-quality randomized, controlled clinical trials comparing proton therapy to traditional radiation therapy. Much of the research into the comparative effectiveness of proton therapy for NSCLC has been in small, short-term clinical trials, often without a control group. Therefore, this study seeks to investigate the efficacy of proton therapy for the treatment of NSCLC on a larger scale while attempting to control for the socio-demographic and disease characteristics that can also influence overall survival. We will use the National Cancer Database to investigate whether proton therapy is associated with longer survival compared to traditional radiation. By implementing propensity score matching, we hope to reduce the effects of confounding and to provide evidence that addresses the uncertain efficacy of proton therapy.

Methods

Data Source and Study Design

Data were from the National Cancer Database (NCDB), a nationwide oncology outcomes database that captures data on approximately 70% of all new invasive cancer diagnoses in the United States each year (Bilimoria, 2008; National Cancer Database, 2015). The NCDB is a joint project of the American Cancer Society and Commission on Cancer. The NCDB maintains that "the data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator" (Winchester, 2004).

Study Population

The NCDB was queried for histologically confirmed NSCLC cases where NSCLC was the patient's primary cancer (N = 1,163,309). Patients were excluded if their tumor had in-situ behavior, if they were missing date of death or last contact, or if they were missing date of treatment start. The study population was restricted to patients diagnosed between the years of 2004 and 2012, patients who received radiation in the lung or chest, and patients who received Protons, External Beam Not Otherwise Specified (EBRT), 3D Conformal (3D CRT), Photons, or intensity-modulated radiation therapy (IMRT) as their first course of treatment.

Variables/Measurement

Study variables were defined by the Participant User Data File dictionary of the NCDB (available at http://ncdbpufbeta.facs.org/?q=node/259)(National Cancer Database, 2015).

Overall survival was defined as the time from the start of radiation treatment to the time of death or last contact. Treatment variables were categorized two different ways. First, a bivariate indicator variable was used to classify cases as either Proton or Non-Proton. The Proton group consisted of those whose primary treatment modality was listed as Proton in the NCDB. The Non-Proton group consisted of those whose primary treatment modality was one of four types of radiation modalities: External Beam NOS, 3D Conformal, Photons, and IMRT. A second categorical treatment variable was created in order to be able to compare proton therapy to each of the individual radiation modalities. This variable had five categories: proton therapy. External Beam NOS, 3D Conformal, Photons, and IMRT that were again determined based on a patient's primary radiation treatment modality as recorded in the NCDB.

There were eight socio-demographic variables of interest. Facility type was categorized as academic/research program, community cancer program/other, comprehensive community cancer program, and integrated network cancer program. Facility location was designated as Northeast, South, Midwest, and West. Sex consisted of male or female. Race was categorized as White, Black, or Other. Insurance type was classified as private insurance, government insurance (Medicare, Medicaid, and other government insurance), or not insured. Income, education, and urban/rural status were all determined based on data from the 2000 United States Census. Median income was measured in quartiles for the patient's area of residence. Education was measured as percentage of people without high school degrees in the patient's Census tract. Urban/rural status was categorized as urban, rural, or metro.

There were sixteen additional patient-specific disease variables of interest. Comorbidity was represented as a modified Charlson-Deyo (CDCC) score reflecting 15 comorbid conditions where patients are classified as having 0, 1, or 2+ comorbidities (Deyo et al, 1992). Year of diagnosis is the year of diagnosis by a physician for the tumor being reported. Primary site was categorized as main bronchus, upper lobe (lung), middle lobe (lung), lower lobe (lung), overlapping lesion of lung, and lung NOS. Laterality refers to the side of the body on which the tumor originated and is classified as Left, Right, or Other. Grade describes the tumor's resemblance to normal tissue and is characterized as well differentiated, moderately differentiated, poorly differentiated, undifferentiated, or unknown. Surgery was a binary variable indicating whether the patient had surgery. Stage group was classified based on the AJCC Analytic Stage Group as Stage 0, Stage I, Stage II, Stage III, or Stage IV. Analytic stage was determined by pathologic stage if the information available and by clinical stage otherwise. A collapsed stage variable was also created with categories Stage 0/I, Stage II/III, and Stage IV.

Histology was categorized as adenocarcinoma, squamous cell carcinoma, or other. Radiation therapy was coded as beam radiation, combination of beam radiation with radioactive implants or radioisotopes, or radiation therapy NOS. Chemotherapy was a binary variable indicated whether the patient received chemotherapy.

Great circle distance, age at diagnosis, regional dose, number of treatments to this volume, and tumor size were all continuous variables. Great circle distance is the distance in miles from the patient's residence zip code centroid to the hospital street address . Age at diagnosis was measured in years. Regional dose was recorded as the most clinically significant total dose of regional radiation therapy delivered to the patient during the first course of treatment and is measured in centiGray. Number of treatments to this volume records the total number of treatment sessions administered during the first course of treatment. Tumor size was measured in centimeters.

Statistical Analyses

Descriptive statistics were calculated for all variables, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Univariate associations with reception of proton therapy were then calculated for all sociodemographic and clinical variables of interest. For categorical covariates, chi-square tests of independence were conducted to evaluate the unadjusted association between each covariate and reception of proton therapy. Independent t-tests and Analysis of Variance (ANOVA) were performed to evaluate whether there was a difference in the mean of each continuous covariate between the proton and non-proton cohorts and between the proton cohort and each of the individual treatment modality cohorts (External Beam NOS, 3D Conformal, Photons, and

IMRT). Univariate associations with the outcome of interest, overall survival, were also calculated for each covariate.

In order to ascertain which factors were associated with receiving proton therapy, we performed multiple logistic regression to develop a prediction model for receipt of proton therapy. The final prediction model was selected using backwards elimination where first, the proton variable and all covariates of interest were included in the initial model. Then the least significant variable was dropped from the model if its p-value was ≥ 0.05. The process was repeated until there were no more variables for which the p-value was ≥ 0.05. The resulting model was the final predictive model.

Multivariable Cox proportional hazards models were then fitted in order to compare overall survival between the proton and non-proton cohorts adjusting for possible confounding variables. Variables that were significantly associated with reception of proton therapy and overall survival as univariate associations were entered as possible confounders. The socio-demographic and disease-related variables that were included as potential confounders were facility type, facility location, sex, race, insurance type, income, education, urban/rural status, CDCC score, year of diagnosis, primary site, laterality, grade, surgery, stage group (collapsed), histology, chemotherapy, great circle distance, and age at diagnosis. The final Cox model was constructed using backwards elimination with an alpha = 0.20 removal criteria. The main variable of interest (receipt of proton therapy) was forced into the model. Kaplan-Meier plots were produced to compare the survival curves of the proton and non-proton cohorts. This process was repeated to develop multivariable Cox proportional hazards models and KM curves to compare survival between the proton cohort and each of the four individual radiation modalities.

Since the data in this study are observational, there may be inherent differences in the proton and non-proton groups. Consequently, propensity score matching was performed to create a subsample of patients adjusted for all potential confounding variables. A propensity score is defined as the probability of treatment assignment conditional on observed baseline characteristics: $e_i = \Pr(Z_i = 1 \mid X_i)$ (Austin, 2011a; Rosenbaum and Rubin, 1983). It is a balancing score such that conditional on the propensity score, the distribution of observed baseline covariates will be similar between treated and untreated subjects (Austin, 2011a). The score can be used to reduce the effects of confounding when using observational data by calculating propensity scores for each subject and then using one of four methods: propensity score matching, stratification on the score, inverse probability of treatment weighting (IPTW), or regression with covariate adjustment using the propensity score. Applying one of these methods allows one to analyze the observational data as if it were a randomized controlled trial and to estimate treatment effect by directly comparing outcomes between the treatment and control group.

Propensity scores for each case were first estimated using a logistic regression model where proton status was regressed on socio-demographic and patient disease characteristics. We then performed one-to-one propensity score matching, which involved forming matched pairs of proton and non-proton patients who share a similar value of propensity score (Rosenbaum and Rubin, 1983; Austin, 2011a). A greedy matching algorithm was chosen where a proton patient is selected at random. A non-proton patient whose propensity score is closest to this proton patient is then matched to the proton patient. This process is repeated until a match is chosen for all of the proton patients. “Closeness” of propensity score is based on nearest neighbor matching within a specified caliper distance (Rosenbaum and Rubin, 1985). We chose a caliper distance of

0.2 of the standard deviation of the logit of the propensity score, which research has shown minimizes the mean squared error of the estimated treatment effect when estimating differences in means and proportions in observational studies in multiple scenarios (Austin, 2011b).This means that for a selected proton patient, all non-proton patients whose propensity score lays within the specified caliper distance are identified. Within that group, the non-proton patient whose propensity score is closest to that of the proton patient is selected as the match.

Once matching was completed, balancing diagnostics were assessed to check whether the propensity score model was adequately specified. The standardized difference was calculated to compare the mean of continuous and binary variables between the proton and non-proton groups; multilevel categorical variables were compared with a set of multiple binary indicator variables. The standardized difference of a continuous covariate is calculated by:

$$d = \frac{(\bar{x}_{proton} - \bar{x}_{non-proton})}{\sqrt{\frac{s^2{}_{proton} + s^2{}_{non-proton}}{2}}}$$

where "$\bar{x}_{proton}$ and $\bar{x}_{non-proton}$are the sample means for the covariate of interest in the proton and non-proton patients, respectively, and $s^2{}_{proton}$ and $s^2{}_{non-proton}$ are the sample variance for the covariate of interest in the proton and non-proton patients. For binary variables, the standardized difference is calculated by:

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

where $\hat{p}_{proton}$ and $\hat{p}_{non-proton}$ are the prevalence or mean of the variable in proton and non-proton patients (Austin, 2011). In terms of assessing balance, we considered a standardized difference <0.1 to be a negligible difference (Normand et al., 2001; Austin, 2011a). Chi-square

tests and independent t-tests were also conducted to see whether there were significant differences in each of the socio-deomgraphic and disease characteristic covariates.

We then fitted a Cox proportional hazards model and produced Kaplan Meier curves with the resulting matched sample to directly compare survival in the proton and non-proton cohorts. If sufficient balance in the matched cohorts was achieved, the only covariate in the Cox model was the indicator for proton therapy. If the standardized differences were > 0.1 for a variable, this variable was also included in the Cox proportional hazards model. Robust variance estimators were used to account for the matching.

The propensity score calculation and matching steps were then repeated in order to create matched cohorts that compared proton versus each of the individual treatment modalities (i.e. there were four sets of matched cohorts—proton versus External Beam NOS, proton versus 3D Conformal, proton versus Photons, and proton versus IMRT). Proportional hazard models and Kaplan Meier curves were generated to compare survival of the proton group compared to each of the four radiation modalities in the matched sample.

We then explored possible interactions between reception of proton therapy and socio-demographic and disease characteristics. Stratified Cox proportional hazard models were used in the matched sample to generate unadjusted stratum-specific treatment hazard ratios for race, sex, facility type, facility location, insurance, income, education, CDCC score, primary site, laterality, histology, and receipt of chemotherapy. Log-rank tests were used to determine whether there were significant differences in the association between receipt of proton therapy and overall survival among the levels within each of the categorical variables.

All data were analyzed using SAS 9.4 (Cary, NC). Odds ratios (OR) and hazard ratios (HR) are presented with 95% confidence intervals. Hypothesis tests were two-tailed and were evaluated at a significance level of $\alpha = 0.05$.

Results

Descriptive Statistics

After applying the inclusion and exclusion criteria, the final analytic cohort consisted of 243,822 patients (Table 1).The vast majority (99.9%) of patients received traditional photon-based radiation therapy, while 348 patients (0.1%) received proton therapy. Among those who received traditional radiation, the majority (57.5%) received Photons, 18.4% received External Beam radiation, 15% received 3D Conformal, and 9.2% received IMRT. Roughly half (52%) of records were from patients at comprehensive community cancer program, 27.9% were from academic/research programs, 14.1% were from community cancer programs or other, and 6.6% were from an integrated network cancer program. Most patients were treated in the South (39.5%) or the Midwest (29.5%). Male patients comprised 56.8% (N = 138,474) of the sample. Most patients were White (85.7%), while 12.2% were Black and 2.1% were of another race.

The majority of patients had either government insurance (68.2%) or private insurance (28.4%). About a third of patients (32%) lived in census tracts with median income >$46,000, while another 30.1% were from census tracts with median income between $36,000 - $45,999. Just under 29% of patients lived in census tracts where <14% of residents had no high school degree. Less than 20% lived in census tracts where >= 29% of residents had no high school degree. Most patients (78.3%) lived in metro areas. Nearly 62% of patients had a modified Charlson-Deyo score of 0, while 11.4% had a CDCC score of 2 or more. Year of diagnosis was spread fairly evenly between 2004 and 2012. Most patients (87.4%) did not have surgery. About

half of patients (49.8%) had Stage III NSCLC, while 25.3% had Stage IV, 10.0% had Stage II and 14.7% had Stage I. Histology type was almost evenly divided between adenocarcinoma (30.6%), squamous cell carcinoma (37.6%), and other (31.8%). About 68% of patients also received chemotherapy. Mean age at diagnosis was about 68 years.

Univariate Association with Reception of Proton Therapy

Univariate associations between receipt of proton therapy and covariates of interest are presented in Table 2. Patients at academic/research programs, in the West, and with government insurance were significantly more likely to receive proton therapy (all $p < 0.001$). Those in census tracts with the highest median income and with the highest proportion of people with a high school degree or above were significantly more likely to receive proton therapy ($p < 0.001$ and $p = 0.006$, respectively). Patients with Stage 0/I cancer were significantly more likely to receive proton therapy. Patients in the proton group were significantly less likely to receive chemotherapy ($p < 0.001$). Proton patients tended to be slightly older than non-proton patients (60.2 years versus 67.7 years, $p = 0.009$).

Predicting Reception of Proton Therapy

The factors associated with receiving proton therapy after stepwise regression are presented in Table 3. Patients at integrated network cancer programs (OR = 0.14 [0.06, 0.30], $p < 0.001$), comprehensive community cancer programs (OR = 0.34 [0.27, 0.44], $p < 0.001$), and community cancer programs/other (OR = 0.23 [0.14, 0.38], $p < 0.001$), were all significantly less likely to receive proton therapy compared to patients at academic/research programs. Patients whose treatment facility was in the West region had significantly higher odds of receiving proton

therapy compared to those in the Northeast (OR = 0.17 [0.12, 0.23], p < 0.001), South (OR = 0.30 [0.23, 0.39], p < 0.001), and the Midwest (OR = 0.08 [0.05, 0.12], p < 0.001). Patients with private insurance were significantly less likely to receive proton therapy compared to those with government insurance (OR = 0.67 [0.51, 0.87], p = 0.003). Patients living in census tracts with median incomes <$30,000 (OR = 0.67 [0.46, 0.97], p = 0.035) and between $30,000 and $35,999 (OR = 0.63 [0.44, 0.90], p = 0.011) had significantly lower odds of receiving proton therapy compared to those in census tracts with median income >$46,000. Patients in urban areas were significantly less likely to receive proton therapy than those in rural areas (OR = 0.32 [0.12, 0.72], p = 0.006). Patients with Stage II/III (OR = 0.59 [0.45, 0.77], p <0.001) or Stage IV (OR = 0.42 [0.29, 0.59], p < 0.001) cancer were significantly less likely to receive proton therapy compared to patients with Stage 0/I cancer.

Univariate Association with Overall Survival

Univariate associations between overall survival and covariates of interest are presented in Table 4. Proton therapy is associated with significantly longer survival compared to receiving traditional radiation (HR = 1.36 [1.20, 1.55], p < 0.001). When examining the individual radiation modalities, patients receiving Photons (HR = 1.43 [1.26, 1.63], p < 0.001), 3D Conformal (HR = 1.26 [1.11, 1.43], p < 0.001), and External Beam NOS (HR = 1.39 [1.23, 1.58], p < 0.001) all had significantly shorter survival compared to those receiving proton therapy. Academic/research program facility type was associated with significantly longer survival than all other facility types (all p < 0.001). Males had significantly shorter survival compared to females (HR = 1.21 [1.20, 1.22], p <0.001). Patients with government insurance had significantly longer survival compared to those without insurance ($HR_{\text{No Insurance}}$ = 1.04 [1.02,

1.07], p < 0.001), but significantly shorter survival compared to those with private insurance (HR = 0.81 [0.80-0.82], p < 0.001).

Multivariable Association with Overall Survival

The final selected multivariable Cox proportional hazard model for comparing survival in proton versus traditional radiation therapy is presented in Table 5. No covariates were removed during the backwards elimination process. After controlling for socio-demographic and disease characteristics, those receiving traditional radiation therapy were 1.21 [1.06, 1.39] times more likely to die compared to those receiving proton therapy (p = 0.005). The Kaplan Meier curves for these cohorts are presented in Figure 1. The median survival for the proton therapy group was 18.6 [15.1, 21.2] months, while the median survival for the non-proton group was 11.7 [11.7, 11.8] months (log rank p < 0.001). Five-year survival rates are 23.1% [17.4%, 29.3%] for proton therapy patients and 13.5% [13.4%, 13.7%] for non-proton patients.

The final selected multivariable Cox proportional hazard model for comparing survival in proton versus individual radiation treatment modalities is presented in Table 6. Photons (HR = 1.25 [1.09, 1.43], p = 0.001), 3D Conformal (HR = 1.16 [1.01, 1.33], p = 0.035), and External Beam NOS (HR = 1.26 [1.10, 1.44], p < 0.001) all had significantly higher odds of death than proton therapy. There were no significant differences in survival times between IMRT and proton therapy (p = 0.524). The Kaplan Meier curves for these cohorts are presented in Figure 2. The longest median survival time was for the proton therapy group (18.6 [15.1, 21.2] months), followed by IMRT (17 [16.6, 17.4] months) and 3D Conformal (13.3 [13.1, 13.6]). External Beam NOS (11.1 [10.9, 11.3]) and Photons (10.8 [10.7, 10.9]) had the shortest median survival. The five-year survival rate is 23.1% [17.4%, 29.3%] for proton therapy patients, 17.2% [16.6%,

17.9%] for IMRT patients, 14.7% [14.3%, 15.2%] for 3D Conformal patients, 13.5% [13.1%, 13.8%] for External Beam NOS, and 12.6% [12.4%, 12.8%] for photon patients.

Propensity Score Matching

The distribution of the logit of the propensity scores calculated in the non-proton and proton cohorts are shown in Figure 3. The two curves are mostly overlapping, suggesting a common support for the propensity scores in the two cohorts. Matching yielded 2 cohorts (proton and non-proton) of 308 patients (Table 7). Patients in the matched cohorts had similar distributions of socio-demographic and patient disease characteristics, except with regards to urban/rural status, CDCC Score, laterality, histology, and great circle distance. The proton cohort had more Metro patients than the non-proton cohort (Std. Diff. = 0.115), while it had fewer Urban patients compared to the non-proton cohort (Std. Diff. = 0.140). There were more patients with zero comorbidities in the non-proton group (Std. Diff. = 0.135) and more patients with 2 or more comorbidities in the proton group (Std. Diff. = 0.144). A greater proportion of the proton cohort had patients whose tumor originated in the right side of the body compared to the non-proton cohort (Std. Diff. = 0.106). More patients in the proton cohort had adenocarcinoma histology (Std. Diff. = 0.111) and fewer had other histology (Std. Diff. = 0.114) compared to the non-proton cohort. Patients in the non-proton cohort were a greater average distance from their treatment facility compared to the proton cohort (Std. Diff. = 0.124).

Overall Survival in Matched Sample

For the univariate Cox proportional hazards model with the matched sample, those in the proton cohort had a median survival of 18.4 [14.8, 21] months, while those in the non-proton

cohort had a median survival of 13.8 [11.2, 17.2] months (Figure 4). The five-year survival rate for the proton cohort was 22.6% [16.6%, 29.2%] and for the non-proton cohort 16.2% [11.3%, 21.8%]. These differences in survival were not significant—being in the non-proton cohort was not associated with a significantly higher hazard (HR = 1.16 [0.97-1.39], p = 0.108) (Table 8). The results for the multivariable Cox proportional hazards model controlling for urban/rural status, CDCC Score, laterality, histology, and great circle distance are presented in Table 9. After further controlling for these covariates, the non-proton group still did not have a significantly higher hazard of death compared to the proton group (HR = 1.13[0.94-1.39], p = 0.188).

When sub-setting the non-proton cohort by modality type, 305 External Beam NOS patients were matched to 305 proton therapy patients. Results showed that there was no significant difference in survival between External Beam NOS and proton therapy (HR = 1.09 [0.90-1.32], p = 0.36) (Table 10). Median survival was 15 months for the External Beam NOS cohort and 18.4 months for the proton cohort (Figure 5). In the matched sample of proton versus 3D Conformal cohorts (300 patients each), there were also no significant differences in survival (HR = 1.06 [0.87-1.28], p = 0.575) (Table 11). The proton group had a median survival of 18.3 months, while the 3D Conformal group had a median survival of 16.6 months (Figure 6). On the other hand, in two cohorts of 308 matched patients, photon therapy was associated with significantly shorter survival than proton therapy patients (HR = 1.24 [1.03-1.49], p = 0.024) (Table 12). The proton cohort had a median survival time of 18.4 [14.8, 21] months, while the photon cohort had a median survival time of 13.5 [11.7, 15.1] months (Figure 7). Among 293 matched pairs when comparing proton therapy to IMRT, there were no significant differences in survival (HR = 1.04 [0.85-1.27], p = 0.693) (Table 13). Median survival was 17.7 months for IMRT and 18.4 for proton therapy (Figure 8).

Stratified Analyses

Results from the stratified Cox proportional hazards model are presented in Table 14. The variables that displayed significant differences in the association between proton therapy and overall survival within their categories were CDCC score and facility type. Among all levels of CDCC score, those who received proton therapy had significantly better survival than those who did not. However, the greatest benefit to survival from proton therapy seemed to occur in those with two or more comorbidities ($HR_{proton/non\text{-}proton}$ = 0.44 [0.23 – 0.85]). Among those who received treatment at academic centers, those receiving proton therapy had significantly lower risk of dying than those who did not ($HR_{proton/non\text{-}proton}$ = 0.66 [0.51-0.87]).

Discussion

In this analysis, we sought to compare the effectiveness of proton therapy versus more traditional forms of radiation therapy for the treatment of NSCLC using Cox proportional hazard models and propensity score matching. Prior to propensity score matching, a multivariable Cox proportional hazard model showed that proton therapy was associated with significantly better survival compared to the non-proton group after controlling for socio-demographic and disease characteristics. When further categorizing the non-proton group into individual treatment modalities, the proton therapy cohort had significantly lower hazard compared to photons and external beam NOS modalities. This suggests that there may be more nuance than a simple proton/non-proton dichotomy; while proton therapy may perform better than plain photons, for instance, it may not provide significant benefits over those achieved by more modern forms of photon therapy like 3D Conformal and IMRT.

Propensity score matching resulted in two cohorts of 308 patients. Although balance in the two cohorts was deemed adequate, there were some slight differences between the two cohorts, likely due to the small sample sizes within levels of categorical variables for the proton therapy cohort. We do not think these differences significantly detract from the validity of our results. The results of the Kaplan Meier analysis and univariate Cox proportional hazards modeling of the matched sample were different from that of the multivariable Cox proportional hazards model controlling for baseline covariates in the unmatched sample that there were no significant differences in survival between the proton and non-proton cohorts. Even after controlling for insufficiently balanced covariates, these differences in survival between the matched proton and non-proton cohorts remained insignificant.

When comparing proton therapy to specific types of traditional radiation therapy, our matched analysis showed that proton therapy yielded significantly better survival compared to photon therapy in our patient population. On the other hand, there were no significant differences in survival between the proton cohort and external beam NOS, 3D conformal, or IMRT cohorts. Both the propensity score matched analysis and multivariable Cox proportional hazards model suggest that proton therapy affords significantly better survival than photons, but that there are no significant differences in survival in proton versus 3D conformal or IMRT. This again suggests that proton therapy may only provide strong survival benefits when compared to certain modalities.

The stratified analyses performed in this study suggest that certain groups might benefit more from proton therapy. Although all levels of CDCC score show significantly better survival with proton therapy, those with two or more comorbidities have the lowest hazard when compared to the non-proton group. Those treated at academic centers with proton therapy also

have significantly lower hazard than non-proton patients at academic centers. These results suggest that those are sicker or are being treated at an academic center may derive the greatest benefit from undergoing proton therapy.

Our study has several strengths. To our knowledge, this is the largest cohort used to assess the effectiveness of proton therapy compared to standard-of-care radiation therapy for the treatment of NSCLC. The use of the NCDB provides us with larger sample sizes than would be possible with clinical trial data alone. Moreover, given that 70% of newly diagnosed cancer cases are recorded in the NCDB, we can better control for disparities in receipt of care and make our results more generalizable.

This study has several limitations due to its methodology and the use of the National Cancer Database as a source of data. Propensity score analyses may be able to balance observed baseline covariates between treatment cohorts, but they do nothing to balance unmeasured characteristics and confounders (Winkelmayer and Kurth, 2004). It is possible that our results are confounded by patient and disease characteristics for which we do not have data. Moreover, this is some disagreement among statisticians about the best way to select variables on which to match. Our analysis matched on variables that were associated with either receipt of proton therapy or with the outcome variable, overall survival. However, it is possible that using different criteria for selecting variables may have resulted in more balanced cohorts.

Another limitation is that 40 proton patients were not matched to a non-proton patient. This non-matching leads to a reduction in both sample size and power. Some researchers argue that this is not a major concern, since these patients may represent extreme cases that are not reflective of typical care situations (Winkelmayer and Kurth, 2004). On the other hand, if the association between receipt of proton therapy and overall survival is inherently different in the

patients who were not matched, there could be effect modification that is not accounted for in this analysis. It would be helpful to look further into the non-matched cohort to see if they share some common characteristics that make them systematically different from those included in the matched analysis.

Although there are advantages to using data from the NCDB, there are some limitations as well. Many more analyses will have significance simply due to the large sample size. Although many of the associations seen in Tables 2, 3, and 4 were statistically significant, they may not be clinically significant. Moreover, there is a lack of specificity for certain clinical variables within the NCDB. For instance, we do not have data on specific treatment regimens, doses, and duration. Some patient-specific demographic details are not available as well—for instance, socioeconomic status of the patient is measured based on the median income for their zip code rather than their actual household income. Education of the patient is measured based on the percentage of residents within their census tract who possess a high school degree, but gives no specific information on the patient's individual education level. More patient-specific information would provide better accuracy in estimating the influence of these sorts of variables on survival outcomes.

Furthermore, 30% of newly diagnosed cancer cases are still missing from the NCDB. Information as to why these cases were excluded is not available, and it is possible that the excluded cases are inherently different from the ones that were included. We are also unable to link the data to specific centers or to other claims data that might provide valuable clinical information. Although this is rightfully due to respect for patient confidentiality, it also means that we are not able to use the full data resources that may be available and that may better explain the relationship between treatment and outcomes.

Further research is still needed regarding the effectiveness of proton therapy compared to standard radiation therapy. Randomized, controlled clinical trials on the use of proton therapy for the treatment of NSCLC should still be conducted since propensity score matching cannot control for unmeasured variables. A properly-conducted randomized trial will be able to address this issue. There are currently several ongoing clinical trials that are recruiting patients. The RTOG 1308 trial is a Phase III trial that will investigate photon versus proton chemo-radiotherapy for inoperable Stage II-IIIB NSCLC (Liao, 2013). There are also clinical trials currently recruiting at the University of Florida and Massachusetts General Hospital. Data from these trials may not be available for several years, however, so it is useful to examine the effectiveness of proton therapy using the cancer registries that are currently available.

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Appendix

Table 1. Characteristics of full study population

Variable	Level	N (%) = 243822
Proton	No	243474 (99.9)
	Yes	348 (0.1)
Treatment	Proton Therapy	348 (0.1)
	External Beam NOS	44687 (18.3)
	3D Conformal	36406 (14.9)
	Photons	140035 (57.4)
	IMRT	22346 (9.2)
Facility Type	Academic/Research Program	67590 (27.9)
	Community Cancer Program/Other	34206 (14.1)
	Comprehensive Community Cancer Program	124810 (51.5)
	Integrated Network Cancer Program	15904 (6.6)
	Missing	1312
Facility Location	Northeast	46270 (19.1)
	South	95796 (39.5)
	Midwest	71603 (29.5)
	West	28841 (11.9)
	Missing	1312
Sex	Male	138474 (56.8)
	Female	105348 (43.2)
Race	White	207549 (85.7)
	Black	29461 (12.2)
	Other	5143 (2.1)
	Missing	1669
Insurance Type	Not Insured	8323 (3.5)
	Private Insurance	68079 (28.4)
	Government Insurance	163616 (68.2)
	Missing	3804
Median Income Quartiles 2000	Not Available	9647
	< $30,000	39691 (16.9)
	$30,000 - $35,999	49199 (21.0)
	$36,000 - $45,999	70439 (30.1)
	$46,000 +	74846 (32.0)

Variable	Level	N (%) = 243822
Percent No High School Degree Quartiles 2000	Not Available	9667
	>=29%	45393 (19.4)
	20-28.9%	63020 (26.9)
	14-19.9%	58112 (24.8)
	< 14%	67630 (28.9)
Urban/Rural 2003	Metro	183565 (78.3)
	Urban	44756 (19.1)
	Rural	6261 (2.7)
	Missing	9240
Charlson-Deyo Score	0	150490 (61.7)
	1	65574 (26.9)
	2	27758 (11.4)
Year of Diagnosis	2004	27148 (11.1)
	2005	27254 (11.2)
	2006	27163 (11.1)
	2007	27150 (11.1)
	2008	27771 (11.4)
	2009	27155 (11.1)
	2010	26493 (10.9)
	2011	26706 (11.0)
	2012	26982 (11.1)
Primary Site	C340 - Main Bronchus	15193 (6.2)
	C341 - Upper lobe, Lung	139351 (57.2)
	C342 - Middle lobe, Lung	8903 (3.7)
	C343 - Lower lobe, Lung	55271 (22.7)
	C348 - Overlapping lesion of lung	3707 (1.5)
	C349 - Lung, NOS	21397 (8.8)
Laterality	Left	132778 (54.5)
	Right	90763 (37.2)
	Other	20281 (8.3)
Grade	Well differentiated, differentiated, NOS	6940 (2.8)
	Moderately differentiated, moderately well differentiated, intermediate differentiation	39980 (16.4)
	Poorly differentiated	80706 (33.1)
	Undifferentiated, anaplastic	4857 (2.0)

Variable	Level	N (%) = 243822
	Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	111339 (45.7)
Surgery	No	212781 (87.4)
	Yes	30627 (12.6)
	Missing	414
AJCC Analytic Stage Group	Stage 0	415 (0.2)
	Stage I	34092 (14.7)
	Stage II	23176 (10.0)
	Stage III	115695 (49.8)
	Stage IV	58742 (25.3)
	Missing	11702
Stage Group (collapsed)	Stage 0 or 1	34507 (14.9)
	Stage 2 or 3	138871 (59.8)
	Stage 4	58742 (25.3)
	Missing	11702
Histology	Adenocarcinoma	74538 (30.6)
	Squamous Cell Carcinoma	91685 (37.6)
	Other	77599 (31.8)
Radiation Therapy at any CoC Facility	Beam radiation	243083 (99.7)
	Combination of beam radiation with radioactive implants or radioisotopes	569 (0.2)
	Radiation therapy, NOS	170 (0.1)
Chemotherapy	No	76101 (31.6)
	Yes	164812 (68.4)
	Missing	2909
Great Circle Distance (Units = 50 mi)	Mean	0.43
	Median	0.17
	Minimum	0.00
	Maximum	95.43
	Std Dev	1.54
	Missing	5532.00
Age at Diagnosis	Mean	67.66
	Median	68.00
	Minimum	18.00
	Maximum	90.00
	Std Dev	10.98

Variable	Level	N (%) = 243822
	Missing	0.00
Regional Dose	Mean	4809.45
	Median	4500.00
	Minimum	1.00
	Maximum	85000.00
	Std Dev	3259.43
	Missing	13456.00
Number of Treatments to this Volume	Mean	27.19
	Median	30.00
	Minimum	1.00
	Maximum	998.00
	Std Dev	22.57
	Missing	24601.00
Tumor Size	Mean	0.58
	Median	0.50
	Minimum	0.00
	Maximum	10.00
	Std Dev	0.48
	Missing	46233.00

Table 2. Univariate associations with proton therapy

Covariate	Statistics	Level	Proton		Parametric P-value*
			No N=243474	Yes N=348	
Treatment	N (Row %)	Proton Therapy	0 (0)	348 (100)	**<.001**
	N (Row %)	External Beam NOS	44687 (100)	0 (0)	
	N (Row %)	3D Conformal	36406 (100)	0 (0)	
	N (Row %)	Photons	140035 (100)	0 (0)	
	N (Row %)	IMRT	22346 (100)	0 (0)	
Facility Type	N (Row %)	Academic/Research Program	67402 (99.72)	188 (0.28)	**<.001**
	N (Row %)	Community Cancer Program/Other	34189 (99.95)	17 (0.05)	
	N (Row %)	Comprehensive Community Cancer Program	124675 (99.89)	135 (0.11)	
	N (Row %)	Integrated Network Cancer Program	15896 (99.95)	8 (0.05)	
Facility Location	N (Row %)	Northeast	46217 (99.89)	53 (0.11)	**<.001**
	N (Row %)	South	95673 (99.87)	123 (0.13)	
	N (Row %)	Midwest	71572 (99.96)	31 (0.04)	
	N (Row %)	West	28700 (99.51)	141 (0.49)	
Sex	N (Row %)	Male	138284 (99.86)	190 (0.14)	0.408
	N (Row %)	Female	105190 (99.85)	158 (0.15)	
Race	N (Row %)	White	207252 (99.86)	297 (0.14)	**0.002**
	N (Row %)	Black	29429 (99.89)	32 (0.11)	
	N (Row %)	Other	5127 (99.69)	16 (0.31)	
Insurance Type	N (Row %)	Not Insured	8317 (99.93)	6 (0.07)	**0.003**
	N (Row %)	Private Insurance	68004 (99.89)	75 (0.11)	
	N (Row %)	Government Insurance	163353 (99.84)	263 (0.16)	
Median Income Quartiles 2000	N (Row %)	< $30,000	39650 (99.9)	41 (0.1)	**<.001**
	N (Row %)	$30,000 - $35,999	49152 (99.9)	47 (0.1)	
	N (Row %)	$36,000 - $45,999	70347 (99.87)	92 (0.13)	
	N (Row %)	$46,000 +	74698 (99.8)	148 (0.2)	
Percent No High School Degree Quartiles 2000	N (Row %)	>=29%	45345 (99.89)	48 (0.11)	**0.006**
	N (Row %)	20-28.9%	62939 (99.87)	81 (0.13)	
	N (Row %)	14-19.9%	58035 (99.87)	77 (0.13)	
	N (Row %)	< 14%	67508 (99.82)	122 (0.18)	
Urban/Rural 2003	N (Row %)	Metro	183267 (99.84)	298 (0.16)	**<.001**
	N (Row %)	Urban	44733 (99.95)	23 (0.05)	
	N (Row %)	Rural	6253 (99.87)	8 (0.13)	
Charlson-Deyo Score	N (Row %)	0	150262 (99.85)	228 (0.15)	0.073
	N (Row %)	1	65499 (99.89)	75 (0.11)	
	N (Row %)	2	27713 (99.84)	45 (0.16)	

Covariate	Statistics	Level	Proton		Parametric P-value*
			No N=243474	Yes N=348	
Year of Diagnosis	N (Row %)	2004	27095 (99.8)	53 (0.2)	**<.001**
	N (Row %)	2005	27219 (99.87)	35 (0.13)	
	N (Row %)	2006	27149 (99.95)	14 (0.05)	
	N (Row %)	2007	27131 (99.93)	19 (0.07)	
	N (Row %)	2008	27752 (99.93)	19 (0.07)	
	N (Row %)	2009	27123 (99.88)	32 (0.12)	
	N (Row %)	2010	26457 (99.86)	36 (0.14)	
	N (Row %)	2011	26657 (99.82)	49 (0.18)	
	N (Row %)	2012	26891 (99.66)	91 (0.34)	
Primary Site	N (Row %)	C340 - Main Bronchus	15181 (99.92)	12 (0.08)	0.221
	N (Row %)	C341 - Upper lobe, Lung	139145 (99.85)	206 (0.15)	
	N (Row %)	C342 - Middle lobe, Lung	8890 (99.85)	13 (0.15)	
	N (Row %)	C343 - Lower lobe, Lung	55194 (99.86)	77 (0.14)	
	N (Row %)	C348 - Overlapping lesion of lung	3704 (99.92)	3 (0.08)	
	N (Row %)	C349 - Lung, NOS	21360 (99.83)	37 (0.17)	
Laterality	N (Row %)	Left	132593 (99.86)	185 (0.14)	**0.005**
	N (Row %)	Right	90614 (99.84)	149 (0.16)	
	N (Row %)	Other	20267 (99.93)	14 (0.07)	
Grade	N (Row %)	Well differentiated, differentiated, NOS	6932 (99.88)	8 (0.12)	0.663
	N (Row %)	Moderately differentiated, moderately well differentiated, intermediate differentiation	39917 (99.84)	63 (0.16)	
	N (Row %)	Poorly differentiated	80600 (99.87)	106 (0.13)	
	N (Row %)	Undifferentiated, anaplastic	4848 (99.81)	9 (0.19)	
	N (Row %)	Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	111177 (99.85)	162 (0.15)	
Surgery	N (Row %)	No	212488 (99.86)	293 (0.14)	0.094
	N (Row %)	Yes	30573 (99.82)	54 (0.18)	
AJCC Analytic Stage Group	N (Row %)	Stage 0	414 (99.76)	1 (0.24)	**<.001**
	N (Row %)	Stage I	33998 (99.72)	94 (0.28)	
	N (Row %)	Stage II	23137 (99.83)	39 (0.17)	
	N (Row %)	Stage III	115541 (99.87)	154 (0.13)	
	N (Row %)	Stage IV	58684 (99.9)	58 (0.1)	
Stage Group (collapsed)	N (Row %)	Stage 0 or 1	34412 (99.72)	95 (0.28)	**<.001**
	N (Row %)	Stage 2 or 3	138678 (99.86)	193 (0.14)	
	N (Row %)	Stage 4	58684 (99.9)	58 (0.1)	
Histology	N (Row %)	Adenocarcinoma	74415 (99.83)	123 (0.17)	0.089
	N (Row %)	Squamous Cell Carcinoma	91555 (99.86)	130 (0.14)	

Covariate	Statistics	Level	Proton		Parametric P-value*
			No N=243474	Yes N=348	
	N (Row %)	Other	77504 (99.88)	95 (0.12)	
Radiation Therapy at any CoC Facility	N (Row %)	Beam radiation	242735 (99.86)	348 (0.14)	0.589
	N (Row %)	Combination of beam radiation with radioactive implants or radioisotopes	569 (100)	0 (0)	
	N (Row %)	Radiation therapy, NOS	170 (100)	0 (0)	
Chemotherapy	N (Row %)	No	75961 (99.82)	140 (0.18)	**<.001**
	N (Row %)	Yes	164608 (99.88)	204 (0.12)	
Great Circle Distance (Units = 50 mi)	N		237952	338	**<.001**
	Mean		0.43	1.37	
	Median		0.17	0.24	
	Min		0	0	
	Max		95.43	44.88	
	Std Dev		1.53	4.64	
Age at Diagnosis	N		243474	348	**0.009**
	Mean		67.66	69.21	
	Median		68	70	
	Min		18	42	
	Max		90	89	
	Std Dev		10.98	9.87	
Regional Dose	N		230064	302	**0.047**
	Mean		4808.96	5181.42	
	Median		4500	5970	
	Min		1	6	
	Max		85000	9999	
	Std Dev		3260.58	2194.68	
Number of Treatments to this Volume	N		218931	290	0.736
	Mean		27.19	27.64	
	Median		30	28	
	Min		1	1	
	Max		998	888	
	Std Dev		22.5	53.17	
Tumor Size	N		197283	306	0.682
	Mean		0.58	0.59	
	Median		0.5	0.5	
	Min		0	0.5	
	Max		10	8.5	
	Std Dev		0.48	0.61	

Table 3. Factors associated with receiving proton therapy

Covariate	Level	Proton=Yes Odds Ratio (95% CI)	OR P-value	Type3 P-value
Facility Type	Integrated Network Cancer Program	0.14 (0.06-0.30)	<.001	**<.001**
	Comprehensive Community Cancer Program	0.34 (0.27-0.44)	<.001	
	Community Cancer Program	0.23 (0.14-0.38)	<.001	
	Academic/Research Program	-	-	
Facility Location	Northeast	0.17 (0.12-0.23)	<.001	**<.001**
	South	0.30 (0.23-0.39)	<.001	
	Midwest	0.08 (0.05-0.12)	<.001	
	West	-	-	
Insurance Type	Not Insured	0.54 (0.24-1.22)	0.141	**0.006**
	Private Insurance	0.67 (0.51-0.87)	0.003	
	Government Insurance	-	-	
Median Income Quartiles 2000	< $30,000	0.67 (0.46-0.97)	0.035	**0.036**
	$30,000 - $35,999	0.63 (0.44-0.90)	0.011	
	$36,000 - $45,999	0.81 (0.62-1.07)	0.134	
	$46,000 +	-	-	
Urban/Rural 2003	Metro	0.75 (0.36-1.55)	0.440	**<.001**
	Urban	0.32 (0.14-0.72)	0.006	
	Rural	-	-	
Year of Diagnosis	2004	0.68 (0.48-0.97)	0.033	**<.001**
	2005	0.42 (0.28-0.64)	<.001	
	2006	0.16 (0.09-0.30)	<.001	
	2007	0.21 (0.12-0.36)	<.001	
	2008	0.21 (0.12-0.35)	<.001	
	2009	0.37 (0.24-0.56)	<.001	
	2010	0.35 (0.23-0.53)	<.001	
	2011	0.53 (0.36-0.76)	<.001	
	2012	-	-	
Primary Site	C340 - Main Bronchus	0.30 (0.14-0.66)	0.003	**0.022**
	C341 - Upper lobe, Lung	0.69 (0.47-1.00)	0.047	

Covariate	Level	Proton=Yes Odds Ratio (95% CI)	OR P-value	Type3 P-value
	C342 - Middle lobe, Lung	0.58 (0.29-1.15)	0.118	
	C343 - Lower lobe, Lung	0.56 (0.37-0.85)	0.007	
	C348 - Overlapping lesion of lung	0.46 (0.14-1.49)	0.194	
	C349 - Lung, NOS	-	-	
Stage Group (collapsed)	Stage 4	0.42 (0.29-0.59)	<.001	**<.001**
	Stage 2 or 3	0.59 (0.45-0.77)	<.001	
	Stage 0 or 1	-	-	
Great Circle Distance (Units = 50 mi)		1.06 (1.04-1.08)	<.001	**<.001**

* Number of observations in the original data set = 243822. Number of observations used = 213811.
** Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Age at Diagnosis, Charlson-Deyo Score, Grade, Percent No High School Degree Quartiles 2000, Sex, Chemotherapy, Histology, Laterality, Race, and Surgery.

Table 4. Univariate associate with overall survival

Covariate	Level	N	Overall Survival (Months)		
			Hazard Ratio (95% CI)	HR P-value	Log-rank P-value
Proton	No	243474	1.36 (1.20-1.55)	**<.001**	**<.001**
	Yes	348	-	-	
Treatment	IMRT	22346	1.06 (0.93-1.21)	0.363	**<.001**
	Photons	140035	1.43 (1.26-1.63)	**<.001**	
	3D Conformal	36406	1.26 (1.11-1.43)	**<.001**	
	External Beam NOS	44687	1.39 (1.23-1.58)	**<.001**	
	Proton Therapy	348	-	-	
Facility Type	Integrated Network Cancer Program	15904	1.05 (1.03-1.07)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	124810	1.09 (1.07-1.10)	**<.001**	
	Community Cancer Program/Other	34206	1.17 (1.15-1.18)	**<.001**	
	Academic/Research Program	67590	-	-	
Facility Location	Northeast	46270	1.00 (0.99-1.02)	0.737	**<.001**
	South	95796	1.06 (1.04-1.07)	**<.001**	
	Midwest	71603	1.03 (1.02-1.05)	**<.001**	
	West	28841	-	-	
Sex	Male	138474	1.21 (1.20-1.22)	**<.001**	**<.001**
	Female	105348	-	-	
Race	Other	5143	0.86 (0.84-0.89)	**<.001**	**<.001**
	Black	29461	1.01 (0.99-1.02)	0.251	
	White	207549	-	-	
Insurance Type	Not Insured	8323	1.04 (1.02-1.07)	**<.001**	**<.001**
	Private Insurance	68079	0.81 (0.80-0.82)	**<.001**	
	Government Insurance	163616	-	-	
Median Income Quartiles 2000	< $30,000	39691	1.13 (1.11-1.15)	**<.001**	**<.001**
	$30,000 - $35,999	49199	1.09 (1.07-1.10)	**<.001**	
	$36,000 - $45,999	70439	1.06 (1.05-1.07)	**<.001**	
	$46,000 +	74846	-	-	
Percent No High School Degree Quartiles 2000	>=29%	45393	1.10 (1.08-1.11)	**<.001**	**<.001**
	20-28.9%	63020	1.07 (1.06-1.09)	**<.001**	
	14-19.9%	58112	1.05 (1.04-1.06)	**<.001**	
	< 14%	67630	-	-	
Urban/Rural 2003	Metro	183565	0.93 (0.90-0.95)	**<.001**	**<.001**
	Urban	44756	0.98 (0.95-1.01)	0.112	
	Rural	6261	-	-	

			Overall Survival (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Charlson-Deyo Score	0	150490	0.79 (0.78-0.80)	**<.001**	**<.001**
	1	65574	0.86 (0.85-0.88)	**<.001**	
	2	27758	-	-	
Year of Diagnosis	2004	27148	1.22 (1.20-1.25)	**<.001**	**<.001**
	2005	27254	1.19 (1.17-1.21)	**<.001**	
	2006	27163	1.18 (1.15-1.20)	**<.001**	
	2007	27150	1.14 (1.12-1.16)	**<.001**	
	2008	27771	1.12 (1.10-1.14)	**<.001**	
	2009	27155	1.09 (1.07-1.11)	**<.001**	
	2010	26493	1.05 (1.03-1.07)	**<.001**	
	2011	26706	1.00 (0.98-1.02)	0.874	
	2012	26982	-	-	
Primary Site	C340 - Main Bronchus	15193	0.97 (0.95-0.99)	**0.004**	**<.001**
	C341 - Upper lobe, Lung	139351	0.74 (0.73-0.75)	**<.001**	
	C342 - Middle lobe, Lung	8903	0.76 (0.74-0.78)	**<.001**	
	C343 - Lower lobe, Lung	55271	0.84 (0.83-0.86)	**<.001**	
	C348 - Overlapping lesion of lung	3707	0.95 (0.92-0.99)	**0.009**	
	C349 - Lung, NOS	21397	-	-	
Laterality	Left	132778	0.80 (0.79-0.82)	**<.001**	**<.001**
	Right	90763	0.80 (0.78-0.81)	**<.001**	
	Other	20281	-	-	
Grade	Well differentiated, differentiated, NOS	6940	0.72 (0.70-0.74)	**<.001**	**<.001**
	Moderately differentiated, moderately well differentiated, intermediate differentiation	39980	0.84 (0.83-0.85)	**<.001**	
	Poorly differentiated	80706	0.96 (0.95-0.97)	**<.001**	
	Undifferentiated, anaplastic	4857	1.02 (0.99-1.06)	0.158	
	Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	111339	-	-	
Surgery	No	212781	2.24 (2.21-2.27)	**<.001**	**<.001**
	Yes	30627	-	-	
AJCC Analytic Stage Group	Stage 0	415	0.33 (0.29-0.37)	**<.001**	**<.001**
	Stage I	34092	0.32 (0.32-0.32)	**<.001**	
	Stage II	23176	0.36 (0.35-0.37)	**<.001**	
	Stage III	115695	0.46 (0.45-0.46)	**<.001**	
	Stage IV	58742	-	-	
Stage Group (collapsed)	Stage 0 or 1	34507	0.32 (0.32-0.33)	**<.001**	**<.001**
	Stage 2 or 3	138871	0.44 (0.43-0.44)	**<.001**	
	Stage 4	58742	-	-	

Covariate	Level	N	Overall Survival (Months)		
			Hazard Ratio (95% CI)	HR P-value	Log-rank P-value
Histology	Adenocarcinoma	74538	0.87 (0.86-0.88)	**<.001**	**<.001**
	Squamous Cell Carcinoma	91685	0.99 (0.98-1.00)	**0.017**	
	Other	77599	-	-	
Chemotherapy	No	76101	1.51 (1.50-1.53)	**<.001**	**<.001**
	Yes	164812	-	-	
Great Circle Distance (Units = 50 mi)		238290	0.99 (0.99-1.00)	**<.001**	-
Age at Diagnosis		243822	1.01 (1.01-1.01)	**<.001**	-
Regional Dose		230366	1.00 (1.00-1.00)	**<.001**	-
Number of Treatments to this Volume		219221	0.98 (0.98-0.98)	**<.001**	-
Tumor Size		197589	1.09 (1.08-1.10)	**<.001**	-

Table 5. Multivariable survival analysis for the main effect of proton therapy versus traditional radiation therapy (non-proton)

		Overall Survival (Months)		
Covariate	**Level**	**Hazard Ratio**	**HR P-value**	**Type3 P-value**
Proton	No	1.21 (1.06-1.39)	0.005	**0.005**
	Yes	-	-	
Facility Type	Integrated Network Cancer Program	1.03 (1.01-1.06)	0.001	**<.001**
	Comprehensive Community Cancer Program	1.05 (1.04-1.07)	<.001	
	Community Cancer Program/Other	1.09 (1.07-1.10)	<.001	
	Academic/Research Program	-	-	
Facility Location	Northeast	1.05 (1.03-1.07)	<.001	**<.001**
	South	1.05 (1.03-1.07)	<.001	
	Midwest	1.05 (1.03-1.07)	<.001	
	West	-	-	
Sex	Male	1.19 (1.18-1.20)	<.001	**<.001**
	Female	-	-	
Race	Other	0.88 (0.85-0.91)	<.001	**<.001**
	Black	0.96 (0.94-0.97)	<.001	
	White	-	-	
Insurance Type	Not Insured	1.08 (1.05-1.11)	<.001	**<.001**
	Private Insurance	0.93 (0.91-0.94)	<.001	
	Government Insurance	-	-	
Median Income Quartiles 2000	< $30,000	1.04 (1.02-1.06)	<.001	**<.001**
	$30,000 - $35,999	1.02 (1.00-1.04)	0.034	
	$36,000 - $45,999	1.01 (0.99-1.02)	0.268	
	$46,000 +	-	-	
Percent No High School Degree Quartiles 2000	>=29%	1.01 (0.99-1.03)	0.238	**0.002**
	20-28.9%	1.03 (1.01-1.04)	<.001	
	14-19.9%	1.02 (1.01-1.03)	0.008	
	< 14%	-	-	
Urban/Rural 2003	Metro	1.00 (0.97-1.03)	0.896	0.195
	Urban	1.01 (0.98-1.05)	0.374	
	Rural	-	-	

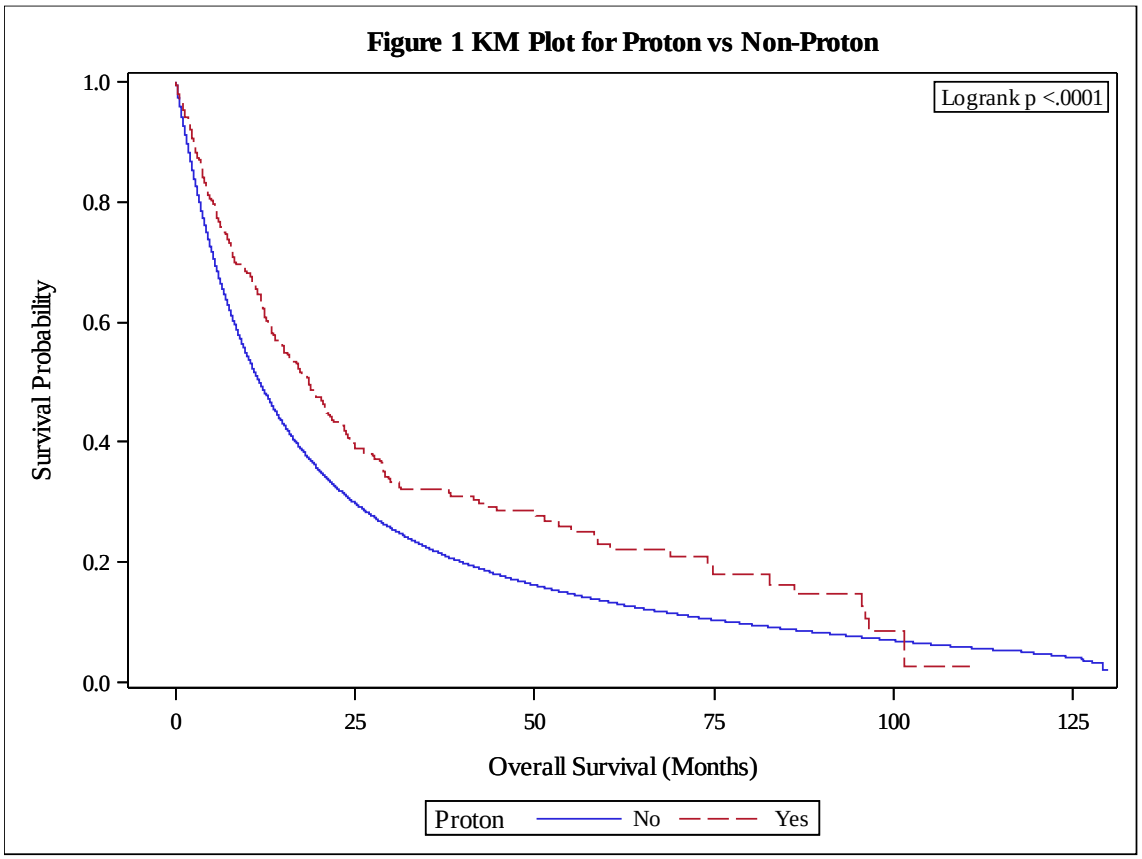
		Overall Survival (Months)		
Covariate	**Level**	**Hazard Ratio**	**HR P-value**	**Type3 P-value**
Charlson-Deyo Score	0	0.79 (0.78-0.80)	<.001	**<.001**
	1	0.89 (0.88-0.91)	<.001	
	2	-	-	
Year of Diagnosis	2004	1.23 (1.20-1.26)	<.001	**<.001**
	2005	1.21 (1.18-1.23)	<.001	
	2006	1.18 (1.16-1.21)	<.001	
	2007	1.13 (1.11-1.16)	<.001	
	2008	1.12 (1.10-1.15)	<.001	
	2009	1.09 (1.07-1.12)	<.001	
	2010	1.04 (1.02-1.07)	<.001	
	2011	0.99 (0.97-1.02)	0.645	
	2012	-	-	
Primary Site	C340 - Main Bronchus	1.10 (1.06-1.15)	<.001	**<.001**
	C341 - Upper lobe, Lung	0.85 (0.83-0.86)	<.001	
	C342 - Middle lobe, Lung	0.90 (0.87-0.92)	<.001	
	C343 - Lower lobe, Lung	0.98 (0.96-1.00)	0.037	
	C348 - Overlapping lesion of lung	1.05 (1.01-1.09)	0.019	
	C349 - Lung, NOS	-	-	
Laterality	Left	1.12 (1.07-1.16)	<.001	**<.001**
	Right	1.10 (1.06-1.14)	<.001	
	Other	-	-	
Grade	Well differentiated, differentiated, NOS	0.85 (0.83-0.88)	<.001	**<.001**
	Moderately differentiated, moderately well differentiated, intermediate differentiation	0.99 (0.98-1.00)	0.179	
	Poorly differentiated	1.07 (1.05-1.08)	<.001	
	Undifferentiated, anaplastic	1.08 (1.05-1.12)	<.001	
	Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	-	-	
Surgery	No	1.83 (1.80-1.86)	<.001	**<.001**
	Yes	-	-	

		Overall Survival (Months)		
Covariate	**Level**	**Hazard Ratio**	**HR P-value**	**Type3 P-value**
Stage Group (collapsed)	Stage 0 or 1	0.26 (0.26-0.27)	<.001	**<.001**
	Stage 2 or 3	0.48 (0.48-0.49)	<.001	
	Stage 4	-	-	
Histology	Adenocarcinoma	0.93 (0.92-0.94)	<.001	**<.001**
	Squamous Cell Carcinoma	1.00 (0.98-1.01)	0.438	
	Other	-	-	
Chemotherapy	No	1.71 (1.69-1.73)	<.001	**<.001**
	Yes	-	-	
Great Circle Distance (Units = 50 mi)		1.00 (0.99-1.00)	0.009	**0.009**
Age at Diagnosis		1.01 (1.01-1.01)	<.001	**<.001**

* Number of observations in the original data set = 243822. Number of observations used = 211080 .

** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.

Figure 1. KM Plot for Proton vs. Non-Proton



Proton	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
No	243474	198845 (82%)	44629 (18%)	11.7 (11.7, 11.8)	49.4% (49.2%, 49.6%)	13.5% (13.4%, 13.7%)
Yes	348	233 (67%)	115 (33%)	18.6 (15.1, 21.2)	63.3% (57.9%, 68.2%)	23.1% (17.4%, 29.3%)

Table 6. Multivariable survival analysis for the main effect of proton therapy versus individual radiation treatment modalities

		Overall Survival (Months)		
Covariate	**Level**	**Hazard Ratio**	**HR P-value**	**Type3 P-value**
Treatment	IMRT	1.05 (0.91-1.20)	0.524	**<.001**
	Photons	1.25 (1.09-1.43)	0.001	
	3D Conformal	1.16 (1.01-1.33)	0.035	
	External Beam NOS	1.26 (1.10-1.44)	<.001	
	Proton Therapy	-	-	
Facility Type	Integrated Network Cancer Program	1.04 (1.02-1.06)	<.001	**<.001**
	Comprehensive Community Cancer Program	1.05 (1.04-1.07)	<.001	
	Community Cancer Program/Other	1.08 (1.06-1.10)	<.001	
	Academic/Research Program	-	-	
Facility Location	Northeast	1.05 (1.03-1.07)	<.001	**<.001**
	South	1.05 (1.03-1.07)	<.001	
	Midwest	1.05 (1.03-1.07)	<.001	
	West	-	-	
Sex	Male	1.19 (1.18-1.20)	<.001	**<.001**
	Female	-	-	
Race	Other	0.88 (0.85-0.91)	<.001	**<.001**
	Black	0.96 (0.94-0.97)	<.001	
	White	-	-	
Insurance Type	Not Insured	1.07 (1.04-1.10)	<.001	**<.001**
	Private Insurance	0.93 (0.91-0.94)	<.001	
	Government Insurance	-	-	
Median Income Quartiles 2000	< $30,000	1.05 (1.03-1.07)	<.001	**<.001**
	$30,000 - $35,999	1.02 (1.01-1.04)	0.010	
	$36,000 - $45,999	1.01 (1.00-1.03)	0.116	
	$46,000 +	-	-	
Percent No High School Degree Quartiles 2000	>=29%	1.01 (0.99-1.03)	0.568	**0.003**
	20-28.9%	1.02 (1.01-1.04)	0.003	
	14-19.9%	1.02 (1.00-1.03)	0.012	
	< 14%	-	-	
Urban/Rural 2003	Metro	1.00 (0.97-1.03)	0.949	0.147
	Urban	1.01 (0.98-1.05)	0.371	

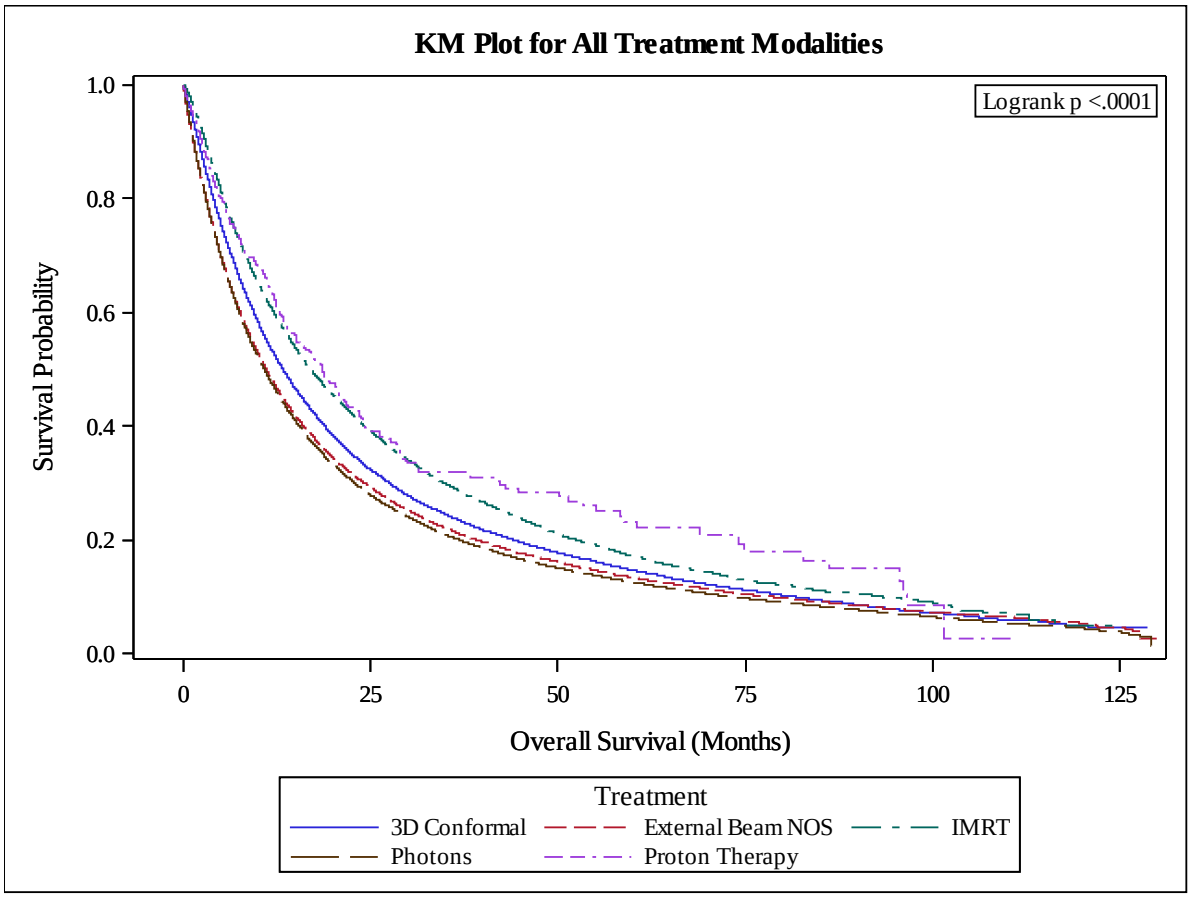
Covariate	Level	Overall Survival (Months)		
		Hazard Ratio	HR P-value	Type3 P-value
	Rural	-	-	
Charlson-Deyo Score	0	0.79 (0.78-0.80)	<.001	**<.001**
	1	0.89 (0.88-0.91)	<.001	
	2	-	-	
Year of Diagnosis	2004	1.18 (1.16-1.21)	<.001	**<.001**
	2005	1.17 (1.14-1.19)	<.001	
	2006	1.15 (1.12-1.17)	<.001	
	2007	1.11 (1.08-1.13)	<.001	
	2008	1.10 (1.08-1.13)	<.001	
	2009	1.08 (1.05-1.10)	<.001	
	2010	1.04 (1.01-1.06)	0.002	
	2011	0.99 (0.97-1.01)	0.420	
	2012	-	-	
Primary Site	C340 - Main Bronchus	1.10 (1.06-1.15)	<.001	**<.001**
	C341 - Upper lobe, Lung	0.85 (0.83-0.86)	<.001	
	C342 - Middle lobe, Lung	0.90 (0.87-0.93)	<.001	
	C343 - Lower lobe, Lung	0.98 (0.96-1.00)	0.092	
	C348 - Overlapping lesion of lung	1.06 (1.01-1.10)	0.010	
	C349 - Lung, NOS	-	-	
Laterality	Left	1.11 (1.07-1.16)	<.001	**<.001**
	Right	1.10 (1.06-1.14)	<.001	
	Other	-	-	
Grade	Well differentiated, differentiated, NOS	0.86 (0.83-0.88)	<.001	**<.001**
	Moderately differentiated, moderately well differentiated, intermediate differentiation	0.99 (0.98-1.00)	0.181	
	Poorly differentiated	1.06 (1.05-1.08)	<.001	
	Undifferentiated, anaplastic	1.08 (1.05-1.12)	<.001	
	Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	-	-	

		Overall Survival (Months)		
Covariate	**Level**	**Hazard Ratio**	**HR P-value**	**Type3 P-value**
Surgery	No	1.83 (1.80-1.86)	<.001	**<.001**
	Yes	-	-	
Stage Group (collapsed)	Stage 0 or 1	0.26 (0.26-0.27)	<.001	**<.001**
	Stage 2 or 3	0.49 (0.48-0.49)	<.001	
	Stage 4	-	-	
Histology	Adenocarcinoma	0.93 (0.92-0.94)	<.001	**<.001**
	Squamous Cell Carcinoma	1.00 (0.98-1.01)	0.554	
	Other	-	-	
Chemotherapy	No	1.70 (1.68-1.72)	<.001	**<.001**
	Yes	-	-	
Great Circle Distance (Units = 50 mi)		1.00 (0.99-1.00)	0.044	**0.044**
Age at Diagnosis		1.01 (1.01-1.01)	<.001	**<.001**

* Number of observations in the original data set = 243822. Number of observations used = 211080 .

** Backward selection with an alpha level of removal of .20 was used. No variables were removed from the model.

Figure 2. KM Plot for all treatment modalities



Treatment	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
3D Conformal	36406	28959 (80%)	7447 (20%)	13.3 (13.1, 13.6)	53.0% (52.5%, 53.6%)	14.7% (14.3%, 15.2%)
External Beam NOS	44687	36380 (81%)	8307 (19%)	11.1 (10.9, 11.3)	47.9% (47.4%, 48.3%)	13.5% (13.1%, 13.8%)
IMRT	22346	15704 (70%)	6642 (30%)	17 (16.6, 17.4)	60.3% (59.6%, 60.9%)	17.2% (16.6%, 17.9%)
Photons	140035	117802 (84%)	22233 (16%)	10.8 (10.7, 10.9)	47.2% (46.9%, 47.4%)	12.6% (12.4%, 12.8%)
Proton Therapy	348	233 (67%)	115 (33%)	18.6 (15.1, 21.2)	63.3% (57.9%, 68.2%)	23.1% (17.4%, 29.3%)

Figure 3. Distribution of the logit of the propensity scores calculated for the non-proton (top) and proton (bottom) cohorts.

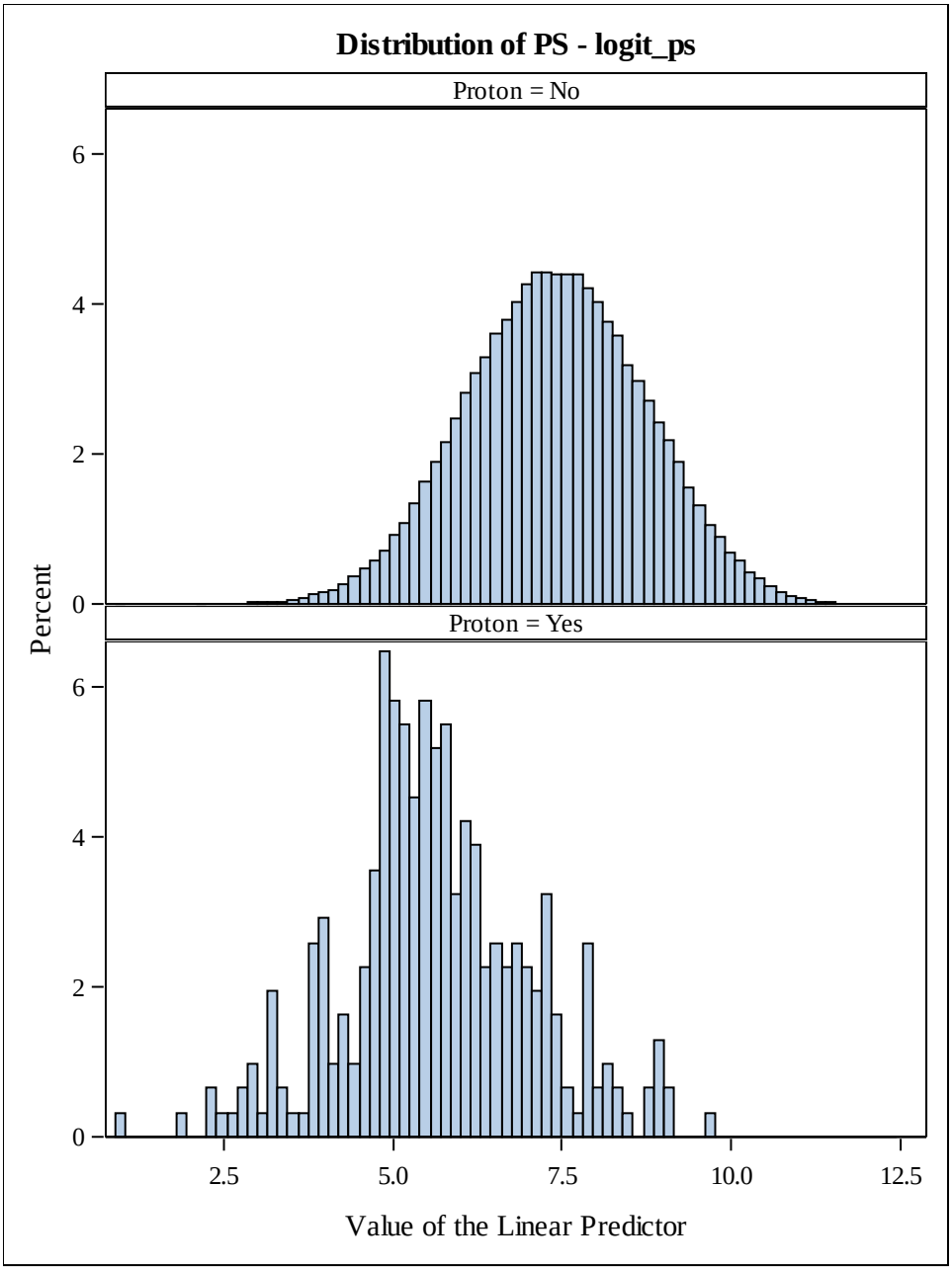


Table 7. Characteristics of patients in matched sample.

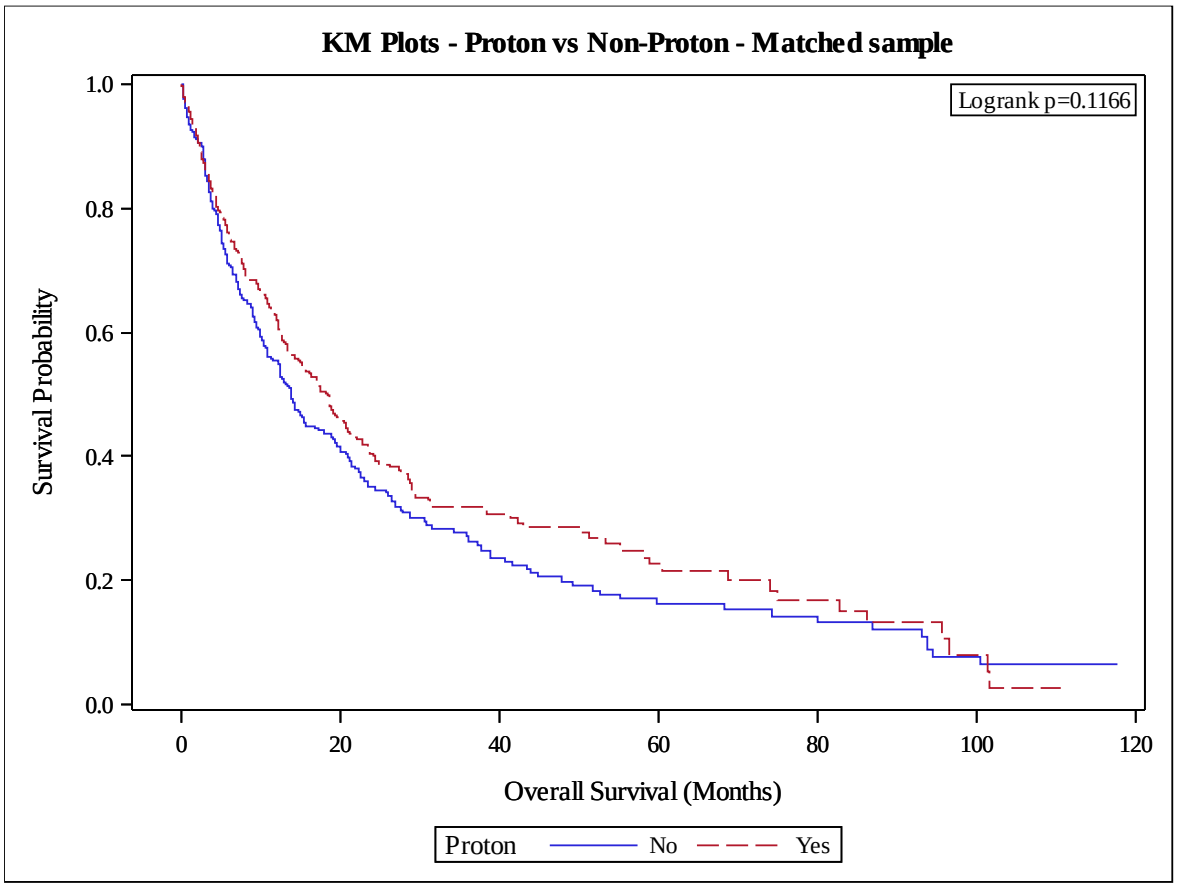
		Proton			
Covariate	**Level**	**No N=308**	**Yes N=308**	**Parametric P-value***	**Standardized Difference**
Race	White	264 (85.71)	264 (85.71)	0.632	0.000
	Black	34 (11.04)	30 (9.74)		0.043
	Other	10 (3.25)	14 (4.55)		0.067
Sex	Male	164 (53.25)	171 (55.52)	0.571	0.046
	Female	144 (46.75)	137 (44.48)		0.046
Facility Type	Academic/Research Program	169 (54.87)	160 (51.95)	0.865	0.059
	Community Cancer Program/Other	13 (4.22)	16 (5.19)		0.046
	Comprehensive Community Cancer Program	120 (38.96)	125 (40.58)		0.033
	Integrated Network Cancer Program	6 (1.95)	7 (2.27)		0.023
Facility Location	Northeast	50 (16.23)	48 (15.58)	0.949	0.018
	South	114 (37.01)	109 (35.39)		0.034
	Midwest	27 (8.77)	27 (8.77)		0.000
	West	117 (37.99)	124 (40.26)		0.047
Insurance Type	Not Insured	8 (2.6)	6 (1.95)	0.863	0.044
	Private Insurance	68 (22.08)	68 (22.08)		0.000
	Government Insurance	232 (75.32)	234 (75.97)		0.015
Median Income Quartiles 2000	< $30,000	48 (15.58)	39 (12.66)	0.643	0.084
	$30,000 - $35,999	49 (15.91)	44 (14.29)		0.045
	$36,000 - $45,999	84 (27.27)	88 (28.57)		0.029
	$46,000 +	127 (41.23)	137 (44.48)		0.066
Percent No High School Degree Quartiles 2000	>=29%	44 (14.29)	45 (14.61)	0.999	0.009
	20-28.9%	77 (25)	76 (24.68)		0.008
	14-19.9%	75 (24.35)	74 (24.03)		0.008
	< 14%	112 (36.36)	113 (36.69)		0.007
Urban/Rural 2003	Metro	269 (87.34)	280 (90.91)	0.217	**0.115**
	Urban	32 (10.39)	20 (6.49)		**0.140**

		Proton			
Covariate	**Level**	**No N=308**	**Yes N=308**	**Parametric P-value***	**Standardized Difference**
	Rural	7 (2.27)	8 (2.6)		0.021
Charlson-Deyo Score	0	225 (73.05)	206 (66.88)	0.136	**0.135**
	1	60 (19.48)	66 (21.43)		0.048
	2	23 (7.47)	36 (11.69)		**0.144**
Primary Site	C340 - Main Bronchus	9 (2.92)	8 (2.6)	0.984	0.020
	C341 - Upper lobe, Lung	187 (60.71)	187 (60.71)		0.000
	C342 - Middle lobe, Lung	10 (3.25)	10 (3.25)		0.000
	C343 - Lower lobe, Lung	60 (19.48)	66 (21.43)		0.048
	C348 - Overlapping lesion of lung	3 (0.97)	3 (0.97)		0.000
	C349 - Lung, NOS	39 (12.66)	34 (11.04)		0.050
Laterality	Left	180 (58.44)	166 (53.9)	0.411	0.092
	Right	116 (37.66)	132 (42.86)		**0.106**
	Other	12 (3.9)	10 (3.25)		0.035
Grade	Well differentiated, differentiated, NOS	5 (1.62)	7 (2.27)	0.871	0.047
	Moderately differentiated, moderately well differentiated, intermediate differentiation	48 (15.58)	54 (17.53)		0.052
	Poorly differentiated	101 (32.79)	97 (31.49)		0.028
	Undifferentiated, anaplastic	11 (3.57)	8 (2.6)		0.056
	Cell type not determined, not stated or not applicable, unknown primaries, high grade dysplasia	143 (46.43)	142 (46.1)		0.007
Chemotherapy	No	124 (40.26)	119 (38.64)	0.680	0.033
	Yes	184 (59.74)	189 (61.36)		0.033

		Proton			
Covariate	**Level**	**No N=308**	**Yes N=308**	**Parametric P-value***	**Standardized Difference**
Stage Group (collapsed)	Stage 0 or 1	76 (24.68)	79 (25.65)	0.920	0.022
	Stage 2 or 3	181 (58.77)	176 (57.14)		0.033
	Stage 4	51 (16.56)	53 (17.21)		0.017
Histology	Adenocarcinoma	94 (30.52)	110 (35.71)	0.264	**0.111**
	Squamous Cell Carcinoma	115 (37.34)	115 (37.34)		0.000
	Other	99 (32.14)	83 (26.95)		**0.114**
Year of Diagnosis	2004	58 (18.83)	50 (16.23)	0.993	0.068
	2005	29 (9.42)	32 (10.39)		0.033
	2006	14 (4.55)	12 (3.9)		0.032
	2007	16 (5.19)	16 (5.19)		0.000
	2008	17 (5.52)	17 (5.52)		0.000
	2009	25 (8.12)	30 (9.74)		0.057
	2010	27 (8.77)	28 (9.09)		0.011
	2011	43 (13.96)	41 (13.31)		0.019
	2012	79 (25.65)	82 (26.62)		0.022
Great Circle Distance (Units = 50 mi)	Mean (Std)	1.98 (7.48)	1.24 (4.03)	0.123	**0.124**
Age at Diagnosis	Mean (Std)	68.16 (10.67)	69.09 (9.83)	0.264	0.090

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

Figure 4. KM Plot for Proton vs. Non-Proton in matched sample



Proton	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
No	308	233 (76%)	75 (24%)	13.8 (11.2, 17.2)	55.4% (49.6%, 60.8%)	16.2% (11.3%, 21.8%)
Yes	308	208 (68%)	100 (32%)	18.4 (14.8, 21)	61.9% (56.1%, 67.1%)	22.6% (16.6%, 29.2%)

Table 8. Association with survival for proton versus non-proton cohorts in matched sample

			Overall Survival (Months)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Proton	No	308	1.16 (0.97-1.39)	0.108	0.117
	Yes	308	-	-	

Table 9. Association with survival in matched survival after controlling for insufficiently balanced covariates.

		Overall Survival (Months)		

Covariate	**Level**	**Hazard Ratio**	**HR P-value**	**Type3 P-value**
Proton	No	1.13 (0.94-1.37)	0.188	0.188
	Yes	-	-	
Laterality	Left	0.52 (0.33-0.83)	0.006	**0.024**
	Right	0.53 (0.33-0.86)	0.009	
	Other	-	-	
Histology	Adenocarcinoma	0.61 (0.48-0.78)	<.001	**<.001**
	Squamous Cell Carcinoma	0.90 (0.72-1.13)	0.378	
	Other	-	-	

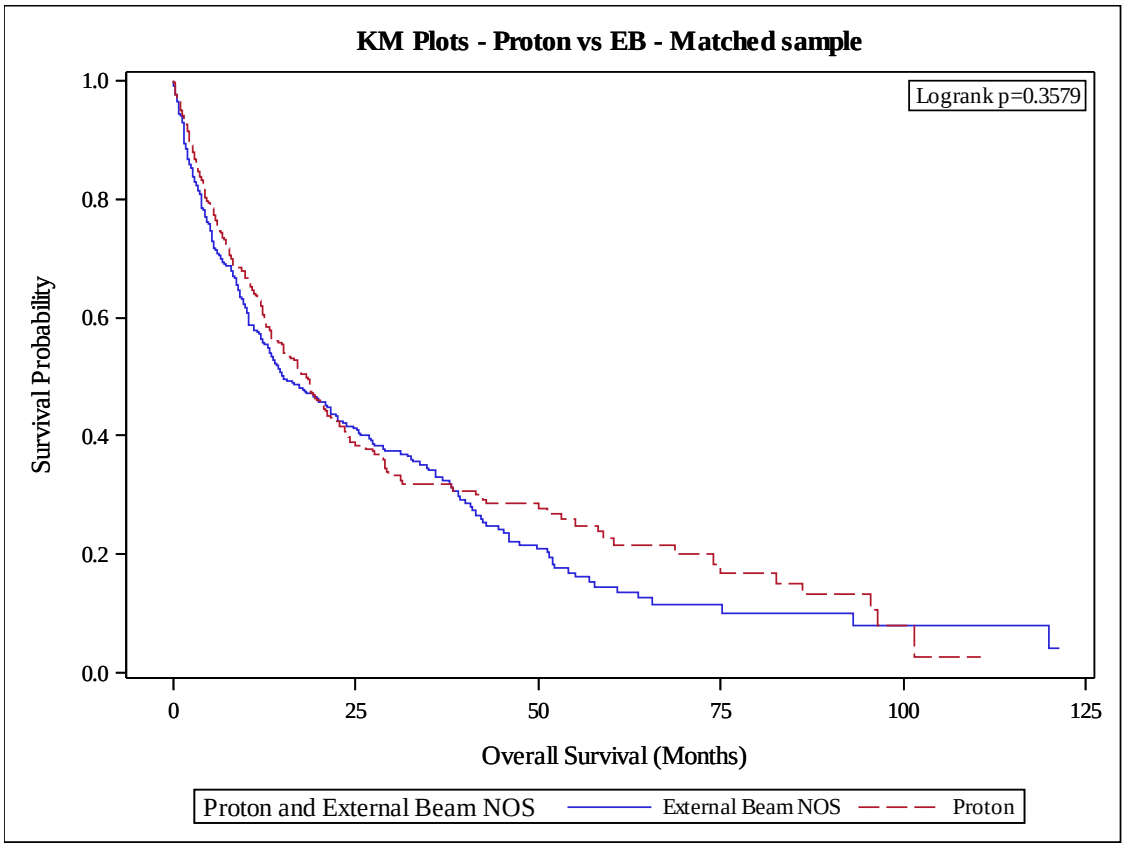
* Number of observations in the original data set = 616. Number of observations used = 616.
** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Charlson-Deyo Score, Great Circle Distance (Units = 50 mi), and Urban/Rural 2003.

Table 10. Association with survival for proton versus External Beam NOS cohorts in matched sample

			Overall Survival (Months)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Proton and External Beam NOS	External Beam NOS	305	1.09 (0.90-1.32)	0.360	0.358
	Proton	305	-	-	

Figure 5. KM Plot for Proton vs. External Beam NOS cohorts in matched sample



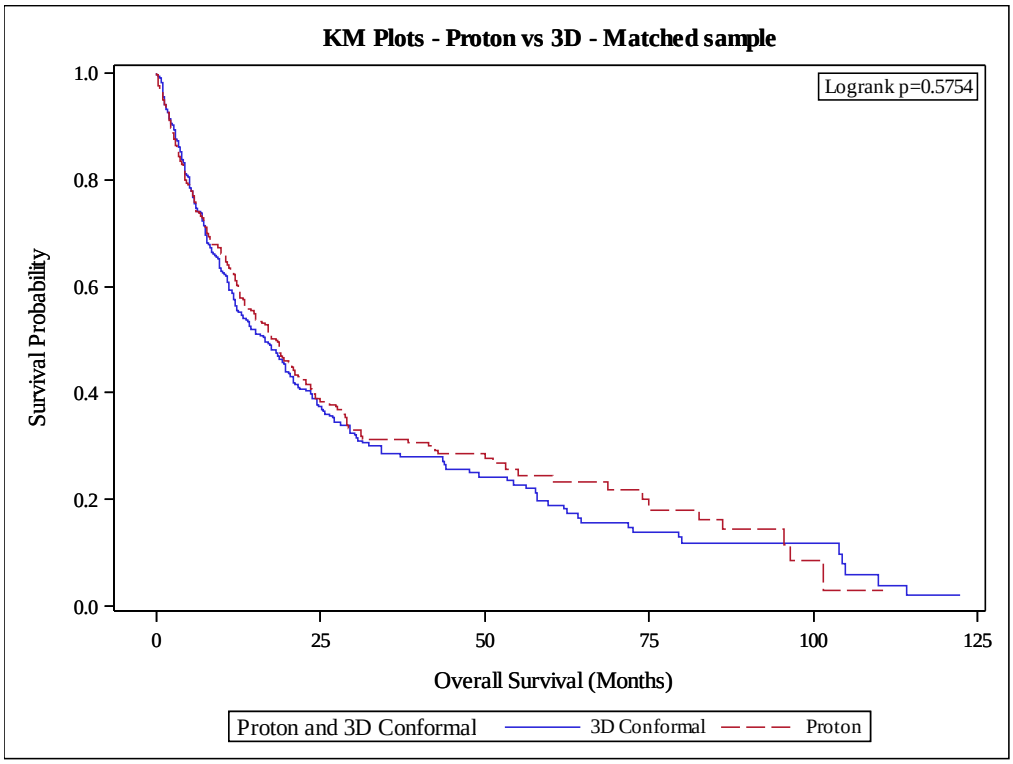
Proton and External Beam NOS	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
External Beam NOS	305	225 (74%)	80 (26%)	15 (12.3, 21.6)	57.1% (51.3%, 62.5%)	14.6% (9.9%, 20.3%)
Proton	305	206 (68%)	99 (32%)	18.4 (14.3, 21)	61.8% (56.0%, 67.1%)	22.7% (16.6%, 29.3%)

Table 11. Association with survival for proton versus 3D Conformal cohorts in matched sample

			Overall Survival (Months)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Proton and 3D Conformal	3D Conformal	300	1.06 (0.87-1.28)	0.576	0.575
	Proton	300	-	-	

Figure 6.

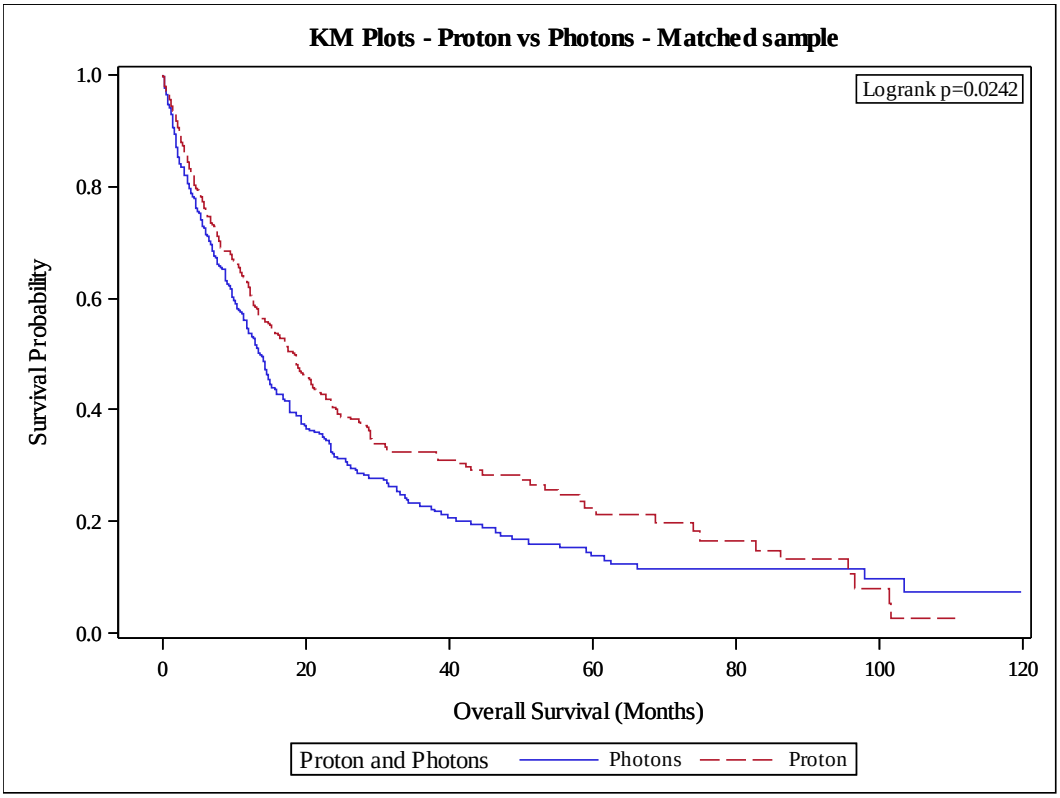


Proton and 3D Conformal	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
3D Conformal	300	222 (74%)	78 (26%)	16.6 (12.1, 19.8)	56.6% (50.7%, 62.1%)	19.0% (13.7%, 25.0%)
Proton	300	201 (67%)	99 (33%)	18.3 (13.7, 21)	61.2% (55.3%, 66.5%)	24.6% (18.6%, 31.1%)

Table 12. Association with survival for proton versus photon cohorts in matched sample

			Overall Survival (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Proton and Photons	Photons	308	1.24 (1.03-1.49)	**0.025**	**0.024**
	Proton	308	-	-	

Figure 7. KM Plot for Proton vs. Photon cohorts in matched sample



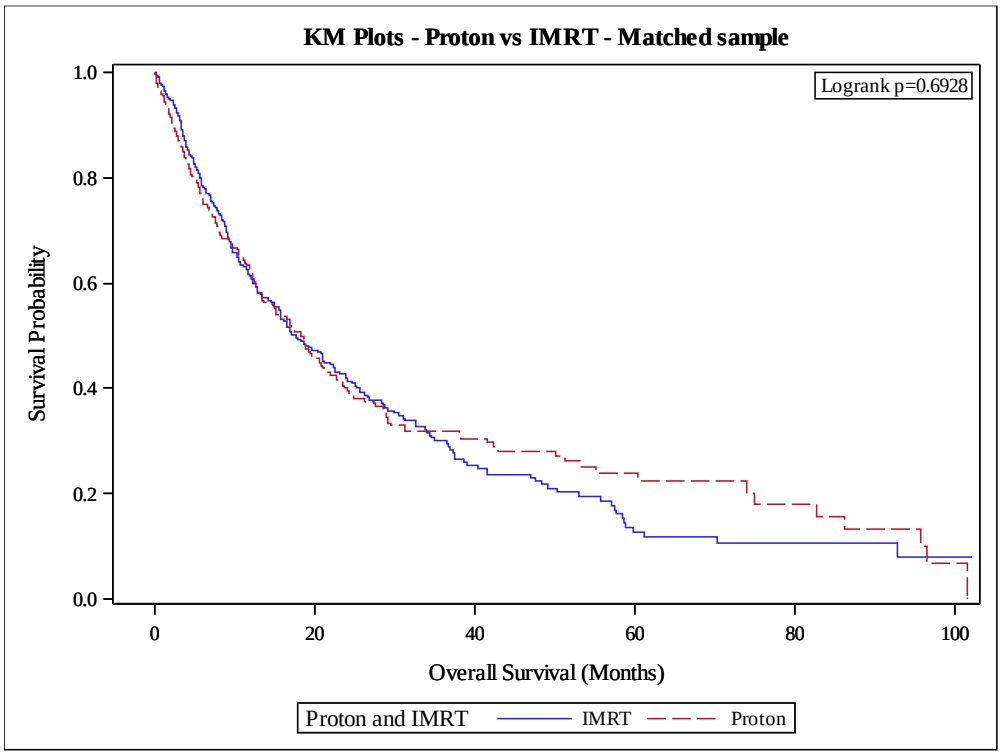
Proton and Photons	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Photons	308	239 (78%)	69 (22%)	13.5 (11.7, 15.1)	54.1% (48.3%, 59.5%)	13.8% (9.4%, 19.1%)
Proton	308	208 (68%)	100 (32%)	18.4 (14.8, 21)	61.9% (56.1%, 67.1%)	22.5% (16.4%, 29.1%)

Table 13. Association with survival for proton versus IMRT cohorts in matched sample

			Overall Survival (Months)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Proton and IMRT	IMRT	293	1.04 (0.85-1.27)	0.697	0.693
	Proton	293	-	-	

Figure 8. KM Plot for Proton vs. IMRT cohorts in matched sample



Proton and IMRT	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
IMRT	293	212 (72%)	81 (28%)	17.7 (14.9, 22.4)	61.0% (55.1%, 66.4%)	12.7% (8.0%, 18.5%)
Proton	293	195 (67%)	98 (33%)	18.4 (14.3, 21)	62.0% (56.0%, 67.3%)	23.8% (17.6%, 30.5%)

Table 14. Results from stratified Cox proportional hazards model.

Stratification	Effect Comparison	Overall Survival (Months) Hazard Ratio (95%CI)	HR P-value	Type3 P-value
			-	-
Facility Type :	**Proton :**	-	-	**0.003**
Academic/Research Program	Yes (n=160) vs. No (n=169)	0.66 (0.51-0.87)	**0.003**	-
Community Cancer Program/Other	Yes (n=16) vs. No (n=13)	0.66 (0.26-1.70)	0.388	-
Comprehensive Community Cancer Program	Yes (n=125) vs. No (n=120)	1.30 (0.98-1.73)	0.069	-
Integrated Network Cancer Program	Yes (n=7) vs. No (n=6)	0.39 (0.13-1.23)	0.108	-
Charlson-Deyo Score :	**Proton :**	-	-	0.087
0	Yes (n=206) vs. No (n=225)	0.95 (0.76-1.19)	0.677	-
1	Yes (n=66) vs. No (n=60)	0.81 (0.54-1.21)	0.310	-
2	Yes (n=36) vs. No (n=23)	0.44 (0.23-0.85)	**0.014**	-

* This table only shows interaction effect with type 3 p-value < 0.1 .
* Excluded interaction effects due to p-value >= 0.1: Proton*race_cat Proton*sex Proton*FACILITY_LOCATION_CD Proton*i