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Clinical Investigation

National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer

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Summary

This study is an analysis of the National Cancer Database, examining survival with photon versus proton radiation for non-small cell lung cancer. Additionally, factors associated with

Purpose: To analyze outcomes and predictors associated with proton radiation therapy for non-small cell lung cancer (NSCLC) in the National Cancer Database.

Methods and Materials: The National Cancer Database was queried to capture patients with stage I-IV NSCLC treated with thoracic radiation from 2004 to 2012. A logistic regression model was used to determine the predictors for utilization of proton radiation therapy. The univariate and multivariable association with overall survival were assessed by Cox proportional hazards models along with log−rank tests. A propensity score matching method was implemented to balance baseline covariates and eliminate selection bias.

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The data used in the study are derived from a deidentified National Cancer Database (NCDB) file. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigator.

Conflict of interest: none.

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receipt of proton therapy were analyzed. Our findings demonstrate that receipt of proton radiation is associated with higher income levels, along with improved survival with proton compared with photon radiation therapy.

Results: A total of 243,822 patients (photon radiation therapy: 243,474; proton radiation therapy: 348) were included in the analysis. Patients in a ZIP code with a median income of <$46,000 per year were less likely to receive proton treatment, with the income cohort of $30,000 to $35,999 least likely to receive proton therapy (odds ratio 0.63 [95% confidence interval (CI) 0.44-0.90]; $P = .011$). On multivariate analysis of all patients, non-proton therapy was associated with significantly worse survival compared with proton therapy (hazard ratio 1.21 [95% CI 1.06-1.39]; $P < .01$). On propensity matched analysis, proton radiation therapy (n = 309) was associated with better 5-year overall survival compared with non-proton radiation therapy (n = 1549), 22% versus 16% ($P = .025$). For stage II and III patients, non-proton radiation therapy was associated with worse survival compared with proton radiation therapy (hazard ratio 1.35 [95% CI 1.10-1.64], $P < .01$).
Conclusions: Thoracic radiation with protons is associated with better survival in this retrospective analysis; further validation in the randomized setting is needed to account for any imbalances in patient characteristics, including positron emission tomography −computed tomography staging.

Introduction

Lung cancer is the leading cause of cancer-related death in the United States for both men and women, with an estimated 86,380 and 71,660 deaths, respectively, in 2015 (1). Clinical outcomes for newly diagnosed non-small cell lung cancer (NSCLC) are best for patients with resectable, early-stage disease, with 5-year overall survival (OS) in these patients ranging from 50% to 70%. However, for patients with locally advanced NSCLC, 5-year survival after treatment with definitive radiation therapy and concurrent chemotherapy remains modest, at approximately 16% (2).

The current standard of care for unresectable, stage III NSCLC is photon-based, external beam radiation therapy with concurrent chemotherapy, set forth by multiple studies showing an OS advantage with the addition of concurrent, platinum-based chemotherapy to daily radiation therapy alone or sequential chemoradiation therapy (3-5). Over the last several decades the most poignant advance in this disease has been the use of concurrent chemotherapy, which yields an absolute survival benefit at 5 years of 5% relative to sequential chemotherapy (6).

In an effort to improve OS for this population, the Radiation Therapy Oncology Group (RTOG) completed RTOG 0617, a large, randomized trial examining standard-dose (60 Gy, 2 Gy per fraction) versus high-dose (74 Gy, 2 Gy per fraction) thoracic radiation with concurrent chemotherapy. This contemporary randomized study demonstrated a median survival of 29 months in the control arm (7). The high-dose arm was found to be inferior, with a median survival of 20 months. Factors predicting inferior survival included the dose to the heart (the V5 and V30 [volume receiving ≥5 Gy and ≥30 Gy, respectively]) and the maximum grade of esophagitis. These findings showed a strong association between radiation doses to normal tissues and OS after concurrent chemoradiation. Thus, technologies that can reduce or spare radiation dose to normal tissues while still delivering full dose to the tumor volume may confer a clinical benefit.

Proton radiation therapy is an advanced treatment modality with a distinct dose deposition pattern known as a Bragg peak that results in minimal to no exit dose and reduced entrance dose compared with photon therapy. This affords an opportunity to increase the therapeutic ratio of radiation therapy for lung cancer given the close proximity of the target volume to multiple sensitive critical organs at risk, such as the heart, lungs, esophagus, spinal cord, and brachial plexus. Multiple studies have demonstrated the dosimetric benefit of proton therapy in comparison with conventional photon therapy (8, 9) and both retrospective and prospective clinical data have demonstrated the safety and efficacy of proton therapy for both early-stage and advanced-stage NSCLC (10-13). However, proton therapy is associated with higher cost and at this time is not universally approved by insurance carriers owing to lack of clinical data showing improved efficacy relative to photon-based radiation.

To that end, the present study utilizes the National Cancer Database (NCDB), a large, prospectively acquired database that captures approximately 70% of newly diagnosed cancers in the United States, to evaluate the impact of proton radiation therapy on OS in NSCLC.

Methods and Materials

Data source

The NCDB is an oncology outcomes database developed in 1989 and jointly administered by the American College of Surgeons and the American Cancer Society. It includes data

from more than 1500 accredited cancer centers across the United States and captures approximately 70% of all newly diagnosed cancer cases annually (14).

Study population

The NCDB was queried to capture patients with stage I-IV NSCLC treated with thoracic radiation from 2004 to 2012. Deindentified patient information was abstracted from the NCDB Participant User File. All patients that received radiation to their lungs or chest as coded for "Proton Therapy," "External Beam NOS" (NOS = not otherwise specified), "3D Conformal," "Photons," and "IMRT" (intensity modulated radiation therapy) were included in the analysis. Patients with missing outcomes were excluded from the analysis.

Outcomes

Overall survival was examined as the primary outcomes, which was defined as time from date of first radiation treatment to death or last follow-up.

Study variables

Patient information related to demographic data included age, sex, race, year of diagnosis, treatment facility type, great circle distance (distance in miles between the patient's residence and the hospital that reported the case), facility location, insurance, and median income at the ZIP code of residence. The treatment facility types were categorized as academic centers (including National Cancer Institute−designated cancer centers), community cancer centers, and comprehensive community cancer programs. Facility type was classified according to the Commission on Cancer accreditation criteria, which provides a general classification of the structural characteristics of each reporting facility. This is based on an institution's caseload and services offered. One hundred to 500 cancer cases per year define community cancer centers, whereas comprehensive community cancer centers must service more than 500 cancer cases per year. Academic/research programs also see more than 500 cancer cases per year but also provide postgraduate medical training for residents and a full range of diagnostic and treatment services on site. Integrated network cancer programs do not have a minimum case requirement and differ in that they are part of a joint venture involving several facilities. The patient residential location was classified and compared as urban versus metro versus rural locations. The Charlson-Deyo Comorbidity Index was used as a measure of comorbidity. It was categorized as 0, 1, or 2 and above to indicate increasing level of comorbid conditions.

Patients of all stages were included in this work and grouped into three cohorts according to American Joint Committee on Cancer (AJCC) Analytic Stage Group (stage 0/I vs stage II/III vs stage IV). Of note, cases are coded using the *AJCC Cancer Staging Manual* edition in use during the year in which the case was diagnosed. Three histology subtypes of NSCLC were examined: adenocarcinoma versus squamous cell carcinoma versus others.

The treatment variables included in this analysis included radiation modality (Proton Therapy, External Beam NOS, 3D Conformal, Photons, and IMRT), chemotherapy, and surgery. Radiation treatment modality is defined as the dominant modality used to deliver the most clinically significant dose to the primary volume of interest. Radiation treatment modality is extracted from the radiation oncologists's summary letter by institutional coders. "External Beam NOS" is defined as insufficient information to determine the specific modality beyond external beam radiation. "Photons" is defined as external beam utilizing photons with energy ranging from 2 MV to >19 MV, also including photon courses with mixed beam energies. "3D Conformal" is defined as an external beam technique beam using multiple, fixed portals shaped to conform to a defined target volume, and clearly described as 3-dimensional therapy in the patient record. "IMRT" is defined as a distinct external beam technique, clearly stated in the radiation summary. "Protons" is defined as treatment delivered using proton therapy.

Of note, when describing all non-proton modalities together, the term "non-proton" is used. The term "Photons" refers to the NCDB classification of treatment modality as defined above.

Statistical analysis

Statistical analysis was conducted using SAS version 9.3 (SAS Institute, Cary NC) and SAS macros or software developed at the Department of Biostatistics and Bioinformatics at our institution (15). The significance level was set at $P<.05$. The univariate association of each covariate with two cohorts of proton and photon (Proton vs External Beam NOS, 3D Conformal, Photons, and IMRT combined together) were assessed using the χ^2 test for categorical covariates and analysis of variance for numerical covariates. This was repeated with cohorts of Proton and one of each of the four other treatment modalities (External Beam NOS, 3D Conformal, Photons, IMRT). The univariate association of each covariate with OS was assessed using Cox proportional hazards models and log−rank tests. A multivariable Cox proportional hazard model was fit by a backward variable selection method applying an $\alpha = .20$ removal criteria. This was performed to compare proton versus photon and to compare proton versus each of the other treatment modalities. Kaplan-Meier (KM) plots were produced to compare the survival curves by treatment subgroups along with log−rank P value.

The propensity score matching method was also implemented to reduce treatment selection bias. A logistic regression model regressing receipt of proton therapy on all

baseline covariates was carried out to estimate the propensity score for each patient. Initial propensity matching was undertaken with a 1:1 match of non-proton to proton patients. Because of the small sample size in the proton cohort, a second propensity matched analysis was undertaken, with five non-proton patients matched to one proton patient through a Greedy algorithm with caliper being 0.2 times of standard deviation of logit propensity score (16). After matching, the balance of covariate between two cohorts was evaluated by the standardized differences, and a value of <0.1 was considered as negligible imbalance (17). The effects were estimated in the matched sample by a Cox model with a robust variance estimator (18) for OS. Propensity score matching was repeated, and KM curves were then produced for proton versus non-proton treatment.

Results

In the NSCLC Participant User File, 243,822 NSCLC patients diagnosed between the years 2004 and 2012 had received thoracic radiation and were included in this analysis. Approximately 0.1% (n = 348) of the patients received proton therapy, compared with 99.9% (n = 243,474) who were treated with photons. Of the patients treated with photons, the modalities were as follows: IMRT, 22,346 (9%); Photons, 140,035 (57%); 3D Conformal, 36,406, (15%); and External Beam NOS, 44,687 (18%). The median age of the population was 68 years, and 57% were male. The majority of patients were stage II and III (60%). Detailed patient and treatment characteristics are provided in Table 1. The median follow-up was 39.6 months for the proton cohort and 59.5 months for the non-proton cohort. The median radiation dose (59.4 Gy for the non-proton group, 60 Gy for the proton group) was not significantly different in patients receiving non-proton radiation versus proton radiation. The median number of fractions given was 30. Univariate associations of covariates with proton and non-proton treatment are shown in Table E2 (available online at www.redjournal.org).

Receipt of proton treatment

Patients treated at comprehensive community cancer programs and community cancer programs were less likely to receive proton therapy compared with academic centers (odds ratios [ORs] 0.34 [95% confidence interval (CI) 0.27-0.44] and 0.23 [95% CI 0.14-0.38], respectively, $P<.001$; details shown in Table 2). Privately insured patients were less likely to receive proton therapy relative to government-insured patients (OR 0.67 [95% CI 0.51-0.87], $P = .003$). Patients in a ZIP code with a median income of <$46,000 per year were also less likely to receive proton treatment, with the income cohort of $30,000 to $35,999 least likely to receive proton therapy (OR 0.63 [95% CI 0.44-0.90]; $P = .011$). Full data for receipt of proton therapy is shown in Table 2.

Table 1 Descriptive statistics for all variables (n = 243,822)

Variable	n (%)
Proton	
No	243,474 (99.9)
Yes	348 (0.1)
Treatment	
Proton Therapy	348 (0.1)
External Beam NOS	44,687 (18.3)
3D Conformal	36,406 (14.9)
Photons	140,035 (57.4)
IMRT	22,346 (9.2)
Facility type	
Academic/research program	67,590 (27.9)
Community cancer program/other	34,206 (14.1)
Comprehensive community cancer program	124,810 (51.5)
Integrated network cancer program	15,904 (6.6)
Missing	1312
Facility location	
Northeast	46,270 (19.1)
South	95,796 (39.5)
Midwest	71,603 (29.5)
West	28,841 (11.9)
Missing	1312
Sex	
Male	138,474 (56.8)
Female	105,348 (43.2)
Race	
White	207,549 (85.7)
Black	29,461 (12.2)
Other	5143 (2.1)
Missing	1669
Insurance type	
Not insured	8323 (3.5)
Private insurance	68,079 (28.4)
Government insurance	16,3616 (68.2)
Missing	3804
Median income quartiles 2000	
Not available	9647
<$30,000	39,691 (16.9)
$30,000-$35,999	49,199 (21.0)
$36,000-$45,999	70,439 (30.1)
$46,000+	74,846 (32.0)
Percent no high school degree quartiles 2000	
Not available	9667
≥29%	45,393 (19.4)
20%-28.9%	63,020 (26.9)
14%-19.9%	58,112 (24.8)
<14%	67,630 (28.9)
Urban/rural 2003	
Metro	183,565 (78.3)
Urban	44,756 (19.1)
Rural	6261 (2.7)
Missing	9240
Charlson-Deyo score	
0	150,490 (61.7)
1	65,574 (26.9)
2	27,758 (11.4)

(*continued on next page*)

Table 1 (*continued*)

Variable	n (%)
Year of diagnosis	
2004	27,148 (11.1)
2005	27,254 (11.2)
2006	27,163 (11.1)
2007	27,150 (11.1)
2008	27,771 (11.4)
2009	27,155 (11.1)
2010	26,493 (10.9)
2011	26,706 (11.0)
2012	26,982 (11.1)
Primary site	
C340, main bronchus	15,193 (6.2)
C341, upper lobe, lung	139,351 (57.2)
C342, middle lobe, lung	8903 (3.7)
C343, lower lobe, lung	55,271 (22.7)
C348, overlapping lesion of lung	3707 (1.5)
C349, lung, NOS	21,397 (8.8)
Laterality	
Left	132,778 (54.5)
Right	90,763 (37.2)
Other	20,281 (8.3)
Grade	
Well differentiated, differentiated, NOS	6940 (2.8)
Moderately differentiated, moderately well differentiated, intermediate differentiation	39,980 (16.4)
Poorly differentiated	80,706 (33.1)
Undifferentiated, anaplastic	4857 (2.0)
Cell type not determined, not stated or not applicable, unknown primaries, high-grade dysplasia	111,339 (45.7)
Surgery	
No	212,781 (87.4)
Yes	30,627 (12.6)
Missing	414
AJCC Analytic Stage Group	
Stage 0	415 (0.2)
Stage I	34,092 (14.7)
Stage II	23,176 (10.0)
Stage III	115,695 (49.8)
Stage IV	58,742 (25.3)
Missing	11,702
Stage group (collapsed)	
Stage 0 or 1	34,507 (14.9)
Stage 2 or 3	138,871 (59.8)
Stage 4	58,742 (25.3)
Missing	11,702
Histology	
Adenocarcinoma	74,538 (30.6)
Squamous cell carcinoma	91,685 (37.6)
Other	77,599 (31.8)
Chemotherapy	
No	76,101 (31.6)
Yes	164,812 (68.4)
Missing	2909
Great circle distance (units = 50 mi)	
Mean	0.43
Median	0.17
Minimum	0.00
Maximum	95.43
SD	1.54
Missing	5532.00
Age at diagnosis (y)	
Mean	67.66
Median	68.00
Minimum	18.00
Maximum	90.00
SD	10.98
Missing	0.00
Tumor size (cm^3)	
Mean	4.90
Median	4.30
Minimum	0.10
Maximum	99.00
SD	4.51
Missing	46,877.00
Regional + boost dose (Gy)	
Mean	54.15
Median	59.40
Minimum	0.01
Maximum	1395.60
SD	36.29
Missing	13,413.00
No. of treatments to this volume	
Mean	27.19
Median	30.00
Minimum	1.00
Maximum	998.00
SD	22.57
Missing	24,601.00

Abbreviations: AJCC = American Joint Committee on Cancer; NOS = not otherwise specified; SD = standard deviation.
Values are number (percentage) unless otherwise noted.

Survival analysis

On univariate survival analysis, non-proton was associated with worse survival compared with proton therapy (hazard ratio [HR] 1.36 [95% CI 1.20-1.55], $P<.001$). Each of the photon modalities was associated with inferior survival compared with proton therapy, except for IMRT (HRs: IMRT 1.06 [95% CI 0.93-1.21], $P=.36$; Photons 1.43 [95% CI 1.26-1.63], $P<.001$; 3D Conformal 1.26 [95% CI 1.11-1.43], $P<.001$; and External Beam NOS 1.39 [95% CI 1.23-1.58], $P<.001$).

The results from univariate analysis were confirmed with multivariable analysis. Non-proton therapy was associated with significantly worse survival (HR 1.21 [95% CI 1.06-1.39], $P=.005$). Except for IMRT, the non-proton modalities were associated with inferior survival on multivariable analysis (Table 3). On multivariate analysis of proton therapy versus Photons (NCDB Photon classification),

Table 2 Multiple Logistic Regression Analysis for factors associated with receipt of proton therapy

Covariate	Proton = yes		
	OR (95% CI)	OR *P*	Type 3 *P*
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/other	0.23 (0.14-0.39)	**<.001**	
Academic/research program	-	-	
Facility location			
Northeast	0.17 (0.12-0.23)	**<.001**	**<.001**
South	0.29 (0.23-0.38)	**<.001**	
Midwest	0.08 (0.05-0.12)	**<.001**	
West	-	-	
Insurance type			
Not insured	0.54 (0.24-1.22)	.138	**.005**
Private insurance	0.65 (0.50-0.86)	**.003**	
Government insurance	-	-	
Median income quartiles 2000			
<$30,000	0.67 (0.46-0.98)	**.038**	**.039**
$30,000-$35,999	0.64 (0.45-0.90)	**.012**	
$36,000-$45,999	0.82 (0.62-1.07)	.142	
$46,000+	-	-	
Urban/rural 2003			
Metro	0.75 (0.36-1.56)	.447	**<.001**
Urban	0.32 (0.14-0.73)	**.006**	
Rural	-	-	
Year of diagnosis			
2004	0.68 (0.48-0.96)	**.031**	**<.001**
2005	0.43 (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	0.98 (0.21-4.62)	.976	**.035**
C341, upper lobe, lung	0.59 (0.40-0.86)	**.006**	
C342, middle lobe, lung	0.52 (0.26-1.05)	.069	
C343, lower lobe, lung	0.48 (0.31-0.74)	**<.001**	
C348, overlapping lesion of lung	0.40 (0.12-1.32)	.134	
C349, lung, NOS	-	-	
Laterality			
Left	3.53 (0.85-14.68)	.083	.120
Right	3.97 (0.95-16.59)	.059	
Other	-	-	
Surgery			
No	0.81 (0.59-1.10)	.179	.179
Yes	-	-	
Stage group (collapsed)			
Stage 0 or 1	2.27 (1.59-3.24)	**<.001**	**<.001**
Stage 2 or 3	1.35 (0.99-1.84)	.058	
Stage 4	-	-	
Great circle distance (units = 50 mi)	1.06 (1.04-1.08)	**<.001**	**<.001**

Abbreviations: CI = confidence interval; OR = odds ratio.

Number of observations in the original data set = 243,822. Number of observations used = 213,494. Backward selection with an α level of removal of .20 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, and race.

Bold values are indicative of statistical significance, $P < .05$

Table 3 Multivariable survival analysis of overall survival (all treatment modalities)

Covariate	Overall survival (mo)		
	HR (95% CI)	HR *P*	Type 3 *P*
Treatment			
IMRT	1.05 (0.91-1.20)	.524	**<.001**
Photons	1.25 (1.09-1.43)	.001	
3D Conformal	1.16 (1.01-1.33)	.035	
External Beam NOS	1.26 (1.10-1.44)	<.001	
Proton Therapy	-	-	

Abbreviations: 3D = 3-dimensional; HR = hazard ratio; IMRT = intensity modulated radiation therapy; NOS = not otherwise specified.

Number of observations in the original data set = 243,822. Number of observations used = 211,080. Backward selection with an α level of removal of .20 was used. No variables were removed from the model.

Bold values are indicative of statistical significance, $P < .05$

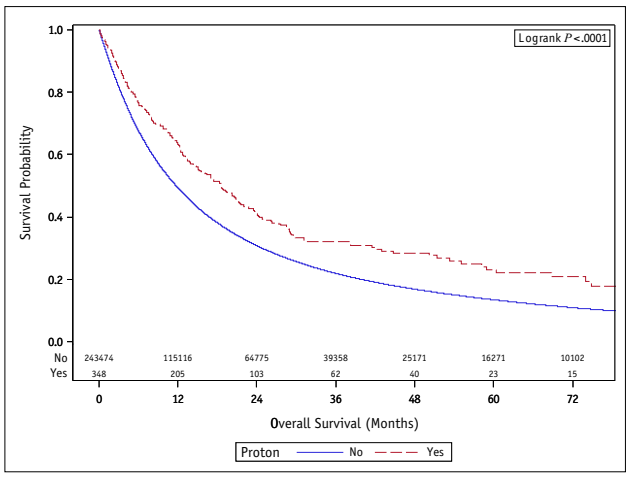
receipt of Photon treatment was associated with an increased risk of death (HR 1.46, $P<.001$).

On KM analysis, patients treated with proton therapy had significantly better OS compared with those treated with non-proton therapy, with a 5-year OS rate of 23.1% versus 13.5% ($P<.0001$; Fig. 1). Proton therapy was also associated with a better 5-year OS rate for all modalities (except for IMRT) when compared with 3D Conformal (14.7%, $P<.01$), External Beam NOS (13.5%, $P<.01$), IMRT (17.2%, $P=.286$), and Photons (12.6%, $P<.01$), $P<.001$ for all comparisons. There was no significant difference in 5-year OS for stage IV patients by treatment modality.

On propensity matched multivariate analysis (308 photon patients with 308 proton patients), non-proton therapy showed a trend for worse OS compared with proton therapy (HR 1.16 [95% CI 0.97-1.39], $P=.12$). To improve statistical power, a second propensity matched analysis was undertaken (though notably this was not the a priori study design) with 5:1 matching (1541 photon patients with 309 proton patients). Non-proton therapy was associated with a higher hazard for OS in the sample of patients of all stages (HR 1.18 [95% CI 1.02-1.37], $P=.026$). On KM analysis of 5:1 matched samples, proton therapy had better 5-year survival rate compared with non-proton therapy (22% vs 16%, $P=.025$; Fig. 2).

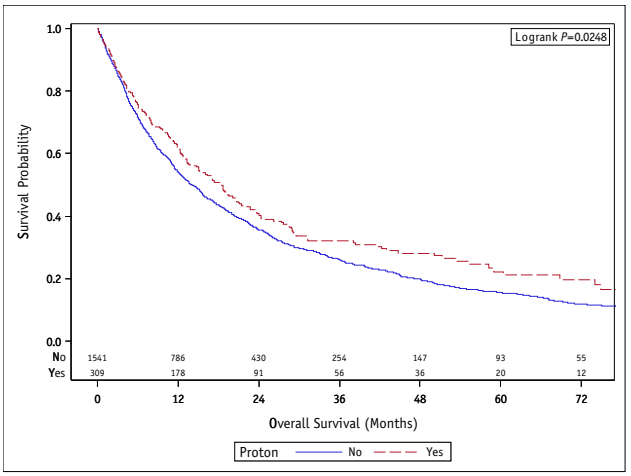
Analysis of stage II and III patients

In all, 138,871 patients with stage II (17%) and III (83%) NSCLC were identified in this cohort. Forty-three percent of patients were female, and 86% were white. Median age was 68 years (range, 18-90 years). Fourteen percent of patients received surgery, whereas 86% of patients did not receive surgery as part of treatment. Chemotherapy was given to 79% of patients. Twenty-eight percent of the patients were treated at academic centers. Forty-one percent of the patients were of squamous cell carcinoma histology, and 29% had adenocarcinomas. Median dose was 60 Gy for patients receiving both proton- and photon-based treatment. There was no significant difference in receipt of chemotherapy between patients treated with protons versus non-protons. Similarly, there were no differences in median age at diagnosis, stage, tumor size, or tumor histology between



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%)

Fig. 1. Survival analysis for proton versus non-proton radiation for all patients, stages I-IV. *Abbreviation:* CI = confidence interval.



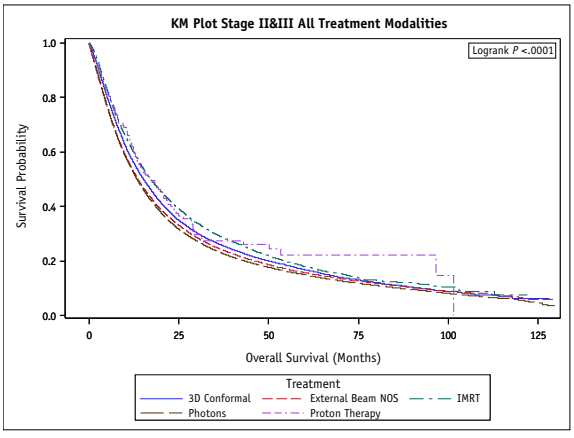
Proton	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
No	1541	1160 (75%)	381 (25%)	14 (12.8, 15.6)	54.2% (51.6%, 56.7%)	15.7% (13.5%, 18.1%)
Yes	309	209 (68%)	100 (32%)	18.4 (14.8, 21.2)	62.0% (56.2%, 67.2%)	22.3% (16.3%, 28.9%)

Fig. 2. Survival analysis for proton versus non-proton treatment with propensity matching, all stages. *Abbreviation:* CI = confidence interval.

patients treated with protons versus non-protons. Univariate associations of covariates with proton and non-proton treatment for stage II and III patients are shown in Table E3 (available online at www.redjournal.org).

Treatment modalities included 3D Conformal (n = 22,369), External Beam NOS (n = 23,553), IMRT (n = 14,328), Photons (n = 78,428), and Proton therapy (n = 193). Detailed patient and treatment characteristics for the stage II and III cohort are provided in Table E1 (available online at www.redjournal.org).

On multivariable analysis for OS in stage II and III, patients with a missing radiation dose value were excluded. Survival was better with proton therapy relative to non-proton therapy. The HR for survival for photon therapy was 1.35 (95% CI 1.10-1.64, $P<.01$). Multivariate analysis was then repeated without excluding patients without a dose value recorded. In this analysis, there was a trend toward worse OS with non-proton therapy, with an HR of 1.19 (95% CI 0.99-1.42, $P=.057$). A third multivariable analysis was then performed, examining each treatment modality separately. This demonstrated that survival was better with Proton therapy relative to External Beam NOS (HR 1.23 [95% CI 1.01-1.43], $P=.04$) and Photons (HR 1.23 [95% CI 1.03-1.47], $P=.02$). For 3D Conformal and IMRT, however, there was not a statistically significant improvement relative to Proton therapy (respectively, HR 1.12 [95% CI 0.94-1.34], $P=.19$; HR 1.02 [95% CI 0.85-1.22], $P=.83$). Figure 3 demonstrates KM analysis for all treatment modalities for stage II and III patients. On propensity matched KM analysis (5:1, 880 non-proton patients, 176 proton patients), there were not statistically significant differences between proton and non-proton therapy (22% vs 17%, $P=.408$).



Treatment	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
3D Conformal	22369	17235 (77%)	5134 (23%)	15.2 (14.9, 15.5)	57.2% (56.6%, 57.9%)	16.9% (16.3%, 17.5%)
External Beam NOS	23553	18556 (79%)	4997 (21%)	13.6 (13.3, 13.9)	53.8% (53.1%, 54.4%)	15.8% (15.3%, 16.4%)
IMRT	14328	9911 (69%)	4417 (31%)	17.2 (16.7, 17.6)	61.1% (60.3%, 61.9%)	18.0% (17.2%, 19.0%)
Photons	78428	64002 (82%)	14426 (18%)	13.4 (13.2, 13.6)	53.3% (53.0%, 53.7%)	15.0% (14.7%, 15.3%)
Proton Therapy	193	123 (64%)	70 (36%)	17.4 (13.4, 21.5)	61.8% (54.4%, 68.4%)	22.3% (14.6%, 31.0%)

Fig. 3. Survival analysis for proton versus photon-modality based radiation in stage II and III patients. *Abbreviations:* 3D = 3-dimensional; CI = confidence interval; IMRT = intensity modulated radiation therapy; KM = Kaplan-Meier; NOS = not otherwise specified.

Discussion

Normal tissue tolerability drives both acute and late side effects of radiation therapy. Patients with unresectable, locally advanced lung cancer are often compromised from a cardiopulmonary standpoint, given the typical history of significant prior or active tobacco use and advanced age at diagnosis. Acute toxicities of thoracic chemoradiation treatment include esophagitis and radiation pneumonitis. Phase 3 data demonstrate that these side effects occur in 10% to 25% of patients with standard, photon-based radiation therapy (2, 7). The RTOG protocol 0617 was a pivotal study that demonstrated the maximum grade of esophagitis during treatment and the heart dose (V5 and V30) were significant predictors of mortality after concurrent chemoradiation.

Strategies to reduce radiation dose to critical organs have evolved over time. Computed tomography (CT)-based simulation and planning with 3D conformal radiation techniques became widely adopted in late 1990s and early 2000s, and they are the current minimum technologic standard. Use of CT-based simulation and 3D planning in stage III lung cancer has been shown to improve survival relative to 2-dimensional radiation techniques, with a 23% relative reduction in the risk of death (19). More advanced radiation techniques, including IMRT or proton radiation therapy, are thought to be appropriate if needed to deliver curative radiation safely (20). Usage of IMRT has increased over time. In RTOG 0617, approximately 50% of patients were treated with IMRT, and the other half received 3D conformal radiation therapy (7). From a technical standpoint, IMRT uses multiple intensity levels across each radiation beam, allowing for improved conformal and homogenous dose distributions over complex target volumes with sparing of adjacent normal structures. There are no prospective, randomized data comparing 3D conformal radiation therapy with IMRT in stage III NSCLC. However, a secondary analysis of RTOG 0617 has been presented in abstract form and found that patients treated with IMRT had larger and less-favorable tumors, but with reduced risk of grade 3 and higher pneumonitis. Additionally, the heart V40 was significantly lower in patients treated with IMRT, and larger heart V40 was associated with worse survival (21). Additionally, retrospective data have shown a survival benefit with IMRT compared with 3D conformal techniques in locally advanced NSCLC and stage T3 and T4 primary tumors (22).

Proton therapy is another strategy to reduce radiation doses to normal tissues. In terms of radiation dosimetry, one of the greatest advantages to proton therapy is the ability to spare dose to the heart. However, because of the

higher cost of proton therapy relative to other radiation modalities, limited availability, and lack of comparative effectiveness data, the role of proton therapy is controversial. At the time of submission, there are 22 operational proton centers within the United States and 14 centers under construction or in development, according to data compiled by the National Association for Proton Therapy.

Owing to the limited clinical experience with proton therapy in lung cancer, little cost-effectiveness data exist. Centers for Medicare and Medicaid 2016 national payor rates are approximately $18,000 for 30 fractions of IMRT, versus approximately $45,000 for 30 fractions of proton therapy (free-standing facilities). Given the increased cost of advanced radiation technologies, and with proton therapy approximately double the cost of IMRT, high level evidence is desirable to support widespread implementation of these therapies. The early clinical experience with thoracic proton radiation includes a phase 2 study from the M. D. Anderson Cancer Center using 74-Gy proton therapy with weekly carboplatin and paclitaxel. Median survival was 29.4 months, and rates of grade 3 or higher esophagitis and pneumonitis were very low. These encouraging results led the RTOG to design RTOG 1308, a randomized, phase 3 trial comparing 70-Gy photon radiation versus 70-Gy proton radiation, with concurrent chemotherapy (platinum-based doublet). This study is currently actively enrolling and will provide prospective data regarding the efficacy of IMRT versus proton radiation in stage II and III NSCLC.

The present study is the largest study to date evaluating proton versus photon radiation therapy. Our analysis found improved survival for patients treated with proton radiation therapy, including the subset of patients with stage II and III NSCLC. Of the photon-based modalities, 5-year survival was highest with IMRT treatment. The clinical experience with proton therapy in lung cancer is still developing, and data such as these support further use of proton therapy as a means to protect normal tissues when delivering thoracic radiation.

Results of a multi-institutional randomized study comparing IMRT with passively scattered proton therapy for locally advanced NSCLC were presented in abstract form at the 2016 American Society of Clinical Oncology annual meeting (23). Investigators found no differences in the study's primary endpoint of treatment failure (defined as local progression or grade $\geq$3 radiation pneumonitis) for IMRT versus passively scattered proton therapy. Overall survival outcomes were not reported. A caveat to this study is that before enrollment, patients had to have IMRT and passively scattered proton therapy plans that both met normal tissue constraints. Conceivably, there are many patients with large tumors that may not meet normal constraints with an IMRT plan but normal tissue sparing could be accomplished with proton therapy, especially sparing of the heart. This therefore could dilute any potential benefit of proton therapy. Additionally, the heart-sparing characteristics of proton therapy are most likely to manifest in an OS endpoint and would be less likely to influence local control or radiation pneumonitis rates.

In the context of these recently reported results, the present study does present OS data that favor proton therapy for stage II and III patients. In the present study, the advantage of protons seems to be strongest when compared with less-advanced radiation modalities, namely the NCDB classifications of External Beam NOS and Photons. On multivariate analysis for OS in stage II and III patients, treatment with Protons compared with IMRT did not demonstrate improvements in OS.

Another important finding of this study is related to patients who receive proton treatment: patients residing in a ZIP code with a median income of $46,000 or higher were more likely to receive proton therapy. This is an important point, because access to emerging healthcare technologies is not uniform in the United States. Further interventions aimed at improving access to proton therapy in underserved populations may be useful and should be incorporated into the design of future clinical trials evaluating proton therapy in lung cancer.

Of note, there are some potential drawbacks to proton therapy, other than the readily apparent cost differential. Proton therapy is more dependent on changes in lung density and tumor size during treatment, which can lead to changes in dose deposition that could be potentially detrimental to both tumor coverage and dose to normal tissues. Proton delivery thus requires more frequent CT imaging to determine whether technical changes need to be made. This adds more complexity to proton delivery relative to IMRT and 3D conformal radiation therapy techniques, requiring more physician treatment planning time and a more robust physics infrastructure.

A major limitation of the present study is the lack of both acute and late toxicity data within the NCDB. Other important data to consider when comparing photon with proton radiation are dose volume histogram data generated during the radiation planning process. These data are used to evaluate whether radiation plans meet accepted normal tissue constraints, and unfortunately are not available within the NCDB. Other important clinical data, such as quality of life outcomes and smoking status, are not accounted for within the database. Additionally, although the data are prospectively collected, they are subject to miscoding errors. Last, the total number of patients treated with proton therapy within the NCDB is modest, given this is an emerging modality. For those reasons, a first analysis was undertaken in all patients independent of stage, with a subgroup analysis performed in stage II and III patients, the population for which proton therapy would be most widely utilized and likely to achieve the greatest benefit in radiation dosimetry sparing of normal structures. Within stage II and III patients, there is heterogeneity of treatment, with some patients receiving surgery as part of therapy. However, the majority of patients in this stage II and III analysis were treated nonsurgically.

Another limitation to this study is the overall small number of patients treated with proton therapy relative to

non-proton/photon therapy, and possible selection bias in patients receiving proton therapy. Over time the number of patients treated with proton therapy will increase and provide a robust analysis of proton versus non-proton/photon therapy; however, at the present time the total number of proton treated patients is small. Patients receiving proton therapy are unique in that they have the means to access an emerging technology. This is a major confounder that cannot be fully accounted for outside of a randomized study. Propensity score analysis using baseline patient characteristics was undertaken to reduce selection bias as much as possible; however, not all proton patients were able to be matched to a photon patient, and it is possible that unaccounted differences in patients who undergo proton therapy exist, thus confounding the relationship between proton therapy and OS seen in this analysis. An additional confounding variable could be positron emission tomography−CT staging. This information is not available within the NCDB; we are thus unable to determine whether both groups had similar rates of positron emission tomography−CT staging, and this could be a potential confounding variable that cannot be addressed within this dataset.

In conclusion, this analysis demonstrates an improvement in survival with proton therapy in NSCLC compared with photon-based radiation. Prospective, randomized data are needed to confirm these findings, and RTOG 1308 is an ongoing randomized trial comparing proton with photon-based radiation for stage II and III NSCLC. Further data are needed to compare toxicities and quality of life for proton versus photon-based thoracic radiation in NSCLC.

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