Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Survival after radiation for stage I and II non-small cell lung cancer with positive margins

Brian C. Gulack, MD, MHS,[a] *Morgan L. Cox, MD,*[a] *Chi-Fu Jeffrey Yang, MD,*[a] *Paul J. Speicher, MD, MHS,*[a] *H. Volkan Kara, MD,*[b] *Thomas A. D'Amico, MD,*[a] *Mark F. Berry, MD, MHS,*[c] *and Matthew G. Hartwig, MD*[a,*]

[a] *Department of Surgery, Duke University Medical Center, Durham, North Carolina*
[b] *Department of Thoracic Surgery, Marmara University Faculty of Medicine, Istanbul, Turkey*
[c] *Department of Cardiothoracic Surgery, Stanford University, Palo Alto, California*

ARTICLE INFO

Article history:
Received 13 July 2017
Received in revised form
7 September 2017
Accepted 12 October 2017
Available online 14 November 2017

Keywords:
Radiation therapy
Positive margins
Non-small cell lung cancer
Lobectomy

ABSTRACT

Background: There is limited data guiding treatment for positive margins following lobectomy for early-stage non-small cell lung cancer (NSCLC). Using data from the National Cancer Data Base, we sought to determine whether radiation therapy following lobectomy for stage I or II NSCLC was associated with improved overall survival in patients with positive margins.

Methods: Patients who underwent lobectomy without induction therapy for stage I or II NSCLC (1998-2006) with positive resection margins were selected. Patients were stratified by administration of radiation therapy following surgery, and overall survival was estimated using the Kaplan–Meier method. The association between radiation therapy and survival was adjusted for nonrandom treatment selection using Cox proportional hazards regression modeling.

Results: Positive margins were recorded in 1934 of 49,563 (3.9%) patients who underwent lobectomy for stage I or II NSCLC. Positive margin status was associated with significantly worse 5-year survival (34.5% *versus* 57.2%, $P < 0.001$). After selection of patients with positive margins and known radiation status and exclusion of patients who had upstaged disease or received radiation therapy for palliative indications, radiation therapy was used in 579 of 1579 patients (38.2%) but was not associated with a significant difference in the likelihood of death during subsequent follow-up (hazard ratio: 1.10, 95% confidence interval: 0.90, 1.35).

Conclusions: Positive margins following lobectomy for stage I or II NSCLC are associated with reduced 5-year survival. Postsurgical radiation is not strongly associated with an improvement in overall survival among these patients.

* *Corresponding author*. Duke University Medical Center, DUMC, Box #3863, Durham, NC 27710. Tel.: +1919 613-5635; fax: +1 919 613-5653.
E-mail address: matthew.hartwig@duke.edu (M.G. Hartwig).
0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2017.10.025

Introduction

Lung cancer is the second most common cancer in the United States, and the number one cause of cancer-related deaths among both men and women.[1] Roughly 30% of patients with non-small cell lung cancer (NSCLC) present with stage I or II disease.[2] Anatomic surgical lobectomy that achieves complete resection is the recommended treatment for early-stage disease if feasible.[3] However, positive surgical margins on pathologic analysis are reported to occur in 4%-6% of patients, most commonly at the bronchial margin, and are associated with significantly reduced long-term survival.[4-6]

Present recommendations regarding the optimal approach to positive margins following lobectomy for stage I or II NSCLC generally rely on expert opinion due to a paucity of literature on the subject. The National Comprehensive Cancer Network (NCCN) guidelines recommend either re-resection or radiation, with or without chemotherapy, in the event of positive margins following resection of stage I or II NSCLC; however, re-resection is preferred.[3] Nevertheless, clinical management of this scenario varies, considering that a recent survey demonstrated that medical oncologists are split almost evenly regarding the use of additional radiation therapy in these patients with 48% of respondents stating they would use radiation therapy and 52% stating that they would not.[7] In this study, we sought to determine whether radiation therapy after surgery was associated with improved overall survival in patients with positive margins following lobectomy for stage I or II NSCLC using a national data set where a large cohort of patients with this relatively uncommon situation could be assembled.

Materials and methods

National Cancer Data Base

The National Cancer Data Base (NCDB) is a clinical oncology database which collects information from over 1500 Committee on Cancer–accredited hospitals.[8] The NCDB captures data on roughly 70% of newly diagnosed cancer cases each year within the United States. This cancer registry includes patient demographics, comorbidities, treatment regimens, postoperative length of stay, readmission, and long-term overall survival.

Patient population

Institutional review board approval for exempt status was obtained before performing the analysis. The NCDB was queried for patients who underwent a lobectomy (defined as Facility Oncology Registry Data System codes 30 and 33) from 1998-2006 for stage I or II NSCLC (defined by the American Joint Committee on Cancer lung cancer staging system, 6th edition). This timeframe was selected because this was the period during which long-term survival was available in the NCDB at the time of data analysis. Patients with unknown follow-up were excluded along with patients who were known to receive neoadjuvant chemotherapy or radiation. Patients who died within 30 days of surgery were unlikely to ever be considered or given additional radiation; therefore, they were also excluded from the analysis in order to prevent selection bias that could overestimate the benefit of additional radiation therapy.

Variables

Patient characteristics, comorbidities, treatment regimens, and follow-up for the study population were obtained from the NCDB. Timing of chemotherapy and radiation were determined either by comparing the time to therapy as compared to the time to definitive surgery, or the variables "systemic surgery sequence" and "radiation surgery sequence." Although the NCDB distinguishes between R1 disease (microscopically positive margins), R2 disease (macroscopically positive margins), and residual tumor not otherwise specified, we chose to group these patients together for the majority of the analysis as the present NCCN guidelines do not differentiate recommended treatment by R1 *versus* R2 status.[3] For all survival analyses, overall survival was defined as the time from diagnosis to either death or loss to follow-up.

Statistical analysis

First, an unadjusted analysis comparing baseline characteristics by margin status was performed to determine factors associated with having a positive margin following lobectomy for stage I or II NSCLC. A Kaplan–Meier analysis was then performed to compare overall survival by margin status. Next, any patient with negative margin status was excluded. Patients who were upstaged to stage III or stage IV disease following surgery were also excluded in order to remove any patients who would have received adjuvant radiation therapy for other indications, such as N2 positivity. Furthermore, any patient receiving radiation therapy for palliative reasons was also excluded. Patients were grouped by whether they received treatment with radiation therapy after surgery and compared with regards to baseline patient and tumor characteristics. Continuous variables were compared using the Wilcoxon rank sum test, whereas categorical variables were compared using Fisher's exact test or the chi-squared test as appropriate based on cohort size.

Multivariable logistic regression was performed in order to determine factors associated with the use of radiation therapy for positive margins following lobectomy. The covariates included in the model were those felt to most likely influence the use of additional radiation therapy which included age, sex, race, private insurance status (as a marker of socioeconomic status), academic center status, pathologic grade, and pathologic stage.

Kaplan–Meier analysis was used to determine the unadjusted association between additional radiation use and long-term survival. Because Charlson/Deyo comorbidity index was felt to potentially have a significant impact on long-term outcomes, the remainder of the analysis only included patients in the NCDB where this data was recorded (the years 2003-2006).

A Cox proportional hazards regression model was utilized in order to adjust for patients' demographic and tumor characteristics. Covariates for adjustment included in the model were determined *a priori* and included age, sex, race, private insurance status, Charlson/Deyo comorbidity index, pathologic grade, and pathologic stage. An adjusted survival curve was created using the Cox proportional-hazards model to illustrate the association between postsurgical radiation therapy and overall survival for a patient of median age with the most common sex, race, insurance status, Charlson/Deyo comorbidity index, pathologic grade, and pathologic stage of the cohort.

A sensitivity analysis including only patients with R1 disease was also performed to determine if the overall findings were consistent among this specific cohort. A second sensitivity analysis was also performed among patients with node negative disease on pathologic examination as these patients are the most likely to receive a cure from surgical resection and therefore are likely the most impacted by positive margins.

Complete case analysis was used for all adjusted models so all subjects with missing variables were excluded. The proportional hazards assumption meaning the hazard functions for survival curves of two strata were proportional over time was tested for all Cox proportional hazards regression models. A P value of <0.05 was used to define statistical significance. All statistical analyses were performed using R software, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 – Baseline characteristics of patients following lobectomy for stage I or II non-small cell lung cancer by margin status.

Variable	Overall	Negative margins	Positive margins	P value
N	49,563	47,629 (96.1%)	1934 (3.9%)	
Age	68 (61, 74)	68 (61, 74)	69 (61, 75)	0.215
Female	24,810 (50.1%)	23,923 (50.2%)	887 (45.9%)	<0.001
Race				0.001
White	44,607 (90.0%)	42,910 (90.1%)	1697 (87.7%)	
Black	3492 (7.0%)	3314 (7.0%)	178 (9.2%)	
Other/Unknown	1464 (3.0%)	1405 (2.9%)	59 (3.1%)	
Private insurance	17,449 (35.2%)	16,785 (35.2%)	664 (34.3%)	0.426
Academic center	16,568 (33.4%)	16,039 (33.7%)	529 (27.4%)	<0.001
Charlson/Deyo comorbidity index				0.299
0	14,071 (55.5%)	13,541 (55.5%)	530 (58.1%)	
1	8580 (33.9%)	8289 (33.9%)	291 (31.9%)	
2+	2681 (10.6%)	2589 (10.6%)	92 (10.1%)	
Tumor size				<0.001
≤2.0 cm	15,731 (32.3%)	15,397 (32.9%)	334 (17.9%)	
2.1-3.0 cm	13,863 (28.5%)	13,389 (28.6%)	474 (25.3%)	
3.0-5.0 cm	13,188 (27.1%)	12,566 (26.8%)	622 (33.3%)	
5.1-7.0 cm	3943 (8.1%)	3674 (7.8%)	269 (14.4%)	
>7.0 cm	1962 (4.0%)	1791 (3.8%)	171 (9.1%)	
Clinical stage				<0.001
1A	25,818 (54.3%)	25,273 (55.2%)	545 (29.8%)	
1B	16,491 (34.7%)	15,728 (34.4%)	763 (41.7%)	
2A	1550 (3.3%)	1457 (3.2%)	93 (5.1%)	
2B	3717 (7.8%)	3289 (7.2%)	428 (23.4%)	
Pathologic stage				<0.001
1A	19,409 (46.2%)	19,173 (47.2%)	236 (16.9%)	
1B	15,076 (35.9%)	14,567 (35.9%)	509 (36.5%)	
2A	2340 (5.6%)	2228 (5.5%)	112 (8.0%)	
2B	5156 (12.3%)	4617 (11.4%)	539 (38.6%)	
Adjuvant chemotherapy	1472 (21.4%)	1363 (20.5%)	109 (42.7%)	<0.001
Adjuvant radiation	3917 (8.0%)	3158 (6.7%)	759 (40.8%)	<0.001
Length of stay (days)	6 (4, 9)	6 (4, 9)	6 (4, 9)	0.426
30-day readmission	1120 (4.6%)	1075 (4.6%)	45 (5.2%)	0.407

Continuous variables are presented as median (interquartile range), whereas categorical variables are presented as frequency (percentage).

Results

A total of 49,563 patients underwent lobectomy for stage I or II NSCLC during the study period, of which 1934 (3.9%) were found to have positive margins following surgery. Patients with positive margins were more likely to be black (9.2% *versus* 7.0%), male (54.1% *versus* 49.8%), and have larger tumors (tumor size >5.0 cm: 23.5% *versus* 11.6%, Table 1). Patients with positive margins were less likely to be treated at an academic center (27.4% *versus* 33.7%). On unadjusted analysis, positive margins status was found to be associated with significantly worse overall survival (5-year survival: 34.5% *versus* 57.2%, $P < 0.001$, Fig. 1).

After selection of patients with positive margins and known radiation status and exclusion of patients who had upstaged disease or received radiation therapy for palliative indications, 1579 patients remained of which 880 (55.7%) had microscopic residual tumor (R1 disease), 63 (4.0%) had macroscopic residual tumor (R2 disease), and 636 (40.3%) had positive margins not otherwise specified. Of these patients, 579 (38.2%) received postoperative radiation therapy. The median time to radiation therapy after surgery was 52 days (interquartile range: 36, 84), and the median radiation dose was 50.4 Gy (interquartile range: 41.4, 60.0).

On unadjusted analysis, patients who received radiation therapy tended to be younger (median age 67 *versus* 70), were more likely to be male (58.7% *versus* 52.9%), were more likely to have private insurance (36.6% *versus* 31.6%), and were less likely to be treated at an academic center (19.5% *versus* 30.8%, Table 2). Patients who received radiation therapy were more likely to have pathologic stage II disease (61.5% *versus* 36.5%) and were more likely to receive adjuvant chemotherapy (58.0% *versus* 27.3%). Following adjustment with multivariable logistic regression, age, academic center status, and pathologic stage remained significantly associated with radiation use (Fig. 2).

Following the removal of patients from before 2003 in order to allow for adjustment with Charlson/Deyo comorbidity index, 739 patients remained with 252 (34.1%) receiving postoperative radiation therapy. On unadjusted analysis, radiation therapy was found to be associated with significantly reduced 5-year survival (33.2% *versus* 43.6%, $P = 0.007$, Fig. 3). However, following adjustment, no significant mortality difference remained (adjusted hazard ratio [HR]: 1.10, 95% confidence interval [CI]: 0.90, 1.35, Fig. 4). Following the selection of only patients with R1 disease, 440 patients remained. Among this cohort, radiation therapy was still not associated with a significant difference in overall survival (adjusted HR: 1.17, 95% CI: 0.90, 1.51).

From the cohort of patients with positive margins, the 452 patients who had no nodal disease on pathologic examination were then selected, of which 132 (29.2%) received radiation therapy. Although radiation therapy was associated with a significantly worse survival on unadjusted analysis (HR: 1.57, 95% CI: 1.23, 2.00), following adjustment, no significant difference in overall survival remained (adjusted HR: 1.27, 95% CI: 0.98, 1.66).

Discussion

Despite previous evidence demonstrating that positive margins following lobectomy for NSCLC are associated with reduced survival, there is still uncertainty regarding the

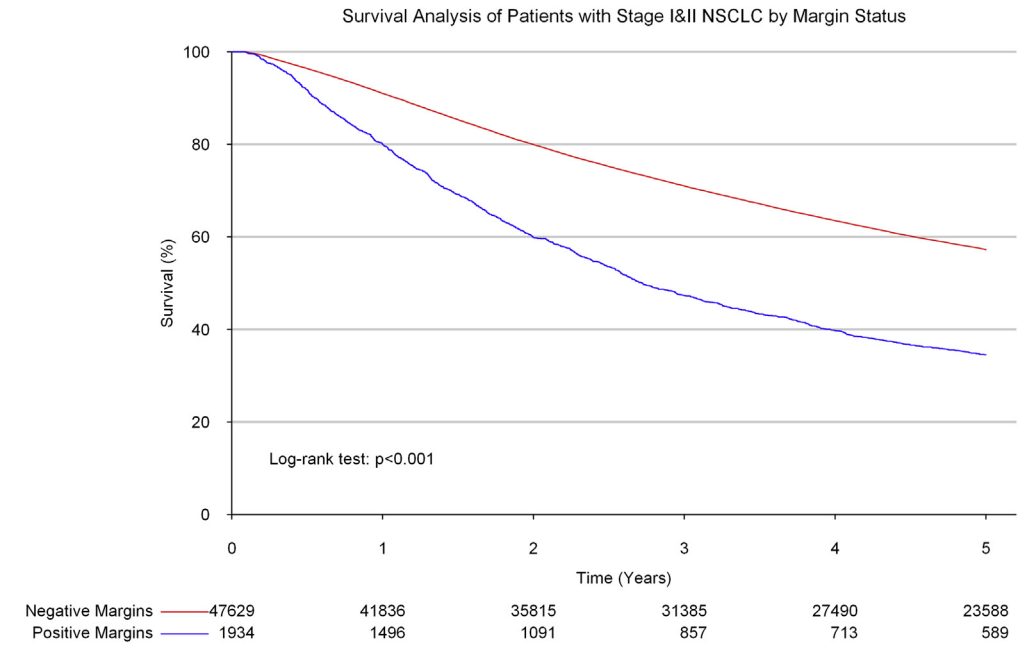

Fig. 1 – Comparison of unadjusted survival by margin status in patients undergoing lobectomy for stage I or II non-small cell lung cancer. (Color version of figure is available online.)

Table 2 – Baseline characteristics of patients with positive margins following lobectomy for stage I or II non-small cell lung cancer by adjuvant radiation treatment.

Variable	Overall	No adjuvant radiation	Adjuvant radiation	P value
N	1579	938 (61.8%)	579 (38.2%)	
Age	69 (61, 75)	70 (62, 76)	67 (60, 73)	<0.001
Female	703 (44.5%)	442 (47.1%)	239 (41.3%)	0.030
Race				0.764
White	1388 (87.9%)	823 (87.7%)	508 (87.7%)	
Black	148 (9.4%)	87 (9.3%)	57 (9.8%)	
Other/Unknown	43 (2.7%)	28 (3.0%)	14 (2.4%)	
Private insurance	534 (33.8%)	296 (31.6%)	212 (36.6%)	0.049
Academic center	418 (26.5%)	289 (30.8%)	113 (19.5%)	<0.001
Charlson/Deyo comorbidity index				0.414
0	432 (57.8%)	275 (56.5%)	154 (61.1%)	
1	242 (32.4%)	164 (33.7%)	73 (29%)	
2+	74 (9.9%)	48 (9.9%)	25 (9.9%)	
Tumor size				<0.001
≤2.0 cm	285 (18.8%)	198 (21.8%)	76 (13.8%)	
2.1-3.0 cm	391 (25.7%)	244 (26.8%)	137 (24.8%)	
3.0-5.0 cm	505 (33.2%)	295 (32.4%)	187 (33.9%)	
5.1-7.0 cm	213 (14.0%)	105 (11.5%)	99 (17.9%)	
>7.0 cm	125 (8.2%)	68 (7.5%)	53 (9.6%)	
Clinical stage				<0.001
1A	460 (30.8%)	330 (37.2%)	115 (20.9%)	
1B	626 (41.9%)	380 (42.8%)	231 (41.9%)	
2A	67 (4.5%)	31 (3.5%)	34 (6.2%)	
2B	341 (22.8%)	146 (16.5%)	171 (31.0%)	
Pathologic stage				<0.001
1A	235 (17.2%)	188 (22.6%)	40 (8.1%)	
1B	497 (36.3%)	340 (40.9%)	149 (30.3%)	
2A	108 (7.9%)	58 (7.0%)	46 (9.4%)	
2B	528 (38.6%)	245 (29.5%)	256 (52.1%)	
Adjuvant chemotherapy	80 (37.6%)	39 (27.3%)	40 (58.0%)	<0.001
Length of stay (days)	6 (4, 9)	6 (5, 10)	6 (4, 9)	0.031
30-day readmission	35 (5.0%)	21 (4.5%)	13 (5.6%)	0.686

Continuous variables are presented as median (interquartile range), whereas categorical variables are presented as frequency (percentage).

optimal management of this clinical scenario.[3,4,6] Here, we have demonstrated that positive margins occur roughly 4% of the time following lobectomy for stage I or II NSCLC, that positive margin status is associated with worse overall survival, and that among patients with positive margins, additional radiation therapy is not associated with a long-term survival benefit.

This study is not the first to demonstrate that there may be no benefit to radiation treatment for positive margins following surgical resection of lung cancer.[5,6,9-11] Hancock *et al.*[5] performed an analysis of the NCDB evaluating patients undergoing any formal surgical resection of NSCLC which was found to be stage I-III on pathologic diagnosis. On multivariable analysis, they did not find a significant association between radiation therapy and improved overall survival for patients with either pathologic stage I or III disease. Interestingly, there was a benefit among patients with pathologic stage II disease. Although using the same database, our analysis adds important findings to the literature as it focuses specifically on patients undergoing a lobectomy for stage I or II disease.

Although adjuvant radiation therapy is an option for the treatment of positive margins following lobectomy for early stage lung cancer, present NCCN guidelines recommend re-resection if possible.[3] Although more radical resections are often associated with a higher perioperative morbidity and mortality, previous studies have demonstrated improved long-term survival associated with re-resection for positive margins following lobectomy for stage I or II NSCLC.[4,11,12] Unfortunately, these data are limited to small single-center reviews. For example, Snijder *et al.*[6] reviewed 28 patients who were found to have microscopic residual disease, five of which underwent re-resection. Median survival following re-resection for these five patients was 38.4 months compared

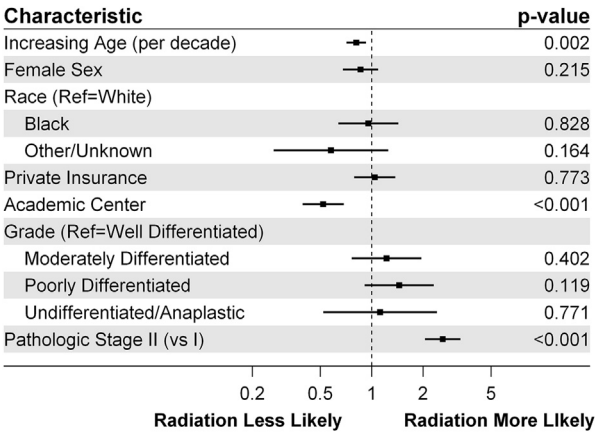

Fig. 2 – Factors associated with receiving postoperative radiation therapy in patients with positive margins following lobectomy for stage I or II non-small cell lung cancer. Adjusted odds ratio is denoted on the x-axis. Error bars indicate the 95% confidence interval.

to 25.5 months in patients who received additional radiation and no re-resection.[6] Likewise, Liewald *et al.*[12] demonstrated improved survival following radical resection as compared to an R1 resection for both stage I and II disease.[4] Unfortunately, due to the nature of the NCDB, we were not able to compare patients who were re-resected for positive margins to determine how patients treated with this methodology fared as compared to patients treated with radiation therapy.

There are important limitations that should be taken into account when interpreting our findings. First and foremost is the possibility of unobserved confounding and bias incurred by performing this study retrospectively. Patients who received radiation following lobectomy for positive margins may have substantial baseline differences as compared to those who did not receive radiation. Although we attempted to adjust for this through the use of multivariable modeling in addition to the exclusion of patients who died within 30 days of surgery, there is still a chance that this significantly affects our findings. Second, although margin status is reported in the NCDB, margin location (bronchial *versus* pleural) is not. Treatment for a positive bronchial margin is much different than that for a positive N1 lymph node, and unfortunately, we could not take this into account in our analysis. Third, although we could determine which patients received postoperative radiation therapy, we could not differentiate why this radiation was given. Therefore, some patients who received radiation may have done so for reasons other than positive margin status, also leading to bias. Furthermore, there have been advances in radiation therapy over the past decade, and it is possible that present therapy provides more benefit than during the time period captured in this study.[13]

Fourth, there is unfortunately a high amount of missing data regarding the timing of chemotherapy, which is why we did not include it in our adjusted analyses. We could not differentiate if patients received neoadjuvant chemotherapy from 2003-2005 as the variable was not yet available. It is possible that some patients who received this therapy remained in the data set. However, investigation of data from 2006 when timing of chemotherapy was available reveals it to be very rare for a patient to get neoadjuvant chemotherapy without also receiving neoadjuvant radiation. Therefore, it is unlikely that many patients who received neoadjuvant chemotherapy remained in the analysis. Fifth, the NCDB does not differentiate the type of disease present in the positive margin. Multiple studies have demonstrated that residual *in situ* disease does not significantly affect survival, and it is possible that some patients included in this analysis had *in situ* residual disease.[6,14] Conversely, it is possible that some of the positive margins were due to peribronchial lymphatic

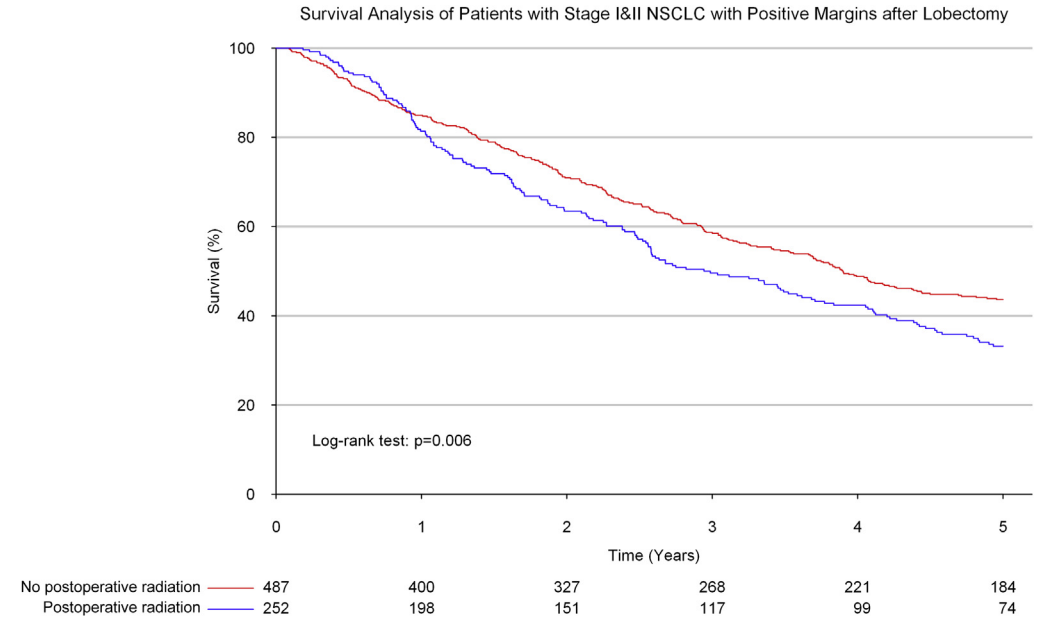

Fig. 3 – Unadjusted overall survival among patients with positive margins following lobectomy for stage I or II non-small cell lung cancer by the use of postoperative radiation therapy. (Color version of figure is available online.)

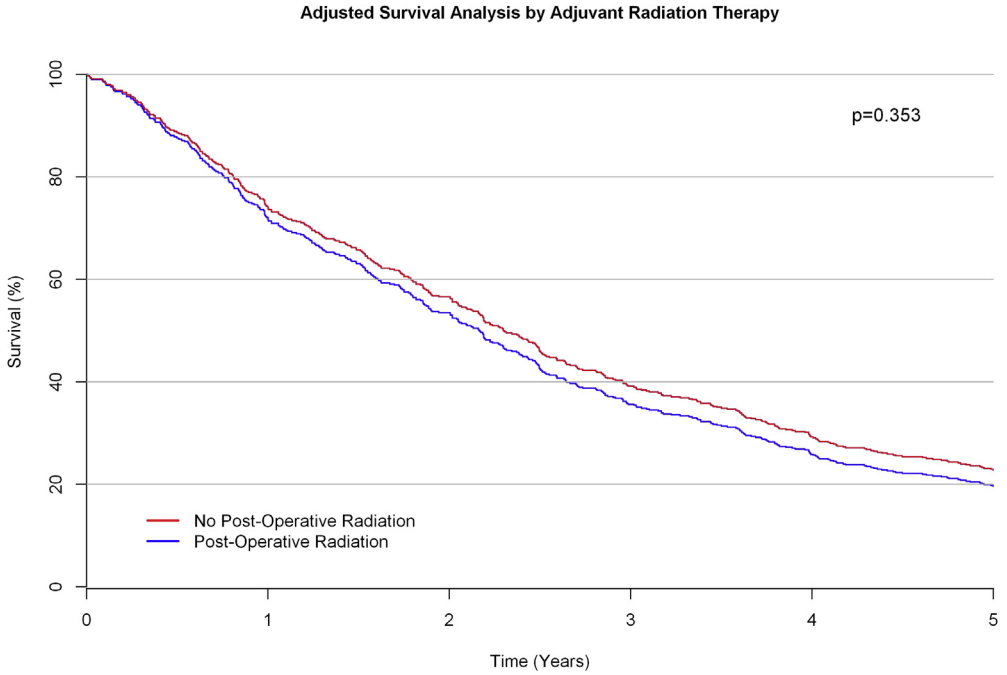

Fig. 4 – Adjusted overall survival by postoperative radiation therapy use among patients who received a lobectomy for stage I or II non-small cell lung cancer with positive margins. (Color version of figure is available online.)

positivity also decreasing the external validity of our findings. Finally, although the NCDB provides a much larger sample of patients than would be available via a single institution or even a multi-institutional study, there is always the chance of a type II statistical error in which we were not able to see a statistically significant difference due to a lack of power, even though there may still be a significant difference. Nonetheless, due to the size of our study and our inability to demonstrate even a nonsignificant benefit with postoperative radiation therapy, if our findings were due to a type II statistical error, the number needed to treat with radiation therapy in order to gain a survival advantage would be so high that it would question the overall feasibility of this treatment.

In conclusion, we have demonstrated that positive margin status following lobectomy for stage I or II NSCLC is associated with significantly reduced survival. Furthermore, the use of radiation therapy in these patients is not strongly associated with a significant improvement in survival. Despite the importance of these findings, there is still potential for substantial bias in this retrospective study, and therefore prospective investigation is necessary in order to validate our results.

Acknowledgment

Authors' contributions: C-F.J.Y., P.J.S., and H.V.K. were involved with the study design, statistical analysis, interpretation of data, and final approval of the manuscript. B.C.G. and M.L.C. were primarily responsible for analysis, interpretation of data, and creation of this manuscript. T.A.D., M.F.B., and M.G.H. were involved in all aspects of this study including design, analysis, manuscript drafting, and final approval.

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in this 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 investigators. The statistical analysis was reviewed and approved by Lin Gu, MS. Additional statistical support was provided by Cindy Green, PhD.

This research did not receive any specific grant from funding agencies in the public, commercial, or non-for-profit sectors.

Disclosure

T.A.D. serves as a consultant for Scanlan. The remaining authors have no conflicts of interest to declare.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65:5–29.
2. Groome PA, Bolejack V, Crowley JJ, et al, IASLC International Staging Committee, Cancer Research and Biostatistics, Observers to the Committee, Participating Institutions. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007;2:694–705.

3. N.C.C.N. (NCCN), NCCN clinical practice guidelines in oncology, Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed February 22, 2017.
4. Wind J, Smit EJ, Senan S, Eerenberg JP. Residual disease at the bronchial stump after curative resection for lung cancer. *Eur J Cardiothorac Surg*. 2007;32:29–34.
5. Hancock JG, Rosen JE, Antonicelli A, et al. Impact of adjuvant treatment for microscopic residual disease after non-small cell lung cancer surgery. *Ann Thorac Surg*. 2015;99:406–413.
6. Snijder RJ, Brutel de la Rivière A, Elbers HJ, van den Bosch JM. Survival in resected stage I lung cancer with residual tumor at the bronchial resection margin. *Ann Thorac Surg*. 1998;65:212–216.
7. Califano R, Karamouzis MV, Banerjee S, et al. Use of adjuvant chemotherapy (CT) and radiotherapy (RT) in incompletely resected (R1) early stage Non-Small Cell Lung Cancer (NSCLC): a European survey conducted by the European Society for Medical Oncology (ESMO) young oncologists committee. *Lung Cancer*. 2014;85:74–80.
8. A.C. of Surgeons, National Cancer Database, Available at: http://www.facs.org/cancer/ncdb. Accessed February 22, 2017.
9. Hofmann HS, Taege C, Lautenschläger C, Neef H, Silber RE. Microscopic (R1) and macroscopic (R2) residual disease in patients with resected non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2002;21:606–610.
10. Gebitekin C, Gupta NK, Satur CM, et al. Fate of patients with residual tumour at the bronchial resection margin. *Eur J Cardiothorac Surg*. 1994;8:339–342. discussion 342-344.
11. Ghiribelli C, Voltolini L, Paladini P, Luzzi L, Di Bisceglie M, Gotti G. Treatment and survival after lung resection for non-small cell lung cancer in patients with microscopic residual disease at the bronchial stump. *Eur J Cardiothorac Surg*. 1999;16:555–559.
12. Liewald F, Hatz RA, Dienemann H, Sunder-Plassmann L. Importance of microscopic residual disease at the bronchial margin after resection for non-small-cell carcinoma of the lung. *J Thorac Cardiovasc Surg*. 1992;104:408–412.
13. Ahmad SS, Duke S, Jena R, V Williams M, Burnet NG. Advances in radiotherapy. *BMJ*. 2012;345:e7765.
14. Massard G, Doddoli C, Gasser B, et al. Prognostic implications of a positive bronchial resection margin. *Eur J Cardiothorac Surg*. 2000;17:557–565.