Prophylactic cranial irradiation is associated with improved survival following resection for limited stage small cell lung cancer

Benjamin J. Resio, Jessica Hoag, Alexander Chiu, Andres Monsalve, Andrew P. Dhanasopon, Daniel J. Boffa, Justin D. Blasberg

Section of Thoracic Surgery, Department of Surgery, Yale School of Medicine, New Haven, CT 06520-8062, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: DJ Boffa, JD Blasberg; (IV) Collection and assembly of data: BJ Resio, JD Blasberg; (V) Data analysis and interpretation: BJ Resio, JD Blasberg; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Justin D. Blasberg, MD. Yale New Haven Hospital, 330 Cedar Street, BB205, New Haven, CT 06520, USA.
Email: Justin.blasberg@yale.edu.

Background: Brain metastases are a major cause of mortality in patients with small cell lung cancer (SCLC). Prophylactic cranial irradiation (PCI) may improve survival among patients that respond to chemotherapy. Less is known about the outcomes of PCI following surgical resection of SCLC. The purpose of this study was to determine if patients who underwent initial surgical resection of SCLC benefit from PCI.

Methods: Adult patients in the National Cancer Database (NCDB) who underwent complete resection for primary, non-metastatic SCLC between 2004 and 2015 were identified. Patients that received preoperative chemotherapy or who did not receive appropriate adjuvant chemotherapy were excluded. Patients were grouped by treatment with or without cranial radiation within 8 months of resection. Survival was estimated using Kaplan-Meier and Cox multivariable analysis, adjusting for patient and tumor characteristics.

Results: A total of 859 patients met inclusion criteria (202 received PCI and 657 did not). Kaplan-Meier analysis demonstrated that patients treated with PCI had significantly improved survival compared to no PCI (5-year survival 59% *vs.* 50%, logrank P=0.0038). Multivariable cox models confirmed a significantly decreased hazard of death for patients receiving PCI (HR: 0.70, 95% CI: 0.55–0.89, P=0.003). In subset analyses, PCI was associated with significantly improved survival for node positive patients, but not node negative patients.

Conclusions: PCI is associated with increased survival for patients following surgical resection of SCLC. Patients with positive lymph nodes appear to benefit the most, while it remains unclear if patients with negative lymph nodes derive a benefit. Further study is warranted to clarify which subsets of patients should be treated with PCI.

Keywords: Lung cancer; surgery; prophylactic cranial irradiation (PCI); small cell lung cancer (SCLC)

Introduction

Brain metastases are a major cause of mortality in patients with small cell lung cancer (SCLC). Even in the best of circumstances, patients who initially respond to chemotherapy have a 50% chance of developing brain metastases within 2 years (1). Consequently, prophylactic cranial irradiation (PCI) has become an important adjuvant therapy to be considered for SCLC patients (2,3).

Over 85% of patients with SCLC present with clinical evidence of locoregional or metastatic disease. As a result, the primary management of SCLC is often limited to systemic chemotherapy for these advanced stage patients (4). In cases of limited stage SCLC, surgical resection followed

by systemic therapy is also a reasonable treatment pathway and is supported by current NCCN guidelines (5). These recommendations additionally extend to surgically managed patients with clinical evidence of non-SCLC and incidental SCLC on pathologic review. While multiple meta analyses and systematic reviews have defined a limited role for PCI in the adjuvant setting to improve outcomes in locoregional or metastatic SCLC (2,3,6,7), much less is known about the outcomes of PCI in patients with limited stage, surgically resected disease (8).

The National Cancer Database (NCDB) captures approximately 70% of new cancer cases in the United States (9) and is an important nationally representative sample from which to evaluate the outcomes associated with SCLC. Therefore, we used the NCDB to determine if patients with surgically resected early-stage SCLC benefit from PCI in additional to standard of care adjuvant chemotherapy.

Methods

Data source

The 2015 participant user file of the NCDB was used for this analysis. The NCDB is a hospital-based tumor registry, run by the Commission on Cancer of the American College of Surgeons and the American Cancer Society, which captures approximately 70% of all newly diagnosed lung cancer cases in the United States, and contains detailed information on patient demographics, tumor staging, treatment, and survival (9). According to the NCDB, "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" (10). This study was approved by the Yale Institutional Review Board with patient consent waived (Protocol #1103008160: Clinical and Molecular Predictors of Survival in Thoracic Malignancies).

Patient selection

All patients who underwent definitive surgery (segmentectomy, lobectomy, pneumonectomy, bronchial sleeve) for primary SCLC between 2004 and 2015 were identified. We excluded patients aged less than 20 at the time of diagnosis, those with evidence of distant metastases, incomplete resection

(positive or unknown margins), no or missing follow up, patients that received preoperative chemotherapy, those who died within 30 days of surgery, or patients with a history of another cancer. Patients were grouped into those who did and did not receive cranial radiation within 8 months of surgery (8 months is the usual window for completion of adjuvant chemoradiation) (11). Patients with an unknown radiation treatment status or who received radiation to the chest/mediastinum were excluded to isolate the impact of PCI alone on survival.

Data elements

Demographic, tumor, and treatment characteristics are listed in *Table 1* as defined in prior publications (12). A full list of variables obtainable in the NCDB can be found online (10).

Statistical analysis

Comparison of patient characteristics was performed using chi square and *t*-test when appropriate. Kaplan-Meier curves were generated for each prognostic group. Multivariable cox proportional hazards regression models were used to estimate hazard ratios of death adjusted for patient age, sex, race, comorbidity index, tumor size, N stage, surgery type, and year of diagnosis. Two-sided P values <0.05 were considered statistically significant. All data analysis was conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

In total, 859 patients were analyzed (202 patients underwent PCI and 657 did not). Patients who received PCI were similar in age (median age 65 *vs.* 67 years), race, sex and comorbidity status, but slightly more likely to be pathologically node negative (78.7% *vs.* 69.9%, P=0.014) (*Table 1*).

Survival

Kaplan-Meier analysis demonstrated that patients who underwent PCI had significantly increased survival compared to no PCI treatment (5-year survival, 59% *vs.* 50%, logrank P=0.0038) (*Figure 1*). In subgroup analysis,

Table 1 Sociodemographic, tumor and treatment characteristics of patients treated with and without prophylactic cranial irradiation (PCI)

Patient characteristics	No PCI (n=657)		Yes PCI (n=202)		P value
	Number	Percent (%)	Number	Percent (%)	
Age (year)					
20–40	2	0.3	0	0.0	0.432
40–60	168	25.6	63	31.2	0.115
60–80	473	72.0	136	67.3	0.202
80+	14	2.1	3	1.5	0.564
Sex					
Male	300	45.7	101	50.0	0.280
Female	357	54.3	101	50.0	0.280
Race					
White	603	91.8	188	93.1	0.553
Non-White	38	5.8	7	3.5	0.196
Unknown	16	2.4	7	3.5	0.428
Charlson-Deyo comorbidity index					
0	311	47.3	94	46.5	0.842
1	242	36.8	83	41.1	0.275
2	85	12.9	19	9.4	0.178
3	19	2.9	6	3.0	0.954
Facility type					
Community	50	7.6	19	9.4	0.412
Comprehensive	297	45.2	88	43.6	0.682
Academic	221	33.6	65	32.2	0.700
Other	89	13.5	30	14.9	0.639
Tumor size (cm)					
0–2	268	40.8	75	37.1	0.353
2–4	279	42.5	94	46.5	0.308
4–6	74	11.3	27	13.4	0.417
6+	34	5.2	6	3.0	0.193
Unknown	2	0.3	0	0.0	0.432
N stage					
0	459	69.9	159	78.7	0.014
1	111	16.9	28	13.9	0.306
2	52	7.9	6	3.0	0.014
3	0	0.0	1	0.5	0.071
Unknown	35	5.3	8	4.0	0.436

Table 1 (*continued*)

Table 1 (*continued*)

| Patient characteristics	No PCI (n=657)		Yes PCI (n=202)		P value
	Number	Percent (%)	Number	Percent (%)	
Surgery type					
Segmentectomy	24	3.7	7	3.5	0.900
Lobectomy	592	90.1	186	92.1	0.401
Pneumonectomy	40	6.1	9	4.5	0.382
Bronchial sleeve	1	0.2	0	0.0	0.579
Year of diagnosis					
2004–2005	83	12.6	23	11.4	0.637
2006–2007	104	15.8	37	18.3	0.404
2008–2009	126	19.2	36	17.8	0.666
2010–2011	113	17.2	40	19.8	0.398
2012–2013	146	22.2	46	22.8	0.870
2013–2014	85	12.9	20	9.9	0.249
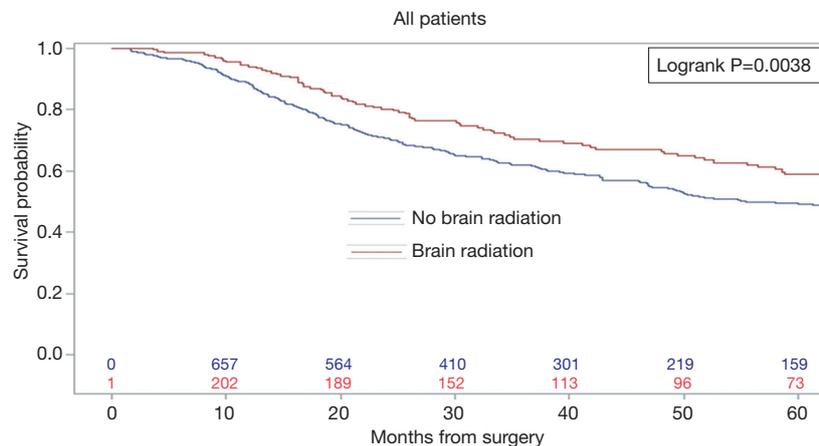
Figure 1 A Kaplan-Meier curve shows the survival of all included patients grouped by whether they received brain radiation (red line) or no brain radiation (blue line). Number of patients at risk at each time interval are shown at the lower margin.

patients with lymph node metastases demonstrated a statistically significant improvement in survival after PCI treatment compared to no PCI (35% *vs.* 20%, logrank P=0.0083) (*Figure 2*). Although there appeared to be a tendency for increased survival in node negative patients treated with PCI compared to not, this difference was not statistically significant (64% *vs.* 59%, logrank P=0.1572) (*Figure 3*).

Multivariable cox models adjusted for patient and tumor characteristics also showed a significantly decreased hazard of death for all patients who underwent PCI (HR: 0.70, 95% CI: 0.55–0.89, P=0.003). This finding was also significant for the subset of patients with lymph node metastases (HR: 0.45, 95% CI: 0.28–0.74, P=0.01), but not for the subset of patients without lymph node metastases (HR: 0.82, 95% CI: 0.61–1.11, P=0.20) (*Table 2*).

Discussion

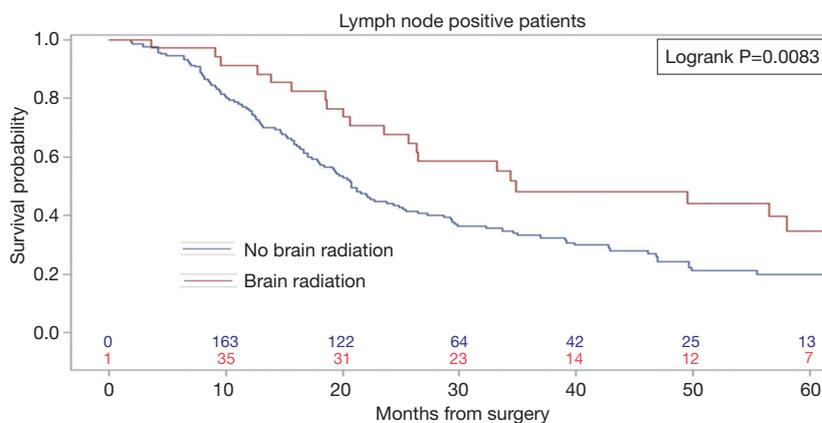This retrospective analysis of the NCDB is the first large

Figure 2 A Kaplan-Meier curve shows the survival of all included lymph node positive patients grouped by whether they received brain radiation (red line) or no brain radiation (blue line). Number of patients at risk at each time interval are shown at the lower margin.
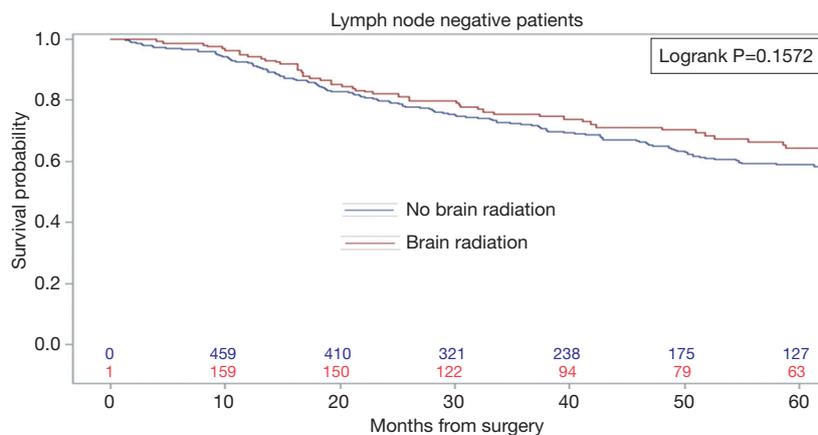

Figure 3 A Kaplan-Meier curve shows the survival of all included lymph node negative patients grouped by whether they received brain radiation (red line) or no brain radiation (blue line). Number of patients at risk at each time interval are shown at the lower margin.

Table 2 Multivariable cox models of PCI *vs.* no PCI (full multivariable models available in *Tables S1-S3*)

Subset	Hazard ratio of death (<1 favors PCI)	95% confidence interval	P value
All patients	0.70	0.55–0.89	0.003
Lymph node negative	0.82	0.61–1.11	0.20
Lymph node positive	0.45	0.28–0.74	0.01

Hazard ratios compare the likelihood of death over 5 years between patients who received PCI and patients who did not receive PCI (a hazard ratio less than 1 suggests a lower risk of death with PCI). While all the groups show lower risk of death for PCI, the difference is only significant in all patients combined and lymph node positive patients.

study to demonstrate a survival advantage associated with adjuvant PCI following surgical resection of early-stage SCLC. Furthermore, PCI seems to be particularly advantageous for patients with pathologically confirmed lymph node involvement that do not receive mediastinal radiation. The benefit of PCI in node negative early stage patients remains unclear.

In its current form, the use of PCI for early-stage surgically managed patients varies by institution, and is not currently endorsed by national consensus guidelines (8).

The support for PCI is largely based on data from small studies of locoregional or metastatic SCLC, given the propensity for the development of systemic failure, including metastatic disease to the brain, in shorter intervals compared to non-SCLC (2,3,6,7). As a result, PCI has largely been used in conjunction with systemic therapy for patients with locoregional or advanced disease. The current results confirm data from prior studies that found PCI was associated with increased survival in limited stage patients who responded to chemotherapy (2,3). Additionally, the results of the current analysis add to conclusions from a previous report derived from NCDB data (11) as well as a single institution study from China (13), which both suggested improved outcomes of PCI in resected SCLC patients. The current study improves on these findings by drawing a large patient population from a national tumor registry, directly comparing PCI to no PCI in a multivariable Cox model, and including patients with positive lymph nodes.

The finding that surgically resected SCLC patients with lymph node metastasis have the largest survival benefit from PCI is congruent with a previous study that found lymphovascular invasion and higher stage after surgical resection were independent risk factors for the development of brain metastases (14). These results are consistent with previously reported single institutional data that also defined a survival benefit for PCI in patients with higher than stage I disease (13). The current study also demonstrated no significant survival benefit for PCI following surgically resected, node negative disease. This is also consistent with previously reported single institutional data (13). However, these results should be viewed with caution as both this present study and prior data were likely underpowered to detect subtle survival differences in the small sample of node negative patients. For example, the current study achieved only 27% power to detect a survival difference in the lymph node negative group at the predicted Hazard Ratio of 0.82. Although the current study had a substantially larger sample compared to prior work, power remains a critical hurdle in evaluating this lung cancer subset. A larger sample or prospective trial is needed to clarify whether early stage lymph node negative patients may benefit from PCI.

The current results should be considered in tandem with the results of a recent randomized controlled trial of PCI in patients with extensive SCLC in Japan that suggested new insight into the mechanism of PCI (15). This study was unique in that it looked at only SCLC patients with confirmed absence of brain metastases by MRI and demonstrated no survival benefit for PCI (15). A suggested interpretation of these findings is that the benefit of PCI is actually due to treatment of subclinical brain metastases in patients that have not been imaged before treatment (16). In terms of the current analysis, the NCDB does not track brain imaging, so this variable could not be included. It is unknown whether necessitating brain imaging before treatment with PCI would change the interpretation of outcomes for patients after resection of limited disease as in the present study. Despite this limitation, the current study implies that PCI for resected patients is associated with improved survival, and therefore an intervention to mitigate brain metastases (whether it be PCI or surveillance brain imaging with cranial radiation when clinically appropriate) may be indicated in these patients.

This analysis identified that current practice patterns do not favor treatment with PCI following surgical resection for early stage SCLC. Previous studies have reported reticence to utilize cranial irradiation due to the dissuasion of cognitive complications associated with treatment, particularly when the treatment goal is prophylaxis (6,7). While the incidence of neurocognitive side effects cannot be determined in this study because this metric is not tracked by the NCDB, previous studies have reported that neurocognitive side effects of PCI vary greatly based on treatment type, dosing, or use of concurrent chemotherapy (incidence of up to 63%) (17,18). Contrarily, two randomized trials that carefully considered cognitive testing found no association between PCI and neurocognitive side effects (19,20). Nevertheless, in the current study only 23% of the total study group and only 19% of lymph node positive patients received PCI, which is significantly lower than previously published. In an analysis of the Quality Research in Radiation Oncology database from 2006–2007, 49% of limited stage SCLC patients were managed with PCI. The current findings may represent a true lower utilization of PCI in this surgical cohort or may be explained by inherent differences of the databases studied (21). Nevertheless, these findings underscore the idea that PCI may be underutilized, may be more clinically relevant than previously considered, and is an area that requires further study.

Several limitations are worth mentioning from this retrospective analysis of registry data. Most importantly, this study was underpowered to demonstrate a survival advantage of PCI for node negative early-stage patients. However, the survival difference for lymph node positive patients was large enough to be significant with our

relatively limited sample size. Attempts to identify other factors associated with benefit from PCI including tumor size, age, sex and lymph-vascular invasion are limited given the sample size of our study population. An additional limitation is that there may be a selection bias for patients who were offered PCI. However, in our post-hoc analysis of patient and tumor characteristics, we found only a few small differences between PCI and non-PCI groups. Additionally, we only included patients who received standard of care multi-agent adjuvant chemotherapy in an attempt to exclude those who were not treated with "intent to cure". This sample limitation may have introduced some level of selection bias. However, we believe our study group was most appropriate to understand the specific advantages associated with PCI in this limited subset. Another limitation is that patients who received mediastinal radiation were excluded from this analysis. Because the NCDB does not report 2 sites of radiation treatment, and that treatment with mediastinal radiation (regarded as the primary site) would eliminate our ability to identify PCI patients, exclusion of mediastinal radiation patients was necessary. Although the minority of patients receive thoracic radiation after resection for SCLC, excluding these patients reduced the sample size available for this analysis and potentially the ability to identify a survival advantage associated with PCI in node negative patients. We analyzed and adjusted for patient and tumor specific factors available in the NCDB, but we acknowledge that there may be other unknown confounders that could bias this retrospective analysis. For example, the NCDB does not track detailed information about recurrence, so the association of PCI with recurrence pattern or the specific mechanism by which PCI increases survival cannot be defined with granularity in this study. However, due to the fact that there is limited data on the impact of PCI in surgically managed patients, this analysis represents an important evidence-based rationale for continuing to consider and evaluate PCI in this limited stage SCLC group.

Conclusions

PCI is associated with increased survival for patients following resection of early-stage SCLC. Patients with pathologically defined local lymph node involvement appear to benefit the most, while it remains unclear if patients without lymph node involvement derive a benefit from PCI. Further prospective study is warranted to clarify which

subsets of patients should be managed with PCI in addition to established adjuvant therapy available to SCLC patients.

References

1. Komaki R, Cox JD, Whitson W. Risk of brain metastasis from small cell carcinoma of the lung related to length of survival and prophylactic irradiation. Cancer Treat Rep 1981;65:811-4.

2. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.

3. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2001;1:5.

4. Wakeam E, Varghese TK, Leighl NB, et al. Trends, practice patterns and underuse of surgery in the treatment of early stage small cell lung cancer. Lung Cancer 2017;109:117-23.

5. Kalemkerian GP, Loo BW, Akerley W, et al. NCCN Guidelines Insights: Small Cell Lung Cancer, Version 2.2018. J Natl Compr Canc Netw 2018;16:1171-82.

6. Alshehadat S, Sahmoun AE. Prophylactic cranial irradiation in limited-stage small-cell lung cancer: a retrospective analysis. Clin Adv Hematol Oncol 2004;2:397-400.

7. Lee JJ, Bekele BN, Zhou X, et al. Decision analysis for prophylactic cranial irradiation for patients with small-cell lung cancer. J Clin Oncol 2006;24:3597-603.

8. Le Pechoux C. Prophylactic Cranial Irradiation or

No Prophylactic Cranial Irradiation after Adjuvant Chemotherapy in Resected Small Cell Lung Cancer? J Thorac Oncol 2017;12:173-5.

9. Boffa DJ, Rosen JE, Mallin K, et al. Using the National Cancer Database for Outcomes Research: A Review. JAMA Oncol 2017;3:1722-8.

10. National Cancer Database [Internet]. American College of Surgeons. Cited 2018 Mar 21. Available online: https://www.facs.org/quality-programs/cancer/ncdb

11. Yang CFJ, Chan DY, Speicher PJ, et al. Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer. J Clin Oncol 2016;34:1057-64.

12. Resio BJ, Chiu AS, Hoag J, et al. Primary Salivary Type Lung Cancers in the National Cancer Database. Ann Thorac Surg 2018;105:1633-9.

13. Zhu H, Guo H, Shi F, et al. Prophylactic cranial irradiation improved the overall survival of patients with surgically resected small cell lung cancer, but not for stage I disease. Lung Cancer 2014;86:334-8.

14. Zhu H, Bi Y, Han A, et al. Risk factors for brain metastases in completely resected small cell lung cancer: a retrospective study to identify patients most likely to benefit from prophylactic cranial irradiation. Radiat Oncol 2014;9:216.

15. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663-71.

16. Daly ME, Palma DA. Prophylactic Cranial Irradiation for Small Cell Lung Cancer: New Insights. Int J Radiat Oncol Biol Phys 2017;99:3-5.

17. Fleck JF, Einhorn LH, Lauer RC, et al. Is prophylactic cranial irradiation indicated in small-cell lung cancer? J Clin Oncol 1990;8:209-14.

18. Yang GY, Matthews RH. Prophylactic Cranial Irradiation in Small-Cell Lung Cancer. Oncologist 2000;5:293-8.

19. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: Results of a multicentre randomised trial. Eur J Cancer 1997;33:1752-8.

20. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic Cranial Irradiation for Patients With Small-Cell Lung Cancer in Complete Remission. J Natl Cancer Inst 1995;87:183-90.

21. Komaki R, Khalid N, Langer CJ, et al. Penetration of Recommended Procedures for Lung Cancer Staging and Management in the United States over 10 Years: A Quality Research in Radiation Oncology Survey. Int J Radiat Oncol Biol Phys 2013;85:1082-9.

Table S1 Full multivariable of all patients

Variable	Comparison	Hazard ratio	P value
N stage	1 *vs.* 0	2.705	<0.0001
	2 *vs.* 0	3.572	<0.0001
	3 *vs.* 0	7.972	0.0431
	Unknown *vs.* 0	0.849	0.4979
Age	20–40 *vs.* 40–60 years	0	0.9723
	60–80 *vs.* 40–60 years	1.328	0.0188
	80+ *vs.* 40–60 years	1.379	0.3412
Sex	Male *vs.* female	1.051	0.6325
Tumor size	2–4 *vs.* 0–2 cm	1.013	0.9104
	4–6 *vs.* 0–2 cm	1.519	0.0106
	>6 *vs.* 0–2 cm	1.205	0.4727
	Unknown *vs.* 0–2 cm	1.773	0.4294
Race	Nonwhite *vs.* white	0.841	0.4704
	Unknown *vs.* white	0.807	0.5786
Charlson-Deyo	1 *vs.* 0	0.984	0.8871
	2 *vs.* 0	1.402	0.0314
	3 *vs.* 0	1.924	0.0119
Surgery type	Wedge *vs.* lobe	0.928	0.8039
	Segment *vs.* lobe	0.693	0.0878
	Pneumonectomy *vs.* lobe	0.809	0.8361
	Sleeve *vs.* lobe	0.697	0.0034
Brain radiation	Yes *vs.* no	1.226	0.2670
Year of diagnosis	2004–2005	1.270	0.1603
	2006–2007	1.203	0.2752
	2008–2009	1.138	0.4647
	2010–2011	0.845	0.5171
	2013–2014	2.705	<0.0001

Hazard ratios compare the likelihood of death over 5 years between patients in each comparison group. For example, the first row below shows that patients with an N stage of 1 had a 2.705 times greater risk of death over 5 years compared to patients with N stage of 0.

Table S2 Full multivariable of lymph node negative patients

Variable	Comparison	Hazard ratio	P value
Age	20–40 *vs.* 40–60 years	0	0.9719
	60–80 *vs.* 40–60 years	1.373	0.0406
	80+ *vs.* 40–60 years	1.325	0.5537
Sex	Male *vs.* female	1.058	0.6780
Tumor size	2–4 *vs.* 0–2 cm	1.102	0.5000
	4–6 *vs.* 0–2 cm	1.667	0.0161
	>6 *vs.* 0–2 cm	1.136	0.7222
	Unknown *vs.* 0–2 cm	0.926	0.9404
Race	Nonwhite *vs.* white	0.781	0.4363
	Unknown *vs.* white	0.588	0.2461
Charlson-Deyo	1 *vs.* 0	1.029	0.8442
	2 *vs.* 0	1.299	0.2312
	3 *vs.* 0	1.830	0.0858
Surgery type	Wedge *vs.* lobe	1.026	0.9433
	Segment *vs.* lobe	1.274	0.5213
	Pneumonectomy *vs.* lobe	0.821	0.2000
Brain radiation	Yes *vs.* no	1.378	0.1819
Year of diagnosis	2004–2005	1.166	0.5011
	2006–2007	1.216	0.3658
	2008–2009	1.052	0.8191
	2010–2011	0.788	0.5063
	2013–2014	0	0.9719

Hazard ratios compare the likelihood of death over 5 years between patients in each comparison group.

Table S3 Full multivariable of lymph node positive patients

Variable	Comparison	Hazard ratio	P value
N stage	2 *vs.* 1	1.218	0.3312
	3 *vs.* 1	5.045	0.1308
Age	60–80 *vs.* 40–60 years	1.353	0.1688
	80+ *vs.* 40–60 years	1.324	0.6140
Sex	Male *vs.* female	0.898	0.5681
Tumor size	2–4 *vs.* 0–2 cm	0.935	0.7593
	4–6 *vs.* 0–2 cm	1.252	0.4508
	>6 *vs.* 0–2 cm	1.639	0.2422
	Unknown *vs.* 0–2 cm	0.851	0.7059
Race	Nonwhite *vs.* white	3.254	0.3146
	Unknown *vs.* white	1.032	0.8816
Charlson-Deyo	1 *vs.* 0	1.933	0.0197
	2 *vs.* 0	2.962	0.0099
	3 *vs.* 0	0.617	0.5249
Surgery type	Wedge *vs.* lobe	0.616	0.0824
	Segment *vs.* lobe	0.734	0.7711
	Pneumonectomy *vs.* lobe	0.454	0.0013
	Sleeve *vs.* lobe	1.203	0.5533
Brain radiation	Yes *vs.* no	1.530	0.1447
Year of diagnosis	2004–2005	1.508	0.1687
	2006–2007	1.324	0.4057
	2008–2009	1.013	0.9738
	2010–2011	1.218	0.3312
	2013–2014	5.045	0.1308

Hazard ratios compare the likelihood of death over 5 years between patients in each comparison group.