CASE REPORT

Prevalence, Prognostic Implications, and Survival Modulators of Incompletely Resected Non–Small Cell Lung Cancer in the U.S. National Cancer Data Base

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ABSTRACT

Introduction: The impact of incomplete lung cancer resection on survival has never been systematically quantified, nor has the value of postoperative adjuvant therapy in this setting been determined.

Methods: We evaluated lung cancer resections in the National Cancer Data Base from 2004 to 2011 to identify factors associated with margin involvement. We compared the survival of patients with and without positive margins and evaluated the impact of postoperative adjuvant therapy.

Results: Of 112,998 resections performed during the 8 years, 5,335 (4.7%) had positive margins. Patient demographic and clinical factors associated with an increased adjusted OR of incomplete resection included black race ($p = 0.006$), age-based Medicare insurance ($p = 0.006$), urban residence ($p = 0.01$), histologic diagnosis of squamous cell carcinoma, high tumor grade, tumor overlapping more than one lobe, and advanced pathologic stage ($p < 0.001$ for all clinical factors). Community cancer programs ($p = 0.002$), institutions with high proportions of underinsured patients ($p = 0.01$), and institutions with a lower volume of cancer resections ($p = 0.006$) also had an increased adjusted OR. The crude 5-year survival rates of patients with complete versus incomplete resections were 58.5% versus 33.8% (log-rank $p < 0.001$). After an incomplete resection, adjuvant chemotherapy was associated with improved 5-year survival across all stages ($p < 0.01$); radiotherapy was associated with worse survival in patients with stage I disease ($p < 0.001$).

Conclusions: Margin involvement significantly impaired survival after lung cancer resection irrespective of stage. Causative institutional and provider practices should be identified to minimize this adverse outcome. Postoperative adjuvant chemotherapy mitigated mortality risk independently of stage, whereas postoperative radiotherapy exacerbated the risk in patients with stage I disease. These findings need validation in prospective trials.

Keywords: Non–small cell; Positive margins; Quality of care; Outcomes; Surgical resection; Survival

Introduction

Lung cancer is the oncologic scourge of the present age, causing 160,000 deaths in the United States annually and accounting for 28% of all cancer mortality in the United States.[1] Only 17% of all patients diagnosed with lung cancer survive up to 5 years.[1] The overwhelming majority of long-term survivors have had surgery as a component of their treatment; however, most patients who undergo surgery for lung cancer die within 5 years.[2] Improving surgical outcomes is therefore a viable

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strategy for improving the overall rate of lung cancer survival.

Attaining the benefit of surgical resection of non–small cell lung cancer requires complete (R0) resection of all evident disease.[3] In relation to lung cancer, however, the term *complete resection* has been ill-defined, with ongoing controversy about the optimal extent of resection of the lung parenchyma[4] and nodal examination.[5–9] Even the prognostic implication of a positive resection margin has been questioned.[5,6,10] Current practice guidelines recognize that patients with microscopic (R1) or macroscopic (R2) positive resection margins are at high risk for death[3]; however, this risk has never been systematically quantified.[11]

Practice guidelines recommend re-resection as the preferred response to margin positivity for patients with stage I and II disease; however, it is infeasible in many cases, and surgeons are often reluctant to subject patients to re-resection in any case.[3] Alternative options to surgery are postoperative adjuvant radiation therapy, chemotherapy, and the combination of modalities in certain situations.[3,11] However, postoperative radiotherapy increases the risk for mortality in patients with completely resected pathologic N0 or N1 non–small cell lung cancer.[12] The benefit of radiotherapy has never been clearly demonstrated in patients with positive margins.[11] The role of chemotherapy in managing patients with positive margins is even less well defined because clinical trials of adjuvant chemotherapy typically exclude patients with positive resection margins.[13,14] Practice guidelines in this area rely predominantly on expert opinion,[3,5] contradictory single-institution reports,[10,15–22] ad hoc secondary analyses of patient subsets in clinical trials designed to answer other questions,[6] or literature reviews.[11]

We analyzed the U.S. National Cancer Data Base (NCDB) to establish the proportion of non-R0 resections in a contemporary multiyear national cohort. We also sought to identify factors associated with resection margin positivity, definitively quantify the survival implications of resection with positive margins, and examine the impact of nonsurgical adjuvant therapies on survival.

Materials and methods

Data sources

The NCDB, which is sponsored jointly by the American College of Surgeons and the American Cancer Society, is a clinical oncology database sourced from hospital registry data that are collected in more than 1500 Commission on Cancer–accredited facilities. Data in the NCDB are used to analyze and track patients with malignant neoplastic diseases, their treatments, and outcomes. The data represent approximately 70% of newly diagnosed cancer cases in the United States.[23] This study was exempted from the informed consent requirement because it analyzes a preexisting, de-identified data set.

Study subjects

We selected patients aged 18 to 90 years who had a first diagnosis of primary non–small cell lung cancer (*International Classification of Disease for Oncology, Ninth Revision, Clinical Modification* [ICD-9-CM] site codes C34.0–C34.9), pathologic stage I through stage IIIA, that was established from 2004 to 2011 and who underwent cancer-directed surgery in a Commission on Cancer–accredited reporting facility within 6 months of diagnosis (Fig. 1). We excluded patients with missing information on gender, administration of radiation therapy, or administration of chemotherapy and those with metastatic disease, unmeasurable tumor, no last contact information, or unknown margin status. Because we were interested in the quality of oncologic resection, we excluded patients who died within 60 days after their operation.

Study outcomes and covariates

The primary outcome was margin status (positive or negative) identified from the final status of the surgical margins after resection of the primary tumor. Positive margin was defined if residual tumor (R1, R2, or not otherwise specified) was recorded in the pathology report. Secondary outcomes were overall survival rates at 1, 3, and 5 years in patients categorized by margin status. Patients were censored if they were lost to follow-up or still alive at the end of the study period.

We examined associations between margin status and patient-level clinical and demographic covariates, as well as institutional covariates. Patient-level demographic covariates included age, sex, race, insurance status, U.S. census region of residence, residence in a rural or urban location, median income level in patients' neighborhood of residence, year of cancer diagnosis and comorbidities. Patient-level clinical covariates included disease characteristics such as tumor histologic features, grade, size, T category, N category, aggregate American Joint Committee on Cancer (AJCC) pathologic stage, and the treatment characteristics extent of resection and lymph node examination results. Institutional covariates included facility type, facility location by census division, proportion of the institution's patients with no insurance or insured by Medicaid (in quartiles), volume of lung cancer operations as a proportion of the institution's entire volume of cancer operations (in quartiles), and total annual volume of cancer operations (in quartiles).

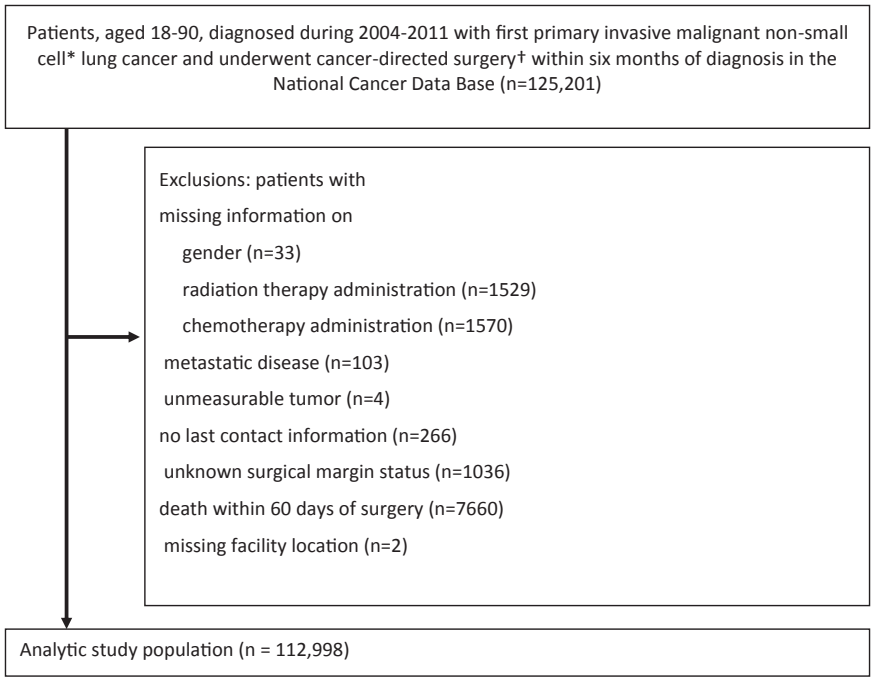

Figure 1. Patient selection scheme. *The histologic diagnosis of non-small cell lung cancer was identified through the following *International Classification of Diseases for Oncology, Third Edition (ICD-O-3)* histologic diagnosis codes: 8010–8040, 8050–8076, 8140, 8143, 8211, 8230–8231, 8246, 8250–8260, 8310, 8320, 8323, 8430, 8470–8490, 8550–8573, 8980, and 8981. †Cancer-directed surgery was identified through site-specific surgical codes (21, 22, 30–70), including those for sublobectomy, lobectomy, bilobectomy, and pneumonectomy.

In secondary analyses, we evaluated the association between use of preoperative adjuvant therapy and margin positivity. We also examined survival after postoperative adjuvant therapy in groups of patients stratified by stage. Adjuvant therapy, including chemotherapy, radiotherapy, or both, was identified if commenced within 6 months before or after surgery. Chemotherapy was identified if administered as a single agent or multiple agents. Radiotherapy was identified if administered at the reporting facility or elsewhere.

Statistical analysis plan

Descriptive analyses were conducted to summarize patient and institutional characteristics. Chi-square tests were used to determine the significance of differences according to margin status. The yearly trend in the incidence of surgical resection with positive margins was evaluated using the Cochran-Armitage test. Univariate and multivariate logistic regression analyses were conducted to evaluate associations between patient and institutional characteristics and positive margins. The multivariate model included the aggregate pathologic stage, and because it is based on the pathological T, N, and M categories, we did not adjust separately for T, N, or M stage to avoid problems with multicollinearity. The results of multivariate logistic regression adjusting either aggregate pathologic stage or T, N, and M categories were similar; therefore, we presented results with aggregate pathologic stage in the model.

In addition, to determine whether use of preoperative adjuvant therapy might be associated with positive margin, three multivariate logistic regression analyses were performed for patients who received preoperative chemotherapy, radiotherapy, or chemoradiation versus those who did not receive preoperative adjuvant therapy.

To examine the impact of a resection with positive margins on survival, 5-year overall survival distributions in patients stratified by margin status were estimated using the Kaplan-Meier method and compared using the log-rank test. Additional stratification by T category, tumor size, and aggregate AJCC stage was conducted to control possible confounding. Furthermore, to assess the impact of postoperative adjuvant therapy use on survival in patients with a positive margin, 5-year overall survival rates stratified by postoperative treatment and aggregate AJCC stage were estimated using the Kaplan-Meier method. Patients who received preoperative adjuvant therapy were excluded from all analyses of the effects of postoperative adjuvant therapy.

To evaluate the impact of including R2 and indeterminate cases as margin-positive, we conducted sensitivity analyses by excluding patients with R2 and/or indeterminate cases. We also analyzed the impact on our results of excluding patients who died within 30, 60, and

Table 1. Factors associated with margin-positive resection (univariate and multivariate analysis)

Patient characteristics and categories	Patients, (N = 112,998), N (%)	Patients with margin-positive resection, (N = 5,335 [4.7%]), N (%)	*p* Value	Unadjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Age							
18-49	6,300 (5.6)	341 (5.4)	<0.001	1		1	
50-64	36,940 (32.7)	1,836 (5.0)		0.91 (0.81-1.03)	0.14	1 (0.88-1.13)	0.99
65-74	42,857 (37.9)	1,915 (4.5)		0.82 (0.73-0.92)	<0.001	0.84 (0.72-0.99)	0.03
75-90	26,901 (23.8)	1,243 (4.6)		0.85 (0.75-0.96)	0.008	0.89 (0.76-1.05)	0.18
Gender							
Male	54,806 (48.5)	2,837 (5.2)	<0.001	1			
Female	58,192 (51.5)	2,498 (4.3)		0.82 (0.78-0.87)	<.001	1 (0.95-1.06)	0.96
Race/ethnicity							
Non-Hispanic, White	88,945 (78.7)	4111 (4.6)	<0.001	1		1	
Hispanic	2,464 (2.2)	119 (4.8)		1.05 (0.87-1.26)	0.63	0.99 (0.81-1.2)	0.88
Black	9,354 (8.3)	531 (5.7)		1.24 (1.13-1.36)	<0.001	1.15 (1.04-1.27)	0.006
Other	2,931 (2.6)	131 (4.5)		0.97 (0.81-1.15)	0.70	0.98 (0.81-1.18)	0.80
Missing	9,304 (8.2)	443 (4.8)		1.03 (0.93-1.14)	0.54	1.05 (0.94-1.16)	0.41
Year of diagnosis							
2004	12,859 (11.4)	606 (4.7)	0.06	1		1	
2005	13,891 (12.3)	638 (4.6)		0.97 (0.87-1.09)	0.64	1.02 (0.9-1.14)	0.78
2006	14,216 (12.6)	662 (4.7)		0.99 (0.88-1.11)	0.83	1.02 (0.91-1.15)	0.73
2007	14,117 (12.5)	618 (4.4)		0.93 (0.83-1.04)	0.19	0.99 (0.88-1.11)	0.81
2008	14,244 (12.6)	676 (4.8)		1.01 (0.9-1.13)	0.90	1.07 (0.95-1.2)	0.28
2009	14,193 (12.6)	659 (4.6)		0.99 (0.88-1.1)	0.79	1.04 (0.93-1.17)	0.48
2010	15,114 (13.4)	791 (5.2)		1.12 (1-1.25)	0.05	0.95 (0.85-1.06)	0.35
2011	14,364 (12.7)	685 (4.8)		1.01 (0.91-1.13)	0.83	0.89 (0.79-0.99)	0.04
Insurance							
Uninsured	2,185 (1.9)	133 (6.1)	<0.001	1.32 (1.1-1.59)	0.003	1.07 (0.88-1.3)	0.49
Medicaid	4,822 (4.3)	274 (5.7)		1.23 (1.08-1.4)	0.002	1.03 (0.9-1.18)	0.70
Younger Medicare	6,392 (5.7)	313 (4.9)		1.05 (0.93-1.19)	0.43	0.99 (0.87-1.13)	0.87
Older Medicare	58,853 (52.1)	2,723 (4.6)		0.99 (0.93-1.05)	0.73	1.16 (1.04-1.3)	0.006
Government	220 (0.2)	10 (4.6)		0.97 (0.51-1.84)	0.93	0.69 (0.36-1.33)	0.27
Private	39,028 (34.5)	1,824 (4.8)		1		1	
Missing	1,498 (1.3)	58 (3.9)		0.82 (0.63-1.07)	0.15	0.86 (0.65-1.13)	0.27
Median income—quartile 2000							
<$30,000	14,702 (13.0)	751 (5.1)	<0.001	1.19 (1.09-1.3)	<0.001	1.09 (0.98-1.21)	0.11
$30,000-$34,999	20,829 (18.4)	1,079 (5.2)		1.21 (1.12-1.31)	<0.001	1.14 (1.04-1.24)	0.004
$35,000-$45,999	31,072 (27.5)	1,498 (4.8)		1.12 (1.05-1.21)	0.001	1.05 (0.98-1.14)	0.18
$46,000+	40,252 (35.6)	1,736 (4.3)		1		1	
Missing	6143 (5.4)	271 (4.4)		1.02 (0.9-1.17)	0.72	1.08 (0.89-1.31)	0.46
Rural/urban							
Rural	21,159 (18.7)	1,030 (4.9)	0.20	1.03 (0.96-1.11)	0.35	0.9 (0.83-0.98)	0.01
Urban	84,715 (74.9)	3,995 (4.7)		1		1	
Unknown	7,124 (6.3)	310 (4.4)		0.92 (0.82-1.04)	0.16	0.98 (0.82-1.17)	0.81
Comorbidity							
0	53,437 (47.3)	2,454 (4.6)	0.11	1		1	
1	40,806 (36.1)	1,993 (4.9)		1.07 (1-1.13)	0.04	1.07 (1-1.14)	0.05
2+	18,755 (16.6)	888 (4.7)		1.03 (0.95-1.12)	0.42	1.02 (0.94-1.11)	0.63
Census region							
Northeast	23,892 (21.1)	946 (4.0)	<0.001	1		1	
Midwest	30,404 (26.9)	1,626 (5.4)		1.37 (1.26-1.49)	<0.001	1.55 (0.93-2.6)	0.10
South	44,324 (39.2)	2,038 (4.6)		1.17 (1.08-1.27)	<0.001	1.17 (0.74-1.86)	0.51
West	14,250 (12.6)	718 (5.0)		1.29 (1.17-1.42)	<0.001	0.98 (0.48-1.97)	0.94
Missing	128 (0.1)	7 (5.5)		1.4 (0.65-3.01)	0.39	1.45 (0.61-3.45)	0.41

(continued)

Table 1. Continued

Patient characteristics and categories	Patients, (N = 112,998), N (%)	Patients with margin-positive resection, (N = 5,335 [4.7%]), N (%)	*p* Value	Unadjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Histologic diagnosis							
NOS	347 (0.3)	18 (5.2)	<0.001	1.37 (0.85-2.2)	0.20	1.05 (0.65-1.72)	0.84
Large cell cancer	5,320 (4.7)	261 (4.9)		1.29 (1.13-1.47)	<0.001	0.98 (0.86-1.13)	0.78
Squamous cell cancer	33,768 (29.9)	2,094 (6.2)		1.65 (1.56-1.75)	<0.001	1.38 (1.29-1.47)	<0.001
Other	5,851 (5.2)	357 (6.1)		1.62 (1.45-1.82)	<0.001	1.34 (1.19-1.51)	<0.001
Adenocarcinoma	67,712 (59.9)	2,605 (3.9)		1		1	
Tumor grade							
Well/moderately differentiated	64,772 (57.3)	2,528 (3.9)	<0.001	1		1	
Poorly differentiated/ undifferentiated	42,668 (37.8)	2,557 (6.0)		1.57 (1.48-1.66)	<0.001	1.14 (1.07-1.21)	<0.001
Unknown	5,558 (4.9)	250 (4.5)		1.16 (1.02-1.33)	0.03	0.98 (0.85-1.13)	0.79
Tumor size							
≤3cm	68,906 (61.0)	2,136 (3.1)	<0.001	1		1	
>3cm-≤5cm	27,971 (24.8)	1,706 (6.1)		2.03 (1.9-2.17)	<0.001	1.65 (1.54-1.77)	<0.001
>5cm	15,518 (13.7)	1,422 (9.2)		3.15 (2.94-3.38)	<0.001	1.94 (1.79-2.1)	<0.001
Unknown	603 (0.5)	71 (11.8)		4.17 (3.25-5.36)	<0.001	2.47 (1.89-3.22)	<0.001
Lymph node examined							
Yes	10,7002 (94.7)	4,858 (4.5)	<0.001	1		1	
No	5,888 (5.2)	467 (7.9)		1.81 (1.64-2)	<0.001	2.14 (1.9-2.41)	<0.001
Unknown	108 (0.1)	10 (9.3)		2.15 (1.12-4.12)	0.02	1.77 (0.9-3.47)	0.10
Primary site							
C340—Main bronchus	725 (0.6)	88 (12.1)	<0.001	2.79 (2.22-3.49)	<0.001	1.4 (1.1-1.78)	0.007
C341—Upper lobe	67,878 (60.1)	3,207 (4.7)		1		1	
C342—Middle lobe	5,451 (4.8)	268 (4.9)		1.04 (0.92-1.19)	0.52	1.19 (1.04-1.35)	0.01
C343—Lower lobe	35,317 (31.3)	1,464 (4.2)		0.87 (0.82-0.93)	<0.001	0.83 (0.78-0.89)	<0.001
C348—Overlapping lesion	1,883 (1.7)	182 (9.7)		2.16 (1.84-2.52)	0.06	1.35 (1.15-1.59)	<0.001
C349—Lung NOS	1,744 (1.5)	126 (7.2)		1.57 (1.31-1.89)	<0.001	1.15 (0.95-1.39)	0.16
Pathologic stage							
Stage I	79,614 (70.5)	1,893 (2.4)	<0.001	1		1	
Stage II	21,550 (19.1)	1,950 (9.1)		4.09 (3.83-4.36)	<0.001	3.79 (3.53-4.07)	<0.001
Stage III	11,834 (10.5)	1,492 (12.6)		5.92 (5.52-6.36)	<0.001	5.77 (5.34-6.23)	<0.001
TNM path T							
T1	55,320 (49.0)	1,115 (2.0)	<0.001	1			
T2	48,028 (42.5)	2,509 (5.2)		2.68 (2.49-2.88)	<0.001		
T3	8,300 (7.4)	1,516 (18.3)		10.86 (10.02-11.79)	<0.001		
T4	667 (0.6)	146 (21.9)		13.62 (11.23-16.52)	<0.001		
Unknown	683 (0.6)	49 (7.2)		3.76 (2.79-5.06)	<0.001		
TNM path N							
N0	85,272 (75.5)	2,818 (3.3)	<0.001	1			
N1	16,187 (14.3)	1,342 (8.3)		2.65 (2.47-2.83)	<0.001		
N2	9,289 (8.2)	975 (10.5)		3.43 (3.18-3.7)	<0.001		
NX	2,021 (1.8)	178 (8.8)		2.83 (2.41-3.31)	<0.001		
Unknown	229 (0.2)	22 (9.6)		3.11 (2-4.83)	<0.001		
Extent of resection							
Sublobectomy	15,671 (13.9)	971 (6.2)	<0.001	1.53 (1.43-1.65)	<0.001	1.96 (1.80-2.15)	<0.001
Lobectomy/bilobectomy	91,017 (80.6)	3,757 (4.1)		1		1	
Pneumonectomy	6,310 (5.6)	607 (9.6)		2.47 (2.26-2.71)	<0.001	0.98 (0.89-1.09)	0.71

(continued)

Table 1. Continued

Patient characteristics and categories	Patients, (N = 112,998), N (%)	Patients with margin-positive resection, (N = 5,335 [4.7%]), N (%)	*p* Value	Unadjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Facility Characteristics							
Facility type							
Community cancer program	8,248 (7.3)	497 (6.0)	<0.001	1.62 (1.42-1.84)	<0.001	1.34 (1.12-1.61)	0.002
Comprehensive community cancer program	53,784 (47.6)	2,647 (4.9)		1.31 (1.18-1.44)	<0.001	1.23 (1.1-1.38)	<0.001
Teaching/research	27,546 (24.4)	1,187 (4.3)		1.14 (1.02-1.26)	0.02	1.06 (0.95-1.19)	0.28
National Cancer Institute program/network	13,418 (11.9)	512 (3.8)		1		1	
Other	10,002 (8.9)	492 (4.9)		1.3 (1.15-1.48)	<0.001	1.23 (1.07-1.4)	0.003
Proportion of Medicaid/ uninsured patients							
Q1 (low)	26,715 (23.6)	1,157 (4.3)	0.003	1		1	
Q2	30,129 (26.7)	1,433 (4.8)		1.1 (1.02-1.19)	0.02	1.07 (0.98-1.16)	0.13
Q3	31,222 (27.6)	1,497 (4.8)		1.11 (1.03-1.2)	0.008	1.08 (0.99-1.18)	0.07
Q4 (high)	24,932 (22.1)	1,248 (5.0)		1.16 (1.07-1.26)	<0.001	1.13 (1.03-1.24)	0.01
Lung cancer resection as a proportion of all surgical procedures							
Q1 (low)	2,690 (2.4)	137 (5.1)	<0.001	1.13 (0.95-1.35)	0.18	1.14 (0.95-1.38)	0.15
Q2	22,445 (19.9)	1,175 (5.2)		1.17 (1.08-1.25)	<0.001	1.24 (1.15-1.34)	<0.001
Q3	38,529 (34.1)	1,789 (4.6)		1.03 (0.96-1.09)	0.42	1.09 (1.02-1.16)	0.02
Q4 (high)	49,334 (43.7)	2,234 (4.5)		1		1	
Total volume of cancer operations							
Q1 (low)	3,377 (3.0)	206 (6.1)	<0.001	1.45 (1.26-1.68)	<0.001	1.17 (0.95-1.43)	0.15
Q2	13,357 (11.8)	739 (5.5)		1.31 (1.21-1.42)	<0.001	1.17 (1.05-1.3)	0.006
Q3	26,773 (23.7)	1,413 (5.3)		1.25 (1.17-1.33)	<0.001	1.19 (1.1-1.28)	<0.001
Q4 (high)	69,491 (61.5)	2,977 (4.3)		1		1	
Census division							
New England	6,993 (6.2)	273 (3.9)	<0.001	1		1	
Middle Atlantic	17,065 (15.1)	681 (4.0)		1.02 (0.89-1.18)	0.75	1.03 (0.89-1.19)	0.72
East North Central	21,333 (18.9)	1,182 (5.5)		1.44 (1.26-1.65)	<0.001	0.87 (0.51-1.47)	0.59
West North Central	9,521 (8.4)	443 (4.7)		1.2 (1.03-1.4)	0.02	0.76 (0.45-1.3)	0.31
South Atlantic	26,279 (23.3)	1,124 (4.3)		1.1 (0.96-1.26)	0.17	0.88 (0.54-1.42)	0.60
East South Central	10,175 (9)	531 (5.2)		1.36 (1.17-1.57)	<0.001	1.03 (0.63-1.67)	0.92
West South Central	7,583 (6.7)	385 (5.1)		1.32 (1.12-1.54)	<0.001	0.98 (0.6-1.6)	0.93
Mountain	3,628 (3.2)	210 (5.8)		1.51 (1.26-1.82)	<0.001	1.41 (0.69-2.9)	0.35
Pacific	10,421 (9.2)	506 (4.9)		1.26 (1.08-1.46)	0.003	1.16 (0.57-2.38)	0.68
Treatment							
Received radiation							
No	10,1731 (90.0)	3,000 (3.0)	<0.001				
Yes	11,267 (10.0)	2,335 (20.7)					
Received chemotherapy							
No	83,513 (73.9)	2,638 (3.2)	<0.001				
Yes	29,485 (26.1)	2,697 (9.2)					

OR, odds ratio; CI, confidence interval; NOS, not otherwise specified.

90 days postoperatively. Because the results were similar, we have reported data using the 60-day exclusion window. All tests of significance were two-sided, and *p* values less than 0.05 were considered statistically significant. All analyses were conducted using SAS Software, Version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient demographic and clinical characteristics and likelihood of margin positivity

Our study cohort consisted of 112,998 individuals, of whom 5,335 (4.7%) had a margin-positive resection

Table 2. Neoadjuvant therapy and the likelihood of a margin-positive resection

		Margin positivity		Likelihood of margin positivity	
	Total N	N (%)	*p* value	OR[a] (95% CI)	*p* value
Preoperative radiation			<0.001		
Yes	590	51 (8.6)		1.59 (1.17-2.15)	0.003
No	107,660	4,896 (4.6)		1	
Preoperative chemotherapy			<0.001		
Yes	1,640	124 (7.6)		1.19 (0.98-1.45)	0.08
No	107,660	4,896 (4.6)		1	
Preoperative chemoradiation			<0.001		
Yes	1,653	151 (9.1)		1.17 (0.98-1.41)	0.09
No	107,660	4,896 (4.6)		1	

[a]Odds ratio adjusted for age at diagnosis, gender, race/ethnicity, insurance, median income level, urban/rural, histologic diagnosis, tumor grade, tumor size, primary site, T stage, N stage, type of surgical procedure, facility type, proportion of Medicaid/uninsured patients, proportion of lung cancer operations, volume of cancer operations.
CI, confidence interval.

(Table 1). The annual margin positivity rate was stable over the 8-year time span (2004–2011), ranging between 4.4%, in 2007 and 5.2% in 2010 (trend test $p = 0.07$). Fifty-seven percent of margin-positive cases were R1, 4% were R2, and 39% were not specified.

Several patient-level demographic characteristics were independently associated with higher adjusted odds of having an incomplete resection (see Table 1). They included black race, older patients with Medicare insurance coverage, and residence in an urban area. Associated patient-level clinical factors were squamous and "other" histologic diagnosis (as opposed to adenocarcinoma), poor histologic differentiation, larger tumors, lymph node involvement (or unknown lymph node status), tumors that overlapped multiple lobes or were located in the middle lobe or in the main-stem bronchus, and advanced stage (in terms of T category, N category, or aggregate stage). Patients with sublobar resections were more likely to have positive margins than were those who had a lobectomy or pneumonectomy.

Institutional characteristics and likelihood of margin positivity

Surgical procedures performed at institutions designated as community cancer programs or comprehensive community cancer programs were more likely to be associated with positive margins than were those performed at teaching or research institutions or at institutions designated as National Cancer Institute programs or networks (see Table 1). Institutions with a higher proportion of patients with Medicaid or no insurance were more likely to have incomplete resections than were those with the lowest proportion of underinsured patients. In addition, institutions at which lung cancer operations constituted a higher percentage of all surgical procedures and those with higher volumes of cancer operations in general had significantly lower odds of performing incomplete resections. Sensitivity analyses, in which we excluded patients with R2 and/or unspecified R status, yielded results similar to those of our primary analyses (Supplementary Table 1).

Pattern of adjuvant therapy use

Radiotherapy was administered to 11,267 patients (10%) in the whole cohort and 2335 (43.8%) of those with positive margins, to 206 (8.8%) of whom it was administered preoperatively and to 2104 (90.1%) of whom it was administered postoperatively. Chemotherapy was administered to 29,845 patients (26.1%) in the whole cohort. This included 2697 (50.6%) patients with positive resection margins, in 277 (10.3%) of whom it was used preoperatively and in 2319 (86%) of whom it was used postoperatively.

Neoadjuvant therapy and incidence of incomplete resection

There was a strong association between use of neoadjuvant therapy and occurrence of a resection with positive margins (Table 2). After adjustment for other factors associated with margin positivity, patients who received preoperative radiotherapy had a significantly greater likelihood of margin positivity than did those who did not receive neoadjuvant therapy (adjusted OR = 1.59, 95% confidence interval: 1.17–2.15, $p = 0.003$).

Survival impact of incomplete resection

The crude overall 5-year survival rate of patients with an R0 resection was 58.5% compared with 33.8% in those with positive margins, log-rank $p < 0.001$, Fig. 2*A*). This survival difference persisted when patients were stratified by T category (Fig. 2*B*), tumor size (Fig. 2*C*), and

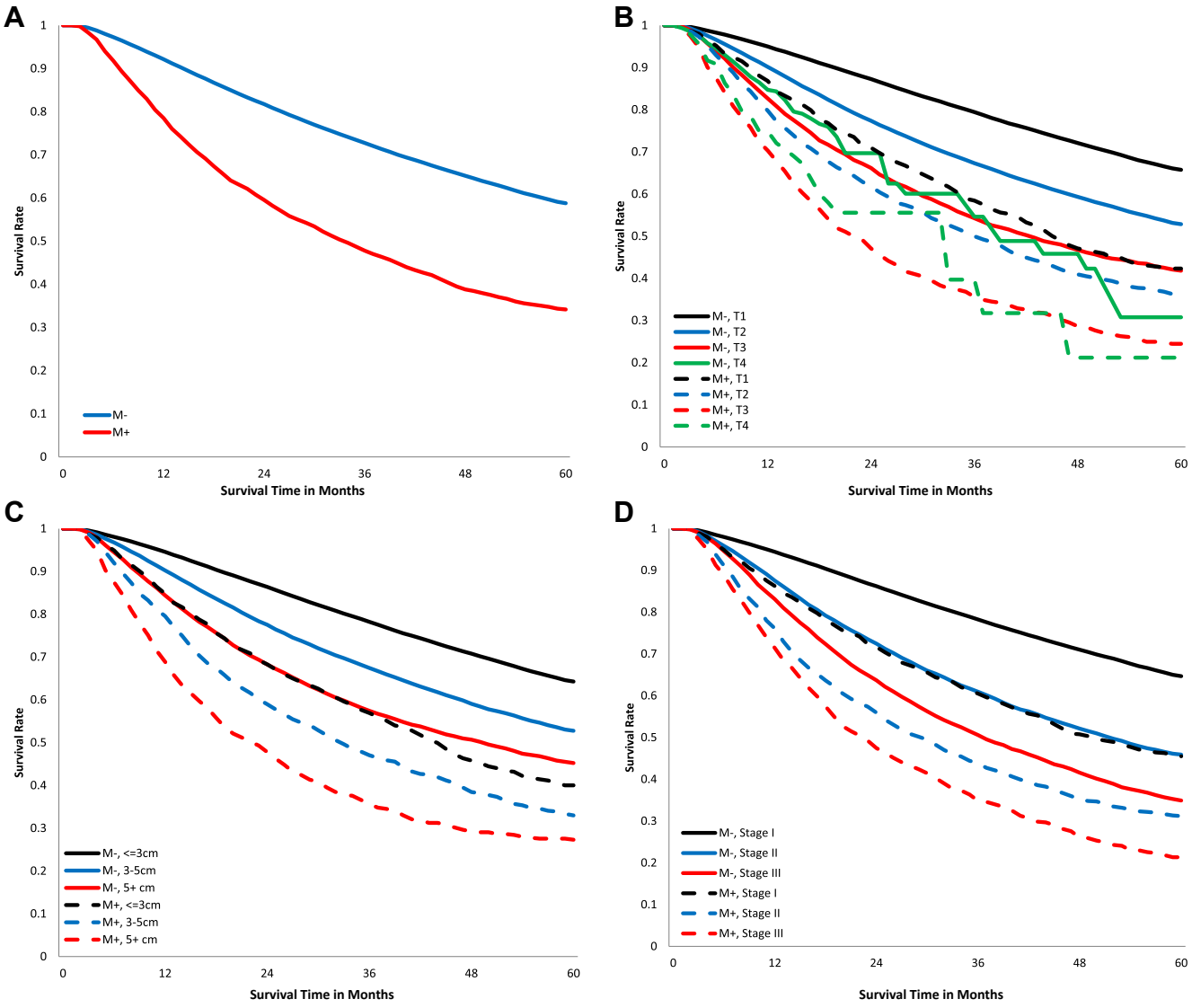

Figure 2. Kaplan-Meier estimates of 5-year overall survival curves stratified by margin status: (*A*) crude; (*B*) stratified by T category; (*C*) stratified by tumor size; and (*D*) stratified by American Joint Committee on Cancer aggregate tumor node metastasis stage. M-, patients with resections with negative margins; M+, patients with resections with positive margins.

aggregate AJCC stage (Fig. 2*D*). Notably, margin-positive patients with pT1 disease had a survival curve overlapping that of patients with pT3 disease who had an R0 resection (see Fig. *2B*). The survival curve of patients with margin-positive stage I disease overlapped that of patients with stage II who had an R0 resection. Patients with incompletely resected stage II disease had a lower survival rate than did those with completely resected stage III disease (see Fig. 2*D*). The survival detriment was consistent at 1, 3, and 5 years (Supplementary Table 2).

Sensitivity analyses, in which patients with an R1 resection were analyzed separately from those with R2 and unspecified R-status revealed similar results (Supplementary Table 3). The results were also similar irrespective of whether eligibility was limited to patients surviving past postoperative day 30, 60, or 90 (Supplementary Table 4).

Survival impact of postoperative adjuvant therapy in patients with positive margins

The 5-year overall survival of patients with positive margins varied by stage and treatment modality (Fig. *3A–C*, Table 3). Receipt of chemotherapy was associated with better survival irrespective of stage. Radiotherapy was associated with significantly lower survival in patients with stage I disease (log-rank $p < 0.001$) but had no significant impact on patients with stage II and III disease. Chemoradiation had no significant impact on patients with stage I disease but

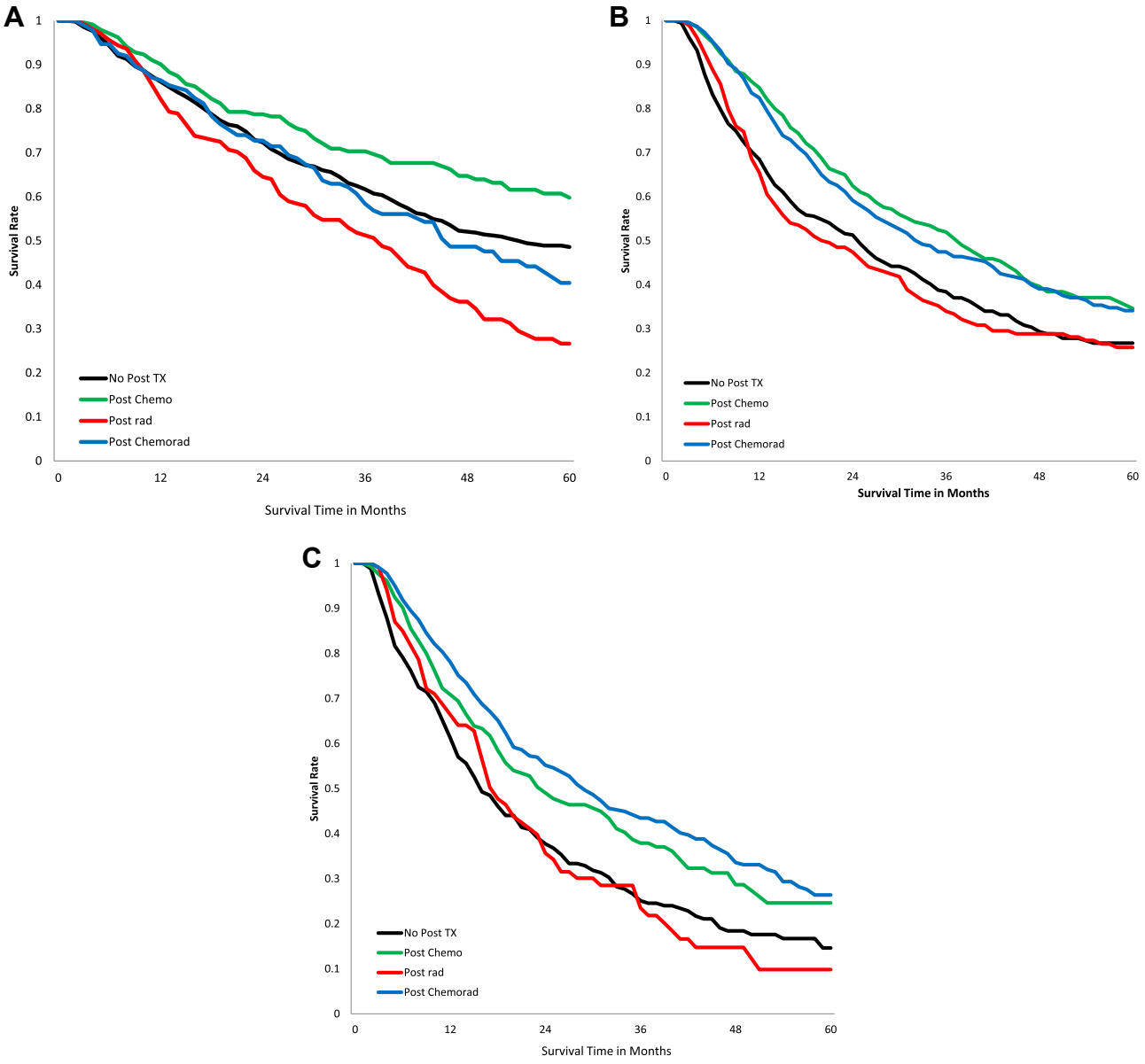

Figure 3. Kaplan-Meier estimates of 5-year overall survival of patients with an incomplete lung cancer resection stratified by postoperative adjuvant treatment and stage: (*A*) patients with stage I disease; (*B*) patients with stage II disease; and (*C*) patients with stage III disease.

was associated with improved survival in patients with stage II and III disease (log-rank $p < 0.001$). The results were similar when margin-positive patients with an R1 resection were analyzed separately from those with R2 or unspecified R status (Supplementary Table 5), and also when the analysis population excluded patients

Table 3. Five-year overall survival rates after incomplete lung cancer resection stratified by stage and postoperative treatment

	Five-year overall survival rate						
Stage	No adjuvant therapy	Chemotherapy	p^a	Radiotherapy	p^a	Chemoradiation	p^a
I	0.49	0.60	0.008	0.27	<0.001	0.40	0.34
II	0.27	0.35	<0.001	0.26	0.66	0.34	<0.001
III	0.15	0.25	<0.001	0.10	0.97	0.26	<0.001

[a]Log-rank survival comparison with patients in a similar stage but without adjuvant therapy.

who died within 30, 60, and 90 days postoperatively (Supplementary Table 6).

Discussion

The goal of all curative intent surgery in oncology is to achieve a disease-free plane of tissue at the microscopic margin of resection, thereby increasing assurance that no disease has been left behind. The adverse survival impact of resection with positive margins has been confirmed for many different types of cancer. Indeed, the rate of resection with positive margins has been proposed as a marker of the quality of rectal cancer care.[24] Since at least 2004, the College of American Pathologists has mandated inclusion of resection margin status in all pathology reports on lung cancer resection. Tacit acknowledgment of the negative impact of incomplete resection of lung cancer has stimulated development of algorithms for the care of such patients.[3]

However, the lung cancer literature on the prognostic implications of margin involvement has been ambiguous. Some studies suggest a negative impact on survival,[15,16,18,20–22,25–33] whereas others suggest little or no impact.[5,10,17,19,34–36] Furthermore, the role of postoperative adjuvant therapy in this situation is unclear. Most reports indicate no benefit from adjuvant radiotherapy.[15–22,30,32] Some reports even recommended it despite evidence of detrimental effects.[20,31] All the previous reports have been small, single-institution studies examining from four to 216 cases. Indeed, the cumulative number of cases in the 28 English-language reports from 1945 to 2010 is approximately 1227.[6,10,11,15–22,25–38] Our 8-year NCDB cohort is more than fourfold larger than the sum of patients in all previous English-language reports.

The size of our cohort has enabled us to definitively address several open questions. The reported rate of margin-positive resection in the existing literature ranged from 1.2% to 17%.[10,38] Our data set, which represents a heterogeneous group of institutions covering more than 70% of the U.S. population, establishes an aggregate annual margin-positive rate consistently under 6%. In addition, we have identified factors associated with the risk for incomplete resection, quantified its negative survival impact, and provided data on the benefit of postoperative adjuvant therapy in such a situation.

Consistent with previous reports, we found that the risk for incomplete resection advances with tumor stage.[11,16,21,22,32,38] However, contrary to previous reports, our study shows that resection with positive margins is not rare in patients with stage I and II non–small cell lung cancer.[16] Such patients represented 35.5% and 36.5% of our cohort, respectively. Also unlike in previous reports, the negative impact of incomplete resection on survival was independent of stage.[21,22,30] Indeed, the impact of incomplete resection was equivalent to at least one level of AJCC stage advancement. Thus, the survival rate of patients with stage I non-R0 cancer was similar to that of patients with stage II R0 disease, and the survival rate of patients with stage II non-R0 cancer was worse than that of patients with stage IIIA R0 disease (see Fig. 2*D*).

We have clarified that a histologic diagnosis of squamous cell carcinoma is associated with a higher risk for incomplete resection than is adenocarcinoma, which is contrary to certain previous reports.[16,38] This association is probably related to the generally more proximal location of these tumors. Patients who undergo lobectomy, bilobectomy, or pneumonectomy are similarly at relatively lower risk than are recipients of sublobar resection. The association between use of preoperative adjuvant therapy and incomplete resection is probably an example of "confounding by indication." Patients who are deemed by clinical staging parameters to be at high risk for incomplete resection are more likely to be offered preoperative adjuvant therapy.

We found a strong association between nonclinical characteristics and the risk for incomplete resection. Resection margin status appears to be a disparate outcome of health care for lung cancer that is associated with patient demographic and institutional characteristics. The specific patient, institutional, and provider-level practices driving this association need to be elucidated to provide a pathway to meaningful quality improvement.[39] We can only speculate on the reasons for this association. One possibility is that certain patients seek care from less proficient providers with access to fewer resources. For example, racial minorities seek care from providers who are less well trained; are less able to provide high-quality care; and have less access to high-quality specialists, diagnostic imaging, and nonemergency care.[40] Reducing the negative impact of incomplete resection requires incidence reduction by elimination of modifiable contributory practices and postincident risk mitigation.

Irrespective of cancer stage, postoperative adjuvant chemotherapy is associated with reduced mortality risk after incomplete resection, thus suggesting the need to consider it for all such patients. However, a key finding of this study is that contrary to current recommendations, postoperative adjuvant radiation may be profoundly harmful to patients with incompletely resected stage I non–small cell lung cancer.[3,11] Clinical trials to confirm these findings and identify the best adjuvant therapy options for the different subsets of patients with an incomplete resection would be ideal. Such trials will be difficult to conduct, partly because providers and institutions with access

to large numbers of eligible patients are unlikely to be actively engaged in clinical trials. However, such a clinical trial may be a suitable challenge for the National Cancer Institute Community Oncology Research Program.

Our study is limited by the retrospective nature of the analysis and the unavailability of some important details about institutional practices (such as intraoperative use of pathologic examination of frozen sections). In addition, we lack information on the anatomic site of margin involvement, the proportion of margin-positive cases with carcinoma in situ at the margin, and disease recurrence patterns. Furthermore, whether the resection was an R1 or R2 resection is unclear in 39% of cases, although our sensitivity analysis suggests that most of these cases were probably R1 resections. In any event, our results are consistent even when the known R1 cases are analyzed separately from the R2 and unspecified R cases. Finally, we lack information on the criteria for selection of the various adjuvant therapy options. Nevertheless, the size of the data set has enabled us to resolve the decades-long debate about the impact of incomplete lung cancer resection on survival and provide evidentiary guidance for developers of clinical management algorithms. Future work should identify causal links with provider and institutional practice. The adjuvant therapy options after incomplete resection of non–small cell lung cancer should also be subjected to prospective clinical trials.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.08.002.

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