Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non–Small-Cell Lung Cancer

Matthew Koshy, MD,† Stacey A. Fedewa, MPH,‡ Renu Malik, MD,† Mark K. Ferguson, MD,§¶ Wickii T. Vigneswaran, MD,§ Lawrence Feldman, MD,‖ Andrew Howard, MD,*† Khaled Abdelhady, MD,# Ralph R. Weichselbaum, MD,*† and Katherine S. Virgo, PhD, MBA‡***

Introduction: Optimal management of clinical stage IIIA-N2 non–small-cell lung cancer (NSCLC) is controversial. This study examines whether neoadjuvant chemoradiation plus surgery improves survival rates when compared with other recommended treatment strategies.

Methods: Adult patients from the National Cancer Database, with clinical stage IIIA-N2 disease definitively treated between 1998 and 2004 at American College of Surgeons Commission on Cancer accredited facilities, were included in the study. Treatment was defined as neoadjuvant chemoradiation plus either lobectomy (NeoCRT+L) or pneumonectomy (NeoCRT+P), lobectomy plus adjuvant therapy (L+AT), pneumonectomy plus adjuvant therapy (P+AT), and concurrent chemoradiation (CRT). Median follow-up and overall survival (OS) were defined from date of diagnosis to last contact. Five-year OS was estimated using Kaplan–Meier methods. Cox proportional hazard regression was used to estimate hazard ratios and 95% confidence intervals (CIs), adjusting for sociodemographic, clinical, and facility characteristics.

Results: Median follow-up was 11.8 months for 11,242 eligible patients. Five-year OS was 33.5%, 20.7%, 20.3%, 13.35%, and 10.9% for NeoCRT+L, NeoCRT+P, L+AT, P+AT, and CRT, respectively ($p < 0.0001$). On multivariable analysis, the estimated hazard ratio was 0.51 (CI: 0.45–0.58) for NeoCRT+L; 0.77 (0.63–0.95) for NeoCRT+P; 0.66 (0.59–0.75) for L+AT; 0.69 (0.54–0.88) for P+AT; and 1.0 (reference) for the CRT group. Comorbidity did not attenuate the relationship between treatment and survival.

Conclusion: This large study demonstrates that patients with clinical stage IIIA-N2 NSCLC, who underwent neoadjuvant chemoradiation followed by lobectomy, were associated with an improved survival.

Key Words: Lung cancer, Neoadjuvant chemoradiation.

(*J Thorac Oncol.* 2013;8: 915-922)

Treating clinical stage IIIA-N2 non–small-cell lung cancer (NSCLC) is a significant challenge.[1] The high rate of local failure seen in the population treated with chemoradiation alone led investigators to examine whether neoadjuvant chemoradiation (NeoCRT) plus curative-intent surgical resection could decrease locoregional recurrence rates and improve survival. The main concern regarding this approach is the potential for increased surgical morbidity and mortality. NeoCRT can cause worsening of inflammation, which may increase the complication rates associated with subsequent surgical resection.[2]

Several phase II studies initially suggested an overall survival (OS) benefit of 10% to 20% from NeoCRT and surgery, with most trials reporting a median survival of 15 to 22 months.[3–8] However, three recent phase III randomized studies, which completed accrual, failed to confirm a clear survival benefit of neoadjuvant therapy.[9–11] Because of these results, the role of neoadjuvant chemoradiation followed by a lobectomy or pneumonectomy in stage IIIA-N2 NSCLC remains controversial.[12]

The purpose of this study was to examine whether neoadjuvant chemoradiation was associated with improved survival compared with other recommended treatment strategies among patients with clinical stage IIIA-N2 NSCLC, using observational data from the National Cancer Database (NCDB), which allows for an analysis of a much larger cohort of patients from a variety of clinical practices than previously published studies.

PATIENTS AND METHODS

The NCDB is a hospital-based cancer registry that collects data from American College of Surgeons (ACoS) Commission on Cancer (CoC) accredited facilities and is jointly sponsored by the ACoS and the American Cancer Society. It includes data on approximately 70% of all

*Department of Radiation Oncology, University of Illinois Hospital, Chicago, Illinois; †Department of Radiation and Cellular Oncology, The University of Chicago, Chicago, Illinois; ‡Health Services Research Program, Intramural Research Department, American Cancer Society, Atlanta, Georgia; §Department of Surgery, The University of Chicago, Chicago, Illinois; ‖Department of Medical Oncology, University of Illinois at Chicago, Chicago, Illinois; ¶The University of Chicago Cancer Center; #Division of Cardiothoracic Surgery, Department of Surgery, University of Illinois at Chicago, Chicago, Illinois; and **Department of Health Policy and Management, Emory University, Atlanta, Georgia.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Matthew Koshy, MD, Department of Radiation Oncology, University of Illinois Hospital, 1801 West Taylor Street, Room C-400, Chicago, IL 60612. E-mail: mkoshy@radonc.uchicago.edu

ISSN: 1556-0864/13/0807-0915

malignant cancers in the United States. The database contains information on patient demographics, primary tumor site, histology, stage at diagnosis, insurance status, first course of treatment, and OS.

Data and Study Population

Eligible patients had histologically confirmed first primary invasive NSCLC and received all or part of their first course of treatment at ACoS CoC accredited facilities.[13] We restricted the analysis to patients aged 19 years and older, with pretreatment clinical stage IIIA-N2 (T1–T3) disease, treated between 1998 and 2004, to allow for a minimum of 5 years of follow-up (n = 39,359). Patients were not required to have histologic confirmation of clinical N2 disease because this information was unavailable in the database. The treatment categories were selected a priori according to a review of the literature. The five recommended treatment strategies in this population, which were consistent with curative therapy, according to evidence-based guidelines released by various oncologic societies for positive clinical N2 nodal status included neoadjuvant chemoradiation plus a lobectomy (NeoCRT+L), neoadjuvant chemoradiation plus a pneumonectomy (NeoCRT+P), lobectomy plus adjuvant therapy (L+AT), pneumonectomy plus adjuvant therapy (P+AT), and concurrent chemoradiation (CRT) alone.[14–18] Adjuvant therapy included chemotherapy alone, radiation alone, and chemoradiation. Patients with missing demographic data (n = 126), missing treatment data (n = 7755), those who did not receive treatment (n = 4358), those who received chemotherapy or radiation therapy alone (n = 9431), or who received treatment that did not meet criteria established for the three categories as mentioned above, such as sequential chemotherapy and radiation, were excluded (n = 6447). All patients were retrospectively classified into each category, based on the actual treatment they received.

The ACoS CoC requires accredited programs to update vital status and other information in 5-year cycles; for example, patients first diagnosed with cancer in 1998 (1998 incident cases) would be initially reported in 2000 and would have their vital status updated in 2005 (which would be the same year when the 2003 incident cases would be reported). After the initial 5-year follow-up, the vital status of the case and follow-up time are updated on an annual basis. The NCDB does not have cause of death data. Therefore, for this study, overall follow-up time was defined as the time from diagnosis to date of death from any cause, or the time from diagnosis to date of last contact for those who were alive at last contact. Patient risk factors that were part of the statistical analysis included histology, T-stage (according to the 6th edition of the American Joint Committee on Cancer Stage), laterality, age at diagnosis, sex, insurance type, race/ethnicity, and geographic region.[19] The variables and categorizations were based on previously published data sets examining prognostic factors in lung cancer patients.[20,21] Among patients who underwent surgery, the surgical margin status of the pulmonary resection was recorded. From 2003, the NCDB began collecting data on comorbidities from the hospital face sheet. A modified version of the 17-item Charlson–Deyo Index (eliminating solid tumors and leukemia) was computed to permit adjustment for comorbidities.[22] The 15-item modified index measured conditions such as diabetes, myocardial infarction, and kidney failure.

Facility-level characteristics included the volume of patients who received care for NSCLC at an ACoS CoC facility during the study period and treatment facility type. Four types of treatment facilities were included in the classification scheme used by the CoC accreditation program, (1) community cancer programs, (2) comprehensive community cancer programs, (3) teaching or research centers, and (4) National Cancer Institute–designated cancer centers. Community cancer centers treat at least 300 cancer patients a year and have a full range of services for cancer care. Comprehensive community cancer centers offer the same range of services as the community hospitals but treat at least 650 cancer patients annually. Teaching/research facilities are affiliated with medical schools, have residency programs, conduct ongoing cancer research, and have no minimum caseload requirement.

Statistical Analysis

Median follow-up was calculated among individuals with censored data.[23] Estimates of OS, stratified by the treatment received, were calculated using Kaplan–Meier survival estimates. The log-rank test was used to estimate whether there were differences in OS rate by treatment type. Differences in treatment type by patient, facility, and area-level characteristics were estimated using χ^2 tests. All statistical tests were two sided, and a 0.05 level of significance was used.

Multivariable Cox proportional hazards (PHs) regression models were used to assess the importance of treatment received as an independent predictor of OS. All statistically significant (at the 0.05 level) data on patient, facility, and area-level variables from the aforementioned bivariate analysis were included in the multivariate Cox PH analysis. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated in models adjusted for the aforementioned covariates of interest. A test for PHs in initial survival models revealed time interactions among several factors, including histopathology, sex, clinical T-stage, laterality, diagnosis year, and age at diagnosis. Because of the violation of PH for these variables, we controlled for these variables by stratification. Stratification allows for different stratum to have different baseline hazard functions and ultimately results in an HR being weighted over the different strata. This procedure allows for simultaneous calculation of HR for those variables that do not violate the PH assumption, but it does preclude the generation of HR estimates for variables that do violate the PH assumption.[24,25] Furthermore, the treatment category violated the PH assumption within the first 4 months of follow-up. The Cox proportional hazards model relies on the hazards to be proportional, meaning that the effect of a given covariate does not change over time. The treatment category violated PH in the first 4 months of follow-up. To correct this, we performed multivariate analysis on patients who survived a minimum of 4 months, after which the treatment variable did not violate the PH assumption (n = 10,058). Use of the 4-month cutoff in the multivariate analysis also reduced potential time biases from differences in the duration of therapy.[26–28]

TABLE 1. Patient, Facility and Area-Level Characteristics by Treatment Type among Clinical Stage IIIA-N2 Non–Small-Cell Lung Cancer Patients, National Cancer Database (NCDB) 1998–2004

Categories	Total	Neoadjuvant Chemoradiotherapy + Lobectomy	Neoadjuvant Chemoradiotherapy + Pneumonectomy	Lobectomy + Adjuvant Therapy	Pneumonectomy + Adjuvant Therapy	Definitive Concurrent Chemoradiotherapy	*p*
	N = 11242	*n* = 564	*n* = 188	*n* = 510	*n* = 123	*n* = 9857	
	%	(4.94)	(1.65)	(4.46)	(1.08)	(86.28)	
	N (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
Sex							<0.0001
Men	6654 (59.19)	313 (55.5)	123 (65.43)	256 (50.2)	90 (73.17)	5872 (59.57)	
Women	4588 (40.81)	251 (44.5)	65 (34.57)	254 (49.8)	33 (26.83)	3985 (40.43)	
Race/ethnicity							0.0003
Non-Hispanic, white	8647 (76.92)	470 (83.33)	140 (74.47)	403 (79.02)	88 (71.54)	7546 (76.55)	
Hispanic	161 (1.43)	*a*	*a*	*a*	*a*	142 (1.44)	
Black	1220 (10.85)	31 (5.5)	18 (9.57)	41 (8.04)	12 (9.76)	1118 (11.34)	
Other	145 (1.29)	10 (1.77)	*a*	10 (1.96)	*a*	120 (1.22)	
Missing	1069 (9.51)	49 (8.69)	24 (12.77)	48 (9.41)	17 (13.82)	931 (9.45)	
Insurance status							<0.0001
Uninsured	311 (2.77)	*a*	*a*	13 (2.55)	*a*	284 (2.88)	
Medicaid	540 (4.8)	22 (3.9)	*a*	20 (3.92)	*a*	484 (4.91)	
Younger medicare	623 (5.54)	27 (4.79)	*a*	24 (4.71)	*a*	562 (5.7)	
Older medicare	4921 (43.77)	153 (27.13)	42 (22.34)	211 (41.37)	29 (23.58)	4486 (45.51)	
Private	4288 (38.14)	330 (58.51)	121 (64.36)	217 (42.55)	71 (57.72)	3549 (36)	
Missing	559 (4.97)	25 (4.43)	*a*	25 (4.9)	*a*	492 (4.99)	
Age, yr							<0.0001
19–59	3351 (29.81)	259 (45.92)	103 (54.79)	165 (32.35)	61 (49.59)	2763 (28.03)	
60–69	3951 (35.14)	217 (38.48)	69 (36.7)	176 (34.51)	42 (34.15)	3447 (34.97)	
70–79	3326 (29.59)	83 (14.72)	16 (8.51)	150 (29.41)	20 (16.26)	3057 (31.01)	
80+	614 (5.46)	*a*	*a*	19 (3.73)	*a*	590 (5.99)	
Year of diagnosis year							<0.0001
1998	834 (7.42)	32 (5.67)	22 (11.7)	48 (9.41)	23 (18.7)	709 (7.19)	
1999	972 (8.65)	59 (10.46)	22 (11.7)	53 (10.39)	22 (17.89)	816 (8.28)	
2000	1405 (12.5)	81 (14.36)	28 (14.89)	67 (13.14)	21 (17.07)	1208 (12.26)	
2001	1787 (15.9)	86 (15.25)	19 (10.11)	70 (13.73)	13 (10.57)	1599 (16.22)	
2002	1792 (15.94)	73 (12.94)	27 (14.36)	63 (12.35)	11 (8.94)	1618 (16.41)	
2003	2290 (20.37)	123 (21.81)	33 (17.55)	100 (19.61)	17 (13.82)	2017 (20.46)	
2004	2162 (19.23)	110 (19.5)	37 (19.68)	109 (21.37)	110 (19.5)	1890 (19.17)	
Histology							<0.0001
Adenocarcinoma	3687 (32.8)	272 (48.23)	54 (28.72)	318 (62.35)	53 (43.09)	2990 (30.33)	
Large-cell	918 (8.17)	47 (8.33)	*a*	37 (7.25)	10 (8.13)	816 (8.28)	
Squamous cell	2298 (20.44)	92 (16.31)	31 (16.49)	35 (6.86)	*a*	2133 (21.64)	
NSCLC NOS	4339 (38.6)	153 (27.13)	95 (50.53)	120 (23.53)	53 (43.09)	3918 (39.75)	
Clinical T-stage							<0.0001
T1	1923 (17.11)	134 (23.76)	20 (10.64)	157 (30.78)	15 (12.2)	1597 (16.2)	
T2	5968 (53.09)	305 (54.08)	100 (53.19)	306 (60)	81 (65.85)	5176 (52.51)	
T3	3351 (29.81)	125 (22.16)	68 (36.17)	47 (9.22)	27 (21.95)	3084 (31.29)	
Laterality							<0.0001
Right	6661 (59.25)	387 (68.62)	90 (47.87)	275 (53.92)	54 (43.9)	5855 (59.4)	
Left	3677 (32.71)	171 (30.32)	80 (42.55)	232 (45.49)	61 (49.59)	3133 (31.78)	
Bilateral	*a*	*a*	*a*	*a*	*a*	*a*	
Unknown	897 (7.98)	6 (1.06)	18 (9.57)	3 (0.59)	8 (6.5)	862 (8.75)	
Facility type							<0.0001
CCP	1803 (16.04)	58 (10.28)	16 (8.51)	57 (11.18)	12 (9.76)	1660 (16.84)	

(*Continued*)

TABLE 1. (*Continued*)

Categories	Total	Neoadjuvant Chemoradiotherapy + Lobectomy	Neoadjuvant Chemoradiotherapy + Pneumonectomy	Lobectomy + Adjuvant Therapy	Pneumonectomy + Adjuvant Therapy	Definitive Concurrent Chemoradiotherapy	*p*
Comprehensive CCP	6251 (55.6)	262 (46.45)	89 (47.34)	237 (46.47)	58 (47.15)	5605 (56.86)	
Teaching/research	2432 (21.63)	165 (29.26)	61 (32.45)	139 (27.25)	32 (26.02)	2035 (20.65)	
NCI	590 (5.25)	68 (12.06)	19 (10.11)	73 (14.31)	17 (13.82)	413 (4.19)	
Missing	166 (1.48)	11 (1.95)	*a*	*a*	*a*	144 (1.46)	
Facility volume							0.17
High	8446 (75.13)	445 (78.9)	151 (80.32)	390 (76.47)	97 (78.86)	7363 (74.7)	
Medium	2448 (21.78)	107 (18.97)	35 (18.62)	104 (20.39)	22 (17.89)	2180 (22.12)	
Low	348 (3.1)	12 (2.13)	*a*	16 (3.14)	*a*	314 (3.19)	
Surgical margin status							0.13*b*
Negative margins	1150 (83.03)	476 (84.4)	165 (87.77)	414 (81.18)	95 (77.24)	N/A	
Positive margins	135 (9.75)	45 (7.98)	11 (5.85)	63 (12.35)	16 (13.01)	N/A	
Margins not evaluable	14 (1.01)	*a*	*a*	*a*	*a*	N/A	
Missing	86 (6.21)	36 (6.38)	*a*	30 (5.88)	*a*	N/A	
Comorbidities (%)*c*							0.10
None	69.99%	73.39%	75.71%	64.59%	57.58%	70.08%	
≥1	30.01%	26.61%	24.29%	35.41%	42.42%	29.92%	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	<0.0001
Age at diagnosis, yr	64.7 (10.11)	60.2 (9.15)	57.4 (9.45)	64 (10.07)	59.4 (9.96)	65.2 (10.04)	

CCP, community cancer program; N/A, patients did not undergo surgery, so margin status is unobtainable; NCDB, National Cancer Database; NCI, National Cancer Institute Designated Facility.

[a] Data cell has <10 patients and is not shown to ensure patient confidentiality, per NCDB Data Use Agreement.

[b] *p* value is among surgical patients only.

[c] Percentages calculated are among the 2003–2004 cohort.

As mentioned above, the NCDB began collecting comorbidity data in 2003. A separate multivariable analysis was performed using data from 2003 to 2004 ($n = 4025$), in which the Charlson-Deyo comorbidity score was also included, as a covariate of interest, to determine whether comorbidity attenuated the relationship between survival and treatment. Because of the very small number of patients in some treatment categories with two or more comorbidities coded, we restricted the comorbidity analysis to two groups, 0, and 1 or more. Data were analyzed using SAS software (version 9.2; SAS Institute Incorporated, Cary, NC).

RESULTS

A total of 11,242 patients met the inclusion criteria. The overall median follow-up time for all patients was 11.8 months (range, <1 month to 60 months) and 60 months among those who were alive at last contact (1279 patients). The median follow-up of patients who lived a minimum of 4 months ($n = 10,058$), which was the cohort analyzed in the multivariable analysis, was 13.5 months. In patients who lived less than 4 months, the median time to treatment was 16 days and median OS was approximately 3 months and the majority received chemoradiation (96%). Of the entire cohort, 4% of patients were lost to follow-up (alive at last contact but followed up for <5 years). The median age at diagnosis was 65 years. Patient characteristics are shown in Table 1. Male patients comprised 59% of the cohort. The majority of patients had either squamous cell carcinoma or adenocarcinoma (20% and 33%, respectively). Among patients who underwent surgical resection, the percentage of patients with positive surgical margins was 9.75% and did not vary significantly among the surgical treatment groups ($p = 0.13$). The 90-day mortality among patients who underwent surgical resection was as follows: 1.6% in the NeoCRT+P group, 0% in the NeoCRT+L group, 2.46% in the P+AT group, and 1.97% in the L+AT group. Approximately 70% of the patients in the cohort were older than 59 years of age. By type of treatment, 4.9% of the cohort underwent NeoCRT+L, 1.7% underwent NeoCRT+P, 4.5% underwent L+AT, 1.1% underwent P+AT, and 86.3% underwent CRT. Among the patients who underwent L+AT or P+AT, similar percentages of patients received adjuvant chemotherapy and radiation therapy (43.4% versus 46.3%, respectively), adjuvant radiation alone (31.1% versus 32.5%), and adjuvant chemotherapy alone (25.5% versus 21.0%). A high proportion of patients treated with NeoCRT+L were white, younger (<70 years), and had larger tumors (T2). Among the cohort who underwent neoadjuvant therapy followed by surgery, 23% had a complete pathologic response. In the 2003–2004 cohort, comorbidity did not vary by treatment type ($p = 0.10$).

The 5-year OS was 33.5%, 20.8%, 20.3%, 13.4%, and 10.9% for the NeoCRT+L, NeoCRT+P, L+AT, P+AT, and CRT groups, respectively ($p < 0.0001$) (Fig. 1). In the cohort that had a complete pathologic response after neoadjuvant chemoradiation the 5-year OS was 40%. For the 10,058 patients, who lived 4 months or longer, age, sex, laterality, T-stage, histology, and diagnosis year were controlled for at

the strata level in multivariate Cox models, as discussed previously. Furthermore, in this cohort there were no significant differences in the patient, facility, and area-level characteristics compared with our initial cohort, as shown in Table 1. The estimated HR was 0.51 (95% CI: 0.45–0.58) for NeoCRT+L; 0.77 (95% CI: 0.63–0.95) for NeoCRT+P; 0.66 (95% CI: 0.59–0.75) for L+AT; 0.69 (95% CI: 0.54–0.88) for P+AT; and 1.0 for the CRT group (reference) (Table 2).

To examine the impact of comorbidities, the adjusted PH analyses were rerun, restricting the cohort to only those patients diagnosed from 2003 to 2004. Despite the existence of a significant association between comorbidity and survival (HR: 1.16; 95% CI: 1.06–1.26), the relationship between treatment and survival was unaltered. Adjusting for comorbidities in the 2003–2004 cohort, the estimated HR was 0.41 (95% CI: 0.33–0.50) for NeoCRT+L, 0.73 (95% CI: 0.52–1.02) for NeoCRT+P, 0.49 (95% CI: 0.40–0.60) for L+AT; 0.59 (95% CI: 0.38–0.93) for P+AT; and 1.0 for the CRT group (reference) (Table 3). We also ran a separate model, restricted to the same 2 years (2003–2004), but excluding comorbidity, and found similar HR and 95% CI for each treatment group (Table 3).

DISCUSSION

This large national hospital-based study examined the outcomes of patients with pretreatment clinical stage IIIA-N2 NSCLC. Representing one of the largest cohorts examined to date, this observational study revealed that patients who underwent NeoCRT+L had a 49% reduced likelihood of death compared with those who underwent CRT after adjusting for other important clinical, sociodemographic, and facility factors.

Neoadjuvant therapy in stage IIIA(N2) NSCLC was introduced in an effort to improve the poor survival rates seen historically in this cohort.[29,30] The recently published phase III study, Intergroup 0139, randomized 396 patients with stage IIIA-N2 disease to either neoadjuvant chemoradiation plus surgical resection and consolidative chemotherapy, or concurrent chemoradiotherapy alone. The median OS rate of 27% in the neoadjuvant group versus 20% in the chemoradiation-alone group did not differ significantly (odds ratio 0.63;95% CI: 0.36–1.10). However, a subgroup analysis revealed a statistically significant 5-year survival advantage for patients who received neoadjuvant chemoradiotherapy plus lobectomy compared with those who underwent chemoradiation alone (36% and 18%, respectively; $p = 0.002$).[9]

The delivery of neoadjuvant chemoradiation is complex and requires high-level multidisciplinary care and coordination.[31] Thus, it was encouraging to note that our nationwide observational study involving patients treated in varying clinical settings, outside the context of a clinical study, had a 5-year OS rate of 34% for the NeoCRT + L group, which is comparable to the 5-year OS rate of 36% seen in the NeoCRT + L subset of the Intergroup 1039 study. This analysis also revealed that patients who had a complete pathologic nodal response had a 5-year survival of 40% and was in almost exact concordance with the findings of the intergroup 1039 study, which revealed a 5-year OS of 42% in patients with a complete pathologic nodal response.

The current study was primarily limited by information that was unavailable in the NCDB database, including types of chemotherapy administered, pretreatment pathologic proof of clinical N2 disease, extent of mediastinal nodal involvement (bulky versus nonbulky), number of mediastinal nodal stations involved, extent of disease, use of positron emission

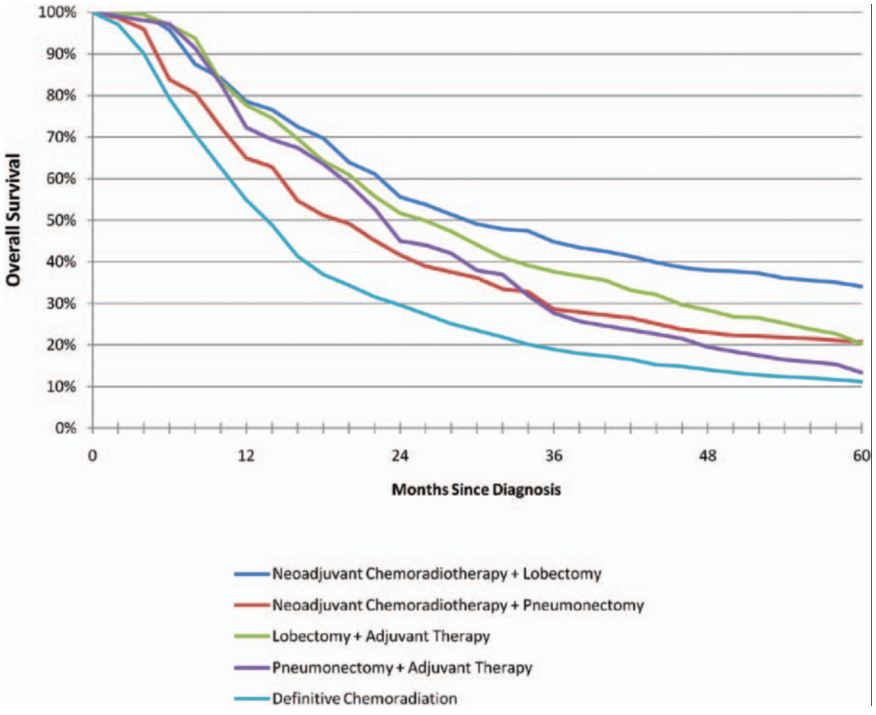

FIGURE 1. Five-year overall survival among clinical stage IIIA-N2 NSCLC patients, National Cancer Database, 1998–2004, $p < 0.0001$. NSCLC, non–small-cell lung cancer.

TABLE 2. Multivariate Cox Proportional Hazard Models Predicting 5-year Overall Survival among Clinical Stage IIIA-N2 NSCLC Patients, NCDB 1998–2004 (n = 10,058)

	5-Year Survival[a,b]	
Parameter	**HR**	**95% CI**
Treatment		
Definitive chemoradiation	1.00	
Neoadjuvant chemoradiotherapy + lobectomy	0.51	(0.45–0.58)
Neoadjuvant chemoradiotherapy + pneumonectomy	0.77	(0.63–0.95)
Lobectomy + adjuvant therapy	0.66	(0.59–0.75)
Pneumonectomy + adjuvant therapy	0.69	(0.54–0.88)
Insurance status		
Private	1.00	
Uninsured	1.1	(0.93–1.30)
Medicaid	1.2	(1.05–1.36)
Younger Medicare	1.09	(0.97–1.23)
Older Medicare	1.06	(0.98–1.13)
Missing	1.4	(1.23–1.59)
Race/ethnicity		
Non-Hispanic white	1.00	
Hispanic	0.77	(0.62–0.96)
Black	0.87	(0.79–0.95)
Other	0.98	(0.78–1.22)
Missing	1.03	(0.95–1.12)
Facility type		
Teaching/research	1.00	
CCP	1.04	(0.94–1.15)
Comprehensive CCP	1.04	(0.97–1.11)
NCI	0.95	(0.84–1.07)
Missing	1.16	(0.92–1.47)
Facility volume		
High	1.00	
Medium	1.04	(0.96–1.12)
Low	1.04	(0.87–1.23)

CCP, community cancer program; CI, confidence intervals; HR, hazard ratio; NCI, National Cancer Institute Designated Facility; NCDB, National Cancer Database; NSCLC, non–small-cell lung cancer.

[a] Models adjusted for age, sex, clinical T-stage, laterality, histology, and diagnosis year at the strata level.

[b] Five-year survival starts at 121 days because of a violation in proportional hazards by treatment within the first 120 days of diagnosis.

tomography scans, performance status, total radiotherapy dosage, overall treatment time, fractionation size, and radiotherapy treatment technique. Furthermore, clinical stage IIIA (N2) NSCLC is a heterogeneous entity because of the extent of nodal involvement. Patients who present with bulky mediastinal adenopathy are considered inoperable and are more likely to undergo chemoradiation, which partially explains the worse survival seen in this cohort.[32] The survival of patients who underwent chemoradation alone was 10.9% versus 20% in the Intergroup 0139 study. This difference is likely because the majority of patients in this study who underwent chemoradiation had inoperable disease, which is associated with a worse prognosis, whereas all patients in the Intergroup study had operable disease. This pretreatment bias was at least partially mitigated because we included a comparison group of patients that underwent lobectomy and adjuvant therapy. Such patients would have had an excellent performance status and nonbulky N2 disease because they were able to tolerate an upfront surgical procedure. Therefore, because of these pretreatment characteristics we would have expected the L+AT group to have an improved survival compared with the other treatment groups. However, the multivariate analysis revealed the opposite, that the NeoCRT+L group had an improved survival (HR: 0.51; CI: 0.45–0.58) compared with the L+AT group (HR: 0.66; CI: 0.59–0.75), lending further evidence to the fact that the differences in survival reflect the differences caused by the treatment. Furthermore, the rates of positive margins did not differ significantly between the surgical groups. Also, the cohort of patients receiving neoadjuvant therapy was small compared with the overall cohort examined, however, this finding is consistent with other studies that have examined the receipt of neoadjuvant therapy in patients having stage III NSCLC.[33,34]

To account for differences in comorbidities between patients which may have explained the difference in OS among treatments, we adjusted for comorbidities among patients treated from 2003–2004, the period when the NCDB began collecting these data. Though comorbidity was significantly associated with survival, it did not attenuate the relationship between treatment and survival. Despite this, we acknowledge that this study has the inherent flaws of being a retrospective analysis, and is limited mainly by pretreatment selection biases, which include patients with better prognostic factors and improved performance status and who may have been more likely to have undergone neoadjuvant chemoradiation followed by surgery. Furthermore, a selection bias is introduced because this analysis only examined the treatment as received, and it was impossible to ascertain how many patients were initially recommended to undergo neoadjuvant chemoradiation followed by surgery but were unable to complete the treatment because of progression or treatment-related toxicity. Another limitation is that variables that violated the PH assumption were used as stratification variables, which does not allow for assessing the impact of these variables on OS. When examining treatment so as to not violate the PH model, we had to exclude deaths within the first 4 months, which may also create a bias toward certain treatment categories. Also, the Charleson–Deyo comorbidity index does not provide as accurate an identification or severity of comorbid illness compared with clinical databases.[35] Thus, because these results come from an observational study, they should be considered as hypothesis-generating and could be considered for confirmation in future prospective studies.

The optimal management of stage IIIA(N2) NSCLC is not well defined and depends on a variety of factors.[36] Appropriate candidates for neoadjuvant chemoradiation followed by surgery include those with T1–T3 disease and ipsilateral positive mediastinal lymph nodes (maximum diameter <3 cm). Furthermore, they should have resectable disease as determined by a thoracic surgeon and have adequate pulmonary function.

TABLE 3. Multivariate Cox Proportional Hazard Models Predicting 5-year Overall Survival among Clinical Stage IIIA-N2 NSCLC Patients with Comorbidity Data, NCDB 2003–2004 (n = 4025)

	5-Year Survival[a,b]			
	Model Includes Comorbidity Data		Model Excludes Comorbidity Data	
Parameter	**HR**	**95% CI**	**HR**	**95% CI**
Treatment				
Definitive chemoradiation	1.00		1.00	
Neoadjuvant chemoradiotherapy + lobectomy	0.41	(0.33–0.50)	0.41	(0.33–0.50)
Neoadjuvant chemoradiotherapy + pneumonectomy	0.73	(0.52–1.02)	0.72	(0.51–1.02)
Lobectomy + adjuvant therapy	0.49	(0.40–0.60)	0.5	(0.4–0.61)
Pneumonectomy + adjuvant therapy	0.59	(0.38–0.93)	0.61	(0.39–0.95)
Insurance status				
Private	1.00		1.00	
Uninsured	1.19	(0.94–1.51)	1.20	(0.95–1.52)
Medicaid	1.12	(0.92–1.36)	1.13	(0.93–1.37)
Younger medicare	1.16	(0.98–1.38)	1.19	(1.00–1.42)
Older medicare	1.08	(0.96–1.22)	1.09	(0.97–1.23)
Missing	1.05	(0.8–1.38)	1.05	(0.80–1.06)
Race/ethnicity				
Non-Hispanic white	1.00		1.00	
Hispanic	0.71	(0.49–1.01)	0.70	(0.49–1.01)
Black	0.92	(0.8–1.05)	0.92	(0.80–1.06)
Other	1.02	(0.73–1.45)	1.01	0.71–1.42
Missing	1.07	(0.95–1.22)	1.07	(0.88–1.32)
Facility type				
Teaching/research	1.00		1.00	
CCP	1.08	(0.91–1.27)	1.09	(0.92–1.28)
Comprehensive CCP	1.11	(1.0–1.23)	1.11	(1.00–1.24)
NCI	1	(0.84–1.20)	1.01	(0.84–1.21)
Missing	1.59	(1.06–2.38)	1.59	(1.06–2.38)
Facility volume				
High	1.00		1.00	
Medium	1.05	(0.94–1.18)	1.05	(0.93–1.18)
Low	0.89	(0.67–1.17)	0.88	(0.67–1.16)
Comorbidity				
None	1.00		N/A	
1 or more	1.16	(1.06–1.26)	N/A	

CCP, community cancer program; CI, confidence intervals; HR, hazard ratio; N/A, patients did not undergo surgery, so margin status is unobtainable; NCI, National Cancer Institute Designated Facility; NCDB, National Cancer Database; NSCLC, non–small-cell lung cancer.

[a] Models adjusted for age, sex, clinical T-stage, laterality, histology, and diagnosis year at the strata level.

[b] Five-year survival starts at 121 days because of a violation in proportional hazards by treatment within the first 120 days of diagnosis.

This study of hospital-based data has important clinical significance because it is one of the largest observational studies to examine this issue, and suggests that neoadjuvant chemoradiation plus lobectomy may be appropriate in carefully selected individuals, and associated with a similar survival to that seen in the Intergroup 0139 study. This study also highlights the importance of patients with locally advanced lung cancer to be initially evaluated in a multidisciplinary setting with a thoracic surgeon, medical oncologist, and radiation oncologist, to determine the most appropriate initial treatment strategy.

ACKNOWLEDGMENT

Supported in part by American Cancer Society Intramural Research Funding.

REFERENCES

1. Rigas JR, Kelly K. Current treatment paradigms for locally advanced non-small cell lung cancer. *J Thorac Oncol* 2007;2 Suppl 2:S77–S85.
2. Anderson CS, Curran WJ. Combined modality therapy for stage III non-small-cell lung cancer. *Semin Radiat Oncol* 2010;20:186–191.
3. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB

non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995;13:1880–1892.
4. Choi NC, Carey RW, Daly W, et al. Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. *J Clin Oncol* 1997;15:712–722.
5. Elias AD, Skarin AT, Leong T, et al. Neoadjuvant therapy for surgically staged IIIA N2 non-small cell lung cancer (NSCLC). *Lung Cancer* 1997;17:147–161.
6. Burkes RL, Shepherd FA, Blackstein ME, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage IIIA (T1-3, N2) unresectable non-small-cell lung cancer: final results of the Toronto phase II trial. *Lung Cancer* 2005;47:103–109.
7. Edelman MJ, Suntharalingam M, Burrows W, et al. Phase I/II trial of hyperfractionated radiation and chemotherapy followed by surgery in stage III lung cancer. *Ann Thorac Surg* 2008;86:903–910.
8. Friedel G, Budach W, Dippon J, et al. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: a single-center study. *J Clin Oncol* 2010;28:942–948.
9. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374:379–386.
10. van Meerbeeck JP, Kramer GW, Van Schil PE, et al.; European Organisation for Research and Treatment of Cancer-Lung Cancer Group. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442–450.
11. Thomas M, Rübe C, Hoffknecht P, et al.; German Lung Cancer Cooperative Group. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008;9:636–648.
12. De Craene S, Surmont V, van Meerbeeck JP. Adjuvant or neoadjuvant chemotherapy in minimal N2 stage IIIA nonsmall cell lung cancer. *Curr Opin Oncol* 2010;22:102–111.
13. Commission on Cancer. *Facility Oncology Registry Data Standards (FORDS); Revised for 2007*. Chicago, IL: American College of Surgeons, 2007.
14. Robinson LA, Ruckdeschel JC, Wagner H Jr, Stevens CW; American College of Chest Physicians. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132(3 Suppl):243S–265S.
15. Pfister DG, Johnson DH, Azzoli CG, et al.; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
16. Pisters KM, Evans WK, Azzoli CG, et al.; Cancer Care Ontario; American Society of Clinical Oncology. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline. *J Clin Oncol* 2007;25:5506–5518.
17. D'Addario G, Felip E; ESMO Guidelines Working Group. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;20 Suppl 4:68–70.
18. Ettinger DS, Akerley W, Bepler G, et al.; NCCN Non-Small Cell Lung Cancer Panel Members. Non-small cell lung cancer. *J Natl Compr Canc Netw* 2010;8:740–801.
19. Greene FL, American Joint Committee on Cancer, American Cancer Society. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*, 6th Ed. New York: Springer-Verlag, 2002.
20. 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.
21. Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P; International Staging Committee and Participating Institutions. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 2008;3:457–466.
22. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–619.
23. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. *Br J Cancer* 2003;89:232–238.
24. Kleinbaum DG, Klein M. Survival analysis. 2012: 700. Available at: http://encompass.library.cornell.edu/cgi-bin/checkIP.cgi?access=gateway_standard%26url=http://dx.doi.org/10.1007/978-1-4419-6646-9. Accessed October 2, 2012.
25. Ata NSM. Cox regression models with nonproportional hazards applied to lung cancer survival data. *Hacc J Math Stat* 2007;38: 157.
26. Park HS, Gross CP, Makarov DV, Yu JB. Immortal time bias: A frequently unrecognized threat to validity in the evaluation of postoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 2012.
27. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983;1:710–719.
28. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;167:492–499.
29. Depierre A, Milleron B, Moro-Sibilot D, et al.; French Thoracic Cooperative Group. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002;20: 247–253.
30. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer* 1980;45: 2744–2753.
31. Kunitoh H, Suzuki K. How to evaluate the risk/benefit of trimodality therapy in locally advanced non-small-cell lung cancer. *Br J Cancer* 2007;96:1498–1503.
32. Roy MS, Donington JS. Management of locally advanced non small cell lung cancer from a surgical perspective. *Curr Treat Options Oncol* 2007;8:1–14.
33. Koshy M, Goloubeva O, Suntharalingam M. Impact of neoadjuvant radiation on survival in stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;79:1388–1394.
34. Wang J, Kuo YF, Freeman J, Markowitz AB, Goodwin JS. Temporal trends and predictors of perioperative chemotherapy use in elderly patients with resected nonsmall cell lung cancer. *Cancer* 2008;112:382–390.
35. Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. *J Clin Epidemiol* 2006;59:265–273.
36. West H, Albain KS. Current standards and ongoing controversies in the management of locally advanced non-small cell lung cancer. *Semin Oncol* 2005;32:284–292.

