Treatment of cT3N1M0/IIIA non–small cell lung cancer and the risk of underuse of surgery

Mohamed Rahouma, MD,[a,b] Mohamed Kamel, MD,[a,b] Abu Nasar, MS,[a] Sebron Harrison, MD,[a] Benjamin Lee, MD,[a] Jeffrey Port, MD,[a] Nasser Altorki, MD,[a] and Brendon M. Stiles, MD[a]

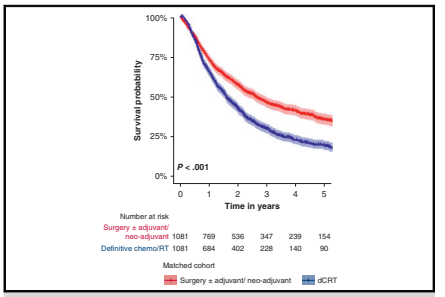
ABSTRACT

Objective: Surgery may be underused for stage IIIA non–small cell lung cancer. Although an argument can be made for definitive chemoradiation for N2/3 mediastinal nodal disease, the role of a nonsurgical strategy is less clear in patients with cT3N1M0 stage IIIA given a lack of randomized data. We sought to determine the outcomes of patients with cT3N1M0 by treatment type from the National Cancer Database.

Methods: The National Cancer Database (2004-2014) was queried for patients with cT3N1M0 non–small cell lung cancer, known treatment modalities, and sequence. Comparisons between groups were performed using Mann–Whitney and chi-square tests. Cox regression was performed to identify predictors of overall survival. Propensity score matching analysis was performed to compare overall survival in surgery versus definitive chemoradiation.

Results: We identified 1937 patients undergoing surgery (1518 up-front and 419 after neoadjuvant treatment) and 1844 patients undergoing definitive chemoradiation. Among patients undergoing surgery without prior treatment, 19% were overstaged and were found to have pN0, whereas 9.6% had pN2/3. Median overall survival was 33.1 months in the surgery group (± adjuvant/neoadjuvant) versus 18 months in definitive chemoradiation. To compare outcomes in balanced groups, we propensity matched 1081 pairs of patients. Median overall survival was 31.1 months in the surgery group compared with 19.1 months in the definitive chemoradiation group ($P < .001$). By multivariable analysis, surgery (hazard ratio, 0.65; confidence interval, 0.59-0.73), female sex (hazard ratio, 0.88; confidence interval, 0.79-0.98), age (hazard ratio, 1.02; confidence interval, 1.01-1.03), squamous histology (hazard ratio, 1.22; confidence interval, 1.07-1.38), and Charlson score of 2 (hazard ratio, 1.31; confidence interval, 1.11-1.54) were predictors of survival.

Conclusions: In the National Cancer Database, approximately half of patients with clinical T3N1M0 were treated with definitive chemoradiation rather than surgery. This practice should be avoided in operable patients, because surgical resection is associated with better survival. (J Thorac Cardiovasc Surg 2021;161:256-63)



Kaplan–Meier OS for matched cohort reflecting better survival in surgery ± (adjuvant/neoadjuvant) versus dCRT ($P < .001$).

CENTRAL MESSAGE

In the NCDB, approximately half of patients with clinical T3N1M0 were treated with dCRT rather than surgery. This practice should be avoided in operable patients, because surgery is associated with better survival.

PERSPECTIVE

In the NCDB, approximately half of patients with clinical T3N1M0 were treated with dCRT rather than surgery. This practice should be avoided in operable patients, because surgery is associated with better survival.

See Commentaries on pages 264 and 265.

Stage IIIA non–small cell lung cancer (NSCLC) includes a heterogeneous group of patients with an overall poor prognosis. Management of patients with clinically stage IIIA disease involves separating patients who have curable local disease from those who essentially have early systemic disease.[1] Evaluation by a multidisciplinary thoracic oncology team remains critical to make individualized treatment recommendations to optimize long-term survival.[1] In appropriate surgical candidates, surgical resection provides optimal local control and has survival benefits beyond chemotherapy and radiation alone.[1] However, surgery in stage IIIA NSCLC disease may be underused. Although

From the [a]Cardiothoracic Department, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY; and [b]Surgical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt.

Read at the 99th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, May 4-7, 2019.

Received for publication June 13, 2019; revisions received Jan 19, 2020; accepted for publication Jan 31, 2020; available ahead of print Feb 24, 2020.

Address for reprints: Brendon M. Stiles, MD, Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Weill Cornell Medicine of Cornell University, Suite M404, 525 East 68th St, New York, NY 10065 (E-mail: brs9035@med.cornell.edu).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.01.097

Abbreviations and Acronyms

CI = confidence interval
dCRT = definitive chemoradiation
HR = hazard ratio
IQR = interquartile range
NCDB = National Cancer Database
NOS = not otherwise specified
NSCLC = non–small cell lung cancer
OS = overall survival

Scanning this QR code will take you to the article title page to access supplementary information.

an argument can be made for definitive chemoradiation (dCRT) for patients with N2 mediastinal nodal disease based on randomized data,[2] the role of a nonsurgical strategy is less clear in patients with cT3N1M0/IIIA given a lack of randomized data. These patients without mediastinal nodal metastases may derive more benefit from surgical resection. We sought to determine outcomes of patients with cT3N1M0 by treatment type from the National Cancer Database (NCDB). We hypothesized that patients with cT3N1M0 who received surgery as part of multimodality therapy would have better survival compared with those who received dCRT.

MATERIALS AND METHODS

Data Source and Study Design

This is a retrospective study of patients with cT3N1M0 stage NSCLC in the NCDB diagnosed from 2004 to 2014. Data were derived from the NCDB participant user data file. The NCDB is a national cancer registry administered jointly through the American College of Surgeons Commission on Cancer and the American Cancer Society.[3] The database contains more than 34 million historical records from more than 1500 participating institutions and captures approximately 70% of newly diagnosed cancer cases in the United States annually. Standardized collection and data definitions have been described.[3] The NCDB collects data on patient and hospital characteristics, cancer diagnosis, staging, treatments, and outcomes. The American College of Surgeons Commission on Cancer is not responsible for the analytic methodology used or the conclusions drawn by the investigators in this study. The study has been exempted from review by the Weill Cornell Medicine institutional review board.

Derivation of the Study Population

Derivation of the study cohort is shown in Figure E1. The study population included adult patients (aged ≥18 years) with clinical stage T3N1M0/IIIA NSCLC and known treatment modalities. Clinical T3 designation was based on the classification in the NCDB and varied by year (patients from 2004-2009 were staged according to the 6th edition, and patients from 2010-2014 were staged according to the 7th edition). Patients were excluded for the following: not cT3N1M0 stage, multiple primary tumors, carcinoid histology, unknown treatment modalities, or unknown treatment modalities sequence. We compared patients who received surgery ± adjuvant/neoadjuvant with those who received definitive chemotherapy/radiotherapy (dCRT) (Figure 1).

Surgery, chemotherapy, and radiotherapy treatment sequence was defined using NCDB variables. Adjuvant chemotherapy was defined as single- or multi-agent systemic chemotherapy given after the surgical resection for the primary site. Per the NCDB-participant user data file data dictionary, postoperative chemotherapy reflects the receipt of at least 2 courses of chemotherapy postoperatively.[3] It also specifies that the recorded treatment information in the NCDB pertains to the first course treatment only. Thus, treatment given for disease recurrence or progression is excluded. Patients in the chemoradiation group were considered to have received dCRT if they did not undergo surgery and chemotherapy was delivered within 3 weeks before or after initiation of radiation.[4,5]

Patient and Treatment Details

Population demographic factors that were examined included age, sex, race, Charlson–Deyo comorbidity condition score. Tumor factors included histology, tumor size, and nodal stage. Treatment details such as the use of neoadjuvant or adjuvant treatment, surgical approach, operation (pneumonectomy, lobectomy or bilobectomy, and less than lobectomy), and surgical margin were collected. For the histology variable, we included 3 categories: adenocarcinoma, squamous cell cancer, and others. The "others" category entailed diverse pathological types as pleomorphic carcinoma, giant cell carcinoma, spindle cell carcinoma, pseudosarcomatous carcinoma, non–small cell carcinoma not otherwise specified (NOS), papillary carcinoma, NOS, lymphoepithelial carcinoma, solid carcinoma, and NOS.

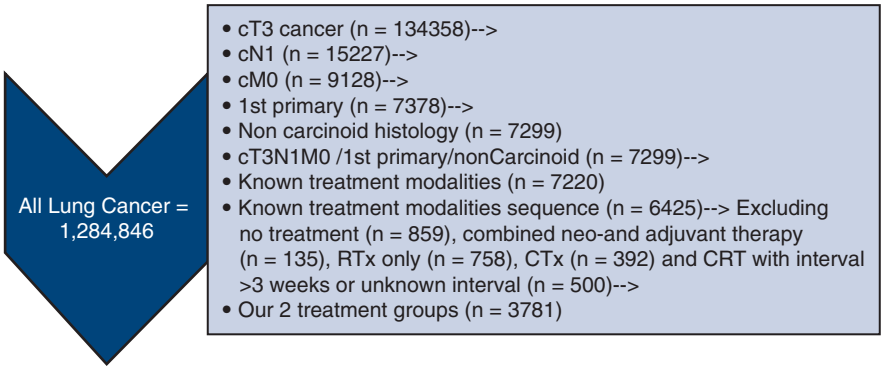


FIGURE 1. Consolidated Standards of Reporting diagram of explaining derivation of our cohorts. *RTx*, Radiation therapy only; *CTx*, chemotherapy only; *CRT*, chemoradiation.

TABLE 1. Demographics and clinical data of the included treatment cohorts

Data from 2004-2014	Surgery ± adjuvant/ neoadjuvant (n = 1937)	Definitive chemotherapy/ radiotherapy (n = 1844)	Total (n = 3781)	*P* value
Age	65 (57-71)	68 (60-75)	66 (58-73)	<.001
Sex				
Male	1196 (61.7%)	1126 (61.1%)	2322 (61.4%)	.667
Female	741 (38.3%)	718 (38.9%)	1459 (38.6%)	
Race				
White	1710 (88.9%)	1566 (85.2%)	3276 (87.1%)	<.001
Black	161 (8.4%)	237 (12.9%)	398 (10.6%)	
Others	52 (2.7%)	34 (1.9%)	86 (2.3%)	
Charlson–Deyo score				
CDCC = 0	1052 (54.3%)	1073 (58.2%)	2125 (56.2%)	.004
CDCC = 1	673 (34.7%)	547 (29.7%)	1220 (32.3%)	
CDCC = 2	212 (10.9%)	224 (12.1%)	436 (11.5%)	
Primary payer				
Private insurance/managed care	750 (38.7%)	485 (26.3%)	1235 (32.7%)	<.001
Medicaid/Medicare/other government	1088 (56.2%)	1250 (67.8%)	2338 (61.8%)	
Not insured	59 (3.0%)	78 (4.2%)	137 (3.6%)	
Insurance status unknown	40 (2.1%)	31 (1.7%)	71 (1.9%)	
Median income quartiles (<$38,000/≥$38,000)	369/1542 (19.3/80.7%)	430/1390 (23.6/67.4%)	799/2932 (21.4/78.6%)	.002
Median income quartiles				
<$38,000	369 (19.3%)	430 (23.6%)	799 (21.4%)	<.001
$38,000-$47,999	490 (25.9%)	545 (29.9%)	1035 (27.7%)	
$48,000-$62,999	526 (27.5%)	461 (25.3%)	987 (26.5%)	
$63,000+	526 (27.5%)	384 (21.1%)	910 (24.4%)	
Urban/rural (urban or metropolitan/rural)	1821/49 (97.4/2.6%)	1740/3.0 (97.0/3.0%)	3561/103 (97.2/2.8%)	.540
Great circle distance (travel distance) (median [IQR])	12.4 (4.9-29.8)	9.3 (4.1-22.7)	10.7 (4.5-25.7)	<.001
Facility type				
Community Cancer Program	179 (9.3%)	275 (14.9%)	454 (12.1%)	<.001
Comprehensive Community Cancer Program	856 (44.5%)	965 (52.4%)	1821 (48.4%)	
Academic/Research Program	711 (37.0%)	431 (23.4%)	1142 (30.3%)	
Integrated Network Cancer Program	178 (9.3%)	171 (9.3%)	349 (9.3%)	
Histology				
Adenocarcinoma	694 (36.1%)	435 (23.7%)	1129 (30.0%)	<.001
Squamous cell cancer	908 (47.2%)	1031 (56.1%)	1939 (51.6%)	
Others	321 (16.7%)	371 (20.2%)	692 (18.4%)	
Tumor size (mm)	65 (40-85)	65 (45-90)	65 (42-89)	<.001

CDCC, Charlson-Deyo Cumulative Comorbidity; *IQR*, interquartile range.

We included bronchioloalveolar carcinoma (n = 24) in adenocarcinoma and large cell (n = 100) in the "others" group. Total dose of radiation therapy was the summation of the regional dose (RAD_REGIONAL_DOSE_CGy) and boost dose (RAD_BOOST_DOS_CGy).[5]

Survival Outcome and Follow-up Data

Overall survival (OS) is the time from date of diagnosis to date of death from any cause or date of last follow-up. Median follow-up time was calculated by reversed Kaplan–Meier method.[6]

Statistical Analysis

After checking for normality, continuous and categoric variables were expressed as median and interquartile range (IQR) and frequency (percentages), respectively, and groups were compared using Mann–Whitney *U* test and chi-square tests. Survival was estimated using Kaplan–Meier curves and compared using log-rank test. Cox regression was done to identify the independent predictors of OS. Variables with *P* values less than .20 in univariate analysis were included in multivariable model.

Propensity score matching analysis (1:1, caliper 0.05, including year of diagnosis, age, sex, race, comorbidities, tumor size, histology, facility type, travel distance, and insurance status) was performed to compare OS in patients undergoing surgery with those treated with dCRT. Matched variables were compared using McNemar test that accounts for the matched nature of the patients. Standardized mean difference before and after matching was compared to assess the matching process with standardized mean difference less than 0.10 after matching reflecting proper balancing of the cohorts.

For statistical analyses, we used "tableone" and "survminer" packages[7,8] in R (version 3.3.3 R Project for Statistical Computing) within RStudio[9] and SPSS version 22.0 (IBM, Armonk, NY).[10-12]

RESULTS

Patients

Among a total of 3781 patients, we identified 1937 patients with cT3N1M0 undergoing surgery (1518 up-front and 419 after neoadjuvant treatment) and 1844 undergoing dCRT. Use of dCRT was more common in elderly patients (aged 68 vs 65 years, $P < .001$), nonwhite patients (14.8% vs 11.1%, $P < .001$), those with more comorbidities (Charlson–Deyo comorbidity condition = 2: 12.1% vs 10.9%, $P = .004$), and those with squamous cell histology (56.1% vs 47.2%, $P < .001$). Detailed demographic differences between the groups are presented in Table 1.

The median total radiation dose was 54 GY (IQR, 45.0-61.2) in the surgery (± adjuvant/neoadjuvant) group (n = 586) versus 63.0 GY (IQR, 59.4-66.6) in those patients receiving dCRT ($P < .001$). Different chemotherapeutic regimens were not recorded in the NCDB; however, among dCRT, 86.3% and 6.4% received multi-agent and single agent chemotherapy, respectively, whereas the type and number of agents were not documented in the remaining 7.3%.

Among the surgical cohort, minimally invasive approach and pneumonectomy were performed in 12.8% and 26.8%, respectively. The 30-day mortality among the up-front surgery group was 3.3% for lobectomy/bilobectomy and 7.1% for pneumonectomy, with 90-day mortality of 6.2% and 14.1%, respectively. For patients receiving neoadjuvant therapy followed by surgery, 30-day mortality was 3.1% for lobectomy/bilobectomy and 4.7% for pneumonectomy, whereas 90-day mortality was 5.1% and 14.0%, respectively. Among patients undergoing surgery without prior treatment, 19% were overstaged and were found to be pN0, whereas 9.6% were upstaged to pN2/3 (Table 2).

TABLE 2. Surgical details among whole cohort and stage accuracy (pathological nodal staging) among patients undergoing surgery without prior treatment

Data from 2004-2014	Surgery ± adjuvant/ neoadjuvant (n = 1937)
Approach	
Robotic assisted	37 (1.91)
Robotic converted to open	7 (0.36)
Thoracoscopic	153 (7.90)
Thoracoscopic converted to open	50 (2.58)
Open or approach unspecified	1026 (52.97)
Missing	664 (34.28)
Extent of resection	
Less than lobectomy	194 (10.0)
Lobectomy or bilobectomy	1224 (63.2)
Pneumonectomy	519 (26.8)
Surgical margin	
Residual tumor, NOS*	142 (7.30)
Microscopic residual tumor	130 (6.70)
Macroscopic residual tumor	23 (1.20)
Indeterminate/unknown	127 (6.60)
Data from 2004-2014	**Surgery ± adjuvant (n = 1518)**
Pathological N stage	(n = 1375 after exclusion of Nx, unknown cases)
N-ve	267 (19.4)
N+ve	1108 (80.6)
Pathological N stage	(n = 1375 after exclusion of Nx, unknown cases)
N0	267 (19.4)
N1	975 (70.9)
N2	131 (9.5)
N3	2 (0.1)

NOS, Not otherwise specified; *N*, nodal stage. *Involvement is indicated, but NOS.

Survival Outcomes

Median follow-up time was 51.9 months (95% confidence interval [CI], 49.6-54.3) for the whole group and 52.5 months (95% CI, 49.7-55.4) for surgery ± adjuvant/neoadjuvant versus 51.7 months (95% CI, 47.0-56.4) for dCRT.

Long-term survival data were available for 86% of the cohort, and patients with missing long-term survival data were excluded from the survival analysis. During the follow-up period, 2166 patients died: 983 (58.3%) in the surgery ± adjuvant/neoadjuvant cohort versus 1183 (75.5%) in the dCRT cohort.

The median and 5-year OS was 33.1 months (95% CI, 29.4-36.8) in the whole cohort: 36.5% in the surgery group (± adjuvant/neoadjuvant) versus 18 months (95% CI, 16.7-19.3) and 17.8% in the dCRT group ($P < .001$) (Figure 2, *A*).

Regarding surgical approach, the median OS in the pneumonectomy cohort was 33.68 (25.12-42.24) versus 36.57 (32.06-41.08) in the lobectomy/bilobectomy cohort ($P = .290$). Therefore, even patients undergoing pneumonectomy had better survival compared with dCRT ($P < .001$). Among patients undergoing surgery without prior treatment, the median OS was 45.4 months (95% CI, 29.2-61.6) for node-negative patients versus 30.5 months (95% CI, 26.7-34.2) for node-positive patients ($P = .015$). By multivariable analysis, surgical resection predicted improved survival (hazard ratio [HR], 0.65; 95% CI, 0.59-0.73), as did female sex (HR, 0.88; 95% CI, 0.79-0.98). Increased age (HR, 1.02; 95% CI, 1.01-1.03), squamous cell histology (HR, 1.22; 95% CI, 1.07-1.38), high pathological grades (HR, 1.13; 95% CI, 1.01-1.26), and Charlson score of 1 and 2 (HR, 1.18; CI, 1.05-1.32 and HR, 1.31; CI, 1.11-1.54, respectively) predicted worse survival (Table 3).

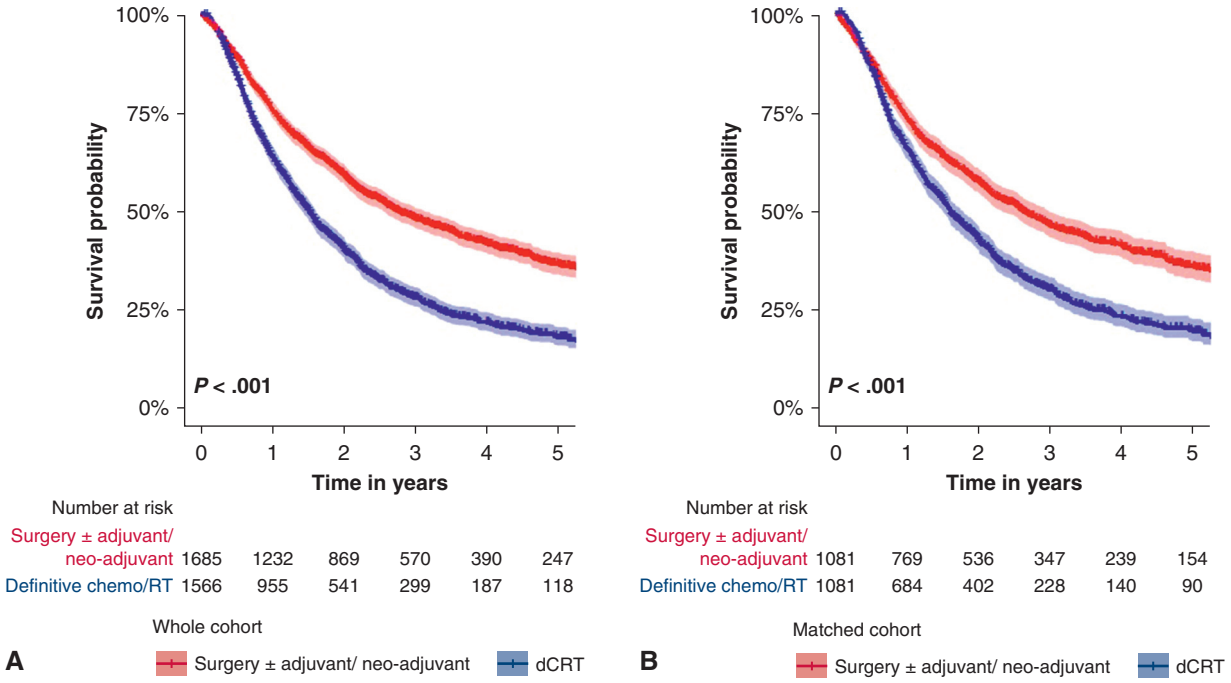


FIGURE 2. Kaplan–Meier OS for (A) unmatched cohorts and (B) matched cohort reflecting better survival in surgery ± (adjuvant/neoadjuvant) versus dCRT ($P < .001$). *dCRT*, Definitive chemoradiation.

Propensity-Matched Groups

To compare balanced groups of patients, we performed propensity matching of the cohorts undergoing surgery (± adjuvant/neoadjuvant) versus the cohort of patients undergoing dCRT (n = 1081 in each group). Groups were well balanced in terms of clinical parameters, comorbidity index, histology, and tumor size (Table 4). We next compared survival in these 2 matched cohorts. Again, OS was significantly improved in patients who underwent surgery (± adjuvant/neoadjuvant) compared with those who underwent dCRT, with a median OS of 31.1 months (27.4-35.2) versus 19.1 months (17.7-20.8). Five-year OS was 35.7% versus 19.0%, respectively ($P < .001$, Figure 2, *B* and Table 4).

DISCUSSION

Patients with clinically staged T3N1M0 NSCLC are underrepresented in clinical trials comparing treatment strategies for patients with clinical stage IIIA disease (range, 12%-30.3%).[2,13,14]

The definition of the T3 classification has changed over time. With the introduction of American Joint Committee on Cancer TNM 8th edition, T3 includes tumors greater than 5 but 7 cm or less or those invading the chest wall, pericardium or phrenic nerve, or separate tumor nodule(s) in the same lobe. In contrast, in the 7th edition, T3 included tumors greater than 7 cm or invading parietal or mediastinal pleura, chest wall, diaphragm, phrenic nerve, parietal pericardium, main bronchus (<2 cm distal to carina), entire left atrium or obstructive pneumonitis, or separate nodule in same lobe.[9,15] T3N2M0 that was considered as stage IIIA in 7th edition currently is considered as IIIB.[9,15]

Despite the adjustments to the T descriptors, most studies comparing treatment modalities for patients with stage IIIA fundamentally focus on the N classification rather than the T classification for allocation into clinical trials.[2,14] For example, Albain and colleagues' trial[2] is an often quoted randomized trial that compared OS and progression-free survival among radiotherapy plus chemotherapy with or without surgical resection for stage III NSCLC (stage T1-3pN2M0). It reported similar OS (HR, 0.87; 95% CI, 0.70-1.10; $P = .24$) when comparing combined modality therapy including surgery with dCRT alone. However, patients with T3 represented only 12% of the whole cohort,[2] and patients with clinical T3N1M0 stage IIIA were not included.[2]

Some data from large retrospective database cohorts are available regarding treatment outcomes for patients with T3 NSCLC. Speicher and colleagues,[16] working on the Surveillance, Epidemiology and End Results database that included 17,378 patients with T3N0-2, reported better survival in patients who received surgery versus those who did not (5-year survival 29% vs 6.8%, respectively). Radiation therapy was given to 47.3% of patients undergoing surgery versus 73.1% of patients who did not undergo surgery.[16] N1 stage represented only 19% of patients among the surgery cohort versus 9.3% among the no surgery cohort compared with 15.9% and 52.1%

TABLE 3. Predictors of overall survival (n = 3781)

	Univariate analysis HR (95% CI), *P* value	Multivariable analysis* HR (95% CI), *P* value
Year of diagnosis		
Age (continuous variable)	1.02 (1.01-1.03), *P* < .001	1.02 (1.01-1.03), *P* < .001
Sex		
Male	Reference	Reference
Female	0.86 (0.78-0.93), *P* < .001	0.88 (0.79-0.98), *P* = .023
Race		
White	Reference	
Black	0.99 (0.87-1.14), *P* = .90	…
Others	0.83 (0.61-1.13), *P* = .24	…
Charlson–Deyo score		
0	Reference	Reference
1	1.13 (1.03-1.24), *P* = .01	1.18 (1.05-1.32), *P* = .004
2	1.36 (1.19-1.55), *P* < .001	1.31 (1.11-1.54), *P* = .001
Histology		
Adenocarcinoma	Reference	Reference
Squamous cell cancer	1.27 (1.15-1.40), *P* < .001	1.22 (1.07-1.38), *P* = .002
Others	1.35 (1.19-1.52), *P* < .001	1.35 (1.16-1.59), *P* < .001
Differentiation grade		
G1-2	Reference	Reference
G3-4	1.11 (0.99-1.23), P0.053	1.13 (1.01-1.26), *P* = .035
Facility type		
Community Cancer Program	Reference	Reference
Comprehensive Community Cancer Program	0.89 (0.78-1.01), *P* = .078	1.03 (0.87-1.22)
Academic/Research Program	0.78 (0.67-0.9), *P* = .001	1.03 (0.86-1.24), *P* = .71
Integrated Network Cancer Program	0.81 (0.67-0.98), *P* = .027	1.06 (0.85-1.33), *P* = .60
Great circle distance		0.999 (0.999-1), *P* = .091
Insurance		
Not insured	Reference	Reference
Private insurance/managed care	0.7 (0.55-0.88), *P* = .002	0.72 (0.55-0.95), *P* = .021
Medicaid/Medicare/other government	1.04 (0.83-1.31), *P* = .71	0.82 (0.621-1.09), *P* = .17
Insurance status unknown	0.75 (0.51-1.11), *P* = .15	0.76 (0.46-1.23), *P* = .258
Median income quartiles		
<$38,000	Reference	Reference
$38,000-$47,999	0.96 (0.86-1.09), *P* = .54	0.96 (0.83-1.11), *P* = .58
$48,000-$62,999	0.91 (0.804-1.03), *P* = .12	0.93 (0.8-1.08), *P* = .334
$63,000 +	0.86 (0.76-0.98), *P* = .021	0.9 (0.77-1.05), *P* = .185
Treatment group		
dCRT	Reference	Reference
Surgery ± (adjuvant/neoadjuvant)	0.58 (0.53-0.63), *P* < .001	0.65 (0.59-0.73), *P* < .001

HR, Hazard ratio; *CI*, confidence interval; *dCRT*, definitive chemoradiation. *Variables with *P* values < .20 in univariate analysis were included in multivariable model.

for N2 stage.[16] These imbalances between the cohorts make for difficult comparisons. Kawaguchi and colleagues[17] reported an OS of 44.9% among their analysis of 531 pT3 cases, of which 66.1%, 15.3%, and 18.5% were N0, N1, and N2, respectively. All these studies reflect the heterogeneity of T3 cohorts and the challenge broadly of including them into clinical trials. Given the equivalence of chemoradiation to surgery in the INT0139 trial and the enthusiasm generated by the PACIFIC trial for the inclusion of immunotherapy into treatment regimens for stage III NSCLC, there is some danger that patients with surgically resectable stage III disease will not be offered surgery.[2,18] This is despite patients with cT3N1 not being included in INT0139 and despite only inoperable patients being included in the PACIFIC trial. However, we think that patients with cT3N1 NSCLC comprise a different group than those included in the INT0139 and PACIFIC trials.[2,18]

TABLE 4. Criteria of the matched cohorts

Data from 2004-2014	Surgery ± (adjuvant/ neoadjuvant) (n = 1081)	Definitive chemotherapy/ radiotherapy (n = 1081)	SMD
Year of diagnosis (median [IQR])	2010 [2008-2012]	2010.00 [2008-2012]	0.032
Age, y (median [IQR])	67 [59-73]	66.00 [59-73]	0.004
Sex = female (%)	398 (36.8)	420 (38.9)	0.042
Race (%)			0.037
White	956 (88.4)	948 (87.7)	
Black	109 (10.1)	112 (10.4)	
Others	16 (1.5)	21 (1.9)	
Charlson–Deyo score (%)			0.028
0	609 (56.3)	624 (57.7)	
1	342 (31.6)	331 (30.6)	
2	130 (12.0)	126 (11.7)	
Histology (%)			0.019
Adenocarcinoma	297 (27.5)	301 (27.8)	
Squamous cell cancer	564 (52.2)	554 (51.2)	
Others	220 (20.4)	226 (20.9)	
Facility type (%)			0.042
Community Cancer Program	140 (13.0)	130 (12.0)	
Comprehensive Community Cancer Program	542 (50.1)	558 (51.6)	
Academic/Research Program	302 (27.9)	291 (26.9)	
Integrated Network Cancer Program	97 (9.0)	102 (9.4)	
Great circle distance (travel distance) (median [IQR])	10.50 [4.60-25.80]	9.60 [4.00-23.40]	0.028
Insurance status (%)			0.035
Not insured	37 (3.4)	44 (4.1)	
Private insurance/managed care	326 (30.2)	327 (30.2)	
Medicaid/Medicare/other government	698 (64.6)	691 (63.9)	
Insurance status unknown	20 (1.9)	19 (1.8)	
Tumor size (median [IQR])	60.00 [40.00-82.00]	58.00 [40.00-76.00]	0.001

SMD, Standardized mean difference; *IQR*, interquartile range.

In the current study, we included a relatively homogenous group of patients with clinically staged T3N1M0 stage IIIA NSCLC. As a first point, it is notable that clinical staging is not always accurate in this group of patients. In the subset of patients who had surgery without neoadjuvant therapy, patients were twice as likely to be pathologically N0 than pathologically N2 or N3 (19.4% vs 9.6%). It is likely that many patients in the dCRT groups were treated without pathological confirmation of N1 disease or without invasive mediastinal staging. We think this practice should generally be avoided in medically operable patients with surgically resectable disease given the discrepancy between clinical and pathological staging, particularly in the current era of personalized treatment recommendations for patients with stage IIIA.

Others have previously reported survival benefits with surgical resection in patients with clinical N1 disease.[19] We further demonstrated a clear survival benefit for surgery with or without neoadjuvant or adjuvant therapy compared with dCRT. Five-year OS was 36.5% versus 17.8% ($P < .001$) in the unmatched patient group and 35.7% versus 19.0% ($P < .001$) in the propensity-matched cohort, favoring the surgical group in each. Even accounting for other patient- and tumor-related factors in a multivariable analysis, surgical resection predicted improved survival (HR, 0.65; 95% CI, 0.59-0.73). We suggest that all of these patients be seen and evaluated by surgeons and offered invasive staging and surgical resection when appropriate. Historically, it has been suggested that patients requiring pneumonectomy for stage III disease may derive no benefit from surgery.[2] In this analysis, however, even patients requiring pneumonectomy had improved survival compared with those undergoing dCRT. This must be tempered by the relatively high 90-day perioperative mortality after pneumonectomy.

Study Limitations

Our results must be interpreted in light of several limitations. Despite our efforts to reduce selection bias using propensity score matching, the possibility of unmeasured confounders persists. Despite a relative balancing of broadly defined comorbidity scores, it is possible that sicker, more frail patients were treated with dCRT and that their comorbidities, rather than their treatment

course, negatively affected their OS. The NCDB does not collect information specific to disease-free survival or recurrence-specific survival; thus, these outcomes cannot be examined. It is to be noted that 14% of included cases had missing long-term follow-up status as being alive or dead. Furthermore, the NCDB does not contain important information such as pulmonary function (eg, forced expiratory volume in 1 second, carbon monoxide diffusing capacity) or technical aspects relating to resection such as central tumors. These could be important confounders in the nonoperative cohort despite matching. Also, details on subgroups of T3 tumors such as parietal pleural invasion, chest wall invasion, multiple nodules in the same lobe, and size alone were not mentioned in the NCDB. Other imbalances may exist with regard to clinical lymph node staging. It is notable that 19% of patients undergoing primary surgery were actually N0 and approximately 10% were N2 or N3. It is not clear that these proportions would be maintained in the dCRT group, and this could not be balanced in the propensity model. It is also notable that specific chemotherapy agents are not specified in the NCDB. Therefore, we cannot analyze the impact of different types of chemotherapy on the outcomes of these patients. Nevertheless, we believe that the current study provides a reasonable comparison between treatment options for patients with cT3N1 NSCLC. Because such options have not been examined rigorously in clinical trials, these data are of significant importance in defining optimal management strategies.

CONCLUSIONS

In the NCDB, 1 in 5 patients with clinically staged T3N1M0 stage IIIA NSCLC was found to have pN0. Despite this, approximately half of patients with cT3N1M0 were treated with dCRT rather than surgery. This practice should be avoided because surgery is associated with markedly improved survival in this subset of patients with cIIIA.

Conflict of Interest Statement

Dr Stiles serves as Chair for the Lung Cancer Research Foundation and discloses personal fees from AstraZeneca, WebMD, Medtronic, and Ribon Therapeutics (his wife is Pharmaceutical Product Development for Pfizer). All other authors have nothing to disclose with regard to commercial support.

References

1. Woodard GA, Jablons DM. The latest in surgical management of stage IIIA non-small cell lung cancer: video-assisted thoracic surgery and tumor molecular profiling. In: Dixon DS, ed. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting*. Alexandria, VA: American Society of Clinical Oncology; 2015:e435-41.
2. Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, 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; 374:379-86.
3. National Cancer Database. American College of Ssurgeons. Available at: https://www.facs.org/quality%20programs/cancer/ncdb. Accessed April 22, 2019.
4. Sher DJ, Koshy M, Liptay MJ, Fidler MJ. Influence of conformal radiotherapy technique on survival after chemoradiotherapy for patients with stage III non-small cell lung cancer in the National Cancer Data Base. *Cancer*. 2014;120: 2060-8.
5. Lin H, Ye H, Kernen KM, Hafron JM, Krauss DJ. National Cancer Database comparison of radical cystectomy vs chemoradiotherapy for muscle-invasive bladder cancer: implications of using clinical vs pathologic staging. *Cancer Med*. 2018;7: 5370-81.
6. Common misunderstandings of survival time analysis. Available at: https://www2.le.ac.uk/departments/health-sciences/research/biostats/youngsurv/pdf/MShanyinde.pdf. Accessed May 2, 2019.
7. Yoshida K. tableone: create 'table 1' to describe baseline characteristics. R package version 0.10.0. Available at: https://CRAN.R-project.org/package=tableone. Accessed October 2, 2018.
8. Kassambara A, Kosinski M, Biecek P. survminer: drawing survival curves using 'ggplot2.' R package version 0.4.6. Available at: https://CRAN.R-project.org/package=survminer. Accessed October 2, 2018.
9. Choi HS, Jeong BK, Jeong H, Lee YH, Ha IB, Song JH, et al. Application of the new 8th TNM staging system for non-small cell lung cancer: treated with curative concurrent chemoradiotherapy. *Radiat Oncol*. 2017;12:122.
10. Hansen BB, Klopfer SO. Optimal full matching and related designs via network flows. *J Comput Graph Stat*. 2006;15:609-27.
11. Hansen BB, Bowers J. Covariate balance in simple, stratified and clustered comparative studies. *Stat Sci*. 2008;23:219-36.
12. Thoemmes F. Propensity Score Matching in SPSS. *ArXiv Prepr*. 2012; ArXiv12016385.
13. Van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non–small-cell lung cancer. *J Natl Cancer Inst*. 2007;99:442-50.
14. Eberhardt WEE, Pöttgen C, Gauler TC, Friedel G, Veit S, Heinrich V, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non–small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol*. 2015;33:4194-201.
15. Detterbeck FC. The eighth edition TNM stage classification for lung cancer: what does it mean on main street? *J Thorac Cardiovasc Surg*. 2018; 155:356-9.
16. Speicher PJ, Englum BR, Ganapathi AM, Onaitis MW, D'Amico TA, Berry MF. Outcomes after treatment of 17 378 patients with locally advanced (T3N0–2) non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2014;47:636-41.
17. Kawaguchi K, Miyaoka E, Asamura H, Nomori H, Okumura M, Fujii Y, et al. Modern surgical results of lung cancer involving neighboring structures: a retrospective analysis of 531 pT3 cases in a Japanese lung cancer registry study. *J Thorac Cardiovasc Surg*. 2012;144:431-7.
18. Antonia SJ. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-29.
19. Bott MJ, Patel AP, Verma V, Crabtree TD, Morgensztern D, Robinson CG, et al. Patterns of care in hilar node-positive (N1) non-small cell lung cancer: a missed treatment opportunity? *J Thorac Cardiovasc Surg*. 2016;151:1549-58.e2.

Key Words: chemoradiation, multimodality treatment, non–small cell lung cancer, stage IIIA

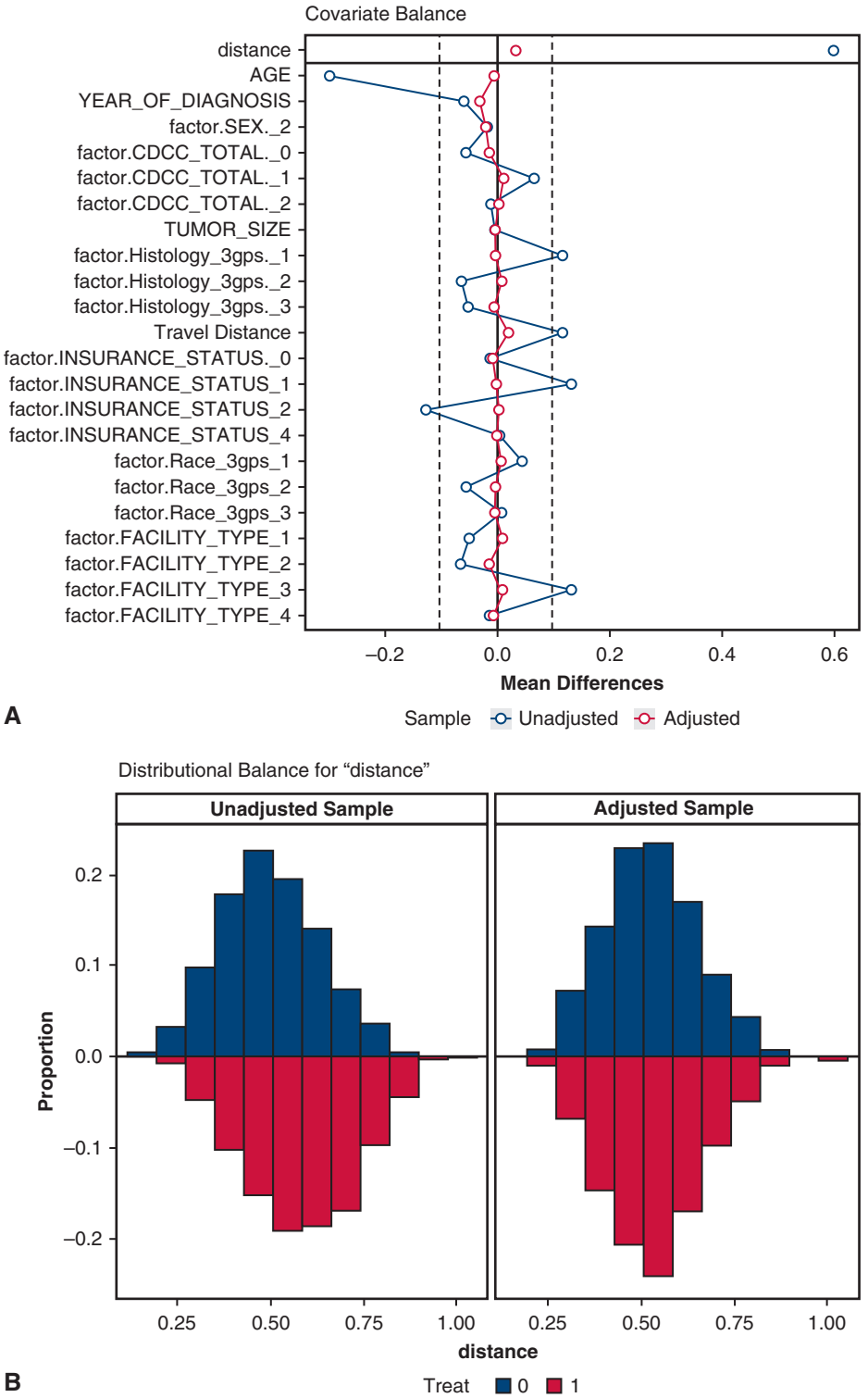


FIGURE E1. Matched cohort criteria. A, Love plot showing different variables included in the propensity score match with the corresponding standardized mean difference before and after matching. B, Mirror histograms before and after matching.