Outcomes of surgery versus chemoradiotherapy in patients with clinical or pathologic stage N3 non–small cell lung cancer

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ABSTRACT

Background: Because surgery is rarely recommended, there is minimal literature comparing the outcomes of surgery and chemoradiation in stage N3 non–small cell lung cancer (NSCLC). We examined the outcomes of definitive chemoradiation versus multimodality therapy, including surgery, for patients with clinical and pathologic stage N3 NSCLC.

Methods: The National Cancer Database was used to identify patients with clinical stage T1 to T3 N3 M0 NSCLC and clinical stage T1 to T3 Nx M0 with pathologic stage N3 NSCLC who were treated with either definitive chemoradiation or surgery between 2004–2015. A 1:1 propensity score–matched analysis was used to compare outcomes for both treatment groups in each analysis. The primary outcome was overall survival.

Results: In 935 matched patient pairs with clinical stage N3 NSCLC, surgery was associated with worse survival (hazard ratio, 1.52; 95% confidence interval, 1.12–2.05) compared with chemoradiation at 6 months, but was associated with a significant survival benefit after 6 months (hazard ratio, 0.54; confidence interval, 0.47–0.63) in multivariable analysis. In 281 pairs of patients with pN3 NSCLC, surgery had similar survival compared with chemoradiation at 6 months (hazard ratio, 1.71; 95% confidence interval, 0.92–3.19), but was associated with improved survival after 6 months (hazard ratio, 0.76; 95% confidence interval, 0.58–0.99). The complete resection rate was 80% and 73% for patients with clinical stage N3 and pathologic stage N3 disease, respectively.

Conclusions: In patients with clinical or pathologic stage N3 NSCLC, surgery is associated with similar or worse short-term but improved long-term survival compared with chemoradiation. In a selected group of patients with stage N3 NSCLC, surgery may have a role in multimodal therapy. (J Thorac Cardiovasc Surg 2019;158:1680–92)

Surgery has survival benefit in N3 NSCLC.

Central Message

In patients with cN3 or pN3 NSCLC, surgery is associated with improved long-term survival compared with chemoradiation.

Perspective

There is minimal literature on the role of surgery for stage N3 lung cancer. Our study demonstrates that surgery is associated with a survival benefit even in persistent, pathologic N3 disease compared with chemoradiation, and suggests that surgery may have a role in multimodal therapy for patients with N3 NSCLC.

See Commentaries on pages 1693 and 1695.

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The National Comprehensive Cancer Network and European Society of Medical Oncology guidelines recommend definitive concurrent chemoradiation as initial therapy for N3 non–small cell lung cancer (NSCLC).^{1,2} Surgery is not recommended for stage N3 disease, which has

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Abbreviations and Acronyms
c = clinical
NCDB = Nation Cancer Database
NSCLC = non–small cell lung cancer
p = pathologic
PACIFIC = Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable non–Small Cell Lung Cancer (Stage III) Who Have not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy

historically been considered unresectable. However, there is minimal literature on the outcomes of surgery for these patients. Several prospective phase 2 trials of surgery following chemotherapy or chemoradiation in stage IIIB NSCLC have been published, but these are limited by small subsets of patients with N3 disease ranging from 7 to 32 patients, variable induction regimens, and variable study design with several excluding patients with supraclavicular node involvement.³⁻¹² These prospective studies rarely contained subgroup analyses of patients with N3 disease, but showed that patients with stage IIIB lung cancer could undergo surgery with a high complete resection rate, up to 81%,⁴ and with acceptable median survival ranging from 13⁸ to 29⁵ months. These prospective studies demonstrated that patients with clinical stage IIIB disease experience a high rate of pathologic nodal downstaging with induction therapy, and that recurrence was both distant and

FIGURE 1. Patient selection schemes for parts of the study. A, Clinical stage (c) N3. B, Pathologic stage (p) N3. NCDB, National Cancer Database; NSCLC, non–small cell lung cancer.

TABLE 1. Background characteristics of propensity score-matched patients with clinical stage N3 non-small cell lung cancer grouped by treatment

Characteristic	Chemoradiation (n = 935)	Surgery (n = 935)	Standard mean difference	P value
Age (y)	67 (59-74)	67 (59-74)	0.01	.98
Sex (female)	405 (43)	402 (43)	0.07	.93
Race				.86
White	818 (88)	811 (87)		
Black	95 (10)	99 (11)	0.01	
Other	22 (2)	25 (3)	0.02	
Year of diagnosis	2010 (2007-2013)	2010 (2008-2012)	−0.007	.80
Charlson-Deyo comorbidity condition score				.75
0	526 (56)	519 (56)		
1	274 (29)	288 (31)	0.03	
2+	135 (14)	128 (14)	−0.02	
Insurance status				.65
Private	339 (36)	331 (35)		
Government	562 (60)	576 (62)	0.03	
None	34 (4)	28 (3)	−0.04	
Facility location				.62
Metro	701 (75)	711 (76)		
Urban	184 (20)	169 (18)	−0.04	
Rural	50 (5)	55 (6)	0.02	
Academic center	336 (36)	344 (37)	0.02	.74
Tumor size (mm)	32 (22-44)	30 (20-45)	−0.05	.11
Histology				.87
Adenocarcinoma	446 (48)	449 (48)		
Squamous cell carcinoma	353 (38)	358 (38)	0.01	
Other	136 (15)	128 (14)	−0.02	
Perioperative chemotherapy		549 (59)	N/A	N/A

Values are presented as median (interquartile range) or n (%). N/A, not available.

locoregional, suggesting that there is a role for definitive local control.

There are no prospective trials and scant observational studies¹³⁻¹⁵ comparing chemoradiation to surgery in patients with clinical stage IIIB NSCLC, including those with clinical stage (c) N3 disease. There are no studies examining the outcomes of patients with pathologic stage (p) N3 disease. The management of patients with limited N3 disease who are otherwise operable and demonstrate response to systemic therapy is not clear, and it is possible that these patients may be treated in a similar manner as operable stage IIIA (ie, N2) NSCLC with acceptable short- and long-term results. We performed a retrospective cohort study examining the outcomes of patients with cN3 and pN3 NSCLC undergoing surgery versus chemoradiation. Given the high incidence of pathologic nodal downstaging and locoregional recurrence in patients with stage IIIB NSCLC, we hypothesized that patients with cN3 NSCLC may experience a survival benefit with surgery compared with definitive chemoradiation treatment. However, we hypothesized that patients with pN3

disease after resection would not have a survival benefit compared with patients with N3 disease who received chemoradiation treatment alone.

METHODS

Data Source

The National Cancer Database (NCDB) is a joint effort of the American Cancer Society and the American College of Surgeons, and contains data collected by certified tumor registrars in 1500 centers. It includes data regarding approximately 80% of cancers diagnosed and treated annually in the United States.¹⁶

Patient Selection

This study was deemed exempt by our institutional review board. In the first part of the study, patients with American Joint Committee on Cancer Eighth Edition clinical T1 to T3 N3 M0 NSCLC were identified in the NCDB (2004-2015). Patients with missing survival, staging, or treatment information were excluded (Figure 1, A). Patients receiving chemoradiation who were not offered surgery due to poor performance status were also excluded, as were patients who received surgery more than 6 months after chemoradiation because of the possibility of a salvage procedure. In the second part of the study, patients with cT1 to cT3 Nx M0 NSCLC with pN3 disease were identified. The same exclusion criteria applied (Figure 1, B).

TABLE 2. Multivariable Cox proportional hazards model for independent predictors of survival for propensity score-matched patients with clinical stage N3 non-small cell lung cancer

Predictor	Hazard ratio (95% Confidence interval)	P value
Age (per year)	1.01 (1.00-1.02)	<.001
Female sex (reference: Male)	0.96 (0.86-1.07)	.46
Race (reference: White)		
Black	1.05 (0.87-1.26)	.61
Other	1.09 (0.76-1.56)	.64
Charlson-Deyo comorbidity condition score (reference: 0)		
1	1.13 (1.00-1.28)	.05
2+	1.26 (1.08-1.49)	.004
Year of diagnosis per year	0.97 (0.95-0.99)	.002
Insurance status (reference: Private)		
Government	1.09 (0.94-1.25)	.25
None	1.01 (0.72-1.40)	.97
Facility location (reference: Metro)		
Urban	1.00 (0.87-1.15)	.98
Rural	1.21 (0.96-1.52)	.11
Academic center	0.87 (0.78-0.98)	.02
Tumor size	1.01 (1.00-1.01)	.005
Histology (ref: Adenocarcinoma)		
Squamous cell carcinoma	0.95 (0.83-1.07)	.38
Other	1.18 (1.01-1.39)	.04
Treatment (reference: Chemoradiation)		
Surgery (≤ 6 mo)	1.52 (1.12-2.05)	.006
Surgery (after 6 mo)	0.54 (0.47-0.63)	<.001

Patients were grouped by treatment: surgery or definitive chemoradiation. Surgery was defined as any operation, including sublobar and lobar resections. Whereas lobar resection is considered most appropriate for patients with NSCLC, not all patients can tolerate lobectomy. To place the burden of proof on patients undergoing surgery, we included all patients who underwent lung resection regardless of type of surgery or receipt of perioperative chemotherapy or radiation to obtain the most conservative estimate of the effect of surgery on survival. We performed subgroup analyses on patients receiving lobar resection alone and those receiving multimodal therapy, including surgery. Patients who received perioperative chemotherapy or radiotherapy as well as those who received no perioperative therapy were included. The NCDB does not contain information on restaging after induction therapy. Definitive chemoradiation was defined as administration of chemotherapy and radiation of 60.0 Grey (Gy) or more, in concordance with the National Comprehensive Cancer Network guidelines. Patients who received either sequential or concurrent chemoradiation were included because not all patients can tolerate concurrent chemoradiation treatment. Although the NCDB does not explicitly code invasive mediastinal staging, a subset of patients who did not receive surgery have pathologic nodal staging recorded in addition to clinical TNM staging, suggesting that the pathologic stage for these patients reflects the findings of invasive nodal staging. Because the second part of the study focused on patients with proven N3 disease, only patients with cNx to pN3 disease receiving definitive chemoradiation were included. Pathologic nodal downstaging is defined as a lower pathologic nodal stage following surgery compared with initial clinical

nodal stage. Because the NCDB does not catalog restaging after neoadjuvant therapy, any downstaging that occurred as a result of neoadjuvant therapy would only be reflected in the postoperative pathologic stage recorded.

Statistical Analysis

Background characteristics between patients in each group were compared using the Wilcoxon rank sum and Pearson χ^2 tests for continuous and categorical variables, respectively. To minimize differences between the study groups, a propensity score-matched analysis was performed in each part of the study using patient and tumor-related variables including age, sex, race, Charlson-Deyo comorbidity condition score, year of diagnosis, insurance status, treatment at an academic center, urban or rural status, histology, and tumor size. A 1:1 nearest-neighbor algorithm¹⁷ was used that utilizes a series of logistic regressions to match control and treatment groups on distance; we used a caliper of 0.15 to eliminate differences and ensure a mean standardized difference ≤ 0.1 for each variable.^{18,19} We report the mean standardized differences in Tables 1 and 2. For the analysis of pN3 disease, clinical nodal status was also included in both the multivariable regression and for propensity matching.

The primary outcome was overall survival, which was evaluated using Kaplan-Meier and Cox proportional hazards estimates. In both parts of the study, the Kaplan-Meier curves intersected at about 6 to 9 months, and the proportional hazards assumption was violated (Schoenfeld residual $P < .05$). To resolve this, the cohorts in each analysis were divided into 2 before the point of intersection (6 months) and modeled as time-varying coefficients in a single multivariable Cox model.²⁰ The following subgroup analyses were performed: cohort limited to patients receiving neoadjuvant therapy (cN3), lobar resection (cN3 and pN3), a complete resection (pN3), or perioperative chemotherapy (pN3).

In survival analyses, missing data were handled with complete case analysis for each variable included in the multivariable Cox models. In other descriptive statistics such as pathologic nodal staging, the fraction of missing data is reported for each group. All statistical analysis was performed using R version 3.5 for Mac (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

cN3 Disease

A total of 6400 patients met study criteria: 5227 underwent chemoradiation treatment (82%) and 1173 underwent surgery (18%). Compared with chemoradiation, surgery patients had a lower T stage, were less likely to have adenocarcinoma, had more comorbidities, and were more likely to be treated at an academic medical center (Table E1). In the surgery group, 616 patients (53%) received perioperative therapies: 209 (18%) received induction chemotherapy with or without radiation and 407 (37%) received adjuvant chemotherapy. The most common operation was lobectomy, followed by wedge resection, and pneumonectomy. A margin-negative (R0) resection was achieved in 80% of patients. The median survival was 20 months (95% confidence interval [CI], 20-21 months) for chemoradiation and 35 months (95% CI, 32-39 months) for surgery (Figure 2, A). In a multivariable Cox model, surgery was associated with worse survival compared with chemoradiation in the first 6 months (hazard ratio [HR], 1.34; 95% CI, 1.07-1.67; $P = .01$). After 6 months, there was a significant

FIGURE 2. Kaplan-Meier survival curves for propensity score-matched patients with clinical stage N3 NSCLC, grouped by treatment of chemoradiation (*chemoRT*) versus surgery, with log-rank test reported as a P value and numbers at risk for each group provided beneath the figure. The y-axis refers to the percentage of patients alive, and the x-axis refers to the time, in years, from diagnosis. A, Overall cohort. B, Propensity score-matched patients only. *ChemoXRT*, Chemotherapy and radiation therapy.

overall survival benefit with surgery compared with chemoradiation (HR, 0.54; 95% CI, 0.48-0.61; $P < .001$). Amongst 5227 chemoradiation group patients with cN3 disease, only 550 had a pathologic nodal stage recorded (30% missing and 59% pNx): 458 (83%) had pN3 disease, 68 (12%) had pN2 disease, 14 (3%) had pN1 disease, and 10 (2%) had pN0 disease. Amongst surgery group patients (6% missing and 26% pNx), 174 (16%) had pN3 disease,

133 (12%) had pN2 disease, 109 (10%) had pN1 disease, and 397 (36%) had pN0 disease.

A total of 935 pairs of patients were identified by 1:1 propensity score matching. Background characteristics of patients in each group are summarized in Table 1. The median survival was 20 months (95% CI, 18-22 months) and 34 months (95% CI, 30-39 months) for chemoradiation and surgery group patients, respectively (Figure 2, B). In

FIGURE 3. Kaplan-Meier survival curves for propensity score-matched patients with clinical stage N3 NSCLC, grouped by treatment of chemoradiation (*chemoRT*) versus surgery following induction therapy with log-rank test reported as a *P* value and numbers at risk for each group provided beneath the figure. The y-axis refers to the percentage of patients alive, and the x-axis refers to the time, in years, from diagnosis.

multivariable analysis, surgery was associated with worse survival compared with chemoradiation within the first 6 months of diagnosis, but after 6 months, surgery was associated with a significant benefit in overall survival compared with chemoradiation (Table 2).

Only 209 patients (18%) undergoing surgery received induction chemotherapy, suggesting that a significant fraction of patients with cN3 disease were downstaged by invasive nodal assessment. We therefore performed a propensity score-matched subgroup analysis of only patients receiving surgery following induction therapy, presuming these patients had pathologically demonstrated N2 or N3 disease at the time of presentation. Surgery and chemoradiation patients had a median survival of 64 months (95% CI, 51-73 months) and 21 months (95% CI, 19-28 months), respectively. In both unadjusted (Figure 3) and adjusted analysis, patients undergoing surgery with induction therapy experienced better survival compared with those receiving chemoradiation (HR, 0.41; 95% CI, 0.31-0.55; *P* < .001). Of surgery patients (7% missing, 20% pNx), 131 (86%) had a lower pathologic N stage compared with initial clinical stage, with 81 (53%) demonstrating pN0 disease.

In a separate subgroup analysis of only patients receiving a lobar resection, 556 matched pairs of patients were identified. Within the first 6 months, there was no difference in survival between surgery and chemoradiation group patients (HR, 1.03; 95% CI, 0.68-2.45; *P* = .88), but surgery was associated with improved survival compared chemoradiation after 6 months (HR, 0.42; 95% CI, 0.35-0.51; *P* < .001).

pN3 Disease

A total of 798 patients with pN3 disease met study criteria, of whom 515 (65%) and 283 (35%) underwent chemoradiation and surgery, respectively. The clinical nodal stage of each treatment group is summarized in Table 3. Compared with chemoradiation group patients, surgery group patients were more likely to have been diagnosed earlier, be treated in a metropolitan area, and be less likely to have adenocarcinoma (Table E2). Of surgery group patients, 184 (66%) underwent perioperative chemotherapy: 31 (12%) received induction chemotherapy and 153 (55%) received adjuvant chemotherapy. The most common operation was lobectomy, followed by wedge resection and pneumonectomy. The R0 resection rate was 73%. The median survival for chemoradiation group and surgery group patients was 22 months (95% CI, 19-25 months) and 24 months (95% CI, 21-29 months), respectively (Figure 4, A). In multivariable Cox regression,

TABLE 3. Clinical nodal staging of patients with pathologic stage N3 non-small cell lung cancer, grouped by treatment

Clinical N stage	Chemoradiation (n = 515)	Surgery (n = 283)
0	10 (2)	43 (15)
1	5 (1)	19 (7)
2	28 (5)	39 (14)
3	458 (89)	174 (61)
X	14 (3)	8 (3)

Values are presented as n (%).

FIGURE 4. Kaplan-Meier survival curves for propensity score-matched patients with pathologic stage N3 NSCLC, grouped by treatment of chemoradiation (*chemoRT*) versus surgery with log-rank test reported as a P value and numbers at risk for each group provided beneath the graph. The y-axis refers to the percentage of patients alive, and the x-axis refers to the time, in years, from diagnosis. A, Overall cohort. B, Propensity score-matched patients only. *ChemoXRT*, Chemotherapy and radiation therapy.

undergoing surgery was associated with worse survival compared with chemoradiation within the first 6 months (HR, 1.69; 95% CI, 1.00-2.83; $P = .05$). Beyond 6 months, surgery was associated with a significant survival benefit (HR, 0.73; 95% CI, 0.58-0.91; $P = .01$).

A 1:1 propensity score-matched analysis identified 221 pairs of patients with pN3 disease. The background characteristics of the patients are summarized in Table 4. The median survival for chemoradiation group and surgery group patients was 22 months (95% CI, 18-28 months) and

24 months (95% CI 19-29 months), respectively (Figure 4, B). In multivariable regression, surgery was not associated with a significant survival benefit compared with chemoradiation within the first 6 months after diagnosis (Table 5). However, surgery was associated with a significant survival benefit after 6 months.

In a subgroup analysis of 136 matched pairs of patients who received perioperative chemotherapy, there was no difference in survival between surgery group and chemoradiation group patients (HR, 1.00; 95% CI, 0.75-1.34; $P = .99$).

TABLE 4. Background characteristics of propensity score-matched patients with pathologic stage N3 non-small cell lung cancer grouped by treatment

Characteristic	Chemoradiation (n = 221)	Surgery (n = 221)	Standard mean difference	P value
Age (y)	66 (58-72)	65 (57-71)	−0.06	.58
Female sex	96 (43)	105 (48)	−0.08	.45
Race				.96
White	192 (87)	192 (87)		
Black	22 (10)	21 (10)	−0.01	
Other	7 (3)	8 (4)	0.02	
Year of diagnosis	2010 (2007-2012)	2010 (2007-2012)	−0.05	.59
Charlson-Deyo comorbidity condition score				.99
0	137 (62)	138 (62)		
1	62 (28)	62 (28)	0.00	
2+	22 (10)	21 (10)	−0.01	
Insurance status				.96
Private	89 (40)	88 (40)		
Government	123 (56)	125 (57)	0.02	
None	9 (4)	8 (4)	−0.02	
Facility location				.24
Metro	189 (86)	176 (80)		
Urban	25 (11)	33 (15)	0.10	
Rural	7 (3)	12 (5)	0.10	
Academic center	82 (37)	86 (39)	0.04	
Tumor size (mm)	28 (18-39)	30 (19-40)	−0.01	.77
Histology				.85
Adenocarcinoma	141 (64)	139 (63)		.44
Squamous cell carcinoma	60 (27)	54 (24)	−0.06	
Other	20 (9)	28 (13)	0.10	
Perioperative chemotherapy	N/A	163 (74)	N/A	N/A

Values are presented as median (interquartile range) or n (%). N/A, not available.

In a separate analysis of patients who underwent lobar resection, there was no difference in survival between surgery group and chemoradiation group patients within 6 months (HR, 1.07; 95% CI 0.49-2.37; $P = .86$), but undergoing surgery was associated with improved survival after 6 months (HR, 0.64; 95% CI, 0.41-0.79; $P = .01$) in 129 matched patient pairs. In a third subgroup analysis limited to patients who received R0 resection, undergoing surgery was again associated with a survival benefit compared with chemoradiation treatment after 6 months in 151 matched pairs of patients (HR, 0.57; 95% CI, 0.41-0.79; $P < .001$).

DISCUSSION

In this propensity score-matched NCDB analysis, patients with both clinical and pathologic N3 NSCLC experienced similar short-term survival and improved long-term survival with surgery compared with definitive chemoradiation. Patients with cN3 disease undergoing surgery had a high rate of pathologic nodal downstaging. To our

knowledge, this is the largest study examining the outcomes of patients with N3 lung cancer, and demonstrates that surgery is associated with superior long-term outcomes in a highly selected group of patients.

Our finding that patients with cN3 NSCLC can experience good overall survival after surgery corroborates the small amount of prospective and retrospective data in the literature. Patients undergoing surgery in our study had a median survival of 35 months, comparable to the range of 13 to 29 months reported in prospective studies.^{3,4,21} Similarly, patients in our study had a pathologic nodal downstaging of 51% after surgery, which is comparable to the 30% to 48% in phase 2 studies.^{3,6,9} Unfortunately, the prospective studies in stage IIIB NSCLC all contained only small subsets of patients with N3 disease, and generally did not examine this population separately in subgroup analyses. Similarly, a previous NCDB analysis¹³ of patients with clinical stage IIIB NSCLC demonstrated that multimodal therapy that included surgery was associated with a survival benefit compared with chemoradiation alone; however,

TABLE 5. Multivariable Cox proportional hazards model for independent predictors of survival for propensity score-matched patients with pathologic stage N3 non-small cell lung cancer

Predictor	Hazard ratio (95% Confidence interval)	P value
Age per year	1.01 (0.99-1.02)	.22
Female sex (reference: Male)	0.97 (0.76-1.22)	.77
Race (reference: White)		
Black	1.06 (0.72-1.57)	.76
Other	1.14 (0.57-2.28)	.71
Charlson-Deyo comorbidity condition score (reference: 0)		
1	1.05 (0.81-1.36)	.72
2+	1.46 (1.00-2.14)	.05
Year of diagnosis per year	0.94 (0.90-0.98)	.002
Insurance status (reference: Private)		
Government	1.01 (0.74-1.38)	.96
None	0.71 (0.35-1.45)	.34
Facility location (reference: Metro)		
Urban	0.92 (0.65-1.29)	.62
Rural	0.90 (0.50-1.63)	.74
Academic center	0.86 (0.68-1.09)	.22
Tumor size	1.01 (1.00-1.01)	.16
Histology (ref: Adenocarcinoma)		
Squamous cell carcinoma	1.08 (0.83-1.42)	.56
Other	0.96 (0.65-1.41)	.84
Treatment (reference: Chemoradiation)		
Surgery (<6 mo)	1.71 (0.92-3.19)	.09
Surgery (after 6 mo)	0.76 (0.58-0.99)	.045

this study did not report a multivariable subgroup analysis of patients with N3 disease, only included surgery patients who received multimodal therapy, and examined patients with clinical stage IIIB disease alone. These studies did demonstrate that failure after multimodal therapy for cIIIB disease manifested as both distant metastases and local recurrence, suggesting that definitive local control in the form of surgical resection and lymphadenectomy may play a role in mitigating recurrence in N3 disease. In addition, the high pathologic downstaging rate in patients who underwent surgery might suggest that there is discordance between clinical and invasive nodal staging in this population, or that patients with response to induction therapy experience superior survival with surgery. The NCDB does not catalog restaging after induction therapy, so we do not know how many patients with cN3 disease were downstaged before or after surgery. However, only 21%

of patients undergoing surgery received neoadjuvant chemotherapy in our study, suggesting that significant downstaging might occur with invasive nodal staging alone. Our study reinforces the importance of invasive nodal staging, especially as studies suggest that a minority of patients nationwide receive invasive staging with significant center variability.^{22,23} Further, in a subgroup analysis of cN3 patients who underwent induction therapy and surgery, we found an 87% pathologic nodal downstaging rate, suggesting that patients with good response to induction therapy were more likely to receive surgery and experience improved survival.

We then expanded our study to investigate the outcomes of patients, regardless of clinical stage, with pN3 disease. As expected, more than half of patients with pN3 disease had cN3 disease, with the remainder being upstaged. Prospective studies in stage III NSCLC have demonstrated that pathologic involvement of mediastinal nodes predicts mortality,^{6,9,21} and we hypothesized that patients with pN3 disease undergoing surgery or chemoradiation would experience similar survival. Our finding that mid to late survival is improved in patients undergoing surgery suggests that in selected patients with persistent N3 disease, surgery can offer acceptable outcomes. Indeed, 1 prospective study of stage III NSCLC found that patients with N2 and N3 disease were equally likely to have sterilization of mediastinal nodes,³ suggesting that patients with N3 disease may have tumor behavior more aligned with N2 rather than T4 disease, and might benefit from multimodal therapy that includes surgery.

In both parts of our study, we found that early survival, less than about 6 months, was either similar between patients undergoing surgery and chemoradiation or worse for surgery patients. Examining the survival curves (Figures 2 and 3), the curves for chemoradiation group patients remain flat early after diagnosis, whereas the curves for surgery group patients fall immediately. This suggests that there might be immortal time bias in patients receiving chemoradiation, who have to survive several weeks to months to successfully receive definitive chemoradiotherapy, whereas patients undergoing surgery shortly after diagnosis may die soon after from complications related to surgery or from comorbidities. Our time-varying Cox models adjust for this finding.

This study allows us to draw inferences on patients with N3 disease who may most benefit from surgery that can be augmented by experience from our institution. Our subgroup analysis of cN3 patients who received neoadjuvant therapy suggests that patients who respond well to neoadjuvant therapy may experience improved long-term survival compared with those receiving chemoradiation. In addition, our subgroup analyses on patients receiving lobar resections and margin-negative resections suggest that patients who may tolerate a lobar resection and with a high probability

Surgery vs. Chemoradiation in N3 Non-Small Cell Lung Cancer

Source: National Cancer Database (2004-2015)
Patients: cN3 or pN3 with NSCLC treated with surgery or chemoradiation
Primary outcome: Overall survival (OS)

In both cN3 and pN3 NSCLC, surgery is associated with improved long-term survival compared to chemoradiation; randomized trials are needed to examine the role of surgery in N3 NSCLC

FIGURE 5. In this National Cancer Database study, surgery was associated with improved long-term overall survival compared with chemoradiation in patients with clinical or pathologic N3 disease. This graphical abstract demonstrates the results of propensity score matched-analysis of clinical and pathologic N3 disease patients with hazard ratios and confidence intervals from time-varying multivariable Cox regression presented in tables and Kaplan-Meier survival curves with numbers at risk. *NSCLC*, Non-small cell lung cancer; *HR*, hazard ratio; *CI*, confidence interval.

of a margin-negative resection may experience a greater survival benefit. Additionally, our time-varying Cox models suggest that patients who are good candidates for surgery and therefore survive beyond the initial few months following surgery are also more likely to benefit from resection. In our institution, surgery is rarely offered for patients with N3 disease. Surgery is offered to patients who exhibit a significant radiographic response to neoadjuvant therapy, who do not have supraclavicular disease, who are good surgical candidates, and who have nonbulky nodal disease.

Our study has several limitations in addition to those already described. As a retrospective cohort study, there is inherent selection bias for which we cannot accommodate. For instance, patients offered surgery rather than chemoradiation for N3 disease likely had nonbulky, single, or oligostation nodal involvement and a good response to induction therapy, if offered. However, none of these variables nor specific N3 disease location are coded in the NCDB. We did attempt to define this selection bias with a subgroup

analysis of cN3 patients undergoing surgery following induction therapy, as discussed above. The NCDB also does not contain information about staging and restaging techniques used. For instance, although we draw inferences about invasive nodal staging from the pathologic nodal stage reported for patients who did not receive a resection, the NCDB does not explicitly catalog invasive nodal staging. Patients offered chemoradiation treatment may also have been poor surgical candidates and consequently experienced worse survival. However, we attempted to adjust for such confounding by excluding chemoradiation patients who were not offered surgery due to poor fitness, as coded in the database, and by using propensity score matching based on variables like age, comorbidity index, treatment at an academic center, and tumor size. Finally, this study period predates that of the Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable non-Small

Cell Lung Cancer (Stage III) Who Have not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC) trial,^{24,25} and as a result, we cannot compare the outcomes of patients receiving surgery with those receiving chemoradiation followed by durvalumab. However, the PACIFIC trial also did not report subgroup analyses on patients with N3 disease, and reported an overall median time to death or distant metastasis of 28 months in the treatment arm, which is comparable to the median survival of 35 months observed in surgery patients with cN3 disease in our study.²⁴ The PACIFIC study also does not contain information on how patients were deemed unresectable, which further limits its interpretation. Future research should focus on the potentially complementary effects of surgery and checkpoint inhibition in multimodal treatment of N3 lung cancer.

CONCLUSIONS

We report the most comprehensive analysis of outcomes following surgery versus chemoradiation in patients with N3 NSCLC, finding that although early survival was similar between the groups, surgery was associated with improved long-term survival compared with chemoradiation in patients with cN3 or pN3 lung cancer (Figure 5). In a selected group of patients with N3 NSCLC, surgery may offer superior survival and can be considered as part of multimodal therapy, although prospective, randomized controlled trials are needed to evaluate the role of surgery in multimodal therapy for this patient population.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Monday_May6/201DF/201DF/S84%20-%20Locally%20advanced%20lung%20cancer/S84_6_webcast_031409114.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

The American College of Surgeons is in a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer-accredited hospitals. The data used in the study are derived from a de-identified National Cancer Database file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic

or statistical methodology used or the conclusions drawn from these data by the investigators.

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Key Words: non-small cell lung cancer, N3, locally advanced, surgery, multimodal therapy

Discussion

Dr James Huang (New York, NY). Thanks for the opportunity to discuss this paper and thank you, Dr Raman, for a nicely presented talk and for sending me the manuscript in advance.

Dr Raman and colleagues have examined the issue of surgery for N3 lung cancer by performing a retrospective analysis of the available data in the National Cancer Database (NCDB), and they conclude that surgery should be considered for selected patients with stage N3 disease. The authors acknowledge that surgery is generally not recommended for stage N3 disease, the National Comprehensive Cancer Center guidelines do not offer an option for surgery for N3 disease, so I think we need to be a little careful about drawing any conclusions that are potentially practice changing from a retrospective observational study. As you know, all retrospective studies are, by definition, hypothesis-generating, and really hypothesis-generating only. So I submit that the real conclusion that you should arrive at is whether or not this question is worthy of further prospective study. A safer conclusion might be that a clinical trial exploring the value of surgery for N3 disease is warranted.

In your analysis, only 21% of the clinical stage N3 patients underwent induction therapy, and you surmise that these patients were downstaged. But I think for clarity's sake what we are really trying to say is that these patients really did not have N3 disease at all. That could explain the survival differences that you see, that most of the surgical patients actually turned out to be stage I or stage II in reality. So I would say another conclusion that you might take away from this analysis might simply be that clinical staging of nodal status is highly inaccurate, or at least in the NCDB.

I have a couple of questions, which I will ask one at a time. Given that surgery is not recommended for N3 disease, do you have a better sense of who exactly these patients are that got operated on?

Dr Vignesh Raman (Durham, NC). I think there are 2 lessons that we can glean from this study. One, like you mentioned, only 21% of patients received induction therapy with clinical stage N3 disease. They could also represent patients who based on their pathologic nodal stage responded very

well to induction therapy, because we do not have any re-staging information from NCDB. So patients with a good to complete response to induction therapy might have been the ones who were ultimately offered surgery; 87% of them were downstaged, as explained.

The second, looking at our time varying Cox models, is that the survival benefit is best for patients beyond the immediate postoperative stage of 7.5 months. So patients who are excellent surgical candidates are probably the ones who benefit most from surgery in this situation.

And I think those are at least 2 specific characteristics that we can infer from the study.

Dr Huang. And clearly selection bias is at play here, and you state that surgery should be offered for selected patients. So can you help guide us as to which patients to select?

Dr Raman. Based on the study, we could argue that patients with limited resectable clinical stage N3 disease who had a good response to induction therapy and who are good surgical candidates might be considered. The reason I add the clause of resectable N3 disease is that we noticed the sort of complete resection rate for patients with N3 disease is 73% to 80%, whether we are looking at clinical or pathologic stage, which is a very high complete resection rate, suggesting that patients who were selected for surgery probably had a pretest probability of resectability.

Dr Huang. In terms of complete resection of N3 disease, how do we resect the N3 disease?

Dr Raman. Unfortunately, there is no information about nodal stations in the NCDB, so it's unclear if these were patients who had an isolated supraclavicular node that was then excisionally biopsied or whether these patients had an isolated node initially in the contralateral mediastinum or hilum that was sterilized by induction therapy.

Dr Huang. And finally, as you have pointed out and as Dr Pass nicely presented earlier, the Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable non-Small Cell Lung Cancer (Stage III) Who Have not Progressed Following Definitive, Platinum-based, Concurrent

Chemoradiation Therapy trial has really changed practice and immunotherapy is here to stay. So in light of that, how should we interpret your results here?

Dr Raman. I think 2 limitations specific to the study that Dr Pass also mentioned in his talk were that we don't know on what basis patients were deemed unresectable, and we don't know what subset of patients with stage IIIB disease had N3 rather than T4 N2 involvement. In that context, you could argue that our results suggest that at least some patients with N3 disease might benefit from enrollment in a future prospective clinical trial examining the role of durvalumab in a perioperative setting.

Dr Huang. Thank you. Congratulations.

Dr Henning Gaissert (*Boston, Mass*). You made a statement about complete resection. How do you do that in N3 disease and how do you confirm that in your patients?

Dr Raman. For the NCDB, the independent tumor registrars look at the surgical pathology reports, and based on that, if there is no margin involvement, code it as an R0 resection. Because there is no station information available, we don't know if these patients had remnant nodal disease: if they had, for instance, an isolated supraclavicular node that was excisionally biopsied and subsequently no other evidence of N3 disease or if these patients initially pre-

sented with a contralateral mediastinal hilar node that was then sterilized by induction therapy. Unfortunately, we do not have the granularity of the NCDB to answer that question specifically and accurately.

Dr Gaissert. I submit R0 resections don't exist in N3 disease.

Dr Raman. Point taken.

Dr Pierre de Delva (*Jackson, Miss*). I was surprised by the 9% incidence of operations for N3 disease. Is it possible that a good number of those patients were patients who went to the operating room with a clinical stage N3 diagnosis, had invasive staging proven not to be N3 disease and go

on to surgery?

Dr Raman. That is entirely possible, which is why we did the subgroup analysis in those with induction therapy and with proven pathologic N3 disease.

Dr Gaissert. I want to know if it's single-station N3 or not single-station N3.

Dr Raman. Unfortunately, a limitation of the NCDB is that there is no station information provided, so we don't know the identity, number, or bulk of involved nodes.

TABLE E1. Background characteristics of patients with clinical stage N3 non–small cell lung cancer grouped by treatment

Characteristic	Chemoradiation (n = 5227)	Surgery (n = 1173)	P value
Age (y)	66 (58-72)	66 (58-73)	.24
Female sex	2381 (46)	510 (44)	.21
Race			.29
White	4384 (84)	1007 (86)	
Black	628 (12)	123 (11)	
Other	180 (4)	38 (3)	
Year of diagnosis	2011 (2008-2013)	2010 (2007-2012)	<.001
Charleston-Deyo comorbidity condition score			<.001
0	3565 (68)	675 (58)	
1	1201 (23)	346 (30)	
2+	461 (9)	152 (13)	
Insurance status			.48
Private	1799 (35)	423 (37)	
Government	3180 (62)	691 (60)	
None	154 (3)	37 (3)	
Facility location			.34
Metro	4044 (77)	905 (77)	
Urban	853 (16)	205 (18)	
Rural	330 (6)	63 (5)	
Academic center	1805 (35)	442 (38)	.05
Type of surgery	N/A		N/A
Wedge resection		185 (16)	
Segmentectomy		28 (2)	
Lobectomy		609 (52)	
Pneumonectomy		75 (6)	
Nodes examined	N/A	7 (2-17)	N/A
Tumor size (mm)	35 (23-49)	30 (20-45)	<.001
Histology			<.001
Adenocarcinoma	2344 (57)	536 (48)	
Squamous cell carcinoma	1546 (37)	170 (15)	
Other	251 (6)	407 (37)	
Perioperative chemotherapy	N/A		N/A
Neoadjuvant		209 (18)	
Adjuvant		407 (35)	
None		536 (47)	
Complete resection rate	N/A	844 (80)	N/A
30-d mortality	N/A	39 (4)	N/A
90-d mortality	N/A	81 (8)	N/A
Radiation treatment volume (Gy)	64.8 (60.0-68.4)	0 (0-50.4)	<.001

Values are presented as median (interquartile range) or n (%). N/A, not available.

TABLE E2. Background characteristics of patients with pathologic stage N3 non-small cell lung cancer grouped by treatment

Characteristic	Chemoradiation (n = 515)	Surgery (n = 283)	P value
Age (y)	65 (57-72)	65 (57-71)	.86
Female sex	251 (49)	132 (47)	.62
Race			.77
White	444 (87)	241 (85)	
Black	48 (9)	31 (11)	
Other	21 (4)	11 (4)	
Year of diagnosis	2010 (2008-2012)	2009 (2007-2012)	.002
Charlson-Deyo comorbidity condition score			.09
0	356 (69)	174 (62)	
1	120 (23)	81 (29)	
2+	39 (8)	28 (10)	
Insurance status			.34
Private	183 (36)	109 (29)	
Government	312 (61)	159 (57)	
None	13 (3)	11 (4)	
Facility location			<.001
Metro	396 (77)	230 (81)	
Urban	83 (16)	40 (14)	
Rural	36 (7)	13 (5)	
Academic center	230 (45)	111 (39)	.16
Type of surgery	N/A		N/A
Wedge resection		63 (22)	
Segmentectomy		7 (3)	
Lobectomy		128 (45)	
Pneumonectomy		21 (7)	
Nodes examined	N/A	7 (3-19)	N/A
Tumor size (mm)	29 (19-42)	29 (19-40)	
Histology			<.001
Adenocarcinoma	274 (66)	151 (61)	
Squamous cell carcinoma	118 (28)	57 (23)	
Other	23 (6)	41 (17)	
Perioperative chemotherapy	N/A		N/A
Neoadjuvant		31 (11)	
Adjuvant		153 (55)	
None		96 (34)	
Complete resection rate	N/A	190 (73)	N/A
30-d mortality	N/A	13 (5)	N/A
90-d mortality	N/A	24 (9)	N/A
Radiation treatment volume (Gy)	66 (61-70)	40 (0-54)	<.001

Values are presented as median (interquartile range) or n (%). N/A, not available.