Original Article

Factors associated with incomplete resection for large, locally invasive non-small cell lung cancer

Whitney S. Brandt[1]^, Zhizhou Yang[1], Brendan T. Heiden[1], Pamela P. Samson[2], Daniel Morgensztern[3], Saiama N. Waqar[3], Bryan F. Meyers[1], Ruben G. Nava[1], G. Alexander Patterson[1], Benjamin D. Kozower[1], Varun Puri[1]

[1]Division of Cardiothoracic Surgery, Department of Surgery, Washington University, St. Louis, MO, USA; [2]Department of Radiation Oncology, Washington University, St. Louis, MO, USA; [3]Division of Oncology, Department of Medicine, Washington University, St. Louis, MO, USA

Contributions: (I) Conception and design: WS Brandt, Z Yang, BT Heiden, V Puri; (II) Administrative support: Z Yang; (III) Provision of study materials or patients: WS Brandt, Z Yang, BT Heiden, V Puri; (IV) Collection and assembly of data: WS Brandt, Z Yang; (V) Data analysis and interpretation: WS Brandt, Z Yang, V Puri, BT Heiden, PP Samson, D Morgensztern, SN Waqar, BF Meyers, RG Nava, GA Patterson; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Whitney S. Brandt, MD. Division of Cardiothoracic Surgery, Department of Surgery, Washington University, 660 Euclid Ave, St. Louis, MO 63110, USA. Email: wbrandt@wustl.edu.

Background: Large, node-negative but locally invasive non-small cell lung cancer (NSCLC) is associated with increased perioperative risk but improved survival if a complete resection is obtained. Factors associated with positive margins in this population are not well-studied.

Methods: We performed a retrospective cohort study using National Cancer Database (NCDB) for adult patients with >5 cm, clinically node-negative NSCLC with evidence of invasion of nearby structures [2006–2015]. Patients were classified as having major structure involvement (azygous vein, pulmonary artery/vein, vena cava, carina/trachea, esophagus, recurrent laryngeal/vagus nerve, heart, aorta, vertebrae) or chest wall invasion (rib pleura, chest wall, diaphragm). Our primary outcome was to evaluate factors associated with incomplete resection (microscopic: R1, macroscopic: R2). Kaplan-Meier analysis and cox multivariable regression models were used to evaluate overall survival (OS), 90-day mortality, and factors associated with positive margins.

Results: Among 2,368 patients identified, the median follow-up was 33.8 months [interquartile range (IQR), 12.6–66.5 months]. Most patients were white (86.9%) with squamous cell histology (47.3%). Major structures were involved in 26.4% of patients and chest wall invasion was seen in 73.6%. Four hundred and seventy-eight patients (20.2%) had an incomplete resection. Multivariable analysis revealed that black race [hazard ratio (HR) 1.568, 95% confidence interval (CI): 1.109–2.218] and major structure involvement (HR 1.412, 95% CI: 1.091–1.827) was associated with increased risk of incomplete resection and surgery at an academic hospitals (HR 0.773, 95% CI: 0.607–0.984), adenocarcinoma histology (HR 0.672, 95% CI: 0.514–0.878), and neoadjuvant chemotherapy (HR 0.431, 95% CI: 0.316–0.587) were associated with decreased risk of incomplete resection. The 5-year OS was 43.7% in the entire cohort and 28.8% in patients with positive margins and 47.5% in patients with an R0 resection. Positive margin was also associated with a significantly higher 90-day mortality rate (9.9% versus 6.7%).

Conclusions: For patients with large, node-negative NSCLC invading nearby structures, R0 resection portends better survival. Treatment at academic centers, adenocarcinoma histology, and receipt of neoadjuvant chemotherapy are associated with R0 resection in this high-risk cohort.

Keywords: Invasive non-small cell lung cancer (invasive NSCLC); resection; positive margin; survival

Submitted Jul 12, 2023. Accepted for publication Mar 08, 2024. Published online May 07, 2024.
doi: 10.21037/jtd-23-989
View this article at: https://dx.doi.org/10.21037/jtd-23-989

^ ORCID: 0000-0003-3839-7667.

Introduction

The 5-year overall survival (OS) for patients with completely resected early-stage non-small cell lung cancer (NSCLC) ranges from 80–90% (1). However, as tumors get larger, the 5-year OS decreases, even in the absence of nodal metastases. A previous study evaluating OS for node-negative NSCLC demonstrated that 5-year OS ranged from 91% for tumors ≤1 cm node-negative tumors to as low as 58% for 6.1–7 cm node-negative tumors (2). The current treatment recommended by National Comprehensive Cancer Network (NCCN) guidelines for large, node-negative NSCLC is upfront surgical resection followed by adjuvant therapy (3). However, resection can be more challenging in these patients, particularly if nearby structures are involved. Previous studies have reported a 2.7–12.5% mortality risk as well as a 21–53% perioperative morbidity risk for large or locally invasive tumors (4,5). Incomplete resection, an important risk factor for diminished survival, is more likely in larger tumors with clinical evidence of local invasion and is seen in 7–16% of patients with suspected chest wall invasion in previous studies (2,6). One study found the 5-year OS for patients with incompletely resected (R1/R2) NSCLC to be 33.8% versus 58.5% in patients with a complete (R0) resection (7).

Given the higher risk of perioperative morbidity and incomplete resection for patients with large, locally invasive, node-negative NSCLC, it is unclear which factors are associated with incomplete resection, who may benefit from attempted resection, and if neoadjuvant chemotherapy is associated with increased complete (R0) resection rates. We address this knowledge gap using a large, nationally representative dataset. We hypothesized that major structure invasion, age of patient, and type and location of surgery would be associated with incomplete resection. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-989/rc).

Highlight box

Key findings

- Survival is improved for patients with large, locally invasive, node-negative non-small cell lung cancer (NSCLC) if complete (R0) resection is obtained. We found that adenocarcinoma, surgery at academic centers, neoadjuvant chemotherapy, and invasion confined to chest wall and diaphragm were all associated with increased risk of complete resection.

What is known and what is new?

- Complete resection is associated with improved survival in all NSCLC. However, when patients have large, locally invasive tumors, one must determine which factors are associated with improved likelihood of complete resection to identify appropriate patients for surgery.
- This work demonstrates that complete resection is associated with improved survival in patients with large, locally invasive NSCLC. Factors associated with incomplete resection for large node negative tumors include squamous cell carcinoma, surgery at a community center, up front surgery, and major structure involvement.

What is the implication, and what should change now?

- In physically fit patients, large, locally invasive tumors, patients may benefit from treatment at an academic center and considered for neoadjuvant therapy as these are associated with R0 resection.

Methods

To test our hypothesis, we performed a retrospective cohort analysis using the National Cancer Database (NCDB). We included patients who had large (>5 cm), clinically node-negative, and documented local structure invasion NSCLC who underwent surgery from 2006 to 2015. We excluded patients with lack of follow-up data, prior malignancy unknown laterality, unknown chemotherapy sequence, neuroendocrine or carcinoid pathology, local tumor destruction (laser ablation, cryosurgery, or electrocautery/fulguration), unknown surgery type, palliative intent treatment, immunotherapy, no definitive treatment, multiple tumor nodules in the same lobe, no invasive tumor, or unconfirmed histology. Patients were also excluded if they had sublobar resection, unknown surgery type, superior sulcus tumor, or induction immunotherapy. The NCDB does not have granular data on how pre-operative mediastinal staging was performed. Follow up was performed by individual institutions and recorded from the NCDB.

Tumor size was obtained from variable "CS tumor size" in NCDB that used a combination of clinical and pathological evidence when available, and was categorized into 5.1–7, 7.1–10, or >10 cm based on a preliminary restricted cubic spline regression against 5-year survival. In the NCDB, major structure involvement includes invasion of the azygous vein, pulmonary artery, pulmonary vein, superior vena cava (SVC), inferior vena cava (IVC), carina, trachea, esophagus, cervical sympathetic chain, recurrent laryngeal nerve, vagus nerve, heart, visceral pericardium, aorta, or vertebrae. Invasion of the chest wall invasion includes invasion of the rib, pleura, chest wall,

or diaphragm. For patients who received neoadjuvant treatment prior to surgical resection, the greatest size and extent of disease was recorded whether determined clinically or pathologically. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Kaplan-Meier survival analysis and multivariable Cox regression model against 5-year OS, as well as binary regression model against 90-day survival and positive surgical margin were performed in this study. Variables used for multivariable analyses were pre-determined based on clinical significance and included age, sex, race, center type, insurance type, Charlson-Deyo score, tumor grade, tumor histology, surgical margin status, tumor size, extent of local invasion, type of surgery (lobectomy or bilobectomy *vs.* pneumonectomy), whether patient received neoadjuvant chemotherapy, and era of diagnosis. For 5-year survival multivariable analysis, we added adjuvant chemotherapy as a variable. Surgical margin status was grouped into positive (R1/R2) and negative (R0 resection) for 90-day mortality multivariable analysis given the small number of events. Multivariable analyses were performed using only patients that have complete variables.

Baseline characteristics were compared using the χ^2 test for categorical variables, and count with proportion (%) was reported. A P value <0.05 was considered statistically significant in all analyses. Our primary endpoint was to evaluate factors associated with positive margin. Secondary endpoints included factors associated with OS and 90-day mortality.

Results

In total, 1,205,501 patients who were >18 years of age, were diagnosed with NSCLC from 2006–2015. After applying exclusion criteria, the study cohort included 2,368 patients with large, clinically node-negative tumors invading nearby structures who underwent surgery (*Figure 1*, consort diagram). Median follow-up was 33.8 [interquartile range (IQR), 12.6–66.5] months. Patient characteristics are listed in *Table 1* and were compared between negative *vs.* positive margin groups.

Among all patients, 20.2% (478/2,368) had an incomplete resection. Of the patients with an incomplete resection, 15% (N=74/478) of patients had neoadjuvant chemotherapy versus 85% (N=404/478) for those that did not get neoadjuvant chemotherapy. In patients with complete variables, we then performed a multivariable analysis against risk of incomplete resection. Black race and major local structure invasion were associated with incomplete resection. On the other hand, surgery at an academic center, adenocarcinoma, and neoadjuvant chemotherapy were associated with higher chance of complete resection (*Table 2*).

The 5-year OS was 43.7% [95% confidence interval (CI): 41.7–45.9%] in the entire cohort (*Figure 2*). Patients with positive margins had a 5-year survival was significantly lower (28.8%, 95% CI: 24.9–33.3%) compared with patients with negative margins patients (47.5%, 95% CI: 45.2–50.0%). Kaplan-Meier survival curves across margin status are shown in *Figure 3*. In multivariable analysis, higher age, surgery at a community center, higher comorbidity score, surgery in an earlier era, incomplete resection (especially R2), pneumonectomy, and larger tumor are associated with worse survival. Neoadjuvant and adjuvant chemotherapy are both associated with better long-term survival (*Table 3*).

Ninety-day mortality in the overall cohort was 7.3% (N=172/2,351). Seventeen patients did not have 90-day mortality data/lost follow-up within 90 days. Positive surgical margin patients had significantly higher 90-day mortality (47/474, 9.9%) compared with negative margin patients (125/1,877, 6.7%; P=0.01). On multivariable analysis, higher age and pneumonectomy were found to be significantly associated with short-term mortality. Surgery at an integrated network cancer program, adenocarcinoma, and surgery in the latest era demonstrated protective effect (*Table 4*).

Discussion

Locally invasive lung cancer poses a particular challenge, as surgery can be more involved than for those with early-stage disease. This is particularly true for those with large tumors but no evidence of lymph node metastases, as local control is paramount and radiation therapy may not be as effective. We therefore evaluated this cohort, patients who had large (>5 cm) NSCLC, which were clinically node-negative and had evidence for local invasion. Not surprisingly, we found that incomplete resection was associated with worse OS in this population. In addition, we found that major structure invasion and Black race were associated with an increased risk of incomplete resection but that neoadjuvant chemotherapy, surgery at an academic center, and adenocarcinoma histology were associated with

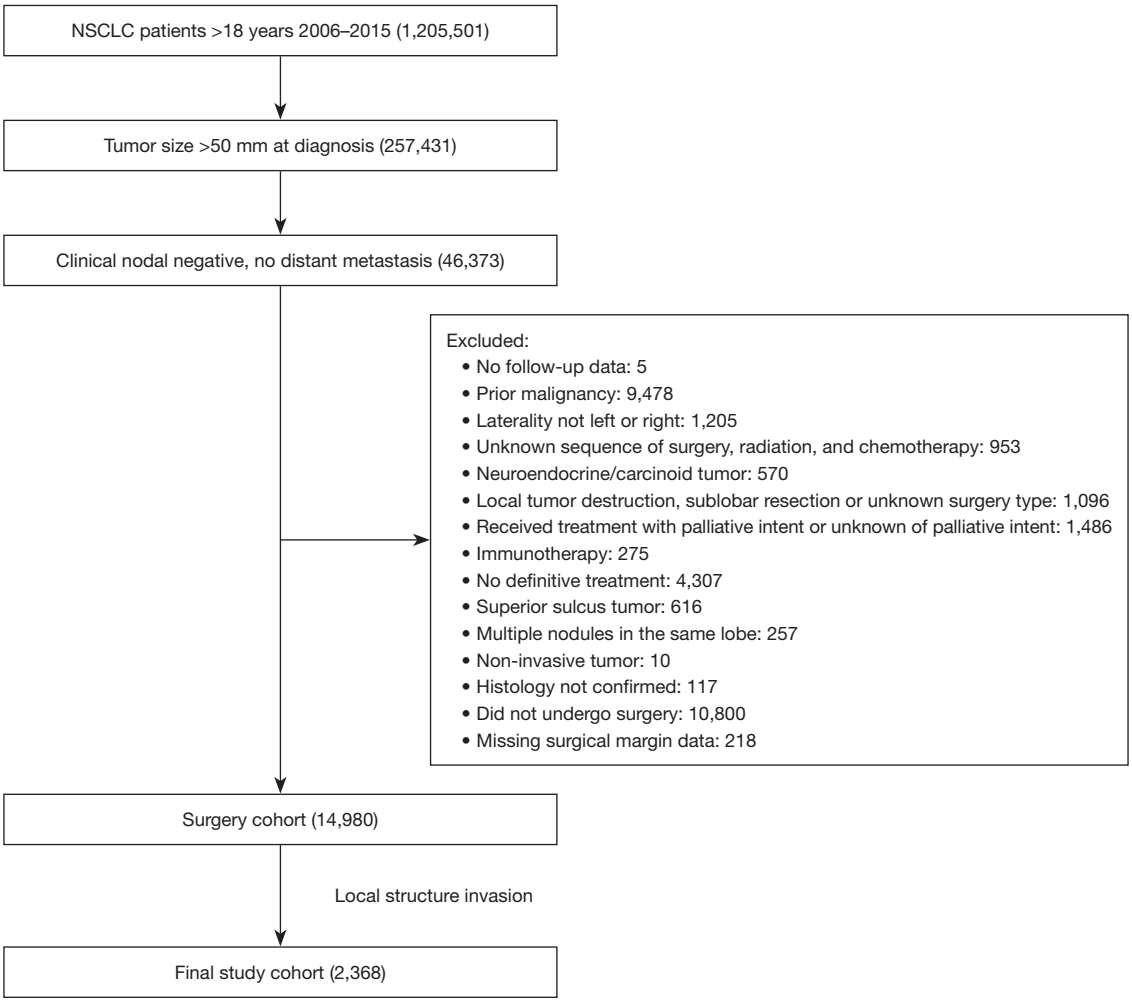

Figure 1 Elimination of certain patients to reach our final cohort of 2,368 patients. NSCLC, non-small cell lung cancer.

decreased risk of incomplete resection.

This study is useful because it uses a large, multi-institutional dataset to compares a unique population of patients who have large locally invasive tumors without nodal metastases. This population is likely to benefit from surgery, should a negative margin be obtained. However, it can be challenging to evaluate pre-operatively which patients are at risk for incomplete resection. Prior studies have not studied the risk factors for incomplete resection in this unique population.

One of the major findings in our study is that adenocarcinoma histology is associated with complete resection. This finding is in line with other studies' results in similar populations. A recent study by Rasing and colleagues evaluated over 7,100 patients in a Dutch national database. They included stage I–IIIA NSCLC regardless of invasive status with a reported 7.1% incomplete resection rate. They found that adenocarcinoma histology as well as cT, cN, sublobar resection, and open approach were associated with increased risk of incomplete resection (6). They validated their findings using the NCDB (6). These results align with ours. For one, lung adenocarcinoma is likely to be peripheral and therefore, less likely to invade mediastinal or hilar structures. Squamous carcinoma, on the other hand, is more commonly centrally located and therefore, may be in proximity to many of the major structures as defined in our study. In our study, we were unable to differentiate the degree of invasion, and therefore, this specific point cannot be evaluated, however. Overall, adenocarcinoma histology appears to be a factor associated with increased likelihood of complete resection.

We also found that treatment at an academic institution

Table 1 Baseline characteristics of the entire cohort

Variables	All (N=2,368)	Negative margin (N=1,890)	Positive margin (N=478)	P value
Age (years)				0.004
≤55	566 (23.9)	465 (24.6)	101 (21.1)	
56–65	742 (31.3)	604 (32.0)	138 (28.9)	
66–75	763 (32.2)	606 (32.1)	157 (32.8)	
>75	297 (12.5)	215 (11.4)	82 (17.2)	
Male	1,511 (63.8)	1,206 (63.8)	305 (63.8)	0.99
Race	N=2,358			0.02
White	2,050 (86.9)	1,653 (87.8)	397 (83.4)	
Black	226 (9.6)	165 (8.8)	61 (12.8)	
Others	82 (3.5)	64 (3.4)	18 (3.8)	
Center type	N=2,345			0.052
Community	1,099 (46.9)	855 (45.8)	244 (51.2)	
Academic	913 (38.9)	750 (40.1)	163 (34.2)	
Network	333 (14.2)	263 (14.1)	70 (14.7)	
Insurance type	N=2,335			0.02
Government	1,304 (55.8)	1,015 (54.5)	289 (61.1)	
Private	933 (40.0)	769 (41.3)	164 (34.7)	
No insurance	98 (4.2)	78 (4.2)	20 (4.2)	
Household income	N=2,176			0.48
Less than $40,227	469 (21.6)	374 (21.8)	95 (20.8)	
$40,227–$50,353	551 (25.3)	427 (24.8)	124 (27.1)	
$50,354–$63,332	516 (23.7)	418 (24.3)	98 (21.4)	
$63,333 or more	640 (29.4)	500 (29.1)	140 (30.6)	
Charlson-Deyo score				0.01
0	1,265 (53.4)	1,032 (54.6)	233 (48.7)	
1	772 (32.6)	599 (31.7)	173 (36.2)	
2	257 (10.9)	208 (11.0)	49 (10.3)	
≥3	74 (3.1)	51 (2.7)	23 (4.8)	
Tumor grade	N=2,083			0.09
Well differentiated	55 (2.6)	47 (2.9)	8 (1.8)	
Moderately differentiated	622 (29.9)	475 (29.0)	147 (33.1)	
Poorly differentiated	1,300 (62.4)	1,039 (63.4)	261 (58.8)	
Undifferentiated	106 (5.1)	78 (4.8)	28 (6.3)	
Histology				0.008
Squamous cell carcinoma	1,121 (47.3)	869 (46.0)	252 (52.7)	
Adenocarcinoma	752 (31.8)	627 (33.2)	125 (26.2)	
Others including large cell	495 (20.9)	394 (20.8)	101 (21.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	All (N=2,368)	Negative margin (N=1,890)	Positive margin (N=478)	P value
Local invasion extension				0.02
Chest wall, diaphragm, parietal pleura, or rib	1,742 (73.6)	1,410 (74.6)	332 (69.5)	
Major structure involvement*	626 (26.4)	480 (25.4)	146 (30.5)	
Tumor size (mm)				0.50
51–70	1,303 (55.0)	1,045 (55.3)	258 (54.0)	
71–100	831 (35.1)	665 (35.2)	166 (34.7)	
>100	234 (9.9)	180 (9.5)	54 (11.3)	
Era				0.29
2006–2009	809 (34.2)	656 (34.7)	153 (32.0)	
2010–2012	778 (32.9)	607 (32.1)	171 (35.8)	
2013–2015	781 (33.0)	627 (33.2)	154 (32.2)	
Procedure				0.01
Lo/bilobectomy	1,992 (84.1)	1,607 (85.0)	385 (80.5)	
Pneumonectomy	376 (15.9)	283 (15.0)	93 (19.5)	
Neoadjuvant chemotherapy	689 (29.1)	615 (32.5)	74 (15.5)	<0.001
Adjuvant chemotherapy	1,045 (44.1)	783 (41.4)	262 (54.8)	<0.001

Data are presented by number of patients (N) and percentage (%). *, major structure involvement: azygos vein, pulmonary artery, pulmonary vein, superior vena cava, inferior vena cava, carina, trachea, esophagus, cervical sympathetic chain (Horner syndrome), recurrent laryngeal nerve, vagus nerve, heart, visceral pericardium, aorta, vertebra.

was associated with decreased risk for incomplete resection. Academic institutions tend to be higher volume and a volume-outcome relationship has been well studied in patients with all types of NSCLC. Previous studies have demonstrated an association between high volume and lower surgical mortality and increased long-term survival in patients (8,9). Though these publications have not specifically focused on invasive NSCLC, one study which evaluated patients with superior sulcus T4N0/1M0 NSCLC demonstrated that both adenocarcinoma and surgery at an academic program were associated with improvement in R0 resection status as well as survival (10). In patients with large, locally invasive tumors, the operations can be technically challenging. Therefore, it is logical that larger academic institutions with well-established collaborative multi-specialty operative teams are more likely to achieve complete resection if structures such as vertebrae, heart, vena cava, etc. require resection. Experienced surgeons from high-volume programs have previously outlined the complexities of resection for lung cancer invading various mediastinal structures and suggested that a multi-disciplinary surgical approach at an academic institution may be better suited for these cases (11).

We also found that invasion of major structures was associated with increased risk for incomplete resection. In our cohort, about 20% of the patients had an R1 resection. Other studies have a similar incomplete resection rate to our study. One study of 44 patients at an academic institution evaluated their experience with NSCLC invading the atrium found that the rate of R1 resection was 18.2% and 0 patient died perioperatively, although 11.4% had major complications (12). The 5-year OS was 39% (12). Another study from 1998–2004 evaluated their experience with seventy patients (52 of which) had lung cancer who had partial (64%) SVC reconstruction or complete replacement (36%). They found that morbidity and mortality were 23% and 7.7% and the 5-year survival was 52% in patients with lung cancer with pN0-1 disease. However, they did not include data on margin status (13). Overall, these findings demonstrate the complexity of patients with invasion of major structures and highlight that survival can be satisfactory considering the extent of

Table 2 Multivariable Cox regression against risk of positive surgical margin (n=2,030)

Variables	Odds ratio (95% CI)	P value
Age (years)		
≤55	Reference	
56–65	0.781 (0.570–1.072)	0.12
66–75	0.822 (0.581–1.165)	0.27
>75	1.119 (0.740–1.690)	0.59
Sex		
Male	Reference	
Female	1.122 (0.892–1.412)	0.32
Race		
White	Reference	
Black	1.568 (1.109–2.218)	0.01
Others	1.233 (0.685–2.216)	0.48
Center type		
Community	Reference	
Academic	0.773 (0.607–0.984)	0.03
Network hospital	0.956 (0.694–1.319)	0.78
Insurance type		
Government	Reference	
Private	0.964 (0.738–1.260)	0.78
No insurance	1.175 (0.658–2.099)	0.58
Charlson-Deyo score		
0	Reference	
1	1.109 (0.871–1.413)	0.40
2	0.875 (0.606–1.263)	0.47
≥3	1.708 (0.987–2.956)	0.056
Tumor grade		
Well differentiated	Reference	
Moderately differentiated	1.628 (0.740–3.585)	0.22
Poorly differentiated	1.424 (0.655–3.095)	0.37
Undifferentiated	1.868 (0.750–4.648)	0.17
Histology		
Squamous cell carcinoma	Reference	
Adenocarcinoma	0.672 (0.514–0.878)	0.004
Others including large cell	0.959 (0.698–1.319)	0.79
Local invasion extension		
Chest wall, diaphragm, parietal pleura, or rib	Reference	
Major structure involvement*	1.412 (1.091–1.827)	0.009
Tumor size (mm)		
51–70	Reference	
71–100	1.075 (0.847–1.365)	0.55
>100	1.230 (0.848–1.783)	0.27
Procedure		
Lo/bilobectomy	Reference	
Pneumonectomy	1.138 (0.839–1.543)	0.40
Neoadjuvant chemotherapy	0.431 (0.316–0.587)	<0.001
Era		
2006–2009	Reference	
2010–2012	1.105 (0.847–1.442)	0.46
2013–2015	1.055 (0.804–1.384)	0.70

*, major structure involvement: azygos vein, pulmonary artery, pulmonary vein, superior vena cava, inferior vena cava, carina, trachea, esophagus, cervical sympathetic chain (Horner syndrome), recurrent laryngeal nerve, vagus nerve, heart, visceral pericardium, aorta, vertebra. CI, confidence interval.

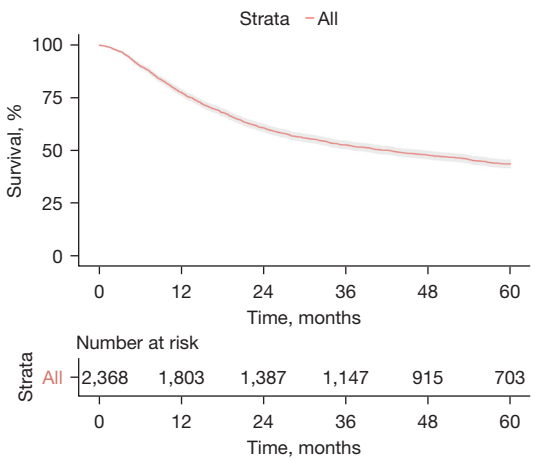

Figure 2 Five-year OS of our entire cohort. OS, overall survival.

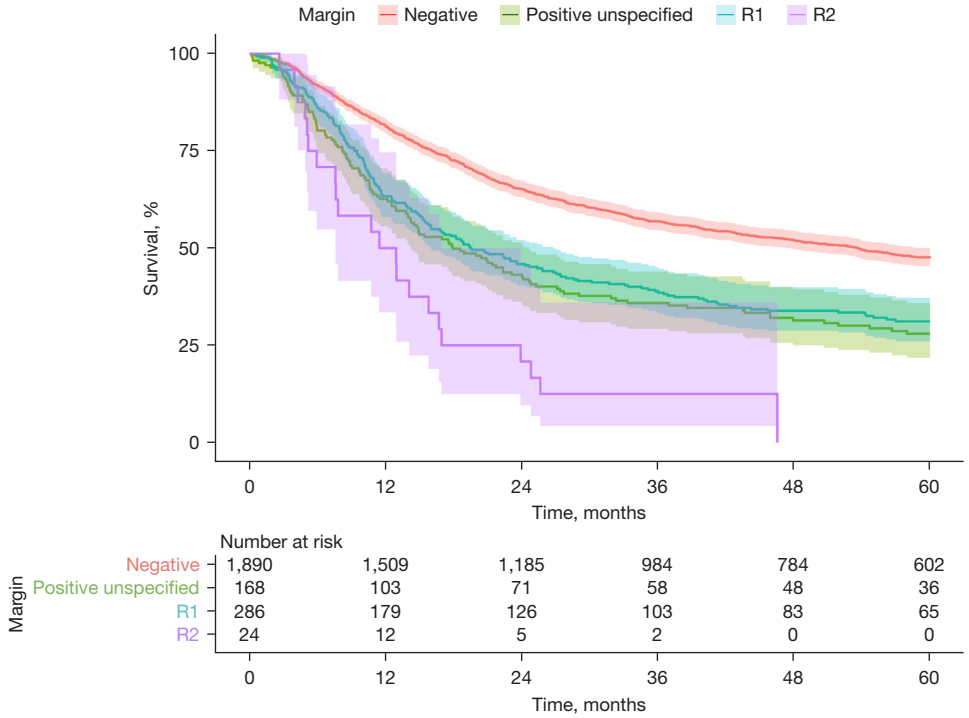

Figure 3 Five-year OS by margin status. OS, overall survival.

the operation.

Finally, we found that receipt of neoadjuvant chemotherapy was associated with greater likelihood of complete resection in our cohort. Previous studies have found that tumors with chest wall invasion have superior outcomes when they receive systemic therapy either before or after surgery. For tumors with major structure invasion this is also true. The Southwest Oncology Group Trial 9416 (intergroup Trial 0160) by Rusch *et al.* demonstrated that patients with superior sulcus tumors benefit from neoadjuvant chemoradiotherapy. Not only was survival acceptable (44% at 5 years) for all patients, but it was even better (54% at 5 years) for patients who completed neoadjuvant chemoradiotherapy and had an R0 resection (14). Our study shows neoadjuvant therapy may be beneficial for patients with local invasion outside of superior sulcus tumors to increase rate of R0 resection. Another study in 65 patients with chest wall invasion demonstrated that receipt of neoadjuvant therapy was associated with a 5-year OS of 69.2% versus 48.5% for those that did not receive neoadjuvant therapy (P=0.02) (15). The majority of these patients had cT3/4 disease and N0 disease (49/65). The R0 resection rate was 93.8% in their entire cohort, which is comparable to all NSCLC cases including stage I. On multivariable analysis, they found that receipt of neoadjuvant therapy, age, and surgical procedure were all associated with OS as well suggesting the increased resection rate (15). Another single institution study evaluated 107 patients with NSCLC invading the chest wall (T3 tumors). They had a complete resection rate of 84%. However, only 50% of the patients were referred for adjuvant chemotherapy (4). For those with pT3N0 disease, the 5-year OS was 68.8% for those who completed adjuvant chemotherapy versus 29.7% for those that did not, suggesting chemotherapy is imperative for improved survival (4). In addition, on multivariable analysis, patients without adjuvant systemic therapy had a greatly increased risk of long-term mortality [hazard ratio (HR) of 4.8, 95% CI: 2.4–9.4] (4). Collectively, these studies and ours demonstrate that chemotherapy is an important consideration for patients with invasion of surrounding structures. In our study, receipt of neoadjuvant therapy was associated with improved complete resection rate which is associated with improved OS.

Given the retrospective nature our study may be subject to potential selection bias in that patients who undergo surgical intervention have a lesser degree that is deemed "resectable". Furthermore, the lack of granular data in the

Table 3 Multivariable Cox regression against 5-year overall survival (n=2,030)

Variables	Hazard ratio (95% CI)	P value
Age (years)		
≤55	Reference	
56–65	1.102 (0.915–1.326)	0.30
66–75	1.471 (1.207–1.794)	<0.001
>75	1.743 (1.381–2.200)	<0.001
Sex		
Male	Reference	
Female	0.777 (0.683–0.884)	<0.001
Race		
White	Reference	
Black	0.871 (0.708–1.072)	0.19
Others	0.938 (0.672–1.308)	0.70
Center type		
Community	Reference	
Academic	0.857 (0.752–0.976)	0.02
Network hospital	0.815 (0.682–0.973)	0.02
Insurance type		
Government	Reference	
Private	0.958 (0.826–1.111)	0.57
No insurance	0.860 (0.600–1.233)	0.41
Charlson-Deyo score		
0	Reference	
1	1.130 (0.989–1.292)	0.07
2	1.227 (1.019–1.476)	0.03
≥3	1.232 (0.907–1.674)	0.18
Tumor grade		
Well differentiated	Reference	
Moderately differentiated	1.086 (0.747–1.579)	0.66
Poorly differentiated	1.111 (0.770–1.602)	0.57
Undifferentiated	1.464 (0.932–2.300)	0.09
Histology		
Squamous cell carcinoma	Reference	
Adenocarcinoma	0.912 (0.791–1.052)	0.20
Others including large cell	0.982 (0.823–1.170)	0.83
Local invasion extension		
Chest wall, diaphragm, parietal pleura, or rib	Reference	
Major structure involvement*	0.951 (0.823–1.099)	0.49
Tumor size (mm)		
51–70	Reference	
71–100	1.253 (1.102–1.425)	<0.001
>100	1.637 (1.347–1.991)	<0.001
Procedure		
Lo/bilobectomy	Reference	
Pneumonectomy	1.284 (1.085–1.518)	0.004
Surgical margin status		
Negative	Reference	
Positive (unspecified)	1.895 (1.547–2.322)	<0.001
R1	1.691 (1.430–1.999)	<0.001
R2	3.668 (2.374–5.667)	<0.001
Neoadjuvant chemotherapy	0.590 (0.499–0.698)	<0.001
Adjuvant chemotherapy	0.565 (0.494–0.645)	<0.001
Era		
2006–2009	Reference	
2010–2012	0.844 (0.732–0.973)	0.02
2013–2015	0.848 (0.731–0.983)	0.02

*, major structure involvement: azygos vein, pulmonary artery, pulmonary vein, superior vena cava, inferior vena cava, carina, trachea, esophagus, cervical sympathetic chain (Horner syndrome), recurrent laryngeal nerve, vagus nerve, heart, visceral pericardium, aorta, vertebra. CI, confidence interval.

NCDB does not allow us to track the location of the which structures are invaded by the tumor and to what extent. This adds to the selection bias. However, the results are as expected that incomplete resection has poor outcomes. Additionally, our study did not include patients who received immunotherapy. Although recent studies suggest immunotherapy may improve survival for patients with large tumors, our study is unable to answer the question whether immunotherapy can help improve survival in patients with large, locally invasive, node-negative NSCLC as it predates the approval for consolidation immunotherapy

Table 4 Multivariable Cox regression against 90-day mortality (n=2,018)

Variables	Odds ratio (95% CI)	P value
Age (years)		
≤55	Reference	
56–65	1.478 (0.753–2.899)	0.25
66–75	2.995 (1.538–5.832)	0.001
>75	4.559 (2.216–9.377)	<0.001
Sex		
Male	Reference	
Female	0.797 (0.545–1.163)	0.23
Race		
White	Reference	
Black	0.863 (0.454–1.641)	0.65
Others	0.436 (0.103–1.849)	0.26
Center type		
Community	Reference	
Academic	0.769 (0.531–1.116)	0.16
Network hospital	0.429 (0.232–0.796)	0.007
Insurance type		
Government	Reference	
Private	0.787 (0.504–1.228)	0.29
No insurance	0.260 (0.034–1.971)	0.19
Charlson-Deyo score		
0	Reference	
1	1.466 (0.997–2.155)	0.052
2	1.370 (0.812–2.311)	0.23
≥3	1.468 (0.620–3.472)	0.38
Tumor grade		
Well differentiated	Reference	
Moderately differentiated	1.495 (0.337–6.620)	0.59
Poorly differentiated	2.217 (0.513–9.575)	0.28
Undifferentiated	2.240 (0.433–11.575)	0.33
Histology		
Squamous cell carcinoma	Reference	
Adenocarcinoma	0.469 (0.289–0.760)	0.002
Others including large cell	0.983 (0.613–1.578)	0.94
Local invasion extension		
Chest wall, diaphragm, parietal pleura, or rib	Reference	
Major structure involvement*	1.187 (0.798–1.767)	0.39
Tumor size (mm)		
51–70	Reference	
71–100	1.246 (0.860–1.806)	0.24
>100	1.490 (0.850–2.615)	0.16
Procedure		
Lo/bilobectomy	Reference	
Pneumonectomy	2.198 (1.428–3.384)	<0.001
Surgical margin status		
Negative	Reference	
Positive	1.254 (0.849–1.853)	0.25
Neoadjuvant chemo	0.801 (0.493–1.302)	0.37
Era		
2006–2009	Reference	
2010–2012	0.732 (0.491–1.091)	0.12
2013–2015	0.486 (0.314–0.752)	0.001

*, major structure involvement: azygos vein, pulmonary artery, pulmonary vein, superior vena cava, inferior vena cava, carina, trachea, esophagus, cervical sympathetic chain (Horner syndrome), recurrent laryngeal nerve, vagus nerve, heart, visceral pericardium, aorta, vertebra. CI, confidence interval.

(PACIFIC), adjuvant immunotherapy (IMpower 010) and neoadjuvant chemoimmunotherapy trials (16-19).

Conclusions

Our study shows that complete tumor resection is a critical prognosticating factor in patients undergoing surgery for large, locally invasive but node-negative NSCLC. Our findings suggest that these patients should be evaluated at experienced centers for multidisciplinary input in treatment planning and complex surgical care. Future studies with targeted therapies, immunotherapy, and neoadjuvant regimens may further improve outcomes in this complex patient population.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-989/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-989/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-989/coif). D.M. serves as an unpaid editorial board member of *Journal of Thoracic Disease* from October 2022 to September 2024. D.M. reports research support from Heat Biologics (Inst), Merck (Inst), Celgene (Inst), AstraZeneca (Inst), Baxter (Inst), Incyte (Inst), AbbVie (Inst), Bristol Myers Squibb (Inst), EpicentRx (Inst), Pfizer (Inst), Roche (Inst), Lilly (Inst), Altum Pharmaceuticals (Inst), Array BioPharma (Inst), Surface Oncology (Inst), Arcus Biosciences (Inst), Boehringer Ingelheim (Inst), Y-mAbs Therapeutics (Inst) and participation on a data safety monitoring board for AbbVie, G1 Therapeutics, Lilly Medical, Mirati Therapeutics, Arcus Biosciences. S.N.W. mentioned support from AbbVie Inc., Ariad Pharmaceuticals, Genentech, Immunomedics, Inc., Millennium Pharmaceuticals Inc., Roche, Astellas Pharma Inc., Daiichi Sankyo, Cullinan Pearl, Verastem Inc., GlaxoSmithKline/GSK, Janssen Research & Development, LLC, Elevation Oncology, Genentech, Loxo Oncology, Takeda Pharmaceuticals, Ribon Therapeutics, Inc., AstraZeneca Pharmaceuticals LP, Advenchen Laboratories, Gilead Sciences for the institution for clinical trials, SWOG-Clinical Trials Partnership, and receives payment for lectures or honoraria for ASCO SEP Editorial board, and she participates on the advisory board for AstraZeneca, Gilead Sciences, Janssen, and Hoosier Cancer Research Network. P.P.S. has speaking honoraria for Varian Medical Systems. B.T.H. is a former consultant at Oncocyte Corporation and a former MBA intern at Eli Lilly and Company. V.P. reports receiving NIH funding (R01CA258681). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
2. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.
3. Network NCC. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): National Comprehensive Cancer Network; 2023. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
4. Lee CY, Byun CS, Lee JG, et al. The prognostic factors of resected non-small cell lung cancer with chest wall invasion. World J Surg Oncol 2012;10:9.
5. Reardon ES, Schrump DS. Extended resections of non-small cell lung cancers invading the aorta, pulmonary artery, left atrium, or esophagus: can they be justified? Thorac Surg Clin 2014;24:457-64.
6. Rasing MJA, Peters M, Moreno AC, et al. Predicting Incomplete Resection in Non-Small Cell Lung Cancer Preoperatively: A Validated Nomogram. Ann Thorac Surg 2021;111:1052-8.
7. Osarogiagbon RU, Lin CC, Smeltzer MP, et al. Prevalence, Prognostic Implications, and Survival Modulators of Incompletely Resected Non-Small Cell Lung Cancer in the U.S. National Cancer Data Base. J Thorac Oncol 2016;11:e5-16.

8. Rosen JE, Hancock JG, Kim AW, et al. Predictors of mortality after surgical management of lung cancer in the National Cancer Database. Ann Thorac Surg 2014;98:1953-60.
9. Jawitz OK, Wang Z, Boffa DJ, et al. The differential impact of preoperative comorbidity on perioperative outcomes following thoracoscopic and open lobectomies. Eur J Cardiothorac Surg 2017;51:169-74.
10. Towe CW, Worrell SG, Bachman K, et al. Neoadjuvant Treatment Is Associated With Superior Outcomes in T4 Lung Cancers With Local Extension. Ann Thorac Surg 2021;111:448-55.
11. Al-Ayoubi AM, Flores RM. Surgery for lung cancer invading the mediastinum. J Thorac Dis 2016;8:S889-94.
12. Galetta D, Spaggiari L. Atrial Resection without Cardiopulmonary Bypass for Lung Cancer. Thorac Cardiovasc Surg 2020;68:510-5.
13. Spaggiari L, Leo F, Veronesi G, et al. Superior vena cava resection for lung and mediastinal malignancies: a single-center experience with 70 cases. Ann Thorac Surg 2007;83:223-9; discussion 229-30.
14. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-8.
15. Sato K, Nakamura S, Kadomatsu Y, et al. Neoadjuvant Therapy for Patients With Non-small Cell Lung Cancer Complicated With Chest Wall Invasion. Anticancer Res 2022;42:5539-46.
16. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344-57.
17. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:1413-22.
18. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:1301-11.
19. Xu K, Yang H, Ma W, et al. Neoadjuvant immunotherapy facilitates resection of surgically-challenging lung squamous cell cancer. J Thorac Dis 2021;13:6816-26.

Cite this article as: Brandt WS, Yang Z, Heiden BT, Samson PP, Morgensztern D, Waqar SN, Meyers BF, Nava RG, Patterson GA, Kozower BD, Puri V. Factors associated with incomplete resection for large, locally invasive non-small cell lung cancer. J Thorac Dis 2024;16(5):2894-2905. doi: 10.21037/jtd-23-989