ORIGINAL ARTICLE

Surgery for Patients With cT3/4N2M0, Stage IIIB NSCLC. Is It Time to Redefine Resectability?

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Received 29 July 2024; revised 5 November 2024; accepted 7 November 2024
Available online - 14 November 2024

ABSTRACT

Introduction: Chemoradiation followed by durvalumab is considered a standard approach for patients with locally advanced NSCLC. With improvements in perioperative and neoadjuvant approaches, there is renewed interest in offering surgery to carefully selected patients with cT3/4N2 stage IIIB cancer. We sought to assess survival outcomes after surgery as part of a multimodality treatment regimen for these patients.

Methods: Patients with cT3/T4N2M0 NSCLC who received surgery (S) as part of a multimodality approach and patients receiving multimodality treatment without surgery (chemoradiation [CRT] or systemic therapy only) were identified in the National Cancer Database (2010–2019). We evaluated factors associated with the receipt of S (logistic regression). After propensity matching, we estimated the overall survival (OS) of patients who received S and compared with those who received CRT (Kaplan-Meier and Cox regression).

Results: A total of 44,756 patients were identified, of whom 3928 (8.8%) underwent S, 29,798 (66.6%) CRT, and 11,030 (24.6%) systemic therapy only. Fewer comorbidities (Charlson-Deyo index 0 or 1, adjusted OR [aOR]: 1.22, 95% confidence interval [CI]: 1.05–1.42), treatment at an academic facility (aOR: 1.70, 95% CI: 1.52–1.89), private insurance (aOR: 2.44, 95% CI: 1.61–3.69), adenocarcinoma histology (aOR: 1.48, 95% CI: 1.22–1.79), and clinical T3 stage (<7 cm, aOR: 1.70, 95% CI: 1.53–1.89) were associated with S. In well-balanced, propensity-matched cohorts, patients selected for S had better OS compared with those who underwent CRT (hazard ratio 0.59, 95% CI: 0.56–0.63, $p < 0.001$) (median OS 49.7 versus 25.0 mo).

Conclusions: In this retrospective cohort analysis, patients with cT3/4N2, stage IIIB NSCLC who underwent surgical resection had better OS compared with those patients treated with CRT. Careful patient selection is undoubtedly critical, but stage IIIB designation alone should not exclude patients from surgical consideration.

Keywords: Unresectable; Definitive chemoradiation; Stage IIIB NSCLC; Neoadjuvant therapy; Perioperative approaches

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Previous presentation: This research study was featured as a podium presentation at the Society of Thoracic Surgeon's annual meeting in San Antonio, Texas, on January 27, 2024.

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Cite this article as: Rodriguez-Quintero JH, Jindani R, Zhu R, et al. Surgery for patients with cT3/4N2M0, stage IIIB NSCLC. Is it time to redefine resectability? *JTO Clin Res Rep* 2025;6:100766.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100766

Introduction

Since the publication of the PACIFIC trial, definitive chemoradiation followed by durvalumab is considered a standard for patients with unresectable stage III NSCLC.[1] Patients designated as having stage IIIB NSCLC may routinely be considered de facto as "unresectable," in large part due to the association of stage IIIB disease with N3 nodal metastases in the seventh edition staging system.[2] Nevertheless, since the adoption of the eighth edition of the staging system, patients with T3 or T4 tumor classifications and N2 nodal classification are also staged as IIIB.[3] The optimal treatment for this subgroup of patients remains debatable, but it is possible that many are considered unresectable based on the IIIB designation alone and thus not considered for surgical resection. Notably, there have been no randomized trials directly comparing surgical with nonoperative approaches for patients with N2 mediastinal nodal metastases and T3/4 tumors.

The concept of surgical resectability has rapidly changed with the addition of immunotherapy and targeted therapies into treatment paradigms for patients with NSCLC. This is particularly evident in the neoadjuvant and perioperative settings, in which several trials have included patients with cIIIA and cIIIB NSCLC, including patients with cT3/4N2 tumors.[4–6] In the perioperative phase II NADIM-2 trial, 72% of patients in the nivolumab plus chemotherapy arm had mediastinal nodal disease, including 39% of patients with multistation N2 disease.[4] Similarly, the phase III AEGEAN trial included 24% of patients with stage IIIB disease in the perioperative durvalumab group, including 9.3% with multistation N2 disease.[5] Last, the KEYNOTE 671 study included 15.6% of patients staged as having IIIB in the perioperative pembrolizumab arm.[6] Considering the promising pathologic response data and survival outcomes of patients in these landmark studies, it is critical for the thoracic oncology community to continue to reevaluate resectability criteria for patients with locally advanced, cT3/4N2 NSCLC. This may be particularly true given the worse-than-expected treatment-related mortality and survival outcomes of the concurrent immunotherapy arm and the control arm in the recently described PACIFIC 2 trial, which was in part attributed to the inclusion of a high proportion of large T4 tumors.[7]

In this study, we investigate treatment patterns and overall survival (OS) outcomes of patients with stage IIIB (T3/4N2M0) NSCLC, focusing on those who underwent surgery as part of a multimodality treatment regimen using real-world data from a multicentric contemporary cohort in the United States. Although we recognize that these patients were carefully selected and that a retrospective analysis cannot fully account for such selection bias, we hypothesized that being selected for surgical resection would be associated with improved OS in patients with T3/4 tumors and N2 nodal disease.

Materials and Methods

National Cancer Database

The National Cancer Database (NCDB) is a hospital-based tumor registry sponsored by the American Cancer Society and the American College of Surgeons. It captures data from approximately 1500 hospitals and includes more than 72% of all newly diagnosed cancers in the United States.[8] The NCDB has not verified and is not responsible for the statistical validity of the data analysis or the conclusions derived by the authors or readers. Because all the information in this study was deidentified, our institutional review board waived the need for informed consent.

Study Population

For this retrospective cohort study, we used the NCDB (version 2020) and included all patients aged 18 years or older who received definitive treatment for clinical T3/4N2M0 (>5 cm tumors with mediastinal nodal disease) NSCLC (staged using American Joint Committee on Cancer eighth edition) diagnosed from 2010 to 2019. Although T-stage designation was used to identify eligible patients, no information other than tumor size (i.e., invasion to adjacent structures) was available on the reason for T-stage. The cohort was stratified based on whether patients underwent surgery, as a formal anatomical resection, and as part of a multimodality regimen (S), or were treated with chemoradiotherapy (CRT), or systemic therapy only (ST) without surgery. In addition, to better understand the outcomes of patients who underwent S over time, we stratified our cohort based on the time of diagnosis as an "early" (2010–2014) and "recent" (2015–2019) treatment groups. Patients were excluded if they had other clinical stages, if they received local therapy (surgery or radiotherapy) without ST, if they had discordant information on staging variables, and if they had missing data on patient, tumor, treatment, and survival variables of interest (Fig. 1). A list of the NCDB variables used is included in Supplementary Table 1. To address missing data, we used a complete-case approach assuming data were missing completely at random.

Study Objectives

Our primary objective was to estimate the association between surgical resection and OS among patients with cT3/4N2M0 disease who were treated with a multimodality treatment regimen. For survival comparisons,

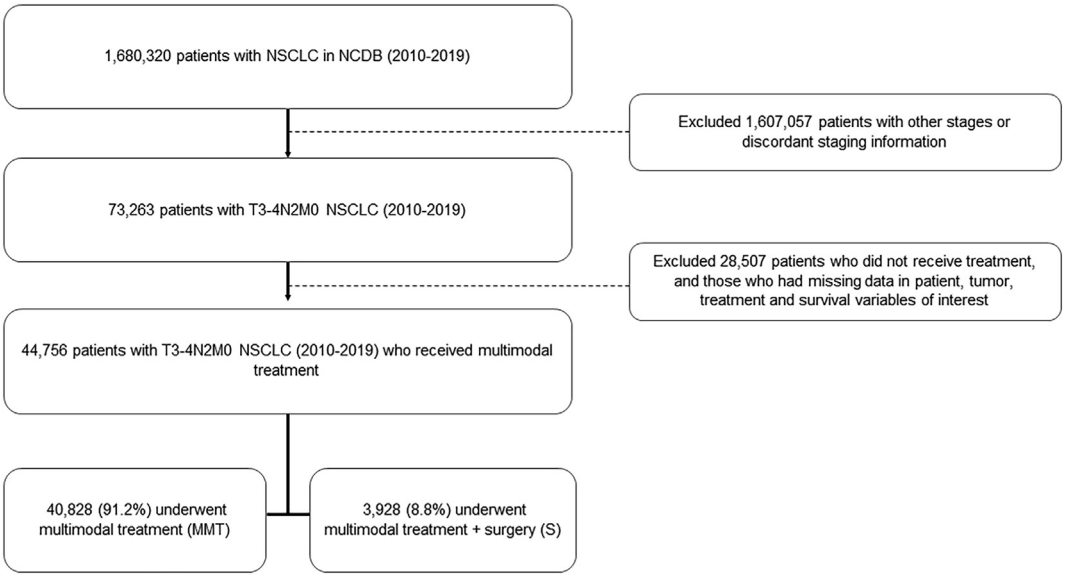

Figure 1. Flowchart of the study participants. NCDB, National Cancer Database.

we excluded patients treated with ST only and compared the outcomes of patients who underwent S to CRT. To better understand the association between the treatment modality and survival over time, we analyzed two different time cohorts and contrasted each group's median OS between time periods. Our secondary objectives included analyzing temporal and geographic trends and patterns of surgery for stage IIIB disease in the United States, identifying factors associated with the use of surgery and identifying factors associated with OS in the S and CRT groups.

Statistical Analysis

Continuous variables were presented as median and interquartile ranges. Categorical variables were presented as frequencies and percentages. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the Mann-Whitney test. The trend of surgery over time was studied using linear regression. To study associations with the receipt of S in the recent cohort, we used a multivariable logistic regression model with stepwise backward elimination ($p = 0.10$ for stepwise removal) including individual patient characteristics (age, sex, race, Charlson-Deyo index), sociodemographic characteristics, (type of facility, location, insurance, area of residence, income), and tumor characteristics (histology, tumor size) in the model.

To compare survival in the balanced groups, three propensity score matched sets (without replacement) were constructed to control for differences between those who received S versus CRT in (1) the whole cohort, (2) the early cohort (2010–2014), and (3) the recent cohort (2015–2019). We only matched patients in the surgery group if they had undergone surgery upfront or less than 180 days from the start of chemoradiation. Salvage resections (performed $\geq$180 d from chemoradiation) were excluded from the survival analysis.[9] For this, a propensity score was created using a logistic regression including the following variables: age, sex, comorbidities, race, type of treating facility, histology, T-stage (based on tumor size). Balanced cohorts were created using one-to-one nearest-neighbor matching using the logit of the propensity score with a caliper width of 0.001. Absolute standardized mean differences were used to assess balance after matching using a threshold of 0.1 for adequate balance.

The Kaplan-Meier method was applied to compute 3-year OS estimates in patients with available follow-up information. OS was defined from the time of diagnosis to the last follow-up or death. The events underwent right censoring at 84 months. Curves were compared using the log-rank test. A Cox proportional hazard regression was used to estimate the hazard ratio (HR) for all-cause mortality and its corresponding 95% confidence interval (CI). A landmark analysis excluding patients who died before the median time from diagnosis to surgery was performed to account for immortal time bias. Last, in the 2015 to 2019 cohort, a multivariable Cox regression analysis was separately performed to evaluate factors associated with OS in the surgery and CRT groups. For this multivariable analysis, we also used stepwise backward elimination ($p = 0.10$ for stepwise removal) selecting covariates based on clinical reasoning, and including factors that have been associated with mortality for patients with NSCLC in

previous literature.[10] All statistical tests were two sided and considered significant with a p value less than 0.05. Statistical analyses were performed using SPSS version 29 (IBM Corporation, Armonk, NY) and R Core Team 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General Characteristics

In the entire cohort, a total of 44,756 patients with T3-4N2M0 NSCLC were identified, of whom only 3928 patients (8.8%) underwent S as part of a multimodality treatment regimen. In contrast, 29,798 patients (66.6%) received CRT and 11,030 patients (24.6%) received ST only. The median age was 68 (interquartile range [IQR] 60–75) years, 25,737 patients (57.5%) were male, and 37,314 patients (83.4%) were white. Patients had T4 and T3 tumors in 77.9% and 22.1% of the cases, respectively. Compared with those patients who received CRT and ST only, patients who underwent S were younger, had fewer comorbidities, and were more likely to be white. In addition, patients who received S were more likely to be treated in an academic facility, to have private insurance, and to have income above median national levels. Patients who underwent S were also more likely to be treated in the early time period of the study (2010–2014), to have adenocarcinoma histology, and to have T3 tumors than those patients who received CRT or ST alone, but were less likely to receive immunotherapy (Table 1).

Among the patients who underwent S, 2255 patients (57.4%) received neoadjuvant ST and 1505 patients (38.3%) received radiotherapy before resection. The most common approach for patients with T3-4N2 NSCLC was open thoracotomy (55.3%), and the most common procedure performed was lobectomy (89.5%). Pneumonectomy was only performed in 0.8% of patients. A total of 83 patients (5.5%) underwent a salvage resection (>180 d after the start of neoadjuvant therapy). The median number of lymph nodes sampled was 11 (IQR 6–17), and 504 patients (12.8%) had positive resection margins. Notably, only 141 patients (3.6%) required a 30-day unplanned readmission, and the proportion of patients with 30- and 90-day mortality were 1.5% and 4.7%, respectively (Table 2). These outcomes were similar when comparing patients operated on in the "early" and "recent" time periods (Supplementary Table 2).

Trends and Geographic Patterns

There was a significant difference in the delivery of S by geographic region, with the highest utilization of S in New England (12.8%) and the lowest in the East South-Central region (6.9%) ($p < 0.001$) (Supplementary Table 3). Over time, there was a trend toward decreased utilization of S, with 9.8% of patients undergoing S in 2010 down to only 6.3% by 2019 ($p < 0.001$) (Fig. 2).

Associations With Surgery for cT3/4N2M0 Disease

In multivariable logistic regression analysis, younger age, the presence of fewer than two comorbidities, treatment at an academic facility, geographic location of the treating facility, insurance status, income above median national levels, adenocarcinoma histology, and T3 as opposed to T4 tumors were independently associated with the use of S (Table 3).

Survival Analysis Among Groups Receiving Definitive Therapy

In the entire (unmatched) cohort (median follow-up 41.6 mo [IQR: 23.5–68.1] in survivors), patients who underwent S had better OS (HR 0.48, 95% CI: 0.46–0.51; median OS: 51.3 versus 19.8 mo, $p < 0.001$) when compared with patients who underwent CRT. After propensity score matching, there were no differences among the groups in the adjusted covariates (Supplementary Tables 4 and 5). Concordantly, after propensity matching (N = 3722 CRT versus N = 3722 S), S was still associated with better OS (HR 0.59, 95% CI: 0.56–0.63; median OS 49.7 versus 25.0 mo, $p < 0.001$) compared with CRT. These findings remained constant when estimating OS differences in distinct propensity-matched cohorts from different time periods: ([2010–2014: N = 2066 CRT versus N = 2066 S, HR: 0.53, 95% CI: 0.50–0.57] [median OS 42.3 versus 19.8 mo, $p < 0.001$]) and ([2015–2019: N = 1543 CRT versus N: 1543 S, HR: 0.59, 95% CI: 0.53–0.65] [median OS 59.1 versus 32.2 mo, $p < 0.001$]) (Fig. 3), and before and after adjusting for immortal time bias (landmark time: 2.66 mo) (Supplementary Tables 6 and 7). Of note, the median OS in both CRT and S groups was longer in the recent than in the early cohort. The median OS of patients who underwent ST only (excluded from matched cohorts) was 8.9 months (Supplementary Table 6). Last, in multivariable Cox regression analysis, patient age, sex, type of treating facility, and type of procedure performed were associated with OS in the S group. In contrast, among patients who received CRT, patient age, Charlson-Deyo index, type of facility, T-stage, and histology were associated with OS (Supplementary Tables 8 and 9).

Discussion

This retrospective review of national data highlights that surgical resection, as part of a multimodality approach, is positively associated with OS for patients with T3/4N2M0 NSCLC. Undoubtedly, these patients

Table 1. Characteristics of All Study Participants

Variable	ST[a] (N = 11,030)	CRT[a] (N = 29,798)	S[a] (N = 3928)	Total[a] (N = 44,756)	*p* Value
Age[b]	72 (64-79)	67 (60-73)	64 (56-70)	68 (60-75)	<0.001
Sex					
Male	6067 (55.0)	17,502 (58.7)	2168 (55.2)	25,737 (57.5)	
Female	4963 (45.0)	12,296 (41.3)	1760 (44.8)	19,019 (42.5)	0.002
Charlson-Deyo index					
0	5918 (53.7)	17,724 (59.5)	2458 (62.6)	26,100 (58.3)	<0.001
1	3067 (27.8)	7846 (26.3)	1005 (25.6)	11,918 (26.6)	
2	1231 (11.2)	2802 (9.4)	339 (8.6)	4372 (9.8)	
≥3	814 (7.4)	1426 (4.8)	126 (3.2)	2366 (5.3)	
Race					
White	9027 (81.8)	24,906 (83.6)	3381 (86.1)	37,314 (83.4)	<0.001
Black	1561 (14.2)	3921 (13.2)	368 (9.4)	5850 (13.1)	
Other	442 (4.0)	971 (3.3)	179 (4.6)	1592 (3.6)	
Treating facility					
Community	5723 (51.9)	15,489 (52.0)	1548 (39.4)	22,760 (50.9)	<0.001
Academic	5307 (48.1)	14,309 (48.0)	2380 (60.6)	21,996 (49.1)	
Geographic region					
New England	624 (5.7)	1727 (5.8)	345 (8.8)	2696 (6.0)	<0.001
Middle Atlantic	1698 (15.4)	4209 (14.1)	775 (19.7)	6682 (14.9)	
South Atlantic	2586 (23.4)	7198 (24.2)	826 (21.0)	10,610 (23.7)	
East North Central	2047 (18.6)	6158 (20.7)	712 (18.1)	8917 (19.9)	
East South Central	1006 (9.1)	2705 (9.1)	276 (7.0)	3987 (8.9)	
West North Central	805 (7.3)	2530 (8.5)	293 (7.5)	3628 (8.1)	
West South Central	812 (7.4)	1915 (6.4)	216 (5.5)	2943 (6.6)	
Mountain	301 (2.7)	762 (2.6)	94 (2.4)	1157 (2.6)	
Pacific	1151 (10.4)	2594 (8.7)	391 (10.0)	4136 (9.2)	
Insurance					
Uninsured/Medicaid	1112 (10.1)	3894 (13.1)	380 (9.7)	5386 (12.0)	<0.001
Government	7925 (71.8)	17,781 (59.7)	1853 (47.2)	27,559 (61.6)	
Private	1993 (18.1)	8123 (27.3)	1695 (43.2)	11,811 (26.4)	
Income level					
< National median	5280 (47.9)	14,188 (47.6)	1525 (38.8)	20,993 (46.9)	<0.001
> National median	5750 (52.1)	15,610 (52.4)	2403 (61.2)	23,763 (53.1)	
Area of residence					
Non-Metropolitan	2054 (18.6)	6293 (21.1)	763 (19.4)	9110 (20.4)	0.13
Metropolitan	8976 (81.4)	23,505 (78.9)	3165 (80.6)	35,646 (79.6)	
Year of diagnosis					
2010-2014	5772 (52.3)	14,776 (49.6)	2246 (57.2)	22,794 (50.9)	<0.001
2015-2019	5258 (47.7)	15,022 (50.4)	1682 (42.8)	21,962 (49.1)	
Histologic type					
Adenocarcinoma	3953 (35.8)	10,007 (33.6)	1951 (49.7)	15,911 (35.6)	<0.001
Squamous	5641 (51.1)	16,230 (54.5)	1598 (40.7)	23,469 (52.4)	
Other	1436 (13.0)	3561 (12.0)	379 (9.6)	5376 (12)	
Immunotherapy	1203 (10.9)	3387 (11.4)	164 (4.2)	4754 (10.6)	<0.001
Clinical T designation					
T3 (5-7 cm or invasion)	2095 (19.0)	6550 (22.0)	1249 (31.8)	9894 (22.1)	<0.001
T4 (>7 cm or invasion)	8935 (81.0)	23,248 (78.0)	2679 (68.2)	34,862 (77.9)	

[a]N, (%).
[b]Median, interquartile range.
CRT, chemoradiotherapy; S, surgical resection as part of multimodality approach; ST, systemic therapy only.

were carefully selected and are not reflective of all patients with stage IIIB NSCLC. Still, our study reveals that the use of surgery has decreased over time and that surgery is not uniformly offered for patients with T3/4N2, stage IIIB NSCLC in all regions of the United States. Last, we identified that the use of surgery may be associated with social determinants of health, highlighting actionable characteristics that may be targeted to prevent widening outcome gaps for patients with locally advanced lung cancer.

Table 2. Characteristics of Patients With T3-4N2 NSCLC Who Underwent Surgery as Part of Multimodality Approach

Variable	S[a] (N = 3928)
Sequence of systemic therapy	
Neoadjuvant	2255 (57.4)
Adjuvant	1584 (40.3)
Unknown	89 (2.3)
Sequence of radiotherapy	
Before surgery	1505 (38.3)
After surgery	1132 (28.8)
No radiotherapy	1291 (32.9)
Days from neoadjuvant to surgery[b,c]	89 (74-113)
Type of approach	
Robotic	238 (6.1)
Thoracoscopic	609 (15.5)
Open	2173 (55.3)
Unknown	908 (23.1)
Extent of resection	
Segmentectomy	381 (9.7)
Lobectomy	3516 (89.5)
Pneumonectomy	31 (0.8)
Salvage resections[d] (N = 1505)	83 (5.5)
Pathologic T-stage	
T1	464 (11.8)
T2	923 (23.5)
T3	1129 (28.7)
T4	382 (9.7)
Unknown	1030 (26.2)
Pathologic N-stage	
N0	1375 (35.0)
N1	473 (12.0)
N2	1442 (36.7)
N3	7 (0.2)
Unknown	631 (16.1)
Number of lymph nodes sampled[b]	11 (6-17)
Number of positive lymph nodes (N = 3419)	
0	1281 (37.5)
1-5	1712 (50.1)
6-10	292 (8.5)
>10	134 (3.9)
Margins	
Negative	3245 (82.6)
Positive	504 (12.8)
Other/Unknown	179 (4.6)
30-d unplanned readmission	141 (3.6)
30-d mortality	59 (1.5)
90-d mortality	185 (4.7)

[a]N, (%).
[b]Median, interquartile range.
[c]In patients who received chemotherapy/radiotherapy before surgery.
[d]Patients who underwent resection more than 180 days after neoadjuvant chemotherapy/radiation.

It is critical to acknowledge that the ideal treatment approach for patients with stage III NSCLC remains undetermined. The value of surgery in this setting was appropriately questioned after several older trials suggested no OS benefit with the addition of surgery to multimodality therapy.[11,12] Unlike our cohort, those trials included a higher proportion of patients undergoing pneumonectomy. In contrast, the low proportion of pneumonectomies observed in our study suggests that surgery is currently often avoided in patients with stage IIIB disease who may require pneumonectomy. Despite improvements in disease-free survival and OS in post hoc subgroup analyses of older trials,[11,12] it has been argued that the potential morbidity of surgical resection may be unjustified given the apparent lack of OS benefit in the intent-to-treat populations. The move away from surgical therapy for patients with stage III lung cancer was further increased after the exceptional outcomes reported in the PACIFIC trial and after the U.S. Food and Drug Administration approval in 2018 of durvalumab for patients with unresectable stage III NSCLC after definitive chemotherapy and radiation.[1] Given the success of that treatment regimen, it seems from our data that surgery has likely been particularly avoided in patients with T3/T4N2 stage IIIB tumors, a stage group generally not considered resectable.[11,12] In this study, only 6.3% of cT3/4N2 patients received surgery in 2019, the most recent year evaluated. Nevertheless, this preference for chemoradiation followed by immunotherapy has been challenged by the increased adoption of neoadjuvant and perioperative chemotherapy and immunotherapy approaches, following positive outcomes reported in several trials which included patients with stage IIIB NSCLC.[6,13]

Data from the present NCDB study, from a time period generally before the incorporation of immunotherapy to the neoadjuvant treatment paradigm, suggest that surgical resection as part of a multimodality treatment approach is unlikely to lead to poor outcomes in carefully selected patients with T3/4N2 stage IIIB disease. In patients selected for surgery, patient age, sex, the type of treating facility, and the procedure performed are associated with improved OS. Importantly, in our study, perioperative morbidity and mortality after surgery did not exceed other contemporary reports.[14] Although these retrospective data (even though propensity matched) do not prove that surgery is a better treatment strategy than chemoradiation, it provides valuable insights into the survival outcomes of patients who were selected for each modality in this setting and supports further prospective trials comparing specific contemporary treatment combinations (such as PACIFIC versus an immunotherapy-based perioperative approach). Clearly, selection bias exists in the group of patients who were considered for surgery. The definition of surgical resectability is highly variable, generally taking several factors into consideration: (1) oncologic factors (the likelihood of subsequent metastatic disease), (2) technical resectability (ability to resect tumor/nodes without compromising vital structures or affecting function), and (3) operability (can the patient tolerate an

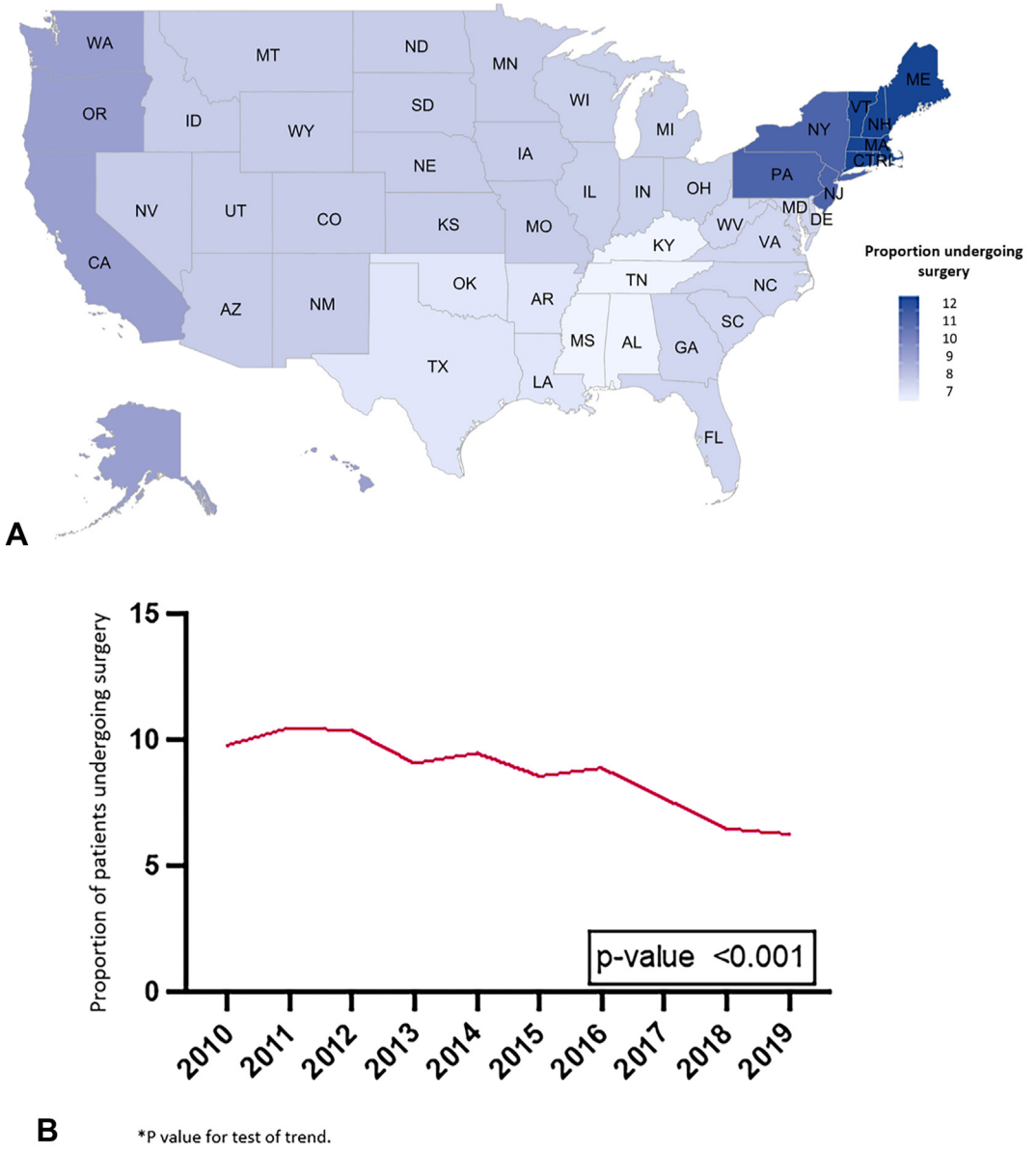

Figure 2. (*A*) Geographic distribution of surgery delivery in the United States. (*B*) Trends in use of surgery over time.

oncologically appropriate operation).[11,12] Nevertheless, if the tumor is deemed resectable and the patient operable, well-selected patients with T3 or T4 tumors and N2 disease may benefit from surgery, regardless of tumor size.[13] Other recent single-institution studies have revealed results consistent with our findings.[15–17]

In the broader treatment context, driven by improvements in both systemic and local therapies, there has been an increase over time in the survival of patients with stage III NSCLC, which was also found in our study.[18] This may be due to better patient selection, new cancer therapeutics, and improved synergy between treatment modalities.[17] Given the exciting potential of neoadjuvant and perioperative chemotherapy and immunotherapy strategies, we believe that patients with stage III NSCLC should at least undergo multidisciplinary evaluation for surgical resection. Another large, retrospective study has also reported associations of surgical resection with OS compared with chemoradiation-based approaches in patients with stage III NSCLC.[19] There may be situations or patient-specific factors where surgery could be considered preferable to chemoradiation, an approach that may have drawbacks in some patients, including increased treatment-related toxicity and potentially lower rates of locoregional control with large tumors.[20] In addition, given that only patients who tolerated chemoradiation and had no progression after treatment were accrued to PACIFIC, the notion that

Table 3. Logistic Regression Analysis for Factors Associated With Surgery

Variable	Adjusted OR	95% Confidence Limits	*p* Value
Age < 68 y (Ref.> 68)	1.52	1.35-1.71	<0.001
CCI 0 or 1 (Ref.: CCI ≥ 2)	1.22	1.05-1.42	0.012
Academic facility (Ref.: community)	1.70	1.52-1.89	<0.001
Geographic location			
East South Central	Ref.	Ref.	<0.001
New England	1.77	1.36-2.30	
Middle Atlantic	1.48	1.18-1.87	
South Atlantic	1.05	0.84-1.31	
East North Central	0.96	0.76-1.21	
West North Central	0.84	0.63-1.12	
West South Central	1.20	0.91-1.59	
Mountain	1.28	0.89-1.85	
Pacific	1.41	1.09-1.81	
Insurance			
Uninsured/Medicaid	Ref.	Ref.	<0.001
Public insurance	1.54	1.02-2.33	
Private insurance	2.44	1.61-3.69	
Above median national income (Ref.: below median)	1.30	1.16-1.45	<0.001
Histology			
Squamous	Ref.	Ref.	<0.001
Adeno	1.48	1.22-1.79	
Other	0.83	0.68-1.06	
Clinical T-3 tumors (Ref.: Clinical T-4 tumors)	1.70	1.53-1.89	<0.001

Note: Covariates in the last step of backward elimination presented. Covariates in first step included the following: age, sex, CCI, race, type of facility, geographic region, insurance, income, area of residence, histology, clinical T-stage.
CCI, Charlson-Deyo index; Ref., reference.

chemoradiation is superior to surgical resection remains speculative, particularly in the case of large tumors. The PACIFIC trial was not designed to determine how many patients are unable to complete chemoradiation or to characterize the treatment-associated morbidity and mortality of chemoradiation. Nevertheless, in the treatment arm of the recently presented PACIFIC 2 trial which assessed patients from the time of treatment allocation (concurrent chemoradiation and durvalumab versus chemoradiation for patients with unresectable stage III NSCLC), adverse treatment events leading to death within 4 months occurred in 6.8% of patients in the concurrent treatment arm.[7] The high treatment-related mortality was suggested in part to be related to the high proportion of cT4 tumors (57.5%) in the cohort. Even in the chemoradiation arm alone, adverse events leading to death within 4 months occurred in 4.6% of patients, which is higher than the 90-day surgical mortality reported in seminal neoadjuvant trials (which admittedly also included patients with less extensive

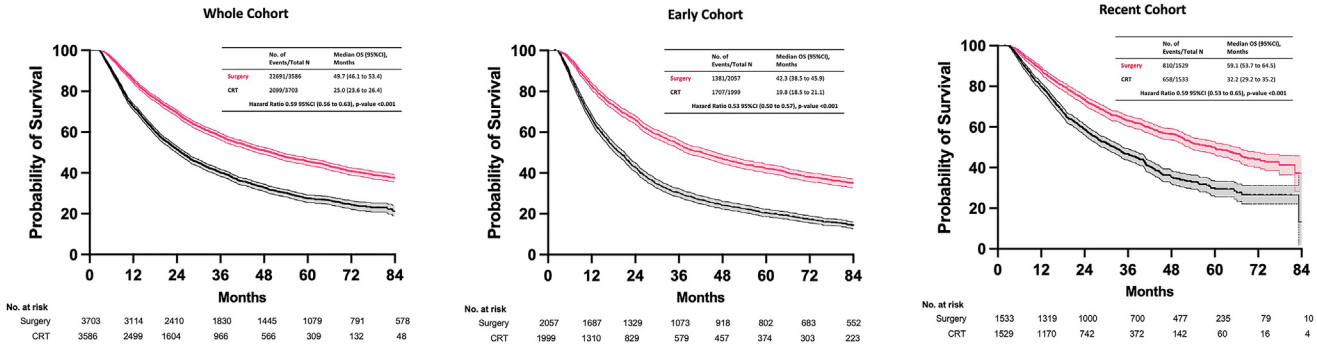

Figure 3. Survival analysis in matched set (adjusted for immortal time bias).

tumors). In addition to describing the treatment-related morbidity and mortality of chemoradiation in patients with large primary tumors, the results of PACIFIC-2 raised concerns regarding the apparent lack of efficacy of concurrent chemoradiation and immunotherapy in these patients (median progression-free survival 13.8 mo) and failed to replicate the survival found in patients in the original PACIFIC trial.[7] It is also notable that the recently published COAST trial reported a worse-than-expected median PFS of only 6.3 months (95% CI: 3.7–11.2) in the control chemoradiation plus durvalumab arm.[21] Clearly, there remain room for improvement in the treatment of patients with "unresectable" stage III NSCLC.

Although we await future trials, it is hoped that, we will be presented with granular details from large neoadjuvant randomized phase 3 studies to help determine which subsets of stage III patients experienced the most benefit from neoadjuvant and perioperative approaches and which patients were at the highest risk for morbidity.[4–6,13] Certainly, appropriate concern exists that the surgical results presented in this study for carefully selected patients may not be replicated in the general population, particularly considering that most patients in our chemoradiation group did not receive immunotherapy. Still, our study highlights that the OS of stage IIIB (N2) patients has improved over time with both therapeutic strategies and lays the foundation for further prospective studies to compare contemporary approaches. In addition, strategies in which neoadjuvant immunotherapy or chemotherapy plus immunotherapy are given before, rather than concurrent with chemoradiation, may be attractive and may allow for more personalized approaches to radiation therapy in patients with large tumor volumes.[22] As advances in systemic treatment allow us to consider more aggressive locoregional approaches in patients with locally advanced disease, patient selection will become critical and the timing for the choice of surgical therapy versus radiation may be best made after neoadjuvant or induction chemotherapy and immunotherapy. In this setting, the potential benefits of surgery must always be balanced with the complexity and potential morbidity of the operation and presented to the patient as part of a shared decision-making process.[10] Nevertheless, uniformly declaring stage IIIB (N2) patients unresectable should not be the standard practice.

Limitations

Our study has several limitations. First, there were significant missing data that can compromise the internal and external validities of our findings. The reasons why surgery was or was not used are not captured. This likely introduces selection bias in favor of the S group and may overestimate its real benefit in comparison with CRT in the general population. Similarly, the NCDB lacked information on the intent-to-treat basis and only captured the ultimately delivered treatment. This limited our ability to identify patients who were considered for surgery but ended up receiving ST only due to disease progression before resection. In addition, although T-classification can reflect either tumor size or invasion of surrounding structures, the NCDB did not provide the reason for T-designation. Similarly, there was no granular information on which N2 nodal stations were positive by clinical staging or whether the nodal disease was considered "bulky" or "multi-station." Thus, more patients in the CRT group may have had technically unresectable tumors (T4 with invasion and bulky/multi-station N2 disease) with potentially worse survival compared with S, where all tumors were thought to be resectable by definition. This could limit the generalizability of our findings to patients with these characteristics. We also had no data on the specific ST agents used, the number of cycles given, and the sequence of different systemic therapies (immunotherapy or chemotherapy). This limits our ability to understand to a granular level whether surgery is particularly synergistic with a specific systemic treatment. We lacked information on whether there was histologic confirmation for clinical N2 disease, disease progression, cause of death, and the delivery of salvage therapies. Our study lacks information on comprehensive molecular testing, program death ligand 1 status, and whether targeted therapy was given. Last, there may be other unmeasured confounders that could affect the associations reported including functional status, pulmonary function tests, extent of nodal involvement, and other patient and tumor factors. Considering these limitations, the study should only be considered to be hypothesis generating to promote further investigation of the outcomes of patients with stage IIIB disease.

Conclusion

In a national retrospective review of patients with clinical T3/4N2M0, stage IIIB NSCLC, undergoing surgical resection as part of a multimodality approach was positively associated with OS outcomes in a contemporary cohort. Despite the potential benefits of surgery, its use has decreased over time and there is marked heterogeneity of utilization by geographic region. Although we await prospective data to validate these findings, the thoracic oncology community should continue to evaluate resectability criteria. Stage IIIB designation alone should not exclude T3-4N2M0 patients from surgical consideration. This study provides a foundation for further prospective studies to be conducted to compare

the efficacy of contemporary treatment modalities in stage IIIB (N2) disease.

CRediT Authorship Contribution Statement

J. Humberto Rodriguez-Quintero: Conceptualization, Formal Analysis, Methodology, Software, Investigation, Data Curation, Writing.

Rajika Jindani: Resources, Methodology, Software, Investigation.

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Isaac Loh: Conceptualization, Methodology, Investigation.

Anne Montal: Conceptualization, Methodology, Investigation.

Marc Vimolratana: Conceptualization, Methodology, Investigation.

Neel P. Chudgar: Conceptualization, Methodology, Investigation.

Nitin Ohri: Conceptualization, Methodology, Investigation, Writing, Supervision.

Balazs Halmos: Conceptualization, Methodology, Investigation, Writing, Supervision.

Brendon M. Stiles: Conceptualization, Methodology, Investigation, Writing, Supervision.

Disclosure

Dr. Stiles reports receiving consulting fees or research support from Medtronic, AstraZeneca, Genentech, Pfizer, Arcus Biosciences, Merck, Bristol Myers Squib, BMS Foundation, Galvanize Therapeutics, Medtronic, and Regeneron. Dr. Halmos reports receiving consulting fees, receiving research support, or serving on the advisory boards of Apollomics, Boehringer Ingelheim, AstraZeneca, Merck, Bristol Myers Squibb, Advaxis, Amgen, AbbVie, Daiichi, Pfizer, GlaxoSmithKline, Beigene, Janssen, Black Diamond Therapeutics, Forward Pharma, Numab, Arrivent, Takeda, Genentech, Eli Lilly, Arcus, Merus, Precede, eFECTOR, and City of Hope. Dr. Ohri reports receiving consulting fees or research support from Merck, Reflexion Medical, AstraZeneca, and Genentech. Dr. Chudgar reports receiving consulting fees from AstraZeneca. Dr. Jindani reports receiving research support (Grant# 312362) from the National Institutes of Health. The remaining authors declare no conflicts of interest.

Acknowledgments

This research was performed by the 1964 Helsinki Declaration and its later amendments and was reviewed by our institutional review board. Institutional review board approval was waived due to the deidentified nature of the data.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100766.

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