En bloc chest wall resection in locally advanced cT3N2 (stage IIIB) lung cancer involving the chest wall: Revisiting guidelines

Joseph F. Zywiciel, BS,[a] Raymond A. Verm, MD,[b] Wissam Raad, MD,[a,b] Marshall Baker, MD, FACS,[a,c,d] Richard Freeman, MD, MBA,[a,b] and Zaid M. Abdelsattar, MD, MS, FACS[a,b,d]

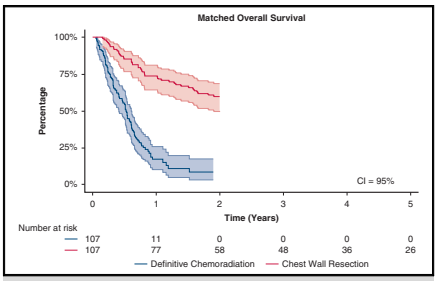
ABSTRACT

Objectives: Current National Comprehensive Cancer Network guidelines recommend definitive chemoradiation rather than surgery for patients with locally advanced clinical stage T3 and N2 (stage IIIB) lung cancer involving the chest wall. The data supporting this recommendation are controversial. We studied whether surgery confers a survival advantage over definitive chemoradiation in the National Cancer Database.

Methods: We identified all patients with clinical stage T3 and N2 lung cancer in the National Cancer Database from 2004 to 2017 who underwent a lobectomy with en bloc chest wall resection and compared them with patients with clinical stage T3 and N2 lung cancer who had definitive chemoradiation. We used propensity score matching to minimize confounding by indication while excluding patients with tumors in the upper lobes to exclude Pancoast tumors. We used 1:1 propensity score matching and Kaplan–Meir survival analyses to estimate associations.

Results: Of 4467 patients meeting all inclusion/exclusion criteria, 210 (4.49%) had an en bloc chest wall resection. Patients undergoing surgical resection were younger (mean age = 60.3 ± 10.3 years vs 67.5 ± 10.4 years; $P < .001$) and had more adenocarcinoma (59.0% vs 44.5%; $P < .001$) but were otherwise similar in terms of sex (37.1% female vs 42.0%; $P = .167$) and race (Whites 84.3% vs 84.0%; $P = .276$) compared with the definitive chemoradiation group. After resection, there was an unadjusted 30- and 90-day mortality rate of 3.3% and 9.5%, respectively. A substantial survival benefit with surgical resection persisted after propensity score matching (log-rank $P < .001$).

Conclusions: In this large observational study, we found that in select patients, en bloc chest wall resection for locally advanced clinical stage T3 and N2 lung cancer was associated with improved survival compared with definitive chemoradiation. National Comprehensive Cancer Network guidelines should be revisited. (JTCVS Open 2024;18:221-31)



Propensity-matched survival analysis of definitive chemoradiation versus chest wall resection.

CENTRAL MESSAGE

Select patients with cT3N2 stage IIIB locally advanced lung cancer invading the chest wall can be treated with en bloc chest wall resection, which is associated with improved overall survival compared with definitive chemoradiation. NCCN guidelines should be revisited.

PERSPECTIVE

The results of this observational study highlight the role of surgery as a potential treatment modality in patients with cT3N2 lung cancer invading the chest wall, contrary to NCCN guidelines.

See Discussion on page 232.

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Patients with stage IIIB non–small cell lung cancer (NSCLC) present a spectrum of challenges to the modern thoracic oncologist.[1] Traditionally, surgical resection is

From the [a]Stritch School of Medicine, Loyola University Chicago, Chicago, Ill; Departments of [b]Thoracic & Cardiovascular Surgery, and [c]Surgery, Loyola University Medical Center, Maywood, Ill; and [d]Edward Hines, Jr VA Hospital, US Department of Veterans Affairs, Hines, Ill.

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Address for reprints: Zaid M. Abdelsattar, MD, MS, FACS, Loyola University Medical Center, 2160 S 1st Ave, Bldg 110, Room 6260, Maywood, IL 60153 (E-mail: Zaid.Abdelsattar@lumc.edu).

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Abbreviations and Acronyms
cT3N2 = clinical stage T3 and N2
NCCN = National Comprehensive Cancer Network
NCDB = National Cancer Data Base
NSCLC = non–small lung cell cancer

not offered to these patients. This is generally the practice for patients presenting with chest wall invasion and mediastinal N2 disease. In fact, the National Comprehensive Cancer Network (NCCN) consensus panel recommends definitive chemoradiation therapy as the only treatment option for $cT3_{(invasion)}N2$ disease and does not explore the role of surgery.[1,2] Although the role of en bloc chest wall resection is established for patients without nodal disease,[3-6] the presence of lymph nodes is commonly viewed as a poor prognosticator.[7,8] Older studies have debated the role of surgery when there is N2 nodal disease.[7,9,10]

However, surgery remains the cornerstone of multimodal therapy and, in many instances, is the only chance for cure for locally advanced lung cancer.[11-13] In the era of minimally invasive approaches, improvements in chemotherapy, immunotherapy, and targeted therapy, one would argue that *select* stage IIIB and particularly non-Pancoast $cT3_{(invasion)}N2$ disease can be resected with favorable outcomes.[14,15] This pattern of locoregional invasion is not common, but it does create a significant knowledge gap on how to best manage these patients because they are not common in randomized trials, and, to date, there have not been any large observational studies clarifying the role of surgery for this tumor presentation.

In this context, we examine treatment patterns and outcomes for locally advanced stage IIIB $cT3_{(invasion)}N2$ NSCLC from a hospital-based, nationally representative database. Specifically, we compare overall survival outcomes for definitive chemoradiation without surgery, which is the current NCCN recommendation, with en bloc chest wall resection with or without multimodal therapy. The findings can help guide tumor board discussions and highlight the need to revisit current consensus guidelines.

MATERIAL AND METHODS

Data Source

We used nationally representative data from the National Cancer Data Base (NCDB) for this study. The NCDB is a prospective national cancer registry maintained by the American College of Surgeons and the American Cancer Society. It collects data from more than 1500 Commission on Cancer–accredited centers across the United States that capture approximately 70% of all newly diagnosed cases of cancer annually and contains more than 34 million patient records and so is a national hospital-based database.[16] It includes data regarding patient demographics, diagnosis, tumor characteristics, staging, treatment strategy, and perioperative and long-term outcomes. The Loyola University Chicago Institutional Review Board reviewed and approved this research study's proposal, deeming it exempt with a waiver of individual consent (LU215469: 11/4/2021).

Patient Population

We included in this study all patients aged 18 years or older diagnosed with NSCLC between 2004 and 2017. Patients were identified using International Classification of Disease Oncology-3 location codes for lung cancer (C34.0-34.9). We only included patients who had clinical stage T3 and N2 (cT3N2) staging in accordance with the American Joint Committee on Cancer 6th and 7th edition staging systems. We then classified patients as having a chest wall resection based on the site-specific surgery code "46", which denotes lobectomy or bilobectomy *with* chest wall resection.[17]

To make the cohort as homogenous as possible, we excluded patients with an upper lobe tumor in an effort to exclude Pancoast tumors and keep the cohort of chest wall resection restricted to non-Pancoast patients. We also excluded patients whose cancer involved the main bronchus, because those patients also could have a T3 descriptor in the American Joint Committee on Cancer 6th and 7th editions. Further, we excluded all patients who underwent surgery for cT3N2 lung cancer but did not undergo en bloc chest wall resection. For patients in the definitive chemoradiation cohort, we acknowledge that we cannot definitively state they had chest wall invasion; they could have a cT3 designation from the size of their tumor. We concede that the approximation is imperfect; however, we believe the assumption is acceptable to generate 2 large, similar cohorts for comparison of this rare disease presentation. We excluded patients with cM + disease. We further excluded patients without a radiation dose available.

Patients were divided into 2 cohorts based on if they had received definitive chemoradiation treatment or en bloc surgical resection. The surgical group consisted of individuals who have undergone en bloc resection with or without systemic or chemotherapeutic therapy before intervention.

Main Exposure and Outcome Variables

The receipt of definitive chemoradiation versus en bloc chest wall resection was the main exposure variable. Patients in the chest wall resection group could have had multimodality therapy. Our primary outcome of interest was overall survival as defined by the time from diagnosis to death due to any cause. Other outcomes that were tracked for the resection cohort included margin status, 30-day mortality, 90-day mortality, and hospital length of stay. The NCDB does not track these outcomes for patients without an operation.

Statistical Analysis

Patients' clinical, demographic, and pathologic variables were compared between those who received definitive chemoradiation and those who received en bloc chest wall resection using Student *t* tests for continuous variables and Pearson chi-square test for categorical variables as appropriate. Missing data for categorical variables were grouped into a separate "unknown" category for analysis.

To minimize confounding by indication, we used propensity score matching. Patients receiving en bloc chest wall resection were 1:1 propensity score matched to patients undergoing definitive chemoradiation using the nearest neighbor method without replacement. Propensity scores for each patient were generated from a multivariable logistic regression adjusting for age, sex, race, insurance status, tumor histology, Charlson-Deyo comorbidity index, and type of treating institution (academic or nonacademic). The quality of the match was assessed by comparing the standardized bias between the groups for each variable included in the match. Standardized bias values less than 10% indicate good balance. Next, we used unmatched and matched Kaplan–Meier survival analyses to compare overall survival between the 2 groups (Figure E1).

All data and statistical analyses were conducted using Stata version 17.0 SE (StataCorp LLC). All tests were 2-sided using a P value less than .05. CIs are reported to a 95% confidence level.

RESULTS

Patient Population

Applying all inclusion and exclusion criteria created a study population of 4677 patients (Figure 1). Of those, 210 patients (4.49%) had an en bloc chest wall resection, whereas 4467 patients (95.51%) underwent definitive chemoradiation. Patients in the definitive chemoradiation group were older (mean age: 67.5 ± 10.4 years vs 60.3 ± 10.3 years; $P < .001$) and more likely to be in a lower income quartile compared with those who underwent en bloc chest wall resection. However, they were similar in sex (42% female vs 37.1%; $P = .167$) and race (Whites 84.0% vs 84.3%; $P = .276$), but the definitive chemoradiation cohort had lower rates of adenocarcinoma (44.5% vs 59.0%; $P < .001$). The comorbidity burden was similar, as shown in Table 1. Tumor size was comparable between the 2 groups (6.7 ± 0.89 cm vs 7.0 ± 3.98 cm; $P = .722$). Fewer patients received care at an academic center in the definitive chemoradiation cohort compared with the resection cohort (1547 [27.2%] vs 100 [44.8%], $P < .001$).

All operations were lobectomy/bilobectomy with en bloc chest wall resection. The majority of patients (84.9%) received systemic therapy. Of those, the majority received it in the neoadjuvant setting (72.8%). Likewise, the majority (74.7%) received radiation therapy, which was most commonly in the neoadjuvant setting (72.7%). A total of 143 patients in the resection group received neoadjuvant chemoradiation, neoadjuvant chemotherapy, or neoadjuvant radiation. A total of 172 patients (77.8%) received a procedure or surgery to obtain a biopsy for staging purposes before definitive surgery.

For patients who received neoadjuvant therapy before surgery, 58% were nodally staged as ypN0, 9.8% were staged as ypN1, 16.8% were staged as ypN2, 0.7% were staged as ypN3, and 12% were coded as ypNx. In patients not receiving neoadjuvant therapy, 34.6% had pN0, 7.7% had pN1, 34.6% had pN2, and 20% were coded as pNx (Table 2).

On Kaplan–Meier analysis of unmatched cohorts (Figure 2), en bloc surgical resection was associated with better overall survival compared with definitive chemoradiation (log rank $P < .001$). Median survival and 5-year survival for the definitive chemoradiation cohort were 12.2 months and 11.6%, respectively. Median survival and 5-year survival by node status for the resection cohort were 39.1 months and 40.9%, respectively. Figure 3, *A* and *B* demonstrate survival by nodal status. The number of observations in the ypN1 group is too small to draw any meaningful conclusions from this graph, but it does show that nodal regression to N0 is associated with better survival. In addition, for patients who did not receive neoadjuvant therapy, inaccuracy in clinical staging may be responsible for improved survival.

Propensity Score–Matched Survival Analysis

With propensity score matching, 107 patients undergoing en bloc surgical resection were successfully 1:1 matched with 107 patients undergoing definitive chemoradiation. After matching on age, sex, race, insurance status, tumor histology, comorbidity index, and treatment at an academic

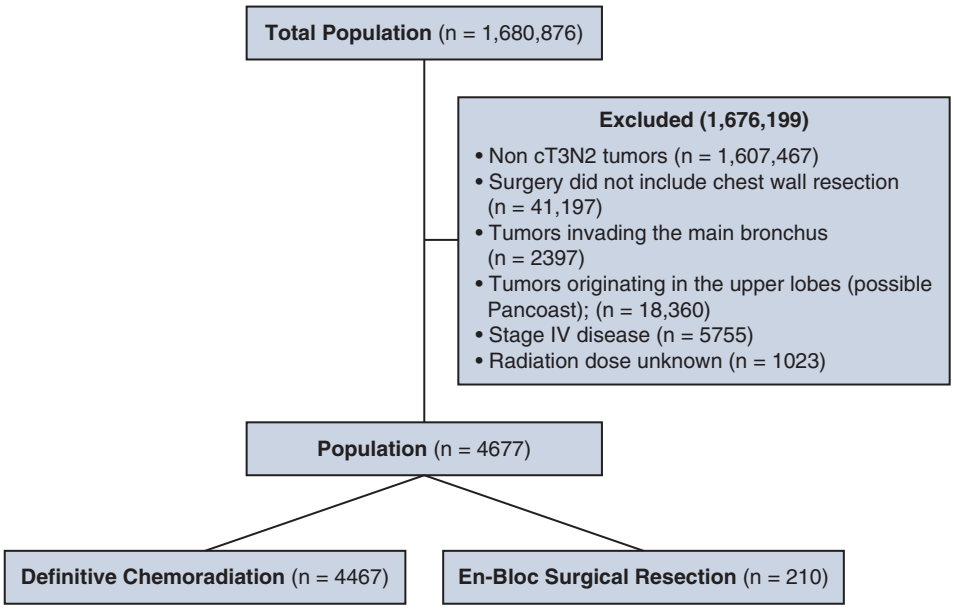


FIGURE 1. CONSORT-type flowchart highlighting exclusion criteria and final cohort.

TABLE 1. Clinical and demographic characteristics of patients undergoing definitive chemoradiation versus en bloc chest wall resection in the overall cohort and matched cohort

	Overall cohort				Matched cohort			
Patient characteristics	Definitive chemoradiation 4467 (95.51)	Chest wall resection 210 (4.49)	*P*	% Standardized bias	Definitive chemoradiation 107 (50)	Chest wall resection 107 (50)	% Standardized bias	*P*
Age, y	67.5 ± 10.4	60.3 ± 10.3	<.001	53.1	67.9 ± 10.1	63.5 ± 8.7	2.1	.996
Female	1874 (42)	78 (37.1)	.167	11.1	34 (31.8)	43 (40.2)	12.3	.200
Race			.276	0.4			21.2	.143
White	3746 (84)	177 (84.3)			86 (80.4)	93 (86.9)		
Black	582 (13.0)	24 (11.4)			20 (18.7)	11 (10.3)		
Other	114 (2.6)	9 (4.3)			1 (0.9)	3 (2.8)		
Unknown	25 (0.6)	0 (0)			0 (0)	0 (0)		
Charlson-Deyo Score			.337	5.8			3.7	.180
0	2669 (59.7)	127 (60.5)			69 (64.5)	67 (62.6)		
1	1250 (28.0)	64 (30.5)			21 (19.6)	30 (28.0)		
≥2	548 (12.3)	29 (9)			17 (15.9)	10 (9.3)		
Insurance status			<.001	14.1			8.6	.144
Uninsured	171 (3.8)	10 (4.8)			6 (5.6)	4 (3.7)		
Private insurance	1237 (27.7)	97 (46.2)			28 (26.2)	43 (40.2)		
Government insurance	2972 (66.5)	98 (46.7)			72 (67.3)	58 (54.2)		
Unknown	87 (1.9)	5 (2.4)			1 (0.9)	2 (1.9)		
Income Quartiles			.007	n/a			n/a	.152
<$38,000	698 (16.6)	23 (11.9)			18 (17.3)	10 (10.2)		
38,000-$47,999	850 (20.2)	30 (15.5)			23 (22.1)	14 (14.3)		
$48,000-$62,999	1286 (30.6)	56 (28.9)			29 (27.9)	32 (32.7)		
≥63,000	1364 (32.5)	85 (43.8)			34 (32.7)	42 (42.9)		
Histology			<.001	17.8			1.7	.051
Adenocarcinoma	1989 (44.5)	124 (59.0)			47 (43.9)	52 (48.6)		
Squamous cell carcinoma	2308 (51.7)	70 (33.3)			56 (52.3)	43 (40.2)		
Other	170 (3.8)	16 (7.6)			4 (3.7)	12 (11.2)		
Tumor size (cm)	6.4 ± 0.89	7.0 ± 3.98	.722	n/a	6.1 ± 2.8	omitted	n/a	n/a
Staging procedure	3796 (85.0)	163 (77.4)	.008	n/a	93 (86.9)	80 (74.8)	n/a	.024
Immunotherapy			.974	n/a			n/a	.364
Did not receive	4427 (99.1)	208 (99.0)			107 (100)	105 (98.1)		
Received	23 (0.5)	1 (0.5)			0 (0)	1 (0.9)		
Unknown	17 (0.4)	1 (0.5)			0 (0.0)	1 (0.9)		
Location			.860	n/a			n/a	.855
New England	278 (6.3)	16 (7.8)			6 (5.6)	9 (8.4)		
Middle Atlantic	626 (14.1)	26 (12.6)			15 (14.0)	14 (13.1)		
South Atlantic	1045 (23.5)	47 (22.8)			34 (31.8)	25 (23.4)		
East North Central	925 (20.8)	48 (23.3)			22 (20.6)	24 (22.4)		
East South Central	433 (9.7)	21 (10.2)			10 (9.3)	10 (9.3)		
West North Central	381 (8.6)	20 (9.7)			7 (6.5)	10 (9.3)		
West South Central	279 (6.3)	9 (4.4)			7 (6.5)	5 (4.7)		
Mountain	135 (3)	4 (1.9)			2 (1.9)	4 (3.7)		
Pacific	343 (7.7)	15 (7.3)			4 (3.7)	6 (5.6)		
Academic institution	1217 (27.2)	94 (44.8)	<.001	28.9	39 (36.4)	33 (30.8)	1.9	.385

Percent standardized bias is reported between prematch and postmatch cohorts. *n/a*, Not available.

TABLE 2. Pathologic nodal status by receipt of neoadjuvant therapy

Pathologic nodal status	Patients, n (%)
Received neoadjuvant therapy	135 (64.29)
ypN0	78 (58.0)
ypN1	13 (9.8)
ypN2	23 (16.8)
ypN3	1 (0.7)
ypNx/Unknown	21 (14.7)
Did not receive neoadjuvant therapy	75 (35.71)
pN0	24 (34.6)
pN1	6 (7.7)
pN2	27 (34.6)
pN3	0 (0)
Unknown	18 (23.1)

Median survival and 5-year survival are reported for entire resection cohort, by neoadjuvant treatment status, and by lymph node status.

center, there were no residual differences between the matched cohorts, except that race became significant. Cohort differences and pre- and postmatch percent standardized bias are reported in Table 1. On Kaplan–Meier analysis of matched cohorts, en bloc surgical resection was still associated with a marked survival benefit (Figure 4, log rank $P < .001$). Median survival and 5-year survival for chemoradiation group were 6.2 months and 0% compared with 27.7 months and 37% for the surgery group, respectively. Pre- and postmatch mirror histograms are reported in Figure 5.

Short-Term Outcomes After Surgery

Unadjusted 30- and 90-day mortality after resection were 3.3% and 9.5%, respectively; 82.8% of patients received an R0 resection, and mean hospital length of stay was 9.28 ± 8.20 days (Table 3). There are no short-term outcomes reported in the NCDB in the absence of surgery. Therefore, no comment can be made on 30-day or 90-day mortality for patients receiving definitive chemoradiation only.

DISCUSSION

In this first and largest nationally representative observational study on patients with non-Pancoast cT3 (invasion) N2 (stage IIIB) lung cancer involving the chest wall, we found that (1) a select few patients (only 4.49%) underwent en bloc chest wall resection; (2) en bloc chest wall resection is associated with substantially improved overall survival even after propensity score matching; and (3) en bloc chest wall resection is safe in the contemporary era. The findings invite revisiting current guidelines and are important to thoracic surgeons and thoracic oncologists as the field continues to evolve multimodal therapeutic options.

The low rate of resection in this subset of patients with locally advanced lung cancer is not surprising given the current guidelines.[1,18] However, tracking the historical evolution of treatment for patients with invasive NSCLC to the chest wall provides some insight. Grillo and colleagues[19] demonstrated in 1966 that invasive tumors to the chest wall were resectable, prolonging survival markedly in some patients. Allen and colleagues[20] pushed treatment further in 1991, noting that N1 disease should not be a contraindication for resection of NSCLC invading the chest wall. Other studies in the early 2000s continued this trend, noting that N2 disease, especially if R0 resection is obtained, is resectable with approximately 20% 5-year survival.[10,21] More recent publications have concluded

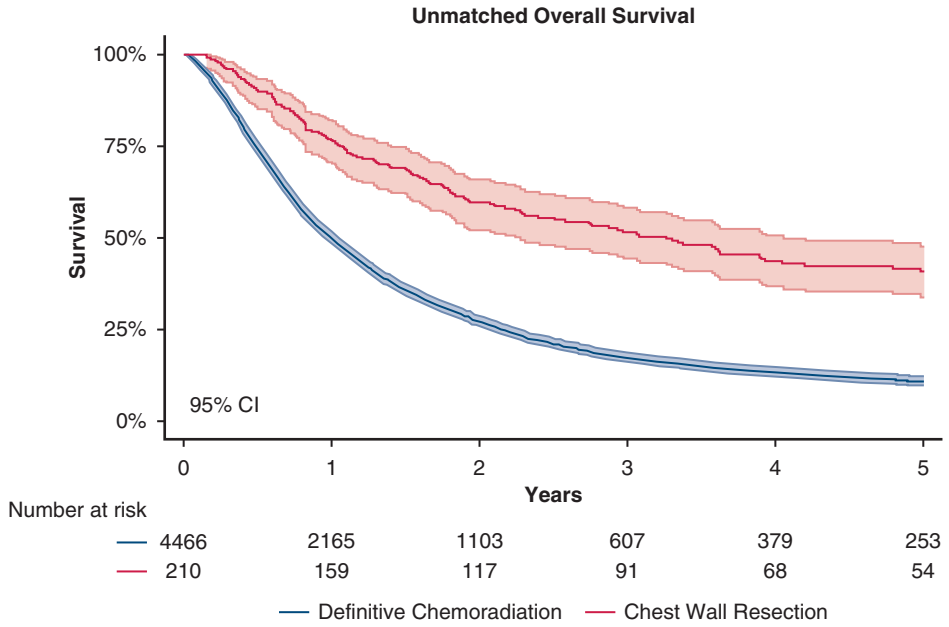


FIGURE 2. Kaplan–Meier survival curve comparing overall survival between unmatched cohorts. *CI*, Confidence interval.

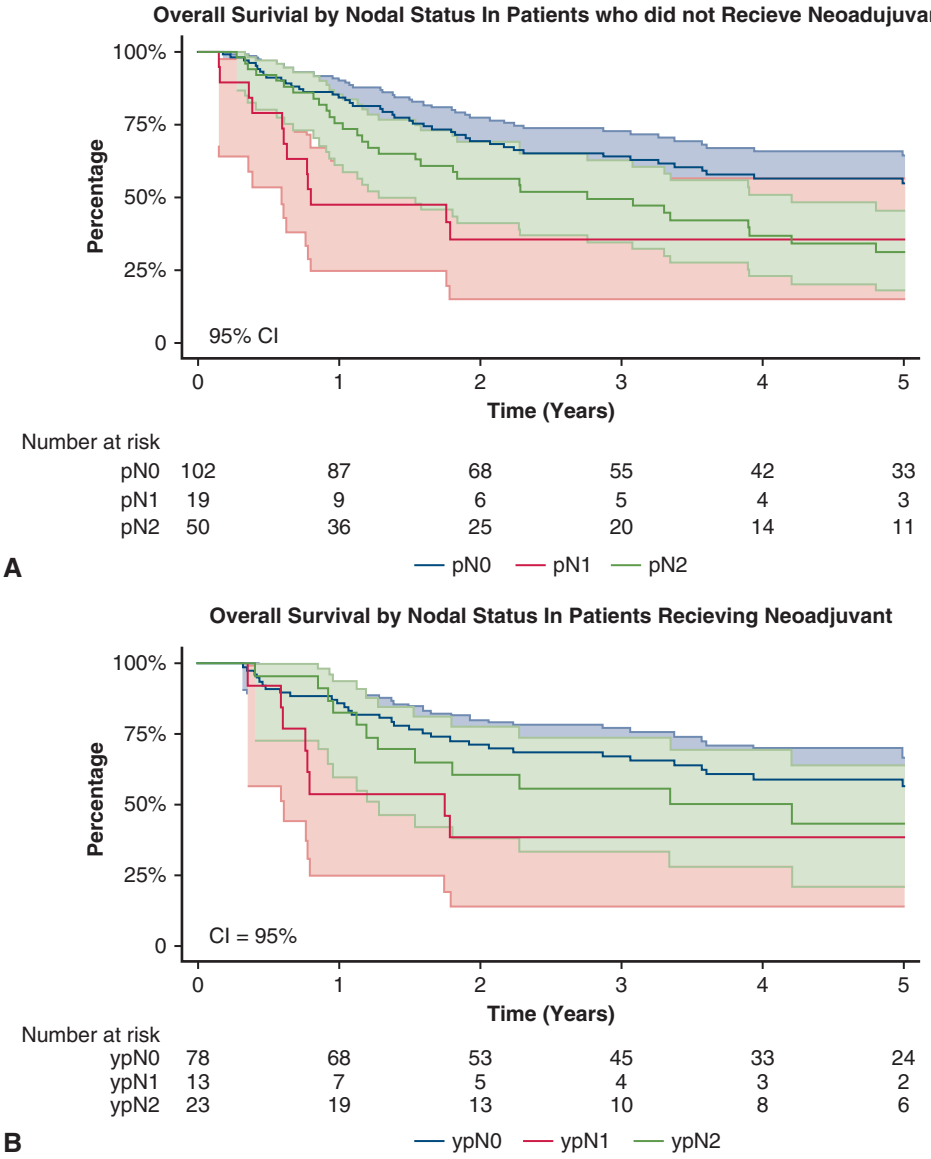


FIGURE 3. Overall survival after en-bloc chest wall resection by pathologic nodal status for patients who (A) did not receive neoadjuvant therapy, and (B) those who received neoadjuvant therapy. *CI*, Confidence interval.

that N2 disease (with or without invading chest wall tumor) should not be used as a contraindication for resection.[12,13,22,23]

We acknowledge that resection of N2 disease in NSCLC is still controversial, especially in the context of invading chest wall tumors.[7,9,24-26] However, due to the rarity of $cT3_{(invasion)}N2$ disease, many of the studies with poor outcomes are older with patients accrued from an era when neoadjuvant chemoradiation was not standard.[7,9,21,26] Additionally, the cohorts were small in several of these studies, which makes drawing statistically significant conclusions difficult.

In this context, we demonstrated 40.9% overall 5-year survival in the unmatched resection cohort compared with 11.6% overall 5-year survival in the definitive chemoradiation cohort. The advancements in systemic chemotherapy for NSCLC should be noted.[14,27] Of 143 patients who had neoadjuvant therapy, 83 (58%) had ypN0 and 14 (10%) had ypN1. The patients with ypN0 had an increased 5-year overall survival of 56%. It is reported that cN2 locally advanced lung cancer was actually pN1 or less in 35% or patients.[23,28] Similarly in our study, 33 of 78 patients who did not receive neoadjuvant therapy were found to be pN0 or pN1. Without a tissue diagnosis of mediastinal nodal

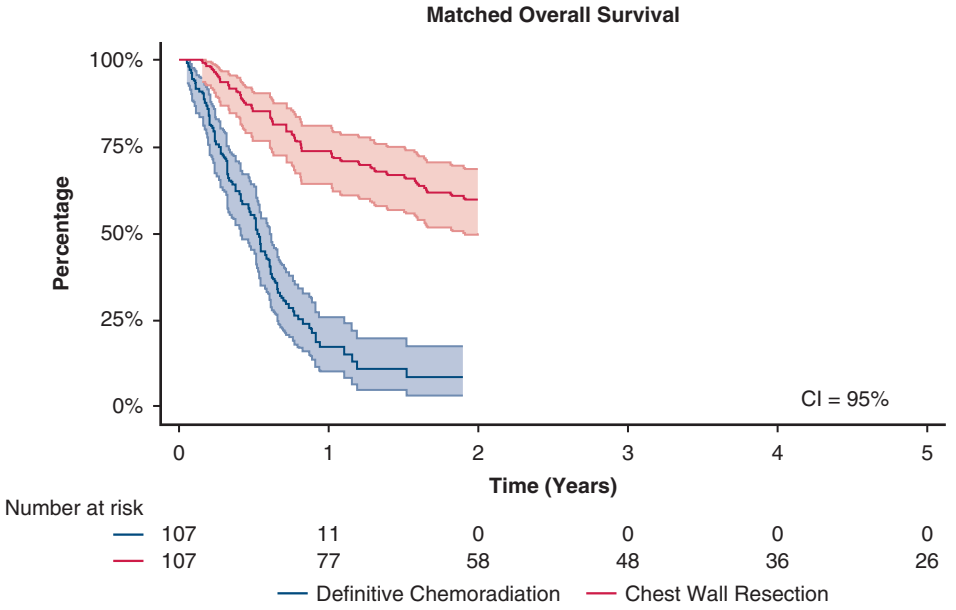


FIGURE 4. Kaplan–Meier survival curve comparing overall survival between propensity-matched cohorts. *CI*, Confidence interval.

disease, patients with resectable disease by current guidelines may not be receiving an appropriate surgery because the designation of cN2 status in general increases the likelihood of nonoperative management.[22] This trend is a possible explanation for why 45% of the resection cohort received care at an academic center and could be confounding the survival outcomes because only 28% of the control arm received care at an academic center. However, the propensity-matched cohort balanced the proportion of patients treated at academic centers (36.3% in control arm and 30.1% in exposure arm) and still yielded a stark and statistically significant difference in overall 5-year survival (median survival 6.2 months for definitive chemoradiation vs 27.7 months in chest wall resection group).

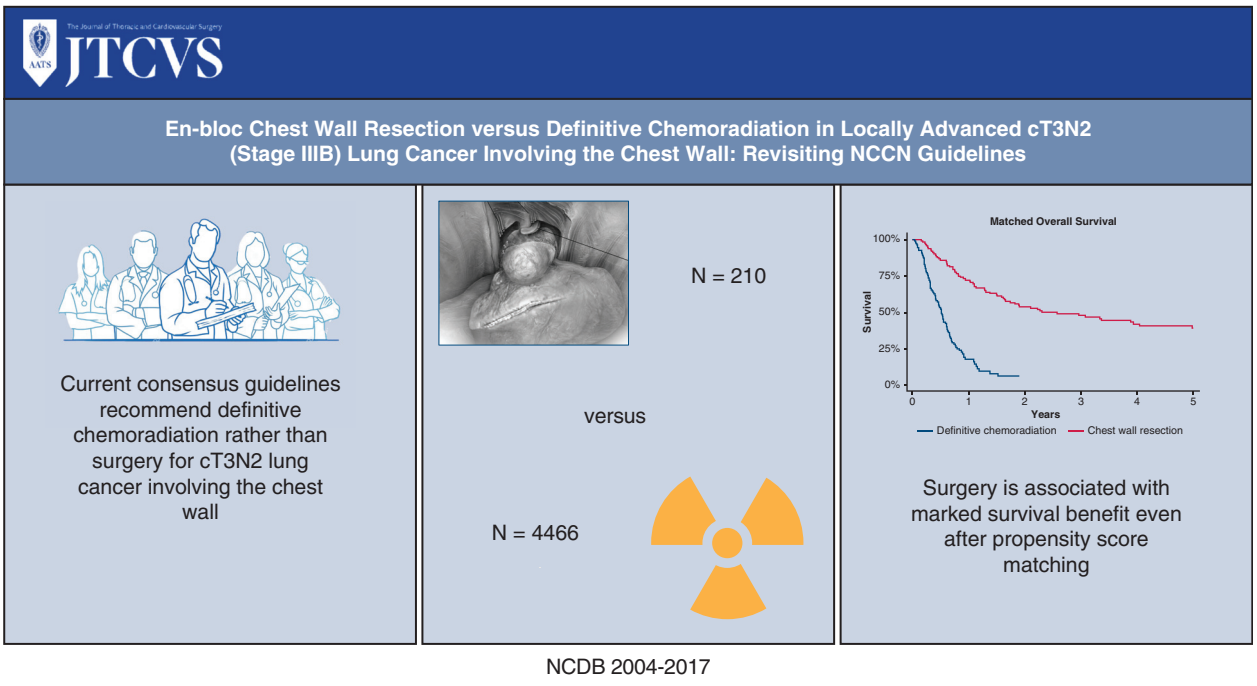


FIGURE 5. Overall study design. *NCCN*, National Comprehensive Cancer Network; *NCDB*, National Cancer Data Base.

TABLE 3. Short-term outcomes after surgery

Characteristic	Outcome
30-d mortality (%)	3.33%
90-d mortality (%)	9.52%
Length of stay (mean, d)	9.28 ± 8.20
Margin status n (%)	
R0	174 (82.8)
R1	21 (10.4)
R2	1 (0.5)
Positive margin NOS	12 (5.4)
Indeterminant	2 (0.9)

NOS, Not otherwise specified.

More recent studies also demonstrate improved survival to patients receiving neoadjuvant therapy plus surgery for locally advanced cT3N2 versus definitive chemoradiation. Darling and colleagues[12] demonstrated 5-year overall survival of approximately 40% in patients with stage IIIA/N2 receiving induction therapy plus surgery compared with approximately 15% for patients receiving only definitive chemoradiation. Pless and colleagues[13] reported overall median survival for neoadjuvant chemoradiation therapy of 37.1 months in stage IIIA/N2 disease, which is within the same spectrum of our reported median survival of 47.2 months for patients who received neoadjuvant therapy. Moreover, the poor survival outcomes in the chemoradiation group are similar to other studies also reporting on definitive chemoradiation outcomes for cT3N2 NSCLC.[22,23] Another factor contributing to our results is an 83% rate of R0 resection. Obtaining negative margins is necessary for optimal survival.[4,5,9,10]

En bloc lung and chest wall resection is a higher-risk surgery than a standard lobectomy. Published data from the Society of Thoracic Surgeons database demonstrate 2.9% 30-day mortality for concurrent chest wall resection with lung resection, which is aligned with our 30-day mortality of 3.3%.[24] Historical perioperative mortality rates from single-institution experiences range from 3.8% to 7%.[10,20,21] Although 9.8% 90-day mortality reported in our study may seem elevated, it is possible that the 30-day mortality metric underrepresents perioperative mortality in complex thoracic surgery.[29,30] Additionally, the single-center series are published from institutions with extensive thoracic oncologic experience, whereas our data are taken from hospitals throughout the country. There is a volume-outcome relationship for complex oncologic surgery.[31] The stark survival differences between surgical resection and definitive chemoradiation for cT3N2 NSCLC begs a balanced patient-centered discussion for the optimal management of these patients. With these results in mind, a careful discussion about balancing short-term risk with long-term benefit is needed. We believe that for the select patient, with good surgeon skill and multidisciplinary judgement, shared decision making, and effective postoperative care at specialized centers, there is utility in this approach.

Looking to the future, assuming novel agents in targeted and immune therapy to treat NSCLC continue to demonstrate promising results, there is hope for increased ability to obtain R0 resections and control disease in this subset of advanced lung cancer. Rusch and colleagues[11] demonstrated neoadjuvant atezolizumab administered to patients with resectable stage IB to IIIB NSCLC was well tolerated, yielded a 20% pathologic response rate, and allowed for a complete surgical resection. Results from the Checkmate 816 trial[32] have changed the paradigm for neoadjuvant therapy and emphasize the role of neoadjuvant chemo-immunotherapy for resectable lung cancer up to stage IIIA. More recently, the results of the Keynote 671 trial[33] demonstrated the role for perioperative chemo-immunotherapy and included resectable stage IIIB lung cancer. We are hopeful new agents such as these have the potential to further improve outcomes in combination with en bloc chest wall resection. However, because of the rarity of this presentation, these patients may be easily overlooked, and surgery automatically ruled out of the equation. Although we did not include superior sulcus or Pancoast tumors in this study, due to historical poor 5-year survival, this may be an avenue where further research using novel agents combined with surgery may show improved survival for this subset and change historical paradigm.[34,35]

Study Limitations

This study has several limitations. First and foremost, this is an observational study that is subject to inherent selection and confounding bias. However, we are not disputing the possibility of selection here, which is a key component of surgical decision making. Rather, we highlight the potential role for surgery for these challenging patients. Surgery is the only chance for meaningful long-term survival based on the results presented herein and in other studies.[12,22,23] Second, the results may not be generalizable because the NCDB only collects data from Commission on Cancer hospitals. Given the rarity and complexity of this disease, patients arguably should be offered surgery only at referral centers. The NCDB also may not capture the diversity of the patient population. Our total patient population was composed of 12.4% Black patients, which is concordant to the percent of the total Black population in the United States (13.6%). However, all other races totaled to 14% of our prematch dataset, which is well below the total percentage of the US population identifying as Hispanic (19.1%), for example.[36] In terms of socioeconomic means, patients were approximately evenly distributed between annual household income quartiles. These limitations should be taken in account during patient surgeon discussions. Third, we do not have data on patients who may have had chest wall invasion clinically, but after neoadjuvant therapy, a chest wall resection may not have

been necessary. Still, one would argue that this should widen the difference in survival observed on the 2 curves. The higher rate of nodal downstaging after resection may suggest inaccuracy in clinical staging and may be one reason for the apparent improved survival to some extent. This confirms the need for accurate invasive mediastinal staging for patients with locally advanced lung cancer. We acknowledge there is a time bias in the surgical cohort due to administration of neoadjuvant therapy. The NCDB is limited in assessing patient operative candidacy because it does not report pulmonary function tests, condenses patient comorbidities into a single score (Charlson-Deyo), and does not provide information on how robust the patient appears to the surgeon, which does not allow for a nuanced discussion of patient fitness for en bloc chest wall resection. There is certainly an increased risk with this operation; therefore, operative candidacy should be determined by an experienced thoracic surgeon due to multidisciplinary discussion. Additionally, the NCDB does not contain data on disease recurrence; therefore, we are unable to draw conclusions on disease-free survival. Also, the NCDB does not capture data on postoperative complications or healthcare-related quality of life. Without these data, we are unable to comment on the quality of life after either modality. However, the stark difference in survival, in our opinion, cannot be overlooked. Finally, a key limitation is that we do not know if the N2 disease was single station or multi-station, bulky disease, or nonbulky disease, which could be the reason that patients in the chemoradiation cohort had worse outcomes. If these patients had more N2 stations involved, it is common practice to not operate. Nonetheless, this highlights the fact that surgery should not be ruled out completely by blanket consensus statements and that surgery can still be considered in highly selected patients. Although the NCDB does not provide pertinent information that can affect treatment decisions, our strict inclusion and exclusion criteria simulate such conditions. Notwithstanding these limitations, we believe our results are valid and relevant to the readership because they provide additional context surrounding clinical decision making for considering surgery in select patients with stage IIIB NSCLC.

The main question left to be answered is, Who is the appropriate patient with cT3N2 lung cancer to be selected for therapy and en bloc resection? On the basis of the data presented, our experience, and extrapolating from current literature, we advocate for the following selection criteria to maintain operative safety and overall survival:

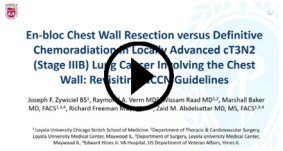
1. Evaluation by an expert multidisciplinary team including a thoracic surgeon who performs complex thoracic resections
2. Ability to achieve R0 resection
3. Nonbulky single-station N2 disease with invasive mediastinal staging
4. Receipt of neoadjuvant therapy
5. No progression on neoadjuvant therapy
6. Good functional status, limited comorbidity burden, and adequate pulmonary function
7. Operation to be performed at a hospital accustomed to caring for patients with complex thoracic pathology

CONCLUSIONS

In this large observational study, en bloc chest wall resection for locally advanced cT3N2 (stage IIIB) lung cancer was associated with substantially improved overall survival compared with definitive chemoradiation and provides some guidance on patient selection. The better overall survival in the resection group may provide evidence that NCCN guidelines can include an item indicating "surgery may be considered in select patients" with advanced cT3N2 (stage IIIB) lung cancer.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/en-bloc-chest-wall-resection-versus-definitive-chemoradiation-in-locally-advanced-c-t3-n2-lung-cancer-involving-the-chest-wall-revisiting-nccn-guidelines.



Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022;20:497-530.
2. Govindan R, Bogart J, Stinchcombe T, Wang X, Hodgson L, Kratzke R, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol*. 2011;29:3120-5.
3. Stoelben E, Ludwig C. Chest wall resection for lung cancer: indications and techniques. *Eur J Cardiothorac Surg*. 2009;35:450-6.
4. Riquet M, Arame A, Le Pimpec Barthes F. Non-small cell lung cancer invading the chest wall. *Thorac Surg Clin*. 2010;20:519-27.
5. Harpole DH Jr, Healey EA, DeCamp MM Jr, Mentzer SJ, Strauss GM, Sugarbaker DJ. Chest wall invasive non-small cell lung cancer: patterns of failure and implications for a revised staging system. *Ann Surg Oncol*. 1996;3:261-9.

6. Facciolo F, Cardillo G, Lopergolo M, Pallone G, Sera F, Martelli M. Chest wall invasion in non-small cell lung carcinoma: a rationale for en bloc resection. *J Thorac Cardiovasc Surg*. 2001;121:649-56.
7. Chapelier A, Fadel E, Macchiarini P, Lenot B, Le Roy Ladurie F, Cerrina J, et al. Factors affecting long-term survival after en-bloc resection of lung cancer invading the chest wall. *Eur J Cardiothorac Surg*. 2000;18:513-8.
8. Burkhart HM, Allen MS, Nichols FC III, Deschamps C, Miller DL, Trastek VF, et al. Results of en bloc resection for bronchogenic carcinoma with chest wall invasion. *J Thorac Cardiovasc Surg*. 2002;123:670-5.
9. Kawaguchi K, Miyaoka E, Asamura H, Nomori H, Okumura M, Fujii Y, et al. Modern surgical results of lung cancer involving neighboring structures: a retrospective analysis of 531 pT3 cases in a Japanese Lung Cancer Registry Study. *J Thorac Cardiovasc Surg*. 2012;144:431-7.
10. Magdeleinat P, Alifano M, Benbrahem C, Spaggiari L, Porrello C, Puyo P, et al. Surgical treatment of lung cancer invading the chest wall: results and prognostic factors. *Ann Thorac Surg*. 2001;71:1094-9.
11. Rusch VW, Nicholas A, Patterson GA, Waqar SN, Toloza EM, Haura EB, et al. Surgical results of the Lung Cancer Mutation Consortium 3 trial: a phase II multicenter single-arm study to investigate the efficacy and safety of atezolizumab as neoadjuvant therapy in patients with stages IB-select IIIB resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2023;165:828-39.e5.
12. Darling GE, Li F, Patsios D, Massey C, Wallis AG, Coate L, et al. Neoadjuvant chemoradiation and surgery improves survival outcomes compared with definitive chemoradiation in the treatment of stage IIIA N2 non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2015;48:684-90; discussion 90.
13. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386:1049-56.
14. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: new biological insights and recent therapeutic advances. *CA Cancer J Clin*. 2011;61:91-112.
15. Strauss GM. Adjuvant chemotherapy of lung cancer: methodologic issues and therapeutic advances. *Hematol Oncol Clin North Am*. 2005;19:263-81, vi.
16. Cancer programs: national cancer database. American College of Surgeons; 2023. Accessed March 1, 2022. https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/
17. National cancer database participant user file: 2019 data dictionary. Accessed June 4, 2023. https://www.facs.org/media/aq3aummh/puf_data_dictionary_2019.pdf
18. Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. *J Clin Oncol*. 2022;40:1356-84.
19. Grillo HC, Greenberg JJ, Wilkins EW Jr. Resection of bronchogenic carcinoma involving thoracic wall. *J Thorac Cardiovasc Surg*. 1966;51:417-21.
20. Allen MS, Mathisen DJ, Grillo HC, Wain JC, Moncure AC, Hilgenberg AD. Bronchogenic carcinoma with chest wall invasion. *Ann Thorac Surg*. 1991;51:948-51.
21. Downey RJ, Martini N, Rusch VW, Bains MS, Korst RJ, Ginsberg RJ. Extent of chest wall invasion and survival in patients with lung cancer. *Ann Thorac Surg*. 1999;68:188-93.
22. Speicher PJ, Englum BR, Ganapathi AM, Onaitis MW, D'Amico TA, Berry MF. Outcomes after treatment of 17,378 patients with locally advanced (T3N0-2) non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2015;47:636-41.
23. Boffa D, Fernandez FG, Kim S, Kosinski A, Onaitis MW, Cowper P, et al. Surgically managed clinical stage IIIA-clinical N2 lung cancer in the Society of Thoracic Surgeons database. *Ann Thorac Surg*. 2017;104:395-403.
24. Towe CW, Servais EL, Grau-Sepulveda M, Kosinski AS, Brown LM, Broderick SM, et al. Impact of chest wall resection on mortality after lung resection for non-small cell lung cancer. *Ann Thorac Surg*. 2022;114:2023-31.
25. McCaughan BC, Martini N, Bains MS, McCormack PM. Chest wall invasion in carcinoma of the lung. Therapeutic and prognostic implications. *J Thorac Cardiovasc Surg*. 1985;89:836-41.
26. Matsuoka H, Nishio W, Okada M, Sakamoto T, Yoshimura M, Tsubota N. Resection of chest wall invasion in patients with non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2004;26:1200-4.
27. Saw SPL, Ong BH, Chua KLM, Takano A, Tan DSW. Revisiting neoadjuvant therapy in non-small-cell lung cancer. *Lancet Oncol*. 2021;22:e501-16.
28. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e211S-50S.
29. McMillan RR, Berger A, Sima CS, Lou F, Dycoco J, Rusch V, et al. Thirty-day mortality underestimates the risk of early death after major resections for thoracic malignancies. *Ann Thorac Surg*. 2014;98:1769-74; discussion 74-5.
30. Mortality field status. The Society of Thoracic Surgeons; 2023. Accessed July 7, 2023. https://www.sts.org/registries-research-center/sts-national-database/mortality-status-fields
31. Birkmeyer JD, Finlayson EV, Birkmeyer CM. Volume standards for high-risk surgical procedures: potential benefits of the Leapfrog initiative. *Surgery*. 2001;130:415-22.
32. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MA, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973-85. https://doi.org/10.1056/NEJMoa220217033
33. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee S-H, Gao S, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. *N Engl J Med*. 2023;389:491-503. https://doi.org/10.1056/NEJMoa2302983
34. Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Johnson D, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg*. 2001;121:472-83.
35. Rusch VW, Parekh KR, Leon L, Venkatraman E, Bains MS, Downey RJ, et al. Factors determining outcome after surgical resection of T3 and T4 lung cancers of the superior sulcus. *J Thorac Cardiovasc Surg*. 2000;119:1147-53.
36. United States Census Bureau. 2023 census data. 2023. Accessed July 7, 2023. https://www.census.gov/quickfacts/fact/table/US/PST045223

Key Words: chemoradiation, chest wall resection, cT3N2 lung cancer, NCCN guidelines

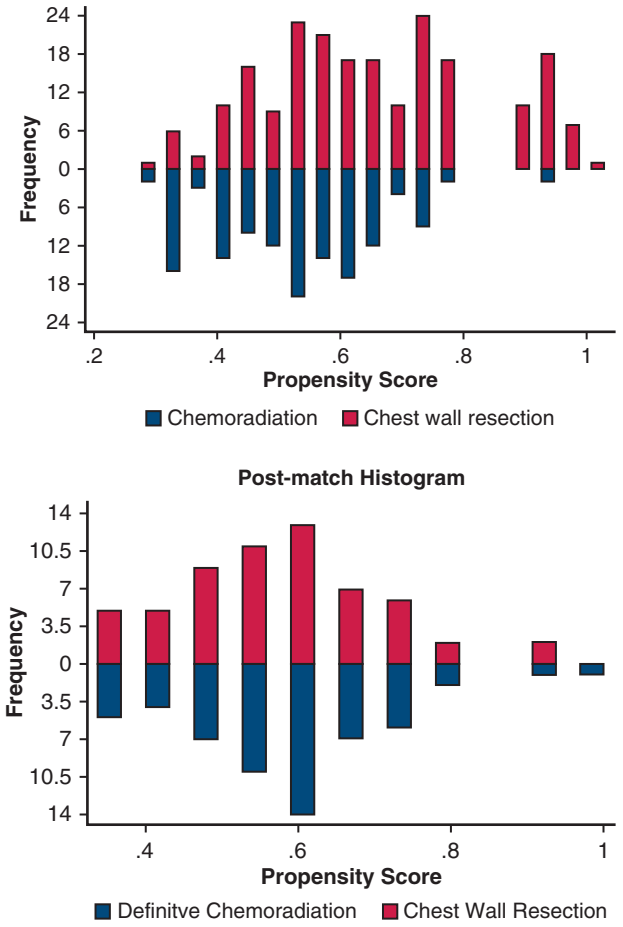


FIGURE E1. Prematch and postmatch histograms for unmatched and matched cohorts.