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Does Pneumonectomy Have a Role in the Treatment of Stage IIIA Non-Small Cell Lung Cancer?

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Abstract

Background—The role of surgical resection for stage IIIA non-small cell lung cancer (NSCLC) is unclear. We sought to examine outcomes after pneumonectomy for patients with stage IIIA disease.

Methods—All patients with stage IIIA NSCLC who had pneumonectomy at a single institution between 1999 and 2010 were reviewed. The Kaplan-Meier method was used to estimate long-term survival, and multivariable Cox proportional hazards regression was used to identify clinical characteristics associated with survival.

Results—During the study period, 324 patients had surgical resection of stage IIIA NSCLC. Pneumonectomy was performed in 55 patients, 23 (42%) of whom had N2 disease. Induction treatment was used in 17 patients (31%) overall and in 11 of the patients (48%) with N2 disease. Perioperative mortality was 9% (n=5) overall and 18% (n=3) in patients that had received induction therapy (p=0.17). Complications occurred in 32 patients (58%). Three-year survival was 36% and five-year survival was 29% for all patients. Three-year survival was 40% for N0-1 patients and 29% for N2 patients (p=0.59). In multivariable analysis, age over 60 (HR 3.65, p=0.001), renal insufficiency (HR 5.80, p=0.007), and induction therapy (HR 2.17, p=0.05) predicted worse survival; and adjuvant therapy (HR 0.35, p=0.007) predicted improved survival.

Conclusions—Long-term survival after pneumonectomy for stage IIIA NSCLC is within an acceptable range, but pneumonectomy may not be appropriate after induction therapy or in patients with renal insufficiency. Patient selection and operative technique that limit perioperative morbidity and facilitates the use of adjuvant chemotherapy are critical to optimizing outcomes.

Keywords

Lung Cancer Surgery; Pneumonectomy; Outcomes

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Introduction

Stage IIIA non-small cell lung cancer (NSCLC) encompasses a heterogeneous group of patients, including T4N0, T3-4N1, and T1-3N2 in the latest staging system [1]. Multimodality therapy with some combination of surgical resection, chemotherapy, and radiation therapy is the preferred treatment approach, but the optimal management strategy is uncertain and controversial [2-7]. In particular, the benefits of pneumonectomy for stage IIIA patients have been questioned. For example, in post-hoc subset analysis of a recent phase III trial of IIIA(N2) patients, induction therapy followed by lobectomy demonstrated a survival benefit over definitive chemoradiation, while pneumonectomy after induction therapy did not [8]. These results suggested the mortality of pneumonectomy limited the potential survival benefit of surgery. However, despite this data, a significant percentage of surgeons still consider pneumonectomy for patients with stage IIIA(N2) disease after induction treatment [7,9]. Additionally, the role of pneumonectomy in the other subsets of stage IIIA disease has similarly not been well established.

Pneumonectomy has been shown to have high rates of perioperative mortality (11-21%) when performed for stage III disease, particularly after induction therapy [8,10-12]. Many clinicians withhold pneumonectomy in patients with stage III disease, likely due to these findings [13]. However, alternative data has demonstrated that pneumonectomy can be performed safely in these patients with acceptable perioperative morbidity and mortality, as well as long-term survival [14-18]. In order to aid in the patient selection process when considering pneumonectomy for stage IIIA NSCLC, we examined short-term and long-term outcomes of patients at our institution, and attempted to identify patient, treatment, and tumor characteristics associated with improved survival.

Patients and Methods

This study was approved by the Duke University Institutional Review Board. All patients who underwent pneumonectomy for stage IIIA NSCLC at Duke University Medical Center between 1999 and 2010 were reviewed retrospectively. Data of patients undergoing lung resection are prospectively collected as part of a quality control process at our institution, with complications recorded by clinical providers based on the definitions of postoperative events maintained by the Society of Thoracic Surgeons General Thoracic Surgery Database. Chart review was utilized for all patients to ensure that all postoperative events were adequately captured. Preoperative patient characteristics, operative details, and postoperative outcomes were noted. Renal insufficiency was defined as creatinine ≥ 2.0 mg/dl or history of end-stage renal disease requiring renal replacement therapy. Perioperative mortality was defined as death within 30 days of surgery or within the same hospitalization after surgery.

Pre-treatment staging involved a combination of non-invasive radiologic evaluations with chest CT, whole-body PET scan, and brain CT/MRI; and invasive evaluations with bronchoscopy and mediastinoscopy. When induction treatment was given, the recorded stage was based on these pre-treatment staging studies. When induction treatment was not given before resection, the recorded stage was based on the pathologic stage. Operative technique involved a posterolateral thoracotomy, with routine use of epidural pain

management and a pneumonectomy tube left in place 1-2 days postoperatively. Coverage of the bronchial stump with a tissue flap was performed at the discretion of the surgeon. . Survival status was determined using medical records and the Social Security Death Index. Median follow-up was calculated from the date of pneumonectomy to death or most recent follow-up at Duke University Medical Center.

Patient and tumor characteristics are presented as raw number (percentage) for categorical data, mean $\pm$ standard deviation for continuous data that are normally distributed, and median (interquartile range) for non-normally distributed variables. Overall survival analyses were performed according to the Kaplan-Meier method. Three- and five-year survivals are presented as percentage (95% confidence interval). Univariate and multivariable adjusted Cox proportional hazards regression was used to identify clinical characteristics associated with post-pneumonectomy survival. Variables to be considered in the screening univariate analysis were chosen because they are clinically known to be important to survival, and included treatment variables (induction treatment and adjuvant treatment), cancer variables (tumor size and nodal status), and patient variables (age, renal insufficiency, gender, coronary disease, and cerebrovascular disease). Variables were considered as covariates in the multivariable analysis if they had $P < 0.1$ in univariate analysis. This strict threshold was chosen to limit the number of covariates, as the number of events was 42.

In order to compare the impact of pneumonectomy and lobectomy on survival for patients with stage IIIA disease, the patients who had pneumonectomy were matched 1:1 with patients who had had a lobectomy for stage IIIA disease during the same time period using a greedy matching algorithm. The matching algorithm calculated a value of the distance between each pneumonectomy patient and potential matched lobectomy patient from a database of patients who had undergone lobectomy for stage IIIA disease using a weighted formula that considered age, induction chemotherapy, induction radiation, N status, tumor size, and smoking history. Lobectomy patients were consecutively identified using a computer program that compared each pneumonectomy patient to all remaining lobectomy patients in the database. The patient from the database with the minimum distance was selected as the control for that study patient and removed from future consideration for other study patients. Survival analyses for the matched lobectomy and pneumonectomy patients were performed according to the Kaplan-Meier method, with the survival of the pneumectomy and lobectomy patients compared using the log rank test. A two-sided probability value of 0.05 was used for all comparisons. Statistical analyses were performed using STATA/SE version 11.2 (Stata Corporation, College Station, TX) and JMP Version Pro 9.0.0 (SAS Institute Inc., Cary, NC).

Results

During the study period, 324 patients had surgical resection of stage IIIA NSCLC. Pneumonectomy was performed in 55 of these patients (Table 1). . Mediastinoscopy was used in 49 of 55 patients (89%) overall. Metastatic involvement of N2 lymph nodes was present in 23 patients (42%, Table 2). Induction therapy was used in 17 (31%) patients overall, and in 11 (48%) of the patients with N2 disease. The six patients who received

induction therapy but did not have N2 disease were treated as part of an institutional protocol that was present during the early years of this study for patients with large, central, locally invasive tumors. All N2 patients receiving induction therapy had pathologic diagnosis of N2 involvement before induction therapy. In 10 of the 12 of patients (83%) with N2 disease who were not given induction treatment, microscopic N2 disease was found after pneumonectomy and mediastinal lymph node dissection, despite a negative pre-resection mediastinoscopy. The remaining two patients with N2 disease who were resected without induction therapy did not have a mediastinoscopy but had a negative mediastinum by CT and PET. Mediastinoscopy was used in 29 of the 32 patients who did not have N2 disease.

Five patients had nodal down-staging after induction therapy (29%), including 2 (12%) with a complete response. R0 resection was achieved in 51 patients (93%). Twenty-five (45%) patients had tissue flaps placed for bronchial stump coverage. Perioperative mortality was 9% (5 patients) overall. Perioperative mortality was 18% (3 patients) among those that received induction therapy versus 5% (2 patients) among those without induction therapy ($p=0.17$). One death was due to pulmonary embolism, one was due to respiratory failure, and the other three occurred outside of the hospital after discharge without a known cause. Three (8.8%) perioperative deaths occurred in patients undergoing left pneumonectomy ($n=34$), and two (9.5%) occurred in patients undergoing right pneumonectomy ($n=21$). Postoperative complications occurred in 32 patients (58%, Table 3). The median hospital stay was 5 days (5,7).

Adjuvant chemotherapy was delivered in 16 (29%) patients, and most often consisted of a platinum-based doublet (69%, 11 of 16 patients). It was unknown whether adjuvant chemotherapy was given in 7 patients (13%). Adjuvant chemotherapy was not delivered in 32 (58%) patients for the following reasons: early death ($n=8$), poor performance status ($n=6$), progressive disease ($n=5$), physician decision ($n=4$), patient preference ($n=3$), postoperative complication ($n=3$), and unknown ($n=3$). Adjuvant radiation was given to 6 (11%) patients. Nine of 16 (56%) patients who received adjuvant therapy had N0-1 disease. Two (13%) of the patients who received adjuvant therapy also received induction therapy. In this subset of patients receiving adjuvant therapy, there were no perioperative deaths and the morbidity rate was 44% ($n=7$).

Mean follow-up was 30 ± 32 months. Recurrence occurred in 17 patients (31%) patients during postoperative follow-up at a median of 10 months (3,16) after pneumonectomy. Median survival was 16.5 months, three-year actuarial survival was 36% (23-49%) and five-year actuarial survival was 29% (17-42%) for all patients after pneumonectomy (Figure 1). Three-year actuarial survival was 40% (23-56%) for N0-1 patients and 29% (12-49%) for N2 patients, and five-year actuarial survival was 36% (19-53%) for N0-1 patients and 20% (6-39%) for N2 patients ($p=0.59$, Figure 2).

Clinical variables associated with survival in univariate analysis are presented in Table 4. In multivariable analysis, age over 60 (hazard ratio [HR] 3.65, $p=0.001$), preoperative renal insufficiency (HR 5.80, $p=0.007$), and induction therapy (HR 2.17, $p=0.05$) predicted worse

survival; and adjuvant therapy (HR 0.35, $p=0.007$) predicted improved survival after pneumonectomy (Table 4).

In order to compare the impact of pneumonectomy and lobectomy on survival for patients with stage IIIA disease, the patients who had pneumonectomy were matched with 55 patients who had had a lobectomy for stage IIIA disease during the same time period. Baseline characteristics of the two groups of matched patients are shown in Table 5. The 2 groups were well matched, aside from mean FEV1, although the magnitude of this difference is relatively small and likely not clinically significant in terms of short- or long-term outcomes (64 vs. 73% predicted). Patients undergoing pneumonectomy had similar survival compared to patients undergoing lobectomy (5-year survival 29% [17-42%] vs. 41% [27-54%]), respectively; $p=0.15$; Figure 3).

Comment

The management of stage IIIA NSCLC is variable and controversial [9]. In particular, the role of pneumonectomy in this group of patients is unclear. We demonstrated that 5-year actuarial survival after pneumonectomy for stage IIIA NSCLC patients was 29%. Patients in this cohort who were treated with adjuvant therapy after pneumonectomy had improved survival. However, induction therapy, preoperative renal insufficiency, and age over 60 years were associated with worse survival. Patients undergoing pneumonectomy had similar survival to a matched set of patients undergoing lobectomy for stage IIIA NSCLC.

Optimizing survival after pneumonectomy for stage IIIA NSCLC clearly involves appropriate selection of patients who are likely to have long-term benefits from surgery. The role of pneumonectomy likely is dependent on T and N stage in heterogeneous IIIA patients. The perioperative morbidity of 58% and mortality of 9% in this study are notable but similar to previously published rates [14,17-20]. Our study did not find a significant difference in survival based on N2 lymph node involvement, but was likely underpowered to detect any such differences, particularly considering that the majority of patients with N2 disease in this study had microscopic disease determined after resection despite negative pre-treatment PET scans and/or mediastinoscopy.

Our study did find that induction therapy was associated with significantly worse long-term survival. Many studies have investigated the impact of induction therapy on short-term outcomes after pneumonectomy, with variable results regarding the risk of pneumonectomy after induction treatment [10,11,14-20]. Induction therapy has been shown to significantly improve long-term survival for patients with stage IIIA disease due to N2 lymph node involvement [3,4]. However, a randomized trial of stage IIIA(N2) patients found that induction chemoradiation followed by surgical resection did not improve survival compared to definitive chemoradiation, with subset analysis suggesting that the lack of benefit seen for surgery was due to poor survival after pneumonectomy [8]. Despite this data, the majority of North American thoracic surgeons still would consider pneumonectomy after induction treatment in this setting [7,9]. Based on the results from both our study and these other studies, we currently do not favor performing pneumonectomy after induction therapy in patients with N2 positive stage IIIA disease.

However, the results of our study do suggest that pneumonectomy can be appropriate for other stage IIIA subsets without N2 disease, that have previously been shown to be at risk for adverse outcome after pneumonectomy [12]. Given the retrospective cohort study design, our study does have a significant limitation of only investigating a group of patients that underwent surgical resection. We are not able to comment on whether a strategy of treatment that involves surgery provides benefits over non-operative therapy with definitive chemoradiation. However, a significant number of the patients in our study met the criteria for stage IIIA disease by having large or locally advanced tumors, potentially along with N1 disease. These patients often have a high rate of local failure with non-surgical therapies [21]. Given the reasonable 40% three-year survival seen in the subset of patients with N0-1 lymph node status in this study, we do feel pneumonectomy is indicated in appropriate operative candidates with large or locally advanced tumors without N2 involvement.

In addition to the survival benefit of pneumonectomy in these patients, the overall quality-of-life after pneumonectomy has been demonstrated to be similar to patients with other chronic diseases [22]. Although physical quality-of-life may be lower than that of the average U.S. population, the mental quality-of-life score is higher, particularly for cancer patients [22]. Furthermore, age has been shown to be significantly associated with physical quality-of-life after pneumonectomy [22]. Thus, particularly in younger patients, pneumonectomy likely allows patients to maintain an adequate quality-of-life in addition to potentially providing an overall survival benefit.

Our study showed that adjuvant therapy was associated with significantly improved survival. Whether this is due to an oncologic effect or whether this is a marker of adequate performance status or avoidance of perioperative morbidity and mortality is uncertain. Patients that could be given adjuvant therapy likely did well after pneumonectomy, and also may have been healthier than the patients who were not given adjuvant therapy. Adjuvant therapy was used in the minority of the patients in this study, and perioperative morbidity, mortality, or poor performance status was the reason adjuvant therapy was not used for 17 of the 32 patients who were not given adjuvant treatment. This finding demonstrates the importance of patient selection when considering pneumonectomy for patients with large or locally advanced tumors. For example, patients over 60 years of age in our study had worse survival compared to younger patients, which is consistent with other studies that have shown an adverse relationship between outcomes and age [18,19,]. Additionally, preoperative renal insufficiency was associated with worse long-term survival in this study. Renal insufficiency has been shown to be associated with increased morbidity after pulmonary resection in elderly patients [23], and renal failure is associated with mortality after completion pneumonectomy [24] although other studies, including an analysis of the Society of Thoracic Surgeons General Thoracic Surgery Database, have not shown this to be the case [19]. Although the sample size of our study does not allow more detailed investigation into the impact of other patient variables such as overall functional status, comorbid conditions, smoking status, and pulmonary function, all of these characteristics must be carefully considered before including pneumonectomy as part of the treatment strategy for this stage of NSCLC.

Patients whose nodal status is downstaged after induction therapy appear to have better survival [8]. The approach at our institution to mediastinal restaging and patient selection for resection after induction therapy has been refined over the long time period of the study. The mediastinum was not routinely restaged invasively in the early part of the study, and patients would undergo resection if they did not have evidence of progressive disease after induction treatment. More recently, we generally use a strategy of restaging the mediastinum before attempting resection to pathologically confirm nodal downstaging and mediastinal disease clearance. The method of restaging is cervical mediastinoscopy if not already performed, and thoracoscopic mediastinal lymph node dissection with frozen section analysis to confirm negative disease prior to proceeding with resection. Re-do mediastinoscopy is generally only considered for patients who had positive 4L lymph nodes prior to induction treatment.

As mentioned above, this study is limited by its retrospective nature and small sample size. As a result, the survival model is limited, and there may be other variables affecting outcome after pneumonectomy that were not assessed. Second, the long timeframe led to inclusion of disparate treatment protocols perioperatively. Third, survival comparisons were calculated from the date of pneumonectomy; thus, patients receiving induction therapy likely had their diagnoses for longer time periods than patients proceeding straight to pneumonectomy. Lastly, this study may be underpowered to detect certain differences between patient subgroups described in this study. However, we have shown that long-term survival after pneumonectomy for stage IIIA NSCLC is within an acceptable range. In addition, our data add to the pessimism regarding pneumonectomy after induction therapy. Patient selection and operative technique that limit perioperative morbidity and allow adjuvant chemotherapy use are critical to optimizing outcomes.

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Figure 1. Kaplan-Meier curve demonstrating the overall survival of patients undergoing pneumonectomy for stage IIIA non-small cell lung cancer. Three-year survival was 36% and five-year survival was 29%.

Figure 2.

Kaplan-Meier curve demonstrating survival of N0-1 patients versus N2 patients with stage IIIA non-small cell lung cancer. Five-year survival was 36% for N0-1 patients and 20% for N2 patients ($p=0.59$).

Figure 3. Kaplan-Meier curve demonstrating the overall survival of patients undergoing pneumonectomy versus a matched group of patients who underwent lobectomy for stage IIIA non-small cell lung cancer. Five-year survival was 29% for pneumonectomy patients and 41% for lobectomy patients.

Table 1

Patient Demographics and Treatment Details

Patient Characteristics	N (%) or Mean $\pm$ S.D.
Age (years)	62 $\pm$ 12
Gender (female)	20 (36)
Race (white)	44 (80)
Previous thoracic surgery	20 (36)
Forced expiratory volume in 1 second (% predicted)	64 $\pm$ 18
Diffusion capacity of carbon monoxide (% predicted)	72 $\pm$ 20
Smoking history	50 (91)
Pack year history of smokers	50 $\pm$ 27
Cigarette smoking within 2 weeks of surgery	8 (15)
Diabetes	9 (16)
Cerebrovascular disease	3 (5)
Renal insufficiency	3 (5)
Hypertension	22 (40)
Coronary artery disease	8 (15)
Staging Technique	
Chest CT	55 (100)
PET	41 (75)
Brain MRI/CT	27 (49)
Bronchoscopy	55 (100)
Mediastinoscopy	49 (89)
Induction Therapy	17 (31)
Preoperative Chemotherapy	4 (7)
Preoperative Chemoradiation	13 (24)
Chemotherapy Regimens	
Carboplatin + Navelbine	n=6
Carboplatin + Taxol	n=4
Cisplatin + Docetaxel	n=2

Patient Characteristics	N (%) or Mean $\pm$ S.D.
Other	n=5

Table 2

Pathology

N (%) or Mean $\pm$ S.D.	
Tumor Size (cm)	5.8 $\pm$ 3.1
Histology	
Squamous Cell Carcinoma	34 (62)
Adenocarcinoma	9 (16)
Large Cell	4 (7)
Carcinoid	2 (4)
Other	6 (11)
TNM Stage	
T3-4N0-1	32 (58)
T4N0	6 (11)
T3N1	23 (42)
T4N1	3 (5)
T1-T3N2	23 (42)
T1N2	1 (2)
T2N2	16 (29)
T3N2	6 (11)

Table 3

Postoperative Complications

Complication	N (%)
Blood product transfusion	16 (29)
Atrial fibrillation	11 (20)
Need for postoperative bronchoscopy	6 (11)
Vocal cord paralysis	6 (11)
Bronchopleural fistula	4 (7)
Pneumonia	4 (7)
Confusion	4 (7)
Urinary tract infection	3 (5)
Need for enteral feeding tube	3 (5)
Re-intubation	3 (5)
Empyema	2 (4)
Other	8 (15)

Table 4

Variables Associated with Survival After Pneumonectomy

	Univariate		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Age (>60 vs ≤60)	2.04 (1.04-3.99)	0.04	3.65 (1.64-8.07)	0.001
Renal Insufficiency	3.54 (1.06-11.78)	0.04	5.80 (1.64-20.61)	0.007
Induction Treatment	1.84 (0.94-3.56)	0.07	2.17 (1.00-4.69)	0.05
Adjuvant Treatment	0.44 (0.22-0.89)	0.02	0.35 (0.17-0.75)	0.007
N2 Disease	1.19 (0.63-2.23)	0.59		
Tumor Size	0.97 (0.87-1.08)	0.56		
Female Gender	0.62 (0.32-1.23)	0.17		
Coronary Artery Disease	0.84 (0.33-2.16)	0.72		
Cerebrovascular Disease	2.53 (0.76-8.38)	0.13		

Table 5

Matched Pneumonectomy and Lobectomy Patients who Underwent Resection for Stage IIIA Non-Small Cell Lung Cancer

Variable	Pneumonectomy (n=55)	Lobectomy (n=55)	P
Age (years)	62 ± 12	62 ± 12	0.8
Gender (male)	20 (36)	20 (36)	1
Forced expiratory volume in 1 second (% predicted)	64 ± 18	73 ± 17	0.02
Diffusion capacity of carbon monoxide (% predicted)	72 ± 20	71 ± 19	0.7
Smoking history	50 (91)	50 (91)	1
Pack year history of smokers	50 ± 27	48 ± 32	0.7
Diabetes	9 (16)	8 (15)	1
Cerebrovascular disease	3 (5)	2 (4)	1
Renal insufficiency	3 (5)	0	0.2
Hypertension	22 (40)	26 (48)	0.6
Coronary artery disease	8 (15)	14 (25)	0.2
Induction chemotherapy	4 (7)	5 (9)	1
Induction chemoradiation	13 (24)	13 (24)	1
Tumor size (cm)	5.8 ± 3.1	5.5 ± 2.9	0.6
TNM Stage			1
T3-4N0-1	32 (58)	32 (58)	
T1-T3N2	23 (42)	23 (42)	
Perioperative mortality	5 (9)	4 (7)	1
Perioperative morbidity	32 (58)	28 (51)	0.6
Hospital Stay (median, IQR)	5 (5,7)	5 (4,7)	0.4

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as raw number (percentage). IQR- interquartile range