Original Article

Pneumonectomy is safe and effective for non-small cell lung cancer following induction therapy

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Background: Uncertainty surrounds the safety and efficacy of pneumonectomy in the setting of induction chemoradiation for non-small cell lung cancer (NSCLC). We sought to evaluate fifteen years of experience with pneumonectomy with and without induction therapy.

Methods: Over a 15-year period [1999–2014], data were extracted from medical records of patients undergoing pneumonectomy for NSCLC. Primary outcomes were 5-year overall survival and mortality at 30, 60 and 90 days following operation. Morbidity data was also reviewed. Statistical comparisons were performed using the Chi-Square test. Kaplan-Meier curves were compared using the log rank test. Significance was defined as a P value less than 0.05. Patients with a prior cancer history, bilateral lung nodules and oligometastatic disease at presentation were excluded.

Results: After exclusion criteria were applied, 240 patients were analyzed and 137 (57%) underwent induction therapy prior to pneumonectomy. Five-year overall survival was 38.5%. Mortality at 90 days was 7.94%. There was no statistically significant difference in perioperative mortality with the addition of induction therapy. In fact, in the subset of patients with N2 disease (n=65), induction therapy was associated with improved 5-year overall survival (10.7% *vs.* 32.7%, P=0.014). Thirty-five percent of patients with N2 disease exhibited a complete response in the nodal basin following induction therapy; however, this did not confer a statistically significant overall or disease-free survival benefit.

Conclusions: Pneumonectomy can safely be performed in the setting of induction chemoradiation. In patients with N2 disease, induction therapy may confer a survival benefit when the surgery can be done with limited morbidity and mortality.

Keywords: Safety; pneumonectomy; induction

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Introduction

The first report of pneumonectomy for lung cancer was published in the *Journal of American Medical Association* (*JAMA*) in 1933 and was performed by Dr. Graham (1). His patient, Dr. Gilmore, an obstetrician from Pittsburgh, would go on to outlive the surgeon himself. As our understanding of the biology of lung cancer and the physiologic consequences of pneumonectomy evolved, so did the techniques and treatments for locally advanced lung cancer, which often include a combination of chemotherapy, radiation and surgery. The Intergroup trial (2), a randomized study published in 2009 and

comparing neoadjuvant chemoradiotherapy plus surgery to chemoradiotherapy alone, issued caution regarding pneumonectomy in the context of multimodality therapy. This was largely due to inexplicable surgical results in this series, which demonstrated morbidity and mortality higher than published averages (26%). Yet pneumonectomy continues to be advocated in this setting by high volume centers that achieve superior surgical morbidity and mortality (3-6). Our initial experience in 73 patients demonstrated favorable morbidity and mortality (7). A systematic review of pneumonectomy followed by neoadjuvant therapy was published in 2012 (8). The report included 27 studies from 1990–2010, and included 4 randomized controlled studies, including the Intergroup trial. Mortality at 30 days was 7% and at 90 days was 12%, suggesting traditional reporting of 30-day mortality may not be the ideal marker of perioperative mortality for pneumonectomy patients. A recently published query of a large-volume national database; however, suggests patients with stage IIIA non-small cell lung cancer (NSCLC) receive neoadjuvant chemoradiotherapy without survival benefit over upfront surgery with adjuvant therapy (9). Importantly, patients with final positive margins were excluded, and mortality was only reported at 30-days. The ideal treatment for patients with locally advanced NSCLC, who require pneumonectomy for resection, remains controversial. This study sought to evaluate the safety and efficacy of pneumonectomy following neoadjuvant chemoradiation therapy in our institution over a 15-year period.

Methods

Institutional Review Board approval was obtained to perform this retrospective review. Individual patient consent was waived for this retrospective study. The age, gender, histopathology, preoperative staging, 90-day mortality, major complications, and survival were recorded for all patients undergoing pneumonectomy for lung cancer at our institution between 1999 and 2014. Patients with a prior history of cancer, with pathology other than NSCLC, and patients with bilateral lung nodules or oligometastatic disease at presentation were excluded from the study. Our institution was involved in a study evaluating the efficacy of extrapleural pneumonectomy for NSCLC in the setting of pleural disease (IIIB). These patients and others undergoing extrapleural pneumonectomy were excluded. Nodal disease was confirmed by histopathology in 81.5% of patients prior to induction therapy. In the remaining 19.5% of patients, mediastinal nodal stations were positron emission tomography (PET)-avid and presumed positive. Median length of follow-up was 2.2 years. Tumors were classified and re-staged according to the 7th edition of the International System for Staging of Lung Cancer. The statistical analysis was performed using STATA 14.1 (Stata Statistical Software, StataCorp LP, College Station, TX, USA). The comparative analysis of the differences between the two groups was performed with the Chi-Square test. Survival was calculated using the Kaplan-Meier method and were statistically evaluated by the log-rank test. A P value of less than 0.05 was considered significant.

Results

Following application of exclusion criteria, 240 patients who underwent pneumonectomy for lung cancer at our institution were analyzed. The most common histology was squamous cell carcinoma (53.3%), followed by adenocarcinoma, and poorly differentiated NSCLC (*Table 1*).

Of those, 137 (57%) underwent induction therapy prior to surgery, 79% received chemoradiation and 21% received chemotherapy alone. There were 65 patients with pathologic N2 disease, and A total of 46 patients underwent induction therapy specifically for this purpose. Twenty-seven patients underwent extended pneumonectomy, which included chest wall resection, partial vertebrectomy, superior vena cava resection and reconstruction, or diaphragmatic resection and reconstruction, in addition to pneumonectomy. Twenty percent of these patients were alive at 5 years.

The overall 5-year survival for all 240 patients was 38.5%, and was not significantly different for patients with or without induction therapy (P=0.4490) (*Figure 1* and *Table 2*). Not surprisingly, the presence of nodal disease conferred a worse prognosis (*Figure 2*). However, 46 patients underwent induction therapy for N2 disease and this subset of patients exhibited a three-fold increase in 5-year overall survival compared to those patients with N2 disease who did not receive induction therapy (32.7% *vs.* 10.7%, P=0.0141) (*Table 2*). Disease-free survival at 5 years was also statistically better for patients with N2 disease who underwent induction therapy prior to pneumonectomy (22.9% *vs.* 11.5%, P=0.033). Mortality at 30-, 60-, and 90-days was 2.08%, 5.0%, and 7.94%, respectively. The most common complication was atrial arrhythmia, affecting 27.5% of patients. Bronchopleural fistula (1.7%), empyema, adult respiratory distress syndrome (ARDS) (2.9%), vocal

Table 1 Characteristics of patients undergoing pneumonectomy for NSCLC, no induction vs. induction, 1999–2014 (N=240)

Characteristics	Total patients (N=240)	Patients with no induction (N=103)	Patients with induction (N=137)	P value
Age				
Mean	62.78	65.91	60.42	0.508
Median	62.51	66.68	60.28	
Min	37.24	43.8	37.24	
Max	88.1	88.1	79.98	
Gender				
Female	91 (37.9%)	37 (35.9%)	54 (39.4%)	0.581
Male	149 (62.1%)	66 (64.1%)	83 (60.6%)	
Smoking status				
Never	12	5	7	0.928
Current	70	35	35	0.155
Former	135	53	82	0.194
No info	23	10	13	0.954
Lung laterality				
Left	148	64	84	0.897
Right	92	39	53	
Tumor histology				
Squamous cell carcinoma	128 (53.3%)	64 (62.1%)	64 (46.7%)	0.018
Adenocarcinoma	87 (36.3%)	31 (30.1%)	56 (40.9%)	0.086
Poorly differentiated	17 (7.1%)	4 (3.9%)	13 (9.5%)	0.094
Other	8 (3.3%)	4 (3.9%)	4 (2.9%)	0.681
Pathologic stage AJCC 7th edition				
Stage 0	15 (6.3%)	0 (0.0%)	15 (10.9%)	0.001
Stage I	31 (12.9%)	9 (8.7%)	22 (16.1%)	0.094
Stage II	93 (38.8%)	43 (41.7%)	50 (36.5%)	0.409
Stage III	101 (42.1%)	51 (49.5%)	50 (36.5%)	0.043
Stage III by TNM classification				
T4N0	9 (8.9%)	3 (5.9%)	6 (12.0%)	0.281
T3N1	41 (40.6%)	30 (58.8%)	11 (22.0%)	0.000
T4N1	7 (6.9%)	4 (7.8%)	3 (6.0%)	0.715
T0-2bN2	22 (21.8%)	4 (7.8%)	18 (36.0%)	0.001
T3N2	15 (14.9%)	6 (11.8%)	9 (18.0%)	0.378
T4N2	7 (6.9%)	4 (7.8%)	3 (6.0%)	0.715
Tumor size (cm)				
Mean	4.99±2.91	5.79±2.66	4.38±2.95	0.390
Median	4.8	5.5	4.3	
Maximum	15	15	15	

NSCLC, non-small cell lung cancer.

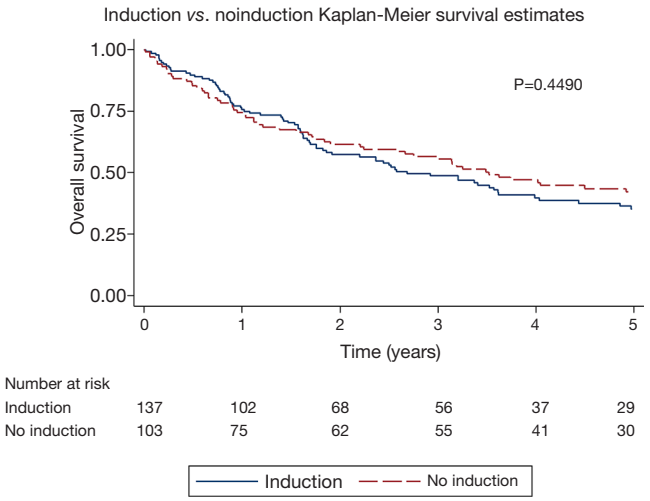

Figure 1 Kaplan-Meier curve for patients undergoing pneumonectomy for NSCLC [1999–2014] with and without induction therapy (central figure). NSCLC, non-small cell lung cancer.

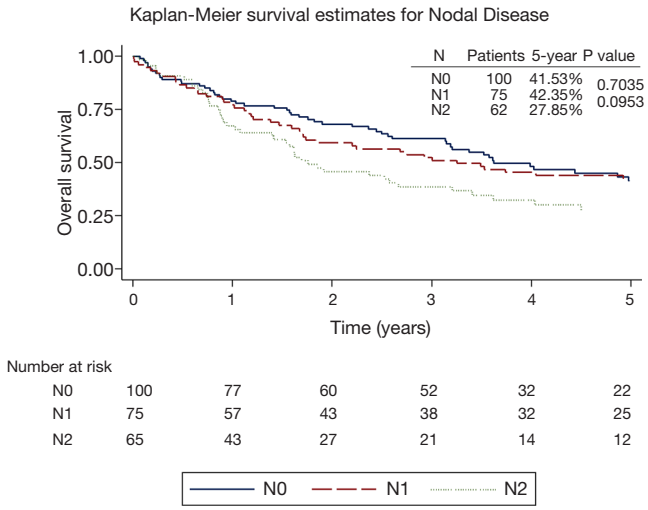

Figure 2 Kaplan-Meier curve for patients undergoing pneumonectomy for NSCLC [1999–2014] stratified by nodal disease.

Table 2 Five-year survival for patients who underwent pneumonectomy for NSCLC, with and without induction therapy (N=240)

Patient characteristics	Total patients		Survival at 5-years		P value	Mortality at 30-days		Mortality at 60-days		Mortality at 90-days	
	N	%	Alive N	%		Events N	%	Events N	%	Events N	%
Overall survival											
Patients with no induction therapy	103	42.9	30	42.2	0.449	3	2.9	6	5.8	10	9.8
Patients with induction therapy	137	57.1	29	35.3		2	1.5	6	4.4	9	6.6
Total	240	100	59	38.5		5	2.1	12	5	19	7.9
Overall survival—N2											
Patients with no induction therapy	14	21.5	1	10.7	0.014	1	7.1	2	14.3	4	28.6
Patients with induction therapy	51	78.5	11	32.7		0	0	1	2	1	2
Total	65	100	12	27.9		1	1.5	3	4.6	5	7.7

cord paralysis (5.0%), pulmonary embolism (2.5%), and pneumonia (4.2%) were much less common, and similar among both groups of patients (*Table 3*). Fourteen (5.8%) patients had final positive margins.

Fifteen (10.95%) of the 137 patients who underwent induction therapy demonstrated complete response on their final pathology, with a 5-year OS of 46.3% (*Table 4*). Sixteen of the 46 patients with N2 disease prior to induction therapy (34.8%) demonstrated pathologic response in the N2 nodal bed, defined as no residual tumor. There was no difference in survival in patients with nodal response compared to those without nodal response to induction therapy (35.0% *vs.* 29.7%) (*Table 4*), nor was there a difference in survival among patients with single-station versus multi-station N2 disease (27.5% *vs.* 28.4%, P=0.669). The most common histology found on final pathologic review for patients with

Table 3 Non-arrhythmia complications of pneumonectomy for NSCLC with and without induction therapy

Postoperative complications	Total patients		Patients with no induction		Patients with induction		P value
	N=240	%	N=103	%	N=137	%	
Overall complications	62	25.8	31	30.1	31	22.6	0.191
ARF	1	0.4	0	0.0	1	0.7	0.385
C. difficile	2	0.8	1	1.0	1	0.7	0.839
DVT	6	2.5	2	1.9	4	2.9	0.631
Pneumonia	10	4.2	6	5.8	4	2.9	0.265
Empyema	4	1.7	2	1.9	2	1.5	0.773
ARDS	7	2.9	5	4.9	2	1.5	0.122
BPF	4	1.7	2	1.9	2	1.5	0.773
PE	6	2.5	3	2.9	3	2.2	0.723
MI	1	0.4	0	0.0	1	0.7	0.385
Ventilation >48 h	20	8.3	9	8.7	11	8.0	0.844
Ventilation >7 days	12	5.0	8	7.8	4	2.9	0.088
Reintubation	14	5.8	5	4.9	9	6.6	0.575
RLN paresis	12	5.0	5	4.9	7	5.1	0.928
Perioperative death	6	2.5	3	2.9	3	2.2	0.723
Take back OR	20	8.3	10	9.7	10	7.3	0.504
Readmit	20	8.3	8	7.8	12	8.8	0.783

ARDS, adult respiratory distress syndrome; BPF, broncopleural fistula; PE, pulmonary embolism; MI, myocardial infarction; DVT, deep vein thrombosis; ARF, acute renal failure; RLN, recurrent laryngeal nerve; OR, operating room.

Table 4 Survival in patients with and without pathologic response to induction therapy

Survival	Total patients		Survival at 5 years		P value
	N	%	Alive N	%	
Overall survival					
Patients with pCR	15	10.9	5	58.3	0.196
Patients without pCR	122	89.1	24	32.0	
Total	137	100.0	29	35.3	
Overall survival—N2					
Patients with nodal pCR	16	34.8	3	35.0	0.171
Patients with no nodal response	18	39.1	4	29.7	
Data not available	12	26.1	1	16.7	
Total	46	100.0	8	27.3	

N2 disease and response to induction chemoradiation, was adenocarcinoma (n=10, 62.5%).

Discussion

Early case series evaluating pneumonectomy following induction chemoradiation reviewed small study populations and reported mortality rates as high as 45% (10). Subsequent data, from a randomized study evaluating surgery for lung cancer following chemoradiation, continued to question the safety of performing pneumonectomy in that setting (2). The 90-day mortality rate of 6.6% reported in this study for patients who underwent induction therapy prior to surgery, is well below the 30-day mortality reported in many studies in the absence of induction therapy, suggesting that pneumonectomy can be safely performed in the setting of induction therapy. Furthermore, the data presented here suggests that induction therapy confers a definite benefit in the subset of patients with N2 disease.

The findings regarding nodal response in patients with N2 disease are important, but warrant further investigation. Our institution has reported on the prognosis of lymph node disease following chemoradiation previously (11). Traditionally, down-staging after induction therapy has been consistent with the hypothesis that the absence of lymphatic involvement at the time of surgery is a predictive marker for the eradication of systemic disease, and is expected to confer at least some cancer-specific survival benefit. While our data indicates that surgery after induction therapy can be accomplished without compromising morbidity or mortality, our study failed to demonstrate a survival benefit with induction therapy despite achieving a complete response in nodal pathology in over 30% of patients. What's more, there was no detectable difference in survival whether nodal disease was single- or multi-station. The survival benefit found for patients who underwent induction therapy compared to those that underwent upfront surgery for N2 disease is intriguing and warrants further review in larger controlled studies. Practically speaking, patients in this subgroup are heterogeneous and not all can expect to benefit from such an aggressive treatment strategy.

The need for additional or extended resection (chest wall resection, left atrial resection, diaphragmatic resection, etc.) in and of itself implies a more invasive tumor. That said, 21% of the patients undergoing extended pneumonectomy were alive at 5 years, and that has significant implications on treatment options, particularly with young and fit patients that wish to be aggressive with treatment strategy.

Our retrospective review has several limitations. While 240 patients are a substantial experience, it may not be an adequate sample size to detect subtle differences in survival among the treatment strategies. Also, out-of-state patients were challenging to track longitudinally, as evidenced by a median follow up of 2.2 years. Patients selected for surgery likely represented patients with favorable physiologic and functional profiles, and we have not included patients who received chemoradiation with the intention of resection, but never went on to surgery, nor patients who were down-staged to a lobectomy, or bilobectomy or sleeve resection following induction therapy. Twelve patients had induction therapy for N2 disease but did not have that station sampled at the time of surgery. Some of the operative reports suggested a particular lymph node basin was surveyed but no lymph nodes were found following induction therapy, but this was not recorded as a nodal response, given the lack of pathologic tissue confirmation. An additional consideration are patients who underwent pneumonectomy prior to any systemic therapy due to concerns related to hemoptysis or post-obstructive pneumonia, which may have negatively affected survival data and perioperative morbidity and mortality data in the upfront surgery group.

Conclusions

Pneumonectomy can be safely performed following induction chemoradiation for NSCLC, achieving morbidity and mortality rates comparable to national standards without chemoradiation. There was a survival benefit to induction therapy prior to pneumonectomy for patients with N2 disease, though cohort size was small. Though 34.8% of patients exhibited a complete pathologic nodal response on final pathology in response to induction therapy, this did not confer a measurable survival benefit at 5 years.

Pneumonectomy continues to be a valid treatment strategy for patients with NSCLC and our study suggests it continues to play a role in multimodality therapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics board of Partners Healthcare (No. 2006P002482). Individual patient consent was waived for this retrospective study.

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