Comparison of Treatment Strategies for Patients With Clinical Stage T1–3/N2 Lung Cancer

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ABSTRACT

Background: The therapeutic strategies for clinical stage T1–3N2 (cT1–3N2) lung cancer are controversial. For operable tumors, treatment can vary by center, region, and continent. This study aimed to identify the optimal therapeutic method and type of surgical strategy for cT1–3N2 lung cancer. **Methods:** This retrospective evaluation analyzed the records of 17,954 patients with cT1–3N2 lung cancer treated in 2010 through 2015 from the SEER database. The effects of different therapeutic methods and types of surgical strategies on overall survival (OS) were assessed. Univariate and multivariate analyses were performed using a Cox proportional hazards model. **Results:** The 5-year OS rates were 27.7% for patients with T1N2 disease, 21.8% for those with T2N2 disease, and 19.9% for T3N2 disease. Neoadjuvant therapy plus operation (OP) plus adjuvant therapy, and OP plus adjuvant therapy, provided better 5-year OS rates than OP alone or concurrent chemoradiotherapy (34.1%, 37.7%, 29.3%, and 16.1%, respectively). In the T1N2, T2N2, and T3N2 groups, lobectomy provided better 5-year OS than pneumonectomy, sublobectomy, and no surgery. Both univariate and multivariate analyses showed that young age, female sex, well-differentiated histologic grade, adenocarcinoma cell type, neoadjuvant and adjuvant therapy, lobectomy, and T1 stage were statistically associated with better 5-year OS rates. **Conclusions:** In cT1–3N2 lung cancer, multimodal treatments tended to provide better 5-year OS than OP alone or concurrent chemoradiotherapy. In addition, lobectomy was associated with better survival than other operative methods.

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Background

Lung cancer is the leading cause of cancer death worldwide among both men and women.¹ Only 14% to 18% of all patients with lung cancer remain alive 5 years after diagnosis.^{2,3} The treatment strategies for stages I, II, IIIb (T4N2 and N3), and IV lung cancer have been well researched and accepted globally. However, the therapeutic methods for clinical T1–3N2 (cT1–3N2) lung cancer remain controversial and differ among centers, regions, and continents. For decades, this issue has been discussed, but no specific therapy has been accepted widely.

Therapeutic methods for cT1–3N2 lung cancer are determined through a multidisciplinary team discussion, including a board-certified thoracic surgeon, who evaluates whether the tumor is operable.⁴ If the tumor is inoperable, the current, widely accepted treatment is concurrent chemoradiotherapy (CCRT) followed by durvalumab. If the tumor is operable, then multimodal therapies may be used, including operation (OP) plus adjuvant chemotherapy (C/T) with or without radiotherapy (RT), and neoadjuvant C/T or chemoradiotherapy (CRT) plus OP plus adjuvant C/T with or without RT. Rocco et al⁵ claimed that North American surgeons, compared with those on other continents, are less likely to offer surgical treatment and more likely to use induction therapy before resection, whereas European surgeons preferred to offer OP followed by adjuvant therapy in select cases of N2 disease.

Different therapeutic methods were compared in previous studies.⁶ Although many issues remain unresolved, most contemporary lung cancer studies include surgery in the multimodal treatment of cT1–3N2 disease.

This study aimed to identify the optimal therapeutic method and surgical strategy for cT1–3N2 lung cancer. We designed a retrospective study and obtained data from the SEER database, which were used to compare the overall survival (OS) rates of patients with cT1–3N2 lung cancer treated using different therapeutic methods and surgical strategies.

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Methods

Patient Population and Selection

Lung cancer cases occurring in 2010 through 2015 (classified using the 7th edition of the *AJCC Cancer Staging Manual*⁷) and their corresponding details were obtained from the SEER public access database using SEER*Stat version 8.3.5. This study was approved by the Institutional Review Board at Changhua Christian Hospital and was deemed exempt from full review by the internal review board because the released information would be used strictly for research purposes.

An independent cohort of cases from 2016 was obtained for cutoff validation. Patients with cT1–3N2M0 lung cancer who underwent surgical resection (pneumonectomy, lobectomy/bilobectomy, or sublobectomy) or C/T, with or without RT, were eligible. Patients were excluded if they received no therapy or if their database records were missing values for therapy or type of surgery.

Baseline patient demographics (age and sex), tumor characteristics (histologic grade, cell type, T stage), and treatment details (surgery type, C/T, RT) were collected from the SEER database. We classified histologic subtypes as adenocarcinoma, squamous cell carcinoma (SCC), and other histologic types. Patients were divided into different cohorts based on T1N2, T2N2, and T3N2 stages. Outcome measures for our study were 1-, 3-, and 5-year OS rates. OS was calculated as the time from date of diagnosis to either death of any cause or the 2016 cutoff. Every observation was staged according to the 7th edition of the *AJCC Cancer Staging Manual* TNM staging system published in 2010.⁷

Statistical Analyses

Survival curves were plotted using the Kaplan-Meier method. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model. The following clinicopathologic factors were included in the analyses: age, sex, histologic grade, cell type, therapeutic methods, type of surgery, and T stage. Chi-square and *t* tests were used to compare differences between categorical and continuous variables, respectively. Cox proportional hazards regression model was used to determine the effects of therapeutic methods and types of surgery on OS. All calculations were performed using SPSS Statistics, version 13 for Windows (SPSS Inc). *P* values <.05 were considered statistically significant.

Results

Data from 17,954 patients with lung cancer were analyzed, among whom 4,436 had stage T1N2, 8,296 had stage T2N2, and 5,222 had stage T3N2 disease (Table 1).

Mean age was approximately 67 years in each group. The proportion of men increased as the T stage advanced (T1 stage, *n*=2,082 [46.93%]; T2 stage, *n*=4,325 [52.13%]; T3 stage, *n*=2,967 [56.82%]).

The predominant histologic grade among patients with N2 lung cancer was poorly differentiated (T1 stage, *n*=1,133 [25.54%]; T2 stage, *n*=2,658 [32.04%]; T3 stage, *n*=1,684 [32.25%]), followed by moderately differentiated, well differentiated, and undifferentiated. Adenocarcinoma was the predominant histologic cell subtype in the T1N2 stage (*n*=1,975; 44.52%) compared with SCC (*n*=775; 17.47%) and others (*n*=1,686; 38.01%). In contrast, SCC was predominant in T3N2 stage (*n*=1,924; 36.84%) compared with adenocarcinoma (*n*=1,542; 29.52%) and others (*n*=1,756; 33.63%).

Most patients with N2 lung cancer received only C/T; a substantial proportion received OP plus adjuvant C/T with or without RT (23.40%, 21.47%, and 14.19% for stages T1N2, T2N2, and T3N2, respectively), and only approximately 3% received neoadjuvant C/T with or without RT followed by OP plus adjuvant C/T with or without RT (2.91%, 3.40%, and 3.45% for stages T1N2, T2N2, and T3N2, respectively). Relatively few patients (~29.7%) with N2 lung cancer received surgical treatment. Lobectomy, the most common surgical type (T1 stage, *n*=1,184 [26.69%]; T2 stage, *n*=2,133 [25.71%]; T3 stage, *n*=844 [16.16%]), was performed significantly more often than pneumonectomy and sublobectomy.

The 1-, 3-, and 5-year OS rates were all significantly different among T1N2, T2N2, and T3N2 stages. Figure 1 illustrates the 5-year OS rates for T1N2, T2N2, and T3N2 stages (27.7%, 21.8%, 19.9%, respectively; *P*<.0001).

Table 2 lists survival rates based on therapeutic methods, which were defined as OP only (group 1); OP plus adjuvant C/T with or without RT (group 2); neoadjuvant C/T with or without RT followed by OP plus adjuvant C/T with or without RT (group 3); only CCRT (group 4); and C/T and others (group 5). Groups 2 and 3 were not significantly different and had better 5-year OS than groups 1 and 4. This result indicates the importance of OP and adjuvant therapy in treating cT1–3N2 lung cancer. Multimodal therapy produced better 5-year OS than single therapy.

Figure 2 shows OS rates based on the different therapeutic methods in all patients with N2 lung cancer, whereas Figures 2B, C, and D display OS rates for those with T1N2, T2N2, and T3N2 disease, respectively. Each figure illustrates significant differences between therapeutic methods (*P*<.0001).

Figure 3 illustrates 5-year OS rates based on different types of surgery. Lobectomy produced the best outcome

Table 1. Baseline Characteristics

	T1N2 n (%)	T2N2 n (%)	T3N2 n (%)	P Value
Patients, N	4,436	8,296	5,222	
Age, mean $\pm$ SD, y	67.45 $\pm$ 9.66	67.34 $\pm$ 10.16	66.85 $\pm$ 9.87	.005
Sex				<.001
Male	2,082 (46.93)	4,325 (52.13)	2,967 (56.82)	
Female	2,345 (53.07)	3,971 (47.87)	2,255 (43.18)	
Histologic grade				<.001
Well-differentiated	177 (3.99)	253 (3.05)	134 (2.57)	
Moderately differentiated	825 (18.59)	1,761 (21.23)	928 (17.77)	
Poorly differentiated	1,133 (25.54)	2,658 (32.04)	1,684 (32.25)	
Undifferentiated	155 (3.49)	284 (3.42)	211 (4.04)	
Unknown	2,146 (48.38)	3,340 (40.26)	2,265 (43.37)	
Cell type				<.001
Adenocarcinoma	1,975 (44.52)	2,967 (35.76)	1,542 (29.52)	
Squamous cell	775 (17.47)	2,542 (30.64)	1,924 (36.84)	
Other	1,686 (38.01)	2,783 (33.55)	1,756 (33.63)	
Therapy group ^a				<.001
1	353 (7.96)	592 (7.14)	235 (4.50)	
2	1,038 (23.40)	1,781 (21.47)	741 (14.19)	
3	129 (2.91)	282 (3.40)	180 (3.45)	
4	1,007 (22.70)	1,371 (16.53)	735 (14.08)	
5	1,909 (43.03)	4,270 (51.47)	3,331 (63.79)	
Surgery type				<.001
Pneumonectomy	27 (0.61)	210 (2.53)	156 (2.99)	
Lobectomy/Bilobectomy	1,184 (26.69)	2,133 (25.71)	844 (16.16)	
Sublobectomy	309 (6.97)	316 (3.81)	161 (3.08)	
None	2,901 (65.40)	5,614 (67.67)	4,052 (77.59)	
Other	15 (3.38)	23 (2.77)	9 (1.72)	
Overall survival rate, %				<.001
1 y	74.6	67.6	61.1	
3 y	41.0	33.2	27.8	
5 y	27.7	21.8	19.1	

Abbreviations: CCRT, concurrent chemoradiotherapy; C/T, chemotherapy; OP, operation; RT, radiotherapy.

^aGroup 1: OP only; Group 2: OP + adjuvant C/T $\pm$ RT; Group 3: neoadjuvant C/T $\pm$ RT + OP + adjuvant C/T $\pm$ RT; Group 4: CCRT; Group 5: C/T and others.

in patients with cT1N2, cT2N2, and cT3N2 lung cancer ($P<.0001$). Pneumonectomy was associated with a slightly better outcome than sublobectomy or no surgery, which may indicate that a clear resection margin is more important than lung function preservation.

Both univariate and multivariate Cox regression models were analyzed (Table 3). Univariate and multivariate analyses both showed that young age, female sex, well-differentiated histologic grade, adenocarcinoma cell type, therapy groups 2 and 3, lobectomy, and T1 stage were statistically significantly associated with better 5-year OS rates.

Discussion

Findings of this retrospective investigation of treatment modalities for patients with lung cancer suggest that multimodal therapies (neoadjuvant C/T with or without RT followed by OP plus adjuvant C/T with or without RT, and OP plus adjuvant C/T with or without RT) tend to be associated with better 5-year OS in patients with cT1–3 N2 lung cancer than OP alone and CCRT.

With regard to induction therapy, Roth et al⁶ compared the treatment strategies of induction C/T plus surgery versus surgery alone and found significantly better outcomes in the combined modality group (2- and 3-year

Figure 1. Kaplan-Meier survival curves of different T stages for all patients with N2 lung cancer.

OS rates of 60% and 56% vs 25% and 15%, respectively). In contrast, another randomized trial that analyzed 62 patients with stage IIIA/N2 non-small cell lung cancer (NSCLC)—half receiving induction C/T plus OP and half receiving OP alone⁸—found that 1- and 3-year OS rates were similar in both groups (68% and 23% for combined modality vs 65% and 26% for OP alone, respectively). The investigators concluded that the result may be explained by limited statistical power. Moreover, induction therapy was reported to have no excessive operative risk (morbidity or mortality) compared with direct surgical treatment.⁹ Our findings revealed that induction therapy provided similar 5-year OS rates in N2 disease (comparing groups 2 and 3), which may be explained by the small number of patients in group 3. Use of induction therapy before surgical treatment requires further evaluation.

Several studies have compared induction CRT and induction C/T alone, with most revealing that induction CRT only increased pathologic response and mediastinal downstaging but did not improve OS or disease-free survival rates.^{10–12} In particular, the large SAKK and WJTOG9903 trials concluded that CRT does not provide better progression-free survival (PFS) and OS than C/T alone.^{13,14} Based on these concordant findings, we categorized induction CRT and induction C/T into the same group (group 3) for comparison.

Some studies have questioned the role of surgery in the treatment of patients with N2 lung cancer. EORTC 08941 concluded that, after induction C/T, surgical resection did not improve OS or PFS compared with RT.¹⁵ The ESPATUE trial concluded that, after induction C/T, there was no evidence of better survival in the surgical

Table 2. Five-Year Overall Survival Rates

Clinical Stage	Therapy Group ^a					P Value
	1	2	3	4	5	
T1N2	0.344	0.420	0.413	0.203	0.000	<.001
T2N2	0.297	0.395	0.377	0.143	0.117	<.001
T3N2	0.237	0.297	0.274	0.156	0.081	<.001

Abbreviations: CCRT, concurrent chemoradiotherapy; C/T, chemotherapy; OP, operation; RT, radiotherapy.

^aGroup 1: OP only; Group 2: OP + adjuvant C/T ± RT; Group 3: neoadjuvant C/T ± RT + OP + adjuvant C/T ± RT; Group 4: CCRT; Group 5: C/T and others.

group compared with the CRT boost group.¹⁶ However, the Intergroup 0139 trial showed that a subgroup of patients who underwent lobectomy after CRT showed improved OS rates compared with those who underwent CRT alone.¹⁷ Our study indicates that patients who underwent OP had better 5-year OS than those who underwent only CCRT or C/T. We suggest that OP is essential for patients with cT1–3N2 lung cancer.

The type of surgery that is selected is an important factor. The GLCCG trial analyzed 524 patients with operable stage III NSCLC and concluded that, after induction with CRT, pneumonectomy should be avoided.¹⁸ The Intergroup 0139 trial showed that OS improved for an OP group that underwent lobectomy but not pneumonectomy.¹⁷ A recent study, published in 2019, reached a similar conclusion and suggested that patients with N2-positive NSCLC treated with fewer pneumonectomy resections experienced favorable OS.¹⁰ Our findings indicated that patients who received surgical treatment had better OS than those who did not. Lobectomy provided the best 5-year OS, followed by pneumonectomy, sublobectomy, and no surgery.

With regard to adjuvant therapy, a meta-analysis integrated data from 47 trials of stage III resectable NSCLC and reported 2 conclusions.¹⁹ First, adding C/T after surgery increased 5-year survival (from 60% to 64%). Second, OP plus adjuvant C/T and RT was associated with a higher 5-year OS rate than OP plus C/T only (33% vs 29%, respectively). Adjuvant therapy played an important role in treating patients with resectable lung cancer, and adding RT provided better outcomes than C/T alone. In our study, we categorized adjuvant C/T and RT into one group and also showed that adding adjuvant therapy provided a significantly better 5-year OS than OP alone.

When treating inoperable tumors, CCRT followed by durvalumab is recommended. Durvalumab was introduced as a lung cancer treatment in 2015. The phase III PACIFIC trial was the largest and most recent investigation of durvalumab in patients with NSCLC.²⁰ It enrolled 709 patients with stage III NSCLC with unresectable tumors who did not experience disease progression after CCRT. A dose of 10 mg per kilogram of

Figure 2. Kaplan-Meier survival curves based on different therapeutic methods for patients with clinical stage (A) T1–3N2, (B) T1N2, (C) T2N2, and (D) T3N2 lung cancer ($P < .0001$ for all).

Abbreviations: CCRT, concurrent chemoradiotherapy; C/T, chemotherapy; OP, operation; OS, overall survival; RT, radiotherapy.

^aWith or without RT.

body weight every 2 weeks for 12 months showed a significant benefit compared with placebo in the 24-month OS rate (66.3% vs 55.6%, respectively), median PFS duration (17.2 vs 5.6 months, respectively), and median time to death or distant metastasis (28.3 vs 16.2 months, respectively). Thus, the standard of care for patients with unresectable stage III NSCLC includes treatment with durvalumab after CCRT.

The well-known RADIANT and SELECT trials indicated that patients with resected *EGFR*-mutant stage

IB–IIIA NSCLC could benefit from adjuvant *EGFR* tyrosine kinase inhibitor treatment. As a result, immunotherapy and targeted therapies have become more popular.^{21,22} The new paradigms in stage IIIA (N2) disease have been studied recently. For example, the ADJUVANT/CTONG1104 trial showed that adjuvant gefitinib led to significantly longer disease-free survival than adjuvant C/T in patients with completely resected stage II–IIIA (N1–N2) *EGFR*-mutant NSCLC.²³ Additionally, the RTOG 0839 trial evaluated panitumumab at a dose of 2.5 mg/kg

Figure 3. Kaplan-Meier survival curves based on different types of surgery for patients with clinical stage (A) T1–3N2, (B) T1N2, (C) T2N2, and (D) T3N2 lung cancer ($P < .0001$ for all).

Abbreviation: OS, overall survival.

weekly for 6 weeks with neoadjuvant CRT, followed by surgery and consolidation C/T²⁴; however, there was an unexpectedly high mortality rate in the panitumumab arm. The combination of immunotherapy and targeted therapies with traditional therapy for stage IIIA (N2) disease must be studied further.

A strength of our study was the inclusion of a large number of patients from multiple centers, which should provide accurate statistical analyses. In addition, we compared common therapeutic methods and different surgical types. However, our study had several limitations. First, the retrospective design may have contributed to

selection bias, which could affect the results. Second, the study period was limited to data available between 2010 and 2015 only, which could have produced inaccurate 5-year OS due to inadequate observations. Third, the SEER database did not indicate whether a patient was treated at an academic medical center or a low-volume center. Several studies have indicated that high-volume centers provide better outcomes than low-volume centers for patients with stage III NSCLC.^{25–27} Fourth, currently, the evaluation of lymph nodes for NSCLC is difficult. In stage IIIA (N2) disease, the lymph node station, histologic type, and numbers of metastatic and

Table 3. Univariate and Multivariate Analysis of Overall Survival

	Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age, y	1.020 (1.018–1.022)	<.001	1.018 (1.015–1.020)	<.001
Sex				
Male	Ref		Ref	
Female	0.790 (0.760–0.822)	<.001	0.818 (0.786–0.852)	<.001
Histologic grade				
Well-differentiated	Ref		Ref	
Moderately differentiated	1.173 (1.029–1.337)	.017	1.165 (1.021–1.330)	.023
Poorly differentiated	1.484 (1.307–1.685)	<.001	1.311 (1.153–1.490)	<.001
Undifferentiated	2.077 (1.780–2.422)	<.001	1.528 (1.306–1.789)	<.001
Unknown	1.653 (1.458–1.875)	<.001	1.219 (1.073–1.386)	.002
Cell type				
Squamous cell	Ref		Ref	
Adenocarcinoma	0.730 (0.695–0.766)	<.001	0.892 (0.848–0.938)	<.001
Other	0.968 (0.923–1.016)	.189	1.082 (1.028–1.139)	.003
Therapy group ^a				
1	Ref		Ref	
2	0.616 (0.560–0.677)	<.001	0.653 (0.594–0.718)	<.001
3	0.576 (0.495–0.669)	<.001	0.648 (0.556–0.755)	<.001
4	1.046 (0.953–1.148)	.343	1.241 (1.036–1.486)	.019
5	1.456 (1.340–1.518)	<.001	1.616 (1.359–1.922)	<.001
Surgery type				
None	Ref		Ref	
Pneumonectomy	0.615 (0.534–0.708)	<.001	0.508 (0.307–0.841)	.008
Lobectomy/Bilobectomy	0.460 (0.436–0.485)	<.001	0.391 (0.241–0.636)	<.001
Sublobectomy	0.723 (0.655–0.798)	<.001	0.601 (0.366–0.987)	.044
Other	0.460 (0.436–0.485)	.008	0.445 (0.246–0.803)	.017
T stage				
T1	Ref		Ref	
T2	1.255 (1.192–1.320)	<.001	1.243 (1.180–1.308)	<.001
T3	1.500 (1.420–1.585)	<.001	1.381 (1.306–1.461)	<.001

Abbreviations: CCRT, concurrent chemoradiotherapy; C/T, chemotherapy; HR, hazard ratio; OP, operation; RT, radiotherapy.

^aGroup 1: OP only; Group 2: OP + adjuvant C/T ± RT; Group 3: neoadjuvant C/T ± RT + OP + adjuvant C/T ± RT; Group 4: CCRT; Group 5: C/T and others.

skip lymph nodes can lead to different outcomes.^{28–30} NCCN Clinical Practice Guidelines in Oncology have not included these as prognostic factors, and the SEER database did not provide lymph node information. Despite these limitations, our findings contribute to the identification of an optimal treatment strategy for patients with N2 lung cancer.

Conclusions

In patients with cT1–3N2 lung cancer, multimodal treatments tended to provide better 5-year OS than OP alone and CCRT. In addition, lobectomy was

associated with better survival than other operative methods.

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