Original Article

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Prognostic analysis of surgical-pathologic N1 disease in non-small cell lung cancer: Single-center experience with 276 cases

Serkan Yazgan, Ahmet Ucvet, Soner Gursoy, Ozgur Samancilar, Ezgi Cimen Guvenc

Abstract:

OBJECTIVE: Patients who receive surgical treatment due to non-small cell lung cancer (NSCLC) and have surgical-pathologic N1 (pN1) disease represent a heterogeneous group. Differences in lymph node (LN) level (hilar or intrapulmonary LNs) may influence patient survival. The aim of this study was to evaluate the prognostic factors, including the level of N1 LN involvement.

METHODS: Patients undergoing complete resection at a single center between January 2000 and January 2017 and diagnosed with surgical-pN1 NSCLC were analyzed retrospectively. Patients were examined in terms of demographic characteristics, preoperative and postoperative management, survival rates, as well as variables affecting survival.

RESULTS: The mean follow-up duration was 50.9 ± 41.2 months (between 2.7 and 204 months); median and 5-year survival rates were 71.5 months and 53.7%, respectively. Five-year survival rates of patients aged 60 and below ($n = 144$) and patients over the age of 60 ($n = 132$) were 59.7% and 46.9%, respectively ($P = 0.001$). Five-year survival rates for patients receiving and not receiving adjuvant therapy were 58.4% and 45.3%, respectively ($P = 0.02$). When surgical-pN1 involvement was assessed with regard to localization, 5-year survival was 59.1% in hilar involvement, 52.4% in intrapulmonary involvement, and 49.4% in involvement of both zones at the same time ($P = 0.58$). In Cox regression analysis, variables affecting survival were age group and adjuvant therapy ($P = 0.001$ and $P = 0.012$, respectively).

CONCLUSION: Surgical-pN1 localization or pleural involvement does not have a significant effect on survival, whereas advanced age and further T classification affect survival adversely. Adjuvant therapy, on the other hand, has a significantly positive effect on survival.

Keywords:

Adjuvant chemotherapy, age groups, lymph node, non-small cell lung cancer, surgery, survival

Department of Thoracic Surgery, University of Health Sciences, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Turkey

Address for correspondence:
Dr. Serkan Yazgan, SBÜ Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Thoracic Surgery, Yenisehir - Konak, Izmir, Turkey.
E-mail: serkanyazgan@gmail.com

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Introduction

Staging in cancer patients not only provides important prognostic information on survival, but also guides us in the selection of optimal treatment modalities. As in all cancers, N status is the most important prognostic factor in non-small cell lung cancer (NSCLC).[1,2]

Although hilar and intrapulmonary nodal involvement does not directly influence surgical decision-making for lung cancer, they have an important place due to their effect on resection size, survival, and recurrence. N1 disease includes early-stage disease and patients with locally advanced cancer. However, it is a heterogeneous group due to various N1 stations. Therefore, the surgical outcome of surgical-pathologic N1 (pN1)

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disease and the efficacy of adjuvant chemotherapy, radiotherapy, or chemoradiotherapy administration are controversial. Our objective in this study was to analyze the postoperative long-term survival outcomes of the patients who underwent surgical treatment due to NSCLC and were diagnosed with pN1 disease and to investigate the prognostic factors affecting survival.

Methods

In this retrospective cohort study, primary NSCLC patients undergoing lobectomy, bilobectomy, or pneumonectomy and diagnosed with pN1 disease between January 2000 and January 2017 were analyzed. Operative mortality, patients with incomplete follow-up, cases of incomplete resection, and Stage IV patients were exclusion criteria. Lung cancer patients were staged according to 8th tumor, node, and metastasis (TNM) classification system.

Preoperative evaluation

Routine blood tests, pulmonary function tests, chest X-ray, thoracic and upper abdominal computed tomography (CT), fiberoptic bronchoscopy, brain magnetic resonance or CT, and internal medicine and anesthesia consultations were performed on all patients. Positron emission tomography scan was used increasingly after 2006. For patients with limited pulmonary function (forced expiratory volume in 1 s [FEV1%] which was <60% of predicted normal values), further evaluation was carried out through arterial blood gas analysis, quantitative perfusion scintigraphy, and stair-climbing test. The predicted postoperative value of 800 mL or more than 40% for FEV1% was considered adequate respiratory function.

Surgical technique

All patients underwent posterolateral thoracotomy with single-lung ventilation and it was aimed to achieve complete resection with all surgical margins negative. Lymph nodes (LNs) which were found suspicious (>1 cm) during the operation were examined by frozen section (F/S). The resection was not extended when complete resection was possible, even if metastasis was observed in N1 LN. Sleeve resection was performed on two patients due to LN involvement. All patients underwent complete mediastinal LN dissection. Patients with any of visceral pleura, parietal pleura, or chest wall involvement were evaluated as having pleural invasion. LN involvement was divided into separate groups according to hilar (# 10) and intrapulmonary (# 11 and more distant) zones.

Postoperative period

Patients were referred to the oncology clinic where they were followed up with the pathology results. Chemotherapy and/or radiotherapy was performed on those patients whose general condition was suitable for additional treatment and who were recommended to receive adjuvant therapy. Afterward, patients were followed up by routine blood tests and thoracic and upper abdominal CT every 3 months in the 1st year, every 6 months in the 2nd year, and then once in a year. For survival information, patients' latest status were checked from the "National Mortality Database" (MERNIS). In addition, all the patients' medical records in the hospital were examined. Even if they were discharged, deaths within the first postoperative 30 days were regarded as operative mortality. Patients whose last status could not be updated from MERNIS were considered as incomplete follow-up and excluded from the study.

Statistical analysis

All statistical data analyses were made using the SPSS 20.0 software program (IBM Corporation, Armonk, NY, USA). Excel software (Microsoft Corp., Seattle, WA, USA) was used to analyze the data. Mean and standard deviations of continuous variables and the number and percentage of categorical variables were given using descriptive statistics. Taking all deaths into account, survival rates were calculated using Kaplan–Meier method and compared by log-rank test. Cox regression analysis was carried out using ten different variables for multivariate analysis. $P < 0.05$ was considered statistically significant, $0.001 \leq P < 0.01$ was considered highly significant, and $0.05 \leq P < 0.10$ was considered as tendency to significance (marginally significant).

Results

Between January 2000 and January 2017, 1948 patients underwent lobectomy, bilobectomy, or pneumonectomy due to Stages I, II, and III primary NSCLC. A total of 305 patients (15.7%) were diagnosed with pN1. Incomplete resection, operative mortality, and patients with incomplete follow-up were excluded from the study and the remaining 276 patients were included in the study.

In the study group consisting of 262 men and 14 women, the mean age was 59.8 ± 8.5 years (between 35 and 79 years) and 47 (17%) patients received neoadjuvant therapy. Either lobectomy or bilobectomy was performed on 161 (58.3%) patients. Seventy-one (25.7%) patients had pleural or chest wall involvement. The most common histopathological type was squamous cell carcinoma and it was observed in 173 (62.7%) patients. The most common pathologic T (pT) status was pT2 with a rate of 37.7% (n = 104) [Table 1]. When LN involvement was analyzed according to hilar and intrapulmonary zones, hilar LN involvement was detected in 74 (26.8%) patients, intrapulmonary LN involvement in 175 (63.4%) patients, and involvement of both zones at the same time in 27 (9.8%) patients. A total of 180 (65.2%) patients

Table 1: General characteristics and survival of pathologic N1 patients undergoing anatomic resection due to non-small cell lung cancer

Characteristics	Number of patient, *n* (%)	5-year survival rate (%)	Median (months)	*P*
Overall survival	276 (100)	53.7	71.5	-
Age				
≤60	144 (52.2)	59.7	102.8	**0.001**
>60	132 (47.8)	46.9	42.9	
Neoadjuvant therapy				
No	229 (83)	54.7	71.5	0.61
Yes	47 (17)	48.7	53.0	
Adjuvant therapy				
No	96 (34.8)	45.3	52.1	**0.02**
Yes	180 (65.2)	58.4	85.9	
Chemotherapy	130 (72.2)	65.2	91.3	0.25
Radiotherapy	35 (19.5)	43.2	49.9	
Chemoradiotherapy	15 (8.3)	46.7	40	
Resection type				
Lobectomy	161 (58.3)	52.0	63.0	0.85
Pneumonectomy	115 (41.7)	55.3	73.6	
Histologic type				
Squamous cell	173 (62.7)	57.7	76.2	0.68
Adenocarcinoma	77 (27.9)	46.1	52.1	
Other	26 (9.4)	50.4	73.6	
N1 localization				
Hilar	74 (26.8)	59.1	73.6	0.58
Intrapulmonary	175 (63.4)	52.4	63	
Hilar and intrapulmonary	27 (9.8)	49.4	40.5	
Tumor size				
3 cm and smaller	107 (38.8)	58.5	76.2	0.19
Larger than 3 cm	169 (61.2)	50.5	62.9	
Stage				
T1N1, T2N1	179 (64.9)	58.1	87.9	0.055
T3N1, T4N1	97 (35.1)	45.0	40.0	
Pleural invasion				
No	205 (74.3)	58.0	78.8	0.13
Yes	71 (25.7)	40.3	37.9	

Bold values represent statistically significant outcomes

received adjuvant therapy and the treatments applied differed according to the oncology clinics patients were referred to; 130 chemotherapy, 35 radiotherapy, and 15 chemoradiotherapy.

In the follow-up with a mean duration of 50.9 ± 41.2 months (between 2.7 and 204 months), median and 5-year survival rates were 71.5 months and 53.7%, respectively [Figure 1]. There was no significant difference between 5-year survival rates of men and women (54.3% and 35.9% respectively; $P = 0.44$). Five-year survival rates of patients aged 60 and below ($n = 144$) and patients over the age of 60 ($n = 132$) were 59.7% and 46.9%, respectively, and the difference was statistically highly significant ($P = 0.001$) [Figure 2]. Five-year survival rates of the patients undergoing lobectomy and pneumonectomy were 52.0% and 55.3%, respectively ($P = 0.85$). For the operations on the right side, 5-year survival rate was 52.5%, while this rate was 54.8% on the left side ($P = 0.88$). Five-year survival rate was 58.1% in the patients with pT1N1 and pT2N1, whereas it was 45% in pT3N1 and pT4N1 patients, and the difference was found to have a tendency to significance in the statistical analysis ($P = 0.055$).

Five-year survival rates of the patients receiving and not receiving adjuvant therapy were 58.4% and 45.3%, respectively, and the difference was statistically significant ($P = 0.02$) [Figure 3]. When survival of the patients receiving adjuvant therapy was examined with regard to treatment modalities, 5-year survival rate was 65.2% in those receiving only chemotherapy, 43.2% in those receiving only radiotherapy, and 46.7% in those receiving chemoradiotherapy ($P = 0.25$) [Figure 4]. Patients who received radiotherapy and chemoradiotherapy, those who received chemotherapy and radiotherapy, and those who received chemotherapy and chemoradiotherapy were compared in terms of survival using univariate analysis and the difference was not statistically significant ($P = 0.9$, $P = 0.12$, and

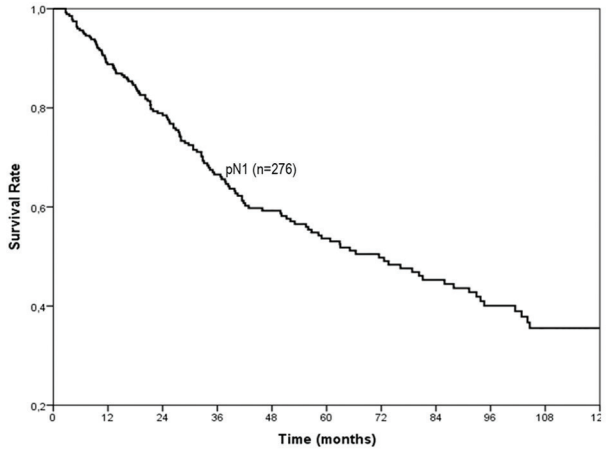

Figure 1: Overall survival curve in N1 disease

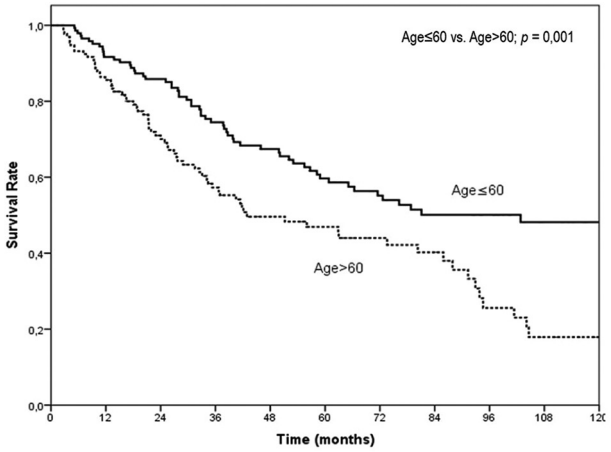

Figure 2: Survival curve according to age in N1 disease

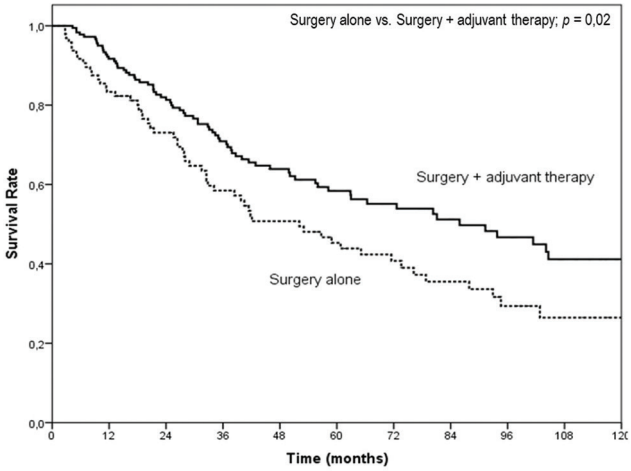

Figure 3: Survival curve of patients receiving and not receiving adjuvant therapy in N1 disease

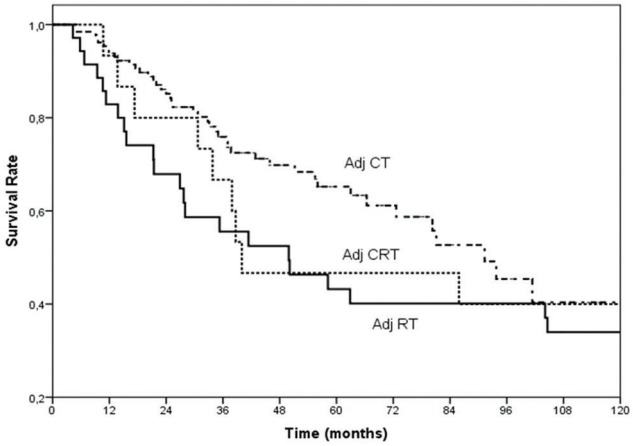

Figure 4: Survival curve according to adjuvant treatment modality applied in N1 disease

P = 0.39, respectively). Hilar and intrapulmonary LNs were classified according to whether they were simultaneously or separately positive and 5-year survival outcomes were compared. Survival was worse when involvement occurred in both zones at the same time (5-year survival: 49.4%); however, the difference was not statistically significant (P = 0.58). When LN involvement was analyzed as single station (n = 246) and multiple stations (n = 30), 5-year survival rates were 54.6% and 47.7%, respectively (P = 0.28).

In univariate analysis, age group and adjuvant therapy were variables affecting survival and this was supported by the Cox regression analysis (P = 0.001 and P = 0.012, respectively) [Table 2].

Discussion

Stage is one of the most important prognostic factors in NSCLC.[3] One of the most important parameters determining the stage is LN metastases.[4] Patients with N0 disease (without regional LN involvement) or N1 disease (ipsilateral intrapulmonary, peribronchial, or hilar LN involvement) are likely to have good long-term outcomes and eligible for surgery.[5] Although several prognostic factors have been identified in the literature for the characteristics of the N1 disease after surgery, no consensus has been reached. The expected 5-year survival rates after resective surgery due to N1 disease have been reported in a wide range of 27.2%–67%.[6] This rate is 53.7% in our series. Conversely, patients with N2 and N3 disease usually receive chemotherapy and/or radiotherapy and 5-year survival rates range from 15% to 30%.[7]

There are two ways in which cancer cells metastasize from the primary tumor to LN. One is metastasis to a separate LN from the primary tumor with lymphatic flow and the other is metastasis directly to the adjacent LN.[2] There are some reports suggesting that these two different ways have different prognostic values

Table 2: Multivariate analysis showing risk factors for N1 patients who underwent resection due to non-small cell lung cancer

Variables	*P*	Risk ratio
Pleural invasion	0.81	-
Gender	0.22	-
Age group (≤60, >60)	**0.001**	**1.82**
Resection type	0.15	-
Tumor size	0.65	-
Neoadjuvant therapy	0.70	-
Adjuvant therapy (yes/no)	**0.012**	**1.58**
Histology (squamous/nonsquamous)	0.54	-
LN localization	0.52	-
pT classification	0.21	-

Bold values represent statistically significant outcomes. LN: Lymph node, pT: Pathologic T

and should be classified in the TNM staging system separately.[2,8] Some groups have reported that location of N1 station involvement (hilar versus intrapulmonary) is an important prognostic factor.[8-10] On the other hand, some studies have reported that the effect of hilar and intrapulmonary pN1 involvement on adjuvant treatment and its prognostic significance are different.[11] In our study, neither the N1 zone nor the number of N1 stations had a statistical significance in terms of long-term survival outcomes. Size of primary tumor, age, and adjuvant treatment were among the noteworthy prognostic factors in our series. In general, no definitive recommendations can be made for the adjuvant chemotherapy of NSCLC resected completely, and this issue requires further research. Some randomized studies on adjuvant treatment have not shown consistent survival benefit for early-stage patients.[12,13] Contrary to this, in our retrospective study, the following adjuvant treatment regimens (especially chemotherapy in recent periods) provided significantly better survival in patients who underwent complete resection. Patients receiving only radiotherapy constituted only the 1st years of the study. In the following years, chemotherapy was the first option in pN1 patients and the group with the best survival rate was the one receiving adjuvant chemotherapy after complete surgery. Five-year survival rate of this group was 65.2%. In our study, the effects of hilar and intrapulmonary pN1 involvement on survival were not statistically different. Based on this, we can say that chemotherapy should be given to patients for pN1 regardless of the LN involvement zone.

In some studies including surgical-pN1 patients, no significant difference among age groups was reported in terms of survival. Fujimoto *et al*.[14] found 5-year survival rate of 40.5% in patients aged 65 and above. This rate was 44.9% in younger patients and the difference was not significant. Similarly, Osaki *et al*.[15] reported that the difference was not statistically significant, although 5-year survival was better in younger patients (60.1% vs. 42.2%). In our study, we found out that patients aged 60 years and older had lower survival than younger patients. According to this, 5-year survival rate was 46.9% in older patients, whereas it was 59.7% in younger patients and the difference was statistically highly significant ($P < 0,001$).

Studies stating that survival gets significantly worse with increasing T classification in surgical-pN1 NSCLC have reported better survival, especially in pT1N1 and pT2N1.[14,15] In some studies claiming otherwise, it was suggested that prognosis in pT3N1 and pT4N1 diseases was not affected by the characteristics of N1 LN involvement, contrary to pT1N1 and pT2N1 diseases.[8] In our series, survival in pT3N1 and pT4N1 patients was adversely affected when compared with pT1N1 and pT2N1 patients. While 5-year survival was 45% in these patients, it was 58.1% in pT1N1 and pT2N1 patients. The difference was considered marginally significant ($P = 0.055$).

In our study group, there were 27 patients receiving neoadjuvant therapy and almost all of them were neoadjuvant chemotherapy patients. Five-year survival rate was 48.7% in the patients receiving neoadjuvant therapy, whereas it was 54.7% in the other patient group who did not undergo this process. In terms of histopathologic tumor type, the group of squamous cell carcinoma had the largest number of patients (62.7%) and the survival rate was higher in these patients than in the other histological types. However, there was no statistically significant difference in both survival analysis according to histologic type and the patient group receiving neoadjuvant treatment. However, some previous studies reported a better prognosis of squamous cell carcinoma histology in pN1 disease.[8,16]

Anatomically, the visceral pleura contains plenty of lymphatic capillaries, which form a network draining into pulmonary lymphatic system. After this network is invaded by primary lung cancer, a pathway for systemic micrometastasis is possible.[14] Nakao *et al*.[2] determined that peripheral localization and pleural involvement were significant prognostic factors in N1 disease. Fujimoto *et al*.[14] reported that pleural invasion was not only a negative prognostic factor for survival, but also increased the incidence of local and distant recurrences significantly. Similar to these studies, patients with pleural invasion had a worse prognosis in our study. However, the difference between the 5-year survival rates, which were 40.3% in pN1 patients with pleural invasion and 58% in pN1 patients without pleural involvement, was not statistically significant.

Many studies have suggested that pneumonectomy in N1 disease establishes a better locoregional control than

lobectomy.[17,18] However, lobectomy is the preferred procedure for N1 disease as long as complete resection is possible, and lobectomy is associated with less operative mortality.[18] In a study, sleeve resection and pneumonectomy were compared in N1 patients and locoregional recurrence was found to be more common among patients who underwent sleeve resection.[19] As a result of the study, the authors recommended sleeve resection for selected cases without LN metastasis. Based on all these findings, it can be speculated that pneumonectomy provides a wider lymphatic clearance than lobectomy or sleeve resection does.[20] However, further work is needed to better illuminate this subject. The incidence of pneumonectomy in N1 disease is reported between 26% and 71%.[9,21] In N1 disease, we performed pneumonectomy on 41.7% of the patients, and the survival rate we obtained in pneumonectomy patients was similar to that in lobectomy patients.

Conclusion

pN1 disease in NSCLC refers to a heterogeneous group. In pN1 disease, advanced age and T classification affect long-term survival adversely ($P = 0.001$ and $P = 0.055$, respectively), while adjuvant therapy has a positive effect on survival ($P = 0.01$). Our results suggest that giving adjuvant therapy to all eligible patients who underwent curative lung resection due to NSCLC could be beneficial to survival in pN1 disease.

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Conflicts of interest
There are no conflicts of interest.

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