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**Original Article**

# Factors affecting survival after resection of stage IIB non-small cell lung cancer

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## ABSTRACT

**Background:** Our aim in this study was to evaluate prognostic factors affecting survival and disease-free survival (DFS) in the subgroups of stage IIB NSCLCs.

**Materials and Methods:** Patients with stage IIB NSCLC who underwent surgery in our hospital between January 2006 and December 2015 were included in the study. The patients were evaluated in two groups: T3N0 patients staged as IIB due to pN0 (Group A) and T1N1/T2N1 patients (Group B).

**Results:** Of the 192 patients were included in the study. There were 47 patients in group A (24.5%) and 145 patients in group B (75.5%). 5-year survival rates was 58.2%. There was no statistically significant difference in survival according to T stage. The 5-year survival rates in the T1, T2, and T3 groups were 69%, 55.3%, and 54.6%, respectively ($p = 0.34$). The main prognostic factors affecting survival were advanced age ($p = 0.02$). The mean DFS was 72 months and the 5-year DFS rate was 54%. Advanced age and male sex, were identified as poor prognostic factors for DFS ($p < 0.005$).

**Conclusions:** The stage IIB category remains heterogeneous despite the updated eighth edition IASCL staging system. The results of our study indicate that age was the main prognostic factors affecting survival in stage IIB NSCLC. However, the effect of visceral pleural invasion and lymph node involvement on survival in stage IIB subgroups was not detected, more comprehensive multicenter studies are still needed.

**Keywords:** lung cancer, stage IIb, survival, prognostic factors, pleural invasion

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## Introduction

Lung cancer currently ranks first in cancer-related deaths [1,2]. Surgical resection is the main treatment method for early non-small cell lung cancer (NSCLC). However, stage IIB NSCLC represents a heterogeneous group of tumors. One of the biggest changes in the eighth edition of the International Association for the Study of Lung Cancer (IASLC) classification for lung cancer was moving the group labeled stage IIA in the seventh edition to stage IIB, while the classification of TIIB (> 5 cm) in the seventh edition is regarded as T3 in the new staging. However, the other T3 factors of a second tumor in the same lobe and parietal pleural invasion remained unchanged. Therefore, patients who were previously considered stage IIA (TIIBN0M0) were included in stage IIB (T3N0M0). This resulted in considerable heterogeneity in the stage IIB group in the eighth edition of the staging system [3]. According to the eighth edition of the IASLC TNM classification, stage IIB includes 3 different subgroups: T1N1, T2N1, and T3N0 [4]. Due to this heterogeneity, there have been publications suggesting that the factors of T stage and N stage have different effects on survival [5]. The present study aimed to evaluate factors affecting survival and prognosis in this heterogeneous group.

Our objective was to evaluate prognostic factors associated with survival and disease-free survival (DFS) in the subgroups constituting stage IIB NSCLC.

## Materials and Methods

Patients who underwent surgical resection of stage IIB NSCLC in our hospital between January 2006 and December 2015 were included in the study. The study was designed retrospectively. Patients who did not receive adjuvant therapy (poor general condition or refused treatment), who received neoadjuvant therapy and were down-staged, or who underwent nonanatomical resection and incomplete resection were excluded from the study. Patients who underwent sleeve resection and had invasion of the chest wall were classified as extended resections. The included patients were evaluated in 2 groups. The first group consisted of pT3N0 patients staged as IIB due to pN0 (group A), while the second group comprised pT1N1 and pT2N1 patients (group B). Sufficient sample size calculated as 88 patients (44 for each groups), alpha value was 0.05, Beta value was 0.02 and the power value of the study calculated as 0.8. The study was approved by the institutional review board and conducted in accordance with the principles of the Declaration of Helsinki (2020-62).

### Patient Selection

Preoperatively, all patients underwent thoracic computed tomography (CT) evaluation as well as positron emission tomography (PET/CT) and cranial magnetic resonance imaging (MRI) for the evaluation of distant metastases. Pulmonary function testing was performed for assessment of pulmonary reserve. Echocardiographic examination was done and the cardiology department was consulted for patients who were > 60 years of age or had a history of cardiac disease. Fiberoptic bronchoscopy was also performed preoperatively to evaluate endobronchial lesions.

The patients underwent curative lobectomy or pneumonectomy. Preoperative mediastinal staging was performed with endobronchial ultrasound bronchoscopy with transbronchial needle aspiration or mediastinoscopy in patients who had mediastinal lymph nodes greater than 1 cm on thorax CT and/or mediastinal hilar pathological uptake of 18-FDG on PET/CT during preoperative period.

Mediastinal lymph node dissection including at least 3 stations was performed. Routine sampling of the paratracheal and subcarinal lymph nodes was done in right-side operations, while the subaortic, paraaortic, and subcarinal lymph nodes together with the other mediastinal and hilar lymph nodes were sampled in left-side operations. Pathologic staging was based on the eighth edition of the IASLC classification [6].

Follow-up information was obtained from all patients through office visits or from their primary physicians. In collaboration with the oncology team, patients were followed by chest CT and physical examination every 3 months for the first 2 years, every 6 months from 2 to 5 years, and once a year thereafter. All patients had postoperative consultation with the oncology department and received adjuvant chemotherapy. Because the study was retrospective and molecular testing is not covered by social insurance, this analysis was not done for all adenocarcinoma patients.

### Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical data, and relationships between

categorical data were evaluated using chi-square ($\chi^2$) or Fisher's exact test. Student's t and Mann–Whitney U tests were used for continuous variables. Overall and disease-free survival were evaluated by Kaplan–Meier analysis and factors were compared using log-rank analysis. P values less than 0.05 were considered statistically significant. All analyses were done using SPSS (version 22, IBM Corp., Armonk, NY, USA) package software.

## Results

A total of 192 patients were included in the study. Of these, 8 (4.2%) were women and 184 (95.8%) were men. The mean age of the patients was 59.3 ± 8.4 years. There were 47 patients in group A (24.5%) and 145 patients in group B (75.5%). In terms of operative characteristics, 87 patients (45.3%) had right-side resections and 105 patients (54.7%) had left-side resections; 147 patients (76.6%) underwent lobectomy and 45 (23.4%) underwent pneumonectomy. Chest wall resection was performed in 6 patients (3.1%) and sleeve resection in 17 patients (8.9%). The mean tumor diameter determined after resection was 4.1 ± 1.5 cm. Postoperative pathologic diagnosis was adenocarcinoma in 67 patients (34.9%), squamous cell carcinoma in 123 patients (64.1%), and adenosquamous cell carcinoma in 2 patients (1%). Comparison of demographic characteristics between groups A and B revealed statistically significant differences in age, visceral pleural invasion, and histopathology ($p < 0.05$). The demographic and operative characteristics of the patient groups are shown in table 1.

Median survival time was 89 months; 5- and 10-year survival rates were 58.2% and 43%, respectively. Median follow-up time was 68 months. There was no statistically significant difference in survival according to T stage. The 5-year survival rates in the T1, T2, and T3 groups were 69%, 55.3%, and 54.6%, respectively ($p = 0.34$). The main prognostic factors affecting survival were advanced age ($p = 0.02$). Table 2 shows prognostic factors associated with survival.

The mean DFS was 72 months and the 5-year DFS rate was 54%. Advanced age and male sex, were identified as poor prognostic factors for DFS ($p < 0.005$). Prognostic factors affecting DFS are shown in table 3.

**Table 1.** Comparison of demographic and histopathological characteristics between the groups.

| Variable | | Group A | | Group B | | p value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| Age (years), mean±SD | | 61.6±7.3 | | 58.5±8.6 | | **0.019** |
| Age (years) | <65 | 28 | 59.6 | 107 | 73.8 | 0.064 |
| | ≥65 | 19 | 40.4 | 38 | 26.2 | |
| Sex | Male | 46 | 97.9 | 138 | 95.2 | 0.682 |
| | Female | 1 | 2.1 | 7 | 4.8 | |
| Side | Right | 24 | 51.1 | 63 | 43.4 | 0.362 |
| | Left | 23 | 48.9 | 82 | 56.6 | |
| Operation | Lobectomy | 47 | 100 | 100 | 69 | **<0.001** |
| | Pneumonectomy | 0 | 0 | 45 | 31 | |
| Resection type | Standard | 40 | 85.1 | 129 | 89 | 0.479 |
| | Extended | 7 | 14.9 | 16 | 11 | |
| Histopathology | Adenocarcinoma | 28 | 59.6 | 39 | 26.9 | **<0.001** |
| | Squamous cell ca | 19 | 40.4 | 104 | 71.7 | |
| | Adenosquamous cell ca | 0 | 0 | 2 | 1.4 | |
| Visceral pleural invasion | No | 22 | 46.8 | 103 | 71 | **0.002** |
| | Yes | 25 | 53.2 | 42 | 29.5 | |

*Bold values indicate statistical significance ($p < 0.05$)*

**Table 2.** Factors associated with survival.

| Variables | | 5-Year Survival (%) | Median survival | Univariate (months) | Multivariate HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Age (years) | <65 | | | **0.019** | 1.5 ( 1,0-2.3) | **0.028** |
| | ≥65 | 47.7 | 59 | | | |
| Sex | Male | 56.4 | 85 | **0.035** | | |
| | Female | 100 | 106 | | | |
| Side | Right | 59.5 | 94 | 0.829 | | |
| | Left | 57.1 | 85 | | | |
| Histopathology | Squamous cell ca | 50.3 | 74 | 0.299 | | |
| | Adenocarcinoma | 62.6 | 91 | | | |
| Stage | Group A | 54.6 | 67 | 0.885 | | |
| | | 59.3 | 91 | | | |
| T Stage | 1 | 69 | 99 | 0.347 | | |
| | 2 | 55.3 | 88 | | | |
| | 3 | 54.6 | 67 | | | |
| Visceral pleural invasion | No | 58.6 | 101 | **0.039** | | |
| | Yes | 47.8 | 71 | | | |
| N1 status | Single-station N1 | 63.3 | 99 | 0.138 | | |
| | Multi-station N1 | 51.1 | 73 | | | |
| Operation | Lobectomy | 59.7 | 91 | 0.316 | | |
| | Pneumonectomy | 53.3 | 73 | | | |
| Resection Type | Standard | 56.1 | 92 | 0.172 | | |
| | | 73.9 | 96 | | | |

*Bold values indicate statistical significance (p < 0.05)*

**Table 3.** Factors associated with DFS.

| Variables | | 5-Year Survival (%) | Median Survival (months) | Univariate p | Multivariate HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Age (years) | <65 | 58.3 | 91 | **0.007** | 1.6 (1.1-2.4) | **0.010** |
| | ≥65 | 40.4 | 48 | | | |
| Sex | Male | 52 | 84 | **0.024** | | |
| | Female | 100 | 105 | | | |
| Side | Right | 44.7 | 64 | 0.983 | | |
| | Left | 57.1 | 74 | | | |
| Histopathology | Squamous cell ca | 61 | 42 | 0.125 | | |
| | Adenocarcinoma | 38.9 | 90 | | | |
| Stage | Group A | 52.5 | 61 | 0.815 | | |
| | Group B | 54.5 | 78 | | | |
| T Stage | 1 | 61.9 | 85 | 0.540 | | |
| | 2 | 51.5 | 74 | | | |
| | 3 | 52.5 | 61 | | | |
| Visceral pleural invasion | No | 55.7 | 90 | **0.045** | | |
| | Yes | 46.3 | 47 | | | |
| N1 status | Single-station N1 | 57.1 | 90 | 0.265 | | |
| | Multi-station N1 | 48.9 | 60 | | | |
| Operation | Lobectomy | 56.3 | 78 | 0.225 | | |
| | Pneumonectomy | 46.7 | 57 | | | |
| Resection Type | Standard | 51.3 | 84 | 0.185 | | |
| | | 73.9 | 90 | | | |

*Bold values indicate statistical significance (p <0.05)*

## Discussion

Stage IIB tumors have always been controversial in lung cancer staging due to the heterogeneity of this group. In particular, factors affecting survival and recurrence prognosis vary [5,7]. Of these factors, the most controversial are older age, pleural involvement, and T and N status.

Especially in lung cancers, age is among the most important prognostic factors for survival [8,9]. Liu et al [10] showed that the survival rate decreased with higher age in patients with pathological stage N1 disease. In contrast, Sayan et al [5] reported that age was not a prognostic factor in overall survival in stage IIB patients. In our study, the 5-year overall survival rate was 62.8% in patients under 65 years of age and 47.7% in patients aged 65 and older. Similarly, DFS was significantly shorter in patients over 65 and advanced age was identified as a significant prognostic factor in multivariate analyses.

Visceral pleural invasion is one of the most heterogeneous factors in the prognosis of stage IIB tumors. Some studies have indicated it to be a significant prognostic factor even in early-stage lung cancer [11-15]. Jiwangga et al [16] also showed that bilateral pleural seeding metastasis was the most common recurrence pattern in stage I lung cancer patients with visceral pleural invasion. In 2019, Shin et al [3] determined that visceral pleural invasion was a poor prognostic factor for recurrence and survival in their study of 122 patients diagnosed with stage IIB (hazard ratio: 1.940). Endo et al [17] reported the DFS rate as 48.6% in stage IIB disease and showed that the most important cause of recurrence was visceral pleural invasion. Van Velzen et al [18,19] and Yin et al [18,19] similarly concluded that visceral pleural invasion is a poor prognostic factor for stage IIB NSCLC. In the present study, the 5-year DFS rate was 46.3% in patients with visceral pleural invasion compared to 55.7% in patients without visceral pleural invasion ($p < 0.05$). Visceral pleural invasion was also found to be the most important factor in terms of recurrence, as in previous studies [5,18]. Consequently, the detection of visceral pleural invasion in stage IIB patients emerged as the most important factor in terms of recurrence follow-up. However, when multivariate analysis was performed, it was found that visceral pleural invasion did not affect survival.

Deterbeck et al [4] reported a survival rate of 56% among patients with pathological stage IIB as in their eighth edition staging system study. In a study comparing the differences between seventh and eighth edition TNM classifications, Goldstraw et al [6] determined the respective 5-year survival rates as 47% and 53% for the stage IIB subgroup. In their comparison of stage IIB subgroups, Asamura et al [20] observed 50% survival of T1N1M0 patients and 38% survival of T3N0M0 patients and reported that tumor diameter was the most important prognostic factor for survival. Dai et al [21] also stated that N status is an important factor for survival and the presence of ≥ 3 N1 lymph nodes is a poor prognostic criterion. However, Maniwa et al [22] did not detect any effect of metastatic lymph node count on survival in N1 patients. In the present study, 5-year overall survival rates were 58.2% among all patients and 69.0%, 55.3%, and 54.6% for T1N1, T2N1, and T3N0 patients, respectively ($p = 0.34$).

Cerfolio et al [23] reported that patients with histopathological diagnosis of adenocarcinoma had higher survival rates compared to other histopathological types. Survival was also longer for squamous cell carcinoma patients than adenocarcinoma patients in the present study (50.3% vs. 62.6%) but the difference was not a statistically significant ($p = 0.29$).

There are differing views on the association between extent of resection and survival in the literature. Patients who undergo pneumonectomy were reported to have poorer survival outcomes [5,24-26]. Sayan et al [5] determined that stage IIB patients who underwent lobectomy and segmentectomy had better survival outcomes compared to those who had pneumonectomy and chest wall resections ($p < 0.05$). Alexiou et al [27] emphasized that although pneumonectomy was associated with worse operative mortality compared to lobectomy, there was a favorable impact on survival. Unlike other publications, Dai et al [21] observed no survival difference between lobectomy patients and pneumonectomy patients ($p = 0.399$). Sezen et al [28] also reported no prognostic relationship between extent of resection and survival in geriatric patients. In contrast to many studies in the literature, resection type was not found to have an effect on survival in the present study. We attribute this to patient selection and believe that patients' performance status influences their survival outcomes.

The main limitation of the study is that attempting to generalize results obtained from a small patient group creates bias. In addition, the retrospective nature of the study, underrepresentation of the female sex, and the inclusion of operations performed by different surgeons.

In conclusion the stage IIB category remains heterogeneous despite the updated eighth edition IASCL staging system. The results of our study indicate that age was the main prognostic factors affecting survival in stage IIB NSCLC. However, the effect of visceral pleural invasion and lymph node involvement on survival in stage IIB subgroups was not detected, more comprehensive multicenter studies are still needed.

## Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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## Ethics approval

The study was approved by the institutional review board of Health Sciences University Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (No: 2020-62).

## Authors' contribution

CA; performed the analysis, co-wrote the paper, contributed data or analysis tools, CBS; conceived and designed the analysis, performed the analysis, co-wrote the paper. MVD, LC, MM, MAB; contributed data, co-wrote the paper, NY, VE; collected the data.

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