Korean J Thorac Cardiovasc Surg 2019;52:131-140 □ CLINICAL RESEARCH □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) https://doi.org/10.5090/kjtcs.2019.52.3.131

Prognostic Factors in Stage IIB Non-Small Cell Lung Cancer according to the 8th Edition of TNM Staging System

Jin Won Shin, M.D.[1], Deog Gon Cho, M.D., Ph.D.[1], Si Young Choi, M.D., Ph.D.[2,*], Jae Kil Park, M.D., Ph.D.[3], Kyo Young Lee, M.D., Ph.D.[4], Youngkyu Moon, M.D., Ph.D.[3,*]

[1]Department of Thoracic and Cardiovascular Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon; [2]Department of Thoracic and Cardiovascular Surgery, St. Paul's Hospital, College of Medicine, The Catholic University of Korea; Departments of [3]Thoracic and Cardiovascular Surgery and [4]Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: The purposes of this study were to evaluate the appropriateness of the stage migration of stage IIA non-small cell lung cancer (NSCLC) in the seventh edition of the tumor, node, and metastasis classification for lung cancer to stage IIB lung cancer in the eighth edition, and to identify prognostic factors in patients with eighth-edition stage IIB disease. **Methods:** Patients with eighth-edition stage IIB disease were subclassified into those with seventh-edition stage IIA disease and those with seventh-edition stage IIB disease, and their recurrence-free survival and disease-specific survival rates were compared. Risk factors for recurrence after curative resection were identified in all included patients. **Results:** Of 122 patients with eighth-edition stage IIB NSCLC, 101 (82.8%) had seventh-edition stage IIA disease and 21 (17.2%) had seventh-edition stage IIB disease. Nonsignificant differences were observed in the 5-year recurrence-free survival rate and the 5-year disease-specific survival rate between the patients with seventh-edition stage IIA disease and those with seventh-edition stage IIB disease. Visceral pleural invasion was a significant risk factor for recurrence in patients with eighth-edition stage IIB NSCLC. **Conclusion:** The stage migration from seventh-edition stage IIA NSCLC to eighth-edition stage IIB NSCLC was appropriate in terms of oncological outcomes. Visceral pleural invasion was the only prognostic factor in patients with eighth-edition stage IIB NSCLC.

Key words: 1. Prognosis
2. Non-small-cell lung carcinoma
3. Stage IIB
4. 8th edition

Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. The eighth edition of the tumor, node, and metastasis (TNM) classification of lung cancer was proposed by the International Association for the Study of Lung Cancer (IASLC) in 2015 and enacted on January 1, 2017 [2]. The changes in the new TNM staging system consist of adjustments of the T descriptors, emphasizing the prognostic impact of tumor size and redefining the classification of additional tumor nodules; a redefinition of malignant

Received: November 27, 2018, Revised: December 27, 2018, Accepted: December 31, 2018, Published online: June 5, 2019

Corresponding author: Youngkyu Moon, Department of Thoracic and Cardiovascular Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
(Tel) 82-2-2030-4507 (Fax) 82-2-2030-2617 (E-mail) mykae@catholic.ac.kr

**Current affiliation: Department of Thoracic & Cardiovascular Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea*

pleural effusion and the subclassification of M1; and a rearrangement of the stage groups; however, the N descriptors were left unchanged [2-4].

The eighth edition of the TNM classification presents many changes in the T categories, which are based on tumor size, as follows: T1a ≤1 cm, T1b ≥ 1 to 2 cm, T1c ≥2 to 3 cm, T2a ≥3 to 4 cm, T2b ≥4 to 5 cm, T3 ≥5 to 7 cm, and T4 ≥7 cm [5]. The previous T3 classification (>7 cm) was upgraded to T4 in the eighth edition. The seventh-edition T2b (>5 cm) classification was also changed in the eighth edition to T3. However, other T3 factors such as lung-to-lung metastasis (same lobe) and parietal pleural invasion were not changed. Therefore, previous stage IIA (T2bN0M0) disease was changed in the eighth edition to stage IIB (T3N0M0) disease. As a result, stage IIB lung cancer in the eighth edition of the TNM classification is a combination of seventh-edition stage IIA (T2bN0M0) and seventh-edition stage IIB (T3N0M0) non-small cell lung cancer (NSCLC).

Even though the N descriptors remained unchanged, because almost all N1 disease was upgraded from stage IIA to stage IIB [5], eighth-edition stage IIB comprises many heterogeneous TNM groups, as follows: T1aN1M0, T1bN1M0, T1cN1M0, T2aN1M0, T2bN1M0, and T3N0M0. In contrast, seventh-edition stage IIB only consisted of T2bN1M0 and T3N0M0 disease. To the best of our knowledge, however, studies have not yet evaluated the appropriateness of combining seventh-edition IIA and seventh-edition stage IIB disease and reclassifying the combination in the eighth edition as stage IIB disease. The eighth-edition stage IIB classification subdivides the T category into 6 groups (T1a to T3) and incorporates several factors that are associated with outcomes (visceral pleural invasion [T2], parietal pleural invasion [T3], lung to lung metastasis [T3], and lymph node metastasis [N1]). Therefore, identifying predictive factors of outcomes in patients with eighth-edition stage IIB disease would potentially enable the subclassification of stage IIB disease into additional subgroups in a future staging system.

The purposes of this study were to evaluate the appropriateness of the stage migration of stage IIA NSCLC in the seventh edition of the TNM classification for lung cancer to stage IIB lung cancer in the eighth edition, and to identify prognostic factors in patients with eighth-edition stage IIB disease.

Methods

1) Patients

From January 2006 to July 2016, 1,551 consecutive patients were diagnosed with and surgically treated for NSCLC at a tertiary hospital in South Korea. Of those patients, 1,126 underwent standard anatomical pulmonary resection (more than lobectomy) with systematic nodal dissection. Patients were reclassified according to the eighth edition of the TNM staging system. Among the reclassified patients, 122 patients were diagnosed with eighth-edition stage IIB NSCLC. None of the study patients received incomplete resection. These consecutive patients were reviewed retrospectively. The clinicopathological characteristics of the tumors and oncological outcomes were analyzed. Patients with eighth-edition stage IIB disease were subclassified into those with seventh-edition stage IIA disease and those with seventh-edition stage IIB disease, and their recurrence-free survival (RFS) and disease-specific survival (DSS) rates were compared. Risk factors for recurrence after curative resection were identified. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, the Catholic University of Korea (IRB approval no., KC19RESI0173).

2) Surgical procedures and systematic nodal dissection

Patients with stage II NSCLC are considered candidates for curative surgery at Seoul St. Mary's Hospital. Every patient underwent surgery, which included more than only lobectomy, and they all underwent mediastinal lymph node dissection of more than 3 mediastinal lymph node stations (operations on the right lobe included paratracheal and subcarinal lymph node dissection, and operations on the left lobe included subaortic and subcarinal lymph node dissection). They all underwent dissection of every visible hilar, peribronchial, and perivascular N1 lymph node. The en bloc resection technique was used for lymph node dissection, including adjacent fat tissue.

Table 1. Clinicopathological characteristics of patients with stage IIB non-small cell lung cancer after curative surgery

Characteristic	Value
Age (yr)	64.6±8.5
Sex	
Male	87 (71.3)
Female	35 (28.7)
Current or former smoker	68 (55.7)
Serum carcinoembryonic antigen level (ng/mL)	10.0±21.8
Maximum standardized uptake value	9.2±5.4
Eighth TNM stage	
T1aN1M0	1 (0.8)
T1bN1M0	7 (5.7)
T1cN1M0	16 (13.1)
T2aN1M0	43 (35.2)
T2bN1M0	11 (9.0)
T3N0M0	44 (36.1)
Involved lobe	
Right upper	37 (30.3)
Right middle	7 (5.7)
Right lower	23 (18.9)
Left upper	28 (23.0)
Left lower	27 (22.1)
Pulmonary function	
Forced expiratory volume in 1 second (%)	92.6±19.4
Diffusing capacity for carbon monoxide (%)	86.7±19.3
Operation	
Lobectomy	113 (92.6)
Bilobectomy	6 (4.9)
Pneumonectomy	3 (2.5)
Video-assisted thoracoscopic surgery	72 (59.0)
Open thoracotomy	50 (41.0)
Postoperative complications	
Total	22 (18.0)
Prolonged air leak	12 (9.8)
Chylothorax	1 (0.8)
Pneumonia	6 (4.9)
Pulmonary thromboembolism	1 (0.8)
Wound infection	2 (1.6)
Operative mortality	1 (0.8)
Adjuvant chemotherapy	76 (62.3)
Total tumor size (cm)	3.9±1.6
Invasive component size (cm)	3.8±1.7
Metastatic lung nodule (stage T3)	1 (0.8)
Location	
Central	37 (30.3)
Peripheral	85 (69.7)
Histology	
Adenocarcinoma	73 (59.8)
Squamous cell carcinoma	41 (33.6)
Others	8 (6.6)
No. of dissected lymph nodes	14.7±7.6
Pleural invasion	
Visceral pleural invasion	33 (27.0)
Parietal pleural invasion	16 (13.1)
Lymphovascular invasion	104 (85.2)

Values are presented as mean±standard deviation or number (%).
TNM, tumor, node, and metastasis.

(Continued to the next page)

3) Histological evaluation and restaging to the eighth-edition staging system

All clinical specimens were examined by pathologists, whose observations were recorded. Each patient report was reviewed for tumor size, location, lymph node status, pleural invasion, and lymphovascular invasion. The presence of visceral pleural invasion was defined as tumor extension beyond the elastic layer of the visceral pleura. Lymphovascular invasion was defined by the presence of tumor cells in the lymphatic or vascular lumen. Histologic features, as well as the presence of pleural invasion, lymphatic invasion, or vascular invasion, were determined by examining slides of tissue sections stained by hematoxylin and eosin. If the findings could not be determined on hematoxylin-and-eosin stained tissue alone, special staining such as the Verhoeff-Van Gieson elastic stain was performed as necessary. In particular, Verhoeff-Van Gieson elastic staining was performed for a detailed evaluation of visceral pleural invasion. TNM staging was based on the eighth IASLC edition of the TNM staging system [2]. To reclassify the T category according to the eighth edition, tumor size was measured again by the pathologist as the greatest dimension of the invasive component on the histopathologic study [6]. In the eighth edition, the N category remained unchanged from the seventh edition, and was thus not reclassified [4].

4) Follow-up evaluations

All patients were evaluated from the day of surgery. For the first 2 years, the patients were evaluated via physical examinations and chest radiography every 3 months, and chest computed tomography (CT) that included cervical and abdominal views every 6 months. Thereafter, they were assessed with physical examinations and chest CT ev-

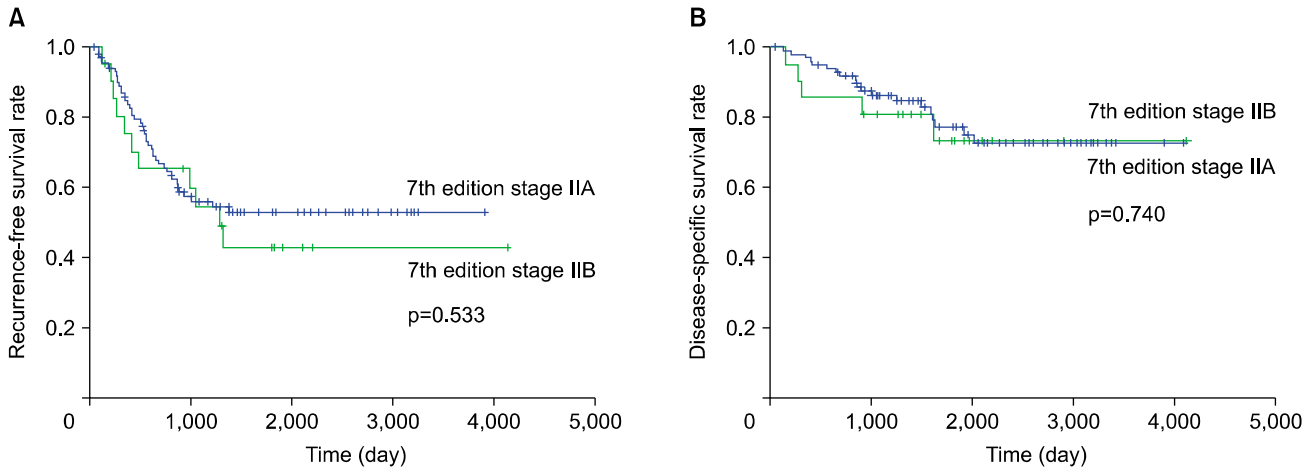

Fig. 1. Comparisons of recurrence-free survival (A) and disease-specific survival (B) rates in patients with eighth-edition stage IIB non-small cell lung cancer after surgery who were subdivided into seventh-edition stage IIA and seventh-edition stage IIB groups.

ery 6 months for 5 years, after which they were evaluated annually.

5) Statistical analysis

The clinicopathological characteristics of the study patients were compared by the Student t-test or the Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher exact test for categorical variables. The Kaplan-Meier method was used to analyze data collected from the interval between the time of surgical resection and the time of the final follow-up visit. RFS and DSS were estimated by the Kaplan-Meier method from the collected data on confirmed cases of recurrence and cancer-related deaths. The Cox proportional hazards model was used in a univariate analysis to determine the risk of recurrence and cancer-related death for all the study patients. A p-value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM SPSS ver. 24.0 software (IBM Corp, Armonk, NY, USA).

Results

The clinicopathological characteristics of the 122 study patients are shown in Table 1. The mean± standard deviation age was 64.6±8.5 years, and there were more male (71.3%) than female patients. The number of patients with stage T1aN1M0, T1bN1M0, T1cN1M0, T2aN1M0, T2bN1M0, and T3N0M0 NSCLC were as follows: 1 (0.8%), 7 (5.7%), 16 (13.1%), 43 (35.2%), 11 (9.0%), and 44 (36.1%), respectively.

There were 22 complications (18.0 %) among the patients, as follows: 12 patients with prolonged air leakage, 1 with chylothorax, 6 with pneumonia, 1 with pulmonary thromboembolism, and 2 with wound infection. All complications were managed successfully during the period of hospitalization for curative surgery. There was 1 (0.8%) postoperative mortality.

Adjuvant chemotherapy was recommended for all patients, and 76 (62.3%) of the study patients did receive adjuvant chemotherapy. The remaining 37.7% of patients did not undergo adjuvant chemotherapy for the following reasons: fear of chemotoxicity, underlying comorbidities, postoperative complications, and advanced age.

The mean size of the total tumor and mean size of the invasive component were 3.9 cm and 3.8 cm, respectively. One patient was diagnosed with stage T3 lung cancer because of unilateral lung metastasis, and 37 patients (30.3%) had central lesions. Most of the patients had adenocarcinoma (59.8%), and the others had squamous cell carcinoma (33.6%) and other histologic types (6.6%). The mean number of dissected lymph nodes was 14.7±7.6. The incidences of visceral pleural invasion, parietal pleural invasion, and lymphovascular invasion were 33 (27.0%), 16 (13.1%), and 104 (85.2%), respectively.

Table 2. Comparison of clinicopathological characteristics between the seventh-edition TNM classifications of IIA and IIB non-small cell lung cancer in patients with eighth-edition stage IIB disease

Variable	Seventh-stage IIA (n=101)	Seventh-stage IIB (n=21)	p-value
Age (yr)	64.5±8.2	64.9±10.1	0.867
Sex			0.033
Male	68 (67.3)	19 (90.5)	
Female	33 (32.7)	2 (9.5)	
Current or former smoker	53 (52.5)	15 (71.4)	0.112
Serum carcinoembryonic antigen level (ng/mL)	8.5±16.4	17.4±38.5	0.335
Maximum standardized uptake value	9.0±5.2	10.3±6.1	0.322
Eighth TNM stage			<0.001
T1aN1M0	1 (1.0)	0	
T1bN1M0	7 (6.9)	0	
T1cN1M0	16 (15.8)	0	
T2aN1M0	42 (41.6)	1 (4.8)	
T2bN1M0	10 (9.9)	1 (4.8)	
T3N0M0	25 (24.8)	19 (90.5)	
Involved lobe			0.106
Right upper	26 (25.7)	11 (52.4)	
Right middle	7 (6.9)	0	
Right lower	20 (19.8)	3 (14.3)	
Left upper	23 (22.8)	5 (23.8)	
Left lower	25 (24.8)	2 (9.5)	
Pulmonary function			
Forced expiratory volume in 1 second (%)	94.3±19.7	84.8±15.9	0.041
Diffusing capacity for carbon monoxide (%)	86.7±19.4	86.8±19.2	0.983
Operation			0.725
Lobectomy	93 (92.1)	20 (95.2)	
Bilobectomy	5 (5.0)	1 (4.8)	
Pneumonectomy	3 (3.0)	0	
Video-assisted thoracoscopic surgery	59 (58.4)	13 (61.9)	0.767
Open thoracotomy	42 (41.6)	8 (38.1)	
Postoperative complications	16 (15.8)	6 (28.6)	0.167
Operative mortality	1 (1.0)	0	1.000
Adjuvant chemotherapy	64 (63.4)	12 (57.1)	0.592
Total tumor size (cm)	3.9±1.6	4.2±1.7	0.370
Invasive component size (cm)	3.7±1.7	4.0±1.7	0.370
Metastatic lung nodule (T3)	0	1 (4.8)	0.172
Location			0.005
Central	36 (35.6)	1 (4.8)	
Peripheral	65 (64.4)	20 (95.2)	
Histology			0.605
Adenocarcinoma	62 (61.4)	11 (52.4)	
Squamous cell carcinoma	32 (31.7)	9 (42.9)	
Others	7 (6.9)	1 (4.8)	
No. of dissected lymph nodes	14.8±7.6	14.2±7.6	0.758
Pleural invasion			<0.001
Visceral pleural invasion	31 (30.7)	2 (9.5)	
Parietal pleural invasion	0	16 (76.2)	
Lymphovascular invasion	85 (84.2)	19 (90.5)	0.736

Values are presented as mean±standard deviation or number (%).
TNM, tumor, node, and metastasis.

1) Comparison of the survival rate between the seventh-edition stage IIA group and the seventh-edition stage IIB group in patients with eighth-edition IIB NSCLC

Among the 122 patients with eighth-edition stage IIB NSCLC, 101 (82.8%) were classified as having seventh-edition stage IIA disease and 21 (17.2%) were classified as having seventh-edition stage IIB disease. We compared the survival rates of these patients (Fig. 1) and their clinicopathological characteristics (Table 2). The differences in most of the clinicopathological characteristics between the 2 groups were not significant. There were differences in T factors between the 2 groups (metastatic lung nodule [T3], parietal pleural invasion [T3]). The patients with seventh-edition stage IIA disease had more central tumors than the patients with seventh-edition stage IIB disease.

The difference in the RFS rate between patients with seventh-edition stage IIA and seventh-edition stage IIB disease was not significant (52.8% versus 42.8%, respectively; p=0.533) (Fig. 1A). The difference in the DSS rate between patients in the 2 groups was also not significant (77.4% versus 73.6%, respectively; p=0.740) (Fig. 1B).

2) Survival analysis and risk factors for recurrence in patients with eighth-edition stage IIB NSCLC after curative surgery

The median follow-up time for patients with eighth-edition stage IIB NSCLC was 1,463 days (range, 37–4,127 days), with recurrence identified in 54 patients (Table 3). Among those 54 patients, locoregional recurrence occurred in 19 patients (35.2%), locoregional recurrence with distant recurrence occurred in 20 (37.0%), and distant recurrence only occurred in 15 (27.8%). The 5-year RFS and DSS rates were 50.6% and 76.8%, respectively (Fig. 2). The results of the univariate analysis are shown in Table 4. The single variable identified as significant ($p < 0.05$) in the univariate analysis was visceral pleural invasion. Visceral pleural invasion (hazard ratio, 1.940; p=0.028) was a significant risk factor for recurrence. Table 5 shows the recurrence pattern of patients with eighth-edition stage IIB disease with visceral pleural invasion. Distant recurrence without locoregional recurrence occurred in 50.0% of the patients who developed recurrence. The 2 major sites of distant recurrence were the contralateral lung and brain.

Table 3. Summary of cases of recurrence in study patients

Variable	No. (%)
Overall recurrence	54 (100.0)
Locoregional recurrence[a)]	19 (35.2)
Distant recurrence	15 (27.8)
Both[b)]	20 (37.0)

[a)]Recurrence within the ipsilateral hemithorax, including the pleura and mediastinal lymph nodes. [b)]Locoregional recurrence+ distant recurrence.

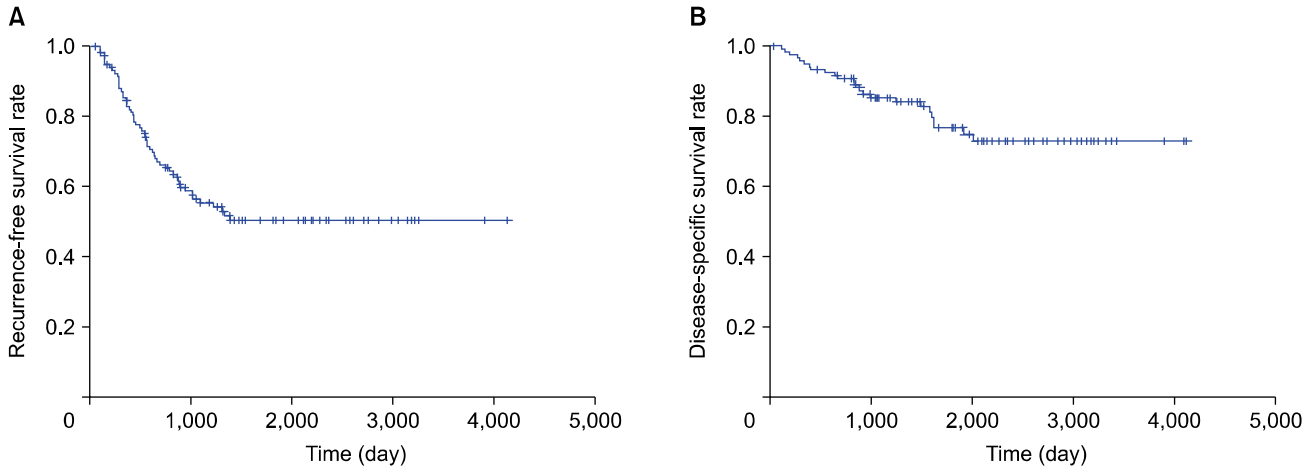

Fig. 2. Recurrence-free survival (A) and disease-specific survival (B) rates of patients with eighth-edition stage IIB non-small cell lung cancer after surgery.

Table 4. Univariate analysis of risk factors for recurrence in patients with eighth-edition stage IIB non-small cell lung cancer after curative surgery

Variable	Hazard ratio (95% confidence interval)	p-value
Age	0.990 (0.958–1.023)	0.551
Sex (male)	1.071 (0.597–1.921)	0.818
Smoker	0.658 (0.386–1.122)	0.124
Serum carcinoembryonic antigen level (ng/mL)	1.009 (0.997–1.022)	0.151
Maximum standardized uptake value	1.004 (0.954–1.057)	0.866
N1	1.053 (0.602–1.843)	0.856
Lobe		0.485
Right upper (reference)	1	
Right middle	0.859 (0.253–2.917)	0.807
Right lower	0.510 (0.202–1.286)	0.154
Left upper	0.990 (0.485–2.023)	0.979
Left lower	1.252 (0.622–2.521)	0.528
Forced expiratory volume in 1 second (%)	0.999 (0.985–1.012)	0.864
Diffusing capacity for carbon monoxide (%)	0.989 (0.974–1.003)	0.131
Video-assisted thoracoscopic surgery	0.728 (0.425–1.246)	0.247
Adjuvant chemotherapy	0.915 (0.533–1.573)	0.748
Invasive component size	1.074 (0.918–1.257)	0.373
Central location	0.596 (0.313–1.134)	0.115
Histology		0.499
Adenocarcinoma (reference)	1	
Squamous cell carcinoma	0.700 (0.377–1.300)	0.259
Others	1.081 (0.384–3.038)	0.883
No. of dissected lymph nodes	0.987 (0.951–1.025)	0.493
Pleural invasion		0.061
Visceral pleural invasion	1.940 (1.076–3.498)	0.028
Parietal pleural invasion	1.837 (0.857–3.938)	0.118
Lymphovascular invasion	0.717 (0.361–1.425)	0.342

TNM, tumor, node, and metastasis.

Table 5. Summary of cases of recurrence in patients with visceral pleural invasion

Variable	No. (%)
Overall recurrence	20 (100)
Locoregional recurrence[a)]	4 (20)
Distant recurrence[b)]	10 (50)
Both[c)]	6 (30)

[a)]Recurrence within the ipsilateral hemithorax, including the pleura and mediastinal lymph nodes. [b)]Distant recurrence (n=10): contralateral lung (n=4), other organ (n=6: brain [n=4], brain+kidney [n=1], brain+supraclavicular node [n=1]). [c)]Locoregional recurrence+distant recurrence.

Discussion

The eighth IASLC edition of the TNM staging system has more subdivisions for T descriptors and M descriptors than the seventh edition of the TNM staging system [2]. Moreover, the stages were also reclassified, leading to stage migration. In the eighth edition, one of the biggest changes was that most stage IIA disease was upstaged to IIB disease. Thus, in the current IASLC staging system, stage IIB comprises many heterogeneous groups of NSCLC. This led to the question of whether patients with eighth-edition stage IIB disease who would have previously been diagnosed with seventh-edition stage IIA disease had outcomes different from those with eighth-edition stage IIB disease who would have previously been diagnosed with seventh-edition stage IIB disease. In this study, the differences between the outcomes (RFS and DSS) of patients with eighth-edition stage IIB grouped according to seventh-edition stage IIA and seventh-edition stage IIB disease were

not significant. The clinicopathological characteristics between the 2 subgroups were also not different, except for T factors and tumor location. Tumor location (central versus peripheral) has also been found to be related to N factors [7,8]. Therefore, the differences in T factors and tumor location were not significant when comparing the outcomes between patients with seventh-edition stage IIA and IIB NSCLC. We therefore concluded that the reclassification of seventh-edition stage IIA disease to stage IIB disease in the eighth edition staging system was appropriate.

The measurement of tumor size was changed in the eighth edition as applied to the T descriptors [5,6,9]. In the seventh edition of the staging system, the total tumor size was measured and the T stage was determined by the maximum size of the total tumor. However, in the eighth edition of the staging system, the T stage is determined by the maximum size of the invasive component without a lepidic component. In this study, there were some T stage migrations (for example, from T2 to T1), but definite stage migration from stage IIB to IIA seldom occurred, because the total tumor size and invasive component size were similar (mean total tumor size, 3.9 cm; mean invasive component size, 3.8 cm). The lepidic component of stage IIB disease in all the patients did not comprise a large proportion of the tumor. The proportion of the lepidic component in advanced cancers is most likely small [10], indicating that this change in the T category is probably not significant for stage IIB patients.

Other studies have reported that visceral pleural invasion was a significant prognostic factor in early-stage lung cancer [11,12]. Liu et al. [13] reported that visceral pleural invasion was significant, irrespective of tumor size. David et al. [14] reported that visceral pleural invasion in patients with large tumors had a negative effect on survival. However, visceral pleural invasion has not previously been studied in patients with stage IIB disease. Our study of patients with stage IIB NSCLC found that visceral pleural invasion was significantly associated with recurrence.

In this study, visceral pleural invasion was found to be the only risk factor for recurrence in patients with stage IIB NSCLC after surgery. In contrast, parietal pleural invasion was not a risk factor for recurrence. In fact, parietal pleural invasion (T3) is a more aggressive form of NSCLC than visceral pleural invasion (T2). In stage IIB disease, patients with visceral pleural invasion were staged T2aN1M0 and T2bN1M0, whereas patients with parietal pleural invasion were staged T3N0M0. Therefore, we can assume that visceral pleural invasion in patients with N1 disease is a worse prognostic indicator than parietal pleural invasion in patients with N0 disease.

In this study, patients with visceral pleural invasion showed an increased tendency for distant metastasis (80.0%). The lungs have a highly developed lymphatic network. It consists of a subpleural superficial plexus located within the connective tissue of the visceral pleura, and a deep peri-bronchovascular plexus located in the connective tissue of the airways, pulmonary arteries, and veins. The subpleural lymphatics pass under the lung surface towards the hilum, where they anastomose with the deep plexus lymphatics. In general, it is accepted that the superficial plexus takes up lymph from visceral pleura and adjoining layers of the subpleural tissues. On occasion, the subpleural lymphatics can collect directly in the mediastinum, thus explaining the existence of skip metastasis in primary lung cancer patients [15]. Tumors with metastatic lymph nodes tend to develop distant metastases, suggesting that if visceral pleural invasion is present in a patient with NSCLC, there is an increased risk of metastasis due to the greater variety and number of possible routes. Jiwangga et al. [16] reported that the most common recurrence pattern of stage I lung adenocarcinoma with visceral pleural invasion was bilateral lung metastasis with pleural seeding. Their findings support our results regarding recurrence in patients with bilateral lung disease and distant metastasis.

This study has limitations. Firstly, it is a retrospective study and the sample size was too small for its results to be generalized. However, this study collected data from patients treated with a relatively standardized protocol. Furthermore, a detailed analysis was possible because detailed information was stored in patients' electronic medical records. Data describing the surgical procedures in detail were used, and we believe that our data can be used as a basis for future investigations. Larger studies should be conducted to confirm our results. Secondly, the follow-up period was relatively short. However, most patients with NSCLC experience recurrence within 2

years after surgery [17], and early recurrence generally reflect long-term outcomes [18].

In conclusion, because the differences in the RFS and DSS rates between study patients with eighth-edition stage IIB NSCLC who had seventh-edition stage IIA disease and those who had seventh-edition stage IIB NSCLC were not significant, the stage migration from seventh-edition stage IIA NSCLC to eighth-edition stage IIB NSCLC was appropriate in terms of oncological outcomes. Despite the heterogeneity of T and N factors in eighth-edition stage IIB NSCLC, all T and N factors except visceral pleural invasion were not prognostic factors in eighth-edition stage IIB NSCLC. Distant metastatic disease tends to develop in patients with stage IIB NSCLC with visceral pleural invasion. Thus, patients with stage IIB lung cancer with visceral pleural invasion should be carefully monitored for distant recurrence. Additional studies that include data from a larger sample and a longer follow-up period might provide more accurate results.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported by a Grant of the Samsung Vein Clinic Network (Daejeon, Anyang, Cheongju, Cheonan; Fund no. KTCS04-122).

ORCID

Jin Won Shin: https://orcid.org/0000-0002-1693-3927
Deog Gon Cho: https://orcid.org/0000-0003-2431-7179
Si Young Choi: https://orcid.org/0000-0002-7372-6959
Jae Kil Park: https://orcid.org/0000-0002-4953-1473
Kyo Young Lee: https://orcid.org/0000-0001-9954-8583
Youngkyu Moon: https://orcid.org/0000-0002-6875-6918

References

1. Didkowska J, Wojciechowska U, Manczuk M, Lobaszewski J. *Lung cancer epidemiology: contemporary and future challenges worldwide*. Ann Transl Med 2016;4:150.
2. Goldstraw P, Chansky K, Crowley J, et al. *The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer*. J Thorac Oncol 2016; 11:39-51.
3. Rami-Porta R, Bolejack V, Crowley J, et al. *The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer*. J Thorac Oncol 2015;10: 990-1003.
4. Asamura H, Chansky K, Crowley J, et al. *The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer*. J Thorac Oncol 2015;10:1675-84.
5. Rami-Porta R, Asamura H, Travis WD, Rusch VW. *Lung cancer: major changes in the American Joint Committee on Cancer eighth edition cancer staging manual*. CA Cancer J Clin 2017;67:138-55.
6. Travis WD, Asamura H, Bankier AA, et al. *The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer*. J Thorac Oncol 2016;11: 1204-23.
7. De Leyn P, Dooms C, Kuzdzal J, et al. *Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer*. Eur J Cardiothorac Surg 2014; 45:787-98.
8. Moon Y, Lee KY, Sung SW, Park JK. *Differing histopathology and prognosis in pulmonary adenocarcinoma at central and peripheral locations*. J Thorac Dis 2016;8:169-77.
9. Rami-Porta R, Eberhardt WE. *Clinical implications of the innovations in the primary tumour and metastasis of the 8(th) edition of the TNM classification for lung cancer*. J Thorac Dis 2018;10(Suppl 22):S2682-5.
10. Moon Y, Sung SW, Lee KY, Kim YK, Park JK. *The importance of the lepidic component as a prognostic factor in stage I pulmonary adenocarcinoma*. World J Surg Oncol 2016;14:37.
11. Huang H, Wang T, Hu B, Pan C. *Visceral pleural invasion remains a size-independent prognostic factor in stage I non-small cell lung cancer*. Ann Thorac Surg 2015;99: 1130-9.
12. Sakakura N, Mizuno T, Kuroda H, et al. *The eighth TNM classification system for lung cancer: a consideration based on the degree of pleural invasion and involved neighboring structures*. Lung Cancer 2018;118:134-8.
13. Liu QX, Deng XF, Zhou D, Li JM, Min JX, Dai JG. *Visceral pleural invasion impacts the prognosis of non-small cell lung cancer: a meta-analysis*. Eur J Surg Oncol 2016;42: 1707-13.
14. David E, Thall PF, Kalhor N, et al. *Visceral pleural invasion is not predictive of survival in patients with lung cancer and smaller tumor size*. Ann Thorac Surg 2013;95:1872-7.
15. Brotons ML, Bolca C, Frechette E, Deslauriers J. *Anatomy and physiology of the thoracic lymphatic system*. Thorac

Surg Clin 2012;22:139-53.
16. Jiwangga D, Cho S, Kim K, Jheon S. *Recurrence pattern of pathologic stage I lung adenocarcinoma with visceral pleural invasion.* Ann Thorac Surg 2017;103:1126-31.
17. Tremblay L, Deslauriers J. *What is the most practical, optimal, and cost effective method for performing follow-up after lung cancer surgery, and by whom should it be done?* Thorac Surg Clin 2013;23:429-36.
18. Kiankhooy A, Taylor MD, LaPar DJ, et al. *Predictors of early recurrence for node-negative t1 to t2b non-small cell lung cancer.* Ann Thorac Surg 2014;98:1175-83.