Original Article

Validation of the 8th edition of the TNM staging system in 3,950 patients with surgically resected non-small cell lung cancer

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Background: The International Association for the Study of Lung Cancer introduced the 8th edition of the tumor, node, and metastasis (TNM) staging system for lung cancer. In this study, we validated the 8th edition of the TNM staging system and compared its discrimination power with that of the previous 7th edition.

Methods: A retrospective analysis was carried out on patients who underwent complete resection with systematic lymph node dissection for non-small cell lung cancer (NSCLC) between 2006 and 2015 at a tertiary referral center in Seoul, South Korea. Cox regression model was used to identify significant differences between adjacent TNM stage groupings. The Concordance index (C-index), Akaike Information Criterion (AIC), and R2 measure were utilized to evaluate the discrimination ability of the staging systems.

Results: A total of 3,950 patients (2,440 male, median age: 63 years) were analyzed. Median follow-up was 59 months (interquartile ranges, 38–88 months). According to the 8th edition, survival curves of overall survival (OS) and recurrence-free survival (RFS) within adjacent stage groupings showed significant differences except for IIA *vs.* IIB. Compared with the 7th edition, the 8th edition showed higher C-index (0.753 *vs.* 0.751), lower AIC (17,517 *vs.* 17,543), and higher R2 (0.178 *vs.* 0.171) values, indicating better discrimination ability.

Conclusions: Stratification based on the 8th edition of the TNM staging system showed favorable prognostic validity compared with the 7th edition. The 8th edition also had superior discrimination ability in terms of OS and RFS.

Keywords: Lung cancer; lung cancer staging; external validation; tumor, node, and metastasis classification (TNM classification)

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Introduction

Despite the recent advances in diagnosis and treatment, lung cancer is the most frequent cause of cancer-related deaths in both men and women worldwide (1). Accurate staging of lung cancer is essential for predicting prognosis and selecting appropriate treatment; as such, the TNM staging system for lung cancer was significantly modified in its 8th edition (2), which was authorized by the American Joint Committee on Cancer (AJCC) on January 1, 2018.

The 8th edition of the TNM system was developed on the basis of extensive investigations by the International Association for the Study of Lung Cancer (IASLC), including the analysis of an international database of 94,708

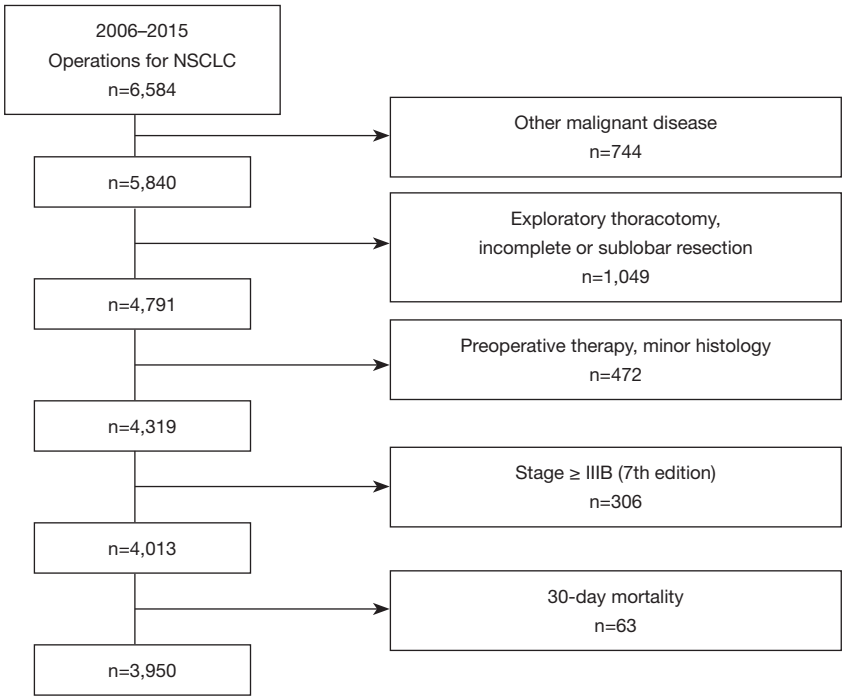

Figure 1 Patient selection process. NSCLC, non-small cell lung cancer.

patients from 46 sites from 19 countries (3). However, the database has some limitations in that a majority of the patients (76.9%) were from two countries (Japan and Denmark) and that the database lacked information on tumor recurrence. In addition, the database consisted of dichotomized patients classified by different LN maps—Naruke-Japanese (4) or Mountain-Dresler modification of the American Thoracic Society (MD-ATS) (5)—and the corresponding analysis was performed without statistical correction (6). Therefore, the IASLC carried out an external validation using the National Cancer Database and showed that the 8th edition had similar discrimination ability (7). Nevertheless, a further robust external validation using a large independent data set from an institution with standardized protocols should be carried out.

As the largest tertiary referral center in Korea, Asan Medical Center has maintained a nearly 100% completion rate for postoperative follow-up and less than 1% surgical mortality in the last decade. In this study, we validated the 8th edition of the TNM staging system by using the prospectively collected lung cancer database from our institution, and compared the discrimination values of the 7th and the 8th editions with respect to the overall survival (OS) and recurrence-free survival (RFS).

Methods

Patients

The clinical records of patients who underwent surgery for non-small cell lung cancer (NSCLC) were retrospectively collected between January 2006 and December 2015 in the thoracic surgery department of Asan Medical Center in Seoul, South Korea. Of these patients (n=6,584), the following patients were excluded: patients with other concurrent malignancies (n=744); patients who underwent sublobar resection (biopsy, wedge resection, and segmentectomy), incomplete resection (R1 and R2 resection) or incomplete lymph nodal dissection (number of resected lymph nodes <6) (n=1,049); patients who received preoperative chemoradiation therapy (n=201); patients who had histology other than adenocarcinoma, squamous cell carcinoma or adenosquamous cell carcinoma (n=271); patients whose stages were higher than IIIB according to the 7th edition (n=306) and/or who died within 30 days after surgery (n=63) (*Figure 1*). Consequently, 3,950 patients who underwent complete resection with systematic lymph node dissection were included. This study was approved by the Asan Medical Center Ethics Committee/Review Board (2019-0544).

The patients were pathologically staged according to the 8th edition in a retrospective manner (2). Adjuvant chemotherapy was used in patients with the 7th edition ≥ IIA and some with high-risk stage IB (lymphovascular invasion, visceral pleural involvement, large tumor size). Systemic chemotherapy with a platinum-based regimen was planned for four to six weeks after surgery, with a total of four courses of treatment. Follow-up information on all patients was obtained through clinic follow-up notes every 6 months during the first 5 years after surgery and every year thereafter. Chest CT scans were performed in sync with clinical visits or at any time when disease recurrence was clinically suspected. Treatment modalities and chemotherapeutic regimens in relapsed cases were determined at the discretion of the attending physician.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges, and categorical variables as percentages. Survival curves of OS and RFS according to the 7th and the 8th editions were estimated using Kaplan-Meier survival analysis and assessed using the log-rank test. Cox proportional hazards model was used for univariate and multivariate analysis to identify prognostic factors of OS and RFS. Selection of the final multivariate model was processed with a stepwise model selection approach ($P \leq 0.1$ for entering the model and $P \leq 0.05$ for staying in the model). Cox proportional hazard analysis was also used to adjust for covariate variables and to calculate hazard ratios (HR) between adjacent TNM staging groupings. Before comparing the discrimination ability, we selected the final model for 7th and 8th editions by using multivariate analysis. Age, sex, and staging groupings were included in the final model for OS, whereas age, histology, history of adjuvant therapy, and staging groupings were included in the final model for RFS. The prognostic values of the two final multivariate models were calculated with the Akaike Information Criterion (AIC) (8) and the R^2 measure (9), and the Concordance index (C-index) (10) was used in the two models to determine the discriminatory power.

All statistical calculations were performed using R version 3.2.5 (The R Foundation for Statistical Computing, Vanderbilt University, Nashville, TN, USA) using the Survival, ggplot2, GGally, and rms packages. *P* values less than 0.05 were considered significant.

Results

Patient characteristics

Clinicopathologic characteristics of the patients are summarized in *Table 1*. The median follow-up period was 59 months (interquartile range, 38–88 months). Lobectomy was performed in 3,663 patients (92.7%), and video-assisted thoracoscopic surgery was performed in 2,427 patients (61.4%). A total of 2,858 (72.4%) patients received adjuvant therapy, including chemotherapy, radiotherapy, or concurrent chemoradiation therapy.

Distribution of patients following the 7th and 8th editions and the association between the two editions is shown in *Table 2*. After applying the 8th edition, patients in the 7th edition stage IA (n=1,463) were subdivided into 8th edition stages IA1 (n=157, 10.7%), IA2 (n=647, 44.2%), and IA3 (n=659, 45.0%), and a portion of the 7th edition stage IB patients were moved to the 8th edition stage IIA (186/991, 18.8%). Due to the change of T1N1 and T2aN1 patients from the 7th edition stage IIA to the 8th edition stage IIB, almost all patients in the 7th edition stage IIA were restaged to the 8th edition stage IIB (526/528, 99.6%). Almost all patients in the 7th edition stage IIB (n=277) were divided into the 8th edition stages IIB (n=138, 49.8%) and IIIA (n=135, 48.7%). In the 7th edition stage IIIA group, 21.3% (147/691) were moved to the 8th edition stage IIIB.

Analysis of OS and RFS

Survival curves of OS and RFS following the 7th and 8th editions are shown, along with median survival time and 5-year survival rates (*Figures 2,3*). The OS curves stratified by the 7th edition showed a stepwise deterioration from stage IA to stage IIIA (*Figure 2A*). A phased degradation was also found within the RFS curves, except that the curves of stage IIA and IIB were not significantly different (P=0.101) (*Figure 2B*). According to the 8th edition, survival curves of OS and RFS displayed sequential deteriorations, but did not show significant differences between stages IIA and IIB (P=0.172 for OS and P=0.144 for RFS) (*Figure 3*).

According to Cox proportional hazard analysis, all HRs between adjacent staging groups were higher than 1.0, indicating gradual deterioration of prognosis according to the staging groups (*Table 3*). However, a significant difference was not observed between stages IIA and IIB in the 8th edition for OS and in both the 7th and the 8th

Table 1 Clinicopathologic characteristics of the patients (n=3,950)

Variable	Number (%) or median [IQR]
Age (years)	63 [56–70]
Sex	
Male	2,440 (61.8)
Female	1,510 (38.2)
Histologic structure	
ADC	2,852 (72.2)
SqCC	1,069 (27.1)
ADSqCC	29 (0.7)
Operative method	
Lobectomy	3,507 (88.8)
Sleeve lobectomy	156 (3.9)
Bilobectomy	168 (4.3)
Pneumonectomy	119 (3.0)
Surgical approach	
VATS	2,427 (61.4)
VATS to open thoracotomy	195 (4.9)
Thoracotomy	1,328 (33.6)
No. of resected lymph nodes	
N0	25 [19–33]
N1	28 [22–36]
N2	28 [21–35]
Tumor size (mm)	28 [20–40]
Tumor location	
Right upper	1,068 (27.0)
Right middle	314 (7.9)
Right lower	949 (24.0)
Left upper	904 (22.9)
Left lower	715 (18.1)
Pathologic tumor factor (8th edition)	
pT1	1,713 (43.4)
pT2	1,534 (38.8)
pT3	491 (12.4)
pT4	212 (5.4)
Pathologic node factor (8th edition)	
pN0	2,889 (73.1)
pN1	476 (12.1)
pN2	585 (14.8)
Adjuvant therapy	
Yes	2,858 (72.4)
No	1,092 (27.6)
Follow-up duration (months)	59 [38–88]

IQR, interquartile ranges; ADC, adenocarcinoma; SqCC, squamous cell carcinoma; ADSqCC, adenosquamous carcinoma; VATS, video-assisted thoracoscopic surgery.

editions for RFS, which is in line with the results from the Kaplan-Meier analysis.

As shown in *Table 4*, the 8th edition had better model fit as indicated by the smaller AIC values (17,517 *vs.* 17,543 for OS, 16,720 *vs.* 16,784 for RFS) and better prediction accuracy as indicated by the higher R^2 values (0.178 *vs.* 0.171 for OS, 0.158 *vs.* 0.143 for RFS). The 8th edition also showed better discriminatory ability as indicated by the higher C-index scores (0.753 *vs.* 0.751 for OS, 0.718 *vs.* 0.716 for RFS).

To evaluate the effectiveness of the modifications in the 8th edition, we compared the survival outcomes of the 7th edition stage IB, IIB, and IIIA divided by the 8th edition (*Table 5*). Using Cox regression models, we found significant differences of the 7th edition stage IB (P=0.048 for OS and P=0.042 for RFS), IIB (P=0.040 for OS and P<0.001 for RFS), and IIIA (P=0.006 for OS and P<0.001 for RFS), depending on whether or not stage migration was present, regardless of OS and RFS.

Discussion

The TNM staging system for malignant tumors is a globally accepted protocol for classifying the degree of tumor extent and invasion, thereby providing accurate prognosis and suggesting the appropriate treatment stratification (11). Several editions of the TNM staging system for lung cancer

Table 2 Relationship between the 7th and 8th edition TNM staging systems

7th edition TNM stage	8th edition TNM stage								
	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	Total, n (%)
IA	157	647	659	–	–	–	–	–	1,463 (37.0)
IB	–	–	–	805	186	–	–	–	991 (25.1)
IIA	–	–	–	–	2	526	–	–	528 (13.4)
IIB	–	–	–	3	1	138	135	–	277 (7.0)
IIIA	–	–	–	–	–	3	541	147	691 (17.5)
Total, n (%)	157 (4.0)	647 (16.4)	659 (16.7)	808 (20.5)	189 (4.8)	667 (16.9)	676 (17.1)	147 (3.7)	3,950

TNM, tumor, node, and metastasis.

have been published following its introduction in 1973 (12); the latest update in 2017 introduced the 8th edition for lung cancer (2), which provided several new categories, especially in the T and M descriptors. As for the T descriptor, T1 and T2 were subdivided into T1a, T1b, T1c, T2a, and T2b by size in 1-cm increments. In addition, tumors larger than 5 and 7 cm were reclassified as T3 and T4, respectively. Tumors causing partial or total lung atelectasis and those involving main stem bronchus regardless of distance from the carina were reclassified as T2. Diaphragm invasion was reclassified as T4 and mediastinal pleural invasion was removed from the T descriptor (13). As for the M descriptor, tumors with extrathoracic metastases were subdivided into M1b involving single distant sites and M1c involving multiple distant sites (14). No changes were recommended for the N descriptor (6). In the new stage grouping, significant changes included subdivision of stage IA into IA1 (T1aN0), IA2 (T1bN0), and IA3 (T1cN0), and introduction of the new IIIC stage representing T3N3 and T4N3 tumors (15).

In our study, the curves of OS and RFS for each stage grouping showed a gradual deterioration (*Figures 2,3*). However, in both the 7th and 8th editions, there were no significant differences between the IIA and IIB groups, which remained the same on Cox analysis adjusted with multiple covariates (*Table 3*). These findings are in line with those from previous studies that validated the 7th edition (16,17) and the 8th edition (18). It is obvious that the absolute values of difference between stage IIA and IIB are not as large as those between other groups. However, relatively low proportions of patients in the 7th edition stage IIB (277/3,950, 7.0%) and the 8th edition stage IIA (189/3,950, 4.8%) also affected these results. In terms of the 7th edition, a small proportion of IIB patients was consistently reported in other external validation studies after the introduction of the 7th stage system (16,17). According to the definition of the 8th edition, almost all patients in the 7th edition stage IIA were restaged to 8th edition stage IIB; moreover, the percentage of stage IIA patients whose tumor size ranged from 4 to 5 cm without lymph node invasion was reduced to 4.8%. Therefore, comparison between the groups with a relatively small difference and a low percentage of patients may be responsible for the insignificant P values.

In our current study, we conducted a retrospective analysis in a large cohort from a single institution in order to determine whether the newly introduced 8th edition of the TNM classification system for NSCLC is a better prognosticator of OS and RFS than the previous 7th edition. Judging from the results adjusted through multivariate Cox analysis, the 8th edition seems to have better prognostic power (higher C-index) for OS and RFS. Considering that the discriminative value becomes higher as the number of prediction variables in a certain model increases (19), this result may be attributed to the subdivision of 7th edition stage IA tumors into 8th edition stages IA1, IA2, and IA3. However, even after applying the AIC and R^2 methods that adjust their predictive value by penalizing the number of increased variables (20), the 8th edition still showed better prognostic ability (lower AIC and higher R^2). Consequently, subdividing the 7th edition stage IA patients into three groups (IA1, IA2, and IA3) is a statistically appropriate modification, and the 8th edition is superior in terms of stratification of prognosis for OS and RFS. Proper migration of stage in patients in the 7th edition stages IB, IIB, and IIIA may also contribute to improved discrimination ability of the 8th edition (*Table 5*).

It is crucial to comment on the clinical guidelines that

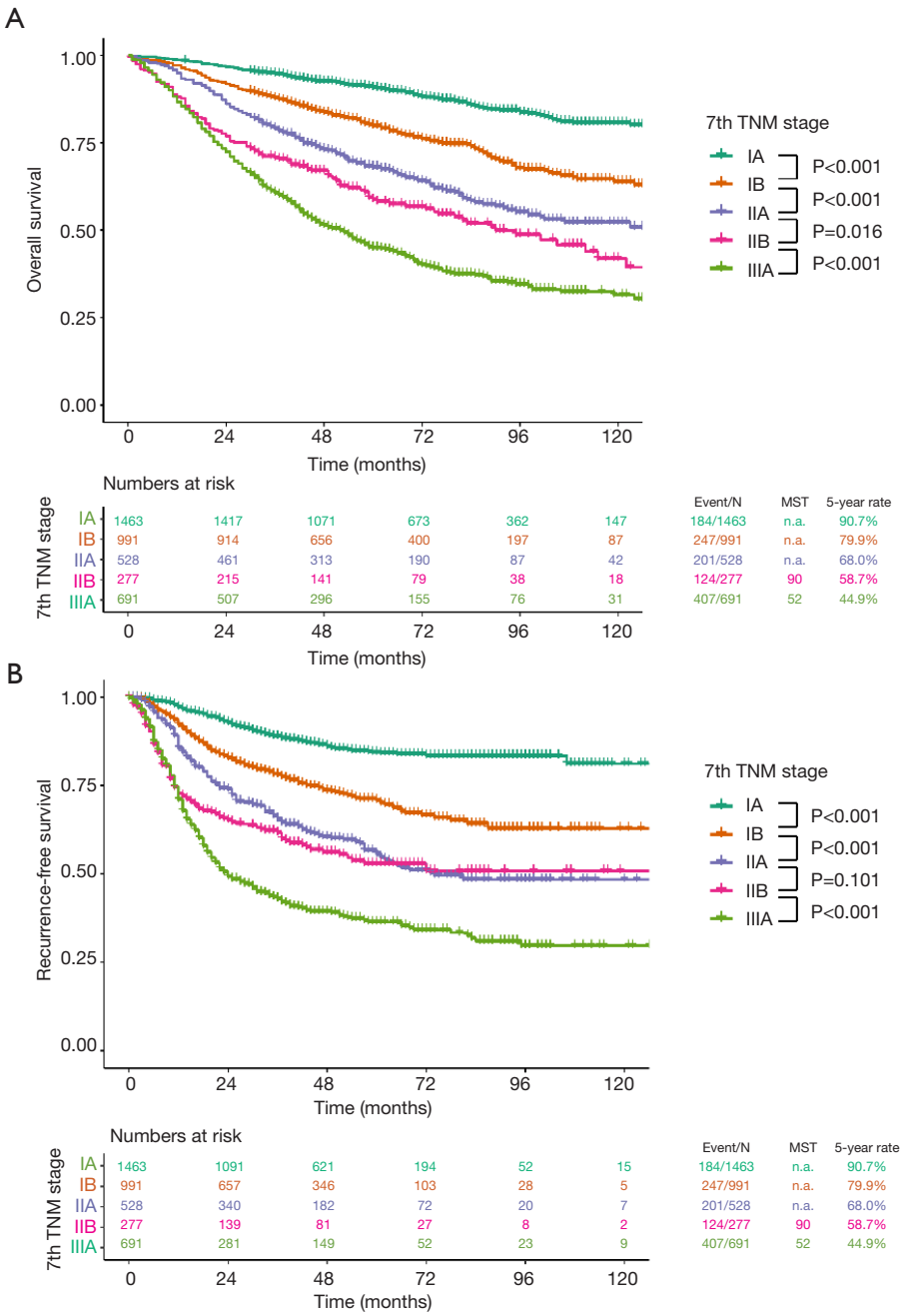

Figure 2 Survival curves of OS (A) and RFS (B) based on the 7th edition of the TNM staging system. OS, overall survival; RFS, recurrence-free survival; TNM, tumor, node, and metastasis; n.a., not applicable.

would be revised as patients move to different stages after applying the 8th edition. For the 7th edition stage IB, patients with tumor size >4 cm are upstaged to the 8th edition stage IIA, which is related to the controversy as to whether the 7th edition stage IB patients with high risk can benefit from adjuvant chemotherapy. Although no definitive agreement has been reached through randomized clinical trials (21,22), there is a consensus that adjuvant chemotherapy is helpful in the 7th edition stage IB patients with tumors >4 cm; as such, the National Comprehensive Cancer Network recommends them as candidates for adjuvant chemotherapy (23), which is reflected in the 8th

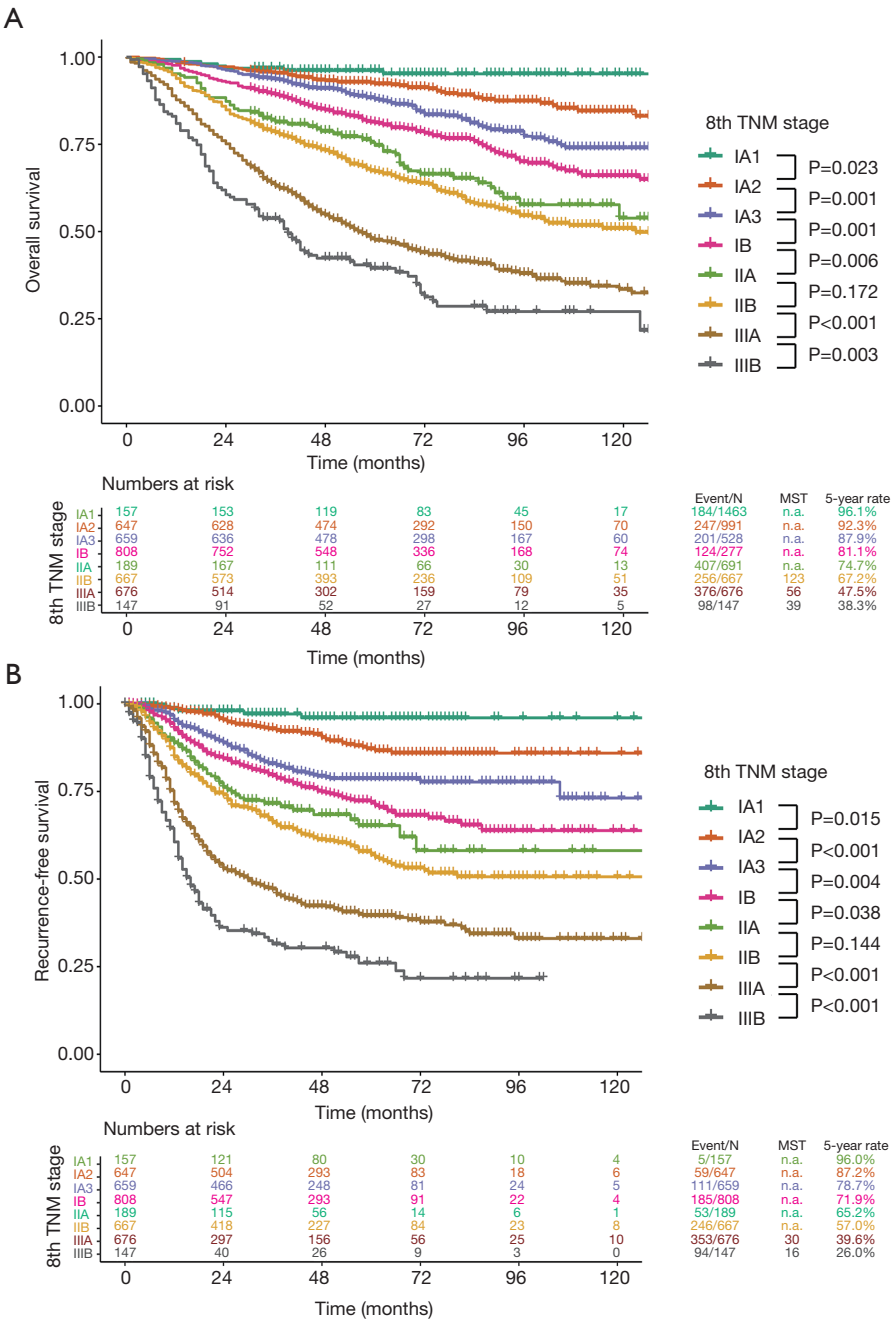

Figure 3 Survival curves of OS (A) and RFS (B) according to the 8th edition of the TNM staging system. OS, overall survival; RFS, recurrence-free survival; TNM, tumor, node, and metastasis; n.a., not applicable.

edition by stage migration. On the other hand, multiple studies reported that patients with visceral pleura invasion (VPI) have significantly worse prognosis within the 7th edition stage IB and proposed them to be upstaged as stage IIA (24-26). However, these patients remain unchanged in the 8th edition. In our study, there was no significant difference of prognosis depending on whether VPI was present (339/727) or not (388/727) among the 8th edition stage IB patients without adjuvant chemotherapy, regardless of OS [HR 0.91, 95% confidence interval (CI):

Table 3 Cox proportional hazards analysis for stage groupings of the 7th and 8th edition TNM staging systems

TNM stage	OS				RFS			
	7th edition		8th edition		7th edition		8th edition	
	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
IA2 *vs.* IA1	–	–	0.042	2.25 (1.03–4.90)	–	–	0.026	2.81 (1.13–7.02)
IA3 *vs.* IA2	–	–	0.004	1.56 (1.15–2.11)	–	–	<0.001	2.00 (1.46–2.75)
IB *vs.* IA3	–	–	0.004	1.41 (1.12–1.79)	–	–	0.003	1.44 (1.14–1.82)
IB *vs.* IA	<0.001	1.95 (1.61–2.36)	–	–	<0.001	2.24 (1.84–2.73)	–	–
IIA *vs.* IB	<0.001	1.64 (1.36–1.97)	0.025	1.39 (1.04–1.86)	<0.001	1.67 (1.36–2.04)	0.025	1.42 (1.05–1.93)
IIB *vs.* IIA	0.023	1.30 (1.04–1.62)	0.084	1.28 (0.97–1.70)	0.093	1.22 (0.97–1.54)	0.177	1.23 (0.91–1.67)
IIIA *vs.* IIB	<0.001	1.56 (1.27–1.90)	< 0.001	1.80 (1.54–2.11)	0.006	1.38 (1.10–1.74)	<0.001	1.65 (1.40–1.96)
IIIB *vs.* IIIA	–	–	0.002	1.43 (1.15–1.76)	–	–	<0.001	1.54 (1.22–1.93)

All the results were adjusted by age (≥70 *vs.* <70 years) and sex for OS and by age, histology, and history of adjuvant therapy for RFS. TNM, tumor, node, and metastasis; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

Table 4 Comparison of prognostic values

N descriptor	AIC	R^2	Harrell's C-index
OS			
7th edition	17,543	0.171	0.751
8th edition	17,517	0.178	0.753
RFS			
7th edition	16,784	0.143	0.716
8th edition	16,720	0.158	0.718

Age (≥70 *vs.* <70 years), sex, and staging groupings were included in overall survival model and age, histology, history of adjuvant therapy, and staging groupings were included in recurrence-free survival model. AIC, Akaike information criterion; C-index, concordance index; OS, overall survival; RFS, recurrence-free survival.

Table 5 Comparisons of the 8th edition stage patients with and without stage migration from 7th edition staging system

7th edition	8th edition	OS			RFS		
		Event/N	P	HR (95% CI)	Event/N	P	HR (95% CI)
IB	IB	189/805	–	1	185/805	–	1
	IIA	58/186	0.048	1.34 (1.01–1.81)	51/186	0.042	1.36 (1.02–1.86)
IIB	IIB	55/138	–	1	43/138	–	1
	IIIA	69/135	0.040	1.46 (1.02–2.09)	67/135	<0.001	1.97 (1.32–2.94)
IIIA	IIIA	307/541	–	1	286/541	–	1
	IIIB	98/147	0.006	1.38 (1.10–1.73)	94/147	<0.001	1.58 (1.25–2.00)

All the results were adjusted by age (≥70 *vs.* <70 years) and sex for overall survival and by age, histology, and history of adjuvant therapy for recurrence-free survival. OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

0.57–1.46, P=0.384] and RFS [HR 1.25, 95% CI: 0.92–1.70, P=0.157]. However, this should be interpreted with caution because there may have been selection bias, considering the exclusion of VPI-positive patients who had more malignant potential (i.e., larger tumor size) and received adjuvant chemotherapy. In fact, among stage IB patients without adjuvant chemotherapy, VPI-positive patients had smaller tumor size than VPI-negative patients (26.6±7.6 *vs.* 33.1±6.4, P<0.001). Consequently, the prognostic effect of VPI is difficult to identify in our study.

Our study utilized a large independent database, and none of the patients were included in the IASLC database. However, our results are limited in generalizability due to the retrospective nature of the study design and the use of observational data from a single institution. Also, because all reviewed data were collected only from patients undergoing surgical treatment, the survival curves might not reflect those of the general NSCLC patient population.

Conclusions

We demonstrate that stratification according to the 8th edition of the TNM staging system is prognostically valid for patients who underwent complete resection of NSCLC. The discrimination ability of the 8th edition was superior to the 7th edition in terms of OS and RFS.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Asan Medical Center Ethics Committee/ Review Board (2019-0544) and written informed consent was obtained from all patients.

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