ORIGINAL ARTICLE

Validation Study for the N Descriptor of the Newly Proposed Ninth Edition of the TNM Staging System Proposed by the International Association for the Study of Lung Cancer

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ABSTRACT

Introduction: The aim of this study was to validate the discriminatory ability and clinical utility of the N descriptor of the newly proposed ninth edition of the TNM staging system for lung cancer in a large independent cohort.

Methods: We retrospectively analyzed patients who underwent curative surgery for NSCLC between January 2004 and December 2019. The N descriptor of patients included in this study was retrospectively reclassified based on the ninth edition of the TNM classification. Survival analysis was performed using the log-rank test and Cox proportional hazard model to compare adjacent N categories.

Results: A total of 6649 patients were included in this study. The median follow-up period was 54 months. According to the newly proposed ninth edition N classification, 5573 patients (83.8%), 639 patients (9.6%), 268 patients (4.0%), and 169 patients (2.5%) were classified into the clinical N0, N1, N2a, and N2b categories and 4957 patients (74.6%), 744 patients (11.2%), 567 patients (8.5%), and 381 patients (5.7%) were classified into the pathologic N0, N1, N2a, and N2b categories, respectively. The prognostic differences between all adjacent clinical and pathologic N categories were highly significant in terms of both overall survival and recurrence-free survival.

Conclusions: We validated the clinical utility of the newly proposed ninth edition N classification for both clinical and pathologic stages in NSCLC. The new N classification revealed clear prognostic separation between all categories (N0, N1, N2a, and N2b) in terms of both overall survival and recurrence-free survival.

Keywords: Lung cancer; Staging; TNM classification; N descriptor

Introduction

Accurate evaluation of lymph node (LN) metastasis is a key component in cancer staging, which allows clinicians to communicate effectively, provide standard treatments, assess prognosis, and perform clinical trials.[1] Since the N descriptor of the TNM staging system for NSCLC was defined as N0, N1, N2, and N3 in 1987 in the fourth edition,[2] this classification has remained unchanged.[3–5] Nevertheless, these four categories are based solely on the anatomical location of metastatic LNs and do not consider disease burden quantification. Thus, questions have consistently been raised about this nodal classification system not adequately reflecting the burden of metastatic LNs, which is known to be a prognostic factor for many other solid malignancies.[6]

Subsequently, this concept of disease quantification was first evaluated in the seventh edition of the TNM staging system for lung cancer and re-explored in the eighth edition by subclassifying according to the number

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of involved LN stations and single versus multiple.[4,5] In addition, the concept of "skip" metastases was newly proposed (a single positive N2 nodal station in the absence of positive N1 nodes).[5] Considering that most data (75.7%) for pathologic N status in the eighth edition were from Japan, various studies were performed for external validation and did provide some evidence of clinical relevance.[7,8] Nonetheless, these subclassified N categories had a critical problem which could only be adopted in pathologic staging.

The Staging and Prognostic Factors Committee (SPFC) of the International Association for the Study of Lung Cancer (IASLC) recently proposed the N descriptor for the ninth edition of the TNM staging system.[9] Compared with the eighth edition, the IASLC recommended subdivision into the simpler single- versus multiple-station metastasis (without a separate "skip" metastasis subgroup) in the ninth edition, as it provided much clearer separation at the N2 level not only in pathologic staging but also in clinical staging. Nevertheless, an apparent gap still exists, in that the study lacks detailed information on patient history or comorbidities that might affect survival outcomes. In addition, this study lacked information on recurrence or progression and did not include the relevant survival analyses, which are important for interpreting oncological outcomes. Thus, there is a need for external validation of the new N descriptors proposed by the IASLC in a large, independent, single-center database.

Our study aimed to evaluate the discriminatory ability and prognostic performance of the proposed N classification in the ninth edition of the TNM staging system based on a large, independent cohort.

Materials and Methods

Patients

This study included patients who underwent curative surgery for NSCLC at the Asan Medical Center in Seoul between January 2004 and December 2019. Surgical treatment included lung parenchymal resection and appropriate lymphadenectomy. Clinicopathologic data of included patients were extracted from electronic medical records stored in a prospective database. Survival information was updated through November 2023. Exclusion criteria were as follows: (1) age below 18 years, (2) SCLC, (3) previous malignancy, (4) concurrent malignancy, (5) neoadjuvant therapy, (6) double primary lung cancer, (7) pathologic M1, (8) number of resected LNs less than six, (9) clinical or pathologic N3, (10) incomplete resection, (11) 30-day mortality, and (12) follow-up loss (Fig. 1). At our institution, the Mountain–Dresler modification of the American Thoracic Society (MD-ATS) and IASLC LN maps have been used for LN station nomenclature until 2009 and from 2009 onward, respectively.[10,11] After a thorough review of the data, experienced surgeons retrospectively reclassified the N descriptor of included patients based on the newly

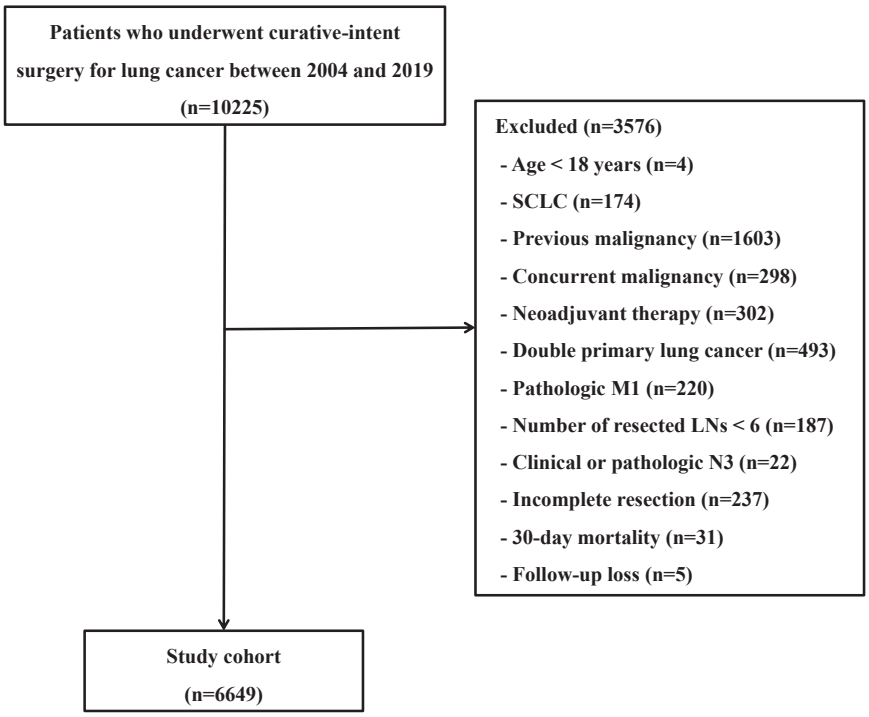

Figure 1. Patient selection flowchart. LN, lymph node.

proposed ninth edition of the TNM classification. This study was approved by the Institutional Review Board of Asan Medical Center (approval no. 2024-0097).

Perioperative Evaluations and Follow-Up

All patients underwent imaging studies such as computed tomography (CT), positron emission tomography–CT (PET-CT), and brain magnetic resonance imaging (MRI). On chest CT, mediastinal and hilar LN enlargement was defined as greater than or equal to 10 mm on the largest short axis. Positive LN uptake on PET-CT was defined as LN uptake greater than mediastinal blood pool. In cases of borderline tumor size or metabolic uptake of mediastinal LNs on CT or PET, biopsies of the involved LNs were selectively conducted with mediastinoscopy, endobronchial ultrasound, or endoscopic ultrasound. Until 2010, before the introduction of endobronchial ultrasound, mediastinoscopy was performed to confirm N2 or N3 nodes. Subsequently, endobronchial ultrasound was primarily used to identify LN metastasis instead of mediastinoscopy. After surgery, adjuvant therapy was provided if indicated. All patients underwent regular outpatient follow-up at 3- or 6-month intervals after surgery. If recurrence was suspected, further evaluation, including laboratory tests, chest CT, and PET-CT, was performed, followed by histologic confirmation if necessary. The date of recurrence was defined as the date of first detection based on imaging studies.

Definition of Variables

As proposed by Asamura et al.,[5] the following N categories were assigned according to the location of metastatic LN station, number of metastatic LN stations, and presence or absence of skip metastasis: N1a (single-station N1 metastasis), N1b (multiple-station N1 metastasis), N2a1 (single-station N2 metastasis without N1 metastasis), N2a2 (single-station N2 metastasis with N1 metastasis), and N2b (ipsilateral multiple-station N2 metastasis). According to the ninth edition N classification, however, N2 disease was simply divided into single-station (N2a) or multiple-station (N2b) metastasis.[9]

The definition of complete resection was based on the Union for International Cancer Control classification for residual tumors, which includes complete resection with no residual tumor (R0) and incomplete resection with microscopic (R1) or macroscopic (R2) residual tumor and continues to be widely used for the intuitive representation of the completeness of surgical resection.[12]

Overall survival (OS) was defined as the period from the date of diagnosis (clinical) or surgery (pathologic) to the date of death from any cause or last follow-up. Recurrence-free survival (RFS) was defined as the period from the date of diagnosis or surgery to the date of recurrence or last follow-up.

Statistical Analysis

Continuous data are presented as mean and SD values; categorical data are presented as frequencies and percentages. OS and RFS were calculated using the Kaplan–Meier method to account for time to death and recurrence, respectively, and compared using the log-rank test; pairwise differences in survival between adjacent N categories were assessed using the log-rank test. Additional sensitivity analyses were performed to confirm the reproducibility of the ninth edition N classification in subgroups according to histology, T descriptor, and year of surgery. As suggested by the IASLC SPFC, a 5-year survival difference of 5% or more between adjacent N categories is considered clinically meaningful.[1] The multivariable Cox proportional hazards model was used to compare N categories after adjusting for age, sex, histology, comorbidity, and year of surgery. Given that the purpose of this study was validation, the variables included in the Cox regression model were selected as suggested by the IASLC SPFC. Furthermore, because the study period was long and improvements in diagnostic and treatment modalities over time may affect survival, we added the year of surgery as a factor to the final COX regression model. R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. Two-sided tests were used for all analyses. p values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

From 2004 to 2019, 6649 patients were included in this study. The median follow-up period was 54 months (interquartile range, 31–77 months). The characteristics of the enrolled patients are summarized in Tables 1 and 2. The mean age was 62.3 ± 9.9 years, and 3955 patients (59.5%) were male. Invasive mediastinal staging was performed for 852 patients (12.8%), of which 641 (9.6%) underwent endobronchial ultrasound. Minimally invasive surgery was performed in 4583 cases (68.9%)—4568 patients (68.7%) underwent video-assisted thoracic surgery and 15 patients (0.2%) underwent robot-assisted thoracic surgery. A total of 5218 patients (78.5%) underwent lobectomy, and 900 patients (13.5%) underwent sublobar resection. The average number of harvested LNs was 26.5 ± 11.1. Adjuvant therapy was provided for 1846 patients (27.8%). The clinicopathologic characteristics of the patients according to the ninth edition N classification are summarized in Supplementary Table 1.

Table 1. Clinical Characteristics of Included Patients (n = 6649)

Variable	Value
Age, y	62.3 ± 9.9
Sex	
Male	3955 (59.5%)
Female	2694 (40.5%)
Smoking history	
Current	821 (12.3%)
Ex-smoker	2757 (41.5%)
Nonsmoker	3071 (46.2%)
Number of comorbidities	
0-1	5315 (79.9%)
2	1028 (15.5%)
≥3	306 (4.6%)
Tumor location	
Right	3990 (60.0%)
Left	2659 (40.0%)
Invasive mediastinal staging technique	852 (12.8%)
Endobronchial ultrasound	641 (9.6%)
Mediastinoscopy	250 (3.8%)
Clinical T category	
cT1	3582 (53.9%)
cT2	2207 (33.2%)
cT3	581 (8.7%)
cT4	279 (4.2%)
Clinical N category (eighth edition)	
cN0	5573 (83.8%)
cN1	639 (9.6%)
cN2	437 (6.6%)
Clinical N category (ninth edition)	
cN0	5573 (83.8%)
cN1	639 (9.6%)
cN2a	268 (4.0%)
cN2b	169 (2.5%)
Surgical approach	
Minimally invasive	4583 (68.9%)
Open thoracotomy	1835 (27.6%)
Thoracotomy conversion	231 (3.5%)
Surgical extent	
Sublobar resection	900 (13.5%)
Lobectomy	5218 (78.5%)
Sleeve lobectomy	125 (1.9%)
Bilobectomy	237 (3.6%)
Pneumonectomy	169 (2.5%)
Adjuvant therapy	1846 (27.8%)
Chemoradiation therapy	618 (9.3%)
Chemotherapy only	968 (14.6%)
Radiotherapy only	256 (3.9%)
None	4803 (72.2%)

Note: Data are presented as numbers (%) or mean ± SD values unless otherwise indicated.

Table 2. Pathologic Characteristics of Included Patients (n = 6649)

Variable	Value
Histologic subtype	
Adenocarcinoma	4826 (72.6)
Squamous cell carcinoma	1427 (21.5)
Others	396 (6.0)
Pathologic T category	
pT1	3139 (47.2)
pT2	2357 (35.4)
pT3	809 (12.2)
pT4	344 (5.2)
Pathologic N category (eighth edition)	
pN0	4957 (74.6)
pN1	744 (11.2)
pN2	948 (14.3)
Pathologic N category (Asamura et al.)	
pN0	4957 (74.6)
pN1a	588 (8.8)
pN1b	156 (2.3)
pN2a1	201 (3.0)
pN2a2	366 (5.5)
pN2b	381 (5.7)
Pathologic N category (ninth edition)	
pN0	4957 (74.6)
pN1	744 (11.2)
pN2a	567 (8.5)
pN2b	381 (5.7)
Histologic grade	
Grade I	867 (13.0)
Grade II	4286 (64.5)
Grade III	941 (14.2)
Not assessable	555 (8.3)
Pathologic tumor size (mm)	31.5 ± 18.4
Visceral pleural invasion	1520 (22.9)
Lymphovascular invasion	1738 (26.1)
Number of harvested LNs	26.5 ± 11.1

Note: Data are presented as numbers (%) or mean ± SD values unless otherwise indicated.
LN, lymph node.

According to the newly proposed N classification, 5573 patients (83.8%), 639 patients (9.6%), 268 patients (4.0%), and 169 patients (2.5%) were classified into the clinical N0, N1, N2a, and N2b categories and 4957 patients (74.6%), 744 patients (11.2%), 567 patients (8.5%), and 381 patients (5.7%) into the pathologic N0, N1, N2a, and N2b categories, respectively. The relationships between pathologic T and pathologic N categories are found in Supplementary Table 2. The relationships between clinical N and pathologic N categories are found in Supplementary Table 3. The concordance rates between the clinical and pathologic N categories were 79.6%, 83.6%, 42.3%, 58.8%, and 75.3% for overall, N0, N1, N2a, and N2b, respectively.

Survival According to the Eighth and Ninth Edition Clinical N Classifications and the Classification Proposed by Asamura et al.[5]

Survival curves and the corresponding median survival time and 5-year survival rates according to the eighth and ninth edition clinical N classifications and the classification proposed by Asamura et al. are presented

in Figure 2 and Supplementary Figure 1. OS was well stratified according to both the eighth and ninth edition clinical N classifications (Fig. 2*A* and Supplementary Fig. 1A), with stepwise deterioration from N0 to N2b (5-y OS: N0, 82.7%; N1, 59.9%; N2, 44.5%; N2a, 51.5%; and N2b, 33.7%). Nevertheless, the OS curves for the classification proposed by Asamura et al. had various overlaps between adjacent N categories, and there were no significant differences except between the N0 and N1a ($p < 0.001$) categories (Fig. 2*C*). Similarly, there was phased degradation in RFS according to both the eighth and ninth edition clinical N classifications (Fig. 2*B* and Supplementary Fig. 1B). Nevertheless, there were several overlaps in RFS between the N1a and N1b ($p = 0.137$), N1b and N2a1 ($p = 0.577$), and N2a2 and N2b ($p = 0.214$) categories of the classification proposed by Asamura et al. Furthermore, phased degradation was inconsistently observed, suggesting that 5-year survival rate of N2a1 was better than that of N1b (31.0% versus 39.1%) (Fig. 2*D*).

The multivariable Cox proportional hazards model was used to calculate the hazard ratios (HRs) for adjacent N categories after adjustments for age, sex, histology, comorbidity, and year of surgery, as suggested by the IASLC SPFC. In the clinical stages, the HRs for OS and RFS between adjacent N categories were higher than 1.0, suggesting phased degradation of prognosis according to both the eighth and ninth edition N classifications, with considerable differences (Table 3 and Supplementary Table 4). With regard to the clinical N classification suggested by Asamura et al., although all HRs for OS were higher than 1.0, there were no differences in OS between the N1a and N1b ($p = 0.758$), N1b and N2a1 ($p = 0.626$), and N2a1 and N2a2 ($p = 0.193$) categories. Furthermore, the HR for RFS between N1b and N2a1 was less than 1.0, which was not an order of survival

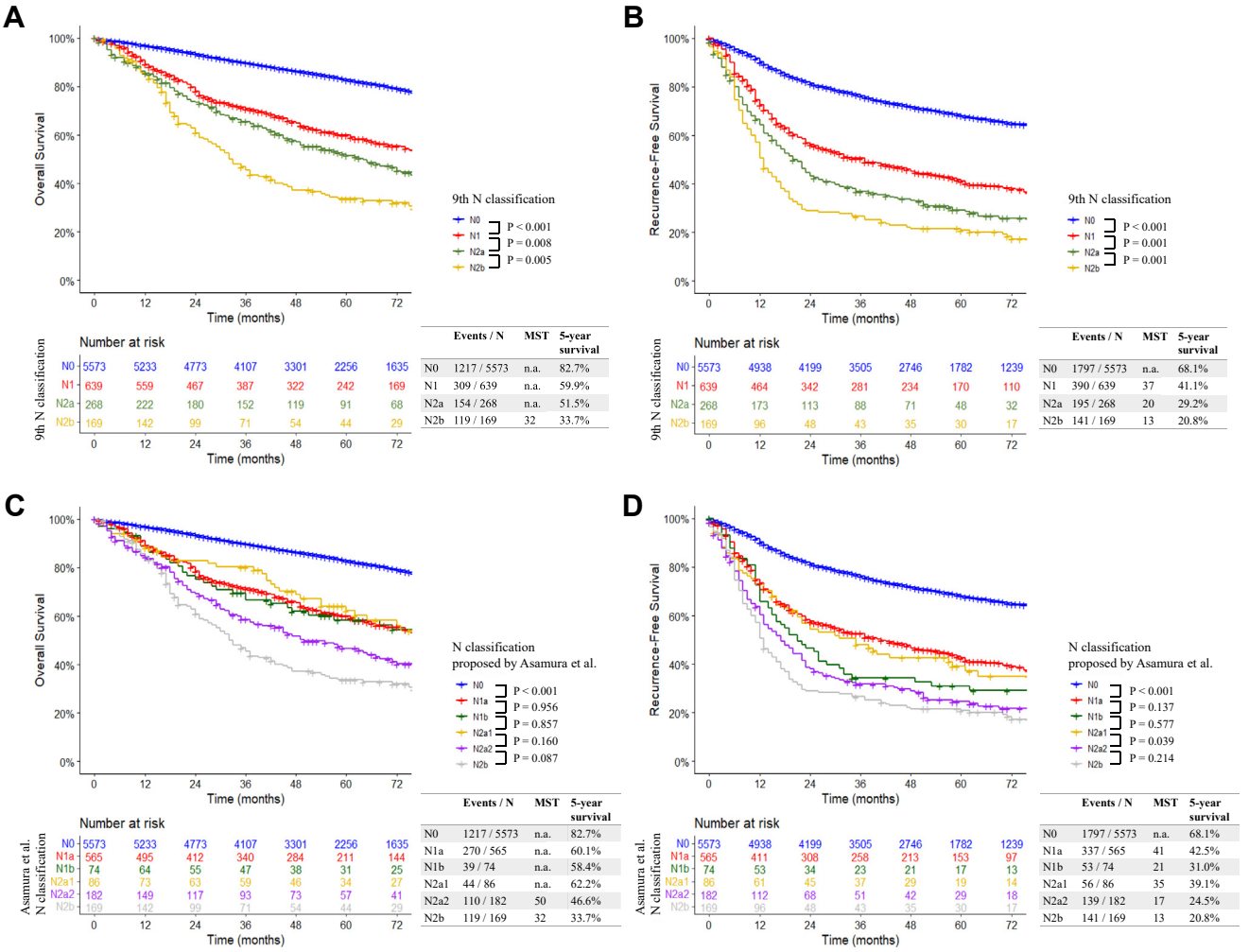

Figure 2. Comparison of the ninth edition clinical N classification and the clinical N classification proposed by Asamura et al. (*A* and *B*) Overall survival and recurrence-free survival according to the ninth edition clinical N classification, and (*C* and *D*) overall survival and recurrence-free survival according to the clinical N classification proposed by Asamura et al. MST, median survival time.

Table 3. Adjusted HRs for OS and RFS Between Adjacent N Categories According to the Ninth Edition N Classification and the N Classification Proposed by Asamura et al.[5] Using the Cox Proportional Hazards Model Adjusted With Age, Sex, Histology, Comorbidity, and Year of Surgery (Clinical and Pathologic Stages)

Clinical Stage

Ninth edition					Asamura et al.				
	OS		RFS			OS		RFS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value		HR (95% CI)	*p* value	HR (95% CI)	*p* value
N1 vs. N0	2.04 (1.79-2.32)	<0.001	2.14 (1.91-2.40)	<0.001	N1a vs. N0	2.02 (1.76-2.32)	<0.001	2.07 (1.83-2.34)	<0.001
N2a vs. N1	1.37 (1.13-1.66)	<0.001	1.49 (1.26-1.77)	<0.001	N1b vs. N1a	1.05 (0.75-1.48)	0.758	1.30 (0.97-1.73)	0.08
N2b vs. N2a	1.55 (1.22-1.98)	<0.001	1.41 (1.13-1.75)	0.002	N2a1 vs. N1b	1.11 (0.72-1.72)	0.626	0.95 (0.65-1.39)	0.801
					N2a2 vs. N2a1	1.26 (0.89-1.79)	0.193	1.39 (1.02-1.89)	0.04
					N2b vs. N2a2	1.44 (1.11-1.88)	0.006	1.27 (1.00-1.60)	0.048

Pathologic Stage

Ninth edition					Asamura et al.				
	OS		RFS			OS		RFS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value		HR (95% CI)	*p* value	HR (95% CI)	*p* value
N1 vs. N0	2.05 (1.80-2.34)	<0.001	2.38 (2.13-2.66)	<0.001	N1a vs. N0	1.86 (1.61-2.15)	<0.001	2.11 (1.87-2.40)	<0.001
N2a vs. N1	1.69 (1.44-1.98)	<0.001	1.46 (1.27-1.68)	<0.001	N1b vs. N1a	1.65 (1.27-2.14)	<0.001	1.78 (1.43-2.21)	<0.001
N2b vs. N2a	1.51 (1.27-1.80)	<0.001	1.62 (1.39-1.88)	<0.001	N2a1 vs. N1b	0.97 (0.72-1.31)	0.838	0.79 (0.61-1.02)	0.066
					N2a2 vs. N2a1	1.28 (1.00-1.63)	0.048	1.30 (1.05-1.61)	0.016
					N2b vs. N2a2	1.39 (1.14-1.68)	0.001	1.48 (1.25-1.75)	<0.001

OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

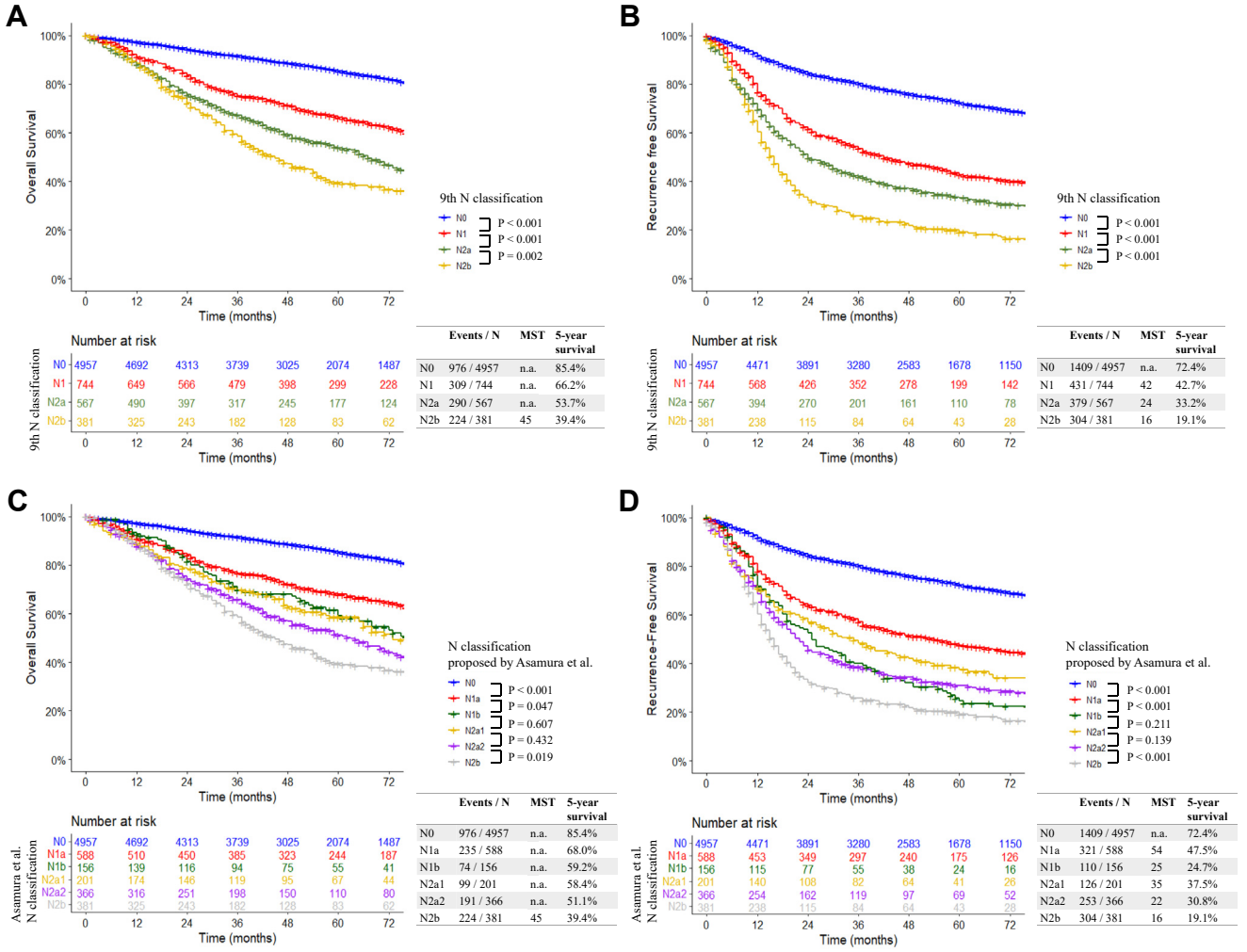

Figure 3. Comparison of the ninth edition pathologic N classification and the pathologic N classification proposed by Asamura et al. (*A* and *B*) Overall survival and recurrence-free survival according to the ninth edition pathologic N classification, and (*C* and *D*) overall survival and recurrence-free survival according to the pathologic N classification proposed by Asamura et al. MST, median survival time.

outcomes among N categories, and there was no significant survival difference between N1b and N2a1 categories ($p = 0.801$) (Table 3).

Survival According to the Eighth and Ninth Edition Pathologic N Classifications and the Classification Proposed by Asamura et al.[5]

Survival curves according to all three pathologic N classifications are presented in Figure 3 and in Supplementary Figure 1. Clear stepwise separations in OS and RFS curves were observed between adjacent N categories according to the eighth and ninth edition pathologic N classifications (Fig. 3*A* and *B*, Supplementary Fig. 1C and D). Nevertheless, there were no differences in OS between the N1b and N2a1 ($p = 0.607$) and N2a1 and N2a2 ($p = 0.432$) categories according to the classification proposed by Asamura et al. (Fig. 3*C*). In addition, there were no differences in RFS between the N1b and N2a1 ($p = 0.211$) and N2a1 and N2a2 ($p = 0.139$) categories. The 5-year survival rate of N1b was worse than that of N2a1 and N2a2, indicating that phased degradation was not observed (Fig. 3*D*).

In the pathologic stages, the HRs for OS and RFS between adjacent N categories were higher than 1.0, indicating stepwise degradation of prognosis according to both the eighth and ninth edition N classifications, with considerable differences (Table 3 and Supplementary Table 4). The HRs for OS and RFS between N1b and N2a1 were 0.97 and 0.79, respectively, according to the classification proposed by Asamura et al., suggesting that the survival outcome of N2a1 tended to be better than that of N1b. Furthermore, there were no significant differences between N1b and N2a1 ($p = 0.838$) regarding OS and between N1b and N2a1 ($p = 0.066$) regarding RFS.

Additional Sensitivity Analyses for Histology, T Descriptor, and Year of Surgery

Various subgroup analyses were performed to confirm the reproducibility of the ninth edition N classification. The survival curves for all subgroup analyses revealed a similar pattern, with a consistent order of survival outcomes among the N descriptors, although some log-rank test p values were not statistically significant, which could have been due to the small sample sizes. In addition, the difference in 5-year OS between the N2a and N2b categories was less than 5% only in the T4 subgroup, whereas in all other subgroups, the survival differences between adjacent N categories were greater than 5% (Supplementary Figs. 2, 3, and 4).

Discussion

The findings of this study revealed the clinical relevance of the newly proposed N descriptor of the ninth edition TNM staging system with patients who underwent curative surgery for NSCLC. We found a clear and consistent prognostic difference between subgroups of patients with N2 disease, namely those with N2a and N2b. In addition, N2a status was associated with worse survival than N1 status, which allowed for a much clearer prognostic separation between all categories compared with that with the eighth edition N classification. The differences between all categories, both clinical and pathologic, remained statistically significant even after adjustment for various cofactors. Moreover, using detailed information from a single large cohort, we validated the clinical utility of the ninth edition N descriptor for RFS and OS.

The N classification of lung cancer is exclusively determined by the anatomical location of the LNs and has no concept of disease burden. Nevertheless, over the years, many studies have reported the disease burden of metastatic LNs and heterogeneity in the N1 and N2 categories.[7,8,13,14] To improve the prognostic discrimination ability based on nodal status, exploratory analyses have been performed before each TNM classification revision. In the seventh edition analysis, disease burden of metastatic LNs at the N1 and N2 levels was evaluated by subdividing into single and multiple LN zones. This categorizing of LN stations into LN zones was introduced to reconcile discrepancies between the MD-ATS and Naruke-Japanese LN maps.[4,10,15] Although the results of this analysis revealed prognostic differences between adjacent N categories, small sample sizes precluded validation of each N category across T categories. In the eighth edition analysis, the disease burden of involved LNs was evaluated according to the number of metastatic LN stations, single versus multiple, and the presence of "skip" metastases. Although the pathologic N classification was observed to have prognostic ability, there was no difference in survival between the N1b and N2a1 categories, and the N1b and N2a2 survival curves overlapped. Furthermore, most of the information for pathologic N status was derived from Japan, and there was still dichotomization of LN maps among the collected data.[5]

Considering these limitations, this classification was re-evaluated with the ninth edition database, which included a larger and more detailed data set obtained through the Electronic Data Capture and adoption of the IASLC LN map as the accepted standard.[16] Nevertheless, there was a still lack of clear separation between adjacent categories. Furthermore, the N2a1 category had no survival difference compared with adjacent categories, increasing the complexity of the staging system. Finally, the IASLC concluded that the proposal did not sufficiently stratify prognostic groups in either clinical or pathologic staging. Nevertheless, clearer prognostic separation between categories was observed when the N1 category was retained and N2 was subdivided on the basis of single (N2a) and multiple (N2b) stations.[9]

In this study, a significant survival difference was observed in terms of pathologic staging between N1a and N1b (HR = 1.65, $p < 0.001$ for OS) (Table 3), which has been consistently reported in other studies including the ninth edition data set.[5,7–9] Nevertheless, the difference between N1a and N1b no longer remained significant when it was applied to clinical staging (HR = 1.05, $p = 0.758$ for OS) (Table 3), which is similar to the results of the survival analysis by the IASLC that used the ninth edition data set.[9] Previously, the IASLC defined the threshold for considering alternative changes in revising the N classification of lung cancer, noting that the ordering of prognostic differences should be maintained in clinical and pathologic staging.[1] This means that clinical N descriptors should be achievable and reasonably capable of discriminating prognosis, regardless of surgical or nonsurgical treatment, even though the magnitude of the difference between survival curves may differ between clinical and pathologic staging. In fact, it is difficult to distinguish and confirm the number of involved N1 LN stations using radiologic and invasive clinical staging procedures.[5,9,17] Thus, we agree with the IASLC's proposal to simply retain the N1 category without separating it into N1a and N1b in the ninth edition N classification.

Similarly, it is reasonable to consolidate into simpler single- versus multiple-station metastasis categories (N2a and N2b) without separating according to the "skip" metastasis (N2a1 and N2a2). Various studies have revealed that the N2a1 category does not have any considerable survival differences compared with adjacent categories, which increases the complexity of the staging system.[4,5,7–9] The same result was obtained in

our study, where there was no significant survival difference between the N1b and N2a1 ($p = 0.838$ for OS) categories. Nevertheless, when N2a1 and N2a2 were combined into N2a in the ninth edition of the TNM staging system, we detected much clearer prognostic separations between all categories (N0, N1, N2a, and N2b) in terms of both clinical and pathologic staging. Notably, in contrast to the N1 category, splitting the N2 category into the N2a and N2b categories was clinically relevant in clinical staging. This is because it is relatively easier to distinguish the number of involved N2 LN stations than that of N1 nodes through imaging tests or invasive staging procedures.

The multivariable Cox proportional hazards model revealed considerable differences between N categories of the ninth edition classification in terms of both clinical and pathologic staging after adjusting for age, sex, histology, comorbidity, and year of surgery. The subgroup analyses survival curves were consistently observed in the order of N descriptors, although some differences between N categories were not statistically significant. Excluding those between the N2a and N2b categories in the T4 subgroup, differences in 5-year survival rates between N categories were consistently observed to be greater than 5%, revealing that the prognostic discriminatory ability is well maintained even across subgroups. Consequently, the ninth edition N classification appropriately reflected the long-standing requirement of integrating a measure of disease burden into the solely location-based system. Moreover, this system did not disrupt the eighth edition classification and is backward compatible. Most importantly, the survival differences between these subgroups were consistent across clinical and pathologic classifications, which may facilitate greater precision from radiologists, practitioners involved in invasive staging procedures, surgeons, and pathologists.

We acknowledge that this study has several limitations. First, information and selection biases are inevitable in a single-center, retrospective study, although the data used in this study were collected prospectively in our database. Second, there was no survival analysis for clinical or pathologic N3 subgroup patients—this study included only patients who underwent surgical treatment, and patients with clinical or pathologic N3 could not be included due to their rarity. Third, patients who underwent neoadjuvant therapy were excluded from this study. Surgical resection after neoadjuvant therapy has become the preferred approach in cases of advanced lung cancer in many institutions. The use of immunotherapy or target agents is also rapidly increasing, and the neoadjuvant chemoimmunotherapy paradigm is rapidly developing.[18,19] Given this trend, even though the proposed N classification was found to have prognostic discrimination ability in the ninth edition data set,[9] it will be necessary to externally validate whether it retains this ability for patients who undergo neoadjuvant therapy. Fourth, performance status and mutation markers are known to be associated with the prognosis of lung cancer. Nevertheless, given the retrospective nature of this study and incomplete data, we could not add these factors to the Cox regression model. Fifth, as only patients who underwent surgical treatment were included in this analysis, the results could differ from those of the overall NSCLC patient population. Finally, our study has a relatively small sample size compared with the IASLC ninth edition data set. Therefore, it may lack statistical power, especially when the N categories are subdivided, as the classification proposed by Asamura et al. In addition, the sample size for various subgroup analyses was relatively small; although there might be clinical differences, statistically significant differences might not be observed.

In summary, we validated the clinical utility of the ninth edition N classification for both clinical and pathologic stages in NSCLC. The newly proposed N classification revealed clear prognostic separation between all categories (N0, N1, N2a, and N2b) in terms of RFS and OS. Thus, it is expected to provide key insights into the heterogeneity of nodal involvement and facilitate the evolution of adequate treatment-related decisions.

CRediT Authorship Contribution Statement

In Ha Kim: Conceptualization, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization.

Jae Kwang Yun: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision.

Geun Dong Lee: Investigation, Formal analysis, Writing - review & editing, Supervision.

Sehoon Choi: Data curation, Writing - review & editing, Supervision.

Hyeong Ryul Kim: Methodology, Writing - review & editing, Supervision.

Yong-Hee Kim: Writing - review & editing, Supervision.

Dong Kwan Kim: Writing - review & editing, Supervision.

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Disclosure

The authors declare no confict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.04.002.

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