CHEST

Role of Pathologic Single-Nodal and Multiple-Nodal Descriptors in Resected Non-Small Cell Lung Cancer

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BACKGROUND: The eighth edition of lung cancer nodal staging assignment includes the location of lymph node metastasis, but does not include single-nodal and multiple-nodal descriptors.

RESEARCH QUESTION: Do the single-nodal and multiple-nodal statuses stratify the prognosis of patients with non-small cell lung cancer (NSCLC)?

STUDY DESIGN AND METHODS: Using the National Cancer Database, we analyzed patients with pathologically staged N1 and N2 NSCLC. Nodal descriptors were classified into pathological single N1 (pSingle-N1), pathological multiple N1 (pMulti-N1), pathological single N2 (pSingle-N2), and pathological multiple N2 (pMulti-N2). Survival analysis was performed using the Kaplan-Meier method and multivariable Cox regression models.

RESULTS: In the general analysis cohort, 24,531, 22,256, 8,528, and 21,949 patients with NSCLC demonstrated pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2 disease, respectively. Patients with pMulti-N1 and pMulti-N2 disease showed a shorter survival than those with pSingle-N1 and pSingle-N2 disease, respectively (hazard ratio, 1.22 [$P < .0001$] for N1 and 1.39 [$P < .0001$] for N2). After adjusting age, sex, and histologic findings, the hazard ratio for pSingle-N2 compared with pMulti-N1 disease was 1.05 ($P = .0031$). Patients with pN1 disease were categorized by metastatic lymph node count (1, 2, 3, $\geq$ 4), showing significant prognostic differences among groups ($P < .0001$). In the sensitivity analysis cohort (limited to R0 resection, lobectomy, or more; survival $\geq$ 30 days; $\geq$ 10 examined lymph nodes; and without neoadjuvant therapy; n = 34,904) and the external validation cohort (n = 708), analyses supported these results.

INTERPRETATION: Patients with NSCLC with one metastatic lymph node, whether in N1 or N2 stations, showed better survival than those with more than one lymph node involved. Patients with NSCLC with a single-skip N2 lymph node metastasis showed survival similar to patients with multiple N1 lymph nodes, and the number of lymph nodes involved in N1 resections up to four or more was sequentially prognostic. CHEST 2024; 166(5):1218-1228

KEY WORDS: lymph node metastasis; non-small cell lung cancer; prognosis; surgery; TNM stage

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ABBREVIATIONS: HR = hazard ratio; IASLC = International Association for the Study of Lung Cancer; NCDB = National Cancer Database; N = node; NSCLC = non-small cell lung cancer; OS = overall survival; pN = pathologic N; pMulti-N1 = pathologic multiple N1; pMulti-N2 = pathologic multiple N2; pSingle-N1 = pathologic single N1; pSingle-N2 = pathologic single N2

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Take-home Points

Study Question: Do the pathologic single-nodal and multiple-nodal statuses stratify the prognosis of patients with non-small cell lung cancer?

Results: Patients with pathologic multiple N1 and N2 involvement showed a significantly shorter survival than those with pathologic single N1 and N2 involvement, respectively, and the prognosis for pathologic single N2 involvement was similar to that for pathologic multiple N1 involvement.

Interpretation: Patients with one metastatic lymph node, whether in N1 or N2 stations, showed better survival than those with more than one lymph node involved.

Lung cancer is one of the most fatal malignancies worldwide, and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases.[1] The overall survival (OS) of patients with NSCLC is predicted using the TNM staging system, which is published and updated every several years by the American Joint Committee on Cancer and the Union for International Cancer Control.[2] Although the American Joint Committee on Cancer and the Union for International Cancer Control are separate organizations, they work together to define a tumor staging system for worldwide use.[3] Stage classification is an important tool in estimating prognosis, determining treatment, and conducting clinical trials.[4] For establishing staging classifications for lung cancer, the American Joint Committee on Cancer and the Union for International Cancer Control rely on the work of the International Association for the Study of Lung Cancer.[4] As more diagnostic and therapeutic technology continues to be developed, the TNM staging system requires regular updates to reflect changes in the diagnosis and management of NSCLC.

In the current TNM classification for lung cancer (the eighth edition), the International Association for the Study of Lung Cancer defines nodal classification depending on lymph node metastasis location to provide an accurate prognosis as follows: N0 (no nodal involvement), N1 (peribronchial, interlobar, or hilar nodal involvement), N2 (ipsilateral mediastinal nodal involvement), or N3 (contralateral mediastinal, contralateral hilar, or supraclavicular nodal involvement).[4] The nodal descriptors are dependent on the anatomic location of the nodal involvement. However, in other malignancies, pathologic nodal classification is assigned depending on the number of lymph nodes with histologic metastases.[5,6] The purpose of this retrospective study was to investigate whether nodal descriptors reflecting the number of metastatic lymph nodes accurately reflect postoperative prognosis in patients with resected NSCLC using the National Cancer Database (NCDB).

Study Design and Methods

National Cancer Database

The NCDB is a joint project between the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB and the hospitals participating in the Commission on Cancer NCDB are the source of the de-identified data used in this study; the NCDB and hospitals have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The data are considered as hospital-based data, rather than population-based data. This study was exempted from institutional review board approval by the authors' institutional review boards.

A general analysis cohort was used and a more restrictive sensitivity analysis cohort was used to perform sensitivity analysis to test the consistency of the results. The study flows of case eligibility of the general and sensitivity analysis cohorts are shown in Figure 1 and e-Figure 1, respectively. For the general analysis cohort, patients with resected NSCLC captured in the NCDB between 2004 and 2019 were selected initially (N = 483,897). Patients with pathologic M1 disease were excluded (n = 13,965); additionally, patients without OS data (n = 53), those with pathologic N3

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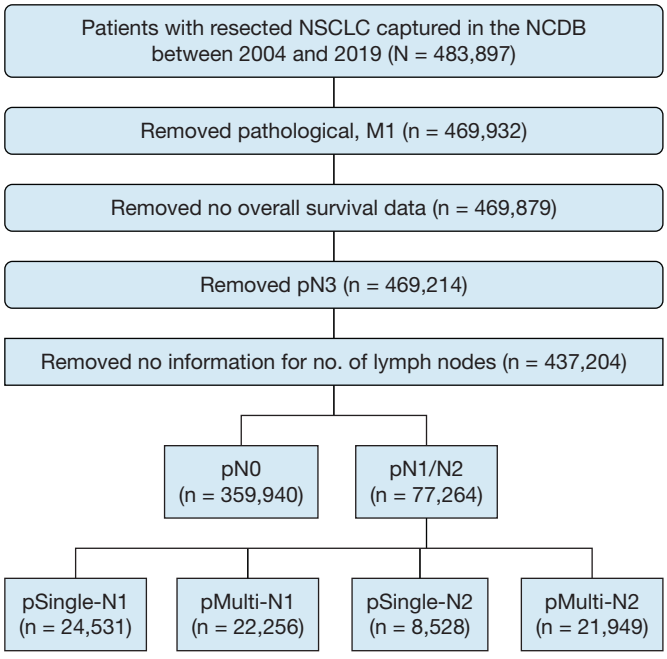


Figure 1 – *Flow diagram showing patient selection in the general analysis cohort. NCDB = National Cancer Database; NSCLC = non-small cell lung cancer; pMulti-N1 = pathologic multiple N1; pMulti-N2 = pathologic multiple N2; pSingle-N1 = pathologic single N1; pSingle-N2 = pathologic single N2.*

(pN3) disease (n = 665), and those without information for number of lymph nodes (n = 32,010) were excluded. Finally, 359,940 patients with pN0 disease, 24,531 patients with pathologic single N1 (pSingle-N1) disease, 22,256 patients with pathologic multiple N1 (pMulti-N1) disease, 8,528 patients with pathologic single N2 (pSingle-N2) disease, and 21,949 patients with pathologic multiple N2 (pMulti-N2) disease were analyzed. For the sensitivity analysis cohort, patients with resected NSCLC captured in the NCDB between 2004 and 2019 were selected initially (N = 483,897). Among this group, we identified 89,438 patients with pN1 and pN2 disease. Patients with pathologic M1 disease were excluded (n = 4,220). Of these, patients with R0 resection, lobectomy or more, and OS of ≥ 30 days were selected (n = 68,198). Patients with neoadjuvant chemotherapy or radiotherapy (n = 6,585) and fewer than 10 examined lymph nodes (n = 26,709) were removed. Finally, 34,904 patients were included in the sensitivity analysis cohort.

Definition of Four Categories for Nodal Descriptors

All cases of pN1 and pN2 disease were classified into four categories using combinations of single or multiple metastatic lymph nodes (pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2). pSingle-N1 and pMulti-N1 disease indicate pN1 with single and multiple metastatic lymph nodes, and therefore are equivalent to pN1a (pN1 single) and pN1b (pN1 multiple) in the International Association for the Study of Lung Cancer (IASLC) staging for the proposed ninth edition staging, respectively.[7] pSingle-N2 disease indicates pN2 with a single metastatic lymph node without pN1, and therefore is equivalent to pN2a1 (pN2 single with skip). pMulti-N2 disease indicates pN2 with multiple metastatic lymph nodes, equivalent to pN2a2 (pN2 single without skip) combined with pN2b (pN2 multiple) in the IASLC staging for the ninth edition staging system.[7]

Validation Data Source

For external validation, we used three electronic medical record databases from Oita University Hospital, National Hospital Organization Kyushu Cancer Center, and Kyushu University Hospital. We selected patients with resected NSCLC with pN1 or pN2 without neoadjuvant therapy from 2013 through 2020 in Oita University Hospital (n = 98), from 2004 through 2018 in National Hospital Organization Kyushu Cancer Center (n = 365), and from 2003 through 2018 in Kyushu University Hospital (n = 245), regardless of surgical procedures, extent of lymph node dissection, neoadjuvant chemotherapy, or radiotherapy. Finally, 708 patients were included in the validation analysis.

Statistical Analysis

The associations between nodal status and clinical demographics were assessed by χ^2 tests. OS was defined

as the time (years) from date of surgery to death resulting from any cause. Kaplan-Meier curves by the nodal classification were compared using log-rank tests. Univariable and multivariable Cox proportional hazards regression analyses were performed using JMP version 14.0 software and SAS version 9.4 software (both SAS Institute, Inc.). All tests were two-tailed, and $P < .05$ was considered statistically significant.

Results

Patient Characteristics

In the general analysis cohort, 359,940 patients (82.3%), 24,531 patients (5.6%), 22,256 patients (5.1%), 8,528 patients (2.0%), and 21,949 patients (5.0%) with NSCLC had pN0, pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2 disease, respectively. The characteristics of the patients with NSCLC in the general and sensitivity cohorts in accordance with the four pN classifications (pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2) are shown in Table 1 and e-Table 1, respectively. Of the total 34,904 patients in the sensitivity cohort, 10,531 patients (30.2%) had pSingle-N1 disease, 12,212 patients (35.0%) had pMulti-N1 disease, 2,207 patients (6.3%) had pSingle-N2 disease, and 9,954 patients (28.5%) had pMulti-N2 disease. Distributions of the metastasized lymph nodes and lymph nodes removed during surgery in the general analysis cohort were shown in e-Figure 2. The median numbers of the metastasized lymph nodes and the lymph nodes removed during surgery were 2 and 11, respectively.

Survival Analysis in Patients With Resected NSCLC in Accordance With pN Classifications

Survival analysis of the general cohort (Fig 1) in accordance with the five pN classifications (pN0, pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2) was performed. As shown in Figure 2, patients with pN0 disease showed a longer OS than those with pSingle-N1 disease (5-year survival rates, 60.0% vs 50.4%, respectively). Patients with pMulti-N1 disease showed a significantly shorter OS compared with those with pSingle-N1 disease (5-year survival rate, 43.6% vs 50.4%, respectively). Patients with pMulti-N2 disease showed a significantly shorter OS compared with those with pSingle-N2 disease (5-year survival rate: 36.4% vs 42.9%, respectively). Patients with pSingle-N2 disease showed an OS comparable with that of those with pMulti-N1 disease (5-year survival rate: 42.9% vs 43.6%, respectively). After adjusting age (≥ 70 years), sex, and histologic findings (adenocarcinoma vs squamous cell carcinoma vs other), the hazard ratios (HRs) for pMulti-N2 disease compared with pSingle-N2 disease, pSingle-N2 disease compared with pMulti-N1 disease, and pMulti-N1 disease compared with pSingle-N1 disease were 1.21 (95% CI, 1.17-1.24; $P < .0001$), 1.05 (95% CI, 1.02-1.08; $P = .0031$), and 1.19 (95% CI, 1.17-1.22; $P < .0001$), respectively.

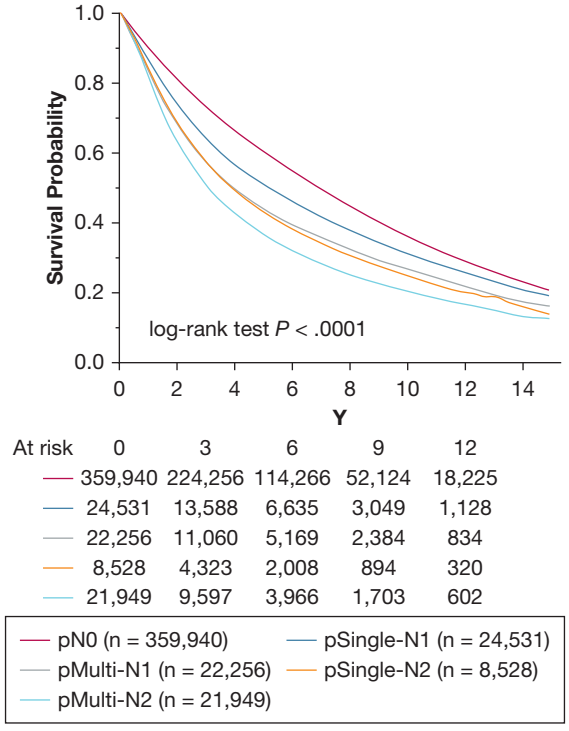
Survival analysis of the sensitivity cohort (e-Fig 1) in accordance with the four pN classifications (pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2) was performed. As shown in e-Figure 3, patients with pMulti-N1 disease showed a significantly shorter OS compared with those with pSingle-N1 disease (5-year survival rate, 48.6% vs 56.3%, respectively). Patients with pMulti-N2 disease showed a significantly shorter OS compared with those with pSingle-N2 disease (5-year survival rate, 39.4% vs 50.3%, respectively). Patients with pSingle-N2 disease showed an OS comparable with that of those with pMulti-N1 disease (5-year survival rate, 50.3% vs 48.6%, respectively). Given that it is possible that PET and invasive mediastinal staging were not implemented properly from 2004 through 2010, subgroup survival analyses were performed by year (2004-2010 vs 2011-2019) (e-Fig 4). In the 2004 through 2010 cohort, patients with pMulti-N1 and pMulti-N2 disease showed a shorter survival than those with pSingle-N1 and pSingle-N2 disease, respectively (5-year survival rates, 44.4% vs 53.0%, respectively, for N1 disease and 34.8 % vs 48.2%, respectively, for N2 disease). Patients with pSingle-N2 disease showed survival comparable with that of those with pMulti-N1 disease (5-year survival rates, 48.2% vs 44.4%, respectively). In the 2011 through 2019 cohort, patients with pMulti-N1 disease and pMulti-N2 disease showed a shorter survival than those with pSingle-N1 disease and pSingle-N2 disease, respectively (5-year survival rates, 50.7% vs 57.8%, respectively, for N1 disease and 41.7% vs 51.6%, respectively, for N2 disease). As can be seen in e-Figure 3, after adjusting for age (≥ 70 years), sex, and histologic findings (adenocarcinoma vs squamous cell carcinoma vs other), the HRs for pMulti-N2

TABLE 1] Clinical Characteristics of Patients With Non-Small Cell Lung Cancer in the General Analysis Cohort in Accordance With Pathologic Nodal Status (N = 77,264)

Factor	Pathologic Nodal Status				*P* Value
	pSingle-N1 (n = 10,531)	pMulti-N1 (n = 12,212)	pSingle-N2 (n = 2,207)	pMulti-N2 (n = 9,954)	
Age, y					
≥ 70	10,272 (42)	8,608 (39)	3,513 (41)	8,491 (39)	< .0001
< 70	14,259 (58)	13,648 (61)	5,015 (59)	13,458 (61)	...
Sex					
Male	12,947 (53)	12,288 (55)	4,107 (48)	10,541 (48)	< .0001
Female	11,584 (47)	9,968 (45)	4,421 (52)	11,408 (52)	...
Race					
White	21,539 (88)	19,623 (88)	7,385 (87)	19,018 (87)	< .0001
Other[a]	2,992 (12)	2,633 (12)	1,143 (13)	2,931 (13)	...
Institution					
Other	16,150 (66)	14,248 (64)	5,514 (65)	13,752 (63)	< .0001
Academic	8,381 (34)	8,008 (36)	3,014 (35)	8,197 (37)	...
Charlson-Deyo score					
≥ 2	3,373 (14)	3,016 (14)	1,158 (14)	2,717 (12)	< .0001
0-1	21,158 (86)	19,240 (86)	7,370 (86)	19,232 (88)	...
Year of diagnosis					
2004-2009	8,674 (35)	7,947 (36)	3,116 (36)	7,367 (33)	< .0001
2010-2017	14,175 (58)	12,811 (57)	4,906 (58)	13,117 (60)	
2018-2019	1,682 (7)	1,498 (7)	506 (6)	1,465 (7)	...
Laterality					
Right/other	13,757 (56)	11,942 (54)	4,653 (55)	12,061 (55)	< .0001
Left	10,774 (44)	10,314 (46)	3,875 (45)	9,888 (45)	...
Histologic findings	...	...	...	...	...
Adenocarcinoma	13,710 (56)	11,820 (53)	5,437 (64)	15,152 (69)	< .0001
Other	10,821 (44)	10,436 (47)	3,091 (36)	6,797 (31)	
Pathologic T stage					
≤ 2	20,031 (82)	17,187 (77)	6,980 (82)	17,250 (79)	< .0001
≥ 3	4,500 (18)	5,069 (23)	1,548 (18)	4,699 (21)	...
Clinical Nodal stage					
N0	16,929 (69)	13,656 (61)	5,245 (62)	12,011 (55)	< .0001
N ≥ 1	7,602 (31)	8,600 (39)	3,283 (38)	9,938 (35)	...
Adjuvant radiotherapy					
Yes	2,275 (9)	2,792 (13)	2,986 (35)	8,749 (40)	< .0001
No	22,256 (91)	19,464 (87)	5,542 (65)	13,200 (60)	...
Adjuvant chemotherapy					
Yes	15,079 (61)	14,484 (65)	6,140 (72)	16,662 (76)	< .0001
No	9,452 (39)	7,772 (35)	2,388 (28)	5,287 (34)	...

pMulti-N1 = pathologic multiple N1; pMulti-N2 = pathologic multiple N2; pSingle-N1 = pathologic single N1; pSingle-N2 = pathologic single N2; T = tumor.
[a]Includes all other races.

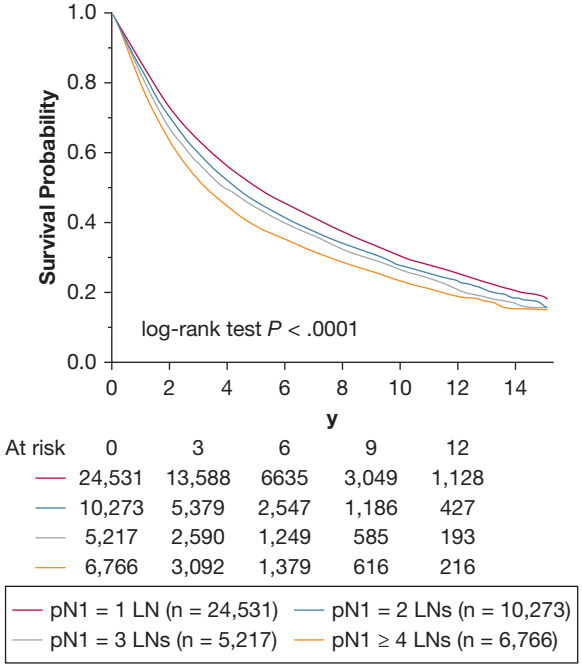
disease compared with pSingle-N2 disease, pSingle-N2 disease compared with pMulti-N1 disease, and pMulti-N1 disease compared with pSingle-N1 disease were 1.39 (95% CI, 1.31-1.47; $P < .0001$), 0.96 (95% CI, 0.90-1.02; $P = .1407$), and 1.22 (95% CI, 1.18-1.27; $P < .0001$), respectively.



pSingle-N1 vs pMulti-N1 vs pSingle-N2 vs pMulti-N2 Comparisons Adjusted for Age ≥ 70 y, Sex, Histologic findings (adenocarcinoma vs squamous carcinoma)		
Comparison	Hazard Ratio (95% CI)	*P* VALUE
pMulti-N1 vs pSingle-N1	1.19 (1.17-1.22)	< .0001
pMulti-N2 vs pSingle-N2	1.21 (1.17-1.24)	< .0001
pSingle-N2 vs pMulti-N1	1.05 (1.02-1.08)	.0031

Group	5-year survival rate (%)	Patients at risk	15-year survival rate (%)	Patients at risk
pN0	60.0	145,162	20.1	3,100
pSingle-N1	50.4	8,474	18.7	199
pMulti-N1	43.6	6,654	15.7	158
pSingle-N2	42.9	2,579	13.3	49
pMulti-N2	36.4	5,282	11.9	104

Figure 2 – *Kaplan-Meier curve showing overall survival in the general analysis cohort of patients with non-small cell lung cancer with pN0, pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2 involvement. pMulti-N1 = pathologic multiple N1; pMulti-N2 = pathologic multiple N2; pN0 = pathologic N0; pSingle-N1 = pathologic single N1; pSingle-N2 = pathologic single N2.*



pN1 = 1LN vs pN1 = 2LNs vs pN1 = 3LNs vs pN1 ≥ 4LNs Comparisons Adjusted for Age ≥ 70 y, Sex, Histologic findings (adenocarcinoma vs squamous carcinoma)		
Comparison	Hazard Ratio (95% CI)	*P* VALUE
pN1 = 2LNs vs pN1 = 1LN	1.11 (1.08-1.14)	< .0001
pN1 = 3LNs vs pN1 = 1LN	1.19 (1.14-1.23)	< .0001
pN1 ≥ 4LNs vs pN1 = 3LNs	1.14 (1.09-1.19)	< .0001

Group	5-year survival rate (%)	Patients at risk	15-year survival rate (%)	Patients at risk
pN1 = 1 LN	50.4	8,474	18.7	199
pN1 = 2 LNs	46.2	3,276	16.6	73
pN1 = 3 LNs	44.4	1,581	15.6	48
pN1 ≥ 4 LNs	39.1	1,801	14.5	40

Figure 3 – *Kaplan-Meier curve showing overall survival in patients with non-small cell lung cancer with pN1 involvement in accordance with the number of metastatic lymph nodes (1, 2, 3, and ≥ 4) in the general analysis cohort. LN = lymph node; pN1 = pathologic N1.*

Survival Analysis in Patients With Resected NSCLC in Accordance With the Number of Metastatic Lymph Nodes in pN1 Disease

We divided patients with pN1 disease into groups in accordance with the number of metastatic lymph nodes (1, 2, 3, and ≥ 4) in the general analysis cohort. A prognostic difference was found among the four groups (Fig 3). After adjusting for age, sex, and histologic findings, the HRs for the pN1 = 2 lymph nodes and pN1 = 3 lymph nodes groups compared with the pN1 = 1 lymph node group were 1.11 (95% CI, 1.08-1.14; $P < .0001$) and 1.19 (95% CI, 1.14-1.23; $P < .0001$), respectively. The hazard ratio (HR) for the pN1 ≥ 4 lymph nodes group compared with the pN1 = 3 lymph nodes group was 1.14 (95% CI, 1.09-1.19; $P < .0001$). The sensitivity analysis cohort analyses performed in a similar manner supported these results (e-Fig 5).

Univariable and Multivariable Analyses of OS in Patients With Resected NSCLC

Univariable and multivariable analyses of OS in the general analysis cohort of patients with resected NSCLC using four categories (pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2) were performed. Univariable analysis revealed that age, sex, race, institution, Charlson-Deyo score, diagnosis period, histologic findings, pT factor, cN status, adjuvant radiotherapy, adjuvant chemotherapy, and pN status were associated significantly with OS (Table 2). Multivariable analyses revealed that age, sex, race, institution, Charlson-Deyo score, diagnosis period, histologic findings, pT factor, cN status, adjuvant radiotherapy, adjuvant chemotherapy, and pN status were associated significantly with OS. In multivariable analysis of OS, the HR of patients with pMulti-N1 disease compared with pSingle-N1 disease was 1.20 (95% CI, 1.17-1.23; $P < .0001$). Additionally, the HR of patients with pSingle-N2 disease compared with those with pSingle-N1 disease (HR, 1.28; 95% CI, 1.24-1.33; $P < .0001$) was much smaller than that of patients with pMulti-N2 disease (HR, 1.57; 95% CI, 1.53-1.61; $P < .0001$).

Univariable and multivariable analyses of OS in the sensitivity analysis cohort of patients with resected NSCLC using four categories (pSingle-N1, pMulti-N1, pSingle-N2, and pMulti-N2) were performed. Univariable analysis revealed that age, sex, race, institution, Charlson-Deyo score, diagnosis period, histologic findings, pT factor, cN status, adjuvant radiotherapy, adjuvant chemotherapy, and pN status were associated significantly with OS (e-Table 2). Multivariable analyses revealed that age, sex, race, institution, Charlson-Deyo score, diagnosis period, histologic findings, pT factor, cN status, adjuvant radiotherapy, adjuvant chemotherapy, and pN status were associated significantly with OS (e-Table 2). In multivariable analyses of OS, the HR of patients with pSingle-N2 disease compared with those with pSingle-N1 disease (HR, 1.19; 95% CI, 1.12-1.27; $P < .0001$) was much smaller than that of patients pMulti-N2 disease (HR, 1.66; 95% CI, 1.60-1.73; $P < .0001$) and even slightly smaller than that of patients with pMulti-N1 disease (HR, 1.22; 95% CI, 1.18-1.26; $P < .0001$).

Validation of Survival Analysis in Accordance with pN Classifications in Patients With Resected NSCLC

Validation of the results was performed using data from three facilities in Japan (Oita University Hospital, National Hospital Organization Kyushu Cancer Center, and Kyushu University Hospital). e-Figure 6 shows the OS curves of patients with pN1a disease (n = 203), pN1b disease (n = 109), pN2a disease (n = 263), and pN2b disease (n = 133) from the validation data. Patients with pN1b disease showed a shorter OS in comparison with those with pN1a disease after adjusting for age, sex, and histologic findings (HR, 1.44; 95% CI, 1.03-2.02; 5-year survival rate, 54.0% vs 63.2%, respectively; $P = .0317$). Patients with pN2b disease showed a shorter OS in comparison with those with pN2a disease after adjusting for age, sex, and histologic findings (HR, 1.35; 95% CI, 1.01-1.81; 5-year survival rate, 42.3% vs 53.8%, respectively; $P = .0445$). Patients with pN2a disease showed a similar OS in comparison with those with pN1b disease after adjusting for age, sex, and histologic findings (HR, 0.88; 95% CI, 0.65-1.21; 5-year survival rate, 53.8% vs 54.0%, respectively; $P = .4563$).

Discussion

The stage of disease is important in predicting the prognosis of patients with NSCLC. In the current study, multivariable analyses confirmed a significant association between pN status in four categories and OS (Table 2). Results from the validation analysis using data from three facilities in Japan supported the findings (e-Fig 6). Of note, the number of patients with NCDB in this study was larger than that used in the previous IASLC lung database (seventh edition analysis).[8] Previous studies reported a potential benefit of combining the number of metastatic lymph nodes and their anatomic locations for prognostic information.[7,9,10] In a previous Japan Lung Cancer Registry Joint

TABLE 2] Univariable and Multivariable Analyses of Overall Survival in Patients With Non-Small Cell Lung Cancer in the General Analysis Cohort With Pathologic Nodal Metastasis (Pathologic Nodal Stage: Single-N1 vs Multi-N1 vs Single-N2 vs Multi-N2; n = 77,264)

	Univariable		Multivariable	
Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y				
≥ 70	1.52 (1.49-1.55)	< .0001	1.41 (1.38-1.43),	< .0001
< 70 (reference)	…	…	…	…
Sex				
Male	1.32 (1.29-1.34)	< .0001	1.28 (1.25-1.30)	< .0001
Female (reference)	…	…	…	…
Race				
White	1.16 (1.13-1.19)	< .0001	1.09 (1.06-1.12)	< .0001
Other (reference)[a]	…	…	…	…
Institution				
Other	1.13 (1.10-1.15)	< .0001	1.12 (1.10-1.14)	< .0001
Academic (reference)	…	…	…	…
Charlson-Deyo score				
≥ 2	1.22 (1.19-1.26)	< .0001	1.17 (1.14-1.19)	< .0001
0-1 (reference)	…	…	…	…
Year of diagnosis	…	…	…	…
2004-2009	1.56 (1.47-1.65)	< .0001	1.52 (1.44-1.61)	< .0001
2010-2017	1.34 (1.27-1.42)	< .0001	1.34 (1.27-1.42)	< .0001
2018-2019 (reference)	…	…	…	…
Laterality				
Left/other	1.01 (0.99-1.03)	.4182	0.99 (0.98-1.01)	.4766
Right (reference)	…	…	…	…
Histologic findings				
Squamous/others	1.16 (1.13-1.18)	< .0001	1.07 (1.05-1.09)	< .0001
Adenocarcinoma (reference)	…	…	…	…
Pathologic T stage				
≥ 3	1.42 (1.39-1.45)	< .0001	1.44 (1.41-1.48)	< .0001
≤ 2/unknown (reference)	…	…	…	…
Clinical Nodal stage				
N ≥ 1	1.08 (1.06-1.10)	< .0001	1.10 (1.08-1.12)	< .0001
N0 (reference)	…	…	…	…
Adjuvant radiotherapy				
Yes	1.08 (1.06-1.11)	< .0001	1.11 (1.09-1.14)	< .0001
No (reference)	…	…	…	…
Adjuvant chemotherapy	…	…	…	…
No	1.76 (1.73-1.80)	< .0001	1.76 (1.73-1.79)	< .0001
Yes (reference)	…	…	…	…
Pathologic Nodal stage				
Multiple N2	1.43 (1.39-1.46)	< .0001	1.57 (1.53-1.61)	< .0001

(Continued)

TABLE 2] *(Continued)*

Factor	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Single N2	1.21 (1.17-1.25)	< .0001	1.28 (1.24-1.33)	< .0001
Multiple N1	1.19 (1.16-1.22)	< .0001	1.20 (1.17-1.23)	< .0001
Single N1 (reference)	...	...	...	...

HR, hazard ratio; pMulti-N1 = pathologic multiple N1; pMulti-N2 = pathologic multiple N2; pSingle-N1 = pathologic single N1; pSingle-N2 = pathologic single N2; T = tumor.
[a]Includes all other races.

Committee database study, Yoshino et al[10] reported that patients with NSCLC with multistation N2 disease showed a significantly worse prognosis than those with single-station N2 disease (5-year survival rate, 22.0% vs 35.8%, respectively). Asamura et al[7] reported similar results, showing that patients with NSCLC with multistation N2 disease showed a significantly shorter OS compared with those with single-station N2 disease (5-year survival rate, 38% vs 49%, respectively). Additionally, patients with NSCLC with multistation N1 disease showed a significantly shorter OS compared with those with single-station N1 disease (5-year survival rate, 50% vs 59%, respectively), and those with multistation N1 disease showed an OS comparable with that of those with single-station N2 disease (5-year survival rate, 50% and 49%, respectively). In that study, most of the data were derived from Japan, with 23,012 patients (59.1%) with cN status and 23,463 patients (74.7%) with pN status. Therefore, the Naruke-Japanese map was used in most patients to designate the location of metastatic lymph nodes and to determine nodal status.[11] The number of data submitted from the United States was small, with 861 patients (2.2%) with cN status and 2,291 patients (7.3%) with pN status. In our study, the number of patients with NSCLC with pN1-2 disease from the United States was 77,264 patients in the general analysis cohort (Fig 1) and 34,904 patients in the sensitivity analysis cohort (e-Fig 1), compared with 8,333 patients with NSCLC analyzed by Asamura et al.[7]

The IASLC Lung Cancer Staging Project recently proposed the revision of the nodal descriptors in the forthcoming ninth edition of the TNM classification of lung cancer.[12] In this revision, the newly established database consisted of 87,043 patients with the data on valid histologic type, survival time, date of diagnosis window, and clinical and pathologic stages.[13] Of the total patients, 10,187 patients(11.7%) were from the United States. The IASLC Lung Cancer Staging Project proposed the addition of new subdescriptors to N2 for single-station involvement (N2a) and multiple-station involvement (N2b) based on the results showing that prognostic differences between N2a and N2b involvement were observed consistently across each subgroup in accordance with completeness of resection, histologic type, T category, and geographic region. In the current study, it was ideal to analyze pN2a2 and pN2b involvement separately; however, because of lack of station information, NCDB could distinguish only pN2a1 from pN2 involvement. Thus, the NCDB showed the prognostic difference only between pSingle-N2 (pN2a1) and pMulti-N2 (pN2a2 plus pN2b) involvement. Regarding the prognostic difference between pN2a and pN2b involvement, analysis of the validation cohort including 708 patients showed that patients with pN2b disease showed a significantly shorter OS compared with those with pN2a disease (e-Fig 6). The proposal of subdivision into pN2a and pN2b disease by the IASLC Lung Cancer Staging Project is considered appropriate. Regarding pN1 disease, NCDB and validation cohort analyses both showed that patients with pN1b disease experienced a significantly shorter OS than those with pN1a disease (Figs 1, 2, e-Fig 6). In the detailed survival analysis in accordance with the number of metastatic lymph nodes in pN1 disease (Fig 3), a difference was found among the multiple pN1 groups, suggesting that the number of metastatic lymph nodes is important. However, the IASLC Lung Cancer Staging Project has not revised the pN1 classification in the ninth edition because clinical staging methods did not permit reliable counting of N1 lymph nodes or stations.

This study has several limitations. First, the findings were derived from pathologic staging and have not been validated in the clinical setting.[7] It is difficult to determine the number of individual metastatic lymph nodes by clinical staging (especially radiologic staging), although the number or location of lymph node metastases is associated with postoperative prognosis in resected NSCLC.[14-21] In breast cancer, the nodal staging system uses separate clinical and pathologic nodal

categories.[6] Clinical nodal classification is defined by the location of metastatic lymph nodes, whereas pathologic nodal staging is determined by the regions of metastatic lymph nodes and the number of ipsilateral axillary metastatic lymph nodes.[6] However, in lung cancer, the idea of separating the approach to clinical staging from that to pathologic staging expressly was rejected in ninth edition of TNM staging because of complexity and likely confusion. Second, the quality of data for the number of lymph node dissection is subject to the surgeons' assessment.[22,23] Although the Commission on Cancer recommends that at least one lymph node in N1 station and three lymph nodes in N2 and N3 stations (three distinct stations) should be examined for resected NSCLC, a question remains regarding the minimum number of lymph nodes that should be evaluated pathologically.[24] The NCDB may identify fewer or more total lymph nodes if the pathologist did not examine the lymph nodes in the specimen adequately or if the surgeon removed some lymph nodes in a piecemeal fashion during lung cancer resection.[25] These issues should be investigated in further prospective studies with a clearly defined protocol. Third, lymph node count was used for this study. This is because the NCDB does not have station-specific information, only number of lymph nodes. Asamura et al[13] proposed a framework for single and multiple lymph node metastases in the eighth edition, but it was not adopted in the ninth edition because of the difficulty in reliably distinguishing between clinical N1a and N1b involvement. The IASLC Lung Cancer Staging Project examined and dismissed the lymph node count approach and opted for lymph node stations as more reliable and reproducible.

Interpretation

This study showed that patients with NSCLC with one metastatic lymph node, whether in N1 or N2 stations, experienced better survival than those with more than one lymph node involved; patients with NSCLC with a single skip N2 lymph node metastasis showed survival similar to that of patients with multiple N1 lymph nodes, and the number of lymph nodes involved in N1 resections up to four or more was sequentially prognostic.

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