The IASLC Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer

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Introduction: Accurate staging of lymph node involvement is a critical aspect of the initial management of nonmetastatic non-small cell lung cancer (NSCLC). We sought to determine whether the current N descriptors should be maintained or revised for the next edition of the international lung cancer staging system.

Methods: A retrospective international lung cancer database was developed and analyzed. Anatomical location of lymph node involvement was defined by the Naruke (for Japanese data) and American Thoracic Society (for non-Japanese data) nodal maps. Survival was calculated by the Kaplan-Meier method, and prognostic groups were assessed by Cox regression analysis.

Results: Current N0 to N3 descriptors defined distinct prognostic groups for both clinical and pathologic staging. Exploratory analyses indicated that lymph node stations could be grouped together into six "zones": peripheral or hilar for N1, and upper or lower mediastinal, aortopulmonary, and subcarinal for N2 nodes. Among patients undergoing resection without induction therapy, there were three distinct prognostic groups: single-zone N1, multiple-zone N1 or single N2, and multiple-zone N2 disease. Nevertheless, there were insufficient data to determine whether the N descriptors should be subdivided (e.g., N1a, N1b, N2a, N2b).

Conclusions: Current N descriptors should be maintained in the NSCLC staging system. Prospective studies are needed to validate amalgamating lymph node stations into zones and subdividing N descriptors.

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Accurate staging of lymph node involvement is a critical aspect of the initial management of patients with nonmetastatic non-small cell lung cancer (NSCLC) that influences decisions about the appropriateness and timing of surgery, radiation, and systemic therapy. Since the lung cancer staging system was first developed in 1973,[1] lymph node involvement has been categorized as N0 (no nodes involved), N1 (peribronchial, interlobar, or perihilar lymph nodes involved), N2 (ipsilateral mediastinal nodes involved), or N3 (contralateral mediastinal or supraclavicular nodes involved). The classification of these N descriptors into the overall tumor stages of I through III has been used to predict outcomes and to assist in treatment selection. During the past 20 years, numerous studies have evaluated the validity of the N descriptors and have suggested that these could be refined to provide more accurate prognostic stratification by subdividing them either according to specific anatomical locations (e.g., N1 peribronchial versus N1 perihilar) or the number of involved lymph nodes (e.g., single versus multiple N2 nodes).[2–27] This study was undertaken as part of the effort by the staging committee of the International Association for the Study of Lung Cancer (IASLC) to determine whether the current international lung cancer staging system required revision in preparation for the seventh edition of the Union Internationale Contre le Cancer (UICC) and American Joint Commission on Cancer (AJCC) cancer staging manuals. We sought to define whether the current N descriptors for NSCLC should be maintained or revised.

METHODS

Data Acquisition and Analysis

The process for the development of the IASLC lung database has been described previously.[28] Briefly, the database was developed through an international consortium of institutions and clinical trials groups that submitted staging

and outcomes data on a total of 100,869 lung cancer cases managed within the time frame of 1990 to 2000. Data were collected retrospectively from 47 preexisting databases, which varied widely in terms of the levels of detail provided. Data management and statistical analyses were provided by coinvestigators at Cancer Research and Biostatistics in Seattle, Washington. Of the 81,015 lung cancer patients and the 67,725 NSCLC patients who met the initial screening requirements of a complete set of tumor, node, metastasis (TNM) by either clinical or pathological staging, known histological type, and survival follow-up, 38,265 patients with no clinical evidence of metastatic disease (cM0) had information on clinical N staging (cN), and 28,371 surgically managed patients provided information on pathologic N staging (pN). Clinical staging included all tests and imaging studies done for initial extent-of-disease evaluation and information obtained from mediastinoscopy, but not from thoracotomy. Positron emission tomography (PET) was not in widespread use internationally during the time frame of this study, so PET data for clinical staging were not available. Pathological staging included all of the information available from clinical staging plus the pathological information from specimens obtained at thoracotomy. Twelve of the 47 databases submitted to the project included data on sampling results (positive, negative, not done) for individual nodal stations. Further analyses of overall survival in relation to subsets of pN1 and pN2 stages were performed for 2876 patients who underwent R0 (microscopically complete) resection without induction therapy and who successfully met logic checks of pN stage for data accuracy (pN stage in relation to highest positive nodal station recorded). Of these, 1721 cases (60%) were submitted from Japan, 701 cases (24%) came from Europe, 380 (13.2%) were from North America, and 74 (2.6%) were from Australia or Taiwan. The minimum lymph node stations for which documentation was available from all contributing groups included nodal level 2 and levels 4 through 9. All but one group provided documentation for levels 11 and 12, and most groups provided documentation for supraclavicular lymph nodes and nodes at levels 1, 13, and 14. Documentation of level 3 nodes was available from half of the contributing groups.

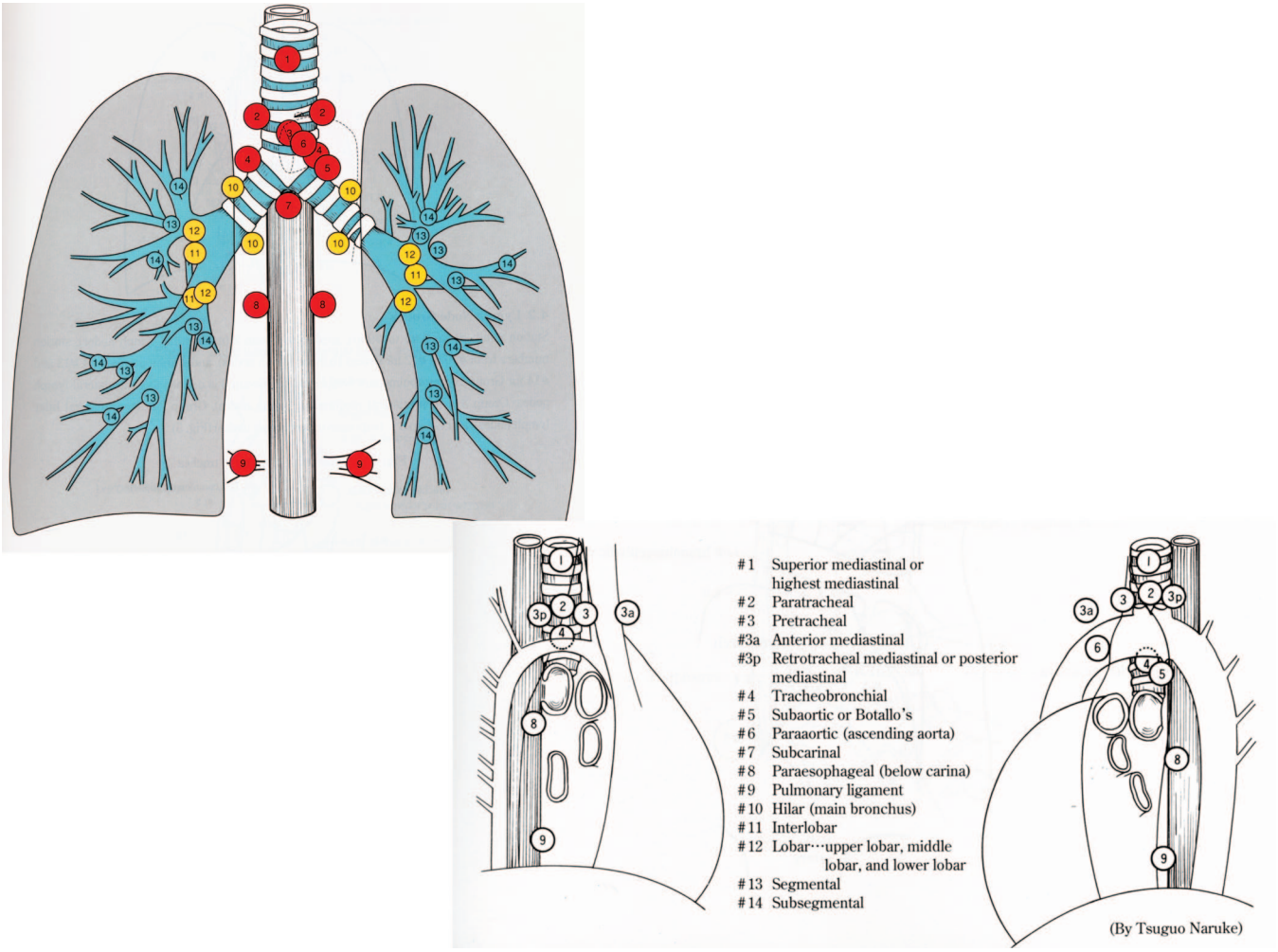


FIGURE 1. Naruke lymph node map. From: The Japan Lung Cancer Society. Classification of Lung Cancer, 1st English Ed. Tokyo: Kanehara & Co., 2000.[29] Used with permission.

Surgical cases from Japan were staged according to the Naruke lymph node map, adopted by the Japan Lung Cancer Society as the official staging map (Figure 1).[29] Those from all other countries were staged according to the Mountain-Dresler modification of the American Thoracic Society (MD-ATS) map (Figure 2).[30–32] From the perspective of grouping lymph node stations into N1 versus N2 categories, the main discrepancy between these two lymph node maps is that the Naruke map considers lymph nodes in the subcarinal space along the inferior border of the mainstem bronchus to be station 10 (hence, N1), whereas these are labeled as level 7 (and, therefore, N2) in the MD-ATS map. Within the context of a retrospective analysis, there was no way to reconcile this inherent difference in the designation of subcarinal lymph nodes. A lesser discrepancy between these two maps occurs in the labeling of lymph nodes from the right paratracheal region. Lymph nodes located between the right main pulmonary artery and the origin of the innominate artery are labeled as right level 4 (R4) in the MD-ATS map, whereas in the Naruke map the upper half of this region is considered level 2 (R2), and only the nodes located between the right main pulmonary artery and the superior border of the azygos vein are considered 4R. Nevertheless, all of these lymph nodes would be considered N2 according to either mapping system. This difference in nomenclature introduces an irreconcilable but likely small discrepancy in data analysis (Table 1).

Statistical Methodology

Survival was measured from the date of entry (date of diagnosis for registries, date of registration for protocols) for clinically staged data and from the date of surgery for pathologically staged data; it was calculated by the Kaplan-Meier method. Prognostic groups were assessed by Cox regression analysis, using the SAS System for Windows version 9.0 PHREG procedure.

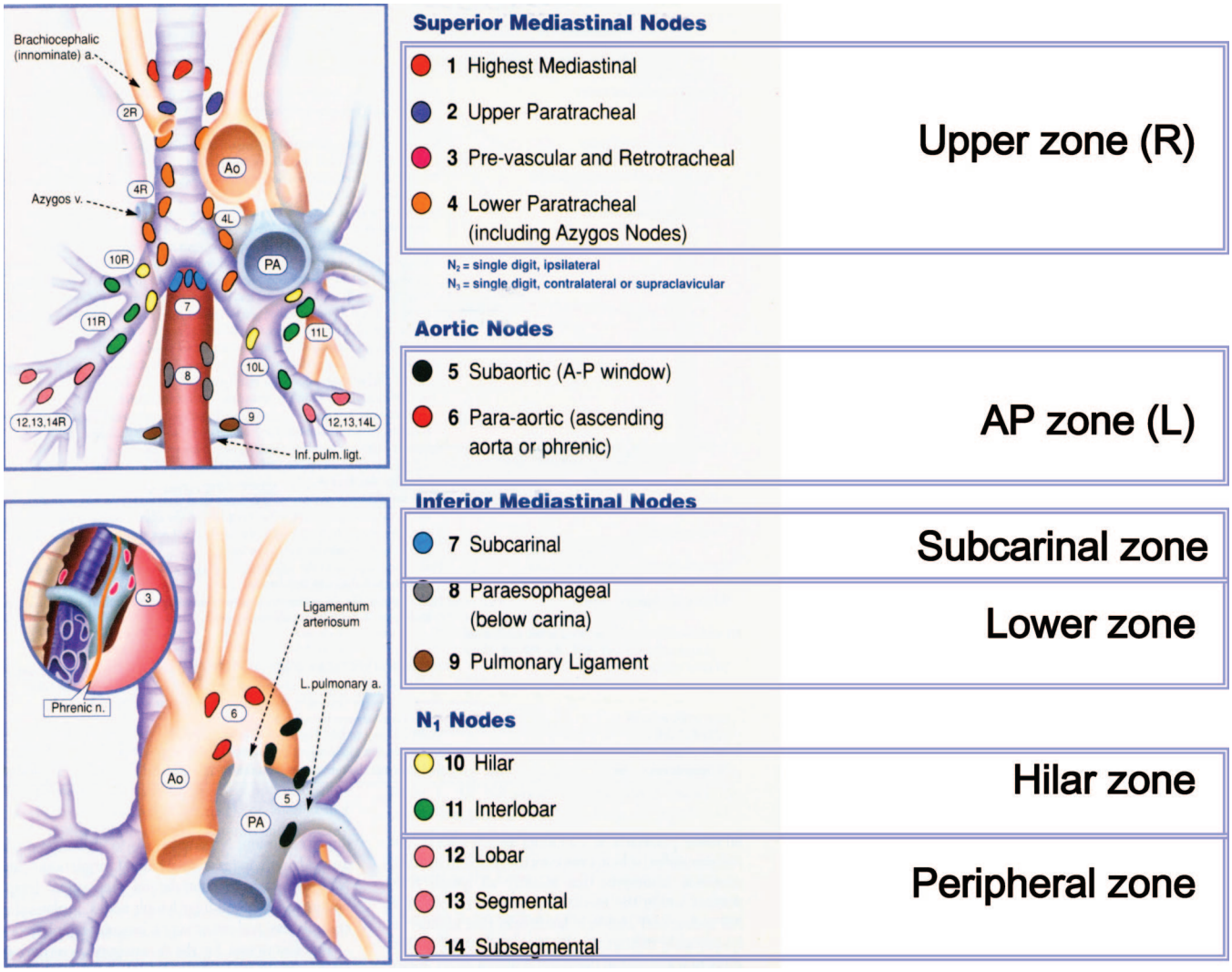


FIGURE 2. Mountain-Dresler lymph node map. The lymph node "zones" used for analyses in this study are shown superimposed on the MD-ATS map. From: Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;111:1718–1723.[30] Used with permission.

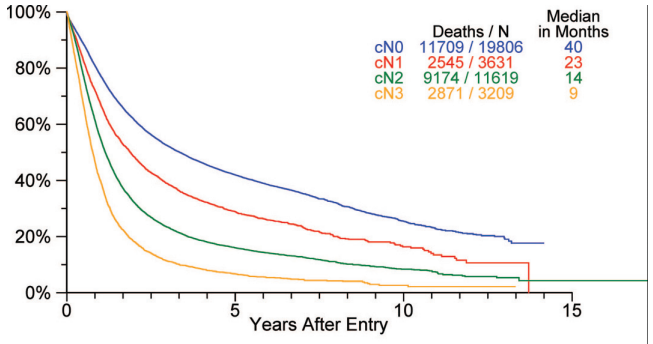
TABLE 1. Comparison of Nomenclature of Lymph Node Stations in the Japanese (Naruke) vs. Mountain-Dresler Modification of American Thoracic Society (ATS) Maps

Japanese	Mountain-Dresler (ATS)
Level 1	Levels 1 and 2
Levels 2, 3, 4R, 4L	Levels 4R and 4L
Levels 7 and 10 (subcarinal)	Level 7

RESULTS

Overall Survival According to Clinical N Staging

The overall survival by cN staging for all 38,265 cM0 (any T stage) patients is shown in Figure 3. These survival curves show clear differences in outcome for each of the cN categories. Additional analyses indicate that these differences in outcome occurred predominantly among the clinically staged patients who underwent surgical treatment. For the clinically staged cM0 patients who were managed nonsurgically (n = 15,451), the median and 5-year survival rates ranged, respectively, from 13 months and 9% for N0 to 9 months and 5% for N3 disease (data not shown). Whether the absence of survival differences for patients managed nonsurgically reflects the lack of efficacy of available treatment, the influence of medical comorbidities, or both, cannot be determined from this database.



	1 Yr	5 Yrs		HR	P
cN0	77%	42%			
cN1	67%	29%	vs cN0:	1.44	<.0001
cN2	55%	16%	vs cN1:	1.49	<.0001
cN3	40%	7%	vs cN2:	1.54	<.0001

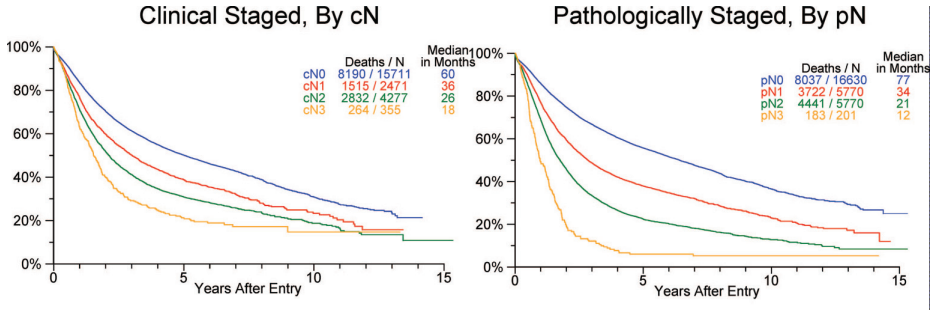
FIGURE 3. Survival by cN for all cM0 patients.

Overall Survival According to Pathological N Staging

The overall survival by pN staging for the 28,371 cM0 (any T stage) patients who were managed surgically (and who had no evidence of intrathoracic M1 disease at thoracotomy) is shown in Figure 4. These survival curves again show significant differences in outcome for each of the pN categories. Figure 4 also shows the survival rates for surgically managed patients for whom cN staging information was available (n = 22,814), again indicating distinct differences in outcome for each N category. Comparison of the survival rates by cN and pN indicates that the additional information provided from pathological staging defines a group of N0 stage tumors with better survival and a group of N3 stage tumors with worse survival than expected from clinical staging alone.

Relationships between the Site of the Primary Tumor and the Presence of Lymph Node Metastases

Information on the site of the primary tumor in relationship to the presence of lymph node metastases (pN) was available from 2538 N1 and N2 cases. There were slightly more upper-lobe (n = 1385; 56%) than lower-lobe tumors. The upper-lobe tumors were associated with the highest frequency of N1 (n = 551; 53%) and N2 (59%) nodal metastases. The right middle lobe was the least common primary tumor site. Among the primary tumors that had only a single involved N2 lymph node station, the most common site of lymph node metastases was level 4R for right upper-lobe tumors (191/280; 68%), levels 5/6 for left upper-lobe tumors (195/251; 78%), and level 7 for middle- and lower-lobe tumors (228/353; 65%).



	1 Yr	5 Yrs		HR	P
cN0	84%	50%			
cN1	77%	39%	vs cN0:	1.37	<.0001
cN2	71%	31%	vs cN1:	1.24	<.0001
cN3	63%	21%	vs cN2:	1.31	<.0001

	1 Yr	5 Yrs		HR	P
pN0	86%	56%			
pN1	77%	38%	vs pN0:	1.63	<.0001
pN2	69%	22%	vs pN1:	1.51	<.0001
pN3	49%	6%	vs pN2:	1.81	<.0001

FIGURE 4. Survival by cN for surgically managed patients.

TABLE 2. Comparison of Survival According to Involvement of Specific Peripheral Lymph Node Stations (2a), Single Lymph Node Zones (2b), and Presence of Skip Metastases (2c)

2a: Specific Peripheral Lymph Node Stations

Lymph Node Station	n	Median Survival (mo)		*p*
12 (or higher) vs. 11, 10				
12+ only	361	51		
12+ 11+ 10−	84	48	12+ 11+ 10− vs 12+ only	0.5876
12+ 11− 10+	46	36	12+ 11− 10+ vs 12+ only	0.0592
12+ 11+ 10+	31	28	12+ 11+ 10+ vs 12+ only	0.0974
			12+ 11+ 10− vs 12+ 11− 10+	0.2340

2b: Single Lymph Node Zones

Lymph Node Station	n	Median Survival (mo)		*p*
Single zone: right				
P only	324	56		
H only	45	63	H only vs P only	0.8548
LM only	8	34	LM only vs P only	0.2303
S only	151	37	S only vs P only	0.0535
			S only vs LM only	0.7775
U only	151	37	U only vs P only	0.0069
			U only vs LM only	0.7131
			U only vs S only	0.8869
Single zone: left				
P only	262	52	P only	
H only	51	40	H only vs P only	0.8156
LM only	9	39	LM only vs P only	0.1422
S only	17	43	S only vs P only	0.2039
			S only vs LM only	0.6688
AP only	64	44	AP only vs P only	0.3923
			AP only vs LM only	0.3189
			AP only vs S only	0.5149

2c: Presence of Skip Metastases

Lymph Node Station	n	Median Survival (mo)		*p*
RUL upper zone+, figure				
U+ P− H−	142	37		
U+ P+ H−	97	44	U+ P+ H− vs U+ P− H−	0.5373
U+ P− H+	23	40	U+ P− H+ vs U+ P− H−	0.8266
U+ P+ H+	55	28	U+ P+ H+ vs U+ P− H−	0.1878
LUL AP zone+, figure				
AP+ P− H−	86	44		
AP+ P+ H−	45	32	AP+ P+ H− vs AP+ P− H−	0.3878
AP+ P− H+	13	27	AP+ P− H+ vs AP+ P− H−	0.6433
AP+ P+ H+	38	24	AP+ P+ H+ vs AP+ P− H−	0.0427

U, upper mediastinal (levels 1–4); AP, aortopulmonary (levels 5 and 6); S, subcarinal (level 7); LM, lower mediastinal (levels 8 and 9); H, hilar (levels 10 and 11); P, peripheral (levels 12–14); RUL, right upper lobe; LUL, left upper lobe.

Survival in Relationship to the Extent of N1 and N2 Disease in Cases with pN Staging

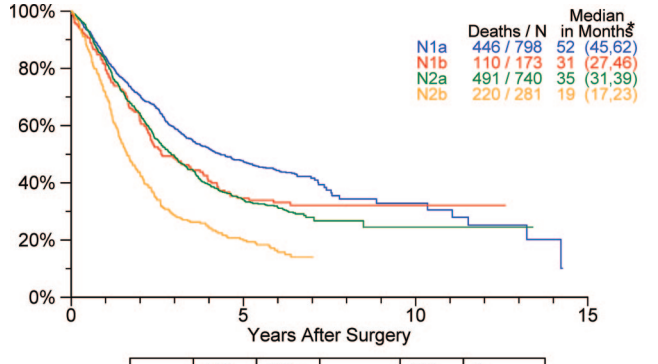
Exploratory analyses were performed to determine whether, in patients with pN staging, survival was influenced by the anatomical location of involved lymph nodes, by the presence of "skip metastases" (N2 disease in the absence of N1), or by the number of involved lymph node stations. The 522 N1 cases with involvement of peribronchial levels 12 to 14 were evaluated to determine whether survival was influenced by involvement of the peribronchial (levels 12–14)

versus the interlobar (level 11) or hilar (level 10) lymph nodes, or by combinations of these. No significant differences in survival could be identified (Table 2a), apart from the general finding that survivorship decreased as the number of positive stations increased.

To reconcile the Naruke and MD-ATS lymph node maps and to permit analyses of cases with N1 and, especially, N2 disease to include larger numbers of patients, lymph node stations were grouped together into anatomical "zones." Lymph nodes at levels 1 through 4 were grouped together into the *upper zone*, levels 5 and 6 into the *aortopulmonary (AP) zone*, level 7 into the *subcarinal zone*, levels 8 and 9 into the *lower zone*, levels 10 and 11 into the *hilar zone*, and levels 12 to 14 into the *peripheral zone* (Figure 2). The appropriateness of grouping lymph node stations into zones was suggested by exploratory analyses that failed to identify significant differences in survival in relation to disease in all of the various N1 and N2 lymph node stations in the data submitted from Japan, from non-Japanese groups, or both (data not shown). As shown in Table 2b, significant differences in survival for patients with lymph node metastases confined to a single zone were seen only for cases of right-sided tumors with upper- or subcarinal zone disease compared with peripheral zone metastases. No differences in survival were identified among patients who had single-zone N2 disease.

Potential differences in survival were analyzed for cases with skip metastases, focusing on upper-lobe tumors, which are thought to be most frequently associated with these. AP zone disease in the absence of N1 metastases was associated with a better survival rate in patients with left upper-lobe tumors, but similar differences in survival were not identified for right upper-lobe tumors with right paratracheal nodal metastases (Table 2c).

The potential impact of the number of involved lymph node zones on survival was then examined. As can be seen in Figure 5, three groups were found to have significantly different survival rates: patients who had N1 single-zone disease, those who had either multiple N1 or single N2 zone metastases, and those who had multiple N2 lymph node zones involved. These prognostically distinct groups suggested that it might be appropriate to subdivide the current N staging descriptors into N1a (single N1 zone), N1b (multiple N1 zones), N2a (single N2 zone), and N2b (multiple N2 zones). To determine whether such a revision to the staging system should be considered, these additional N categories were analyzed in conjunction with each T stage category (e.g., T1N1a, T1N1b, T1N2a, T1N2b, etc.) rather than across all T stages, as was done for all of the preceding analyses. Nevertheless, the number of patients available in each of these subsets was too small to yield statistically valid analyses. Therefore, on the basis of the available data, we cannot recommend altering the current N stage descriptors.



	1 Yr	5 Yrs		HR	P
N1a	86%	48%			
N1b	79%	35%	vs N1a:	1.32	<.0090
N2a	83%	34%	vs N1b:	1.04	0.7137
N2b	71%	20%	vs N2a:	1.65	<.0001

*estimates of median survival, followed by 95% confidence intervals in parentheses

FIGURE 5. Survival by N status and number of involved N zones.

DISCUSSION

Accurate staging of lymph node involvement has long been recognized as a key aspect of the initial management of NSCLC that helps in selecting treatment and predicting outcome. In patients undergoing surgery for possible resection of NSCLC, careful assessment of potential nodal disease has gradually become an accepted part of the operation since Cahan first described radical mediastinal lymph node dissection in the early 1950s.[1,33] For similar reasons, mediastinoscopy and imaging studies such as CT (computed tomography) and PET scanning have become standard components of the initial clinical staging of NSCLC.[31] The development of the Naruke and, subsequently, of the ATS lymph node maps, provided standard nomenclature used by all clinicians and pathologists involved in the care of NSCLC patients to assist in uniform N staging. Traditionally, these maps labeled N2 or N3 nodes with single-digit numbers (nodal stations 1–9) and N1 nodes with double-digit numbers (nodal stations 10–14). From the inception of the AJCC and UICC lung cancer staging systems in 1973, the N0, N1, N2, and N3 descriptors were used to help establish stage classifications for both clinical and pathological staging. The fifth edition of the lung cancer staging system, based on a database developed by Dr. Clifton Mountain of 5319 cases (4351 patients treated at the MD Anderson Cancer Center, and 968 from other North American centers), led to a revision of the stage classifications but maintained the existing distinctions among the N descriptors.[34] In the absence of compelling alternative data, no changes were made to the sixth edition of the AJCC and UICC staging system. The current IASLC database includes a much larger number of cases from databases around the world on which to test the validity of the current staging system. Our data show that the N0, N1, N2, and N3 descriptors, whether derived from clinical or pathological staging, clearly identify prognostically distinct groups of patients, and it is therefore appropriate to maintain these descriptors in the upcoming seventh version of the lung cancer staging system. Notably, the IASLC database is the first international database that has shown these descriptors to have internal and external validity.

TABLE 3. Results of Series Reporting the Outcome of Patients Who Underwent Resection for Non-small Cell Lung Cancer with N1 Disease

		5-Year Survival (%)			
Authors (Year)	**No. of Patients**	**Overall**	**(+) Hilar**	**(+) Interlobar**	**(+) Peripheral**
Ferguson et al.[2] (1986)	34	30.2	NS	NS	NS
Maggi et al.[3] (1990)	157	46.1	NS	NS	NS
Martini et al.[4] (1992)	214	39	NS	NS	NS
Yano et al.[5] (1994)	78	49.2	39.7*		64.5
van Velzen et al.[6] (1996)	57	45.7	23.3*		55.6
van Velzen et al.[7] (1997)	369	37.8	30.3*		57.3
van Velzen et al.[8] (1999)	111	27.2	NS	NS	NS
Sawyer et al.[9] (1999)	107	32	NS	NS	NS
Riquet et al.[10] (1999)	256	47.5	38.5*		52.6
Yoshino et al.[11] (1999)	43	50.2	47.4*		55
Asamura et al.[12] (2000)	180	67	54	70†	
Marra et al.[13] (2003)	535	40	30	39	41

NS, not shown.
*Hilar and interlobar were analyzed as a single group.
†Interlobar and peripheral were analyzed as a single group.

During the past 25 years, numerous studies have examined the patterns of lymphatic drainage of the lung and have analyzed the influence of N1 and N2 lymph node involvement on overall survival. These series are retrospective, are based on pathological staging, and include relatively small numbers of patients.[2–27] Among patients undergoing surgery for NSCLC, our data corroborate the findings of other studies, including a higher frequency of upper-lobe tumors and a predominance of lymphatic drainage to the superior mediastinum for right upper-lobe tumors, to the AP region for left upper-lobe tumors, and to the subcarinal area for middle- and lower-lobe tumors.[18,20,24–26,35] Previous studies suggest that survival is significantly worse in patients who have hilar or interlobar rather than only peribronchial lymph node involvement or that multiple levels of N1 nodal disease are associated with a worse outcome than single-level disease (Table 3). We were unable to identify differences in outcome for patients with peripheral versus hilar N1 disease, but we found that survival was significantly worse in cases of multiple versus single levels of N1 nodal metastases.

Differences in nomenclature between the Naruke and the MD-ATS lymph node maps pose challenges for the

TABLE 4. Results of a Series Reporting the Outcome of Patients Who Underwent Resection for Non-small Cell Lung Cancer with N2 Disease

		5-Year Survival (%)			
Author (Year)	**No. of Patients**	**Overall**	**Single Level**	**Multi Level**	***p***
Naruke et al.[14] (1978)	77	18.8	NR	NR	NR
Martini et al.[15] (1983)	151	29	25	33	NR
Miller et al.[16] (1994)	147	23.7	30	0–30, depending on number of stations	0.02
Goldstraw et al.[17] (1994)	149	20.1	30 (3 yr)	25 (3 yr)	0.05
Riquet et al. (1995)[18]	237	18.8	26.3	8.3	0.0003
Vansteenkiste et al.[35] (1997)	140	20.8	19.5	22	0.20
Okada et al.[19] (1999)	141	26	39	11	0.0001
Asamura et al.[20] (1999)	166	35	48	18	0.006
Sagawa et al.[21] (1999)	178	28	41	13	0.001
Andre et al.[22] (2000)	702	18	25	7	<0.0001
Naruke et al.[23] (2001)	736	19.9	NR	NR	NR
Ichinose et al.[24] (2001)	402	31	43	17	<0.0001
Ueda et al.[25] (2003)	96	30	35	19	0.019
Inoue et al.[26] (2004)	154	28.1	42.7	15.5	0.0001
Keller et al.[27] (2004)	172	NR	32	NR	NR

NR, not reported.

analysis of an international database. Reconciliation of these maps is the subject of a separate study (which is being undertaken by the IASLC staging committee) and is, therefore, not discussed in detail here. Nevertheless, our exploratory analyses suggested that for the purposes of analyzing N stages, it was statistically appropriate to consolidate several lymph node stations from both mapping systems together into zones. This approach allowed us to address the findings of previous studies that skip metastases and single-level N2 disease are both associated with better survival rates than involvement of multiple N2 lymph node stations (Table 4). In contrast with previous studies,[36–43] we were able to identify a better survival rate only for patients with left upper-lobe tumors with AP zone N2 disease—not for patients with right upper-lobe tumors with metastases confined to the superior mediastinum. These results should be interpreted with caution because the numbers of patients available for these subset analyses are relatively small.

The most salient finding with respect to pN staging in our database is that patients fall into three prognostically distinct categories, depending on the extent of nodal metastases: single-zone N1, multiple-zone N1 or single-zone N2, and multiple-zone N2. In conjunction with our other analyses, these results suggest that the overall disease burden, rather than just the anatomical location of lymph node involvement, may have the most important influence on outcome. These three categories have not been clearly identified in previous studies (Table 3 and 4), which have focused predominantly on comparing survival relative to varying levels of either N1 or N2 disease. Validating this finding in a way that would be statistically sound enough to warrant a change in the N descriptors for the staging system would clearly require a prospective study of even larger numbers of patients with meticulous pN staging. Nevertheless, our results provide the impetus for such a study and the rationale for stratifying patients according these three prognostic groups in clinical trials.

In summary, analyses of clinical and pathological N staging in the IASLC database support the continued use of the current N descriptors in the lung cancer database. Additional analyses suggest that consolidation of multiple lymph node stations into zones and stratification of patients into three groups according to the extent of nodal disease may be appropriate and warrant inclusion in future studies.

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APPENDIX 1

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