ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groups in the Forthcoming (Ninth) Edition of the TNM Classification for Lung Cancer

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ABSTRACT

Introduction: The TNM classification of lung cancer is periodically revised. The International Association for the Study of Lung Cancer collected and analyzed a new database to inform the forthcoming ninth edition of the TNM classification. The results are herewith presented.

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Methods: After exclusions, 76,518 patients from a total of 124,581 registered patients were available for analyses: 58,193 with clinical stage, 39,192 with pathologic stage, and 62,611 with best stage NSCLC. The proposed new N2 subcategories (N2a, involvement of single ipsilateral mediastinal or subcarinal nodal station, and N2b, involvement of multiple ipsilateral mediastinal nodal stations with or without involvement of the subcarinal nodal station) and the new M1c subcategories (M1c1, multiple extrathoracic metastases in one organ system, and M1c2, multiple extrathoracic metastases in multiple organ systems) were considered in the survival analyses. Several potential stage groupings were evaluated, using multiple analyses, including recursive partitioning, assessment of homogeneity within and discrimination between potential groups, clinical and statistical significance of survival differences, multivariable regression, and broad assessment of generalizability.

Results: T1N1, T1N2a, and T3N2a subgroups are assigned to IIA, IIB, and IIIA stage groups, respectively. T2aN2b and T2bN2b subgroups are assigned to IIIB. M1c1 and M1c2 remain in stage group IVB. Analyses reveal consistent ordering, discrimination of prognosis, and broad generalizability of the proposed ninth edition stage classification of lung cancer.

Conclusions: The proposed stages for the ninth edition TNM improve the granularity of nomenclature about anatomic extent that has benefits as treatment approaches become increasingly differentiated and complex.

Keywords: Lung cancer prognosis; Lung cancer stages; Lung cancer stage classification; Prognostic factors; TNM classification

Introduction

Lung cancer stages, that is, coalescing the categories of the anatomic extent of the primary tumor (T), lymph node involvement (N), and number and location of metastases (M) into a practical system of groups, were introduced in the second edition of the TNM classification published by the Union for International Cancer Control (UICC) in 1975 and in the first edition of the staging manual of the American Joint Committee on Cancer (AJCC) published two years after.[1] The revisions in this second UICC edition were based on the analyses of a North American database with 2155 patients. In their seminal article of 1974, Mountain et al.[2] reported graphs with distinct survivals for the three T categories (T1, T2, and T3), the three N categories (N0, N1, and N2), the two M categories (M0 and M1), and for stages I, II, and III, the latter including tumors invading beyond the lung (T3), mediastinal nodal disease (N2), and distant metastatic spread (M1). The survival curves of the different T, N, and M categories and of the three stages were so clearly different that no statistical comparisons were made and no *p* values revealed. Although this classification and stage grouping were meant for clinical stage only, the authors posited that more precise evaluations of the extent of disease could be provided by an exploratory thoracotomy (surgical evaluative classification) and by the examination of the resected specimen (postsurgical treatment classification). The former, including invasive procedures, such as mediastinoscopy, thoracoscopy, and even exploratory thoracotomy, is now part of clinical classification, and the latter is called pathologic classification.

Stage IV, exclusively including distant metastatic disease, was introduced in the TNM classification of lung cancer in the third edition of the UICC manual in 1978. Nine years after, the fourth edition of the UICC manual included innovations based on another article by Mountain[3] analyzing a larger database of 3753 patients with lung cancer. Stage III was subdivided into stage IIIA, for T3 and N2 tumors, and stage IIIB, for those classified as T4 and N3, a new nodal category introduced in this edition of the classification. The final changes in stages based on the North American database appeared in the fifth edition of the UICC manual and emanated, once more, from further analyses of an even larger database of 5319 patients reported by Mountain[4] in 1997. In this edition, stage I was split into IA for T1N0M0 tumors and IB for T2N0M0 tumors and stages II into IIA for T1N1M0 tumors and IIB for T2N1M0 and T3N0M0 tumors. There were no changes to the sixth edition.

In agreement with the UICC and the AJCC, the International Association for the Study of Lung Cancer (IASLC) took over the responsibility of revising future editions of the TNM classifications of thoracic malignancies, namely, lung cancer, pleural mesothelioma, and thymic epithelial tumors.[5,6] Further revisions to the lung cancer classification system were based on international databases compiled by the IASLC. In the seventh edition, although some tumors were recategorized upward or downward, there were no changes in the structure of the stage groups.[7] For the eighth, the granularity and the quality of the data registered in the IASLC database allowed the subclassification of stage IA into IA1, IA2, and IA3 to accommodate the newly defined T1a, T1b, and T1c subcategories; the creation of stage IIIC for T3N3M0 and T4N3M0 tumors; and the subdivision of stage IV into IVA for intrathoracic and single extrathoracic metastases and IVB for multiple extrathoracic metastases.[8]

This article reports the analyses performed to inform revisions of the stage groups for the forthcoming ninth edition of the TNM classification of lung cancer. These

analyses, led by the Stage Group Subcommittee of the IASLC Staging and Prognostic Factors Committee (SPFC), are based on a new database of prospective and retrospective data especially collected to update the ninth edition TNM categories and descriptors.[9]

Materials and Methods

Population

Data on 124,581 patients with histologically proven lung cancer were submitted to the IASLC database from 78 unique sites across 25 countries. Each participating institution was required to obtain institutional review board approval and sign a data use agreement to share a limited or deidentified data set as defined by the U.S. Health Insurance Portability and Accountability Act Privacy Rule. This structure meets the standards in most countries that allow individual patient consent to be waived. A total of 23,548 patients (19%) were entered in an electronic data capture (EDC) system housed by Cancer Research And Biostatistics (CRAB), and 101,033 (81%) were submitted as retrospective "batch" data sets that were manually mapped and harmonized to the EDC data fields (Supplementary Fig. 1). A detailed overview of the IASLC ninth edition database was previously published.[9]

Inclusion and Exclusion Criteria

For the analysis of TNM stage groups, only patients with a histologic diagnosis of NSCLC, excluding squamous cell carcinoma in situ, were included. Patients were also required to have valid survival time, date of diagnosis between January 1, 2011, and December 31, 2019, with follow-up truncated as of December 2021, and sufficient T, N, and M data to assign the stage group according to the AJCC/UICC eighth edition system, excluding stage 0 and occult disease (Supplementary Fig. 2). An exception was made for one large registry data set where all patients were diagnosed in 2010, outside of the prespecified time window, and one site was excluded from the final analysis due to concerns about aberrant patterns of correlation between clinical and pathologic N-category information. The patients who passed the inclusion criteria for the clinical, pathologic, and best stage analyses are described in Table 1.

Patients included in the clinical (c) stage analysis (n = 58,193) were required to have clinical T, N, and M categories and descriptors that allowed assignment of an eighth or proposed ninth edition TNM stage classification. Overall survival (OS) was assessed from the date of diagnosis to death. Patients included in the pathologic (p) stage analysis (n = 39,192) were required to have pathologic T, N, and M categories and descriptors that allowed assignment of an eighth or proposed ninth edition TNM stage classification, with OS assessed from the date of surgery to death. In addition, all patients included in the pathologic analysis had nonmetastatic tumors (M0), were managed surgically, and did not receive neoadjuvant treatment. Patients receiving neoadjuvant treatment were included in the pretreatment clinical stage analysis and analyzed in a separate pathologic stage analysis (yp). Best (b) stage (n = 62,611) was defined as pathologic stage or clinical stage if pathologic stage was unavailable, the patient received neoadjuvant treatment, or the patient had metastatic tumor by clinical assessment. OS was the primary end point for all analyses.

Patients included in the assessment of the eighth edition stage groups were not required to have complete T, N, and M descriptors recorded provided the stage groups could be reliably assigned but were excluded if any reported descriptors indicated a higher eighth edition T, N, or M category than was reported, suggesting a possible data entry error. Patients included in the assessment of the ninth edition stage proposals were required to have sufficiently detailed tumor descriptors to assign them to the newly proposed N and M categories.

When primary tumor size was the determinant of the T category and the stage group, the eighth edition definitions were used whenever available—that is, solid by imaging for clinical and invasive for pathologic tumor size. Nevertheless, for approximately half of the cases, a T (and N and M) category was available without details of how size was measured. This reflects the fact that the eighth edition recommendations for size measurement were not published until partway through the data inclusion period. These cases were combined; in general, separate analyses based on the type of size measurement used were deemed inappropriate due to confounding by time period. Nevertheless, a secondary analysis was conducted among patients with clinical and pathologic T1N0 tumors (where the type of size measurement is likely to have the most impact) using only the cases in which the solid (imaging) or invasive (pathologic) size variable was provided, to verify separation of the IA1, IA2, and IA3 and IB stage categories. Nevertheless, it is possible that in a few of these cases, the provided size might have erroneously represented total rather than solid or invasive size, due to the time it takes for awareness to disseminate and local data collection systems to adapt. Patients with tumors classified as T1mi or higher before resection but which were determined to be adenocarcinoma in situ on resection were included in the clinical stage analysis but excluded from the pathologic stage analysis.

Statistical Analysis

Candidate proposals for the TNM stage groups were developed accounting for the proposed changes to the N

Table 1. Characteristics of All Assessable Patients

	Clinical Stage		Pathologic Stage		Best Stage	
Specific Item	n	(%)	n	(%)	n	(%)
Grand total	58,108	(100)	39,135	(100)	62,542	(100)
Region						
Asia	33,883	(58)	26,939	(69)	38,465	(62)
Europe	12,639	(22)	4321	(11)	11,443	(18)
North America	10,184	(18)	6457	(16)	10,493	(17)
Rest of world	1402	(2)	1418	(4)	2141	(3)
GDP						
Low	14,361	(25)	9827	(25)	13,811	(22)
Mid	23,655	(41)	19,505	(50)	28,665	(46)
High	20,092	(35)	9803	(25)	20,066	(32)
Sex						
Male	29,923	(51)	18,921	(48)	32,369	(52)
Female	28,182	(48)	20,212	(52)	30,170	(48)
No data	3	(0)	2	(0)	3	(0)
Age						
Less than 65 y	25,055	(43)	17,212	(44)	26,981	(43)
65 y or older	32,973	(57)	21,863	(56)	35,485	(57)
No data	80	(0)	60	(0)	76	(0)
NSCLC histology						
AIS	685	(1)	0	0	137	(0)
Adenocarcinoma	41,832	(72)	29,202	(75)	45,395	(73)
Adenosquamous	853	(1)	717	(2)	939	(2)
Large cell	789	(1)	536	(1)	880	(1)
NSCLC NOS	1549	(3)	128	(0)	1351	(2)
Squamous	12,400	(21)	8552	(22)	13,840	(22)
Resection						
Nonsurgical	17,007	(29)	0	(0)	16,142	(26)
Surgical R0	34,754	(60)	36,788	(94)	40,789	(65)
Surgical R1 or R2	1334	(2)	1055	(3)	1409	(2)
Surgical R unknown	3249	(6)	1292	(3)	2624	(4)
Surgical status unknown	1764	(3)	0	(0)	1578	(3)

AIS, adenocarcinoma in situ; GDP, gross domestic product; NSCLC NOS, non-small cell lung cancer not otherwise specified.

and M categories by the N and M Subcommittees.[10,11] No changes were proposed for the T category definitions.[12] A summary of ninth edition T, N, and M categories and descriptors is found in Table 2. Discrimination between the TNM categories aimed to separate patients into distinct subsets with similar within-group survival but different between-group survival. Several candidate proposals were evaluated using the training data set (two-thirds of the data, balanced by year of diagnosis, and data source: EDC or batch data sets). Proposals were evaluated considering the totality of evidence in accordance with the IASLC-SPFC's methodologic principles,[13] including the strength and consistency of statistical evidence, clinical relevance, and practical considerations such as backward compatibility and application in real-world settings.

The final proposal was evaluated with multiple approaches. One method involved recursive partitioning and amalgamation-generated survival trees[14] using the M0 best stage data set, stratified by the data source. The algorithm generates a tree-based model using the R packages RPART[15] and RSPLIT[16] to maximize differences in survival between subsets created by an ordered variable for the current T-categories and newly proposed N-categories. Log-rank test statistics for the recursive partitioning and bootstrap resampling to correct for the adaptive nature of the splitting algorithm produces terminal nodes containing patients with similar survival outcomes.

Another method involved graphically evaluating OS curves generated using the Kaplan-Meier method[17] for clinical, pathologic, and best stage, with log-rank tests[18] for pairwise comparisons intended to reveal the presence or absence of expected survival differences among newly assigned TNM subsets. This included analyses assessing homogeneity within proposed subgroups and discrimination between proposed subgroups.

Furthermore, Cox proportional hazards regression models[19] stratified by data source were created for both clinical and pathologic stage with adjustment for

Table 2. Proposed T, N, and M Categories and Descriptors for the Ninth Edition of the TNM Classification for Lung Cancer

T: Primary tumor	
Tx	Primary tumor cannot be assessed[a]
T0	No evidence of primary tumor
Tis	Carcinoma in situ[b]
T1	Tumor surrounded by lung or visceral pleura or in a lobar or more peripheral bronchus[c]
T1mi	Minimally invasive adenocarcinoma[d]
T1a	Tumor ≤1 cm in greatest dimension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor with any of the following features:
T2a	Tumor >3 cm but ≤4 cm in greatest dimension invades visceral pleura invades an adjacent lobe involves main bronchus (up to but not including the carina) or is associated with atelectasis or obstructive pneumonitis, extending to the hilar region, involving either part of or the entire lung
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor with any of the following features: tumor >5 cm but ≤7 cm in greatest dimension invades parietal pleura or chest wall invades pericardium, phrenic nerve, or azygos vein[e] invades thoracic nerve roots (i.e., T1, T2) or stellate ganglion separate tumor nodule(s) in the same lobe as the primary
T4	Tumor with any of the following features: tumor >7 cm in greatest dimension invades mediastinum, thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus, or diaphragm invades heart, great vessels (aorta, superior or inferior vena cava, intrapericardial pulmonary arteries or veins), supra-aortic arteries, or brachiocephalic veins invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus (i.e., trunks, divisions, cords, or terminal nerves) separate tumor nodule(s) in a different ipsilateral lobe than that of the primary
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial or ipsilateral hilar or intrapulmonary lymph nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal or subcarinal lymph node(s)
N2a	Metastasis(es) in a single ipsilateral mediastinal or in the subcarinal nodal station
N2b	Metastases in multiple ipsilateral mediastinal nodal stations with or without involvement of the subcarinal nodal station
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Tumor with pleural or pericardial nodules or malignant pleural or pericardial effusions,[f] separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis in a single organ system[g]
M1c	Multiple extrathoracic metastases in a single or multiple organ system(s)
M1c1	Multiple extrathoracic metastases in a single organ system[h]
M1c2	Multiple extrathoracic metastasis in multiple organ systems

Note: Changes to the eighth edition are in bold.

[a]This includes tumors proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

[b]This includes adenocarcinoma in situ—Tis (AIS)—and squamous cell carcinoma in situ—Tis (SCIS).

[c]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

[d]Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension in any one focus.

[e]Although these structures lie within the mediastinum, the degree of mediastinal penetration by the tumor needed to invade these structures is not counted as T4.

[f]Most pleural (or pericardial) effusions in patients with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (or pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

[g]This includes involvement of a single nonregional node.

[h]For example, the skeleton is considered one organ. Several metastases in a single bone or in several bones are classified as M1c1.

baseline traits including age (<65 y versus ≥65 y), sex (male versus female), histologic type (squamous versus nonsquamous), and region (Europe, North America, or the Rest of the World [ROW] versus Asia).

The R^2 value was calculated to estimate the percent of variance explained by the models,[20] where larger values indicate an improvement in the goodness of fit. The R^2 values for models using the eighth edition staging criteria versus the proposed ninth edition staging criteria were compared to confirm that the proposed criteria had performance that met or exceeded the existing status quo.

Generalizability was assessed with subgroup analyses to confirm similar ordering of TNM subsets by data source (EDC, batch), histologic type (squamous, nonsquamous), geographic region (Asia, Europe, North America, ROW), Zubrod performance status (PS) (0, ≥1), time period (≤2017, ≥2018), and treatment approach (surgical, nonsurgical, complete [R0] resection, neoadjuvant therapy). Finally, the proposed ninth edition stage classification was applied to the previous IASLC eighth edition data set for external validation (i.e., in an independent data set). All analyses were conducted using the SAS statistical software package 9.4 (SAS Institute, Cary, NC) or R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Geographic and Stage Distribution of the Data

From a total of 58,108 clinical stage tumors by eighth edition criteria, Asia contributed 33,883 (58%), Europe 12,639 (22%), North America 10,184 (18%), and ROW 1402 (2%). Tumors in clinical stage IA were the most common, with 22,676 (39%) cases, followed by clinical stages IVA, with 8341 (14.4%), and IVB, with 7899 (13.6%) cases (Supplementary Fig. 3). Asia also contributed the largest number of pathologic stage tumors (26,939; 69%), followed by North America (6457; 16%), Europe (4321; 11%), and the ROW (1418; 4%); and stage IA was again the most common (18,063; 46%, Supplementary Fig. 4). The same pattern was found in the numbers of best stage tumors, with Asia in the lead followed by Europe and North America, and with best stages IA, IVA, and IVB being the most common (Supplementary Fig. 5). Supplementary Tables 1a and b reveal the sample sizes of tumors with complete clinical and pathologic ninth edition T, N, and M categories, respectively.

Validation of the Eighth Edition Stage Groups

OS by eighth edition clinical and pathologic stage groups was tested in the population of patients in the ninth edition database. The OS by clinical and pathologic stages followed the same pattern found in the eighth edition database, with the expected worsening of survival as tumor stage increased. Survival was significantly different in all stages ($P < .0001$), except in clinical stages IIIC versus IV, where no difference was found ($P = .7926$), as was previously found in the survival analyses of the eighth edition database[8] (Supplementary Figs. 6 and 7). It had been deemed appropriate to classify IIIC and IVA as distinct groups nevertheless, because of the fundamental difference between M0 and M1.[8] This validation analysis established that the eighth edition structure remained a solid foundation to build on for potential refinements in the ninth edition classification.

Identification and Alignment of New Subgroups

The decision to subdivide the N2 category into N2a and N2b created new subgroups, namely T1N2a, T1N2b, T2aN2a, T2aN2b, T2bN2a, T2bN2b, T3N2a, T3N2b, T4N2a, and T4N2b. New subgroups are also created by the decision to subdivide M1c into M1c1 and M1c2. The question for the Stage Group Subcommittee was how to coalesce these new subgroups in a manner that reflects important differences and is clinically useful. Prognosis serves as an important tool to assess which groups align together, but application in the context of clinical care is the ultimate purpose of stage classification.

Several potential models of alignment of TNM subgroups into stage groups were considered. These were evaluated using several approaches and assessments of homogeneity within and discrimination between potential new stage group definitions. In addition, the committee considered how well potential models would align with current and evolving treatment strategies, including how disruptive potential changes to the stage classification would be. For simplicity, this paper focuses only on the analyses involving the stage group model that was ultimately deemed best.

The recursive partitioning and amalgamation survival tree analysis provides an unbiased approach to assessing which subgroups appear prognostically aligned or distinct. The result from one such analysis (in a training set of 31,087 best stage M0 tumors) is found in Figure 1; Supplementary Table 2 illustrates the terminal nodes with their respective sample sizes and hazard ratios. This approach suggests, regarding the new N2 subgroups, that T1N2a aligns with other (eighth edition) stage IIB subgroups; T2N2a, T3N2a, and T1 N2b align with other (eighth edition) stage IIIA subgroups; T4N2a, T2N2b, T3N2b, and T4N2b align with other (eighth edition) stage IIIB subgroups. In addition, the survival tree analysis suggested that T1N1 aligns more with other (eighth edition) IIA subgroups than with (eighth edition)

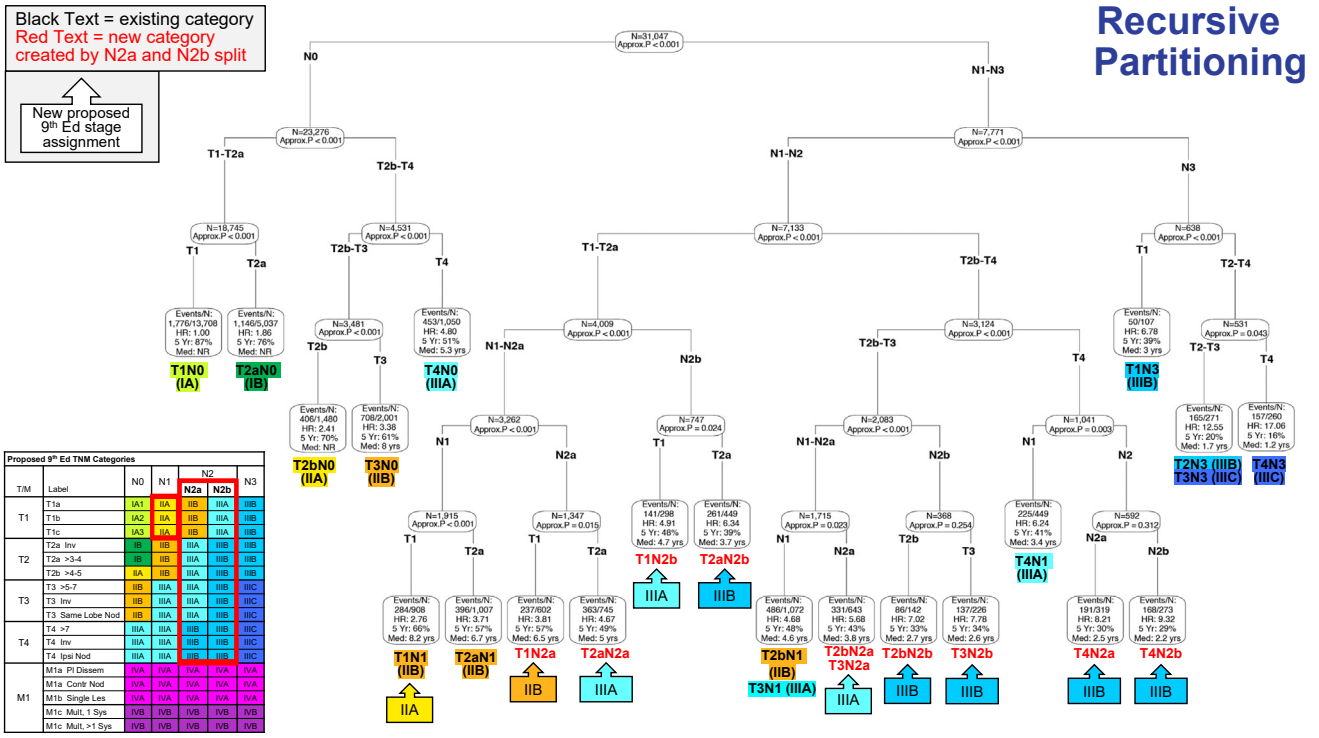


Figure 1. Recursive partitioning and amalgamation-generated survival tree based on best stage for 31,087 M0 training set cases. T and N categories are modelled as ordered variables. Stratified hazard ratios are revealed relative to the leftmost terminal node, that is, T1aN0. The analysis was stratified by data source. Approx, approximate; Contr Nod, contralateral separate tumor nodule; Inv, invasion; Ipsi Nod, ipsilateral separate tumor nodule; Med, median survival time; Mult, multiple; NR, not reached; Pleur, pleural or pericardial involvement; Sat, Satellite, that is, separate tumor nodule.

IIB. This alignment is reflected in the proposed ninth edition stage groups found in Figure 2.

This was further evaluated using survival graphs of patients with tumors involving the potential new subgroup alignment described in the preceding paragraph. Homogeneity within potentially aligned subgroups was confirmed for the new (ninth edition) stage groups IIA and IIB (Supplementary Figs. 8 and 9) and the new stage groups IIIA and IIIB (Supplementary Figs. 10 and 11). Specifically, in the total data set (validation and training sets), comparisons of TN subgroups within each potential new stage group revealed little difference, with only a few minor inconsistencies in some comparisons that were marginally clinically meaningful or statistically significant.

Next, evidence was sought that the TN subgroups to be potentially reassigned to a different stage group in the ninth edition exhibited distinct survival outcomes from the eighth edition group assignment. These analyses in the total data set (validation and training sets) confirmed clinically relevant and statistically significant differences. Specifically, T1N1 was distinct from the stage IIB cohort ($P = .001$ for clinical stage and $P < .0005$ for pathologic stage) and T1N2a from the stage IIIA cohort ($P = .04$ for clinical stage and $P = .002$ for pathologic stage) (Supplementary Figs. 12 and 13). Similarly, T3N2a was distinct from the stage IIIB cohort ($P < .0001$ for clinical stage and $P = .03$ for pathologic stage) and T2N2b from the stage IIIA cohort ($P < .0001$ for clinical and pathologic stages) (Supplementary Figs. 14 and 15).

Effect of New M1 Categories on Stage Group Assignment

The analyses of the M Subcommittee confirmed the previous eighth edition finding regarding similar survival of patients with intrathoracic metastases (M1a) and those with a single extrathoracic metastasis (M1b). In addition, it was found that multiple extrathoracic metastases in a single organ system had significantly worse prognosis than M1b ($P < .0001$) and significantly better prognosis than multiple extrathoracic metastases in multiple organ systems (M1c) ($P < .0001$). This finding was the basis to subdivide the eighth edition M1c into M1c1 (multiple extrathoracic metastases in a single organ system) and M1c2 (multiple extrathoracic metastases in several organ systems). Nevertheless, these changes did not affect stage IV because M1a and M1b remained in stage IVA, and M1c1 and M1c2 were

8th Ed TNM Categories

8th Ed TNM Categories					
T/M	Label	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a Inv	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIB	IIIC
	T3 Same Lobe Nod	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Pl Dissem	IVA	IVA	IVA	IVA
	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1b Single Les	IVA	IVA	IVA	IVA
	M1c Mult Les	IVB	IVB	IVB	IVB

Proposed 9th Ed TNM Categories

Proposed 9th Ed TNM Categories						
T/M	Description	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural / pericardial dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple lesions, 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple lesions, >1 organ system	IVB	IVB	IVB	IVB	IVB

Figure 2. Proposed ninth edition TNM stage groups. Mult, multiple.

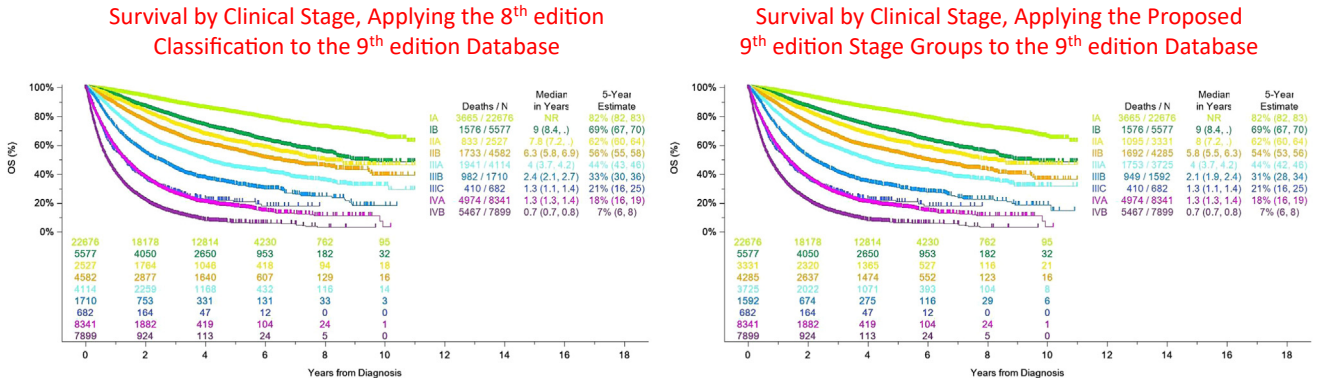
assigned to stage IVB, consistent with the eighth edition M1 classification.[11] The decision to assign different M categories to intrathoracic metastases and single extrathoracic metastasis was based on the fact that, although they have similar prognosis, they represent different forms of anatomic tumor extent that justify a different code in the TNM classification. In the same way, M1c1 and M1c2, although having different prognosis, have worse prognosis than M1b, which supports both their distinction as specific subsets and their assignment to stage IVB.

Validation of Proposed Ninth Edition Stage Groups

On the basis of the aforementioned analyses and considerations, the Stage Group Subcommittee developed the proposed ninth edition stage groups found in Figure 2. This proposed model was then validated in multiple ways. Kaplan-Meier survival curves for patients with tumors involving the proposed stage groups confirmed clinically relevant survival differences between stage groups that were consistent in both training and validation data sets and for clinical, pathologic, and best stage (Supplementary Fig. 16*A* and *B*).

Figure 3 illustrates survival graphs and 5-year survival rates of clinical stages of the eighth edition and of the proposed ninth edition models applied to the complete ninth edition data set. The graphs illustrate the expected degradation of survival as clinical stage increases, both using the eighth edition and the proposed ninth edition stage groups—with the exception of stages IIIC and IV that do not reveal significant survival differences in both stage models ($P = .0630$ for 8th edition clinical stages and $P = .0643$ for 9th edition clinical stages). Figure 4 illustrates the OS graphs and the 5-year survival rates of pathologic stage groups of the eighth edition and of the proposed ninth edition models. As for clinical stage, in both models, survival decreases progressively as tumor stage increases.

Cox multivariable analyses that adjusted for major prognostic factors are also found for the eighth edition and proposed ninth edition models in Figure 3 for clinical stage and in Figure 4 for pathologic stage. In clinical stage, in both models, patients below 65 years of age, women, patients from Asia, and those with nonsquamous cancers have a significantly better prognosis than older patients, men, patients from Europe, North America, and the ROW, and those with squamous cancers ($P < .0001$ for all comparisons). Similarly, in pathologic stage in both models, significantly better prognosis is found in patients below 65 years old, patients from Asia, and those with nonsquamous cancers ($P < .0001$ for all comparisons), but women had equal



Multivariable Cox Model	8th Ed Clinical TNM Stage Groups n=55,986; R^2=64.9454				
	n/N	(%)	HR	(95% CI)	P-value
IB (vs IA)	5,513/55,986	(9.85%)	1.77	(1.67-1.88)	<.0001
IIA (vs IB)	2,487/55,986	(4.44%)	1.18	(1.08-1.28)	0.0002
IIB (vs IIA)	4,494/55,986	(8.03%)	1.21	(1.11-1.32)	<.0001
IIIA (vs IIB)	3,471/55,986	(6.20%)	1.40	(1.31-1.50)	<.0001
IIIB (vs IIIA)	1,608/55,986	(2.87%)	1.42	(1.31-1.54)	<.0001
IIIC (vs IIIB)	632/55,986	(1.13%)	1.72	(1.53-1.94)	<.0001
IVA (vs IIIC)	7,931/55,986	(14.17%)	1.10	(0.99-1.23)	0.0630
IVB (vs IVA)	7,309/55,986	(13.06%)	1.68	(1.61-1.75)	<.0001
Age ≥65 (vs <65)	31,754/55,986	(56.72%)	0.70	(0.68-0.72)	<.0001
Female (vs Male)	27,370/55,986	(48.89%)	1.20	(1.17-1.24)	<.0001
Europe (vs Asia)	11,875/55,986	(21.21%)	1.31	(1.27-1.36)	<.0001
North America (vs Asia)	9,811/55,986	(17.52%)	1.10	(1.05-1.14)	<.0001
Rest of World (vs Asia)	1,294/55,986	(2.31%)	1.78	(1.62-1.95)	<.0001
Squamous (vs Non-squamous)	12,304/55,986	(21.98%)	0.70	(0.68-0.72)	<.0001

Multivariable Cox Model	9th Ed Clinical TNM Stage Groups n=55,986; R^2=65.0371				
	n/N	(%)	HR	(95% CI)	P-value
IB (vs IA)	5,513/55,986	(9.85%)	1.77	(1.67-1.88)	<.0001
IIA (vs IB)	3,280/55,986	(5.86%)	1.18	(1.09-1.28)	<.0001
IIB (vs IIA)	3,701/55,986	(6.61%)	1.25	(1.16-1.35)	<.0001
IIIA (vs IIB)	3,590/55,986	(6.41%)	1.33	(1.24-1.43)	<.0001
IIIB (vs IIIA)	1,489/55,986	(2.66%)	1.53	(1.41-1.66)	<.0001
IIIC (vs IIIB)	632/55,986	(1.13%)	1.62	(1.44-1.83)	<.0001
IVA (vs IIIC)	7,931/55,986	(14.17%)	1.10	(0.99-1.23)	0.0643
IVB (vs IVA)	7,309/55,986	(13.06%)	1.68	(1.61-1.75)	<.0001
Age ≥65 (vs <65)	31,754/55,986	(56.72%)	0.70	(0.68-0.72)	<.0001
Female (vs Male)	27,370/55,986	(48.89%)	1.20	(1.17-1.24)	<.0001
Europe (vs Asia)	11,875/55,986	(21.21%)	1.30	(1.26-1.35)	<.0001
North America (vs Asia)	9,811/55,986	(17.52%)	1.10	(1.05-1.14)	<.0001
Rest of World (vs Asia)	1,294/55,986	(2.31%)	1.78	(1.62-1.95)	<.0001
Squamous (vs Non-squamous)	12,304/55,986	(21.98%)	0.70	(0.68-0.72)	<.0001

Figure 3. Survival by clinical stage in the ninth edition entire database, applying the eighth edition classification (left graph) and applying the proposed ninth edition stage groups (right graph). Data involve all assessable patients with NSCLC including M1, pretreatment (including surgical, nonsurgical, neoadjuvant, and other forms of treatment). The table illustrates HRs comparing adjacent stage subgroups calculated by multivariable Cox regression, adjusting for covariates of age, sex, region, cell type, and stratified by data source. This analysis reveals ordered, step-wise and statistically significant discrimination between each stage subgroup, with progressively worse survival (HR > 1), using both the eighth edition classification and the proposed ninth edition classification. CI, confidence interval; HR, hazard ratio; OS, overall survival; R^2, percent of variance explained statistic.

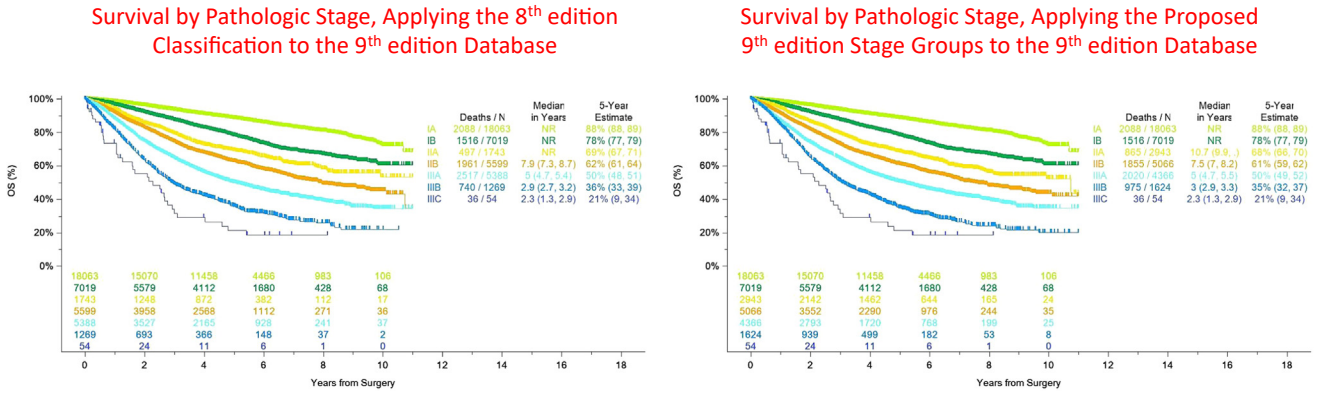
prognosis to that of men ($P = .3049$ for the 8th edition model and $P = .1725$ for the 9th edition model). The salient point is that the multivariable Cox analyses adjusted for these factors and revealed that the stage groups in both eighth edition and proposed ninth edition models retained strong discrimination between adjacent stage groups (hazard ratios > 1, statistically significant in each adjacent group comparison).

The R^2 statistic for the proposed ninth edition clinical stage groups (65.0371) is slightly higher than that for the eighth edition stages (64.9454). The R^2 statistic for pathologic stage groups is also slightly higher for the proposed ninth edition stage model (46.0529) compared with that for the eighth edition (45.5623).

Additional analyses were performed to validate the stage I subgroups IA1, IA2, IA3, and IB among patients where eighth edition size measurement was provided. Supplementary Figure 17 reveals that in the ninth edition database, survival of the three clinical and pathologic I subgroups differs significantly from each other and from stage IB ($P < .0001$ for all comparisons for clinical and pathologic stages), with the expected reduction of survival as tumor stage increases. This justifies maintaining these subgroups in the proposed ninth edition classification.

Subset Analyses for Generalizability of the Proposed Ninth Edition Stage Groups

To ensure generalizability of the proposed stage classification broadly across patient cohorts, tumors, regions, and settings, consistent discrimination between the proposed stage groups was assessed in multiple subset analyses. With few exceptions, survival graphs and 5-year survival rates in both clinical and pathologic stage reveal a consistent, ordered, and step-wise decline of survival as tumor stage increases. Supplementary Figures 18*A* and *B*, 19*A* and *B*, 20*A* to *D*, 21*A* and *B*, and 22*A* and *B* reveal the survival of patients with tumors in ninth edition clinical and pathologic stages registered in the EDC and as batch; the survival of those with squamous and nonsquamous cancers; of those from Asia and Europe; of those from North America and ROW; of those with Zubrod PS 0 and greater than or equal to 1; and of those diagnosed in an early versus later time period, respectively. Supplementary Figure 23*A* and *B*



Multivariable Cox Model	8th Ed Pathologic TNM Stage Groups n=38,280; R^2=45.5623 n/N	(%)	HR	(95% CI)	P-value
IB (vs IA)	6,990/38,280	(18.26%)	1.84	(1.73-1.97)	<.0001
IIA (vs IB)	1,733/38,280	(4.53%)	1.33	(1.20-1.47)	<.0001
IIB (vs IIA)	5,570/38,280	(14.55%)	1.29	(1.17-1.43)	<.0001
IIIA (vs IIB)	4,688/38,280	(12.25%)	1.62	(1.53-1.72)	<.0001
IIIB (vs IIIA)	1,259/38,280	(3.29%)	1.48	(1.36-1.61)	<.0001
IIIC (vs IIIB)	52/38,280	(0.14%)	1.71	(1.21-2.42)	0.0024
Age ≥65 (vs <65)	21,478/38,280	(56.11%)	0.61	(0.58-0.64)	<.0001
Female (vs Male)	19,824/38,280	(51.79%)	1.02	(0.98-1.07)	0.3049
Europe (vs Asia)	4,227/38,280	(11.04%)	1.52	(1.43-1.62)	<.0001
North America (vs Asia)	6,351/38,280	(16.59%)	1.53	(1.44-1.62)	<.0001
Rest of World (vs Asia)	1,393/38,280	(3.64%)	1.56	(1.41-1.73)	<.0001
Squamous (vs Non-squamous)	8,431/38,280	(22.02%)	0.70	(0.67-0.73)	<.0001

Multivariable Cox Model	9th Ed Pathologic TNM Stage Groups n=38,280; R^2=46.0529 n/N	(%)	HR	(95% CI)	P-value
IB (vs IA)	6,990/38,280	(18.26%)	1.84	(1.72-1.97)	<.0001
IIA (vs IB)	2,928/38,280	(7.65%)	1.40	(1.29-1.52)	<.0001
IIB (vs IIA)	4,375/38,280	(11.43%)	1.25	(1.15-1.36)	<.0001
IIIA (vs IIB)	4,329/38,280	(11.31%)	1.49	(1.40-1.59)	<.0001
IIIB (vs IIIA)	1,618/38,280	(4.23%)	1.70	(1.57-1.83)	<.0001
IIIC (vs IIIB)	52/38,280	(0.14%)	1.60	(1.13-2.25)	0.0074
Age ≥65 (vs <65)	21,478/38,280	(56.11%)	0.61	(0.58-0.64)	<.0001
Female (vs Male)	19,824/38,280	(51.79%)	1.03	(0.99-1.07)	0.1725
Europe (vs Asia)	4,227/38,280	(11.04%)	1.51	(1.42-1.61)	<.0001
North America (vs Asia)	6,351/38,280	(16.59%)	1.55	(1.46-1.65)	<.0001
Rest of World (vs Asia)	1,393/38,280	(3.64%)	1.58	(1.43-1.75)	<.0001
Squamous (vs Non-squamous)	8,431/38,280	(22.02%)	0.68	(0.65-0.72)	<.0001

Figure 4. Survival by pathologic stage in the ninth edition entire database, applying the eighth edition classification (left graph) and applying the proposed ninth edition stage groups (right graph). Data involve all assessable patients with NSCLC, M0, R-any, post-treatment who underwent surgery (excluding those who underwent neoadjuvant therapy). The table illustrates HRs comparing adjacent stage subgroups calculated by multivariable Cox regression, adjusting for covariates of age, sex, region, cell type, and stratified by data source. This analysis reveals ordered, step-wise, and statistically significant discrimination between each stage subgroup, with progressively worse survival (HR > 1), using both the eighth edition classification and the proposed ninth edition classification. CI, confidence interval; HR, hazard ratio; OS, overall survival; R^2, percent of variance explained statistic.

illustrates the survival of patients with clinical stage tumors who underwent surgical and nonsurgical treatments, of those who underwent complete (R0) resection, and of those who received neoadjuvant therapy.

The few instances of overlapping survival primarily involved clinical stages IIIC and IVA; specifically, similar survival is observed in patients with such tumors whose data were submitted through the EDC (Supplementary Fig. 18*A* and *B*); in those from Asia (Supplementary Fig. 20*A* and *B*); in those from the ROW (Supplementary Fig. 20*C* and *D*); and in those with Zubrod PS 0 (Supplementary Fig. 21*A* and *B*). This overlapping was also found in the analyses of the eighth edition database. At that time, a decision was made to keep these two stages separate, despite the fact of having the same survival, because they represent different forms of anatomic tumor spread: stage IIIC groups locally advanced tumors, whereas stage IVA represents distant spread. In addition, in patients with clinical stage tumors who underwent nonsurgical treatment, the survival of those with stages IIB, IIIA, IIIB, IIIC, and IVA is similar, suggesting that other factors besides the extent of tumor spread may be the greater determinant of prognosis in patients managed nonsurgically (Supplementary Fig. 23*A*).

Pathologic Stage Groups After Neoadjuvant Treatment

Chemotherapy only, administered to 408 (68.3%) patients, was the most common neoadjuvant treatment, followed by chemoradiotherapy, which was given to 94 patients (15.7%). Other combinations included radiotherapy only in 68 patients (11.4%), chemoimmunotherapy in 17 (2.8%), immunotherapy only in six (1.0%), and chemoradioimmunotherapy in four (0.7%). Among patients who received neoadjuvant treatment, those with tumors in pathologic stages IA to IIIA (yp stage) had worse absolute survival compared with their corresponding counterparts who underwent complete resection without neoadjuvant therapy (p-stage). The few patients with tumors in pathologic stage IIIB and IIIC after neoadjuvant therapy (208 and 12, respectively) had better absolute survival compared with their counterparts who underwent complete resection without neoadjuvant therapy (Supplementary

Fig. 23*B*). In the comparison of adjacent stages, only yp stages IIA versus IIB ($P = .0290$), IIB versus IIIA ($P = .0098$), and IIIA versus IIIB ($P = .0129$) had statistically significant different survival. This may reflect small patient numbers in some groups and that other factors besides anatomic tumor extent can affect survival.

External Validation of the Proposed Ninth Edition Stage Groups Using the Previous Eighth Edition Data Set

For external validation of the proposed ninth edition stage classification system in an independent data set, the previous eighth edition IASLC database was used (patients diagnosed between 1999 and 2010). The analysis (Supplementary Fig. 24) involves pathologic stage cases; there was insufficient granularity regarding the clinical N2 status to assign proposed ninth edition subgroups (using the separation of N2a and N2b) in the clinical stage cohort. Nevertheless, consistent ordering and discrimination is found by pairwise comparisons of each adjacent subgroup and by multivariable Cox regression.

Discussion

The IASLC ninth edition database has a similar number of assessable cases to the previous databases used to inform the seventh and the eighth editions of the TNM classification of lung cancer,[9] but its greater granularity allowed the identification of a way to quantify nodal disease that can be applied to clinical and pathologic classifications, that is, division of the N2 category into N2a and N2b subcategories.[10] The prognostic relevance of quantifying nodal disease was evident in the previous two editions of the TNM classification, either by the number of involved nodal zones[21] or by the number of involved nodal stations.[22] In the seventh and the eighth editions, the greater the number of involved nodal zones or nodal stations, respectively, the worse the prognosis. Nevertheless, this type of quantification was found only in pathologic classification, using a selected group of patients who had undergone resection and a proper intraoperative nodal assessment. In both editions, these forms of quantifying nodal disease could not be validated in clinical classification.

The two subcategories of N2 have produced new TN subsets with different prognosis that have to be assigned to stage groups. Thus, T1N2a was assigned to ninth edition stage IIB and T3N2a to ninth edition IIIA. T2bN2b was assigned to ninth edition stage IIIB. The new subsets T1N2b, T2aN2a, and T2bN2a remained in stage IIIA and T3N2b, T4N2a, and T4N2b remained in stage IIIB. In addition, T1N1 was downstaged from eighth edition stage IIB to ninth edition stage IIA. All these changes were adequately validated in subset analyses involving both clinical and pathologic stage cohorts (Supplementary Figs. 8–15).

The proposed assignment of T1N2a to ninth edition stage IIB is the most radical change in the ninth edition of the TNM classification. Despite the changes that have occurred in the stage groups since their introduction in the second edition of the TNM classification, N2 has remained in stage III. Clinical trials testing new therapeutic modalities, even in the era of targeted therapies and immunotherapy,[23,24] are based on traditional anatomic stage classification, and the trials specifically studying therapies for N2 have included the full range of mediastinal nodal involvement, from a single lymph node to multiple nodal stations.[25]

Quantifying nodal disease in the way the proposed new N2 subcategories indicate will have clinical and therapeutic implications. From the clinical point of view, computed tomography (CT), positron emission tomography (PET), or their combination (PET-CT) will have to be read carefully to assess and report the magnitude of mediastinal nodal disease. This seems to be possible, because in the ninth edition database, the different prognosis of N2a and N2b was confirmed using mainly imaging techniques to determine clinical stage. At invasive clinical stage evaluation, needle aspirations at ultrasound-guided bronchoscopy will have to be as thorough as possible for histologic proof of single or multiple nodal involvement. It has been suggested that relying on examining the largest lymph node or performing a nodal sampling may not be enough to assess whether the tumor can be classified as N2a or N2b.[26,27] The minimal requirements for an acceptable mediastinoscopy, recommended by the European Society of Thoracic Surgeons (biopsies of right and left inferior paratracheal and subcarinal lymph nodes),[28] may underestimate the quantification of mediastinal nodal disease, especially compared with video-assisted mediastinoscopic lymphadenectomy, which offers the highest yield in identifying mediastinal nodal disease especially when invasive staging is indicated despite a normal mediastinum by PET-CT.[29] The assessment of nodal involvement with the highest certainty is relevant not only to indicate resection but also to plan the radiotherapy field with maximum precision. At resection, the alternative lobe-specific systematic nodal dissection[30] may leave involved lymph nodes behind that would be removed with the higher standard of systematic nodal dissection, that is, the removal of the fatty tissue and the lymph nodes of all ipsilateral mediastinal nodal stations.[31] When these lymph nodes are involved, prognosis is worse.[32] Clinical judgment will have to be exercised carefully to apply the best procedure for the most reliable staging. Although the thoroughness of intraoperative nodal assessment is essential for the

quality of pathologic stage assessment,[33] the selective application of lesser procedures, such as lobe-specific nodal sampling, may be adequate in early stages.[34,35]

Treatment of T1N2a tumors should not change from what the clinical guidelines recommend for stage IIIA cancers (the stage for which we have recommendations based on trials).[36] As it has been emphasized before, a mere change in the classification of the anatomic extent does not imply an automatic change in treatment.[37,38] Changing the name assigned to the anatomic extent of disease does not alter the existing data regarding treatment results. Treatment recommendations should derive from properly designed clinical trials and not from taxonomic changes.

The other changes in the upstaged and downstaged TN subsets, important as they are because they refine the prognosis of patients with clinical and pathologic stage tumors, will not seem as drastic as the assignment of T1N2a to stage IIB, because, even if they change from substages A or B, they remain in their stage II or III. Likewise, the downstaged T1N1 from IIB to IIA remains in stage II.

The subcategorization of M1c into M1c1 (multiple extrathoracic metastasis in a single organ system) and M1c2 (multiple extrathoracic metastases in multiple organ systems) does not imply a change of stage because both remain in stage IVB. The subdivision is relevant to refine prognosis. In clinical practice, as with the determination of mediastinal nodal disease, the identification of number and location of metastatic implants will be key to proper categorization of the M component of the classification.

The proposed ninth edition stage groups (Fig. 2) have been found to be generalizable across time, regions, settings, and a spectrum of patients and tumor types. Specifically, subgroup analysis revealed consistent ordering and discrimination by type of data base (EDC and batch) (Supplementary Fig. 18*A* and *B*); type of tumor (squamous and nonsquamous) (Supplementary Fig. 19*A* and *B*); geographic region (Asia, Europe, North America, and ROW) (Supplementary Fig. 20*A*–*D*); Zubrod PS (0 and 1+) (Supplementary Fig. 21*A* and *B*); time period (Supplementary Fig. 22*A* and *B*) and in surgically treated patients and in those in whom resection was complete (Supplementary Fig. 23*A* and *B*).

Among the patients with clinical stage tumors who did not undergo resection, the survival curves of locally advanced cancers and of those in stage IVA are not so clearly distinct from each other as those of the other analyzed subgroups, and they tend to meet quite early after diagnosis. The proposed ninth edition stage groups work relatively well in those tumors that have received neoadjuvant treatment (yp), but their absolute survival, stage by stage, is generally lower than the survival of their pathologic stage counterparts that have been completely resected without neoadjuvant treatment.

The AJCC seeks to ideally fulfil five criteria of a stage classification for formal adoption. These five proposed AJCC criteria include the following: discrimination, calibration, generalizability, clinical relevance, and parsimony. Discrimination, defined as the ability of the proposed stage classification to distinguish between patients with different prognoses, was established with log-rank pairwise comparisons of survival between adjacent groups in adjusted multivariable Cox models. In addition, the SPFC suggested at least a 5% difference in survival between neighboring groups to justify the subdivision of a group to ensure a clinically meaningful difference in survival.

Calibration, the agreement between predicted and observed outcomes, is primarily applicable to a prognostic prediction model. Prognostic models should account for traits beyond the TNM stage group of the tumor, including patient-related, environment-related, and treatment-related factors. Thus, prognostication is not a stated goal of IASLC's Staging Project.[39] We welcome external applications that use the TNM stage classification in combination with other patient traits to assess calibration tools but find this endeavor to be outside the scope of the current analysis.

Generalizability, the ability of the classification system to work well in different populations and settings, is a major focus of the SPFC's initiative. The proposed ninth edition TNM stage groups were evaluated in clinical, pathologic, and best stage, and within several meaningful subgroups: histologic types, geographic region, PS, and treatment modality.

Clinical relevance, the usefulness of the classification system in clinical practice, highlights that stage classification systems should provide clinically relevant information that can be used to guide treatment decisions. The decision to split N2 into N2a and N2b and to subcategorize M1c into M1c1 and M1c2 was based on evidence suggesting that heterogeneous survival and different burdens of disease were inadequately described in the eighth edition's combined categories. These characteristics are often already considered when identifying the preferred treatment approach. We anticipate that these changes to the stage classification system will better describe current practices of clinical management and allow for deeper investigation of these traits in the future.

Finally, parsimony refers to a stage classification system that is simple and easy to use. To uphold a parsimonious system, the clinical and pathologic TNM stage categories remain identical, and the same tumor descriptors continue to be used for both. In addition, for the proposed ninth edition criteria, existing stage

classifications were retained whenever possible to allow for backward compatibility and ease of adoption.

The R^2 statistics of the proposed model for the ninth edition clinical and pathologic stage groups are higher than those for the model of the eighth: 65.0371 and 64.9454 for ninth and eighth edition clinical stages, respectively; and 46.0529 and 45.5623 for ninth and eighth edition pathologic stages, respectively (Figs. 3 and 4). Although the anatomic tumor extent explains a major part of the prognosis associated with lung cancer, the anatomic stage classification system is not designed to be a prognostic model. Prognosis is multifactorial and depends on tumor-, patient-, environment-, and treatment-related factors.[40] Developing a prognostic model is complex. It must be flexible to allow for inclusion of newly identified prognostic factors and user friendly to be useful in making decisions in current clinical practice.[41] The ninth edition database includes nonanatomic elements, including biomarkers,[9] that will be used to build prognostic groups, that is, the association of different prognostic factors that predicts prognosis better than any of the individual prognostic factors.[42,43] This will start being explored for the ninth edition TNM but will be more relevant in the tenth edition as more detailed data will be collected.

As was the case for the seventh and the eighth edition databases, the number of patients from the different geographic regions is unbalanced. In the ninth edition database, cases from Asia and Europe predominate and those from North and South America, Africa, and the ROW are underrepresented. Nevertheless, the trend is toward an increasing number of cases from South America and, for the first time in the history of the IASLC Lung Cancer Staging Project, there are cases from Africa and the Middle East.[9] This imbalance of geographic origin does not invalidate the recommendations for the ninth edition because they have been solidly supported by their validation in clinical and pathologic staging and in different subgroups and have revealed generalizability in different geographic regions. It is also clear that the quality of batch data is suboptimal compared with data registered in the EDC system, and that the latter should be the favored system for data collection in future revisions of the TNM classification of lung cancer. Nevertheless, good quality batch data should not be discarded because, in spite of their limitations, the proposed ninth edition recommendations could be validated in both EDC and batch databases, revealing that batch data, if adequately complete, can be reliable enough for analysis.

The eighth edition stage classification proposals, which were adopted by the UICC and AJCC in 2017, were to report both solid/invasive size and total size (including a ground-glass component for clinical and a lepidic/noninvasive component for pathologic assessment), but to use the solid (clinical) or invasive (pathologic) measurement to define the size.[44–46] Although information was submitted on the solid/invasive size in the latter portion of the accrual period, very few cases included information on the total size. Therefore, we were not able to validate in the ninth edition database that solid/invasive size is a better prognostic predictor than total size, as had been found in the eighth edition analysis (and many other studies). Adjustment for invasive rather than total size in pathologic stages I to IIA nonmucinous lung adenocarcinomas has been found to downstage 22% of tumors.[47] More detailed data collection will be an emphasis for the tenth edition of TNM classification.

The main limitation of this study is that it incompletely accounts for confounders. Developing a stage classification system requires confidence that prognosis, which is used as the primary tool, largely reflects the impact of the anatomic tumor features instead of confounding factors. Associated confounders that cannot be altered (e.g., age, comorbidity, PS) are less concerning than those that are under our control, such as treatment strategy, which can change significantly as we are constantly striving to improve patients' prognosis. We were only partially able to adjust for the impact such factors have on prognosis in the analyses conducted by the SPFC.

In conclusion, the rearrangement of new TNM subsets conditioned by the split of the N2 category into N2a and N2b and of the M1c category into M1c1 and M1c2 improves the granularity of nomenclature about anatomic extent that has benefits as treatment approaches become increasingly differentiated and complex.

CRediT Authorship Contribution Statement

Ramón Rami-Porta: Conceptualization, Methodology, Investigation, Writing—original draft.

Katherine K. Nishimura, Dorothy J. Giroux: Methodology, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review and editing.

Frank Detterbeck, Conceptualization, Methodology, Investigation, Writing—original draft, Writing—review and editing.

Giuseppe Cardillo, John G. Edwards, Kwun M. Fong, Meredith Giuliani, James Huang, Kemp H. Kernstine, Edith M. Marom, Andrew G. Nicholson, Paul Van Schil, William D. Travis, Ming S. Tsao, Shunichi Watanabe: Conceptualization, Writing—review and editing.

Hisao Asamura: Conceptualization, Methodology, Investigation, Writing—review and editing.

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Appendix 1.

IASLC Staging and Prognostic Factors Committee

Hisao Asamura (chair), Keio University, Tokyo, Japan; Valerie Rusch (chair elect), Memorial Sloan Kettering Cancer Center, New York, New York, USA; Ramón Rami-Porta (past chair), Hospital Universitari Mútua Terrassa, Terrassa, Spain; Luiz Henrique Araujo, Brazilian National Cancer Institute, Rio de Janeiro, Brazil; David Beer, University of Michigan, Ann Arbor, Michigan, USA; Pietro Bertoglio, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; Ricardo Beyruti, University of São Paulo Medical School, São Paulo, Brazil; Andrea Billè, Guy's Hospital, London, United Kingdom; Souheil Boubia, Department of Thoracic Surgery, University Hospital Ibn Rochd, Laboratoire de Pathologie Cellulaire et Moléculaire Hassan II University of Casablanca, Casablanca, Morocco; Elisabeth Brambilla, Centre Hospitalier Universitaire, Grenoble, France, University of Grenoble Alpes, Grenoble, France; A. K. Cangir, Ankara University Faculty of Medicine, Ankara, Turkey; David Carbone, The Ohio State University, Columbus, Ohio, USA; Vanessa Cilento, Cancer Research And Biostatistics, Seattle, Washington, USA; Casey Connolly, IASLC, Denver, Colorado, USA; Gail Darling, University of Toronto, Toronto, Canada; Frank Detterbeck, Yale University School of Medicine, New Haven, Connecticut, USA; Daniel Dibaba, Cancer Research And Biostatistics, Seattle, Washington, USA; Xavier Benoit D'Journo, Aix-Marseille University, Marseille, France; Jessica Donington, University of Chicago, Chicago, Illinois, USA; Wilfried Eberhardt, West German Cancer Centre, University Hospital Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Megan Eisele, Cancer Research And Biostatistics, Seattle, Washington, USA;

Jeremy Erasmus, M. D. Anderson Cancer Center, Houston, Texas, USA; Wentao Fang, Department of Thoracic Surgery, Shanghai Chest Hospital, Jiaotong University Medical School, Shanghai, People's Republic of China; Dean Fennell, Leicester Cancer Research Centre, Department of Genetics and Genome Biology, University of Leicester and University Hospital of Leicester National Health Service Trust, Leicester, United Kingdom; Kwun Fong, University of Queensland Thoracic Research Centre, Brisbane, Australia; Françoise Galateau-Sallé, Centre Hospitalier Universitaire, Caen, France; Oliver Gautschi, Cancer Center, Cantonal Hospital Lucerne, Lucerne, Switzerland; Ritu R. Gill, Beth Israel Lahey Health, Boston, Massachusetts, USA; Dorothy Giroux, Cancer Research And Biostatistics, Seattle, Washington, USA; Meredith Giuliani, The Princess Margaret Cancer Centre/University Health Network, Toronto, Ontario, Canada; Department of Otolaryngology - Head and Neck Surgery, The University of Toronto, Toronto, Ontario, Canada; Jin Mo Goo, Seoul National University, Seoul, Republic of Korea; Seiki Hasegawa, Hyogo College of Medicine, Nishinomiya, Japan; Emily Goren, Cancer Research And Biostatistics, Seattle, Washington, USA; Fred Hirsch, Center for Thoracic Oncology, Tisch Cancer Institute, Mount Sinai Health System, New York, New York, USA; Antje Hoering, Cancer Research And Biostatistics, Seattle, Washington, USA; Hans Hoffman, Technical University of Munich, Munich, Germany; Wayne Hofstetter, M. D. Anderson Cancer Center, Houston, Texas, USA; James Huang, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Philippe Joubert, Quebec Heart and Lung Institute, Quebec, Canada; Kemp H. Kernstine, The University of Texas Southwestern Medical Center, Dallas, Texas, USA; Keith Kerr, University of Aberdeen, School of Medicine and Dentistry, Aberdeen, United Kingdom; Young Tae Kim, Seoul National University, Seoul, Republic of Korea; Hong Kwan Kim, Samsung Medical Center, Seoul, Republic of Korea; Hedy Kindler, The University of Chicago Medical Center, Chicago, Illinois, USA; Yolande Lievens, Radiation Oncology Department, Ghent University Hospital and Ghent University, Ghent, Belgium; Hui Liu, Sun Yat-Sen University Cancer Center, Guangdong Sheng, People's Republic of China; Donald E. Low, Virginia Mason Medical Center, Seattle, Washington, USA; Gustavo Lyons, Buenos Aires British Hospital, Buenos Aires, Argentina; Heber MacMahon, University of Chicago, Chicago, Illinois, USA; Alyson Mahar, School of Nursing, Queen's University, Ontario, Canada; Mirella Marino, IRCCS Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, University of Tel Aviv, the Chaim Sheba Medical Center, Tel Aviv, Israel; José-María Matilla, Valladolid University Hospital, Valladolid, Spain; Jan van Meerbeeck, Antwerp University and Antwerp University Hospital, Antwerp, Belgium; Luis M. Montuenga, Center of Applied Medical Research, University of Navarra, Pamplona, Spain and Centro de Investigación Biomédica en Red de Cáncer, Spain; Andrew G. Nicholson, Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust and Imperial College, London, United Kingdom; Katie Nishimura, Cancer Research And Biostatistics, Seattle, Washington, USA; Anna Nowak, University of Western Australia, Perth, Australia; Isabelle Opitz, University Hospital Zurich, Zurich, Switzerland; Meinoshin Okumura, National Hospital Organization Osaka Toneyama Medical Center, Osaka, Japan; Raymond U. Osarogiagbon, Baptist Cancer Center, Memphis, Tennessee, USA; Harvey Pass, New York University, New York, New York, USA; Marc de Perrot, University of Toronto, Toronto, Canada; Helmut Prosch, Medical University of Vienna, Vienna, Austria; David Rice, M. D. Anderson Cancer Center, Houston, Texas, USA; Andreas Rimner, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Adam Rosenthal, Cancer Research And Biostatistics, Seattle, Washington, USA; Enrico Ruffini, University of Torino, Torino, Italy; Shuji Sakai, Tokyo Women's Medical University, Tokyo, Japan; Paul Van Schil, Antwerp University and Antwerp University Hospital, (Edegem) Antwerp, Belgium; Navneet Singh, Postgraduate Institute of Medical Education and Research, Chandigarh, India; Francisco Suárez, Clínica Santa María, Santiago, Chile; Ricardo M. Terra, University of São Paulo, São Paulo, Brazil; William D. Travis, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Ming S. Tsao, Princess Margaret Cancer Centre, Toronto, Canada; Paula Ugalde, Brigham & Women's Hospital, Boston, Massachusetts, USA; Shun-ichi Watanabe, National Cancer Center Hospital, Tokyo, Japan; Ignacio Wistuba, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA; Murry Wynes, IASLC, Denver, Colorado, USA; Yasushi Yatabe, National Cancer Center Hospital, Tokyo, Japan.

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Mark Ferguson, The University of Chicago, Chicago, USA.

Advisory Board to the Mesothelioma Domain

Jennifer Sauter, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Andrea Wolf, Icahn School of Medicine at Mount Sinai, New York, New York, USA.

Appendix 2. Chairpersons and Members of the Subcommittees of the Lung Cancer, Thymic Epithelial Tumors, Pleural Mesothelioma and Esophageal Cancer Domains of the IASLC Staging and Prognostic Factors Committee

IASLC Staging and Prognostic Factors Committee Chair: Hisao Asamura.

Lung Cancer Domain

Lung Cancer Domain Chair: Paul Van Schil.

Lung Cancer Domain Vice Chair: Kemp H. Kernstine.

Lung Cancer Domain T Descriptors Subcommittee. Hisao Asamura (chair), Young Tae Kim (co-chair), Pietro Bertoglio, A. K. Cangir, Jessica Donington, Wentao Fang, Yolande Lievens, Hiu Liu, Gustavo Lyons, Shuji Sakai, William Travis, Paula Ugalde, Paul Van Schil, Jeff Yang, Masaya Yotsukura.

Lung Cancer Domain N Descriptors Subcommittee. James Huang (chair), Raymond U. Osarogiagbon (co-chair), Andrea Billè, Giuseppe Cardillo,

Kemp H. Kernstine, Hong Kwan Kim, Kaoru Kubota, Yolande Lievens, Eric Lim, Edith M. Marom, Helmut Prosch, Paul Martin Putora, David Rice, Gaetano Rocco, Valerie Rusch, Paul Van Schil, Isabelle Opitz, Francisco Suárez, Jeff Yang, Shun-ichi Watanabe.

Lung Cancer Domain M Descriptors Subcommittee. Kwun Fong (chair), Wilfried Eberhardt (co-chair), Jeremy Erasmus, Yolande Lievens, Mirella Marino, Edith M. Marom, Paul Martin Putora, Navneet Singh, Francisco Suárez.

Lung Cancer Domain Lepidic and GGO Subcommittee. William Travis (chair), Philippe Joubert (co-chair), Hisao Asamura, Frank Detterbeck, Giuseppe Cardillo, Wendy Cooper, Ritu R. Gill, Jin Mo Goo, Young Tae Kim, Ho Yun Lee, Heber MacMahon, Edith M. Marom, David Naidich, Andrew G. Nicholson, Mizuki Nishino, Helmut Prosch, Ramón Rami-Porta, Valerie Rusch, Shuji Sakai, Yasushi Yatabe, Shun-ichi Watanabe.

Lung Cancer Domain Neuroendocrine Tumors Subcommittee. Ming Tsao (chair), Andrew G. Nicholson, (co-chair), Ricardo Beyruti, Frank Detterbeck, Wilfried Eberhardt, Pier Luigi Filosso, Yolande Lievens, Eric Lim, Geoffrey Liu, José-María Matilla, Natasha Rekhtman, William Travis, Jeff Yang, Yasushi Yatabe.

Lung Cancer Domain Stage Group Subcommittee. Hisao Asamura (chair), Giuseppe Cardillo, Frank Detterbeck, John Edwards, Kwun Fong, Meredith Giuliani, James Huang, Kemp H. Kernstine, Edith M. Marom, Andrew G. Nicholson, Ramón Rami-Porta, William Travis, Ming Tsao, Paul Van Schil, Shun-ichi Watanabe.

Lung Cancer Domain Lymph Node Chart Subcommittee. Shun-ichi Watanabe (chair), Jin Mo Goo (co-chair), Hisao Asamura, Hans Hoffman, James Huang, Kemp H. Kernstine, Yolanda Lievens, Raymond U. Osarogiagbon, Paul Martin Putora, Ramón Rami-Porta, Valerie Rusch, Paul Van Schil, Jeff Yang.

Lung Cancer Domain Validation and Methodology Subcommittee. Frank Detterbeck (chair), Alyson Mahar (co-chair), Hisao Asamura, Meredith Giuliani, Mirella Marino, Raymond U. Osarogiagbon, Valerie Rusch.

Lung Cancer Domain Prognostic Factors Subcommittee. Frank Detterbeck (chair), Raymond U. Osarogiagbon (co-chair), Alex Brunelli, Kwun Fong, James Huang, Young Tae Kim, Mark Krasnik, Hiu Liu, Jan van Meerbeeck, Luis M. Montuenga, Andrew G. Nicholson, Valerie Rusch, Robert Samstein, Navneet Singh, Martin Tammemägi, Ricardo M. Terra, Ming Tsao, Akif Turna, Terence Williams.

Lung Cancer Domain R Factor Subcommittee. John Edwards (chair), Marcin Ostrowski (co-chair), Souheil Boubia, Jessica Donnington, Hans Hoffman, Maurizio Infante, Mirella Marino, Edith M. Marom, Jun Nakajima, Andrew G. Nicholson, Paul Van Schil, William Travis, Ming Tsao, Yasushi Yatabe.

Lung Cancer Domain Imaging Subcommittee. Jim Mo Goo (chair), Ritu R. Gill (co-chair), Helmut Prosch (co-chair), Samuel Armato, Hui Liu, Heber MacMahon, Edith M. Marom, David Naidich, Charles Powell, Paul Van Schil, William Travis.

Lung Cancer Domain Multiple Pulmonary Nodules Subcommittee. Frank Detterbeck (chair), Alyson Mahar (co-chair), Sarit Appel, Jason Chang, Keneng Chen, Nicolas Girard, Jin Mo Goo, Young Tae Kim, Heber MacMahon, Andrew G. Nicholson, Paul Martin Putora, Natasha Rekhtman, M. Patricia Rivera, Lynn Tanoue, Ricardo M. Terra, William Travis, Paula Ugalde.

Lung Cancer Domain Molecular Subcommittee. David Carbone (co-chair), Fred Hirsch (co-chair), Luiz Henrique Araujo, Hisao Asamura, Elisabeth Brambilla, Jason Chang, Frank Detterbeck, Oliver Gautschi, Nagla Karim, Keith Kerr, Peter Kneuertz, Eric Lim, Philip Mack, José-María Matilla, Luis M. Montuenga, Andrew G. Nicholson, Raymond U. Osarogiagbon, Harvey Pass, Carolyn J. Presley, Ramón Rami-Porta, Natasha Rekhtman, Harry Ren, Robert Samstein, Kenichi Suda, Ricardo M. Terra, William Travis, Ming Tsao, Terence Williams, Ignacio Wistuba, Dawei Yang, Yasushi Yatabe.

Lung Cancer Domain Database. Paula Ugalde (chair), Pietro Bertoglio (co-chair), Sarit Appel, Philippe Joubert, Catherine Labbe, Hongxu Liu, Gustavo Lyons, José-María Matilla, Robert Samstein, Ricardo M. Terra, Maria Teresa Ruiz Tzukazan, Benny Weksler.

Cancer Research And Biostatistics. Vanessa Cilento, Daniel Dibaba, Megan Eisele, Dorothy Giroux, Emily Goren, Antje Hoering, Katie Nishimura, Adam Rosenthal.

Thymic Epithelial Tumors Domain

Enrico Ruffini (chair), James Huang (co-chair), Usman Ahmad, Sarit Appel, Andrea Billè, Souheil Boubia, Cecilia Brambilla, A. K. Cangir, Frank Detterbeck, Conrad Falkson, Wentao Fang, Pier Luigi Filosso, Giuseppe Giaccone,

Nicolas Girard, Francesco Guerrera, Maurizio Infante, Dong Kwan Kim, Marco Lucchi, Mirella Marino, Edith M. Marom, Andrew Nicholson, Meinoshin Okumura, Andreas Rimner, Anja Roden, Charles B. Simone II.

Thymic Domain T Descriptor: Andrew Nicholson (chair), Cecilia Brambilla, A. K. Cangir, Maurizio Infante, Mirella Marino, Edith M. Marom, Meinoshin Okumura.

Thymic Domain N Descriptor: Wentao Fang (chair), Frank Detterbeck, Pier Luigi Filosso, Marco Lucchi, Edith M. Marom, Charles B. Simone II.

Thymic Domain M Descriptor: Nicolas Girard (chair), Usman Ahmad, Sarit Appel, Conrad Falkson, Wentao Fang, Giuseppe Giaccone, Dong Kwan Kim, Edith M. Marom, Andreas Rimner.

Thymic Domain Database Subcommittee: Pier Luigi Filosso (chair), Usman Ahmad, Andrea Billè, Souheil Boubia, Frank Detterbeck, Wentao Fang, Nicolas Girard, Francesco Guerrera, James Huang, Dong Kwan Kim, Meinoshin Okumura, Enrico Ruffini.

Pleural Mesothelioma Domain

Valerie Rusch (chair), Anna K. Nowak (co-chair), Pietro Bertoglio, Andrea Billè, Ayten K. Cangir, Dean Fennell, Françoise Galateau-Salléé, Ritu R. Gill, Seiki Hasegawa, Hong Kwan Kim, Hedy Kindler, Joseph Friedberg, Jan van Meerbeeck, Isabelle Opitz, Harvey Pass, Marc de Perrot, David Rice, Andreas Rimner, Robert T. Ripley, Jennifer Sauter, Ming S. Tsao, David Waller, Andrea Wolf.

Esophageal Cancer Domain

Wentao Fang (chair), Xavier D'Journo (co-chair), Gail Darling, Jeremy Erasmus, Mark Ferguson, Wayne Hofstetter, Hong Kwan Kim, Donald Low, Paula Ugalde.

Appendix 3. Participating Institutions in the Third Phase of the IASLC Lung Cancer Staging Project

Participating Institutions Ordered by Number of Eligible Cases Submitted

I. Yoshino, Japanese Joint Lung Cancer Registry, Chiba, Japan (23,663 cases); T. Muley, Thoraxklinik, University Hospital Heidelberg, Heidelberg, Germany (8887 cases); W. Li, CAALC: West China Hospital, Sichuan University, Chengdu, People's Republic of China (7345 cases); Y. Kim, Korean Association for Lung Cancer, Seoul, Republic of Korea (4622 cases); H.K. Kim, Samsung Medical Center, Seoul, Republic of Korea (4130 cases); F. Griesinger, CRISP, Berlin, Germany (5482 cases)*; J. Huang, Memorial Sloan Kettering Cancer Center, New York, New York, USA (3146 cases); R. Osarogiagbon, Baptist Memorial Hospital, Memphis, Tennessee, USA (3021 cases); S. Park, Seoul National University Hospital, Seoul, Republic of Korea (2542 cases); G. Liu, Princess Margaret Cancer Center, Toronto, Canada (2280 cases); N. Singh, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India (2060 cases); P. Ugalde Figueroa, IUCPQ - Université Laval, Quebec, Canada (2018 cases); P. Kneuertz, The Ohio State University, Columbus, Ohio, USA (1819 cases); J. Shih, Taiwan Society of Pulmonary and Critical Care Medicine, Taipei, Taiwan, Republic of China (1481 cases); S. Jordan, The Royal Brompton Hospital & E. Beddow, Harefield Hospital, Part of Guy's & St. Thomas' NHS Foundation Trust, London, UK (1434 cases); B. McCaughan, University of Sydney, Newtown, Australia (1368 cases); H. Liu, Liaoning Cancer Hospital, Shenyang, People's Republic of China (1161 cases); A. Cangir, Ankara University School of Medicine, Ankara-Sihhiye, Turkey (887 cases); A. Billè, Guy's Hospital, London, UK (882 cases); F. Leo, S Luigi Hospital, University of Turin, Orbassano, Torino, Italy (840 cases); H. Liu, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China (825 cases); M. Redman, SWOG-0819, Seattle, USA (782 cases); H. Pass, NYU Langone Medical Center and Cancer Center, New York, New York, USA (762 cases); J. Sun, CAALC: Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, People's Republic of China (634 cases); K. Fong, The University of Queensland TPCH Thoracic Research Centre, Brisbane, Australia (577 cases); R. Terra, University of São Paulo Medical School, São Paulo, Brazil (555 cases); N. Wu, Second Department of Thoracic Surgery, Peking University Cancer, Beijing, People's Republic of China (455 cases); K. Chen, First Department of Thoracic Surgery, Peking University Cancer Hospital, Beijing, People's Republic of China (451 cases); A. Mohan, All India Institute of Medical Sciences, New Delhi, India (448 cases); P. Van Schil, University Hospital Antwerp, Department of Pneumology, Edegem, Belgium (304 cases); P. Bertoglio, IRCCS Sacro Cuore-Don Calabria Hospital, Negrar, Italy (298 cases); C. Yang, Massachusetts General Hospital, Boston, Massachusetts, USA (295 cases); R. Moises, Hospital de Rehabilitación Respiratoria María Ferrer, Buenos Aires, Argentina (264 cases); A. Turna, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey (238 cases); A. Celik, Gazi University Faculty of Medicine, Ankara, Turkey (193 cases); M.

** CRISP is an AIO study (project no. AIO TRK-0315) under the medical leadership of the Executive Committee (Prof. F. Griesinger [Oldenburg], Prof. M. Thomas [Heidelberg], Dr. M. Sebastian [Frankfurt], and Dr. W. Eberhardt [Essen]). CRISP is conducted by AIO-StudiengGmbH (sponsor) in cooperation with iOMEDICO (conception, project management, analysis). CRISP is supported by AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, Lilly Deutschland GmbH, MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG, and Takeda Pharma Vertrieb GmbH & Co. KG. Nevertheless, these companies have no input into or influence over data analysis, data interpretation, or writing of the manuscript.*

Modesto Alapont, GCCB3: Consorcio Hospitalario Provincial de Castellón, Castellón, Spain (165 cases); L. Sánchez Moreno and M. Zabaleta Murguiondo, GCCB3: Hospital Universitario Marqués de Valdecilla, Santander, Spain (165 cases); C. Longo, Instituto COI, Rio de Janeiro, Brazil (150 cases); H. Zhou, Suining Central Hospital, Suining, Sichuan, People's Republic of China (147 cases); E. Pirondini, ASST San Gerardo, Monza, Italy (144 cases); G. Lyons, Hospital Británico de Buenos Aires, Buenos Aires, Argentina (143 cases); I. Gkiozos, Athens School of Medicine, Athens, Greece (133 cases); K. Kernstine, UT Southwestern Medical Center at Dallas, Dallas, Texas, USA (132 cases); M. Serra Mitjans and R. Costa, GCCB3: Hospital Universitari Mútua Terrassa, Barcelona, Spain (124 cases); M. Genovés Crespo and A. Nuñez Ares, GCCB3: Complejo Hospitalario Universitario of Albacete, Albacete, Spain (114 cases); C. Lee, Seoul National University Bundang Hospital, Seongnam, Republic of Korea (104 cases); Y. K. Pang, Malaysian Thoracic Society, Kuala Lumpur, Malaysia (99 cases); N. Evans, Thomas Jefferson University Hospital, Philadelphia, USA (98 cases); F. Hirsch, Icahn School of Medicine at Mount Sinai, New York, New York, USA (84 cases); M. Ridai, University Hospital of Casablanca, Casablanca, Morocco (83 cases); C. Martínez Barenys and J. Sanz Santos, GCCB3: Hospital Universitari Germans Trias i Pujol, Badalona, Spain (77 cases); J. Sauleda Roig, Hospital Universitari Son Espases, Palma de Mallorca, Spain (76 cases); H. Hoffmann, University of Munich - Division of Thoracic Surgery, Munich, Germany (75 cases); M.A. Iñiguez-García, National Institute of Respiratory Diseases, Mexico City, Mexico (74 cases); L. H. de Lima Araujo, Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil (72 cases); C. Grohé, Evangelische Lungenklinik Berlin - NET Registry, Berlin, Germany (71 cases); D. Ball, Peter MacCallum Cancer Institute, Melbourne, Australia (70 cases); J. C. Peñalver Cuesta, GCCB3: Fundación Instituto Valenciano de Oncología, Valencia, Spain (65 cases); N. Tarek, Ain Shams University Hospitals, Cairo, Egypt (64 cases); D. Yang, CAALC: Zhongshan Hospital Fudan University, Shanghai, People's Republic of China (63 cases); D. Sánchez, GCCB3: Hospital Clínic, Barcelona, Spain (62 cases); J. A. Gullón Blanco, GCCB3: Hospital Universitario San Agustín, Avilés, Asturias, Spain (61 cases); L. M. Montuenga and M. A. Mesa-Guzmán, CIMA/Clínica Universidad de Navarra, Pamplona, Spain (55 cases); G. Galán Gil and R. Guijarro Jorge, GCCB3: Hospital Clínico Universitario de Valencia, Valencia, Spain (52 cases); C. García Rico, J. M. Matilla and B. de Vega Sánchez, GCCB3: Hospital Clínico Universitario de Valladolid, Valladolid, Spain (50 cases); A. Rodríguez Fuster and V. Curall, GCCB3: Hospital del Mar, Barcelona, Spain (50 cases); L. Miravet, GCCB3: Hospital La Plana, Castellón, Spain (49 cases); J. Abal Arca and I. Parente Lamelas, GCCB3: Complexo Hospitalario Universitario Ourense, Ourense, Spain (48 cases); E. Melis, IRCCS Regina Elena National Cancer Institute, Rome, Italy (41 cases); S. García Fuika, GCCB3: Hospital UA Txagorritxu, Vitoria-Gasteiz, Spain (34 cases); K. Tournoy, University Hospital Ghent, Ghent, Belgium (33 cases); M. Zuil Martín, GCCB3: Hospital Royo Villanova, Zaragoza, Spain (31 cases); L. García Aranguena, GCCB3: Hospital Sierrallana, Torrelavega, Cantabria, Spain (28 cases); O. Arrieta, Instituto Nacional de Cancerología, Mexico City, Mexico (28 cases); M. G. Blum, Penrose Cancer Center, Colorado Springs, Colorado, USA (28 cases); D. Mishra, B. P. Koirala Institute of Health Sciences, Dharan, Nepal (25 cases); J. M. García Prim, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain (25 cases); M. Mariñán Gorospe, Hospital San Pedro de Logroño, Logroño, Spain (24 cases); R. Stirling, The Alfred Hospital, Melbourne, Australia (23 cases); B. Steen, GCCB3: Hospital de Alcorcón, Madrid, Spain (23 cases); D. Chimondeguy, Hospital Universitario Austral, Buenos Aires, Argentina (22 cases); F. J. Montoro Zulueta, GCCB3: Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain (22 cases); M. Paradela de la Morena and A. Souto Alonso, GCCB3: Complejo Hospitalario Universitario de A Coruña, La Coruña, Spain (21 cases); R. Cordovilla and T. Gómez Hernández, GCCB3: Hospital Universitario de Salamanca, Salamanca, Spain (21 cases); C. Thomas, Mayo Clinic Rochester, Rochester, Minnesota, USA (20 cases); J. Hernández Hernández and I. Lobato Astiárraga, GCCB3: Complejo Asistencial de Ávila, Ávila, Spain (19 cases); I. Macía Vidueira and S. Padrones, GCCB3: Hospital de Bellvitge, Barcelona, Spain (16 cases); J. R. Jarabo Salcedo and B. 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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.2024.02.011.

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