The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours

Peter Goldstraw, FRCS, John Crowley, PhD,† Kari Chansky, MS,† Dorothy J. Giroux, MSc,† Patti A. Groome, PhD,‡ Ramon Rami-Porta, MD,§ Pieter E. Postmus, PhD,‖ Valerie Rusch, MD,¶ and Leslie Sobin, MD,# on behalf of the International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions*

Introduction: The seventh edition of the *TNM Classification of Malignant Tumors* is due to be published early in 2009. In preparation for this, the International Association for the Study of Lung Cancer established its Lung Cancer Staging Project in 1998. The recommendations of this committee for changes to the T, N, and M descriptors have been published. This report contains the proposals for the new stage groupings.

Methods: Data were contributed from 46 sources in more than 19 countries. Adequate data were available on 67,725 cases of non-small cell lung cancer treated by all modalities of care between 1990 and 2000. The recommendations for changes to the T, N, and M descriptors were incorporated into TNM subsets. Candidate stage groupings were developed on a training subset and tested in a validation subset.

Results: The suggestions include additional cutoffs for tumor size, with tumors >7 cm moving from T2 to T3; reassigning the category given to additional pulmonary nodules in some locations; and reclassifying pleural effusion as an M descriptor. In addition, it is suggested that T2b N0 M0 cases be moved from stage IB to stage IIA, T2a N1 M0 cases from stage IIB to stage IIA, and T4 N0–1 M0 cases from stage IIIB to stage IIIA.

Conclusions: Such changes, if accepted, will involve a reassessment of existing treatment algorithms. However, they are based on an intensive and validated analysis of the largest database to date. The proposed changes would improve the alignment of TNM stage with prognosis and, in certain subsets, with treatment.

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The current (sixth) *TNM Classification of Malignant Tumours*, introduced in 2002,[1] made no changes to the previous edition with regards to lung cancer. The proposals with regard to lung cancer in the fifth edition, published in 1997,[2] were based on a relatively small database of 5319 cases of non-small cell lung cancer (NSCLC) accumulated since 1975. During this time, there had been many refinements to the techniques available for clinical staging, principally the routine use of computed tomography. The database was largely from a single institution, containing cases predominantly treated surgically. Repeated iterations of the *TNM Classification of Malignant Tumours* had seen the recommendations for lung cancer staging evolve with little internal validation and no external validation of the descriptors or the stage groupings. Increasingly reports from other databases were challenging some of the descriptors and suggesting revised stage groupings. The next edition of the *TNM Classification of Malignant Tumours*, the seventh, was due to be published early in 2007, now 2009. In preparation for this the International Association for the Study of Lung Cancer (IASLC) established its Lung Cancer Staging Project in 1998 to bring together the large databases available worldwide and to form recommendations for the seventh edition that would be intensively validated. The history of the project and details of the database have been described elsewhere.[3] The project has been recognized by the International Union Against Cancer as the primary source for recommendations for revisions to the sixth edition of the *TNM Classification of Malignant Tumours* and has received funding from the

*Royal Brompton Hospital, Imperial College, London, United Kingdom; †Cancer Research and Biostatistics, Seattle, Washington; ‡Queen's Cancer Research Institute, Kingston, Ontario, Canada; §Hospital Mutua de Terrassa, Terrassa, Spain; ‖Vrije Universiteit University Medical Center, Amsterdam, The Netherlands; ¶Memorial Sloan-Kettering Cancer Center, New York, New York; #Armed Forces Institute of Pathology, Washington, DC.

See Appendix for participants.

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Address for correspondence: Peter Goldstraw, FRCS, Department of Thoracic Surgery, Royal Brompton Hospital, Sydney Street, London, SW3 6NP UK. E-mail: p.goldstraw@rbht.nhs.uk

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American Joint Committee on Cancer to separately submit proposals for its revision of the staging manual. The recommendations of the staging committee have been submitted to the International Union Against Cancer and are shortly to be submitted to the American Joint Committee on Cancer.

METHODS

At a workshop held in London in February 2001, a number of groups presented the data held in their institutions. Our chosen biosciences partner, Cancer Research and Biostatistics, in discussion with the committee members, subsequently developed the data fields and dictionary. It was decided that the study period should enlist cases diagnosed between 1990 and 2000. This interval was chosen as it represented a relatively short period during which staging methods had been constant and allowed 5 years of follow-up before analysis. Cases treated by all modalities of care, including multimodality treatment, were included. From the core of contributors who presented at the workshop, data acquisition was widened to eventually involve 46 sources in more than 19 countries. These additional sources were identified from the literature by their response to advertisements in the journals or by contact from individual members of the committee. A total of 100,869 cases were submitted to the data center at Cancer Research and Biostatistics. After an initial sift to exclude cases outside the study period, those for whom cell type was not known, cases not newly diagnosed at the point of entry, and those with inadequate information on stage, treatment, or follow-up, 81,015 cases remained for analysis. Of these, 67,725 were NSCLC and 13,290 were small-cell lung cancer (SCLC). Only the NSCLC cases were included in the analyses of the T, N, and M descriptors and the subsequent analysis of TNM subsets and stage groupings. Survival was measured from the date of entry (date of diagnosis for registries, date of registration for protocols) for clinically staged data and the date of surgery for pathologically staged data and 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.

Where the analyses showed descriptors to have a prognosis that differed from the other descriptors in any T or M category, two alternative strategies were considered: (1) Retain that descriptor in the existing category, identified by alphabetical subscripts. For example, additional pulmonary nodules in the lobe of the primary, considered to be T4 in the sixth edition,[1] would become T4a, whereas additional pulmonary nodules in other ipsilateral lobes, designated as M1 in the sixth edition,[1] would become M1a. (2) Allow descriptors to move between categories, to a category containing other descriptors with a similar prognosis, e.g., additional pulmonary nodules in the lobe of the primary would move from T4 to T3, and additional pulmonary nodules in other ipsilateral lobes would move from M1 to T4. The first strategy had the advantage of allowing, to a large extent, retrograde compatibility with existing databases. Unfortunately, this generated a large number of descriptors (approximately 20) and an impractically large number of TNM subsets (>180). For this reason, backward compatibility was compromised and strategy (2) was preferred for its clinical utility. The resultant TNM subsets and the numbers of cases in each subset by clinical stage and pathologic stage are shown in Table 1. A small number of candidate stage grouping schemes were developed initially using a recursive partitioning and amalgamation algorithm.[4] S-PLUS Version 7.0 was the statistical software used to apply this algorithm and draw the initial tree. The analysis grouped cases based on best stage (pathologic, if available, otherwise clinical) after determination of best-split points based on overall survival on indicator variables for the newly proposed T/M categories and an ordered variable for N category, excluding NX cases. This analysis was performed on a randomly selected training set comprising two thirds of the available data that met the requirements for conversion to newly proposed T and M categories (n = 17,726), reserving 9133 cases for later validation. The random selection process was stratified by type of database submission and time period of case entry (1990–1995 versus 1995–2000).

The recursive partitioning and amalgamation analysis generated a tree-based model for the survival data using log rank test statistics for recursive partitioning and, for selection of the important groupings, bootstrap resampling to correct

TABLE 1. Total Number of International Database Cases Classifiable According to Proposed TNM Stage Subsets for Clinical Stage and Pathologic Stage

Clinical Stage

	N Stage				
Proposed T/M Stage	**N0**	**N1**	**N2**	**N3**	**Total**
T1a	419	12	66	13	510
T1b	442	14	78	5	539
T2a	1345	71	326	39	1781
T2b	411	33	107	14	565
T3	2452	691	2355	616	6114
T4	144	17	134	44	339
M1a	213	41	220	157	631
M1b	626	221	1151	790	2788
Total	6052	1100	4437	1678	13,267

Pathologic Stage

	N Stage				
Proposed T/M Stage	**N0**	**N1**	**N2**	**N3**	**Total**
T1a	1965	226	191	4	2386
T1b	1796	343	327	6	2472
T2a	3186	1123	905	18	5232
T2b	937	382	285	4	1608
T3	2188	1015	1114	74	4391
T4	224	118	217	12	571
M1a	99	42	94	4	239
M1b	15	7	11	5	38
Total	10,410	3256	3144	127	16,937

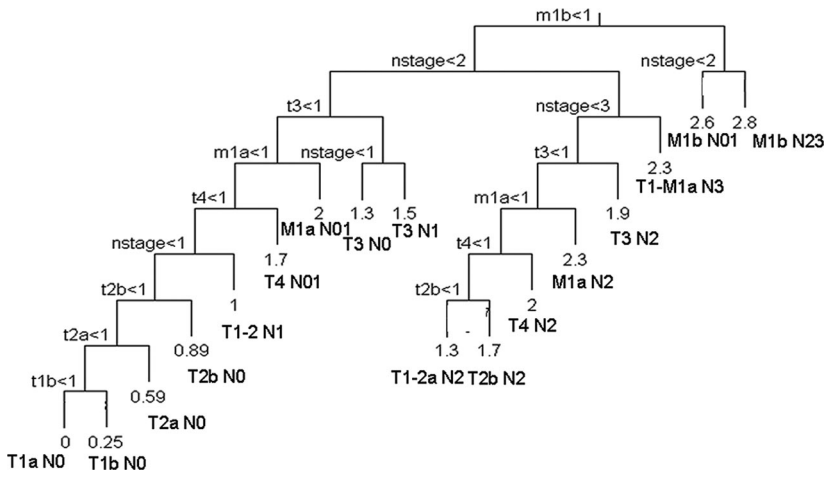

FIGURE 1. Recursive partitioning and amalgamation–generated survival tree based on best stage for 17,726 cases. T and M stages (from proposed new T and M) are combined as 0/1 indicators. N stage is ordered. The number below each terminal node is the log hazard ratio, with the T1aN0M0 category as baseline.

TABLE 2. Terminal Nodes from T/M and N Survival Tree, Ordered by Hazard Ratio

Terminal Node	Sample Size (Training Set)	Hazard Ratio
T1a N0	1373	1.00
T1b N0	1257	1.28
T2a N0	2346	1.80
T2b N0	673	2.44
T1ab–T2ab N1	1460	2.72
T3 N0	2466	3.67
T1–2a N2	1253	3.67
T3 N1	1066	4.48
T4 N01	354	5.47
T2b N2	250	5.47
T3 N2	2006	6.69
M1a (N0–1)	301	7.39
T4 N2	239	7.39
M1a (N2)	212	9.97
T1-M1a N3	630	9.97
M1b (N0–1)	553	13.46
M1b (N2–3)	1287	16.44

Sample size is the number of cases in the training set classifiable by best stage.

for the adaptive nature of the splitting algorithm (Figure 1). An ordered list of groupings from the terminal nodes of the survival tree, with group sizes and hazard ratios, is shown in Table 2. With this as a guide, several proposed stage groupings were created by combining adjacent groups. Selection of a final stage grouping proposal from among the candidate schemes was based on its statistical properties in the training set and its relevance to clinical practice and was arrived at by consensus.

RESULTS

The changes proposed to the current T and M descriptors are highlighted in the full list of descriptors shown in Table 3. These changes have been reported in detail in this journal.[5,6] The existing N descriptors were validated, and no changes are proposed.[7] The changes proposed suggest that size cutoffs in addition to the 3-cm limit that separates T1 from T2 tumors be established. Tumors that fulfill the definition for T1 and are ≤2 cm in greatest dimension should be designated T1a, whereas those that are >2 cm but ≤3 cm in greatest dimension be designated T1b. Those tumors that fulfill the present definition of T2 and are ≤5 cm in greatest dimension become T2a, whereas those that are >5 cm but ≤7 cm in greatest dimension become T2b. Tumor dimension >7 cm becomes a T3 descriptor. Additional tumor nodules in the lobe of the primary become T3, nodules in other ipsilateral lobes become T4, whereas nodules in the contralateral lung remain M1 disease. The presence of a malignant pleural effusion, pleural dissemination, or pericardial disease becomes an M descriptor. The M category is subdivided into M1a, which includes the new descriptors added to this category, i.e., cases with pleural nodules or malignant pleural or pericardial effusion and additional pulmonary nodules in the contralateral lung and M1b for those cases with other distant metastases.

These proposed changes were incorporated into the data and, after analysis of each TNM subset, the resultant stage groupings were identified. These are summarized in Table 4, in which are highlighted those TNM subsets that it is proposed should move from their present stage grouping. The moving of some cases from within a descriptor in the present staging system to another in the proposals for the seventh edition of the TNM classification and the creation of new descriptors has led to the migration of certain TNM subsets between stage groups. For example, of 1789 cases in the database designated as T2 N1 M0 according to the sixth edition, 400 were allocated to the new subset of T2b N1 M0 and another 205 migrate into the T3 N0 M0 subset. Consequently, those cases remaining T2a N1 M0 had a survival equivalent to that of stage IIA and not stage IIB as in the sixth edition. The numbers driving this, and other changes, are evident in Table 5. Those T2 tumors >5 cm but ≤7 cm in greatest dimension are reclassified as T2b, and if node negative migrate to stage IIA from stage IB. Those T2 tumors >7 cm in greatest dimension would become T3 tumors and move to stage IIB from IB if node negative and to stage IIIA from IIB if associated with N1 disease. If

TABLE 3. Proposed Definitions for T, N, and M Descriptors

T (Primary Tumor)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumor ≤2 cm in greatest dimension
T1b	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm in greatest dimension
T2b	Tumor >5 cm but ≤7 cm in greatest dimension
T3	Tumor >7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe
N (Regional Lymph Nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (Distant Metastasis)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion[b]
M1b	Distant metastasis

[a] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

[b] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

TABLE 4. Descriptors, Proposed T and M Categories, and Proposed Stage Groupings

Sixth Edition T/M Descriptor	Proposed T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (>5–7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in bold indicate a change from the sixth edition for a particular TNM category.

those cases with additional tumor nodules in the same lobe as the primary are moved to T3 from T4 as proposed, then such cases move from stage IIIB to IIB if node negative and to stage IIIA if associated with N1 or N2 disease. The changes to the T4 descriptor, the removal of cases with additional tumor nodules in the lobe of the primary and cases with pleural or pericardial disease, and the addition of cases with additional tumor nodules in other ipsilateral lobes result in a lower stage being assigned to most TNM subsets containing the T4 descriptor. Those cases with pleural or pericardial disease, if assigned to an M descriptor, would consequently fall within stage IV disease.

Figures 2 and 3 show survival by stage according to the sixth edition of TNM and by the newly proposed TNM stage based on the entire set of cases available for reclassification. (Cases without data on age, sex, and histology are excluded.) Tables 6 and 7 show the statistics from Cox proportional hazards regression modeling of the sixth edition of TNM and the proposed new system for clinical and pathologic stage, respectively. Stage was parameterized both as a set of indicator variables and also by ordered variables (Tables 6 and 7), adjusted for cell type, sex, region, and age (younger than 60 versus 60 and older).

The proposed system better delineates the early stage cases, where problems with overlap between IB and IIA have been noted with the sixth edition of TNM[8] and are clearly seen here on clinical staging. Improvement is also seen in the distinction between clinical IIA and IIB, as well as the proportion of cases assigned to stage IIA (a weakness of the sixth edition of TNM).

For both the clinical and pathologic stage models, there is an increase in the value for R^2, an estimate of the percentage of variance explained by the model.[9] The new system makes use of well-justified changes to T and M and may serve to identify subsets of patients with tumors of different sizes with differing prognoses. Both the proposed new system and the sixth edition of TNM yielded a reversal on pathologic staging from the expected hazards for advanced stage disease

TABLE 5. Sample Sizes for TNM Subsets Providing the Basis for Proposed Changes T1–T3 by Best Stage, T4 by Best Stage, and M1 by Best Stage

T1–T3 by Best Stage		N0		N1		N2		N3	
Sixth Edition Descriptor	**Proposed T/M**	**Overall Stage**	**Sample Size**	**Overall Stage**	**Sample Size**	**Overall Stage**	**Sample Size**	**Overall Stage**	**Sample Size**
T1 (≤2 cm)	T1a	IA	2134	IIA	242	IIIA	257	IIIB	19
T1 (>2–3 cm)	T1b	IA	1902	IIA	360	IIIA	412	IIIB	13
T2 (≤5 cm)	T2a	IB	3547	**IIB–>IIA**	**1184**	IIIA	1198	IIIB	60
T2 (>5–7 cm)	T2b	**IB–>IIA**	**1016**	IIB	400	IIIA	374	IIIB	20
T2 (>7 cm)	T3	**IB–>IIB**	**457**	**IIB–>IIIA**	**205**	IIIA	211	IIIB	5
T3 (invasion)		IIB	3113	IIIA	1329	IIIA	2735	IIIB	642
T4 (same lobe nodules)		**IIIB–>IIB**	**174**	**IIIB–>IIIA**	**70**	**IIIB–>IIIA**	**127**	IIIB	5

T4 by Best Stage		N0–N1		N2–N3	
Sixth Edition Descriptor	**Proposed T/M**	**Overall Stage**	**Sample Size**	**Overall Stage**	**Sample Size**
T4 (extension)	T4	**IIIB–>IIIA**	**432**	IIIB	320
M1 (ipsilateral lung)		**IV–>IIIA**	**97**	**IV–>IIIB**	**86**

M1 by Best Stage		Any N	
Sixth Edition Descriptor	**Proposed T/M**	**Overall Stage**	**Sample Size**
T4 (pleural dissemination)	M1a	**IIIB–>IV**	**683**
M1 (contralateral lung)		IV	230
M1 (distant)	M1b	IV	2800

Cells in bold indicate a change from the sixth edition for a particular TNM category. Samples sizes for T/M descriptors are summarized across N-stage categories where possible to highlight the decision points for the proposed stage groupings.

(IIIB and IV). This result, although anomalous, can most likely be explained by the nature of advanced-stage surgical cases. By virtue of their expected resectability, they consisted primarily of small effusions or additional nodules discovered at surgery or of cases with single isolated central nervous system or adrenal metastases.

In summary, the proposed system results in improved R^2 values for both clinical and pathologic stages, improved separation between stages IIB and IIA for clinical and pathologic stages, a more even distribution among the stage groupings for both clinical and pathologic stages, and an increase in the hazard ratio for stage when modeled as an ordered variable. These advantages, combined with enhanced clinical utility and incorporation of the refined T and M criteria, make this system a strong candidate for a revised staging system. The proposed stage groupings are summarized in Table 8.

Validation

The proposals derived from the training set of 17,726 cases were internally validated against the validation set of 9133 cases. Details of these analyses are provided in the companion paper on the validation process and results.[10] In brief, the validation set generated survival curves that were generally similar to those in the training set and Cox proportional hazards regression analyses that calculated the hazard ratios between each pair of adjacent stage groups while controlling for cell type, sex, age, and region were all statistically significant using the pathologic staging data. There were some nonsignificant differences in the early-staged clinical cases, but this problem was present using both the proposed system and the existing sixth edition of TNM and may be the result of an unstable comparison as the validation set contained only 3863 cases.

External validation was assessed against the Surveillance, Epidemiology, and End Results Program database, which records best stage and details of this comparison along with survival curves are provided in our validation paper.[10] The Surveillance, Epidemiology, and End Results Program survival curves using the sixth edition of the *TNM Classification of Malignant Tumours* and the IASLC proposed system were compared. Generally, both the new system and the existing performed well, but the separation between the IB and IIA curves was better in the proposed system, whereas the new IIA and IIB curves converged at 5 years.

DISCUSSION

Previous revisions to the TNM classification for lung cancer contained very little internal and no external validation information. In 1974, the second edition of the *TNM Classification of Malignant Tumours* [11] incorporated all of the descriptors suggested by the American Joint Committee on Cancer Task Force on Lung Cancer.[12] Although T, N, and M

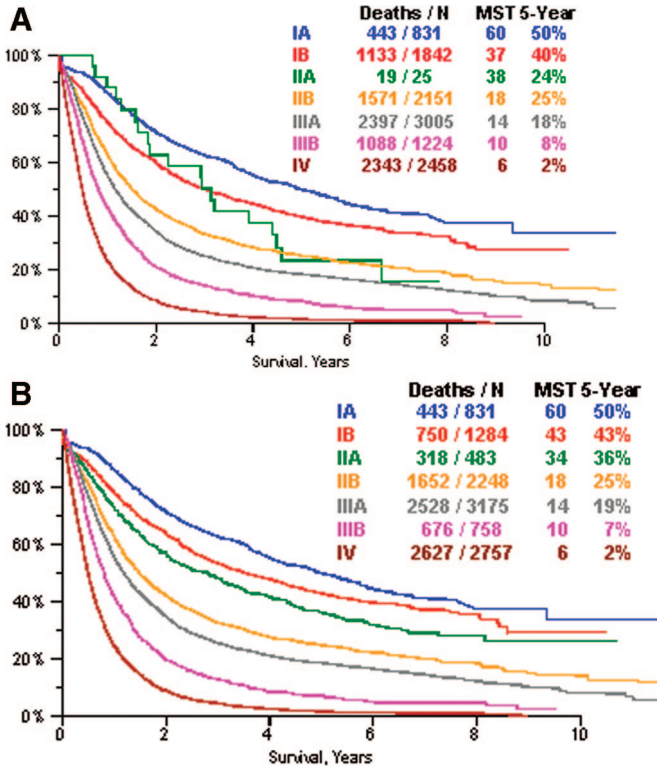

FIGURE 2. Overall survival, expressed as median survival time (MST) and 5-year survival, by clinical stage using the sixth edition of TNM (*A*) and proposed International Association of the Study of Lung Cancer recommendations (*B*).

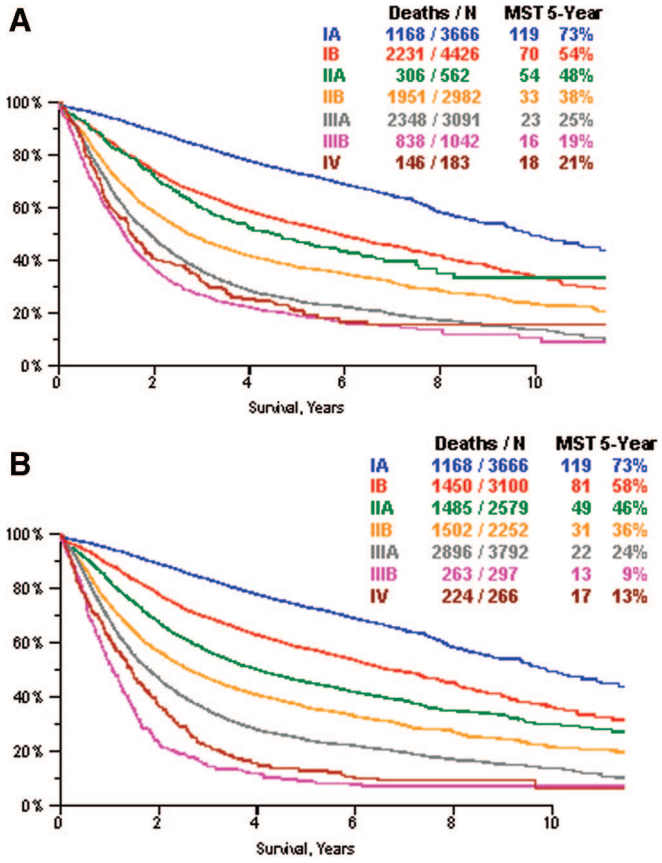

FIGURE 3. Overall survival, expressed as median survival time (MST) and 5-year survival, by pathologic stage using sixth edition of TNM (*A*) and proposed International Association of the Study of Lung Cancer recommendations (*B*).

categories were shown to have differing prognoses, there was no validation presented to justify the individual descriptors. In addition, of the 18 possible TNM subsets in that edition, seven contained fewer than 100 cases, some as few as 24 cases, and four other subsets contained too few cases for any analysis. In successive revisions, new descriptors were added as deemed necessary. In some situations, as with additional pulmonary nodules,[2] these were added to existing T, N, and M categories retaining the existing TNM stage subsets and stage groupings. In other revisions, for example, the division of T3 and T4 in the fourth edition,[13] existing descriptors were expanded and divided into new TNM subsets and new stage groupings. Although changes in TNM subsets and stage groupings were internally validated in a limited way, there was no external validation presented and individual descriptors were not validated. To a large extent, the creation of new descriptors in earlier revisions and their accommodation within the TNM classification for lung cancer was driven largely by existing treatment algorithms.

The validation process has been an integral part of this project. The internal and external validation of the T, N, and M descriptors proposed by this project[5–7] and that of the TNM stage groupings suggested in this article will be presented in another article in this journal.[10] Such intensive validation has only been possible by the enormous size of the database and the international spread of the contributions to this project from the lung cancer community. This has, however, led us to arrive at decisions that we recognize will create problems for our colleagues in this field. The necessity to sacrifice backward compatibility with existing databases in the search for a staging system that is manageable in clinical practice has already been mentioned. We further recognize that moving some descriptors within stage categories and the proposed changes to the stage groupings will cut across established treatment algorithms. The moving of the larger, node-negative T2 tumors (T2b cases >5 cm in greatest dimension) and tumors >7 cm in greatest dimension (which would become T3) from stage IB into stage IIA and stage IIB, respectively, will clearly raise the question as to whether such cases should have adjuvant chemotherapy after complete resection. Although there is still doubt as to the value of adjuvant chemotherapy after complete resection for node negative cases in stage IB,[14,15] at least two large trials have shown a benefit for node-positive cases in stages II and IIIA.[16,17] The question as to whether these larger node-negative tumors benefit from adjuvant therapy will only be resolved by large, prospective, randomized trials. The reassignment of cases with additional nodules in an ipsilateral, nonprimary tumor–bearing lobe into a T4 descriptor rather than an M1 descriptor and the relocation of T4 N0 M0 and T4 N1 M0 cases into stage IIIA will also lead to questions as to

TABLE 6. Cox Proportional Hazards Regression Models for the Sixth Edition of TNM and Proposed Clinical Stage Groupings (IASLC)

Clinical Stage (Sixth Edition and IASLC Proposed) Modeled as Indicator Variables

	Hazard Ratio		*p*	
Comparisons	**Sixth Edition**	**IASLC**	**Sixth Edition**	**IASLC**
IB vs. IA	1.31	1.19	<0.0001	0.0035
IIA vs. IB	1.35	1.23	0.1978	0.0020
IIB vs. IIA	1.20	1.46	0.4344	<0.0001
IIIA vs. IIB	1.30	1.27	<0.0001	<0.0001
IIIB vs. IIIA	1.47	1.54	<0.0001	<0.0001
IV vs. IIIB	1.71	1.64	<0.0001	<0.0001
R^2	25.86	26.77		

Clinical Stage (Sixth Edition and IASLC Proposed) Modeled as Ordered Variables

	Hazard ratio		*p*	
Variable	**Sixth Edition**	**IASLC**	**Sixth Edition**	**IASLC**
Stage	1.36	1.38	<0.0001	<0.0001

Adjusted for cell type, sex, age, and region (n = 11,536 (8944 events). IASLC, International Association of the Study of Lung Cancer.

TABLE 7. Cox Proportional Hazards Regression Models for the Sixth Edition TNM and Proposed Pathologic Stage Groupings (IASLC)

Pathologic Stage (Sixth Edition and IASLC Proposed) as Indicator Variables

	Hazard Ratio		*p*	
Comparisons	**Sixth Edition**	**IASLC**	**Sixth Edition**	**IASLC**
IB vs. IA	1.72	1.55	<0.0001	<0.0001
IIA vs. IB	1.28	1.44	<0.0001	<0.0001
IIB vs. IIA	1.26	1.29	0.0002	<0.0001
IIIA vs. IIB	1.48	1.47	<0.0001	<0.0001
IIIB vs. IIIA	1.27	1.79	<0.0001	<0.0001
IV vs. IIIB	0.91	0.86	0.2921	0.0974
R^2	29.44	30.40		

Pathologic Stage (Sixth Edition and IASLC Proposed) Modeled as Ordered Variables

	Hazard Ratio		*p*	
Variable	**Sixth Edition**	**IASLC**	**Sixth Edition**	**IASLC**
Stage	1.35	1.40	<0.0001	<0.0001

Adjusted for cell type, sex, age, and region (n = 15,952 (8988 events). IASLC, International Association of the Study of Lung Cancer.

TABLE 8. Proposed TNM Stage Groupings

Occult Carcinoma	**TX**	**N0**	**M0**
Stage 0	Tis	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a, b

the appropriate treatment algorithm. The limitations of our database do not allow us to be certain whether this reassignment is appropriate for cases with multiple additional tumor nodules or for all T4 cases. Multimodality treatment models, some including surgery, will no doubt evolve, informed by appropriate trials. In other situations, the changes suggested for inclusion in the seventh edition of the *TNM Classification of Malignant Tumours* might better reflect current practice as with the move of cases with malignant pleural effusions into an M category from a T category. Within our database, there was a clear difference in prognosis between patients with metastases to the ipsilateral pleura or contralateral lung and those with metastases at distant sites outside the thorax. In general, the latter have the worst prognosis and have been historically considered as stage IV and candidates for primarily systemic treatment. Within the cases proposed in an expanded stage IV, there is still a prognostic difference between those with spread within the thorax and those with metastases to distant sites, and therefore differentiating between M1a and M1b seems to be of relevance.

These recommendations have been based on the findings of a large international database. The number of cases recruited is 15 to 20 times larger than that which informed any previous revision. Data have been donated by 46 sources in 19 countries. We are all immensely grateful for the support offered by colleagues around the world. Although the treatment of these NSCLC cases included surgery in 53% of the patients, there were 30% in which chemotherapy was used and 29% in which radiotherapy was used. The data were collected from cases treated over a relatively short period during which the techniques used in clinical staging were reasonably standardized worldwide. The recommendations have been, for the first time, intensively validated. Internal validation has ensured that the recommendations are supported by data from all geographic areas and across all types of databases. External validation has been established against the Surveillance, Epidemiology, and End Results Program database.

There are, however, limitations to this project. The volume of data and the international nature of the data sources have made data audit extremely difficult, and, as a result, only limited checks for consistency have been possi-

ble. There are glaring deficiencies in the global distribution of the data with no data at all being included from Africa, South America, or the Indian subcontinent. Other vast countries such as Russia, China, and Indonesia are not represented or only poorly represented. Although less surgically dominated than previous databases, the spread of treatment modalities does not reflect the practice in most institutions. The time period under study predates the widespread and routine use of positron emission tomography, which has had an enormous impact on clinical staging algorithms. In any retrospective database, one has to collect the data that was considered important by each source, and this reflects the use for which the data were collected. Although we have an enormous amount of data on some descriptors, such as tumor dimension, we have too little on many to prove or disprove the validity of some descriptors.

We hope that our colleagues in clinical practice will recognize that the changes suggested by this project are driven by the data available to us from a database of more than 68,000 cases. Even with the acknowledged limitations of the database, its breadth has allowed the application of evidence-based standards in terms of statistical power, reliability, and scientific validity that were not possible in previous revisions. Inevitably, existing treatment algorithms will be challenged, but we hope by such rigorous analysis of large volumes of data, the utility of the TNM classification for lung cancer will be strengthened. It is our intention to ensure that the expansion of the database, including the prospective collection of data over the coming years, will ensure further, carefully validated proposals concerning thoracic malignancies for the eighth edition of the *TNM Classification of Malignant Tumours* and beyond.

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APPENDIX

IASLC International Staging Committee

P. Goldstraw (Chairperson), Royal Brompton Hospital, London, UK; H. Asamura, National Cancer Centre Hospital, Tokyo, Japan; D. Ball, Peter MacCallum Cancer Centre, Melbourne, Australia; V. Bolejack, Cancer Research and Biostatistics, Seattle, WA, USA; E. Brambilla, Laboratoire de Pathologie Cellulaire, Grenoble Cedex, France; P. A. Bunn, University of Colorado Health Sciences, Denver, CO, USA; D. Carney, Mater Misericordiae Hospital, Dublin, Ireland; K. Chansky, Cancer Research and Biostatistics, Seattle, WA, USA; T. Le Chevalier, Institute Gustave Roussy, Villejuif, France; J. Crowley, Cancer Research and Biostatistics, Seattle, WA, USA; R. Ginsberg (deceased), Memorial Sloan-Kettering Cancer Center, New York, NY, USA; D. Giroux, Cancer Research and Biostatistics, Seattle, WA, USA; P. Groome, Queen's Cancer Research Institute, Kingston, Ontario, Canada; H. H. Hansen (retired), National University Hospital, Copenhagen, Denmark; P. Van Houtte, Institute Jules Bordet, Bruxelles, Belgium; J.-G. Im, Seoul National University Hospital, Seoul, South Korea; J. R. Jett, Mayo Clinic, Rochester, MN, USA; H. Kato (retired), Tokyo Medical University, Tokyo, Japan; C. Kennedy, University of

Sydney, Sydney, Australia; M. Krasnik, Gentofte Hospital, Copenhagen, Denmark; J. van Meerbeeck, University Hospital, Ghent, Belgium; T. Naruke (deceased), Saiseikai Central Hospital, Tokyo, Japan; E. F. Patz, Duke University Medical Center, Durham, NC; P. E. Postmus, Vrije Universiteit Medical Center, Amsterdam, The Netherlands; R. Rami-Porta, Hospital Mutua de Terrassa, Terrassa, Spain; V. Rusch, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; J. P. Sculier, Institute Jules Bordet, Brussels, Belgium; Z. Shaikh, Royal Brompton Hospital, London, UK; F. A. Shepherd, University of Toronto, Toronto, Ontario, Canada; Y. Shimosato (retired), National Cancer Centre, Tokyo, Japan; L. Sobin, Armed Forces Institute of Pathology, Washington, DC; W. Travis, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; M. Tsuboi, Tokyo Medical University, Tokyo, Japan; R. Tsuchiya, National Cancer Centre, Tokyo, Japan; E. Vallieres, Swedish Cancer Institute, Seattle, WA, USA; J. Vansteenkiste, Leuven Lung Cancer Group, Leuven, Belgium; Yoh Watanabe (deceased), Kanazawa Medical University, Uchinada, Japan; and H. Yokomise, Kagawa University, Kagawa, Japan.

Participating Institutions

O. Visser, Amsterdam Cancer Registry, Amsterdam, The Netherlands; R. Tsuchiya and T. Naruke (deceased), Japanese Joint Committee of Lung Cancer Registry, Japan; J. P Van Meerbeeck, Flemish Lung Cancer Registry-VRGT, Brussels, Belgium; H. Bülzebruck, Thorax-Klinik am Universitatsklinikum, Heidelberg, Germany; R. Allison and L. Tripcony, Queensland Radium Institute, Herston, Australia; X. Wang, D. Watson and J. Herndon, Cancer and Leukemia Group B (CALGB), USA; R. J. Stevens, Medical Research Council Clinical Trials Unit, London, UK; A. Depierre, E. Quoix, and Q. Tran, Intergroupe Francophone de Cancerologie Thoracique (IFCT), France; J. R. Jett and S. Mandrekar, North Central Cancer Treatment Group (NCCTG), USA; J. H. Schiller and R. J. Gray, Eastern Cooperative Oncology Group (ECOG), USA; J. L. Duque-Medina and A. Lopez-Encuentra, Bronchogenic Carcinoma Co-operative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S), Spain; J. J. Crowley, Southwest Oncology Group (SWOG), USA; J. J. Crowley and K. M. W. Pisters, Bimodality Lung Oncology Team (BLOT), USA; T. E. Strand, Cancer Registry of Norway; S. Swann and H. Choy, Radiation Therapy Oncology Group (RTOG), USA; R. Damhuis, Rotterdam Cancer Registry, The Netherlands; R. Komaki and P. K. Allen, M. D. Anderson Cancer Center–Radiation Therapy (MDACC-RT), Houston, TX, USA; J. P. Sculier and M. Paesmans, European Lung Cancer Working Party (ELCWP); Y. L. Wu, Guangdong Provincial People's Hospital, P. R. China; M. Pesek and H. Krosnarova, Faculty Hospital Plzen, Czech Republic; T. Le Chevalier and A. Dunant, International Adjuvant Lung Cancer Trial (IALT), France; B. McCaughan and C. Kennedy, University of Sydney, Australia; F. Shepherd and M. Whitehead, National Cancer Institute of Canada (NCIC); J. Jassem and W. Ryzman, Medical University of Gdansk, Poland; G. V. Scagliotti and P. Borasio, Università Degli Studi di Torino, S. Luigi Hospital, Orbassano, Italy; K. M. Fong and L. Passmore, Prince Charles Hospital, Brisbane, Australia; V. W. Rusch and B. J. Park, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; H. J. Baek, Korea Cancer Centre Hospital, Seoul, South Korea; R. P. Perng, Taiwan Lung Cancer Society, Taiwan; R. C. Yung, A. Gramatikova, Johns Hopkins University, Baltimore, MD, USA; J. Vansteenkiste, Leuven Lung Cancer Group (LLCG), Leuven, Belgium; C. Brambilla and M. Colonna, Grenoble University Hospital–Isere Cancer Registry, Grenoble, France; J. Hunt and A. Park, Western Hospital, Melbourne, Australia; J. P. Sculier and T. Berghmans, Institute of Jules Bordet, Brussels, Belgium; A. K. Cangir, Ankara University School of Medicine, Ankara, Turkey; D. Subotic, Clinical Centre of Serbia, Belgrade, Serbia; R. Rosell and V. Aberola, Spanish Lung Cancer Group (SLCG), Spain; A. A. Vaporciyan and A. M. Correa, M. D. Anderson Cancer Center–Thoracic and Cardiovascular Surgery (MDACC-TCVS), Houston, TX, USA; J. P. Pignon, T. Le Chevalier and R. Komaki, Institut Gustave Roussy (IGR), Paris, France; T. Orlowski, Institute of Lung Diseases, Warsaw, Poland; D. Ball and J. Matthews, Peter MacCallum Cancer Institute, East Melbourne, Australia; M. Tsao, Princess Margaret Hospital, Toronto, Ontario, Canada; S. Darwish, Policlinic of Perugia, Perugia, Italy; H. I. Pass and T. Stevens, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; G. Wright, St. Vincent's Hospital, Victoria, Australia; and C. Legrand and J. P. van Meerbeeck, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium.