ORIGINAL ARTICLE

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

Peter Goldstraw, FRCS,[a,*] Kari Chansky, MS,[b] John Crowley, PhD,[b] Ramon Rami-Porta, MD,[c] Hisao Asamura, MD,[d] Wilfried E. E. Eberhardt, MD,[e] Andrew G. Nicholson, FRCP,[f] Patti Groome, PhD,[g] Alan Mitchell, MS,[b] Vanessa Bolejack, MPH,[b] on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions

[a]*Department of Thoracic Surgery, Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College, London, United Kingdom*
[b]*Cancer Research and Biostatistics, Seattle, WA, USA*
[c]*Department of Thoracic Surgery, Hospital Universitari Mutua Terrassa, University of Barcelona, and CIBERES Lung Cancer Group, Terrassa, Barcelona, Spain*
[d]*Division of Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan*
[e]*West German Cancer Centre, University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany*
[f]*Department of Pathology, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, United Kingdom*
[g]*Queen's Cancer Research Institute, Kingston, ON, Canada*

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ABSTRACT

The IASLC Staging and Prognostic Factors Committee has collected a new database of 94,708 cases donated from 35 sources in 16 countries around the globe. This has now been analysed by our statistical partners at Cancer Research And Biostatistics and, in close collaboration with the members of the committee proposals have been developed for the T, N, and M categories of the 8th edition of the TNM Classification for lung cancer due to be published late 2016. In this publication we describe the methods used to evaluate the resultant Stage groupings and the proposals put forward for the 8th edition.

Keywords: Lung cancer; Staging; Prognostic factors

Introduction

The seventh edition of the tumor, node, and metastasis (TNM) classification for lung cancer was published in September 2009[1,2] and enacted in January 2010.[3,4] The revision was novel in that the changes were based entirely on the proposals of the International Association for the Study of Lung Cancer (IASLC) International Staging Project.[5–13] The project was organized and funded by the IASLC and collected and analyzed more than 100,000 cases contributed by colleagues at 46 centers in more than 19 countries around the world. Data entry and analysis were performed by Cancer Research and Biostatistics (CRAB), a not-for-profit organization based in Seattle, Washington. Validation, both internal and external, was more rigorous than that undertaken in any previous revision.[14] The success of this project led the IASLC to expand the remit of its Staging and Prognostic

*Corresponding author.

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Address for correspondence: Peter Goldstraw, FRCS, 33, Ridge Hill, Dartmouth, TQ6 9PE, UK. E-mail: p.goldstraw@imperiaL.ac.uk

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Factors Committee and, with other collaborating organizations, develop proposals for the eighth edition of the TNM classification for other thoracic malignancies in addition to lung cancer.

In preparation for the impending eighth edition of TNM staging for lung cancer, the committee and partners in CRAB developed a new database. The characteristics of the new database[15] and the committee's proposals for changes to the T, N, and M descriptors[16–18] have been published elsewhere; here we present the proposals for the resultant TNM stage groupings. All these proposals will be submitted to the Union for International Cancer Control and the American Joint Committee on Cancer for inclusion in the eighth edition of the TNM classification for lung cancer, which is due to be published in late 2016 and enacted in January 2017.

Methods

During the transition from adopting the seventh edition to working toward the eighth edition, a new data dictionary was developed in conjunction with a new Electronic Data Capture (EDC) system. Housed at CRAB, the EDC system has provided a total of 4667 cases that were used in this latest revision, and another 90,041 cases have been contributed by individual sites in retrospective fashion and mapped to be compatible with the EDC data fields.[15] The database contains cases that were treated using all modalities of care, including multimodality treatment, and diagnosed between 1999 and 2010. For the analyses of TNM categories presented here, only cases with a histologic diagnosis of non–small cell lung cancer and complete staging information were included. For cases in which chemotherapy was received before surgery (yp cases), only clinical stage was considered.

Candidate proposals for overall TNM stage groups were developed in conjunction with proposed changes to the T and M categories.[16,17] The proposed changes are highlighted in the full list of T, N, and M descriptors shown in Table 1, which also incorporates the subsequent recommendations of the IASLC on classification of minimally invasive adenocarcinoma.[18] The existing N descriptors were validated, and no changes were proposed for the eighth edition.[19]

The new T and M proposals were applied to the training data set, and the resultant TNM subsets and the numbers of cases in each subset by clinical stage and pathologic stage are shown in Tables 2 and 3. A small number of candidate stage grouping schemes were developed initially on the basis of the M0 cases by using a recursive partitioning and amalgamation algorithm.[20] The analysis was applied using the statistical package R, Version 3.1.0 (R Project for Statistical Computing, Vienna, Austria). The algorithm generates 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 for the adaptive nature of the splitting algorithm (Fig. 1). The tree-based analysis was stratified on the basis of type of data submission: registry versus all others. The analysis grouped cases on the basis of the best stage (pathologic if available, otherwise clinical) after determination of best split points on the basis of overall survival using an ordered variable for the newly proposed T categories and the current N categories (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 the newly proposed T and M categories (N = 25,911 M0 cases plus 599 M1 cases), with 12,931 cases reserved for subsequent internal validation. The random selection process was stratified by type of database submission and time period of case entry (1999–2004 versus 2005–2010). M1 cases were also split but were not the focus of the tree-based analysis.

An ordered list of groupings was constructed from the terminal nodes of the survival tree. With this list 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 relevance to clinical practice and was arrived at by consensus.

Candidate TNM stage grouping schemes were evaluated in part by assessing overall survival by clinical, pathologic, and best stage. Survival was measured from the date of diagnosis for clinically staged tumors and from the date of surgery for pathologically staged tumors and calculated by the Kaplan-Meier method. Adjusted survival curves[21,22] were drawn using inverse probability weights applied to the survival calculations on the basis of the proportion of cases that were from registry databases (versus others) in each stage category. This method was used in light of the different overall survival prognosis in registry databases in general, combined with the disproportionate representation of registry cases in some of the stage groups. Contrasts between adjacent stage groups were evaluated by Cox regression analysis, adjusted for baseline factors (age, performance status, and cell type) and type of database submission by using the SAS System for Windows Version 9.4 PHREG procedure (SAS, Cary, NC).

Table 1. Proposed T, N, and M descriptors for the eighth edition of TNM classification for lung cancer

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by 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(mi)	**Minimally invasive adenocarcinoma**[b]
T1a	**Tumor ≤1 cm in greatest dimension**[a]
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension**[a]
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension**[a]
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features[c]: - **Involves main bronchus regardless of distance from the carina but without involvement of the carina** - Invades visceral pleura - **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm,** mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
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	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis**[e]
M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition are in bold.
[a]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.
[b]Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.
[c]T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and 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.
[e]This includes involvement of a single distant (nonregional) lymph node.

Results

Figure 1 shows the survival tree based on best stage in the training set with M0 cases only (N = 25,911). The ordered list of terminal nodes, with stratified hazard ratios relative to the best prognosis node (T1aN0), is shown in Table 4. The proposed eighth edition of the TNM stage groupings are summarized in Table 5, in which those TNM subsets that the proposals advocate moving from their present stage grouping are highlighted. The transfer of some cases from within a category in the present staging system to another in the proposals for the eighth edition of the TNM classification

Table 2. Distribution of T, N, and M categories in the training set (clinical classification)

Proposed T/M categories	N category				
	N0	N1	N2	N3	Total
T1a	781	7	19	6	813
T1b	3105	68	124	30	3327
T1c	2417	142	208	32	2799
T2a	1928	268	372	50	2618
T2b	585	131	183	36	935
T3	837	191	344	77	1449
T4	1711	392	1642	909	4654
M1a	64	9	77	127	277
M1b	39	16	67	85	207
M1c	67	15	120	196	398
Total	11,534	1239	3156	1548	17,477

T, tumor; N, node; M, metastasis.

and creation of new descriptors and categories have led to the migration of certain TNM subsets between stage groups. For example, an N0 case that involves either diaphragm invasion or a 7-cm tumor that is classified as T3 according to the definitions in the seventh edition, moves from stage IIB to IIIA by virtue of being redefined as T4 by the eighth edition. A new stage, IIIC, consists of T3–T4N3M0 cases, which showed a worse prognosis than the others. The numbers of available cases (training and validation sets combined) occupying each of these T, N, and M categories by best stage are shown in Table 6.

Figures 2 and 3 show weighted survival by stage according to the seventh edition of TNM and the newly proposed TNM stage based on the entire set of cases available for reclassification, including the M1 cases: 17,477 cases clinically staged I–IV and 31,836 cases with a pathologic stage. Tables 7 and 8 show the statistics from adjusted Cox proportional hazards regression modeling based on the seventh edition of TNM and the proposed new system for clinical and pathologic stage, respectively, using the new database collected for the eighth edition. The hazard ratios between adjacent stage group categories are uniformly significant for stage in both the seventh edition and the more finely parsed proposed eighth edition. The additional stage categories within stage I and stage III in the proposed system are sufficiently distinct from one another. The weighted clinical survival estimates for the proposed eighth edition (Fig. 2B) show overlap between stages IIIC (T3–T4N3) and IVA (M1a cases with metastases restricted to the thoracic cavity and M1b cases with single metastasis outside the thoracic cavity). This overlap is not evident in the multivariate analyses, in which the hazard ratio for the comparison between stage IVA and stage IIIC is 1.75 ($p < 0.0001$). The overlap in the survival curves may be partly a result of the distribution of registry and non-registry cases despite the attempt to correct for this by weighting. There are no registry cases in the stage IV groups, which had to have a sufficient description of metastatic disease to be classified as M1a, M1b, or M1c.

Table 3. Distribution of T, N, and M categories in the training set (pathologic classification)

Proposed T/M categories	N categories				
	N0	N1	N2	N3	Total
T1a	1390	45	49	2	1486
T1b	5638	311	392	7	6348
T1c	4403	484	515	13	5415
T2a	6102	1223	1526	55	8906
T2b	1640	485	490	16	2631
T3	2683	795	1025	39	4542
T4	1447	546	613	30	2636
Total	23,303	3889	4610	162	31,964

T, tumor; N, node; M, metastasis.

For both the clinical and pathologic stage models, there is a slight increase in the value for R^2, which is an estimate of the percent variance explained[23] by the models described earlier, for the proposed eighth edition of the staging scheme. For clinical stage, the R^2 value for the seventh edition of the staging scheme in the complete data set is 67.5. The R^2 value for the scheme in the proposed eighth edition is 68.3. Likewise, for pathologic stage, the R^2 value for the seventh edition of the classification is 45.7 versus 46.9 for the proposed classification.

The proposed stage groupings are summarized in Table 9.

Validation

The proposals derived from the training set were internally validated against the validation set of 12,931 cases (5785 classifiable by clinical stage and 10,558 classifiable by pathologic stage). The validation set generated survival curves that were generally similar to those in the training set, and the 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 database type were all statistically significant for the clinical and the pathologic staging data, with one exception. The comparison of clinical stage IIA versus IB disease was not significant, with a hazard ratio of 1.35 and a p value of 0.18. The hazard risk is slightly higher than that found when analyzing the combined training and validation sets; however, the p value is reduced, possibly because the validation set contains only 183 cases in the clinical stage IIA.

External validation against an outside database is desirable. In this regard, the North American Surveillance, Epidemiology, and End Results Registries (SEER) database was a valuable tool for development of the

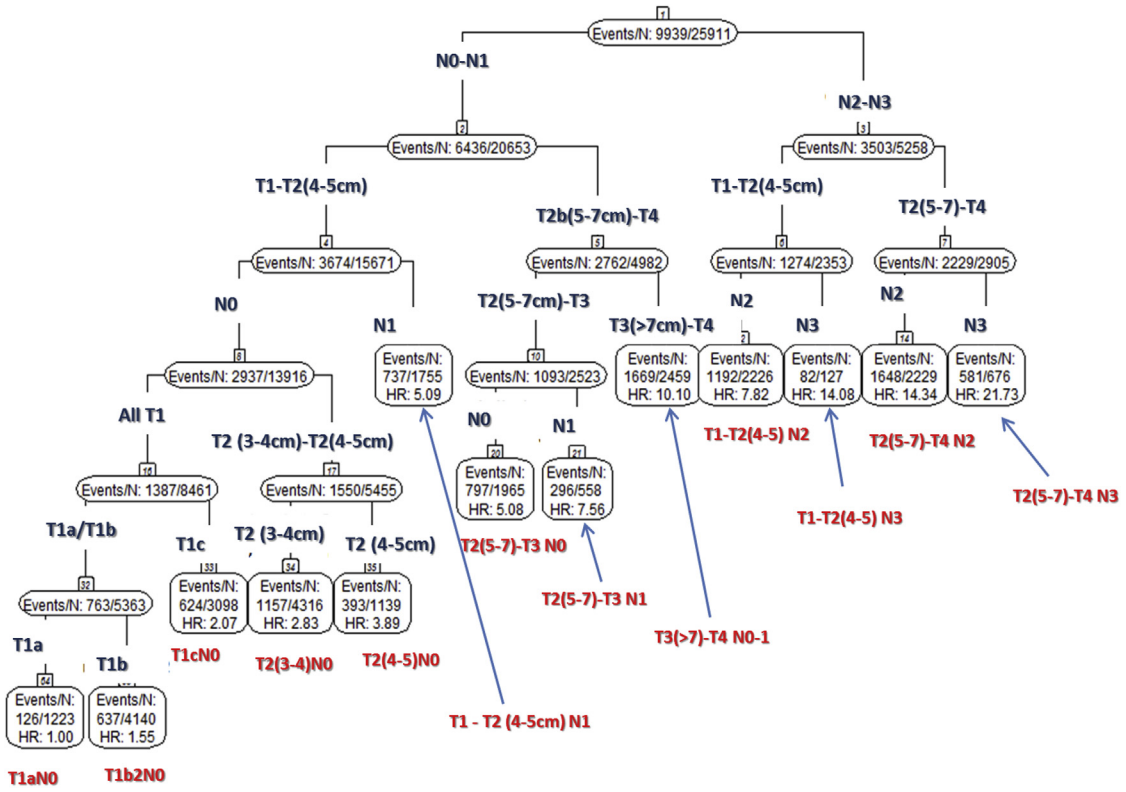


Figure 1. Recursive partitioning and amalgamation-generated survival tree based on best stage for 25,911 M0 training set cases. T and N categories are modeled as ordered variables. Stratified hazard ratios are given relative to the leftmost terminal node, T1aN0.

seventh edition. For the current proposal, certain cases in the SEER data cannot be classified. Although additional site-specific factors have been collected during recent years (2010–2012), it is, for example, impossible to identify and reclassify cases with diaphragm invasion that were classified as T3 in the seventh edition. In any case, given the fact that the additional site-specific factors were not in effect for earlier years, too few cases with the appropriate time frame are available to be classified. The SEER data have been classified according to the seventh edition, however. Consequently, a comparison of the IASLC database with SEER from the standpoint of overall survival across stage categories in the seventh edition was performed to assess the validity of the IASLC database.

Table 4. Terminal nodes defined on the basis of best stage from a stratified tree-based analysis (recursive partitioning analysis) of the training data set. Hazard ratios are relative to the best prognosis group (T1aN0) and are stratified on type of database submission: registry versus others

Terminal node	Sample size (training set)	Hazard ratio
T1a N0	1223	1.00
T1b N0	4140	1.55
T1c N0	3098	2.07
T2a N0	4316	2.83
T2b N0	1139	3.89
T3 N0	1965	5.08
T1a-T2b N1	1755	5.09
T3 N1	558	7.56
T1a-T2b N2	2226	7.82
T4 N0-N1	2459	10.10
T1a-T2b N3	127	14.08
T3-T4 N2	2229	14.34
T3-T4 N3	676	21.73

T, tumor; N, node.

Supplemental Figure 1 shows survival according to stage in the seventh edition for the SEER database and the IASLC database. Stage for stage, the median survival time is consistently higher in the IASLC database, which is not unexpected given the various data sources, only a portion of which originated from a national registry. When the difference in survival between the SEER data and the IASLC data is explored by using Cox regression analysis with stage and member database as factors, however, adjusting for surgical management diminishes the difference between the two databases. The adjusted hazard ratio for overall survival is 0.91 in favor of the IASLC database (95% confidence interval 0.85–0.96, $p < 0.0001$). The analysis data set for TNM stage from the IASLC database is 87% surgically managed cases

Table 5. Descriptors and T and M categories in the seventh edition and as proposed for the eighth edition[a]

		N categories			
		Overall stage			
Descriptor in 7th edition	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

[a]Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
T, tumor; M, metastasis.

versus 31% of the SEER cases used for the comparison. The unadjusted hazard ratio is 0.73 (95% confidence interval 0.68–0.77).

Discussion

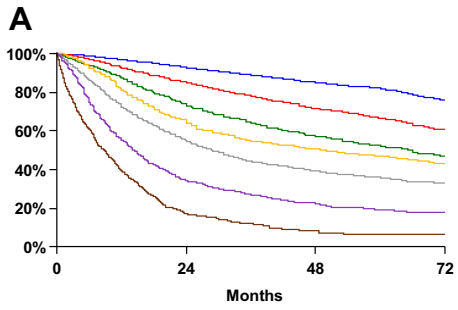
This publication sets out the IASLC proposals for stage groupings in the eighth edition of the TNM Classification for Lung Cancer. The database used in this analysis consisted entirely of cases of non–small cell lung cancer; a separate publication addresses the recommendations for small cell lung cancer.[24]

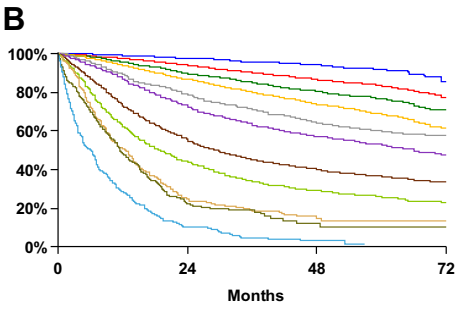
The IASLC Staging and Prognostic Factors Committee remains committed to the accumulation of prospectively acquired data using the data set specifically

Table 6. Sample sizes for TNM subsets providing the basis for proposed changes, best stage

		N0		N1		N2		N3	
Descriptor in seventh edition	Proposed T/M	Overall stage	Sample size	Overall stage	Sample size	Overall stage	Sample size	Overall stage	Sample size
T1 ≤ 1 cm	T1a	IA ≥ IA1	1765	IIA ≥ IIB	47	IIIA	59	IIIB	4
T1 > 1-2 cm	T1b	IA ≥ IA2	6127	IIA ≥ IIB	321	IIIA	444	IIIB	20
T1 > 2-3 cm	T1c	IA ≥ IA3	4606	IIA ≥ IIB	492	IIIA	596	IIIB	37
T2 > 3-4 cm	T2a	IB	6382	IIA ≥ IIB	1250	IIIA	1666	IIIB	89
T2 > 4-5 cm	T2b	IB ≥ IIA	1689	IIA ≥ IIB	497	IIIA	559	IIIB	35
T2 > 5-7 cm	T3	IIA ≥ IIB	1244	IIB ≥ IIIA	418	IIIA ≥ IIIB	455	IIIB ≥ IIIC	45
T3 structures	T3	IIB	1666	IIIA	432	IIIA ≥ IIIB	736	IIIB ≥ IIIC	55
T3 > 7 cm	T4	IIB ≥ IIIA	870	IIIA	316	IIIA ≥ IIIB	320	IIIB ≥ IIIC	33
T3 diaphragm	T4	IIB ≥ IIIA	47	IIIA	16	IIIA ≥ IIIB	22	IIIB ≥ IIIC	0
T3 endobronchial location/atelectasis									
>3-4 cm	T2a	IIB ≥ IB	18	IIIA ≥ IIB	18	IIIA	10	IIIB	1
>4-5 cm	T2b	IIB ≥ IIA	11	IIIA ≥ IIB	2	IIIA	9	IIIB	1
T4	T4	IIIA	1862	IIIA	538	IIIB	1770	IIIB ≥ IIIC	893
M1a	M1a	IV ≥ IVA	62	IV ≥ IVA	11	IV ≥ IVA	100	IV ≥ IVA	145
M1b single lesion	M1b	IV ≥ IVA	38	IV ≥ IVA	13	IV ≥ IVA	68	IV ≥ IVA	74
M1b multiple lesions	M1c	IV ≥ IVB	59	IV ≥ IVB	18	IV ≥ IVB	128	IV ≥ IVB	191

TNM, tumor, node, metastasis.





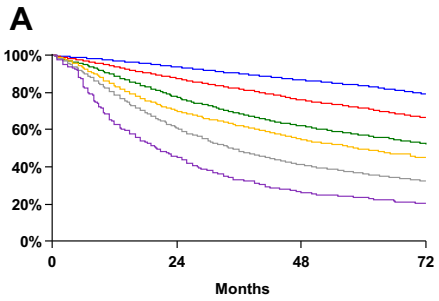
7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

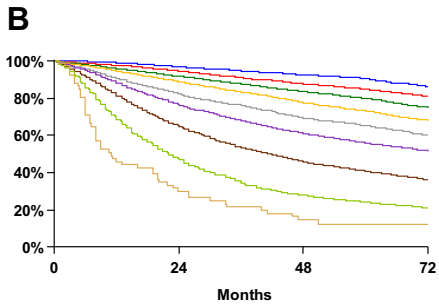
Figure 2. Overall survival by clinical stage according to the seventh edition (*A*) and the proposed eighth edition (*B*) groupings using the entire database available for the eighth edition. MST, median survival time. Survival is weighted by type of database submission: registry versus other.

designed to inform revisions to the TNM classification.[25] However, the added complexity of such data accrual has resulted in our continuing to depend largely on retrospective accrual of data that were collected mostly for other purposes. The committee accepted the advice of its statisticians and epidemiologists that new cases be kept separate from the data accrued for the seventh edition. This decision has been vindicated by the improved survival by stage for the newly acquired data set. This improved survival may reflect improvements in diagnosis, such as the increasing vogue for computed tomography (CT) screening; improvements in the staging algorithm with the widespread use of positron emission tomography scanning and less invasive mediastinal staging by endobronchial ultrasound and endoscopic ultrasound; and improvements in treatment, including the following: the use of adjuvant therapy after complete resection, the availability of radical options for treating less fit individuals with stereotactic body radiation therapy and minimally invasive surgical options, and targeted agents providing improved results in stage IV disease because their toxicity profile allows consideration of such treatment in patients with worse performance levels. Differences also exist between the data sets developed for the revisions leading to the seventh and eighth editions of the TNM classification for lung cancer, however. The new data set has a higher proportion of cases from Asia—mostly from Japan, which contributed 41% of the total—and this difference has in turn resulted in the proportion of cases including surgery as a component of their treatment rising from 53% in the previous data set to 85% in the new one. In addition, there was an increase in the proportion of cases derived from registry data and a lack of cases from clinical trials. The net effect of all these variations was that although stage-for-stage survival increased in all stages, there was a relative worsening of survival for advanced stages, especially stage IIIB. We attempted to correct these biases by performing the tree-based analysis stratified by type of database and adjusting the survival curves by inverse probability weighting.

Changes to some T and M descriptors will result in these cases being assigned to a different stage than that to which they would have been assigned in the seventh edition. In addition, some TNM subsets have been moved to a new stage grouping. Although such changes might raise the issue of whether consequent changes to treatment algorithms are needed, it is important to remind ourselves that stage does not dictate treatment. Stage is one, and perhaps the single most important, of several prognostic factors that guide the appropriate treatment option(s) to offer the patient. Any change to established treatment



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1837 / 11423	NR	94%	83%
IB	2168 / 7711	NR	87%	71%
IIA	1514 / 3702	NR	77%	57%
IIB	1325 / 2776	58.9	70%	49%
IIIA	3467 / 5818	35.0	61%	36%
IIIB	364 / 506	20.0	45%	23%



Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

Figure 3. Overall survival by pathologic stage according to the seventh edition (*A*) and the proposed eighth edition (*B*) groupings using the entire database available for the eighth edition. MST, median survival time. Survival is weighted by type of database submission: registry versus other.

algorithms should be based on clinical judgment informed by prospective trials.

The seventh edition of the TNM classification for lung cancer placed additional emphasis on tumor size and, as could have been anticipated, size cut points have further proliferated in the proposals for the eighth edition, such that size will now be a descriptor in all T categories.

Some new stage groupings are proposed for the eighth edition of the TNM classification for lung cancer. The division of the category T1 into T1a, T1b, and T1c on the basis of new size cut points of 1 cm and 2 cm has resulted in these cases (when associated with the categories N0 and M0) being assigned to stage IA1, IA2, and IA3, respectively, and thus reflecting the statistically different

Table 7. Cox proportional hazards regression model output for the seventh edition of the TNM classification and proposed eighth edition clinical stage groupings using the entire database available for the eighth edition. Adjusted for age (70 years or older), sex, and histologic diagnosis (adenocarcinoma versus others). Stratified by type of database submission (registry versus others)

	Hazard ratio		*p*	
Stages Compared	7th edition	Proposed 8th edition	7th edition	Proposed 8th edition
IA2 vs. IA1	–	1.82	–	<0.0001
IA3 vs. IA2	–	1.40	–	<0.0001
IB vs. IA	1.75	–	<0.0001	–
IB vs. IA3	–	1.29	–	<0.0001
IIA vs. IB	1.57	1.30	<0.0001	0.0012
IIB vs. IIA	1.22	1.30	0.0046	0.0008
IIIA vs. IIB	1.28	1.48	<0.0001	<0.0001
IIIB vs. IIIA	1.57	1.38	<0.0001	<0.0001
IIIC vs. IIIB	–	1.36	–	<0.0001
IVA vs. IIIC	–	1.75	–	<0.0001
IVB vs. IVA	–	1.91	–	<0.0001
IV vs. IIIB	2.61	–	<0.0001	–

TNM, tumor, node, metastasis.

Table 8. Cox proportional hazards regression model output for the seventh edition of the TNM classification and proposed eighth edition pathologic stage groupings using the entire database available for the eighth edition. Adjusted for age (70 years or older), sex, histologic diagnosis (adenocarcinoma versus others), and type of database submission (registry versus others)

	Hazard ratio		*p*	
Comparison	7th edition	Proposed 8th edition	7th edition	Proposed 8th edition
IA2 vs. IA1	–	1.44	–	<0.0001
IA3 vs. IA2	–	1.31	–	<0.0001
IB vs. IA	1.68	–	<0.0001	–
IB vs. IA3	–	1.32	–	<0.0001
IIA vs. IB	1.66	1.29	<0.0001	<0.0001
IIB vs. IIA	1.22	1.40	<0.0001	<0.0001
IIIA vs. IIB	1.61	1.66	<0.0001	<0.0001
IIIB vs. IIIA	1.58	1.67	<0.0001	<0.0001
IIIC vs. IIIB	–	1.85	–	<0.0001

TNM, tumor, node, metastasis.

Table 9. Proposed stage groupings for the eighth edition of the TNM classification for lung cancer

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1a(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a-c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a-c**	**N2**	**M0**
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a-c**	**N3**	**M0**
	T2a-b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**

Note: Changes to the seventh edition are highlighted in bold and underlined.
TNM, tumor, node, metastasis; Tis, carcinoma in situ; T1a(mi), minimally invasive adenocarcinoma.

prognosis of such cases. These new cut points and the stage groupings should be used in any trials of novel therapies, such as sublobar resection and nonsurgical treatment options. They should not in themselves be taken as a constraint on the use of structured surveillance in studies of CT screening because the proportion of screen-detected tumors in our data set is unknown.

A new stage grouping has also been created for the most advanced local disease categories, T3 and T4 associated with N3 disease but category M0. Such cases will now be classified as stage IIIC, reflecting their worse outcome than that of cases involving tumors that remain in stage IIIB. The prognosis for stage IIIC cases is similar to that for stage IVA cases, but the separation is justified by the different treatment approaches used in such cases.

Finally, changes to classification of stage IV disease have been proposed. Cases with intrathoracic metastatic disease to the contralateral lung or with pleural/pericardial dissemination will remain classified as M1a disease. The category M1b will now be assigned to cases with is a single metastatic deposit (in one organ), and M1a and M1b cases will be moved to a new stage grouping, stage IVA. Although the survival rates in these two M1 categories are sufficiently similar to justify their inclusion in a single stage grouping, the committee believed that it would be useful to retain the separate M categories M1a and M1b for future data collection and analysis because some patients with oligometastatic disease are now receiving more aggressive local therapy in addition to systemic treatment. The more common situation involving multiple metastatic deposits, usually in more than one organ, will now be classified as M1c and staged as IVB.

Other changes to the stage groupings have been proposed. In some cases, the change will result from a T descriptor being allocated to a higher stage in the eighth edition, such as has occurred with T3 tumors, which have been thus classified because of invasion of the chest wall or some mediastinal structures when associated with N2 disease moving from stage IIIA in the seventh edition to IIIB in the eighth and, when associated with N3 disease, moving from stage IIIB to IIIC. Similarly, all subdivisions of the category T1 that are now associated with N1 disease will move from stage IIA to IIB. In other situations tumors may be allocated to a different T category in the eighth edition, which results in a change of stage as for the reclassification of tumors associated with diaphragmatic invasion to T4, and hence when associated with N0 disease, moving from stage IIB to IIIA. For some T and N categories both influences may affect the stage grouping assigned to a case. For example, the shift of tumors larger than 5 cm from T2b to T3 led to them being assigned to a higher stage grouping whatever the N category. When associated with N0 and N1 disease, such tumors move from IIA to IIB and from IIB to IIIA, respectively, because of the change in T category, whereas when they are associated with N2 or N3 disease, the shift from IIIA to IIIB and from IIIB to IIIC is the result of the change of stage that has been proposed for that TNM subset in the eighth edition.

Like the seventh edition, the eighth edition includes instances in which the power of the data requires changes that at first sight might appear counterintuitive. The transfer of tumors larger than 5 cm to the T3 category, leaving T2a for tumors larger than 3 cm but no larger than 4 cm and T2b for tumors larger than 4 cm but no larger than 5 cm should, if a variant of stage migration were in effect, result in a lower stage being assigned to these tumors for all N categories. In reality, the new data set showed that such cases should remain in the same stage grouping as assigned in the seventh edition, except when T2a cases were associated with N1 disease, which would mean that a higher stage grouping was appropriate. Will this change encourage wider consideration of adjuvant chemotherapy after the

complete resection of such small tumors (4 cm and smaller)? Such questions challenge us all to reconsider the treatment algorithms and test new options with appropriate clinical trials.

Central to the greater emphasis on tumor size as a descriptor that is now proposed in all T categories is the need to study an appropriate way in which to measure size. Appropriate measurement of size is especially important when dealing with mixed attenuation tumors, which are being found increasingly frequently as CT screening for lung cancer becomes more widely adopted and with the recently revised classification for adenocarcinoma. A discussion document on this topic has been published by the IASLC Staging and Prognostic Factors Committee.[18]

When presenting its proposals for the seventh edition of the TNM classification for lung cancer, we expressed the hope that through the support of the pharmaceutical industry and with the cooperation of its members and the generous donation of hard-earned data, the IASLC could go on to develop validated proposals for the eighth edition and beyond. This article is an important step in realizing that ambition.

As more detailed data are accrued, our survival analyses will inevitably permit sharper distinction between subsets within the present T, N, and M categories and the resultant stage groupings, thereby leading to proliferation of such categories and stage groupings, as well as to added complexity of the staging system. The IASLC Staging and Prognostic Factors Committee has strived to limit such changes to those that appear to have clinical relevance. Even so, the changes proposed for the eighth edition will further reduce backward compatibility within existing databases. This fact is certain to be an increasing issue with future revisions, and we can but caution those collecting data to "future proof" their data by collecting raw data wherever possible, especially when documenting tumor size.

The Staging and Prognostic Factors Committee of the IASLC presents these recommendations to inform the discussions leading to the eighth edition of the TNM classification for lung cancer. We hope that the thoracic oncology community finds the proposals of value and that when accepted, they will have a positive impact on the effectiveness of treatment for lung cancer, which will benefit patients around the globe.

Appendix

IASLC Staging and Prognostic Factors Committee

Peter Goldstraw, past chair, Royal Brompton Hospital and Imperial College, London, United Kingdom; Ramón Rami-Porta, chair, Hospital Universitari Mutua Terrassa, Terrassa, Spain; Hisao Asamura, chair elect, Keio University, Tokyo, Japan; David Ball, Peter MacCallum Cancer Centre, Melbourne, Australia; David G. Beer, University of Michigan, Ann Arbor, Michigan, United States; Ricardo Beyruti, University of São Paulo, Brazil; Vanessa Bolejack, Cancer Research And Biostatistics, Seattle, Washington, United States; Kari Chansky, Cancer Research And Biostatistics, Seattle, Washington, United States; John Crowley, Cancer Research And Biostatistics, Seattle, Washington, United States; Frank Detterbeck, Yale University, New Haven, Connecticut, United States; Wilfried Ernst Erich Eberhardt, West German Cancer Centre, University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Françoise Galateau-Sallé, Centre Hospitalier Universitaire, Caen, France; Dorothy Giroux, Cancer Research And Biostatistics, Seattle, Washington, United States; Fergus Gleeson, Churchill Hospital, Oxford, United Kingdom; Patti Groome, Queen's Cancer Research Institute, Kingston, Ontario, Canada; James Huang, Memorial Sloan-Kettering Cancer Center, New York, New York, United States; Catherine Kennedy, University of Sydney, Sydney, Australia; Jhingook Kim, Samsung Medical Center, Seoul, Republic of Korea; Young Tae Kim, Seoul National University, Seoul, Republic of Korea; Laura Kingsbury, Cancer Research And Biostatistics, Seattle, Washington, United States; Haruhiko Kondo, Kyorin University Hospital, Tokyo, Japan; Mark Krasnik, Gentofte Hospital, Copenhagen, Denmark; Kaoru Kubota, Nippon Medical School Hospital, Tokyo, Japan; Antoon Lerut, University Hospitals, Leuven, Belgium; Gustavo Lyons, British Hospital, Buenos Aires, Argentina; Mirella Marino, Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, M. D. Anderson Cancer Center, Houston, Texas, United States; Jan van Meerbeeck, Antwerp University Hospital, Edegem (Antwerp), Belgium; Alan Mitchell, Cancer Research And Biostatistics, Seattle, Washington, United States; Takashi Nakano, Hyogo College of Medicine, Hyogo, Japan; Andrew G. Nicholson, Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College, London, United Kingdom; Anna Nowak, University of Western Australia, Perth, Australia; Michael Peake, Glenfield Hospital, Leicester, United Kingdom; Thomas Rice, Cleveland Clinic, Cleveland, Ohio, United States; Kenneth Rosenzweig, Mount Sinai Hospital, New York, New York, United States; Enrico Ruffini, University of Torino, Torino, Italy; Valerie Rusch, Memorial Sloan-Kettering Cancer Center, New York, New York, United States; Nagahiro Saijo, National Cancer Center Hospital East, Chiba, Japan; Paul Van Schil, Antwerp University Hospital, Edegem (Antwerp), Belgium; Jean-Paul Sculier,

Institut Jules Bordet, Brussels, Belgium; Lynn Shemanski, Cancer Research And Biostatistics, Seattle, Washington, United States; Kelly Stratton, Cancer Research And Biostatistics, Seattle, Washington, United States; Kenji Suzuki, Juntendo University, Tokyo, Japan; Yuji Tachimori, National Cancer Center, Tokyo, Japan; Charles F. Thomas Jr., Mayo Clinic, Rochester, Minnesota, United States; William Travis, Memorial Sloan-Kettering Cancer Center, New York, New York, United States; Ming S. Tsao, The Princess Margaret Cancer Centre, Toronto, Ontario, Canada; Andrew Turrisi, Sinai Grace Hospital, Detroit, Michigan, United States; Johan Vansteenkiste, University Hospitals, Leuven, Belgium; Hirokazu Watanabe, National Cancer Center Hospital, Tokyo, Japan; Yi-Long Wu, Guangdong General Hospital, Guangzhou, People's Republic of China.

Advisory Board of the IASLC Mesothelioma Domain

Paul Baas, The Netherlands Cancer Institute, Amsterdam, The Netherlands; Jeremy Erasmus, M. D. Anderson Cancer Center, Houston, Texas, United States; Seiki Hasegawa, Hyogo College of Medicine, Hyogo, Japan; Kouki Inai, Hiroshima University Postgraduate School, Hiroshima, Japan; Kemp Kernstine, City of Hope, Duarte, California, United States; Hedy Kindler, The University of Chicago Medical Center, Chicago, Illinois, United States; Lee Krug, Memorial Sloan-Kettering Cancer Center, New York, New York, United States; Kristiaan Nackaerts, University Hospitals, Leuven, Belgium; Harvey Pass, New York University, New York, United States; David Rice, M. D. Anderson Cancer Center, Houston, Texas, United States.

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Advisory Board of the IASLC Esophageal Cancer Domain

Eugene Blackstone, Cleveland Clinic, Ohio, United States.

Participating Institutions in the new IASLC Lung Cancer Staging Project

F. Abad Cavaco and E. Ansótegui Barrera, Hospital La Fe, Valencia, Spain; J. Abal Arca and I. Parente Lamelas, Complejo Hospitalario de Ourense, Ourense, Spain; A. Arnau Obrer and R. Guijarro Jorge, Hospital General Universitario de Valencia, Valencia, Spain; D. Ball, Peter MacCallum Cancer Centre, Melbourne, Australia; G. K. Bascom, Good Samaritan Hospital, Kearney, Nebraska, United States; A. I. Blanco Orozco and M. A. González Castro, Hospital Virgen del Rocío, Sevilla, Spain; M. G. Blum, Penrose Cancer Center, Colorado Springs, USA; D. Chimondeguy, Hospital Universitario Austral, Argentina; V. Cvijanovic, Military Medical Academy, Belgrade, Serbia; S. Defranchi, Hospital Universitario-Fundacion Favaloro, Buenos Aires, Argentina; B. de Olaiz Navarro, Hospital de Getafe, Getafe, Spain; I. Escobar Campuzano and I. Macía Vidueira, Hospital de Bellvitge, L'Hospitalet de Llobregat, Spain; E. Fernández Araujo and F. Andreo García, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; K. M. Fong, Prince Charles Hospital, Brisbane, Australia; G. Francisco Corral and S. Cerezo González, Hospital La Mancha Centro, Ciudad Real, Spain; J. Freixinet Gilart, Hospital Universitario "Dr. Negrín," Las Palmas de Gran Canaria, Spain; L. García Arangüena, Hospital Sierrallana, Torrelavega, Spain; S. García Barajas, Hospital Infanta Cristina, Badajoz, Spain; P. Girard, L'Institut Mutualiste Montsouris, Paris, France; T. Goksel, Turkish Thoracic Society, Turkey; M. T. González Budiño, Hospital General Universitario de Oviedo, Oviedo, Spain; G. González Casaurrán, Hospital Gregorio Marañón, Madrid, Spain; J. A. Gullón Blanco, Hospital San Agustín, Avilés, Spain; J. Hernández Hernández, Hospital de Ávila, Avila, Spain; H. Hernández Rodríguez, Hospital Universitario de Tenerife, Santa Cruz de Tenerife, Spain; J. Herrero Collantes, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain; M. Iglesias Heras, Hospital de Ávila, Ávila, Spain; J. M. Izquierdo Elena, Hospital Nuestra Señora de Aránzazu, Donostia, Spain; E. Jakobsen, Danish Lung Cancer Registry, Denmark; S. Kostas, Athens School of Medicine, Athens, Greece; P. León Atance and A. Núñez Ares, Complejo Hospitalario de Albacete, Albacete, Spain; M. Liao, Shanghai Lung Tumor Clinical Medical Center, Shanghai, China; M. Losanovscky, Clinica y Maternidad Suizo Argentina, Buenos Aires, Argentina; G. Lyons, Hospital Britanico de Buenos Aires, Buenos Aires, Argentina; R. Magaroles and L. De Esteban Júlvez, Hospital Joan XXIII, Tarragona. Spain; M. Mariñán Gorospe, Hospital de San Pedro de Logroño, Logroño, Spain; B. McCaughan and C. Kennedy, University of Sydney, Sydney, Australia; R. Melchor Íñiguez, Fundación Jiménez Díaz, Madrid, Spain; L. Miravet Sorribes, Hospital La Plana, Castellón, Spain; S. Naranjo Gozalo and C. Álvarez de Arriba, Hospital Universitario Marqués de Valdecilla, Santander, Spain; M. Núñez Delgado, Hospital de Meixoeiro, Vigo, Spain; J. Padilla Alarcón and J. C. Peñalver Cuesta, Instituto Valenciano de Oncología, Valencia, Spain; J. S. Park, Samsung Medical Center,

Seoul, Republic of Korea; H. Pass, New York University Langone Medical Center and Cancer Center, New York, New York, United States; M. J. Pavón Fernández, Hospital "Severo Ochoa," Leganés, Spain; M. Rosenberg, Alexander Fleming Institute and Hospital de Rehabilitación Respiratoria, Buenos Aires, Argentina; E. Ruffini, University of Torino, Torino, Italy; V. Rusch, Memorial Sloan-Kettering Cancer Center, New York, New York, United States; J. Sánchez de Cos Escuín, Hospital de Cáceres, Cáceres, Spain; A. Saura Vinuesa, Hospital de Sagunto, Sagunto, Spain; M. Serra Mitjans, Hospital Universitari Mutua Terrassa, Terrassa, Spain; T. E. Strand, Cancer Registry of Norway, Norway; D. Subotic, Clinical Centre of Serbia, Belgrade, Serbia; S. Swisher, M. D. Anderson Cancer Center, Houston, Texas, United States; R. Terra, University of São Paulo Medical Center, São Paulo, Brazil; C. Thomas, Mayo Clinic Rochester, Rochester, Minnesota, United States; K. Tournoy, University Hospital Ghent, Belgium; P. Van Schil, Antwerp University Hospital, Edegem (Antwerp), Belgium; M. Velasquez, Fundacion Clinica Valle del Lili, Cali, Colombia; Y. L. Wu, Guangdong General Hospital, Guangzhou, China; K. Yokoi, Japanese Joint Committee for Lung Cancer Registry, Osaka, Japan.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.09.009.

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