ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the Revision of the M Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer

Kwun M. Fong, M.B.B.S., PhD,[a,*] Adam Rosenthal, MS,[b] Dorothy J. Giroux, MS,[b] Katherine K. Nishimura, PhD, MPH,[b] Jeremy Erasmus, MD,[c] Yolande Lievens, MD, PhD,[d] Mirella Marino, MD,[e] Edith M. Marom, MD,[f] Paul Martin Putora, MD, PhD,[g] Navneet Singh, MD, DM, FRCP,[h] Francisco Suárez, MD,[i] Ramon Rami-Porta, MD,[j] Frank Detterbeck, MD,[k] Wilfried E. E. Eberhardt, Priv.-Doz.,[l,*] Hisao Asamura, MD,[m,*] and the Members of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Members of the Advisory Boards, and Participating Institutions of the Lung Cancer Domain[**]

[a]*Department of Thoracic Medicine, The Prince Charles Hospital, University of Queensland Thoracic Research Centre, Brisbane, Australia*
[b]*Cancer Research And Biostatistics (CRAB), Seattle, Washington*
[c]*Department of Thoracic Imaging, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[d]*Department of Radiation Oncology, Ghent University Hospital and Ghent University, Gent, Belgium*
[e]*Department of Pathology, IRCCS Regina Elena National Cancer Institute, Rome, Italy*
[f]*Department of Diagnostic Imaging, Chaim Sheba Medical Center, Tel-Aviv University, Ramat Gan, Israel*
[g]*Department of Radiation Oncology, Kantonsspital St. Gallen, St. Gallen, Switzerland and Department of Radiation Oncology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland*
[h]*Lung Cancer Clinic, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*
[i]*Department of Thoracic Surgery, Clínica Santa María, Universidad de Los Andes, Santiago, Chile*
[j]*Department of Thoracic Surgery, Hospital Universitari Mutua Terrassa, University of Barcelona, Terrassa, Barcelona, Spain and Network of Centres for Biomedical Research in Respiratory Diseases (CIBERES) Lung Cancer Group, Terrassa, Barcelona, Spain*
[k]*Department of Surgery, Division of Thoracic Surgery, Yale University School of Medicine, New Haven, Connecticut*
[l]*Department of Medical Oncology, West German Cancer Center, University Medicine Essen and Ruhrlandklinik, University Duisburg-Essen, North Rhine-Westphalia, Germany*
[m]*Division of Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan*

Received 8 November 2023; revised 24 January 2024; accepted 31 January 2024
Available online - 4 February 2024

ABSTRACT

Introduction: This study analyzed all metastatic categories of the current TNM classification of NSCLC to propose modifications of the M component in the next edition (ninth) of the classification.

Methods: A database of 124,581 patients diagnosed between 2011 and 2019 was established; of these, 14,937 with NSCLC in stages IVA to IVB were available for this analysis. Overall survival was calculated using the Kaplan-Meier method, and prognosis was assessed using multivariable-adjusted Cox proportional hazards regression.

*Corresponding author.
**See Appendices
Address for correspondence: Kwun M. Fong, M.B.B.S., PhD, The Prince Charles Hospital, Rode Road Chermside, Brisbane, QLD 4032, Australia.
E-mail: kwun.fong@health.qld.gov.au

© *2024 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.*

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2024.01.019

Results: The eighth edition M categories revealed good discrimination in the ninth edition data set. Assessments revealed that an increasing number of metastatic lesions were associated with decreasing prognosis; because this seems to be a continuum and adjustment for confounders was not possible, no specific lesion number was deemed appropriate for stage classification. Among tumors involving multiple metastases, decreasing prognosis was found with an increasing number of organ systems involved. Multiple assessments, including after adjustment for potential confounders, revealed that M1c patients who had metastases to a single extrathoracic organ system were prognostically distinct from M1c patients who had involvement of multiple extrathoracic organ systems.

Conclusions: These data validate the eighth edition M1a and M1b categories, which are recommended to be maintained. We propose the M1c category be divided into M1c1 (involvement of a single extrathoracic organ system) and M1c2 (involvement of multiple extrathoracic organ systems).

© 2024 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

Keywords: Lung cancer; Non–small cell lung cancer; Stage classification; Metastases; Stage IV lung cancer

Introduction

The objective of this investigation was to explore whether the M categories developed by the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee (SPFC) for the eighth edition of the TNM classification for lung cancer require modification. For this purpose, a new prospective IASLC database was developed. Since the IASLC published their recommendations for the eighth edition M categories for NSCLC,[1] multiple developments in diagnosis, imaging, and treatment of NSCLC have emerged. Particularly relevant is the emerging concept of oligometastatic disease as a unique entity with specific and possibly curative treatment options.[2–6]

Since the last database which consisted of patients diagnosed and treated between 1999 and 2010, clinical practice now routinely includes positron emission tomography staging, minimally invasive endoscopic and surgical methods for diagnostic evaluation. A consensus definition of oligometastatic disease has been proposed with several issues remaining unresolved such as the role and optimal modality of local therapy in the setting of targeted therapies and immunotherapy, selection for local therapy, and varying definitions of oligometastases and oligoprogression.[7,8] Therapy has also rapidly involved to include local ablative therapies such as surgical resection and precision stereotactic ablative body radiotherapy (SABR) for both primary and metastatic lesions, particularly metastases-directed SABR in select cases with a low tumor burden when combined with targeted therapy or immunotherapy.[9] New systemic treatments, including immune checkpoint inhibitors and molecular-targeted agents in tumors with actionable driver mutations, are now standard of care, supplementing conventional chemotherapy. Collectively, these novel treatments have improved systemic control of NSCLC for many.

The improvement in systemic control of metastatic disease, together with global diffusion of advanced imaging such as positron emission tomography, and new possibilities for definitive treatment of single metastatic lesions mandate critical analyses of the prospectively collected IASLC ninth edition 2011 to 2019 database to develop proposals for the M categories of the ninth edition TNM classification.[10]

On the basis of the recommendations of the IASLC SPFC, the prospective data set had included several variables for potentially relevant revisions of the M categories. The collected information (number of variables and sample size) far exceeded that available for the eighth edition TNM stage classification of lung cancer. The data were evaluated by the IASLC SPFC M factor subcommittee.

Here, the overall findings generated from the ninth edition database are reported based on published guiding principles.[10] Additional possible research directions for future developments are also proposed based on documentation of parameters for the next database revision.

Material and Methods

Population Analyzed for the M Descriptors

The process for data acquisition and analysis of the IASLC lung cancer database has already been described in detail in the introductory manuscript to the ninth edition stage classification initiative and the manuscripts covering the proposals for the T, N descriptors and stage groups of the ninth edition of the TNM classification.[10–14]

The analysis population for this manuscript includes a subset of tumors from the ninth edition IASLC database diagnosed with lung cancer between January 2011 and December 2019 with follow-up data until December 2021, collected through the electronic data capture (EDC) system or batch data sets.

In the eighth edition revision, the final analyses were restricted to the patient population with data captured through the EDC due to lack of information on single versus multiple lesions in the batch data. This ninth edition analysis evaluated both EDC and batch data sets that provided sufficient information on the multiplicity

of metastatic lesions. The number of tumors used in a particular analysis was based on the availability of data to address the analysis question. For example, analyses of the number of lesions required discrete lesion counts per organ system, whereas analysis of the number of metastatic extrathoracic sites required only identification of the sites and whether single site/single lesion or single site/multiple lesions or multiple sites were involved. Notably, for the ninth edition revision, international participants contributed more batch data, from which tumors were excluded if the batch data lacked essential elements needed for revision of the TNM classification.[15]

Statistical Methods

The data set used for the M component analyses consisted of patients submitted to the IASLC ninth edition database as described, consisting of 87,043 patients with lung cancer, of whom 73,197 (84%) had NSCLC and are included in this paper.[15] The analyses described in this paper are based solely on clinical stage. General statistical methodology was similar to that used for the analysis of the T and the N components and stage groups of the ninth edition of the TNM classification.[10,12–14]

Overall survival (OS) was measured from the date of diagnosis to the date of death. Survival was estimated using the Kaplan-Meier method, with the log-rank test used to compare survival outcomes. Optimal cutpoints for continuous variables with respect to a survival outcome were identified using the running log-rank method, with a permutation test used to identify the approximate p value of the cutpoint. Primary comparisons of survival between groups of tumors with neighboring M categories and between stage groups IVA versus IVB were assessed using multivariable Cox proportional hazards regression, adjusting for covariates of age, sex, region, cell type, and stratifying the analysis by the ability to identify integer counts of metastatic lesions per organ system based on data source. All survival and regression analyses were performed using SAS System for Windows, version 347 9.4.

Three questions were considered for potential revisions of the M categories, which are as follows:

1. Is there a prognostic difference whether a presumed malignant pleural effusion is cytologically confirmed or not?
2. Can prognostic thresholds be identified based on the following:
   a. size of the largest metastatic lesion?
   b. number of metastatic lesions?
   c. number of metastatic sites (organs)?
3. Can stage classification be refined to reflect the prognostic interaction between the number of extrathoracic metastatic sites (organs) and the number of metastatic lesions?

Results

Details of the Analysis Data Set

A total of 14,937 patients with M1 NSCLC had data available for analysis (Table 1). This includes 2839 patients with data entered directly into the EDC system and 12,098 patients with data submitted by means of batch data sets.[15] Of the 12,098 batch data patients, 780 were from the North American SWOG 0819 study, for which M descriptors including the number of metastatic lesions were entered directly into the EDC system. In combination with data exclusively entered by EDC, this yields a total of 3619 patients from data sets with integer counts of lesions per metastatic organ system, in contrast to the remainder of batch patients (11,318), where only the organ systems and distinction of single versus multiple lesions were recorded. As such, many key results feature analyses of patients grouped or stratified by EDC and SWOG-0819 versus the rest to reflect grouping of patients by the ability to quantify metastatic lesions.

The 14,937 total patients were classifiable as having M1a (5410), M1b (1929), or M1c (7598) disease (Table 1).

Adenocarcinoma was the most common histologic type (n = 11,108, 74.4%); squamous cell carcinoma was the next most common (n = 2531, 16.9%).[15] Of the 14,210 patients with available data on therapy to the primary tumor, 13,500 (95%) were treated with a nonsurgical approach. The median follow-up for patients from the EDC and SWOG-0819 versus the rest of the patients was 50 months versus 62 months, respectively. Additional details for the study cohort can be found in Supplementary Table 1a to d.

Validation of Eighth Edition M Categories in the Ninth Edition Database

To establish that the eighth edition M categories were an appropriate starting point for further refinements, the eighth edition M categories were analyzed using the ninth edition database. This was done in a similar manner to the eighth edition analysis by adjusting for confounders (age, sex, histology, and geographic region) and stratified by data source (EDC + SWOG-0819 versus Batch, excluding SWOG-0819). Applying the unchanged eighth edition M categories (M1a, M1b, M1c) to the ninth edition data revealed progressively worse survival (hazard ratio [HR] > 1) for each eighth edition M category when compared with M1a; these differences were statistically significant after adjustment and stratification by data source (Supplementary Table 2 and

Table 1. Number of Cases by Source, Region, and Eighth Edition M Categories in the Ninth Edition Database

			By Eighth Edition			By Proposed Ninth Edition			
			M Categories			M Categories			
Data Source	Geographic Region	Assessable Cases	M1a	M1b	M1c	M1a	M1b	M1c1	M1c2
EDC and SWOG-0819	Europe	592	164	171	257	164	171	155	102
	North America	1259	322	319	618	322	319	383	235
	Asia/Australia	1443	537	331	575	537	331	334	241
	South/Central America	286	116	49	121	116	49	67	54
	Africa/Middle East	39	10	10	19	10	10	8	11
	Total	3619	1149	880	1590	1149	880	947	643
Batch, Excluding SWOG-0819	Europe	5513	1613	502	3398	1613	502	2197	1201
	North America	142	78	11	53	78	11	46	7
	Asia/Australia	5663	2570	536	2557	2570	536	2199	358
	South/Central America	0	0	0	0	0	0	0	0
	Africa/Middle East	0	0	0	0	0	0	0	0
	Total	11,318	4261	1049	6008	4261	1049	4442	1566
All patients	Global	14,937	5410	1929	7598	5410	1929	5389	2209

EDC, electronic data capture; SWOG, Southwest Oncology Group.

Supplementary Fig. 1). This provides validation of the eighth edition classification in an independent analysis (i.e., using the ninth edition database).

Prognostic Impact of Malignant Pleural Effusion With and Without Cytologic Confirmation

Analyses were conducted to evaluate the prognostic impact of cytologic confirmation of a pleural effusion classified as malignant, compared with a clinically diagnosed malignant pleural effusion without or unsuitable for cytologic confirmation. In addition, separate analyses were performed for tumors whose M1a category by eighth edition stage classification criteria was determined by the presence of any subset of M1a descriptors including associated pleural effusions and for tumors whose M1a category designation was solely determined by the presence of a pleural effusion.

Among patients with tumors categorized as M1a due to a pleural effusion along with other potential M1a descriptors, there was no strong evidence of a survival difference for those with positive cytology result (n = 432) compared with those without cytologic confirmation (n = 386) (p value = 0.09, Supplementary Fig. 2*A*). Similarly, in patients with M1a disease exclusively due to malignant pleural effusion, there was no strong evidence of a survival difference for those with positive cytology result (n = 203) compared with those without cytologic confirmation (n = 238) (p value = 0.22, Supplementary Fig. 2*B*). These finding should be interpreted with caution due to potential confounders, for example, investigators who categorized cytologically negative pleural effusions as M1a for database submission were doing so because the clinical context strongly suggested this diagnosis given the observation that up to half of malignant pleural effusions can test as cytologically negative, including potential sample size/power limitations.

Prognostic Impact of Maximum Size of Largest Metastatic Lesion

A limited number of tumors were eligible for these analyses (Supplementary Table 3); thus, the results should be considered as hypothesis generating. The most frequent metastatic organ systems for which lesion size data were available were the brain (n = 244), liver (n = 120), adrenals (n = 108), bone (n = 84), and lymphatic system (n = 76). Altogether, 552 patients had at least one assessable lesion with size data available. For the lesion of maximum size for these 552 patients, the mean size was 2.6 cm (SD 2.2), median size was 2.0 cm with a range of 0.1 to 19.2 cm after removal of zero values (three patients), and outliers were reported as 60 cm or greater (two tumors).

An optimal cutpoint analysis with respect to OS was undertaken for this limited data set of 552 patients with eighth edition stages of M1b or M1c. The optimal cutpoint was identified at 1.2 cm (Supplementary Fig. 3*A*).

An exploratory analysis revealed better survival for patients with tumors with a maximal metastatic lesion size below a cutpoint of 1.0 cm (rounded) compared with larger metastatic lesions (p value = 0.02, Supplementary Fig. 3*B*). Overall differences in outcome were also observed between patient subgroups when grouped simultaneously by M component (M1b versus M1c) and maximum metastatic lesion size (p value = 0.003, Supplementary Fig. 3*B*).

Nevertheless, the number of cases with a recorded metastatic lesion size was insufficient to permit validation of the cutpoint or to allow evaluation of the

generalizability of the prognostic impact. More extensive data and further research are needed before maximal metastasis size can be considered as a descriptor in the M component of stage classification.

Prognostic Impact of the Number of Extrathoracic Metastatic Lesions

Altogether, 1258 cases were assessable for prognosis according to the number of metastatic lesions. Specifically, sufficient numbers of cases were available to allow several analyses, including division into multiple subgroups with empiric thresholds of three, five, or seven metastatic lesions (Supplementary Table 4), which have been suggested by other investigators.

An optimal cutpoint analysis identified seven lesions as the optimal cutpoint (i.e., seven or fewer compared with eight or more; Supplementary Fig. 4*A*). Nevertheless, this was not a training set/validation set analysis due to the number of cases.

Kaplan-Meier survival curves revealed a trend toward progressively worse OS of patient subgroups with an increasing number of metastatic lesions (2–3, 4–5, 6–7, and 8+ lesions, p value < 0.0001, Supplementary Fig. 4*B*). Although each of the subgroup was statistically different compared with the subgroup with a single metastasis (eighth edition M1b), the differences of the adjacent subgroups with 2 to 3, 4 to 5, 6 to 7 and 8+ lesions were not statistically different.

The prognostic impact of the number of lesions was also analyzed by dichotomizing according to the empiric thresholds suggested by others. Each of the examined empiric thresholds ($\leq$3 versus $\geq$4; $\leq$5 versus $\geq$6; $\leq$7 versus $\geq$8) revealed significantly different outcomes in the dichotomized multiple lesion categories (Supplementary Fig. 4*C*) and in comparison to patients with a single metastasis (eighth edition M1b).

Thus, the number of metastatic lesions seems to be a continuum, without a clear inflection point. Furthermore, there were insufficient data to investigate the impact of confounding by treatment—that is, patients with less extensive metastatic disease may have been treated more aggressively, including definitive local therapy of metastases. There were also insufficient data to investigate the thoroughness of stage evaluation.

Prognostic Impact of the Number of Extrathoracic Metastatic Organ Systems

Survival curves were plotted (Supplementary Fig. 5*A*) for patients with tumors involving increasing numbers of metastatic organ systems (1, 2, 3, $\geq$4 sites) and for comparison tumors with a single metastasis (M1b). This analysis revealed progressively worse survival with increasing number of organ systems with metastases, with statistically significant differences for each group compared with the next adjacent group ($p < 0.0001$).

The prognostic impact of the number of organ systems with metastases was further according to M1c subgroups dichotomized by the following three empiric candidate thresholds: greater than or equal to two sites (versus one), greater than or equal to three sites (versus one to two), and greater than or equal to four sites (versus one to three). For each of these thresholds, statistically significant differences were noted between one metastasis (M1b), the M1c subgroup below the threshold, and the M1c subgroup above the threshold ($p < 0.0001$, Supplementary Fig. 5*B*).

Potential confounding from possible prognostic differences related to specific organs was investigated (e.g., brain compared with liver). Among patients with tumors involving a single metastasis (eighth edition M1b), those with a brain metastasis experienced the best survival, with a median OS of 1.6 years (1.3, 1.9) and a statistically significant difference relative to other frequently involved organs (p value < 0.0001, Supplementary Fig. 6*A*). Nevertheless, there were no OS differences by organ system for patients with tumors involving multiple lesions in a single organ system (p value $= 0.40$, Supplementary Fig. 6*A*).

Furthermore, OS was compared in patients with brain lesions versus those with metastatic lesions at any other distant site among cohorts with a single metastasis and with multiple metastases confined to a single site. The analyses similarly confirmed a better prognosis for patients with M1b single brain metastasis versus other M1b sites (log-rank p value < 0.0001) but not for patients with multiple extrathoracic metastases in the brain compared with patients with multiple extrathoracic metastases in other sites (log-rank p value $=$ 0.22, Supplementary Fig. 6*B*).

A sensitivity analysis evaluated the OS of patients with tumors involving a single metastasis versus single site with multiple lesions versus multiple site tumors, after excluding the brain, liver, and either brain or liver metastasis (Supplementary Fig. 7*A*). Distinct survival curves were observed between patients with eighth edition M1a versus M1b (single metastasis) tumors when brain lesions but not liver lesions were excluded. Nevertheless, survival differences persisted whether or not brain or liver metastases were excluded for patients with tumors involving a single metastasis versus a single organ system with multiple metastases, versus multiple organ systems.

Prognostic differences according to the extrathoracic metastatic site were still evident when the analyses excluding the brain and liver and either liver or brain lesions were run separately for only EDC and SWOG-

0819 cases or for only batch cases (Supplementary Fig. 7*B*).

Similarly, when survival curves for patients with M1c tumors were compared with the reference group of patients with M1b tumors, the Kaplan-Meier curves seem heterogeneous for the common extrathoracic metastatic sites of the brain, liver, and bone (Supplementary Fig. 7*C*), again supporting the hypothesis of differing prognostic impact by organ system. We could not assess whether these observations reflect inherent biologic differences related to the site of metastases or differences in treatment policies (e.g., increased use of SABR or resection of brain metastases as compared with other sites of metastasis).

Refining M Categories to Reflect the Prognostic Interaction Between the Number of Extrathoracic Metastatic Sites (Organs) and the Number of Extrathoracic Metastatic Lesions

In the eighth edition classification system, similar OS was observed in patients with tumors involving multiple extrathoracic metastatic lesions in one organ system versus in multiple organ systems. The survival of both of these groups was also significantly worse than those with M1a tumors and those with a single metastatic extrathoracic lesion in one organ system (M1b). This was the basis for the eighth edition M1a, M1b, and M1c categories (p value < 0.0001, Fig. 1).

The ninth edition data set involves a much larger population consisting of both EDC and batch data (Fig. 1), whereas the eighth edition was based exclusively on data entered into the EDC system.

Kaplan-Meier analyses of the current database reveal that patients with tumors involving multiple metastatic extrathoracic lesions in one organ system have survival outcomes (median OS 1.0 [0.9, 1.0] y) that fall in-between that of patients with tumors involving a single extrathoracic metastatic lesion (eighth edition M1b, median survival 1.2 [1.1, 1.3] y) and that of patients with tumors involving metastatic lesions at multiple organ systems (median OS 0.6 [0.6, 0.7] y, p value < 0.0001, Fig. 1).

Stemming from this analysis, the M subcommittee extensively investigated the following four M1 categories: intrathoracic metastases (same as eighth edition M1a, i.e., pleural/ pericardial involvement or contralateral separate tumor nodules), a single extrathoracic metastasis (same as eighth edition M1b), multiple metastases at a single extrathoracic organ system (M1c1), and multiple metastases involving multiple organ systems (M1c2). These four categories are referred to as "proposed 9th edition M1 categories" in this paper.

Sensitivity subset analyses consistently revealed the progressively lower OS of patients with tumors involving a single extrathoracic metastasis (M1b) versus multiple lesions at one extrathoracic organ system (M1c1) versus multiple metastases at multiple extrathoracic sites (M1c2). The differences between these three patient cohorts were apparent when viewing the EDC/SWOG data or only the batch data (Supplementary Fig. 8*A*). The OS differences remained generally consistent when stratified by treatment received, performance status, and histologic

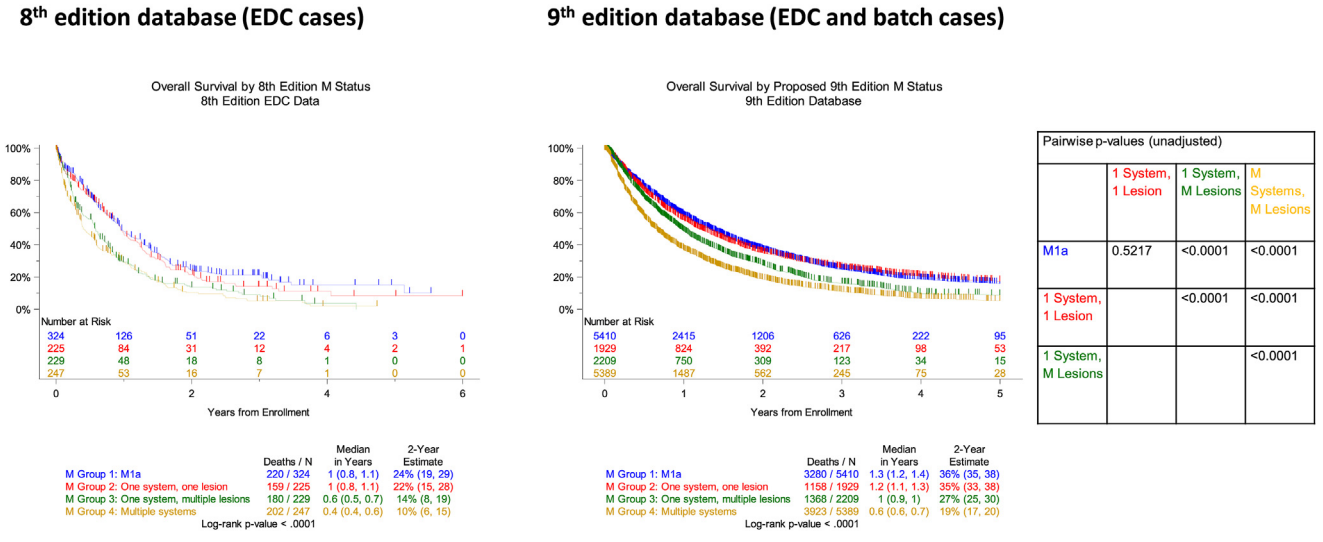

Figure 1. Prognostic impact of proposed ninth edition M1 categories applied to the eighth and ninth edition databases. Survival outcomes of patients according to the proposed 9th edition M1 categories applied to the 8th and 9th edition data sets. The 9th edition data, with a much larger sample size, shows similar trends from M1a to M1b to M1c compared to the 8th edition data, and reveals that patients with tumors involving multiple lesions in one site have superior survival than patients with tumors involving multiple metastatic sites. EDC, electronic data capture.

type (Supplementary Fig. 8*B*, *C*, and *D*, respectively), although diminishing sample sizes sometimes hamper the statistical assessment. Similarly, the differences between the three cohorts of patients with extrathoracic metastases also remained reasonably evident in patients from all regions (the smaller sample sizes in analyses involving Australia and South/Central America limited the statistical assessment; Supplementary Fig. 8*E*).

Survival of patients in the EDC data set was better than that in the batch data set, particularly for tumors with less metastatic burden (M1a and one extrathoracic metastasis [M1b]). Batch data sets frequently had missing data and were generally not constructed in a way conducive to determining whether missing data were simply missing or indicative of negative results for key data fields such as prior therapies received, pretreatment testing, and comorbidities. This deficiency presented an impediment to identifying causes of the apparent survival discrepancies found when comparing the data sources (Supplementary Table 1c and d).

Finally, stratified multivariable Cox regression modelling was undertaken to compare the OS of patients with tumors involving one of the proposed ninth edition M1 categories—eighth edition M1a, a single extrathoracic metastasis (eighth edition M1b), multiple lesions in one organ system (M1c1), and multiple extrathoracic organ systems (M1c2), while adjusting for four key predictors of age (≥65 y versus younger), sex, histology (squamous versus other), and geographic region (Asia versus other), and stratifying by data source (EDC + SWOG-0819 versus batch, excluding SWOG-0819). The data source stratification provides a more precise HR estimate by adjusting for baseline hazard differences, arising in part from differences in availability of lesion count data between data sources (Supplementary Table 2).

The stratified multivariable analyses in Table 2 reveal progressively worse survival for patients with tumors involving the four potential ninth edition M1 categories (eighth edition M1a, single extrathoracic metastasis [M1b], single metastatic organ system/multiple lesions [M1c1], and multiple metastatic organ systems [M1c2]). Each potential M category reveals an increased HR (worse survival) compared with M1a, and each of these comparisons is statistically significant after adjustment for other factors (HRs for these are also revealed).

Table 3 reveals results for the stratified adjusted multivariable regression analysis when the proposed ninth edition M1 categories are applied to proposed stage groups. The proposed stage groups would maintain the traditional alignment, namely including M1a and M1b in stage IVA, and include the two proposed M1c categories in stage IVB. It can be found that stage IVB exhibits significantly worse survival (HR > 1) compared with stage IVA after stratification and adjustment for confounders.

Discussion

The eighth edition of the TNM classification for lung cancer separated prognostically distinct categories of metastatic disease and has been well validated since its inception.[16,17] It classified M1 categories as M1a, M1b (single metastatic lesion), and M1c (multiple extrathoracic metastases in either a single organ or multiple organ systems). Patients with tumors involving a single extrathoracic metastasis (M1b) were found to have a prognosis similar to patients with tumors in the M1a

Table 2. Cox Regression for Overall Survival by Number of Lesions and Sites, Stratified by Data Source; Analysis of M Categories

Category	Variable	n/N (%)	HR (95% CI)	*p* Value
Proposed M1 categories: M1a, M1b, M1c1 (single organ system), and M1c2 (multiple organ systems)				
M1a	M1a	5406/14,926 (36%)	(reference level)	-
M1b	M1b; single organ system, single lesion (vs. M1a)	1927/14,926 (13%)	1.18 (1.10, 1.27)	<0.001
M1c1 single organ system	M1c1; single organ system, multiple lesions (vs. M1b)	2207/14,926 (15%)	1.17 (1.08, 1.27)	<0.001
M1c2 multiple organ systems	M1c2; multiple organ systems, multiple lesions (vs. M1c1 single organ system)	5386/14,926 (36%)	1.33 (1.25, 1.41)	<0.001
Adjustment factors:				
	Age ≥ 65 y	8577/14,926 (57%)	1.35 (1.30, 1.41)	<0.001
	Male	8838/14,926 (59%)	1.32 (1.27, 1.38)	<0.001
	Squamous	2529/14,926 (17%)	1.34 (1.27, 1.41)	<0.001
	Region: Asia (vs. other)	6872/14,926 (46%)	0.93 (0.89, 0.97)	<0.001

CI, confidence interval; HR, hazard ratio; n, number of cases; N, total number of evaluable cases; N/A, not applicable.

Table 3. Cox Regression for Overall Survival by Number of Lesions and Sites, Stratified by Data Source; Analysis of Stage IV Groups

Category	Variable	n/N (%)	HR (95% CI)	*p* Value
Impact of proposed M1 categories on stage groups (maintaining inclusion of M1a and M1b in stage IVA, and including the proposed M1c categories in stage IVB)				
Stage IVA	M1a+M1b	7333/14,926 (49%)	(reference level)	-
Stage IVB	M1c (1 and 2) (vs. M1a+M1b)	7593/14,926 (51%)	1.63 (1.56, 1.70)	<0.001
Adjustment factors:				
	Age ≥ 65 y	8577/14,926 (57%)	1.34 (1.29, 1.40)	<0.001
	Male	8838/14,926 (59%)	1.32 (1.26, 1.37)	<0.001
	Squamous	2529/14,926 (17%)	1.33 (1.26, 1.40)	<0.001
	Region: Asia (vs. other)	6872/14,926 (46%)	0.95 (0.91, 0.99)	0.015

CI, confidence interval; HR, hazard ratio; n, number of cases; N, total number of evaluable cases; N/A, not applicable.

category. Patients with tumors involving a single extrathoracic metastasis had better prognosis than those with tumors involving multiple extrathoracic metastatic lesions in one or multiple organs (M1c).

Since then, the value of metastasis-directed ablative therapies has emerged, particularly in the setting of modern targeted therapies and immunotherapy, leading to a need to consider refinements to the M categories. The ninth edition database involves prospectively collected cases of lung cancer diagnosed between 2011 and 2019; data were submitted to the IASLC database through the EDC or by batch data sets. The ninth edition data set was much larger than the eighth edition data set, particularly with respect to the M category. Importantly, the eighth edition M categories were validated in the ninth edition database (Supplementary Fig. 1). The data suggest generally improved survival in stage IV patients in the ninth edition database compared with the previous edition database (Fig. 1).

The data elements for the ninth edition database were designed and implemented in 2011 and could not anticipate the dramatic evolution of how stage IV NSCLC is managed. Specifically, the importance of molecular profiling, the number of metastatic lesions, and the treatments used were not as apparent in 2011.[18,19] Further limitations arose from incompleteness of data submitted for some variables. It is thus strongly recommended that future data submissions are made to an updated and revised EDC database in preference to batch data, to capture all relevant data systematically and comprehensively to avoid the heterogeneity and inconsistency encountered for this edition.

The effort to develop proposals for revision of the M categories focused on several clinical questions. One issue was to explore whether an optimal definition of oligometastatic disease could be identified. Specifically, the current ninth edition database was interrogated for information on the number of metastatic lesions, size of individual metastatic lesions (size of largest lesion), and number of involved organs with metastatic lesions. In addition, the M subcommittee explored whether survival of patients with a presumed malignant pleural effusion was altered whether the effusion was cytologically confirmed or not.

Regarding the M1a pleural effusion designation, we do not propose any changes to the Union for International Cancer Control TNM Classification of Malignant Tumors, eighth edition descriptor footnote: "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 nonbloody 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."

We attempted to analyze tumor burden using the size of the largest metastatic lesion as a crude index. Optimal cutpoint analysis suggested a threshold of 1.2 cm (Supplementary Fig. 3*A* and *B*). Although this size threshold correlated with a statistically significant impact on OS, the sample size was too small to permit validation and assessment of generalizability. Thus, these observations are considered to be hypothesis generating. Although the concept is intuitively plausible, there are also likely confounders, such as the ability to ablate smaller versus larger lesions. It may be that metastatic lesion size is more appropriate as a parameter for treatment guidelines than for stage classification. Ongoing data collection is recommended with sufficient detail for further evaluation in the future tenth edition revision.

The M subcommittee investigated whether a definition of oligometastatic disease could be identified from the data and included as an M descriptor. The unbiased optimal cutpoint analysis of available data without training/test set division suggested the optimal statistical cutpoint was seven lesions (i.e., seven or fewer compared with eight or more) (Supplementary Fig. 4*A*),

and a statistically significant OS difference was apparent when multiple extrathoracic metastasis was dichotomized at this threshold. Nevertheless, OS differences were also noted when other dichotomized thresholds (e.g., three or five) were used, and a non-dichotomized analysis suggested that there is a continuum of worsening prognosis with an increasing number of metastatic lesions.

Furthermore, the data available do not allow analysis of the potential interaction between the number of lesions and how often definitive local therapy was used. From a stage classification perspective, it is important to identify characteristics that inherently affect prognosis—these are likely to remain relatively stable and generalizable. Nevertheless, it is crucial to distinguish inherent prognostic characteristics from characteristics that drive treatment selection. Treatment selection is eminently controllable by the provider; the associated prognosis is by nature constantly changing as treatment evolves. Furthermore, treatment selection characteristics are best assessed as a continuum that is weighed along with other considerations. Therefore, the M subcommittee concluded that the number of lesions is best left as a clinical consideration; the analysis suggests this is not amenable to dichotomization at a threshold that reflects an inherent biologic inflection point.

Analysis of the much larger ninth edition database was able to reveal that the eighth edition M1c category consists of two prognostically distinct groups. Patients with tumors involving multiple metastatic lesions at one extrathoracic organ system (M1c1) have significantly better OS than patients with tumors involving metastatic lesions at multiple extrathoracic organ systems (M1c2). This was consistent in several statistical approaches and in multiple subset analyses (Fig. 1, Supplementary Fig. 8*A–E*, and Table 2). This is also consistent with external literature, albeit in a smaller retrospective cohort.[20]

There is an argument for biological plausibility to support separating the M1c category into metastases at a single organ system versus multiple metastatic organ systems—the former could be expected to have a lower metastatic tumor burden and a better prognosis as suggested by clinical studies.[21–24] Unfortunately, the current data set did not allow us to adequately quantify metastatic tumor burden. We strongly recommend collecting granular lesion size and count data to inform analyses for the next revision of the TNM classification, specifically to enable an adequately powered analysis of the prognostic interaction of combined number of extrathoracic metastatic organ systems and number of metastases. This analysis will be important for validating empiric definitions of oligometastatic disease, such as the popular definition of five or fewer metastatic lesions in three or fewer extrathoracic organ systems.

An issue is how an organ system should be defined. This question is not addressed in the general stage classification rules of the Union for International Cancer Control or American Joint Committee on Cancer. This is straightforward when dealing with a localized single organ such as the brain or the liver. We consider paired organs such as the kidneys or adrenals also to represent one organ system. Conceptually, more difficult is how to view diffuse organs such as the skeleton. In the data available for our analysis, such lesions at such sites were considered to involve one organ system—for example, multiple metastases involving only the skeleton were analyzed in the M1c1 group. Therefore, the M1c1 definition should be applied to an organ system, regardless whether the organ is solitary, paired, or diffuse throughout the body.

Another issue is whether there should be a limit to the number of metastatic lesions in a single organ system. We do not have data to address this. Furthermore, this is likely a clinical issue that plays into judgment about the optimal treatment strategy for a patient and not an issue amenable to dichotomization according to a biologically inherent threshold. From a ninth edition stage classification standpoint, any number of metastases more than one at a single extrathoracic site should be classified as M1c1. At the same time, we recognize that the clinical management of M1c1 patients may be varied and influenced by the number of lesions (and other factors).

Exploratory analysis has suggested potential prognostic differences between M1 subsets of EDC tumors compared with batch data (Supplementary Fig. 8*A*) and between M1 subsets involving different organs, in particular M1 tumors with brain involvement (Supplementary Fig. 7*A*), which may stimulate research for the tenth edition revision.

In conclusion, the following proposals are made for the M1 descriptors in the ninth edition of TNM classification of lung cancer (Table 4):

1. M1a—no change from the eighth edition
2. Size of largest metastatic lesion is not recommended to be included as a descriptor
3. The number of metastatic lesions is not recommended to be included as a descriptor
4. M1c is subdivided into (a) multiple extrathoracic metastases in a single organ system (proposed M1c1) and (b) multiple extrathoracic metastases in multiple organ systems (proposed M1c2)
5. No change to stage groups IVA and IVB

Stage classification is a nomenclature to describe the anatomic extent of a cancer. By providing a universal

Table 4. Proposed M Descriptors for the Ninth Edition Classification

M0	No distant metastasis
M1	Distant metastasis
M1a	Tumor with malignant pleural or pericardial nodules or effusions[a] or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis in a single organ system[b]
M1c	Multiple extrathoracic metastases
M1c1	Multiple extrathoracic metastases in a single organ system[c]
M1c2	Multiple extrathoracic metastasis in multiple organ systems

[a]Pleural effusions are excluded that are cytologically negative and clinically judged not to be due to cancer (e.g. transudative, non-bloody).
[b]This includes involvement of a single non-regional node.
[c]A diffuse organ system, such as the skeleton, is considered one organ – i.e., metastases limited to several bones are classified as M1c1.

language, it fosters communication about specific patients, the applicability of clinical trial results to a particular patient and helps define prognosis of a collection of patients with a similar anatomic extent of cancer. Nonetheless, it is important to note the distinction between prognosis and tumor extent, the latter is what the TNM system determines. Stage classification has historically focused more on tumors with limited extent rather than metastatic disease. In part, this is due to the available data, and in part, because anatomic extent is an important characteristic when local therapies are considered, and less important relative to other tumor characteristics (e.g., molecular profiling) when systemic therapies are appropriate. Over time, however, patient management increasingly involves a combination of systemic and local therapies. The greater number of advanced stage cases allowed the committee to assess and propose refinements of the M categories. Although further work is needed, it represents an evolution of stage classification, specifically seeking to define anatomic tumor characteristics of advanced lung cancer which are generalizable and useful in discussions of individual patient management.

However, it is strongly emphasized that introduction of the new M categories for the ninth edition is not intended to affect contemporary best practice.[25] For instance, a patient with a single brain metastasis and a single bone metastasis would be staged as M1c2 with the new proposal, whereas a patient with multiple (e.g., nine) metastatic lesions in a single extrathoracic organ system (e.g., liver) would have the lower M1c1 stage. Nevertheless, in clinical practice, the former patient could be treated as having "oligometastatic disease" with more aggressive metastasis-directed treatment with anticipation of a better outcome than the latter patient in the lower M1 category. This example underscores that a stage classification cannot address all nuances and cannot define what the optimal treatment strategy is for an individual. Moreover, the ninth edition proposals were unable to be stratified by actionable mutation therapy or immunotherapies received, both of which can lead to meaningful survival benefits for individuals.

Nonetheless, these ninth edition proposals should help to identify subsets of tumors with a more favorable prognosis and patients for whom curative treatments could be considered and start the journey to collate enough data of sufficient granularity to optimally describe the "oligometastatic" state; "the devil is in the detail." The proposed changes to the M categories maintain the compatibility with the M categories of the previous edition, help us to better understand the concept of oligometastatic disease, and improve our capacity to indicate prognosis and offer optimal treatments, which is the ultimate objective of the TNM classification in lung cancer.[1,10,15,26,27]

CRediT Authorship Contribution Statement

Kwun M. Fong: Conceptualization, Methodology, Writing—original draft, Writing—review and editing, Project administration.

Wilfried Eberhardt: Conceptualization, Methodology, Writing—original draft, Writing—review and editing.

Adam Rosenthal: Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review and editing.

Dorothy J. Giroux: Formal analysis, Investigation, Resources, Data curation, Writing—review and editing.

Katherine K. Nishimura: Formal analysis, Investigation, Resources, Data curation.

Jeremy Erasmus: Methodology, Writing—original draft, Writing—review and editing.

Yolande Lievens: Methodology, Writing—original draft, Writing—review and editing.

Mirella Marino: Methodology, Writing—original draft, Writing—review and editing.

Paul Martin Putora: Methodology, Writing—original draft, Writing—review and editing.

Navneet Singh: Methodology, Writing—original draft, Writing—review and editing.

Francisco Suárez: Methodology, Writing—original draft, Writing—review and editing.

Ramon Rami-Porta: Writing—review and editing.

Frank Detterbeck: Writing—review and editing.

Hisao Asamura: Conceptualization, Methodology, Project administration.

Disclosure

Dr. Fong reports receiving grants and contracts from MRFF EPCDR, NHMRC Ideas Grant, MRFF Next Generation Clinical Researchers Program, NHMRC; receiving funds from UpToDate as reviewer and Cochrane Clinical Answers as reviewer; and receiving equipment support from Olympus and Mevis Veolity. Mr. Rosenthal reports receiving fees for service from IASLC to complete work associated with publication. Ms. Giroux reports receiving fees for service from IASLC to complete work associated with publication. Dr. Nishimura reports receiving fees for service from IASLC to complete work associated with publication. Dr. Erasmus reports receiving honoraria from Canadian Association of Radiologists. Dr. Lievens reports receiving grants and contracts for the ImmunoSABR EU Project, HERO-VBHC chair; consulting fees from AstraZeneca; and honoraria from Merck Sharp & Dohme. Dr. Marom reports receiving honoraria from Boehringer Ingelheim, Merck, and AstraZeneca. Dr. Putora reports receiving grants or contracts from Bayer, Takeda, and AstraZeneca. Dr. Suárez reports receiving consulting fees from AstraZeneca and Roche; honoraria from AstraZeneca. The remaining authors declare no conflict of interest.

Acknowledgments

This research is supported by a grant from AstraZeneca. This research was also supported, in part, through the National Institutes of Health/National Cancer Institute (NIH/NCI) Cancer Center Support Grant (P30 CA008748 and R01CA172253). The authors thank the International Association for the Study of Lung Cancer (IASLC) for supporting the employees of the Cancer Research And Biostatistics (CRAB) to attend the IASLC World Conference on Lung Cancer for the Staging Project as statistical consultants. The co-authors and members of the IASLC Staging and Prognostic Factors Committee (SPFC) also thank Patricia Vigues, SPFC Project Coordinator, for providing administrative support for the project and the SPFC as a whole.

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; Ramón Rami-Porta (past chair), Hospital Universitari Mutua Terrassa, Terrassa, Spain; Luiz Henrique Araujo, Brazilian National Cancer Institute, Rio de Janeiro, Brazil; David Beer, University of Michigan, Ann Arbor, Michigan; Pietro Bertoglio, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; Ricardo Beyruti, University of São Paulo Medical School, Sao Paolo, Brazil; Andrea Bille, 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, Morocco; Elisabeth Brambilla, Centre Hospitalier Universitaire, Grenoble, France, University of Grenobles Alpes, Grenoble, France; A. K. Cangir, Ankara University Faculty of Medicine, Ankara, Turkey; David Carbone, The Ohio State University, Columbus, Ohio; Vanessa Cilento, Cancer Research And Biostatistics, Seattle, Washington; Casey Connolly, IASLC, Denver, Colorado; Gail Darling, University of Toronto, Toronto, Canada; Frank Detterbeck, Yale University School of Medicine, New Haven, Connecticut; Daniel Dibaba, Cancer Research And Biostatistics, Seattle, Washington; 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; Jeremy Erasmus, M. D. Anderson Cancer Center, Houston, Texas; 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-Salle, Centre Hospitalier Universitaire, Caen, France; Oliver Gautschi, Cancer Center, Cantonal Hospital Lucerne, Lucerne, Switzerland; Ritu R. Gill, Beth Israel Lahey Health, Boston, Massachussetts, USA; Dorothy Giroux, Cancer Research And Biostatistics, Seattle, Washington; Meredith Giuliani, The Princess Margaret Cancer Centre/University Health Network, Toronto, ON, Canada; Department of Otolaryngology - Head and Neck Surgery, The University of Toronto, Toronto, ON, Canada; Jin Mo Goo, Seoul National University, Seoul, Republic of Korea; Seiki Hasegawa, Hyogo College of Medicine, Nishinomiya, Japan; Fred Hirsch, Center for Thoracic Oncology, Tisch Cancer Institute, Mount Sinai Health System, New York, NY, USA; Hans Hoffman, Technical University of Munich, Munich, Germany; Wayne Hofstetter, M. D. Anderson Cancer Center, Houston, Texas; James Huang, Memorial Sloan Kettering Cancer Center, New York, New York; Philippe Joubert, Quebec Heart and

Lung Institute, Quebec, Canada; Kemp Kernstine, The University of Texas Southwestern Medical Center, Dallas, Texas; Keith Kerr, University of Aberdeen, School of Medicine and Dentistry, Aberdeen, United Kingdom; Young Tae Kim, Seoul National University, Seoul, Republic of Korea; Dong Kwan Kim, Samsung Medical Center, Seoul, Republic of Korea; Hedy Kindler, The University of Chicago Medical Center, Chicago, Illinois; Yolande Lievens, Ghent University Hospital, Gent, 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; Gustavo Lyons, Buenos Aires British Hospital, Buenos Aires, Argentina; Heber MacMahon, University of Chicago, Chicago, Illinois; Alyson Mahar, University of Manitoba, Manitoba, Canada; Mirella Marino, IRCCS Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, M.D. Anderson Cancer Center, Houston, Texas, and 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 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; Anna Nowak, University of Western Australia, Perth, Australia; Isabelle Opitz, University Hospital Zurich, Zurich, Switzerland; Meinoshin Okumura, Osaka University, Osaka, Japan; Raymond U. Osarogiagbon, Baptist Cancer Center, Memphis, Tennessee; Harvey Pass, New York University, New York, New York; 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; Andreas Rimner, Memorial Sloan Kettering Cancer Center, New York, New York; Adam Rosenthal, Cancer Research And Biostatistics, Seattle, Washington; 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 Sao Paulo, Sao Paulo, Brazil; William D Travis, Memorial Sloan Kettering Cancer Center, New York, New York; 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; Murry Wynes, IASLC, Denver, Colorado; Yasushi Yatabe, National Cancer Center Hospital, Tokyo, Japan.

Advisory Board to the Lung Cancer Domain

Samuel Armato, The University of Chicago, Chicago, USA; Lawek Berzenji, University of Antwerp, Antwerp, Belgium; Alex Brunelli, St. James's University Hospital, Leeds, UK; Giuseppe Cardillo, Azienda Ospedaliera San Camilo Forlanini, Rome, Italy; Jason Chang, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Keneng Chen, Peking University, Beijing Cancer Hospital, Beijing, China; Wendy Cooper, Royal Prince Alfred Hospital, NSW Health Pathology, Sydney, Australia; Pier Luigi Filosso, University of Torino, Torino, Italy; Liyan Jiang, Shanghai Chest Hospital, Shanghai, People's Republic of China; Nagla Karim, Inova Cancer Institute-University of Virginia, Virginia, USA; Peter Kneuertz, The Ohio State University College of Medicine, Ohio, USA; Mark Krasnik, Gentofte University Hospital, Copenhagen, Denmark; Kaoru Kubota, Nippon Medical School Hospital, Tokyo, Japan; Catherine Labbe, Quebec Heart and Lung Institute, Quebec, Canada; Ho Yun Lee, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Eric Lim, Imperial College and the Royal Brompton Hospital, London, United Kingdom; Geoffrey Liu, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; Hongxu Liu, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Liaoning, China; Philip Mack, Mount Sinai, New York, USA; David Naidich, NYU-Langone Medical Center, New York, USA; Mizuki Nishino, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts, USA; Marcin Ostrowski, Medical University of Gdańsk, Gdańsk, Poland; Charles Powell, Mount Sinai School of Medicine, New York, USA; Carolyn Presley, The Ohio State University, Ohio, USA; Paul Martin Putora, Kantonsspital St.Gallen, St. Gallen, Switzerland; Natasha Rekhtman, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Harry Ren, Shanghai Pulmonary Hospital, Shanghai, China; M Patricia Rivera, University of North Carolina, Dept of Medicine, chapel Hill, NC, USA; Gaetano Rocco, Memorial Sloan Kettering Cancer Center, New York, New York; Maria Teresa Ruiz Tzukazan, Pontifical Catholic University of Rio Grande do Sul, PUCRS, Porto Alegre, Brazil; Robert Samstein, Mount Sinai, New York, USA; Yu Yang Soon, National University Hospital, Harvard University Hospital, Singapur; Kenichi Suda, Kindai University Faculty of Medicine, Osaka, Japan; Martin Tammemägi, Department of Community Health Sciences, Ontario, Canada; Lynn Tanoue ,Yale University, Dept of Medicine,

New Haven CT, USA; Akif Turna, Istanbul Univ Cerrahpasa Medical School, Istanbul, Turkey; Benny Weksler, University of Tennesse Health Science Center, Tennessee, USA; Terence Williams, City of Hope comprehensive cancer center, California, USA ; Dawei Yang Zhongshan Hospital Fudan University, Shanghai, China; Jeff Yang, Massachusetts General Hospital/Harvard Medical School, Massachusetts, USA; Masaya Yotsukura, Dep of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan.

Advisory Board to the Thymic Tumor Domain

Usman Ahmad, Cleveland Clinic, Cleveland, Ohio, USA, Thoracic Surgery. Heart, Vascular and Thoracic Institute. Cleveland Clinic and Cleveland Clinic Abu Dhabi, United Arab Emirates; Sarit Appel, Sheba Medical Center, Ramat Gan, Israel; Cecilia Brambilla, Royal Brompton and Harefield hospital, Guy's and St. Thomas NHS foundation trust, UK; Conrad B. Falkson, Queen's University, Kingston, Ontario, Canada; Pier Luigi Filosso, University of Torino, Torino, Italy; Giuseppe Giaccone, Weill-Cornell Medicine, New York, USA; Francesco Guerrera, University of Torino, Torino, Italy; Maurizio Infante, University and Hospital Trust Azienda Ospedaliera Universitaria Integrata, Verona, Italy; Dong Kwan Kim, Asan Medical Center, Seoul, and University of Ulsan College of Medicine, Seoul, Republic of Korea; Marco Lucchi, Division of Thoracic Surgery, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Charles B. Simone II, New York Proton Center and Memorial Sloan Kettering Cancer Center, New York, USA.

Advisory Board to the Esophageal Cancer Domain

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

Advisory Board to the Mesothelioma Domain

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

Appendix 2. Chairpersons and Members of the Subcommittees of the Lung Cancer, Epithelial Thymic 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 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 Bille, Giuseppe Cardillo, Kemp 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 & 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 Nicholson, Mizuki Nishino, Helmut Prosch, Ramon 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. Hisao Asamura (chair), Giuseppe Cardillo, Frank Detterbeck, John Edwards, Kwun Fong, Meredith Giuliani, James Huang, Kemp 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 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 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. Jin 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 Terra, Maria Teresa Ruiz Tzukazan, Benny Weksler.

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

Epithelial Thymic Tumors Domain

Enrico Ruffini (chair), James Huang (co-chair), Usman Ahmad, Sarit Appel, Andrea Bille, Souheil Boubia, Cecilia Brambilla, A K Cangir, Frank Detterbeck, Conrad Falkson, Wentao Fang, Pier Liugi Filosso, Giuseppe Giaccone, Nicholas Girard, Francesco Guerrera, Maurizio Infante, Hong Kwan Kim, Marco Lucchi, Mirella Marino, Edith M. Marom, Andrew Nicholson, Meinoshin Okumura, Andreas Rimner, 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: Nicholas Girard (chair), Sarit Appel, Conrad Falkson ,Wentao Fang, Giuseppe Giaccone, Hong Kwuan Kim, Edith M. Marom, Andreas Rimner.

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

Pleural Mesothelioma Domain

Valerie Rusch (chair), Anna Nowak (co-chair), Pietro Bertoglio, Andrea Billè, Dean Fennell, Françoise Galateau, Ritu R. Gill, Seiki Hasegawa, Hong Kwan Kim, Hedy Kindler, Jan van Meerbeeck, Isabelle Opitz, Harvey Pass, Marc de Perrot, David Rice, Andreas Rimner, Jennifer Sauter, Ming 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, University Hospital Heidelberg, Heidelberg, Germany (8887 cases); W.Li, CAALC: West China Hospital, Sichuan University, Chengdu, China (7345 cases); Y.Kim, Korean

Association for Lung Cancer, Seoul, South Korea (4622 cases); H.K.Kim, Samsung Medical Center, Seoul, South Korea (4130 cases);F.Griesinger, CRISP, Berlin, Germany (5482 cases)*; J.Huang, Memorial Sloan Kettering Cancer Center, New York, USA (3146 cases); R. Osarogiagbon, Baptist Memorial Hospital, Memphis, USA (3021cases); S.Park, Seoul National University Hospital, Seoul, South 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, USA (1819 cases); J.Shih, Taiwan Society of Pulmonary and Critical Care Medicine, Taipei, Taiwan (1481 cases); Simon Jordan, The Royal Brompton Hospital & Emma 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, 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, China (825 cases); M.Redman, SWOG-0819, Seattle, USA (782 cases); H.Pass, NYU Langone Medical Center and Cancer Center, New York, USA (762 cases); J.Sun, Shanghai Chest Hospital, Shanghai, China (634 cases); J.Sun, CAALC: Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China (634 cases); K.Fong, The University of Queensland TPCH Thoracic Research Centre, Brisbane, Australia (577 cases); R.Terra, University of Sao Paulo Medical School, Sao Paulo, Brazil (555 cases); N.Wu, Second Department of Thoracic Surgery, Peking University Cancer, Beijing, China (455 cases); K.Chen, First Department of Thoracic Surgery, Peking University Cancer H, Beijing, China (451 cases); A.Mohan, All India Institute of Medical Sciences, New Delhi, India (448 cases); P.Van Schil, University Hospital Antwerp, Dept of Pneumology, Edegem, Belgium (304 cases); P.Bertoglio, IRCCS Sacro Cuore-Don Calabria Hospital, Negrar, Italy (298 cases); C.Yang, Massachusetts General Hospital, Boston, 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. 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, 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, USA (132 cases); M.Serra Mitjans and R. Costa, GCCB3: Hospital Mútua Terrassa. Barcelona (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, South 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, 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); N.Tarek, Ain Shams University Hospitals, Cairo, Egypt (64 cases); D.Yang, CAALC: Zhongshan Hospital Fudan University, Shanghai, 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.Montuenga, 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 and J.M. Matilla, 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:

** 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-Studien-gGmbH (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. However, these companies have no input into or influence over data analysis, data interpretation, or writing of the manuscript.*

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.T.Rosell Abós, GCCB3: Hospital Royo Vilanova, 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, USA (28 cases); D.Mishra, BP 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, Minessota, USA (20 cases); J. Hernández Hernández, 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.Morales Chacón, GCCB3: Hospital Clínico San Carlos, Madrid, Spain (16 cases); Y. L. Wu, Guangdong General Hospital, Guangzhou, China (15 cases); E.Martínez Tellez and J.C.Trujillo, GCCB3: Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (14 cases); L.Bai, CAALC: Xinqiao Hospital, No. 3 Army Medical University, Chongqing, China (14 cases); R. Magaroles and L. de Esteban Júlvez, Hospital Universitari Joan XXIII, Tarragona, Spain (14 cases); R. Melchor Íñiguez, Fundación Jiménez Díaz, Madrid, Spain (14 cases); IR.Embun Flor and P.Teller Justes, GCCB3: Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain (13 cases); C.M. Ariza Prota, GCCB3: Hospital Universitario Asturias, Oviedo, Spain (13 cases); M. J. Pavón Fernández, Hospital Severo Ochoa, Leganés, Spain (13 cases); J. Menéndez, Hospital General de Agudos José M. Penna, Buenos Aires, Argentina (11 cases); S. Defranchi, Hospital Universitario-Fundación Favaloro, Buenos Aires, Argentina (11 cases); E. Martínez Tellez, Hospital de Terrassa, Terrassa, Spain (11 cases).

The following institutions submitted ten eligible cases or less listed alphabetically

M.Curado, A.C. Camargo Cancer Center, Sao Paulo, Brazil; A.Badawy, Alexandria University, Alexandria, Egypt; X.Zhang, CAALC: Henan Provincial People's Hospital, Zhengzhou, China; Q.Wang, CAALC: The Second Hospital of Dalian Medical University, Dalian, China; S.Han, CAALC: Zhongda Hospital Affiliated to Southeast University, Nanjing, China; D.Levy Faber, Carmel Medical Center, Haifa, Israel; P. García Herreros, Clínica Cardiovid, Medellín, Antioquia, Colombia; F.Suárez, Clínica Santa María, Santiago de Chile, Chile; D. Subotic, Clinical Center of Serbia, Belgrade, Serbia; J. Abal Arca and I. Parente Lamelas, Complejo Hospitalario de Ourense, Ourense, Spain; T. Horvath, Czech Republic-Urazova nemocnice Brno, BRNO, Czech Republic; M.Velásquez, Fundación Clínica Valle del Lili, Cali, Colombia; J.C. Peñalver Cuesta, GCCB3: Fundación Instituto Valenciano de Oncología, Valencia, Spain; S.García García, GCCB3: Complejo Asistencial Universitario de León, León, Spain; O.Bernadich Márquez, GCCB3: Hospital Althaia Red Asistencial Universidad de Manresa, Barcelona, Spain; J.García, GCCB3: Hospital Gregorio Marañón, Madrid, Spain; T.Ruiz Albi, GCCB3: Hospital Río Hortega, Valladolid, Spain; O.Castro Añón, GCCB3: Hospital Universitario Lucus Augustí, Lugo, Spain; M.Serraj, Hassan II University Hospital, Fez, Morocco; V.Baysungur, Health Science University Sureyyapasa Thoracic and Chest Disease, Istambul, Turkey; M.Raíces, Hospital Italiano de Buenos Aires, Argentina; J.R. Hernández-Hernández, Hospital Nuestra Señora de Sonsoles, Ávila, Spain; Luis Berlanga, Hospital San Pedro Alcántara, Cáceres, Spain; M.J. Pavón Fernández, GCCB3: Hospital Severo Ochoa, Leganés, Madrid, Spain; H. Hernández Rodríguez, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Canary Islands, Spain; F. Abad Cavaco and E. Ansótegui Barrera, Hospital Universitario La Fe, Valencia, Spain; V. Cvijanovic, Military Medical Academy, Belgrade, Serbia; M.Zereu, Pavilhao Pereira Filho, Santa Casa de Porto Alegre, Brazil; W.Aguiar, SECITOR - Servico de Cirurgia Toracica de Recife, Recife, Brazil.

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.2024.01.019.

References

1. Eberhardt WE, Mitchell A, Crowley J, et al. The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of

the tnm classification of lung cancer. *J Thorac Oncol*. 2015;10:1515–1522.
2. Giaj-Levra N, Giaj-Levra M, Durieux V, et al. Defining synchronous oligometastatic non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 2019;14:2053–2061.
3. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019;37:1558–1565.
4. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4:e173501.
5. Kavanagh BD, McGarry RC, Timmerman RD. Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. *Semin Radiat Oncol*. 2006;16:77–84.
6. Wang XS, Bai YF, Verma V, et al. Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic eGFR-mutated NSCLC. *J Natl Cancer Inst*. 2023;115:742–748.
7. Dingemans AC, Hendriks LEL, Berghmans T, et al. Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report. *J Thorac Oncol*. 2019;14:2109–2119.
8. Levy A, Hendriks LEL, Berghmans T, et al. Eortc lung cancer group survey on the definition of NSCLC synchronous oligometastatic disease. *Eur J Cancer*. 2019;122:109–114.
9. Kroeze SGC, Pavic M, Stellamans K, et al. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the Eortc-estro Oligocare consortium. *Lancet Oncol*. 2023;24:e121–e132.
10. Detterbeck FC, Nishimura KK, Cilento VJ, et al. The International Association for the Study of Lung Cancer staging project: methods and guiding principles for the development of the ninth edition tnm classification. *J Thorac Oncol*. 2022;17:806–815.
11. Detterbeck FC, Asamura H, Rami-Porta R, Rusch VW. The only constant is change: introducing the International Association for the Study of Lung Cancer proposals for the ninth edition of TNM stage classification of thoracic tumors. *J Thorac Oncol*. 2023;18:1258–1260.
12. Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19:766–785.
13. Rami-Porta R, Nishimura KK, Giroux DJ, et al. 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. *J Thorac Oncol*. 2024. https://doi.org/10.1016/j.jtho.2024.02.011.
14. Van Schil PE, Asamura H, Nishimura KK, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the revisions of the T-descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19:749–765.
15. Asamura H, Nishimura KK, Giroux DJ, et al. IASLC lung cancer staging project: the new database to inform revisions in the ninth edition of the tnm classification of lung cancer. *J Thorac Oncol*. 2023;18:564–575.
16. Hwang JK, Page BJ, Flynn D, et al. Validation of the eighth edition tnm lung cancer staging system. *J Thorac Oncol*. 2020;15:649–654.
17. Okami J, Shintani Y, Okumura M, et al. Demographics, safety and quality, and prognostic information in both the seventh and eighth editions of the TNM classification in 18,973 surgical cases of the Japanese joint committee of lung cancer registry database in 2010. *J Thorac Oncol*. 2019;14:212–222.
18. Metzenmacher M, Griesinger F, Hummel HD, et al. Prognostic factors in nonsmall cell lung cancer: insights from the German Crisp registry. *Eur Respir J*. 2023;61:2201336.
19. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: the lung cancer mutation consortium experience. *J Thorac Oncol*. 2015;10:768–777.
20. Dias M, Antunes A, Campainha S, Conde S, Barroso A. Prognostic impact of M descriptors of the 8th edition of TNM classification of lung cancer. *J Thorac Dis*. 2017;9:685–691.
21. Higuera Gomez O, Moreno Paul A, Ortega Granados AL, et al. "High Tumor Burden" in metastatic non-small cell lung cancer: defining the concept. *Cancer Manag Res*. 2021;13:4665–4670.
22. Lee P, Bazan JG, Lavori PW, et al. Metabolic tumor volume is an independent prognostic factor in patients treated definitively for non-small-cell lung cancer. *Clin Lung Cancer*. 2012;13:52–58.
23. Tarantino P, Marra A, Gandini S, et al. Association between baseline tumour burden and outcome in patients with cancer treated with next-generation Immunoncology agents. *Eur J Cancer*. 2020;139:92–98.
24. Zhang H, Wroblewski K, Appelbaum D, Pu Y. Independent prognostic value of whole-body metabolic tumor burden from FDG-PET in non-small cell lung cancer. *Int J Comput Assist Radiol Surg*. 2013;8:181–191.
25. Iyengar P, All S, Berry MF, et al. Treatment of oligometastatic non-small cell lung cancer: an astro/estro clinical practice guideline. *Pract Radiat Oncol*. 2023;13:393–412.
26. Postmus PE, Brambilla E, Chansky K, et al. The Iaslc lung cancer staging project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the tnm classification of lung cancer. *J Thorac Oncol*. 2007;2:686–693.
27. Rami-Porta R, Bolejack V, Giroux DJ, et al. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2014;9:1618–1624.