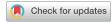




## The IASLC Lung Cancer Staging Project: A Renewed Call to Participation



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#### ABSTRACT

Over the past two decades, the International Association for the Study of Lung Cancer (IASLC) Staging Project has been a steady source of evidence-based recommendations for the TNM classification for lung cancer published by the Union for International Cancer Control and the American Joint Committee on Cancer. The Staging and Prognostic Factors Committee of the IASLC is now issuing a call for participation in the next phase of the project, which is designed to inform the ninth edition of the TNM classification for lung cancer. Following the case recruitment model for the eighth edition database, volunteer site participants are asked to submit data on patients whose lung cancer was diagnosed between January 1, 2011, and December 31, 2019, to the project by means of a secure, electronic data capture system provided by Cancer Research And Biostatistics in Seattle, Washington. Alternatively, participants may transfer existing data sets. The continued success of the IASLC Staging Project in achieving its objectives will depend on the extent of international participation, the degree to which cases are entered directly into the electronic data capture system, and how closely externally submitted cases conform to the data elements for the project.

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Keywords: Lung cancer; Lung cancer databases; Lung cancer staging; TNM classification

#### Introduction

The International Association for the Study of Lung Cancer (IASLC) established an international staging committee, now referred to as the Staging and Prognostic Factors Committee (SPFC), in 1997 to collect and combine lung cancer data sets to inform changes to the TNM staging system for lung cancer with representation worldwide and including all treatment modalities. The TNM staging system was developed by Pierre Denoix between 1943<sup>1</sup> and 1952,<sup>2</sup> and until the IASLC initiative,

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\*\*See Appendix 1 for the members of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee and advisory boards and Appendix 2 for the chairpersons and members of the subcommittees of the Lung Cancer Domain of the IASLC Staging and Prognostic Factors Committee.

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revisions to the lung cancer staging system had been based almost exclusively on a single data set established by Dr. Clifton Mountain at M. D. Anderson Cancer Center<sup>3</sup> in the United States.

This first phase of the staging project resulted in a database of 81,495 evaluable lung cancer cases from 45 sources in 20 countries that were diagnosed from 1990 to 2000 and included all treatment modalities. 4 This database was the foundation for the committee's core recommendations for changes to the staging system, which was published in 2007<sup>5-9</sup> along with additional publications on SCLC, 10,11 carcinoid tumors, 12 and prognostic factors for lung cancer in general<sup>13</sup> and surgically managed NSCLC.<sup>14</sup> In planning for future collaboration, a new international nodal map 15 was proposed to resolve differences in the two maps in use at the time, and standard criteria were proposed to measure depth of pleural invasion.<sup>16</sup> All of these recommendations were adopted by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) in 2009 in the seventh editions of their staging manuals for lung cancer. 17,18 They were also published in the first edition of the IASLC Staging Manual in Thoracic Oncology and the IASLC Staging Handbook in Thoracic Oncology. 19,20 A catalog of presentation slides describing the recommendations and the supportive data is also posted on the IASLC website for public use.

The second phase of the staging project began in 2009 with a call to participants to contribute data using a centralized, electronic data capture (EDC) system.<sup>21</sup> Alternatively, participants were encouraged to collect the published data elements using their own platforms and still contribute standardized data sets in this way. These data elements were drafted in a series of meetings of the chair and subcommittee chairs in 2007-2008 and circulated among the full committee membership for review. Ultimately, a number of large national registries were combined with the EDC data to yield a database of 94,708 patients around the world with lung cancer diagnosed from 1999 to 2010. Approximately 6% of the cases in this second international database were submitted according to the prescribed data dictionary, including 4667 cases entered through the EDC and a database of 1427 from Memorial Sloan Kettering Cancer Center.<sup>22</sup> From this second, international database, the IASLC SPFC developed recommendations toward the eighth edition of the TNM staging system. These recommendations were published in 2015, 2016, and 2017<sup>23-33</sup> and were once again accepted by the UICC34 and AJCC35 in 2017 (with AJCC implementation effective in 2018) and included in the second edition of the IASLC Staging Manual in

Thoracic Oncology and the IASLC Staging Handbook in Thoracic Oncology. 36,37

### Data Elements for the Project

The project is now entering its third cycle, with the goal of developing recommendations for the ninth edition of TNM. The population to be studied consists of patients with lung cancer newly diagnosed between January 1, 2011, and December 31, 2019. The data elements and other documentation describing the project, including application materials, a protocol to facilitate ethics review, and screenshots of the data entry screens, are posted online at https://iaslc.crab.org/LC/ LCStagingProject9Ed.pdf. Briefly, data elements include patient characteristics; baseline laboratory values and results of pulmonary function tests and positron emission tomography; an indication of which clinical tests were used to establish pretreatment T, N, and M categories; clinical TNM category plus supporting evidence and pathologic TNM category; treatment; molecular markers; and survival.

Pretreatment TNM category is collected for all cases; postsurgical or pathologic TNM category is collected if resection of the primary tumor is attempted. T descriptors include size and degree of tumor extension, with further description of pretreatment carcinomatous lymphangitis and attributes of the primary tumor documented during the surgical procedure that are not currently T descriptors. Nodal station involvement is described by station by using the IASLC 2009 nodal map, with additional collection of the number of nodes sampled, the number of positive nodes, and the presence of extracapsular involvement. M descriptors qualify the presence of pleural/pericardial effusions, contralateral/ bilateral lung nodules, and contralateral/bilateral pleural nodules and quantify metastatic lesions at specific distant sites. Genetic biomarkers, copy number alterations, and protein alterations identified at any time during the course of systemic treatment, as well as the specific systemic agents administered, are new data elements in the ninth edition effort, introduced by the recently created Molecular Taskforce Subcommittee of the SPFC.

In all, the database consists of 474 fields collected in 18 data forms. Although the majority of these fields are check boxes, entering a complete baseline form set can be expected to take 1 to 2 hours. This time estimate is based on the October 2017 release of the EDC system (before molecular forms were added) and reflects the experience of the first institutions in using the new system—primarily, the Cooperative Group of Bronchogenic Carcinoma III–Spanish Society of Pulmonology and Thoracic Surgery.

# Areas of Focus for the Next Revision of the TNM Classification

The initial retrospective staging project was based exclusively on existing data sets that were not designed to address questions about lung cancer staging, and the limitations of this method of case selection have been described. For example, proposals for change regarding T descriptors were limited to tumor size, additional tumor nodules, and pleural effusion in the seventh edition recommendations partly because of a lack of detail in the data submitted to explore other questions regarding tumor extension.<sup>22</sup> In the eighth edition database, many of the large staging-related data sets and registry data were pivotal in providing the empirical evidence on which the T1a, T1b, and T1c categories are based and provided context to the stage groupings analysis. However, with the exception of the Japanese series, these data sets were less informative to decisions regarding atelectasis (reclassified as T2 whether partial or total) or involvement of the main bronchus (reclassified as T2) or diaphragm (reclassified as T4), for example.<sup>22</sup> They also generally lacked the distinction between single and multiple distant metastatic lesions necessary to explore the committee's predefined objectives regarding M descriptors. By contrast, the subset of cases that were directly entered through the EDC from Spain, China, and other countries in Europe and South America were fundamental to the eighth edition recommendations to subdivide extrathoracic metastases into M1b (single lesion) and M1c (multiple lesions), as these data suggested that the M1b category had a prognosis similar to that of the M1a category and significantly different from that of the M1c category.<sup>25</sup> For these reasons, increasing online registration through the EDC is the highest priority of the IASLC SPFC in terms of recruitment of cases in the ninth edition database.

The primary aim of the IASLC Lung Cancer Staging Project is to inform future revisions to the staging criteria. The research objectives related to the T, N, and M descriptors, as well as other nonanatomic considerations for staging and prognosis, are as outlined in Table 1. Further implementation and evaluation of prognostic differences based on tumor size will be a special area of focus for the ninth edition, given the increasing emphasis on tumor size as a determinant of T classification and the new guidelines regarding the measurement and pathologic staging of adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma,<sup>38</sup> which were added to the WHO Classification in 2015.<sup>39</sup> Other burning questions for the ninth edition in particular include the assessment of the prognostic impact of single versus multiple station involvement in N1 and N2 locations, skip N2 disease, and reassessment of newly implemented proposals regarding multiple lesions after increasing the follow-up for survival of these patients. Although criteria for complete resection in lung cancer were already published in 2005 by an IASLC working group specifically looking at residual (R) disease, the precise impact of the different R categories on survival has not been clearly established. 40 A recent publication 41 and data presented at the presidential session of the 18th World Conference on Lung Cancer<sup>42</sup> show that patients with uncertain resections have a poorer outcome that do patients with complete (R0) resections. Most patients in the uncertain category have inadequate lymph node dissection; so, particular attention should be paid to mediastinal staging and intraoperative lymph node evaluation. Guidelines for surgical evaluation during staging and definite treatment of lung cancer will be provided, with clarification of the description of the different lymph node stations for specific surgical purposes. Also, oligometastatic disease is currently a major topic of interest, with controversial opinions regarding the best management. More prospective data will provide useful information regarding refinement of the category M1b: is there a significant survival difference between patients with one, two, or three metastases in one specific distant organ? Are these survival rates comparable to the survival rates in patients with two or three distant metastases in two or three different organs? Finally, survival models should be developed that incorporate additional biomarker profiles and specific gene mutations as prognostic variables in addition to anatomic TNM and classic predictors of survival such as age, sex, and performance status. In this respect, the creation of prognostic groups combining anatomic and nonanatomic parameters will be one of the most challenging activities of the third phase of the IASLC Staging Project.

## Call to Participation

At this time, the IASLC SPFC is issuing a call to participation to all who wish to contribute data to this effort to ensure that decisions regarding the staging of lung cancer are based on sound empirical evidence. The current time line for the project, as shown in Table 2, allows recruitment of cases through 2019, with follow-up for survival through 2021, for the ninth edition recommendations to be developed in 2022. As in past years, these findings will be shared with the worldwide lung cancer community through a series of publications to be submitted to the *Journal of Thoracic Oncology*. The recommendations and supportive data will also be submitted to the UICC and AJCC for consideration in the next

Table 1. Study Objectives						
Component	Objective					
Т	<ul><li>a) Assess the prognostic impact of tumor size</li><li>b) Assess the classification capacity of each descriptor defining T status</li><li>c) Study new conditions not included in the present T (e.g., differences between parietal pleura invasion and rib invasion)</li></ul>					
N	<ul> <li>a) Assess the prognostic impact of N status</li> <li>b) Assess the prognostic impact of <ul> <li>i. Nodal extent (single vs. multiple station involvement in N1 and N2 locations)</li> <li>ii. Number of involved lymph nodes</li> <li>iii. Lymph node ratio (i.e., number of involved lymph nodes divided by the number of removed lymph nodes)</li> <li>iv. Nodal size (i.e., largest involved node within the relevant N category)</li> <li>v. Individual nodes involved in each nodal category</li> </ul> </li> <li>c) Assess the prognostic impact of extracapsular extension</li> <li>d) Assess the prognostic impact of the N3 nodal location (i.e., contralateral mediastinum and ipsilateral or contralateral supraclavicular fossa)</li> </ul>					
М	<ul> <li>a) Assess the prognostic impact of M status</li> <li>b) Assess the prognostic impact of <ol> <li>Single metastasis in a single organ</li> <li>Multiple metastases in a single organ</li> <li>Multiple metastases in several organs</li> </ol> </li> </ul>					
Other	<ul> <li>a) Assess the prognostic impact of histologic type and grade</li> <li>b) Assess the reliability of staging methods utilized in clinical staging (for those tumors with pretreatment and postsurgical classification)</li> <li>c) Assess the prognostic impact of complete, incomplete, and uncertain resections according to the proposed definitions of the International Association for the Study of Lung Cancer</li> <li>d) Assess the prognostic impact of clinical factors, including comorbidity and pulmonary function tests</li> <li>e) Assess the prognostic impact of maximum standard uptake value (SUV<sub>max</sub>) at the primary site and in any positive nodal sites for those patients with positron emission tomography scans in the pretreatment staging</li> </ul>					
Prognostic groups	<ul> <li>a) Assess the prognostic relevance of individual molecular parameters</li> <li>b) Create prognostic groups based on the combination of anatomic and nonanatomic parameters, including molecular markers, clinical and epidemiological features, and other parameters, such as lung function tests, blood analyses and SUV<sub>max</sub></li> </ul>					

 $SUV_{max}$ , maximum standardized uptake value.

revisions of their staging manuals, which are expected to be published in 2024.

Contributing to the IASLC database is both personally and professional rewarding for those interested in improving lung cancer staging on account of the long-standing nature of this international project, which has proved to be very successful in the past two revisions of the TNM classifications of thoracic maliganancies. Contributors are acknowledged in the appendix of every paper published by the committee. In addition, contribution of cases through the EDC system provides sites with the ability to download institutional data, with

range checks and data consistency checks having been applied.

Each institution that contributes data to the project will retain full access and publishing rights to its own data; however, the collective database is the property of the IASLC, and Cancer Research And Biostatistics is responsible for its management, storage, and analysis. Publications related to the objectives of the IASLC SPFC (i.e., publications providing recommendations for changes in the TNM classification for lung cancer) will be planned, researched, analyzed, and written by the members of the respective subcommittees and will

Table 2. Time Line									
Year:	2018	2019	2020	2021	2022	2023	2024		
Activity:		registration ective to 2011)	Follow-up prelimi	o and inary analysis	Final data analysis	Publication of recommendations in the Journal of Thoracic Oncology Submission of recommendations to the UICC and AJCC	Publication of the ninth edition of the TNM classification by the UICC and AJCC		

follow the same authorship pattern used for the publications regarding the seventh and eighth edition proposals: chair of the subcommittee, members of the subcommittee in alphabetical order, chair of the IASLC SPFC on behalf of the committee, and participating institutions.

Readers with ideas on the inclusion of elements not included in the present data set should contact the chair of the IASLC SPFC, Hisao Asamura, MD (thymoma1983@gmail.com), and explain the rationale behind these proposals.

There are several ways to become a member of the IASLC SPFC: (1) by invitation (invitations are sent to specialists who have shown special interest in staging or who can contribute cases from their institutions or scientific societies, (2) by recommendation from an IASLC board member (these are usually included in point 1), (3) by application (the IASLC has a system of self-nomination to apply for membership on the IASLC different committees; the applications are reviewed by the IASLC and discussed with the chair of the SPFC and chairs of the respective subcommittees), and (4) by contacting the chair of the SPFC and expressing interest in participating.

In all cases, membership in the SPFC is subject to approval by the president and board of directors of the IASLC. Current active IASLC membership is generally required to serve on IASLC committees, though exceptional circumstances may be considered at the discretion of the SPFC chair.

To indicate your interest in contributing data to the project or to obtain more information, please send an email to webhelpIASLC@crab.org (Supplementary Fig. 1) with IASLC Lung Cancer Staging Project in the subject line.

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## Appendix 1

#### IASLC Staging and Prognostic Factors Committee

Hisao Asamura (chair), Keio University, Tokyo, Japan; Valerie Rusch (chair elect) Memorial Sloan Kettering Cancer Center, New York, New York; Ramón Rami-Porta (past chair), Hospital Universitari Mutua Terrassa, Terrassa, Spain; Luiz Henrique Araujo, Brazilian National

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#### Advisory Board to the Lung Cancer Domain

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### Advisory Board to the Esophageal Cancer Domain Eugene Blackwell, Cleveland Clinic, Cleveland, Ohio; Thomas Rice, Cleveland Clinic, Cleveland, Ohio.

# Appendix 2: Chairpersons and Members of the Subcommittees of the Lung Cancer Domain of the IASLC Staging and Prognostic Factors Committee

IASLC Staging and Prognostic Factors Committee Chair

Hisao Asamura.

Lung Cancer Domain Chair Paul Van Schil.

Lung Cancer Domain Vice Chair Kemp Kernstine.

# Lung Cancer Domain T Descriptors Subcommittee Hisao Asamura (chair), A. K. Cangir, Hui Liu, Jessica Donnington, Wentao Fang, Gustavo Lyons, William Travis, Young Tae Kim, Shuji Sakai, Paula Ugalde, Pietro Bertoglio.

# Lung Cancer Domain N Descriptors Subcommittee James Huang (chair), Kemp Kernstine, Raymond U. Osarogiagbon, Francisco Suárez, Valerie Rusch, David Rice, Ricardo Beyruti, Hong Kwan Kim, Paul Van Schil, Shun-ichi Watanabe, Helmut Prosch, Edith Marom.

### Lung Cancer Domain M Descriptors Subcommittee Kwun Fong (chair), Navneet Singh, Dean Fennell, Wilfried Eberhardt, Yolande Lievens, Mirella Marino,

Jeremy Erasmus, Paul Martin Putora, Edith Marom, Francisco Suárez.

# Lung Cancer Domain Ground Glass Opacities and Adenocarcinoma In Situ Subcommittee

William Travis (chair), Hisao Asamura, Shun-ichi Watanabe, Shuji Sakai, Yasushi Yatabe, Helmut Prosch, Hans Hoffman, John Edwards, Philippe Joubert, Ritu Gill, Jin Mo Goo, Andrew G. Nicholson, Young Tae Kim, Heber MacMahon, Frank Detterbeck, Edith Marom.

#### Lung Cancer Domain Neuroendocrine Tumors Subcommittee

Ming Tsao (cochair), Andrew G. Nicholson, (cochair), Wilfried Eberhardt, Ricardo Beyruti, Yasushi Yatabe, William Travis, José-María Matilla, Yolande Lievens, Frank Detterbeck, Eric Lim.

#### Lung Cancer Domain Stage Subcomittee

Hisao Asamura (chair), Ramón Rami-Porta, James Huang, Kwun Fong, William Travis, Ming Tsao, Shun-ichi Watanabe, Andrew G. Nicholson, Frank Detterbeck, John Edwards, James Brierley, Paul Van Schil, Kemp Kernstine, Edith Marom.

#### Lung Cancer Domain Lymph Node Chart Subcommittee

Shun-ichi Watanabe (chair), Hisao Asamura, Valerie Rusch, Ramón Rami-Porta, Hans Hoffman, Paul Van Schil, Kemp Kernstine, Raymond U. Osarogiagbon, Jin Mo Goo, Edith Marom.

#### Lung Cancer Domain Validation and Methodology Subcommittee

Frank Detterbeck (chair), James Brierley, Raymond U. Osarogiagbon, Paul Beckett, Mirella Marino, Hisao Asamura, Valerie Rusch, Eric Lim.

#### Lung Cancer Domain Prognostic Factors Subcommittee

Frank Detterbeck (chair), Andrew G. Nicholson, Kwun Fong, Young Tae Kim, James Huang, Jan van Meerbeeck, Ming Tsao.

#### Lung Cancer Domain R Factor Subcommittee

John Edwards (chair), Hans Hoffman, Souheil Boubia, Jun Nakajima, Paul Van Schil, Jessica Donnington, Elisabeth Brambilla, Edith Marom, Andrew G. Nicholson, Mirella Marino, Françoise Galateau, Bill Travis, Yasushi Yatabe, Ming Tsao.

# Lung Cancer Domain Radiology and Imaging Subcomittee

Heber MacMahon (chair), Edith Marom, Jim Mo Goo, Ritu Gill.

#### Lung Cancer Domain Multiple Pulmonary Nodules Subcommittee

Frank Detterbeck (chair), Edith Marom, Andrew G. Nicholson, William Travis, Paula Ugalde, Ricardo M. Terra, Eric Lim.

#### Lung Cancer Domain Molecular Database Subcommittee

David Carbone (cochair), Fred Hirsch (cochair), Ignacio Wistuba, Keith Kerr, Elisabeth Brambilla, Oliver Gautschi, Yasushi Yatabe, Luiz Henrique Araujo, Harvey Pass, Ming Tsao, Ramón Rami-Porta, William Travis, Frank Detterbeck, Andrew G. Nicholson, Hisao Asamura, Philippe Joubert, Luis Montuenga, Ricardo M. Terra, Raymond U. Osarogiagbon, José-María Matilla, Dean Fennell, David Beer, Jacinta Wiens, Eric Lim.

#### Cancer Research And Biostatistics

John Crowley, Kari Chansky, Dorothy Giroux, Vanessa Bolejack, Amy Stoll-D'Astice, Hong Wei Wang, Katie Nishimura.

#### 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.2018.02.012.

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