Forty Years of the International Association for Study of Lung Cancer Pathology Committee

Ming-Sound Tsao, MD, FRCPC,* William D. Travis, MD,† Elisabeth Brambilla, MD, PhD,‡ Andrew G. Nicholson, MD, FRCPath,§ Masayuki Noguchi, MD, PhD,|| and Fred R. Hirsch, MD, PhD,¶ on behalf of the IASLC Pathology Committee

Abstract: Lung cancer classification during the last four decades has undergone major changes and evolution, mostly lead by pathologists who were actively involved in the International Association for the Study of Lung Cancer (IASLC) Pathology Committee. The Committee members have led the development and writing of the second (1981), third (1999 and 2004), and fourth (2015) editions of the World Health Organization classifications on lung tumors. Committee members were responsible for defining and refining the classifications of small-cell carcinoma and adenocarcinoma subtypes that are relevant to their clinical behavior. Particularly notable was development of the 2011 IASLC/American Thoracic Society/European Respiratory Society international, multidisciplinary lung adenocarcinoma classification. The multidisciplinary approach that represents the IASLC culture in research, education, and practice in clinical management of lung cancer patients have paved the way for integrating pathology practice into the new era of personalized cancer care.

Key Words: World Health Organization classification, Histopathology, Molecular pathology, Epidermal growth factor receptor, Anaplastic lymphoma kinase.

(J Thorac Oncol. 2014;9: 1740–1749)

The International Association for the Study of Lung Cancer (IASLC) was established in 1974 to promote all aspects of research in lung cancer and thoracic malignancies and improve lung cancer patient outcome through prevention, better diagnosis, and treatment. As an international and multidisciplinary organization, the pathology community was engaged to play a role in this effort. The development and role of Pathology Committee has been an evolution, with large parts being intimately associated with the development of lung cancer classification during the last four decades (Fig. 1). However, with more recent advances on molecular diagnoses in lung cancer, the committee has also assumed leadership roles in the development of guidelines and standards on molecular testing for lung cancer. This article is meant to highlight and archive some of the important works and roles that IASLC Pathology Committee and its members have undertaken, in the context of the 40th Anniversary of IASLC.

EVALUATION OF IASLC PATHOLOGY PANEL/COMMITTEE

1970s and 1980s

In 1982, the Pathology Panel of the IASLC was officially recognized by the IASLC Board and approved by the General Assembly as recorded in the IASLC Newsletter, September 29, 1982. However, leading up to this event, a group of lung cancer pathology experts (Fig. 2) coordinated by Dr. Raymond Yesner (New Haven, CT) had already been working together on the lung cancer classification. In 1977, Dr. Yesner was asked by the World Health Organization (WHO) to be the chairman of the 2nd edition of the WHO classification of lung tumors and to coordinate this group through 1981, when the World Health Organization, Histological Typing of Lung Tumours, 2nd edition was published.

After the 1981 WHO classification was published, a proposal was made to the IASLC Board to form a Pathology Panel by Drs. Mary J. Matthews, Fred R. Hirsch, Adi Gazdar, Yukio Shimosato, and Raymond Yesner. The purpose of the Panel at that time was summarized in Table 1. After formal constitution of the Panel, the group focused on the classification of small-cell lung cancer (SCLC) and its subtypes: the classical “oat cell” carcinoma (lymphocyte-like), the intermediate subtype, and the combination of SCLC and non–small-cell lung cancer (NSCLC). Based on ongoing cell line studies, mainly performed at the National Cancer Institute, Bethesda, MD, evidence emerged that there were significant biologic differences between classical oat cell carcinoma (“classical” cell lines) and the intermediate subtypes (corresponding to “variant” cell lines). The biologic differences in
characteristics of the cell lines encouraged the IASLC pathology group to evaluate differences in clinical characteristics for SCLC patients having classical oat cell carcinoma versus those with intermediate subtypes. The latter morphologic subtype was also termed 22/40 based on the mixture of SCLC (in the WHO classification termed 22) and the large-cell carcinoma (in the WHO classification termed 40). Some clinical studies were performed showing that patients with tumor of the 22/40 subtype had a poorer response to chemotherapy and shorter survival compared with patients with the pure SCLC morphology. However, other studies showed no difference, and the IASLC Pathology Panel tried to determine whether the differences in clinical outcome were based on different histopathologic interpretation of the WHO subtypes. Several publications were made from the IASLC pathology group on this issue including a proposal for modification of the histologic subclassification of small-cell carcinoma. However, through these studies, the morphologic and biologic heterogeneity of malignant lung tumors was recognized, and further studies emerged demonstrating the heterogeneity in NSCLC. Clinical studies emerged and also demonstrated chemotherapy effect of certain histologic subtypes of NSCLC, and the tasks for the IASLC Pathology Panel expanded as more pathologists became involved in its activity (Table 2).

FIGURE 1. IASLC contribution to the progress made in pathology of thoracic malignancies during the last 40 years. Upper panel illustrates the milestone in histologic classification of lung cancer and contribution by members of IASLC pathology committee. Lower panel highlights major progress in pathology research during each decade since 1970s. IASLC, International Association for the Study of Lung Cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.
The late Dr. Mary Matthews served as the first Panel chairman until the 1991 sixth World Conference on Lung Cancer (WCLC) in Melbourne, Australia, when Dr. Fred Hirsch assumed chairmanship for the period of 1991–1998. In 1994, with the encouragement of Dr. Shimosato, two projects were initiated that focused on lung neuroendocrine tumors and adenocarcinoma. This led to a series of publications on lung neuroendocrine tumors from the Panel as well as new ideas that contributed to revisions in the 1999 WHO classification. During this period, new members were recruited to the committee including those shown in Table 2. In 1996, Dr. Travis was asked by the WHO to coordinate the revision of the international classification of lung tumors, and a collaboration between WHO and IASLC was initiated.8

Between 1994 and 1998, the Panel members contributed and reviewed a group of neuroendocrine lung tumors and adenocarcinomas (Fig. 3) allowing for development of better
<table>
<thead>
<tr>
<th>Year</th>
<th>Chairperson</th>
<th>Members</th>
<th>Major Accomplishment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983–1991</td>
<td>Mary Matthews (USA)*</td>
<td>Seena Aisner (USA), Onofrio Campopopbasso (Italy),¹ Bryan Corrin (UK), J. D. Elema (Netherlands), Adi Gazdar (USA), Samuel P. Hammar (USA), Fred R. Hirsch (Denmark), Bruce Mackay (USA), Magnus Nasiell (Sweden), Mary Sheppard (UK), Yukio Shimosato (Japan), Richard H. Steele (Australia), Raymond Yeener (USA),¹ and L. Zettergren (Sweden)</td>
<td>Second edition of WHO Classification of Lung Tumors (published in 1981)</td>
</tr>
<tr>
<td>1991–1998</td>
<td>Fred R. Hirsch (Denmark)</td>
<td>Seena Aisner (USA), Emilio Alvarez-Fernandez (Spain), Elisabeth Brambilla (France), Thomas V. Colby, M.D. (USA), Bryan Corrin (UK), Adi Gazdar (USA), Samuel P. Hammar (USA), Philip S. Hasleton (UK), Bruce Mackay (USA), Helmut Popper (Austria), Mary Sheppard (UK), Yukio Shimosato (Japan), Richard Steele (Australia), and William D. Travis (USA)</td>
<td>Third edition of WHO Histological typing of lung and pleural tumours (published in 1999)</td>
</tr>
<tr>
<td>1999–2005</td>
<td>William D. Travis (USA)</td>
<td>Seena Aisner (USA), Emilio Alvarez-Fernandez (Spain), Elisabeth Brambilla (France), Thomas V. Colby, M.D. (USA), Bryan Corrin (UK), Wilbur Franklin (USA), Fred Hirsch (USA), Samuel P. Hammar (USA), Philip S. Hasleton (UK), Masayuki Noguchi (Japan), Helmut Popper (Austria), and Mary Sheppard (UK)</td>
<td>WHO Classification of Tumors—Pathology and Genetics, Tumours of the Lung, Pleura, Thymus and Heart (published in 2004)</td>
</tr>
<tr>
<td>2005–2009</td>
<td>Elisabeth Brambilla (France)</td>
<td>Douglas B. Flieder (USA), Wilbur Franklin (USA), Adi Gazdar (USA), Kim R. Geisinger (USA), Philip S. Hasleton (UK), Douglas Henderson (Australia), Bruce E. Johnson (USA), Andrew Nicholson (UK), Masayuki Noguchi (Japan), Victor Roggli (USA), F. B. J. M. Thunnissen (Netherlands), William D. Travis (USA), and Ming-Sound Tsao (Canada)</td>
<td>IASLC/ATS/ERS International multidisciplinary classification of lung adenocarcinoma. (published in 2011)</td>
</tr>
<tr>
<td>2009–2011</td>
<td>Masayuki Noguchi (Japan)</td>
<td>Seena Aisner (USA), Elisabeth Brambilla (France), Federico Cappuzzo (Italy), Lucian Chirieac (USA), Fred Hirsch (USA), Kim Geisinger (USA), Keith Kerr (UK), Andrew Nicholson (UK), Masayuki Noguchi (Japan), Victor Roggli (USA), Dirk Nalle (Germany), Iver Petersen (Germany), David Travis (USA), and Ming-Sound Tsao (Canada)</td>
<td>CAP/IASLC/AMP guideline on EGFR and ALK testing for lung cancer patients (published in 2013)</td>
</tr>
<tr>
<td>2011–2013</td>
<td>Ming-Sound Tsao (Canada)</td>
<td>Seena Aisner (USA), Elisabeth Brambilla (France), Lucian Chirieac (USA), Sanja Dacic (USA), Rafal Dziadziuszko (Poland), Kim Geisinger (USA), Fred Hirsch (USA) Keith Kerr (UK), Yuichi Ishikawa (Japan), Iver Petersen (Germany), Andrew Nicholson (UK), Masayuki Noguchi (Japan), Victor Roggli (USA), Dirk Nalle (Germany), Iver Petersen (Germany), David Travis (USA), and Ming-Sound Tsao (Canada)</td>
<td>IASLC ATLAS of ALK Testing in lung cancer. (published in 2014)</td>
</tr>
<tr>
<td>2013–2015</td>
<td>Andrew Nicholson (UK)</td>
<td>Mary Beth Beasley (USA), Elisabeth Brambilla (France), Johan Bottling (Sweden), Lucian Chirieac (USA), Sanja Dacic (USA), Kim Geisinger (USA), Fred Hirsch (USA), Giuseppe Pelosi (Italy), Keith Kerr (UK), Yuichi Ishikawa (Japan), Nirush Lertprasertboon (Thailand), Andre Moreira (USA), Masayuki Noguchi (Japan), Iver Petersen (Germany), Erik Thunnissen (Netherlands), Kafai To (China/Hong Kong), William D. Travis (USA), and Ming-Sound Tsao (Canada)</td>
<td>CAP/IASLC/AMP guideline on EGFR and ALK testing for lung cancer patients (published in 2013)</td>
</tr>
</tbody>
</table>

¹IASLC Newsletter, November 1983.
understanding of these tumors and consensus on the histologic subclassification. These efforts and the publication documenting 100% 5-year survival for solitary small peripheral bronchioalveolar carcinomas (BACs)9 led to major revisions in criteria for neuroendocrine lung tumors and adenocarcinoma adopted in the 1999 WHO classification. Collaborations among panel members resulted in a number of publications that contributed to our better understanding of the clinical, biologic, and molecular aspects of lung cancer.10–20 The panel for the 1999 WHO Histologic Typing of Tumours of the Lung and Pleura consisted of the IASLC panel as well as additional members added for broader expertise and international representation (Table 2). Dr. Travis became chair of the Pathology Panel in 1999 and the panel met once or twice a year to address problems in the pathology of lung tumors.

In 2003, Drs. Travis and Brambilla were asked to be co-editors of the 2004 WHO Blue Book on classification of tumors, together with Drs. H. Konrad Müller-Hermelink (Würzburg, Germany) and Curtis C. Harris (Bethesda, MD). For this effort in addition to members of the IASLC Pathology Panel, almost 200 co-authors were involved in the writing of this document.21 A writing committee of the lead authors and staff from the International Association for Research on Cancer met in March of 2004 in Lyon, France to assemble the book (Fig. 4).

In November 4, 2004, at a multidisciplinary workshop on BAC22 sponsored by the IASLC and the American Society of Clinical Oncology, the IASLC Pathology Panel co-chaired by Drs. Travis and Franklin worked closely with a panel of radiologists coordinated by Dr. Kavita Garg (Denver, CO) to address problems in classification of BAC and lung adenocarcinoma.23 In preparation for this meeting, a panel of pathologists met at the Armed Forces Institute of Pathology in August of 2004 to review histologic slides from a set of lung adenocarcinomas contributed for the workshop (Fig. 5). The pathology group reviewed a series of 131 cases with surgical biopsies and computed tomography scans and a consensus document was published in 2005.23 In 2005, the IASLC Pathology Panel was reformed (Table 2, 2005–2009) and Dr. Brambilla became the Chair and Dr. Noguchi the Chair-Elect.

2005 to Present

As a follow-up of the Bronchioloalveolar Workshop meeting, the panel organized a series of meetings and workshop to address the classification of pulmonary neuroendocrine tumors and adenocarcinoma. An IASLC International Symposium on Advances in Pulmonary Neuroendocrine Tumors was held in December 2007 at the Royal Brompton Hospital in London, United Kingdom.24 The meeting, led by 14 international faculties in the disciplines of pathology, surgery, medicine, oncology, endocrinology, nuclear medicine, diagnostic imaging, and biostatistics aimed to develop the IASLC International Pulmonary Neuroendocrine Tumors Registry. The meeting highlighted the difference in presentation of the tumors, management options for early and advanced stage disease including the use of novel agents and approaches.
The need, process, and approach to an International Registry were emphasized. International collaboration to develop a retrospective registry, prospective data collection, virtual tissue bank, and collaborative clinical trials were universally agreed as the best way to advance our understanding and treatment of these rare tumors. These recommendation remains as an ongoing project for the current Pathology Committee.

The concept of developing the next version of lung adenocarcinoma classification that is based on multidisciplinary inputs followed the 2005 IASLC/American Society of Clinical Oncology BAC workshop. The concept was proposed to and received approval by the IASLC Board of Directors at the 2007 12th WCLC meeting, and subsequently received co-funding approval by the American Thoracic Society (ATS) and the European Respiratory Society (ERS). The first International Multidisciplinary Lung Adenocarcinoma Classification meeting took place at the Memorial Sloan Kettering Cancer Center (MSKCC, New York) during March 28–31, 2008, to address the pathology, clinical, surgical, imaging, and molecular issues pertaining to lung adenocarcinoma classification. In addition to the pathologist members, more than 20 IASLC leaders in medical oncology, thoracic surgery, respiriologists/pulmonologists, thoracic radiologists, and lung molecular biologists were invited and attended this meeting. After this meeting, a systematic literature review on all aspects of lung adenocarcinoma involving more than 60 international lung cancer experts was completed during August 2008 to February 2009. This was followed by a second International Lung Adenocarcinoma Multidisciplinary meeting in March 2009 at the MSKCC, during which the concept of “adenocarcinoma in situ (AIS) and “minimally invasive adenocarcinoma (MIA)” to replace the classical yet confusing term “BAC” was presented, extensively discussed and adopted by majority vote. In addition, the adenocarcinoma classification was revised to group tumors based on the predominant histologic patterns while retaining the rare variants. After presentations of the new classification at the 13th WCLC (San Francisco, CA), ATS (San Diego, CA), and ERS (Vienna, Austria) meetings, the manuscript was finally published in the February 2011 issue of the *Journal of Thoracic Oncology*.

After Dr. Masayuki Noguchi became the Chair of the panel, the committee devoted 2010 to the completion of the new classification manuscript, and conducted a study to assess the feasibility of adopting the “predominant pattern” approach.
for classifying lung adenocarcinoma with mixed histologic patterns. The results of this extensive study were the topic of discussion during the committee meetings in January and October of 2011 at Tsukuba, Japan. The study concluded that in pulmonary adenocarcinomas with classic morphology, which comprise the majority of cases, there was good reproducibility in identifying a predominant pattern. However, more precise definitions and better education on interpretation of existing terminology are required to improve recognition of purely in situ disease, which becomes an area of increasing importance.

Dr. Ming-Sound Tsao became Chair of the Committee in October 2011 and focused the committee efforts and meetings during 2011–2013 to two areas: (1) molecular classification and biomarkers for treatment in NSCLC and (2) revision of classifications of other types of lung cancers aside from adenocarcinoma (Fig. 6). This period marked an important extension of the Committee’s activities into the field of molecular pathology and biomarkers, especially on issues related to tissue utilization and assay standardization in biomarker testing. In collaboration with the College of American Pathologists and the Association of Molecular Pathologists, representative members of the IASLC Pathology Committee participated in the systematic review and publication of a guideline on molecular testing of epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements in lung cancer patients. In addition, the Committee convened a workshop that resulted in the publication of the IASLC Atlas on ALK testing in lung cancer. The Atlas was freely distributed to all registrants at the 15th WCLC and worldwide. The Atlas provided guidance on the use of fluorescence in situ hybridization for detecting ALK gene arrangement, as well as the use of alternative methods for ALK testing, selection of patients for testing, sample acquisition and processing, comparison of testing platforms, and reporting guidelines. Its goal was to help pathologists, laboratory scientists, and practicing physicians better understand the background, protocol, and interpretation of results of ALK testing in patients with advanced NSCLC.

After the 15th WCLC meeting, Prof. Andrew Nicholson became the Chair of the Committee. As a priority in making further revision of the lung cancer histologic classification, the committee convened a multidisciplinary meeting at the MSKCC in New York on December 5–7, 2013. This meeting, led by Dr. William Travis, discussed proposals extensively for new classification system for lung cancer, in addition to the new classification of lung adenocarcinoma published in 2011. In addition to the Pathology Committee members, more than 20 IASLC leaders in clinical oncology and lung cancer genome scientists were invited to discuss critical issues that would impact on the new classification system being drafted for the 4th edition of the *WHO Classification of Tumors of the Lung Pleura, Thymus and Heart* to be published in January 2015, with three members of the IASLC Pathology Committee, Drs. William Travis (lead editor), Elisabeth Brambilla, and Andrew Nicholson serving as the invited co-editors of this new book, and many committee members are lead co-authors of its major chapters.

**HIGHLIGHTS OF PATHOLOGY RESEARCH DURING FOUR DECADES**

**1970–1979**

One of the most important reports in pathology during 1970s was by Oscar Aurbach et al., who documented the significant decrease in the prevalence of bronchial epithelial...
aberrations related to smoking during 1955–1960 and 1970–1977, which coincides with the introduction of filter-tip cigarettes. Although the authors concluded that the finding supported a great drop during 25 years in the tar and nicotine content of the smoke from cigarettes consumed in the USA, it did not address the fact that such changes in cigarette manufacture resulted in a shift in the histology and location of lung cancer from more common central squamous/small-cell carcinoma to peripheral adenocarcinoma. Another important development was reports that cytology examination of exfoliated lung cancer cells can be accurately classified according to the histologic types diagnosed in resection specimens.30,31 These reports led to the widespread adoption of cytology and the standard of care as the primary method of diagnosis especially in advanced lung cancer patients.

1980–1989

Two important areas of development occurred during the 1980s. The first was a proposal by the IASLC Pathology Committee to revise the 1981 WHO classification of small-cell carcinoma by combining the “oat cell” and “intermediate” variants into a single “small cell” entity, and recognizing the “mixed small cell/large cell” and “combined small-cell carcinoma” variants as new variants with potential prognostic and therapeutic implication.7,32 This new proposed classification has subsequently been adopted in the 1997 and 2004 WHO classifications. The other development was several institutional and population-based studies that reported a changing incident pattern of histologic type of lung cancer during the 1970s, with an increase in adenocarcinoma type.33,34

1990–1999

One of the important developments in lung cancer pathology during this period was reports by Dr. Elisabeth Brambilla et al.35,36 on basaloid carcinoma as a new subtype of non–small-cell carcinoma with distinct histopathologic features and very poor prognosis. Tumors that fit into this subtype were identified in 38 of 671 lung cancers that were resected over a 7-year period, with 22 stage 1 and 2 patients having a very poor median survival of 22 months. This tumor subtype has subsequently been incorporated into the WHO classification.1,8,21

In 1995, Drs. Noguchi and Shimosato published for the first time a pioneer paper35 on the pathologic prognostic indicator in small-cell (size: ≤2 cm) lung adenocarcinoma on a series of 236 surgically resected small 2 cm maximum diameter adenocarcinoma. They distinguished patients with type A (localized BAC) and type B (with foci of collapse) adenocarcinoma, in contrast with other subtypes with invasion (C, D, E, and F), showed no lymph node metastasis and the most favorable prognosis with 100% 5-year survival. Based on this article, the concept of AIS and MIA emerged and these entities were subsequently proposed in the 2011 IASLC/ATS/ERS lung adenocarcinoma classification.22 At the molecular pathology front, an important step was achieved toward the comprehension of multistep and multicentric carcinogenesis field cancerization with the discovery of multiple clonal abnormalities in the bronchial epithelium of patients with lung cancer.33 Multiple small clones or larger clonal patches containing clonally related molecular abnormalities are present in normal or slightly dysplastic bronchial epithelium, distant to the tumor in smoking patient with lung cancer, indicating that normal epithelium of smokers is not normal.

2000–2009

In 2004, the new WHO classification “blue book” on Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart Classification was published.23 The new classification recognized that 85% of adenocarcinoma are mixed type and do not fit within one defined histologic pattern, due to the frequent histologic heterogeneity. Importantly, EGFR mutations that conferred sensitivity to EGFR tyrosine kinase inhibitor gefitinib was reported to be significantly more frequent in the BAC subtype.18 This publication has led to increased awareness among clinicians and pathologists on the importance of histologic typing of adenocarcinoma. The second highlight of this decade was the discovery of EML4-ALK gene fusion as a lung cancer driver oncogene,29 and subsequent clinical trials showing that ALK rearranged lung cancers are tractable by specific kinase inhibitors.30,41 This discovery consolidated the concept of “oncogene addiction” as a highly efficacious strategy to treat cancer patients.
2010–2013

In 2011, the IASLC, ATS, and ERS published a new proposal for classifying lung adenocarcinoma. This new classification, which was developed by the IASLC Pathology Committee and with extensive collaboration with a multidisciplinary team of clinicians and scientists from the three societies, proposed major changes to the 2004 WHO lung adenocarcinoma classification that would bring greater clinical relevance for the classification and practical application in the age of molecular pathology and targeted therapy. Major changes included the proposal to discontinue the use of the term BAC from the classification system and replace it with new categories of AIS and MIA, to reflect lesions that may have 100% survival if completely resected by surgery. The new proposal also for the first time provides recommendations on how to approach classification in small biopsy/cytology specimens, and guidelines for good practice in pathologic work-up and diagnosis of lung cancer specimens. Subsequent to the publication of this new proposal, several independent studies have validated the prognostic relevance of the classification.

CONCLUSION

The multidisciplinary approach that represents the IASLC culture in research, education, and practice in clinical management of lung cancer patients has paved the way for integrating pathology practice into the new era of personalized cancer care based on more accurate diagnosis, molecular characterization of tumor, and effective targeted therapy. As the molecular genotype and phenotype of different histologic types of lung cancers are being deciphered, there is expectation that the IASLC Pathology Committee will continue to lead in improving lung cancer diagnosis for better survival outcome of lung cancer patients.

ACKNOWLEDGMENTS

The authors thank Drs. Paul Bunn, Raymond Yesner, and Yukio Shimosato for review of part of this document and for contributing photographs.

REFERENCES