Progress in Lung Cancer

Celebrating 40 years of the IASLC and Research Advancements 1974-2013
Support for *Progress in Lung Cancer: Celebrating 40 Years of the IASLC and Research Advancements* (1974-2013) from Eli Lilly is gratefully acknowledged.
Dedication

To the men and women who have dedicated their professional lives to the optimum care of people with lung cancer and other thoracic malignancies, and to the eventual eradication of these diseases.
**Acknowledgment**

**IASLC Conquering Thoracic Cancer Worldwide**

Since the 1970s, the International Association for the Study of Lung Cancer (IASLC) has promoted research into all aspects of lung cancer and other thoracic malignancies, as well as encouraged worldwide cancer prevention efforts. Under the leadership of the IASLC Board of Directors, IASLC experts have participated in a historical review and documentation of the seminal and influential research that has impacted the treatment and prevention of thoracic cancers worldwide over the past 4 decades.

The vision and tireless efforts of Paul Bunn, Jr, MD, has driven the work involved in documenting this 40-year history of the progress in lung cancer alongside the continuing guidance and vision of the IASLC Board of Directors. The following IASLC leaders in particular are acknowledged for their individual contributions: Hisao Asamura, David Ball, Elisabeth Brambilla, David Carbone, Hak Choy, Carolyn Dresler, David Gandara, Adi Gazdar, Peter Goldstraw, Dominique Grunenwald, Fred R. Hirsch, James Jett, Karen Kelly, John Minna, Alex Molasiotis, James Mulshine, Silvia Novello, Patti Palmer, Ming Tsao, Wilma Uyterlinde, and Johan Vansteenkiste.

Others involved in creating this recognition of the 40-year history progress in lung cancer include Kristal Griffith, IASLC Director of Communications; Deb Whippen, Publisher and Editor, Editorial Rx, Inc; Amy Boches, Graphic Designer, Biographics; Pia Hirsch, IASLC Director of Education, Industry Relations, and Governance; Kristin Richeimer, Director of Membership; and John Wetherington, IASLC COFO.

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Advancement of the understanding of thoracic cancers and their treatment as well as enhancement of the quality of cancer care is the mission of the IASLC. The story of the progress made in research and care of lung cancer is a demonstration of this mission in action and reflects the dedication and commitment of lung cancer specialists worldwide over the past 40 years.
The IASLC has worked since 1974 to promote research into all aspects of lung cancer and thoracic malignancies, as well as encouraging worldwide cancer prevention efforts. The IASLC has grown from 200 members in its first year (1974) to over 3,500 members in 2013. The Association grew and developed over the past 40 years through the dedication of its members and leaders and has had an important impact on the care of people with thoracic cancers. A celebration of this history offers the opportunity to acknowledge and honor the advances made in the science and practice of lung cancer medicine.

This assembly of lung cancer research and IASLC historical information follows a timeline from the early 1970s to the present, and concludes with a look into the future. A systematic literature review was performed on all English language articles with lung cancer in the title. All references were categorized and the number of citations of each provided. These articles were categorized by topic and reviewed by experts in the field. The experts selected the most important research findings by time period using the citation rating, their expert opinion, and impact on research and patient care. Reported here are the most impactful research articles that advanced progress in lung cancer research as well as the accomplishments and programs of the IASLC that communicated these advances to the global community of lung cancer specialists.

The celebration of IASLC’s 40-year history is launched at the 2013 World Conference in Lung Cancer (WCLC) and will continue throughout the years thereafter. Included in this historical review program are this print monograph, a video program accessible through the IASLC website (www.iaslc.org), and an exhibit program at pivotal IASLC educational programs including the 2013 and 2015 WCLCs.

The lung cancer science of the future will continue to translate into the daily clinical medicine provided to patients with lung cancer. Clinical medicine alone will not, of course, address the problems of global tobacco use and tobacco cessation remains of critical importance. Patients with lung cancer will continue to rely on specialists who also work as or among clinical and science researchers to ensure that advances benefit all patients, present and future. The IASLC will continue its leadership in supporting today’s and tomorrow’s lung cancer researchers and practitioners, as well as its vital role communicating information and new developments in thoracic oncology. The IASLC’s organizational vision of conquering lung and other thoracic cancers looks ahead to the future of lung cancer medicine and to continuing the global progress in lung cancer through research, education, prevention, and treatment in a multidisciplinary manner.
Lung cancer, unfortunately, accounts for more deaths worldwide than any other malignant neoplasm. Globally, in 2008 this disease was responsible for 12.7% of all new cancers and 1.38 million deaths. In most developed countries, it is the leading cause of cancer death in both men and women. Even though the majority of lung cancers are caused by tobacco smoking, lung cancer in never-smokers is still a formidable problem. As a result, most lung cancer disease is preventable. In more developed economies, as the smoking prevalence is finally decreasing there is an increasing proportion of lung cancers in people who have never smoked.

By the early 1970s it was clear that lung cancer was the leading cause of cancer death worldwide and was likely to remain so for many decades. A group of leading international experts in many facets of the lung cancer problem recognized that it would take a concerted and organized international and multidisciplinary effort to combat this dreaded disease. “Diseases desperate grown by desperate appliance relieved, or not at all,” wrote William Shakespeare.

Advances in one specialty area of lung cancer research has informed advances in other areas as well. During the 1970s into the 1980s, there were key research breakthroughs and new understandings that had clinical applicability in the care of patients with lung cancer. The range of lung cancer specialties is representative of the multidisciplinary involvement, approach, and global resources invested in lung cancer research. These specialty areas include biology and molecular biology, epidemiology, pathology, pulmonology and pulmonary medicine, medical oncology, radiation oncology, thoracic surgery, radiology and interventional radiology, and public health and supportive care.

1970s Research Highlights

Epidemiology

Lung cancer was linked to cigarette smoking as early as the 1930s. However, it was the key epidemiologic studies from the 1950s in both the UK and the US that more definitively demonstrated causation, most notably the 1950 landmark article in the *British Medical Journal* (Doll and Hill, 1950). Further epidemiologic research during the 1970s and into the 1980s was critical in addressing not only the association between smoking and lung cancer but in confirming other environmental, synergistic factors for the development of lung cancer.

The relationship between asbestos and lung cancer was established in a breakthrough *International Journal of Cancer* article in which a model for the asbestos-smoking interaction on human lung cancer was demonstrated. A *New England Journal of Medicine* article by Blot et al the following year confirmed the relationship between asbestos, smoking, and lung cancer. The link between uranium mining, radiation, and lung cancer was also established in the 1970s by Saccomanno et al who studied miners in the western slope of Colorado, USA.


MILESTONES

- 70 71 72 73 74
- • Lymph node mapping introduced
- • Radiotherapy included in combined modality treatment trials for SCLC and NSCLC
- • ACTH research identified SCLC as an ectopic hormone-producing tumor
- • First data-driven revision of TNM classification of lung cancer
- • Sublobular resection found to be adequate for limited-stage lung cancer
- • First International Workshop for Therapy of Lung Cancer, Virginia, USA
- • First IASLC Board of Directors convenes
Biology

During the 1970s most of the focus for biological research regarding lung cancer was focused on small-cell lung cancer (SCLC). Because of the progress achieved in the treatment of SCLC with systemic chemotherapy, it was urgent to learn the biology of this "disease," which was facilitated by the success of making continuous cell cultures from human SCLC tumors.

In 1974, the Nobel Prize Laureate Rosalyn Sussman Yalow described ectopic adrenocorticotropin (ACTH) in patients with bronchogenic carcinomas (Gewirtz and Yalow, 1974). The ACTH was slightly different from the pituitary ACTH, and was called "Big ACTH" due to a different amino acid composition. However, the finding sparked clinical research on different hormones produced by SCLC, which led to the characterization of SCLC as an ectopic hormone-producing tumor with several recognized paraneoplastic clinical syndromes (i.e., diabetes insipidus [ACTH], hyponatremia [ADH], hypercalcemia [calcitonin], etc). Many different ectopic hormones were found to be produced in patients with SCLC, including also calcitonin, ACTH, and melanin-stimulating hormones (MSH) (Abe et al, 1977) and estrogen (Munck and Brink-Johnson, 1974).

Because there are few circulating cancer cells in lung cancers, a source of cells for study was critical. Several permanent cell lines were established, mainly from the US National Cancer Institute (eg, NCI H-###) (Gazdar et al, 1980), but also from other institutions (Pettengill et al, 1980; Sorenson GD et al, 1981). From the 1970s the cell line studies revealed significant biological characteristics about SCLC; the ectopic hormone production that was demonstrated in patients with SCLC was also demonstrated in cell lines such as immunoreactive ACTH, lipotropin and β-endorphins (Bertagna et al, 1978).
1970s Research Highlights


Pathology

One of the most important reports in pathology during 1970s was by Auerbach et al, who documented the significant decrease in the prevalence of bronchial epithelial aberrations related to smoking during 1955-60 and 1970-77, 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 United States, it did not address the fact that such changes in the cigarette manufacture resulted in a shift in the histology and location of lung cancer from more commonly central squamous/small cell carcinoma to peripheral adenocarcinoma. The other 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 (Oswald et al, 1971; Kanhouwa and Matthews, 1976). These reports led to the widespread adoption of cytology as the primary method of diagnosis especially in patients with advanced-stage lung cancer.

Staging

The study by Mountain et al, conducted under the auspices of the Task Force on Lung Cancer of the American Joint Committee on Cancer Staging and End Results Reporting (subsequently the American Joint Committee on Cancer), was the first attempt at data driven revision of the TNM classification for lung cancer, published by the Union for International Cancer Control (UICC) in 1968 (Mountain et al, 1974). The authors collected a data base of 2,155 cases of histologically confirmed bronchogenic carcinoma with information on 28 clinically established characteristics. Many of the descriptors in use.
today and incorporated into the 7th edition of the TNM classification derive from this study.

By the 1970s, the importance of the assessment of regional lymph node metastasis in lung cancer had been recognized as an important predictor of prognosis influencing the choice of treatment modality. Dr. Pearson showed that candidates for curative resection could be appropriately selected using mediastinoscopy and the vast majority of patients with positive mediastinoscopy could be spared unrewarding thoracotomy (Pearson et al, 1972). For the uniform description of location of nodes, Dr. Naruke introduced the concept of “lymph node mapping.” In this landmark publication, Naruke and colleagues provided the global lung cancer community with an explicit illustration and detailed definitions of each nodal station, a concept still in use today after several revisions (Naruke et al, 1978).

- Mountain CF, Carr DT, Anderson WAD
  A System for the Clinical Staging of Lung Cancer. 

- Naruke T, Suemasu K, Ishikawa S Lymph node mapping and curability at various levels of metastasis in resected lung cancer. 
  *J Thorac Cardiovasc Surg.* 1978; 76:832-839

**Prevention**

Two articles dominated the field of lung cancer prevention during the decades of the 1970s. Both papers were authored by the pair of British epidemiologists, Sirs Richard Doll and Richard Peto. The hallmark of their research was to use large datasets to address logically simple important questions. In this case the nature of smoking exposure across two decades in a large prospective cohort of male British doctors (Doll and Peto, *Br Med J*, 1976), and the impact of tobacco exposure as smokers age (Doll and Peto, *J Epidemiol Community Health*, 1978). One measure of this impact of this research is the estimate that nearly 800,000 smokers in the United States alone were saved by smoking cessation related reductions in lung cancer between 1975-2000 (Moolgavkar al, *J Natl Cancer Inst.* 2012). Also of interest, this prospective cohort was the first study of its kind in the world and demonstrated the ability of epidemiology to define causation of disease. Prior to Doll’s and his mentor’s—Bradford Hill—groundbreaking work in applying mathematics and statistics to medicine, the Koch postulates had been held sacrosanct—that an organism must be demonstrated to cause disease. Also, this ground-breaking prospective cohort was the first time that it was demonstrated that smoking caused cardiovascular deaths (Keating 2009).

Sir Richard Peto, FRS, with Sir Richard Doll, MD, KBE, CH, FRS.
1970s Research Highlights

- Doll R, Peto R
  Mortality in Relation to Smoking: 20 Years’ Observations on Male British Doctors.
- Doll R, Peto R
  Cigarette Smoking and Bronchial Carcinoma: Dose and Time Relationships Among Regular Smokers and Lifelong Non-smokers.
  *J Epidemiol Community Health.* 1978; 32:303-313
- Keating C
  *Smoking Kills: The Revolutionary Life of Richard Doll.*
  Oxford, United Kingdom: Oxford University Press; 2009
- Moolgavkar SH, Holford TR, Levy DT, et al
  *J Natl Cancer Inst.* 2012; 104:541-548

Screening/Radiology

Before the 1970s, there were a number of trials aimed at early detection of lung cancer with chest radiographic imaging. These included studies in the German Democratic Republic, the South London Study, Philadelphia Pulmonary Neoplasm Project, and others (Cooperative Study Group for Early Detection of Lung Cancer in the German Democratic Republic, 1978; Nash et al, 1968; Weiss et al, 1975). However, these studies were inconclusive as to the benefit of screening in high-risk individuals (males). The US NCI sponsored the Early Lung Cancer Cooperative Group, which evaluated the role of chest x-ray and sputum cytology for screening of lung cancer. The three screening programs were at Mayo Clinic, Johns Hopkins University, and Memorial-Sloan Kettering Cancer Center. These randomized screening trials started accrual in the early 1970s. Screening was confined to “high-risk” individuals and consisted of men, 45 years of age or older who smoked one package or more of cigarettes each day at study entry or within the prior year. The Mayo Lung Project screened participants with chest radiographs and sputum cytology every four months and the control group was advised to have usual care but was not contacted for return visits (Fontana et al, 1975). At Johns Hopkins, the screened group received chest radiographs annually and sputum cytology every four months (Stitik et al, 1978). The control group had an annual chest radiograph alone. The Memorial-Sloan Kettering Cancer Center study used a similar design (Melamed et al, 1977) and each of the three centers randomized approximately 10,000 participants. The preliminary reports from these trials observed that the chest x-ray was best at detecting peripheral cancers and cytology was better able to detect centrally located cancers many of which were roentgenographically occult.

- Cooperative study group for early detection of lung cancer in the German Democratic Republic. Roentgenographic chest screening in the detection and survival of patients with lung cancer.
- Fontana RS, Sanderson DR, Woolner LB, et al
  The Mayo lung project for early detection and localization of bronchogenic carcinoma: A status report.
  *Chest.* 1975; 67:511-522
  Preliminary report of the lung cancer detection program in New York.
  *Cancer.* 1977; 39:369-382
- Nash FA, Morgan JM, Tomkins JG
  South London lung cancer study.

Pulmonology

In lung cancer screening studies based on chest x-ray and sputum cytology, “radio-occult lung cancer” (ROLC, i.e., lung cancer detectable by sputum cytology only, with the primary tumor undetectable radiographically or during standard bronchoscopy) emerged as a new diagnostic challenge (Cortese and McDougall, 1979; Doiron et al, 1979). Localizing ROLC with fluorescence bronchoscopy—a fiberoptic bronchoscope with special violet-transmitting light conductor that could detect previously injected hematoporphyrin derivatives concentrated in early endobronchial lesions—proved to be a scientific accomplishment in pilot studies (Sanderson et al, 1974). Occult cancers were now diagnosed with the flexible fiber optic bronchoscope, which had been introduced in the late 1960s by Dr. Shigeto Ikeda (Ikeda et al, 1968).

Furthermore, fluoroscopy applied to the diagnostic algorithm is able to improve the sensitivity of fibrobronchoscopy to obtain diagnosis of lung cancer and at the same time to better identify the endoscopic location of the tumor, even in absence of radiologic alterations (Zavala, 1975).

- Cortese DA, McDougall JC
  Biopsy and Brushing of Peripheral Lung Cancer with Fluoroscopic Guidance.
  Chest. 1979; 75:141-145.

- Doiron DR, Profio E, Vincent RG, et al
  Fluorescence bronchoscopy for detection of lung cancer.

- Ikeda S, Yanai N, Ishikawa S
  Flexible bronchofiberscope.
  The Keio Journal of Medicine 1968; 17:1-16

- Sanderson DR, Fontana RS, Woolner LB, et al
  Bronchoscopic localization of radiographically occult lung cancer.
  Chest. 1974; 65:608-612.

- Zavala DC
  Diagnostic fiberoptic bronchoscopy: Techniques and results of biopsy in 600 patients.


Various biopsy instruments (brushes, forceps, and curette).
Lung Cancer Management

Management of lung cancer usually involves multidisciplinary care. Over the last four decades, treatment options have included surgery, radiation therapy, chemotherapy, and immunotherapy, depending on the type and stage of lung cancer. The historical development of treatment options has enhanced patient clinical care with each new scientific advance.

Surgery

In an attempt to preserve pulmonary function, Jensik and colleagues were the first to suggest that resection less than lobectomy might be adequate for lung cancer (Jensik et al, 1973). They reported the results of segmentectomy in 119 patients. The patients were categorized into three groups: previous resection (n=16), palliative resection (n=37), and curative resection (n=69). In the last group, the survival rate was 56.4% at 5 years, comparable to that for lobectomy at that time. These findings opened the field of exploring the role of sublobar resection for limited-stage lung cancer, a subject of renewed interest in the present era of computed tomography screening.

Adjuvant and neoadjuvant chemotherapy and surgery:

By the late 1970s, it was recognized that the majority of relapses after surgical resection of early-stage lung cancers occurred in distant sites (Br Med J, 1971). Thus, it was clear that improvement in cure rates would need to come from the use of systemic therapies before or after surgery. At the time, chemotherapies such as cyclophosphamide and methotrexate were producing dramatic responses in patients with lymphomas and leukemias. Thus, these therapies were given after surgery in attempt to delay and prevent subsequent distant relapse. Unfortunately, these early attempts were not successful due to the relative lack of efficacy of the chemotherapeutic agents.

Radiation Oncology

Two of the most important developments in this decade were (a) the introduction of computed tomography of the chest for disease staging and radiotherapy planning (Emami et al, 1978)—without which modern conformal radiotherapy would not be possible—and (b) the emergence of combined modality therapy for both small cell and non-small cell lung cancers (SCLCs) as illustrated by the prospective phase III trial of radiotherapy with (groups A and B) and without (group C) cyclophosphamide (Bergsagel et al, 1972).

It was also early in this decade that a possible role for prophylactic cranial irradiation in SCLC was suggested for the first time by Hansen (Hansen HH, 1973).

Survival of treatment groups from start of therapy. Group A, radiotherapy plus eight courses of cyclophosphamide; Group B, radiotherapy plus four courses of cyclophosphamide, or Group C, radiotherapy alone. Reproduced from Cancer, Bergsagel et al, 30:621-627, Copyright © 1972, with permission from John Wiley and Sons.

Bergsagel DE, Jenkins, RDT, Pringle, JF et al
Chemotherapy

Development of cisplatin-based combination therapy, given together with etoposide (Cavalli et al, 1978), represented an advance in chemotherapeutic management of both non-small-cell lung cancer (NSCLC) and SCLC (Einhorn et al, 1976), which has stood the test of time. Still employed today, some 35 years after its initial development in the 1970s, two seminal initial publications are those by Gralla et al (1979), and Sierocki et al (1979) in which clinical response was demonstrated with cisplatin-based therapy.


Immunotherapy

Following up on the clinical observation of decreased recurrence in patients with postoperative empyema, this study describes a prospective randomized clinical trial in early stage lung cancer patients of a single postoperative injection of intrapleural BCG compared to controls treated with postoperative isoniazid orally for 12 weeks (McKneally et al, 1976). None of 17 BCG-treated stage I patients relapsed with one year of followup, while nine of 22 patients randomized to isoniazid therapy relapsed. No difference was seen in smaller numbers of stage II or III patients. Although subsequent trials showed that BCG did not improve outcomes in surgically resected patients, the findings stimulated the field of immunotherapy and vaccine therapy that is beginning to show survival effects 40 years later.


Supportive Care

Supportive care of patients with lung cancer during the 1970s into the early 1980s was largely provided by allied health professionals and publications in this area focused on case-driven issues of palliative and end-of-life care. Little original clinical research was reported and there was a gap in the continuum of therapeutic care to end-of-life. Changes in smoking patterns in parts of the world began to result in a change in the disease of lung cancer and in the options available to those with the disease. The multidisciplinary approach to research and education in lung cancer, in large part driven by the IASLC, was yet to make an impact on supportive care options during the 1970s.
The IASLC has from its beginnings brought together international experts from all disciplines involved in the research and treatment of lung cancer. At its first informal meeting in October 1972—the First International Workshop for Therapy of Lung Cancer—115 individuals from 15 countries discussed the benefit of a multidisciplinary approach and the development of an organization to address lung cancer. In August 1973, the first formal outline of the organization was circulated and by the middle of 1974, approximately 250 individuals comprised the founding membership. The first formal IASLC meeting was held in 1974, in Florence, Italy, where the inaugural slate of officers and board of directors was selected.

The goals of the 1st WCLC (1978) included presentation and evaluation of current knowledge relating to prevention, diagnosis, and treatment of lung cancer and synthesis of appropriate ideas into recommendations to the medical community. The purpose of the first WCLC was to be a scientific forum for sharing current knowledge and research. This program structure has been applied to subsequent WCLCs and expanded upon in additional IASLC’s educational and scientific programs developed over time.

The first WCLC was sufficiently successful to allow for the planning of a second WCLC, which was held in Copenhagen, Denmark from June 9-13, 1980 with Dr. Heine Hansen serving as the Congress President. During this period (1978–1980) Dr. George Higgins served as IASLC President.

At the first international Workshop for Therapy of Lung Cancer, which was held at Arlie House Conference Center in Virginia, USA in 1972, attendees chose David T. Carr, MD to chair an international committee to organize a professional society. This committee developed a constitution and bylaws, membership criteria, and selection processes and held an organizational meeting at the XIth International Cancer Congress sponsored by UICC in Florence, Italy, October 1974. At this meeting the bylaws
were approved as were the founding officers and Board of Directors. The Founding Officers were Oleg Selawry, president, David Carr, Vice President, Clifton Mountain, President-elect, Lawrence Broder, Secretary and George Higgins, Treasurer. The Board of Director’s included Drs. Pierre Alberto, Johannes Clemmensen, Shichiro Ishikawa, Lucien Israel, F.G. Pearson, and Roy Ritts.

Dr. Selawry resigned as President in May 1976 and Dr. David Carr, then vice president, became President for the remainder of 1976. Dr. Clifton Mountain served as President in 1977 and 1978. During this period Dr. Mountain led the plans for the first WCLC, which was held at the Hyatt on Hilton Head Island, South Carolina, USA from May 10-13, 1978. The conference was attended by 106 participants from 16 countries and had the following goals: to present a meaningful evaluation of current knowledge of prevention, diagnosis, and treatment of lung cancer based on the best available evidence; to critically examine the causes of failure in each program area, through bringing into focus the primary need for new approaches; to examine the pertinent spectrum of basic science, and other new knowledge to improve outcomes; and to synthesize ideas that emerge from this interaction into a statement of recommendations to the medical community.

The IASLC logo was designed by Mrs. Laura Palmer, the daughter of Dr. George Higgins, in 1978 when it appeared on the cover of the program for the first WCLC. The logo depicts a sword to symbolically represent the staff of Aesculapius (the god of Healing) and the caduceus of Hermes as a symbol of medicine conquering lung cancer represented by the tracheobronchial tree, the lungs, and the world. Interestingly, despite being the daughter of prominent thoracic surgeon the symbol appears to show 3 lobes to both the right and left lungs!

Newsletter and Journal: The IASLC instituted a newsletter in April, 1975 with Lawrence Broder, MD as the editor. Dr. Broder was the Secretary of the IASLC and started the newsletter to inform the increasing number of members about the activities of the Association and the members. The newsletter was the only official IASLC publication until the launch of the journal *Lung Cancer* in 1985. *Lung Cancer Therapy Annuals* was published by Taylor and Francis annually from 2000–2006.

Lung Cancer Staging: The first TNM based classification for lung cancer was published by the UICC in 1966. In 1973, the American Joint Committee on Cancer (AJCC) Task Force on Lung Cancer proposed a system for the clinical staging of lung cancer using the tumor-node-metastasis (TNM) system based on 2,155 lung cancer cases in the MD Anderson database. In 1974, the International Union Against Lung Cancer (UICC; now named the Union for International Cancer Control) accepted the AJCC TNM lung cancer system in its second edition of the *TNM Classification of Malignant Tumors*, ensuring the uniformity of staging throughout the World. The role of the IASLC in providing data to allow precise prognosis associated with the TNM classification has continued to the present.
**Pathology:** In 1977 Dr. Raymond Yesner was asked by the World Health Organization (WHO) to chair the second edition of the WHO Classification of Lung Tumors. Dr. Yesner chaired this group through 1981 when the second edition was published. This group subsequently became the IASLC Pathology Panel as described later in the text.

**Centers of Excellence in Lung Cancer:** Several institutions around the world, recognizing the importance of lung cancer, established Centers of Excellence that shaped many of the activities of the IASLC and progress in lung cancer. In the US, the NCI created a separate branch to focus its efforts on lung cancer in a multidisciplinary manner. This branch was located at the Washington VA Hospital. Dr. Oleg Selawry was the first branch chief and the first IASLC president, Dr. Broder, and treasurer, Dr. Higgins, were part of the branch. Dr. Mary Matthews, one of the founders of the IASLC Pathology Panel, was also a branch member. Dr. Heine Hansen was one of the first visiting fellows. Dr. Selawry decided to relocate to Florida during the mid-1970s and Dr. John Minna was recruited to head the branch. In 1976, Dr. Minna recruited Drs. Adi Gazdar, Daniel Ihde, and Paul Bunn to become senior investigators within the branch. These investigators used biopsies from patients to start human tumor cell lines now referred to as NCI-H### cell lines, which are widely used in lung cancer research through the present. Many of the branch’s faculty and trainees—including Drs. Eli Glatstein, Allen Lichter, Desmond Carney, James Mulshine, Bruce Johnson, Fred R. Hirsch, Jacqueline Whang-Peng, Gerold Bepler, Edward Sausville, Frank Cuttitta, James Battey, Steve Rosen—became leaders in lung cancer research and in the IASLC.

Dr. Heine Hansen, one of the Branch’s visiting fellows, returned to the Finsen Institute in Copenhagen, Denmark where he organized a similar national center.

In the University of Toronto, Princess Margaret Hospital developed a strong program with leadership from thoracic surgeons (Dr. Robert Ginsberg, Joel Cooper), medical oncology (Ronald Feld and Frances Shepherd), and radiation oncology (David Payne). At MD Anderson Cancer Center in the USA, Dr. Clifton Mountain led a strong group of thoracic surgeons subsequently led by Jack Roth.

In Japan, the Tokyo Medical University and the National Cancer Center developed strong leadership activities and included academic surgeons led by Drs. Shichiro Ishikawa, Yoshihiro Hayata, K. Suemasu, Tsuguo Naruke, H. Kato, with pathologist Dr. Yukio Shimosato.

This growth in leadership of IASLC experts from all disciplines paralleled the pivotal advancements in the lung cancer research and treatment that occurred in the 1980s.

"Progress in lung cancer is a step-by-step march toward declining mortality."
1980s–Uniting Internationally
Research Highlights

**Epidemiology**

In the 1980s, evidence began to grow demonstrating the impact of secondhand smoke on lung cancer incidence. One of the earliest studies was by Dr. Hirayama in Japan who followed a cohort of Japanese women and the smoking behaviors of their husbands over 14 years (Hirayama, 1981). This study demonstrated a risk factor of 2 for developing lung cancer in never-smoking women if their husbands smoked 20+ cigarettes per day. This study overwhelming is the most attributed paper in the 1980s; however, there were substantial other studies, also highly recognized, that addressed the issue of secondhand smoke and its causation of lung cancer in never smokers (Correa et al, 1983). Progressively thereafter through the 1980s and onward, were numerous other studies, cohort and case-control series, that strengthened the epidemiologic evidence of the causation of lung cancer from secondhand smoke and that the risk was greater as the person who smoked had the great consumption (Garfinkel et al, 1985; Dalager et al, 1986).


**Biology**

The period of 1980-1989 was characterized by establishment of more than 100 SCLC cell lines (Carney et al, 1985; Gazdar et al, 1985). Through studies of the established lung cancer cell lines, autocrine growth factors were identified and factors necessary for growth in serum-free conditioned medium were established (Carney et al, 1981). Neuroendocrine features were typical for the SCLC cell lines and among the most frequently growth factors produced was gastrin-releasing peptide (GRP), a mammalian homologue to bombesin (Carney et al, 1987).

Most SCLC cell lines/tumors were “classical SCLC” with retained SCLC morphology, some SCLC cell lines (10% to 15%) had varying degree of morphologic and biologic alterations and they were called “variant SCLC” cell lines, often corresponding to mixed small cell/large cell morphology (Hirsch et al, 1988). Classic cell lines grew as floating aggregates while variant cell lines attached to the plastic dishes.

In most instances, cell lines were aneuploidy and had the same DNA index that corresponded to the human tumors (Bunn et al, 1983). The myc-gene family was frequently amplified (Kok et al, 1989), and “variant SCLC” cell lines frequently overexpressed c-myc oncogene (Gazdar et al, 1985) or other myc-family oncogenes such as N-myc and L-myc. The SCLC cell lines also revealed a consistent deletion of a DNA sequence at chromosomal region 3p (14-23) in all major types of lung cancer (Whang-Penn et al, 1982). The cell line studies also demonstrated that the lung cancer, particularly

**MILESTONES**

- 60 Gy most effective dose in NSCLC
- IASLC Pathology Panel formed
- 2nd WCLC, in Copenhagen, Denmark
- IASLC Pathology Committee proposes revision of WHO classification of SCLC
- First IASLC workshop, on SCLC, at Ashford Castle, Ireland
- 3rd WCLC, in Tokyo, Japan
- Impact of secondhand smoke on lung cancer demonstrated
- Etoposide approved by FDA
- Mediastinal lymph node staging less invasive with flexible transbronchial needle aspiration
SCLC, frequently suffer allelic loss and inactivation of anti-oncogenes including the retinoblastoma (Rb) gene (Harbour et al, 1988) and following the discovery of cytogenetic abnormalities of chromosome region 17p allele loss in lung cancer, the assignment of p53 to this region, it was found inactivation of the p53 gene in lung cancer (Takahashi et al, 1989), and it was suggested that p53 act as an anti-oncogene and that loss of the p53 gene (inactivation/mutation) is an significant event in lung carcinogenesis, eventually through activation of dominantly acting oncogenes (Minna et al, 1986).


- Quality-of-life assessment tools validated
- Chest x-ray and sputum screening for lung cancer not recommended
- Paraplatin approved by FDA for NSCLC

• More than 100 SCLC cell lines established
• Methotrexate approved by FDA
• Increase in adenocarcinoma histologic type of lung cancer
• New staging system for lung cancer proposed
• Thoracic radiotherapy plus chemotherapy improves locoregional control in SCLC
• Chemotherapy established as care standard for good PS SCLC patients, despite toxicity
• Adjuvant chemotherapy has survival impact after NSCLC carcinoma resection
• 4th WCLC, in Toronto, Canada
• IASLC journal Lung Cancer, Heine H. Hansen, MD, Editor
• 5th WCLC, in Interlaken, Switzerland
• Paraplatin approved by FDA for NSCLC
Pathology

Two important areas of development in the area of pathology 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 (Yesner, 1985; Hirsch et al, 1988). These histopathologic studies paved the way of recognizing the tumor heterogeneity of lung cancer, which also at that time was verified biologically through several cell line studies. This new proposed histopathologic 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 (Wu, 1986; Dodds et al, 1986).

Staging

Based upon a database of 3,753 patients with lung cancer a new staging system for lung cancer was proposed (Mountain, 1986). This ultimately formed the basis of the 4th edition of TNM for lung cancer published by the Union for International Cancer Control (UICC) and the 3rd edition of the American Joint Committee on Cancer (AJCC) Staging Manual. A new category of N3 was added and some more extensive tumors previously classified as T3 were re-classified as T4. From the present-day viewpoint, the database was a small, single institution collection of predominately surgically treated cases. However, this was the first attempt to create an international consensus on the staging system for lung cancer.

- Mountain CF

Prevention

During the 1980s, considerable interest focused on the contribution of vitamin A in the regulation of respiratory epithelial growth. Epidemiologic studies conclusively demonstrated the relationship between low vitamin A levels and increased risk of lung cancer (Peto et al, 1981). This formed a rationale for a randomized lung chemoprevention trial conducted in Seattle, Washington (CARET study) involving supplementation of vitamin A either by the oral administration of beta carotene or retinol in a cohort of high at-risk for lung cancer individuals based on exposure to cigarette smoke and/or asbestos (2). This was the most frequently cited paper of the decade. The two vitamin A precursors for this trial were selected as they were much better tolerated as a chronic medication than the parent vitamin A molecule. While the impact of these agents on the increasing levels of vitamin A in lung tissue with trial subjects was not examined, this is an early example of science driven translational research, which showed that epidemiologic studies of nutrient levels did not predict for a chemoprevention effect of high-dose vitamins.

- Peto R, Doll R, Buckley JD, et al
  Can dietary beta-carotene materially reduce human cancer rates?
  Nature. 1981; 290:201-208

- Omenn GS
  A double-blind randomized trial with beta-carotene and retinol in persons at high risk of lung cancer due to occupational asbestos exposures and/or cigarette smoking.

Screening/Radiology

Two studies from Japan evaluated screening with chest roentgenograms annually (Tokyo Metropolitan Government Study) or biennial chest radiographs (atomic bomb survivors study) (Hyata et al, 1982; Hayabuchi et al, 1983). Neither study had a control group. Chest x-rays detected more early stage lung cancers than nonscreened lung cancers from the population, but 5-year survivals for all cancers in the screened population was <20%. A study from Czechoslovakia screened individuals with chest radiographs and sputum cytology and had a no-screening control group (Kubik and Polak, 1986). Another study from Germany combined screening every six months versus every 18 months (Wilde, 1989). Neither the Czechoslovakian or German study demonstrated any decrease in lung cancer mortality in the more frequently screened participants. In the report of the prevalence screen, the three US centers screened over 10,000 subjects each and had a prevalence of <1%. Sputum cytology was helpful for central cancers that were almost always squamous cell carcinomas (Frost et al, 1984; Flehinger et al, 1984; Fontana et al, 1984).

The final results of the three USA randomized trials established that adding biannual sputum cytology to an annual chest x-ray does not decrease lung cancer mortality (Melamed et al, 1984; Tockman et al, 1986). Similarly, performing chest radiographs and sputum cytology every four months did not decrease lung cancer mortality compared to the control group (Fontana et al, 1986). In 1989, a report from the Center for Health Policy Research from Duke University in the USA concluded that, because of lack of benefit and due to potential harms and cost, chest x-ray and sputum screening for lung cancer is not recommended (Eddy, 1989).

- Eddy DM
  Screening for lung cancer.

  Early lung cancer detection: results of the initial (Prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study.

- Fontana RS, Sanderson DR, Taylor WF, et al
  Early lung cancer detection: results of the initial (Prevalence) radiologic and Cytologic screening in the Mayo Clinic study.

- Fontana RS, Sanderson DR, Woolner LB, et al
  Lung cancer screening: the Mayo program.
1980s Research Highlights


Pulmonology

Two  Several advances in the preoperative work-up of lung cancer had their start in the 1980s. Staging of mediastinal nodes traditionally relied on surgical techniques only. The technique of transbronchial needle biopsy with an 18-gauge needle with a beveled stylet allowed sampling of histologic cores during rigid bronchoscopy (Wang et al, 1985). This technique was further refined for the fiberoptic bronchoscopy: flexible transbronchial needle aspiration (TBNA) yielded cytopathologic specimens, which allowed mediastinal lymph node staging in a far less invasive way (Wang, 1983).

More structural data to define functional operability came in place. On the one hand, calculation of predicted postoperative FEV1 (FEV1-ppo) and diffusing capacity (DLCO-ppo) was more precisely estimated with the combination of baseline pulmonary function tests and preoperative pulmonary scintigraphy.

FEV1-ppo and DLCO-ppo of more than 40% of predicted normal value—rather than absolute units—could be linked with postoperative mortality (Markos et al, 1989). Cycle spiroergometry testing became more standardized. In multivariate analyses including several parameters, oxygen uptake at peak exercise level (VO2max, mL/kg/min) —a value that reflects capability of O2 transport by the cardiopulmonary system—proved to be an important predictor of tolerability of lung resection (Olsen et al, 1989).


Lung Cancer Management

Surgery

The North American Lung Cancer Study Group conducted a series of clinical trials in the 1980s, including ground-breaking studies on the role of adjuvant therapy.
in resected NSCLC (Holmes et al, 1985; Holmes et al, 1986). These articles reported on the use of various and combined modalities of adjuvant chemotherapy, immunotherapy, and radiotherapy dependent upon stage and cell type. In these studies the authors demonstrated the importance of systemic therapy to control unsuspected distant metastases and set the scene for successful trials around the turn of the millennium, which proved a positive impact of adjuvant chemotherapy on survival following complete resection of early-stage non-squamous carcinoma. These trials showed favorable results compared to surgery alone and were followed by trials employing two-drug platinum-based combinations that later became standard.

- Holmes EC, Hill LD, Gail M
- Holmes EC, Gail M
  Surgical adjuvant therapy for stage II and III adenocarcinoma and large cell carcinoma. J Clin Oncol. 4: 710-715, 1986

Radiation Oncology

During the 1980s, a series of randomized trials demonstrated the importance of radiotherapy in achieving locoregional control in parallel studies in NSCLC and SCLC. The landmark RTOG 7301 trial demonstrated that 60 Gy was the most effective dose in NSCLC, and it has remained a standard of care to the present day (Perez et al, 1980). In a trial of the Lung Cancer Study Group, postoperative radiotherapy also reduced locoregional failure in patients who had had complete resection of squamous cell carcinoma of the lung but survival was not affected (NEJM, 1986). This impact on local control was largely seen in patients with mediastinal lymph node involvement.

In SCLC, the addition of thoracic radiotherapy to chemotherapy improved locoregional control and this resulted in longer survival (Bunn et al, 1987). Subsequent meta-analyses provided guidelines evidence to treat with concurrent chemoradiotherapy. The timing of the radiotherapy was debated in the 1980s with most studies showing early initiation at the outset or with two cycles of chemotherapy was superior to the addition of chest radiotherapy late in the course. A Canadian study of two different doses of thoracic radiotherapy demonstrated that a higher dose (37.5 Gy vs 25 Gy) was associated with better local control and survival (Coy et al, 1988), confirming the presence of a dose-response relationship as in NSCLC.

- {no authors}
- Bunn PA Jr, Lichter AS, Makuch RW, et al
- Perez CA, Stanley K, Rubin P, et al

Chemotherapy

A Canadian NCI study randomized 233 patients with NSCLC to two different doublet chemotherapy options, vs. placebo and showed that patients on the trial had a median survival of 32.6 weeks when treated with vindesine and cisplatin; 24.7 weeks with cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), and cisplatin; and 17 weeks with BSC. This is the first study...
that established the survival benefit of chemotherapy (albeit modest), compared to best supportive care in patients with NSCLC, and established the paradigm that therapy should be the standard of care for good performance status patients, in spite of the high toxicity of the platinum-containing regimens in an era before effective anti-emetic regimens. Many subsequent trials and meta-analyses of these trials confirmed these results (Bonomi et al, 1989; Ruckdeschel et al, 1986; Hirsch et al, 1987; Klastersky et al, 1989): thus 2-day platinum-based combinations remain the standard of care today.

In limited-stage SCLC the results of the first randomized trials comparing combined chemotherapy and radiotherapy were reported and showed superior survival for the combined approach (Bunn et al, 1987, see reference citation in Radiation Oncology 1980s section). There were no available therapies for relapsed SCLC, but the reintroduction of EP was shown to produce high response rates in late relapse and remains the standard approach for this indication today (Batist et al, 1983).


Immunotherapy

In the 1980s, attempts were made to use cytokines and natural extracts to build on the hints from the empyema and intrapleural BCG data of the 1970s and earlier (Watanabe and Iwa, 1984). Technologies for the culture and therapeutic re-infusion of T-cells, pioneered by Steven Rosenberg at the Surgery Branch of the NCI, much more developed for melanoma and other cancers, saw early clinical application in lung cancer (Rosenberg et al, 1987). Small randomized trials of vaccine therapy showed no benefit for the vaccines in both SCLC and NSCLC (Yasumoto et al, 1987).

Clinical studies on patient-reported outcomes led to the development and call for validity testing of lung cancer-specific quality-of-life tools such as the EORTC-QOL lung questionnaire, the Functional Living Index (FLIC), and the Linear Analogue Self-Assessment (LASA) scales that were carried on in the 1990s. Another practice-changing theme centered around the exploration of performance status, age, psychosocial support, and emotional health's effects on the overall prognosis of patients treated with therapy, radiation, and chemotherapy, for lung cancer (Kaasa et al, 1989; Cella et al, 1987). Conclusive evidence was found for the positive effect of good performance status and overall prognosis, a treatment tenant that still holds true today. Studies also looked closely at the relationship of continued smoking and prognosis with conflicting results (Johnston-Early et al, 1980; Bergman and Sorenson, 1988).

These studies laid the groundwork for further study and the conclusion that there was a benefit in prognosis if patients stopped smoking. In the area of symptom management the majority of the citations looked at using total parenteral nutrition (TPN) to reverse cachexia associated with lung cancer concluding that the risks associated with TPN were much greater than the benefits in prognosis and that successful treatment of cancer was the most effective treatment of cancer cachexia (Weiner et al, 1985). Other papers reviewed the patient’s perception of dyspnea, causes and treatment for dyspnea, offered guidelines for treatment of chemotherapy-related side effects (specifically nausea and vomiting and renal insufficiency with cisplatin), pain control, and home care guidelines for lung cancer patients as care moved from primarily hospital to outpatient (Brown et al, 1986; Foote et al, 1986). Finally, there were a few studies that began to look at long-term survivors and the complications of successful treatment. Specifically suggesting that prophylactic brain irradiation in SCLC was related to long-term cognitive changes and also describing secondary leukemias in survivors who had received multi-agent chemotherapy for SCLC (Frytak et al, 1989; Bradley et al, 1982). The overall theme of supportive care in the 80s decade was to critically look at the risk and benefits of treatment for lung cancer and realize that for some patients the risk was much greater that the benefit and that not everyone should be offered aggressive treatment. However, on a positive note, there were long-term survivors of lung cancer in the 1980s and the beginning of research about surviving lung cancer is also seen.

- Bergman B, Sorenson S
  Smoking and effect of chemotherapy in small cell lung cancer.

- Bradley EC, Schechter GP, Matthews MJ, et al
  Erthroleukemia and other hematologic complications of intensive therapy in long term survivors of small cell lung cancer.

- Brown ML, Carrieri V, Janson-Bjerklie S, et al

- Cella DF, Orofiamma B, Holland JC, et al
  *Cancer*. 1987; 60:1661-1667.

- Foote M, Sexton DL, Pawlik L.
  Dyspnea: a distressing sensation in lung cancer.

  Leukoencephalopathy in small cell lung cancer patients receiving prophylactic cranial irradiation.

- Johnston-Early A, Cohen MH, Minna JD, et al
  Smoking abstinence and small cell lung cancer survival. An association.
  *JAMA*. 1980; 244:2175-2179.

- Kaasa S, Mastekassa A, Lund E
  Prognostic factors for patients with inoperable non-small cell lung cancer, limited disease. The importance of patient’s subjective experience of disease and psychosocial well being..

- Weiner RS, Kramer BS, Clamon GH, et al.
  Effects of intravenous hyperalimentation during treatment in patients with small-cell lung cancer.
The **1980s—Steady Growth of the IASLC**

**WCLCs:** The IASLC entered the 1980s with a fabulous start centered on the 2nd WCLC with Heine Hansen, MD as the Conference President. This conference attracted more than 1,000 registrants from more than 38 countries. There were 283 submitted abstracts. The conference highlighted the many advances in lung cancer including surgical techniques and staging systems refinements, new chemotherapy and radiotherapy studies especially in SCLC and new biology findings. Dr. Hansen also instituted many social activities that became a staple of ensuing WCLCs. These included an opening ceremony with local dignitaries, including the Queen of Denmark, a half-day tour of local sites, an evening of entertainment and a closing ceremony. Tokyo, Japan was selected as the site of the 3rd WCLC with Dr. Shiohiro Ishikawa as Congress President and Dr. Yoshihio Hayata as Vice-President.

The 3rd WCLC was held in Tokyo, Japan from May 17-20, 1982 and was attended by more than 1,500 registrants from more than 30 countries. There were 388 abstracts. The IASLC flag was introduced at the Conference and it became a tradition to present the flag to the next WCLC Congress President who would hold the flag until the following WCLC. While the 3rd WCLC was a scientific success, it was decided to hold the WCLCs on an every 3rd year basis because it was felt there was not sufficient scientific advances to warrant conferences every other year. Toronto, Canada was selected to hold the 4th WCLC with Dr. Ronald Feld as Conference President (Secretary General) and Dr. Robert Ginsberg as Vice President (Program Chair).

The 4th WCLC was held on August 25-30, 1985 and had 1,064 registrants from 33 countries. There were 600 submitted abstracts. The 4th WCLC was the first WCLC to be “smoke free” as tobacco smoking was banned in all the meeting places. At the time, this was a major change. At the meeting, the Board decided that the IASLC should sponsor small workshops and conferences to take place between WCLCs. The society provided funds for Dr. Hansen to conduct IASLC business from his Copenhagen office.

The 5th WCLC was held in Interlaken, Switzerland from August 28–September 1, 1988 with Dr. Rudolf Joss as the Conference President (Secretary General), Dr. Kurt Brunner was Program Leader (conference co-President). The meeting had 1,100 registrants, 880 submitted abstract and 50 invited speakers. Social highlights included an excursion to the Ballenberg museum and a boat cruise over Lake Brienz. Abstracts were published as a supplement to the new IASLC journal *Lung Cancer*. 

**Presentation of the IASLC flag at the 3rd World Conference on Lung Cancer.**
Workshops: Because the WCLCs were held on an every 2-3 year basis, the need arose for workshops on selected topics. The workshop topics and workshop chairs were approved by the IASLC Board of Directors but were organized by the chairs. During the 1980s there were 14 of these workshops, which were varied in topic and included three on SCLC in 1981, 1984, and 1989; one on SCLC antigens in 1987; one on mesothelioma in 1981; three on biology or biologic features in 1984, 1985, 1987; one on treatment of NSCLC; one on surgical therapy one on combined modality therapy; and three on varied topics. The majority of these workshops were held in Europe (10) and three were in North American and one in Asia. Several of these workshops developed state of the art consensus statements that were published in *Lung Cancer*.

First workshop on Small Cell Lung Carcinomas at Ashford Castle, Ireland September 1981.

**Lung Cancer—Official IASLC Journal:** The IASLC contracted with Elsevier to start the society’s first journal, *Lung Cancer*. Dr. Heine Hansen was appointed as the Editor. From 1985 to 1989 there were quarterly issues annually that were typewritten in Copenhagen and

**IASLC 80s Workshops/Symposia**

1981 First Workshop on Small Cell Lung Cancer, Asford Castle, Ireland.
1984 Second Workshop on Small Cell Lung Cancer, Gleneagles, Scotland.
1984 Peptide Hormones and Lung Cancer, Marburg, Germany.
1984 Colloquium on Surgical and Bronchological Aspects of Lung Cancer, Rome, Italy.
1985 Postgraduate Course on Chest Tumors, Pomerio Castle, Italy.
1987 International Conference on Hormones, Growth Factors and Oncogenes in Pulmonary Carcinoma, Hanover, New Hamshire, USA.
1987 Workshop on Combined Treatment of Lung Cancer, Le Havre, France.
1987 The Guangzhou First Symposium on Lung Cancer, China.
1987 Treatment of Non–Small Cell Lung Cancer, Key Biscayne, Florida, USA.
1989 Third Workshop on Small Cell Lung Cancer, Elsinore, Denmark.
The 1980s—Steady Growth of the IASLC

published and distributed by Elsevier. There were two sections: 1) society news, meeting reports, information from cooperative groups, member surveys, and 2) submitted manuscripts. Starting in 1989 there were bi-monthly publications typeset and distributed by Elsevier. The journal changed to focus on peer-reviewed articles and meeting abstracts rather than society news.

By 1988, Exerpta Medica accepted Lung Cancer for inclusion but Current Contents did not accept Lung Cancer because Lung Cancer had few citations due to the large number of abstracts and meeting reports. Then Lung Cancer decided to focus on full length original articles at the Board meeting at the 5th WCLC in 1988. The Board also decided to publish bimonthly issues starting in 1989. Bodil Diemer and Susanne Justesen were employed to oversee both the journal editorial office and the IASLC office in Copenhagen, Denmark.

Pathology Panel: After the publication of the 2nd Edition of the WHO Histologic typing of lung tumors in 1981, the IASLC Board accepted the recommendation of Drs. Mary Matthews, Fred R. Hirsch, Adi Gazdar, and Raymond Yesner to form a Pathology Panel. During the 1980s, the Panel focused on the classification of SCLC and its subtypes. The proposed classification included the classic "lymphocyte-like, oat-cell subtype (22) and intermediate subtype with large cells mixed with lymphocyte-like cells (22/40) and mixed subtypes with mixtures of small cells with adenocarcinoma." It became recognized that SCLCs had neuroendocrine properties and were frequently associated with paraneoplastic syndroms that were due to tumor production of various peptides such as ACTH and AVP.

Pathology Panel Members 1980-1994

Mary J. Matthews, Bethesda, USA*† (Chair 1983-1991)
Fred R. Hirsch, Copenhagen, Denmark* (Secretary, 1982-1991; Chair 1991-1998)
Seena Aisner, Newark, USA*
Onofrio Campopbasso, Turin, Italy*†
Bryan Corrin, London, England
J.D. Elema, Groningen, Netherlands*
Adi Gazdar, Dallas, USA
Samuel P. Hammar, Bremerton, USA
Bruce Mackay, Houston, USA*
Magnus Nasiell, Sweden*
Mary Sheppard, London, England
Yukio Shimosato, Tokyo, Japan*
Richard H. Steele, Woolloongabba, Australia*
Raymond Yesner, New Haven, USA† (Chair, 1981 WHO Panel)
L. Zettergren, Sweden*

*Original IASLC Pathology Panel Members recorded in IASLC Newsletter, April, 1985
†Members of 1981 WHO Lung Tumor Expert Committee on Lung Cancer

Mary Matthews, Chair, IASLC Pathology Panel 1983-1990 (right) and Seena Aisner, Member IASLC Pathology Panel 1983-2005 (left).
Board and Officers: The IASLC bylaws called for elections of officers and Board members at the time of the WCLC. In the late 1970s it became a tradition to rotate the Presidency between Europe, Asia/Rest of World, and North America just as the WCLCs rotated through these regions. In 1980, Dr. Pierre Alberto, a medical oncologist/hematologist from Geneva, Switzerland was elected as President for the term from 1980–1982. Dr. Shiohiro Ishikawa, a thoracic surgeon from the National Cancer Center in Tokyo, Japan was elected and served as President from 1982-1985. Dr. Ronald Vincent, a thoracic surgeon from the Roswell Park Memorial Institute in Buffalo, NY, USA succeeded Dr. Ishikawa and served as President from 1985–1988. Dr. Heine Hansen, a medical oncologist from the Finsen Institute in Copenhagen, Denmark succeeded Dr. Vincent and was President from 1988-1991.

It also became a tradition to balance Board membership by region, and specialty. During the 1980s, Board meetings occurred primarily at the WCLCs and occasionally at other IASLC workshops. The office was located in Copenhagen, Denmark.

IASLC Board Members

1980-1982
President: Pierre Alberto, Switzerland
President-Elect: Shichiro Ishikawa
Past-President: George A. Higgins
Vice-President: Norman M. Bleehen
Treasurer: David T. Carr, USA
Directors: Robert Fontana, USA; Clifton Mountain, USA; Yoshihiro Hayata, Japan; Paul Nettesheim, USA; Tadeusz Lewinski, Poland; Keiichi Suemasu, Japan.

1982-1985
President: Shichiro Ishikawa, Japan
President-Elect: Ronald Vincent, USA;
Vice-President: Karl Karrer, Austria
Treasurer: Guntel Seydel, USA
Directors: Normal Bleehen, UK; Yoshihiro Hayata, Japan; Ronald Feld, Canada; John Minna, USA; Magnus Nasiell, Sweden; David Sanderson, USA.

1985-1988
President: Ronald Vincent, USA
President-Elect: Heine H. Hansen, Denmark
Vice-President: Karl Karrer, Germany
Treasurer: Gunter H Seydel, USA
Directors: Norman Bleehen, UK; Adi Gazdar, USA; Yoshihiro Hayata, Japan; Rudolf A. Joss, Switzerland; David Sanderson, Keiichi Suemasu, Japan.

1988-1991
President: Heine H. Hansen, Denmark
Vice President: Norman M. Bleehen, UK
President-Elect: Yoshiro Hayata, Japan
Past-President: Ronald G. Vincent
Treasurer: Rudolf A. Joss, Switzerland
Directors: Rodrigo D. Arriagada, France; David Ball, Australia; Paul A. Bunn, USA; Anna Gregor, Scotland; George D. Sorenson, USA; Keiichi Suemasu, Japan.
Epidemiology

Studies in which the relationship between air pollution and an increased risk of lung cancer was assessed required control for cigarette smoking. Dockery et al (1993) performed a prospective cohort study in six USA cities that estimated the effects of air pollution on mortality, while controlling for risk factors, including smoking history. They demonstrated a 1.26 (95% confidence interval, 1.08-1.47) adjusted mortality-rate ratio in the most polluted cities. Lung cancer and cardiopulmonary deaths were positively associated with fine particulates, including sulfates. An additional study published a few years later from some of the same authors, strengthened this relationship between lung cancer and cardiopulmonary deaths from fine particulate air pollution (Pope et al, 1995). This study examined data from 151 US cities with individual risk factors in 552,138 adults who lived in these cities. Again, the conclusion was significant, when controlled for multiple risk factors, including smoking, for increased lung cancer and cardiopulmonary mortality, but not mortality from other causes from fine particulate air pollution at levels commonly measured in USA cities.

Richard Doll and Richard Peto started a pivotal study in the 1950s in male physicians in the UK that initially defined the relationship between smoking and lung cancer. They demonstrated the cumulative risk of death from lung cancer in persistent smokers not only in males, but also, now in females. In this article, the authors reported an increased risk of lung cancer deaths in women in 1990—as compared with women in 1950—due to persistent smoking (Peto et al, 2000). This report was an early demonstration of the decrease in lung cancer deaths correlated to the age of smoking cessation. Smoking cessation was shown to significantly and relatively rapidly decrease the risk of lung cancer, with the effects increasingly reduced the younger the age of cessation. A notable quote from this paper about smoking is: “Stopping before middle age avoids more than 90% of the risk attributable to tobacco.”


Biology

The 1990s were a decade during which the widespread application of earlier methods of molecular analyses was applied to lung cancer. In contrast to the present genome wide approaches, individual genes or small
numbers of genes were studied, usually in a modest number of samples or cell lines. It also represented a period during which larger numbers of investigators from Asia and Europe began to enter the field, converting the study of lung cancer biology into a truly international effort.

Among the major molecular findings were defining the role of KRAS mutations, although they had been described earlier (Slebos and Rodenhuis, 1992). Early relatively crude allelotyping efforts had identified multiple chromosomal regions of allelic loss in lung cancers (Virmani et al, 1998). These efforts, combined with earlier cytogenetic studies, indicated that there were multiple regions of loss on the short arm of chromosome 3, harboring several crucial tumor suppressor genes including FHIT and RASSF1A (Sozzi et al, 1996; Dammann et al, 2000). The role of amplification of the MYC family of oncogenes was defined in SCLC, and later found to be over-expressed in NSCLC.

While RB gene mutations had been identified in SCLC earlier, the crucial role of inactivation of this gene in SCLC was put into perspective (Shimizu et al, 1994). By contrast, RB inactivation was relatively uncommon in NSCLC, which had frequent inactivation of the p16INK4A2 gene (Otterson et al, 1994). The inverse correlation of RB and p16INK4 expression confirmed a common P16-INK4A2/RB growth suppressor pathway in human lung cancers with different mechanisms affecting the pathway in SCLC and NSCLC.

The vast majority of lung cancer tumors (Hiyama et al, 1995) and cell lines were found to express telomerase activity, a hallmark of cancer. However, up to 20% of NSCLC did not express telomerase, indicating the presence of alternative pathways for maintaining telomere length.

These early molecular characterization studies of lung cancer set the stage for the dramatic genome wide advances that were to follow in the new century.

1990s Research Highlights

Pathology

An important development in pathology during 1990-1995 was reported by Brambilla et al (1992), who proposed “basaloid carcinoma” as a new subtype of NSCLC with distinct histopathologic features and very poor prognosis. This initial report provided the histologic criteria for the diagnosis of basaloid carcinoma of the lung. 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 I-II patients having a very poor median survival of 22 months. This tumor subtype has subsequently been incorporated into the WHO classification.

In 1995 another pioneering article reported the pathologic prognostic indicators in small size (≤ 2 cm) lung adenocarcinoma in a series of 236 surgically resected adenocarcinomas (Noguchi et al, 1995). These authors distinguished type A (localized bronchioloalveolar carcinoma) and type B with foci of collapse. In contrast with other subtypes (C, D, E, F), A and B types showed no lymph node metastasis and the most favorable prognosis: patients had 100% 5-year survival. Interestingly, four B type tumors had vascular invasion or pleural invasion showing that the concept of adenocarcinoma in situ deserved future refinements and waited for definitive concept. From the molecular pathology point of view, an important step toward the comprehension of multistep and multicentric carcinogenesis field cancerization was the discovery of multiple clonal abnormalities in the bronchial epithelium of patients with lung cancer (Park et al, 1999). 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 patients with lung cancer. So normal-appearing epithelium of smokers is not normal molecularly.

Staging

The diagnostic value of regional and whole-body positron emission tomography (PET) was prospectively determined in the evaluation of lung cancer in comparison with computed tomography (CT) and surgical findings. It was demonstrated that imaging with PET was more accurate than CT for diagnosis of mediastinal and distant metastasis (Valk et al, 1995). This study demonstrated that unnecessary thoracotomy could be avoided by performing PET before treatment, and established PET as an indispensable component of pre-operative staging prior to thoracotomy for lung cancer.

The 5th edition of the TNM Classification of Malignant Tumours for lung cancer was published in 1997 (Sobin and Wittekind, eds). In this revision, stages I and II were further divided as new stages IA, IB, IIA, and IIB. Based upon the prognostic assessment, T3N0M0 moved from IIIA to IIB stage. Furthermore, the additional tumor nodules in the same lobe as primary site and those in the different lobes regardless of the side were newly defined as new T4 and M1, respectively.

This new classification was presented at an IASLC Workshop at the Brompton Hospital in 1996, a few weeks ahead of their implementation (Goldstraw, 1996). It was at this workshop that the members decided to lobby the IASLC to take an active role in future revisions of the TNM classification for lung cancer. Here we see the passing of the baton for future revisions from Clifton Mountain, MD, to the IASLC.

Selected References

- Brambilla E, Moro D, Veale D, et al
  Basal cell (basaloid) carcinoma of the lung: a new morphologic and phenotypic entity with separate prognostic significance.
  Small adenocarcinoma of the lung. Histologic characteristics and prognosis.
- Park IW, Wistuba, II, Maitra A, et al
  Multiple clonal abnormalities in the bronchial epithelium of patients with lung cancer.
The decade of the 1990s was a time of great excitement related to success with combination therapies in advanced disease. In preventing smoking-induced cancers of the upper aerodigestive tract, many researchers expected vitamin A analogues to have a similar impact in lung cancer and clinical research explored, for example, adjuvant treatment with high-dose vitamin A in stage I lung cancer (Pastorino et al, 1993). Two of the most cited references of the 1990s emerged from workshops conducted to explore new molecularly defined options to intercept lung carcinogenesis (Ihde and Lippman, 1992; Roth et al, 1992). The first report reviewed the opportunity with a population of stage I resected lung cancer since these patients developed new second lung cancers at a predictable rate, which provided a test bed to validate the chemopreventive effect of a vitamin A analog. Ihde was a strong early influence on the IASLC focus on rigorous clinical trial methodology. In the second prescient article, Dr Roth and colleagues made the case for epidermal growth factor receptor (EGFR) as an attractive target for prevention and treatment of lung cancer (Roth et al, 1992). Through the prism of retrospection, this was a golden age of translational research. Ideas, energy and resources have never again been in such balance and so a challenge going forward is to re-establish this equilibrium.


Prevention

Additional reports of the miss rate of lung cancer detection with chest radiographs appeared in the literature and were reported to be 19% in one series of 259 lung cancers (Quekel et al, 1999). Miss rates as high as 80% had previously been reported in prospective screening trials with chest x-rays. The first reports of screen-detected lung cancer with low-dose CT scans were reported from Japan and the USA (Kaneko et al, 1996; Sone et al, 1998; Henschke et al, 1999). The lung cancer detection rate varied from 0.3% to 2.7% in the various screened populations. These studies confirmed that the simultaneous chest radiographs missed approximately 70% of the lung cancers detected by CT. CT screening detected more early-stage lung cancers than was usually observed in clinical practice. No randomized trials with CT screening were reported. Initial reports appeared during this decade testing biomarkers of early lung cancer in the breath (Phillips et al, 1999) and sputum (Payne et al, 1997; Tockman et al, 2000). The search for biomarkers of early detection continues with no clinically proven early biomarker in the blood, urine, sputum, or breath at this time.
1990s Research Highlights


Pulmonology

The continuous efforts in discovering new bronchoscopic techniques led at the beginning of 1990s to the comparison of the novel fluorescence imaging system with conventional white light bronchoscopy. The fluorescence system uses a nonlinear discriminant function combining the red and green image intensity values to form a pseudo-image that, when displayed on a monitor, allows the detection and delineation of abnormal areas. The two methods were found to have the same specificity; however, the sensitivity of the fluorescence system was found to be 50% greater than that of the white light bronchoscopy in detecting dysplasia and carcinoma in situ (Lam et al, 1993; Hung et al, 1991). Investigators continued to evaluate the use of fluorescence imaging with hematoporphyrin derivative for localization of early endobronchial cancers (Lam et al, 1990). However, toxicity issues from hematoporphyrin led to the discovery and eventual transition to autofluorescence bronchoscopy with the promise that it would be a tool for early detection (Lam et al, 1998).

Various stent models have been developed for the treatment of inoperable stenoses of the central airways caused by external compression: the silicone stents designed by Dumon are easily inserted and removed, well tolerated and efficacious in relieving respiratory symptoms caused by extrinsic airway compression. Other types of stents were used and evaluated in this period of time, such as the Gianturco expandable metallic stents (Bolliger et al, 1993; Sawada et al, 1993).

Pleuroscopy, historically started in the tuberculosis era in the 1950s, became of age in this period. This “medical” thoracoscopy as compared with “surgical” thoracoscopy or VATS had the advantage of being considerably less invasive and less expensive (performed under local anesthesia or conscious sedation in endoscopy suite). It allowed very high diagnostic yields in pleural effusions and offered the most effective pleurodesis.

The first reports on using endoluminal ultrasound for staging of mediastinal nodes by guided needle aspiration came out. The first reported an accuracy of 84% with esophageal ultrasound (EUS) guided aspirations to assess subcarinal or posterior mediastinal lymph nodes (Gress et al, 1997). Another article reported on the initial use of endobronchial ultrasound (EBUS) (Kurimoto et al, 1999). The five-layer structure of the cartilaginous portions of bronchi were described, and then used to successfully determine the depth of tumor invasion in the tracheobronchial wall.

- Bolliger CT, Probst R, Tschopp K, et al
- Kurimoto N, Murayama M, Yoshioka S, et al
- Lam S, Kennedy T, Unger M, et al
- Lam S, MacAulay C, Hung J et al
- Loddenkemper R
- Mathur PN, Loddenkemper R

Lung Cancer Management

Surgery

The important prospective study by the Lung Cancer Study Group (1995) was undertaken to assess the relative effectiveness of lobectomy versus limited resection (segmentectomy or wedge resection) in 276 patients confirmed to have T1N0 NSCLC at thoracotomy. The results indicated that there was an observed 75% increase in recurrence rates, 30% increase in overall death rate, and 50% increase in death with cancer rate in patients undergoing limited resection. Wedge resection appeared to result in worse outcomes than segmentectomy. This randomized trial established the appropriate extent of resection for T1N0 lung cancer to be lobectomy for patients with conventionally detected stage I NSCLC. Also in the 1990s, a landmark article by Grunenwald and Spaggiari (1997) described a novel surgical approach to the apical lung cancer invading the anterior part of the chest wall with a good preservation of the osteomuscular structures. This technique ensures the excellent exposure of subclavian vessels and brachial plexus with preservation of function of the pectoral girdle. Nowadays, most of the surgeons employ “Grunenwald’s approach” for the difficult, challenging tumors with such unique locations.
Adjuvant and neoadjuvant chemotherapy with surgery: There were numerous studies in the 1980s that evaluated chemotherapy before or after surgery. These studies employed chemotherapy combinations such as MVP (mitomycin C, vindesine, cisplatin) or CAP (cyclophosphamide, Adriamycin, cisplatin) that were subsequently shown to be more toxic and no more effective than two-drug combinations (Burkes et al, 1992). In 1995, a seminal article was published in the *British Medical Journal*, evaluating the role of cytotoxic chemotherapy for NSCLC. The article combined data from 14 trials and 4,357 patients involving post-operative chemotherapy. NSCLC had previously been considered a chemoresistant disease, so a meta-analysis demonstrating a survival benefit with surgery plus cisplatin-based chemotherapy vs. surgery alone was particularly noteworthy. However, although the hazard ratio was 0.87 (13% reduction in the risk of death, equivalent to an absolute benefit of 5% at 5 years) for regimens containing cisplatin, the *P* value was borderline at 0.08. Toward the end of the decade, a neoadjuvant approach with newer paclitaxel/carboplatin chemotherapy produce very favorable results (Pisters et al 2000), which led to a large randomized phase III trial of this combination reported in 2010 (see next section). The favorable results led to subsequent randomized trials comparing adjuvant and neoadjuvant two-drug combinations to surgery alone.

- **No authors**

- **Burkes RL, Ginsberg RJ, Shepherd FA, et al**

- **Ginsberg RJ, Rubinstein LV**

- **Grunenwald D, Spaggiari L**

- **Pisters KM, Ginsberg RJ, Giroux DJ, et al**

**Radiation Oncology**

A major step forward in the curative treatment of NSCLC occurred with the demonstration that the addition of cisplatin-based chemotherapy to radical radiotherapy (55 to 60 Gy) increased the survival of patients with inoperable disease, compared with radiotherapy alone. This benefit was observed both when the chemotherapy was given prior to (Dillman et al, 1990) and concomitantly (Schaake-Koning et al, 1992) with radiotherapy.

In SCLC, a Canadian randomized trial demonstrated that in patients with limited disease, the administration of thoracic radiotherapy resulted in longer survival if given early with the second cycle of chemotherapy, rather than later with the last cycle (Murray et al, 1993). The median (21 months) and 5-year survival rates (20%) observed in the early thoracic irradiation arm set new benchmarks for this disease.

The potential for lung dose volume metrics derived from analysis of dose volume histograms of 3D treatment plans to predict risk of lung radiation toxicity was first recognized by Martel and colleagues, and has become a standard tool in radiotherapy plan evaluation (Martel et al, 1994).

Further progress was made in the use of chemoradiation for patients with stage III NSCLC in the late 1990s when the West Japan Lung Cancer Group demonstrated that concomitant administration of cisplatin-based chemotherapy was superior to sequential (Furuse et al, 1999) and has remained the standard of care to the present day.

The importance of keeping overall treatment time short when delivering radiotherapy was supported by the results of trials in both NSCLC and SCLC. In the CHART...
In a practice changing meta-analysis, the Prophylactic Cranial Irradiation Overview Collaborative Group was able to demonstrate that in patients with SCLC who had achieved complete remission, prophylactic cranial irradiation not only reduced the incidence of brain metastases, but also lengthened survival (Auperin et al, 1999).


Chemotherapy

Research in the 1990s changed the way we treated both SCLC and NSCLC. In NSCLC, a meta-analysis of randomized trials reported by the NSCLC collaborative group confirmed that cisplatin-based chemotherapy could prolong survival in advanced NSCLC compared to best supportive care (BMJ, 1995, see reference citation in Surgery 1990s section). Further studies indicated that two-drug cisplatin-based combinations were superior to...
single-agent therapy. A large European study reported in 1992 demonstrated that the two-drug combinations of cisplatin with either vinorelbine or vindesine were superior to vinorelbine alone (Le Chevalier et al, 1994). These results were confirmed in a large North American SWOG trial randomizing patients to cisplatin alone or cisplatin with vinorelbine (Wozniak et al, 1988). In other NSCLC studies, cisplatin was combined with many new drugs as they were introduced including etoposide, vindesine, and later gemcitabine, paclitaxel, and docetaxel. Meta-analyses subsequently confirmed the superiority of single agents and doublets to best supportive care and the superiority of doublets over single agents. Thus, two-drug combinations such as those studied by Le Chevalier et al remain the standard of care.

In SCLC, the trial of Roth et al demonstrated that three-drug combinations were not superior to two-drug combinations and the two-drug combination of etoposide/cisplatin had less toxicity and has been the standard since that time. Aside from related advances in adjuvant therapy for NSCLC and chemo-radiation for extensive-stage SCLC, the “tools” (drugs) available to practitioners caring for patients were quite limited in activity in this decade.

In the 1990s randomized trials in SCLC compared the two-drug etoposide/cisplatin (EP) combination to three- and four-drug combinations such as CAP, CAV, CODE, or alternating combinations (Roth et al, 1992; Fukuoka et al, 1991; Murray et al, 1999). There was very little difference in efficacy parameters but the EP combination was less toxic, so it was widely adopted. Topotecan was shown to be superior to combination chemotherapy in relapsed SCLC and remains the only drug approved in this indication. (von Pawel et al, 1999).

**Immunotherapy**

Attempts at clinical development of cytokine and interleukin therapies continued, but with the definition of the mechanisms of T-cell and B-cell recognition of cancer-specific genes came several studies evaluating oncogene/tumor suppressor gene-specific immune responses, both humoral and cellular (Winter et al, 1992; Yanuck et al, 1993).

In the late 1990s it became clear that the immune system can highly specifically recognize antigens that were abundantly present in tumor cells, but for some reason did not (Chen et al, 1996; Chen et al, 1996 letter). Mutational mechanisms were defined that cause the loss of antigen presentation, but so were regulatory ones (Gabrilovich et al, 1996).

- **Chen HL, Gabrilovich D, Tampé R, et al**

- **Chen HL, Gabrilovich D, Virmani A, et al**

- **Gabrilovich DI, Chen HL, Girgis KR, et al**

- **Winter SF, Minna JD, Johnson BE, et al**

- **Yanuck M, Carbone DP, Pendleton CD, et al**

**Supportive Care**

The 1990s focused more attention on the supportive care of patients with lung cancer. Quality of life (QOL) was identified as an independent prognostic factor (Ganz et al, 1991) and the EORTC-QLQ-LC13 and the FACT-L QOL scales (Bergman et al, 1994; Cella et al, 1995) that are now used as an outcome measure in most of the drug trials were validated. The Lung Cancer Symptom Scale, developed in 1993, paid particular attention to symptoms including weight loss, emesis in cisplatin-treated patients (particularly with the introduction of the new 5-HT3 receptor antagonists early in this decade) and breathlessness and also was validated. A strong focus on the psychosocial aspects of lung cancer, particularly depression, occurred and a new non-pharmacological intervention for the management of breathlessness (Bredin et al, 1999) shaped the way that we currently treat this symptom. Furthermore, IASLC organized its first workshop on improving QOL and supportive care in 1993.

- **Bergman B, Aaronson NK, Ahmedzai S, et al**

- **Bredin M, Corner J, Krishnasamy M, et al**

- **Cella DF, Bonomi AE, Lloyd SR, et al**

- **Ganz PA, Lee JJ, Siau J**
The 1990s were a time of major growth for the IASLC, even though their major conference, the WCLC was held only every 3 years in 1991, 1994, and 1997. Growth in membership continued. Membership by region was relatively constant with roughly one third from Europe, one third from North America, and one third from Asia/ROW. Because of the growth, the Board decided to create the position of Executive Director and Dr. Heine Hansen was chosen for this position immediately upon completion of his term as president in 1991. Dr. Yoshihiro Hayata, a thoracic surgeon from Tokyo Medical College, Japan was elected President for a term from 1991-1994. Dr. Paul A. Bunn, Jr., a medical oncologist from the University of Colorado in Denver, Colorado, USA was elected as President to succeed Dr. Hayata for a term from 1994-1997. During Dr. Bunn’s term the Board decided to hold additional Board meetings that were not associated with the WCLCs; these Board meetings were held at various IASLC workshops and as a separate meeting at least once annually. Dr. Bunn was succeeded by Dr. Giovanni Motta, a thoracic surgeon from Genoa, Italy, who was President from 1997–2000.

As Executive Director, Dr. Hansen created the IASLC office in Copenhagen with the assistance of Bodil Diemer. Dr. Hansen held the position of Executive Director until WCLC 2003 in Vancouver.

During the 1990s the Board decided to form several committees to assist the Board. These included a Nominating Committee to select the candidates for election, a WCLC Selection Committee to select the sites for the WCLC, and a Workshop Committee to approve and oversee the workshops and conferences.

In recognition of the importance of prevention and early detection of lung cancer, Dr. Fred R. Hirsch proposed with support from the IASLC President, Professor H. Kato, to establish a Prevention and Early Detection Committee.

**1990s WCLCs:** The 6th WCLC was held in Melbourne, Australia from November 10-14, 1991, with Dr. David Ball as Conference President (Secretary General). There were more than 1,240 registrants from 47 countries with 647 submitted abstracts. There were more than 60 invited speakers. The social highlights included an excursion to the gold mines at Ballarat. The traditions of the Opening and Closing ceremonies were continued. This was the first WCLC that provided travel grants for individuals from developing countries.

The 7th WCLC was held at the Broadmoor conference center in Colorado Springs, CO, USA from June 26-July 1, 1994. Dr. Paul A. Bunn, Jr. was the Conference President. Attendees totaled 1,347 from 40 countries and there were 726 submitted abstracts. In addition to travel...
awards from developing countries, there were travel awards for young investigators. Both of these awards were based on the merit of submitted abstracts.

The 8th WCLC was held at the University College in Dublin, Ireland from August 10-15, 1997. Dr. Desmond Carney was the Conference President (Secretary General). There were 2,505 registrants from 63 countries with 927 submitted abstracts. Social highlights included a speech from Mary Robinson, the President of Ireland, at the opening ceremony. This WCLC had record attendance and record abstract submission and was the most revenue-positive WCLC for the IASLC to date.

Awards (1990–2000): The first IASLC award was the IASLC Merit Award given to Clifton Mountain in 1991. The award was supported by a generous contribution from Dr. Giovanni Motta. The IASLC Merit awards are given to a member for extraordinary contributions to the organization. Subsequent awardees during the 1990s included Dr. Y. Shimosato in 1994, Dr. Heine Hansen in 1997, and Dr. Desmond Carney in 2000.

The Mary Matthews Pathology Award is given to an IASLC member for lifetime scientific achievement in pathology-translational research of thoracic cancers. The first award presented in the 7th WCLC in Colorado Springs in 1994 went to Geno Saccamanno, MD, a leader in lung cancer cytology, early detection, and etiology (uranium exposure). The second award was presented to Dr. William Travis in 1997 for his contributions to the pathologic classification of lung tumors.

The IASLC Scientific Award was also initiated at the 7th WCLC in Colorado Springs. The award is given for lifetime achievement in scientific contributions to thoracic cancer research. The first award was given to Robert Ginsberg, MD, thoracic surgeon from Toronto, Canada, for his contributions to the surgical treatment of early-stage lung cancer. The second award in 1997 was given to John Minna, AMD, medical oncologist from UT Southwestern Cancer Center, Texas, US for developing lung cancer cell lines and for understanding the molecular changes. These early scientific achievement awards were supported by industry grants from Bristol-Myers Squibb.

The Joseph Cullen Prevention Award for lifetime scientific achievement was also started at the 7th SCLC in Colorado Springs, CO, USA. The first was awarded to Jesse Steinfeld, MD, who was the US Surgeon General when the sentinel 1964 Surgeon General’s report on tobacco was first issued. The second award in 1997 was given to Clifford E. Douglas, JD, for discovery of the tobacco company papers and the successful litigation of the USA versus the tobacco companies.

Fellowships (1990–2000): In 1999 the IASLC and the Cancer Research Foundation of America established a fellowship program in lung cancer prevention and translational research. This fellowship award, based on scientific merit, was first given to Dr. Junr Zhang, China, for 2000-2002, for his work on detection of microsatellite alterations in serum DNA for early diagnosis of lung cancer.
**Tobacco Policies (1990–2000):** The IASLC recommendations on tobacco policy were established at the 7th WCLC in Colorado Springs in 1994. This program was widely distributed including publication in *Lung Cancer* and the *Annals of Oncology* and sent to governments and health organizations throughout the world. This tobacco policy was revised and updated at the 9th WCLC in Tokyo with the Tokyo Declaration on Tobacco in 2000.

**Lung Cancer Journal (1990–2000):** From 1990 to 1994 subscriptions to *Lung Cancer* increased by approximately a third with growth in both library and member subscriptions. The number of articles published grew from about 20 in 1990 to 250 in 2000. This growth in manuscripts led to an expansion of circulation to monthly issues. Manuscripts were submitted from all regions of the world with about 45% from Europe, 25% from North America, 30% from Japan/Australia/Asia. The first impact factor was reported in 1996 and was 0.6 and this increased to 1.9 by 1999. Online versions of the journal were first available in 1999.

**Pathology Panel (1990–2000):** From 1991-1998, the Pathology Panel was chaired by Fred R. Hirsch, MD, PhD. In 1996, Dr. William Travis, a panel member, was asked by the WHO to coordinate a revision of the international classification of lung tumors, and led to publication of the *Histologic Typing of Lung and Pleura Tumours* (3rd Edition; Berlin, Springer, 1999). The revised classification created new subcategories of adenocarcinomas and neuroendocrine tumors.

**Pathology Panel Members 1994-1999**

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>Fred R. Hirsch</td>
<td>Copenhagen, Denmark (Chair 1991-1998)</td>
</tr>
<tr>
<td>Seena Aisner</td>
<td>Newark, USA</td>
</tr>
<tr>
<td>Emilio Alvarez-Fernandez</td>
<td>Madrid, Spain</td>
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<tr>
<td>Elisabeth Brambilla</td>
<td>Grenoble, France</td>
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<tr>
<td>Thomas V. Colby, MD</td>
<td>Scottsdale, USA</td>
</tr>
<tr>
<td>Bryan Corrin</td>
<td>London, England</td>
</tr>
<tr>
<td>Adi Gazdar</td>
<td>Dallas, USA</td>
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<tr>
<td>Samuel P. Hammar</td>
<td>Bremerton, USA</td>
</tr>
<tr>
<td>Philip S. Hasleton</td>
<td>Manchester, England</td>
</tr>
<tr>
<td>Bruce Mackay</td>
<td>Houston, USA</td>
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<tr>
<td>Helmut Popper</td>
<td>Graz, Austria</td>
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<tr>
<td>Mary Sheppard</td>
<td>London, England</td>
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<tr>
<td>Yukio Shimosato</td>
<td>Tokyo, Japan</td>
</tr>
<tr>
<td>Richard Steele</td>
<td>Woolloongabba, Australia</td>
</tr>
<tr>
<td>William D. Travis</td>
<td>Washington, DC, USA</td>
</tr>
</tbody>
</table>

**Staging (1990–2000):** The 5th revision of the TNM classification was completed in 1997 ( Sobin LH, Wittekind C, *TNM Classification of Malignant Tumours*. Wiley-Liss). By this time, Dr. Mountain’s database had grown to 5,319 cases including 4,351 consecutive patients undergoing surgical resection at the MD Anderson Cancer Center and 968 cases from other centers. At an IASLC staging workshop in London, UK in 1996, the proposed 5th revision was presented and approved. At this time, it was recognized that the IASLC was in the best position to expand the basis for future revisions because of the
The IASLC therefore expanded the Staging Committee membership, obtaining additional funding, and created its own database for cases. Planning meetings were held in London in 1999 and 2000.

**Workshops (1990–2000):** The IASLC sponsored a total of 39 workshops during the 1990s on a wide variety of topics including biology, therapy of NSCLC, Central European Lung Cancer Conferences, quality of life/supportive care, prevention, etiology and lifestyle, mesothelioma, metastases, staging, early diagnosis, and prognostic and predictive factors. These meetings were held in multiple countries and continents including Europe, North America, Asia, Africa, and the Middle East. The workshops in Central Europe, Biology, Perugia, and Bruges were held on a recurring basis and are described in more details in the 35-year history of the IASLC (History of the International Association for the Study of Lung Cancer 1972-2007. H. Hansen, Editorial Rx Press, 2009).

**IASLC Board Members**

**1991–1994**
- President: Yoshihiro Hayata, Japan
- Vice-President: NM Bleehen, UK
- President-Elect: Paul A. Bunn, Jr., USA
- Past-President: Heine H Hansen, Denmark
- Treasurer: Rudolf A. Joss, Switzerland
- Secretary: Ugo Pastorino
- Directors: Arriagada R, France; David L. Ball, Australia; Anna Gregor, UK; PA Rocmans, Belgium; Y Shimosato, Japan; George D. Sorenson, USA.

**1994–1997**
- President: Paul A. Bunn, Jr., USA
- Vice-President: George D. Sorenson, USA
- President-Elect: Giovanni Motta, Italy
- Past-President: Yoshihiro Hayata, Japan
- Treasurer: Jens B Sørensen, Denmark
- Executive Director: Heine H. Hansen, Denmark
- Directors: Carmack E. Holmes, USA; Frances A. Shepherd, Canada; Yukio Shimosato, Japan; Tsuguo Naruke, Japan; Pierre A. Rocmans, Belgium; Raymond P. Abratt, South Africa.

**1997–2000**
- President: Giovanni Motta, Italy
- Vice-President: Frances Shepherd, Canada
- President-Elect: Harubumi Kato, Japan
- Past-President: Paul A. Bunn, Jr., USA
- Treasurer: Jens B Sørensen, Denmark
- Executive Director: Heine H. Hansen, Denmark
- Directors: Raymond P. Abratt, South Africa; James Bishop, Australia; Desmond N. Carney, Ireland; Peter Harper, UK; Carmack E. Holmes, USA; Daniel Ihde, USA; Tsuguo Naruke, Japan; Valerie Rusch, USA; Nagahiro Saijo, Japan.
Epidemiology

Approximately 50 years after the first epidemiologic evidence that smoking caused lung cancer, the most referenced article for the first decade of the new millennium demonstrated the health risk of long-term exposure to fine particulate air pollution. Over the previous decades, exposure to even low levels of fine particulate matter (FPM)- or particles measuring less the 2.5 microns, was shown to increase substantially the risk for lung cancer. The article by Pope et al (2002) used the large dataset for approximately 1.2 million adults in the American Cancer Society’s Cancer Prevention II study (CPSII) to more definitively address the relationship of FPM and risk for lung cancer. By combining the comprehensive health and diet histories of CPSII, and individually assigning a metropolitan area of residence based on their enrollment address, the authors were able to assess the exposure to air pollution–measured by FPM. The results were quite conclusive demonstrating that each 10 microgram/m3 increase in FPM exposure increased lung cancer mortality risk by 8%. The article also demonstrated that this same 10 microgram/m3 elevation would increase all-cause mortality by 4% and cardiovascular mortality by 6%. Although previous studies had also shown this increase in mortality from long-term exposure to FPM, this study was the largest and best controlled for potential confounders and definitively delineated the substantial increased risk for lung cancer.

Genome-wide association studies allow for the investigation of genetic variants to assess their susceptibility risk for lung cancer. In the first study (Amos et al, 2008) 315,450 single nucleotide polymorphisms (SNPs) were analyzed in 1,154 current and former patients who smoked with lung cancer of European ancestry and 1,137 matched controls. Two SNPs mapped to region 15q25.1—which includes two nicotinic acetylcholine receptor subunit genes. The odds ratio for these two SNPs was 1.32 (p<1x10(-17) for both SNPs). A follow-up publication by the same research group, examining 511,919 SNPs in 1,952 cases and 1,438 controls confirmed their early results with the most significant association found at 15q25.1 (Wang et al, 2008). In addition, two other identified risk loci were found at 6p21.33 and 5p15.33–both with significant associations. The authors identified genetic variants that conferred significant risk for developing lung cancer. The results need to be confirmed in additional studies or meta-analyses and assessed whether they exist in other racial groups.


### MILESTONES

- Increase in lung cancer deaths among women due to smoking demonstrated
- “Chemotherapy efficacy plateau” demonstrated
- Zoledronic acid approved by FDA
- Gefitinib for NSCLC with EGFR mutations by FDA, distribution later limited
- Discovery that certain EGFR mutations associated with response to EGFT TKIs
- Prostacyclins shown to have chemopreventive effects in animal models
- Erlotinib for NSCLC approved by FDA
- FDG-PET+ CT shown to improve target volume definition for NSCLC RT treatment planning
- 4-D CT useful for tumor motion and localization
This decade was characterized by the development of targeted therapies selected for patients with lung cancer using predictive biomarkers and thus, the paradigm of "personalized medicine." New technologies for sequencing the genome discovered "oncogenic drivers" in NSCLC, and concomitant development of specific oral small molecule tyrosine kinase inhibitors (TKIs), made an entirely new therapeutic approach to the management of NSCLC patients, particularly those with advanced disease.

In previous decades the EGFR was recognized to be highly overexpressed in NSCLC tumors and shown to play an important role in lung carcinogenesis. Agents that could inhibit the EGFR pathway activation were developed, both as TKIs as well as monoclonal antibodies against EGFR. Clinical studies with single-agent erlotinib in unselected patient populations who progressed on one or two prior chemotherapy regimens demonstrated a small but statistically significant improvement in survival compared to placebo. However, the combination of EGFR TKIs with chemotherapy was no better than chemotherapy alone in four large randomized trials in unselected patients.

The discovery that certain EGFR mutations (deletions in exon 19 or point mutations in exon 21) were associated with response to EGFR TKIs was published simultaneously by two groups in Boston in 2004 (Lynch et al, 2004; Paez et al, 2004). An interesting discovery regarding the EGFR mutations was also that the mutation rate in Asia was much higher than in Western NSCLC populations (40% versus 10%), which gave rise to study differences in genetic abnormalities based on ethnicities for NSCLC patients. The EGFR mutations were most frequently found in never-smokers and younger females with pulmonary adenocarcinomas (Mok et al, 2009). Other second gatekeeper mutations in EGFR such as the T790M point mutation in exon 20 were shown to cause resistance to EGFR TKI therapy in up to half of all patients.

The anaplastic lymphoma kinase (ALK) gene was shown to be activated by fusion to another chromosome 2 gene, EML4, in 2007 by Soda et al (2007). The fusion was reported to drive the growth of NSCLCs and to occur in about 2% to 3% of NSCLC patients with adenocarcinoma, again most frequently in never-smokers and younger women; in practice, ALK-EML4 was mutually exclusive from EGFR mutations despite the prevalence in the same group of NSCLC (Shaw et al, 2009). However, no difference in ALK gene rearrangement has been found between Asian and Western NSCLC populations. Several variants of the EML4 fusion partners to the ALK gene are detected (up to 2013 at least 13 different EML4 variants are identified). The ALK-EML4 fusion gene can be detected by several methods (fluorescence in situ hybridization [FISH], immunohistochemistry...
[IHC], and polymerase chain reacton [PCR]). The FISH assay was shown to correlate with response to ALK TKIs and was approved for clinical use as a companion diagnostic. Encouraged by the molecular discoveries of EGFR mutations and ALK gene rearrangement and its particular therapeutic relevance, a search for many other "oncogenic drivers" in NSCLC was initiated, which was facilitated by a rapid development of multiplex diagnostic platforms, making it possible to identify multiple mutations on the same diagnostic platform (and later also other genetic abnormalities on the same platforms such as Next Generation Sequencing). Crizotinib, an ALK TKI, was under phase I study at the time the ALK fusions were reported; patients with ALK fusions demonstrated high response rates with long progression-free survival (Kwak et al, 2010). During this decade up to 60% of pulmonary adenocarcinomas had potential targetable genetic abnormalities detected (i.e., c-MET, BRAF, KRAS, HER2, IGFR)–a number of which in the next decade increased significantly.


Pathology

In 2004, the new World Health Organization classification (Travis et al, 2004) (classification: pathology and genetics) published the new rules for lung cancer classification, introducing many changes recognizing that 85% of adenocarcinoma are mixed type and cannot fit within one defined histological pattern, such admitting their huge heterogeneity. EGFR mutation and sensitivity to gefitinib was shown significantly more often in the bronchioloalveolar carcinoma subtype.

Preinvasive lesions were thoroughly revisited, definitely for squamous lesions, but not for precursors of adenocarcinoma; only atypical adenomatous hyperplasia (AAH) was considered as preinvasive lesions. The new context of adenocarcinoma in situ had to wait.

The most important molecular discoveries during 2000-2009 included the finding that certain "hot spot" mutations in the EGFR gene increased the sensitivity to EGFR TKIs by altering the structure of the drug and ATP (Lynch et al, 2004; Paez et al, 2004; see reference citations in Biology 2000-2009 section). The ALK oncogenes binding site and fusions between EML4 or other genes on chromosome 2 were discovered to activate ALK.
Soda et al (2007, see reference citation Biology 2000-2009 section) used the retroviral cDNA library prepared from DNA of a lung adenocarcinoma to transform mouse 3T3 fibroblasts. The transforming clone was found to be a fusion of the intracellular kinase domain of ALK and the N-terminus of EML4. The authors demonstrated that the ALK-EML4 fusion gene was a powerful oncogene in nude mice assay, and subsequent screening in additional lung and non-lung cancers confirmed its unique occurrence as a lung cancer oncogene. This discovery consolidated the concept of “oncogene addiction” as a highly efficacious strategy to treat patients with cancer. The break apart FISH probe became a validated predictive biomarker.


TNM Staging

To inform discussions leading to the 7th edition of TNM for Lung Cancer, the IASLC Staging Committee collected and analyzed over 100,000 cases worldwide to determine prognosis associated with T, N, and M variables and published recommendations for the new classification (Goldstraw et al, 2007). These recommendations were subsequently adopted by the UICC and AJCC and form the basis of the current staging classification.

The Japanese members of the Staging Committee committed a large number of cases (6,644) and these data indicated the need for changes to the 6th edition of the staging classification (Goya et al, 2005). The IASLC Staging Committee results also demonstrated the prognostic value of the 7th edition of TNM classification for SCLC (Vallières et al, 2009). This classification should replace the old VA classification of limited/extension stage because of the large differences between stage I-IIA and IIB-IIIA with the role of lobectomy for stages IA-IIA.

In recognition of the central role that the Association played in the development of the 7th edition of TNM cancer staging for lung cancer, the IASLC was accorded the honor of being first to publish the new classification for lung cancer, ahead of the UICC Handbook and AJCC Cancer Staging Manual. The IASLC Staging Manual in Thoracic Oncology and its companion IASLC Staging Handbook, were the first ever site-specific


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cancer staging publication in thoracic oncology. These publications and accompanying educational materials were launched at the 13th World Conference on Lung Cancer, which allowed conference attendees and IASLC members 3 months in which to study and prepare for the new staging system prior to its implementation in January 2010.

- **Goldstraw P, Crowley J, Chansky K, et al**
  The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours.

- **Goldstraw P (ed).**
  *IASLC Staging Manual in Thoracic Oncology.*

- **Goya T, Asamura H, Yoshimura H, et al**

- **Vallières E, Shepherd FA, Crowley J, et al**
  The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer.

### Prevention

A highly visible trial of the early 2000s was a randomized evaluation of oral isotretinoin compared to placebo in 1,166 patients with pathologic stage I NSCLC (6 weeks to 3 years from definitive resection and no prior radiotherapy or chemotherapy). Patients received either a placebo or the retinoid isotretinoin for 3 years in a double-blind fashion (Lippmann et al, 2001). Unfortunately, long-term follow-up did not show any benefit to the retinoid chemoprevention. A smaller randomized phase II trial of 13-cis-retinoic acid with or without alpha tocopherol versus observation also showed no benefit with respect to bronchial dysplasia (Kelly et al, 2009).

The most provocative chemoprevention report of the second half of the first decade of the new millennium was a prospective cohort study of over 10,000 veterans with known diagnosis of COPD (Parimon et al, 2007). This study explores the observation of Dr. Tom Petty, that lung cancer is the leading cause of death in COPD cohorts (Petty, 2005). Over the 4 years of follow up, in excess of 400 lung cancers were detected. For the individuals receiving in excess of 1,200 g/d of inhaled corticosteroid, the hazard ratio for developing lung cancer was 0.56. This result was persistent after correcting for all other risk factors such as smoking rates. A trend for lower lung cancer rates with inhaled corticosteroids was reported previously as well (Sin et al, 2005).

During this decade, prostacyclins were shown to have chemopreventive effects in animal models (Keith et al, 2004).

- **Keith RL, Miller YE, Hudish TM, et al**
  Pulmonary prostacyclin synthase overexpression chemoprevents tobacco smoke lung carcinogenesis in mice.

- **Kelly K, Kittelson J, Franklin WA, et al**
  A randomized phase II chemoprevention trial of 13-CIS retinoic acid with or without alpha tocopherol or observation in subjects at high risk for lung cancer.

- **Lippman SM, Lee JJ, Karp DD, et al.**
  Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer.

- **Parimon T, Chien JW, Bryson CL, et al.**
  Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease.

- **Petty TL.**
  Are COPD and lung cancer two manifestations of the same disease?

- **Sin DD, Wu L, Anderson JA, et al.**
  Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease.
Screening/Radiology

Non-randomized low-dose screening computed tomography (LDCT) trials from Japan, Europe, and North America (Sone et al, 2001; Swensen et al, 2005; Novello et al, 2005) showed LDCT was more sensitive than chest x-rays for detecting pulmonary nodules. However, these trials showed a high rate of non-calcified nodules (20% to 50%) and the vast majority of these were benign (Swensen et al, 2005; Novello et al, 2005; van Klaveren et al, 2009). The incidence of lung cancer was generally 0.5% to 2.0% in these LDCT trials screening high-risk individuals. Of the lung cancers detected, 50% or more were stage I (Swensen et al, 2005; Novello et al, 2005; van Klaveren et al, 2009; International Early Lung Cancer Action Program [IELCAP] Investigators, 2006). Several small randomized screening trials demonstrated that participants would accept randomization to screening with LDCT or chest radiograph (Garg et al, 2002; Gohagan et al, 2004; Infante et al, 2011). These trials were too small to demonstrate any mortality reduction with LDCT screening. Additional risks of screening were identified that included operations for benign disease (van Klaveren et al, 2009; Crestanello et al, 2004) and the potential of radiation-induced cancers (Brenner et al, 2007). A potential benefit of screening was a significant rate of smoking cessation for participants in screening studies. The IELCAP trial demonstrated a very high survival rate for resected stage I cancers detected by the LDCT (IELCAP et al, 2006). Research on biomarkers of early disease continued especially in the areas of volatile organic compounds in the breath as well as sputum and blood markers (Mazzone et al, 2007; Varella-Garcia et al, 2010).

The introduction of VATS as a possible approach for lobectomy in early-stage NSCLC requires a precise functional evaluation: VATS lobectomy leads to a 15% loss in vital capacity and forced expiratory volume in 1 second, whereas open thoracotomy leads to losses of 23% and 29%, respectively (Nagahiro et al., 2001). At the same time, functional tests have optimal predictive value for severe toxicities in patients treated with concomitant chemo-radiotherapy (the pretreatment measured DLCO and FEV1 predict for severe radiation pneumonitis) (Robnett et al., 2000).

A primary lung cancer is a challenging disease frequently requiring endobronchial interventional therapy. A variety of interventional modalities, including laser, stenting, photodynamic therapy and endoluminal brachytherapy are valid approaches to relieve airway obstruction and bleeding. The systematical use of different bronchoscopic techniques is nowadays required to produce and maintain palliation (Stephens et al., 2000; Santos et al., 2004).

The diagnostic tools for suspected peripheral lung cancer were further expanded in the 2000s with two new techniques. The first is EBUS in which a radial ultrasound probe is inserted through the bronchoscope working channel to provide images of lesions. Specific echoic image patterns to differentiate malignant versus benign lesions were described (Chao et al., 2006). Lesion detection also guided the bronchoscopist to the best place for biopsy, which greatly increased the possibility to obtain a pathologic diagnosis for lesions above 2 cm in diameter (Asahina et al., 2005).

The second diagnostic tool is the electromagnetic navigation bronchoscopy, which uses a position sensor encapsulated in the tip of a steerable bronchoscopy probe, allowing for real-time correlation with previously acquired multiplanar CT images, in order to direct the biopsy of a peripheral nodule (Gildea et al., 2006).

For locoregional lung cancer staging, endoscopic techniques were further refined, allowing a true mapping of the mediastinal nodes by less invasive techniques. With EBUS-guided transbronchial needle aspiration (TBNA), the paratracheal, subcarinal, and hilar lymph nodes can be punctured under real-time guidance in sampling, while EUS fine-needle aspiration (FNA) is able to assess lymph nodes located in the left and posterior mediastinum, adjacent to the esophagus. In addition, the two procedures were shown to be feasible with one single dedicated linear EBUS bronchoscope (Herth et al., 2010).

Lung Cancer Management

Surgery

By the turn of the millennium, patients with pathologically confirmed N2 disease evaluated as resectable, non-bulky, and often limited to single-station involvement were considered for surgery after induction chemotherapy/chemoradiotherapy, mostly when induction treatment was shown to have eliminated mediastinal nodal disease. There was debate over the best technique to re-evaluate the mediastinum, when primary staging had utilized mediastinoscopy or video-mediastinoscopy. Repeat mediastinoscopy was known to be more difficult than in the primary setting, but in experienced hands was safe. The sensitivity with which re-mediastinoscopy correctly identified residual nodal disease was lower (70% to 75%) (Mateu-Navarro et al, 2000; Van Schil et al, 2002; Stamatis et al, 2005) but higher than when PET was used (50% to 60%). However, others found the sensitivity of re-mediastinoscopy to be as low as 29% (De Leyn et al, 2006). In situations in which the multidisciplinary team was involved from an early point in evaluation, a compromise evolved of using EBUB +/- EUS to confirm and evaluate the extent of mediastinal involvement, reserving mediastinoscopy for re-evaluation after induction therapy.

The French Society of Thoracic and Cardiovascular Surgery created the Epithor data set used to collect information on 15,183 adult patients undergoing thoracic procedures in a 3-year period at 39 centers (Falcoz et al, 2007). Analysis of this data base allowed the construction of a model predictive for in-hospital death, using only nine variables, validated in a random split between training and testing sub-sets. Excellent c-indices confirm that the model performs well in most sub-groups of patients. This risk-adjusted model allows meaningful comparison of in-hospital mortality between surgeons and institutions, assisting efforts to inform the decisions made by patients and health care providers.

Adjuvant and neoadjuvant chemotherapy with surgery: Multiple randomized trials evaluating post-operative platinum-based chemotherapy reported improved 5-year survival rates (Arriagada et al, 2004 and 2010; Scagliotti et al, 2003; Winton et al, 2005; Douillard et al, 2006). A 2008 meta-analysis of the largest of these showed an overall hazard ratio of death of 0.89 (95% CI, 0.82-0.96; P =0.005 [Pignon et al, 2008]). This survival benefit corresponded to a 5% absolute benefit in 5-year survival. The benefit varied by stage, with no benefit by stage I and considerable benefit by stages II and IIIA. While the majority of these trials used cisplatin-based doublet chemotherapy, the CALGB utilized paclitaxel/carboplatin in stage IB disease. Overall there was a trend toward improved survival (hazard ratio 0.83; P = 0.12) but in an exploratory subset analysis patients with tumors > 4 cm in diameter had a hazard ratio of 0.69 (P = 0.4) (Strauss et al, 2008). The study leaves unanswered the question of whether this carboplatin regimen is as good as cisplatin-based doublet combinations and a confirmation that patients with large tumors have improved outcomes with chemotherapy.

2000s Research Highlights


**Radiation Oncology**

Two major practice-changing developments occurred during the 2000s: fluorodeoxyglucose (FDG)-PET in combination with CT was shown to improve target volume definition for radiation treatment planning for NSCLC (Bradley et al, 2004) compared with CT alone and is now the standard of care. FDG-PET has also proved to provide more accurate post treatment response information (Mac Manus et al, 2003).

The first reports of the use of hypofractionated stereotactic ablative radiotherapy (SABR) for the treatment of inoperable stage I NSCLC indicated that it was associated with rates of local control in excess of 90% (Uematsu et al, 2001). A subsequent phase I dose escalation study demonstrated that doses as high as 60 Gy in 3 fractions were safely achievable (Timmerman et al, 2003). SABR continues to be an area of intense research interest for both primary lung cancers and oligometastases.

New technology had a major influence on radiotherapy planning and delivery during this period. Two developments in particular had applicability for more precise treatment of lung cancers. These were four-dimensional CT (Keall et al, 2004), especially useful for taking account of tumor motion, and on-board imaging with cone-beam CT, enabling precise localization of the tumor immediately before treatment (image guided radiotherapy) (Dawson et al, 2007). Image guidance is now an essential pre-requisite for SABR of the lung.
Chemotherapy

In 2000-2009, the “chemotherapy efficacy plateau” was demonstrated (Schiller et al, 2002; Kelly et al, 2001) in large randomized trials that showed equivalent results when different two-drug platinum-based combinations were compared. A major exception to the equivalence rule was discovered in a trial that randomized advance NSCLC patients to receive gemcitabine/cisplatin or pemetrexed/cisplatin (Scagliotti et al, 2008). The overall results show no difference in outcomes. However, in non-squamous cancers, the pemetrexed/cisplatin combination produced significantly longer progression-free survival and overall survival. In contrast, the gemcitabine/cisplatin combination was superior in squamous carcinomas. Similar findings that the improved outcomes from pemetrexed were observed only in non-squamous tumors were found in the maintenance (Ciuleanu et al, 2009) and second-line (Hanna et al, 2004) settings. Thus, these trials created a paradigm by which histology must be confirmed before initiating therapy. Attempts to add targeted therapy to chemotherapy resulted in the realization that simple approaches to additive benefits would be hard to come by (Herbst et al, 2004). Randomized trials showed benefits for platinum doublet therapy in elderly as well as PS 2 patients (Lilenbaum et al, 2005; Gridelli et al, 2004).

During this time, the role of second-line chemotherapy was established (Shepherd et al, 2000; Hanna et al, 2004; Shepherd et al, 2005) docetaxel, pemetrexed, and erlotinib were shown to improve survival. The benefits of pemetrexed were limited to non-squamous histology in the first-line, maintenance, and second-line settings.

A meta-analysis of post-operative radiation therapy (PORT) trials showed no survival advantage (Pignon et al, 2008, see reference citation in Surgery 2000-2009 section). In fact, survival may have been compromised in stage I and II disease. An analysis of USA data showed no survival advantage for stage II or III NSCLC patients receiving post-operative radiotherapy (Lally et al, 2006). In stage IIIA the role of chest radiotherapy remains controversial with some studies showing an advantage and others showing no advantage.

Anti-angiogenic agents were studied in combination with chemotherapy. Two phase III trials in advanced non-small cell lung cancer were conducted in the US. The ECOG 4599 trial for non-squamous NSCLC patients receiving the carboplatin and paclitaxel combination with bevacizumab (an anti-VEGF antibody) compared to the same chemotherapy alone (Sandler et al, 2006). This study showed a significant improvement in response, progression-free survival, and overall survival in the bevacizumab arm. The second randomized trial, termed AVAIL, showed that the addition of bevacizumab to the cisplatin/gemcitabine combination prolonged the progression-free interval but not overall survival (Reck et al, 2009). Both trials showed increased toxicity in the bevacizumab arm, especially in the elderly.

The 2004 discovery that activating mutations in the EGFR gene were more common in Asians, adenocarcinomas, and never-or-light smokers and could serve as a predictive biomarker, led to a sentinel randomized trial in Asia, comparing an oral EGFR TKI, gefitinib, to combination chemotherapy (Mok et al, 2009, see reference citation in Biology 2000-2009 section). In patients with
an activating EGFR mutation, gefitinib was superior with regards to efficacy, safety, and patient-reported outcomes whereas chemotherapy was superior in patients without these mutations. These observations were confirmed in a number of subsequent randomized trials comparing gefitinib, erlotinib, and afatinib to chemotherapy as first-line therapy in patients with EGFR mutations. The new era was established of personalized medicine where predictive biomarkers could be used to select the optimal therapy for an individual patient.

Randomized trials evaluating the anti-EGFR monoclonal antibody cetuximab showed small benefits with both positive and borderline statistical effects on survival. The ultimate role of this agent will await subsequent biomarker driven study results (Pirker et al, 2009; Lynch et al, 2004, see reference citation in Biology 2000-2009 section).


Immunotherapy

In the early 2000s, molecular definition of subsets of immune cells with negative regulatory capability were defined, and the molecular mechanisms underlying these defects was further clarified (Woo et al, 2001; Butts et al, 2005). More sophisticated clinical trials were conducted with defined antigen vaccines and possible signals of benefit (Carbone et al, 2005). PD-1 was defined as a novel target (Blank et al, 2004).

In the late 2000s, there was better definition of cell-cell interactions that regulate immune responses, and ipilimumab (anti-CTLA4) was being studied with success in melanoma. Combinations of chemotherapy and immune therapy suggested that they could work together, that immune effects could be long-lasting, and that sequencing mattered (Antonio et al, 2006). Genetically modified autologous vaccines demonstrated anecdotal responses, but proved too impractical (Nemunaitis et al, 2006). In this period, attention was focused on targeted therapies in lung cancer and immunotherapy was relatively out of favor.

- Antonia SJ, Mirza N, Fricke I, et al
  PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 2004; 64:1140-1145
- Carbone DP, Ciernik IF, Kelley MJ, et al
- Nemunaitis J, Jahan T, Ross H, et al

Supportive Care

In this decade, more work was diverted to the management of dyspnea, pain, fatigue, anorexia/cachexia and psychological distress as symptom control remains one of the key areas of unmet needs among lung cancer patients (Linssen et al, 2007). New clinical issues in supportive care first appeared, including the side effects of EGFR TKIs, which were introduced as possible treatment options of lung cancer, confronting patients with newly introduced toxicities like acneform rash, hypomagnesemia, diarrhea, and hypertrichosis, for which management protocols have since been published (Melosky, 2012). QOL studies demonstrated the EGFR TKIs provided superior outcomes compared to chemotherapy in patients with EGFR mutations. The contribution of supportive and palliative care in lung cancer on survival and treatment compliance was demonstrated (Temel et al, 2010).

  A web site on lung cancer: who are the users and what are they looking for? J Thorac Oncol. 2:813-818, 2007
- Melosky B
- Temel JS, Greer JA, Muzikansky A, et al
This decade was marked by significant changes within the IASLC including completion of Dr. Hansen’s term as CEO, the new CEO Dr. Paul Bunn, a new executive office in Aurora, USA, replacement of Bodil Diemer by Pia Hirsch as the IASLC Executive Administrator, a new journal—Journal of Thoracic Oncology, a new newsletter with Dr. Fred Hirsch as editor, completion of the first formal and comprehensive strategic plan, institution of regional meetings, new staging and pathology classifications, and highly successful WCLCs.

**2000s WCLCs:** The 9th WCLC was held in Tokyo, Japan from September 11-15, 2000 with Dr. Y. Hayata as Conference President. There were 1,130 abstracts and 2,135 participants from 64 countries. The Opening Ceremony was held at the Tokyo Opera House with attendance of their Imperial Highnesses, Prince and Princess Takamado and tradition Japanese performers. The Tokyo Declaration on Tobacco requesting governments worldwide to take action against tobacco consumption due to the rapid increasing lung cancer mortality rates was adopted. The IASLC Board elected to support Lung Cancer Awareness days. At the time of the 9th WCLC, the IASLC Board decided to re-institute the policy of holding WCLC’s every other year starting in 2003. The decision was based on the increasing scientific advances, increasing conference attendance and increasing membership.

The 10th WCLC was held in Vancouver, Canada from August 10-14, 2003 with Dr. Nevin Murray as the Conference President. The meeting had a record of 3,224 delegates from 77 countries with 1,149 abstracts. The Opening Ceremony featured cultures and traditions from the Pacific Northwest and the closing Gala Dinner at British Columbias Place Stadium, featured entertainers from the Cirque Pacifique.

The WCLC was held July 3-6, 2005 in Barcelona, Spain with Dr. Rafael Rosell as Conference President and Laureano Molins as Co-President. There was another record of attendance of 4,987 registrations from 92 countries. There were 1,488 abstracts and 175 invited speakers. The Opening Ceremony was held at the Forum Convention Center and the closing Gala was held at the Palau Sant Jordi.

After the 2005 WCLC, the IASLC Board of Directors decided that the IASLC should contract with a Professional Congress Organization (PCO) to organize each WCLC to ensure continuity and the best conference organization. A request for proposal (RFP) process led to applications from many qualified PCOs including International Conference Services (ICS) that organized the 10th WCLC in Vancouver, Imedex that organized the 11th WCLC in Barcelona, as well as others. In the final review, the Board selected ICS, which holds the PCO contract through 2019.

The 12th WCLC was held from September 2-6, 2007 at the COEX Convention Center in Seoul, South Korea. The Conference President was Dr. Jin Soo Lee. There were 4,769 registrants from 84 countries with 1,294 abstracts. The Opening Ceremony included remarks from the Prime Minister of Korea Han Duck-soo and traditional Korean musical performances. The Tobacco Declaration was updated at this meeting.

The 13th WCLC was held at the Moscone West Convention Center in San Francisco, USA from July 31 to August 4, 2009. The Conference President and Co-President were Dr. David Gandara and Dr. David Jablons. There were 6,215 registrants from 85 countries.
The program included 1,531 abstracts and 375 invited speakers. The Opening Ceremony featured performances by the famous Glide Memorial Choir as well as Beach Blanket Babylon. The Gala dinner included music by Dr. Jablons daughter Josie Jablons and opera singer, Zheng Cao as well as an unforgettable performance by the Beach Boys who rocked the stage for more than an hour. There was a Faculty Dinner at the Academy of Sciences in Golden Gate Park.

Beginning with the WCLC in San Francisco, the program planning was done by committee that included members of the local organizing committee with international committee members selected with the main conference topic areas.

Awards 2000–2010: In 2000, the IASLC Merit Award was given to Dr. Desmond Carney who previously was Conference President at the 8th WCLC and subsequently elected IASLC President for 2005-2007. Dr. Carney established the principle that the nominating committee should balance Board elections by region, specialty, and gender. In 2000, the Mary Matthews Pathology Award was given to Dr. Y. Shimosato for his lifelong achievements in the changing pathologic classification of lung cancers. The 2000 IASLC Scientific award was supported by Bristol-Myers Squibb and was awarded to Dr. Daniel C. Ihde. Dr. Ihde was one of the founding faculty of the NCI VA and Navy Branches and Deputy Director of the NCI. Dr. Ihde was a pioneer in the multidisciplinary approach to treating SCLC and the natural history and optimal chemotherapy combinations for SCLC.

In 2003 the IASLC Merit Award was given to Dr. Paul A. Bunn, Jr, MD, for his contributions as former Conference President (7th WCLC), and as former IASLC President and former Board member. Dr. Bunn was involved in many IASLC activities including the writing of the first tobacco policy and in the publication of annual textbooks on advances in lung cancer with Dr. Hansen. The Mary Matthews Award was given to Dr. Adi Gazdar. Dr. Gazdar had worked with Dr. Matthews for many years at the NCI VA and Navy Medical Branches. He had served on the IASLC Pathology panel and was instrumental in characterizing the biologic and molecular features of clinical samples and cell lines.

The IASLC Scientific Merit Award was given to Paul Van Houtte, MD, for his contribution in the combined modality therapy of lung cancer. In 2005, the IASLC Merit Award was given to Dr. Harubumi Kato who had served on the IASLC Board from 1997–2003 and served as IASLC President from 2000–2005. Dr. Kato was the 9th WCLC co-President in Tokyo in 2000.

The 2005 Mary Matthews Award winner was Elisabeth Brambilla, MD, from Grenoble, France. Dr. Brambilla had been a long serving Pathology Panel member and worked closely with Dr. Travis on the prior and subsequent WHO Pathology classification. The 2005 IASLC Scientific Award was presented to Dr. Thierry Le Chevalier. Dr. Le Chevalier was instrumental in defining the role of adjuvant chemotherapy in the cure of patients with resected lung cancers.

The 2005 Prevention Award went to Nigel Gray, MD, of Australia. Dr. Gray played an instrumental role in disclosing the chemical contents of tobacco products and the disparate ways these were being regulated globally.

The 2007 IASLC Merit Award was given to Peter Goldstraw of the United Kingdom for his sentinel contribution to the TNM staging classification. Dr. Goldstraw provided leadership for creating the database housed at the Cancer Research and Biostatics Office in Seattle, WA, USA for getting international participation and for publication in the JTO and IASLC publications. In 2007, Mary Matthews Award was presented to Fred R. Hirsch, MD, PhD, for his

President, Harubumi Kato presents IASLC Distinguished Service Award to Heine Hansen at the 10th WCLC (left) and President Frances Shepherd presents the Mary Matthew’s Award to Elisabeth Brambilla at the 11th WCLC, 2005.
many contributions on the Pathology Panel and for his work in defining prognostic and predictive biomarkers. Dr. Hirsch worked with Dr. Matthews in many pathology projects before her untimely death. The 2007 IASLC Scientific Award went to Dr. Frances Shepherd for her sentinel accomplishments in defining the best therapies for lung cancer including the role of novel targeted therapies such as EGFR TKIs. The 2007 Joseph Cullen Prevention Award was presented to Dr. James Mulshine for his tireless efforts on early detection, especially spiral CT screening.

The 2009 IASLC Merit Award was presented to Dr. Giorgio Scagliotti for service on the IASLC Board, for chairing the Nominating Committee for serving as Co-Editor of the IASLC textbook and for his role on many IASLC committees and meetings planning. The 2009 IASLC Scientific Achievement Award was presented jointly to Drs. Thomas Lynch and Bruce Johnson for their definition of EGFR mutations as critical oncogenic drivers in some lung cancers and for their use as predictive biomarkers for therapy selection. The 2009 Mary Matthews Pathology Award was presented to Dr. Mayayuki Noguchi. Dr. Noguchi was instrumental in defining precursor lesions for adenocarcinomas and for defining the outcomes associated with in situ adenocarcinomas and minimally invasive adenocarcinomas. The 2009 Joseph Cullen Prevention Award was presented to Dr. Stephen Lam from Canada. Dr. Lam’s study defined the role of sputum cytology in early detection and risk assessment, improved on understanding of premalignant lesions, and set standards for chemoprevention studies.

Fellowships 2000–2010: The IASLC Fellowship and Young Investigator awards developed and flourished during this period. These awards were designed to provide 2 years of support for fellows in training and for junior faculty.

More details of these awards and a list of recipients can be found on the www.iaslc.org/fellowship website. These awards have been supported by industry and advocacy groups as well as the IASLC. Advocacy supporters have been the Lung Cancer Foundation of America, The Prevent Cancer Foundation, and the National Lung Cancer Partnership. Commercial supporters over the decade included Bristol-Myers Squibb, Roche, Genentech, Lilly, Celgene, Amgen, GlaxoSmithKline, Sanofi-Aventis, AstraZeneca, Pfizer, OSI, Daiichi-Sankyo, and Merck KGaA.

Workshops 2000–2010: The IASLC continued to sponsor and endorse educational meetings and workshops during the 2000-2010 period. As these evolved, some of the meetings became recurring meetings that were sponsored and supported solely by the IASLC. Among these were regional meetings with scientific research abstracts as well as educational invited speakers. The first of these originated as the Chicago Multidisciplinary Conference on Cancer of the Lung and Head and Neck. The first of these was held in Chicago in 2001 with joint sponsorship of the University of Chicago chaired by Dr. Everett Vokes and contributions from Rush Presbyterian, Northwestern, and Loyola medical schools. These conferences were held in 2001, 2004, 2006, 2008, 2010, and 2012. In 2008 a decision was made to partner these conferences with the American Society of Clinical Oncology (ASCO), The American Society for Radiation Oncology (ASTRO), and the University of Chicago. These meetings were held in the even numbered years when no World Conferences were scheduled. Meeting chairs rotate between the societies and the planning committee members are distributed equally between the societies.

The IASLC also decided to hold regional meetings every other year in Europe in partnership with the European Society of Medical Oncology (ESMO). The ESMO and IASLC Executive Directors Aage Schultz and Paul Bunn planned for these meetings at the IASLC Targeted Therapy meeting in Taormina, Italy in 2006. These European Lung Cancer Conference (ELCC) meetings began in Geneva, Switzerland in 2008 and continued in even number years. Abstract submissions increased from 1,253 in 2008 to 1,358 in 2012 and attendance increased from 800 in 2008 to 1,476 in 2012. When the IASLC decided to have the WCLCs on an annual basis starting in 2016, the IASLC and ESMO decided to also hold the ELCC meetings on an annual basis beginning in 2015. The meetings are co-chaired by one IASLC and one ESMO member. Committee members were split between the societies.

The first Latin America Lung Cancer (LalCa) conference was held outside Sao Paulo, Brazil in 2004, chaired
by Dr. Nise Yamaguchi. This meeting was highly successful with over 1,000 registrants in attendance. The meeting highlighted the role of governments in approving oncology drugs and the importance of tobacco control programs with a full tobacco symposium chaired by Dr. Yamaguchi. These tobacco forums have been a part of every LalCa meetings since the first one and have played a role in reducing tobacco consumption throughout Latin America. Subsequent LalCa conferences were held every other year in even numbered years in Cancun, Mexico (2006), Vina del Mar, Chile (2008), Buenos Aires, Argentina (2010) and Rio de Janeiro, Brazil (2012); with a 2014 meeting scheduled for Lima, Peru.

In Asia, Dr. Sumitra Thongprasert organized the first Asia-Pacific lung cancer conference in Chiang Mai, Thailand in 2004. Dr. Thongprasert also started a committee called the Asia Pacific Lung Cancer Conference (APLCC) Committee, with representations from various Asian countries. In association with the IASLC, subsequent APLCC regional meetings were held in Guangzhou, China in 2006; Hyderabad, India in 2008; and, Seoul, Korea in 2010.

Targeted Therapy of Lung Cancer 2000–2010: The IASLC originally endorsed meetings on the Targeted Therapy of Lung Cancer that were held in North America and in Europe. The North American meetings were originally started in 2001. The first two meetings were held in Aspen, CO, USA, and in Scottsdale, AZ, USA. Beginning in 2003, the IASLC decided to take over the conference management and program. Since that time, the meeting has been held on an annual basis in February in Santa Monica, CA, USA. Beginning in 2003 the meeting has been started with a keynote address highlighting new transformational research. The conference has been co-chaired by Drs. Paul A. Bunn, Jr., David Johnson, and Roy Herbst since 2001. The meeting highlights have been published annually in the Journal of Thoracic Oncology.

The Targeted Therapy of Lung Cancer meetings in Europe have been held approximately every other year starting in 2003. These meetings have always been endorsed by the IASLC and in some instances have been endorsed by ESMO and ASCO. The meetings have been chaired by Dr. Fred R. Hirsch. Attendance at the meetings has been limited to 150 invited participants.

Additional Meetings: Other recurring meetings that have been endorsed by IASLC but not supported/conference managed by IASLC include the Central European Lung Cancer Conferences held every year or every other year since 2001, and the British Thoracic Oncology Group meetings held annually.

The IASLC has also endorsed the recurring Clinical Oncology Society of Australia (COSA) Lung Cancer meetings. The IASLC has endorsed a number of other meetings on a variety of topics including screening, mesothelioma, biology, and supportive care.

IASLC Journal 2000–2010: In 2003, the IASLC decided that it should own the society’s journal name and copyright to the content published in the society’s journal. The journal Lung Cancer was owned by Elsevier. The IASLC issued an RFP for publishers that would publish the IASLC journal with the IASLC owning the name, copyright, and content. Lippincott, Williams and Wilkins (subsequently Wolters Kluwer) was chosen and a new journal title, Journal of Thoracic Oncology (JTO), was selected to reflect the societies interest in all chest malignancies. Dr. James Jett, a pulmonologist from the Mayo Clinic in the USA, was chosen as the first editor. The first issue was published in January, 2006 with an international Board of Associate Editors. There were nine issues of JTO in 2006 and monthly issues began in 2007. In March 2007 the JTO was accepted by the National Library of Medicine for listing in MEDLINE and Pub Med. Over the years various editors have also been published in different languages including Spanish, Japanese and Chinese. The number of submissions and the quality of the manuscripts has increased year by year. In 2011, 28% of the submitted articles were from Europe, 27% from North America, and 43% from Asia and Australia. JTO’s initial Impact Factor was 3.5 and its current impact factor is 4.473.
**2000s–IASLC Roots Sprout**

**Pathology Panel:** In 2003 Drs. Travis and Brambilla were asked to co-edit the 2004 WHO classification together with Dr. H. Muller-Hermelink of Germany and Dr. Curtis Harris of the USA and the IASLC Pathology Panel members. The WHO subsequently published this revision in 2004. In November 2004 a workshop on bronchoalveolar carcinomas (BAC) sponsored by IASLC and ASCO was held to address the problems in the classification of BAC including the radiologic and clinical issues. The chairs were Drs. Travis and Wilbur Franklin with radiologic input from Dr. Kavita Garg (USA) and clinical input from Dr. F. Cappuzzo (Italy). In 2007 the IASLC Pathology Panel published an update on the pathologic classification of neuroendocrine carcinomas. The group also began working on changes to the pathologic classification of lung adenocarcinomas. This effort varied from prior classifications as it included radiologists and clinicians as did the BAC effort.

**Staging Committee:** The Staging Committee worked diligently to collect a large number of international cases to inform the 7th Edition of the TNM classification system. By 2010 the committee had collected data on more than 100,000 cases from 46 sources in over 20 countries worldwide. The goal was to complete collection and analyses by 2005 for the 2007 scheduled revision. Support for the effort was obtained by Eli Lilly and Company and the data collection center was at the Cancer Research and Biostatistics office in Seattle. The Committee presented data at the 2005 WCLC in Barcelona and published their results in a series of articles in JTO in 2007. These data were incorporated in the 7th TNM edition formally adopted in January 2009. The committee and IASLC worked with Editorial Rx Press (Deb Whippen, Publisher and Editor) to distribute the information in a variety of ways (see next section). Numerous articles appeared in the literature confirming the prognostic features of the new 7th edition TNM classification.

The Staging Committee began work on the 8th edition with Dr. Ramon-Rami Porta (Spain) as chair. The committee decided to include cases of thymoma and mesothelioma in its next TNM revision. The Cancer Research and Biostatistics office continued to provide the database and statistical support.

**IASLC Textbooks:** The IASLC developed a number of textbooks during 2000-2009, including the *Lung Cancer Therapy Annual* (first edition published in 2000 through the 6th edition, 2008). Editors included Drs. Heine Hansen (all editions), Paul Bunn (first through third editions), and Karen Kelly (third edition), publisher Taylor and Francis. These texts briefed the oncology community about the most recent developments in lung cancer by reviewing the literature from the previous year.

In 2006 the *IASLC Textbook of Prevention and Detection of Early Lung Cancer* was published, edited by Fred R. Hirsch, MD, PhD, with Paul A. Bunn, Jr, MD, Harubumi Kato, MD, PhD, and James L. Mushine, MD, and published by Taylor and Francis. This textbook examined the various methods and interventions used in screening in lung cancer and presented a detailed review of the approaches to prevention and treatment of early disease.

The IASLC published a number of textbooks in 2009, including *History of the IASLC: 1972–2007* by Dr. Heine H. Hansen (Editorial Rx Press). This text was provided as a member benefit to all IASLC members following the WCLC 2009 in San Francisco, and was dedicated by Dr. Hansen to the founding members of the IASLC.

In this same year, the IASLC also produced the *IASLC Staging Manual in Thoracic Oncology* and the *IASLC Staging Handbook in Thoracic*.
Oncology, thanks to the efforts of the Staging Committee chaired by Dr. Peter Goldstraw. These were distributed and sold at the WCLC 2009. The materials were incorporated into electronic applications for the iPad, iPhone, Android and Blackberry mobile devices and were available in seven languages. Thoracic oncology staging information published in these texts and electronic publications was also widely distributed in reference card and poster formats. Editorial Rx Press (Florida, USA) supported the IASLC in the global publication and distribution of these vital materials.

In the late 2000s, IASLC decided to work with and support Dr. Harvey Pass and his co-editors in the development of the 4th edition of the textbook, *Principles & Practice of Lung Cancer: The Official Reference Text of the International Association for the Study of Lung Cancer* (Lippincott Williams & Wilkins). This text became the official IASLC textbook of lung cancer and was officially published in 2010. It was translated into Chinese due to the efforts of Dr. Li Hou-Wen.

**Strategic Planning:** The IASLC Board and office instituted a formal strategic planning effort that began in 2008 and was completed in September 2011 under the leadership of IASLC President, Dr. David Gandara. The IASLC hired a consulting firm, David Kushner Consulting, to assist in this effort. Early discussions considered the organizational structure, location, size and role of the head office that had been rotating to the location of the Executive Director (Copenhagen, Denmark from 1994–2003 and Aurora, CO, USA from 2003–2008). The Board decided that the IASLC office should have a permanent site and should not rotate locations and that the office should remain permanently in Aurora, CO, USA. The Board also decided that the Executive Director should become the Chief Executive Officer (CEO) and that the time commitment for this position should increase from 50% to 75%. The Board created a new organizational chart that created three permanent departments: Education and Industry Relations, Membership, and Communications. Each of these Departments would have a Department Director. A new position of Chief Financial and Operations Officer was also created. Pia Hirsch, who had been serving as the Executive Administrator running the IASLC Office since 2003 became the Director of Education, Industry Relations, and Governance. The other positions were to be filled with national searches.

**IASLC Board Members**

**2000-2003**
- **President:** Harubumi Kato, Japan
- **Vice-President:** Andrew T. Turrisi, USA
- **President-Elect:** Frances A. Shepherd, Canada
- **Past President:** Giovanni Motta, Italy
- **Treasurer:** Anna Gregor, Scotland
- **Executive Director:** Heine H. Hansen, Denmark
- **Directors:** James Bishop, Australia; Desmond N. Carney, Ireland; Adi F. Gazdar, USA; Peter Harper, UK; James Jett, USA; Reury-Perng Perng, Taiwan; Rafael Rosell Spain; Valerie Rusch, USA; Nagahiro Saijo, Japan.

**2003-2005**
- **President:** Frances Shepherd, Canada
- **Vice-President:** Andrew T. Turrisi, USA
- **President-Elect:** Desmond N. Carney, Ireland
- **Past-President:** Harubumi Kato, Japan
- **Treasurer:** Anna Gregor, Scotland
- **Executive Director:** Paul A. Bunn, Jr., USA
- **Directors:** Masahtoh Fukuoka, Japan; Adi Gazdar, USA; James Jett, USA; Ritsuko Komaki, USA; Reury-Perng P. Perng, Taiwan; David R. Gandara, USA; Giorgio V. Scagliotti, Italy; Ryosuke Tsuchiya, Japan; Pieter E. Postmus, Netherlands.

**2005-2007**
- **President:** Desmond N. Carney, Ireland
- **President-Elect:** Nagahiro Saijo, Japan
- **Past-President:** Frances Shepherd, Canada
- **Treasurer:** Andrew T. Turrisi, USA
- **Executive Director:** Paul A. Bunn, Jr., USA
- **Directors:** M. Fukuoka, Japan; R Komaki, USA; David Gandara, USA; Giorgio Scagliotti, Italy; R. Tsuchiya, Japan; Pieter Postmus, The Netherlands; Jack Roth, USA; Nobuyuki Yamamoto, Japan; Nico van Zandwijk, The Netherlands; Fred R. Hirsch, USA; David H. Johnson, USA.

**2007-2009**
- **President:** Nagahiro Saijo, Japan
- **President-Elect:** David Gandara, USA
- **Past-President:** Desmond N. Carney, Ireland
- **Treasurer:** Andrew T. Turrisi, USA
- **Executive Director:** Paul A. Bunn, Jr., USA
- **Directors:** Jack Roth, USA; Nobuyuki Yamamoto, Japan; Nico van Zandwijk, Australia; Fred R. Hirsch, USA; David H. Johnson, USA; Wilfried Eberhardt, Germany; Joan Schiller, USA; Elisabeth Brambilla, France; Harvey Pass, USA; Tony Mok, China; Kwun Fong, Australia; Masahiro Tsuboi, Japan
Epidemiology

Genetic variants have been widely explored to identify predictors of risk and disease. Of particular interest has been the increasingly focused attention on the genes for the nicotinic acetylcholine receptor and its variants as they relate to increased risk for lung cancer in people who smoke. These genetic variants are even more intriguing as they also predict increased risk for nicotine dependence. The SNP genes encoding for nicotinic acetylcholine receptor subunits genes CHRNA3 and CHRNA5 have demonstrated increased risk for nicotine dependence and lung cancer risk. The study led by Timofeeva et al (2011) with an investigation in the largest group to date (894 cases and 1,805 controls) showed that SNPs in CHRNA5 and CHRNA3 had higher cotinines and higher risks for lung cancer. Similarly, Wassenaar et al (2011), demonstrated increased lung cancer risk in CHRNA5-A3-B4 gene cluster polymorphism. In addition, this group demonstrated the correlated relationship between smoking behavior, nicotine dependence, lung cancer risk and associated genetic variants. Perhaps as these genetic variants are further elucidated, there might be the ability to genetically assess risk for becoming nicotine dependent and furthermore, assess lung cancer risk.


Biology

The brief period since 2010 has been characterized by major advances in the biology of lung cancer due to the application of new technologies in an integrated fashion. These technologies, including next generation sequencing for mutational analysis, and global approaches for gene expression, copy number, methylation and microRNA have resulted in a comprehensive understanding of the basic biology of lung cancer with major translational applications. While the NCI-sponsored The Cancer Cell Genome (TCGA) project (http://cancergenome.nih.gov) has spearheaded this effort, multiple other groups have made important contributions as described later. They have led to the confirmation that each major form of lung cancer consists of multiple molecular and biological subtypes, and that the “one shoe fits all” concept for therapy will be replaced by precision (personalized) therapy for the patients’ individual tumor. A decade after the human genome was deciphered, we are beginning to tap into the full potential of the era of “omics.”

While adenocarcinoma is a relatively well-studied tumor with over 50% of cases having known or potential

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**MILESTONES**

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<td>• Targetable genetic abnormalities identified in up to 60% of pulmonary adenocarcinomas</td>
<td>• Paclitaxel in combination with carboplatin for NSCLC approved by FDA</td>
<td>• Crizotinib approved by FDA for NSCLC patients who have ALK-positive tumors</td>
<td>• Afatinib for NSCLC with EGFR-activating mutations approved by FDA</td>
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<td>• Use of biomarkers established for identifying optimal therapy, age of personalized medicine</td>
<td>• Clinical activity of targeting the PD-1/PD-L1 pathway in lung cancer demonstrated</td>
<td>• Erlotinib for maintenance treatment for NSCLC approved by FDA</td>
<td>• 14th WCLC, in The Netherlands</td>
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<td>• Contribution of supportive and palliative lung cancer care to survival and treatment compliance demonstrated</td>
<td>• CAP/IASLC/AMP Molecular Testing Guideline published</td>
<td>• 15th WCLC, in Australia</td>
<td>• Erlotinib for metastatic NSCLC with EGFR-activating mutations approved by FDA</td>
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target driver oncogenes, recent studies have identified new mutations targeting relatively small but clinically relevant subpopulations (Imielinski et al, 2012; Peifer et al, 2012).

Compared to lung adenocarcinomas, squamous cell carcinomas represented “terra incognita” with relatively little known about their molecular characterization. That has altered dramatically, with the publication of the TCGA study, and several other reports (The Cancer Genome Atlas Research Network, 2012). Recurrent mutations were found in 11 genes, including mutation of TP53 in nearly all specimens. Significantly altered pathways included NFE2L2, KEAP1, squamous differentiation, phosphatidylinositol-3-OH kinase pathway, CDKN2A, RB1 and HLA-A class I major histocompatibility genes.

During the last 25 years there have been very few important molecular studies on SCLC having potential translational applications (Haddadin and Perry, 2011). As with the other major types of lung cancer, the last few years have changed this landscape. Sequencing of a SCLC cell line in 2010 demonstrated over 20,000 somatic substitutions, many having characteristics of being tobacco exposure driven (Pleasance et al, 2010). Two recent studies (Peifer et al, 2012; Rudin et al, 2012) identified inactivation of TP53 and RB1 in almost all SCLC tumors and recurrent mutations in the CREBBP, EP300 and MLL genes that encode histone modifiers. Also mutations in PTEN, SLIT2 and EPHA7, as well as focal amplifications of the FGFR1 tyrosine kinase and SOX2 were identified.

While smoke exposure is by far the major causative agent for the vast majority of lung cancers, and an important and possibly growing percentage of lung cancers arise in lifetime never smokers, lung cancers in smokers and never smokers show many clinical, pathological and molecular differences. The molecular differences between these two very different forms of lung cancer have been highlighted by recent comprehensive studies (Imielinski et al, 2012; Govindan et al, 2012).

The major socio-environmental risk factor involved in the development of lung cancer is cigarette smoking. However, there are multiple genetic factors, which may also play a role in lung cancer risk. Genome-wide association studies (GWASs) have unraveled a large number of cancer risk alleles. While these reports began about 5 years ago, several recent studies have placed them in focus, and demonstrated the differences between cancers based on smoking status, ethnicity and gender (VanderWeele et al, 2012; Shiraishi et al, 2012; Lan et al, 2012; Fehringer et al, 2012; Dong et al, 2012). Risk-associated variants at 15q25 lie in a region of strong linkage disequilibrium (LD) that comprises several genes including several nicotinic acetylcholine receptor genes.

- Cancer Genome Atlas Research Network
  Comprehensive genomic characterization of squamous cell lung cancers.
  Nature. 2012; 489:519-525

  Association analyses identify multiple new lung cancer susceptibility loci and their interactions with smoking in the Chinese population.

  Association of the 15q25 and 5p15 lung cancer susceptibility regions with gene expression in lung tumor tissue.

- Govindan R, Ding L, Griffith M, et al
  Genomic landscape of non-small cell lung cancer in smokers and never-smokers.

- Haddadin S, Perry MC
  History of small-cell lung cancer.

- Imielinski M, Berger AH, Hammerman PS, et al
  Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing.
  Cell. 2012; 150:1107-1120.

- Lan Q, Hsiung CA, Matsuo K, et al
  Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia.
2010 Onward–Research Highlights

- Peifer M, Fernandez-Cuesta L, Sos ML, et al
  Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer.

- Pleasance ED, Stephens PJ, O'Meara S, et al
  A small-cell lung cancer genome with complex signatures of tobacco exposure.

- Rudin CM, Durinck S, Stawiski EW, et al
  Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer.

  A genome-wide association study identifies two new susceptibility loci for lung adenocarcinoma in the Japanese population.

- VanderWeele TJ, Asomaning K, Tchetgen Tchetgen EJ, et al
  Genetic variants on 15q25.1, smoking, and lung cancer: an assessment of mediation and interaction.

Pathology

In 2012, the IASLC, American Thoracic Society (ATS) and European Respiratory Society (ERS) published a new proposal for classifying lung adenocarcinoma (Travis et al, 2012). 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 remove the term bronchioloalveolar carcinoma (BAC) from the classification system and replace it with new categories of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), to reflect lesions that may be associated with 100% survival if completely resected by surgery. The new proposal also for the first time provided recommendations on how to apply the classification to small biopsy/cytology specimens, and guidelines for good practice in pathological 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.

- Travis WD, Brambilla E, Noguchi M, et al
  International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma.

Staging

A landmark study in which a group of thoracic surgeons trained in EBUS-TBNA and mediastinoscopy undertook a comparison of these 2 techniques in the pre-operative detection of N2 and N3 disease. Cases deemed to need further assessment of the mediastinum on the basis of clinical features, CT scan, and, in approximately 50% of cases by PET, first underwent EBUS-TBNA under general anaesthesia, followed under the same anaesthetic by mediastinoscopy. Cases not
Preclinical work by M You’s group demonstrated the ability of aerosolized delivery of such combination therapy to directly target these pathways using aerosol delivery (Fu et al, 2011). The conceptual attraction of aerosolized drug delivery for the early stages of lung cancer relates to the features of first-pass pharmacological delivery, which provides for a favorable therapeutic index. Finding well-tolerated chemoprevention for lung cancer has been a critical problem. Aerosolized delivery of peroxisome proliferator-activated receptor ligands is a favorable approach since it would reduce the rare chance of hepatic toxicity and address the distribution of early lung cancer mediated by the bronchogenic distribution of tobacco-combustion products that occurs with contemporary filtered cigarettes. Studies of volatile organic compounds in breath indicated that these analyses could be used to help distinguish benign from malignant pulmonary nodules after LDCT screening (Peled et al, 2012).

Prevention

Lai and colleagues (2012) examined data sets from 1 million claims derived randomly for National Health Insurance sources in Taiwan from a 5-year period starting in the year, 2000. The incidence of lung cancer was determined in the nearly 20,000 newly diagnosed cases of diabetes mellitus compared to a reference cohort was reduced by 39% to 45% in individuals tin individuals who took antidiabetes drugs, such as metformin, thiazolidinediones, or alpha-glucosidase inhibitors. This observation builds on an earlier observations (Chang and Szabo, 2000; Nemenoff et al, 2008) that peroxisome proliferator-activated receptors are critical regulators of lung cancer cell growth and regulation. Thiazolidinediones target that pathway. Avis and co-workers (2005) demonstrated the complex interplay of this signaling pathway with other pathways in lung cancer cells. Clinical studies showed that oral iloprost could improve bronchial dysplasia in former smokers (Keith et al, 2011) and preclinical studies indicated that the prostacyclin activity is mediated through PPAR activation (Nemenoff et al, 2008).

shown to have N2 or N3 disease underwent surgery with systematic nodal dissection. EBUS-TBNA and mediastinoscopy were found to have equal sensitivity, negative predictive value and diagnostic accuracy.


Schematic diagram of aerosol delivery system. A custom-built atomizer was used to generate budesonide droplets. Aerosol flow was then passed through two diffusion dryers containing active carbon to removedimethyl sulfoxide and ethanol. The resulting dry aerosol flow of budesonide particles was introduced into thenose-only exposure chamber from the top inlet. Effluent aerosol was discharged from an opening at the bottom of the chamber. Reproduced from Molecular Carcinogenesis, Fu et al, 50:915-921, Copyright © 2011, with permission from John Wiley and Sons.
2010 Onward–Research Highlights


**Screening/Radiology**

The Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial of chest radiograph versus usual care for 4 years had enrolled over 75,000 participants on each arm and followed participants through 13 years (Oken et al, 2011). Annual screening with chest radiograph did not reduce lung cancer mortality. Two randomized controlled screening trials with low-dose helical computed tomography (LDCT) were reported from Denmark and Italy (Saghir et al, 2012; Pastorino et al, 2012). The trials were small with less than 2,100 participants per arm and did not show a decrease in lung cancer mortality. The National Lung Screening Trial (NLST) was a randomized clinical trial that compared screening with LDCT or chest x-ray for three years (Aberle et al, 2011). Over 53,000 high-risk participants were enrolled and followed for a mean of 6.5 years. The trial demonstrated a 20% reduction in lung cancer mortality in the LDCT screening arm. Additionally, there was a 6.7% all cause mortality reduction in the LDCT arm. Based on a systematic review of screening trials with LDCT (Humphrey et al, 2013), the United Stated Prevention Services Task Force has issued a recommendation in favor of annual screening for lung cancer with LDCT in persons at high risk for lung cancer based on age and smoking history (US Preventive Services Task Force, 2013).


The last 40 years were characterized by great clinical and technological achievements in pulmonary medicine: fiberoptic bronchoscopy, TBNA for pathological mediastinal lymph node assessment, video-assisted pleuroscopy, autofluorescence bronchoscopy, various methods of endobronchial interventional therapy, such as laser resection, brachytherapy or stent placement, electromagnetic navigation bronchoscopy, and EUS/EBUS guidance to sample peripheral lung lesions and locoregional lymph nodes.

Our current reality, however, dictates that we aim for the best quality health care for our patients, but in acknowledgment of the need for financial prudence. All technological advances will increasingly be evaluated for their cost-effectiveness.

One good example in the field of endoscopy is the randomized controlled trial that compared mediastinal nodal staging by either surgical mediastinoscopy or EUS/EBUS guided sampling followed by mediastinoscopy in case of negative EUS/EBUS results only (Annema et al, 2010). The endoscopic approach was more sensitive in detection of N2/N3 metastases (79% vs. 94%, \( P = 0.02 \)), had less complications, and led to fewer unnecessary thoracotomies (18% vs. 7%, \( P = 0.02 \)). The 6-month cost of the EUS/EBUS approach was £9713 per patient vs. £10,459 for the surgical arm, so the EUS/EBUS strategy was cheaper and more effective (Sharples et al, 2012).


### Lung Cancer Management

**Surgery**

A randomized trial from the American College of Surgery Oncology Group addressed the question; does radical mediastinal lymph node dissection (MLND) improve survival compared to “sampling”? The result, that survival in the two arms was equivalent, might suggest that “sampling” is adequate (Darling et al, 2011). However, the study population was a closely defined group of early stage cases in whom one would expect a low percentage of “unexpected” N2 disease, proving to be only a fourth of the estimate used in the power calculations. Also the nodal assessment defined in preliminary “sampling” was more rigorous than many surgeons use in routine practice. The authors concluded that MLND is still merited in “all patients with resectable NSCLC.”

A large database “developed for quality and utilization information” was used to identify 3,961 patients who underwent lobectomy for lung cancer in 2007/2008 by “thoracic” surgeons at 201 institutions (Swanson et al, 2012). Open thoracotomy was utilized in 2,907 cases and a VATS approach in 1,054. VATS was associated with lower costs, especially when related to the surgeon’s experience over the previous 6 months, due probably to shorter hospital stay and less adverse events. This is the

![Esophageal and EndoBronchial UltraSound (EUS/EBUS).](image)
best data we are likely to get on the probable advantages of the VATS approach as it is unlikely we will ever see randomized phase III evidence.

**Adjuvant and neoadjuvant chemotherapy with surgery:** This decade produced results of randomized trials and meta-analyses that showed small but statistically significant survival advantage for neoadjuvant chemotherapy. The Southwest Oncology Group trial of neoadjuvant paclitaxel/carboplatin showed a survival advantage but the differences were not significant (Pisters et al, 2010), perhaps due to the fact that the trial ended early due to the meta-analysis of adjuvant trials showing surgery alone was an inferior treatment. Similar results were reported by the Spanish Lung Group that described better results for neoadjuvant approach compared to the adjuvant approach (Felip et al, 2010). Both approaches were better than surgery alone. A meta-analysis of all neoadjuvant trials confirmed an improvement in survival of a magnitude similar to that from adjuvant therapy (Song et al, 2010). Thus, either approach can be used.

- **Darling GE et al**

- **Felip E, Rosell R, Maestre JA, et al**

- **Pisters KM, Vallières E, Crowley JJ, et al**

- **Song WA, Zhou NK, Wang W, et al**

- **Swanson SJ, Meyers BF, Gunnarsson CL, et al**

**Radiation Oncology**

Two large individual patient data meta-analyses in NSCLC were published that have had a major impact on 2010 to today. The first was a comparison of sequential versus concomitant chemotherapy in patients receiving chemoradiotherapy for locally advanced NSCLC (Auperin et al, 2010). It confirmed that concomitant chemotherapy resulted in superior local control and longer survival but at a cost of more severe esophagitis. As a result, concomitant chemoradiotherapy is now established as the standard of care. The second meta-analysis demonstrated that altered fractionation, predominantly accelerated treatment (as in CHART), resulted in longer survival compared with conventional fractionation (Maugen et al,
2012). This information has had less impact on practice to date, but should have implications for the design of future studies. One of the most important advancements during this time period is the development and implementation of SABR for medically inoperable early-stage lung cancer patients (Timmerman et al, 2010). In SCLC, the recommended dose for prophylactic cranial irradiation was settled by a large international randomized trial at 25 Gy in 2 weeks, which was as effective as a higher dose in reducing the incidence of cerebral metastases (Le Pechoux et al, 2009).


### Chemotherapy

In earlier first-line chemotherapy of advanced NSCLC, results were limited to patients with performance status of 0-1 and to younger patients, principally due to the toxicities associated with platinum-based chemotherapy. Randomized studies of carboplatin-based combinations such as carboplatin/paclitaxel and carboplatin/pemetrexed confirmed earlier trials that these combinations improved survival in elderly patients (Weiss et al, 2006) and PS2 patients (Lilenbaum et al, 2005, see reference citation in Chemotherapy 2000-2009 section; Zukin et al, 2013).

Research on continuation maintenance chemotherapy for patients with NSCLC showed overall survival benefits and set the tone for increased emphasis on histologic subtyping in the therapeutic decision-making for advanced-stage disease (Paz-Ares et al, 2013). The randomized PARAMOUNT trial demonstrated a progression-free survival and overall survival advantage for maintenance pemetrexed after initial pemetrexed/platinum-doublet induction showed that pemetrexed improved survival as both continuation and switch maintenance. Erlotinib was also shown to improve progression-free survival and overall survival in the switch maintenance setting irrespective of histology but with a larger benefit in those with activating EGFR mutations (Capuzzo et al, 2010). The issue of whether two agent maintenance such as both bevacizumab and pemetrexed would be superior was initiated in the AVAPERL randomized trial that showed significant benefit in progression-free but not overall survival (Barlesi et al, 2013). An ongoing ECOG trial may provide the answer. These results represent a paradigm shift stemming from the addition of maintenance treatment to the treatment...
algorithm for NSCLC. Clinical decision-making for these patients now includes whether to offer maintenance or switch maintenance therapy versus close observation. Ongoing and future research is continuing to focus on optimizing maintenance therapy in this NSCLC, including multiple-agent combination maintenance, when second-line regimens should be offered as first-line, and the predictive value for EGFR expression (Scagliotti et al, 2011).

- Segquist JY, Yang JC, Yamamoto N, et al Phase III study of afatinib or cisplatin plus pemetrexed in patients with meta-


Immunotherapy

Multiple clinical trials reported convincing clinical activity of targeting the PD-1/PD-L1 pathway in lung cancer, launching multiple new clinical trials in different settings and in different combinations (Brahmer et al, 2012; Topalian et al, 2012). Also under investigation as a treatment option in NSCLC is ipilimumab, an anti-CTLA-4

Ipilimumab blocks negative Signaling from CTLA-4. Adapted from Lebbée’ et al ESMO 2008. Courtesy of Global Resource for Advancing Cancer Education.
antibody, the long-term benefit of which on overall survival has been demonstrated (Haanen et al, 2010). Identification of prognostic and predictive biomarkers for the use of ipilimumab in NSCLC as well as other immunotherapies such as MAGE-A3, belagenpumatucel-L, BLP25 liposome vaccine, and saccharomyces-CEA vaccine are also areas of ongoing research.


**Supportive Care**

The use of health-related QOL assessment and patient-reported outcomes (PRO), even in daily practice, has become common and widely accepted. The need for information on coping with distress and physical impairment is realized (Maguire et al, 2012 [a]). However, people with lung cancer have a complex array of supportive care needs that impact on various life aspects and knowledge about these needs still remains fragmentary (Maguire et al, 2012 [b]).

The complexity of symptoms in lung cancer has recently been published, showing the existence of a respiratory distress symptom cluster (Molassiotis et al, 2011). Follow-up models in the lung cancer patient population and outcomes research following lung cancer surgery have been focal areas of research (Schmidt-Hansen et al, 2012; Schmidt-Hansen et al, 2013).

The contribution of supportive and palliative care in lung cancer on survival and treatment compliance has been demonstrated and continues to be an area of scrutiny (Greer et al, 2012; Gustafson et al, 2013; Irwin et al, 2013).

- Schmidt-Hansen M, Baldwin DR, Hasler E. What is the most effective follow-up model for lung cancer patients? A systematic review. *J Thorac Oncol.* 2012; 7:821-824
The fourth decade of the IASLC began with focused efforts to fulfill its mission and create a strategic plan. In 2012 the Board set as a priority expanding attendance of the WCLCs, expanding the number of abstracts submitted, and improving scientific study results in lung cancer. WCLCs will be offered on an annual basis starting with the 17th WCLC to be held in Vienna, Austria. The Board also chose to change the WCLC program planning such that beginning with the WCLC in Yokohama, Japan, the local organizing concept will be expanded to a regional organizing concept with planning members from multiple countries with the region of the WCLC (eg, North America/Europe/Asia/ROW).

Strategic Plan: The strategic planning process begun in 2008 concluded with a 2-day meeting retreat in September 2011 dedicated solely to the strategic plan development. The Board of Directors hired Deb Whippen, Editorial Rx, Inc, to assist with the process and created the three leadership task forces—which focused on IASLC mission, internal affairs, and external affairs—to prepare for the retreat in Aurora, CO, USA.

At the conclusion of the strategic retreat, the Board of Directors approved revised society mission and vision statements that incorporated all thoracic malignancies in their scope and adopted strategic goals in Mission, Education, Research and Science, Organizational Growth, Professional Membership Association, Charitable Giving and Philanthropic Relationships, and Operational Soundness. The Board also adopted the organizational tagline “Conquering Thoracic Cancer Worldwide” to represent the forward vision of the society.

The IASLC Board of Directors, as part of the strategic plan, decided to form new committees to increase the role and participation of advocates, the public and family members and to increase education and activities of nurses and allied health professionals.

Membership: The membership of the IASLC in 2012 consisted of 3,790 members from all regions of the world. The six major specialties represented by IASLC members are medical oncology, thoracic surgery, pulmonary medicine, radiation oncology, basic science and cancer research, and pathology. Under the direction of Kristin Richeimer, Director of Membership, the membership application, dues, and directory were converted to an electronic format. Membership directories were distributed in an electronic PDF format beginning in 2013. The Membership Committee also tested several ideas to increase membership including offering 1-year free membership to registrants at the WCLC and offering 1-year discounted membership to members of regional societies.

Council of Regents: Under President Dr. Peter Goldstraw’s leadership, a Council of Regents was established, the goal of which is to increase awareness of the IASLC and to increase membership worldwide. Council members were nominated by regional specialty societies.

Education: The IASLC Board of Directors, Education Committee, and staff decided that the society should become a certified provider of continuing medical education (CME). The society applied for certification by the
Accreditation Council of Continuing Medical Education (ACCME), which was approved in 2012. Thus, the IASLC has been the CME provider for its meetings and web-based educational offering since July 2012. The IASLC Education Committee with approval by the Board of Directors established a CME Subcommittee to oversee the society’s CME-certified programs.

In addition to selecting meetings for IASLC endorsement, the Education Committee also reviews educational webinars. The webinars are available in live WebEx presentations and are permanently archived on the IASLC website. The Education Committee is developing a plan for an IASLC thoracic curriculum that uses relevant current education from IASLC meetings, WebEx’s, webinars, and society publications.

Tobacco Control and Smoking Cessation Committee:
In 2011, the IASLC Board decided to form a Tobacco Policy and Smoking Cessation Committee that would be distinct from the Prevention and Early Detection Committee. Dr. Michael Cummings became the first committee chair. The committee conducted a survey of members on the smoking cessation practices and needs. The results were published in the May 2013 issue of the Journal of Thoracic Oncology. The committee is working on policy statements, contributing to educational programs, and will link with anti-tobacco programs of other medical organizations.

IASLC Office and Staff: Permanent space for the IASLC Offices was obtained in Aurora, CO, USA (just outside Denver, CO). The space was designed by Camille Bunn and Pia Hirsch and occupied by staff in February 2012. A national search selected John Wetherington as the CFO/COO. Kristin Richeimer was selected as Membership Director and Renee McGaw was selected as Director of Communication. Pia Hirsch continued in her role as Director of Education, Industry Relations, and Governance. In 2012 Kristal Griffith replaced Renee McGaw as Director of Communication.

The Publication Committee with Board approval decided that the IASLC should create and publish its own textbook of thoracic oncology and this should be available electronically as well as in print form. Dr. Harvey Pass, Executive Editor, and Drs. Giorgio Scagliotti and David Ball, Editors, were selected and the official name “The IASLC Multidisciplinary Approach to Thoracic Oncology” was created. The first chapters of the book were made available at the Sydney WCLC with the entire book sales and distribution scheduled for late spring 2014.

IASLC Website and Newsletter: A major effort to create a new society website was undertaken, as overseen by the Communications Committee, chaired by Dr. Heather Wakelee, and staffed by Kristal Griffith, Director of Communications. The new website IASLC.org launched July 2013. Given the opportunity provided by

the enhanced website, the Communications Committee updated the newsletter such that upon the completion of Dr. Fred R. Hirsch’s term as Editor in July, 2013, the Editor of the redesigned newsletter will be the Chair of the Communications Committee. The first edition of the revised newsletter was sent on August 15, 2013 and can be viewed at https://www.iaslc.org/membership/newsletters/august-2013.

**IASLC e-Library:** Under the leadership of Dr. Paul Bunn, an effort spearheaded by John Wetherington, Chief Operating & Finance Officer, and with input from the Publications Committee, includes the launch of an IASLC-e-Library, which will include all future textbooks, atlases, handbooks, manuals, posters and meeting materials. All educational materials will be incorporated in an “IASLC-e-library” and be searchable and available on the IASLC website. An IASLC Post publication is also under consideration with the purpose of disseminating new and scientific achievements in thoracic malignancies to a broader community.

**Industry Task Force and Patient Education Task Force:** The IASLC Board formed two task forces to consider issues related to industry and public education. The first, the Industry Task Force, was initially chaired by Dr. Rolf Stahel. This task force recommended that the IASLC develop a foundation to raise funds to support its mission. This foundation is expected to receive IRS and Board approval in 2014. The Task Force also suggested that IASLC set up: 1) grants for members from developing nations to visit large academic centers in the region of the WCLC before or after the WCLC in that region. This grant mechanism was first established for the WCLC in Sydney with plans to continue it in the future. And, 2) travel grants to academic sites or to industry sites to allow members to receive advanced training in specialty techniques. These grants could last 2 weeks to 6 months and could be extended if funded and mutually agreeable. Work on the details of the program is continuing. The Task Force is providing recommendations to the IASLC regarding meeting regulations for potential meetings in various cities under consideration for meeting sites. The Industry Task Force recommended the development of additional patient-oriented materials. This suggestion was referred to a new task force described below.

Dr. Goldstraw established a Patient Education Task Force, chaired by Dr. Silvia Novello. This Task Force surveyed members about their perceived need for such materials. The Task Force decided that its first task would be to take inventory of useful materials from all parts of the world and in multiple languages. Links to this material will be place on the IASLC.org website. The task force will then develop materials in areas that were not well covered already.

The IASLC Board of Directors and staff developed new ways to distribute the messages and information presented at its meetings. The office initiated a plan to sponsor “Best of WCLC” meetings that would take highlighted presentations from the Sydney WCLC and have them presented in various world wide locations with selected local thought leaders. For 2013-2014 there are 17 such “Best of WCLC” meetings planned.

**IASLC Finances:** During the period of 2010–2014 there were some changes in the IASLC finances. Despite increasing attendance and increasing abstracts to the WCLCs, meeting expenses increased at a greater rate than meeting income meaning that the WCLCs were less profitable. The increase in office expenses due to the costs associated with the new staff, new website, etc, meant that operating expenses would exceed income.

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IASLC Member Dues 1974-2014. All amounts are USD.
in even number years when there was no WCLC. There were a large number of new projects that diversified the sources and amounts of revenue. Among these were the development of webexs and webinars, the development of staging and pathology manuals, handbooks and atlases, new meetings including the “Best of WCLC” series and self-publishing the society’s own textbooks. The plans for an annual WCLC were also designed to improve the overall revenues and recap the cost savings associated with annual meetings. The IASLC Board decided to increase the member dues for members from developed countries from $200/year to $250/year to shore up the finances and ensure the fiscal stability of the organization. Dues for members of developing countries, nurses and allied health professionals remain at $50 annually with continued free membership for members in training. The year-end net assets increased yearly from 2010-2012 as shown in Table.

WCLCs 2010–2013: The 2011 14th WCLC was held in Amsterdam, The Netherlands, with Dr. Pieter Postmus as Conference President and Dr. Nico van Zandwijk as Conference co-President. Once again, records were set for the number of submitted abstracts—1,880—and the number of registrants was 6,989. The Opening Ceremony was held at the Rai Convention Center and featured a “live version” of the famous Dutch painting “the Nightwatch.” The Opening Ceremony was held at the Convention Center and featured the famous Dutch Singer Karin Bloemen who wrote a song especially for

- **2003** $3,589,000
- **2004** $4,285,000
- **2005** $4,677,000
- **2006** $5,072,000
- **2007** $5,784,000
- **2008** $4,943,000
- **2009** $7,210,000
- **2010** $7,834,000
- **2011** $8,541,000
- **2012** $8,616,000

IASLC Total net assets 2003–2012.

**IASLC Board Members**

**2009-2011**
- **President:** David Gandara, USA
- **President-Elect:** Peter Goldstraw, UK
- **Past President:** Nagahiro Saijo, Japan
- **Executive Director:** Paul A. Bunn, Jr., USA
- **Treasurer:** Fred R. Hirsch, USA
- **Directors:** Wilfried Eberhardt, Germany; Joan Schiller, USA; Elisabeth Brambilla, France; Harvey Pass, USA; Tony Mok, China; Kwun Fong, Australia; Masahiro Tsuboi, Japan; Hisao Asamura, Japan; Johan Vansteenkiste, Belgium; Rolf Stahel, Switzerland; Dominique Grunenwald, France; Hak Choy, USA; Karen Kelly, USA; David Carbone, USA; Keunchil Park, South Korea.

**2011-2013**
- **President:** Peter Goldstraw, UK
- **President-Elect:** Tony Mok, Hong Kong
- **Past President:** David Gandara, USA
- **Executive Director:** Paul A. Bunn, Jr., USA
- **Treasurer:** Fred R. Hirsch, USA
- **Directors:** Alex Adjei, USA; Hisao Asamura, Japan; David Carbone, USA; Hak Choy, USA; Carolyn Dresler, USA; Dominique Grunenwald, France; Karen Kelly, USA; Christian Manegold, Germany; Tetsuya Mitsudomi, Japan; Kazuhiko Nakagawa, Japan; Silvia Novello, Italy; Keunchil Park, South Korea; Rolf Stahel, Switzerland; Sumitra Thongprasert, Thailand; Johan Vansteenkiste, Belgium.

**2013-2015**
- **President:** Tony Mok, Hong Kong
- **President-Elect:** David Carbone, USA
- **Past President:** Peter Goldstraw, UK
- **Chief Executive Officer:** Fred R. Hirsch, USA
- **Treasurer:** David Gandara, USA
- **Directors:** Alex Adjei, USA; Carolyn Dresler, USA; Laurie Gaspar, USA; Pasi A. Janne, USA; Keith Kerr, UK; Christian Manegold, Germany; Franciose Mornex, France; Tetsuya Mitsudomi, Japan; Kazuhiko Nakagawa, Japan; Silvia Novello, Italy; Yuichiro Ohe, Japan; Solange Peters, Switzerland; Sumitra Thongprasert, Thailand; William D. Travis; Yi-long Wu, China.
the occasion. The Gala dinner finished with a performance by Caro Emerald, a rising star in Europe, whose grooving jazz, infectious mambos, and banging beats filled the dance floor.

The 15th WCLC was held at the Darling Harbour Convention Center in Sydney, Australia. There were a record number of submitted abstracts—2,316. The Conference President is Dr. Michael Boyer with Dr. Kwun Fong as Co-Conference President. The meeting featured increased input from advocates and from nursing and allied health professionals. The Opening Ceremony, which was preceded by a tobacco cessation session, featured a keynote presentation by The Honourable Nicola Roxon, Australia as well as an overview of the research in lung cancer and IASLC's 40-year history presented by Dr. Fred R. Hirsch. The Gala dinner program included an amazing journey through Australia including regional cuisine, indigenous culture, and life music.

The WCLCs leading up to and including the 15th WCLC in Sydney were scheduled over 4½ days and included cultural activities/tours planned to stimulate member interactions and local cultural awareness. Beginning with the 15th WCLC in Sydney the conferences schedule was shortened to 3 days and the social-featured half-day omitted.

The WCLCs through the 15th WCLC also included a Presidential Reception and a faculty dinner in addition to the Opening and Closing ceremonies. The outgoing President presented awards to outgoing Board of Directors members, committee chairs, and past presidents at the President's Reception. All invited faculty were invited to a faculty dinner. Because of the shortened days of the 15th WCLC, the President’s Reception and faculty dinner were combined into one event.

**2010–2014 Meetings:**

*European Lung Cancer Conference*—In 2010 and 2012, regional IASLC-sponsored and -supported meetings continued in Europe with ESMO at the European Lung Cancer Conferences (ELCCs) in Geneva, Switzerland. Both ESMO and IASLC agree to expand the partnership of the ELCC to include the European Thoracic Society (ETS) and the European Society of Therapeutic radiologists (ESTRO) for the annual meetings starting in 2015.

*Latin American Lung Cancer Conference*—The Latin American Lung Cancer Conferences were held in Buenos Aires, Argentina, in 2010 and in Rio de Janeiro, Brazil, in 2012. The 2014 LaLCa meeting will be held in Lima, Peru and the 2016 meeting will be held in Panama City, Panama. It is expected that more than 1,000 attendees will participate in this meeting.

*Chicago Multidisciplinary Symposium in Thoracic Oncology*—The Chicago Multidisciplinary Symposium in Thoracic Oncology was held jointly with ASTRO, ASCO, and the University of Chicago every other year since 2008. The most recently held Symposium was in 2012, with 657 attendees. The meeting chairs, numbers of attendees and numbers of abstracts are also illustrated.

*Asia Pacific Lung Cancer Conference*—The Asia Pacific Lung Cancer Conference was held in Chiang Mai, Thailand in 2004, Guangzhou, China in 2006, Hyderabad, India in 2008, Seoul, Korea, in 2010, and in Fukuoka, and Japan, in 2012. The 2014 APLCC meeting is scheduled for Kuala Lumpur, Malaysia, in November 2014. In 2011, the IASLC Board decided to formally include the APLCC as a standing IASLC committee and Dr. Sumitra Thongprasert was appointed as the first committee chair.

*AACR-IASLC Joint Conference on the Molecular Origins of Lung Cancer*—The IASLC Board of Directors decided to co-sponsor a continuing series of meetings on the Molecular Origins of Lung Cancer with the American Association for Cancer Research (AACR) starting in 2010 in San Diego, CA, USA, with the second meeting occurring in 2012. Members of the Program Planning Committee for these conferences are split evenly between the societies. The program of the 2014 Conference will cover a range in topics spanning prevention, early detection, cancer stem cells, genomics, epigenetics, novel therapeutics, clinical trials, and patient advocacy.
**Targeted Therapy of Lung Cancer Meeting:** The Targeted Therapy of Lung Cancer meetings chaired by Drs. Paul A. Bunn, David H. Johnson, and Roy Herbst have been offered annually from 2010–2013 in Santa Monica, CA, USA. Meeting highlights were published in the *Journal of Thoracic Oncology*. The meeting continues its unique formats of scientific presentations on novel targets, presentations of drug developments and biomarkers for these targets, trial design and discussion. This invitation-only meeting highlights interactions between government, academia and industry with strong input from pathology, basic scientists, and statistics. The next Targeted Therapy of Lung Cancer meeting is scheduled to be held February 19-22 2014 and is expected to occur annually thereafter.

The IASLC continued to endorse and/or provide fiscal support for other workshops and meetings. There were 11 of these meetings in 2010, five in 2011, six in 2012 and four in 2013.

**2010–2014 Awards:** The IASLC Merit award in 2011 presented at the Amsterdam WCLC was awarded to Dr. David Ball for extraordinary contributions to the combat of lung cancer and to the IASLC. Dr. Ball was President of a World Conference, served on the Board of Directors, chaired the Nominating Committee, played a key role in the development of combined modality therapies, and lectured and attended more IASLC meetings and workshops than perhaps most other members. The 2011 IASLC Achievement Award was presented to Dr. Nagahiro Saijo for his studies on the pharmacology of lung cancer therapeutics, for developing the chemotherapy field in Japan, and for developing combination chemotherapy combinations that became worldwide standards. The 2011 IASLC Mary Matthews Pathology Award went to Dr. Philip Hasleton, Professor of Pulmonary Pathology at the University of Manchester, UK, for his studies of lung cancer and mesothelioma. Dr. Hasleton has served as the Editor of *Spencer’s Pathology of the Lung* textbook for many years—the most recent being the 6th edition (Cambridge University Press, 2013)—among many other leadership roles and IASLC accomplishments. The 2011 IASLC Joseph Cullen Prevention Award was presented to Dr. John Field for his unwavering efforts in the prevention and early detection of lung cancer. Dr. Field developed a risk score for lung cancer based on clinical and smoking histories. He chaired the IASLC Prevention Committee, headed the IASLC efforts to prepare statements on CT-screening, and chaired several IASLC-sponsored workshops.

The 2013 IASLC awards were presented at the WCLC in Sydney, Australia. The IASLC Merit Award was given to Dr. James Jett for his many contributions to the IASLC and lung cancer research. Dr. Jett was the Founding Editor of the *Journal of Thoracic Oncology*. The 2013 IASLC Scientific Achievement Award was presented to Dr. David Gandara for his career in translational and clinical lung cancer research. Dr. Gandara chaired the Southwest Oncology Group (SWOG) Lung Cancer Committee for many years and their scientific accomplishments reflect his leadership. In addition his studies at the University of California, Davis have identified novel agents and targets. The 2013 Mary Matthews Pathology Award was presented to Dr. Tetsuya Mitsudomi from Japan for his studies on the molecular biological pathogenesis of lung cancer. Dr. Mitsudomi is the first surgeon to receive this award for molecular pathology. The 2013 Joseph Cullen Award for Prevention and Early Detection was presented to Dr. Pieter Postmus from the Netherlands for studies on early detection and chemoprevention of lung cancer.

**2010–2013 Fellowship Award:** The IASLC Fellowship and Young Investigator Awards developed and flourished during this period. These awards were designed to provide 2 years of support for fellows in training and for junior faculty.

Details about these awards and lists of recipients can be found on www.iaslc.org/fellowship. These awards have been supported by industry and advocacy groups as well as the IASLC. Advocacy supporter have been the Lung Cancer Foundation of America, The Prevent Cancer Foundation, and the National Lung Cancer Partnership. Commercial supporters over the decade included Bristol-Myers Squibb, Roche, Genentech, Lilly, Celgene, Amgen,
2010-2014—IASLC Fulfills Its Strategic Mission

GlaxoSmithKline, Sanofi-Aventis, AstraZeneca, Pfizer, OSI, Daiichi-Sankyo, and Merck KGaA.

Journal of Thoracic Oncology 2010–2014: Dr. James Jett completed his term as editor of JTO on December 31, 2012. After an international search, Dr. Alex Adjei was selected as the second editor of the JTO with a term starting January 1, 2013. Comments from the outgoing and incoming editors were both published in the January 2013 issue of JTO. During Dr. Jett’s term as editor, the journal grew from a circulation of nine monthly issues per year to 12 monthly issues and the annual manuscript submissions increased from 300 in 2006 to over 1,100 in 2012. The impact factor was first issued in 2008 and was 3.5; the most recent impact factor is 3.66.

As the new editor, Dr. Adjei plans to build on the journal’s foundation and track record created by Dr. Jett, and lead the journal to meet continuing and evolving goals for high-quality research articles beginning with a revamped and international new editorial board (http://journals.lww.com/jto/pages/editorialboard.aspx).

Pathology Panel: The IASLC Pathology Panel began this period with recommendations on the classification of lung adenocarcinoma, as published in the JTO (Travis et al, 2011). This classification addressed both resected specimens and small biopsies and cytology and eliminated the terms bronchiolalveolar carcinoma (BAC) and mixed subtype adenocarcinoma. For resection specimens the terms adenocarcinoma in situ and minimally invasive adenocarcinomas were developed for small solitary adenocarcinomas with pure lepidic growth (AIS) or predominant lepidic growth with <5 mm invasion (AIA). Invasive adenocarcinomas were classified by predominant pattern (lepidic, acinar, papillary, solid, and micropapillary). This new classification was followed by articles showing the radiologic implications of the classification (Lee HJ et al. J. Thorac Imaging 27: 340-353, 2012), articles showing that classification is a stage-independent prediction of survival (Warth A et al. J Clin Oncol 30: 1436-1446, 2012), could be used in small biopsies and cytology specimens (Travis WD et al. Arch Pathol Lab med 137: 668-684, 2013), and had relevance in clinical practice and clinical trials (J Clin Oncol 31: 992-1001, 2013). Additional studies demonstrated that classification had implications for surgical therapy and was of prognostic value even in stage I disease (Travis WD et al. Arch Pathol Lab Med 137: 685-705, 2013 and Hung JJ et al. Ann Surg, 2013).

Members of the IASLC Pathology Panel as well as clinician members participated in the Development of the Molecular Testing Guideline for Selection of Lung Cancer patients for EGFR and ALK tyrosine kinase inhibitors with the College of American Pathology (CAP) and the Association for Molecular Pathology (Lindeman N et al. JTO 2013). The guideline provides 15 recommendations for molecular testing.


Staging Committee: The Staging Committee, under the leadership of Dr. Peter Goldstraw and subsequently Dr. Rami-Porta, published proposals on the TNM classification for small cell lung cancer in 2009 (Vallieres E et al. JTO 4: 1049–1059, 2009) strengthening the
recommendation to use TNM staging for all SCLC cases. In 2009 the group also published its proposal for a new international lymph node map (Rusch VW et al. JTO 43: 568-577, 2009). In 2010 the Staging Committee published data showing that standardized uptake value measured on PET scans is prognostic for survival (Paesman M et al. JTO 5:612–619, 2010). Subsequent studies showed that tumor size has an effect on prognosis in patients treated with radical radiotherapy or chemotherapy (Ball D et al. JTO 8: 315–321, 2013). The staging group also published recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma, a consensus report (Rice D et al. JTO 6: 1304–1312, 2011). The group also published an initial analysis of the IASLC mesothelioma database (Rusch VW et al. JTO 7: 1631–1634, 2012). The Staging Committee will include lung cancers, thymomas, and mesotheliomas in their revisions for the 8th TNM revisions.

Prevention/Early Detection: The publication of the results of the NLST stimulated debate on whether the data were sufficient to change public policy. The data provided compelling data showing a 20% reduction in lung cancer mortality and a 6% reduction in overall mortality. However, the early results showed a 96% false positive rate, a positivity rate of 26% and a large number of evaluations performed to follow-up on false positives. There was no cost effectiveness data and results from many other trials were still not known. Thus the IASLC released a statement regarding the pros and cons of low dose spiral CT screening and published an article in JTO summarizing their conclusions. (References available at iaslc.org.) As of 2014 the committee continues to work on ways to inform the public and governments regarding early detection.

The IASLC's commitment to lung cancer screening has been long-term. Collaborative work in this area has been influential, including on the recently issued draft recommendation and evidence review regarding annual screening for lung cancer by the US Preventive Services Task Force (http://www.uspreventiveservicestaskforce.org/). As of 2014 the committee continues to work on ways to inform the public and governments regarding early detection.

Leadership: The President of the IASLC from 2009–2011 was Dr. David Gandara, a medical oncologist from the US. Dr. Gandara was the WCLC Congress President in 2009 and spearheaded the strategic planning process completed in 2011. Dr. Peter Goldstraw was IASLC President from 2011–2013. Dr. Goldstraw is a thoracic surgeon from the United Kingdom who chaired the staging committee prior to his election. Dr. Goldstraw started the Board of Regents, new committees on Advocacy, Nurses/Allied Health Professional and task forces on Public Education and Industry Relations. Dr. Tony Mok, a medical oncologist from the University of Hong Kong is President from 2013–2015 and Dr. David Carbone, a medical oncologist from Ohio State’s Comprehensive Cancer Center, USA, is President-Elect. Dr. Fred R. Hirsch served as the Treasurer from 2009–2013. Dr. Gandara was elected Treasurer for a 4-year term from 2013–2017.

The second term of Dr. Paul A. Bunn, Jr. as CEO of the IASLC was completed at the Sydney WCLC in 2013. The IASLC Board of Directors conducted an international search and Dr. Fred R. Hirsch was chosen as CEO for a 5-year term starting at the Sydney WCLC for 2013–2018.
Two Executive Directors moving the IASLC forward!

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<th>Name</th>
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**Save the Date**
IASLC 16th World Conference on Lung Cancer
September 6–10, 2015
Denver, CO, USA

www.iaslc.org