

April 2002

Lung  
Cancer

# Frontiers

## Newsletter Enters Seventh Year

Comments may be submitted to:

**Lung Cancer Frontiers**

1850 High Street  
Denver, CO 80218  
or by e-mail to  
tlpdoc@aol.com

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“The purpose of *Lung Cancer Frontiers* is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.”

**L**ung Cancer Frontiers was launched in 1996. Its purpose is to stimulate interest in all aspects of lung cancer, with an emphasis on early identification and intervention. Today *Lung Cancer Frontiers* reaches all board certified pulmonologists in the United States and Canada. Plans to expand our readership are underway. This 12th issue of *Lung Cancer Frontiers* launches this year's series. We are grateful for the new support of Astra-Zeneca, which, through an unrestricted grant, provides additional support for three issues this year. Hopefully this will be sufficient to continue to cover the exciting new developments that are occurring in lung cancer around the world. We hope to return to quarterly issues in 2003. Also, our web site, lungcancerfrontiers.org, has been revitalized. All previous issues can be viewed on line.

This issue presents selected abstracts from the peer-reviewed literature with accompanying editorial comments. Subsequent issues will deal with highlights from lung cancer conferences as we have done in the past, as well as selected citations from the contemporary literature.

### National Lung Health Education Program/Association of Respiratory Care Alliance

**T**he alliance between the NLHEP and the AARC continues to flourish. NLHEP aims to involve all primary care physicians in the early identification and intervention in COPD and related disorders. Of course, lung cancer, heart attack, and stroke all relate to COPD. The linkage is through smoking and, perhaps, other factors including heredity. In any case, spirometry can be the first step in finding patients at risk of progressive COPD, as well as associated lung

cancer. Abnormal spirometry is also a strong indicator of increased risk of heart attack and stroke. In fact, abnormal spirometry is associated with all causes of mortality (Shennemann HJ et al: *Chest* 2000;118:656-664).

At the annual meeting of the AARC in December 2001, a “Train the Trainer Program” was provided for over 100 respiratory therapists. Already, a pilot project designed to demonstrate a pragmatic approach to early assessment of lung function has been established in Hanover, Pennsylvania under the direction of pulmonologist Michael Ader. Other pilot projects will be established in the future. Respiratory therapists represent 130,000 “foot soldiers” on the front lines and are involved in the day-to-day functions of virtually all of our nation's hospitals. Thus, a true grass roots campaign for early identification and intervention in COPD and related disorders is at hand.

Soon, this alliance will begin to focus on the early identification of lung cancer.

### New Lung Cancer Screening Trial Approved by the National Cancer Institute

The Cancer Letter, Nov 23, Vol 27, No 43

**T**he Board of Overseers of the National Cancer Institute has approved a lung cancer screening trial that will test whether spiral CT screening can detect lung cancers early enough to reduce mortality. The approval commits \$200 million over the next eight years during which 50,000 current or former smokers between 55-74 will be randomly assigned to screening by either spiral CT or standard chest x-ray. This represents the first new

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**Lung Cancer Frontiers**  
1850 High Street  
Denver, CO 80218  
or by e-mail at  
tlpdoc@aol.com

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large randomized clinical trial comparing screening methods measuring mortality and other outcomes.

### Design

All participants will receive an initial screen and two subsequent yearly screens. 50% will be randomized to spiral CT screening and 50% to chest x-ray screening.

All current smokers will be referred to local smoking cessation programs. The trial will measure incidence, mortality, survival, stage, sensitivity, predictive value, and harmful effects of screening, diagnostic testing, treatment, cost-effectiveness and quality of life.

### Eligibility

Participants must be between 55 and 74 with a smoking history of at least 30-pack years and current smokers or former smokers who have quit within ten years. Excluded are those who have had a spiral CT in the last 24 months, a known history of lung cancer, currently undergoing treatment for another cancer other than skin cancer (non-melanoma), participation in another screening or cancer prevention trial.

### Editorial (TLP) Comment:

The Lung Cancer Newsletter of November 23, Volume 27 No. 43, announced a new lung cancer screening trial that would test whether spiral CT screening can detect lung cancers early enough to reduce mortality. The proposed controlled clinical trial commits a huge expenditure of funds for what is presented as early lung cancer screening. Sadly, this study is already flawed and cannot answer the question of early identification and intervention in lung cancer using modern technology. This study ignores the importance of sputum cell markers for early central lesions. These lesions are often 2 to 3 mm roentgenographically occult intraepithelial, mostly squamous carcinomas, many of which are *in situ* or stage I. We have established these lesions can be detected through sputum cytology followed by white light fiberoptic bronchoscopy<sup>1,2</sup>, but most accurately through fluorescent endoscopy<sup>3</sup>. Failure to do dual screening will miss approximately 25% of lung cancers which could be cured if they were identified and treated early.

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“Sadly, this study is already flawed and cannot answer the question of early identification and intervention in lung cancer using modern technology. This study ignores the importance of sputum cell markers for early central lesions.”

“We already know that screening in high risk patients yields a high prevalence of lung cancer.”

“The other troubling issue is the age of entry criteria. Why age 55? There are plenty of high risk patients who develop lung cancer in their 40’s and early 50’s.”

“Thus when the results of this study are known in approximately 10 years, the technologies for the diagnosis of early lung cancer will have evolved further.”

patients yields a high prevalence of lung cancer. Jim Jett (Am J Respir Crit Care Med 2001;163:A484) enrolled 1520 patients in a new screening study at the Mayo Clinic in Rochester. Three lung cancers were only found through sputum cytology. In a further analysis of this cohort, 25 cancers were found (1.6%) (Jim Jett personal communication February 2002).

The other troubling issue is the age of entry criteria. Why age 55? There are plenty of high risk patients who develop lung cancer in their 40’s and early 50’s. Since we already know that we can find, treat and cure early lung cancer in high risk patients, it is the opinion of the editor that heavy smokers with airflow obstruction should be **excluded** in the new NCI trial. Such patients should receive dual screening at least twice, which will result in a yield of between 2 and 5% early stage lung cancers.

Another problem with the new study is that it will require eight or more years to enroll patients and more time to analyze the results. Thus when the results of this study are known in approximately 10 years, the technologies for the diagnosis of early lung cancer will have evolved further. Thus, this study is destined to be obsolete at the outset. And think of the missed opportunities to diagnose, treat and cure lung cancer in hundreds of thousands of high risk patients, for which we have a practical diagnostic approach right now! It just doesn’t make sense.

1 Bechtel JJ, Kelley WR, Petty TL, Patz DS, Saccomanno G. Outcome of 51 patients with roentgenographically occult lung cancer detected by sputum cytologic testing: A community hospital program. Arch Intern Med 1994;154:975-980.

2 Bechtel JJ, Petty TL, Saccomanno G. Five year survival and later outcome of patients with x-ray occult lung cancer detected by sputum cytology. Lung Cancer 2000;30:1-7.

3 Lam S, Kennedy T, Unger M, et al: Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 1998;113:691-702.

## Early Lung Cancer Action Project

Henschke CI, Naidich DP, Yankelevitz DF, et al: Lung Cancer Action Project. Cancer 2001;92:153-9.

**B**ackground. The Early Lung Cancer Action Project (ELCAP) was designed to evaluate the usefulness of annual computed tomography (CT) screening for lung carcinoma. With the baseline results having been reported previously, the focus of the current study was on the early results of the repeat screenings.

**Methods:** A cohort of 1000 high-risk individuals was recruited for baseline and annual repeat CT screening. At last follow-up, a total of 1184 annual repeat screenings had been performed. A positive result from the screening test was defined as newly detected, one to six noncalcified pulmonary nodules with interim growth. The diagnostic workup of the individuals was guided by recommendations supplied by the ELCAP investigators to the collaborating clinicians.

**Results:** Of the 1184 repeat CT screenings, the test result was positive in 30 (2.5%). In 2 of these 30 cases, the individual died (of an unrelated cause) before diagnostic workup and the nodule(s) resolved in another 12 individuals. In the remaining 16 individuals, the absence of further growth was documented by repeat CT in 8 individuals and further growth was documented in the remaining 8 individuals. All eight individuals with further nodular growth underwent biopsy and malignancy was diagnosed in seven. Six of these seven malignancies were nonsmall cell carcinomas (five of which were Stage IA and one of which was Stage IIIA) and the one small cell carcinoma was found to be of limited stage. The median size dimension of these malignancies was 8 mm. In another two subjects, symptoms prompted the interim diagnosis of lung carcinoma. Neither of these malignancies was nodule-associated but rather were endobronchial; one was a Stage IIB nonsmall cell carcinoma and the other was a small cell carcinoma of limited stage.

**Conclusions:** False-positive screening test results are uncommon and usually manageable without biopsy; compared with no screening, such screenings permit diagnosis at substantially earlier and thus more curable stages. Annual

“False-positive screening test results are uncommon and usually manageable without biopsy; compared with no screening, such screenings permit diagnosis at substantially earlier and thus more curable stages.”

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“Idiopathic pulmonary fibrosis (IPF) was reported to be associated with increased risk of lung cancer as a result of the occurrence of atypical or dysplastic epithelial changes in fibrosis which progressed to invasive malignancy.”

repetition of CT screening is sufficient to minimize symptom-prompted interim diagnoses of nodule-associated malignancies.

#### Editorial (TLP) Comment:

It is not surprising that the rescreening of 1,000 high risk patients yielded more lung cancers. Note that two were endobronchial, again underscoring the importance of sputum cytology.

### Can Semi-automated Image Cytometry on Induced Sputum Become a Screening Tool for Lung Cancer?

Evaluation of Quantitative Semi-automated Sputum Cytometry on Radon- and Uranium-exposed Workers. Marek W, Kotschy-Lange N, Muti A, et al: Can Semi-automated Image Cytometry on Induced Sputum Become a Screening Tool for Lung Cancer? *Eur Respir J* 2001;18:942-950.

The correlations between semi-automated sputum cytometry (ASC), conventional cytology and the final diagnosis were investigated in industrially-exposed workers. Slides of sputum samples from 201 former uranium miners with silicosis, 100 patients with asbestosis, 103 workers resected for lung cancer, and 200 controls (50% smokers), were stained using the Papanicolaou (Pap) method and the Feulgen reaction with thionin. Cytometry was performed using the Cyto-Savant automated system.

Atypical nuclei were found in 72 of 404 patient samples, 327 samples were normal and five were inadequate for ASC analysis. Thirteen tumours (Pap IV, Pap V) and 11 cases of severe dysplasia were identified by cytology. Lung cancer was confirmed in 20 patients. Compared to the final diagnosis of lung cancer, the sensitivity of ASC was 75% (15 out of 20) and specificity 89.8% (520 out of 579). The results represent a diagnostic efficiency of 89.3%. The combination of ASC with cytology increased sensitivity to 80% (16 out of 20) without significant loss of specificity (89.7% or 523 out of 581).

In this investigation of a limited number of patients with occupational radon or asbestos exposure, semi-automated sputum cytometry

appears to be sensitive and reliable for the detection of malignant changes in the tracheobronchial mucosa. Together with conventional cytology, it would be reasonable to test the validity of the combined methods in a large-scale feasibility study of early lung cancer detection.

#### Editorial (TLP) Comment:

This new semi-automated sputum cytology technology appears to be sensitive and reliable enough for mass screening in high risk patients. Certainly, easy access to affordable sputum cytology is a high priority in lung cancer screening.

### Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis

Park J, Kim DS, Shim TS, et al: Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis. *Eur Respir J* 2001; 17:1216-1219

Idiopathic pulmonary fibrosis (IPF) was reported to be associated with increased risk of lung cancer as a result of the occurrence of atypical or dysplastic epithelial changes in fibrosis which progressed to invasive malignancy. In that situation, the cancer will develop in the area of major fibrosis. To investigate the direct relationship between fibrosis and cancer development, the real concordance rate of the two lesions in the chest computed tomography (CT) was analysed and compared to the histological types of lung cancer.

The subjects included 63 patients with combined lung cancer and IPF (IPF-CA), 218 patients with lone IPF, and 2,660 patients with primary lung cancer. All patients were diagnosed at Asan Medical Center during the same period.

The age, percentage of smokers, and the male sex were significantly higher in IPF-CA compared with lone IPF. The odds ratio of smoking was 2.71 compared to nonsmoking IPF controls. In IPF-CA, 56% of the cancer was located in the periphery of the lung and 52% in the upper lobe. The majority of the cancers (64%) were found in the nonfibrotic area at chest CT. The most frequent cell type was squamous cell carcinoma (35%), and there was no significant difference in

the cancer cell type between IPF-CA and total lung cancer population.

These findings suggest that in combined lung cancer and idiopathic pulmonary fibrosis patients, the features of the lung cancer are similar to the total lung cancer population.

**Editorial (TLP) Comment:**

It is well established that chronic obstructive pulmonary disease increases the prevalence of lung cancer four to six times in patients with equal smoking, family and occupational histories, compared with those who have normal airflow. The present study also implicates idiopathic fibrosis as a risk factor for lung cancer. Thus, when spirometric abnormalities are present, either in obstructive or restrictive diseases, indications for lung cancer screening are present.

**An Evaluation of Screening for Lung Cancer in Niigata Prefecture, Japan: A Population-based Case-control Study.**

Tsukada H, Kurita Y, Yokoyama A, et al: An Evaluation of Screening for Lung Cancer in Niigata Prefecture, Japan: A Population-based Case-control Study. *BR J Cancer* 2001; 9:1326-1331. Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan.

**A**lthough an annual screening programme for lung cancer has been carried out widely in Japan since 1987, there is insufficient evidence to confirm its efficacy in terms of reducing mortality. In order to evaluate the efficacy of the lung cancer screening which has been widely carried out in Japan since 1987, a case-control study was conducted in Niigata Prefecture, Japan. In the study area, chest X-ray examinations for all participants and sputum cytology for high-risk participants were offered annually. Case subjects, who had died from lung cancer (174), and control subjects matched by sex, year of birth, residence and smoking status (801), who had been alive at the time of diagnosis of the corresponding case, were selected from the National Health Insurance holders. Screening histories of the subjects were compared between cases and matched controls for the identical

calendar period before the time of diagnosis of the cases. The odds ratio of death from lung cancer for those screened within 12 months vs those not screened was 0.401 (95% CI: 0.272-0.591) with adjustment by smoking index. Our results suggest that annual lung cancer screening might reduce mortality from lung cancer by approximately 60%. Copyright 2001 Cancer Research Campaign

**Editorial (TLP) Comment:**

This study adds additional evidence favoring modern lung cancer screening over ordinary diagnostic approaches. Although not a randomized controlled clinical trial, the large body of evidence strongly suggests that screening can improve survival in lung cancer.

**Role of p53 as a Prognostic Factor for Survival in Lung Cancer: A Systematic Review of the Literature with a Meta-analysis**

Steels E, Paesmans M, Berghmans T, et al: Role of p53 as a Prognostic Factor for Survival in Lung Cancer: A Systematic Review of the Literature with a Meta-analysis. *Eur Respir J* 2001;18:705-719. Dept de Medecine et Laboratoire d'Investigation Clinique H.J. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Universite Libre de Bruxelles, Brussels, Belgium.

**T**he role of p53, as a prognostic factor for survival in lung cancer, is controversial and the purpose of the present systematic review of the literature is to determine this effect. Published studies were identified with the objective to aggregate the available survival results after a methodological assessment using a scale specifically designed by the European Lung Cancer Working Party (ELCWP). To be eligible, a study had to deal with p53 assessment in lung cancer (primary site) only, and to provide a survival comparison according to the p53 status. Among the 74 eligible papers, 30 identified p53 abnormalities as a univariate statistically significant poor prognostic factor and 56 provided sufficient data to allow survival results aggregation. There was no significant difference between the trials that either showed or did not

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show a prognostic effect of p53 according to the methodological score or to the laboratory technique used. The studies were categorized by histology, disease stage, treatment and laboratory technique. Combined hazard ratios suggested that an abnormal p53 status had an unfavourable impact on survival: in any stage non-small cell lung cancer (NSCLC) the mean (95% confidence interval) was 1.44 (1.20-1.72) (number of studies included in the subgroup was 11), 1.50 (1.32-1.70) in stages I-II NSCLC (n=19), 1.68 (1.23-2.29) in stages I-III NSCLC (n=5), 1.68 (1.30-2.18) in stages III-IV NSCLC (n=9), 1.48 (1.29-1.70) in surgically resected NSCLC (n=20), 1.37 (1.02-1.85) in squamous cell carcinoma (n=9), 2.24 (1.70-2.95) in adenocarcinoma (n=9), 1.57 (1.28-1.91) for a positive immunohistochemistry with antibody 1801 (n=8), 1.25 (1.09-1.43) for a positive immunohistochemistry with antibody DO-7 (n=16), and 1.65 (1.35-2.00) for an abnormal molecular biology test (n=13). Data were insufficient to determine the prognostic value of p53 in small cell lung cancer. In each subgroup of non-small cell lung cancer, p53 abnormal status was shown to be associated with a poorer survival prognosis.

## Expression of Vascular Endothelial Growth Factor (VEGF) in Non-small Cell Lung Cancer (NSCLC): Association with p53 Gene Mutation and Prognosis.

Niklinska W, Burzykowski T, Chyczewski L, et al: Expression of Vascular Endothelial Growth Factor (VEGF) in Non-small Cell Lung Cancer (NSCLC): Association with p53 Gene Mutation and Prognosis. *Lung Cancer* 2001;34 Suppl 2:S59-S64. Department of Histology, Medical Academy of Bialystok, Bialystok, Poland.

**V**ascular endothelial growth factor (VEGF) is a multifunctional cytokine that increases microvascular permeability and directly stimulates endothelial cell growth and angiogenesis. Recent evidence suggests that the genetic regulation of angiogenesis is also of crucial importance and that oncogenes and tumor suppressor genes can regulate it. The aim of this study was to determine the prognostic

value of VEGF and its possible association with p53-gene mutation in 89 stage I-IIIa surgically treated NSCLC patients. DNA sequencing of the p53 gene (exons 5-8) showed 40 mutations (45%). Among the 89 NSCLC patients, immunoreactivity for VEGF was weakly, moderately and strongly positive in 35 (39%), 36 (40%) and 18 (20%) cases, respectively. A strong, statistically significant association was found between the presence of a p53 gene mutation and expression of VEGF ( $P < 0.001$ ). The positive result of the p53 mutation increased the odds of observing a higher level of VEGF expression approximately 9.5 times (95% confidence interval: [3.44, 25.89]). In the univariate analysis of survival, increasing levels of VEGF expression were associated with poor prognosis ( $P < 0.001$  for trend). In the multivariate analysis, after adjusting for the presence of a p53-gene mutation, gender, TNM stage and histological type, the prognostic effect of VEGF expression level was marginally non-significant ( $P = 0.077$ ). When the two-category quantification of the VEGF level was considered (low vs. intermediate/high), a marginally significant ( $P = 0.024$ ), unfavorable effect of intermediate/high levels of VEGF expression, independent of the effect of the presence of a p53-gene mutation, was found. In conclusion, we found that the p53 mutation was closely related to VEGF expression. Additionally, we observed that an intermediate/high expression of VEGF might be a useful indicator of prognosis in NSCLC. This latter conjecture, suggested by an analysis of the data, ought however, to be independently verified in further studies.

“The positive result of the p53 mutation increased the odds of observing a higher level of VEGF expression approximately 9.5 times (95% confidence interval: [3.44, 25.89]).”

## Prognostic Molecular Markers in Non-small Cell Lung Cancer.

Niklinski J, Niklinska W, Laudanski J, et al: Prognostic Molecular Markers in Non-small Cell Lung Cancer. *Lung Cancer* 2001;34 Suppl 2:S53-S58. Department of Thoracic Surgery, Medical Academy of Bialystok, Bialystok, Poland

**A**lthough TNM stage is the most significant prognostic parameter in lung cancer, additional parameters are required for explaining variability of survival. Hence molecular alterations in lung cancer have been extensively studied. Most prominent among them are alterations in the p53-p21 pathway, controlling the G(1)/S transition. They are the most commonly observed aberrations in non-small cell lung cancer (NSCLC). The results of p53 mutations on an individual patient's changes for survival are rather controversial. In a recent study however, after analyzing p53 abnormalities both by direct sequencing and immunohistochemistry together with evaluation of bcl-2 protein expression, we have found that p53 alterations were significantly associated with poor overall survival. Recently, a more sensitive yeast functional assay for altered p53 protein has been developed, with about 70% positivity in NSCLC patients and a correlation with shortened survival. The clinical significance of p21(waf1), the protein encoded by the target gene of p53 transcription, is still controversial; however expression has been associated with favorable prognosis in squamous cell carcinoma type. The 'Rb pathway' involving two oncogenes (cyclins D and E) and two tumor suppressor genes (Rb and p16) represents another major source of molecular alterations in lung cancer. Loss of Rb does not seem to significantly influence prognosis, while loss of p16 has been shown repeatedly to be a factor for poor survival. Hypermethylation of the promoter region has been proposed as an alternative mechanism for inactivation of the p16 gene. The relation between cyclin D and E expression and prognosis, still is matter of controversy. Ras mutations are reported especially in adenocarcinoma; considered alone they bear no clear relation with prognosis, in opposition when considering them together with other molecular alterations. As a conclusion, a variety of

molecular markers have been implicated in the prognosis of NSCLC. However, conflicting results were reported in the literature. Thus further investigations will be required, especially the use of newer molecular assays and the development of appropriate markers or panels of molecular markers.

### Editorial (TLP) Comment:

These three papers give additional information about p53 mutations associated with lung cancer and related prognosis, and the intriguing relationship with VEGF.

## Proposed Biological Staging for Lung Cancer. A Biological Staging Model for Operable Non-small Cell Lung Cancer.

Cox G, Jones JL, Andi A: et al: A Biological Staging Model for Operable Non-small Cell Lung Cancer. *Thorax* 2001;56:561-566. Department of Medical Oncology, Leicester Royal Infirmary, Leicester LE1 5WW, UK.

**B**ackground: Currently the best prognostic index for operable non-small cell lung cancer (NSCLC) is the TNM staging system. Molecular biology holds the promise of predicting outcome for the individual patient and identifying novel therapeutic targets. Angiogenesis, matrix metalloproteinases (MMP)-2 and -9, and the erb/HER type I tyrosine kinase receptors are all implicated in the pathogenesis of NSCLC.

**Methods:** A retrospective analysis of 167 patients with resected stage I-IIIa NSCLC and >60 days postoperative survival with a minimum follow up of 2 years was undertaken. Immunohistochemical analysis was performed on paraffin embedded sections for the microvessel marker CD34, MMP-2 and MMP-9, EGFR, and c-erbB-2 to evaluate the relationships between and impact on survival of these molecular markers.

**Results:** Tumour cell MMP-9 [HR 1.91 (1.23-2.97)], a high microvessel count [HR 1.97 (1.28-3.03)], and stage [stage II HR 1.44 (0.87-2.40), stage IIIa HR 2.21 (1.31-3.74)] were independent prognostic factors. Patients with a high microvessel count and tumour cell MMP-9 expression had a worse outcome than cases with

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“Angiogenesis, EGFR, and MMP-9 expression provide prognostic information independent of TNM stage, allowing a more accurate outcome prediction for the individual patient.”

only one [HR 1.68 (1.04-2.73)] or neither [HR 4.43 (2.29-8.57)] of these markers. EGFR expression correlated with tumour cell MMP-9 expression ( $p < 0.001$ ). Immunoreactivity for both of these factors within the same tumour was associated with a poor prognosis [HR 2.22 (1.45-3.41)].

**Conclusion:** Angiogenesis, EGFR, and MMP-9 expression provide prognostic information independent of TNM stage, allowing a more accurate outcome prediction for the individual patient. The development of novel anti-angiogenic agents, EGFR targeted therapies, and MMP inhibitors suggests that target specific adjuvant treatments may become a therapeutic option in patients with resected NSCLC.

#### **Editorial (TLP) Comment:**

Angiogenesis inhibitors represent a new, therapeutic target in lung cancer staging and management. Further developments are expected, as intense research is ongoing in this area.

## **Angiogenesis Inhibitors in the Staging and Treatment of Lung Cancer.**

Shepherd FA: Angiogenesis Inhibitors in the Treatment of Lung Cancer. *Lung Cancer* 2001;34 Suppl 3:81-89. Division of Medical Oncology, Department of Medicine, Princess Margaret Hospital, 610 University Avenue, 5-104, University of Toronto, Ont., M5G 2M9, Toronto, Canada

**N**umerous inhibitors of angiogenesis are currently under study in lung cancer. Four trials of adjuvant interferon after chemotherapy for small cell lung cancer (SCLC) were negative. Several metalloproteinase inhibitors (MMPi's) are now in study in SCLC and non-small cell lung cancer (NSCLC). Two large randomized trials have closed recently in which Marimastat 10 mg bid was compared to placebo in responding patients with SCLC. Two randomized studies of Prinomastat versus placebo with combination chemotherapy in advanced NSCLC have also completed accrual. The results of these trials are not yet available, but should be reported in mid-2001. A Phase III trial of BMS-275291, a broad-spectrum MMPi in

combination with paclitaxel and carboplatin is open for patients with advanced NSCLC. Neovastat, a standardized shark cartilage extract is under study in inoperable Stage III NSCLC. VEGF gene expression is increased in many tumors including NSCLC, and may act as a paracrine mediator of growth. A randomized Phase II trial of paclitaxel and carboplatin with or without a recombinant humanized anti-VEGF has been undertaken in NSCLC. Modestly better response and survival were seen with anti-VEGF and a large Phase III trial is planned. Numerous receptor tyrosine kinases (TK) have been found to be directly or indirectly involved in angiogenesis including Flk-1, Flt-1, Tie-1 and Tie-2. SU5416 is a small molecular TK inhibitor and potent inhibitor of VEGF-mediated Flk-1 receptor signaling. Another TK inhibitor SU6668 blocks VEGF, bFGF and PDGF receptor signaling. It is orally available, and it may be evaluated in lung cancer trials in the near future. ZD4190 is an inhibitor of KDR/Flk-1 that may be evaluated in SCLC. Thalidomide has recently been shown in pre-clinical models to be anti-angiogenic. A randomized trial of paclitaxel/carboplatin and radiation with or without thalidomide is open for patients with Stage IIIB NSCLC in the United States. Numerous other anti-angiogenesis agents are in early clinical trials, but have not been evaluated in lung cancer yet.

## **Featured Thoracic Surgery Studies:**

### **Investigating Extrathoracic Metastatic Disease in Patients with Apparently Operable Lung Cancer**

The Canadian Lung Oncology Group: *Ann Thorac Surg* 2001;71:425-434. Dalhousie University, Halifax, Nova Scotia; Laval University, Quebec City, Quebec; University of Ottawa, Ottawa, Ontario; University of Toronto, Toronto, Ontario; McMaster University, Hamilton, Ontario; The University of Western Ontario, London, Ontario; and the University of British Columbia, Vancouver, British Columbia, Canada.

**B**ackground: The optimal approach to the investigation of possible distant metastases in patients with apparently operable non-small cell lung cancer who do not

“Numerous inhibitors of angiogenesis are currently under study in lung cancer.”

“Background: The optimal approach to the investigation of possible distant metastases in patients with apparently operable non-small cell lung cancer who do not have symptoms suggesting metastatic disease is controversial.”

“Full investigation for metastatic disease in patients with non-small cell lung cancer without symptoms or signs of metastatic disease may reduce the number of thoracotomies without cure.”

have symptoms suggesting metastatic disease is controversial.

**Methods:** We conducted a randomized, controlled trial in thoracic surgery services at mainly academic tertiary- and secondary-care general hospitals. We recruited 634 patients with apparently operable, suspected or proven non-small cell carcinoma of the lung without findings on history, physical examination, laboratory testing, or imaging suggesting extrathoracic metastases. Patients were randomly allocated to receive either mediastinoscopy and computed tomography of the chest and then, depending on the results, immediate thoracotomy or bone scintigraphy and computed tomographic scanning of the head, liver, and adrenal glands.

**Results:** The relative risk of thoracotomy without cure (the combination of open and closed thoracotomy, incomplete resection, and thoracotomy with subsequent recurrence) in the full investigation group versus the limited investigation group was 0.80 (95% confidence interval [CI], 0.56 to 1.13;  $p=0.20$ ). Forty-three patients in the full investigation group and 61 patients in the limited investigation group underwent a thoracotomy but subsequently had recurrence (relative risk, 0.70; 95% CI, 0.47 to 1.03;  $p=0.07$ ). Patients in the full investigation group were more likely to have avoided thoracotomy because of extrathoracic metastatic disease than those in the limited investigation group (22 patients versus 10 patients, respectively; relative risk, 2.19; 95% CI, 1.04 to 4.59;  $p$  value = 0.04). The total number of negative invasive tests was six in the full investigation group and one in the limited investigation group (relative risk, 6.1; 95% CI, 0.72 to 51.0;  $p=0.10$ ) and the total number of invasive tests, 11 versus six, respectively (relative risk, 1.84; 95% CI, 0.68 to 4.98;  $p=0.23$ ). The full investigation strategy cost \$823 less per patient (95% CI's 2,482 to -725).

**Conclusions:** Full investigation for metastatic disease in patients with non-small cell lung cancer without symptoms or signs of metastatic disease may reduce the number of thoracotomies without cure. The higher the threshold for considering symptoms to suggest metastatic disease, the more likely it is that investigation will spare patients futile thoracotomy.

#### Editorial (TLP) Comment:

Although this study was not conclusive, a trend toward fewer thoracotomies was evident when a full metastatic evaluation was done, compared with CT and mediastinoscopy alone. The Study was probably underpowered to prove that a more extensive evaluation is cost effective.

## Postoperative Fluorescence Bronchoscopic Surveillance in Non-small Cell Lung Cancer Patients.

Weigel TL, Kosco PJ, Dacic S, et al: Postoperative Fluorescence Bronchoscopic Surveillance in Non-small Cell Lung Cancer Patients. *Ann Thorac Surg* 2001;71:967-970. Thoracic Surgery Service, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA. [weigelt@mskcc.org](mailto:weigelt@mskcc.org)

**Background:** Second lung primaries occur at a rate of 1% to 3% per patient-year after complete resections for non-small cell lung carcinoma (NSCLC). Fluorescence bronchoscopy appears to be a sensitive tool for surveillance of the tracheobronchial tree for early neoplasias.

**Methods:** Patients who were disease-free after complete resection of a NSCLC were entered into a fluorescence bronchoscopy surveillance program. All suspicious lesions were biopsied along with two areas of normal mucosa to serve as negative controls.

**Results:** A total of 73 fluorescence bronchoscopies were performed after conventional bronchoscopy in 51 patients at a median of 13 months postresection. The majority (46 of 51) of patients had stage I or II NSCLC, whereas 10% (5 of 51) had stage IIIA. Three intraepithelial neoplasias and one invasive carcinoma were identified in 3 of 51 patients (6%), all current or former smokers. Of the four lesions identified, three were in the 20 patients with prior squamous cell carcinomas. No intraepithelial neoplasias were identified by white-light bronchoscopy, whereas two of three were detected by fluorescence examination. The one invasive cancer detected was apparent on both white-light and fluorescence bronchoscopic examinations

**Conclusions:** Surveillance with fluorescence

“Fluorescence bronchoscopy appears to be a sensitive tool for surveillance of the tracheobronchial tree for early neoplasias.”

“Surveillance with fluorescence bronchoscopy identified lesions in 6% of postoperative NSCLC patients thought to be disease-free.”

bronchoscopy identified lesions in 6% of postoperative NSCLC patients thought to be disease-free. Patients with prior squamous cell carcinomas appear to be a population that may warrant future prospective study of postoperative fluorescence bronchoscopic surveillance.

“...the risk of secondary or tertiary cancers remains high for months or years following treatment of the original lung cancer.”

## Editorial (TLP) Comment:

This important study employs the latest bronchoscopic technology, light intensified fluorescent endoscopy (LIFE), to look for recurrent lesions. Although sputum cytology will also be helpful in identifying recurrent lesions, the tumor must be localized for staging and possible further surgery and/or radiation therapy. In the Grand Junction, Colorado study<sup>1,2</sup> 12 recurrent or metachronic cancers occurred between 9 and 111 months following initial surgery (n=29) or radiation therapy (n=16) for cure. Nine of these patients had positive for sputum cytology, which was the only indication for further diagnostic studies by bronchoscopy and imaging. Thus, the risk of secondary or tertiary cancers remains high for months or years following treatment of the original lung cancer.

1 Bechtel JJ, Kelley WR, Petty TL, Patz DS, Saccomanno G. Outcome of 51 patients with roentgenographically occult lung cancer detected by sputum cytologic testing: A community hospital program. *Arch Intern Med* 1994;154:975-980.

2 Bechtel JJ, Petty TL, Saccomanno G. Five year survival and later outcome of patients with x-ray occult lung cancer detected by sputum cytology. *Lung Cancer* 2000;30:1-7.

“These cancers were found by sputum cytology or imaging. It may well be that sputum cytology will emerge as the most cost efficient method of post treatment surveillance.”

## Regular Follow-up After Curative Resection of Nonsmall Cell Cancer: A Real Benefit for Patients?

Egermann U, Jaeggi K, Habicht JM, Perruchoud AP, Dalquen P, Soler M. *ERS Journals Ltd.* 2002. ©*Eur Respir J* 2002;19:464-468.

**A**bstract: Even though complete resection is regarded as the only curative treatment for nonsmall cell lung cancer (NSCLC), >50% of resected patients die from a recurrence or a second primary tumour of the lung within 5 yrs. It remains unclear, whether follow-up in these patients is cost-effective and whether it can improve the outcome due to early detection of recurrent tumour.

The benefit of regular follow-up in a consecutive series of 563 patients, who had undergone potentially curative resection for NSCLC at the University Hospital, was analysed. The follow-up consisted of clinical visits and chest radiography according to a standard protocol for up to 10 yrs. Survival rates were estimated using the Kaplan-Meier analysis method and the cost-effectiveness of the follow-up programme was assessed.

A total of 23 patients (6.4% of the group with lobectomy) underwent further operation with curative intent for a second pulmonary malignancy. The regular follow-up over a 10-yr period provided the chance for a second curative treatment to 3.8% of all patients.

The calculated costs per life-yr gained were 90,000 Swiss Francs. The cost-effectiveness of the follow-up protocol was far above those of comparable large-scale surveillance programmes. Based on these data, the intensity and duration of the follow-up was reduced.

**Editorial (TLP) Comment:** It is well known that subsequent, ie recurrent or methchronous, cancers commonly occur following an apparently successful resection for early stage lung cancer. In the Grand Junction Study, we reported on 12 new cancers in the followup following attempts at cure by surgery (n=27) or radiation therapy (n=19). Bechtel, et al. *Lung Cancer* 2000, 30: 1-7. These cancers were found by sputum cytology or imaging. It may well be that sputum cytology will

emerge as the most cost efficient method of post treatment surveillance.

## Earley Results of a Prospective Study of Limited Resection for Bronchioloalveolar Adenocarcinoma of the Lung.

Yamato Y, Tsuchida M, Watanabe T, et al: Early Results of a Prospective Study of Limited Resection for Bronchioloalveolar Adenocarcinoma of the Lung. *Ann Thorac Surg* 2001;71:971-974. Department of Thoracic and Cardiovascular Surgery, Niigata University School of Medicine, Japan. [yamato@med.niigata-u.ac.jp](mailto:yamato@med.niigata-u.ac.jp)

**B**ackground: We reported that bronchioloalveolar adenocarcinoma (BAC) without active fibroblastic proliferation of the lung had no lymph node and pulmonary metastasis and had a favorable prognosis. However, there has been no prospective trial regarding limited pulmonary resection for this type of BAC. The purpose of this study is to confirm the effectiveness of limited resection for histologically confirmed BAC without active fibroblastic proliferation.

**Methods:** From 1996 through 1999, 42 patients who had small peripheral lung tumors (<or= 20 mm), suspected of being BAC, were enrolled in this trial. The patient population consisted of 24 men and 18 women with a mean age of 58.4 years. Limited resection was completed when BAC, without both active fibroblastic proliferation and lymph node metastasis, was confirmed histologically by intraoperative pathologic examination.

**Results:** Limited resection was completed in 36 patients, wedge resection in 34, and segmentectomy in 2 patients. In 6 patients, the procedure was converted into lobectomy because of pathologic invasive sign in 3, active fibroblastic proliferation in 1, and for other reasons in 2 patients. All patients have been followed for a median follow-up period of 30 months and are alive without sign of recurrence.

**Conclusions:** Our early results indicate that limited resection may be an acceptable alternative

to lobectomy for histologically confirmed BAC without active fibroblastic proliferation.

### Editorial (TLP) Comments:

Many small nodules may be observed to grow on low radiation dose helical CT surveillance studies. Among these suspicious shadows will be bronchoalveolar carcinomas, possibly beginning with a pre-malignant stage known as atypical adenomatous hyperplasia (AAH). The authors of this article proposed six subtypes in bronchoalveolar carcinoma. The best survival (100%) five-year survival in small lesions without fibroblastic proliferation. Those with fibroblastic proliferation have a less favorable prognosis (75% at five years). Limited resection was planned in 36 of 42 patients enrolled in this study. Six were changed to lobectomy at time of surgery on the basis of intraoperative examination. All 30 patients with a limited resection are currently alive after a median follow-up period of 30 months. The authors concluded that a limited resection may be an acceptable alternative to lobectomy in small peripheral adenocarcinomas that did not reveal any active fibroblastic proliferation.

## Myeloperoxidase -463 (G→A) Polymorphism Associated with Lower Risk of Lung Cancer.

Kantarci OH, Lesnick TG, Yang P, et al: Myeloperoxidase -463 (G→A) Polymorphism Associated with Lower Risk of Lung Cancer. *Mayo Clin Proc* 2002;77:17-22. Department of Neurology, Mayo Clinic, Rochester, Minn 55905, USA.

**O**bjective: To study the association of the myeloperoxidase (MPO) -463 (G→A) polymorphism with lung cancer risk.

**Patients and Methods:** We performed a paired case-control analysis of 307 patients with primary lung cancer and an equal number of age-, sex-, and ethnicity-matched controls to evaluate the effect of the MPO -463 (G→A) polymorphism on disease susceptibility. We also performed conditional logistic regression analyses to evaluate the effect of the polymorphism adjusted for smoking status and chronic obstructive pulmonary disease, 2 established risk factors. We used 2 models for

“...bronchioloalveolar adenocarcinoma (BAC) without active fibroblastic proliferation of the lung had no lymph node and pulmonary metastasis and had a favorable prognosis.”

“We performed a paired case-control analysis of 307 patients with primary lung cancer and an equal number of age-, sex-, and ethnicity-matched controls to evaluate the effect of the MPO -463...”

“The AA genotype was inversely associated with susceptibility to lung cancer (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.15-1.00).”

these analyses: one to compare homozygous (AA) genotypes with wild type (GG) and heterozygous (GA) genotypes and one to compare carriers (heterozygotes and AA homozygotes) with GG genotypes. Finally, we combined the results from the published studies of this putative association and performed a stratified analysis.

**Results:** The AA genotype was inversely associated with susceptibility to lung cancer (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.15-1.00). There was no association in heterozygotes. However, in the stratified analysis, we found an association between patients with the AA (OR, 0.44; 95% CI, 0.27-0.68) and GA (OR, 0.77; 95% CI, 0.64-0.93) genotypes vs the GG genotype.

**Conclusion:** Our results are consistent with previous reports and show that homozygotes of the less common A allele of MPO -463 polymorphism have a 2.6-fold lower risk of lung cancer.

#### Editorial (TLP) Comments:

The AA genotype may have been protective by decreasing the expression of myeloperoxidase which generates hypochlorous acid and other reactive oxygen intermediates that damage DNA.

## Lung Cancer Risk in a Population-based Cohort of Patients Hospitalized for Asthma in Sweden

Boffetta P, Ye W, Boman G, et al: Lung Cancer Risk in a Population-based Cohort of Patients Hospitalized for Asthma in Sweden. *Eur Respir J* 2002;19:127-133.

It has been suggested that asthma increases the risk of lung cancer in males but not in females. However, previous studies may suffer from report bias and are based on a small numbers of cases.

The objective of the present study was to assess the incidence of lung cancer in males and females using a nationwide Swedish cohort of asthma patients.

Patients (n=92,986) aged >20 yrs with a hospital-discharge diagnosis of asthma and who were alive and free from malignancy 1 yr after first hospitalization were followed-up, for incidence of lung cancer during the period 1965-

1994 (average duration of follow-up, 8.5 yrs). Their incidence of lung cancer was compared with that of the national population.

The authors observed 713 lung cancers (standardized incidence ratio (SIR) 1.58, 95% confidence interval (CI) 1.47-1.70). The SIR was 1.51 in males (95% CI 1.38-1.65, 492 cases) and 1.78 in females (95% CI 1.55-2.03, 221 cases). The SIR decreased with duration of follow-up and increased with calendar period and age at first hospitalization. The risk of lung cancer was higher for squamous cell and small cell carcinoma than for adenocarcinoma, and it was higher in patients with other diseases as the main diagnosis and in patients hospitalized in departments other than internal and respiratory medicine.

It was confirmed that asthma patients are at increased risk of lung cancer, but there is no heterogeneity in risk between the sexes. Several indirect arguments point towards a noncausal explanation of these findings; in particular, confounding by tobacco smoking is a plausible explanation.

#### Editorial (TLP) Comment:

The history of heavy smoking and airflow obstruction indicates a high risk of lung cancer. This is primarily in the context of chronic obstructive pulmonary disease. Asthma is also a chronic obstructive pulmonary disease, but one characterized by reversibility. Is asthma, in the absence of smoking, a risk factor for lung cancer? The answer is not provided by this study. Since asthmatics generally smoke much less than those without asthma, one could conclude that asthma, without smoking, is a risk factor. Perhaps the mechanism is chronic inflammation. Looking for lung cancer in non-smokers will probably not be an efficient endeavor.

“It was confirmed that asthma patients are at increased risk of lung cancer, but there is no heterogeneity in risk between the sexes.”

## Lung Cancer—Time to Move on From Chemotherapy

Carney, MD: Lung Cancer—Time to Move On From Chemotherapy; *N Engl J Med*; 2002;346:126-128.

### Editorial (TLP) Comment:

This editorial accompanies two reports indicating very modest improvements in the survival in both small cell lung cancer and non-small lung cancer by new chemotherapeutic strategies. The editorial concludes that chemotherapy just isn't beginning to solve the problem of advanced, inoperable lung cancer. The argument is made that new therapeutic approaches are needed. These should include prevention, screening and early detection, and novel treatments based upon our understanding of the molecular biology of lung cancer. The editorial goes on to predict that chemoprevention in patients at risk, attack upon epidermal growth factors, and inhibition of the growth factor receptor growth by monoclonal antibodies and also against the extracellular domain of the receptor in the tyrosine kinase region of the receptor with new inhibitors may have antitumor activity in advanced non-small cell carcinoma, even in patients in whom previous therapy have failed. Hopefully, new approaches will yield better results.

## Cochrane Review on Screening for Breast Cancer with Mammography

Olsen O, Gotzsche PC.: Cochrane review on screening for breast cancer with mammography. *Lancet* 2001;358:1340-1342.

In 2000, we reported that there is no reliable evidence that screening for breast cancer reduces mortality. As we discuss here, a Cochrane review has now confirmed and strengthened our previous findings. The review also shows that breast-cancer mortality is a misleading outcome measure. Finally, we use data supplemental to those in the Cochrane review to show that screening leads to more aggressive treatment.

“The argument is made that new therapeutic approaches are needed. These should include prevention, screening and early detection, and novel treatments based upon our understanding of the molecular biology of lung cancer.”

### Editorial (TLP) Comments:

This article and the commentary that accompanies it begin to question the value of mammography screening in the early identification of breast cancer. Again, the issue of identifying slow-growing lesions that are clearly harmless is suggested. Tell that to women at risk of breast cancer. If mammography screening does not work, why is it that mortality from breast cancer has been falling, paralleling the increased use of mammography? Both the *Wall Street Journal* (February 8, 2002) and *Time Magazine* (February 18, 2002 Vol. 159 No. 7) have commented on what is sure to become a growing controversy. Marisa Weiss, an oncologist and founder of *breastcancer.org* is quoted in the *Wall Street Journal* article as saying, “My perspective is that mammography is the only proven screening test for breast cancer. You don't trash what you have until you find something better.” The NCI still maintains that women over 50 should have mammography every 1-2 years.

## Tobacco Trivia

In addition to the historical vignettes that have been cited in some previous issues of *Frontiers*, we are adding a new feature known as “Tobacco Trivia.” The point of this section is to put a face on tobacco and its lethal toxins.

When **Joe DiMaggio** died of lung cancer at age 84, few knew that his son, **Joe DiMaggio, Jr.**, died of emphysema from smoking at age 57. **Babe Ruth** died of lung cancer at age 52. He was a heavy smoker. **Larry Linville**, who played Frank Burns in “Mash” television series, died of lung cancer at age 60. **Michael Landon**, an actor known for his role in “Bonanza,” died of pancreatic carcinoma associated with smoking at age 54. **RJ Reynolds, Sr.**, founder of Reynolds Tobacco Company, was a tobacco chewer and died of pancreatic cancer at age 67. **RJ Reynolds, Jr.** was a cigarette smoker and died of emphysema at 58. **RJ, the III** smoked cigarettes and died of emphysema at age 60. Many of the men featured in Marlboro ads died of lung cancer.

## In Memory of Professor Shigeto Ikeda Pioneer of Flexible Bronchoscopy

**O**n December 25, 2001, the world lost the pioneer of flexible bronchoscopy.

Professor Ikeda was a very gifted individual. Following his training in engineering, he entered medical school and graduated from Keio University School of Medicine in 1952. He then joined the Department of Thoracic surgery of his alma mater. While training under Professor Yasuyuki Kano, he showed a special interest in chest diagnosis through bronchoscopy and bronchography. To overcome the limitations of rigid bronchoscopy in gaining access to the upper lobes and to extend the range of the examination to more peripheral airways, he put together the specifications for a flexible bronchofiberscope in 1964. The first prototype was made by Machida Endoscope Co. Ltd (later taken over by Pentax) and Olympus Optical Co. Ltd. in 1966. He demonstrated the use of the flexible bronchoscope with his impressive motion pictures at the 9th International Congress on diseases of the Chest held in Copenhagen in 1966. An improved version of the bronchoscope was introduced into the United States in 1969. Professor Ikeda presented a prototype flexible fiberoptic bronchoscope to Professors Arthur Olsen and David Sanderson at the Mayo Clinic, Professor Bernard Marsh at Johns Hopkins University and Professor Myron Melamed at the Memorial Sloan-Kettering Cancer Center. Chest physicians worldwide rapidly recognize this landmark development. Within a short few years, the flexible bronchoscope became an indispensable tool in chest diagnosis especially for lung cancer diagnosis. Even if lesions in distal airways cannot be visualized, brush, curette or flexible forceps can obtain material for cytological or histological diagnosis.

Under Dr. Ikeda's leadership, the arts and science of bronchology continue to evolve. A number of ancillary devices have been developed resulting in significant new capabilities for patient management and clinical research. A second milestone was achieved in 1984, with the invention of the CCD-tipped videobronchoscope along with his then younger colleague,



*Professor Shigeto Ikeda*

**“To overcome the limitations of rigid bronchoscopy in gaining access to the upper lobes and to extend the range of the examination to more peripheral airways, he put together the specifications for a flexible broncho-fiberscope in 1964.”**

Dr. Ryosuke Ono. This invention opens up the possibility of digital image processing of endoscopic images and electronic transfer of information in addition to superior image resolution.

In 1962, Professor Ikeda was appointed Chief of the Division of Broncho-esophagology at the then newly established National Cancer Center Hospital in Tokyo. This was the first institute of its kind in Japan, created to meet the rising incidence of cancer including lung cancer. He remained the chief there until his retirement following a stroke. In addition to numerous publications and lectures nationally and internationally, he had personally trained many bronchoscopists worldwide. His atlas of flexible bronchofiberscopy first published in 1974 is a classic. He had also set a standard for video recording, which provides an excellent tool for training bronchoscopists and to share information among colleagues.

Professor Ikeda was tireless in disseminating the arts and science of bronchology worldwide. In 1978, he organized the first meeting of World

Association for Bronchology in Tokyo. He was voted the founding president of the association. He remained the Chair of the Board of Regent of WAB until his death. He inspired the formation of bronchology associations in other countries such as the American and Spanish Associations of Bronchology. Even after losing part of his English language ability with his stroke, he continued to show an interest in on-going development of bronchology. His attendance by wheelchair in the last World Association of Bronchology Meeting in Yokohama two years ago brought encouragement to all who attended the meeting.

In 1979, I had the privilege of studying under Professor Ikeda at the National Cancer Center Hospital. His intimate knowledge of the bronchial anatomy and lung cancer pathology, his dexterity and skill in examining the bronchial tree, the accuracy of his diagnosis, his knowledge of devices as well as his ability to translate new knowledge to industries to produce new generations of bronchoscopic devices were most inspiring. He took great care to instruct his students—even body position and handling of the bronchoscope in an ergonomic fashion. He gently persuaded his students to build a bronchial tree model as a tool to learn the complex branching system and nomenclature which most people outside of Japan had difficulty remembering. Through this experience and the experience gained from observing and doing bronchoscopies in addition to participation in rounds where selective bronchography, pulmonary angiogram and CT scan images of each patient were presented, I and many others were equipped to carry out the type of detailed examination that is required for diagnosis of early lung cancer. His ideas and inventions will continue to stretch our imagination to develop better methods to advance the field of early lung cancer diagnosis and management.

Although we have lost a pioneer, a mentor and a friend, Professor Ikea's motto—"more hope with the bronchoscope" will live on. All of us who have benefited from his work will carry his torch by continuing to push the frontiers of lung cancer management through early diagnosis and treatment. (SL)

**"In 1962, Professor Ikeda was appointed Chief of the Division of Bronchoesophagology at the then newly established National Cancer Center Hospital in Tokyo. This was the first institute of its kind in Japan, created to meet the rising incidence of cancer including lung cancer."**

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