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# Frontiers

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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.”

## John Nakhosteen Early Lung Cancer Symposium

This issue of *Lung Cancer Frontiers* features selected manuscripts from a recent conference conducted in Germany, along with selected abstracts from the peer reviewed literature and some additional editorial comments about early diagnosis of lung cancer. The editors hope you will find this year's final issue of *Lung Cancer Frontiers* both interesting and stimulating.

### Introduction to the John Nakhosteen “Retirement” Symposium.

By: Thomas L. Petty, M.D., Editor

The following manuscripts were selected from a special symposium held in Bochum Germany to commemorate the retirement of the Chief of the Augusta Teaching Hospital Program in Pulmonology. Professor John Nakhosteen has been a leader in pulmonology with special emphasis in bronchology in Europe for many years. It is appropriate to include the brief review of the sentinel contributions of the late Shigeto Ikeda, who introduced the flexible fiberoptic bronchoscopic and taught many around the world in its use. This advance revolutionized the field of bronchoscopy and provided an instrument that would become the standard for localizing and diagnosing lung cancer in early stages. (Also see *Lung Cancer Frontiers* 13, August 2002) The two papers that follow give an update on the RIDTELC Lung Study for the automated diagnosis of the various stages of atypia and early stages of lung cancer using

sputum cytology. The interim results of a large scale feasibility study is reported, along with a discussion of recruitment obstacles. Two additional articles from the Symposium will appear in *Lung Cancer Frontiers* 15. One will be about endobronchial treatment options for early stage lung cancer and a thorough analysis of the epidemiology of lung cancer in Germany with extensive references. I hope that the North American readership of *Lung Cancer Frontiers* will appreciate this opportunity to see what is going on in Germany and elsewhere in Europe in the arena of the early diagnosis and treatment of lung cancer by the publication of selected papers from this symposium. The proceedings will be published in two installments beginning with this issue of *Lung Cancer Frontiers* 14 and concluded in the first issue of *Lung Cancer Frontiers* 15 in 2003.

### Shigeto Ikeda, A Revolutionary in Pulmonary Medicine—in Memoriam

John A. Nakhosteen

**Introduction.** Considering a range of topics that we planned for this symposium with Dr. Barbara Khanavkar in the spring of 2001, we touched on the contributions Shigeto Ikeda made to pulmonary endoscopy. I knew then that Ikeda was very ill and unable to travel long distances. Unfortunately, his health continued to deteriorate, and he died on Christmas day, 2001. To both of us it seemed only fitting that this symposium be dedicated to his memory. In this

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short essay I will discuss some aspects of his education and training, his life-long struggle against disease, his motivation for and development of the flexible bronchoscope, and, as a case in point of his influence on pulmonary specialists world-wide, his impact on my own career.

**Education, Training, Career.** Born on July 1, 1925, Shigeto Ikeda graduated from Keio Medical School, Tokyo, in 1952, where he went on to obtain his M.D. in 1960. After eight years (1954-62) as staff surgeon at the same institution, he continued his training with two years in the Department of Radiology of the National Cancer Center Hospital, Tokyo. He was named Chief of the Division of Bronchoesophagology of that institution in 1964, retaining that position until 1977, when he became Chairman of the Department of Endoscopy, a post he occupied until 1991. He was the moving force behind the establishment of the World Association for Bronchoscopy, founded in 1978, and presided over the first World Congress on Bronchoscopy in Tokyo in the same year. The association holds biennial meetings alternately in Asia, the Americas, and Europe, and the 12th WCB (now fused with the World Association for Bronchoesophagology or WCBE) was held in June, 2002, in Boston, with Dr. John Beamis as president.

**Struggle against disease.** All his adult life, Ikeda was afflicted with severe acute and chronic illness. He contacted acute tuberculous pleurisy in his third year of medical school, while doing volunteer field work after a major earthquake, living in a cold, wet tent. Although streptomycin was available to American troops in Japan, it was unaffordable for the Japanese in 1948, and Ikeda was ill for two years. His treatment included pneumolysis, partial decortication, and resection of four ribs. He was the surgeon's second only patient for thoracoplasty, and after he awakened from general anesthesia on the surgical ward, fellow patients told him that the first, also a young man, had died three hours post-operatively. Later, in the 1980's, he developed diabetes, and, subsequently, thromboembolic disease. He had two cardiac arrests in the 90's; at least once, pulmonary edema, and a number of ischemic cerebral episodes with varying degrees of transient, incomplete paralysis, leading, ultimately, to right-sided spastic hemiplegia. He



*The author with Ikeda at a traditional Japanese ceremony during the 1st World Congress for Bronchoscopy (Tokyo, June, 1978).*

**“The cells of the brush smears were identical to those Saccomano had discovered previously in the patients’ sputum smears. ‘We were both,’ said Ikeda, ‘very happy and excited on that day.’”**

spent his last 10 years in a wheel chair. His gastrointestinal system was exquisitely sensitive, and nervous stress, constant travelling, continual hard work, and the slightest wavering from his strict diet led to regular bouts of vomiting and diarrhea.

In spite of all these health problems, Ikeda never thought of even slowing the pace of his professional work, let alone quitting. It was not uncommon for him to go directly to his hospital office after discharge from his many, brief periods of in-patient care, from which he inevitably discharged himself against his doctors’ advice. He confessed to being a “very difficult patient.” He continued attending national and international congresses, accompanied and supported by his devoted wife, and by his trusted aid and secretary, Mr. Shimizu, until just a few months before his death. “Never give up,” the title of his autobiography,<sup>1</sup> was his motto, and he lived it.

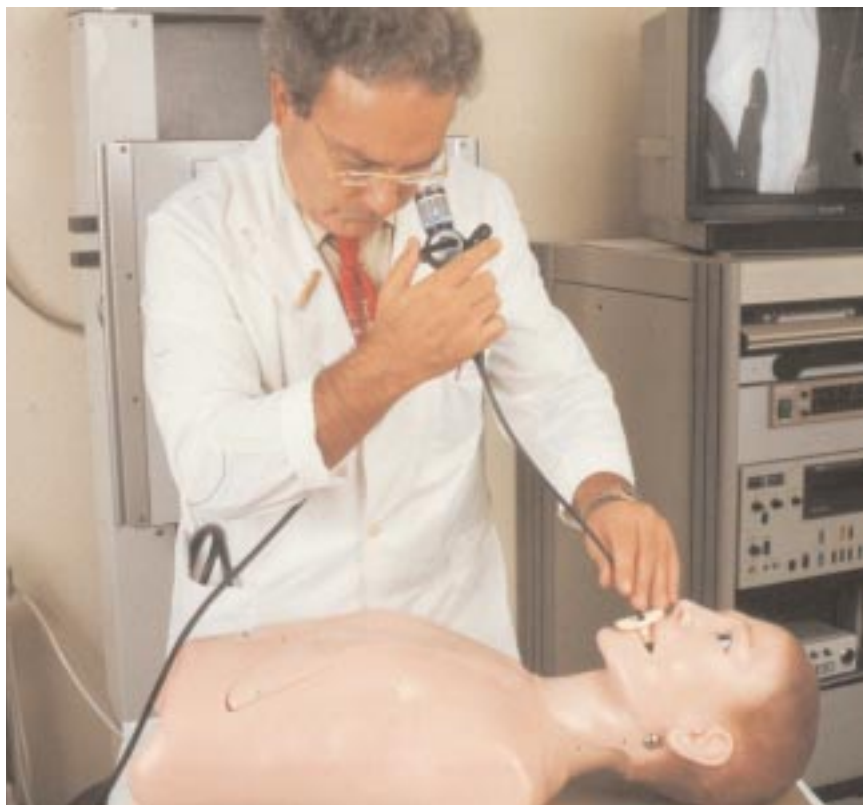
**Ikeda and the fiberoptic bronchoscope.** While still in thoracic surgery Ikeda became interested in the diagnosis of early lung cancer as a means of improving survival from this disease. Realizing the limitations of open tube systems, he conceived the idea of a flexible endoscope in

1964, listing ten specifications, which he presented first to Machida Endoscopes (later Asahi-Pentax) and subsequently to Olympus Optical Company, as guidelines for constructing the first fiberoptic bronchoscopes. The concept was revolutionary and truly a spark of genius.

He worked closely with Mr. Haruhiko Machida of the firm of the same name and they jointly constructed, tested and improved six prototypes, number seven (designated Machida One) was the instrument Ikeda introduced into the West. Essentially, he required a maximal outer shaft diameter of 6mm, maximal diameter of individual glass fibers of 15µ, and a minimum of 15,000 fibers in the objective fiber bundle, with at least 10,000 in the light guide. Today’s instruments have outer diameters from 1.8-7.0mm; fiber diameter has been reduced to the theoretical minimum of 9µ, and fiber bundles contain almost 30,000 individual glass filaments.

The original fiberscopes had a distal angulation of 60°, today (2002) the bend is 180° up and 180° down. And the angle of vision has been increased from 80° to 120°. Finally, while all of today’s bronchoscopes have instrumentation channels, the original ones did not. Hence Ikeda provided the original stimulus, and subsequent modifications and improvements (many under his guidance) have rendered today’s flexible bronchoscopes incomparably better than the original instruments. Ikeda also played a key role in the development of the miniaturized TV camera chip for the videobronchoscope.

During a 4-month stay in the United States in 1972 Ikeda visited Dr. Geno Saccomano, who had been using his fixative for longitudinal sputum cytology studies in uranium miners in Grand Junction, Colorado. Saccomano had followed three cases of severe atypia which had progressed to *Carcinoma-in-situ*, but he had no way of localizing them. Using his flexible scope in topical anesthesia, Ikeda identified and brush-biopsied all three lesions, demonstrating the endoscopic findings to the astounded pathologist. The cells of the brush smears were identical to those Saccomano had discovered previously in the patients’ sputum smears. “We were both,” said Ikeda, “very happy and excited on that day.”<sup>1</sup> Although Ikeda returned to Japan full of enthusiasm for the Saccomano fixative, being a clinician, he was not taken seriously at first, and sputum cytology did not become established in



*The author with Broncho Boy, whose many versions can be used for anesthesiology, rigid and fluorescence scoping, and pediatric endoscopy (Broncho Junior) CLA, Coburg, Germany.*

**“Ikeda introduced the flexible bronchoscope to Europe in 1967, at the International Congress on Diseases of the Chest in Copenhagen.”**

Japan until four years later, in 1976, after Ikeda had convinced a leading Japanese cytopathologist also to visit Saccomano.

In such an eventful life, scientific controversy is almost inevitable. In his autobiography<sup>1</sup> Ikeda makes a point of correcting an “existing inaccurate statement,” viz., that Professor Shohei Horie was the first to conceive the bronchofiberscope—with Mr. Machida’s help—before Ikeda subsequently took over, expanded the concept, and further improved the instrument. Ikeda, citing a number of mostly Japanese publications, takes some pains to set the record straight as to who—namely, Ikeda—is the true “father of flexible bronchoscopy.”

**Personal encounters with Ikeda and his work.** Ikeda introduced the flexible bronchoscope to Europe in 1967, at the International Congress on Diseases of the Chest in Copenhagen. In 1969 he demonstrated the instrument to the Mayo Clinic pulmonary specialists in Rochester, and in 1972

he published the English version of his Atlas of Flexible Bronchoscopy.<sup>2</sup> I first learned of flexible bronchoscopy, and Ikeda, in 1974, but found no possibility of training in the technique in Germany. In renowned pulmonary centers, the procedure was heard of, but, considered “not to have a great future,” and not routinely practiced. I decided to go to Brompton Chest Hospital in London in the summer of 1975 to learn from Drs. Stuart W. Clarke, John Collins, and Richard Stapleton. Subsequently I became very active in promoting the flexible bronchoscope in Germany, with my own bronchoscopy out-patients even while completing my residency in internal medicine, lecturing and publishing diligently, persistently highlighting the merits of flexible as compared to rigid bronchoscopy, thus becoming quite a nuisance to the German pulmonary establishment. I then moved on to do my pulmonary subspecialty at the Ruhrlandklinik in Essen in 1977, under Professor Werner Maassen, with whom I had an occasionally tense, always mutually respectful, and academically productive relationship. Then as now, I consider Maassen one of the greats of German pulmonology and lung surgery.

Several developments came into play while I was completing my subspecialty training under Maassen.

The first was the alarming number of severe, some fatal, bronchospastic complications in patients with obstructive airways disease undergoing bronchoscopy.<sup>3</sup> My interest in asthma therapy led me to the idea that if steroids were administered prior to endoscopy and diluted salbutamol instilled intraluminally, asthmatic reactions could be attenuated, even if not completely avoided. I designed and conducted a small double-blind trial in 24 COPD in-patients and found a significant drop of post-bronchoscopy FEV<sub>1</sub> in the controls and no change in the treatment group. The paper was published in *Respiration*.<sup>4</sup> I submitted an abstract to the First World Congress for Bronchoscopy (1st WCB) in Tokyo, organized and presided over by Ikeda. Before leaving for Tokyo in June, 1978, I asked Maassen whether we should not attempt bringing the 2nd WCB to Germany His response: “I’ll do the president’s job if you take on the secretary general’s,” the answer I had hoped for, and anticipated.

My first meeting with Ikeda was at the 1st

WCB in Tokyo (Fig. 1)—he was a man of rather small, almost diminutive stature, with bright, alert eyes, full of energy and unquestionably on a mission to change the face of pulmonary endoscopy. At the 1st WCB the World Association for Bronchoscopy was founded, and Ikeda named president, by acclamation. During my four days there I was able to convince Ikeda and key members of the newly-constituted Board of Regents of the WAB to agree having the second world congress in Duesseldorf, under Maassen's presidency. The few days in Tokyo were just as strenuous as successful for me; the first night in Hong Kong on my return trip I slept 23 hours in one stretch. The revised proceedings of the 1980 congress were published in book form in 1981.<sup>5</sup>

A parallel development came from my observation that worldwide there was no bronchoscopy teaching model which integrated the airway system with a head and torso. Both Ikeda and Don Zavalla of Iowa had board- or box-mounted tracheobronchial trees, but these were obviously inadequate for learning nasotracheal and orotracheal intubation. I contacted Hans Sommer, owner and CEO of CLA, a firm with a then 100-year family tradition of manufacturing high-quality teaching aids, and suggested jointly developing an integrated trainer. Sommer's enthusiasm equaled mine, and we jointly developed the first Broncho Boy Trainer, the original model (Fig. 2) has been modified many times to meet worldwide market demands. In a notable trend reversal, the Japanese market has proven very lively for the Broncho Boy series. Current prototypes scheduled for production in the last quarter of 2002, include a pediatric trainer (Broncho Junior) and a tracheobronchial tree with mediastinal, hilar, and segmental nodal anatomy.

My final encounter with Ikeda was in June, 2000, at the 11th WCB and WCBE in Yokohama. He had spastic right-sided hemiplegia and incomplete aphasia, but his eyes were as lively and he was mentally as alert as ever. He asked me, as usual, about flexible bronchoscopy in Germany, and I responded that over 90% of routine diagnostic procedures were done in flexible technique but that there were still some die-hards who persisted with open-tube bronchoscopy and general anesthesia. He smiled and said, "Next generation, smarter. Will change."

He died on December 25, 2001.

**Conclusion.** Ikeda was a creative researcher and clinician who will go down in history as the Father of Flexible Bronchoscopy. For me personally he was an inspiration and role model, not just for innovative thinking, but in particular for treading uncharted paths undeterred by a self-satisfied establishment not often limited by envy and scientific myopia. Notwithstanding severe, chronic and recurring health problems, he persevered: "Never give up," he espoused in his autobiography. In the eternal interplay between destiny and the propensity of individuals to effect change, Ikeda exemplified the individual's power to challenge and modify fate.

The interest Ikeda had forty years ago for detection of early, hilar type, squamous cell lung cancer is as important today as it was then, and the clinical researchers presenting their results in this journal show first signs of true progress in unraveling the complexities of lung cancer.

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**“The interest Ikeda had forty years ago for detection of early, hilar type, squamous cell lung cancer is as important today as it was then...”**

## Interim Results from the RIDTELC Lung Study—Feasibility

### I. Study design and results of the radiological entry examinations

Barbara Khanavkar, Augusta-Teaching Hospital, Bochum for the RIDTELC-Study Group\*

**Introduction:** New methods for early detection of lung cancer have emerged during the last 10 years. After a research lag of more than a decade on the subject of early lung cancer publications on low dose spiral CT, autofluorescence (AF) bronchoscopy and sputum cell analysis with the help of genetic or cytochemical markers and image cytometry now are numerous.<sup>1</sup> It seems feasible to identify lung cancer in earlier stages, when the prognosis is still favorable.

Yet, the lung cancer screening dogma of the eighties remains unchallenged by perpetuation of the conclusion that screening does not reduce lung cancer mortality and therefore cannot be recommended as general policy.<sup>2</sup> It remains to be seen if present day technical development in diagnostic and therapeutic procedures can reduce lung cancer mortality.

Seven years ago the Clinic for Pulmonology at the Augusta Teaching Hospital acquired two new technologies with high potentials for early lung cancer diagnosis: the Cytosavant (Oncometrics, Vancouver, BC) for sputum image cytometry (Fig. 1) and the LIFE-Lung-System (Xillix, Vancouver, BC) for the application of AF analysis of bronchial mucosa during flexible bronchoscopy (Fig. 2).

**Hypothesis:** Automated sputum cytology<sup>3</sup> and AF bronchoscopy<sup>4</sup> can result in a stage shift towards earlier stages of the disease, resulting in early treatment and a reduction in lung cancer mortality.

**Study design** (Fig. 3): 5000 individuals with a high risk for lung cancer (aged between 50 and 75, smokers of >30 pack years, active smoking no longer than 10 years ago) will be recruited through public announcements (the local press, television, internet). Another 1000 very high-risk individuals from a radon and asbestos exposed population will be included through a surveillance program of an institution for occupational medicine in East Germany. The

total prevalence of lung cancer in the study population is expected to be around 1-2%.

This study is presently underway and thus incomplete. Thus the plans and results are presented as goals and interim accomplishments. All suitable candidates will first receive a digital chest x-ray. Individuals with x-ray changes suggestive of pulmonary neoplasms will be offered appropriate further investigations, and in case a pulmonary neoplasm is confirmed, suitable therapy, usually resectional surgery. All other candidates as well as those for whose with non-malignant appearing x-ray-changes will have sputum induction will be randomized into a diagnostic (DG) and a control group (CG). Both groups will initially submit induced sputum.

DG-sputa are analyzed immediately (cytology and cytometry), suspicious results (cytology – severe dysplasia or worse, cytometry – grade II or worse) are followed by an AF bronchoscopy (lung cancer prevalence evaluation). If endoscopic localization cannot be achieved sputum induction is repeated 6 months later. Chest x-ray and AF bronchoscopy are offered to individuals with a second suspicious sputum result. Normal second sputa or a second failed localization will lead to regrouping of these individuals with the “normal” fraction in DG.

CG sputa will not be evaluated on entry, but retrospectively with a second sample collected from all participants 3 years later. At that point all individuals are re-x-rayed as well (LC incidence evaluation).

For the time of study duration all candidates (DG and CG) are encouraged to answer a short questionnaire inquiring about their general and respiratory health status at yearly intervals.

At the end of the three year observation period comparison of DG and CG will supply information on the difference of tumor stages diagnosed with the help of sputum analysis (cytometry and cytology) and AF-bronchoscopy. Positive and negative predictive values for cytometry, AF-bronchoscopy and digital chest x-ray will be calculated.

Additionally on entry participants will receive a lung function test<sup>5</sup> (spirometry) and a detailed questionnaire about living conditions and occupational exposures. A relationship between impaired lung function or socioeconomic factors and lung cancer development may be established through the evaluation of these data.<sup>5</sup>

“the lung cancer screening dogma of the eighties remains unchallenged by perpetuation of the conclusion that screening does not reduce lung cancer mortality...”

“Automated sputum cytology and AF bronchoscopy can result in a stage shift towards earlier stages of the disease...”



**Figure 5:**  
Digital chest x-ray – adenocarcinoma



**Figure 6:**  
Final results for radiologically abnormal chest x-rays

**Progress report:  
Results of radiological screening**

| Category        | No. |
|-----------------|-----|
| Lung cancers    | 17  |
| Other diagnoses | 65  |
| Normal CTs      | 51  |
| No diagnosis    | 5   |
| Total           | 138 |

required at least twice, the region of recruitment was limited to a radius of easy traveling. Unfortunately due to logistic problems and lack of financial support other initially interested centers in Germany did not participate. Therefore other regions for recruitment of suitable candidates could not be included.

Since January 2002 the KAS Gentofte Hospital, Copenhagen, however, joined the study and has been entering candidates since.

Age distribution is presented Fig. 4. This reveals an overrepresentation of younger age groups. We were not successful in recruiting older subjects, even though promotion was focused on the older generation.

**c. Compliance.** Approximately 25% of suitable individuals failed the appointment for the entry examination after telephone contact. Dropout from further radiological testing if required during the first year was 4 of 45 (8.9%). Increased effort of the study coordinator subsequently led to a considerable reduction of

non-compliance with follow up of radiological abnormalities, only 3 of 138 (2.2%). Failure to attend an appointment for bronchoscopy, however, could not be lowered beyond 26 of 89 (29%) in spite of considerable contacting efforts with individuals involved and their physicians. The return on interim questionnaires was 70%.

**d. Complications.** No serious side effects from sputum induction or bronchoscopy were encountered up to the present. In the early phase some individuals complained of headaches and dizziness after sputum induction. This led to a modification in operating instructions. Bronchospasm after inhalation with hypertonic saline requiring intravenous medication and a 2 hour observation period occurred once only.

Two of 63 bronchoscopies had to be performed as in-patient procedures with increased sedation and antiinflammatory premedication because of severe cough or laryngospasm. 2 bronchoscopies could not be conducted satisfactorily including white light and autofluorescence inspection.

**e. Radiological screening.** Chest x-ray results are grouped into three categories: no abnormality detected, abnormalities not suggestive of lung cancer (participant's physician informed if appropriate) and changes suggestive of lung cancer. Reading of x-ray films is done by a radiologist not aware of clinical details, all non-normal chest films are reread by the pulmonologist not blinded to the radiologist's report. With lung cancer suspicion participants and their physicians are contacted for either of the following next steps: compare earlier radiological studies, perform further radiological investigations such as a computer tomogram of the chest or initiate bronchoscopy with biopsies and further staging procedures.

Two years from the start of the study in April 2000 2547 candidates were recruited and x-rayed. Changes requiring further investigations were detected in 138 (5.4%) individuals (108 male; 30 female, age 60.9 ± 5.04 years) (Fig. 5).

Comparison with previous chest x-rays in 7 cases confirmed no growth in lesions detected, these were assumed to be benign without further diagnostic tests.

CTs of the chest were reported as normal in a further 51 individuals. Other non malignant conditions were diagnosed in 65 participants by CT, sonography, fluoroscopy or operation (4

“No serious side effects from sputum induction or bronchoscopy were encountered up to the present.”

benign tumors, 15 pleural shadows, residual scarring from previous processes in 29, 2 had active infection, 5 granulomas, 9 miscellaneous changes).

There were 16 NSCLCS (12 adenocarcinomas, 3 squamous cell carcinomas of the following tumor stages: I n=5, II n=4, III n=5, IV n=2) and one small cell cancer (limited disease), a prevalence of 0.67%.

The proportion of individuals with lung cancer in the group subjected to further investigations was 17/138, 12.3 %.

Three (3) of 138 refused further investigations. Results of further diagnostic tests are awaited in two more candidates (Fig. 6).

With the study in progress 3 interim-carcinomas were identified, 2 in DG, 1 in CG. None of the tumors were visible on the entry chest x-ray.

**Conclusions.** Two years into the study 42% of the expected number of participants were recruited. Radiological screening by digital chest x-ray led to fewer further diagnostic procedures for participants than known from historical controls (5.4% vs. 9%), and the proportion of true positives in this group was larger than reported before (12.3% vs. 10.7%).<sup>7</sup>

The majority of tumors diagnosed were of the prognostically favorable stages I and II. The prevalence of lung cancer is comparable to reports on similarly recruited populations and corresponds to the rate expected.<sup>6</sup> The overrepresentation of younger age individuals in this voluntary group has to be taken into account as well as the fact, that the very high risk individuals with radon and asbestos exposure have not been included yet. Occult cancers of CG will also have to be taken into account later.

Recruitment for a study of such magnitude is a crucial factor. Its success by numbers is essential for achievement of study goals. Dynamics of recruitment determine the time frame for which financial means (personnel costs) will have to be calculated. Motivation of patient compliance to a certain extent can be influenced through effort and qualification of the personnel involved. Still a sizable number of voluntary participants even after being informed about initial pathologic investigations are reluctant to enter into more invasive investigations such as bronchoscopy. This will have to be considered in the planning of larger screening trials.

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“The majority of tumors diagnosed were of the prognostically favorable stages I and II.”

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## RIDTELC Lung Study, Interim Results

### II. Sputum-Screening

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**Introduction.** Sputum cytology is a non-invasive screening method for early lung cancer.<sup>1,2</sup> Aerosolized hypertonic saline can be used safely for supervised sputum induction.<sup>3,4,5</sup> The RIDTELC Lung Study was initiated to test the efficiency of a RIDTELC research tool, semi-automated image cytometry (ASC) for the screening of lung cancer parallel to conventional cytology in heavy smokers with normal chest x-rays.<sup>6</sup>

**Methods.** Following lung function testing all eligible volunteers (see Interim Results Part I) had a sputum induction with hypertonic saline (3%) and 2.5mg salbutamol for 20 minutes as previously described.<sup>7,8</sup> After cyto-spinning the sample the cell pellet was resuspended in 0.5 to 2.5ml Saccomanno solution, depending on the pellet weight. Air-dried slides of two drops each of the suspension were stained for cytology (Papanicolaou) and by a modified Feulgen's reaction with thionin for ASC.

Cytology classification of results followed a modified Papanicolaou scheme (Table 1). For all candidates with a sputum classification of Pap IIIDs and worse an autofluorescence bronchoscopy was recommended.

Quantitative cytometry was performed with a semi-automated image-cytometer (Cyto-Savant, Oncometrics).<sup>9,10</sup> Data collection was achieved using a dedicated software for exfoliative cells from the respiratory tract including a diffraction correction. Adjustment of the original program was made according to the recommendations of ESACP (Task Force on Standardization of Diagnostic Image Cytometry) and Haroske et al.<sup>11,12</sup> Up to 2000 nuclei were collected and saved (of 1000 epithelial cells, up to 200 cells with a DNA-index between 1.25 and 2.5, another 100 with a DNA-index of more than 2.5, additionally 200 of each lymphocytes, granulocytes and 100 alveolar macrophages). (*DNA-index 1.0 corresponds to the DNA content of normal diploid (2c) epithelial nuclei*).

Three parameters were calculated based on the DNA content of epithelial cells: the rate of cells with more than 5c (5cER), the 2c deviation index (2cDI) and a malignancy grade (multiplication of 2cDI and 5cER with logarithmic transformation).

Cytometry classification of results had three subgroups (Table 2).

“Three parameters were calculated based on the DNA content of epithelial cells: the rate of cells with more than 5c (5cER), the 2c deviation index (2cDI) and a malignancy grade (multiplication of 2cDI and 5cER with logarithmic transformation).”

Table I

#### Modified Papanicolaou-Classification

| PAP            | Description                          |
|----------------|--------------------------------------|
| 0              | Inadequate                           |
| I              | Normal cells                         |
| II             | Inflammation, mild, moderate, severe |
| III            | Unclear result, cellular metaplasia  |
| IIID, mild     | Mild dysplasia                       |
| IIID, moderate | Moderate dysplasia                   |
| IIID, severe   | Severe dysplasia                     |
| IV             | <i>Carcinoma in situ</i>             |
| V              | Invasive cancer                      |

Table II

#### Classification of ASC

| Grade | Description  |
|-------|--|
| 0     | Inadequate   |
| I     | Normal or benign, MG<0.1   |
| II    | Suspicious, MG>0.1 or MG<0.1 but with suspicious nuclei in cell gallery. |

**Results**

**1. Patients.** 2443 volunteers were recruited between May 2000 and April 2002 and randomized into a diagnostic (n=1257) and a control group (n=1186). Sputum from all participants was processed immediately, but cytological and cytometrical evaluation was performed for the diagnostic group sputa only. Control group sputa were saved for retrospective analysis three years later. 71% of participants were male, the average age was 59 yrs. Female participants were 2 years younger, 57 yrs. Male smokers had a cumulative cigarette burden of 61.7 ± 25.9 pack years, significantly more so than female smokers with 50.7 ± 20.5 pack years (p<0.0005). Lung function parameters showed a significant deviation from predicted values of EC (Table 3).

**2. Sputum induction.** 1192 participants in the diagnostic group produced sufficient sputum for analysis on site. Sputum vials were taken home by those who failed and within 3 to 4 days another 65 submitted a satisfactory sample. Volume of sputum samples and cell counts did not differ significantly between jet- or ultrasonic nebulizer method as well as spontaneous collection.

**3. ASC.** 1158 of 1257 evaluable sputa were classified as grade I (92%), 87 as grade II (6.9%). There were 12 insufficient samples (grade 0, 0.9%).

**4. Cytology and overlap.** There were 8 highly pathological samples: 2 PAP IIID, severe, 3 PAP IV and 3 invasive tumors, PAP V (0.6%), 20 samples were not evaluable cytologically (1.6%). The overlap between cytology and ASC was 6, 2 samples were abnormal in cytology and not cytometry, 81 with abnormal ASC were cytologically without high grade lesions.

**5. Bronchoscopy.** Eighty-nine (89) participants were invited for further evaluation, only 65 (59 with grade II ASC, 2 with abnormal cytology and 4 with both) agreed to an autofluorescence bronchoscopy (73%). Endoscopic findings were 4 clinically relevant lesions: 2 stage II squamous cell carcinomas, 1 CIS and 1 PAP IIID, severe. All lesions were detected in white light as well as with autofluorescence. 5 months post bronchoscopy a peripheral stage III adeno carcinoma was diagnosed radiologically.

**Table III**

**Anthropometrical Data from Participants of RIDTELC-Lung-Study**

|                               |          | Males       | Females     |
|-------------------------------|----------|-------------|-------------|
| Number                        |          | 1802 (71%)  | 741 (29%)   |
| Age (Years)                   | MW ± Std | 59.7 ± 6.1  | 57.8 ± 5.3  |
|                               | Median   | 59          | 57          |
| Packyears                     | MW ± Std | 61.7 ± 25.9 | 50.7 ± 20.5 |
|                               | Median   | 56          | 46          |
| FEV <sub>1</sub> (%pred)      | MW ± Std | 90.4 ± 21.2 | 93.6 ± 20.4 |
|                               | Median   | 92.5        | 94.5        |
| FVC (%pred)                   | MW ± Std | 92.5 ± 16.6 | 99.3 ± 16.6 |
|                               | Median   | 92.8        | 99.4        |
| FEV <sub>1</sub> %FVC (%pred) | MW ± Std | 90.4 ± 21.2 | 93.6 ± 20.4 |
|                               | Median   | 98.4        | 100         |
| MEF <sub>50</sub> (%pred)     | MW ± Std | 50 ± 25     | 52.55 ± 25  |
|                               | Median   | 52          | 57          |

All lesions occurred in ASC positive cases, one was abnormal in cytology as well. “low grade” lesions (metaplasias, mild and moderate dysplasias) were found in a further 21 volunteers.

**Summary and Conclusions.** Eighty-nine (89) of 1257 sputum samples submitted by the diagnostic group were classified as abnormal, 81 by ASC, 2 by cytology and 6 by both methods (7.1%).

Among those 65 investigated by bronchoscopy 5 “high grade” lesions (7.6 %) were found and another 31 “low grade” lesions in 21 participants. The 4 endoscopically evident lesions were white light and autofluorescence positive. 3 radiologically occult tumors were detected and treated (0.24%) as well as one severe dysplasia.

Not including occult tumors in the control group the total number of bronchial carcinomas in the population recruited was 21, a prevalence of 0.8%. 16 tumors were ASC grade II, for 81 grade II sputa no clinically significant lesion could be found. This adds up to a sensitivity of 73% and a specificity of 93% for ASC. Further development of tumors (incidence study) in both groups will provide information on the predictive power of ASC/cytology for a very high risk group justifying more intensive monitoring.<sup>13,14</sup>

*continued*

“Eighty-nine (89) of 1257 sputum samples submitted by the diagnostic group were classified as abnormal...”

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## Citations from the Literature

### Combined expression of p53, Bcl-2, and p21WAF-1 proteins in lung cancer and premalignant lesions: association with clinical characteristics.

Kalomenidis I, Orphanidou D, Papamichalis G, Vassilakopoulos T, Skorilas A, Rasidakis A, Papastamatiou H, Jordanoglou J, Roussos C. Department of Pulmonary and Critical Care Medicine, Medical School of Athens University, Evangelismos Hospital, Athens, Greece. jkalomenidis@hotmail.com  
Lung 2002;179:265-278

**W**e examined p53, p21WAF-1, and Bcl-2 protein expression in malignant and nonmalignant bronchial specimens obtained during bronchoscopy from 60 lung cancer patients. Twenty-six (43.3%), 36 (60%), and 20 (33.3%) of the tumors were p53, p21WAF-1, and Bcl-2 positive, respectively. High-level p53 and Bcl-2 expression characterized advanced preneoplastic lesions, while hyperplasias, squamous metaplasias, and mild dysplasias exhibited low levels of expression. There was no difference between early and advanced preneoplastic lesions in the level of p21WAF-1, expression. A history of heavy smoking was associated with p21WAF-1, expression in preneoplastic lesions ( $p=0.022$ ) and tumors ( $p=0.032$ ). p53(-)/p21WAF-1(++)/bcl-2(-) was the only significant independent predictor of lower clinical stage (OR: 0.88,  $p=0.038$ ). In univariate analysis, survival of NSCLC patients was affected by disease stage ( $p<0.001$ ) and tumor histology ( $p=0.018$ ). While single-protein expression was not associated with prognosis, the combined immunophenotype p53(-)/p21WAF-1(++)/bcl-2(-) predicted longer survival ( $p=0.03$ ). In multivariate analysis, only the TNM stage was found to be a prognostic factor for NSCLC. We conclude that p53 and Bcl-2 alterations may happen early in bronchial carcinogenesis and that absence of these alterations in combination with p21WAF-1, overexpression may be associated with a less aggressive tumor behavior.

**Editorial (TLP) Comment.** This is one of many clinical studies which seeks to identify molecular

markers of various stages of lung cancer. The present study adds some evidence that molecular markers may be predictive of tumor biology and aggressiveness and may supplement the TNM stage for prognostic purposes.

### Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis.

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Mayo Clinic Proc 2002;77:763-770

**O**bjective. To identify distinguishing characteristics between patients with idiopathic pulmonary fibrosis (IPF) and primary lung carcinoma and patients with either IPF or carcinoma alone.

**Patients and Methods.** The study group consisted of 24 patients with histologically proven usual interstitial pneumonia and lung carcinoma identified through a search of the Rochester Mayo Clinic database for 1990 to 1998. Medical records, radiographs, and histological slides were reviewed. Several variables including survival were compared in 2 control groups, IPF only and carcinoma only, by using various statistical methods.

**Results.** Our study group included 21 men and 3 women (mean age, 72.3 years). Twenty-two were past or current smokers. Approximately half of the lung carcinomas were incidental findings. Of the 14 patients with preoperative computed tomographic scans, 12 had peripheral tumors situated in areas of fibrosis. Squamous cell carcinoma was the most common histological type, accounting for 16 cases. Almost all patients underwent surgical treatment; nearly 40% developed postoperative complications, and 3 died within 30 days of surgery. The ratio of men to women in patients with IPF and carcinoma was 7:1 compared with 1:1 in patients with IPF only ( $P=0.003$ ). Patients with IPF and carcinoma were also older, with a mean age of 72.3 years compared with 64.4 years ( $P=0.001$ ), and were more often smokers ( $P=0.002$ ). Carcinomas involved the lower lobes in 42% of patients with

“Mean survival in patients with IPF and lung carcinoma was 2.3 years after the diagnosis of IPF and 1.6 years after that of carcinoma.”

IPF and carcinoma compared with 29% of patients with carcinoma only ( $P=.004$ ) and were mainly composed of squamous cell carcinoma ( $P=.004$ ). Mean survival in patients with IPF and lung carcinoma was 2.3 years after the diagnosis of IPF and 1.6 years after that of carcinoma. This finding did not differ significantly from survival of patients with either IPF or carcinoma alone. However, statistical power was limited.

**Conclusion.** Carcinoma in patients with IPF arises in older male smokers and usually presents as peripheral squamous cell carcinoma. The prognosis is poor

**Editorial (TLP) Comment.** It is well known that lung cancer is far more common in patients with airflow obstruction than with normal airflow with all other risk factors being equal. Another family of pulmonary diseases, i.e., idiopathic pulmonary fibrosis, is also associated with an increased prevalence of lung cancer. Interestingly, cancers are often peripheral squamous cell carcinomas with poor prognosis. In the presence of airflow obstruction, adenocarcinoma is most common and squamous carcinoma usually has a central location and with a better prognosis.

The widespread use of spirometry will identify patients not only with airflow obstruction but with restriction; thus the spirometric abnormalities should alert the clinician to a high risk of lung cancer.

## Anti-angiogenic strategies and vascular targeting in the treatment of lung cancer

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*Eur Respir J.* 2002;14:557-570

**T**he generation of new blood vessels, angiogenesis, is important for tumour proliferation and metastasis. This involves a number of interacting processes and factors, such as growth factors and the receptor tyrosine kinases, matrix metalloproteinases and integrins. Studies have shown that tumour vascularity and the overexpression of growth factors and their receptors are of independent prognostic importance in different cancers, including lung cancer. The present article provides a background to angiogenesis and describes the potential targets for anti-angiogenic and vascular targeting strategies in cancer, focusing specifically on carcinoma of the lung. It also describes the anti-angiogenic drugs presently under phase I, II and III investigation and highlights some of the problems associated with the standard methodologies for assessing tumour response and drug efficacy using these agents.

**Editorial (TLP) Comment.** This important article highlights the growing interest in vascular targeting strategies in the management of cancer in various stages. A great amount of basic and clinical science is currently focusing on this topic.

## Editorial Comments by: Thomas L. Petty, M.D.

**T**hree items in the July issue of *Chest* focus once again on the controversies concerning lung cancer screening.

**Improved survival and higher mortality: the conundrum of lung cancer screening.** (*Chest* 2002;122:329-337), the author continues the seemingly endless dissertation that is confusing to me. I believe this is a smoke screen. For example, “... if an increase in longevity resulting from intervention in some individuals was offset by delayed decrease in longevity in others, survival

“...I have never seen a pseudo lung cancer. It’s either cancer or it isn’t.”

would improve and mortality would remain unchanged. Survival and mortality are not complementary measures.” Here is where I am having trouble. If one has a disease and survives it for however many years—say five or ten—and does not die of the disease or any other disease, then the patient must have lived, which to me is the flip side of died. The author goes on to criticize population screening on the basis of false positive findings resulting in anxiety and complications. Terms like “pseudo disease” and “nonaggressive lung cancer” permeate the discussion. The problem that I have with these mystical terms is that I have never seen a pseudo lung cancer. It’s either cancer or it isn’t. In addition, I have never seen a nonaggressive lung cancer in nearly 40 years of practice, but perhaps one may exist.

Two accompanying editorials in the same issue (Chest 2002;122:1-2;ibid 3) draw different conclusions—the first favoring lung cancer screening and the other (predictably) cautioning against it. Still another article concludes that CT screening is suitable for routine health examinations and is quite sensitive in finding early stage lung cancer. The most appropriate re-screening interval remains to be determined (Chest 2002;122:15-20).

As readers of *Lung Cancer Frontiers* must know by now, I have taken a simplistic view to so-called screening.

I have likened the results of screening to the successful fisherman who knows where the fish are and catches many compared with his colleague who fishes in a barren pond and catches nothing.<sup>1</sup> I have made the point several times that lung cancer is highly prevalent in smokers with airflow obstruction. The airflow obstruction as judged by simple spirometry, of course, may be mild, moderate or severe. Approximately five percent of heavy smokers over the age of 45 with airflow obstruction have or will soon develop clinically overt lung cancer if offered sputum cytology and CT scanning. In the Grand Junction study, the actual survival beyond five years was more than 50% with no lung cancer deaths after 8 years, meaning the cancer or cancers found years before including metachronous cancers, were cured.<sup>2,3</sup> Although none of the cured patients were questioned about their quality of life, many lived beyond 10 years, suggesting an opportunity to pursue life’s

pleasant and rewarding experiences. Those who die of lung cancer are denied this privilege.

Consider the following hypothetical scenario. You have 200 heavy smokers with airflow obstruction in a room and you are lecturing to them about smoking cessation. You get an idea. After gaining their attention, you simply say, “Ten of you (5%) have lung cancer right now. Would you rather find it now or find it later?” Then you go on to say that if you find it now (based upon the Grand Junction study), more than half (50%) of you will live beyond five years and many for more than ten years. If you don’t find it now and wait for symptoms, only 1-2 (15%) of you will live five years. What is your choice?

Thus, I continue to believe that we should look for lung cancer in the high-risk patients. These are smokers with airflow obstruction and those with an occupational risk or strong family history risk. Many will have only mild airflow obstruction and can lead normal lives following surgical resection. Those with greater age or comorbidity or unfavorable tumor location can be candidates for alternative therapies, such as attempts at curative radiation therapy, brachytherapy, photodynamic therapy or other forms of intrabronchial therapy.

My view is that it is time to end the diatribe of “should we screen or not.” Screen where the fish are. If we follow this simple plan, we will find, treat and cure lung cancer in individual patients. They will live, as an alternative to dying, which seems to be the objective of most patients and their physicians.

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“Approximately five percent of heavy smokers over the age of 45 with airflow obstruction have or will soon develop clinically overt lung cancer if offered sputum cytology and CT scanning.”

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