17 Number

The Forum for Early Diagnosis and Treatment of Lung Cancer

October 2003

Lung Cancer 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."

Highlights of the 10th International Congress on Lung Cancer Vancouver, British Columbia August 10-14, 2003

Following a most cordial introduction by Conference Chairman Nevin Murray MD (British Columbia Cancer Agency) on behalf of the International Association for the Study of Lung Cancer (IASLC), a large audience, representing most of the 3200 participants enjoyed an impressive opening ceremony. Delegates from 77 countries attended. In addition to the over 140 invited speakers participating in Meet the Professor sessions, plenary sessions, interactive sessions and poster sessions, 307 presentations were selected from 1159 abstracts submitted; 600 posters, and 14 satellite symposia. The attendance greatly exceeded the 2000 attendees from 64 countries at the 9th International Congress held in Tokyo in 2000. The first international conference was held in Copenhagen 30 years ago with only a few hundred in attendance.

Dr. Murray's welcome was followed by a welcoming address by President H. Kato (Figure 1), Tokyo Medical College. (Dr. Kato has been an esteemed member of the editorial board of Lung Cancer Frontiers since its inception.) Dr. Kato introduced Founding Executive Director Heine H. Hansen of Copenhagen (Figure 2) and announced that he will turn over the reins of executive management to Dr. Paul Bunn, Denver,

Figure 1 President H. Kato

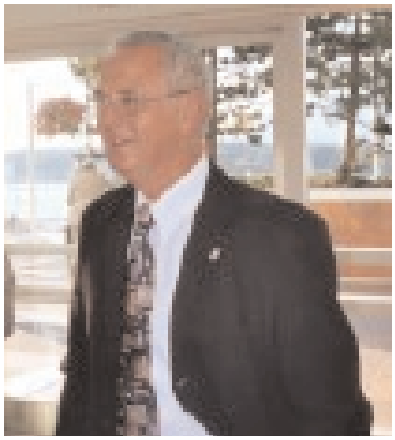

Figure 2 Founding Executive Director Heine H. Hansen

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Colorado at the end of this session.

Dr. Hansen will remain editor of Lung Cancer. Dr. Hansen reviewed the brief history of IASLC covering 31 years. The journal Lung Cancer was launched in 1985 and has grown rapidly from less than 100 pages per year in the first volume to over 1400 pages in the year 2003.

Paul Bunn received the Fifth IASLC Merit Award since its inception in 1991. Adi Gazdar, Dallas, Texas received the Mary Williams Award for Excellence in Lung Cancer Pathology. The first of these awards was given Geno Saccomanno in Colorado Springs in 1994. President-elect Frances A. Shepherd (Toronto) (Figure 3) gave a moving tribute to the late Robert J. Ginsburg who was praised for his many contributions to IASLC. All were saddened by his recent death in 2003 from lung cancer.

Figure 3 President-elect Frances A. Shepherd

"...both EFGR receptor inhibitors and anti-angiogenesis drugs offer new therapeutic targets."

Selected Highlights

Amongst the 14 satellite sessions that drew huge audiences was "Novel HER1/EGFR – Targeted Agents for NSCLC: Current State of the Art." This session was opened by Chairman Guiseppe Giaccone of the Netherlands and co-chaired by Dr. Frances Shepard.

Ulrich Gatzemeier, Hamburg, Germany, reviewed the HER1/EGFR: Regulating Several Functions to Determine Cell Proliferation in Survival. This receptor occurs frequently in lung cancer and leads to a poor prognosis and resistance to chemotherapy.

A new HER1/EGFR tyrosine kinase inhibitor, erlotinib (TARCEVA) and just-released gefitinib (Iressa) are effective in late phase trials. The key is the challenge to learn which patients are likely to benefit. Although dramatic individual responses and remissions were observed with this class of drugs in both Phase II and Phase III studies, overall survival in these controlled clinical trials along with chemotherapy in a large number of patients has not shown statistically significant differences. Erlotinib is effective in a 150 mg daily dosing in some patients. Drug accumulation does not occur on daily dosing. Like gefitinib, It seems to have a particular role in non-smoking bronchoalveolar cell carcinoma and works much better in never-smokers than smokers. Many current studies are combining HER1/EGFR receptor inhibitors given in earlier stages of disease or in combination with platinum-based chemotherapy.

It appears that cutaneous reactions indicate drug activity with erlotinib. Patients with moderate to severe cutaneous reactions have a

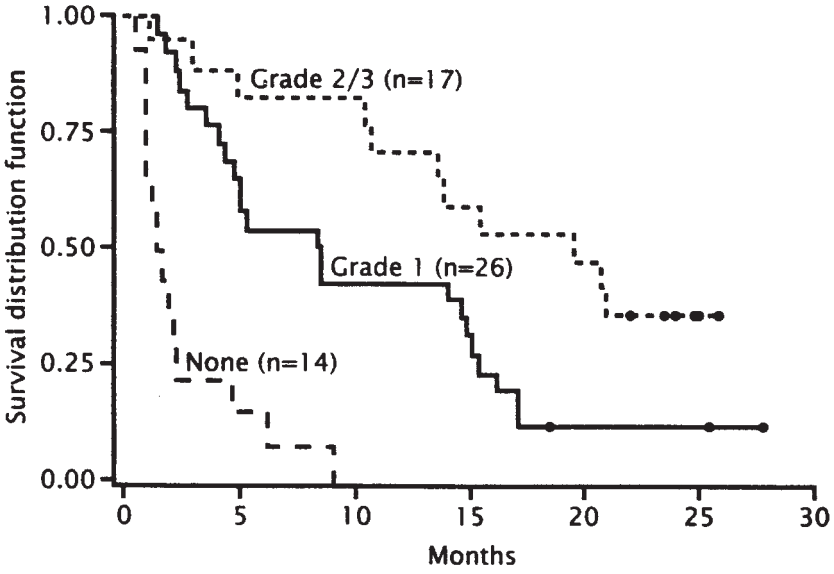

Figure 4 Survival of patients by grade of rash

"The illusion of a safer cigarette is nothing more than that."

far better survival, than those with only mild reactions and much better than those with no cutaneous manifestations of drug effects. (Figure 4)

Certainly both EGFR receptor inhibitors and anti-angiogenesis drugs offer new therapeutic targets. A new strategy, possibly using these drugs in combination will produce interesting results.

Editorial Comment (TLP):
My own view is that these drugs are a valuable new approach to advanced stage lung cancer, but may have their greatest benefit as adjutants to surgery or other therapy in early stage resectable lung cancers, Stages 1A and 1B.

Plenary Session

The first plenary session following the first day's satellite sessions appropriately focused on "The Tobacco Pandemic: Challenges for the 21st Century." This session was introduced by Chairman Nevin Murray and Co-Chairman Paul Bunn.

The failure of global tobacco policy and the production of low tar and nicotine cigarettes has not been successful and has resulted in products with toxicities equal to unfiltered tar cigarettes. David Burns (San Diego) pointed out that the pattern of smoking has shifted when filters have been used to smoking more cigarettes rapidly and deeply and creating holes in the filters to admit more air. All of this creates the illusion of light or ultra light tobacco products. Filtering and reduction in tar have been replaced by increased production of nitrosamines, which has more carcinogenics and tend to produce adenocarcinomas. The illusion of a safer cigarette is nothing more than that. Neal Benowitz (San Francisco) reviewed the pharmacological basis of nicotine addiction, which began in 1884 with the mass production of automated cigarette rolling machines. Details of nicotine dependence and the genetic, as well as ethnic basis, predicting addiction in some individuals was stressed. Nicotine use transiently augments the release of pleasurable neurotransmitters used to reduce irritability, depression and improve cognitive functions.

"Strategies in Cessation" was discussed by Ellen Gritz (Houston). The increasing array of nicotine replacement products, ranging from gum, lozenge, patch, spray, and inhaler to the anti-depressant bupropion used alone or together can greatly enhance the rate of biologically-proven smoking cessation, which is at least twice as great as with advice or behavior modification alone.

Editorial Comment (TLP):
Although significant progress has been made in the basic understanding of nicotine addiction and the growing number of products to mitigate nicotine withdrawal have been useful, no major breakthroughs have yet to be achieved.

Highlights on Early Detection and Chemoprevention

(Abstracts from Lung Cancer 2003, Supplements 2 & 3)
Evaluation of nodules detected by screening for lung cancer with low dose spiral computed tomography.
David E Midthun, Stephen J Swensen, James R Jett, Thomas E Hartman, Mayo Clinic, Rochester, USA

Screening with low dose fast spiral CT of the chest may be an effective means of detecting lung cancer at an early stage. Screening CT has a high false positive rate and the appropriate evaluation of nodules detected by CT screening is unclear.

Goal: To determine rates of malignancy for nodules of differing size detected by CT screening in high-risk individuals.

Methods: We enrolled 1,520 participants (735 women, 785 men) from January 20, 1999 through December 1, 1999. All participants have completed the prevalence spiral CT, 97% the 1st annual scan, 96% the 2nd annual scan, and 95% the 3rd annual scan.

Results: Single or multiple uncalcified nodules were identified in 782 of 1,520 participants (51%) at baseline. A total of more than 1,646 nodules were identified (32 participants had >6 nodules). The largest nodule identified was <3 mm in 39%, 4–7 mm in 50%, 8–20 mm in 10%, and >21 mm in 1%. Our recommendations were as follows : for nodules <3 mm F/U CT in 6 months and at one year; for nodules 4–7 mm F/U CT in 3 months, 6 months, and at one year for nodules >8 mm thin section CT and CT contrast enhancement, biopsy or resection. To date CT has identified 28 prevalence lung cancers (1.7% of the nodules): 26 NSCLC and 2 limited stage small-cell carcinomas. Based on size at time of detection, likelihood of malignancy was 0.2% for nodules < 3 mm, 0.9% for nodules 4–7 mm; 18.7% for nodules 8–20 mm; and 50% for nodules >20 mm. Other nodules were detected in 75% of the participants found to have lung cancer.

Conclusions: Spiral CT (prevalence) screening has a high rate of nodules detection and over 98% of the nodules so far identified are likely benign. Seven of the 1547 nodules detected <7 mm at initial screening have been found to be malignant; observation of nodules of this size appears appropriate. Complete three-year follow-up data was presented.

Editorial Comment (TLP):
This study concluded, as reported before, that spiral CT (prevalence) screening has a high rate of nodule detection. Over 98% of the nodules identified so far are benign. Only seven nodules detected of less than 7 mm turned out to be malignant. Accordingly, observations of nodules of small size, i.e., less than 7 cm appears to be appropriate (approximately at six months to one year). The ancillary diagnoses made through screening, including other cancers such as renal, abdominal aortic aneurism and other to serious illnesses such as atrial myxoma and pheochromocytoma were collateral benefits of the Mayo study.

"Screening CT has a high false positive rate and the appropriate evaluation of nodules detected by CT screening is unclear."

Screening for lung cancer with low-dose helical CT and sputum cytology: Results of Anti-Lung Cancer Association Project:

Masahiro Kaneko, Toshiaki Kobayashi, Noriyuki Moriyama, et al, National Cancer Center Research Institute, Tokyo Japan

CT, with its high contrast resolution, shows superior capability to demonstrate small and faint lesions in the lung fields even those concealed by anatomic structures such as the mediastinum. The Anti-Lung Cancer Association (ALCA) is a for-profit organization that was established in 1975 to thoroughly screen dues-paying members for lung cancer. From September 1975 to August 1993 (the first time period), 26,338 examinations were performed with chest radiography and sputum cytologic studies. From September 1993 to August 2002 (the second time period), 15,342 examinations were performed with low-dose helical CT along with chest radiography and sputum cytologic

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"15,342 examinations were performed with low-dose helical CT along with chest radiography and sputum cytologic studies."

studies. Forty-three lung cancers were detected in the first time period (0.16%), and 61 lung cancers were detected in the second time period (0.40%). In the first time period, 15 of the 43 tumors were detected with sputum cytology, and 38 of the 43 were detected with chest radiography. In the second time period, 12 of the 61 tumors were detected with sputum cytology, 15 of the 61 were detected with chest radiography, and 55 of 61 were detected with low-dose helical CT; some were detected with two or three modalities, but no cases were detected by chest radiography alone. In the first period, 43% (18 of 43 tumors) were stage 1A, but in the second time period, 85% (52 of 61 tumors) were stage 1A. Introducing helical CT to lung cancer screening, the detection rate especially early stage lung cancer is increased. But there are some problems in performing the CT screening for lung cancer worldwide. The first problem is time-consuming image interpretation, which will be improved by a recently developed computer-aided diagnosis (CAD) system. The second is inappropriate diagnostic accuracy, which should be improved by developing appropriate assessment criteria considering follow-up period in order not to subject patients to unnecessary invasive procedures. The third is insufficient proof of efficacy, which is expected to be shown by several epidemiological and clinical studies which are being carried out by study groups of the Ministry of Health, Labour and Welfare in Japan.

"...no cases were detected by chest radiography alone."

Editorial Comment (TLP):
These new studies on screening for lung cancer with low-dose helical CT and sputum cytology gave evidence that more early stage lung cancer is found with modern CT scanning, than in earlier years of less precise CT scanning where 43% of cancers found were Stage 1A. With improved spiral CT scanning, there is an 80% survival rate at five years, compared with a 50% survival rate during the first five years of the study of a ten-year study.

Lung Cancer Screening with Helical CT: Evidence for a Stage Shift

Melvyn S Tockman, Todd Hazelton, Lynn Coppage, et al, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Objective: Conduct a single arm cohort study of lung cancer screening with helical CT and biomolecular markers. We hypothesize that screening will increase (stage-shift) the percentage of detected Stage 1 lung cancers 3-fold from the current 20% to at least 60%.

Methods: To observe 50 lung cancer cases during an initial screening plus 4 annual re-examinations, the study design sought 1,150 high-risk participants, i.e., age >45 years, current and former smokers of >30 pk-year, with at least mild obstruction on spirometry ($FEV_1/FVC < 70\%$). Sufficient lung cancer cases allowed removal of the obstruction entry requirement after 2/3 of participant accrual. Eligible subjects underwent sputum induction and low-dose helical CT scanning (10 mm image collimation and reconstruction, 2:1 pitch, no IV contrast, 120 kV, 20–85 mA). Abnormal studies were evaluated for lesion growth with follow-up diagnostic CT: lesions between 1–5 mm required repeat diagnostic CT at intervals of 3, 6, 12 and 24 months, lesions 6–10 mm required diagnostic assessment and possible biopsy; nodules > 10 required clinical evaluation. Nodules were evaluated with PET prior to further follow-up (nodule is PET negative) or therapy (nodule is PET positive). Individuals with lung cancer receive appropriate staging and therapy and are taken off study.

Prevalence Results: 1,151 high risk individuals have been enrolled (mean age 60.2; gender, 59% male; mean smoking 57.9 pk-yr; and mean FEV_1/FVC 65.5%). 35% of initial CT examinations were abnormal. Lung cancer was diagnosed in 28 subjects for a prevalence of 2.4%. This high risk population has a prevalence 3-fold greater than the Johns Hopkins Lung Project (JHLP), one of the NCI collaborative trials. Of 28 lung cancers, 24 (86%) were non-small cell. Of these, 14 were

Stage I (58%), 2 Stage II (8.3%), 3 Stage III (12.5%), and 5 Stage IV (20.8%). This stage distribution is similar to the 79 JHLP prevalence cases (58% early stage, 42% advanced stage). The Stage I rate in our CT screening (14/1151, 1.2%) is 3-fold greater than the rate of Stage I in the JHLP (42/10387 0.4%), while the advanced stage rate (8/1151, 0.7%) is 2.2-fold (33/10387 0.32%) greater.

Conclusion: Conclusive stage shift is not yet demonstrated.

Editorial Comment (TLP):
This study concluded that although more Stage I carcinomas are found with CT screening, there has not been a reduction in Stages III and IV cancers. Accordingly conclusive stage shift is yet to be determined.

An Alternative Approach to Lung Cancer Screening

Annette M McWilliams, John May, Sharyn MacDonald, et al, Vancouver General Hospital, Vancouver, Canada

Aim: Thoracic computed tomography (CT) is a sensitive method for detecting early peripheral lung cancer, but it has a number of limitations including a high false-positive rate and low sensitivity for central lesions. We assessed the role of quantitative image analysis of sputum cells as the first step screening method and the use of combined thoracic CT scan and autofluorescence bronchoscopy as second line investigations in an early lung cancer detection program. We assessed the ability of image analysis of sputum cells to improve the detection of early lung cancer by identifying individuals at highest risk and also present the findings of 12 months of CT followup in subjects with an abnormal CT scan.

Method: Sputum cells, obtained by simultaneous high frequency chest wall oscillation and hypertonic saline induction, were analyzed by automated quantitative image cytometry. Subjects were also offered an autofluorescence bronchoscopy. Spiral thoracic CT was performed in 561 volunteers >50 years of age with a smoking history of >30 pack/years. Subjects with an abnormal CT scan are being followed for 2 years with serial CT scans.

Results: Sputum atypia was found in 70% of subjects and an abnormal baseline CT scan was found in 46% of subjects. Thirteen cancers were detected in subjects with sputum atypia – 9 by CT and 4 carcinoma in-situ/micro-invasive cancers by autofluorescence bronchoscopy. One cancer was diagnosed in a subject with normal sputum at baseline. A total of 592 nodules or non-solid opacities were detected in 259 subjects. During follow-up a further 130 new nodules developed, 426 more nodules were seen in retrospect, 33 nodules increased in size, 33 nodules became smaller, 58 nodules resolved and 74 were seen to be benign. Of the enlarged nodules 2 were diagnosed as cancer, and 3 required resection and were benign.

Conclusion: The use of quantitative image analysis of sputum cells in addition to CT improved the detection rate of lung cancer from 1.8% to 3.1%. One third of cancers would have been missed if CT alone was used. Sputum atypia was seen in 93% of subjects with lung cancer. An abnormal CT scan result is seen in half of subjects screened requiring intensive CT scan followup. Although 14% of all lesions decreased in size or found to be benign over 12 months, more than 500 more nodules were seen. Therefore, sputum analysis has the potential of reducing both the number of initial CT scans required by at least 30% and significant downstream investigations, workload and costs.

Editorial Comment (TLP):
This study concluded that the use of automated quantitative image analysis of cells, in addition to CT, improved the detection rate of lung cancer from 1.8% to 3.1%. One-third of the cancers would have been missed if CT alone was used. Sputum atypia was seen in 93% of the subjects with lung cancer and abnormal CT scan results were seen in half of the subjects requiring intensive CT scan follow-up. It was interesting that 14% of the lesions decreased in size and were found to be benign over 12 months for more than 500 nodules seen. This study concludes that sputum analysis is a

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"Thirteen cancers were detected in subjects with sputum atypia –9 by CT and 4 carcinoma *in-situ*/micro-invasive cancers by autofluorescence bronchoscopy."

"One third of cancers would have been missed if CT alone was used."

potential for reducing both the number of initial CT scans required by at least 30% and in reducing physician workload.

High-Prevalence of Endobronchial Malignancy in High-Risk Patients Who Have Moderate Dysplasia in Sputum

Timothy C Kennedy, Wilbur A Franklin, Robert L Keith, et al, University of Colorado Health Science Center, Denver

Hypothesis: Moderate dysplasia in sputum is an important indicator of occult central airway lung cancer in high risk subjects, defined by 30 or more pack years of tobacco smoking and airflow obstruction.

Study Population: Current or former heavy smokers at least 30 pack-years of cigarette use with airflow obstruction defined by $FEV_1/FVC <$ 70% predicted and FEV_1 ratio of less than 70% (N=83), with moderate dysplasia in sputum cytology who had no evidence of malignancy on chest radiograph, at the time bronchoscopy was scheduled.

Results: Lung cancer was found by combined white-light and fluorescence bronchoscopy in six of 83 (7.2%, 95% CI=1.6%–12.8%) consecutive high-risk patients. In two of these six, the biopsy showed carcinoma *in situ*, while four were invasive. In addition, seven patients (8.4%, 95%CI=2.2%-14.2%) has severe dysplasia found at fluorescence bronchoscopy. over all 13 of 83 (15.6%, 95% CI=7.9%–23.5%) of the patients had malignancy or severe pre-neoplastic changes at bronchoscopy. Moderate dysplasia in sputum appears to be an important marker of risk for occult endobronchial malignancy in high risk subjects.

Conclusion: A significant fraction of patients with moderate dysplasia found by sputum cytology evaluation had radiologically occult endobronchial cancer discovered on combined white-light and fluorescence bronchoscopy.

"Moderate dysplasia in sputum appears to be an important marker of risk for occult endobronchial malignancy in high risk subjects."

"We have been developing a quantitative sputum test based on a fully automated, high resolution image cytometer."

Editorial Comment (TLP):
A significant fraction of patients with moderate dysplasia had occult endobronchial lung cancer and, accordingly, are candidates for both white-light and fluorescent endoscopy.

The Role of Automated Quantitative Cytology Sputum Test in the Early Detection of Lung Cancer

Roger Kemp, Bojana Turic, Jayson Eppler, et al, British Columbia Cancer Agency, Perceptronix Medical Inc., Vancouver, Canada

The last two decades are marked with exponential growth of the knowledge and utilization of image analysis. There is a high expectation that these advances will be translated into further improvement in the care of cancer patients, especially in the areas of prevention and diagnosis. We have been developing a quantitative sputum test based on a fully automated, high resolution image cytometer. The test involves measurements of several thousand cell nuclei per sputum sample stained with a DNA specific and stoichiometric stain. The digital images of the nuclei are captured at the limit of optical (spatial and photometric) resolution with the cytometer and over one hundred nuclear features are then calculated from each nucleus. In a large field study a total of 1220 sputum samples were collected and 293 patients were subsequently confirmed by histopathology diagnoses of lung cancers (nearly half of which were from state 0 and stage I lung cancers) and 927 from matching (high risk) subjects with no known malignancy. The results of the quantitative sputum test (sensitivity and specificity) as analyzed by Automated Quantitative Sputum (AQC) Cytology were then compared to those derived by conventional cytology. In addition, buccal mucosa samples were taken simultaneously from about one third of the subjects to further test the hypothesis that buccal cells, too, could be used to assess the probability of the presence/absence of lung cancer. The results of the AQC test from sputum cells as well as from the buccal cells show a

several fold increase of sensitivity (35%–60% depending on the lung cancer stage and type versus 5–25% by conventional cytology) at a moderately reduced specificity (90% versus 98%, for AQC and conventional cytology, respectively). The role of the AQC cytology test in a comprehensive approach to detection of early (non-invasive and minimally invasive) lung cancers will also be discussed.

Editorial Comments (TLP):
The role of AQC in the comprehensive approach to early detection appears to be bright. More prospective studies are needed. AQC could help revolutionize the approach to lung cancer case finding in high risk patients and be practical in broader screening for occult lung cancer.

"AQC could help revolutionize the approach to lung cancer case finding in high risk patients..."

Mulshine, NCI, Bethesda summarized and commented about the early morning presentations, which focused on early identification and intervention. He emphasized the stage distribution shift in the current Mayo studies compared with the National model. (New Mayo study: Stage I, –74%, Stages II and III, –23%, Stage IV, –2%; American Cancer Society Historical Data: Stage I, –17%, Stages II and III, –20%, Stage IV, –48%) It seems highly likely that expanded, systematic case finding in high risk groups will continue to identify more patients with early stages of disease, where a favorable outcome can be expected.

"Angiogenic squamous dysplasia is a unique lesion found in the proximal bronchial epithelium of current and former smokers consisting of capillary blood vessels projecting into metaplastic and dysplastic squamous bronchial epithelium."

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www.lungcancerfrontiers.org

Selected Posters

Robert L. Keith presented an update on his work in angiogenic squamous dysplasia in a poster presentation (Figure 5). Related abstracts proffered in the same session follow.

Figure 5 Robert L. Keith

Angiogenic Squamous Dysplasia (ASD): A Biomarker Highly Associated with Squamous Cell Lung Carcinoma

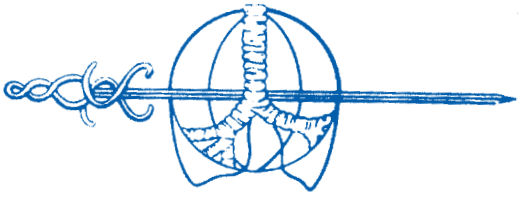
Robert L Keith, York E Miller, Timothy C Kennedy, et al, University of Colorado SPORE in Lung Cancer, Denver, CO

Angiogenic squamous dysplasia is a unique lesion found in the proximal bronchial epithelium of current and former smokers consisting of capillary blood vessels projecting into metaplastic and dysplastic squamous bronchial epithelium. Ongoing clinical trials at the University of Colorado involving fluorescence bronchoscopy have identified a large cohort of

patients with ASD (n=105). ASD is seen almost exclusively in current and former smokers when compared to non-smoker (p=0.006). Patients with ASD on bronchial biopsy (when compared to those without ASD) are more commonly male (p=0.045) and have significantly more severe airflow limitation (based on FEV_1/FVC ratio (p=0.028). Among the current and former smokers with and without ASD, there were no significant differences in age, race or tobacco exposure. In analysis of our entire cohort of 264 subjects undergoing LIFE bronchoscopy, ASD occurred at high frequency in patients with squamous carcinoma at the time of bronchoscopy; was present in 13/18 patients with squamous carcinomas, in only 1/10 patients with non-squamous carcinoma and in 91 of 236 patients with no lung cancer at the time of bronchoscopy (Chi-test p=0.003). We conclude that ASD occurs frequently in the central bronchi of high risk smokers, is important evidence of neovascularization of the bronchial tissue before and in association with invasive lung cancer. ASD may be an important target for chemoprevention of squamous cell lung cancer.

"The angiogenic activity was associated with increased VEGF RNA expression..."

"...a trend toward higher VEGF expression was seen in dysplastic lesions with histologic features of angiogenesis (angiogenic squamous dysplasias)..."



Angiogenic activity in bronchial dysplasia and invasive lung cancer: Features of vascular endothelia growth factor (VEGF) express

Daniel T Merrick, Jerry Haney, Michio Sugita, et al, Denver Veterans Affairs Medical Center, University of Colorado Health Sciences Center, Denver, US

Quantitative RT-PCR (qRT-PCR) and microvessel densities (MVDs) were employed to study alterations in VEGF expression in preneoplastic and invasive lung lesions and relate these changes to evidence of angiogenic activity. Elevated MVDs were found in dysplastic and invasive lesions as compared to normal tissue. The angiogenic activity was associated with increased VEGF RNA expression demonstrated in qRT-PCR analyses to dysplastic bronchial epithelium (6.00 x 107 copies/mcg) and invasive lung cancer (5.79 x 108 copies/mcg) as compared to normal bronchial tissue (2.57 x 107 copies/mcg). In contrast, the reactive lesion, basal cell hyperplasia, did not demonstrate VEGF overexpression (2.06 x 107 copies/mcg). ELISA VEGF protein analysis in lung carcinomas revealed a strong correlation between VEGF RNA and protein levels ($r2 = .45$; $p < .001$) validating qRT-PCR as a measure of VEGF expression. VEGF levels were not different between low and high-grade dysplasias. However, a trend toward higher VEGF expression was seen in dysplastic lesions with histologic features of angiogenesis (angiogenic squamous dysplasias) as compared to dysplasias without these features (7.9 x 107 copies/mcg vs. 5.16 x 107 copies/mcg). Interestingly, VEGF levels showed statistically significant increases in normal bronchial epithelium from patients with dysplasia elsewhere in their airways (3.12 x 107 copies/mcg) versus normal epithelium from patients without associated dysplasias (1.11 x 107 copies/mcg), and in patients with 50 pack-year histories (1.06 x 107 copies/mcg) suggesting a field effect in regard to VEGF expression. A qualitative analysis of VEGF isoform expression revealed increased normal parenchymal tissue, but showed significant

expression of only VEGF121 in a limited number of normal and dysplastic bronchial biopsy specimens analyzed. Preliminary studies using conditioned media from lung cancer derived cultures showed a two-fold increase in endothelial cell proliferation as compared to endothelial cells grown in basal media. This increased proliferation was equivalent to that seen in endothelial cells grown in media supplemented with 1 ng/ml of recombinant VEGF165. Future studies using conditioned media from dysplasia and carcinoma derived cultures will be aimed at demonstrating VEGF specific proliferative effects and evaluating the efficacy of inhibitory compounds in blocking VEGF mediated activities.

Detection and Follow-Up of Premalignant Bronchial Lesions Using Laser-Induced Fluorescence Endoscopy (LIFE) in Patients at High Risk for Lung Cancer

M Patricia Rivera, Robbert J C Slebos, William K Funkhouser, et al, The Multidisciplinary Thoracic Oncology Program, University of North Carolina at Chapel Hill, Chapel Hill, USA, National Institutes of Environmental Health Sciences, NIH Research Triangle Park, USA

Lung cancer remains a disease without effective screening. The strongest risk factors for lung cancer are tobacco exposure, family history of lung cancer and previous history of lung or head and neck (H&N) cancer. Although LIFE bronchoscopy has been shown to be a sensitive method for detection or premalignant bronchial lesions, the natural history of such lesions is not well known. We conducted a prospective study in high-risk patients using LIFE bronchoscopy as a screening tool for premalignant lesions. At baseline, all patients had a chest radiograph, spirometry and bronchoscopy. Biopsies were taken from four pre-determined sites and from any abnormal areas. Serial bronchoscopies followed if any premalignant lesion(s) were detected at baseline. If carcinoma *in situ* (CIS) or cancer was found, a chest computed tomograph (CT) scan was obtained and treatment initiated.

Results: To date, 36 subjects have been enrolled: 33 males, median age 61, mean FEV_1 percent-predicted 65%; 20 with prior lung cancer (3/20 also had H&N cancer), 1 H&N cancer only, and 15 heavy smokers without prior cancer. 8/36 had a family history of lung cancer. Of 183 biopsies collected to date, 122 were collected at baseline bronchoscopies (see table). The patient found to have squamous cell carcinoma at baseline was treated with surgery. The patient with CIS at baseline had a corresponding mass on CT, which was dysplasia and one with severe dysplasia at baseline progressed to CIS. Despite laser therapy, CIS persisted in 1 patient and progressed to invasive carcinoma in the other. Both subjects have since been treated with photodynamic therapy with excellent results. Of the 7 subjects found to have dysplasia, CIS, or cancer, 5 had a prior history of cancer and 3 had a family history of lung cancer.

Conclusion: LIFE identified premalignant or malignant lesions in 7 (19%) high-risk subjects. Prior history of cancer and family history of cancer correlated with abnormal findings on LIFE. Severe dysplasia may progress to CIS. Additional baseline and follow-up data will be presented.

" Preliminary studies using conditioned media from lung cancer derived cultures showed a two-fold increase in endothelial cell proliferation..."

"Of the 7 subjects found to have dysplasia, CIS, or cancer, 5 had a prior history of cancer and 3 had a family history of lung cancer.

Histology at Baseline Bronchoscopy	Histology at Follow-Up Bronchoscopy (N)							
	Normal	Metaplasma	Mild Dysplasia	Severe Dysplasia	CIS[1]	Cancer	Lost to Follow-up	Pending
Normal (N-94)	21	4						69[2]
Metaplasia (N=19)	1	10						8[2]
Mild Dysplasia (N=4)		2			1			1
Severe Dysplasia (N=3)	1				1		1	
CIS (N=1)								
Carcinoma[3] (N=1)								

[1]Carcinoma *in situ*; [2]2-year follow-up bronchoscopy pending

"Advances in the molecular biology of lung cancer and new clinical approaches to early diagnoses and treatment created an ebullient atmosphere."

Perspectives on the 10th International Conference on Lung Cancer Vancouver—August 2003

You could feel the excitement that permeated the plenary sessions, state of the art presentations, and the Meet the Professor session, and smaller venues that gave "proffered papers."

Advances in the molecular biology of lung cancer and new clinical approaches to early diagnoses and treatment created an ebullient atmosphere.

New developments in the chemotherapy of late stage lung cancer impressed both oncologists and pulmonologists, and others of various backgrounds. The session on supportive therapy and an improved quality of life were well attended and appropriately so, because today we are faced with growing numbers of patients with advanced disease with varying impairments and a poor quality of life. It is an exciting fact that advances in chemotherapy are extending life with survival increased by approximately 5%. This equals the chemotherapy advances recently achieved in breast and colon cancer and should be big news, particularly to pulmonologists who have historically been nihilistic about lung cancer chemotherapy for advanced stages of disease.

"It is an exciting fact that advances in chemotherapy are extending life with survival increased by approximately 5%."

The control of chemotherapy-related anemia with erythropoietin received appropriate emphasis, but there was insufficient attention paid to pain control, nutritional aspects and oxygen for the respiratory insufficiency of advanced stages of disease.

"More pulmonologists must become involved in lung cancer and make necessary improvements in all aspects of lung cancer diagnosis and management."

More pulmonologists must become involved in lung cancer and make necessary improvements in all aspects of lung cancer diagnosis and management. More emphasis on early diagnosis and treatment and chemoprevention as an alternative to late stage disease will emerge. Hopefully we will see evidence of this at the 11th IASLC in Barcelona Spain in July 2005.

Additional highlights of the 10th World Conference on Lung Cancer will be carried in *Lung Cancer Frontiers* No. 18.

Highlights of the Battenkill River Lung Conference

A unique conference for pulmonologists, who are also fly-fishing enthusiasts, was held at The Inn at Willow Pond in Manchester, Vermont, co-sponsored by the Vermont Lung Association and the Pulmonary Division of the University of Vermont. Organizers were Gerald S. Davis MD, Albee Budnitz MD, Charles G. Irvin PhD, Polly Parsons MD and Robert C. Uerz MeD (of the Vermont Lung Association).

The conference program included a complete review of COPD: It's Past, Present and Future," as well as "Managing Exacerbations, Pulmonary Rehabilitation, Office Spirometry, Smoking Cessation, an Update on Lung Volume Reduction Surgery, and Cor Pulmonale." A special highlight of the conference was the emphasis on lung cancer, with a review of epidemiology and etiology, and screening strategies for lung cancer. Jim Jett MD (Rochester MN) discussed new techniques including optical coherence tomography and CT PET fusion. Simon Spivac MD (Albany NY) discussed molecular and other biological markers of lung cancer. Richard Matthay MD (New Haven) emphasized that the highest prevalence of lung cancer is today in Eastern Europe. Tom Petty MD (Denver) commented about the success of the Grand Junction Colorado study that is cited in *Lung Cancer Frontiers* No. 16.

Future conferences are planned. The format is very much like the original Pombine conferences with informality and interaction. Consecutive case presentations will be considered in the future. Look for future announcements of Battenkill River Lung Conferences at www.battenkillriverlungconference.org

Gerald S. Davis MD

Richard A. Matthay MD

Citations From the Peer Reviewed Literature

Impact of Limited Pulmonary Function on the Management of Resectable Lung Cancer

Lung Cancer 2003;41:71-79

Aims: Limited pulmonary function (LPF) related to obstructive disease and emphysema or due to significant lung toxicity resulting from chemotherapy regimens are frequent co-morbidity factors in lung cancer patients. Purpose of this study was to investigate the frequency of LPF in lung cancer and its impact on surgical eligibility and postoperative outcome. Materials and methods: We analyzed a series of 255 consecutive patients with otherwise resectable lung cancer, admitted to our department between January 1998 and December 1999. Patients were considered affected by LPF if their forced expiratory volume in one second (FEV_1%) and/or diffusing lung capacity for carbon monoxide (DLCO%) was less than 50% of predicted normal values. Perioperative mortality, major and minor complications were analysed according to lung function status.

Results: A total of 42 (16.5%) patients presented with significant limitations of the pulmonary function (LPF). Of these, 11 (26%) cases were excluded from surgery because of the severity of pulmonary disease. In the higher frequency of preoperative induction therapies (42 vs. 30%) and sublobar resections (33 vs. 8%) in comparison with the other 213 resected cases. However, no difference was observed in median hospital stay (7 days in both groups), major morbidity (13 vs. 11%) or mortality (0 vs. 1.4%). Studies that relate preoperative assessment of lung function to postoperative values were cited (Markos J, Mullan BP, Hillman DR, et al: Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis 1989;139:902-910.

Conclusions: A strict and careful selection of patients, guided by concurrent analysis of

"A total of 42 (16.5%) patients presented with significant limitations of the pulmonary function (LPF)."

different functional tests, allowed to offer surgery with a very low complication rate to the majority of patients with limited pulmonary function. A lung volume reduction effect was evident in selected patients with severe emphysema.

Editorial Comment (TLP):
This study adds to other evidence that even in the face of moderate to severe ventilatory impairment as judged by FEV_1 and FVC, major resections, including pneumonectomy, can be done for localized lung cancer. Pre-operative diffusion tests of great than 60% of predicted and a predicted postoperative FEV_1 or more than 40% of predicted are considered reasonable guidelines. A lung volume reduction affect, particularly in apical disease, may be expected in selected patients. Since most lung cancer is found in the upper lung zones, resection of apical lesions with surrounding emphysema may not sacrifice lung function at all, and could possibly improve it.

Diagnosis of Airflow Limitation Combined With Smoking Cessation Advice Increases Stop-Smoking Rate

Gorecka D, Bednarek M, Nowinski A, et al
Chest 2003;123:1916-1923

"...FEV_1 percent predicted ($p < 0.01$) proved to be significant predictors of success in stopping smoking."

Objectives: To assess how the diagnosis of airflow limitation (AL) combined with advice to stop smoking in middle-aged smokers influence the smoking cessation rate and to identify predictors of successful outcome.

Design: Prospective, single-center, comparative study of the effects of smoking intervention in smokers with diagnosed al and in smokers with normal lung function (NLF).
Setting: University hospital, out-patient clinic.
Participants: Of 659 smokers participating in a population spirometric screening for COPD combined with smoking cessation advice, 558 (AL, 297 smokers; NLF, 261 smokers) were invited for a follow-up after 1 year.
Intervention: At follow-up, spirometry was repeated and smoking status was assessed. Nonsmoking status was validated with carbon monoxide measurements in exhaled air. Patients who did not come for the follow-up visit were considered to be smokers.

Results: Of 558 smokers invited, 368 (66%) presented for the follow-up visit. All had tried to reduce their smoking habit. The number of cigarettes smoked per day (CPD) at 1 year was −5.2 ($p < 0.01$) in patients with AL and −2.7 (not significant (NS) in those with NLF. The 1-year cessation rate in smokers with AL was 10.1% vs 8.4% in smokers with NLF (NS). After stratifying the patients according to AL severity, the highest cessation rate was observed in smokers with moderate and severe AL (16.5%) compared to smokers with mild AL (6.4%; $p < 0.001$) and smokers with NLF 8.4%; $p < 0.05$). In a univariate analysis, the cessation of smoking was correlated with older age ($p < 0.001$), later age when starting smoking ($p < 0.005$), lower tobacco exposure (in pack-years; $p < 0.01$, fewer cpd ($p < 0.001$), and lower lung function ($p < 0.05$). No interaction effect was observed for any of the studied variables using two-way analysis of variance. In a stepwise logistic regression analysis, age ($p < 0.001$), tobacco exposure (in pack-years; $p < 0.001$), and FEV_1 percent predicted ($p < 0.01$) proved to be significant predictors of success in stopping smoking.
Conclusion: All smokers, irrespective of their lung function, tried to modify their habit as the result of screening for COPD combined with smoking cessation advice. The diagnosis of AL motivated smokers to attempt to quit smoking. Older age, lower tobacco exposure, and lower lung function were the predictors of success in quitting smoking.

Editorial Comment (TLP):
This important study offers powerful evidence that spirometric testing combined with advice in smoking cessation can be successful.

It is particularly noteworthy that a much higher smoking cessation rate was observed in smokers with moderate and severe airflow limitation (16.5%) compared with those with mild airflow obstruction (6.4%), $p < 0.001$ in smokers with normal lung function (8.4%) $p < 0.05$. The advice on not smoking resulted in a decrease of cigarette consumption in all

subjects. Some critics of spirometric testing have expressed a concern that knowledge of normal lung function simply encourages the continuation of smoking. The fact that 8.4% smokers **with normal lung function** could quit as proven biologically by exhaled carbon monoxide testing, indicates otherwise. Patients with only mild airflow obstruction who had even less success than smokers with normal lung function in quitting (6.4% vs 8.4%). Focusing on smokers with mild airflow obstruction and learning better methods in smoking cessation may yield the greatest improvement in reducing the risk of lung cancer (see *Lung Cancer Frontiers* No. 16).

Release of Iressa Criticized!

Criticism that the FDA approval of Iressa (Gefitinib), (as announced by the FDA on May 5), was done prematurely and inappropriately, is astonishing. The criticism was voiced by Thomas Fleming PhD, a biostatistician (JAMA 2003;289:3227). Although controlled clinical trials using Iressa with chemotherapy versus chemotherapy alone have thus far failed to show improved survival in large groups of patients, highly impressive anecdotal remissions have been recognized by clinical researchers and practicing clinicians alike during the conduct of these and earlier Phase II clinical trials. Today Iressa is available for use alone, following failure of two chemotherapy trials.

I have had one such patient, a non-smoking woman with diffuse alveolar cell carcinoma occupying all lung fields, with engorged Kerley's B lines and cancer cells seen in every high-powered field, on VATS biopsy. This woman was symptomatic and required oxygen therapy. Now she has experienced a ten-month remission, improved quality of life, and a reduction in oxygen need. Why should any physician or scientist quarrel with such an outcome? It is a fact that there are significant side effects associated with Iressa involving acute interstitial pneumonitis, (particularly reported in Japan but much less common in the United States), but these side effects are relatively rare. Considering the simplicity of using an oral agent, Iressa has more than "something to offer." to persons who have failed two courses of chemotherapy and have no where else to turn. To quarrel with these observations is unconscionable. True, it is difficult to predict who will respond to Iressa and treatment costs must be considered. Nonetheless, approval of such a novel agent with extensive, worldwide use already in highly selected patients, is an advance that should not be under-estimated. Biostatisticians are not clinicians. They do not have to deal with death and dying. They can amuse themselves by statistical masturbation, but they should not try to obstruct progress.

International Conference

Lung Cancer Screening and Early Diagnosis Como, Italy November 8, 2003

This is on the fifth anniversary of the Varese Conference held in 1998. The importance of early identification and intervention was liberally discussed at the first conference, which represented a major departure from the dogma that has held back early diagnosis and screening for many years. This year's conference promises to be equally exciting and deals with new approaches and perspectives. Registration is possible online at www.predica.it/comoference/registration .

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