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**LUNG  
CANCER****FRONTIERS****7TH PERSPECTIVES IN LUNG  
CANCER CONFERENCE  
ATHENS GREECE**Comments may be  
submitted to:**Lung Cancer  
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**Lung Cancer Frontiers** is published by The Snowdrift Pulmonary Conference and supported by a generous grant from the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida. It is hoped that the next series of issues will help to disseminate knowledge based on our experiences in early lung cancer identification and treatment, based upon studies originally conducted in Grand Junction, Colorado.

"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."

The Editorial Board calls everyone's attention that all issues of **Lung Cancer Frontiers** beginning with their inception in 1996 are available on the internet at [www.lungcancerfrontiers.org](http://www.lungcancerfrontiers.org).

By Paul Baas, M.D.

The 7<sup>th</sup> "Perspectives in Lung Cancer" took place in Athens on September 8 and 9, 2006. The meeting was well attended with approximately 350 persons from mostly European countries. Besides general talks, a variety of issues was presented like rare tumors, endobronchial therapies, and pathology issues.

The State of the Art lectures were well balanced and gave a good, up-to-date overview. The rising incidence of lung cancer in females was addressed by Carolyn Dressler (Lyon). She discussed the epidemiology of the still-rising incidence of (adeno) carcinoma while the overall incidence of lung cancer is decreasing in Northwestern Europe. In the Eastern and Southern countries, incidence of lung cancer in both male and females is still

increasing. Publications on the advantages of low tar and nicotine cigarettes have been criticized by the fact that the experimental set-up does not take into account the increase in inhalation depth and frequency. Most smokers need a minimal amount of nicotine which is quickly achieved in standard cigarettes and only slowly in the so-called "safer" cigarettes.

Giorgio Scagliotti (Turin) discussed the pathology of the Broncho Alveolar Carcinoma (BAC). A "pure" BAC is a rare tumor according to the WHO classification of 1999 and accounts for 3% of all lung cancers. On the contrary, adeno carcinomas with BAC-like features have been reported in up to 20% of the cases. Scaliotti underscored the importance of making this distinction since tumors with BAC features seem to have an improved survival.

With the implementation of low

# The Forum for Early Diagnosis and Treatment of Lung Cancer

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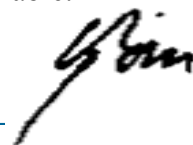
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## SNUFF AS A SMOKING AID?

The widespread use of the tobacco product snuff in Sweden appears to have been successful in reducing the lung cancer mortality rate in Sweden to 22.6 per 100,000, which is far better than any other country such as the UK with 42.9 and Belgium with 69.9 lung cancer deaths per 100,000 population. Dissolvable tobacco pellets are popular and are sometimes used by women. Women, however, continue to smoke at rates nearly equivalent to the rest of Europe and they still have one of the highest lung cancer rates. Oral disease rates in Sweden are lower than other countries than where snuff is not used, although it is recognized that snuff does have an oral cancer risk. Certainly the nicotine in snuff is equally addicting as smoked tobacco, but the risk of exposure to nitrosamines is far less, thus explaining the reduction of lung cancer.

The US smokeless tobacco market now exceeds 3 billion per year compared with 70 billion for cigarettes. Only about two percent of Americans use tobacco, compared with 22% who smoke.

My own view is that we have better methods of nicotine replacement and non-nicotine stop smoking drugs. Use of these agents by prescription, rather than snuff or over the counter, seems highly preferable.



dose helical CT screening studies, it is clear that slow-growing BACs and pre-malignant stages like Atypical Adenomatous Hyperplasia (AAH) can be detected. The question arises what the clinical significance of these disorders is and how it will affect the timing of a proposed therapeutic intervention. Biological analysis of BACs reveals a higher expression of p53, cyclin D1 and p21. With respect to the therapy, surgery remains the primary choice of treatment when the disease is localized. Chemotherapy is only moderately effective and the use of Tyrosine Kinase Inhibitors in unselected patients will could be simplified. The difference between the atypical carcinoid and the LCNEC is based on the number of mitosis in the biopsy specimen. For AC it is 3-9/10HPF and for LCNEC >10. The clinical behavior, however, is different with respect to growth rate and metastatic potential, making it difficult to decide on a choice of therapy. Thierry le Chevalier (Paris) discussed the therapeutic options and concluded that primary surgical resection with adjuvant chemotherapy (cisplatin based) should be given. There are no clear data on the indication of adjuvant radiation therapy so far. He considers the use of the TKI in this disease as new treatment possibility.

Nick Thatcher (Manchester) discussed issues concerning SCLC. It is clear that the anatomical staging, which is currently used, is insufficient and the choice of therapy should also include factors as LDH and performance score. In the last year, three publications (including abstracts) indicated that there was no sign of differences between the use of cisplatin/etoposide vs cyclophosphamide/doxorubicin/etoposide in patients with extensive stage SCLC. There was a clear difference in hematological toxicity, which was more pronounced when CDE was used. In patients with poor prognostic factors (PS  $\geq 2$ , >70 years, abnormal biochemistry) single agent carboplatin gave a similar survival and less toxicity compared with a multidrug regimen. So far, two studies in the US/Europe have failed to attain the promising results reported by the Japanese groups who used irinotecan and cisplatin. Patients with SCLC in the good prognostic group should

be treated with a platinum regimen (PE or ICE) when combined with radiation therapy. The RT should be given as early as possible during the treatment. Nowadays more emphasis is given to the incorporation of new agents and the use of newer methods of radiation. With this approach we hope to reduce the toxicity to the normal surrounding organs and to increase the dose or efficacy of the radiation. The new compounds currently under investigation are pemetrexed and anti-angiogenic agents.



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# ADVANCEMENT IN TARGETED THERAPY FOR LUNG CANCER

In its fall newsletter, the Cleveland Clinic promoted the use of targeted therapy for lung cancer including “smart drugs,” such as bevacizumab Avastin recently approved by the FDA for advanced colon cancer. Bevacizumab is an antibody which binds to vascular and epithelial growth factor leading to interruption of blood vessels and tumors. Preliminary reports are showing improved survival.

*Editorial Comment: Second generation antiangiogenesis drugs are now under study, such as sunitinib (Sutent), sorafenib (Nexavar), and an experimental drug called ZD6474 (Zactima).*

The Cleveland Clinic is also promoting stereotactic radiation therapy for lung cancer. In the 45 lung cancer patients treated in the last two years, the mortality rate has been zero. The Clinic is promoting multi-modality treatment programs that can increase the survival by 30-40 percent. Such aggressive therapy appears to be best in locally advanced cancer. Of course, patient selection is critical as with any multi-modality therapy. It is encouraging that at least one major medical center is now pushing for improved mortality. It is hoped that they will get behind a concerted effort in targeted screening for earlier stage lung cancer in high risk groups where the survival rate is much more satisfactory than in locally

**Previous studies have treated severe dysplasia (SD) and carcinoma-in-situ (CIS) ....**

## **Citations from the Peer Reviewed Literature**

1. Thorax 2006 Aug (ahead of print)  
Surveillance for the detection of early lung cancer in patients with bronchial dysplasia  
George PJ, Banerjee A, Read CA, et al

UCL Hospitals NHS Foundation Trust, United Kingdom.

**BACKGROUND:** The natural history of bronchial pre-invasive lesions and the risk of developing lung cancer in patients harbouring these lesions are not clear. Previous studies have treated severe dysplasia (SD) and carcinoma-in-situ (CIS) on the assumption that the majority

**To define the natural history of pre- invasive lesions and assess lung cancer risk in patients harbouring these lesions.**

**Five separate cancers developed at remote sites in patients harbouring high-grade lesions.**

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**The utility of DLight/ AFB in the detection of pre-cancerous lesions was compared to the standard white light bronchoscopy (WLB).**

will progress to invasive carcinoma. AIMS: To define the natural history of pre-invasive lesions and assess lung cancer risk in patients harbouring these lesions. Hypotheses: The majority of pre-invasive lesions will not progress to invasive carcinoma but patients harbouring these lesions will be at high risk. METHODS: A cohort of patients with pre-invasive lesions underwent fluorescence bronchoscopy every 4-12 months and chest CT annually. The main endpoint was the development of invasive carcinoma. RESULTS: Twenty-two patients with 53 lesions were followed for 12-85 months. Eleven cancers were diagnosed in 9 patients. Of 36 high-grade lesions (SD and CIS), 6 progressed to invasive cancers. Five separate cancers developed at remote sites in patients harbouring high-grade lesions. All cancers were N0M0 and curative treatment was given to 8/9 patients. The cumulative risk of developing lung cancer in a patient harbouring a high-grade lesion was 33% and 54% at 1 and 2 years respectively. Of 17 low-grade lesions, none progressed to invasive carcinoma. CONCLUSIONS: Although the risk of malignant progression of individual preinvasive lesions is relatively small, patients harbouring high-grade lesions are at high lung cancer risk. Surveillance facilitated early detection and treatment with curative intent

in the majority of patients.

Editorial Comment (TLP): This important study adds to other evidence that dysplasia frequently, though not always, progresses to invasive carcinoma. This additional evidence supports both sputum cytology and CT screening in the early identification of early stage lung cancer.

2.

J Korean Med Sci  
2006;21:242-246

Detection of pre-invasive endobronchial tumors with D-light/autofluorescence system

Jang TW, Oak CH, Chun BK, et al

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Autofluorescence bronchoscopy (AFB) is one of the newly developed diagnostic tools to detect the pre-cancerous lesions in the bronchial tissue. The utility of DLight/AFB in the detection of pre-cancerous lesions was compared to the standard white light bronchoscopy (WLB). In 113 patients (male 106,

**The specificity of adjunctive AFB and WLB alone were 0.91 and 0.5, respectively.**

**White light (WLB) and autofluorescence bronchoscopy (AFB) examination were performed sequentially in the same session.**

**For the 8 patients who had lesion with histological grade moderate dysplasia or worse, 5 patients were found to have lung cancer:**

female 7), who visited hospital for evaluation of lung cancer, WLB and AFB were done and 364 biopsy specimens were obtained from November 2001 to August 2002. The bronchoscopic findings on WLB and AFB were compared to the pathological findings. The pathologic diagnoses of the specimens were as follows: normal in 96; hyperplasia in 69; metaplasia in 32; mild dysplasia in 13, moderate dysplasia in 6, severe dysplasia in 4; carcinoma in situ in 6; invasive carcinoma in 57. The relative sensitivity of adjunctive AFB to WLB vs. WLB alone was 1.5 in moderate dysplasia or worse lesions, and 3.2 in intraepithelial neoplasia. The specificity of adjunctive AFB and WLB alone were 0.91 and 0.5, respectively. The adjunctive AFB to the standard WLB increased the detection rate of the localized pre-invasive lesions. However, there was high rate of false positive in AFB.

(See Editorial Comment below)

3.

Eur Respir J 2006; Jul 26 (ahead of print)

The clinical value of autofluorescence bronchoscopy for the diagnosis of lung cancer

Lam B, Wong MP, Fung SL, et al

University Dept of Medicine.

To evaluate the role of autofluorescence bronchoscopy in routine work-up of lung cancer. Consecutive patients with atypical cells/suspicious cells in sputum or bronchial aspirate, non-localizing radiological examination, and non-diagnostic white light bronchoscopic examination were recruited. White light (WLB) and autofluorescence bronchoscopy (AFB) examination were performed sequentially in the same session. All abnormal areas detected by WLB, AFB or both were biopsied and sent for histological examination. Sixty-two patients were recruited within the 32 months study period. Seventeen had no endobronchial lesion detected. Among the 45 patients with endobronchial lesions: 37 had lesions with histopathology grade mild dysplasia or less; For the 8 patients who had lesion with histological grade moderate dysplasia or worse, 5 patients were found to have lung cancer: 2 had invasive lung cancer and 3 had intraepithelial neoplasm (severe dysplasia). Lesions with moderate dysplasia or worse were more commonly found in patients with "suspicious cells" than patients with "atypical cells" in sputum examination. AFB is more sensitive than WLB (91% Vs 58%) in detecting these lesions though less specific (26% Vs

**Subjects received four annual posteroanterior CXRs for the early detection of lung cancer.**

**These two articles indicate that the techniques of white light bronchoscopy and autofluorescent bronchoscopy are complimentary.**

**..... pulmonary fibrosis was significantly associated with an increased risk of lung cancer with a hazard ratio (HR) ....**

50%). The combination of WLB and AFB can increase the diagnostic yield of this invasive procedure in patients with abnormal sputum cytology.

Editorial Comment (TLP): Autofluorescent bronchoscopy is beginning to become more widely used because of its increased sensitivity in the diagnosis of lung cancer. These two articles indicate that the techniques of white light bronchoscopy and autofluorescent bronchoscopy are complimentary.

4.  
Chest 2006;130:688-693

Abnormalities on chest radiograph reported in subjects in a cancer screening trial

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BACKGROUND: Chest radiographs (CXRs) are commonly performed for diagnostic and other purposes. There is little literature either on the prevalence in the general population of various abnormalities seen on CXRs or on the risks associated with these abnormalities.

METHODS: We followed up > 70,000 men and women who were enrolled in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Subjects received four annual posteroanterior CXRs for the early detection of lung cancer. Radiologists noted the presence of non-cancer-related abnormalities as well as nodules/masses that were suspicious for lung cancer. Subjects were followed up for mortality and cancer incidence. RESULTS: Abnormalities that were not suspicious for lung cancer were observed on 35% of examinations, compared to 8% of examinations with findings that were suspicious for cancer. The most commonly reported noncancer abnormalities were granuloma (10.7% of examinations), scarring/pulmonary fibrosis (8.2% of examinations), bone/soft tissue lesions (5.5% of examinations), cardiac abnormalities (4.4% of examinations), pleural fibrosis (3.6% of examinations), and COPD/emphysema (2.5% of examinations). Most noncancer abnormalities were more prevalent in men, older subjects, and smokers. Controlling for age, smoking, and other factors, scarring/pulmonary fibrosis was significantly associated with an increased risk of lung cancer with a hazard ratio (HR) of 2.0, while cardiac abnormalities (HR, 2.1), scarring/pulmonary fibrosis (HR, 1.4), COPD (HR, 1.7), and pleural fluid (HR, 2.3) were significantly associated with increased overall (ie, non-lung cancer) mortality. CONCLUSION: Abnormalities that are not suspicious for lung cancer are common in a

population undergoing screening. Some of these abnormalities are associated with an increased risk for lung cancer incidence and/or overall mortality.

Editorial Comment (TLP):  
Although the “routine” or “screening” of chest x-rays have fallen into disfavor, the present study indicates significant value in older subjects and those at high risk. The chest x-ray is not obsolete in the diagnosis of lung cancer.

## American Cancer Society Report

In its September 6 report on the “Annual Report to the Nation on the Status of Cancer 1975-2003,” the American Cancer Society pats itself on the back for the reduction in cancer in both men and women. However, lung cancer in women is up by 0.3 percent, along with pancreatic cancer at a 0.1 percent increase. Both are smoking related diseases. The ACS continues to refuse to support screening for lung cancer, for which effective screening exists today. Not so with pancreatic cancer, but in high risk patients with family history of pancreatic or other gastrointestinal cancer, expanding the range of the CT scan into the upper abdomen would seem to make sense. The need for stepped-up screening in the 35 million Hispanics in this country was appropriately mentioned. The ACS admits that “cancer of the lung and rectum, prostate and female cervix among those detected in later stages among Hispanics and there are effective screening techniques for several of these cancers.” So where is the emphasis on screening for lung cancer? The head in the sand