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**LUNG  
CANCER****FRONTIERS****PROGRESS IN  
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."

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**RECENT EVENTS AND  
ADVANCES IN LUNG CANCER**

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**I. EPIDEMIOLOGY & ETIOLOGY**

Jemal and colleagues at the American Cancer Society<sup>1</sup> analyzed historical cancer incidence and mortality data and reported that for the years between 1990 and 2004 the **number** of deaths from lung cancer decreased by 2% in males and increased by 36% in females. They also reported that between 1999 and 2003, the five states with the highest lung cancer incidence among males (expressed per 100,000 population) were Kentucky (137.9), West Virginia (118), Arkansas (114.9), Louisiana (114) and Oklahoma (111.2); Utah had the lowest incidence among males (41.8). Among females, the five states with the highest incidence were Kentucky (73.5), Nevada (71.2), West Virginia (68.4), Delaware (63) and Maine (62.8). These findings closely parallel the report in *Morbidity and Mortality Weekly Report* (MMWR) showing that among all adults in 2004 the states with the highest

prevalence of current cigarette smoking were Kentucky (27.6%), West Virginia (26.9%), Oklahoma (26.1%) and Tennessee (26.1%).<sup>2</sup> The lowest smoking prevalence was in Utah (10.5%).<sup>2</sup>

Jemal and coworkers<sup>1</sup> also analyzed trends in 5-year survival rates in the United States for selected cancers, focusing on the years 1975 through 2002. The 5-year survival rate for lung cancer during that time increased from 13% to 16%, the smallest increase in any of the major cancers; the survival rate in prostate cancer increased from 69% to 99-100%, breast cancer increased from 75% to 89%, and colon cancer increased from 51% to 65%.



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# The Forum for Early Diagnosis and Treatment of Lung Cancer

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## LUNG CANCER BIOMARKERS

This issue has been developed by Richard Matthay of Yale, one of LCF's most loyal editors. It represents a general update indicating progress with the diagnosis and treatment of lung cancer. It also points out remaining disappointments, and painfully slow improvement in mortality.

I continue to believe that apart from primary prevention through smoking cessation, case finding in high risk populations, and early aggressive treatment holds the best hope for improved mortality. Whether CT screening is really superior to chest x-ray diagnosis, will soon be answered by studies in progress, but all cancers do better if diagnosed early, and CT is superior to chest x-rays in the diagnosis of early stage lung cancer, according to many studies done in North America, Europe and Japan.



**Relationship between reduced forced expiratory volume in one-second and the risk of lung cancer: a systematic review and meta-analysis.**

**Thorax 2005;60-570-575.**

**Wasswa-Kintu S, Gan WQ, Man SFP, et al  
Center for Cardiovascular & Pulmonary  
Research, St. Paul's Hospital, Vancouver,  
B.C., Canada.**

**BACKGROUND:** It is well-known that patients with severely impaired lung function as assessed by forced expiratory volume in 1 second (FEV<sub>1</sub>), have an increased risk of lung cancer. Wasswa-Kintu and colleagues<sup>3</sup> assessed whether milder reductions in FEV<sub>1</sub> increase the risk of lung cancer and whether both sexes are similarly affected.

**METHODS:** The authors searched the PubMed database from January 1966 to January 2005, limiting their search to studies that examined the relationship between FEV<sub>1</sub> and lung cancer, that were population-based, employed a prospective design, included at least 5,000 participants, and adjusted for cigarette smoking status.

**RESULTS:** Twenty-eight abstracts were identified; six of which did not report FEV<sub>1</sub> and eight did not adjust for smoking. Included in this report were four studies that reported FEV<sub>1</sub> in quintiles. The risk of lung cancer increased with decreasing FEV<sub>1</sub>. Compared with the highest quintile of FEV<sub>1</sub> (> 100% of predicted), the lowest quintile (< approximately 70% of predicted) was associated with a 2.23 fold increase in the risk of lung cancer in men and a 3.97 fold increase in women. Even relatively small decrements in FEV<sub>1</sub> (to approximately 90% of predicted) increase the risk for lung cancer by 30% in men and 2.64 fold in women.

**CONCLUSION:** Reduced FEV<sub>1</sub> is strongly associated with lung cancer, and even a relatively modest reduction is a significant predictor of lung cancer, especially among women.

**Editorial Comment (RAM):** This study produced four especially important findings. First, independent of cigarette smoking, decreases in FEV<sub>1</sub> increases the risk of lung cancer in the general population. Second, the relationship is severity-dependent such that patients

with the worst lung function have the highest risk, whereas those with preserved lung function have the lowest risk. Third, the relationship is alinear: relatively small differences in FEV<sub>1</sub>, which are commonly considered to be within the normal range (e.g., from 90% to 100% of predicted), increase the risk of lung cancer by 30% to 60%. Fourth, the risk appears to more pronounced in women.

## II. PREVENTION

Khurana and colleagues<sup>4</sup> carried out a Veterans Affairs Health Care System Retrospective Case-Control Study of almost half a million patients from eight states in the south central United States from 1998-2004. This study assessed whether the lipid-lowering agents HMG-CoA reductase inhibitors (statins) were protective against lung cancer. In the study, 163,662 patients (33.8%) were receiving statins, and 7,280 patients (1.5%) had a primary diagnosis of lung cancer. Statin therapy for more than 6 months was associated with a risk reduction of lung cancer of 55% (odds ratio 0.45; CI 0.42-0.48; P < 0.01). Moreover, the protective effect of statin therapy was evident across age and racial groups and irrespective of the presence of diabetes, smoking, or alcohol use. The authors conclude that statins appear to be protective against the development of lung cancer and recommend well-designed randomized prospective double-blinded placebo controlled clinical trials to validate the potential value of statin chemoprevention for lung cancer.

**Editorial Comment (RAM):** This study highlights the current focus on chemoprevention in lung cancer. Potential chemoprevention agents previously studied have been shown to be ineffective. Statins, which are a cornerstone in the treatment of atherosclerotic disease, have been shown to

*“It is well-known that patients with severely impaired lung function as assessed by forced expiratory volume in 1 second (FEV<sub>1</sub>), have an increased risk of lung cancer.”*

*“The risk of lung cancer increased with decreasing FEV<sub>1</sub>. Compared with the highest quintile of FEV<sub>1</sub> (> 100% of predicted), the lowest quintile (< approximately 70% of predicted) was associated with a 2.23 fold increase in the risk of lung cancer in men and a 3.97 fold increase in women.”*

*“Moreover, the protective effect of statin therapy was evident across age and racial groups and irrespective of the presence of diabetes, smoking, or alcohol use.”*

have anti-tumor effects in vitro. These agents increase apoptosis,<sup>5</sup> suppress angiogenesis through their effects on vascular endothelial growth factor,<sup>6</sup> and alter invasion and metastatic potential through interaction with adhesion molecules.<sup>5-7</sup> Epidemiologic data have shown an association between the use of statins and a decrease in cancer incidence.<sup>8,9</sup> In addition to the study by Khurana et al,<sup>4</sup> two meta-analyses<sup>10,11</sup> found no beneficial or detrimental effect of statins in relation to overall cancer risk or cancer death. Given the weaknesses of the retrospective analysis by Khurana and colleagues,<sup>4</sup> future prospective controlled phase III trials are needed to assess the effects of statins on lung cancer incidence and/or mortality.

*“The results of both studies indicate that CT screening increases the diagnosis of lung cancer and the earlier institution of treatment, but that screening may not reduce the risk of advanced lung cancer or lung cancer mortality rates.”*

*“Endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) have separately increased the diagnostic yield of bronchoscopic diagnosis of peripheral lung lesions.”*

### III. SCREENING

Two studies assessed the potential value of computed tomography (CT) screening in early lung cancer detection and outcomes<sup>12,13</sup>. The results of both studies indicate that CT screening increases the diagnosis of lung cancer and the earlier institution of treatment, but that screening may not reduce the risk of advanced lung cancer or lung cancer mortality rates. Swensen and colleagues at the Mayo Clinic<sup>13</sup> completed a 5-year phase II prospective study of low-dose helical CT in 1520 persons (52% men, 48% women) who were older than 50 years of age and had at least a 20 pack-year history cigarette smoking; 61% were current smokers and 39% former smokers. Uncalcified nodules were detected in 1,118 (74%) of participants after 5 years of annual CT scans: 68 lung cancers were diagnosed of which 61% were at stage I. However, there was a 96% false-positive rate for both prevalence and incidence cancers. Moreover, there was no evidence of stage shift when the cohort was analyzed.

Bach and colleagues<sup>12</sup> conducted a longitudinal analysis of 3,246 asymptomatic current or former smokers in either one of two screening trials in the United States or Italy with a follow-up of 3.9 years. Outcomes with spiral CT were compared with predicted number of new lung cancer resections, advanced lung cancer cases, and deaths from lung

cancer: 144 cases of lung cancer were diagnosed, whereas 44.5 were expected; there were 109 lung resections in the screened group, whereas 10.9 were expected. However, there was no evidence for a reduction in the number of advanced lung cancer diagnoses (42 diagnosed; 33 expected) or deaths from lung cancer (38 deaths; 38 expected).

### EDITORIAL COMMENT: (RAM)

Both of these studies suggest that CT screening detects early-stage lung cancer. However, screening results in a high false-positive rate, no observed stage shift in the cancers detected, and no effect on the mortality rate from lung cancer.

### IV. DIAGNOSTIC TECHNIQUES

**Multimodality bronchoscopic diagnosis of peripheral lung lesions—a randomized controlled trial.**

**Am J Respir Crit Care Med  
2007;176:36-41**

**Eberhardt R, Anantham D, Ernst A et al  
Department of Pneumology &  
Critical Care Medicine, University of  
Heidelberg, Heidelberg, Germany and  
Interventional Pulmonology, Beth  
Israel Deaconess Medical Center,  
Harvard Medical School, Boston, MA.**

**BACKGROUND:** Endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) have separately increased the diagnostic yield of bronchoscopic diagnosis of peripheral lung lesions. However, the role of combining these modalities to overcome each individual technique's limitations and, consequently, to further increase the diagnostic yield remains untested. **OBJECTIVES:** Eberhardt and colleagues carried out a prospective randomized control trial involving three diagnostic arms (EBUS alone, ENB alone, and a combined procedure) to assess whether combining these modalities further increased the diagnostic yield.<sup>14</sup> **METHODS:** All procedures were performed via flexible bronchoscopy and transbronchial forceps biopsies were obtained with fluoroscopic guidance. In the combined group, after electromagnetic navigation, the ultrasound probe was

*“Combined EBUS and ENB improves the diagnostic yield of flexible bronchoscopy for peripheral lung lesions without compromising safety.”*

*“It is questionable whether the high diagnostic yields reported in this study can be achieved outside expert centers.”*

*“Mediastinoscopy was infrequently performed in patients undergoing surgery for non-small cell lung cancer, and in those that it was performed fewer than half underwent a lymph node biopsy”*

passed through an extended working channel to visualize the lesion. Biopsy specimens were taken if ultrasound visualization showed that the extended working channel was within the target. Primary outcome was diagnostic yield. The reference “gold standard” was a surgical biopsy if bronchoscopic biopsy did not reveal a definite histologic diagnosis compatible with the clinical presentation.

**MEASUREMENTS & MAIN RESULTS:** Of the 120 patients recruited, 118 had a definitive histologic diagnosis and were included in the final analysis. The diagnostic yield of the combined procedure (88%) was greater than that of EBUS alone (69%) or ENB alone (59%) (P =0.02). The combined procedure’s yield was independent of the size of the lesion or its lobar distribution. The pneumothorax rates ranged from 5% to 8%, with no significant difference between the groups.

**CONCLUSIONS:** Combined EBUS and ENB improves the diagnostic yield of flexible bronchoscopy for peripheral lung lesions without compromising safety.

**EDITORIAL COMMENT (RAM):** As Silvestri<sup>15</sup> points out in an accompanying editorial, despite excitement generated by this new technology, troubling questions remain. EBUS and ENB are separately expensive with disposables that significantly drive up the per case cost. Moreover, in the United States, reimbursement has not been well-established. Accordingly, patients may need to be referred to high-volume centers for use of these techniques. Hospitals, bronchoscopy laboratories, and physicians must decide which technology(ies) to purchase. Nevertheless, it is likely that these technologies will be incorporated into clinical practice.

## V. STAGING

Patterns of surgical care of lung cancer patients.

Ann Thorac Surg 2005;80:2051-6  
Little, AG, Rush, VW, Bonner, JA, et al  
Department of Surgery, Wright State University School of Medicine, Dayton, Ohio

Memorial Sloan-Kettering Center, New York, New York  
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Department of Radiology, University of California, San Francisco, California  
American College of Surgeons and the National Cancer Data Base, Chicago, Illinois

**BACKGROUND:** Little and colleagues<sup>16</sup> assessed patterns of surgical care provided patients with non-small cell lung cancer.

**METHODS:** In conjunction with the American College of Surgeons, they carried out patient care surveys in the year 2001 in 729 hospitals with detailed information abstracted for patients with non-small cell lung cancer, including patient history, diagnostic evaluation, pathology, and surgical treatment.

**RESULTS:** Of the 11,668 patients treated surgically, only 27.1% underwent mediastinoscopy, and of those only 46% underwent mediastinal lymph node sampling.

**CONCLUSIONS:** Mediastinoscopy was infrequently performed in patients undergoing surgery for non-small cell lung cancer, and in those that it was performed fewer than half underwent a lymph node biopsy.

**Editorial Comment (RAM):** Mediastinoscopy remains the “gold standard” for staging the mediastinum in lung cancer. Little and colleagues showed that in practice mediastinoscopy is carried out in only about one-quarter of patients undergoing lung cancer surgery with curative intent. Even more concerning is the fact that less than one-half of patients undergoing mediastinoscopy had a lymph node biopsy. Thus, patients undergoing mediastinoscopy had lymph nodes evaluated visually but no histopathologic confirmation. Because treatment varies widely depending on whether there is lymph node involvement with tumor, this is an extremely disturbing finding.

**Real-time endobronchial ultrasound-guided transbronchial needle aspiration for sampling mediastinal lymph nodes.**

**Thorax 2006;61:795-798**

**Herth FJ, Eberhardt R, Villman T., et al  
Department of Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg, Germany  
Department of Surgical Gastroenterology, Gentofte University Hospital, Copenhagen, Denmark  
Department of Cardiothoracic Surgery, Gentofte University Hospital, Copenhagen, Denmark  
Interventional Pulmonology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA**

**BACKGROUND:** Mediastinal lymph nodes are currently evaluated by mediastinoscopy, thoracoscopy, blind transbronchial needle aspiration, endoscopic ultrasound with fine-needle aspiration, and endobronchial ultrasound with fine-needle aspiration.

**METHODS:** Herth and colleagues<sup>17</sup> studied endobronchial ultrasound-guided transbronchial needle aspiration for sampling mediastinal lymph nodes in 502 consecutive patients referred for transbronchial needle aspirate. When a lymph node was detected, a puncture was performed under real-time ultrasound guidance. The primary endpoint was the number of successful biopsy specimens obtained.

**RESULTS:** Of the 502 patients who underwent endobronchial ultrasound, 572 lymph nodes were biopsied. The biopsy specimens were taken from the following regions: 2 L, 2 R, 3, 4 R, 4 L, 7, 10 R, 10 L, 11 R, and 11 L. The mean diameter of lymph nodes was 1.6 cm. Sensitivity was 94% and specificity 100%, and there were no complications.

**CONCLUSION:** The endobronchial ultrasound-guided transbronchial needle aspirate technique is an excellent method for obtaining samples from the mediastinal lymph nodes. In addition, the technique can be performed in the out-patient setting with minimal complications.

**Editorial Comment (RAM):** Although mediastinoscopy remains the “gold

standard” for staging the mediastinum, endobronchial ultrasound is safe and accurate, and can assess lymph node stations that are not accessible by mediastinoscopy. The only two lymph node stations that endobronchial ultrasound apparently cannot reach are level 5 and level 6, both in the anterior mediastinum. This technology is superior to blind transbronchial needle aspirate and may in the future be the gold standard for staging the mediastinum.

## **VI. COMPLICATIONS**

Wilson and colleagues<sup>18</sup> provide a thorough review of the superior vena cava (SVC) syndrome. This syndrome occurs in approximately 15,000 patients in the United States each year. Increased venous pressure in the upper body results in edema of the head, neck, and arms, often with cyanosis, plethora, and distended subcutaneous vessels. Edema may cause functional compromise of the larynx or pharynx manifested as cough, hoarseness, dyspnea, stridor, and dysphagia. Cerebral edema may result in headache, confusion, and coma. Moreover, decreased venous return may result in hemodynamic compromise, a potential consequence of intrinsic or extrinsic obstruction of the superior vena cava, compression of the heart by a large mass in the chest, or both. Symptoms develop over a period of two weeks in approximately a third of affected patients and over longer periods in other cases.

Malignant causes of SVC syndrome include non-small cell lung cancer (50%), small cell lung cancer (22%), lymphoma (12%), metastatic cancer (9%), germ-cell cancer (3%), thymoma (2%), mesothelioma (1%) and other cancers (1%). Symptoms include facial edema (82% of patients), distended neck veins (63%), distended chest veins (53%), arm edema (46%), and facial plethora (20%). Contrast-enhanced chest CT scan is required to evaluate the superior vena cava. When placement of a stent or surgery is planned, venography may be warranted. Magnetic resonance imaging (MRI) is useful for patients who cannot tolerate contrast medium. Positron emission tomography (PET) may be useful in designing the radiotherapy field. Histologic diagnosis is necessary to

*“When a lymph node was detected, a puncture was performed under real-time ultrasound guidance.”*

*“Cerebral edema may result in headache, confusion, and coma.”*

*“When placement of a stent or surgery is planned, venography may be warranted.”*

confirm the presence of malignant conditions. Pleural effusion is common, affecting about two-thirds of patients with SVC syndrome, and thoracentesis with cytologic analysis may yield the diagnosis in up to 50% of patients. Bronchoscopy has a diagnostic yield of 50-70%; transthoracic needle-aspiration biopsy approximately 75%; and mediastinoscopy or mediastinotomy more than 90%. Approximately 3% of patients undergoing mediastinoscopy or mediastinotomy develop major hemorrhage.

***“Management of SVC syndrome depends on the severity of symptoms and the underlying malignant condition, in addition to the anticipated response to treatment.”***

***“Sixteen genes that correlated with survival in non-small cell lung cancer were identified and risk scores were established.”***

Management of SVC syndrome depends on the severity of symptoms and the underlying malignant condition, in addition to the anticipated response to treatment.<sup>18</sup> Two weeks of radiation therapy alleviates symptoms of obstruction in 78% of patients with small-cell lung cancer and 63% of patients with non-small cell lung cancer. Relief of symptoms is often apparent within 72 hours. Similarly, systemic chemotherapy completely relieves symptoms of vena cava obstruction in approximately 80% of patients with non-Hodgkin's lymphoma or small cell lung cancer and in 40% of patients with non-small cell lung cancer. There is apparently no clinically significant difference in the rate of relief of symptoms from the SVC syndrome whether chemotherapy, radiation therapy, or chemotherapy with radiation therapy is used.

Percutaneous placement of an intravascular stent to bypass the obstruction of the superior vena cava is an additional possible intervention. A stent can be placed before a tissue diagnosis is made and can be useful for patients with severe symptoms (such as respiratory distress) that require urgent intervention. Cyanosis is often relieved within hours and edema can resolve within 48-72 hours after placement of a stent.<sup>18</sup>

## VII. PROGNOSIS

### **A 5-gene signature and clinical outcome in non-small cell lung cancer.**

**N Engl J Med 2007;356:11-20  
Chen HY, Yu SL, Chen CH, et al  
Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan 100**

**BACKGROUND:** Current staging methods do not adequately predict the outcome of treatment of non-small lung cancer. Chen and colleagues<sup>19</sup> developed a 5-gene signature

that is closely correlated with survival in patients with non-small cell lung cancer.

**METHODS:** These investigators utilized computer-generated, random numbers to assign 185 frozen specimens from microarray analysis with real-time reverse-transcriptase polymerase chain reaction (RT-PCR) analysis. Gene expression was studied in frozen specimens of 125 randomly selected patients who had undergone surgical resection for lung cancer, and the correlation between the level of expression and survival was evaluated. Next, they used risk scores and decision-tree analysis to develop a gene expression model for the prediction of outcome. They also used a validation group to confirm their findings.

**RESULTS:** Sixteen genes that correlated with survival in non-small cell lung cancer were identified and risk scores were established. Five genes were ultimately used in a decision-tree analysis. The five-gene signature was an independent predictor of relapse-free and overall survival. The model was validated with an independent cohort of 60 patients with known non-small cell lung cancer. **CONCLUSION:** The five-gene signature is closely correlated with relapse-free and overall survival in patients with non-small lung cancer.

**EDITORIAL COMMENT (RAM):** This study shows the potential value of genomics in the diagnosis, prognosis, and potential treatment options available in patients with non-small cell lung cancer. These prognostic gene signatures may be relied upon in the future to guide the type of treatment patients should receive, as well as their prognosis.

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## SELECTIONS FROM THE PEER-REVIEWED LITERATURE

1. **Radiology, 2007;243:329-249**

### **CT Screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project**

#### **New York Early Lung Cancer Action Project Investigators**

**PURPOSE:** To evaluate prospectively the diagnostic performance of the New York Early Lung Cancer Action Project (NY-ELCAP) regimen in the diagnosis of early lung cancer at baseline and annual repeat computed tomographic (CT) screenings.

**MATERIALS AND METHODS:** Informed consent and institutional review board approval were obtained for this HIPAA-compliant study of baseline and annual repeat low-dose

CT screening performed with a common regimen in asymptomatic individuals at 12 institutions in New York State. All 6295 participants were aged 60 years or older, had smoked for at least 10 pack-years, had no prior cancer, had not undergone chest CT in the previous 3 years, and were medically fit to undergo thoracic surgery. Median age was 66 years, and median smoking history was 40 pack-years. The proportion (and 95% exact confidence intervals [CIs]) of subjects with a positive result, as determined by using nodule size; the diagnoses of lung cancer resulting from subsequent work-up; and the distribution by cancer stage and cell type were determined. When relevant, 95% CIs for the proportions were calculated.

**RESULTS:** Initial CT imaging led to recommendations for further work-up in 14.4% (95% CI: 13.5%, 15.3%) of the 6295 baseline screenings and 6.0% (95% CI: 5.1%, 6.6%) of the 6014 annual repeat screenings. Of 101 patients in whom the diagnosis of lung cancer resulted from baseline screening and three in whom a diagnosis of lung cancer was prompted by symptoms prior to the first scheduled repeat screening, 95 (91.3%) had no clinical evidence of metastases. Of the 20 patients in whom the diagnosis of lung

*“Of 101 patients in whom the diagnosis of lung cancer resulted from baseline screening and three in whom a diagnosis of lung cancer was prompted by symptoms prior to the first scheduled repeat screening, 95 (91.3%) had no clinical evidence of metastases.”*

*“Of the 134 recommended biopsies, 125 (93.3%) resulted in diagnosis of lung cancer or another malignancy . . . . .”*

cancer resulted from annual repeat screening, 17 (85%) showed no evidence of metastases. Of the 134 recommended biopsies, 125 (93.3%) resulted in diagnosis of lung cancer or another malignancy, while none of the 24 biopsies performed outside of the recommendation of the regimen resulted in diagnosis of lung cancer. CONCLUSION: The NY-ELCAP regimen of screening revealed that annual CT screening for lung cancer resulted in identification of a high proportion of patients with early-stage disease.

**Editorial Comment (TLP): This is the latest in the University of Cornell ELCAP study, which continues to encourage annual screening for lung cancer because it has continued to be reliable in diagnosing a high proportion of patients with early stage disease since the original report (Lancet, 1999). Although other non randomized controlled clinical trials have reached the same conclusion, the purists amongst us are still holding out for the “gold standard” study, sponsored by the National Cancer Institute, which itself is quite flawed.**

**2.  
Lung Cancer 2007; Aug 3 (ahead of print)**

**Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography.**

**Sone S, Nakayama T, Hondo T, et al**

Department of Radiology, JA Nagano Azumi General Hospital, Ikeda, Nagano 399-8695, Japan.

Early diagnosis and treatment are important for improvement of the low survival rate of patients with lung cancer. The objective of this study was to evaluate the long-term survival rate of patients identified to have lung cancer by our population-based baseline and annual repeat low-radiation dose computed tomography (low-dose CT) screenings, conducted in 1996-1998. A total of 13,037 CT scans were obtained from 5480 subjects (2969 men, 2511 women) aged 40-74 years at the initial CT screening. Lung cancer was detected in 63 subjects (57 were detected by CT scans and

underwent surgery; 1 was detected by sputum cytology and underwent surgery; 3 rejected treatment; and 2 were interval cases that developed symptoms prior to the next annual repeat CT screening). Follow-up study included review of medical records. Death certificates were examined to check for any deceased interval case among participants. Postoperative follow-up of the 50 survived patients ranged from 70 to 117 (median, 101) months. Eight patients died during follow-up (6 due to lung cancer from 20 to 67 months after surgery and 2 deaths unrelated to lung cancer, each 7 and 60 months following surgery). Three patients who rejected treatment died 14 months to 6 years after positive screening CT scans, and the 2 interval cases died at each 17 and 30 months, respectively, following negative screening CT scans. Survival was analysed in 59 patients with lung cancer detected by low-dose CT screening (excluding two patients; one was detected by sputum cytology and the other had mass lesion already noted on the chest radiograph of the previous year). The 10-year survival calculated by the Kaplan-Meier method was 83.1% (95% CI: 0.735-0.927) for death from all causes and 86.2% (95% CI: 0.773-0.951) for death from lung cancer. The survival rate was excellent for never-smokers, patients with BAC and adenocarcinoma/mixed types with non-solid CT density pattern, associated with Noguchi's type A or B and pathologic stage IA. A poorer prognosis was noted in smokers with adenocarcinomas/mixed types, associated with part-solid or solid CT density pattern and Noguchi's type C or D. All patients with non-solid tumours measuring 6-13.5mm at presentation are alive, patients with part-solid tumours, measuring 17mm or more, or solid tumours, measuring 13mm or more at presentation were associated with increased risk of lung cancer-related morbidity or mortality. The estimated rate of possible over-diagnosis was 13% in total and we failed to cure 17% of patients encountered in the programme. Low-dose CT screening substantially improves the 10-year survival for lung cancer with minimal use of invasive treatment procedures.

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**Editorial Comment (TLP): This extensive study from Japan also supports low dose CT screening for early stage lung cancer and offers evidence that suggests an improvement in ten-year survival of lung cancer following algorithms established in this study.**

3.  
**Cancer 2007;110:835-844**

**A study of the volatile organic compounds exhaled by lung cancer cells in vitro for breath diagnosis.**

**Chen X, Xu F, Wang Y, Pan Y, et al**

Biosensor National Special Laboratory, Department of Biomedical Engineering, Key Laboratory of Biomedical Engineering of National Education Ministry, Zhejiang University, Hangzhou PR China.

**BACKGROUND:** The specific volatile organic compounds (VOCs) exhaled by lung cancer cells in the microenvironment are the source biomarkers of lung cancer and also serve as direct evidence that the diagnosis of lung cancer by breath is possible. However, to the authors' knowledge, few articles published to date have provided accurate VOCs in the microenvironment, thereby leading to different points of view with regard to searching for biomarkers in the breath from lung cancer patients. In this article, an innovative pathologic analysis method of lung cancer and the early diagnosis of lung cancer at the cellular level were introduced for this purpose. **METHODS:** Solid-phase microextraction combined with gas chromatography is used as the detection system to determine the VOCs in the culture medium of several target cells, including different kinds of lung cancer cells, bronchial epithelial cells, taste bud cells, osteogenic cells, and lipocytes. As a result, each kind of cells has a unique chromatogram. There are 4 special VOCs that were found to exist in all culture mediums of lung cancer cells, which are the metabolic products of lung cancer cells and can be viewed as markers of lung cancer. **RESULTS:** The authors were able to determine a correlation between VOCs in the metabolic products of lung cancer cells and VOCs in the breath of lung cancer patients, some of whom had stage I and II disease, and eventually hope to certify the biomarkers in the breath of lung

cancer patients. **CONCLUSIONS:** This research is significant and provides the basis for the noninvasive detection and the breath diagnosis of lung cancer using an electronic nose.

**Editorial Comment (TLP): The continued inquiry into research that diagnose lung cancer by breath analysis is exciting and worthwhile. Whether or not early stage lung cancer can be so diagnosed remains to be determined by more extensive studies.**

4.  
**Mod Pathol 2007;20:905-913**

**EGFR expression as an ancillary tool for diagnosing lung cancer in cytology specimens.**

**Wei EX, Anga AA, Martin SS, et al**

1Department of Hematopathology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA.

Lung cancer evolves in a multistep process, and its early detection portends a better prognosis. Bronchial washings/brushings and fine-needle aspirations are often used as early screening and cytological diagnosis of lung cancer. In some cases, it is difficult to differentiate morphologically malignant from reactive cells. Epidermal growth factor receptor (EGFR) is a transmembrane receptor overexpressed in high percentage lung cancers, and contributes to tumor growth. Assessing EGFR expression levels by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) may provide critical information of tumor marker abnormalities, assist in the cytological diagnosis, and stratify patients for EGFR inhibitor therapy. Fifty patients with bronchial washings/brushings or fine-needle aspiration specimens, and corresponding histologically confirmed lung biopsies, were studied for EGFR expression with FISH and IHC. Copy numbers of the EGFR gene locus were analyzed with those of chromosome 7 by FISH. EGFR and FISH results were compared to our FISH data with combined EGFR, c-myc, 5p15.2, and chromosome 6 probes in selected cases. Cell blocks, if available, and tissue biopsy sections were used for

*“There are 4 special VOCs that were found to exist in all culture mediums of lung cancer cells, which are the metabolic products of lung cancer cells and can be viewed as markers of lung cancer.”*

*“Epidermal growth factor receptor (EGFR) is a transmembrane receptor overexpressed in high percentage lung cancers, and contributes to tumor growth.”*

EGFR IHC. The intensity of IHC was scored, and quantified. Only balanced aneuploidy of EGFR was identified by FISH. Gene amplification was not detected. The chromosomal abnormalities of EGFR were often accompanied by other chromosomal aneuploidies demonstrated in c-myc (8q24), 5p15.2 or 6p, indicating a general genomic instability. About half of the specimens with confirmed malignancy showed EGFR balanced aneuploidy by FISH, and gene copy number was not coupled with protein expression in many cases. The benign or reactive cytology specimens confirmed by biopsies had high specificity by FISH (96%) and IHC (88%). FISH and IHC analysis of EGFR, possibly along with other tumor markers, may be a useful ancillary tool to classify difficult cytology cases and inform clinicians arranging targeted chemotherapy. *Modern Pathology* (2007) 20, 905-913; doi:10.1038/modpathol.3800939; published online 20 July 2007.

*“FISH and IHC analysis of EGFR, possibly along with other tumor markers, may be a useful ancillary tool to classify difficult cytology cases and inform clinicians arranging targeted chemotherapy.”*

**Editorial Comment (TLP): FISH and IHC analysis of the epidermic growth factor receptor (EGFR), along with other tumor markers, may help classify and diagnose cancers identified by sputum cytology alone.**

5.  
**Lung Cancer 2007 Aug 13 (ahead of print)**

**Photodynamic therapy for lung cancers based on novel photodynamic diagnosis using talaporfin sodium (NPe6) and autofluorescence bronchoscopy.**

**Usuda J, Tsutsui H, Hondo H, et al**

Department of Thoracic Surgery, Tokyo Medical University Hospital, Tokyo 160-0023, Japan.

**BACKGROUND:** We had previously developed the possibility of use of a photodynamic diagnosis (PDD) system using a tumor-selective photosensitizer and laser irradiation for the early detection and photodynamic therapy (PDT) for centrally located early lung cancers. Recently, we established the autofluorescence diagnosis system integrated into a videoendoscope (SAFE-3000) as a very useful technique for the early diagnosis of lung cancer.

**PATIENTS AND METHODS:** Twenty-nine patients (38 lesions) with centrally located early lung cancer received PDD and PDT using the second-generation

photosensitizer, talaporfin sodium (NPe6). Just before the PDT, we defined the tumor margin accurately using the novel PDD system SAFE-3000 with NPe6 and a diode laser (408nm). **RESULTS:** Red fluorescence emitted from the tumor by excitation of the photosensitizer by the diode laser (408nm) from SAFE-3000 allowed accurate determination of the tumor margin just before the PDT. The complete remission (CR) rate following NPe6-PDT in the cases with early lung cancer was 92.1% (35/38 lesions). We also confirmed the loss of red fluorescence from the tumors immediately after the PDT using SAFE-3000. We confirmed that all the NPe6 in the tumor had been excited and photobleached by the laser irradiation (664nm) and that no additional laser irradiation was needed for curative treatment.

**CONCLUSIONS:** This novel PDD system using SAFE-3000 and NPe6 improved the quality and efficacy of PDT and avoided misjudgement of the dose of the photosensitizer or laser irradiation in PDT. PDT using NPe6 will become a standard option of treatments for centrally located early lung cancer.

**Editorial Comment (TLP): Although photodynamic therapy has been under study for over 30 years, its appropriate place in management remains to be established. Some strategy to ablate small central tumors and preserve lung function is certainly needed.**

6.  
**Prim Care Respir J 2007;16:41-48**

**COPD screening efforts in primary care: what is the yield?**

**Tinkelman DG, Price D, Nordyke RJ., et al**

Health Initiatives, National Jewish Medical and Research Center, Denver, USA.

**INTRODUCTION:** Underdiagnosis of COPD appears to be common, although the degree of underdiagnosis is rarely measured. To document the extent of underdiagnosis in a high risk group of ambulatory patients, we

*“Participants underwent pre- and post-bronchodilator spirometry.”*

*“Screening of smokers over 40 in general practice may yield 10 - 20% undiagnosed COPD cases, with a substantial proportion of these having moderate to severe disease.”*

performed spirometry in smokers aged 40 years and over drawn from general practices in two countries. METHODS: Subjects were recruited from primary care practices in Aberdeen, Scotland, and Denver, Colorado, via random mailing. Current and former smokers aged 40 or older with no prior diagnosis of chronic obstructive respiratory disease (and no respiratory medications within the past year) were enrolled. Participants underwent pre- and post-bronchodilator spirometry. A study diagnosis of COPD was defined as post-bronchodilator FEV1/FVC < 0.70. RESULTS Spirometric examination was complete in 818 patients, of whom 155 (18.9%) had a study diagnosis of COPD. Using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity criteria, the COPD was mild in 57.4%, moderate in 36.8%, and severe in 5.8%. No patients had very severe disease according to GOLD criteria. DISCUSSION: Screening of smokers over 40 in general practice may yield 10 - 20% undiagnosed COPD cases, with a substantial proportion of these having moderate to severe disease. Earlier diagnosis through targeted case-finding will allow early, aggressive smoking cessation efforts and may lead to a reduction in the burden of COPD symptoms and a reduced impact of the disease on health-related quality of life in these patients.

**Editorial Comment (TLP): Again, screening of smokers over the age of 40, by spirometry in general practice, has a very high yield of undiagnosed COPD cases and ancillary diseases such as coronary artery disease. It is a little known fact that overall mortality correlates with spirometric abnormalities—a fact that has been known for many years but rarely acted upon.**