

January 2000

Lung
Cancer

Frontiers

Comments may be submitted to:

Lung Cancer Frontiers

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Lung Cancer Frontiers is funded by The Snowdrift Pulmonary Conference through Bristol-Myers Squibb

“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.”

New Support for Lung Cancer Frontiers

As Editor in Chief of *Lung Cancer Frontiers*, I am delighted to announce an unrestricted grant made available from Bristol-Myers Squibb to support future issues of *Lung Cancer Frontiers*, (*LCF*). The Editorial Board joins me in expressing its appreciation. For the year 2000, we plan quarterly issues. In keeping with our original mission, we will focus upon new developments in lung cancer early identification and intervention, where many exciting new developments are rapidly happening. We will also provide news about new therapeutic strategies in more advanced stages of disease, whenever appropriate. It is the purpose of *LCF* to disseminate new information primarily to pulmonologists and other specialists who need to become involved in lung cancer identification and treatment. Historically, nihilism has permeated the field of lung cancer diagnosis and treatment. This must be replaced by enlightenment, made possible through new knowledge and technological developments.

We will send copies of the first five issues of *LCF* upon request, as long as our supply lasts.

Editorial Board News

Stephen Lam has agreed to serve as Deputy Editor of *LCF*. We welcome his increased involvement in this publication. Steve has been a leader in promoting techniques of early identification, most notably, the application of fluorescent endoscopy, to diagnose early intraepithe-

lial lesions. We hope that all who read *LCF* will benefit from an expanding body of knowledge and technology that could help us change the outcome of lung cancer. The future promises more tools that will ultimately lead to the solution of the most common fatal malignancy of men and women not only in the United States, but around the world.

We welcome two new members to the *LCF* Editorial Board. Dr. James R. Mault, is Assistant Professor of Cardiothoracic Surgery at the University of Colorado Health Sciences Center, in Denver. Jim's main interest is treatment of lung cancer in all stages, with emphasis in early identification and intervention. Jim is an extremely enthusiastic young thoracic surgeon who is representative of a new group of thoracic surgeons who will develop new surgical approaches to treat lung cancer.

Dr. M. Patricia Rivera is Assistant Professor of Medicine at the University of North Carolina in Chapel Hill. She is Co-director of the Multidisciplinary Thoracic Oncology Program at her institution and is Co-director of the Pulmonary Fellowship Training Program. She represents a growing group of pulmonologists who are taking a comprehensive approach to lung cancer identification, staging, and treatment.

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**Geno Saccomanno, Ph.D., M.D.
(1915–1999)**



This issue of *Lung Cancer Frontiers* honors the memory of Geno Saccomanno, the pioneer who developed the current method of sputum cytology, which is used around the world. Geno was truly a renaissance man. Following training at St. Louis University, he returned to the Rockies to join the staff of St. Mary's Hospital in Grand Junction, Colorado in 1948. This city is near his childhood home of Moab, Utah. In the early 1950's, until the time of his death on July 10, 1999, Geno was the prime mover in the development and promotion of sputum cytology. He knew that someday his technique would be valuable in the early identification and treatment of occult central lung cancers. Geno's contributions, along with new imaging techniques, including rapid low-dose CT scanning, discussed elsewhere in this issue, offer an effective strategy in lung cancer screening. New endoscopic techniques, also provide new tools to find and treat most central lung cancers in their earliest and most treatable stages. The Editorial Board dedicates all four issues of *LCF* in 2000 to the spirit of Geno Saccomanno. He will be missed, but always remembered, not only for his

enormous contributions to medicine, but for his humanism and contributions to the Grand Junction community.

The first two contributions to this issue of *LCF* were written especially for this issue. The other citations concentrate mightily to the armamentarium we are amassing to be able to identify and treat early stages of lung cancer.

Lung Cancer Identification Based on Molecular Markers

James L. Mulshine, M.D., National Cancer Institute, National Institutes of Health, Melvyn S. Tockman, Ph.D., M.D. H. Lee Moffitt Cancer Center and Research Institute

Despite Dr. Geno Saccomanno's many decades of important and pioneering work, over the last several years he related a mild sense of chagrin. He sensed that the tools to finally bring lung cancer back under control were coming into focus and he regretted that he was not going to play a role in the resolution of the greatest scourge of the 20th century. Despite grave medical problems, Dr. Saccomanno was still in the chase for his great white whale. Immediately prior to his death, he was developing a clinical trial to evaluate a new technique for sputum induction. His energy, dedication, and decency were a joy to all that had the privilege to work with him.

In considering the future of molecular detection of lung cancer, it is useful to reflect on how Dr. Saccomanno approached early lung cancer detection. He had a pragmatic approach to the problem that was tempered by the reality of clinical practice. The fixation fluid that bears Dr. Saccomanno's name was developed because of the practical need to standardize the conditions for evaluating nuclear detail of the bronchial epithelial cells recovered in the sputum. The appearance of the nucleus was particu-

larly useful in Dr. Saccomanno's mind because it revealed the position of the cell along the progressive transformation from squamous maturation toward squamous neoplasia. In the process of carcinogenesis, the normal regulation of cell cycle control is perturbed and for squamous cancer, this dysregulation is most reliably reflected in the nuclear detail. Routine clinical identification of early lung cancer in high risk populations depends upon the consistent identification of discriminating signals to allow for reliable case detection. The complexity of cytopathology detection of cancer becomes evident as computerized image analysis has been applied to cervical cancer screening. Of the many companies that attempted to provide this service, only a few still exist. As the experience with automated cellular detection of cervical cancer matures, the prescience of Saccomanno's approach to cytomorphological detection becomes evident.

As we move to molecular-based detection of early lung cancer, the same principles apply. Fastidiousness in defining the specimen preservation and handling techniques is essential. Defining conditions to ensure optimal preservation of the informative signals is the challenge. From a conceptual level, molecular detection techniques still involve an element of cytomorphological discrimination. As Saccomanno and co-workers so clearly demonstrated, in the airway of a chronic smoker, there are numerous scattered foci of injured cells. The ones with the most advanced cytomorphological changes are typically from areas of dysplastic squamous growth. We think about such cells as being part of an evolving cancer clone. With molecular approaches we still want to find those evolving cancer clones, but we want to cast the net more broadly so we find more than just early squamous cancers. The goal with image analysis is to find all of the cells in the sputum that could be members of clonal populations of bronchial epithelial cells. Undifferentiated, metabolically active bronchial epithelial cells have been recognized in

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the sputum by early cytopathologists such as Doctors Geno Saccomanno and John Frost, but many of these cells are from individuals that will have a benign course. The co-incidence of these cells in the sputum which also display large amounts of the molecule, heterogeneous nuclear ribonucleoprotein A2/B1 are the cases that we have consistently found to go on to lung cancer. We think that hnRNP A2/B1 is a molecular beacon in that setting. We have previously published that in other settings. The over-expression of the molecule is not diagnostic for cancer but rather this molecule may play an important role in lung development. For example, since this molecule is also widely expressed in inflammatory cells, we must first use morphology to identify bronchial epithelial cells. We anticipate that this approach of analyzing molecular expression in clonal populations of epithelial cells will be essential for other markers that would indicate the emergence of a bronchial epithelial cancer. In the face of intense cost pressure for diagnostics, the logical path combines economical, automated analyses of sputum morphology with molecular detection. We have started with one of the successful, automated cervical cancer screening systems. This platform could be modified to add molecular analysis of the sputum cells. This essential describes a development process that we have engaged in with Bayer Diagnostics and TriPath to enable high throughput cell-based early lung cancer detection. To be successful, such a system will have to automate the critical steps that Saccomanno outlined forty years ago. As this process proceeds, continued attention to practical detail will also be essential, so even with sophisticated, high speed, image processing platforms we will remain Geno's students.

Suggested Readings

1. Tockman MS, Mulshine JL, et al. LCEWDG Investigators, YTC Investigators. Prospective detection of preclinical lung cancer: Results from two

studies of heterogeneous nuclear ribonucleoprotein A2/B1 overexpression. *Clin Cancer Res* 1997;3:2,237-2,246.

2. Tockman MS, et al. Sensitive and specific monoclonal antibody recognition of human lung cancer antigen on preserved sputum cells: A new approach to early lung cancer detection. *J Clin Oncol* 1988;6:1,685-1,693.

3. Fielding P, et al. Heterogeneous nuclear ribonucleoprotein A2/B1 up-regulation in bronchial lavage specimens. A clinical marker of early lung cancer detection. *Clin Cancer Res* 1999;5:4,048-4,052.

Current Status of Fluorescence Bronchoscopy and the Future of Optics in Localisation and Intervention of Early Lung Cancer

Stephen Lam, M.D., FRCPC
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In 1990, fluorescence bronchoscopy using tissue autofluorescence without the use of exogenous fluorescence drugs such as porphyrin compounds was developed at the British Columbia Cancer Agency to enhance the ability of endoscopists to visualize and biopsy pre-invasive and micro-invasive cancers (*IEEE Eng Med Biol* 1990;1291:1,142-1,143). Fluorescence bronchoscopy makes use of the absorption and fluorescence properties of chromophores in bronchial tissues to provide information on the biochemical and functional changes in the bronchial tissues. Upon illumination by violet or blue light (400 nm to 450 nm), normal tissues fluoresce strongly in the green (500 nm to 520 nm). As the bronchial epithelium changes from normal, to dysplasia, to carcinoma *in situ*, and then to invasive cancer, there is a progressive decrease in the fluorescence

intensity especially in the green region, with comparatively less reduction in the red. This reduction in fluorescence intensity is due to a decrease in the concentration of short lifetime chromophores such as reduced or protein-bound flavins, increase in the epithelial thickness that impedes the emission of the fluorescent light to the bronchial surface and an increase in blood volume due to angiogenesis in pre-malignant and malignant tissues.

The differences in fluorescence between normal and abnormal tissues are very subtle. In the current FDA-approved fluorescence imaging device (LIFE-Lung System, Xillix Technologies Corporation; Richmond, British Columbia, Canada), two image-intensified cameras are used to amplify the red and green fluorescence intensity differences between normal and abnormal tissues. Other devices, such as the D-Light/AF system (Karl Storz, Tuttlingen, Germany) and the SAFE-1000 (Pentax, Japan) are currently under clinical trials. In the D-Light/AF system, a non-image intensified color CCD camera is used. However, to record the weak fluorescence, the exposure time has to be increased to 1/8 to 1/15 second instead of the conventional video rate of 1/60 second to collect enough light for visualization. In addition, a small amount of reflected blue is used to increase the brightness of the image (*Diagn Ther Endosc* 1999;5:71-75). As a result, time-delay and movement artifacts may occur unless the endoscopist has steady hands and inserts the bronchoscope smoothly. Bronchial secretions may have a bluish hue from the reflected blue light. The advantage of the system in terms of instrumentation is its compact size and the high quality of the fiberoptic bronchoscope that is specially adapted for fluorescence examination. The SAFE-1000 system is consisted of a single image-intensified camera (*Diagn Ther Endosc* 1999;5:91-98). The design is similar to an earlier version of the LIFE-Lung System (Palcic B et al. *Chest* 1991;99:742-743), except a non-laser

light source is used.

Published data on the use of the LIFE-Lung device in over 1,400 patients worldwide showed that white light bronchoscopy alone localized 40% of the pre-invasive lesions with a range of 27% to 51% in different countries. The addition of fluorescence examination increased the detection rate by an average of two-fold (range 71% to 88%) (*Diagn Ther Endosc* 1994;1:75-78; 1997;3:197-201; 1999;5:77-84; 1999;5:85-90; Lam S et al. *Chest* 1998;113:696-702; Kurie JM et al. *J Natl Cancer Inst* 1998;90:991-995; Khanavkar B et al. *Pneumologie* 1998;52:71-76; *Atemw Lungenkrkh* 1997; 23:211-217; Vermylen P *Eur Resp J* 1997;10:425S; *J Bronchology* 1997;4:205-208; 1998;5:280-283).

There is a learning curve to achieve optimal results. Most bronchoscopists are familiar with the changes associated with invasive cancer but have little experience in recognizing the subtle changes of small, pre-invasive cancer. For example, in the North American multi-center clinical trial (Lam S et al. *Chest* 1998;113:696-702), the number of pre-invasive lesions identified in part one of the study to become familiar with the changes associated with these lesions was much lower than that in the actual clinical trial that followed (0.14 lesions per subject in Part I versus 0.59 per subject in Part II). The ability to perform a careful examination without traumatizing the bronchial mucosa is extremely important in performing fluorescence bronchoscopy, because trauma would result in a dark image due to absorption of the blue light by blood. Minor degrees of trauma such as from strong suctioning can create changes that mimic abnormal fluorescence. Optimal results also require pathologists who are experienced in the diagnosis of pre-invasive lesions. These factors may explain some of the discrepancy in the literature from studies involving very small number of patients (Lam S, Palcic B *J Natl Cancer Inst* 1999;91:561-562). (*continued*)

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With the development of early detection methods using sputum cells that are more sensitive than conventional sputum cytology, examination such as computer-assisted image analysis of exfoliated sputum cells (Payne PW et al. *Mayo Clinic Proc* 1997;72:697-704), immunostaining of transformed epithelial cells (Tockman MS et al. *Clin Cancer Res* 1997;3:2,237-2,246) and PCR-based assays to detect oncogene mutations (Mao L et al. *Cancer Res* 1994;54:1,634-1,637), the size of pre-invasive lesions discovered by these screening tests will likely be smaller. The role of fluorescence bronchoscopy to localize these lesions will become even more important.

Although there is great excitement in the prospect of using low-dose spiral CT in the detection of early, curable lung cancer in the peripheral airways not accessible by the conventional fiberoptic bronchoscope, the specificity of spiral CT is low (Sone S et al. *Lancet* 1998;351:1,242-1,245; Henschke CI et al. *Lancet* 1999;354:99-105; Kaneko M et al. *Radiology* 1996;201:798-802; *Eur Radiol* 1997;S143). Depending on the geographic region, non-malignant lung nodules can be found in 20% to 40% of the high risk subjects that are screened by spiral CT. Less than 3% were ultimately confirmed to have lung cancer. Instead of performing serial CT scans or a chest x-ray every few months or performing invasive diagnostic procedures to delineate the etiology of these lung nodules, optical diagnostic methods may provide a better alternative to localize and to determine the nature of these nodules. Optical probes can be made much smaller than the conventional fiberoptic bronchoscope. Optical methods offer the possibility of real time, high resolution imaging of the morphological and/or biochemical changes associated with these lesions. For example, Optical Coherence Tomography (Tearney GJ *Science* 1997;276:2,037-2039; Optics Express 1998;3:219-229) can provide in-depth information. Elastic scattering (Mourant JR et al. *Lasers Surg Med*

1995;17:350-357), may be able to determine the pathology of the lesion *in vivo* by measuring the nuclear size and density. Raman spectroscopy can be used to probe the biochemical composition of molecules in cells such as lipids, proteins, and nucleic acids (*J Biomedical Optics* 1996;1:31-70) to fingerprint lesions. These techniques are still in the developmental stage. Hopefully, they will be available for clinical use in a few years.

The importance of finding stage 0 lung cancer is that a number of curative endobronchial treatment modalities are now available in addition to surgery. The 5-year survival for stage 0 lung cancer after photodynamic therapy (Furuse K et al. *J Clin Oncol* 1993;11:1,852-1,857) electrocautery (van Boxem TJ *Eur Resp J* 1998;11:169-172) or YAG laser therapy (*J Bronchology* 1994;1:105-111) or surgery is > 90% (Cortese DA et al. *J Thorac Cardiovasc Surg* 1983;86:373-380). Stage IA lung cancer also has a very favorable 5-year survival of > 80% after surgical resection.

The development of optical imaging methods to localize the source of the abnormal cells found in examination of sputum specimens or to determine the nature of small lung nodules on spiral CT is an integral part of the diagnostic armamentarium in the overall management of early lung cancer.

Early Lung Cancer Action Project

The study design and findings of the Early Lung Cancer Action Project, (ELCAP), published recently in *Lancet* (Henschke CI et al. *Lancet* 1999;354:99-105) received tremendous notoriety in both the medical and lay press. In brief, ELCAP enrolled 1,000 symptom-free volunteers who were 60 years or older and who had smoked at least 10 pack-years, and who had no previous evidence of cancer. Subjects were excluded if they were “not medically fit to undergo thoracic surgery.” Low-dose computer tomography, (CT), scanning for

“With the development of early detection methods using sputum cells that are more sensitive than conventional sputum cytology, examination such as computer-assisted image analysis of exfoliated sputum cells... the size of pre-invasive lesions discovered by these screening tests will likely be smaller.”

non-calcified nodules revealed 233 (23%) compared with only 68 (7%) with standard chest x-rays. Malignant disease was detected in 27 (2.7%) by CT, but only 7 (0.7%) by ordinary chest x-rays. Stage I disease was found in 23 of 27 patients. Of these 27 patients, 26 were resectable for apparent cure. No participant had a thoracotomy for a benign nodule. The key to the success of this screening by CT scanning, according to the protocol was, recommended follow-up by high resolution CT three months later. There had been no growth of the high resolution CT scans at six, 12, and 24 months. If no growth was noted over two years, the nodule was classified as benign, for lesions 5.0 mm or less.

For lesions 6.0 mm to 10.0 mm, the protocol recommended assessment on an individual basis with the possibility of percutaneous transthoracic CT-guided fine needle biopsy or video-assisted thorascopic procedures. In patients where a biopsy was not possible, follow-up at intervals described above, was recommended. For lesions 11.0 mm or more in size, the protocol recommended a biopsy according to current standards of care by fine needle aspiration video-assisted thoracostomy, bronchoscopy, or a combination. Lesions that increased in size were the ones that were resected. Amazingly, all were early stage adenocarcinomas. In this study, malignant disease was detected four times more frequently on low-dose CT scanning than by standard chest roentgenology. Of the 27 malignant nodules, 22 were stage IA, one stage IB, one stage IIA, two stage IIIA, and one stage IIIB. Thus, all but one were potentially resectable for cure.

In discussion, the authors emphasize that the cost of low-dose CT scanning is only slightly higher than standard chest roentgenology. Once low-dose CT screening becomes commonplace, and the volume of tests increase, the unit cost may decrease further.

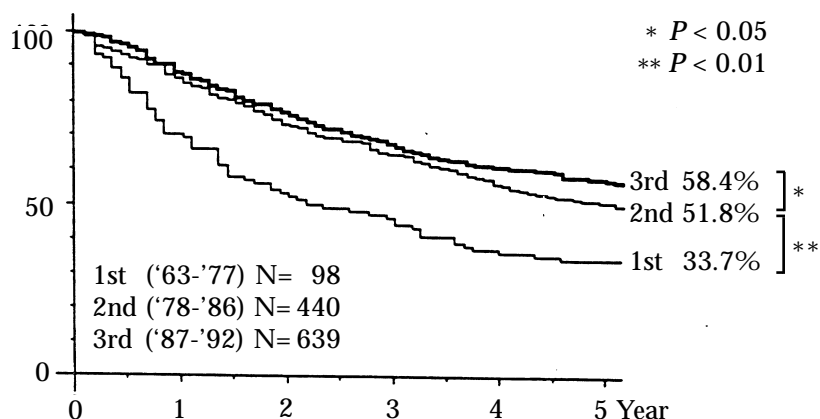
Comment: These and other studies of the efficacy of high resolution rapid low intensity CT scanning are convincing that this is the best way to detect peripheral malignant nodules, most of which are adenocarcinoma. This approach may not be suitable for small central lesions, which are best detected by sputum cytology and bronchoscopy. A recent comparison of fluorescent endoscopy with white light endoscopy, indicates a superiority of fluorescent endoscopy with small lesions of approximately 3.0 mm in size (Lam S et al. *Chest* 1998;113:696-702).

The Impact of Lung Cancer Screening in Japan

The influence of lung cancer mass screening on surgical results was reported by Kioke et al., from Japan (Kioke T et al. *Lung Cancer* 1999;24:75-80). This study evaluated the effectiveness of lung cancer screening on survival. A total of 177 primary lung cancer patients who underwent surgery from 1963 to 1992 were retrospectively reviewed. They were grouped according to the changes in the mass screening system from the first

Figure 1
Postoperative 5-year survival rate. The 5-year survival improved significantly, from 33.7% in the first period to 51.8% in the second and then, 58.4% in the third. Differences between groups: first versus second period, $P < 0.01$; second versus third period, $P < 0.05$.

Figure 1 Percent of Survival



period when screening was mostly done for tuberculosis (1963 to 1977). This was before lung cancer screening was initiated in the second period (1978 to 1986), in this study supported by the local government. Finally, in the third period screening after 1987, after the launching of the national screening program was studied, the rate of cases detected by mass screening over time and the 5-year survival rate improved markedly. Survival was 33.7% in the first period, 51.8% in the second period, and 58.4% in the third period. This improvement in the survival is due to the increase in stage I cases. The increase in the number of patients with stage IA peripheral-type lesions and roentgenographically occult lung cancer by standard roentgenology, is remarkable. The survival of the three periods is presented in Figure 1 on page 7.

Comment: There seems to be no doubt that mass screening to identify early stage disease results in improved survival. With these data in hand, a randomized prospective clinical trial to compare the outcome of smokers at high risk of lung cancer who were screened compared to smokers at equal risk who were not screened, would probably not be necessary. In fact, it would probably be unethical. Mass screening for lung cancer is now the standard of care in Japan where a mobile spiral computed scanner is used in rural areas (Sone S et al. *Lancet* 1998; 351:1,242-1,245).

Both airway cell markers of malignancy and imaging for peripheral lesions are necessary in the detection of early stages of lung cancer.

Screening for Lung Cancer with Low-dose Spiral CT Scan of the Chest and Sputum Cytology

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In 1999, there will be approximately 170,000 new cases of lung cancer in the United States. The overall 5-year survival is 14% (Landis SH et al. *CA Cancer J Clin* 1999;49:8-31). Lung cancer alone accounts for more cancer deaths than the next three most common cancer causes of death combined (Table 1). Currently, 45% of all lung cancers occur in women, and more women die of lung cancer than breast cancer in America.

What is striking from Table 1 is the disparity of the 5-years survival for lung cancer compared to the other most common cancer causes of death. Of these four most common cancer killers, lung cancer is the only one for which screening is not recommended. We know that symptomatic lung cancer is usually an advanced cancer, stage IIIA/B or IV and associated with a 5-year survival of 10% or less. According to recent data from the SEER (National Cancer Institute's Surveillance Epidemiology and End Result Program), only 15% of lung cancers are localized at the time of diagnosis.

Why then is screening for lung cancer not recommended? Past screening trials with chest radiographs and sputum cytology conducted at Mayo Clinic, Johns Hopkins and Memorial Sloan Kettering Cancer Center were unable to demonstrate a decrease in lung cancer mortality in the screened population. These NCI-sponsored studies were conducted in the 1970's and are now 20 years old (Fontana RS et al. *J Occup Med* 1986;28:746-750; Melamed MR et al. *Chest* 1984;86:44-53; Tockman MS *Chest* 1986;89:324S-325S).

“What is striking from Table 1 is the disparity of the 5-years survival for lung cancer compared to the other most common cancer causes of death.”

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Research in the last 20 years has revealed a great deal about the biology of lung cancer, and along with technologic advances, has led to the development of a number of promising new tools that may lead to effective screening. The most promising of the new tools is the spiral CT chest scanner. Several recent reports have documented the ability of low-dose spiral CT scans to detect lung cancer at an early stage. Trials have been conducted in Japan, Germany and the United States.

Two different groups of Japanese investigators screened male smokers > 50 years (Kaneko M et al. *Radiology* 1996;201:798-802; Sone S et al. *Lancet* 1998;351:1,242-1,245). The first group reported 15 lung cancers detected by spiral CT, and only 4 of those were visible by chest radiograph. Most promising was the fact that 14 of 15 cancers were stage I and had an average tumor diameter of 1.6 cm (Kaneko M et al. *Radiology* 1996;201:798-802). The second group found similar results, reporting 80% of detected lung cancer in stage I (Sone S et al. *Lancet* 1998;351:1,242-1,245).

At the 1999 American Society of Clinical Oncology meeting, the first of these groups updated their results (Ohmatsu H *Proc Am Soc Clin Oncol* 1999;18:463A). With a total of 9,452 low-dose spiral CT chest examinations, they have detected 35 primary lung cancers (0.37% detection rate). Of these, 27 were stage IA, and the mean tumor diameter was 15 mm. Their 3-year survival was 83%. At the 1999 American Thoracic Society meeting, Henschke and associates reported the results of their 1,000 subject spiral CT screening trial from New York (Henschke CI et al. *Am J Respir Crit Care Med* 1999;159:A60). They detected non-calcified nodules in 24% (n=240), and 22 of these individuals were subsequently proven to have lung cancer. Only 5 of the 22 cancers were visible on standard chest radiograph. To date, none of their participants have had a thoracotomy for benign disease, but five individuals underwent percutaneous or video-assisted thoracoscopic biopsy for benign disease.

In clinical practice today, only 20% to 25% of all new lung cancers are diag-

“The potential to detect 80% of lung cancers in stage I (while few are detectable by standard chest radiograph) could very well lead to a reduction in lung cancer mortality”

Table 1 Three Most Common Cancer Causes of Death¹

Primary Site of Cancer	No. of New Cases (Estimated 1999)	No. of New Deaths (Estimated 1999)	5-Year Survival (1989–1994)
Lung	171,600	158,900	14%
Colorectal	129,400	56,600	63%
Breast	176,300	43,700	85%
Prostate	179,300	37,000	93 %

¹ Data from American Cancer Society (Landis SH et al. *CA Cancer J Clin* 1999;49:12-13).

“In addition to standard sputum cytology, investigators are evaluating sputum, bronchoalveolar lavage fluid, and bronchial biopsy specimens for DNA biomarkers indicative of premalignant changes in an effort to identify individuals at very high risk for developing lung cancer.”

nosed in stage I/II. The NCI screening trials used chest radiographs and sputum cytology as screening tools and detected 40% to 50% of lung cancers as stage I. The potential to detect 80% of lung cancers in stage I (while few are detectable by standard chest radiograph) could very well lead to a reduction in lung cancer mortality (Mountain CF *Chest* 1997;111:1,710-1,717). Screening with spiral CT scan is by far the most exciting and promising new tool in several decades for early lung cancer detection.

In the NCI screening trials, sputum cytology detected 25% of all lung cancers and was the only means of detection in 15% of cases. Recently, physicians from the University of Colorado obtained screening sputum cytology results in smokers with mild or greater degrees of obstructive lung disease and identified carcinoma cells or severe dysplasia in 2.5% of screened subjects (Kennedy TC et al. *Cancer Res* 1996;56:4,673-4,678). Another 25% had moderate dysplasia of the sputum, which is believed to be a precursor of lung cancer. Patients with moderate dysplasia were further evaluated with standard white light bronchoscopy and the new autofluorescent bronchoscope (LIFE-Lung System; Xillix Technologies Corporation; Richmond, British Columbia, Canada) capable of detecting dysplasia and carcinoma *in situ* that may not be visible with standard bronchoscopy. The autofluorescent bronchoscope is another new tool that may have a role in screening trials when the sputum cytology shows moderate or severe dysplasia (Lam S et al. *Chest* 1998;113:696-702).

In addition to standard sputum cytology, investigators are evaluating sputum, bronchoalveolar lavage fluid, and bronchial biopsy specimens for DNA biomarkers indicative of premalignant changes in an effort to identify individuals at very high risk for developing lung cancer (Belinsky SA et al. *Proc Natl Acad Sci* 1998;95:11,891-11,896; Sozzi G et al. *Cancer Res* 1998;58:5,032-5,037; Ahrendt SA et al. *J Natl Cancer Inst*

1999;91:332-339; Wistuba II et al. *J Natl Cancer Inst* 1997;89:1,366-1,373). While there are no sputum tests other than cytology that are clinically proven and commercially available for detection of early lung cancer, the monoclonal antibody test against heterogeneous nuclear ribonucleoprotein on sputum cells shows great promise. In a preliminary report of patients with previously resected stage I lung cancer, this sputum test demonstrated a sensitivity of 77% and specificity of 82% for detection of a second primary lung cancer (Tockman MS et al. *Clin Cancer Res* 1997;3:2,237-2,246). The positive predictive value was 67% (10 of 15). This trial and others are ongoing, but it is likely to be at least a few years before this test is commercially available.

In January, 1999, Mayo Clinic physicians launched a lung cancer screening trial that is being supported by a grant from the NCI. Eligibility criteria for the study are as follows: 50 years of age or greater; current or former smoker (quit < 10 years ago) of 20 pack-years or more; not on supplemental oxygen; life expectancy of 5-years; and no prior cancer within the last 5 years (except skin, localized prostate cancer, or cervical carcinoma *in situ*). The enrollment target of 1,500 individuals has been reached. All patients will have a low-dose fast spiral CT scan of the chest performed at the time of enrollment and yearly for 3 years and a sputum cytology performed on a yearly basis. All study tests will be performed free of charge to the patient. The dose of radiation associated with the low-dose spiral CT scan is equivalent to or less than that associated with mammography. The goal of the study during the incidence screen (after the baseline scan) is to determine if we can detect 75% or more lung cancers while they are stage I and likely to be associated with excellent long-term survival.

(Henschke CI et al. *Am J Respir Crit Care Med* 1999;159:A60).

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A Breath Test for Lung Cancer?

A number of volatile organic compounds, (VOCs), which are mainly alkanes and benzene derivatives have been identified in the exhaled air from patients with lung cancer. In a study of 108 patients who had abnormal chest radiographs and who were scheduled for bronchoscopy, samples were collected with a portable apparatus and assayed by gas chromatography or mass spectroscopy. Lung cancer was confirmed in 60 patients. A combination of 22 breath VOCs, predominantly alkanes, alkane derivatives, and benzene derivatives, discriminated between patients with and without lung cancer, regardless of stage (all $p < 0.0003$), for stage 1 lung cancer. The 22 VOCs had 100% sensitivity and 81% specificity. This study suggests that prospective studies are needed to confirm the usefulness of breath VOCs in detecting lung cancer in the general population.

Comment: This test might be most useful in high risk populations who have smoked 30 or more pack-years in the presence of airflow obstruction. It would be interesting to compare the yield of breath testing with sputum cytology.

Adapted from: Phillips M, et al. Volatile organic compounds in breath as markers of lung cancer: A cross-sectional study. *Lancet* 1999;353:1,930-1,933.

The Bronchoscope in Historical Perspective

John A. Nakhosteen, member of the Editorial Board of *LCF*, and a renowned bronchologist who teaches, does research, and practices in Bochum, Germany, offers the following historical vignette on the beginnings of bronchoscopy and the landmark development of Ikeda's fiberoptic bronchoscope, which has transformed modern bronchology. The fiberoptic bronchoscope has provided a major new tool, not

only for the surgeon and the otolaryngologist, but most notably, the pulmonologist. Lam's, (Deputy Editor of *Frontiers*), development of the light intensified fluorescent endoscope, (LIFE), is discussed in further detail in the contribution he makes to this issue of *LCF*.

Historical Vignette

In his paper "On Direct Bronchoscopy" at the sixth meeting of the South German Society of Laryngologists on May 29, 1898, Gustav Killian described the extraction of tracheobronchial foreign bodies from three patients using a modified esophagoscope in topical cocaine anesthesia. Others had previously inspected the trachea through a rigid tube, but, as Kirstein had noted in 1894, manipulation may have perforated the trachea where aortic pulsation could be seen, causing fulminating hemorrhage. However, Killian knew of work done by another investigator, Pieniasek, who had done direct lower tracheoscopy through a tracheostoma without complications. He spent the period between 1887 and 1894 intensively studying direct visualization of the tracheobronchial tree.

First, he introduced bronchoscopes through tracheostomas, noticing that both trachea and bronchi were pliable and elastic; only the diameter of the bronchus limited deeper advancement of the instrument. Concurrently, he intubated many cadavers orotracheally. Once he felt confident enough, he performed bronchoscopies on a janitor working at Freiburg University, who readily volunteered for repeat bronchoscopies in return for some pocket money (and, perhaps with time, the cocaine anesthesia). Then, on March 31, 1897, came the dramatic case, the first of the three presented the year after, of the Black Forest farmer who had aspirated a bone fragment - and rigid bronchoscopy was born! (*continued*)

"Ikeda's dream of improved diagnosis of early lung cancer with the flexible instrument could not be fulfilled, however, until this instrument could be combined with more sensitive imaging techniques."

Killian's emulators included Chevallier Jackson Sr., Chevallier Jackson, Jr., Lundy, Foregger, and Gillespie, who all contributed to the development of the rigid bronchoscope. But the fundamental device conceived by Killian remained unchanged until Ikeda developed the fiberoptic bronchoscope in 1964. Ikeda's dream of improved diagnosis of early lung cancer with the flexible instrument

could not be fulfilled, however, until this instrument could be combined with more sensitive imaging techniques. Perhaps, with innovations such as Lam's autofluorescent bronchoscope, we are now at the threshold of reaching this elusive goal of early lung cancer detection approximately one-hundred years after Killian's discovery of open tube bronchoscopy!

Lung Cancer

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January 2000

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