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Lung
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“The purpose of *Lung Cancer Frontiers* is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.”

Selected Highlights of the 12th World Congress for Bronchology and 12th World Congress for Bronchoesophagology— Boston, Massachusetts, June 16-19, 2002

The 12th World Congress for Bronchology was opened by President John Beamis (Burlington, MA). This was a joint meeting with the 12th World Congress for Bronchoesophagology. This was welcomed by Hirokuni Yoshimura (Yokohama).

In a Combined Symposium on Early Detection of Lung and Head and Neck Cancer, Barbara Khanavkar (Bochum) presented two papers on behalf of John Nakosteen and co-investigators involved in the RIDTELC early lung cancer identification project. The studies represent seven years of experience with both LIFE bronchoscopy and the Cyto-Savant® automated sputum cytology analyser (see *Lung Cancer Frontiers* No. 12; April 2002, for the initial report from the RIDTELC project). A preliminary report was made on the study that aims to randomly enroll 6000 heavy smokers into a program. Thus far 2547 subjects have been enrolled in the three-year study. All the participants received a digital chest x-ray at entry. Seventeen cancers were detected. The lung cancer prevalence was 0.67%. Those who were cancer-free on chest x-ray were randomized to an active screening group with annual sputum cytology examination or a control group where sputum specimens were collected but will be analyzed retrospectively. Of the first 1107 patients enrolled in the active study group, 89 had high grade atypia or cancer in their sputum—86 of which were detected by cytometry. Sixty-three received bronchoscopy and five cancers were found (7.9%). No cancers were detected in sputum negative patients. Thus

far it can be concluded that recruitment is difficult. Twenty-six percent failed to show up in the initial appointment. Twenty-nine percent refused bronchoscopy and 30% did not return for their annual monitoring.

Harabumi Kato (Tokyo) reported on the Japanese program for early lung cancer diagnosis. Since 1987 annual lung cancer screening has been offered by the Health Insurance of the Association of the Elderly in Japan. Anyone over age 40 can have an annual chest x-ray. At age 50, both annual CT and sputum cytology screening is the standard of care. A 0.8% rate of identification is currently found in Japan. Newer techniques of sputum identification, including malignancy associated changes (MAC) (see Ikeda below) is routinely used along with spiral CT. The group is also experimenting with the use of Optical Coherence Tomography in collaboration with Pentax to determine the depth of tumor infiltration. Photodynamic therapy has become the standard treatment for early hilar lesions that are almost always squamous cell carcinomas. Brachytherapy is used for larger, more invasive tumors in the central bronchi.

Norihiko Ikeda (Tokyo) reported on malignant associated changes (MAC) as tumor bio-markers. MAC is emerging to a practical diagnostic tool. R. Kim Davis (Salt Lake) also reported upon tumor markers in the context of evaluation of the pathology of cancers of the head and neck. The H&E staining of biopsy materials is still the gold standard. Emerging technologies include identification of

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cytokeratins, the p53 mutation which has an inconstant relationship with tumor biology and outcome, and HER2 receptors.

Annette McWilliams (Canada) reported the results of lung cancer screening from the British Columbia Cancer Agency. Using image analysis of sputum cells obtained by high frequency chest wall oscillation and quantitative cytology with the Cyto-Savant® device, 423 heavy smokers above 50 years of age with sputum atypia underwent spiral CT and LIFE-Lung bronchoscopy. Thirteen cases of lung cancer (3%) were found—9 by CT and 4 by LIFE-Lung bronchoscopy. Eighty-six percent of the cancers were Stage 0/I. In a concurrent cohort of 138 smokers without sputum atypia by image analysis, no cancer or high grade dysplasia were found by CT or bronchoscopy. The BCCA group concluded that image analysis should be considered as the first screening step. It would reduce the number of spiral CT's and unnecessary follow-ups for false-positive lung nodules.

Stanley Shapshay (Boston) discussed the potential of optical biopsies in trimoidal spectroscopy as a painless, non-invasive approach to evaluate clinically suspicious lesions in the upper airway.

Editorial (TLP) Comment:

It is obvious that emerging technologies will improve our ability to identify early cancer and pre-cancers in the aerodigestive tract, but with emphasis on lung cancer. Although there are 8,000 head and neck cancer deaths per year and many are painful and disfiguring, there are 155,000 lung cancer deaths. It is certain that the key to improving lung cancer mortality is early identification and intervention.

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“The overuse of bronchoscopy for therapeutic purposes, such as removal of mucus plugs or simply for cough was criticized.”

“Photodynamic therapy is still not widely accepted in the United States, but is well established elsewhere, most notably regions of Japan...”

Udaya Prakash (Rochester, Minnesota) reviewed the techniques of flexible fiberoptic bronchoscopy, citing evolving techniques and honoring the pioneering work of the late Shigeto Ikeda (1925-2001). He reviewed two surveys he had completed in 1989 and 1999 respectively, published in *Chest*, 1991;100:1668-1675 and *J Bronchology* 2000;7:1-3. Each survey identified prerequisite tests that were deemed necessary before fiberoptic bronchoscopy in those two surveys done a decade apart. The least chosen test was spirometry and the most common were chest x-rays, coagulation studies, complete blood tests and EKG. Prakash concluded that coagulation tests and EKG were not necessary prerequisites for bronchoscopy, nor was spirometry, because virtually any patient with any degree of airflow obstruction can, when needed, have diagnostic or therapeutic bronchoscopy. The presence of uremia was a risk factor for bleeding.

The overuse of bronchoscopy for therapeutic purposes, such as removal of mucus plugs or simply for cough was criticized. It was interesting that patients who were being prepared for bronchoscopy had more concerns about finding lung cancer than the procedure itself.



Thomas Sutedja, MD with John Beamis, MD

John Beamis (Burlington, MA) reviewed the evolution of therapeutic bronchoscopy. The first use of bronchoscopy was the removal of foreign bodies and the management of benign airway stenosis. The CO₂ laser was introduced in the 1970s, followed by ND:YAG and other technologies designed to open up blocked bronchi, usually from tumor. A discussion of the use of stents followed. Stents provide for an extension of a comfortable life to selected patients with obstructive malignant lesions of the large central airways. The field of “interventional pulmonology” has developed in recent years. The evolving use of photodynamic therapy beginning in 1970 was also reviewed. Photodynamic therapy is still not widely accepted in the United States, but is well established elsewhere, most notably regions of Japan (Kato).

In the mini-symposium that followed “New Frontiers in Bronchology; From Gross to Microscopic to Biochemical,” Stephen Lam (Vancouver) gave a brief comprehensive introduction about the objectives in modern diagnostic bronchoscopy in identifying early stages of lung cancer. The evolution of new techniques that can probe cellular and biochemical changes in the airways and improve our understanding of the effect of pharmacological/mechanical treatment in patients with asthma, improve the accuracy of diagnosis of central and peripheral early lung cancers as well as provide a non-biopsy method to evaluate outcomes of chemoprevention were presented.

Noriaki Kurimoto (Hiroshima) reported on Endobronchial Ultrasonography (EBUS) using 20 or 30 Mhz to study the laminated structures of the bronchial wall. There are five to seven layers in the extra pulmonary bronchus and five or fewer layers in the intrapulmonary bronchi. EBUS can identify hypo or hyper echoic regions in the airway walls to identify the depth of tumor invasion and spread beyond the basement membrane. Metastatic nodes can be identified by EBUS for biopsy.

James Fujimoto (Cambridge, MA, Department of Electrical Engineering, Massachusetts Institute of Technology) reported on the evolution optical coherence tomography (OCT). This technique has its origins in ophthalmology. OCT can be used on any epithelial surface or intravascularly to evaluate the early stages of arteriosclerotic plaques. “Optical biopsies can characterize

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pre-malignant or malignant lesions. An optical biopsy is chosen when the tissue aspiration or excisional biopsy is risky, such as in the retina. OCT is also useful where there is the likelihood of a high prevalence of false negative lesion and to evaluate tissue tumor margins, extremely tiny probes capable of passage through the suction channel of the bronchoscope, as small as a 27G needle (450 microm.) can actually visualize peripheral lesions.

Mary-Ann Mycek (Hanover, NH) reported upon advances in biomedical optics to noninvasively evaluate the structure and function of bronchial tissues in real time. Identification and quantitation of intracellular fluorophores such as NADH and flavins, can be obtained from the emitted wavelengths and decay times. The technique, known as time resolved fluorescence, is employed in the diagnosis of early stage lung cancer. Use of this technique is now moving into the clinic.

Calum MacAulay (Vancouver) discussed confocal microendoscopy. Briefly, this is a miniature microscope that fits in the suction channel of a fiberoptic bronchoscope and provides microscopic images. Using the native optical properties of the tissue (differences in back scattering intensity between the cytoplasm and nuclei or tissue autofluorescence), this method allows the imaging of individual cells without staining from the tissue surface down to 150 um deep into the tissue. It is highly sensitive in identifying dysplastic patterns in the evolutionary stages of lung cancer.

Editorial (TLP) Comment:

This section gave an excellent historical review of the evolving technologies which allow the clinician to not only identify lung cancer early but also to understand the evolving tumor biology involved in the neoplastic/malignant processes. Although none of these new developments are ready for “prime time,” they are all evolving technologies that will find their place in the future. Each of these new advances, of course, has a high price tag and it remains to be seen which ones will become practical in the drive to help advance the frontier of lung cancer diagnosis, knowledge and treatment.

In a session in new technologies for analysis of bronchial samples, four international investigators lead by Michael Unger (Philadelphia) gave an overview of tumor markers of materials obtained from bronchial washings, brushes, biopsies and sputum cytology. Advances in our concepts of the processes of lung carcinogenesis are evolving. Understandings of the epithelial/stroma interaction result from both environmental stimuli and host susceptibility factors. The transition of various stages of cell dysplasia and growth control exaggerate the responses to growth stimuli and inhibitory signals, as well as the breakdown of the escape signal for apoptosis. The result is uncontrolled cell proliferation at the expense of differentiation.

Since only 10% of smokers get lung cancer, what are the susceptibility factors? The answer is not known, but there is no question that lung cancer clusters in families. There is no one specific biomarker and there are many candidates including AKT, activation EGFR receptors,



Michael Unger, MD

mutation of the p16 gene and p53. The biomarkers are KUS, CEA, neuron specific, enolase, tissue peptide antigen (TPA), CYFR21-I, and tissue peptide specific antigen TPSA. Some of these tumor markers will be indicators of positive responses to chemoprevention. Chemoprevention strategies may work with some systemic agents. The goal is to stop the progress of carcinogenesis by chemoprevention. There is great promise in understanding the proteomics involved in carcinogenesis.

Giuseppe Marciano (Sienna Italy) considered the bronchoscope the extension of the microscope. The bronchoscope is used for lavage, brush, and biopsy in the analysis of epithelial dysplastic and neoplastic changes. The polymerase chain reaction and other automated techniques can be employed to find one abnormal cell in 10,000! Although the p53 mutation is common in lung cancer, there is also lung cancer without the p53 mutation. No one marker can be equated with the emergence of lung cancer. As there are more markers for lung cancer, which increase both sensitivity and specificity, there are also more costs.

Takehito Fujisawa (Chiba, Japan) discussed the handling of biopsies, an emphasized studies focused on the interesting lesion of angiosquamous dysplasia as an important step in carcinogenesis evolution. A combination of increased telomerase levels, p53 and k-ras are progressively correlated with higher grades of dysplasia and the evolution into carcinoma *in situ* and invasive carcinoma.

Editorial (TLP) Comment:

Although there is a tremendous increase in techniques and studies that help explain the biological nature of lung cancer and new methods of practical diagnostic potential to aid the clinician, again it is true that what will emerge in terms of cost effective technology remains to be established through empiric studies and controlled clinical trials.

History of Bronchoscopy

A series of three thrilling presentations on the history of bronchoscopy opened each morning session.

Heinrich Becker (Heidelberg Germany) discussed the pioneering work of Gustav Killian, who is credited with introducing the first rigid bronchoscope. His first bronchoscopic procedure was on March 30, 1897, when he removed a piece of bone from a young man. He perfected and popularized his technique during the time he was in Freiberg Germany. He introduced bronchoscopy to the United States in 1907 at the annual meeting of the American Medical Association.

On another morning, Stern Zeifels (Boston) presented a review of highlights of the fine work of the Chevalier Jacksons in Philadelphia. The Jacksons produced new bronchoscopic designs and introduced the Jackson tracheostomy tube, which remained in use until the 1960s.

A particularly exciting review of the history of bronchology in Japan was presented by Taeko Shirakawa (Kumimoto, Japan). In her beautiful presentation, she featured the original work of Inikichi Kubo, who became known as Ino Kubo, the first bronchologist in Japan. He was a pioneer in early otolaryngology and also the originator and editor of the first journal on otolaryngology in Japan. In 1903, he went to Freiberg to study under Killian. He became Killian's "top student." In 1907 he became Professor of Otolaryngology in Fukuoka. He learned that could avoid tracheostomy for the removal of a foreign body. He removed a tack from a 14-year-old boy in 1907. Over 2000 foreign bodies were removed at Kioshi University under his tutelage. Upon his retirement, he was replaced by Professor Joe Ono, who had studied in Philadelphia and received his MD at Jefferson Medical Center. Ono had studied under Chevalier Jackson and he brought the Jackson bronchoscope to Fukuoka on his return. In that era, rigid bronchoscopy was primarily used to deal with foreign bodies and benign obstructive lesions of the trachea. By the late 40s bronchoscopy was also used in the diagnosis and treatment of tuberculosis. Ono was an enthusiastic proponent of bronchoscopy and taught, in all, 51 courses on bronchoscopy

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Taeko Shirakawa, MD and David Sanderson, MD

“Ikeda introduced a new classification of the bronchopulmonary segments, including naming the sub-segments.”

around the country. The Japanese Society of Bronchoesophagology was formed in 1949. During this period, Ono became concerned about social issues in foreign body aspiration and convinced the toy manufacturers to make safer play things. Pencil caps were required to have a hole in them to avoid suffocation, if aspirated.

The third and most monumental leader was Shigeto Ikeda, who helped Ono make a movie of a human bronchoscopy because of his interest in movie camera and 8 mm films. Both bronchoscopy and bronchography became key steps in the evaluation of tuberculosis for patients requiring surgery. Ikeda hit on the idea of using fiberoptic bundles to transmit light. After a series of seven different designs, finally the first practical fiberoptic bronchoscope was developed in 1967. Ikeda introduced his bronchoscope at the Johns Hopkins Medical School in 1968. In 1970 he came to the Mayo Clinic, during the

period of the rapid acceptance of his new technology.

Ikeda quickly applied the new technology to the diagnosis of early hilar lung cancer. He realized that it was complementary to sputum cytology. He advised chest x-rays for peripheral lesions and cytology for central lesions.

By 1993 the Anti Lung Cancer Association of Japan was promoting dual screening for lung cancer. Since that time, the survival rate of lung cancer diagnosed early elevated to 83% at five years. Ikeda introduced a new classification of the bronchopulmonary segments, including naming the sub-segments. He founded the World Association of Bronchology in 1974, as its first president. He also was instrumental in developing the video bronchoscope, which was the third revolution in bronchology. Even as he fell into poor health, Ikeda continued to accept students and teach. “Never give up,” was his motto until his death.

Bronchoscopic treatment of early cancer

(Summary by Thomas Sutedja, Amsterdam)

The majority of lung cancer patients are beyond cure due to the advanced stage when diagnosed. Surgery provides the best chance for cure if the tumor can be completely resected in the absence of lymph node and distant metastases. Even after radical resection, many remain at risk for distant metastasis, local recurrence and to develop subsequent primaries. Heavy (ex-) smokers with COPD are known to be particularly at risk to develop lung cancer. In addition, smoking related problems such as COPD and poor cardiovascular status, may limit our abilities to apply the best treatment strategies because of unacceptable morbidity and mortality. Squamous cell cancer (SCC) gradually develops from normal bronchial epithelium in a period of up to ten years and can be multifocal because of field carcinogenesis (multiple synchronous or metachronous cancer lesions). It is then prudent to look for minimally invasive techniques that can be appropriately used for early detection and treatment, to preserve quality of life in the individuals at risk.

Carcinoma *in situ* (CIS) is recognized to consist of 4–38 cell layers, while the majority of these lesions are only about 5 cell layers thick. In early SCC, 61% of the lesions had depth abnormalities of ≥ 6 cells' layer. It is obvious that these early SCC lesions are easily missed during routine bronchoscopy, even in sputum positive individuals. This may result in diagnostic delay of up to two years, which is counterproductive for the concept of stage shift to treat early stage N0 tumors. Fortunately, autofluorescence bronchoscopy (AFB LIFE-Xillix, Richmond, Canada) is shown to be 2–4 fold more accurate for the detection and accurate localization of pre-invasive lesions (80–100% range) and in finding 10% unforeseen occult synchronous lesions in patients with lung cancer primaries. All CIS ultimately progressed to SCC and should be treated promptly.

“Early stage” SCC should be assessed with regard to tumor margins and depth of tumor invasion in the bronchial wall and endobronchial ultrasonography (EBUS) has recently been used to predict the involvement of the cartilage layer. The role of PET-scan to exclude lymph node involvement has to be investigated further. The use of both AFB and HRCT can help select individuals suitable for intraluminal bronchoscopic treatment (IBT). As early hilar lung cancer is minute, superficial and intraluminal, ibt e.g. Nd-YAG laser, photodynamic therapy, cryotherapy, electrocautery and argon plasma coagulation are obviously less traumatic than surgical resection, provided nodal involvement has been ruled out. Many phase II studies have dealt with the efficacy of IBT for treating occult SCC, showing its curative potential at the 80–90% rate, which is comparable to the surgical cure rate previously published.

Ideally, phase III studies comparing surgery versus various IBT modalities will be required - (regarding epidemiological controversy about overdiagnosis and treatment of a pseudo-disease – a randomized study between treatment and no treatment). However, early stage SCC is usually detected by chance, which makes the realization of such a study difficult. Some individuals are considered poor surgical candidates (e.g. COPD, poor cardiovascular status, previously resected syn-, meta-chronous tumors). IBT is an alternative for surgery and is a parenchyma

conserving technique. Twenty-two out of 39 patients with early stage SCC were spared surgery after initial PDT treatment in the Mayo study. Any IBT modality prior to surgery should be considered to enable less extensive surgical resections.

In conclusion, minimal invasive bronchoscopic techniques can be used for early detection, accurate staging and treatment of early hilar cancers, or as an adjunct to surgical resection, to offer cure and long-term local control in the individuals at risk and in preserving quality of life. Although surgical resection is the standard treatment for early lung cancer, it has a significant morbidity and mortality. Resectional surgery is wasteful of functioning lung tissue in early hilar SCC. Bronchoscopists should be aware that their active role in the integrated management of early detection with regard to studying carcinogenesis, accurate localization, staging, and minimally invasive early treatment is warranted. One often argues that so far, data generated by the bronchoscopists regarding IBT has been limited, but this is because many early SCC are detected by chance. The recognition that lung cancer may develop slowly up to ten years should also remind proponents of “immediate surgical intervention” to reflect whether the aim of treatment is always cure. One should realize that for patients with inherent risks of dying from non-lung cancer related deaths, already suffering from non-lung cancer related diseases, a balance between preservation of quality of life and suffering from additional lung cancer is a delicate one.

Honor Lectures

T. Petty, Denver, reported on Practical Approaches to Screening for Early Lung Cancer in High Risk Patients. His motto is “Now is the time.” “We have the knowledge and technology to change lung cancer, if applied in selected patients today. We know that patients who are heavy smokers, i.e., 30 or more pack years and who have any degree of airflow obstruction, even mild, have four to six times the prevalence of lung cancer, compared with patients with equal smoking, occupational and family histories, but with normal airflow. Thus we should look for lung cancer in all smokers with airflow

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obstruction beginning at age 45. When we do, approximately 4–5% lung cancer is found in virtually every study. Thus, after the smoking history, the spirometer becomes key to lung cancer diagnosis. Sputum cytology or fiberoptic bronchoscopy is the next step. CT scanning will identify peripheral lesions. PET scanning may be useful in staging.”

Petty reported preliminarily on a new community study done in Grand Junction, Colorado during one calendar year, 2001. Of 1296 questionnaires from patients done by all 15 primary care physicians in the community, 430 were eligible for spirometry because of smoking, at age 45, symptoms or occupational exposures. One hundred twenty-six of these had airflow obstruction. Eighty-seven received sputum cytology, CT or standard chest x-rays. Four cancers were found. Two additional cancers were found during the same period that were not formally enrolled. Thus in all, six cancers were found in one year in a community study directing surveillance at high-risk patients. The cost in real dollars for finding these six lung cancers is currently being analyzed and is approximately \$7,000 per cancer found.

R. Feins, (Rochester, NY) discussed the difficulties with lung cancer research. Why the five year survival rate remains 15% or less was reviewed and lamented. The requirements for rigid prospective controlled clinical trials to prove the reduction of lung cancers was addressed. High costs, huge sample sizes, difficulties in enrollment, and study management issues were all limitations to the progress.

Editorial (TLP) Comment:

If we wait for randomized prospective controlled clinical trials to show that early lung cancer treatment can improve survival, we will waste a lot of time, spend a lot of money, and probably draw the wrong conclusions once again. Today's technology advances are happening more rapidly than knowledge about their applications. By the time a multiyear controlled prospective trial is completed, the technologies will already be obsolete.

It seems perfectly reasonable to diagnose and treat lung cancer in high risk patients now. In fact, this position is now meekly embraced by the American Cancer Society in the following statement: “The ACS does not recommend testing

for early lung cancer detection in asymptomatic individuals at risk of lung cancer. However, because of the limitations of the trials of chest radiography and sputum cytology, as well as a more favorable survival rate associated with diagnosis of resectable tumors during *case finding*, the ACS historically has maintained that *physicians may decide to have these screening tests done on an individual basis.*” This is a rather tepid comment, but a step in the right direction. Let's look for lung cancer in high-risk patients. The time is now!

Summary of Late Breaking News Session

Although spiral CT is a very sensitive method to detect early lung cancer, 40%–50% of smokers above the age of 50 will have one or more non-calcified nodules. The majority of these nodules are non-malignant. Many of them are very small (<7 mm in diameter) and are very difficult to biopsy. Even if transthoracic needle aspiration biopsy under CT guidance can be performed, the procedure carries a significant risk of pneumothorax. Follow-up CTs to determine stability of the nodule can generate anxiety from the patients. An endoscopic method that can access and biopsy these nodules would be a great advance.

Asano et al from the National Health Insurance Sekigahara Hospital, in Gifu, Japan reported their results in 30 peripheral lung nodules with a mean size of 18.3 x 13.3 mm. CT was performed using a GE High Speed Fx/I and the area from the involved segmental bronchus to the lesion was scanned with a collimation width of 1–2 mm at a table transfer rate of 1–3mm/0.8sec/rotation at reconstruction intervals of 0.5–1.0 mm. Virtual bronchoscopy (VB) images were produced with a GE navigator. Based on VB images, an ultrathin bronchoscope (Olympus XP40: external diameter 2.8 mm) was inserted under direct vision into the target bronchus. After the position was confirmed by thin section CT, biopsy was performed. VB images to the 3rd to 11th (mean 6th) order bronchi could be produced. Observation to the 4th to 11th (mean 6.9th) order bronchi was possible using an ultrathin bronchoscope. VB was found to be

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useful for advancing the ultrathin bronchoscope. In 28 of the 30 lesions, the biopsy apparatus reached the lesion and 11 lesions were diagnosed as lung cancer and 15 as inflammation.

VB images beyond the 11th order are difficult to produce. D. Tolkowski and Y. Shwarz presented an even more sophisticated solution/approach from Super Dimension Ltd., Israel. Using a small 1-mm steerable catheter and a standard CT to fix the coordinates, the catheter could be navigated under electromagnetic wave control outside the body to the desired location. Using a sheath over the wire as a guide, the area of interest could be biopsied. The technology is scheduled for clinical trial in early 2003.

Bronchoscopists often struggle with obtaining a diagnosis of small peripheral lung lesions. Both technologies offer the opportunity to biopsy small lung nodules that could not be achieved previously. Having a “smart” catheter is certainly the route to go. These are exciting development that will revolutionize how small lung nodules will be managed. If these nodules can be biopsied, they can also be treated endoscopically such as by radiofrequency or photodynamic therapy.

Selected Reports from Recent Publications:

Endobronchial ultrasound: where are we now?
(Comments on Recent Reports by T. Sutedja)

Recently there have been two articles published regarding the use of endobronchial ultrasound (EBUS) for intraluminal assessment of early stage tumor located in the central airways [Baba et al. in *Lung Cancer* 2002;35:65-71 and Miyazu et al. in *Am J Resp Crit Care Med* 2002;165:832-837].

High-frequency ultrasound endoscopy in the GI tract has been accepted as a very sensitive tool for assessing the depth of tumor infiltration in the esophagus, hence the interest to use the same technique for assessment of tumor infiltration in the bronchial wall. Apart from this, EBUS can image parabranchial lymph nodes, large vessels and other structures to properly evaluate topographical anatomical

correlation of any suspicious mass in the central tracheobronchial tree and its relation to central organs within the mediastinum, important for assessing resectability.

EBUS is less invasive than standard surgical staging and its potential to accurately define possible tumor infiltration into the tracheobronchial wall may prove valuable. Patients with early stage hilar cancer have to be accurately staged as tumor dimension and local growth pattern are important determinants for choosing the most appropriate treatment. Recent interest in early detection and the desire to treat lesions at the earliest stage possible, may improve the cure rate by applying less invasive and morbid intraluminal bronchoscopic treatment (IBT) such as photodynamic therapy. IBT is justified in case early squamous cell cancer is strictly intraluminal without any nodal involvement. So far, surgical data have shown that intraluminal lesions <1 cm in size with visible tumor margins seem to be free of nodal involvement. IBT may then be applied as a tissue conserving treatment alternative for surgical resection.

Baba et al. reported their experience in using EBUS with the ultrasonic probe of 20 MHz radial scanner for the evaluation of tracheobronchial wall structure and comparing EBUS image with the actual microscopic findings regarding the depth of tumor invasion. Sixty-one patients have been subjected to this study, 40 patients had peripheral malignancy. In 21 patients with central airway tumors, clinical “*in vivo*” bronchoscopic EBUS findings of five thickened, nine nodular and seven polypoid intraluminal tumors seemed to define no invasion to the cartilage layer. All of these sites were confirmed histologically to have involvement of the cartilage layer. EBUS was not able to image the basement membrane clearly enough to differentiate between carcinoma *in situ* and submucosal invasion. Limitations in using EBUS were discussed by the authors: 1. Necessity for 10–15 manipulations to obtain clear images which may be improved by increasing expertise; 2. the inability for radial type ultrasonic probe to clearly image bronchial wall structure at bronchial bifurcations and in the small sub-segmental bronchi. Especially *in vivo*, the latex balloon sheath may prevent clear discrimination in the assessment of tumor

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invasion in the bronchial wall. The cartilage layer is however, easily identified by EBUS, allowing clear distinction of cases with tumor invasion through the cartilage layer, therefore EBUS can be used to select patients who will not be appropriate candidate for IBT.

Miyazu et al. in their meticulous study reported the use of EBUS using similar brand and type of instruments as Baba et al. as they also acknowledged the importance of accurate local staging to exclude deep invasion into the tracheobronchial wall prior to photodynamic therapy. Twelve patients were selected for this study and both high resolution CT (HRCT) scan and EBUS were performed. In cases with clear invasion of the bronchial cartilage, the resected specimens confirmed these findings in six patients. EBUS findings were more accurate than HRCT in two of eleven cases showing cartilage invasion. They also showed that five of the 14 lesions <1cm size did protrude beyond the cartilage.

What can be learnt from these data? EBUS as an emerging technique seems to be able to increase our sensitivity for assessing intraluminal tumor growth allowing more accurate staging, especially regarding mucosal tumor infiltration through the distinct border of bronchial cartilage, by showing hypoechoic mass of tumor infiltration beyond the cartilage layer. However, more data are needed to show the consistency of EBUS technique, as complementary technologies such as HRCT and optical coherence tomography are also being developed. The learning curve as indicated by Baba et al. may prove a major hurdle for many institutions, as not many centers deal daily with occult central airway tumors. The HRCT machines are being developed further with improved resolution such as the multi-slice CT. Nevertheless, both studies show that there are additional ways to improve our staging, allowing clinicians to be increasingly more accurate in choosing the best treatment strategy for each individual case of early stage hilar cancer, before proceeding to the currently acceptable standard of “relatively morbid and wasteful” surgical resection. This should be kept in mind, especially in patients with small intraluminal, early stage squamous cell cancer in their central airways, in whom smoking history has led to limited pulmonary reserve capacity and the fact that

many are at risk to develop subsequent primaries. Increasing accuracy in determining stage and lymph node involvement allow the oncology team to choose the most appropriate therapy for each particular individual who harbors early stage squamous cell cancer in their central airways.

“The cartilage layer is however, easily identified by EBUS...”

“The HRCT machines are being developed further with improved resolution such as the multi-slice CT.”

Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial.

Harm van Tinteren, Otto S. Hoekstra, Egbert F Smith, et al: *Lancet* 2002;359:1388-1392

Background: Up to 50% of curative surgery for suspected non-small-cell lung cancer is unsuccessful. Accuracy of positron emission tomograph (PET) with 18-fluorodeoxyglucose (¹⁸FDG) is thought to be better than conventional staging for diagnosis of this malignancy. Up to now, however, there has been no evidence that PET leads to improved management of patients in routine clinical practice. We did a randomised controlled trial in patients with suspected non-small-cell lung cancer, who were scheduled for surgery after conventional workup, to test whether PET with ¹⁸FDG reduces number of futile thoracotomies.

Methods: Before surgery (mediastinoscopy or thoracotomy), 188 patients from nine hospitals were randomly assigned to either conventional workup (CWU) or conventional workup and PET (CWU+PET). Patients were followed up for 1 year. Thoracotomy was regarded as futile if the patient had benign disease, explorative thoracotomy, pathological state IIIA-N2/IIIB, or postoperative relapse or death within 12 months of randomisation. The primary outcome measure was futile thoracotomy. Analysis was by intention to treat.

Findings: 96 patients were randomly assigned CWU and 92 CWU+PET. Two patients in the CWU+PET group did not undergo PET. 18 patients in the CWU group and 32 in the CWU+PET group did not have thoracotomy. In the CWU group, 39 (41%) patients had a futile

thoracotomy, compared with 19 (21%) in the CWU+PET group (relative reduction 51%, 95% CI 32–80%; $p=0.003$).

Interpretation: Addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer.

Editorial (TLP) Comment:

Although this new imaging technique can identify occult metastases, it is still not sufficiently sensitive to identify the very small lesions of micrometastasis.

Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial.

Ann M Moller, Nete Villebro, Tom Pedersen, et al: *Lancet* 2002;359:114-117.

Background: Smokers are at higher risk of cardiopulmonary and wound-related postoperative complications than non-smokers. Our aim was to investigate the effect of preoperative smoking intervention on the frequency of postoperative complications in patients undergoing hip and knee replacement.

Methods: We did a randomised trial in three hospitals in Denmark. 120 patients were randomly assigned 6–8 weeks before scheduled surgery to either the control ($n=60$) or smoking intervention (60 group). Smoking intervention was counselling and nicotine replacement therapy, and either smoking cessation or at least 50% smoking reduction. An assessor, who was masked to the intervention, registered the occurrence of cardiopulmonary, renal, neurological, or surgical complications and duration of hospital admittance. The main analysis was by intention to treat.

Findings: Eight controls and four patients from the intervention group were excluded from the final analysis because their operations were either postponed or canceled. Thus, 52 and 56 patients, respectively, were analysed for outcome. The overall complication rate was 18% in the smoking intervention group and 52% in controls ($p=0.0003$). The most significant effects of intervention were seen for wound-related

complications (5% vs 31%, $p=0.001$), cardiovascular complications (0% vs 10%, $p=0.08$), and secondary surgery (4% vs 15%, $p=0.07$). The median length of stay was 11 days (range 7–55) in the intervention group and 13 days (8–65) in the control group.

Interpretation: An effective smoking intervention programme 6–8 weeks before surgery reduces postoperative morbidity and we recommend, on the basis of our results, this programme be adopted.

Editorial (TLP) Comment:

Of course stopping smoking is key to preventing or forestalling all of the smoking-related diseases that these patients risk.

Smoking Cessation Following CT Screening for Early Detection of Lung Cancer

Jamie S Ostroff, Natasha Buckshee, Carol A Mancuso, et al: *Preventive Medicine* 2001;33:613-621

Background: This study was conducted to assess the impact of lung cancer screening participation on smoking cessation.

Methods: Individuals ($n=134$) who reported active smoking at the time of enrollment in our Early Lung Cancer Action program (ELCAP) completed a brief, follow-up telephone interview assessing any changes in smoking patterns following lung cancer screening. Using logistic regression, we estimated the probability of decreasing or quitting smoking using each enrollee's background information and computed tomography (CT) scan results.

Results: Most survey respondents (74%) agreed that participation in the ELCAP increased their motivation for quitting smoking. In terms of self-reported changes in smoking behavior, 31 (23%) reported that they had quit and 35 (27%) decreased their smoking patterns. Several significant covariates of smoking cessation were identified: perceived benefit of quitting (OR 4.02), cancer anxiety (OR 2.49), younger age (OR 2.47), and abnormal CT finding (1.97).

Conclusions: Our analyses suggest that low-dose helical CT scanning may serve as a strong catalyst for smoking cessation and that delivery

“The most significant effects of intervention were seen for wound-related complications...”

“Most survey respondents (74%) agreed that participation in the ELCAP increased their motivation for quitting smoking.”

“...helical CT scanning may serve as a strong catalyst for smoking cessation and that delivery of effective smoking cessation interventions along with CT scanning represents a potential opportunity...”

of effective smoking cessation interventions along with CT scanning represents a potential opportunity to increase the overall cancer prevention benefit of lung cancer screening.

Editorial (TLP) Comment:

This is an interesting “side benefit of CT screening for early lung cancer.” The success probably relates to a high level of cancer concern in the subjects who sought screening. Isn’t this an expensive approach to smoking cessation? Probably not since many lung cancer screening programs offer CT at times of slow activity in the CT units for as little as \$250. This is less expensive than most commercial stop smoking programs, which currently cost \$500–\$1,000, such as SmokeEnders.

“Certainly finding lung cancer and occult, asymptomatic coronary artery disease, particularly in high-risk individuals is better than not finding it.”

Direct-To-Consumer Marketing of High-Technology Screening Tests

Thomas E. Lee, MD, Troyen A. Brennan, MD:
N Engl J Med 2002;346:529-531

Increasingly, entrepreneurs, including physicians, are offering to the general public high-technology screening tests that are not covered by most health insurance plans. These tests are frequently being marketed directly to consumers by radio, the print media, the Internet, and other media. People who undergo these tests pay fees that generally range from \$300 to \$1,000.

Editorial (TLP) Comment:

This “Sounding Board” editorial is critical of the use of new technology for the purpose of diagnosing occult diseases, such as early coronary artery disease or lung cancer. It argues that a high false positive rate and the creation of anxiety and costs are a disservice to patients. But patients have what they have, whether diagnosed or not. Certainly finding lung cancer and occult, asymptomatic coronary artery disease, particularly in high-risk individuals is better than not finding it. If we wait for randomized controlled clinical trials to prove their worth of early diagnosis, we will wait 8–10 years and by then the technologies under study today will be

“Daily intake of NSAIDs for at least 2 years prior to interview was associated with a 68% reduction in the relative risk of lung cancer...”

“But maybe we should take a more simplistic approach and study chemoprevention in all current and former smokers with airflow obstruction!”

obsolete. It is not reasonable to go through this agonizing expense when we know we can find, treat and cure lung cancer in high-risk persons.

Chemoprevention of lung cancer by non-steroidal anti-inflammatory drugs among cigarette smokers.

Harris RE, Beebe-Donk J, Schuller HM: *Oncol Rep* 2002;9:693-695

We conducted an epidemiologic case control study of NSAIDs among 489 lung cancer patients and 97 control subjects. The case patients were diagnosed and treated during 1996–1999 at the James Cancer Hospital and Research Institute, Columbus, OH. Each lung cancer diagnosis was verified by examination of the pathology report. Population controls free of disease were obtained from health screening clinics and frequency-matched to the cases at a 2:1 rate. Matching characteristics included age, gender, and pack-years of cigarette smoking. In order to assess the effects of NSAIDs on tobacco carcinogenesis, only heavy smokers were included in the control group. Information on the use of aspirin, ibuprofen, and prescription NSAIDs was obtained by personal interviews. Effects of NSAIDs lung cancer risk were assessed by estimating odds ratios (relative risks) with 95% confidence intervals and performing trend tests. Daily intake of NSAIDs for at least 2 years prior to interview was associated with a 68% reduction in the relative risk of lung cancer (RR, 0.32; 95% CI, 0.23–0.44; $p < 0.01$). The inverse trend of lung cancer risk with increasing NSAID use was highly significant ($p < 0.01$). Results were similar for men (RR, 0.41) and women (RR, 0.22), and for the individual compounds, aspirin (RR 0.25) and ibuprofen (RR, 0.39). These results combined with the current molecular evidence suggest the regular NSAID intake may prevent tobacco carcinogenesis through COX-2 blockade.

Editorial (TLP) Comment:

Establishment of effective strategies for chemoprevention is a critical next step in reducing the prevalence of lung cancer. Candidates for chemoprevention studies are patients with dysplastic changes in sputum

cytology or those with molecular markers indicative of lung cancer. But maybe we should take a more simplistic approach and study chemoprevention in all current and former smokers with airflow obstruction!

“...the intercurrent survival, which is associated with non-cancer related death, was 60.1% in patients with COPD and 86.2% in patients without COPD at 5 years...”

Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC.

Sekine Y, Behnia M, Fujisawa T: *Lung Cancer* 2002;1:95-101

Purpose: The purpose of our study was to determine the incidence of various types of postoperative pulmonary complications and to evaluate the impact of chronic obstructive pulmonary disease (COPD) on the long-term survival of patients with non-small cell lung cancer (NSCLC) undergoing pulmonary resection.

Methods: We performed a retrospective chart review of 244 patients who had undergone lung resection for NSCLC at Indiana University. COPD, defined as predicted forced expiratory volume in 1 s (FEV_1) $\leq 70\%$ and $FEV_1/FVC \leq 70\%$, was determined based on preoperative pulmonary function testing in 78 of 244 patients (COPD group). The remaining 166 patients were classified as non COPD. The incidence of postoperative complications, which included air leaks of ≥ 10 days, atelectases pneumothorax, pneumonia, bronchopleural fistula, empyema, acute respiratory distress syndrome, mechanical ventilation of ≥ 7 days, and outpatient oxygen supplementation were compared between the two groups. Long-term survival and mortality due to respiratory failure were analyzed between the two groups using the Kaplan-Meier method and log rank test.

Results: All of the above-stated postoperative pulmonary complications occurred more frequently in the COPD than in the non-COPD patients ($P < 0.01$). The overall 5-year survival rate was 36.2% in the COPD and 41.2% in the non-COPD patients ($P = 0.1023$). Five-year cancer related survival was 43.2% in the COPD and 41.2% in the non-COPD patients ($P = 0.357$). There was no significant difference in survival among patients with different stages of lung

cancer. However, the intercurrent survival, which is associated with non-cancer related death, was 60.1% in patients with COPD and 86.2% in patients without COPD at 5 years ($P < 0.0001$). The major cause of non-cancer related death in the COPD group was respiratory failure ($P = 0.0008$).

Conclusion: The presence of COPD is an acceptable predictor of postoperative pulmonary complications in patients with NSCLC, COPD is also a significant risk factor for development of respiratory-related complications, which may explain the poor long-term survival in these patients.

Editorial (TLP) Comments:

Of course, more complications will be expected in patients with COPD due to the reduced pulmonary function and a greater likelihood of infection and air leaks. The strong connection between COPD and lung cancer will continue to challenge our ability to deal with both diseases. Or are COPD and lung cancer two different diseases, or different manifestations of the same disease?

“VATS lobectomy as specifically defined is an anatomic lobectomy using individual hilar dissection and node sampling or dissection and 2–4 small incisions without rib spreading.”

Late Breaking Reports

Results of CALGB 39802: Feasibility of video-assisted thoracic surgery (VATS) lobectomy for early stage lung cancer: Swanson S J, Herndon J, D'Amico A, et al: *Am Assoc Clin Oncol* 2002;21:290a

Objective: Evaluate feasibility VATS lobectomy for small lung cancers using a prospective, multi-institutional design.

Methods: VATS lobectomy as specifically defined is an anatomic lobectomy using individual hilar dissection and node sampling or dissection and 2–4 small incisions without rib spreading. Lobes are removed in a bag through one port enlarged up to 8 cm. Eleven VATS lobectomy credentialed surgeons from 6 institutions participated. Between 1998 and 2001, 128 patients with nodules in outer half of lung suspected as non-small cell lung cancer < 3 cm, CT-scan confirmed clinical stage I disease, and without evidence of adenopathy were prospectively

“There were 511 patients (430 males and 81 females) whose age averaged 63+/-10 years who underwent 515 lung resections.”

“VATS lung resection with lymph node dissection achieved a 5-year survival similar to that achieved by the conventional approach.”

registered for VATS lobectomy. At lobectomy mediastinoscopy or ipsilateral thoracoscopic mediastinal node sampling ruled out N2 disease in all patients and complete, standard resection insured by rigorous protocol guidelines.

Feasibility, primary endpoint, was determined by perioperative measures and defined as successfully completing a VATS lobectomy in >85% of patients without excess morbidity (<10%). Secondary endpoints, long-term morbidity, local recurrence and survival were also measured.

Results: 128 patients, 66 males, median age 66 (37–86), PS 0 (67%) or 1 (20%) underwent surgery. 106 (83%) had stage I lung cancer. 97/111 (87%) patients with evaluable data had successful VATS lobectomies. Lobes resected were (using standard abbreviations): RUL 23 (24%), RML 2 (2%), RLL 18 (19%), LUL 35 (36%), LLL 12 (12%), not specified 7 (7%). Median procedure length was 130 minutes (47–428), median chest tube duration 3 days (1–14). At time of lobectomy, 58/97 (60%) patients had a diagnostic biopsy. Within 30 days, 2 in 97 (2.1%) deaths occurred, neither directly related to VATS technique; 8/97 (8.2%) patients had grade 3/> complications, only one intraoperative bleeding.

Conclusions: Specifically defined VATS lobectomy avoiding rib spreading is feasible in a prospective, multi-institutional setting. A follow-up Phase III study is being written to define its benefit.

VATS is an adequate oncological operation for state I non-small cell lung cancer.

Thomas P, Doddoli C, Yena S, et al: *Eur J Cardiothorac Surg* 2002;6:1094-1099

Objectives: This study was designed to determine the long-term prognosis of video-assisted thoracic surgery (VATS) vs. open lung resections for patients with pathological stage I non-small cell lung cancer (NSCLC).

Materials and Methods: The medical records of all patients who underwent lung resection for a pathological stage I NSCLC were reviewed for the period from 1990 to 1999, by screening of a

database into which data were entered prospectively. There were 511 patients (430 males and 81 females) whose age averaged 63+/-10 years who underwent 515 lung resections. Our VATS experience began in 1993 with selected stage I patients, and since that date an average of one patient in four was managed with VATS. Lung resections consisted of 25 wedge resections or segmentectomies (seven VATS), 390 lobectomies (92 VATS), 19 bilobectomies (one VATS) and 81 pneumonectomies (ten VATS). Lymph node dissection was performed in all cases.

Results: There were significantly more females ($P=0.01$) and adenocarcinoma ($P=0.02$) in the VATS group ($n=110$) when compared to the open group ($n=405$). Tumour size averaged 4+/-2cm in the open group and 3+/-2cm in the VATS group ($P=0.04$). The distribution of T1/T2 tumours was 97/308 and 50/60, respectively ($P=0.0001$). At follow-up, cancer recurrence could be documented in 117 patients, with no difference of incidence between the two groups (22.5 vs. 24.5%; $P=0.64$). Estimated Kaplan-Meier 5-year survival rates, including the operative mortality as well as any cancer-related and unrelated death, were 62.8% (confidence interval (CI): 56.8–68.7%) vs. 62.9% (CI: 51.4–74.4%), respectively ($P=0.60$). The advent of VATS did not influence the patients' survival: 5-year survival rate was 63.9% (CI: 55.3–72.5%) for the period from 1990 to 1992, and 58.8% (CI: 51.7–65.9%) for the period from 1993 to 1999 ($P=0.65$). Subgroups survival analysis according to the T status did not show any statistically significant difference between the two groups.

Conclusions: VATS lung resection with lymph node dissection achieved a 5-year survival similar to that achieved by the conventional approach. VATS is a valuable option for the management of selected patients with an early-stage NSCLC.

Editorial (TLP) Comment:

As we move into the new era of early diagnosis and treatment of small lung cancers, we will need new approaches to treatment. A less traumatic approach to lobectomy appears to be an advance in the surgical treatment of lung cancer.

Historical Vignette

The Origins of the Forced Expiratory Volume in One Second (FEV₁) and a Tribute to Robert Tiffeneau (1910-1961)

Although only a minority of pulmonologists can answer the question, who invented the spirometer (John Hutchinson of London in 1846), only intense and sometimes compulsive zealots of the history of respiratory physiology give Robert Tiffeneau credit for adding the concept of time to the expiratory vital capacity. This was the foundation of the timed vital capacity, the forerunner of the forced expiratory volume in one second (FEV₁). Tiffeneau and other Frenchmen did not like the maximum breathing capacity (MBC) test that was used to diagnose and monitor diseases with airflow obstruction, i.e., asthma and COPD. The MBC required a 12 to 15 second sustained deep and rapid breathing and this was fatiguing to the patient and not very reproducible.

Tiffeneau of Paris, a pharmacologist, was interested in epinephrine as a bronchodilator in asthma and acetylcholine and histamine as bronchoconstrictors. He was probably the first to do

clinical bronchoprovocation clinical challenges in asthma. He surmised that epinephrine would prevent the bronchoconstriction by acetylcholine, but cortisone would not. Cortisone, however, blunted the responses to inhaled antigens, that caused bronchoconstriction. These early observations formed the basis of combining a beta agonist with an inhaled corticosteroid in the management of chronic asthma!

Tiffeneau's work was ignored by British and American pulmonologists, probably because of the poor ability of English speaking pulmonologists to read French. Gaensler popularized the timed vital capacity in North America and designed a device, the Gaensler-Collins Spirometer, that mechanically indicated the FEV₁ and FVC.^{3,4}

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