

## Frontiers

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how it can be most  
quickly and effec-  
tively diagnosed  
and treated.”

## Selected Highlights of the 9th World Conference on Lung Cancer

**M**ore than 2,000 attendees from some 64 countries attended the opening ceremony of the 9th IASLC

International Conference on Lung Cancer in Tokyo, Japan. The banner prominently displayed at the Tokyo Opera City Concert Hall proclaimed the theme: “Prevention and Eradication for Human Development.”

Clinicians, comprised of oncologists, pulmonologists, surgeons, radiologists, and pathologists were joined by basic scientists, nurses, therapists, governmental officials, and representatives from industry to take the next step in lung cancer study, treatment, and control.

The impressive opening ceremony, attended by their Imperial Highnesses, Prince and Princess Takamado, cast a solemn and earnest mood as the attendees stood with respect of the Japanese ceremonial icons. A thundering brass band solute in the awesome Tokyo Opera House was deafening.

Congress President, Yoshihiro Hayata’s opening welcome was followed by remarks in both Japanese and English by the Prince, who had lost his uncle to lung cancer. Thus, he is no stranger to the challenges that lie ahead in the treatment and prevention of the world’s most common fatal malignancy.

The attendees were next greeted by a succession of Japanese governmental officials who emphasized the chilling fact that cancer is the most common cause of death in Japan. In 1999, 32% of all cancer deaths (some 50,000) were from malignancies of the lungs. The imperative to prevent teens from smoking, to eliminate smoking, and to increase smoking cessation efforts are top priorities for Japan. Outgoing President of IASLC, G. Motta, (Genova, Italy), extended his greetings to the Conference before the dramatic award ceremony.



Yukio Shimosato, M.D., D. Med., S.C.:  
Mary J. Matthews award winner.

### Mary J. Matthews Award Given to Dr. Yukio Shimosato.

**A** highlight of each International Lung Cancer Conference is the presentation of awards. The Mary J. Matthews citation, established in 1994, honors persons for excellence in lung cancer pathology. The first recipient of this award was the late Geno Saccomanno at the 7th International Congress held in Colorado Springs, CO. This year the award went to Yukio Shimosato, (Tokyo, Japan). Dr. Shimosato is known for many contributions to our understanding of lung cancer, including the rebuttal of the “scar carcinoma concept.” He showed the scar develops not before, but after the development of peripheral lung cancer (Prognostic implications of fibrotic focus [scar] in small peripheral lung cancers. *Am J Surg Path* 1980;4:365-373). Dr. Shimosato also recognized atypical adenomatous hyperplasia without scar as a preneoplastic lesion of many peripheral adenocarcinomas of the lung and the stepwise malignant progression in peripheral

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adenocarcinoma from atypical adenomatous hyperplasia to bronchoalveolar carcinoma.

This year's Conference appropriately asked for the prohibition of smoking at any of the formal sessions. Alas, this principle was not well embraced by many of the attendees at the reception following the impressive opening ceremony.

### Plenary Session 1: Tuesday, September 12: Recent Advances in Molecular Genetics of Lung Cancer.

**T**he many new important observations covering the molecular and cellular events that result in pre-clinical and clinical lung cancer, attracted a large audience. J. D. Minna, (Chairman), opened the session with a dazzling display of the various patterns of genetic abnormalities, which are associated with the different cell types, and clinical stages of a large number of lung cancers. The software for these studies is available for all investigators.

An emerging hypothesis is that some 10 to 20 different genetic abnormalities in dominant oncogenes and/or tumor suppressor genes results in the cellular evolutionary processes that result in clinical lung cancer. This research has major implications for directing the search for specific diagnostic and therapeutic targets. A multiplicity of allele losses are associated with preneoplastic/pre-invasive lesions. Genetic abnormalities differ between non-small-cell lung cancer, (NSCLC), and small-cell lung cancer and between the various types of NSCLC in smokers. These same genetic losses were not found in never smokers. Tumor-acquired hypermethylation is a frequent mutational mechanism in lung cancer. Many of these extensive observations are ready for the development of new clinical strategies in the diagnosis and risk assessment aimed at prevention and control of lung cancer.

C. C. Harris, (Bethesda, MD), offered new insights into the molecular epidemiology and pathogenesis of human lung cancer. People differ in their susceptibility to the carcinogenicity of tobacco smoke. Long-term former smokers or never smokers appear to have either a genetic or an acquired susceptibility to carcinogens from tobacco smoke, e.g., benzo[a] pyrene, glutathione S-transferase M1, (GSTM1). Environmental tobacco smoke is responsible for approximately 45% of cancer, particularly in women, who have genetic patterns of susceptibility. Critical mechanisms of defense against lung cancer appear to be in the tumor suppression gene p53. "p53 is at the crossroads of cellular stress."

**Impressions of the 9th Conference.**

*There is a huge and growing international interest in lung cancer.*

*Discussions of multimodality therapy and the organization of comprehensive diagnostic and treatment clinics were heard in packed sessions. Comments about evolving practices were frequently overheard in informal discussions.*

*New challenging approaches to the early identification and treatment of lung cancer are emerging.*

*Increasing evidence of interest in early identification exists, particularly in high prevalence areas such as Japan, eastern Europe, and South America.*

Depending on the functional integrity of p53, cell repair, death, or malignant transformation may occur. Systematic clinical studies with the analysis of lung cancer gene markers is needed to further pursue the p53 hypothesis.

L. Mao, (Houston, TX), spoke on "Molecular Changes in Early Carcinogenesis of the Lung." The evolution of lung cancer is a multi-step process and involves the accumulation of genetic epigenetic alterations. How the molecular processes continue in some, but not all former smokers is a huge basic science and clinical challenge. Studies of allele gene expression in bronchoscopic biopsies done serially, may point the way to better preventive strategies.

W. K. Hong, (Houston, TX), discussed chemopreventive approaches to upper aerodigestive tract cancers during the past 15 years. Although chemopreventive strategies have been successful with other cancers, similar success has not been achieved in lung cancer in active smokers. Perhaps a continued bombardment of the bronchial epithelium with too advanced genetic abnormalities already present at the time of introduction of chemopreventive strategies, or poor adherence to chemopreventive strategies may explain these negative results of chemoprevention studies with vitamin E, beta carotene, or the retinoids. Randomized prospective placebo controls of chemoprevention in former smokers, now underway, may result in a more favorable outcome. Such studies may be complete in two to three years. Developing alternative approaches to chemoprevention via the aerosolized medications may be another potential strategy.

**Plenary Session 2: Wednesday, September 13: New Diagnostic Strategies for Lung Cancer.**

**T**he new technologies that are rapidly emerging for the diagnosis of early stages of lung cancer are truly astonishing. The dismal state of conventional diagnostic approaches, at least in the United States, have not improved lung cancer survival in any material way in the past 30 years. Abundant evidence exists that we simply must take a new approach to lung cancer diagnosis as the basis of finding cancer in early stages for potentially curative treatment and to develop new treatment strategies.

The four plenary presentations attracted a large early morning audience. K. Furukawa, (Tokyo, Japan), described his experience with a new fluorescence bronchoscopic device. Instead of a laser light source, such as is used in the LIFE-

Lung system, now being used in North America, the SAFE-1000 device (Pentax) uses a filtered xenon light source for tissue excitation. Normal tissue autofluorescence is a function of riboflavins, flavins, elastin, and collagen. In high-grade dysplasia and cancer, autofluorescence is reduced by disordered tissue. This results in cold spots devoid of fluorescence which guide the site of biopsy. The sensitivity of the SAFE-1000 system is superior to conventional white-light bronchoscopy. The specificity is somewhat reduced, but the relative detection rate of the SAFE-1000 system is higher than white-light bronchoscopy and similar to the LIFE-Lung system.

A. F. Gazdar, (Dallas, TX), summarized the emerging molecular approaches to early lung cancer diagnosis, the evolution of premalignant lesions, and lung cancer risk assessment. He summarized the major molecular marker differences that are associated with sequential bronchial changes in squamous vs adenocarcinomas. Premalignant changes with abnormal molecular markers are much less common in small-cell carcinoma. How molecular markers can be applied to clinical management, risk assessment, and early diagnosis, remain to be established. New therapeutic targets based on molecular markers associated with lung cancer are being developed.

J. L. Mulshine, (Bethesda, MD), reported on the continued effort to develop high throughput computer-assisted sputum markers in lung cancer early diagnosis. An airway cell marker for lung cancer is needed for central lesions, which are most often squamous cell cancers, representing 25% to 30% of all lung cancers. A practical airway cell marker will someday replace conventional sputum cytology. Airway cell markers are needed to complement low-dose helical CT scanning, which is rapidly emerging as a practical method of identifying small peripheral lesions, which are most often adenocarcinomas. Mulshine also described the advantages of dealing with the problem of field carcinogenesis, which is so effectively induced by cigarettes, a highly effective carcinogen delivery device to the lungs and oropharynx. Chemoprevention agents, such as the retinoids, can be effectively delivered throughout the lungs via an electrospray device, which is currently under evaluation. It is entirely made of plastic and resembles a metered-dose device used in bronchodilator and corticosteroid delivery. Direct topical therapy will deal with lung cancer, which begins, in the epithelium, particularly in the apices of the lungs. Aerosol

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therapy will likely greatly reduce the toxicity of chemopreventive drugs such as the retinoids and should have a greater effect in promoting lung repair, than when delivered systemically.

J. G. Fujimoto, (Cambridge, MA), spoke on new diagnostic imaging technology known as optical coherence tomography, (OCT), for the diagnosis of neoplasia. This was a true spell-binder. Originally developed for ophthalmological use in the early 1900's, OCT provides an optical biopsy. It is analogous to B-mode ultrasonography, but rather than utilizing a sound signal, it uses light. This is possible with optical bundles which reflect signals with a high degree of resolution. Signal processing involves what is known as interferometry, which is basically the analysis for reflected light waves from normal versus altered tissue. OCT is used not only in ophthalmology, but also in the analysis of uterine-cervical dysplasia and cancer, bladder cancer, esophageal, gastric, ampullar, and brain lesions via fiberoptic probes inserted into solid tumors. It is eminently suitable for use in the diagnosis of bronchial tumors, including those at the extreme periphery. An approximately 1 mm optic probe will be introduced through the suction channel of a standard bronchoscope and on reaching tissue, gives an optical signal of abnormality with an “optical fingerprint” that can be equivalent to a tissue diagnosis. This type of technology is already being evaluated in the clinic, and may someday make more conventional technology obsolete. More likely, it will complement the existent fiberoptic imaging devices that we have employing both white-light and fluorescence technology.

**Editor's (TLP) comment:** This plenary session was fascinating. The rapid emergence of new technology is truly mind-boggling. The question, however, must always focus on practicality. What should we be advising primary care physicians to do today? Right now, it remains the identification of patients at high risk with sputum cytology for the evaluation for central lesions and CT techniques for peripheral lesions. We need to develop not only new diagnostic but treatment paradigms for an increasing number of patients we will be encountering in the future. As Mulshine so effectively pointed out in this session, our new approaches to screening will be no stronger than the weakest link of a chain. Screening the right population, the follow-up of early lesions, communication, follow-up of patients, and helping to enlighten the profession and the public, as well as government officials, and those in control of reimbursement, are all requirements for success.

## Selected Highlights From Pulmonary Imaging Sessions.

**A** preliminary report of the lung cancer screening program with low-dose spiral CT at the Mayo Clinic, was reported by D. E. Midthun, et al, (Rochester, MN). The study has already enrolled 1,520 participants (735 women and 785 men) from January 20, 1999 through December 1, 1999. Participants were over age 50, current or former smokers, and had quit less than ten years before. The smoking intensity threshold was set at 20 pack-years. The average age at enrollment was 59 years. 61% were current smokers. Non-calcified lung nodules were found in 51% of the participants. To date, 17 primary lung cancers (15 NSCLC and two limited stage small-cell cancers) have been identified. Staging included ten 1A, three 2A, and two 3A tumors. Four lesions were determined as benign on resection. Repeat annual screening had been completed in 632 subjects. In 21%, nodules were found to be present in the first scan in retrospect. New nodules were detected in 11% of the participants. Two incidence cancers have been diagnosed so far: one Stage IIB non-small-cell lung cancer, and one small-cell lung cancer.

**Editors' (TLP and SL) comments:** Achieving an approximately 1% prevalence rate is a high yield compared to other cancer screenings such as mammography, where the detection rate is 0.5% to 0.8%. The majority of the lung cancers detected were early stage disease amenable to curative resection. However, this and other studies showed that 20% to 50% of the individuals screened with spiral CT have non-calcified lung nodules, especially in regions where fungal disease such as histoplasmosis is endemic. Since the majority of nodules less than 10 mm are benign, a major area of research is to separate malignant nodules from benign disease, to avoid unnecessary surgery or repeated follow-up CTs. Some of this ongoing research, such as density analysis and contrast-enhanced dynamic CT, were reported in this meeting (see below). False-negative CT can occur. Computer-aided diagnosis will reduce this possibility. Some cancers can also appear within a year. This and other studies will increase our understanding of the value of CT scanning and estimate the magnitude of length bias.

H. van Tinteren, et al., (Rotterdam, The Netherlands), reported on the cost-effectiveness of PET scanning, added to conventional diagnostic strategies for non-small lung cancer. These investigators showed a significant reduction in unnecessary thoracotomy using PET

scan criteria. PET scans cost in Holland is \$1,750, but this does not increase the cost of evaluation and treatment, because unnecessary surgery can be eliminated in 20%. This approximately equals the additional cost of PET scanning.

R. Kakinuma, et al., (Tokyo and Tokushima, Japan), reported on evaluations of performance of computer-aided diagnosis to detect lung cancer by helical CT screening. This technique promises to improve upon the diagnosis of the smallest lesions, and should assist radiologists in the detection of significant abnormalities that otherwise might have been missed.

A. Mochizuki, et al., (Kawasaki, Japan), reported upon different patterns seen in solitary nodules, based upon vascular supply patterns with first-pass dynamic CT. This provides a low invasive approach to the evaluation of solitary pulmonary nodules. The aortic supply via the bronchial system patterns is a good indicator of primary lung cancer. When the blood supply appears to come from the pulmonary artery, it strongly indicates metastatic tumor or inflammatory nodule. The third pattern, i.e., reduced flow from its vascular source is frequently seen in benign lesions.

Z. G. Yang, et al., (Matsumoto, Japan), reported upon the CT features of small peripheral lung cancers found in CT screening. Three types of nodules are found on CT. A ground-glass attenuation nodule corresponding with a lepidic growth pattern was most often seen in bronchoalveolar carcinoma. A heterogeneous nodule with a higher density central zone was most often seen in well-differentiated adenocarcinomas. A solid homogeneous soft tissue density was most often seen in poorly differentiated adenocarcinomas, squamous cell carcinomas, and small-cell carcinomas.

K. J. Jung, et al., (Seoul, Korea), reported upon the frequency of extrathoracic metastasis in T1 lung cancer, found in CT. Extrathoracic metastases are evidence in presentation in 13% of patients, and at one year in an additional 11% of patients. Prevalence of extrathoracic metastasis is significantly lower in tumors with ground-glass attenuation, suggesting bronchoalveolar carcinoma.

**Editor's (SL) comment:** The approach taken by Jung and co-workers should have been taken by E.F. Patz, Jr., et al. in their study recently reported in the June issue of *Chest*. Patz, Jr., et al. reported that in patients with Stage IA lung cancer, there was no correlation between the tumor size and outcome, implying that detecting

smaller tumors with spiral CT may have no impact in reducing lung cancer mortality. A more valid study to determine if detecting smaller tumors would alter survival, is to correlate tumor size in all patients with T1 disease (not just those with N0M0 status) with the frequency of nodal and extrathoracic metastases, as well as subsequent survival.

#### Presidential Symposium: Thursday, September 14: Lung Cancer Control Strategy in the New Millennium.

(Lam S, Palcic B, Garner D, et al. *Lung Cancer Suppl.* 2000;29:145).

**P** rimary prevention measures, aiming at curbing tobacco smoking, especially among young people, should remain a priority of government policy. However, to reach the goal of a significant reduction in lung cancer mortality in the next several decades, requires evaluation and implementation of an additional strategy of early detection and chemoprevention. Although low-dose spiral chest CT offers a significant improvement in early lung cancer detection compared to chest x-ray, CT mainly detects peripheral adenocarcinomas. In addition, the specificity of spiral CT can be as low as 50%. Conventional sputum cytology is the only non-invasive method to detect pre-invasive (Stage 0) lung cancer. However, although the specificity is high (98%), the sensitivity is very low (about 10% to 15%) for detecting Stage 0/I lung cancer and peripheral adenocarcinoma.

To overcome these deficiencies, a fully automated method, using computer-assisted image analysis, (CAIA), of sputum cells has been developed that can greatly improve the sensitivity of sputum cytology for the detection of early lung cancers, including adenocarcinoma. A blinded, randomized clinical trial showed that Stage 0/I lung cancer and adenocarcinoma can be detected with a sensitivity of 70% to 80%, at 90% specificity. This study breaks the conventional thinking that sputum cytology is not effective in detecting peripheral adenocarcinoma. Combining a sputum biomarker such as CAIA of sputum cells with low-dose spiral CT may yield the best sensitivity and specificity. This approach should be tested in large scale randomized clinical trials.

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“At least three types of MMPI have entered clinical trials.”

## Satellite Symposium on Medical Application of Synchrotron Radiation—Trial for Lung Cancer Diagnosis.

**A**n extremely exciting satellite symposium reported on the development of synchrotron radiation, which is orbital radiation emitted when a path of electron beams are traveling at almost the speed of light, and are bent by a magnetic field. It continuously covers a wide range of wave lengths, and provides several orders of magnitude higher intensities than those of conventional x-ray tubes. It is possible to make the x-ray beam highly monochromatic and parallel by reflecting the silicon crystals. This was reported by Professor J. Chikawa, (Hyogo, Japan), Professor of High Energy Physics at Tokyo University Medical Center. The resulting x-ray image is 100 billion times more intense than that produced by an x-ray tube. Extremely high resolution, down to tenths of millimeters, can be achieved. This technology is capable of imaging individual alveoli and cilia. Since no absorption agent is needed, the method's energy toxicity is extremely low. Such methods would be suitable for a serial study of any organ, because radiation toxicity is essentially avoided.

In the second part of this symposium, T. Tsuchida, (Tokyo, Japan), demonstrated how this technology interfaced with a gold-derived fluorescence inducer that can identify mouse tremors as small as 0.3 mm.

**Editor's (TLP) comment:** Thus, the advances in technology continue to increase our ability to see structure at the microscopic level in our pursuit of more knowledge in early evolutionary changes in lung cancer.

## Plenary Session 3: Friday, September 15: New Treatment Paradigms.

**N**ew understanding of the biology of lung cancer was reviewed by P. A. Bunn, Jr., (Denver, CO). A succession of mutations determine the transformation from normal cells through successive stages of hyperplasia, metaplasia, the various stages of dysplasia, and finally neoplasia. Numerous growth factors control these evolutionary stages. Evidence of overexpression of dominant oncogenes genetic instability and the squelching of suppressor genes have been identified. Not surprisingly, these genes are involved in the regulation of growth, DNA repair, and apoptosis. There is no precise order of gene loss, but some genes appear to be lost earlier than others are (3p greater than 9p, greater than 53p,

greater than RB). p53 is probably the suppressor oncogene that is lost most frequently, but p53 loss may occur at a later time in the development of lung cancer. Overexpression of dominant oncogenes appears to occur later than loss of suppressor genes. The most common overexpressed oncogenes in lung cancer appear to be the mitomycin, ifosfamide, and cisplatin, (MIC), family in small-cell lung cancers. Mutations in Ras occur most frequently in adenocarcinoma. Multiple genetic defects are found in premalignant epithelia, including those that appear cytologically normal. Proliferation, inflammation, invasion, and angiogenesis produce “rogue” clones that evolve into lung cancer. Cell cycle regulation under the control of signaling and growth factor, plus an attack upon cell surface antigens, offers new therapeutic targets.

**Editor's (TLP) comment:** Understanding the biology of lung cancer is rapidly helping to guide new therapeutic strategies. Industry is responding to this new knowledge by the production of novel agents designed not only to be cytotoxic, but also to be suppressive to tumor activity through a variety of independent and interrelated mechanisms.

P. Bonomi, (Chicago, IL), reported on the importance of matrix metalloproteinases, (MMP's), in lung cancer pathogenesis. Malignant tumors have the ability to invade their surrounding environment and to spread to distant sites, via MMP mechanisms. MMP is in a family of proteolytic enzymes that are involved in creating an environment for damage and invasion of the basement membrane, stimulation of angiogenesis, and inhibition of apoptosis. More than 20 MMP's have been identified. MMP's are collagenases, gelatinases, stromelysins, elastases, and the unclassified metalloproteinases which work on different substrates. Their normal function is the regulation of the matrix under conditions of stress and wound healing. MMP enhance the growth of primary tumors and metastases. Inhibitors of MMP's (MMPI), are capable of blocking these pressures. Pre-clinical trials with MMPI show that these compounds reduce tumor size and tend to inhibit metastases. At least three types of MMPI have entered clinical trials. So far, the results of these new clinical strategies are inconclusive. The role of MMPI in the treatment of lung cancer will be determined by numerous studies, which are now underway.

Some of the interesting dilemmas faced by oncologists today are the rapid proliferation of new therapeutic strategies, who to treat, what are the best strategies for chemotherapy, and how should chemoprevention be strategized.

**Editor's (TLP) comment:** There is no doubt that the combination of better understandings of the basic biology of lung cancer and targets against basic cellular mechanisms will be the approach to treating lung cancer in the future. It was not surprising that all presenters stressed the importance of initiating treatment early in the evolution of lung cancer, or even better, in chemoprevention.

New molecular targets for cancer chemotherapy, according to N. Saijo, (Tokyo, Japan), may hold new promise for treatment of late stage lung cancer which has been already substantially improved through development of new drugs and the understanding of better therapeutic strategies through controlled clinical trials. But, there is a great need to take other approaches.

Numerous molecular targets of cancer chemotherapy have been identified based on the progress of molecular biological studies. To each molecular target, many new compounds have been developed to treat advanced stages of lung cancer. They include inhibitors of transduction, CDK inhibitors, anti-angiogenesis agents, matrix metalloproteinase inhibitors, and other novel compounds. Target-based drugs have an effect on specific molecular events in the evolution of lung cancer. They can be potentially used selectively in various molecular targets, rather than just to kill abnormal cells. Accordingly, it can be much less toxic. Since they are only predatory to the powerful processes involved in lung cancer, it must be used when the tumor burden is small. Future chemotherapy may be customized, individualized, personalized, or tailor-made, based upon molecular markers that reliably can be targeted to deal with the basic biological aberrations, the precursors of invasive and lethal lung cancer.

**Editor's (TLP) comment:** It's a Star Wars-type of era that we are now in with anti-rocket warfare going on at the molecular level.

### Selected Reports on Malignant Pleural Mesothelioma, (MPM).

Currently, there is no standard treatment for unresectable malignant pleural mesothelioma, (MPM). Three abstracts presented at the IASLC meeting were of particular interest. J.W. van Haarst, (Heidelberg, Germany), reported on behalf of a cooperative group study (Multicenter Phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Lung Cancer* 2000;29:185-195, abstract #56). Thirty-two patients with unresectable MPM were treated with gemcitabine (1,250 mg/m<sup>2</sup>) on day 1 and 8 and cisplatin (80

mg/m<sup>2</sup>) on day 1 every 3 weeks. The pathology and radiologic responses underwent a central review to ensure quality. They observed 4 partial responses and 18 stable disease for an overall response rate of 15%, (as reported at the meeting). The median survival time was 10 months.

**Editor's (JRJ) comment:** This trial is important because it refutes the results of a previously reported trial (Byrne MJ, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: A Phase II study. *J Clin Oncology* 1999;17:25-30) from Australia that reported a 48% major response rate with the same combination with a slightly different treatment schedule. It is unclear why there is such a major discrepancy in the response rate between the two trials.

J.P.C. Steel, (London, England), reported the results of a single institution Phase II trial. They treated 65 patients with MPM with weekly IV administration of vinorelbine (30 mg/m<sup>2</sup>) for six weeks followed by a two-week break and then re-treatment if the patient was stable or responding. They observed 12 partial responses from 57 evaluable patients, for a response rate of 21%. There were 37 patients with stable disease. The median survival time was an encouraging 13.4 months (Steele JPC, et al. Vinorelbine (Navelbine) given as a single agent for malignant pleural mesothelioma. Results from 65 patients at a single centre. *Lung Cancer* 2000;29:185, abstract #55).

A Calvert, (Newcastle-upon-Tyne, United Kingdom), evaluated a new drug, ALIMTA™, in combination therapy (Calvert A, et al. ALIMTA™ in combination with carboplatin demonstrates clinical activity against malignant mesothelioma in a Phase II trial. *Lung Cancer* 2000;29:195-205, abstract #59). ALIMTA™ is a novel anti-folate that inhibits several folate-dependent enzymes and has demonstrated activity against a number of solid tumors. This was a Phase I trial (dose escalating). On day 1, patients received ALIMTA™ by ten-minute infusion followed by carboplatin. The dose level of ALIMTA™/carboplatin ranged from 400 mg/m<sup>2</sup>/AUC 4 to 500 mg/m<sup>2</sup>/AUC 6, which was the maximum tolerated dose. Of 25 evaluable patients, they observed 10 partial responses for a response rate of 40%. The median survival time was 410 days.

**Editor's (JRJ) comment:** These last two trials are of interest because of the encouraging response rate noted with either single agent vinorelbine, (21%) or the combination of ALIMTA™ and carboplatin, (40%). The London group is currently evaluating the combination of

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vinorelbine and oxaliplatin (a newer platinum agent in use in gastrointestinal cancers), and the group from Newcastle has plans to move the ALIMTA™ and carboplatin into a Phase II trial.

The most encouraging point about the entire session in which these abstracts were presented is that the field of investigation for new treatments of MPM is alive and prospering. While we still do not have a “standard therapy,” there are promising new results. Accordingly, I would encourage my pulmonary and thoracic surgery colleagues to refer their patients with MPM to medical oncology colleagues who are offering these patients participation in clinical trials. Without clinical trials, no progress will be made.

## Satellite Symposium on Photodynamic Therapy and Other Selected Presentations.

**P**hotodynamic Therapy, (PDT), played a small but important role at the recent 9th World Conference on Lung Cancer.

Immediately preceding the meeting, was a morning symposium entitled “Photodynamic Therapy—Valuable Tool in the Treatment of Lung Cancer.” This symposium was chaired by two world experts in the use of PDT in lung, Drs. H. Kato, (Tokyo, Japan), and D. A. Cortese, (Jacksonville, FL). Dr. Cortese delivered the first presentation on PDT in late stage lung cancer. This was followed by E. S. Edell’s, (Rochester, MN) presentation on PDT for early lung cancer. The final presentation was by T. Okunaka, (Tokyo, Japan), on the topic of PDT for bronchogenic carcinoma. Each of the presenters discussed both the possible utility of PDT in specific types of lesions/patients as well as possible problems. All data presented was based on long-term (> 5 year) follow-up.

During the meeting, there were two additional key presentations discussing PDT. These were by Dr. T. G. Sutedja, (Amsterdam, The Netherlands), and the Tokyo Medical University group of Drs. C. Konaka, T. Okunaka, K. Furukawa, and H. Kato, (Tokyo, Japan). The interesting fact is that the discussion following both the symposium presentations and these other key presentations was very similar and revolved around two key areas. The areas were the “actual” stage of the lesion and the critical end point of the therapy. Discussing the latter area first, the authors and discussants felt it was critical to define what was meant by the utility of PDT. In some cases utility was to be defined as “cure,” the long-term elimination of the lesion. In other cases PDT had utility in “down staging” the patient. This had several different end points

ranging from converting an inoperable patient to an operable one, and to reducing the extent of the necessary surgical procedure to even the elimination of the need for surgery.

The discussion of the “stage” of the lesion was more complex, and was interrelated to many presentations related to new diagnostic methods. Many so-called “early” lesions in the data presented at the meeting and in the published literature differed widely in size (<.5 cm to >2.0 cm) and stage (severe dysplasia to invasive carcinoma). It was generally agreed that it was these differences which were strongly associated with the observed differences in response to PDT. Long-term cures of over 90% of treated lesions could be obtained with PDT but only in the smaller (<1.0 cm) and early stage (CIS, T1) lesions. This discussion was, however, intertwined with the discussion throughout the meeting of “over diagnosis.” Were these early lesions, now being detected by new CT and optical methods, true malignancies in need of treatment? This topic will be left to another discussion.

## Selected Abstracts from the 11th World Congress of Bronchology, June 7–10, 2000, (Yokohama, Japan).

**The Follow-up of Dysplasias Diagnosed by the Fluorescent Bronchoscopy.** Hoshino H, et al., (Chiba, Japan).

**B**ackground: Some of dysplasias in the bronchial epithelium are thought to be a precancerous lesion that may develop to squamous cell carcinoma.

**Purpose:** To clarify the details of the periodic follow-up of dysplasias localized by the fluorescence bronchoscopy.

**Patients and Methods:** From October 1997, to December 1999, we diagnosed 79 dysplasias in the 43 patients by the fluorescence bronchoscopy. We could follow-up 39 dysplasias in the 19 patients approximately every 6 months. In addition, assessed of the correlation between histological outcome and smoking status, and telomerase activity of biopsy specimens. The features of the 19 patients include that male/female: 19/0. Age: 55 to 75 year-old (mean: 68). Pack-years: 11.5 to 156 (mean 61.1).

**Results:** Of 39 dysplasias, 2 developed to squamous cell carcinoma, 14 maintained dysplasia, 5 metaplasia, 2 hyperplasia, and 16

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“To clarify the details of the periodic follow-up of dysplasias localized by the fluorescence bronchoscopy.”

regressed to bronchitis or normal bronchial epithelium (mean follow-up period: 6.8 months). Though there was no significant difference ( $P=0.063$ ), dysplasia tended to regress in the patient who stopped smoking. Also, dysplasia with high telomerase activity tended to remain dysplasia.

**Conclusions:** Some of dysplasias developed to squamous cell carcinoma. The patient with localized dysplasia should be carefully followed up and be motivated to stop smoking.

**Editor's (SL) comment:** Approximately 10% of patients with bronchial dysplasia progressed to invasive cancer with a mean follow-up of less than a year. This points out that dysplasia is not a benign entity. Also, dysplasia with high telomerase activity tended to persist or progress. Telomerase activity may be a useful indicator of the biological behavior of these lesions.

#### Micromachines. Mizuno H. Olympus Optical Co, Ltd., (Tokyo, Japan).

**R**ecently micromachine technology has been actively introduced to the endoscope. It has allowed endoscope to get into the organs that it could not before. Also, micromachine technology enables us to obtain various images and data that lead to advanced diagnosis. As examples of the above, the following devices are introduced:

Active bending catheter, with SMA, (Shape Memory Alloy), realizes accurate bending of the distal end by remote control and ensures clear observation.

Micro tactile sensor, which is fabricated by micromachining technique, can measure the hardness of tissue.

Ultra-thin video endoscope is the thinnest video endoscope in the world. We developed Ultra-thin video endoscopy by using micro fabricating technology and micro assembling technology.

Endoscopic Optical Coherence Tomography is a novel technique based on low-coherence interferometry that provides non-invasive, surface, high resolution imaging of biological ultrastructure. The optical component inside the probe is fabricated using miniaturization technology.

Micro confocal scanning microscope is a laser-scanning microscope extremely miniaturized with micromachine technology and is built into the distal end of the probe. It realizes the observation of the cellular architecture of biological tissue with resolution on the micro scale *in vivo* without biopsies.

Micromachine technology has enhanced the diagnostic capability of endoscopes. It enables endoscopes to reach deeper parts of various organs and obtain much more diagnostic information. Consequently, endoscopes can contribute to less-invasive and more precise diagnosis.

At Olympus, we continue technical challenges to realize the Capsule Endoscope as a dream endoscope.

#### Assessment of Usefulness of Endobronchial Ultrasonography, (EBUS), in Determination of Depth of Tracheobronchial Tumor Invasion. Kurimoto N, et al., (Higashi-Hiroshima, and Iwakuni, Japan).

**P**urpose: We reported that the cartilaginous portion are depicted as five layers. The membranous portion appears as three layers with the 20 MHz probe, and that we got the correct diagnosis on 23 cases of 24 resected tracheobronchial tumors in water. The purpose of this study is to assess the usefulness of EBUS (balloon probe), in determination of depth tumor invasion in clinical cases.

**Method:** We compared EBUS images (balloon probe), and histopathologic findings of resected specimens. The probe is a miniature probe (20 MHz radial type, diameter 2.6 mm UM-BS20-26R Olympus).

**Result:** In our 26 clinical lung cancer cases, depth of tumor invasion by the ultrasonograms and the histopathologic findings was the same in 23 of the 26 lesions (88.5%). We had three cases where the EBUS findings did not correlated with the histopathologic findings. In one case, tumor invaded to the adventitia whereas I diagnosed beyond adventitia. The depth of tumor invasion of the other 2 cases was carcinoma *in situ* on histopathological findings. We are not able to detect the carcinoma *in situ* on EBUS, because the tumor is included in the first hyperechoic marginal echo. We classified the depth of tumor invasion in 1) submucosa, 2) cartilage, 3) adventitia, and 4) beyond adventitia.

**Conclusion:** This method by the balloon probe allows visualization of the laminar structure of the trachea and bronchial wall, which is impossible with other diagnostic imaging methods.

“Some of dysplasias developed to squamous cell carcinoma. The patient with localized dysplasia should be carefully followed up and be motivated to stop smoking.”

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“In our 26 clinical lung cancer cases, depth of tumor invasion by the ultrasonograms and the histopathologic findings was the same in 23 of the 26 lesions (88.5%).”

## Brief History of International Association for the Study of Lung Cancer, (IASLC).

*Sponsored by the National Cancer Institute, the 1st International Workshop for Therapy of Lung Cancer was held in Airlie House Conference Center near Washington D.C. in October, 1972. At the end of this landmark meeting, Dr. David. T. Carr, (Houston, TX), introduced the idea of developing an international organization to foster the fruitful exchange of ideas about how to deal with the growing worldwide problem of lung cancer. Thus, the IASLC was born.*

*By mid 1974, the new association had 250 members. An organizational planning meeting was held in Florence, Italy in October, 1974 in conjunction with the 11th International Cancer Congress. A formal organization resulted. Shortly afterwards, the association was incorporated as a non-profit corporation, (IASLC).*

(continued)

## Utility of Endobronchial Ultrasonography in the Diagnosis of Nodular Lesions in the Peripheral Lung. Matsuo K, et al., (Okayama, Japan).

**W**e examined the utility of endobronchial ultrasonography, (EBUS), in the diagnosis of nodular lesions in the peripheral lung field. Since September, 1998, EBUS was performed in 48 patients (29 male, 19 female, age 27 to 86), with nodule lesions in the peripheral lung field using 20 MHz radial probe (UM-3R Olympus). Echo probe reached the lesions in 37 out of 48 cases and we were able to get echo images. These patients include 23 cases of lung cancer, 3 cases of metastatic lung cancer, 3 cases of organizing pneumonia, and 1 case of pneumonia lung abscess, atypical mycobacteriosis, aspergilloma, BOOP, MALT lymphoma, respectively.

EBUS was thought to be very useful in the diagnosis of nodular lesion in the peripheral lung and the images of EBUS showed very suggestive findings in the differential diagnosis between malignant and benign inflammatory lesion.

## Evaluation of the Bronchial Wall Invasion and the Peribronchial Nodal Metastasis Using Endobronchial Ultrasonography, (EBUS), in Malignant Lung Tumors. Baba M, et al., (Chiba, Japan).

**O**bject: To demonstrate the ability of EBUS to image the bronchial wall invasion and peribronchial lymph nodes in malignant lung tumors.

**Materials and Methods:** 27 patients with endobronchial tumor-findings associated with malignant tumors who underwent surgical resection or forceps biopsy were used. Malignant tumors included 25 primary lung cancers and 2 metastatic lung tumors. EBUS was performed during bronchoscopy using the thin ultrasonic probe UM-BS20-24R (20 MHz Olympus) via the channel of the bronchoscope BF-XT (Olympus) preoperatively. Bronchial invasion was estimated in 26 cases paying attention to the continuity of the cartilage layer in the EBUS images. Endobronchial tumor-findings consisted of 14 nodular, 7 polypoid, 5 superficial infiltration. Peribronchial nodes were considered as metastasized when the short axis was 10 mm or more and the shape was round or oval. The assessment of intrapulmonary nodal metastasis by EBUS in 8 primary cancers were compared with the diagnosis by CT.

**Results:** All tumors were considered by EBUS not to invade the cartilage layer in 8 endobronchial tumor lesions without cartilage

destruction confirmed by histology, and all tumors revealed extrabronchial tumor tissue by EBUS in 18 malignant tumors confirmed their endobronchial and extrabronchial tumor extent by histology. In 8 peribronchial lymph node stations including 1 interlobar or 3 segmental nodes which were confirmed as metastasized histologically, 3 (15%) were assessed as positive by EBUS whereas none was judged by CT (Fisher's exact probability test:  $p=0.071$ ).

**Conclusions:** With the use of high resolution thin ultrasonic probes, the bronchial wall structure can be clearly imaged including peribronchial lymph nodes. EBUS appears to be useful to judge the depth of tumor invasion to the bronchial walls or intrapulmonary nodes to be metastasized.

## Ultrathin Bronchoscopy as a New Tool in the Diagnosis of Peripheral Lung Lesions. Schoenfeld N, et al., (Berlin, Germany).

**B**ackground: The diagnostic yield of conventional bronchoscopy for peripheral lesions is limited because of lacking visibility beyond the segment level and the frequent inability to reach the lesions even under fluoroscopic guidance.

**Methods:** A 2.8 mm thin flexible bronchoscope ("babyscope" prototype BF-XP40 Olympus Optical) was tested in 48 bronchoscopies in the same number of patients with peripheral lung lesions and with normal macroscopic findings during conventional bronchoscopy. In 40 patients (12 women, 28 men), there is a definite diagnosis available so far.

**Results:** Visibility was found up to the 10th generation of bronchi. The lesion size varied from one to nine cm. Under fluoroscopy 38/40, (95%) lesions appeared reachable for the babyscope. In 13/32, (40%) patients with malignancy babyscope revealed macroscopically direct or indirect signs of peripheral tumour growth. Malignancy was proven either by histology and/or cytology in 13/32, (40%) patients by babyscope. 3/8 benign conditions could be diagnosed as well.

**Conclusion:** The babyscope is a new and probably complementary tool in the diagnosis of peripheral lung lesions. The study is ongoing to obtain more precise data on specific indications for the method.

**Real Time Observation of Ciliary Beat of the Bronchial Epithelium Through the Bronchofiberscope Modified for High-power Magnification. Sakurada A, et al., (Sendai, Japan).**

**Background:** The ciliary beat of the bronchial epithelium has been observed *in vitro* and *ex vivo* through the stereoscopic zoom microscope. Through endoscope, the real time observation of ciliary beat is possible, it is very useful to detect a variety kind of disorders of the bronchial epithelium, including inflammation, ischemia, and malignant change.

**Objective:** To clarify whether the modified bronchofiberscope has an ability to visualize ciliary beat or another useful information, which have never been obtained through conventional bronchofiberscopes.

**Methods:** We made prototypes by modifying the optical system of conventional bronchovideoscope in cooperation with Olympus Optical Corporation. We observed the bronchial surface of resected lung in human and pig through stereoscopic zoom microscope and through the prototype high magnification videoscope (XBF-200HM2), which can magnify objects 100 times.

**Results:** Through the high magnification videoscope we could recognize: 1) ciliary beat as fine vibrations of light reflection, 2) the details of known structure, for example, winding of microvessels.

**Conclusion:** Although some additional modifications are needed, high magnification videoscope can be a novel and powerful diagnostic tool.

**Editor's (SL) comment:** Technological advances make it possible to assess the extent of bronchial wall invasion and even peribronchial lymph node spread to separate *in situ* carcinoma from invasive cancer using endobronchial ultrasonography, (EBUS). This will help to select patients for curative endobronchial treatment such as photodynamic therapy or electrocautery treatment. The nature of small peripheral lung nodules (benign versus malignant), may now be diagnosed using ultra-thin bronchoscopes or EBUS. High magnification bronchoscopes that can magnify the bronchial surface 100 to 200 times, enable visualization of fine details in the bronchial epithelium, although movement artifacts need to be overcome. Confocal microscopy can provide cellular details with cell by cell depth resolution. These developments complement the rapid and sensitive, but not as specific scanning capability of fluorescence

bronchoscopy, to determine the nature of the lesion, hopefully, without taking a biopsy in the future. Wireless capsule endoscopy has been recently reported by Israeli investigators for the GI tract (Iddan G, et al. Wireless capsule endoscopy. *Nature* 2000;405:417). Whether similar wire/wireless capsule technology can be applied to examine deeper parts of the lung, is an intriguing possibility provided one can invent a capsule that would not stimulate the cough reflex.

**“And the Beat Goes On.”**

**T**he emergence of new technologies has reawakened interest in screening for early stages of lung cancer. Low radiation dose, helical CT scanning for peripheral adenocarcinomas and improved airway cell markers for central squamous cell carcinomas are being evaluated as early detection clues. Today, the five-year survival rate for lung cancer remains a dismal 13% to 15% in the U.S.A. By contrast, it is nearly 60% in Japan, as a direct result of screening.

The results of the National Cancer Institute-sponsored studies of the mid-1970's, continue to dictate that targeted screening for early lung cancer does not alter outcome. The problem with these naive studies is that they were destined to draw the wrong conclusion when they were designed. The flaws are that they screened low levels of smoking intensity, enrolling smokers of only 20 cigarettes or more during the year before screening (mean age of smoker screened was 20 pack-years). Only men were screened. The strong association between the presence of chronic airflow obstruction and lung cancer was also not appreciated at that time. Also, evidence of presence of lung cancer was missed with the sputum tests used at that time. Lastly, many persons randomized to receive “usual care” in the era of the 1970's received annual chest x-rays, which was the standard of care in that foregone era. Thus, these persons had the opportunity of some chance of early diagnosis by standard chest x-rays.

Now, a late follow-up of the Mayo Clinic component of the screening study, recently published (Marcus PM, et al. Lung cancer mortality in the Mayo Lung Project: Impact of extended follow-up. *J Natl Cancer Inst* 2000;92:1308-1316) continues to conclude that early screening does not work.

**Editor's (TLP) comment:** Are we to remain forever in the dark by following the dogma of this obsolete and inadequate study? Fortunately,

**Brief History of IASLC (continued)**

*The 1st World Congress on Lung Cancer was held in Hilton Head, South Carolina in May, 1978. Dr. Ronald Vincent served as Conference Chairman.*

*The 2nd World Congress was held in Copenhagen in June, 1980, chaired by Dr. Heine H. Hansen. Over 1,000 participants from around the world attended. Dr. Hansen later founded the peer-reviewed journal, Lung Cancer, the official publication of IASLC.*

*Subsequent Conferences were held in Tokyo, Toronto, Interlaken, Melbourne, Colorado Springs, CO, and Dublin at an established three-year interval. This year's Conference was held in Tokyo from September 12th through 15th, 2000.*



many who recognize that today we have the knowledge and technology to be able to change the outcome of lung cancer are beginning to light candles. "The darkness of night will not prevent morn." (African proverb).

## Cancer Chemotherapy 2000 Commentary

**A** study of the 948 abstracts of the 9th World Conference on Lung Cancer indicates that approximately 80% of the presentations were related to cancer chemotherapy. These are published in *Lung Cancer* 2000;29:15-2985. They are also available on a CD-ROM sponsored by Bristol-Myers Squibb. The extended abstracts covered the plenary presentations and are available in Supplement 2 in *Lung Cancer*, September, 2000. This embodies 196 pages of very interesting material.

It is clear that huge advances have been made in cancer chemotherapy in recent years. No longer should anyone, particularly pulmon-

ologists, consider advanced stage lung cancer untreatable or futile. Even in Stage III-B or IV lung cancer, the median survival has gradually increased to over 8 months. The one-year survival is approximately 36%. This is accomplished with very acceptable toxicity, even in older people. Patients with good performance status, Stage 0 or I and occasionally Stage II under the Eastern Cooperative Oncology Group, (ECOG), performance classification, (this is different from the Karnofski classification where high scores were good), should receive cancer chemotherapy unless there are severe comorbidities or anything that might destabilize the patient. It is time for pulmonologists to get more active in cancer chemotherapy by referring patients to oncologists rather than to learn cancer chemotherapy themselves as more and more pulmonologists are starting to do. Of course, the emphasis needs to be on early identification and intervention, which is the goal of *Lung Cancer Frontiers*.

**"No longer should anyone, particularly pulmonologists, consider advanced stage lung cancer untreatable or futile."**

**"It is time for pulmonologists to get more active in cancer chemotherapy by referring patients to oncologists rather than to learn cancer chemotherapy themselves as more and more pulmonologists are starting to do."**

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