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**LUNG
CANCER****FRONTIERS**

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HOPES FOR 2005***Diminishing the Dogma Drag***

by Editor Thomas L. Petty, M.D.

Lung Cancer Frontiers is funded by The Snowdrift Pulmonary Conference and a generous grant from the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida. It is hoped that the unrestricted grant to expand and report our experiences in early lung cancer identification and treatment, based upon studies originally conducted in Grand Junction, Colorado, will provide new and exciting material for *Lung Cancer Frontiers*.

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

The Editorial Board calls everyone's attention that all issues of **Lung Cancer Frontiers** beginning with their inception in 1996 are available on the internet at

www.lungcancerfrontiers.org.

It is becoming progressively clear that the early diagnosis of lung cancer results in the identification of a high proportion of Stage I cancers that are amenable to cure. Please note this quote from the AMA News, 12/27/04, "The early Lung Cancer Action Program, led by Claudia I. Henscke, M.D., PhD, principle investigator and Professor of Radiology at Cornell Medical Center In New York, reported on more than 300 cancers found in 26000 people, who received CT scanning since 1993. Eighty-two percent (82%) were early stage cancer with a high cure rate." She recommends screening those high risk patients on an annual basis.

This has been my position for many years. It is certain that we know that lung cancer risk is associated with smoking and family history, as evidenced by the lead article in this issue of LCF. The additional risk of airflow obstruction has been reported by many. Our work in Grand Junction shows that asymptomatic lung cancer can be found in an efficient way at a relatively low cost. The follow-up of an earlier series of patients diagnosed with early stage lung cancer

shows an approximate 50% cure rate after ten years of treatment (Lung Cancer; 2000;30:1-7). More and more centers are beginning to embrace "case finding" through CT and sputum cytology in patients at highest risk. Unfortunately, we still have to deal with the current dogma that lung cancer screening is not recommended by the US Preventative Service Task Force (Ann Int Med 2004;140:738-739). All the points of the Task Force that cancer found by screening may be biologically and clinically indolent appear to be wrong as documented in the article by Bianchi, page 13, abstract 19.

We also have to deal with the mentality of people in high places, such as Edward J. Patz, Jr., Professor of Radiology and Pharmacology and Cancer Biology at Duke University, North Carolina, is also quoted from the AMA News: "But right now there are no data that suggest screening will actually reduce mortality." This attitude is curious, since more and more studies are showing that survival, which means that you live rather than you die from lung cancer, is now occurring through early diagnosis. It should be emphasized once again that annual CT scanning and sputum cytology are the standard of care in Japan for all smokers over the age of 45, because the survival rates are far higher in the Japanese populations so iden-

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THIS JANUARY ISSUE OF LCF IS THE FIRST OF FOUR QUARTERLY ISSUES PLANNED FOR 2005. WE NEED TO HEAR FROM YOU ABOUT YOUR SATISFACTION WITH OUR ELECTRONIC VERSION OF LCF.

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Lung Cancer 2005: Challenges and Solutions

CME PROGRAM FOR CLINICIANS MARCH 5, 2005 DENVER, COLORADO

Update by International Leaders

- David P. Carbone** — Nashville, TN
“Lung Cancer From Molecular Biology to Clinical Control”
- Claudia I. Henscke** – New York, NY
“New Frontiers in Imaging”
- Stephen Lam** – Vancouver BC
“New Developments in Bronchology and Sputum Cytology”
- York E. Miller** and **Robert H. Keith** – Denver, CO
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tified.

Someday reason will prevail and we will have systematic programs for early identification, treatment and cure of lung cancer, that are not only cost effective but reduce the ravages and burdens of dealing with advanced stages of lung cancer, which is the state of the situation today in the United States today. Progress will be made in 2005. Happy New Year!

NOTEWORTHY ABSTRACTS

FAMILIAL RISK OF LUNG CANCER BETTER DEFINED

1. JAMA 2004;292:2977-2983

Familial risk of lung carcinoma in the Icelandic population.

Jonsson S, Thorsteinsdottir U, Gudbjartsson DF, Jonsson HH, Kristjansson K, Arnason S, Gudnason V, Isaksson HJ, Hallgrimsson J, Gulcher JR, Amundadottir LT, Kong A, Stefansson K.

Department of Medicine, Landspítali-University Hospital, Reykjavik, Iceland.

CONTEXT: The dominant role of tobacco smoke as a causative factor in lung carcinoma is well established; however, an inherited predisposition may also be an important factor in the susceptibility to lung carcinoma. **OBJECTIVE:** To investigate the contribution of genetic factors to the risk of developing lung carcinoma in the Icelandic population. **DESIGN, SETTING, AND PARTICIPANTS:** Risk ratios (RRs) of lung carcinoma for first-, second-, and third-degree relatives of patients with lung carcinoma were estimated by linking records from the Icelandic Cancer Registry (ICR) of all 2756 patients diagnosed with lung carcinoma within the Icelandic population from January 1, 1955, to February 28, 2002, with an extensive genealogical database containing all living Icelanders and most of their ancestors since the settlement of Iceland. The RR for smoking was similarly estimated using a random population-based cohort of 10,541 smokers from the Reykjavik Heart Study who had smoked for more than 10 years. Of these smokers, 562 developed lung cancer based on the patients with lung cancer list from the ICR. **MAIN OUTCOME MEASURES:** Estimation of RRs of close and distant relatives of patients with lung carcinoma and comparison with RRs for close and distant relatives of smokers. **RESULTS:** A familial factor for lung carcinoma was shown to extend beyond the nuclear family, as evidenced by signifi-

cantly increased RR for first-degree relatives (for parents: RR, 2.69; 95% confidence interval [CI], 2.20-3.23; for siblings: RR, 2.02; 95% CI, 1.77-2.23; and for children: RR, 1.96; 95% CI, 1.53-2.39), second-degree relatives (for uncles/aunts: RR, 1.34; 95% CI, 1.15-1.49; and for nephews/nieces: RR, 1.28; 95% CI, 1.10-1.43), and third-degree relatives (for cousins: RR, 1.14; 95% CI, 1.05-1.22) of patients with lung carcinoma. This effect was stronger for relatives of patients with early-onset disease (age at onset < or =60 years) (for parents: RR, 3.48; 95% CI, 1.83-8.21; for siblings: RR, 3.30; 95% CI, 2.19-4.58; and for children: RR, 2.84; 95% CI, 1.34-7.21). The hypothesis that this increased risk is solely due to the effects of smoking was rejected for all relationships, except cousins and spouses, with a single-sided test of the RRs for lung carcinoma vs RRs for smoking. **CONCLUSIONS:** These results underscore the importance of genetic predisposition in the development of lung carcinoma, with its strongest effect in patients with early-onset disease. However, tobacco smoke plays a dominant role in the pathogenesis of this disease, even among those individuals who are genetically predisposed to lung carcinoma.

Editorial Comment (TLP):

This lead article in the JAMA is extremely important because it further defines the genetic risk factors in lung cancer. Author and editorial board member, Steinn Jonsson, elaborates on his findings below.

2.

Editorial Comments (SJ):

In a case-control study published in 1963, Tokuhata and Lilienfeld¹ first observed a 2-fold increase in the development of lung cancer in 1st degree relatives of lung cancer patients. The study was controlled for smoking, age and gender and suggested a familial or genetic predisposition to lung cancer. More recently studies by Seller et al, using segregation analysis, showed similar results and suggested an autosomal co-dominant pattern of inheritance². Since these early reports the notion of familial or genetic risk in lung cancer has been studied extensively but has remained controversial. Thus a study of 15924 pairs of twins failed to show any evidence of a genetic predisposition to lung cancer.³

In a study recently published in JAMA⁴ investigators at the university of Iceland Hospi-

“These results underscore the importance of genetic predisposition in the development of lung carcinoma, with its strongest effect in patients with early-onset disease.”

“... An inherited predisposition may also be an important factor in the susceptibility to lung carcinoma.”

“In this study they were able to estimate the risk ratios (RR) for 1st, 2nd and 3rd degree relatives of lung cancer patients by linking information on all lung cancer patients.”

“This study is an important step towards resolving the long-standing debate on genetic susceptibility . . .”

“ . . . The study was not designed to elucidate the mode of inheritance.”

“For all groups of relatives the RRs were significantly increased for patients diagnosed with lung cancer ≥60 years of age when compared to relatives of all lung cancer patients.”

tals, Icelandic Heart Association and Decode Genetics in Reykjavik, Iceland, have studied the familial risk of lung carcinoma in the Icelandic population using a unique set of data. In this study they were able to estimate the risk ratios (RR) for 1st, 2nd and 3rd degree relatives of lung cancer patients by linking information on all lung cancer patients diagnosed within the Icelandic population in the period of 1955-2002, to an extensive genealogical database containing all 284,000 living Icelanders and most of their ancestors.⁵

Comparing the 2756 patients with controls in the Icelandic genealogical database the 1st degree relatives (parents, siblings and children) of lung cancer patients showed a RR of 2.69, 2.02 and 1.96, respectively. Risk ratios of 2nd degree relatives aunts/uncles and nephews/nieces (1.34 and 1.26) were lower than that of 1st degree relatives but were also significantly greater than 1 as was the RR for cousins (1.14). The RR for mates was also significantly elevated at 1.75, although lower than that of 1st degree relatives and indicates the presence of smoking or smoke exposure as a shared environmental factor.

For all groups of relatives the RRs were significantly increased for patients diagnosed with lung cancer ≥60 years of age when compared to relatives of all lung cancer patients. Thus the RRs for 2nd degree relatives (1.96 and 1.94) of early onset patients were as high as those for the 1st degree relatives of all lung cancer patients. This provides further evidence for a familial or genetic predisposition.

This is the first study that demonstrates that the familial risk of lung cancer extends beyond the immediate family. This is particularly important in a disease where the environmental factor is so strong as in lung cancer. In more distant relationships the shared environment is likely to be of less importance.

Since smoking information was available only on a small proportion of all lung cancer patients and their relatives it was not possible to calculate RR of lung cancer directly, taking smoking into account. Instead the RRs of smoking for relatives of smokers were compared to the RR for lung cancer among relatives of lung cancer patients. The authors show mathematically that assuming that the familial clustering of lung cancer is entirely explained by the familial clustering of smoking, then the RR of smoking must be greater than that of lung cancer. The hypothesis that this increased risk of lung cancer was solely due to the effects of smoking was rejected with a single sided test on the RR of lung cancer versus that of smoking. Thus the RR of lung cancer was greater than the RR for smok-

ing for all categories of relatives except cousins. And importantly the RR of smoking was significantly greater than the RR for lung cancer among the mates of the lung cancer patients.

This study is an important step towards resolving the long-standing debate on genetic susceptibility in lung cancer. The data indicate that there is indeed a genetic predisposition to the development of lung cancer which is strongest in early-onset patient and that this predisposition is not only present among first degree relatives, but also extends to second and third degree relatives with a step-wise falloff in RR as you get further from the proband. In a recent report a major lung susceptibility locus was mapped to chromosome 6q23-25⁶ also supporting the conclusion that there is a genetic predisposition to the development of lung cancer.

The authors acknowledge that the study was not designed to elucidate the mode of inheritance. Furthermore it cannot answer the fundamental question of how much of the lung cancer risk is attributable to familial factors as compared to smoking. Many theories have been advanced which could explain individual differences in susceptibility to tobacco carcinogens and are likely to include genes involved in decreasing or increasing the activity of carcinogens (e.g. CYP1A, CYP2E and GSTM1) and genes involved in monitoring and repairing tobacco carcinogen induced DNA damage (e.g. p53 and ERCC1).

But how will this knowledge be put to use? We know that treatment results in lung cancer have remained poor and only insignificant gains have been made in recent decades. This is because 65-70% of all patients with lung cancer are diagnosed in an advanced stage (III or IV) where the prognosis is dismal. Even among patients diagnosed at an early stage (I-II) a substantial proportion of patients relapse and succumb to the disease.

It is clear that a new approach to the epidemic of lung cancer is needed. The importance of prevention cannot be overemphasized and efforts to curb smoking with public education, anti-smoking laws and smoking cessation programs have already resulted in falling smoking rates and lung cancer incidence among men in some western countries. The incidence among women has however continued to increase. Furthermore the rising problem of lung cancer in developing countries where the situation is different with respect to public education and awareness is likely to more than offset gains in the developed world. Lung cancer is therefore going to remain the largest cancer killer in the world for the foreseeable future with death rates exceeding those from the next four cancer killers combined, namely breast, prostate, colon and pancreas.

Advances in screening with low dose helical CT and promising new technologies relating to cytology and tumour markers⁷ are now shifting the em-

“Advances in screening with low dose helical CT and promising new technologies relating to cytology and tumour markers are now shifting the emphasis in research towards detecting and treating lung cancer at an early stage.”

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phasis in research towards detecting and treating lung cancer at an early stage⁸. Although prior screening studies have proven fruitless, the opportunity of finding a tumour several doubling times earlier creates better opportunities for early diagnosis and treatment than previously possible. In this context it is vitally important to gain additional understanding of the predisposing factors in lung cancer. All smokers are not equal when it comes to susceptibility to lung cancer development as shown in the study cited above and many others. Furthermore the notion that all smokers are suitable for screening seems implausible if only for logistical reasons.

The factors already known to influence lung cancer risk are smoking, family history and the presence of reduced lung function particularly airway obstruction⁹. Information gained from new epidemiological and genetic studies may prove crucial in allowing for more accurate risk stratification, which will be important for both early detection and prevention. The combination of family history, smoking history and lung function tests looking for airflow obstruction may in the future provide better information on the population, which might benefit the most from screening and other preventive strategies.

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Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan.

Chen CL, Hsu LI, Chiou HY, Hsueh YM, Chen SY, Wu MM, Chen CJ; Blackfoot Disease Study Group.

Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan.

CONTEXT: Arsenic has been documented as a lung carcinogen in humans in only a few follow-up studies, which were limited by a small number of cases or the lack of information on cigarette smoking. OBJECTIVES: To elucidate the dose-response relationship between ingested arsenic and lung cancer and to assess the effect of cigarette smoking on the arsenic-lung cancer association. DESIGN, SETTING, AND PARTICIPANTS: A total of 2503 residents in southwestern and 8088 in northeastern arseniasis-endemic areas in Taiwan were followed up for an average period of 8 years. Information on arsenic exposure, cigarette smoking, and other risk factors was collected at enrollment through standardized questionnaire interview. MAIN OUTCOME MEASURES: The incidence of lung cancer was ascertained through linkage with national cancer registry profiles in Taiwan (January 1985-December 2000). The joint effect of arsenic and cigarette smoking was estimated by both etiologic fraction and synergy index. RESULTS: There were 139 newly diagnosed lung cancer cases during a follow-up period of 83,783 person-years. After adjustment for cigarette smoking and other risk factors, there was a monotonic trend of lung cancer risk by arsenic level in drinking water of less than 10 to 700 microg/L or more ($P < .001$). The relative risk was 3.29 (95% confidence interval, 1.60-6.78) for the highest arsenic level compared with the lowest. The etiologic fraction of lung cancer attributable to the joint exposure of ingested arsenic and cigarette smoking ranged from 32% to 55%. The synergy indices

“The joint effect of arsenic and cigarette smoking was estimated by both etiologic fraction and synergy index.”

“... the diagnosis of lung cancer in asymptomatic patients in the private practice setting is not even on the radar screen for the editors of the major primary care journals.”

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“... The story behind the story.”

ranged from 1.62 to 2.52, indicating a synergistic effect of ingested arsenic and cigarette smoking on lung cancer. CONCLUSIONS: There was a significant dose-response trend of ingested arsenic on lung cancer risk, which was more prominent among cigarette smokers. The risk assessment of lung cancer induced by ingested arsenic should take cigarette smoking into consideration.

Editorial Comment (TLP):

Arsenic is a well known lung cancer risk and a common component of tobacco smoke. This article indicates that local water supplies in various parts of the world are confirmed as a carcinogen and co-carcinogen, along with tobacco, in lung cancer. These two articles are discussed in an accompanying editorial in the JAMA, “Lung cancer etiology: independent and joint effects of genetics, tobacco, and arsenic. JAMA 2004;292:3026-3029.”

4. **STUDY FINALLY ACCEPTED!**

Grand Junction Study Finally Accepted!

Readers of LCF will recall that I have made several comments about an important study, conducted in Grand Junction, Colorado. It has finally been accepted for publication in a forthcoming issue of *CHEST*. This commentary is "the story behind the story". Since the study was conducted in the offices of all 15 primary practitioners within one calendar year, and it focused on patients that come to a doctor for ANY reason, we naturally thought that publication in a primary care journal would be most appropriate. We first sent the manuscript to the JAMA and The Archives of Internal Medicine. It was returned within a week without review. The same happened with the Annals of Internal Medicine, and the American Journal of Medicine! What this means is that the diagnosis of lung cancer in asymptomatic patients in the private practice setting is not even on the radar screen for the editors of the major primary care journals.

This is a sad commentary on the status of lung cancer in the minds of all too many. Actually the Grand Junction study will have a tremendous impact in the future. The practitioners had 1296 of their patients over age 50, complete a simple one page questionnaire to determine high risk. High risk was defined as heavy smoking, a family history of lung cancer or an occupational risk. 430 patients

were identified as high risk individuals. Simple office spirometry was done in all 430. 126 had spirometric abnormalities, mostly various stages of obstructive airways disease. All were offered a chest x-ray, chest CT and sputum cytology. Only 88 would actually complete these tests. The result was the identification of 8 cancers, four early stage and four more advanced. All 8 received treatment. All four of the early stage patients are alive, following resectional surgery for more than three years, thus far. We are also following the entire cohort of 430 for at least five years to get the rest of the story. (study funded by the Flight Attendants Medical Research Institute, Miami, FL). No matter what the final outcome, it will be interesting. I predict that the Grand Junction Study will be a model for other community based identification programs in the future. Look for the Chest article in early 2005. (TLP)

5. Eur Respir J 2004;24:898-904

Lung cancer: clinical presentation and specialist referral time.

Buccheri G, Ferrigno D.

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Many textbooks describe symptoms and signs of lung cancer but refer to old series of patients. To update knowledge about lung cancer presentation, a study was carried out on 1,277 consecutive lung cancer patients, who were seen in a single Institution from January 1989 to October 2002. A set of 33 anthropometric, clinical, physical, laboratory, radiological, pathological and follow-up variables was prospectively recorded for all patients. In addition, information was obtained concerning symptoms of alarm (i.e. potential concern), times to specialist referral and the mix of symptoms at presentation. Patients were carefully followed-up and their subsequent clinical course was recorded. Casual discovery with absence of symptoms occurred more frequently towards the end of the study period and the prevalence of chest pain became less common. No other time-dependent changes were found in the presenting symptoms. Delay in specialist referral was longer when presentation was provoked by cough or by the occurrence of systemic symptoms, such as weight loss, anorexia and asthenia. Referral delay was longer towards the end of the study, perhaps related to an increase in the number of elderly patients with co-morbidities. Both alarm and prevalence symptoms were strong predictors of the clinical outcome, as found in both univariate analysis (favourable: casual discovery and chest infection; unfavourable: chest pain, dyspnoea, systemic symptoms and symptoms of

“Delay in specialist referral was longer when presentation was provoked by cough or by the occurrence of systemic symptoms, such as weight loss, anorexia and asthenia.”

“Early presentation of lung cancer is characterized by a specific symptomatic pattern.”

“Physicians are most often sued by patients in their 50s(mean age, 58.9 years; range, 34 to 80 years . . .”

“Over the past 12 years, there appears to have been a substantial increase in awards to patients with lung cancer who sue their physicians.”

local or systemic dissemination) and in multivariate analysis (favourable: chest infection). Early presentation of lung cancer is characterised by a specific symptomatic pattern. Knowledge of this pattern may help to improve the rate of early diagnosis.

Editorial Comment (TLP):

Reducing the interval between the first evidence of lung cancer and its diagnosis and treatment is key to improving survival. But symptoms most commonly identify late stages of lung cancer. It is so much better to have an approach such as that conducted in Grand Junction in order to diagnose asymptomatic lung cancer at an earlier and more curable stage.

6. Chest 2004;126:1672-1679

Why do physicians who treat lung cancer get sued?

McLean TR.

Third Millennium Consultants, LLC, 4970 Park, Shawnee, KS 66216, USA. tmclean@dnamail.com

BACKGROUND: Minimal information exists on why malpractice actions are filed against physicians who treat lung cancer. OBJECTIVE: To review currently available data on lung cancer malpractice litigation to develop litigation-avoidance strategies. DESIGN: A retrospective review of a publicly available database containing verdicts and settlements of malpractice cases. Data were then compared to the Physician Insurers Association of America (PIAA) Lung Cancer Study, which was published in 1992. The PIAA report is considered the best available data on malpractice and lung cancer. RESULTS: There were 89 patients in the current study and 213 patients in the PIAA study. Physicians are most often sued by patients in their 50s (mean age, 58.9 years; range, 34 to 80 years [current study]; vs 55 years; range, 17 to 75 years [PIAA study]). Primary care physicians (60% cases in the current study vs 33% cases in the PIAA study) and radiologists (20% cases in the current study vs 55% cases in the PIAA study) were named as defendants in > 75% of suits. Failure to diagnosis lung cancer was the most common reason physicians were sued (80% case in the current study vs 23.3% cases in the PIAA series). Despite the similarity in litigation profiles, the mean award to plaintiffs, in constant dollars, increased from \$172,271 in the PIAA study to \$632,261 in the current study. CONCLUSIONS: (1) Recommended strategies to avoid litigation depend on physician subspecialties. While primary care physicians would benefit most from setting up a chest radiograph tracking system,

radiologists would benefit most from initiating a continuous quality improvement system to substantially decrease the misinterpretation rate of chest radiographs. (2) Over the past 12 years, there appears to have been a substantial increase in awards to patients with lung cancer who sue their physicians. However, this finding may be artificial because of differing study design. Further investigation on this subject is recommended.

Editorial Comment (TLP):

There are many clues to the presence of lung cancer in the symptom complex or from imaging of patients with lung cancer that should suggest its diagnosis. Often imaging abnormalities that are missed or not pursued lead to a delay in diagnosis, treatment, and sometimes a trip to the courthouse.

7. Lung Cancer 2004;46:233-245

Influence of age, comorbidity and performance status on the choice of treatment for patients with non-small cell lung cancer; results of a population-based study.

de Rijke JM, Schouten LJ, ten Velde GP, Wanders SL, Bollen EC, Lalisang RI, van Dijck JA, Kramer GW, van den Brandt PA.

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BACKGROUND: In the Netherlands in 1997, 43% of patients with newly diagnosed lung cancer were over 70. Large age-specific differences in treatment exist. We examined whether age, comorbidity, performance status and pulmonary function influenced treatment. PATIENTS AND METHODS: Data on patients with newly diagnosed non-small cell lung cancer (N = 803) were obtained: comorbidity, performance status, pulmonary function (FEV1) and initial treatment. Age-specific differences in treatment according to the guidelines were examined. Odds ratios were calculated by means of logistic regression analyses. RESULTS: 82% with stage I or II disease received treatment according to the guidelines; this applied to 48% with stage IIIA disease and to 54% with stage IIIB disease. For all stages, this proportion decreased with increasing age. In stage IV disease, 36% did not receive any treatment; this applied to 52% of the elderly patients (75+ years). Multivariate analyses showed associations between comorbidity and treatment choice, but none with performance

“Data on patients with newly diagnosed non-small cell lung cancer (N=803) were obtained . . .”

status. Age of 75+ years appeared to be the most important factor for not receiving treatment according to guidelines. CONCLUSION: A substantial proportion of elderly patients with non-small cell lung cancer did not receive standard treatment. Performance status and comorbidity seldom formed the underlying reason. Calendar rather than biological age seemed to play the most important role in choice of treatment for patients with non-small cell lung cancer.

Editorial Comment (TLP):

Although lung cancer is common in old age, this fact does not rule out aggressive treatment on the basis of age alone. Co-morbidity and performance status did not influence this somewhat surprising outcome.

8. J Cell Physiol 2004;25 (Epub ahead of print)

Early diagnosis of lung cancer by detection of tumor liberated protein.

Tarro G, Perna A, Esposito C.

Department of Diagnostics, Unit of Molecular Biology, "D. Cotugno" Hospital, Naples, and Unit of Pathology "M. Scarlato" Hospital, Scafati (SA), Italy.

Tumor liberated protein (TLP) is a protein that can be used to reveal the early development of a tumor. Besides being formed in the tumor, TLP is released in the blood when a patient starts producing cancer cells, which in turn enables the physician to intervene at a stage when the cancer is operable. To date, the available studies of tumor markers in lung cancer patients are CEA, NSE, TPA, Chromogranine, CA125, CA19-9, and Cyfra 21-1. The sensitivity and specificity for serum markers ranges between 50 and 90%, depending on the study and the clinical samples analyzed. Most of these markers show an increased rate of positivity as the stage advances. There are very limited data on TLP to draw any firm conclusion regarding the diagnostic value of this marker. TLP has been detected in 53.1% of non-small cell lung cancer (NSCLC) patients (N = 534) with 75% being positive in the early stage (stage I) and dropping to 45% in the late stage (stage IV). However, 7.6% blood donor sera and 17.4% chronic lung disease sera have also tested positive. In a confirmation study, the specificity was 89.94% and the sensibility was 63.63% from stage III to IV NSCLC patients. In an initial study of TLP as a marker for early

“Age of 75+ years appeared to be the most important factor for not receiving treatment according to guidelines.”

“Most of these markers show an increased rate of positivity as the stage advances.”

detection in stage I, NSCLC patients showed a sensitivity of 66.7% and a specificity of 80% for TLP compared to a sensitivity of 33.3% for CA19-9, 11.1% for Cyfra 21-1 and CA125, and 0% for CEA; the specificity for all four of the latter markers was 100%. Using immunohistochemical analysis with peroxidase anti-peroxidase (PAP), we observed that NSCLC cells were positive; we used the specific rabbit antiserum to TLP, which turned out negative in the presence of 1 mg/ml of the synthesized peptide. The pre-serum was also negative. The same reactivity was found early in the modified epithelial cells of interstitial lung fibrosis and might be a predictive marker of cell transformation. The site of the peroxidase positivity was cytoplasmic, of diffuse and/or granular type. Copyright 2004 Wiley-Liss, Inc.

9. Ann Thorac Cardiovasc Surg 2004;10:213-217
Lung cancer-related genes in the blood.

Sonobe M, Tanaka F, Wada H.

Department of Thoracic Surgery, Kyoto University Hospital, Kyoto, Japan.

Tumor-related genes can be found circulating in the blood of cancer patients. These genes may be derived from circulating cancer cells or from the patient's primary tumor directly by a process referred to as "gene shedding." Selective and sensitive detection of tumor-related genes in the blood of cancer patients has been made possible by the advent of polymerase chain reaction-based technology that can detect mutations, polymorphisms, microsatellite instability, loss of heterozygosity, and promoter hypermethylation. Several reports have documented the clinical potential of using circulating tumor-related genes as a molecular marker for the early detection of lung cancer, and as a prognostic tool in these patients; larger, prospective studies will be needed to test the feasibility of this approach. Certainly, such an approach in lung cancer patients would be attractive since it is noninvasive and employs relatively easy and rapid methodologies.

Editorial Comment (TLP):

Finding reliable markers of lung cancer in the blood of patients is a huge and as yet unsolved problem. Studies such as these two and the other cited in LCF 20, "Detecting lung cancer in plasma with the use of multiple genetic markers: Andriani F, Conte D, Mastrangelo T, et al: Int J Cancer 2004;108:91-96," show approaches that are being taken to solve this problem.

“Several reports have documented the clinical potential of using circulating tumor-related genes as a molecular marker for the early detection of lung cancer, and as a prognostic tool in these patients . . .”

“A total of 155 transthoracic core biopsies with touch imprint smears were performed under ultrasound guidance, with 127 malignant and 28 benign lesions.”

“Subjects had chronic obstructive pulmonary disease and > or = 30 pack-years of tobacco use, and aneusomy was tested using a multi-target DNA FISH assay . . .”

10. *Cancer Detec Prev* 2004;28:244-251

Multi-target interphase fluorescence in situ hybridization assay increases sensitivity of sputum cytology as a predictor of lung cancer.

Varella-Garcia M, Kittelson J, Schulte AP, Vu KO, Wolf HJ, Zeng C, Hirsch FR, Byers T, Kennedy T, Miller YE, Keith RL, Franklin WA.

Department of Medicine, School of Medicine, University of Colorado Health Sciences Center, Cancer Center, Campus Box B188, Denver 80262, USA. marileila.garcia@uchsc.edu

Survival rates for lung cancer are low because patients have disseminated disease at diagnosis; therefore tests for early diagnosis are highly desirable. This pilot study investigated occurrence of chromosomal aneusomy in sputum from a 33 case-control cohort matched on age, gender, and date of sample collection. Subjects had chronic obstructive pulmonary disease and > or = 30 pack-years of tobacco use, and aneusomy was tested using a multi-target DNA FISH assay (LAVysion, Abbott/Vysis). In specimens collected within 12 months of lung cancer diagnosis, abnormality was more frequent among the 18 cases (41%) than the 17 controls (6%; $P = 0.04$). Aneusomy had no significant association with cytologic atypia, which might indicate that molecular and morphological changes could be independent markers of tumorigenesis. Combining both tests, abnormality was found in 83% of the cases and 20% of the controls ($P = 0.0004$) suggesting that FISH may improve the sensitivity of cytologic atypia as a predictor of lung cancer.

Editorial Comment (TLP):

This is another test proposed as a useful sputum marker in the early detection of lung cancer.

11. *Eur Respir J* 2004;24:905-909

Value of imprint cytology for ultrasound-guided transthoracic core biopsy.

Liao WY, Jerng JS, Chen KY, Chang YL, Yang PC, Kuo SH.

Dept of Laboratory Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, 7 Chung-Shan S. Road, Taipei 100, Taiwan.

The aim of this study was to investigate the possible additional diagnostic information provided by imprint cytology when performing ultrasound-guided

transthoracic core biopsy and to evaluate whether it could optimise the biopsy procedure. A total of 155 transthoracic core biopsies with touch imprint smears were performed under ultrasound guidance, with 127 malignant and 28 benign lesions. The imprint smears were stained using Riu's method and interpreted by a cytopathologist. These were compared with the histopathology of core biopsy specimens and the final diagnosis of malignant versus benign disease. The overall diagnostic accuracy of imprint cytology was 94% (146 out of 155). Histopathological analysis showed an overall accuracy of 94% (146 out of 155), with a sensitivity of 94% (119 out of 127) and negative predictive value of 79% (27 out of 34). The combination of these two methodologies had an increased overall accuracy and negative predictive value of 98% (152 out of 155) and 90% (28 out of 31), respectively. The results of imprint cytology and histopathology were in agreement in 143 patients (92%). In conclusion, imprint cytology of ultrasound-guided transthoracic core biopsy is a sensitive procedure for diagnosing peripheral thoracic lesions, and it may increase the diagnostic accuracy and cancer negative prediction of biopsy alone. With an on-site approach, imprint cytology may help to assess the adequacy of biopsy specimens and optimise the biopsy procedure.

Editorial Comment (TLP):

Imprint cytology of needle biopsies of peripheral tumors appears appealing to help identify the nature of tiny tumors that require local resection.

12. *Lung Cancer* 2004;46:11-19

Human small cell lung cancer cells express functional VEGF receptors, VEGFR-2 and VEGFR-3.

Tanno S, Ohsaki Y, Nakanishi K, Toyoshima E, Kikuchi K.

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Studies have suggested that the vascular endothelial growth factors (VEGFs)/VEGF receptors (VEGF-Rs) system plays an important role in tumour growth and metastasis. We conducted the present study to clarify whether small cell lung cancer (SCLC) cells express functional VEGF-Rs and VEGFs, and their biological significance in the SCLC progression. We examined expression of VEGF and VEGF-C, and their receptors, VEGFR-2 and VEGFR-3, in five SCLC cell lines, NCI-H82, H209, H510, H526 and H660, by Western blotting. We evaluated whether hypoxic

conditions up-regulate these protein expressions. We also examined whether VEGF addition and VEGF-D addition cause phosphorylation of the mitogen-activated protein kinase (MAPK) as well as VEGFR-2 and VEGFR-3. Further, we investigated whether VEGF addition and VEGF-D addition induced the proliferation and migration of the SCLC cells. VEGF, VEGF-C, VEGFR-2 and VEGFR-3 were detectable by Western blotting in all five SCLC cell lines. The VEGF-Rs and VEGFs expression levels were increased by an incubation under hypoxic conditions in NCI-H82. VEGF addition and VEGF-D addition caused phosphorylation of MAPK as well as the VEGF-Rs themselves, and induced proliferation and migration of the SCLC cells. These results suggested potential of VEGF signal-pathway inhibitors as anti-cancer agents in SCLC treatment disturbing growth and migration of the cancer cells.

“We conducted the present study to clarify whether small cell lung cancer (SCLC) cells express functional VEGF-Rs and VEGFs, and their biological significance in the SCLC progression.”

“Metastases were found in an additional 5 patients (16%) at autopsy, 1 of whom had 2 sites involved.”

Editorial Comment (TLP):

We have commented upon the role of VEGF in the earlier stages of angio-squamous dysplasia which may be a forerunner of squamous cell lung cancer in earlier issues. Hopefully, an array of cytologic tumor markers will soon be of sufficient specificity and sensitivity to be particularly useful in early diagnosis in multiple types of lung cancer.

13. Mayo Clin Proc 2004;79:1409-1414

Autopsy results after surgery for non-small cell lung cancer.

Finke NM, Aubry MC, Tazelaar HD, Aughenbaugh GL, Lohse CM, Pankratz VS, Deschamps C.

Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minn 55905, USA.

OBJECTIVE: To determine the percentage of metastatic and unexpected residual lung cancer at autopsy in patients considered for curative resection of non-small cell lung cancer during a time when computed tomography was available as a preoperative staging tool. **MATERIAL AND METHODS:** Clinical data and surgical and autopsy slides of all patients who underwent curative resection of non-small cell lung cancer at the Mayo Clinic in Rochester, Minn, between 1985 and 1999 and who underwent autopsy within 30 days of surgery were reviewed retrospectively for the presence of residual or metastatic disease. **RESULTS:** The study group consisted of 25 men and 7 women, with a mean age of 70 years. A pulmonary metastasis was identified at surgery in 1 patient (3%). Metastases were found in an additional 5 patients (16%) at autopsy, 1 of whom had 2 sites involved. These sites included the

“The advent of computed tomography as a staging tool has decreased the percentage of patients with undiagnosed metastatic disease at surgery; however, preoperative understaging in lung cancer remains a problem.”

liver in 2 and lung, epicardium, adrenal gland, and kidney in 1 each. The average diameter of metastases was 1.6 cm. No factor studied was found to be significantly associated with the presence of unrecognized metastatic disease at autopsy. **CONCLUSION:** The advent of computed tomography as a staging tool has decreased the percentage of patients with undiagnosed metastatic disease at surgery; however, preoperative understaging in lung cancer remains a problem. Editorial Comment (TLP):

Fortunately, computer tomography and other imaging such as PET scanning will reduce the incidence of non-recognized carcinoma prior to surgical resection.

14. Ann Thorac Surg 2004;77:1774-1780

Accuracy of virtual bronchoscopy to detect endobronchial lesions.

Lacasse Y, Martel S, Hebert A, Carrier G, Raby B.

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BACKGROUND: Virtual bronchoscopy (VB) could obviate flexible bronchoscopy (FB) if no endobronchial lesion is detected in patients presenting with a suspicion of malignancy. Our objectives were to evaluate the accuracy (in terms of sensitivity and specificity) of VB in detecting endobronchial lesions, and to determine the anatomical limit of detection of endobronchial lesions by VB. **METHODS:** This study involved, in a blind comparison of VB and FB, consecutive patients presenting with symptoms or plain chest radiography abnormalities raising the suspicion of pulmonary neoplasm. After the standard chest computed tomography (CT), additional helical CT data were acquired from the aortic arch to the origin of the segmental bronchi of the inferior lobes in one 20-second breath hold using a helical CT scan (3.0-mm collimation with a pitch of 1.5 and 1.5-mm reconstruction intervals). **RESULTS:** One hundred ninety patients were enrolled; 136 patients (including 63 with an endobronchial lesion at FB) contributed to the primary analysis. The sensitivity and specificity of VB to detect endobronchial lesions were 68% (95% confidence interval [CI]: 55% to 79%) and 90% (95% CI: 81% to 96%), respectively. Overall, the agreement between VB and FB regarding the location on endobronchial lesions was substantial (weighted kappa: 0.66). However, VB detected only 26 of the 34 lobar lesions (sensitivity: 76%; CI: 59% to 89%) and 11 of the 23 segmental le-

sions (sensitivity: 48%; CI: 27% to 69%). CONCLUSIONS: Beyond the mainstem bronchi, VB is not accurate enough to detect endobronchial lesions and to obviate FB in patients presenting with a suspicion of malignancy.
Editorial Comment (TLP):

Virtual bronchoscopy appears appealing but the need to biopsy suspicious areas will remain.

15. Eur Respir J 2004;24:348-352

Endobronchial brachytherapy in the treatment of malignant lung tumours.

Escobar-Sacristan JA, Granda-Orive JI, Gutierrez Jimenez T, Delgado JM, Rodero Banos A, Saez Valls R.

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A prospective study was made to assess the short-term clinical and endoscopic response to high-dose-rate endobronchial brachytherapy (HDREB) in patients with malignant endobronchial tumours. From July 1995 to May 2000, 288 HDREB sessions were carried out on 81 patients. The mean patient age was 61.57 yrs (range 34-82); males were predominant (87.65%). Tumours were primary in 76 patients (93.82%) and metastatic in five patients (6.18%). The inclusion criteria were malignant endobronchial tumour and either palliative treatment for incurable disease or intent-to-cure treatment for residual malignancy on the bronchial resection surface after surgery or an inoperable tumour. The exclusion criteria were as follows: impediments to catheter placement, expected survival <2 months, Karnofsky index <60, or absence of informed consent. The clinical response of a symptom was categorised as complete (disappearance of the symptom), partial (less than complete) or absent. The endoscopic response was considered to be complete if lesions disappeared and biopsy findings remained negative 1 month after the last radiation session; partial if lesions improved to some extent, but the biopsy findings were positive; and absent if there was no change in relation to baseline. The technique consisted of delivering high-dose irradiation from an Ir192 source to a target volume using one or two endobronchial catheters inserted under optical or video bronchoscopic guidance. Four sessions were scheduled at weekly intervals and 500 cGy was applied per session over a length of 1-9 cm, measured 0.5-1 cm from the centre of the source. In total, 85% of the symptoms analysed (haemoptysis, cough, dyspnoea, expectoration, and stridor) disappeared with HDREB, which was categorised as a complete response. The endoscopic response was complete in 56.79% of patients, partial or less than complete in

“... 136 patients (including 63 with an endobronchial lesion at FB) contributed to the primary analysis.”

“The technique consisted of delivering high-dose irradiation from an Ir 192 source to a target volume using one or two endobronchial catheters inserted under optical or video bronchoscopic guidance.”

“... 288 HDREB sessions were carried out on 81 patients. The mean patient age was 61.57 years (range 34-82); males were predominant (87.65%).”

40.74% and absent in 2.46%. One major complication occurred (bronchial fistula 1.2%), but no lethal haemoptysis. Minor complications (pneumonitis, bronchospasm and bronchial stenosis) each occurred in one patient (1.2%). High-dose-rate endobronchial brachytherapy is a good palliative treatment for endoluminal lung neoplasms, effectively alleviating symptoms and endoscopic evidence in many cases with an acceptable rate of complications. High-dose-rate endobronchial brachytherapy can be carried out as an intent-to-cure procedure in highly selected cases.

Editorial Comment (TLP):

This is one of many attempts to treat small endobronchial cancers with tissue-sparing in mind.

16. Lung Cancer 2004;46:341-347

Synchronous lesions detected by autofluorescence bronchoscopy in patients with high-grade preinvasive lesions and occult invasive squamous cell carcinoma of the proximal airways.

Pierard P, Faber J, Hutsebaut J, Martin B, Plat G, Sculier JP, Ninane V.

Department of Internal Medicine, Institut Bordet, CH Etterbeek-Ixelles and Chest Service, Saint-Pierre Hospital, Rue Haute, 322, 1000 Brussels, Belgium.

The cancerization field concept implies that lung cancer multicentricity may be a frequent event and primary studies using white-light bronchoscopy (WLB) have reported a high prevalence of multicentricity in patients with roentgenographically occult lung cancer. We have used autofluorescence bronchoscopy (AFB) to reassess the prevalence of synchronous lesions in patients referred for the staging and/or treatment of occult lesions initially detected during WLB. All the patients referred with high-grade preinvasive lesions (severe dysplasia, DYS S and carcinoma in situ, CIS) and occult invasive squamous cell carcinoma (CIV) of the bronchus initially detected during WLB at other centers, underwent AFB. Data were prospectively collected and retrospectively analyzed to assess the prevalence of synchronous occult lesions. From January 1996 to December 2001, 28 patients (26 males, 2 females; mean age: 65 +/- 11) were assessed. After re-evaluation, in two cases, the referred lesions corresponded only to metaplasia and were discarded from analysis. The 26 other patients were referred for 28 lesions (3 DYS S, 19 CIS and 6 CIV; 2 patients were referred with two synchronous le-

“Forty-nine (72.1%) of the total 68 lesions exhibited ground-glass opacity on high-resolution CT (HRCT).”

“Of 17 patients with bilateral synchronous cancers, simultaneous bilateral pulmonary resection was performed in 14 patients . . . “

“The high prevalence of synchronous lesions in this series of patients with occult DYS S, CIS and occult CIV suggests that AFB may be a useful adjunct in the pretreatment evaluation.”

sions). AFB revealed, in these 26 patients, six additional lesions (1 DYS S, 4 CIS and 1 CIV). Multicentricity in this group, initially estimated to amount to 7% with WLB alone, raised to 23% by using AFB. The high prevalence of synchronous lesions in this series of patients with occult DYS S, CIS and occult CIV suggests that AFB may be a useful adjunct in the pretreatment evaluation.

17. Ann Thorac Surg 2004;78:1194-1199

Surgical treatments for multiple primary adenocarcinoma of the lung.

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BACKGROUND: The aim of this study was to identify the clinical characteristics of multiple primary adenocarcinomas and to evaluate the efficacy of surgical treatments. **METHODS:** Three-hundred sixty-nine patients who underwent pulmonary resection for adenocarcinoma from January 1994 to December 2002 were reviewed. **RESULTS:** Thirty-one patients (8.4%) were determined to have multiple primary adenocarcinomas that could be detected on chest x-rays or computed tomography (CT). Twenty-six patients were synchronous and five patients were metachronous with a median interval of 59.0 months. Forty-nine (72.1%) of the total 68 lesions exhibited ground-glass opacity on high-resolution CT (HRCT). Pathologically well-differentiated adenocarcinoma with mixed bronchioloalveolar pattern was the most common subtype (39.7%). Taking into consideration pulmonary function, size, location, and HRCT findings of the lesions the procedures performed were lobectomy with mediastinal lymph-node dissection for 32 patients, segmentectomy with hilar node dissection for 8 patients, and wedge resection for 28 patients. Of 17 patients with bilateral synchronous cancers, simultaneous bilateral pulmonary resection was performed in 14 patients including simultaneous bilateral video-assisted thoracic surgery (VATS) in 11 patients. After a median follow-up period of 27.7 months, the 3-year overall survival rate was 92.9% and the 3-year disease-free survival rates of synchronous cancer and metachronous cancer were 77.9% and 100%, respectively. **CONCLUSIONS:** The incidence of multiple primary adenocarcinomas was relatively common. Early radiographic detection and surgical excision could yield a favorable prognosis. The use of VATS, even for synchronous bilateral patients, was a safe and beneficial procedure.

Editorial Comments (TLP):

Synchronous lesions may be identified by bronchoscopy and treated with appropriate individual modalities with the aim of cure.

18. Chest 2004;126:1742-1749

Benchmarking lung cancer mortality rates in current and former smokers.

Bach PB, Elkin EB, Pastorino U, Kattan MW, Mushlin AI, Begg CB, Parkin DM.

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STUDY OBJECTIVES: To develop and validate a model for estimating the risk of lung cancer death in current and former smokers. The model is intended for use in analyzing a population of subjects who are undergoing lung cancer screening or receiving lung cancer chemoprevention, to determine whether the intervention has altered lung cancer mortality. **Design/setting/patients:** Model derivation was based on analyses of the placebo arm of the Carotene and Retinol Efficacy Trial. Model validation was based on analyses of three other longitudinal cohorts. **MEASUREMENTS:** Observed and predicted number of deaths due to lung cancer. **RESULTS:** In internal validation, the model was highly concordant and well calibrated. In external validation, the model predictions were similar to what was observed in all of the validation analyses. The predicted and observed deaths within 6 years were very similar when assessed in the Johns Hopkins Hospital trial of chest radiography and sputum cytology screening (176 predicted, 184 observed, $p = 0.53$), the Memorial Sloan-Kettering Cancer Center trial of chest radiography and sputum cytology screening (108 predicted, 114 observed, $p = 0.57$), and the National Health and Nutrition Evaluation Survey part I (24 predicted, 21 observed, $p = 0.52$). **CONCLUSIONS:** The number of lung cancer deaths in a population of current or former smokers can be accurately predicted, making model-based evaluations of prevention and early detection interventions a useful adjunct to definitive randomized trials. We illustrate this potential use with a small example.

Editorial Comment (TLP):

Although the number of lung cancer deaths based upon smoking histories may be predicted, it is far better to use smoking histories along with other risk factors such as family history and the occupa-

tional risks, for the purpose of early diagnosis and intervention as earlier citations in this issue argue.

“Correspondence analysis has demonstrated that nine genes were differentially expressed, although with a high variability across the samples that prevented distinguishing the two groups of tumors.”

“The predicted and observed deaths within 6 years were very similar when assessed in the Johns Hopkins Hospital trial of chest radiography and sputum cytology screening (176 predicted, 184 observed, $p = 0.53$), the Memorial Sloan-Kettering Cancer Center trial of chest radiography and sputum cytology screening (108 predicted, 114 observed, $p = 0.57$), and the National Health and Nutrition Evaluation Survey part I”

“Recent improvements with spiral CT technology applied to detect early lung cancer in high risk populations have also enhanced the prospect of finding locally confined primary lung cancers.”

19. Clin Cancer Res 2004;15:6023-6028

Lung cancers detected by screening with spiral computed tomography have a malignant phenotype when analyzed by cDNA microarray.

Bianchi F, Hu J, Pelosi G, Cirincione R, Ferguson M, Ratcliffe C, Di Fiore PP, Gatter K, Pezzella F, Pastorino U.

Cancer Research UK Tumor Pathology Group, Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, Oxford, United Kingdom.

PURPOSE: Spiral computed tomography (CT) can detect lung cancer at an early stage, but the malignant potential is unknown. The question is, as follows: do these small lesions have the same lethal potential as do symptomatic tumors? **EXPERIMENTAL DESIGN:** We used a cDNA microarray platform and compared the gene expression profile of spiral CT-detected lung carcinomas with a matched case-control population of patients presenting with symptomatic lung cancer. **RESULTS:** CT-detected and symptomatic tumors have shown a comparable gene expression profile. Correspondence analysis has demonstrated that nine genes were differentially expressed, although with a high variability across the samples that prevented distinguishing the two groups of tumors. Analysis of these nine genes has suggested that early-detected tumors have higher levels of retinoic acid production and higher expression levels of caveolin 2, matrix Gla, and cystatin A, which are already known to be lost during tumor progression. **CONCLUSIONS:** All of the tumors observed are histologically malignant according to the WHO Classification. Early lung cancers that are detected by screening have a gene expression pattern similar to, but not identical to, that of symptomatic lung carcinomas.

Editorial Comment (TLP):

This interesting study shows that tumors diagnosed by screening, have similar gene expressions compared with those that are diagnosed as symptomatic stages of disease. This argues strongly against the myth that small lesions may be “indolent” and thus slow growing, as is the case with prostate cancer.

20. Lung Cancer 2004;46:387-392

Epithelial-directed drug delivery: influence of formulation and delivery devices.

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Technology to deliver drugs reliably throughout the entire respiratory tract has greatly improved in part because of asthma- and infectious disease-related applications. Recent improvements with spiral CT technology applied to detect early lung cancer in high risk populations have also enhanced the prospect of finding locally confined primary lung cancers. In this setting, the need to safely and economically manage the local regional phase of early lung cancer is assuming great strategic importance. At the same time the growing knowledge regarding the molecular and biochemical events driving the progression of lung cancer is allowing the development of targeted drug that may be useful in arresting lung cancer progression. The questions considered in this forum is whether improvements in these areas are sufficiently mature to allow application of local regional drug delivery with targeted drug agents to improve the management of early lung cancer.

Editorial Comment (TLP):

This interesting therapeutic approach, like photodynamic therapy, may be used to minimize unnecessary sacrifice of lung function through resection. An accompanying editorial by James L. Mulshine and John N. Weinstein, “Is the Gene Expression Pattern of Lung Cancer Detected by Screening With Spiral Computed Tomography Different from That of Symptom-Detected Lung Cancer. Clinical Cancer Research 2004;10:5973-5974,” makes the point that there is no conclusive evidence of benign activity in lung cancer, as some argue, in studies of prostate cancer that is found by autopsy. Reference: Humphrey LL, Teutsch S, Johnson M: Lung cancer screening with sputum cytological examination, chest radiography and computer tomography: An update for the U.S. Preventive Task Force. Ann Internal Med 2004;140:740-753.

“ . . . Whether improvements in these areas are sufficiently mature to allow application of local regional drug delivery with targeted drug agents to improve the management of early lung cancer.”

CME PROGRAM

We have organized the CME program (described on page two) to help publicize our new Center For Lung Cancer Diagnosis and Treatment at the Swedish Hospital.

Please consider attending this full day program on March 5, which features four internationally known speakers and local experts who will bring us to the cutting edge of lung cancer diagnosis and treatment. We will feature emerging practical and successful approaches to early diagnosis in high risk individuals.

This is a "can't miss" opportunity. Learn the latest, get 8 CME hours with free registration, interact with your friends and colleagues in a brand new hotel, and have a glass of wine while you get all of your questions about practical aspects of lung cancer that will be immediately useful to your practice.

Reasons not to attend include, (1) you need to work on your taxes; (2) your kids have the SUV for the day; (3) you want to clean out the garage; (4) you do not treat lung cancer in your practice; (5) you would rather go skiing.

Take the weekend off. Stay at the brand new JW Marriott Hotel, in Cherry Creek. Ski on Sunday. Give your spouse a vacation and full use of the credit cards while you learn.

Call Cindy at 877-SMC-LUNG or email Catherine.Battaglia@HealthONEcares.com to register. We hope to see you in Denver on March 5.

Your friends,
James T. Good, Jr., M.D. and Thomas L. Petty, M.D.