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**LUNG  
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**Landmark Trials of Adjuvant Chemotherapy  
Following Complete Surgical Resection**

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**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](http://www.lungcancerfrontiers.org).**

Two extremely important adjuvant chemotherapy trials were presented at the spring meeting of the American Society of Clinical Oncology in New Orleans in June of 2004. The following summarizes those two trials:

The first trial was conducted by the CALGB in cooperation with two other cooperative groups that included NCCTG and RTOG (1). Dr. Gary Strauss presented the results. Patients with surgically resected and pathologic stage T2, NO (Stage IB) were randomized to receive no treatment or four cycles of adjuvant chemotherapy with paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC = 6) every 21 days for four cycles. Patients were stratified for histologic cell type and presence or absence of mediastinal lymph node staging. Patients with small cell lung cancer were not eligible for study. Three hundred forty-four patients were randomized on study between September of 1996 and November of 2003. Sixty-four percent were males with a median age of 61 years for all participants. Grade 3-4 neutropenia was observed in 36% of patients. A total of 85% percent of participants received all four planned cycles of chemotherapy. There were no treatment-related deaths.

Overall, there were more deaths in the no treatment arm (52 vs. 36) and more lung cancer deaths in the no treatment arm (34 vs. 19). The absolute survival at four years was 71% for those individuals who received adjuvant chemotherapy as compared to 59% for those randomized to the observation-only

arm.  $p = 0.028$ . The lung cancer mortality at four years was 15% on the adjuvant chemotherapy arm and 26% on the no-adjuvant therapy arm. These results were strikingly in favor of adjuvant chemotherapy with four cycles of paclitaxel and carboplatin following resection of Stage IB non-small cell lung cancer.<sup>1</sup>

The second trial was conducted by the National Cancer Institute of Canada in cooperation with ECOG and SWOG.<sup>2</sup> In this trial patients with completely resected and pathologic staged T2, NO (Stage IB) or Stage II (except T3, NO) non-small cell lung cancer were randomized observation only or treatment with vinorelbine (25 mg/m<sup>2</sup>) weekly times 16 weeks plus cisplatin (50 mg/m<sup>2</sup>) on day one and eight every four weeks for four cycles. Patients were stratified based on the presence of N1 lymph node or N0 lymph node involvement.

A total of 425 patients were randomized between 1994 and 2001. The median age of participants was 61 years with 65% males. Grade 4 neutropenia (life threatening) was common with chemotherapy. Febrile neutropenia occurred in 7% of patients treated. Other side effects of chemotherapy included fatigue, nausea, anorexia and sensory neuropathy in approximately 45% of patients. There were two treatment-related deaths on the chemotherapy arm. Fifty-three percent of all participants had an adenocarcinoma. Forty-five percent of all participants were Stage IB with the rest of patients being Stage II A/B.

The five-year survival was 69% for those individuals receiving adjuvant chemotherapy as compared to 54% for patients randomized to no adjuvant treatment. The hazard ratio of

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death was 0.69 in favor of adjuvant therapy (p = 0.011).<sup>2</sup>

These two adjuvant studies produced remarkably similar and very striking results in favor of adjuvant therapy for patients with totally resected Stage IB or Stage IIA or IIB non-small cell lung cancer. In the Strauss study the four-year survival advantage was an absolute 12% improvement while in the Winton study the five-year survival advantage was 15% for those individuals who received adjuvant chemotherapy. These results are remarkably better than the previous reports of the IALT trial published in the New England Journal of Medicine in 2004 (NEJM 350:351-360, 2004). That International and Multi-Center Trial showed an absolute 4% improvement in five-year survival for individuals who received adjuvant chemotherapy as compared to observation alone following complete resection. Based on results of these two adjuvant trials, in conjunction with the previously reported IALT Trial, adjuvant chemotherapy with four cycles of platinum-based chemotherapy is now considered to be the standard in patients with completely resected Stage IB or IIA and IIB non-small cell lung cancer. Many practicing oncologists believe that this data can also be extrapolated to include patients with totally resected Stage IIIA non-small cell lung cancer. The results of these two trials from the American Society of Clinical Oncology this year have changed the current status of practice in favor of administering adjuvant chemotherapy.

**“That International and Multi-Center Trial showed an absolute 4% improvement in five-year survival for individuals who received adjuvant chemotherapy as compared to observation alone following complete resection.”**

**“Many practicing oncologists believe that this data can also be extrapolated to include patients with totally resected Stage IIIA non-small cell lung cancer.”**

**“The application of non- and minimal invasive techniques for early detection, staging and treatment will become increasingly important.”**

**Pasic A, Postmus PE, Suttedja TG.** Department of Pulmonary Medicine, Vrije Universiteit Medical Center, P.O. Box 7057, 1007 MB, Amsterdam, The Netherlands.

The dismal cure rate of patients with lung cancer and the stage shift hypothesis have propelled the interest to perform screening at large, despite that previous randomized clinical trials failed to show any mortality benefit and the controversial issue of overdiagnosis. Due to early detection programs, a larger number of individuals at risk will be found to harbor small and potentially malignant early stage lesions. The application of non- and minimal invasive techniques for early detection, staging and treatment will become increasingly important. This review deals with the available clinical, surgical and pathological data focusing on early lung cancer lesions <=1cm. Literature data from both centrally located and parenchymal lesions <=3cm. have been analyzed. For all sub-centimeter lesions, minimal invasive staging and treatment approaches must still be considered inappropriate. Less invasive and less extensive treatment methods may be considered in high risk individuals with <=1cm. peripheral lesion showing >=50 ground glass opacity on high resolution CT scan and those with superficial lesion in their central airways without deeper tumor invasion in the bronchial wall. Caution is necessary, however, as clinical staging remains inferior to pathological staging which is based on tissue samples collected after complete tumor removal and mediastinal lymph nodes dissection have been performed.

Editorial Comment (Suttedja TG):  
It is paramount to clearly define what is early stage lung cancer in current activities regarding early intervention i.d. screening, staging and treatment. Understandably, one can easily agree that early stage lung cancer indicates the point of no return, meaning that a detected lung lesion containing pre-malignant clonal cells which will irreversibly progress towards cancer.

However, it is much more difficult to indicate in clinical practice how accurate one can be. Obviously, the TNM classifications are the gold standard in taking care of lung cancer

## REFERENCES

1. Strauss G, Herndon J, Maddaus, M et al: Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in Stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. (Abstract #7019). Am Soc Clin Oncol 23:621S, 2004
2. Winton, T, Livingston, R, Johnson, D et al: A prospective randomized trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non-small cell lung cancer (NSCLC) Intergroup JBR.10. (Abstract #7018). Am Soc Clin Oncol 23:621S, 2004

## ABSTRACTS FROM THE PEER-REVIEWED LITERATURE

1. Lung Cancer 2004;45:267-77  
**What is early lung cancer?; A review of the literature.**

“... We can now analyze clonal cells with malignant potential years before disease become clinical apparent.”

“... 33 lung cancers were diagnosed through the early detection project: complete resection by radical lobectomy was achieved in 31 (94%) of them and 24 (73%) were pathological stage I.”

“Annual spiral CT ± PET is a safe approach to early detection, with low frequency of invasive diagnostic procedures and absence of screening-related mortality.”

patients. However, it also becomes clear that in this era of early detection (use of sputum cytology, autofluorescence bronchoscopy to detect pre-neoplastic lesions, use of 32 bit CT that can visualize parenchymal changes in the order of mm size) with the exploration of molecular biology, we can now analyze clonal cells with malignant potential years before disease become clinical apparent.

To remain practical, one therefore has to indicate clinical workable parameters which can be used in the daily practice. The limits of what is currently regarded as early stage cancer within the perspective of minimal invasive techniques need to be define.

To be clinical relevant, early interventional issues should not focus only on early lung cancer per se, but to keep in mind that individuals at risk need to be provided with a targeted approach exploiting the time window before local disease disseminates to lymph nodes and distant organs by considering various factors including the preservation of quality of life.

Clinical, surgical and pathological data seem to indicate that size definition alone for central and peripheral early stage lung cancers are still inadequate for a proper decision analysis. However, the use of non- and minimally invasive parameters (bronchoscopy, CT scan) may indicate certain cohort within stage IA disease with tumor size <1 cm; in which one can exploit the advancements of less invasive or minimally invasive therapeutic measures."

Further comment (TLP): Reference is also made to a previous report of Dr. Sut-edja:

**Clin Lung Cancer 2001;2:264-270**  
**Sutedja TG van Boxem AJ, Postmus PE**  
**The curative potential of intraluminal bronchoscopic treatment for early-state non-small cell lung cancer.**

2.

**2004 ASCO Annual Meeting Abstract No. 7040**  
**Impact of early lung cancer**

## detection on surgical mortality

**U. Pastorino, P. Borasio, P. Solli, M. Bellomi, C. Fava, F. Leo, S. Novello, G. Scagliotti; Istituto Nazionale Tumori, Milano, Italy; S. Luigi Hospital, Orbassano, Italy; Istituto Europeo di Oncologia, Milano, Italy.**

**Background:** Pilot studies in high risk individuals have shown that spiral CT can detect early cancer, with high resectability rate and nearly 80% stage I disease. However, concern has been raised that competing risks of death and screening-related mortality may overcome the benefits of early detection. To evaluate the impact of early lung cancer detection on peri-operative mortality, we compared the death rate in the first Italian early detection project with a consecutive series of lung cancers resected in the same institutions and period of time. **Methods:** In 2000, a pilot trial was launched at the European Institute of Oncology of Milan and the S.Luigi Hospital of Orbassano, to test the value of annual low dose CT and positron emission tomography (PET) in a cohort of 1555 volunteers, aged 50 years or older who had smoked for 20 pack-years or more. A total of 1396 lung cancer resections, performed after standard detection in the same two institutions from 1998 to 2002, were analysed as control group. **Results:** At the end of 2002, 33 lung cancers were diagnosed through the early detection project: complete resection by radical lobectomy was achieved in 31 (94%) of them and 24 (73%) were pathological stage 1. No perioperative death (within 31 days or related to surgery) were observed. After standard detection, the overall mortality was 1.9%, being related to resection volume (pneumonectomy 3.7% vs. lobectomy 1.7%) and extent of disease (stage I 1%, stage II 2.3%, stage III-IV 3.4%). In the early detection project, 6 subjects (0.4%) underwent a surgical biopsy for benign disease, without perioperative mortality. **Conclusions:** Early lung cancer resection has a favorable effect on surgical mortality, by preventing the need of pneumonectomy and reducing mortality after lobectomy. Annual spiral CT ± PET is a safe approach to early detection, with low frequency of invasive diagnostic procedures and absence of screening-related mortality.

	Standard Detection		Early Detection
Stage I	6/611	1%	0/24
Stage II	7/309	2.3%	0/2
Stage III-IV	13/384	3.4%	0/5
Pneumonectomy	9/244	3.7%	-
Lobectomy	17/991	1.7%	0/31

3.  
**Chest 2004;126:108-113**  
**The natural history of radiographically occult bronchogenic squamous cell carcinoma: a retrospective study of overdiagnosis bias.**

**Sato M, Saito Y, Endo C, Sakurada A, Feller-Kopman D, Ernst A, Kondo T.** Department of Thoracic Surgery, Institute of Development, Aging, and Cancer, Tohoku University, Sendai 980-8575, Japan. m-sato@idac.tohoku.ac.jp

**OBJECTIVE:** An overdiagnosis bias occurs with the diagnosis of a disease that does not produce signs or symptoms before the patient dies from other causes. We sought to determine whether overdiagnosis bias is a factor when screening for squamous cell carcinoma of the lung. **DESIGN:** Retrospective study of the Miyagi Population-Based Lung Cancer Screening Registry for high-risk patients who were seen between January 1, 1982 (when sputum cytology tests were added for men with long smoking histories), and December 31, 1996. **SETTING:** Miyagi Prefecture, Japan. **PATIENTS:** A total of 251 patients (all men) who had sputum cytology test results that were positive for squamous cell carcinoma but had normal radiograph findings, 44 of whom declined cancer treatment (mean age, 70 years) and 207 of whom were treated with resection within 12 weeks of diagnosis (mean age, 65.5 year). **END POINTS:** Five-year and 10-year survival rates from primary lung cancer in both groups as of August 15, 2001. **RESULTS:** Among the 44 untreated patients, 15 (34%) remained asymptomatic. The survival rate due to primary lung cancer death in the untreated group was 53.2% at 5 years and 33.5% at 10 years. The survival rate among treated patients was 96.7% at 5 years and 94.9% at 10 years. Of the 125 treated patients who died, 14 (11.2%) died from primary lung cancer. **CONCLUSION:** Given that the two thirds of the untreated patients with squamous cell carcinoma of the bronchus died from lung cancer within 10 years, overdiagnosis bias does not appear to be a factor in screening for this disease. Thus, we recommend that patients with radiographically occult squamous cell carcinoma of the bronchus undergo tumor treatment after localiza-

“We sought to determine whether overdiagnosis bias is a factor when screening for squamous cell carcinoma of the lung.”

“The survival rate due to primary lung cancer death in the untreated group was 53.2% at 5 years and 33.5% at 10 years.”

“The current authors prospectively studied 27 patients with 31 histologically proven severe dysplasia (SD) and carcinoma in situ (CIS), with repeated bronchoscopy and endobronchial treatment.”

tion.

Editorial Comment (TLP):

These are two extremely important studies that show that pre-malignant in-situ stage intrabronchial squamous cell carcinoma, which is frequently radiographically occult, is clinically significant. The use of sputum cytology is particularly effective in the diagnosis of early central lesions. The prognosis is dramatically improved by early identification and intervention. Hopefully, sputum cytology and bronchoscopy for dysplasia or early stage lung cancer can join CT screening as a standard of care for the early diagnosis of patients at high risk. Fluorescent bronchoscopy increases the sensitivity of early diagnosis of pre-malignant and in situ lesions but at the cost of reduced specificity.

4.  
**Eur Respir J 2004;24:24-29**  
**Clinical prognostic indicators of high-grade pre-invasive bronchial lesions.**

**Moro-Sibilot D, Fievet F, Jeanmart M, Lantuejoul S, Arbib F, Laverribe MH, Brambilla E, Brambilla C.**

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Lung cancer arises from multistep genetic damage of bronchial epithelium, driving multifocal progressive dysplastic lesions. However, the risk of progression of high-grade pre-invasive bronchial lesions to cancer is poorly assessed. The purpose of this study was to better define the parameters that predict the outcome of these lesions. The current authors prospectively studied 27 patients with 31 histologically proven severe dysplasia (SD) and carcinoma in situ (CIS), with repeated bronchoscopy and endobronchial treatment. The influence of respiratory-cancer history, histopathological classification, tobacco consumption, and number of biopsies on the progression rate into cancer was studied. The actuarial progression rate to cancer was 17% at 1 yr and 63% at 3 yrs. A total of 11 cases of CIS progressed to invasive cancer, 17 were stable or regressed during the study, two with SD regressed and one progressed to

“A total of 11 cases of CIS progressed to invasive cancer . . . “

“The 1 year survival rate is significantly better for BAC patients relative to other histological subtypes of NSCLC.”

invasive cancer. Progression of CIS appeared more frequent in lesions diagnosed as "questionable CIS". Persistence of smoking did not influence high-grade lesion outcome. The existence of synchronous lung cancer did not seem to impact on progression. The number of biopsies did not influence the outcome. In conclusion, the current study suggests that the outcome of high-grade pre-invasive lesions is not modified by the number of biopsies performed on these lesions. Careful pathological examination of these lesions and pathological revision seem necessary, since questionable cases have the worse progression rate.

Editorial Comment (TLP):

This study also offers good evidence of the malignant potential of severe dysplasia and the progression of carcinoma in situ to more invasive lesions. Some lesions regress over time for unknown reasons. All such lesions should be followed closely or treated with ablative therapy or resected in selected patients.

5.  
**Lung Cancer 2004;45:137-142**

**The epidemiology of bronchioloalveolar carcinoma over the past two decades: analysis of the SEER database.**

**Read WL, Page NC, Tierney RM, Piccirillo JF, Govindan R.**

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Bronchioloalveolar carcinoma of the lung (BAC) is a subtype of adenocarcinoma of the lung. Although traditionally grouped with other non-small cell lung carcinomas (NSCLC), BAC has unique morphological features and clinical behavior such as bilateral lung involvement, indolent course and lack of association with smoking. Some epidemiologic studies report a significant increase in the incidence of BAC. We used the SEER database to compare the incidence, demographics, and overall survival of BAC patients as compared to other NSCLC types over the past two decades (1979-

1998). Although the incidence of BAC has increased over the past two decades, BAC represents less than 4% of all NSCLC in every time period evaluated. The 1 year survival rate is significantly better for BAC patients relative to other histological subtypes of NSCLC. There has not been a marked increase in the incidence of BAC reported to SEER over the past 20 years.

Editorial Comment (TLP):

The epidemiology of Bronchioloalveolar carcinoma (BAC) appears to be changing. The early diagnosis of BAC results in improved survival (*Lung Cancer 2004;44:61-68*). In addition, the knowledge of mutational changes in epidermoid receptor factors and the knowledge about the accompanying molecular changes that deal with epithelial receptor factor antagonists (*NEJM 2004;350:2129-2139*) is creating an expanding and fascinating aspect of lung cancer today.

6.

**Am J Hum Genet 2004;75:460-474**

**A major lung cancer susceptibility locus maps to chromosome 6q23-25.**

**Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, de Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, Klein C, Gazdar A, Rothschild H, Mandal D, Coons T, Slusser J, Lee J, Gaba C, Kupert E, Perez A, Zhou X, Zeng D, Liu Q, Zhang Q, Seminara D, Minna J, Anderson MW.** National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA.

Lung cancer is a major cause of death in the United States and other countries. The risk of lung cancer is greatly increased by cigarette smoking and by certain occupational exposures, but familial factors also clearly play a major role. To identify susceptibility genes for familial lung cancer, we conducted a genomewide linkage analysis of 52 extended pedigrees ascertained through probands with lung cancer who had several first-degree relatives with the same disease. Multipoint linkage analysis, under a simple autosomal dominant model, of all 52 families with three or more individuals affected by lung, throat, or laryngeal cancer, yielded a maximum

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“Analyses of tumour-associated gene expression showed positive results, with at least one marker in the lavage supernatants of all 25 patients.”

“These results localize a major susceptibility locus influencing lung cancer risk to 6q23-25.”

“Promoter hypermethylation of at least one of the genes studied was detected in all 31 lung primary tumors . . .”

pedigrees ascertained through probands with lung cancer who had several first-degree relatives with the same disease. Multipoint linkage analysis, under a simple autosomal dominant model, of all 52 families with three or more individuals affected by lung, throat, or laryngeal cancer, yielded a maximum heterogeneity LOD score (HLOD) of 2.79 at 155 cM on chromosome 6q (marker D6S2436). A subset of 38 pedigrees with four or more affected individuals yielded a multipoint HLOD of 3.47 at 155 cM. Analysis of a further subset of 23 multigenerational pedigrees with five or more affected individuals yielded a multipoint HLOD score of 4.26 at the same position. The 14 families with only three affected relatives yielded negative LOD scores in this region. A predivided samples test for heterogeneity comparing the LOD scores from the 23 multigenerational families with those from the remaining families was significant ( $P=.007$ ). The 1-HLOD multipoint support interval from the multigenerational families extends from C6S1848 at 146 cM to 164 cM near D6S1035, overlapping a genomic region that is deleted in sporadic lung cancers as well as numerous other cancer types. Parametric linkage and variance-components analysis that incorporated effects of age and personal smoking also supported linkage in this region, but with somewhat diminished support. These results localize a major susceptibility locus influencing lung cancer risk to 6q23-25.

Editorial Comment (TLP):

It appears that the chromosome that indicates a risk of familial lung cancer has been identified. This is obviously important as was zero in on genetic factors resulting in lung cancer.

7.

**Eur J Cancer 2004;40:452-460**

### **Detection of cell-free nucleic acids in bronchial lavage fluid supernatants from patients with lung cancer.**

**Schmidt B, Carstensen T, Engel E, Jandrig B, Witt C, Fleischhacker M.**

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The aim of this study was to determine whether nucleic acids are detectable in cell-free bronchial lavage supernatants, and whether it is possible to find alterations in this DNA and RNA of genes known to be present in lung tumour cells. DNA was isolated from cell-free lavage supernatants from 30 and RNA from 25

lung cancer patients. The DNA was examined for microsatellite alterations (MA) and the RNA analysed for the expression of seven tumour-associated genes. Intact DNA and mRNA could be isolated from all cell-free bronchial lavage supernatants. MA were found in lavage supernatants of 12/30 patients and in lavage cells of 6/30 patients. Altogether alterations were found in 14/30 patients. Analyses of tumour-associated gene expression showed positive results, with at least one marker in the lavage supernatants of all 25 patients. Thus, we could demonstrate, for the first time, that it is possible to isolate intact DNA and RNA from cell-free bronchial lavage supernatants. Their quantity and quality is sufficient for further amplification by polymerase chain reaction (PCR)/reverse transcriptase (RT)-PCR. Altogether, tumour-associated changes were detected in DNA samples from 47% of the patients and in RNA samples from all of the patients analysed.

8.

**Clin Cancer Res 2004;10:2284-2288**

### **Detection of promoter hypermethylation of multiple genes in the tumor and bronchoalveolar lavage of patients with lung cancer.**

**Topaloglu O, Hoque MO, Tokumaru Y, Lee J, Ratovitski E, Sidransky D, Moon CS.**

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**PURPOSE:** Aberrant promoter hypermethylation of several known or putative tumor suppressor genes occurs frequently during the pathogenesis of lung cancers and is a promising marker for cancer detection. We investigated the feasibility of detecting aberrant DNA methylation in the bronchoalveolar lavage (BAL) samples of lung cancer patients. **EXPERIMENTAL DESIGN:** We examined the tumor and the matched BAL DNA for aberrant methylation of eight gene promoters (CDH1, APC, MGMT, RASSF1A, GSTP1, p16, RAR-beta 2, and ARF) from 31 patients with primary lung tumors by quantitative fluorogenic real-time PCR. BAL from 10 age-matched noncancer patients was used as a control. **RESULTS:** Promoter hypermethylation of at least one of the genes studied was detected in all 31 lung primary tumors; 27 (87%) CDH1, 17 (55%) APC, 14 (45%) RASSF1A, 12 (39%) MGMT, 7 (23%) p16, 3 (10%) GSTP1, 3 (10%) RAR-beta 2, and 0 (0%) ARF. Methyla-

“Overall, 21 (68%) of 31 BAL samples from cancer patients were positive for aberrant methylation.”

“... genetic markers in plasma identified 29 of 45 (64.4%) of all stages and 15 of 22 (68.2%) of stage I patients whose tumors had an alteration.”

“The goal of this study was to validate a panel of molecular markers for lung cancer detection in plasma DNA.”

tion was detected in CDH1 (48%), APC (29%), RASSF1A (29%), MGMT (58%), p16 (14%), GSTP1 (33%), RAR-beta 2 (0%), and ARF (0%) of BAL samples from matched methylation-positive primary tumors, and in every case, aberrant methylation in BAL DNA was accompanied by methylation in the matched tumor samples. BAL samples from 10 controls without evidence of cancer revealed no methylation of the MGMT, GSTP1, p16, ARF, or RAR-beta 2 genes whereas methylation of RASSF1, CDH1, and APC was detected at low levels. Overall, 21 (68%) of 31 BAL samples from cancer patients were positive for aberrant methylation. CONCLUSION: Our findings suggest that promoter hypermethylation in BAL can be detected in the majority of lung cancer patients. This approach needs to be evaluated in large early detection and surveillance studies of lung cancer.

Editorial Comment (TLP):

These two papers are encouraging because they appear to identify lung cancer molecular markers that have clinical relevance. Bronchoalveolar lavage to identify an increasing number of lung cancer biological markers is evolving in the detection of early stage and even occult lung cancer. Finding the same genetic markers in expectorated sputum would be even more advantageous.

9.  
**Int J Cancer 2004;108:91-96**  
**Detecting lung cancer in plasma with the use of multiple genetic markers.**

**Andriani F, Conte D, Mastrangelo T, Leon M, Ratcliffe C, Roz L, Pelosi G, Goldstraw P, Sozzi G, Pastorino U.**  
Department of Experimental Oncology, Istituto Nazionale Tumori, Milan, Italy. francesca.andriani@istitutotumori.mi.it

Recent studies have demonstrated the possibility to detect genetic changes in plasma DNA of cancer patients. The goal of this study was to validate a panel of molecular markers for lung cancer detection in plasma DNA. Three markers, p53, FHIT and microsatellite alterations at loci on chromosome 3, were used to detect mutations in tumor and plasma DNA of 64 stage I-III non small cell lung cancer patients. p53 mutations were studied by direct se-

quencing of exons 5 through 8 in tumor DNA and by plaque hybridization assay and sequencing in plasma DNA. Allelic losses were evaluated by fluorescent PCR in tumor and plasma DNA. p53 genomic mutations were detected in 26 (40.6%) of 64 tumor DNA samples and the identical mutation was identified in plasma of 19 (73.1%) of them. Microsatellite alterations at FHIT and 3p loci were observed in 40 (62.5%) tumors and in 23 (35.9%) plasma samples. Of the 40 patients showing microsatellite alterations in tumors, 19 (47.5%) displayed the same change in plasma DNA. At least 1 of the 3 genetic markers (p53, FHIT and 3p) was altered in plasma of 51.6% of all patients and 60.7% of stage I patients. Moreover, genetic markers in plasma identified 29 of 45 (64.4%) of all stages and 15 of 22 (68.2%) of stage I patients whose tumors had an alteration. These results provide the proof of principle that plasma DNA alterations are tumor-specific in most cases and support blood testing as a noninvasive strategy for early detection. Copyright 2003 Wiley-Liss, Inc.

10.  
**Int J Cancer 2004;110:891-895**  
**Genetic abnormalities in plasma DNA of patients with lung cancer and other respiratory diseases.**

**Khan S, Coulson JM, Woll PJ.**  
Cancer Research UK Department of Clinical Oncology, University of Nottingham and Nottingham City Hospital, Nottingham, United Kingdom.

The detection of tumour-associated genetic alterations in plasma DNA has been proposed as a simple method for the early diagnosis of lung cancer and for identifying individuals at high risk of lung cancer who might be included in screening or chemoprevention programmes. To evaluate the practicality of this approach, we screened a panel of 16 plasma DNA markers in a lung cancer population to identify those with the highest genetic alteration rate. These were then used to study plasma DNA in 206 hospital outpatients with lung cancer and other respiratory diseases. Plasma and lymphocyte DNA were isolated from blood samples collected from hospital outpatients. Polymerase chain reaction was carried out with 16 microsatellite markers covering chromosomal regions 3p,

8p, 9p, 13q and 17p, using DNA from 32 lung cancer patients. The 3 markers most commonly affected were selected for use in a larger study of 86 lung cancer patients and 120 patients with other respiratory diseases. In the pilot study, 3 primer pairs (D3S1300, D3S1560, D8S201) together detected genetic alterations in plasma DNA in 60% of lung cancer patients. In the larger study, significantly higher genetic alteration rates were observed in lung cancer patients than in patients with other respiratory diseases for the two markers D3S1560 and D8S201. The overall genetic alteration rate was 69% in the lung cancer patients and 42% in the patients with other respiratory diseases ( $p < 0.001$ ). Analysis of plasma and lymphocyte DNA to detect genetic alterations typical of lung cancer is possible in large studies. The genetic alteration rate we found in lung cancer patients was comparable with other studies. Although the genetic alteration rate was significantly higher in the lung cancer than the respiratory disease patients, it did not have good positive predictive value in this population. Longitudinal studies are required to determine whether genetic changes in plasma DNA of non-cancer patients indicate a high risk of later lung cancer. Copyright 2004 Wiley-Liss, Inc. Editorial Comment (TLP):

“ . . . Significantly higher genetic alteration rates were observed in lung cancer patients than in patients with other respiratory diseases for the two markers D3S1560 and D8S201.”

“Higher concentrations of exhaled ET-1 were found in NSCLC patients (8.3 +/- 0.7 pg/ml) compared to controls . . .”

These two articles report the finding of lung cancer markers in serum. Obtaining serum, of course, is easier than by bronchoalveolar lavage. These serum markers of lung cancer along with markers in bronchoalveolar lavage will continue to tantalize basic scientists and clinicians interested, particularly in the early stages of lung cancer.

11.

**Oncology 2004;66:180-183**

### **Endothelin-1 is increased in the breath condensate of patients with non-small-cell lung cancer.**

**Carpagnano GE, Foschino-Barbaro MP, Resta O, Gramiccioni E, Carpagnano F.**  
Institute of Respiratory Disease, University of Bari, Bari, Italy.

One recent line of cancer research is currently directed to the study of growth factors. Of increasing interest is endothelin-1 (ET-1), a mitogenic factor already investigated in several human cancer cell lines, which has been found to participate in the development and progression of tumours. This peptide has an important role also in non-small-cell lung cancer (NSCLC) where ET-1 expression has been found in 100% of cell lines. OBJECTIVES: The aim of

this study was to measure ET-1 concentrations in the airways of patients with NSCLC using a completely non-invasive procedure--the breath condensate--and to verify the involvement of this peptide in the growth of lung tumours. METHODS: We enrolled 30 patients (17 men, median age 63 years; range 53-74) with histological evidence of NSCLC and 15 healthy controls (9 men, median age 59 years; range 52-70). ET-1 was measured in the exhaled breath condensate by means of a specific enzyme immunoassay kit. RESULTS: Higher concentrations of exhaled ET-1 were found in NSCLC patients (8.3 +/- 0.7 pg/ml) compared to controls (5.2 +/- 0.5 pg/ml,  $p < 0.0001$ ). A statistically significant difference was observed between patients with distant metastases (stage IV) of NSCLC (8.9 +/- 0.6 pg/ml) and those with locoregional disease (stage I-III) (7.9 +/- 0.5 pg/ml). A significant reduction in ET-1 levels was found in 14 patients after surgical removal of the tumour either associated with or without adjuvant chemotherapy (6.3 +/- 0.5 vs. 7.9 +/- 0.4 pg/ml,  $p < 0.0001$ ). CONCLUSIONS: These findings suggest that the measurement of ET-1 in the breath condensate of patients with NSCLC could be proposed as a marker for early detection of NSCLC as well as for monitoring reduction or progression of the neoplasm in the follow-up of treated patients. Copyright 2004 S. Karger AG, Basel

Editorial Comment (TLP):

How about a breath test for lung cancer? This has been suggested before (Lancet 1999;353:1930-1933 cited in *Lung Cancer Frontiers No. 6*). I hope we are moving closer to non-invasive convenient markers of early stage of malignancy or pre-malignancy.

12.

**Curr Opin Pulm Med 2004;10:242-247**

### **Recent developments in biomarkers for the early detection of lung cancer: perspectives based on publications 2003 to present.**

**Chanin TD, Merrick DT, Franklin WA, Hirsch FR.**

University of Colorado Health Sciences Center, Department of Pathology and University of Colorado Cancer Center, Denver, Colorado 80262, USA.

PURPOSE OF REVIEW: Given the poor prognosis associated with lung cancer, the ability to diagnose lung cancer in its early

“Novel potential biomarkers have been identified via new techniques including cDNA microarray analysis, comparative genomic hybridization, and proteomics.”

stages is considered crucial to achieving decreased lung cancer mortality. Herein, we discuss recent advances in biomarker discovery and evaluation of their potential application in the clinical setting. RECENT FINDINGS: Novel potential biomarkers have been identified via new techniques including cDNA microarray analysis, comparative genomic hybridization, and proteomics. These factors have been evaluated in various validation studies including tissue microarrays, RT-PCR, and assays of bioactivity. The characterization of these potential biomarkers through analysis of pathways that have been associated with neo-plastic transformation may help to identify the precursor lesions that are associated with subsequent progression to invasive carcinoma. In addition, the past year has also produced intriguing results regarding the detection of biomarkers in easily accessible screening specimens such as sputa, serum, and exhaled breath. Recent advances in these aspects of biomarker identification for the early detection of lung cancer are reviewed. SUMMARY: Identification of new candidate biomarkers and improved applications of previously detected biomarkers show great promise for the ultimate establishment of practical lung cancer screening. While recent studies engender optimism for the creation of clinically applicable screening tests, the biomarkers that have been identified need larger, follow-up validation studies and further characterization as to their biologic importance.

“Identification of new candidate biomarkers and improved applications of previously detected biomarkers show great promise for the ultimate establishment of practical lung cancer screening.”

Editorial Comment (TLP):

The Editorial Board rarely publishes reviews, but a summary of recent developments in biomarkers for the early identification in recent years is of particular value. For this reason this citation is included.

13.

**Thorax 2004;59:237-241**

### **Screening for lung cancer using low dose CT scanning.**

**MacRedmond R, Logan PM, Lee M, Kenny D, Foley C, Costello RW.**

Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland. rmacredmond@rcsi.ie

BACKGROUND: Lung cancer is the most common cause of cancer related death in Ireland. The majority of lung cancers are inoperable at the time of diagnosis and consequently the overall 5 year survival is less than 10%. The objective of the ProActive Lung Cancer Detection (PALCAD) study was to evaluate whether low dose chest computed tomographic scan-

ning (LDCCT) can detect early stage asymptomatic lung cancer in a high risk urban population. METHODS: Four hundred and forty nine subjects of median age 55 years (range 50-74) with a median pack year smoking history of 45 years (range 10-160), with no previous cancer history and medically fit to undergo thoracic surgery were recruited. After informed consent, LDCCT was performed on all subjects. Non-calcified nodules (NCNs) of  $\geq 10$  mm in diameter were referred for biopsy. Follow up with interval LDCCT at 6, 12 and 24 months to exclude growth was recommended for NCNs  $< 10$  mm in diameter. RESULTS: Six (1.3%) NCNs of  $\geq 10$  mm were detected of which one (0.23%) had non-small cell lung cancer stage 1; 145 NCNs of  $< 10$  mm were detected in 87 (19.4%) subjects. Mediastinal masses were detected in three subjects (0.7%)-one small cell lung cancer and two benign duplication cysts. Incidental pathology was noted in 276 patients (61.5%), most commonly emphysema and coronary artery calcification. CONCLUSION: The prevalence of resectable lung cancer detected by LDCCT at baseline screening was low at 0.23%, but there was a high rate of significant incidental pathology.

Editorial Comment (TLP):

CT scanning continues to evolve as the most popular method of lung cancer screening. The fact that it identifies many benign lesions and requires follow-up are important limitations.

14.

### **Acad Radiol 2004;11:233-237** **Consistency of reporting basic characteristics of lung nodules and masses on computed tomography.**

**Burns J, Haramati LB, Whitney K, Zelefsky MN.**

Department of Radiology, Albert Einstein College of Medicine, Montefiore Medical Center and Jacobi Medical Center, Bronx, NY, USA.

RATIONALE AND OBJECTIVES: To assess the consistency of chest computed tomography (CT) reports in describing basic characteristics of lung nodules and masses. MATERIALS AND METHODS: We retrospectively identified 107 consecutive patients with pre-operative chest CT scans before resection of a lung nodule or mass over a 4-year period within a single institution. There were 54 men

“We retrospectively identified 107 consecutive patients with preoperative chest CT scans before resection of a lung nodule or mass over a 4-year period within a single institution.”

“Radiologists described the margins of the nodule or mass in 64% (68/107) cases, similar in frequency to 66% of pathologists (71/107).”

“Current indications for PET in the staging of newly diagnosed NSCLC are mainly the patients who are considered to be candidates for radical treatment.”

and 53 women with a mean age of 64 years (range, 37-86) years. The CT scans were reported by a cohort of 20 board-certified radiologists, three of whom reviewed more than 10 CT scans (n = 60 exams). The CT reports were reviewed for lesion characteristics including size, location, and description of margins, presence or absence of calcification, fat and cavitation, and the diagnosis or differential diagnosis. Pathology reports were reviewed for the same characteristics and the final diagnosis. Both CT and pathologic reports of emphysema were noted in lobectomy specimens. The differences between the interpreting radiologists were also sought. RESULTS: A diagnosis or differential diagnosis was provided in 90% (96/107) of CT reports. The diagnosis of bronchogenic carcinoma was made in 78% (59/76) of those with bronchogenic carcinoma, compared with 65% (20/31) of those with other diagnoses (P = NS). Radiologists described the margins of the nodule or mass in 64% (68/107) of cases, similar in frequency to 66% of pathologists (71/107). Radiologic description of an irregular/spiculated margins predicted bronchogenic carcinoma in 86% of cases (42/49), while a smooth/lobulated margins predicted a diagnosis other than bronchogenic carcinoma in 58% (11/19; P < .05). The presence or absence of calcification was noted in 7% (5/76) of cases of bronchogenic carcinoma and 32% (10/31) of those with other diagnoses (P < .05, chi square). Both radiologists and pathologists consistently reported the size of the lesions with a correlation coefficient between radiology and pathology reports of 0.88. CT reporting of the characteristics of the lesion did not differ among lesions of different sizes. There was no significant difference between major reporters (more than 10 cases) in this study. Emphysema in the surrounding lung was reported in 25% (20/81) of radiology and 38% (31/81) of pathology reports (P = NS). CONCLUSION: This series demonstrates a lack of consistent reporting of the margins of resected lung nodules both on CT and on pathologic specimens. The presence or absence of calcification was inconsistently reported, although more frequently noted in diagnoses other than bronchogenic carcinoma. As large-scale CT screening for lung cancer becomes more common, radiologists should prioritize developing and adopting standardized reporting criteria for the CT evaluation of lung nodules.

Editorial Comment (TLP):

We old “grey-haired pulmonologists” used to try and predict lung cancer on the basis of a smooth border versus irregular or “spiculated” margins on solitary nodules visible on standard chest x-rays. Now with CT scanning, these

patterns have become more complex. Certainly some sort of consistent reporting of nodular features including margins, at least among radiologists and pulmonologists, is needed.

15.

## **Hematol Oncol Clin North Am 2004;18:269-288** **Positron emission tomography in the management of non-small cell lung cancer.**

**Vansteenkiste JF, Stroobants SG.**

Respiratory Oncology Unit, Department of Pulmonology, Leuven Lung Cancer Group, University Hospital Gasthuisberg, Catholic University, Herestraat 49, B-3000 Leuven, Belgium. johan.vansteenkiste@uz.kuleuven.ac.be

In the past 10 years, FDG-PET has become an important imaging modality in NSCLC. Its indication in the assessment of lung nodules and staging is based on large prospective experience, further supported by some meta-analyses. This evidence has important consequences for patient management, which recently was proved in a randomized trial that showed a reduction in the number of futile thoracotomies by preoperative PET. The use of FDG-PET could become more widespread when commercial isotope distributors are able to deliver FDG so that an on-site cyclotron is no longer a prerequisite. FDG has a half-life of 110 minutes, so a practical distribution radius of 200 km should be feasible. Current indications for PET in the staging of newly diagnosed NSCLC are mainly the patients who are considered to be candidates for radical treatment. The technique does not have a clinical indication in other patients—for example, when metastatic lymph nodes are detected at clinical examination, when a simple ultrasound study already points to diffuse hepatic metastases, or in cases of poor performance status. PET also has prognostic value; it can be used for the evaluation of response or restaging after radiotherapy or chemotherapy and for early detection of relapse. The combination of CT and PET improves radiotherapy planning and it is to be expected that combined CT-PET-guided planning devices will further refine three-dimensional conformal radiotherapy. Finally, a whole new field of application of PET in molecular biology using new radiopharmaceuticals is in development. FDG, with its possibility to study tumor glucose metabolism, has paved the way for PET in clinical oncol-

“... Excellent prognosis can be expected even with limited surgical resection.”

“New tracers that have showed their promise in early clinical studies include 18F-fluorothymidine ...”

“Video-assisted thoracic surgery may be appropriate for management of small pure ground-glass opacities.”

ogy. It is hoped that PET examinations with new molecular tracers will allow ever better specificity and become sufficiently reliable and manageable to evaluate receptors, transport proteins, and intracellular enzymes so that very early response monitoring during chemotherapy or radiotherapy, evaluation of novel molecular-targeted lung cancer therapies, or even gene therapy becomes possible. New tracers that have showed their promise in early clinical studies include 18F-fluorothymidine (a proliferation marker that might give better specificity in the assessment of solitary pulmonary nodules or better accuracy in the evaluation of early response), (99m)Tc-Annexin V (Apomate; an apoptosis-imaging agent that could be correlated with overall and progression-free survival in phase I data), or 18F-fluoromisonidazole (which can be used to quantify regional hypoxia in human tumors with PET).

Editorial Comment (TLP):

PET scanning or combined PET-CT is emerging as an increasingly popular way of both assessing the likelihood of malignancy and in staging lung cancer. It is great to have this evolving technology, but the final diagnostic value remains with the perspective of the radiologists and managing clinicians.

16.

**Ann Thorac Surg 2004;77:1911-1915**  
**Video-assisted thoracic surgery for pure ground-glass opacities 2 cm or less in diameter.**

**Yamada S, Kohno T.**

Department of Thoracic Surgery, Toranomon Hospital, Tokyo, Japan. yamada.shunsuke@hachioji-hosp.tokai.ac.jp

**BACKGROUND:** Small, well-circumscribed pure ground-glass opacities on high-resolution computed tomography can represent either localized bronchioloalveolar carcinoma without foci of active fibroblastic proliferation, or atypical adenomatous hyperplasia. Since neither lesion displays lymph node metastasis, excellent prognosis can be expected even with limited surgical resection. In this study, video-assisted thoracic surgery was performed for patients with pure ground-glass-opacity to evaluate efficacy for both diagnostic and therapeutic purposes. **METHODS:** Thirty-nine patients with pure ground-glass opacity less than or equal to 2 cm in diameter (62 lesions) underwent video-assisted thoracic surgery with

wedge resection as primary therapy. Histologic diagnoses were made according to Noguchi classifications. **RESULTS:** Single lesions were observed in 30 patients, with multiple lesions (mean, 4 lesions) in 9 patients. Twenty-eight patients underwent wedge resection. Seven patients underwent lobectomy or segmentectomy for technical reasons. Four patients underwent conversion of wedge resection to lobectomy (due to active fibroblastic proliferation in 2 patients, and other reasons in 2 patients). All procedures were performed under videoscopic observation. Histologic diagnoses comprised localized bronchioloalveolar carcinoma without active fibroblastic proliferation either alone or in combination with atypical adenomatous hyperplasia in 29 patients, atypical adenomatous hyperplasia in 8 patients, and localized bronchioloalveolar carcinoma with active fibroblastic proliferation in 2 patients. All patients with localized bronchioloalveolar carcinoma underwent follow-up for a median period of 29.3 months, and have survived without sign of recurrence. **CONCLUSIONS:** Video-assisted thoracic surgery may be appropriate for management of small pure ground-glass opacities.

Editorial Comment (TLP):

Early diagnosis of small peripheral alveolar cell carcinoma allows for tissue sparing surgery and apparent cure!

17.

**Ann Thorac Surg 2004;77:1896-903**  
**Preoperative pulmonary function as a prognostic factor for stage I non-small cell lung carcinoma.**

**Iizasa T, Suzuki M, Yasufuku K, Iyoda A, Otsuji M, Yoshida S, Sekine Y, Shibuya K, Saitoh Y, Hiroshima K, Fujisawa T.**  
Department of Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan.

**BACKGROUND:** The aim of this study was to clarify preoperative lung function as a prognostic factor for the long-term survival of, and to discuss the appropriateness of lobectomy for, patients with stage I non-small cell lung carcinoma who have poor preoperative pulmonary function. **METHODS:** The study group consisted of 402 lobectomized patients with stage I non-small cell lung carcinoma treated by complete resection from 1985 to 1997. Preoperative percent forced vital capacity [(forced vital capacity/predicted forced vital capacity) x 100], FEV(1)% [(forced expiratory volume in 1 second/forced vital capacity

“The study group consisted of 402 lobectomized patients with stage I non-small cell lung carcinoma treated by complete resection . . .”

ity) x 100], arterial carbon dioxide tension, and smoking were statistically analyzed as prognostic factors together with other host and tumor biologic factors. RESULTS: Multivariate analysis demonstrated that tumor size ( $p < 0.0001$ ) was the most significant prognostic factor for survival from primary lung cancer. Age ( $p < 0.0001$ ), sex ( $p = 0.0036$ ), and FEV(1)% ( $p = 0.0046$ ) were found to be independent prognostic factors for survival from death by nonprimary lung cancer-related causes. Smoking was highly correlated with FEV(1)% (correlation coefficient =  $-0.511$ ;  $p < 0.0001$ ). The 100 patients with a preoperative FEV(1)% less than 70% included 34 patients with nonprimary lung cancer-related deaths, whereas the 302 patients with an FEV(1)% of 70% or greater included only 23 patients ( $p < 0.0001$ ). CONCLUSIONS: Along with tumor size, FEV(1)% is the most significant prognostic factor for patients with stage I non-small cell lung carcinoma with regard to survival from death by other causes. Lobectomy may not be preferred as an appropriate surgical modality for patients with stage I non-small cell lung carcinoma with small peripheral nodules who exhibit poor pulmonary function, especially lowered FEV(1)%.

Editorial Comment (TLP):

Pulmonary function sparing surgery for the curative resection of lung cancer is clearly important in an aging population with reduced pulmonary reserve. Pre-operative spirometry is a must for these patients!

18.

**J Thorac Cardiovasc Surg 2004;127:1323-1331**

**Lung cancer resection combined with lung volume reduction in patients with severe emphysema.**

**Choong CK, Meyers BF, Battafarano RJ, Guthrie TJ, Davis GE, Patterson GA, Cooper JD.**

Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine, and Jacqueline Mariitz Lung Center at Barnes-Jewish Hospital, St Louis, MO 63110, USA.

OBJECTIVE: Certain patients with resectable lung cancer and severe respiratory limitation due to emphysema may have a suitable operative risk by combining cancer resection with lung volume reduction surgery. The purpose of this study is to review our experience with such patients. METHODS: A review was conducted

on 21 patients with lung cancer in the setting of severe emphysema who underwent an operation designed to provide complete cancer resection and volume reduction effect. RESULTS: In the 21 patients, the mean preoperative forced expiratory volume in 1 second was  $0.7 \pm 0.2$  L (29% predicted), residual volume was  $5.5 \pm 1.0$  L (271%), and diffusing capacity for carbon monoxide was  $8.0 \pm 2.2$  mL/min/mm Hg (34% predicted). In 9 patients, the cancer was located in a severely emphysematous lobe and the lung volume reduction surgery component of the procedure was accomplished with lobectomy alone. In the remaining 12 patients, the cancer resection lobectomy ( $n = 9$ ) and wedge resection ( $n = 3$ ) were supplemented with lung volume reduction surgery. Final pathologic staging was stage I in 16 patients, stage II in 2 patients, and stage III in 2 patients. One patient was found to have stage IV disease due to multifocal tumors in separate lobes. There were no hospital deaths. Postoperative complications included prolonged air leak in 11 patients, atrial fibrillation in 6 patients, and reintubation for ventilatory assistance in 2 patients. All patients showed improved lung function postoperatively. Survival was 100% and 62.7% at 1 and 5 years, respectively. CONCLUSIONS: Patients with severe emphysema and resectable lung cancer who have a favorable anatomy for lung volume reduction surgery may undergo a combined cancer resection and lung volume reduction surgery with an acceptable risk and good long-term survival.

Editorial Comment (TLP):

This is a true “blue plate special.” Just notice the survival of one in five years! Too bad patients have to wait until they have advanced emphysema and require lung volume reduction surgery to get attention to their lung cancer.

19.

**Ann Thorac Surg 2003;76:1821-1827**  
**Quality of life after tailored combined surgery for stage I non-small-cell lung cancer and severe emphysema.**

**Pompeo E, De Dominicis E, Ambrogi V, Mineo D, Elia S, Mineo TC.**

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“Lobectomy may not be preferred as an appropriate surgical modality for patients with stage I non-small cell lung carcinoma with small peripheral nodules who exhibit poor pulmonary function . . .”

“Patients with severe emphysema and resectable lung cancer who have a favorable anatomy for lung volume reduction surgery may undergo a combined cancer resection and lung volume reduction surgery . . .”

**BACKGROUND:** We analyzed the early and long-term quality of life changes occurring in 16 patients undergoing tailored combined surgery for stage I non-small-cell lung cancer (NSCLC) and severe emphysema. **METHODS:** Mean age was 65 +/- 5 years. All patients had severe emphysema with severely impaired respiratory function and quality of life. Tumor resection was performed with sole lung volume reduction (LVR) in 5 patients, separate wedge resection in 3 patients, segmentectomy in 2 patients, and lobectomy in 6 patients. A bilateral LVR was performed in 5 patients. Quality of life was assessed at baseline and every 6 months post-operatively by the Short-form 36 (SF-36) item questionnaire. **RESULTS:** Mean follow-up was 44 +/- 21 months. All tumors were pathologic stage I. There was no hospital mortality nor major morbidity. Significant improvements occurred for up to 36 months in the general health ( $p = 0.02$ ) domain and for up to 24 months in physical functioning ( $p = 0.02$ ), role physical ( $p = 0.005$ ), and general health ( $p = 0.01$ ) SF-36 domains. Associated improvements regarded dyspnea index (-1.3 +/- 0.6) forced expiratory volume in one second (+0.28 +/- 0.2L), residual volume (-1.18 +/- 0.5L) and 6-minute-walking test distance (+86 +/- 67 m). Actuarial 5-year survival was similar to that of patients with no cancer undergoing LVRS during the same period (68% vs 82%,  $p =$  not significant). **CONCLUSIONS:** Our study suggests that selected patients with stage I NSCLC and severe emphysema may significantly benefit from tailored combined surgery in terms of long-term quality of life and survival.

“Women are targeted in tobacco advertising, and teenage girls are often drawn to cigarette smoking under a variety of social pressures.”

“There are no hospital mortality nor major morbidity.”

Editorial Comment (TLP):

It is remarkable that even in severe emphysema patients may have significantly better quality of life and survival with combined surgery for the purpose of increasing elastic recoil and also curing associated carcinoma.

20.

**JAMA 2004;291:1763-1768**

### **Lung cancer in US women: a contemporary epidemic.**

**Patel JD, Bach PB, Kris MG.**

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Lung cancer is the leading cause of cancer death in US women and is responsible for as many deaths as breast cancer and all gynecological cancers combined.

Most lung cancer is caused by cigarette smoke. Despite all that is known about the devastating effects of cigarettes, one quarter of women in the United States continue to smoke. Women are targeted in tobacco advertising, and teenage girls are often drawn to cigarette smoking under a variety of social pressures. Following the increase in smoking, the death rate from lung cancer in US women rose 600% from 1930 to 1997. Women may be more susceptible than men to the carcinogenic properties of cigarette smoke. In addition, differences in the biology of lung cancer exist between the 2 sexes with higher levels of DNA adduct formation, increased CYP1A1 expression, decreased DNA repair capacity, and increased incidence of K-ras gene mutations in women. The novel estrogen receptor beta has also been detected in lung tumors and suggests that estrogen signaling may have a biological role in tumorigenesis. Given these differences and given the enormous toll this disease has on US women, undertaking sex-specific research in lung cancer is crucial. Finally, disseminating information about this epidemic may prevent a similar epidemic in other parts of the world where women are just now becoming addicted to tobacco.

21.

**J Natl Cancer Inst 2004;96:826-834**

### **Lung cancer rates in men and women with comparable histories of smoking.**

**Bain C, Feskanich D, Speizer FE, Thun M, Hertzmark E, Rosner BA, Colditz GA.**  
School of Population Health, University of Queensland, Brisbane, Queensland, Australia.

**BACKGROUND:** Recent case-control studies suggest that, given equal smoking exposure, women may have a higher relative risk of developing lung cancer than men. Despite prospective data that conflict with this hypothesis, mechanistic studies to find a biologic basis for a sex difference continue. **METHODS:** We addressed the hypothesis directly by analyzing prospective data from former and current smokers in two large cohorts--the Nurses' Health Study of women and the Health Professionals Follow-up Study of men. We calculated incidence rates and hazard ratios of lung cancer in women compared

with men, adjusting for age, number of cigarettes smoked per day, age at start of smoking, and time since quitting, using Cox proportional hazards models. We also reviewed published results from prospective analyses. RESULTS: From 1986 through 2000, 955 and 311 primary lung cancers were identified among 60 296 women and 25 397 men, respectively, who ranged in age from 40 to 79 years. Incidence rates per 100 000 person-years for women and men were 253 and 232, respectively, among current smokers and 81 and 73, respectively, among former smokers. The hazard ratio in women ever smokers compared with men was 1.11 (95% confidence interval = 0.95 to 1.31). Six published prospective cohort studies allowed assessment of comparative susceptibility to lung cancer by sex. None supported an excess risk of lung cancer for women. CONCLUSIONS: Women do not appear to have a greater susceptibility to lung cancer than men, given equal smoking exposure. Research should be focused on enhancing preventive interventions for all.

Editorial Comment (TLP):

These two timely articles with mutually conflicting conclusions still leave question marks. However, it is unlikely that women are really more susceptible than men with equal degrees of smoking, after studying both papers. In any case, women are certainly just as likely to have lung cancer as equally-smoking men. We know that women are more likely to die of emphysema than men. High risk women smokers need screening for the early diagnosis of lung cancer.

“Women do not appear to have a greater susceptibility to lung cancer than men, given equal smoking exposure.”

22.

**Cancer 2004;101:3-27**  
**Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival.**

**Jemal A, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, Wingo PA, Howe HL, Anderson RN, Edwards BK.**

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BACKGROUND: The American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Insti-

“The 5-year relative survival rates improved for all cancers combined and for most, but not all, cancers over 2 diagnostic periods . . .”

tute (NCI), and the North American Association of Central Cancer Registries (NAACCR) collaborate annually to provide updated information regarding cancer occurrence and trends in the U.S. This year's report features a special section on cancer survival. METHODS: Information concerning cancer cases was obtained from the NCI, CDC, and NAACCR and information concerning recorded cancer deaths was obtained from the CDC. The authors evaluated trends in age-adjusted cancer incidence and death rates by regression models and described and compared survival rates over time and across racial/ethnic populations. RESULTS: Incidence rates for all cancers combined decreased from 1991 through 2001, but stabilized from 1995 through 2001 when adjusted for delay in reporting. The incidence rates for female lung cancer decreased (although not statistically significant for delay adjusted) and mortality leveled off for the first time after increasing for many decades. Colorectal cancer incidence rates also decreased. Death rates decreased for all cancers combined (1.1% per year since 1993) and for many of the top 15 cancers occurring in men and women. The 5-year relative survival rates improved for all cancers combined and for most, but not all, cancers over 2 diagnostic periods (1975-1979 and 1995-2000). However, cancer-specific survival rates were lower and the risk of dying from cancer, once diagnosed, was higher in most minority populations compared with the white population. The relative risk of death from all cancers combined in each racial and ethnic population compared with non-Hispanic white men and women ranged from 1.16 in Hispanic white men to 1.69 in American Indian/Alaska Native men, with the exception of Asian/Pacific Islander women, whose risk of 1.01 was similar to that of non-Hispanic white women. CONCLUSIONS: The continued measurable declines for overall cancer death rates and for many of the top 15 cancers, along with improved survival rates, reflect progress in the prevention, early detection, and treatment of cancer. However, racial and ethnic disparities in survival and the risk of death from cancer, and geographic variation in stage distributions suggest that not all segments of the U.S. population have benefited equally from such advances. Published 2004 by the American Cancer Society.

Editorial Comment (TLP):

I included this article because of the commentary on improved survival rate and the fact that it reflects “progress in the prevention, early detection, and treatment of can-

“The continued measurable declines for overall cancer death rates and for many of the top 15 cancers, along with improved survival rates, reflect progress in the prevention, early detection, and treatment of cancer.”

cer.” Notice that it comes from the American Cancer Society that today fails to recommend screening for the early detection of lung cancer. What hypocrisy!

23.

**JAMA 2004;292:470-484**  
**Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis.**

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CONTEXT: Randomized trials have demonstrated that adding a drug to a single-agent or to a 2-agent regimen increased the tumor response rate in patients with advanced non-small-cell lung cancer (NSCLC), although its impact on survival remains controversial. OBJECTIVE: To evaluate the clinical benefit of adding a drug to a single-agent or 2-agent chemotherapy regimen in terms of tumor response rate, survival, and toxicity in patients with advanced NSCLC. DATA SOURCES AND STUDY SELECTION: Data from all randomized controlled trials performed between 1980 and 2001 (published between January 1980 and October 2003) comparing a doublet regimen with a single-agent regimen or comparing a triplet regimen with a doublet regimen in patients with advanced NSCLC. There were no language restrictions. Searches of MEDLINE and EMBASE were performed using the search terms non-small-cell lung carcinoma/drug therapy, adenocarcinoma, large-cell carcinoma, squamous-cell carcinoma, lung, neoplasms, clinical trial phase III, and randomized trial. Manual searches were also performed to find conference proceedings published between January 1982 and October 2003. DATA EXTRACTION: Two independent investigators reviewed the publications and extracted the data. Pooled odds ratios (ORs) for the objective tumor response rate, 1-year survival rate, and toxicity rate were calculated using the fixed-effect model. Pooled median ratios (MRs) for median survival also were calculated using the fixed-effect model. ORs and MRs lower than unity (<1.0) indicate a benefit of a doublet regimen compared with a single-agent regimen (or a triplet regimen compared with a doublet regimen). DATA SYNTHESIS: Sixty-five trials (13 601 patients) were eligible. In the trials comparing a doublet regimen with a single-

“Adding a second drug improved tumor response and survival rate.”

agent regimen, a significant increase was observed in tumor response (OR, 0.42; 95% confidence interval [CI], 0.37-0.47; P<.001) and 1-year survival (OR, 0.80; 95% CI, 0.70-0.91; P<.001) in favor of the doublet regimen. The median survival ratio was 0.83 (95% CI, 0.79-0.89; P<.001). An increase also was observed in the tumor response rate (OR, 0.66; 95% CI, 0.58-0.75; P<.001) in favor of the triplet regimen, but not for 1-year survival (OR, 1.01; 95% CI, 0.85-1.21; P =.88). The median survival ratio was 1.00 (95% CI, 0.94-1.06; P =.97). CONCLUSION: Adding a second drug improved tumor response and survival rate. Adding a third drug had a weaker effect on tumor response and no effect on survival.

Editorial Comment (TLP):

Few pulmonologists use chemotherapy in the treatment of lung cancer. However, as comprehensive thoracic oncology treatment centers emerge and pulmonologists become appropriately more involved, they will have to learn and provide lung cancer chemotherapy. This can't be any more difficult to learn than the re-treatment of multiple drug resistant tuberculosis.

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**The Precautionary Principle, epidemiology and the ethics of delay.**

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Ethics tells us: do good and do no harm and invokes the norms of justice, equity and respect for autonomy in protecting and promoting health and well-being. The Precautionary Principle, a contemporary re-definition of Bradford Hill's case for action, gives us a common sense rule for doing good by preventing harm to public health from delay: when in doubt about the presence of a hazard, there should be no doubt about its prevention or removal. It shifts the burden of proof from showing presence of risk to showing absence of risk, aims to do good by preventing harm, and subsumes the upstream strategies of the Driving Forces Pressure Stress Exposure Effect Action model and downstream strategies from molecular epidemiology for detection and prevention of risk. The Precautionary Principle has emerged because of the ethical import of delays in de-

tection of risks to human health and the environment. Ethical principles, the Precautionary Principle, the DPSEEA model and molecular epidemiology all imply re-emphasizing epidemiology's classic role for early detection and prevention. Delays in recognizing risks from past exposures and acting on the findings (e.g., cigarette smoking and lung cancer, asbestos, organochlorines and endocrine disruption, radiofrequency, raised travel speeds) were examples of failures that were not only scientific, but ethical, since they resulted in preventable harm to exposed populations. These may delay results from, among other things, external and internal determinants of epidemiologic investigations of hazard and risk, including misuse of tests of statistical significance. Furthermore, applying the Precautionary Principle to ensure justice, equity, and respect for autonomy raises questions concerning the short-term costs of implementation to achieve long-term goals and the principles that guide compensation.

“The Precautionary Principle has emerged because of the ethical import of delays in detection of risks to human health and the environment.”

Editorial Comment (TLP):

This philosophical article deserves citation because it speaks to the ethical issues of delay in diagnosis. This is certainly true in lung cancer. Thus we need to be aware of the ethical aspects of failing to diagnose lung cancer when we have the knowledge and technology which could change its outcome.

“ . . . Applying the Precautionary Principle to ensure justice, equity, and respect for autonomy raises questions concerning the short-term costs of implementation . . . ”

## **CHANGES IN EDITORIAL BOARD**

The editorial board is delighted to announce the appointment of two new members: Elisabeth Brambilla of Grenoble Cedex France and Paul Baas of Amsterdam Netherlands.

Dr. Baas spends most of his time doing clinical and scientific studies of mesothelioma lung cancer and is also heavily involved in endobronchial techniques. He is particularly interested in the preventive aspects of pulmonary medicine, including smoking cessation. In addition to his MD, he has a PhD in photodynamic therapy. He is involved in many European and international

lung cancer-related activities.

Professor Elisabeth Brambilla is a lung pathologist with much interest in both interstitial and tumor pathologies. She is Chair of the Department of Pathology in university Hospital of Grenoble. She is also author and editor of the last classification of thoracic tumors. Her main interest is in the molecular pathology in relation with carcinogenic process in preinvasive lesions and tumors.

These new appointments reflect the editorial board's interest in increasing representation in Europe and other countries in *Lung Cancer Frontiers*. We also acknowledge the rotation off the board of Branko Palcic of Vancouver and John L. Stauffer of Research Triangle Park, North Carolina.