

October 2001

Lung  
Cancer

# Frontiers

## Lung Cancer Frontiers Still Viable

Comments may be submitted to:

**Lung Cancer Frontiers**  
1850 High Street  
Denver, CO 80218  
or by e-mail to  
tlpdoc@aol.com

*Lung Cancer Frontiers* is jointly funded by The Snowdrift Pulmonary Conference, the British Columbia Cancer Agency and a generous grant from AstraZeneca.

“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.”

Regular readers of *Lung Cancer Frontiers*, will note that our previous edition, *LCF 10*, appeared in January, 2001.

Unfortunately, we had to suspend publication of our planned April and July issues, because we lost the support that had allowed us to produce quarterly issues beginning with issue 6, January, 2000. As Editor-in-chief, I am pleased to say that our prognosis remains good, even though we are deficient in a certain critical nutrient that makes publication possible, namely money. The Snowdrift Pulmonary Conference, the British Columbia Cancer Agency, and a generous grant from AstraZeneca jointly sponsor this issue. We are seeking full support once again for quarterly issues in 2002 and beyond. Hopefully, we will find a sponsor that recognizes the importance of our goals, as stated in our first issue, which was launched in January, 1996. “Our purpose is to acquire and to disseminate new knowledge about lung cancer and about how it can be most quickly and effectively diagnosed and treated with an improvement in the dismal cure rate which has persisted for the past 30 years.” From all feedback that we have received from our readers, we have begun to achieve this goal.

Since the 6th issue, *LCF* has been mailed to all board-certified pulmonologists and internists in the U.S. and Canada (nearly 10,000). We feel it critical to stimulate the interest of pulmonologists in getting involved in lung cancer, particularly in early identification and intervention. Of perhaps greater importance is the fact that since the 6th issue, *LCF* has appeared on the Internet at our web site: [www.lungcancerfrontiers.org](http://www.lungcancerfrontiers.org). The Editorial Board is committed to at least continuing electronic versions of *LCF* as a life support measure. But, before we retreat to our fall-back position, we offer you *LCF 11* in the printed format. We are committed to publishing at least one issue in 2002 with existing resources.

*LCF* publishes abstracts from the contemporary peer-reviewed medical literature,

with editorial comments from experts in the field, and covers selected highlights of regional and international conferences. Thus, we devoted *LCF 9* to selected highlights of the 9th World Congress on Lung Cancer, held in Tokyo, Japan in September, 2000. This issue sites highlights from two conferences: The Liverpool Symposium in June, 2001 and Reykjavik, Iceland program in August. These conferences were attended by the following members of the *LCF* Editorial Board: Fred R. Hirsch, James R. Jett, Timothy C. Kennedy, Stephen Lam, York E. Miller, and James L. Mulshine. The editors are grateful to those who contributed to this issue. In addition, selected citations or commentaries of contemporary literature are included.

We continue to believe that at a time when knowledge and technology is changing so rapidly, fortunately in the direction of early identification and intervention, that this communication vehicle remains important. Its greatest value may be to stimulate both interest and controversy so that, ultimately, we can make progress in our approach to lung cancer in all of its stages.

## Lung Cancer Frontiers Editorial Board News

The newest member of the *LCF* Editorial Board is Dr. John L. Stauffer, Professor of Medicine, Penn State University, Hershey, Pennsylvania. Jack replaces James R. Mault. We thank Jim for his service. Jack is a senior pulmonologist and a seasoned clinician on the full-time faculty of the Hershey Medical Center. Following residency training at the University of California in San Francisco where he served as Chief Resident, Jack received his fellowship training at the University of Colorado program. During his training, he spent some time with the late Geno Saccomanno in Grand Junction, Colorado. Jack had formal training in pathology. Very early in his career, he was interested in the

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Frontiers**  
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or by e-mail at  
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possibility of employing sputum cytology on a widespread basis for the early diagnosis of lung cancer. He became a disciple of Geno Saccomanno. We welcome Jack, and look forward to his contributions.

## Enlarging the Debate on Lung Cancer Screening

The Journal of the American Medical Association (JAMA), article, Screening Strategies for Early Detection of Lung Cancer: The Time is Now (Petty TL. JAMA 2000;284:1977-1980) resulted in an invitation from Erich E. Brueschke, Editor of Disease-a-Month to write an expanded dissertation on the subject. This has now appeared in the June issue (Petty TL. Disease-a-Month 2001;47:197-264). This is a 67-page review with historical perspectives on the development of sputum cytology, the evolution of modern imaging techniques, and how sputum cytology and modern imaging are complementary in the screening and diagnosis of lung cancer, particularly in high-risk patients. Many members of the LCF Editorial Board feel that sputum cytology or an evolving sputum biomarker should be the first test in screening in high-risk patients (i.e., heavy smokers with airflow obstruction).

In 2001, an estimated 169,500 Americans will be diagnosed with lung cancer. Lung cancer represents 13% of all incident cancers annually in the United States and 29% of all cancer deaths. Lung cancer is the leading cause of cancer death for both men and women and kills more patients than the next five most common cancers combined. Eighty-five percent of patients who develop lung cancer die from it. Although lung cancer mortality rates began to decline in 1990 for men (about 1.7% per year), the mortality rates for women continued to increase until very recently. Smokers who give up smoking after the age of 50 retain a significant risk for lung cancer (Peto R, et al. B Med J 2000;321:323-329). Approximately 50% of newly diagnosed lung cancers occur in former smokers. Therefore, for long-term heavy smokers, an additional strategy such as early detection is needed in addition to smoking cessation for lung cancer control in the next several decades.

To address this important issue, the National Cancer Institute held several meetings to assess the current state of science in early lung cancer detection and management, as well as developing recommendations for further research in this

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area. International workshops were organized by John Field in the Roy Castle Lung Cancer Foundation in Liverpool, United Kingdom in June, 2001 and by Fred Hirsch in Reykjavik, Iceland from August 8 through August 12, 2001.

Central to the discussion on early detection and treatment was what constitutes “early” lung cancer. How do we define the biological, molecular, and phenotypic profile of “early” lung cancer? The ability to define what is an early lung cancer is of great importance in terms of risk assessment, design of new chemopreventive agents, development and validation of early detection methods, as well as establishing management guidelines.

Although the risk of lymph node metastases increase with the tumor size (Oda M, et al. Lung Cancer 1998;22:23-30), data from the Mayo Clinic, Cornell University, and Japan showed that as much as 7% of patients with lung cancer  $\leq 1$  cm in diameter can have N1 or N2 lymph node involvement. Some of these cancers appear to grow rapidly. Studies reported by Sone, Henschke, and Jett and their co-workers suggest that approximately 18% of lung cancers detected on annual repeat computed tomography (CT), were invisible on the prior CT scan. Thus, they must appear from what is below the CT detection limit in the interval. But fortunately, they can be detected in the next annual repeat examination. The incidence of interval cases diagnosed because of symptoms in these trials appears to be very low (approximately 5% or less). However, the study by Sone (see abstract on page 6) also suggests a word of caution. The mean tumor volume doubling time was 500 days for adenocarcinoma, with a range of 60 to 1,700 days. Most of these slow-growing cancers appear to be bronchoalveolar carcinoma without fibroblastic proliferation or foci of adenocarcinoma. They usually appear as non-solid or part-solid nodules on spiral CT. The tumor volume doubling time was also found to be longer in non-smokers compared to smokers. The implications of these findings are that for a tumor to grow from 3 mm to 15 mm in diameter, it would take 7 years with a doubling time of one year, and 14 years if the doubling were 2 years. The detection of these slow-growing tumors in the elderly or those with short life expectancy would not reduce lung cancer mortality.

In evaluating the potential usefulness of screening tests, it is important to define the target lesion. A test that can detect invasive cancer may not work for *in situ* carcinoma or sub-centimeter tumors. In early detection, specificity of the screening test is more important than sensitivity.

The positive predictive value of a test is usually lower than 10% when the specificity is less than 90%. Tests that have low positive predictive values will result in unnecessary diagnostic testing and treatment with associated morbidity and mortality. They also generate greater costs without corresponding benefits. Some of the biomarkers reported in these meetings, such as methylation markers in sputum cells, are important developments. However, much more work is needed. These and other biomarkers have differential sensitivity for different cell types. Combining several markers may improve the sensitivity but may also decrease the specificity.

The general consensus of these meetings is that lung cancer screening, such as using spiral CT, should only be conducted in a clinical trial setting. This would allow development of sufficiently accurate CT criteria that can differentiate sub-centimeter malignant nodules from benign lesions using computer-assisted technologies. Methods for CT image acquisition and measurement of lesion size, need to be validated and standardized. There is a need for improved transthoracic or endoscopic biopsy methods for small lung nodules. The methods of specimen collection, processing, and analysis and pathology/cytology interpretation need to be standardized. The role of minimally invasive treatments, such as radiofrequency surgery or photodynamic therapy, should also be further investigated.

A comprehensive program of lung cancer control by early detection and treatment has several components: screening, localization, diagnosis, treatment, and risk reduction for those with premalignant lesions. Each of these components must be in place before large-scale screening studies are initiated, so the same mistakes of the 1970's are not repeated. This is best achieved in collaborative controlled trials. The momentum is gaining worldwide for these collaborative studies. ■

## Highlights of the 2nd International Lung Cancer Molecular Biomarkers Workshop: A European Strategy for Developing Lung Cancer Molecular Diagnostics in High-Risk Populations.

June 27-30, 2001, Liverpool, United Kingdom.

### Early Lung Cancer Action Project: Findings on Baseline and Annual Repeat Screening CT and Future Projects.

Henschke CI, Principal Investigator of ELCAP, Weill Medical College of Cornell University, New York, NY.

**Purpose:** The Early Lung Cancer Action Project (ELCAP) is designed to evaluate baseline and annual repeat screening by low radiation dose computed tomography (low-dose CT) in persons at high-risk for lung cancer.

**Methods:** Since starting in 1993, the ELCAP has enrolled 1,000 asymptomatic persons, 60 years of age or older, with at least 10 pack-years of cigarette smoking, no prior cancer, and medically fit to undergo thoracic surgery. After a structured interview and informed consent, baseline chest radiographs (CXR) and low-dose CT were obtained on each subject. Low-dose CT was repeated on an annual basis as long as no malignancy was found. The diagnostic work-up of screen-detected noncalcified pulmonary nodules (NCN's) was guided by ELCAP recommendations which included short-term high-resolution CT (HRCT) follow-up for the smallest NCN's.

**Baseline Screening Results:** On low-dose CT at baseline as compared to CXR, NCN's were detected three times as commonly (23% vs 7%), malignancies four times as commonly (2.7% vs 0.7%), Stage I malignancies six times as commonly (2.3% vs 0.4%). Of the 27 CT-detected cancers, 96% (26/27) were resectable; 85% (23/27) were Stage I, 19 (83%) of the 23 were not seen on CXR. Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCN's; 27 had a malignant NCN and one had a benign one. Another three individuals underwent biopsy

outside of the ELCAP recommendations, all had benign NCN's. No one had thoracotomy for a benign nodule.

**Annual Repeat Screening Results:** In the 1,184 repeat screenings, the test result was positive in 30 (2.5%). In two of these 30 instances, the subject died (of unrelated cause) before diagnostic work-up; the nodule(s) resolved in another 12; and absence of further growth was documented by repeat CT in eight of the remaining 16. Further growth was documented in all of the remaining eight; all eight were biopsied and malignancy was diagnosed in seven of them. Six of the seven malignancies were non-small-cell carcinomas, five of Stage IA and one of Stage IIIA, and the one small-cell carcinoma was of limited stage. The median diameter of these malignancies was 8 mm. In another two subjects, symptoms prompted interim diagnosis of lung cancer, neither one of these nodule-associated (but endobronchial instead); one was a non-small cell carcinoma of Stage IIB and the other a small-cell carcinoma of limited stage.

**Conclusion:** Annual CT screening for lung cancer provides for detecting the disease at earlier and presumably more commonly curable stages in a cost-effective manner.

**Future Projects:** The ELCAP report, in turn, inadvertently led to considerable public and professional interest in the practice of CT-based screening for lung cancer; and within Cornell it led to two carefully-considered initiatives: the planning and fundraising for a project experimentally to screen 10,000 high-risk persons in what got to be called the New York ELCAP (NY-ELCAP) and the International Conferences on Screening for Lung Cancer. The latter initiative also was an outgrowth of the Cornell team's already extensive role in helping other investigator groups in various institutions initiate research projects patterned after the original ELCAP, including sharing with them a web-based management and data-recording system and its associated teaching files.

Integral to this international collaboration is pooling of the data, which represents the final element in what is now being launched as the International-ELCAP (I-ELCAP), simultaneously with the NY-ELCAP and with a shared set of not only principles but protocol as well. The I-ELCAP protocol represents an update of that in the original ELCAP, as is to be expected in this novel and rapidly evolving area of medical technology and its requisite evaluation toward the knowledge-base of future practice.

At any given time, the I-ELCAP focuses on the then-most-promising regimen of early (pre-

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symptomatic) diagnosis of lung cancer; and in respect to any such regimen, the first-order aim is to determine how early the diagnoses are achieved. This is a matter of determining the distribution of the diagnosed cases according to indicators such as stage and size, and status as to symptoms and signs, jointly considered. The diagnostic distribution is considered separately for baseline and for post-baseline diagnoses, and as for the latter, separately for interim (symptom-prompted) and screen-prompted diagnoses. The diagnostic subclassification is further refined by other prognostic indicators, notably cell type and, for the earliest diagnoses, CT-based measures of the tumor's rate of growth. Focus is on diagnoses in the practice-relevant sense of intervention-guiding, pre-surgical diagnosis.

For each of the diagnostic-prognostic categories, the broad aim is to determine their respective degrees of significance. This involves determining their associated case-fatality rates without and with intervention (in the absence of competing causes of death), together with the respective timings of fatal outcomes. Implied by these are the category-specific proportions of overdiagnosed cases, curability rates for progressive cases, and the time lags to deaths preventable by early intervention. With sufficiently detailed diagnostic-prognostic categories, these parameters presumably are general over various regimens of early diagnosis.

The category-specific, fundamental results under these two aims (frequency and significance) imply the overall case-fatality and curability rates associated with the regimen of early diagnosis, and also that specific to screen-detected cases (both of these for genuine, progressive cases of lung cancer). They also imply the timing of the deaths prevented by screening-associated early intervention.

An ancillary aim is to assess the frequency (prevalence) of cases diagnosable by the regimen, the way this depends on the risk indicators involved in the definition of indications for the screening (at baseline and subsequently).

**Editorial (TLP) comment:** Certainly, Henschke's approach to early lung cancer diagnosis has created a tremendous interest in the widespread application of low-dose radiation helical CT screening, which is particularly appropriate for high-risk populations. Her systematic approach is impressive in finding early lesions that are amenable to cure. However, a large risk of missing central lesions in high-risk patients is a concern. Sputum cytology followed by fluorescent bronchoscopy when high levels of dysplasia or carcinoma are found in expectorated

sputum, is complementary to imaging. Together, both airway cell markers and peripheral images can be the most effective diagnostic approach. Two prospective studies are currently underway in Grand Junction and Denver, Colorado, to learn the outcome and cost of screening high-risk patients, i.e., smokers at any age with 30 pack-years consumption, and with airflow obstruction, as judged by simple spirometry.

## Aberrant Methylation of Genes in the Pathogenesis of Lung Cancer.

Wistuba II, Zöchbauer-Müller S, Virmani AK, Toyooka S, Minna JD, Gazdar AF. Catholic University, Santiago, Chile; and Hamon Center for Therapeutic Oncology Research, UT; Southwestern Medical Center, Dallas, TX.

**A**berrant methylation of several known or putative tumor suppressor genes occurs frequently during the pathogenesis of lung cancers, including genes RASSF1A, RAR $\beta$ , FHIT, APC, CDH13, TIMP-3, P16<sup>INK4a</sup> and MGMT (19%). In lung cancer, methylation of genes has been associated with loss of gene expression, which is restored after treatment with the demethylating agent 5'-aza-2-deoxycytidine. Different aberrant methylation patterns have been demonstrated between SCLC (small-cell lung cancer) and NSCLC (non-small-cell lung cancer) tumor and cell lines specimens. Recently, geographic, smoking related and histologic (squamous cells vs. adenocarcinoma) differences in the methylation profiles of NSCLC have been identified. Methylation of RAR $\beta$ , CDH13, p16<sup>INK4a</sup> and RASSF1A genes can be detected in the respiratory epithelium of nearly 50% of heavy smokers with sputum atypia. In general, methylation occurs more frequently in samples from the central airways (sputum, bronchial bushes) compared to the peripheral airways (BAL [bronchoalveolar lavage] fluids), and only occasionally in the oropharynx. These findings suggest that detection of methylation should be investigated as an intermediate marker for lung cancer risk assessment and response to chemopreventive regimens.

**Editorial (TLP) comment:** This appears to be an attractive biomarker of different lung cancer histologic types. Also see the abstract by Palmisano WA, et al. in selected abstracts from the literature on page 13. ■

'For each of the diagnostic-prognostic categories, the broad aim is to determine their respective degrees of significance.'

'Sputum cytology followed by fluorescent bronchoscopy when high levels of dysplasia or carcinoma are found in expectorated sputum, is complementary to imaging.'

## Highlights of the International Association for the Study of Lung Cancer (IASLC) 3rd International Conference on Prevention and Early Detection of Lung Cancer.

August 8-12, 2001 Reykjavik, Iceland.

### The Possibility of Clinical Application of Malignancy Associated Changes (MAC) for Early Detection of Lung Cancer.

Ikeda N, Ohira T, Hirano T, Honda H, Yoshida K, Saito M, Konaka C, Kato H. Department of Surgery, Tokyo Medical University.

**O**bjectives: Lung cancer is the leading cause of cancer death in both sexes. The need exists for effective means for detection at its earliest stage. Malignancy associated changes (MAC) are subtle changes that could be measured in the nuclei of visually normal cells growing in the vicinity of malignant lesions. The authors postulated that the detection rate of cancer would improve by the existence of MAC unless cancer cells were proved.

**Methods:** A total of 106 sputum samples, 52 from lung cancer patients, 54 from non-cancer patients, was analyzed. After staining with DNA specific stain, cells were measured by high-resolution image cytometer (AcCell-Savant system, AccuMed, Chicago). 2,000 to 3,000 normal cells were measured per case and 120 nuclear features were analyzed per case. MAC cells were defined by the combination of several nuclear texture features and MAC expression in each case was calculated. Also this analysis was performed in buccal mucosa smears.

**Results:** This approach yields an increased sensitivity of sputum cytology (77% at a specificity of 70%) compared to conventional sputum cytology (sensitivity 19%). MAC expression in buccal mucosa of lung cancer patients were higher than that of non-cancer subjects.

**Conclusions:** The application of MAC was useful in improving detection rate of lung cancer at an earlier stage.

### Bronchoscope Treatment (BT) of Medically Inoperable Patients with Radiographically Occult Lung Cancer: A Follow-up Study.

Vonk-Noordegraaf A, Postmus PE, Sutedja TG. Department of Pulmonary Medicine, Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

**S**creening for lung cancer (early detection) will be futile if there is no treatment alternative for medically inoperable patients with radiographically occult lung cancer (ROLC). Thirty-two patients with ROLC (all microinvasive cancer, excluding carcinoma *in situ*) were offered BT with curative intent. BT was performed using electrocautery in 24 patients, argon plasma coagulation in two, Nd-YAG laser therapy in one and photodynamic therapy in five patients. Follow-up evaluation at 3 to 4 month interval[s] included high-resolution CT scans, both conventional and autofluorescence bronchoscopy and the sampling of biopsy specimens and brush cytology for histological evaluation.

The average follow-up period was 4.6 years (range: 1 to 9). In three patients local recurrence was again successfully treated with electrocautery. Sixteen patients died during follow-up, eight of them due to lung cancer (25%). Seven of these eight patients had a previous resection of a more advanced stage lung cancer. The remaining eight patients' cause of death was definitely unrelated to ROLC. Sixteen patients are still alive, without any tumor recurrence.

Current data show BT to have a  $\geq 75\%$  cure rate for medically inoperable patients with ROLC.

### Approaches to Population Based Screening.

Sone S, Shinshu University, Matsumoto, and Azumi General Hospital, Ikeda, Nigano, Japan.

**I**n order to significantly improve the prognosis of patients with lung cancer we should detect and treat the lung cancer in the early stages. Detection of tumors measuring 2 cm or less, which are less likely to be associated with lymph node metastasis, or possibly even tumors measuring 1.5 cm or less, which are very rarely associated with metastasis, should lead to improved therapeutic outcomes.<sup>1-5</sup> CT screening can detect many of these small lung cancers,

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'Screening for lung cancer (early detection) will be futile if there is no treatment alternative for medically inoperable patients with radiographically occult lung cancer (ROLC).'

'CT screening can detect many of these small lung cancers, unlike chest radiography, which can rarely identify such small cancers.'

unlike chest radiography, which can rarely identify such small cancers.<sup>6-9</sup>

This paper describes briefly the results of the use of CT scanning for annual lung cancer screening, including the characteristics of the patients and growth rates of lung cancers found in the screening, and discusses the age of subjects to be screened and an appropriate frequency of screening.<sup>10,11</sup>

We conducted a population based, low-dose CT screening for lung cancer during the 3-year period from 1996 to 1998, in Nagano Prefecture in Japan.<sup>5,7</sup> Among a total of 13,786 subjects, in the 40- to 74-year age group, we found 60 patients who had the lung cancer surgically confirmed, which was 0.44% of the total number of CT screening examinations and comprised 10% of the patients who had undergone further work-up examinations for suspicious lesions found in the CT screening. These results were

significantly different from the data, reported by the Japanese Research Committee of Studies on Evaluation of Effectiveness of Cancer Screening (Japanese publication, 1998), for lung cancer screening in the elderly health and insurance program (fiscal 1995), in which the total number of participants was approximately 6.7 million. The number of subjects requiring further work-up examinations was nearly 170,000 (2.5% of the total), and the number of lung cancers detected was 3,144 (0.05% of the total and 1.9% of those requiring further work-up). The detection rate for lung cancer in CT screening is approximately 9 times higher than that in the conventional standard method, by the use of chest radiographs (0.44/0.05), indicating excellent sensitivity. In other words, (if) the CT screening detected 9 lung cancers, 8 cancers would theoretically be missed by the standard mass screening. In our CT screening program,

**‘The detection rate for lung cancer in CT screening is approximately 9 times higher than that in the conventional standard method, by the use of chest radiographs...’**



**Figure 1**  
Example of a part-solid nodule in the left upper lobe detected by spiral CT. Following surgery, a histological diagnosis of a mucin-producing adenocarcinoma was established.  
(courtesy of S. Stone)

lung cancers were identified in 10% of those who required work-up examinations. This means that 9 of 10 were false-positives with regard to the presence of lung cancer. However, these false-positive cases were not free of disease. On the other hand, in the group requiring work-up examinations in the standard mass screening, 1.9% were reported to have lung cancer. In other words, of 100 subjects, 98 were false-positives and underwent work-up examinations. Therefore, CT screening showed far better specificity. In addition, there were significant differences in the details of the lung cancers detected. Many of the lung cancers detected by CT screening were small and were more likely to be curable (see Figure 1). Most of the tumors were 5 mm to 2 cm in diameter, and 53 (88%) were pathologically confirmed to be stage IA (Table 1).

Characteristics of patients with lung cancers detected by CT screening and the subjects to be screened: No lung cancers were detected in patients in their early 40's or younger. They were detected in patients over 45 years of age, and more tumors were seen in patients over 55 years of age. Benefits may be higher with CT screening being conducted in patients older than their 50's (Table 2).

Lung cancers were detected in 27 women, 33 men, 31 non-smokers, and 29 smokers. This means that lung cancers were identified in women and regardless of the subject's smoking history. It may not be appropriate to exclude non-smokers from screening. However, as described later, many of the lung cancers detected in non-smokers and women were well differentiated adenocarcinomas, which tend to progress slowly. (Initial screening revealed well differentiated

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**Table 1**

**Characteristics of lung cancers detected by low-dose CT screening**

Number of lung cancer patients	60
<b>Size</b>	
< 10 mm	21
11 to 15 mm	23
16 to 20 mm	13
21 to 47 mm	3
<b>Stage (pathological)</b>	
IA	53
IB	2
IIA	1
IIB	1
IIIA	1
IIIB	1
IV	1
<b>Histological diagnosis</b>	
<b>Total (non-smokers/smokers)</b>	
Adenocarcinoma (well-differentiated)	42 (28/14)
Adenocarcinoma (moderately to poorly differentiated)	9 (2/7)
Squamous cell carcinoma	6 (1/5)
Small cell carcinoma	3 (0/3)

**Table 2**

**Ages of 60 cases of lung cancer detected by low-dose CT screening**

Number of lung cancers	60
Average age (years)	65
<b>Age distribution</b>	
<b>Total (women/men)</b>	
40–44 years	0 (0/0)
45–49 years	4 (3/1)
50–54 years	2 (1/1)
55–59 years	7 (2/5)
60–64 years	14 (6/8)
65–69 years	17 (8/9)
70–74 years	16 (7/9)
<b>Subtotal</b>	60 (27/33)
<b>Smoking history</b>	
<b>Non-smokers/smokers (&gt;1 pack-year)</b>	
40–44 years	0/0
45–49 years	3/1
50–54 years	1/1
55–59 years	2/5
60–64 years	9/4
65–69 years	8/9
70–74 years	8/9
<b>Subtotal</b>	31/29

From: Sone S, Li F, Yang Z-G, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Ca 2001;84:29.

**'Most of the tumors were 5 mm to 2 cm in diameter, and 53 (88%) were pathologically confirmed to be stage IA.'**

**'No lung cancers were detected in patients in their early 40's or younger.'**

**Table 3**

**Summary of approximate tumor volume doubling time (TVDT) values (mean-1 SD) of lung cancers**

**1. Differences of TVDT's according to CT type**

1. Tumors containing mainly GGO (type 1): 800 days (mean-1 SD: 438 days, mean+1 SD: 1,188 days)
2. Tumors with peripheral GGO and a central higher density (type 2): 450 days (mean-1 SD: 197 days)
3. Tumors containing mainly soft tissue density (type 3), mean: 150 days (mean-1 SD: 24 days, but minimum TVDT based on actual calculation: 52 days)

**2. Differences between smokers and non-smokers**

1. Smokers:	300 days
2. Non-smokers:	600 days (mean-1 SD: 215 days)

**3. Differences according to histological type**

1. Adenocarcinomas	530 days
2. Squamous cell carcinomas	130 days
3. Small cell carcinomas	100 days

GGO=ground glass opacities

From: Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol* 2000;73:1255.

adenocarcinoma in many women and non-smokers. In annual repeat screening, poorly differentiated adenocarcinomas, squamous cell carcinomas, and small cell carcinomas were seen in a relatively larger proportion, mainly in men and smokers.) Therefore, such subjects are not thought to require annual repeat CT screening.

Growth rates of lung cancers detected by CT screening were investigated based on the tumor volume doubling time (TVDT).<sup>12</sup> TVDT of tumors containing mainly GGO ([ground glass opacities] type 1), tumors with peripheral GGO and a higher density central zone (type 2), and tumors containing mainly soft tissue density (type 3)<sup>13,14</sup> were appropriately 800 days, 450 days, and 150 days, respectively. The TVDT index for slower growth, seen in type 1 (GGO lung cancers), was approximately 3 years (mean + 1 SD: approximately 1,200 days = approximately 3 years). The minimum TVDT, seen in type 3 (lung cancers, containing mainly soft tissue opacity) was approximately 50 days. An interesting finding was that TVDT in smokers was approximately one half that in non-smokers indicating that lung cancers in smokers tend to grow more rapidly (Table 3).

Appropriate intervals for CT screening (number of examinations) should be determined to ensure precision and efficiency in CT screening.

Relevant items are listed in Table 3. A tumor measuring 3 mm or less is difficult to identify in low-dose CT images. On the other hand, a tumor measuring 15 mm or more is associated with an increased risk of hilar lymph node metastasis, and lung cancer surgery should ideally be performed before the tumor size exceeds 15 mm. The TVDT needs to be repeated 7 times before a 3-mm tumor grows to 15 mm. This fact should be considered in determining the appropriate screening intervals based on objective analysis. Annual repeat CT screening permits lung cancers measuring 20 mm or less to be detected in most cases. Lung cancers in smokers grow at a rapid rate (e.g., a TVDT of 50 days), and CT screening must be performed once a year to detect lung cancers measuring 15 mm or less (50 days x 7 = 350 days). However, annual screening is not sufficient for lung cancers that grow at even faster rates (e.g., a TVDT of 30 days). CT screening every 4 years is thought to be sufficient for lung cancers in non-smokers, which grow slowly, with an assumed TVDT of approximately 200 days (mean - 1 SD). However, to be on the safe side, screening every 3 years may be preferable. Such calculations will become more reliable when a larger number of subjects have been studied, which will hopefully lead to the establishment of

**‘Growth rates of lung cancers detected by CT screening were investigated based on the tumor volume doubling time (TVDT).’**

**‘An interesting finding was that TVDT in smokers was approximately one half that in non-smokers...’**

practical guidelines for economical and effective CT screening.

Other questions that arise regarding the application of CT to lung cancer screening are related to radiation exposure to the participant and costs. These issues have already been addressed by the advocates of CT screening in Japan (Japanese publication, 1992). The benefits of the detection of early lung cancers by low-dose CT screening as commonly practiced in Japan are expected to be higher than the risk of radiation exposure in a population with a lung cancer incidence rate of 10/100,000 per year. These benefits were thought to be definitely higher in a population with a rate of 50 to 100 or more per 100,000 per year. In addition, the actual data obtained from CT screening performed later demonstrated benefits beyond those anticipated, with greater benefits in patients older than their 40's and significantly greater benefit in patients older than their 50's. Costs have also been investigated.<sup>11</sup> Based on the data obtained from our CT screening program, the actual cost per subject has been calculated to be approximately 5,000 yen (\$50 U.S.), and this figure can be expected to fall with the further penetration of CT screening, leading to reduced system prices and improved processing capabilities.

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**'Appropriate intervals for CT screening (number of examinations) should be determined to ensure precision and efficiency in CT screening.'**

**'Other questions that arise regarding the application of CT to lung cancer screening are related to radiation exposure to the participant and costs.'**

**'Based on the data obtained from our CT screening program, the actual cost per subject has been calculated to be approximately 5,000 yen (\$50 U.S.)...'**

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## PET Scan Can Detect Radiologically ‘Occult’ Lung Cancer in the Central Airways.

Herder G, Breuer R, Comans E, Risse E, van Mourik J, Postmus PE, Sutedja TG. Department of Pulmonology, Nuclear Medicine and Clinical PET Centre, Pathology, Surgery, Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

**A**s patients with lung cancer have a dismal prognosis, there is an increasing interest in the medical community to screen the population at risk, in order to diagnose, localize and treat lung cancer at the earliest possible moment. Sputum cytology screening and radiological screening may detect patients with

early stage lung cancer and this issue has become a heated debate lately. For patients with early stage squamous cell cancer in the central airways, however, low-dose spiral CT is relatively insensitive for detecting these tumours. There is an increasing role for bronchoscopic detection using autofluorescence bronchoscopy and bronchoscopic treatment, because these lesions are small and superficial at an early stage. We have used positron emission tomography (PET) using the glucose analogue <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>FDG) with the intention to exclude nodal metastasis as part of the tumour staging procedure. PET proved to be quite sensitive to detect occult cancers in the central airways, including carcinoma *in situ*, of  $\geq 2$  mm size (Table 4).

‘For patients with early stage squamous cell cancer in the central airways, however, low-dose spiral CT is relatively insensitive for detecting these tumours.’

**Table 4**

**Six patients with seven radiologically occult lung cancers, additionally staged by autofluorescence bronchoscopy and positron emission tomography (PET)**

Lesion	Location	Diagnosis	AFB, T-size	PET Scan:	Follow-up, T-size, if resected
1*	RB6	CIS	Polypose 2 mm	+	Progression to SCC within 3 months, locally treated with PDT and later on, external irradiation
2*	LMB	Superficial spreading type SCC	AFB: DM?	+	Pneumectomy (left) T=Three microinvasive fields: 0.18, 0.19, and 0.36 mm N0
3	RUL	SCC	AFB: DM?	+	Lobectomy RUL, T=3 mm N0
4	LUL	SCC	AFB: DM?	-	Lobectomy LUL, T=5 mm N0
5	Carina ML	SCC	Granular T 2-3 mm	+	IBT, curative
6	Distal BI RB6	CIS	Flat superficial 5 mm	+	IBT, curative
7	LMB	SCC	AFB: DM?	+	Lobectomy:15 mm N0

**Abbreviations:**

\* =synchronous cancer in the same patient; RB6=right superior basal segment; LMB=left main bronchus; LUL=left upper lobe; RUL=right upper lobe; ML=middle lobe; BI=bronchus intermedius; CIS=carcinoma *in situ*; SCC =microinvasive squamous cell cancer; AFB=autofluorescence bronchoscopy; DM?=distal tumour margin invisible on AFB; T-size=tumour size; PDT=photodynamic therapy; IBT=intraluminal bronchoscopic therapy with curative intent.

## Clinical Usefulness of hnRNP B1 Protein for Detection of Early Lung Cancer

Sueoka E, Sueoka N, Suganuma M, Fujiki H. Saga Medical School, Nabeshima, Japan and Saitama Cancer Center, Ina, Kitaadachi-gun, Saitama, Japan.

To improve detection of early lung cancer, the molecular targets of lung cancer need to be intensively studied. In this sense, Drs. Tockman's and Mulshine's finding that overexpression of hnRNP A2/B1 is a good biomarker for early detection of lung cancer, is exciting.

To increase the specificity of hnRNP A2/B1, we raised anti-hnRNP B1 antibody, which was produced in rabbits using 19-mer synthetic peptide (amino acid residues 3-20+cysteine) for hnRNP B1. We found that hnRNP B1 showed stronger specificity in human lung cancer than hnRNP A2/B1 does, as follows:

1) hnRNP B1 protein is an onco-developmental protein in human lung, but not in other organs; 2) overexpression of hnRNP B1 protein was observed in stage I lung cancer tissues (100%) and adenocarcinoma tissues (70.8%); and 3) anti-hnRNP B1 antibody stained roentgenographic occult lung cancer (58.1%) and bronchial dysplasia (63.6%). All the results indicated that the positivity of lung lesions with anti-hnRNP B1 antibody is an accurate predictor of malignant progression.

Study at the molecular level is now needed in order to determine how hnRNP B1 protein is involved in the carcinogenesis of lung cancer. Since overexpression of hnRNP B1 protein was also found in squamous cell carcinoma of oral and esophageal tissues, including oral leukoplakia, the molecular function of hnRNP B1 in the lung is probably generalized in squamous cell carcinomas.

Since hnRNP B1 protein is one of the largest complexes of the hnRNP protein family, its clinical usefulness demands further discussion.

## Lung Cancer Incidence and Selenium Supplementation. An Update of a Clinical Trial.

Reid ME, Duffield-Lillico A, Garland L, Turnbull B, Clark LC, Marshall JR. Arizona Cancer Center and Arizona College of Public Health, University of Arizona, Tucson, AZ; and School of Operations Research, Cornell University, Ithaca, NY.

Interest in the chemopreventive effects of the trace element selenium has spanned the past three decades. Of more than 100 studies that have investigated the effects of selenium in carcinogen-exposed animals, two-thirds have observed a reduction in tumor incidence and/or preneoplastic endpoints. The Nutritional Prevention of Cancer Trial (NPC) reported by Clark et al. (Clark, 1996) a randomized clinical trial showed as a secondary endpoint, a statistically significant decrease in lung cancer incidence with selenium supplementation. The unadjusted relative risk (RR) of 0.54; 95% CI=0.30, 0.96,  $p=0.04$  and the adjusted Cox Proportional Hazards Ratio (HR) of 0.56; 95% CI=0.31, 1.01,  $p=0.05$ . These results for selenium supplementation were based on active follow-up of 1,312 participants through December 31, 1993.

This re-analysis is based on an extended NPC participant follow-up through the end of the blinded clinical trial on February 1, 1996. The addition of 3 years of follow-up added 8 cases to the selenium treated group and 4 cases to the placebo group. The RR of .70 (95% CI=.40, 1.21,  $p=.18$ ), is not statistically significant. The HR, which was adjusted for age and smoking status, is also now non-significant (HR of .74; 95% CI=.44, 1.24;  $p=.26$ ), but was in the same direction as the original analysis.

Adenocarcinoma ( $n=14$ ), squamous cell ( $n=22$ ) and small cell carcinoma ( $n=11$ ) were the most common histologies and were equally distributed between treatment groups. There is a statistically significant inverse association between selenium supplementation and lung cancer incidence among subjects with baseline plasma selenium in the lowest tertile (HR of .42; 95% CI=.18, .96;  $p=.04$ ). The models for the middle and highest tertiles of baseline showed HR's of .91 and 1.25. The current re-analysis, the most definitive with data up to unblinding, indicates that selenium supplementation significantly decreases lung cancer incidence only among individuals with low baseline selenium levels. ■

'To improve detection of early lung cancer, the molecular targets of lung cancer need to be intensively studied.'

'Interest in the chemopreventive effects of the trace element selenium has spanned the past three decades.'

Selected Abstracts From  
Peer-reviewed Literature:

**Predicting Lung Cancer by  
Detecting Aberrant Promoter  
Methylation in Sputum.**

Palmisano WA, Divine KK, Saccomanno G, Gilliland FD, Baylin SB, Herman JG, Belinsky SA. Lovelace Respiratory Research Institute, Lung Cancer Program, Albuquerque, NM; St. Mary's Hospital, Grand Junction, CO; Department of Preventive Medicine, Division of Occupational and Environmental Health, University of Southern California, Los Angeles, CA; and Johns Hopkins University Medical Institutions, the Johns Hopkins Comprehensive Cancer Center, Baltimore, MD. *Cancer Res* 2000;60:5954-5958.

**Abstract:** Despite the promise of using DNA markers for the early detection of cancer, none has proven universally applicable to the most common and lethal forms of human malignancy. Lung carcinoma, the leading cause of tumor-related death, is a key example of a cancer for which mortality could be greatly reduced through the development of sensitive molecular markers detectable at the earliest stages of disease. By increasing the sensitivity of a PCR approach to detect methylated DNA sequences, we now demonstrate that aberrant methylation of the *p16* and/or *O*<sup>6</sup>-methylguanine-DNA methyltransferase promoters can be detected in DNA from sputum in 100% of patients with squamous cell lung carcinoma up to 3 years before clinical diagnosis. Moreover, the prevalence of these markers in sputum from cancer-free, high-risk subjects approximates the lifetime risk for lung cancer. The use of aberrant gene methylation as a molecular marker system seems to offer a potentially powerful approach to population-based screening for the detection of lung cancer, and possibly the other common forms of human cancer.

'Despite the promise of using DNA markers for the early detection of cancer, none has proven universally applicable...'

'RT-PCR-based amplification of transcripts expressed in cancer but not in normal non-neoplastic cells is increasingly used...'

**Sensitive Detection of Rare  
Cancer Cells in Sputum and  
Peripheral Blood Samples of  
Patients with Lung Cancer by  
PreproGRP-specific RT-PCR.**

Lacroix J, Becker HD, Woerner SM, Rittgen W, Drings P, von Knebel Doeberitz M. Division of Molecular Diagnostics and Therapy, Department of Surgery, University of Heidelberg; Thoraxklinik der LVA Baden; and Biostatistics Unit, German Cancer Research Center, Heidelberg, Germany. *Intl J Cancer* 2001;92:1-8.

**Abstract:** RT-PCR-based amplification of transcripts expressed in cancer but not in normal non-neoplastic cells is increasingly used for the sensitive detection of rare disseminated or exfoliated cancer cells to improve cancer staging and early detection protocols. However, these assays are frequently hampered by false-positive test results due to low-level transcription of the marker genes in normal cells. To overcome these limitations, target transcripts have to be identified that are tightly suppressed in normal non-neoplastic tissues, whereas they should be actively transcribed in the respective cancer cells. Here, we tested RT-PCR assays for 7 neuroendocrine marker transcripts including NCAM, PGP 9.5, gastrin, gastrin receptor, synaptophysin, preprogastrin-releasing peptide (preproGRP) and GRP-receptor to detect rare exfoliated tumor cells in peripheral venous blood and sputum samples from patients with lung cancer. Among these preproGRP, RT-PCR was the only assay with which illegitimate transcription in blood or sputum samples from healthy donors or patients with unrelated disease did not interfere. However, it reproducibly detected up to 10 small-cell lung cancer cells diluted in either 10 ml blood or 5 ml sputum samples. Single blood and sputum samples were collected directly before diagnostic bronchoscopy from 175 patients suspected to have lung cancer. Twenty-six of these had small-cell lung cancer (SCLC). Thereof, 13 patients (50%) tested positive in the blood sample and 5 of 23 patients (22%) tested positive in the sputum sample. Moreover, among 92 patients with non-small-cell lung cancer (NSCLC) 25 patients (27%) had disseminated cancer cells in peripheral blood. Amplification of preproGRP transcripts from clinical samples is a sensitive and specific assay to detect disseminated or exfoliated lung cancer cells either in peripheral blood or sputum samples.

'In sputum cytology suspicious or positive for malignancy, the diagnosis of preinvasive bronchial lesions was greatly enhanced in the LIFE group...'

'Overall 5-year survival after the first resection was 70% and after the second resection was 26%.'

## Fluorescence Bronchoscopy in the Detection of Preinvasive Bronchial Lesions in Patients With Sputum Cytology Suspicious or Positive for Malignancy.

Shibuya K, Fujisawa T, Hoshino H, Baba M, Saitoh Y, Iizasa T, et al. Department of Surgery, Institute of Pulmonary Care Research, and Department of Pathology, Institute of Pulmonary Cancer Research, Chiba University School of Medicine, Inohana, Chuo-ku, Chiba, Japan. *Lung Cancer* 2001;32:19-25.

### Abstract:

**Background:** A new strategy in the treatment of squamous cell carcinoma of the tracheobronchial tree is the detection and eradication of preinvasive bronchial lesions before they become invasive cancers. It is, however, difficult to detect preinvasive lesions by conventional white-light bronchoscopy alone.

**Purpose:** We conducted a detailed investigation on the use of fluorescence bronchoscopy in the detection of preinvasive bronchial lesions in patients with sputum cytology suspicious or positive for malignancy.

**Methods:** 64 participants with sputum cytology suspicious or positive for malignancy were examined with both white-light and fluorescence bronchoscopy (LIFE group). Earlier to this study, before fluorescence bronchoscopy became available in our institute, 48 participants having sputum cytology suspicious or positive for malignancy were examined with white-light bronchoscopy alone (control group). Biopsy specimens for pathological examinations were taken of all abnormal areas discovered by white-light or fluorescence bronchoscopy examination.

**Results:** In sputum cytology suspicious or positive for malignancy, the diagnosis of preinvasive bronchial lesions was greatly enhanced in the LIFE group as compared with the control group (45 vs. 7 lesions). The percentage of participants with preinvasive bronchial lesions was also significantly higher in the LIFE group than in the control group (40.6 vs. 12.5%,  $P=0.00087$ , respectively).

**Conclusions:** Our study suggests that the use of fluorescence bronchoscopy in addition to conventional white-light examination could greatly enhance the detection and localization of preinvasive bronchial lesions in patients with sputum cytology suspicious or positive for malignancy.

## Survival After Resection of Metachronous Non-small Cell Lung Cancer in 127 Patients.

van Rens, MTM, Zanen P, de la Rivière AB, Elbers HRJ, van Swieten HA van den Bosch JMM. Departments of Pulmonary Diseases, Pathology, and Thoracic Surgery, Sint Antonius Hospital, Nieuwegein, and Department of Thoracic Surgery, University Medical Center, Utrecht, The Netherlands. *Ann Thorac Surg* 2001;71:309-313.

**Background:** In a number of patients with treated primary non-small cell lung cancer (NSCLC) a second primary tumor will be diagnosed. Our experience with surgery in these patients was analyzed and possible prognostic parameters were defined.

**Methods:** Patients with metachronous NSCLC ( $n=127$ ) who underwent resection from 1970 through 1997 were analyzed. All tumors were classified postsurgically. Median interval between the tumors was 3.7 years. Actuarial survival time was estimated and risk factors influencing survival were evaluated.

**Results:** Overall 5-year survival after the first resection was 70% and after the second resection was 26%. Patients with stage IA of the second primary tumor did have a significantly better survival ( $p<0.005$ ) as compared with patients with higher staged second primaries. Stage of second primary tumor and age were significant predictors of survival, whereas stage of first tumor, interval between resections, histology, and type of resection were not.

**Conclusions:** Survival of patients with metachronous NSCLC and resection of both tumors is high, but poorer than after resection of the first tumor. Irrespective of the interval, patients with stage IA second primary tumor may benefit more from pulmonary resection.

## The Influence of Hospital Volume on Survival After Resection for Lung Cancer.

Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. Health Outcomes Research Group, the Departments of Epidemiology and Biostatistics, Medicine, and Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY. *N Engl J Med* 2001;345:181-188.

### Abstract

**Background:** Among patients who have undergone high-risk operations for cancer, postoperative mortality rates are often lower at hospitals where more of those procedures are performed. We undertook a population-based study to estimate the extent to which the number of procedures performed at a hospital (hospital volume) is associated with survival after resection for lung cancer.

**Methods:** We studied patients 65 years old or older who received a diagnosis of stage I, II, or IIIA non-small-cell lung cancer between 1985 and 1996, resided in 1 of the 10 study areas covered by the Surveillance, Epidemiology, and End Results Program, and underwent surgery at a hospital that participates in the Nationwide Inpatient Sample (2,118 patients and 76 hospitals).

**Results:** The volume of procedures at the hospital was positively associated with the survival of patients ( $P < 0.001$ ). Five years after surgery, 44 percent of patients who underwent operations at the hospitals with the highest volume were alive, as compared with 33% of those who underwent operations at the hospitals with the lowest volume. Patients at the highest-volume hospitals also had lower rates of postoperative complications (20% vs. 44%) and lower 30-day mortality (3% vs. 6%) than those at the lowest-volume hospitals.

**Conclusions:** Patients who undergo resection for lung cancer at hospitals that perform large numbers of such procedures are likely to survive longer than patients who have such surgery at hospitals with a low volume of lung-resection procedures.

‘The volume of procedures at the hospital was positively associated with the survival of patients.’

## Lung Cancer in Patients Under 50 Years Old

Radzikowska E, Roszkowski K, Glaz P. III Department of Tuberculosis and Lung Diseases, National Tuberculosis and Chest Disease Research Institute, Warsaw 01-138, Plocka 26 Street, Poland. *Lung Cancer* 2001;33:203-211.

### Abstract:

**Purpose:** The community based lung cancer registry was set up and the results were analysed to assess the differences in clinicopathological parameters and survival between patients under and over 50 years of age.

**Patients and Methods:** The Pulmonary Outpatient Clinics supplied the data on 5404 lung cancer patients diagnosed in Poland in 1995. Data regarding demographic, smoking, histology, clinical stage, performance status, family history of cancer, therapy and survival were obtained.

**Results:** At time of diagnosis 757 (14%) patients were under 50 years of age. In this group the frequency of females was higher as compared to this in the group of older patients (24.2% vs. 12.1%;  $P < 0.001$ ). Also the incidence of adenocarcinoma (12.6% vs. 7.6%;  $P < 0.001$ ) and small cell cancer (22.9% vs. 14.8%;  $P < 0.001$ ) were significantly higher in younger patients. Young patients had better performance status (55.4% vs. 46.6%;  $P < 0.001$ ) than old. The incidence of cancer in families of younger patients was higher both among the mothers (4.7% vs. 3.0%;  $P < 0.001$ ) and among the fathers (7.6% vs. 4.1%;  $P < 0.001$ ). Surgery or chemotherapy were more often applied to patients under 50 years in comparison to older ones ( $P < 0.001$ ). Young patients had better prognosis. Higher percentage of them survived one year (32.6% vs. 28.9%;  $P < 0.049$ ). In multivariate analysis, age over 50 at diagnosis, male gender, diagnosis of small cell lung cancer, advanced stage of the disease, bad performance status, and non-surgical therapy were independent negative prognostic factors.

**Conclusion:** Among young patients, over-representation of women, subjects with positive family history of cancer, with better performance status, with adenocarcinoma and small cell lung cancer were noticed. Young patients were treated more aggressively and had better prognosis than patients over 50 years of age.

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Lung Cancer

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