Special Support for Lung Cancer Frontiers Volume 18

The Editorial Board deeply appreciates the generous support of the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida, which provides the support for Lung Cancer Frontiers No. 18. 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 three-year grant awarded to the editor specially supports the expansion of the early identification and treatment initiatives, including the Grand Junction project (cited below) and other community projects under development.

In addition, 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. In the future, we will likely put greater reliance upon electronic publishing for the worldwide communication and messages.


Lung Cancer Frontiers No. 17 carried several highlights of the 10th International Conference on Lung Cancer, sponsored by the International Association for the Study of Lung Cancer (IASLC). Additional highlights follow:

Comments on the Endobronchial Diagnosis and Treatment (10th IASLC Conference on Lung Cancer, Vancouver BC, August 2003)
By T. G. Sutedja, M.D.

The awareness that early detection and treatment is necessary to improve the dismal survival rate of lung cancer patients has created a high interest in the minimally invasive techniques. Minimally invasive techniques, such as the use of many bronchoscopic techniques is critical when dealing with individuals who have limited pulmonary function or are medically inoperable due to age, comorbidity, or tumor location (e.g., carina).

Bronchoscopic procedures use miniaturized biopsy forceps and probes of ≈2 mm cross section which can be passed
through the suction channel of the fiberoptic bronchoscope. Lesions outside the visibility spectrum of the bronchoscope are not appropriate for this technique, such as the assessment of tumor invasion into the airway wall and cancer location or extension in the distal segmental bronchi or peripheral parenchyma. Therefore, from the bronchoscopists’ point of view, there are two challenges for early intervention: sub-millimeters central airway lesions in the tracheobronchial tree at the clonal stage of carcinogenesis such as in the dysplasias, and sub-centimeter lesions in the lung parenchyma distal to the segmental bronchi that are beyond reach of the fiberoptic bronchoscope which currently become increasingly visualized by spiral-CT detection.

The ultimate proof of malignancy remains based on the gold standard of microscopic
classification of biopsy specimens, but many diagnostic procedures for collecting representative specimens are invasive and traumatic. This creates the drive to further refine established and emerging minimally invasive techniques for early and accurate staging.

The recognition that accurate staging rather than treatment technique per se, will be the key for the justification of local treatment in the absence of nodal and distant disease, be it “limited” surgery (wedge resection without lymph node dissection in small parenchymal lesions with <50% ground glass opacity (ggo) on spiral CT as so far they have been proven to be Noguchi A/B type adenocarcinoma N0 and surgical bronchoplasty for centrally early stage squamous cancer) or “less invasive therapeutic alternatives” (conformal stereotactic radiotherapy, radiofrequency ablation, transthoracic photodynamic therapy (PDT)). All efforts are aimed to preserve lung function quality in applying the most optimal strategy for each individual patient.

This imperative has been the stimulus to develop non-invasive, sensitive early detection tools on size, growth, metabolic and bio-molecular characteristics (spiral CT, PET scan, sputum cytology, sputum cytometry, polymerase chain reaction (PCR) and immunohistochemical (IHC) stains based early detection tools). Despite the huge numbers of individuals at risk, the prevalence of lung cancer in a general population is “relatively” low. Thus, test of high sensitivity but low specificity is currently the hallmark of present day screening tools. These limitations will lead to the necessity for repeat and additional tests to ultimately prove or exclude the presence of early cancer.
Because of this, one should consider whether the use of or addition of minimally invasive procedures, rather than repetitive non-invasive approaches alone, may be more cost effective. The initial screening step — provided it is highly specific — may help reduce the enormous burden of too many false positives including the emotional burden of prolonged insecurity by the patient until the ultimate diagnosis of cancer is made or can be ruled out.

The serial use of spiral CT and PET scan (Pastorino U et al. Lancet 2003; 362:593-7) is an example of this. Although serial use of highly sensitive tests may significantly reduce the need for a more frequent repeat CTs, futile invasive treatment interventions due to false positives cannot be prevented.

For bronchoscopists, an accurate minimally invasive test should be done with the assistance of precise navigational tool for collection of representative materials.

Autofluorescence bronchoscopy (AFB) has an established role in central airway lesions, both for studying squamous cell carcinogenesis and finding early, and stage (pre-) neoplastic lesions. A multicenter study using the D-Light system (Storz“) for AFB performed in six academic centers (Beamis et al: Lung Cancer 2003;41:abstract S49) has confirmed the increased detection rate of suspicious early stage lesions in a prospective non-randomized clinical study if compared with white light (WL) bronchoscopy alone. Three hundred patients have been enrolled and 901 biopsy specimens collected. Higher relative sensitivity of 61.2% (vs. to WL 10.6%) was found at the cost of lower specificity 75.3% (vs. WL 94.6%).

To further improve the bronchoscope imaging system especially in studying squamous dysplasia - with the aim to reduce false positive detection rate of non-malignant mucosal lesions by AFB described or improved their broncho-videoscope system (Shibuya et al: Lung Cancer 2003;41: abstract S158) with the initial report in Thorax 2003; 58: 989-95. This refinement offered a more detailed examination of the micro-vascular network of angiogenic squamous dysplasia (ASD), a lesion believed to represent a pre-malignant lesion among
the many dysplasias found in the bronchial mucosa of the individuals at risk. (Keith RL et al. Clin Cancer Res 2000; 6: 1616-25). Therefore, it seems now feasible to visualize the vascular networks of different dysplastic lesions in the central airway mucosa which may match the corresponding microscopic method for studying squamous cell carcinogenesis. This is an example of further refinement towards optical biopsy techniques, i.e. micro-dynamic imaging without taking any biopsy, to understand early carcinogenesis without the necessity for removing the clonal cells’ groups involved. It has been shown that complete removal of the target tissue at the initial examination may occur.

Near infrared Raman spectroscopy for optical diagnosis based on vibrational energy of molecules in the target cells is another method being explored (Huang Z et al: Lung Cancer 2003;41:S550). Due to Raman spectral differences between normal cells and malignant cells related to the protein and lipid contents in nucleic acids, the prospect of optical biopsy is becoming closer.

The big hurdle of accurately localizing small parenchymal lesions (beyond the fiberoptic bronchoscope’s reach and the visibility range of the bronchoscopist) has to be pursued.

Dr. H. Becker (Heidelberg, Germany) presented preliminary data in using the super Dimension electromagnetic navigation system, in performing catheter based localisation of small peripheral parenchymal lesions detected by spiral CT programs. Accuracy is currently at the 80% level rate for lesions up to 4 cm in size (personal communication, see also Schwarz Y et al. Electromagnetic navigation during flexible bronchoscopy, Respiration 2003; 70:516-22). This is a technique using generated low frequency electromagnetic waves based on the previously acquired 3D CT images, being an alternative approach for the virtual bronchoscopy method (see also Finkelstein et al. Chest 2003;124:1834).

Bronchoscopists can now explore the feasibility to increase cost-effectiveness of early intervention for peripheral parenchymal lesion, in order to provide the ultimate answer as soon as possible, whether lesions are early cancer or benign. This may prove to be the alternative for repeat tests that generate enormous emotional burdens and costs.

However, more data is needed. The problems of accurate localisation and approaching early parenchymal (sometimes multiple) lesions of ≈ 5 mm will have to be accomplished within the average time of any fiberoptic bronchoscopy session of 20-30 minutes, including sampling. This is not an easy task, as it is known that especially the 4D effect due to respiratory movements and cardiac beats may lead to tumor hysteresis up to 2.5 cm, largely in the ventral-dorsal and cranio-caudal directions (Seppenwoolde et al. Int J Radiation Oncology Biol Phys 2002; 53: 822). This is a problem of accurate targeting both in term of detection, localisation and treatment.

Perhaps the additional use of endobronchial ultrasound (EBUS) using the radial type transducer may ease the navigational approach (Herth FJ et al. Respiration 2003; 70:87-94). The additional use of bronchoscopic techniques in the total approach of a lung cancer screening setting will be certainly very cost-effective, as the estimation of incremental costs of spiral CT screening is staggering; being US$ 116,300 per QALY gained and up to US$ 2,322,700 for former smokers (Mahadevia PJ et al. JAMA 2003; 289:313). The reimbursement for one bronchoscopy session in the Netherlands being ≈ 80.00 is very favorable compared to CT scan. This justifies further research of bronchoscopic navigation in early detection, localisation and treatment of central and peripheral lung lesions.
New Practice Based Pragmatic Approach to Early Lung Cancer Diagnosis
Grand Junction, Colorado.

The confluence of the Colorado and the Gunnison Rivers near the Utah border, has been the sight for interesting studies in asymptomatic and roentgenographically occult lung cancer for more than a decade. St. Mary’s Hospital, the venue for the landmark work of the late Geno Saccomanno who perfected and popularized the present cytological techniques that are used worldwide, though most commonly in Japan and Canada, but with increasing frequency in the United States. Previous studies from Grand Junction have shown that roentgenographically occult lung cancer, when diagnosed by sputum cytology and treated either surgically or with radiation when early stage disease is found shows a survival rate of greater than 50% beyond five years (Bechtel JJ et al. Ann Intern Med 1994; 154:975–80; Bechtel JJ et al. Lung Cancer 2000; 30:17).

This community just completed another landmark study wherein all primary care physicians of the community were persuaded to provide a simple one-page questionnaire to patients over the age of 50 to determine subjects at high risk. In the calendar year 2000–2001, physicians in the rural town of a population of 40,000 but with a drawing area of 250,000 had 5236 patient visits. High risk questionnaires were completed in 1296 adults with the criteria of high risk, i.e., a family history of cancer of the aerodigestive tract, smoking of 30 pack years or more, exposure to asbestos and coal dust. Four hundred and thirty completed questionnaires indicated high risk. Of these 430 patients, all of whom received spirometry, 126 had an airflow abnormality. Eighty-eight of these agreed to have sputum cytology and CT scanning. Amongst those with airflow obstruction, a total of eight cancers were found. Details of this report were submitted to a peer-reviewed publication and have been previously described in abstract form in Lung Cancer Frontiers Volume 16. Follow-up of all 430 patients, both with and without airflow obstruction, is planned for a total of five years. This study will shed additional light upon the value of spirometry and the one-page questionnaire (Table 1, opposite) offers a pragmatic approach in the very highest risk patients. The study will allow analysis of the cost of diagnosing and treating lung cancer and its ultimate outcome.
Table 1

Saccomanno Research Institute pilot project in community screening questionnaire.

LUNG HEALTH SCREENING SURVEY

1) Name_________________________ Date_____________ Age*_______

Telephone Number: ________________________

Type of insurance: Rocky Mountain HMO Other No insurance coverage

2) Please circle the answer that best describes your smoking habits:

I have never smoked I currently smoke* I smoked in the past, but no longer smoke*

Packs per day:_______ Year or age started:_______ Year or age stopped:________

3) Please circle the answers that apply to you:

I currently work or have previously worked in one or more of these occupations:

Underground Mining Construction Railroad

I have had significant industrial and/or occupational exposure to the following substances:

Asbestos Silica Dust Coal Dust

4) Please circle the answer that best describes who in your family has been diagnosed with cancer of the lung and/or larynx:

No One Self Parent Brother or Sister Children

I would like to get more information about this important project: No Yes*

Thank you. Please stop here. Your doctor will complete the remainder of the information.

8) FEV₁ Actual / Predicted % of Predicted FVC Actual / Predicted % of Predicted FEV₁/FVC Ratio Actual / Predicted % of Predicted

Date & Initials Notes:

Chest x-ray ordered by physician during this office visit? No Yes
Abstracts and Other Material from the Peer Reviewed Literature

Lung cancer: the importance of seeing a respiratory physician.

Fergusson RJ, Thomson CS, Brewster DH, Brown PH, Milroy R; Scottish Cancer Trials Lung Group; Scottish Cancer Therapy Network. Western General Hospital, Lothian University Hospitals NHS Trust, Edinburgh, UK. ron.fergusson@luht.scot.nhs.uk Eur Respir J 2003;21:565-566

Patients with lung cancer present to and are managed by a variety of clinicians. In this study the effect of involvement by a respiratory physician on the diagnosis, staging, treatment and survival of a large unselected group of lung cancer patients was investigated. The study population was derived from the Scottish Cancer Registry.

A total of 3,855 patients diagnosed during 1995 with lung cancer were studied. The data were validated and supplemented by references to medical records. The study found that a respiratory physician had been involved in the initial management of 2,901 (75.3%) patients. These patients were found more likely to have had the cancer diagnosis confirmed by histological methods and to have received active treatment with surgery, radiotherapy or chemotherapy. Survival, 1 yr after diagnosis was higher in patients who saw a respiratory physician (24.4 versus 11.1%) and benefit was found to have remained 3 yrs after diagnosis (8.1 versus 3.7%). Although the patients who had not seen a respiratory physician were generally older, and had more extensive disease, after correcting for age, stage and other prognostic factors, the relative hazard ratio of death for those not managed by a respiratory physician was 1.44. The data from this study supports the recommendations of recent lung cancer guidelines for the early involvement by a respiratory physician.

Editorial Comment (TLP): Specialists are more likely to be aware of new diagnostic and treatment approaches to lung cancer than non-specialists. Today there is a departure from the nihilism about lung cancer which has been well ingrained in the minds of specialists and generalists alike.

Variations in lung cancer risk among smokers.

Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, Hsieh LJ, Begg CB. The Health Outcomes Research Group, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. bachp@mskcc.org J Natl Cancer Inst. 2003;95:470-478

Background: Although there is no proven benefit associated with screening for lung cancer, screening programs are attracting many individuals who perceive themselves to be at high risk due to smoking. We sought to determine whether the risk of lung cancer varies predictably among smokers.

Methods: We used data on 18,172 subjects enrolled in the Carotene and Retinol Efficacy Trial (CARET)—a large, randomized trial of lung cancer prevention—to derive a lung cancer risk prediction model. Model inputs included the subject’s age, sex, asbestos exposure history, and smoking history. We assessed the model’s calibration by comparing predicted and observed rates of lung cancer across risk deciles and validated it by assessing the extent to which a model
Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis.

Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, Chan JK, Owens DK. Pulmonary Section (111P), Veterans Affairs Palo Alto Health Care System, Palo Alto, California 94304, USA. gould@stanford.edu
Ann Intern Med 2003;139:879-892

Purpose: To compare the diagnostic accuracy of computed tomography (CT) and positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) for mediastinal staging in patients with non-small-cell lung cancer and to determine whether test results are conditionally dependent (the sensitivity and specificity of FDG-PET depend on the presence or absence of enlarged mediastinal lymph nodes on CT).

Data Sources: Computerized search of MEDLINE, EMBASE, BIOSIS, and Cancer Lit through March 2003 and reference lists of retrieved studies and review articles.

Study Selection: Studies in any language that examined FDG-PET for mediastinal staging in patients with known or suspected non-small-cell lung cancer, enrolled at least 10 participants (including at least 5 participants with mediastinal metastasis), and provided enough data to permit calculation of sensitivity and specificity for identifying lymph node involvement.

Data Extraction: One reviewer (of non-English-language studies) or 2 reviewers (of English-language studies) independently evaluated studies for inclusion, rated methodologic quality, and abstracted relevant data.

Data Synthesis: Thirty-nine studies met estimated on data from five CARET study sites could predict events in the sixth study site. We then applied the model to evaluate the risk of lung cancer among smokers enrolled in a study of lung cancer screening with computed tomography (CT).

Results: The model was internally valid and well calibrated. Ten-year lung cancer risk varied greatly among participants in the CT study, from 15% for a 68-year-old man who has smoked two packs per day for 50 years and continues to smoke, to 0.8% for a 51-year-old woman who smoked one pack per day for 28 years before quitting 9 years earlier. Even among the subset of CT study participants who would be eligible for a clinical trial of cancer prevention, risk varied greatly.

Conclusions: The risk of lung cancer varies widely among smokers. Accurate risk prediction may help individuals who are contemplating voluntary screening to balance the potential benefits and risks. Risk prediction may also be useful for researchers designing clinical trials of lung cancer prevention.

Editorial Comment (TLP): Lung cancer screening for high risk patients makes good sense. See Grand Junction studies reported herein and in the previous issue of Lung Cancer Frontiers (Volume 17).

Previous and Current issues of Lung Cancer Frontiers are available on line at
www.lungcancerfrontiers.org

“The model was internally valid and well calibrated. Ten-year lung cancer risk varied greatly among participants in the CT study, from 15% for a 68-year-old man who has smoked two packs per day for 50 years and continues to smoke, to 0.8% for a 51-year-old woman who smoked one pack per day for 28 years before quitting 9 years earlier.”
inclusion criteria. Methodologic quality varied, but few aspects of study quality affected diagnostic accuracy. The authors constructed summary receiver-operating characteristic curves for CT and FDG-PET. Positron emission tomography with 18-fluorodeoxyglucose was more accurate than CT for identifying lymph node involvement (P<0.001). For CT, median sensitivity and specificity were 61% (interquartile range, 50% to 71%) and 79% (interquartile range, 66% to 89%), respectively. For FDG-PET, median sensitivity and specificity were 85% (interquartile range, 67% to 91%) and 90% (interquartile range, 82% to 96%), respectively. Fourteen studies provided information about the conditional test performance of CT and FDG-PET. Positron emission tomography with 18-fluorodeoxyglucose was more sensitive but less specific when CT showed enlarged lymph nodes (median sensitivity, 100% [interquartile range, 90% to 100%]; median specificity, 78% [interquartile range, 68% to 100%]) than when CT showed no lymph node enlargement (median sensitivity, 82% [interquartile range, 65% to 100%]; median specificity, 93% [interquartile range, 92% to 100%]; P=0.002).

Conclusions: Positron emission tomography with 18-fluorodeoxyglucose is more accurate than CT for mediastinal staging. Positron emission tomography with 18-fluorodeoxyglucose is more sensitive but less specific when CT shows enlarged mediastinal lymph nodes.

Editorial Comment (TLP): The combined use of CT and PET scanning in a single instrument to give us more information about the cost-effectiveness of dual image scanning. See next abstract.

Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography.

Divisions of Thoracic Surgery, University Hospital of Zurich, Zurich, Switzerland.

Background: We compared the diagnostic accuracy of integrated positron-emission tomography (PET) and computed tomography (CT) with that of CT alone, that of PET alone, and that of conventional visual correlation of PET and CT in determining the stage of disease in non-small-cell lung cancer.

Methods: In a prospective study, integrated PET-CT was performed in 50 patients with proven or suspected non-small-cell lung cancer. CT and PET alone, visually correlated PET and CT, and integrated PET-CT were evaluated separately, and a tumor-node-metastasis (TNM) stage was assigned on the basis of image analysis. Nodal status was identified according to the mapping system of the American Thoracic Society. The standard of reference was histopathological assessment of tumor stage and node stage. Extrathoracic metastases were confirmed histopathologically or by at least one other imaging method. A paired sign test was used to compare integrated PET-CT with the other imaging methods.

Results: Integrated PET-CT provided additional information in 20 of 49 patients (41 percent), beyond that provided by conventional visual correlation of PET and CT. Integrated PET-CT had better diagnostic accuracy than the other imaging methods. Tumor staging was significantly more accurate with integrated PET-CT than with CT alone (P<0.001), PET alone (P<0.001), or visual correlation of PET and CT (P=0.013);
node staging was also significantly more accurate with integrated PET-CT than with PET alone (P=0.013). In metastasis staging, integrated PET-CT increased the diagnostic certainty in two of eight patients.

Conclusions: Integrated PET-CT improves the diagnostic accuracy of the staging of non-small-cell lung cancer. Copyright 2003 Massachusetts Medical Society

Editorial Comment (TLP): These additional studies suggest that integrated CT-PET scanning increases the diagnostic accuracy of combined screening.

Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer.


Background: On the basis of a previous meta-analysis, the International Adjuvant Lung Cancer Trial was designed to evaluate the effect of cisplatin-based adjuvant chemotherapy on survival after complete resection of non-small-cell lung cancer.

Methods: We randomly assigned patients either to three or four cycles of cisplatin-based chemotherapy or to observation. Before randomization, each center determined the pathological stages to include, its policy for chemotherapy (the dose of cisplatin and the drug to be combined with cisplatin), and its postoperative radiotherapy policy. The main end point was overall survival.

Results: A total of 1867 patients underwent randomization; 36.5 percent had pathological stage I disease, 24.2 percent stage II, and 39.3 percent stage III. The drug allocated with cisplatin was etoposide in 56.5 percent of patients, vinorelbine in 26.8 percent, vinblastine in 11.0 percent, and vindesine in 5.8 percent. Of the 932 patients assigned to chemotherapy, 73.8 percent received at least 240 mg of cisplatin per square meter of body-surface area. The median duration of follow-up was 56 months. Patients assigned to chemotherapy had a significantly higher survival rate than those assigned to observation (44.5 percent vs. 40.4 percent at five years [469 deaths vs. 504]; hazard ratio for death, 0.86; 95 percent confidence interval, 0.76 to 0.98; P<0.03). Patients assigned to chemotherapy also had a significantly higher disease-free survival rate than those assigned to observation (39.4 percent vs. 34.3 percent at five years [518 events vs. 577]; hazard ratio, 0.83; 95 percent confidence interval, 0.74 to 0.94; P<0.003). There were no significant interactions with prespecified factors. Seven patients (0.8 percent) died of chemotherapy-induced toxic effects.

Conclusions: Cisplatin-based adjuvant chemotherapy improves survival among patients with completely resected non-small-cell lung cancer. Copyright 2004 Massachusetts Medical Society

Editorial Comment (TLP): This well designed and conducted study will probably set a new standard of care of patients with completely resectable lung cancer. It still concerns me that a 39.3% of the patients were Stage III, meaning relatively late diagnosis. How much better it would be if we could deal primarily with Stage I disease through early identification, at least in high risk groups.
Racial differences pertaining to a belief about lung cancer surgery: results of a multicenter survey.


Background: Patients at the Philadelphia Veterans Affairs Medical Center frequently voice concern that air exposure during lung cancer surgery might cause tumor spread. Several African-American patients asserted that this belief was common in the African-American community.

Objective: To assess the prevalence of the belief that air exposure during lung cancer surgery might cause tumor spread and gauge the influence of this belief on the willingness of African-American and white patients to have lung cancer surgery.

Design: Prospective questionnaire survey.

Setting: Philadelphia Veterans Affairs Medical Center and University of Pennsylvania, Philadelphia, Pennsylvania; Los Angeles Veterans Affairs Medical Center, Los Angeles, California; and Medical University of South Carolina, Charleston, South Carolina.

Patients: 626 consecutive patients in pulmonary and lung cancer clinics.

Measurements: None.

Results: 38% of patients (61% of whom were African American and 29% of whom were white) stated that they believe air exposure at surgery causes tumor spread. The most significant predictor of belief was African-American race (odds ratio, 3.5 (95% CI, 1.9 to 6.5)), even after controlling for other relevant variables in a multivariable analysis. Nineteen percent of African Americans stated that this belief was a reason for opposing surgery, and 14% would not accept their physicians’ assertion that the belief is false. These rates were also statistically significantly higher among African-American than white patients.

Conclusions: Belief in accelerated tumor spread at surgery is prevalent among general pulmonary outpatients and lung cancer clinic patients facing lung surgery, particularly among African-American patients. Our findings may pertain to key racial disparities in lung cancer surgery and survival rates and suggest that culturally sensitive physician training or outreach programs directed at disparate beliefs and attitudes may help to address racial discrepancies in health care outcomes.

Editorial Comment (TLP): I remember a similar concern about lung cancer surgery in black patients when I was an intern in Philadelphia in 1958-1959!

Long-term survival and prognostic factors of five-year survivors with complete resection of non-small cell lung carcinoma.


Objective: We analyzed the long-term follow-up data on cancer-related death in 5-year survivors of complete resection of their non-small cell lung cancer and examined the prognostic factors having an impact on subsequent survival.

Methods: Of 848 consecutive patients with proven primary non-small cell carcinoma who underwent complete removal of the primary tumor together with hilar and mediastinal lymph nodes, 421
patients (49.6%) survived 5 years or longer after the initial surgical treatment. Of all the data analyzed, only death related to cancer was treated as death.

**Results:** The median follow-up of 5-year survivors was 84 months from the original treatment (range, 60 to 200 months). Their overall survival rate at 10 years was 91.0%. Multivariable Cox analysis demonstrated that although advanced surgical-pathological stage \( (P=0.001) \), nodal involvement \( (P=0.0245) \), male gender \( (P=0.0313) \), and nonsquamous type of the tumor \( (P=0.0034) \) were significant, independent, unfavorable prognostic determinants in all patients, none of the variables investigated significantly influenced the long-term survival of 5-year survivors.

The rate of recurrence beyond 5 years was much lower compared with that within 5 years. In contrast, the rate of occurrence of new malignancies was unchanged throughout the long-term postoperative period.

**Conclusions:** Among 5-year survivors of complete resection of non-small cell lung cancer, neither stage, nodal status, sex, nor histologic condition further affected subsequent survival, suggesting that the 5-year interval might be sufficient to declare that a patient with lung cancer has been cured.

**Editorial Comment (TLP):** A five-year follow-up is probably not sufficient to declare cure. In a previously reported study of 46 roentgenographically occult lung cancer followed for many years, there were 12 patients with a second or third cancer detected, however only one occurred after 5 years (111 months) following the original resection. Five year survival was 54.3% including patients who received radiation therapy for cure. (Bechtel, et al: Lung Cancer 2000;30:1-7)

---

**Histology-related variation in the treatment and survival of patients with lung carcinoma in Canada.**

Xie L, Ugnat AM, Morriss J, Semenciw R, Mao Y. Surveillance and Risk Assessment Division, Center for Chronic Disease Prevention and Control, Population and Public Health Branch, Health Canada, 120 Colonnade Road, Address Locator 6702A, Ottawa, Ont., Canada K1A 0K9.

**Lung Cancer** 2003;42:127-139

**Objectives:** The aim of the study was to examine histologic differences in lung cancer treatment and survival, and to define recent survival trends in Ottawa, Canada.

**Methods:** From 1994 to 2000, 3,237 patients with invasive lung cancer were registered at the Ottawa Regional Cancer Centre (ORCC) and were followed up to 31 December 2001. Five-year relative survival rates (rsr) and relative excess risks (rer) of dying were calculated by stage and dominant initial treatment modalities for major cellular histologies using a relative survival model.

**Results:** The overall 5-year survival rate was 14%, and female patients had significantly better survival. Patients with stage I and II non-small cell lung cancer (nsclc) who were treated by surgery alone were more likely to survive (5-year rsrs were 72 and 48%, respectively) than those who received other treatments. Patients with stage III nsclc had a 5-year survival rate of 9% after chemotherapy plus radiotherapy, whereas stage IV patients who received only chemotherapy had better survival for up to 2 years than patients with other treatments. In cases of limited-stage small cell lung cancer (sclc), survival was better for patients who received chemotherapy plus radiotherapy than for those who received only chemotherapy.

**Conclusions:** The relatively superior survival of surgical patients with stage I...
NSCLC implies that a considerable number of patients have the potential to be treated successfully. The overall poor survival of lung cancer patients suggests a need for more national public health emphasis on lung cancer prevention, improved screening and early diagnosis, and better treatment.

Editorial Comment (TLP): Again, another strong vote for screening for lung cancer, particularly in high risk individuals.


Context: In the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, alpha-tocopherol supplementation decreased prostate cancer incidence, whereas beta-carotene increased the risk of lung cancer and total mortality. Postintervention follow-up provides information regarding duration of the intervention effects and may reveal potential late effects of these antioxidants.

Objective: To analyze postintervention effects of alpha-tocopherol and beta-carotene on cancer incidence and total and cause-specific mortality.

Design, Setting, and Participants: Postintervention follow-up assessment of cancer incidence and cause-specific mortality (6 years (May 1, 1993-April 30, 1999)) and total mortality (8 years (May 1, 1993-April 30, 2001)) of 25,563 men. In the ATBC Study, 29,133 male smokers aged 50 to 69 years received alpha-tocopherol (50 mg), beta-carotene (20 mg), both agents, or placebo daily for 5 to 8 years. End point information was obtained from the Finnish Cancer Registry and the Register of Causes of Death. Cancer cases were confirmed through medical record review.


Results: Overall post-trial relative risk (RR) for lung cancer incidence (n=1037) was 1.06 (95% confidence interval (CI), 0.94-1.20) among recipients of beta-carotene compared with nonrecipients. For prostate cancer incidence (n=672), the RR was 0.88 (95% CI, 0.76-1.03) for participants receiving alpha-tocopherol compared with nonrecipients. No late preventive effects on other cancers were observed for either supplement. There were 7261 individuals who died by April 30, 2001, during the posttrial follow-up period; the RR was 1.01 (95% CI, 0.96-1.05) for alpha-tocopherol recipients vs nonrecipients and 1.07 (95% CI, 1.02-1.12) for beta-carotene recipients vs nonrecipients. Regarding duration of intervention effects and potential late effects, the excess risk for beta-carotene recipients was no longer evident 4 to 6 years after ending the intervention and was primarily due to cardiovascular diseases.

Conclusions: The beneficial and adverse effects of supplemental alpha-tocopherol and beta-carotene disappeared during postintervention follow-up. The preventive effects of alpha-tocopherol on prostate cancer require confirmation in other trials. Smokers should avoid beta-carotene supplementation.

Editorial Comment (TLP): This follow-up study raises more questions than it answers. Certainly there is no evidence that beta-carotene protects against lung cancer and may be a contributing factor in smokers.
Diagnosis of airflow limitation combined with smoking cessation advice increases stop-smoking rate.

Gorecka D, Bednarek M, Nowinski A, Puscinska E, Goljan-Geremek A, Zielinski J. Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland. d.gorecka@igichp.edu.pl

Chest 2003;123:1916-1923

Objectives: To assess how the diagnosis of airflow limitation (AL) combined with advice to stop smoking in middle-aged smokers influence the smoking cessation rate and to identify predictors of successful outcome.

Design: Prospective, single-center, comparative study of the effects of smoking intervention in smokers with diagnosed AL and in smokers with normal lung function (NLF).

Setting: University hospital, out-patient clinic.

Participants: Of 659 smokers participating in a population spirometric screening for COPD combined with smoking cessation advice, 558 (AL, 297 smokers; NLF, 261 smokers) were invited for a follow-up after 1 year.

Interventions: At follow-up, spirometry was repeated and smoking status was assessed. Nonsmoking status was validated with carbon monoxide measurements in exhaled air. Patients who did not come for the follow-up visit were considered to be smokers.

Results: Of 558 smokers invited, 368 (66%) presented for the follow-up visit. All had tried to reduce their smoking habit. The number of cigarettes smoked per day (CPD) at 1 year was −5.2 (p < 0.01) in patients with AL and −2.7 (not significant (NS)) in those with NLF. The 1-year cessation rate in smokers with AL was 10.1% vs 8.4% in smokers with NLF (NS).

Conclusion: All smokers, irrespective of their lung function, tried to modify their habit as the result of screening for COPD combined with smoking cessation advice. The diagnosis of AL motivated smokers to attempt to quit smoking. Older age, lower tobacco exposure, and lower lung function were the predictors of success in quitting smoking.

Editorial Comment (TLP): This is another study that strongly suggests that knowledge of abnormal spirometry may be a mitigating factor in smoking cessation, in particular with more advanced stages of COPD. How to mitigate smoking cessation with patients with mild airflow obstruction remains a major challenge!