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**LUNG
CANCER****FRONTIERS****NEW GENOMIC AND PROTEOMIC
STUDIES IN LUNG CANCER
BIOMARKER DETECTION**

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"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."

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New Genomic and Proteomic Studies in Lung Cancer Biomarker Detection
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Lung cancer is the leading cause of cancer death in both men and women in the United States with a dismal 5-year survival rate of <15%.¹ Approximately 80-85% of cases are non-small cell lung cancer (NSCLC) and 25% are eligible for surgical resection.² Unfortunately, recurrence still remains unacceptably high among patients who undergo surgical resection. Lung cancer represents a group of heterogeneous diseases that despite similar morphology exhibit different growth rates, metastatic potential and response to therapies.³ Determining which early lesions could benefit from adjuvant therapies is essential. In addition to tobacco cessation and current therapies, personalizing our approach to lung cancer through the use of new modalities for early detection, molecular

characterization of disease phenotypes and identification of new molecular targets remains important to improving overall survival. To date, researchers have examined primary tumors, sputum, airway samples, blood, pleural fluid and exhaled breath condensate for genetic alterations in order to identify biomarkers of disease.

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The Forum for Early Diagnosis and Treatment of Lung Cancer

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LUNG CANCER BIOMARKERS

This issue of *Lung Cancer Frontiers*, prepared by Dr. Patrick Nana-Sinkam of Ohio State University, contains important updates on the current status of biomarkers in the diagnosis and assessment of prognosis in various stages of lung cancer. It is an important finding and not surprising that molecular markers are far more accurate than morphologic classifications of disease states in determining overall prognosis and response to therapy. This issue also includes a summary of highlights of the 2007 Annual Meeting of the American Society of Clinical Oncology (ASCO) recently held in Chicago, Illinois in June 2007.

Continued progress in this area will hopefully lead to better diagnostic approaches. In the future we may be able to rely upon breath, sputum, or blood markers before we order CT and PET scans or bronchoscopy.

I continue to believe that the entire armamentarium will be useful as we emerge from an era of doing very little for lung cancer to an aggressive approach particularly in earlier stages of disease.



Such biomarkers could then serve to stratify high risk patients, personalize treatment plans, predict response to therapy, prognosis and define risk of disease recurrence. In the last several years we have witnessed the development of new targeted therapies such as epidermal growth factor inhibitors (Erlotinib and Gefitinib) which are of therapeutic benefit in distinct subgroups of lung cancer patients.^{4,5}

High throughput genomic platforms such as DNA microarrays may be used to screen for thousands of potential biomarkers. Genomic platforms have become powerful tools in identifying histological subcategories of disease, new molecular targets, prognostication and predicting response to therapies. A major limitation of gene expression profiling has been the loose association between mRNA and protein expression and inter-laboratory variability. However, in the last year there have been several studies supporting the use of microarray technology as a platform for biomarker detection. Last year, Potti et al. conducted a retrospective study published in the *New England Journal of Medicine* utilizing gene expression profiling in NSCLC (N=89 from two previous studies ACOSOG Z0030 and CALGB 9761). The authors identified a distinct set of genes (termed lung metagene) in a test cohort that predicted disease recurrence in NSCLC (defined as within 2.5 years) better than traditional clinical prognostic factors regardless of stage.⁶ The potential implications of this study are significant. Early stage lung cancers should be stratified into high and low risk lesions. Future risk stratification may incorporate both clinical information as well as genomic platforms which could affect medical decision making. Individuals with high risk lesions should perhaps be considered for adjuvant therapies and undergo tighter surveillance.

Several investigators are focusing on profiling the expression and function of cancer cell related proteins (Proteomics) as a platform for identifying novel biomarkers. Proteomics based analyses are being applied to biological specimens for the purposes of early diagnosis, prognostication and evaluating response to therapy.⁷ In a recent study by Taguchi et al., investigators conducted proteomic analysis termed matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) on serum from NSCLC patients prior to therapy with either erlotinib or gefitinib. The authors were successful in generating an algorithm that could predict patients with a good versus poor outcome following epidermal growth factor inhibitor treatment.⁸ In another recent study, investigators identified a proteomic signature

associated with relapse-free and overall survival in early stage lung cancer.² Such profiles could eventually be a component in a personalized treatment plan.

In our search for new biomarkers, one particular issue that arises is the ability to accurately profile disease in areas other than primary tumor tissue. Investigators have profiled sputum, bronchial biopsies, pleural fluid and serum. Whether expression patterns correlate with the primary tumor remains unclear. In a study published in the *Annals of Oncology*, Taillade and colleagues compared preoperative biopsies with corresponding resected tumor for five biomarkers.⁹ While the authors examined a small number of samples (N=41), they observed high correlation between the expression of markers for DNA repair, Ki-67 and cellular immortality in preoperative biopsies and surgical specimens. The authors were not able to detect high correlation for EGFR expression. The findings suggest that integrating preoperative biopsy molecular information into any algorithm for risk stratification and targeted therapy should be done with caution. There is developing evidence that gene expression patterns in the peripheral blood may be utilized as a noninvasive biomarker for disease diagnosis and prognosis. Several groups have identified malignant epithelial cells in the peripheral circulation of patients with carcinoma.¹⁰ Rarely, these malignant cells form a metastatic focus in a distant organ/site (hematogenous metastasis). Recent techniques allow for the sensitive detection of cells in the circulation. Investigators are currently investigating the role of serum tumor markers in lung cancer but there are a limited number of biologically relevant markers.^{11,12}

In the last decade we have seen the emergence of a new mode of gene regulation. MicroRNAs (MiRNAs, *mir*) are a family of small non-coding RNAs expressed in many organisms including animals, plants, and viruses. MiRNAs are integral to several biological functions including gene regulation, apoptosis, hematopoietic development and the maintenance of cell differentiation. MiRNAs target other RNAs for either degradation or inhibition of translation. To date over 400 miRNAs have been identified. Researchers have identified abnormal expression of miRNAs in several types of malignancies including Chronic Lymphocytic Leukemia (CLL), colorectal neoplasia, lymphoma, glioblastoma ,

breast, lung and hepatocellular carcinoma.¹³⁻¹⁵ MiRNAs may function as either tumor suppressors or oncogenes but most miRNA targets have yet to be identified. MiRNAs are located throughout the genome but the majority of miRNAs are located in fragile sites or regions that are altered in expression in cancer.¹⁶

Our knowledge of miRNA biology in lung cancer is limited. Johnson et al. identified that multiple mir-let-7 family genes can identify the 3'-untranslated region (UTR) of nematode RAS gene (let-60) in *C. elegans*.¹⁷ Overexpression of let-7 inhibits the expression of RAS protein and let-7 complementary sites are seen in human NRAS and KRAS 3'-UTR. RAS signaling is believed to help initiate the deletions of human let-7 genomic regions in lung cancer. Accordingly, let-7 expression was decreased in lung cancer samples but not in breast or colon cancer samples when compared to normal adjacent tissue. Indeed reduced let-7 expression in 143 resected lung cancer cases correlated to worse prognosis. Recently, Yanaihara et al. through the use of miRNA chip analysis identified distinct miRNA profiles in 104 pairs of primary lung cancers and corresponding non-cancerous tissue.¹⁸ The investigators identified five distinct miRNAs (*mir-155*, *17-3p*, *let-7a-2*, *145* and *21*) whose alteration in expression predicted prognosis among patients with adenocarcinoma.

Genomic and proteomic platforms have become powerful tools in identifying histological subcategories of disease, new molecular targets, prognostic tools and response to therapies. In the last year, several studies have served to strengthen their place in how we will determine phenotypes of disease. With the advent of miRNA, we have added another potential layer of complexity. Each of these technologies has their limitations and none of the modalities should supplant current clinical models but rather complement them. It appears that a systems-based approach of integrating several platforms of analysis will be required to better clarify the molecular heterogeneity in lung cancer.

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Lung Cancer Highlights of ASCO 2007

Chicago, Illinois
June 1—5, 2007

Shubham Pant, MD and
Miguel A. Villalona-Calero, MD, FACP

A number of interesting studies that pertain to the clinical management of patients with lung cancer were presented at the American Society of Clinical Oncology (ASCO) June 2007 meeting in Chicago.

Small cell lung cancer: This subset of lung cancer has always been the most challenging; traditionally very few studies have led to significant changes in clinical practice. However, this year's plenary session included the presentation of the EORTC 08992-22993 trial.¹ This study randomized patients with extensive disease small cell lung cancer (ED-SCLC) who had demonstrated partial or complete responses to 4-6 cycles of chemotherapy to either receive prophylactic cranial irradiation (PCI) (doses ranging from 20 Gy/5 fractions to 30 Gy/12

fractions) or no PCI. The primary end point was the cumulative incidence of symptomatic brain metastasis (BM). Two hundred eighty six patients entered the trial, 76% with residual disease in the thorax and 71% at distant sites. Acute toxicity was mild. The patients randomized to PCI had a significant reduction in the risk of symptomatic brain metastases, with the 1-year cumulative incidence being 14.6% on PCI (CI 8.3–20.9) versus 40.4% in controls (CI 32.1–48.6). Therapy with PCI significantly prolonged progression-free survival time (PFS) (P=0.0218, HR=0.76, CI: 0.59–0.96) and overall survival (P=0.0033, HR=0.68, CI: 0.52–0.88). The 1-year survival rate was 27.1% for the PCI and 13.3% for the control arm. Based on these results, the authors concluded that PCI should be offered to all ED-SCLC patients showing a response to initial chemotherapy.

Other trials worth mentioning include the failure of the oral inhibitor of vascular endothelial and epidermal growth factor receptors vandetanib (V) in the maintenance of partial or complete response to platinum based chemotherapy.² Neither progression free survival (2.7 months vs. 2.8 months) or overall survival (10.6 month for V vs. 11.9 months for placebo) were affected by the addition of this agent. In an attempt to confirm efficacy of irinotecan in first line ED-SCLC, another study compared irinotecan versus etoposide in carboplatin containing doublets.³ Although, the overall survival was 8.5 months vs. 7.1 months (p=0.04) in favor of the irinotecan arm, and the prior evidence of a Japanese trial supporting efficacy of irinotecan in ED-SCLC,⁴ the use of a non-conventional regimen as the comparator (oral etoposide/carboplatin) and an American trial failing to show differences between cisplatin/etoposide and irinotecan/cisplatin in the same setting,⁵ makes it unlikely that this trial will result in any significant changes in clinical practice.

Advanced NSCLC: As an expected follow up to the Eastern Cooperative Oncology Group (ECOG) 4599 demonstrating a benefit in overall and PFS with the addition of bevacizumab (B) to carboplatin/paclitaxel (CP) in patients with non-squamous histology,⁶ the AVAIL trial was designed to try and investigate if the addition of bevacizumab to another commonly used regimen (gemcitabine/cisplatin) had any impact on survival.⁷ Patients were randomized to placebo, B 7.5 mg/kg or B 15 mg/kg (plus chemotherapy), every three weeks. Progression free survival was higher in the B containing arms: 6.7/6.5 months versus 6.1 months. Hazard ratios were 0.75 (p=0.002) and 0.82 (p = 0.03) for B 7.5 mg/kg and 15 mg/kg, respectively. The response rates were 34%, 30% and 20% for B 7.5 mg/kg, B 15 mg/kg and placebo, respectively, and toxicity was similar. Although overall survival has not yet been presented, this study would give support that B could be added to other NSCLC chemotherapy regimens resulting in clinical benefit. The higher doses of 15 mg/kg, currently used in NSCLC, yet not in colon cancer, may not be needed to achieve this benefit.

The database of the ECOG 4599 study referenced above,

was re-analyzed retrospectively to compare outcomes in elderly patients (≥ 70 old) with the rest of patients in the study.⁸ Out of the 850 patients enrolled, 26% were elderly. A trend towards superior response rate (29% vs. 17%, $P = 0.067$) and median PFS (5.9 mo. vs. 4.9 mo., $p = 0.063$) with CPB when compared to CP, was observed, although there was no difference in overall survival (CPB = 11.3 mo.; CP = 12.1 mo.; $P = 0.4$). Eighty seven percent of elderly patients treated with CPB experienced grades 3–5 toxicities compared to 61% ($P < 0.001$) in the CP arm. Treatment-related death rates with CPB vs. CP were 6.3% vs. 1.8% (non significant) for the elderly. When compared to younger patients, the elderly experienced more neutropenia (34% vs. 22%), febrile neutropenia (6% vs. 0.9%), bleeding (7.9% vs. 3.2%), proteinuria (7.9% vs. 1.3%), hypertension (6% vs. 0.9%) muscle weakness (7.9% vs. 2.2%) and motor neuropathy (3.5% vs. 0.6%) with CPB. Although this analysis is limited by its post-hoc, retrospective nature, extra caution when treating elderly patients appears warranted. It is also of interest that females did not appear to have a survival benefit in ECOG 4599, despite an enhanced response rate. Subgroups analyses on the AVAIL and other ongoing trials in this setting should shed more light on this issue.

Epidermal Growth Factor Receptor (EGFR) inhibitors have been a welcome addition to our armamentarium in NSCLC patients failing chemotherapy treatment. Unfortunately, these agents have failed to improve outcomes when combined with chemotherapy compared to chemotherapy alone. Preclinical data suggested that addition of erlotinib before or after chemotherapy instead of concurrently may improve outcomes. This led to a randomized phase II trial,⁹ presented at ASCO in which patients (all current or former smokers) were assigned to one of three arms: erlotinib 150 mg on days 1,2, and chemotherapy (CP) on day 3; erlotinib 1500 mg on days 1, 2 and chemotherapy on day 3; or chemotherapy on day 1 and erlotinib 1500 mg on days 2,3. Patients received up to six 21-day cycles of treatment. The primary end point was overall response rate (PR+CR) using RECIST. The overall response rate in the three arms was 25%, thus the pre-clinical hypothesis failed to translate into clinical benefit.

Loco-Regional disease: Without doubt, the most controversial of all trials presented was the assessment of docetaxel as consolidation following concurrent chemo-radiation in a phase III trial (first time ever) of patients with inoperable stage III NSCLC.¹⁰ This approach has become common clinical practice based on SWOG S9504, which reported very encouraging 2 and 3 year survival with this strategy.¹¹ Patients received cisplatin (C) 50 mg/m² iv on days 1,8,29,36 and Etoposide (E) 50 mg/m² iv on day 1-5,29-33 concurrently with chest XRT to 5940 cGy. They were then randomized to receive 75 mg/m² of docetaxel i.v. every 21 days for 3 cycles vs. observation (O). Eligible patients had inoperable stage III A/B NSCLC, PS 0-1, FEV₁ ≥ 1 Lt and $<5\%$ weight loss.

The trial was designed to demonstrate a difference in median survival time of 25 months vs. 15 months (5%, 2 sided alpha, 80% power), but upon evidence of futility (predefined as $p > 0.7271$) the Data Safety Monitoring Board (DSMB) recommended early termination of the trial. The PFS was 12.3(D) vs. 12.9 months (O).

A significant rate of severe toxicities for the D arm (10.9% febrile neutropenia, 8.2% pneumonitis, 28.8% hospitalizations and 5.5% deaths) may account for the lack of clinical benefit in this trial. It is still to be seen, if patient selection and the use of prophylactic colony stimulating factors may make this approach feasible for clinical practice.

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SELECTIONS FROM THE PEER- REVIEWED LITERATURE:

1. **DNA Synthesis and Repair Genes RRM1 and ERCC1 in Lung Cancer** [N Engl J Med.](#) 2007 Feb 22;356(8):800-8

Zhong Zheng, M.D., Ph.D., Tingan Chen, M.D., Ph.D., Xueli Li, M.D., Eric Haura, M.D. Anupama Sharma, M.D., and Gerold Bepler, M.D., Ph.D.

BACKGROUND: RRM1, the regulatory subunit of ribonucleotide reductase, is involved in carcinogenesis, tumor progression, and the response of non-small-cell lung cancer to treatment. **METHODS:** We developed an automated quantitative determination of the RRM1 protein in routinely processed histologic specimens. In these specimens, we measured the expression of RRM1 and two other proteins that are relevant to non-small-cell lung cancer: the excision repair cross-complementation group 1 (ERCC1) protein and the phosphatase and tensin

homologue (PTEN). We compared the results with the clinical outcomes in 187 patients with early-stage non-small-cell lung cancer who had received only surgical treatment. **RESULTS:** RRM1 expression correlated with the expression of ERCC1 ($P < 0.001$) but not with the expression of PTEN ($P = 0.37$). The median disease-free survival exceeded 120 months in the group of patients with tumors that had high expression of RRM1 and was 54.5 months in the group with low expression of RRM1 (hazard ratio for disease progression or death in the high-expression group, 0.46; $P = 0.004$). The overall survival was more than 120 months for patients with tumors with high expression of RRM1 and 60.2 months for those with low expression of RRM1 (hazard ratio for death, 0.61; $P = 0.02$). Among these 187

“We developed an automated quantitative determination of the RRM1 protein in routinely processed histologic specimens.”

“The overall survival was more than 120 months for patients with tumors with high expression of RRM1 and 60.2 months for those with low expression of RRM1 . . .”

“... the survival advantage was limited to the 30% of patients with tumors that had a high expression of both RRM1 and ERCC1.”

patients, the survival advantage was limited to the 30% of patients with tumors that had a high expression of both RRM1 and ERCC1. CONCLUSIONS: RRM1 and ERCC1 are determinants of survival after surgical treatment of early-stage, non-small-cell lung cancer.

Editorial Comment: Ribonucleotide reductase (RRM1) expression has previously been identified to correlate with survival in NSCLC. RRM1 is biologically relevant to tumor invasiveness and metastases. This extremely important study adds to our current knowledge by demonstrating a correlation between elevated levels of RRM1, the excision repair cross-complementation group 1 (ERCC1) and survival in patients with early stage lung cancer. Risk stratification among early stage respectable patients is essential to identifying those that may benefit from adjuvant therapies.

“Statins appear to be protective against the development of lung cancer, and further studies need to be done to define the clinical utility of statins as chemo protective agents.”

2.
Statins Reduce the Risk of Lung Cancer in Humans*
A Large Case-Control Study of US Veterans [Chest](#). 2007 May;131(5):1282-8
Vikas Khurana, MD; Hanmanth R. Bejjanki, MD; Gloria Caldito, PhD and Michael W. Owens, MD

BACKGROUND: Statins are commonly used cholesterol-lowering agents that are noted to suppress tumor cell growth in several in vitro and animal models. **METHODS:** We studied the association of lung cancer and the use of statins in patients enrolled in the Veterans Affairs (VA) Health Care System. A retrospective case-control study nested in a cohort study was conducted using prospectively collected data from the Veterans Integrated Service Networks 16 VA database from 1998 to 2004. We analyzed data on 483,733 patients from eight states

“We analyzed data on 483,733 patients from eight states located in south central United States.”

located in south central United States. The primary variables of interest were lung cancer and the use of statins prior to the diagnosis of lung cancer. Multiple logistic regression analysis was done to adjust for covariates including age, sex, body mass index, smoking, diabetes, and race. Statistical software was used for statistical computing. **RESULTS:** Of the 483,733 patients in the study, 163,662 patients (33.8%) were receiving statins and 7,280 patients (1.5%) had a primary diagnosis of lung cancer. Statin use > 6 months was associated with a risk reduction of lung cancer of 55% (adjusted odds ratio, 0.45; 95% confidence interval, 0.42 to 0.48; $p < 0.01$). Furthermore, the protective effect of statin was seen across different age and racial groups and was irrespective of the presence of diabetes, smoking, or alcohol use. **CONCLUSIONS:** Statins appear to be protective against the development of lung cancer, and further studies need to be done to define the clinical utility of statins as chemo protective agents.

Editorial Comment: This is a potentially important study investigating the role of statins in lung cancer risk. There are several limitations to the study including evaluation of a primarily male population, uncertainty of other risk factors for the development of lung cancer in the cohort and lack of clarity of the interaction between tobacco use and statins. Nevertheless, statins as a chemopreventive agent may merit further study.

3.
Expression of nicotinic acetylcholine receptor subunit genes in non-small-cell lung cancer reveals differences

between smokers and nonsmokers.

Cancer Res. 2007 May 15;67 (10):4638-47

[Lam DC](#), [Girard L](#), [Ramirez R](#), [Chau WS](#), [Suen WS](#), [Sheridan S](#), [Tin VP](#), [Chung LP](#), [Wong MP](#), [Shay JW](#), [Gazdar AF](#), [Lam WK](#), [Minna JD](#).

Nicotine and its derivatives, by binding to nicotinic acetylcholine receptors (nAChR) on bronchial epithelial cells, can regulate cellular proliferation and apoptosis via activating the Akt pathway. Delineation of nAChR subtypes in non-small-cell lung cancers (NSCLC) may provide information for prevention or therapeutic targeting. Expression of nAChR subunit genes in 66 resected primary NSCLCs, 7 histologically non-involved lung tissues, 13 NSCLC cell lines, and 6 human bronchial epithelial cell lines (HBEC) was analyzed with quantitative PCR and microarray analysis. Five nonmalignant HBECs were exposed to nicotine in vitro to study the variation of nAChR subunit gene expression with nicotine exposure and removal. NSCLCs from nonsmokers showed higher expression of nAChR alpha6 ($P < 0.001$) and beta3 ($P = 0.007$) subunit genes than those from smokers, adjusted for gender. In addition, nAChR alpha4 ($P < 0.001$) and beta4 ($P = 0.029$) subunit gene expression showed significant difference between NSCLCs and normal lung. Using Affymetrix GeneChip U133 Sets, 65 differentially expressed genes associated with NSCLC nonsmoking nAChR alpha6beta3 phenotype were identified, which gave high sensitivity and specificity of prediction. nAChR alpha1, alpha5, and alpha7 showed

“Delineation of nAChR subtypes in non-small-cell lung cancers (NSCLC) may provide information for prevention or therapeutic targeting.”

“NSCLCs from nonsmokers showed higher expression of nAChR alpha6 ($P < 0.001$) and beta3 ($P = 0.007$) subunit genes than those from smokers, adjusted for gender. In addition, nAChR alpha4 . . .”

significant reversible changes in expression levels in HBECs upon nicotine exposure. We conclude that between NSCLCs from smokers and nonsmokers, different nAChR subunit gene expression patterns were found, and a 65-gene expression signature was associated with nonsmoking nAChR alpha6beta3 expression. Finally, nicotine exposure in HBECs resulted in reversible differences in nAChR subunit gene expression. These results further implicate nicotine in bronchial carcinogenesis and suggest targeting nAChRs for prevention and therapy in lung cancer.

Editorial Comment: This is an interesting observational study that seeks to delineate the role of differential expression of nicotinic acetylcholine receptors in NSCLC. The authors successfully characterize patterns of nAChR subunit expression in primary NSCLC tumors, normal lung tissue, cancer cell lines and normal bronchial epithelial cells. This is an important first step in understanding the role that nAChR expression may play in nicotine addiction and disease pathogenesis.

4. A 25-signal proteomic signature and outcome for patients with resected non-small-cell lung cancer.

J Natl Cancer Inst. 2007 Jun 6;99 (11):858-67

[Yanagisawa K](#), [Tomida S](#), [Shimada Y](#), [Yatabe Y](#), [Mitsudomi T](#), [Takahashi T](#).

BACKGROUND: Among patients with non-small-cell lung cancer (NSCLC), those with poor prognosis cannot be distinguished from those with good prognosis. METHODS:

“Frozen resected tissue specimens were randomly divided into a training set (116 NSCLC and 20 normal lung specimens) . . .”

Matrix-assisted laser desorption-ionization mass spectrometry was used to analyze protein profiles of 174 specimens from NSCLC tumors and 27 specimens from normal lung tissue and to derive a prognosis-associated proteomic signature. Frozen resected tissue specimens were randomly divided into a training set (116 NSCLC and 20 normal lung specimens) and an independent, blinded validation set (58 NSCLC and seven normal lung specimens). Mass spectrometry signals from training set specimens that were differentially associated with specimens from patients with a high risk of recurrence (i.e., who died within 5 years of surgical treatment because of relapse) compared with those from patients with a low risk of recurrence (i.e., alive with no symptoms of relapse after a median follow-up of 89 months) were selected by use of the Fisher's exact test, the Kruskal-Wallis test, and the significance analysis of microarray test. These signals were used to build an individualized, weighted voting-based prognostic signature. The signature was then validated in the independent dataset. Survival was assessed by multivariable Cox regression analysis. Proteins corresponding to individual signals were identified by ion-trap mass spectrometry coupled with high-performance liquid chromatography. All statistical tests were two-sided. RESULTS: From 2630 mass spectrometry signals from specimens in the training cohort, we derived a signature of 25 signals that was associated with both relapse-free survival and overall survival. Among stage I NSCLC patients in the validation set, the signature was statistically significantly

“. . . . we derived a signature of 25 signals that was associated with both relapse-free survival and overall survival.”

associated with both overall survival (hazard ratio [HR] of death for patients in the high-risk group compared with those in the low-risk group = 61.1, 95% confidence interval [CI] = 8.9 to 419.2, $P < .001$) and relapse-free survival (HR of relapse = 11.7, 95% CI = 3.1 to 44.8, $P < .001$). Proteins corresponding to signals in the signature were identified that had various cellular functions, including ribosomal protein L26-like 1, acylphosphatase, and phosphoprotein enriched in astrocytes 15. CONCLUSIONS: We defined a mass spectrometry signature that was associated with survival among NSCLC patients and appeared to distinguish those with poor prognosis from those with good prognosis.

Editorial Comment: The identification of a distinct proteomic profile that correlates with disease prognosis can alter medical decision making and help to personalize our approach in lung cancer treatment. The primary limitations are those of the technology which continue to improve.

4. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the T Descriptors in the Forthcoming (Seventh) Edition of the TNM Classification for Lung Cancer

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Ramón Rami-Porta, MD, David Ball, MD, FRANZCR, John Crowley, PhD, Dorothy J. Giroux, MS, James Jett, MD, § William D. Travis, MD, Masahiro Tsuboi, MD, Eric Vallières, MD, and Peter Goldstraw, MB, FRCS on behalf of the

International Staging Committee, a Cancer Research and Biostatistics, b Observers to the Committee, c and Participating Institutions, d

PURPOSE: To propose changes in the seventh revision of the tumor, node, metastasis (TNM) classification for lung cancer.

METHODS: Data on 100,869 patients were submitted to the international database, and data for 18,198 of these patients fulfilled the inclusion criteria for the T component analysis. Survival was calculated for clinical and pathologic T1, T2, T3, T4NOMO completely resected (R0), and for each T descriptor. A running log-rank test was used to assess cutpoints by tumor size. Results were internally and externally validated. **RESULTS:** On the basis of the optimal cutpoints, pT1NOR0 was divided into pT1a ≤ 2 cm ($n = 1816$) and pT1b ≥ 2 to 3 cm ($n = 1653$) with 5-year survival rates of 77 and 71% ($p = 0.0001$). The pT2NOR0 cutpoints resulted in pT2a ≥ 3 to 5 cm ($n = 2822$), pT2b ≥ 5 to 7 cm ($n = 825$), and pT2c ≥ 7 cm ($n = 364$). Their 5-year survival rates were 58, 49, and 35% ($p = 0.0001$). For clinically staged N0, 5-year survival was 53% for cT1a, 47% for cT1b, 43% for cT2a, 36% for cT2b, and 26% for cT2c. pT3NO ($n = 711$) and pT4 (anyN) ($n = 340$) had 5-year survival rates of 38 and 22%. pT4 (additional nodule(s) in the same lobe) ($n = 363$) had a 5-year survival rate of 28%, similar to pT3 ($p = 0.28$) and better than other pT4 ($p = 0.0029$). For pM1 (ipsilateral pulmonary nodules) ($n = 180$), 5-year survival was 22%, similar to pT4. For cT4-malignant pleural effusion/nodules, 5-year survival

“Data on 100,869 patients were submitted to the international database, and data for 18,198 of these patients fulfilled the inclusion criteria for the T component analysis.”

“For clinically staged N0, 5-year survival was 53% for cT1a, 47% for cT1b, 43% for cT2a, 36% for cT2b, and 26% for cT2c. pT3NO ($n = 711$) and pT4 (anyN) ($n = 340$) had 5-year survival rates of 38 and 22%.”

was 2%. **CONCLUSION:** Recommended changes in the T classification are to subclassify T1 into T1a and T1b, and T2 into T2a and T2b; and to reclassify T2c and additional nodule(s) in the same lobe as T3 nodule(s) in the ipsilateral non-primary lobe as T4, and malignant pleural or pericardial effusions as M1.

Editorial Comment: The data presented represent the results of a long term studies examining our current TNM classification. The recommendations support previous studies to suggest that traditional T1 staging contains a heterogeneous group of patients with differing prognoses that should be subdivided along lines of tumor size. In addition, the recommendations propose downstaging of lesions in separate lobes and upstaging of malignant pleural/pericardial effusions. Modifying clinical staging is essential to risk stratification and determining individual treatment plans.

6. Natural history of stage 1 non-small cell lung cancer: implications for early detection.

CHEST 2007;132:194-199

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BACKGROUND: Concern has been raised that early detection of lung cancer may lead to the treatment of clinically indolent cancers. No

“ . . . the natural history of patients with stage I NSCLC who receive no surgery, chemotherapy, or radiation therapy.”

“Long-term survival with untreated stage I NSCLC is uncommon, and the vast majority of untreated patients die of lung cancer. Given that median survival is only 13 months in patients with T1 disease”

“ 1,432 did not undergo surgical resection or receive treatment with chemotherapy or radiation.”

population-based study has examined the natural history of patients with stage I NSCLC who receive no surgery, chemotherapy, or radiation therapy. Our hypothesis is that long-term survival in patients with untreated stage I non-small cell lung cancer (NSCLC) is uncommon. METHODS: A total of 101,844 incident cases of NSCLC in the California Cancer Center registry between 1989 and 2003 were analyzed; 19,702 patients had stage I disease, of whom 1,432 did not undergo surgical resection or receive treatment with chemotherapy or radiation. Five-year overall survival (OS) and lung cancer-specific survival were determined for this untreated group, for subsets of patients who were recommended but refused surgical resection, and for T1 tumors. RESULTS: Only 42 patients with untreated stage I NSCLC were alive 5 years after diagnosis. Five-year OS for

untreated stage I NSCLC was 6% overall, 9% for T1 tumors, and 11% for patients who refused surgical resection. Five-year lung cancer-specific survival rates were 16%, 23%, and 22%, respectively. Among these untreated patients, median survival was 9 months overall, 13 months for patients with T1 disease, and 14 months for patients who refused surgical resection. CONCLUSION: Long-term survival with untreated stage I NSCLC is uncommon, and the vast majority of untreated patients die of lung cancer. Given that median survival is only 13 months in patients with T1 disease, surgical resection or other ablative therapies should not be delayed even in patients with small lung cancers.

Editorial Comment (TLP):

This article helps to clarify the natural history of early stage cancer, and tends to debunk the lead time, length time and indolent tumor dogma, which old-time clinicians know is bunk.