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Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

Jeffrey A. Kern, MD Named Editor in Chief of *Lung Cancer Frontiers*

By Esther L. Langmack, MD

In January 2010, Dr. Jeffrey A. Kern, Professor of Medicine at National Jewish Health, became Editor in Chief of *Lung Cancer Frontiers*. He assumed leadership of the publication after the death of Thomas L. Petty, MD, the founder and former Editor in Chief of *Lung Cancer Frontiers*, in December 2009.

Dr. Kern joined National Jewish Health in December 2009 as Chief of the new Division of Oncology and Vice Chair of the Department of Medicine. Dr. Kern's goal is to develop a comprehensive program in thoracic oncology at National Jewish Health, based on state-of-the-art diagnostic and treatment modalities, with an emphasis on personalized treatment selection. In addition, he will coordinate basic science and translational research in lung cancer focusing on his interest in epithelial cell biology and tyrosine kinase signaling. His research focuses on the role of the epidermal growth factor receptor family and other receptor tyrosine kinases in lung cancer tumorigenesis. With the implementation of a thoracic oncology program, Dr. Kern plans to expand the Oncology Division into other aerodigestive malignancies such as head and neck, esophageal and gastrointestinal cancers.

Before he came to National Jewish Health, Dr. Kern was Chief of Pulmonary, Critical Care and Sleep Medicine at University Hospitals Case Medical Center, Professor of Oncology, and Professor of Physiology and Biophysics at Case Western Reserve University. During his career he has helped build nationally recognized thoracic oncology programs at Case Western Reserve University and the University of Iowa.

Dr. Kern recently served on the Editorial Boards of the *Journal of Laboratory and Clinical Medicine* and the *Journal of Investigative Medicine*. He is a reviewer for several prominent medical journals, including the *New England Journal of Medicine*, the *American Journal of Respiratory and Critical Care Medicine*, and *Cancer*.

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.

Access current and past issues of *Lung Cancer Frontiers* via the Internet at LungCancerFrontiers.org

In this issue

As Editor in Chief of *Lung Cancer Frontiers*, Dr. Kern will work with the Editorial Board to continue to bring current information about lung cancer to pulmonologists and other front-line practitioners. "I'm truly honored to carry forward the mission Dr. Petty started with *Lung Cancer Frontiers*," said Dr. Kern. "Our understanding of how best to diagnose and treat lung cancer is rapidly evolving, particularly in the area of genetics and molecularly targeted therapies," he noted. "These

advances will change fundamentally how we care for patients with lung cancer, as well as the role of pulmonologists in delivery of primary therapy, and are cause for great optimism. *Lung Cancer Frontiers* will expand its scope and readership to keep practitioners informed of the latest developments. More importantly, I hope to put many of these advances into perspective, to point out the real applications of new discoveries."

The Role of Immuohistochemistry in Lung Cancer
By Steve D. Groshong, MD, PhD

Steve D. Groshong, MD, PhD, is Head of the Section of Pathology and Assistant Professor of Medicine at National Jewish Health. He is also Assistant Professor in the Division of Pulmonary Medicine and Critical Care Sciences at the University of Colorado Denver School of Medicine. His interests include pathologic classifications and mechanisms of pulmonary fibrosis and lung cancer. He is a member of the **Lung Cancer Frontiers** Editorial Board.

Lung cancer is not a single disease. There are many different cell types in the normal lung, and each cell type can transform to become cancerous and give rise to a specific tumor type. To complicate matters even further, the lung is a common site of metastasis for tumors that arise elsewhere in the body. The correct classification of a tumor, both in terms of its organ of origin and specific subtype, is the first step towards effective therapy. With the recognition that specific mutations that predict treatment response are more common in specific histologic subtypes,[1] and with U.S. Food and Drug Administration (FDA) approval of drug regimens for specific histologic subtypes, such as pemetrexed (Alimta®) for adenocarcinoma and large-cell carcinoma, and bevacizumab (Avastin®) for non-squamous non-small cell lung cancer (NSCLC), we can no longer simply lump lung cancers into non-small cell and small cell categories. With the advent of molecularly targeted therapies and regimens, specific histologic classifications are critical.

Even in an era of sophisticated molecular and proteomic analysis, the "gold standard" for lung cancer classification continues to be the tumor's appearance on a microscope slide using the routine histologic stain, hematoxylin and eosin

(H & E). The pathologist first separates lung tumors into small cell and non-small cell categories. Tumors composed of small, easily crushed cells that appear predominantly blue under the microscope due to their scant cytoplasm and high nucleus/cytoplasm ratio are considered small cell carcinoma. Large, polygonal cells with abundant cytoplasm, and therefore a much lower nucleus/cytoplasm ratio, that grow in sheets are classified as squamous cell carcinoma. Large cells with prominent nucleoli forming glandular structures are classified as adenocarcinoma. Finally, tumors composed of large cells that are typical of neither adenocarcinoma nor squamous cell carcinoma are classified as large cell carcinoma.

Immunohistochemical Markers to Identify Tumor Type

In most cases, the appearance of the tumor by H & E staining is sufficient to accurately classify a tumor, but there are situations in which additional immunohistochemical studies are necessary. Immunohistochemical staining uses antibodies that target specific proteins or glycosylated epitopes to allow their visualization in the biopsy tissue. One of the most

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useful tissue-specific stains routinely employed to distinguish a primary lung cancer from a metastasis, or confirm the diagnosis of primary lung cancer, is thyroid transcription factor-1 (TTF-1). TTF-1 is a 38 kDa nuclear protein member of the NKX2 homeobox 1, or NKX2-1, family of transcription factors. In humans, TTF-1 is a 371 amino acid polypeptide encoded by a single gene. It was first discovered in the follicular epithelial cells of the thyroid and then in the lung (Clara cells and alveolar type II pneumocytes) and cells of the diencephalon. It has recently also been found in the pituitary, parathyroid gland and parafollicular C-cells of the thyroid. In the lung, TTF-1 regulates transcription of surfactant proteins A, B, C and D, as well as Clara cell secretory protein. When considering lung nodules, if a thyroid malignancy can be excluded, TTF-1 positivity is convincing evidence that a tumor is a primary of the lung and not a metastasis to the lung from a distant primary. In the lung, the vast majority of small cell carcinomas (>88%), approximately 84% of adenocarcinomas and half of all large cell carcinomas retain TTF-1 expression (*Table 1*). In contrast, lung squamous cell carcinomas only rarely express TTF-1. Although most adenocarcinomas and small cell carcinomas express TTF-1, some lose expression due to the considerable genetic instability and heterogeneity often present in tumors, particularly poorly differentiated ones. There may also be subpopulations, or subclones, within a tumor that have different patterns of expression. Morphologic subtypes of lung adenocarcinomas do not seem to confound expression, however, as acinar, papillary and bronchioloalveolar subtypes all express TTF-1. Mucin-producing adenocarcinomas,

however, can be an exception and are often TTF-1 negative, while other neuroendocrine tumors (carcinoid, large cell neuroendocrine carcinoma) variably express TTF-1.

Although TTF-1 positivity is helpful in confirming that a tumor is a primary of the lung, the absence of TTF-1 does not exclude the possibility of a lung primary because of the variability of expression in certain histologic subtypes and the lack of staining in all adenocarcinomas. Therefore, additional immunohistochemical staining for other lung-specific markers is performed (*Table 1*). Cytokeratins (CKs) are the next useful markers that are analyzed. Cytokeratins are intermediate filaments of the cell's cytoskeleton found in epithelial cells and are made up of keratin-containing proteins. The CKs are coded by a family of 30 different genes, of which 20 are expressed in epithelial cells. Epithelial cell CK expression depends on the type of epithelium and its differentiation state. Cytokeratin expression is often organ- or tissue- specific, allowing a CK profile to assist in the classification of the organ or cell of origin of a cancer. In epithelial cells, CKs are broadly divided into type I CKs (CKs 1-9), which are acidic, and type II CKs (CKs 10-20), which are basic or neutral. Though extremely helpful in classifying a tumor's primary cell of origin, the CKs are less specific markers than TTF-1. Squamous cell and small cell carcinomas of the lung typically do not express either CK 7 or CK 20. Squamous cells, however, strongly express CK 5 and 6. Small cell carcinomas rarely express CK 7 or CK 20, but do express CK 18. In contrast, lung adenocarcinomas express CK 7 and are negative for CK 20, CK 5 and CK 6. Unfortunately, adenocarcinomas of the breast and of gynecologic origin also

Table 1. Immunohistochemical Staining Results in Lung Cancer					
Tumor Cell Type	**TTF-1**	**CK 5/6**	**CK 7**	**CK 20**	**Chromogranin/ synaptophysin/CD 56**
Squamous	-	+	-	-	-
Adeno	+	-	+	-	-
Large cell	+/-	-	+	-	-
Large cell neuroendocrine	+/-	-	+/-	-	+
Small cell	+	-	-	-	+
Carcinoid	+/-	-	+/-	-	+

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show this pattern of CK expression and must be excluded radiographically. Tumors of the gastrointestinal tract typically have the reverse profile: they are CK 7 negative, but CK 20 positive. Some tumors, such as renal carcinomas, are negative for both CK 7 and CK 20, while others express both of these CKs, such as pancreatic carcinoma.

In cases in which radiographic imaging is clearly consistent with a lung primary, or cases in which the tumor expression of TTF-1, CK 7 and CK 20 are consistent with a tumor of pulmonary origin, the second step is to classify the tumor into one of the subcategories of lung carcinoma. Although most tumors fall clearly into one of the histologic categories based on H & E staining characteristics, some tumors are so poorly differentiated that they no longer retain the characteristic architecture of their lineage. Historically, tumors that are not small cell carcinoma and lack the characteristic features of either an adenocarcinoma or squamous cell carcinoma have been placed in the enigmatic category of large cell carcinoma. The question naturally arises, is large cell carcinoma truly a different type of tumor, or is it really just poorly-differentiated adenocarcinoma or squamous cell carcinoma? In this scenario, immunohistochemical staining for CK expression is the most useful. Squamous cells in the body, both benign and malignant, express large amounts of CK 5 and 6 and inconsistently express CK 7. Adenocarcinoma and large cell carcinomas of the lung, on the other hand, do not express CK 5 or 6 but do express CK 7.

Cytokeratin staining profiles can handily distinguish squamous cell tumors from the adenocarcinomas and large cell undifferentiated lung cancers, but how do we separate adenocarcinomas from large cell carcinomas? This distinction becomes problematic, even marshalling the vast array of immunostains at our disposal. Currently, no stain can definitively separate adenocarcinoma from the general category of large cell carcinoma, although a specific subcategory of large cell carcinoma, large cell neuroendocrine carcinoma (LCNC), can be identified by histologic appearance and immunohistochemistry. Neuroendocrine cells are found in almost every organ and give rise to both carcinoid tumors and small cell carcinomas in various organs. While carcinoids are generally benign, they behave unpredictably and can be clinically aggressive, despite a rather bland appearance. However, small cell carcinomas, the least well-differentiated

neuroendocrine carcinomas, behave aggressively and are treated very differently from other types of lung cancer. For many years, small cell carcinoma and typical/atypical carcinoid were the only recognized neuroendocrine tumors in the lung. With the advent of immunohistochemistry, it became evident that a subset of large cell carcinomas expressed the same neuroendocrine markers found in small cell carcinoma and carcinoid, namely chromogranin A, synaptophysin and CD 56 (*Table 1*). Chromogranin A is a member of the chromogranin family of neuroendocrine secretory peptides and is found in secretory vesicles of neurons and endocrine cells. It is the precursor to many neuroendocrine peptides such as catestatin, pancreastatin and vasostatin. Synaptophysin is a glycoprotein typically found in neuroendocrine cells that participates in synaptic transmission, but its function is not clear. Due to its presence in neuroendocrine cells as a marker of synapses, it has also become a biomarker for neuroendocrine tumors. CD 56 is also called neural cell adhesion molecule (NCAM). It also is a glycoprotein expressed on the cell surface and normally expressed by NK cells, activated T cells, brain and cerebellar tissue, as well as neuroendocrine tissue. It is found in a number of tumors besides small cell lung cancer including myeloma, myeloid leukemia, neuroendocrine tumors, Wilms' tumor, adult neuroblastoma, NK/T cell lymphomas, pancreatic acinar cell carcinoma, pheochromocytoma, and paraganglioma.

When a series of large cell carcinomas with neuroendocrine differentiation (LCNC), defined by both histology and immunohistochemistry (chromogranin A, synaptophysin, CD 56) were studied, it became apparent that this subset behaved far more aggressively than typical large cell carcinoma and shared the same poor prognosis as small cell carcinoma. In a case series comparing the survival of patients with various neuroendocrine tumors of the lung,[2] there was no difference in stage-specific survival between small cell carcinoma and LCNC. Given the small numbers of LCNC tumors available for study, it is not clear if there is a relationship between the degree of neuroendocrine differentiation, as reflected by the number of neuroendocrine markers expressed, and tumor behavior. Given the apparent change in prognosis with any degree of neuroendocrine differentiation, some have suggested that at least three different neuroendocrine markers should be used to enhance sensitivity in diagnosing this subtype of large cell carcinoma.[3]

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Immunohistochemical Markers In Guiding Therapy

In addition to providing important prognostic information, immunohistochemistry can be used to guide pharmacologic therapy for cancer. The use of immunohistochemistry for this purpose began with the determination of steroid hormone receptor (estrogen and progesterone) status in breast cancer and advanced with the identification of HER2 as a prognostic and therapeutic target in breast cancer. Tamoxifen, newer anti-estrogen agents, and the anti-HER2 drugs trastuzumab (Herceptin®) and lapatanib (Tykerb®) are effective therapy for a subset of women whose tumors express the estrogen receptor and/or HER2. Therefore, staining breast tumors for steroid hormone receptors and HER2 has become standard practice in pathology and guides therapy. Given studies of HER2 test performance,[4] immunohistochemistry is often used as the first-line test for HER2 expression due to its low cost, with more expensive *in situ* hybridization for HER2 gene amplification used in cases with borderline staining.

Unlike breast cancer, the role of immunohistochemistry in predicting pharmacologic response in lung cancer has been somewhat more problematic. Many lung cancers express high levels of the epidermal growth factor receptor (EGFR) and are therefore potential targets for pharmacologic therapies that directly target EGFR or antagonize EGFR tyrosine kinase, such as erlotinib (Tarceva®) and gefitinib (Iressa®). Cetuximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody that binds to EGFR with high specificity and with a higher affinity than epidermal growth factor, thus blocking ligand-induced phosphorylation of EGFR. In addition, its human IgG1 backbone seems to trigger immunological mechanisms that further potentiate these effects. It has not yet been approved by the U.S. FDA for use in lung cancer but is under investigation. Contrary to expectations, however, there is not a clear relationship between the expression of EGFR by immunohistochemisty, EGFR gene amplification by fluorescence *in situ* hybridization (FISH) and the response of the tumor to the anti-EGFR therapy cetuximab (Erbitux®).[5,6] The discordance between immunohistochemistry, which identifies protein expression, and FISH, which identifies gene amplification or translocation, may reflect a number of potential discrepancies such as transcriptional regulation or the effect of mutations on both the stability of EGFR mRNA

and the resultant protein. More importantly, the proliferative effect of EGFR is related to its activation status rather than the mass of its expression. Therefore, understanding EGFR's activation status may be a better predictor of response to receptor antagonists. Since the presence of mutations in EGFR can lead to constitutive activation of the receptor, molecular mutation analysis via polymerase chain reaction (PCR) has become important in the clinical management of patients, guiding the use of small molecule tyrosine kinase inhibitors (erlotinib, gefitinib).[7] Molecular studies for EGFR mutation are typically 20 times more costly than immunohistochemical approaches. Currently, immunohistochemical stains for specific protein epitopes only present in the mutated EGFR protein are under development, but they are difficult to devise because the antibody must have very high affinity and specificity for a relatively small epitope of the protein.

Another promising development in the treatment of lung cancer is the finding that many non-small cell lung cancers have a translocation of the anaplastic lymphoma kinase (ALK) gene. The genetic translocation creates a fusion gene that enhances the growth and survival of tumor cells. Drugs that specifically inhibit ALK are under development with early results that appear promising. Currently, FISH is the technique of choice for identifying this translocation. Since the gene translocation leads to a unique fusion protein composed of the N-terminal end of echinoderm microtubule-associated protein-like 4 (EML4) fused to the intracellular kinase domain of ALK,[8] there is the potential that antibodies could be generated to the unique epitopes of the fusion protein. While at this time neither mutation/translocation-specific nor activation-specific receptor antibodies are in widespread use by clinical laboratories, it is hoped that mutation/translocation/activation-specific immunohistochemistry may provide a more cost-effective approach to directed therapy in lung cancer in the future.

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Emerging Data in Lung Cancer Screening

By James L. Mulshine, MD

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Lung cancer remains the most lethal cancer in the world. The majority of new lung cancers are detected in the advanced stages when long term survival is improbable.[1] Thomas L. Petty, MD, whose recent death was a loss to all of us, was an enthusiastic advocate of early lung cancer management strategies. Over the last decades of his rich life, he focused his passionate efforts with Geno Saccamano, PhD, MD, Joel Bechtel, MD and others, on proving the benefits of early lung cancer detection. This work was motivated by their shared experience in dealing with the inevitable outcome of advanced lung cancer.

A number of new publications outline significant successes with aspects of CT-based lung cancer screening. While this strategy to systematically find lung cancer earlier has inherent appeal, there are a number of reports that question the theoretical as well as actual benefit of lung cancer screening. Against this backdrop, an intense debate is swirling about the value of screening for other cancers, such as breast cancer and prostate cancer.[2,3] It has been challenging to understand how the same evidence base could support such disparate conclusions about efficacy. However, with colon cancer screening, where the data showing benefit is established, the poor compliance rates suggest confusion on the part of the public as well as the medical profession about the benefit of population-based, early detection efforts.[4] In this tumultuous setting, the remarkable progress occurring with CT-based lung cancer screening is easily overlooked or misunderstood. Therefore, it is timely to briefly explore the positive trends emerging with lung cancer screening research.

Does size matter?

An early challenge to the potential value of detection of pre-symptomatic lung cancer was the assertion that finding smaller tumors using screening CT would not improve lung cancer outcomes.[5] This so-called "does size matter question" has been squarely resolved with the comprehensive analysis by the IASLC staging group.[6] This massive effort using clinical outcomes from over 67,000 patients has definitively reconfirmed the earlier findings of Mountain, Martini and others that larger tumor size does correlate highly with poorer disease outcome.[7,8]

From two CT screening trials involving high-risk individuals published in the *New England Journal of Medicine*, detection of stage I lung cancer ranged from a frequency of 73.7% (42 cases) on annual follow up in over 7,000 subjects in the NELSON study,[9] to 85% (412 cases) in over 31,000 subjects in the I-ELCAP series.[10] In the I-ELCAP series, the mean size of the detected baseline tumors was 1.5 cm and 0.9 cm for annual follow up cases. The expected outcomes with these smaller screen-detected primary cancers is likely to be much more favorable based on the new lung cancer staging classification.[6]

Are 98 percent of lung nodules falsely positive?

The systematic identification of lung cancer in large populations of high-risk individuals is a new pattern of care and has been a stressful challenge at virtually all institutions starting lung cancer screening programs. Reports in the literature comment on the difficulty in sorting through many pulmonary abnormalities in the search for clinically significant lung cancer.[11] The transition from the standard workup of a solitary pulmonary nodule in a patient presenting with lung cancer to the efficient workup of a high-risk individual undergoing screening involves a significant learning curve. In their commentary, Swensen and co-workers[11] reported that 70% of participants had one or more non-calcified lung nodules, and that 98% of these nodules

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were falsely positive. This and similar articles suggest that the complexity of finding clinically significant lung cancer employing CT-based screening was a paralyzing challenge in screening implementation.

There have, however, also been reports describing a systematic approach to nodule workup in CT-based screening studies. Libby and co-workers presented a more disciplined approach to the diagnostic workup of the CT scan-identified lung nodule.[12] Other groups have also reported more efficient approaches to the workup of suspicious nodules in the screening setting.[13,14] The recent paper by Croswell[15] suggested a false positive rate with spiral CT screening of about 33% after two annual screening rounds. However, in this report of a small pilot study that included an undefined number of older single detector scans using 0.5 cm collimation, a 3 mm cut-off for the baseline suspicious nodule, and an undefined diagnostic workup protocol, we are reminded how fast this field has progressed over the last decade.

This reported high false positivity rate underscores the importance of optimizing screening management parameters along the lines of the study design of the randomized NELSON trial, which was associated with profoundly more favorable diagnostic efficiency.[9] A key strategy to reduce the rate of false-positive diagnosis in lung cancer screening trials was to use the rate of nodule growth to differentiate clinically aggressive lung cancer from benign lesions.[16] Yankelevitz and co-workers[16] introduced the approach of measuring the interval growth of suspicious nodules to determine which nodules were growing at a rate consistent with a clinically significant lung cancer. This approach was recently applied by the NELSON screening program, a population-based lung cancer screening trial in the Netherlands and Belgium.[9] The NELSON group adapted this growth rate-filter strategy for their diagnostic workup in over 7,000 subjects evaluated in the experimental arm of their randomized trial. With this approach, they achieved a diagnostic sensitivity of 95% and a specificity of 99% on the baseline scan. They also reported a similar diagnostic workup accuracy rate on the annual follow up scan. While these performance numbers are not optimal, they compared quite favorably to diagnostic efficiency associated with other types of cancer screening tools, including those for breast cancer and prostate cancer.[17,18] The diagnostic sensitivity of screening mammography has been reported to

be on the order of 68%. Prostate cancer screening detection using prostate-specific antigen (PSA) has been reported to have a sensitivity of 78-100% with a specificity of 6-66%. Decades of research, especially for breast cancer, have been required to define the currently accepted diagnostic approach. In contrast, the diagnostic workup for CT-based early detection of lung cancer is still a new process, and there has been only limited research in the area of screening workup optimization.

The performance of the diagnostic approach in the NELSON trial is not an isolated finding. In a rigorous analysis of a published series of CT-based lung cancer screening trials, the mean sensitivity of cancer detection was 97%.[19] Therefore, acceptable performance of a diagnostic approach to finding lung cancers in asymptomatic, high-risk populations does seem feasible. The favorable results reported by the NELSON investigators reflect the rigor with which they approached the process of population-based CT screening. Like the investigators from the I-ELCAP, each step in the screening process was isolated and analyzed to optimize the process. In both efforts, quality control measures were defined and implemented across all study sites. The need for rigor and quality control in the lung cancer screening process is a critical component of minimizing the potential harm inherent in the screening process.[20]

Inherent to the screening process is the possibility of finding lung cancers that may not be sufficiently aggressive to constitute a mortality threat to an individual. This concept of "overdiagnosis" has been a focus of considerable discussion about screening benefit. In a large study of the California State Tumor Registry involving over 100,000 cases of lung cancer,[21] stage I lung cancer was lethal in over 90% of cases in which the patient declined care. The conclusion of that large analysis was that compelling evidence did not exist for a major contribution for overdiagnosis in the California experience.

Another positive finding in this regard is that serial, large epidemiological studies have led to the development of lung cancer risk models that use information beyond smoking history and age to more precisely define elevated risk for lung cancer.[22,23] While none of these tools has yet been validated for use in lung cancer screening trials, it is possible that identifying a population at higher risk for lung cancer with great precision will allow more efficient and potentially more economical lung cancer detection.

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To come full circle, the five year follow up of the use of a simple risk assessment tool in lung cancer screening was the subject of one of Dr. Petty's last research papers. This study,[24] by Dr. Joel Bechtel and colleagues, demonstrates how even a small group can contribute to the research process of defining the optimal approach to finding asymptomatic lung cancer. In Grand Junction, CO, the investigators evaluated the use of a simple questionnaire to elucidate a "higher risk" group based on known lung cancer risk factors (age ≥ 50, and at least one of the following: ≥ 30 pack year smoking history, asbestos or mining dust exposure, or family history of lung, esophageal, or laryngeal cancer) so that their early lung cancer detection efforts could be more efficient. Grand Junction, CO holds a special place in the history of lung cancer research, as this is where Dr. Geno Saccomanno conducted his pioneering work on sputum cytology-based early lung cancer detection. He worked in the Colorado plateau because that area contained an abundance of uranium and heavily smoking uranium miners. The combination led to an extraordinary rate of lung cancer in that area prior to the involvement of OSHA several decades ago to reduce miner exposure to radiation. This cluster of lung cancers in Western Colorado and his cytopathological early lung cancer detection work is what initially brought Drs. Saccomanno and Petty together.

In closing, smaller lung cancers have conclusively better outcomes. The diagnostic workup for suspicious thoracic nodules is becoming more efficient, and large study groups are achieving excellent results. Tools to identify clinically aggressive lung cancer are emerging, but the predominant behavior of clinically identified lung cancer is very aggressive. These developments bode well for the eventual objective validation of CT-based lung cancer screening, but this will require continued focus on implementing and then continuously improving the CT screening clinical management process. Dr. Petty was excited about the potential of CT-based lung cancer screening. More than once he commented that the positive results emerging in this field were one of the few things that made him wish to be a young man again.

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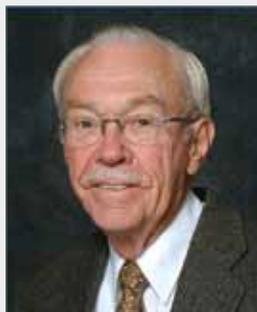
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