Lung Cancer Treatment: Many Disciplines, One Goal

Lung cancer is the leading cause of cancer death in both men and women in the United States, with more than 150,000 deaths annually. This is more than the next three leading causes of cancer death combined.

For years, there was not much new to report about lung cancer, and there has not been a significant improvement in lung cancer survival in the past 25 years. Fortunately, the future holds promise, thanks in part to novel screening methods, innovative diagnostics, new treatment techniques, and personalized medicine approaches, all of which are being developed and employed at UPMC and the University of Pittsburgh Cancer Institute (UPCI).

UPMC CancerCenter Lung Cancer Specialty Care, co-directed by David Wilson, MD, MPH, of the Division of Pulmonary, Allergy and Critical Care Medicine, Mark Socinski, MD, of the Division of Hematology/Oncology, and James Luketich, MD, Department of Cardiothoracic Surgery, is a multidisciplinary clinical and research program that provides patients with convenient access to pulmonologists, medical oncologists, radiation oncologists, and thoracic surgeons, all focused on lung cancer.

Complementing the clinical services is a large and varied research program that includes the endowed Georgia Cooper Lung Cancer Research Registry, the Specialized Program of Research Excellence (SPORE) in lung cancer — one of only nine in the United States — and many clinical trials for all types and stages of lung cancer that offer exciting new treatment options.

Research into defining new biological tools for the identification of lung cancer is leading to new options for prevention and early detection. This issue of Respiratory Reader highlights some of these detection and treatment methods through a discussion of lung cancer screening, a case of stereotactic body radiotherapy (SBRT), approaches to personalized lung cancer treatment, and a review of advanced bronchoscopy techniques.

Through the combined clinical and research efforts of the Division of Pulmonary, Allergy and Critical Care Medicine; UPCI; UPMC CancerCenter Lung Cancer Specialty Care; the Division of Hematology/Oncology; and the Department of Cardiothoracic Surgery, UPMC is moving closer to advancing the diagnosis, treatment, and management of patients with lung cancer. Experts from these disciplines aim to reach the ambitious goals of improving long-term outcomes for lung cancer patients and their families, as well as developing innovative methods to support prevention and early detection.
Lung Cancer Screening

Christopher N. Faber, MD
Associate Professor, Division of Pulmonary, Allergy, and Critical Care Medicine

Toni Opalko, RN
Outpatient Nurse Coordinator, Division of Pulmonary, Allergy, and Critical Care Medicine

Cancer is second only to heart disease as the leading cause of death in the United States, and lung cancer is the most common cause of cancer-related deaths in both men and women. Risk factors for lung cancer include smoking, environmental exposures (second-hand smoke, asbestos, radiation), pulmonary fibrosis, and HIV infection. Overall, the five-year survival rate for lung cancer is poor; currently estimated at about 16%. Prognosis of non-small-cell lung cancer is related to stage, with median survivals of about four to five years for Stage I disease, two to two-and-a-half years for Stage II disease, and about one year for Stage III disease. Prognosis of non-small-cell lung cancer is also related to histologic cell type. Bronchoalveolar cell carcinoma, now termed adenocarcinoma in situ or minimally invasive adenocarcinoma, has the best survival rate; large-cell and invasive adenocarcinomas carry the worst prognosis.

Given the dismal survival for advanced stage disease, one would assume that early detection of lung cancer would lead to improved outcomes. Prior to 2010, this had not been proven. An early attempt at screening, the Mayo Lung Project, showed that screening with chest films and sputum cytology could detect more resectable lung cancers, but resulted in no difference in lung cancer mortality between those subjects who were aggressively monitored with radiographs and cytology and those who were not. The Pittsburgh Lung Screening Study (PLuSS) evaluated the use of low-dose CT as a means for screening from 2002 to 2005. In more than 3,400 smokers or ex-smokers, age 50 to 79, 40.6% had lung nodules detected by low-dose CT. There were 80 lung cancers detected in this population; 53 noted at the first screen and the remainder at follow-up. Of the 80 cancers found in the PLuSS study, half were early stage. About one-third (28/80) of the cancers were not present on the original CT. Of these subsequent cancers, 37% (10/27) were small-cell carcinomas. 82 patients underwent thoracotomy or video-assisted thoracic surgery (VATS) for lung nodules. Of these patients, 54 had lung cancer and 28 had a non-cancer diagnosis. The PLuSS study concluded that CT detects many indeterminate nodules, as well as early lung cancer and that there was a tendency toward “overly aggressive” diagnostic evaluation.

Between 2002 and 2004, the National Lung Screening Trial (NLST) screened nearly 50,000 patients between the ages of 55 and 74 who were current or ex-smokers and who had at least a 30 pack-year history of smoking. Half of the study population received yearly CT scans and half received yearly chest films for a total of three imaging studies in two years. At the time of publication, there was a six-year follow-up. The overwhelming majority of positive screens (96.4% of CT scans and 94.5% of chest x-rays) were false positive studies. Lung cancer caused 25% of the deaths during this period. Lung cancer mortality was reduced by 20% in the CT-screened group, and overall mortality was reduced by 6.7%. So, 320 patients would need to be screened in order to prevent one cancer-related mortality. The NLST was the first trial to demonstrate improved mortality with lung cancer screening.

There are several real and potential disadvantages to screening CT. First, CT scans expose patients to radiation. A low-dose CT is about the equivalent to 15 chest x-rays. A standard CT is equivalent to 80 chest x-rays (as a means of comparison, mammography is equivalent of four chest x-rays). Secondly, the many false positive studies can potentially lead to additional tests and procedures that add cost and risk to the patient with no tangible benefit, while causing undue worry and stress. Finally, many of the abnormalities detected by screening CT were ground glass opacities, which often represent adenocarcinoma in situ or minimally invasive adenocarcinomas (formerly bronchoalveolar carcinomas). These cancers tend to have a longer doubling time and have less impact on overall lung cancer mortality.

Detection of these cancers by screening CT may result in interventions that are not ultimately beneficial to the patient. Therefore, it is essential that the patient follow up with specialists knowledgeable in screening CT and in lung cancer management.

The true cost benefit of lung cancer screening with low-dose CT has yet to be accurately calculated. Therefore, neither the Center for Medicine Services (CMS) nor private insurance carriers cover screening CT. Furthermore, there is no CPT code that allows physicians to order the low-dose CT screening study. In response to the anticipated demand for this service before the publication of the NLST results in June 2011, the UPMC Comprehensive Lung Center, in collaboration with the Department of Imaging Services at UPMC Presbyterian, established a Lung Cancer Screening Clinic at the Oakland campus. This clinic is run as a group visit model and is directed by a nurse. Patients are charged a flat fee and receive a 20-minute presentation on the program, including the benefits and limitations of screening CT. They then receive a low-dose CT, after which both the patient and their primary care physician (PCP) receive a letter with follow-up recommendations. If there are no abnormalities, they are instructed to follow up in one year, according the NLST protocol. To date, 36 patients have been screened; 39% had lung nodules, none of them suspicious for lung cancer, and 47% had coronary calcifications indicative of coronary atherosclerosis.

Suggested reading:
CASE PRESENTATION: Personalized Medicine: Use of Genetics to Individualize Lung Cancer Therapy

Liza C. Villaruz, MD  
Assistant Professor, Division of Hematology/Oncology

Mark A. Socinski, MD  
Professor of Medicine, Division of Hematology/Oncology

Genetic-based medical therapy was once a futuristic consideration that only researchers could use. Now, with new breakthroughs and increased availability of genetic testing, personalized medicine is practiced every day at UPMC. We present two cases here for discussion and review.

Case 1
A 67-year-old never-smoking female presented with a one-month history of progressive shortness of breath and was found on chest X-ray and CT scan to have a large left-sided pleural effusion and post-obstructive consolidation of the left upper lobe, in addition to innumerable bilateral pulmonary nodules, multiple bony metastases, a hypoattenuating lesion of the liver, and a 5 cm right kidney mass. Thoracic surgery subsequently performed a flexible bronchoscopy, a left-sided video-assisted thoracoscopic surgery with drainage of the pleural effusion, talc pleurodesis, and pleural biopsies.

The patient was found to have a TTF-1-positive adenocarcinoma of lung origin. Subsequent mutational testing revealed an EGFR exon 19 deletion, which is a sensitizing mutation to targeted therapy with erlotinib, an EGFR tyrosine kinase inhibitor (TKI). The patient underwent whole-brain radiotherapy and was placed on erlotinib with a dramatic response in both her CNS and systemic disease (Figure 1).

Case 2
A 53-year-old never-smoking male, originally treated with a right middle lobectomy for a T1N0 lung adenocarcinoma, recurred with significant increase in his mediastinal lymphadenopathy. A subsequent mediastinoscopy confirmed recurrent lung adenocarcinoma, and the patient was treated with platinum-based doublet chemotherapy. He had progression of his disease and was treated with erlotinib for one year after which he had further disease progression. He was then placed on pemetrexed and bevacizumab for 19 cycles with a partial response to therapy. The patient experienced myelosuppression and was given a treatment holiday. He then resumed therapy with pemetrexed and received two cycles, during which time he was admitted with rapidly progressive dyspnea and decline in his performance status. He was found to have a right perihilar mass and a malignant right-sided pleural effusion, for which he had a therapeutic thoracentesis. The patient had never been genotyped; standard mutational testing revealed a chromosomal translocation involving the ROS1 gene, a receptor tyrosine kinase of the insulin receptor family, which is a novel oncogenic driver associated with significant responses to crizotinib therapy. The patient was placed on crizotinib and had a complete response with improvement in his performance status (Figure 2).

Non-small-cell lung cancer (NSCLC) was historically treated as a single disease entity, and palliative chemotherapy in the metastatic setting resulted in modest survival gains and preservation of quality of life. The identification of driver mutations and the development of molecularly targeted agents have permanently shifted the landscape of NSCLC therapy toward a personalized approach. The Lung Cancer Mutation Consortium (LCMC) represents a 14-institution cooperative effort, in which the University of Pittsburgh participates, which accrued and genotyped 1,000 patients with advanced adenocarcinomas. An underlying oncogenic driver was identified in 60% of patients, and the vast majority of these mutations (97%) are mutually exclusive (Figure 3).
**CASE PRESENTATION:**
The Emerging Role of Stereotactic Body Radiotherapy in Early-Stage Lung Cancer

A 55-year-old male with a 40-pack-year history of smoking is found to have a 1.5 cm suspicious right upper lobe nodule on CT of the chest (see Figure 1A). CT-guided biopsy of this nodule revealed a diagnosis of non-small-cell lung cancer (NSCLC), adenocarcinoma type (see Image 1B). Subsequent staging PET-CT study showed no evidence of distant metastasis; however noted equivocal mediastinal lymph nodes. He was ultimately referred to the Comprehensive Stereotactic Radiosurgery Program, part of UPMC CancerCenter.

Evaluated by both thoracic surgery and radiation oncology the same day, the patient was deemed medically inoperable based on advanced COPD and an associated poor pulmonary reserve. However, he was thought to be a potential candidate for definitive stereotactic body radiotherapy (SBRT) should an endobronchial-ultrasound-guided sampling of the equivocal mediastinal lymph nodes be negative for metastatic disease. The sampling was negative, and he elected to proceed with SBRT for his medically inoperable Stage I NSCLC.

Figure 1 A, B, C, D: Pretreatment CT (A) and PET/CT (B) showing 1.5 cm peripheral NSCLC in right upper lobe with near complete response on repeat CT (C) and PET/CT (D) 4-month post-SBRT.

Figure 2: SBRT treatment plan delivering 60Gy in 3 fraction of highly conformal radiotherapy to the right upper lobe lesion using Varian Trilogy Intensity Modulated Radiosurgery.
Using Varian Trilogy® Intensity Modulated Radiosurgery with dynamic respiratory compensation, he went on to receive 60 Gy in 3 SBRT fractions to the right upper lobe lesion over seven elapsed days without toxicity (see Figure 2). Four months post-SBRT, a follow-up PET-CT study was obtained (see Figure 1C and 1D) and showed a complete metabolic response and no evidence of treatment-related toxicity.

Despite advances in multimodality management, lung cancer remains the leading cause of cancer-related mortality. While only a minority of newly diagnosed NSCLC patients present as localized disease (15-20%), increased adoption of high-risk screening may translate into increased early detection. Surgical resection is the standard of care for Stage I NSCLC; however many patients, such as the case presented in this report, represent poor operative candidates due to baseline pulmonary dysfunction and comorbidities.

Building upon advances in radiation planning and delivery, SBRT has emerged as a noninvasive definitive therapy for early-stage NSCLC delivering high doses of increasingly conformal radiation therapy with an accuracy less than 1 mm that integrates radiation delivery with respiratory cycle motion (1). Multiple single institutional series, including pioneering collaborations between UPMC CancerCenter Radiation Oncology and Thoracic Surgery, suggest excellent local control less than 90% and minimal toxicity in medically inoperable patients (2).

These results were recently further substantiated in a cooperative Phase 2 study (RTOG-0236), demonstrating a three-year local control of 98% approaching, if not exceeding, prior reported surgical series for early-stage NSCLC (3). Building on these promising results in medically inoperable patients, numerous ongoing international trials including, Dutch ROSEL, RTOG 0618, and JCOG 0403, are comparing SBRT to definitive surgical resection in operable patients. The Comprehensive Stereotactic Radiosurgery Program offers patients with early-stage NSCLC a state-of-the-art, noninvasive definitive therapy in a multidisciplinary approach where radiation oncologists and thoracic surgeons collaboratively optimize the application of emerging technologies, such as SBRT, promising to challenge current paradigms and improve outcomes in the management of early-stage NSCLC.

**REFERENCES:**

CASE PRESENTATION:
Evolving Role of Advanced Bronchoscopy in Thoracic Oncology

James Luketich, MD
Henry T. Bohnson Professor and Chair,
Department of Cardiothoracic Surgery

David O. Wilson, MD, MPH
Associate Professor, Division of Pulmonary,
Allergy, and Critical Care Medicine

Jonathan D’Cunha, MD, PhD
Associate Professor, Department of
Cardiothoracic Surgery

Arjun Pennathur, MD
Assistant Professor, Department of
Cardiothoracic Surgery

Advanced bronchoscopy, including endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA) of mediastinal lymph nodes and electronavigational bronchoscopy (ENB) and biopsy for peripheral lung nodules, has greatly expanded the utility of bronchoscopic techniques in thoracic oncology. Accurate staging, and therefore management, of lung cancer requires access to the mediastinum for lymph node sampling.

A 64-year-old woman was referred for the evaluation of pathologically enlarged metabolically active mediastinal lymphadenopathy (Figure 1) on a routine restaging PET-CT scan. She was originally diagnosed with ER/PR/HER 2 negative breast cancer in 2009, and was treated with chemoradiation, but the chemotherapy was incomplete due to toxicity. She had a supraclavicular lymph node recurrence in 2007 treated with additional chemoradiation. A routine restaging PET-CT scan in March 2010 showed new pathologically enlarged and metabolically active mediastinal lymph nodes, and the patient was referred for biopsy. She felt well and was asymptomatic. She had a 40-pack-year smoking history, and her grandmother and uncle died of lung cancer.

It was felt the patient either had recurrent and metastatic breast cancer or sarcoid-like granulomatous inflammation in the mediastinal lymph nodes. EBUS-guided TBNA of level 4 paratracheal (Figure 2) and level 7 subcarinal lymph nodes was performed as an outpatient procedure, and recurrent and metastatic breast cancer was confirmed.

**EBUS**

There are multiple approaches to biopsy mediastinal lymph nodes (Table 1). Lymph node enlargement on CT scan does not constitute proof of metastatic disease. In contrast to mediastinoscopy and/or mediastinotomy, EBUS-TBNA allows access to posterior subcarinal and hilar lymph node stations that would otherwise be inaccessible. EBUS-TBNA also can be performed in situations where mediastinoscopy is difficult or overly risky, such as in patients with a tracheostomy or cervical spine deformity, or in patients with a prior mediastinoscopy. The advantages of EBUS-TBNA are 1) easily accomplished in outpatient bronchoscopy lab with IV sedation, 2) safest risk profile, and 3) most time-efficient.

EBUS-TBNA provides access to paratracheal (level 4), subcarinal, including posterior (level 7), and hilar (levels 10, 11) lymph nodes. Dedicated biopsy needles (21-gauge) are inserted through the 2 mm working channel to perform aspirations (Figure 2) for cytology. If there are difficulties achieving adequate EBUS images, a saline-filled balloon surrounding the transducer can be inflated to improve image quality. There also are Doppler capabilities to allow vascular structure differentiation, minimizing unintended vascular puncture. Many well-designed studies have demonstrated that the diagnostic yield from

Figure 1A: Fused PET/CT image showing enlarged metabolically active right and left level 4 paratracheal lymphadenopathy.

Figure 1B: Fused PET/CT image showing enlarged metabolically active level 7 subcarinal and right level 10 hilar lymphadenopathy.
EBUS-TBNA can approach 90% sensitivity and negative predictive value, with 100% specificity. In addition, EBUS-TBNA is superior to CT or PET-CT at detecting hilar and mediastinal metastatic disease, especially identifying regional nodal metastases in radiographically “normal” lymph nodes. Given the importance of accurate mediastinal lymph node assessment in lung cancer staging, treatment, and prognosis, the ability of EBUS to allow for more accurate staging is a significant advance.

UPMC specialists have been performing EBUS-TBNA since October 2006. Our initial experience has been published (1, 2) and confirms the safety and clinical utility of this procedure as a diagnostic tool in patients with mediastinal lymphadenopathy. EBUS-TBNA is especially useful for mediastinal staging for lung cancer, with the added benefit that it can be repeated, such as post neoadjuvant chemotherapy for pathologic restaging. It has become the procedure of choice for the diagnosis of sarcoidosis. It is very useful for documenting cancer recurrence as in the case presented.

The patient was treated with chemotherapy and achieved remission. Three years later, a routine restaging CT chest showed a growing 9 mm LUL nodule that was present in retrospect the year before (Figure 3). The nodule was adjacent to a bronchovascular bundle and had a positive bronchus sign (see arrow Figure 3). There were no mediastinal abnormalities.

It was felt that the new, growing solitary LUL nodule most likely represented malignancy. The issue was whether it was recurrent and metastatic breast cancer, or lung cancer. If it was lung cancer, surgical resection or stereotactic radiation would be favored. If it was recurrent breast cancer, then additional systemic therapy would be indicated. Despite the relative small size of the nodule, the presence of a bronchus sign is a favorable indicator for the success of ENB. Given the patient’s prior favorable experience with EBUS, she elected to proceed and ENB was carried out in the bronchoscopy suite under IV sedation. The procedure was well-tolerated and the patient was discharged home within four hours of her arrival. The biopsy showed adenocarcinoma, with primary lung cancer favored based on immunohistochemistry profile of the tumor.

ENB

ENB works on the same triangulation principle as a global positioning system and allows the bronchoscopist to direct a steerable probe through the airways to a peripheral target. ENB combines three technologies: 1) planning software that converts DICOM images from a CT scan into 3D reconstruction and virtual bronchoscopy of the airways, 2) steerable sensor probe designed with the ability to navigate turns in the endobronchial tree, and 3) electromagnetic navigational board that emits low frequency electromagnetic waves and is connected to a computer containing the planning data. Volumetric high-resolution CT images are acquired using a specialized algorithm from which a virtual pathway fused with real-time bronchoscopy images is constructed allowing access to peripheral lung lesions as small as 1 cm that would otherwise be hidden. To do this, the bronchoscopist passes the steerable sensor through the bronchoscope to the targeted lesion utilizing known landmarks in the patients airways determined by triangulation from the electromagnetic field surrounding the patient. Acknowledging a rather steep learning curve for ENB, the diagnostic yield approaches 70% in experienced centers such as UPMC. Factors that improve the diagnostic yield include larger nodule size and presence of bronchus sign (3).

Suggested reading:

MEDIASTINAL SAMPLING

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Table 1

| Techniques for mediastinal lymph node biopsy |

Figure 2: EBUS guided transbronchial needle aspiration of subcarinal lymph node.

Figure 3: CT image of LUL nodule with bronchus sign.
MEET THE LUNG CANCER TEAM

Division of Pulmonary, Allergy, and Critical Care Medicine

David O. Wilson, MD, MPH
Associate Professor of Medicine
Co-Director, Lung Cancer Center
Email: wilsondo@upmc.edu

Maria M. Crespo, MD, FCCP
Assistant Professor of Medicine
Email: crespomm@upmc.edu

Michael Donahoe, MD
Associate Professor of Medicine
Email: donahom@upmc.edu

Christopher N. Faber, MD
Assistant Professor of Medicine
Email: fabecn@upmc.edu

Khaled Fernainy, MD
Assistant Professor of Medicine
Email: fernainyke@upmc.edu

Bruce Johnson, MD
Assistant Professor of Medicine
Email: johnsonba2@upmc.edu

John W. Kreit, MD
Professor of Medicine
Email: kreitjw@upmc.edu

Phillip E. Lamberty, MD
Assistant Professor of Medicine
Email: lambertype@upmc.edu

Matthew E. Woodske, MD
Assistant Professor of Medicine
Email: woodskeme@upmc.edu

Department of Cardiothoracic Surgery

James D. Luketich, MD
Henry T. Bahnson Professor and Chair
Department of Cardiothoracic Surgery
Co-Director, Lung Cancer Center
Email: luketichjd@upmc.edu

Ghulam Abbass, MD, MHCM
Assistant Professor of Cardiothoracic Surgery
Email: abbasg@upmc.edu

Neil A. Christie, MD
Assistant Professor of Cardiothoracic Surgery
Email: christiena@upmc.edu

Jonathan D’Cunha, MD, PhD
Associate Professor of Cardiothoracic Surgery
Email: ddcunha@upmc.edu

Ryan M. Levy, MD
Assistant Professor of Cardiothoracic Surgery
Email: levyrm@upmc.edu

Arjun Pennathur, MD
Assistant Professor of Cardiothoracic Surgery
Email: pennathura@upmc.edu

Matthew J. Schuchert, MD
Assistant Professor of Cardiothoracic Surgery
Email: schuchertmj@upmc.edu

Department of Hematology/Oncology

Mark A. Socinski, MD
Professor of Medicine
Co-Director, Lung Cancer Center
Email: socinskima@upmc.edu

Steven A. Burton, MD
Assistant Professor of Medicine
Email: burtons@upmc.edu

David M. Friedland, MD
Assistant Professor of Medicine
Email: friedlandd@upmc.edu

Daniel P. Petro, MD
Assistant Professor of Medicine
Email: petrod@upmc.edu

Liza C. Villaruz, MD
Assistant Professor of Medicine
Email: villaruzl@upmc.edu

Department of Radiation Oncology

Brian J. Karlovits, DO
Assistant Professor of Radiation Oncology
Email: karlovitsbj@upmc.edu

Austin Vargo, MD
Radiation Oncology Resident
Email: vargoja2@upmc.edu

Referring a Patient

Referrals to UPMC for advanced bronchoscopy procedures, such as EBUS or ENB, or for consultation, can be made by calling the Lung Cancer Specialty Care Center at 412-623-5864.

Referrals to the UPMC Comprehensive Lung Center can be made by calling 412-692-2400.

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