LUNG CANCER TREATMENT: MANY DISCIPLINES, ONE GOAL

Lung cancer is the leading cause of cancer death in the U.S., with more than 150,000 deaths annually — more than the next three leading causes of cancer death combined. In the last 25 years, there have not been significant improvements in survival rates. Fortunately, novel screening methods, innovative diagnostics, new treatment techniques, and personalized medicine approaches all hold promise, and all are being developed and employed at UPMC and the University of Pittsburgh Cancer Institute (UPCI).

UPMC CancerCenter Lung Cancer Specialty Care is a multidisciplinary program that gives patients access to pulmonologists, medical oncologists, radiation oncologists, and thoracic surgeons, all focused on lung cancer. The program’s research program is large and varied, including the endowed Georgia Cooper Lung Cancer Research Registry, the Specialized Program of Research Excellence (SPORE) in lung cancer (one of only a few in the country), and many clinical trials for all types and stages of lung cancer.

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 Cancer Insights highlights some of these detection and treatment methods through literature reviews and case studies.

Through the combined clinical and research efforts of the Division of Pulmonary, Allergy and Critical Care Medicine at UPMC; 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 improve patients’ long-term outcomes, as well as develop innovative methods to support prevention and early detection — and, ultimately, save lives.
Immunotherapy and Lung Cancer: A New Frontier

The treatment of advanced lung cancer has undergone several revolutions since it became standard to aggressively treat patients, following studies in the late 1980s that showed an advantage over best supportive care (1). Early explorations of nonspecific immunotherapies, including animal-based monoclonal antibodies, failed to show any impact on survival and were largely abandoned.

As chemotherapy became established as standard treatment for advanced non-small-cell lung cancer (NSCLC) and regimens were refined, simultaneously researchers were developing chimeric and humanized monoclonal antibody technology. This structural refinement allowed trials to integrate the two approaches and resulted in landmark trials showing a survival advantage, albeit modest, with the integration of the monoclonal antibodies bevacizumab and cetuximab (2,3). One such trial randomized patients to standard chemotherapy using the regimen of paclitaxel and carboplatin plus or minus bevacizumab, which was to continue until disease progression. The bevacizumab arm showed a statistically significant survival advantage of two months (10.3 vs. 12.3 months), and the FDA approved this in 2006 as a standard treatment option (3).

While passive immunotherapy approaches were unsuccessful in improving outcomes in patients with lung cancer, more subtle manipulation of the immune response appears to be a potentially viable treatment option for patients with advanced disease. The ongoing study of tumor immunology has led to the understanding of immune checkpoints such as PD-1 (Figure 1). This inhibitory surface receptor on cytotoxic T-cells, when blocked, potentiates the antitumor immune response. The ligands for PD-1 are PD-L1 and PD-L2. Early trials of monoclonal antibodies directed against PD-1 and PD-L1 have shown consistent antitumor activity against pre-treated NSCLC, with response rates of 10 to 24% and progression-free interval of greater than six months in up to 31% (4,5,6). These exciting findings have led to a randomized clinical trial comparing docetaxel, a standard second line cytotoxic chemotherapy agent, to nivolumab, an anti–PD-1 antibody in patients with locally advanced or metastatic tumors. N Engl J Med 2015;372:2070-80. Erratum in: N Engl J Med 2015;372:2071

Active immunotherapy is another rapidly advancing branch of cancer immunotherapy. As previously mentioned, nonspecific vaccines such as BCG have been tested and are ineffective in lung cancer.

REFERENCES:

Figure 1: Immunotherapy mechanisms under investigation in lung cancer.
CASE STUDY: 
Personalized Medicine: Use of Genetics to Individualize Lung Cancer Therapy

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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. An MRI of the brain demonstrated innumerable supratentorial and infratentorial metastatic lesions. 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).
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, but 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.

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 medical comorbidities.
Most importantly, all targets, with the exception of AKT1, have linked clinical trials with single and combination agents. The importance of molecular profiling in the diagnostic evaluation of lung adenocarcinomas cannot be underestimated because of the therapeutic implications of finding a potentially druggable oncogenic driver. This paradigm is exemplified by the unprecedented response rates (70%) seen in EGFR-mutant NSCLC when treated with EGFR TKI therapy, ALK- positive NSCLC when treated with crizotinib (response rates also of 70%), and in the discovery and targeting of other novel oncogenic drivers like the ROS1 gene rearrangement.

As part of our participation in the LCMC, the University of Pittsburgh Cancer Institute performs routine molecular testing on all lung adenocarcinomas utilizing an eight-gene panel which consists of EGFR, KRAS, BRAF, PIK3CA, ALK, c-Met, RET, and ROS1. We currently have opened, or are in the process of opening, a clinical trial targeting each of these genomic subsets. The “old approach” to the diagnosis of lung cancer placed more emphasis on noninvasive techniques, often fine needle aspiration (FNA), with the goal of distinguishing small cell lung cancer (SCLC) from NSCLC. The “modern approach” has shifted toward more invasive approaches with an emphasis on core biopsies to ensure adequate tissue to both distinguish histology (not just SCLC from NSCLC, but also non-squamous from squamous cell carcinoma) and to complete molecular profiling. Bone lesions are no longer acceptable, as the decalcification process precludes interrogation of the DNA. The modern molecularly-driven treatment of NSCLC necessitates a multidisciplinary approach to the issue of tissue acquisition, and requires a close collaborative effort between medical oncologists, pulmonologists, thoracic surgeons, and interventional radiologists.

**REFERENCES:**

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 in greater 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:**
Advanced bronchoscopy, including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-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 metastatic breast cancer or sarcoid-like granulomatous inflammation in the mediastinal lymph nodes. EBUS-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 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 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 electronavigational bronchoscopy (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.

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

**Figure 3:** CT image of LUL nodule with bronchus sign.

**Table 1**

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**Suggested reading:**


**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).
**UPMC CancerCenter’s Network of Care**

The channels through which patients come to the community locations of UPMC CancerCenter for comprehensive cancer care may differ, but once a patient enters the system, they have access to an entire network of medical, radiation, and surgical oncologists, evidence-based treatment options, and the latest advances in cancer clinical care.

**A Network of Physicians and Locations**

At UPMC CancerCenter, we employ a hub-and-spoke model, anchored by our clinical and academic hub, Hillman Cancer Center, to offer cancer patients throughout western Pennsylvania and beyond convenient access to cancer care and innovative treatments close to home. This model of patient care provides easy access to care to an aging western Pennsylvania population and accommodates referrals between specialists at Hillman and our more than 35 locations.

With more than 180 affiliated oncologists, this network represents a collection of some of the nation’s most highly qualified and respected physicians and researchers in cancer medicine.

**Clinical Pathways Program**

Cancer care in your community at a UPMC CancerCenter offers the same high-value standards of care that you would expect at Hillman Cancer Center, thanks to the Clinical Pathways program. Developed by UPMC CancerCenter clinicians, Clinical Pathways provides uniform treatment plans for different types of cancer based on specific disease and patient parameters. Pathways, used throughout the UPMC CancerCenter, are constructed and maintained by disease-specific teams of physicians led by experts in academic and clinical medicine.

These physicians review published literature and clinical experience to determine the optimal treatment for a specific disease, stage-by-stage, taking into account common patient characteristics and presentations.

If more than one treatment regimen fits the “best” category, then our experts choose the regimen with the most favorable toxicity profile.

As a top priority for each Pathway, whenever applicable, patients are recommended to participate in relevant clinical trials. Pathways take into account current patient health status when recommending therapy, so that efficacy is maximized while toxicity is minimized. The program recognizes that there will always be circumstances where the recommended treatment is not appropriate for a given patient and allows for physician discretion in this and all circumstances.

All of UPMC CancerCenter use this system to be sure that each and every patient has access to the best available care and allows the CancerCenter to continuously monitor success and make adjustments vital to promoting the very best outcomes for all of our patients.

**Access to Clinical Trials**

Physicians understand that breakthroughs in research won’t make a real impact until they reach the patient. At UPMC CancerCenter and the University of Pittsburgh Cancer Institute (UPCI), our physicians and researchers collaborate to rapidly translate basic science into effective new strategies for the prevention, detection, and treatment of cancer.

Strategies include the development of vaccines to block the progression of many cancers, the incorporation of new technologies that allow physicians to more precisely target treatment, as well as advances in minimally-invasive surgical procedures that are leading to reduced recovery times and better outcomes for patients.

Our research efforts have been recognized continuously by the National Cancer Institute, which has awarded UPCI the top distinction of Comprehensive Cancer Center since 1990, cementing our commitment to developing a comprehensive research infrastructure that ultimately supports superior cancer care.

As one of the nation’s top centers for care and research, our nationally and internationally recognized specialists are changing the landscape of oncology.

For consults and referrals, call 412-647-2811.