

Thoracic Oncology Program

The Minimally Invasive Tissue Issue and the Thoracic Interventional Program

By Jonathan Puchalski, MD, MEd

Advances in diagnosing or treating lung lesions over the past several years can be likened to those in consumer electronics: TV has become high definition; the telephone has become cellular; and the internet has become high speed. In pulmonary and thoracic disease, the bronchoscope has become EBUS, fluoroscopy has become electromagnetic navigation, and tumor ablation has become lasers and more. In this edition of "advances," my colleagues and I discuss minimally invasive modalities employed by the Thoracic Interventional Program (TIP) to diagnose and treat lung cancer. TIP offers a comprehensive diagnostic and therapeutic team for patients with lung cancer. Our concentrated attention provides experience and expertise that distinguishes TIP as a unique program of excellence.

My focus is on diagnostic and therapeutic strategies for diseases that include mediastinal abnormalities, parenchymal lesions, and tumors obstructing the airways. When making a diagnosis, tissue is truly the issue. However, this extends not only to quality specimens, but also to tissue quantity. The diagnosis of medi-

astinal and parenchymal abnormalities has been *revolutionized* by the introduction of endobronchial ultrasound (EBUS) and electromagnetic navigation (EMN). EBUS comes in two major varieties: central and peripheral. Central EBUS enables the bronchoscopist to biopsy lymph nodes and masses in real-time and can be likened to mediastinoscopy, the current gold standard. The addition of on-site cytology can enable the **same day** diagnosis and staging of lung cancer, without any incisions. This technique far surpasses the diagnostic yield from "blind" transbronchial needle aspiration (TBNA).

The second type of endobronchial ultrasound, peripheral EBUS, uses a miniaturized ultrasound probe that goes through the bronchoscope into the periphery of the lung. Diagnostic yield is improved with peripheral EBUS as the bronchoscopist can confirm whether the biopsy tools are within, adjacent to, or outside of the lesion in question. This is something bronchoscopists can only make an educated guess about with fluoroscopy or older techniques.

Finally, a separate entity called electromagnetic navigation (EMN) provides "GPS" mapping of the airways into the lungs. Integrating the patient's CT scan, computer technology, and an electromagnetic platform, the bronchoscopist can navigate into distal generation bronchi and be guided to peripheral lesions. By combining this and peripheral ultrasound, the precision of the biopsy is greatly enhanced and incomparable to traditional methods of diagnosis. The risk of pneumothorax is less than transthoracic biopsies and the yield is naturally greater than parenchymal biopsies guided only by fluoroscopy. The cost of the equipment and training required to learn the technical aspects of these procedures has thus far limited its wide-spread use. Yale-New Haven Hospital boasts the most EBUS experience and the only EMN system in Connecticut. Both of these technologies provide significant advantages when obtaining tissue for a diagnosis or guiding treatment that is critical to the patient's care.

Sometimes, when a tumor is obstructing the patient's airway, the continued on page 2 ▶

The Cutting Edge of Thoracic Surgery: Getting More for Less

By Anthony W. Kim, MD, FACS

As outlined in the other articles in this "tissue issue," defining the diagnosis and stage of a patient's lung cancer with sufficient accuracy and detail is crucial in choosing the optimal treatment approach. Thoracic surgery plays an integral part in this process, meshing with the other disciplines of medicine and surgery (i.e., radiology, pathology, pulmonary medicine, medical, and radiation oncology).

There is an increased recognition that exactly how a test is performed has considerable impact on the accuracy of the results (1). Advances in technology and expertise in thoracic surgery have resulted in more tissue and greater accuracy through smaller and less painful incisions (2). As a part of the Yale Cancer Center Thoracic Oncology Program (TOP), dedicated thoracic continued on page 4 >



Editor's Letter


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Advances in the field of medicine sometimes improve our ability to make specific diagnoses. Other times, they make procedures less invasive, thereby decreasing morbidity or even mortality. It isn't often that medical advances truly revolutionize an entire field of patient care. In this issue, we analyze how new technology has enabled pulmonologists, thoracic surgeons, and medical oncologists to evaluate patients and individualize patient care in a way that escalates the treatment of lung cancer to a level that previously could only be imagined.

The Thoracic Interventional Program (TIP) was conceptualized by the leaders of the Thoracic Oncology Program (TOP). TIP enables a unique collaboration between pulmonologists and thoracic surgeons at Yale that focuses strictly on advancing patient care. Technological advances erase a blind approach and enable enhanced visualization during the biopsy of mediastinal lymph nodes, lung nodules or masses, and pleural disease. These advances include ultrasound (thoracic ultrasound, endobronchial ultrasound, or EBUS), electromagnetic navigation (GPS-type technology), and minimally invasive exploration of the pleura (thoracoscopy, pleuroscopy). By obtaining the right tissue in the least invasive manner, patients and clinicians can quickly advance to the next stages of care.

The medical oncologist relies on an accurate diagnosis for treating lung cancer. Whereas this used to mean strictly a microscopic examination, it now must often include genetic analyses in order to individualize patient care. By targeting chemotherapy based on gene mutations of each patient, oncologists can provide a new standard of care. At Yale, we emphasize not only high-quality biopsies that provide a diagnosis, but that also provide enough tissue to analyze specimens at the molecular level. The treatment of lung cancer in 2010 is much more advanced than a few years ago.

There has been exponential growth at Yale-New Haven Hospital with a dedicated interest in lung cancer. Whereas Smilow Cancer Hospital provides the physical plant, every discipline described in this issue has expanded. Dr. Puchalski has joined Dr. Tanoue and others in pulmonary medicine. Dr. Kim united with Drs. Detterbeck and Boffa in thoracic surgery. Dr. Decker has teamed up with Dr. Wilson in radiation oncology. Finally, Dr. Lynch teamed with Dr. Gettinger in medical oncology. Together, we provide a multidisciplinary approach that offers advanced technology in a minimally invasive approach to diagnosing and treating lung cancer. This premise fulfills a new promise for lung cancer, and is the basis for our minimally invasive tissue issue of *Advances*.

Sincerely,

 Jonathan Puchalski, MD, MEd

diagnosis is easier than the treatment. Lung cancer may cause significant airway obstruction which severely limits the quality and quantity of the patient's life. TIP offers a full spectrum of treatment and unique expertise in rigid bronchoscopy, stenting, and ablative techniques. The rigid bronchoscope provides a safe way of treating complex airway lesions with speed, better visualization, and improved control compared to flexible bronchoscopy alone. Not many physicians can claim expertise in rigid bronchoscopy. When the airway patency needs to be reestablished and rigid bronchoscopy alone fails, additional ablative strategies are employed. These techniques include electrocautery, argon plasma coagulation (APC), and laser surgery within the airway, and each requires expertise. Finally, the choice of stents (silicone, metal or hybrid; straight or Y-shaped; length, size and configuration) must be made by a physician trained in the placement and management of these devices. Despite the complex nature of these procedures, they are performed minimally invasively and often in the outpatient setting. They can seemingly instantaneously improve a patient's ability to breathe and offer major palliation as an integral component of care.

Finally, no review of interventional pulmonary techniques can be complete without discussing the critical management of pleural disease. Pleural effusions affect hundreds of thousands of people every year. At a basic level, the safety of a diagnostic thoracentesis improves with real-time ultrasonographic visualization of the pleural space. Ultrasound may also be used to place tunneled pleural catheters, a procedure for malignant pleural effusions that can typically be done as an outpatient without any radiation exposure. Defining pleural pathology is sometimes difficult and requires additional techniques that are minimally invasive. In his article beginning on page 1, Dr. Anthony Kim discusses techniques used in our multidisciplinary approach to pleural disease diagnosis and management. We take pride in our dedication to the evaluation and treatment of pleural disease, both in a clinical capacity and with our research interests.

In summary, the Thoracic Interventional Program (TIP) at Smilow Cancer Hospital at Yale-New Haven and Yale Cancer Center combines physicians from multiple specialties into one cohesive group to diagnose and manage complex thoracic disease. The diagnosis is enhanced by EBUS and EMN while the treatment could not be complete without options of ablative therapy. Finally, the extension of our pleural program facilitates the comprehensive evaluation and treatment of patients with diseases of the chest. When tissue is the issue, patients deserve the most sophisticated technology available using the least invasive techniques. This is the standard of the state's only comprehensive, collaborative group of physicians and care providers known as TIP.

CLINICAL TRIALS Thoracic Oncology Program



HIC 0904005074

A Phase III Randomized Trial of Adjuvant Chemotherapy With or Without Bevacizumab for Patients With Completely Resected Stage IB (≥ 4 cm) - IIIA Non-Small Cell Lung Cancer

PI: Scott Gettinger, MD
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HIC 0707002901

A Phase II Trial of Induction Carboplatin/Paclitaxel with Bevacizumab Followed by Concurrent Thoracic Conformal Radiation Therapy with Carboplatin/Paclitaxel, Bevacizumab and Erlotinib in Stage IIIA/B Non-Small Cell Lung Cancer

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HIC 0904005075

A Phase I Study of IPI-504 and Docetaxel in Patients with Advanced Solid Tumors

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HIC 0805003786

A Phase I/II Study of XL184 with or without Erlotinib in Subjects with Non-Small Cell Lung Cancer

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HIC 0708002987

A Phase I/II Study to Investigate the Safety, Tolerability, and Potential Activity of IPI-504 in Relapsed and/or Refractory Stage IIIb (with Malignant Pleural or Pericardial Effusion) or Stage IV NSCLC Patients

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HIC 0907005473

A Phase III, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 versus Docetaxel or Pemetrexed in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus

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HIC 0907005475

A Phase II Trial of PF-02341066 in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus

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HIC 0909005674

A Randomized Discontinuation Phase II Trial of Deforolimus in Non-Small Cell Lung Cancer Patients with KRAS Mutations

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HIC 0809004248

Sorafenib Long Term Extension Program (STEP)

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HIC 0811004507

Evaluation of Vorinostat in Combination with Palliative Radiotherapy for Patients with Non-Small Cell Lung Cancer

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HIC 0807004099

A Phase Ib, Open-label, Multi-dose, Multicenter, Dose-escalation Study of MDX-1106 in Subjects with Selected Advanced or Recurrent Malignancies

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HIC 0908005567

A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors (NSCLC and SCLC)

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HIC 0812004584

Vibration Resonance Imaging for Prediction of Postoperative Lung Function: A Multi-institutional Study

PI: Frank Detterbeck, MD
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surgeons who specialize exclusively in thoracic diseases, are at the forefront of these developments.

Mediastinoscopy is still the gold standard staging procedure to evaluate mediastinal lymph nodes in patients with lung cancer. Traditional mediastinoscopy involves getting small fragments of tissue via a 1 cm view at the end of a 15 cm lighted shaft. Through the addition of high-definition video technology to standard mediastinoscopy, videomediastinoscopy provides a full screen view, showing details and structures not previously able to be seen (Figure 1). The expanded view afforded by videomediastinoscopy allows complete dissection of the mediastinal structures, and

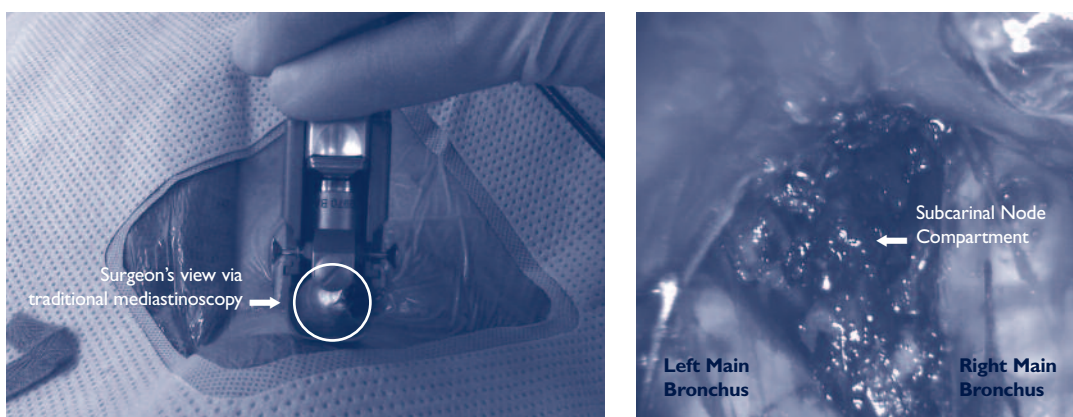
based on cytology alone. Thoracic surgery is a key component of the Yale Thoracic Interventional Program (TIP), which is an integrated service that works to achieve accurate diagnoses reliably using either needle-based techniques or thoracoscopy, as needed. The benefit of high accuracy rates cannot be overstated: either inappropriately assuming a malignant diagnosis when an effusion is benign or assuming it is benign when it is malignant results in major differences in care.

In the context of a probable malignant effusion, thoroscopic inspection almost always allows for the immediate confirmation of the presence or absence of pleural involvement by malignancy. If

approaches (i.e., thoroscopic lobectomy or laparoscopic/thoroscopic esophagogastrectomy). This approach not only minimizes pain and speeds recovery, but allows for better integration of multimodality care; patients have a much improved ability to receive adjuvant therapy, when needed, after a thoroscopic resection (3,4).

Yale Thoracic Surgery, in conjunction with the Yale Thoracic Interventional Program, offers the full spectrum of advanced techniques available. This expertise permits the accurate diagnosis and staging of patients, which is crucial in the management of thoracic malignancies. When appropriate, Yale physicians can secure large

Figure 1
left - View using traditional mediastinoscopy (white circle)
right - View on monitor using video mediastinoscopy



complete removal of all mediastinal nodes (lymphadenectomy). This changes a procedure that formerly required a thoracotomy into one that is almost painless and can be done in the outpatient setting. It not only provides the ultimate in staging accuracy (1), but may be therapeutic and increase the effectiveness of other modalities, such as radiation therapy, by altering the treatment fields necessary. Videomediastinoscopy is routine at Yale whereas it is available in only a minority of hospitals in the United States. The thoracic surgeons at Yale also provide expertise in extended cervical mediastinoscopy and extended mediastinal lymphadenectomy, procedures that are available at only a handful of institutions around the world.

The view provided by videot technology also extends to the pleural space. Misdiagnoses of the nature of a pleural effusion are common when

and when a malignancy is confirmed, immediate therapeutic maneuvers, such as a talc pleurodesis, can then be performed in the same setting to most effectively reduce the potential of a symptomatic recurrence. In the setting of lung entrapment in which parietal and visceral pleural apposition is not possible and recurrence is essentially inevitable, pleural catheter placement can still be performed. Although these catheters do not typically require a thoroscopic approach, the thoroscopic approach provides the versatility to address this problem while confirming the entrapment of the lung.

Aside from pleural-based disease, thoracoscopy also allows for better selection of patients for surgery providing a minimally invasive evaluation of tumor extent. In fact, the majority of surgical resections of thoracic malignancies performed at Yale are done using minimally invasive

amounts, or even all, of the tissue in question (lymphadenectomy, lobectomy) using advanced techniques that have minimal patient morbidity and are associated with maximal patient benefit.

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Individualizing Therapy in Lung Cancer: More Tissue Please

By Scott Gettinger, MD

Systemic therapies for non-small cell lung cancer (NSCLC) are increasingly individualized based on histological and molecular characterization. Further advances in the treatment of NSCLC will depend on procurement of adequate tissue for such analysis. This will require minimally invasive procedures that will allow core biopsies pre-treatment, and in some cases post-treatment, to determine mechanisms of sensitivity and resistance to chemotherapy and novel targeted agents. This will not only improve outcomes in patients, but will ultimately be more cost effective and spare patients toxicity from ineffective therapies.

To date, two drugs have been restricted by the Food and Drug Administration (FDA) based on NSCLC histology. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor, a key mediator of angiogenesis, is approved for use only in patients with non-squamous cell histology, as early experience with this drug found increased rates of fatal hemoptysis in those with squamous cell NSCLC (1,2). Pemetrexed, a newer antifolate whose primary target is thymidylate synthetase (TS), has recently been restricted to use in non-squamous cell carcinoma as well, based on subset analyses of three randomized NSCLC clinical trials suggesting benefit limited to those without squamous cell histology (3). Further efforts are underway to determine if TS expression, which is generally higher in squamous cell NSCLC (4), is the driver of sensitivity to Pemetrexed.

Perhaps the most striking example of the power of individualized therapy is use of the small

molecule inhibitors of the epidermal growth factor receptor (EGFR) such as erlotinib and gefitinib in patients with EGFR mutant NSCLC. Response rates on the order of 70% have been reported in patients with activating EGFR mutations receiving these orally administered agents (5). Such responses tend to be dramatic both clinically and radiographically, with less toxicity than that experienced with traditional chemotherapy. Despite this, the routine commercial testing of EGFR mutational status is not standard, even in enriched populations (never/light smokers). This is largely due to inadequate tissue for molecular analysis.

Many additional oncogenic targets have been recognized in lung cancer, and a handful of targeted agents are presently being evaluated in molecularly defined populations in the clinic. These include inhibitors of ALK, MET, and KRAS, with several other agents being developed. Such efforts will depend on minimally invasive access to sufficient tumor tissue to select initial therapies, and further define mechanisms of acquired resistance allowing subsequent targeted therapy.

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INDIVIDUALIZED THERAPY THROUGH CLINICAL TRIALS AT YALE CANCER CENTER

Several molecularly defined cohorts of non-small cell lung cancer are emerging. These include EGFR mutant, KRAS mutant, and ALK rearranged NSCLC. Another population of interest is those with acquired resistance to small molecule inhibitors of EGFR. Clinical trials targeting each of these four groups are currently available at Yale Cancer Center (see page 3).

Additional studies are being designed to target other subpopulations of lung cancer patients and will be updated online at www.yalecancercenter.org/trials. As part of this effort, genotyping of patients seen in the Thoracic Oncology Program will be routinely done starting in mid-2010, offering an extensive menu of molecular alterations that will help direct therapy.

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Yale-New Haven Hospital is the primary teaching hospital of Yale School of Medicine and is ranked among the nation's best hospitals by U.S. News and World Report. Smilow Cancer Hospital at Yale-New Haven works in partnership with Yale Cancer Center.

Together, we provide a multidisciplinary approach that offers advanced technology in a minimally invasive approach to diagnosing and treating lung cancer.