MAYO CLINIC

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INSIDE THIS ISSUE

Screening for Lung Cancer: The Evolving Challenge

Cancer of the lung is the leading cause of cancer death in both women and men in the United States. In the year 2012, the estimate is for 226,160 new cases of lung cancer in the US, and 164,770 deaths; the five-year survival rate for lung cancer is 16%. This sobering outlook is due primarily to the fact that most patients have advanced disease at the time of presentation. Nonsmall cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer diagnoses. For this subset of patients, surgery is often curative if presentation is early (stages I and II). Unfortunately, only approximately 30% of diagnoses fall within this early-stage category.

Nearly a quarter of the US population actively smokes, and at the same time contributes to the downstream effects of secondhand smoke. While prevention remains the most important strategy to stem the epidemic of lung cancer, until that goal is realized there remains an urgent need for new and improved means of early diagnosis.

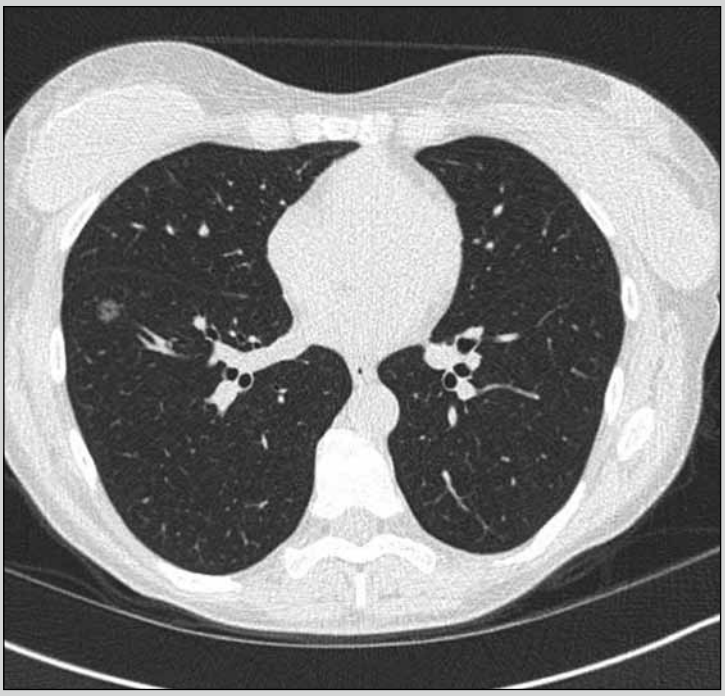

Figure. *A 9 x 8 mm groundglass nodule in the anterior basal segment of the right lower lobe found incidentally on a CT abdomen obtained for evaluation of trauma.*

Effective Screening

Screening as a means to achieve early diagnosis has always sounded like a good idea but until recently, no screening test had been shown to impact deaths from lung cancer. Prior studies, including the Mayo Lung Project and the Prostate, Lung, Colon and Ovary (PLCO) study, utilized chest radiograph (CXR), with or without sputum cytology. Results showed that CXR screening does not result in lives saved from lung cancer.

Computed tomography (CT) has been in clinical use since the mid 1970s, but it wasn't until technical advances allowing for rapid scanning at low

dose that screening became feasible. Single-arm studies of CT screening reported detection of more cancers, more early stage cancers and with a high resectability rate. The Mayo CT study enrolled over 1,500 participants; the baseline nodule detection rate was 51% and, after 5 annual scans, 74% of the participants had 1 or more nodules. The vast majority of nodules were found to be benign. There were a total of 68 lung cancers; 79% of the incident (not present on the baseline scan) NSCLC were stage I. However, due to the biases inherent to screening, a suggested survival improvement was insufficient proof of effectiveness.

National Lung Screening Trial

The large randomized controlled trial, the National Lung Screening Trial (NLST)—has now shown that screening with low-dose CT scanning, compared to CXR—results in fewer deaths from lung cancer. Results were published in the *New England Journal of Medicine* August 4, 2011, edition. The NLST compared two methods of detecting lung cancer. Data showed that patients screened with low-dose CT scanning had a 20% lower risk of dying from lung cancer compared to patients who received standard CXR.

Investigators at Mayo Clinic in Rochester and Florida participated in the NLST. The study included 53,454 subjects considered high-risk for lung cancer, ages 55 to 74, who were current or former smokers with at least a 30 pack-year history. Participants were randomized to either low-dose spiral CT or chest X-ray at baseline, year 1, and year 2, with follow-up over about 6 years.

Findings: CT vs CXR

The finding on CT of a non-calcified nodule of at least 4 mm was considered a positive result, and 27% in the CT arm had a positive baseline screen, of which 96% were false positives. There were 649 prevalent cancers detected by CT and an additional 367 cancers in the CT-arm diagnosed during follow-up after screening. On CXR, any non-calcified nodule visualized was considered a positive result; 9% were positive at baseline, of which 94% were false positives. In the CXR arm, there were 279 cancers detected and 525 subsequently diagnosed during follow-up post screening.

Within the CT arm, 63% of the lung cancers detected by CT were stage I; only 29.8% were stages III or IV. Among those detected by CXR, 47.6% were stage I, and 43.2% were stage III or IV. CT demonstrated the ability to shift stage at diagnosis from advanced disease to more frequent detection in early stage and potentially curative early disease.

There were 356 lung cancer deaths among those in the CT arm versus 443 deaths among those in the CXR arm—a 20.0% reduction with CT screening. In the NLST the number of high risk participants needed to screen with CT to save one life from lung cancer was 320.

Several other smaller randomized CT screening trials are currently under way in Europe. Recent results from the Danish Lung Cancer Screening Trial (DLCST), where 4,104 subjects were randomized to CT versus no screening showed that, although a higher proportion of early-stage disease was detected by CT screens, there was no difference in either the diagnosis of advanced-stage disease or mortality after 5 annual screenings.

David E. Midthun, MD

"The odds of saving one's life are much greater with smoking cessation than they are with CT screening."

David Midthun, MD

Performing the CT is technically simple; the difficulty lies in interpretation and in limiting unintended consequences. CT screening presents issues of false positive scans, resection of benign nodules, overdiagnosis, harmful effects of radiation, and cost. For the most part , now that low-dose rapid-scanning CT has been shown to reduce mortality, the problems of CT screening are recognized as manageable, with the possible exception of cost. (See sidebar, "Uncertainties of Lung CT Screening").

Next Steps

Widespread implementation of screening programs largely depends upon resolution

of these uncertainties, particularly the reimbursement issues.

Mayo Clinic has developed a program that would include screening patients who fit the NLST criteria for enrollment and others who are at equal or higher risk. Risk is determined on the basis of a diagnosis of chronic obstructive pulmonary disease (COPD) or family history as supported by the National Comprehensive Cancer Network guidelines. Greater precision is needed in clarifying indications for screening and for determing who among those with CT abnormalities have lung cancer. This level of clinical detail is likely to be gained by the application and refinement of novel tests of blood, urine, sputum, mucosa, or breath analysis that are currently in development.

For more information visit: www.cancer.gov/clinicaltrials/noteworthy-trials/nlst.

Uncertainties of Lung CT Screening

With the favorable findings on computed tomography (CT) from the National Lung Screening Trial (NLST) published in 2011, there is a growing urgency to address the uncertainties and apparent limits of CT screening, including:

- **High rates of false positive scans.** A non-calcified nodule of any size will be found in approximately 50% of those undergoing CT screening and 98% of those will be false positives. Tests to distinguish malignant nodules from benign are imperfect, and could subject patients to unnecessary procedures. In single-arm CT screening studies, 15% to 25% of the surgical procedures were performed for benign histology. Researchers at Mayo Clinic are developing imaging techniques such as CANARY (see story on p. 4) that may help predict malignant behavior among CT abnormalities, and, by so doing, limit the number of thoracic procedures performed for benign disease.
- **Overdiagnosis.** This term refers to cancers identified and treated that, if otherwise gone undetected, would not have impacted long-term morbidity or mortality. Many cases of overdiagnosis in lung cancer screening have been attributed to ground-glass opacities (GGOs), which have a long tumor-doubling time. In the Mayo CT screening study, 27% of the screen-detected NSCLC exhibited doubling times of > 400 days, suggesting these may have been overdiagnosis cancers. The findings of the Danish Lung Cancer Screening Trial have also raised the possibility of overdiagnosis. Awareness of this issue, it is hoped, will help reduce unnecessary surgery for these indolent cancers.
- **Radiation Risks.** There is concern over the risks of radiation exposure associated with serial CT imaging and its role in the development of future lung or other cancers. Comparatively, a single, low-dose CT scan delivers about 1.5 millisieverts (mSv) of radiation, ambient radiation exposure associated with inhabiting planet Earth is estimated at 3 mSv per year, while a standard diagnostic CT of the chest delivers 7-8 mSv.
- **Cost-effectiveness.** In this era of intense focus on health care cost containment, questions about the cost-effectiveness of CT screening for lung cancer will continue to arise. The NLST found that the number of high-risk patients needed to screen with CT to save one life from lung cancer was 320. While this number compares favorably to those associated with mammography and colonoscopy, the actual cost per quality-adjusted life-year (QALY)—a standardized measure of cost-effectiveness—is projected to be several-fold higher for CT screening for lung cancer. Estimates of the cost of CT screening have varied from as low as $19,000 to about $169,000 per life-year saved. Further cost information results from the NLST are eagerly anticipated and will be critical to shaping the acceptance of CT screening by third-party payers.

Importantly, it should not be forgotten that smoking cessation programs are a cost-effective preventive measure that has far-reaching downstream effects on reducing deaths from lung cancer.

Innovative, Minimally Invasive Strategies for Lung Cancer: A Paradigm Shift

Developing more effective diagnostic tools for early detection and staging of lung cancer—both more accurate and less invasive—and ongoing research efforts are poised to usher in a paradigm shift in patient care. Advances in endoscopic techniques and in imaging help achieve these goals. Among endoscopy techniques are endobronchial ultrasound (EBUS), electromagnetic navigation (EMN) with volumetric high-resolution computed tomography (HRCT), and early detection of endobronchial mucosal abnormalities by autofluorescence bronchoscopy and narrow-band imaging. Mayo Clinic is designing a novel imaging technique for staging subsolid lesions, known as CANARY (See sidebar on p. 5). Through an integrated multidisciplinary approach, this is among the many innovative and minimally invasive strategies used at Mayo Clinic in the management of lung cancer.

Endobronchial Ultrasound and Staging

Accurate staging, and therefore management, of lung cancer requires access to the mediastinum for lymph node sampling. This has historically been accomplished by mediastinoscopy, a surgical procedure requiring a small skin incision and general anesthesia, but which gives only partial access to thoracic lymph node stations. By contrast, the convex endobronchial ultrasound (EBUS) bronchoscope provides real-time guidance for transbronchial needle aspiration (TBNA) and allows access to more lymph node stations than mediastinoscopy. EBUS is generally performed as an outpatient procedure under conscious sedation. It affords excellent sampling precision and minimal complications and has been routinely used at Mayo Clinic Rochester since 2006, with more than 400 procedures performed annually. A growing body of evidence suggests that EBUS-TBNA has a diagnostic accuracy similar to mediastinoscopy. For lymph node stations not accessible via bronchoscopic EBUS, combining with transesophageal endoscopic ultrasound has proven complementary and allows complete mediastinal staging with excellent sensitivity and specificity. Importantly, EBUS-TBNA samples provide sufficient tissue for molecular analyses (see section on Individualized Lung Cancer Treatment, p. 7) in the vast majority of cases, precluding the need for more invasive sampling procedures.

Early Diagnosis of Peripheral Lung Cancers

Many lung cancers present as peripheral lesions. For definitive diagnosis, transthoracic needle aspiration—or even surgical lung biopsy—is required. Both procedures are associated with a risk of morbidity, complications, and occasional sampling error. Mayo Clinic bronchoscopists now use electromagnetic navigation (EMN), which takes advantage of volumetric high-resolution computed tomography (HRCT) acquisition protocols to provide a virtual pathway to peripheral lesions. These pathways are fused with real-time bronchoscopy images, allowing access to lesions that are otherwise hidden. To do this, the physician advances a probe through the bronchoscope. Its location is determined relative to the targeted lesion by triangulation, which involves measuring the angles to it from known points as the patient lies within an electromagnetic field. A sheath is left in place within a bronchus, through which biopsy forceps or needles can be advanced to biopsy the lesion. This revolutionary technology substantially increases the diagnostic yield of bronchoscopy and has minimal complications. Continuing refinements in the technology are promising and suggest that EMN will likely occupy an increasingly important role in the diagnosis of lung cancer.

Autofluorescence Bronchoscopy and Narrow Band Imaging

Some cancers arise from the bronchial epithelium and are preceded by premalignant lesions not easily visualized by conventional bronchoscopy. Autofluorescence bronchoscopy (AB) and narrow-band imaging rely on certain patterns of absorption by abnormal tissues when exposed to light emitted at specified wavelengths. AB, also known as "blue light bronchoscopy," can reveal abnormalities in tissue that may not be visible with white light. These techniques may be utilized to detect pre-invasive endobronchial lesions amenable to early treatment which may prevent progression to invasive lung cancer. Furthermore, as the airway is not typically well characterized by CT imaging, these bronchoscopic techniques may prove complementary to CT screening for the early detection of lung cancer.

Novel Visualization Approach To Speed Diagnosis: A CANARY in a Coal Mine?

The use of imaging modalities such as computed tomography (CT) continues to expand, regardless of lung cancer screening programs. As a consequence, clinicians are encountering an increasing number of incidentally detected peripheral lung subsolid lesions, for which management strategies have not been well established. A key innovative, non-invasive technique that may help clarify the role of these lesions has been developed by a team of Mayo Clinic physicians and scientists led by Fabien Maldonado, MD. Known as CANARY—Computer-Aided Nodule Assessment and Risk Yield—it is a novel technology that can help categorize lesions and may aid prognosis (Figure).

About Ground Glass Opacity (GGO)

Persistent GGO are usually classified as adenocarcinomas, ranging from premalignant lesions (atypical adenomatous hyperplasia) to invasive disease. They are generally slow-growing lesions. Because their significance can be difficult to determine, optimal follow-up and management are not clearly known. The prognosis of these lesions is driven by their histologic characteristics, which are available only after surgical resection.

The Mayo Clinic team tackling the uncertainties of GGO's includes biomedical imaging engineers, pathologists, pulmonologists, and radiologists. They are developing CANARY as a non-invasive quantitative imaging tool designed to differentially categorize CT-detected peripheral subsolid lung nodules and predict underlying pathology and prognosis. Preliminary data suggest that CANARY, utilizing volumetric histogram density analysis (so-called "radiologic biopsies"), effectively risk-stratifies these nodules.

To further validate this technology, CANARY researchers are using data from the National Lung Screening Trial (NLST) and partnering with the American College of Radiology Imaging Network. Early detection and categorization of GGOs by CANARY could ultimately result in significant advances in understanding and treating this subtype of lung cancer. The ability of CANARY to non-invasively identify tumors exhibiting aggressive behavior could avoid unnecessary delays in management and result in improved patient outcomes. Importantly, the ability to predict indolent behavior would help avoid unnecessary surgery.

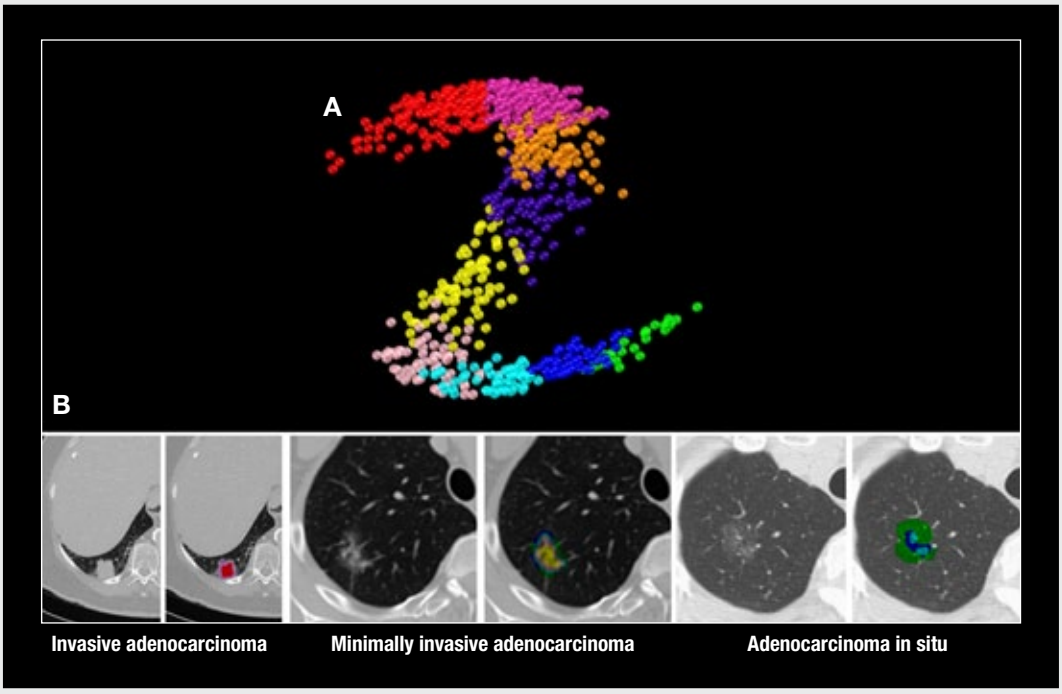

Figure. *CANARY is a non-invasive quantitative imaging tool under development by Mayo Clinic scientists and physicians that uses robust, state-of-the-art machine learning and novel visualization techniques (A) to model the building blocks of the lesion (color-coded density histograms based on volumetric analysis). Subsequently (B), the lung nodules on high-resolution computed tomography (HRCT) scans are risk-stratified based on the distribution of the building blocks.*

Expanding Surgical Options for Lung Cancer Treatments

Surgical options are expanding for the treatment of patients with lung cancer. One of the most important has been the development of minimally invasive techniques, particularly video-assisted thoracic surgery (VATS).

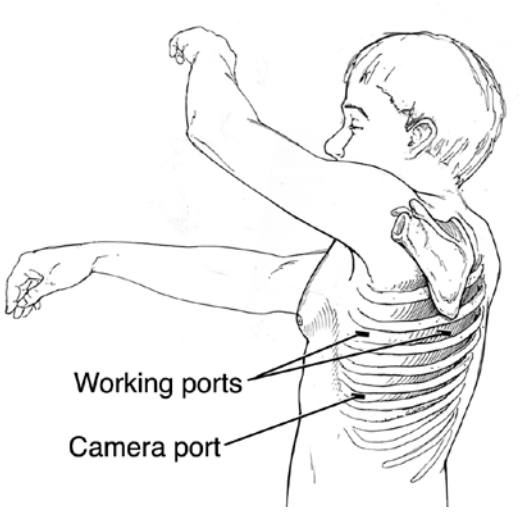

Figure 1. *Representative image of skin incisions used during a VATS procedure.*

VATS

In VATS, small incisions are made on the chest wall through which a thoracoscopic camera is passed, which allows mediastinal lymph node dissection as well as lobectomy (Figure 1).

VATS lobectomy is the preferred care for surgical resection of early stage (stage I or II) non-small cell lung cancer (NSCLC) at Mayo Clinic, where hundreds of these procedures have been performed, with outcomes equivalent to—or better than—those found within the multi-institutional Society of Thoracic Surgeons' database.

With ongoing developments in surgical optics and instrumentation continuing to improve this approach, most patients are candidates for thoracoscopic lobectomy.

Robot Assistance

Robot-assisted surgery is an emerging field that transcends multiple disciplines; advanced centers such as Mayo Clinic are rapidly adapting it to thoracic surgery. During a robotic procedure, the surgeon operates the surgical instruments while sitting at a console a few feet away from the patient (Figure 2).

Robot-assisted surgery offers several potential advantages over conventional procedures. Chief among them are better visualization of the surgical field, as well as improved stability and enhanced mechanics of instruments, with less invasiveness than traditional approaches.

Natural Orifices: NOTES

Another emerging advanced technique is natural orifice transluminal endoscopic surgery (NOTES). NOTES is an experimental surgical technique that relies on natural orifices to provide surgical access. Refined in 2009 by a Mayo Clinic gastrointestinal endoscopic surgical team, NOTES is the culmination of years of research into a new generation of endoscopic tools, techniques and physiologic responses, and ushers in a new era of surgery—scarless and pain-free.

The potential that NOTES offers to lung cancer surgery patients is the elimination of skin wounds by using natural anatomic passages for access, such as openings in the mouth, endoscopically through the esophagus, or endoscopically through an incision in the trachea which allows access to the pleural space and mediastinum. Several investigational approaches for non-cancerous conditions are being explored for NOTES thoracic surgery, including endoscopic myotomies for achalasia.

In its leadership role in the refinement of novel surgical methods, Mayo Clinic is committed to expanding and improving surgical options. The goal is to offer lung cancer patients options that lead to optimal outcomes with the least trauma.

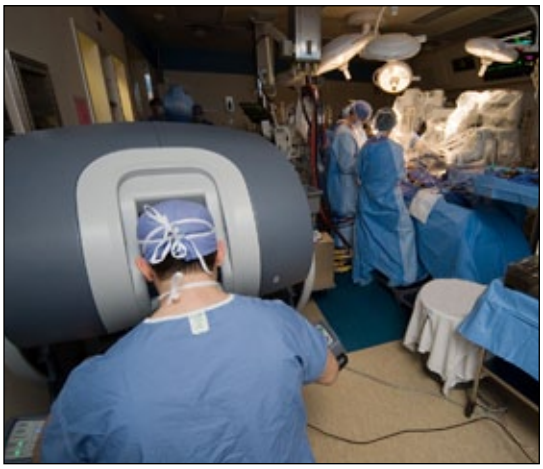

Figure 2. *This surgeon controls instruments in the surgical field while sitting at a console.*

Stereotactic Body Radiation Therapy Offers Option to High-Risk Surgery Patients

Severe chronic obstructive pulmonary disease (COPD) may be a contraindication to surgical therapy in patients with early-stage non-small-cell lung cancer (NSCLC). In carefully selected patients, stereotactic body radiation therapy (SBRT) is a relatively new treatment that expands treatment options. Utilizing multiple radiation beam angles to target a tumor (typically < 5 centimeters in size) with high-ablative radiation doses, SBRT also minimizes radiation to adjacent normal tissue. While the therapeutic course of traditional radiation treatments is 6 to 7 weeks, SBRT can be completed in just 3 to 5 days over 1 to 2 weeks. SBRT is generally delivered without concurrent chemotherapy.

Prospective observational (phase II) studies of SBRT in stage I or II NSCLC (T1 or T2) have shown short-term outcomes similar to surgery. Data on long-term outcomes are not yet available.

There is a subset of patients with early-stage NSCLC and comorbid illness in whom surgical risk is higher, though not necessarily prohibitive. For such patients, the standard of care is not yet known. Limited resection surgeries or SBRT could be offered for many. To help answer these questions, Mayo Clinic is participating in a phase III randomized trial comparing sublobar resection (with or without brachytherapy) with SBRT in higher-risk (FEV1 or DLCO < 50% predicted) surgical patients with T1 disease.

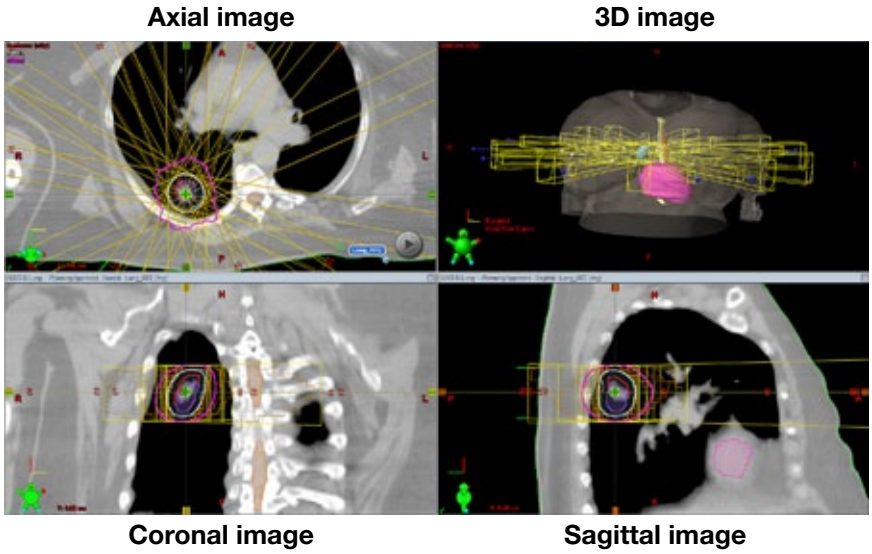

Figure. *Representative axial/coronal/sagittal slices of an SBRT plan that delivers 5400 cGy in 3 fractions (white isodose line encompassing planning tumor volume in light blue). The red line is the internal target volume, which accounts for respiratory movement of the tumor. The magenta 3000 cGy isodose line shows rapid dose fall off outside the tumor, minimizing radiation to the normal lung and chest wall. The 3D image shows the entrance and exit of 10 coplanar beams utilized for treatment. The heart is outlined in pink.*

Individualizing Lung Cancer Treatment

State-of-the-art management of lung cancer includes individualized treatment as a means of optimizing care. Personalized genomic cancer care is the pinnacle of this approach, and has far-reaching implications for both the medical and surgical treatment of lung cancer patients. There are various lung cancer subtypes based on mutation status that might warrant different treatment approaches, and genomic analysis through profiling can help inform clinical-decision in the context of each individual. These spaces are rapidly evolving and a number of Mayo Clinic investigators are at the forefront of advancing these fields.

Molecular maps allow physicians to tailor more specific drug therapy—referred to as targeted therapy—on the basis of an individual's genetic makeup. Molecule-specific agents are designed to work against a specific aberrant molecular pathway. They are increasingly used in the treatment of lung cancer to enhance therapeutic efficacy and limit toxicity. Mayo Clinic researchers have perfected a tumor assay that can quickly identify 187 mutations from 10 oncogenes commonly altered in lung cancer cells.

Mayo Clinic utilizes a protocol for treating

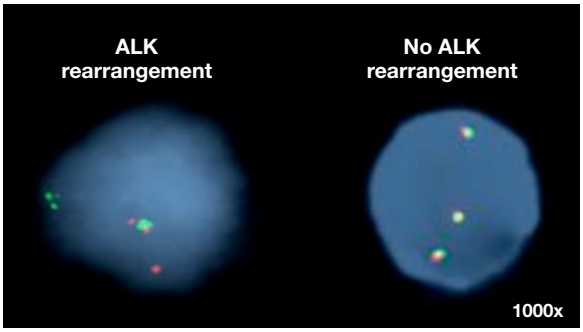

Figure. *Representative images of ALK rearrangement. The normal cell on the right shows 3 intact ALK signals in close proximity to one another; the left cell exhibits an ALK rearrangement with a separation of the 5′ (green) and 3′ (orange) FISH signals.*

Mayo Clinic
Clinical Update

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locally advanced disease in patients with mutations in the EGFR gene or the ALK translocation. Such patients can be treated in a neoadjuvant manner with targeted therapy. How best to combine targeted therapies with traditional treatment approaches such as systemic chemotherapy and/or radiation therapy is an active area of investigation at Mayo.

To date, the most therapeutically important mutations to identify in molecular mapping for optimized lung cancer treatments include:

- **Epidermal growth factor receptor (EGFR).** EGFR mutations are more common in women and those of Asian descent. Furthermore, an EGFR mutation is estimated to be present in approximately 10% to 15% of all adenocarcinomas but is present in nearly 50% of individuals with lung cancer who have never smoked.
- **The EML4-ALK gene fusion.** The EML4-ALK fusion is present in approximately 3% to 6% of adenocarcinomas, and is also more common in never-smokers. Mayo pathologists routinely perform a fluorescent in situ hybridization (FISH—see figure on p. 7) assay that assesses the abnormal fusion between the echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (EML4-ALK).
- **V-Ki-ras2 oncogene (KRAS).** In contrast to the tendency for EGFR gene mutations and EML4-AKL fusion to occur in those who have never smoked, KRAS mutations are more common in past or current smokers.

The three most commonly utilized targeted agents against EGFR mutations are gefitinib (*Iressa*), erlotinib (*Tarceva*), and cetuximab (*Erbitux*).

For treatment of lung cancer with the EML4-ALK fusion, the drug crizotinib (Xalkori) is approved. Multiple other agents are in development or in clinical trials that target other genes such as PIK3CA, c-MET, and BRAF.

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Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

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Resources

mayoclinic.org/medicalprofs

Clinical trials, CME, Grand Rounds, scientific videos, and online referrals

Educational Opportunities

Transfuse 2013: Transformative Fusion of Innovative Blood Management Technologies

March 13-16, 2013, Phoenix, AZ
In this 3-day multidisciplinary conference, clinicians from all fields will learn innovative and strategic blood management with the goal of mastering state-of-the-art blood management practice. This is a one-of-a-kind summit designed by leaders in blood management from Mayo Clinic, Hartford Hospital and Cleveland Clinic. Faculty from all three organizations will lead highly targeted, lively and productive sessions. For more information, visit www.mayo.edu/cme/anesthesiology-2013r106 or call 507-288-5620.

Point of Care Ultrasonographyy

March 22-24, 2013, Rochester, MN
Designed to help attendees improve practical use of ultrasonography, this course will focus on innovative and effective procedures that have a direct impact on patient care. Through presentations, discussions, hands-on training and workshops with state-of-the-art technology, attendees will improve both their machine operation and image acquisition skills, as well as deepen their clinical understanding of the role of ultrasonography in best-practices care. For more information, visit www.mayo.edu/cme/emergency-medicine-2013r138 or call 800-323-2688.

2013 Multidisciplinary Update in Pulmonary and Critical Care Medicine

April 11-14, 2013, Scottsdale, AZ
This course is designed for pulmonary physicians, internists, hospitalists and specialists in critical care medicine. The goal is to provide a comprehensive approach to the current evaluation and management of various respiratory diseases.
Leaders in pulmonary and critical care medicine will lecture, demonstrate, discuss case studies and engage in interactive sessions on topics that include pulmonary pathology, radiology and critical care medicine. For information, visit www.mayo.edu/cme/pulmonary-medicine-2013s963 or call 480-301-4580.

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