Lung cancer remains one of the leading causes of cancer-related mortality and morbidity. In the year 2015, it was estimated that 221,200 new cases of lung cancer would be diagnosed in United States and 158,040 patients would die of lung cancer. Non-small cell lung cancer accounts for approximately 85 percent of lung cancer diagnoses and carries an overall five-year survival rate of 17.4 percent. Effective implementation of lung cancer screening, as is currently done at Mayo Clinic using low-dose computerized tomography (LDCT) of the chest, is expected to improve associated mortality and morbidity, with a demonstrated 20 percent relative reduction in mortality shown in the National Lung Screening Trial (NLST). Based on the NLST result, the U.S. Preventive Services Task Force, as well as many professional societies, recommends annual screening for lung cancer with LDCT in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Of screening-detected nodules, however, less than 4 percent will prove to be malignant with the remaining 96 percent requiring serial follow-up, invasive diagnostic maneuvers or both. With that ability to safely and effectively sample, diagnose and potentially treat screening-detected abnormalities takes on additional importance, and has become a major focus of investigation and innovation in interventional pulmonary medicine and thoracic surgery.

Lung tumors, depending on their location in the tracheobronchial tree, are categorized as central or peripheral. Central tumors, according to American College of Chest Physician (ACCP) guidelines, are sampled easily under direct bronchoscopic visualization with an 88 percent diagnostic yield. Early-stage lung cancer, however, frequently presents as a peripheral pulmonary nodule and is often curable by surgical resection. ACCP guidelines for establishing the diagnosis of lung cancer report the diagnostic yield of bronchoscopy decreases from 63 percent to 34 percent when the peripheral pulmonary nodule is smaller than 2 centimeters, creating a particular challenge for bronchoscopists in establishing a diagnosis in smaller lesions using traditional bronchoscopic techniques. In the NLST, the vast majority of screening-detected nodules were less than 10 millimeters in size, with almost two-thirds less than 7 millimeters. Radial endobronchial ultrasound and navigation bronchoscopy are emerging technologies especially well-suited for the diagnosis of small peripheral nodules, demonstrating a diagnostic yield of 73 percent and 71 percent respectively. This compares with the pooled sensitivity of transthoracic needle aspiration (TTNA) of 90 percent, but TTNA also trends toward lower sensitivity for nodules less than 2 centimeters in diameter at a higher complication rate than bronchoscopically sampled nodules. A complication rate of up to 30 percent is noted for TTNA compared with a complication rate of 2 percent for navigation bronchoscopy.
Mayo Clinic bronchoscopists routinely use a combination of specialized bronchoscopes, electromagnetic navigation, endobronchial ultrasound localization and rapid on-site histopathologic diagnosis in their assessment of suspicious peripheral lung nodules (Figures 1, 2, 3, 4 and 5). More recently, Mayo has incorporated the use of real-time chest computerized tomography to further aid in nodule localization. This, in concert with electromagnetic navigation, which provides a 3-D road map of the lungs and real-time information about the position of a steerable probe during bronchoscopy, further optimizes diagnostic yield and facilitates dye and fiducial marker placement to direct surgical and radiotherapy treatment options. This continued collaboration between interventional pulmonology, radiation oncology and thoracic surgery specialists has resulted in successful localization and management of pulmonary nodules smaller than 1 centimeter. At times when it may be difficult for a thoracic surgeon to localize and feel a ground-glass or soft nodule, especially in patients with underlying lung disease, dye placement by interventional pulmonary specialists using methylene blue just before surgery has resulted in successful resection and a decrease in operative time.

Going forward, these localization and diagnostic tools and techniques offer the promise of less invasive treatments of lung cancer in patients who are deemed poor surgical candidates. In high-risk surgical patients, bronchoscopic localization and confirmation of lung cancer may allow opportunities to perform nonsurgical tumor treatment using cryoablation or microwave ablation.

Safety and Efficacy of Cryoablation for Metastatic Lung Tumors (ECLIPSE), a recent multicenter study including Mayo Clinic, describes the successful use of percutaneous CT-guided cryoablation in local treatment of up to five metastatic lesions each less than 3.5 centimeters in diameter. This technique was shown to be effective in treating various types of metastases with up to a 96 percent local control rate at 12 months (Figures 6, 7 and 8).

A larger multicenter study involving Mayo Clinic and Gustave Roussy, Paris, called the Study of Cryoablation for Metastatic Lung Tumors (SOLSTICE), is currently enrolling patients, as is The Emprint Ablate and Resect Study in Patients With Metastatic Lung Tumors (EMPRESS), a multicenter study investigating the percutaneous use of the Emprint microwave ablation system to treat metastatic and primary lung tumors. Likewise, several manufacturers are investigating the use of bronchoscopically deployed ablative devices, which, if successful, will further limit the risks posed by the percutaneous approach.

In the meantime, Mayo Clinic investigators are actively engaged in the testing of various percutaneous ablative devices using both cold and thermal energy sources, and a multidisciplinary lung ablation committee meets regularly to review cases for potential ablative therapies.

To learn more about current studies using novel ablative devices, or to have a case reviewed at the lung ablation meeting, contact Shanda Blackmon, M.D., M.P.H., Thoracic Surgery, at blackmon.shanda@mayo.edu.

For additional information about the Mayo Clinic Lung Cancer Screening Program, contact David E. Midthun, M.D., Pulmonary and Critical Care Medicine, at midthun.david@mayo.edu.
Diffuse parenchymal lung diseases comprise a group of noninfectious, non-neoplastic lung diseases, each characterized by varying degrees of inflammation or fibrosis or both of the parenchyma of both lungs. The evaluation and management of patients with these diseases, particularly those with idiopathic interstitial pneumonias, often involves a multidisciplinary team approach. The differentiation of these disorders may require biopsy material, particularly in patients with atypical clinical or radiological presentations.

The diagnostic accuracy of standard forceps transbronchial biopsies ranges from 50 to 70 percent but also depends on the underlying disease. Poor results are seen in usual interstitial pneumonia, pneumoconiosis, respiratory bronchiolitis associated interstitial lung disease, nonspecific interstitial pneumonia and Langherhans’s cell histiocytosis. These patients may require surgical lung biopsy to obtain a confident diagnosis. Unfortunately, surgical lung biopsies have a risk of serious complications, including a 30-day mortality ranging from 2.7 to 12 percent in patients with interstitial lung disease. Short-term mortality has been as high as 21 percent for patients with idiopathic pulmonary fibrosis undergoing thoracotomy or video-assisted thoracoscopic surgery.

A potential alternative to forceps transbronchial biopsies or surgical biopsies is biopsies obtained with the use of a flexible cryoprobe. Cryobiopsies offer specialists the advantage of being able to collect much larger specimens than can be collected with forceps biopsy, plus preserve of the underlying lung architecture similar to a frozen section specimen. The biggest disadvantage of the lung biopsy with a cryoprobe is a higher risk of substantial bleeding and pneumothorax.

No systematic controlled trials have compared cryobiopsies with standard forceps biopsies or thoracoscopic biopsies in idiopathic interstitial pneumonias, but several centers have reported case series using cryobiopsies. These case series have demonstrated advantages of cryobiopsies (Figure 1) over forceps biopsies (Figure 2), including sample size and the presence of alveolar tissue without the crush artifacts. Biopsies with more alveolar tissue enable the addition of immunohistochemistry and thus an increased diagnostic
Persistent postoperative air leaks can be troubling and lead to prolonged hospitalization, increased cost of care and the need for repeated surgical interventions. Overall their occurrence is not insignificant, occurring in up to 4 percent of lung resections. Many are successfully addressed with prolonged thoracostomy tube placement. However, for others innovative approaches are evolving that may aid in the resolution of the air leak and avoid the need for additional surgery.

Among these innovations is the use of bronchoscopically positioned endobronchial valves that completely stop or decrease the extent of the air leak and may facilitate resolution. These valves are designed to limit airflow to the portions of the lungs distal to the valve, while still allowing mucus and air movement in the proximal direction.

Since 2008, this alternative to surgery has been available through interventional pulmonology to select patients at Mayo Clinic under a Food and Drug Administration-approved humanitarian use protocol through the Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE Study). Use of the valves is limited to the control of prolonged air leaks, or significant air leaks that are likely to become prolonged after lobectomy, segmentectomy or lung volume reduction surgery. Additional information about patient eligibility for this option can be obtained from Eric S. Edell, M.D., primary investigator, Pulmonary and Critical Care Medicine. Team members include pulmonologists, pathologists, radiologists, interventional pulmonologists and thoracic surgeons, who combine their expertise in the assessment, diagnosis and treatment of these patients.

For more information, contact Dr. Moua at moua.teng@mayo.edu. To refer a patient or request an appointment, call 507-266-0415.

Evolving Management Strategies for Persistent Air Leaks and Chronic Obstructive Pulmonary Disease Using Endobronchial Valves

Persistent postoperative air leaks can be troubling and lead to prolonged hospitalization, increased cost of care and the need for repeated surgical interventions. Overall their occurrence is not insignificant, occurring in up to 4 percent of lung resections. Many are successfully addressed with prolonged thoracostomy tube placement. However, for others innovative approaches are evolving that may aid in the resolution of the air leak and avoid the need for additional surgery.

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For more information, contact Dr. Moua at moua.teng@mayo.edu. To refer a patient or request an appointment, call 507-266-0415.
unknown. It is for this reason that interventional pulmonology and thoracic surgery specialists are jointly engaged in a multicenter study, the Spiration Valves Against Standard Therapy (VAST), designed to study the role of endobronchial valves in this patient population. The target enrollment is 200 patients randomized to either standard therapy or standard therapy augmented by valve therapy. The primary outcome is time from randomization to cessation of air leak, with secondary outcomes including time to chest tube removal, hospital length of stay, need for additional interventions and rate of air leak recurrence (Figures 1, 2 and 3).

Additional information about this study, including eligibility and assistance enrolling a patient, can be obtained from the study’s co-primary investigators, K Robert Shen, M.D., Thoracic Surgery, at shen.krobert@mayo.edu or John J. Mullon, M.D., a specialist in interventional pulmonology, at mullon.john@mayo.edu.

**COPD**

It is estimated that 16 million people have chronic obstructive pulmonary disease (COPD) in the United States alone. Emphysema, a common form of COPD, affects 3 to 4 million people. The disease produces hyperinflation and functional limitations of the chest wall and diaphragm, resulting in inefficient ventilatory mechanics. Progressive physical activity limitations become evident, and these patients experience increasing dyspnea and poor quality of life.

Pharmacological treatments have limited benefit, and no medical therapy can provide relief from the progressive disability of severe emphysema. The National Emphysema Treatment Trial (NETT) studied lung volume reduction surgery (LVRS) and established that it improved survival, in addition to health status, dyspnea, and exercise capacity and lung function, when compared with medical treatment. Unfortunately, approximately 80 percent of the patients referred for LVRS are ineligible for this surgical treatment. A significant group of these patients are ineligible due to concern regarding the morbidity of surgical intervention.

These data indicate that there is a significant medical need to investigate a less invasive, nonsurgical approach to help this patient group. Extensive research efforts began about 10 years ago worldwide, with the goal of investigating the feasibility of achieving lung volume reduction through bronchoscopic methods. These investigations included evaluation of the use of bronchial valves placed in the airways to block aeration to an area of the lung, thereby inducing absorption atelectasis.

Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function (EMPROVE) is a multicenter, prospective, randomized, controlled study designed to evaluate the safety and long-term effectiveness of the Spiration Valve System in patients with emphysema. Additional information about this study and assistance getting your patient enrolled can be obtained from Jorge M. Mallea, M.D., primary investigator, Pulmonary Medicine, at mallea.jorge@mayo.edu.

**For more information**


Update in Pleural Disease

Recurrent pleural effusions
Recurrent pleural effusions are one of the most common, yet challenging, problems encountered by pulmonologists. A thorough history, physical examination and pleural fluid analysis can point to a specific cause in over 75 percent of pleural effusions, but with over 1 million new pleural effusions diagnosed in the United States annually, an enormous number remain difficult to diagnose or treat with conventional methods.

Recurrence of pleural effusions
In 1972, Richard W. Light, M.D., demonstrated that effusions caused by usually local inflammatory processes called “exudative” effusions could be separated from effusions from systemic, “transudative” processes by simple pleural chemistry and blood tests. There are numerous etiologies that cause exudative pleural effusions, but a specific diagnosis may be difficult to determine even after an exhaustive laboratory, radiographic and microbiologic search.

In much of the world, both pleural tuberculosis and occult malignancy are the chief concerns, but in the United States, pleural-based malignancy is more common. By performing two separate thoracenteses with cytologic analysis, an effusion caused by malignancy will be diagnosed 60 to 75 percent of the time. While very useful, this implies that many patients will ultimately require a pleural biopsy for diagnosis.

Options for pleural biopsy are many and include closed biopsy techniques, such as the Abram’s needle, CT- or ultrasound-guided biopsy, or direct visually guided biopsy with video-assisted thoracoscopic surgery (VATS) or medical thoracoscopy, also known as pleuroscopy. The pleural surface area is very large and direct visually guided biopsy has advantages, particularly in cases when a possible target lesion is not visible on imaging. Figures 1, 2 and 3 show three common pleural findings on pleuroscopy.

Chronic pleuritis
A lymphocytic exudative effusion often triggers clinicians to think of tuberculosis, malignancy or an autoimmune pleuritis. However, we have found that in a substantial amount of cases, the only pathologic diagnosis obtained by pleural biopsy is a nonspecific pleuritis, also known as chronic pleuritis (Figure 2). Often these patients have no other explanation, such as an underlying autoimmune disease. These are challenging scenarios. Around 90 percent of the time, malignancy never develops and treatment is aimed at effusion management. However, in the remaining 10 percent a pathologic diagnosis of chronic pleuritis may represent inadequate sampling or could herald the development of mesothelioma in the future. For this reason, a multidisciplinary team is important to diagnose, manage and continue to monitor patients with chronic pleuritis.

Currently Pulmonary and Critical Care Medicine is enrolling for Prospective Evaluation of the Prevalence of Infectious Pathogens in Culture-Negative, Non-Specific Pleuritis Patients, an ongoing study evaluating the prevalence of viral pathogens in pleural fluid for patients with nonspecific chronic pleuritis. For more information, contact Darlene R. Nelson, M.D., primary investigator, Pulmonary and Critical Care Medicine, at nelson.darlene@mayo.edu.

Pleural disease management at Mayo Clinic
In recognition of the rapid growth of diagnostic and management strategies for recurrent pleural effusions, Mayo Clinic has established a dedicated pleural clinic with interventional pulmonologists, thoracic surgeons and nurses who are all specialized in treating patients with both malignant and nonmalignant pleural disease. The clinic provides full consultative services as well as thoracentesis, pleural manometry, thoracostomy and tunneled catheter placement and management, and same-day outpatient pleuroscopy.

For patients diagnosed with mesothelioma or other pleural-based malignancy, the team expands to include radiation oncologists, medical oncologists and pulmonary pathologists. All patients with any pleural-based malignancy are presented in multidisciplinary tumor board meetings. Conducted every Monday, the tumor board involves thoracic surgeons, interventional pulmonologists, medical and radiation oncologists, radiologists, and pathologists. Cases cared for at Mayo Clinic in Rochester, Minnesota, as well as Mayo Clinic Health System sites are discussed.

To have a case reviewed by the tumor board, contact Dennis Wigle, M.D., Ph.D., Thoracic Surgery, at wigle.dennis@mayo.edu or Shanda Wigle, M.D., Ph.D., Thoracic Surgery, at wigle.dennis@mayo.edu.
Mesothelioma team at Mayo Clinic
Mesothelioma is an uncommon, aggressive and almost universally fatal malignancy. It primarily develops in people with previous (20 to 60 years ago) asbestos exposure. Other risk factors include:

- Exposure to other fibrous minerals, such as erionite
- Prior radiation therapy
- Genetic causes such as BRCA1 associated protein-1 (BAP1) cancer syndrome

Mesothelioma typically arises from mesothelial cells lining the pleural cavity but can also develop in the peritoneal cavity, pericardium or the tunical vaginalis (scrotum). There are approximately 3,500 newly diagnosed cases of malignant pleural mesothelioma (MPM) in the United States. Overall the incidence of malignant pleural mesothelioma peaked in the United States in 2000, but continues to rise worldwide due to a continued rise in parts of Europe, Asia and Australia.

Patients often present with dyspnea and chest pain with an associated pleural effusion. Although the effusion will typically have exudative characteristics, pleural fluid cytology is generally insufficient for the diagnosis of mesothelioma and suspicious cytology results have to be confirmed by tissue biopsy before a diagnosis of mesothelioma is established.

The most commonly utilized techniques for tissue biopsy include pleuroscopy, VATS and computerized tomography-guided biopsy. The diagnostic sensitivity of direct pleural biopsy by pleuroscopy or VATS method is 98 percent. Due to the high rate of entrance site metastasis, at Mayo Clinic pleural exploration is deliberately limited to a single port placed in the location of a future incision that may be removed or excised in the future.

Due to the complexity of diagnosis, staging and treatment of mesothelioma guidelines, Mayo specialists recommend that these patients be evaluated and treated in centers with specialized and dedicated mesothelioma programs. Mayo offers just such a multidisciplinary program, staffed by interventional pulmonologists, thoracic surgeons, radiation and medical oncologists, thoracic pathologists, and thoracic radiologists. Every case of mesothelioma is carefully reviewed in a multidisciplinary fashion and individualized treatment plans established.

Currently available treatment options at Mayo include neoadjuvant radiotherapy followed by extrapleural pneumonectomy (SMART protocol) and neoadjuvant chemotherapy followed by pleurectomy decortication and intensity-modulated radiation therapy.

All patients with mesothelioma should also be offered participation in ongoing clinical trials at Mayo Clinic:

- For information about the Intrapleural Measles Virus Therapy in Patients With Malignant Pleural Mesothelioma study, contact Tobias Peikert, M.D., primary investigator, Pulmonary and Critical Care Medicine, at peikert.tobias@mayo.edu.
- For information about the Intrapleural Cryotherapy for Malignant Pleural Mesothelioma study, contact Shanda Blackmon, M.D., M.P.H., primary investigator, Thoracic Surgery, at blackmon.shanda@mayo.edu.

Refer patients with confirmed or suspected malignant mesothelioma directly to the Pleural Disease Clinic by calling 507-266-0415 or emailing John J. Mullon, M.D., medical director, at mullon.john@mayo.edu.

For more information


Education Opportunities
For more information or to register for courses, visit https://ce.mayo.edu/pulmonary-medicine/node/1664, call 800-323-2688 (toll-free) or email cme@mayo.edu.

Multidisciplinary Update in Pulmonary and Critical Care Medicine 2016
April 7-10, 2016, in Scottsdale, Ariz.
Mayo Clinic specialists in pulmonary and critical care medicine, pulmonary pathology, and radiology provide a comprehensive approach to the current evaluation and management of various respiratory diseases.
Current Studies and Clinical Trials

The Emprint Ablate and Resect Study in Patients With Metastatic Lung Tumors (EMPRESS)
Principal investigator: Shanda Blackmon, M.D., M.P.H.
Synopsis: Post-market prospective, nonrandomized, single-arm, multicenter study designed to demonstrate dose response of the Emprint ablation system using a percutaneous approach in patients with metastatic or primary lung tumors. Once the ablation procedure is complete, the scheduled surgical tumor resection will be performed.
Contact: Thoracic Surgery Clinical Research Unit, 877-526-9172 (toll-free)
Study coordinators: Karlyn E. Pierson, M.A.N., R.N., CCRP, and Bettie J. Lechtenberg, CCRP
NCT02323854

Pilot Study to Evaluate the Effects of Intrapleural Cryotherapy on Tumor-Infiltrating Lymphocytes in Malignant Pleural Mesothelioma Using Cryospray Therapy Followed by Pleurectomy
Principal investigator: Shanda Blackmon, M.D., M.P.H.
Synopsis: Pilot study evaluating the effects of intrapleural cryotherapy on tumor-infiltrating lymphocytes in malignant pleural mesothelioma. Soon to be open to enrollment.
Contact: Thoracic Surgery Clinical Research Unit, 877-526-9172 (toll-free)
Study coordinators: Karlyn E. Pierson, M.A.N., R.N., CCRP, and Bettie J. Lechtenberg, CCRP
NCT: None

MARK 1A Series: Percutaneous Microwave Ablation for Patients With Lung Tumor(s)
Principal investigator: Shanda Blackmon, M.D., M.P.H.
Synopsis: This is a single-arm pilot trial designed to characterize new ablation technology with regard to clinical outcomes of lung ablation in patients deemed to be surgically high risk.
Contact study coordinators: Karlyn E. Pierson, M.A.N., R.N., CCRP, and Bettie J. Lechtenberg, CCRP, 877-526-9172 (toll-free)

Humanitarian Device for Use in the Control of Prolonged Air Leaks
Principal investigator: Eric S. Edell, M.D.
Summary: Humanitarian use. The Spiration IBV Valve System is intended to control prolonged air leaks of the lung or significant air leaks that are likely to become prolonged air leaks after lobectomy, segmentectomy or lung volume reduction surgery.
Contact: Eric S. Edell, M.D., 507-284-3822, and John J. Mullon, M.D., 507-284-5398
Study coordinator: Kathleen S. Mieras, 800-753-1606 (toll-free)
NCT: None

Prospective Evaluation of the Prevalence of Infectious Pathogens in Culture-Negative, Non-Specific Pleuritis Patients
Principal investigator: Darlene R. Nelson, M.D.
Aims, purpose or objectives: To describe the prevalence of viral pathogens in pleural fluid among adult patients with a diagnosis of biopsy-proven, culture-negative, nonspecific pleuritis.
Contact study coordinator: Kathleen S. Mieras, 800-753-1606 (toll-free)
NCT: none

Intrapleural Measles Virus Therapy in Patients With Malignant Pleural Mesothelioma
Principal investigator: Tobias Peikert, M.D.
Summary: This phase I clinical trial investigates the side effects and the best dose of local intrapleural measles virus therapy in treating patients with malignant pleural mesothelioma. The investigators anticipate that the intrapleural of the vaccine strain measles virus will enable the virus to specifically infect and kill cancer cells and spare, without damaging, normal cells. Furthermore, the investigators expect the measles virus to trigger an anti-tumor immune response that will result in additional destruction of the tumor by immune cells.
Contact: Medical Oncology Clinical Research Unit, 507-284-8440
Study coordinator: Jill K. Burton, CCRP
NCT01503177

A Prospective, Randomized, Controlled Multicenter Clinical Study to Evaluate the Safety and Effectiveness of the Spiration Valve System for the Single Lobe Treatment of Severe Emphysema (EMPROVE)
Principal investigator: Jorge M. Mallea, M.D.
Primary outcome measure: The primary effectiveness endpoint will be the difference between the treatment and control groups in the mean change in forced expiratory volume in 1 second (FEV1).
Time frame: Baseline and 6 months
Contact study coordinators: Verna J. Skinner, CCRP; Estela Skaggs; Iris Orenjo, R.N., CCRP; Johnathan (Jonathan) J. Wright, C.C.R.C.; 904-783-7719
NCT01812447

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