Lung cancer is abnormal proliferation arising within the airways or tissue of the lung. Traditionally divided into non-small cell and small cell carcinoma. Small cell carcinoma accounts for approximately 16% of all cases of lung cancer. Unusual tumor types such as carcinoid tumor account for approximately 5% of cases. The remainder of cases are attributable to non-small cell carcinoma.

Lung Cancer: Epidemiology

• Lung cancer is the second most common cancer in the United States
• Lung cancer is the #1 cause of cancer-related mortality in the United States
• The American Cancer Society (ACS) estimates that in the United States in 2012:
  – 226,160 new cases of lung cancer
  – 160,340 lung cancer related deaths
  – Lung cancer will account for 28% of all cancer-related deaths


Lung Cancer: Epidemiology

• Lung cancer is the leading cause of years of life lost to cancer in the United States
  – Estimated 15 years of life lost on average per person dying of lung cancer


Lung Cancer: Epidemiology

• It is estimated that 7% of everyone born today will be diagnosed with lung cancer during their lifetime and nearly 6% will die from lung cancer
• Lung cancer rates have been increasing steadily in recent years throughout the world, and differences between countries have largely mirrored differences in smoking rates
• Worldwide estimated 1.6 million new cases and 1.4 million deaths from lung cancer in 2008

Lung Cancer: Risk Factors

- Smoking is greatest risk factor for lung cancer
- Smoking is responsible for approximately 85% of lung cancer cases in the United States
- Worldwide, smoking accounts for 75-80% of cases of lung cancer in men and not less than 50% of cases in women
- Smoking most associated with small cell and squamous cell carcinoma and less associated with adenocarcinoma, including adenocarcinoma in situ (AIS)


Lung Cancer: Risk Factors

- How many smokers are there?
  - NCI estimated that in 2006-2007, approximately 37% of the US population were current or former smokers
  - In 2008, an estimated 7 million Americans between ages 55-75 had at least a 30 pack-year smoking history
  - Estimated 19% of US population in 2010 were current smokers.
  - Projected that 17% of the US population will be current smokers by the year 2020


Lung Cancer: Risk Factors

- Other risk factors for lung cancer:
  - Age: Incidence of lung cancer significantly increases with age
  - Environmental radon exposure
  - Family history
  - COPD
  - Pulmonary fibrosis
  - Exposure to second hand smoke
  - Indoor cooking fumes
  - Occupational exposures including asbestos, arsenic, chromium, and coal tar

Lung Cancer: Risk Factors

- Women may be at higher risk than comparably exposed men according to some studies
- Blacks are nearly twice as likely as whites to die of tobacco-related malignancy
  - Race/ethnicity may play a role
- Lung cancer may be higher in patients with disadvantaged socioeconomic status
  - This may reflect unmeasured confounding tobacco use


Lung Cancer: Natural History

- Lung cancer traditionally has poor prognosis, causing death in 90% of affected patients
- Stage at diagnosis is a strong predictor of mortality, but overall carries a 16% 5-year survival (all stages combined)
- 75% of patients present with symptoms due to locally advanced or metastatic lung cancer which is not able to be cured


Lung Cancer: Natural History

- Survival for patients with lung cancer related to stage (in addition to many other factors)
- 5 year survival for NSCLC:
  - Stage IA: 49%
  - Stage IB: 45%
  - Stage IIA: 30%
  - Stage IIB: 31%
  - Stage IIIA: 14%
  - Stage IIIB: 5%
  - Stage IV: 1%

NCI SEER Database 1998-2000
Lung Cancer: Natural History

- 5 year survival for SCLC:
  - Stage I: 31%
  - Stage II: 19%
  - Stage III: 8%
  - Stage IV: 2%

NCI SEER Database 1988-2001

Recent Mortality Statistics

- At least 167,133 cancer deaths in the United States in 2014 were caused by cigarette smoking
- Indiana is #12 overall, with 4099 cancer deaths caused by cigarette smoking

JAMA Intern Med. Published Online October 24, 2016
What Makes Lung Cancer a Good Target for Screening?

• High Morbidity and Mortality
• Relatively high prevalence in high risk populations
• Mortality and survival in lung cancer related to initial stage of diagnosis, therefore, early diagnosis may be beneficial
• Based on this, an effective screening program for early diagnosis and treatment may have a significant impact on the high mortality of lung cancer


What Makes a Good Screening Test?

• The condition or disease should be an important health problem
• There should be an identifiable latent or early symptomatic stage
• The natural history of the condition or disease should be adequately understood, including progression from latent to symptomatic disease
• There should be an accepted treatment for the condition and an agreed upon policy on whom to treat
• High sensitivity and specificity
• Acceptable to patients and providers
• Cost effective
• Non-invasive or minimally invasive
• Facilities for diagnosis and treatment should be widely available
• Screening should be a continuous process rather than a “once and done” proposition

Background Information:

- Several studies have been completed using plain chest radiographs with or without sputum cytology for lung cancer screening
- These studies have all been negative
- There have also been 3 other smaller European trials of low dose CT screening have shown no benefit to LDCT screening

Randomized trial of 3 annual LDCT scans (n=26,722) versus 3 annual single view PA chest radiographs (n=26,732)

- Total n=53,454
- Enrollment between August 2002 and April 2004 at 33 centers
- Data regarding cases of lung cancer and death from lung cancer collected through December 31, 2009
National Lung Cancer Screening Trial

• Adherence to screening was >90%
• Positive screening result obtained in 24.2% of LDCT and 6.9% of chest x-rays over all 3 rounds of screening
• A total of 96.4% of positive results in the LDCT group and 94.5% in the chest x-ray group were FALSE POSITIVES
• Incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23)

National Lung Cancer Screening Trial

• There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group
• Relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P = 0.004)

National Lung Cancer Screening Trial

• Death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P = 0.02)
<table>
<thead>
<tr>
<th>Organization</th>
<th>Groups Eligible for Screening</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Family Practice</td>
<td>Evidence is insufficient to recommend for or against screening.</td>
<td>2013</td>
</tr>
<tr>
<td>American Association for Thoracic Surgery</td>
<td>1. Age 55 to 79 years with ≥ 30 pack-year smoking history. 2. Long-term lung cancer survivors who have completed 4 years of surveillance without recurrence, and who can tolerate lung cancer treatment in order to detect second primary lung cancer until the age of 79. 3. Age 50 to 79 years with ≥ 20 pack-year smoking history and additional comorbidity that produces a cumulative risk of developing lung cancer ≥ 5% in 5 years.</td>
<td>2012</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>Age 55 to 74 years with ≥ 30 pack-year smoking history, either currently smoking or have quit within the past 15 years, and who are in relatively good health.</td>
<td>2013</td>
</tr>
</tbody>
</table>
### Lung Cancer Screening Guidelines and Recommendations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Groups Eligible for Screening</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Chest Physicians (CHEST)</td>
<td>Age 55 to 74 years with ≥ 30 pack-year smoking history and either continue to smoke or have quit within the past 15 years.</td>
<td>2013</td>
</tr>
<tr>
<td>American College of Chest Physicians and American Society of Clinical Oncology</td>
<td>Age 55 to 74 years with ≥ 30 pack-year smoking history and either continue to smoke or have quit within the past 15 years.</td>
<td>2012</td>
</tr>
<tr>
<td>American Lung Association</td>
<td>Age 55 to 74 years with ≥ 30 pack-year smoking history and no history of lung cancer.</td>
<td>2012</td>
</tr>
</tbody>
</table>
| National Comprehensive Cancer Network (NCCN) | 1. Age 55 to 74 years with ≥ 30 pack-year smoking history and smoking cessation < 15 years.  
2. Age ≥ 50 years and ≥ 20 pack-year smoking history and 1 additional risk factor (other than secondhand smoke). | 2012  |
| U.S. Preventative Services Task Force (USPSTF) | Age 55 to 80 years with ≥ 30 pack-year smoking history and smoking cessation < 15 years. | 2013  |

**Figure 3: Meta-Analysis of Lung Cancer Mortality**

<table>
<thead>
<tr>
<th>Study, year (Y)</th>
<th>F/Y</th>
<th>Mean age (Yr)</th>
<th>Mean pack-years (Yr vs. Ctrl)</th>
<th>Screening lines (Yr)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIST, 2011**</td>
<td>59% male</td>
<td>53</td>
<td>56</td>
<td>0,1,2</td>
<td>0.89 (0.73 to 0.93)</td>
</tr>
<tr>
<td>DANTE, 2008**</td>
<td>2.8% 100% male</td>
<td>56</td>
<td>63</td>
<td>47.3 vs. 47.2</td>
<td>0.83 (0.45 to 1.54)</td>
</tr>
<tr>
<td>DL-CRP, 2010**</td>
<td>56% male</td>
<td>56</td>
<td>64</td>
<td>26.4 vs. 26.9</td>
<td>1.27 (0.63 to 2.67)</td>
</tr>
<tr>
<td>Overall (I² = 0%) p = 0.405</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91 (0.72 to 1.19)</td>
</tr>
</tbody>
</table>

*Var 10,000 person-years

**Abbreviations: Ctrl = control; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Techniques and Historical Categorization; DL-CRP = Computed Lung Cancer Screening Trial; F/Y = follow-up; L = intervention; NIST = National Lung Screening Trial; RR = relative risk; vs. = versus; yr. = year.


**Figure 4: Meta-Analysis of All-Cause Mortality**

<table>
<thead>
<tr>
<th>Study, year (Y)</th>
<th>F/Y</th>
<th>Mean age (Yr)</th>
<th>Mean pack-years (Yr vs. Ctrl)</th>
<th>Screening times (Yr)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIST, 2011**</td>
<td>59% male</td>
<td>53</td>
<td>56</td>
<td>0,1,2</td>
<td>0.93 (0.86 to 0.99)</td>
</tr>
<tr>
<td>DANTE, 2008**</td>
<td>2.8% 100% male</td>
<td>56</td>
<td>63</td>
<td>47.3 vs. 47.2</td>
<td>0.85 (0.56 to 1.27)</td>
</tr>
<tr>
<td>DL-CRP, 2010**</td>
<td>56% male</td>
<td>56</td>
<td>64</td>
<td>26.4 vs. 26.9</td>
<td>1.46 (0.60 to 3.45)</td>
</tr>
<tr>
<td>Overall (I² = 61%) p = 0.077</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.02 (0.78 to 1.33)</td>
</tr>
</tbody>
</table>

*Var 10,000 person-years

**Abbreviations: Ctrl = control; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Techniques and Historical Categorization; DL-CRP = Computed Lung Cancer Screening Trial; F/Y = follow-up; L = intervention; NIST = National Lung Screening Trial; RR = relative risk; vs. = versus; yr. = year.

EBUS and EBUS-TBNA in Lung Cancer Staging

Definition of terms

- **EBUS**: Endobronchial Ultrasound
- **TBNA**: Transbronchial Needle Aspiration
- **EBUS-TBNA**: Endobronchial Ultrasound Guided Transbronchial Needle Aspiration
TYPES OF EBUS

- Two types of endobronchial ultrasound (EBUS) exist:
  - Radial Probe EBUS (RP-EBUS)
  - Convex Probe EBUS (CP-EBUS)

What is EBUS?

- Types of Endobronchial Ultrasound:
  - Radial Probe (RP-EBUS)

20 MHz Probe. Less depth of penetration. Greater axial and lateral resolution.
What is EBUS?

- **Types of Endobronchial Ultrasound**:
  - Convex Probe (CP-EBUS)

7.5 MHz Probe: Increased depth of penetration. Less axial and lateral resolution

Convex-probe EBUS (CP-EBUS)
Olympus BF-UC180F

- 2.2 mm Instrument Channel
- Scanning Range: 50 degrees

Outer Diameter:
- Distal end: 6.9mm
- Insertion tube: 6.3 mm

Direction and field of View:
- 35 degrees forward oblique
- 80 degree field of view

Ridges for balloon
### RP vs CP EBUS

- RP-EBUS typically has higher resolution than CP-EBUS such that airway structure and parenchymal lesions are visualized in better detail.
- However, unlike CP-EBUS, RP-EBUS cannot be used to biopsy targets in real time. Thus, for the purposes of sampling, CP-EBUS is more frequently used to acquire tissue, while RP-EBUS is often used to locate a target lesion suitable for sampling (e.g., peripheral nodules).

### CLINICAL APPLICATIONS

- Visualize mediastinal and peribronchial
  - lymph nodes and metastases and allow EBUS-guided TBNA
- Determine depth of tumor invasion of tracheobronchial lesions
- Define positional relationships with pulmonary
  - artery and veins and hilar structures
- Localize and diagnose peripheral pulmonary
  - lesions (benign or malignant)

### Specifications at a Glance

**BF-UC180F**

<table>
<thead>
<tr>
<th><strong>Optical System</strong></th>
<th><strong>Insertion Tube</strong></th>
<th><strong>Instrument Channel</strong></th>
<th><strong>Bending Section</strong></th>
<th><strong>Total Length</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view</td>
<td>36° forward oblique</td>
<td>Channel inner diameter</td>
<td>Angulation range</td>
<td>890 mm</td>
</tr>
<tr>
<td>Direction of view</td>
<td>60°</td>
<td>Channel outer diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth of field</td>
<td>2-50 mm</td>
<td>Insertion tube outer diameter</td>
<td>Up 120°, down 90°</td>
<td></td>
</tr>
</tbody>
</table>

- Balloon water supply port is in the groove
- Objective lens
- Instrument channel outlet
CLINICAL APPLICATIONS

- Staging of non-small cell lung cancer (NSCLC)
- Diagnosis and to evaluate pathologic conditions like pulmonary sarcoma and pulmonary embolism
- Extrinsic compression of the airway by peri-bronchial process
- Submucosal disease
- Diagnosis of endobronchial lesions with necrotic tumor, hemorrhagic tumor, predicting line of surgical resection
- Follow up of small cell tumors, lymphoma

ADVANTAGES

- EBUS is a minimally-invasive
- Real-time imaging permits the sampling of lymph nodes that are smaller than 10 mm in short axis and/or near major blood vessels
- High diagnostic yield
- Safe procedure that can be performed on an outpatient basis using local anesthesia and conscious sedation or general anesthesia.
- EBUS can access a wide range of mediastinal lymph nodes as well as hilar lymph nodes (2R, 2L, 3P, 4R, 4L, 7, 10R, 10L, 11R, 11L), and sample centrally located pulmonary lesions with high sensitivity.
- Complications are uncommon, while sampling is performed in real time.

DISADVANTAGES

- EBUS cannot image or sample subaortic and para-aortic lymph nodes (stations 5 and 6).
- Its availability is institution-specific, and expertise is required to interpret images and obtain diagnostic samples.
- Small sample size.
Obtaining the sample

EBUS-TBNA principle

EBUS Scope: Obtaining the Sample
Orientation

POSTERIOR

CAUDAL

CRANIAL

ANTEOR

DEDICATED 21,22-GAUGE NEEDLE

Echogenic dimpled tip design combined with a stopping mechanism for safe, reliable TBNA in the bronchi.

Features:
- Surface of the needle tip has an echogenic dimpled design to improve visibility on ultrasound images.
- Maximum advancing stroke is 20 mm.
- To prevent accidental perforation in oleary use, a removable safety mechanism stops the needle at 20 mm.
- Specifically designed for use with the Olympus EBUS-TBNA scope.
- Pre-shaped and angle cure.
- Two types of needle gauge available: 22 gauge and 21 gauge.
- "One-piece design of the needle is designed to allow increased space for operating room use.
- "In vitro designs of the needle is designed to provide more stiffness for a better needle penetration.
- "Designed to offer more flexibility for easier accessibility.

Olympus Vizishot EBUS-TBNA Needles
Where are the Regional Lymph Nodes and How are they Named?
Lymph Nodes Accessible by Cervical Mediastinoscopy

- Lymph node stations 2R, 2L, 4R, 4L, and station 7 lymph nodes are accessible by standard cervical mediastinoscopy.
- Lymph node stations 1R and 1L are above the suprasternal notch and are not accessible by standard mediastinoscopy.

Lymph Nodes Accessible by Extended Mediastinoscopy

- Lymph node stations 5 (subaortic) and 6 (paraaortic) are accessible by extended mediastinoscopy.
- Alternative to anterior mediastinotomy (Chamberlain procedure).
- More technically challenging than standard cervical mediastinoscopy.

Lymph Nodes Accessible by EUS-FNA

- Lymph node stations 2R, 2L, 4R, 4L, 7, 8 (paraeosophageal), and 9 (pulmonary ligament) are accessible by EUS-FNA.
- Also allows access to the left lobe of the liver and adrenal glands, particularly the left adrenal gland.
Figure 1. Regional lymph node stations for lung cancer staging accessible by EBUS (white circle) and EUS (green circle). Yellow circle = MRCS + EUS; gray circle = Nonaccessible by EBUS or EUS.

### Accuracy of Staging in Lung Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Studies</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinoscopy</td>
<td>35</td>
<td>10,648</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>EUS</td>
<td>26</td>
<td>2,443</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>EBUS</td>
<td>26</td>
<td>2,756</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>EBUS/EUS</td>
<td>7</td>
<td>811</td>
<td>91</td>
<td>100</td>
</tr>
</tbody>
</table>

Silvestri et al. CHEST 2013; 143(5)(Suppl):e211s-e250s
ACCP Lung Cancer Guidelines 2013

- In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no discrete metastases), a needle technique (EBUS-NA, EUS-NA, or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test

Silvestri et al. CHEST 2013; 143(5)(Suppl):e211S–e250S

Safety and Complications

- Overall, very safe with minimal reported complications
- Complications of conscious sedation/general anesthesia
- Rarely, infection has been reported following EBUS-TBNA including infectious pericarditis/pericardial effusion, tumor bed infection, mediastinal abscess, mediastinitis
- Mechanism likely related to introduction of oral contaminants
- Rare bleeding complications, even in a series which did not hold Plavix prior to EBUS-TBNA

Safety and complications

- EBUS pneumothorax rate 0.2%
  - TBBx pneumothorax rate 1-6% (4.0%)
- EBUS-TBNA bleeding rate 0.2%
  - TBBx bleeding rate 2-9% (2.1%)
Clinical Pearls

- Central tumor or suspected N1 disease, 20-25% change of N2 or N3 nodal involvement
- We usually sample the highest lymph node station
  - First: N3→N2→N1
- Time to treat should be 1 month or less
- Usual number of aspirations are 3-4 needle passes
- Need 4 additional passes for mutational analysis.
- Need 500 cells to perform EGFR, 50 cells for ALK
- Non-diagnostic EBUS-TBNA: blood and bronchial epithelial cells with no malignant cells identified.
- Confirm negative EBUS with mediastinoscopy before resection

Recommended Reading


Recommended Reading