Lung Cancer Update: Prevention, Screening, Diagnosis and Treatment

Talmadge E. King, Jr., M.D.
Julius R. Krevans Distinguished Professorship in Internal Medicine
Chair, Department of Medicine
University of California San Francisco (UCSF)
San Francisco, CA

Disclosure Statement

Dr. King has served on a Scientific Advisory Board for the following companies:

- InterMune
- ImmuneWorks
- Boehringer Ingelheim
- Daiichi Sankyo Pharma
- UpToDate

Outline of Presentation

- Burden of lung cancer
- Risk factors for lung cancer
- Types of lung cancer
- Lung cancer screening
- Lung cancer diagnosis
- Staging of lung cancer
- Treatment

Take Home Messages

1. Lung cancer is the most common cause of cancer mortality worldwide for both men and women.
2. Cigarette smoking is responsible for ~85-90% of cases of lung cancer.
3. When a patient presents with suspected NSCLC, the diagnosis should be confirmed and both the histologic type and disease stage should be determined. The disease stage is a measure of the extent of disease, which is used to determine prognosis and guide management.
4. Annual screening with low-dose CT (LDCT) scanning:
   - Adults aged 55 to 80 years
   - 30 pack-year smoking history
   - Current smoker or quit within the last 15 years
Take Home Messages

5. The clinical manifestations of lung cancer due to:
   – intrathoracic effects (eg, cough, hemoptysis, pleural disease),
   – extrathoracic metastases (most commonly, liver, bone, brain),
   – paraneoplastic phenomena (eg, hypercalcemia, Cushing’s syndrome, hypercoagulability disorders, various neurologic syndromes).

6. Integrated PET/CT, if available, is preferred over an initial CT of the chest followed by whole body PET.

7. The prevention of smoking and cessation of smoking offer the most important route to decreasing the morbidity and mortality associated with this disease.

LUNG CANCER: LEADING CAUSE OF CANCER-RELATED MORTALITY IN MEN AND WOMEN.

• More individuals die of lung cancer than of colon, breast, prostate and pancreas cancers combined.

Worse of the Worse!
Significant Decreases Reported in Annual Lung Cancer Rates

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>3.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>35</td>
<td>1.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>45</td>
<td>0.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>55</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>65</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>75</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Burden of Lung cancer: 2014

- **New cases: 224,210**
  - 116,000 in men (Black ~20% more likely)
  - 108,210 in women
  - Lifetime risk of lung cancer diagnosis: 7%
- **Deaths: 159,260**
  - 86,930 in men
  - 72,330 in women
  - 27% of all cancer deaths
  - Lifetime risk of lung cancer death: 5.8%

RISK FACTORS FOR LUNG CANCER

- **Smoking**—~87% of lung cancers are related to smoking.
- **Secondhand smoke** is also a risk factor.
- Unfortunately, worldwide tobacco consumption = epidemic for years to come!
RISK FACTORS FOR LUNG CANCER

• Many tobacco-related carcinogens; two major classes are the N-nitrosamines and polycyclic aromatic hydrocarbons.
• Other factors that influence the risk:
  – Age at which smoking began,
  – Number of cigarettes smoked per day,
  – Duration of smoking,
  – Intensity of smoking,
  – Depth of inhalation,
  – Composition of the cigarette.

RISK FACTORS: Type of Cigarettes

• Shift from nonfiltered to filtered cigarettes; “light” low-tar cigarettes, “all natural” or menthol.
• Only altered the most frequent type of lung cancer, shifting from Sq Cell Ca to adenocarcinoma.

RISK FACTORS: Marijuana

• Produces histologic and molecular changes in the bronchial epithelium that are similar to the metaplastic premalignant alterations seen among tobacco smokers.
• Users probably at increased risk for lung cancer, although the magnitude of risk has not been well quantified.

Lung Cancer in Never Smokers

• “Never smoker” = smoked <100 cigarettes in lifetime.
• Worldwide, lung cancer in never smokers comprises an ~15 to 20% of cases in men and >50% in women.
• Major geographic differences, particularly in Asia, where 60 to 80 percent of women with the disease are never smokers.
• The incidence of small cell lung cancer in never smokers is exceedingly small.
OTHER RISK FACTORS FOR LUNG CANCER

• ≈2% to 9% of lung cancers related to occupational exposures
• Radon, arsenic, asbestos, chromium, radioactive dust, bis-chloromethyl ether, formaldehyde, ionizing radiation, nickel, polycyclic aromatic hydrocarbons, hard metal dust, and vinyl chloride.

GENETIC FACTORS & LUNG CANCER

• Poorly understood.
• First-degree relatives of individuals with lung cancer have an increased risk of developing lung cancer (relative risk 1.8, 95% CI 1.6-2.0)
  – Greatest in relatives of patients diagnosed with lung cancer at a young age;
  – Those with multiple affected family members.
• The increased risk in relatives of patients with early onset lung cancer appears to extend to non-lung malignancies.

OTHER RISK FACTORS FOR LUNG CANCER

• COPD is an independent risk factor.
  – risk increases as the forced expiratory volume in 1 second (FEV₁) decreases.
• IPF and tuberculosis

FACTORS THAT MODIFY RISK FOR LUNG CANCER

• Higher consumption
  – Fruits and vegetables = reduced lung cancer risk,
  – Increased dietary fat intake = a higher risk.
• Supplementation with vitamins A and E, and beta carotene has not positively influenced risk.
Types Of Lung Cancer

• There are two main types of lung cancer:
  —non-small cell (NSCLC)
  —small cell
• These categories are used for treatment decisions and determining prognosis (prospect of recovery).

Non–small Cell Lung Cancer (NSCLC)

• Adenocarcinoma
• Squamous cell carcinoma
• Large cell carcinoma, and
• Variants.
**Adenocarcinoma**
- 35-40% of all lung cancers.
- Arising from the bronchial mucosal glands
- It usually occurs in a peripheral location within the lung.
- Subtype observed most commonly in persons who do not smoke.

**Bronchoalveolar Carcinoma**
- Classic manifestation as an interstitial lung disease on chest radiograph.
- Arises from type II pneumocytes and grows along alveolar septa.
- May manifest as a solitary peripheral nodule, multifocal disease, or a rapidly progressing pneumonic form.
- In advanced disease = voluminous watery sputum.

**Squamous Cell Carcinoma**
- 25-30% of all lung cancers
- Central parts of the lung
- Classic manifestation + cavitary lesion in a proximal bronchus.
- Type most often associated with hypercalcemia.

**Squamous Cell Carcinoma**
- Characterized histologically by the presence of keratin pearls
- Can be detected with cytologic studies because it has a tendency to exfoliate.
**Large cell carcinoma**

- 10-15% of lung cancer
- Typically manifesting as a large peripheral mass on chest radiograph;
- Decreasing in incidence
- Histologically, this type has sheets of highly atypical cells with focal necrosis, with no evidence of keratinization (typical of SCC) or gland formation (typical of adenocarcinomas).

**Small Cell Lung Cancer**

- Several types:
  - pure small cell,
  - mixed small cell, and
  - combined small cell.
- Usually more aggressive than NSCLC
- Central lesion with hilar and mediastinal invasion along with regional adenopathy.
- Metastatic disease at diagnosis (bones, liver, adrenal glands, pericardium, brain, and spinal cord)

**LUNG CANCER SCREENING**
Lung Cancer and Early Detection

- No tests are recommended for screening the general population
- We should discuss the benefits and limitations of a screening CT scan in any person who is at increased risk due to smoking or asbestos exposure.

Screening Approaches

- NO
  - Chest x-ray
- NO
  - Sputum
- YES
  - Low dose CT scans

US Preventive Services Task Force (USPSTF)

- Independent panel of nonfederal experts in prevention and evidence-based medicine
  - Volunteer members represent primary care disciplines
  - No substantial financial, intellectual, or other conflicts that would impair the scientific integrity of the work of the Task Force

US Preventive Services Task Force (USPSTF)

- Rigorous review of existing peer-reviewed evidence
  - Ratings reflect the strength of the evidence on the harms and benefits of a preventive service
  - Task Force does not consider the costs of providing service or make recommendations for coverage
**US Preventive Services Task Force**

- **Annual screening** with low-dose CT (LDCT) scanning:
  - Adults aged 55 to 80 years
  - 30 pack-year smoking history
  - Current smoker or quit within the last 15 years

- **Discontinue screening** in those who either:
  - have not smoked for >15 years or
  - who have developed a health condition that will substantially limit their life expectancy or
  - the feasibility of or their willingness to undergo curative lung surgery

---

**Low-dose helical CT scanning**

- Noncontrast study with a multidetector CT scanner
  - Single maximal inspiratory breath-hold; scanning time <25 seconds.
  - High-resolution (1.0 to 2.5 mm interval) images reconstructed using a soft tissue or thin-section algorithm.

- Overall average effective dose of low-dose CT is 2 mSv, compared with 7 mSv for a standard-dose diagnostic chest CT

**USPSTF Recommends: Structured Screening Process**

- Careful patient selection
- Not screening patients with lower risk or comorbid conditions that limit life expectancy or suitability for resection.
- Most false-positive results should be resolved without invasive procedures.
USPSTF Recommends: Structured Screening Process

• Screening in organized programs
  – discussion of benefits and harms;
  – smoking cessation counseling for active smokers;
  – standardized approach to scanning, image interpretation,
  – ensuring follow-up;
  – adherence to quality standards;
  – participation in a registry;
  – validation of results of the NLST.

CT: Potential Concerns

• Complications from invasive diagnostic evaluation procedures infrequent
  – At least one major complication: 10.8%
  – Death following procedure: 1.4%
• False-positive scan
• Benign nodule resections
• Over diagnosis
• Patient anxiety
• Radiation
• Cost

CT: Potential Concerns
~7 million eligible Americans

Who will evaluate people who are interested in or should consider CT screening for lung cancer.

• primary care physicians
• pulmonologists
• nurse practitioners
• radiologists

LUNG CANCER DIAGNOSIS
Presentation of Lung Cancer

- Often insidious; may produce no symptoms until the disease is well advanced.
- Early recognition of symptoms may be beneficial to outcome.
- At initial diagnosis,
  - 20% of patients have localized disease,
  - 25% of patients have regional metastasis, and
  - 55% of have distant spread of disease

The Most Common Symptoms

- Persistent cough
- Coughing up blood
- Chest pain
- Hoarseness
- Sudden onset of wheezing
- Shortness of breath
- Weight loss and loss of appetite
- Recurrent respiratory infections, such as pneumonia
- Fatigue
- If cancer has spread, symptoms include bone pain, difficulty breathing, abdominal pain, headache, weakness, and confusion

INITIAL EVALUATION

- Cell type non-small cell lung cancer versus small cell lung cancer (NSCLC versus SCLC)
- Stage of disease
- Functional status of the patient

How is Lung Cancer Evaluated?

- Chest x-ray or CT scan of the chest is performed
- Diagnosis must be confirmed with a biopsy
- The location(s) of all sites of cancer is determined by additional CT scans, PET (positron emission tomography) scans, and MRI (magnetic resonance imaging)
- It is important to find out if cancer started in the lung or somewhere else in the body.
**Initial Testing**

- Chest radiographs **NOT** recommended screening method in asymptomatic persons.
- **Chest radiographs** may show:
  - Pulmonary nodule, mass, or opacity
  - Mediastinal widening
  - Atelectasis
  - Hilar enlargement
  - Pleural effusion

**Methods of Confirming Diagnosis**

- Bronchoscopy
- Sputum cytology
- Mediastinoscopy
- Thoracentesis
- Thoracoscopy
- Transthoracic needle biopsy (CT- or fluoroscopy-guided)

**LUNG CANCER STAGING**

**TESTS FOR LUNG CANCER**

- **Computed tomography (CT) scan** of the lungs to identify abnormal tissue masses
- **Positron emission tomography (PET) scan** of the lungs to look for cancer cells
- **Bone scan** to determine whether the cancer has spread to the bones
What is Lung Cancer Staging?

• Staging is a way of describing a cancer, such as the size of the tumor and where it has spread
• Staging is the most important tool doctors have to determine a patient’s prognosis
• The type of treatment a person receives depends on the stage of the cancer
• Staging is different for non-small cell lung cancer and small cell lung cancer

Staging: Chest CT scan

• The TNM (tumor-node-metastasis) staging system used for all lung carcinomas except small-cell lung cancer.
• The TNM takes into account the following key pieces of information:
  – T describes the size of the primary tumor
  – N describes the spread of cancer to regional lymph nodes
  – M indicates whether the cancer has metastasized

Positron Emission Tomography (PET)

• PET or PET-CT useful in the initial staging to identify sites of tumor involvement.
• Integrated PET-CT has been shown to improve staging over PET scanning alone.
• A tumor’s metabolic activity using the standardized uptake value (SUV) to assess the tumor uptake of fluorodeoxyglucose (FDG).
  – HIGH SUV = associated with a poor prognosis
  – LOWER FDG uptake associated with a better prognosis

Primary tumor (T) involvement

• Tx - Primary tumor cannot be assessed
• T0 - No evidence of tumor
• Tis - Carcinoma in situ
• T1, T2, T3, T4: size and/or extension of the primary tumor
**Lymph node (N) involvement**

- **Nx** - Regional nodes cannot be assessed
- **N0** - No regional node metastasis
- **N1** - Metastasis in ipsilateral peribronchial and/or ipsilateral hilar nodes and intrapulmonary nodes, including involvement by direct extension
- **N2** - Metastasis in ipsilateral mediastinal and/or subcarinal node
- **N3** - Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene node, or supraclavicular node

**Metastatic (M) involvement**

- **M0** - No metastasis
- **M1** - Distant metastasis

**Stage I: Non-Small Cell Lung Cancer**

- Cancer is found only in the lung
- Surgical removal recommended
- Radiation therapy and/or chemotherapy may also be used

**Stage II: Non-Small Cell Lung Cancer**

- Cancer has spread to lymph nodes in the lung
- Treatment is surgery to remove the tumor and nearby lymph nodes
- Chemotherapy recommended; radiation therapy sometimes given after chemotherapy
Stage III: Non-Small Cell Lung Cancer

- Cancer has spread to the lymph nodes outside the lung
- **Stage IIIA** cancer spread to lymph nodes in the chest, on the same side where the cancer originated
- **Stage IIIB** cancer has spread to lymph nodes on the opposite side of the chest, under the collarbone, or the pleura.
- Surgery or radiation therapy with chemotherapy recommended for stage IIIA
- Chemotherapy and sometimes radiation therapy recommended for stage IIIB

Stage IV: Non-Small Cell Lung Cancer

- The cancer has spread to different lobes of the lung or to other organs, such as the brain, bones, and liver
- Stage IV non-small cell lung cancer is treated with chemotherapy

Small Cell Lung Cancer—All Stages

- Patients with limited stage (confined to one area of the chest) small cell lung cancer are treated with simultaneous radiation therapy and chemotherapy.
- Patients with extensive stage (not confined to one area of the chest) small cell lung cancer are treated with chemotherapy only.
- Because small cell lung cancer can spread to the brain, preventative radiation therapy to the brain is routinely recommended to all patients whose tumors disappear following chemotherapy and radiation therapy
How is Lung Cancer Treated?

• Many factors must be taken into account to determine the best treatment for an individual diagnosed with lung cancer.
  – Specific type of cell,
  – Location of the lung tumor,
  – Stage of the disease with possible metastasis,
  – General health of the individual.

How is Lung Cancer Treated?

• Treatment depends on the stage and type of lung cancer
  – Surgery
  – Radiation therapy
  – Chemotherapy
  – Targeted therapy
• Lung cancer is usually treated with a combination of therapies
• Skilled palliative care

Cancer Treatment: Surgery

• Treatment of choice for stage I and stage II NSCLC.
• The tumor and the nearby lymph nodes in the chest are typically removed to offer the best chance for cure.
• For NSCLC, a lobectomy, has shown to be most effective
• Surgery may not be possible in some patients

Cancer Treatment: Chemotherapy

• ~80% of all patients considered for chemotherapy during the course of their illness.
• Multiple trials and meta-analyses confirm superiority of combination chemotherapy regimens up front for advanced NSCLC.
• May be prescribed before or after surgery, or before, during, or after radiation therapy
• Can improve survival and lessen lung cancer symptoms in all patients, even those with widespread lung cancer
Cancer Treatment: Chemotherapy

- ASCO guidelines recommend that first-line treatment for NSCLC should include a platinum combination.
  - Younger patients, with a good performance status or in the adjuvant setting, cisplatin is preferred
  - Older patients or those with significant comorbidities, carboplatin may be substituted

Cancer Treatment: Chemotherapy

- 2 drugs, often given for 4 to 6 cycles followed by single chemo or targeted drug -- maintenance therapy
- Paclitaxel (Taxol®)
- Albumin-bound paclitaxel (nab-paclitaxel, Abraxane®)
- Docetaxel (Taxotere®)
- Gemcitabine (Gemzar®)
- Vinorelbine (Navelbine®)
- Irinotecan (Camptosar®)
- Etoposide (VP-16®)
- Vinblastine
- Pemetrexed (Alimta®)

Best Treatment for an Individual With Lung Cancer.

- The current standard of care for advanced NSCLC is to determine the chemotherapies to use on the basis of precise histologic subtype.
- In advanced, non-squamous cell carcinoma, molecular characterization for epidermal growth factor receptor (EGFR) mutations and/or anaplastic lymphoma kinase (ALK) alterations also helps to guide treatment decisions.

Personalized, genotype-directed therapy

- Activating mutations in the epidermal growth factor receptor (EGFR)
  - Define a subset of patients with adenocarcinoma that typically affects patients who are never smoking, women, and/or of Asian ethnicity.
  - Generally highly responsive to EGFR tyrosine kinase inhibitors (erlotinib, gefitinib) and have a significantly better prognosis than those without EGFR mutations.
- Presence of the EML4-ALK fusion oncogene defines
  - NSCLC subset that is more frequent in nonsmokers or former smokers and occurs at a younger age.
  - Highly responsive to crizotinib, an inhibitor of the anaplastic lymphoma kinase (ALK).
- Bevacizumab (Avastin®): targets vascular endothelial growth factor (VEGF), a protein that helps new blood vessels to form.
Cancer Treatment: Radiation Therapy

- Radiation is a reasonable option for lung cancer treatment among those who are not candidates for surgery.
- It is important that the radiation treatments avoid the healthy parts of the lung.

American Society Clinical Oncology (ASCO)

Cancer Treatment: Radiation Therapy

- Beta blockers have been found to improve overall survival, disease-free survival, and distant metastasis-free survival, though not locoregional progression-free survival, in patients with NSCLC undergoing radiotherapy.
- Side effects include fatigue, malaise (feeling unwell), loss of appetite, and skin irritation at the treatment site.
- Radiation pneumonitis occurs in 15% of patients.

Prognosis: 5-yr relative survival rate

- ~15.7%
- Survival rate varies markedly, depending on how advanced the disease is at diagnosis:
  - 49% for local disease
  - 16% for regional disease
  - 2% for distant stage disease

5-year survival rates for specific stages

- Stage IA - 75%
- Stage IB - 55%
- Stage IIA - 50%
- Stage IIB - 40%
- Stage IIIA - 10-35%
- Stage IIIB - Less than 5%
- Stage IV - Less than 5%
Follow-Up Care

• Quitting smoking helps recovery and health.
  – Patients who have developed lung cancer who then stop live longer.
  – It is never too late to stop smoking

“Quitting smoking is easy. I’ve done it a thousand times.”
Mark Twain

Take Home Messages

1. Lung cancer is the most common cause of cancer mortality worldwide for both men and women.
2. Cigarette smoking is responsible for ~85-90% of cases of lung cancer.
3. When a patient presents with suspected NSCLC, the diagnosis should be confirmed and both the histologic type and disease stage should be determined. The disease stage is a measure of the extent of disease, which is used to determine prognosis and guide management.
4. Annual screening with low-dose CT (LDCT) scanning:
   – Adults aged 55 to 80 years
   – Current smoker or quit within the last 15 years

Take Home Messages

5. The clinical manifestations of lung cancer due to:
   – intrathoracic effects (eg, cough, hemoptysis, pleural disease),
   – extrathoracic metastases (most commonly, liver, bone, brain), or
   – paraneoplastic phenomena (eg, hypercalcemia, Cushing’s syndrome, hypercoagulability disorders, various neurologic syndromes).
6. Integrated PET/CT, if available, is preferred over an initial CT of the chest followed by whole body PET.
7. The prevention of smoking and cessation of smoking offer the most important route to decreasing the morbidity and mortality associated with this disease.

THANK YOU FOR YOUR ATTENTION
**Paraneoplastic Syndromes**

- Paraneoplastic syndromes can occur before the primary tumor appears and thus can be the first sign of disease or an indication of tumor recurrence.
- Paraneoplastic endocrine syndromes occur when the tumor produces hormones.
- The three most common are ectopic Cushing’s syndrome, the syndrome of inappropriate antidiuretic hormone (SIADH), and humoral hypercalcemia of malignancy.
  - **Ectopic Cushing’s syndrome** occurs in 2% to 10% of patients with small cell carcinoma. The clinical manifestations are less prominent than in Cushing’s disease; biochemical abnormalities predominate, whereas the physical changes are less prominent.
  - **The SIADH** is also more common in small cell carcinoma, occurring in 7% to 11% of patients. The manifestations of hyponatremia [mental status changes, lethargy, or seizures] are often absent despite very low sodium levels, because the rate of decline is typically prolonged.
  - **Humoral hypercalcemia of malignancy**, resulting from the production of parathyroid hormone-related protein by the tumor, is most commonly associated with squamous cell carcinoma. Fatigue, mental status changes, weakness, gastrointestinal symptoms, polypnea, and electrocardiogram changes may occur.

**Paraneoplastic Syndromes**

- Paraneoplastic neurologic syndromes affect all parts of the nervous system.
  - An immune response to tumor antigens that cross-react with common antigens expressed in the nervous system seems to take place. This leads to manifestations that vary depending on where in the nervous system these antigens are expressed.
  - Paraneoplastic limbic encephalitis is characterized by mood and behavior changes, memory problems, and seizures; paraneoplastic cerebellar degeneration manifests with ataxia, nystagmus, dysarthria, and diplopia; and paraneoplastic opsoclonus-myoclonus manifests with involuntary eye movements, myoclonus, truncal ataxia, dysarthria, and encephalopathy. Each of these is more common with small cell carcinoma, can occur in the presence of anti-Hu antibodies, and can occur as part of a more diffuse anti-Hu

**Paraneoplastic Syndromes**

- Other paraneoplastic neurologic syndromes include:
  - Cancer associated retinopathy (most common with small cell carcinoma), rapid vision loss, ring scotomata, photosensitivity, night blindness, and color vision loss can occur in association with autoantibodies directed against retinal proteins.
  - Lambert-Eaton myasthenic syndrome is the most common of the neurologic paraneoplastic syndromes and is present in 3% of small cell carcinomas. Proximal muscle weakness (which might improve with exercise) is most prominent in the lower extremities, and autonomic features predominate. Autoantibodies directed against P/Q type voltage-gated calcium channels are believed to be responsible.

**Paraneoplastic Syndromes**

- Other paraneoplastic neurologic syndromes include:
  - Other paraneoplastic syndromes include
    - skeletal and connective tissue syndromes (clubbing, hypertrophic pulmonary osteoarthropathy),
    - coagulation and hematologic disorders,
    - cutaneous and renal manifestations, and
    - systemic symptoms (anorexia, cachexia, and weight loss).