Early Stage, Inoperable Non-Small Cell Lung Cancer

Christine Lauro, MD
Radiation Oncology
Rocky Mountain Mountain Oncology
February 22, 2015
Objectives

- Review NSCLC epidemiology & screening
- Review radiation treatment alternatives for early NSCLC
- Compare/contrast radiation treatment with other alternatives
- Review radiation treatment techniques
Epidemiology

Worldwide:

1.8 million patients
1.6 million deaths in 2012

US:

224,000 cases*
159,000 deaths in 2014

*116,000 men, 72,000 women
Epidemiology

- **Lifetime Risk:**
  - 1 in 13 men
  - 1 in 16 women

- **Average age at diagnosis: 70**
  - However, 2% of lung cancers are diagnosed in patients <45
Epidemiology

- Smoking is considered cause of lung cancer
  - 90% men
  - 80% women

- Majority of lung cancers diagnosed in people who do not presently smoke
  - 50% former smokers
  - 15% never smokers
NSCLC Survival

![Graph showing relative survival rates for different stages of NSCLC.](image-url)

- **Stage I**: 71.12% 1 year survival, 35.33% 5 year survival
- **Stage II**: 48.15% 1 year survival, 20.89% 5 year survival
- **Stage III**: 34.59% 1 year survival, 6.32% 5 year survival
- **Stage IV**: 14.36% 1 year survival, 5.79% 5 year survival
- **Stage Not Known**: 16.61% 1 year survival, 9.68% 5 year survival
- **All Stages**: 32.16% 1 year survival, 9.68% 5 year survival
Survival

Source: CHEST © 2007 American College of Chest Physicians
Diagnosis

- Malignancies that are difficult to diagnose early:
  - Lung
  - Pancreas
  - Ovarian
  - Myeloma
Risk Assessment Tool for Lung Cancer

- Unexplained hemoptysis
- Persistent for > 3 weeks:
  - Cough
  - Shoulder pain
  - Chest pain
  - Hoarseness
- Other signs:
  - Unresolved chest infection
  - Finger clubbing
  - Cervical or supraclavicular lymphadenopathy
  - Pleural effusion
- Other models:
  - Family history
  - Anemia
  - Thromboembolism
  - Age
  - Smoking history
  - Weight loss
Lung Cancer Screening Guidelines (ACS 2013)

- Patients aged 55-74
- Smoking history of 30+ pack years
- Current smokers or quit within last 15 years

Why?

20% relative reduction in mortality from lung cancer with low-dose CT screening

NCCN Screening Guidelines

NCCN Guidelines Version 1.2015
Lung Cancer Screening

RISK ASSESSMENT

- Smoking history
  - Present or past
- Radon exposure
- Occupational exposure
- Cancer history
- Family history of lung cancer
- Disease history (COPD or pulmonary fibrosis)
- Smoking exposure (second-hand smoke)
- Absence of symptoms or signs of lung cancer (if symptoms, see appropriate NCCN Guidelines)

RISK STATUS

High risk:
- Age 55-74 y and
- ≥30 pack-year history of smoking and
- Smoking cessation <15 y (category 1) or
  - Age ≥50 y and
  - ≥20 pack-year history of smoking and
  - One additional risk factor (other than second-hand smoke)

For patients eligible for screening, shared patient/physician decision making is required, including a discussion of benefits/risks

Moderate risk:
- Age ≥50 y and
- ≥20 pack-year history of smoking or second-hand smoke exposure
- No additional risk factors

Routine lung cancer screening not recommended

Low risk:
- Age <50 y and/or
- <20 pack-year history of smoking

Routine lung cancer screening not recommended

See Screening and Findings (LCS-2)
# NSCLC Staging

## NCCN Guidelines Version 4.2014 Staging
Non-Small Cell Lung Cancer

### Table 1. Definitions for T, N, M*

<table>
<thead>
<tr>
<th>T</th>
<th>Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumor ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 2 cm but ≤ 3 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T2</th>
<th>Tumor &gt; 3 cm but ≤ 7 cm or tumor with any of the following features:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Involves main bronchus, ≥ 2 cm distal to the carina</td>
</tr>
<tr>
<td></td>
<td>Invades visceral pleura</td>
</tr>
<tr>
<td></td>
<td>Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt; 3 cm but ≤ 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt; 5 cm but ≤ 7 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T3</th>
<th>Tumor &gt; 7 cm or one that directly invades any of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or tumor in the main bronchus ≤ 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T4</th>
<th>Tumor of any size that invades any of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

---

*a The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchi, is also classified as T1.

*b T2 tumors with these features are classified T2a if ≤ 5 cm or if size cannot be determined, and T2b if > 5 cm but ≤ 7 cm.

*Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an effusion. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.
Early NSCLC (T1-2 N0 M0)

Patient factors
- Medically inoperable
- Medically operable

Location
- Peripheral
- Central

Medically Inoperable NSCLC
Stereotactic Body Radiation Therapy (SBRT)

• Breathing control is key
• Highly conformal
• Tight margins
• Pre-RT onboard imaging
RTOG 0236: SBRT for Medically Inoperable Peripheral Early Stage NSCLC

- Non-small cell lung cancer - biopsy proven
- T1, T2 (≤ 5 cm) and T3 (chest wall only, ≤ 5 cm), N0, M0
- Medical problems preclude surgery (e.g. emphysema, heart disease, diabetes)
- No other planned therapy

Timmerman et al, JAMA 303(11):1070-6, 2010
Eligibility

Only allowed peripheral tumors outside “zone of proximal bronchial tree”

Timmerman et al, JAMA 303(11):1070-6, 2010
Protocol Specified Severe Toxicity

» Lungs/bronchi: decline in pulmonary function tests (PFTs), pneumonitis, pulmonary fibrosis, hypoxemia, pleural effusion
» Esophagus: dysphagia, esophagitis, stricture, ulceration
» Heart: pericarditis, effusion, cardiomyopathy, ventricular dysfunction
» Nerve: myelitis, neuropathy (both cranial and motor)
» Pulmonary blood vessel: hemorrhage

Timmerman et al, JAMA 303(11):1070-6, 2010
RTOG 0236

- Opened May 2004 and closed October 2006
- 59 patients enrolled (55 evaluable)
- 62% female, median age 72 years
- Zubrod performance 0 (12 patients), 1 (35), 2 (8)
- 44 patients with T1 tumors, 11 with T2 tumors

Timmerman et al, JAMA 303(11):1070-6, 2010
RTOG 0236 Local Control

- Median follow-up = 24.8 months (range 4.9-43.7 months)
- 1 failure within PTV

Timmerman et al, JAMA 303(11):1070-6, 2010
RTOG 0236
Regional and Distant Failure

- 2 patients developed regional failure, both after 2 years (2.8 and 3.0 years)

- Eleven patients (20%) had distant failure

Timmerman et al, JAMA 303(11):1070-6, 2010
RTOG 0236 Disease Free Survival

Timmerman et al, JAMA 303(11):1070-6, 2010
RTOG 0236 Overall Survival

Overall Survival (%)

0 25 50 75 100

Months after Start of SBRT

0 6 12 18 24

Patients at Risk

55

Dead: 24
Total: 55

24 month overall survival = 72% (CI: 58-82%)

Timmerman et al, JAMA 303(11):1070-6, 2010
RTOG 0236 Toxicity

- No grade 5 toxicities (treatment deaths)

- 2/55 patients (4%) grade 4 protocol specified toxicity (decline in PFTs to <25% predicted, and hypocalcemia)

- 7/55 patients (13%) grade 3 protocol specified toxicities

- 3/55 patients (5%) had grade 3 rib and skin toxicity associated with chest wall tumors

_Timmerman et al, JAMA 303(11):1070-6, 2010_
RTOG 0236 Summary

- Local control was very high at 98%
- Survival high at 72% (2 years)
- 12/55 patients (22%) had grade 3-4 toxicity with no treatment related deaths

Timmerman et al, JAMA 303(11):1070-6, 2010
Xiao Y et al, IJROBP 2009;73(4):1235-42
Stereotactic Body Radiation Therapy
Stage I NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient #</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uematsu 2001</td>
<td>50</td>
<td>50 Gy/5 fx</td>
<td>LC 94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 yr OS 66%</td>
</tr>
<tr>
<td>Timmerman 2003</td>
<td>37</td>
<td>24-60 Gy/3 fx</td>
<td>LC 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 m DFS 50%</td>
</tr>
<tr>
<td>Ricardi 2009</td>
<td>62</td>
<td>45 Gy/3 fx</td>
<td>3 yr LC 87.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 yr OS 57.1%</td>
</tr>
<tr>
<td>Timmerman 2010</td>
<td>55</td>
<td>60 Gy/3 fx (54 Gy corrected)</td>
<td>2 yr LC 98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 yr LS 72%</td>
</tr>
<tr>
<td>Senan 2009 abstract</td>
<td>193</td>
<td>60 Gy/3- 8 fx</td>
<td>3 yr LC 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 yr OS 46%</td>
</tr>
</tbody>
</table>
Characteristic development of stable fibrosis after SBRT

McCammon R et al, IJROBP 73(1):112-8, 2009
SBRT-related Treatment Changes

- Differentiating treatment effect from recurrence
  - Favors treatment effect
    - Not FDG-avid
    - Ground glass changes
    - Wedge/triangular shaped atelectasis downstream on coronal images
    - Does not enlarge on serial scans
  - Favors recurrence
    - FDG-avid
    - Nodularity (differing from atelectasis) on CT
    - Enlarges on serial scans
- Should fuse follow-up CT with SBRT plan to determine if changes correlate with isodose curves
Extra caution needed when near the proximal airways

Timmerman et al, J Clin Oncol, 2006
RTOG 0813: Phase I/II SBRT for Proximal Medically Inoperable

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose per Fraction</td>
<td>8 Gy</td>
<td>8.5 Gy</td>
<td>9 Gy</td>
<td>9.5 Gy</td>
<td>10 Gy</td>
<td>10.5 Gy</td>
<td>11 Gy</td>
<td>11.5 Gy</td>
<td>12 Gy</td>
</tr>
<tr>
<td>Total Dose</td>
<td>40 Gy</td>
<td>42.5 Gy</td>
<td>45 Gy</td>
<td>47.5 Gy</td>
<td>50 Gy</td>
<td>52.5 Gy</td>
<td>55 Gy</td>
<td>57.5 Gy</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>

- T1-2, N0 M0
- T ≤ 5 cm
- Thoracic surgeon deems tumor potentially resectable but patient medically inoperable
- Started at 50 Gy in 5 fx over 1.5-2 weeks
SBRT Medically Inoperable

- No phase III studies planned to compare with non-radiation therapy

- Standard of care to offer for both peripheral and central location

- What other options can or should be mentioned?
## Conventional Radiation Stage I

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Patient #</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley 2005</td>
<td>77</td>
<td>70.9-83.8 Gy</td>
<td>LC 75%</td>
</tr>
<tr>
<td>Langerwaard 2002</td>
<td>113</td>
<td>60-72 Gy (Median 66 Gy)</td>
<td>LC 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 yr OS 25%</td>
</tr>
<tr>
<td>Rosenzweig 2001</td>
<td>32</td>
<td>48.6-81 Gy (Median 70.2 Gy)</td>
<td>2 yr LC 43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 yr OS 33%</td>
</tr>
<tr>
<td>Sibley 1998</td>
<td>156</td>
<td>50-80 Gy (Median 64 Gy)</td>
<td>LC 51%</td>
</tr>
</tbody>
</table>
Radiofrequency Ablation (RFA): RAPTURE study

Multinational trial: 106 patients, 183 lung tumors, <3.5 cm NSCLC (n=33), CRC mets (n=53), other mets (n=20)

Unsuitable for surgery, RT or chemo

Outcomes: correct placement of device 99%, complete response 88% at 1 year

Complications: 25% pneumothorax (n=27), 4% pleural effusion (n=4).

PLANNING AND TECHNICAL ASPECTS OF LUNG SBRT

CT simulation
Accounting for tumor/organ motion
Daily imaging
Immobilization: 4D CT, Alphacradle
Management of Respiratory-Associated Tumor Motion: 4D-CT, Creation of ITV
Management of Respiratory-Associated Tumor Motion: Axial View
Image Guided Treatment delivery

- Daily CBCT
- Used to align with CT sim images/treatment plan
- Checked by physician prior to treatment
Treatment Plan
Potential side effects:

- Fatigue
- Others are uncommon:
- Radiation pneumonitis (parallel pattern) is not a primary dose limiting toxicity (occurs in <5%)
- Bronchial toxicity (serial pattern) is primary pattern of lung injury
  - Fibrosis
  - Downstream atelectasis/collapse
  - Post-obstructive pneumonia
- “Chest Wall volume receiving more than 30 Gy predicts risk of severe pain and/or rib fracture after lung SBRT” Dunlap et al; ASTRO 2008
  - Med time to CW toxicity 7.1mo
- Brachial Plexopathy
### Clinical Assessment

#### Stage IA
- Peripheral T1ab, N0
- **PFTs (if not previously done)**
- Bronchoscopy (intraoperative preferred)
- Pathologic mediastinal lymph node evaluation (category 2B)
- PET/CT scan (if not previously done)

#### Stage IB
- Peripheral T2a, N0
- Central T1ab–T2a, N0
- T1ab–T2b, N0
- **PFTs (if not previously done)**
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation (category 2B)
- PET/CT scan (if not previously done)
- Brain MRI (Stage II, Stage IB [category 2B])

### Pretreatment Evaluation

<table>
<thead>
<tr>
<th>Operable</th>
<th>Medically Inoperable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative mediastinal nodes</strong></td>
<td><strong>Definitive RT including stereotactic ablative radiotherapy (SABR)</strong></td>
</tr>
<tr>
<td><strong>Positive mediastinal nodes</strong></td>
<td><strong>Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling</strong></td>
</tr>
</tbody>
</table>

### Initial Treatment

- **Operable**: Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- **Medically Inoperable**: Definitive RT including stereotactic ablative radiotherapy (SABR)

**See Stage IIIA (NSCL-C) or Stage IIIB (NSCL-D)**

#### Stage IIA
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Consider adjuvant chemotherapy (category 2B) for high-risk stages IB-II

**See Stage IIIA (NSCL-C) or Stage IIIB (NSCL-D)**

### Notes
- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**See Principles of Radiation Therapy (NSCL-C).**

**See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).**

**Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors excluding well-differentiated neuroendocrine tumors), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (N0). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.**

**See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).**
# Early NSCLC Summary

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically inoperable, Peripheral</td>
<td>SBRT (54 Gy 3-5 fx) or Accelerated</td>
</tr>
<tr>
<td>Medically inoperable, Central</td>
<td>SBRT (50 Gy 5 fx) or Accelerated</td>
</tr>
<tr>
<td>Medically operable, Peripheral</td>
<td>Surgery</td>
</tr>
<tr>
<td>Medically operable, Central</td>
<td>Surgery</td>
</tr>
</tbody>
</table>
Thank You