The Management of Lung Cancer

Dr. David Palma, MD, MSc, PhD, FRCPC
Radiation Oncologist, London Health Sciences Centre, London, Canada
Clinician-Scientist, Ontario Institute for Cancer Research
Disclosures

for the following presenter

David Palma

Employment Relationship

- London Health Sciences Centre: Radiation Oncologist

Compensation, Remuneration, Funding

- Ontario Institute for Cancer Research: Research Grant

Ownership or Investment Interests

- Group patent on a computer analysis technique used to assess CT scans after patients have radiation treatment. No income made. Not licensed.

Leadership Positions

- None
Today’s Roadmap

• Part I: The Basics (15 min)
  • Epidemiology, Screening, and Staging

• Part II: Non-Small Cell Lung Cancer (40 min)
  • Stage I
  • Stage II/III – Resectable and Unresectable
  • Stage IV
    • Oligometastases
    • Palliative Approaches (covered this afternoon)

• Part III: Small Cell Lung Cancer (20 min)
Links to Articles

• **Key Articles** are identified with this icon:

• All Key Articles available to you as PDFs via Dropbox
• Shortened URL – type this into your browser:

  [www.goo.gl/WmkgZ9](http://www.goo.gl/WmkgZ9)

• Password is: refresher
• **Folder will be available to you for 24 hours**
Links to Articles

www.goo.gl/WmkgZ9
Lung cancer is the leading cause of cancer death in the world.
A Public Health Problem
A Public Health Problem
Risk Factors

• **Active Cigarette Smoking**
• **Other causal agents**: Secondhand smoke, ionizing radiation (including radon), occupational exposures (arsenic, chromium, nickel, asbestos), indoor and outdoor pollution
• **Additional risk indicators**: Age, male sex, family history, acquired lung disease (e.g. IPF)
Screening

• At least 6 large RCTs evaluated lung cancer screening with CXR, and none showed a mortality benefit to screening.

• Refinements in low-dose CT technology led to the NLST:
  • Average dose 2 mSv.

• Eligible patients:
  • 55-74 years
  • 30 pack years of smoking; if quit, then within 15 years
  • 53,454 randomized to 3 annual LDCTs vs. 3 annual CXRs

NEJM Aug 2011: 365(5)
## Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Dose CT</th>
<th>Chest Radiography</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>Total positive tests</td>
<td>7191 (100.0)</td>
<td>6901 (100.0)</td>
<td>4054 (100.0)</td>
</tr>
<tr>
<td>Lung cancer confirmed</td>
<td>270 (3.8)</td>
<td>168 (2.4)</td>
<td>211 (5.2)</td>
</tr>
<tr>
<td>Lung cancer not confirmed †</td>
<td>6921 (96.2)</td>
<td>6733 (97.6)</td>
<td>3843 (94.8)</td>
</tr>
</tbody>
</table>

NEJM Aug 2011: 365(5)
Screening

- 20% relative reduction in lung cancer mortality
- 6.7% relative reduction in all-cause mortality
- Subsequent NEJM publication: ICER = $81,000 per QALY

NEJM Aug 2011: 365(5)
Staging Investigations

• History, Physical, Appropriate Labs
• CXR, CE-CT chest/upper abdomen
• Whole body PET/CT
  • 2 RCTS show that use of PET (or PET/CT) avoids unnecessary surgery in ~10-20%
  • MRI head for stage III/IV
Getting Tissue from the Thorax

• Sputum cytology
• Bronchoscopy
• Endobronchial ultrasound
• Esophageal ultrasound
• Transthoracic biopsy
• Mediastinoscopy
• Electromagnetic navigation
• VATS

• Notes:
  • When nodes are positive on imaging, nodal biopsy is preferred first attempt at tissue as it provides diagnosis and stage
  • Histopathology preferred over cytology
Addressing the Mediastinum

Supracleavicular zone
1. Low cervical, supracleavicular, and sternal notch nodes

**Superior Mediastinal Nodes**
Upper zone
- 2R: Upper Paratracheal (right)
- 2L: Upper Paratracheal (left)
- 3a: Pre-vascular
- 3p: Retrotracheal
- 4R: Lower Paratracheal (right)
- 4L: Lower Paratracheal (left)

**Aortic Nodes**
AP zone
- 5: Subaortic
- 6: Para-aortic (ascending aorta or phrenic)

**Inferior Mediastinal Nodes**
Subcarinal zone
- 7: Subcarinal

Lower zone
- 8: Paraesophageal (below carina)
- 9: Pulmonary ligament

**N3 Nodes**
Hilar/Interlobar zone
- 10: Hilary
- 11: Interlobar

Peripheral zone
- 12: Lobular
- 13: Segmental
- 14: Subsegmental
Needle or Surgical Approach?

Surgical Approaches
Cervical: 1, 2, 3, 4, 7, +/- 10
Anterior: predominantly 5, 6

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)
Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)
EBUS-TBNA or EUS-FNA
Controversial

Lymph node stations: 1 = Supraclavicular, 2 = Upper paratracheal, 3 = Prevascular and retrotracheal (not shown), 4 = Lower paratracheal, 5 = Subaortic, 6 = Para-aortic (not shown), 7 = Subcarinal, 8 = Paraesophageal, 9 = Pulmonary ligament, 10 = Hilal, 11 = Interlobar, 12 = Lobar
Neede vs. Surgical

Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer
A Randomized Trial

- 241 patients with resectable NSCLC in whom mediastinal staging was indicated
- Randomized to surgical staging vs. combined EUS-FNA and EBUS-TBNA followed by surgical staging if negative

Annema et al, JAMA 2010
Needle vs. Surgical

- 47% in EUS/EBUS arm avoided surgical staging

### Table 2. Diagnostic Performance

<table>
<thead>
<tr>
<th>Nodal Invasion, N2/N3</th>
<th>Surgical Staging ( (n = 118) )</th>
<th>Endosonography and Surgical Staging ( (n = 123) )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>41/52 (79) [86-88]</td>
<td>62/66 (94) [85-98]</td>
<td>.02</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>66/77 (86) [76-92]</td>
<td>57/61 (93) [84-97]</td>
<td>.18</td>
</tr>
</tbody>
</table>

### Table 3. Secondary Outcomes

<table>
<thead>
<tr>
<th>Unnecessary thoracotomies, all ( (n = 118) )</th>
<th>Endosonography and Surgical Staging, No. ( (n = 123) )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>pN2</td>
<td>pN2</td>
<td></td>
</tr>
<tr>
<td>Combination pN2/death</td>
<td>Combination pN2/pT4</td>
<td></td>
</tr>
<tr>
<td>Combination pN2/pM1</td>
<td>Combination pN2/pM1</td>
<td></td>
</tr>
<tr>
<td>pT4(^a)</td>
<td>pT4(^a)</td>
<td>.02</td>
</tr>
<tr>
<td>pM1</td>
<td>pM1</td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>Small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td>Exploratory thoracotomy</td>
<td>Exploratory thoracotomy</td>
<td></td>
</tr>
<tr>
<td>Benign lesion</td>
<td>Benign lesion</td>
<td></td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>Death within 30 days</td>
<td></td>
</tr>
</tbody>
</table>

Annema et al., JAMA 2010
“When EBUS-TBNA (+/- EUS-FNA) is negative or inconclusive, disease can be missed and staging is imprecise. Thus, in this setting further biopsy is indicated.”
# Staging System

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong> Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus*</td>
<td><strong>N0</strong> No regional lymph node metastases</td>
<td><strong>M0</strong> No distant metastasis</td>
</tr>
<tr>
<td><strong>T1a</strong> Tumor ≤2 cm in diameter</td>
<td><strong>N1</strong> Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
<td><strong>M1</strong> Distant metastasis</td>
</tr>
<tr>
<td><strong>T1b</strong> Tumor &gt;2 cm but ≤3 cm in diameter</td>
<td><strong>N2</strong> Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
<td><strong>M1a</strong> Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td><strong>T2</strong> Tumor &gt;3 cm but ≤7 cm, or tumor with any of the following features:</td>
<td><strong>N3</strong> Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or suoradavicular lymph node(s)</td>
<td><strong>M1b</strong> Distant metastasis (in extrathoracic organs)</td>
</tr>
<tr>
<td>Involves main bronchus, ≥2 cm distal to carina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involves visceral pleura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2a</strong> Tumor &gt;3 cm but ≤5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2b</strong> Tumor &gt;5 cm but ≤7 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Tumor &gt;7 cm or any of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus ≤2 cm from carina (without involvement of carina)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atelectasis or obstructive pneumonitis of the entire lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Separate tumor nodules in the same lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong> Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Staging System

<table>
<thead>
<tr>
<th>T/M</th>
<th>Subgroups</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>T1</td>
<td>T1a</td>
<td>IA</td>
<td>II A</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>IA</td>
<td>II A</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>T2</td>
<td>T2a</td>
<td>IB</td>
<td>II A</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>II A</td>
<td>II B</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>T3</td>
<td>T3 &gt;7</td>
<td>II B</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td></td>
<td>T3 Inv</td>
<td>II B</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td></td>
<td>T3 Satell</td>
<td>II B</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>T4</td>
<td>T4 Inv</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
<td>III B</td>
</tr>
<tr>
<td></td>
<td>T4 Ips Nod</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
<td>III B</td>
</tr>
<tr>
<td>M1</td>
<td>M1a Contr Nod</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
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<tr>
<td></td>
<td>M1a Pl Dissem</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
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</table>

Detterbeck, Chest 2010
Management: Stage I NSCLC
The role of radiotherapy in treatment of stage I non-small cell lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>BED (acute)</th>
<th>Local failure alone (%)</th>
<th>Any local failure (%)</th>
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<tbody>
<tr>
<td>Krol et al. [15]</td>
<td>–</td>
<td>27.8</td>
<td>65.7</td>
</tr>
<tr>
<td>Hayakawa et al. [8]</td>
<td>68.1</td>
<td>11.1</td>
<td>19.4</td>
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<tr>
<td>Kaskowitz et al. [16]</td>
<td>65.1</td>
<td>41.5</td>
<td>43.4</td>
</tr>
<tr>
<td>Slotman et al. [9]</td>
<td>76.4</td>
<td>0</td>
<td>6.4</td>
</tr>
<tr>
<td>Jeremic et al. [4]</td>
<td>71</td>
<td>–</td>
<td>45</td>
</tr>
<tr>
<td>Sibley et al. [20]</td>
<td>–</td>
<td>16.3</td>
<td>19.1</td>
</tr>
<tr>
<td>Slotman et al. [17]</td>
<td>–</td>
<td>19.1</td>
<td>25.2</td>
</tr>
<tr>
<td>Sandler et al. [18]</td>
<td>62.8</td>
<td>42.8a</td>
<td>42.8a</td>
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<tr>
<td>Haffty et al. [19]</td>
<td>59</td>
<td>39</td>
<td>39</td>
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<tr>
<td>Noordijk et al. [13]</td>
<td>63.4</td>
<td>–</td>
<td>70</td>
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<tr>
<td>Morita et al. [14]</td>
<td>65.3</td>
<td>–</td>
<td>44.3</td>
</tr>
<tr>
<td>Gauden et al. [5]</td>
<td>62.5</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Qiao et al, Lung Cancer 2003
Stereotactic Radiation by Two Names

SBRT
Stereotactic Body Radiation Therapy

təˈmeɪtou

SABR
Stereotactic Ablative Radiation Therapy

təˈmaːtou
Features of Lung SABR

Accounting for Motion
• 4D Planning

Small tumour volumes
• Small margins

Many Beam Directions
• 7-11 Beams / Arc Therapy

Steep dose gradients
• Inhomogeneous target dose

Accurate Targeting
• CBCT pre-RT

High dose per fraction
• Short total treatment duration
60 Gy in a Different Way

Older RT

- PTV X 60 Gy
- 57 Gy

SABR

- PTV X 75 Gy
- 60 Gy (80%)

- PTV X 100 Gy
- 60 Gy (60%)

Senan, Palma, Lagerwaard, J Thorac Dis 2011
Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

- Multicenter phase II trial
- Equivalent of 54 Gy in 3 fractions
- Primary tumor control 98%
- Lobar control 91%

- 2014 ASTRO update -- 5-year outcomes: primary tumor recurrence 7%, involved lobar recurrence 20%, regional recurrence 38% and distant recurrence 31%.
Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis

Sashendra Senthil, Frank J. Logenwaard, Cornelis J. A. Hazebroek, Ben J. Slotman, Suresh Senan

5 yr LC 89.5%
5 yr RC 87.3%
5 yr DC 80.1%

Senthil et al Lancet Oncology 2012
# VUmc: A Risk–Adapted Strategy

<table>
<thead>
<tr>
<th>Tumor description</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Older algorithms</td>
</tr>
<tr>
<td>T1 tumor surrounded by lung tissue</td>
<td></td>
</tr>
<tr>
<td>T2 tumor or broad contact with chest wall</td>
<td></td>
</tr>
<tr>
<td>Central tumor or near brachial plexus</td>
<td></td>
</tr>
</tbody>
</table>
Dose*: How much and where?

Extracranial stereotactic RT
Dose-response in stereotactic irradiation of lung tumors

Joern Wulf, Kurt Baier, Gerd Mueller, Michael P. Flentje

*Department of Radiotherapy, University of Wuerzburg, Wuerzburg, Germany,
Department of Radiotherapy, Lindenhofspital, Bern, Switzerland

PTV-margin

Isocenter

BED_{(w/10)} [Gy]

Local control [%]

48/4
60/8

Timmermann 3 x 20 Gy/80%
Timmermann 3 x 16 Gy/80%
Blomgren 3 x 15 Gy/65%
Zimmermann 3 x 12.5/60%
Nagata 4 x 12 Gy/80%
Fritz 1 x 30 Gy/100%
Hertarth-Hof 1 x 26 Gy/100%
Zimmermann 3 x 10 Gy/60%
Central Tumors

- Meta-analysis (Senthi 2012):
  - $BED_{10} \geq 100$ to maximize local control
  - $BED_{3} \leq 240$ to keep risk of fatal toxicity to 1%

Timmerman et al JCO 2006
Haasbeek et al JTO 2011
## Central Tumors: RTOG 0813

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose per Fraction</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 Gy</td>
<td>40 Gy</td>
</tr>
<tr>
<td>2</td>
<td>8.5 Gy</td>
<td>42.5 Gy</td>
</tr>
<tr>
<td>3</td>
<td>9 Gy</td>
<td>45 Gy</td>
</tr>
<tr>
<td>4</td>
<td>9.5 Gy</td>
<td>47.5 Gy</td>
</tr>
<tr>
<td>5</td>
<td>10 Gy†</td>
<td>50 Gy</td>
</tr>
<tr>
<td>6</td>
<td>10.5 Gy</td>
<td>52.5 Gy</td>
</tr>
<tr>
<td>7</td>
<td>11 Gy</td>
<td>55 Gy</td>
</tr>
<tr>
<td>8</td>
<td>11.5 Gy</td>
<td>57.5 Gy</td>
</tr>
<tr>
<td>9</td>
<td>12 Gy</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>
Tumors were in different locations so different OARs at risk
# Results – Dose Limiting Toxicity (DLT)

<table>
<thead>
<tr>
<th>SBRT dose</th>
<th># of evaluable pts</th>
<th># of DLTs (Probability*)</th>
<th>DLT Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>10x5</td>
<td>8</td>
<td>0 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>10.5x5</td>
<td>6</td>
<td>1 (2.7%)</td>
<td>Hemoptysis (G5)</td>
</tr>
<tr>
<td>11x5</td>
<td>13</td>
<td>1 (4.3%)</td>
<td>Bradycardia (G5)</td>
</tr>
<tr>
<td>11.5x5</td>
<td>32</td>
<td>2 (5.7%)</td>
<td>Hypoxia (both G3)</td>
</tr>
<tr>
<td>12x5</td>
<td>30</td>
<td>1 (7.2%)</td>
<td>Pneumonitis (G3)</td>
</tr>
</tbody>
</table>

*Probability based on a Bayesian logistic model with $\alpha=1.266$ and 95% CI = (1.089,1.049).
Still need to be cautious

Central-Airway Necrosis after Stereotactic Body-Radiation Therapy

Corradaeti, Haas, Rengan NEJM 2012
Is SABR better than older techniques?

Timmerman J Clin Oncol 32:2847-2854
SABR vs. older techniques

• Several population-based studies suggest SABR better for OS:
  • Palma, Amsterdam Cancer Registry, JCO 2010
  • Haasbeek, Netherlands Cancer Registry, Annals of Oncology 2011
  • Shirvani, SEER-Medicare, IJROBP 2012

• At least 3 RCTs launched comparing SABR with standard or less-hypofractionated regimens
  • SPACE (Sweden) - completed
  • CHISEL (Australia)
  • LUSTRE (Canada)
RCT #1: SPACE

**Stereotactic Precision And Conventional radiotherapy Evaluation**

**Comparison**

66 Gy in 3 fractions (0.5 – 1 cm margin)

vs. 70 Gy in 35 fractions (2 cm margin)

**Major Inclusion Criteria**

- T1-2 N0 M0
- Medically Inoperable or Refusing Surgery
- WHO 0-2
- Biopsy proven or growing on CT with positive PET

Nyman et al, ESTRO 2014, OC–0565
# Stereotactic Precision And Conventional radiotherapy Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>SABR N=49</th>
<th>Conventional N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>72.7</td>
<td>75.3</td>
</tr>
<tr>
<td>Male</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td>COPD</td>
<td>71%</td>
<td>64%</td>
</tr>
<tr>
<td>T2</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>SCC</td>
<td>18%</td>
<td>28%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>45%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Nyman et al, ESTRO 2014, OC-0565
Stereotactic Precision And Conventional radiotherapy Evaluation

- No differences in local control or survival outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>SABR N=49</th>
<th>Conventional N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (any)</td>
<td>16%</td>
<td>34%</td>
</tr>
<tr>
<td>Esophagitis (any)</td>
<td>9%</td>
<td>32%</td>
</tr>
<tr>
<td>Any toxicity G3–5</td>
<td>18%</td>
<td>16%</td>
</tr>
</tbody>
</table>

- SABR appears to improve the therapeutic ratio compared to older techniques

Nyman et al, ESTRO 2014, OC–0565
SABR without histology

When Is a Biopsy-Proven Diagnosis Necessary Before Stereotactic Ablative Radiotherapy for Lung Cancer?
A Decision Analysis

- Decision analysis and Markov model assessing QALYs achieved, comparing 3 approaches to a nodule ≥1 cm
  - Surveillance
  - PET then biopsy if PET+
  - PET, the treat if PET+

- Sensitivity analysis to determine factors influencing outcome

Louie et al Chest, 2014; 146(4):1021-1028
When Is a Biopsy-Proven Diagnosis Necessary Before Stereotactic Ablative Radiotherapy for Lung Cancer? A Decision Analysis

Louie et al Chest, 2014; 146(4):1021-1028
Stage I Inoperable: Summary

- SABR has been widely adopted as standard treatment for inoperable patients
- Non-randomized comparisons suggest better local control, better survival than with conventional treatments
- Convenience of SABR probably improves access to care
- Preliminary randomized data (SPACE) suggests that long-course treatments can also achieve good local control
- More randomized data is coming
Randomized Trial of Lobectomy Versus Limited Resection for T1 N0 Non-Small Cell Lung Cancer

Lung Cancer Study Group (Prepared by Robert J. Ginsberg, MD, and Lawrence V. Rubinstein, PhD)

• 247 patients with T1N0 NSCLC analyzed

<table>
<thead>
<tr>
<th>Event</th>
<th>Limited Resection</th>
<th>Lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Rate (per person/y)</td>
</tr>
<tr>
<td>Recurrence (excluding second primary)</td>
<td>38</td>
<td>0.101</td>
</tr>
<tr>
<td>Recurrence (including second primary)</td>
<td>42</td>
<td>0.112</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>21</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Fig 1. Time to death (from any cause) by treatment for 247 eligible patients.

Annals of Thoracic Surgery 1995
Operable Patients: Types of Surgical Resections

- Pneumonectomy
- Sleeve lobectomy
- Wedge resection
- Lobectomy
- Segmentectomy
LR was defined as recurrence within the primary tumor lobe at the staple line (local progression), recurrence within the primary tumor lobe away from the staple line (involved lobe failure), or recurrence within hilar lymph nodes.
SABR in Operable Patients

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>United States (1)</th>
<th>Japanese National Cancer Center (2)</th>
<th>Japanese National Survey (3)</th>
<th>SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>61</td>
<td>71</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>IB</td>
<td>40</td>
<td>44</td>
<td>60</td>
<td>64</td>
</tr>
</tbody>
</table>

Abbreviation: SBRT = stereotactic body radiotherapy. Values are percentages.

Onishi et al IJROBP 2011
The Debate
SABR vs. Surgery: Systematic Review

• 20 comparative effectiveness studies comparing survival after surgery vs. SABR

• 12 found no difference between SABR and surgery

• 8 found surgery superior to SABR
  • 4 of these had no statistical adjustment for baseline factors
SABR vs. VATS lobectomy

Stage I–II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis


Annals of Oncology Mar 2013
SEER–Medicare: SABR vs. other techniques

Table 4  Proportional hazards models for propensity-matched pairs of SABR cases and non-SABR controls

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Overall survival</th>
<th>Lung cancer-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P &gt; χ²</td>
</tr>
<tr>
<td>Lobectomy vs SABR</td>
<td>0.71 (0.45-1.12)</td>
<td>.14</td>
</tr>
<tr>
<td>Sublobar resection vs SABR</td>
<td>0.82 (0.53-1.27)</td>
<td>.38</td>
</tr>
<tr>
<td>Conventional XRT vs SABR</td>
<td>1.97 (1.31-2.96)</td>
<td>.001</td>
</tr>
<tr>
<td>Adj for age and grade</td>
<td>1.96 (1.28-3.00)</td>
<td>.002</td>
</tr>
<tr>
<td>Observation vs SABR</td>
<td>2.10 (1.37-3.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adj for tumor size</td>
<td>2.03 (1.24-3.07)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* SABR is the referent group for all comparisons.
High Risk Patients: Severe COPD

• Systematic Review of the Literature
  • Four papers reported patients with severe/very severe COPD or ppo-FEV1<40%
  • All reported local control of ≥89%
  • 30 day mortality: all SABR studies = 0%, surgical average = 10%

Palma et al IJROBP 2011
In Search of Level 1 Evidence…

the gold standard
Randomized Trials

**ROSEL study**
- Peripheral stage IA tumors
- **Primary**: 2- and 5-year local+ regional control, QoL and treatment costs.
- **Secondary**: Overall survival, quality adjusted life years (QALYs), pulmonary function, total costs (direct and indirect)

**STARS study**
- Stage IA tumors; T2 if ≤4cm
- **Primary**: 3-year overall survival.
- **Secondary**: DFS, PFS at 3 years; acute and chronic toxicities; predictive value of pre- and post-treatment PET scans

- **The Lone Star State**
PROTOCOL ACTIVATION: MAY 2, 2011

**TITLE**
ACOSOG Z4099/RTOG 1021: A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

**SCHEMA**

1. Histologically confirmed NSCLC with negative mediastinal lymph nodes
2. STRATIFY: Planned brachytherapy yes/no, Performance status
3. RANDOMIZE
4. ARM 1: Sublobar Resection (SR) ± Brachytherapy
5. ARM 2: Stereotactic Body Radiation Therapy (SBRT)
6. FOLLOW
Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang*, Suresh Senan*, Marinus A Paul, Reza Mehran, Alexander V Louie, Peter Balter, Harry JM Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben EE M van den Borre, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kriesel, Anne-Marie Dingemans, Omar Dowood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smits†, Jack A Roth†

3-year overall survival (95% CI):
- SABR 95% (85-100)
- Surgery 79% (64-97)

HR (95% CI): 0.14 (0.017-1.190)

log-rank p=0.037

Lancet Oncology 2015
STARS–ROSEL: Other Outcomes

Toxicity

• SABR:
  • 3 grade 3 events (10%)

• Surgery
  • 1 death (4%)
  • 1 grade 4 event (4%)
  • 11 grade 3 events (40%)

Locoregional Recurrence Events

• SABR:
  • 5 (1 local, 4 regional)

• Surgery
  • 1 (regional)

Lancet Oncology 2015
Local vs Lobar Recurrence

- 90% “local control” at 3 years is our standard quote
- Primary tumor control is different than lobar control
Patient reported outcomes in lung cancer

Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: Results from the ROSEL multicenter randomized trial

Summary: Stage I Treatment

• Surgery remains standard of care, but non-randomized data suggests that SABR can achieve comparable outcomes

• New trials being launched: STABLEMATES, VALOR, and in China

• SABR beats 3D-CRT on convenience and toxicity, but early RCT data suggests that good local control can also be achieved with very prolonged fractionation schedules
Management of Stage III NSCLC
Unresectable: RT alone

• Perez et al RTOG RCT (IJROBP 1986) established 60 Gy in 30 fractions based on highest rates of local control (no survival differences vs. 40 or 50 Gy).

• Altered fractionation provides a 2.5% benefit in 5-year survival (meta-analysis JCO 2012) at the expense of increased esophagitis
Chemo + RT vs. RT alone

**Improved Survival in Stage III Non-Small-Cell Lung Cancer: Seven-Year Follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial**


**Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary Results of a Phase III Trial in Regionally Advanced, Unresectable Non-Small-Cell Lung Cancer**


![Graph showing survival probability over months for RT Only and CT-RT arms](image-url)
Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer

Anne Auperin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Khyonuki Puruse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Caneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cécile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>RT + ConC CT</th>
<th>RT + Seq CT</th>
<th>O/E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 8831</td>
<td>45/48</td>
<td>39/45</td>
<td>2.4</td>
<td>30.9</td>
<td></td>
<td>1.12</td>
<td>(0.73 to 1.72)</td>
</tr>
<tr>
<td>WJLCG</td>
<td>131/156</td>
<td>142/158</td>
<td>-16.8</td>
<td>67.3</td>
<td></td>
<td>0.76</td>
<td>(0.61 to 0.99)</td>
</tr>
<tr>
<td>RTOG 9410</td>
<td>183/264</td>
<td>182/263</td>
<td>-20.5</td>
<td>91.1</td>
<td></td>
<td>0.80</td>
<td>(0.65 to 0.98)</td>
</tr>
<tr>
<td>GMMA</td>
<td>15/15</td>
<td>15/15</td>
<td>-1.0</td>
<td>7.0</td>
<td></td>
<td>0.67</td>
<td>(0.41 to 1.02)</td>
</tr>
<tr>
<td>Antunes 95</td>
<td>87/102</td>
<td>96/103</td>
<td>-9.9</td>
<td>45.0</td>
<td></td>
<td>0.60</td>
<td>(0.60 to 1.07)</td>
</tr>
<tr>
<td>GLOT-GFPC NPC</td>
<td>63/90</td>
<td>66/78</td>
<td>-0.3</td>
<td>31.9</td>
<td></td>
<td>0.98</td>
<td>(0.69 to 1.39)</td>
</tr>
<tr>
<td>EORTC 08872</td>
<td>52/602</td>
<td>547/602</td>
<td>-46.4</td>
<td>263.1</td>
<td></td>
<td>0.94</td>
<td>(0.74 to 0.99)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 3.24$, $P = .68$, $I^2 = 0\%$

Auperin, JCO 2012
Optimal Chemotherapy Unknown

Most common options in U.S. are carboplatin/paclitaxel and cisplatin/etoposide.

No phase III data to compare these:
- Pneumonitis rates appear higher with carbo/paclitaxel
- Phase II survival data favors cisplatin/etoposide
- Cis-Vinca alkaloid also reasonable
# Predicting Radiation Pneumonitis After Chemoradiation Therapy for Lung Cancer: An International Individual Patient Data Meta-analysis

David A. Palma, MD, MSc, PhD, * Suresh Senan, MRCP, FRCR, PhD, † Kayoko Tsujino, MD, ‡ Robert B. Barriger, MD, † Ramesh Rengan, MD, PhD, ‡ Marta Moreno, MD, † Jeffrey D. Bradley, MD, ** Tae Hyun Kim, MD, †† Sara Ramella, MD, †‡ Lawrence B. Marks, MD, §§ Luigi De Petris, MD, PhD, ††† Larry Stitt, MSc, ††‡ and George Rodrigues, MD, MSc*.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Multivariable analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Age (per 10-y increase)</td>
<td>1.24</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cisplatin-etoposide</td>
<td>1</td>
</tr>
<tr>
<td>Carboplatin-paclitaxel</td>
<td>3.33</td>
</tr>
<tr>
<td>Other</td>
<td>1.38</td>
</tr>
<tr>
<td>Volume of lung receiving ≥20 Gy (V&lt;sub&gt;20&lt;/sub&gt;)</td>
<td>1.03</td>
</tr>
</tbody>
</table>

*STRIVE Pneumonitis Meta-analysis*
Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer

Luhua Wang, Shixiu Wu, Guangfei Ou, Nan Bi, Wenfeng Li, Hua Ren, Jianzhong Cao, Jun Liang, Junling Li, Zongmei Zhou, Jima Lv, Xiangru Zhang

log-rank test: p=0.04

Overall Survival Probability

Time (months)
Cis/Etoposide or Carbo/Paclitaxel?

Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer

Luhua Wang, Shixiu Wu, Guangfei Ou, Nan Bi, Wenfeng Li, Hua Ren, Jianzhong Cao, Jun Liang, Junling Li, Zongmei Zhou, Jima Lv, Xiangru Zhang

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Treatment-related toxicities.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PE</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>25 (78.1%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>28 (87.5%)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>PLT</td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>27 (84.4%)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Grade 2/3</td>
<td>12 (37.5%)</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>24 (75%)</td>
</tr>
<tr>
<td>Grade ≥2</td>
<td>8 (25%)</td>
</tr>
</tbody>
</table>
Optimal RT Dose – RTOG 0617

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIA or IIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study


<table>
<thead>
<tr>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm A</strong></td>
<td></td>
</tr>
<tr>
<td>Concurrent chemotherapy: Carboplatin &amp; Paclitaxel</td>
<td>Consolidation chemotherapy: Carboplatin &amp; Paclitaxel</td>
</tr>
<tr>
<td>RT to 60 Gy, 5 x per week for 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Arm B</strong>: Closed 6/17/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent chemotherapy: Carboplatin &amp; Paclitaxel</td>
</tr>
<tr>
<td>RT to 74 Gy, 5 x per week for 7.5 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Arm C</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab Loading Dose: Week 1, Day 1</td>
</tr>
<tr>
<td>then Concurrent chemotherapy: Carboplatin &amp; Paclitaxel, and Cetuximab</td>
</tr>
<tr>
<td>RT to 60 Gy, 5 x per week for 6 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Arm D</strong>: Closed 6/17/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab Loading Dose: Week 1, Day 1</td>
</tr>
<tr>
<td>then Concurrent chemotherapy: Carboplatin &amp; Paclitaxel, and Cetuximab</td>
</tr>
<tr>
<td>RT to 74 Gy, 5 x per week for 7.5 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Consolidation Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab and Carboplatin &amp; Paclitaxel</td>
</tr>
</tbody>
</table>

Western University - Canada

OICR - Ontario Institute for Cancer Research
- Factors predictive of OS: Radiation dose (60 Gy), maximum esophagitis grade, PTV size, heart V5 and V30
Unresectable Stage III – Summary

• Concurrent chemoradiotherapy is preferred
  • Optimal chemotherapy is an open question

• Randomized evidence best supports a total dose of 60 Gy in 2 Gy daily fractions with chemotherapy

• Sequential chemoradiation, and radiation alone are options in less-fit patients
Resectable Stage III NSCLC

- Options for curative-intent treatment:
  - Surgery
  - Chemo ± RT
  - Surgery
  - ± RT
  - ChemoRT
  - Surgery
  - Concurrent ChemoRT
  - Others: sequential chemoRT
    - RT alone

Sobering quote:
“While there are many potential treatment options, none yields a high probability of cure.”
– Schild et al, utdol.com
• Insufficient randomized data to identify which option is best

• Some RCTs include non-standard arms – this makes conclusions difficult

• **Overarching Theme of This Section:**
  - Randomized trials have consistently failed to show that two local treatments are better than one local treatment.
Resectable Stage III NSCLC

- Options for curative-intent treatment:

  - Surgery → Chemo ± RT
  - Chemo → Surgery → ± RT
  - ChemoRT → Surgery
  - Concurrent ChemoRT
Option 1: Surgery first

- In carefully selected patients with limited stage IIIA disease that can be completely resected, initial surgery is often the treatment of choice
  - Examples include T3N1 disease, or T4 disease due to multiple tumor nodules in one lung.

- Superior sulcus (Pancoast) tumors are a special case
  - SWOG 9416 evaluated neoadjuvant chemoRT for T3-T4 N0/1 superior sulcus tumors (45 Gy with concurrent cis/eto then resection)
  - 2-year survival 55%
Surgery first? Then what…?

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dumant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier

![Graph showing survival rates with chemotherapy vs. no chemotherapy over time.](image)
Post–Operative Radiotherapy: PORT

• Why consider PORT?
  • R1 resection (positive margins)
  • R0 resection with positive nodes
PORT: Positive Margins

**JOURNAL OF CLINICAL ONCOLOGY**  **ORIGINAL REPORT**

Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non–Small-Cell Lung Cancer

Elyn H. Wang, Christopher D. Corso, Charles E. Rutter, Henry S. Park, Aileen B. Chen, Anthony W. Kim, Lynn D. Wilson, Roy H. Decker, and James Byunghoon Yu

---

**Fig 1.** Percent distribution by year of diagnosis of patients receiving postoperative radiotherapy.
PORT Based on Nodal Status

**Table 3: Details of radiotherapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Radiotherapy delivery (day)</th>
<th>Prescription technique</th>
<th>Machine used</th>
<th>Average field size (cm)</th>
<th>Clinical target volume</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>60</td>
<td></td>
<td>Co60</td>
<td>15x9</td>
<td>Bronchial stump, hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>LCSG 773</td>
<td>50</td>
<td></td>
<td>Co60 &amp;</td>
<td>60 &amp;</td>
<td>Bronchial stump, hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>CAMS</td>
<td>60</td>
<td></td>
<td>Co60 &amp;</td>
<td>15x9</td>
<td>Bronchial stump, hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>Lille</td>
<td>45-60</td>
<td></td>
<td>Co60 &amp;</td>
<td>15x9</td>
<td>Hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>EORTC 08861</td>
<td>56</td>
<td></td>
<td>Co60 &amp;</td>
<td>15x9</td>
<td>Bronchial stump, hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>MRC LU11</td>
<td>40</td>
<td></td>
<td>Co60 &amp;</td>
<td>15x9</td>
<td>Bronchial stump, hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>GETCB 04CB88</td>
<td>60</td>
<td>Isocentre</td>
<td>Scattering</td>
<td>2.0-2.5</td>
<td>Bronchial stump, hilum, mediastinum</td>
<td>OF, LF</td>
</tr>
<tr>
<td>Slovenia</td>
<td>30</td>
<td></td>
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<td>15x9</td>
<td>Hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
<tr>
<td>GETCB 05CB88</td>
<td>60</td>
<td>Isocentre</td>
<td>Co60</td>
<td>15x9</td>
<td>Hilum, mediastinum</td>
<td>SCB, OF, LF</td>
</tr>
</tbody>
</table>

SCB = spinal cord blocks; OF = oblique fields; LF = lateral fields; linac = linear accelerator; Co60 = cobalt-60.

*Information not available; †For upper lobe tumours.

Many centers used old techniques (Cobalt, APPA) and large doses per fraction.
PORT Based on Nodal Status

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

PORT Meta-analysis Trialists Group

Lancet 1998
PORT Based on Nodal Status

- Several subsequent observational studies suggest some value for PORT
  - Data sources:
    - ANITA trial (post hoc analysis – IJROBP 2008)
    - SEER (JCO 2006)
    - National Cancer Database (JTO 2014)

- PORT in N2 disease is the current topic of the Phase III European LUNG-ART randomized trial (EORTC 22055) – dose is 54 Gy in 30 fractions

Lancet 1998
### Variations in Target Volume Definition for Postoperative Radiotherapy in Stage III Non-Small-Cell Lung Cancer: Analysis of an International Contouring Study

<table>
<thead>
<tr>
<th>Surgically involved mediastinal nodes</th>
<th>LN stations to be included in the CTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2R</td>
<td>1–2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>1–2L</td>
<td>1–2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>3 (Right -sided tumor)</td>
<td>3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>3 (Left-sided tumor)</td>
<td>3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>4R</td>
<td>2R, 4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>4L</td>
<td>2L, 4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>5</td>
<td>2L, 4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>6</td>
<td>2L, 4L, 5, 6, 7 Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>7 (Right-sided tumor)</td>
<td>4R, Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*</td>
</tr>
<tr>
<td>7 (Left-sided tumor)</td>
<td>4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*</td>
</tr>
<tr>
<td>8 (Right-sided tumor)</td>
<td>4R, 7, 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction</td>
</tr>
<tr>
<td>8 (Left-sided tumor)</td>
<td>4L, 5, 6, 7 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction</td>
</tr>
</tbody>
</table>

* Abbreviations: LN = lymph node; CTV = clinical target volume.

* Unless other nodes are involved.
Resectable Stage III NSCLC

- Options for curative-intent treatment:
  - Surgery
  - Chemo ± RT
  - Chemo → Surgery → ± RT
  - ChemoRT → Surgery
  - Concurrent ChemoRT
Option 2: Chemo before surgery

- Pre-operative chemotherapy improves survival compared to surgery alone (Meta-analysis, Lancet 2014).

- But, compared to post-operative chemotherapy, outcomes are similar (NATCH RCT).

- Induction chemotherapy may be considered in patients planned for surgery who have low volume/microscopic mediastinal disease.
Option 2: Chemo before surgery

• If choosing induction chemotherapy before surgery, should you deliver induction chemoradiation instead?
Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

Milos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Fröh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijedovic, Adrian Ochsenbein, Urs R Meier, Christoph Marnot, Daniel Rauch, Oliver Gaultchi, Daniel C Betticher, René-Olivier Minimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group

232 patients randomized to cis-doc vs. cis-doc-RT (44Gy) before surgery

2 older RCTs showed similar results (Shah, ATS 2012)
Option 2: Chemo before surgery or RT?

Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer


No. of patients registered: 582
  3 patients excluded because of lack of informed consent

No. of included patients: 579

No. of patients off study: 247 (43%)
  - progressive or stable disease or death: 175
  - toxicity or refusal: 37
  - other: 35

No. of patients randomized: 332 (57%)
  Stratified for type of response, histological subtype and institution

No. allocated to Radiotherapy: 165
  No. not irradiated: 11 (7%)
    - operated: 3
    - unfit for Radiotherapy: 8
  Radiotherapy: 154 (93%)

No. allocated to Surgery: 167
  No. not operated: 13 (8%)
    - irradiated: 5
    - unfit for Surgery: 8
  Surgery: 154 (92%)

60-62.5 Gy

JNCI 2007
“In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment.”

JNCI 2007
Resectable Stage III NSCLC

• Options for curative-intent treatment:

- Surgery → Chemo ± RT
- Chemo → Surgery → ± RT
- ChemoRT → Surgery
- Concurrent ChemoRT

Not better than option 1
Not better than chemo followed by RT
Resectable Stage III NSCLC

- Options for curative-intent treatment:

  - Surgery → Chemo ± RT
  - Chemo → Surgery → ± RT
  - ChemoRT → Surgery
  - Concurrent ChemoRT
Option 3: ChemoRT first – or alone

Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyau Chen, Robert B Livingstone, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, William T Sause, James D Cox

Lancet 2009
Albain Trial

- Pneumonectomy operative mortality rate: 26% (15/54)
Albain Trial – Exploratory Analysis

Lobectomy vs. Matches

Pneumonectomy vs. Matches

Lancet 2009
Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA (N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

Wilfried Ernst Erich Eberhardt, Christoph Piétre, Thomas Christoph Gaudes, Godehard Frisdal, Stefanie Voit, Vanessa Heinrich, Stefan Wehner, Wilfried Budach, Werner Spengler, Martin Kornisch, Berthold Fischer, Heinrich Schmidhauser, Dirk De Breycker, Claus Helka, Sebastian Cordes, Rodrigo Hepp, Diana Lütke-Brintrop, Nils Lehmann, Martin Schuler, Karl-Heinz Jäckel, Georgios Stoumbris, and Martin Strobl
ESPATUE Trial

Fig 2. Overall survival of randomly assigned arms.

Table 3. Surgical Procedures and Maximum Postoperative Toxicity Observed in Arm B.

<table>
<thead>
<tr>
<th>Toxicity by Procedure</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy (n = 39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Other GI or renal</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous infection</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonectomy (n = 23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilobectomy (n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Segmentectomy (n = 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other GI or renal</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Resectable Stage III NSCLC

• Options for curative-intent treatment:

  - Surgery → Chemo ± RT
  - Chemo → Surgery → ± RT
  - ChemoRT → Surgery
  - Concurrent ChemoRT

Not better than concurrent chemoRT overall. May be considered when lobectomy needed.
Resectable Stage III NSCLC

- Options for curative-intent treatment:
  - Surgery → Chemo ± RT
  - Chemo → Surgery → ± RT
  - ChemoRT → Surgery
  - Concurrent ChemoRT

- No strong evidence as to which approach is best.
- The “Two Local Modality” approach has failed in several RCTs
- Treatment decisions must be individualized
Resectable Stage III – Summary

• Based on randomized data, outcomes appear to be similar whether the definitive local treatment is surgical or radiotherapy based

• **Primary surgical patients:** adjuvant chemotherapy is standard, PORT is indicated if margin positive and debatable for N2.
  • The benefit of neoadjuvant treatment in resectable cases is unclear (compared to just post-operative chemotherapy)

• **Primary chemoradiotherapy:** benefit of adding surgery afterward, or instead of RT, is unclear
Adjuvant radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline


Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline

European Organization for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer

Dirk De Ruyscher, Corinne Faivre-Finn, Ursula Nestle, Coen W. Hurkmans, Cécile Le Péchoux, Allan Price, and Suresh Senan
Oligometastatic NSCLC
Oligomets: A Hot Topic
NSCLC Phase II Data

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

*Long-Term Results of a Prospective Phase II Trial (Nct01282450)

Dirk De Raeymaeker, MD, PhD,* Rianus Wunders, MD,* Angela van Baardwijk, MD, PhD,* Anne-Marie C. Dingemans, MD, PhD,† Bart Reynen, MD,* Rund Houven, MSc,* Gerben Bootma, MD, PhD,‡ Cordula Pitt, MD, PhD,§ Linda van Eijden, MD,§ Wiel Geraedts, MD,‖ Brigitta G. Baumert, MD, PhD,* and Philippe Lambin MD, PhD*  

<table>
<thead>
<tr>
<th>Localization metastasis</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal gland</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>Bone</td>
<td>7 (17.9%)</td>
</tr>
<tr>
<td>Brain</td>
<td>17 (43.9%)</td>
</tr>
<tr>
<td>Gastro-hepatic ligament</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Lung</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>Muscle</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Pleura</td>
<td>3 (7.7%)</td>
</tr>
</tbody>
</table>

Number metastases

<table>
<thead>
<tr>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34 (87.2%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (2.6%)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Overall survival (n = 39).
An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non—Small-Cell Lung Cancer

**ALL PATIENTS**
(T: n=363, V: n=168)
1yr OS: T: 71.9% (V: 68.5%)
2yr OS: T: 51.8% (V: 47.5%)
3yr OS: T: 41.4% (V: 36.1%)
4yr OS: T: 35.1% (V: 33.6%)
5yr OS: T: 30.5% (V: 27.5%)

**Metachronous**
(T: n=101, V: n=45)
LOW RISK
1yr OS: T: 88.4% (V: 87.7%)
2yr OS: T: 66.3% (V: 66.3%)
3yr OS: T: 59.8% (V: 59.8%)
4yr OS: T: 50.4% (V: 56.4%)
5yr OS: T: 47.8% (V: 51.7%)

**Synchronous**
(T: n=262, V: n=123)
N Stage: N0
(T: n=140, V: n=61)
INTERMEDIATE RISK
1yr OS: T: 76.2% (V: 74.6%)
2yr OS: T: 57.4% (V: 50.0%)
3yr OS: T: 42.9% (V: 36.8%)
4yr OS: T: 40.9% (V: 34.5%)
5yr OS: T: 36.2% (V: 29.2%)

N Stage: N1 or N2
(T: n=122, V: n=62)
HIGH RISK
1yr OS: T: 53.6% (V: 48.9%)
2yr OS: T: 34.1% (V: 32.1%)
3yr OS: T: 25.4% (V: 20.0%)
4yr OS: T: 18.3% (V: 12.3%)
5yr OS: T: 13.8% (V: 12.1%)

Ashworth, Clin Lung Ca 2014
MDACC/Colorado Trial

First-line treatment for oligometastatic stage IV NSCLC (1-3 metastases)

Acceptable regimens:
- ≥4 cycles of platinum-based doublet+/BV
- erlotinib and crizotinib are acceptable for patients with EGFR mutations and EMLA-ALK fusions, respectively.
- CNS metastases can be treated prior to enrollment

No local consolidation therapy (LCT) arm**

Physician choice for standard maintenance or surveillance*

Non-PD Enroll, randomize

LCT arm

Local consolidation (surgery and/or radiation to primary and metastases)

Physician choice for standard maintenance or surveillance*

PD

Eligibility
- 1-3 mets after completion of first-line treatment
- Non-PD
- PS 0-2
- Candidate for local therapy

Covariates
- Number of mets (1 vs. 2-3)
- Response to first-line chemo (SD vs. PR/CR)
- N0/N1 vs. N2/N3
- CNS Mets (yes/no)
- EGFR/EML4-ALK status

**Recommended systemic therapy options include bevacizumab, pemetrexed, and erlotinib

Results submitted to ASCO 2016
The COMET Trial

STEREOTACTIC ABLATIVE Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): A Randomized Phase II Trial

Patients with up to 5 metastatic lesions from any primary tumor site, meeting inclusion criteria

RANDOMIZATION

(1:2 ratio of randomization to Arm 1 vs. Arm 2)

ARM 1: STANDARD OF CARE
Palliative RT to any symptomatic sites
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP

ARM 2: STANDARD OF CARE + SABR
SABR to all sites of known disease
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP

Principal Investigators
D. Palma, S. Senan

Target Sample Size
99

Open Sites
London, ON
Amsterdam, NL
BCCA
Surrey, BC
Sudbury, ON
Hamilton, ON

Opening Soon:
Beatson, Scotland
McGill
Royal Alfred, Australia

http://clinicaltrials.gov/ct2/show/NCT01446744
Palma et al, BMC Cancer 2012, 12:305
Small Cell Lung Cancer
Epidemiology

• Approximately 15% of lung cancers – small decrease over past 30 years, higher proportion of women

Fig 1. The diagnosis of small-cell lung cancer, as a percent of all lung cancers, over 30 years.

Govindan, JCO 2006
Pathology

- Small round blue cell tumor
- Virtually all are reactive for keratin and epithelial membrane antigen
- 75% have one more neuroendocrine markers
  - Chromogranin, synaptophysin, NSE, etc.
NCCN Definitions

**Limited Stage**

- AJCC (7th edition) Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

**Extensive Stage**

- AJCC (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
Stage Distribution and Survival

Fig 5. The diagnosis of small-cell lung cancer by stage.

Fig 10. The all-cause survival trends in limited-stage small-cell lung cancer.

Fig 7. The all-cause survival trends in extensive-stage small-cell lung cancer.

Govindan JCO 2006
Unique Scenario: T1–T2N0 lesions

- Surgery alone provides poor outcomes, but in combination with chemotherapy, outcomes are reasonable
- IASLC data: 439 patients with resected SCLC. In patients with stage I disease, 5-yr OS = 48%
Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer

Chi-Pu Jeffrey Yang, Derek Y. Chiu, Paul J. Speicher, Brian C. Golack, Xiaofei Wang, Matthew G. Hartwig, Mark W. Onaitis, Betty C. Yong, Thomas A. D’Amico, Mark F. Berry, and David H. Harpole

No. at risk
No adjuvant therapy | 388 | 320 | 247 | 192 | 151 | 105
Adjuvant chemotherapy | 354 | 219 | 256 | 210 | 167 | 116
Adjuvant chemo, RT to brain | 99 | 91 | 98 | 75 | 62 | 48
Adjuvant chemo, RT to lung | 87 | 75 | 57 | 45 | 40 | 30
Adjuvant RT to lung | 17 | 14 | 11 | 9 | 7 | 7

Log-rank P < .01
The Role of Radiotherapy

- Similar data from two meta-analysis from 1992: Pignon, NEJM: 13 trials: 5.4% OS benefit at 3-years
Role of Chemoradiotherapy in Elderly Patients With Limited-Stage Small-Cell Lung Cancer


Fig 3. Kaplan-Meier overall survival stratified by treatment regimen for propensity score-matched cohort. CRT, chemoradiotherapy; CT, chemotherapy.

Fig 4. Kaplan-Meier overall survival analysis stratified by sequential or concurrent chemoradiotherapy.
419 patients enrolled, all patients received 45 Gy starting with cycle 1 of EP: 45/30 BID vs. 45/25 OD

Patients with CR offered PCI
Which Fractionation?

- OS benefit at a cost of increased esophagitis
- Control arm (45/25) may be a low bar to clear
Which Fractionation?

- 2 cycles of paclitaxel + topotecan
- 70 Gy in 35 fractions with EP
- Phase II design, 63 patients

**Table 5. Comparison of INT-0096 and CALGB 39808**

<table>
<thead>
<tr>
<th>Trial</th>
<th>INT-0096</th>
<th>CALGB 39808</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic radiotherapy regimen</td>
<td>45 Gy</td>
<td>70 Gy</td>
</tr>
<tr>
<td></td>
<td>twice daily</td>
<td>every day</td>
</tr>
<tr>
<td>Patient and tumor characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58%</td>
<td>54%</td>
</tr>
<tr>
<td>Weight loss &gt; 5%</td>
<td>18%</td>
<td>31%</td>
</tr>
<tr>
<td>Age, years (median)</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Supraclavicular adenopathy</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Toxicity profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>87%</td>
<td>83%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>32%</td>
<td>21%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median overall survival</td>
<td>20.3 months</td>
<td>22.4 months</td>
</tr>
<tr>
<td>2-year overall survival</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>2-year DFS</td>
<td>29%</td>
<td>31%</td>
</tr>
</tbody>
</table>

IJROBP 2004
Ongoing Trials

• Two ongoing trials:
  • CALGB 30610: 70 Gy/35 OD vs. 45 Gy/30 BID
  • CONVERT: 66 Gy/33 OD vs. 45 Gy/30 BID

• Reasonable doses include:
  • 60-70 Gy in 1.8 – 2 Gy per fraction
  • 45 Gy in 30 fractions BID (or similar short-course regimens)
Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel B. Fried, David E. Morris, Charles Poole, Julian G. Rosenman, Jan S. Halle, Frank C. Detterbeck, Thomas A. Hensing, and Mark A. Socinski

Fig 1. Two-year overall survival risk ratio forest plot for early vs late thoracic radiation therapy (RT).

JCO 2007
The SER: Start date to End of RT

SER = 12 weeks

SER = 6 weeks

SER = 3 weeks
The SER: Start date to End of RT

- Survival decrease of 1.86% per 1 week prolongation of SER
- Increased esophagitis with low SER
Two RCTs have compared Pre-chemotherapy vs. Post-chemotherapy volumes

- SWOG study (started in 1979) used wide-field vs. limited-field 2-D planning
- Chinese study used 3D planning
- No differences in relapse rates or toxicity

- Dutch phase II data suggests that ENI is not required if a PET/CT is done for staging, but in the absence of PET/CT, isolated nodal relapse may be >10%.
Caveats:

- In some trials, CR was defined by CXR
- A subsequent RCT showed no benefit to doses >25 Gy in 10 fractions
Extensive Stage SCLC

- Majority of SCLC patients have extensive stage disease
- Disease is highly responsive to chemotherapy, but median survival is 8-13 months
- Multiple RCTs have evaluated chemotherapy combinations and timing. Two-drug regimens are better than single-drug regimens, but >2 is not very beneficial but more toxicity
- Platinum + Etoposide (4-6 cycles) remains standard first-line in most centers
- Can radiation help improve survival?
PCI in ES–SCLC

• 286 patients with ES-SCLC randomized after any response to chemotherapy: PCI vs no PCI
• Several fractionations allowed: 20 Gy/5 and 30 Gy/10 most common
• Brain imaging was not part of standard staging and follow-up procedures, unless symptoms present
PCI in ES–SCLC

**Figure 1.** Cumulative Incidence of Symptomatic Brain Metastases.

The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001), by Gray’s method.

**Figure 3.** Overall Survival.

Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Slotman 2007
Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

By Branislav Jeremic, Yuta Shibamoto, Nebojsa Nikolic, Biljana Miličić, Slobodan Milošavljević, Aleksandar Dagošević, Jasna Aleksandrović, and Gordana Radosavljević-Asić

Fig 1: Treatment schema. VP-16, etoposide.

Fig 2: Overall survival in group 1 (—), group 2 (— — — —), group 3 (— — — — —), group 4 (— — — — — —), and group 5 (— — — — — — —).

MST | % Alive
--- | ---
1 | 17 65 38 22 13 6.1
2 | 11 46 28 13 5.6 3.7
3 | 8 35 8.8 2.9 0 0
4 | 0 21 3.0 0 0 0
5 | 0 0 0 0 0 0

JCO 1999
Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Prang, Joost I. Kneijens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Fauve-Finn*, Suresh Senan*

ED-SCLC without brain metastases or pleural involvement
Any response to 4-6 cycles chemotherapy

RANDOMIZE

Thoracic radiotherapy (10x3Gy)

No Thoracic radiotherapy

All patients will receive PCI

Lancet 2014
Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost I. Kneegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keljser, Corinne Faivre-Finn*, Suresh Senan*

1° Endpoint: 1-yr OS:
33% (TRT) vs. 28% (no TRT)
HR 0.84, p=0.066

2° Endpoint: 2-yr OS:
13% (TRT) vs. 3% (no TRT)
p=0.004
Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harn van Tinteren, John O Praga, Joost I. Kneijens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faiivre-Finn*, Suresh Senan*
Thoracic Radiotherapy for Extensive Stage Small-Cell Lung Cancer: A Meta-Analysis

David A. Palma, Andrew Warner, Alexander V. Louie, Suresh Senan, Ben Slotman, George B. Rodrigues

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slotman</td>
<td>0.840</td>
<td>0.694</td>
<td>1.016</td>
<td>-1.794</td>
</tr>
<tr>
<td>Jeremic</td>
<td>0.726</td>
<td>0.529</td>
<td>0.996</td>
<td>-1.985</td>
</tr>
<tr>
<td></td>
<td>0.808</td>
<td>0.686</td>
<td>0.951</td>
<td>-2.561</td>
</tr>
</tbody>
</table>

Overall Survival

<table>
<thead>
<tr>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

Favours TRT  Favours No TRT

Random effects p=0.01
Q=0.598  df=1  p=0.439  I²=0%

Clinical Lung Cancer 2015
Oligometastatic SCLC: RTOG 0937

Also noted is a disproportionate distribution of grade 4 and 5 toxicities.

**PCI only arm (n=40):** 16 deaths, no grade 4 or 5 toxicities.

**PCI + consolidative RT (n=39):** 23 deaths, 7 patients with grade 4 or 5 toxicities.

Patients still on the investigational arm (Arm 2) should discontinue and convert to appropriate standard of care.
Oligometastatic SCLC: RTOG 0937

Overall Survival

HR 1.44 (95% CI: 0.82-2.43)
1yr OS: 60.1% vs 50.8%

Time Since Randomization (Months)

<table>
<thead>
<tr>
<th>PCI</th>
<th>PCI+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>37</td>
<td>39</td>
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<td>20</td>
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<td>17</td>
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</table>

<table>
<thead>
<tr>
<th>PCI</th>
<th>PCI+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>15</td>
</tr>
</tbody>
</table>

# of Patients | Dead | Alive | Median Survival (95% CI) | p-value
---|------|-------|--------------------------|------
PCI | 42   | 22    | 20  | 15.8 (8.8, 27.6) | 0.2080
PCI+RT | 44   | 29    | 15  | 13.8 (6.3, 18.0) |
SCLC: Take Home Messages

• Limited Stage
  • Chemoradiotherapy (with early RT)
  • Several reasonable radiation fractionations
    • 45/30 BID, 70/35 (CALGB), 60/30, 40/15 (NCIC BR-6)
  • PCI in responders

• Extensive Stage
  • Doublet platinum-based chemotherapy
  • In patient with a response, consider thoracic radiotherapy and PCI
CRITICAL REVIEW

RADIOThERAPY IN SMALL-CELL LUNG CANCER: LESSONS LEARNED AND FUTURE DIRECTIONS

Ben J. Slotman, M.D., Ph.D., and Suresh Senan, M.R.C.P., F.R.C.R., Ph.D.

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

Although chemotherapy is an essential component in the treatment of small-cell lung cancer, improvements in survival in the past two decades have been mainly achieved by the appropriate application of radiotherapy. The aim of the present study was to review the key developments in thoracic radiotherapy and prophylactic cranial radiotherapy and to discuss the rationale behind key ongoing studies in small-cell lung cancer. © 2011 Elsevier Inc.
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Questions? david.palma@lhsc.on.ca