The Management of Lung Cancer

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University of Washington

ASTRO Spring Refresher Course
March 8, 2014
Overview

- Introduction
- Screening and Workup
- Early Stage NSCLC
  - Operable
  - Medically Inoperable
- Locally Advanced NSCLC
  - Surgery-based options for IIIA Disease
  - Inoperable
- Small Cell Lung Cancer
- Conclusions
• 213,380 patients are diagnosed yearly with lung cancer in the US with approximately 160,390 deaths
Introduction: The Scope of the Problem

The Challenge of Treating NSCLC

- Lung cancer is aggressive
- Normal lung is very radiosensitive
- The lung is a vital organ
- The uninvolved lung doesn’t work
Improving Clinical Outcome

local control

Toxicity

Probability

Dose of Radiation

Treatment Intensification
Improving Clinical Outcome

Disease Control

Toxicity

Treatment Intensification
(more RT; more chemo; surgery)

Probability

Treatment Intensity
Screening and Diagnostic Workup
Early lung cancer detection → cure
CT is effective in detecting early lung cancer
However:
  • Prior studies of CXR: No mortality advantage
  • Studies demonstrating increased survival subject to lead time and over diagnosis bias etc
  • Impact of false positive studies?
Screening

NLST Protocol Schema

Final: October 2010
Kaplan-Meier curves for lung cancer mortality

Probability of survival: ALL participants

Years from randomization

CT arm
CXR arm
Lung cancer case survival Kaplan Meier curve

Probability of survival: Participants with lung cancer

Years from randomization

CT arm
CXR arm
Kaplan-Meier curves for *all-cause mortality*

- **CT arm**
- **CXR arm**

Probability of survival: ALL participants

Years from randomization

0 1 2 3 4 5 6 7 8
Diagnostic Workup: Patient Selection

Stage IIIA/IIIB NSCLC
N=153

Hicks et al JNM 2001
Diagnostic Workup: Impact of mediastinal nodal involvement

<table>
<thead>
<tr>
<th>Stage</th>
<th>5yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>75%</td>
</tr>
<tr>
<td>Stage IB</td>
<td>55%</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>50%</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>40%</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>10-35%</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>5-8%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Invasive staging of mediastinum: cervical mediastinoscopy

- **Gold standard is surgical staging with cervical mediastinoscopy**
  - Sensitivity is 44-92% with 100% specificity
- **Invasive procedure**
  - Risk of complications (rare)
- **Requires skilled thoracic surgeon (operator dependent)**
- **Often omitted in inoperable patients**
Mediastinal LN Biopsy

## Diagnostic Workup: Methods for staging mediastinum

<table>
<thead>
<tr>
<th>Lymph Node Levels</th>
<th>2</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8-9</th>
<th>10</th>
</tr>
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<tbody>
<tr>
<td><strong>EBUS-FNA</strong></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>EUS-FNA</strong></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Mediastinoscopy:</strong> Cervical</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Mediastinoscopy:</strong> Chamberlain</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Combination of EBUS + Mediastinoscopy had higher sensitivity (94%) than Mediastinoscopy alone (79%) or EBUS alone (85%) (p=0.02)

- EBUS alone vs mediastinoscopy alone: no difference in lymph node sensitivity

- 18% vs 7% futile thoracotomy rate in the mediastinoscopy vs EBUS group (p=0.02)

Annema et al JAMA 2010
Diagnostic Workup: Impact of mediastinal nodal involvement

- Is PET alone adequate for staging the mediastinum?

<table>
<thead>
<tr>
<th></th>
<th>SEN</th>
<th>SPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>50-71</td>
<td>66-89</td>
</tr>
<tr>
<td>PET/CT</td>
<td>67-91</td>
<td>82-96</td>
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<table>
<thead>
<tr>
<th></th>
<th>SEN</th>
<th>SPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED</td>
<td>44-92</td>
<td>100</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>87-96</td>
<td>100</td>
</tr>
</tbody>
</table>

**INVASIVE**

Kim et al JTO S2:S59 2007

Gould et al AIM 139:3 T 2003
Diagnostic Staging and Workup: Summary points

• Staging workup should include PET/CT for all lung cancer patients

• For all non-metastatic patients invasive staging of the mediastinum should be performed when possible
  – Including all medically inoperable patients

• UW approach
  – All patients undergo PET/CT
  – All patients undergo invasive staging
    • Operable patients undergo additional mediastinoscopy
    • Subset of inoperable patients undergo EBUS-TBNA alone
Early Stage Disease
Stage IA/IB
Early Stage Operable Disease

- 276 patients, intraoperatively T1N0
  - Lobectomy vs limited resection
    - registered 771 patients (clinical T1N0), but excluded 495 due to benign disease, tumor location, size or nodal status.
- LCSG showed trend towards increased likelihood of death with limited resection
- LCSG showed three-fold increase in local failure with wedge resection vs. lobectomy

![Fig 1. Time to death (from any cause) by treatment for 247 eligible patients.](image1)

![Fig 2. Time to recurrence (excluding second primaries) by treatment for 247 eligible patients.](image2)
Early Stage Operable Disease: High Risk Patients

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

Fig 2. Time to recurrence (excluding second primaries) by treatment for 247 eligible patients.
Is there a ‘lumpectomy’ for the lung?
Early Stage Operable Disease: High Risk Patients
## Studies of Brachytherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santos (Surg 2003;134:691-6)</td>
<td>102</td>
<td>2%</td>
</tr>
</tbody>
</table>
Z4032

A Randomized Phase III Study of Sublobar Resection (SR) vs Sublobar Resection plus Brachytherapy (SRB) in High-risk patients with NSCLC, 3cm or smaller
• There was no significant difference between the arms in time to local recurrence (HR = 0.87; 5% CI: 0.41, 1.86, p=0.72).
• There was no difference in the rate of local recurrence between SR and SRB arms (12.8% versus 12.5%, p=0.94).
• There was no difference in the location of local recurrence between SR and SRB arms: At the staple line (6.4% versus 4.8%, p=0.94); away from the staple line (3.7% versus 3.8%, p=1.00); nodal (1.8% versus 3.8%, p=0.44).
• SRB did not reduce the rate of local recurrence in patients with a compromised surgical margin (margin < 1cm; margin:tumor ratio <1; positive staple line cytology).
• There was no significant difference in overall survival between SR (71%) and SRB (72%) (p=0.81) at 3 years.
• Brachytherapy does not improve clinical outcome over SR alone in this patient population.
Surgery - Medically Inoperable

- Cor pulmonale
- Severe coronary artery disease
- Renal failure
- Poor pulmonary function
  - DLCO <50%
  - FEV1/FVC ratio < 50 – 75% of predicted
- Impaired nutritional status
## Medically Inoperable Early Stage: Role of RT

<table>
<thead>
<tr>
<th>Study Author</th>
<th>n</th>
<th>Dose (Gy)</th>
<th>5-yr survival</th>
<th>5-yr CSS</th>
<th>5-yr local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosoretz</td>
<td>152</td>
<td>60-69</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krol</td>
<td>108</td>
<td>60-65</td>
<td>15%</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td>Kaskowitz</td>
<td>53</td>
<td>63</td>
<td>6%</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Sibley</td>
<td>141</td>
<td>55-70</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenzweig</td>
<td>32</td>
<td>70.2</td>
<td>33%</td>
<td>39%</td>
<td>43%</td>
</tr>
</tbody>
</table>
Fig. 1  The dose plan for a 75-year-old woman with poor lung function and a 3 cm adenocarcinoma in the right upper lobe. PTV was 44 cm$^3$ and five coplanar fields were used.

Nyman et al Lung Cancer 2006
SBRT: Indiana University Phase II Trial

- 70 patients cT1/T2 NO Medically Inoperable NSCLC
  - 35 patients cT1N0 20Gy x 3
    - Safety
    - Preliminary Efficacy
  - 35 patients cT2N0 22Gy x 3
    - Safety
    - Preliminary Efficacy
Early Stage NSCLC, Medically Inoperable: Is SBRT Effective?

- Indiana U., Phase II (Timmerman, et al.): efficacy

Local Control
95% at 2yrs
88% at 3 yrs

Overall Survival
55% at 2yrs
43% at 3 yrs

JCO, 2006
<table>
<thead>
<tr>
<th>Author</th>
<th># of Patients</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onishi et al.</td>
<td>245</td>
<td>56% (3-yr)</td>
</tr>
<tr>
<td>Timmerman</td>
<td>70</td>
<td>55% (2-yr)</td>
</tr>
<tr>
<td>Nyman</td>
<td>45</td>
<td>71% (2-yr)</td>
</tr>
<tr>
<td>Xia</td>
<td>43</td>
<td>78% (3-yr)</td>
</tr>
<tr>
<td>Nagata</td>
<td>31</td>
<td>79% (2-yr)</td>
</tr>
<tr>
<td>Uematsu</td>
<td>50</td>
<td>66% (3-yr)</td>
</tr>
<tr>
<td>Fukumoto</td>
<td>25</td>
<td>47% (2-yr)</td>
</tr>
<tr>
<td>Wulf</td>
<td>20</td>
<td>32% (2-yr)</td>
</tr>
</tbody>
</table>
Grade 3-5 Toxicity: Location

Grade 3-5 Toxicity Free Survival Zone of the Proximal Bronchial Tree Status

Percent without Toxicity

Months since Therapy

- location
  - inside
  - outside

p = 0.003
**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0813**

**SEAMLESS PHASE I/II STUDY OF STEREOTACTIC LUNG RADIOThERAPY (SBRT) FOR EARLY STAGE, CENTRALLY LOCATED, NON-SMALL CELL LUNG CANCER (NSCLC) IN MEDICALLY INOPERABLE PATIENTS**

**Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>†Level 5</th>
<th>Level 6</th>
<th>Level 7</th>
<th>Level 8</th>
<th>Level 9</th>
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</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>

†Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.
Correspondence

Central-Airway Necrosis after Stereotactic Body-Radiation Therapy

Central lesion SBRT

Outcomes of Stereotactic Ablative Radiotherapy for Centrally Located Early-Stage Lung Cancer

Median follow-up of 35 months
No grade IV/V toxicities
SBRT Dose and IGRT
SBRT Dose and IGRT

- 505 patients receiving SBRT for early stage NSCLC
  - All patients underwent daily OBI with CBCT
- LR was 4% for BED 105 or greater
  - 12Gy x 4 (BED=105.6 Gy); 20Gy x 3 (BED=180Gy); 10Gy x 5 (BED=100Gy)
  - \( \text{BED}_{10} = \text{nd}(1 + d/10) \alpha/\beta=10 \)

\( \text{BED}_{10} < 105 \text{ Gy} \)
\( \text{BED}_{10} \geq 105 \text{ Gy} \)
SBRT Dose and IGRT

Radiation Therapy Oncology Group (RTOG) Protocol 0915:
A Randomized Phase II Study Comparing 2
Stereotactic Body Radiation Therapy (SBRT)
Schedules for Medically Inoperable Patients with
Stage I Peripheral Non-Small Cell Lung Cancer Videtic ASTRO 2013

- 34Gy x 1 (Arm 1) vs 12Gy x 4 (Arm 2)
- 86 evaluable patients (41 in arm 1, 45 in arm 2)
- Median follow up was 20.6 months
- OS at 1 year was 85.4% (95% CI: 70.3-93.1%) for arm 1 patients and 91.1% (95% CI: 78.0-96.6%) for arm 2
- PFS at 1 year was 78.0% (95% CI: 62.1-87.9%) for arm 1 and 84.4% (95% CI: 70.1-92.3%) for arm 2
- The PC rates at 1 year were 97.1% (95% CI: 85.1-99.9%) for arm 1 and 97.6% (95% CI: 87.1-99.9%) for arm 2
- Both regimens are safe and effective
- 34Gy x 1 will be experimental arm in next RTOG phase III trial
24 patients treated with SBRT with CBCT
Compared setup with tattoo alone vs CBCT
CBCT reduced margin requirements from 9-13mm to 1-2mm
SBRT and IGRT

- 87 patients receiving SBRT for medically inoperable stage I NSCLC
- Determine need for CBCT over KV-KV matching along
- IGRT procedure: position with KV-KV; then perform CBCT
  - ~20% of patients required shift of 3mm or greater after KV-KV
- Conclusion: CBCT is critical to avoid marginal misses in SBRT

Corradetti et al PRO 2012
SBRT For Operable Disease
SBRT for Operable Disease

- Similar local control, locoregional control and CSS to wedge

Grills et al JCO 2010
SBRT for Operable Disease

• RTOG 0618: **Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients (ASCO 2013)**
  – 18Gy x 3
  – 33 patients enrolled, 26 evaluable
  – 2-year local failure 7.7%; OS 84%
  – One patient required surgical salvage with lobectomy for recurrence

• RTOG 1021: SBRT vs sublobar resection- closed due to poor accrual

• ROSEL: SBRT vs surgical resection (lobectomy or sublobar)- closed due to poor accrual
SBRT: Practical Considerations

- **Dose and fractionation**
  - Peripheral lesions 12Gy x4 to 20Gy x 3 all reasonable (BED > 105Gy)

- **Simulation**
  - 4DCT is essential to account for tumor motion

- **Margins**
  - IGTV→ PTV usually 3-5mm margin

- **IGRT**
  - Volumetric IGRT is essential given small # of fractions and small margins
    - Grills et all (IJROBP); Corradetti et al (PRO 2012)
SBRT: Practical Considerations

- **My approach**
  - 12.5Gy x 4 for peripheral lesions
  - 10Gy x 5 for apical or chest wall proximate lesions
    - Chest wall invasion treated with standard fractionation
  - 7.5Gy x 5 for central lesions on registry protocol
    - Proton trial in development for central lesions (Simone PI)

- **RTOG**
  - 0915 12Gy x 4 vs 30Gy x 1 showed equivalent control results ~97% LC in both arms; similar toxicity (ASTRO 2013)
  - 0813 pending 10Gy x 5 for centrally located lesions
    - Grade 5 toxicities have been observed
  - 0618 pending for operable early stage
Early Stage NSCLC

• IA/IB:
  – Good pulmonary function: lobectomy
  – Marginal function: sublobar resection
  – Inoperable: High-dose radiation alone

• IIA/B: Surgery or RT with either neoadjuvant or adjuvant chemotherapy
LOCALLY ADVANCED NSCLC
Locally Advanced NSCLC

- **T 3 N1**
  - Positive ipsilateral hilar/ peribronchial nodes (N1)

- **T 1-2-3, N2**
  - Positive ipsilateral mediastinal/ subcarinal nodes (N2)

- **T4, N0-3, M0**
  - Locally invasive
  - Pleural/ pericardial effusion
  - Satellite nodules in primary-tumor lobe

- **T1-4, N3, M0**
  - Contralateral mediastinal/ hilar nodes
  - Any scalene or supraclavicular nodes
Treatment of IIIA: Surgery Based Options

Surgery $\rightarrow$ Chemo +/- RT
- Chemo (IALT/ANITA)
- RT (PORT/ANITA)

Chemo $\rightarrow$ Surgery
- Roth, Rosell, Depierre

Chemorads $\rightarrow$ surgery
- Albain, Rusch
Adjuvant Chemotherapy

N=1867

I(0.36)-II(0.25)-III(0.39) NSCLC R0 resections

- Observation (935)
- cDDP based (922)

+/- RTx ≤ 60 Gy

Le Chevalier, NEJM 2004
Adjuvant Chemotherapy IALT n=1867

1995-2000

- 33 countries, initial accrual goal was 3300
- 80/20 M/F
- Mean age 59
- Squamous 47%, ACAs 40%
- Chemo to start ≤ 60 days after surgery
- Median f/up is 56 months

Le Chevalier, NEJM 2004
<table>
<thead>
<tr>
<th></th>
<th>+ chemo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (months)</td>
<td>50.5</td>
<td>44.4</td>
</tr>
<tr>
<td>Median DFS (months)</td>
<td>40.2</td>
<td>30.5</td>
</tr>
<tr>
<td>OS 5 years (%)</td>
<td>44.5</td>
<td>40.4</td>
</tr>
</tbody>
</table>

Le Chevalier, NEJM 2004
Surgery → Chemotherapy

Cisplatin-based CT for completely resected disease

- **IALT - 2004**
  - 1867 pts with resected stage I-III: Post-op cis-based CT vs observation, ~25% received post op XRT
  - 5 year OS improved at 45% versus 40% (p = 0.03)

- **ANITA - 2004**
  - 840 pts with resected stage Ib-III: Post-op cis/ VLB x4 vs observation
  - 5 year OS improved at 42% vs 26% for stage IIIA patients

Surgery → XRT

Adjuvant XRT in IIIA Disease

- **Lung Cancer Study Group 773 - 1986**
  - 230 pts with stage II or III squamous cell lung cancer
  - Randomized post-op to XRT (50Gy) vs observation
  - ↓ local recurrence, but no improved OS

- **PORT Meta-analysis – 1998 updated in 2005**
  - 9 trials that compared adjuvant XRT to observation
  - Accrual 1966-1994, stage I-III pts, XRT 30-60Gy
  - 18% increased risk of death in XRT group
    - Subset analysis: No OS difference in stage III

PORT Meta-Analysis

![Graph showing survival rates with and without PORT]

- **PORT**
  - Events: 707
  - Total: 1056
  - Patients at risk:
    - Months: 0, 12, 24, 36, 48, 60
    - Values: 1056, 743, 493, 340, 242, 160

- **No PORT**
  - Events: 661
  - Total: 1072
  - Patients at risk:
    - Months: 0, 12, 24, 36, 48, 60
    - Values: 1072, 802, 541, 396, 295, 224
PORT Meta-Analysis: Impact

Bekelman et al IJROBP 2006
PORT Meta-Analysis: A Closer Look Radiation Treatment Details

PORT Meta-Analysis

3D-CRT
PORT Meta-Analysis

Is this result really at all RELEVANT?
PORT: Who can benefit?

Not detrimental in N2 disease
PORT: Who can benefit? N2 Patients

1987 patients
1998-2002

p=0.0036

Lally et al JCO 2006
PORT in the era of chemotherapy: Is there a role? ANITA

Overall Survival in N2 patients

Median survival OVERALL:
- CT + PORT: 47.4 m.
- CT: 23.8 m.
- OBS: 20 m.

Survival Distribution Function

Duration of Survival (_months)
Surgery → XRT Summary

– Post op chemo for stage III disease: IALT/ANITA

– Post op chemoRT for surprise N2 disease: Using modern RT techniques
  • 5040cGy for R0 resection
  • Start RT 4-6 weeks after last cycle of chemo

– Post op chemoRT for positive margins
  • 6120cGy
  • Start RT first alone or with concurrent chemotherapy 4-6 weeks after surgery
Treatment of IIIA: Surgery Based Options

- Surgery → Chemo +/- RT
  - Chemo (IALT/ANITA)
  - RT (PORT/ANITA)

- Chemo → Surgery
  - Roth, Rosell, Depierre

- Chemorads → surgery
  - Albain, Rusch
Neoadjuvant Chemotherapy: Rationale

Surgical Rationale

• Initial response may facilitate local therapy
• Reduced incidence of (+) surgical margins
• Potential use of less radical surgery and organ preservation

Chemotherapy/Systemic Rationale

• Improved drug delivery through intact vasculature
• Possible eradication of occult regional and distant micrometastases
• Useful in vivo assessment of tumor responsiveness: implications for molecular staging and further treatment
### Induction Chemotherapy + Surgery in Stage III NSCLC: Results of Randomized Trials

<table>
<thead>
<tr>
<th>Investigators</th>
<th>RX</th>
<th># Pts.</th>
<th>Resect Rate (%)</th>
<th>Med Surv (mo)</th>
<th>5-yr Surv (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT+Surgery</td>
<td>13</td>
<td>85</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>CT+Surgery</td>
<td>28</td>
<td>61</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Rosell et al (1994)</td>
<td>Surgery</td>
<td>30</td>
<td>90</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>CT+Surgery</td>
<td>29</td>
<td>85</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>CT+Surgery</td>
<td>119</td>
<td></td>
<td>37</td>
<td>39</td>
</tr>
</tbody>
</table>

Chemo → Surgery Summary

• If operable and goal is to get to surgery for N2 disease:
  – Platin doublet → surgery → chemo/RT as indicated

• My Approach regarding post-operative therapy:
  – Deliver PORT after surgery if residual N2 disease is identified
  – If multiple nodes are identified, consider additional adjuvant chemotherapy (switch regimen)
  – Observe patients who obtain clearance of mediastinum (~30%)
Treatment of IIIA: Surgery Based Options

Surgery ➔ Chemo +/-RT
- Chemo (IALT/ANITA)
- RT (ANITA)

Chemo ➔ Surgery
- Roth, Rosell,
- Depierre

Chemorads ➔ surgery
- Albain, Rusch
Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Kathy SA Albain, RSuzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuh-chyou Chen, Robert B Livingston, 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
INT 0139: Definitive CT/RT vs Induction CT/RT → Surgery for Stage IIIA NSCLC

Stage IIIA (T1-3, pN2, M0) NSCLC
N = 429 (396 eligible)

RANDOMIZE

Cis/VP16 x 2 cycles w/concurrent XRT 45Gy
Surgery
Cis/VP16 x 2 cycles

Cis/VP16 x 2 cycles w/concurrent XRT 45Gy
Continue RT to 61GY
Cis/VP16 x 2 cycles

Albain et al. Lancet 2009
Lung Intergroup Trial 0139

**Objectives**

1. Determine if resection after CT/RT results in improved outcome compared to CT plus full-course RT (arms based on SWOG 8805 and SWOG 9019)

2. Analyze progression-free, overall, and long-term survival; toxicity; and patterns of failure
Trimodality therapy: The Results of INT 0139

Progression-free survival (A) and overall survival (B) of intention-to-treat population
CT/RT/S=chemotherapy plus radiotherapy followed by surgery (group 1, n=202).
CT/RT=chemotherapy plus radiotherapy (group 2, n=194).
median follow-up for all patients was 22.5 months (range 0.9–125.1)

Albain et al Lancet 2009
Trimodality therapy: The Results of INT 0139

- Pathological N0 (n=76)
- Pathological N1–3, unknown (n=88)
- No surgery (n=38)

MS = 7.9 Months
5-yr survival = 3% (point estimate)
38/202 = 18% of patients

Albain et al Lancet 2009
The Risks of Trimodality Therapy

Preoperative Chemoradiotherapy
45 to 50 Gy

4-6 weeks
The Risks of Trimodality Therapy

4-6 weeks

15-20Gy?

Minimal chance of cure

Surviving Cells After 45-50Gy
### INT 0139 Treatment-Related Deaths on CT/RT/S Arm (n=16)

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Total (of n=202)</th>
<th>Deaths n (% total)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>38</td>
<td>1 (3%)</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Exploration only</td>
<td>9</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Wedge</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>98</td>
<td>1 (1%)</td>
<td>ARDS</td>
</tr>
<tr>
<td>Pneumonecctomy</td>
<td>54</td>
<td>14 (26%)</td>
<td>ARDS/respiratory 11; miscellaneous, 3</td>
</tr>
<tr>
<td>(R) simple</td>
<td>17</td>
<td>5 (29%)</td>
<td>45% (13/29) of T0N0 pts underwnt pneumonecctomy</td>
</tr>
<tr>
<td>(R) complex</td>
<td>12</td>
<td>6 (50%)</td>
<td></td>
</tr>
<tr>
<td>(L) simple</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(L) complex</td>
<td>19</td>
<td>3 (16%)</td>
<td></td>
</tr>
</tbody>
</table>
INT 0139 Exploratory Survival Analysis

- All but 1 postoperative death followed a pneumonectomy

- Hypothesized survival advantage for CT/RT/S if lobectomy performed and for CT/RT if pneumonectomy

- Patients on CT/RT/S were matched with those on CT/RT arm on 4 presstuday factors (KPS, age, sex, T stage); match feasible for 90/98 lobectomies and 51/54 pneumonectomies
INT 0139 Overall Survival of Pneumonectomy Subset versus Matched CT/RT Subset


### Months from Randomization

<table>
<thead>
<tr>
<th></th>
<th>CT/RT/S</th>
<th>CT/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>19 mos.</td>
<td>29 mos.</td>
</tr>
</tbody>
</table>
INT0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset

% Alive

Months from Randomization

Dead/Total

CT/RT/S 57/90
CT/RT 74/90

Logrank p = 0.002

CT/RT/S
CT/RT

MS 34 mos. 22 mos.
5 yr OS 36% 18%
INT0139 Overall Survival Matched CT/RT Subset

- **CT/RT (Pneumonectomy)**
  - Median Survival (MS): 29 months
  - 5-year OS: 24%

- **CT/RT (Lobectomy)**
  - MS: 22 months
  - 5-year OS: 18%
Issues with this exploratory analysis

- Unplanned and retrospective
- Matching criteria are not necessarily valid
- Cannot reliably predict *a priori* who will require lobectomy vs pneumonectomy
  - 45% of pT0N0 patients in trimodality arm underwent a pneumonectomy
ChemoXRT ➔ Surgery Summary

– Trimodality therapy is stressful!
  • Coordination with surgeon and medonc from day 1

– Trimodality therapy should not be used to “convert” a marginally resectable patient to resectable
  • This approach only applies to resectable patients
  • Surgery has to be planned from the start

– Absolute contraindication if patient requires a right pneumonectomy

– Lobectomy candidates may benefit from this approach
  • Needs to be confirmed in a prospective trial
ChemoXRT → Surgery (Superior Sulcus)

SWOG 9416/Intergroup 0160 (Rusch)

- 111 pts superior sulcus T3-4N0-1, (-) MEAD
- 2 cycles of Cis/etop + 45 Gy concurrent RT
- Responder underwent resection 3-5 weeks later followed by 2 additional cycles of adjuvant chemotherapy
- 95/83 had a thoracotomy and 76 (92%) had a complete resection
- 54 (65%) showed pCR or microscopic residual disease
- 2 yr OS 55% for all patients and 70% for those with complete resection

Operable Stage IIIA Disease

Chemotherapy/Surgery vs Chemoradiotherapy?
Operable Stage IIIA Disease

EORTC 08941: STUDY DESIGN

III A NSCLC
579 pts
“unresectable”
N2 disease

CDDP chemo
3 cycles

Response assessment
332 responders

SURGERY

RADIATION
60 Gy
6 weeks

JNCI 2007
Operable Stage IIIA Disease

SURGERY 16.4 MONTHS
RADIATION 17.5 MONTHS
NO DIFFERENCE
Definitive Chemoradiotherapy for Stage III
Treatment of IIIA/B: ChemoXRT

• Sequential Chemoradiotherapy
  – Chemotherapy → Radiotherapy vs RT alone
  – Dillman, Sause

• Concurrent Chemoradiotherapy
  – Concurrent chemoradiotherapy vs RT alone
  – Schaake-Koning, Jeremic

• Sequential vs Concurrent Chemoradiotherapy
  – Sequential vs Concurrent chemoradiotherapy
  – RTOG 9410, Furuse, Fournel, Auperin meta-analysis

• Augmentation Strategies
  – Chemotherapy → Concurrent Chemoradiotherapy vs Concurrent Chemoradiotherapy
    • CALGB 39807 Vokes
  – Concurrent Chemoradiotherapy → Chemotherapy vs Concurrent Chemoradiotherapy
    • HOG/LUN Hanna
  – Targeted Agent addition
    • SWOG 0023
  – Local Augmentation
    • RTOG 0617
# Chemotherapy → XRT

<table>
<thead>
<tr>
<th></th>
<th>CALGB 8433 Dillman</th>
<th>RTOG 88-08 Sause</th>
<th>CEBI 138 LeChevalier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>77/ 78</td>
<td>149/ 151/ 152</td>
<td>177/ 176</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>I XRT alone II Cis/VBL → XRT</td>
<td>I QD XRT II BID XRT III Cis/ VBL → XRT</td>
<td>I XRT alone II Chemo → XRT → Chemo*</td>
</tr>
<tr>
<td><strong>XRT</strong></td>
<td>60 Gy</td>
<td>60 Gy (69.6 in BID)</td>
<td>65 Gy (2.5 Gy fx)</td>
</tr>
<tr>
<td><strong>MST (mo)</strong></td>
<td>9.7/ 13.8 (SS)</td>
<td>11.4/ 12.0/ 13.2 (SS)</td>
<td>9/ 12</td>
</tr>
<tr>
<td><strong>OS (% 2 yr)</strong></td>
<td>13 / 26 (SS)</td>
<td>19/ 24/ 32 (SS)</td>
<td>14/ 21 (SS)</td>
</tr>
<tr>
<td><strong>OS (% 5 yr)</strong></td>
<td>6/ 17 (SS)</td>
<td>5/ 6/ 8 (NS)</td>
<td>3/ 5 (NS)</td>
</tr>
<tr>
<td><strong>% LF</strong></td>
<td>Not analyzed</td>
<td>41/ 45/ 41 (NS)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td><strong>% DM</strong></td>
<td>Not analyzed</td>
<td>35/ 37/ 24 (p=0.045,FF)</td>
<td>40/ 27 (3yr) p&lt;0.001</td>
</tr>
</tbody>
</table>

* “sandwich” regimen of induction chemotherapy with videstine/ lomustine/ cisplatin/ cyclophosphamide
Chemo → XRT

- Relative to XRT alone:
  - Significantly fewer distant mets demonstrated in RTOG 88-08 and CEBI 138
  - No local control improvement with chemo
  - Survival advantage likely due to delayed distant metastases
  - 5 year OS still disappointing
## Concurrent ChemoRT

<table>
<thead>
<tr>
<th>EORTC 8844 Shaake-Koning</th>
<th>Jeremic, 1995</th>
<th>Jeremic, 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>108/ 102/ 96</td>
<td>61/ 52/ 56</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>I XRT alone</td>
<td>I XRT alone</td>
</tr>
<tr>
<td></td>
<td>II Cis qwk + XRT</td>
<td>II Carbo/ VP16 q3wk + XRT</td>
</tr>
<tr>
<td></td>
<td>III Cis qday + XRT</td>
<td>III Carbo/ VP16 qwk + XRT</td>
</tr>
<tr>
<td><strong>XRT</strong></td>
<td>55 Gy split</td>
<td>BID to 64.8 Gy</td>
</tr>
<tr>
<td><strong>MST (mo)</strong></td>
<td>10.5/ 11/ 12.5 (p=0.009)</td>
<td>8/ 13/ 18 (p&lt;0.05)</td>
</tr>
<tr>
<td><strong>OS (% 2yr)</strong></td>
<td>13/ 19/ 26 (p=0.009)</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>OS (% 3yr)</strong></td>
<td>2/ 13/ 16 (p=0.009)</td>
<td>6.6/ 16/ 23 (p&lt;0.05)</td>
</tr>
<tr>
<td><strong>LRFS (%2y)</strong></td>
<td>19/ 30/ 31 (p=0.003)</td>
<td>35/ 30/ 42 (p=0.76)</td>
</tr>
<tr>
<td><strong>DMFS(%2y)</strong></td>
<td>8/ 9/ 13 (p=0.16)</td>
<td>42/ 52/ 52 (p=0.54)</td>
</tr>
</tbody>
</table>
Concurrent chemoradiotherapy

• Relative to XRT alone:
  – Significantly improved LOCAL CONTROL demonstrated in EORTC and Jeremic
  – No reduction in distant mets with chemo
  – Survival advantage likely due to improved local control
  – 5 year OS still disappointing
Sequential vs Concurrent

• Speaks directly to the question of the value of local control in locally advanced disease

• Concerns about increased toxicity with concurrent regimens
Sequential vs Concurrent

– RTOG 94-10: Curran et al – 2011

  • 597 pts, Stage II-III
  • Cisplatin/vinblastine → 60Gy vs cisplatin/vinblastine and concurrent 60Gy vs cisplatin/oral VP-16 with concurrent BID 69.6Gy

– Furuse et al -1999

– NPC 95-01: Fournel et al – 2005

– Auperin meta-analysis

Curran WJ et al. JNCI 2011
Auperin A, J Clin Oncol 2010 May 1;28(13):2181-2190
## Sequential vs Concurrent

<table>
<thead>
<tr>
<th></th>
<th>Furuse et. al.</th>
<th>RTOG 9410 Curran</th>
<th>NPC 95-01 Fournel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>156/158</td>
<td>597 total</td>
<td>103/102</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>I cis/vind/MM → XRT</td>
<td>I cis/VBL → XRT</td>
<td>I cis/vinor → XRT</td>
</tr>
<tr>
<td></td>
<td>II cis/vind/MM + XRT</td>
<td>II cis/VBL + XRT</td>
<td>II cis/VP16 + XRT → cis/vinor X 2</td>
</tr>
<tr>
<td><strong>XRT</strong></td>
<td>56 Gy (split in arm II)</td>
<td>60 Gy (BID to 69.6)</td>
<td>66 Gy</td>
</tr>
<tr>
<td><strong>MST (mo)</strong></td>
<td>13.3/16.5 (p&lt;0.05)</td>
<td>14.6/17.0 (SS)/15.2</td>
<td>14.5/16.3 (NS)</td>
</tr>
<tr>
<td><strong>OS (% 3yr)</strong></td>
<td>14.7/22.3 (p&lt;0.05)</td>
<td>17/26/23</td>
<td>18.6/24.8 (p=0.24)</td>
</tr>
<tr>
<td><strong>OS (% 5yr)</strong></td>
<td>8.8/15.8 (p&lt;0.05)</td>
<td>12/21 (SS)/17 (4 yr)</td>
<td>14/20.7 (4 yr) (NS)</td>
</tr>
<tr>
<td><strong>% LF</strong></td>
<td>39/33 (p = 0.27)</td>
<td>65/56/47</td>
<td>70/53 (p = 0.17)</td>
</tr>
<tr>
<td><strong>% DM</strong></td>
<td>No significant diff</td>
<td>Not available</td>
<td>47/58 (p = 0.17)</td>
</tr>
</tbody>
</table>
Sequential vs Concurrent: Meta-analysis

- 1205 patients pooled
- Median f/u 6 years
- OS benefit with concurrent chemo RT (HR 0.84, SS); 3-years absolute benefit 5.7% (18% to 24%), 5-years 4.5% (11% to 15%)

Auperin A, J Clin Oncol 2010 May 1;28(13):2181-2190
Decrease in locoregional progression (HR 0.777, SS); absolute decrease of 6% at 5 years (35% to 29%)

No difference in PFS (HR 0.9, p=0.07). No difference on distant progression (HR 1.04, NS), with 5-year rate of ~40%

Toxicity: Acute Grade 3-4 esophageal toxicity worse (RR 4.9, SS), increase from 4% to 18%; no significant difference in acute pulmonary toxicity
Concurrent ChemoXRT Summary

• OS improved with concurrent chemoXRT (with platinum based chemo)
• Improvement in local control demonstrated in EORTC and by Jeremic (1996)
• Toxicity tolerable for selected patients
Concurrent Chemoradiotherapy: Augmentation Strategies

• Systemic Augmentation
  – Cytotoxic chemotherapy
    • Induction chemotherapy → Chemoradiotherapy
      – CALGB 39801
    • Concurrent chemoradiotherapy → Consolidative chemotherapy
      – HOG/LUN trial
  – Targeted agents
    • Concurrent chemoradiotherapy → Gefitinib
      – SWOG 0023

• Local Augmentation
  – Surgery
    • Concurrent chemoradiotherapy → Surgery
      – INT 0139 (Albain)
  – RT Dose
    • Concurrent chemoradiotherapy 60Gy vs 74Gy
      – RTOG 0617
Systemic Augmentation: Induction chemotherapy

- Inoperable Stage IIIA/IIIB patients
- CALGB PS 0 or 1
- No weight loss exclusion

JCO 2007
No significant differences in survival

- ITT MS 12 vs 14 months (p=NS)
- Good PS <5% weight loss MS 16 vs 14 months (p=NS)

Toxicity

- Maximum toxicity reported were higher with induction (40% vs 26% G4) p=0.004
### Systemic Augmentation: Consolidation chemotherapy

#### HOG LUN 01-24/USO 02-033

**ChemoRT**

- Cisplatin 50 mg/m² IV d 1, 8, 29, 36
- Etoposide 50 mg/m² IV d 1-5 and 29-33
- Concurrent RT 59.4 Gy (1.8 Gy/fr)

**Randomize**

Stratification variables:
- PS 0-1 vs 2
- IIIA vs IIIB
- CR vs non-CR

- **Docetaxel 75 mg/m² q3 wk x 3**
- **Observation**

**Study end points**

- **Primary:** Overall survival – accrue 210 to demonstrate an increase in MST from 15 mo → 24 mo with > 80% power
- **Secondary:** Progression-free survival and toxicity

Hanna N, et al. JCO
Systemic Augmentation: Consolidation chemotherapy

- **Observation**: Median: 24.1 ms (18.0-34.2)  
  3 year survival rate: 27.6%
- **Docetaxel**: Median: 21.5 ms (17.0-34.8)  
  3 year survival rate: 27.2%

P-value: 0.940
Systemic Augmentation: Targeted Agents

**Fig 2.** Overall survival for patients receiving gefitinib or placebo.

- **PLACEBO**
- **GEFITINIB**

*Median In Months*
- 23 (17, 29)
- 35 (25, 40)
Local Augmentation: More RT Dose

<table>
<thead>
<tr>
<th>INST.</th>
<th>No. of Patients</th>
<th>Stage III (%)</th>
<th>Dose (Gy)</th>
<th>ENI</th>
<th>Induction (%)</th>
<th>Esophagitis ≥ Grade 3 (%)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke</td>
<td>94</td>
<td>74</td>
<td>73.6-80</td>
<td>Yes</td>
<td>27</td>
<td>3</td>
<td>IIIA 13.0 IIIB 10.0</td>
</tr>
<tr>
<td>UM</td>
<td>104</td>
<td>66</td>
<td>63-102.9</td>
<td>No</td>
<td>24</td>
<td>7</td>
<td>III 16.0</td>
</tr>
<tr>
<td>RTOG 9311</td>
<td>179</td>
<td>47</td>
<td>70.9-90.3</td>
<td>No</td>
<td>14</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Shanghai</td>
<td>50</td>
<td>92</td>
<td>69-78</td>
<td>Yes</td>
<td>100</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Carolina</td>
<td>44</td>
<td>98</td>
<td>73.6-86.4</td>
<td>Yes</td>
<td>100</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>CALGB 30105</td>
<td>43</td>
<td>100</td>
<td>74</td>
<td>Yes</td>
<td>Concurrent</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>MSKCC</td>
<td>35</td>
<td>100</td>
<td>64-84</td>
<td>No</td>
<td>89</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>
RTOG 0617

A Randomized Phase III Comparison of Standard Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab In Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer

Intergroup Participation:
RTOG, NCCTG, CALGB
### Schema

<table>
<thead>
<tr>
<th>Stratify</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT Technique</strong></td>
<td><strong>Zubrod</strong></td>
<td><strong>PET Staging</strong></td>
</tr>
<tr>
<td>1. 3D-CRT</td>
<td>1. 0</td>
<td>1. No</td>
</tr>
<tr>
<td>2. IMRT</td>
<td>2. 1</td>
<td>2. Yes</td>
</tr>
</tbody>
</table>

*Carboplatin and paclitaxel
Primary Objective

• To compare the overall survival of patients treated with high-dose versus standard-dose conformal radiation therapy with concurrent chemotherapy.

• To compare the overall survival of patients treated with cetuximab versus without cetuximab with concurrent chemoradiotherapy.
<table>
<thead>
<tr>
<th>Pretreatment Characteristics</th>
<th>60 Gy (n=213)</th>
<th>74 Gy (n=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>125 (58.7%)</td>
<td>120 (58.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>88 (41.3%)</td>
<td>86 (41.7%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26 (12.2%)</td>
<td>29 (14.1%)</td>
</tr>
<tr>
<td>White</td>
<td>187 (87.8%)</td>
<td>177 (85.9%)</td>
</tr>
<tr>
<td>RT Technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3DCRT</td>
<td>115 (53.9%)</td>
<td>109 (52.9%)</td>
</tr>
<tr>
<td>IMRT</td>
<td>98 (46.1%)</td>
<td>97 (47.1%)</td>
</tr>
<tr>
<td>PET Staging</td>
<td>91.1%</td>
<td>88.8%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>84 (39.4%)</td>
<td>71 (34.5%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>89 (41.8%)</td>
<td>97 (47.1%)</td>
</tr>
<tr>
<td>NSCLC NOS</td>
<td>40 (18.7%)</td>
<td>38 (18.4%)</td>
</tr>
<tr>
<td>AJCC Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>143 (67.1%)</td>
<td>131 (63.6%)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>70 (32.9%)</td>
<td>75 (36.4%)</td>
</tr>
</tbody>
</table>
Overall Survival

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Standard (60 Gy)</th>
<th>High dose (74 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>213</td>
<td>206</td>
</tr>
<tr>
<td>Dead</td>
<td>90</td>
<td>117</td>
</tr>
<tr>
<td>Median Survival Time</td>
<td>28.7 months</td>
<td>19.5 months</td>
</tr>
<tr>
<td>HR</td>
<td>1.56 (1.19, 2.06)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0007</td>
<td></td>
</tr>
</tbody>
</table>

18-Month Survival Rate

- Standard: 66.9%
- High dose: 53.9%
## RTOG 0617: Dosimetric Data Distribution

<table>
<thead>
<tr>
<th>Metric</th>
<th>60 Gy (n=203) Mean (Median)</th>
<th>74 Gy (n=197) Mean (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV Volume (cc)</td>
<td>124.7 (92.2)</td>
<td>128.5 (96.4)</td>
</tr>
<tr>
<td>Heart V5 (%)</td>
<td>47.4 (45.7)</td>
<td>45.6 (46.1)</td>
</tr>
<tr>
<td>Heart V50 (%)</td>
<td>7(4.2)</td>
<td>11(5.6)</td>
</tr>
<tr>
<td>Lung V20 (%)</td>
<td>28.7 (28.8)</td>
<td>30.9 (31.9)</td>
</tr>
<tr>
<td>Esophagus Dose (Gy)</td>
<td>24.7 (25.1)</td>
<td>29.8 (28.9)</td>
</tr>
<tr>
<td>Esophagus V60 (%)</td>
<td>15 (13)</td>
<td>25.6 (25.7)</td>
</tr>
<tr>
<td>Mean Margin CTV to PTV (mm)</td>
<td>7.9 (6.6)</td>
<td>7.7 (6.6)</td>
</tr>
</tbody>
</table>
Local Progression Rate (%)

- Months since Randomization: 0, 3, 6, 9, 12, 15, 18
- Patients at Risk:
  - Standard (60 Gy): 213, 205, 187, 165, 137, 113, 85
  - High dose (74 Gy): 206, 197, 170, 134, 105, 80, 62

Local Progression Rate:
- Fail: 65, 81
- Total: 213, 206

HR = 1.37 (0.99, 1.89)  p = 0.0319

18-Month Local Progression Rate
- Standard (60 Gy): 25.1%
- High dose (74 Gy): 34.3%
## Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison (RL)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation dose</td>
<td>60 Gy v 74 Gy</td>
<td>1.51 (1.12, 2.04)</td>
<td>0.007</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam v Squam</td>
<td>1.31 (0.99, 1.75)</td>
<td>0.061</td>
</tr>
<tr>
<td>Max esophagitis grade</td>
<td>&lt;3 vs ≥3</td>
<td>1.52 (1.06, 2.20)</td>
<td>0.024</td>
</tr>
<tr>
<td>Heart Contour</td>
<td>Per Protocol vs. Not per protocol</td>
<td>0.67 (0.47, 0.96)</td>
<td>0.029</td>
</tr>
<tr>
<td>GTV</td>
<td>Continuous</td>
<td>1.001 (1.000, 1.002)</td>
<td>0.038</td>
</tr>
<tr>
<td>Heart V50(%)</td>
<td>Continuous</td>
<td>1.017 (1.004, 1.030)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Backwards Selection: Exit criteria p>0.10
Two-sided p-values
Removed from model: Age (continuous), overall RT review (per protocol vs. not per protocol), and lung V5 (continuous)
My interpretation

• Level 1 evidence against high dose is compelling in unselected stage III NSCLC
  – Prospective trials aimed at ‘adaptive’ dose escalation are underway

• Difficult to justify doses of 70Gy and beyond
  – Although improving local control is still important

• My standard is 6660cGy/180cGy fraction for locally advanced NSCLC
HYPOFRACTIONATION
HYPOFRACTIONATION

• 79 patients enrolled all treated with IFRT
• 57 to 85.5Gy in 25 fractions
• Involved field only
• Median f/u 17 months
• MTD is maximum dose that yielded <20% risk of severe toxicity
• MTD was 63.25 (second dose level)
• MS was 16 months, 3-year survival 29%

Cannon et al JCO 2013
Locally Advanced NSCLC: What is the right dose?

- 4/8/07: New diagnosis of NSCLC. Undergoes bronchoscopy with biopsy and debulking and diagnostic thoracentesis
- 4/18/07: Seen in RadOnc by me. Undergoes PET/CT
  - 4.5 x 3.8 intensely FDG-avid mediastinal nodal conglomerate
  - RLL primary tumor; small non-FDG avid nodules in RML
  - Malignant PE confirmed (small volume)
  - Simulated for RT to encompass mediastinal nodes and RLL tumor
- 4/22/07: Presents to ED with hemoptysis. Repeat bronch shows complete recurrence of right BI tumor
- **Date of Scan: 2/26/13**
- **Dose received: 250 x 14 (3500cGy) from 4/23-5/11 2007**
Target Delineation and IGRT
Locally Advanced NSCLC: Treatment Volume

- What is the right volume? IFRT vs ENI
  - Most studies show EN failure rate to be 4-8%
- IFRT reduces toxicity

Rosenzweig et al JCO 2007
Fernandes et al R&O 2010
Target Delineation

Identification of Occult Tumor

CT simulation

FDG-PET scan

Register

Derive GTV - PTV

Treatment planning

Paraesophageal node seen on PET, but not CT

CT - defined PTV
Target Delineation

The importance of image registration
Target Delineation

Concordance Rate Non-registered: 61%
Concordance Rate Registered: 70%
p<0.05

Fox et al IJROBP 2005
CBCT with carina match was superior to both CBCT spine and tattoos
Locally Advanced NSCLC: Practical Considerations

- **RT Dose**
  - 60-66.6Gy in 1.8Gy/fraction (RTOG 0617)

- **Simulation**
  - 4D PET/CT simulation

- **Target Delineation**
  - IFRT as defined on PET/CT (Fox et al IJROBP)

- **IGRT**
  - Daily CBCT with match to carina (PMH IJROBP)

- **Chemotherapy**
  - Platin doublet, given concurrently. No clear role for induction or consolidation
Locally advanced NSCLC: Summary

- Local control
- Toxicity

Probability vs. Dose of Radiation

Treatment Intensification

- Black line: Standard treatment
- Red line: Intensified treatment
We may have reached a therapeutic plateau for treatment intensification in locally advanced disease (More RT-0617; Induction chemo-CALGB 39801; Consolidation chemo-HOG Surgery-0139).
Locally advanced NSCLC: Summary

- All treatments are equally good/bad
  - Patient KPS, tumor burden, institutional preference all play a role

  - UW approach:
    - Concurrent chemoradiotherapy with cisplatin/etoposide for excellent PS patients
    - Concurrent chemoradiotherapy with carbo/taxol for intermediate PS patients
    - Poor PS patients sequential chemoradiotherapy

- Until systemic therapy improves local treatments will have diminished importance
Small Cell Lung Cancer
~15% lung cancers are small cell
Declining in incidence
SEER database reports SCLC cases declined from 17% to 13% in the past 30 years
Female incidence is increasing
Risk factors: SMOKING, uranium exposure, radon exposure
Clinical Presentation

• Symptoms related to central location:
  – SOB, cough, dyspnea, chest pain, PNA, hoarseness, dysphagia, **SVC syndrome**
  – Hemoptysis less common because of submucosal location

• Radiographs
  – Usually is a large central lesion
  – Usually with extensive lymphadenopathy

• 2/3 present with mets at diagnosis: Bone, liver, adrenals, bone marrow, brain
LS-SCLC: Malignant Pleural Effusion

- Veteran’s Affairs Lung Study Group
  - **Limited SCLC (L-SCLC) – 1/3**
    - Confined to one hemithorax
    - Regional nodes that can be encompassed in a reasonable radiation port
    - May include ipsilateral SCV Nodes
  
  - **Extensive SCLC (E-SCLC) – 2/3**
    - Including Malignant Pleural Effusion

- Marburg Definition
  - Included patients with small pleural effusion
  - Defined a separate cohort ED I (Large volume disease, malignant PE); ED2 had distant mets
    - LS and EDI had similar median survival ~12 vs ~11 months
    - ED2 had poorer survival ~6 months
Initial Workup

- CT: Chest, including adrenals
- MRI Brain (including asymptomatic pts)
  - Positive in ~8% of asymptomatic patients
- PET/CT (~10% of patients are upstaged from LS to ES and 25% reveal unsuspected nodal mets that could alter RT plan)
  - Survival advantage to PET stage LS-SCLC (Xanthopoulos et al in press)
- CBC, CMP, LDH
- Consider bone marrow biopsy if counts are low
- PFT’s
Outcomes

- Untreated: Median survival time of patients with unresectable disease randomized to receive supportive care only
  - **L-SCLC**: 12 weeks
  - **E-SCLC**: 5 weeks

<table>
<thead>
<tr>
<th>Stage</th>
<th>Complete Response</th>
<th>Median Survival</th>
<th>2 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L-SCLC</strong></td>
<td>60-75%</td>
<td>18-24 months</td>
<td>25-50%</td>
</tr>
<tr>
<td><strong>E-SCLC</strong></td>
<td>20-35%</td>
<td>6-12 months</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
LIMITED STAGE
Etoposide + cisplatin or carboplatin (4-6 cycles)
Concomitant RT (twice-daily if feasible)

EXTENSIVE STAGE
Etoposide + cisplatin or carboplatin (4-6 cycles)

COMPLETE RESPONSE
PCI
Observe for progression
Smoking cessation
If long term remission, surveillance for 2nd primary

PARTIAL RESPONSE
Observe for progression
Smoking cessation

PROGRESSION (Performance status 0-2)
Topotecan or CAV
What about the role of surgery?

- Historically, surgery had little to no role
- Recent data suggests good survival in stage I patients
- Penn approach- surgery not used except if incidental at thoracotomy

Chemotherapy is still given postoperatively, followed by PCI
Radiotherapy in LS-SCLC
Role of Radiation

- 13 randomized trials, 2140 patients
- Limited disease only
- 5% improvement in overall survival at 3 yrs
- Trend favored benefit for younger patients
Timing: Early vs. Late

Early thoracic radiotherapy is superior

- Early defined as starting Cycle 1 or Cycle 2; less than 9 weeks after start of chemo

Significance diminishes with longer timepoints
Treatment Volume: Pre-chemo vs. Post-chemo

• NCCTG/Mayo retrospective study
  – Most failures in the treatment field, so supported post-chemo volumes

• SWOG randomized trial
  – No change in recurrence rate

• Not relevant if giving early RT!
Treatment Volume: ENI vs. IFRT

• IFRT appears ok in PET-staged patients
• ENI was utilized in Turrisi trial
• IFRT being investigated prospectively in Europe and RTOG
• Penn approach
  – Use ENI when feasible
Fractionation

Turrisi et al. NEJM 1999 (Intergroup 0096):

- Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide.
  - Randomly assigned 417 patients with L-SCLC
    - 45 Gy TRT QD/5 weeks
    - 45 Gy BID/3 weeks
  - Concurrent chemo: cisplatin + etoposide (4 cycles of cisplatin 60 mg/m2 and etoposide 120 mg/m2 (EP) Q3W)
  - TRT begun at cycle 1 of 4 planned
  - TRT:
    - Target volume was gross tumor and bilateral mediastinal and ipsilateral hilar nodes
    - Margin 1-1.5cm
    - Supraclavicular fossa not treated if not involved
  - PCI offered at 12 weeks for CR

Turrisi Trial: Results

BID TRT benefit:
- median survival significantly longer:
  - 23 vs. 19 months
- 2yr survival:
  - 47% vs. 41%
- 5yr survival:
  - 26% vs. 16%
- Local failure
  - QD 52% vs BID 36% (p=0.06)

- Toxicity: Grade 3 esophagitis QD 11% vs. 27%, no difference in Grade 4 esophagitis
- Summary: established 45 Gy given twice daily over 3 weeks as standard regimen
Dose Escalation

• Phase II Study
  • CALGB 39808
    – Demonstrated safety of 70 Gy in 2 Gy fractions with concurrent chemotherapy

<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 twice daily</td>
<td>70 Gy 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>

Bogart et al. IJROBP 2004
### CALGB 30610 Phase III

<table>
<thead>
<tr>
<th>ARM</th>
<th>Regimen</th>
<th>Study</th>
<th>BED</th>
<th>2-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>45 Gy (1.5Gy BID/3 weeks)</td>
<td>INT 0096</td>
<td>52</td>
<td>47%</td>
</tr>
<tr>
<td>B</td>
<td>70 Gy (2Gy QD/7 weeks)</td>
<td>CALGB 39808</td>
<td>84</td>
<td>48%</td>
</tr>
<tr>
<td>C</td>
<td>61.2 (1.8 Gy Concomitant Boost for final 9 days/5 weeks)</td>
<td>RTOG 0239</td>
<td>72</td>
<td>37%</td>
</tr>
</tbody>
</table>

Concurrent Chemotherapy: Cisplatin/Etoposide

Currently Accruing
Prophylactic Cranial Irradiation

- 987 patients in CR from 7 randomized trials between 1977-1995
- RR of death 0.84 in PCI group compared to control (observation only)
- 5.4% increase in 3 year survival: 15.3 vs. 20%
- 25.3% decrease in 3 yr incidence of brain metastases with PCI
- Unable to assess impact of PCI on cognitive function
Dose for PCI

- PCI 99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01 randomized trial
  - Eligible patients:
    - LS-SCLC
    - CR after thoracic RT and chemotherapy
  - Low Dose (25 Gy/10fxn (std)) vs High Dose (36 Gy/18 fxn or 36 Gy/24 fxn (1.5 Gy bid))
  - With Median FU=39 mo, no difference in
    - 2 year incidence of brain mets (29%LD vs 23%HD, p=0.18)
    - 2 year OS (42%LD vs 37%HD, p=0.05)
- Conclusion: PCI at 25 Gy remain the standard of care

Péchoux CL et al Lancet Oncology 2009
Consequence of higher PCI dose

• Combined analysis was performed across all 4 trials
  – No significant difference across all QOL and Cognitive parameters over 3 years between LD and HD arm
  – Some critical individual domains (intellectual deficit, etc) were poorer in HD arm
• Secondary endpoint analysis of phase II randomized trial (RTOG 0212)
  – Neurophychologic tests and QOL assessments prior to PCI, then at 6 mo, 12 mo and annually for 3 years.
  – ND and CNT at 12 mo sig higher in high dose arms 2&3 (p=0.02)
• My approach: 25 Gy in 10 fractions
Extensive stage small cell lung cancer

- Role for thoracic radiotherapy in extensive stage
  - Primary site of failure is intrathoracic
  - Improved median survival: 17 vs. 11 months
  - 5 year OS 9.1 vs. 3.7%, P = 0.041

- **RTOG 0937**: Ongoing Randomized Phase II Trial Comparing PCI Alone to PCI + Consolidative Thoracic RT (QD IFRT: 300cGy x15) for E-SCLC

- My approach: Excellent PS patients with extrathoracic CR, will consider
Extensive stage small cell lung cancer: PCI

- Brain a significant site of failure in extensive stage disease
- EORTC randomized trial demonstrated a survival benefit to ES-responders
- Criticism- no brain imaging required. Patients screened clinically for brain mets (HA, N/V, Visual, Cognitive, Seizure, FNS)
- My approach: Use PCI in ES disease on case-by-case basis
Small Cell Lung Cancer: Practical Considerations

• Treatment approach for LS-SCLC
  – ENI to 45Gy in 1.5BID fractions
  – Alternate options
    • 1.8-2Gy QD to 70Gy (RTOG 9712)
    • IFRT if ENI is not feasible (JJCO 2012)

• Simulation
  – Use PET/CT for staging and to inform treatment planning if IFRT is used

• IGRT
  – No clear data, but given the rapid volume change- would use CBCT if available

• Treatment delivery technique
  – 3D-CRT, all-fields daily (Rengan in submission, presented Chicago lung)

• PCI
  – 2.5Gy x 10 to 25Gy is standard
Summary

- **L-SCLC:**
  - Chemo plus XRT (Turissi and Pignon meta-analysis)
  - Early XRT (Murray and Fried Meta-analysis)
  - Performance status should be always be considered
  - 45 Gy twice daily in 1.5 Gy fractions or ~70 Gy daily in 1.8 - 2Gy fractions (Turrisi or CALGB 39808)

- **Ongoing** **CALGB 30610**

- **E-SCLC**
  - Platin doublet
  - Thoracic radiotherapy in excellent PS with extrathoracic CR

- **PCI reasonable option in L-SCLC or E-SCLC**
  - Auperin Meta-analysis and Slotman Trial
THANK YOU!