The Management of Lung Cancer

ASTRO Spring Refresher Course
JW Marriott Hotel

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Department of Radiation Oncology

Friday March 22, 2013
Learning Objectives

At the conclusion of this activity, the learner will be able to do the following:

1. Discuss the standard of care for the radiotherapeutic management of non-small cell lung cancer.
2. Discuss the standard of care for the radiotherapeutic management of small cell lung cancer.
1. A 63-year old woman is incidentally found to have a 2 cm peripheral lung nodule in the right upper lobe. Fine needle aspiration reveals adenocarcinoma. PET CT scan reveals abnormal FDG avidity within the right upper lobe lesion only. The hilum and mediastinum are without adenopathy. She has a history of chronic emphysema with FEV1 32% predicted and DLCO 55% predicted. Her performance status is satisfactory but is limited by exertional dyspnea. Which of the following statements is true for this patient?

a) Even if she were an appropriate surgical candidate, definitive stereotactic body radiation therapy (SBRT) should be offered as an acceptable first-line treatment.

b) Conventional thoracic irradiation (66 Gy delivered in 2Gy fractions) would provide equivalent primary local tumor control and overall survival as SBRT (54 Gy delivered in 18Gy fractions).

c) Primary tumor control rates with SBRT are superior to those observed with lobectomy for similarly staged patients.

d) SBRT (54Gy delivered in 18Gy fractions) would be appropriate if this patient’s lesion was located 1.5 cm from the right hilum.

e) Image guidance to confirm position of target with each fraction is necessary for safe SBRT delivery.
TAKE SURVEY NOW!

Penn Radiation Oncology
Penn Medicine
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
Introduction: The Scope of the Problem

213,380 patients are diagnosed yearly with lung cancer in the US with approximately 160,390 deaths
Introduction: The Scope of the Problem

Lung cancer is aggressive

Normal lung is very radiosensitive

The lung is a vital organ

The uninvolved lung doesn’t work
Improving Clinical Outcome

PROBABILITY

local control

toxicity

DOSE OF RADIATION

Treatment Intensification
Improving Clinical Outcome

Disease Control

Treatment Intensification (more RT; more chemo; surgery)

Toxicity

PROBABILITY

Treatment Intensity
Screening and Diagnostic Workup
Early lung cancer detection \(\rightarrow\) 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

High Risk Subjects

Intervention
- Experimental Group
  CT
- Control Group
  CXR

Randomize

Follow-up

Time

0 1 2 3 4 5 6 7 8 9 10 11 years

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

Probability of survival: ALL participants

Years from randomization

CT arm

CXR arm
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**

<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>
</thead>
<tbody>
<tr>
<td>EBUS-FNA</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>EUS-FNA</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinoscopy: Cervical</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Mediastinoscopy: Chamberlain</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**ASTER Trial**

- 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>
</tr>
</tbody>
</table>

<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>

Gould et al AIM 139:879 2003  
Kim et al JTO S2:S59 2007  
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

- **Penn approach**
  - All patients undergo PET/CT
  - All patients undergo EBUS-TBNA
    - Operable patients undergo additional mediastinoscopy
    - 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**

![Graph 1](image1.png)

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

![Graph 2](image2.png)

*Fig 2. Time to recurrence (excluding second primaries) by treatment for 247 eligible patients.*
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?
# Studies of Brachytherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santos</td>
<td>102</td>
<td>2%</td>
</tr>
<tr>
<td>(Surg 2003;134:691-6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>33</td>
<td>6.1%</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
Surgery - Medically Inoperable

- Cor pulmonale
- Severe coronary artery disease
- Renal failure
- Poor pulmonary function
  - DLCO <50%
  - FEV1/FVC ratio < 50% 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>
Medically Inoperable Early Stage: Stereotactic Body Radiotherapy

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 cm³ 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
Indiana U., Phase II (Timmerman, et al.): efficacy

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

- **Overall Survival**
  - 55% at 2 yrs
  - 43% at 3 yrs
Medically Inoperable Early Stage: Hypofractionated Stereotactic Radiation

<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
- location outside

p = 0.003
SBRT: Central Lesion Toxicity

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

<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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<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.
Medically Inoperable Early Stage: Hypofractionated Stereotactic Radiation

Correspondence

Central-Airway Necrosis after Stereotactic Body-Radiation Therapy


Michael N. Corradetti, M.D., Ph.D.
Andrew R. Haas, M.D., Ph.D.
Ramesh Rengan, M.D., Ph.D.
Hospital of the University of Pennsylvania
Philadelphia, PA
renan@uphs.upenn.edu
Central lesion SBRT

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

FIGURE 1. Patient examples with early-stage non-small cell lung cancer (NSCLC) in central tumor locations: (A) tumor adjacent to the aortic arch, (B) tumor adjacent to the left ventricle, and (C) tumor in a hilar location, extending to the chest wall. The patient in panel (C) is the patient who developed a rib fracture after treatment.

FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

TABLE 3. Early and Late Toxicity After SABR in 63 Patients with Central Stage Early-Stage NSCLC (Absolute Patient Numbers)

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5</td>
<td>2</td>
<td></td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>1</td>
<td></td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rib fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (% of patients)</td>
<td>29 (62)</td>
<td>6 (10)</td>
<td>1 (2)</td>
<td>11 (17)</td>
<td>9 (14)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

SABR, stereotactic ablative radiotherapy; NSCLC, non-small cell lung cancer.

Median follow-up of 35 months
No grade IV/V toxicities

Cornelis J. A. Haasbeek, MD, PhD, Frank J. Lagerwaard, MD, PhD, Ben J. Slotman, MD, PhD, and Suresh Senan, MRCP, FRCR, PhD
SBRT Dose and IGRT
SBRT Dose and IGRT

505 patients receiving SBRT for early stage NSCLC

- 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)
  - BED_{10} = \text{nd}(1 + d/10) \alpha/\beta=10

- All patients underwent daily OBI with conebeam CT
SBRT and IGRT

- 24 patients treated with SBRT with CBCT
- Compared setup with tattoo alone vs CBCT
- CBCT reduced margin requirements from 9-13mm to 1-2mm

Grills et al IJROBP 2008
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
SBRT: Practical Considerations

- **Dose and fractionation**
  - Peripheral lesions 12Gy x 4 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 al (IJROBP); Corradetti et al (PRO 2012)
SBRT: Practical Considerations

♦ Penn 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
  • 0914 pending 12Gy x 4 vs 30Gy x 1
  • 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 +/- brachytherapy
  • 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 → Chemo +/- RT
  - Chemo (IALT/ANITA)
  - RT (PORT/ANITA)

- Chemo → Surgery
  - Roth, Rosell, Depierre

- Chemorads → surgery
  - Albain, Rusch
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(.36)-II(.25)-III(.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
## Adjuvant Chemotherapy IALT N=1867

<table>
<thead>
<tr>
<th></th>
<th>+ chemo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>50.5</td>
<td>44.4</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median DFS</td>
<td>40.2</td>
<td>30.5</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS 5 years</td>
<td>44.5</td>
<td>40.4</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></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
PORT Meta-Analysis: Impact

CASE CLOSED

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

PORT Meta-Analysis

3D-CRT
Is this result really at all RELEVANT?
PORT: Who can benefit?

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

Lally et al JCO 2006

1987 patients
1998-2002

p=0.0036

No. at risk:
Observation  521  298  177  101  65
PORT       944  590  420  321  239

Surviving (%)
0  1  2  3  4  5
Survival (years)
100  75  50  25
PORT in the era of chemotherapy: Is there a role? ANITA
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>
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<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

- Penn Approach
  - Deliver PORT after surgery if residual N2 disease is identified
  - If multiple nodes are identified, consider adjuvant chemotherapy
  - 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 S Alibain, RSuzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyan 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 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
38/202= 18% of patients
5-yr survival= 3% (point estimate)

Albain et al Lancet 2009
The Risks of Trimodality Therapy

Preoperative Chemoradiotherapy
45 to 50Gy

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>Pneumonectomy</td>
<td>54</td>
<td>14 (26%)</td>
<td>ARDS/respiratory 11; miscellaneous, 3</td>
</tr>
</tbody>
</table>

- **(R) simple**: 17, 5 (29%)
- **(R) complex**: 12, 6 (50%)
- **(L) simple**: 6, 0
- **(L) complex**: 19, 3 (16%)

45% (13/29) of T0N0 pts underwent pneumonectomy.
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 prestudy 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

<table>
<thead>
<tr>
<th>Months from Randomization</th>
<th>CT/RT/S</th>
<th>CT/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 mos.</td>
<td>36%</td>
<td>45%</td>
</tr>
<tr>
<td>22%</td>
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</table>

3 yr OS

<table>
<thead>
<tr>
<th>Months from Randomization</th>
<th>CT/RT/S</th>
<th>CT/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 mos.</td>
<td>22%</td>
<td>24%</td>
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</tbody>
</table>

5 yr OS

logrank p = NS

INT0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset

Logrank p = 0.002

% Alive

Dead/Total

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

CT/RT/S
34 mos.  36%
5 yr OS

CT/RT
22 mos.  18%

Months from Randomization

Penn Radiation Oncology
Penn Medicine
INT0139 Overall Survival Matched CT/RT Subset

**CT/RT (Pneumonectomy)**
- Months to Survival (MS): 29 mos.
- 5 yr OS: 24%

**CT/RT (Lobectomy)**
- Months to Survival (MS): 22 mos.
- 5 yr 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?
Locally Advanced NSCLC

EORTC 08941: STUDY DESIGN

IIIA NSCLC
579 pts
“unresectable”
N2 disease

CDDP chemo
3 cycles

Response assessment
332 responders

SURGERY

RADIATION
60 Gy
6 weeks

JNCI 2007
Locally Advanced NSCLC

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
## Chemotherapy → XRT

<table>
<thead>
<tr>
<th></th>
<th>CALGB 8433 Dillman</th>
<th>RTOG 88-08 Sause</th>
<th>CEBI 138 LeChevalier</th>
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</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</td>
<td>I QD XRT</td>
<td>I XRT alone</td>
</tr>
<tr>
<td></td>
<td>II Cis/VBL → XRT</td>
<td>II BID XRT</td>
<td>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 $\rightarrow$ 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></th>
<th>EORTC 8844 Shaake-Koning</th>
<th>Jeremic, 1995</th>
<th>Jeremic, 1996</th>
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</thead>
<tbody>
<tr>
<td><strong>Arms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>XRT alone</td>
<td>I XRT alone</td>
<td>I XRT alone</td>
</tr>
<tr>
<td>II</td>
<td>Cis qwk + XRT</td>
<td>II Carbo/ VP16 q3wk + XRT</td>
<td>II Carbo/VP16 qday + XRT</td>
</tr>
<tr>
<td>III</td>
<td>Cis qday + XRT</td>
<td>III Carbo/ VP16 qwk + XRT</td>
<td></td>
</tr>
<tr>
<td><strong>XRT</strong></td>
<td>55 Gy split</td>
<td>BID to 64.8 Gy</td>
<td>BID to 69.6 Gy</td>
</tr>
<tr>
<td>MST (mo)</td>
<td>10.5/ 11/ 12.5 (p=0.009)</td>
<td>8/ 13/ 18 (p&lt;0.05)</td>
<td>14/ 22 (p&lt;0.05)</td>
</tr>
<tr>
<td>OS (% 2yr)</td>
<td>13/ 19/ 26 (p=0.009)</td>
<td>Not reported</td>
<td>24/ 43 (p&lt;0.05)</td>
</tr>
<tr>
<td>OS (% 3yr)</td>
<td>2/ 13/ 16 (p=0.009)</td>
<td>6.6/ 16/ 23 (p&lt;0.05)</td>
<td>9/ 23 (4 year) (p&lt;0.05)</td>
</tr>
<tr>
<td>LRFS (%2y)</td>
<td>19/ 30/ 31 (p=0.003)</td>
<td>35/ 30/ 42 (p=0.76)</td>
<td>19/ 42 (4y,p=0.015)</td>
</tr>
<tr>
<td>DMFS(%2y)</td>
<td>8/ 9/ 13 (p=0.16)</td>
<td>42/ 52/ 52 (p=0.54)</td>
<td>33/ 39 (4y,p=0.33)</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>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>156/ 158</td>
<td>597 total</td>
<td>103/ 102</td>
</tr>
<tr>
<td>Arms</td>
<td>I cis/vind/MM → XRT II cis/vind/MM + XRT</td>
<td>I cis/VBL → XRT II cis/ VBL + XRT III cis/VP16 + BID XRT</td>
<td>I cis/vinor → XRT II cis/VP16 + XRT → cis/vinor X 2</td>
</tr>
<tr>
<td>XRT</td>
<td>56 Gy (split in arm II)</td>
<td>60 Gy (BID to 69.6)</td>
<td>66 Gy</td>
</tr>
<tr>
<td>MST (mo)</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>OS (% 3yr)</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>OS (% 5yr)</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>% LF</td>
<td>39/ 33 (p = 0.27)</td>
<td>65/56/47</td>
<td>70/ 53 (p = 0.17)</td>
</tr>
<tr>
<td>% DM</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
**Systemic Augmentation: Induction chemotherapy**

- **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)

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

**Randomize**

- **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.
Local Augmentation: More RT Dose

RTOG 7301 (Perez et al.)
- RCT of unresectable NSCLC
- T1-3 N0-2 tumors randomized to:
  - 4000 cGy split course
  - 4000 /5000 /6000 cGy continuous course
- Dose response for local control:
  - Local failure:
    - 51% 4000cGy; 42% 5000cGy; 35% 6000cGy (p = 0.006)
  - No survival differences
## 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>
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</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>
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<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>
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<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>
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<tr>
<td>Shanghai</td>
<td>50</td>
<td>92</td>
<td>69-78</td>
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<td>100</td>
<td>4</td>
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<td>Carolina</td>
<td>44</td>
<td>98</td>
<td>73.6-86.4</td>
<td>Yes</td>
<td>100</td>
<td>9</td>
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<tr>
<td>CALGB 30105</td>
<td>43</td>
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<td>74</td>
<td>Yes</td>
<td>Concurrent</td>
<td>16</td>
<td>24</td>
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<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>
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Local Augmentation: More RT Dose

**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>RT Technique</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
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<tbody>
<tr>
<td></td>
<td>1. 3D-CRT</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>2. IMRT</td>
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<tr>
<td>Zubrod</td>
<td>1. 0</td>
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<td></td>
<td>2. 1</td>
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<td></td>
<td>2. Yes</td>
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<td>1. Squamous</td>
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<td>2. Non-Squamous</td>
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<td></td>
<td><strong>Arm A</strong> Concurrent chemotherapy*</td>
<td>Arm A Consolidation chemotherapy*</td>
</tr>
<tr>
<td></td>
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<td>RT to <strong>60 Gy</strong>, 5 x per wk for 6 wks</td>
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<tr>
<td></td>
<td></td>
<td><strong>Arm B</strong> Concurrent chemotherapy*</td>
<td>Arm B Consolidation chemotherapy*</td>
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<tr>
<td></td>
<td></td>
<td>RT to <strong>74 Gy</strong>, 5 x per wk for 7.5 wks</td>
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<tr>
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<td></td>
<td><strong>Arm C</strong> Concurrent chemotherapy* and Cetuximab</td>
<td>Arm C Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT to <strong>60 Gy</strong>, 5 x per wk for 6 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Arm D</strong> Concurrent chemotherapy* and Cetuximab</td>
<td>Arm D Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT to <strong>74 Gy</strong>, 5 x per wk for 7.5 wks</td>
<td></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 chemotheraphy.

- To compare the overall survival of patients treated with cetuximab versus without cetuximab with concurrent chemoradiotherapy.
## Pretreatment Characteristics

<table>
<thead>
<tr>
<th>Pretreatment Characteristics</th>
<th>60 Gy (n=216)</th>
<th>74 Gy (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median)</strong></td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>127 (58.8%)</td>
<td>119 (57.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>89 (41.2%)</td>
<td>89 (42.8%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>27 (12.5%)</td>
<td>30 (14.4%)</td>
</tr>
<tr>
<td>White</td>
<td>189 (87.5%)</td>
<td>178 (85.6%)</td>
</tr>
<tr>
<td><strong>RT Technique</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3DCRT</td>
<td>116 (57.3%)</td>
<td>113 (54.3%)</td>
</tr>
<tr>
<td>IMRT</td>
<td>100 (46.3%)</td>
<td>95 (45.7%)</td>
</tr>
<tr>
<td><strong>PET Staging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91.2%</td>
<td></td>
<td>88.9%</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>86 (39.8%)</td>
<td>73 (35.1%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>86 (39.8%)</td>
<td>96 (46.2%)</td>
</tr>
<tr>
<td>NSCLC NOS</td>
<td>39 (18.1%)</td>
<td>33 (15.9%)</td>
</tr>
<tr>
<td><strong>AJCC Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>138 (65.7%)</td>
<td>131 (63.6%)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>72 (34.3%)</td>
<td>75 (36.4%)</td>
</tr>
</tbody>
</table>
Overall Survival

Patients at Risk

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Total</th>
<th>Dead</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy</td>
<td>213</td>
<td>58</td>
<td>213</td>
</tr>
<tr>
<td>74 Gy</td>
<td>204</td>
<td>70</td>
<td>204</td>
</tr>
</tbody>
</table>

**Overall Survival (%)**

- **0** months: 100%
- **3** months: 75%
- **6** months: 50%
- **9** months: 25%
- **12** months: 0%

**HR = 1.45 (1.02, 2.05)**

**p* = 0.02**

*One-sided p-value, left tail
# RTOG 0617: Dosimetric Data Distribution

<table>
<thead>
<tr>
<th></th>
<th>60 Gy (n=216) Mean (Median)</th>
<th>74 Gy (n=208) Mean (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV Volume (cc)</td>
<td>134.9 (106.1)</td>
<td>122.7 (85.6)</td>
</tr>
<tr>
<td>Lung Volume (cc)</td>
<td>512.5 (463.4)</td>
<td>514.3 (440.0)</td>
</tr>
<tr>
<td><strong>Lung V20 (%)</strong></td>
<td><strong>30.2 (30.3)</strong></td>
<td><strong>29.8 (31.5)</strong></td>
</tr>
<tr>
<td>Esophagus Dose (Gy)</td>
<td>28.1 (28.1)</td>
<td>27.5 (27.3)</td>
</tr>
<tr>
<td>Esophagus V60 (%)</td>
<td>22.1 (22.1)</td>
<td>20.4 (20.1)</td>
</tr>
<tr>
<td>Esophagus V20 (%)</td>
<td>48.4 (48.7)</td>
<td>47.6 (46.8)</td>
</tr>
<tr>
<td>Mean Margin CTV to PTV (mm)</td>
<td>8.0 (7.0)</td>
<td>7.9 (6.6)</td>
</tr>
</tbody>
</table>
### RTOG 0617

**Definitely, Probably, or Possibly Related to Treatment**

<table>
<thead>
<tr>
<th>September 2011</th>
<th>Arm A: 60 Gy +/- Cetuximab (n=192)</th>
<th>Arm B: 74 Gy +/- Cetuximab (n=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>79 (41.1%)</td>
<td>85 (46.4%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>14 (7.3%)</td>
<td>17 (9.3%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>4 (2.1%)</td>
<td>8 (4.4%)</td>
</tr>
</tbody>
</table>

- **Worst non-hematologic**
  - Arm A: 60 Gy +/- Cetuximab
    - Grade 3: 79 (41.1%)
    - Grade 4: 14 (7.3%)
    - Grade 5: 4 (2.1%)
  - Arm B: 74 Gy +/- Cetuximab
    - Grade 3: 85 (46.4%)
    - Grade 4: 17 (9.3%)
    - Grade 5: 8 (4.4%)

- **Worst overall**
  - Arm A: 60 Gy +/- Cetuximab
    - Grade 3: 84 (43.8%)
    - Grade 4: 45 (23.4%)
    - Grade 5: 4 (2.1%)
  - Arm B: 74 Gy +/- Cetuximab
    - Grade 3: 78 (42.6%)
    - Grade 4: 52 (28.4%)
    - Grade 5: 8 (4.4%)

- **Grade 5 Events**
  - Arm A: 60 Gy +/- Cetuximab (n=4)
    - 2 Pulmonary
    - 1 Thrombosis
    - 1 Death NOS
  - Arm B: 74 Gy +/- Cetuximab (n=8)
    - 2 Pulmonary
    - 1 Thrombosis
    - 1 Upper GI Hemorrhage
    - 1 Pulmonary Hemorrhage
    - 1 Pneumonia NOS
    - 1 Esophageal
    - 1 Death NOS

- As scored by institution
- No significant difference
### Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Dose</td>
<td>60 Gy v 74 Gy</td>
<td>0.038</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam v</td>
<td>0.025</td>
</tr>
<tr>
<td>GTV/ITV</td>
<td>Continuous</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Histology is important in stage III NSCLC with non-squamous “better” than squamous.... .......similar to stage IV disease)
My interpretation

- Level 1 evidence against high dose is compelling
- Difficult to justify doses of 70Gy and beyond
- No clear role for photon beam dose escalation with concurrent chemotherapy at present
- Penn standard is 6660cGy/180cGy fraction for locally advanced NSCLC
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 bronchoscopy shows complete recurrence of right BI tumor
- 4/23 started RT to mediastinal conglomerate and dominant RLL mass

Post-RT CT of Chest: rt change only - no residual disease

Date of Scan: 2/26/13

Dose received: 250 x 14 (3500 cGy) from 4/23 to 5/11 2007
Target Delineation and IGRT
What is the right volume? IFRT vs ENI

- Most studies show EN failure rate to be 4-8%

- IFRT reduces toxicity
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

**DOES REGISTRATION OF PET AND PLANNING CT IMAGES DECREASE INTEROBSERVER AND INTRAOBSERVER VARIATION IN DELINEATING TUMOR VOLUMES FOR NON–SMALL-CELL LUNG CANCER?**

Jana L. Fox, M.D.,* Ramesh Rengan, M.D., Ph.D.,* William O’Meara, M.D.,* Ellen Yorke, Ph.D.,† Yusuf Erdi, Ph.D.,† Sadek Nehme, Ph.D.,† Steven A. Leibel, M.D.,* and Kenneth E. Rosenzweig, M.D.,*

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

Volumetric Image Guidance Using Carina vs Spine as Registration Landmarks for Conventionally Fractionated Lung Radiotherapy
Caroline Lavioie, MD,* Jane Higgins, BSc,* Jean-Pierre Bissonnette, PhD,* Lisa W. Le, MSc,* Alexander Sun, MD,* Anthony Brade, MD, PhD,* Andrew Hope, MD, BC,* John Cho, MD, PhD,* and Andre Bejjak, MD*

Grade 3: Tumor outside PTV
Grade 2: Tumor inside PTV
Grade 1: Tumor inside IGTV
Grade 0: Tumor inside GTV

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

![Graph showing the relationship between local control, toxicity, and dose of radiation. The graph illustrates the concept of Treatment Intensification.](Image)
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**
Locally advanced NSCLC: Summary

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

  - **PENN 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
Background

Changing Epidemiology of Small-Cell Lung Cancer in the United States Over the Last 30 Years: Analysis of the Surveillance, Epidemiologic, and End Results Database

Ramanayam Govindan, Nathan Page, Daniel Morgensztern, William Read, Ryan Tierney, Anna Vlahiotis, Edward L. Spitznagel, and Jay Pecturilla

JCO 2006

- ~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

![Graph](image1.png)  
**Fig 1.** The diagnosis of small-cell lung cancer, as a percent of all lung cancers, over 30 years.

![Graph](image2.png)  
**Fig 3.** The diagnosis of small-cell lung cancer by sex.
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>L-SCLC</td>
<td>60-75%</td>
<td>18-24 months</td>
<td>25-50%</td>
</tr>
<tr>
<td>E-SCLC</td>
<td>20-35%</td>
<td>6-12 months</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

DeVita et al. Principles and Practice of Oncology, 2008
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

Smoking cessation
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

Meta-Analysis of Thoracic Radiotherapy
Pignon, NEJM, 1992
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

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 Petoa, Julian G. Rosenman, Jan S. Halle, Frank C. Derenneck, Thomas A. Hersting, and Mark A. Scocinski

JCO 2004
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

*Comparison of Treatment Outcomes Between Involved-field and Elective Nodal Irradiation in Limited-stage Small Cell Lung Cancer*

JJCO 2012
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

**Prophylactic Cranial Irradiation for Patients with Small-Cell Lung Cancer in Complete Remission**

Anne Auperin, M.D., Rodrigo Arruabarrena, M.D., Jean-Pierre Fignon, M.D., Ph.D., Cécile Le Pechoux, M.D., Anna Gregor, M.D., Richard J. Stephens, P.A.S., E.G. Kristjansdottir, M.D., Ph.D., Bruce E. Johnson, M.D., Hiroshi Uchida, M.D., Henry Wagner, M.D., and Joseph Asinari, M.D., for the Prophylactic Cranial Irradiation Overview Collaborative Group

- **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/10 fxn (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
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
1. A 63-year old woman is incidentally found to have a 2 cm peripheral lung nodule in the right upper lobe. Fine needle aspiration reveals adenocarcinoma. PET CT scan reveals abnormal FDG avidity within the right upper lobe lesion only. The hilum and mediastinum are without adenopathy. She has a history of chronic emphysema with FEV1 32% predicted and DLCO 55% predicted. Her performance status is satisfactory but is limited by exertional dyspnea. Which of the following statements is true for this patient?

a) Even if she were an appropriate surgical candidate, definitive stereotactic body radiation therapy (SBRT) should be offered as an acceptable first-line treatment.

b) Conventional thoracic irradiation (66 Gy delivered in 2Gy fractions) would provide equivalent primary local tumor control and overall survival as SBRT (54 Gy delivered in 18Gy fractions).

c) Primary tumor control rates with SBRT are superior to those observed with lobectomy for similarly staged patients.

d) SBRT (54Gy delivered in 18Gy fractions) would be appropriate if this patient’s lesion was located 1.5 cm from the right hilum.

e) Image guidance to confirm position of target with each fraction is necessary for safe SBRT delivery.
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