Non-small Cell Lung Cancer: SBRT, Protons & Improvements in Tumor Control and Normal Tissue Toxicities with Advanced Technologies

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Disclosures

• National Institutes of Health
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  – R01 5-R01-CA-154562

• Department of Defense
  – W81XWH-09-2-0174
Lung Cancer Background

• Second most common malignancy among men and women
  – ~221,000 cases annually in the US

• Most common cause of death from cancer
  – ~158,000 deaths annually in the US
  – As many deaths as colorectal, pancreas, breast, and prostate (#’s 2-5) combined
Histology

- Adenocarcinoma 44%
- Squamous 23%
- Small cell 15%
- Large cell 11%
- Other NSCLC 7%

- Adenocarcinoma vs. squamous cell carcinoma
  - Primary location
    - Adeno: typically peripheral
    - Squamous: typically central
  - Patterns of Failure
    - Brain Mets: adenoca (2x) > squamous
  - Association with smoking
    - Nearly all non-smoking related lung cancers are adenocarcinoma
Early Stage NSCLC and SBRT
Lung Cancer Stage and Survival

- Trend towards improved survival for stage I: SBRT for medically inoperable
- Trend towards improved survival for stage III and IV: palliative care, change in malignant effusions (IIIB), stage migration and targeted therapies (IV)
- AJCC 7th Ed median survival (mo): 115 (IA), 76 (IB), 47 (IIB), 24 (IIIB), 17 (IIIA), 10 (IIIB), 7 (IV)

Early Stage Operable NSCLC

- Lung Cancer Study Group: limited resection vs. lobectomy (T1N0)
  - 30% increase in overall death rate (p=0.08)
  - Tripling of local recurrence rate (p=0.008)

- Brachytherapy can decrease local recurrence rates with sublobar resection to <10% (similar to lobectomy)

Medically Inoperable

• PFTs
  – FEV1 <1.2 L, <0.8 L post-op predicted, ≤40-50% predicted
  – DLCO ≤40-50% predicted
  – FEV1/FVC <50%

• Oxygenation
  – PCO₂ >45-50 mm Hg
  – Resting or exercise Pa02 ≤55 mm Hg or peripheral O2 sat ≤88%

• Comorbidities
  – Cor pulmonale, severe pulmonary hypertension, poor left ventricular function, severe dyspnea, inability to walk 1 flight of stairs

• Age
  – Operative mortality by age: <60 yrs ~2%, >70 yrs ~8%
    • May be less relevant with increasing use of minimally invasive surgery
    • Age ≥75 years may be more predictive
  – 2013 ACCP Guidelines: age alone is not a reason to deny surgery
Radiotherapy Treatment Options for Medically Inoperable Stage I NSCLC

• Definitive Conventionally Fractionated External Beam Radiation Therapy
  – 6-8 weeks, 30-40 fractions

• Stereotactic Body Radiotherapy
  – 1-2 weeks, 1-10 fractions
# Definitive Conventionally Fractionated Radiotherapy for Early-stage NSCLC

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Stage</th>
<th># pts.</th>
<th>Dose (Gy)</th>
<th>5-yr. OS (%)</th>
<th>5-yr. CSS (%)</th>
<th>5-yr. LC (%)</th>
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</thead>
<tbody>
<tr>
<td>Dosoretz, 1996</td>
<td>I-II</td>
<td>152</td>
<td>60-69</td>
<td>10</td>
<td>-</td>
<td>68</td>
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<tr>
<td>Krol, 1996 (Leiden)</td>
<td>I</td>
<td>108</td>
<td>60-65</td>
<td>15</td>
<td>31</td>
<td>25</td>
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<td>Sibley, 1998 (Duke)</td>
<td>I</td>
<td>141</td>
<td>55-70</td>
<td>13</td>
<td>32</td>
<td>78</td>
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<tr>
<td>Bradley, 2003 (Wash U.)</td>
<td>I</td>
<td>56</td>
<td>60-83</td>
<td>34 (3 yr)</td>
<td>51 (3 yr)</td>
<td>63 (3 yr)</td>
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<tr>
<td>Rosenzweig, 2001 (MSKCC)</td>
<td>I-II</td>
<td>32</td>
<td>70.2</td>
<td>33</td>
<td>39</td>
<td>43</td>
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<tr>
<td>Jeremic, 1999 (Yugoslavia)</td>
<td>II</td>
<td>67</td>
<td>69.6 (BID)</td>
<td>25</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

*Compared w/ surgery: more comorbidities, clinical understaging

Principals of Stereotactic Body Radiotherapy (SBRT) for Stage I Non-small Cell Lung Cancer

• Also called stereotactic ablative radiotherapy (SABR)
• Stereotactic: implies targeting, planning, and directing therapy using beams of irradiation along any trajectory in 3-D space toward a target of known 3-D coordinates
• Imaging guided set-up verification and external or internal markers are used to increase treatment accuracy, decrease target margin
• Typically for medically inoperable pts with tumors <5-7 cm
• Large doses per fraction to a small conformal volume with the intention of increasing the delivered effective dose of therapy
• Use beam energies of 6-10 MV to improve target coverage and limit penumbra
Tumor Motion

- Can account for tumor motion during treatment from respiration using a 4D simulation

- Ways to mitigate tumor motion:
  - Abdominal compression
  - Accelerator beam gating with the respiratory cycle
  - Dynamic tumor tracking
  - Active breathing control
  - Coaching/biofeedback techniques

Max Inhale  Max Exhale

Csiki I and Simone CB 2\textsuperscript{nd}. *J Vis Exp.* 2015; in press.
Early Reports on SBRT for NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Overall Survival</th>
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<tbody>
<tr>
<td>Onishi</td>
<td>245</td>
<td>56% (3-yr)</td>
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<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>
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</table>

3-year primary tumor control rate - **97.6%**

## Modern Prospective SBRT Studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>Patients</th>
<th>Treatment</th>
<th>3 Yr Local Control</th>
<th>3 Yr Overall Survival</th>
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</thead>
<tbody>
<tr>
<td>Nagata</td>
<td>45</td>
<td>48 Gy, 4 fx</td>
<td>97.8%</td>
<td>83% stage IA, 72% stage IB</td>
</tr>
<tr>
<td>Koto</td>
<td>31</td>
<td>45 Gy, 3 fx (peripheral); 60 Gy, 8 fx (near organs at risk)</td>
<td>77.9% T1 40.0% T2</td>
<td>71.7%</td>
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<tr>
<td>Baumann</td>
<td>57</td>
<td>45 Gy, 3 fractions</td>
<td>92% overall 100% T1a 74.6% T1b 59.2% T2a</td>
<td>60% (not different by T stage)</td>
</tr>
<tr>
<td>Fakiris</td>
<td>70</td>
<td>60 Gy, 3 fx (T1); 66 Gy, 3 fx (T2)</td>
<td>88.1%</td>
<td>42.7% (MS 38.7 mo T1, 24.5 mo T2)</td>
</tr>
<tr>
<td>Ricardi</td>
<td>62</td>
<td>45 Gy, 3 fx</td>
<td>87.8%</td>
<td>57.1% (not different for stage IA vs. IB)</td>
</tr>
<tr>
<td>Timmerman</td>
<td>55</td>
<td>54 Gy, 3 fx</td>
<td>97.6%</td>
<td>55.8% (MS not reached for T1, 33.7 mo T2)</td>
</tr>
</tbody>
</table>

UPenn Stage I SBRT Experience

• 186 patients with 204 lesions treated from 6/2009-7/2013 for cT1-2aN0M0 stage I NSCLC
  – 85% inoperable after thoracic surgeon evaluation
  – 50 Gy in 4 (peripheral) or 5 (central) fractions

• 2-year local control 97%
  – Better for T1a-T1b than T2a (p=0.05)

• Operable patients refusing surgery
  – Similar local control (100% v 96%, p=0.28), nodal failure (7% v 14%, p=0.33), distant failure (7% v 4%, p=0.45), cause-specific survival (96% v 96%, p=0.86)
  – Trended to better 2-year (85% v 69%, p=0.09) and median (not reached vs. 34 months, p=0.12) survival

• Toxicity
  – No grade >2 acute or late toxicity
  – Grade 2 rib fracture 1%, chest wall syndrome 6%, pneumonitis 3%

Surgery vs. SBRT

- William Beaumont retrospective study
  - 124 pts with stage I NSCLC ineligible for lobectomy
  - SBRT (n=58; 48Gy T1, 60Gy T2, 4-5 fx) vs. wedge resection (n=69)
  - SBRT pts older, higher comorbidity scores
  - SBRT pts had a lower risk of local recurrence (5% vs. 24%, p=0.05) and locoregional recurrence (5% vs. 29%, p=0.03)
  - No difference in cause-specific survival (93% vs. 94%, p=0.53)
  - SBRT pts had inferior overall survival (72% vs. 87%, p=0.01)

SBRT Trials for Operable NSCLC

- **RTOG 0618**: “A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer”
  - Closed, publication pending
  - 2013 ASCO: 2-yr primary tumor failure rate 7.7%, PFS 65.4%, OS 84.4%

- **Netherlands**: “Randomized Clinical Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer” (ROSEL)
  - 2012 closed due to poor accrual

- **International**: “Randomized Study of Lobectomy vs. CyberKnife for Operable Lung Cancer” (STARS)
  - Randomization closed due to poor accrual, reopened as registry

- **ACOSOG Z4099/RTOG 1021**: “Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)”
  - 2013 closed due to poor accrual
Randomized Comparison Results

- Pulled analysis of the STARS and ROSEL randomised, phase III trials
  - STARS trial: ≤4 cm, resection +/- chemo vs. SABR 54/18 Gy (peripheral) or 50/12.5 Gy (central)
  - ROSEL trial: ≤3 cm, resection (lobectomy preferred) vs. SABR 54/18 Gy (peripheral) or 60/12 Gy (central and tumors with broad contact to the thoracic wall)
  - 58 patients randomized, no differences in characteristics between arms
- Survival: higher with SABR (p=0.037; HR 0.14; 1-yr 100% vs. 88%, 3-yr 95% vs. 79%)
  - Potentially related to post-operative complications and morbidities
- Disease control at 3 yrs: no difference in local control (SABR 96% vs. surgery 100%, p=0.44), regional nodal control (90% vs. 96%, p=0.32), metastatic-free survival (97% vs. 91%, p=0.42), or recurrence-free survival (86% vs. 80%, p=0.54)
- Toxicity
  - SABR arm: no grade 4 or 5 toxicities, 3 patients with grade 3 toxicities
  - Surgery arm: 1 grade 5 toxicity, 44% with grade 3 or 4 toxicities

Increasing Use of SBRT

- 600% increase between 2004 and 2010
- Collaboration across specialties

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Provider</th>
<th>2012 RVU Total</th>
<th>2013 RVU Total</th>
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<tbody>
<tr>
<td>32701</td>
<td>Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment</td>
<td>Thoracic surgeons Pulmonologists, General surgeons, Interventional radiologists</td>
<td>N/A</td>
<td>5.83</td>
</tr>
<tr>
<td>77435</td>
<td>Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions</td>
<td>Radiation Oncologists</td>
<td>13.00</td>
<td>11.87</td>
</tr>
</tbody>
</table>

Empiric SBRT Primary Tumor Considerations

• Patient refusal of biopsy
• Risks of biopsy thought to be prohibitive
• Biopsy attempted and nondiagnostic or nodule inaccessible to minimally invasive biopsy
• Nodule growth over time and rate of nodule growth
• Nodule PET avidity (greater than normal tissue)
• Nodule size (>8-10 mm)
• Patient smoking history
• Presence of nodule spiculations
• Lack of benign-appearing calcifications within the nodule

Central SBRT Toxicity

- 70 patient phase II study using 3 x 20 Gy (T1) or 22 Gy (T2)
  - 6 deaths attributable to therapy (4 in patients with perihilar/central tumors)
  - Median time to toxicity 10.5 months
- 2-year freedom from toxicity: peripheral 83% vs. central 54%, p=0.004
- 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

Proton Therapy: Rationale and Stage I
Proton Radiation Therapy

- External beam radiation therapy
- Largely equivalent in efficacy to photons
- More advanced form of targeted therapy
  - Can more precisely localize radiation therapy dosage
- 14 centers in the US, over 75,000 patients treated worldwide
- Protons stop, photons do not
Rationale for Proton Therapy for Thoracic Malignancies

• Reduce normal tissue dose
  – Reduced treatment toxicities
• Allows treatment of tumors close to critical organs (spinal cord) potentially not treatable with photon therapy
• Dose escalation
  – Increased local control (→ ? survival benefit)
• May be more safely and effectively combined with chemotherapy and surgery
• May allow for retreatment of recurrent tumors not safely retreatable with photon therapy
The Physics of Proton Therapy

The diagram shows the dose distribution in tissue for different types of proton beams compared to a photon beam. The horizontal axis represents the depth in tissue (cm), while the vertical axis shows the dose (%).

- **PHOTON beam 6MV**
- **modified PROTON beam 250MeV**
- **native PROTON beam 250MeV**

The graph highlights the Bragg peak, which is the point where the dose is maximized just before it drops to zero. This characteristic is particularly advantageous in proton therapy as it allows for more targeted treatment of tumors while minimizing damage to surrounding healthy tissue.
Proton Therapy for Stage I NSCLC

• Prospective study of 80 patients with stage I NSCLC who were medically inoperable or refused surgery treated with protons (n=57) or carbon-ions (n=23) most commonly to 60 CGE in 10 fractions
  – 3-year overall survival 75%, cause-specific survival 86%, local control 82%
  – Grade 2 pneumonitis 11%, grade 3 pneumonitis 2%

• Phase II prospective study of 111 patients with stage I NSCLC who were medically inoperable or refused surgery treated in 10 fractions to escalated doses of 51 CGE, 60 CGE, 70 CGE
  – 4-yr overall survival increased with increasing dose level (18% vs. 32% vs. 51%, p=0.006)
  – No clinical radiation pneumonitis requiring steroid therapy

ROCOCO Stage I NSCLC

- 25 patients with stage I NSCLC prescribed to 60 Gy in 8 fractions

<table>
<thead>
<tr>
<th>Structure</th>
<th>Measure</th>
<th>IMRT</th>
<th>RapidArc</th>
<th>CyberKnife</th>
<th>Protons</th>
<th>Carbon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Mean</td>
<td>5.0</td>
<td>4.4</td>
<td>4.6</td>
<td>4.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Heart</td>
<td>D2</td>
<td>6.1</td>
<td>4.7</td>
<td>7.6</td>
<td>2.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Mean</td>
<td>3.2</td>
<td>2.4</td>
<td>2.6</td>
<td>0.29</td>
<td>0.45</td>
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<tr>
<td>Cord</td>
<td>D2</td>
<td>8.6</td>
<td>11.3</td>
<td>5.8</td>
<td>0.68</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- “Given the ability of RapidArc and CyberKnife to limit doses to OARs compared with IMRT, the incremental additional benefit of particle therapy irradiation for stage I NSCLC may not be the most relevant indication for IMPT or IMIT.”

Wink KC, Roelof E, Simone CB 2nd, et al. Submitted, 2015 ASTRO
Locally Advanced NSCLC
Sequential vs. Concurrent Chemoradiation

- RTOG 94-10: 610 pts w/ unresected stage II-III NSCLC w/ KPS >70, wt loss<5% randomized from 7/94-7/98

**Arm 1:**
vinblastine 5 mg/m² IV bolus weekly first 5 weeks
cisplatin 100 mg/m² IV over 30-60 minutes, days 1 & 29

(starting day 50)
63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

**Arm 2:**
vinblastine 5 mg/m² IV bolus weekly first 5 weeks
cisplatin 100 mg/m² IV over 30-60 minutes, days 1 & 29
63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

**Arm 3:**
oral etoposide 50 mg twice daily x 10 only on RT treatment days 1-5, 8-12, 29-33 and 36-40 (75 mg/day if body surface area < 1.7 m²)
cisplatin 50 mg/m² IV over 30-60 minutes on days 1 and 8 and 29 and 36
69.6 Gy/6 wks/58 x 1.2 Gy twice-daily fractions (at least 6 hours apart)

RTOG 94-10

- 582/610 patients dead at time of analysis (11/2009)
- Sequential vs. Concurrent Daily
  - MST: 14.6 mo vs. 17.0 mo (p=0.046)
  - 5-yr OS: 10% vs. 16%
  - Response rate: 61% (30% cCR) vs. 70% (42% cCR) (p<0.05)
  - 2-yr in-field failure: 39% vs. 30% (p=0.09)
  - Concurrent with increased acute toxicity, equivalent late toxicity
- Sequential vs. Concurrent HFX
  - MST: 14.6 mo vs. 15.6 mo (p=0.46)
  - 5-yr OS: 10% vs. 13%
  - Response rate: 61% (30% cCR) vs. 65% (33% cCR) (NS)
  - 2-yr in-field failure: 39% vs. 29% (p=0.053)
  - Concurrent with increased acute toxicity, equivalent late toxicity

### RTOG 94-10 Toxicity

**Chemotherapy and acute radiotherapy toxicities, No. (%)**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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<th>Grade 4</th>
<th>Grade 5</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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</thead>
<tbody>
<tr>
<td>Granulocytopenia</td>
<td>Arm 1 (n = 195)</td>
<td>37 (19)</td>
<td>111 (57)</td>
<td>2 (1)</td>
<td>40 (21)</td>
<td>114 (59)</td>
<td>3 (2)</td>
<td>51 (27)</td>
<td>46 (25)</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Arm 2 (n = 193)</td>
<td>68 (35)</td>
<td>42 (22)</td>
<td>1 (&lt;1)</td>
<td>64 (33)</td>
<td>94 (49)</td>
<td>4 (2)</td>
<td>76 (40)</td>
<td>61 (27)</td>
<td>1 (&lt;1)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>Arm 3 (n = 187)</td>
<td>4 (2)</td>
<td>5 (3)</td>
<td>0</td>
<td>11 (6)</td>
<td>6 (3)</td>
<td>1 (&lt;1)</td>
<td>14 (7)</td>
<td>16 (9)</td>
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<td>Worst hematological</td>
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<td>40 (21)</td>
<td>114 (58)</td>
<td>2 (1)</td>
<td>46 (24)</td>
<td>117 (61)</td>
<td>4 (2)</td>
<td>77 (41)</td>
<td>53 (28)</td>
<td>3 (2)</td>
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<td>Pulmonary</td>
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<td>13 (7)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>6 (3)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>3 (2)</td>
<td>1 (&lt;1)</td>
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<tr>
<td><strong>Esophagus</strong></td>
<td>Arm 1 (n = 195)</td>
<td>7 (4)</td>
<td>0</td>
<td>0</td>
<td>40 (21)</td>
<td>3 (2)</td>
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<td>78 (42)</td>
<td>6 (3)</td>
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<td>Cardiac</td>
<td>Arm 2 (n = 193)</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
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<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>4 (2)</td>
<td>3 (2)</td>
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<td>Mucositis</td>
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<td>21 (11)</td>
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<td>39 (21)</td>
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<td>Nausea/Vomiting</td>
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<td>36 (19)</td>
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<td>Anemia</td>
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<td>31 (17)</td>
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<tr>
<td>Other nonhematological</td>
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<td>21 (11)</td>
<td>7 (4)</td>
<td>5 (3)</td>
<td>33 (17)</td>
<td>9 (5)</td>
<td>1 (&lt;1)</td>
<td>42 (22)</td>
<td>8 (4)</td>
<td>3 (2)</td>
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<tr>
<td>Worst nonhematological</td>
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<td>47 (24)</td>
<td>14 (7)</td>
<td>7 (4)</td>
<td>82 (42)</td>
<td>20 (10)</td>
<td>1 (&lt;1)</td>
<td>90 (48)</td>
<td>31 (17)</td>
<td>3 (2)</td>
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<tr>
<td>Worst overall toxicity</td>
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<td>47 (24)</td>
<td>114 (57)</td>
<td>7 (4)</td>
<td>50 (26)</td>
<td>121 (63)</td>
<td>4 (2)</td>
<td>79 (42)</td>
<td>75 (40)</td>
<td>3 (2)</td>
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**Late radiotherapy toxicities, No. (%)**

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<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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<tbody>
<tr>
<td>Granulocytopenia</td>
<td>Arm 1 (n = 176)</td>
<td>1 (1)</td>
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<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
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<td>Leukopenia</td>
<td>Arm 2 (n = 184)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
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<td>Thrombocytopenia</td>
<td>Arm 3 (n = 171)</td>
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<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Worst hematological</td>
<td></td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
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<td></td>
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<tr>
<td>Pulmonary</td>
<td></td>
<td>20 (11)</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>20 (11)</td>
<td>0</td>
<td>3 (2)</td>
<td>24 (14)</td>
<td>3 (2)</td>
<td>2 (1)</td>
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<tr>
<td>Esophagus</td>
<td></td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>5 (3)</td>
<td>1 (1)</td>
<td>0</td>
<td>6 (4)</td>
<td>0</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0</td>
<td>7 (4)</td>
<td>1 (1)</td>
<td>0</td>
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<tr>
<td>Nausea/Vomiting</td>
<td></td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>Anemia</td>
<td></td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other nonhematological</td>
<td></td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>8 (4)</td>
<td>2 (1)</td>
<td>0</td>
<td>4 (2)</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst nonhematological</td>
<td></td>
<td>24 (14)</td>
<td>5 (3)</td>
<td>2 (1)</td>
<td>29 (16)</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>31 (18)</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td></td>
<td></td>
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<tr>
<td>Worst overall toxicity</td>
<td></td>
<td>25 (14)</td>
<td>7 (4)</td>
<td>2 (1)</td>
<td>30 (16)</td>
<td>5 (3)</td>
<td>3 (2)</td>
<td>32 (19)</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sequential vs. Concurrent Meta-analysis

- 6 trials, 1205 pts
- Concurrent improved
  - OS (HR 0.84, p=0.004)
  - 3-yr absolute survival benefit of 5.7% (from 18.1% to 23.8%)
  - 5-yr benefit 4.5% (10.6% to 15.1%)
  - Locoregional progression (HR 0.77, p=0.01)
  - 5-yr absolute LRP benefit of 6.0% at 5 years (35.0% to 28.9%)
- No difference in PFS (p=0.07)
- No difference in distant progression (p=0.69)
- Increased acute grade 3-4 esophageal toxicity from 4% to 18% (RR 4.9, p<0.001)
- No difference in acute pulmonary toxicity

Sequential vs. Concurrent Therapy

Summary

• Overall survival improved with concurrent therapy
• Toxicity tolerable for selected patients
• Significant improvement still needed
  – Induction and/or consolidation chemotherapy
  – Hyperfractionation and changes in XRT techniques
  – Novel chemotherapeutic agents

Incidence of Brain Metastases as a Function of Chemotherapy Sequencing

Elective Nodal vs. Involved Field Radiation Therapy
MSKCC

- 524 pts with NSCLC treated with 3DCRT from 1991-2005
  - Target: only nodal regions initially involved with tumor (biopsy, imaging)
  - Dose: mean 66 Gy (50-90 Gy)
  - Elective nodal failure (ENF) = recurrence in initially uninvolved LN in the absence of local failure
- 6.1% with ENF (median time 6 months)
- 2-yr primary tumor control 51% vs. elective nodal control 92.4%

Incidental Irradiation

- 23 consecutive stage IIIA-B NSCLC (contralateral N3 excluded) patients treated with definitive IMRT (median 72 Gy, range 50-80 Gy), corresponding 3DCRT plans generated.

• 200 pts w/ inoperable stage III NSCLC w/ tumor/nodal masses ≤6 cm randomized to IFI or ENI
  – Induction chemotherapy x 2 cycles (21 days): cisplatin 25 mg/m² D1-3 + etoposide 75 mg/m² D1-5 → concurrent chemoradiation
  – IFI: 68-74 Gy in 1.8-2.0 Gy fx
  – ENI: 60-64 Gy in 1.8-2.0 Gy fx

Shandong Cancer Hospital, China

- Results
  - Overall response rate: 90% (IFI) > 79% (ENI), p=0.032
  - 5-yr LC: 51% > 36%, p=0.032
  - Radiation pneumonitis: 17% < 29%, p=0.044
  - IFI: trend towards lower rates of RT esophagitis, RT pericarditis, myelosuppression
  - 2-yr OS: 39.4% > 25.6%, p=0.048
  - 5-yr OS: 25.1% vs. 18.3%, p>0.05

FIGURE 1. Overall survival curve for patients with IFI or ENI.

Elective Nodal vs. Involved Field Radiation Therapy Summary

• Involved field irradiation
  – Regional failure rates low
  – Decreases treatment toxicity → allows for dose escalation
    • Improved response rates
    • Improved local control rates
    • Potential improvement in overall survival
Radiation Dose Escalation
RTOG 73-01

- 375 pts w/ stage I-II medically inoperable or stage III unresectable (T1-2N2, T3N0-2) NSCLC treated with definitive radiation therapy alone

<table>
<thead>
<tr>
<th>Dose</th>
<th>In-field Recurrence</th>
<th>Median Survival</th>
<th>3-yr OS</th>
<th>5-yr OS</th>
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<tbody>
<tr>
<td>40 Gy split course</td>
<td>53%</td>
<td>37 wks</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>40 Gy conventional</td>
<td>58%</td>
<td>45 wks</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>50 Gy</td>
<td>49%</td>
<td>41 wks</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>60 Gy</td>
<td>35%</td>
<td>47 wks</td>
<td>15%</td>
<td>6%</td>
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</table>

Other Dose Escalation Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Stage III (%)</th>
<th>Dose (Gy)</th>
<th>ENI</th>
<th>Induction (%)</th>
<th>Concurrent</th>
<th>Esophageal Toxicity ≥ Grade 3 (%)</th>
<th>Toxicity ≥ Grade 3 (%)</th>
<th>Median Survival (months)</th>
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</thead>
<tbody>
<tr>
<td>Maguire et al\textsuperscript{34}</td>
<td>94</td>
<td>74</td>
<td>73.6-80</td>
<td>Yes</td>
<td>27</td>
<td>No</td>
<td>3</td>
<td>16</td>
<td>13.0 IIIA / 10.0 IIIB</td>
</tr>
<tr>
<td>Sim et al\textsuperscript{35}</td>
<td>152</td>
<td>100</td>
<td>50-81</td>
<td>No</td>
<td>54</td>
<td>No</td>
<td>3</td>
<td>14</td>
<td>18.1 CMT / 11.7 RT alone</td>
</tr>
<tr>
<td>Hayman et al\textsuperscript{36}</td>
<td>104</td>
<td>66</td>
<td>63-102.9</td>
<td>No</td>
<td>24</td>
<td>No</td>
<td>7</td>
<td>1</td>
<td>16.0 III</td>
</tr>
<tr>
<td>Bradley et al\textsuperscript{37}</td>
<td>179</td>
<td>41</td>
<td>70.9-90.3</td>
<td>No</td>
<td>14</td>
<td>No</td>
<td>3</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>Wu et al\textsuperscript{38}</td>
<td>50</td>
<td>92</td>
<td>69-78</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Marks et al\textsuperscript{39}</td>
<td>44</td>
<td>98</td>
<td>73.6-96.4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>7</td>
<td>18</td>
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<tr>
<td>Socinski et al\textsuperscript{10}</td>
<td>62</td>
<td>100</td>
<td>60-74</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>0</td>
<td>24</td>
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<tr>
<td>Belderbos et al\textsuperscript{40}</td>
<td>55</td>
<td>53</td>
<td>54-101.3</td>
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<td>10</td>
<td>No</td>
<td>0</td>
<td>5</td>
<td>NR</td>
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<tr>
<td>Current study</td>
<td>29</td>
<td>100</td>
<td>78-90</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>16</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 4. Three-Dimensional Conformal Radiotherapy Dose-Escalation Trials in NSCLC

Abbreviations: NSCLC, non–small-cell lung cancer; ENI, elective nodal irradiation; CMT, chemotherapy; RT, radiation therapy; NR, not reported.

*Percentages refer to the percentage of all patients entered receiving induction chemotherapy. The yes or no designation refers to whether or not chemotherapy was administered concurrently with thoracic conformal radiation therapy.
RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609

A RANDOMIZED PHASE III COMPARISON OF STANDARD-DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

• 257 patients received cetuximab
• Median survival: cetuximab 25.0 months vs. 24.0 months (p=0.29)
• Cetuximab results crossed protocol-specified futility boundaries
• Cetuximab increased grade ≥3 toxic effects (86% vs. 70%, p<0.0001)
• Patients with EGFR IHC H-score ≥ 200 may have more benefit with cetuximab

RTOG 0617 By Radiation Dose

<table>
<thead>
<tr>
<th></th>
<th>60 Gy</th>
<th>74 Gy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 Pulmonary</td>
<td>20%</td>
<td>19%</td>
<td>0.71</td>
</tr>
<tr>
<td>Grade ≥3 Pneumonitis</td>
<td>7%</td>
<td>4%</td>
<td>0.25</td>
</tr>
<tr>
<td>Grade ≥3 Esophagitis</td>
<td>7%</td>
<td>21%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade ≥3 Any</td>
<td>76%</td>
<td>79%</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 5 Toxicity</td>
<td>N=3</td>
<td>N=8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Median overall survival: 28.7 months (60 Gy) vs. 20.3 months (74 Gy), p=0.0042

RTOG 9410 concurrent daily arm median overall survival: 17.0 months

RTOG 0617 Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Dead/Total RL</th>
<th>Dead/Total Group 2</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Level</td>
<td>Standard Dose (RL) vs. High Dose</td>
<td>121/208</td>
<td>136/199</td>
<td>1.34 (1.04, 1.73)</td>
<td>0.0213</td>
</tr>
<tr>
<td>Maximum related esophagitis/dysphagia grade</td>
<td>Maximum grade &lt; 3 (RL) vs. Maximum grade ≥ 3</td>
<td>210/349</td>
<td>47/58</td>
<td>1.54 (1.11, 2.15)</td>
<td>0.0102</td>
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<tr>
<td>Volume of PTV</td>
<td>Continuous</td>
<td>257/407</td>
<td></td>
<td>1.000 (1.000, 1.001)</td>
<td>0.0729</td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>257/407</td>
<td></td>
<td>1.007 (1.002, 1.011)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Zubrod PS</td>
<td>0 (RL) vs. 1</td>
<td>151/240</td>
<td>106/167</td>
<td>1.14 (0.89, 1.47)</td>
<td>0.3045</td>
</tr>
<tr>
<td>PET Staging</td>
<td>No (RL) vs. Yes</td>
<td>30/39</td>
<td>227/367</td>
<td>0.77 (0.52, 1.13)</td>
<td>0.1766</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (RL) vs. Female</td>
<td>153/240</td>
<td>104/167</td>
<td>0.97 (0.74, 1.26)</td>
<td>0.7975</td>
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<tr>
<td>Histology</td>
<td>Non-squamous (RL) vs. Squamous</td>
<td>146/228</td>
<td>111/179</td>
<td>1.01 (0.78, 1.31)</td>
<td>0.9380</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Non-smoker/former light smoker (RL) vs.</td>
<td>39/60</td>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Former heavy/current smoker vs. Unknown</td>
<td>206/328</td>
<td></td>
<td>1.14 (0.80, 1.63)</td>
<td>0.4617</td>
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<tr>
<td></td>
<td></td>
<td>12/19</td>
<td></td>
<td>1.44 (0.74, 2.80)</td>
<td>0.2776</td>
</tr>
</tbody>
</table>

RL = reference level, HR = hazard ratio, CI = confidence interval
*Two-sided log-rank p-value
17 patients are missing dose-volume and/or smoking history information and are excluded from this model

RTOG 0617

• Potential reasons for decreased survival with 74 Gy
  – Increase in grade 5 toxicities (n=8 vs. n=3)
  – More squamous cell histology (47% vs. 42%)
  – Fewer with PET staging (89% vs. 91%)
  – More stage IIIB (37% vs. 34%)
  – Increased heart dose (V50 – 11% vs. 7%)
  – Cardiac toxicity
MDACC – Cardiac Toxicity

- 532 patients with NSCLC treated with concurrent chemoradiation at MDACC
  - Mean heart dose:
    - 22.3 Gy – 3DCRT
    - 15.1 Gy – IMRT
    - 6.5 Gy – Protons
- Retrospective multivariate analysis:
  mean heart doses >25th percentile associated with increased risk of death (HR 1.4)

OS with mean heart dose above or below the median per RT dose subgroup
Proton Therapy Studies

- MDACC phase II trial of 44 pts with stage III NSCLC
  - Protons to 74 CGE with concurrent carboplatin + paclitaxel
  - MS 29.4 mo
    - Best survival ever reported in a phase II or III trial for stage III NSCLC
  - 20.5% local failure
  - Toxicity: 11% with grade 3 esophagitis and dermatitis, 2% with pneumonitis, no grade 4-5 toxicity

Proton Therapy Studies

- **RTOG 1308**: Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIIB NSCLC
  - Protons vs. photons to 70 Gy with concurrent chemotherapy (platinum-based doublet) +/- consolidation chemotherapy
  - Primary outcome: overall survival
  - Secondary outcomes: progression-free survival, grade ≥3 adverse events, QOL/PROs, cost-effectiveness outcomes, pulmonary function changes, technological parameters
  - 560 patient targeted accrual, enrollment started 2014

- **MDACC/Harvard randomized trial of protons versus photons**
  - Stage II/III NSCLC to 74 Gy with IMRT or protons (2 Gy/CGE fractions)
  - Primary outcomes: local control, grade ≥3 pneumonitis, esophagitis

- **Proton Collaborative Group LUN-005**: Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer
  - Phase I: Proton RT with concurrent chemotherapy to 60 CGE in $24 \rightarrow 20 \rightarrow 17 \rightarrow 15$ fractions [find maximum tolerated dose]
  - Phase II: 31 patients treated with MTD [primary endpoint: 1-yr OS]
NSCLC Mutations/Translocations

- EGRF mutations
  - 10% Western, 50% Asian
  - Associated with TKI therapy response
  - Typically mutually exclusive with KRAS mutations (intrinsic TKI resistance)
- EML4-ALK translocation
  - 3% of NSCLC
  - ALK inhibitors (ie. crizotinib)
- RTOG1306/Alliance 31101: A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC)
  - EGFR mutation: erlotinib
  - ALK translocation: crizotinib
## Improving Outcomes in LA-NSCLC RTOG Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>RT</th>
<th>Chemo</th>
<th>Sequence</th>
<th>MST</th>
<th>5 y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0617</td>
<td>74 Gy (SDFx)</td>
<td>Pac-Carbo +/- C225</td>
<td>Con-Consol</td>
<td>19.5 m</td>
<td>N/A</td>
</tr>
<tr>
<td>0617</td>
<td>60 Gy (SDFx)</td>
<td>Pac-Carbo +/- C225</td>
<td>Con-Consol</td>
<td>28.7 m</td>
<td>N/A</td>
</tr>
<tr>
<td>0324</td>
<td>63 Gy (SDFx)</td>
<td>Pac-Carbo-C225</td>
<td>Con-Consol</td>
<td>22.7 m</td>
<td>N/A</td>
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<tr>
<td>0229</td>
<td>61.2 Gy (SDFx) → Sx</td>
<td>Pac-Carbo</td>
<td>Con-Consol</td>
<td>26.7 m</td>
<td>N/A</td>
</tr>
<tr>
<td>0117</td>
<td>74 Gy (SDFx)</td>
<td>Pac-Carbo</td>
<td>Con-Consol</td>
<td>21.6 m</td>
<td>N/A</td>
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<tr>
<td>9801</td>
<td>69.6 Gy (BID Fx)</td>
<td>Pac-Carbo/Amif</td>
<td>Ind-Con</td>
<td>17.3 m</td>
<td>17%</td>
</tr>
<tr>
<td>9801</td>
<td>69.6 Gy (BID Fx)</td>
<td>Pac-Carbo</td>
<td>Ind-Con</td>
<td>17.9 m</td>
<td>16%</td>
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<tr>
<td>9410</td>
<td>63 Gy (SDFx)</td>
<td>VBL-DDP</td>
<td>Con</td>
<td>17.0 m</td>
<td>16%</td>
</tr>
<tr>
<td>9410</td>
<td>63 Gy (SDFx)</td>
<td>VBL-DDP</td>
<td>Seq</td>
<td>14.6 m</td>
<td>10%</td>
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<tr>
<td>9410</td>
<td>69.6 Gy (BID Fx)</td>
<td>VP-16DDP</td>
<td>Con</td>
<td>15.6 m</td>
<td>13%</td>
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</table>
Trimodality Therapy
INT 0139: Definitive Chemorads vs Neoadjuvant Chemorads and 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

Median F/u: 22.5 mo

INT 0139: Results

Progression-free survival
Sx 12.8 mo vs. 10.5 mo, p=0.017
5-yr PFS: 22% vs. 11%

Overall survival
Sx 23.6 mo vs. no sx 22.2 mo, p=0.24
5-yr OS: 27% vs. 20%, p=0.10

INT 0139: Surgery Group

- Pathologic CR in 18%
- Down staging with nodal clearance in 46%
- pN0 median survival 34.4 mo
- pN0 5-yr survival 41%

INT 0139 Overall Survival of Pneumonectomy Subset versus Matched CT/RT Subset

- **CT/RT/S**
  - 3 yr OS: 36%
  - 5 yr OS: 22%
  - Median Survival (MS): 18.9 mos.
  - Dead/Total: 38/51
- **CT/RT**
  - 3 yr OS: 45%
  - 5 yr OS: 24%
  - Median Survival (MS): 29.4 mos.
  - Dead/Total: 42/51

Logrank p = NS

INT 0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset

Dead/Total

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

Logrank p = 0.002

MS 33.6 mos. 36%
5 yr OS
CT/RT/S
CT/RT 21.7 mos. 18%

INT0139 Summary

- Survival was not increased in the surgical arm despite improved PFS
- Nodal status at the time of surgery predicts 5-yr survival
- Trimodality approach not optimal if pneumonectomy required
  - Particularly for right side
- Surgery may be considered for fit patients if lobectomy feasible, minimal bulk disease
- Increased treatment-related deaths in sx arm: 8% vs. 2%
  - Only 1 of 14 deaths after lobectomy

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Number</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>L lobectomy</td>
<td>1</td>
<td>PE</td>
</tr>
<tr>
<td>R bilobectomy</td>
<td>1</td>
<td>ARDS</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>12</td>
<td>ARDS 8 Respiratory misc 4</td>
</tr>
<tr>
<td>R simple</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>R complex</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>L complex</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**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 miscellaneous, 3</td>
</tr>
<tr>
<td>(R) simple</td>
<td>17</td>
<td>5 (29%)</td>
<td></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 0160/SWOG 9416

- Surgeries performed
  - Lobectomy + chest wall: 66%
  - Lobectomy: 14.8%
  - Pneumonectomy +/- chest wall: 3.4%
  - Exploratory thoracotomy: 2.3%
  - Other: 13.2%

- pCR or minimal microscopic disease in 56% (improves survival)

- 5-yr survival 44%
  - 54% after complete resection

INT 0160/SWOG 9416

pCR improved survival (p=0.02)

No difference in T3 vs. T4

Neoadjuvant Chemoradiation to Definitive RT Dose

- RTOG 02-29: phase II trial of 57 pt with pathologically proved N2 or N3 stage III NSCLC
- Induction carboplatin/paclitaxel → concurrent chemoradiation (50.4 Gy mediastinum + primary, boost to 61.2 Gy to all gross disease) → surgery
  - Primary endpoint: 63% pCR in mediastinum
  - 14% grade 3 pulmonary toxicity, 3% grade 5 postop toxicity
  - 2-yr OS 54% (75% if pCR in mediastinum, 52% if residual nodal disease, 23% if not eligible/no surgery, p=0.0002)

Surgical Conclusions

• Induction therapy prior to surgery may be of benefit in a subset of fit patients with non-bulky stage III NSCLC
  – More clear benefit for T3-4 N0-1
  – Chemotherapy alone unless superior sulcus (chemoradiation)

• For N2 disease, trimodality therapy is:
  – Less favorable if pneumonectomy required
  – Best performed on clinical trial
  – Not shown to be superior to definitive chemoradiation
    • Improved patient selection and modern radiation and surgery techniques may lead to improved outcomes with trimodality therapy for a subset of IIIA patients
Proton Therapy in Trimodality Therapy

• Proton therapy may allow for more safer implementation of trimodality therapy
• MDACC experience of 444 patients treated with surgery after chemoradiation for esophageal cancer from 1998-2011

• UPenn: Phase I/II Trial of Preoperative Proton Beam Radiotherapy with Concurrent Chemotherapy for Resectable Stage IIIA or Superior Sulcus NSCLC – 50.4 CGE → 59.4 CGE → 66.6 CGE

Rationale for Postoperative Radiotherapy

- Rate of local-regional failure (LRF) after surgery for pN+ NSCLC is 20-60%

- Distant metastases (DM) remain the primary determinant of OS
  - No chemotherapy in PORT Meta-analysis → LRF even more important in modern studies with chemotherapy use

- LRF can present as site of isolated first failure (20-30%) or be identified at the same time as DM (up to 60%) but may still be the driver for DM
Correlation Between LRC and OS

- Meta-analysis of 6 trials, 1205 patients of sequential vs. concurrent chemoradiation
  - No difference in distant progression (p=0.69)
  - 5-yr absolute LRP benefit 6.0% (35.0% to 28.9%) (HR 0.77, p=0.01)
  - 5-yr absolute OS benefit 4.5% (10.6% to 15.1%) (HR 0.84, p=0.004)

- 1390 LA-NSCLC patients from 7 RTOG trials treated with chemoradiation
  - 3-yr LRC 38%
  - LRC was association with overall survival (p<0.0001) on univariate and multivariate analyses

<table>
<thead>
<tr>
<th>Table 2. Multivariate Cox Proportional Hazards Models of Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>LRC endpoint = freedom from local progression (FFLP-LRC)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>KPS</td>
</tr>
<tr>
<td>Chemotherapy Order</td>
</tr>
<tr>
<td>BED</td>
</tr>
<tr>
<td>LRC endpoint = response-mandatory local-regional control (strict-LRC)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>KPS</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Chemotherapy Order</td>
</tr>
<tr>
<td>BED</td>
</tr>
</tbody>
</table>

PORT Meta-Analysis and Toxicity

• 2,343 patients from 11 trials
  – No chemotherapy; outdated RT techniques, included stage I-III NSCLC
  – Significant adverse effect of PORT on survival HR 1.18
• Benefit of improved local-regional control of PORT on survival thought to be offset by excess toxicity and death from treatment
  – Causes of death thought to be primarily cardiac and pulmonary

<table>
<thead>
<tr>
<th></th>
<th>NSCLC</th>
<th>Treatment</th>
<th>Other</th>
<th>Non-Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORT</td>
<td>82%</td>
<td>4%</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>No PORT</td>
<td>89%</td>
<td>2%</td>
<td>9%</td>
<td>11%</td>
</tr>
</tbody>
</table>

• PORT toxicities related to:
  – Volume (whole mediastinum → involved field)
  – Technique (cobalt → Linac; lateral fields → conformal/IMRT)
  – Total dose (50-60 Gy → 50-54 Gy)
  – Dose per fraction (1.8-3.0 Gy → 1.8-2.0 Gy)
  – Patient age/comorbidities

Modern Population-Based PORT Studies

- **SEER:** 7,465 patients from 1988-2002 with stage II-III NSCLC s/p lobectomy/pneumonectomy
  - 47% received PORT (more common in: age <50 years, higher stage, T3-4 primary, larger tumor size, advanced node stage, greater number of + LNs, higher +LN/LN sampled ratio)
  - PORT improved survival for pN2 nodal disease (HR 0.855; 95% CI 0.762 to 0.959; p=0.0077)
  - PORT decreased survival for pN0 (HR 1.176; 95% CI 1.005 to 1.376; p=0.0435) and pN1 (HR 1.097; 95% CI 1.015 to 1.186; p=0.0196)
- **NCB:** 4,483 patients with pN2 stage III NSCLC s/p R0 surgery from 2006-2010
  - All received chemo, 41% received PORT
  - PORT increased median (45.2 v 40.7 months) and 5-year OS (39.3% v 34.8%) [p=0.014]

Postoperative Radiotherapy

• LungART trial in Europe is an ongoing phase III trial of chemo +/- PORT for IIIA(N2) NSCLC

• RADCOMP multi-centered trial of adjuvant protons vs. photons for patients with stage III pN2 NSCLC
  – Primary: major cardiovascular events
  – Secondary: radiation pneumonitis, cardiopulmonary mortality, HRQOL/PROs, toxicity, loco-regional relapse, lung-cancer specific survival, OS
Stage IV NSCLC
Survival in Advanced NSCLC

- Changing Face of Stage IV NSCLC
  - With improved systemic therapy, patients are living longer
  - We are being asked to treat patients with metastatic or recurrent disease with a goal of local control and not simple palliation
UPenn Stage IV Chemorads Experience

• 29 NSCLC oligometastatic patients from 1/2004-8/2010 with ≤4 sites of metastasis treated with thoracic chemoradiation to ≥50 Gy
  – Median survival 22 months
    • Local control associated with improved survival (p=0.02)
  – In matched subset analysis, median survival 9 months (p<0.01) in patients who received chemotherapy alone
    • Median time to local progression: 18 mo vs. 6 mo (p=0.01)
  – Improved survival on multivariable analysis: radiation (p<0.01, OR=0.33), fewer metastasis (p<0.01, OR=2.14), female gender (p<0.01, OR=0.41)

What to do at TKI Progression (Acquired Resistance)

- Resistance to TKIs after a median of 10-16 months
- **New Concepts: Oligometastatic vs. Oligoprogression**

Upenn Stage IV SBRT Experience

• Pts with 1-5 pulmonary metastases and limited extrathoracic disease treated from 5/2010-8/2013 with SBRT to pulmonary metastases
  – 52 pts with 67 pulmonary metastases
  – 12.5 Gy x 4 (48%) or 10 Gy x 5 (31%) a median of 32.2 months (range 6.9-167.7 mo) after initial diagnosis
  – Stage IV NSCLC (24 pts, 32 lesions) or other malignancies (28 pts, 35 lesions)
    • Melanoma most prevalent (7 pts, 9 lesions)
  – Median follow-up of 18 months from SBRT

Upenn Stage IV SBRT Experience

- Local control 94% (NSCLC 91% vs. other 97%, p=0.26)
- Nodal failure 19% (NSCLC 24% vs. other 14%, p=0.27)
- Distant failure 34% (NSCLC 47% vs. other 23%, p=0.04)
  - Distant failure the most common failure pattern after SBRT, especially in NSCLC pts
- Overall survival 63% (NSCLC 53% vs. other 71%, p=0.12)
  - Trended higher in NSCLC pts with disease confined to thorax than NSCLC pts with extrathoracic metastasis (64% vs. 40%, p=0.13)
  - Melanoma pts had similar distant failure rates as NSCLC pts but higher distant failure than all other non-NSCLC pts (p=0.03)
- 40.4% of pts free of any failure after SBRT
- Toxicity
  - Grade 2 toxicity: chest wall syndrome (2%), pneumonitis (2%)
  - No grade >2 acute or late toxicity

Phase II Data for SBRT of Oligometastasis

- Single arm phase II study of stage IV NSCLC patients with ≤6 sites of extracranial disease who failed early systemic chemotherapy treated with SBRT to all sites of disease and concurrent erlotinib until disease progression
  - 24 patients treated to 52 sites

- Outcomes
  - Median PFS 14.7 months, median OS 20.4 months
  - Only 3 of 47 measurable lesions recurred within the SBRT field
  - Two grade 3 toxicities

NRG Study for Lung Oligometastasis SBRT

NRG ONCOLOGY

NRG-BR001

A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

SCHEMA

Patients with metastatic breast, adenocarcinoma of the prostate or non-small cell lung cancer with ≤ 4 metastases; all metastases not resected must be amenable to SBRT
See Section 3.0 for details

\[ \downarrow \]

REGISTER

\[ \downarrow \]

SBRT (in 3 or 5 fractions) to all existing metastases in 1-3 weeks
See Table 6-1 in Section 6.1 for dose levels and Table 13-1 in Section 13.3 for Dose Limiting Toxicities (DLTs)

<table>
<thead>
<tr>
<th>Metastatic Locations</th>
<th>Initial Starting Dose</th>
<th>Decreased DLT Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung—Peripheral</td>
<td>45 Gy (3 fractions)</td>
<td>42 Gy (3 fractions)</td>
</tr>
<tr>
<td>Lung—Central</td>
<td>50 Gy (5 fractions)</td>
<td>47.5 Gy (5 fractions)</td>
</tr>
<tr>
<td>Mediastinal/Cervical Lymph Node</td>
<td>50 Gy (5 fractions)</td>
<td>47.5 Gy (5 fractions)</td>
</tr>
<tr>
<td>Liver</td>
<td>45 Gy (3 fractions)</td>
<td>42 Gy (3 fractions)</td>
</tr>
<tr>
<td>Spinal/Paraspinal</td>
<td>30 Gy (3 fractions)</td>
<td>27 Gy (3 fractions)</td>
</tr>
<tr>
<td>Osseous</td>
<td>30 Gy (3 fractions)</td>
<td>27 Gy (3 fractions)</td>
</tr>
<tr>
<td>Abdominal-pelvic metastases (lymph node/adrenal gland)</td>
<td>45 Gy (3 fractions)</td>
<td>42 Gy (3 fractions)</td>
</tr>
</tbody>
</table>
Stage IVA - Pleural

• NSCLC with pleural spread carries a dismal prognosis of 6-10 months median survival
• Standard treatment is palliative chemotherapy
• Surgery typically has no role
  – Prior studies show no survival benefit and high rates of local recurrence of up to 90% due to microscopic residual disease following resection
• Phase II trial of patients with NSCLC with pleural metastasis treated from 1997-2012 with definitive surgery with intent of achieving a gross total resection and intraoperative photodynamic therapy (PDT) to target microscopic residual disease
Intrapleural Photodynamic Therapy

- Light therapy administered intraoperatively at the time of surgery to attempt to kill microscopic residual cancer cells
- Photosensitizer (photofrin 2 mg/kg) given IV 24 hrs prior to surgery to make cancer cell more susceptible to damage with light therapy
- On the day of surgery
  - Gross microscopic resection (or <5 mm residual tumor)
  - Light therapy is administered to the entire chest cavity
# Patient Characteristics (N=34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>55 yrs (35-73 yrs)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (50.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (50.0%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>29 (85.3%)</td>
</tr>
<tr>
<td>African American</td>
<td>4 (11.8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td><strong>Smoking History</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (73.5%)</td>
</tr>
<tr>
<td>Second Hand</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>None</td>
<td>4 (11.8%)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (41.2%)</td>
</tr>
<tr>
<td>1</td>
<td>20 (58.8%)</td>
</tr>
<tr>
<td><strong>Pleural Metastasis at Diagnosis</strong></td>
<td>33 (97.1%)</td>
</tr>
<tr>
<td><strong>Side of Pleural Dissemination</strong></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>24 (70.6%)</td>
</tr>
<tr>
<td>Left</td>
<td>10 (29.4%)</td>
</tr>
<tr>
<td><strong>Histologic Subtype</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>27 (79.4%)</td>
</tr>
<tr>
<td>Poorly Differentiated</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Malignant Pleural Fibrous</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td><strong>Preoperative Clinical Stage</strong></td>
<td></td>
</tr>
<tr>
<td>T4N0</td>
<td>10 (29.4%)</td>
</tr>
<tr>
<td>T4N1</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>T4N2</td>
<td>22 (64.7%)</td>
</tr>
<tr>
<td><strong>Postoperative Pathologic Stage</strong></td>
<td></td>
</tr>
<tr>
<td>T4N0</td>
<td>8 (23.5%)</td>
</tr>
<tr>
<td>T4N2</td>
<td>26 (76.5%)</td>
</tr>
<tr>
<td><strong>Prior Definitive Surgery</strong></td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td><strong>Neoadjuvant Chemotherapy</strong></td>
<td>32 (94.1%)</td>
</tr>
<tr>
<td><strong>Neoadjuvant Radiotherapy</strong></td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td><strong>Adjuvant Chemotherapy</strong></td>
<td>17 (50.0%)</td>
</tr>
<tr>
<td><strong>Adjuvant Radiotherapy</strong></td>
<td>20 (58.8%)</td>
</tr>
<tr>
<td>Median Dose</td>
<td>54 Gy (30-72 Gy)</td>
</tr>
</tbody>
</table>
## Surgical Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N (%)</th>
<th>Gross Total Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable</td>
<td>2 (5.9%)</td>
<td>0/2</td>
</tr>
<tr>
<td>Extrapleural Plenumonectomy</td>
<td>19 (55.9%)</td>
<td>18/19</td>
</tr>
<tr>
<td>Radical Pleurectomy and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (2.9%)</td>
<td>1/1</td>
</tr>
<tr>
<td>Wedge Resection</td>
<td>2 (5.9%)</td>
<td>0/2</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>1 (2.9%)</td>
<td>1/1</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>5 (14.7%)</td>
<td>5/5</td>
</tr>
<tr>
<td>Lobectomy + Segmentectomy</td>
<td>1 (2.9%)</td>
<td>1/1</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>3 (8.8%)</td>
<td>3/3</td>
</tr>
</tbody>
</table>

- 2 pts unresectable
  - 1 pericardial effusion
  - 1 trans-diaphragmatic extension
- 4 pts (3/19 EPP, 1/13 lung-sparing) suffered peri-operative mortalities (day 11-98)
  - 1 death attributable to PDT (ARDS, day 11)
- Pleural recurrence free survival, PFS, and OS similar for EPP and lung-sparing surgery (all p>0.05)

Simone CB 2nd, et al. 2015; in press.
# Patterns of Failure After Surgery/PDT

<table>
<thead>
<tr>
<th>Site(s) of First Failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated Pleural</td>
<td>9.4%</td>
</tr>
<tr>
<td>Isolated Locoregional</td>
<td>15.6%</td>
</tr>
<tr>
<td>Isolated Distant</td>
<td>34.4%</td>
</tr>
<tr>
<td>Pleural and Locoregional</td>
<td>3.1%</td>
</tr>
<tr>
<td>Locoregional and Distant</td>
<td>6.3%</td>
</tr>
<tr>
<td>Pleural and Distant</td>
<td>3.1%</td>
</tr>
<tr>
<td>Pleural, Locoregional, and Distant</td>
<td>6.3%</td>
</tr>
<tr>
<td>No Recurrence</td>
<td>21.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall Cumulative Site(s) of Failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>34.4%</td>
</tr>
<tr>
<td>Locoregional</td>
<td>31.3%</td>
</tr>
<tr>
<td><strong>Distant</strong></td>
<td>53.1%</td>
</tr>
<tr>
<td>Any Site</td>
<td>78.1%</td>
</tr>
</tbody>
</table>

Simone CB 2nd, et al. 2015; in press.
Pleural Recurrence Free Survival

Median PRFS 29.9 mo, 95% CI (23.5, NA)
Mean PRFS 33.8 mo, 95% CI (24.4, 43.2)
PRFS at 1 yr = 73%, 2 yr = 63%, 3 yr = 48%, 5 yr = 48%

Simone CB 2nd, et al. 2015; in press.
Overall Survival

Median OS 22.0 mo, 95% CI (8.5, 29.0)
[median OS 27.6 months from pleural diagnosis]
Mean OS 27.8 mo, 95% CI (16.2, 39.5)
OS at 1 yr = 59%, 2 yr = 40%, 3 yr = 17%, 5 yr = 10%

Simone CB 2nd, et al. 2015; in press.
Thoracic Reirradiation
Rationale for Thoracic Reirradiation and Protons

• Local failures occur in 30-50% of patients with locally advanced NSCLC
  – Isolated first failures occurs locoregionally in 20-30% patients after chemoradiation and are potentially curable with additional local therapy but are traditionally treated with chemotherapy alone due to excessive toxicities associated with photon reirradiation
    • Chemotherapy: 4-6 month progression free survival
  
• Protons provide opportunity for reirradiation in the thorax when there would otherwise be few radiotherapy options
  – Allows for escalation of reirradiation dose
  – Lack of exit dose significantly decreases cord and contralateral lung doses, as well as heart, esophagus, ipsilateral lung doses
  – May also be critical for distal wall of mainstem bronchus/carina
Thoracic Reirradiation – Example Case

- Surgery for pT2N2M0 NSCLC (right paratracheal node) → adjuvant chemotherapy
- Reimaging before planned adjuvant RT = right paratracheal recurrence
- Treated to the right paratracheal node and mediastinum to 66.6 Gy
  - Spinal cord received >44 Gy from this first course
- First surveillance scan 3 months after RT = response
- 6 months after RT = progression in the right paratracheal node
- Second line chemotherapy → isolated right paratracheal progression
- Proton reirradiation to 66.6/1.8 Gy → alive, without recurrence ~3.5 yrs after reirradiation
UPenn Proton Prospective Reirradiation Trial

- 49 pts with recurrent NSCLC in or near their prior thoracic irradiation portal treated at 3 proton therapy centers:
  - University of Pennsylvania: n=37
  - CDH Proton Center, Warrenville, IL: n=10
  - Procure Proton Therapy Center, Oklahoma City: n=2

- Tumor volume
  - Low volume (CTV ≤250 cc; n=42), high volume (CTV >250 cc; n=7)

- Disease status
  - Alive without recurrence n=7 (14%)
  - Alive with locoregional recurrence n=14 (29%)
  - Alive with distant metastasis n=3 (6%)
  - Deceased n=25 (51%)
  - ***Only 1/49 (2%) with an in-field recurrence***
Treatment Planning
Simulation

• Supine position
• Torso supported, partially immobilized
  – Arm positioning dependent on tumor location
• Arms above head allows more options for lateral/oblique fields
• CT planning
  – Scan from larynx to L2
  – CT/PET preferable to CT alone for GTV delineation
  – IV contrast for better target, normal tissue delineation
Simulation

• Quiet, steady respiration vs. more formal respiratory arrest (deep breathing, breath holding, abdominal compression) or gaitting
  – Decrease dose to normal tissues
  – 4D CT (individualizes respiratory motion) increasingly utilized
    • Replaced assessing breathing under fluoro and CT of max inhale/exhale

• Patients receiving induction chemotherapy
  – Consider baseline planning CT in pts with good pulmonary function so initial RT fields cover pre-chemo tumor volume
    • Cone-down fields to cover post-chemotherapy tumor volume

• Plan with heterogeneity corrections
Radiation Energy, Technique

- **Energy**
  - 4-10 MV generally recommended
  - 15-18 MV for separation >20 cm or large mediastinal tumors
    - Potentially increases dose to lung through lateral scatter, underdoses tumor at air-tissue interface
- **2D: AP-PA until cord tolerance → off-cord laterals/obliques**
- **3D conformal:** increases number of beams used and volume of lung receiving some RT, decreases volume receiving high RT doses
- **IMRT** (esp. if tumor fixed to vertebral body, at superior sulcus, involves b/l mediastinum/hilum)
  - Increasingly used
- **Proton therapy**
- **Use daily imaging (IGRT) when treating with conformal techniques**
Unresectable NSCLC Fields

• Tumor Volumes: RTOG 0617
  – GTV: primary tumor and clinically positive LNs (> 1 cm on planning CT, pretreatment PET scan SUV >3)
  – CTV: GTV + 0.5-1.0 cm margin
    • Elective treatment of mediastinum and supraclavicular fossae not done
  – 3D planning PTV: CTV + ≥1.0 cm sup/inf and 0.5 cm axial plan (internal motion) + 0.5 cm (additional set-up margin) [total 1.0-1.5 cm]
  – 4D planning PTV: CTV + ≥ 1.0 cm sup/inf and 0.5 cm axial plan

• Tumor Volumes: RTOG 1308
  – GTV → iGTV (tumor motion) → ITV (iGTV + 8 mm) → PTV (ITV + 5 mm)
  – GTV → CTV (GTV + 8 mm) → ITV (CTV + motion) → PTV (ITV + 5 mm)
  – Exclude uninvolved organs (esophagus, heart, bone) in CTV/ITV
Planning Instructions

Dose Targets and Constraints – Current Course

<table>
<thead>
<tr>
<th>Priority (option)</th>
<th>Volume Name</th>
<th>Max Dose (cGy)</th>
<th>Min Dose (cGy)</th>
<th>Mean Dose (cGy)</th>
<th>Relative Volume Constraint 1</th>
<th>Relative Volume Constraint 2</th>
<th>Absolute Volume Constraint</th>
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<tbody>
<tr>
<td></td>
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<td>Volume %</td>
<td>Min %</td>
<td>Mean %</td>
<td>Volume %</td>
<td>Min %</td>
<td>Mean %</td>
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<tr>
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<td>BRACHIALPLEXUS</td>
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<table>
<thead>
<tr>
<th>Organ</th>
<th>1308 Per Protocol</th>
<th>1308 Variation Acceptable</th>
<th>0617 Per Protocol</th>
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</thead>
<tbody>
<tr>
<td>Lung minus GTV</td>
<td>V20 ≤ 37%; MLD ≤ 20 Gy (RBE); lung V5 ≤ 60%</td>
<td>V20 ≤ 40% or MLD ≤ 22 Gy (RBE); lung V5 ≤ 65%</td>
<td>V20 ≤ 37%, MLD ≤ 20 Gy</td>
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<tr>
<td>Esophagus</td>
<td>Max dose: 74 Gy (RBE) ≤ 1cc of partial circumference</td>
<td>Max dose: 74 Gy (RBE) ≤ 1.5 cc of partial circumference</td>
<td>Mean ≤34 Gy</td>
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<tr>
<td>Brachial Plexus</td>
<td>V66 ≤ 2.0 cc</td>
<td>V66 ≤ 2.5 cc</td>
<td>Dmax &lt;66 Gy</td>
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<tr>
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<td>V70 ≤ 1.0 cc</td>
<td>V70 ≤ 1.5 cc</td>
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<tr>
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<td>V74 ≤ 0.5 cc</td>
<td>V74 ≤ 1.0 cc</td>
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<tr>
<td></td>
<td>V75 ≤ 0.1 cc</td>
<td>V75 ≤ 0.5 cc</td>
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<tr>
<td>Spinal Cord</td>
<td>V50 &lt; 0.03 cc</td>
<td>V52 &lt; 0.03 cc</td>
<td>Dmax &lt;50.5 Gy</td>
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<td>Heart</td>
<td>V30 ≤ 50%</td>
<td>V30 ≤ 55%</td>
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<td>V45 ≤ 35%</td>
<td>V45 ≤ 40%</td>
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<td>Max Dose to 0.03cc ≤ 70 Gy</td>
<td>Max Dose to 0.03cc ≤ 75 Gy</td>
<td>3/3 &lt;40 Gy</td>
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Proton Beam Arrangement

• Most lung cancer patients have been treated with scattered beams due to difficulties in accounting for motion using smearing with pencil beam scanning (PBS)
• Definitive locally advanced NSCLC is typically treated with 2-3 beams
  – 2 fields: posterior and posterior oblique or anterior and anterior oblique
    • The angle between the anterior and anterior oblique or posterior and posterior oblique beams must balance skin overlap (at small angles of separation) with increased lung dose (at large angles of separation)
  – 3 fields: posterior or anterior, lateral, and oblique
  – Beam angles are robust with respect to target coverage and there is minimal uncertainty in cord dose
  – Oblique angle should be chosen to block the cord with the aperture
  – Oblique angle must avoid the corner of the treatment table
Proton Beam Arrangement

- PORT for NSCLC is typically treated with two anterior beams
  - Beams are typically an anterior and anterior oblique
  - Considerations for PBS given less movement for mediastinal targets
Conclusions

• Radiation therapy should be individualized
  – Maximize tumor dose, limit normal tissue dose
  – Options: conventional photons (3D conformal or IMRT), SBRT, protons
• For early stage NSCLC, SBRT increases local control and survival
• For locally-advanced NSCLC, concurrent chemoradiation improves survival
  – IFRT has largely replaced ENI for definitive chemoradiation
  – Radiation pneumonitis is dose limiting
    • 4D CT (intrafractional tumor motion), daily imaging (IGRT), lung DVH, IMRT/protons
  – RT can be used as adjuvant (pN2) or neoadjuvant (superior sulcus or single station, non-bulky N2) therapy with surgery
  – In selected patients, protons can reduce normal tissue dose which may:
    • Lead to fewer acute and late toxicities
    • Treat lesions potentially not treatable with photon therapy
    • More safely allow for dose escalation
    • More safely allow for trimodality therapy
    • Allow for retreatment of recurrent tumors
• Radiotherapy may have increasing roles in stage IV NSCLC
  – NSCLC: Definitive chemoradiation, SBRT for oligometastasis, surgery/PDT