What Dose is optimal?
Locally Advanced NSCLC...

Dr P Vijay Anand Reddy
Director
Apollo Cancer Institute, Hyd
# TNM Staging of Lung Cancer

## Stage 0

- **T0**: Carcinoma in situ

**Occult Carcinoma (Tx, N0, M0)**

- Including direct extension to intrapulmonary nodes
- Including superior sulcus tumor

**Including**

- and
- or
- and/or

## Stage I

**Stage I A**

- T1
- N0
- M0

**Stage I B**

- T1
- N1
- M0

## Stage II

**Stage II A**

- T2
- N0
- M0

**Stage II B**

- T2
- N1
- M0

## Stage III

**Stage III A**

- T3
- N1
- M0

**Stage III B**

- T3
- N2
- M0

**Stage IV**

- Any T, any N

### METASTASES (M)

- **M0**: Absent
- **M1**: Present

Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1

### Primary Tumor (T)

- **Criteria**
  - a. Size
  - b. Endobronchial location
  - c. Local Invasion
  - d. Other
Locally Advanced NSCLC

- >50% of all lung cancers
- Chemo-radiotherapy +/− Chemotherapy
- Poor survival (5yr OS 5-20%)
- Dismal local control rates
- Local failure a harbinger for distant metastases and survival*

* Malissard L, IJROBP’91; Sibley GS, IJROBP’98
Radiation Therapy in Stage III NSCLC

**Therapeutic Ratio**

- Chemotherapy concurrent

**Dose Escalation**
  - Dose escalation - Standard fractionation
  - Altered Fractionation Schedules
  - SBRT
  - Proton Therapy

**Modern Techniques:**
3D Conformal RT, IMRT, IGRT, Volumatric Arc etc,
Concurrent Chemoradiotherapy in NSCLC

19 RCTs of concurrent CTRT vs RT alone:
- Sig reduction in risk of death (HR 0.71) & improvement in PFS (HR 0.69) with CTRT

6 RCTs of Concurrent vs Sequential Chemo-radiation:
- 10% abs survival benefit at 2yrs
- Increased severe esophagitis in concurrent arm

Concurrent is even more better!
Dose Escalation...

- Dose escalation - Standard fractions
- Altered Fractionation - Hyper, Hypo #
- SBRT
- Proton Therapy
**Original Contribution: Clinical**

**IMPACT OF TUMOR CONTROL ON SURVIVAL IN CARCINOMA OF THE LUNG TREATED WITH IRRADIATION**

**Carlos A. Perez, M.D.,**¹ **Madeleine Bauer, Ph.D.,**² **Sharon Edelstein, B.S.,**² **Brenda W. Gillespie, M.S.,**² **and Robert Birch, Ph.D.**³

**4000 Vs 5000 vs 6000 cGy**

The long-term results in tumor response, intrathoracic tumor control and survival are reported in patients with medically inoperable or unresectable non-oat cell and small cell carcinoma of the lung. In 376 patients with stages T1–3, NO-2 carcinoma of the lung tumors, accessioned to a Radiation Therapy Oncology Group (RTOG) randomized study to evaluate different doses of irradiation, a higher complete response rate (24%), intrathoracic tumor control (67%) and three year survival (15%) was observed with 6000 cGy, compared with lower doses of irradiation (4000 or 5000 cGy). Increased survival was noted in patients with complete tumor response. Three year survival in complete responders was 23%, in partial responders, 10%, and in patients with stable disease, 5%. Patients treated with 6000 cGy had an overall intrathoracic failure rate of 33% at 3 years, compared with 42% for those treated with 5000 cGy, 44% for patients receiving 4000 cGy with split course, and 52% for those treated with 4000 cGy continuous course ($p = 0.02$). Patients surviving 6 or 12 months exhibited a statistically significant increased
## Results

376 patients

<table>
<thead>
<tr>
<th></th>
<th>4000 cGy, continuous</th>
<th>4000 cGy, split course</th>
<th>5000 cGy, continuous</th>
<th>6000 cGy, continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR rate</td>
<td>48%</td>
<td></td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td>Local rec</td>
<td>58%</td>
<td>53%</td>
<td>49%</td>
<td>35%</td>
</tr>
<tr>
<td>3-yr OS rate</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>5-yr OS rate</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Carlos Parez et al, RTOG 7301, IJROBP 1986*
Dose escalation study based on vol of lung irradiated
Percentage of the lung volume which receives radiation doses of 20 Gy or more. (with subtraction of the vol involved by lung cancer - PTV)

The risk for radiation pneumonitis depends on V20

V20 = 22% risk for radiation pneumonitis is nearly zero. V 20 = 33% radiation induced pneumonitis is 10 -15% V20 of 35%, 40%  - radiation pneumonitis nearly 50%.
RTOG 9311: Trial Schema

179 pts

Phasel/II
Stage 1-3 unresectable
3DCRT, 2.15Gy fr

Group 1:
V20Gy<25%:
70.9Gy/33frs to 90.3Gy/42frs

Group 2:
V20Gy – 25-36%
70.9Gy/33frs to 77.4Gy/36frs

Group 3:
V20>37%
Closed early
RTOG 9311 : Conclusions

• RT dose was safely escalated using the 3D CRT
• 83.8 Gy for pts with V20 values of <25% Grp I,
• 77.4 Gy for pts with V20 values 25% - 36% Grp 2,
• The 90.3 Gy dose was too toxic (deaths 2 pts)
• Using fraction size of 2.15 Gy.
• Elective nodal failure occurred in <10 pts

Jafrey Badley IJRBP vol 61, No 2, 318-328, 2005
To identify the risk factors for developing Rad Pneumonitis

CLINICAL DOSE–VOLUME HISTOGRAM ANALYSIS FOR PNEUMONITIS AFTER 3D TREATMENT FOR NON-SMALL CELL LUNG CANCER (NSCLC)

MARY V. GRAHAM, M.D., JAMES A. PURDY, Ph.D., BAHMAN EMAMI, M.D., WILLIAM HARMS, B.S., WALTER BOSCH, D.Sc., MARY ANN LOCKETT, M.B.A., AND CARLOS A. PEREZ, M.D.

Radiation Oncology Center, Washington University Medical Center, St. Louis, MO

Purpose: To identify a clinically relevant and available parameter upon which to identify non-small cell lung cancer (NSCLC) patients at risk for pneumonitis when treated with three-dimensional (3D) radiation therapy. Methods and Materials: Between January 1991 and October 1995, 99 patients were treated definitively for inoperable NSCLC. Patients were selected for good performance status (96%) and absence of weight loss (82%). All patients had full 3D treatment planning (including total lung dose–volume histograms [DVHs]) prior to treatment delivery. The total lung DVH parameters were compared with the incidence and grade of pneumonitis after treatment.

Results: Univariate analysis revealed the percent of the total lung volume exceeding 20 Gy ($V_{20}$), the effective volume ($V_{eff}$) and the total lung volume mean dose, and location of the tumor primary (upper versus lower lobes) to be statistically significant relative to the development of ≥ Grade 2 pneumonitis. Multivariate analysis revealed the $V_{20}$ to be the single independent predictor of pneumonitis.

Conclusions: The $V_{20}$ from the total lung DVH is a useful parameter easily obtained from most 3D treatment planning systems. The $V_{20}$ may be useful in comparing competing treatment plans to evaluate the risk of pneumonitis for our individual patient treatment and may also be a useful parameter upon which to stratify patients or prospective dose escalation trials. © 1999 Elsevier Science Inc.
Factors influencing the Rad. pneumonitis

- Percent of the total Lung vol exceeding 20 Gy (V20)
- The total lung vol mean dose
- The location of the primary tumor (Upper vs Lower)

*Were statistically related to Grd II pneumonitis*

**Multivariate analysis : V20 the single most independent predictor of pneumonitis**
RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A RANDOMIZED PHASE III COMPARISON OF STANDARD-DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL +/- CETUXIMAB (IND #103444) IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

60 Gy vs 74 Gy
<table>
<thead>
<tr>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm A</strong></td>
<td></td>
</tr>
<tr>
<td>Concurrent chemotherapy: Carboplatin &amp; Paclitaxel</td>
<td>Consolidation chemotherapy: Carboplatin &amp; Paclitaxel</td>
</tr>
<tr>
<td>RT to 60 Gy, 5 x per week for 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th><strong>Arm D: Closed 6/17/11</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab Loading Dose:</td>
<td>Consolidation therapy:</td>
</tr>
<tr>
<td>Week 1, Day 1 then Concurrent chemotherapy, Carboplatin &amp; Paclitaxel, and Cetuximab</td>
<td>Cetuximab and Carboplatin &amp; Paclitaxel</td>
</tr>
<tr>
<td>RT to 74 Gy, 5 x per week for 7.5 weeks</td>
<td></td>
</tr>
</tbody>
</table>
## RTOG 0617: Interim Analysis

### 419 patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Dose (60 Gy)</th>
<th>High Dose (74 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med surv, months</td>
<td>28.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Estimated 18-mo OS%</td>
<td>66.9</td>
<td>53.9</td>
</tr>
<tr>
<td>Local rec rates, %</td>
<td>25.1</td>
<td>34.3</td>
</tr>
<tr>
<td>Distant rec rates, %</td>
<td>35.3</td>
<td>44.0</td>
</tr>
<tr>
<td>Treatment-related deaths, n</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

*Proc ASTRO 2011*
RTOG 0617 60 Gy vs 74 Gy

**Overall Survival**

- **18-Month Survival Rate**
  - Standard (60 Gy): 53.9%
  - High dose (74 Gy): 66.9%

- **Median Survival Time**
  - Standard: 28.7 months
  - High dose: 19.5 months

- **HR** = 1.56 (1.19, 2.06)  \( p = 0.0007 \)

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Patients at Risk (Standard)</th>
<th>Patients at Risk (High dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>213</td>
<td>206</td>
</tr>
<tr>
<td>3</td>
<td>207</td>
<td>197</td>
</tr>
<tr>
<td>6</td>
<td>190</td>
<td>178</td>
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<tr>
<td>9</td>
<td>177</td>
<td>159</td>
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<td>12</td>
<td>161</td>
<td>135</td>
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<tr>
<td>15</td>
<td>141</td>
<td>112</td>
</tr>
<tr>
<td>18</td>
<td>108</td>
<td>87</td>
</tr>
</tbody>
</table>
RTOG 0617: 60 Gy vs 74 Gy

• Higher radiation dose is not superior to standard dose

• Outcomes better with standard dose

• High dose arms closed for further accrual
RTOG 0617: 
Patient Reported QOL Outcomes

Meaningful decline in QOL

• 3mths after starting treatment in high dose arm
• Persistent decline in QOL at one year follow-up
Altered Fractionation…

- Hyper fractionation
- CHART
- Hypofractionation
A phase I/II trial of hyperfractionated (HFX) radiation therapy for non–small-cell carcinoma of the lung (NSCCL) was conducted by the Radiation Therapy Oncology Group (RTOG) between 1983 and 1987. Fractions of 1.2 Gy were administered twice daily with ≥ 4 hours between fractions. Patients were randomized to receive minimum total doses of 60.0, 64.8, and 69.6 Gy. After acceptable risks of acute and late effects were found, 74.4 Gy and 79.2 Gy arms were added, and the lowest total dose arms were closed. No significant differences in the risks of acute or late effects in normal tissues were found among the 848 patients analyzed in the five arms; risks of severe or life-threatening pneumonitis were 2.6% for 60.0 to 64.8 Gy, 5.7% for 69.6 to 74.4 Gy, and 8.1% for 79.2 Gy. Among 350 patients who had the same criteria as Cancer and Leukemia Group B (CALGB) protocol 84-33 (American Joint Committee on Cancer Staging [AJCCS], 1984, stage III; Karnofsky performance status [KPS] 70 to 100; < 6% weight loss), there was a dose response for survival: survival with 69.6 Gy (median, 13.0 months; 2 years, 29%) was significantly (P = .02) better than the lower total doses. There were no differences in survival among the three highest total-dose arms. Comparisons with results in similar patients treated with 60 Gy in 30 fractions of 2.0 Gy 5 days per week for 6 weeks suggest benefit from HFX radiation therapy with 69.6 Gy. Improvement in survival with HFX radiation therapy at 69.6 Gy total dose without increase in normal tissue effects, justifies phase III comparison with standard fractionation alone and combined with systemic chemotherapy in this common presentation of NSCCL. 

RTOG 83-11… Hyperfractionation trial

• 848 pts,
• Locally advanced unresectable.
• 1.2Gy BID
• trend toward prolonged survival between 60 Gy and 69.6 Gy
• No difference beyond!
  69.9 Gy and 74.4 Gy and 79.2 Gy

James D Cox et al, JCO - 8, 1543-1555
Hyper # vs CT + RT
Final Results of Phase III Trial in Regionally Advanced Unresectable Non-Small Cell Lung Cancer*

Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group

William Sause, MD, FCCP; Patricia Kolesar; Samuel Taylor IV, MD; David Johnson, MD; Robert Livingston, MD; Ritsuko Komaki, MD; Bahman Emami, MD; Walter Curran, Jr., MD; Roger Byhardt, MD; A. Rashid Dar, MD; and Andrew Turrisi III, MD

Study objectives: The purpose of this phase III clinical trial was to test whether chemotherapy followed by radiation therapy resulted in superior survival to either hyperfractionated radiation or standard radiation in surgically unresectable non-small cell lung cancer.

Design: Patients were prospectively randomized to 2 months of cisplatin, vinblastine chemotherapy followed by 60 Gy of radiation at 2.0 Gy per fraction or 1.2 Gy per fraction radiation delivered twice daily to a total dose of 69.6 Gy, or 2.0 Gy per fraction of radiation once daily to 60 Gy. Patients were enrolled from January 1989 through January 1992, and followed for a potential minimum period of 5 years.

Setting: This trial was an intergroup National Cancer Institute–funded trial within the Radiation Therapy Oncology Group, the Eastern Cooperative Oncology Group, and the Southwest Oncology Group.

Patients: Patients with surgically unresectable non-small cell lung cancer, clinical stage II, IIIA, and IIIB, were required to have a Karnofsky Performance Status of ≥ 70 and a weight loss of < 5% for 3 months before study entry. Four hundred ninety patients were registered on trial, of which 458 patients were eligible.

Conclusion: Overall survival was statistically superior for the patients receiving chemotherapy and radiation vs the other two arms of the study. The twice-daily radiation therapy arm, although better, was not statistically superior in survival for those patients receiving standard radiation. Median survival for standard radiation was 11.4 months; for chemotherapy and irradiation, 13.2 months; and for hyperfractionated irradiation, 12 months. The respective 5-year survivals were 5% for standard radiation therapy, 8% for chemotherapy followed by radiation therapy, and 6% for hyperfractionated irradiation.

(CHEST 2000; 117:358–364)
Phase III trial Locally advanced NSCLC
RTOG, ECOG & SWOG

448 pts

Three Arms

RT alone 60 Gy

Chemo + RT 60 Gy

Hyperfractionation 69.6 Gy

RT alone vs CT=>RT vs Hyper #

Phase III trial - RTOG, ECOG & SWOG

- Unresectable stg II, IIIA, IIIB, PS > 70
- 458 pts were eligible for analysis
- 1989 to 1992; 5 yrs follow up

60Gy@2Gy; Cisp + VBN => RT; Hyper #1.2 Gy BD 69.6Gy

Phase III trial
RTOG, ECOG & SWOG

<table>
<thead>
<tr>
<th></th>
<th>RT alone</th>
<th>CT =&gt; RT</th>
<th>Hyper fr 69.6Gy</th>
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</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>11.4%</td>
<td>13.2%</td>
<td>12%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>5%</td>
<td>8%</td>
<td>6%</td>
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</tbody>
</table>

Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial

Michele Saunders, Stanley Dische, Ann Barrett, Angela Harvey, Della Gibson, Mahesh Parmar, on behalf of the CHART Steering Committee

Summary

Background Human tumour cells can proliferate rapidly, and giving radiotherapy in many small fractions may reduce by the addition of cytotoxic chemotherapy, and by hypoxic cell radiosensitisation.

Lancet 1997; 350: 161–65
Continuous hyper-fractionated accelerated radiotherapy

- Overcome proliferation of tumor cells during conventional RT
- Minimize long-term normal tissue toxicity by the use of multiple small #

563 patients - 13 centres

60 Gy/30# /6 weeks  54 Gy/36# - 1.5 Gy 3 tid daily in 12 consecutive days

Saunders M et al. Radiotherapy and Oncology: 1999
<table>
<thead>
<tr>
<th>Patient characteristics</th>
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</thead>
<tbody>
<tr>
<td>Total patients</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Sex</td>
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<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Age</td>
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<td>31–40</td>
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<td>41–50</td>
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<td>51–60</td>
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<td>71+</td>
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<td>IB</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td>IIIA</td>
</tr>
<tr>
<td>IIIB</td>
</tr>
<tr>
<td>Unknown</td>
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Saunders M et al.  Radiotherapy and Oncology:1999
## Results

### Results of statistical analysis of primary endpoints for all patients

<table>
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<tr>
<th>Endpoints</th>
<th>2-Year</th>
<th></th>
<th></th>
<th>3-Year</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conventional (%)</td>
<td>CHART</td>
<td>Difference</td>
<td>95% C.I.</td>
<td>Conventional</td>
<td>CHART</td>
<td>Difference</td>
<td>95% C.I.</td>
<td>Hazard ratio</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>All patients</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>21</td>
<td>30</td>
<td>9</td>
<td>2.16</td>
<td>13</td>
<td>20</td>
<td>7</td>
<td>2.13</td>
<td>0.78</td>
<td>0.65–0.94</td>
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</tr>
<tr>
<td>Local tumour control</td>
<td>16</td>
<td>23</td>
<td>7</td>
<td>1.15</td>
<td>12</td>
<td>17</td>
<td>5</td>
<td>1.14</td>
<td>0.86</td>
<td>0.70–1.06</td>
<td></td>
</tr>
<tr>
<td>Disease-free interval</td>
<td>13</td>
<td>18</td>
<td>5</td>
<td>−2.11</td>
<td>9</td>
<td>12</td>
<td>3</td>
<td>−1.10</td>
<td>0.79</td>
<td>0.63–0.98</td>
<td></td>
</tr>
<tr>
<td>Metastasis-free interval</td>
<td>44</td>
<td>48</td>
<td>4</td>
<td>−5.13</td>
<td>33</td>
<td>40</td>
<td>7</td>
<td>−4.14</td>
<td>0.89</td>
<td>0.69–1.14</td>
<td></td>
</tr>
</tbody>
</table>

*Saunders M et al. Radiotherapy and Oncology:1999*
CHART : Morbidity

**Early : 3 months**

<table>
<thead>
<tr>
<th></th>
<th>Conv.</th>
<th>CHART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical RP</td>
<td>19 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Radiological RP</td>
<td>65 %</td>
<td>56 %</td>
</tr>
</tbody>
</table>

**Late : >6 months**

<table>
<thead>
<tr>
<th>Radiation Pneumonitis</th>
<th>Dysphagia @ 2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 2 yrs - ↑ CHART</td>
<td>Conv. - 5 %</td>
</tr>
<tr>
<td>After 2 yrs - ↑ Conv.</td>
<td>CHART – 7 %</td>
</tr>
</tbody>
</table>

Saunders M et al. Radiotherapy and Oncology:1999
**CHART** is superior to conventional RT in achieving

- Local tumor control and
- Reduction in distant mets and
- Long term Survival

_Saunders M et al. Radiotherapy and Oncology:1999_
Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non–Small-Cell Lung Cancer

Donald M. Cannon, Minesh P. Mehta, Jarrod B. Adkison, Deepak Khuntia, Anne M. Traynor, Wolfgang A. Tomé, Richard J. Chappell, Ranjini Tolakanahalli, Pranshu Mohindra, Søren M. Bentzen, and George M. Cannon

- Prospective phase 1 trial
- 79 pts NSCLC, all stages
- IMRT over 25 days, 1 fr/day
- 95% pts with Tomotherapy

Dose Levels:

- 57Gy @ 2.28Gy fr
- 63.2Gy @ 2.53Gy fr
- 69.25Gy @ 2.77Gy fr
- 75Gy @ 3Gy fr
- 80.5Gy @ 3.22Gy fr
- 85.5Gy @ 3.4Gy fr
Results
No grade 3 pneumonitis was observed and an MTD for acute toxicity was not identified during patient accrual. However, with a longer follow-up period, grade 4 to 5 toxicity occurred in six patients and was correlated with total dose ($P = .004$). An MTD was identified at 63.25 Gy in 25 fractions. Late grade 4 to 5 toxicities were attributable to damage to central and perihilar structures and correlated with dose to the proximal bronchial tree.

Conclusion
Although this dose-escalation model limited the rates of clinically significant pneumonitis, dose-limiting toxicity occurred and was dominated by late radiation toxicity involving central and perihilar structures. The identified dose-response for damage to the proximal bronchial tree warrants caution in future dose-intensification protocols, especially when using hypofractionation.

Median f/u 17mths
Median OS 16mths
3yr OS 29%
No difference in local control

Median tolerance dose identified as 63.25 in 25 fr @ 253 cGy/fr
Stereotactic Body Radiation Therapy

- **Stereotactic**
  - precise positioning of the target volume in 3 dimensions.

- High dose per fraction.

- Delivery techniques
  - arcs, static fields, protons

- Technology
  - Novalis TX, Tomotherapy, Cyberknife, Proton
Stereotactic Body Radiotherapy

Radiobiology

- **High ablative dose**
  - SRS = single Fx  SBRT = 2-5 Fx
  - Overwhelms repair/repopulation mechanisms
  - BED important? (>100)

- **Short time (1-5 treatments)**

- **Tight targets and rapid dose fall-off**
  - Damages everything in high dose area
  - Critical to limit toxicity
  - Need target tracking or gating system
Clinical Investigation: Thoracic Cancer

Stereotactic Body Radiation Therapy Can Be Used Safely to Boost Residual Disease in Locally Advanced Non-Small Cell Lung Cancer: A Prospective Study

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Boost by SBRT is feasible with no increased toxicity (Rad Pneumonitis)

to the residual primary tumor, consisting of 10 Gy × 2 fractions (20 Gy total) for peripheral tumors, and 6.5 Gy × 3 fractions (19.5 Gy total) for mediastinal tumors using the Radiation Therapy Oncology Group protocol 0813 definitions. The primary endpoint was the development of grade ≥3 radiation pneumonitis (RP).

Results: After a median follow-up of 13 months, 4 patients developed acute grade 3 RP, and 1 (2.9%) developed late and persistent grade 3 RP. No patients developed grade 4 or 5 RP. Mean lung dose, V2.5, V5, V10, and V20 values were calculated for the SBRT boost, and none were found to significantly predict for RP. Only advancing age (P = .0147), previous smoking status (P = .0505), and high CRT mean lung dose (P = .0295) were significantly associated with RP development. At the time of analysis, the actuarial local control rate at the primary tumor site was 82.9%, with only 6 patients demonstrating recurrence.

Conclusions: Linear accelerator-based SBRT for dose escalation of limited residual NSCLC after definitive CRT was feasible and did not increase the risk for toxicity above that for standard radiation therapy. © 2013 Elsevier Inc.
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Proton Beam Therapy

Unique depth dose compared to photons, electrons

(Bragg Peak Effect)
Clinical Potential of Proton Therapy:

- Reduced side effects
- Increase tumor control probability through “dose escalation”?
- Facilitate combined modality therapy
- Re-treatment is possible
CLINICAL INVESTIGATION

PROTON BEAM THERAPY OF STAGE II AND III NON–SMALL-CELL LUNG CANCER

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35 patients, Median age 70.3 yrs
Median Proton dose 78.3 Gy
Local PFS 93.3% @ 1 yr, 65.9% @ 2 yrs
Overall survival 81.8% @ 1 yr, 58.9% @ 2 yrs
Toxicity Grade I 42.9% Grd II 17.1%

a median observation period of 16.9 months. Four patients (11.4%) developed local recurrence, 13 (37.1%) developed regional recurrence, and 7 (20.0%) developed distant metastases. The progression-free survival rate for Stage II-III patients was 59.6% at 1 year and 29.2% at 2 years. The overall survival rate of Stage II-III patients was 81.8% at 1 year and 58.9% at 2 years. Grade 3 or greater toxicity was not observed. A total of 15 patients (42.9%) developed Grade I and 6 (17.1%) Grade 2 toxicity.
Conclusion: PBT for Stage II-III non–small-cell lung cancer without chemotherapy resulted in good local control and low toxicity. PBT has a definite role in the treatment of patients with Stage II-III non–small-cell lung cancer who are unsuitable for surgery or chemotherapy.
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Conclusions

• Dose Escalation appears to be safe, but with strict quality control and accuracy

• What dose?
  • Stnd # : 60Gy/30#,  
  • Hyper# : 68.6Gy/1.2Gy BID,  
  • CHART: 54 Gy/36#, 1.5Gy 3 tid 12d  
  • Hypo: 63.25 in 25 fr @ 253 cGy/fr

• Boost by SBRT, Proton is feasible

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Take Home Message

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Continued..
Conclusions

- Further Dose escalation with less toxicity - Whether it is going to improve surv?
- Long term follow-up imperative
- Results of RTOG 0617 surprising! needs to be thoroughly analyzed!
- CTRT more accepted than HF
Way Forward..

To improve outcome with RT

- Dose intensification
  - with modern techniques, altered #, SBRT, Proton

- Redefining dose constraints V5, V20?

- Integration of CT with RT

- Appropriate pt. selection
Thank you

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