IMRT for Lung Cancer

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Washington University and
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## IMRT Issues in Lung Cancer

<table>
<thead>
<tr>
<th><strong>IMRT advantages</strong></th>
<th><strong>IMRT disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformal high dose volumes</td>
<td>Larger lower dose volumes (i.e. V5)</td>
</tr>
<tr>
<td>Reduced normal lung dose</td>
<td>More sensitive to tumor motion</td>
</tr>
<tr>
<td>Reduced heart dose</td>
<td>Sharper dose fall off</td>
</tr>
<tr>
<td>Reduced esophagus dose</td>
<td></td>
</tr>
</tbody>
</table>
Scientific issues relating to lung cancer

1. what was the PRINCIPAL dose-limiting toxicity that precluded giving adequate radiation doses to the cancer with CRT?
Radiation Dose in Lung Cancer?

1. How can we push the RT Dose up w/o increasing Toxicity?
Effects of Esophagitis

- Treatment Interruptions; shortened survival
- Failure to Complete XRT
- Failure to Complete Systemic Therapy
- Inability to Advance the Field with new Combinations!
- Dehydration
- Malnutrition
- Infection
- Decreased QOL

Treatment Interruptions; shortened survival

Failure to Complete XRT

Failure to Complete Systemic Therapy

Inability to Advance the Field with new Combinations!

Dehydration

Malnutrition

Infection

Decreased QOL
<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>102</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>227</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>201</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>585</td>
<td>100</td>
</tr>
</tbody>
</table>

Werner-Wasik M et al.
Figure 1: Time Courses of Maximum Esophagitis and Grade $\geq 3$ Esophagitis

Partial Sparing of the Esophageal Circumference: IMRT Approach

No need for a randomized trial to prove advanced technology is better and CRT in reducing Esophagitis! The real issue is “Local Tumor Control”!
Time Course of \textgreater Grade 3 Late Pneumonitis
Radiation Pneumonitis after Concurrent Chemoradiation for Lung Cancer:

Fig. 1. Relation between $V_{20}$ and RP grade.

KAYOKO TSUJINO, Hyogo Medical Center

Radiation Pneumonitis after Concurrent Chemoradiation for Lung Cancer

\[ V_{20} \geq 25\% \]

\[ V_{20} \leq 25\% \]

P < .0001

Cumulative incidence

Follow-up period (months)
3D Vs IMRT

Dosimetric Comparision between 3D Vs IMRT for NSCLC

Table 3. Summary of the total lung $V_5$, $V_{10}$, and $V_{20}$, $V_{\text{eff}}$, mean dose, and integral dose for 3D-CRT and IMRT plans

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3D-CRT</th>
<th>IMRT</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung $V_5$ (%)</td>
<td>52 (28–86)</td>
<td>59 (25–78)</td>
<td>0.424</td>
</tr>
<tr>
<td>Total lung $V_{10}$ (%)</td>
<td>45 (22–64)</td>
<td>38 (18–59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung $V_{20}$ (%)</td>
<td>35 (17–55)</td>
<td>25 (13–43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung $V_{\text{eff}}$ (%)</td>
<td>71 (33–101)</td>
<td>58 (28–95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung mean dose (Gy)</td>
<td>19 (10–29)</td>
<td>17 (9–27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung integral dose (J)</td>
<td>19 (5–36)</td>
<td>16 (5–34)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
3DCRT vs. 4DCT/IMRT in NSCLC
Longitudinal study

- N=409 patients treated between 1996 – 2006 at MD Anderson (318 and 91 pts)
- All patients received 63 Gy definitive RT
- In mid 2004, they switched to 4DCT/IMRT treatment planning and delivery
- Imbalance of PET/CT (49% of 3D and 82% of 4D)
- Mean f/u:
  - 3DCRT = 2.1 years
  - 4DCT/IMRT = 1.3 years

Liao et al. IJROBP 2009
Liao et al. IJROBP 2009

(a) Change in technology of treatment delivery

Proportion free of LRP

Freedom from local progression

CT/3DCRT

4DCT/IMRT

Years after start of RT

(b) Change in technology of treatment delivery

Proportion free of DM

Freedom from DM

CT/3DCRT

4DCT/IMRT

Years after start of RT

(c) Change in technology of treatment delivery

Overall survival

Overall Survival

CT/3DCRT

4DCT/IMRT

Years after start of RT

(d) Change in technology of treatment delivery

Freedom from grade 3 or higher radiation pneumonitis

Freedom from pneumonitis

CT/3DCRT

4DCT/IMRT

Years after start of RT
### RTOG 0617 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>91.2%</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

Overall Survival (%)

Months since Randomization

0 3 6 9 12

*One-sided p-value, left tail

Patients at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>60 Gy</th>
<th>74 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>213</td>
<td>204</td>
</tr>
<tr>
<td>Dead</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>HR</td>
<td>1.45</td>
<td>1.45</td>
</tr>
<tr>
<td>(1.02, 2.05)</td>
<td>1.02, 2.05</td>
<td></td>
</tr>
<tr>
<td>p*</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

HR = 1.45 (1.02, 2.05) p* = 0.02
## Cox Univariate Analysis for OS

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>Other Covariates</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous</td>
<td></td>
<td>1.02 (1.00, 1.04)</td>
<td>0.027</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam vs Squam</td>
<td></td>
<td>1.55 (1.10, 2.20)</td>
<td>0.013</td>
</tr>
<tr>
<td>Gender</td>
<td>Male v Female</td>
<td></td>
<td>0.60 (0.41, 0.87)</td>
<td>0.007</td>
</tr>
<tr>
<td>RT Technique</td>
<td>3D v IMRT</td>
<td></td>
<td>0.93 (0.65, 1.32)</td>
<td>0.68</td>
</tr>
<tr>
<td>PET Staging</td>
<td>No v yes</td>
<td></td>
<td>0.93 (0.65, 1.32)</td>
<td>0.68</td>
</tr>
<tr>
<td>Max Related Tox</td>
<td>&lt;grade 3 vs ≥grade 3</td>
<td></td>
<td>1.13 (0.79, 1.78)</td>
<td>0.42</td>
</tr>
<tr>
<td>Overall RT Review</td>
<td>Per protocol vs not</td>
<td></td>
<td>1.33 (0.84, 2.11)</td>
<td>0.22</td>
</tr>
<tr>
<td>GTV</td>
<td>Continuous</td>
<td></td>
<td>1.002 (1.001, 1.004)</td>
<td>0.005</td>
</tr>
<tr>
<td>PTV</td>
<td>Continuous</td>
<td></td>
<td>1.001 (1.000, 1.002)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean Margin to PTV</td>
<td>Continuous</td>
<td></td>
<td>0.95 (0.89, 1.02)</td>
<td>0.16</td>
</tr>
<tr>
<td>Lung V5</td>
<td>Continuous</td>
<td></td>
<td>1.012 (1.000, 1.024)</td>
<td>0.0537</td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td></td>
<td>1.013 (1.006, 1.019)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Multivariate Cox Model
Backwards Selection

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation dose</td>
<td>60 Gy v 74 Gy</td>
<td>1.55 (1.07, 2.23)</td>
<td>0.020</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam v Squam</td>
<td>1.37 (0.94, 1.98)</td>
<td>0.097</td>
</tr>
<tr>
<td>GTV (ITV if GTV unavailable)</td>
<td>Continuous</td>
<td>1.002 (1.000, 1.003)</td>
<td>0.034</td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>1.010 (1.004, 1.017)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Exit criteria = \( p > 0.10 \); radiation dose and histology forced to remain.
Covariates dropped from the model were: gender, age, lung V5.
Clinical, dosimetric, and spatial factors to predict local control and toxicity in non-small cell lung cancer (2 datasets)

Washington University Team
Joseph O. Deasy - MSKCC
Andrew J. Hope – PMH Toronto
Patricia E. Lindsay - PMH
Issam El Naqa – McGill University
Jeffrey D. Bradley
1991-2000 Study population

- 228 patients with non-small cell lung cancer (NSCLC) treated definitively with radiation +/- chemotherapy

- All have:
  - 3D treatment plan archives available
  - Heterogeneity corrected dose distributions
  - Minimum six months follow-up post-treatment unless patient developed pneumonitis
Computational Environment for Radiotherapy Research (CERR)

- Custom software extracts dose, volume, and structure data automatically
- http://radium.wustl.edu/cerr
Tumor position vs. failure

**GTV-cord separation (less separation = more failures)**

Univariate Spearman’s rank correlation \((Rs) = 0.45\)
### WU Data. Parameters for local control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rs (Spearman)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV/cord separation</td>
<td>0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior-posterior tumor position</td>
<td>-0.38</td>
<td>0.003</td>
</tr>
<tr>
<td>GTV volume</td>
<td>-0.37</td>
<td>0.004</td>
</tr>
<tr>
<td>GTV V75</td>
<td>0.28</td>
<td>0.04</td>
</tr>
<tr>
<td>Prescription dose</td>
<td>0.27</td>
<td>0.04</td>
</tr>
<tr>
<td>Age</td>
<td>0.27</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Radiation Pneumonitis

Does IMRT help reduce risk?
WU Data: Tumor location associated with risk of pneumonitis

Superior 25%: 15.9% (7/44)

“Middle” 25%: 30.2% (42/139)

Inferior 50%: 44.4% (20/45)

Right Lung: 47/137 (34.3%)

Left Lung: 22/91 (24.2%)

Hope, Deasy, Bradley et al.
Pneumonitis by location

RTOG 9311

WU (n = 228)

WU (n = 129)

4% (1/24)

15% (11/74)

26% (8/31)

9% (9/101)

25% (25/100)

35% (35/100)

p = 0.474

p = 0.576

p = 0.945

p = 0.025

p = 0.004

p = 0.209
WU/RTOG 9311: Pneumonitis Data
Multi-metric Modeling

Percentage frequency

Models

[MLD, COM-SI]
[V65, COM-SI]
[D25, MLD]
[MLD, PreTxChemo]
[D35, V70]
[D35, COM-AP]
[V25, V75]
[MLD, COM-LAT]
Figure 1. This nomogram embodies the derived equation for the risk of pneumonitis. As shown, it is used by placing a straight-edge across all axes given the planned normal lung mean dose and the estimated center of the largest high-dose region (1 = most superior lung position, 0 = most inferior lung position).
IMRT 3DCRT
WU RP Risk Calculator

**IMRT**

**Patient Name:** ANDERSON, ARTHUR,  
**Plan:** IMRT  
**Trial:** NEW PLAN FINAL  
**Date:** 4/18/2008  

Most Superior Slice of RT LUNG: -52.25  
Most Inferior Slice of RT LUNG: -26.1501  
Lung Length: 26.0999  
Slice with GTV center on it: -34.40005  
GTV position: 0.32  
(0=inferior, 1=superior)  
Mean total lung-gtv Dose (in Gy): 13.48 Gy  

**RP Risk:** 0.298

**Desired risk level (RP):** 0.2  
**Max MLD to achieve this:** 8.81 Gy

---

**3DCRT**

**Patient Name:** ANDERSON, ARTHUR,  
**Plan:** IMRT  
**Trial:** 3D  
**Date:** 4/18/2008  

Most Superior Slice of RT LUNG: -52.25  
Most Inferior Slice of RT LUNG: -26.1501  
Lung Length: 26.0999  
Slice with GTV center on it: -34.40005  
GTV position: 0.32  
(0=inferior, 1=superior)  
Mean total lung-gtv Dose (in Gy): 16.95 Gy  

**RP Risk:** 0.386

**Desired risk level (RP):** 0.2  
**Max MLD to achieve this:** 8.81 Gy
2001-2010 Data
Stage III NSCLC treated with CRT

Huang, Deasy, Bradley et al
Does Heart Dose Matter?

Spearman Correlation with RP

Heart
Lung

x(%) in Dx
Does Heart Dose Matter?

Spearman Correlation with RP

- Heart
- Lung

x (Gy) in Vx

0 20 40 60 80 100
Huang et al., Figure 11.
Summary

- IMRT reduces lung and heart normal tissue high dose volumes
- IMRT facilitates avoidance of critical structures (i.e. spine)
- RTOG 0617 shows no difference in toxicity, tumor control, or survival outcomes when comparing 3D vs IMRT delivery method
- Heart dose may be more important than lung dose to predict pneumonitis! More work needs to be done