Innovations in Radiation Therapy, Including SBRT, IMRT and Cancer Proton Beam Therapy

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Primary Goals: Radiation Therapy

- Control the local disease
- Minimize side effects
When you think of Radiation Therapy...

• Nobody thinks about radiotherapy
  - Common, but not sexy
    Surgery is sexy: “I can get it all!”
    Surgery cures (“I got it all!”)
    Radiotherapy **mops up** after surgery
    Chemo/Targeted Therapy is sexy
  - Something to do in a basement

• Radiotherapy is/was **SLOW**
  - Takes weeks and months to complete a course
    Even for small tumors
Why is radiotherapy so slow (and boring)?

- **CUMULATIVE DAMAGE**

- Understand that **both** normal tissue than tumor typically get irradiated to high dose
  - Often normal tissue volume irradiated is bigger than the tumor (intentionally or not)

- **Tumors accumulate damage faster than normal tissues**
  
  IF you give the radiotherapy very slowly
  Damage in the tumor > damage in the normal tissue
Sexy Radiotherapy?

- There was a time…
  - Radiotherapy was fast
  - Radiotherapy was exciting
1895 – A New Kind of Ray

Wilhelm Röntgen

1897 – Radioactive Substances

Marie Curie
1914 – Erlanger Method of Hypofractionation using Teletherapy
1921 – The Sky Fell

LATE radiation toxicity: ulceration, denervation, devasculization, stenosis, fibrosis, devitalization
Why did the sky fall?

- **Technology problems**
  - Very low energy beams (most dose into the skin)
  - Crude guidance
  - Poor understanding of radiation interactions (unable to represent dose)

- **Biology problems**
  - As with tumor, normal tissues poorly tolerant of radiation therapy

- **Clinical problems**
  - Crude understanding of tumor location
  - Normal tissues extensively irradiated
Radiotherapy in early 1900

- Tumor control was NOT the problem
  - Amazing tumor shrinkage (response) and eradication
  - General feeling that cancer was finally “cured”

- Toxicity was the problem
  - Poor understanding of normal tissue response
  - Very crude technology with little ability to “spare”

- Eventually Radiation Therapy was considered
  - “Appalling aberration” and “Barbaric”
  - Patients referred to as “victims”
Next 90 years...

- Protracted radiation delivery dominates
  - 30+ daily treatments over 6+ weeks renamed “conventionally fractionated radiotherapy”

- Radiotherapy is used on a wide scale
  - Clinics set up to deliver many daily treatments
  - Reimbursement ($$) encourages fractionation
Technological Breakthroughs
More Recent Technological Advances

- **IMRT:**
  - Intensity Modulated Radiation Therapy
  - Dose painting with x-rays

- **4DCT**
  - Accounting for tumor motion during breathing
  - X, Y, Z, and time

- **IGRT:**
  - Image-guided Radiation Therapy
  - Daily imaging on the treatment machine
3-D RT Vs IMRT radiation therapy
3D Vs IMRT

[CT images showing 3D and IMRT treatment plans for a patient's chest and larynx, with arrows indicating differences in coverage and dose distribution.]
### Comparison of 2D VS 3d VS IMRT in Post Operative RT for NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Heart V30(%)</th>
<th>Lung V20(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>3DCRT</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>IMRT</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

Rosenzweig et. al. (IASLC 2005)
IMRT
THE RADIATION BOOM
Radiation Offers New Cures, and Ways to Do Harm
By WALT BOGDANICH
Published: January 23, 2010

As Technology Surges, Radiation Safeguards Lag
By WALT BOGDANICH
Published: January 26, 2010
RTOG 0617: IMRT allowed (1st NCI trial)

NCI Guidelines -

- Protocol must specify patient and tumor immobilization and localization
- Tumor motion should be ≤5 mm using spirometry, abd compression, 4DCT or inhalation/exhalation techniques
- Protocol provides rationale for IM and SM components of PTV margin
- Heterogeneity corrected doses
- *Institutional credentialing and central QA*
What About Protons?
Relative Dose

Depth of tumor

3D vs Proton for NSCLC

Photon 3-DCRT

Proton

JOE Y. CHANG,
What About Protons?

- Obvious issues of cost and access
- Currently heading down the same path as IMRT

Conventionally fractionated radiotherapy (Lot of Fractions = Lot of $)  
Because of IMRT, world is suspicious. Outcomes will be scrutinized.

- BUT, protons and charged particles can do more
  - High quality radiation that could be used for SBRT and hypofractionated IGRT

**ECOG 4599:**  
Overall Survival by Treatment

<table>
<thead>
<tr>
<th>Month</th>
<th>PC, %</th>
<th>PCB, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>43.7</td>
<td>51.9</td>
</tr>
<tr>
<td>24</td>
<td>16.9</td>
<td>22.1</td>
</tr>
</tbody>
</table>

HR 0.77 (0.65-0.93), P<0.007

Medians: 10.2, 12.5
What About Carbons?
Why 12C over conventional photon or proton delivery systems?

- Minimal relative dose to tissues either in front of, or behind tumors (1)
- Greater biological dose delivered (2)
- Less spread of Bragg Peak for more precise deposition (3)
Why 12C over conventional photon or proton delivery systems?

**RBE**: Relative Biological Effect

**Figure 2.** The structure of a proton and a carbon track in nanometre resolution are compared with a schematic representation of a DNA molecule. The higher density of the secondary electrons produced by carbon ions, creates a large amount of clustered DNA damage.
## Dose-Fractionation in Carbon ion RT at NIRS

<table>
<thead>
<tr>
<th>Site</th>
<th>Dose-Fractionation (GyE/fr/week)</th>
<th>Gy/fr</th>
<th>BED (α/β=10)</th>
<th>BED (α/β=2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H &amp; N:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC, MM, etc.</td>
<td>57.6/16/4</td>
<td>3.6</td>
<td>78.3</td>
<td>140.5</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>70.4/16/4</td>
<td>4.4</td>
<td>101.4</td>
<td>194.3</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull Base</td>
<td>58.0/20/5</td>
<td>2.9</td>
<td>74.8</td>
<td>125.3</td>
</tr>
<tr>
<td><strong>NSCLC:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Stage I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>90.0/18/5</td>
<td>5.0</td>
<td>135.0</td>
<td>270.0</td>
</tr>
<tr>
<td></td>
<td>72.0/9/3</td>
<td>8.0</td>
<td>129.6</td>
<td>302.4</td>
</tr>
<tr>
<td></td>
<td>60.0/4/1</td>
<td>15.0</td>
<td>150.0</td>
<td>420.0</td>
</tr>
<tr>
<td>Hilar</td>
<td>32.0/1/1 dy</td>
<td>36.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>57.6/9/3</td>
<td>6.4</td>
<td>94.5</td>
<td>205.1</td>
</tr>
<tr>
<td><strong>Liver:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>79.5/15/5</td>
<td>5.3</td>
<td>121.6</td>
<td>248.0</td>
</tr>
<tr>
<td></td>
<td>69.6/12/3</td>
<td>5.8</td>
<td>110.0</td>
<td>231.1</td>
</tr>
<tr>
<td></td>
<td>58.0/8/2</td>
<td>7.2</td>
<td>100.1</td>
<td>226.2</td>
</tr>
<tr>
<td></td>
<td>52.8/4/2</td>
<td>13.2</td>
<td>122.5</td>
<td>331.6</td>
</tr>
<tr>
<td></td>
<td>33.6/2/2 dys</td>
<td>16.8</td>
<td>90.0</td>
<td>259.4</td>
</tr>
<tr>
<td><strong>Bone/soft tissue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.4/16/4</td>
<td>4.4</td>
<td>101.4</td>
<td>194.3</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>66.0/20/5</td>
<td>3.3</td>
<td>87.8</td>
<td>153.1</td>
</tr>
<tr>
<td><strong>Pancreas:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op.</td>
<td>38.4/12/3</td>
<td>3.2</td>
<td>50.7</td>
<td>87.6</td>
</tr>
<tr>
<td>Radical</td>
<td>30.0/8/2</td>
<td>3.8</td>
<td>41.3</td>
<td>75.0</td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73.6/16/4</td>
<td>4.6</td>
<td>107.5</td>
<td>209.0</td>
</tr>
</tbody>
</table>
But, Real Question?

- Can the benefits of Advanced Radiation Technology be recognized NSCLC patients?
  - YES
  - EVIDENCE
  - SBRT
    - RTOG 0236 and many other publications
• First North American cooperative group trial using SBRT

• Non-small cell lung cancer - biopsy proven

• T1, T2 ($\leq 5$ cm) and T3 (chest wall only, $\leq 5$ cm), N0, M0

• Medical problems precluding surgery (e.g. emphysema, heart disease, diabetes)

• No other planned therapy
Stereotactic Body Radiation Therapy

RTOG 0236: 2000 cGy X 3
RTOG 0236: Local Control

36 month local control = 98% (CI: 84-100%)

1 failure within PTV, 0 within 1 cm of PTV

Patients at Risk | 55 | 54 | 47 | 46 | 39 | 34 | 23

Fail: 1
Total: 55
RTOG: 0236 Disseminated Recurrence

- 6 patients (11%) disseminated within 1 year of Rx

36 month disseminated recurrence = 22% (CI: 12-38%)
Overall Survival

36 month overall survival = 56% (CI: 42-68%)

Dead: 26
Total: 55
MST: 48.1
(95% CI): (29.6, not reached)
## Local Control with SBRT in Inoperable Stage I/II

<table>
<thead>
<tr>
<th>Series</th>
<th>Dose</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America/Europe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timmerman, 2006</td>
<td>20-22 Gy X 3</td>
<td>95% (2+ years)</td>
</tr>
<tr>
<td>Bauman, 2006</td>
<td>15 Gy X 3</td>
<td>80% (3 years)</td>
</tr>
<tr>
<td>Fritz, 2006</td>
<td>30 Gy X 1</td>
<td>80% (3 years)</td>
</tr>
<tr>
<td>Nyman, 2006</td>
<td>15 Gy X 3</td>
<td>80% (crude)</td>
</tr>
<tr>
<td>Zimmerman, 2005</td>
<td>12.5 Gy X 3</td>
<td>87% (3 years)</td>
</tr>
<tr>
<td>Timmerman, 2003</td>
<td>18-24 Gy X 3</td>
<td>90% (2 years)</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xia, 2006</td>
<td>5 Gy X 10</td>
<td>95% (3 years)</td>
</tr>
<tr>
<td>Hara, 2006</td>
<td>30-34 Gy X 1</td>
<td>80% (3 years)</td>
</tr>
<tr>
<td>Nagata, 2005</td>
<td>12 Gy X 4</td>
<td>94% (3 years)</td>
</tr>
</tbody>
</table>
Legitimate Alternative to Lobectomy for Stage I NSCLC

• Requirements:
Legitimate Alternative to Lobectomy for Stage I NSCLC

- Requirements:
  - Local control 90% or more at 5 years (actuarial)
  - Survival 60% - 80% at 5 years (actuarial)
  - Grade III or higher toxicity <15 - 20%
  - Ideally less invasive than thoracotomy
  - Ideally more convenient
  - Ideally less costly
  - All proven by prospective testing

Lung Cancer Study Group
Ginsberg, et al.

Ann Thorac Surg 1995;60:615
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RTOG 0618

- Small pilot study in operable patients:
- Build on experience, guidelines, and QA program from RTOG 0236 using 18-20 Gy X 3 fractions (54-60 Gy) given in about one week
- Primary objective = 2 year local control, secondary objectives survival and toxicity
- Target local control = 90% (similar to lobectomy) justifying treatment dose.
- Accrual Completed in 5/2010
“High Risk” Operable AKA “Marginally” Operable Patients randomized to SABR will receive 18Gy in three fractions, for a total dose of 54Gy. Brachytherapy is allowed with SR.
Stereotactic Body Radiotherapy

Outpatient

20-60 Minutes Per Treatment

Entire course of Rx in 1-2 weeks

No Sedation or Anesthesia (painless)

1-5 Treatments qd or qod

Immediate Return To Activities
Barriers/Threats to Implementation

- Training radiation oncologists to be “experts” in advanced radiation technology and techniques
- Need effective systemic treatments
- “Because we can do it” rationale confounds legitimacy
- Peer scrutiny should require that the treatment does some tangible good for the patient (i.e., conduct prospective trials)
- Ideally, protocol should test hypotheses aimed at improving cure, quality of life, or cost of therapy (i.e., not trials simply enrolling patients with lung cancer expecting P value to be statically significant)