The Promise of Protons in Cancer Therapy

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American Association of Physics Teachers
Jacksonville, Florida  January 12, 2011
A neutron walks into a bar and asks: “Hey, how much for a beer?”
A neutron walks into a bar and asks: "Hey, how much for a beer?"
The bartender says, "For you, no charge."

source: http://www.jokebuddha.com/Proton#ixzz1Al50LTYf
A proton walks into a bar, sits down and orders a drink. After finishing the drink, the bartender says, "Would you like another drink?".
A proton walks into a bar, sits down and orders a drink. After finishing the drink, the bartender says, "Would you like another drink?".

The proton says, "No, thanks."
A proton walks into a bar, sits down and orders a drink. After finishing the drink, the bartender says, "Would you like another drink?"

The proton says, "No, thanks."

A few minutes later, the bartender approaches the proton again and says, "Are you sure you don't want another drink?"
A proton walks into a bar, sits down and orders a drink. After finishing the drink, the bartender says, "Would you like another drink?".

The proton says, "No, thanks."

A few minutes later, the bartender approaches the proton again and says, "Are you sure you don't want another drink?"

To which the proton says, "I'm positive." (Protons know when to stop!!)

source: http://www.jokebuddha.com/Proton#ixzz1Al50LTyf
Objectives

• Cancer

• Radiation Therapy Basics
  – Mechanism of Action
  – Non-specific Effects
  – Therapeutic Ratio
  – Dose distribution

• The Promise of Protons

• The University of Florida Project

• Clinical Applications
Cancer
The Cancer Problem

• Cancer affects 1 in every 3 to 4 Americans
• 2nd leading cause of death in US
• Affects men, women, children, all races and ages
• Most cancers arise from a single cell that has mutated.

• The main clinical characteristic of cancer is its aberrant growth pattern.
Cancer Growth

• Cancer grows **locally**, beyond the usual normal tissue boundaries, compressing or destroying adjacent tissues.

• In addition, most cancers **can metastasize** by shedding cells into the bloodstream, lymphatic fluid, or other body fluids that can travel to and colonize a distance site.
Except in leukemia, systemic therapy rarely sufficiently effective to eradicate local disease.
Radiation Therapy
Radiation Therapy

• Radiation is used
  – alone or with surgery
  – for cure or palliation
  – in most types of cancers

• ~50% all cancer patients
• ~2 m radiation treatments in F1/yr
Types of Radiation

Radiation Therapy

External Beam

Electromagnetic

Gamma Rays

X-Rays

Electrons

Neutrons

Heavy Ions

Particulate

Brachytherapy

Proton
Mechanism of Action in Radiation Therapy
Radiation Therapy Basics

- Radiation damage is non-specific.
- Response* probability dose-related and volume-related.
- Dose distribution key to outcome.

*Cancer control and normal tissue damage.
Radiation Therapy

In radiation oncology, dose distribution is the main challenge. . .

Oftentimes radiation doses are limited to avoid toxicity.

Sometimes the price of cure is a complication.
Conventional Radiation in Head & Neck Cancers

<table>
<thead>
<tr>
<th>Site</th>
<th>Dose</th>
<th>Local Control</th>
<th>Gr. 3-4 Toxicity</th>
<th>Therapeutic Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocal Cord*</td>
<td>63 Gy</td>
<td>94%</td>
<td>&lt;1</td>
<td>&gt;94</td>
</tr>
<tr>
<td>Sinus**</td>
<td>~75 Gy</td>
<td>79% SX + RT</td>
<td>27% unilateral blindness</td>
<td>1.8-15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49% RT alone</td>
<td>5% bilateral blindness</td>
<td></td>
</tr>
</tbody>
</table>

*Small volume tumor with no critical structures around.
**Large volume tumor close to visual apparatus.
 Radiation dose distribution is key to improving therapeutic ratio
Promise of Protons
Radiation Dose Distribution: The Bragg Peak

- 200 KV
- 60 Cobalt
- 22 MV X-rays
- 22 MEV Electrons
- Proton Bragg Peak
- Spread Out Proton Peak
The Promise of Proton Therapy

• No exit dose, less entrance dose means less normal tissue damage
• Less normal tissue damage means higher doses to tumor possible
• Higher doses to tumor means higher cure rates
The Promise of Protons

- Less toxicity.
- Higher cure rates.
- Potential reduction in health care costs.
University of Florida Proton Therapy Institute Site Selection

- UFPTI to serve Florida & SE US.
- UF has two healthcare campuses: Gainesville and Jacksonville.
- JAX strategically located with international air and sea ports and interstate highway.
- Strong long-visioned and principle-guided city and state legislative support for UFPTI.
- UFPTI sited adjacent to UF affiliated tertiary hospital, ambulatory diagnostic radiology, and close to pediatric hospital.
University of Florida Cancer Center
Production of Proton Beams

- **Cyclotron:** 230 MeV proton beams (~33 cm depth in water)
- **Energy degrader:** reduce energy to the desired value
- **Beam line:** guide the proton beam to the treatment room
- At the end of the beam line, the proton beam is
  - Small and narrow
  - Monoenergetic (almost)
Production of Clinically-Useful Proton Beams
Proton Accelerators - CYCLOTRON
Production of Clinically-Useful Proton Beams

Beam Line

- Protons are Charged Particles
  - Dipoles – Bend, guide the proton beam
  - Quadrupoles – Focus the proton beam
  - Steering Coils – Fine-tune direction of beam
IBA Isocentric Gantry
Gantry in Motion
Mono-energetic pencil beam → Treatment Nozzle

Depth Dose Distribution

Lateral Dose Distribution

3D dose distribution
Double Scattering

Rotating Range Modulator

Fixed Scatterer

Second Scatterer

Aperture & Bolus

P+
Range modulation / RM wheels

IBA design (3 tracks on single wheel, gating used to adjust modulation)

Photos courtesy MGH / IBA
Range modulation / RM wheel

<table>
<thead>
<tr>
<th>Step#</th>
<th>thickness</th>
<th>angular width</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1.8 cm.H20</td>
<td>76 deg</td>
</tr>
<tr>
<td>2</td>
<td>2.3 cm.H20</td>
<td>27 deg</td>
</tr>
<tr>
<td>3</td>
<td>2.9 cm.H20</td>
<td>20 deg</td>
</tr>
<tr>
<td>4</td>
<td>3.4 cm.H20</td>
<td>14 deg</td>
</tr>
<tr>
<td>5</td>
<td>4.0 cm.H20</td>
<td>11 deg</td>
</tr>
</tbody>
</table>

1. \( E_1 = 147 \text{ MeV} - w_1 = 89\% \)
2. \( E_2 = 143 \text{ MeV} - w_2 = 30\% \)
3. \( E_3 = 139 \text{ MeV} - w_3 = 25\% \)
4. \( E_4 = 135 \text{ MeV} - w_4 = 19\% \)
5. \( E_5 = 130 \text{ MeV} - w_5 = 16\% \)
Range-compensated contoured scatterer

Diagram: Gottschalk
Field-specific aperture:
- Used to conform the dose to the lateral shape of the target
- Brass
- 2-6.5 cm thickness
- Positioned as close to the patient as possible
Field-specific range compensator

- Used to conform the dose to the distal end of the target
- Lucite
- 0-15 cm thickness
- Positioned as close to the patient as possible (2 cm from skin)
Applications for Proton Therapy
Brain Tumors: Craniopharyngioma
Craniopharyngioma
Colorwash Representation of Radiation Dose:

Range from ~105% (pink) to ~20% (aqua)

Desired target dose is 100% (red)

Target outlined in thin black line

Courtesy: D Louis, D Yeung, Z Li, C Li
Radiation Therapy Progress

- Opp 6X ~1980
- Opp 15X ~1985
- 3 Field ~1990
- IMRT ~2005
- Proton ~2009

Colors and Radiation Levels:
- Pink = 105%
- Red = 100%
- Yellow = 90%
- Green = 50%
- Aqua = 20%

V20 = 22% for IMRT vs 5.6% for protons

Courtesy: D Louis, D Yeung, Z Li, C Li, N Mendenhall
Craniospinal Axis Irradiation for CNS Tumors
Paranasal Sinus

IMXT (X rays)

Protons

Dose Difference

PSI
Prostate Cancer
Prostate Cancer: bPFS and Grade 3+ GI Toxicity in Dose Escalation Studies

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>d/Fx</th>
<th>bPFS</th>
<th>Gr 3+GI</th>
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<tbody>
<tr>
<td>Dutch¹</td>
<td>78</td>
<td>2</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>MRC²</td>
<td>74</td>
<td>2</td>
<td>71</td>
<td>6</td>
</tr>
<tr>
<td>MDA³</td>
<td>78</td>
<td>2</td>
<td>73</td>
<td>7</td>
</tr>
<tr>
<td>PROG⁴</td>
<td>79.2</td>
<td>1.8</td>
<td>91⁴</td>
<td>1</td>
</tr>
<tr>
<td>UFPTI*</td>
<td>78-82</td>
<td>2</td>
<td>--</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

¹Peeters et al, 2006; ²Dearnaley et al, 2007; ³Kuban et al, 2008; ⁴Zeitman et al, 2010, for low risk disease bPFS was 97%; UFPTI PR010203 2 Y.
Lung Cancer
Proton Beam Results in Lung Cancer

Stage I/II

*87% Local Control

*63% Disease Free


Treatment given intensely over 2 weeks rather than traditional 8 weeks, increasing effectiveness and reducing costs.
Hodgkin’s Lymphoma
Background: General

Childhood Cancer Survivor Study- Oeffinger et al. NEJM 2006
HL survivors (as a group) were: highest risk of severe or life threatening chronic health conditions (highest risk of second cancer and heart disease)

Ng JCO 2002
## RT dose & late effects HL survivors

<table>
<thead>
<tr>
<th>Author</th>
<th>Disease</th>
<th>Dose</th>
<th>RR</th>
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</thead>
<tbody>
<tr>
<td>Travis et al 2002</td>
<td>Breast Cancer</td>
<td>≥ 4 Gy</td>
<td>3.2</td>
</tr>
<tr>
<td>Travis et al 2003</td>
<td>Lung Cancer</td>
<td>≥ 5 Gy</td>
<td>5.9</td>
</tr>
<tr>
<td>Van Den Belt-Dusebout 2009</td>
<td>Gastric Cancer</td>
<td>≥ 11 Gy</td>
<td>3</td>
</tr>
<tr>
<td>Mulrooney et al 2009</td>
<td>CHF</td>
<td>≥ 15 Gy</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>≥ 15 Gy</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Pericardial</td>
<td>≥ 15 Gy</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Valvular</td>
<td>≥ 15 Gy</td>
<td>3.3</td>
</tr>
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</table>
1 field- AP- Cardiac Sparing
1 field- AP- Cardiac Sparing
Cardiac & Breast Sparing
<table>
<thead>
<tr>
<th>PROSTATE</th>
<th>HEAD&amp;NECK</th>
<th>LYMPHOMA</th>
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<tbody>
<tr>
<td>Prostate PR01</td>
<td>NX 01</td>
<td>HL01</td>
</tr>
<tr>
<td>Prostate PR02</td>
<td>PS 01</td>
<td>LUNG</td>
</tr>
<tr>
<td>Prostate PR03</td>
<td>OX 01</td>
<td>LG01</td>
</tr>
<tr>
<td>Prostate PR04</td>
<td>SK01</td>
<td>LG02</td>
</tr>
<tr>
<td>Prostate PR05</td>
<td>SARCOMA</td>
<td>CENTRAL NERVOUS SYSTEM</td>
</tr>
<tr>
<td>Prostate PR06</td>
<td>CH01</td>
<td>PI01</td>
</tr>
<tr>
<td>Prostate PR08</td>
<td>SA01</td>
<td>CN01</td>
</tr>
<tr>
<td>PANCREAS</td>
<td>SA02</td>
<td>SJEP(SJCP)</td>
</tr>
<tr>
<td>PC01</td>
<td>GENERAL</td>
<td></td>
</tr>
<tr>
<td>PC02</td>
<td>OT01</td>
<td></td>
</tr>
</tbody>
</table>
Promise of Proton Therapy

- **Reduced toxicity** (brain function, vision preservation, gastrointestinal damage, pulmonary damage, thyroid and reproductive organ function, cardiovascular disease and second malignancy)

- **Increased cure rates** through dose escalation and or intensification.

- **Reduced health care costs** through lowering costs of recurrence and toxicity and reducing overall treatment time.

- **Main barrier** to proliferation of proton facilities for treatment is cost.
The Slide Rule

1980: ~$12.50
The Hewlett-Packard HP-35

1980: ~$399.00
The Slide Rule

1980: ~$12.50

2011: ~$33.00
The Slide Rule and The HP-35

Accuracy

Efficiency

Increased potential for good
The Hewlett-Packard HP-35

1980: $399.00
2010: ~$79.99
Walmart Price 2010: ~$7.99
Acknowledgements

Clinical JAX
Nancy Price Mendenhall, MD
Randy Henderson, MD
Robert Malyapa, MD, Ph.D.
William Mendenhall, MD
Chip Nichols, MD
Danny Indelicato, MD
Rusty Marcus, MD
Brad Hoppe, MD
Amy Sapp, RN
Kristi Helow, RN
Karen, Bunk, RN,
Gail Sarto, RN
Marilyn Hataka, RN
Maggie Simmons
Sheryl Martin
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