The Science behind Proton Beam Therapy

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Principles underlying Radiotherapy

• Radiation related complications do not occur in un-irradiated tissues

• Normal tissue irradiation does not benefit patient

• One can optimize the therapeutic ratio by maximizing radiation dose to the tumor and minimizing normal tissue dose
History of Radiation Oncology

- Understanding of radiation biology

- Improvements in imaging:
  • For visualizing normal tissues and tumor
  • For planning
  • For on-treatment verification

- Improvements in computing power:
  • 3-D planning
  • Intensity modulation

- Improvements in delivery systems
A century of “delivery tools” in radiation oncology
Clinical gains

Technological sophistication

The “arrow of progress”
Protons – “The Point of the Arrow”

• **Traditional X-rays (photons)**
  - Attenuate progressively with depth
    - Continue to deposit dose beyond target
      - Unwanted dose to normal tissue

• **Particles with charge and mass**
  - Defined range in tissue
    - Proportional to energy
    - Deposit dose in sharp Bragg Peak
      - No dose delivered beyond that point
Radiation deposition in tissue for radiation beams

Radiation dose deposited vs. Depth in tissue
Proton Radiation Therapy

• **1929:** Cyclotron invented by Ernest Lawrence as a way to accelerate nuclear particles to very high speeds.

• **1946:** Robert Wilson, professor of physics at Harvard first proposes using protons for the treatment of cancer.

• **1954:** J. Lawrence treats first patient with protons at Berkeley for pituitary tumor

• **1957:** First European proton Rx in Uppsala, Sweden.
Proton Radiation Therapy

- **1961**: First patient treated at Harvard Cyclotron by Kjellberg
- **1974**: MGH protons for cancers including eye, skull base, prostate
- **1988**: FDA approves protons for selected cancers
- **1990**: Loma Linda Medical Center synchrotron opens
- **2001**: Francis H. Burr Proton Therapy Center opens
- **2004-2015**: Multiple new facilities built, planned
- **2015**: 42 operating centers worldwide
How are clinical proton beams generated?

1. **Cyclotron**
   Using magnetic fields, the cyclotron can accelerate the hydrogen protons to two-thirds the speed of light.

2. **Electromagnets**
   The magnets focus the proton beams toward the gantry.

3. **Gantry**
   The gantry can rotate 360° around the patient to position the nozzle.

4. **Nozzle**
   A 21,000-pound magnet guides the beam to the patient through a nozzle.
How are clinical proton beams generated?

Cost: $30-180M
“Spot scanned” beams – the new wave

The dynamic application of scanned and modulated proton pencil beams

Images courtesy of Eros Pedroni
Proton beam therapy – US treatment centers

Over 20 more in planning stages
Protons: Potential Clinical Advantages

Lower integral dose and absence of exit dose:

- Improve acute treatment tolerance:
  - Allows integration with systemic chemotherapy
  - Allows delivery of higher radiation doses

- Reduce late effects
Pediatric cancers – the very best indication for proton beam

Children are uniquely sensitive to radiation:

- Profound effects on growth and development
- Substantial risk of radiation-induced cancers
MEDULLOBLASTOMA

PHOTONS

PROTONS

PHOTONS

PROTONS

Courtesy T. Yock, N. Tarbell, J. Adams
Orbital Rhabdomyosarcoma

Courtesy T. Yock, N. Tarbell, J. Adams
Pediatric Studies

Traditional Comparative Effectiveness Research does not exist:

- No RCTs because no equipoise
- Unanimity among radiation oncology community globally
Protons: Reduction in Second Malignancies among Pediatric Patients

Comparative Treatment Planning studies:

Protons vs. Photons (Conformal or IMRT)

- **Rhabdomyosarcoma**
  - Protons reduce risk 2nd tumors by factor of > 2

- **Medulloblastoma**
  - Protons reduce risk 2nd tumors by factor of 8-15

Proton beam therapy – UK treatment centers

Government Commission:
1 facility per 30m population
Accepted adult indications for protons:

- Skull base tumors
- Eye tumors
- Spine and sacral tumors

Not that evidence is strong. More that alternatives are unacceptable.
Adult Cancer Studies

For more common cancers

Do the physical advantages translate into measurable clinical benefit?

• Cancer control
• Quality of life
• Second malignancies
The trouble with randomized trials testing proton therapy

• Ethical objections
• Advantages small and trials large
• Advantages late and trials long
• Huge initial investment for protons
• Slow the engine of discovery
Reducing the incidence of second cancers

How many patients would one need to demonstrate a significant reduction in 2nd tumors?

- Assume 60% decrease in 0.5% incidence at 15 y (NCI)
- For 80% power at $p=0.05$.

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<thead>
<tr>
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<th>1-sided</th>
<th>2-sided</th>
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</thead>
<tbody>
<tr>
<td>5 y average FU</td>
<td>13509</td>
<td>17280</td>
</tr>
<tr>
<td>10 y average FU</td>
<td>6759</td>
<td>8646</td>
</tr>
<tr>
<td>15 y average FU</td>
<td>4510</td>
<td>5768</td>
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<td>Expected 2nd cancers</td>
<td>32</td>
<td>41</td>
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<table>
<thead>
<tr>
<th></th>
<th>photons</th>
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<td>9</td>
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Sample size smaller by increasing FU from 10 y to 15 y

Courtesy of Beow Yeap, PhD
Second Malignancies in adults

• Matched retrospective cohort study

  – 1,450 Harvard proton patients and photon cohort in SEER cancer registry

  – Matched 558 HCL proton pts (1972-2001) with 558 SEER pts. Median FU 6 years

  – 6.4% of proton patients developed another malignancy, versus 12.8% of photon patients

Chung et al Int J Radiat Oncol Biol Phys 2014
Studies in prostate cancer

Protons

IMRT
Does proton beam cure patients?

- Randomized trial 393 men T1-2 tumors
- 70 vs. 79Gy    Median FU 8.9 years

Zietman J Clin Oncol 2010, 28:1106
Does it cure more patients than brachytherapy?

Case-matched analysis: $n = 141 + 141$
Does it cure more patients than other kinds of external beam?

2000-2007

<table>
<thead>
<tr>
<th>Method</th>
<th>Count</th>
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<tr>
<td>Conformal</td>
<td>6310</td>
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<tr>
<td>IMRT</td>
<td>6666</td>
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<tr>
<td>Protons</td>
<td>684</td>
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</tbody>
</table>

Min FU 1 year, median 50 months

Endpoints: hip fractures, ED, GI morbidity, additional cancer treatment

Sheets et al JAMA 2012, 307:1611
Does it cure more patients than other kinds of external beam?

Likelihood of additional treatment

Sheets et al JAMA 2012, 307:1611
Does it reduce morbidity?

U Florida
1285 patients with median FU 3.5 years

Colaco et al IJROBP 2014, 91:172
Does it reduce morbidity?

Data from 3 prospective cohort studies

Gray et al cancer 2013, 119:1729
Does it reduce morbidity?

Two contemporaneous cohorts:

- Protons 9.4 years
- Conventional 5.9 years

<table>
<thead>
<tr>
<th></th>
<th>Protons</th>
<th>Conventional</th>
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<tbody>
<tr>
<td>Number</td>
<td>280</td>
<td>97</td>
</tr>
<tr>
<td>Age at survey</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>Urinary obst/irr</td>
<td>24.0</td>
<td>21.8</td>
</tr>
<tr>
<td>Incontinence</td>
<td>10.2</td>
<td>11.2</td>
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<tr>
<td>Bowel problems</td>
<td>7.8</td>
<td>10.6</td>
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<tr>
<td>Sexual problems</td>
<td>67.1</td>
<td>76.3</td>
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*Talcott et JAMA 2010, 303:1046*
Does it **increase** morbidity?

<table>
<thead>
<tr>
<th>IMRT vs Protons</th>
<th>HR</th>
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<tr>
<td>GI diagnoses</td>
<td>0.66</td>
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<tr>
<td>Hip fractures</td>
<td>NS</td>
</tr>
<tr>
<td>ED</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary incontinence, diagnoses, and procedures</td>
<td>NS</td>
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Sheets et al JAMA 2012
Low-Intermediate Risk Prostate Cancer

N=350

IMRT

Proton Beam

ENDPOINTS

Patient-Reported Quality of Life
Cost-Effectiveness
Physics/Biology

79.2 Gy (RBE)

79.2 Gy
New opportunities:

- Left-sided breast cancer
- Pancreas
- Retroperitoneal sarcomas
- Paranasal sinus tumors
- Lung
- Liver
STAGE III Non-Small Cell Lung Cancer

Randomized Phase II Study in Progress at MDACC/MGH

Highest dose that can be achieved: 74 Gy, 66 Gy, (60 Gy) dose levels

Image courtesy of Joe Chang MD, MDACC
New opportunities- Hepatocellular Cancer

Standard Photons

Protons

Willett C, Adams J
Proton Therapy 2015

• Accurate and effective treatment

• Rides the “minimally invasive” wave

• Technical and biological advances: scanned beam biophysical optimization, “personalized” dose

• New centers being established globally
Proton Therapy 2015

- Treatment of choice for pediatric solid tumors and selected adult tumors

- Relative benefit versus photons in adult patients being studied in randomized, controlled trials

- Cost reduction and efficiency a research priority

- An economic “development trap” exists.