AAPM 50th Annual Meeting

CE - Therapy

PROTON THERAPY

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Topics Covered

- History of Proton Therapy
- Worldwide Facilities
- Rationale for Proton Therapy
- Physics of Proton Beams
- Treatment Delivery Techniques
- Proton Treatment Technology
- Clinical Commissioning
- Treatment Planning
History and Current Status of Proton Therapy
Abbreviated History of Protons

- 1919  Rutherford proposed existence of protons
- 1930  E. O. Lawrence built first cyclotron
- 1946  Robert Wilson proposed proton therapy
- 1955  Tobias et al. treated patients at LBL
- 1972  MGH received first NCI grant for proton studies at HCL using large field fractionated treatments
- 1991  First hospital-based proton facility at LLUMC
- 2008  First spot scanning treatments in US at MDACC
- 2008  25 facilities worldwide treating patients.
Proton Therapy Facilities

25 facilities worldwide treating patients.

- **6 in Japan (4 hospital-based)**
  - Chiba, NCC East-Kashiwa, HIBMC-Hyogo, PMRC-Tsukuba, WERC-Wakasa, Shizuoka Cancer Center
- **6 in the United States (4 hospital-based)**
  - LLUMC, MGH, MDACC, Univ. of Florida, Univ. of Indiana, UC Davis
- **9 in Europe/Russia**
- **4 Additional facilities (UK, China, Korea, South Africa)**
- **15 additional institutions worldwide are developing new facilities.**

>55,000 patients have been treated with proton beams
Particle Therapy Facilities Worldwide

Treating: Protons 25, Carbon ions 3

In operation  In preparation  Considering

Courtesy of Takashi Ogino, MD, PhD, NCC Kashiwa, Japan
Rationale for Proton Therapy
## Need for Improved Local Control in Cancer Treatment (selected sites)

(all numbers are estimates)

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Deaths/Year</th>
<th>Deaths due to Local Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck</td>
<td>22,000</td>
<td>13,200 (60%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>135,000</td>
<td>54,000 (40%)</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>28,000</td>
<td>14,000 (50%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>55,000</td>
<td>27,500 (50%)</td>
</tr>
<tr>
<td>Lung</td>
<td>160,000</td>
<td>40,000 (25%)</td>
</tr>
<tr>
<td>Breast</td>
<td>41,000</td>
<td>4,920 (12%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>20,000</td>
<td>2,400 (12%)</td>
</tr>
<tr>
<td>Skin, Bone, Soft Tissue</td>
<td>15,000</td>
<td>5,000 (33%)</td>
</tr>
<tr>
<td>Brain</td>
<td>12,000</td>
<td>10,800 (90%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>488,000</strong></td>
<td><strong>171,820 (35%)</strong></td>
</tr>
</tbody>
</table>

Over 1,350,000 new cancer patients per year in the US
Fundamental Things to Remember about Protons

- Protons Stop!
- Photons don’t stop.
- Proton dose at depth (target) is greater than dose at surface.
- Photon dose at depth (target) is less than dose at $d_{max}$. 
Rhabdomyosarcoma of Paranasal Sinus (7 y old boy)

6 MV Photons (3 field)

Photon IMXT (9 field)

160 MeV Protons (2 field)

Proton IMRT (9 field)
Proton Physics

- The physics of proton beams
- Passive scattering systems
- Pencil beam scanning systems
Electromagnetic energy loss of protons

Mass Electronic Stopping Power is the mean energy lost by protons in electronic collisions in traversing the distance $dx$ in a material of density $\rho$.

$$S/\rho = 1/\rho[\text{d}E/\text{d}x] \propto 1/v^2$$

Where $v$ = proton velocity

The Bragg peak is “broadened” by two effects:

1. The incident beam has a narrow energy spread (not monoenergetic)
2. Range straggling caused by statistical differences in energy losses in individual proton paths.
Normalized (at peak) Bragg Curves for Various Proton Incident Energies

Range Straggling will cause the Bragg peak to widen with depth of penetration

Normalized (at entrance) Bragg Curves for Various Proton Incident Energies
Dose depositions in water from 160 MeV protons. Beam slit delimiters with width W cm. Uniform particle distributions.

Loss of in-scattering (charged particle equilibrium) results in deterioration of Bragg peak and non uniformity of SOBP.

George Ciangaru

Narayan Sahoo
Multiple Coulomb Scattering

- Protons are deflected frequently in the electric field of the nuclei
- Beam broadening can be approximated by a Gaussian distribution

Lateral dose fall-off: Protons vs. Photons

80/20 Penumbra Comparison

- Protons
- 15 MV Photons

Approximately 17 cm
RESIDUAL RANGE 12.55 (gm/cm²)
MODULATION 11.8
DEPTH 3 cm
NO LUCITE

Airgap (cm)
12
6
NO GAP

% DOSE

DISTANCE (cm)
A certain fraction of protons undergo nuclear interactions, mainly on $^{16}$O.

Nuclear interactions lead to secondary particles and thus to local and non-local (neutron) dose deposition.

In passive scattering systems neutrons are produced in the first and second scatterers, modulation wheel, aperture, range compensator in addition to those produced in the patient.
Effect on the lateral dose distribution

Pedroni et al PMB, 50, 541-561, 2005

Primary fluence

Secondaries from nuclear interactions

Effect on Depth Dose

Total Absorbed Dose

230 MeV protons

'Results' Dose

'Secondary' Dose

Depth in Water [cm]
Proton Therapy
Beam Delivery Technology
Physics of the Passive Scattering Mode of Proton Beam Delivery

Passive Scattering Nozzle with Range Modulation Wheel

Hitachi Passive Scattering Nozzle
How a Spread Out Bragg Peak (SOBP) is formed.

- Modulation wheel rotates in the beam.
- Pull-back (energy shift) determined by height of step.
- Weight determined by width of step.
- Multiple SOBPs can be obtained by gating beam.
Deficiencies of Proton Passive Scattering Techniques

- Uniform SOBP - excess normal tissue dose.
- Requires custom aperture and compensator
- Inefficient - high proton loss produces activation and neutron production.

The Pencil Beam Scanning Mode of Proton Beam Delivery

Active Scanning

Dynamic changes of the proton energy

Dynamically varying sweeping magnets (in and out of plane)

No compensator, and generally no collimator needed

Evolution of the lateral beam profile

No wasted protons

Patient

Target

Variable SOBP

Pencil Beam Scanning Nozzle

**Performance**

- **Range**: 4 – 36 g/cm²
- **Adjustability**: 0.1 g/cm²
- **Max. field size**: 30 x 30 cm
- **Beam size in air**: 6 – 10 mm \( \sigma \)
- **SAD**: > 2.5 m
- **Dose compliance**: +/- 3% (2 \( \sigma \))
- **Irradiation time**: < 2 min to deliver 2 Gy to 1 liter
Proton Accelerators
Isocentric Gantries
Typical Facility
Typical Accelerators used in proton therapy facilities

- Hitachi 250 MeV synchrotron ring
- 7 MeV Linac injector
- IBA 230 MeV Cyclotron
- ACCEL Superconducting Cyclotron
- 250 MeV
Evolution of commercial Cyclotron systems

**IBA C230**
- First commercially available cyclotron for PT
- 230 MeV protons
- Dedicated to therapy

**ACCEL K250**
- Compact superconducting cyclotron
- Higher magnetic field - less volume/mass
- High extraction efficiency and reproducible beam parameters

**Next Generation?**
- Energy: 250 MeV Protons
- Diameter: 1.7 m
- Magnetic field: 8.5 Tesla
- Beam structure: Pulsed, 1 kHz
M. D. Anderson Gantry
Hitachi
190 tons

Siemens
Heidelberg

600 tons

Gantries

Proton

120 tons

Carbon

NPTC GANTRY

Commercial bearing

Chain drive

Commercial bearing

9.2 m diam / 12.7m long
156 Tons rotating mass

Counterweight
Proton Therapy Center - Houston

PTC-H
3 Rotating Gantries
1 Fixed Port
1 Eye Port
1 Experimental Port

Accelerator System (slow cycle synchrotron)

Pencil Beam Scanning Port
Passive Scattering Port
Experimental Port
Large Fixed Port
Eye Port
New Technologies

• Single Room Proton Therapy Systems
• Laser Acceleration
• Dielectric Wall Acceleration
<table>
<thead>
<tr>
<th>Potential advantages of single room proton therapy solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cost effective proton therapy solution for small, community-based hospitals - reduced floor space and building costs. Lower cost entry into proton therapy</td>
</tr>
<tr>
<td>• All components mounted on the rotating gantry thus reducing the length of the beam transport system</td>
</tr>
<tr>
<td>• No competition for beam with other treatment rooms</td>
</tr>
<tr>
<td>• If multiple rooms are used, the entire proton treatment capability is not lost if one accelerator goes down.</td>
</tr>
</tbody>
</table>
Potential disadvantages of a single room proton therapy solution

- Not necessarily cheaper per treatment room.
- If demand for proton therapy increases, additional rooms may have to be installed. If several treatment rooms are eventually needed, the cost effectiveness of the single-room concept will be lost.
- For some systems, it may be difficult to use spot scanning techniques.
- No track record for reliability, maintainability, robustness, etc.
Laser Accelerated Proton Beams

Proton acceleration is achieved by focusing a high-power laser on a thin target. The short \((10^{-16}\text{ sec})\) laser pulse width produces a high peak power intensity that causes massive ionization in the target, expelling a large number of relativistic electrons. The sudden loss of electrons gives the target a high positive charge and this transient positive field accelerates protons to high energies. The resultant proton beams have a broad energy spectrum and therefore a magnetic spectrometer must be used to select a narrow energy band. This selection process throws away about 99.5% of the beam.
Acceleration, Particle Selection and Beam Collimation

Movable aperture to select protons of desired energy

0.5 to 1 m

10 TW = 10^{15} watts

Fs = 10^{-15} seconds

Time Line: 7-10 years.
Conventional accelerator cavities have an accelerating field only in the gaps which occupy only a small fraction of their length. In a DWA, the beam pipe is replaced by an insulating wall so that protons can be accelerated uniformly over the entire length of the accelerator yielding a much higher accelerating gradient.
The enabling technologies are the high gradient insulator (HGI*), SiC switching**, and new dielectric materials**.

An electric field propagates down the bore of the accelerator pushing the proton “packet” in front of it.

Conventional accelerators have a gradient of ~ 1-2 MeV/meter
DWA produce a gradient of \( \geq 20 \text{ MeV/meter} \)
The goal is to have a full scale prototype in ~ 4-5 years, which will be installed at UC Davis CC.

Thomotherapy is the private sector partner.
A Proton + Light Ion Facility built in two phases

Phase I
Protons only

PHASE II
Add Light ions
Treatment Planning

- Acquisition of imaging data
- Delineation of regions of interest
- Selection of beam directions
- Dose calculation
- Optimization of the plan
Treatment Planning (Protons vs. Photons)

Hounsfield Units (HU)

Photon Planning System
HU versus electron density

Proton Planning System
HU versus rel. stopping power
Proton beams (fields) have an end of range (i.e. pointing to critical structures is an option)
Treatment Planning (Protons vs. Photons)

Planned to the PTV

Dose versus time

Isodose levels
20
50
80
95
100

© Martijn Engelsman, MGH
Treatment Planning

- Passive scattered proton beams
- Scanned proton beams
- Intensity modulated proton beams
- Comparative treatment plans
Dose shaping for passive scattered protons

Double scattering system

High-Density Structure

Target Volume

Critical Structure

Body Surface

Aperture

Beam

© Hanne Kooy, MGH
SOBP Modulation

- Prescription:
  - Range
  - Modulation
  - Compensator
  - Aperture

© Hanne Kooy, MGH
Aperture and Range Compensator

To be ‘designed’ by the planning system!

© Hanne Kooy, MGH
1. Range and Modulation Width for each field

- **Beam range: 17.19 cm**
  - Modulation width: 6.78 cm

- **Beam range: 13.47 cm**
  - Modulation width: 8.65 cm

- **Beam range: 12.0 cm**
  - Modulation width: 4.0 cm
2. Absolute dosimetry for each field

Volume for absolute dosimetry

\[
\text{Output - Factor} \approx \frac{D_{\text{cal}}}{i_{ic}} \left[ \frac{cGy}{MU} \right]
\]
A SIMPLE EXAMPLE: Para-spinal case using 3 fields
Field Patching

- Useful if target is close to critical structures
- Not necessarily homogeneous dose to the target for each beam (IM!)
- Range and penumbra uncertainties need to be considered
A COMPLICATED EXAMPLE: Nasopharynx case using 14 fields (plus additional photon fields to the lower neck)
• GTV 76 Gy
  – CTV1 60-66 Gy
  – CTV2 60 Gy
• Nodes 54 Gy
Treating moving targets with protons
Effect of respiration on dose

- Rescanning
- Beam Gating
- Real-time tumor tracking with markers

Range fluctuations due to respiration in the lung

© Shinishiro Mori, MGH
FH Burr Proton Therapy Center (2001-)

Patient Population

- Brain 32%
- Spine 23%
- Prostate 12%
- Skull Base 12%
- Head & Neck 7%
- Trunk/Extremity Sarcomas 6%
- Gastrointestinal 6%
- Lung 6%

In general, 1-3 fields / day / patient
Currently ~ 45 patients / day

© Thomas DeLaney, MGH
Treatment Planning

- Passive scattered proton beams
- **Scanned proton beams**
- Intensity modulated proton beams
- Comparative treatment plans
Beam Scanning

Typical Spot
Beam in Water

© Eros Pedroni, PSI
1. Evenly spaced/weighted spots to achieve uniform field

2. 1mm spot error due to delivery error or patient motion.

3. Optimum spacing/weighting to achieve sharper penumbra

© Eros Pedroni, PSI
Dosimetry and QA of pencil beams

• Energy/Range
  • large number of energies required
  • energy spacing must provide dose uniformity over all depths

• Spot size and shape
  • spot size/shape may depend on energy
  • spot position accuracy

• Measurements require methods for rapid collection of large amounts of data

• Real-time beam information
Orthogonal IC array measurements performed at different water depths using a computer controlled water column and compared with calculations.

'Beam's-eye-view' of dose in water

Scintillating screen viewed with a CCD through a 45° mirror

Scintillating Plate, Mirror and CCD Camera used for pencil beam scanning QA.

© Alfred Smith, MDACC
Treatment Planning

- Passive scattered proton beams
- Scanned proton beams
- Intensity modulated proton beams
- Comparative treatment plans
IMPT Treatment Planning

- Bragg peaks of pencil beams are distributed throughout the planning volume
- Pencil beam weights are optimized for several beam directions simultaneously (inverse planning)
Intensity-Modulated Proton Therapy–IMPT

© Alex Trofimov, MGH
Treatment Planning

• Passive scattered proton beams
• Scanned proton beams
• Intensity modulated proton beams
• Comparative treatment plans
Example
(standard protons vs. photons)

Medulloblastoma
Medulloblastoma

Protons

Photons

Copyright © MGH/NPTC 2003
Example
(protons vs. IM photons)

Prostate
Prostate carcinoma:
(GTV + 5mm) to 79.2 Gy
(CTV + 5mm) to 50.4 Gy

© Alex Trofimov, MGH
Example
(protons / IM protons / IM photons)

Nasopharynx
(case shown earlier)
A Composite plan
(14 proton fields, 4 photon fields)

- proton fields
  CTV to 59.4 GyE (33 x 1.8 Gy)
  GTV to 70.2 GyE (+ 6 x 1.8 Gy)
- Photon fields
  lower neck, nodes to 60 Gy

© Alex Trofimov, MGH
B IMXT plan
(7 coplanar photon beams)
C IMPT plan
(4 coplanar proton beams)
DVH for target structures

Comparable target coverage

© Alex Trofimov, MGH
DVH for some critical structures

Brainstem

Minor Salivary

Major Salivary

Rt Temporal

Suprahyoid muscles

Lt + Rt Subling

© Alex Trofimov, MGH
Summary

- Proton planning offers more options in terms of beam directions and field shaping than photon planning
- IMRT and 3D protons can be comparable in terms of dose conformality
- Protons are able to reduce the dose to most critical structures compared to photons
- Proton therapy is able to reduce the integral dose compared to photons by up to a factor of 3
- IMPT is the method of choice
Some remarks on biology

• Neutrons in proton therapy
• The proton RBE
Integral dose (protons vs. photons)
Neutron dose as a function of lateral distance

Neutron radiation weighting factor

From: Annals of the ICRP; ICRP Publication 92; Relative Biological Effectiveness (RBE), Quality Factor (Q), and Radiation Weighting Factor ($w_R$)
Neutron RBE as a function of endpoint

Estimates of $RBE_M$ for neutron carcinogenesis in mice

<table>
<thead>
<tr>
<th>Mouse Strain</th>
<th>Sex</th>
<th>Tissue-tumor</th>
<th>$\eta_n$</th>
<th>$\gamma$</th>
<th>$RBE_M$</th>
<th>Approximate S.E. of $RBE_M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFM</td>
<td>♂</td>
<td>Thymic lymphoma</td>
<td>0.56 ± 0.004</td>
<td>0.021 ± 0.02</td>
<td>27</td>
<td>± 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian tumor</td>
<td>0.52 ± 0.04</td>
<td>0.0</td>
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<tr>
<td></td>
<td></td>
<td>Pituitary</td>
<td>0.41 ± 0.21</td>
<td>0.007 ± 0.005</td>
<td>59</td>
<td>± 52</td>
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<tr>
<td></td>
<td></td>
<td>Harderian gland</td>
<td>0.54 ± 0.03</td>
<td>0.015 ± 0.004</td>
<td>36</td>
<td>± 10</td>
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<tr>
<td></td>
<td></td>
<td>Lung tumor</td>
<td>1.7 ± 0.15</td>
<td>0.29 ± 0.151</td>
<td>6</td>
<td>± 3</td>
</tr>
<tr>
<td>BALB/c</td>
<td>♂</td>
<td>Lung adenocarcinoma</td>
<td>0.76 ± 0.19</td>
<td>0.041 ± 0.009</td>
<td>19</td>
<td>± 6</td>
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<tr>
<td></td>
<td></td>
<td>Mammary carcinoma</td>
<td>1.14 ± 0.27</td>
<td>0.035 ± 0.01</td>
<td>33$^b$</td>
<td>± 12</td>
</tr>
</tbody>
</table>

NCRP Report No. 104, The Relative Biological Effectiveness of Radiations of Different Quality
RBE in proton therapy:

Clinical (generic) RBE = 1.1*

* Based on experiments at the Harvard cyclotron done in the 70’s
RBE values *in vivo* (center of SOBP; relative to $^{60}$Co)

Mice data:
Lung tolerance, Crypt regeneration, Acute skin reactions, Fibrosarcoma NFSa

- **RBE as a function of LET**
  - be careful when using the end of range next to a critical structure

- **RBE as a function of dose**
  - dose dependency seems to be small

- **RBE as a function of biological endpoint**
  - variation seems to be small
  - Note: RBE for cell kill can be different than for mutation/carcinogenesis
RBE as a function of particle energy / LET

Radiation is more effective when energy depositions are more concentrated in space.
Thanks to

Hanne Kooy
Alex Trofimov
George Chen
Martijn Engelsman
Judy Adams

for providing some slides and figures.