Particle beam Therapy

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Learning objective

- Particle beam therapy?
- Interaction of charge particle with matter
- Rational of particle beam therapy
- Carbon vs Proton
- Historical development of proton beam therapy
- How it work?
- Accelerator technology (Cyclotron / Synchrotron)
- Passive Scattering and Pencil beam scanning
- Benefit of Proton beam therapy
- Clinical Indications
Ionizing Radiation
- Deposited energy is high enough to ionize the traversed material

Charge
- Electron
- Light charge particles (Proton)
- Heavy charge particles (C, He)

Un-charge
- Photons/ MV X-rays
- Neutrons
Particle / hadron / ion beam therapy

- Specific type of EXRT
- Use high energy neutron, proton, other heavy +ve ions
- Most commonly used particle in Hadron therapy
  - Proton
  - Carbon
  - Helium
Interaction of charge particle with matter

- Nucleus of the hydrogen atom.
- Unit positive charge \((1.6 \times 10^{-19} \text{ C})\)
- Mass of \(1.6 \times 10^{-27} \text{ kg} (\sim 1,840 \text{ times the mass of electron})\).
Why particle therapy??

- Physical depth dose characteristics
  - Finite range (e.g. R90)
  - No exit dose
- Radiobiology (RBE)
  - Proton = 1.1 (0.7 – 1.5)
  - Carbon = 2-5

\[
RBE = \frac{\text{Dose of 150 V X-rays required to cause effect } x}{\text{Dose of radiation required to cause effect } x}
\]
Dosimetric benefit of particle therapy
Depth dose characteristics of charge particles

**Electrons**
- Very high peak to plateau ratio
- Better penumbra
- Fragment tail
- Higher RBE
- Extremely high cost

**Protons**

**Anti-Protons**

**Helium**

**Carbon**
- Very high peak to plateau ratio
- Better penumbra
- Fragment tail
- Higher RBE
- Extremely high cost

**Iron**
Fragment tail of Carbon

- Fragment tail beyond Bragg peak of carbon ion
- Tails are of low physical dose & relatively high RBE
- Extend up to 15 cm
- BED from fragmental tail not negligible
- Limited use of carbon in paediatric patient
Historical development

- Initial proposal by Robert Wilson in 1946
- Spread out Bragg Peak (SOBP) using range modulating wheel
  - Proton energies → Depth of the tumours
  - Number of proton energies → Tumour extent in beam direction

Courtesy: Harald Paganetti; AAPM Summer School 2015
Historical development

- First patient treated at LBL in 1954
- Metastatic breast cancer treated for pituitary gland for hormone suppression.
- The bony landmarks made targeting of the beam feasible.
- The plateau of the depth dose curve of 340 MeV Proton
- Cross-firing technique
Progress in Proton Beam Therapy

- 1990: First Hospital based PT facility at Loma Linda University Medical center
- Present status of PT facility
  - 109 in operation
  - 37 under construction
  - 29 in planning
- Exponential increase in peer-reviewed publication
- Technological development
- Cost effective solution (Single room)

Proton Therapy Physics (2nd Edition) by Prof Harald Paganetti
How does it work??
Proton Therapy System Architecture

- Accelerator (Cyclotron/Synchrotron)
- Energy selection system (ESS)
- Beam Transport System (BTS)
- Beam delivery System (BDS)
- Positioning system
- Patient positioning and verification system
- Therapy safety system (TSS)

TCS : Treatment control system

Beam management system
Position management system
Proton Accelerator: Cyclotron-1932

- Fixed-energy cyclic particle accelerator
- Designed to generate proton beams of up to 250 MeV

Energy gain per rotation = 2
Energy = \( \frac{mv}{qB} \)

\( r = \frac{mv}{qB} \)

Angular frequency

\( \bar{F}_{\text{magn}} = q (\bar{v} \times \bar{B}) \)
Cyclotron Type

Proton revolving frequency $= \frac{1}{2\pi}$.

Proton angular frequency $= 2\pi = \frac{qB}{m} = \frac{qB}{m_0}$.

**CLASSICAL: (original)**
- Operate at fixed frequency $(\omega = \frac{qB}{m})$ and ignore the mass increase
- Works to about 25 MeV for protons $(\omega = 1.03)$

**SYNCHROCYCLOTRON:** let the RF frequency $\omega$ decreases as the energy increases
- $\omega = \omega_0 / \omega$ to match the increase in mass $(m = m_0)$
- Uses same decreasing field with radius as classical cyclotron

**ISOCHRONOUS:** raise the magnetic field with radius such that the relativistic mass increase is just cancelled
- Pick $B = B_0$ {this also means that $B$ increases with radius}
- Then $\omega = \frac{qB}{m} = \frac{qB_0}{m_0}$ is constant.
- Field increases with radius- magnet structure must be different
- 1.7-2.15 T in C230
Proton Accelerator: Synchrotrons

- Variable energy cyclic particle accelerator
- Suitable for both light (Proton) and heavy ions (Z>1, C12, He4, etc)
- 1st Synchrotron was Built by Fermilab and started operation in 1992 at LomaLinda University.
- Low energy proton (2-7MeV) are injected
- An alternating voltage adds energy to the proton on each rotation
- Magnetic field must be increase each cycle to keep the proton circulating on the same radius
- Commercial system
  - Hitachi
  - Mitsubishi
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Synchrotron</th>
<th>Isochronous Cyclotron</th>
<th>Synchrocyclotron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical Size (Dia in meter)</td>
<td>6 - 8 + Injection system</td>
<td>3.0 – 4.5 m</td>
<td>2.5 – 1.8</td>
</tr>
<tr>
<td>Time structure beam intensity</td>
<td>Spill structure</td>
<td>Continuous</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Fast energy scanning</td>
<td>Wait for next spill During extraction</td>
<td>Degrader</td>
<td>Degrader</td>
</tr>
<tr>
<td>Activation</td>
<td>No problem</td>
<td>Degrader need shielding</td>
<td>Degrader need shielding</td>
</tr>
<tr>
<td>Beam intensity</td>
<td>Limited in magnitude &amp; range</td>
<td>“Any” Adjustable within &lt;1ms</td>
<td>“Any” but low on average. Adjustable within a few mS</td>
</tr>
<tr>
<td>Intensity stability</td>
<td>10-20%</td>
<td>2 - 5%</td>
<td>20%</td>
</tr>
<tr>
<td>Scattering</td>
<td>Suitable</td>
<td>Suitable</td>
<td>Suitable</td>
</tr>
<tr>
<td>Spot Scanning</td>
<td>Suitable</td>
<td>Suitable</td>
<td>Long time needed</td>
</tr>
<tr>
<td>Beam gating</td>
<td>Suitable</td>
<td>Suitable</td>
<td>Suitable</td>
</tr>
<tr>
<td>Fast continuous scanning</td>
<td>Difficult due to pulse structure</td>
<td>Suitable</td>
<td>Not possible due to pulse structure</td>
</tr>
</tbody>
</table>

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2. Energy Selection System

- Beam Degrader:
  - Degrade the beam energy to requested value up to 70 MeV
  - Scatter beam transversely & generate a spread of beam energies
- Collimate beam transverse phase space and to limit the beam energy spread
- Much of the beam is lost in ESS at lower energy

C230: 
\[ p^+ \text{ 230 MeV} \]
Ambient neutron and photon dose around PT facility

Neutrons and photons are produced during beam losses at various location along beam path when proton hits matter

Cyclotron (230 MeV on Cu/Fe)

Degrader (230 MeV on Cu)

Collimator (70-230 MeV on Ta)

Divergence Slits (70-230 MeV on Ni)

Momentum Slit (70-230 MeV on Ni)

Nozzle (70-230 MeV on Brass)

Patient (70-230 MeV on Tissue)

H^+(10) < 1 mSv/yr
3. Beam Transport System

- Reduced peak to plateau ratio

- Figure showing beam delivery system components: Range modulator, First Scatterer, Second Scatterer, Shaped Aperture, Range Compensator, Prescription Dose spillage.
Proton beam therapy with passive scattering techniques

- Seating/sleeping position
- Planar radiograph for target localization
- Limited Clinical site
- Logistic issues
- Manpower
- Neutron contamination
Beam delivery system: Active scanning

- Reduced
  - Proximal, entrance, integral dose
  - Preparation time
  - In-room therapist time
  - Easy Adaptive therapy
  - Neutron contamination
- Increase conformity
- Disadvantages
  - Sensitivity to patient motion (interplay effect)
  - Slower irradiation
  - Poorer target conformity at lower energies due to increase penumbra
Contemporary PT

- Pencil Beam Scanning only
- Image-Guided PT (2D, 2.5D, 3D)
- 6D Robot
- Motion Management (AlignRT SGRT)
- Optimized shallow tumor treatment
Contemporary PT facility at APCC

- 85 cm bore S-CT
- 3T MRI
- Digital PET/CT
- RadiXact HT
- MOSAIC OIS Server
- Thin Client RayStation TPS workstations (6 Nos.)
- RayStation TPS Server
- LAN
Benefit PBT

• **Dosimetric benefit**
  • Reduction of OAR doses
  • Reduction of Integral dose

• **Impact**
  • Reduction of toxicity profile
  • Possibility of dose escalation
  • Reduction or avoidance of radiation induced carcinogenesis

• **Clinical outcome**
Dosimetric benefit of Proton Therapy

- Reduction of Dose to OARs
- In CSI, mandible, parotid gland, thyroid gland, lung, kidney, heart, ovary, uterine, and other non-target intracranial structures (St Clair 2004 IJROBP, Lee 2005 IJROBP, Howell 2012 IJROBP)


Robustly optimized hybrid intensity-modulated proton therapy for craniospinal irradiation
Dosimetric benefit of Proton Therapy

Dose escalation:
Sacral chordoma (Radio-resistant)

- Reduction of Second Cancer
- Expected to improve further with Pencil beam scattering Technique
Clinical benefit of proton therapy

- Datas emerging
- PSI & Orsay clinical outcome data for Chondrosarcoma: 1996 to 2015,
- 251 patients (mean age, 42.0 ± 16.2 years)
- protons with \( n = 135 \); 53.8% or without photons \( n = 116 \); 46.2%.
- Median delivered dose was 70.2 Gy\(_{\text{RBE}}\).
- Median follow-up of 88.0 months
- 7-year Failure Free Survival was 93.1%.
- 7-year OS was 93.6%.
- 7-year Toxicity Free Survival was 84.2%.
## Recommended indications for CPT

<table>
<thead>
<tr>
<th>Country</th>
<th>Document</th>
<th>Group 1 (medically necessary)</th>
<th>Group 2 (potential indications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>ASTRO&lt;sup&gt;a&lt;/sup&gt; Model Policy</td>
<td>- Eye tumors</td>
<td>- All other solid tumors, including: &lt;ul&gt; - Head and neck cancers &lt;li&gt; - Thoracic malignancies &lt;li&gt; - Abdominal cancers &lt;li&gt; - Pelvic cancers &lt;p&gt; - Chordoma and chondrosarcoma &lt;li&gt; - Spine tumors&lt;sup&gt;b&lt;/sup&gt; &lt;li&gt; - Hepatocellular carcinoma&lt;sup&gt;c&lt;/sup&gt; &lt;li&gt; - Pediatric tumors&lt;sup&gt;d&lt;/sup&gt; &lt;li&gt; - Patients with genetic syndromes&lt;sup&gt;e&lt;/sup&gt; &lt;li&gt;</td>
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<tr>
<td>UK</td>
<td>Clinical indications for treatment overseas by protons</td>
<td>- Skull-base and spinal chordoma &lt;li&gt; - Skull-base chondrosarcoma &lt;li&gt; - Spine and paraspinosal soft-tissue sarcomas&lt;sup&gt;f&lt;/sup&gt; &lt;li&gt; - Pediatric tumors &lt;li&gt;</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>AIRO&lt;sup&gt;e&lt;/sup&gt; indications for government reimbursement</td>
<td>- Skull base and spine chordomas and chondrosarcomas&lt;sup&gt;g&lt;/sup&gt; &lt;li&gt; - Adenoid cystic carcinoma of the salivary glands&lt;sup&gt;h&lt;/sup&gt; &lt;li&gt; - Mucosal malignant melanoma&lt;sup&gt;h&lt;/sup&gt; &lt;li&gt; - Ocular melanoma &lt;li&gt; - Osteosarcomas&lt;sup&gt;h&lt;/sup&gt; &lt;li&gt; - Pediatric tumors &lt;li&gt;</td>
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<tr>
<td>Denmark</td>
<td>Aarhus University, indications for the Danish National Center for Particle Therapy</td>
<td>■ Chordoma and chondrosarcoma ■ Ependymoma ■ Primitive neuroectodermal tumors ■ Pituitary adenoma ■ Acoustic neuroma ■ Arterovenous malformations ■ Germinoma ■ Eye tumors ■ Lymphomas ■ Selected sarcomas ■ Nasopharyngeal cancer recurrence ■ Pediatric tumors</td>
<td></td>
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<tr>
<td>The Netherlands</td>
<td>Health Council of the Netherlands on Proton Therapy&lt;sup&gt;1&lt;/sup&gt;</td>
<td>■ Skull base and spine chordomas and chondrosarcomas ■ Meningioma ■ Pediatric tumors</td>
<td>■ Re-irradiations ■ Paranasal sinus tumors ■ Nasopharyngeal carcinoma ■ Retroperitoneal sarcoma</td>
</tr>
<tr>
<td>Canada</td>
<td>AHS&lt;sup&gt;1&lt;/sup&gt; Proton Therapy Referral Committee Report</td>
<td>■ Chordomas and chondrosarcomas ■ Ocular melanomas&lt;sup&gt;k&lt;/sup&gt; ■ Pediatric tumors</td>
<td>■ Benign tumors of the CNS ■ Paranasal sinus and nasal cavity tumors</td>
</tr>
</tbody>
</table>
## Ongoing phase-III randomized clinical trials

<table>
<thead>
<tr>
<th>Brief title</th>
<th>Sponsor</th>
<th>Start date</th>
<th>Condition</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPT&lt;sup&gt;a&lt;/sup&gt; versus IMRT&lt;sup&gt;b&lt;/sup&gt; for head and neck cancers</td>
<td>MDACC&lt;sup&gt;c&lt;/sup&gt;, USA</td>
<td>August 2013</td>
<td>Oropharyngeal cancer</td>
<td>Protons&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X-rays&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Proton therapy versus IMRT&lt;sup&gt;b&lt;/sup&gt; for prostate cancer</td>
<td>MGH&lt;sup&gt;e&lt;/sup&gt;, USA</td>
<td>July 2012</td>
<td>Low or intermediate risk prostate cancer</td>
<td>Protons</td>
<td>X-rays</td>
</tr>
<tr>
<td>Proton beam therapy versus IMRT&lt;sup&gt;b&lt;/sup&gt; trial for esophageal cancer</td>
<td>MDACC&lt;sup&gt;c&lt;/sup&gt;, USA</td>
<td>April 2012</td>
<td>Esophageal cancer</td>
<td>Protons&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X-rays&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comparing photon therapy to proton therapy to treat patients with lung cancer</td>
<td>RTOG&lt;sup&gt;f&lt;/sup&gt;, USA</td>
<td>February 2014</td>
<td>Stage II-III NSCLC&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Protons&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X-rays&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pragmatic randomized trial of proton versus photon therapy for breast cancer</td>
<td>PTCORI&lt;sup&gt;b&lt;/sup&gt;, USA</td>
<td>2015</td>
<td>Post-mastectomy stage II or III breast cancer</td>
<td>Protons</td>
<td>X-rays</td>
</tr>
<tr>
<td>Trial of proton versus carbon ion radiation therapy in patients with chondrosarcoma</td>
<td>Heidelberg University, Germany</td>
<td>August 2010</td>
<td>Low and inter-mediate grade chondrosarcoma of the skull base</td>
<td>Protons</td>
<td>C-ions</td>
</tr>
<tr>
<td>Randomised trial of proton versus carbon ion radiation therapy in patients with chordoma</td>
<td>Heidelberg University, Germany</td>
<td>July 2010</td>
<td>Chordoma of the skull base</td>
<td>Protons</td>
<td>C-ions</td>
</tr>
<tr>
<td>First French prospective randomised study of the medical and financial potential of carbon ion therapy</td>
<td>Lyon University Hospitals</td>
<td>2016</td>
<td>Adenoid cystic carcinoma and sarcomas</td>
<td>C-ions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IMRT</td>
</tr>
<tr>
<td>Prospective trial comparing carbon ions to IMRT&lt;sup&gt;b&lt;/sup&gt; in pancreatic cancer</td>
<td>NCI&lt;sup&gt;i&lt;/sup&gt;, USA</td>
<td>2016</td>
<td>Locally advanced pancreatic adenocarcinoma</td>
<td>C-ions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X-rays&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Acknowledgement

Thank You