Proton Radiation Therapy Technology and Clinical Indications

Niek Schreuder
Vice President and Chief Medical Physicist

Marcio Fagundes MD - Medical Director
Matt Ladra MD (Pediatrics)
Allen Meek MD
Tamara Vern Gross MD
Provision Health Alliances
Proton Therapy Alliances

Provision Health Alliance (PHA)
A comprehensive clinical outpatient healthcare center consisting of multiple physician practice groups, comprehensive diagnostic imaging, advanced chemotherapy and radiation therapy, wellness center, physical therapy, a cyclotron and nuclear pharmacy, and clinical trials and research capabilities.

Provision Center for Proton Therapy (PCPT)
The key cancer radiation therapy component of PHA at Dowell Springs which together with the rest of PHA distinguishes PHA from all other outpatient cancer centers in the world. Currently, there are 11 proton centers in the US.

ProNova Solutions, LLC (ProNova)
A US-based developer, manufacturer, and distributor of multi-room proton therapy equipment and solutions which together with PHA and PCPT distinguishes us from all other proton therapy manufacturers and centers in the world.
Provision Center for Proton Therapy
Facility – 1st Floor
Physics of Protons

• Protons are directly ionizing particles
• Energy Loss is proportional to $1/v^2$
  – Bragg Peak
  – finite range in matter
• Multiple Scattering
  – lateral broadening of beam
• Nuclear interactions
The Physics of Protons

Depth Dose Curves for Different Treatment Modalities

- **8 MV X-Rays**
  - SSD = 100 cm
  - 5 cm SOBP
  - Depth of Tumor

- **200 MeV Protons**

![Graph showing depth dose curves for different treatment modalities.](image-url)
Where do we get the Protons?

Protons are the nucleus of the hydrogen atom.

Protons are created by stripping (ionizing) the electron from the hydrogen atom.
Accelerating Protons

In order for protons to be clinically useful for radiotherapy, they must be accelerated to high energy.

Radiotherapy is performed with protons of energy up to 250 MeV (mega-electron volts). mega = 10^6 = 1,000,000

- “room temperature” atoms have energies of ~25 meV (milli-electron volts). milli = 10^-3 = 1/1000
- so we have to increase their energy by a factor of ~10 billion for clinical use.

A 200 MeV proton travels at ~1/2 the speed of light.

There are several techniques for accelerating protons: Synchrotrons, linear accelerators, cyclotrons
“High Energy” can be Misleading

**electron volts in perspective**

- A light bulb consumes $\sim 10^{20} \text{ eV/second.}$
- Bowl of Wheaties $\sim 10^{24} \text{ eV.}$

- A fly travelling only 1 meter/second has an energy of $\sim 10 \text{ billion MeV.}$

Protons are tiny – they are $\sim 10^{-15}$ meters in radius and have a mass of $\sim 10^{-27}$ kilograms.
How a Cyclotron Works

1. Protons (ionized hydrogen) are injected at low energy.

2. Voltage alternates to give the protons a “kick” every time they cross the gap.

3. Magnetic field keeps protons bound in a circular orbit.

4. As the proton’s energy increases, its orbital radius increases.

5. High energy protons are kicked out.
Early Cyclotrons

First Cyclotron, 1931

- 4 inch diameter
- 80,000 eV

Original publication in 1932.

Ernest Lawrence won the Nobel Prize in 1939 for his work on the cyclotron.
How do we use Protons

- *The same way than x-rays – conventional radiotherapy*
Classical Radiation Therapy
Classical Proton Therapy: 
oldest form of IMRT – depth dose modulation
Beam Delivery Systems

- Passive Scattering
  - Single Scattering
  - Double Scattering

- Active Scanning
  - Uniform Scanning (Wobbling)
  - Pencil Beam Scanning (IMPT)
  - Continuous / Raster Scanning
  - Spot Scanning

vs
Active scanning

Proton pencil beam

‘Range shifter’ plate

Magnetic scanner

Target

Patient

SGSMP/FMH Physics lectures 2011

Prof Dr Tony Lomax, Proton therapy
Pencil Beam Scanning Proton Therapy: Best form of IMRT
Spot Scanning Principle

Pictures - With compliments from PSI

Few Spots

Single Spot

Total Picture
Pencil Beam Scanning (PBS)
– Filling the target with spheres of Radiation dose
“There is no advantage whatsoever to irradiating uninvolved healthy tissue”

Dr. Herman Suit
Harvard / MGH Proton Center (1)

The Goal of Radiation Therapy for 100 years:

Therapeutic Ratio = Tumor Control / Normal Tissue Complications

Potential improvement in quality of life

Cost savings by decreasing complications
How does Radiation Kill cells?
How does Radiation Kill cells?

**Physical Effects**
- Electron$^-$
- Atom $\rightarrow$ Ion$^+$
- Photon

**Biological Effects**
- Formation of radicals within the cytoplasm
- $H_2O \rightarrow H_2O^+ + e^-$
- $H_2O^+ \rightarrow H^+ + OH^-$
- $e^- + H_2O \rightarrow H + OH^-$

**Alternative**
- Damage to DNA
- Biological effects on all cells

**Identical**
The Value of Protons

Protons are physically superior to X-rays:

X-Rays do not stop Continue to travel into normal tissues beyond the target
Individualized treatment - NTCP-models and *in silico* studies

With Compliments – Dr Hans Langendijk - UMCG

Conversion of: *Dose difference* to: *Clinical benefit (NTCP-value)*

Mean dose

NTCP (%)
Proton therapy → Categories of indications

Main clinical use PREVENTION:
- Complications
- Secondary tumors

Source: Horizon scanning report (Health council of the Netherlands 2009)

With Compliments – Dr Hans Langendijk - UMCG
Proton Therapy – Past and Current Environment

• First patient treatment in the U.S. occurred at Berkeley in 1954
  - First IMRT treatment didn’t occur until the early 1990s

• Harvard - MGH began treating patients in 1961

• The first hospital based proton center in the U.S. was built at the Loma Linda University Medical Center in 1990
  - Loma Linda initially treated prostate, brain, and some head and neck tumors

• Currently: 15 operating centers in the U.S. and over 30 worldwide
  - There are another 30+ proton centers in development in the U.S.

• Medicare has paid for proton therapy since 1997

• Every major national insurance carrier has paid for proton therapy
What Cancers Can Protons Treat?

Classic indications:

- Base of skull tumors
- Eye (uveal) melanomas
- Brain tumors
- Pediatric tumors
- Spinal / Paraspinal tumors
- Prostate cancers
- Lung
- Liver
- Breast
- Esophagus
- Pelvic tumors
- Large sarcomas
- Mediastinal tumors
- Reirradiation of recurrent tumors
Pediatric Treatments
The Value of Protons

Protons are physically superior to X-rays:

Protons avoid unnecessary radiation to heart, lungs, intestines delivered by X-rays.

X-Rays do not stop. Continue to travel into normal tissues beyond the target.
Medulloblastoma Longitudinal IQ
IMRT vs. IMPT

IQ = 93.00 + (0.024 x Age – 0.0091 x Mean Dose) x time*

Mean Dose (supratentorial brain volume); time (months)

Quality of Life

QOL for children 2-18 yrs treated at MGH (n=57) or Stanford (n=60)

Protons scored 10 pts higher in Psychosocial and Physical domains vs photons

Significant differences seen in Total QoL scores for Medulloblastoma, Ependymoma/High Grade Glioma, and Low Grade Glioma
Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

Christine S. Chung, MD, MPH,* Torunn I. Yock, MD, MCh,† Kerrie Nelson, PhD,‡ Yang Xu, MS,§ Nancy L. Keating, MD, MPH,‖ and Nancy J. Tarbell, MD†∥

558 proton pts treated from MGH (1973 to 2001) compared with 558 matched photon pts (SEER)

Protons=5.4%

Photons=8.6%

Hazard ratio = 0.52
(CI 0.32-0.85, p=0.009)
Recent Cases At Provision
Bifocal Germinoma
Tectal Glioma 50.4 CGE
Prostate Cancer
Radiotherapy for Prostate Cancer

Conventional radiotherapy X-rays (IMRT) exposes more healthy tissue to radiation.

Higher dose to healthy tissues:
Pelvis, rectum and bladder

Proton therapy
Less healthy tissue exposed to radiation with protons.
Proton and IMRT – Prostate Plan

**Dose Volume Histogram Comparison**

- **Irradiated Volume** vs **Delivered Dose**
- **IMRT Dose Outside the Prostate**
- **Proton dose outside the Prostate**

**IMRT (10 liters)**

**PROTONS**

<table>
<thead>
<tr>
<th>Irradiated Volume (l)</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 liters</td>
<td>0</td>
</tr>
<tr>
<td>2 liters</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>4000</td>
</tr>
<tr>
<td></td>
<td>6000</td>
</tr>
<tr>
<td></td>
<td>8000</td>
</tr>
</tbody>
</table>
Lung Cancer
Why Protons for Lung Cancer?

Conventional radiotherapy
X-rays (IMRT)

Protons

Difference
Protons decrease unnecessary dose to:
Left lung
Esophagus
Heart
Spinal cord
Clinical Case 1

Right Lung Middle Lobe, 70 Gy (RBE) in 10 Fractions

Pre Treatment

Post Treatment – 1 month after treatment
M.D. Anderson treatment related toxicity data for inoperable locally advanced lung cancer:

**NSCLC treated with radiation therapy + chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>3D CRT</th>
<th>IMRT</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>63 Gy</td>
<td>63 Gy</td>
<td>74 CGE</td>
</tr>
<tr>
<td>% patients stage IIIA-B2</td>
<td>87%</td>
<td>91%</td>
<td>87%</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagitis – G3+</td>
<td>18%</td>
<td>44%</td>
<td>5%</td>
</tr>
<tr>
<td>Pneumonitis – G3+</td>
<td>30%</td>
<td>9%</td>
<td>2%</td>
</tr>
</tbody>
</table>

## Lung Cancer Proton Therapy Trials

<table>
<thead>
<tr>
<th>Study name</th>
<th>Trial type</th>
<th>Modalities</th>
<th>Description</th>
<th>Selection criteria (inoperable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton with chemo</td>
<td>Phase II</td>
<td>Protons and chemo</td>
<td>-Primary goal is to improve survival</td>
<td>Stage IIIA and IIIB</td>
</tr>
<tr>
<td>M.D. Anderson</td>
<td>Phase II</td>
<td>Protons and chemo</td>
<td>-Chemo and 74 CGE of proton therapy</td>
<td></td>
</tr>
<tr>
<td>Loma Linda</td>
<td>Phase I/II</td>
<td>Protons and chemo</td>
<td>-Chemo with accelerated proton therapy</td>
<td>Stage II, IIIA or IIIB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-5 week RT (first two weeks – daily; final three weeks – twice daily)</td>
<td></td>
</tr>
<tr>
<td>University of Florida</td>
<td>Phase II</td>
<td>Protons and chemo</td>
<td>-Chemo with higher 74 CGE dose delivered by protons</td>
<td>Stage IIIA or IIIB</td>
</tr>
<tr>
<td>UPENN</td>
<td>Phase I/II</td>
<td>Protons and chemo</td>
<td>- Chemo with 5.5 – 7.5 weeks of proton radiation (total dose not disclosed)</td>
<td>Stage IIIA that are eligible for surgery</td>
</tr>
<tr>
<td>UPENN</td>
<td>Phase I</td>
<td>Protons and Nelfinavir</td>
<td>-Goal is to test the highest safest dose of proton therapy that can be given concurrently with drug</td>
<td>Stage IIIA or IIIB</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D. Anderson</td>
<td>Phase II</td>
<td>Protons and x-rays</td>
<td>-Randomize between x-rays and protons</td>
<td>Stage II-IIIIB</td>
</tr>
<tr>
<td>PCG</td>
<td>Phase III</td>
<td>Protons and x-rays</td>
<td>-Randomize between x-rays and protons</td>
<td>Stage IIIA - IIIB</td>
</tr>
<tr>
<td>Hypofractionation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.D. Anderson</td>
<td>Phase I</td>
<td>Protons</td>
<td>-Hypofractionating starting at 45 Gy in 15 Fx to 60 Gy in 15 Gy</td>
<td>-NSLC, small cell lung cancer, thymic or carcinoid tumors</td>
</tr>
<tr>
<td>University of Florida</td>
<td>Phase II</td>
<td>Protons</td>
<td>Hypofractionating:</td>
<td>Stage I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-48 CGE in 4 fx (peripherally located)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-60 CGE in 10 fx (centrally located)</td>
<td></td>
</tr>
<tr>
<td>Dose escalation</td>
<td></td>
<td></td>
<td>-Dose escalation to 87.5 CGE in 35 Fx</td>
<td>Stage IA, IB, and selected stage II</td>
</tr>
</tbody>
</table>
Rectal Re-irradiation

A. Berman and J. Plastaras – U PENN (PTCOG – Essen 2013)
Breast Cancer
Breast Cancer Treatment

• Many breast cancer patients will receive radiation therapy as part of their course of treatment

• Patients are at risk for post treatment complications resulting from radiation to the heart, lungs and contralateral breast
  - These risks may increase if patients:
    a) Receive cardio-toxic chemotherapy drugs
    b) Have smoking history
    c) Left sided breast cancer

• Protons can spare critical structures and can deliver approximately 10 times less radiation to the heart than conventional X-Ray radiation
Coronary Exposure to Radiation in Conventional Radiotherapy for Breast Cancer

Stenosis of the main coronary artery left anterior descending (LAD)
Conventional Radiotherapy

Use Protons

Spare the heart and coronaries
Sweden and Denmark: Population-based study of 2168 pts post-radiation therapy for Breast Cancer

Risk of major coronary events: Myocardial infarction
Coronary revascularization
Death from ischemic heart disease

...were correlated with mean radiation dose delivered to the heart.

The Risk of major coronary event increases by 7.4% per gray of exposure to the heart\textsuperscript{1}
Heart toxicity (cont)

ASTRO states that “in patients with breast cancer, it is recommended that the irradiated heart volume be minimized to the greatest possible degree without compromising the target dose”¹

<table>
<thead>
<tr>
<th></th>
<th>3DCRT</th>
<th>IMRT</th>
<th>Tomo</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD mean dose</td>
<td>23.7</td>
<td>19.9</td>
<td>10.6</td>
<td>5.8 Gy</td>
</tr>
<tr>
<td>Heart mean dose</td>
<td>7.3</td>
<td>8.2</td>
<td>10.5</td>
<td>0.9 Gy</td>
</tr>
<tr>
<td>Total Lung V5 Gy</td>
<td>33.6%</td>
<td>54.6%</td>
<td>46.3%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Contral. Breast mean</td>
<td>1.5</td>
<td>3.9</td>
<td></td>
<td>0.2 Gy</td>
</tr>
<tr>
<td>Unspecified normal tissue volume &gt; 10 Gy (cc)</td>
<td>2817</td>
<td></td>
<td></td>
<td>353</td>
</tr>
</tbody>
</table>


57.5% reduction in the Risk of major coronary event
“Direct Radiation Complications Never Occur In Unirradiated Tissues”

Dr. Herman Suit
Harvard / MGH Proton Center

Treatment Modality Evolution

Percentage Depth Dose

Depth in water (mm)

Relative Dose

DXR

Co-60

8MV X-rays

Protons
Cost of Complications

- The average lifetime cost of a severe heart attack has been estimated to be about $1 million\(^1\)
- \(~75\%~\) of health care costs in the U.S. goes to the treatment of chronic diseases\(^2\)
- In 2010 the cost of cardiovascular disease / stroke in the U.S. was about $432 billion (1 in every 6 dollars spent on healthcare)\(^3\)

The best way to reduce the overall cost of cancer care is to eliminate the chronic side effects of treatment

\(^1\) National Business Group On Health.
The Future of Proton therapy
Leveraging Technology

• Superconducting magnets have multiple benefits
  - Dramatically smaller size, weight, and power
  - 2X higher magnetic field, 0.5X bend radius

• ProNova leverages superconducting magnet technology
  - Maintains 360° rotation similar to radiation therapy
  - Ample room for full ring imaging at isocenter
  - Simplified shipping and installation reducing cost and time to market
Open square room provides improved patient access

Open room provides clear access for lasers, projectors, Optical imaging, & intercom

Projection screens provide easy review of therapy information
1 Massachusetts General Hospital, Boston
2 Loma Linda University Medical Center, Calif.
3 Midwest Proton Radiotherapy Institute, Bloomington
4 MD Anderson Cancer Center, Houston (PTCH)
5 University of Florida Proton Therapy Institute, FL
6 ProCure Proton Therapy Center Oklahoma City, OK
7 University of Pennsylvania Health System, Philadelphia
8 Hampton University Proton Therapy Institute, Hampton
9 ProCure Proton Center, Chicago
10 ProCure Proton Center, New Jersey
11 ProCure Proton Therapy Center, Seattle
12 Washington University, St. Louis
13 Provision Center for Proton Therapy, Knoxville
14 Scripps Proton Therapy, San Diego
15 Willis Knight Shreveport LA
The future of Proton Therapy

- All truth passes through three stages.
  - First, it is ridiculed.
  - Second, it is violently opposed.
  - Third, it is accepted as being self-evident —
    - Arthur Schopenhauer (1788–1860)

The Truth of Proton Therapy is now almost through the second Phase
Provision Center for Proton Therapy

Thank You