Proton Therapy:
Where Are We Now and Where Are We Going?

Erin Davis MSN, CRNP, ACNP – BC
Lead Nurse Practitioner

Genevieve Hollis MSN, CRNP, ANP-BC, AOCN
Oncology Nurse Practitioner
Advanced Senior Lecturer-B

September 17, 2016
Proton Therapy Centers in the US
Proton Therapy Centers Globally
Challenges and Unanswered Questions

- **Data**
  - Efficacy
  - Toxicity

- Improvement in conventional therapy

- Cautionary tale: neutron beam therapy

- Cost

- Reimbursement

- Treatment delivery technology
Objectives

- Identify potential therapeutic and toxicity advantages and disadvantages of Proton radiation therapy

- Discuss current and future indications for Proton radiation therapy
Broad Overview

- 65-80% of all cancer patients receive radiation therapy

- Treatment of local and regional disease
  - Effects occur only in the radiation field
  - Kill cancer cells while minimizing damage to normal tissues

- Ionizing radiation
  - Transfer of high energy from radiation source to tissues
  - Direct and indirect damage to DNA
    - Double strand breaks
    - If cell tries to divide before it repairs DNA, the cell will die
Radiosensitivity

- Rapidly dividing cells are the most radiosensitive
  - Cancer and normal cells
  - Cancer cells generally divide faster than normal cells, not as good repairing DNA
  - Therefore, cancer cells are much more vulnerable to RT, some more than others

<table>
<thead>
<tr>
<th>Tumors/Tissues</th>
<th>Radiosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>High</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>Fairly High</td>
</tr>
<tr>
<td>Vascular Connective</td>
<td>Medium</td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>Fairly Low</td>
</tr>
<tr>
<td>Renal Cell</td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
</tr>
<tr>
<td>Muscular Sarcomas</td>
<td>Low</td>
</tr>
</tbody>
</table>

- Cell cycle phase
  - Most radiosensitive: Late G2 and mitosis (M)
  - Most radioresistant: Late synthesis (S)

- Small, well oxygenated, poorly differentiated cells more sensitive
Dose, Radiobiology, Tissue Tolerance

- **4 Rs of Radiobiology**
  - Repair of sub-lethal damage of normal cells
  - Repopulation of normal tissues
  - Reassortment of tumor cells to more radiosensitive cell cycle phase
  - Re-oxygenation of previously hypoxia tumor cells

- **1 Gy = 100 cGy** standard unit of measuring radiation absorption

- **Tumor radiation dose limited by normal surrounding tissue tolerance**
  - Dose normal tissues can be irradiated and continue to function, acceptable treatment complications
  - **LIFE TIME** radiation tolerance

- **Fractionation**: total dose of radiation is divided into equal
  - Allows normal tissue repair, Increase tumor effect
  - Standard fractions 1.8 Gy, 2 Gy daily
Treatment Volumes

GTV = Gross Tumor Volume (macroscopic cancer)

CTV = Clinical Target Volume (microscopic cancer)

PTV = Planning Target Volume (internal margin + setup margin)

Site Specific QI
Radiation Toxicities

- Generalized fatigue

- Only within radiation field

- Depends on
  - Type of radiation absorbed
  - Field size
  - Fraction dose, total dose, schedule
  - Site (tissues and structures in energy path).
  - Concurrent (prior) chemotherapy/biotherapy
  - Co-morbid conditions
  - Smoking, nutrition status
  - Performance status
  - Patients constitutional genome

- Acute, Late, Chronic
External Beam Radiation Therapy

- **Photon (XRY)**
  - LINAC
    - 3-D conformal radiation
    - IMRT
  - Cobalt

- **Electrons**

- **Particles**
  - Proton
What is Photon Radiation Therapy?

Ionizing Radiation
- Penetrates
- Breaks DNA
Photon: Box Field
Photon: 3D conformal...

- Computers
- Ability to sculpt the radiation dose
- Increase dose
  - To improve tumor control
  - Reduce normal tissue side effects.

Courtesy of Varian Medical Systems
Photon: IMRT

- Multiple “beamlets” of variable strength and angles to conform dose to target
- More conformal, smaller treatment volumes
- Lower radiation doses to normal tissue
  - Fewer side effects
- Low-moderate dose is spread over many tissues
  - Increases total body exposure
  - 2nd cancer risk,
- Treatment time increases
- Cost increases
What is a Proton Radiation Therapy?

Diagram showing the relative dose of protons, electrons, and photons with distance in millimeters.
Spread Out Braggs Peak

- Beam direction
  - X-ray (photon) beam
- Proton beam #1
  - SOBP region
    - (12 proton beams)
- Tissues:
  - Skin
  - Shallow tissues
  - Tumor
  - Deep tissues
IBA Cyclotron

Beam-line
Gantry
Each of the three gantries is three-stories tall and weighs 200,000 lbs.
Proton delivery options

Double Scatter (DS)
Uniform Scanning (US)
Pencil-beam Scanning (PBS)

Diagram courtesy of Varian Medical Systems
Passive scattering (double scattering)

Passive scattering in practice

- Each delivered field (incident direction of irradiation) requires specific collimator and compensator.
- As range shifter is up-stream of scatterer(s), extent of SOBP is fixed across field.

Tony Lomax - Paul SCHERRE INSTITUTE
Active scanning, Pencil Beam Scanning

- Proton pencil beam
- Magnetic scanner
- ‘Range shifter’ plate

Tony Lomax - Paul SCHERRE INSTITUTE
Potential Advantages of Proton Therapy

- Precisely delivers energy to an optimal dose to the tumor.
- **Dose escalation**
  - Increase the dose within a confined treatment volume
  - Increase long term, progression-free survival rates
- **Decrease entrance and exit dose**
  - Reduces the probability and/or severity of toxicities.
  - Retreat previously radiated tissues
Potential Disadvantages of Proton Radiation Therapy

- More technically complex
- More conformal, more concerns for motion (internal and external)

- Relative biological effectiveness (RBE)
  - End of beam
- Potential toxicity concerns
  - More late effects with re-treatment
  - Developed of unexpected toxicities
- Clinical data regarding efficacy and toxicity, higher cost, reimbursement challenges, limited resource, treatment delivery technology
<table>
<thead>
<tr>
<th></th>
<th>Photon/ IMRT</th>
<th>Proton/IMPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin sparing</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Entrance dose vs. target</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Exit dose vs. target</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Target conformality</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td># Beams required</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Motion &amp; Heterogeneity</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
When to Consider Protons?

- Maximize sparing normal tissues
  - Proximity to critical “High real estate” areas

- Where dose escalation is beneficial

- Regions of predictable target motion and tissue homogeneity

- Retreatment of cases that have reached organ tolerances
Why Not Always Use Proton?

- Indication for treatment may be served by photons
  - Current conventional photon therapy give excellent results
  - Proton plan not always better then photon
    - Field size, tissue homogeneity, motion, DVHs
  - Palliative treatment
  - Urgent radiotherapy
  - Patient clinical condition

- Limited resource

- Cost & insurance related issues
Penn Vision for Future Directions for Proton

- Expand the clinical indications for proton
  - Rare tumors
  - Dose escalation
  - Combined modality
  - Retreatment with radiation

- Generate data regarding proton efficacy, toxicity, and supportive care

- Develop techniques and technology for treatment delivery
  - Improving target with soft tissue imaging (CBCT)
  - Mobilizations
  - PBS
  - IMPT

- Expand knowledge of Proton radiobiology

- Decrease cost and increase efficiency
Distribution of PENN Proton Patients 2013-15

- N=1594

- Breast: 3%
- Endocrine: 4%
- GU/Prostate: 17%
- Gastrointestinal: 17%
- Gynecology: 2%
- Head & Neck: 9%
- Lymphoma: 6%
- Metastases: 2%
- Missinng: 0%
- Neuro/CNS: 16%
- Sarcoma/Musculoskeletal: 8%
- Thoracic: 16%
- Skin: 0%
- Other: 0%
-\n- Penn Radiation Oncology
- Penn Medicine
Studies

- All patients treated at Penn are on clinical trial or registry
- Randomized Controlled Trials
  - Pragmatic Phase III Randomized Trial of Proton Vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer Receiving Comprehensive Nodal Radiation: A Radiotherapy Effectiveness (RADCOMP) Consortium Trial
  - Phase III Randomized Trial Comparing Overall Survival After Photon vs. Proton Chemoradiotherapy for inoperable Stage II-IIIB NSCLC
  - PARTIQoL: Prostate Advanced Radiation Technologies Investigating Quality of Life: A Phase III Randomized Clinical Trial of Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer.
- CNS
  - Therapeutic trials, radiosensitizers
  - Neurocognitive differences
- Thoracic
  - Trimodality, transponder
Studies

- **GI**
  - Esophageal
  - Anal
- **GU**
  - Propstate RCT, Hypofractionation
- **Pediatric**
- **Retreatment**
  - H& N, Thoracic, Abdominal, Pelvic & Extremity
- **Registry**
Research Limitations

- Small numbers of oncology patients participate clinical trials
- Most difficulties in recruitment are well known
- How does that affect recruitment/participation in proton trials?
  - Limited centers
  - Insurance caveats
  - Attrition particularly in RCT
Thymoma & Thymic Carcinoma

- Prospective Study
- 27 patients treated between 2011 and 2015
- Included patients receiving definitive (22%), adjuvant (63%) and salvage (15%) treatment
- Assessing for toxicity as well as local control
- No ≥ Grade 3 toxicity
- Grade 2 toxicities
  - Dermatitis, fatigue, esophagitis and pneumonitis
  - Late grade 2 – single patient with chronic dyspnea
- Follow Up
  - Median follow up at 2 years: 100% local control
  - 3 year follow up
    - Regional control 96%
    - Distant control 74%
    - Overall survival 94%

Thymus

Rx: 5940cGy
Neoadjuvant Chemoradiation for Locally Advanced Rectal Cancer Using Pencil Beam Scanned Proton Radiotherapy
Preop Rectal Cancer: PBS vs IMRT
## Rectal Cancer: Comparing PBS to IMRT

<table>
<thead>
<tr>
<th>Patients (Mean Age)</th>
<th>PBS PT</th>
<th>IMRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26 (61.2)</td>
<td>39 (58.5)</td>
<td>.35</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 53.8%</td>
<td>21 53.8%</td>
<td>.61</td>
</tr>
<tr>
<td>Female</td>
<td>12 46.2%</td>
<td>18 46.2%</td>
<td></td>
</tr>
<tr>
<td>Tumor Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2</td>
<td>4 15.4%</td>
<td>5 12.8%</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>19 73.1%</td>
<td>29 74.4%</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>0 0.0%</td>
<td>3 7.7%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 11.5%</td>
<td>2 5.1%</td>
<td>.26</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>17 65.4%</td>
<td>27 69.2%</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>8 30.8%</td>
<td>11 28.2%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 3.8%</td>
<td>1 2.6%</td>
<td>.88</td>
</tr>
<tr>
<td>Chemo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>10 38.5%</td>
<td>8 20.5%</td>
<td></td>
</tr>
<tr>
<td>CI 5-FU</td>
<td>16 61.5%</td>
<td>31 79.5%</td>
<td>.162</td>
</tr>
</tbody>
</table>

Batra S et al. Lower Rates of Acute GI Toxicity with Pencil Beam Proton Therapy Relative to IMRT In Neo-Adjuvant Chemoradiation for Rectal Cancer. ASCO GI 2015.
Batra S, Comisar L, Both S, Giantonio B, Mahmoud N, Lukens JN, Ben-Josef E, Metz JM, Plastaras JP. Lower Rates of Acute GI Toxicity with Pencil Beam Proton Therapy Relative to IMRT In Neo-Adjuvant Chemoradiation for Rectal Cancer. ASCO GI 2015.
## Preop Rectal Toxicity: PBS vs IMRT

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>PBS PT</th>
<th>IMRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade &gt;= 2 Diarrhea</td>
<td>3 (12%)</td>
<td>15 (39%)</td>
<td>.013</td>
</tr>
<tr>
<td>Grade &gt;= 2 Dehydration</td>
<td>2 (6%)</td>
<td>8 (22%)</td>
<td>.136</td>
</tr>
<tr>
<td>Grade &gt;= 2 Fatigue</td>
<td>2 (8%)</td>
<td>11 (29%)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Batra S, Comisar L, Both S, Giantonio B, Mahmoud N, Lukens JN, Ben-Josef E, Metz JM, Plastaras JP. Lower Rates of Acute GI Toxicity with Pencil Beam Proton Therapy Relative to IMRT In Neo-Adjuvant Chemoradiation for Rectal Cancer. ASCO GI 2015.
Definitive Chemoradiation for Anal Squamous Cell Cancer Using Pencil Beam Scanned Proton Radiotherapy
Anal Cancer

PBS

RA
Prospective Clinical Trial: PRT for Anal SCC

- A Pilot Feasibility Study of Definitive Concurrent Chemoradiation With Pencil Beam Scanning Proton Beam in Combination With 5-Fluorouracil and Mitomycin-C for Carcinoma of the Anal Canal

- PI: Wo, Jennifer (MGH Lead Site)

Primary Outcome:
- Feasibility of administration of pencil beam scanning proton beam radiation with chemotherapy for anal cancer:
  - Proton radiotherapy will be considered feasible if grade 3+ skin toxicity seen on this protocol is less than 48% (reported grade 3+ dermatologic toxicity from RTOG 98-11)

ClinicalTrials.gov Identifier: NCT01858025
RCT

- ASCO June 2016
- RCT NSCLC
- 255 locally advanced NSCLC randomized to proton therapy vs. standard IMRT
- Proton group had larger target volumes, higher tumor doses and larger lung volumes in 30-80 Gy range
- No difference in treatment failure (Grade 3 or more radiation pneumonitis or local recurrence in 12 months)
- No improvement in overall survival with proton therapy
- Equivalent mean doses to lung and esophagus; significant reduction in mean dose to the heart with protons
Cone Beam CT (CBCT)

- Volumetric imaging for increased accuracy
- 3D Imaging
- Accurate patient positioning
- Rapidly assess current treatment dose
- Motion & increased sensitivity to anatomic changes
  - Tumor enlargement or regression, weight change, other anatomic change
Intensity-Modulated Proton Therapy (IMPT)

- Currently being tested
- New scanning beam nozzles in development will permit complex beam shaping needed for IMPT.
- Critical in improving precision, driving the expansion of proton therapy into other tumor types
- Enable proton therapy to complete with traditional radiation therapy.
Nursing Implications

- **Up to Date on the science, implications & treatment decision making with proton therapy**
- **Patient Education**
  - Side effects
- **Supportive care**
  - Thinking about how it may or may not differ from a patient receiving photon therapy
- **Opportunities for Nursing Research**
  - Supportive Care
    - Dermatitis, preservation of sexual function
    - Mucosal toxicities
  - QOL Metrics