Introduction to Proton Therapy at UAB

Adam Kole, MD, PhD
Assistant Professor
Department of Radiation Oncology
University of Alabama at Birmingham
Part 1: Why talk about proton therapy?
The number of patients treated with proton therapy is growing

~30 proton facilities currently in the US

9 additional US facilities under construction
UAB Proton Therapy Center
UAB Proton Therapy Center

Construction
Start 1/2/18

Building Ready for Equipment 2/11/19

Cyclotron Arrival 2/28/19

Construction
Jan 2, 2018 - Jun 10, 2019

Proton Treatment Facility
Part 2: What is proton radiation?
Review of photon (X-ray) radiation

X-ray:

Tumor
Review of photon (X-ray) radiation

- Characteristics of X-ray RT:
  - Unnecessary exit dose
  - Maximum dose from each beam is near skin surface

Review of photon (X-ray) radiation

![Diagram showing dose vs. depth with a shaded area around the tumor](image)
Review of photon (X-ray) radiation
Modern Photon RT

Static Field IMRT:
Modern Photon RT – Large Areas of Low Dose

Conventional (X-ray) vs. Proton RT

X-ray:

Proton:
Conventional (X-ray) vs. Proton RT

Modified from Stokkevåg et al, Acta Oncol, 2014
Physics of Proton RT

Dose vs. Depth graph showing the Bragg peak and the tumor area.

Bragg peak

Tumor
Many possible applications of proton RT

Leeman et al, Lancet Oncol, 2017
Part 3: How are protons delivered?
Current Beam Lines at PSI

- **Cyclotron**: 70 – 250 MeV protons
- **Custom PBS gantries** designed in-house
- **Passive scattering for ocular tumors**
- **Varian ProBeam (PBS)**
Physics of Proton RT

Bragg peak

Dose

Depth

Tumor
Physics of Proton RT
Physics of Proton RT

"Spread out Bragg peak"
Types Of Proton Beam Delivery

- Passive Scattering
- Pencil Beam (Spot) Scanning
Passive Scattering

Scatterers

Aperture

Range modulator

Dose Delivered

Tumor
Pencil Beam (Spot) Scanning

Passive Scattering:

- Scatterers
- Aperture
- Compensator
- Dose Delivered
- Tumor
Pencil Beam (Spot) Scanning

Passive Scattering:

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Pencil Beam

Steering Magnets

Tumor
Pencil Beam (Spot) Scanning

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Dose Delivered

Pencil Beam

Steering Magnets

Tumor
Types Of Proton Beam Delivery

Passive Scattering:
- Major advantages of PBS:
  - Allows conformality in 3-dimensions with a single beam
  - No need to manufacture patient-specific devices (e.g. apertures, compensators)
  - Improved skin sparing
  - Dose modulation within different portions of tumor volume is possible (i.e. IMPT)
  - Fewer secondary neutrons

Pencil Beam Scanning:
Comparison of RT Techniques

IMRT  Proton Passive Scattering  Proton Pencil Beam Scanning

Grosshans et al., Neuro Oncology, 2017
Part 4: Are there possible disadvantages to proton RT?
Range Uncertainty

- Proton range depends on beam energy and composition/thickness of material it is passing through

- Important considerations:
  - Changes in anatomic compartments
    - Sinus/bowel/bladder filling
    - Weight loss
    - Tumor growth/shrinkage
  - CT artifacts
  - Patient set-up errors
  - Stopping power calibration uncertainties
  - Uncertainties in precision of beam energy selection and spot placement
Range Uncertainty - Examples

- Sinus filling during treatment

Placidi et al, *IJROBP*, 2017
Range Uncertainty - Examples

- Tumor shrinkage during treatment
Range Uncertainty - Solutions

- Appropriate beam angle selection
  - Short beam paths
  - Avoid regions prone to anatomic change (e.g., air cavities, seromas, etc.)
  - Avoid hardware and other heterogeneities if possible

- Consider use of “robust optimization” during planning

- IGRT and careful attention to patient set up

- Monitor weight loss / anatomic changes closely

- Re-calculate RT plan if concerned and adapt plan if necessary
Range Uncertainty - Solutions

Less robust

More robust

%
Part 5: What are the indications for proton therapy?
Proton Therapy Indications

ASTRO Model Policies

PROTON BEAM THERAPY (PBT)

- Written to communicate when proton RT should be covered by insurance

- Two groups
  - Group 1: Proton RT supported
  - Group 2: Suitable in the context of clinical trial or registry
Proton Therapy Indications

- **ASTRO Group 1:**
  - Base of skull tumors
    - Chordoma
    - Chondrosarcoma
  - Primary CNS tumors (benign or malignant)
  - Unresectable head & neck cancers
  - Tumors of paranasal sinus
  - Retroperitoneal sarcomas

- Primary or metastatic tumors of the spine
- Solid tumors in children
- Re-irradiation cases, when photon RT would exceed dose tolerance
- Patients with genetic syndromes (eg. NF1, Rb) where total volume of RT should be reduced
- Ocular tumors (especially when dedicated beam line present)
Proton Therapy Indications

• ASTRO Group 2:
  • Resectable head & neck cancer
  • Thoracic cancers (non-metastatic)
    • Lung cancer
    • Esophageal
    • Lymphoma
  • Abdominal cancers (non-metastatic)
    • Pancreatic
    • Biliary
    • Adrenal
  • Pelvic cancers (non-metastatic)
    • Lower GI: rectal and anal
    • Bladder
    • Cervical
  • Breast cancer
  • Prostate cancer
Simplified Indications for Proton RT

- **Excellent candidates:**
  - Patients with long life expectancy
  - Tumors with high chance for long-term control
  - Cases which require high dose adjacent to critical structures
  - Cases where reducing low-medium dose would reduce toxicity

- **Poor candidates:**
  - Any emergent treatment
    - Spinal cord compression
    - SVC syndrome
  - Most metastatic or palliative cases
  - Diseases with particularly poor prognosis (e.g. GBM)
Part 6: Any data available comparing proton to photon RT?
Clinical Evidence Overview

- Available data promising, but mostly:
  - *In silico* analyses of proton vs. photon dose distribution
  - Retrospective comparisons of proton vs. photon cohorts
  - Single-arm proton studies (some long-term and prospective)

- Currently, there is no level 1 evidence showing superiority of protons vs. photons

- Randomized trials between protons vs. photons are either ongoing, have not been performed, or will not be performed
Base of Skull Tumors

- Chordoma / Chondrosarcoma
  - Frequently present in the clivus or sacrum
  - Challenging location (brainstem, optic chiasm)
Base of Skull Tumors

- **Chordoma / Chondrosarcoma**
  - Frequently present in the clivus or sacrum
  - Challenging location (brainstem, optic chiasm)
  - Disease control very poor historically (doses ~50 Gy):

Fig. 3. Progression-free survival for 36 patients with overt disease treated with radical intent.

Fig. 1. Overall survival for all 45 cases, with a comparison of survival from diagnosis for those presenting with clival and non-clival tumours.

Base of Skull Tumors

- Chordoma / Chondrosarcoma
  - Dose escalation to 70-74 Gy possible with proton therapy
  - Dramatically improved recurrence / survival rates

Weber et al, IJROBP, 2016
Head and Neck – Dosimetric Comparison

Unilateral RT

Bilateral RT

Leeman et al, Lancet Oncol, 2017
Head and Neck – Clinical Outcomes

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Disease sub-site</th>
<th>Methodology</th>
<th>Toxicity evaluated</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photon vs Proton</td>
<td>p value</td>
</tr>
<tr>
<td>Romesser et al (2016)</td>
<td>18 proton beam therapy, 23 intensity modulated radiotherapy</td>
<td>Unilateral head and neck cancer (major salivary gland or cutaneous primary)</td>
<td>Retrospective cohort comparison</td>
<td>Mucositis, grade 2 or worse; nausea, grade 1 or worse; dysgeusia, grade 1 or worse; fatigue, grade 1 or worse; dermatitis, grade 2 or worse</td>
</tr>
<tr>
<td>McDonald et al (2016)</td>
<td>14 proton beam therapy, 12 intensity modulated radiotherapy, 14 proton beam therapy to primary site and intensity modulated radiotherapy to neck</td>
<td>Nasopharyngeal, nasal cavity or paranasal sinus cancer</td>
<td>Retrospective cohort comparison</td>
<td>Gastrostomy tube dependent at completion of radiotherapy; gastrostomy tube dependent 1 month after radiotherapy; equivalent morphine dose greater than baseline at end of radiotherapy</td>
</tr>
<tr>
<td>Sio et al (2016)</td>
<td>35 intensity modulated proton therapy, 46 intensity modulated radiotherapy</td>
<td>Oropharyngeal cancer</td>
<td>Retrospective cohort comparison</td>
<td>Subacute food taste symptoms; subacute appetite symptoms; chronic appetite symptoms; subacute mucous symptoms (% with moderate-severe symptoms)</td>
</tr>
<tr>
<td>Blanchard et al (2016)</td>
<td>50 intensity modulated proton therapy, 100 intensity modulated radiotherapy</td>
<td>Oropharyngeal cancer</td>
<td>Retrospective case-matched control comparison</td>
<td>Patient-rated xerostomia, grade 2-3, 3 months after radiotherapy; gastrostomy tube presence or weight loss &gt;20%, 1 year after radiotherapy</td>
</tr>
<tr>
<td>Holliday et al (2015)</td>
<td>10 intensity modulated proton therapy, 20 intensity modulated radiotherapy</td>
<td>Nasopharyngeal cancer</td>
<td>Retrospective case-matched control comparison</td>
<td>Gastrostomy tube needed during or after treatment</td>
</tr>
<tr>
<td>Patel et al (2014)</td>
<td>286 charged particle (proton, carbon ion, helium ion, or other), 1186 photon (41 studies included)</td>
<td>Nasal cavity and paranasal sinus cancer</td>
<td>Systematic review and meta-analysis</td>
<td>Neurological toxicity (95% CI)</td>
</tr>
</tbody>
</table>

MDASI-HN = MD Anderson Symptom Inventory-Head and Neck. *Proton vs photon odds ratio (95% CI). †Mean MDASI-HN score.

Table 1: Direct comparisons of photon versus proton toxicity in head and neck cancer

- **Note:** All retrospective analyses
- Improved acute toxicity during unilateral RT (except skin; note passive scattering technique)
- Reduced PEG tube dependence for nasopharyngeal / nasal / paranasal cancers
- Improved taste, appetite, mucositis in oropharynx patients
- Reduced grade 2+ xerostomia and PEG tube dependence
- Reduced PEG tube dependence in nasopharyngeal carcinoma
- Worse toxicity, but improved OS among patients receiving particle therapy for nasal / paranasal cancers

Breast Cancer – Dosimetric Comparison

Proton radiotherapy for chest wall and regional lymphatic radiation; dose comparisons and treatment delivery

Shannon M MacDonald, Rachel Jimenez, Peter Paetzold, Judith Adams, Jonathan Beatty, Thomas F DeLaney, Hanne Kooy, Alphonse G Taghian and Hsiao-Ming Lu

- 11 left-sided PMRT patients planned with:
  - Partially wide tangents
  - Matched photon/electron fields
  - Protons (passively scattered)

- Dosimetric advantage of proton RT:
  - Improved target coverage with better homogeneity
  - Reduced cardiac dose
  - Reduced ipsilateral lung dose

Figure 2 Dose volume histograms for chest wall (a) and internal mammary nodes (b) averaged over the patients for the three treatment techniques PWTF (dashed), P/E (thin solid) and 3D CRT (thick solid).

Figure 4 Dose volume histograms for heart (a) and left lung (b) over the patients for the three treatment techniques PWTF (dashed), P/E (thin solid) and 3D CRT (thick solid).
MDACC/MGH Phase II randomized trial for inoperable advanced NSCLC

All patients received definitive chemoRT, between 66 to 74 Gy

Primary end points: grade 3+ pneumonitis, local failure
Primary end points:

- No significant difference in local failure or radiation pneumonitis between protons and IMRT

Liao et al, JCO, 2018
• Dosimetric findings:

→ Unexpected: important lung metrics (mean lung dose, lung V20) were not better with protons

Liao et al, JCO, 2018
Lung Cancer

• Considerations:
  • Proton learning curve?
    • Patients treated with protons in early portion of the trial had highest pneumonitis rates
    • Proton cases with pneumonitis were re-planned years later → improved lung metrics observed

Liao et al, JCO, 2018
Lung Cancer

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  • Tumor differences?
    • GTV size in “early” proton group was 2-3x larger than IMRT group

<table>
<thead>
<tr>
<th></th>
<th>IMRT Early</th>
<th>IMRT Later</th>
<th>P Value</th>
<th>PSPT Early</th>
<th>PSPT Later</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross target volume, cm³, median (range)</td>
<td>69.0 (5.9-686.6)</td>
<td>62.4 (5.8-355.5)</td>
<td>0.743</td>
<td>150.6 (1.9-673.7)</td>
<td>56.0 (12.0-221.3)</td>
<td>0.011</td>
</tr>
</tbody>
</table>
Lung Cancer

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  - Suboptimal conformality with passive scattering proton RT?

Liao et al., JCO, 2018

Passive Scattering

Pencil Beam Scanning
Lung Cancer

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  - Tumor differences?
    - GTV size in “early” proton group was 2-3x larger than IMRT group
  - Suboptimal conformality with passive scattering proton RT?
  - Proton range uncertainties given heterogeneous anatomy, moving tumors, tumor shrinkage?
  - Is better patient selection needed?
    - 6% of patients excluded from trial because proton plan > IMRT plan; these patients not randomized
  - Ongoing trial: RTOG 1308 phase III proton vs. IMRT inoperable advanced NSCLC
Part 7: Summary
Proton Therapy Summary

- Proton therapy is growing and coming to Alabama
- Protons have inherent advantages over photon therapy
  - Elimination of unnecessary exit dose
  - Majority of dose delivered at depth, where tumor is located
- Pencil beam scanning is most modern delivery technique available
- Range uncertainty must be carefully considered
- Clinical data are encouraging
Questions?