The Clinical Application of Proton Pencil Beam Scanning for High-Dose Spatially Fractionated Radiation (GRID) Therapy

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Disclosures

• Nothing to disclose

Learning Objectives

• To learn some of the historical background of high-dose spatially fractionated radiation therapy (GRID Therapy)

• To recognize the common clinical indications for GRID therapy.

• To appreciate how PBS protons can provide clinical effectiveness and improve patient safety in a sub-set of patients where GRID therapy is indicated.
The early problems of deep seated targets and Ortho-voltage X-Ray

An alternative approach to space skin

- 1895: Roentgen discovers X-Ray
- In 1902: first reported treatment using X-ray
- In 1909: Kohler introduced a method to spare some skin in the irradiated field by using a perforated screen initially made of Pb and rubber.
- Produced a “Grid” pattern of X-ray intensity over the field of 100-400kVp
- Able to increase doses 20X's higher with tolerable dose to the skin

Treatment Planning: 101

- Rule #1: Cover the target with dose to control disease
- Rule #2: Limit dose to critical structures to minimize the probability of toxicities

Nevertheless GRID therapy produced good clinical outcomes
A second look at GRID Therapy

- Renewable interest published by Mohiuddin in 1990.
- Spatially fractionated radiotherapy was similar to a brachytherapy boost
  - Goal: safe delivery of high doses without exceeding normal tissue tolerance
- 22 patients, already treated with:
  - maximal surgery
  - maximum conventional chemotherapy
  - maximum conventional radiotherapy
  - massive tumor bulk

- Single GRID Field with 6MV Peak doses of 10 – 15Gy
- All patients were treated with intent of palliation
  - 6 had prior irradiation of > 50Gy
  - 14 had EBRT in addition to GRID
  - 4 had GRID Tx repeated after a 4 week interval
- Reported complication
  - 1 O-phosphate, 2 Al do cases and Noces and Cahil
  - 1 late bowel obstruction, 70Gy + 10Gy GRID
- Excellent response rates
  - 20 of 22 achieved "dramatic relief of severe symptoms"

<table>
<thead>
<tr>
<th>Table 3: Response Rate as a Function of the Four Most Common Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Oedema</td>
</tr>
<tr>
<td>Late bowel obstr.</td>
</tr>
<tr>
<td>CR: complete response; PR: partial response; NR: no response</td>
</tr>
</tbody>
</table>
A slowing growing interest in SFRT

So what is going on to make GRID therapy work??

- GRID treatments minimize the toxicity of high dose radiations by limiting the volume of normal tissues irradiated.
- Although the entire target is not covered by the high dose, GRID treatment remain clinically effective.
- For these extremely inhomogeneous radiation fields, there exists signal-mediated effects:
  - near the tumor (bystander effects)
  - at distance sites (abscopal effects)

Bystander effects:
- Cellular and biological effects occur on un-irradiated tumor cells (located in the valleys) in response to signals from irradiated cells within the peak portion of the radiation.
- Genes survive in the valleys are much less than what is expected by the dose delivered in these regions.
- Overexpression of DNA repair, apoptosis, cell cycle control, heat shock protein and antioxidant/pro-oxidant genes
- TNFa, a cytokine associated with tumor killing was increased from baseline levels in 32% of GRID patients and correlated with improved clinical response


So what is going on to make GRID therapy work??

- Abscopal effects:
  - An action at a distance from the irradiated volume, but within the same organism.

<table>
<thead>
<tr>
<th>Radiation Field</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Full Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>X X 10%</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>X X 20%</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>X X 50%</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Full Field</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
A new need ... in a new time... with new technology

• Skin sparing to treat deep targets is no longer the primary motivation

• Now treating large, bulky, poorly responding targets with limited alternative treatment options

• Spatial fractionation (spatial dose inhomogeneities) is the primary goal

• High-energy linear accelerators are the X-ray source

Linac Based GRID Therapy: Describing the beam

• How do we quantify the GRID Dose?
  - Hole Size and Spacing
    • Hexagonal pattern (equidistant holes)
    • i.e. 1cm diam. holes spaced 2cm apart
  - Valley to Peak Ratio (VP)

  \[
  \text{VP} (\text{Depth}, \text{E}, \text{GRID}) = \frac{\text{Dose valley}}{\text{Dose peak}}
  \]

  Dose prescribed a (D(max)) in the center of an open hole
Linac Based GRID Therapy: Creating the GRID

- **Physical Block**
  - Cerrobend / Brass

- **3-D Printed** *
  - Poured Cerrobend


Linac Based GRID Therapy: Creating the GRID

- **MLC Based GRID Patterns**


Linac Based GRID Therapy: Creating the GRID

- **3-D Conformal, VMAT or Tomotherapy methods**

Linac Based GRID Therapy: Creating the GRID

• 3-D Conformal, VMAT or Tomotherapy methods

**The Physics of Protons**

**Depth Dose Curves for Different Treatment Types**

- **High Energy X-Rays**
- **Spread Out Bragg Peak (SOBP)**

With protons, a few questions arise....

- Can PBS spot patterns be configured to deliver GRID type dose distributions?
  - Similar peak to peak (hole) positioning
  - Similar valley to peak (VP) ratios
  - Some different assumptions would need to be made depth dose shape
With regards to PBS protons, a few question arise....

- Feasibility Study
  - Phantom plans of simple shapes
  - Dosimetric verifications
  - Common GRID parameters compared

- Early report on clinical implementation
  - Two of the first four cases are presented

Shallow Depth and a Deep Depth Simulation

Shallow Target: 20cm X 20cm X 12cm
- Central depth 6cm
- Proximal depth at surface

Deep Target: 15cm X 15cm X 8cm
- Central depth 14cm
- Proximal depth = 10cm

Shallow Target: 20cm X 20cm X 12cm
- Central depth 6cm
- Proximal depth at surface

Deep Target: 15cm X 15cm X 8cm
- Central depth 14cm
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Spot Spacing
Match GRID Block
2cm spacing
PBS Protons: Energy Stacking to create the SOBP

Dose gradient with depth on traditional GRID

PBS energy stacking can be optimized to match photon PDD's
PBS energy stacking can be optimized to match photon PDD's

PDD optimizations for the Shallow and Deep targets

Valley to Peak Ratios: Comparison to photon block GRID

- PBS plan were created using RayStation treatment planning system (RaySearch Labs, Sweden) and IBA Universal Nozzle proton machine (IBA, Belgium).
- Valley / Peak Ratios (VP) are a function of:
  - Depth
  - Spot/Hole spacing
  - Local scatter conditions
- Gold standard: 6MV and 18MV commercially available Photon GRID blocks, 1cm holes spaced at 2cm
- Our evaluation of the VP ratios of the different modalities demonstrates that the proton GRID distributions are clinically equivalent to photon GRID.
Profile optimizations for the Shallow and Deep targets

Valley to Peak Comparisons

<table>
<thead>
<tr>
<th>Depth (cm)</th>
<th>Description</th>
<th>Photon 6 MV</th>
<th>Photon 10 MV</th>
<th>Photon PBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 cm</td>
<td>Shallow target</td>
<td>0.23</td>
<td>0.34</td>
<td>0.23</td>
</tr>
<tr>
<td>5.0 cm</td>
<td>Shallow target</td>
<td>0.27</td>
<td>0.38</td>
<td>0.34</td>
</tr>
<tr>
<td>10.0 cm</td>
<td>Deep target</td>
<td>0.29</td>
<td>0.37</td>
<td>0.31</td>
</tr>
<tr>
<td>15.0 cm</td>
<td>Deep target</td>
<td>0.36</td>
<td>0.40</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Verification of Valley to Peak Ratios: Measured vs. Calculated

- Beamlet distributions were calculated using Raystation with MC algorithm and 1 mm calc point spacing.
- Profiles measured with IBA Dosimetry Lynx and MatrixPT.
- Lynx (Scint plate and CCD) used for relative, high spatial resolution (0.5 mm).
- MatrixPT used as absolute dosimeter. Ion chamber array chamber size 4.5 mm spaced 7.6 mm apart.
- Lynx data was down sampled to match spatial resolution of the MatrixPT chamber. Then, a least squares method was used to correct the Lynx data obtained using a least squares method.
Verification of Valley to Peak Ratios: Measured vs. Calculated

Real patient Proton GRID Planning Strategies

- Start with spots centered 2 cm apart and verify VP ratios in the target are ~0.25 – 0.30. If needed, open spot spacing. Attempt to place spots only inside the target.
- Because of the high single fraction doses (15-20 Gy\textsubscript{RBE}), maximum MU/spot constraints may be exceeded. A simple fix on our IBA system was to force layer repainting.
- Keep spots away from very critical OAR’s. Consider dosimetric consequences of:
  - Remember, it is not necessary to cover the entire target! Plan conservatively.
  - Do not use extremely low energy proton layers to provide some skin sparing (max ~95% at surface)

GRID Therapy at our center

- 14 patients treated thus far using the methods described here
- Doses ranged for 15-20Gy\textsubscript{RBE}, most patients receive and additional short course of Std Fx RT.
- Retrospective analysis of first 10 patients has been submitted for publication and was presented at the “Workshop on Understanding High-Dose, Ultra-dose rate, and Spatial Fractionated Radiotherapy” held on August 21, 2018 in Bethesda, MD.
  - Response rates very consistent with previously published works with a 90% local response rate and a similar side-effect profile.
- We are considering a Phase I study to determine optimal Proton GRID Doses / VP Ratios
Case Studies

Case 1

68 yo male, recurrent sarcoma of the back
50Gy XRT 2 years prior followed by a re-section
1 year after RT had another resection

Aortic valve replacement
Hypertension
Bowel perforation

Referred for Proton GRID of 18Gy(RBE)
\[ + 15 \times 2.5\text{Gy(RBE)} = 37.5\text{Gy(RBE)} \] Total
Case 1

85 yo male, 3 years ago diag with head/neck undifferentiated carcinoma Rt lip possible salivary primary

Resection. 24 of 38 +LN Rt side, and 2 of 16 + Lt side Chemo + 64Gy to upper lip and Bilateral neck, Lt side treated to 45-50Gy

2 years later recurrence in Lt Neck, metastatic to the skin. De-bulking surgery and Chemo.

Trouble swallowing and speaking, PET showed involvement encasing the carotid and brachial plexus

Referred for 20Gy(RBE) GRID + XRT Boost of ~30Gy

Case 2

85 yo male, 3 years ago diag with head/neck undifferentiated carcinoma Rt lip possible salivary primary

Resection. 24 of 38 +LN Rt side, and 2 of 16 + Lt side Chemo + 64Gy to upper lip and Bilateral neck, Lt side treated to 45-50Gy

2 years later recurrence in Lt Neck, metastatic to the skin. De-bulking surgery and Chemo.

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Referred for 20Gy(RBE) GRID + XRT Boost of ~30Gy
In conclusion.....

• Modern GRID Therapy can be a clinically effective treatment for some advanced, bulky tumors

• Pencil Beam Scanned Proton Beamlets can be used to generate the inhomogeneous GRID doses with similar properties to historical photon GRID blocks.

• The use of a PBS Proton GRID can be provide a safe and effective treatment option in cases where photon GRID treatments may be difficult.

THANK YOU