The State of the Art: Proton Therapy

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Yoshiya Yamada MD FRCPC
Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center
Disclosures

• Varian Medical Systems. Consultant, research funding
• BrainLab. Consultant
• University of Wollongong. Consultant Professor
• N = 186 “Separation surgery”
• 40 = Single fraction SRS (2400cGy)
• 37 = High dose hypofractionated SRS (3 fractions)
• 109 = low dose hypofractionated (5 fractions)
• 144 = radioresistant
• Prior RT N = 91
• Histology = NS
• High dose significantly higher LC (900cGy×3) vs low dose (600cGy×5) (p=0.04)
• RT failures did no worse than RT naïve patients after separation surgery and high dose SBRT in MVA
40Gy/5 Salvage SBRT

(Moore et al ASTRO 2022)

- Retrospective analysis of 63 consecutive patients salvaged with 800cGy×5 after prior SBRT for spine metastases.
- Median FU 11.9 months (1.8-39.6 months)
- 5 patients with late toxicity
  - G1 = 2
  - G2 = 1
  - G3 = 2 (1 subacute pneumonitis)
- Fracture risk
  - 3 patients post salvage kypho (4.8%)
  - 7 patients post salvage surgery (11.3%)

12% cumulative incidence of LF at 12 months
Reirradiation: Where Are We?

- Reirradiation – The most widely accepted indication for spine SBRT
  - Ablative nature of SBRT overcomes radioresistant clones (Laufer et al)
  - SBRT limits dose exposure to previously irradiated normal tissue resulting in acceptable toxicity
  - SBRT can be effective in salvage of SBRT failures (Moore)

- *Is there a role for proton based salvage spine SBRT?*
Photons

Protons

Esophagus

Esophagus

Esophagus

Esophagus

Courtesy Jessie Liang PhD
## Proton vs Photon SRS: 24 Gy x 1 to T7

<table>
<thead>
<tr>
<th></th>
<th>Photon (cGY)</th>
<th>Proton (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV Dmin</td>
<td>1371.9</td>
<td>1463.0</td>
</tr>
<tr>
<td>PTV Dmax</td>
<td>2986.0</td>
<td>2958.5</td>
</tr>
<tr>
<td>Cord Dmax</td>
<td>1431.7</td>
<td>1441.8</td>
</tr>
<tr>
<td>Cord Dave</td>
<td>472.2</td>
<td>452.1</td>
</tr>
<tr>
<td>Cord Dmin</td>
<td>77.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Esophagus Dmin</td>
<td>66.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Esophagus Dave</td>
<td>705.4</td>
<td>345.2</td>
</tr>
<tr>
<td>Esophagus Dmax</td>
<td>2142.3</td>
<td>2082.0</td>
</tr>
</tbody>
</table>
“Flash” Radiotherapy

• Ultra high dose rate radiotherapy: RT delivered 400x (>40Gy/s) faster than conventional radiotherapy (5Gy/min).
  – Normal Tissue Sparing
    • Lung fibrosis
      – 17Gy FLASH = minimal fibrosis vs 17Gy Conventional Dose Rate RT
      – 30Gy FLASH = 17Gy CDR Fibrosis rate
    • Brain (juvenile mice WBRT)
      – FLASH 8Gy x 1 = control group (No RT) vs CDR 8Gy (significant determent)
<table>
<thead>
<tr>
<th>Model (Site of Irradiation)</th>
<th>Assay/Endpoint</th>
<th>Dose (Gy)</th>
<th>Dose Rate (Gy/s)</th>
<th>Radiation Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice (WBI) ¹</td>
<td>Memory tests, neurogenesis</td>
<td>10</td>
<td>&gt;100</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (WBI) ¹</td>
<td>Neurocognitive tests, mature/immature neurons, growth hormone levels</td>
<td>8</td>
<td>$4.4 \times 10^6$</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (WBI) ¹</td>
<td>Neurocognitive tests, dendritic spine density, microglial activation, inflammation</td>
<td>30</td>
<td>200/300</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (WBI) ¹</td>
<td>Neurocognitive tests, neuroinflammation, neuronal morphology</td>
<td>10</td>
<td>&gt;100</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (WBI) ¹</td>
<td>Neurocognitive tests, hippocampal cell division, astrogliosis</td>
<td>10</td>
<td>37</td>
<td>X-ray</td>
</tr>
<tr>
<td>Mice (thorax)</td>
<td>Survival, dermatitis, breathing function, lung pathology</td>
<td>15/17.5/20</td>
<td>40</td>
<td>Proton</td>
</tr>
<tr>
<td>Mice (thorax)</td>
<td>Lung fibrosis, skin dermatitis, survival</td>
<td>15/17.5/20</td>
<td>40</td>
<td>Proton</td>
</tr>
<tr>
<td>Mice (thorax)</td>
<td>Lung fibrosis, TGF-β signaling, apoptosis</td>
<td>17</td>
<td>40–60</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (thorax)</td>
<td>Cellular proliferation, pro-inflammatory gene expression, DNA damage (53BP1/γH2AX foci), senescence</td>
<td>17</td>
<td>40–60</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (abdomen)</td>
<td>Survival</td>
<td>10–22</td>
<td>70–210</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice (abdomen)</td>
<td>Survival, stool production, crypt cell regeneration, apoptosis, DNA damage</td>
<td>12–16</td>
<td>216</td>
<td>Electron</td>
</tr>
</tbody>
</table>

## FLASH: Tumor Control

<table>
<thead>
<tr>
<th>Model</th>
<th>Assay/Endpoint</th>
<th>Dose (Gy)</th>
<th>Dose Rate (Gy/s)</th>
<th>Radiation Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice, HBCx-12A, and Hep-2 human xenografts (local)</td>
<td>Tumor growth</td>
<td>17–25</td>
<td>60</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice, orthotopic engrafted lung carcinoma luciferase+ TC-1 cells (thorax)</td>
<td>Tumor growth</td>
<td>15–28</td>
<td>60</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice, ID8 syngeneic ovarian cancer (thorax)</td>
<td>Tumor number/weight</td>
<td>14</td>
<td>216</td>
<td>Electron</td>
</tr>
<tr>
<td>Mice, orthotopic engrafted Lewis lung carcinoma (thorax)</td>
<td>Tumor size</td>
<td>18</td>
<td>40</td>
<td>Proton</td>
</tr>
<tr>
<td>Mice, pancreatic <a href="https://example.com">MH641905</a> flank tumor</td>
<td>Tumor growth</td>
<td>12/15</td>
<td>78</td>
<td>Proton</td>
</tr>
<tr>
<td>Cat, nasal planum SCC (local)</td>
<td>Tumor growth</td>
<td>25–41</td>
<td>130–390</td>
<td>Electron</td>
</tr>
<tr>
<td>Human, CD30+ T-cell cutaneous lymphoma</td>
<td>Tumor response</td>
<td>15</td>
<td>167</td>
<td>Electron</td>
</tr>
</tbody>
</table>
• No difference in tumor control vs CDR RT
• Normal tissue sparing = opportunity for dose escalation
  – 15Gy CDR = 20% LC in implanted lung tumor vs 70% with 28Gy FLASH
  – CDR lungs significant fibrosis, minimal with FLASH

Standard Rate RT (0.9 Gy/s) and FLASH (78Gy/s) Mouse Model

Flash: spares proliferating crypt cells (a), greater regeneration of crypt cells (b) with significant less fibrosis 8 weeks post RT (c)

Flash: no impact on probability of tumor control at 12Gy x 1 (d) or 18Gy x 1 (e) compared to standard rate RT
Role of Proton SRS/SBRT in Spine Tumors

• Advantages of Protons: Sparing Normal Tissue
  – Dosimetric
    • Sparing the esophagus
    • Pneumonitis risk
    • Bowel toxicity
  – Biologic
    • FLASH reduce toxicity by 50% equivalent dose.
• Ideal platform for reirradiation SBRT
  – Technical considerations/challenges:
    • Managing uncertainties
      – Patient related factors
      – Beam related factors
      – Surgical hardware
    • Treatment planning
• Reirradiation-a critical need
  – Potential for proton SBRT cannot be understated
FLASH: Technical Considerations/Challenges

• Ultra accurate patient set up
• Beam delivery
  – Developing tools for FLASH QA
  – Passive scatter vs scanning
  – Scanning + ridge filter for range modulation

• Treatment planning systems need to be adapted to provide FLASH compatible conditions
  – Increasing beam intensity
  – Reducing beam spots
  – Optimal number of fields
The Future of Spine SBRT: Proton FLASH

• Dosimetric and biologic advantages for normal tissue.
  – Esophagus
  – Spinal Cord
  – Bowel
  – Large volumes

• Normal tissue sparing will allow for tumor dose escalation and biologic effective dose escalation