Perils of Proton Therapy

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Are there any issues with these illustrations?

Expansion of tumor

- 250 MeV carbon ions
- 135 MeV protons
- 18 MV photons

Penetration depth (cm)

Relative Dose

Siemens Particle Therapy 2007

Proton spot scanning (from PSI home page, Pedroni et al)
Yes, they have made Proton Therapy prone to hyperbole

“Proton therapy can strike a tumor with millimeter accuracy, yet spare healthy tissue around the tumor and cause very few, if any, side effects. In the Proton Therapy Center, we’re able to deliver energy like never before.”

“It sounds like power belonging only to a superhero: a high-powered beam that is able to zap a millimeter area within someone’s body, and yet not harm the surrounding healthy cells. Heroic — yes, but this is not in comic books. It’s happening in real life, in nearby XXXXXX.”

“When treated with Proton Beam Therapy, radiation is controlled while inside the body, that enables the physician to deliver full or higher doses while sparing surrounding healthy tissues and organs. It allows to deliver necessary dose of radiation without causing damage to healthy tissues.”

“With protons.. energy can be very precisely controlled to place the Bragg peak within a tumor or other tissues that are targeted to receive the radiation dose. Because the protons are absorbed at this point, normal tissues beyond the target receive very little or no radiation”. 
Promises of Proton Therapy

Compared to external beam photon therapy, proton therapy:

• Decreases the integral dose due to the “finite range” of protons
• Reduces the volume of normal tissue exposed to low doses, potentially lowering the risk of second malignancies. This risk is notably higher for young patients, as they are more at risk to future radiation induced cancers.
• Has demonstrated advantage for treating small tumor volumes at shallow depths (eye tumors and CNS such as chordomas and chondrosarcomas)
• Has demonstrated advantage for treating a few select cases in almost all disease site
Perils of Proton Therapy

1. Uncertainties:
   - Consequences of nuclear interactions (neutrons)
   - Multiple Coulomb scattering (lateral penumbra)
   - Intrinsic basic physics uncertainty (I-values)
   - CT numbers (stopping powers; range)
   - Dose calculation errors due to complex inhomogeneities,
   - Intra-fractional organ motion,
   - Inter-fractional changes in anatomy and motion patterns,
   - Mis-registration of tissue compensators (passively scattered proton beams,
   - Uncertainties in immobilization devices and patient support devices

2. Evaluation of proton plans
   - How to evaluate a proton plan in the presence of various uncertainties?
     - PTV?
     - Error bars of dose distributions?
Nuclear Interactions

About 20% (~1%/g.cm\(^{-2}\)) of primary protons lost to interactions with atomic nuclei.

- Effect on the depth dose curve
  - Pristine Bragg peak
  - Proton fluence
  - Resultant Bragg peak

- Effect on the lateral dose distribution
  - Secondary particle fluence resulting from nuclear interactions
  - Primary fluence

Lomax : AAPM SS 2003
Proton Scattering

A proton pencil beam

$\sigma_{\text{MCS}}$

Dose per proton (nGy)

0 1 2 3

Depth in water (cm)

0 5 10 15 20 25

Sigma MCS (mm)

$\sigma_{\text{tot}} = f(\sigma_{\text{ips}}, \sigma_{\text{MCS}})$

(80-20%) lateral dose fall-offs at 10cm depth

Protons – 5-8mm

6MV photons – 6mm

Lomax : AAPM SS 2003
Proton Depth Dose (PDD)

Depth-dose curve for 177 MeV protons

**Proton De**p**th Dose (PDD)**

- **Peak-to-plateau ratio**: 3-5 (depending on width of energy spectrum)
- **Range straggling in medium and initial energy spectrum**; typically 8 mm for 177 MeV protons

\[
dE \propto \frac{1}{(\beta c)^2}
\]
PDD as a function of SOBP widths

1. Excitation/ionization; Nuclear interaction
2. Excitation/ionization (Bragg Peaks); Nuclear interaction
3. Range straggling and energy spread
4. Neutrons from nuclear interactions

Note increase in entrance dose with increase in modulation.
Intrinsic basic physics uncertainty (I-values)

The peak spread increases with energy.

P Andreo, Phys Med Biol, 2009
122 MeV Protons on water: $I_w$ - dependence

$P_{122} I_w = 67\text{eV}$

$P_{122} I_w = 75\text{eV}$

$P_{122} I_w = 80\text{eV}$

Peak spread is $.7 \text{g/cm}^2$ for 230 MeV protons

Intrinsic basic physics uncertainty makes the argument of “sub-millimeter precision” an issue, which deserves careful consideration

P Andreo, Phys Med Biol, 2009
164 MeV protons on various tissues
(+/- 10% change in I-values)

Peak spread assuming 10% uncertainty in I-values

P Andreo, Phys Med Biol, 2009
Range uncertainty due to CT calibration is generally taken as 3.5%. However, it can be minimized with better calibration techniques.
HU-Stopping Power Conversion Uncertainties
Results in Range Uncertainties

Large prostate patient, Right lateral field

Proximal PTV Edge

Distal PTV Edge

Small prostate patient, Right lateral field

Pediatric spine patient, Anterior field

Head patient, Left lateral field

Range Uncertainty [%]
Impact of CT Hounsfield number uncertainties on dose distributions

Individualized patient determination of tissue composition along the complete beam path, rather than CT Hounsfield numbers alone, would probably be required even to reach “sub-centimeter precision”
CT Artifacts and Hounsfield Numbers

“It is imperative that body-tissue compositions are not given the standing of physical constants and their reported variability is always taken into account” (ICRU-44, 1989).
Range compensator conforms dose to distal edge target volume; the aperture shapes field in lateral direction.
Misalignment of the compensator with Target Volume

Correct alignment of the compensator and target volume

Patient is shifted left

Patient is rotated clockwise

ICRU Report 78
Proton Range Uncertainty in the Presence of heterogeneities

\[ \Delta R_{\text{hom}} \]

\[ \Delta R_{\text{inho}} \]

Lomax : AAPM SS 2003
Impact of Organ Motion on Proton Dose Distributions
Impact of Organ Motion on Proton Dose Distributions

Treatment planned based on single Free-breathing (FB) CT image (conventional approach)

The same treatment plan calculated on 4D CT images

Y. Kang et al. IJROBP. 67, 906-914 (2007)
Comparing Proton Therapy with IMRT

It is incontrovertible that dose distributions of protons can be theoretically superior to those of high energy photons.

Protons Therapy

Ca Oropharynx

Photon IMRT

Yeung UFPTI
# Ca Oropharynx

**Concomitant Boost (7200 cGy)**

(95% PTV receives prescription dose, 99% PTV receives 93% of prescription dose and 20% PTV receives <110% of prescription dose)

<table>
<thead>
<tr>
<th>Tumor Coverage</th>
<th>Photon IMRT</th>
<th>PROTONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% of PTV 5400/7200</td>
<td>7320 (101.6%)</td>
<td>7178 (99.7%)</td>
</tr>
<tr>
<td>99% of PTV 5400/7200</td>
<td>7221 (100.3%)</td>
<td>6975 (96.7%)</td>
</tr>
<tr>
<td>20% of PTV 5400/7200</td>
<td>7722 (107.3%)</td>
<td>7243 cGy (106%)</td>
</tr>
<tr>
<td>Brain stem (0.1 c.c.)</td>
<td>5020</td>
<td>2685</td>
</tr>
<tr>
<td>Spinal cord (0.1 c.c.)</td>
<td>4400</td>
<td>546</td>
</tr>
<tr>
<td>Contralateral parotid (mean dose ≤ 2600)</td>
<td>2529</td>
<td>1482</td>
</tr>
<tr>
<td>Contralateral submandibular gland (mean dose ≤ 2600)</td>
<td>6928</td>
<td>6148</td>
</tr>
</tbody>
</table>

Please note that this is **ONLY** a synthetic comparison of two modalities of treatment.

Yeung UFPTI
The Clinical Challenge

Accurately deliver ionizing radiation to the real dynamic patient
Intra-Fraction Prostate Motion
Due to Breathing and Bladder Filling
Rectal DVH from multiple post treatment PET/CT

Uncertainties in Rectal $V_{74}$ and $V_{39}$

<table>
<thead>
<tr>
<th></th>
<th>Mean ± Dev.</th>
<th>Rel. Dev. ± Dev.</th>
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<tbody>
<tr>
<td>$V_{74}$</td>
<td>9.6%±7.2%</td>
<td>73.9%±20.5%</td>
</tr>
<tr>
<td>$V_{39}$</td>
<td>25.2%±11.4%</td>
<td>42.1%±15.3%</td>
</tr>
</tbody>
</table>

Yin: UFPTI, 2008
Anatomic Variations During Course of RT

Planning CT

Three Weeks into RT

Impact of Tumor Shrinkage on Proton Dose Distribution

Original Proton Plan

Dose recalculated on the new anatomy

Bucci et al. ASTRO Abstract, 2007
Intensity Modulated Proton Therapy (IMPT)

Passive scattering

Spot scanning

IMPT

1 field

1 field

1 field

3 fields

3 fields

3 fields

Lomax/PSI
Plan DVH Evaluation (PTV)
What you see is not what you always get....
Plan DVH Evaluation (PRV)

What you see is not what you always get..
Plan Evaluation

What you see is not what you always get....

IMXT Plan
(with Confidence-weighted Isodose Distribution)

IMPT Plan

There is no easy way to show what patient will get in proton therapy

180 160 120 80 40 cGy
Summary 1

• Proton beams stop - no exit dose
  – Although we don’t know exactly where they stop

• Proton beams are more sensitive to
  – CT Hounsfield number/Stopping Power accuracy
  – Organ motion
  – Anatomy changes

• Proton plans are difficult to evaluate
  – “What you see is not what is delivered”

• Protons demonstrate excellent low dose sparing
Summary 2

- IMPT shows additional benefits both in low dose sparing and high dose conformality
- IGRT and Adaptive RT will play an important role
- Inter/Intra-fractional variations have far more significant consequences in patients treated with proton therapy
  - Approaches and data to deal with this issue is still lacking
    - Minimize it and develop strategies to deal with the residual motion
Summary 3

• Empirical approaches used in defining margins for range uncertainties, smearing, and smoothing are questionable
  – No real data exist to support any of these approaches
• Repeat imaging and reevaluation based on deformable registration may be necessary
  – In some cases repeat planning may be clinically beneficial
• Biologically Effective Dose
  – Little published data on end of range RBE
General Observations Regarding Proton Therapy Technology

• State-of the Art in Proton Therapy is still an accelerator with multi-room configuration and scattered beam delivery system. These are far from “turnkey” systems

  – Scanning and IMPT are still a works-in-progress.
  – Subsystem integration is far from complete
    • It impacts clinical workflow and throughput

• Development of new proton beam production technologies are being fueled by the promise of proton therapy in normal tissue sparing.
  – Developing a technology is lot simpler and quicker than its seamless and safe integration in existing clinical work flow.
    • Historically, routine application of new developments in radiation oncology has taken at least 5 years from the time its FDA approval (e.g. MLC, IMRT, IGRT, etc.)

• Promise of Proton Therapy will only hold if we take the most advantage of the state-of-the art in conventional radiation therapy
  – We must not be satisfied with less than the best in technology available for immobilization, imaging, treatment planning, patient/target position verification, and treatment delivery.