Reducing uncertainties in particle therapy – status and perspectives

Katia Parodi, Ph.D.

Professor and Chair, Department of Medical Physics,
Ludwig-Maximilians-Universität München, Munich, Germany

Challenges in clinical practice of ion therapy

Improved physical selectivity  BUT  increased sensitivity to uncertainties in beam delivery
- Anatomical changes (inter- and intra-fractions)
- Tissue stopping power (relative to water, SPR)

M. Engelsman et al, Seminars Rad. Onc. 2013
J. Bauer et al, HIT
Mitigating range uncertainties in clinical practice

Usage of safety margins (non-isotropic)
\[ \approx 2.5\%-3.5\% + 1\text{-}3\text{ mm} \]

and conservative choice of beam angles

Paganetti, PMB 2012
Poll and Parodi, Phys Today 2015

In-room imaging for ion beam therapy

Anatomical imaging (as in modern photon therapy)
- Horizontal/vertical CT
- On-board Cone Beam CT (CBCT)
- Magnetic Resonance Imaging

Source: TPC, Northwestern Medicine, Oncoray Dresden, MGH Boston, IBA, MedPhoton; Hoffmann ... Parodi, RadOnc 2020
Beyond (CB)CT/MR imaging for ion therapy planning

**Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)**

**Dual Energy X-ray CT (DECT)**
- Commercially available
- Enables patient-specific calibration
- Improves SPR estimation accuracy

**Ion transmission imaging**
- Under development
- Enables direct SPR estimation
- Low-dose imaging

**Theory:**
$$\text{SPR} \propto \rho e \frac{\ln \left( \frac{2m_e c^2 \beta^2}{I (1 - \beta^2)} \right)}{\ln \left( \frac{2m_e c^2 \beta^2}{I_{\text{water}} (1 - \beta^2)} \right)} - \beta^2$$

- Wolfahrt et al, IJROBP 2017
- Niepel...Landry, Parodi, PMB 2020, Berthold et al, IJROBP 2021
- Dickmann,...Parodi, Dedes, Landry, PMB 2021

**In-room imaging for ion beam therapy**

**Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)**

- Confirmation of promising DECT SPR-based estimation in tissue samples regardless of used conversion method

- Niepel, Stanislawski..., Landry, Parodi, PMB 2021

- Competitive performance of proton CT prototype vs dual-source DECT
- MAPE: 0.55% vs 0.67% at ~20 reduced dose (though not yet dose-optimized)

- Dedes, ..., Landry, Parodi, PMB 2019
**In-room imaging for ion beam therapy**

**Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)**

Further dose reduction possibilities in combination with fluence modulation

*Dedes...Parodi, Landry Med Phys 2018*

*Dickmann,...Parodi, Landry, Dedes PMB 2020*

First commercial prototype close to clinical translation for proton radiography

*Dedes et al SU-J-207-1 (Sunday, 7/10/2022)*

<table>
<thead>
<tr>
<th>noise in beam</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose outside beam</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Enhancement of in-room CBCT with proton/ion radiography or dual energy/spectral imaging capabilities?**

*DFG Project HIGH-ART (PI: C. Gianoli & K. Parodi)*

*PhD project G. Hu (in collaboration with LMU Klinikum, Manuscript submitted to Front Oncol)*

**PET/PG imaging for on-site treatment verification**

**Detection of energetic photons resulting from nuclear interactions**

**In-beam PET**

3D imaging of irradiation-induced β⁺-activity ideally during irradiation, integrating signal over ≈ s – min

*Ferraro et al, Sci Rep 2018*

**PG imaging**

So far 1-2D detection of irradiation induced PG after mechanical collimation, integrating signal of a few pencil beams (≈ ms – s)

*Richter et al, Radiother Oncol 2016*

*Tattenberg et al, WE-E-BRA-5 (Wednesday 7/13/2022)*

**Detection of energetic photons resulting from nuclear interactions**

*Planned Measured*

*Richter et al, Radiother Oncol 2016*

*Tattenberg et al, WE-E-BRA-5 (Wednesday 7/13/2022)*

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*Tattenberg et al, WE-E-BRA-5 (Wednesday 7/13/2022)*
Confirmation of improved SPR determination

First-In-Human Validation of CT-Based Proton Range Prediction Using Prompt Gamma Imaging in Prostate Cancer Treatments

Niepel et al, TH-F-201-6 (Thursday, 7/14/2022)

Expected clinical impact of range uncertainty reductions...

NTCPs have been quantified as a function of range uncertainty

S. Tattenberg PhD project, MGH & LMU
Novel beam arrangements will have additional benefits

Study | Site | NTCP | ΔRange uncertainty [pp] | ΔNTCP [pp] |
--- | --- | --- | --- | --- |
Van de Water et al. | Oropharynx | Various | 2 (3%-1%) | μ = 0.4 |
Wagenaar et al. | H&N | Various | 1 | μ = 0.9 |
Tattenberg et al. | Clivus | Optic chiasm (blindness) | 3 (4%-1%) | ≤0.9 (nominal) ≤2.2 (worst-case) |
| | Brainstem necrosis | | | ≤1.3 (nominal) ≤2.9 (worst-case) |
| | Brain & skull base | | | ≤1.8 (nominal) ≤3.2 (worst-case) |

But biological implications have to be considered…

Can We Advance Proton Therapy for Prostate? Considering Alternative Beam Angles and Relative Biological Effectiveness Variations When Comparing Against Intensity Modulated Radiation Therapy

Toward new treatment planning strategies accounting for range verification and biological effects

Range retrieval accuracy and precision crucially depend on PB statistics and PG-dose correlation

TABLE 3: The mean dose-averaged linear energy transfer \( \langle \text{LET} \rangle \) within the brachistion for all 10 cases

<table>
<thead>
<tr>
<th>Patient</th>
<th>Traditional</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5</td>
<td>5.2</td>
</tr>
<tr>
<td>2</td>
<td>3.3</td>
<td>3.3</td>
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<td>3.7</td>
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<tr>
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<td>5.7</td>
</tr>
<tr>
<td>10</td>
<td>4.0</td>
<td>4.3</td>
</tr>
</tbody>
</table>

The mean dose-averaged linear energy transfer \( \langle \text{LET} \rangle \) within the brachistion for all 10 cases included in this study. All values concern the nominal scenario of the treatment plan only robust to setup errors of \( \pm 2 \) mm.

Tian, ... Parodi, PMB 2018, 2019, 2020
Invert prediction to estimate dose from PG for monitored high statistics PBs & put back in progressive plan adaptation

And explore tradeoffs in number of high statistics PB for PG monitoring and other considerations (eg. biology from LET)

**Conclusion & Outlook**

- Promising techniques for reduction of range uncertainties in clinical practice close to or just starting clinical translation & evaluation
- Reduction of range uncertainties at planning & delivery stage will enable more accurate dose delivery and likely impact clinical outcome
- Understanding of biological uncertainties and development of reliable models is mandatory to fully exploit the benefit of range uncertainty reduction, and all information could be used in new planning strategies
Acknowledgement

Thank you for your attention

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www.med.physik.uni-muenchen.de