Treatment Planning and Delivery for Proton Thoracic Therapy
An European Center’s Experience

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Department of Radiation Oncology
# Disclosures

<table>
<thead>
<tr>
<th></th>
<th>COI status</th>
<th>Names of companies / organizations</th>
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<tr>
<td>①</td>
<td>No</td>
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<tr>
<td>⑥</td>
<td>YES</td>
<td>Department of Radiation Oncology has research collaborations with Elekta, IBA, RaySearch, Siemens and Mirada Dutch Cancer Society Project 11518</td>
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</table>
Outline

- Introduction
- Motion assessment
- Robust planning
- Robustness evaluation
- Retrospective 4D dose reconstruction
- Future Developments
IMPT Thoracic indications@UMCG

- Lung
- Lymphoma
- Esophagus
- Breast
Lung IMPT: Reduced Heart & Lung Dose

Patient qualifies for protons?

<table>
<thead>
<tr>
<th></th>
<th>Photon plan</th>
<th>Proton plan</th>
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<tbody>
<tr>
<td>Heart</td>
<td>11.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Lung</td>
<td>15.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Esophagus</td>
<td>18.5</td>
<td>12.3</td>
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</table>

**GRADE 2 Complications**

<table>
<thead>
<tr>
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<th>NTCP Photons</th>
<th>NTCP protons</th>
<th>ΔNTCP DSS</th>
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</thead>
<tbody>
<tr>
<td>Radiation Pneumonitis</td>
<td>36.9%</td>
<td>24.2%</td>
<td>12.8%</td>
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<tr>
<td>Dysphagia</td>
<td>44.5%</td>
<td>30.3%</td>
<td>14.2%</td>
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</table>

**Grade 5 complications**

<table>
<thead>
<tr>
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<th>NTCP Photons</th>
<th>NTCP protons</th>
<th>ΔNTCP DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year mortality</td>
<td>55.8%</td>
<td>40.2%</td>
<td>15.7%</td>
</tr>
</tbody>
</table>

**Decision Support System**

- **Result**: Yes
- **Protons**
  - Mean Dose (Gy): 1.0

**DSS**

- **Threshold**:
  - >10%
  - >10%
  - >15%
  - >2%

Outline

• Introduction
• **Motion assessment**
• Robust planning
• Robustness evaluation
• Retrospective 4D dose reconstruction
• Future Developments
Motion induced dose variations
Interplay effect

- Dynamic treatment
  ‘interplay’ dynamic beam & patient geometry
Established in pre-clinical study: Knopf, A et al. (2019) *IJROBP*

The REACT-REpeated 4D CTs and Cbcts to Prepare for Pencil Beam Scanned Proton Therapy (PBS-PT) in Lung and Esophagus Patients

Target Motion Evaluation: 4DCT
Coregistered INHALE+EXHALE
Exhale Def. Field Vector, target

**Clinical Pt NSCLC 05**
**DIR**
- Max inhale vs. max exhale
- Superimposed on max exhale
Outline

• Introduction
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Robust planning
AveCT robust clinical plan recalculated on the 4DCT to check robustness

ROBUST planned protons

Inoue T et al. 2016 Limited Impact of Setup and Range Uncertainties, Breathing Motion & Interplay ...
IJROB
Robust planning

- LUNG : 25 x 2.4 Gy(RBE)
- 3 beams
- Monte Carlo( Raysearch)
- Planning on ITV & average of 4DCT
- Density override ITV( muscle density)
- Robustness Settings( setup/range)
Relative residual range errors

\[(\text{Rel. range error})^{-1} = \text{WET}\]

A Meijers et al: Assessment of range uncertainty in lung-like tissue using a porcine lung phantom and proton radiography, PMB, Vol.65, 2020
Mean rel. range error 1.0 %
(1.5SD 2.2%)

A Meijers et al: Assessment of range uncertainty in lung-like tissue using a porcine lung phantom and proton radiography, PMB, Vol.65, 2020
Robust planning

• Repainting of Pencil Beam spots Energy Layer wise

BEV
1 in layer rescanning

BEV
5 in layer rescanning

• Optional: enlargement of the spot size
Spot size & Interplay

- Small spots: $\sigma \sim 5$ mm vs. Big spots: $\sigma \sim 10$ mm

Bigger spots can correct for Interplay.

3D vs. 4D Robust planning optimization

Preclinical study

*Comprehensive 4D Robustness evaluation

+ Setup errors
+ Proton range uncertainty
+ Breathing motion
+ Interplay effect
+ Beam delivery accuracy
+ Fractionation
+ Anatomical variations

*Ribeiro, CO et al. (2019) Radiother Oncol Comprehensive 4D Robustness Evaluation ..
Ribeiro, CO et al. (2019) IJROBP Towards the Clinical Implementation of Pencil Beam Scanned Proton ..
Outline

• Introduction
• Motion assessment
• Robust planning
• Robustness evaluation
• Retrospective 4D dose reconstruction
• Future Developments
Pre-treatment robustness evaluation

Setup errors
Proton range uncertainty

Planning
CT
Pre-treatment robustness evaluation

*Goal: D98 > 95%

Clinical Pt NSCLC 05

95% isodose

*Korevaar, EW et al. (2019) Radiother Oncol Practical robustness evaluation in radiotherapy ..
Pre-treatment robustness evaluation

Patient position errors  0.6 cm
Proton range uncertainty  3%

*Korevaar, EW et al. (2019) Radiother Oncol Practical robustness evaluation in radiotherapy ..
On treatment robustness evaluation on AVECT with \( \text{Vox}_{\text{min}} \) and \( \text{Vox}_{\text{max}} \) eval(3%/2mm)

Fraction 08

Fraction 13

Fraction 22

Clinical Pt NSCLC 5

Voxel-wise min

95% isodose

Goal: D98 > 95%

<table>
<thead>
<tr>
<th>Frct</th>
<th>Dose</th>
<th>ROI/POI</th>
<th>Clinical goal</th>
<th>Value</th>
<th>Result</th>
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<tbody>
<tr>
<td>08</td>
<td>Perturbed dose (RBE):...</td>
<td>CTV_6000</td>
<td>At least 5700 cGy (RBE) dose at 98.00 % volume</td>
<td>5790 cGy (RBE)</td>
<td>✔️</td>
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<tr>
<td>13</td>
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<td>CTV_6000</td>
<td>At least 5700 cGy (RBE) dose at 98.00 % volume</td>
<td>5761 cGy (RBE)</td>
<td>✔️</td>
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<td>CTV_6000</td>
<td>At least 5700 cGy (RBE) dose at 98.00 % volume</td>
<td>5774 cGy (RBE)</td>
<td>✔️</td>
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</table>
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Daily 4D dose reconstruction

ANZAI breathing signal

Delivery log files

Meijers, A et al. Evaluation of interplay and organ motion effects by means of 4D dose reconstruction and accumulation”, Radiotherapy and Oncology 150 (2020) 268-274
On treatment robust evaluation

The platform architecture: core units (in grey) and external components (in white).

### Characteristics of treatment course preparation

10 consecutive patients treated with IMPT@UMCG

<table>
<thead>
<tr>
<th>Pat. #</th>
<th>Indication</th>
<th>Prescription</th>
<th>ITV volume, cm³</th>
<th>Mean motion, mm</th>
<th>Point-max motion mm</th>
<th>ITV V95 vox-min³</th>
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</thead>
<tbody>
<tr>
<td>01</td>
<td>Lymphoma</td>
<td>15 × 2.0 Gy$_{RBE}$</td>
<td>166</td>
<td>0.9</td>
<td>&lt;5</td>
<td>98.13</td>
</tr>
<tr>
<td>02</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>44</td>
<td>2.2</td>
<td>&lt;6</td>
<td>99.42</td>
</tr>
<tr>
<td>03</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>243</td>
<td>0.9</td>
<td>&lt;6</td>
<td>99.77</td>
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<tr>
<td>04</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>131</td>
<td>0.7</td>
<td>&lt;5</td>
<td>99.82</td>
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<tr>
<td>05</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>357</td>
<td>0.7</td>
<td>&lt;7</td>
<td>99.06</td>
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<tr>
<td>06</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>217</td>
<td>1.1</td>
<td>&lt;5</td>
<td>99.74</td>
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<tr>
<td>07</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>298</td>
<td>1.2</td>
<td>&lt;9</td>
<td>98.41</td>
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<tr>
<td>08</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>202</td>
<td>1.4</td>
<td>&lt;8</td>
<td>98.41</td>
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<tr>
<td>09</td>
<td>NSCLC</td>
<td>25 × 2.4 Gy$_{RBE}$</td>
<td>336</td>
<td>0.6</td>
<td>&lt;6</td>
<td>99.49</td>
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<tr>
<td>10</td>
<td>Lymphoma</td>
<td>15 × 2.0 Gy$_{RBE}$</td>
<td>339</td>
<td>2.1</td>
<td>&lt;20</td>
<td>99.67</td>
</tr>
</tbody>
</table>

A. Meijers, et al.  Evaluation of interplay and organ motion effects by means of 4D dose reconstruction and accumulation”, Radiotherapy and Oncology 150 (2020) 268-274
Daily 4D Dose reconstruction

Lung & Mediastinal Lymphoma:
- Similar motion
- Different Target Volumes
- Small vs. Enlarged Spots
- Larger hot/cold spots
- Similar cumulative dose

A. Meijers, et al. Evaluation of interplay and organ motion effects by means of 4D dose reconstruction and accumulation", Radiotherapy and Oncology 150 (2020) 268-274
Lung Big Movers Study

• Thoracic indications
  - 9 lung + 1 thymoma cancer
    ➢ Large CTV motion amplitudes (>10 mm)
  - IMPT_3D plans
    ➢ Clinically approved
    ➢ 4DREM
      ✖ Machine log files
      ✖ Patient weekly repeated 4DCTs
      ✖ End-exhale planning CT phase

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location</th>
<th>Planning 4DCT</th>
<th>Planning 4DCT</th>
<th>Verification 4DCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung (right-lower)</td>
<td>&lt; 12</td>
<td>5.1</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>2</td>
<td>Lung (right-middle)</td>
<td>&lt; 12</td>
<td>8.9</td>
<td>7.0 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>Anterior mediastinum</td>
<td>&lt; 15</td>
<td>9.7</td>
<td>8.9 ± 1.0</td>
</tr>
<tr>
<td>4</td>
<td>Lung (right-upper)</td>
<td>&lt; 12</td>
<td>1.5</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>5</td>
<td>Lung (right-middle)</td>
<td>&lt; 16</td>
<td>5.0</td>
<td>4.1 ± 0.8</td>
</tr>
<tr>
<td>6</td>
<td>Lung (left-lower)</td>
<td>&lt; 15</td>
<td>9.0</td>
<td>8.2 ± 0.8</td>
</tr>
<tr>
<td>7</td>
<td>Lung (right-middle)</td>
<td>&lt; 11</td>
<td>10.9</td>
<td>7.7 ± 1.6</td>
</tr>
<tr>
<td>8</td>
<td>Lung (right-middle)</td>
<td>&lt; 12</td>
<td>5.9</td>
<td>7.6 ± 0.3</td>
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<tr>
<td>9</td>
<td>Lung (left-upper)</td>
<td>&lt; 12</td>
<td>4.9</td>
<td>4.4 ± 0.8</td>
</tr>
<tr>
<td>10</td>
<td>Lung (right-upper)</td>
<td>&lt; 12</td>
<td>5.4</td>
<td>5.0 ± 0.1</td>
</tr>
</tbody>
</table>

C.O. Ribeiro: Patient and machine specific evaluation of intensity-modulated proton therapy (IMPT) for thoracic indications with large motion. PTCOG 2021
• **4DREM (with dose-fraction-smoothening effect)**

14 4D accumulated scenario dose distributions = 14 possible fractionated treatment courses of the nominal plan

Results – Target coverage

Lung cancer patient 5

\[ V_{95}(iCTV/CTV) \% \]

Graph showing comparison of nominal and 4DREM treatments for lung cancer patient 5.
OARs (lungs and heart)

Nominal

4DREM = scenarios

Patient

$D_{\text{mean}}(\text{lungs-GTV})$ [Gy$_{\text{RBE}}$]

Patient

$D_{\text{mean}}(\text{heart})$ [Gy$_{\text{RBE}}$]

$4DREM = \text{scenarios}$

$9.74 \pm 0.59 \text{ Gy}_{\text{RBE}}$

$1.09 \text{ Gy}_{\text{RBE}}$

$10.27 \pm 0.42 \text{ Gy}_{\text{RBE}}$

$0.86 \text{ Gy}_{\text{RBE}}$

C.O. Ribeiro : PTCOG 2021
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FUTURE:

Automatize treatment planning and QA processes on our clinical control platform for daily treatment monitoring and model based adaptive proton therapy workflows based on:

- Quality of Life based robust optimized planning
- daily 3D /4D synthetic CT generated from 3D /4D CBCT
- patient treatment log File / machine File
- “end to end “ treatment verification such as proton radiography measurements

Thummerer A.: Neural Network Based Synthetic CTs for Adaptive Proton Therapy of Lung Cancer, Oral Presentation, ESTRO 2021
Conclusions:

• Rescanned delivered 3D robustly optimized and evaluated IMPT based on 4DCT can treat moving targets in free breathing for an increasing range of motion.

• Use of enlarged spots further robustify IMPT.

• Treatment adaptations are mostly due to anatomical changes.

• 4D dose reconstructions are a good predictor for plan robustness assessing the delivered dose considering patient anatomy and breathing pattern changes as the treatment progresses.
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