One year experience with model-based selection in head and neck cancer

IBA Proton Therapy Symposium (Milan, 27 April, 2019)

Professor Hans Langendijk (MD, PhD)
Department of Radiation Oncology, University Medical Center Groningen
Indications proton therapy

- Improvement local control: 15%
- Prevention of complications: 85%

Head and neck cancer
Model-based approach
Three basic conditions

1. Bio-equivalent target dose (similar local control)
2. Lower dose to relevant OAR ($\Delta$Dose)
3. $\Delta$Dose should translate into $\Delta$NTCP = difference in complication rate

Langendijk, et al. Sem Radiat Oncol 2018
Model-based approach

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Model-based selection

Plan comparison

Dose VMAT plan

Dose IMPT plan

NTCP-model

PHOTON therapy

Low ΔNTCP

PROTON therapy
National Indication Protocol Proton Therapy

HEAD and NECK CANCER
# National indication protocol

## Head and neck cancer (primary setting)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>NTCP-models (6 months after end of RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xerostomia grade ≥ 2 (^1)</td>
</tr>
<tr>
<td>(D_{\text{mean}}) contralateral parotid gland</td>
<td></td>
</tr>
<tr>
<td>(D_{\text{mean}}) oral cavity</td>
<td></td>
</tr>
<tr>
<td>(D_{\text{mean}}) superior PCM</td>
<td></td>
</tr>
<tr>
<td>(D_{\text{mean}}) inferior PCM</td>
<td></td>
</tr>
<tr>
<td>(D_{\text{mean}}) cricopharyngeal muscle</td>
<td></td>
</tr>
<tr>
<td>Baseline xerostomia</td>
<td></td>
</tr>
<tr>
<td>Baseline dysphagia</td>
<td></td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
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<tr>
<td>Weigh losss prior to RT</td>
<td></td>
</tr>
<tr>
<td>T-stage</td>
<td></td>
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</tbody>
</table>

\(^1\) Beetz et al, R&O 2011; \(^2\) Christianen et al. R&O 2012; \(^3\) Wopken, et al. R&O 2016
CASE EXAMPLE
Case

- cT3N2cM0
- Base of tongue carcinoma
- Planned for concurrent chemoradiation
- Baseline toxicity:
  - Grade I xerostomia
  - Grade II dysphagia
  - No weight loss
Plan comparison
Model-based optimization using VMAT (photons)

Overview
Superior PCM
Oral cavity
Contrateral parotid gland
Inferior PCM
Crico-pharyngeus

Phons

Dysphagia grade ≥ 2
Xerostomia grade ≥ 2
Tube feeding dependence

Overview
Superior PCM
Oral cavity
Contrateral parotid gland
Inferior PCM
Crico-pharyngeus

Phons

Dysphagia grade ≥ 2
Xerostomia grade ≥ 2
Tube feeding dependence
Plan comparison
Proton therapy treatment planning

- Similar dose prescription and fractionation as for VMAT
  - $35 \times 2.00 \text{ Gy} / 5 \text{ times per week} = 70.00 \text{ Gy}$
  - $35 \times 1.55 \text{ Gy} / 5 \text{ times per week} = 54.25 \text{ Gy}$

- IMPT Pencil beam scanning
  - Standard 4-field beam configuration with post hoc adjustment of beam set up
  - Robust treatment planning:
    - $5 \rightarrow 3 \text{ mm set up inaccuracy}$
    - $3\% \text{ range uncertainty}$
  - Robustness evaluation
Plan comparison
Model-based optimization using IMPT (protons)

<table>
<thead>
<tr>
<th>Overview</th>
<th>Superior PCM</th>
<th>Oral cavity</th>
<th>Contrateral parotid gland</th>
<th>Inferior PCM</th>
<th>Crico-pharyngeus</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
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</table>
Plan comparison
Model-based optimization using IMPT (protons)

Overview

Superior PCM

Photons

Protons (VMAT)

Protons (IMPT)
Plan comparison
Model-based optimization using IMPT (protons)
Model-based selection

Step 2: Plan comparison to determine $\Delta$Dose

<table>
<thead>
<tr>
<th>Overview</th>
<th>Superior PCM</th>
<th>Oral cavity</th>
<th>Contrateral parotid gland</th>
<th>Inferior PCM</th>
<th>Cricopharyngeus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photons</td>
<td>40.9</td>
<td>32.4</td>
<td>20.5</td>
<td>41.9</td>
<td>34.6</td>
</tr>
<tr>
<td>Protons</td>
<td>17.9</td>
<td>23.4</td>
<td>20.5</td>
<td>15.5</td>
<td>22.3</td>
</tr>
</tbody>
</table>

- PCM superior
- Oral cavity
- Parotid gland CL
- PCM inferior
- Cricopharyngeus

Start: PCM

VMAT: Red
IMPT: Green
ΔNTCP-profile

Step 3: Does THIS patient qualify for protons?

NTCP-profiles

<table>
<thead>
<tr>
<th>Condition</th>
<th>VMAT</th>
<th>IMPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerostomia grade ≥ 2</td>
<td>52,1%</td>
<td>45,6%</td>
</tr>
<tr>
<td>Dysphagia ≥ 2</td>
<td>37,0%</td>
<td>18,8%</td>
</tr>
<tr>
<td>Tube feeding dependence</td>
<td>2,5%</td>
<td>7,5%</td>
</tr>
</tbody>
</table>
Treatment

Daily ConeBeam CT
Treatment

Weekly Repeat CT

Dose reconstruction, robustness evaluation and plan adaptation
First experience UMCG (15 months)
Primary setting (n=159)

VMAT

Pre-selection tool

Negative

60%

Positive

Plan comparison

Negative

35%

Plan comparison

35%

Positive

IMPT

40%

Not suited for protons

10%

40%
Dose comparison \((n=120)\)  
**BEST** protons compared with **BEST** photon technique

**Patient qualifying for IMPT**

**Patient NOT qualifying for IMPT**

OAR used for dose optimization
Model-based clinical validation

Study design

PROTON therapy yes

Excluded: treated with photons

Observed toxicity rates

Comparison

yes

no

Excluded: treated with photons

PROTON therapy

N/TCP

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

N/TCP

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

∆N/TCP

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

N/TCP

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

∆N/TCP

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

Photons

Protons

Xerostomia

Dysphagia

Tube feeding dependence

52,1%

37,0%

7,5%

0%

10%

20%

30%

40%

50%

60%

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

5,2%

1,1%

1,3%

0%

10%

20%

30%

40%

50%

60%

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

45,0%

18,8%

2,5%

0%

5%

10%

15%

20%

25%

Xerostomia grade ≥ 2

Dysphagia grade ≥ 2

Tube feeding dependence

6,5%

18,2%

5,0%

0%

5%

10%

15%

20%

25%
Model-based versus RCT validation

Randomized controlled trial

- **Observed** toxicity rate after PROTON therapy
- **Observed** toxicity rate after PHOTON therapy

Model-based clinical validation

- **Observed** toxicity rate after PROTON therapy
- Each patient is its own control
- **Predicted** toxicity rate (NTCP) based on PHOTON therapy plan
## Head and neck cancer radiotherapy

Toxicity profiles of concurrent chemoradiation

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Acute toxicity</th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W1</td>
<td>W2</td>
</tr>
<tr>
<td>Dysphagia (grade≥2)</td>
<td>16%</td>
<td>25%</td>
</tr>
<tr>
<td>Tube feeding dependent</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Xerostomia (grade≥2)</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Sicky saliva (grade≥2)</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Loss of taste (grade≥2)</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>Oral mucositis (grade≥3)</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Aspiration (grade≥3)</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Osteoradionecrosis (grade≥3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism (grade≥3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Acute toxicities in week 3-12 during RT**

**Selection criteria national indication protocol**

Percentage with toxicity

Prospective HEAD & NECK Data Registration Program UMCG
Patient characteristics

<table>
<thead>
<tr>
<th>Mean age</th>
<th>62</th>
<th>(27-80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>71%</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>29%</td>
</tr>
<tr>
<td>Tumour site</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>27</td>
<td>71%</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>4</td>
<td>11%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>Larynx</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>P16</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Positive OPC</td>
<td>14</td>
<td>52%</td>
</tr>
<tr>
<td>Negative OPC</td>
<td>13</td>
<td>48%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage UICC v7</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>6</td>
<td>16%</td>
</tr>
<tr>
<td>Stage III</td>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>29</td>
<td>76%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiation</td>
<td>19</td>
<td>50%</td>
</tr>
<tr>
<td>Conventional radiotherapy</td>
<td>13</td>
<td>34%</td>
</tr>
<tr>
<td>Accelerated radiotherapy</td>
<td>4</td>
<td>11%</td>
</tr>
<tr>
<td>Radiotherapy + cetuximab</td>
<td>2</td>
<td>5%</td>
</tr>
</tbody>
</table>

Prospective HEAD & NECK Data Registration Program UMCG
Model-based clinical validation (n=38)
Acute xerostomia grade ≥ 2

Expected Photons

Observed protons
NTCP-reductions by protons

Acute XEROSTOMIA grade ≥ 2

Observed versus expected:
(W3-W12): p = 0.007
Model-based clinical validation (n=38)
Acute dysphagia grade ≥ 2

Expected Photons

Observed protons
NTCP-reductions by protons

Acute DYSPHAGIA grade ≥ 2

<table>
<thead>
<tr>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>-11.6%</td>
<td>-9.1%</td>
<td>-6.3%</td>
<td>-4.0%</td>
<td>-7.7%</td>
<td>-16.6%</td>
</tr>
</tbody>
</table>

Observed versus expected (W3-W12): p = 0.031
Model-based clinical validation (n=38)
Acute dysphagia grade ≥ 3

Expected Photons
Observed protons
NTCP-reductions by protons

Acute DYSPHAGIA grade ≥ 3

Week 3: -9.5%
Week 4: -18.8%
Week 5: -21.3%
Week 6: -23.0%
Week 7: -18.6%
Week 12: -28.1%

Observed versus expected (W3-W12): p < 0.001
NTCP-reductions by protons
Acute xerostomia and dysphagia

Week 3: -11.6% - 9.5%
Week 4: -9.1%
Week 5: -6.3%
Week 6: -4.0%
Week 7: -7.7%
Week 12: -16.6%

TOXICITY RATE REDUCTION
Dysphagia grade ≥ 2
Dysphagia grade ≥ 3
Summary and conclusions

• Model-based selection of head and neck cancer patients is logistically feasible:
  – ~ 30-40% eligible

• NTCP-guided model-based optimization with IMPT results in dose reduction in multiple OARs
  – Expected to result in more favourable toxicity profile
  – Especially with new technological developments
Summary and conclusions

- Model-based validation show a significant and marked reduction of acute xerostomia and dysphagia
- The benefit exceeds the toxicity endpoints used for model-based selection
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