History of particle therapy in the Netherlands

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GRONINGEN
The Netherlands
Disclosures

• Department research agreements with:
  – RaySearch
  – Philips
  – IBA
  – Mirada

• Speaker for IBA symposium with honorarium (UMCG Research BV)

• Conference sponsorship by IBA
# Milestones

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• Should proton therapy be part of Specific Medical Procedures Act (WBMV)
  – Requires formal governmental license

• Considerations regarding the need for RCT and alternative evidence-based methods

• Overview of indications

• Estimation of the number of patients with an expected benefit from proton therapy
  – Which capacity is needed?
Estimation of numbers
Example (breast cancer)

<table>
<thead>
<tr>
<th>Indication group</th>
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<th>Number of patients treated with RT</th>
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<td>12,171</td>
<td>10,102</td>
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- Annual incidence based on the Dutch Cancer Registry (2005)
- Percentage and number of patients treated with radiotherapy based on CCORE Report
- Percentage and number of irradiated patients with expected benefit from protons

Horizon Scanning Report (Health Council 2009)
## Estimation of numbers

### Example (breast cancer)

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Horizon Scanning Report

Indication grouping

• Standard indications
• Prevention of secondary tumours
• Potential indications
• Model-based indications
### Standard indications

#### Number of patients

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<td>Standard indications</td>
<td>550</td>
<td>299</td>
<td>84%</td>
<td>252</td>
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- Generally accepted indications for proton therapy world wide:
  - Paediatric tumours
  - Base of skull tumours
  - Ocular melanoma
## Prevention secondary tumours

**Number of patients**

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<tr>
<td>Prevention secondary tumours</td>
<td>15,867</td>
<td>11,289</td>
<td>7%</td>
<td>807</td>
</tr>
</tbody>
</table>

- Young patients (18-40 years) with tumours with favourable prognosis:
  - Early stage breast cancer
  - Hodgkin lymphoma
  - Seminoma testis
Potential indications
Number of patients

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<tr>
<td>Potential indications</td>
<td>21,061</td>
<td>14,471</td>
<td>8%</td>
<td>1,215</td>
</tr>
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</table>

- Target dose escalation
  - Individual:
    - when the required dose cannot be given without exceeding the threshold dose for critical structures (e.g. spinal cord)
  - Within framework of RCT
## Model-based indications

### Number of patients

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<td>Model-based indications</td>
<td>52,305</td>
<td>34,578</td>
<td>14%</td>
<td>4,824</td>
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- Proton therapy indicated based on expected benefit in terms of clinically relevant risk reduction of radiation-induced side effects
- Model-based selection and validation

Horizon Scanning Report (Health Council 2009)
Step 1: NTCP-model
Example: Tube feeding dependence (n=350)
Step 2: Dose comparison
Assessment ΔDose (individual patient)

- **Standard IMRT (parotid glands)**
  - Dmean superior PCM: 66 Gy

- **Swallowing sparing IMRT (parotid glands and superior)**
  - Dmean superior PCM: 60 Gy

- **Swallowing sparing IMPT (parotid glands and superior PCM)**
  - Dmean superior PCM: 50 Gy

Van der Laan et al, Acta Oncol 2012
Step 3: Clinical benefit
Translate ΔDose into ΔNTCP

Risk tube feeding dependence (NTCP)

Chemoradiation

Photon

Protons

Mean dose superior PCM

Translation from Δdose to ΔNTCP

Langendijk et al, Radiother Oncol 2013
Step 3: Clinical benefit
Translate ΔDose into ΔNTCP

Translation from Δdose to ΔNTCP

Langendijk et al, Radiother Oncol 2013
Step 3: Clinical benefit
Translate ΔDose into ΔNTCP

Translation from Δdose to ΔNTCP

Langendijk *et al.*, Radiother Oncol 2013
Step 3: Selection
Which threshold should be used?

$\Delta$NTCP varies widely among individual patients with apparently similar tumour characteristics

Langendijk et al, Work in Progress
NVRO consensus
Thresholds for ΔNTCP

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<th>CTCAE Grade</th>
<th>Threshold for ΔNTCP</th>
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<tr>
<td>I</td>
<td>No indication</td>
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NOTE:
Separate algorithms in case of multiple complications
Step 3: Selection
Which threshold should be used?

Threshold for grade III or higher side effects: 5%

Langendijk et al, Work in Progress
# Model-based indications

Four major examples

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<td>Prostate cancer</td>
<td>8,773</td>
<td>5,264</td>
<td>10%</td>
<td>526</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>9,801</td>
<td>5,264</td>
<td>15%</td>
<td>1,118</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>2,487</td>
<td>2,288</td>
<td>45%</td>
<td>1,069</td>
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Horizon Scanning Report

Indications for proton therapy (4 categories)

- Prevention of complications: 4,824 patients per year
- Target dose escalation: 1,215 patients per year
- Prevention secondary tumours: 807 patients per year
- Standard indications: 252 patients per year

Total number with expected benefit: 7,098 patients per year (based on Cancer Registry in 2005)
Advice: Keep initial capacity below 4,000 patients per year
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Health Insurance Board
Introduction

• Main task:
  – Review scientific evidence to accept a new treatment modality / drug / technology to be part of the Basic Health Insurance Package
    • If YES, all patients will be reimbursed
    • If NO, reimbursement depends on individual Health Insurance Company

• Main problem in 2010:
  – Only level I-II evidence accepted as evidence-based medicine
Health Insurance Board
Reports

  – Recognition of the model-based approach

  – Positive advice
  – Insured care (252 patients per year)

  – Positive advice
  – 3,218 patients per year
    • requires indication protocols per tumour site
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Planning Directive PT
Ministry of Health

• Based on reports from:
  – Health Council (2009)
  – Health Insurance Board (2009-2012)
  – Consensus with all proton therapy initiatives

• Main issues:
  – Specific Medical Procedures Act (WBMV)
  – Maximum license for 2,200 patients per year
  – 4 centres
    • Optimal geographic distribution
    • Optimal accessibility for patients
  – Re-evaluation after full capacity reached
Proton therapy facilities

Geographic distribution

Groningen (GPTC)
- Treatment rooms: 2
- Capacity: 600 patients
- Vendor: IBA
- Operational: Q4-2017

Amsterdam (APTC)
- Treatment rooms: 3
- Capacity: 600 patients
- Set on hold

Delft (HollandPTC)
- Treatment rooms: 3
- Capacity: 600 patients
- Vendor: Varian
- Operational: Q3-2017

Maastricht (ZonPTC)
- Treatment rooms: 1 gantry
- Capacity: 400 patients
- Vendor: Mevion
- Operational: Q4-2018
Planning Directive PT
Background and license conditions

• High accessibility for patients ➔ optimal geographic distribution

• Realistic business cases regarding maximum capacity:
  – Limited experience with PBS + image-guidance + real time adaptation
  – Maximum capacity: 600 patients

• Existing radiotherapy department:
  – Efficient use of existing experience/infrastructure
  – Better integration with existing multidisciplinary pathways
Planning Directive PT
Background and license conditions

- Direct involvement of University Medical Centre:
  - Strong clinical scientific track record
  - Research plan
    - Clinical validation of benefits of protons
    - Cost effectiveness

- Uniform national prospective data registration
  - Involvement of 7 university departments ➔ optimal environment for clinical studies with high patient accrual
Planned capacity
In relation to expected future indications

Horizon Scanning Report
All standard and model-based indications
Planned capacity

Assumed ramp up of 30%-60%-90%-100%
Planned capacity
In relation to total number of RT treatments

Number of photon therapy treatment per year

Assumed ramp up of 30%-60%-90%-100%
Next steps
NVRO consensus
Thresholds for ΔNTCP

Thresholds for 1 complication

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NOTE:
Separate algorithms in case of multiple complications

Which NTCP models should be used for model-based selection?
NTCP-models

Minimal requirements for high quality model-based selection

• Prospective data collection of toxicity
• Sufficient number of patients/events
• Multivariable analysis
• Clinical Decision Rule
  – Formula, nomogram or graph
• Internal validation (correct for overfitting)
  – Bootstrapping and/or cross-validation
• Model performance

## NTCP-models

Levels of evidence (TRIPOD Statement)

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<th>Description</th>
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<td><strong>Type 4</strong></td>
<td>External validation of published <em>High quality NTCP-model</em> in separate dataset in other institution</td>
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<tr>
<td><strong>Type 3</strong></td>
<td>Development and validation of <em>High quality NTCP-model</em> using one data set for development and a separate dataset for validation</td>
</tr>
<tr>
<td><strong>Type 2b</strong></td>
<td>Non-random split-sample development and validation</td>
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<tr>
<td><strong>Type 2a</strong></td>
<td>Random split-sample development and validation</td>
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<tr>
<td><strong>Type 1b</strong></td>
<td>Development and validation using resampling</td>
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<td>Development only</td>
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*High quality refers to requirements for NTCP-models*

Model-based selection
Decision support system

\[ \Delta \text{NTCP} \text{ criteria fulfilled?} \]

\[ \text{IMRT} \]

\[ \text{IMPT} \]

\[ \Delta \text{NTCP-profile} \]

- Hypothyroidism
- Sticky saliva
- Xerostomia
- Dysphagia
- Tube feeding

\[ 0\% \quad -5\% \quad -10\% \quad -15\% \]
Model-based selection
Decision support system

IMRT

NO

ΔNTCP criteria fulfilled?

IMPT
Model-based approach
Rapid Learning Health Care (RLHC) system

Knowledge stage
- NTCP-model
- NTCP-optimisation
- Model-based validation

Data stage
- Prospective data registration
- IMPT protons
- IMRT photons

Application stage
- IMPT dose optimisation
- IMRT dose optimisation

Evaluation stage
- Indication protocol
- NTCP-model library

Most relevant dose
Volume factors

Conclusions

• The introduction of proton therapy on a national basis is a long and time-consuming process

• The model-based approach can be used as an alternative for RCT and should be implemented within the framework of a rapid learning health care system
  – Continuous quality improvement
  – Selection of patients
  – Clinical validation
Conclusions

• Main challenges
  – Indication protocols and NTCP-model selection
  – Model-based selection work flow
  – Uniform national prospective data registration