History of particle therapy in the Netherlands

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ENLIGHT

Disclosures

- Department research agreements with:
  - RaySearch
  - Philips
  - IBA
  - Mirada
- Speaker for IBA symposium with honorarium (UMCG Research BV)
- Conference sponsorship by IBA

Milestones

Year	Milestone
2009	Horizon Scanning Report (Health Council)
2010-2012	Advisory Reports (Health Insurance Board)
2013	Planning Directive Proton Therapy (Ministry of Health)
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2017	First patient treatment planned
2020-2022	Full capacity available

Horizon Scanning Report
Contents

- 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?

Horizon Scanning Report (Health Council 2009)

Estimation of numbers
Example (breast cancer)

Indication group	Annual incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
Breast cancer	12,171	10,102	**5%**	505

- 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)

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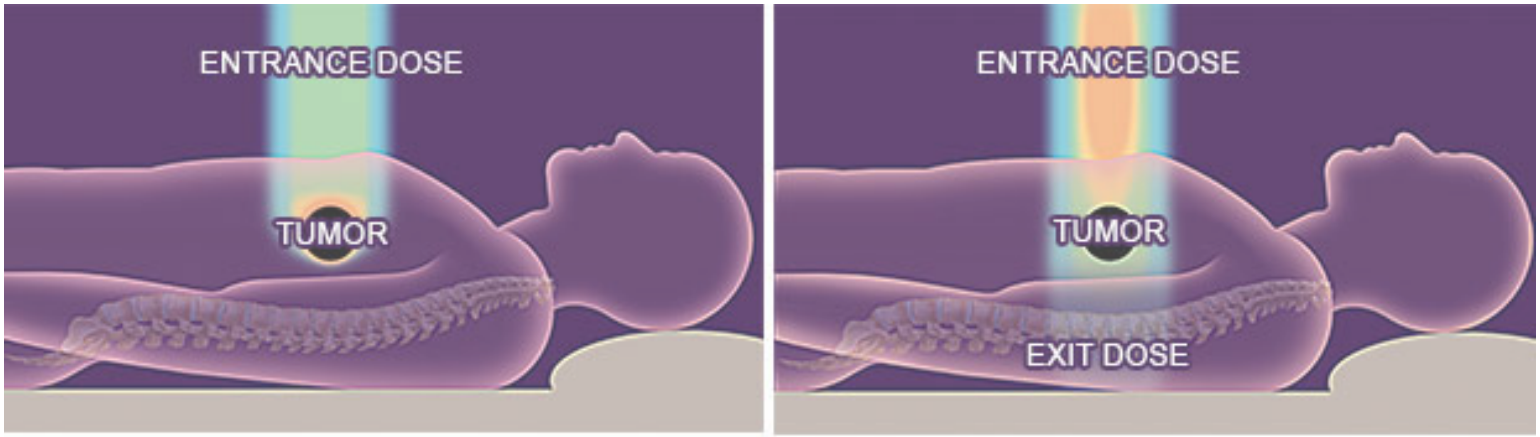
Horizon Scanning Report (Health Council 2009)

Horizon Scanning Report

Indication grouping

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



Horizon Scanning Report (Health Council 2009)

Standard indications

Number of patients

Indication group	Incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
Standard indications	550	299	84%	252

- Generally accepted indications for proton therapy world wide:
  - Paediatric tumours
  - Base of skull tumours
  - Ocular melanoma

Horizon Scanning Report (Health Council 2009)

Prevention secondary tumours

Number of patients

Indication group	Incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
Prevention secondary tumours	15,867	11,289	7%	807

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

Horizon Scanning Report (Health Council 2009)

Potential indications
Number of patients

Indication group	Incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
Potential indications	21,061	14,471	8%	1,215

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

Horizon Scanning Report (Health Council 2009)

Model-based indications

Number of patients

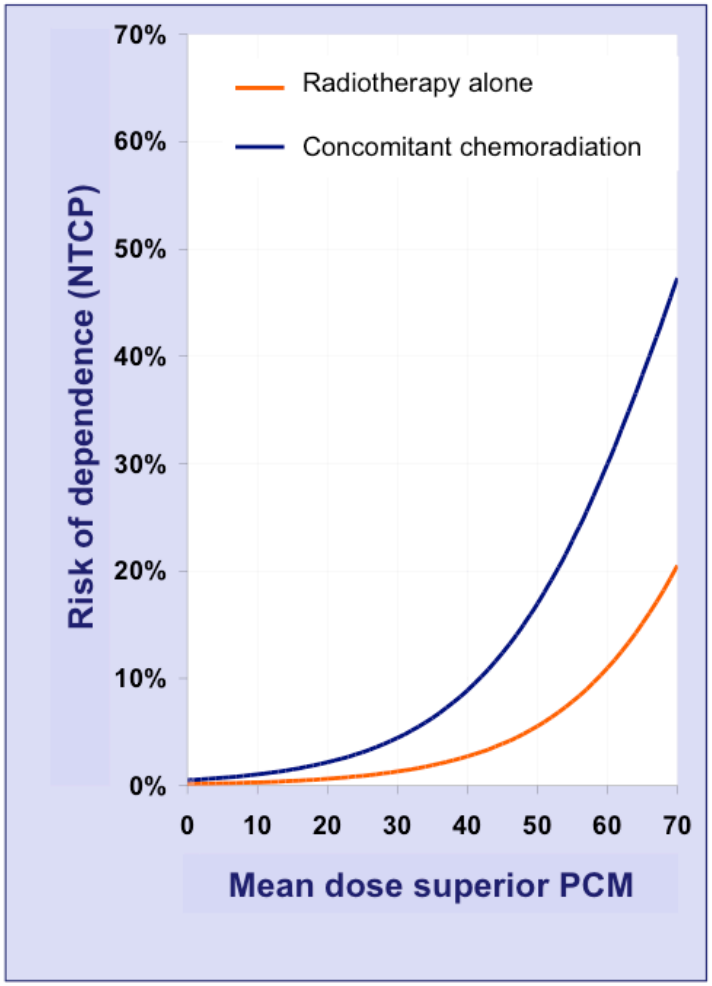
Indication group	Incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
Model-based indications	52,305	34,578	14%	4,824

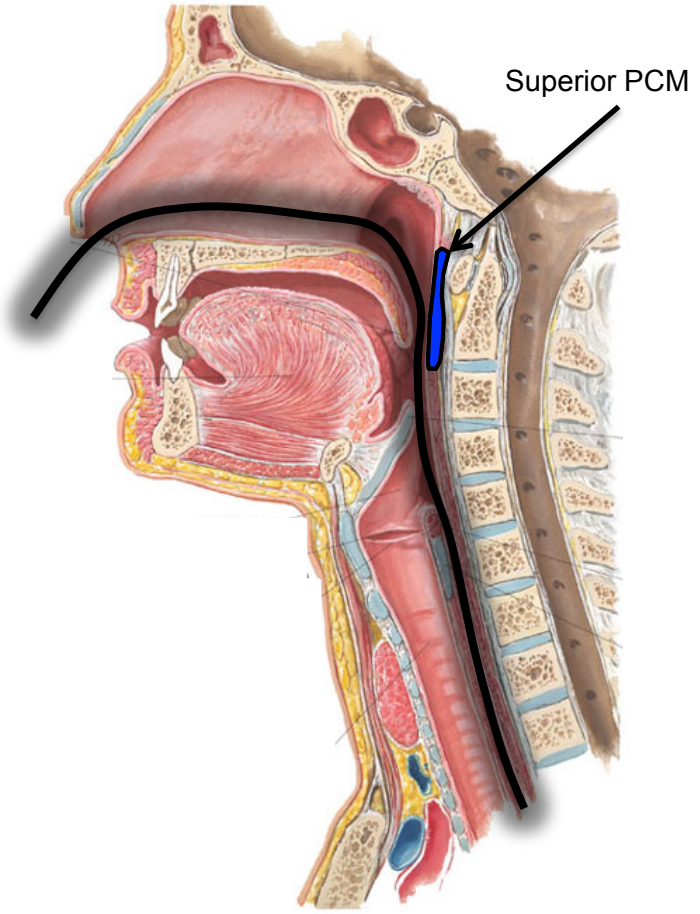
- Proton therapy indicated based on expected benefit in terms of clinically relevant risk reduction of radiation-induced side effects
- Model-based selection and validation

Horizon Scanning Report (Health Council 2009)

Step 1: NTCP-model

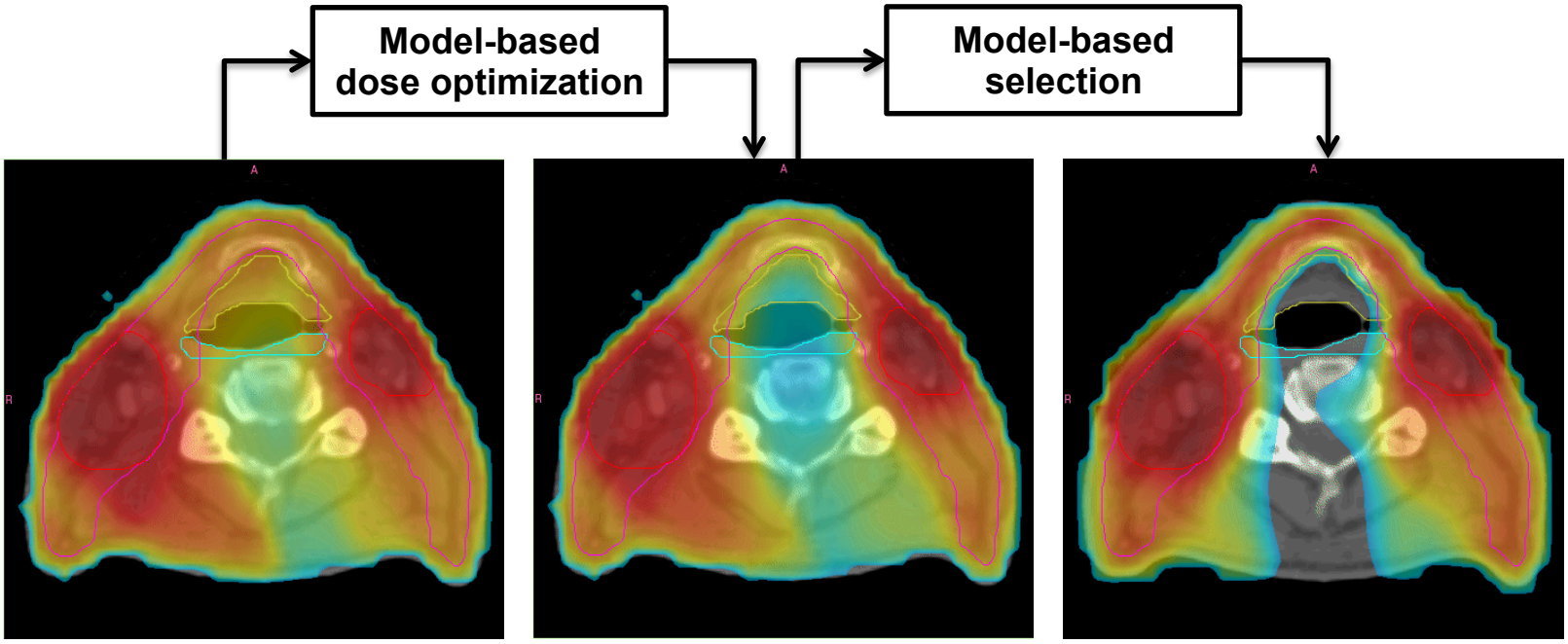
Example: Tube feeding dependence (n=350)





Step 2: Dose comparison

Assessment ΔDose (individual patient)

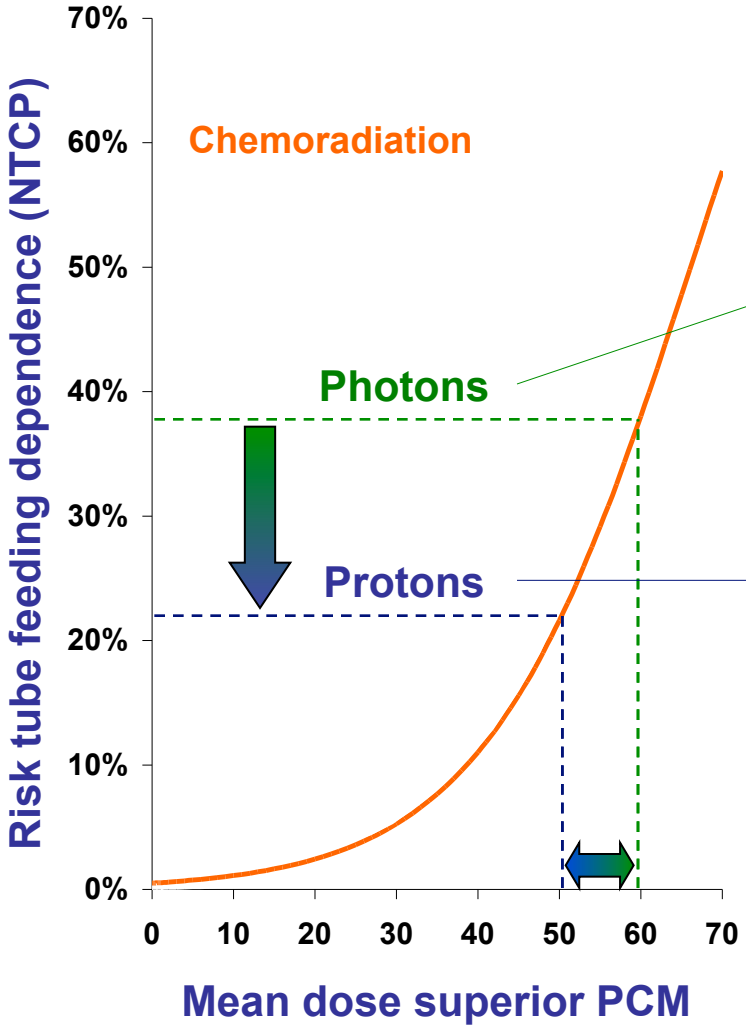


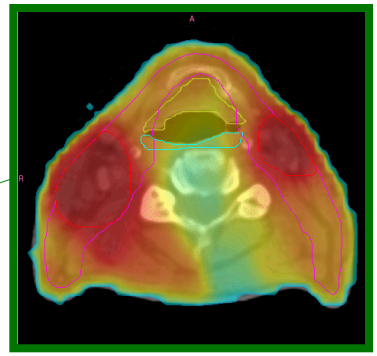
Standard IMRT (parotid glands)	Swallowing sparing IMRT (parotid glands and superior	Swallowing sparing IMPT (parotid glands and superior PCM)
Dmean superior PCM: 66 Gy	Dmean superior PCM: 60 Gy	Dmean superior PCM: 50 Gy

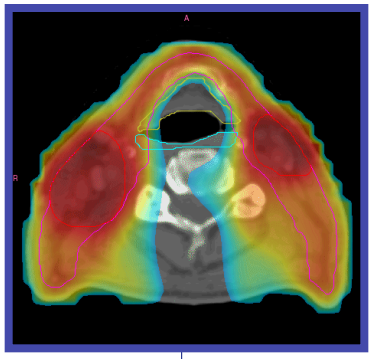
Van der Laan *et al*, Acta Oncol 2012

Step 3: Clinical benefit

Translate ΔDose into ΔNTCP







Translation from Δdose to ΔNTCP

Langendijk *et al*, Radiother Oncol 2013

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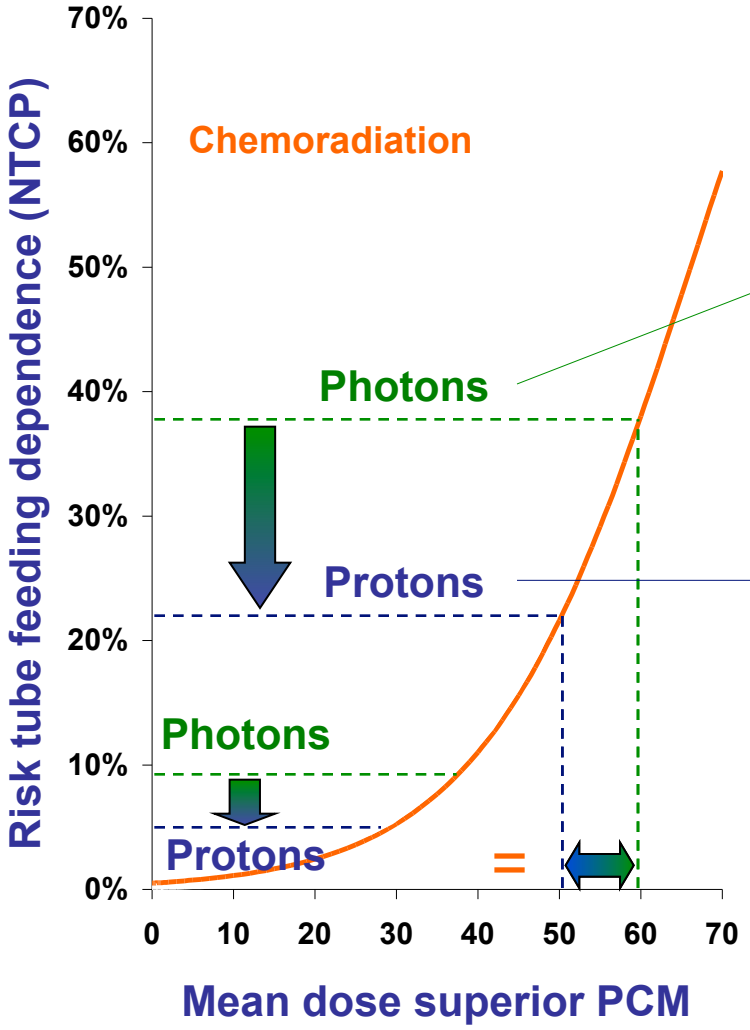

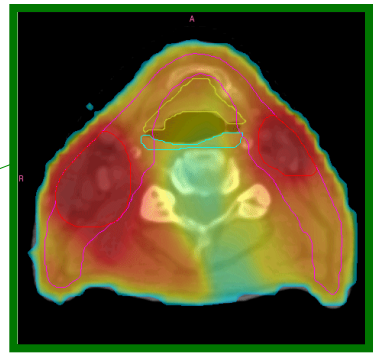

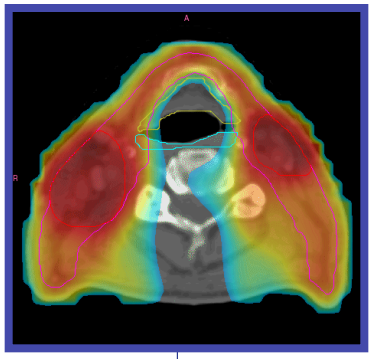

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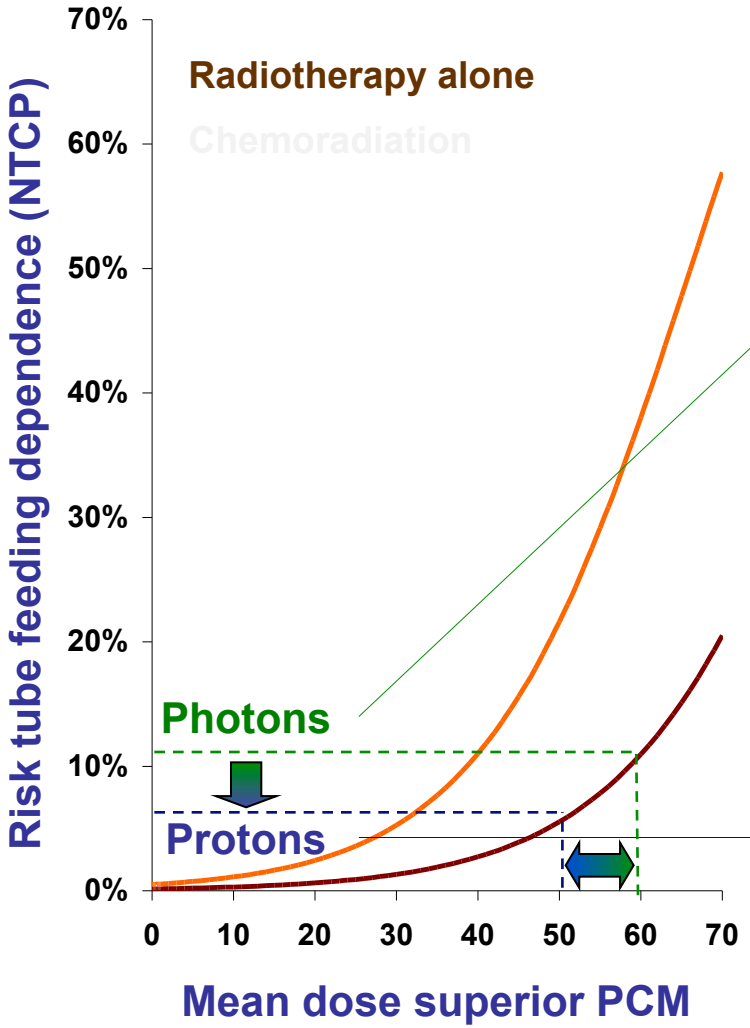
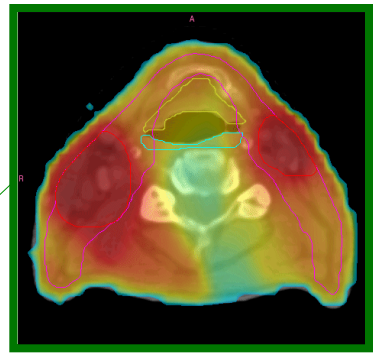
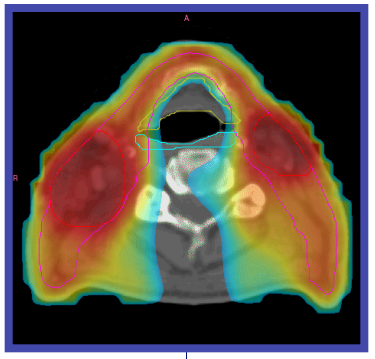




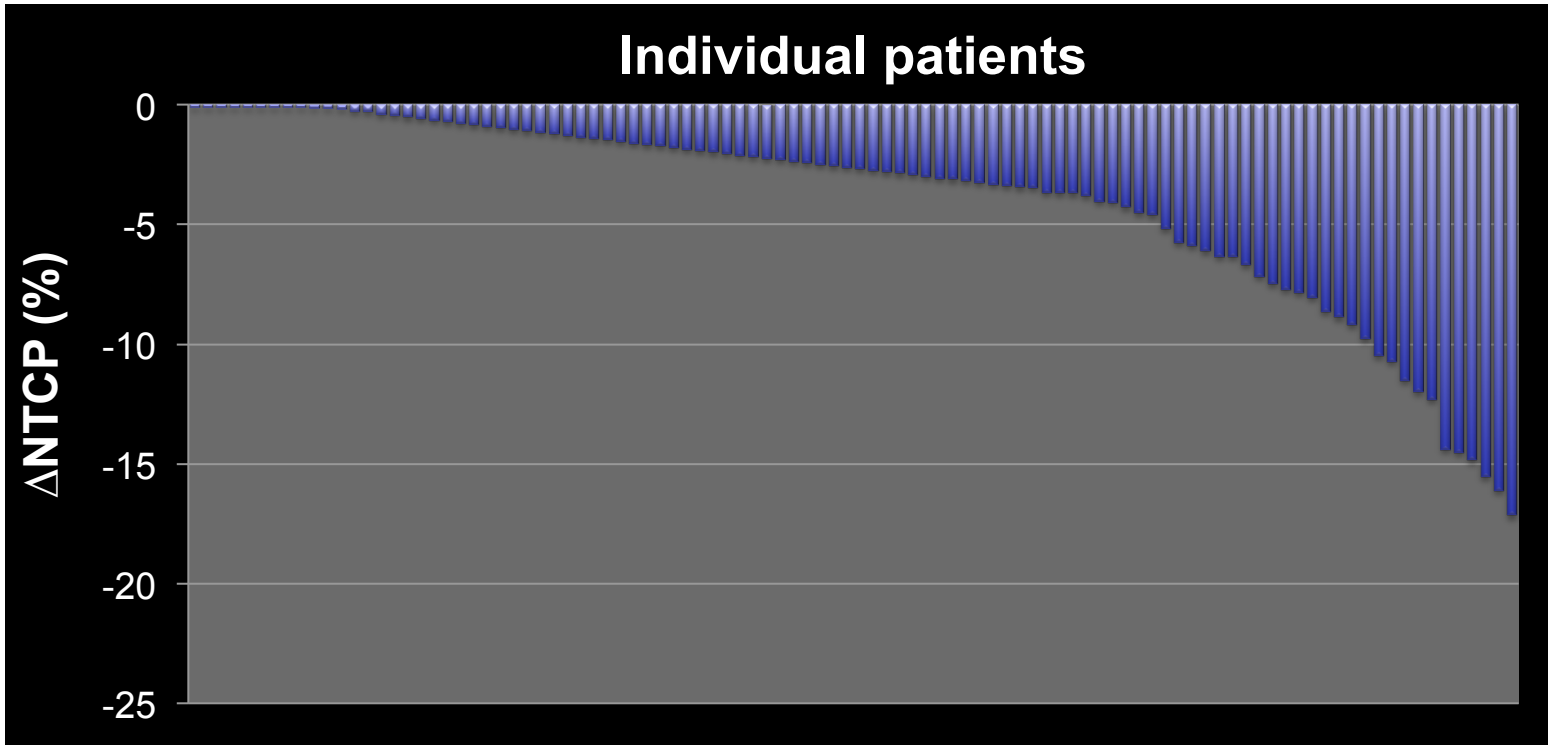


Translation from Δdose to ΔNTCP

Langendijk *et al*, Radiother Oncol 2013

Step 3: Selection

Which threshold should be used?



ΔNTCP varies widely among individual patients with apparently similar tumour characersitics

Langendijk *et al*, Work in Progress

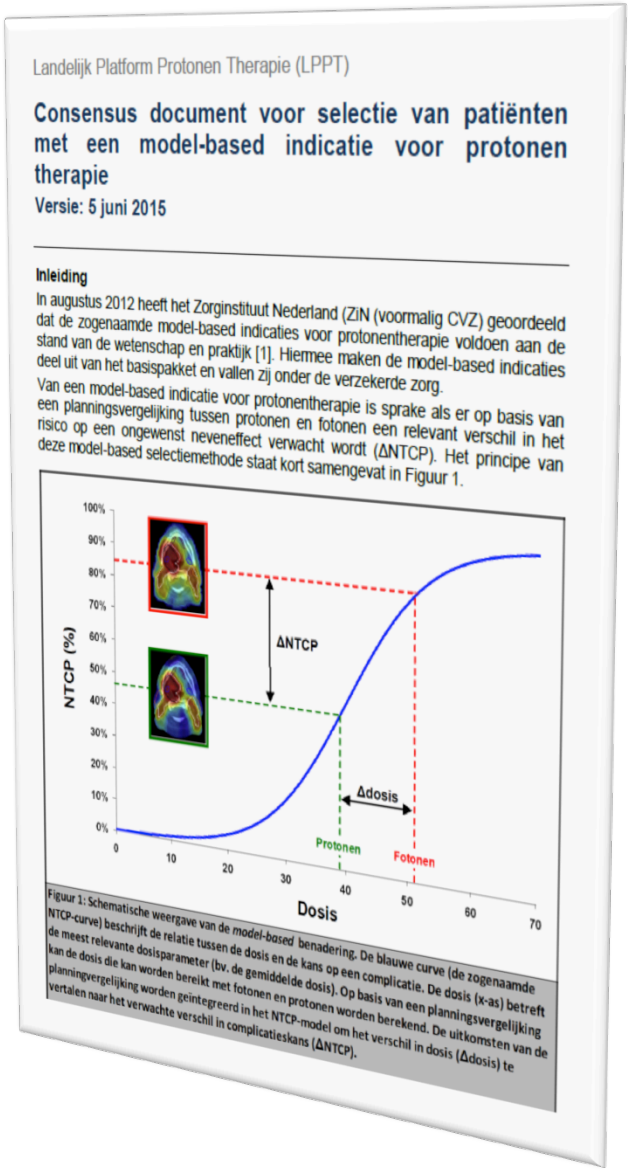
NVRO consensus

Thresholds for ΔNTCP

Thresholds for 1 complication

CTCAE Grade	Threshold for ΔNTCP
I	No indication
II	≥ 10%
III	≥ 5%
IV-V	≥ 2%

NOTE:
Separate algorithms in case of multiple complications



Landelijk Platform Protonen Therapie (LPPT)

Consensus document voor selectie van patiënten met een model-based indicatie voor protonen therapie

Versie: 5 juni 2015

Inleiding

In augustus 2012 heeft het Zorginstituut Nederland (ZiN (voormalig CVZ) geoordeeld dat de zogenaamde model-based indicaties voor protonentherapie voldoen aan de stand van de wetenschap en praktijk [1]. Hiermee maken de model-based indicaties deel uit van het basispakket en vallen zij onder de verzekerde zorg.

Van een model-based indicatie voor protonentherapie is sprake als er op basis van een planningsvergelijking tussen protonen en fotonen een relevant verschil in het risico op een ongewenst neveneffect verwacht wordt (ΔNTCP). Het principe van deze model-based selectiemethode staat kort samengevat in Figuur 1.

Figuur 1: Schematische weergave van de *model-based* benadering. De blauwe curve (de zogenaamde NTCP-curve) beschrijft de relatie tussen de dosis en de kans op een complicatie. De dosis (x-as) betreft de meest relevante dosisparameter (bv. de gemiddelde dosis). Op basis van een planningsvergelijking kan de dosis die kan worden bereikt met fotonen en protonen worden berekend. De uitkomsten van de planningvergelijking worden geïntegreerd in het NTCP-model om het verschil in dosis (Δdosis) te vertalen naar het verwachte verschil in complicatieskans (ΔNTCP).

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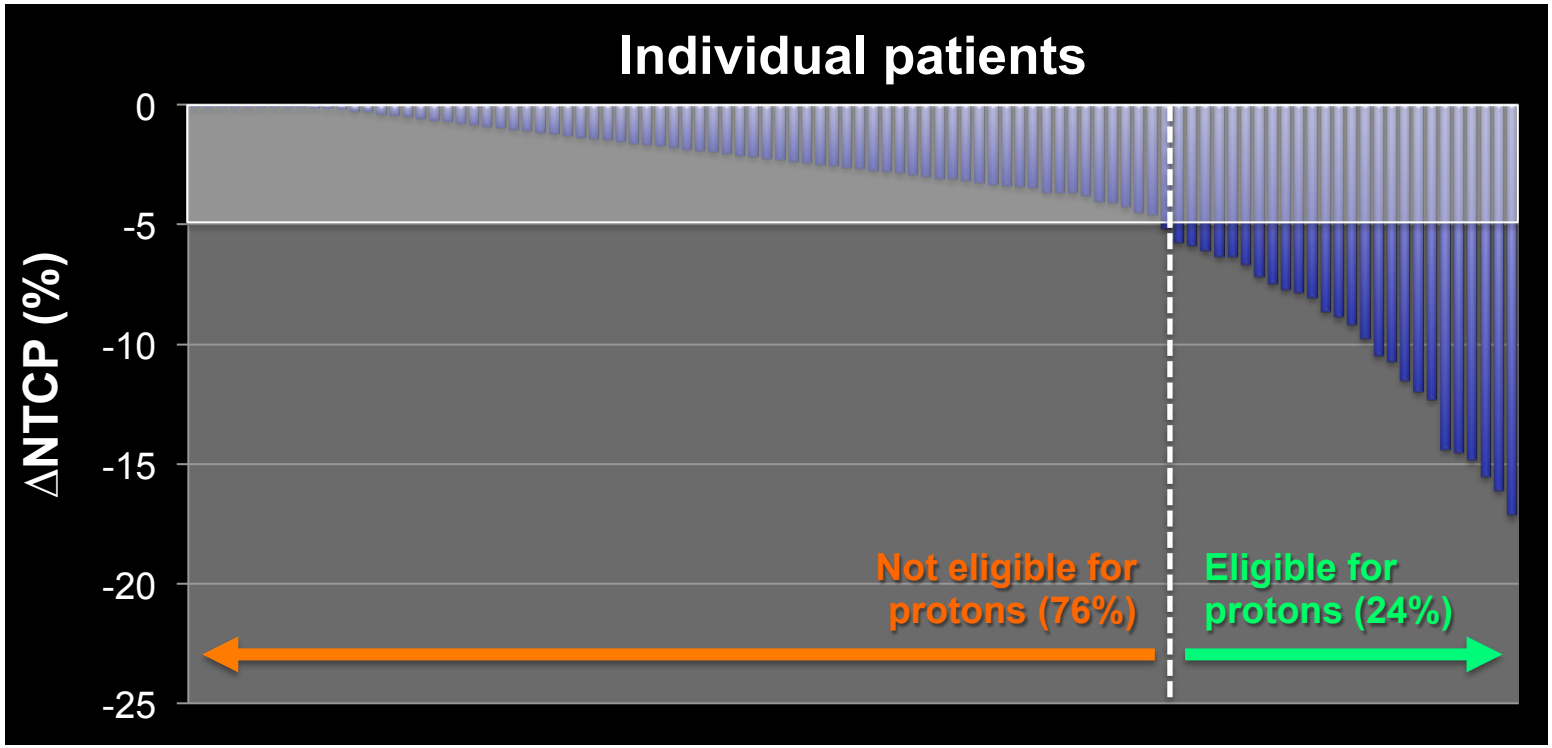


Threshold for grade III or higher side effects: 5%

Langendijk *et al*, Work in Progress

Model-based indications

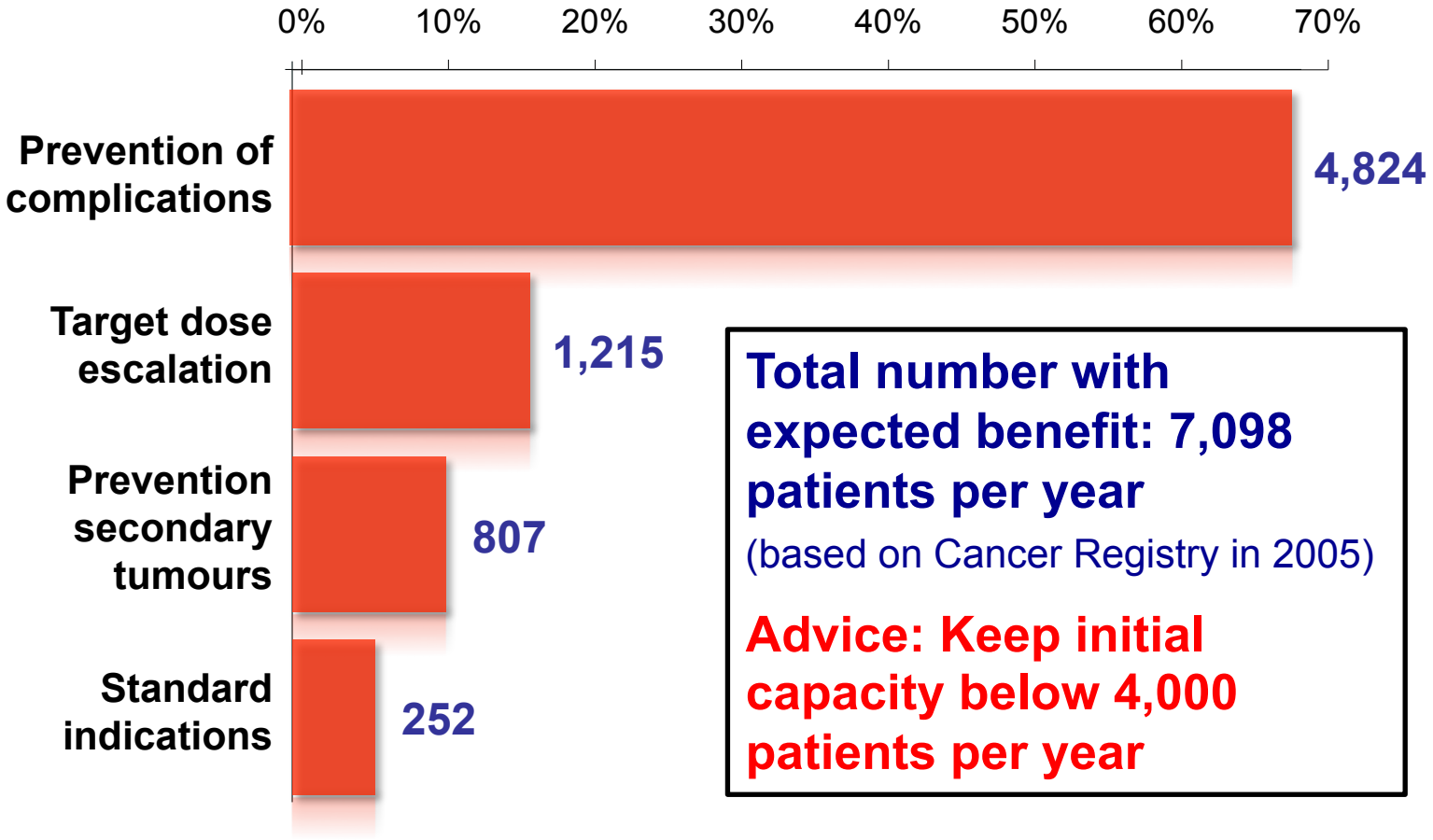
Four major examples

Indication group	Incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
Breast cancer	12,171	10,102	**5%**	505
Prostate cancer	8,773	5,264	**10%**	526
Lung cancer	9,801	5,264	**15%**	1,118
Head and neck cancer	2,487	2,288	**45%**	1,069

Horizon Scanning Report (Health Council 2009)

Horizon Scanning Report

Report of the Dutch Health Council (2009)



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

Indications for proton therapy (4 categories)

Milestones

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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

- Report: '**Proton Therapy**' (2009)
  - Recognition of the model-based approach
- Report: '**Indications for proton therapy part I: the standard indications**' (2010):
  - Positive advice
  - Insured care (252 patients per year)
- Report: '**Indications for proton therapy part II: the model-based indications**' (2012)
  - 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

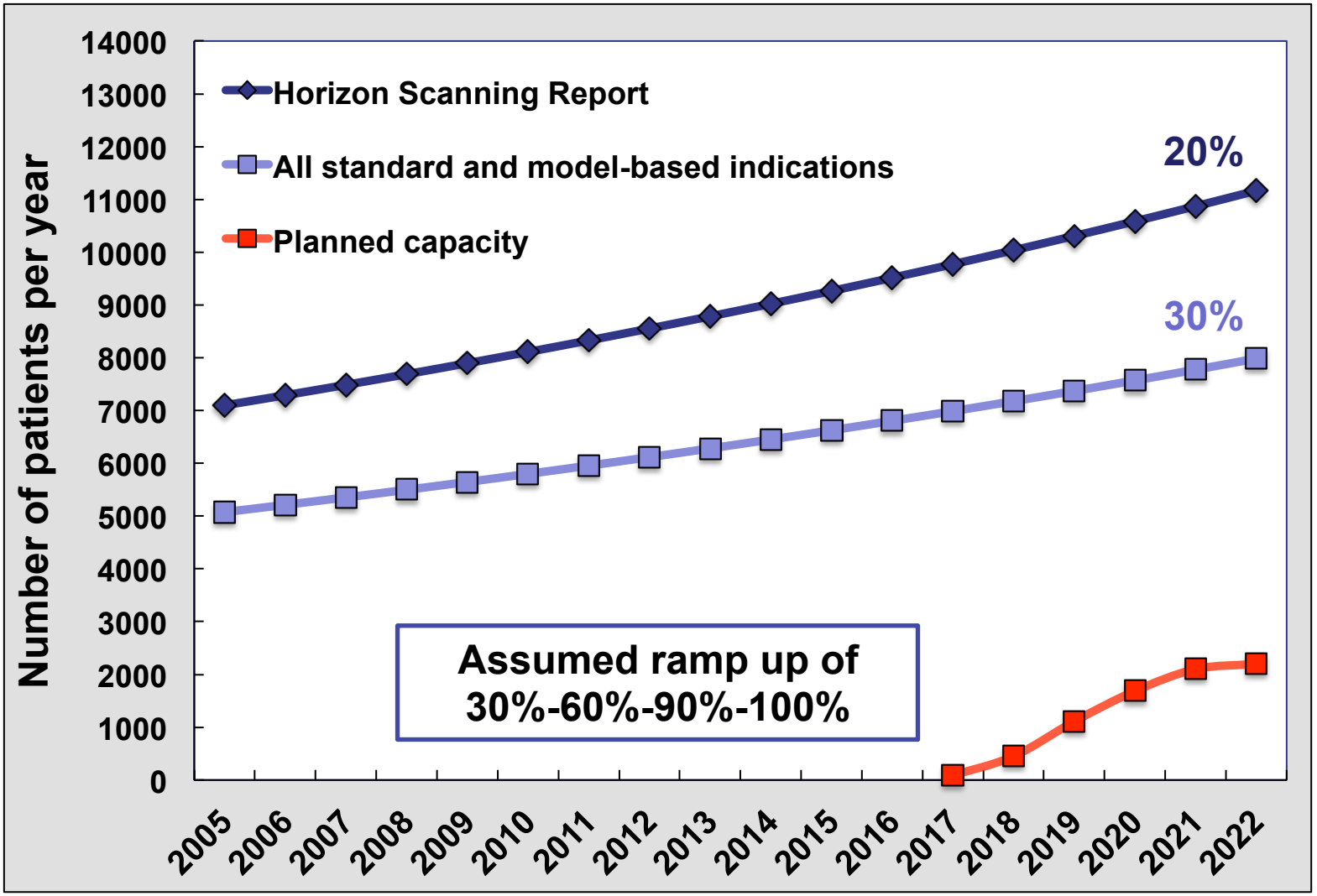
Planning Directive PT

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

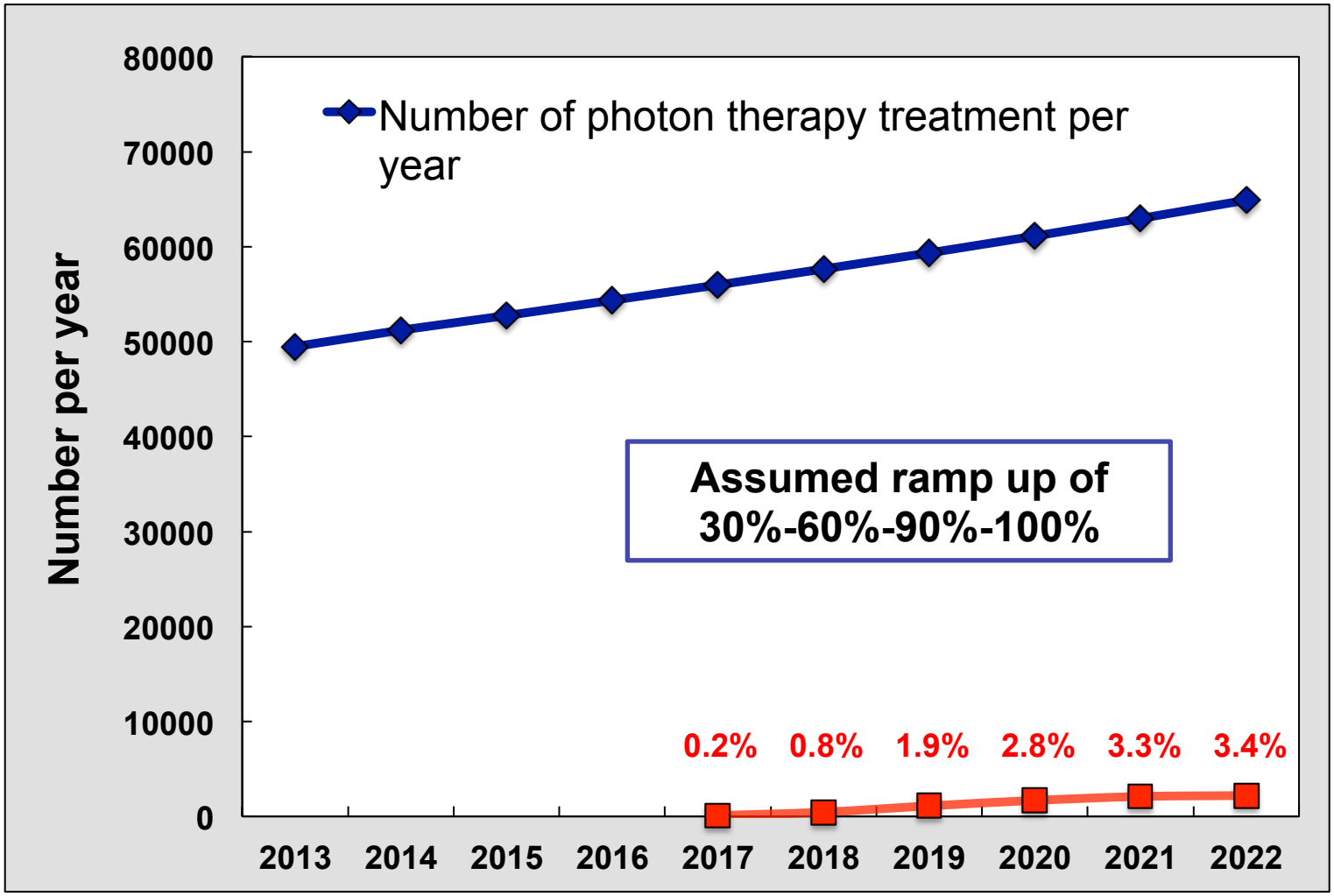
Planned capacity

In relation to expected future indications



Planned capacity

In relation to total number of RT treatments



Next steps

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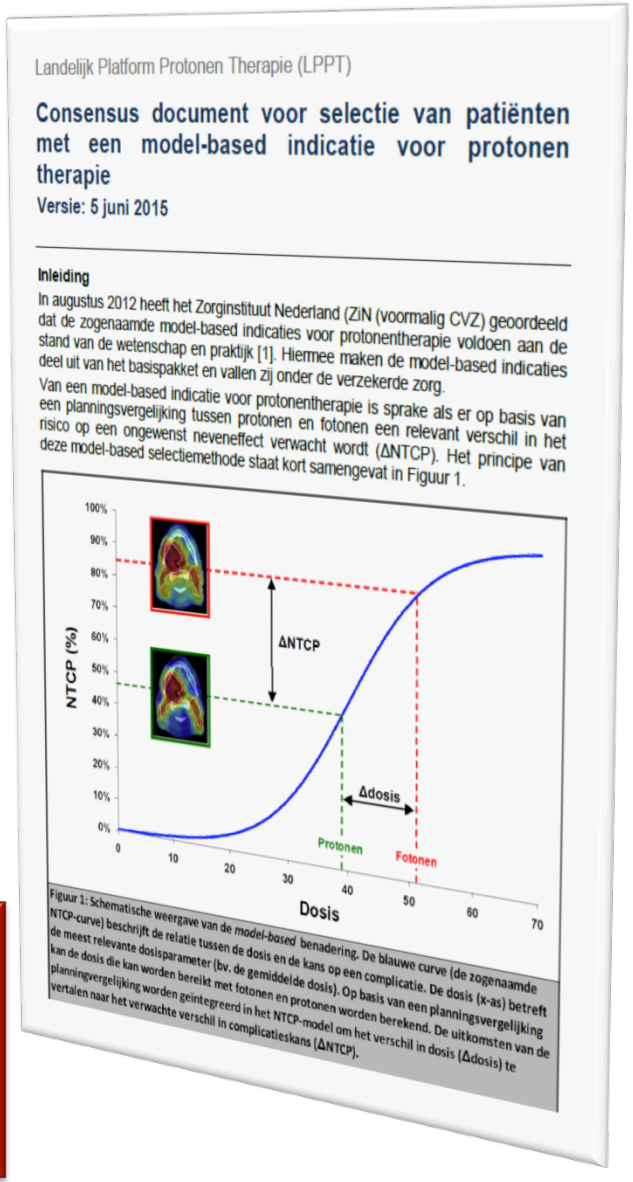

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NTCP-models

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

Collins, et al. Ann Int Med 2015

NTCP-models

Levels of evidence (TRIPOD Statement)

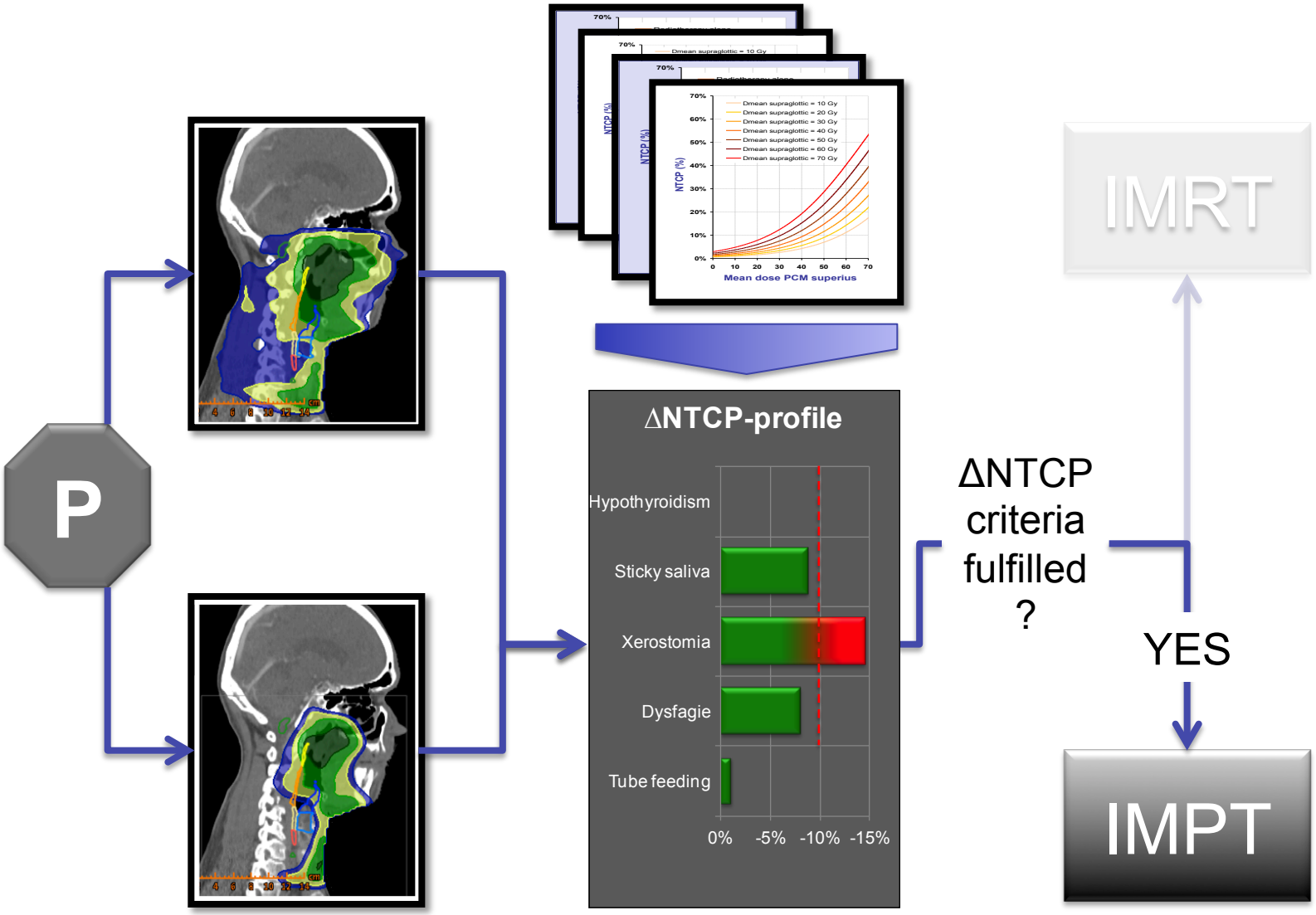
TRIPOD Type	Description
Type 4	External validation of published *High quality NTCP-model* in separate dataset in other institution
Type 3	Development and validation of *High quality NTCP-model* using one data set for development and a separate dataset for validation
Type 2b	Non-random split-sample development and validation
Type 2a	Random split-sample development and validation
Type 1b	Development and validation using resampling
Type 1a	Development only

High quality refers to requirements for NTCP-models

Derived from: Collins, et al. Ann Int Med 2015

Model-based selection

Decision support system



Model-based selection

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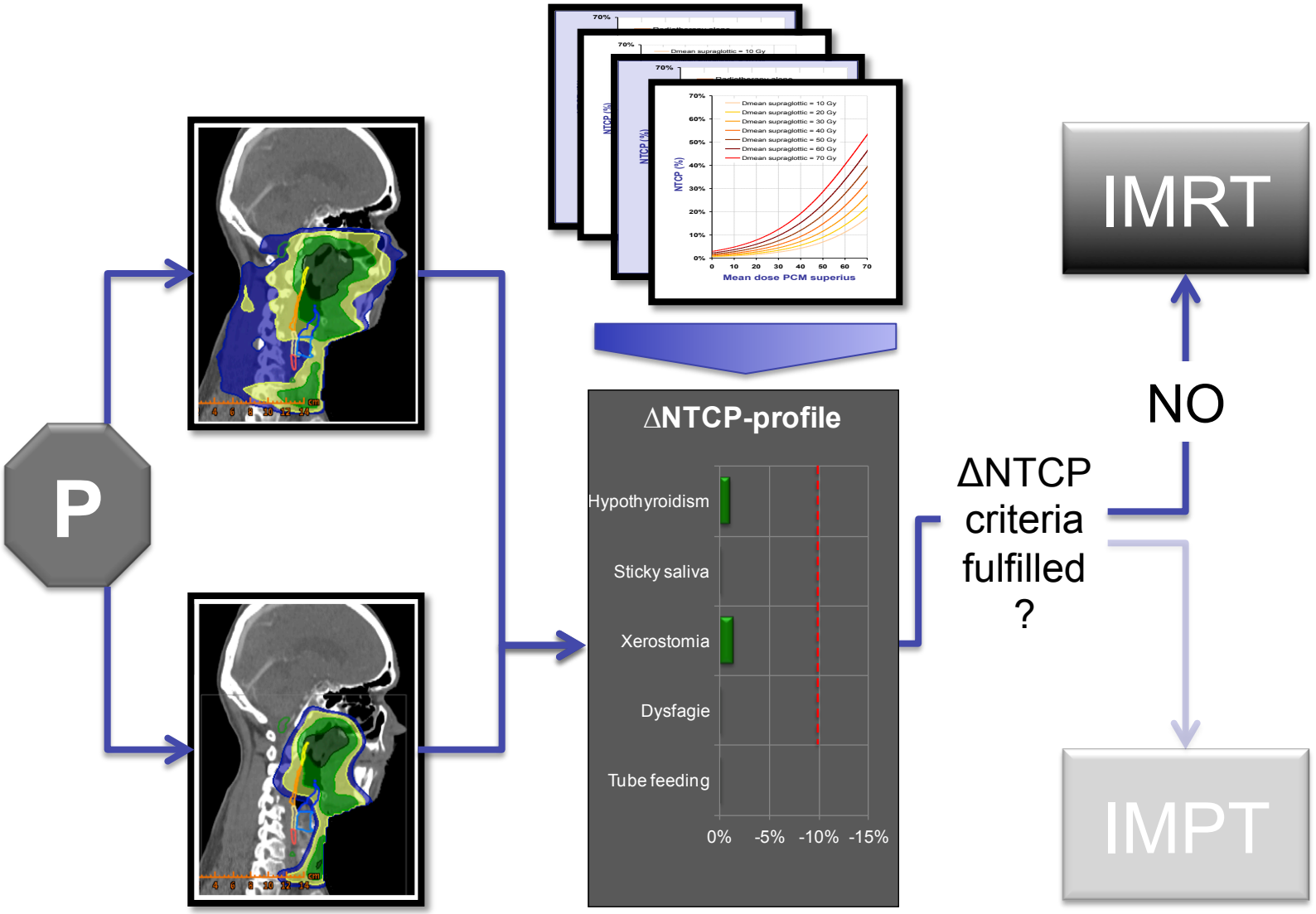
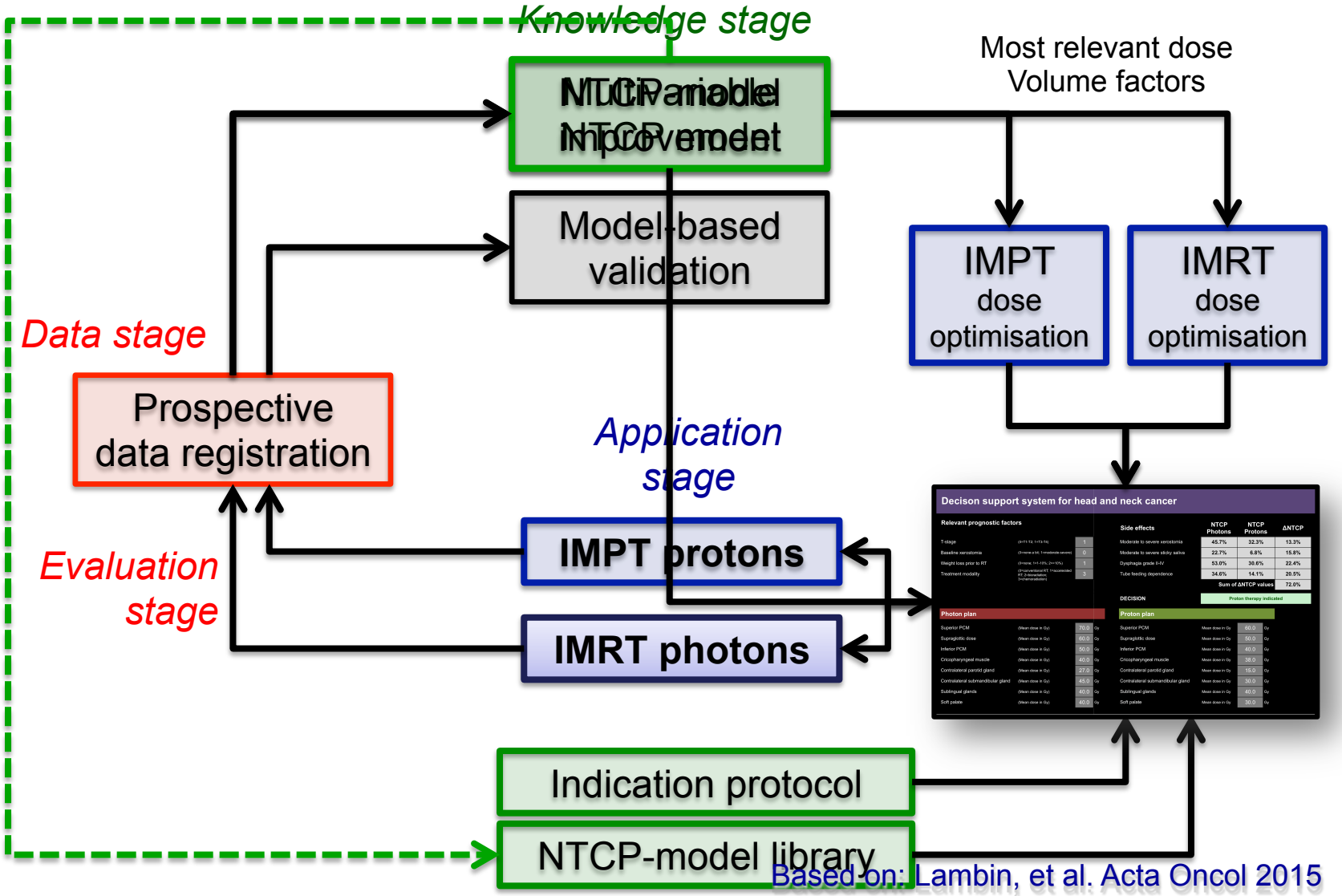


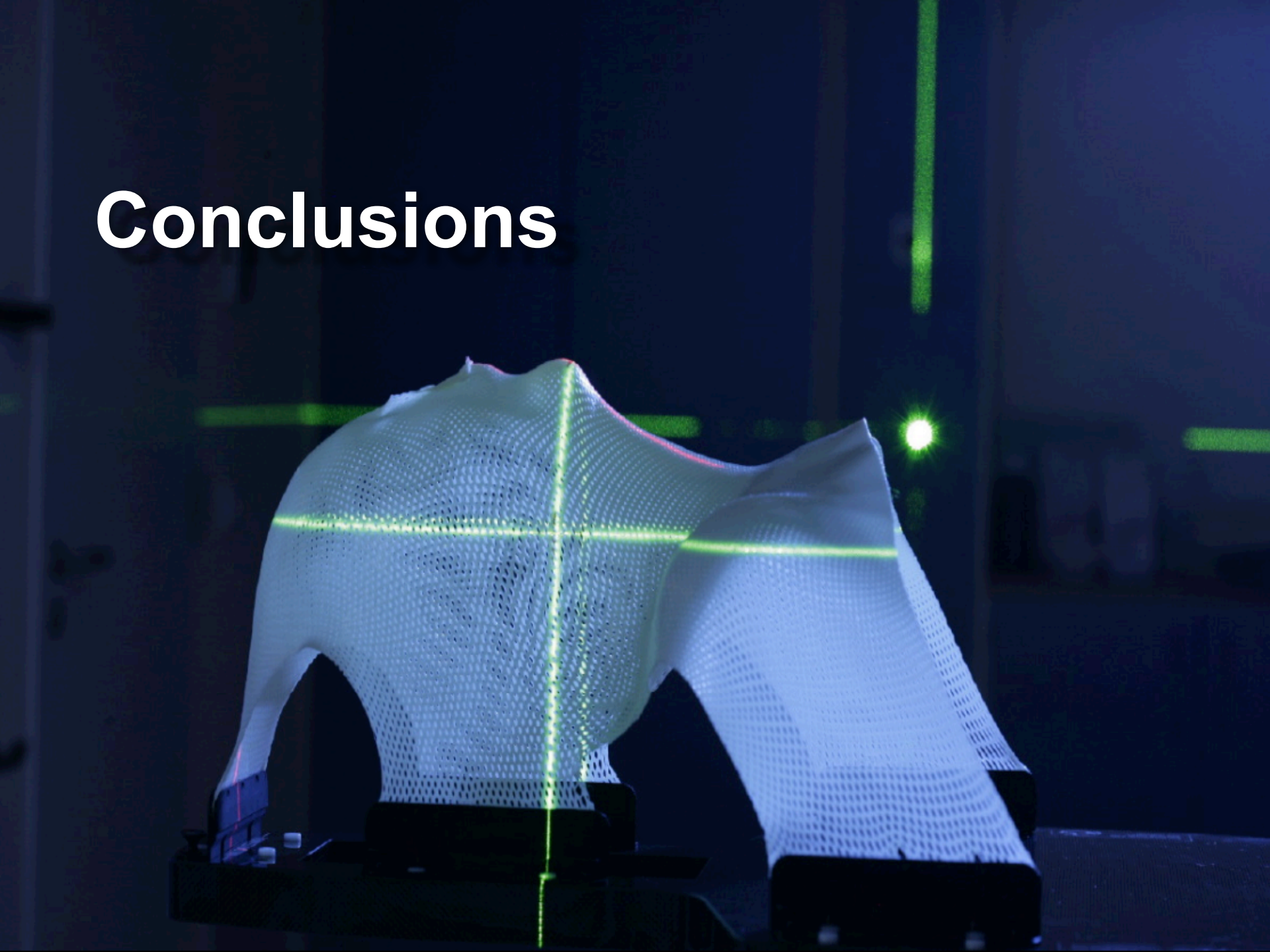
Model-based approach

Rapid Learning Health Care (RLHC) system



Based on: Lambin, et al. Acta Oncol 2015

Conclusions



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