Current status of proton therapy in the Netherlands

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GRONINGEN

The Netherlands

ICTR-PHE 2016

Uniting physics, biology and medicine for better healthcare

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)
2015	Start construction of first two Dutch Proton therapy centres
2017	First patient treatment planned
2020-2022	Full capacity available

Horizon Scanning Report
Health Council

- Formal request of Minister of Health (2007)

- Main purpose:
  - To provide information for political decision making on the introduction of proton therapy in the Netherlands

- Background:
  - Complex infrastructure with special expertise
  - Higher capital outlay and operational costs with higher costs per treatment

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)

Estimation of numbers
Example (breast cancer)

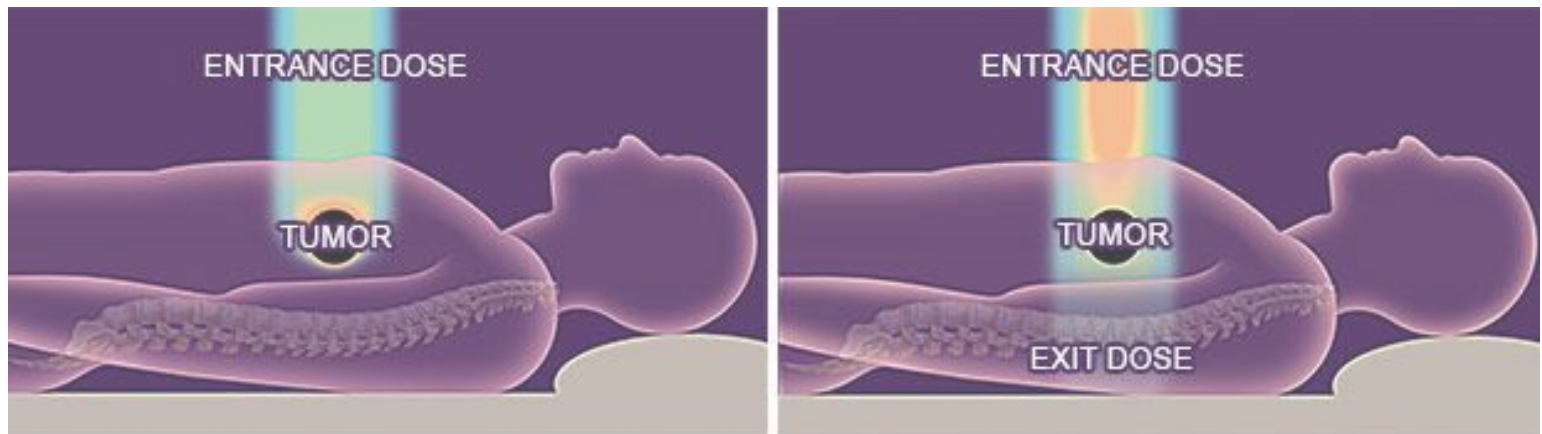| Indication group	Annual incidence in 2005	Number of patients treated with RT	Expected percentage with benefit from protons	Number of patients with benefit of protons
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Horizon Scanning Report (Health Council 2009)

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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
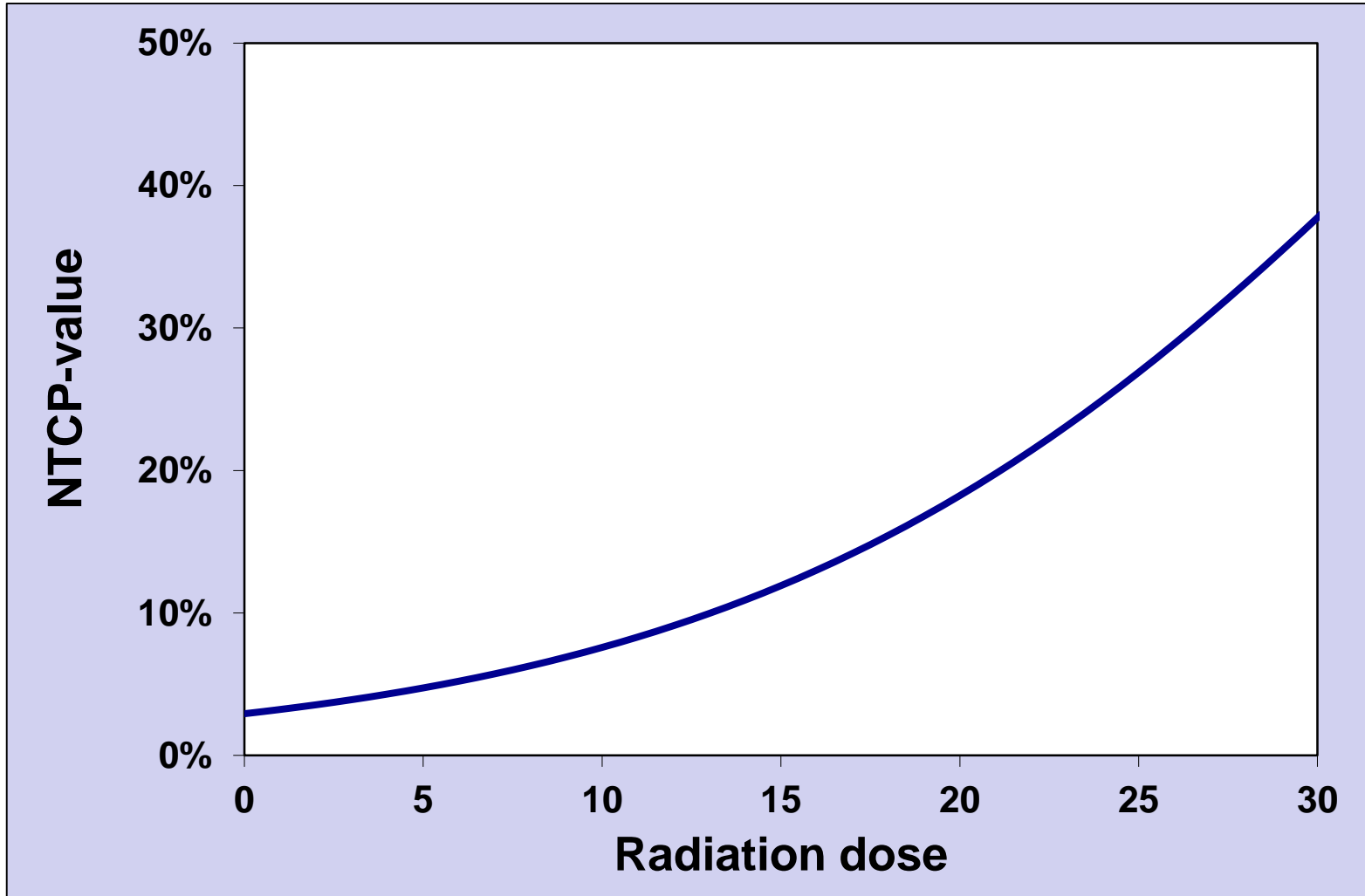 - Seminoma testis

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

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
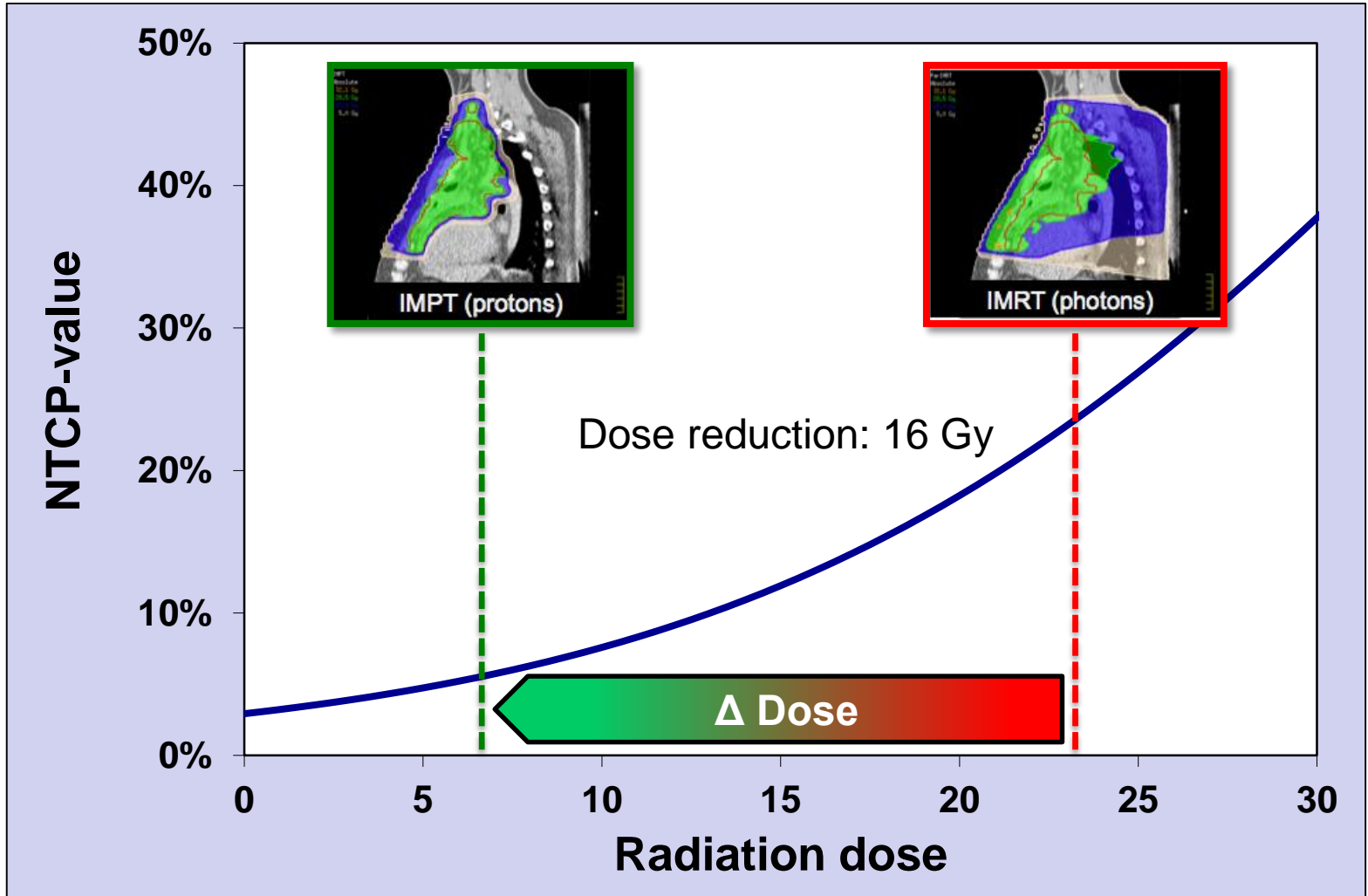
- Model-based selection and validation

Horizon Scanning Report (Health Council 2009)

Model-based approach
Step 1: NTCP-model

Virtual data

Model-based approach
Step 2: Dose comparison photons *vs.* protons

Virtual data

Model-based approach
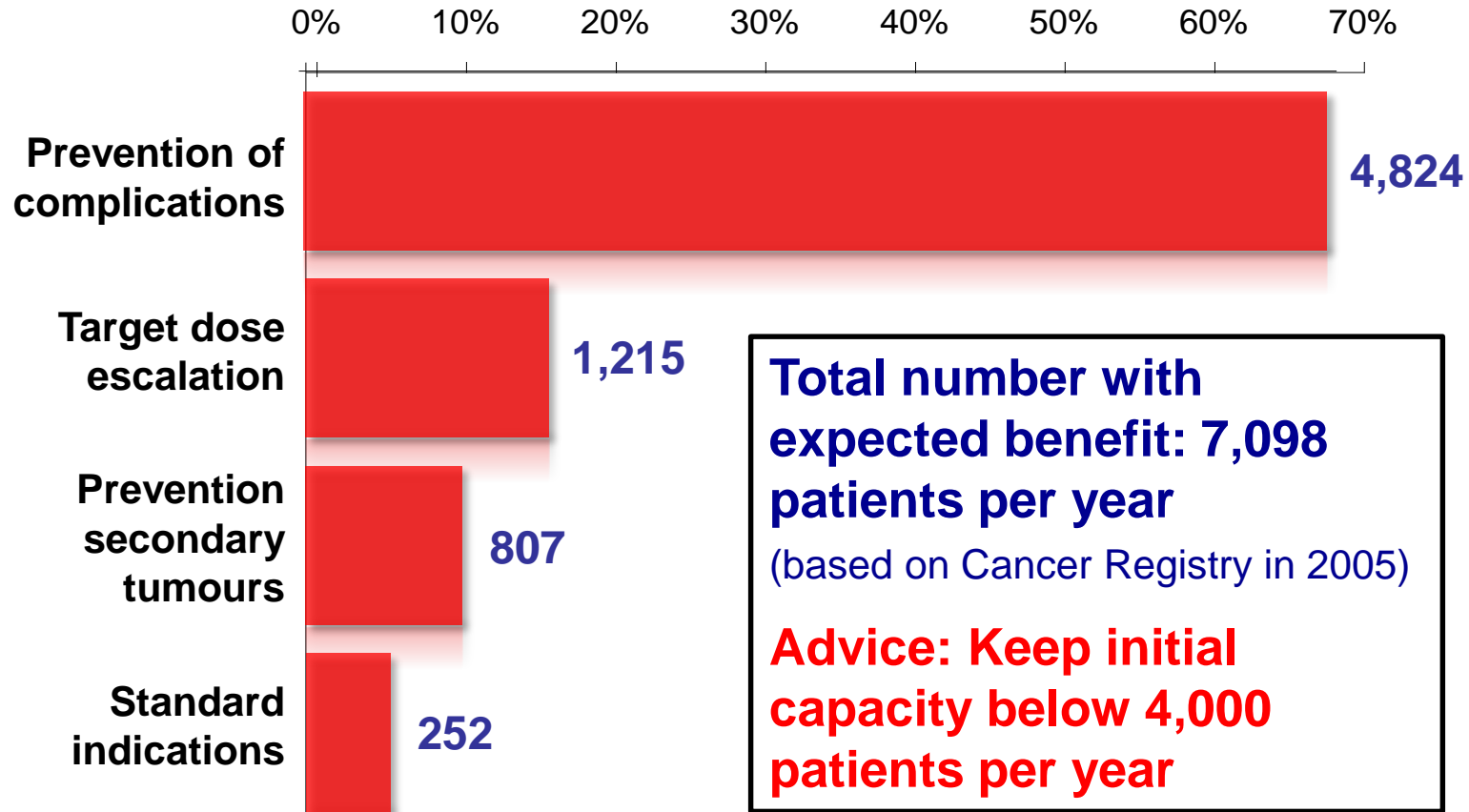## Step 3: Translate ΔDose ➔ 🔻NTCP (risk reduction)
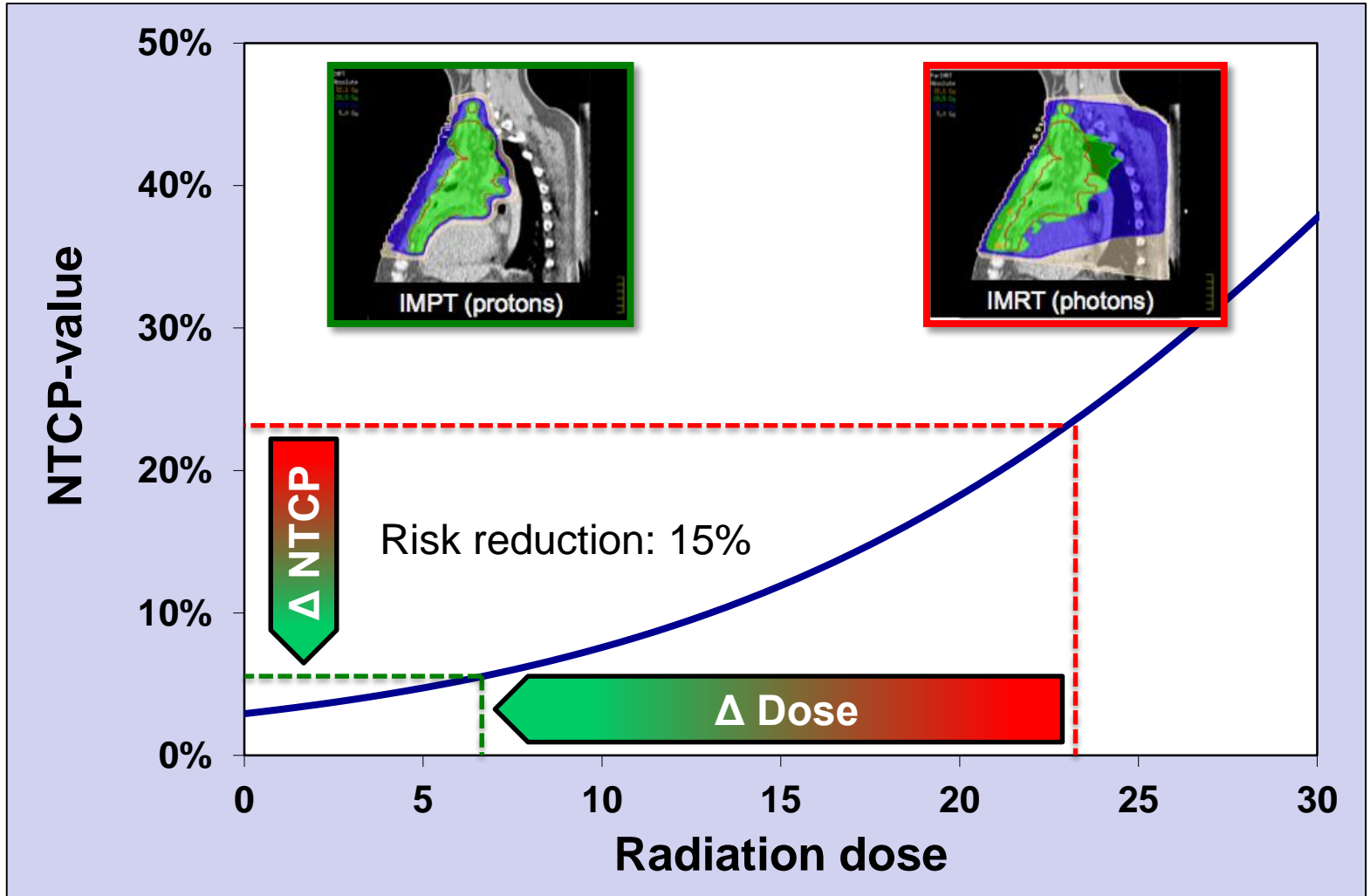
Model-based indications
Four major examples

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
Report of the Dutch Health Council (2009)

Indications for proton therapy (4 categories)

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

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

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

Milestones

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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
Vendor: ProNova
Operational: Q4-2018

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
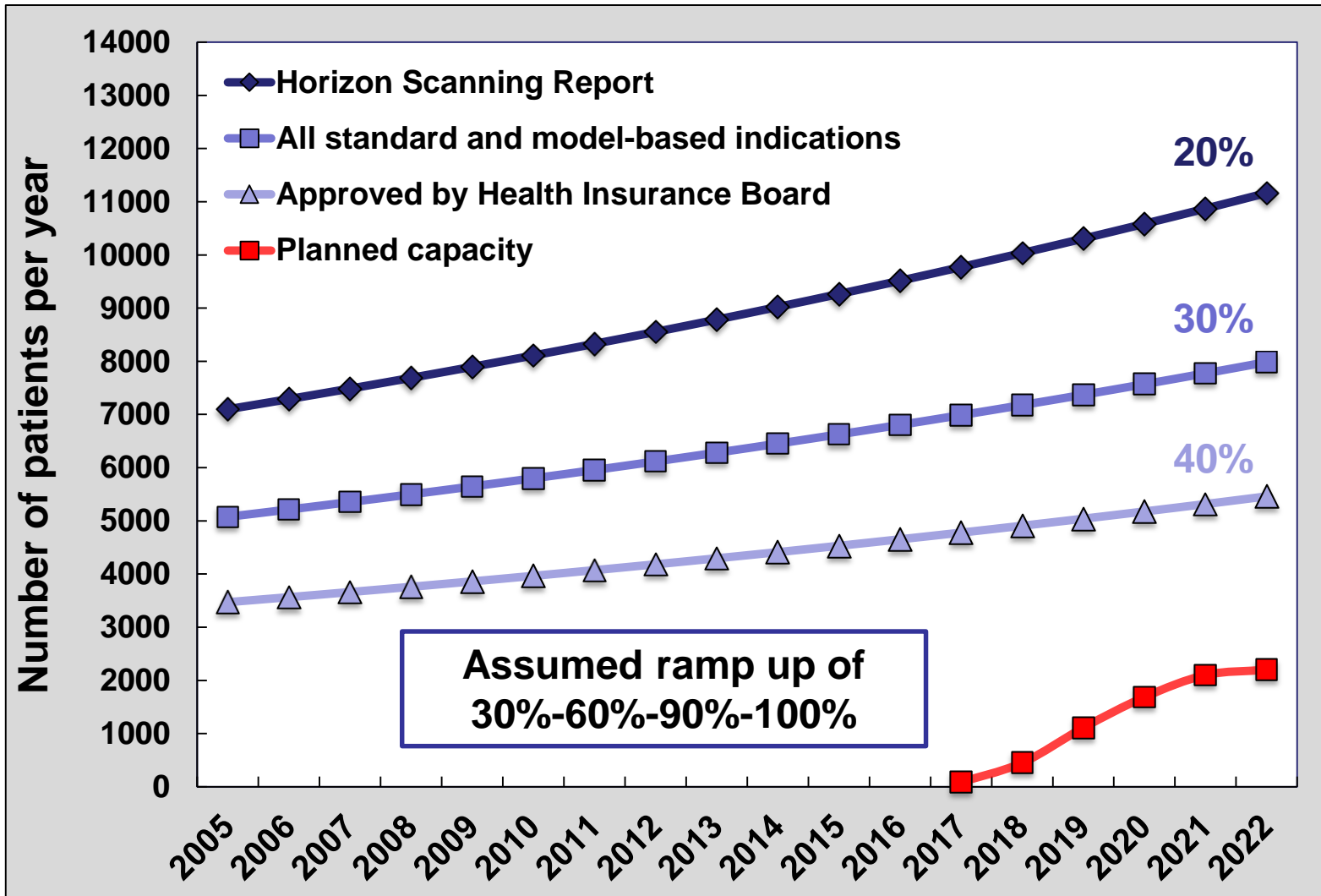 - Better integration with existing multidisciplinary pathways

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
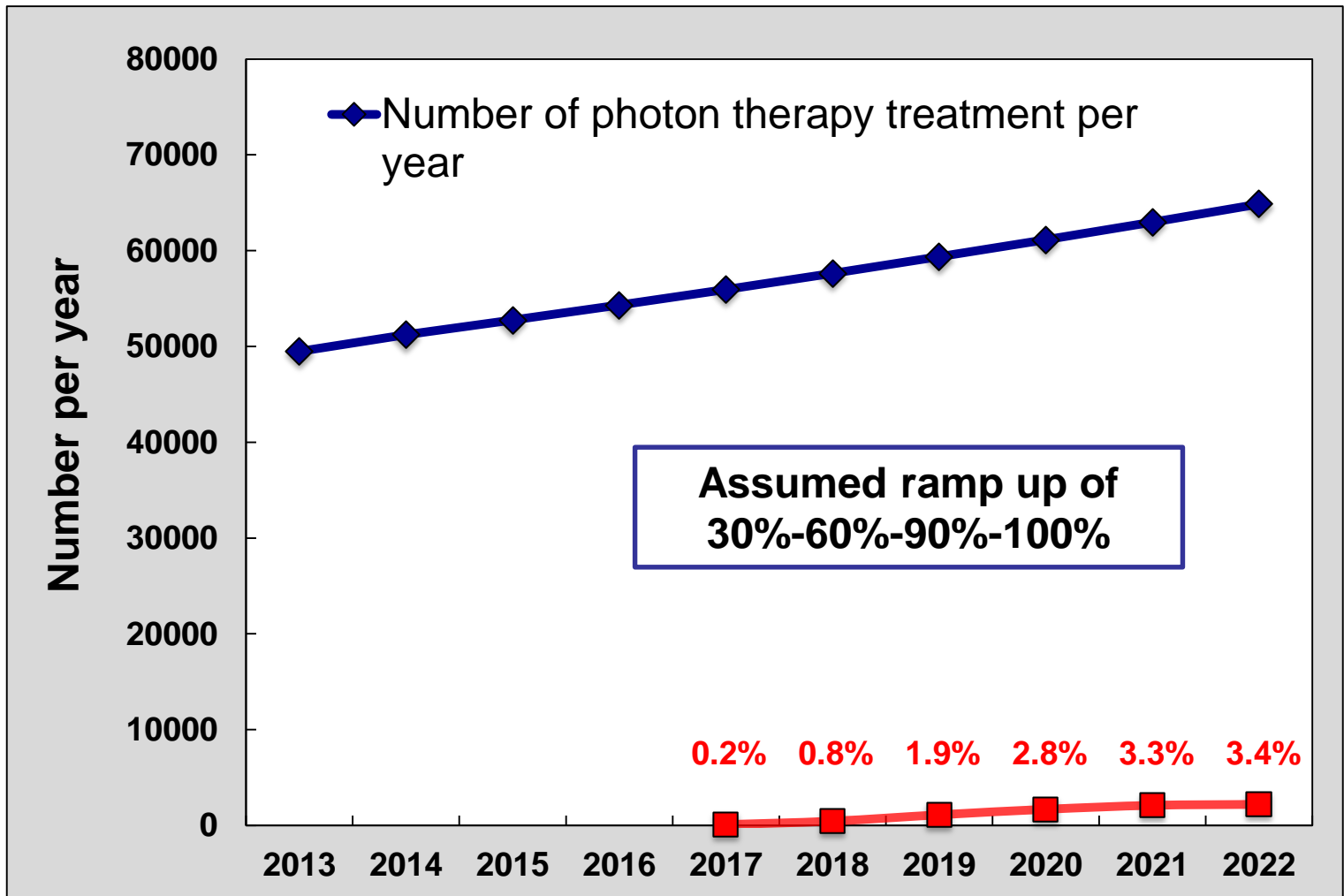
Planned capacity
In relation to total number of RT treatments

Number of photon therapy treatment per year

Number per year

80000
70000
60000
50000
40000
30000
20000
10000
0

Assumed ramp up of
30%-60%-90%-100%

0.2%   0.8%   1.9%   2.8%   3.3%   3.4%

2013   2014   2015   2016   2017   2018   2019   2020   2021   2022

Next steps

Implementation
Organization

- National Proton Therapy Platform
  - All 22 radiotherapy departments represented
  - Main task:
    - Define quality criteria for protons centres
    - Initiate indication protocol development
    - Prospective data registration
    - Define efficient referral workflow

- Expert Group Health Insurance Board
  - All relevant stakeholders
  - Main task:
    - To guide and facilitate clinical introduction of proton therapy

Model-based approach
Step 3: Translate ΔDose ➜ ↓NTCP (risk reduction)

Risk reduction: 15%

IMPT (protons)

IMRT (photons)

Δ NTCP

Δ Dose

NTCP-value

Radiation dose
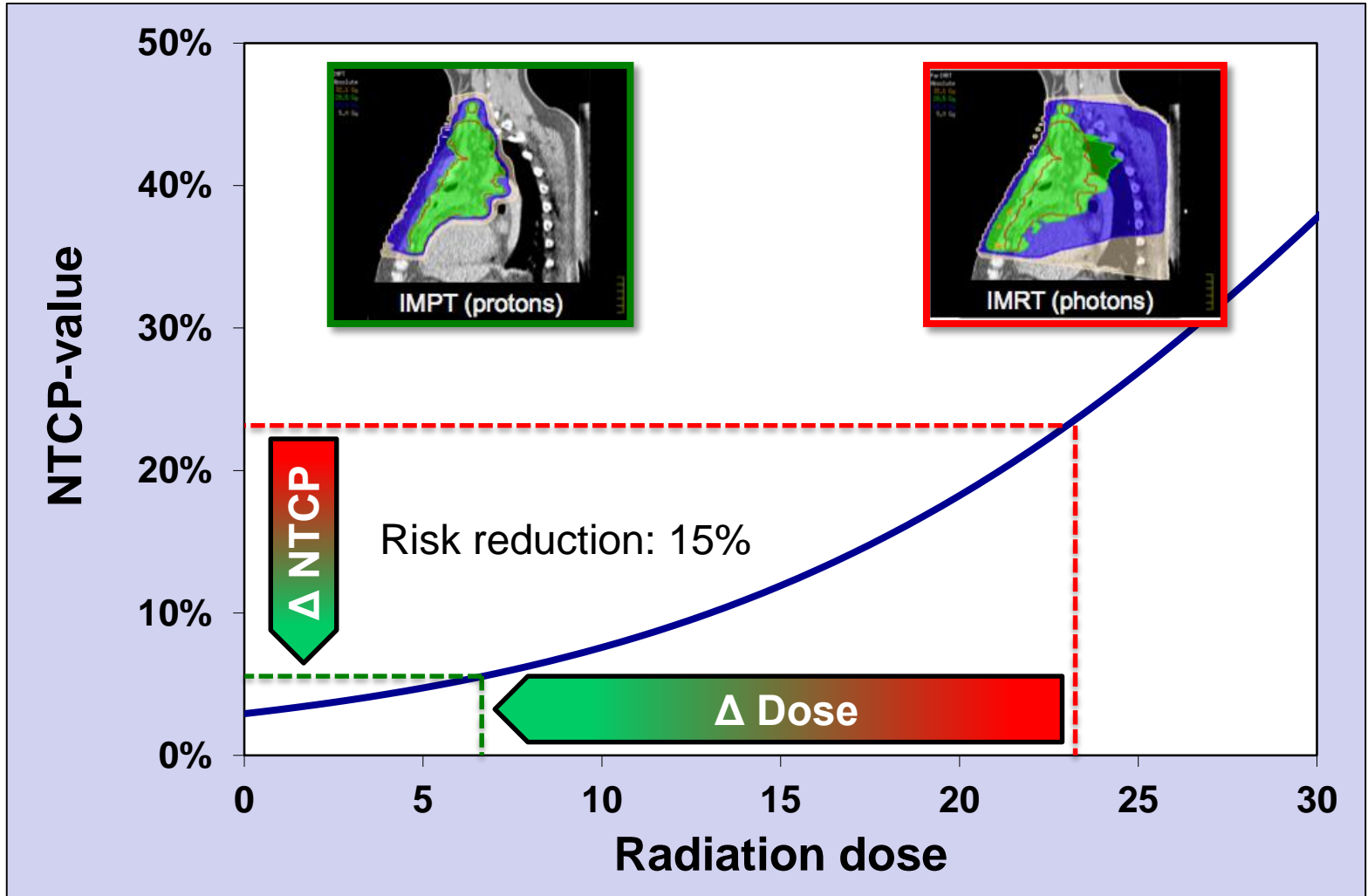
Virtual data

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.
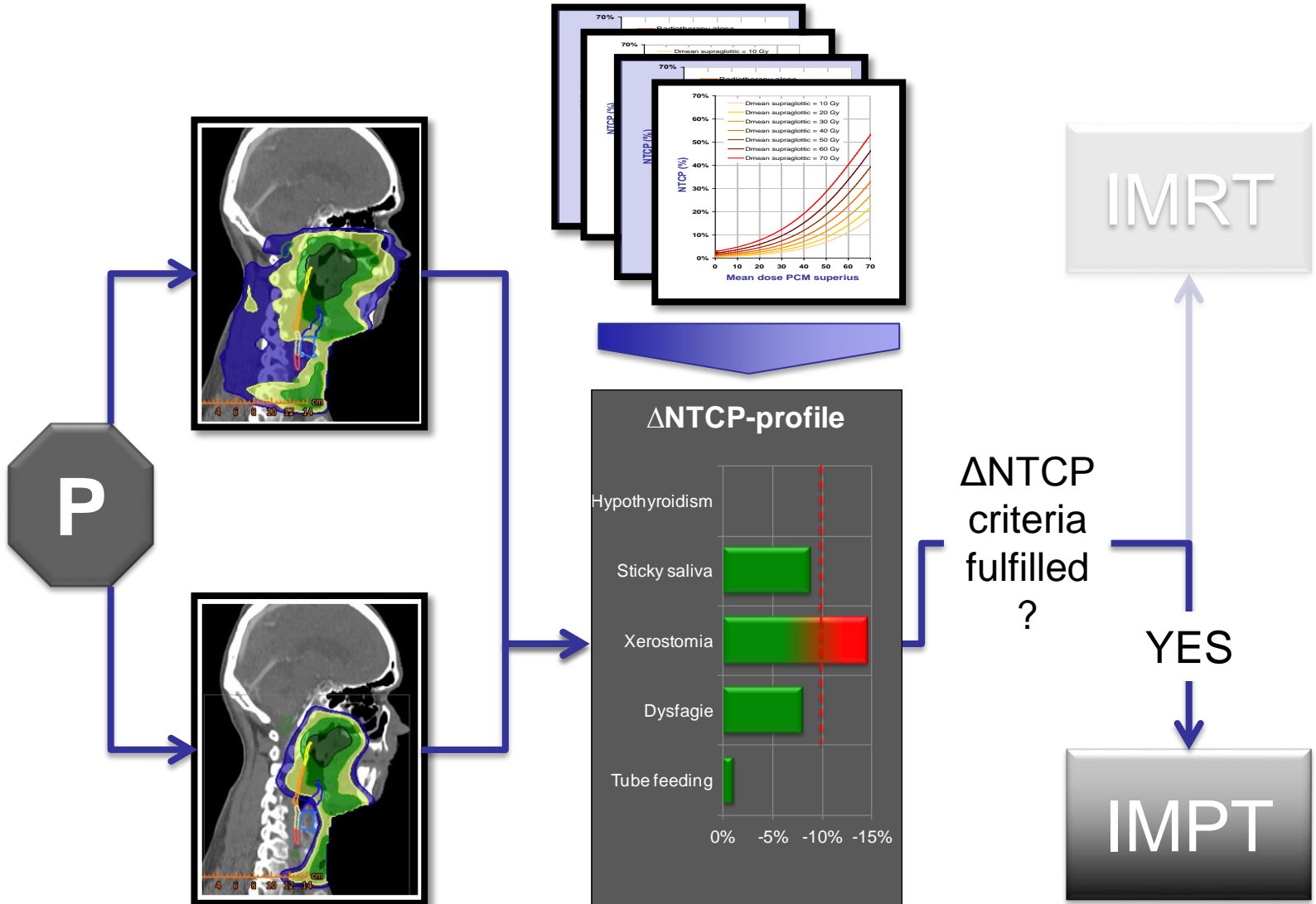
Van een model-based indicatie voor protonentherapie is sprake als er op basis van een planningsvergelijking tussen protonen en fotonen een relevant verschil in het risico op een ongewenst neveneffect verwacht wordt (ΔNTCP). Het principe van deze model-based selectiemethode staat kort samengevat in Figuur 1.
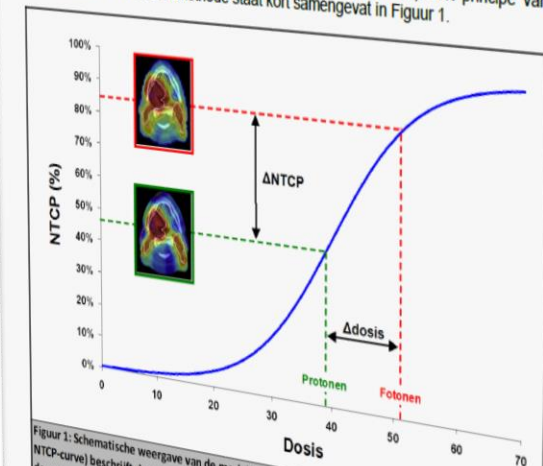
Figuur 1: Schematische weergave van de model-based benadering. De blauwe curve (de zogenaamde NTCP-curve) beschrijft de relatie tussen de dosis en de kans op een complicatie. De dosis (x-as) betreft de meest relevante dosisparameter (bv. de gemiddelde dosis). Op basis van een planningsvergelijking kan de dosis die kan worden bereikt met fotonen en protonen worden berekend. De uitkomsten van de planningsvergelijking worden geïntegreerd in het NTCP-model om het verschil in dosis (Δdosis) te vertalen naar het verwachte verschil in complicatiekans (ΔNTCP).
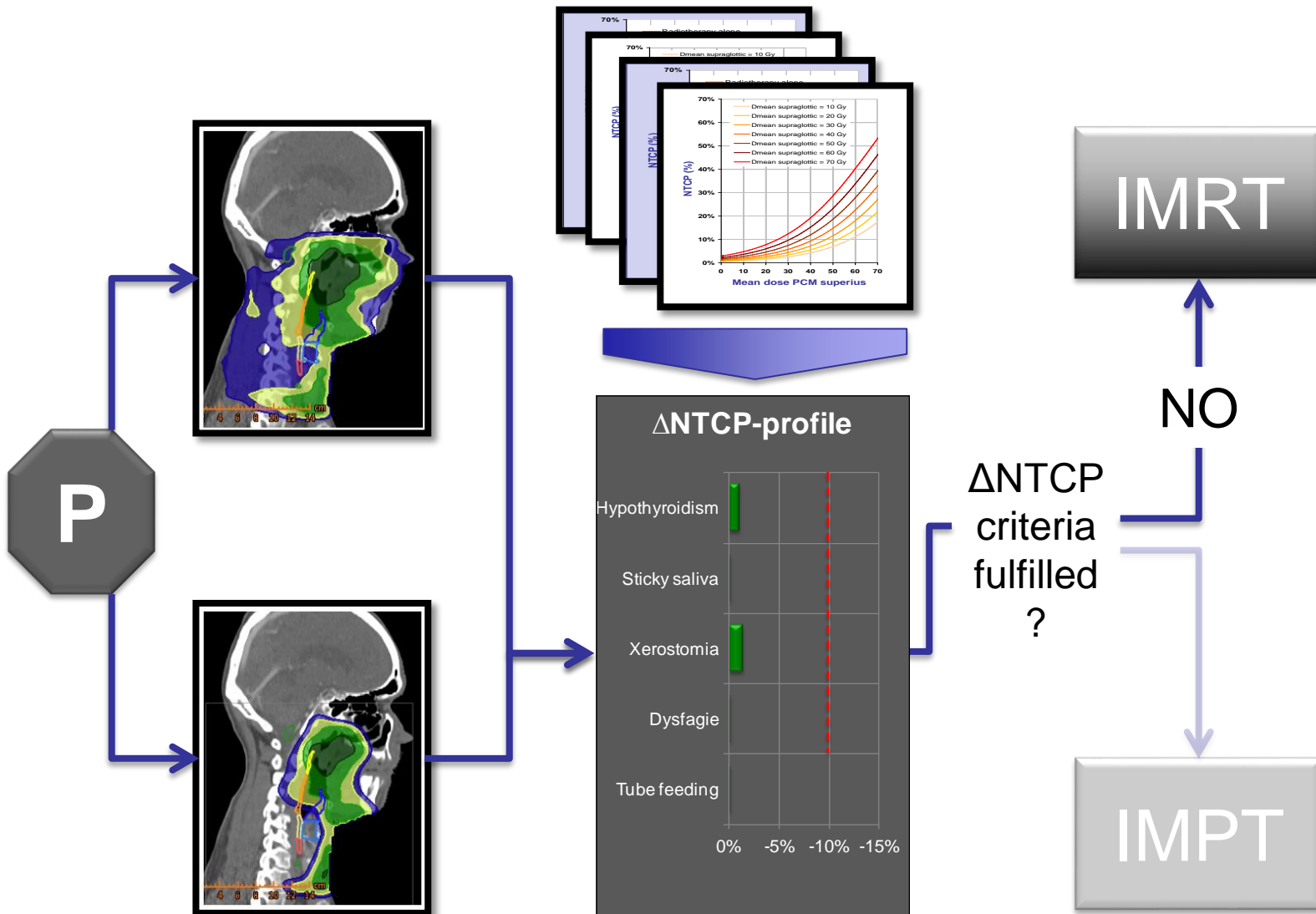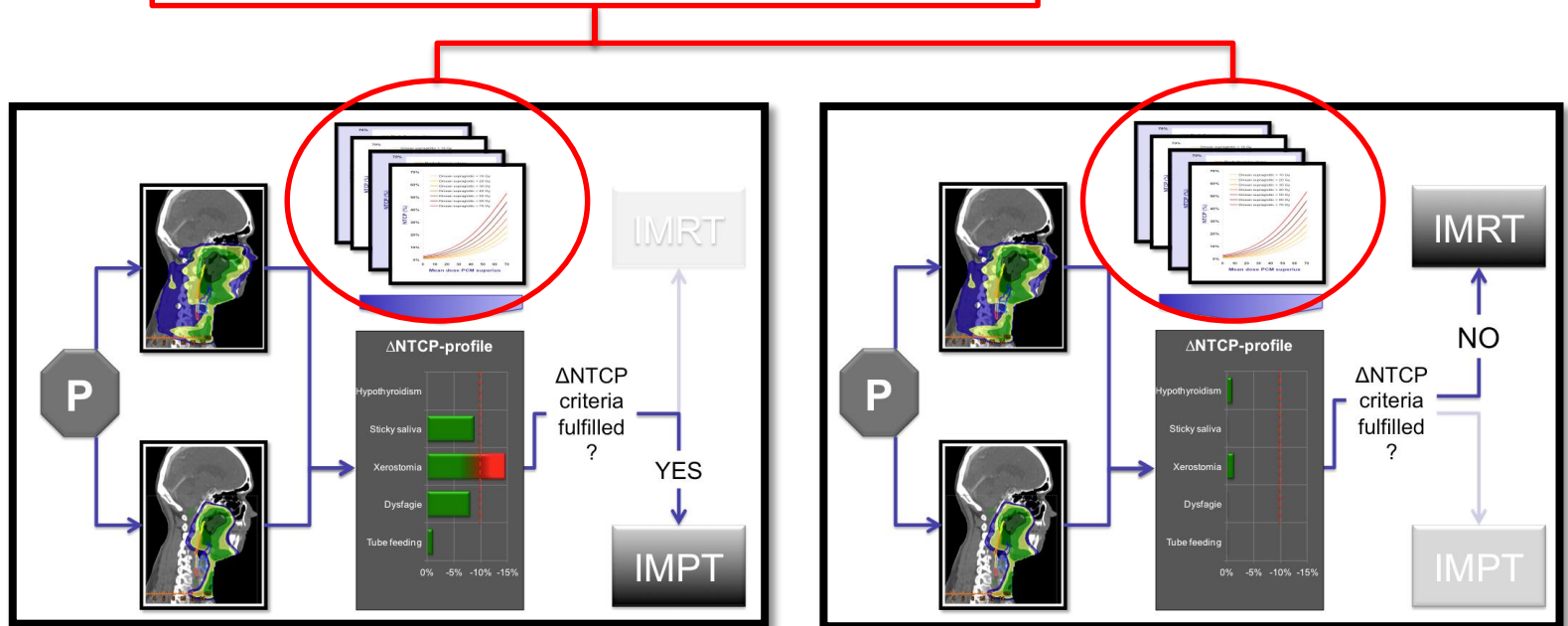
Model-based selection
Decision support system

Indication protocols

- Indication protocol based on:
  - National consensus guidelines for ΔNTCP
  - NTCP-models (to be selected)

Indication protocols
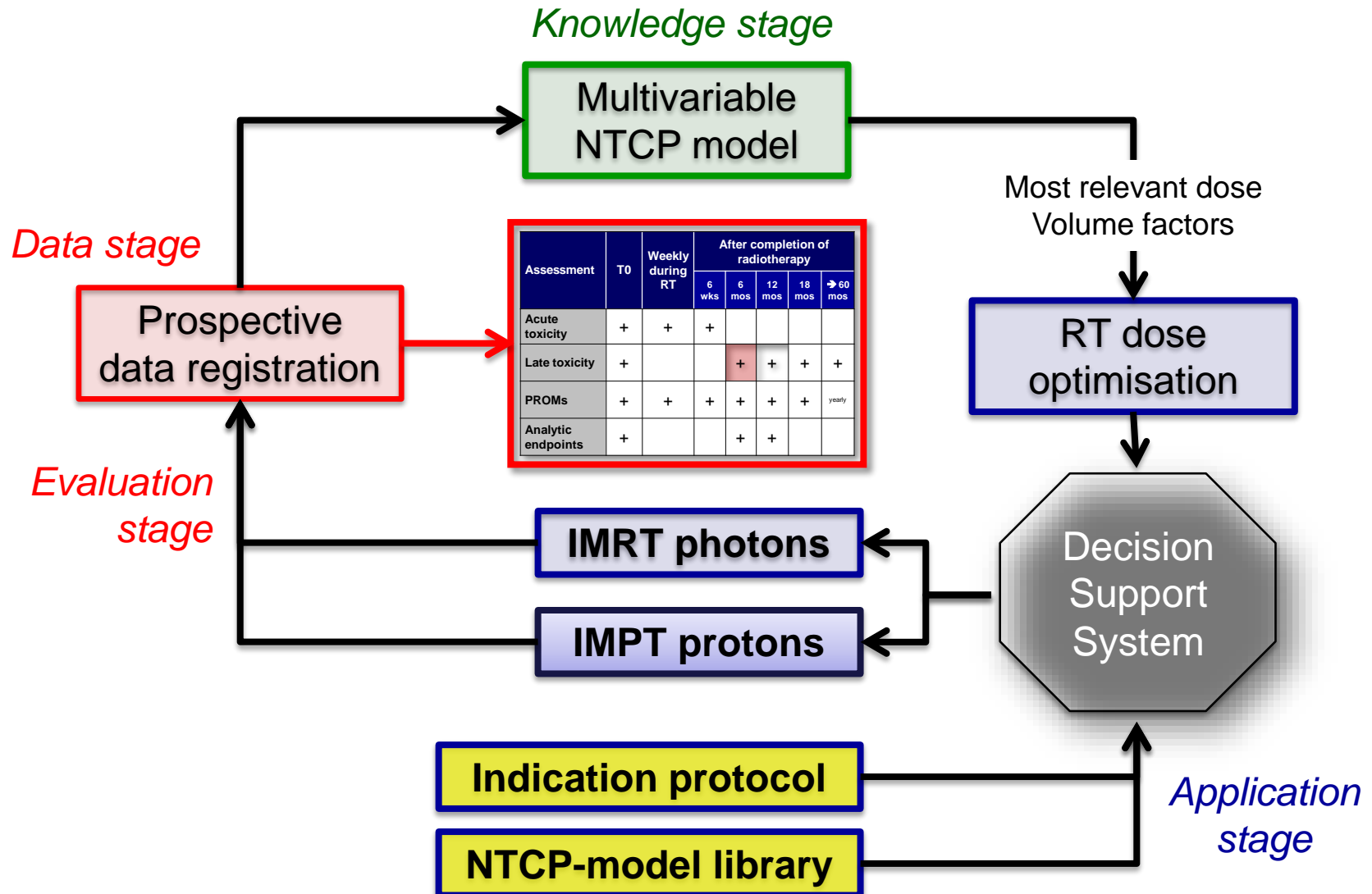## NTCP-model selection (level of evidence)

Level	Description
Level 1a	High quality NTCP-model with evaluation of the model performance in a separate dataset of another institution (external validation)
Level 1b	High quality NTCP-model with evaluation of the model performance in a separate subsequent dataset of the same institution (external validation)
Level 1c	High quality NTCP-model derived from meta-analysis of one or more cohort studies, using resampling (e.g. bootstrapping of cross-validation) techniques to evaluate model performance and overfitting

High quality refers to e.g. study design, number of patients, prospective or retrospective assessment of toxicity, etcetera..
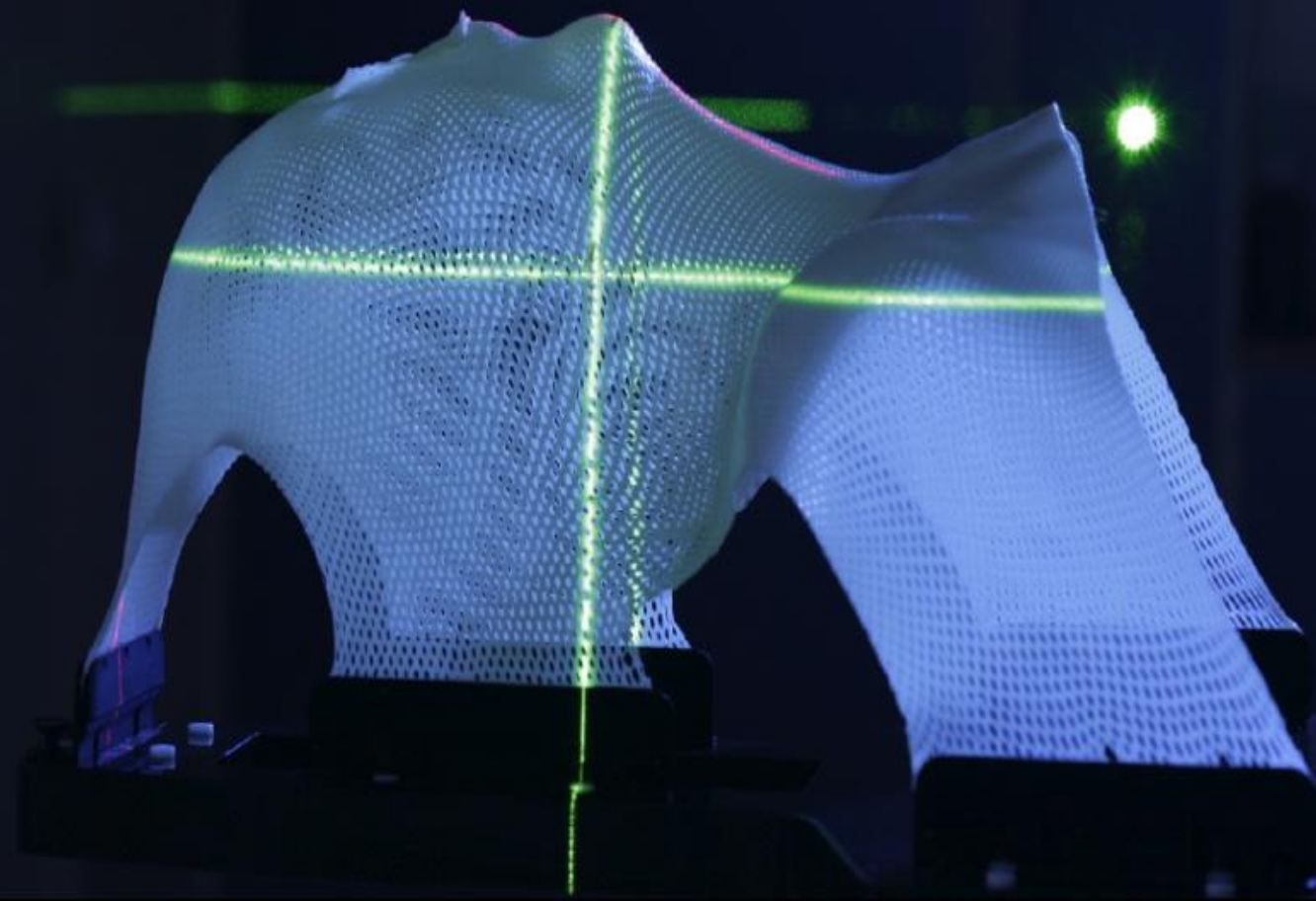
Derived from: Collins, et al. Ann Int Med 2015

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

Knowledge stage

Multivariable NTCP model

Most relevant dose Volume factors

Data stage

Prospective data registration

Assessment	T0	Weekly during RT	After completion of radiotherapy				
			6 wks	6 mos	12 mos	18 mos	→ 60 mos
Acute toxicity	+	+	+				
Late toxicity	+			+	+	+	+
PROMs	+	+	+	+	+	+	yearly
Analytic endpoints	+			+	+		

RT dose optimisation

Evaluation stage

IMRT photons

IMPT protons

Decision Support System

Indication protocol

NTCP-model library

Application stage

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 with 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