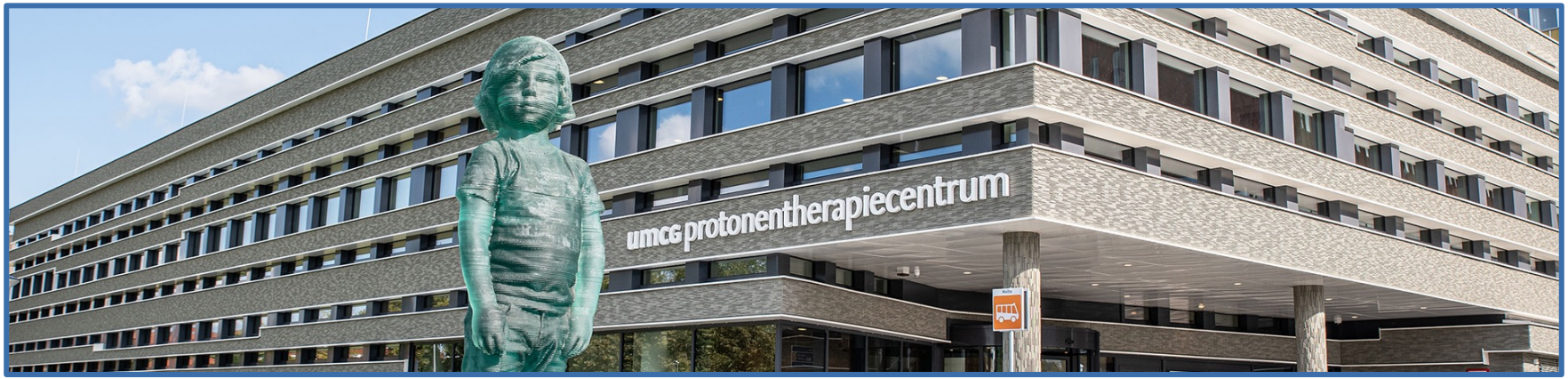


Randomized clinical trials, limitations and possible alternatives: The Dutch experience

Prof. Johannes (Hans) A. Langendijk, MD, PhD
Radiation Oncologist / Department Chair
Department of Radiation Oncology
University Medical Center Groningen
Groningen
The Netherlands

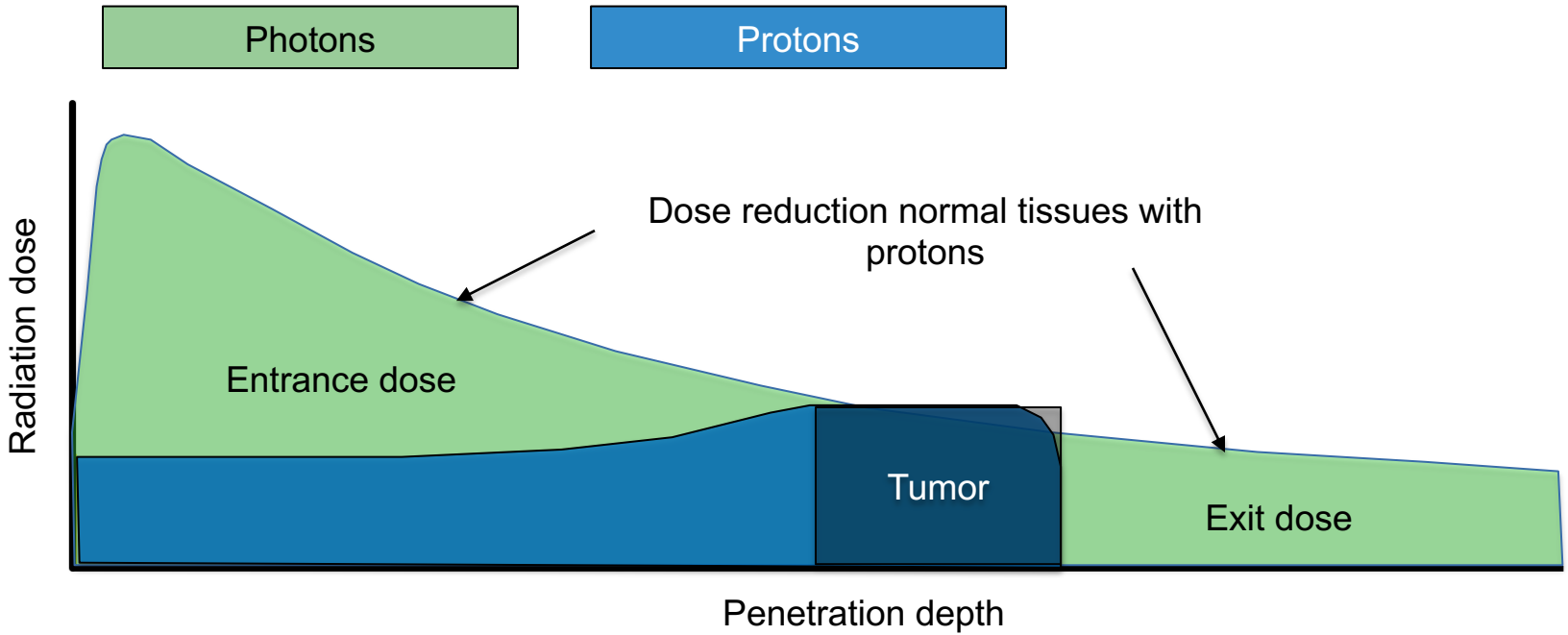
DANSKE KRÆFTFORSKNINGSDAGE 2022
25. & 26. AUGUST 2022, COMWELL KOLDING

Disclosures

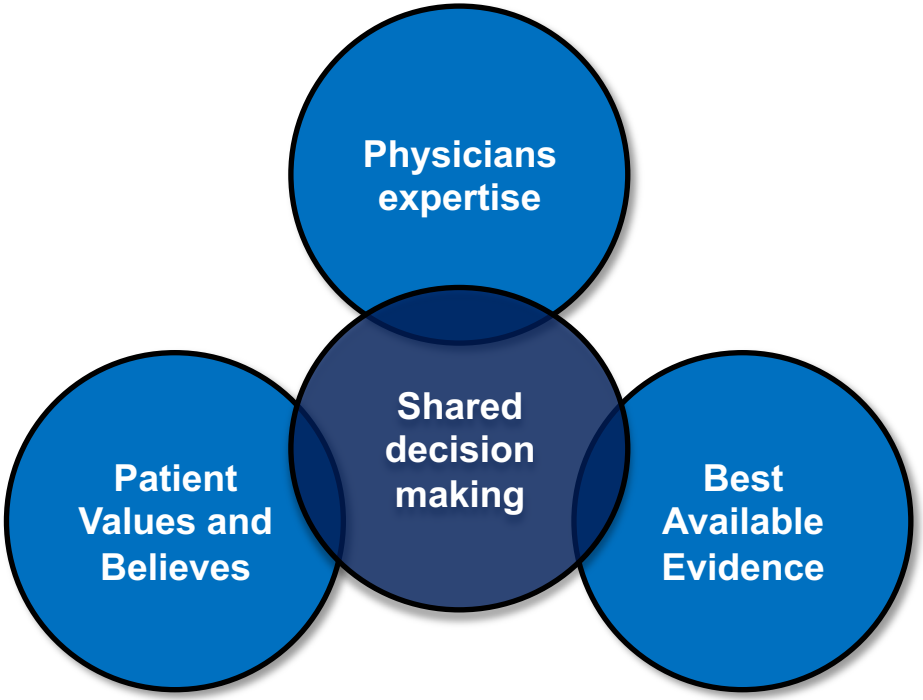
	COI status	Names of companies / organizations
Post of executive / consultant	YES	Honorarium from IBA for consultancy and presentation at IBA symposia paid to UMCG Research BV Member of the Global Advisory Board IBA, Belgium Member of the RayCare Clinical Advisory Board, Sweden
Grant / Research funding	YES	Department of Radiation Oncology has research collaborations with Elekta, IBA, RaySearch, Siemens, Leoni and Mirada

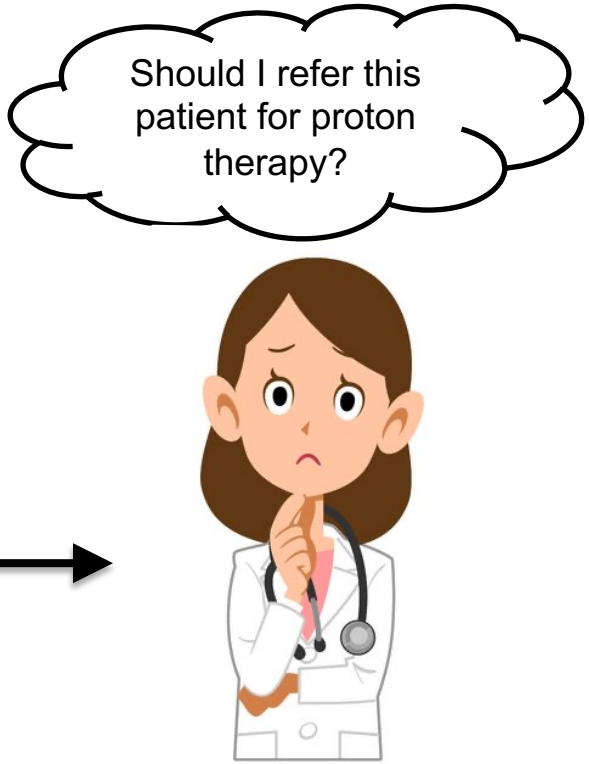
Protons versus photons

Beam properties

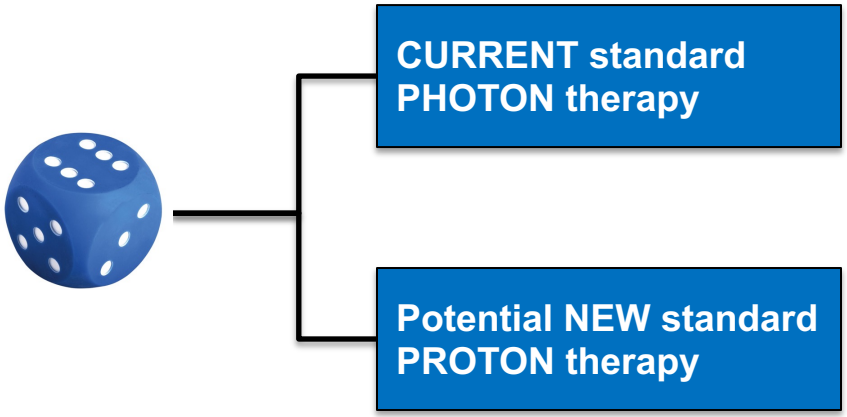


Evidence-based medicine

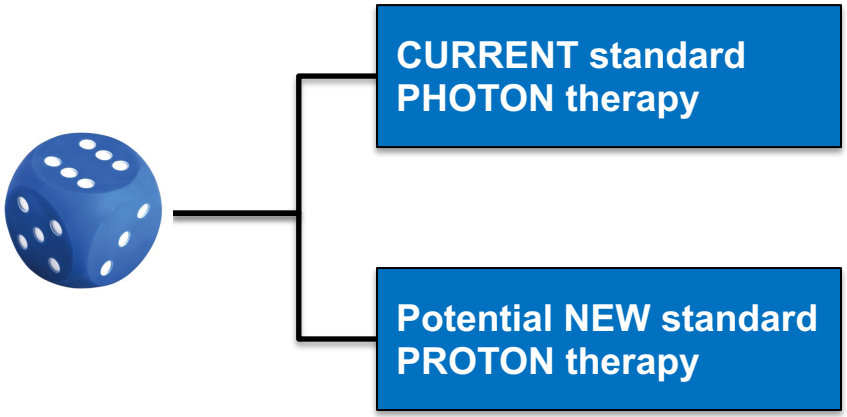




Evidence-based medicine

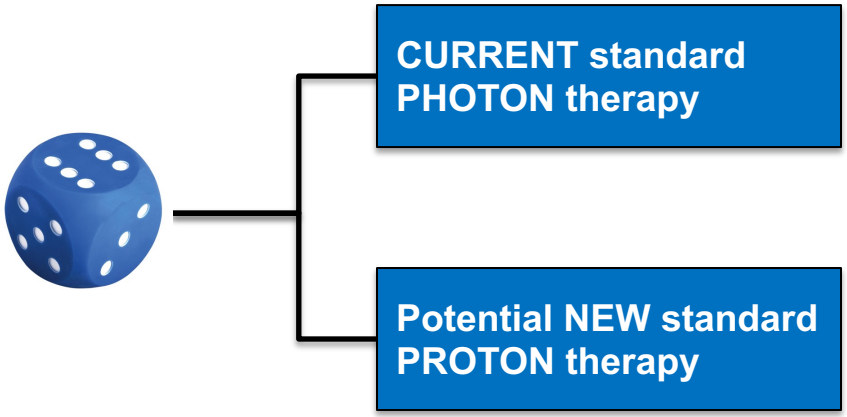


Best available evidence?



- Best approach when protons are used for **target dose escalation**

Best available evidence?



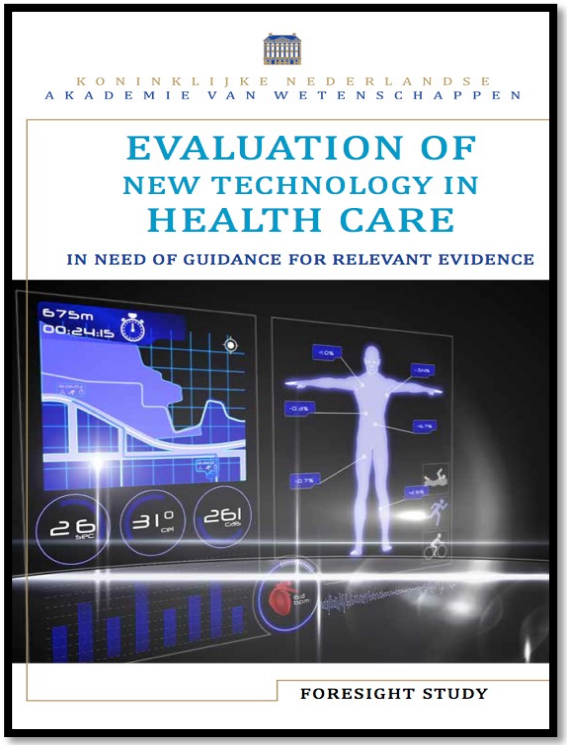
- **Prevention** of radiation-induced side effects ?
  - Similar target dose
  - Lower dose healthy tissues

Foresight Report

Dutch Academy of Arts and Sciences

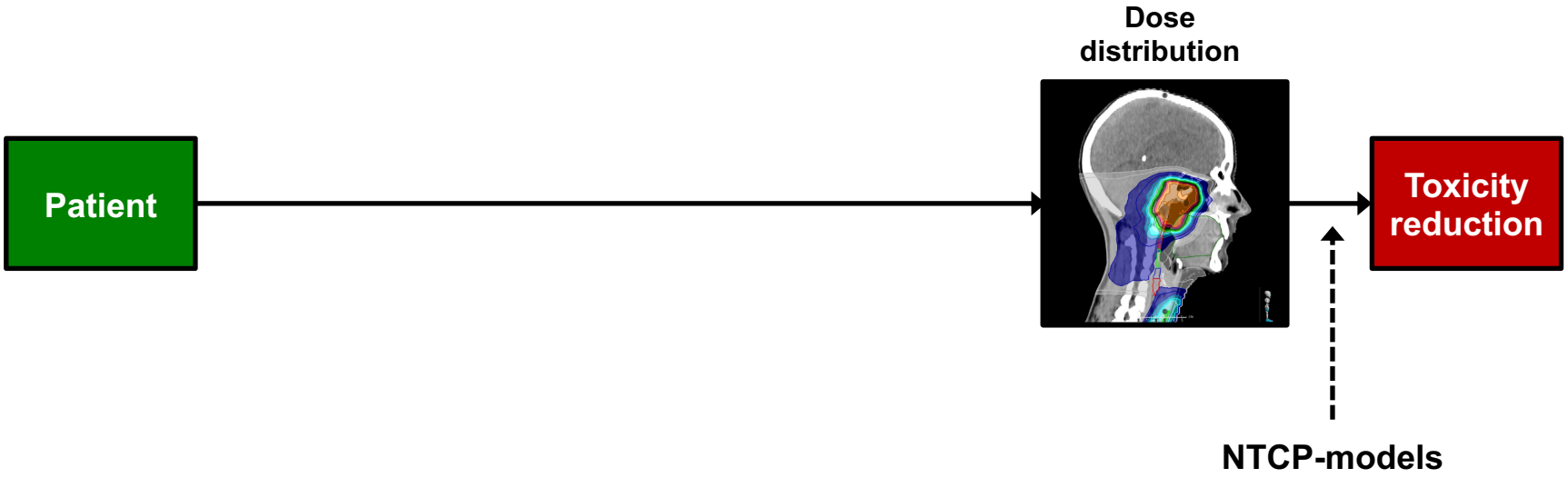
RCT's mostly not suitable / feasible for testing new technologies

- Technological developments
- Technology-user interplay

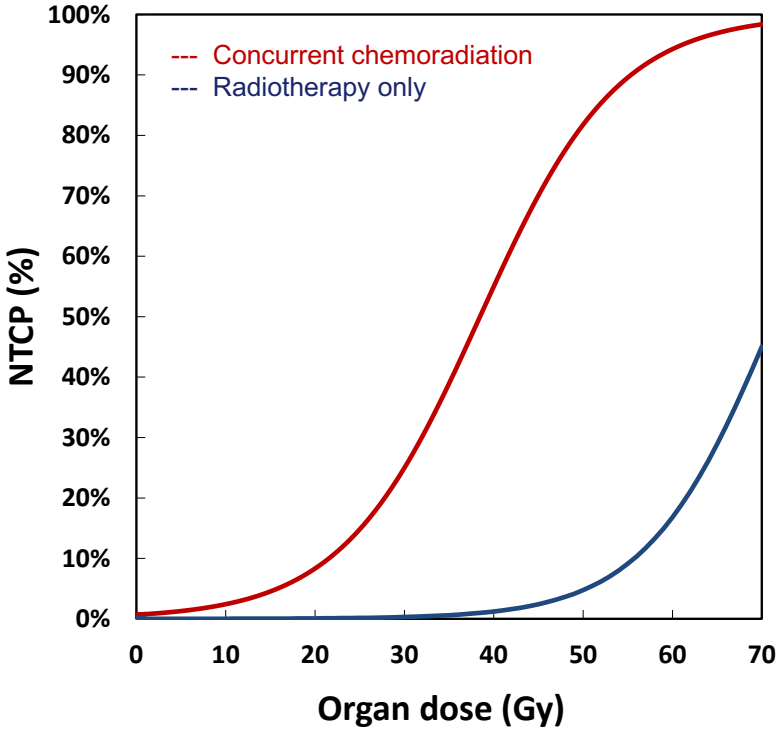


www.knaw.nl/nl/actueel/publicaties/evaluation-of-new-technology-in-health-care

How to reduce toxicity?



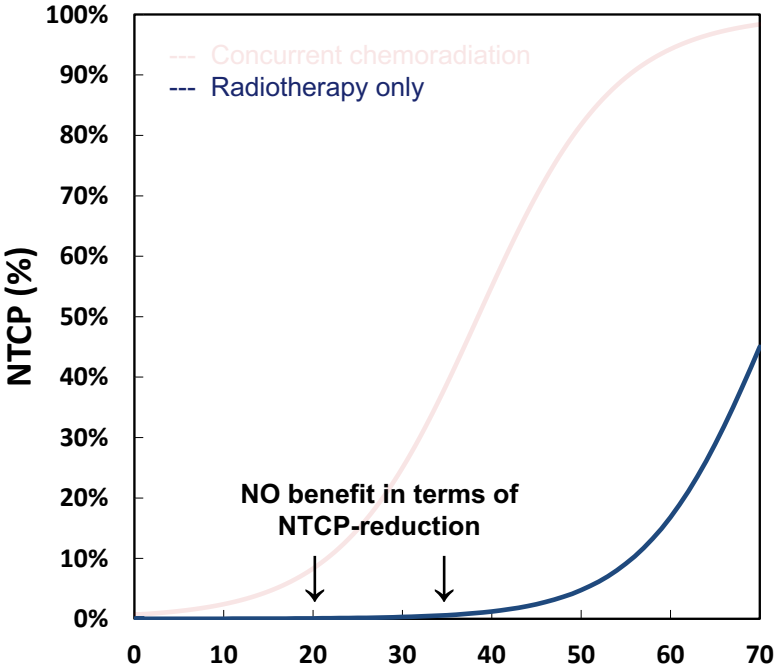
NTCP-model

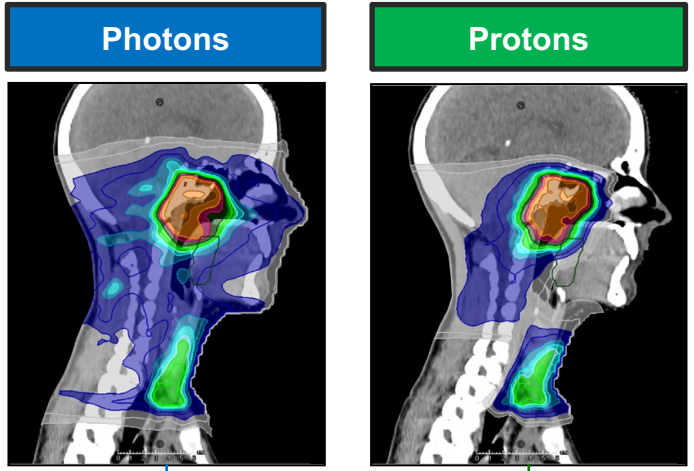


NTCP-model

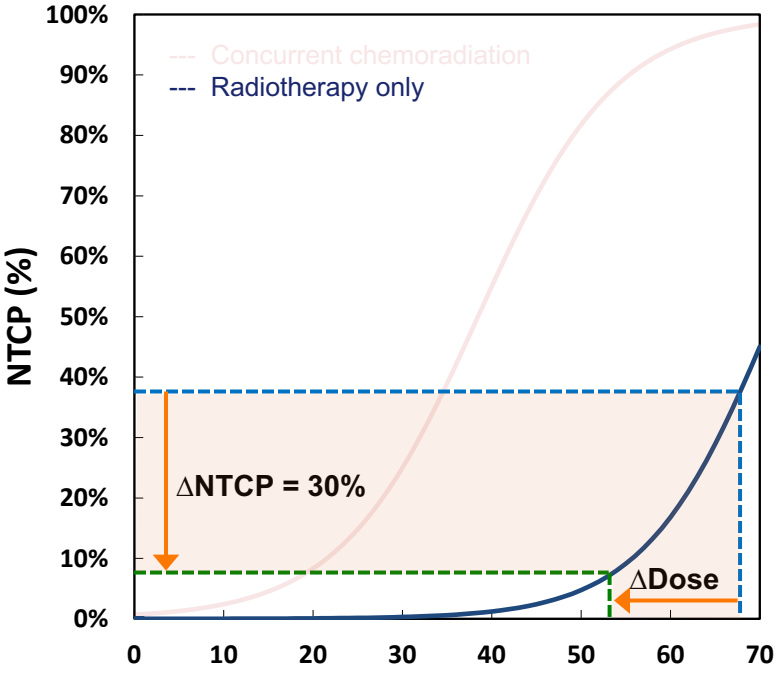
= Normal Tissue Complication Probability

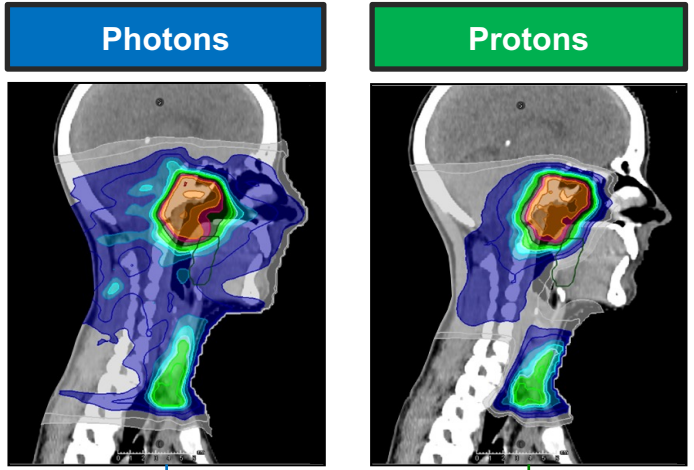
From ΔDose to ΔNTCP



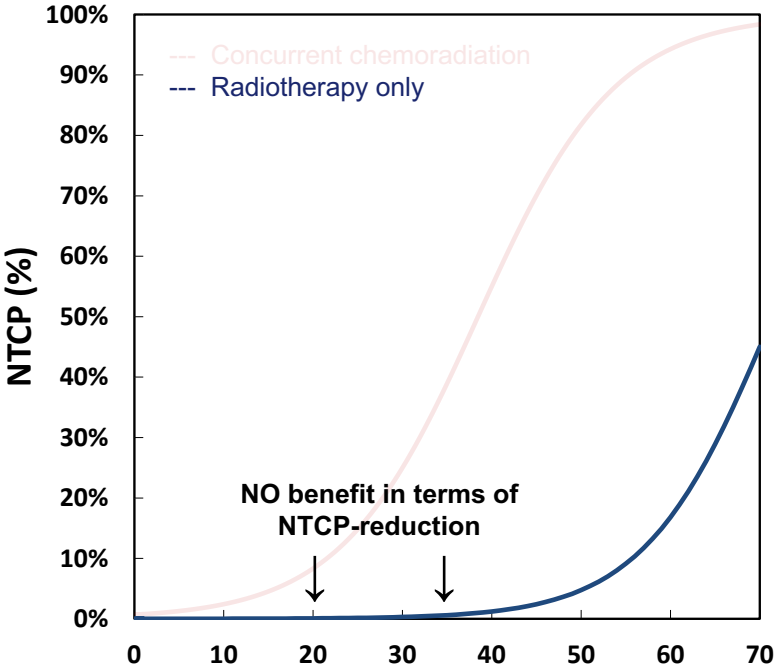


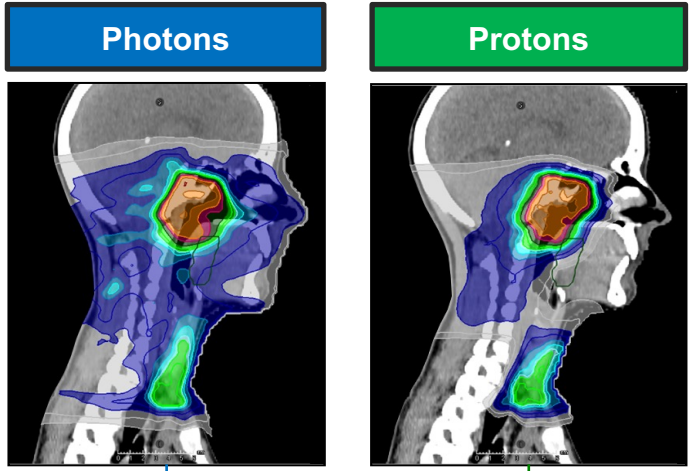
From ΔDose to ΔNTCP



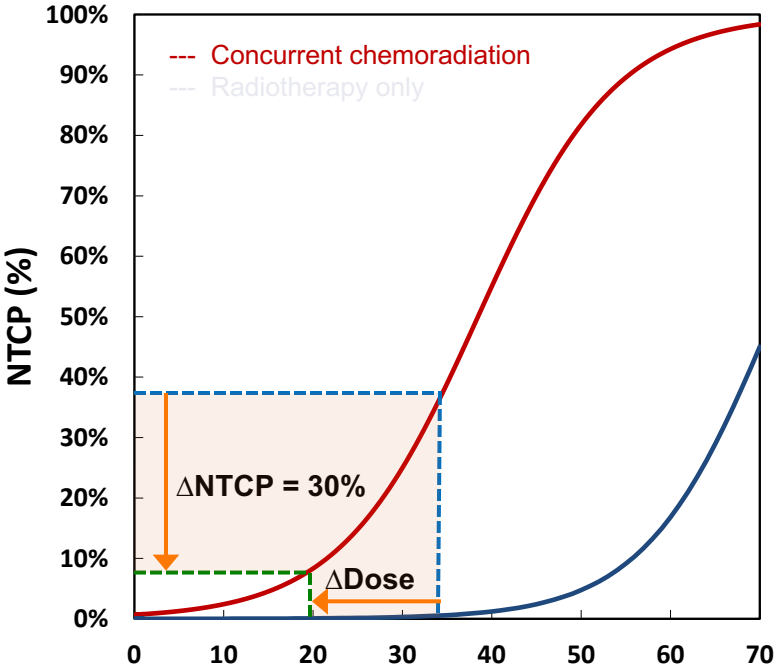


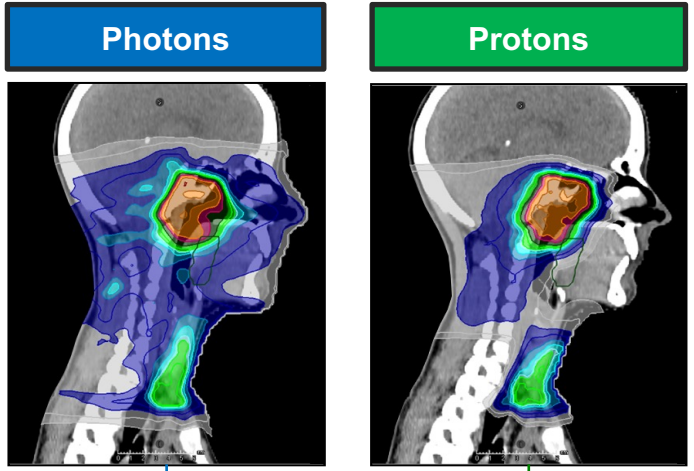
From ΔDose to ΔNTCP



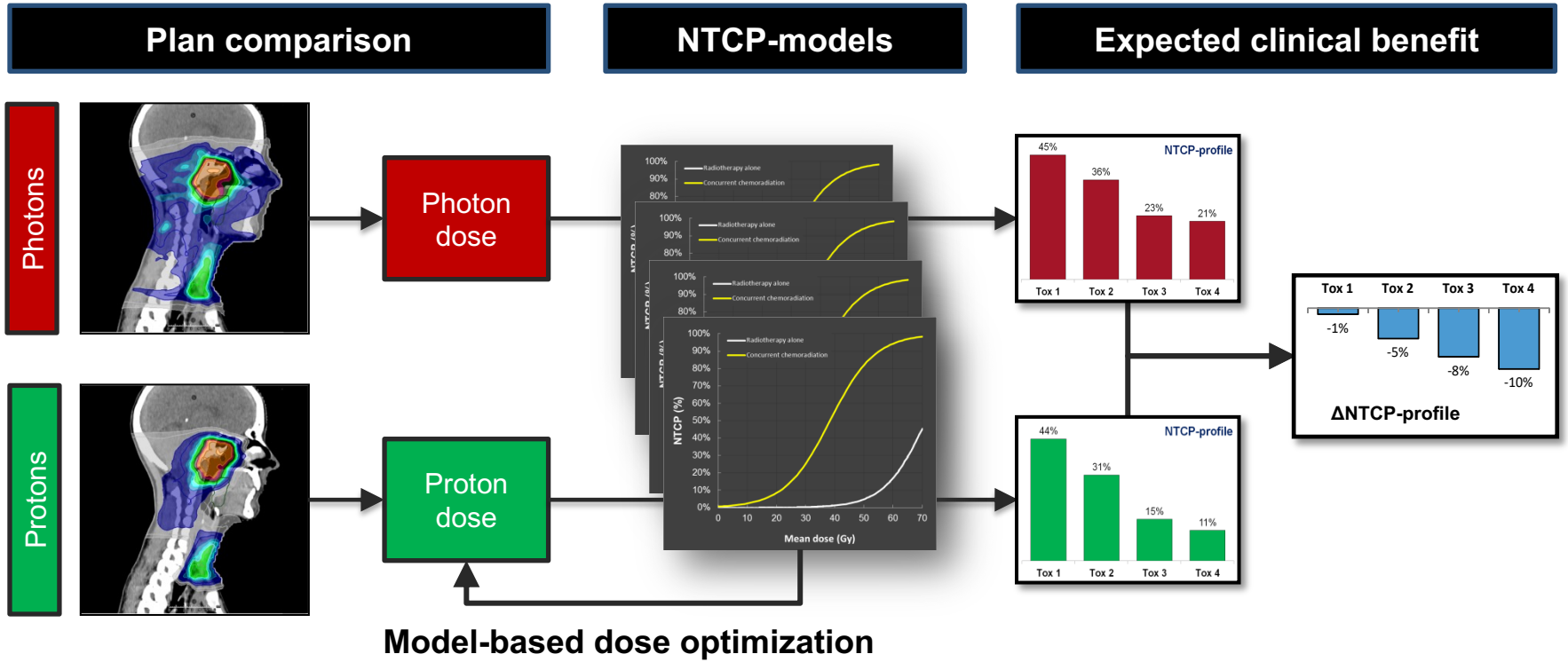


From ΔDose to ΔNTCP





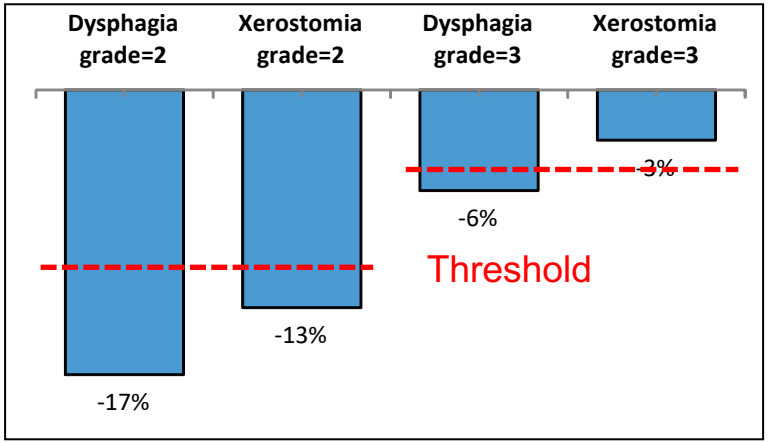
Model-based selection procedure



ΔNTCP-profile

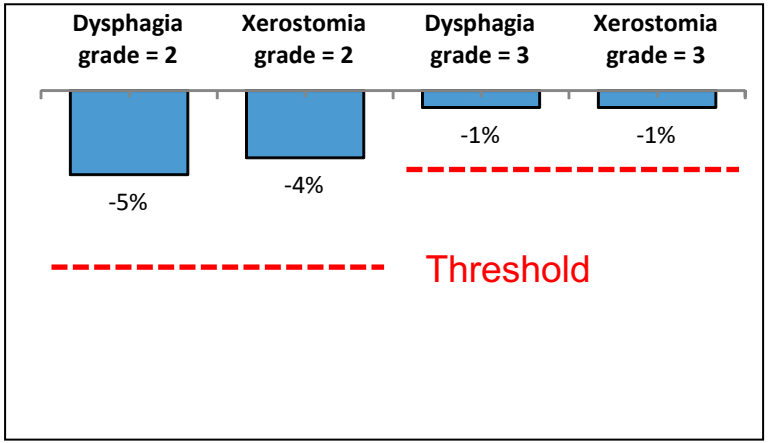
Biomarker expected benefit of protons

High benefit ΔNTCP-profile

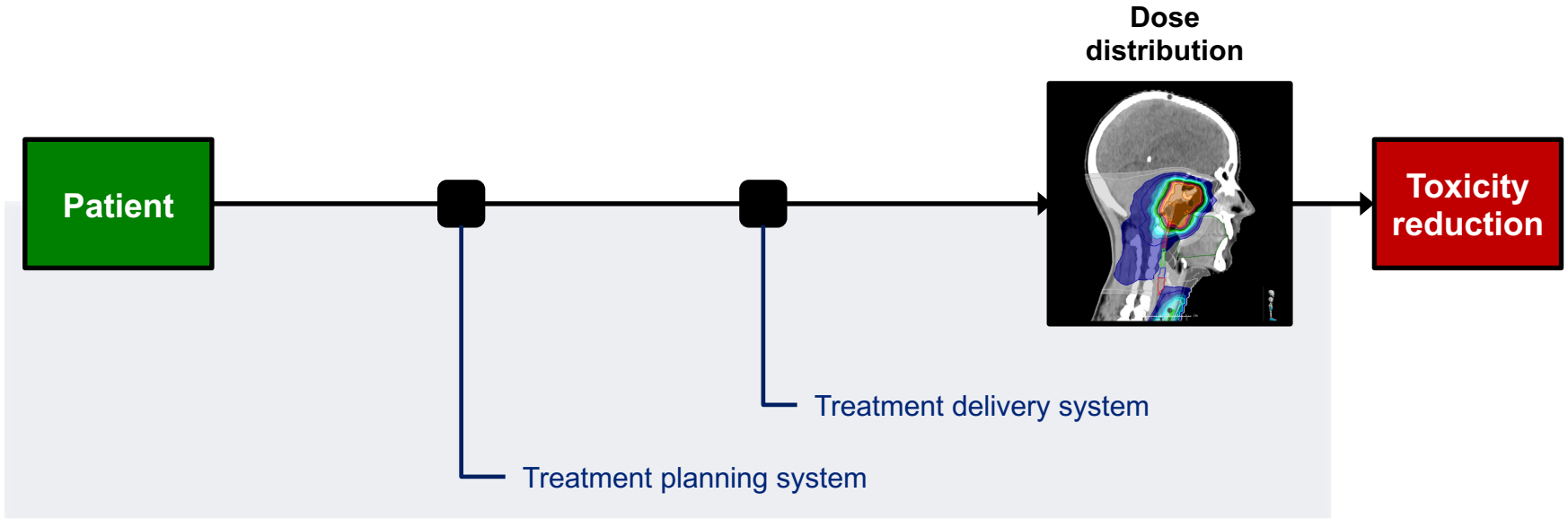


Qualifies for protons

Low benefit ΔNTCP-profile

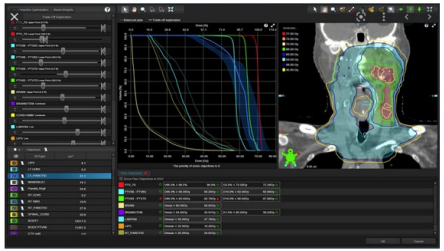


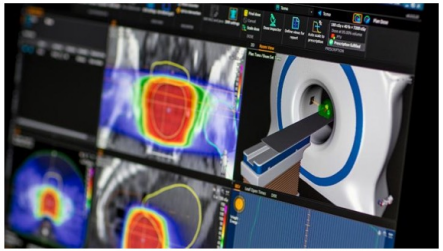
Does NOT qualify for protons

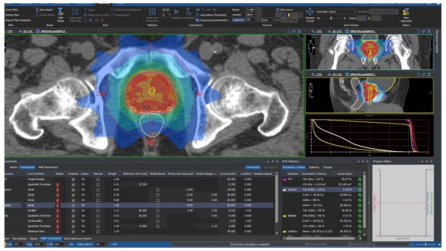

Dose distribution
Patient
Toxicity reduction
Treatment delivery system
Treatment planning system

Technology

Differences in technology specifications





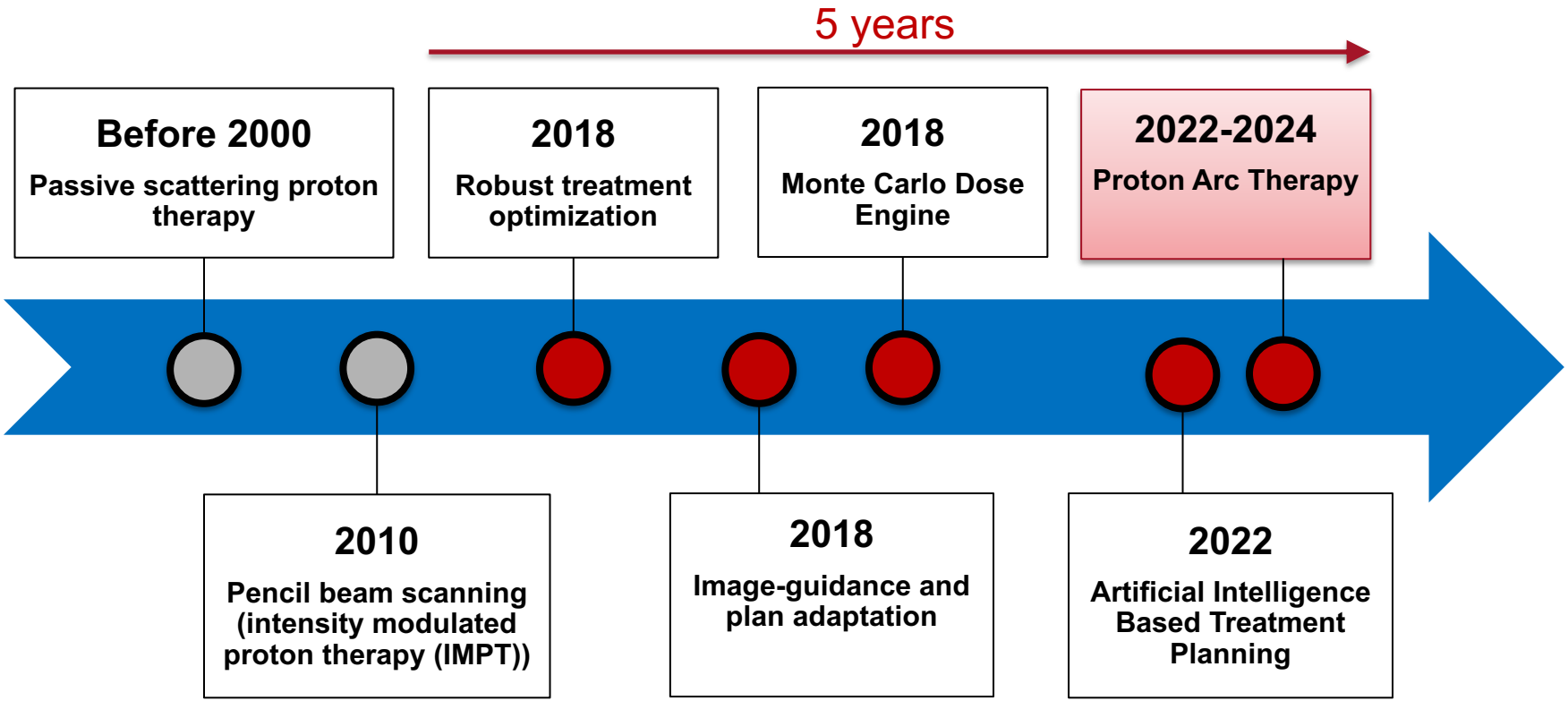


Treatment PLANNING systems

Treatment DELIVERY systems

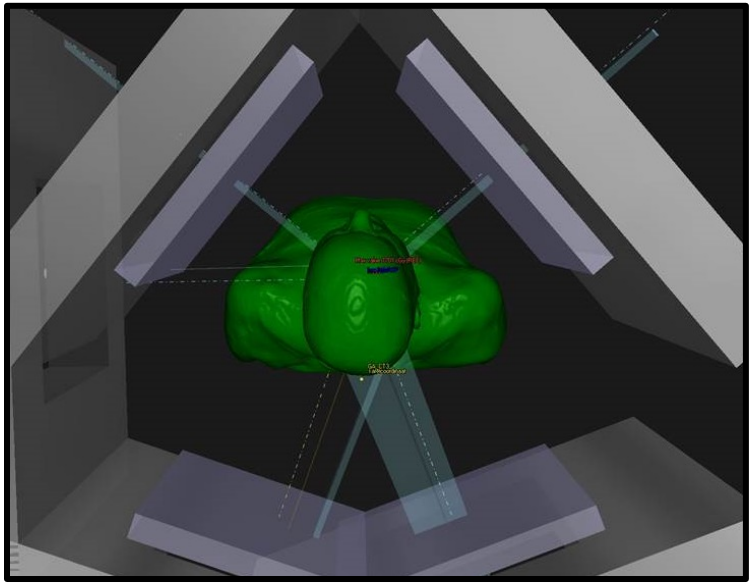
Technological developments

Proton therapy



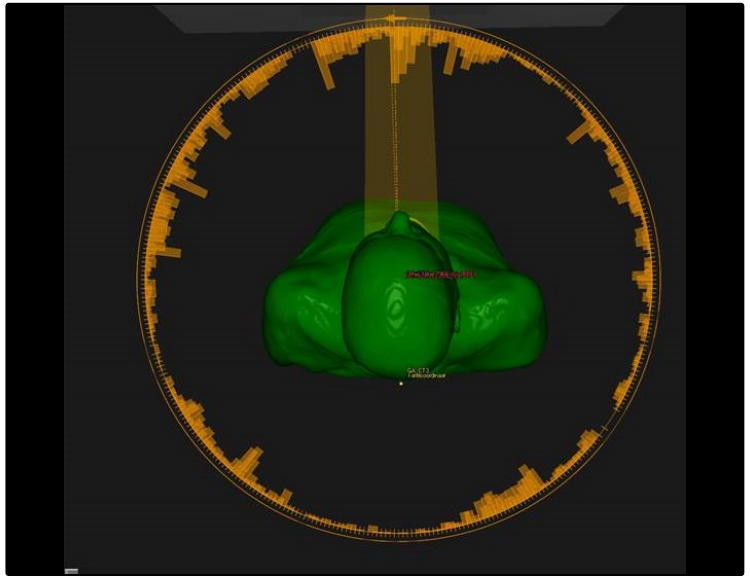
Technological development
Proton Arc Therapy (PAT)

IMPT
Current standard proton technique



4 fixed beams

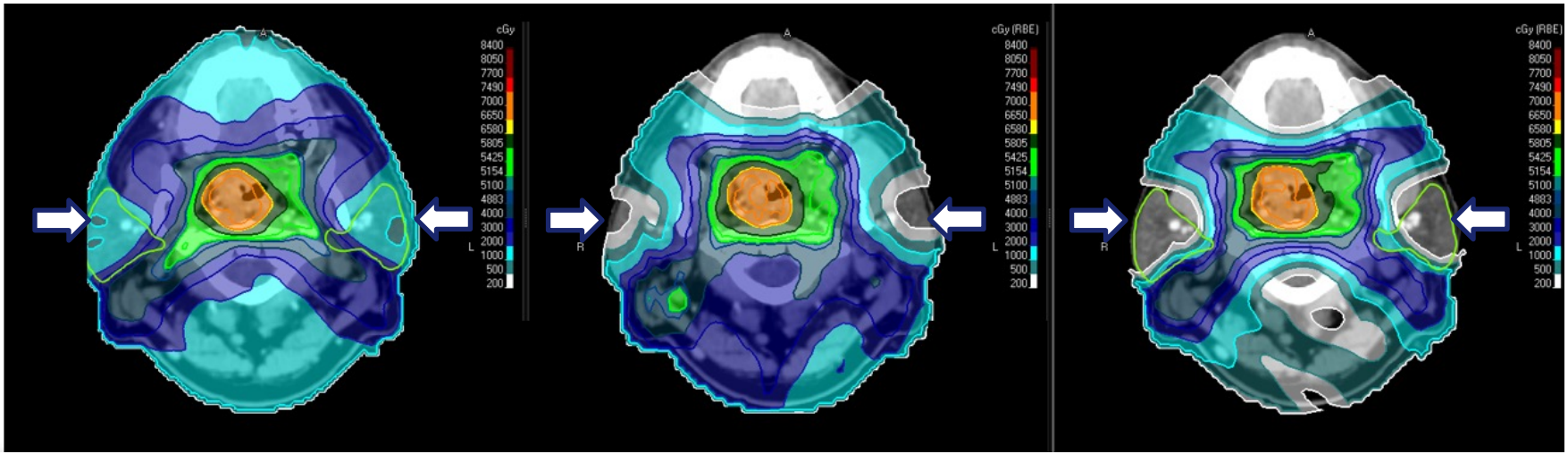
Proton Arc Therapy (PAT)
New proton technique



Full Arc 360^0

Technological development

Proton Arc Therapy (PAT)

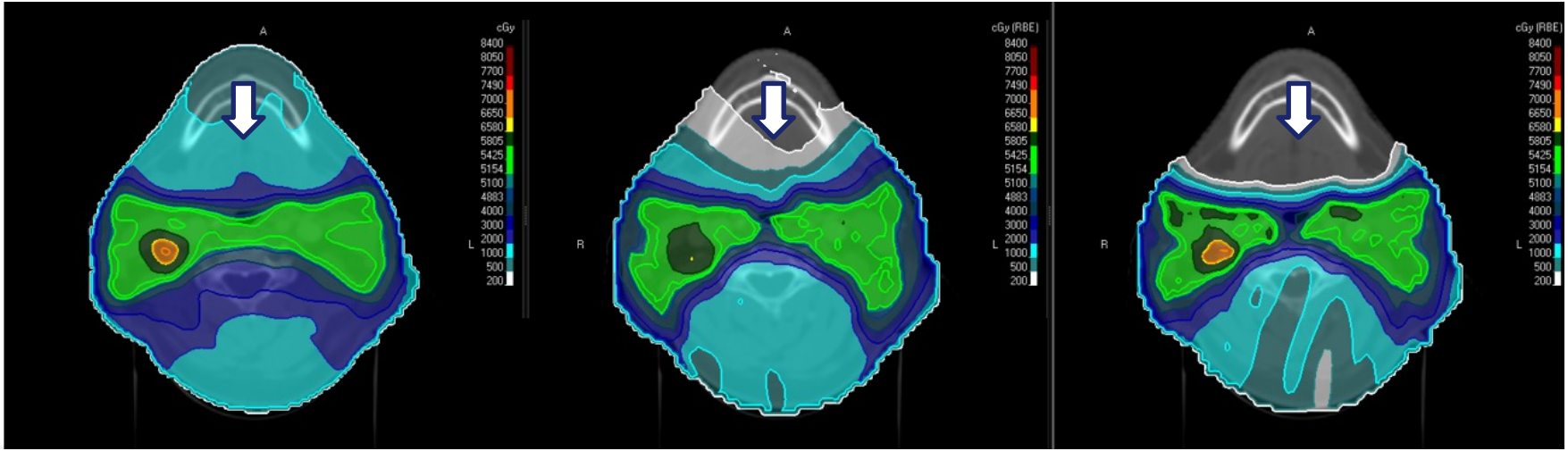


VMAT (photons)
Current technique

IMPT (protons)
Current technique
(since 2018)

Step and shoot Arc (protons)
New technique
(Start 2022)

Technological development
Proton Arc Therapy (PAT)

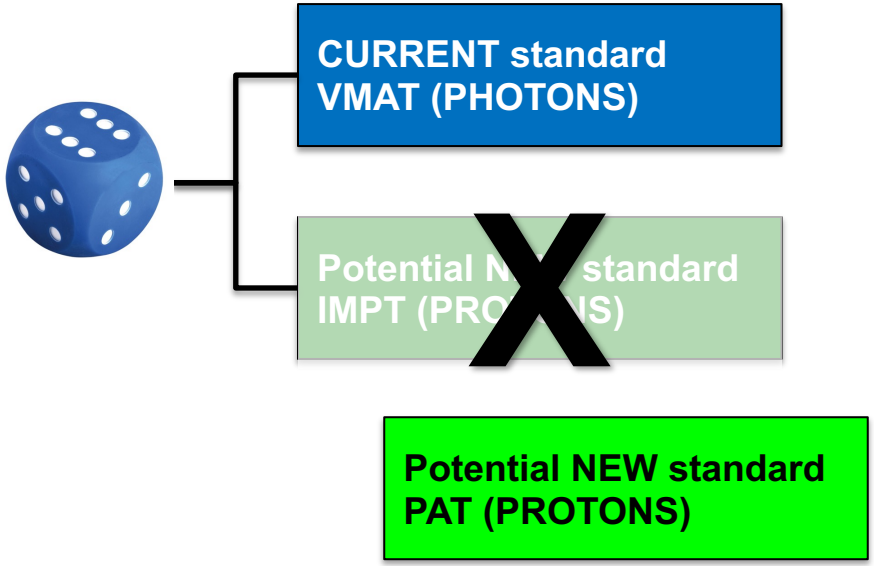


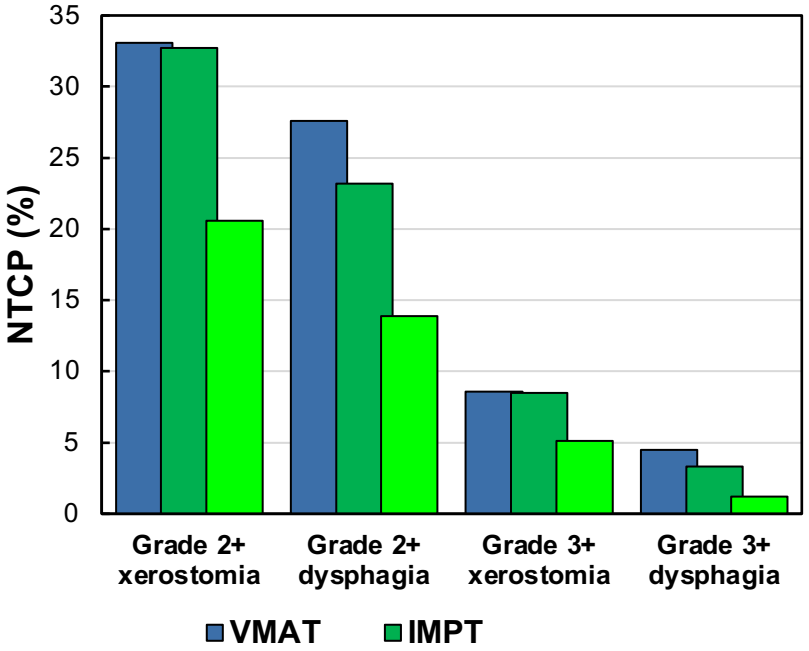
VMAT (photons)

IMPT (protons)
Current technique
(since 2018)

Step and shoot Arc (protons)
New technique
(Start 2022)

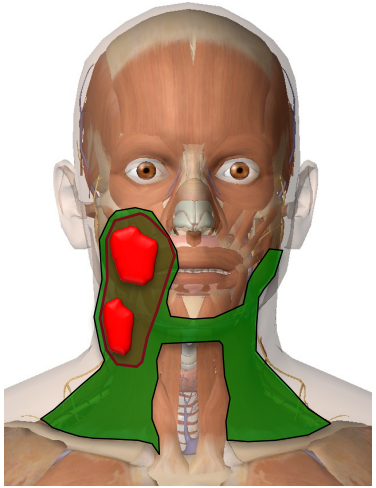
Technological development
Proton Arc Therapy (PAT)





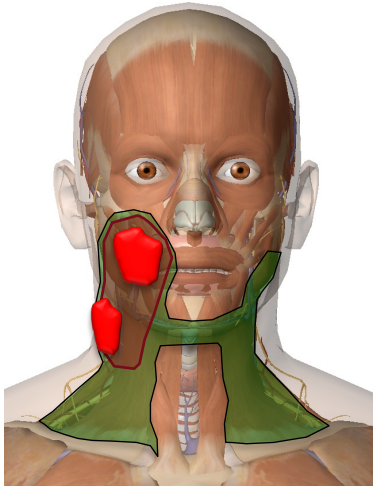
Medical developments

Elective nodal irradiation in HPV+ oropharyngeal cancer



Current standard

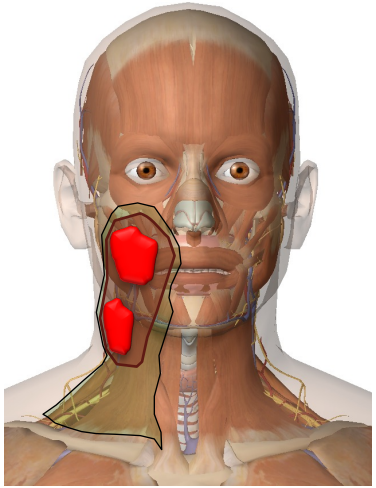
High dose: **70** Gy
Elective dose: 54 Gy



Lower elective dose

High dose: **70** Gy
Elective dose: **40** Gy

Deschuymer, et al. 2021



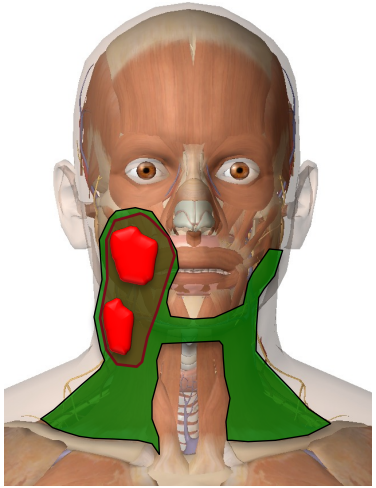
Unilateral neck only

High dose: **70** Gy
Elective dose: **40** Gy

Ongoing trial

Medical developments

Elective nodal irradiation in HPV+ oropharyngeal cancer



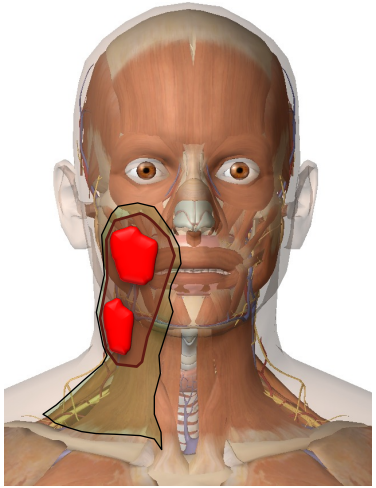
PAST standard

High dose: **70** Gy
Elective dose: 54 Gy

CURRENT standard
PHOTON therapy

Potential NEW standard
PROTON therapy

?



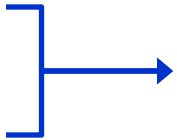
NEW standard

High dose: **70** Gy
Elective dose: **40** Gy

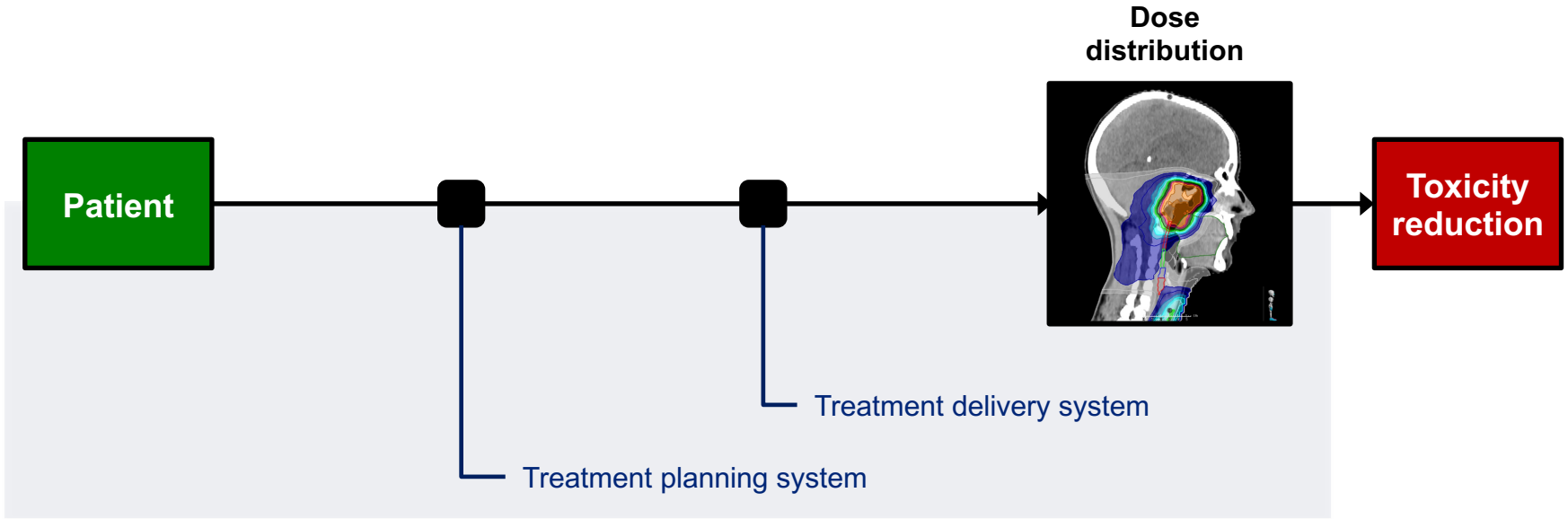
Ongoing trial

Consequences

- Technological developments
- Medical developments

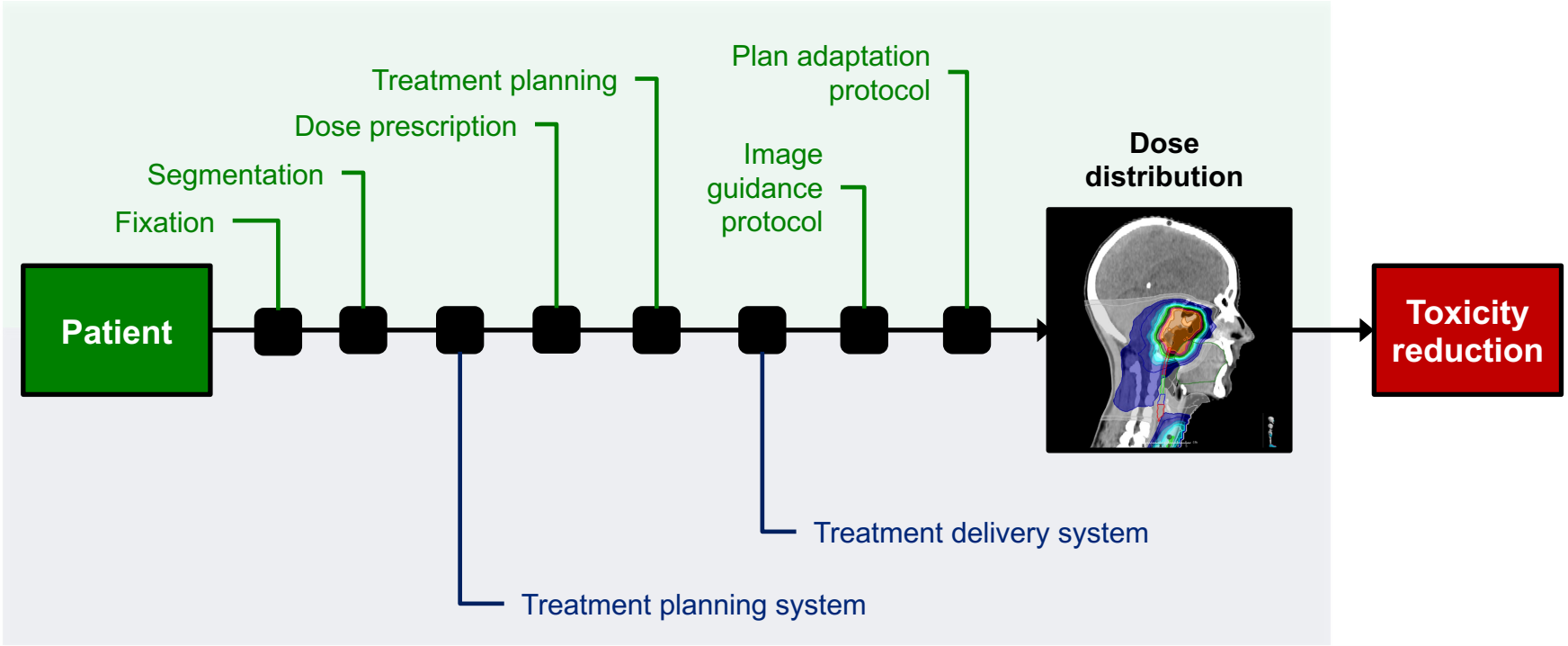


↓ **sustainability**


Dose distribution
Patient
Toxicity reduction
Treatment delivery system
Treatment planning system

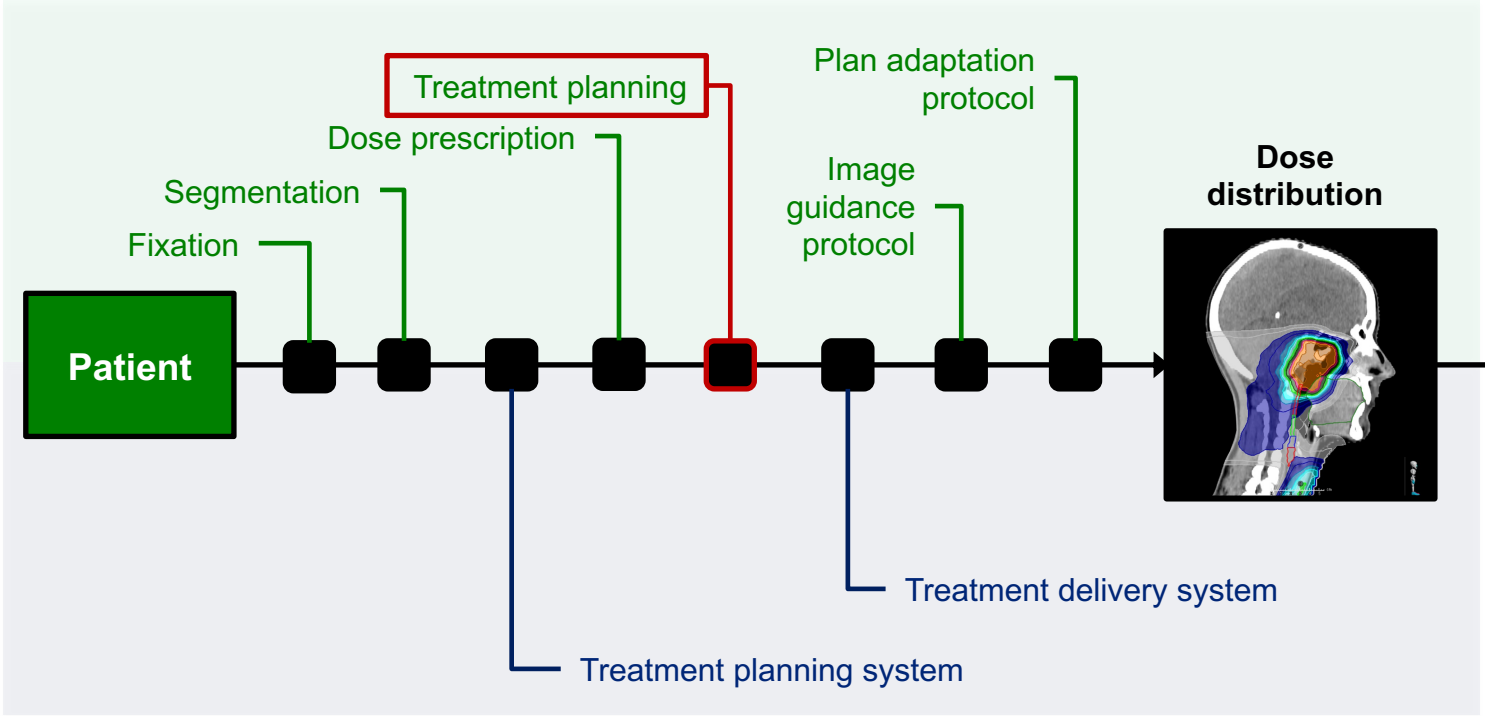
Technology

Technology-user interplay



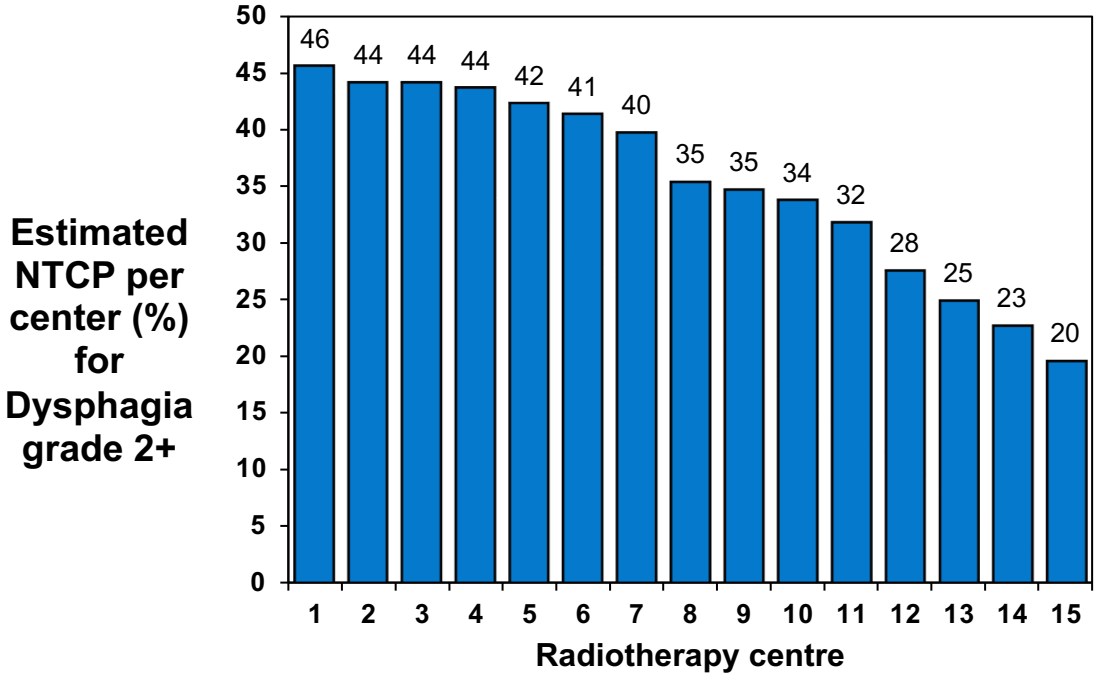
Technology

Technology-user interplay



Technology

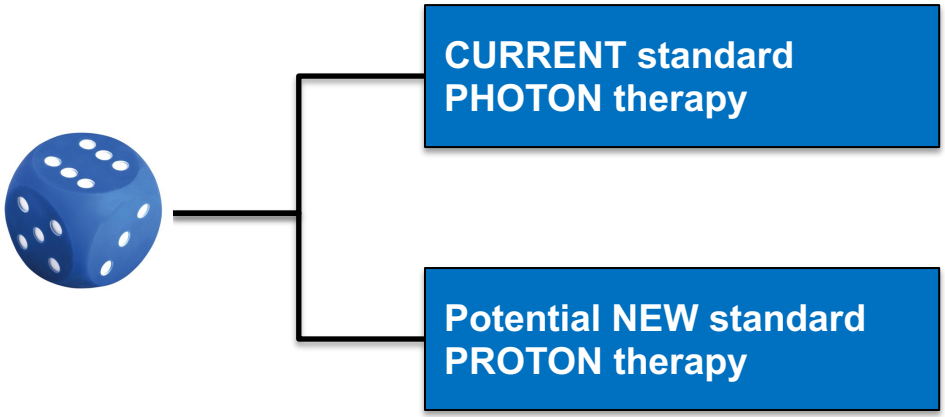
Current standard?
IMRT (photon) treatment planning



- Planning comparison study
- Multicenter (n=15)
- One patient
  - One set of targets
  - One of OAR's

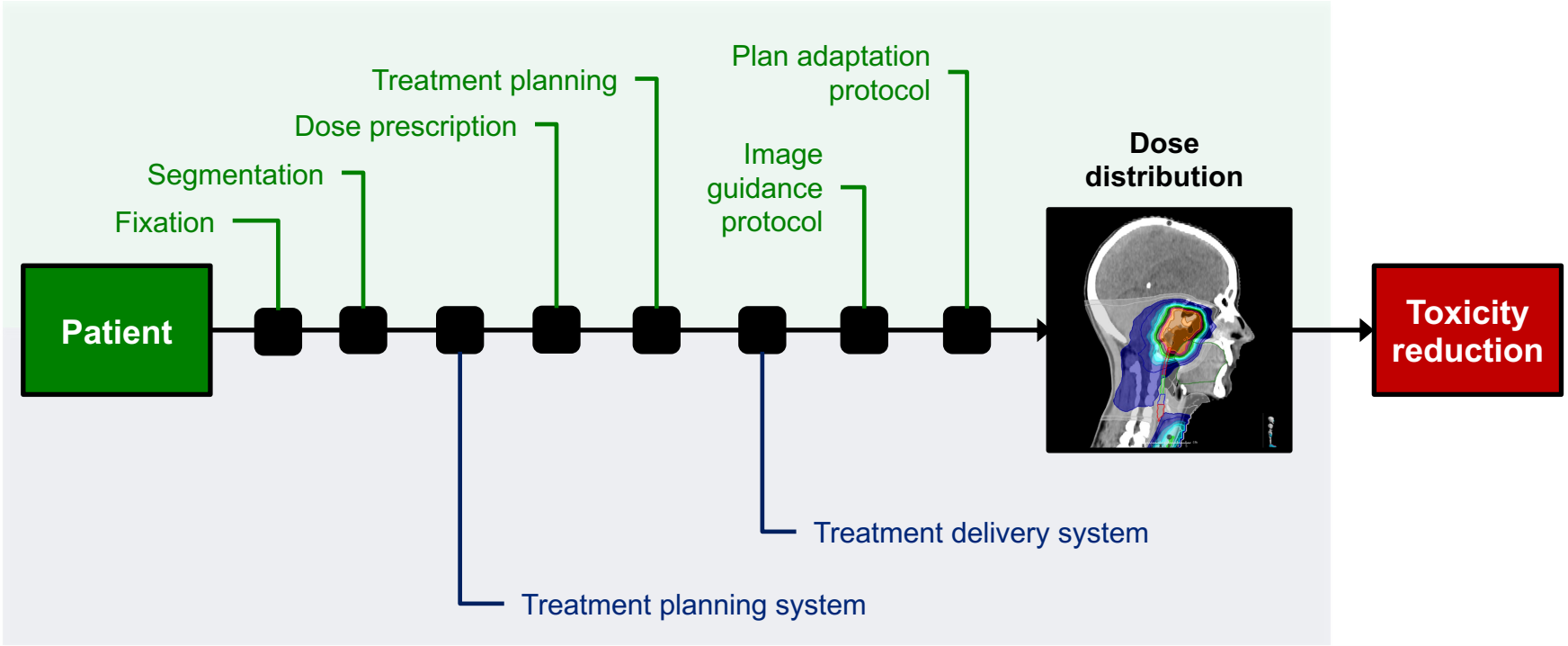
Courtesy: Wilco Verbakel

Best available evidence?



- How can IMRT be standard, if there is no standard IMRT?

Technology-user interplay

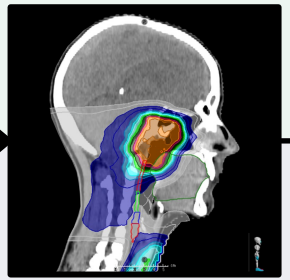


Technology

Technology-user interplay ← The HUMAN factor

Patient

Dose distribution

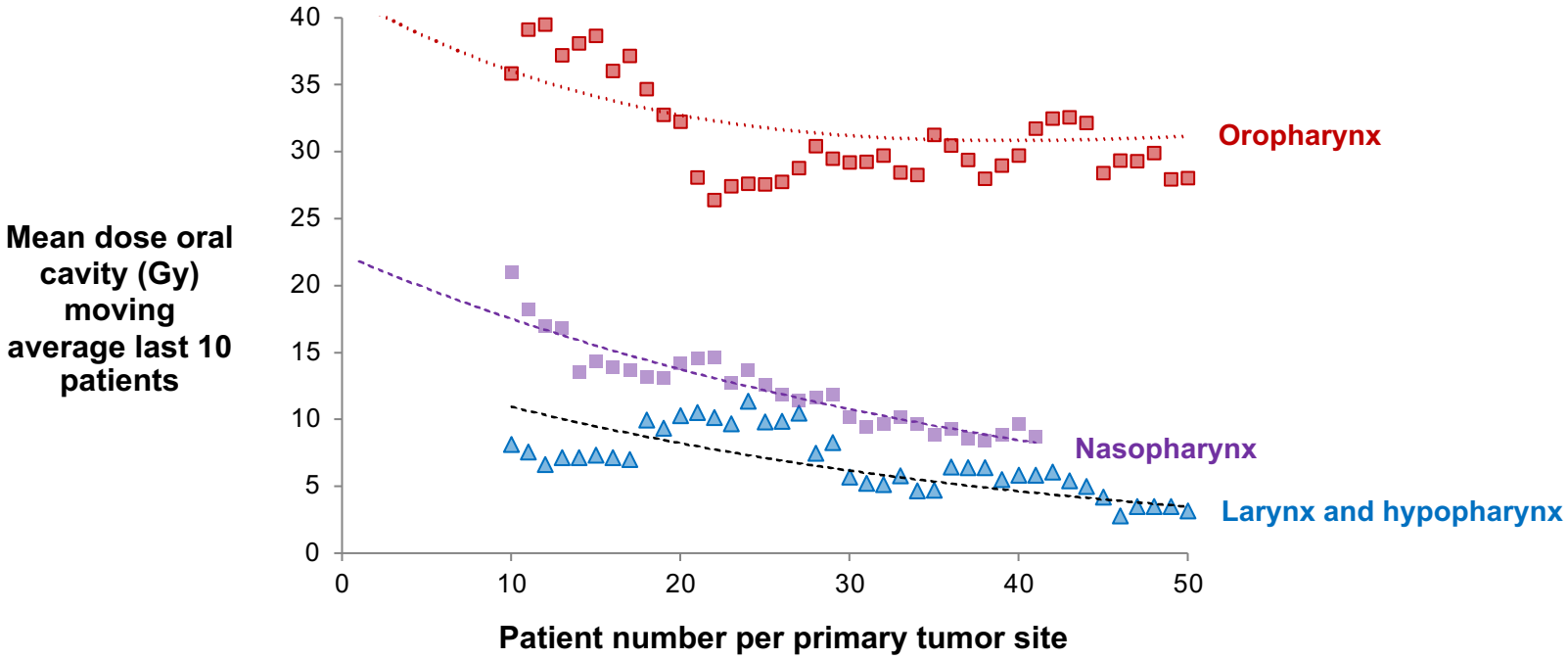


Toxicity reduction

Technology

Learning curve

Proton therapy 2018-2021 (head and neck)



Prospective Data Registration Program UMCG

Consequences

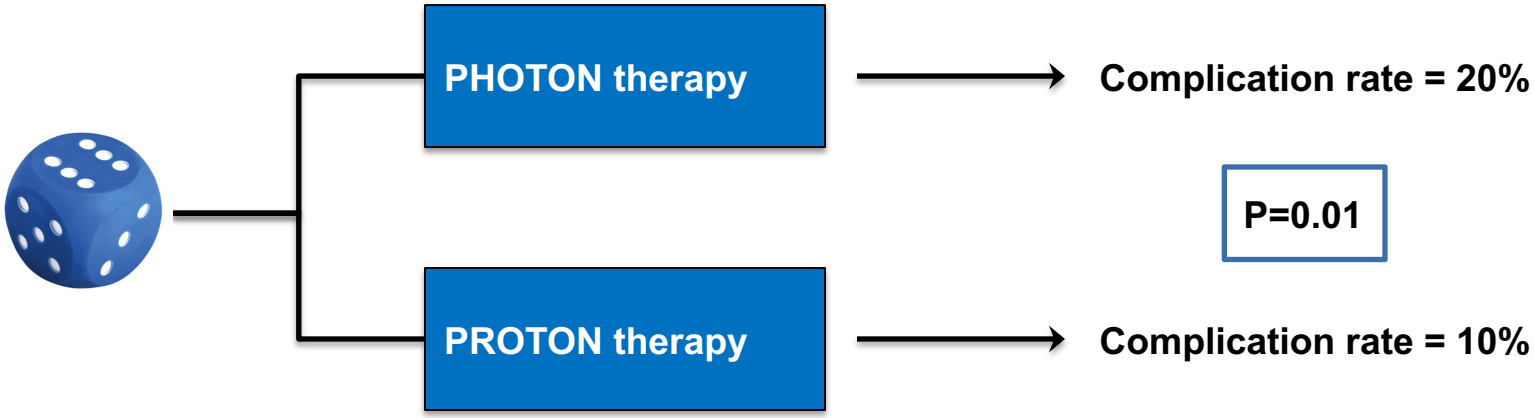
- Technological developments
- Medical developments

→ ↓ **sustainability**

- Technological specifications
- Technology-user interplay
- Learning effect

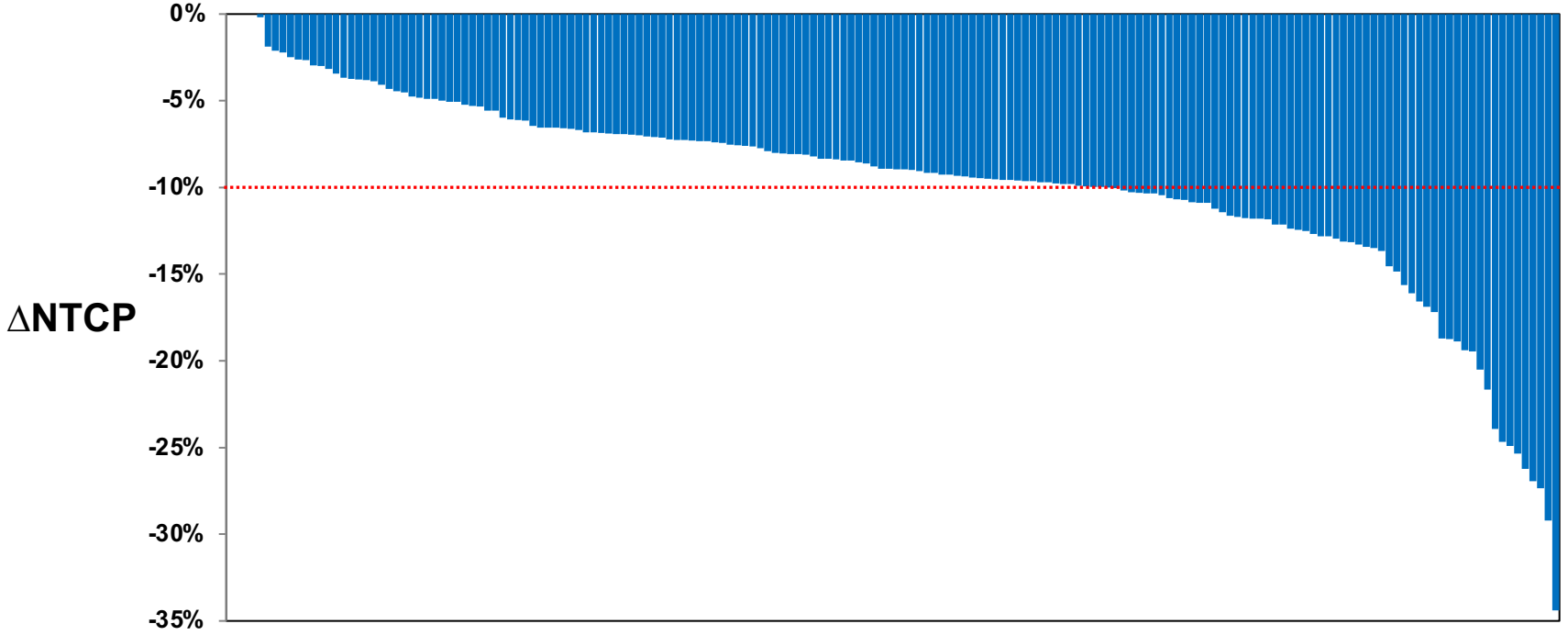
→ ↓ **generalisibility**

Positive RCT



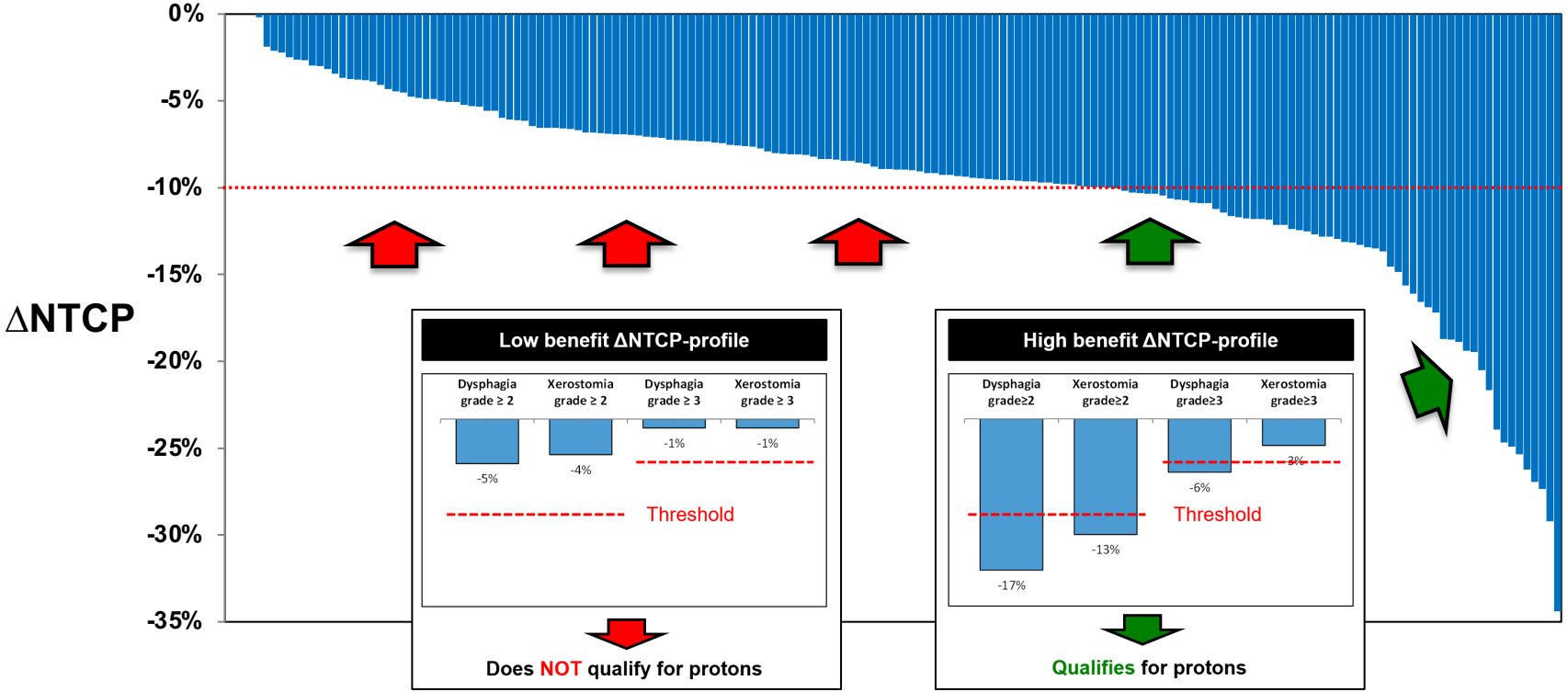
Positive RCT

Underlying ΔNTCP-values per patients



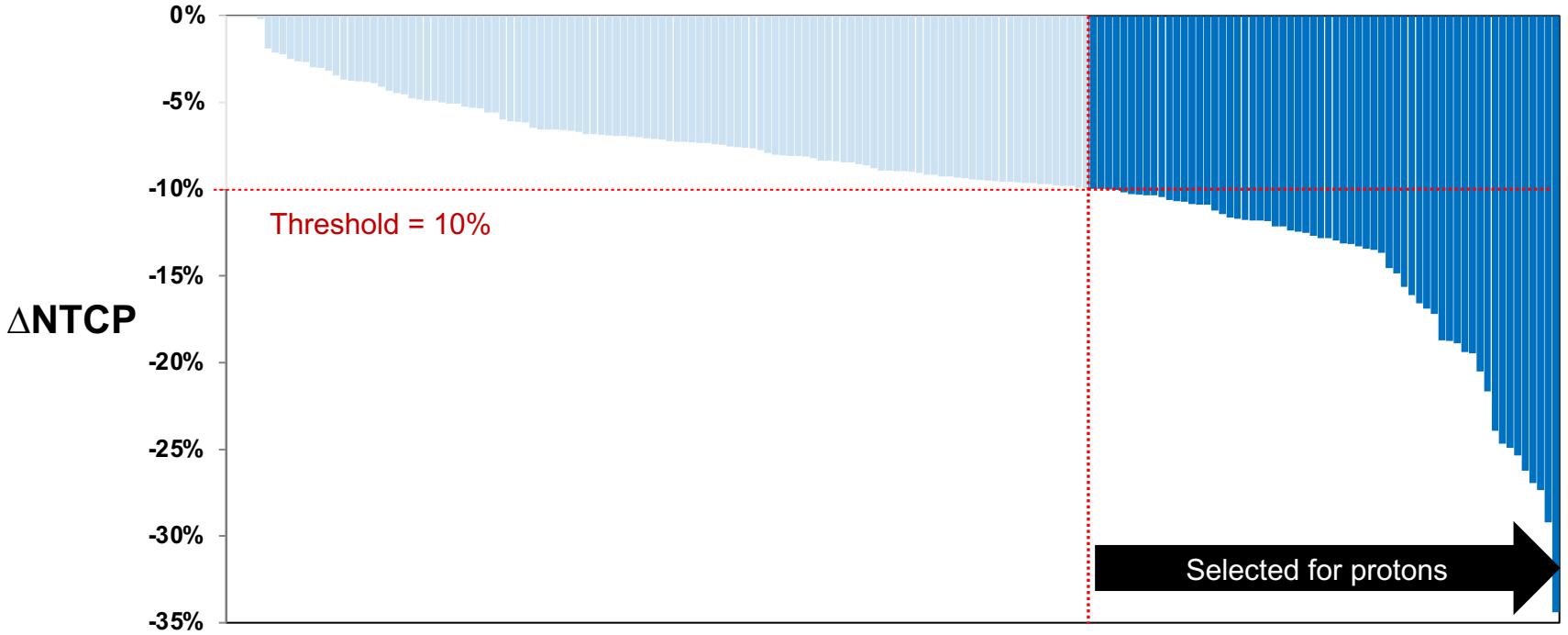
Positive RCT

Underlying ΔNTCP-values per patients



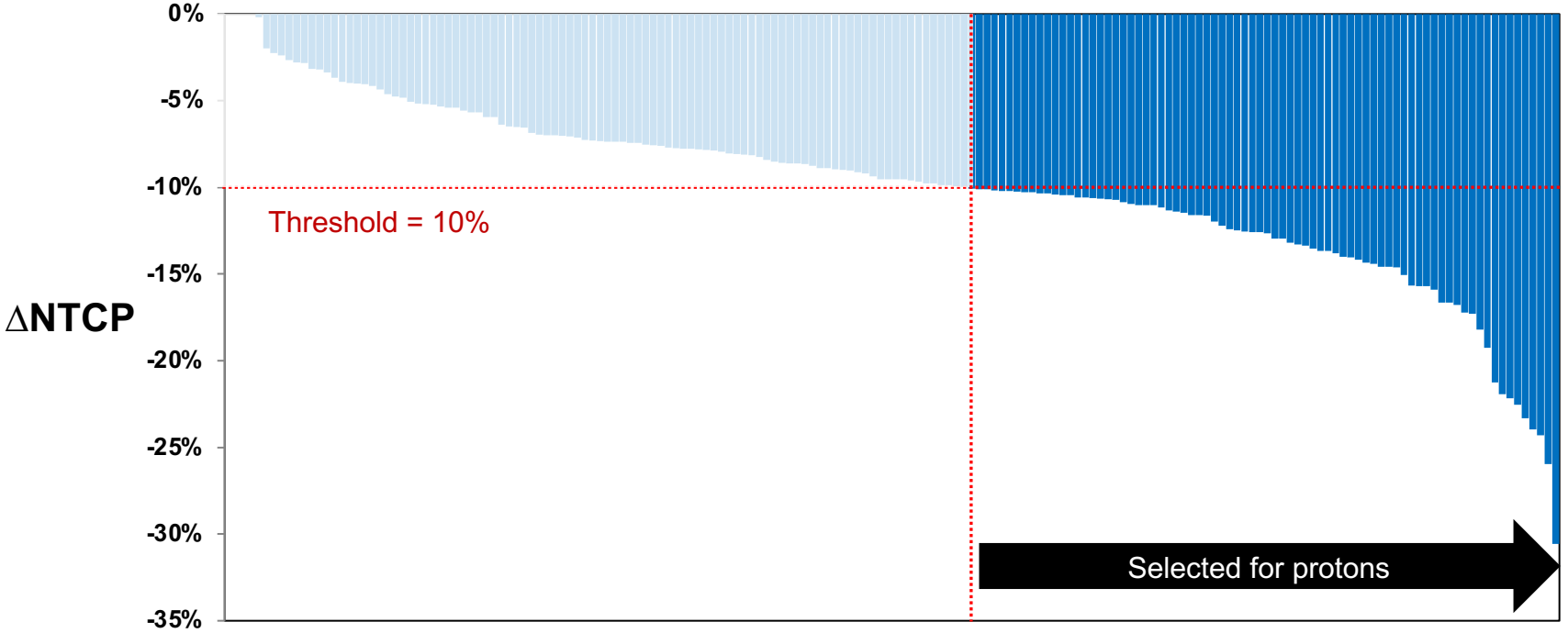
ΔNTCP threshold

Based on current technology



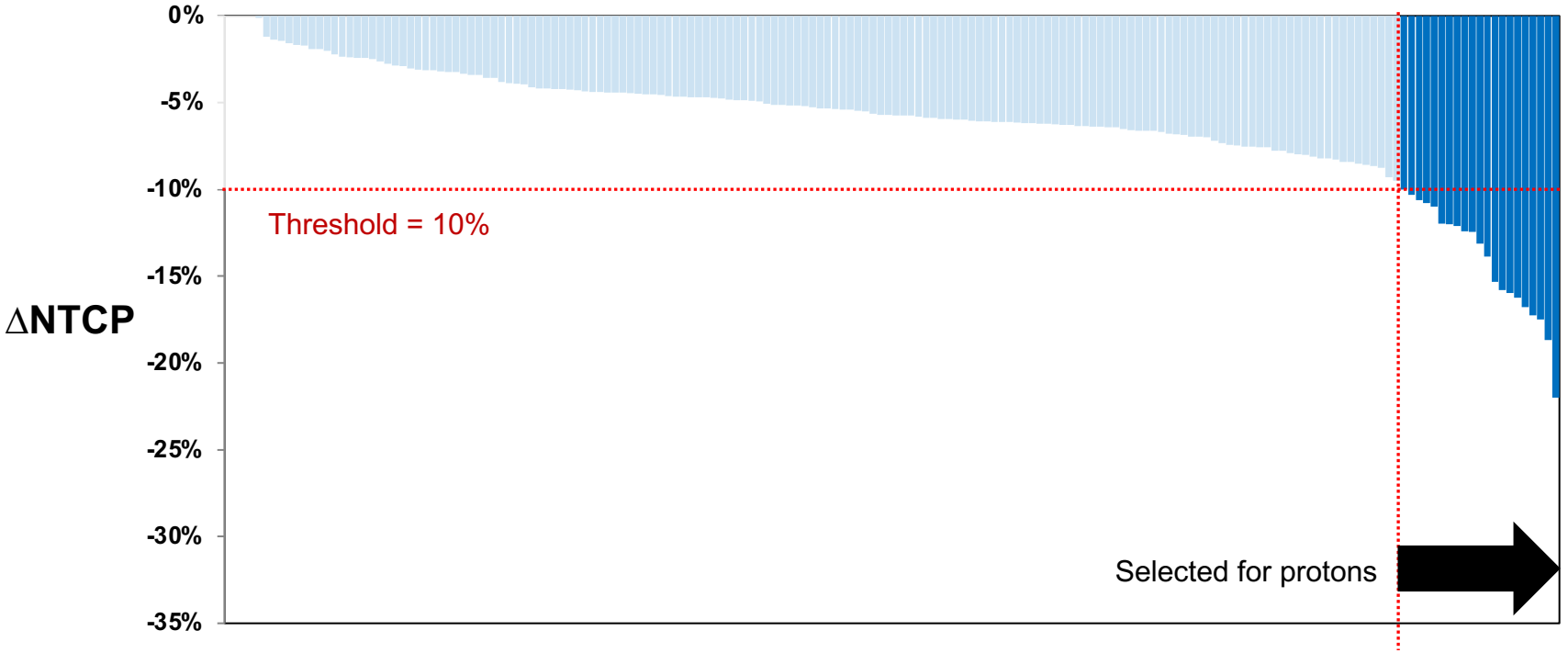
ΔNTCP threshold

Effect of small improvement in proton therapy performance

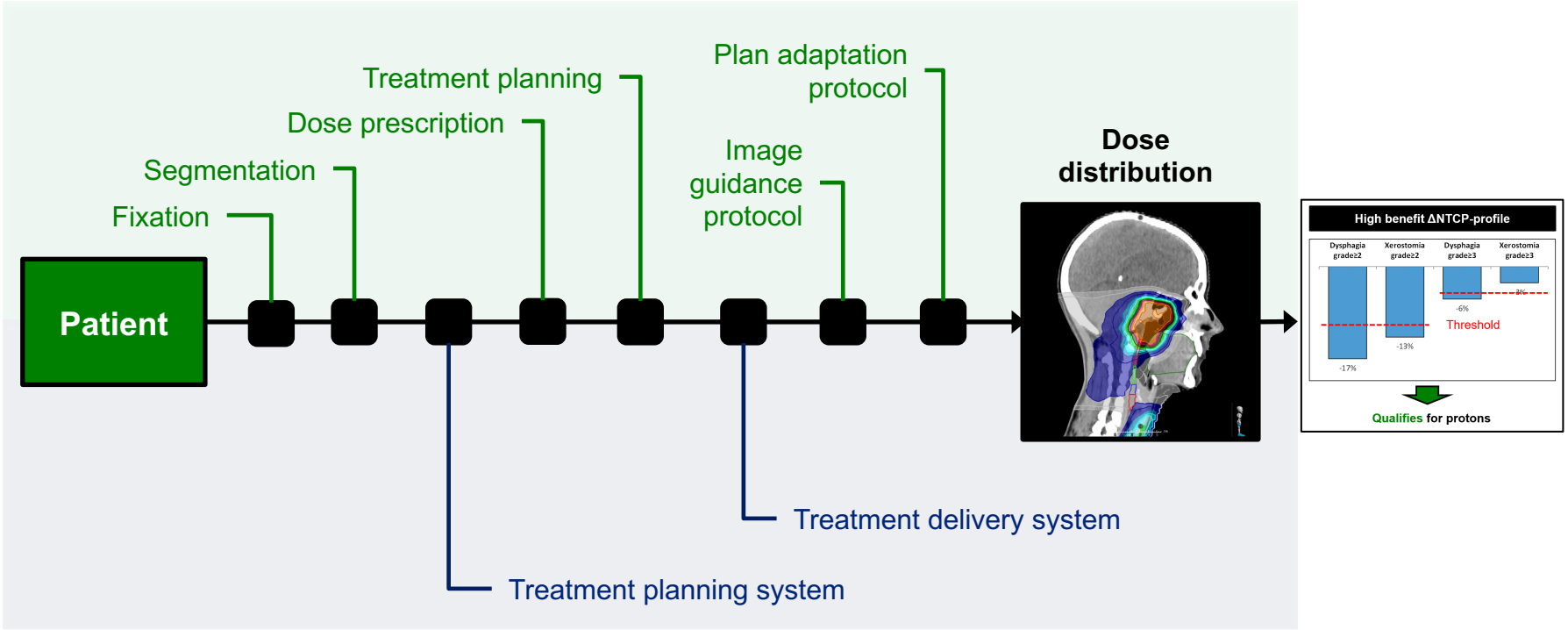


ΔNTCP threshold

Early phase learning curve / medical developments (lower elective dose)



Technology-user interplay

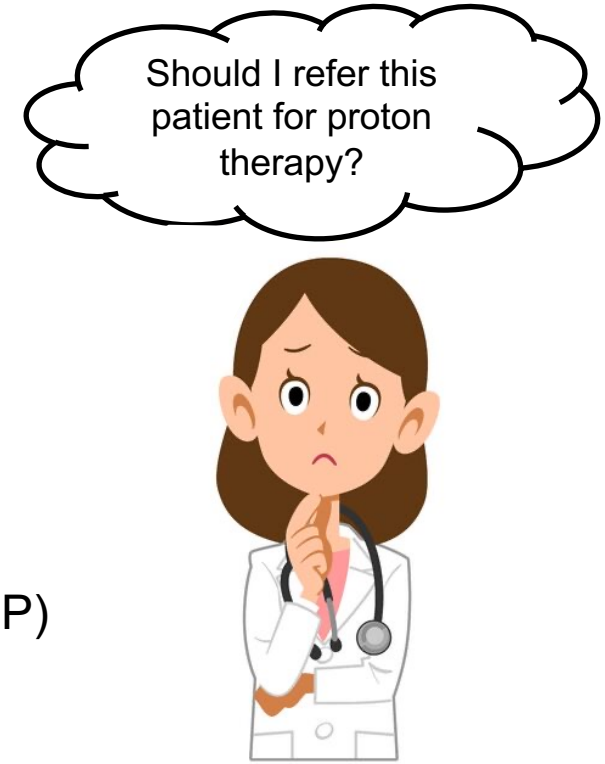


Technology

ΔNTCP-profile

Accounts for all components

1. Technological and medical developments
2. Technology-user interplay
3. Institutional performance
4. Individual patient characteristics (Δdose →ΔNTCP)



Model-based approach

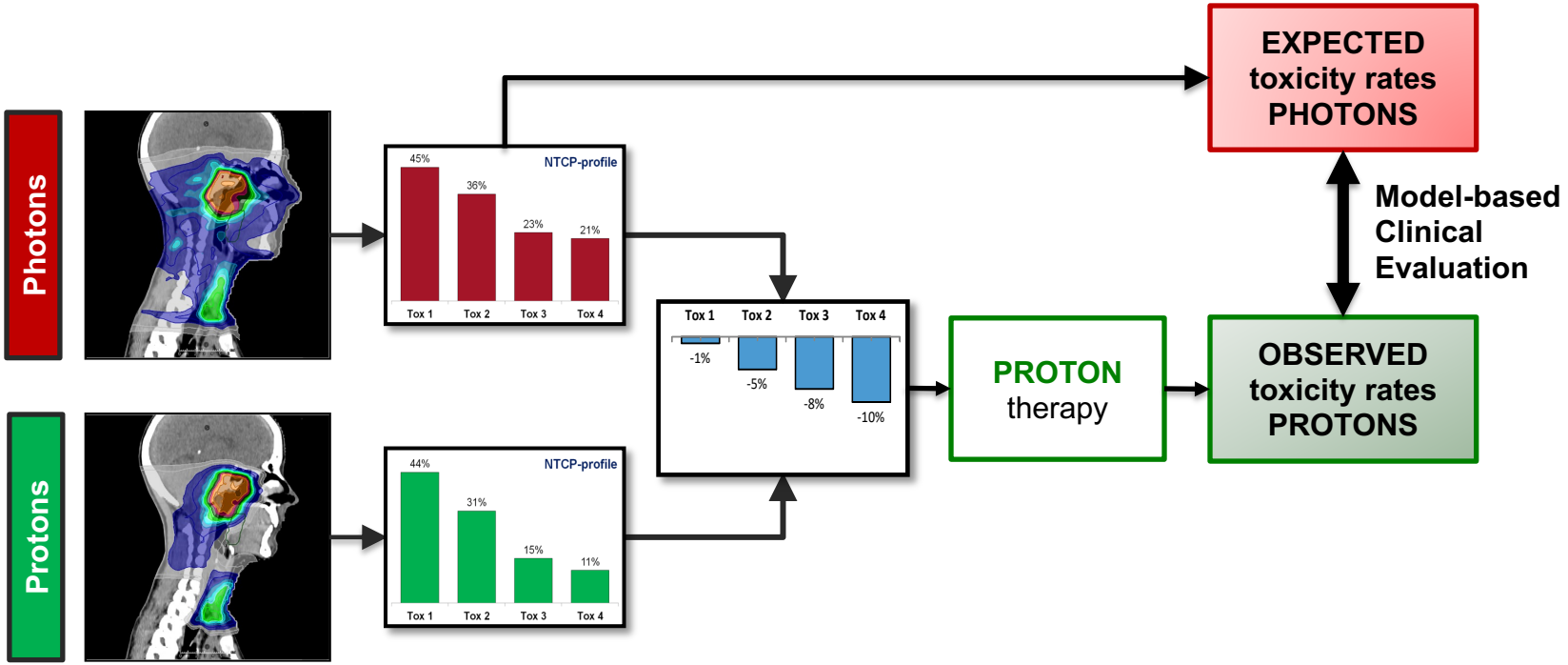
1. Model-based selection
   - **Identify patients** who will benefit most from proton therapy in terms of complication risk reduction

2. Model-based validation
   - **Evaluate the benefit** protons when used to reduce complication risk

Langendijk, et al. Radiother Oncol 2013
Langendijk, et al. Sem Radiat Oncol 2018

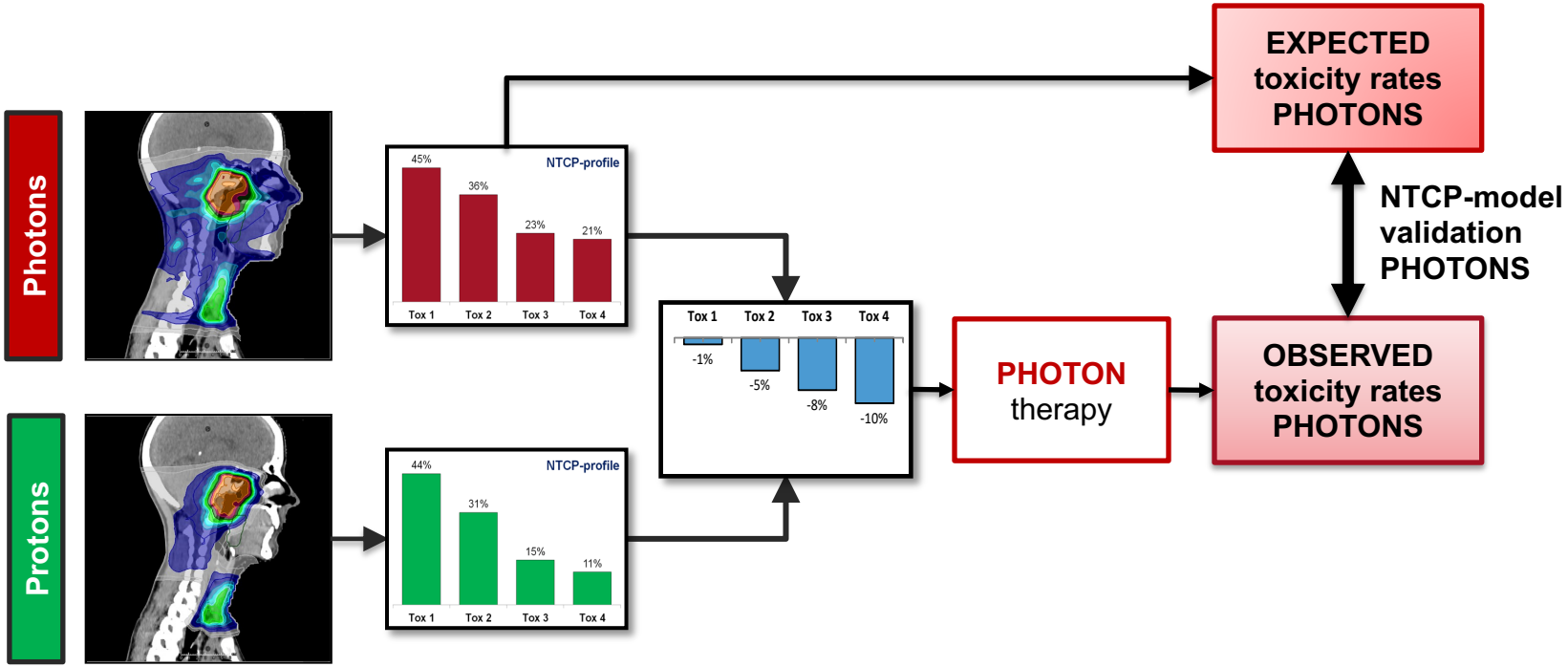
Model-based validation

Study design *Model-based Clinical Evaluation*



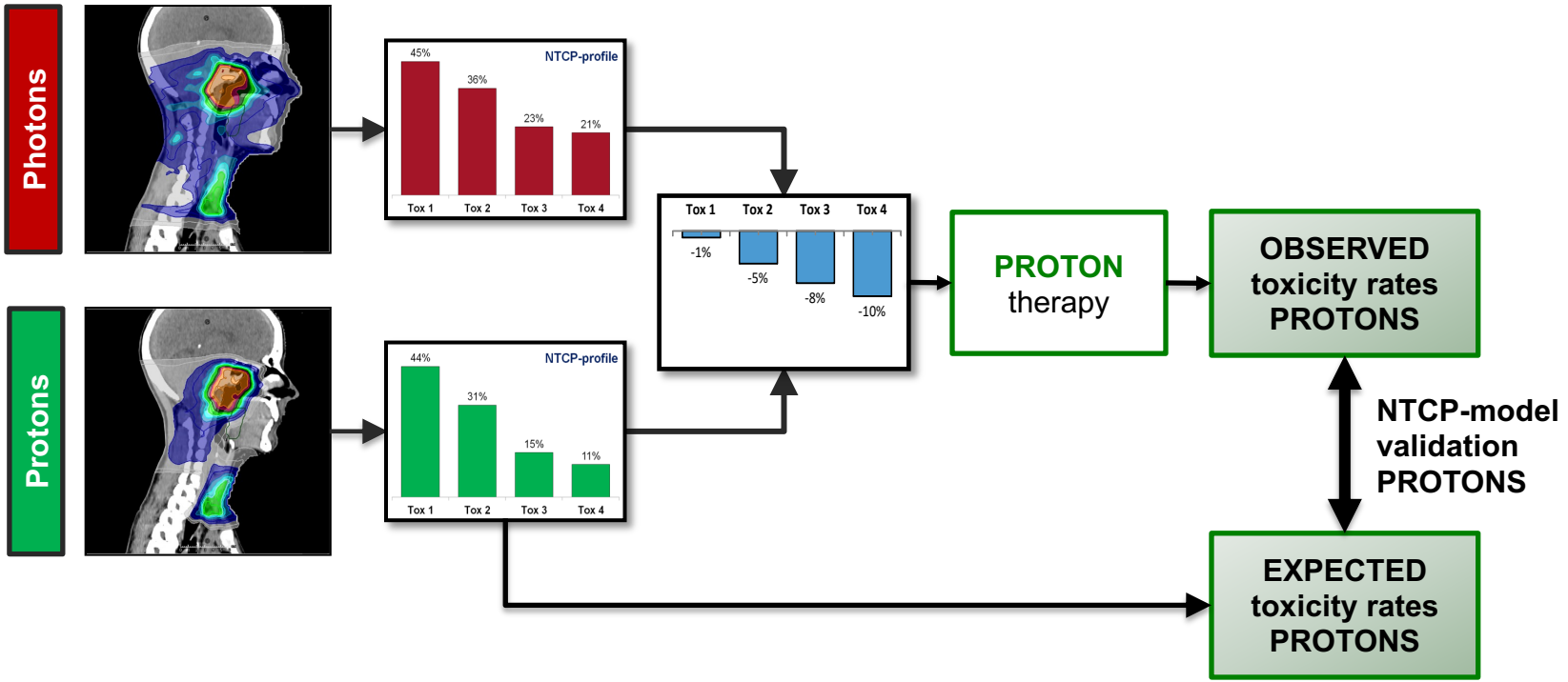
Model-based validation

Study design *Model-based Clinical Evaluation*

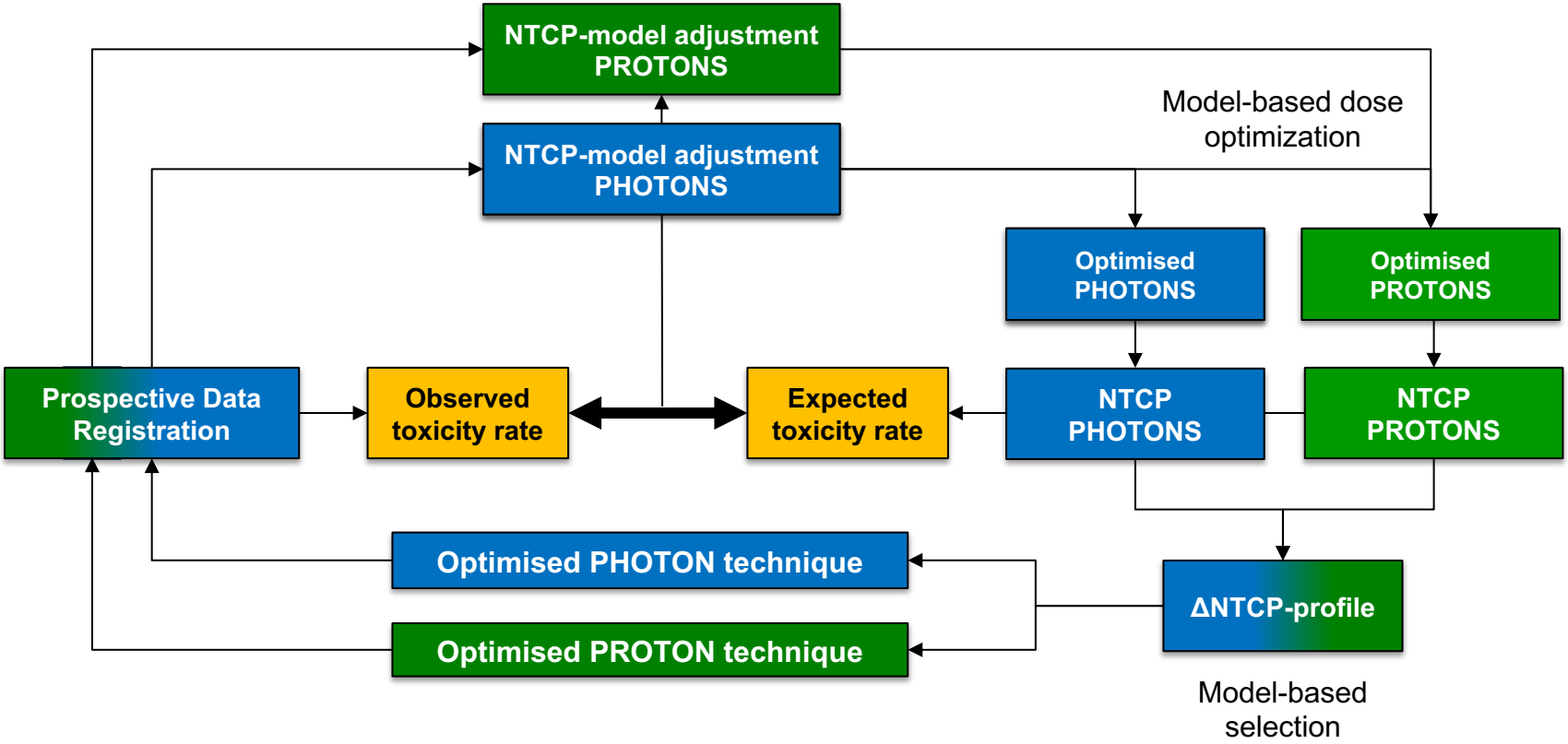


Model-based validation

Study design *Model-based Clinical Evaluation*



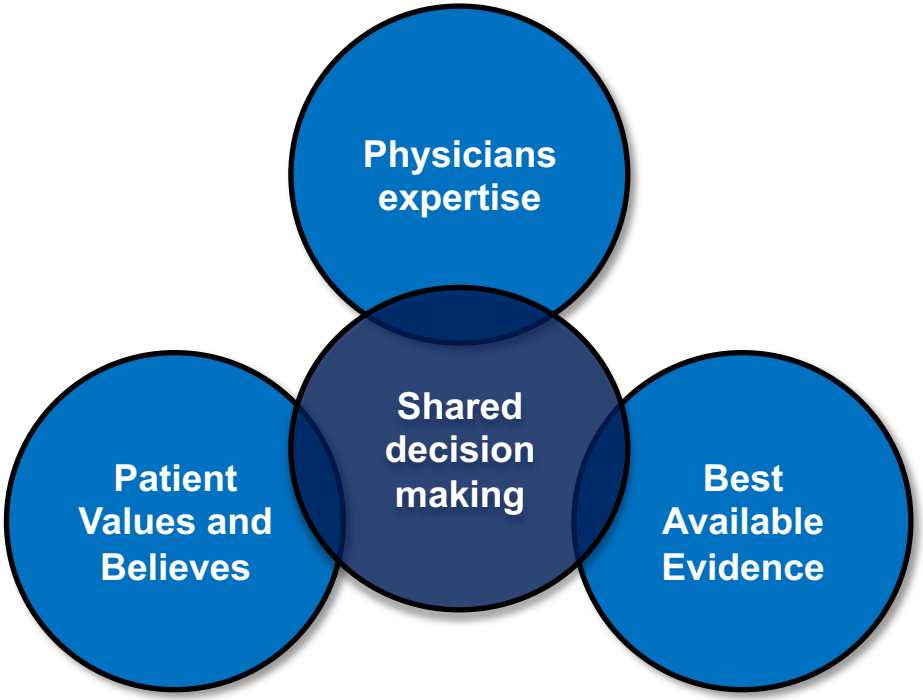
Learning Radiation Health Care System (ProTRAIT)

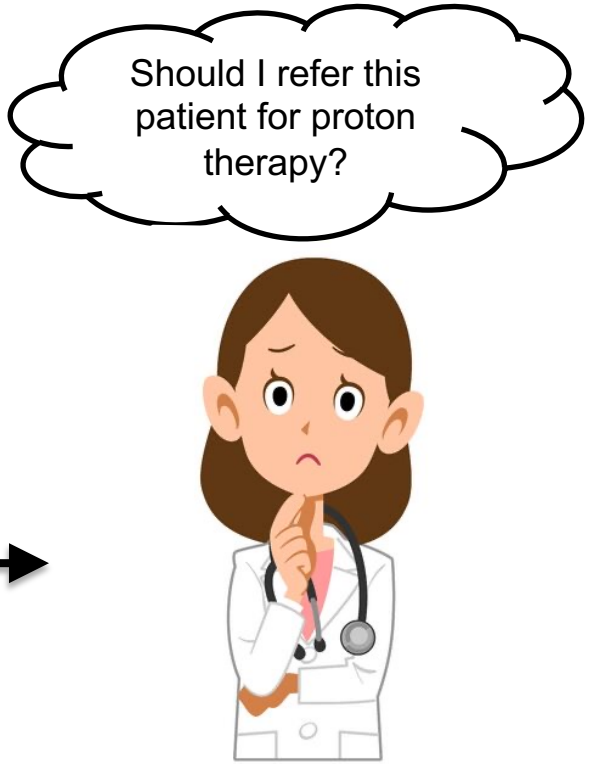


Summary and conclusions

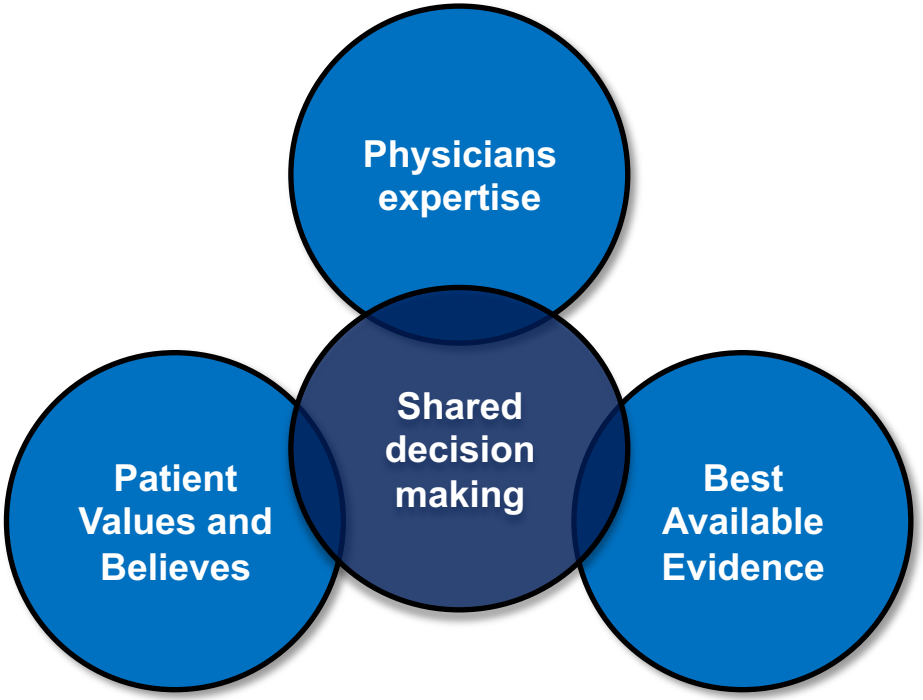
- Evidence-based medicine ≠ RCT's
  - Translation RCT's hampered by:
    - Technological and medical developments
    - Technology-user interplay
- Model-based selection (ΔNTCP-profile) is robust for these effects and accounts for how Δdose translates into ΔNTCP
- Continuous learning system based on real-world data
  - Optimize and enrich ΔNTCP-profiles

Evidence-based medicine

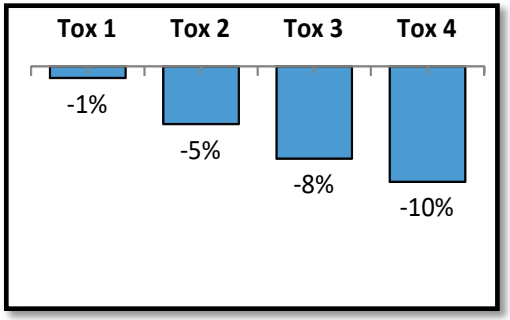




Evidence-based medicine



ΔNTCP-profile provides essential and updated information for shared decision-making



Acknowlegements

Department of Radiation Oncology
Anne van den Hoek, MD
Miranda Kramer, MD PhD
Tineke Meijer-van Zon, MD PhD
Edwin Oldehinkel, MD
Roel Steenbakkers, MD PhD

Prof. Stefan Both, PhD
Jeffrey Free
Hans Paul van der Laan, PhD
Henriette van der Laan-Boomsma
Dan Scandurra
Arjen van der Schaaf, PhD
Lisa van den Bosch, MD

Julius Center Utrecht
Prof. Carl Moons, PhD
Hans Reitsma, PhD
Ewoud Schuit, PhD

Maastro
Prof. Andre Dekker, PhD
Prof. Liesbeth Boersma, MD PhD

HollandPTC
Prof. Marco van Vulpen, MD PhD
Prof. Mischa Hoogeman, PhD

LUMC
Prof. Coen Rasch, MD PhD

Erasmus MC
Prof. Remi Nout, MD PhD

And many others

KWF

HORIZON 2020

EURATOM

UMCG Kanker Researchfonds

umcg