


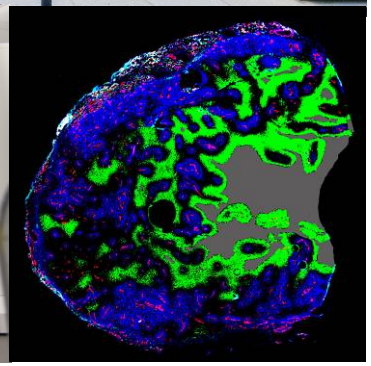

Medical perspectives of particle therapy:

# Needs of the medical community – impulse statement

Michael Baumann

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Medical Faculty and Univ. Hospital, TU Dresden

OncoRay – Natl. Center for Radiation Research in Oncology, Dresden

Institute of Radiation Oncology,
HZDR Dresden

German Cancer Consortium (DKTK),
Partnersite Dresden

National Center for Tumor Disease (NCT),
Partnersite Dresden

OncoRay
National Center for Radiation Research in Oncology Dresden

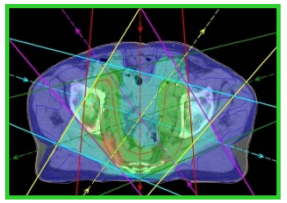
TECHNISCHE UNIVERSITÄT DRESDEN

HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

Universitätsklinikum Carl Gustav Carus

# Radiation Oncology

- 50% of all cancer patients
- Highly individualized treatment
- 50% of cures – radiotherapy sole treatment or major component
- Organ- and function sparing, well tolerable
- More than 4m long term survivors in Europe
- Favorable cost/benefit



# Radiotherapy needs

## Cancer burden, patients needing radiotherapy

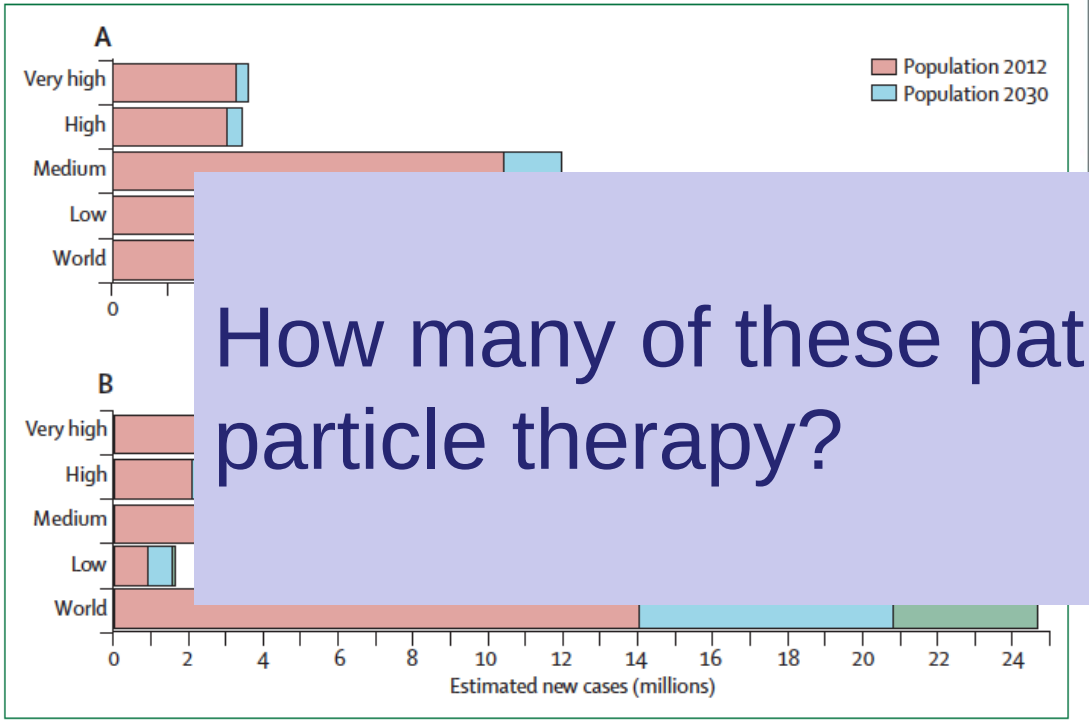



*Figure 5:* **Population increases (A) and predicted increases in cancer burden based on demographic and risk changes (B) by HDI level, 2012–30**


How many of these patients profit from particle therapy?

Benefits
2012 1.5m pts. LC, 0.58m OS
2035 2.5m pts. LC, 0.95m OS

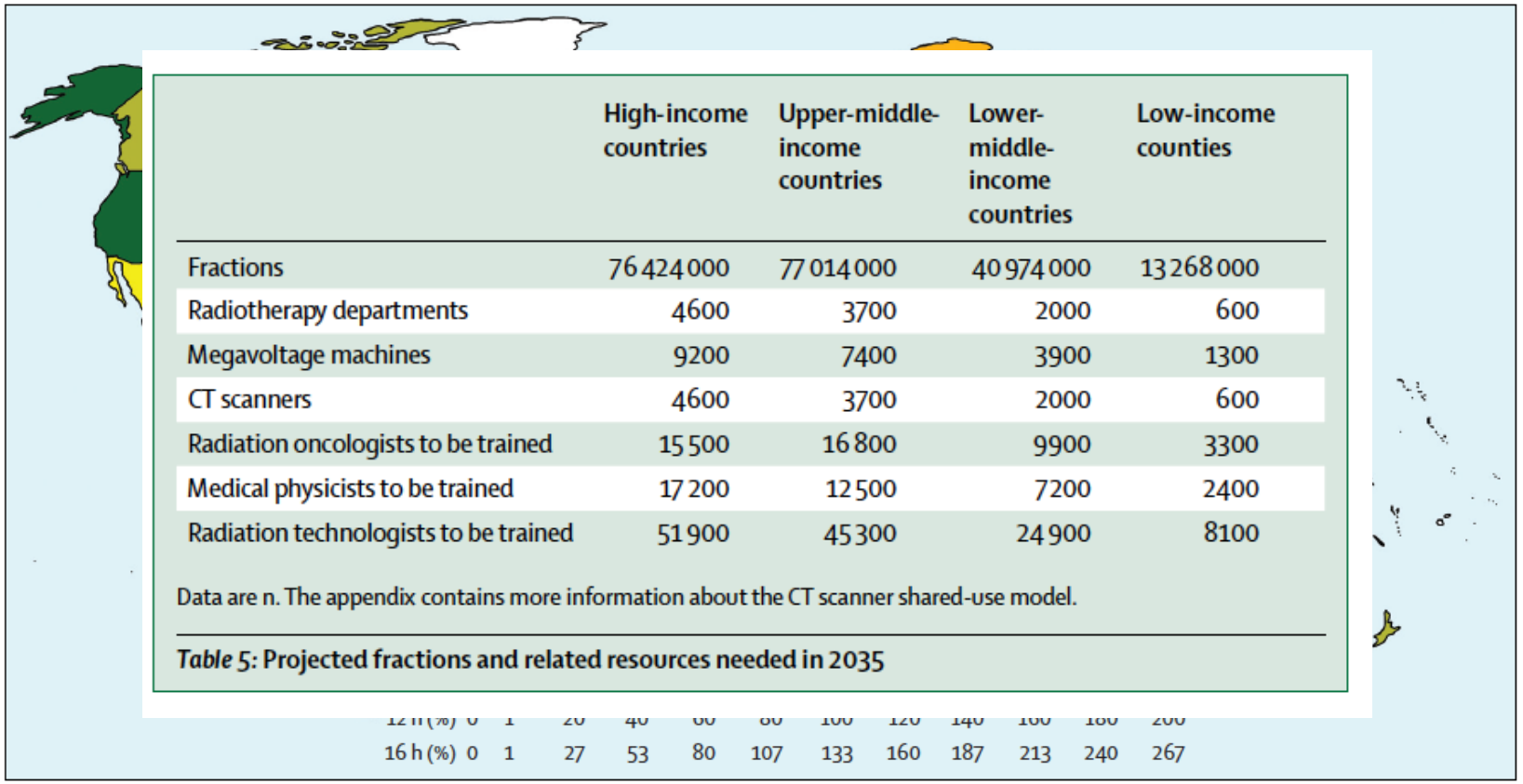
Plus palliation

Atun et al., Lancet Oncol 16:1153-86, 2015

# Radiotherapy

## Coverage of services, population benefits of scale-up

Only 40-60% of patients with cancer have access to radiotherapy



| | High-income countries | Upper-middle-income countries | Lower-middle-income countries | Low-income counties |
|---|---|---|---|---|
| Fractions | 76 424 000 | 77 014 000 | 40 974 000 | 13 268 000 |
| Radiotherapy departments | 4600 | 3700 | 2000 | 600 |
| Megavoltage machines | 9200 | 7400 | 3900 | 1300 |
| CT scanners | 4600 | 3700 | 2000 | 600 |
| Radiation oncologists to be trained | 15 500 | 16 800 | 9900 | 3300 |
| Medical physicists to be trained | 17 200 | 12 500 | 7200 | 2400 |
| Radiation technologists to be trained | 51 900 | 45 300 | 24 900 | 8100 |

Data are n. The appendix contains more information about the CT scanner shared-use model.

*Table* 5: **Projected fractions and related resources needed in 2035**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 h (%) | 0 | 1 | 20 | 40 | 60 | 80 | 100 | 120 | 140 | 160 | 180 | 200 |
| 16 h (%) | 0 | 1 | 27 | 53 | 80 | 107 | 133 | 160 | 187 | 213 | 240 | 267 |

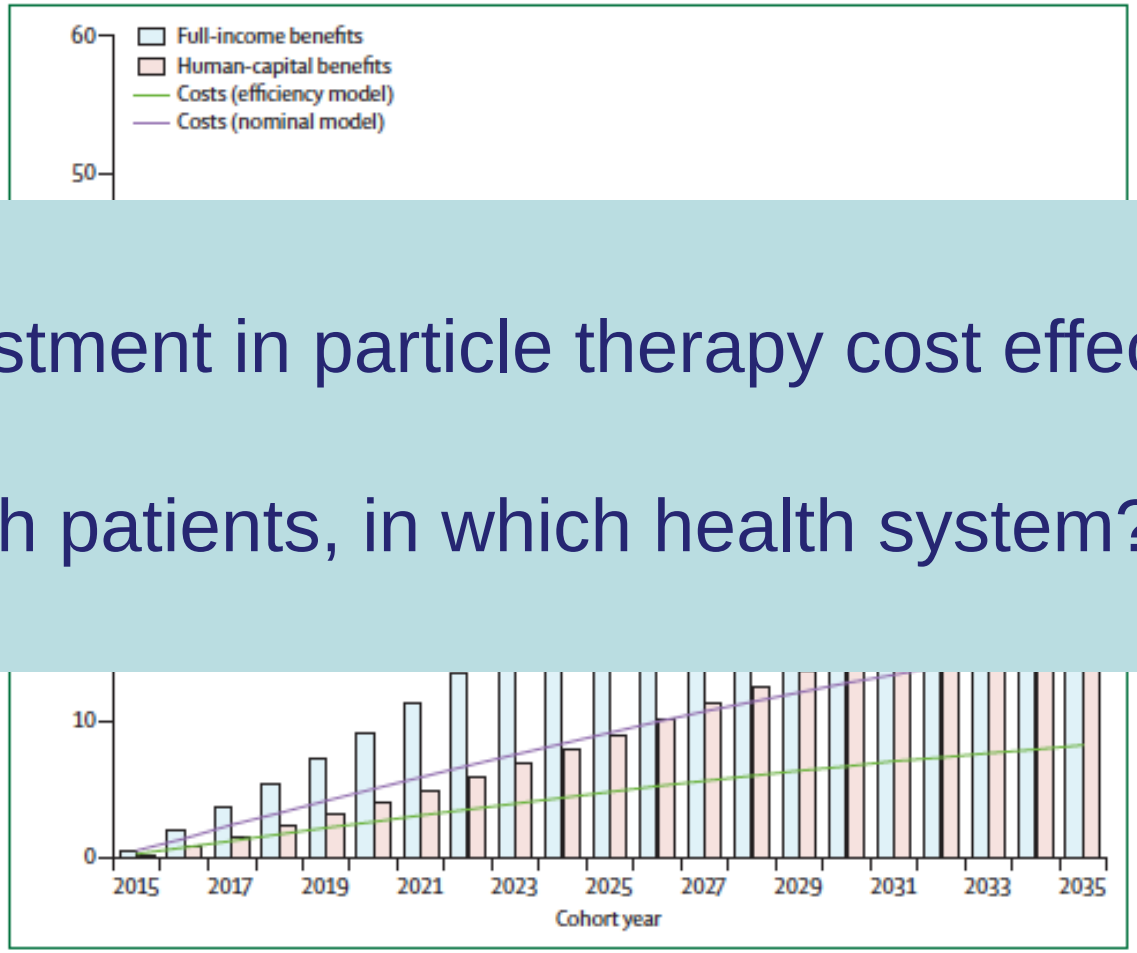
***Figure* 9: Coverage of radiotherapy services according to country as determined by global equipment databases, an activity-based operations model, cancer incidence, and evidence-based estimates of radiotherapy need**

Estimates depend on the nature of equipment use. The colour bar shows the operational model: 12 h operation was used as the feasible case, but 8 h and 16 h were also modelled to capture typical and potential capacity, respectively.

Atun et al., Lancet Oncol 16:1153-86, 2015

# Radiotherapy

## Cost benefit of scaling-up RT to demand




Are investment in particle therapy cost effective?

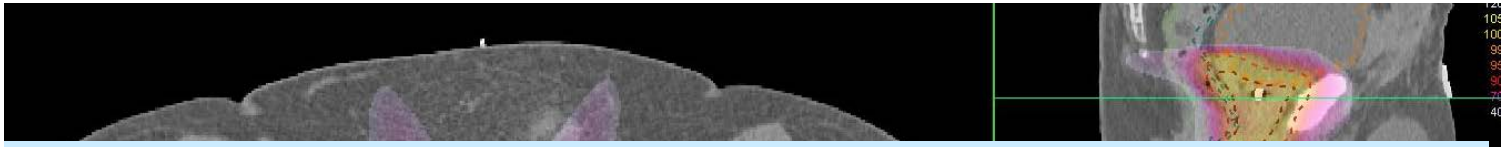
For which patients, in which health system?

***Figure 11:*** **Cost and benefits of investments to scale up radiotherapy services in low-income and middle-income countries, 2015–35**

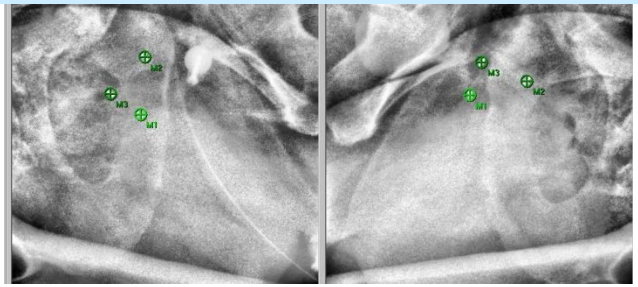
The costing models are described in the text and include both operational and capital costs.

# State of the art

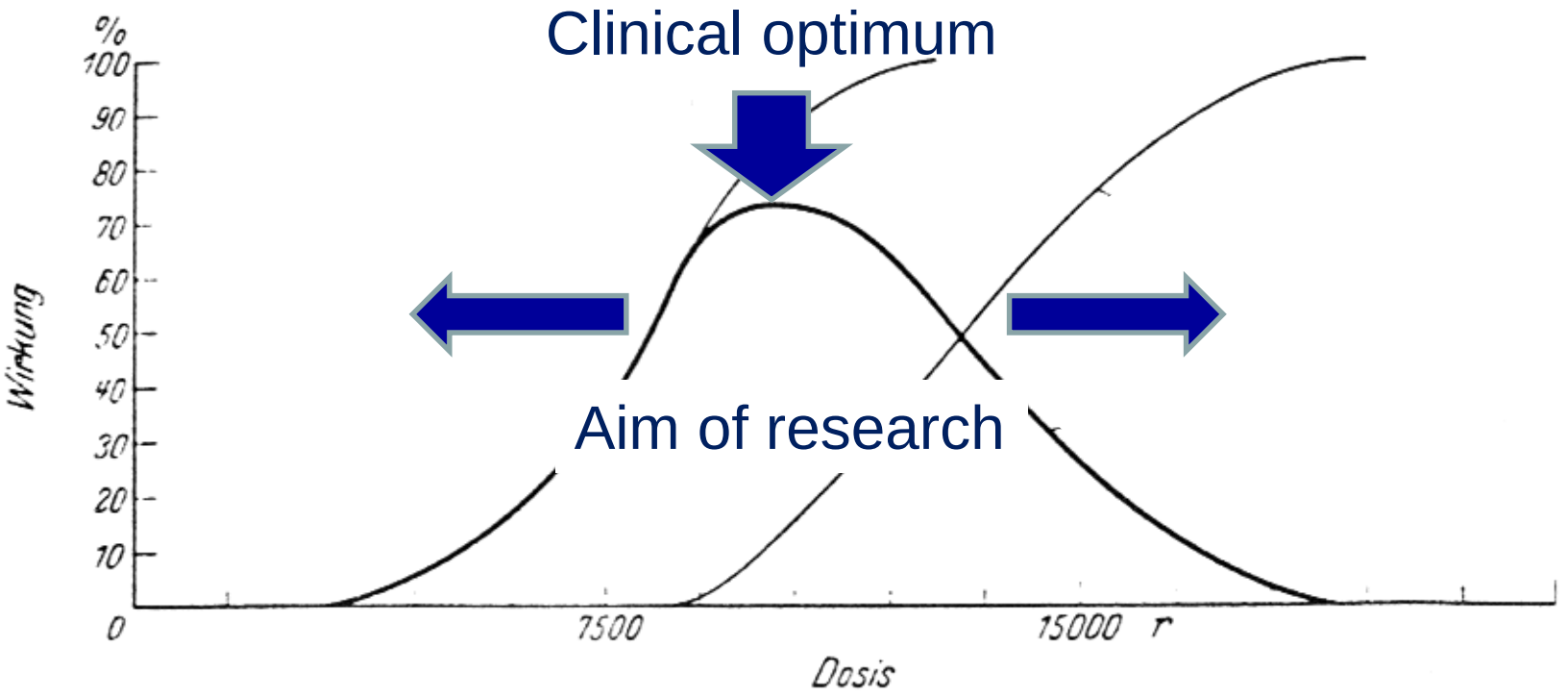
## Image guided, conformal (IMRT), photon therapy (Linacs)



- 35% local recurrence
- Preventable distant metastases
- Large volumes irradiated
- Early, late and very late normal tissue damage



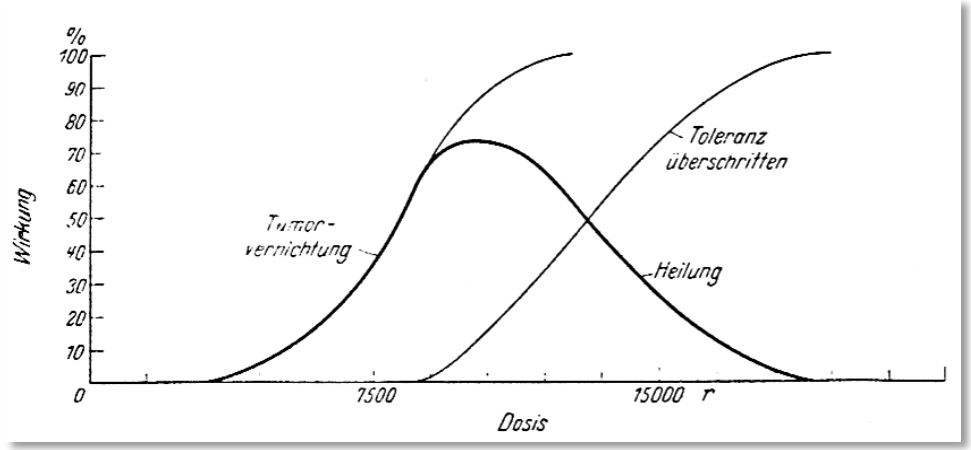
# Aim of radiotherapy




*) Vortrag vor der Deutschen Röntgengesellschaft am 24. April 1936

Holthusen, Strahlentherapie 57: 254-268,1936

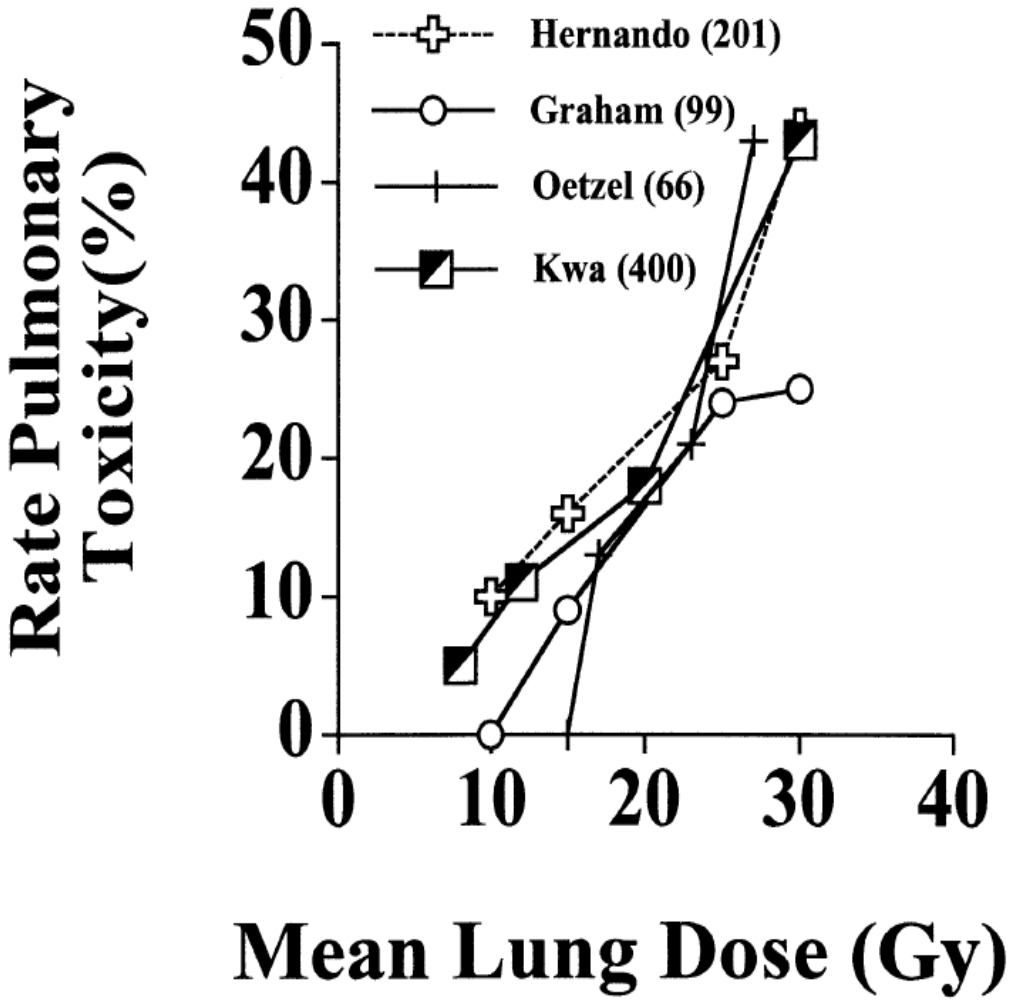
# Aim of radiotherapy




High precision technology

(Radio) Biology

# Dose-volume-effects of normal tissue toxicity

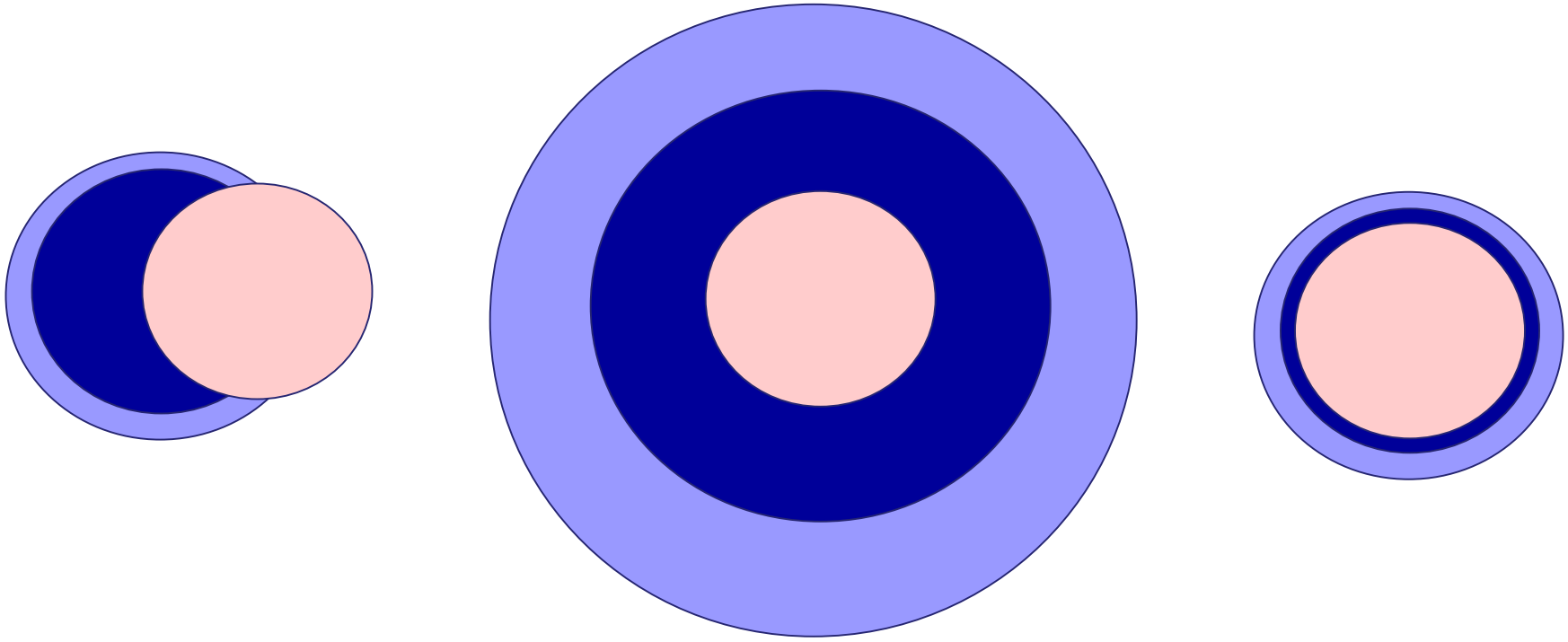


# Concept of precision radiotherapy

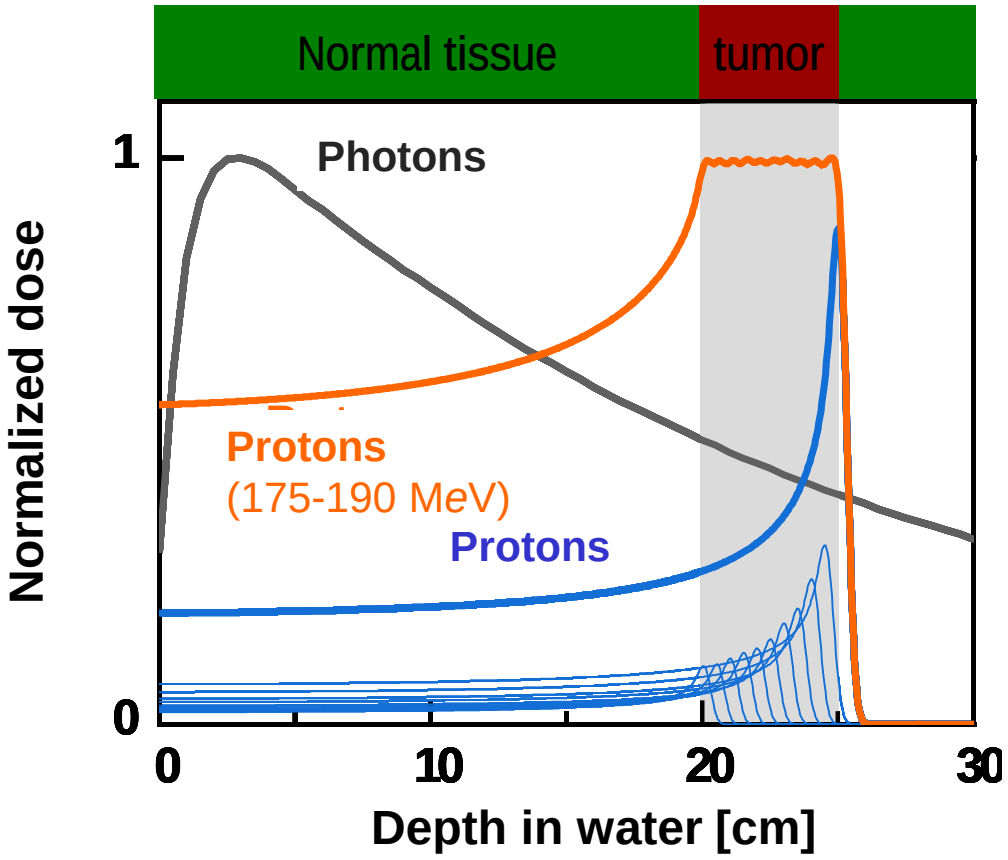
Missing the tumor–
local recurrence

Wide margins–
Increased normal
tissue toxicity

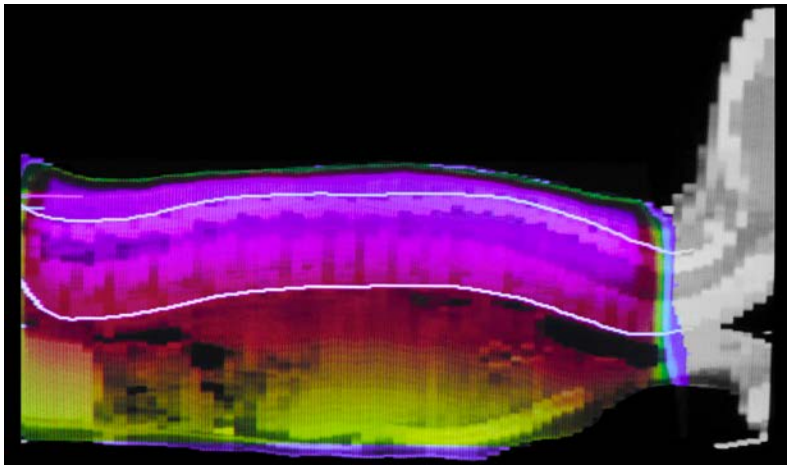
Optimal

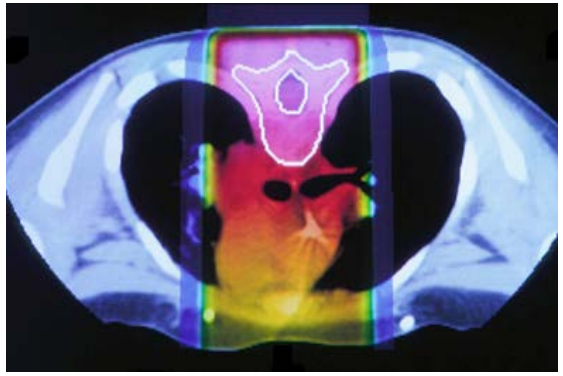


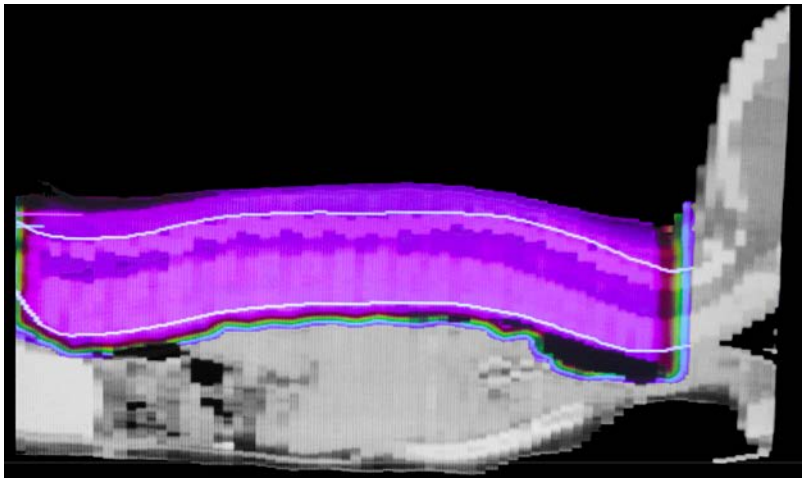
# Physical basis



# Potential of particle therapy

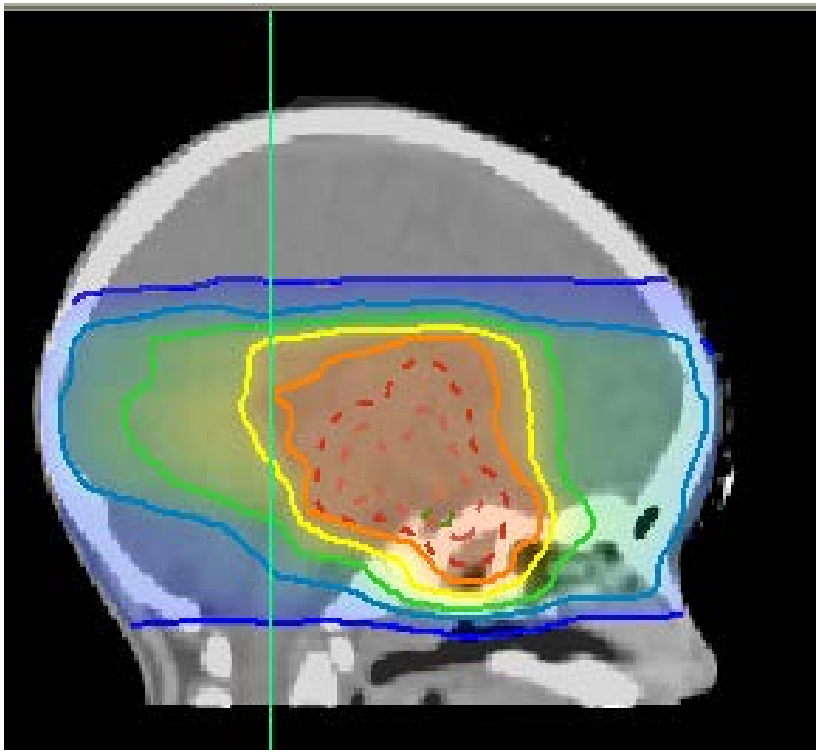






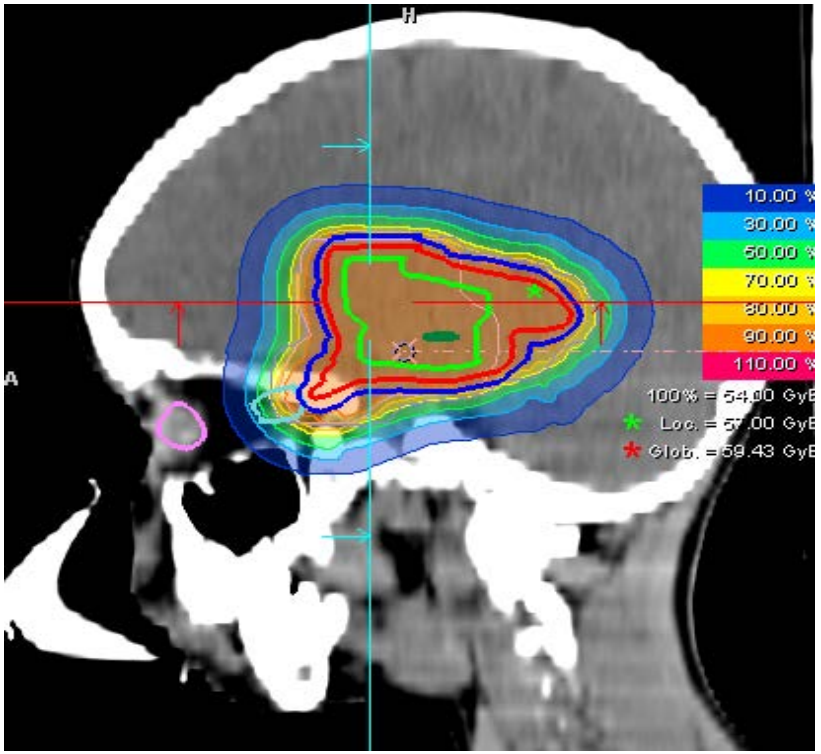
# Potential of particle therapy

Photon-IMRT



Universitätsklinikum Dresden

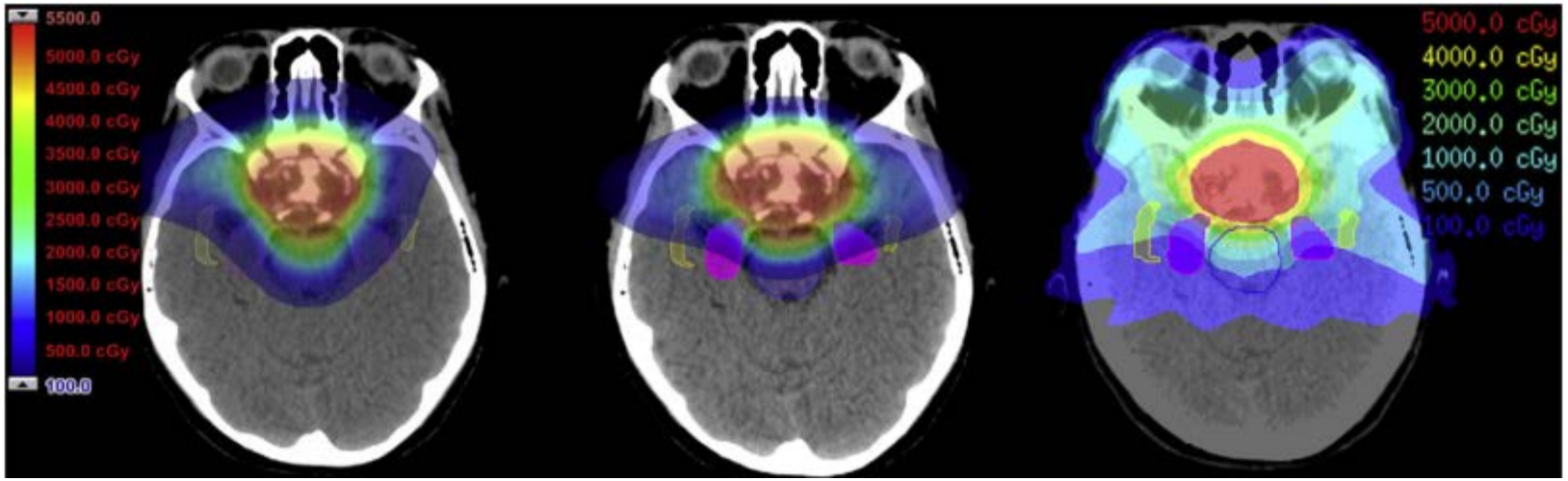
Protons

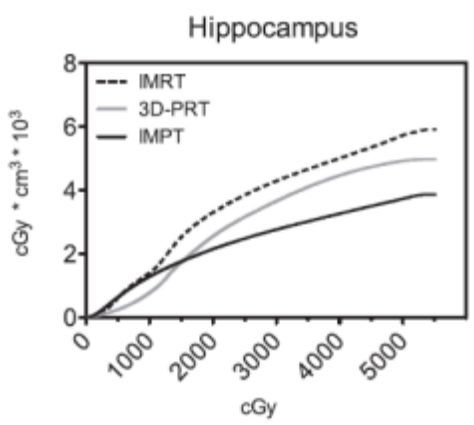


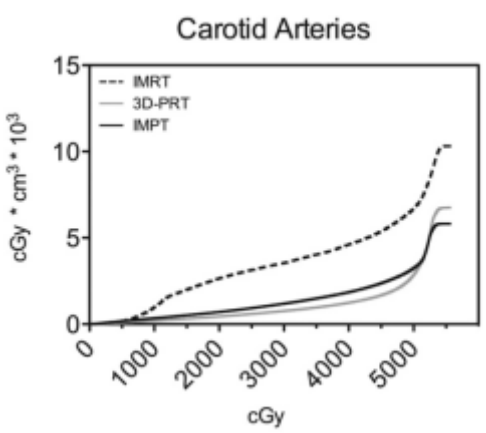

HIT, Heidelberg

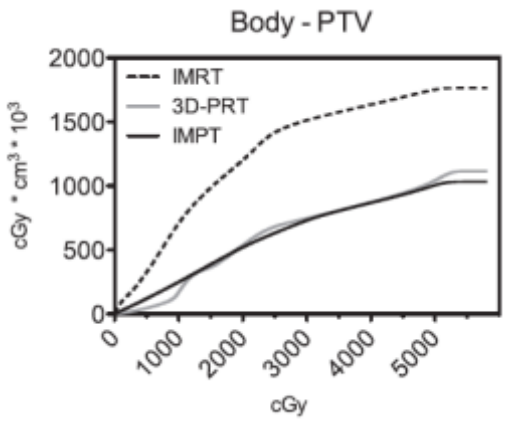
# Potential of particle therapy

3D-PRT IMPT IMRT



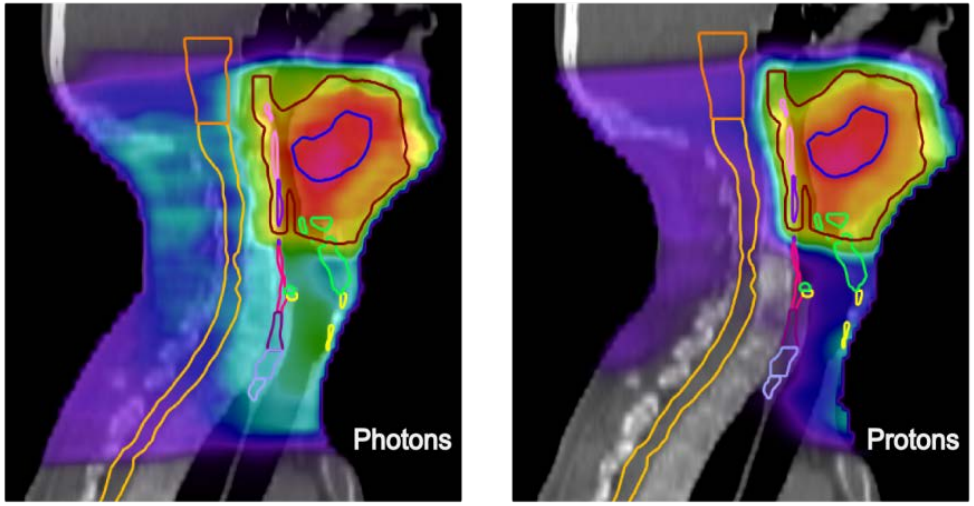



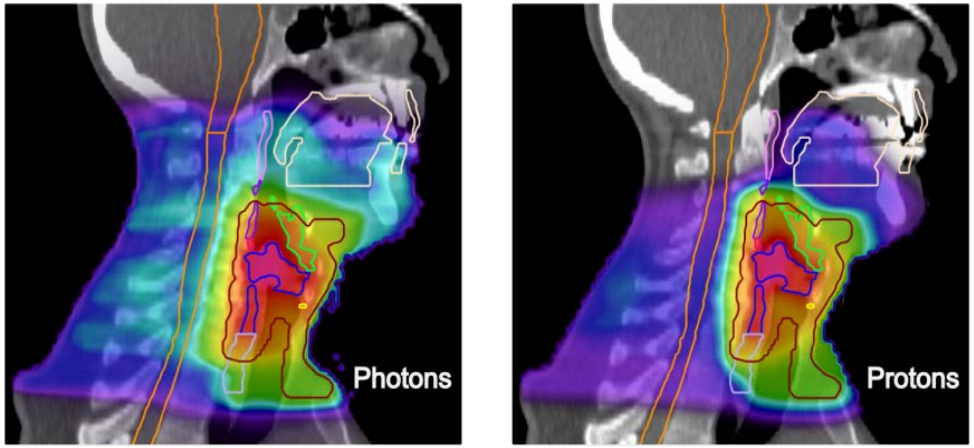

Boehling et al., IJROBP 82, 643-52, 2012

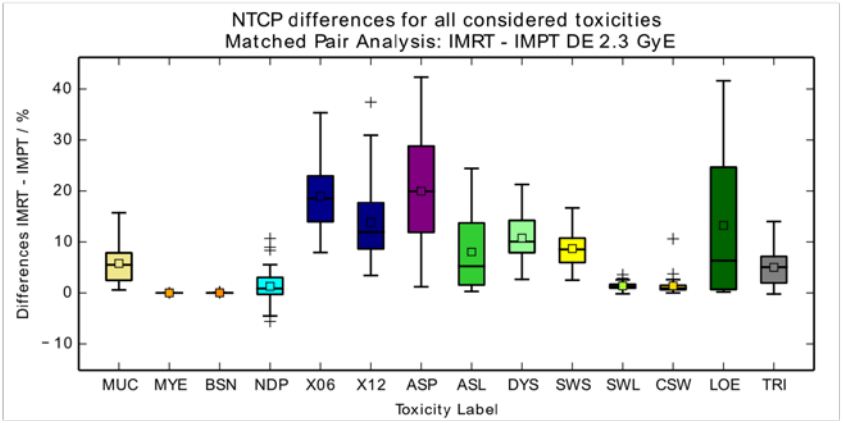
# Potential of particle therapy

(c) Representative patient of group A




Representative patient of group B

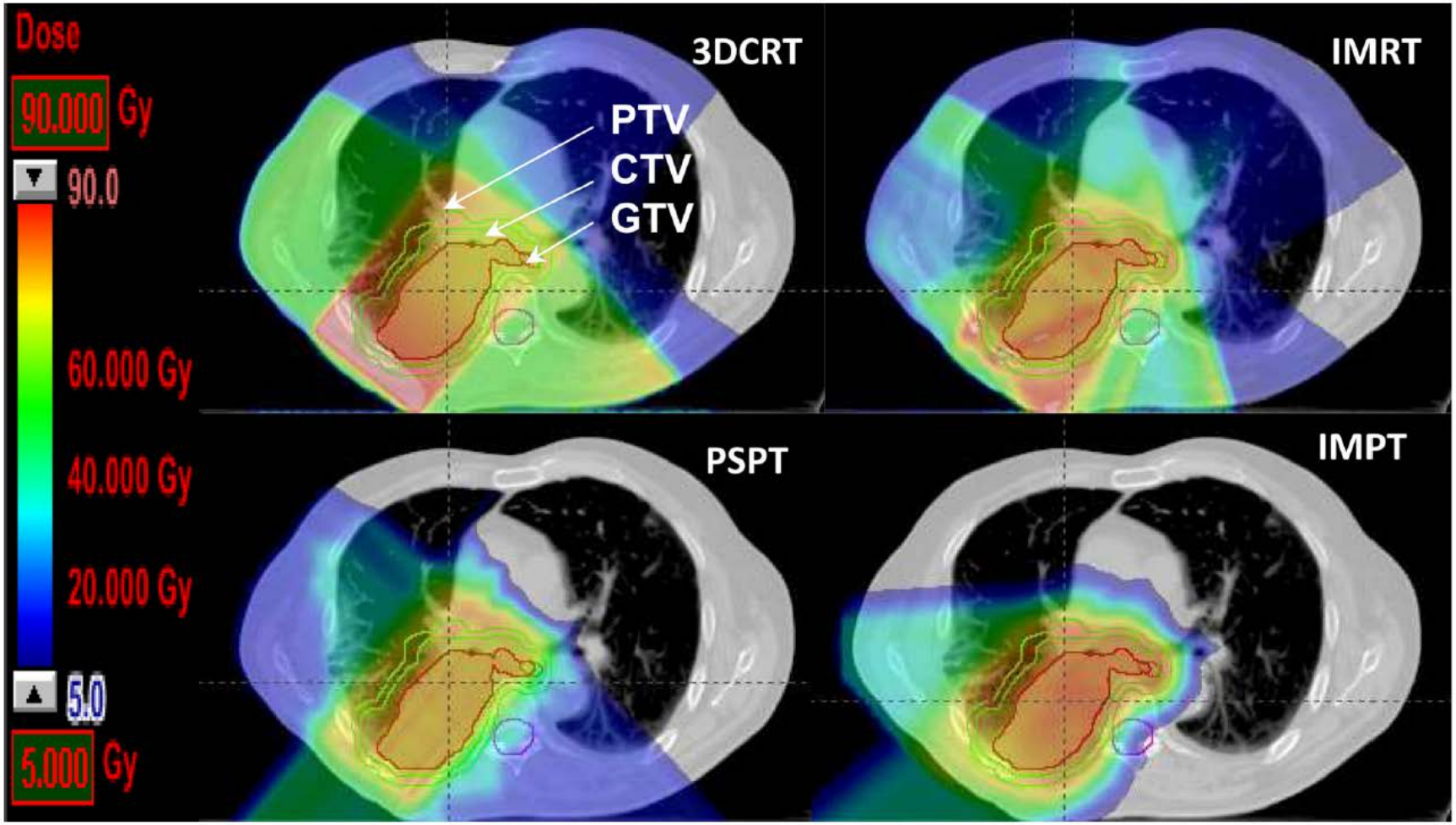



MUC: Oral mucositis
MYE: Myelopathy
BSN: Brain stem necrosis
NDP: Nerve damage of brachial plaxus
X06: Xerostomia after 6 months
X12: Xerostomia after 12 months
ASP: Aspiration based on pharyngeal constrictor muscles
ASL: Aspiration based on larynx
DYS: Physician-rated swallowing dysfunction
SWS: Patient-rated problems swallowing solid food
SWL: Patient-rated problems swallowing liquids
CSW: Patient-rated choking when swallowing
LOE: Laryngeal oedema
TRI: Trismus

Jakobi et al., IJROBP 2015

# Potential of particle therapy




Chang et al., *Semin Radiat Oncol 20(3)*: 171-177, 2010

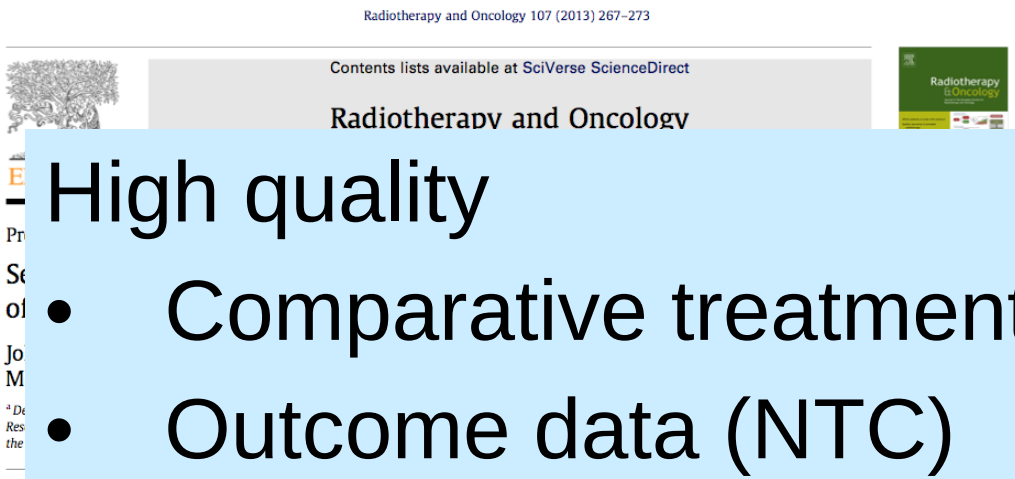
# Potential of particle therapy to explore

We do not know much about the impact of low and intermediate doses and dose volume relationship on normal tissue reactions

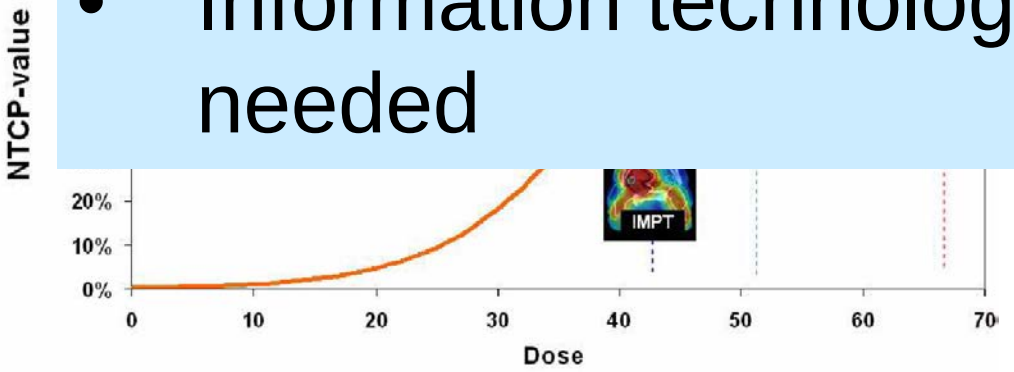
We also do not know a lot about the clinical benefit of partial organ/structure sparing

We therefore can also not make good predictions about the option of dose-escalation

# Clinical evaluation in prospective trials




- High quality
  - Comparative treatment planning
  - Outcome data (NTC)
  - National international networks (numbers)
  - Information technology and modelling needed



# Particle centers in Europe


Advanced planning / under construction

Operating

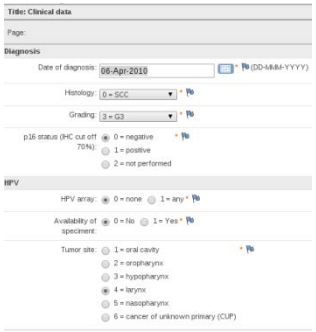
# European Particle Centers Network


| WP | Title | Coordinators |
|---|---|---|
| 1 | **Scoring of normal tissue reactions and tumor response particle/photon RT; endpoint definitions, outcome database** | Hans Langendijk, Mechthild Krause, Roberto Orrechia |
| 2 | **Dose assessment, quality assurance, dummy runs, technology inventory** | Dietmar Georg, Oliver Jäckel, Sairos Safai |
| 3 | **Trials inventory (website); „Towards joint clinical trials“** | Karin Hausterman, Cai Grau, Daniel Zips, Jacques Balosso |
| 4 | **Image Guidance in particle therapy** | Aswin Hoffmann, Alessandra Bolsi |
| 5 | **TPS in particle therapy** | Hakan Nystrom, Tony Lomax |
| 6 | **Radiobiology, RBE** | Bleddyn Jones, Jörg Pawelke, Jan Alsner, Martin Prutschy, Manjit Dosanjh |
| 7 | **Health Economy** | Yolande Lievens, Klaus Nagels |

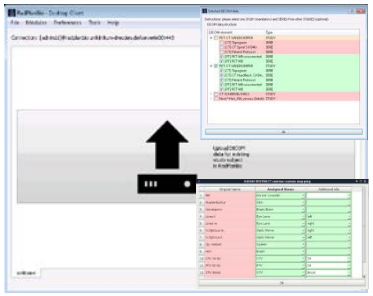
# DOSE PLAN DATA BANKS
# RADPLANBIO (DKTK ROG)

## 1. Clinical data

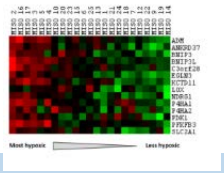
### eCRF




### DICOM Data



### Bio-Data



## 2. Dataexport

- Data sets
- Statistics
-DICOM data port (offline)
-DICOM data port (online = WADO)
- ….

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

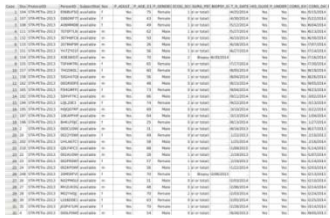
…eating a data exchange strategy for radiotherapy research: Towards federated databases and anonymised public datasets

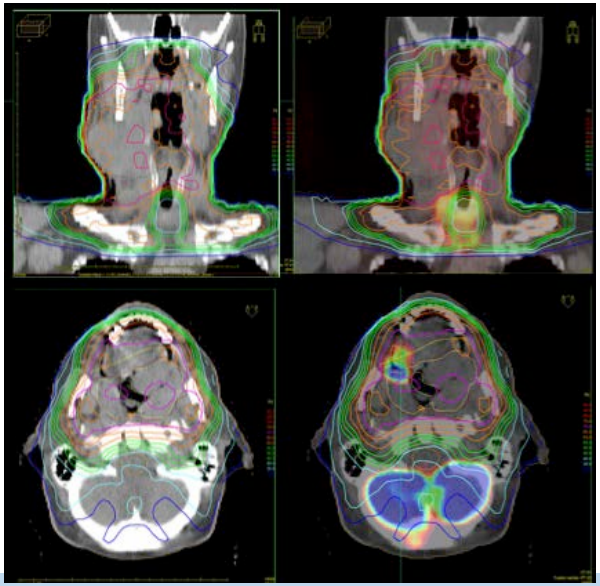
Tomas Skripcak [a,*], Claus Belka [b], Walter Bosch [c], Carsten Brink [d,ae], Thomas Brunner [e], Volker Budach [f], Daniel Büttner [a], Jürgen Debus [g], Andre Dekker [h], Cai Grau [i], Sarah Gulliford [j], Coen Hurkmans [k,l,m], Uwe Just [n], Mechthild Krause [a,n,o,p], Philippe Lambin [h], Johannes A. Langendijk [q], Rolf Lewensohn [r], Armin Lühr [s,o], Philippe Maingon [t,f], Michele Masucci [u], Maximilian Niyazi [b], Philip Poortmans [v], Monique Simon [a], Heinz Schmidberger [w], Emiliano Spezi [x], Martin Stuschke [w], Vincenzo Valentini [x], Marcel Verheij [y], Gillian Whitfield [z], Björn Zackrisson [aa], Daniel Zips [ab,ac,ad], Michael Baumann [a,n,o,p]

[a] German Cancer Consortium (DKTK) Dresden and German Cancer Research Center (DKFZ) Heidelberg; [b] German Cancer Consortium (DKTK) Munich and German Cancer Research Center (DKFZ) Heidelberg, Germany; [c] Dept. of Radiation Oncology, Washington University, St. Louis, MO, USA; [d] Laboratory of Radiation Physics, Odense University Hospital, Odense, Denmark; [e] German Cancer Consortium (DKTK) Freiburg and German Cancer Research Center (DKFZ) Heidelberg; [f] German Cancer Consortium (DKTK) Berlin, German Cancer Research Center (DKFZ) Heidelberg; [g] German Cancer Consortium (DKTK) Heidelberg and German Cancer Research Center (DKFZ) Heidelberg, Germany; [h] Dept. of Radiation Oncology (MAASTRO), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands; [i] CIRRO Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [j] Joint Department of Physics, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK; [k] Dept. of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands; [l] EORTC-Radiation Oncology Group; [m] EORTC-Global Clinical Trial QART Harmonisation Group, Brussels, Belgium; [n] Dept. of Radiation Oncology, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden; [o] OncoRay – National Center for Radiation Research in Oncology, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden and Helmholtz-Zentrum Dresden-Rossendorf; [p] Institute of

## 3. Data analysis

- Advanced (Re) TPS
- Spatially resoluted – dose corrected outcome
- Radiomics
- TCP/NTCP
- Complex models
- trial hypotheses
- secondary analysis
- machine learning
- …





# MOLECULAR STRATIFICATION BY HPV
## (Retrospective, post-OP RCT)

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

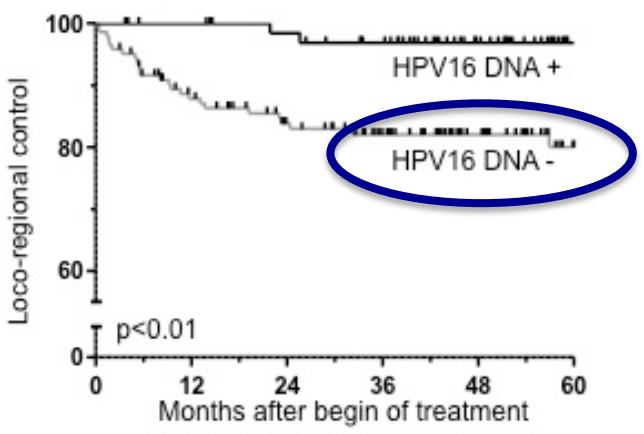
HPV in postoperative RT of oropharynx

### HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: Results from a multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

Fabian Lohaus [a,i,j,1], Annett Linge [a,i,j,1], Inge Tinhofer [b,k], Volker Budach [b,k], Eleni Gkika [c,l], Martin Stuschke [c,l], Panagiotis Balermpas [m], Claus Rödel [d,m], Melanie Avlar [e,n], Anca-Ligia Grosu [e,o], Amir Abdollahi [f,p,q,r], Jürgen Debus [f,p,q,s], Christine Bayer [g], Claus Belka [g,t], Steffi Pigorsch [g,u], Stephanie E. Combs [g,u], David Mönnich [h,v], Daniel Zips [h,v], Cläre von Neubeck [a,j], Gustavo B. Baretton [a,w,x], Steffen Löck [j], Howard D. Thames [z], Mechthild Krause [a,i,j,y], Michael Baumann [a,i,j,y,*], for the DKTK-ROG

***Radiotherapy & Oncology*** 113:317-23, December 2014

post-OP RCT

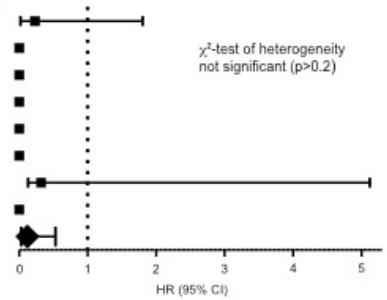



nts at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| HPV16 DNA + | 72 | 69 | 65 | 58 | 43 | 24 |
| HPV16 DNA - | 143 | 116 | 102 | 86 | 60 | 36 |

| Treatment centre | Loco-regional control, HR (95% CI) | | HPV16 DNA positive Events | HPV16 DNA positive Total | HPV16 DNA negative Events | HPV16 DNA negative Total |
|---|---|---|---|---|---|---|
| Centre 1 | 0.23 | (0.02-1.80) | 1 | 12 | 9 | 30 |
| Centre 2 | 0 | * | 0 | 7 | 4 | 20 |
| Centre 3 | 0 | * | 0 | 11 | 3 | 20 |
| Centre 4 | 0 | * | 0 | 10 | 3 | 20 |
| Centre 5 | 0 | * | 0 | 9 | 4 | 23 |
| Centre 6 | 0 | * | 0 | 4 | 2 | 17 |
| Centre 7 | 0.32 | (0.02-5.12) | 1 | 13 | 1 | 4 |
| Centre 8 | 0 | * | 0 | 6 | 1 | 9 |
| **Overall** | **0.13** | **(0.03-0.54)** | **2** | **72** | **27** | **143** |

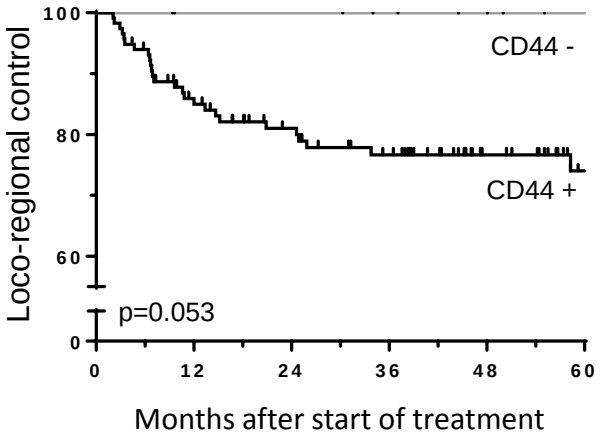
* No CI was calculated in case of no event in the HPV16 DNA positive group



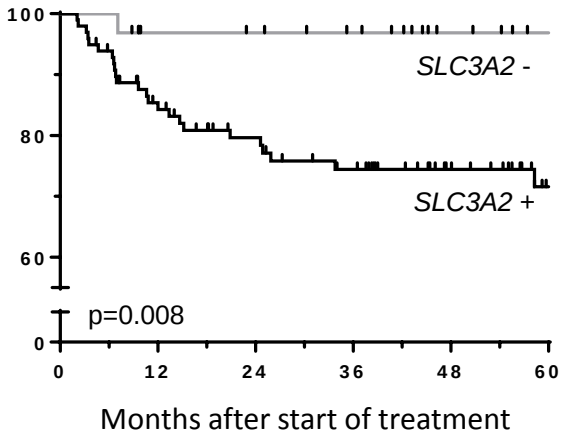
# PROGNOSTIC BIOMARKERS
## CSC marker in HPV-negative tumors

Locally advanced HNSCC, post-OP RCT, n= 143

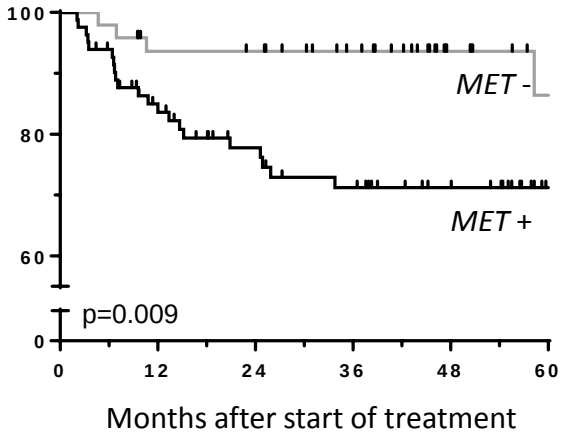
### CD44
IHC




### *SLC3A2* (CD98)
nanostring mRNA

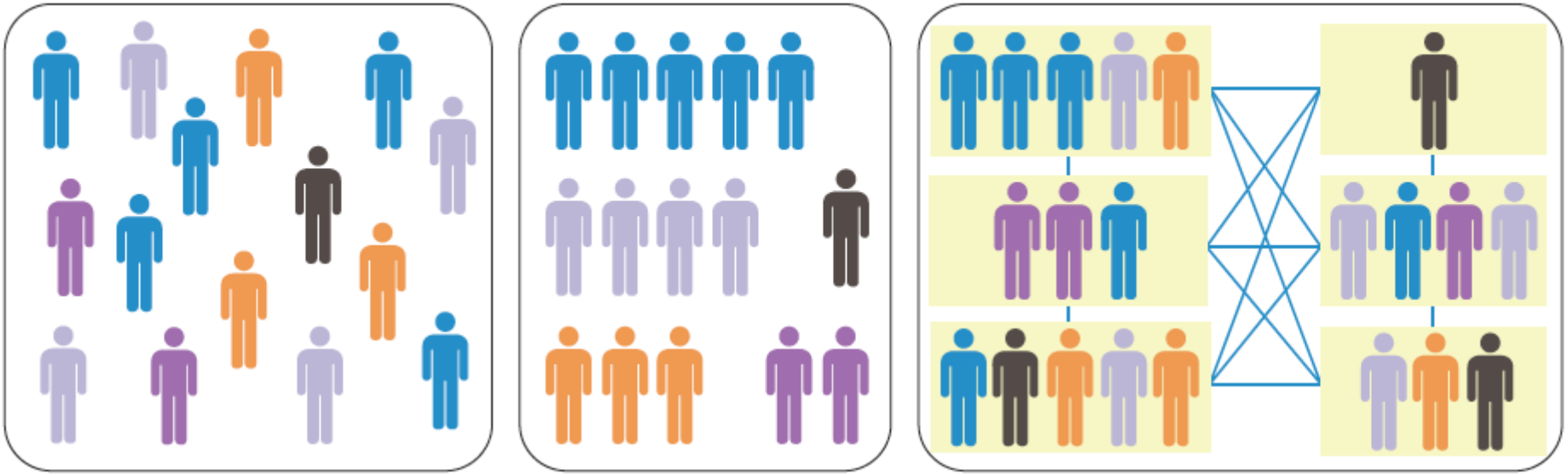



### *MET* (c-MET, MET)
nanostring mRNA




*Linge et al., Clin Cancer Res, epub 2016*

# Radiation oncology in the era of precision medicine



- Patients with same tumour disease and stage have typically received similar treatments
- Large clinical trials possible

- Biomarkers allow stratification into small subgroups
- Trials for treatment individualisation

- Small numbers of patients per subgroup per centre
- Networks necessary
- Novel trial designs needed

Nature Reviews | Cancer

Baumann, Krause, Overgaard, Debus, Bentzen, Daartz, Richter, Zips, Bortfeld, *NRC* in press 2016

# But this is not all…

Motion, anatomic changes during treatment,
biological changes during treatment

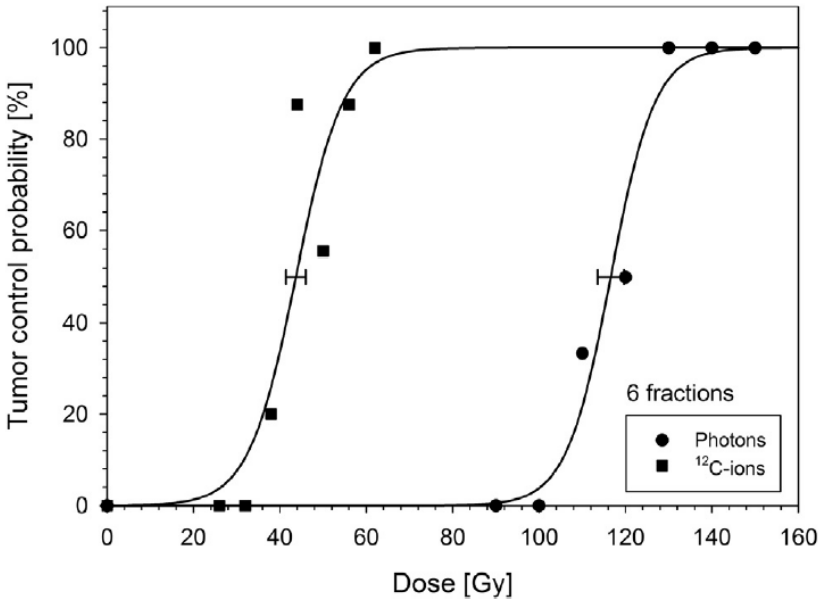
Taking full advantage of particle therapy in terms of physics requires:

- Full image guidance (real time)
- Reduced range uncertainties (real time beam imaging)
- In vivo dosimetry
- Highest level treatment planning
- Adaptive algorithms incluing all items above
- Very rapid and exact dose delivery (repaiting, tracking)
- ....

# But this is not all…

## Lung, Mice, 200 MV P+

| Time after irradiation | Number of fractions | DL50/Gy $^{60}$Co | DL50/Gy Protons | RBE* |
|---|---|---|---|---|
| 180 days | 1 | 12.0 (10.8–13.1) | 11.5 (10.3–12.7) | 1.04 |
| | 3 | 17.9 (15.2–20.0) | 16.4 (13.8–18.5) | 1.09 |
| | 10 | 27.7 (19.8–31.1) | 32.2 (28.0–46.3) | 0.86 |
| 210 days | 1 | 10.9 (9.3–12.2) | 9.1 (7.3–10.4) | 1.20 |
| | 3 | 16.3 (13.2–18.4) | 15.2 (12.4–17.3) | 1.07 |
| | 10 | 26.1 (21.0–19.1) | 27.2 (24.2–31.0) | 0.96 |
| 240 days | 1 | 9.6 (7.7–11.1) | 7.3 (4.8–8.9) | 1.33 |
| | 3 | 14.2 (9.2–16.7) | 13.8 (9.7–16.2) | 1.02 |
| | 10 | 23.7 (11.7–27.7) | 22.5 (14.2–26.3) | 1.05 |
| 270 days | 1 | 8.6 (6.4–10.1) | 5.5 (2.5–7.4) | 1.55 |
| | 3 | 12.4 (3.7–15.7) | 11.7 (3.8–14.8) | 1.06 |
| | 10 | 21.1 (7.8–25.4) | 20.6 (11.4–24.1) | 1.02 |




| Study | RBE ± SE (90% CI) |
|---|---|
| 1 Fraction* | 2.30 ± 0.08 (2.17-2.44) |
| 2 Fractions* | 2.39 ± 0.16 (2.15-2.68) |
| 6 Fractions | 2.67 ± 0.15 (2.43-2.94) |

# But this is not all…

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Biology based treatment stratification
and treatment planning requires:

- RBE assessment for a large range of beam qualities, energies and positions on the depth curve and beyond
- RBE assessment for a large range of clinical relevant cell systems and organ systems
- In the context of combinations used in patients
- Under knowledge of emerging molecular biomarkers and functional imaging
- Mechanistic understanding
- Systems biology approaches for development of comprehensive models for patient use

Dose (Gy)

# Needs of medical community

- High quality clinical data for high level evidence
- Health economic assessments;
  global epidemiological assessments
- Improved clinical research structures, including IT
- Radiobiological core data (e.g. RBE)
- Integration into precision medicine era
  (e.g. biomarkers, combined modality effects)
- Full image guided, range uncertainty reduced,
  adaptive RT equipment
- Lower cost
- ….