HIRO
Heidelberger Institut für Radioonkologie
Nationales Zentrum für Strahlenforschung in der Onkologie Heidelberg

RadioOnkologie
Behandeln
Forschen
Lehren

HIT
Heidelberger Ionenstrahl-Therapiezentrum

UniversitätsKlinikum Heidelberg

Jürgen Debus

indications and challenges of clinical trials in particle therapy


1946 - Robert D. Wilson publishes the concept of Proton-based therapy

Radiological Use of Fast Protons

ROBERT R. WILSON
Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been -pplied to medical problems. This has, in -e part, been due to the very short -ation in tissue of protons, deut- -particles from prese- -r-energy mach- - how-

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate inter- -ly a strictly localized region -

Radiology 47: 487-491, 1946

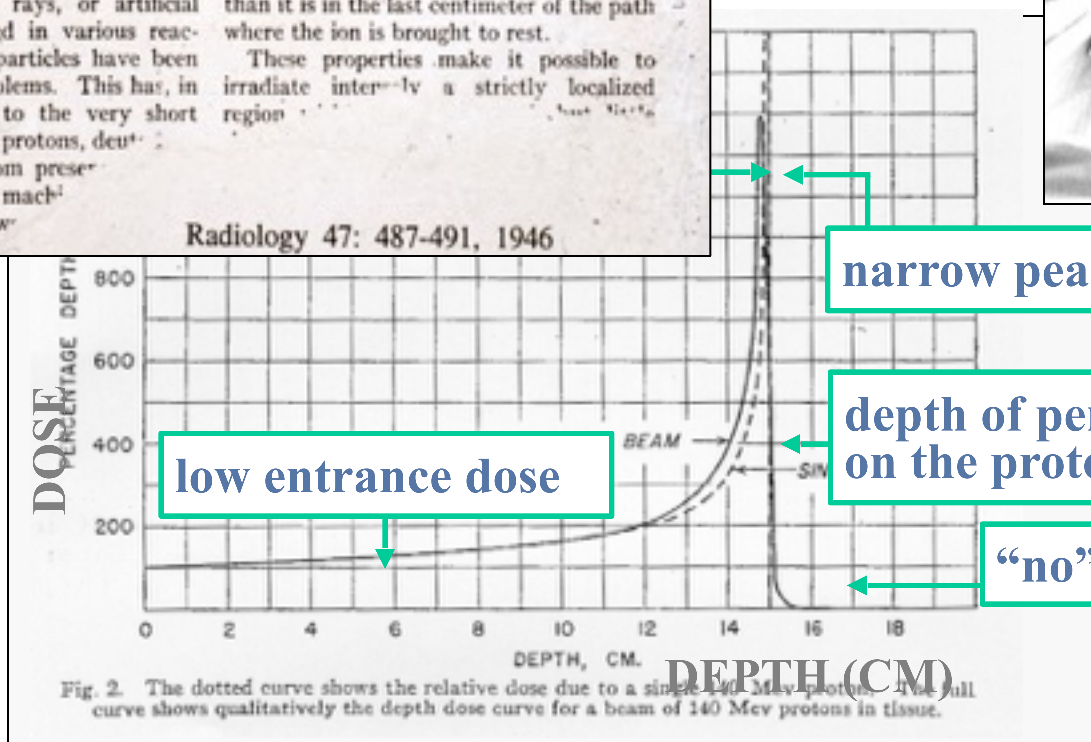
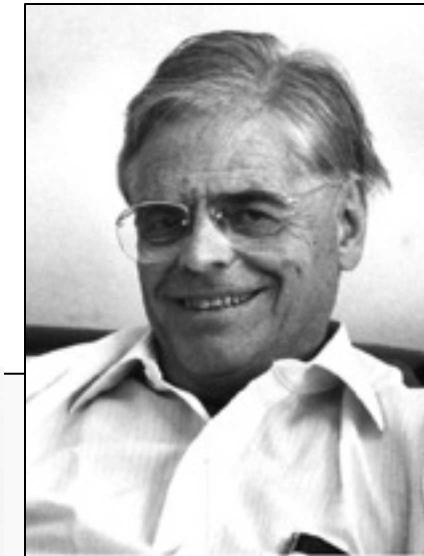


Fig. 2. The dotted curve shows the relative dose due to a single 140 Mev proton. The full curve shows qualitatively the depth dose curve for a beam of 140 Mev protons in tissue.



History of Protons

Radiological Use of Fast Protons in *1946*

"These properties (of protons, as described before) make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose."

"One naturally asks what are the advantages of fast protons over high-energy electrons such as those from a betatron. This question can be answered only by medical workers, and the answers will probably be different for different kinds and sizes of tumors."

Robert Wilson, 1946

27 years prior to the introduction of individually shaped blocks

First proton treatments at Harvard Cyclotron / Mass. General Hospital

HCL-MGH pioneers of proton radiation therapy

The first large field treatment with protons at the Harvard Cyclotron in ***1973***, for a pediatric pelvic rhabdo-myosarcoma.
The patient died several years later from probably a marginal tumor progression or relapse

The second large field treatment, for a chondrosarcoma of the base of skull.
The patient is alive and active, though diagnosed with local relapse more than 30 years after proton radiation therapy

Slides courtesy of M. Goitein

Protons and carbon ions

Protons

Universität Zürich

The future role of Proton Radiotherapy in the framework of modern Photon-RT

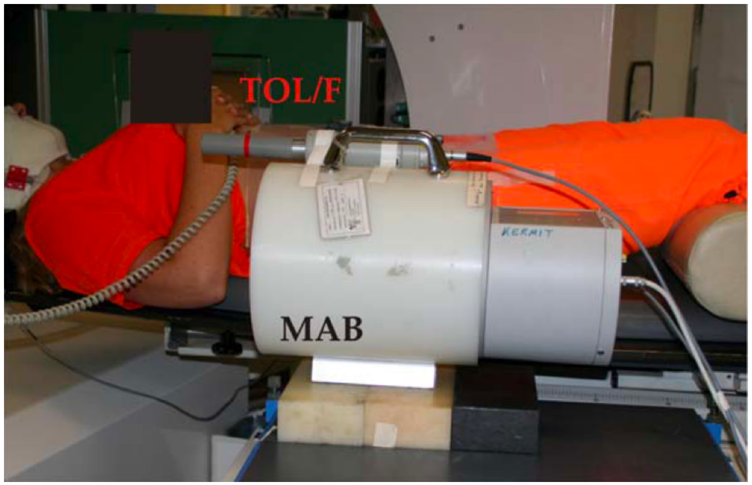
The 2 (historic) legs of Proton Radiotherapy

High-Dose Target coverage

Reduction of low-moderate dose volume

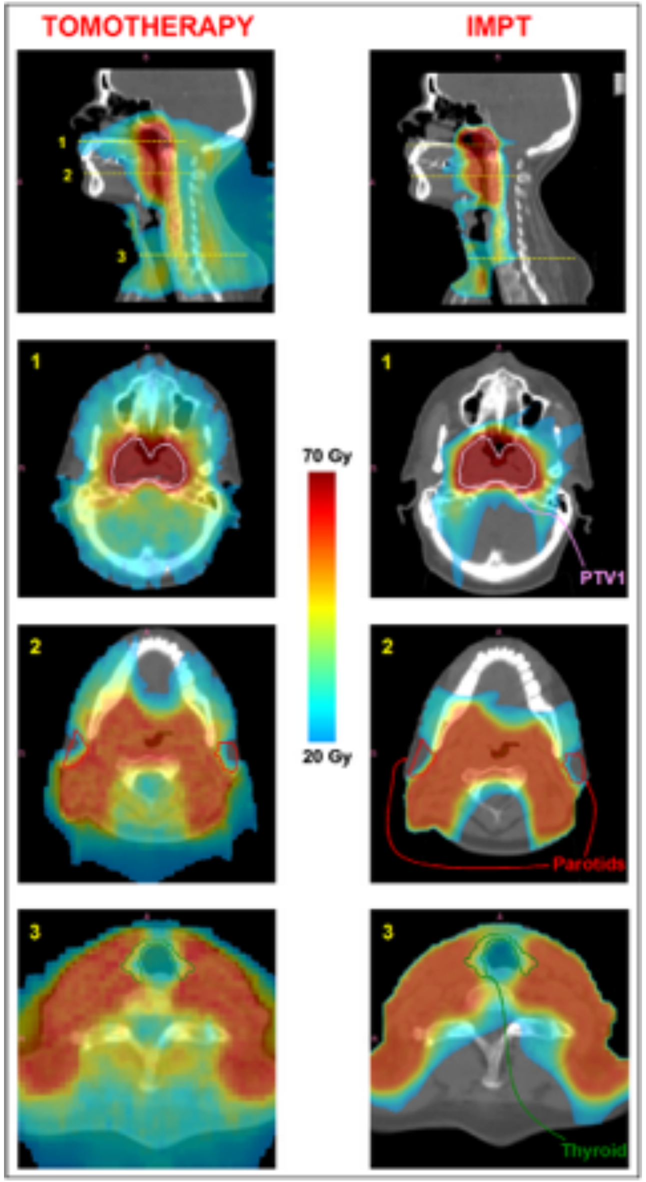
Eugen Hug, 2011

Carbon Radiotherapy In A Pregnant Patient: low scattered dose to the fetus

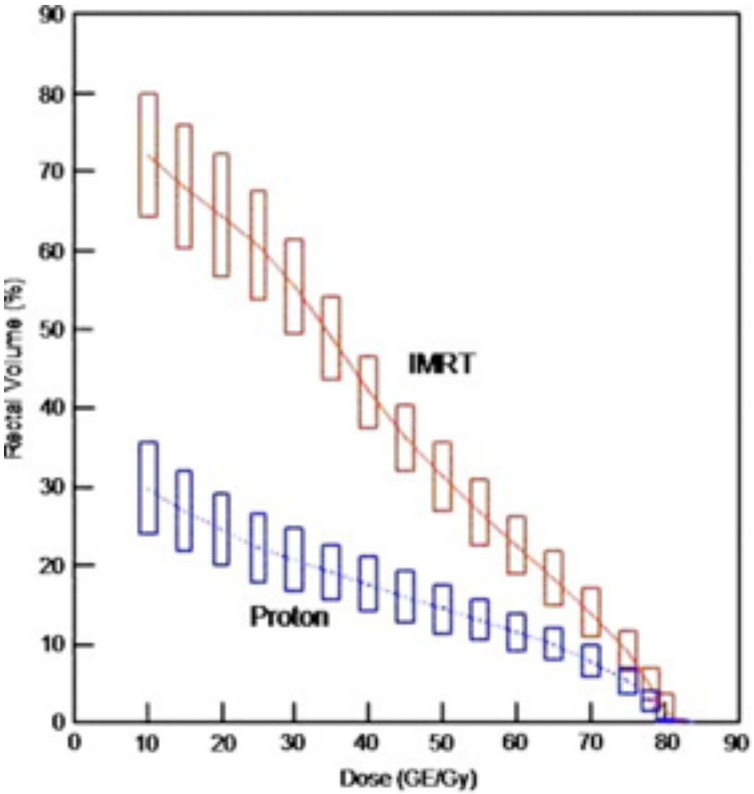


	photon dose (µSv/fraction)	neutron dose (µSv/fraction)	Number of fractions	Total dose (µSv)
Normal field	3.0 *	1.4	15	66
Boost field	2.2 **	1.0	5	16
Total treatment			20	**82**

Muenter MW, Fertil Steril 2010



L. WIDESOTT, M. SCHWARZ.
IJROBP 72(2):589, Oct. 2008

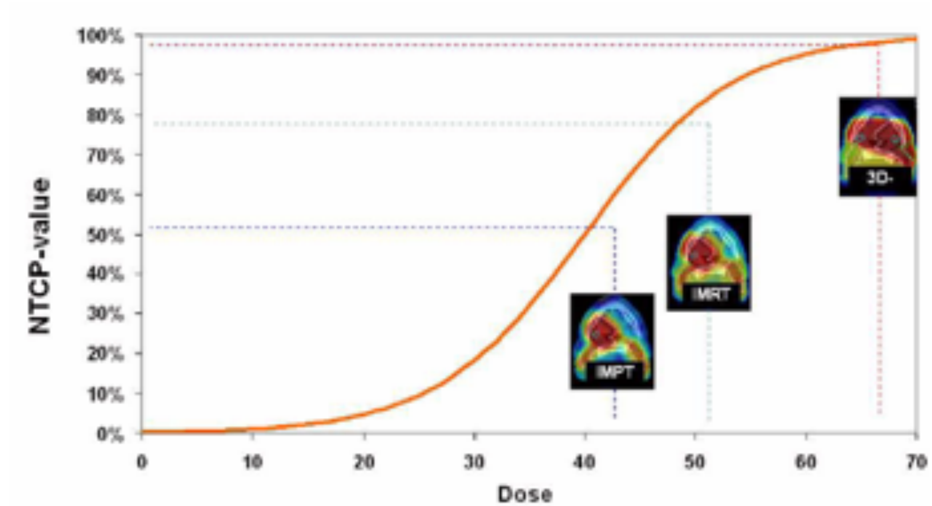


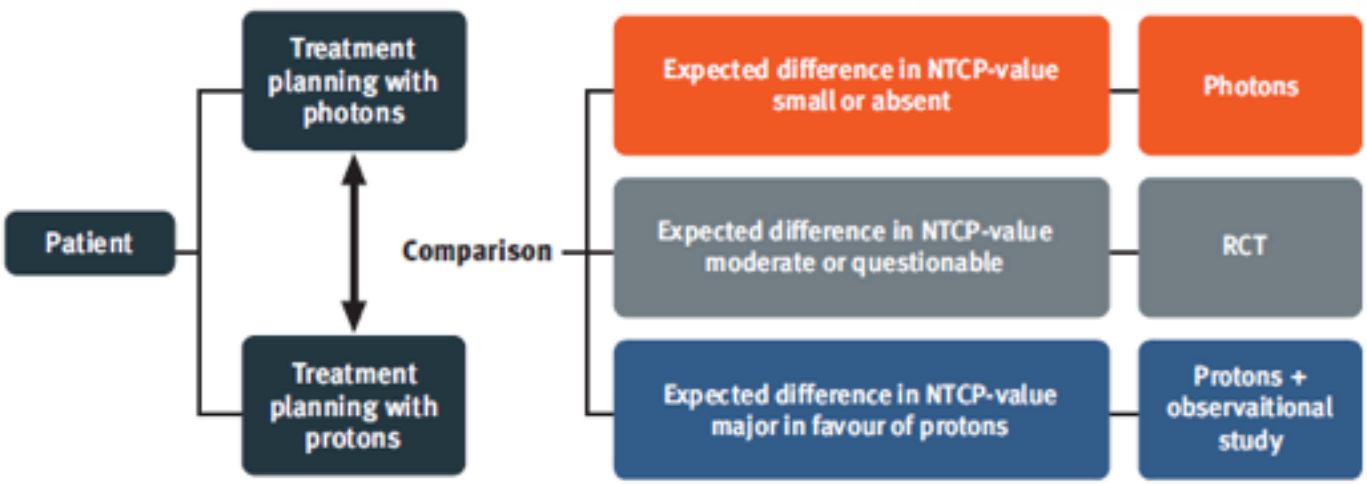
Combined rectal dose–volume curves for proton therapy and intensity-modulated radiotherapy (IMRT) (n = 20 plans)

Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer
Vargas et al, IJROBP 2008, 70(3):744

Protocol Strategies: Comparative Photon / Proton planning

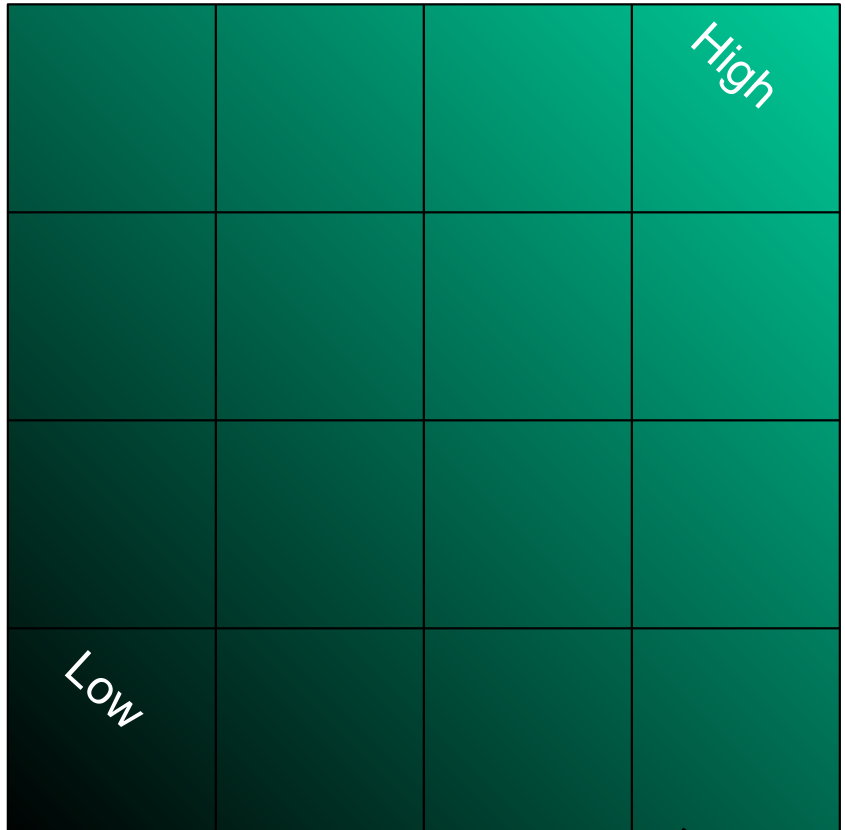
EU-ALLEGRO
Consortium





Thanks to J. Langendijk; J. Overgaard/ C. Grau

NCI: Indices of clinical relevance



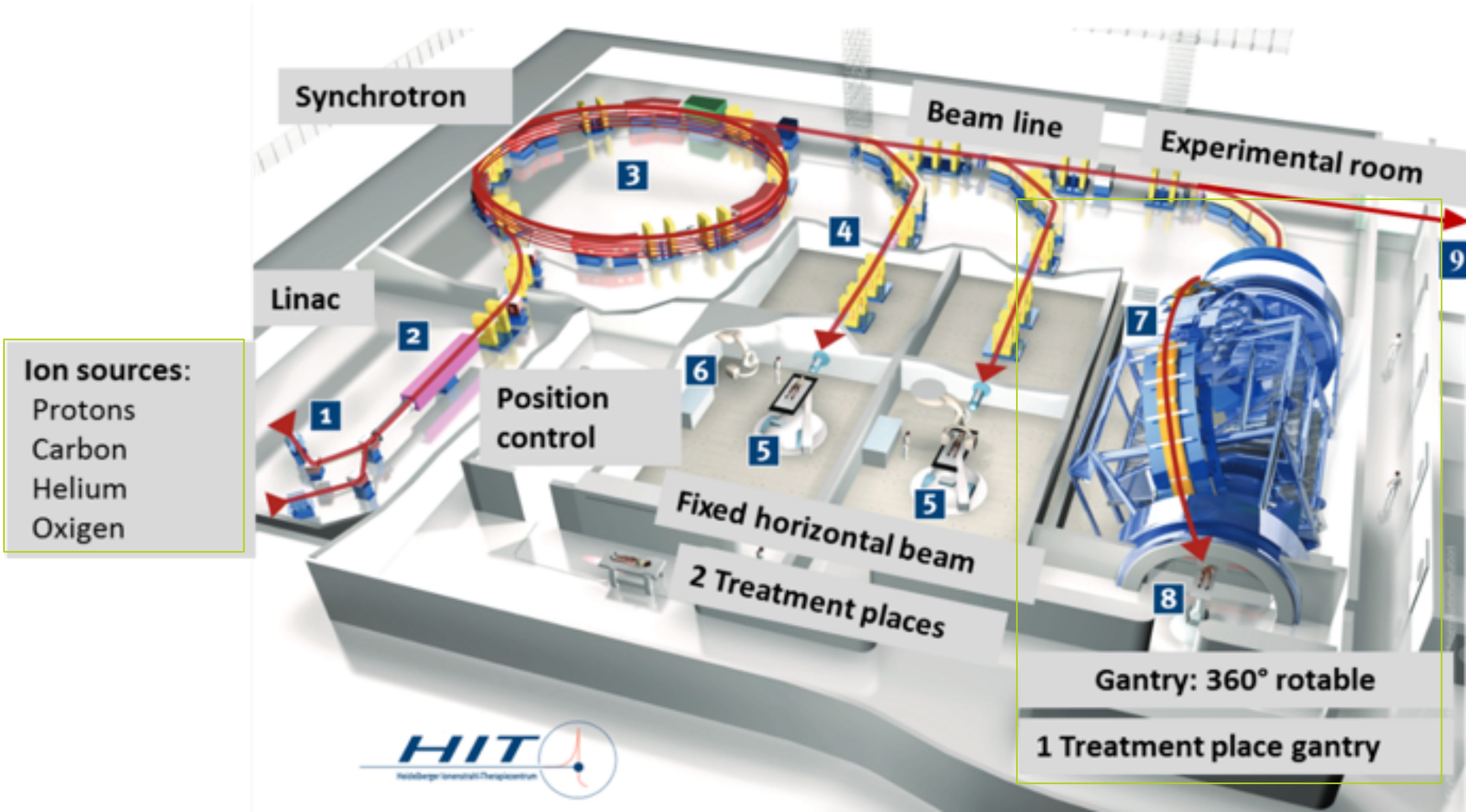
Caveat:

„Local Tumor Control“ only a „low-strength“ endpoint

HIT: Heidelberg Ion Therapy Center

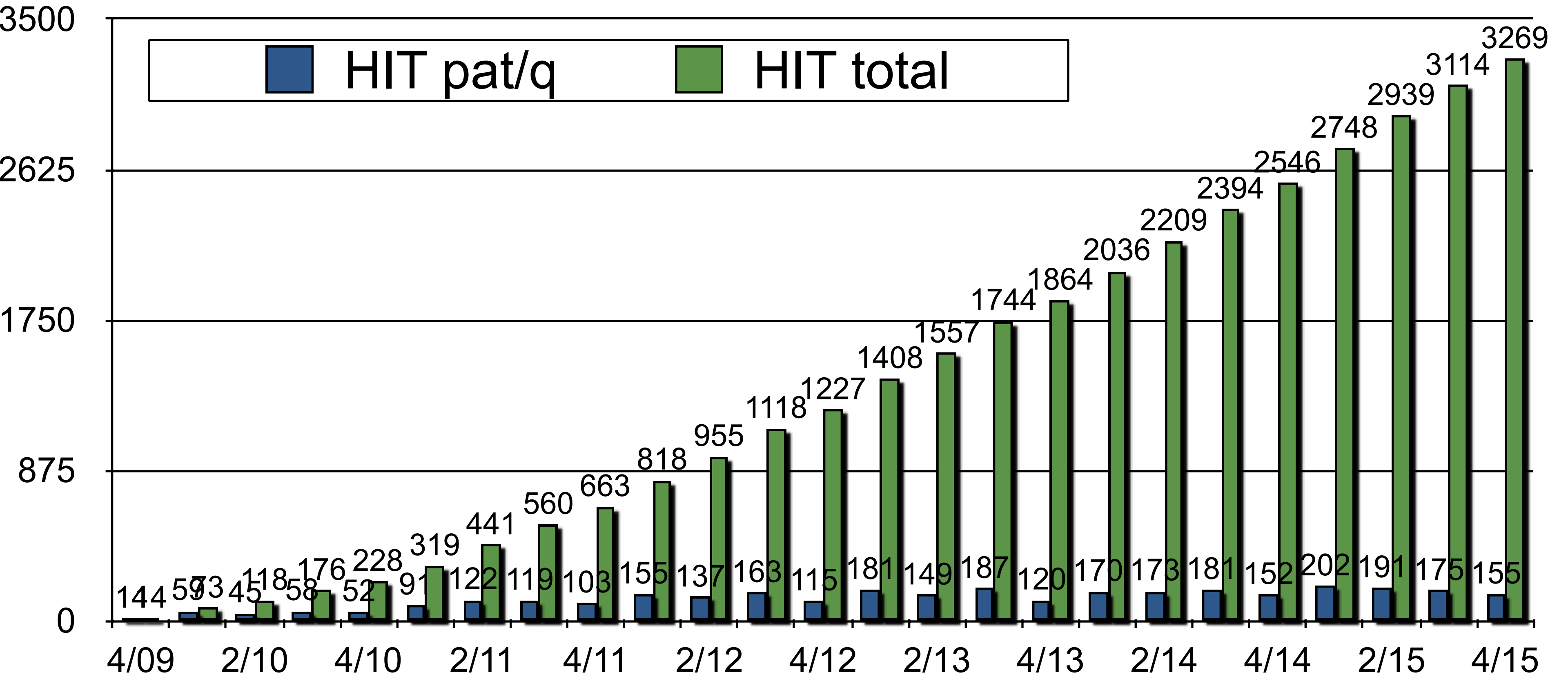
- HIT is Europe's first combined treatment facility using **protons and heavy ions** for radiation therapy.

- HIT is the world's first heavy ion treatment facility with a **360° rotating beam delivery** system (gantry).



Patients @ HIT / MIT

Protonen- und Schwerionentherapi seit 11/2009, ~3300 patients treated



2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
14	**214**	**435**	**570**	**637**	**676**	**723 (HIT)**

MIT: Marburg Ionbeam Therapy center

MIT
Marburger Ionenstrahl-Therapiezentrum

Operation started in 10/ 2015

MIT: Marburg Ionbeam Therapy center

- 3 treatment places at horizontal beam -1 treatment place at 45° beam
- clinical operation since 10/2015: 106 patients treated

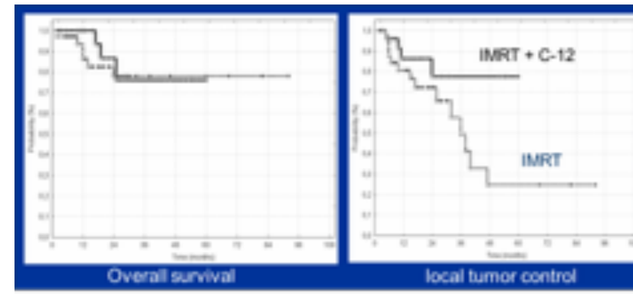
Clinical trials @ HIT+MIT

- SB chordomas: H1 vs. C12 recruiting (71/319)
- SB chondrosarcomas: H1 vs. C12 recruiting (49/154)
- CLEOPATRA (H1 vs. C12 boost RT; prim. glioblastoma) recruiting (97/150)
- CINDERELLA (C12 recurrent gliobastoma) recruiting (56/56 Phase 1)
- MARCIE (C12 boost RT, meningeomas grade 2) recruiting (15/40)
- **COSMIC** (C12 boost RT; salivary glands) published
- TPF-C HIT (C12 boost RT; head&neck) closed
- IMRT HIT-SNT (C12 boost RT; sinu-nasal cancer) recruiting (9/36)
- ACCEPT (C12 boost RT + Erbitux for ACC) recruiting (17/49)
- PROMETHEUS (C12 for HCC) recruiting (11/36)
- **OSCAR** (H1 + C12 boost; inoperable osteosarkoma) recruiting (15/20)
- PANDORA (C12 for recurrent rectal carcinoma) recruiting (11/51)
- IPI (C12/H1 for prostate cancer) f/u phase
- ISAC (C12/H1 for sacral chordoma) recruiting (35/100)
- PROLOG (hypofract. H1 for prostate cancer recurrence) f/u phase
- **INKA** (neoadj. C12 for inop. sulcus superior tumors) recruiting (5/20)
- KOLOG (hypofract. C12 for Prostate cancer recurrence) recruiting (8/40)

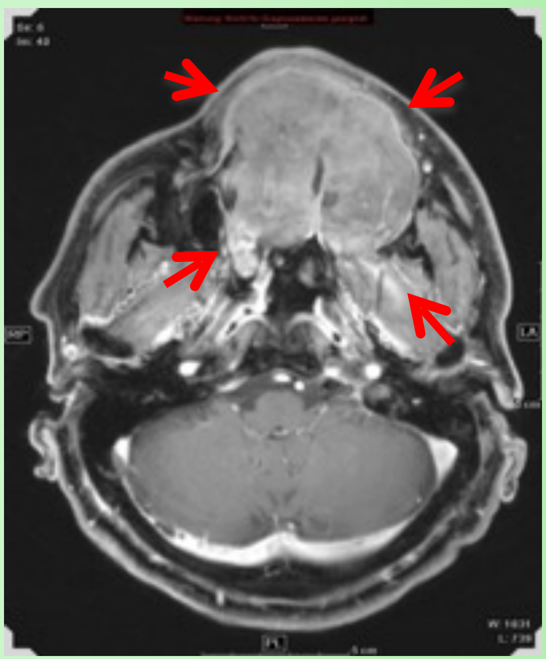
COSMIC- trial

Combined therapy of **m**alignant **s**alivary gland tu**m**ors with **I**MRT and **c**arbon ions

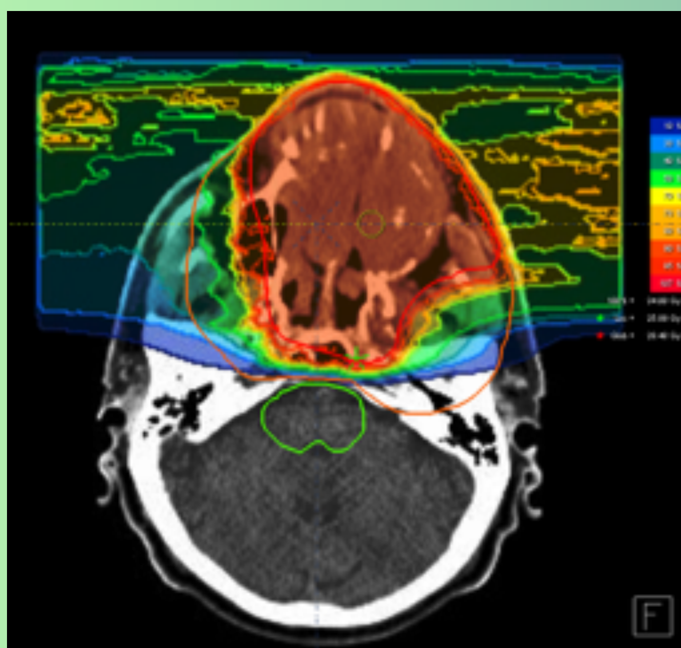
- Phase II feasibility study
  - ➢ No dose limitting acute toxicity
  - ➢ Late Toxicität G > CTC grade 2 < 5%



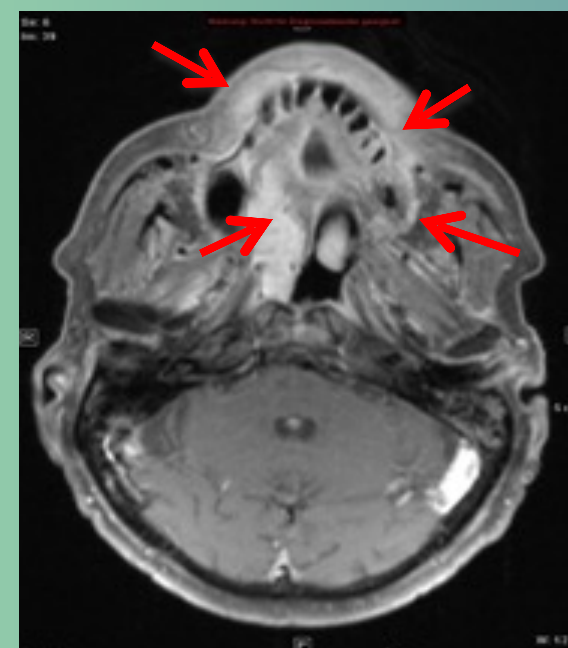
Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44



Pre-treatment situation



Treatment planning
C-12 boost

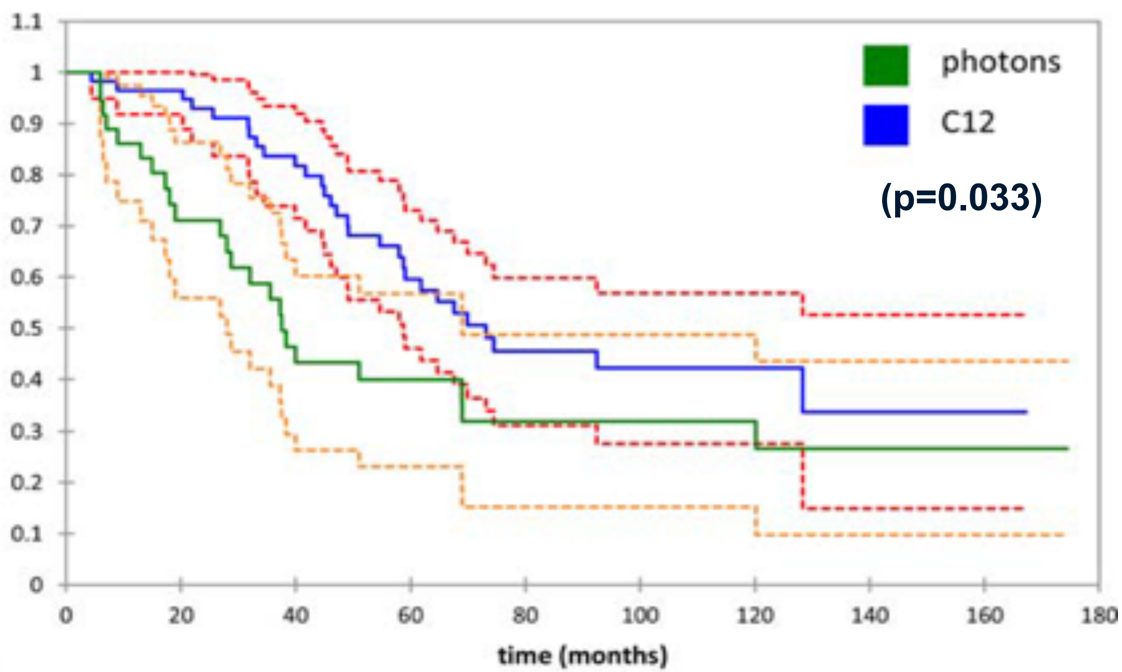


6 weeks post RT

COSMIC- trial

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma

Local control



numbers at risk:

C12:	58	55	43	28	17	11	8	5	2
photons:	37	24	15	12	9	7	7	5	2

Cancer

Original Article

Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

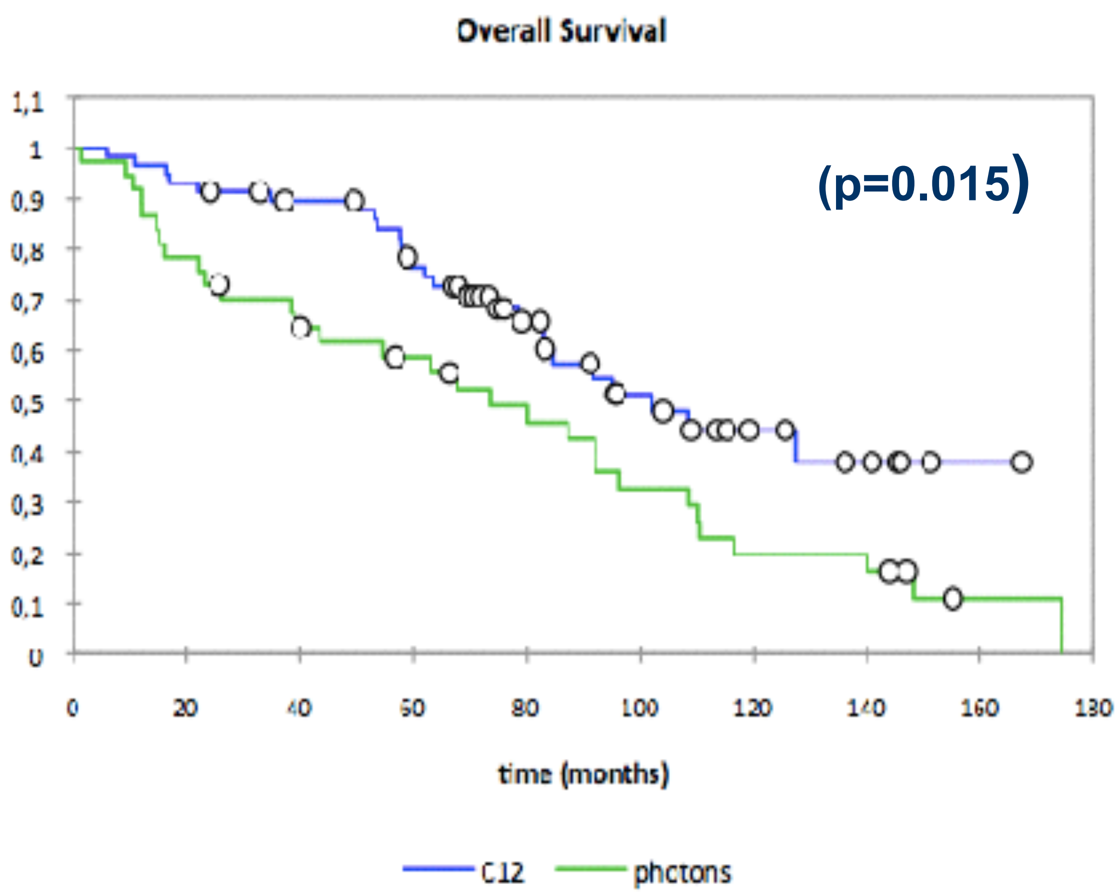
Alexandra D. Jensen MD, MSc, Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W Münter MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

First published: 4 June 2015 Full publication history
DOI: 10.1002/cncr.29443 View/save citation
Cited by: 0 articles Check for new citations

Jensen et al. 2015, Cancer

COSMIC- trial

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma



Cancer

Original Article

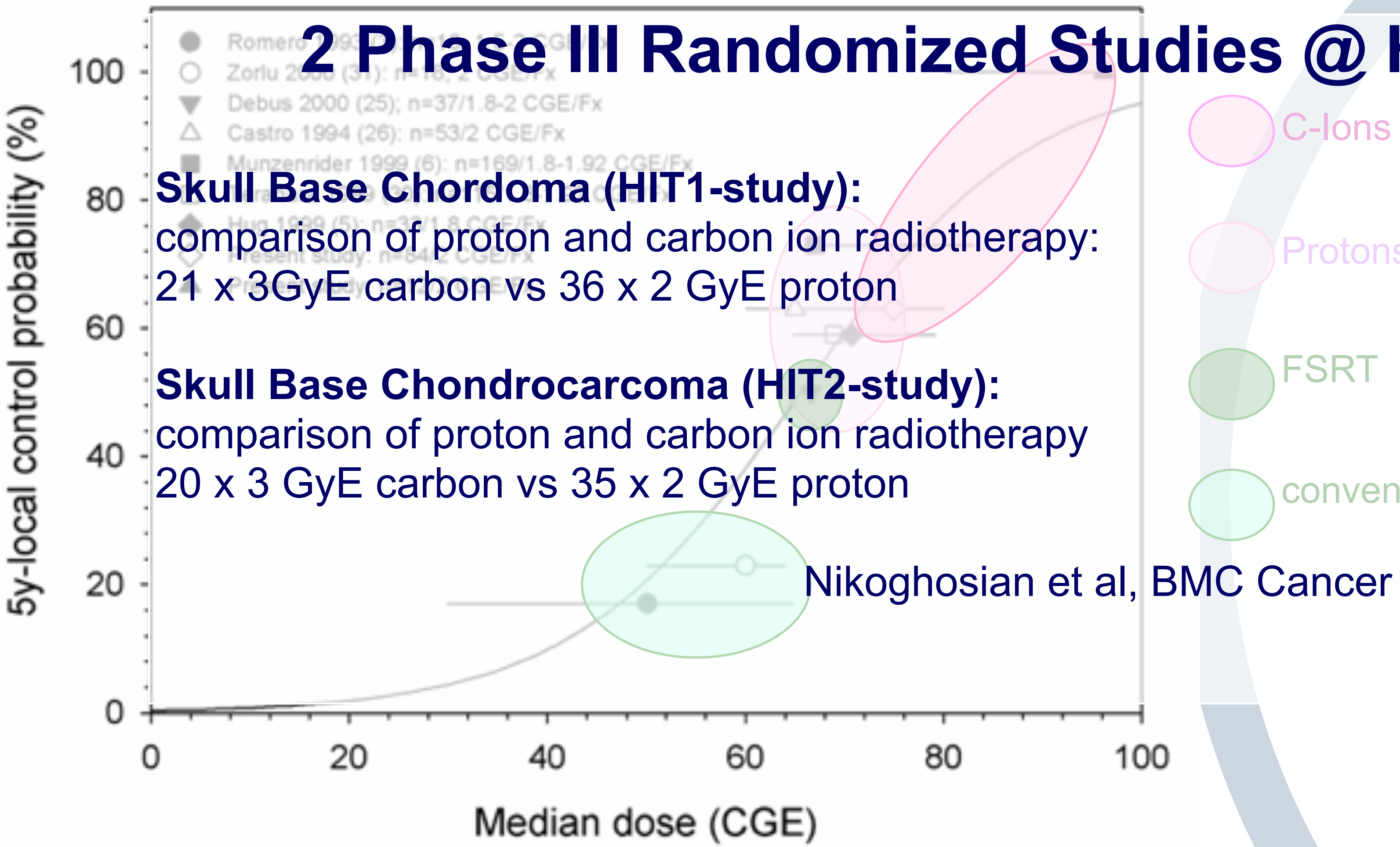
Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

Alexandra D. Jensen MD, MSc, Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W Münter MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

First published: 4 June 2015 Full publication history
DOI: 10.1002/cncr.29443 View/save citation
Cited by: 0 articles Check for new citations

Jensen et al. 2015, Cancer

Hypothesis: Dose Response Relationship Radiotherapy of Skull Base Chordomas



2 Phase III Randomized Studies @ HIT:

Skull Base Chordoma (HIT1-study):
comparison of proton and carbon ion radiotherapy:
21 x 3GyE carbon vs 36 x 2 GyE proton

Skull Base Chondrocarcoma (HIT2-study):
comparison of proton and carbon ion radiotherapy
20 x 3 GyE carbon vs 35 x 2 GyE proton

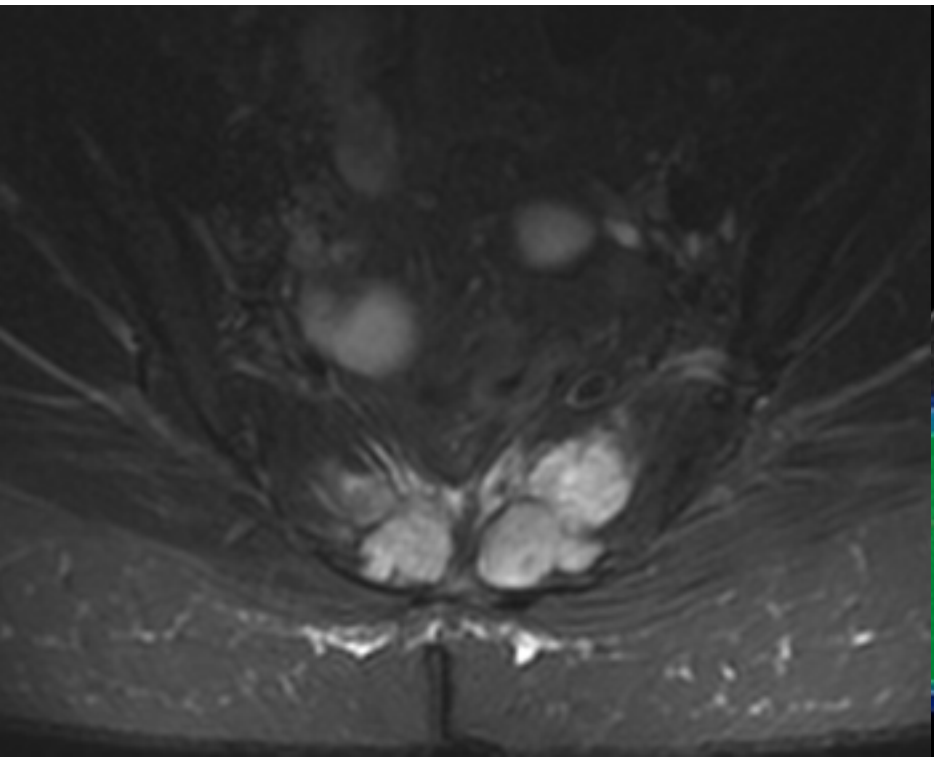
Nikoghosian et al, BMC Cancer 2010, 10:606

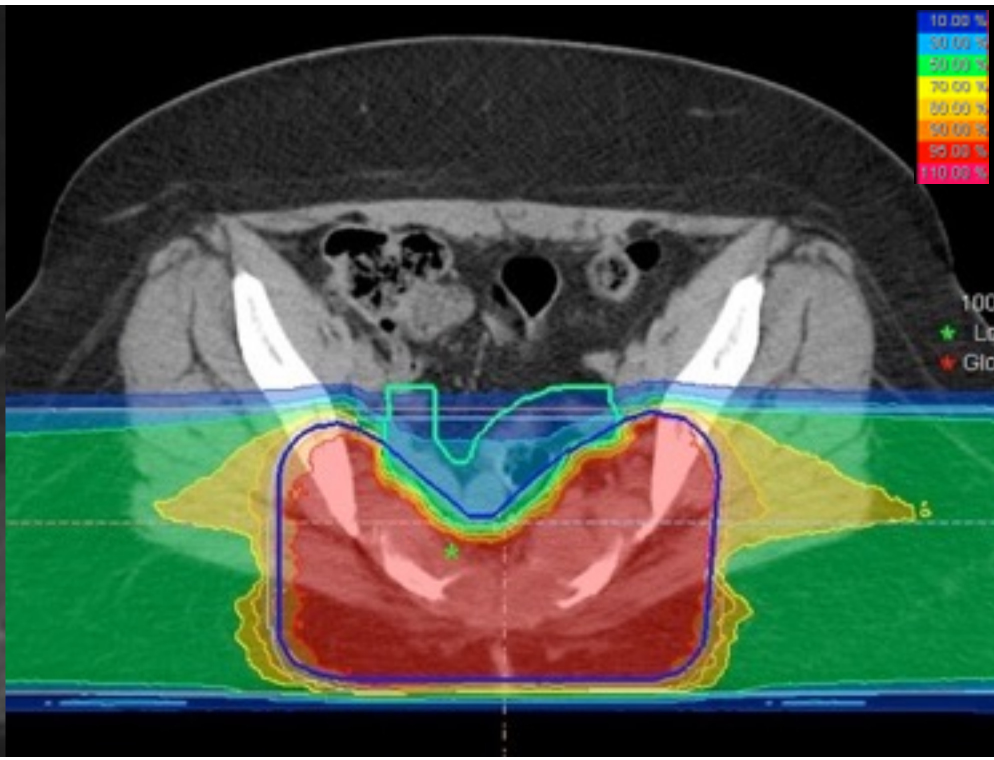
[Schulz-Ertner, IJROBP 2007]

Sacral Chordoma

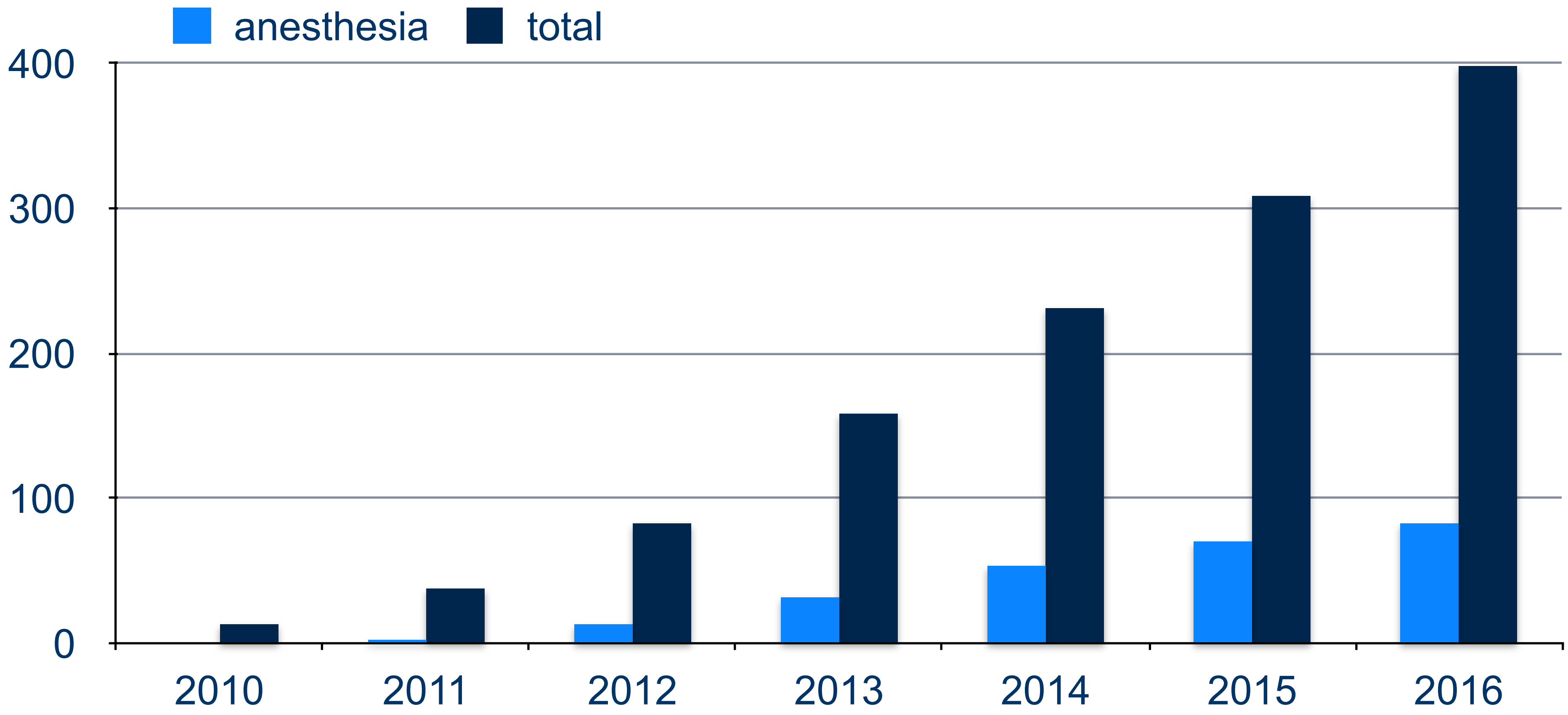
ISAC trial: randomized phase II

16 x 4 GyE C12 vs. 16 x 4 GyE H1





Pediatric Patients at HIT



2010
- / 13

2011
3 / 25

2012
11 / 45

2013
18 / 76

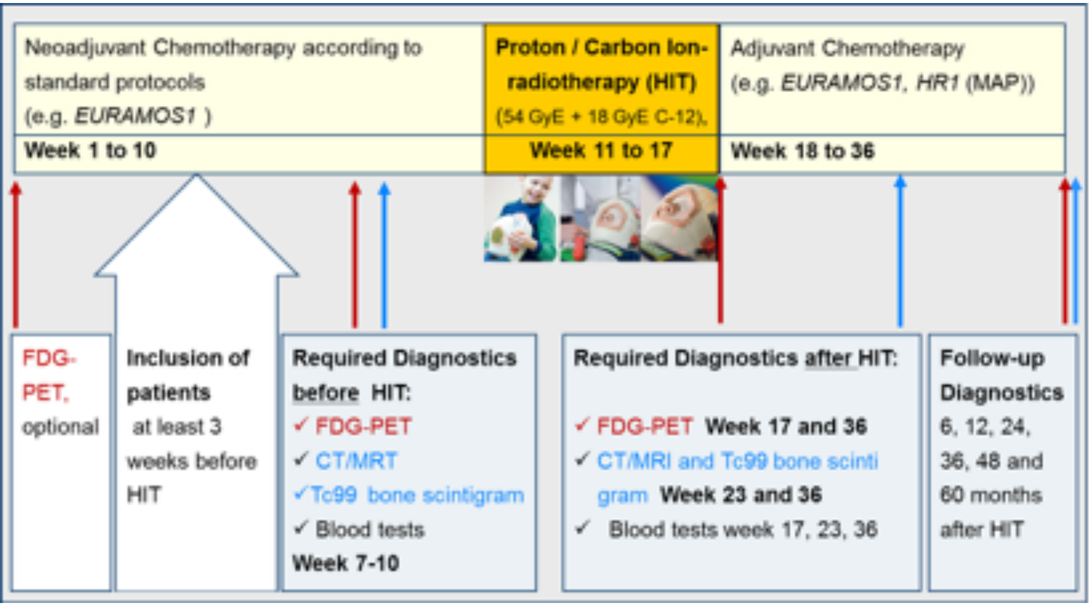
2014
21 / 73

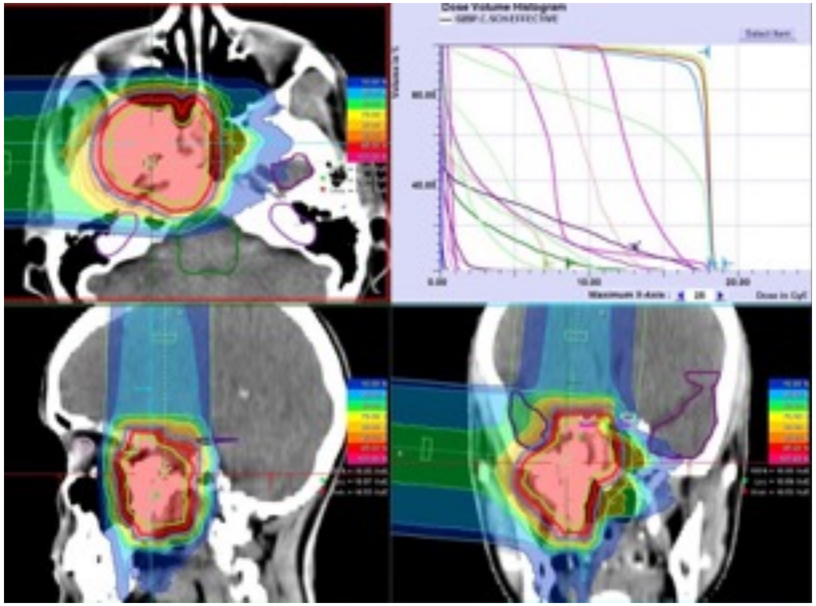
2015
18 / 77

OSCAR- trial

OSteosarcoma – CArbon Ion Radiotherapy: Phase I/II therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with inoperable osteosarcoma

Secondary endpoints: local control disease-free and progression-free survival, Overall survival, role of FDG-PET in response monitoring



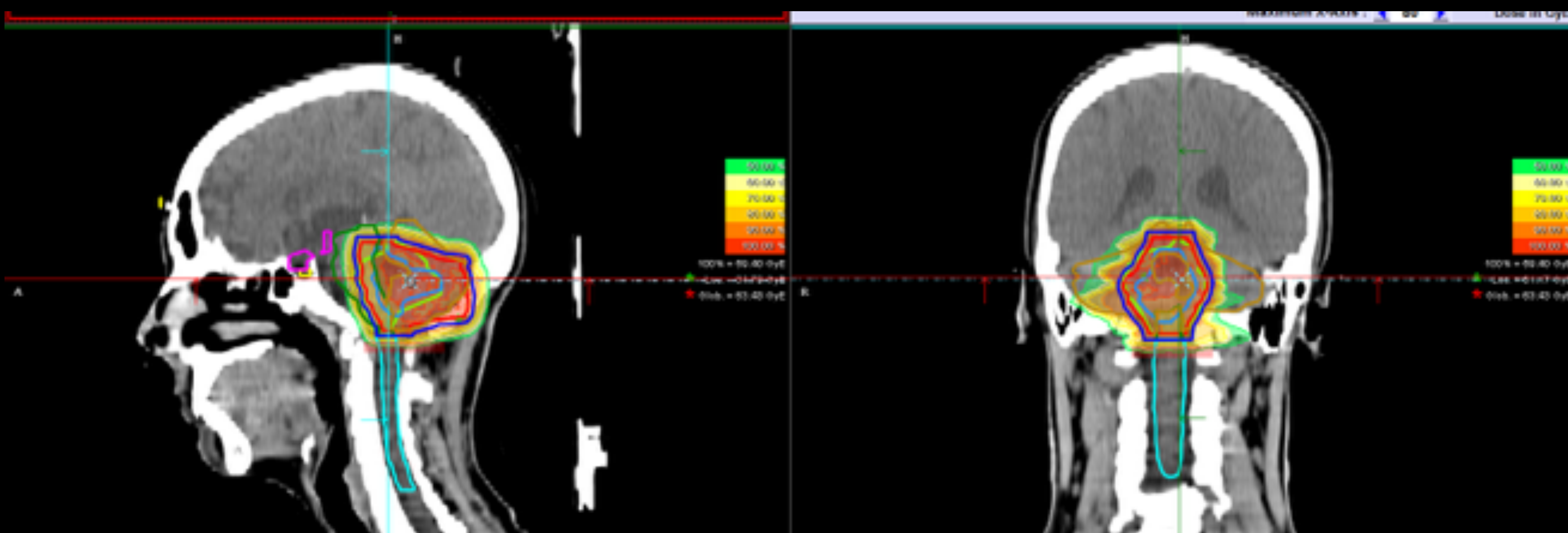


Challenges: Changes Due Molecular Diagnostics

12 years old girl
Diagnosis post surgery:
Ependymoma °III on reference pathology

Localization infratentorial,
IV Ventricle

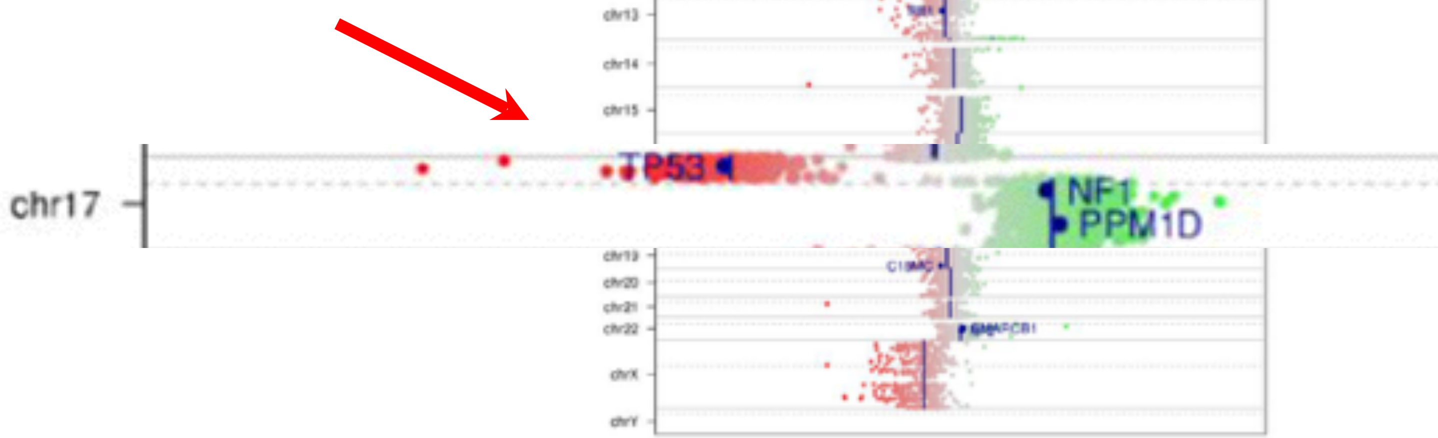
Residual Tumor:
59.4 GyE Proton (HIT)
in 1.8Gy Fx (33 Fx total)

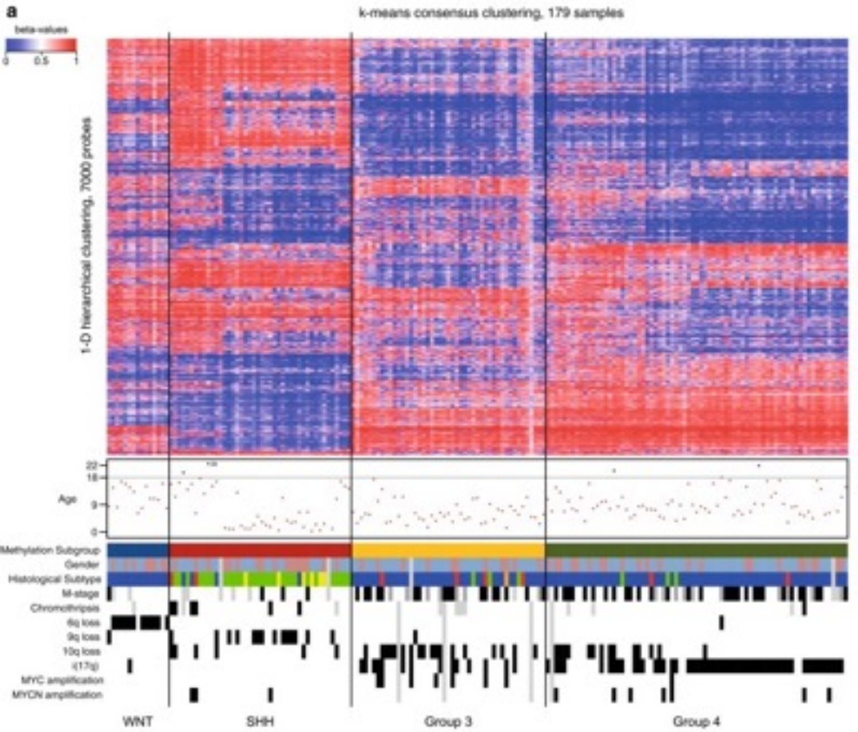


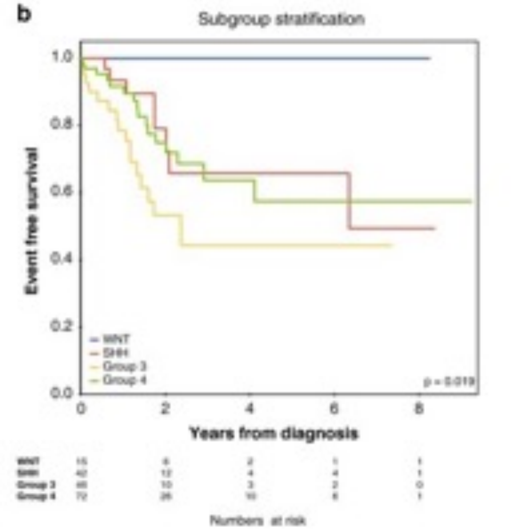
450k Methylome/CNV + NGS analysis

No, GLI-, MYC, MYCN amplif.
No mut. in 130 NGS Ultra Deep Seq

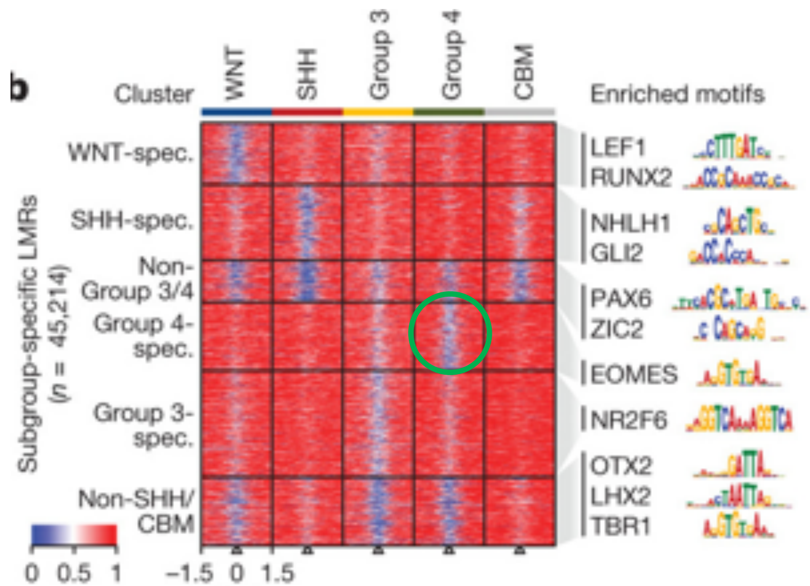
Isochromosome 17q
2 identical long q arms
Loss of the p arm







Localized lowly methylated regions (LMRs)



Our case:

Non-SHH,
non-WNT,
no p53 mut

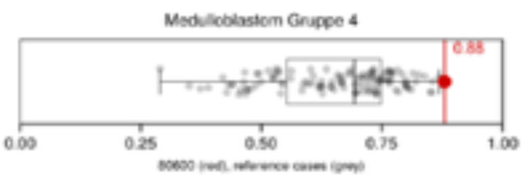
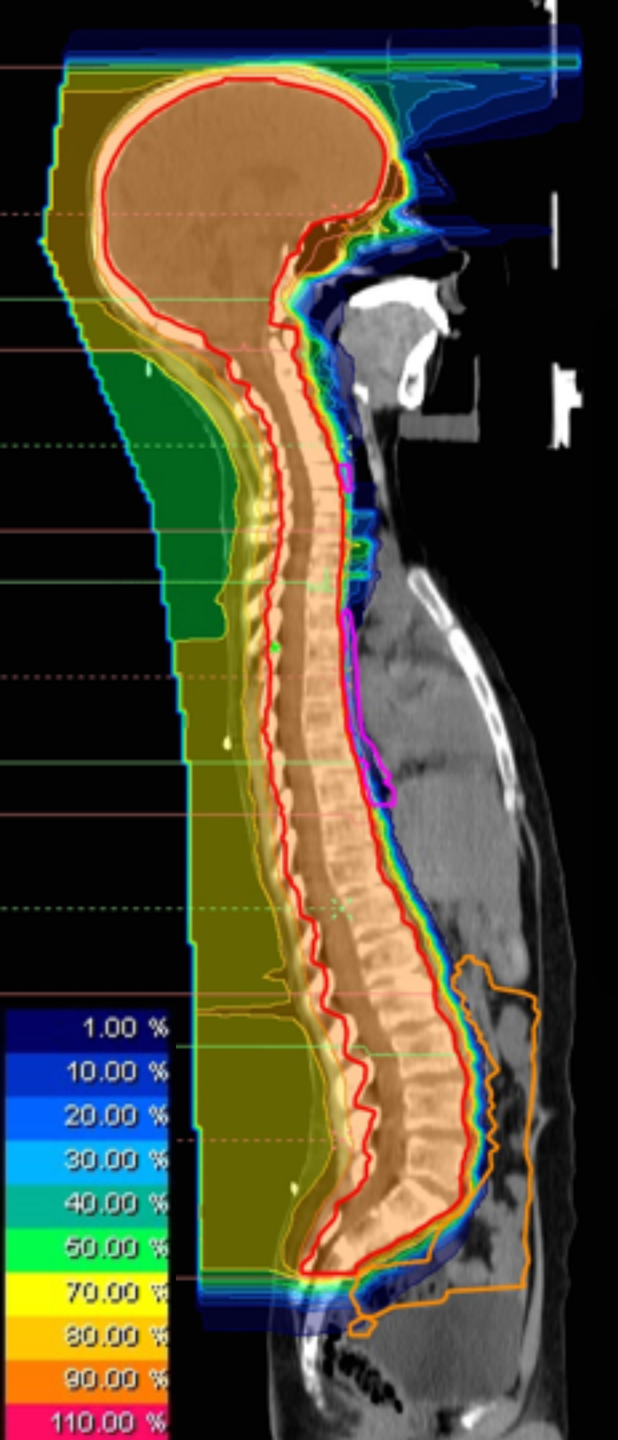
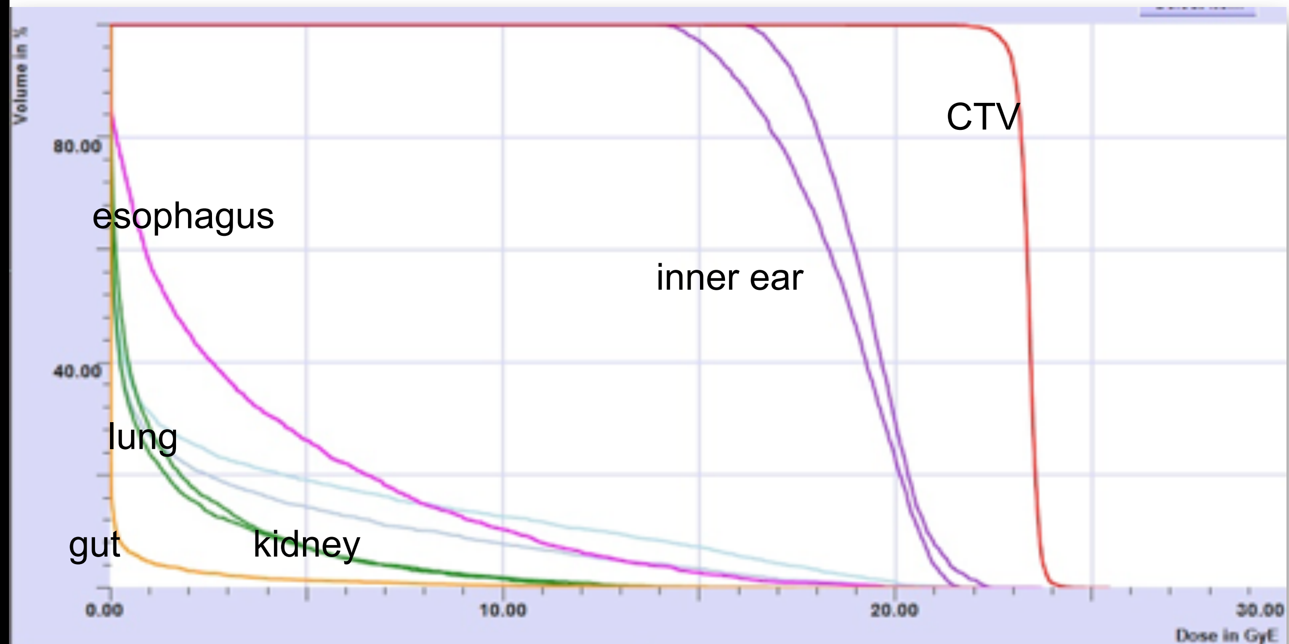


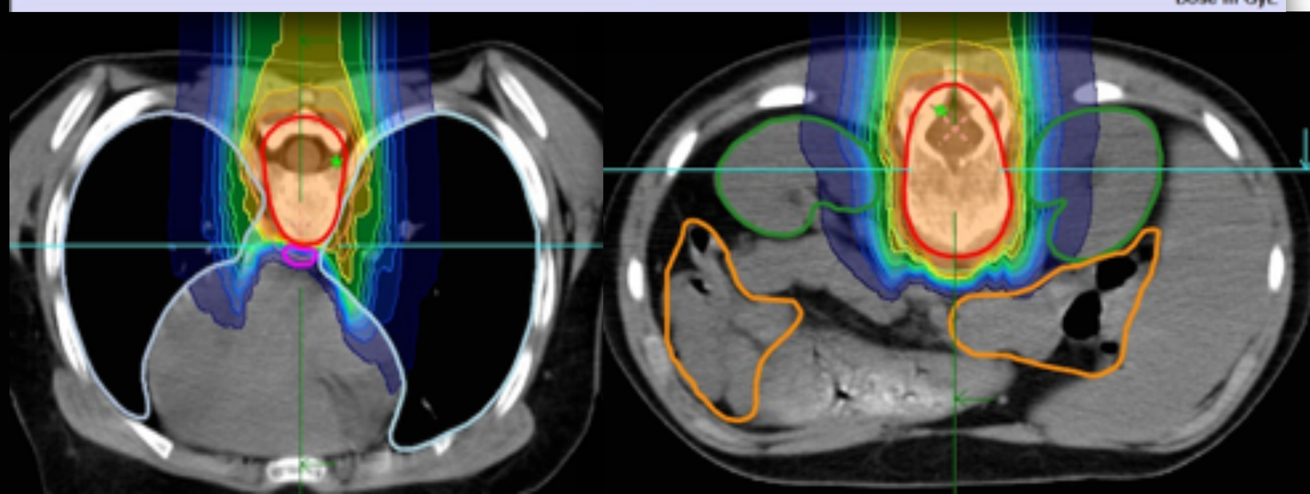
Figure adapted from Hovestadt et al. *Nature* and *Acta Neuropathol*. 2014

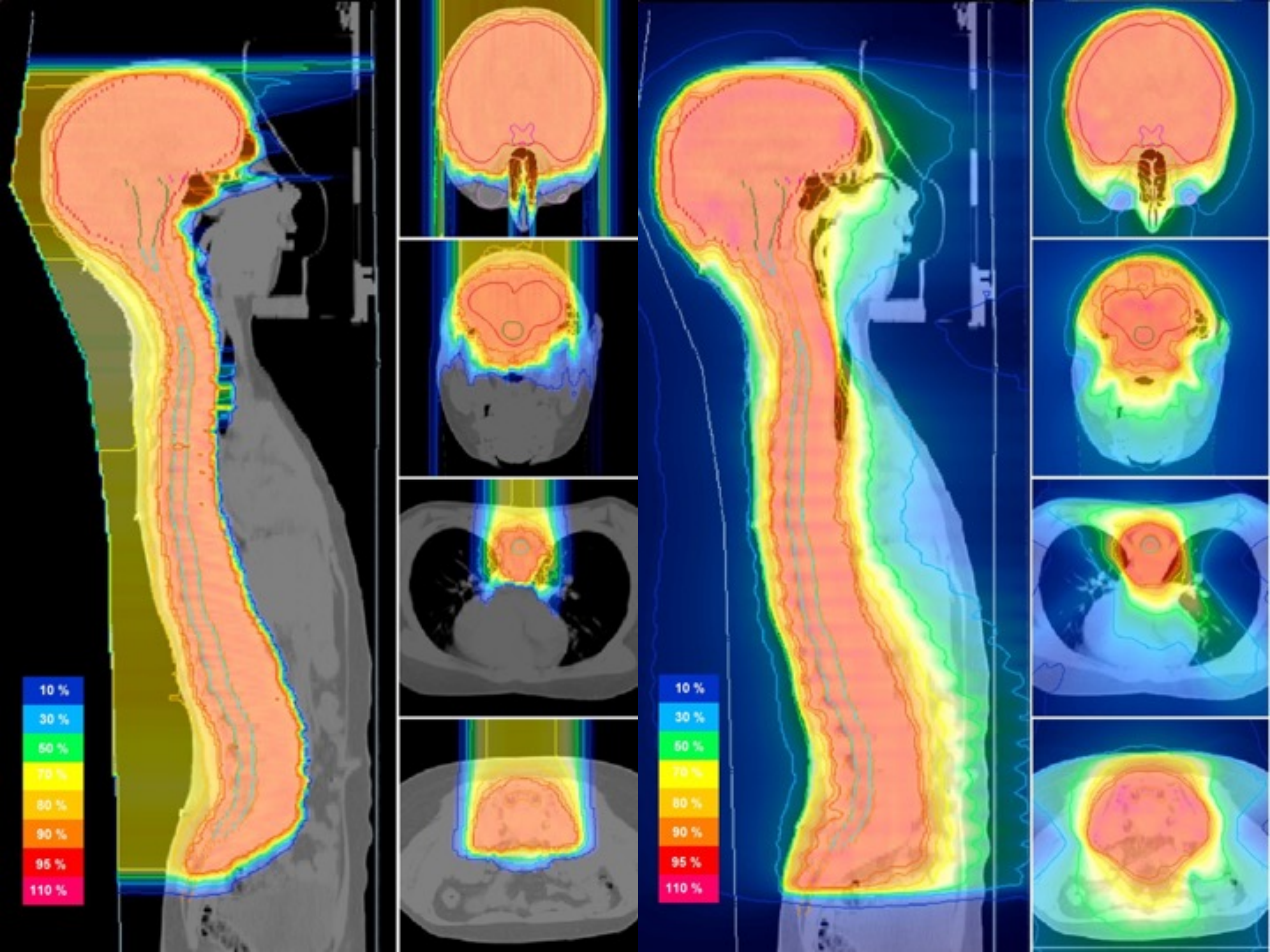
MEDULLOBLASTOMA WHO Grad IV
(Group 4)

cranio spinal irradiation: protons

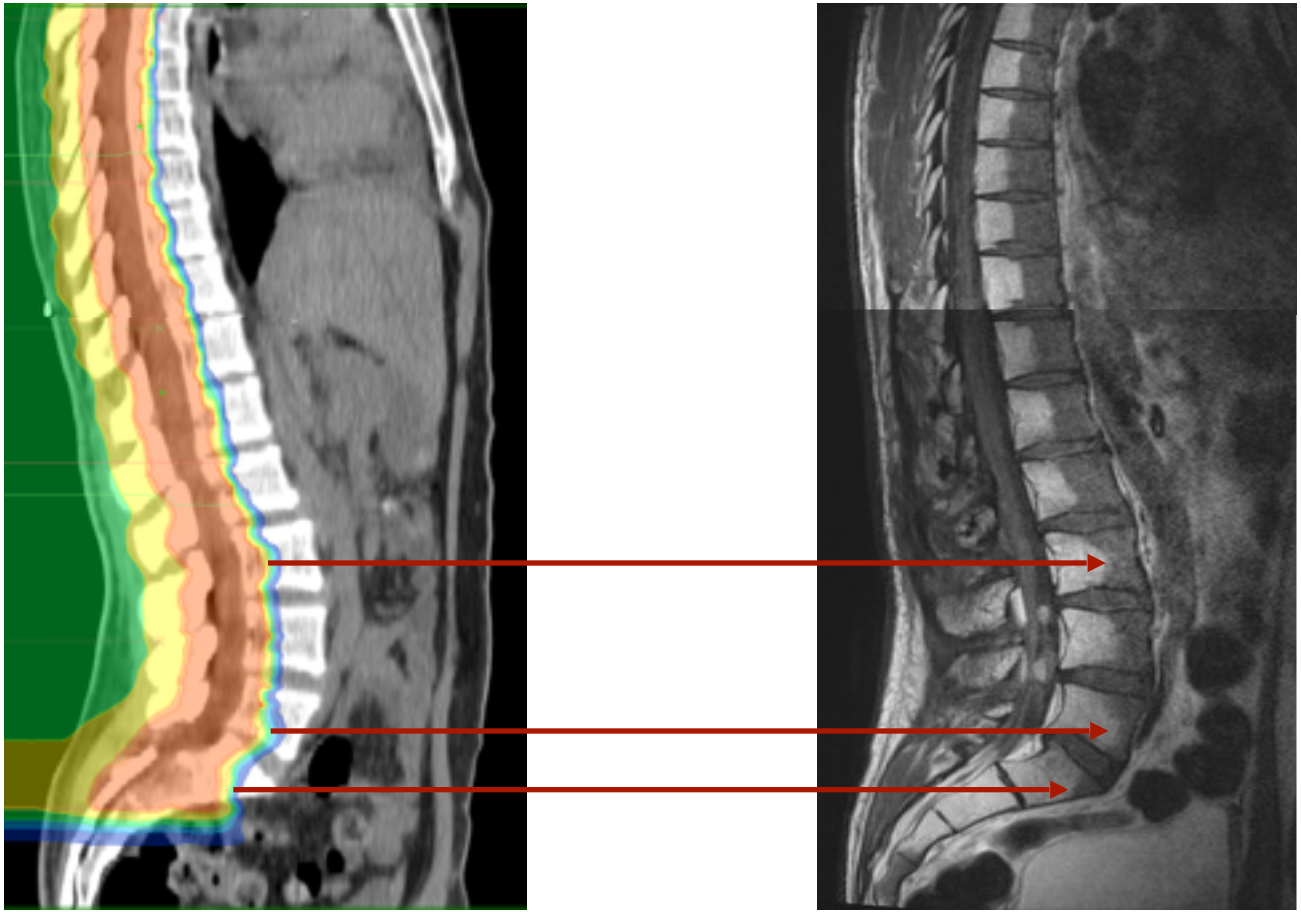







10 %
30 %
50 %
70 %
80 %
90 %
95 %
110 %
10 %
30 %
50 %
70 %
80 %
90 %
95 %
110 %

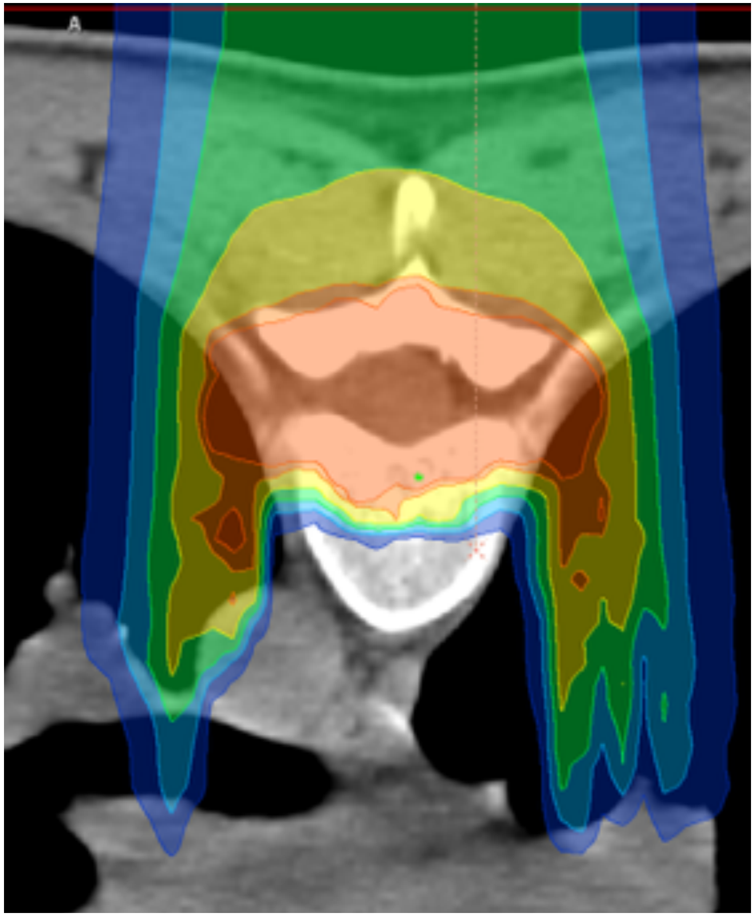
Proof of principle: CSI



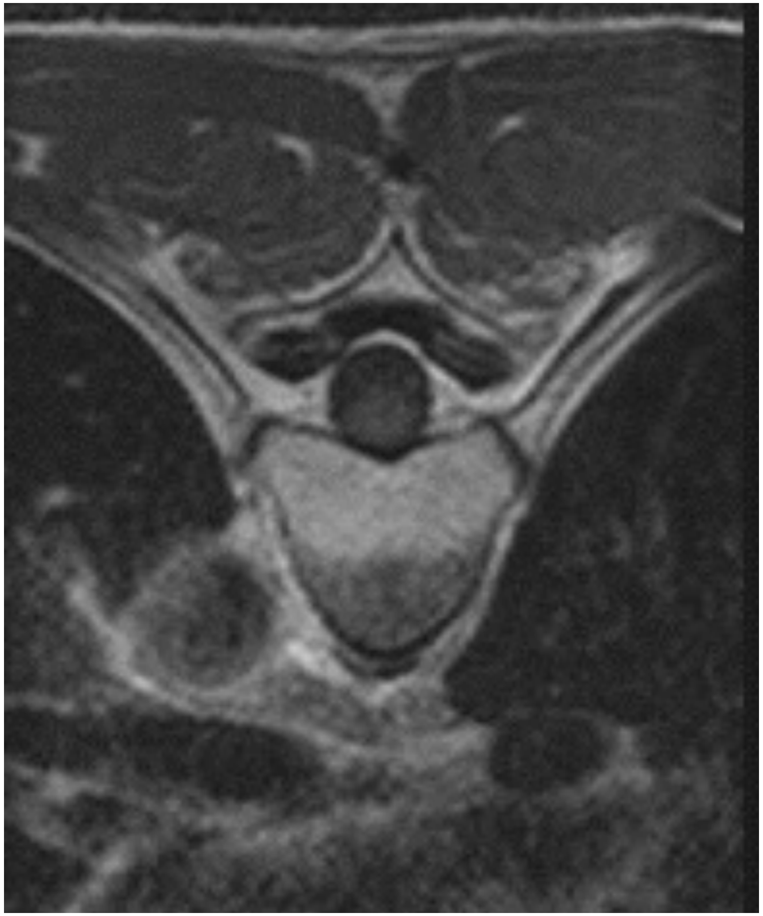
treatment plan

6 months after therapy

Proof of principle: CSI



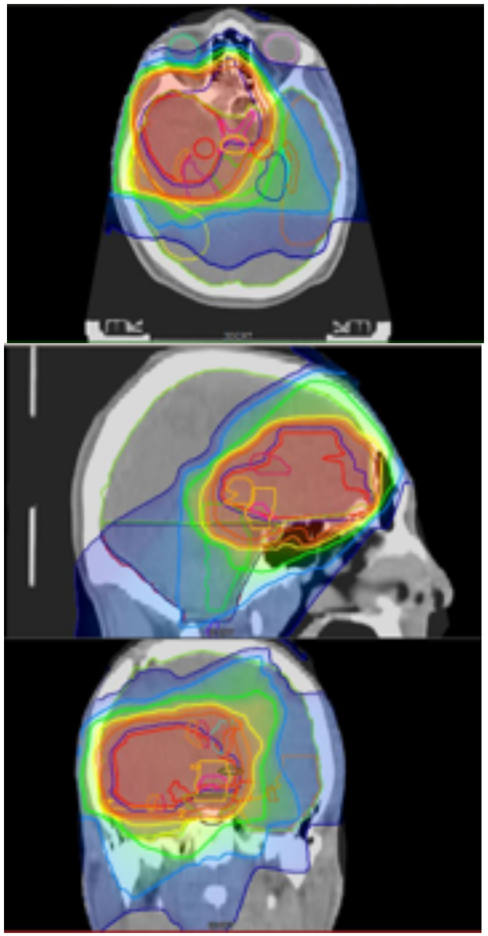
treatment plan



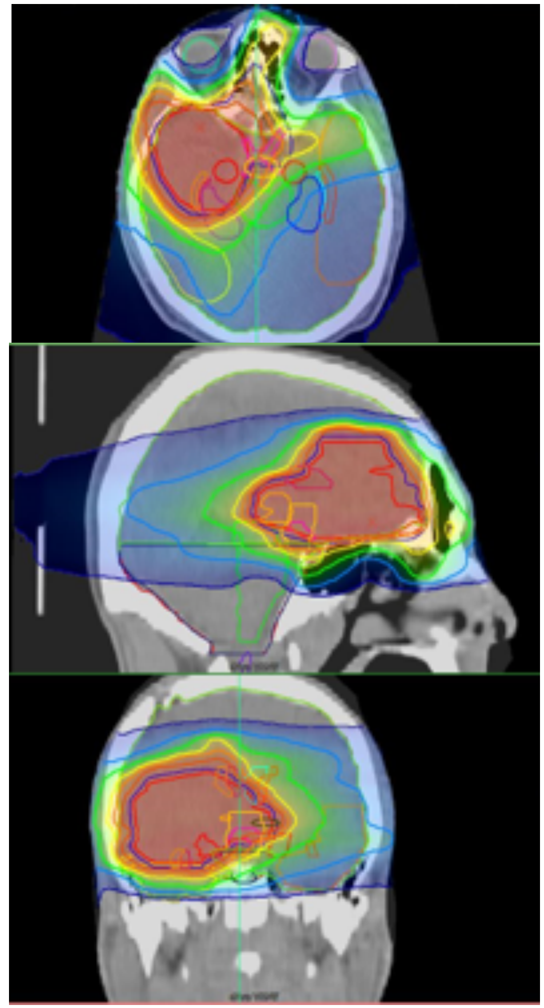
6 months after therapy

Low grade glioblastoma

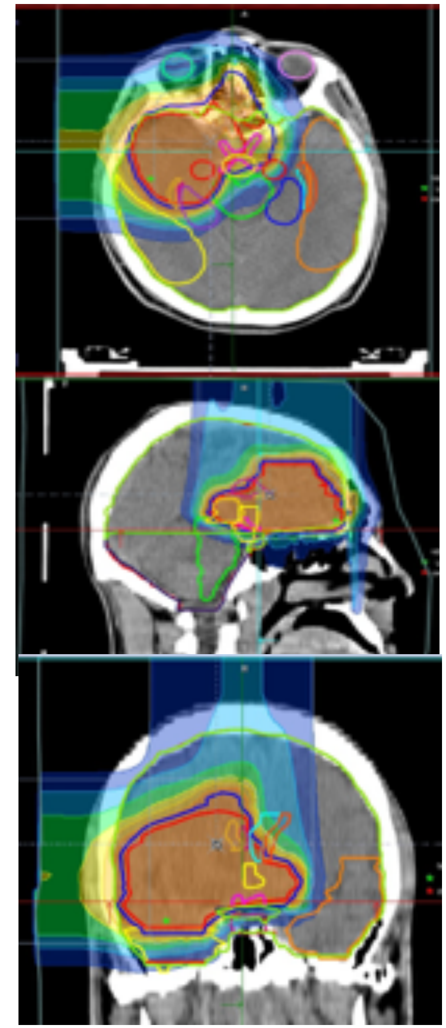
3D-CRT



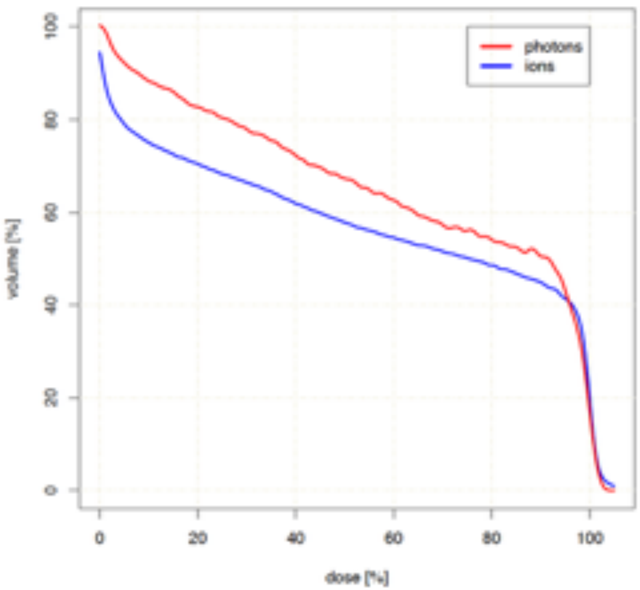
VMAT

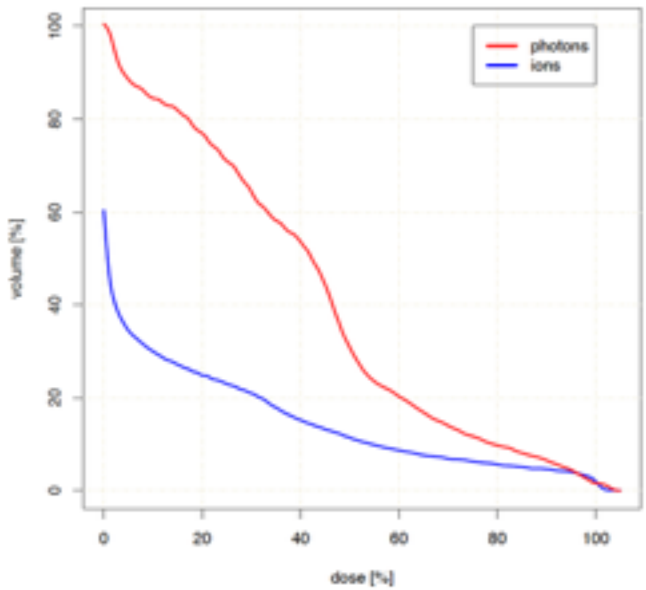


PRT



Result: dose reduction





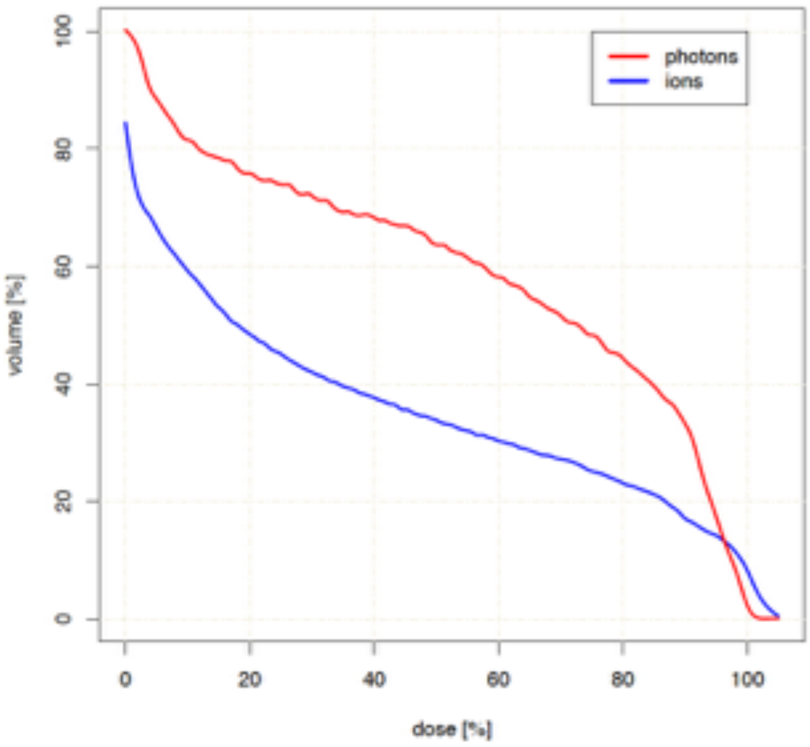
Hippocampus ipsilateral:

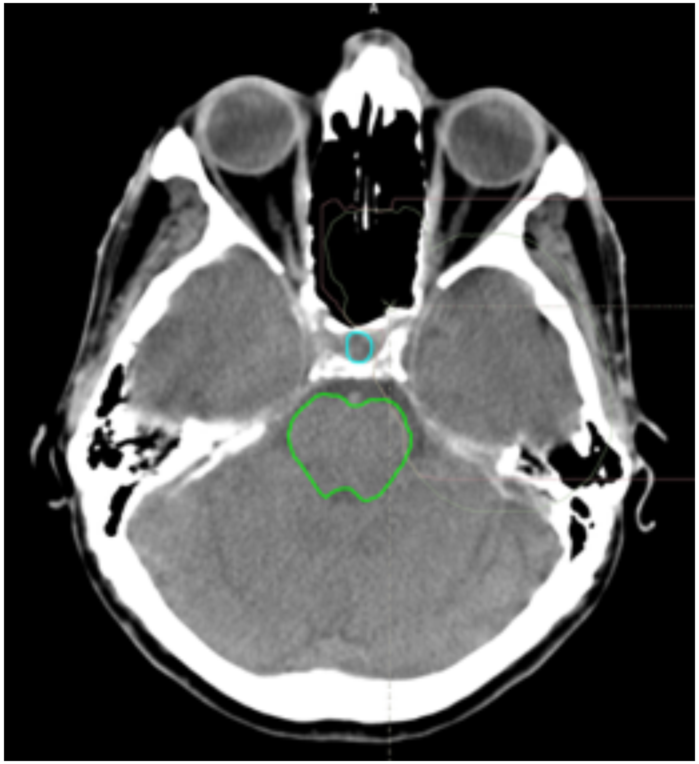
Dmax: -5.5%
Dmean: -15.3%
Mean ID: -16.5%

Hippocampus contralateral:

Dmax: -37.2%
Dmean: -64.5%
Mean ID: -62.7%

Result: dose reduction

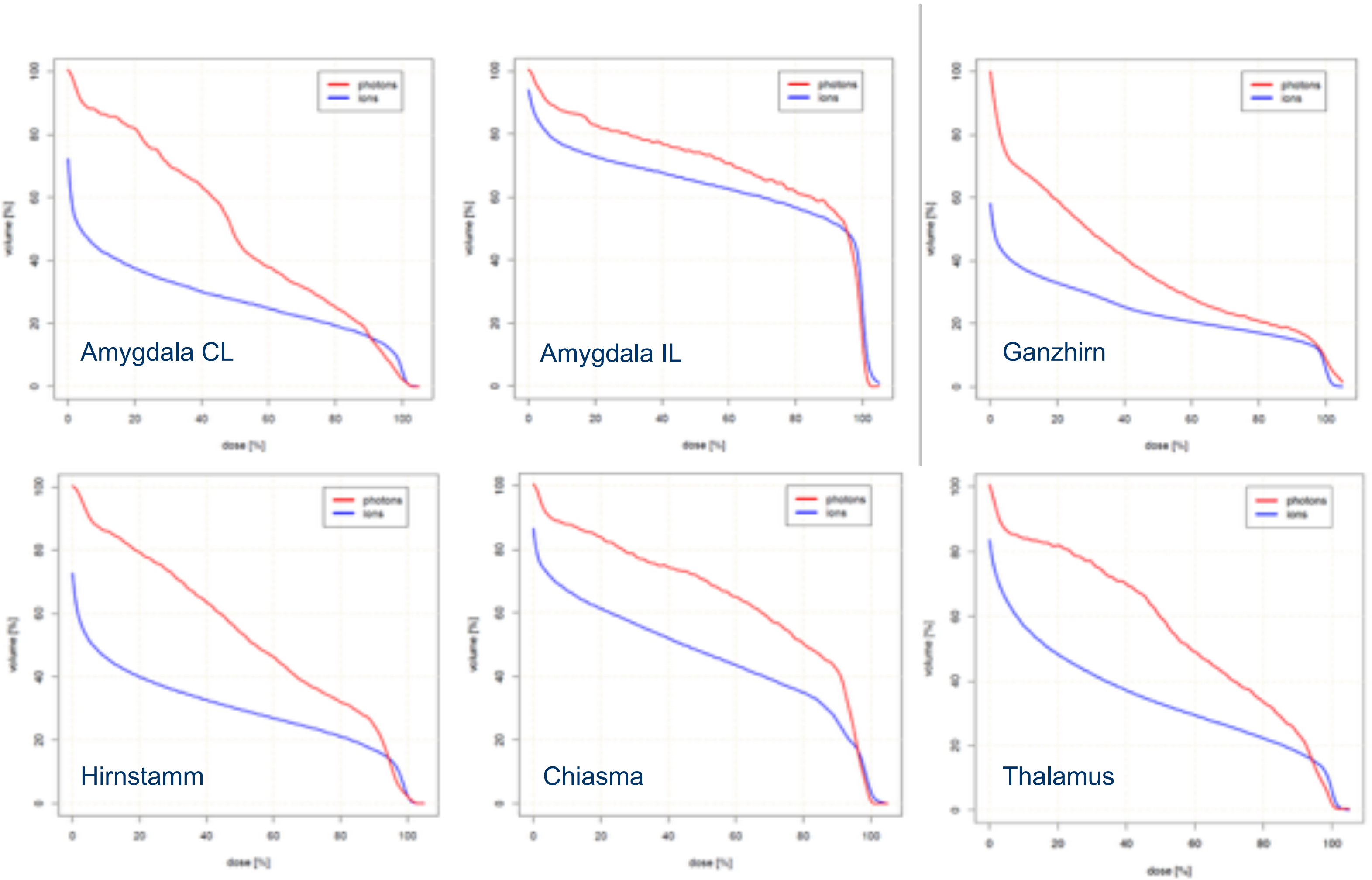




Hypophyse

Dmax: -24.6%
Dmean: -40.9%
Mean ID: -37.8%

Result: dose reduction



Mediastinal lymphoma

Dosimetric plan comparison: Methods

Proton therapy (PT):

Raster-Scan

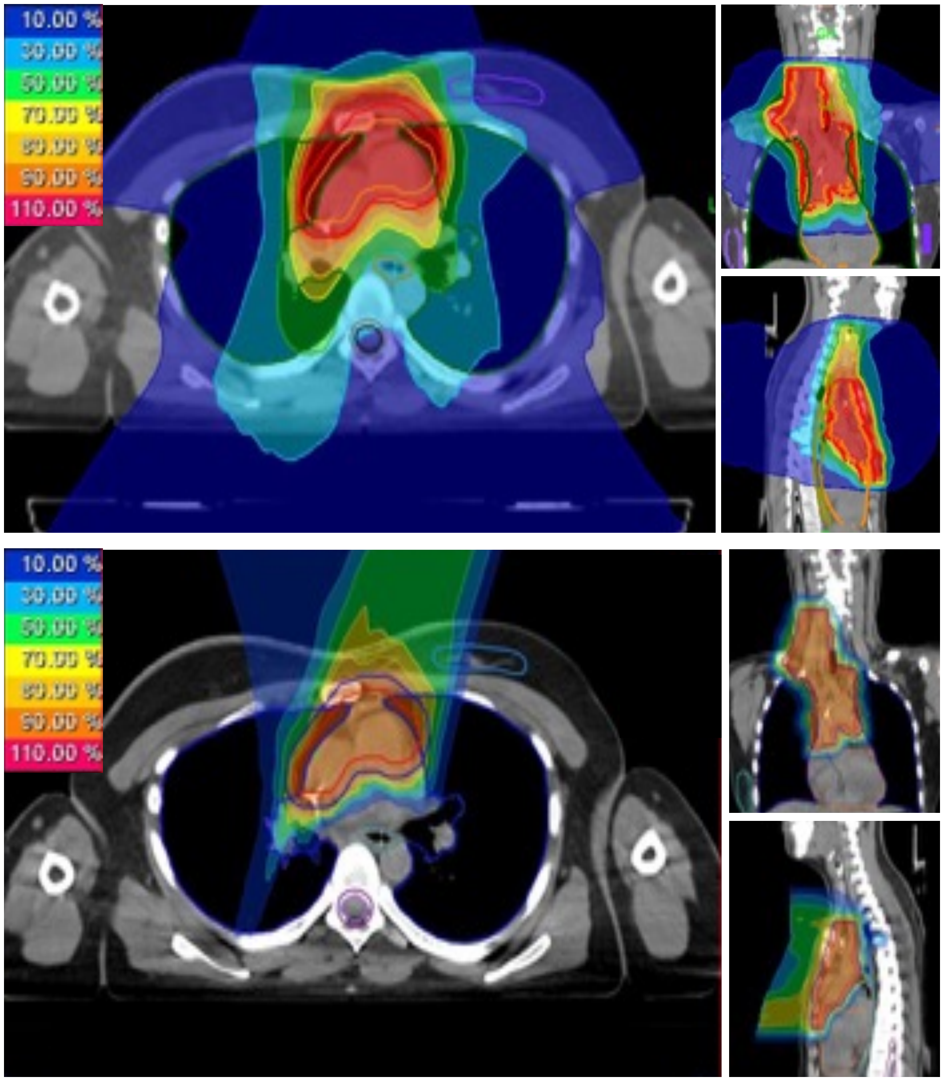
Helical TomoTherapy® :6 MV, binary MLC

Planning: 4D-BPL-CT
Target volume definition: PTV: CTV + 5mm

16 Patients (11 w, 5 m), Median age: 29,5 years (21-54 years)

indikation for protons : age, pericard involvement, high dose expected in mamma

Mediastinal lymphoma



IMRT

PT

27 LJ, f, DLBCL
St. IIA mit med. Bulk

RT: 36 Gy RBE in 18 Fx (ED 2,0 Gy RBE)

D_{mean} myocard:
3,5 Gy RBE vs. 7,2 Gy

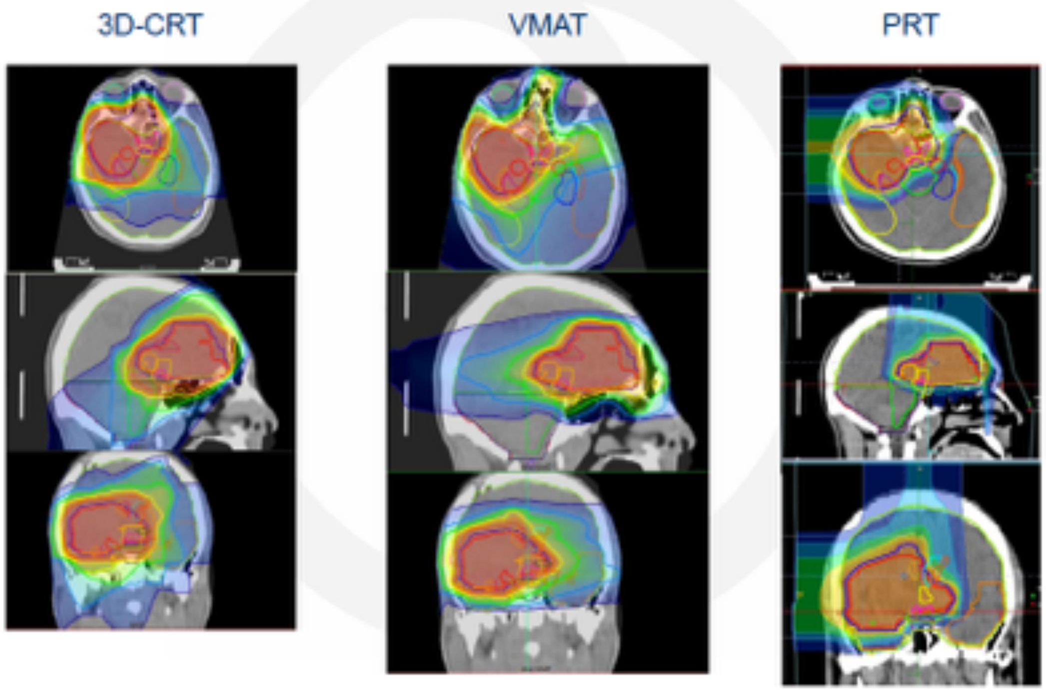
D_{mean} breast right.:
0,1 Gy RBE vs. 1,4 Gy

D_{mean} breast left.:
1,7 Gy RBE vs. 2,4 Gy

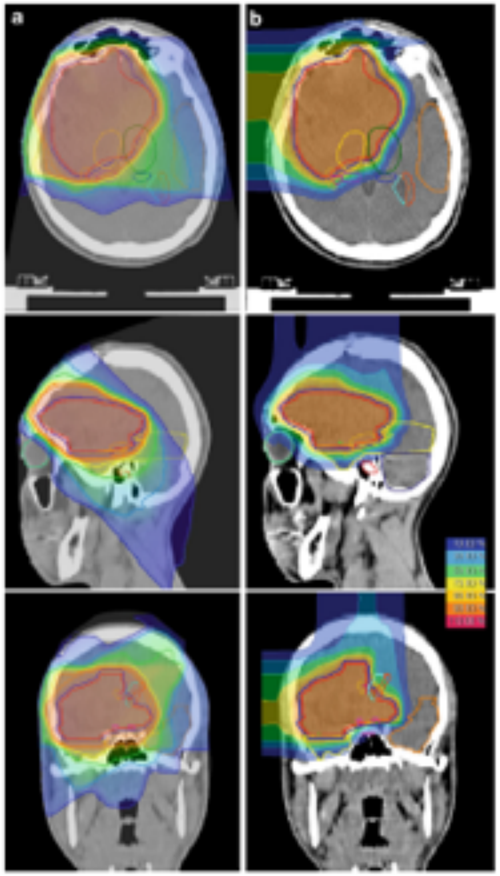
Dose reduction OAR: Protontherapy Of Mediastinal Lymphoma

	PT (Gy)	IMRT (Gy)	Absolute Reduction (Gy)	Relative Reduction (%)	p-value
D_{mean} heart (myocard)	3,2	7,1	-3,9	-54,9%	≤ 0,001
D_{mean} right breast	0,1	1,4	-1,3	**-92,9%**	≤ 0,001
D_{mean} left breast	1,4	2,4	-1,0	-41,7%	≤ 0,001
D_{mean} esophagus	7,0	10,9	-3,9	-35,9%	≤ 0,001
D_{max} spinal chord	1,6	16,2	-14,7	**-90,4%**	≤ 0,001

Low grade glioma



Adeberg et al., SUON 2016

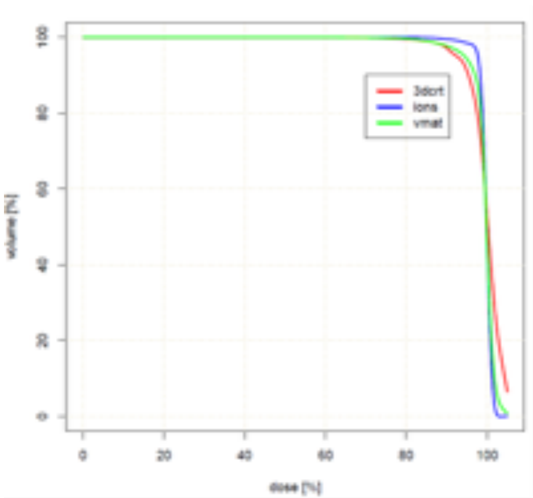


Harrabi,…,Adeberg et al., SUON 2016

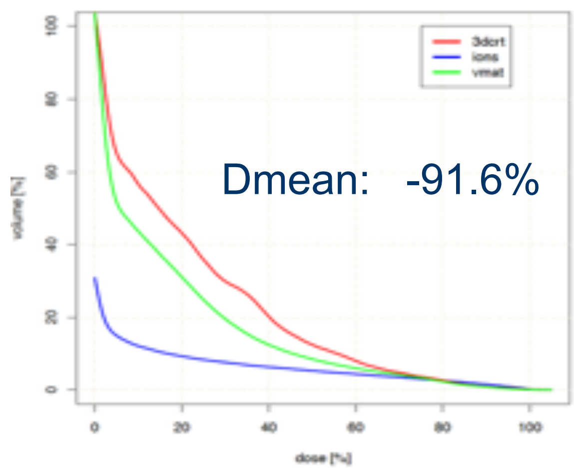
Fig. 4 Comparison of dose distribution for a patient with low grade glioma. **a** Three-dimensional conventional radiotherapy plan, **b** proton beam therapy plan. CTV is delineated in *red*, the corresponding planning target volume in *blue*. The potential for dose reduction is especially eminent at the contralateral site

Low grade glioma

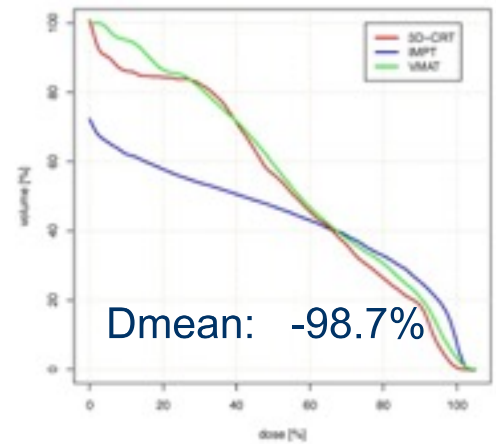
Plan comparisons: IMPT vs IMRT vs 3D-CRT



Dose coverage



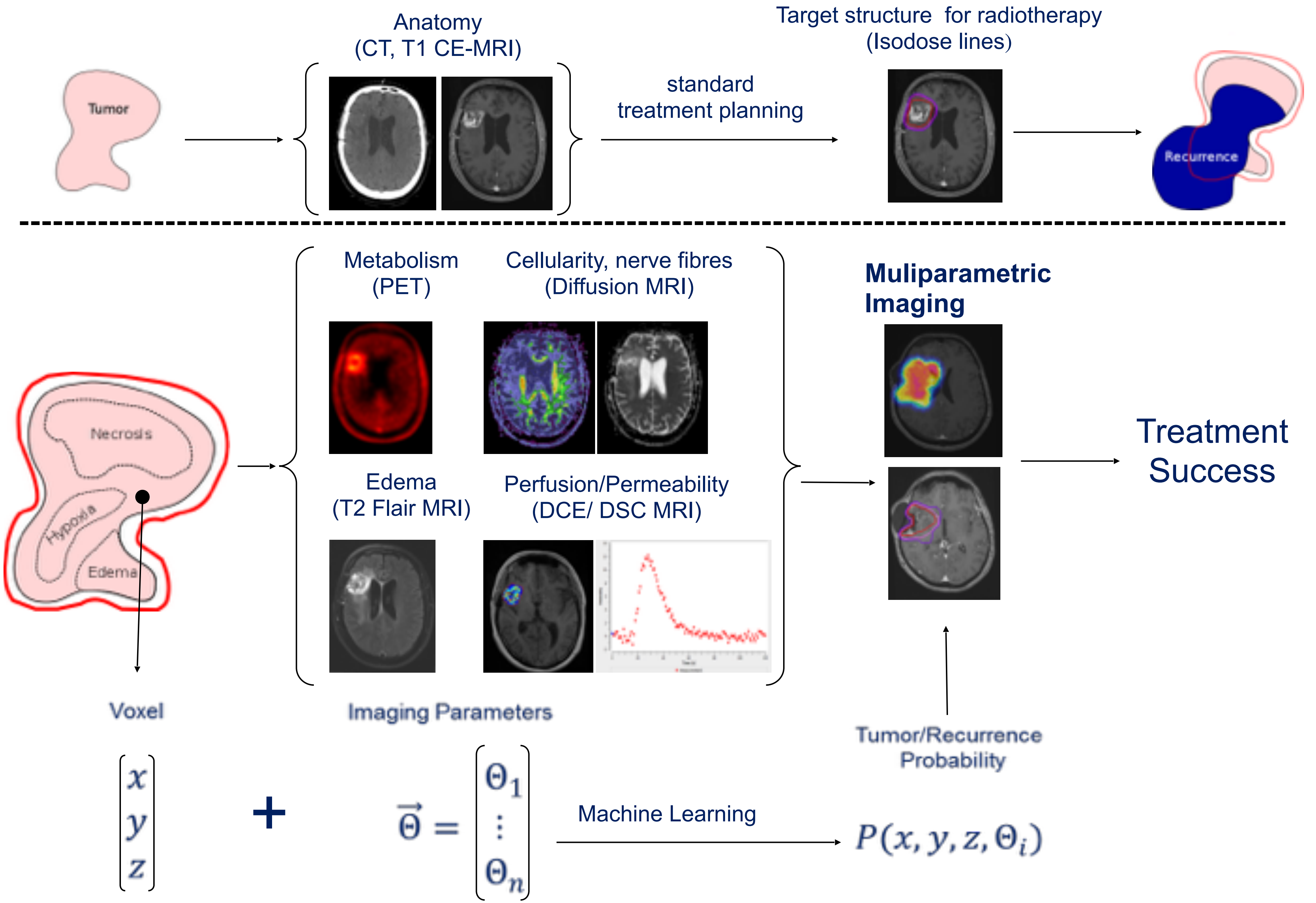
Brainstem



CL Hippocampus

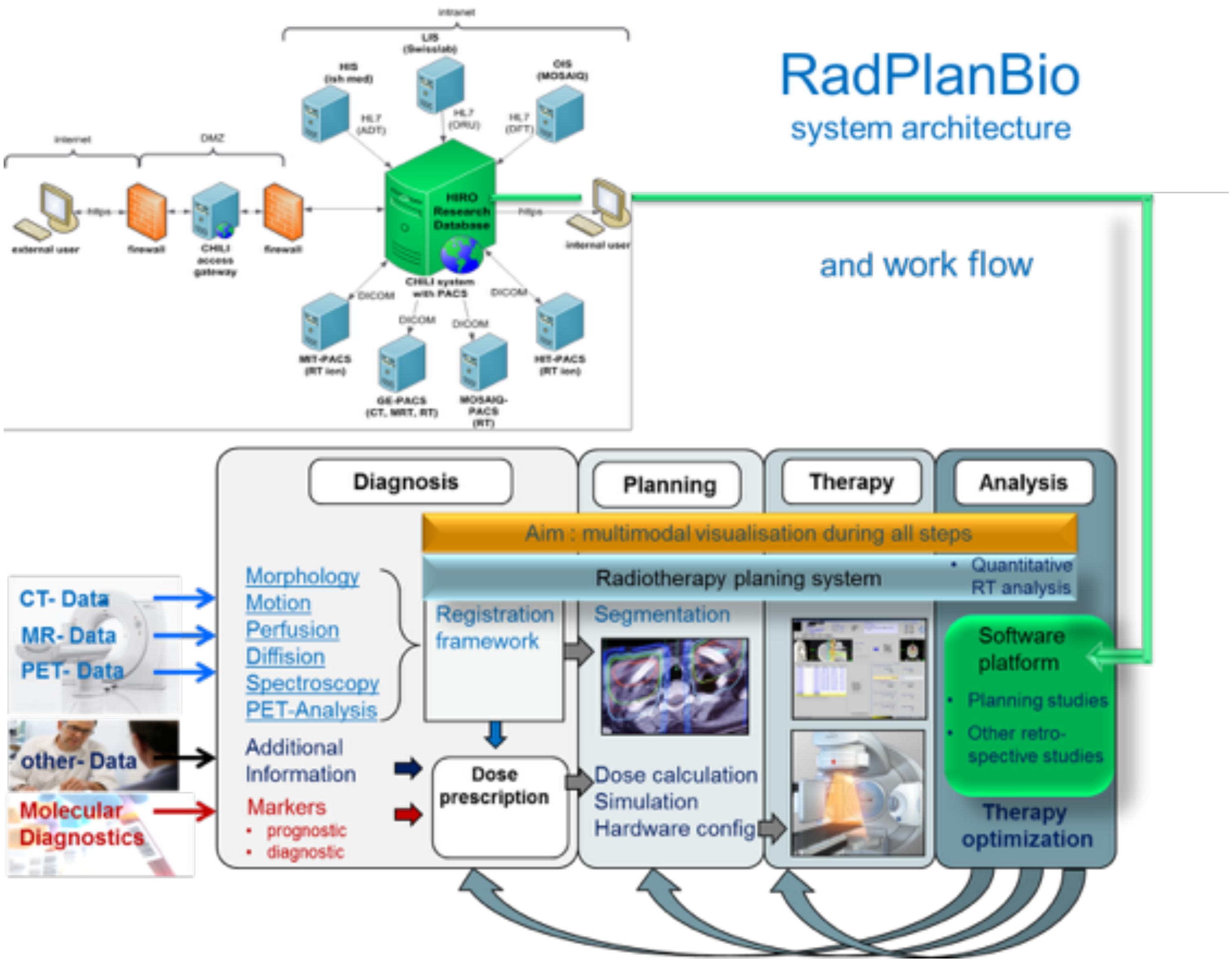
Adeberg et al., SUON 2016

New Ways Of Learning



Future aims

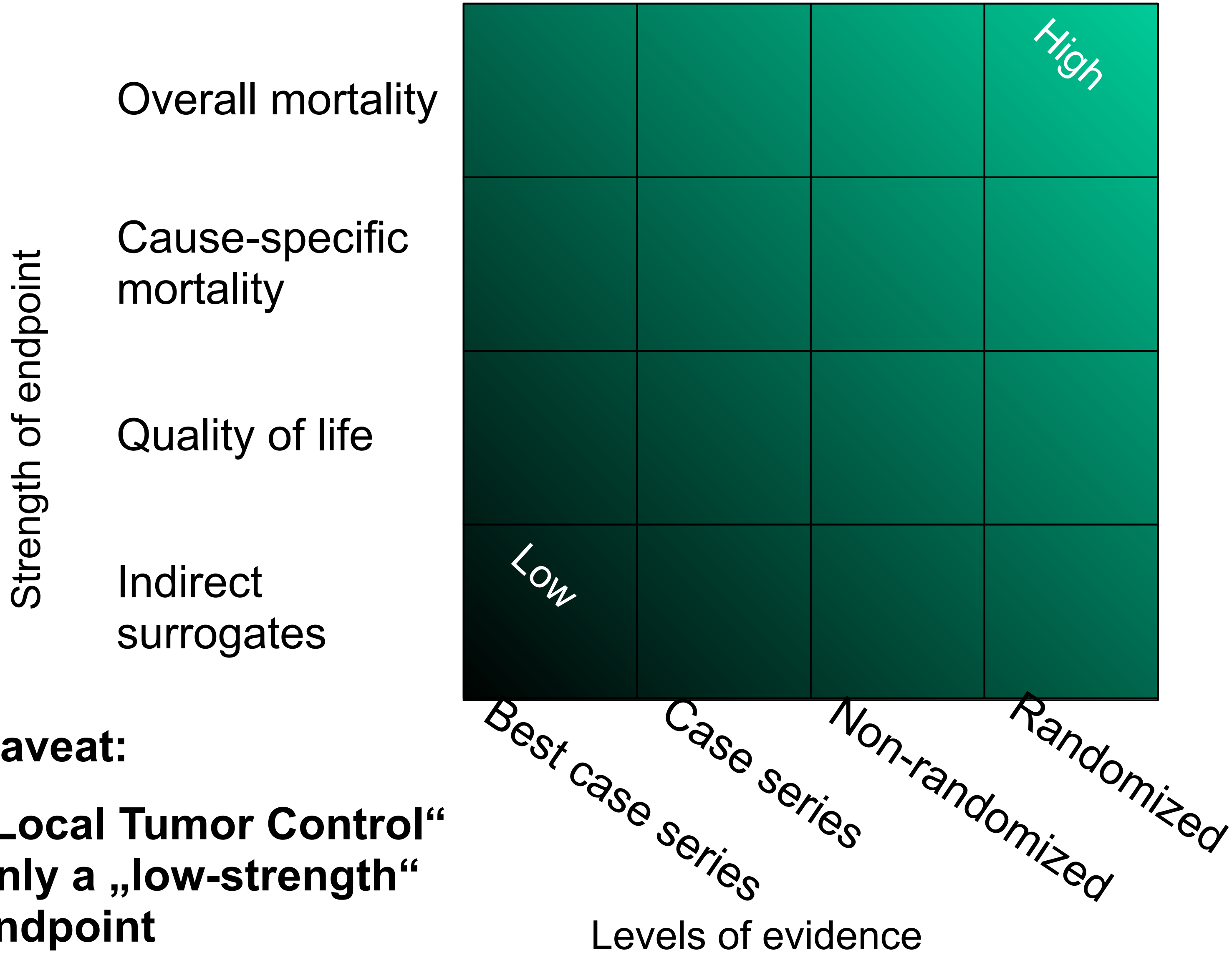
Systematic assessment of long term effects of particle therapy



Pitfalls

- Commercial priorities: financial pressure
- Not sufficient time for ramp-up
- Underestimation of training needs: CTV / PTV
- Lack of trials interesting for 1) advancing cancer care and for 2) health authorities/ insurances
- Too optimistic estimation of recruitment for studies
- Quick progress of photon radiotherapy (IGRT, ART) comparison with standard of care
- Too rapid shifts from standard treatments (e.g. hypofractionation)
- Underestimation of current shortcomings of particle vs. photon therapy (moving targets, range detection/QM, TPS, on-board imaging, IMRT, …….)

NCI: Indices of clinical relevance



Caveat:

„Local Tumor Control“ only a „low-strength“ endpoint

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

dkfz.

UniversitätsKlinikum Heidelberg

Partners:

HIRO
Heidelberger Institut
für Radioonkologie

OncoRay
Radiation Research in Oncology

GSI

HZDR
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

UKGM
UNIVERSITÄTSKLINIKUM GIESSEN UND MARBURG

MIT
Marburger Ionenstrahl-Therapiezentrum

HIT
Heidelberger Ionenstrahl-Therapiezentrum