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Radiation Oncology Concepts for Recurrent Tumors – Particles an Option?

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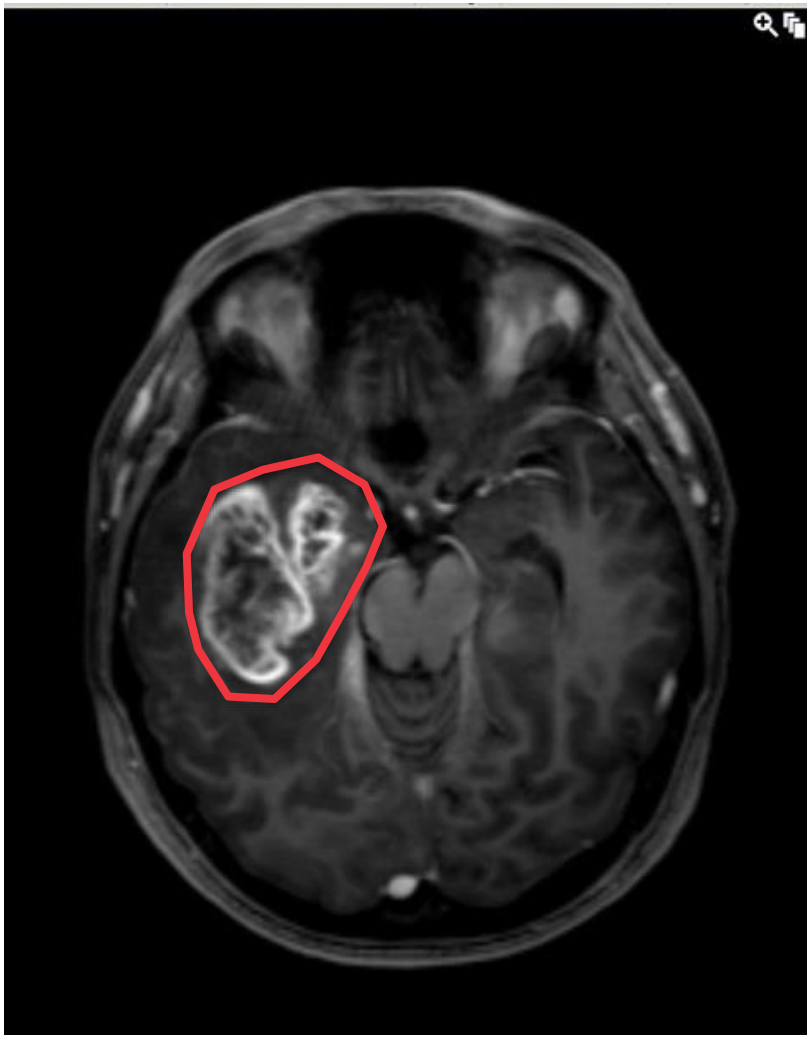
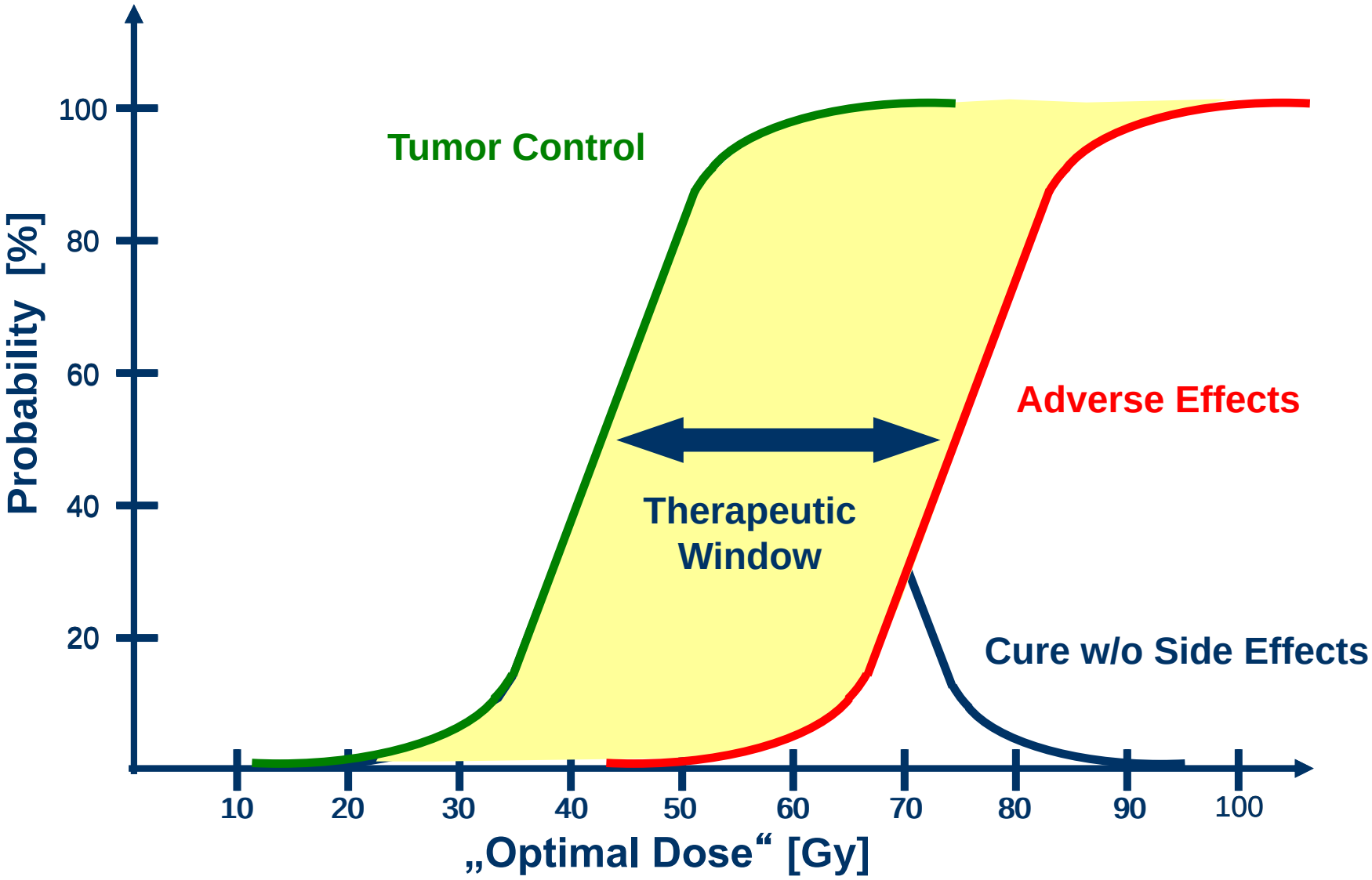
Director, Institute of Innovative Radiotherapy (*i*RT), HMGU

Radiotherapy of a Patient with a Brain Tumor

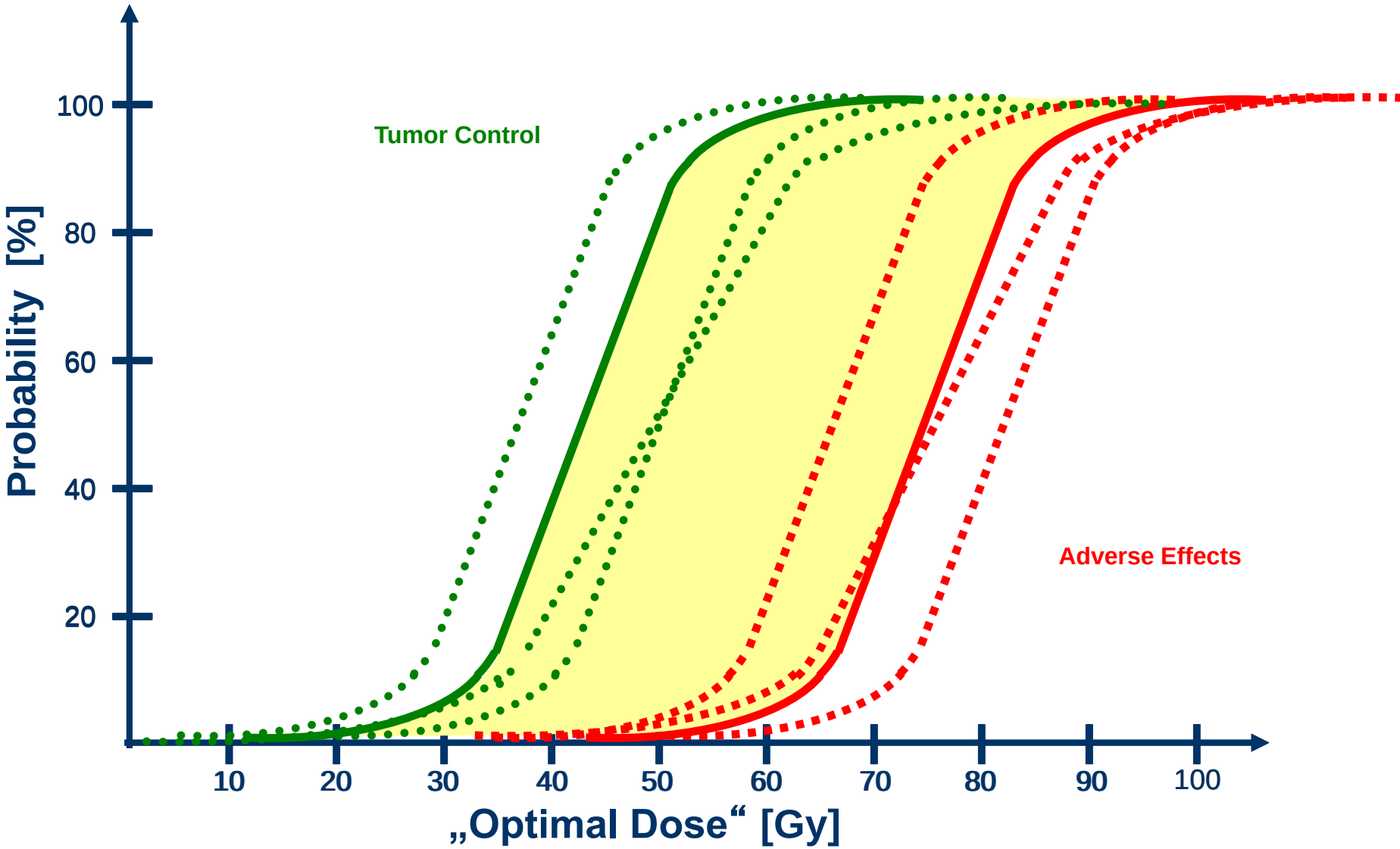


Holthusen-Curve: Dose-Response-Relationship



After: Holthusen, H. und Braun, R. (1933) :
Grundlagen und Praxis der Röntgenstrahldosierung, Thieme Verlag, Leipzig

Holthusen-Curve: Dose-Response-Relationship



After: Holthusen, H. und Braun, R. (1933) :
Grundlagen und Praxis der Röntgenstrahldosierung, Thieme Verlag, Leipzig

Improving the Therapeutic Window: Clinical Rationale for Particle Therapy

What are the „new possibilities“ I can use with particle therapy?

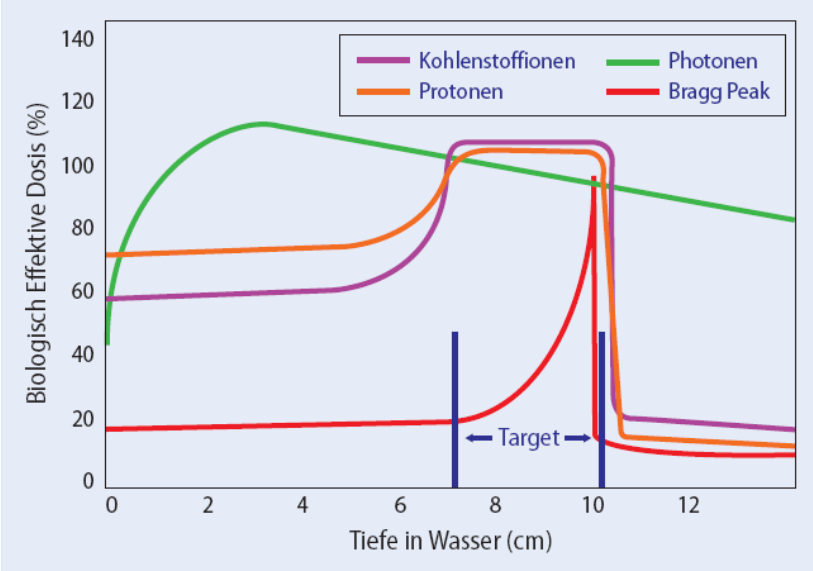
How is my efficacy? What biology is in the background?

Which patients most probably have the best benefit?

Do I have increased precision, i.e. can I reduce dose do non-involved areas?

- Reduction of integral dose
- sparing of normal tissue
- minimizing side effects, especially long-term toxicity
- imaging: CT-Cone beam, conventional X-ray? Issues of positioning
- **Normal tissue tolerance does not change – independently of radiation modality...**

Physical and biological Benefit of Ion Beams



- inverse dose profile
- high local dose deposition in „Bragg Peak“
- sparing of normal tissue

Combs SE et al. Chirurg, 2007

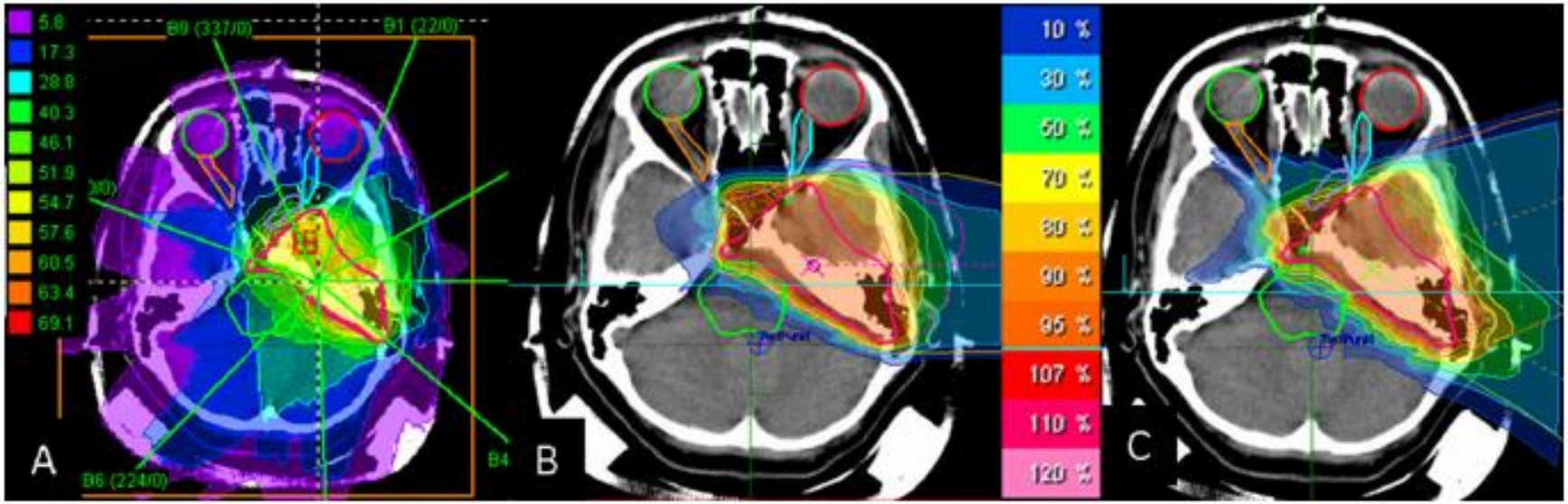


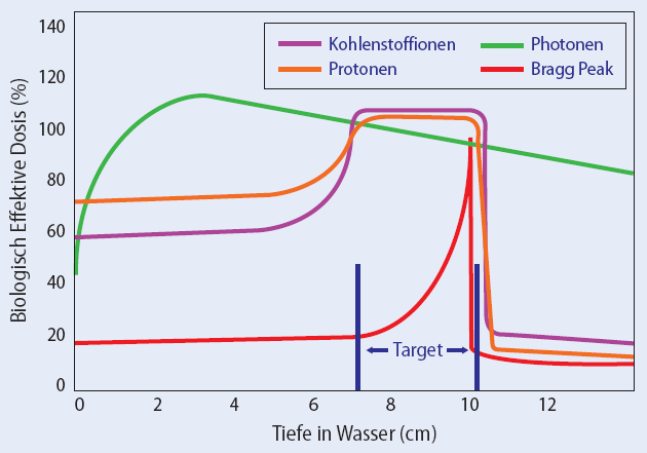
Figure 4 Dose distributions for (A) photon IMRT plan, (B) proton plan with horizontal beams, (C) proton plan with gantry beams.

Kosaki K,...Combs SE, 2012

Protons have an Inverted Dose Profile

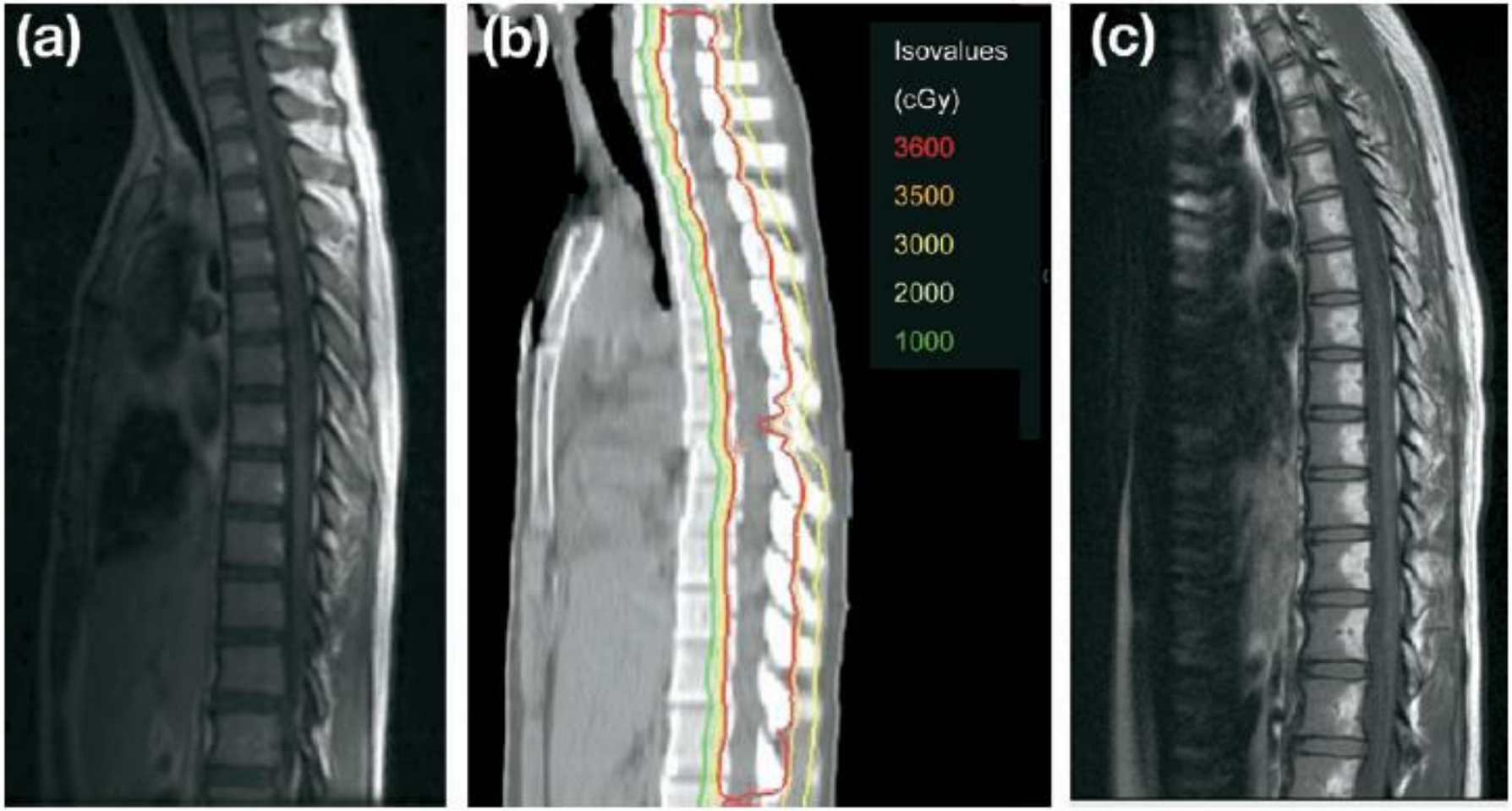
Clinical Benefit

- Sparing of Normal Tissue
- Potential Dose Increase in Treatment Volumes
- Reduction of Side effects



- Visual Impairment
- Neurological Deficits
- Xerostomia
- Growth Deficits, Deformities
- Secondary Malignancies
- Hormonal Deficits
- etc.

Combs SE et al., Der Chirurg, 2006



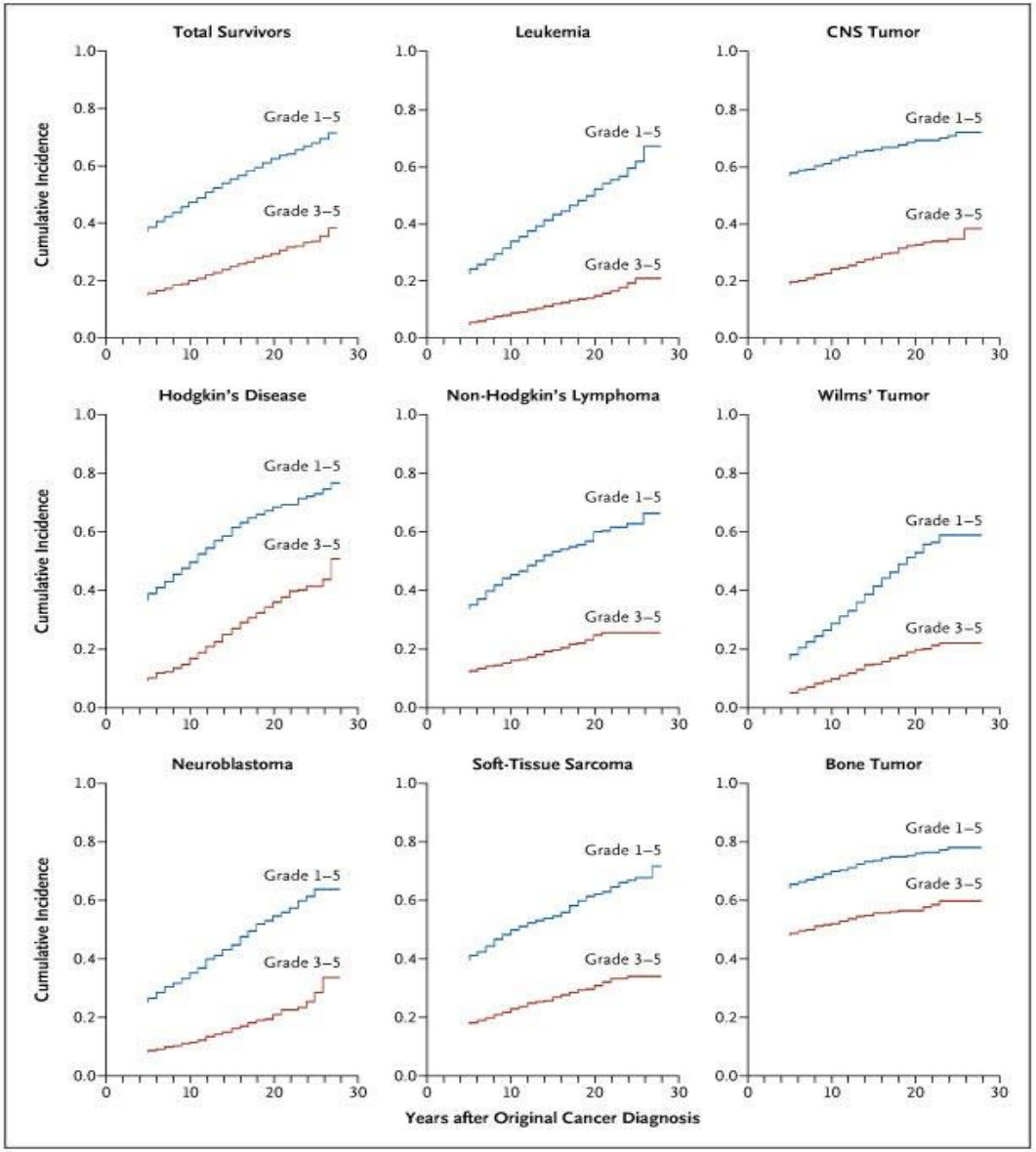
Krejcarek et al., IJROBP, 2007

Chronic Health Conditions in Adult Survivors of Childhood Cancer: The Childhood Cancer Survivor Study

Oeffinger et al. (MSKCC).
NEJM 355(15):1572-82, 2006

Cumulative Incidence of Chronic Health Conditions among 10,397 Adult Survivors of Pediatric Cancer, Severity of subsequent health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3) as:

mild (grade 1),
moderate (grade 2),
severe (grade 3),
life-threatening or disabling (grade 4),
or fatal (grade 5).



Predictive Factors for IQ Deficits *(Merchant, JCO, 2009)*

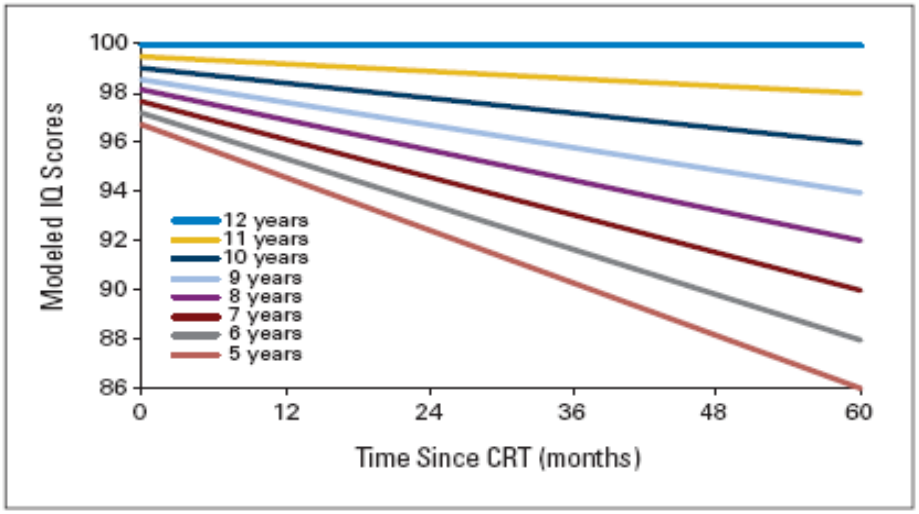


Fig 1. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age for pediatric low-grade glioma. Age is measured in years, and time is measured in months after the start of CRT.

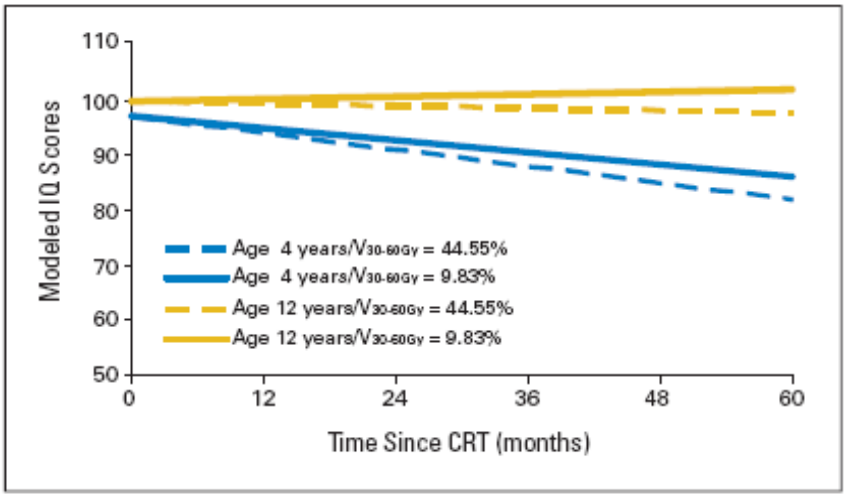
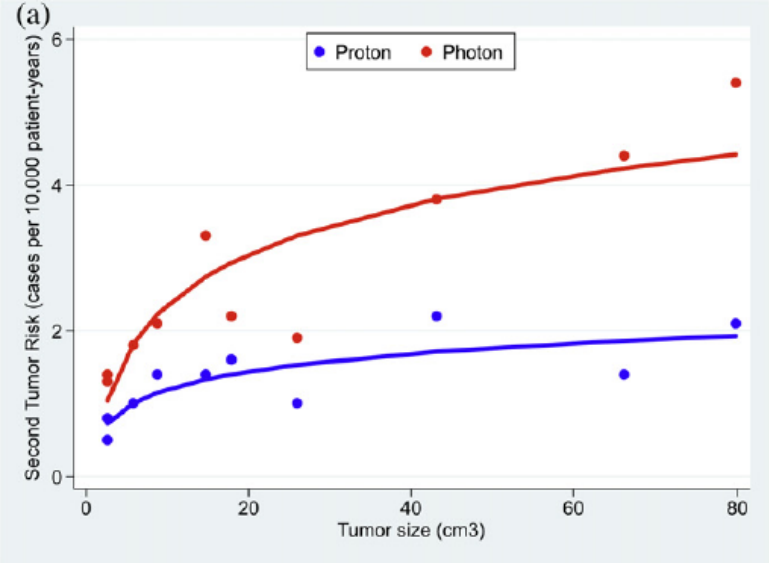


Fig 2. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age and supratentorial brain dose-volume intervals for pediatric low-grade glioma. Age is measured in years, and time is measured in months after CRT. The dose-volume intervals $V_{0\text{-}30Gy}$ and $V_{30\text{-}60Gy}$ represent the percent volume of the supratentorial brain that received dose within the specified interval.

Age at RT and Dose to Normal Tissue as important factor

Proton Therapy für the Treatment of Skull Base Tumors



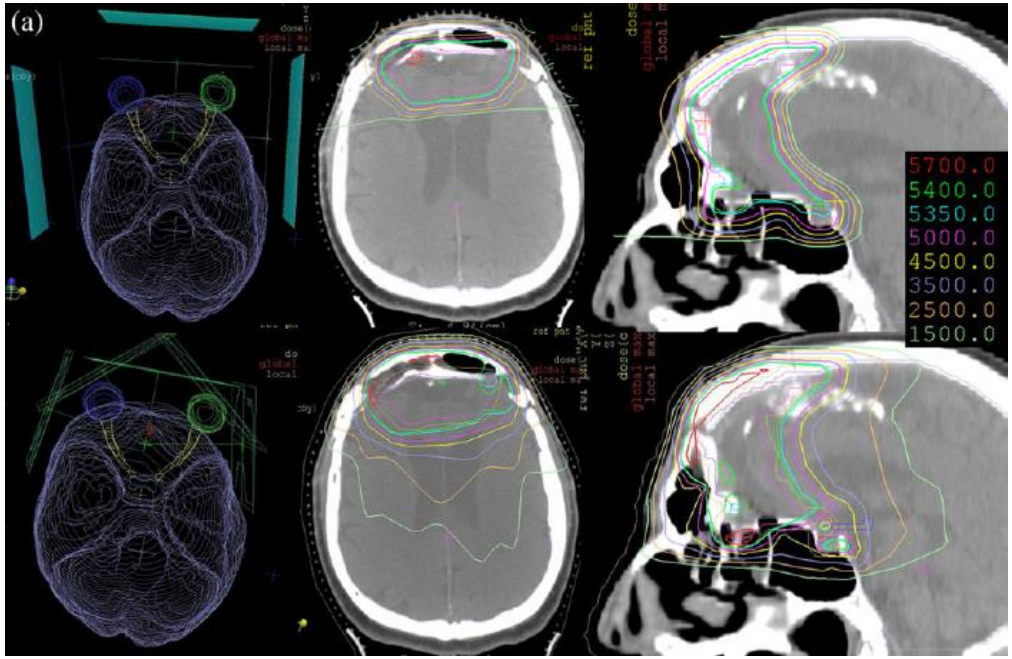


Table 4 Projected second tumor risk and late toxicities after proton vs. photon radiotherapy

Late effect	Proton RT	Photon RT	p*
Excess risk of RT-associated tumor†	1.34	2.76	0.002
Mean NTCP (%) ± SE‡			
Brainstem	0.02 ± 0.02	0.17 ± 0.16	0.36
Temporal lobe			
Left	0.06 ± 0.02	0.14 ± 0.09	0.27
Right	0.16 ± 0.14	0.21 ± 0.18	0.24
Optic chiasm	0.60 ± 0.57	0.48 ± 0.45	0.34
Optic nerve			
Left	0.02 ± 0.01	0.08 ± 0.06	0.34
Right	0.01 ± 0.004	0.01 ± 0.01	0.30

Abbreviations: RT = radiotherapy; NTCP = normal tissue complication probability; SE = standard error.

* Paired t test.

† Cases per 10,000 patient-years.

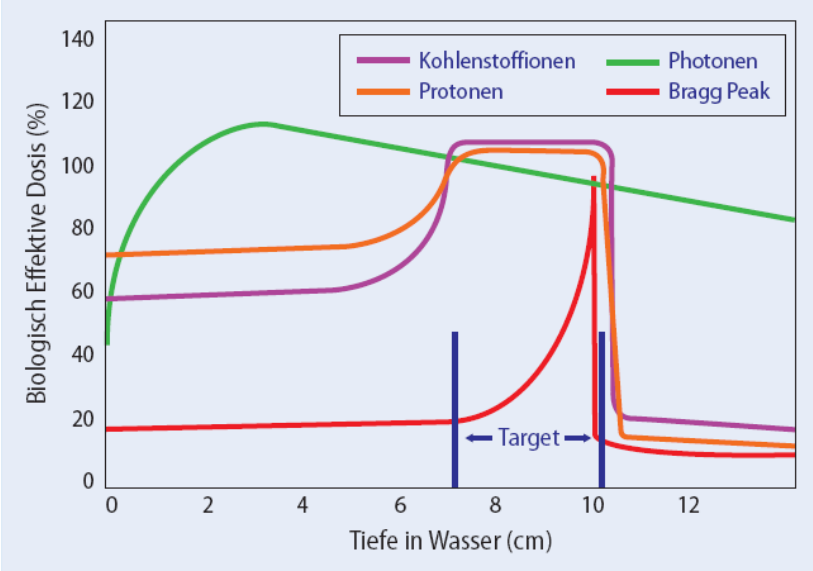
‡ The NTCP data are not presented for hippocampi, cochlea, pituitary gland, and hypothalamus owing to lack of reliable NTCP data for these structures at the doses received.

→ **Reduction of Long-Term Side effects**

→ **To date not data of clinial superiority**

Arvold et al., IJROBP 2012

Physical and biological Benefit of Ion Beams



- inverse dose profile
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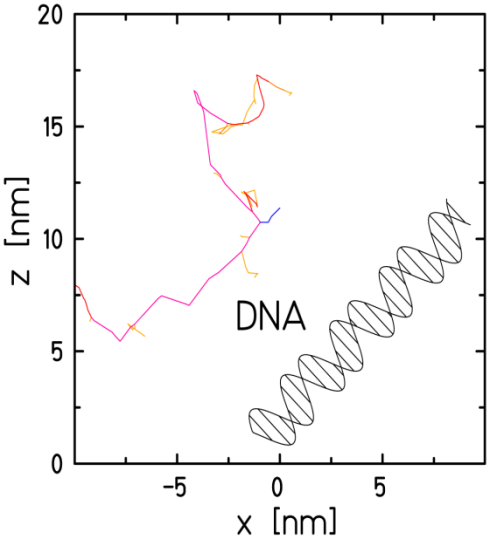
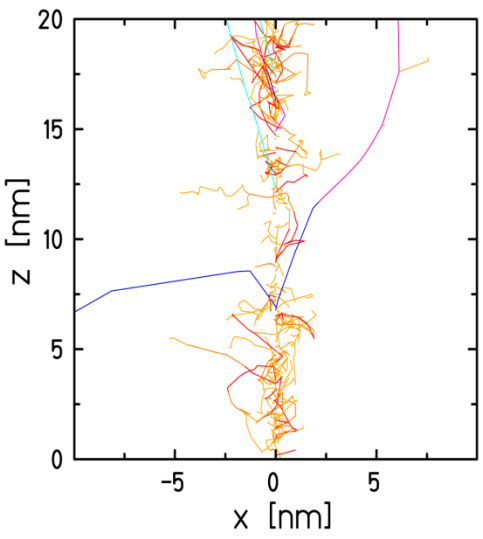
- sparing of normal tissue

Combs SE et al. Chirurg, 2007

Low-LET



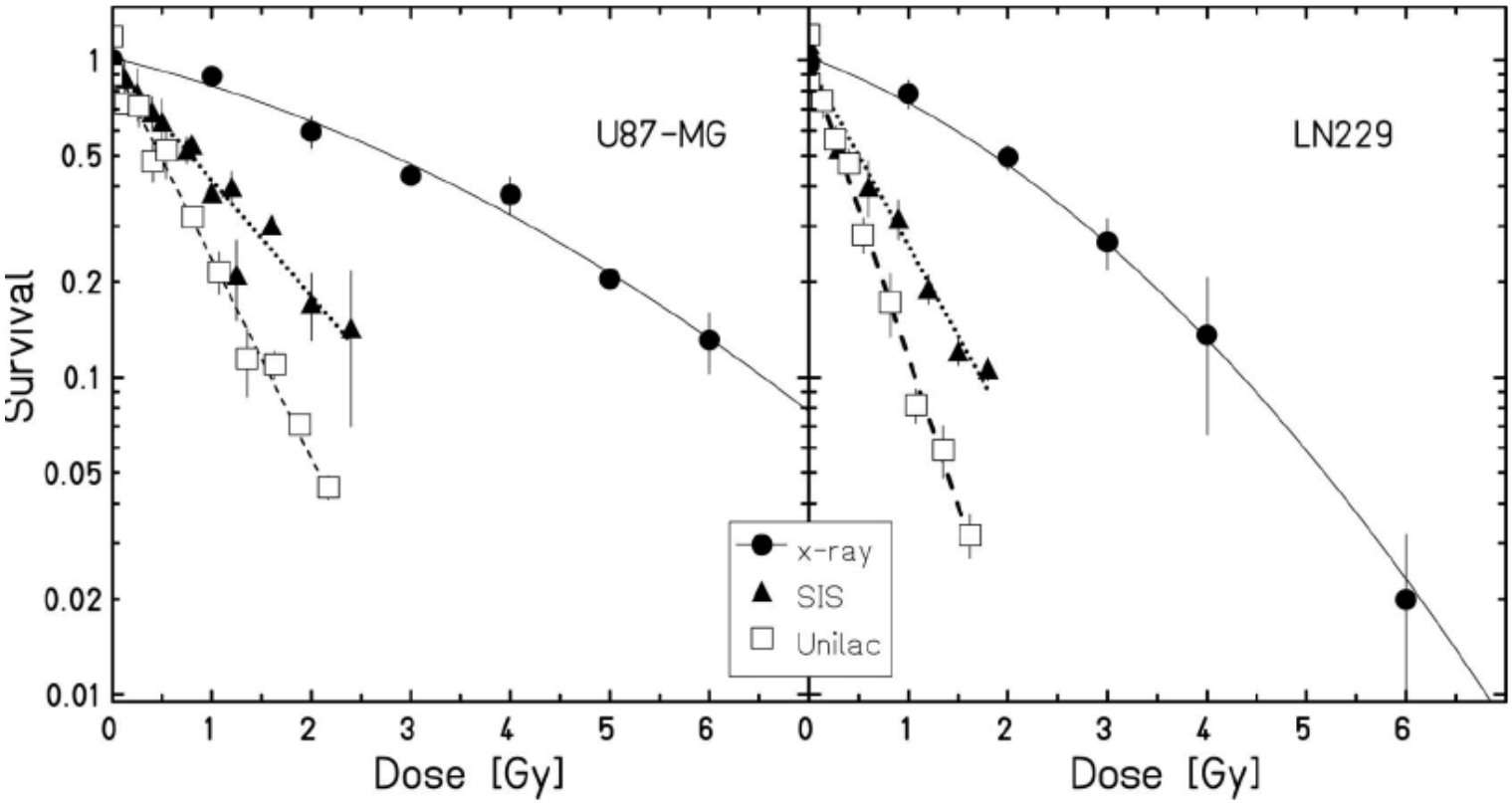
High-LET



- carbon ions: higher relative biological effectiveness (RBE)
- difficult to repair radiation damage, i.e. double strand breaks
- correlation with repair proteins, e.g. p21

M. Scholz et al. Rad. Res. 2001

Radiobiological evaluation and correlation with the local effect model (LEM) of carbon ion radiation therapy and temozolomide in glioblastoma cell lines



Combs SE et al. Int J Radiat Biol, 2009

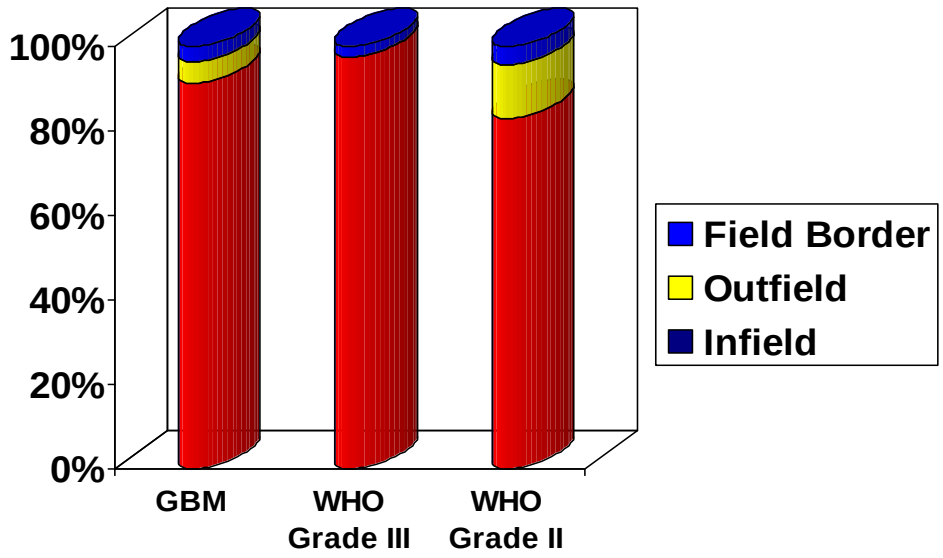
Clinical Evidence for Particle Therapy for Re-Irradiation

- several small reports (< 50 patients)
- few published prospective trials
- protons – carbon ions
- alleged superiority of dose distributions – What about the RBE and the Bragg Peak?
- Heterogeneous patient cohorts – clinical properties are „not standardized“ in the recurrent situation
  - volume of the tumor
  - time to recurrence
  - possibility of surgery
  - previous systemic treatment
  - patient performance score
  - patients‘ preference
  - Center‘s possibilities and experience

Re-irradiation of recurrent gliomas
- limits and risks -

- previous radiotherapy: majority of recurrences within the prior target volume
- patient performance, age etc.
- size and location of the lesion

Location of recurrences after primary radiotherapy



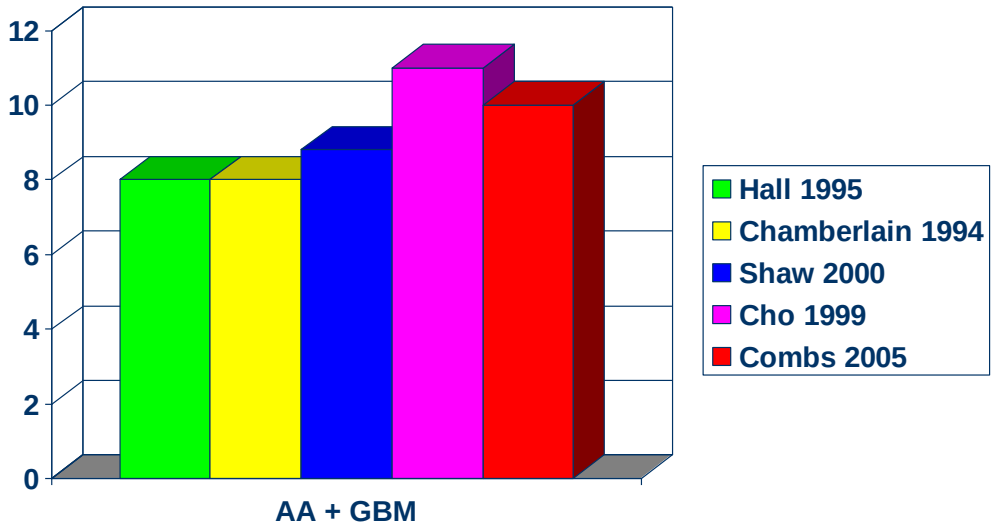
Combs SE et al., J Clin Oncol, 2005

Radiotherapeutic Options for Recurrent Gliomas
Stereotactic Radiosurgery (SRS)

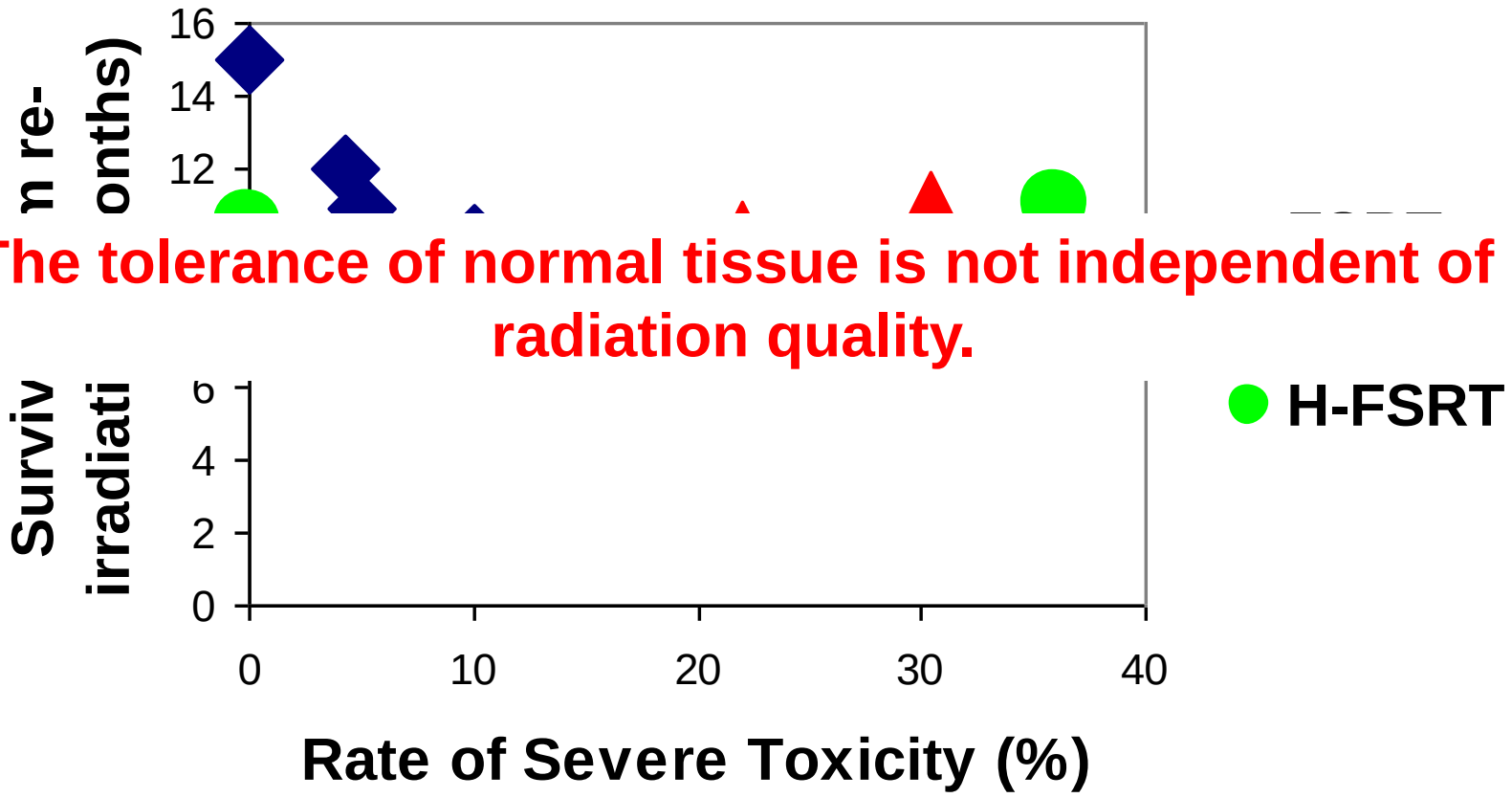
- Dose application in one fraction
- High local dose deposition
- Short treatment times

To take into consideration....

- Risk for treatment-related side effect increases with irradiation volume / recurrence volume



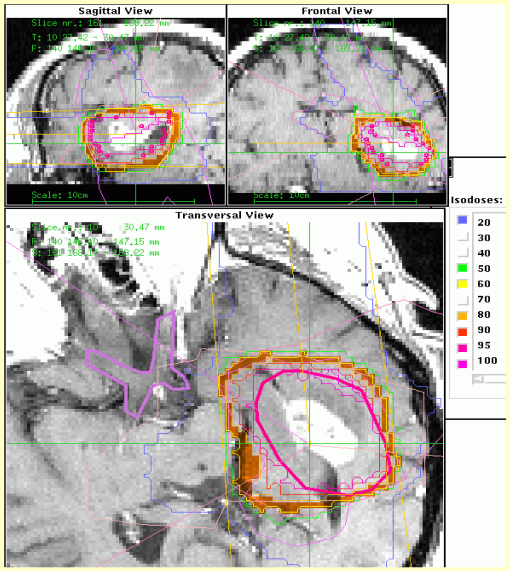
Severe Side Effects after Re-Irradiation



The tolerance of normal tissue is not independent of radiation quality.

Combs SE et al., BMC Cancer, 2007

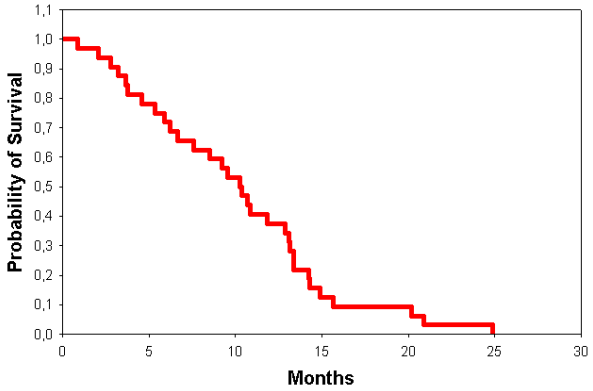
Fractionated Sterotactic Radiotherapy (FSRT)



-172 patients with recurrent glioma
- individuelle mask fixation
- GTV – contrast enhancement in T1-MRT
- CTV 5-10 mm safety margin
- median total dose 36 Gy (5*2Gy/Week)

Combs SE et al., JCO 2005
Combs SE et al., Strahlenther Onkol, 2005
Combs SE et al., J Neurooncol, 2005
Combs SE et al., J Neurooncol, 2005

Stereotactic Radiosurgery (SRS)



- 32 recurrent glioblastoma
- GTV contrast enhancement in T1-MRT
- PTV 1-2mm safety margin
- median total dose 15 Gy (range 10-20 Gy)
- median survival 10 months

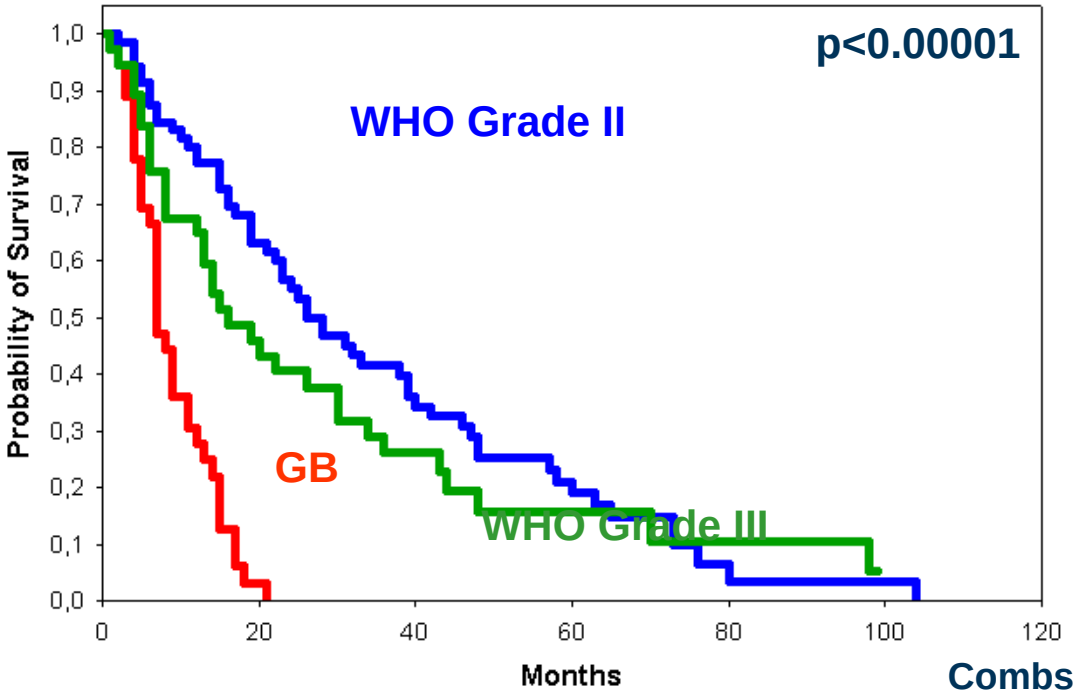
Combs SE et al., Cancer , 2005

Survival after FSRT

Radiotherapeutic Options for Recurrent Gliomas

Fractionated Stereotactic Radiotherapy (FSRT)

- Dose application in a number of fractions
- Fractionation effect beneficial with respect to side effects (normal tissue toxicity ↓)
- Less toxicity, increased treatment safety



Combs SE et al., J Clin Oncol, 2005

Randomised Phase I/II Study to Evaluate ***C***arbon ***Io****n* Ra***d***ioth***e***rapy ve***r***sus Fractionated Stereotactic R***a***diotherapy in Patients with Recurrent or Progressive G***l***iom***a***s: *The CINDERELLA Trial*

- unifocal recurrent glioma post 1 or 2 treatments
- no other re-irradiation performed
- largest diameter of contrast enhancement: 4cm

Phase I:
Dose Escalation

R

Arm A: Experimental Arm

C12

„Best-Dose“ of Phase I

10 x 3Gy E to 16 x 3 Gy E Single Dose

Arm B: Standard Arm

FSRT
Combs SE, JCO 2005
36 Gy / 2 Gy single dose

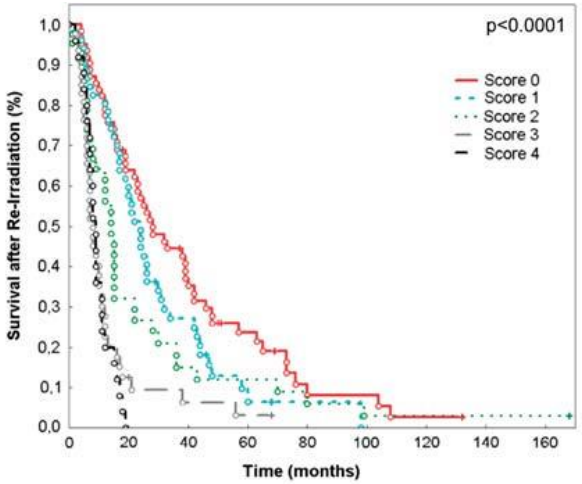
Study Coordinator: Combs SE
in cooperation with:
Prof. Dr. Wolfgang Wick, Neuroonkology
Prof. Dr. Andreas Unterberg, Neurosurgery
Dr. L. Edler, Dr. I. Burkholder, dkfz-Biostatistics

Combs SE et al., BMC Cancer 2010

Which patients benefit from re-irradiation?
Is beam quality really THE factor for outcome?

Table II. Factors identified as signficiantly influencing survival after re-irradiation used for the generation of the prognostic score.

Prognostic factor	Subgroups	Value for prognostic score
Histology	WHO Grade IV	2
	WHO Grade III	1
	WHO Grade II	0
Age	< 50 years	0
	≥ 50 years	1
Time betweeen RT and re-RT	≤ 12 months	1
	> 12 months	0



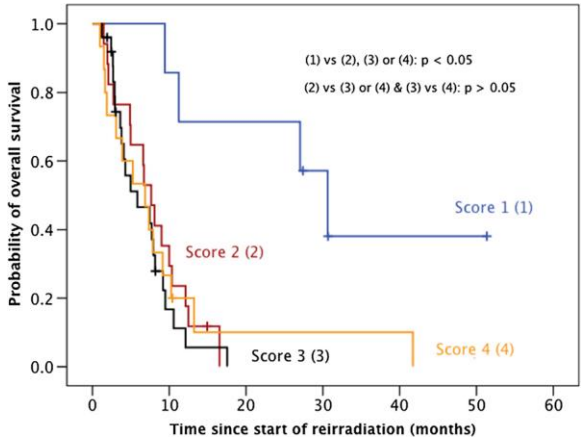


Figure 4 Re-assessment of the prognostic score recently suggested by Combs et al. to predict overall-survival after reirradiation of relapsed HGG.

- Patient age, histology, tumor volume are „classical“ prognostic factors
- Time point of re-irradiation – „the earlier the better“ but not < 6 months after first radiotherapy
- treatment dose, treatment technique
- target volume

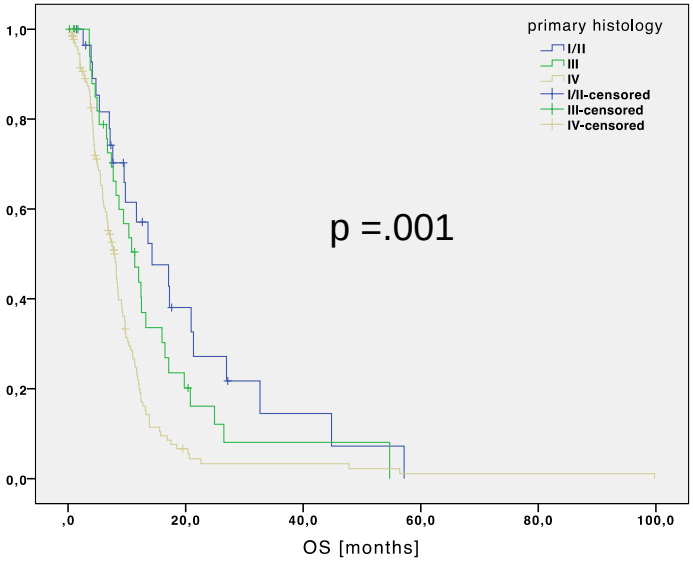
Combs SE et al., Acta Oncol, 2012; Scholtyssek et al., 2013; Combs SE et al., Cancers 2016

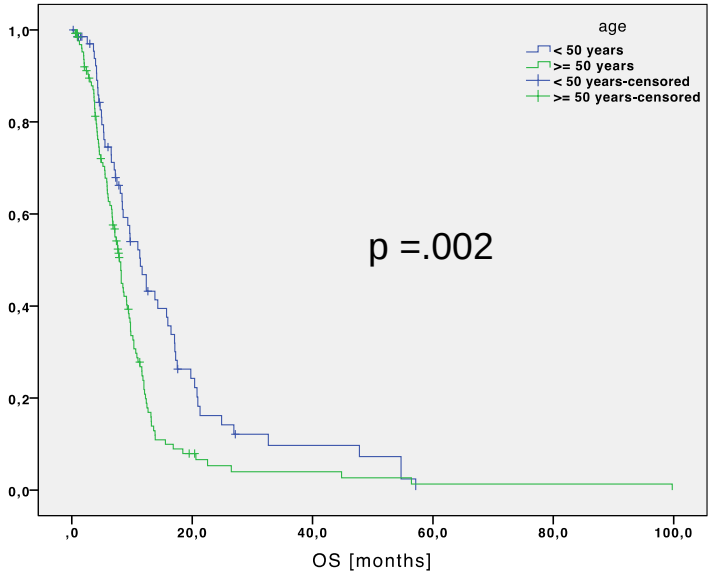
Validation of the prognostic core: TUM cohort

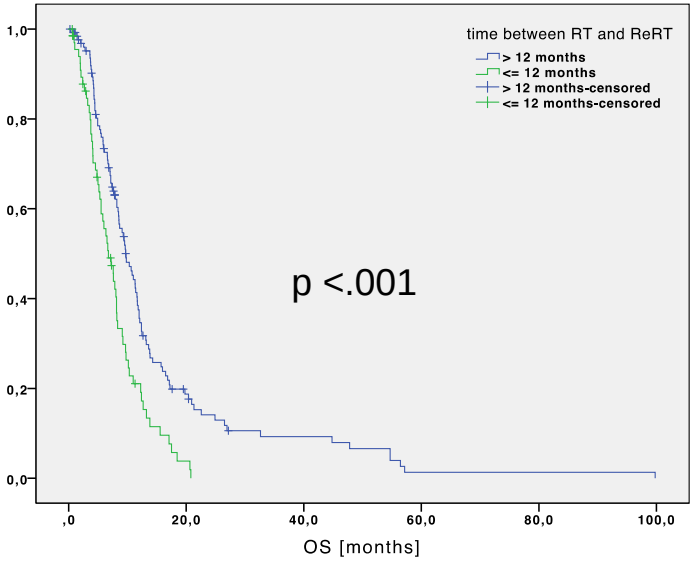
- 199 patients (female 87, male 112)
- Primary histology
  - 133 Pat: WHO IV
  - 37 Pat: WHO III
  - 29 Pat: WHO I/II
- Median time between primary RT and Re-RT [months]
  - 14.4 (1.9 – 77.7): WHO IV
  - 19.1 (5.8 – 175.7): WHO III
  - 34.0 (1.0 – 228.1): WHO I/II
- Re-resection
  - 96 Pat: no re-resection
  - 77 Pat: 1
  - 26 Pat: >= 2

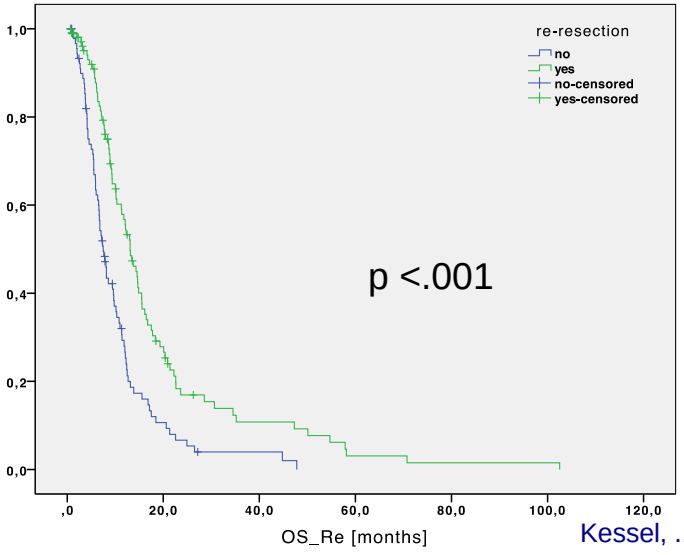
Kessel, ..., Combs, 2017

Validation of the prognostic core: TUM cohort





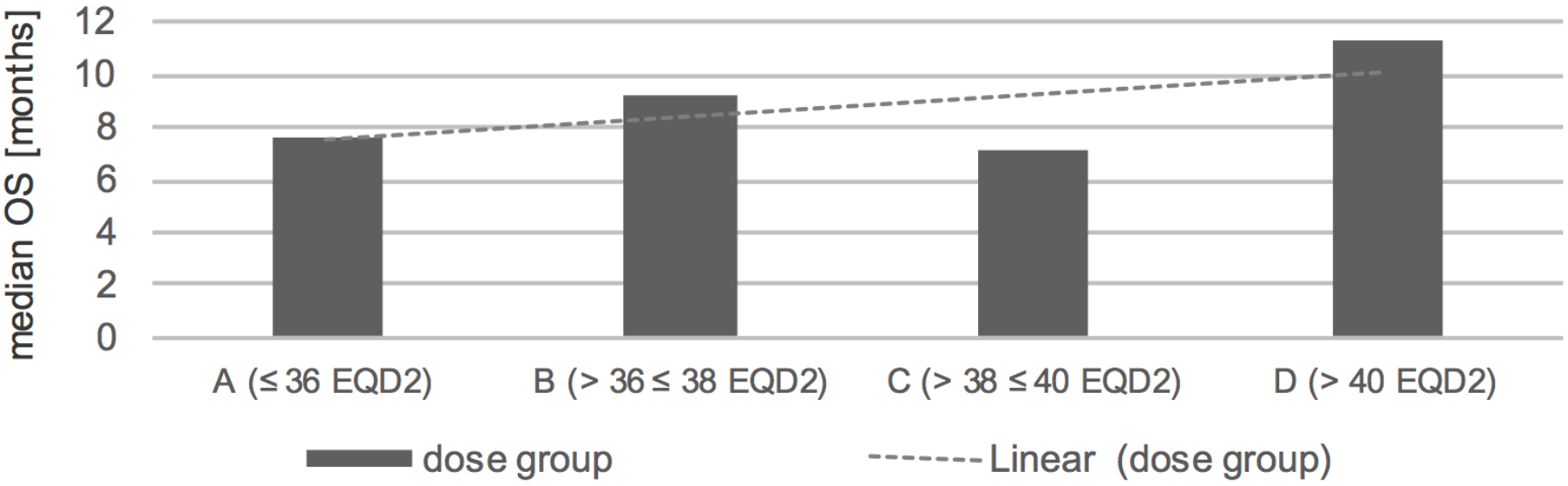




Kessel, ..., Combs, 2017

Validation of the prognostic core: TUM cohort

Outcome according to dose



Combs SE et al., Neurosurgery 2018

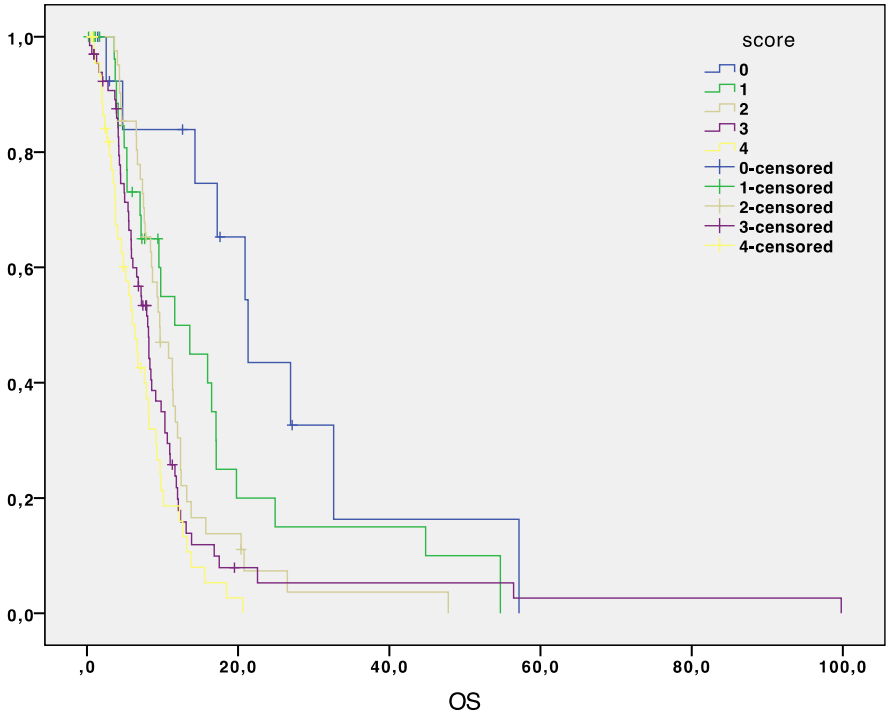
Old score vs. New score

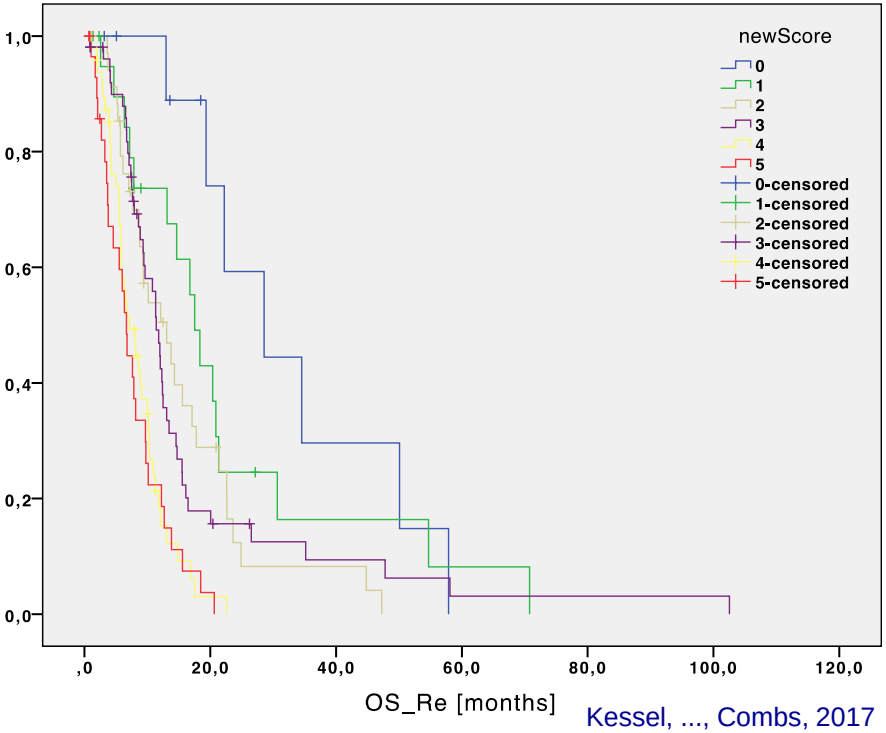
Including prognostic factors

- Primary histology (WHO IV vs. III vs. I/II)
- Age (<50y vs. ≥50y)
- Time between primary RT and Re-RT (>12m vs ≤12m)

Including prognostic factors

- Primary histology (WHO IV vs. III vs. I/II)
- Age (<50y vs. ≥50y)
- Time between primary RT and Re-RT (>12m vs ≤12m)
- **added: Re-resection** (yes vs. no)





Kessel, ..., Combs, 2017

ORIGINAL RESEARCH

Re-irradiation of recurrent gliomas: pooled analysis and validation of an established prognostic score—report of the Radiation Oncology Group (ROG) of the German Cancer Consortium (DKTK)

Stephanie E. Combs[1,2,3], Maximilian Niyazi[3,4], Sebastian Adeberg[3,5], Nina Bougatf[3,5], David Kaul[3,6], Daniel F. Fleischmann[3,4], Arne Gruen[6], Emmanouil Fokas[3,7], Claus M. Rödel[3,7], Franziska Eckert[3,8], Frank Paulsen[3], Oliver Oehlke[3,9], Anca-Ligia Grosu[3,9], Annekatrin Seidlitz[3,10], Annika Lattermann[3,10,11], Mechthild Krause[3,10,11], Michael Baumann[3,10,11,12,13], Maja Guberina[3,14], Martin Stuschke[3,14], Volker Budach[3,6], Claus Belka[3,4], Jürgen Debus[3,5] & Kerstin A. Kessel[1,2,3]

Table 2. Scoring scheme of the original [14] and new [15] score.

Prognostic factor	Prognostic value of the original score	Prognostic value of the new score
Primary histology at diagnosis		
WHO IV	2	2
WHO III	1	1
WHO I/II	0	0
Age		
≥50 years	1	1
<50 years	0	0
Time from primary RT to re-RT		
≤12 months	1	1
>12 months	0	0
KPS		
<80%		1
≥80%		0
Tumor volume (PTV)		
>47 mL		1
≤47 mL		0
Reresection performed		
No		1
Yes		0

re-RT, re-irradiation; KPS, Karnofsky Performance Score; PTV, Planning target volume.

Table 3. OS analysis of the prognostic factors and scores.

	Univariate analysis		
Prognostic factor	HR	95% CI	*P*-Value
Primary histology at diagnosis	1.28	1.06–1.54	0.010*
Age (≥50 y vs. <50 y)	1.45	1.21–1.75	<0.001*
Time from primary RT to re-RT (≤12 m vs. >12 m)	1.18	0.98–1.41	0.074
KPS (<80% vs. ≥80%)	2.02	1.67–2.43	<0.001*
Tumor volume (PTV) (>47 mL vs. ≤47 mL)	1.23	1.02–1.49	0.032*
Reresection performed (no vs. yes)	0.82	0.65–1.04	0.101
MGMT status (methylated vs. not methylated)**	0.67	0.52–0.86	0.002*
Score			
Original score	1.20	1.10–1.32	<0.001*
New score	1.22	1.11–1.34	<0.001*

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Re-irradiation of recurrent gliomas: pooled analysis and validation of an established prognostic score—report of the Radiation Oncology Group (ROG) of the German Cancer Consortium (DKTK)

Stephanie E. Combs[1,2,3], Maximilian Niyazi[3,4], Sebastian Adeberg[3,5], Nina Bougatf[3,5], David Kaul[3,6], Daniel F. Fleischmann[3,4], Arne Gruen[6], Emmanouil Fokas[3,7], Claus M. Rödel[3,7], Franziska Eckert[3,8], Frank Paulsen[3], Oliver Oehlke[3,9], Anca-Ligia Grosu[3,9], Annekatrin Seidlitz[3,10], Annika Lattermann[3,10,11], Mechthild Krause[3,10,11], Michael Baumann[3,10,11,12,13], Maja Guberina[3,14], Martin Stuschke[3,14], Volker Budach[3,6], Claus Belka[3,4], Jürgen Debus[3,5] & Kerstin A. Kessel[1,2,3]

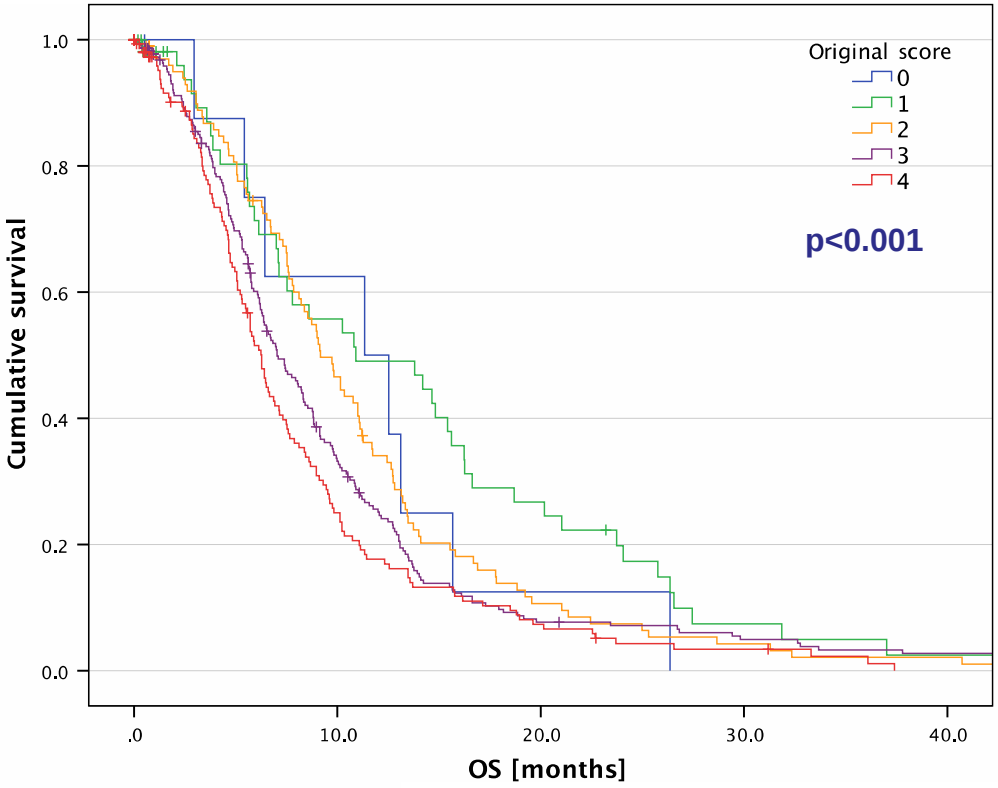


Table 4. Median OS and life table for both scores.

	n	Median OS	Proportion surviving after re-RT	
			6 months (%)	12 months (%)
Original score				
0	9 (2%)	12.0	75	50
1	60 (11%)	11.3	76	49
2	106 (19%)	9.7	76	35
3	224 (41%)	7.5	64	26
4	153 (28%)	6.6	57	18
New score				
a	2 (1%)	16.8	100	100
b	67 (19%)	9.4	75	34
c	199 (56%)	9.4	75	34
d	88 (25%)	6.1	50	12

OS, Overall survival; *n*, number of patients.

Combs SE et al., 2018

Re-irradiation of gliomas

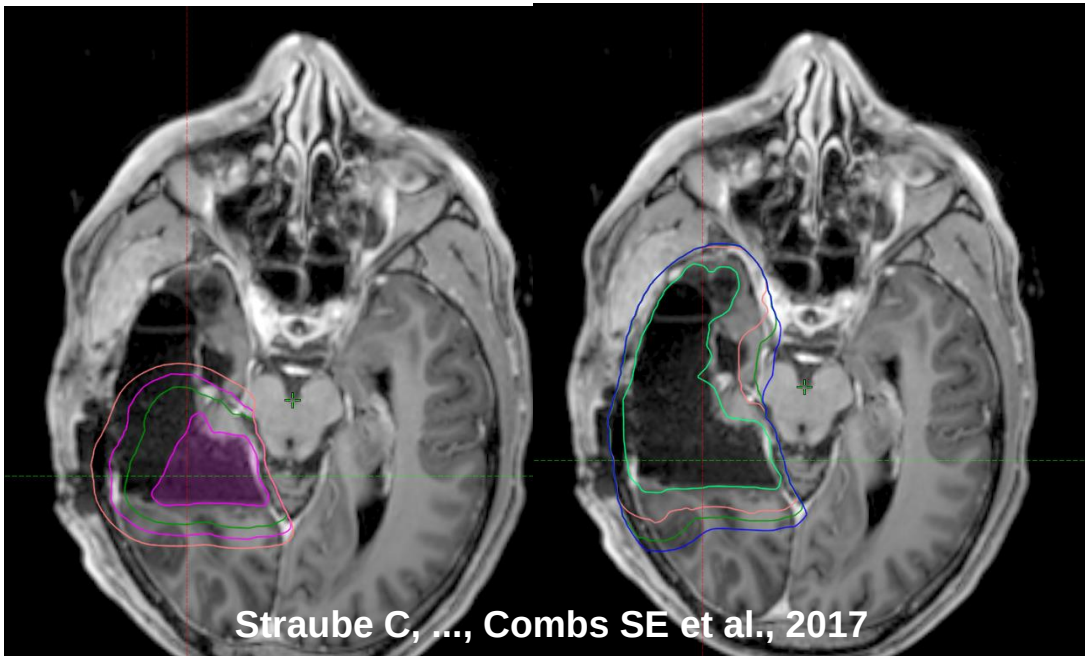
- ... Has been established in clinical routine
- various fractionation concepts
- indication generally in incompletely resected tumors (on MRI and/or PET)
- alone or in combination with chemotherapy
- Information of recurrence and risk patterns?
- Target volume?
- Influence of any biomarkers?
- But – we randomize photons vs. Carbon based on macroscopic tumor

- question: “complete resection“?

No real evidence..

Definition of target volumes for re-irradiation of the resection cavity: Integration of CT, MRI and PET

- Pt. With previous irradiation
- „complete resection“ of the recurrence
- Target volume generation with different safety margins:
  - Resection cavity primary tumor
  - Resection cavity recurrence
  - Margins?
  - Organs at risk (OAR)- normal brain, eloquent regions, hippocampus



GlioCave – NOA 17 Trial

A Phase-II Trial comparing adjuvant stereotactic fractionated radiotherapy to the resection cavity in recurrent glioblastoma to observation

- recurrent glioblastoma after standard treatment (surgery, chemoradiation)
- no prior re-irradiation
- „complete resection“

Phase II

R

Arm A: Experimental Arm

High precision-RT

46 Gy/2 Gy / 36 Gy, 3 Gy

(resection cavity, margin)

Arm B: no RT

PI: Stephanie E. Combs
In cooperation with:
Prof. Dr. Bernhard Meyer, Neurochirurgie TUM
Prof. Dr. Claus Zimmer, Neuroradiologie, TUM
Study Coordinator: Dr. C. Straube, TUM RadOnk

Straube S, ..., Combs SE, BMC Cancer 2017

GlioCave – NOA 17 Trial

A Phase-II Trial comparing adjuvant stereotactic fractionated radiotherapy to the resection cavity in recurrent glioblastoma to observation

- pre-operative imaging (PET, MRI)
- surgical resection
- collection of serum, tumor tissue, primary cell cultures
- characterization of migration, invasion, other biomarkers for radiation (γH2AX)
- treatment according to study protocol
- MRI during treatment - @10 fractions – including T1, T2 weighted sequences, DTI
- correlation of biological and clinical data

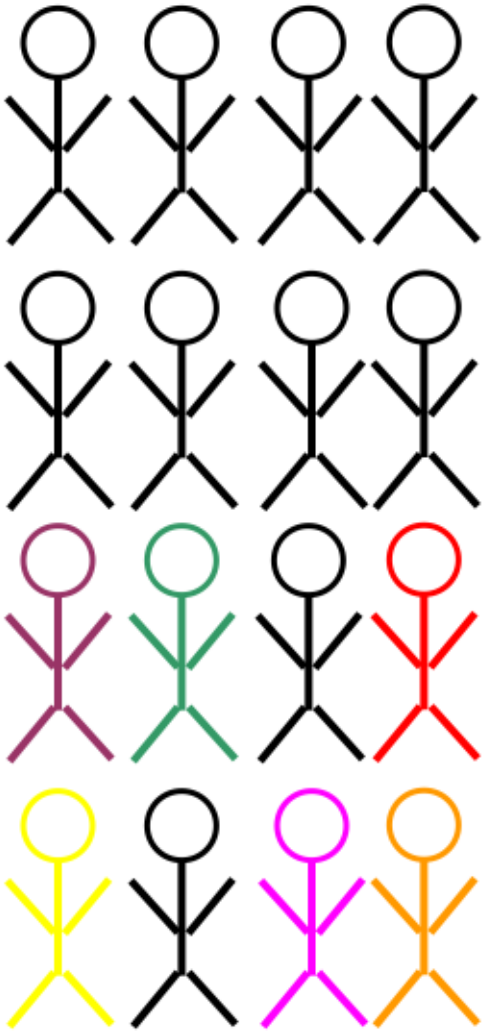
PI: Stephanie E. Combs
In cooperation with:
Prof. Dr. Bernhard Meyer, Neurochirurgie TUM
Prof. Dr. Claus Zimmer, Neuroradiologie, TUM
Study Coordinator: Dr. C. Straube, TUM RadOnk

Straube S, ..., Combs SE, 2017

Re-Irradiation of Gliomas

- Has an etasblished role in the multimodal treatment of gliomas
- Optimal dose and target volumes yet need to be defined
- Radiosurgery vs. Fractionated – impact of volume, location etc.
- Potential benefit of high single doses ?!?
- Combination with systemic treatment safe and certainly possible depending on the individual pre-treatment
- Prognostic scores reflect the heterogeneity of gliomas
- Benefit of particles? Not proven yet...

Innovative Radiotherapy (*i*RT) Concepts



Radiotherapy

- histopathological characteristics
- molecular markers
- individual radiation sensitivity
- immunological properties
- patient-individual factors such as Karnofsky Performance Status, diabetes, nutritional state etc.

Individualized Radiotherapy (*i*RT)

Combs SE, Langenbecks Archives of Surgery, 2015

Improving the Therapeutic Window: Clinical Rationale for Particle Therapy

What are the „new possibilities“ I can use with particle therapy?

How is my efficacy? What biology is in the background?

Which patients most probably have the best benefit?

Do I have increased precision, i.e. can I reduce dose do non-involved areas?

- Reduction of integral dose
- sparing of normal tissue
- minimizing side effects, especially long-term toxicity
- **Normal tissue tolerance does not change – independently of radiation modality...**

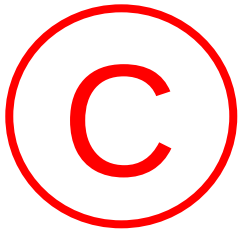
High-LET Radiotherapy, e.g. Carbon Ions

- High-LET radiotherapy
- Relative Biological Effectiveness (RBE) > 1
- Higher relative biological effectiveness
- However, data on biological „uncertainties“, e.g. increase in RBE at distal end
- Biological Models, „dose painting“...
- Incoming Data on Proton/Carbon Biology:
  - Proton irradiation suppresses angiogenic genes and impairs cell invasion and tumor growth (Radiat Research 2012)
  - Uncertainties in RBE

Phase I/II Study evaluating the treatment of patients with Recurrent Rectal Cancer with Carbon Ion Radiotherapy: *The PANDORA-01 Trial*

- histologically confirmed recurrent rectal cancer
- macroscopic tumor
- localized, no metastases

RRC



Arm A: Experimental Arm

Carbon Ion Radiotherapy

Dose Escalation

12 x 3 Gy E

Increasing fraction number

18 x 3 Gy E

Arm B: Historical Controls

Study Coordinator Combs SE
in cooperation with
Prof. Dr. Jürgen Weitz & Prof. Dr. Dr. M Büchler, Surgery
Prof. Dr. Dr. Jäger, NCT/Oncology
Prof. Dr. M. Kieser, Biostatistics
ULICE-Framework

Combs SE et al., BMC Cancer 2014

Re-Irradiation for Recurrent Meningiomas

Table 1 Patient characteristics

Age at re-irradiation (years)			
	Mean (SD)	53	13,4
	Median (Q1-Q3)	53	47–61
	Median (range)	53	18–77
		n=	%
Gender			
	male	17	40,5%
	female	25	59,5%
Histology			
	WHO I	10	23,8%
	WHO II	25	59,5%
	WHO III	6	14,3%
	unknown	1	2,4%
Location			
	skull base	31	73,8%
	falx	6	14,3%
	convexity	5	11,9%
Karnofsky performance score			
	≥ 80%	34	81,0%
	< 80%	8	19,0%
Previous radiotherapy			
	IMRT	16	38,1%
	3DCRT	16	38,1%
	SRS/FSRT	8	19,0%
	radiopeptide	1	2,4%
	carbon ions	1	2,4%
Recurrence			
	infield / field border	38	90,5%
	outfield	4	9,5%
Particle therapy			
	protons	8	19,0%
	carbon ions	34	81,0%

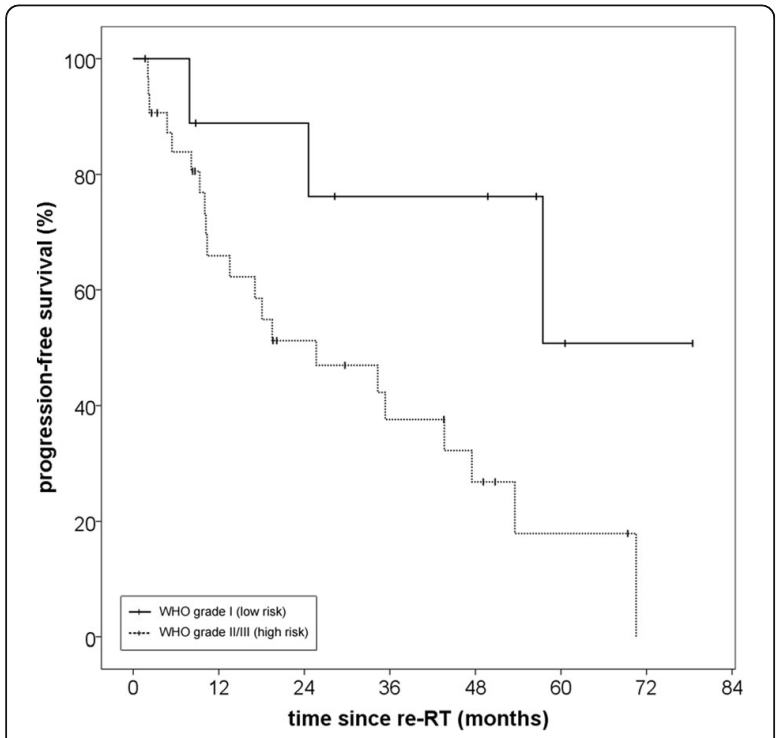


Fig. 2 Impact of histology on progression-free survival when classified as low-risk (WHO grade I) and high-risk (grades II and III). The difference between the two groups was significant ($p = 0{,}03$)

El Shafi R, ..., Combs SE, Radiat Oncol 2018

Re-Irradiation for Recurrent Meningiomas

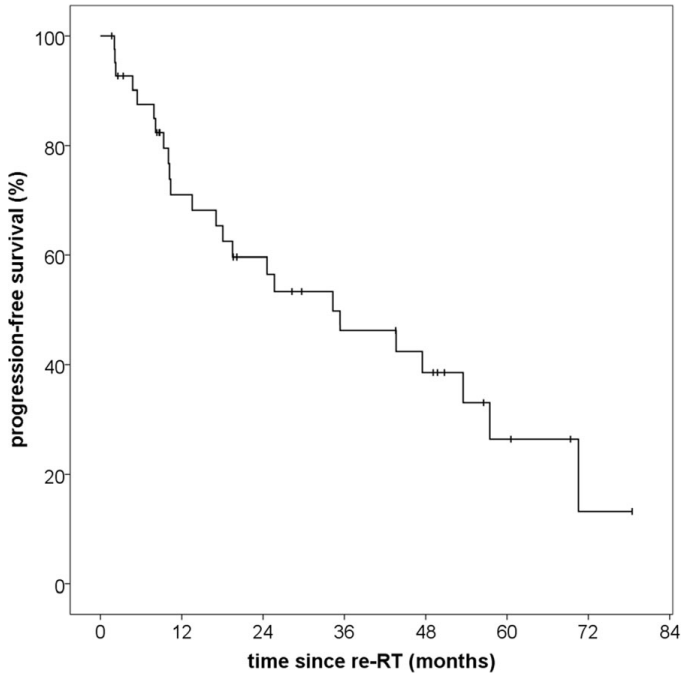


Fig. 1 Progression-free survival for patients with recurrent meningioma regardless of histology after re-irradiation with particle therapy

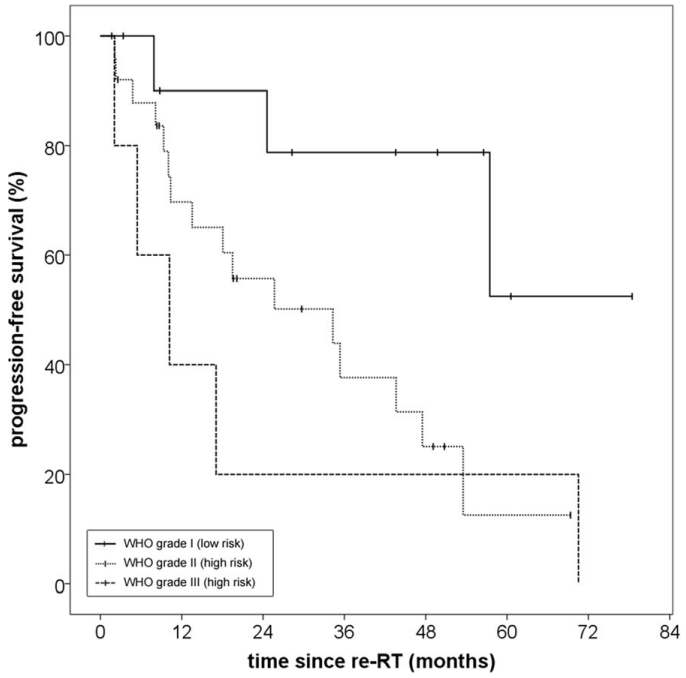


Fig. 3 Impact of histology on progression-free survival regarding all WHO grades separately: The difference between grades I and III was significant ($p = 0.02$) but not between grades II and III ($p = 0{,}43$)

El Shafi R, ..., Combs SE, Radiat Oncol 2018

Re-Irradiation for Recurrent Meningiomas

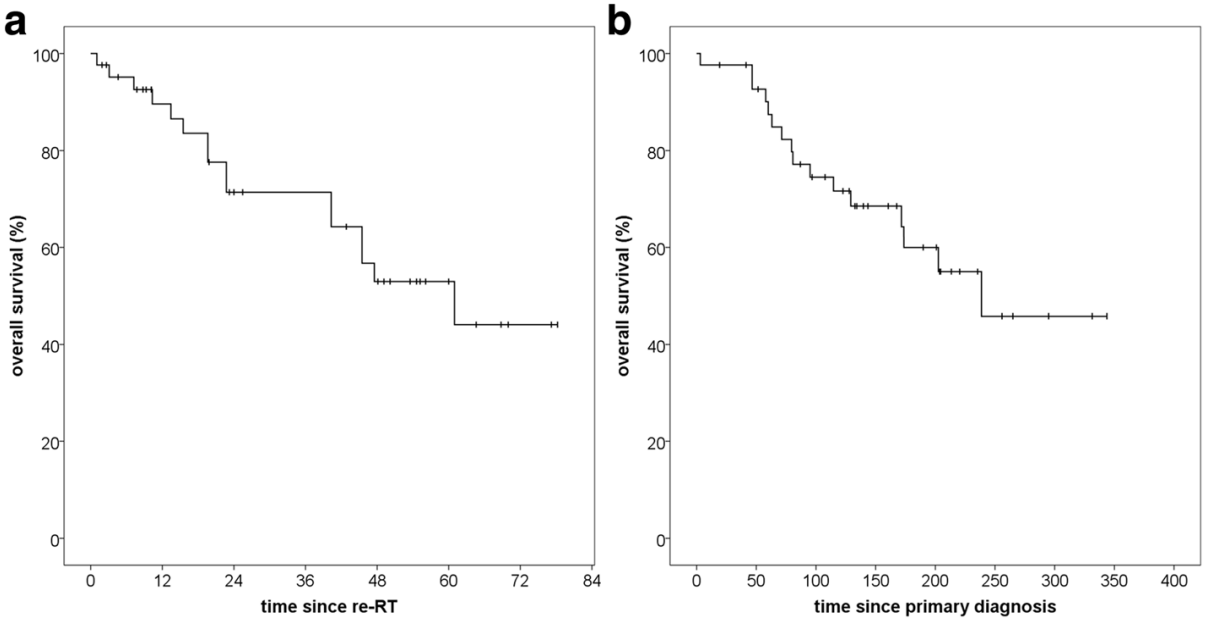


Fig. 4 Overall survival for patients with recurrent meningioma regardless of histology after re-irradiation with particle therapy, calculated from date of re-irradiation (**a**) and from date of primary diagnosis (**b**)

El Shafi R, ..., Combs SE, Radiat Oncol 2018

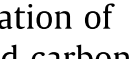
Re-Irradiation of Adenoid-Cystic Carcinomas

Table 1
Patient characteristics and radiotherapy.

Patient characteristics		
	Pts	%
Re-treatment site		
Paranasal sinus	19	36.5
Base of skull/intracranial	11	21.2
Parotid	10	19.2
Submandibular gland	3	5.8
Nasopharynx	2	3.8
Pterygopalatine fossa	2	3.8
Orbit	2	3.8
Lacrimal gland	1	1.9
Auditory canal	1	1.9
Jaw angle	1	1.9
Re-treatment stage		
T2	2	3.8
T3	10	19.2
T4	40	76.9
T4a	6	11.5
T4b	34	65.4
N1	1	1.9
N2a	1	1.9
N2b	3	5.8
N2c	1	1.9
M1	15	28.8
Prior surgery	7	13.5
Macroscopic tumour at re-RT	45	86.5
Radiotherapy		
IMRT + C12-boost	4	7.7
C12 only	48	92.3
	Median (Gy/GyE)	Range (Gy/GyE)
Prior radiotherapy		
Nominal dose	66	20–115
BED	66	20–133
Re-irradiation		
Nominal dose	51	36–74
BED	63	45–82
Cumulative life-time dose		
BED	128	67–182
Interval between RT courses	61 mo	9–620 mo
Treatment volume		
CTV (C12)	93 ml	6–618 ml
CTV (IMRT); 4 pts only!	334 ml	211–344 ml

Adenoid cycstic carcinoma

Re-irradiation of adenoid cystic carcinoma: Analysis and evaluation of outcome in 52 consecutive patients treated with raster-scanned carbon ion therapy



Jensen et al., 2017

Re-Irradiation of Adenoid-Cystic Carcinomas

Adenoid cycstic carcinoma

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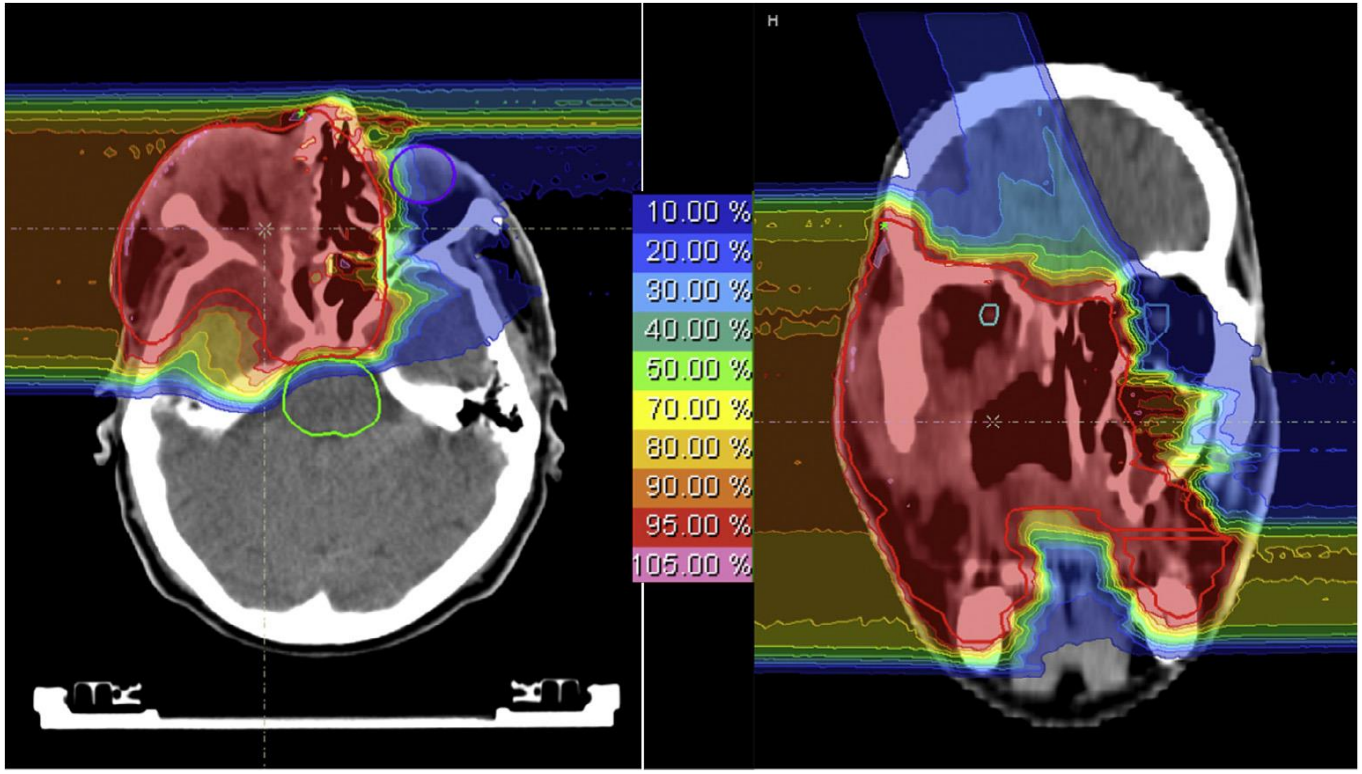
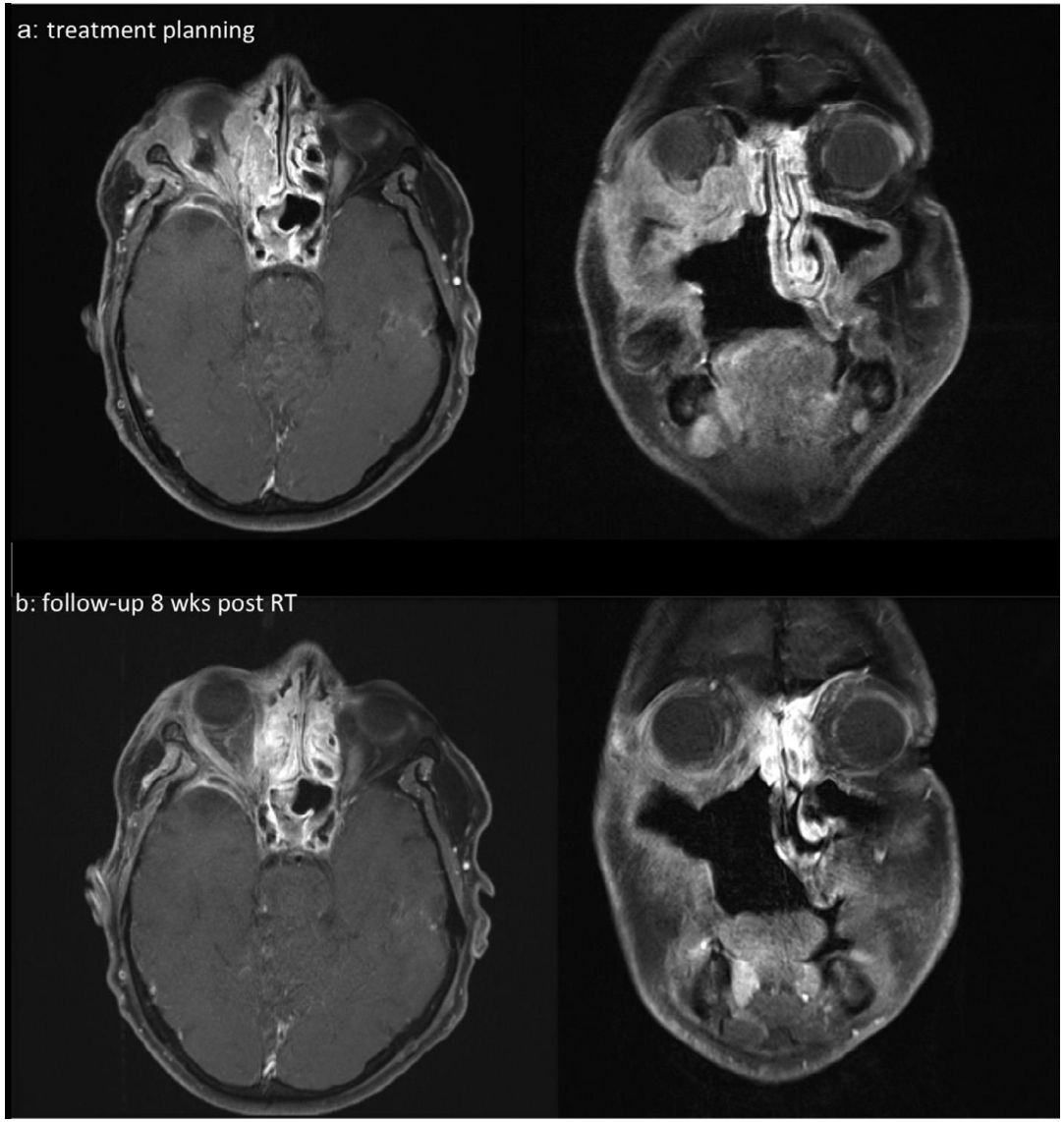


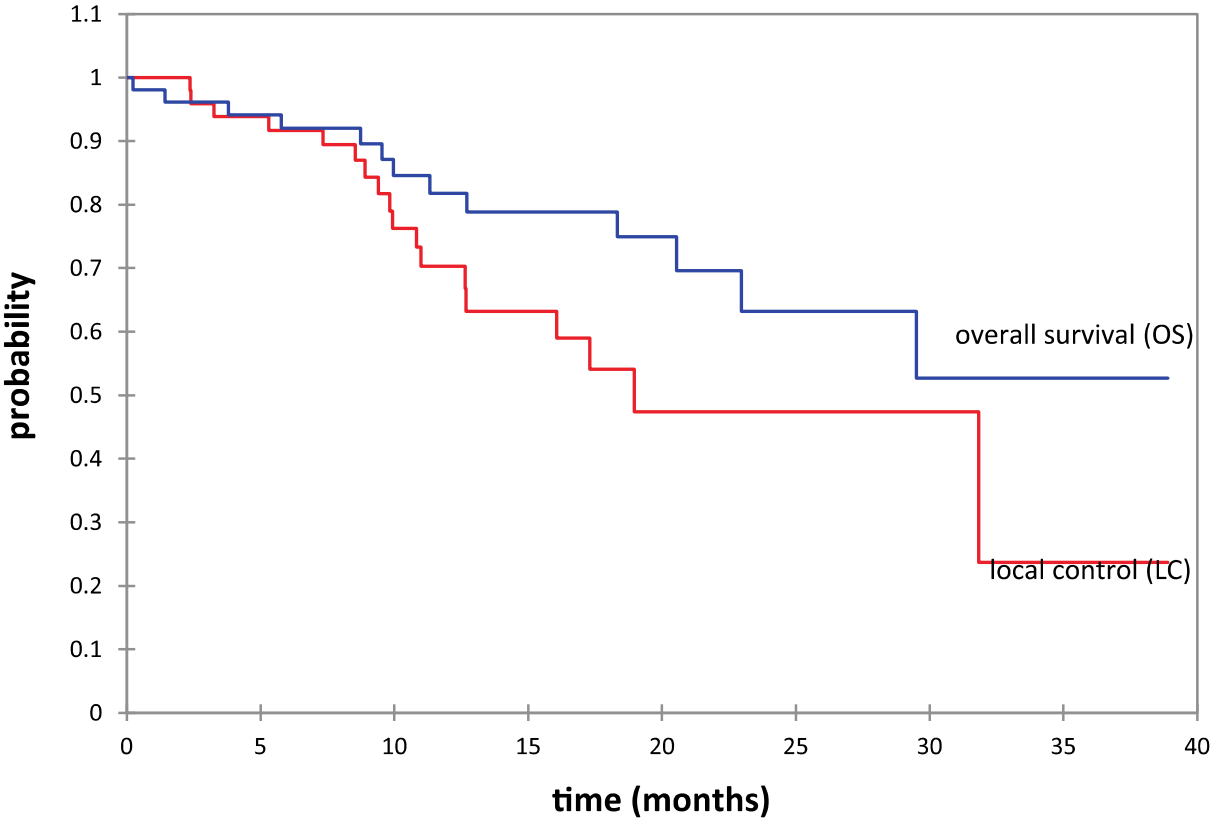
Jensen et al., 2017

Re-Irradiation of Adenoid-Cystic Carcinomas



Jensen et al., 2017

Re-Irradiation of Adenoid-Cystic Carcinomas



numbers at risk:

OS:	52	47	35	24	17	9	6	4
LC:	52	46	28	17	8	4	4	2

Jensen et al., 2017

Re-Irradiation of Head and Neck Tumors with Protons

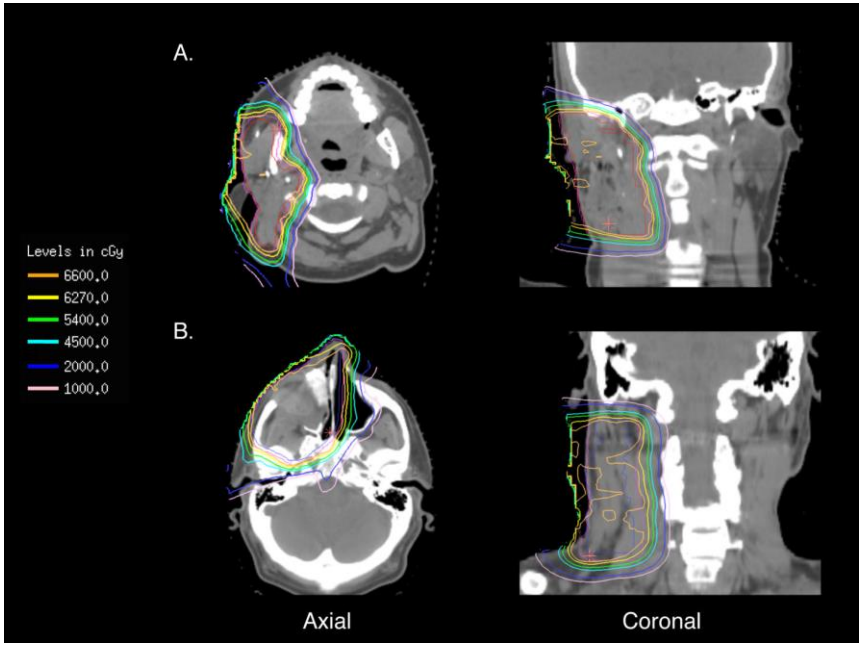
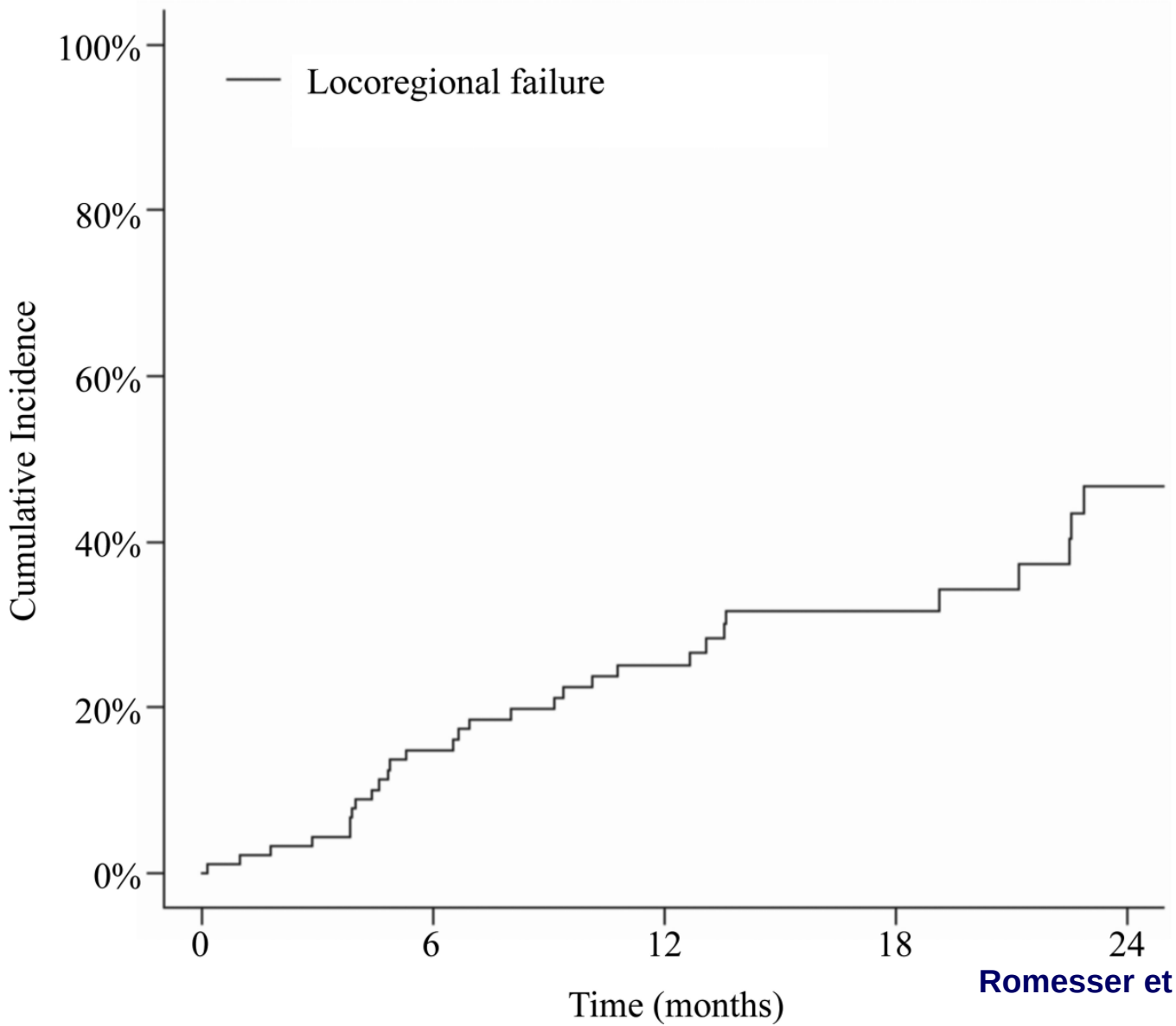


Figure 3.
Representative isodose plans for patients under going re-RT for (3a) recurrent poorly differentiated carcinoma with squamous features previously treated to 48Gy with concurrent cisplatin and etoposide after a superficial parotidectomy who developed a local recurrence ~3 years later who underwent re-irradiation with PBRT to 66Gy (RBE) in 33 fractions with concurrent cisplatin in the post-operative setting for a positive margin after a right parotidectomy with right masseter muscle resection, rectus abdominus free flap reconstruction, and selective right neck dissection and (3b) recurrent olfactory neuroblastoma previously treated to 55.8 Gy after endoscopic resection who developed a local recurrence ~2.5 years later who underwent re-irradiation with PBRT to 66Gy (RBE) in 33 fractions in the post-operative setting for a positive margin after a right maxillectomy, extranasal ethmoidectomy, dacryocystorhinostomy, and right modified neck dissection for a positive margin, cortical bone invasion, perineural invasion, and four positive nodes with extracapsular extension. The PTV is in magenta and CTV is in red.

	All	SCC	non-SCC
	N (%)	*N (%)*	*N (%)*
Gender			
Male	65 (70.7%)	38 (73.1%)	27 (67.5%)
Female	27 (29.3%)	14 (26.9%)	13 (32.5%)
KPS			
≥80	65 (70.7%)	41 (78.8%)	24 (60.0%)
<80	18 (19.6%)	7 (13.5%)	11 (27.5%)
Not recorded	9 (9.8%)	4 (7.7%)	5 (12.5%)
Initial disease site			
Oropharynx	17 (18.5%)	17 (32.7%)	0 (0.0%)
Nasal cavity/paranasal sinuses	12 (13.0%)	4 (7.7%)	8 (20.0%)
Oral cavity	12 (13.0%)	9 (17.3%)	3 (7.5%)
Salivary glands	11 (12.0%)	0 (0.0%)	11 (27.5%)
Larynx/ hypopharynx	10 (10.9%)	9 (17.3%)	1 (2.5%)
Nasopharynx	9 (9.8%)	5 (9.6%)	4 (10.0%)
Other	21 (22.8%)	8 (15.4%)	13 (32.5%)

Romesser et al., 2016

Re-Irradiation of Head and Neck Tumors with Protons



Romesser et al., 2016

Re-Irradiation of Head and Neck Tumors with Protons

Table 3

Acute toxicity[1]

	Total	Grade 0	(%)	Grade 1	(%)	Grade 2	(%)	Grade 3	(%)	Grade 4	(%)
Dysphagia[2]	66	25	37.9%	19	28.8%	16	24.2%	6	9.1%	0	0.0%
Mucositis	91	37	40.7%	29	31.9%	16	17.6%	9	9.9%	0	0.0%
Nausea	91	63	69.2%	21	23.1%	7	7.7%	0	0.0%	0	0.0%
Dysgeusia	91	50	54.9%	23	25.3%	18	19.8%	0	0.0%	0	0.0%
Esophagitis[2]	66	41	62.1%	12	18.2%	7	10.6%	6	9.1%	0	0.0%
Dermatitis	91	10	11.0%	38	41.8%	40	44.0%	3	3.3%	0	0.0%

[1] Data unavailable for one patient, admitted during treatment

[2] Limited to patients without G-tube in place or symptoms prior to treatment

Romesser et al., 2016

Basic Original Report

Reirradiation of thoracic cancers with intensity modulated proton therapy

Jennifer C. Ho MD [a], Quynh-Nhu Nguyen MD [a], Heng Li PhD [a], Pamela K. Allen PhD [a], Xiaodong Zhang PhD [b], Zhongxing Liao MD [a], X. Ronald Zhu PhD [b], Daniel Gomez MD [a], Steven H. Lin MD, PhD [a], Michael Gillin PhD [b], Ritsuko Komaki MD [a], Stephen Hahn MD [a], Joe Y. Chang MD, PhD [a,*]

[a]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
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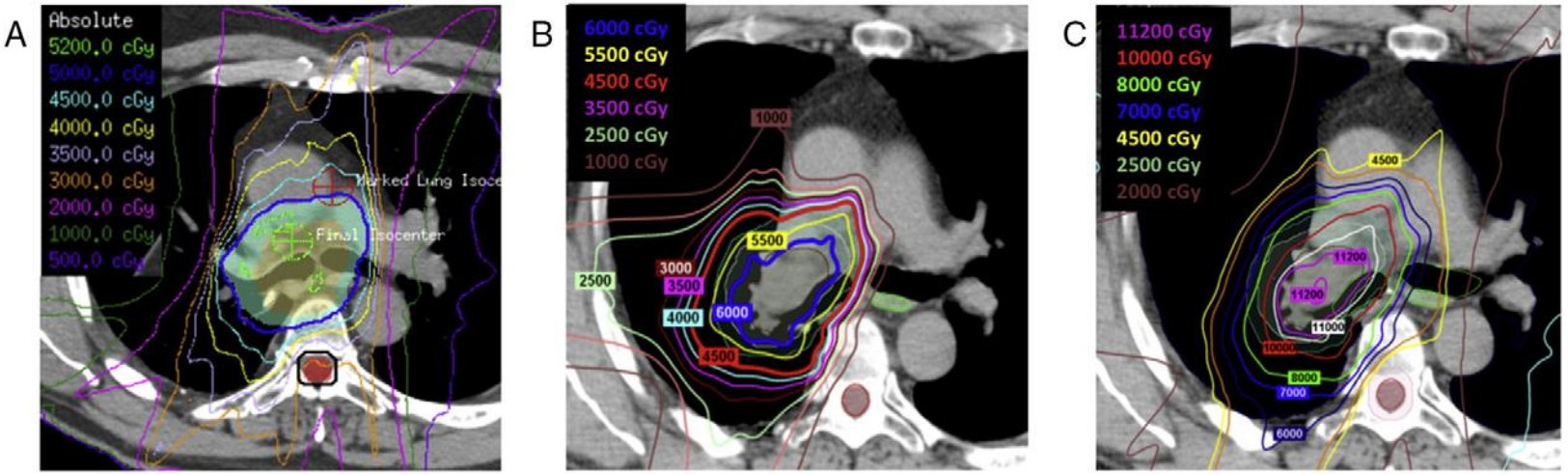

Figure 1 A representative plan showing a patient's (A) previous intensity modulated radiation therapy plan (50 Gy in 25 fractions), (B) reirradiation intensity modulated proton therapy plan (60 Gy in 30 fractions), and (C) composite plan.

Ho et al., 2017

Conclusions: These data represent the largest series of patients treated with IMPT for definitive reirradiation of thoracic cancers. They demonstrate that IMPT provided durable local control with minimal toxicity and suggest that higher doses may improve outcomes.

27 patients between 2011 - 2016

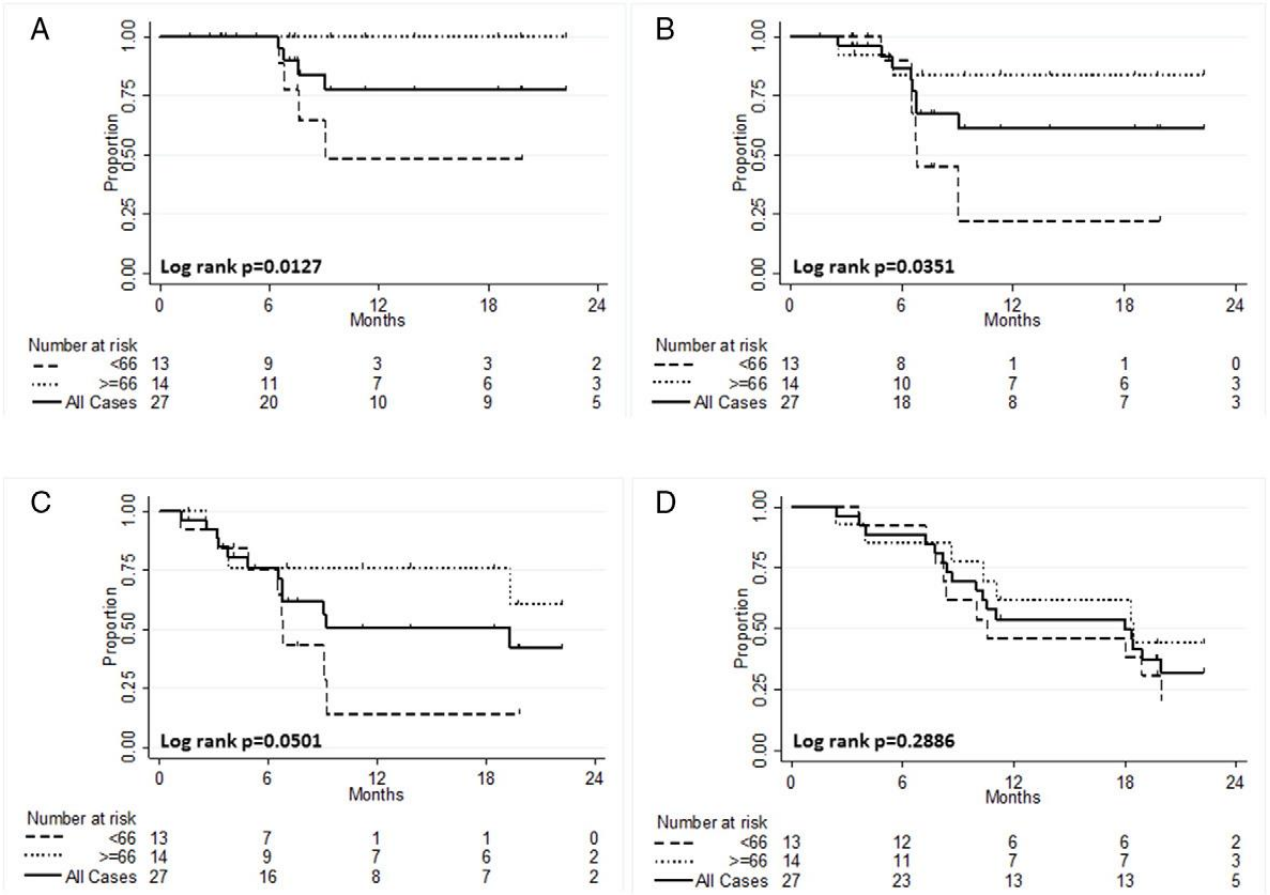

Figure 2 (A) Freedom from local failure, (B) freedom from locoregional failure, (C), progression-free survival, and (D) overall survival among all patients (solid line), patients who received an equivalent dose in 2-Gy fractions of ≥66 Gy (small dashed line), and patients who received <66 Gy (large dashed line).

Ho et al., 2017

Improving the Therapeutic Window: Clinical Rationale for Particle Therapy for Re-RT

- Improved sparing of normal tissue in certain cases
- Depending on tumor type, certain benefit of high-RBE
- Is it dose to the target of really radiation quality?
- Benefit of modern image-guided RT
- Heterogeneous biology & other factors influence outcome
- Small patient cohorts until now, difficult to do randomized trials
- Individual decision making and interdisciplinary discussion essential
- if possible in a timely manner, particles should be considered

Department of Radiation Oncology/Institute of Innovative Radiotherapy

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

iRT.

Klinik Biologie Informatik Physik

MiRO