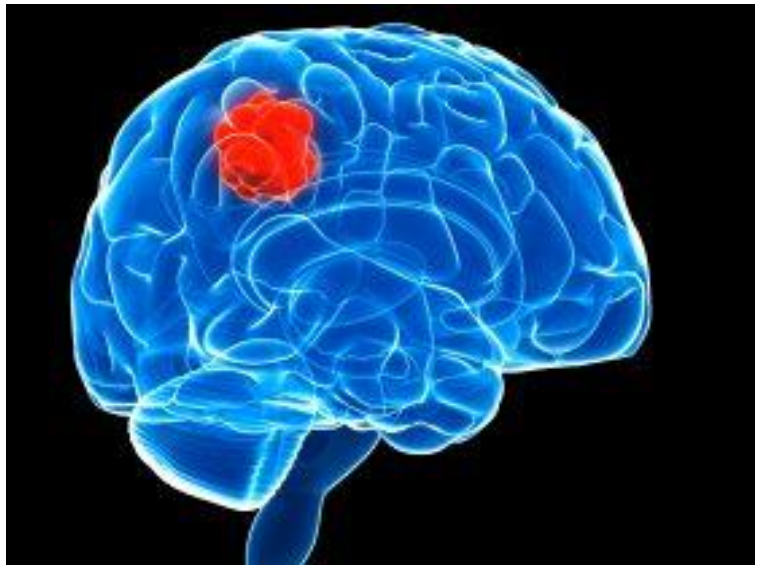
HITRI plus
Heavy Ion Therapy Research Integration

re-irradiation of central nervous system tumors



DR. MED. SEMI B. HARRABI

HIT

HEIDELBERG ION-BEAM THERAPY CENTER

HIT
Heidelberger Ionenstrahl-Therapiezentrum

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Rationale for re-irradiation

- What are we trying to achieve?
  - A second chance of cure
  - A long term local control
  - A meaningful palliation
- What dose do we need for each aim?
- And at what cost?

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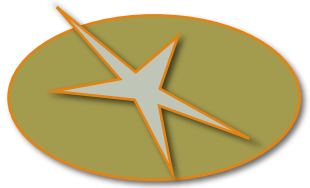
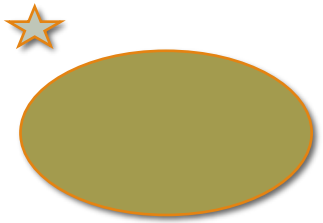
Rationale for re-irradiation

Tumor recurrence after RT:

Initial radiotherapy



Re-growth of residual tumor cells



Re-RT ?

Secondary tumor due to RT

Re-RT ?

There is no rationale to repeat an inefficient treatment!

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How to improve outcome of re-irradiation

Modifiers:

radiation sensitizers and radiation protectants

- Hyperthermia combined with re-RT
- Chemotherapy
- New drugs

Improved imaging:

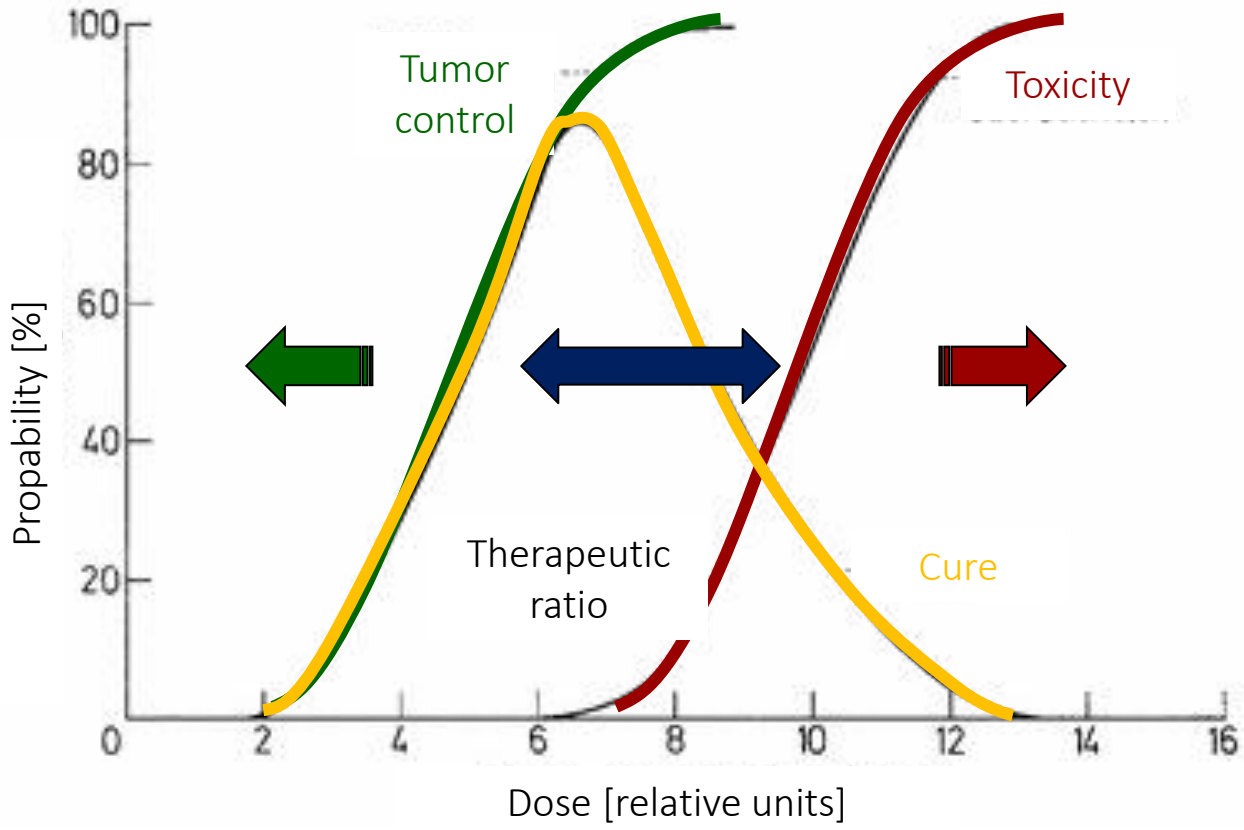
to detect recurrences earlier / precise targeting

- FDG-PET /CT
- (functional) MRI, MRI-guided RT

Other radiation modalities :

“new beams”

- Protons
- Carbon ions
- Helium? Oxygen?



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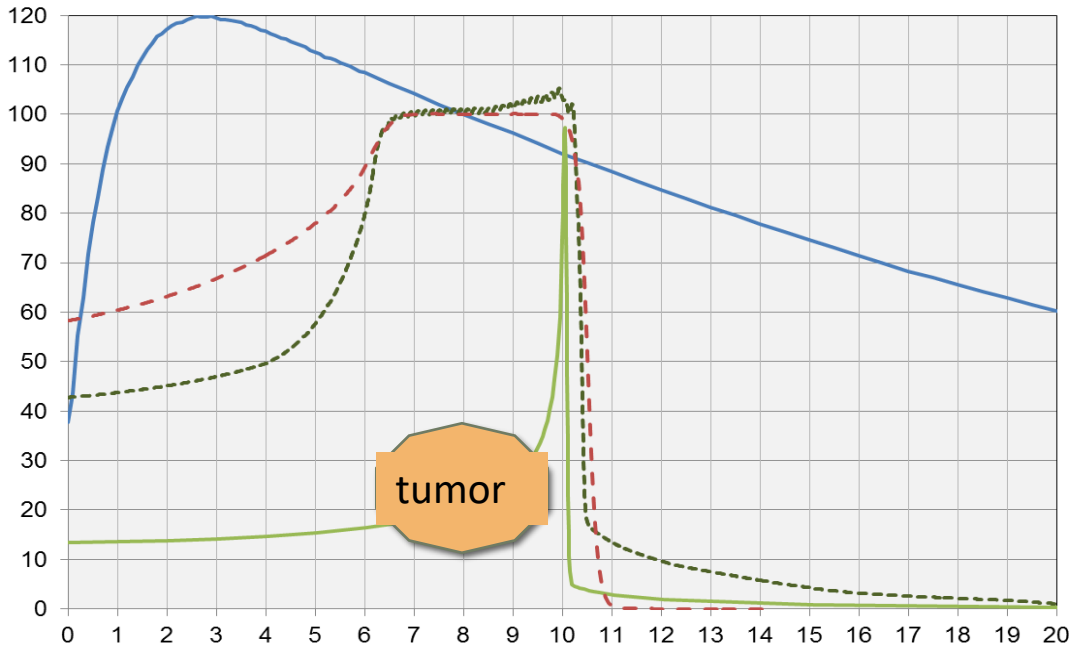
Modified from Scherer (Ed.) Strahlentherapie (1987, Springer)

Physical rationale for protons and other ions



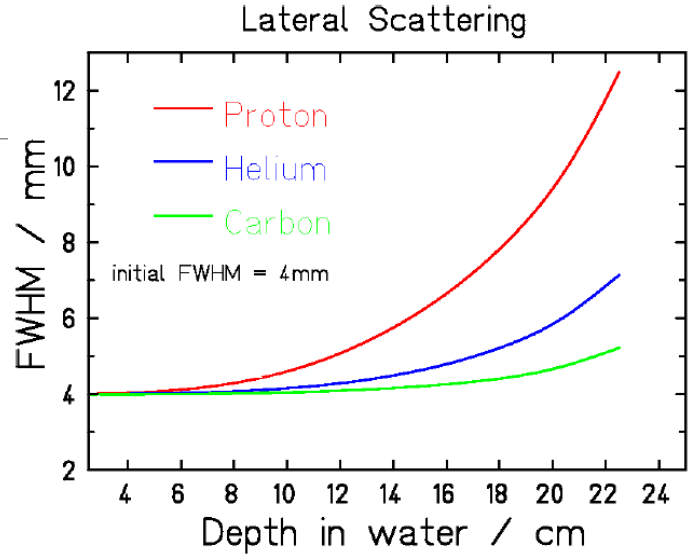
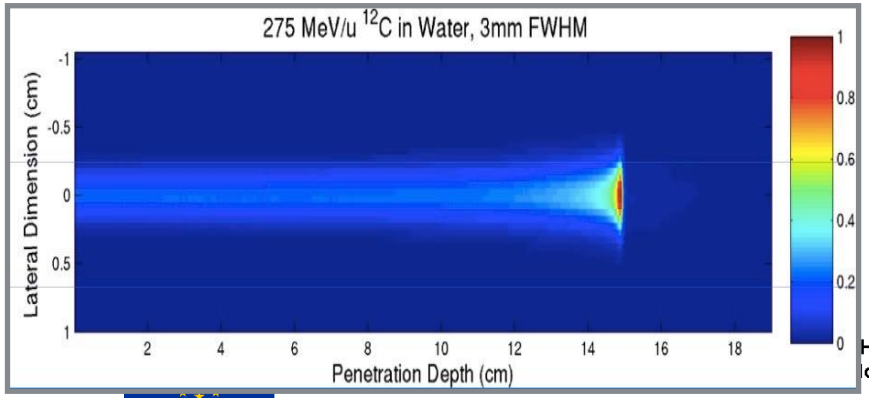


Image: Weber 2005

Advantageous physical properties:

- Less entry dose
- No or less exit dose



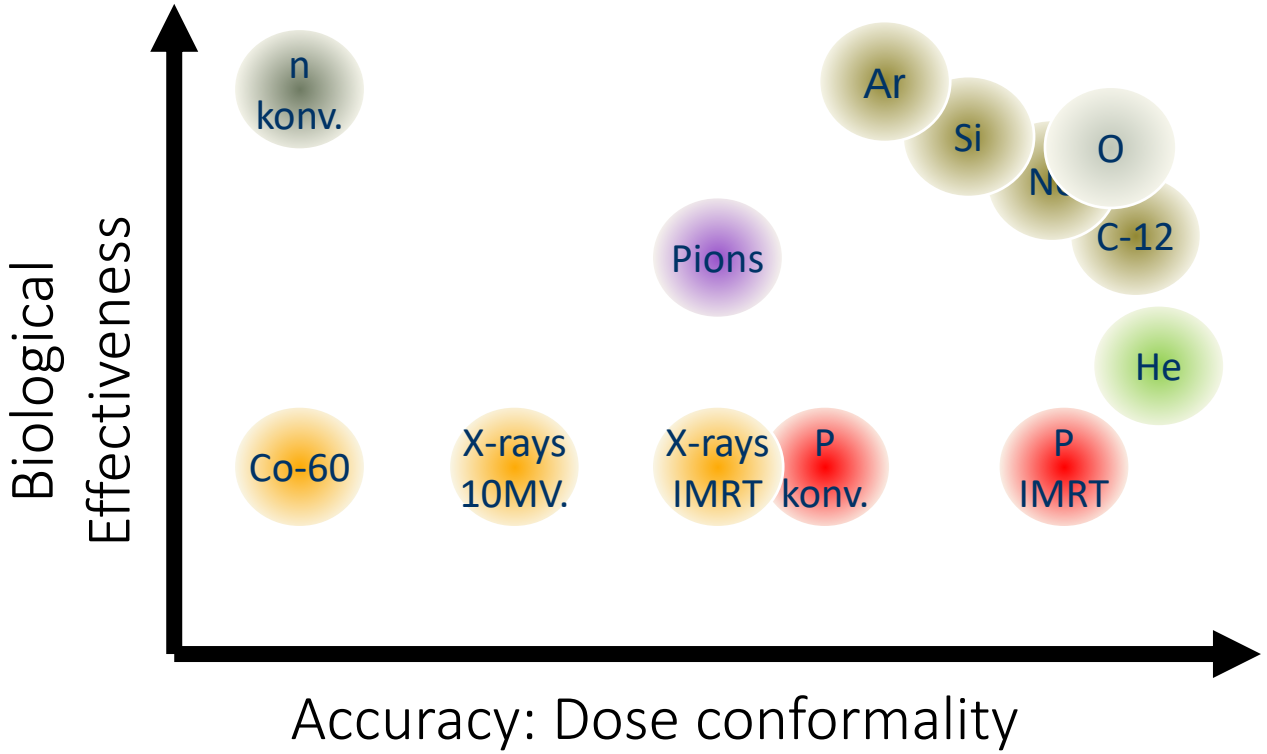
HITRI

Horizon 2020
lo 101008548

Sparing of normal tissue, dose escalation, better tumor coverage


Spoilt for choice?
Si
He
n
konv.
Ar
O
P
IMRT
C-12
Ne
X-rays
10MV.
X-rays
IMRT
P
konv.
Co-60
Pions

Biological rationale for helium and carbon ions



Advantageous biological properties of light ions:

- Higher biological effectiveness
- More efficient in killing hypoxic tumor cells

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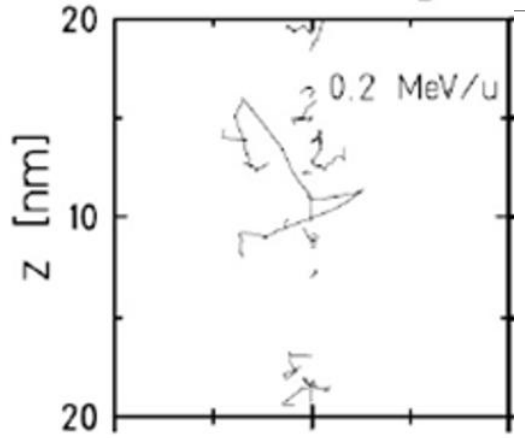
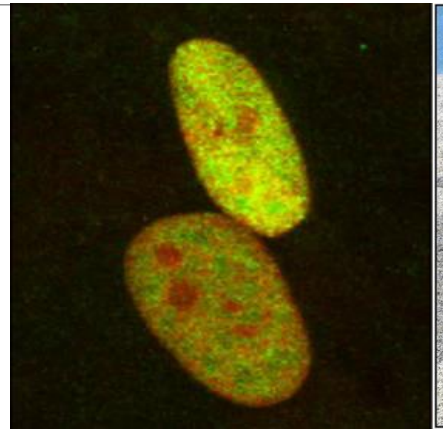
Biological rationale for helium and carbon ions

ionisation tracks | **damage (in nucleus)**

low LET

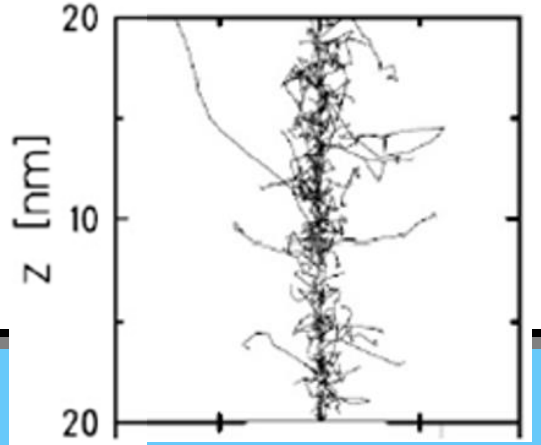


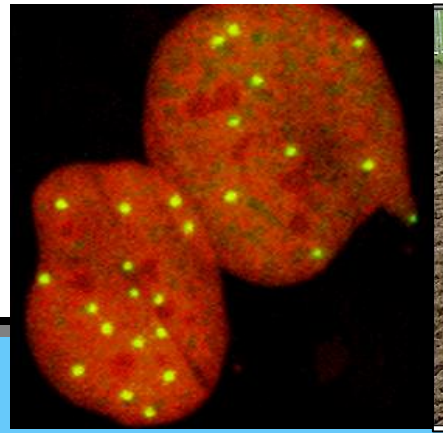


Photons, protons

Increase of **direct radiation damage** and **RBE** for high-LET radiation

high LET





Carbon ions

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ding from the European Union's Horizon 2020
ramme under grant agreement No 101008548

modified from Kraft et al., 2003

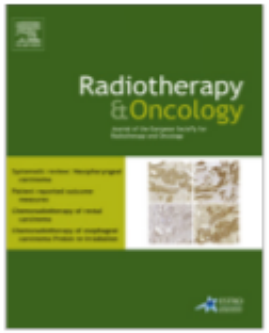
re-irradiation of brain tumors

Radiotherapy and Oncology 116 (2015) 301–308

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Proton re-irradiation

Use of proton therapy for re-irradiation in pediatric intracranial ependymoma

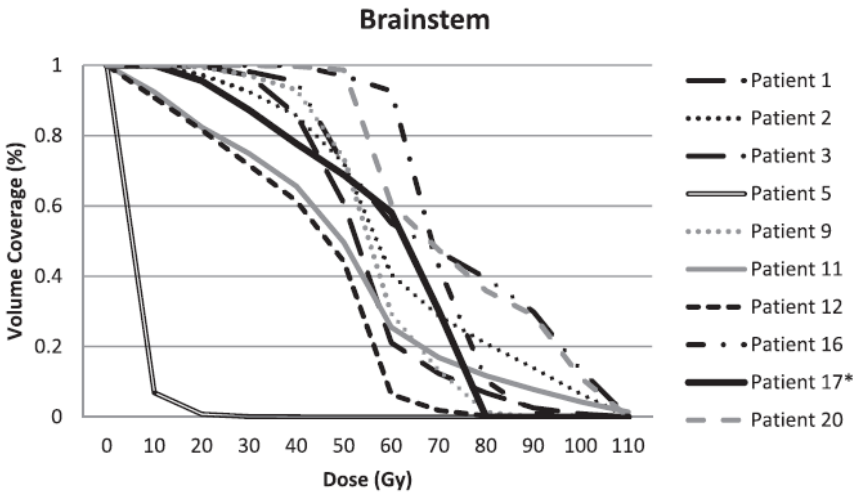
Bree R. Eaton [a], Varun Chowdhry [a], Kenneth Weaver [a], Li Liu [a], David Ebb [b], Shannon M. MacDonald [a], Nancy J. Tarbell [a], Torunn I. Yock [a,*]

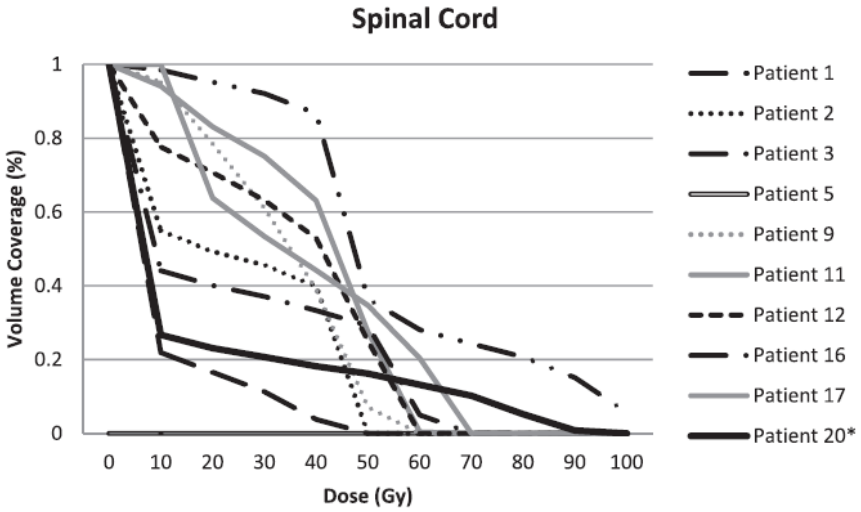
[a] *Department of Radiation Oncology; and* [b] *Department of Pediatrics, Massachusetts General Hospital, Boston, USA*

re-irradiation of brain tumors

Results (N=20):
First failure was local (55%), distant (30%) or both (15%)
at a median time of 23.9 months from first treatment.

Salvage therapy
re-resection (75%),
chemotherapy (60%)
IFPRT (70%) to a median dose 50.4 GyRBE (35–55.8)





rizon 2020
101008548

Eaton et al. / Radiotherapy and Oncology 2015

re-irradiation of brain tumors

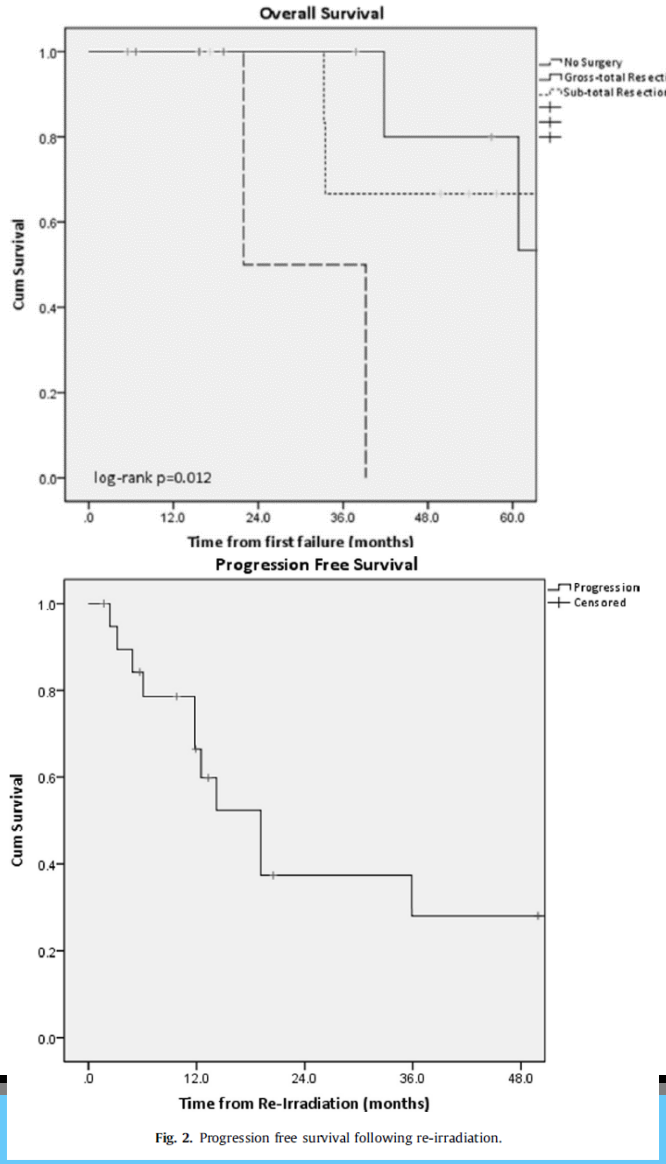


Fig. 2. Progression free survival following re-irradiation.

Median follow-up 37.8 months (5.5–138.0).

Three year OS 78.6% and PFS 28.1%.

Longer OS was significantly associated with surgical resection of recurrent disease (HR 9.19, 95% CI 1.27–66.44, p = 0.028).

Pattern of second failure after re-irradiation was directly related to the pattern of first failure ($p < 0.01$).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Eaton et al. / Radiotherapy and Oncology 2015

re-irradiation of brain tumors

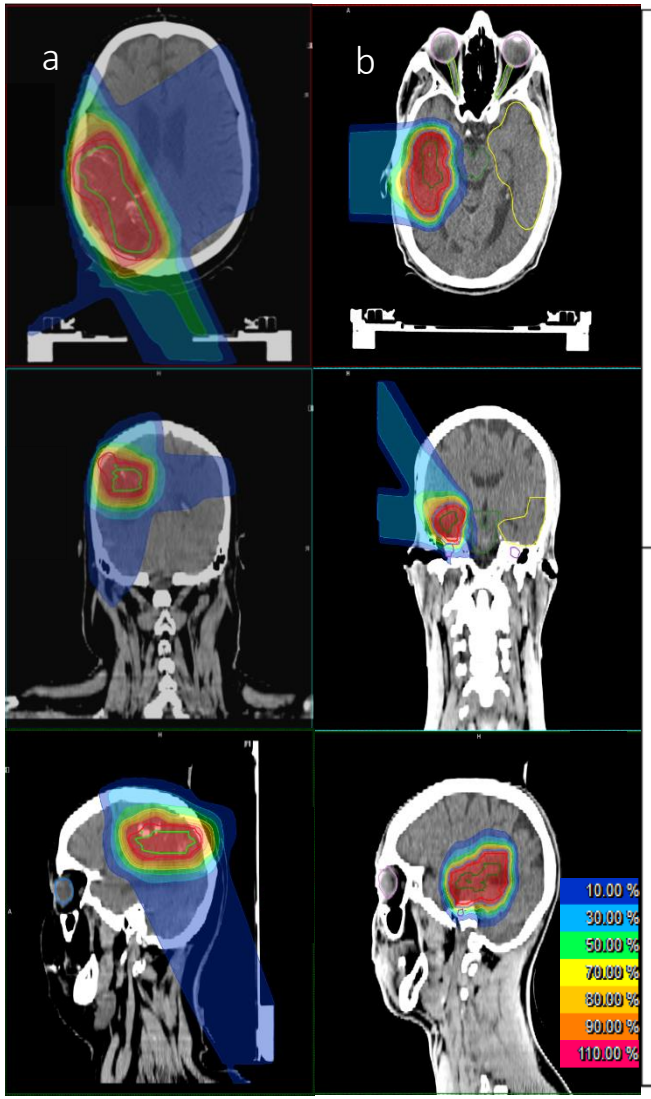
Matched pair analysis

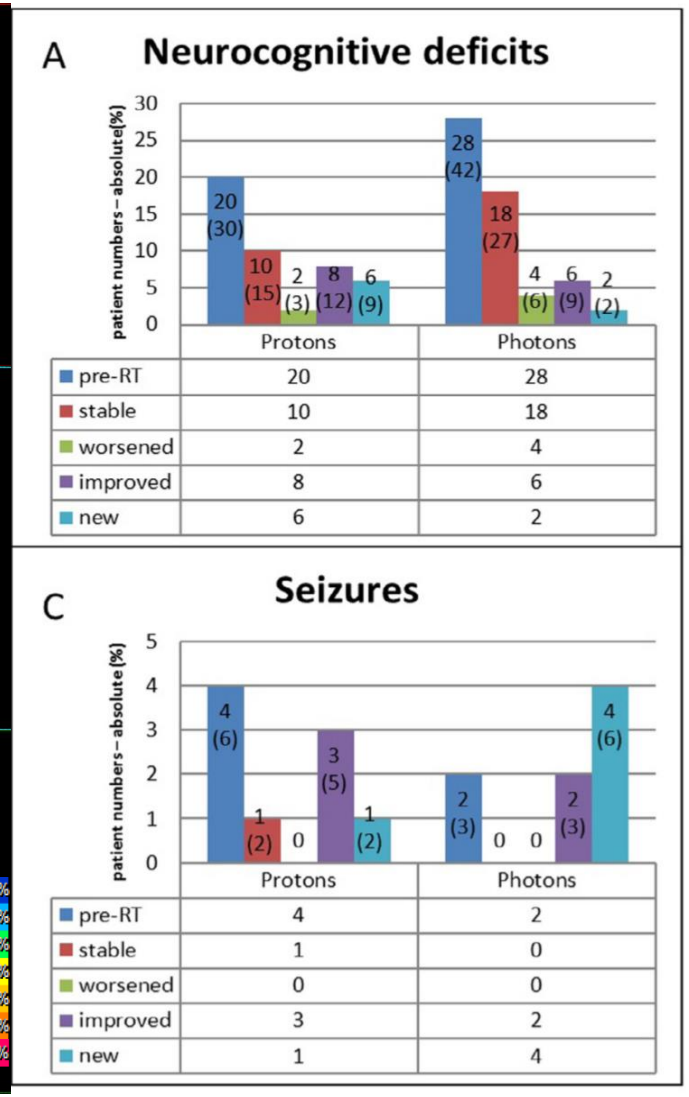
N = 66

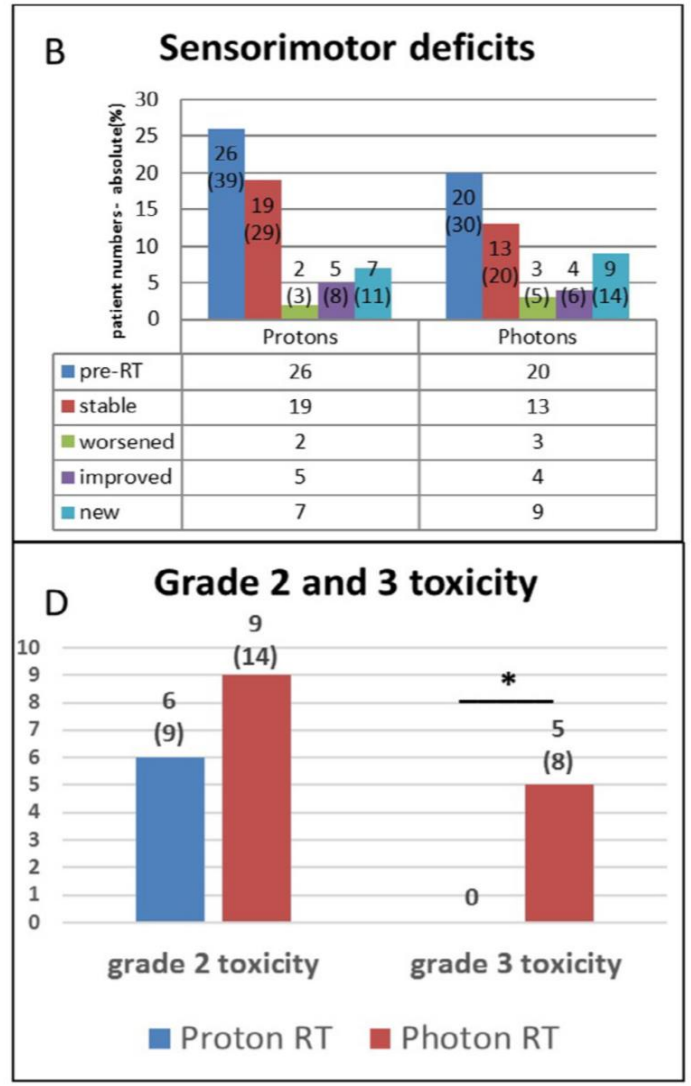
WHO grade 3 / 4

60 Gy IMRT
vs
50 Gy IMRT + 10Gy

Same efficacy
Less toxicity







Adeberg et al, 2017

re-irradiation of brain tumors

prospective phase II

N = 84

WHO grade 4

60 Gy (RBE)
Radiochemotherapy
(concurrent TMZ)

Less grade 3
lymphopenia

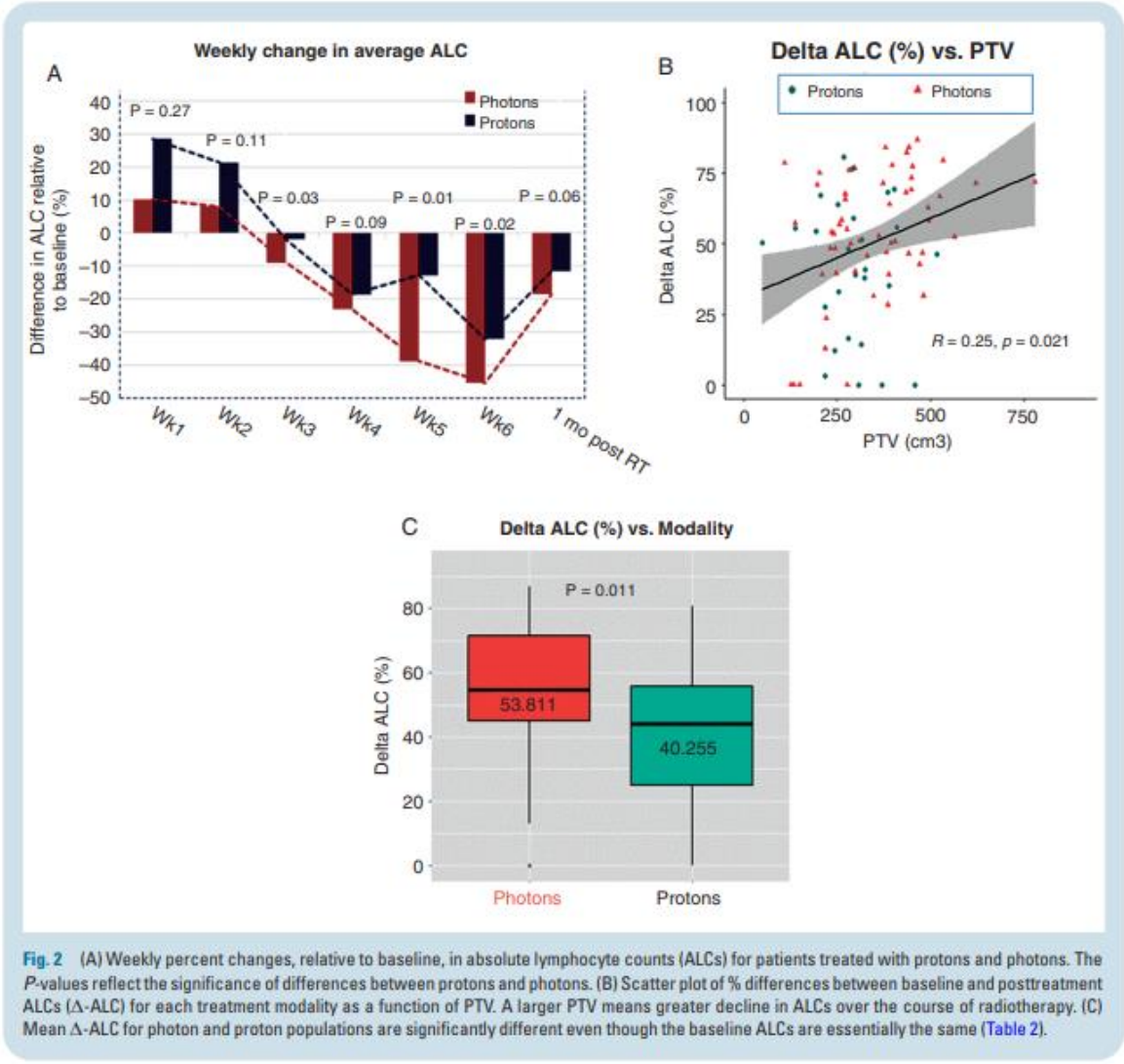


Fig. 2 (A) Weekly percent changes, relative to baseline, in absolute lymphocyte counts (ALCs) for patients treated with protons and photons. The *P*-values reflect the significance of differences between protons and photons. (B) Scatter plot of % differences between baseline and posttreatment ALCs (Δ-ALC) for each treatment modality as a function of PTV. A larger PTV means greater decline in ALCs over the course of radiotherapy. (C) Mean Δ-ALC for photon and proton populations are significantly different even though the baseline ALCs are essentially the same (Table 2).

	Multivariate Regression Analysis	
Variable	**OR (95% CI)**	***P*-value**
Sex (Female)	6.193 (1.951–22.37)	0.0029
Baseline ALC (K/μL)	0.179 (0.052–0.511)	0.0027
Whole brain V20 (%)	1.072 (1.028–1.125)	0.0021

*Variables with statistically significant association.
Abbreviations: BMI, body mass index; GTV, gross tumor volume; CTV, clinical target volume; PTV-50 and PTV-60, planning target volumes receiving higher than 50 and 60 Gy respectively; DVH, dose-volume histogram; ALC, absolute lymphocyte count; WBC, white blood cells count (in units of 109 cells per liter); V5, V10, . . . , brain volumes receiving greater than 5, 10, . . . Gy(RBE) dose.

Heavy Ion Therapy Research Integration

Mohan et al, Neuro Oncol 2021

original report

Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis

pCSI resulted in significantly **improved CNS PFS and OS** compared with IFRT in **patients with metastatic NSCLC and breast cancer**, with LM with no increase in high-grade adverse events.

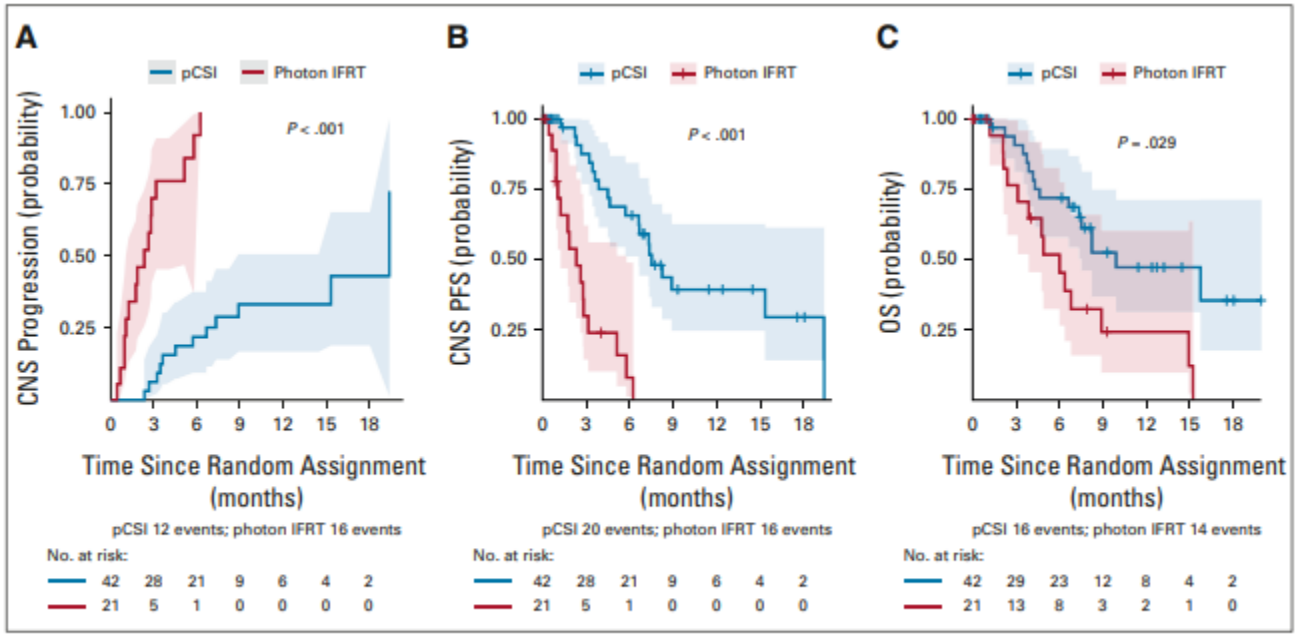


FIG 2. Patients who were randomly assigned to pCSI had significantly improved (A) CNS time to progression, (B) CNS PFS, and (C) OS. IFRT, involved-field radiotherapy; OS, overall survival; PFS, progression-free survival; pCSI, proton craniospinal irradiation.

improved CNS PFS
7.5 months (pCSI)
vs
2.3 months (IFRT)

improved OS
9.9 months (pCSI)
vs
3.9 months (IFRT)

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Yang et al, JCO 2022

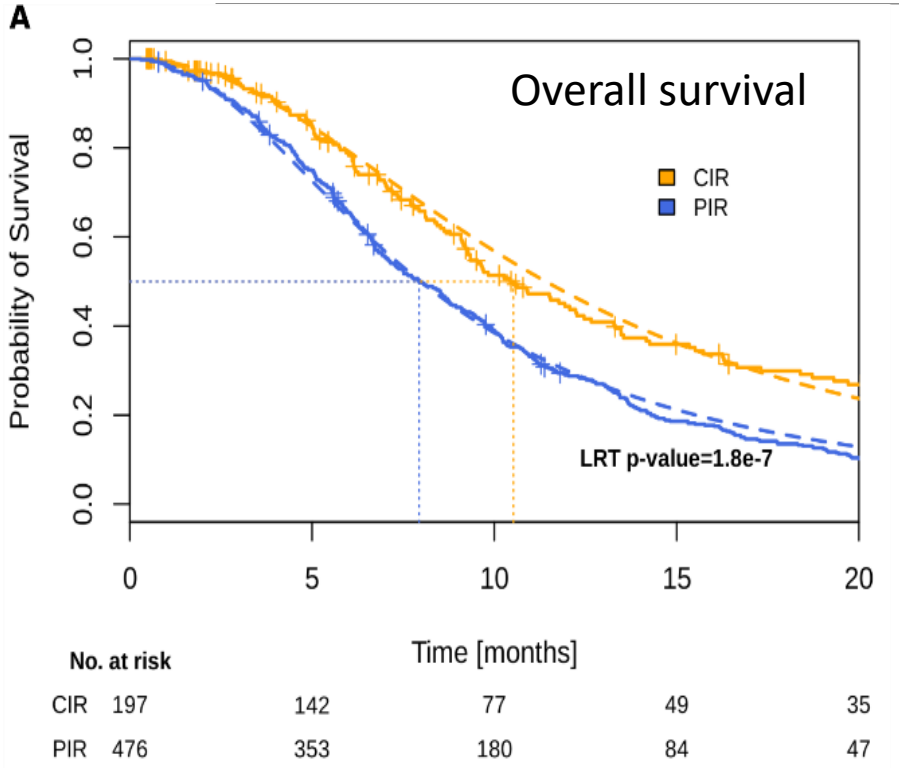
re-irradiation of brain tumors

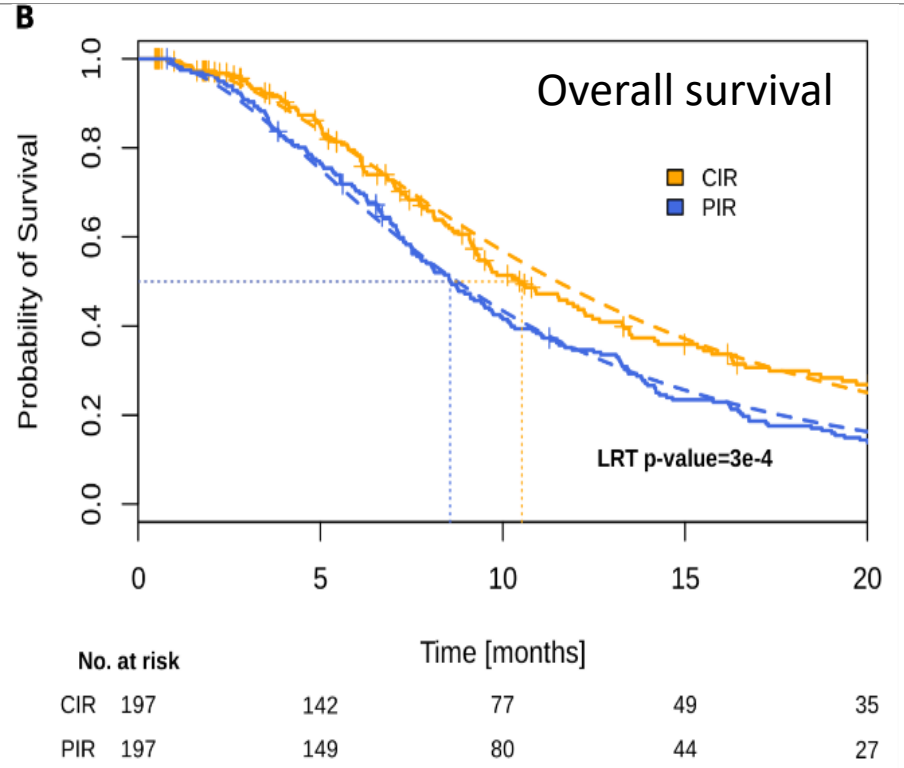
Combs et al, Radiother Oncol, 2018.

Knoll, M. et al. 2019, J Clin Oncol suppl

Complete cohorts

re-irradiation risk score (RRRS) matched cohorts





Median OS was 10.5 [9.3-12.7] months (grade III: 28.2, grade IV: 8.53) after CIRT compared to 7.9 [7.2-8.8] M (grade III: 10.89, grade IV: 7.93) after XRT.

In DKTK-ROG multicenter cohort n:**565** rHGG patients (grade III: 63, IV: 479) underwent RiP between 1997-2016 with a median dose of 36 Gy in 12 fractions

197 patients with rHGG (grade III: 71, IV: 126) received RiCi between Nov 2009 and Feb 2018 at **HIT** with a median dose of 42GyRBE in 14 fractions

Median follow up: 34.2 months for RiCi 7.1 months for RiP (DKTK)

Limiting dose tolerance of organs at risk

- What are the most critical organs at risk?
- How much dose have they absorbed before?
- What are their tolerance doses?
- What is their potential for recovery?

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Organ/tissue	Accepted re-irradiation dose-fractionated (Gy)	Accepted re-irradiation dose-stereotactic (Gy)	Accepted time interval between RT courses	Extent of OAR recovery
Soft tissue/ muscle	Doses over 50 Gy conventional EBRT produce better control[16,17]		>12 months	Large scale data not available; only case serie's present
Brain/ brainstem	Cumulative BED not exceed 130-159 Gy with an α/β ratio equal 2 Gy2[18]		>12 months	Partial
	30-40 Gy in fractionated RT[19]	24 Gy for involved volume <20 mm, 18 Gy for volume 21-30 mm and 15 Gy for volume 31-40 mm[6]		
Spinal Cord	cumulative BED should not exceed 130 Gy2[18]		>12 months	Partial
	20-24 Gy in10-12 fractions[13,14]	dose threshold for thecal sac 10 Gy in single fraction and nBED of 30-35 Gy 2/2 for up to five fractions		
Heart	Cumulative dose to the heart (BED_{3Gy}) should not exceed 70 Gy_3 and the point dose (0.1 cc) Dmax not >49 Gy_3[20]		>24 months	Partial
Great vessels	cumulative BED should not exceed 90-100 Gy2[21]		>36 months interval can produce estimated 65% OAR recovery[21]	1%-2% aortic toxicities noted; carotid blowout
Head and neck soft tissues	The dose ranges from 58-60 Gy[22]	18-40 Gy in 3-5 fractions to the 65%-85% isodose line over consecutive days[6]	>6 months-1 year	Lesser volume and more mucosa means more OAR recovery
Mandible	Cumulative dose not defined, but tolerance below 100 Gy_3 without cortical breach			
Parotid	Can tolerate cumulative dose of 45 Gy[23]		>12-18 months	
Optic structures	Re-irradiation constraints limited to <8-10 Gy for 10 cm^3 volume[24]		>12 months	
Urinary bladder	Can tolerate point cumulative doses of up to 120 Gy3[25]		>6 months-1 year	
Pelvic ureter	Can tolerate point cumulative doses of up to 110 Gy3[26]		>24 months	Ureteric stenosis
Rectal mucosa and wall	Total cumulative doses 70-100 Gy with a median total dose of 85 Gy[27,28]	IORT dose of 10-20 Gy[26,28]		Peripheral neuropathy most commonly seen with IORT
Femoral heads	Blood supply to the femoral head is defining point of action. Constraint similar to blood vessels; cumulative BED should not exceed 90-100 Gy2		>2-3 years gap can help recovery	Avascular necrosis of the head is the catastrophic event
Breast soft tissues	40-50 Gy given within 4 days with PDR brachy minimum re-radiation dose in fractionated schedule is 40 Gy		Minimum 6 months	Moderate skin and subcutaneous tissue side effects seen; mainly erythemas and skin telangiectasias
				Expected full OAR recovery

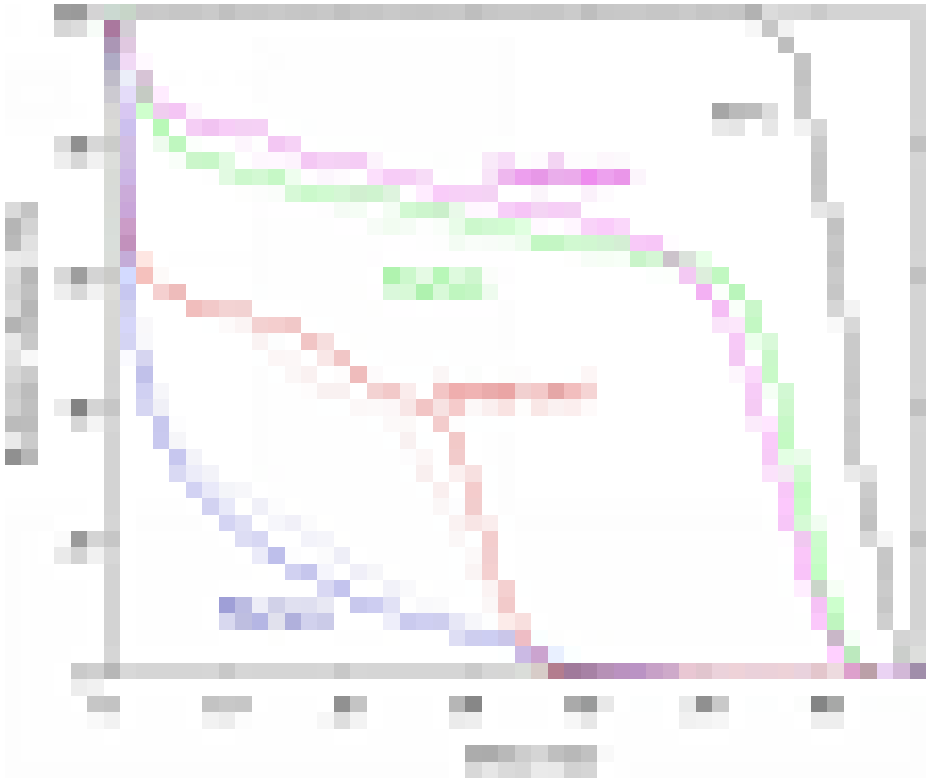
BED: Biological equivalent dose, RT: Radiotherapy, EBRT: External beam radiation therapy, IORT: Intraoperative radiotherapy, PDR: Pulsed dose rate, OAR: Organ at risk

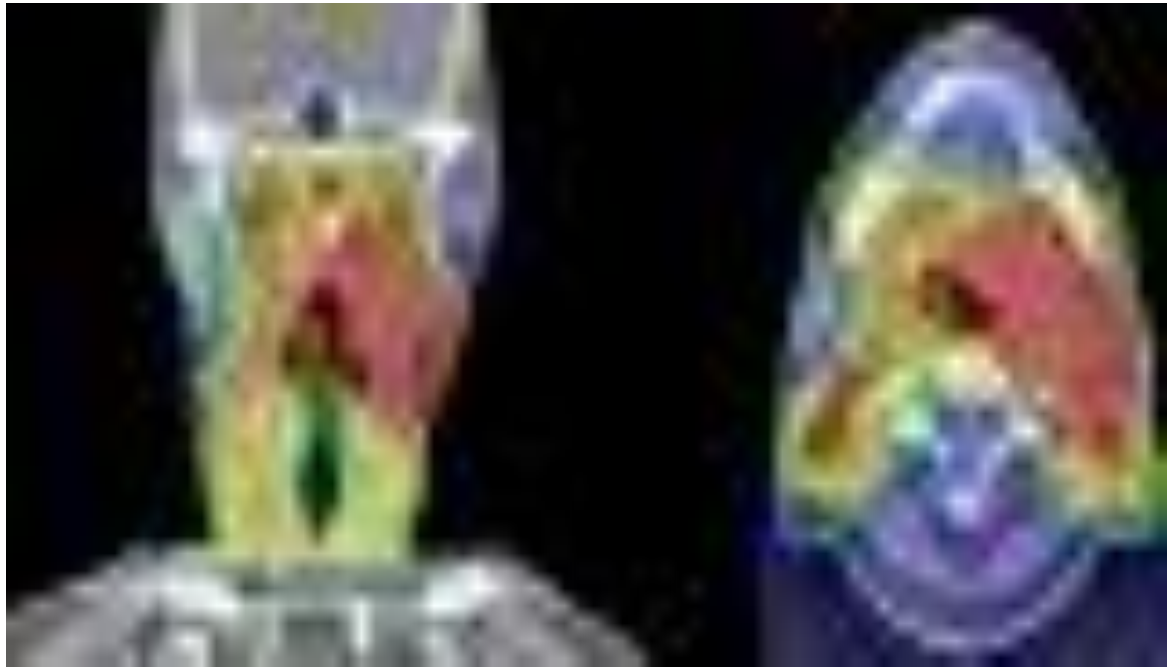
HITB
Heavy Ion Therapy Research In

t has received funding from the European Union's Horizon 2020
nd innovation programme under grant agreement No 101008548

Das et al, Journal of current oncology 2018

previous irradiation always as DICOMs





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summary

- Particle Therapy offers a chance for re-treatment of previously irradiated tumor sites
- ion beams enable more favorable dose distributions and thus highly individualized treatment concepts
- Helium and Carbon ions offer the advantage of higher biological effectiveness in radioresistant tumors
- First clinical studies show promising results in re-irradiated patients with reasonable outcome and relatively low toxicity.
- More clinical studies and longer follow-up is needed to assess late toxicities and to discriminate patients that clearly benefit from re-irradiation from those who only suffer side effects.


THANK YOU