HITRI plus
Heavy Ion Therapy Research Integration

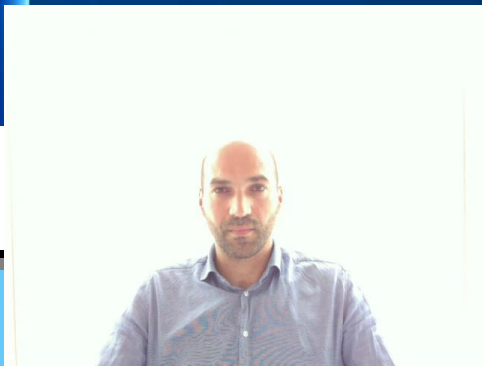
skull base tumors

DR. MED. SEMI B. HARRABI

HIT

HEIDELBERG ION-BEAM THERAPY CENTER

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



overview

- ~~**Chordoma & Chondrosarcoma**~~

(-> see lecture on Tuesday given by Giulia Riva)

- Pituitary adenoma
- Juvenile angiofibroma
- Craniopharyngioma

- Esthesio neuroblastoma
- Meningioma
- Schwannoma

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Oncological Dilemma

DAMAGE

eradication of
all tumor cells

achieving local control

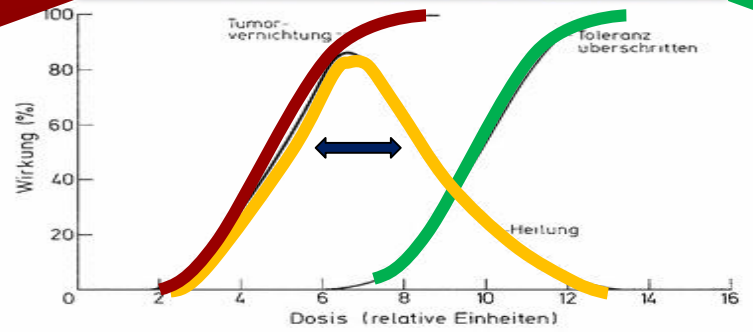
improving survival

REPAIR

protection of
surrounding healthy tissue

organ preserving

reducing late sequelae



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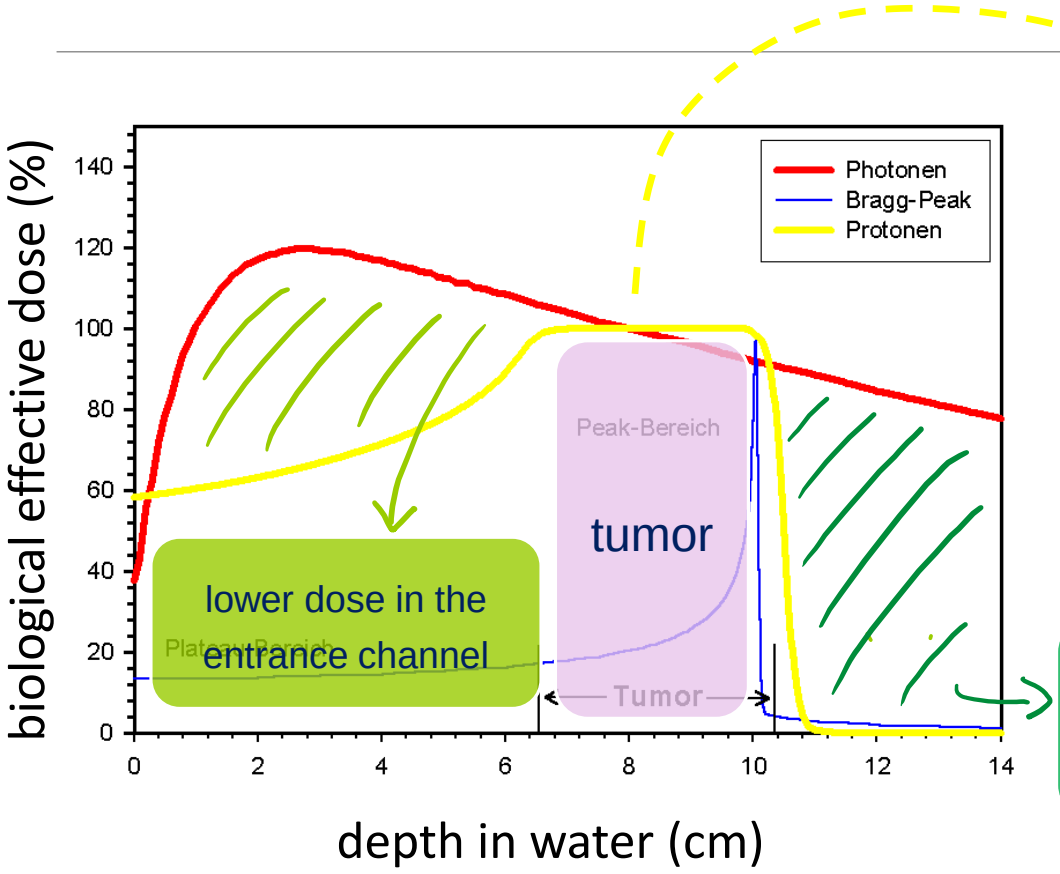
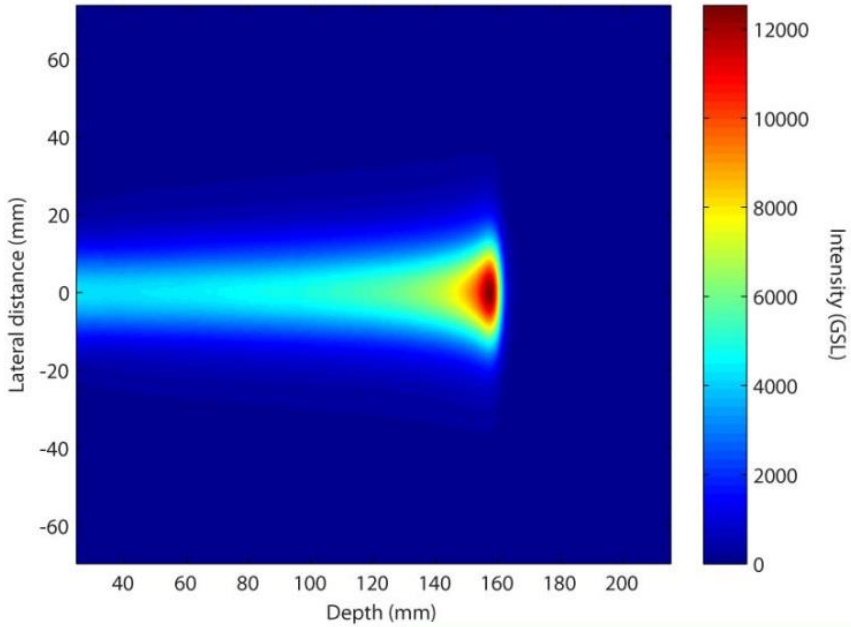
Depth dose profile: photons vs protons



SOBP

Spread Out Bragg Peak



no dose distal to the tumor

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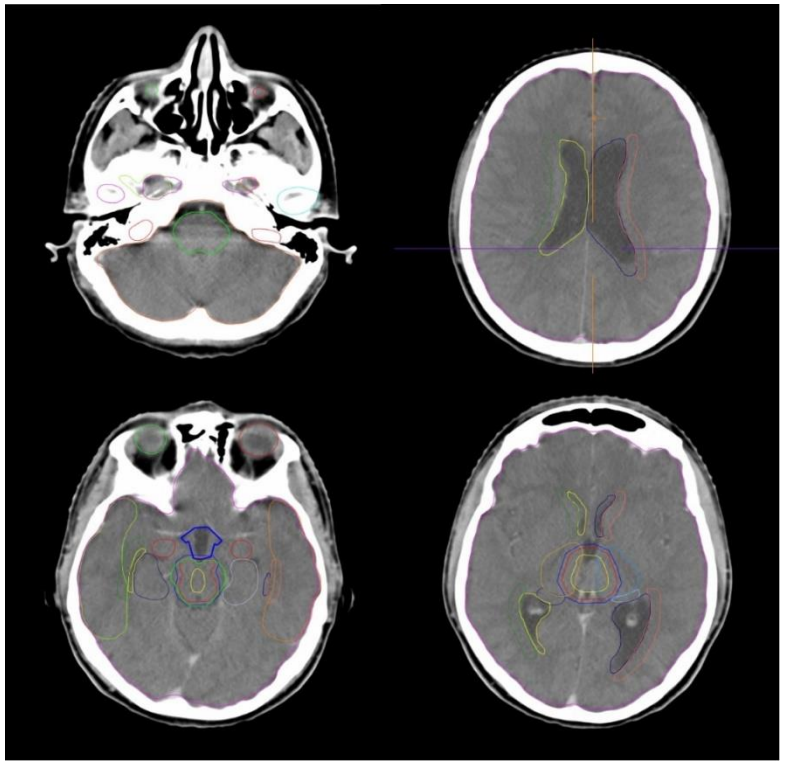
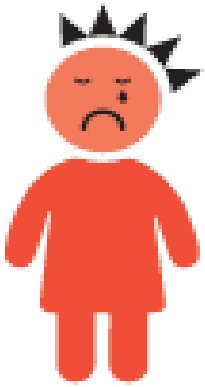
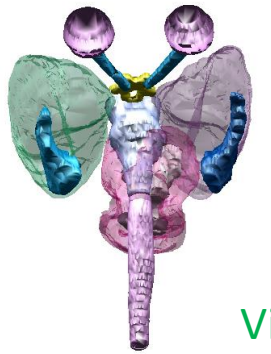
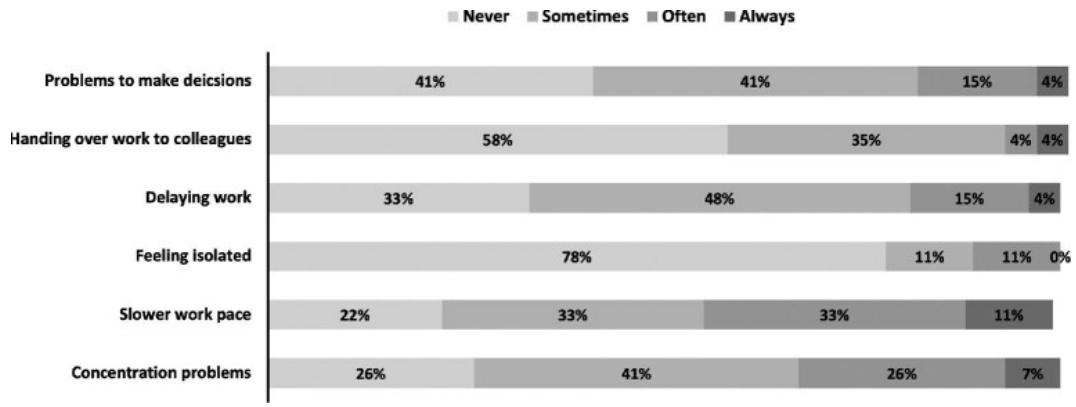
rationale of particle therapy for skull base tumors



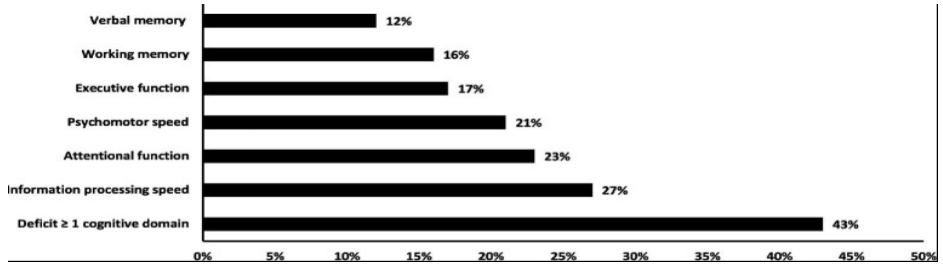
potential sequelae







Visual impairment / loss of hearing



Secondary malignancies

neurocognitive function ↓

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Quality of life ↓

Hypopituitarisms

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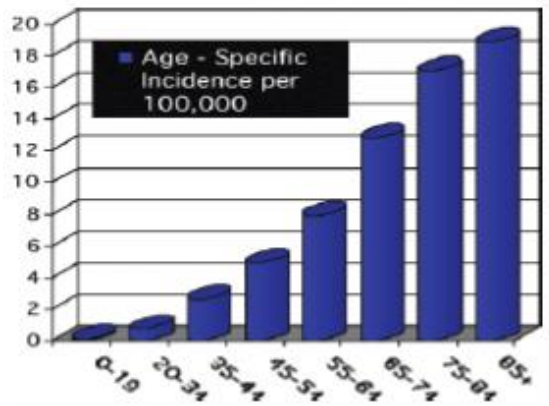
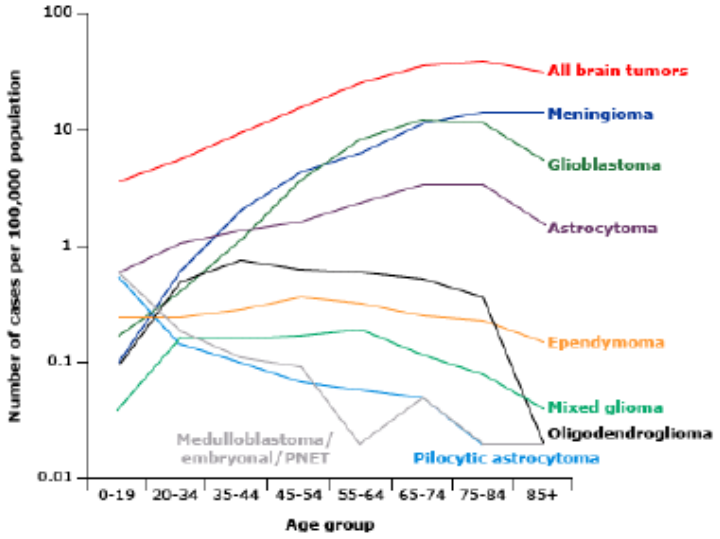
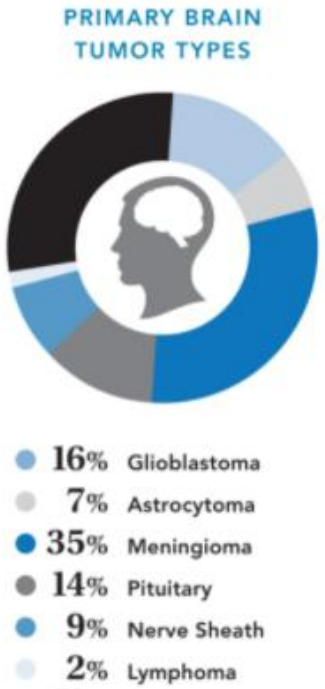
background: meningioma

- most frequent primary intracranial tumor in adults
- incidence ~ 2/100.000, female > male (3:1)
- risk factors: inter alia st.p. radiotherapy,
  NF2 (75% life time risk)
- median age ~ 65 y







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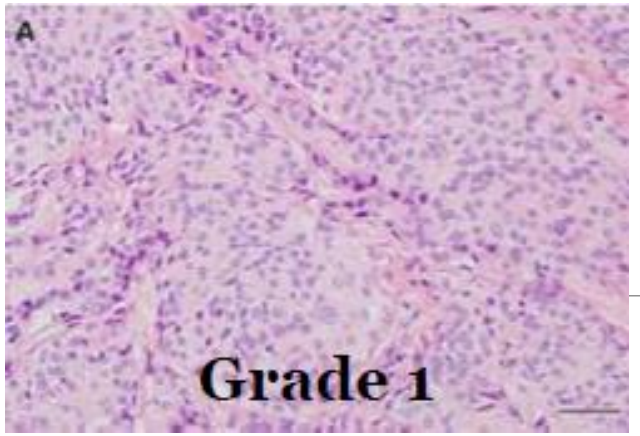

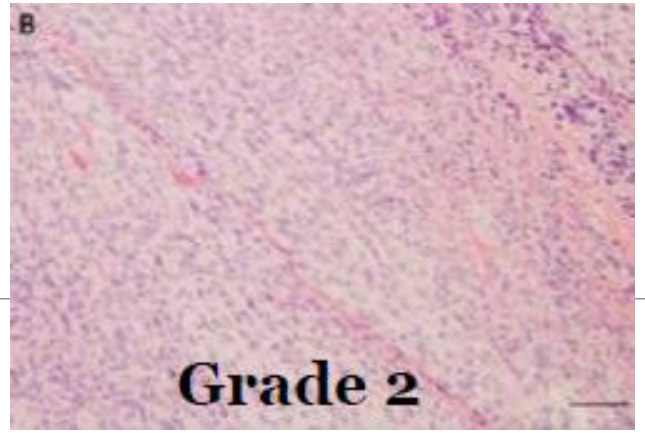

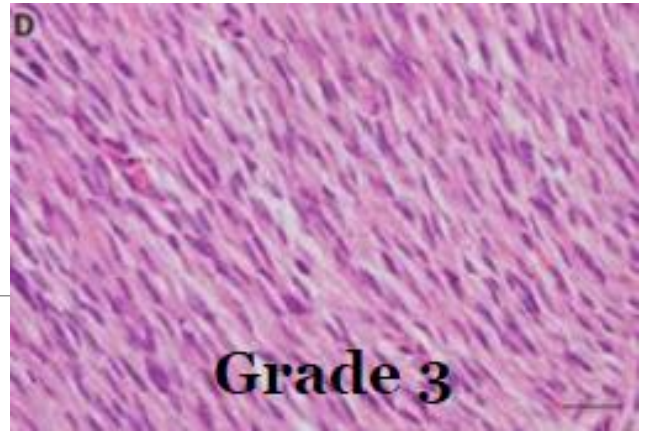

benign (80-85%)

low mitotic rate with less than 4 per 10 HPF
absence of brain invasion
nine subtypes

10y OS: 80-90%
10y PFS: 75-90%

atypical (15-18%)

mitotic rate 4-19/ HPF
OR brain invasion
OR three of five histologies:
spontaneous necrosis, sheeting, prominent nucleoli, high cellularity and small cells

10y OS: 50-79%
10y PFS: 23-78%

malignant (1-3%)

mitotic rate >20/HPF
OR specific histologies:
papillary or rhabdoid

10y OS: 14-34%
10y PFS

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Louis et al., The 2016 WHO Classification, Acta Neuropathologica 2016; Bi et al., Frontiers in Neurosurgery 2016

proton beam therapy for meningioma WHO I

highly conformal RT yields better sparing of critical organs at risk (and potentially less side effects)

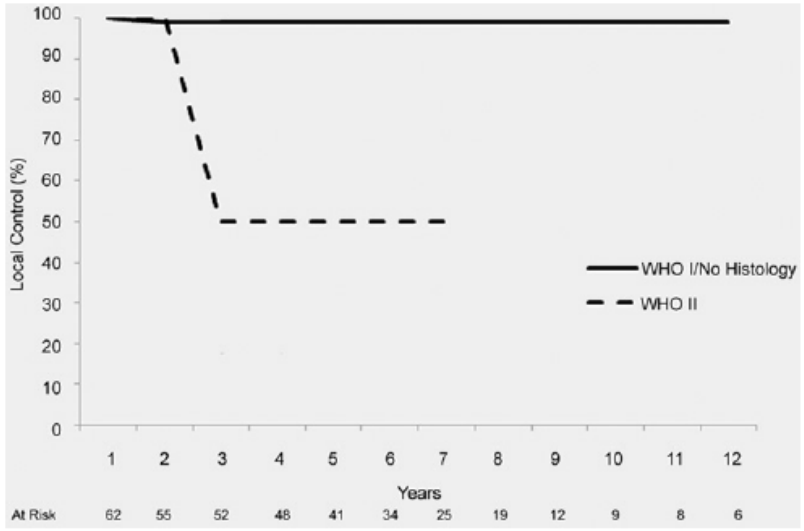
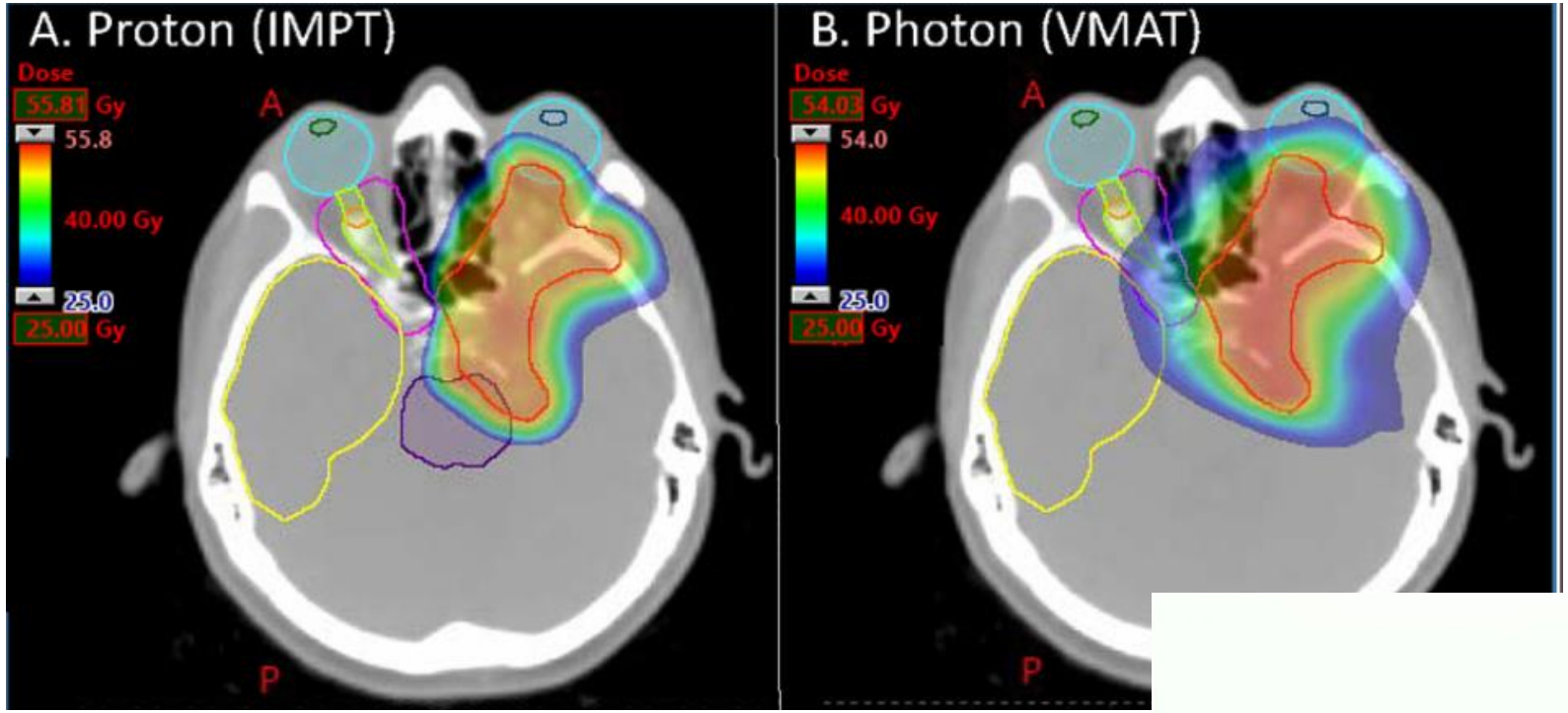


Fig. 3. Kaplan-Meier curve showing local disease control in terms of histologic findings.



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Slater et al., Int. J. Rad Oncol Biol. Phys. (2012)

Weber et al., Front Oncol (2020)

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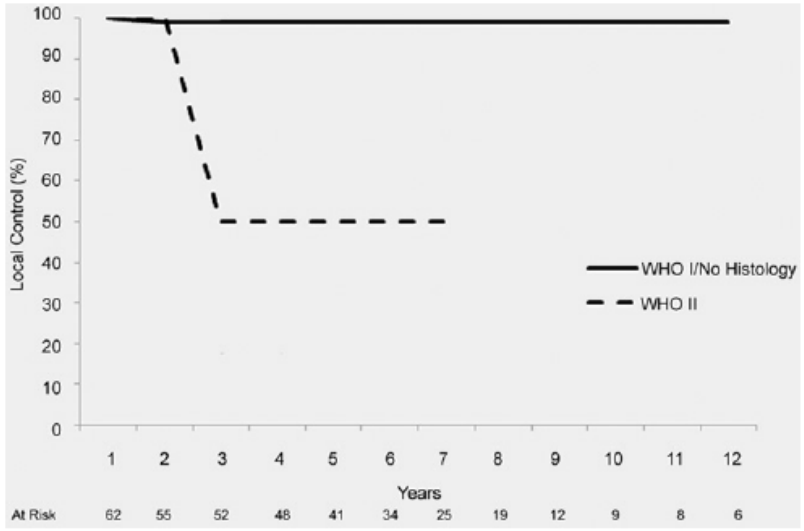

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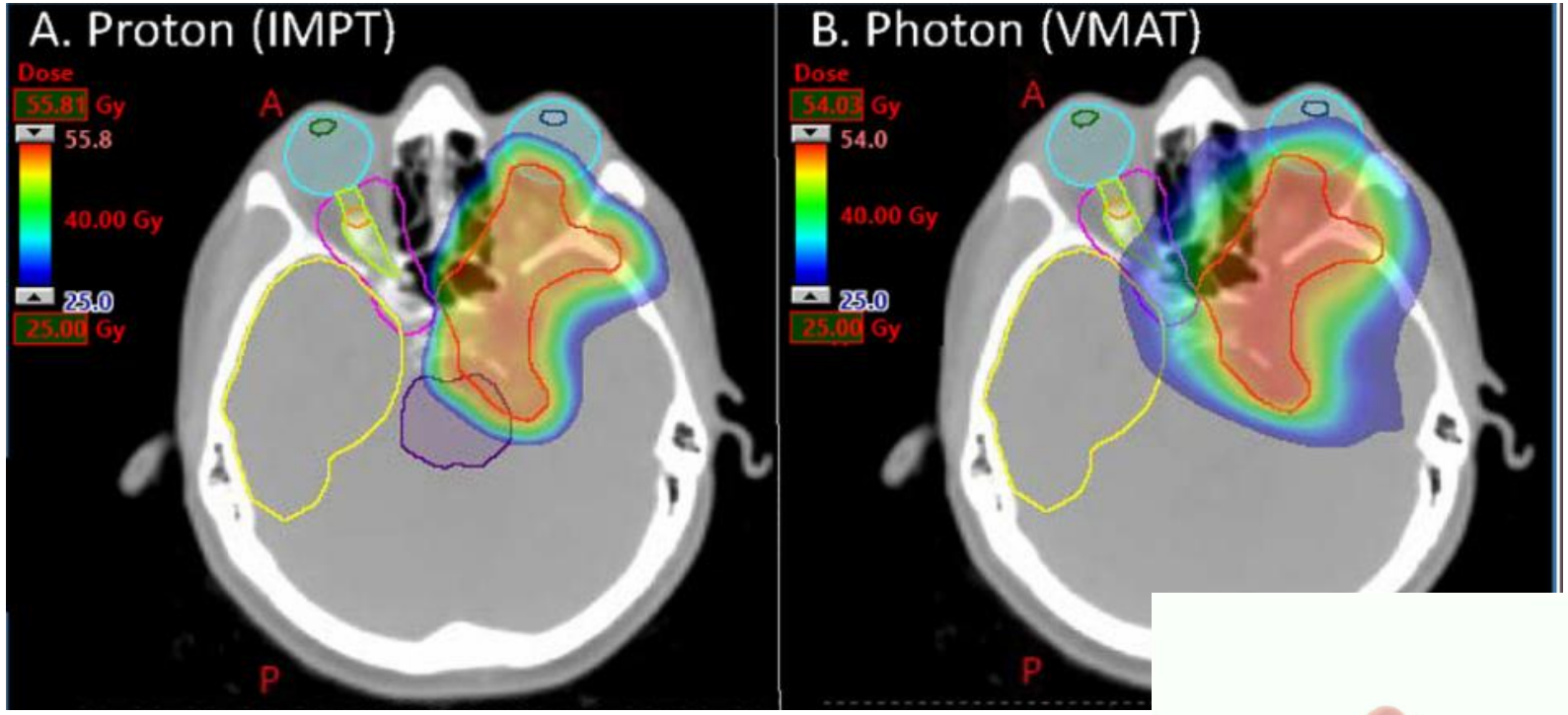

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Slater et al., Int. J. Rad Oncol Biol. Phys. (2012)

Weber et al., Front Oncol (2020)

local control is dose dependent (in meningioma ≥ grade II)

Dose escalation > 60 GyRBE yields better local control

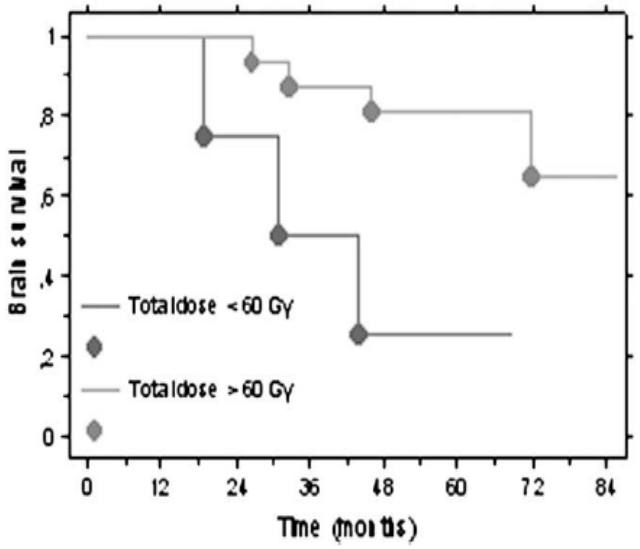

Fig. 4. Cause-specific survival curves for 24 patients undergoing combined proton and photon radiotherapy for atypical and malignant meningiomas, divided according to the delivered total dose. Cause-specific survival is prolonged in patients receiving a total dose of >60 Gy ($p = 0.01$).

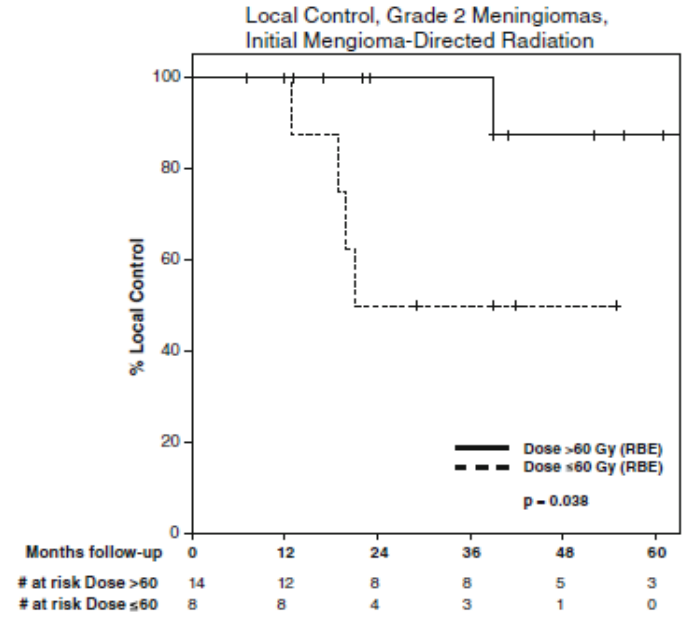

Fig. 1 Local tumor control outcomes stratified by radiation dose for patients receiving their initial meningioma-directed radiotherapy for grade 2 meningiomas

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Boskos et al., Int. J. Rad Oncol Biol. Phys. (2009)

McDonald et al., J Neurooncol (2015)

Efficacy and toxicity of particle radiotherapy in WHO grade II and III meningioma: a systematic review

TABLE 1. Literature summary of 11 studies on WHO grade II and III meningiomas treated with particle therapy

Authors & Year (tumors studied)	Cohort Size*	Type of Radiotherapy†	Median Cohort Age in yrs‡	Median Dose	Local Control Rates	Overall Survival Rates	Median FU (mos)	Level of Evidence§
Boskos et al., 2009 (Gr II–III meningiomas)	24	Proton + photon (24)	52.5	34 CGE	46.7% (5 yrs)	53.2% (5 yr)	32.2	IV
Chan et al., 2012 (Gr II–III meningiomas)	6	Proton + photon (6)	46	68.4 Gy (Gr II), 72 Gy (Gr III)	83.3% (end of FU)	100% (Gr II), 0% (Gr III)	145	IV
Combs et al., 2013[18] (multiple tumor types)	36	Photon + carbon boost (36); proton (176); carbon (84)	NA (48)	NA	54% (1 yr)	NA	12	IV
Combs et al., 2013[19] (Gr I–III meningiomas)	27	Proton (38); carbon (17); photon + carbon (15)	NA (55)	50 GyE + 18 Gy boost	81.4% (end of FU)	100% (end of FU)	6	IV
Combs et al., 2010 (Gr II–III meningiomas)	10	Photon + carbon (10)	52	50.4 GyE + 18 Gy boost	86% (5 yrs)	90% (5 yrs)	77	IV
El Shafie et al., 2018[22] (Gr I–III meningiomas)	31	Proton (8); carbon (34)	NA (54)	60 Gy (Gr II), 56 Gy (Gr III)	71% (1 yr)	238.7 mos (Gr II), 173.6 mos (Gr III)	NA	IV
El Shafie et al., 2018[23] (Gr I–III meningiomas)	8	Proton (2), photon + carbon (6)	NA (52)	Proton (NA), photon + carbon (50 Gy + 18 Gy)	100% (3 yrs), 96.6% (5 yrs)	96.2% (5 yrs), 92% (7 yrs)	46.8	IV
Hug et al., 2000 (Gr II–III meningiomas)	31	Photons + protons (16)	49¶	160 MeV protons, 62 Gy photons¶ (Gr II), 58 Gy photons¶ (Gr III)	80% (5 yrs)	89% (5 yrs, Gr II), 51% (5 yrs, Gr III)	59	IV
McDonald et al., 2015 (Gr II–III meningiomas)	22	Proton (22)	42	62 Gy (Gr II, III)	71.1% (5 yrs)	100% (end of FU)	39	IV
Murray et al., 2017 (Gr I–III meningiomas)	35	Proton (96)	NA (52.8)	NA	86.4% (5 yrs)	88.2% (5 yrs)	56.9	IV
Weber et al., 2012 (Gr I–III meningiomas)	10	Proton (39)	NA (48.3¶)	56 Gy	84.8% (5 yrs)	81.8% (5 yrs)	28.7	IV

CGE = Cobalt Gray equivalent; FU = follow-up; GR = grade; GyE = Gray equivalent; NA = not available.

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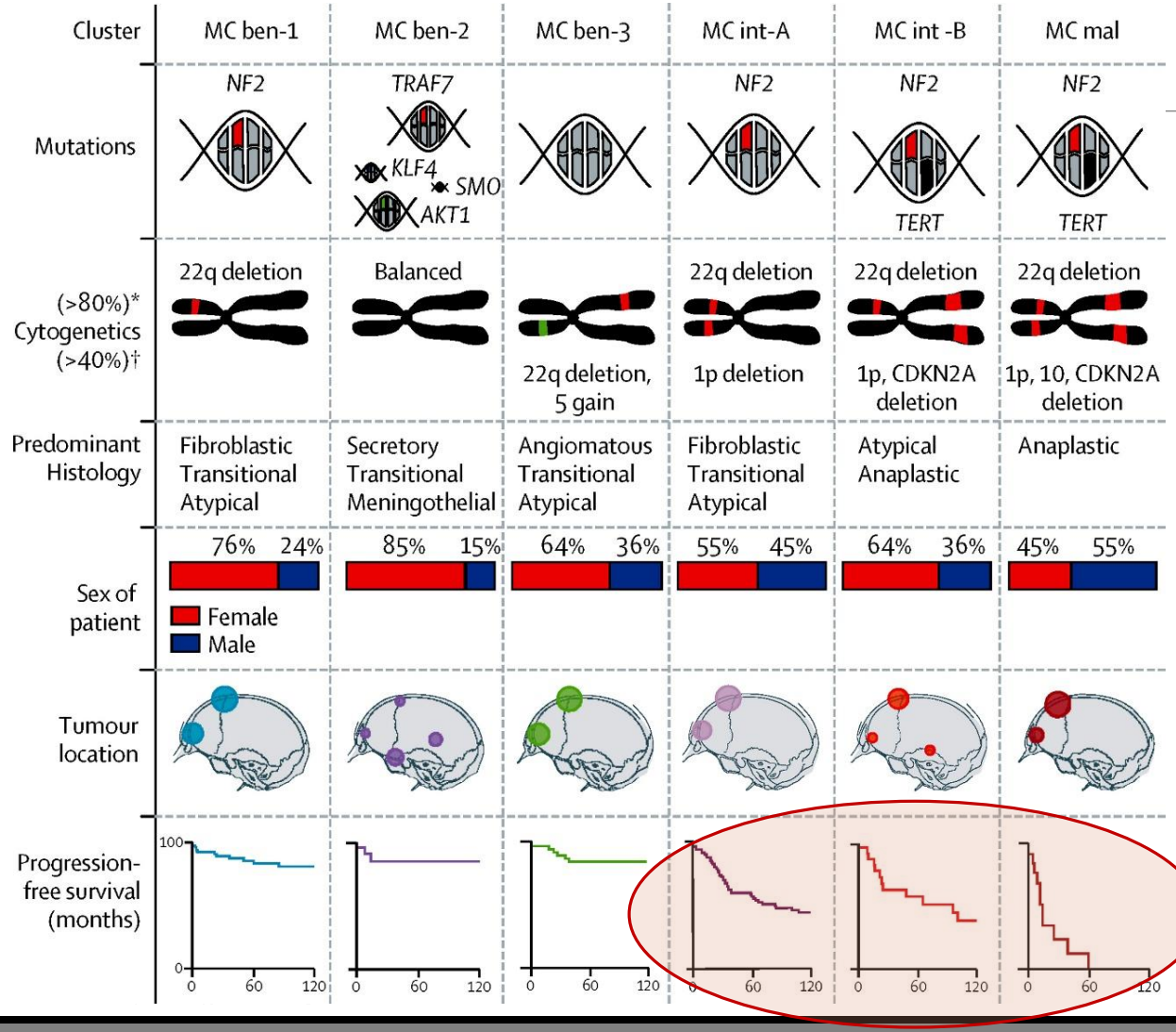
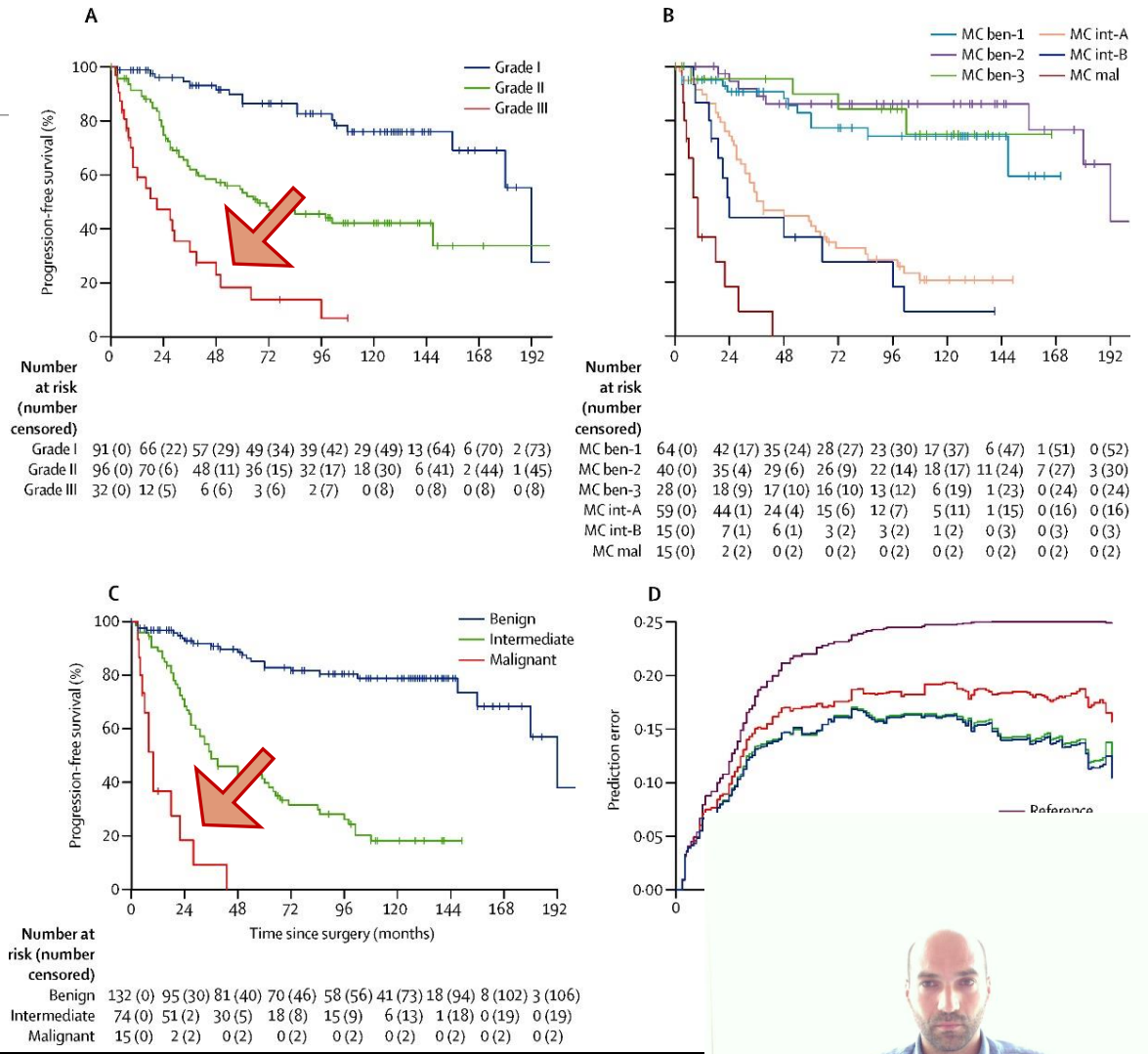
Wu et al., Neurosurg Focus 46 (6):E2, 2019

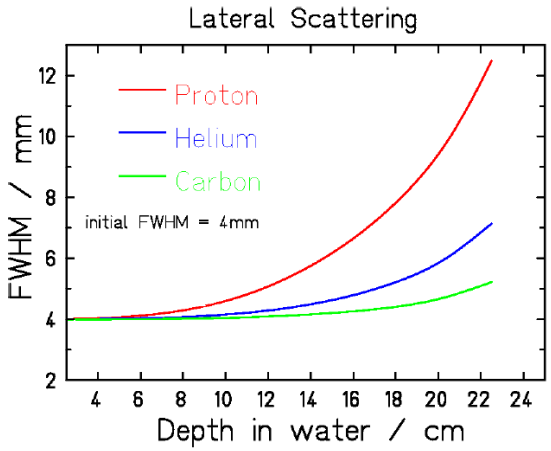
prognosis for malignant meningioma remains poor

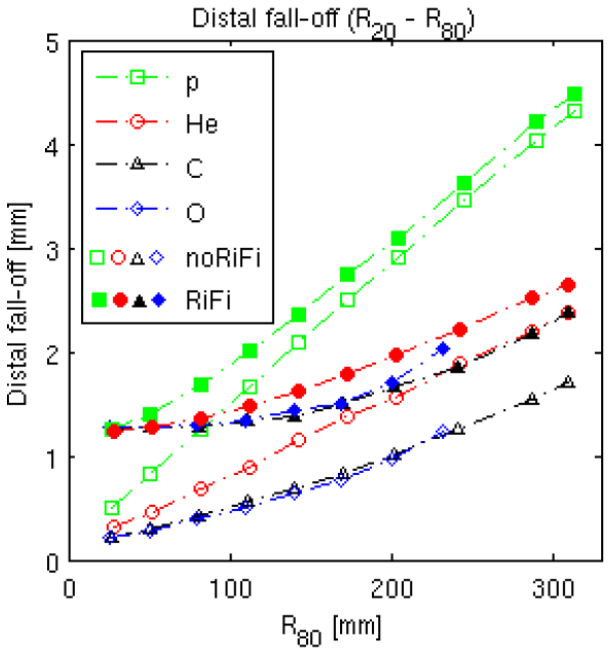


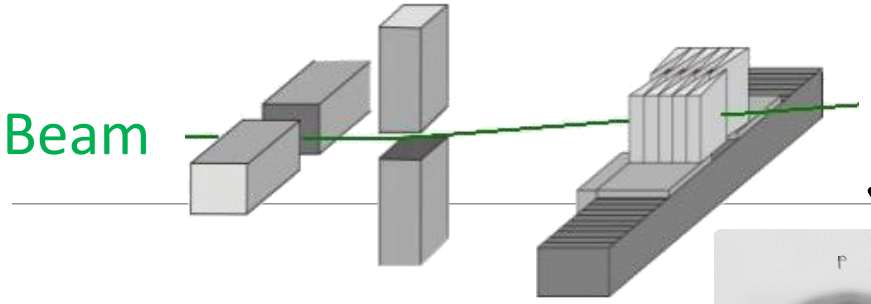


Sahm et al., Lancet Oncol (2017)

(physical) rationale for ions other than protons



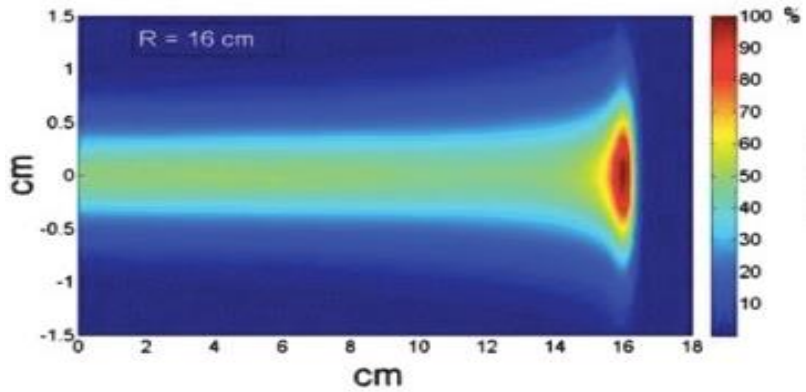


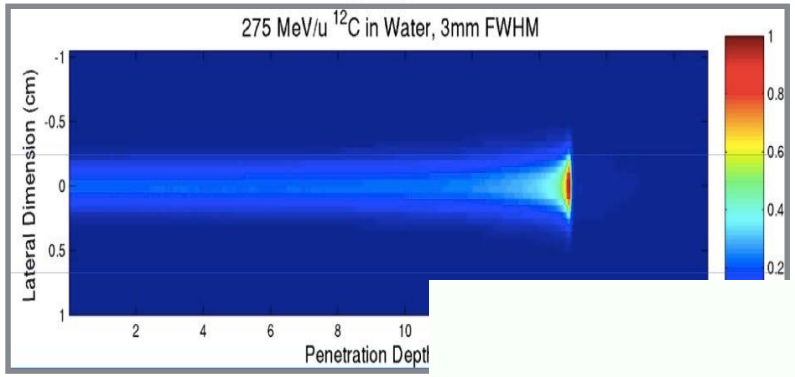


Protons
175 MeV

Helium ions
175 MeV/u

Carbon ions
330 MeV/u





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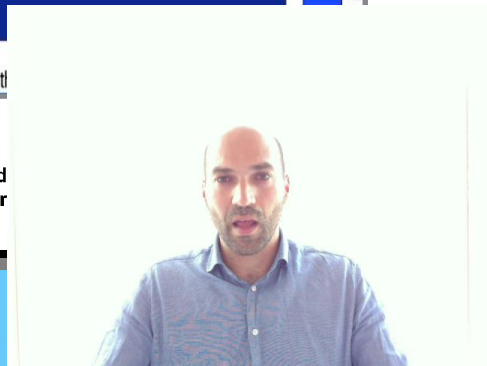


(biological) rationale for ions other than protons

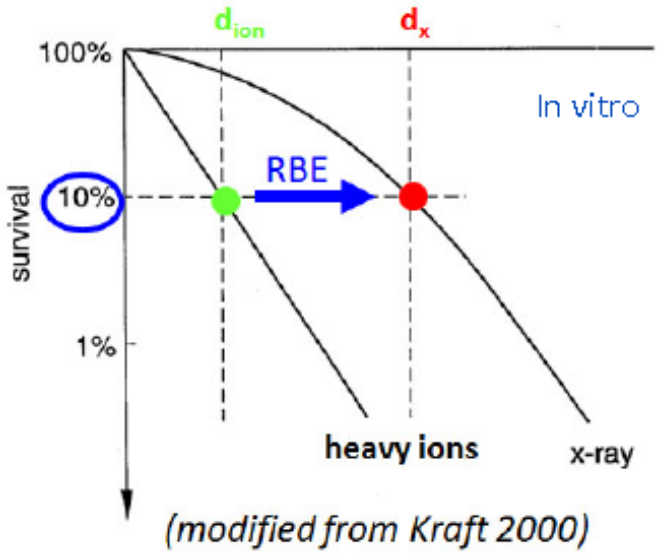
- For a given dose (in Gy), heavy ions are more effective than photons
- This is quantified by the **R**elative **B**iological **E**ffectiveness (RBE)

$$RBE = \left.\frac{d_{x-rays}}{d_{ions}}\right|_{\substack{same\\endpoint}}$$

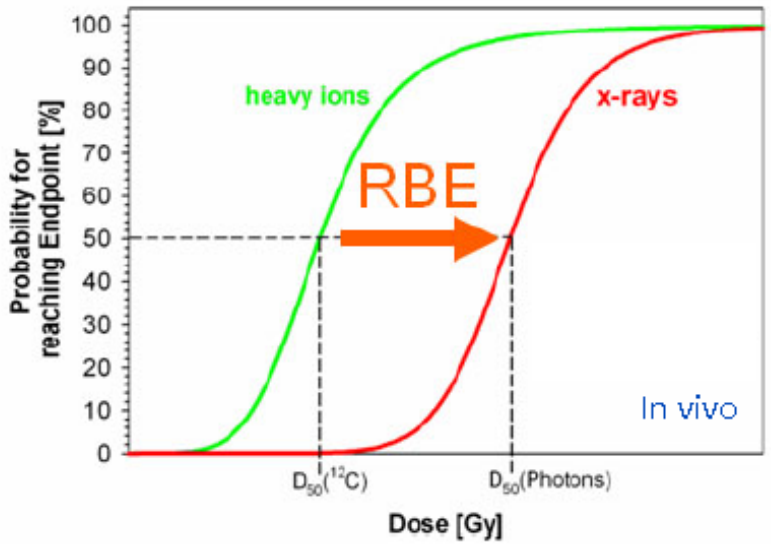
- Iso-effective x-ray dose

$$d_{x-rays} = RBE \times d_{ions}$$

- d is the fractional dose!
- All our clinical experience refers to the effectiveness of photons



(modified from Kraft 2000)



RBE is often determined at 10% cell survival

10 Gy with photons

2.85 Gy with high LET

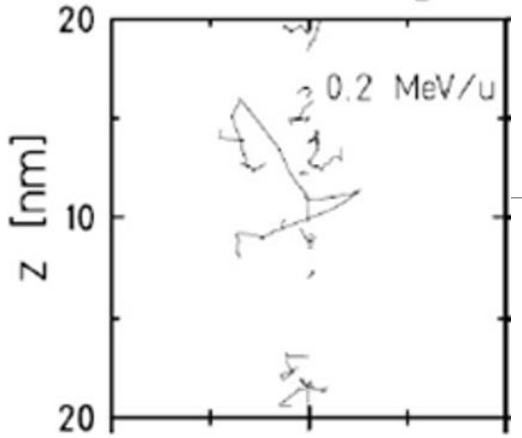
$RBE_{0.1}$ = **10 Gy** / **2.85 Gy**

$RBE_{0.1}$ = 3.5

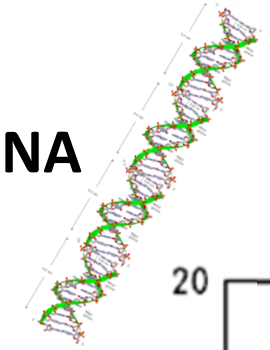
ionisation tracks

damage (in nucleus)

protons / photons **low LET**

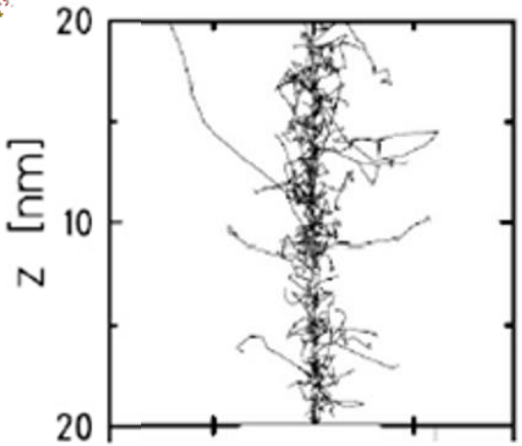


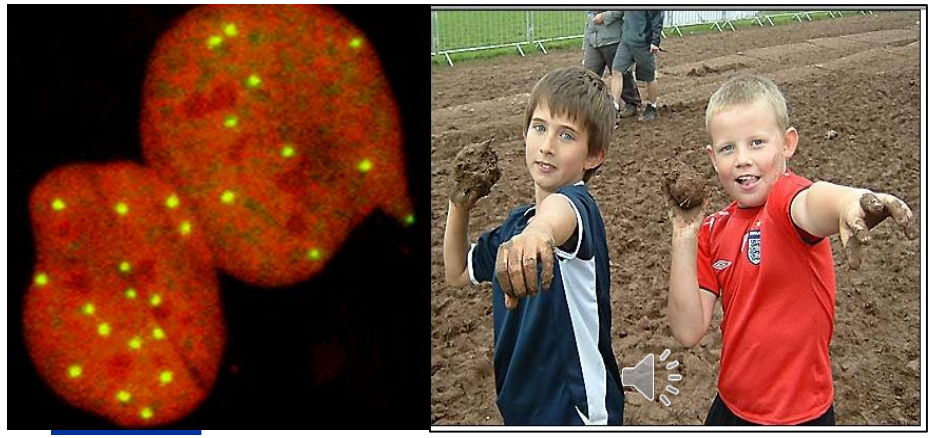
DNA



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

Carbon ions **high LET**





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modified from Kraft et al., 2003

malignant meningioma: prospective (particle therapy) trials

TABLE 3. Ongoing clinical trials exploring particle therapy in high-grade meningioma

Study ID	Study Name	Phase	Enrollment (no. of patients)	Intervention	Primary Outcome	Secondary Outcome	Completion Date	Associated Publications
NCT01166321	Carbon Ion Radiotherapy for Atypical Meningiomas (MARCIE)	II	40	Carbon boost	PFS (3 yrs)	OS (3 yrs)	12/2020	Combs et al., 2010
NCT01795300	Comparison of Proton and Carbon Ion Radiotherapy With Advanced Photon Radiotherapy in Skull Base Meningiomas: The PINOCCHIO Trial	NA	80	Carbon RT, proton RT, HF photon RT, photon RT	Toxicity (1 yr)	OS (3 yrs)	5/2022	NA
NCT02693990	A Trial of Increased Dose Intensity Modulated Proton Therapy (IMPT) for High-Grade Meningiomas	I/II	60	IMPT	Toxicity (2 yrs)	Local control (5 yrs), OS (2 yrs), linear energy transfer	2/2024	NA
NCT03267836	Neoadjuvant Avelumab and Hypofractionated Proton Radiation Therapy Followed by Surgery for Recurrent Radiation-refractory Meningioma	I	12	Avelumab + proton RT	Immunogenicity (2 yrs)	Toxicity (7 mos), radiological & pathological response (3 mos), PFS (2 yrs), OS (2 yrs)	7/2020	NA
NCT02978677	Proton Dose Escalation for Patients With Atypical or Anaplastic Meningiomas (PANAMA)	NA	90	Photon/proton RT/ boost	PFS (5 yrs)	Toxicity (late/acute; 5 yrs), OS (5 yrs), recurrence (5 yrs), QOL (5 yrs)	12/2028	NA

HF = hypofractionated; IMPT = intensity-modulated proton therapy; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RT = radiotherapy.
A total of five ongoing clinical studies investigating the utility of particle therapy in atypical and anaplastic meningioma were identified. Toxicity is measured according to the Common Terminology Criteria for Adverse Events (CTCAE). Quality of life is graded according to the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients (EORTC-QLQ-C30) and Brain Cancer Patients (EORTC-QLQ-BN20) criteria.

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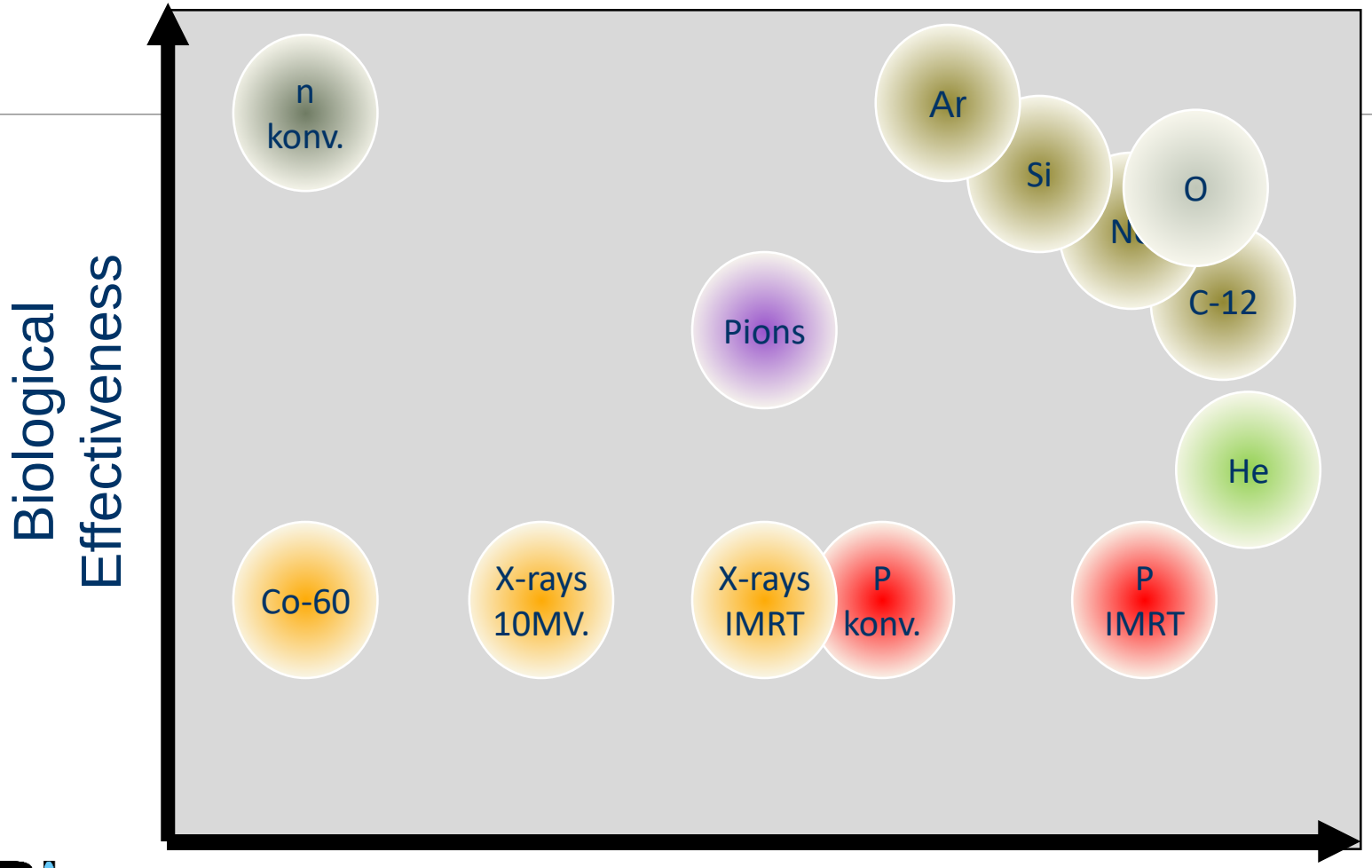
Wu et al., Neurosurg Focus 46 (6):E2, 2019

future topic: new ion types



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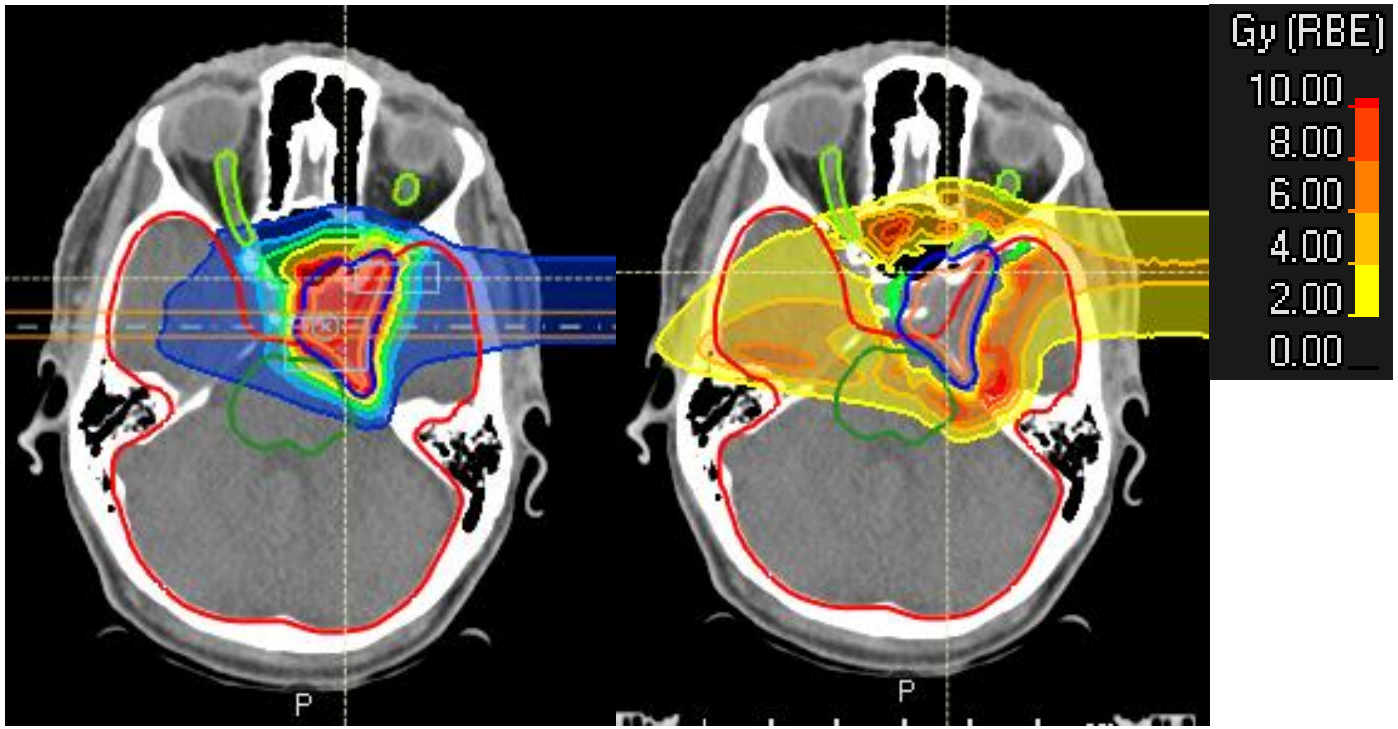
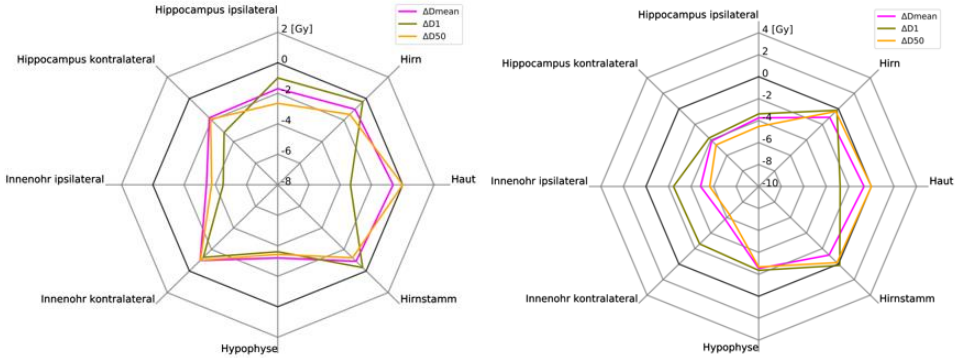
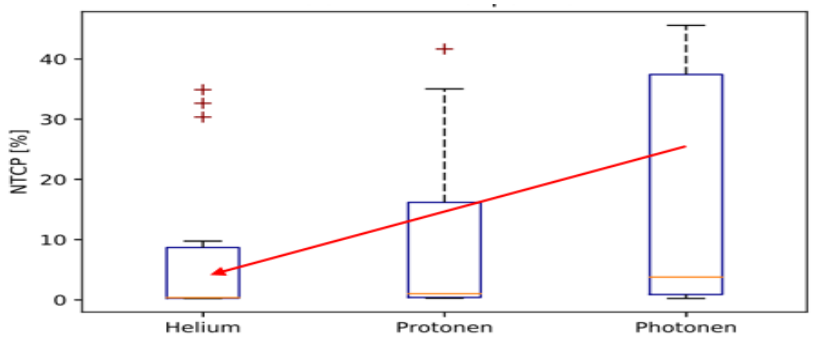
clinical rationale for helium ions



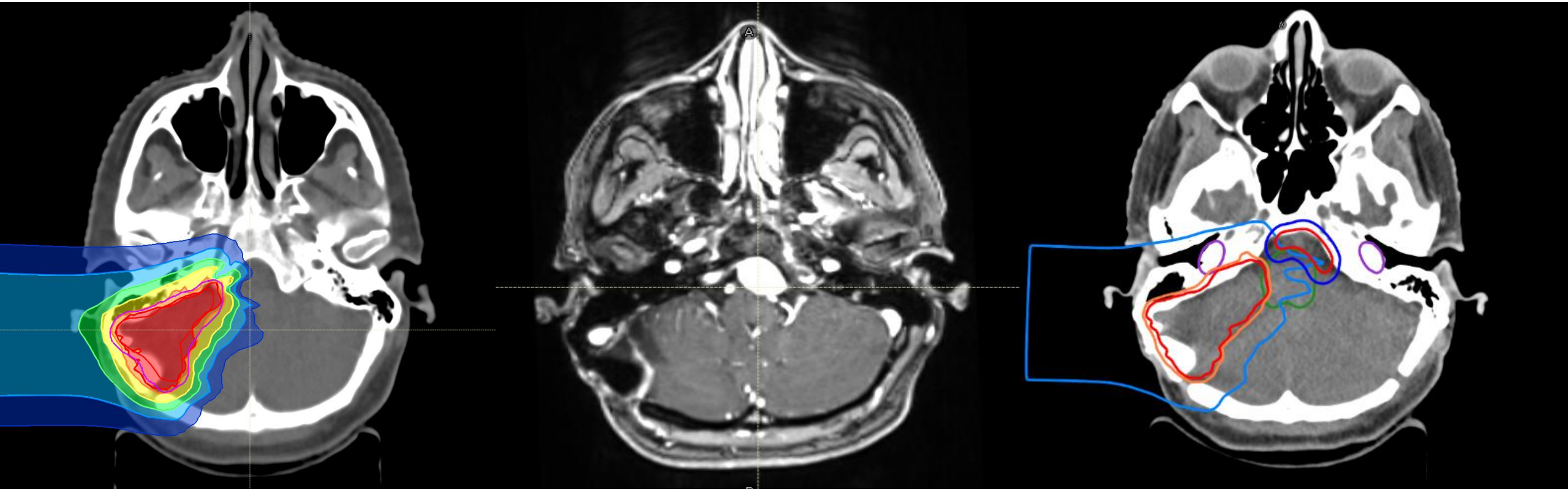




HITRI
Heavy Ion Therapy Research Integration

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

1st treatment with scanned helium beams



Recurrent solitary fibrous tumor of the dura

2015: 60 GyRBE carbon ions

summer 2021: 60GyRBE helium ions – 30 fractions / Re-irradiation

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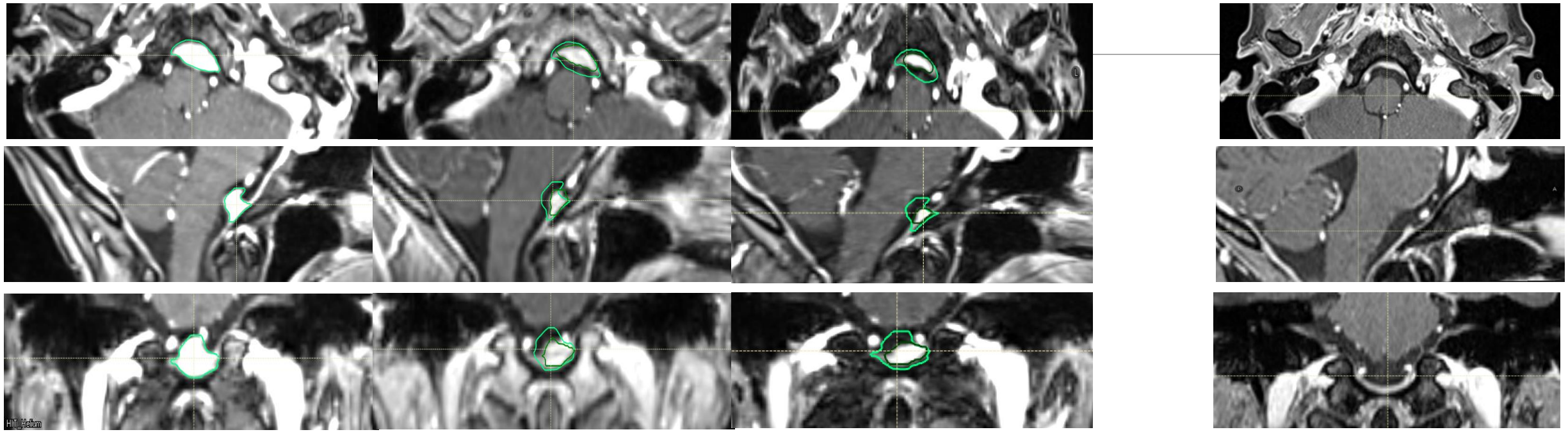
1st treatment with scanned helium beams

Baseline MRI | six weeks post RT | six months post RT | one year post RT



GTV pre RT
0,8 ml

GTV post RT
0,3 ml

GTV post RT
0,2 ml

complete remission

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Thank you!

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