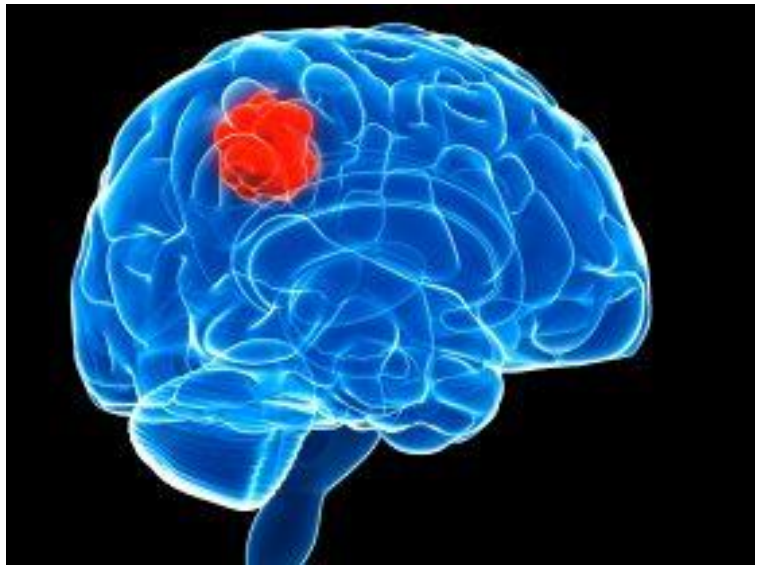
HITRI plus
Heavy Ion Therapy Research Integration

tumors of the central nervous system



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

Table 1 2021 WHO Classification of Tumors of the Central Nervous System. Provisional Entities are in Italics

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Glioblastoma, IDH-wildtype
Pediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, *MN1*-altered
Glioneuronal and neuronal tumors
Ganglioglioma
Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
Dysembryoplastic neuroepithelial tumor
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
Papillary glioneuronal tumor
Rosette-forming glioneuronal tumor
Myxoid glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Gangliocytoma
Multinodular and vacuolating neuronal tumor
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Ependymal tumors
Supratentorial ependymoma
Supratentorial ependymoma, *ZFTA* fusion-positive
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma
Spinal ependymoma, *MYCN*-amplified
Myxopapillary ependymoma
Subependymoma

Table 1 Continued

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Choroid plexus tumors
Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma
Embryonal tumors
Medulloblastoma
Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and *TP53*-wildtype
Medulloblastoma, SHH-activated and *TP53*-mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined
Other CNS embryonal tumors
Atypical teratoid/rhabdoid tumor
Cribriform neuroepithelial tumor
Embryonal tumor with multilayered rosettes
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
CNS embryonal tumor
Pineal tumors
Pineocytoma
Pineal parenchymal tumor of intermediate differentiation
Pineoblastoma
Papillary tumor of the pineal region
Desmoplastic myxoid tumor of the pineal [illegible] *CB1*-mutant
Cranial and paraspinal nerve [illegible]rs
Schwannoma
[illegible]fibroma
[illegible]eriomas
Hybrid nerve sheath tumor
Malignant melanotic nerve sheath tumor
Malignant peripheral nerve sheath tumor
Paraganglioma
Meningiomas
Meningioma
Mesenchymal, non-meningothelial tumors
Soft tissue tumors
Fibroblastic and myofibroblastic tumors
Solitary fibrous tumor
Vascular tumors
Hemangiomas and vascular malformations
Hemangioblastoma
Skeletal muscle tumors
Rhabdomyosarcoma
Uncertain differentiation
Intracranial mesenchymal tumor, FET-CREB fusion-positive
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Ewing sarcoma

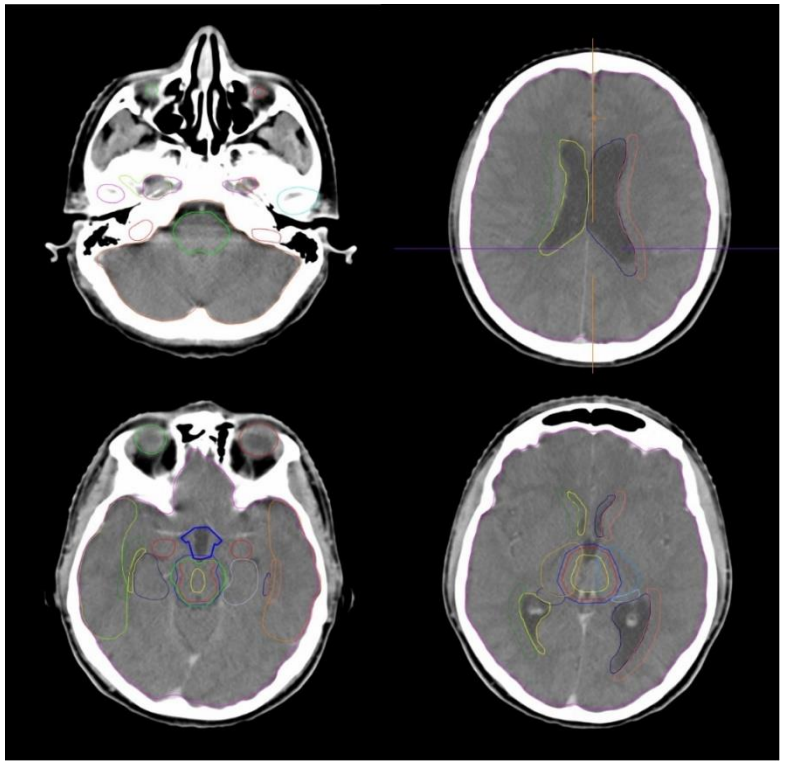
Table 1 Continued

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Chondro-osseous tumors
Chondrogenic tumors
Mesenchymal chondrosarcoma
Chondrosarcoma
Notochordal tumors
Chordoma (including poorly differentiated chordoma)
Melanocytic tumors
Diffuse meningeal melanocytic neoplasms
Meningeal melanocytosis and meningeal melanomatosis
Circumscribed meningeal melanocytic neoplasms
Meningeal melanocytoma and meningeal melanoma
Hematolymphoid tumors
Lymphomas
CNS lymphomas
Primary diffuse large B-cell lymphoma of the CNS
Immunodeficiency-associated CNS lymphoma
Lymphomatoid granulomatosis
Intravascular large B-cell lymphoma
Miscellaneous rare lymphomas in the CNS
MALT lymphoma of the dura
Other low-grade B-cell lymphomas of the CNS
Anaplastic large cell lymphoma (*ALK*+/*ALK*–)
T-cell and NK/T-cell lymphomas
Histiocytic tumors
Erdheim-Chester disease
Rosai-Dorfman disease
Juvenile xanthogranuloma
Langerhans cell histiocytosis
Histiocytic sarcoma
Germ cell tumors
Mature teratoma
Immature teratoma
Teratoma with somatic-type malignancy
Germinoma
Embryonal carcinoma
Yolk sac tumor
Choriocarcinoma
Mixed germ cell tumor
Tumors of the sellar region
Adamantinomatous craniopharyngioma
Papillary craniopharyngioma
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma
Pituitary adenoma/PitNET
Pituitary blastoma
Metastases to the CNS
Metastases to the brain and spinal cord parenchyma
Metastases to the meninges

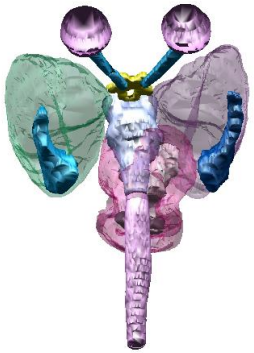
Abbreviations: CNS, central nervous system; IDH, isocitrate dehydrogenase; NK, natural killer; PitNET, pituitary neuroendocrine tumor; SHH, sonic hedgehog.

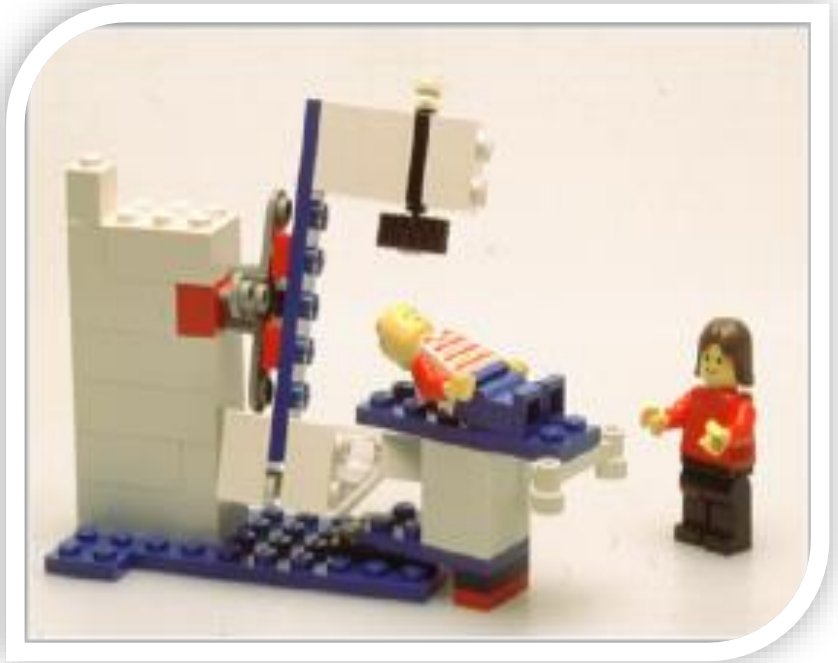
Focus on glioma !

rationale of particle therapy for brain tumors



potential sequelae





Secondary malignancies

Visual impairment / loss of hearing

Hypopituitarisms

Quality of life ↓

neurocognitive function ↓

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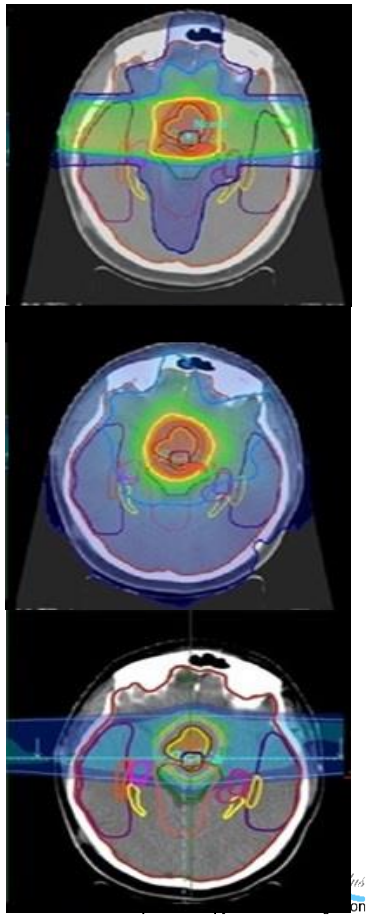
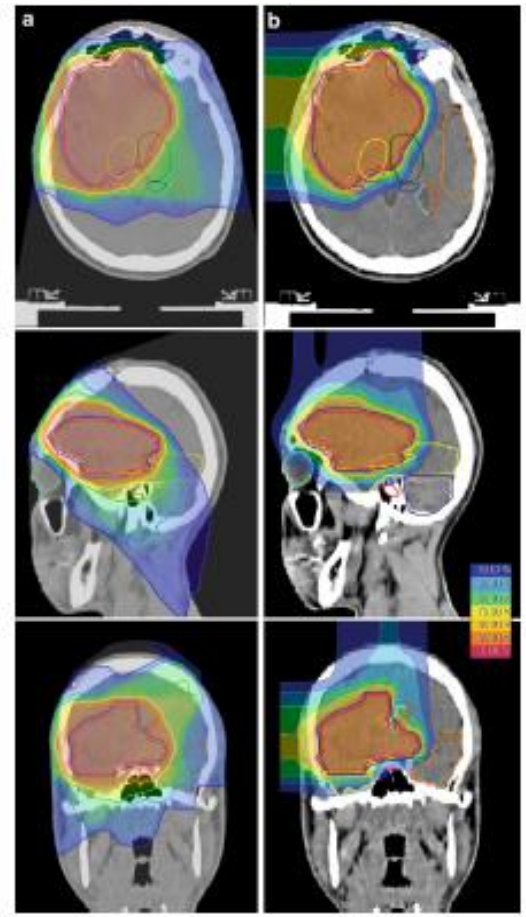
rationale of particle therapy for brain tumors

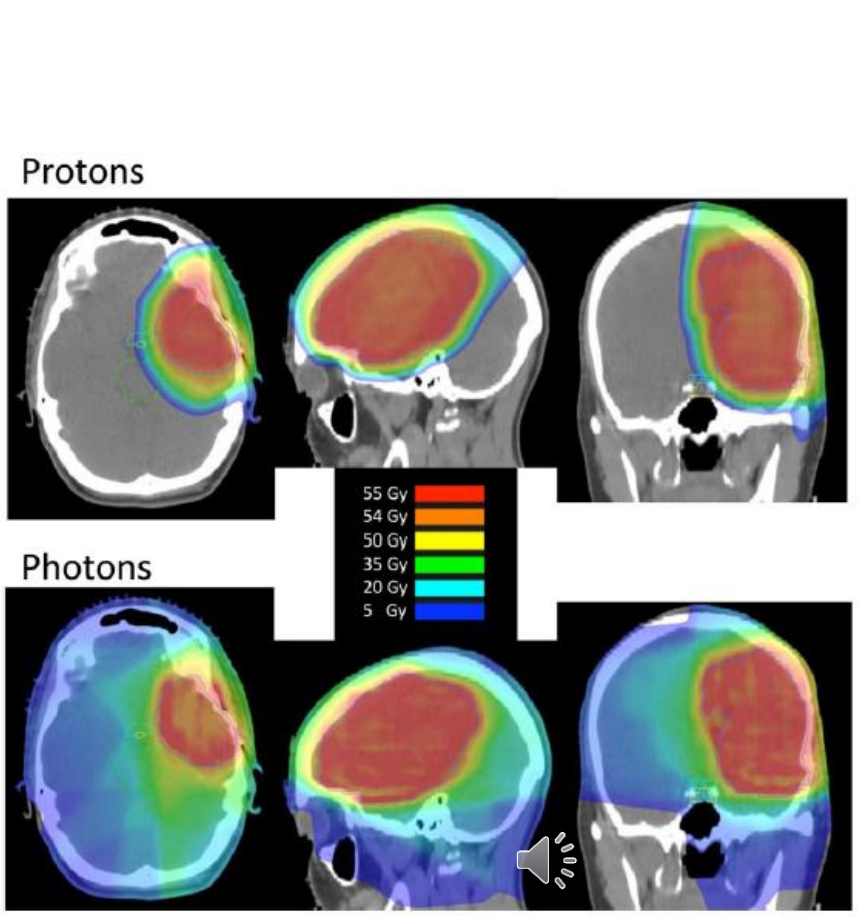


3D-CRT

VMAT

Ions

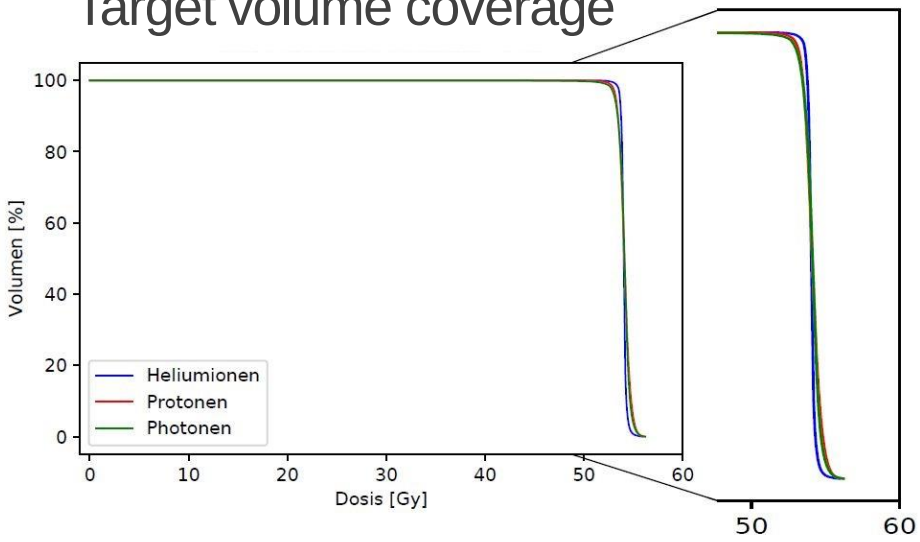


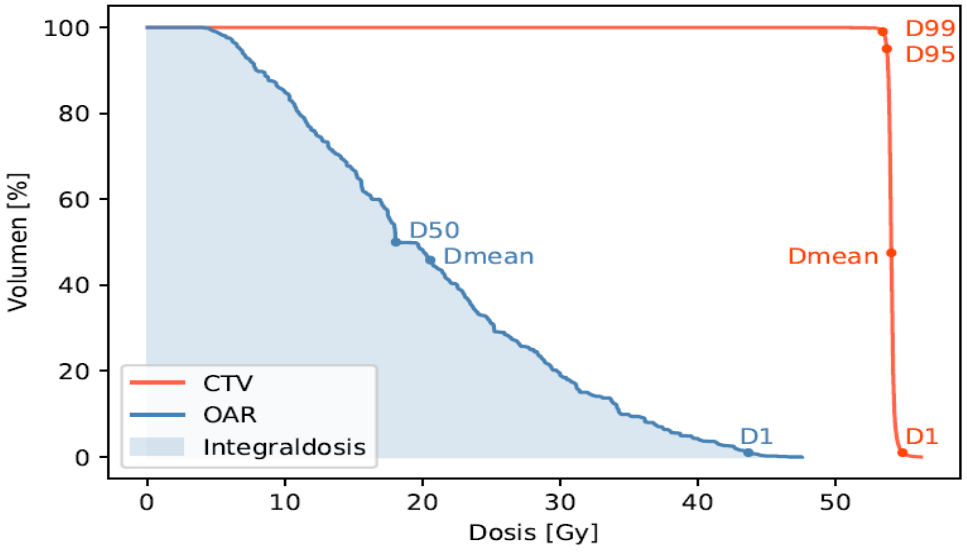


Harrabi et al. 2016 *Shih et al 2015*

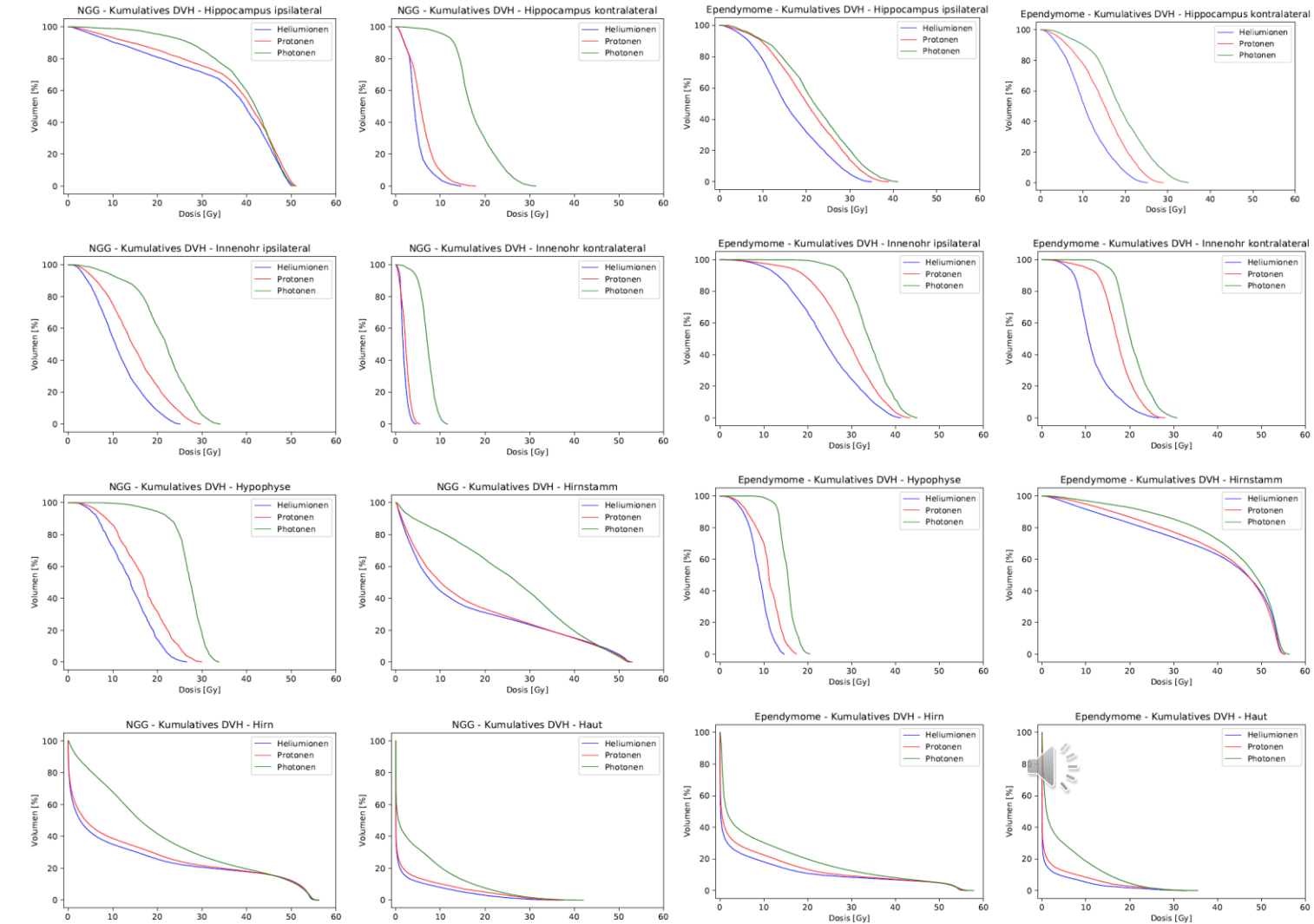
quantification of the dosimetric potential

Target volume coverage

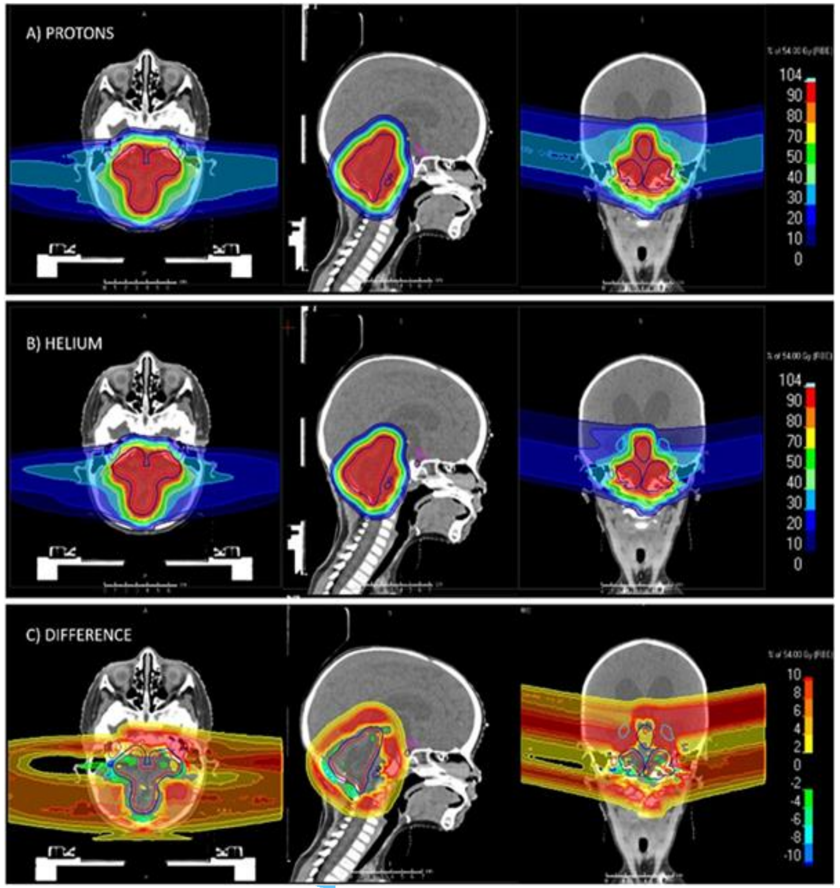




Organs at risk



quantification of the dosimetric potential



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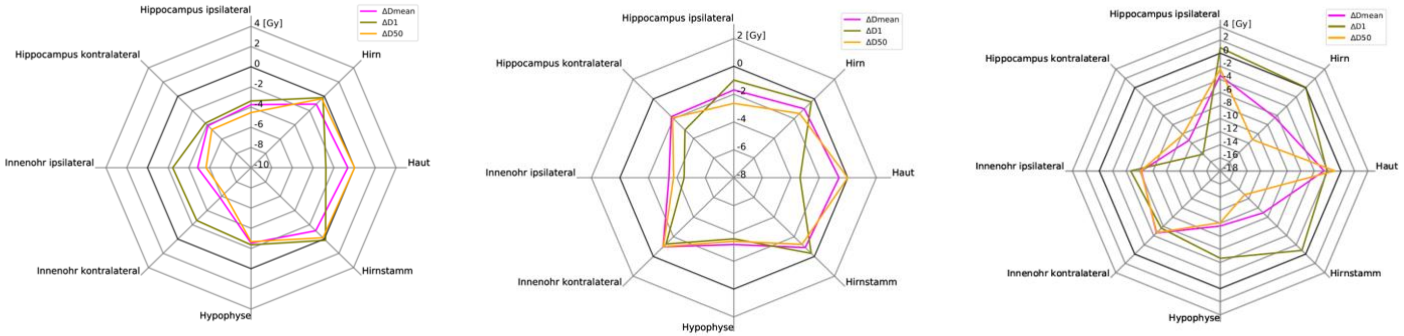

- For patients with low grade glioma absolute dose reduction of up to 5 GyRBE
- Biggest dose sparing potential for pituitary and ipsilateral cochlea

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Clinical outcome

Neurocognitive effects of proton radiation therapy in adults with low-grade glioma

20 patients mit low grade glioma WHO °II

Indication for PBT: age >/= 40 Jahre
MiB1 >/=3%
tumor size >/= 6cm
tumor progression

dose: 54 GyRBE in 30 fractions

median f/u 5,1 year
5-year OS 84%

results

- **stable cognitive function**
- Left sided tumor significantly increased impairment of speech
- Improvement of speach memory with left sided tumors better than with right sided tumors

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Sherman et al. J Neurooncol (2016) 126:157–164 DOI 10.1007/s11060-015-1952-5

Clinical outcome

Proton Therapy for Low-Grade Gliomas: Results From a Prospective Trial

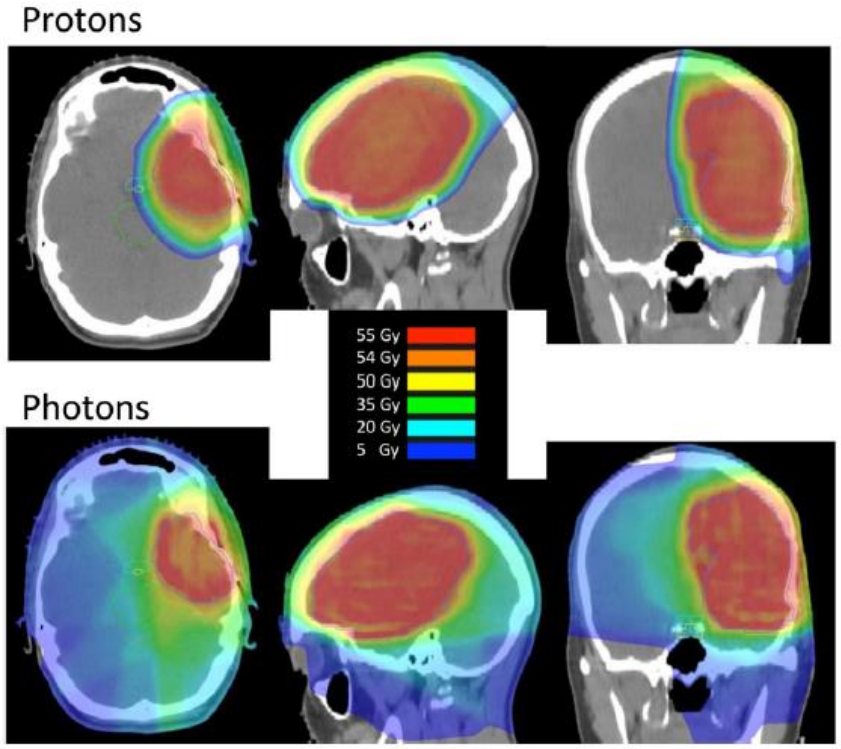
20 patients with low grade glioma WHO °II

dose 54GyRBE in 30 fractions

Median f/u 5.1 years

New endocrine impairment in six patients

PFS after 3 years 85%
PFS after 5 years 40%



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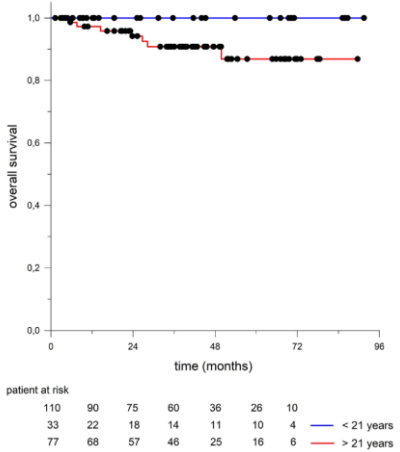
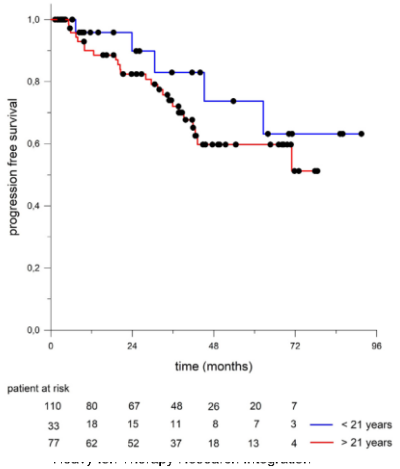
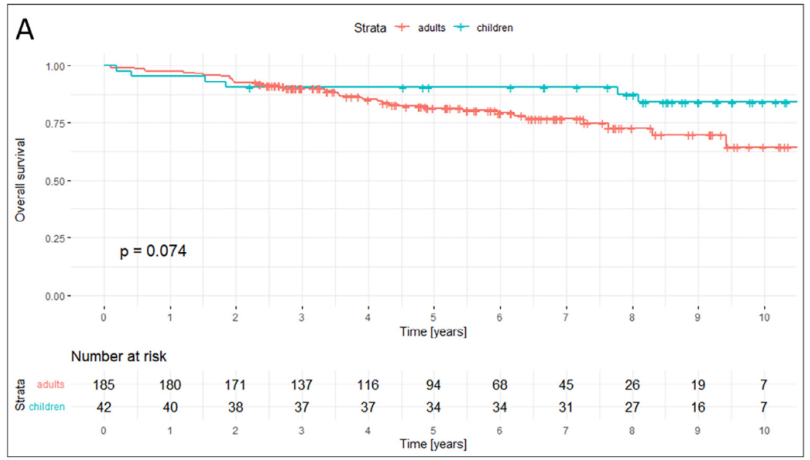
Shih et al., Cancer 2015;121:1712-9 DOI: 10.1002/cncr.29237

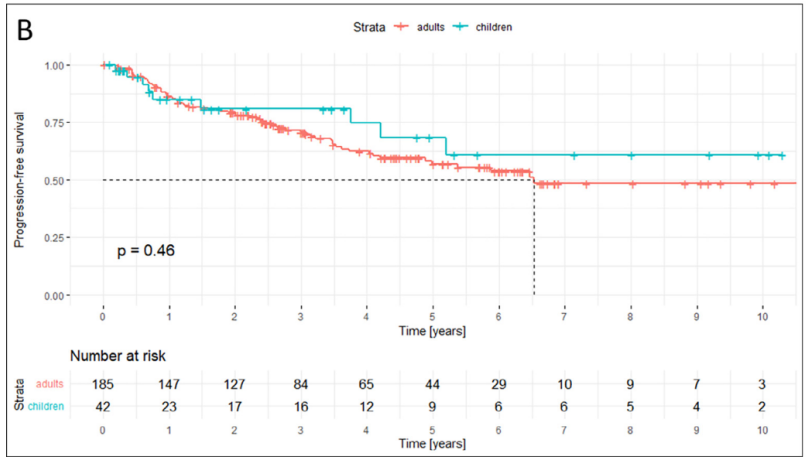
Clinical outcome:

brain tumors with low to intermediate malignancy (CNS grade I and II)









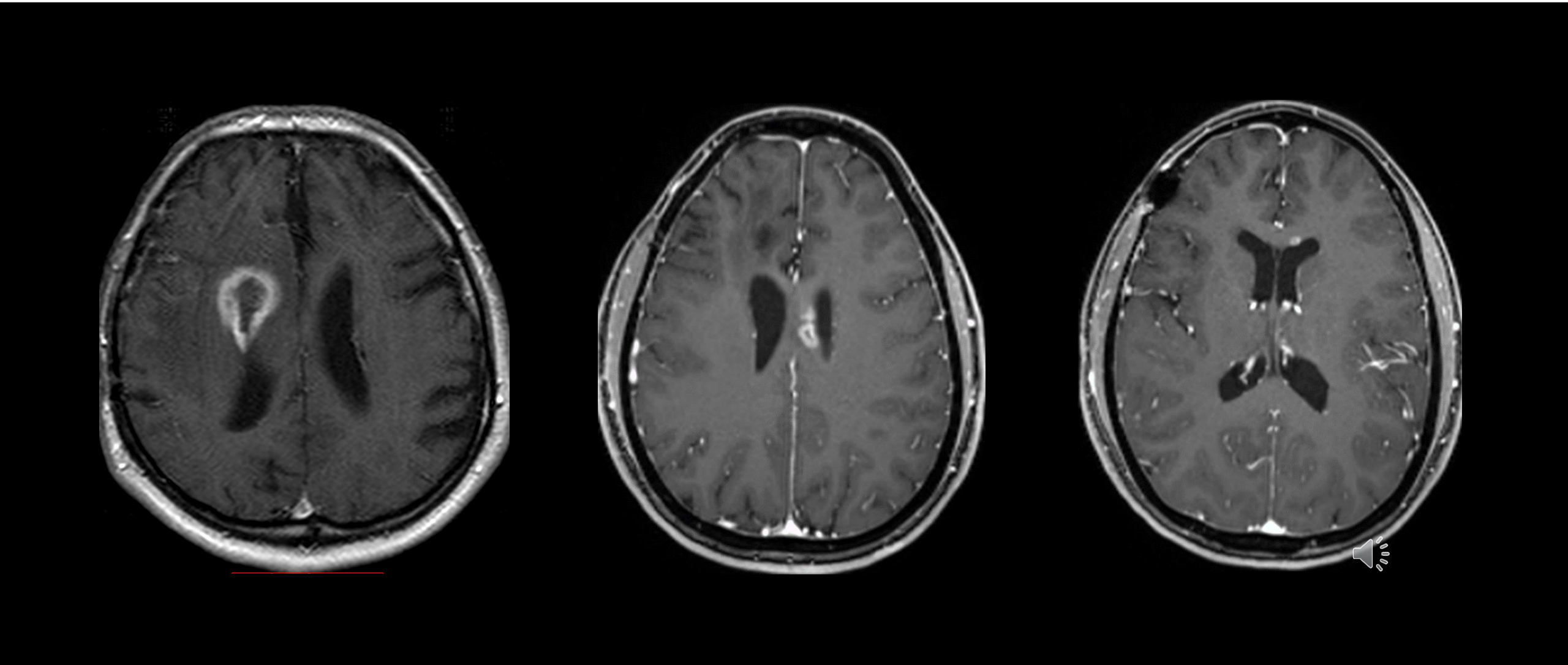
A) Patients	overall cohort *n* = 227 [%]	Adults *n* = 185	Children *n* = 42
Gender			
female	99 [43.6%]	79 [42.7%]	20 [47.6%]
male	128 [56.4%]	106 [57.3%]	22 [52.4%]
Age at primary diagnosis			
median	31.5	34.7	7.7
minimum – maximum	0.2–76	13–76	0.2–19.2
Karnofsky Performance Status	***n* = 182 [%]**	***n* = 152 [%]**	***n* = 25 [%]**
<70	19 [10.5%]	19 [12.1%]	0 [0%]
80	25 [13.7%]	20 [12.7%]	5 [20%]
90	78 [42.9%]	66 [42.1%]	12 [48%]
100	60 [33.0%]	52 [33.1%]	8 [32%]
Diagnosis	***n* = 227 [%]**	***n* = 185**	***n* = 42**
Astrocytoma	148 [65.2%]	113 [61.1%]	35 [83.3%]
Oligodendroglioma	52 [22.9%]	52 [28.1%]	0 [0%]
Other/mixed glioma	27 [11.9%]	20 [10.8%]	7 [16.7%]
WHO grade	***n* = 227 [%]**	***n* = 185**	***n* = 42**
1	51[22.5%]	22 [11.9%]	29 [69.0%]
IDH status available	14 [27.5%]	8 [9.1%]	6 [20.7%]
IDH wildtype	12 [85.7%]	7 [87.5%]	5 [83.3%]
IDH mutation	2 [14.3%]	1 [12.5%]	1 [16.7%]
2	170 [74.9%]	160 [86.5%]	10 [23.8%]
IDH status available	146 [85.9%]	142 [88.8%]	4 [40.0%]
IDH wildtype	15 [10.3%]	14 [9.9%]	1 [25.0%]
IDH mutation	131 [89.7%]	128 [90.1%]	3 [75.0%]
1–2	6 [2.6%]	3 [1.6%]	3 [7.2%]
IDH status available	2 [33.3%]	2 [66.7%]	0 [0%]
IDH wildtype	0 [0%]	0 [%]	-
IDH mutation	2 [100%]	2 [100%]	–
1p/19q LOH deletion	***n* = 99 [%]**	***n* = 96 [%]**	***n* = 3 [%]**
no	38 [38.4%]	37 [38.5%]	1 [33.2%]
yes	61 [61.6%]	59 [61.5%]	2 [66.7%]
MGMT promotor methylated	***n* = 72 [%]**	***n* = 66 [%]**	***n* = 6 [%]**
no	20 [27.8%]	16 [24.2%]	4 [66.7%]
yes	52 [72.2%]	50 [75.8%]	2 [33.3%]
Past surgery	***n* = 211 [%]**	***n* = 175 [%]**	***n* = 36 [%]**
no surgery	5 [2.4%]	2 [1.1%]	3 [8.3%]
biopsy	81 [38.4%]	75 [42.9%]	6 [16.7%]
subtotal resection	68 [32.2%]	50 [28.6%]	18 [50%]
total resection	57 [27.0%]	48 [27.4%]	9 [25%]
Chemotherapy	***n* = 227 [%]**	***n* = 185 [%]**	***n* = 42 [%]**
none	87 [38.3%]	56 [30.3%]	31 [73.8%]
PCV	44 [19.4%]	41 [22.1%]	3 [7.1%]
temozolomide	79 [34.8%]	74 [40.0%]	5 [11.9%]
other	17 [7.5%]	14 [7.6%]	3 [7.1%]

Harrabi et al. Radiother Oncol 2022

Eichkorn et al. Radiother Oncol 2022

Clinical outcome:

brain tumors with low to intermediate malignancy (CNS grade I and II)



Clinical outcome:

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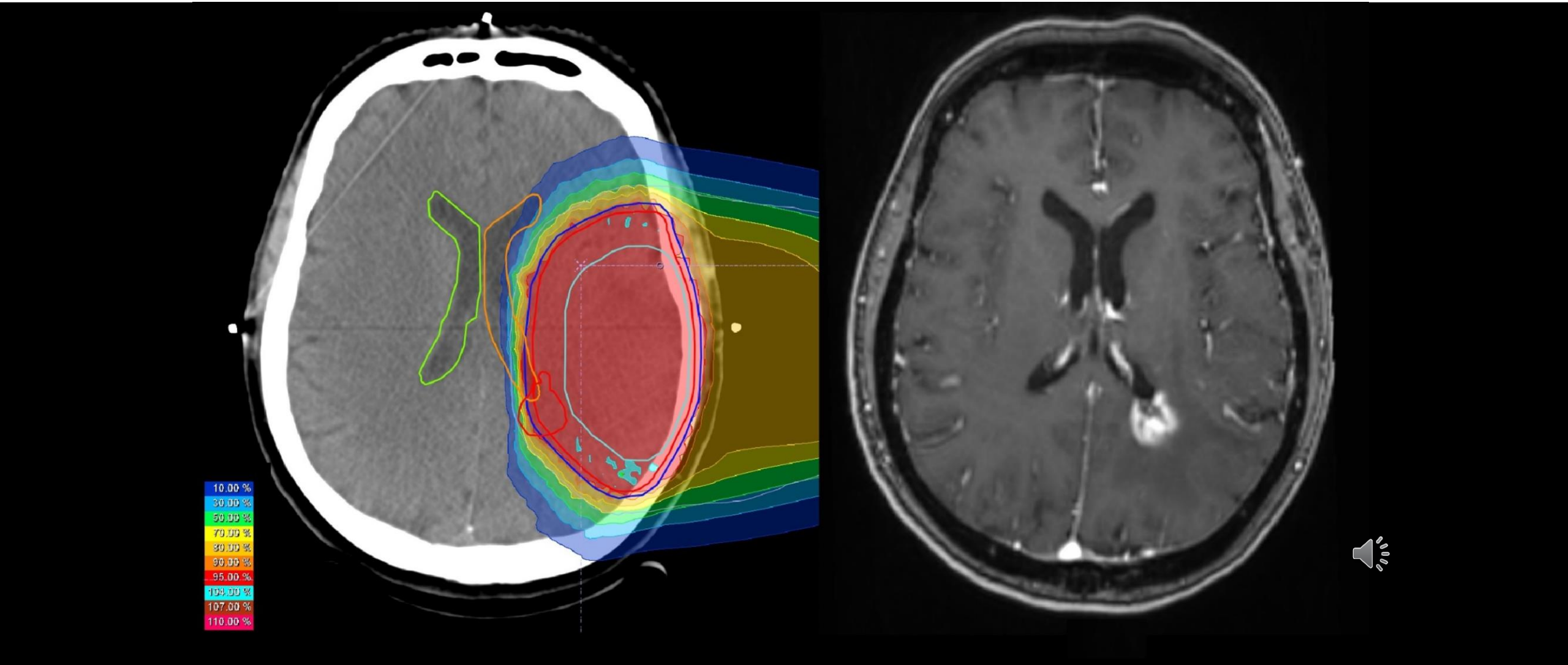
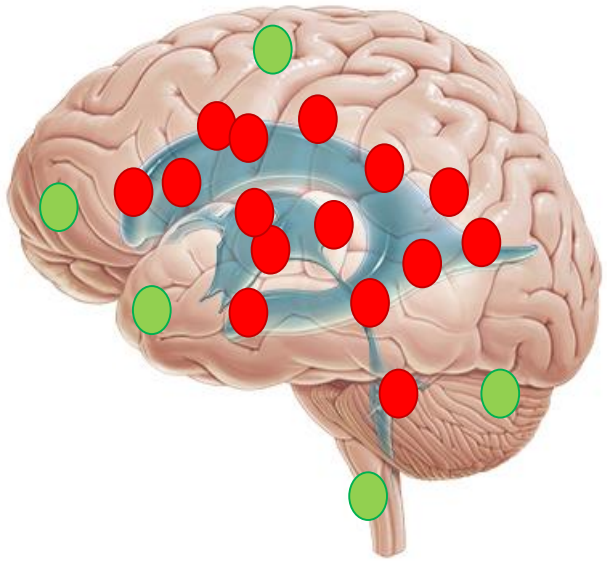
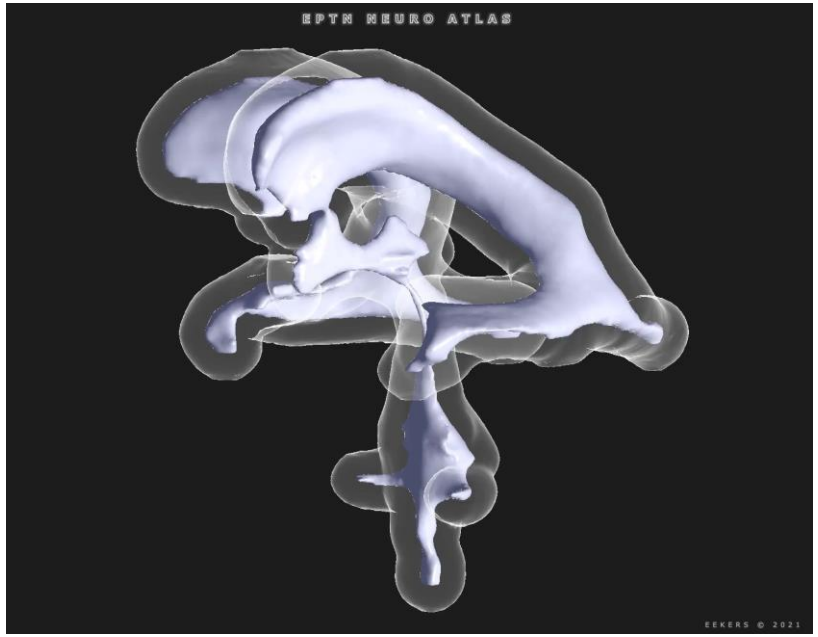


Clinical outcome:

characteristics of radiation induced brain injuries



Number of patients	**51**
Total number of lesions	108
age	41 years
Median time to occurence	13 months
Median size at first diagnosis	0,63 ml
Anatomical localisation (periventricular)	90/108
Distal part of the SOBP	99/108



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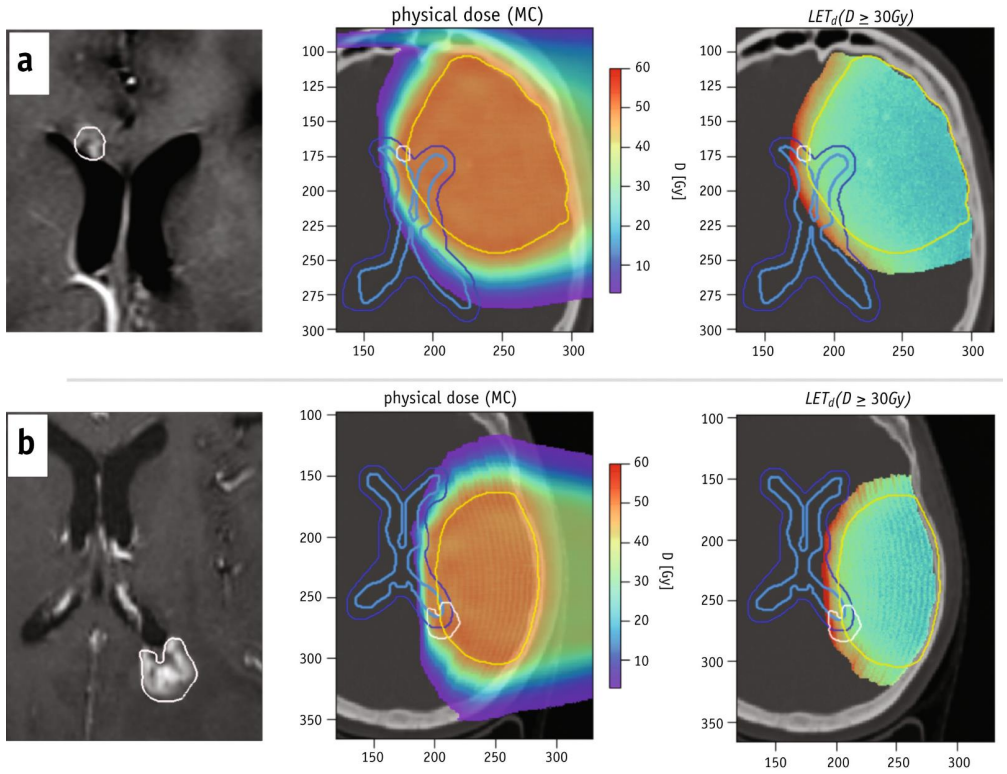
Clinical outcome:

development of a new model



Why does it happen?

What if we could predict where it happens?

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Bahn et al., IJROBP 2020

	Indication	patients with PRT	Median dose	Follow up	Conclusion
Gunther et al [17]	Ependymoma	37	59.4 GyRBE	40 months	Postradiation MRI changes are more common with PBRT and in patients less than 3 years of age at diagnosis and treatment. It is difficult to predict causes for development of imaging changes that progress to clinical significance.
Indelicato et al [18]	Ependymoma Craniophayryngioma LGG other (incl. extracranial)	73 68 66 106	n/a	24 months	Association of increased-LET and endothelial damage hypothesized. Utilization of current national brainstem dose guidelines is associated with a low risk of brainstem toxicity in pediatric patients.
Acharya et al [28]	Oligodendroglioma and Astrozytoma	37	54 GyRBE	29 months	The study showed that 1p/19q codeleted oligodendroglioma was a significant risk factor associated with radiation necrosis.
Peeler et al	Ependymoma	34	54 GyRBE	n/a	correlation of changes on MR images after proton therapy with increased LET constitutes the first clinical evidence of variable proton biological effectiveness
Niemierko et al	Head and neck, skull base and intracranial	50	≥59.4 GyRBE	n/a	In this patient cohort, LET adjusted for dose was not found to be associated with risk of brain necrosis.
Grabacz et al	Skull base	45	70 GyRBE	n/a	When looking at standard dosimetric parameters, the higher dose associated with vRBE seems to be responsible for an enhanced risk of radiographic changes. However, as revealed by avoxel-based analysis, the large inter-patient variability hinders the identification of a clear effect for high LETd
present study	LGG	110	54 GyRBE	39 months	The increased incidence of asymptomatic radiation-induced brain injuries with an increased average LET seen in this cohort provides strong clinical evidence for the hypothesis of a variable relative biological effectiveness of protons being different than the fixed factor of 1.1 currently used worldwide.

Harrabi et al. Radiother Oncol 2022

Clinical outcome:

development of a new model: why does it happen?

Study of dose/LET on risk of necrosis

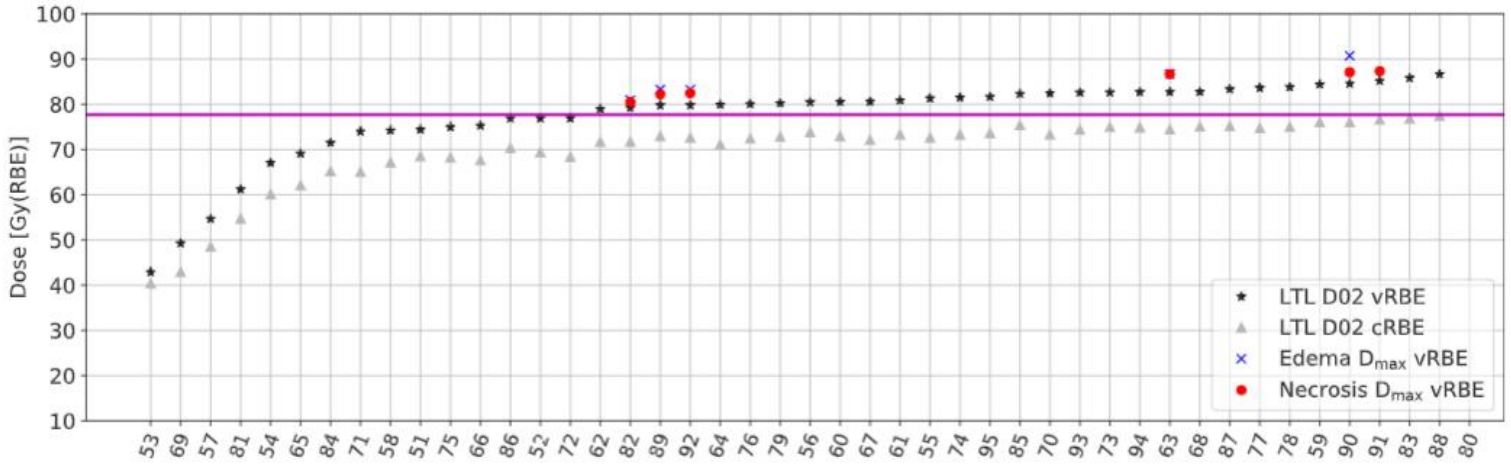

Fig. 2. D02 for left temporal lobe calculated with constant and variable RBE and D_{max} in necrosis/edema calculated with vRBE. Solid magenta line indicates the dose constraint at 77.7 Gy(RBE).

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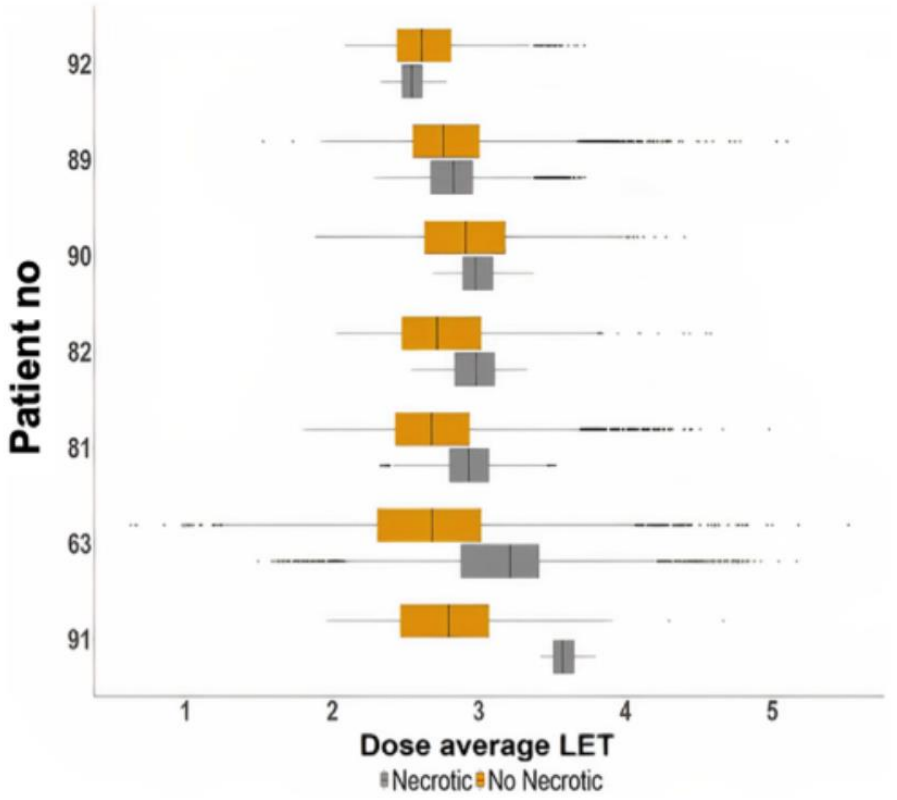
Clinical outcome:

development of a new model: why does it happen?

Patient no	Mean LET (keV/μm)		Mean Difference (keV/μm)	Nr of necrotic voxels
	Necrotic	Non-necrotic		
92	2.54	2.66	-0.12±0.02	699
89	2.81	2.80	0.01±0.01	7602
90	2.99	2.93	0.07±0.03	554
82	2.97	2.79	0.18±0.04	494
81	2.94	2.72	0.22±0.02	2506
63	3.13	2.68	0.45±0.02	5236
91	3.58	2.82	0.76±0.09	102
Mean	2.99	2.77	0.22±0.03	2456.14



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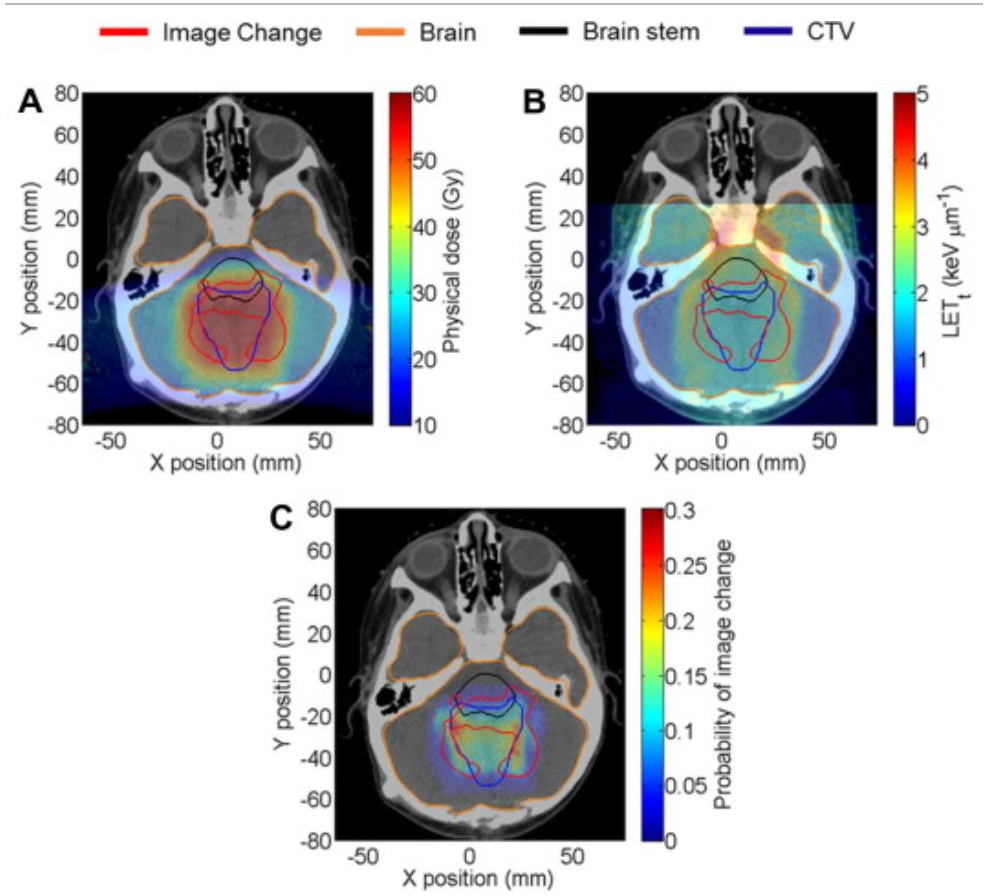
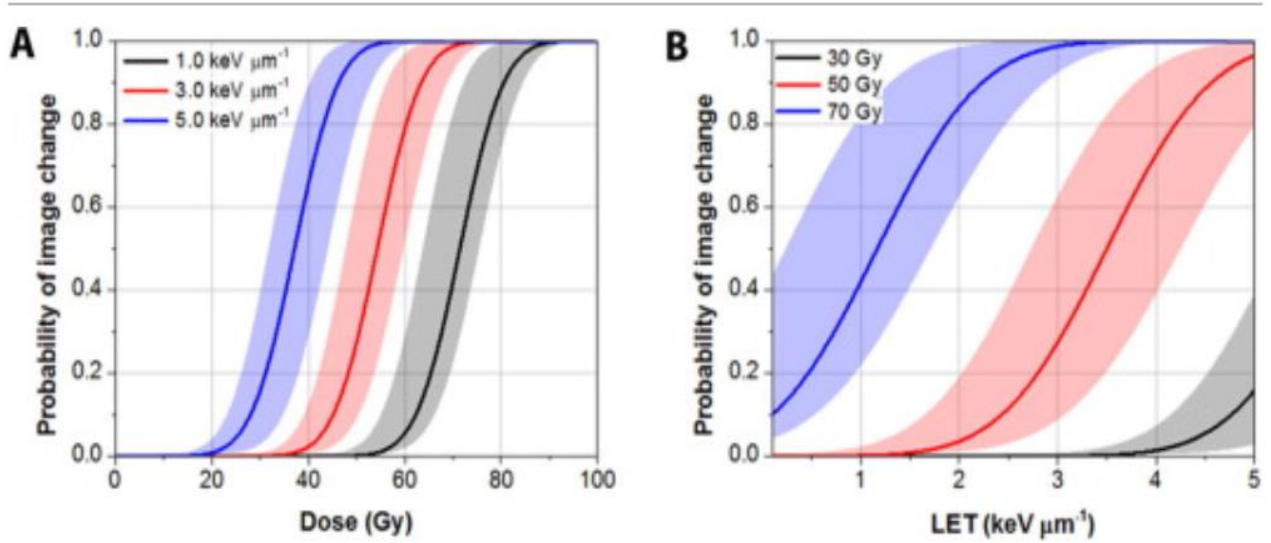
Garbacz et al., Radiother Oncol 2021

Clinical outcome:

development of a new model: why does it happen?





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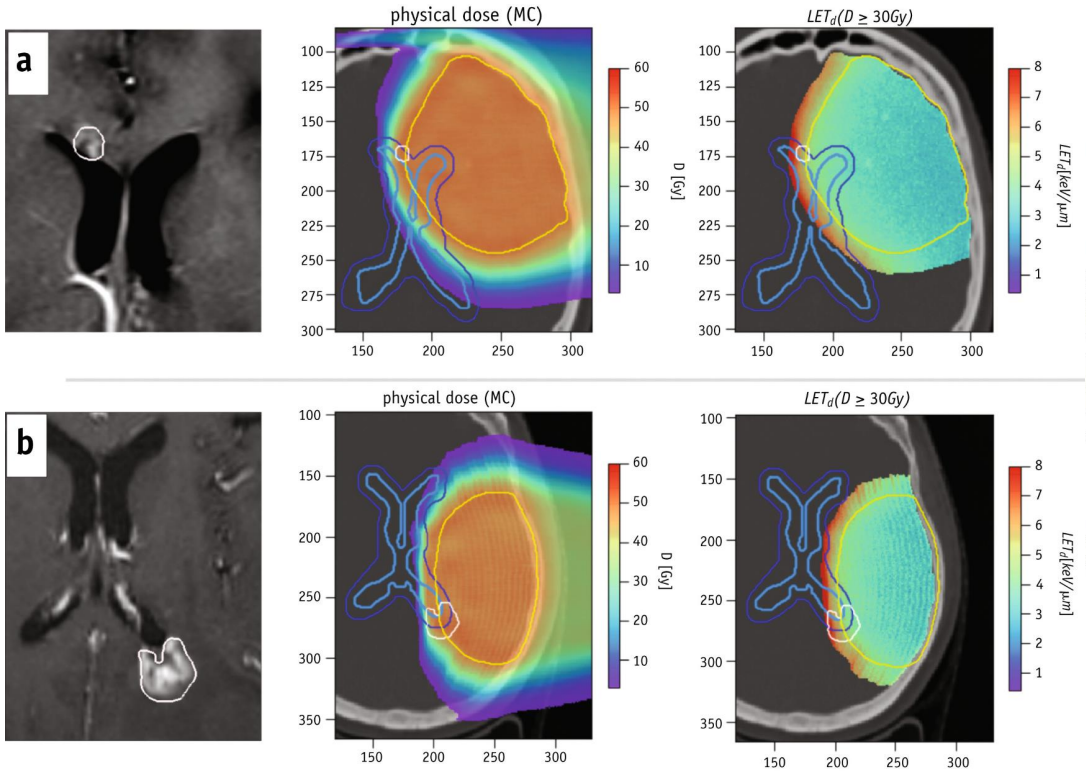
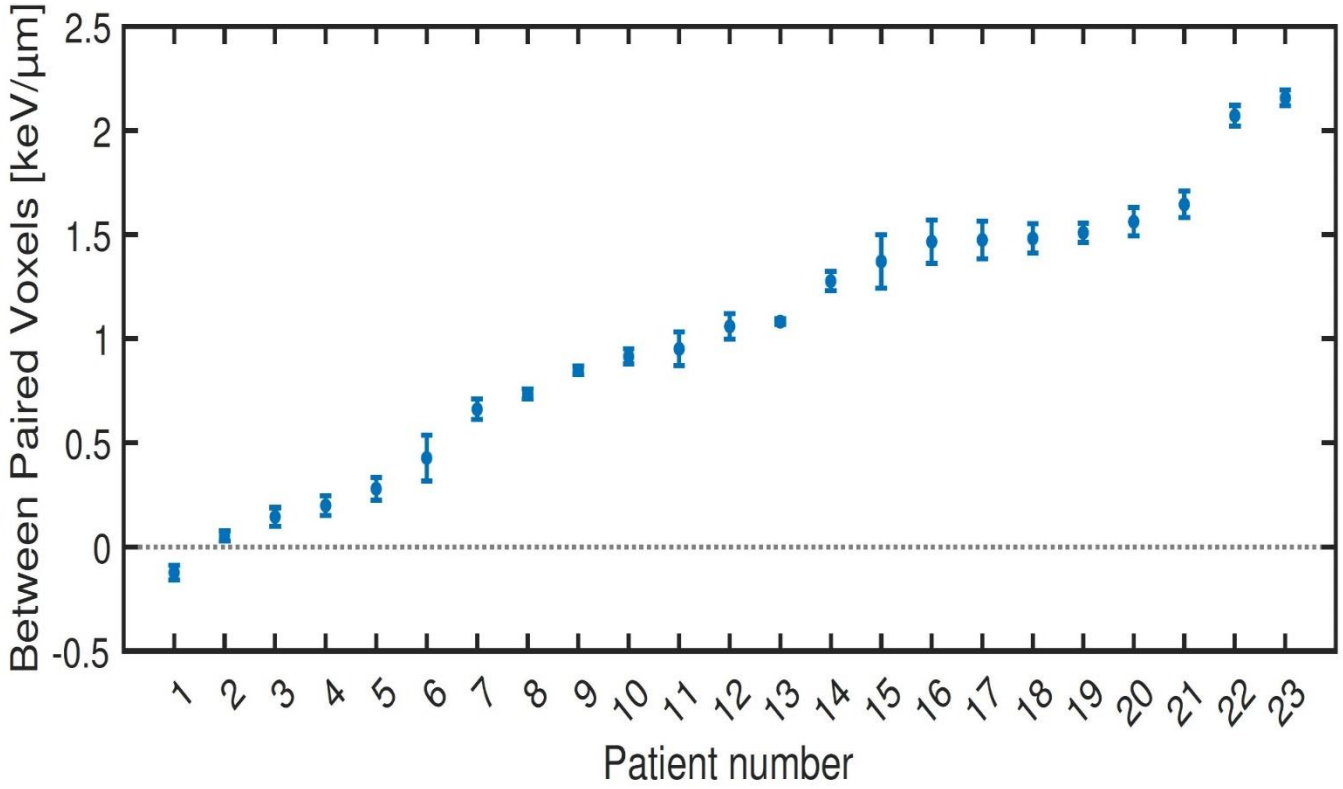
Peeler et al., IJROBP 2016

Clinical outcome:

development of a new model: why does it happen?





HITRI
Heavy Ion Therapy Research Integration

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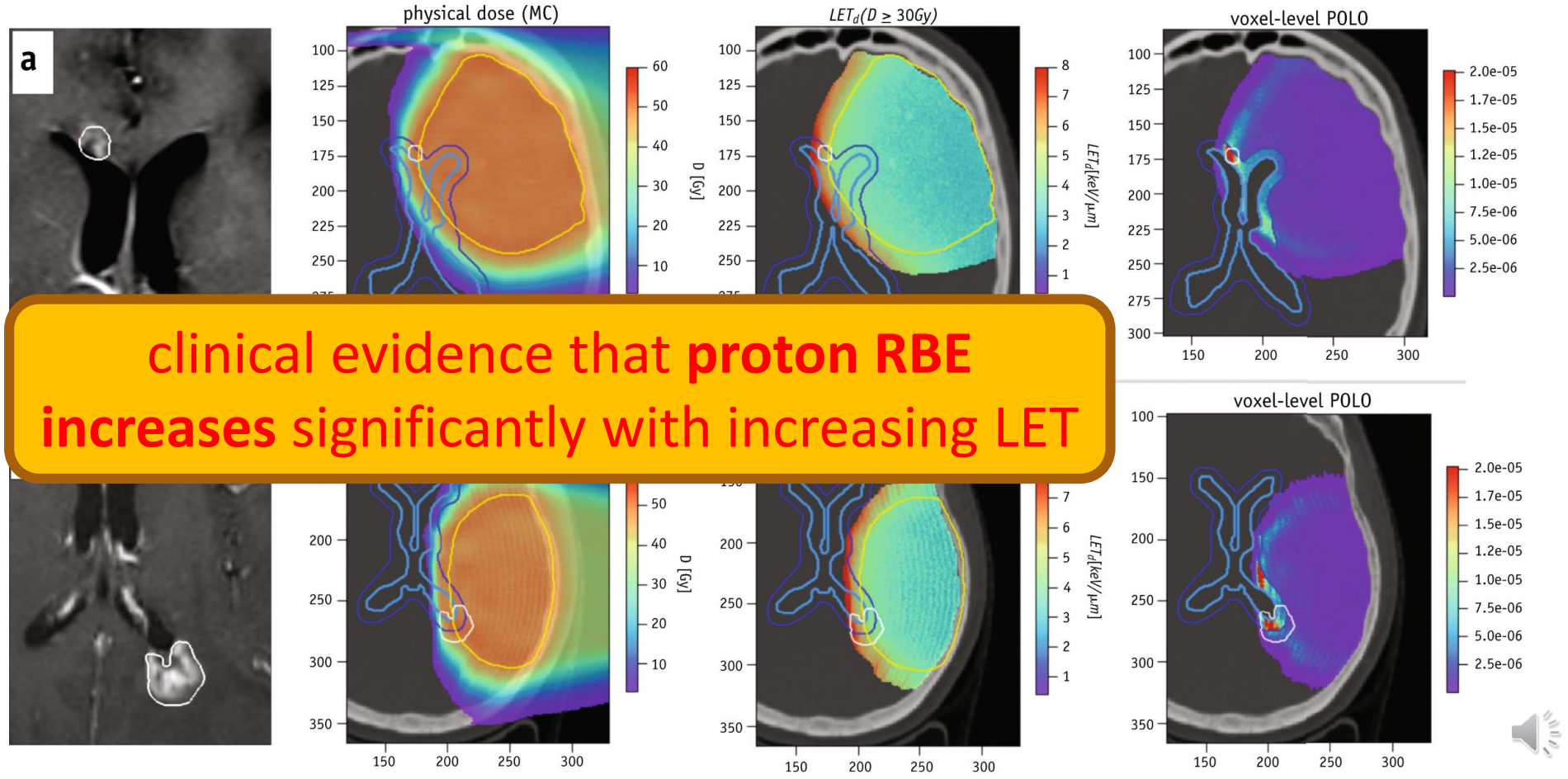
Bahn et al., IJROBP 2020

Harrabi et al. Radiother Oncol 2022

Clinical outcome:

development of a new model: how to predict?

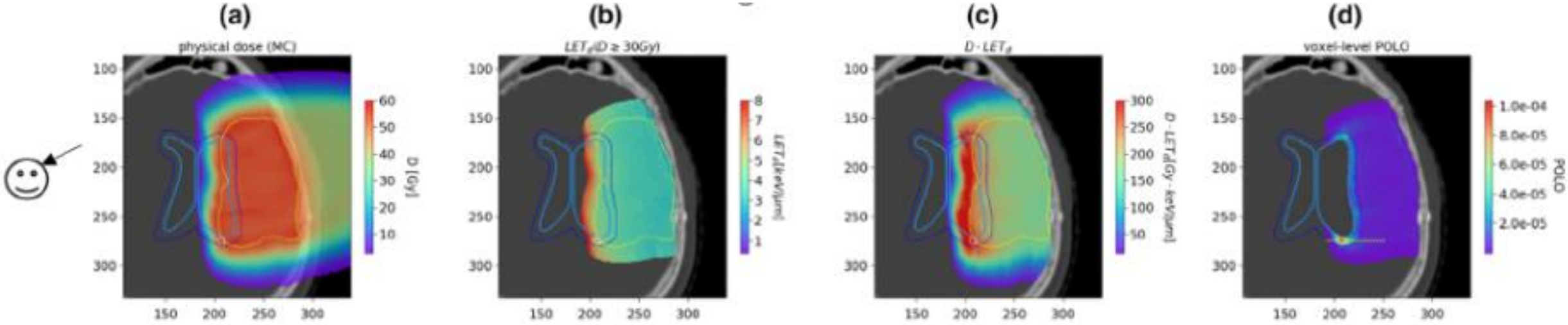


clinical evidence that **proton RBE increases** significantly with increasing LET

Clinical outcome:

development of a new model: how to avoid?

Clinical-1F



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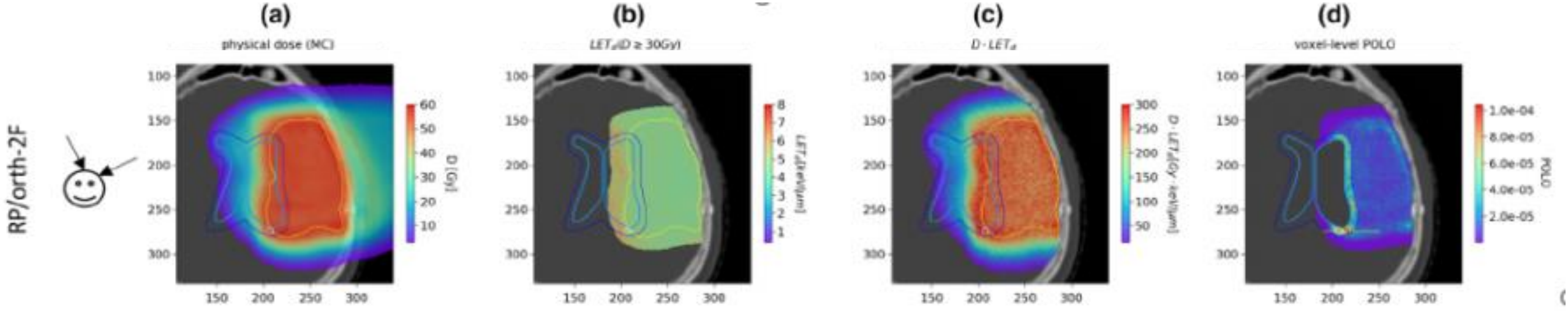
Clinical outcome:

development of a new model: how to avoid?



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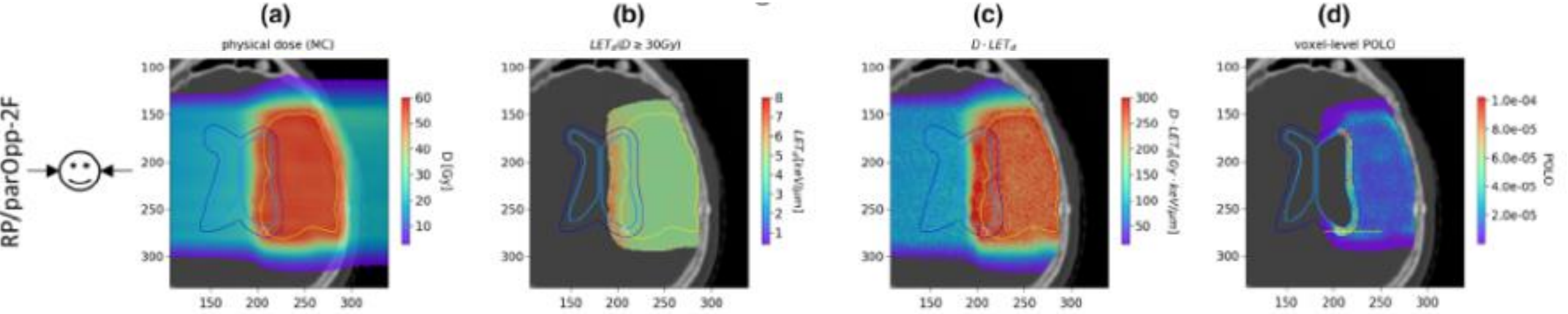
Clinical outcome:

development of a new model: how to avoid?



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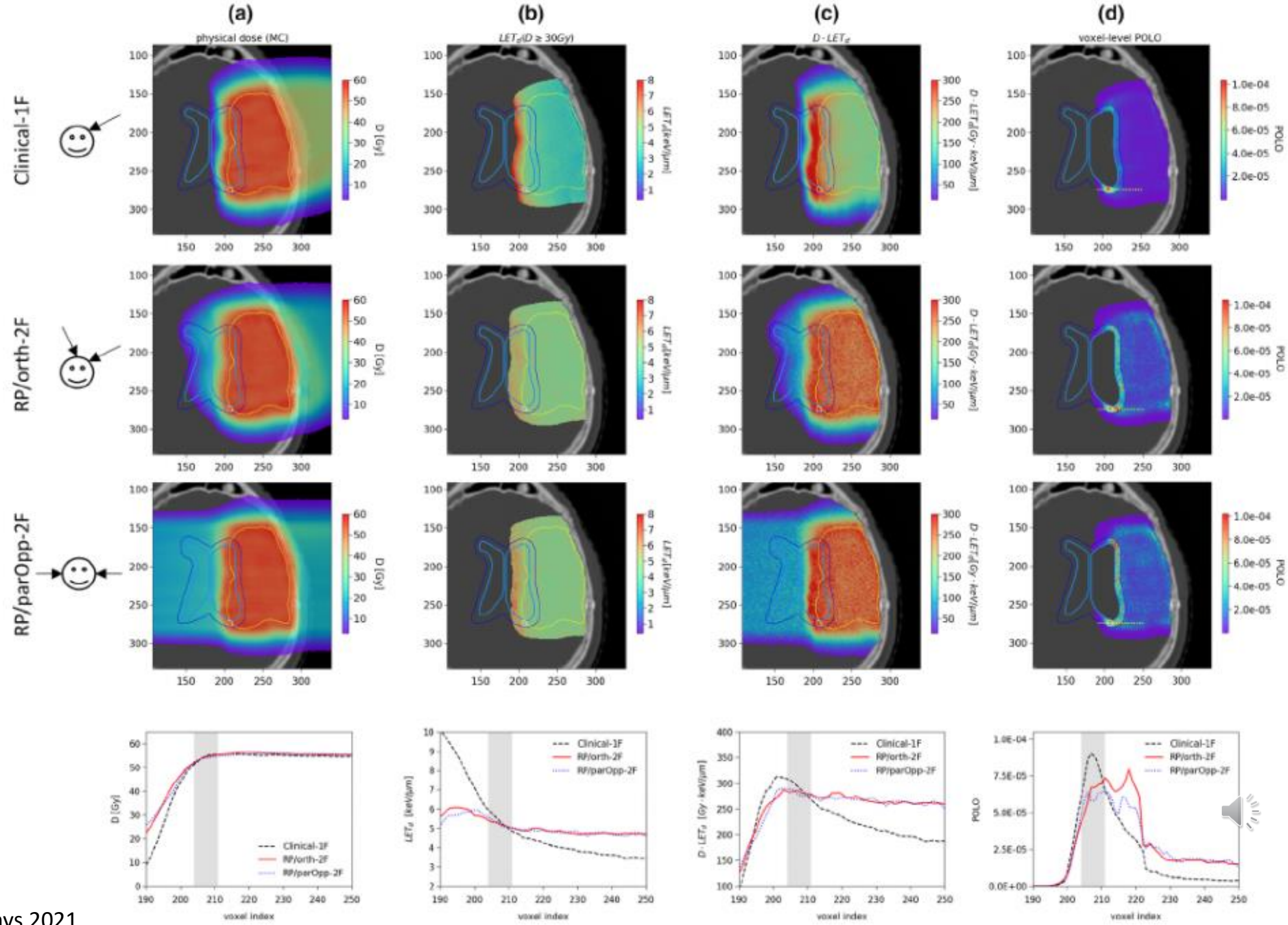

Bauer et al., Med Phys 2021

Clinical need for (biologically) optimized treatment planning: INDIGO trial

Key hypothesis:

model-guided risk avoidance reduces the risk for contrast enhancing brain lesions

multicentric, prospective interventional, randomized, observer blind two arm (active control), investigator initiated phase II trial

120 patients to be enrolled (60 per group)

HITRI
Heavy Ion Therapy Research Integration

Gefördert durch
DFG Deutsche Forschungsgemeinschaft

THANK YOU!

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