



CIRT at MedAustron: the first 200 patients

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EBG MedAustron GmbH



No Conflict of Interest to disclose

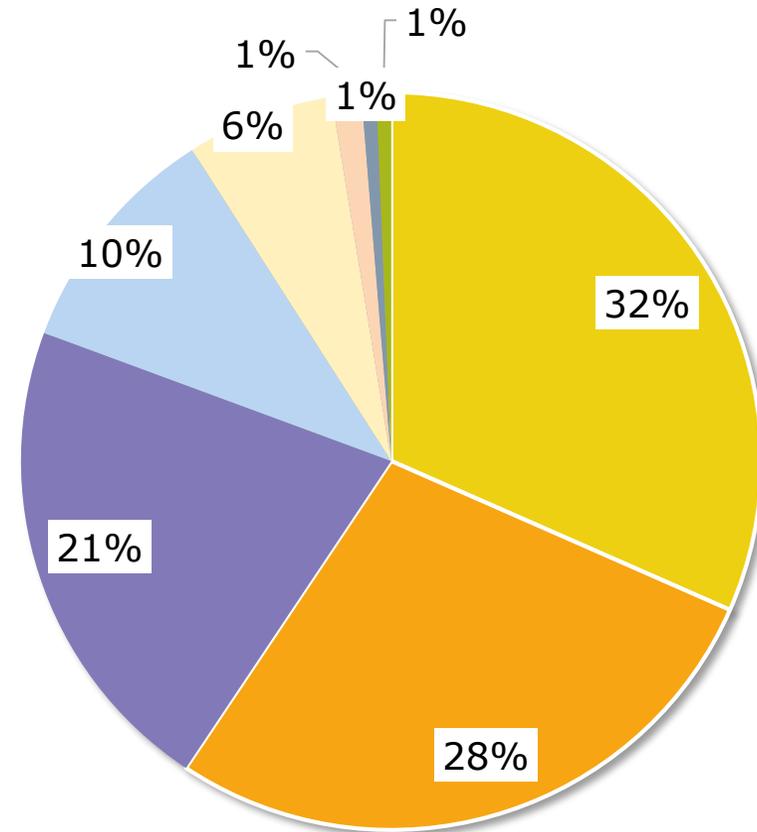


CIRT at MedAustron: some of the first
200 patients (and some of the ongoing
research projects)

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Carbon ions patient Jul 2019 – Oct 2021

n= 200



→
Rebestrahlungen

Indications

■ HNO

■ Re-irradiatio

davon

6,5% HNO

5,8% GU

4,5% others

3,9% GI

3,2% Chordoma /Chondrosarcoma / Skull base

1,3% Meningeom

1,3% salivary gland

1,3% Paraspinal TU

■ Sarkome

■ Prostata

■ Chordome & Chondrosarkome Schädelbasis

■ Varia

■ Pädiatrische Tumore

■ Gastrointestinal (oberer)

MedAustron approach

Skull base

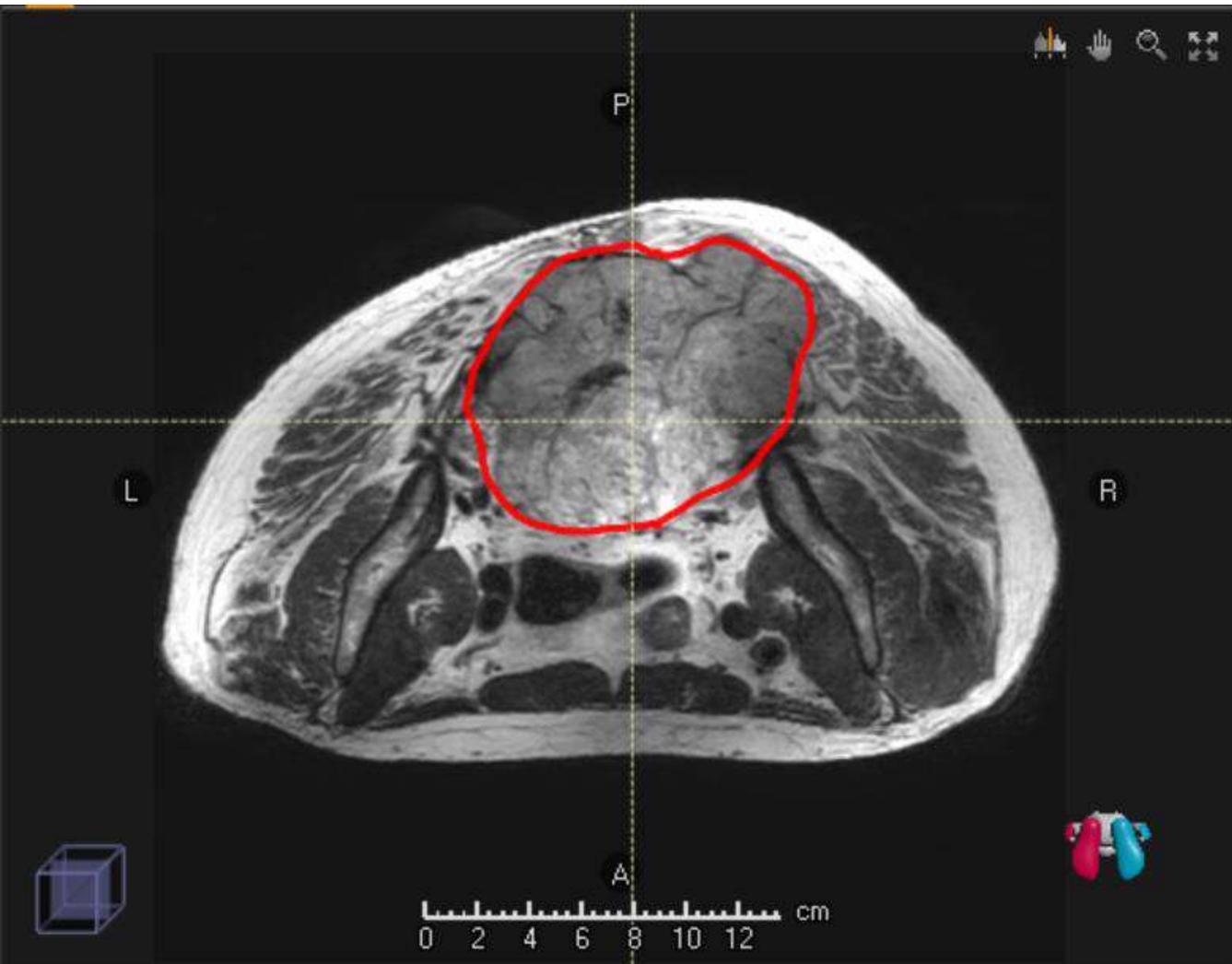
- German approach
- $d = 3$ Gy RBE
- $D = 60-66$ Gy RBE
- 20-22 fractions
- 5 fractions per week

Body

- Japanese approach
- 16 fractions
- 4 fractions per week
- $d = 4.6$ Gy RBE
(Chordoma/chondrosarcoma) or
 4.8 Gy RBE (Osteosarcoma and
other histologies)
- $D = 73.6 / 76.8$ Gy RBE

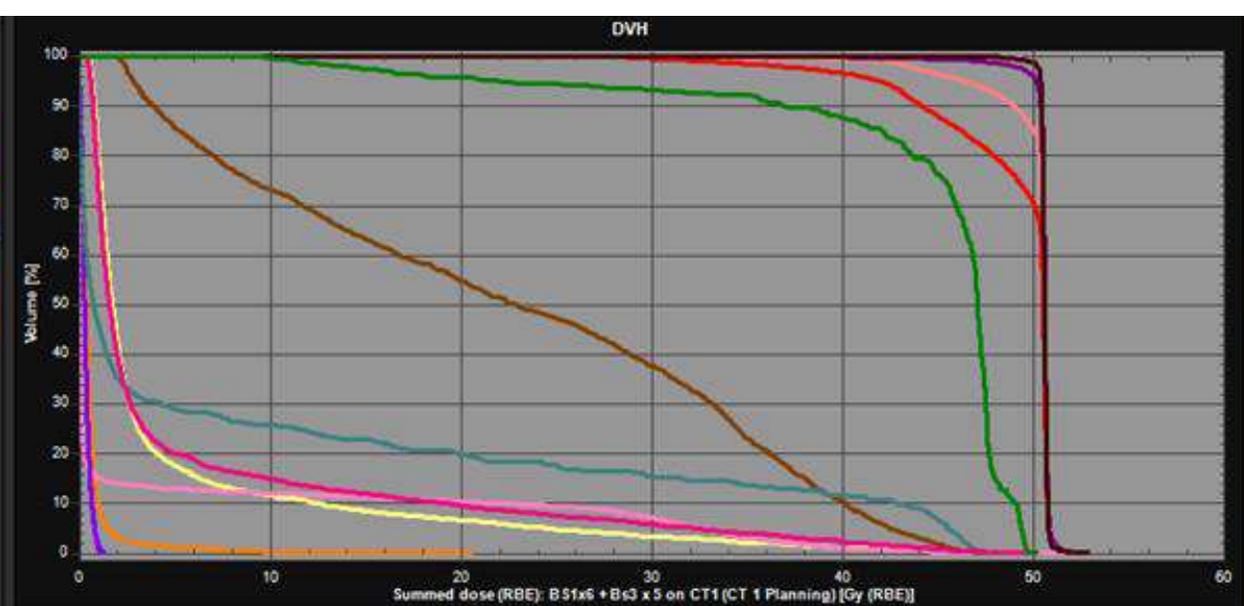
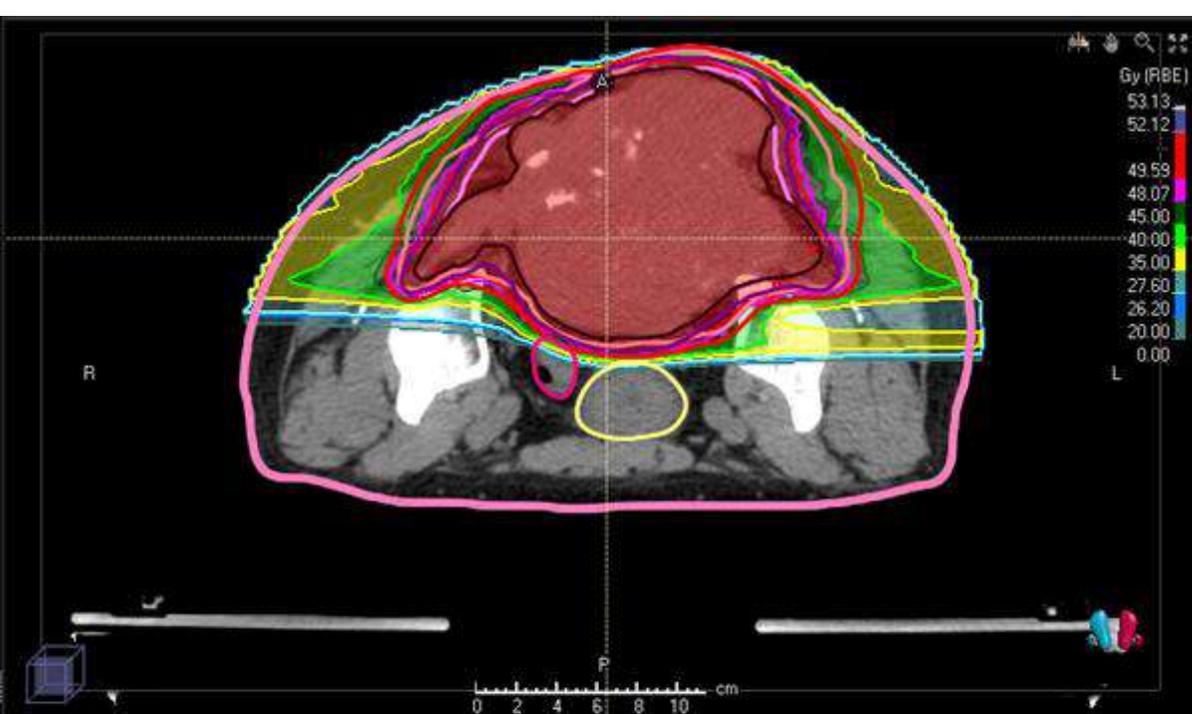
Sacral chordoma

- Male 41 YO
- November 2019 sacral pain, urinary incontinence (preexisting major neurological deficit due to spinal trauma)
- April 2020 an MRI demonstrated a large sacral lesion of 13.5 x 12 x 9.5 cm involving S2
- Surgery would be at high risk of double incontinence and is refused by patient.
- CIRT is delivered as curative local therapy (200 ml of macroscopic tumor)



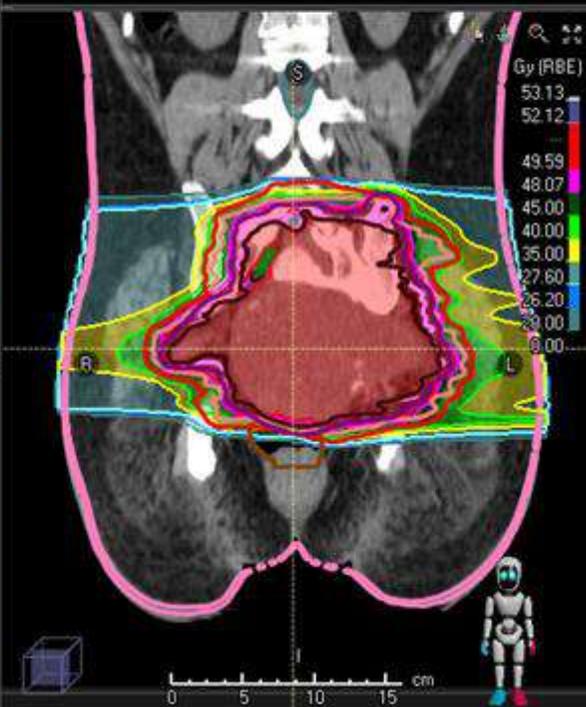
prescription

- 73.6 Gy RBE in 16 fractions of 4.6 Gy RBE over 4 weeks (4fr per week)
- PTV1 9 fr to 41.4 Gy RBE
- Sequential Boost to PTV2 with additional 7 fr.
- GTV = macroscopic disease
- CTV1 = GTV + piriform muscles bilaterally + margin > 1cm in gluteal muscle + sacral bone up to the sacro iliac joints
- CTV2 = GTV + 1 cm adapted to anatomy
- 2 set up: prone and lateral decubitus2 set up: prone and lateral decubitus

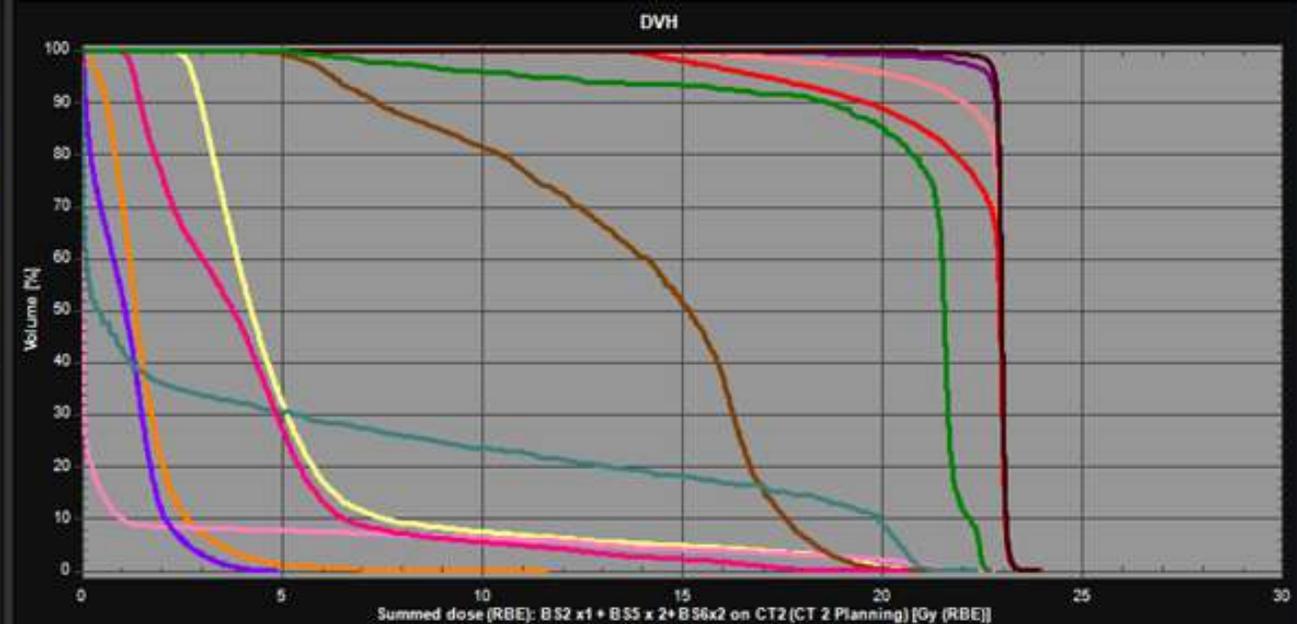
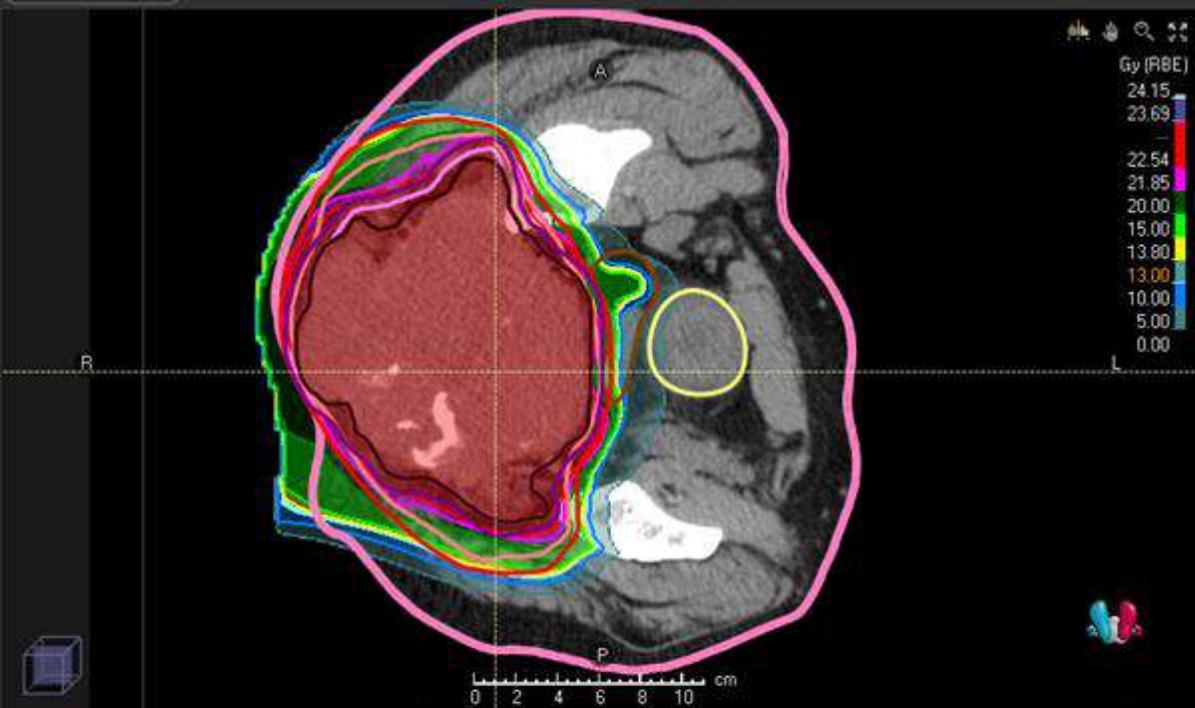


Dose axis: Absolute Relative max Relative dose [Gy (RBE)]:

Volume axis: Relative Absolute



ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]						
		D99	D98	D95	Average	D50	D2	D1
bladder	177.43	0.54	0.59	0.70	4.60	1.74	35.29	40.80
bowelloops	229.01	0.00	0.00	0.00	0.56	0.37	2.83	5.68
cauda	24.30	0.00	0.00	0.00	9.24	0.76	46.48	46.85
colon	129.65	0.00	0.00	0.00	0.34	0.29	0.97	1.05
CTV1	2411.74	42.06	43.47	46.35	50.04	50.58	51.02	51.24
CTV2	1640.32	49.72	50.22	50.39	50.59	50.61	50.92	51.10
GTV1	1554.49	49.69	50.22	50.40	50.59	50.61	50.91	51.08
nerveroots	5.57	11.38	13.91	21.72	44.30	47.08	49.55	49.60
PTV1	3019.04	32.32	36.51	41.91	48.95	50.53	50.99	51.20
PTV2	2121.22	47.08	48.95	50.16	50.49	50.60	51.08	51.31
rectum	63.78	2.25	2.38	2.85	22.42	22.83	44.83	45.64
sigma	111.54	0.48	0.53	0.62	5.56	1.60	40.74	44.12
skin	1140.02	0.00	0.00	0.00	3.77	0.02	37.04	39.78



ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]						
		D99	D98	D95	Average	D50	D2	D1
bladder	214.69	2.55	2.63	2.79	5.26	4.25	19.41	19.81
bowelloops	489.74	0.08	0.19	0.44	1.54	1.35	4.41	5.15
cauda	25.31	0.01	0.01	0.01	5.05	0.37	20.73	20.88
colon	281.35	0.04	0.05	0.07	1.11	1.09	3.29	3.64
CTV1	2406.64	16.09	17.79	20.39	22.64	22.99	23.22	23.27
CTV2	1653.88	22.29	22.68	22.84	22.98	23.00	23.22	23.27
GTV1	1565.74	22.25	22.67	22.84	22.98	23.00	23.22	23.28
nerveroots	5.36	6.09	7.01	11.11	20.51	21.56	22.49	22.54
PTV1	3032.47	14.32	14.96	17.01	22.11	22.96	23.20	23.26
PTV2	2146.70	20.32	21.79	22.69	22.92	23.00	23.23	23.29
rectum	63.65	5.16	5.61	6.28	13.82	15.18	19.03	19.46
sigma	130.23	1.13	1.20	1.32	4.20	3.79	15.37	16.76
skin	1134.73	0.00	0.00	0.00	1.29	0.01	20.16	20.96

- During the treatment the patient experienced a marked improvement in symptoms with pain decreasing in intensity.
- No GI or GU symptoms. No sexual deficit. No skin toxicity. No other toxicity

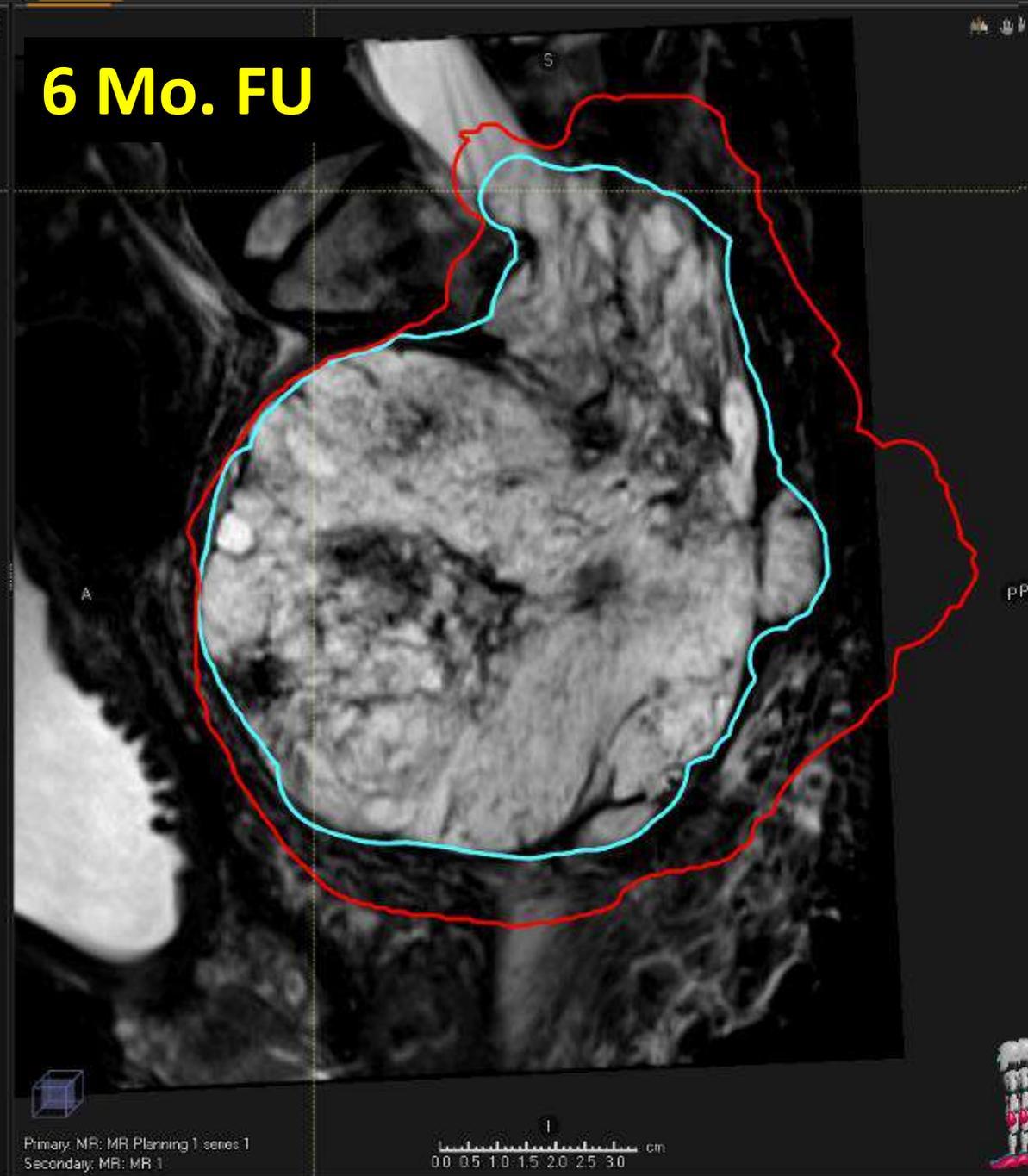
After 6 months:

- complete resolution of urinary incontinence (he no longer needs a diaper)
- major improvement in pain. He has discontinued all pain medications.
- dimensional response with 33% shrinkage (from 1178 cc to 790 cc)

PRE CIRT



6 Mo. FU

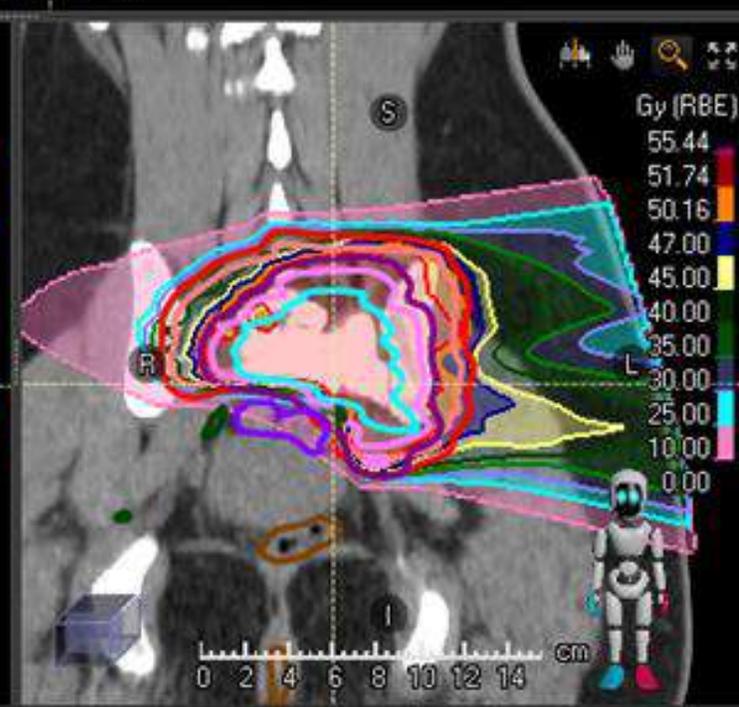
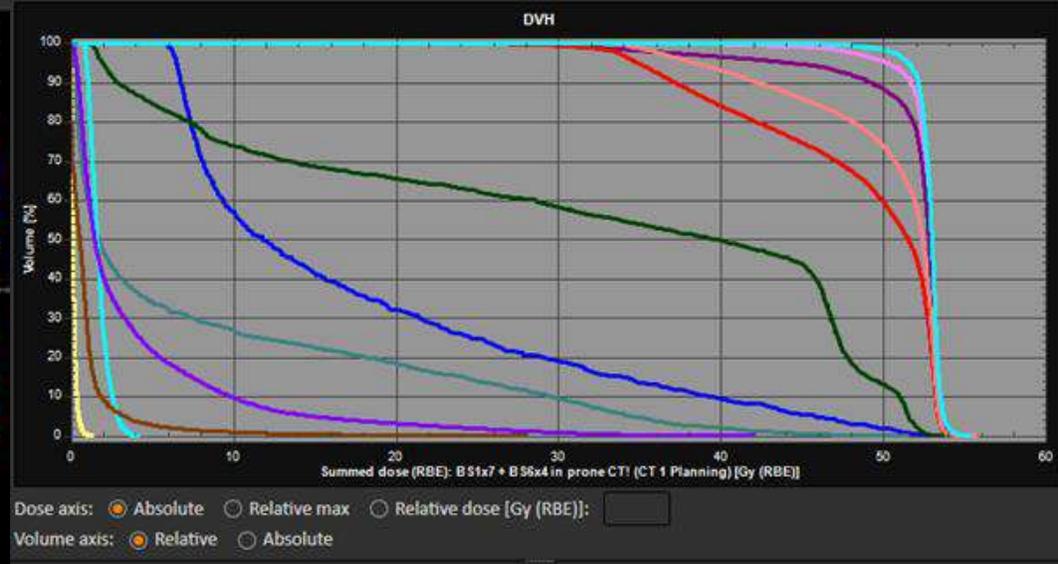
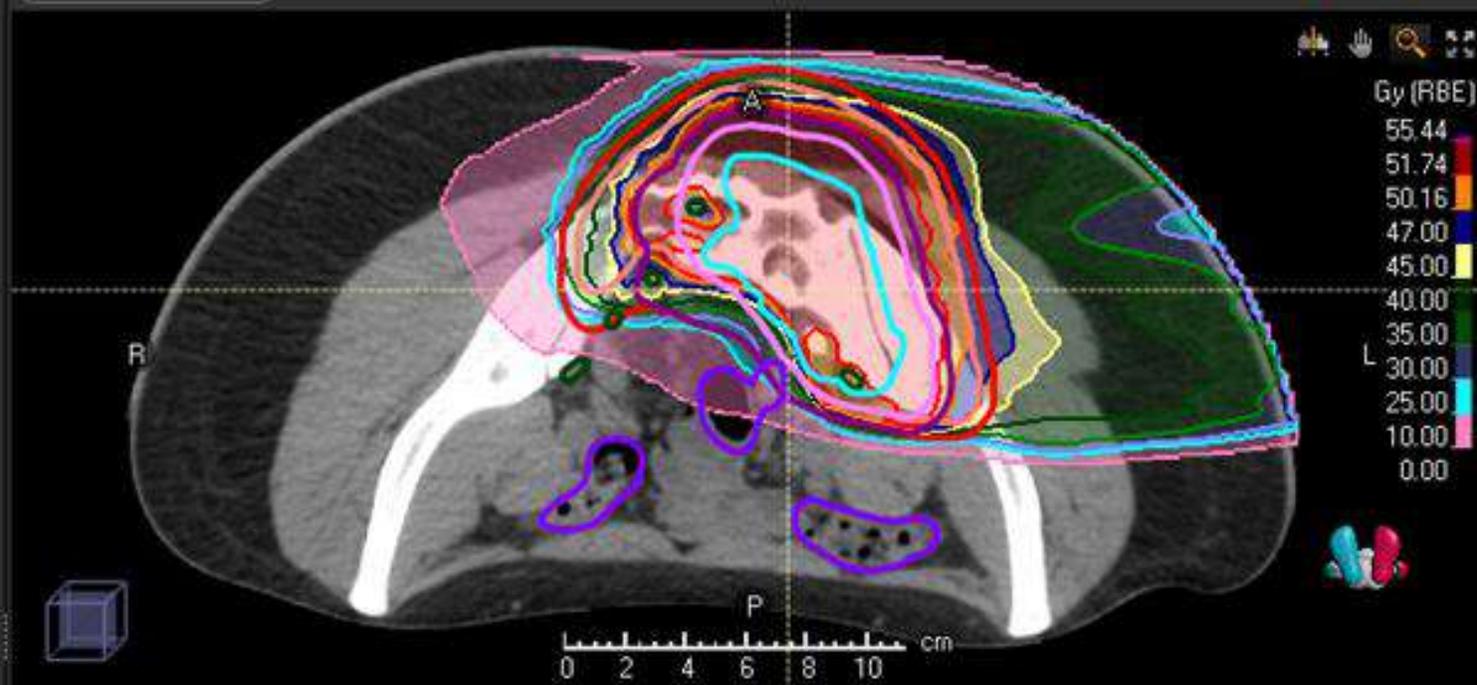


PELVIC OSTEOSARCOMA

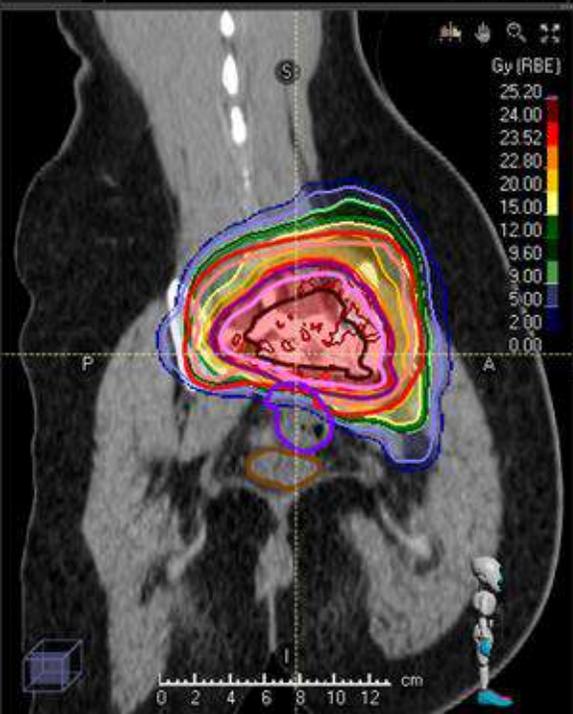
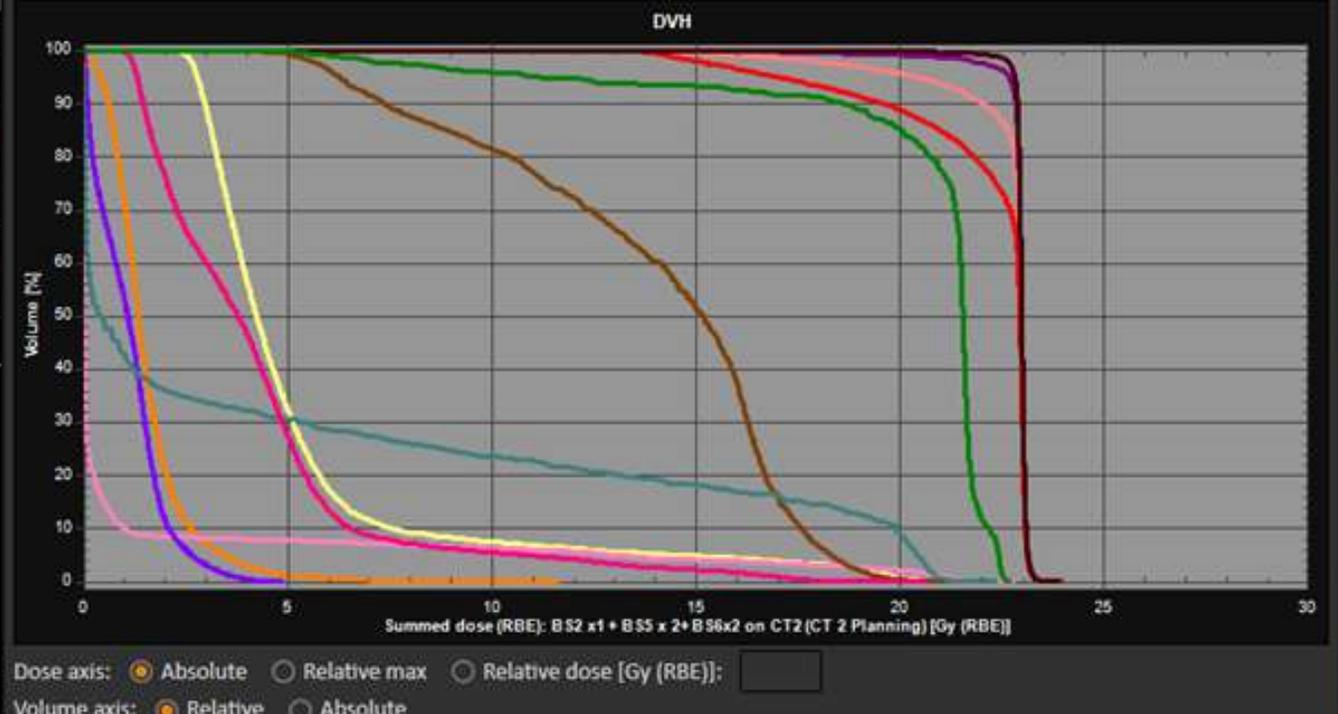
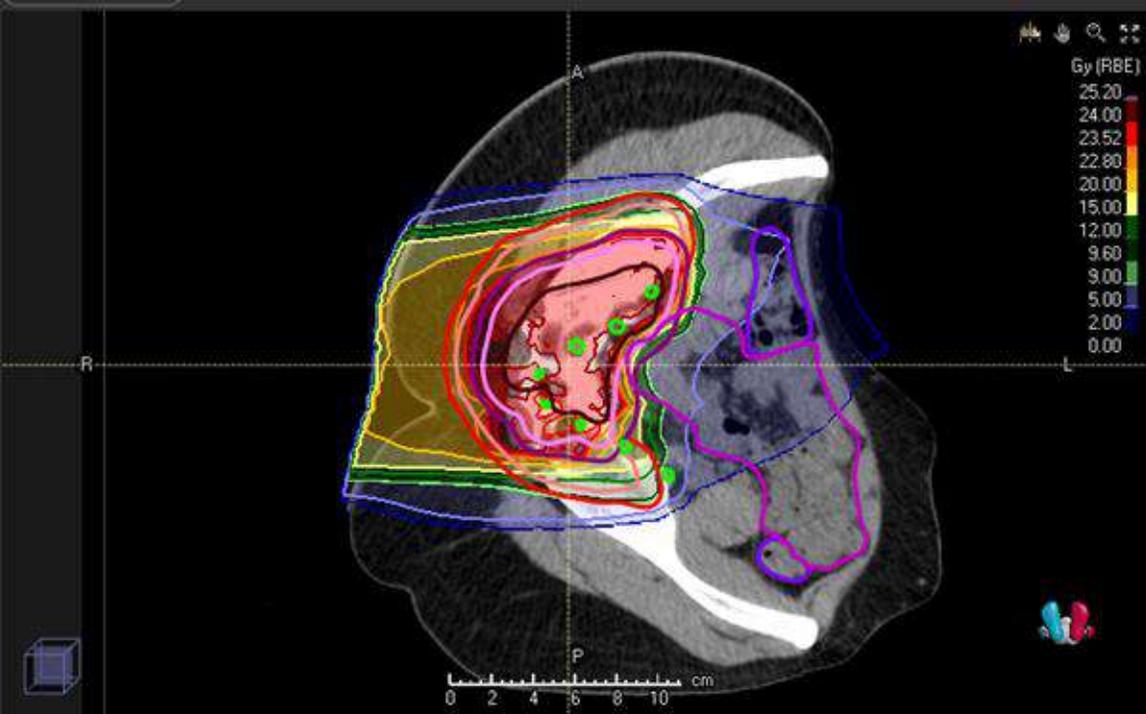
- Female 25 YO
- Jan 2020 pain in the right gluteus: diagnosis of high grade pelvic osteosarcoma at sacroiliac junction
- Jan-Jun 2020 5 cycles chemo according to EURAMOS protocol with SD
- Surgery would result in permanent colo- and uro-stoma.
- CIRT is delivered as curative local therapy (200 ml of macroscopic tumor)

prescription

- 76.8 Gy RBE in 16 fractions of 4.8 Gy RBE over 4 weeks (4fr per week)
- PTV1 9 fr to 43.2 Gy RBE
- Sequential Boost to PTV2 with additional 7 fr.
- GTV = visible tumor in CT and MRI
- CTV1 = GTV + areas at risk (sacrum, biopsy tract, retro sacral soft tissue, posterior part of right iliac wing, cranial part of right piriform muscle)
- CTV2 = GTV + areas at high risk of tumor infiltration (GTV + 1 cm margin adapted to anatomy)
- 2 set up: prone and lateral decubitus



ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]						
		D99	D98	D95	Average	D50	D2	D1
bladder	40.66	0.02	0.02	0.03	0.19	0.15	0.66	0.79
cauda	12.23	0.16	0.17	0.22	8.21	1.69	39.80	42.76
colon	310.65	0.21	0.25	0.34	3.75	1.48	24.04	28.60
CTV1	821.72	34.51	35.70	38.33	50.19	52.42	53.62	53.80
CTV2	386.76	45.31	47.45	50.19	52.53	52.91	53.79	54.08
GTV1adapt30062020	199.07	48.85	50.25	51.53	52.82	52.99	54.00	54.31
left Ovary	15.15	0.88	0.91	0.98	1.74	1.64	3.22	3.45
nervrootstospare	12.48	1.44	1.57	1.97	30.90	39.64	52.09	52.40
PTV1	1107.06	31.26	33.30	34.84	48.20	51.51	53.57	53.73
PTV2	580.53	31.65	35.21	44.14	51.60	52.81	53.71	53.96
rectum	51.99	0.00	0.00	0.00	0.94	0.56	6.08	9.56
right Ovary	4.65	6.07	6.25	6.51	17.68	11.83	49.57	51.02

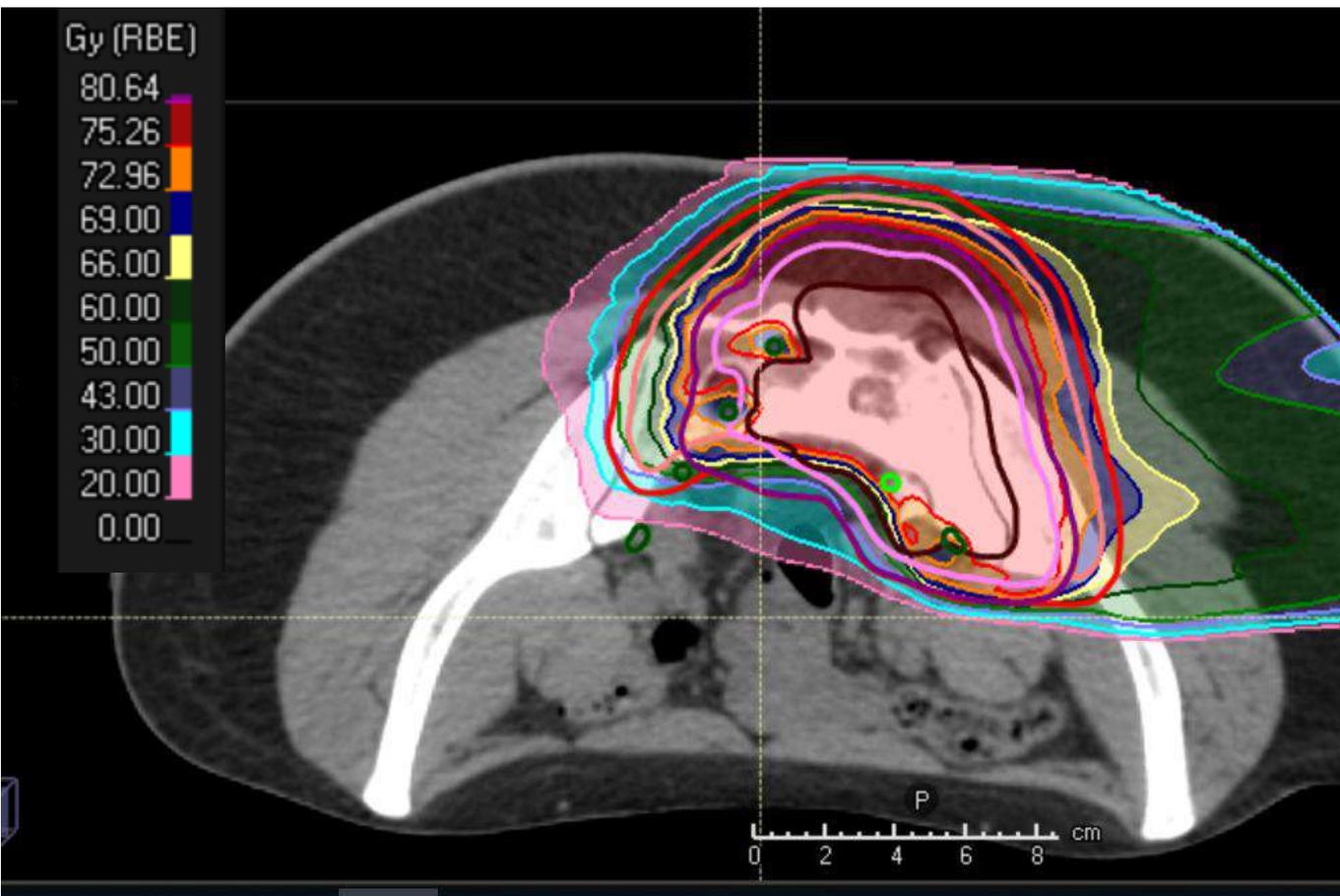


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bowelloops	489.74	0.08	0.19	0.44	1.54	1.35	4.41	5.15
cauda	25.31	0.01	0.01	0.01	5.05	0.37	20.73	20.88
colon	281.35	0.04	0.05	0.07	1.11	1.09	3.29	3.64
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PTV1	3032.47	14.32	14.96	17.01	22.11	22.96	23.20	23.26
PTV2	2146.70	20.32	21.79	22.69	22.92	23.00	23.23	23.29
rectum	63.65	5.16	5.61	6.28	13.82	15.18	19.03	19.46
sigma	130.23	1.13	1.20	1.32	4.20	3.79	15.37	16.76
skin	1134.73	0.00	0.00	0.00	1.29	0.01	20.16	20.96

Selective sparing of non involved nerve roots

Gy (RBE)

80.64
75.26
72.96
69.00
66.00
60.00
50.00
43.00
30.00
20.00
0.00



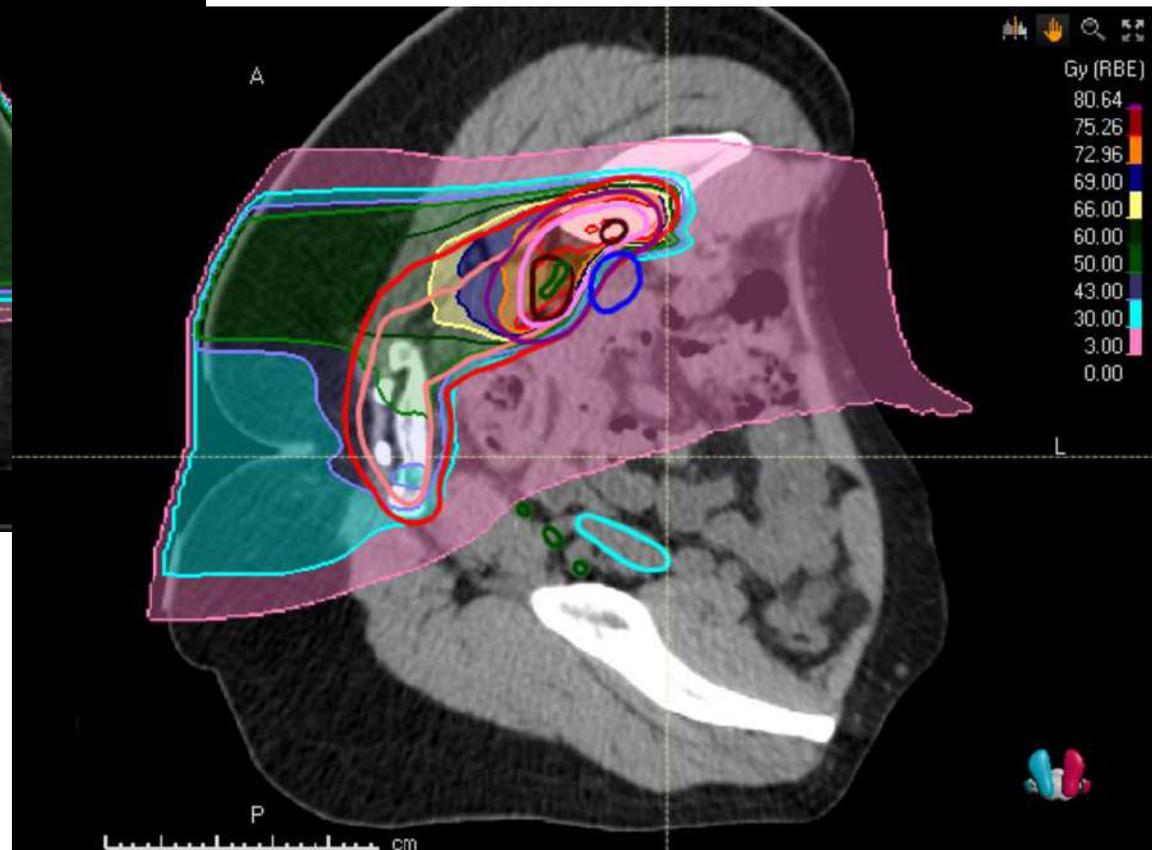
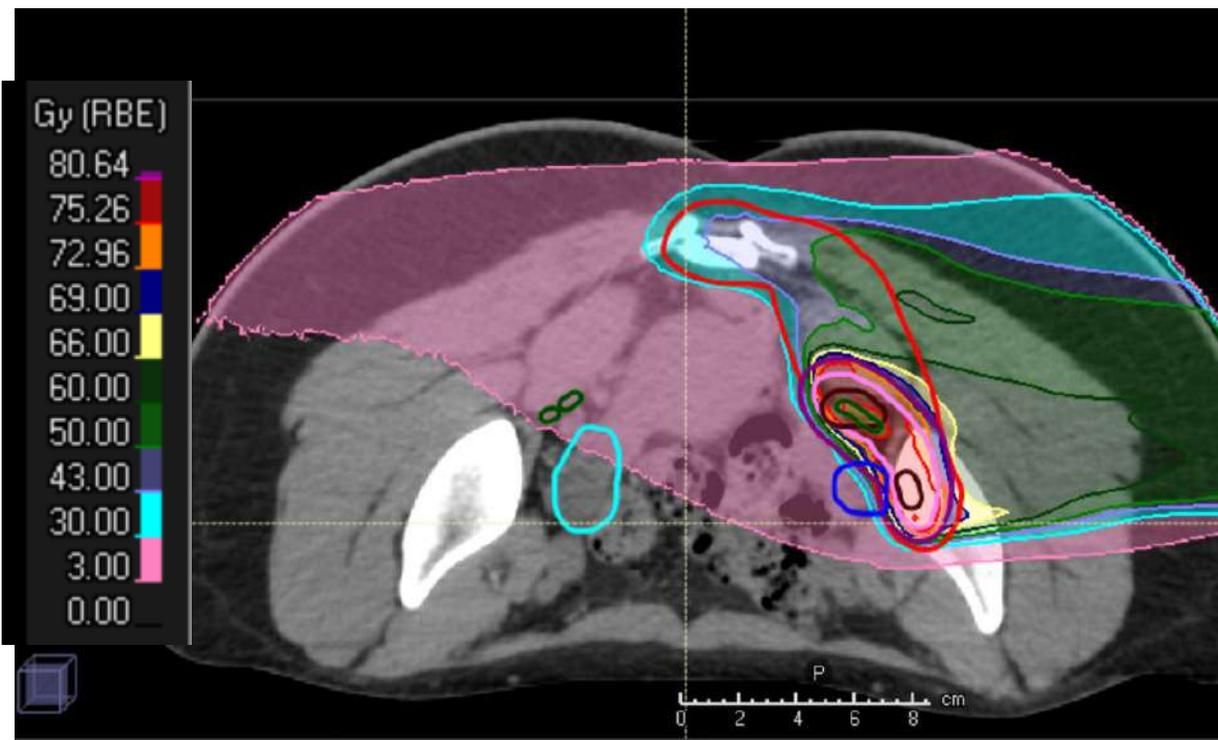
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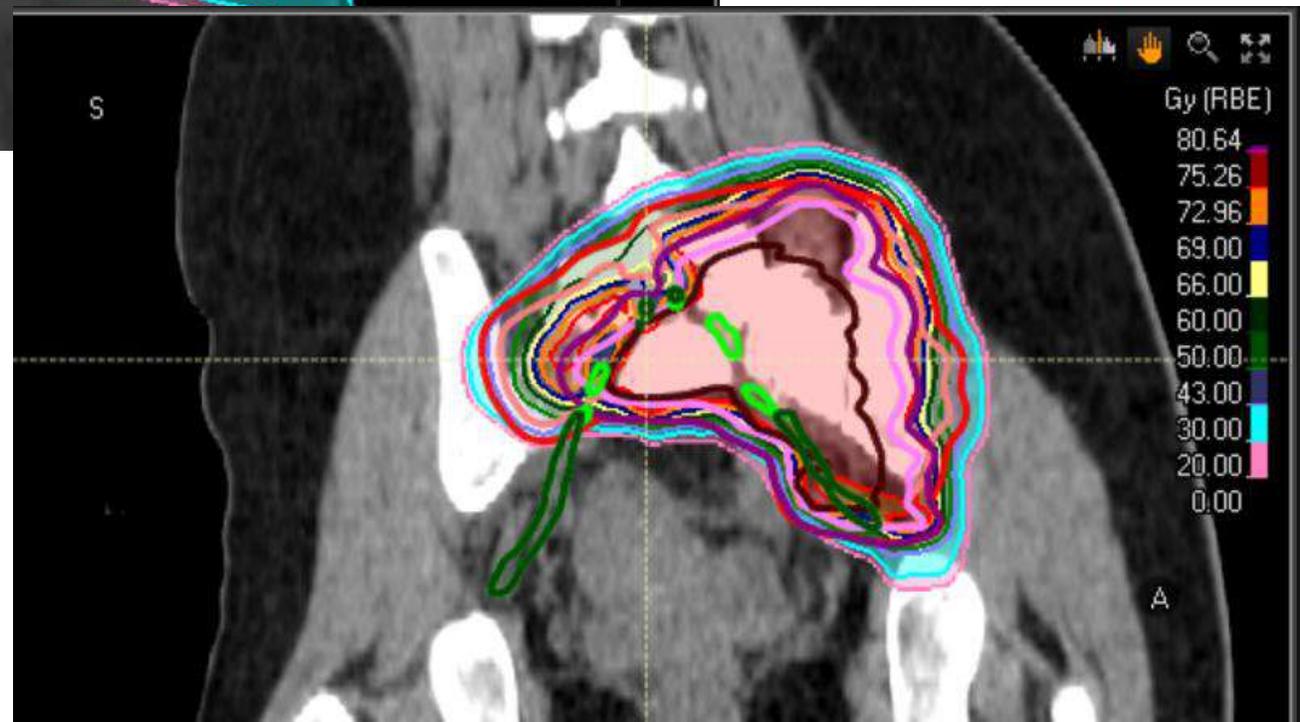
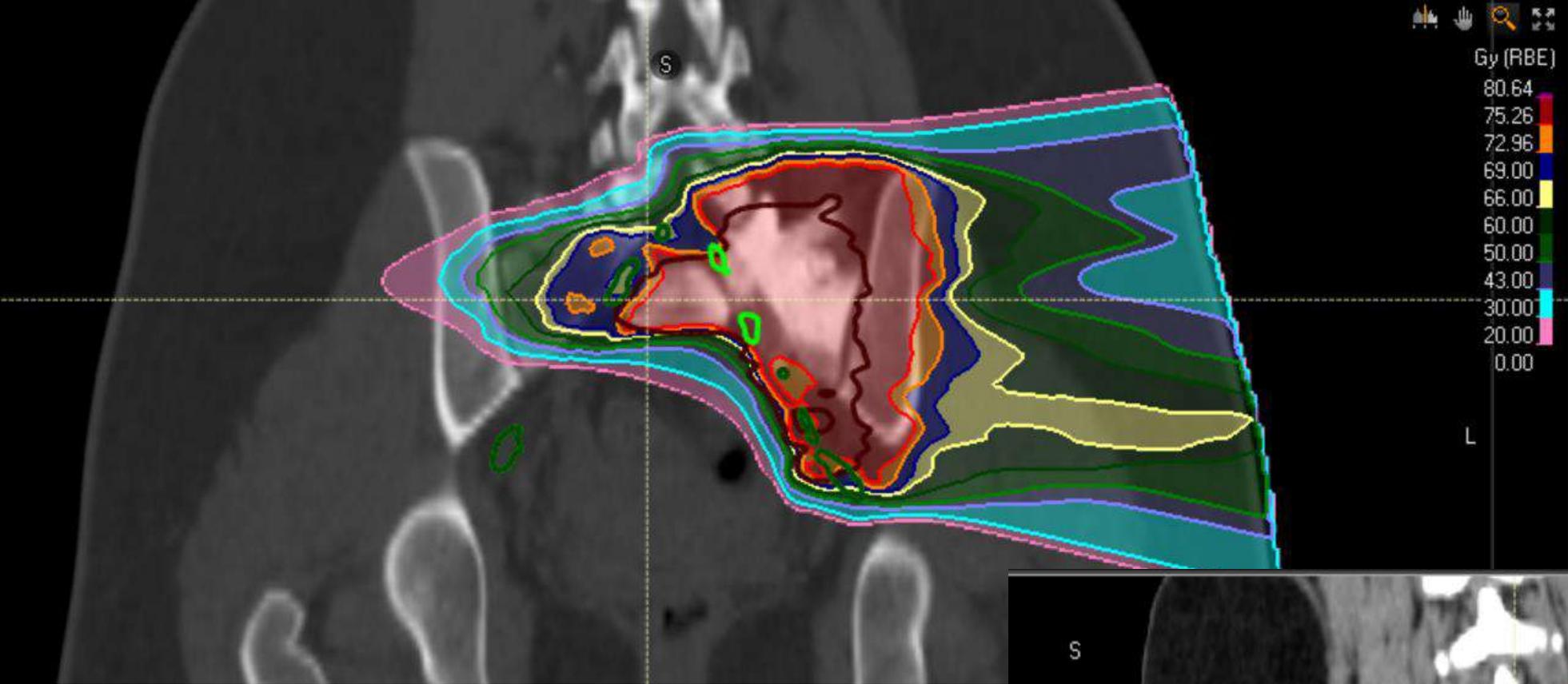
Gy (RBE)

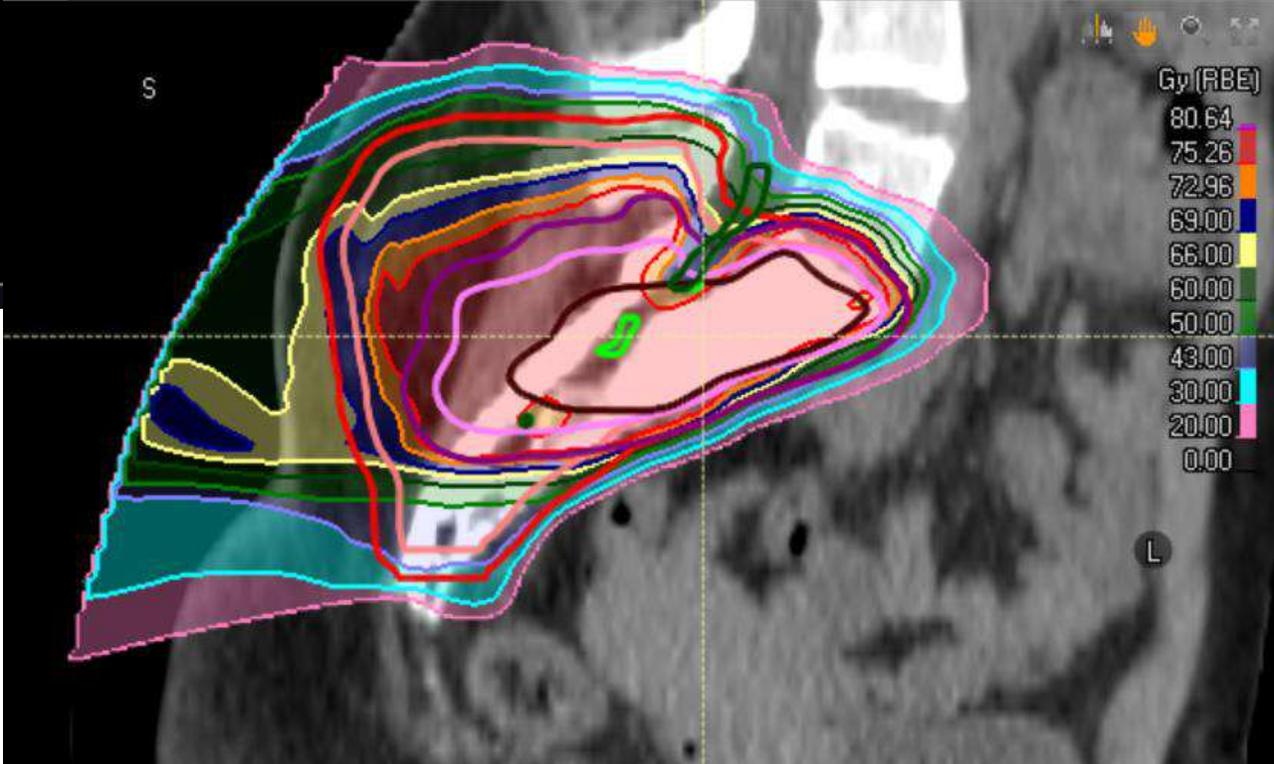
80.64
75.26
72.96
69.00
66.00
60.00
50.00
43.00
30.00
20.00
0.00



Sparing of contralateral ovary







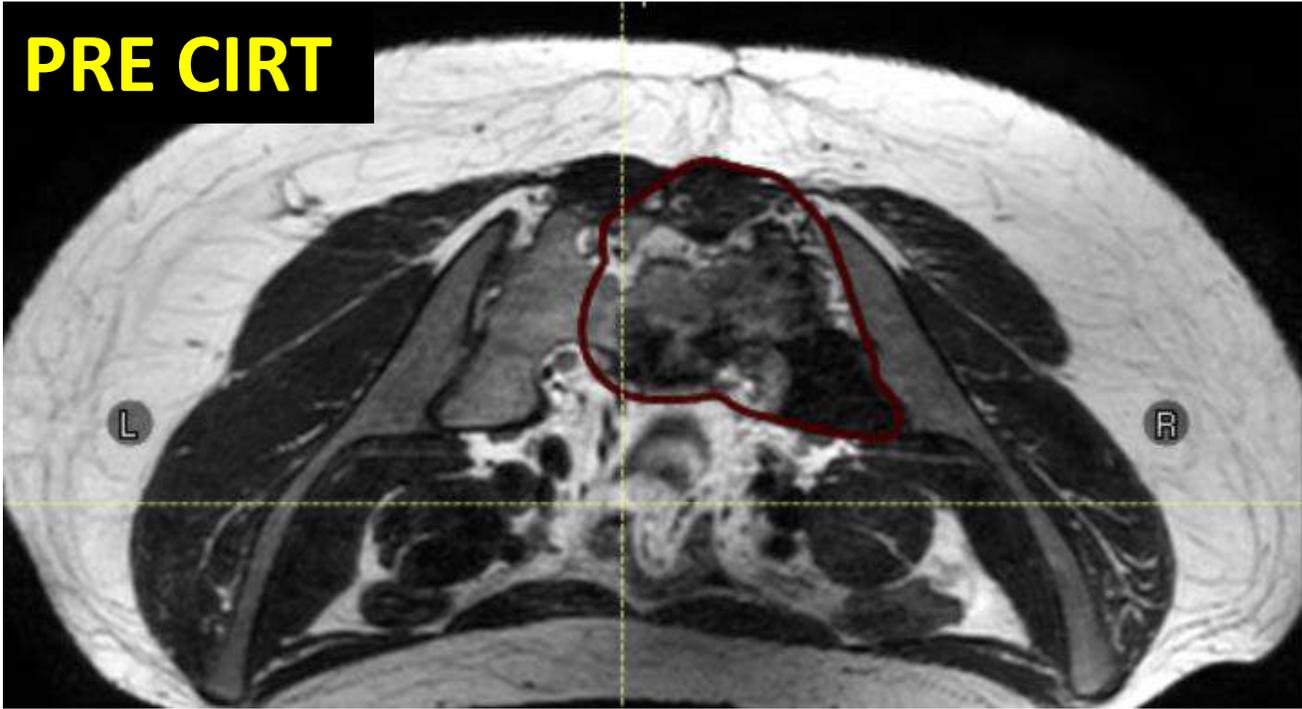
- Toxicity at end of treatment:
- Local pain G0
- Fatigue G1
- GI G0
- GU G0
- Skin G1
- All other toxicities G0

After the end of CIRT additional 3 cycles of chemo

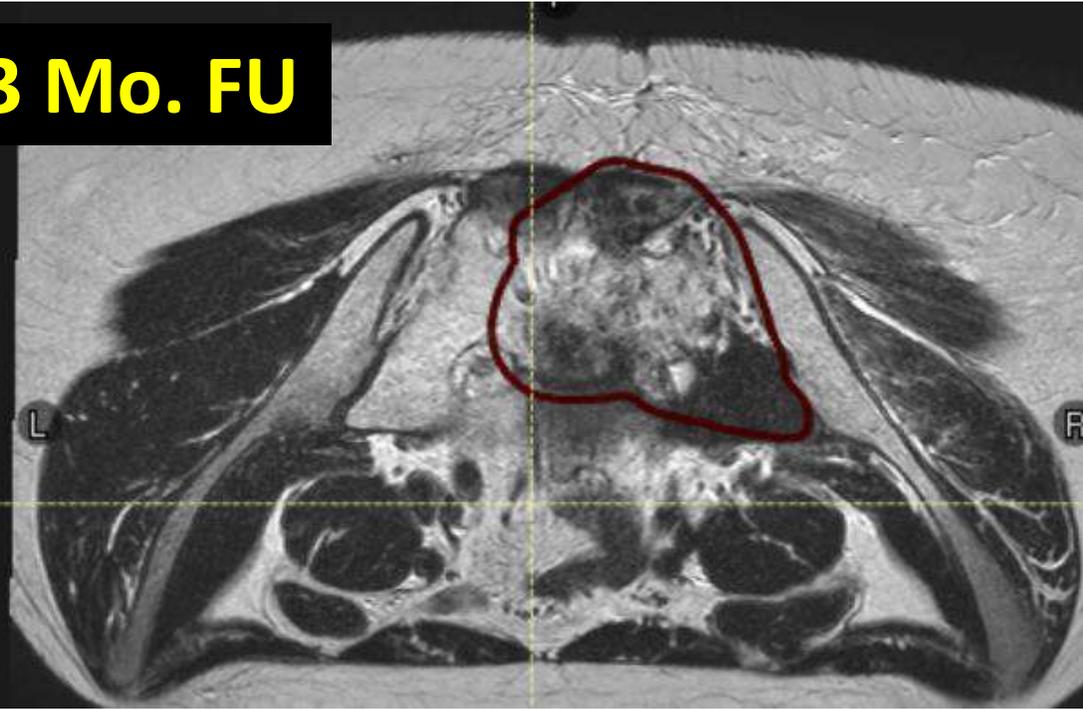
- At 6 months local tox G0

SD at MRI at 3 Months

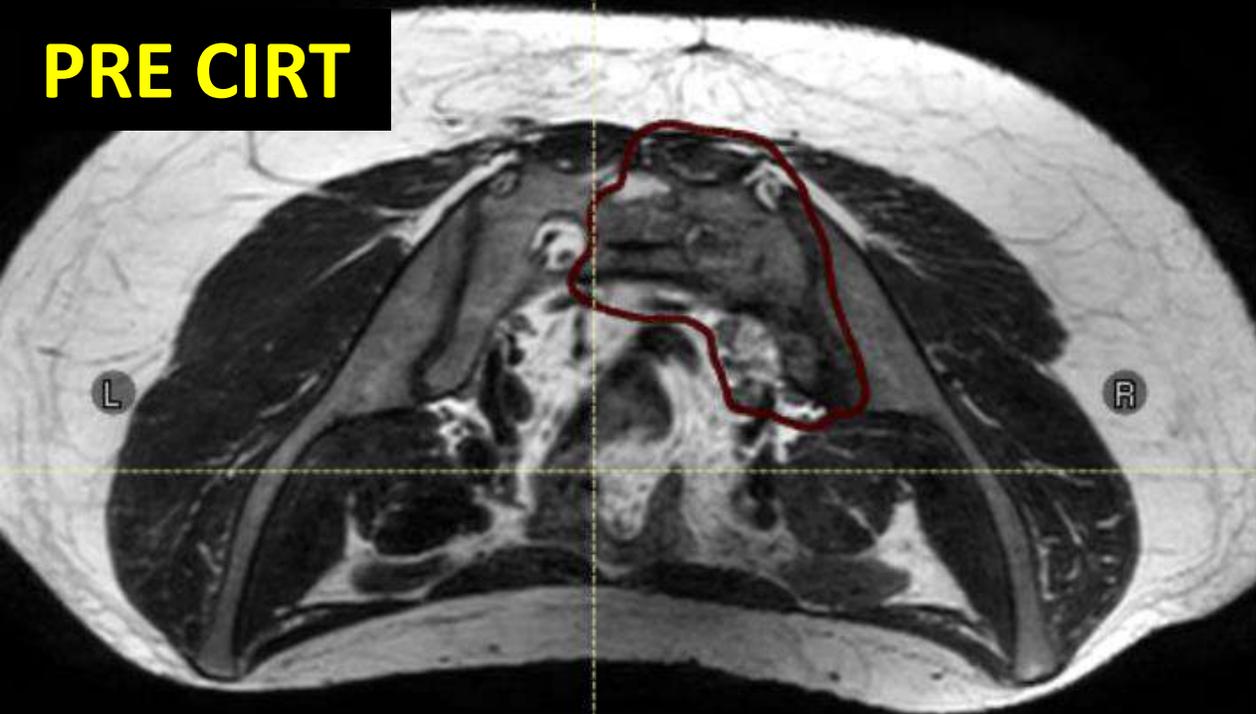
PRE CIRT



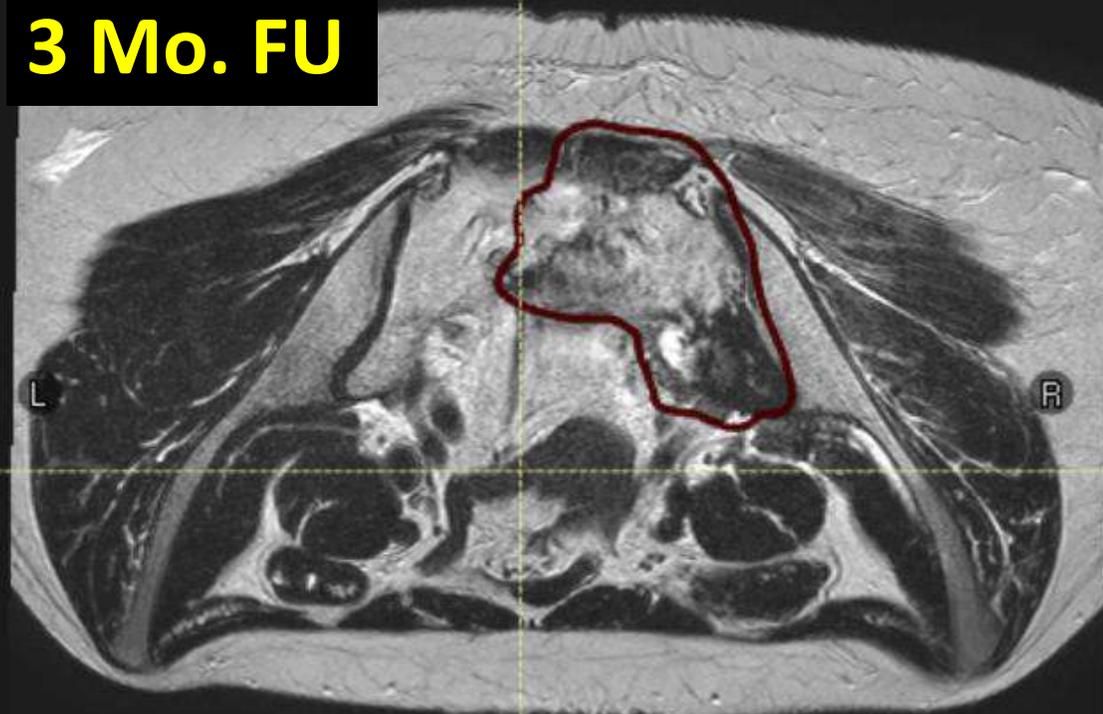
3 Mo. FU



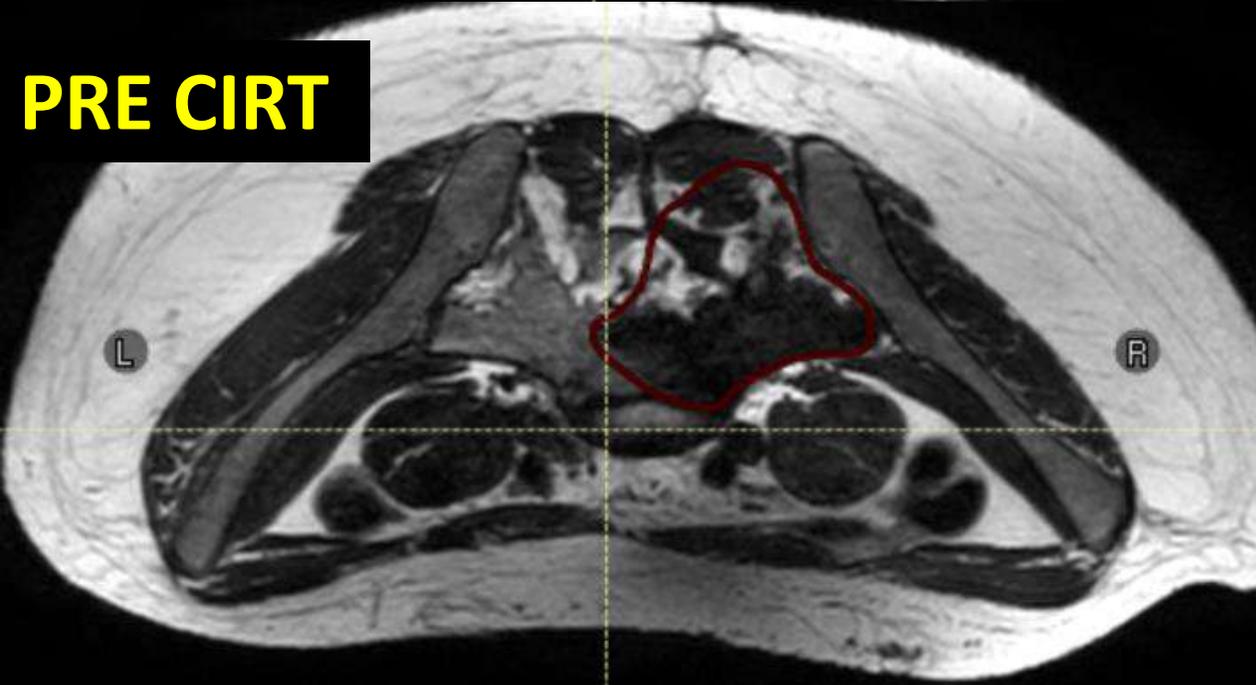
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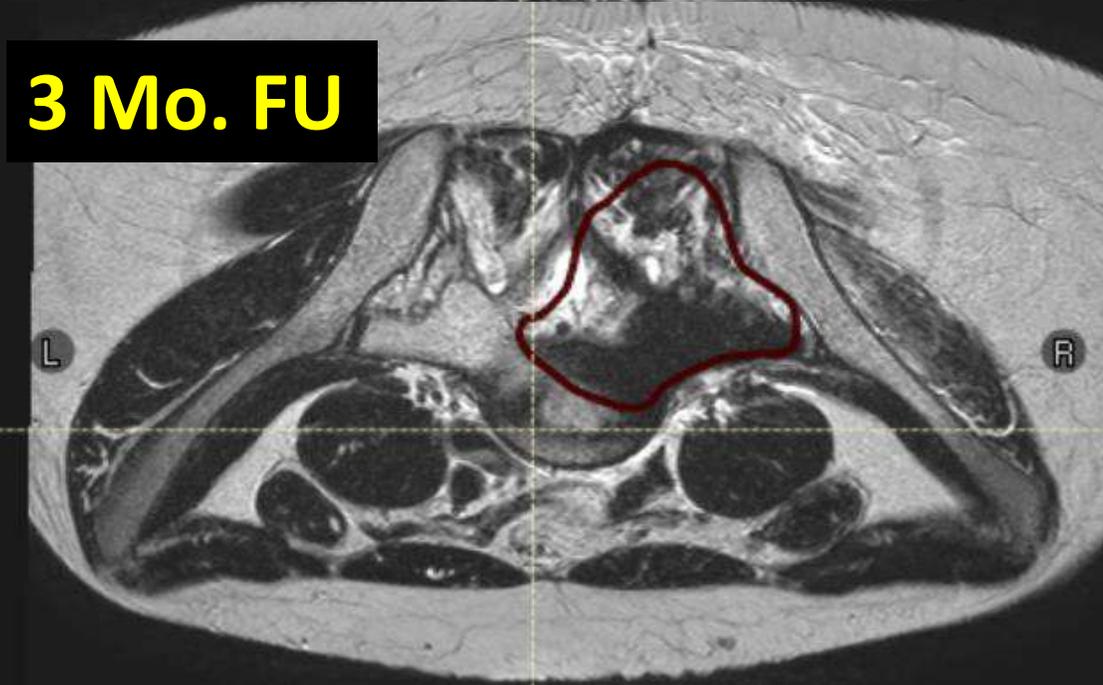
3 Mo. FU



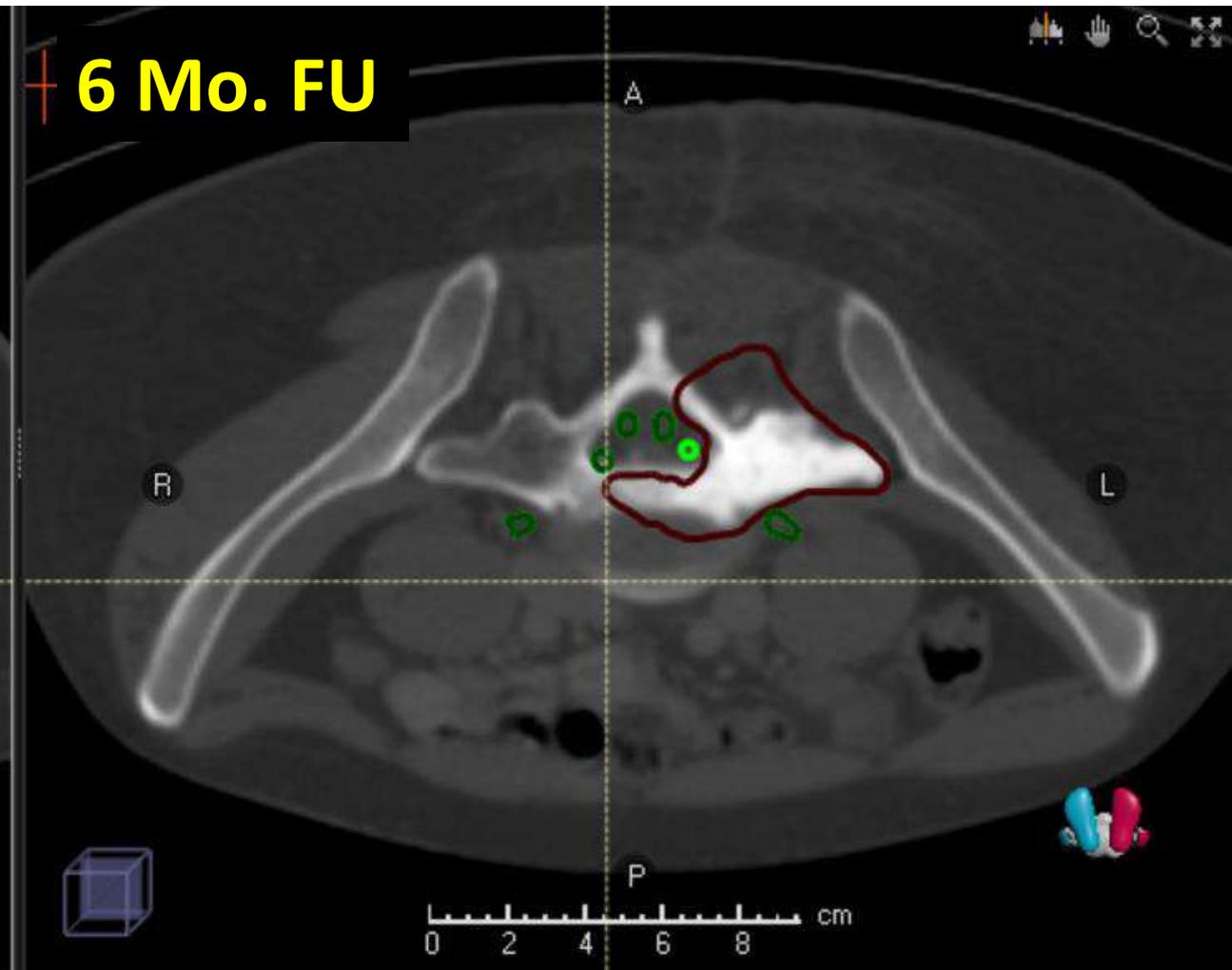
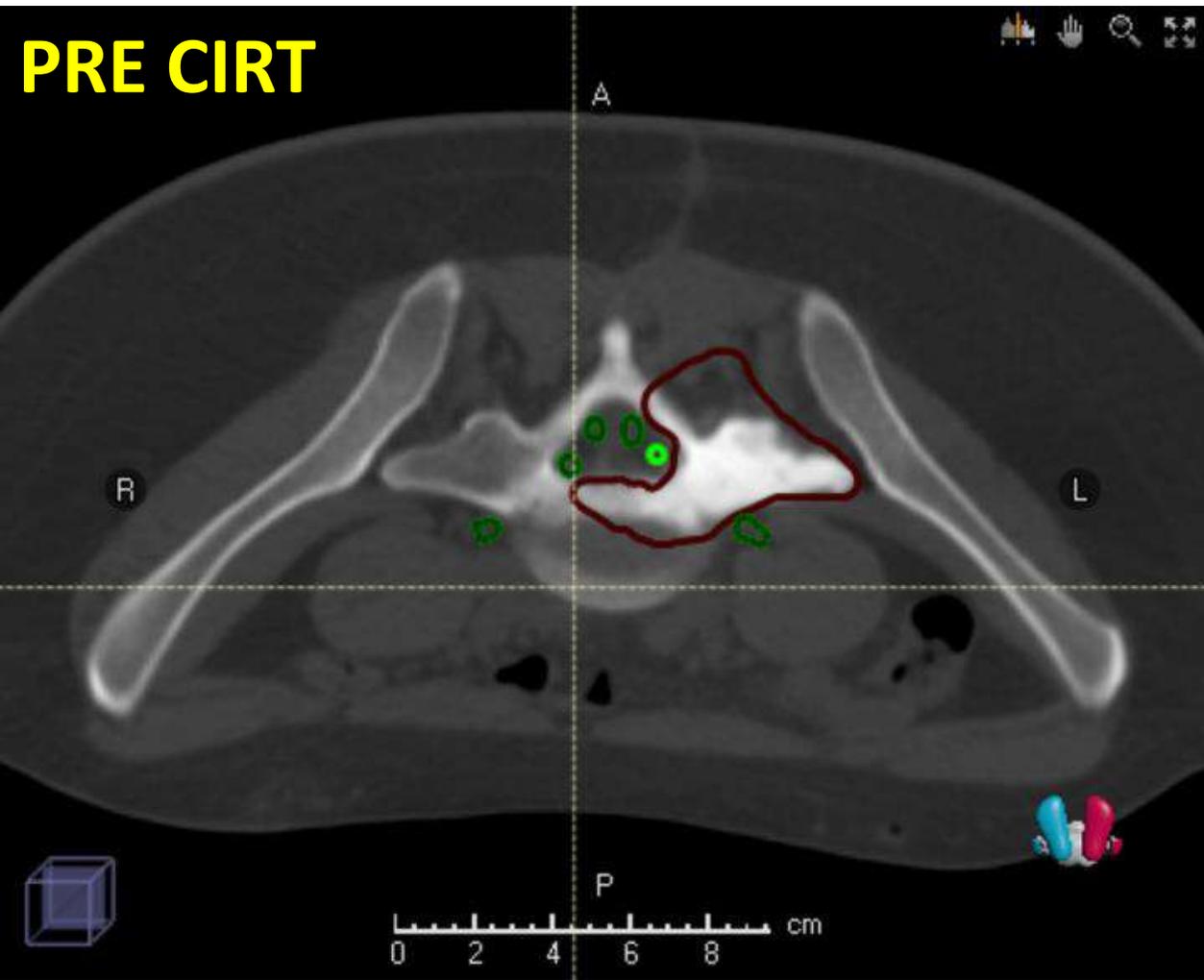
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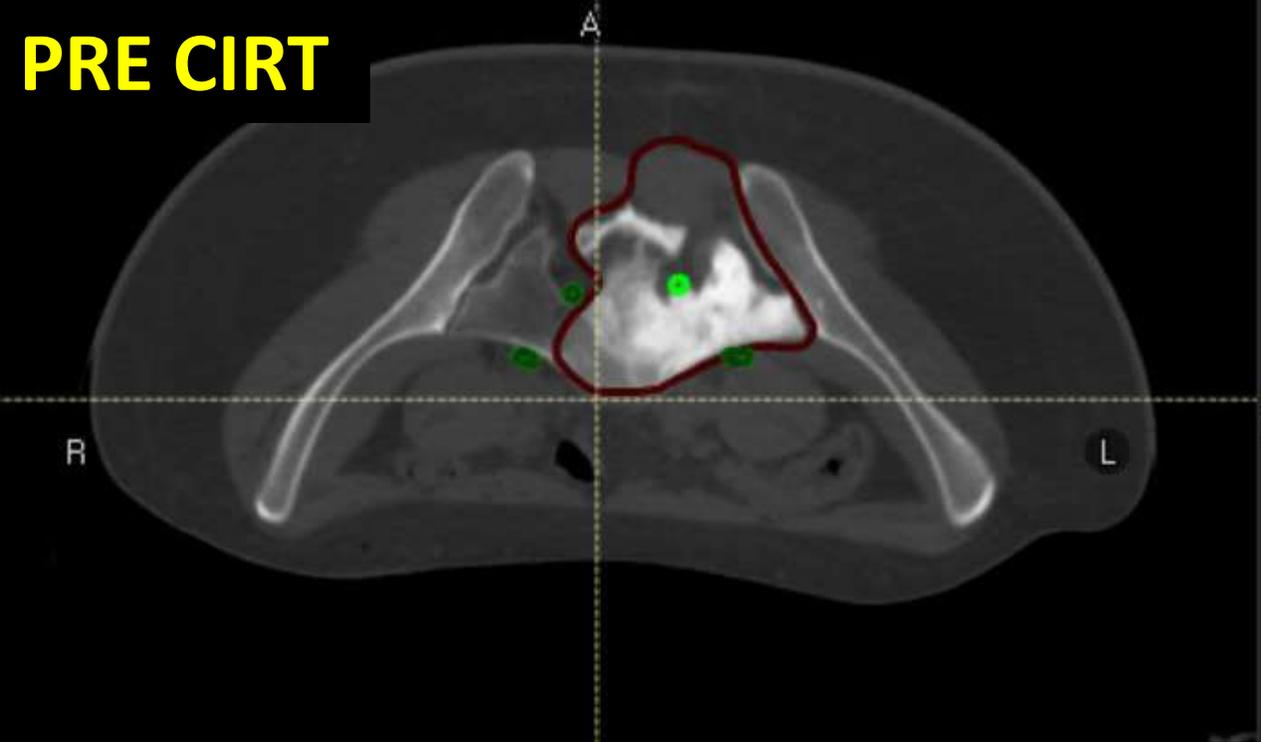
3 Mo. FU



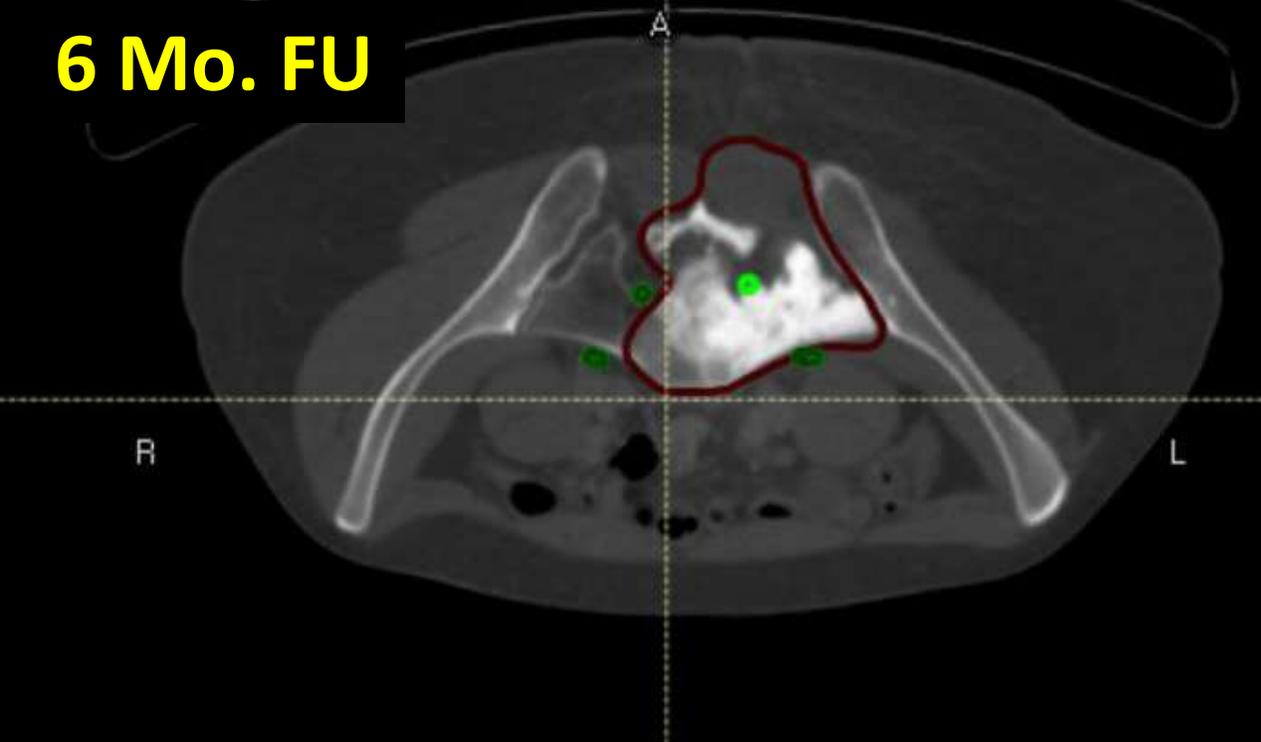
SD at CT at 6 Months



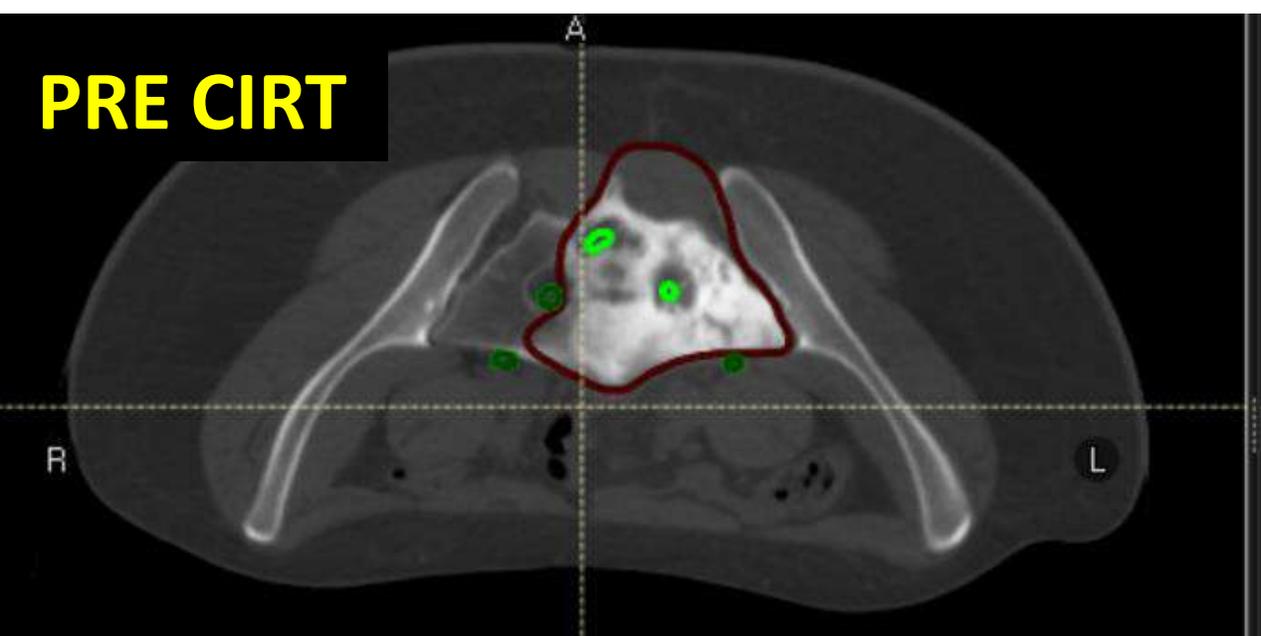
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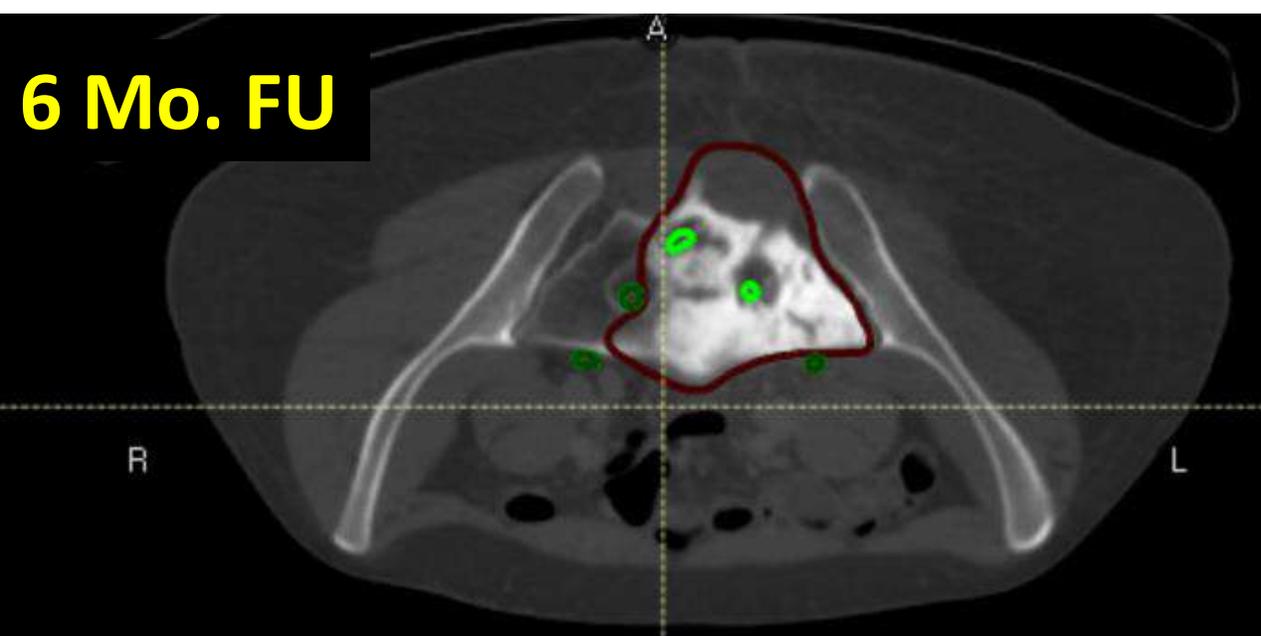
6 Mo. FU



PRE CIRT



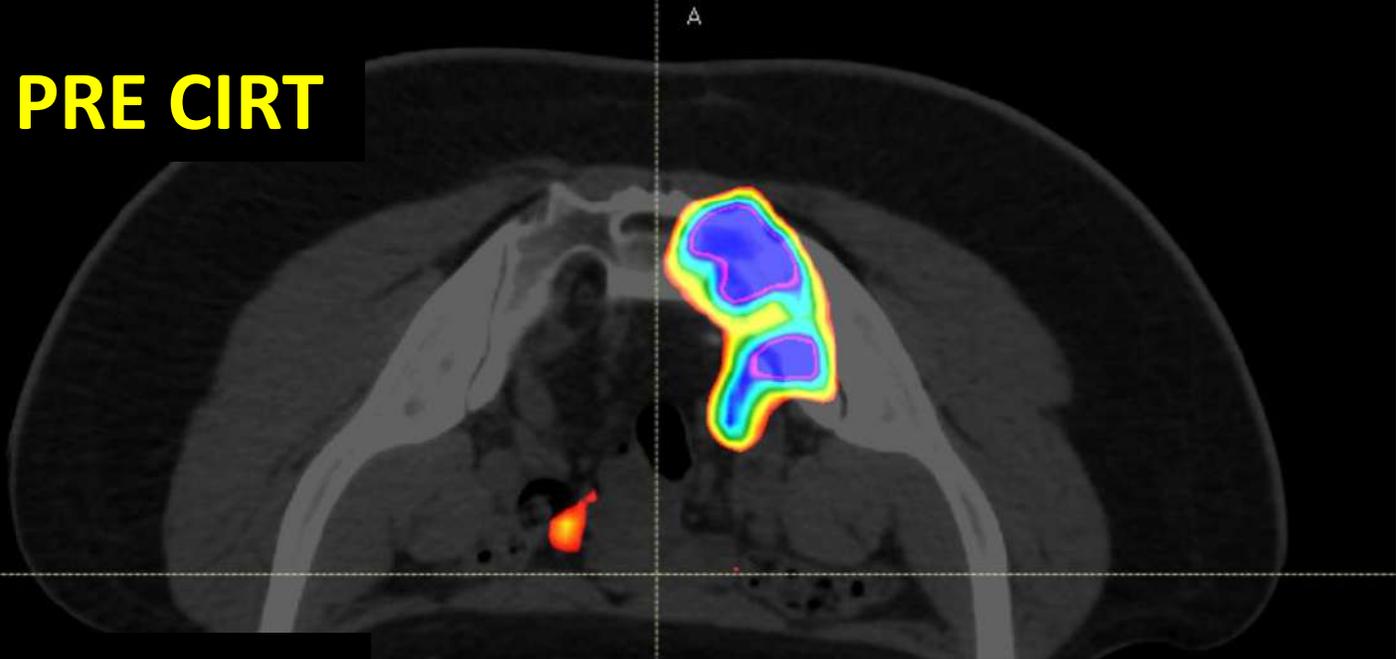
6 Mo. FU



But complete metabolic response

- “Currently, no intrapelvic pathologic hypermetabolic locations
Skeletal: in os sacrum currently without pathologically increased
glucose metabolism”

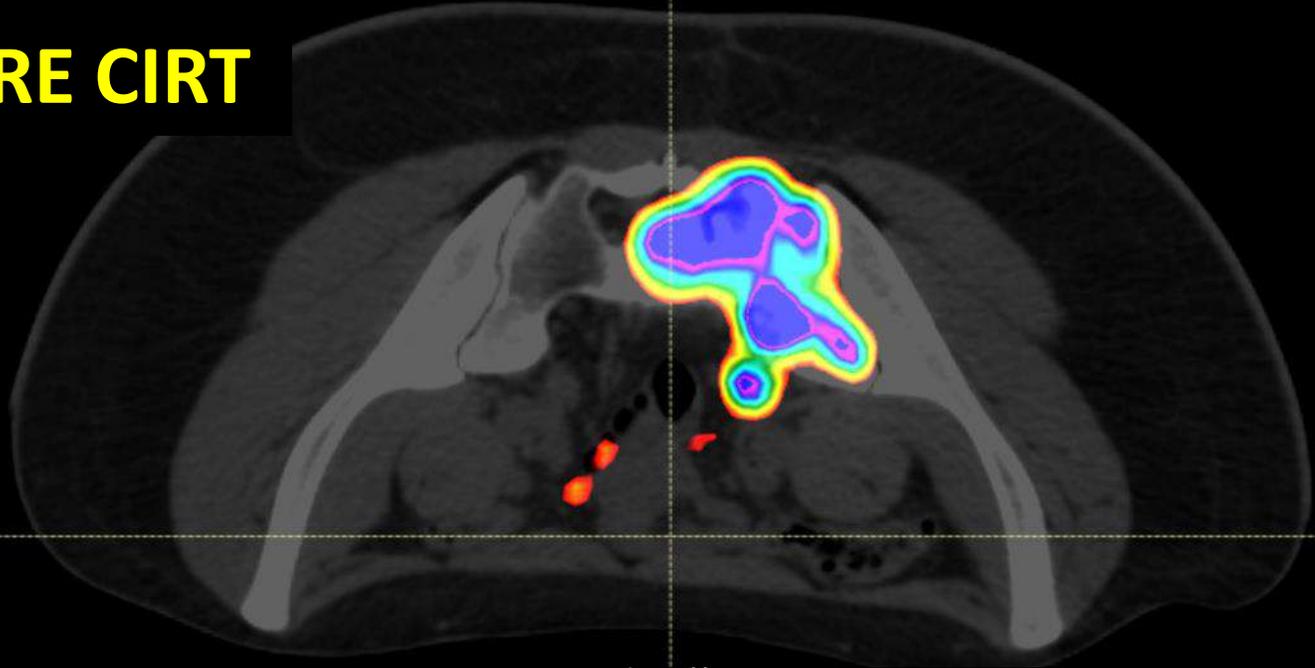
PRE CIRT



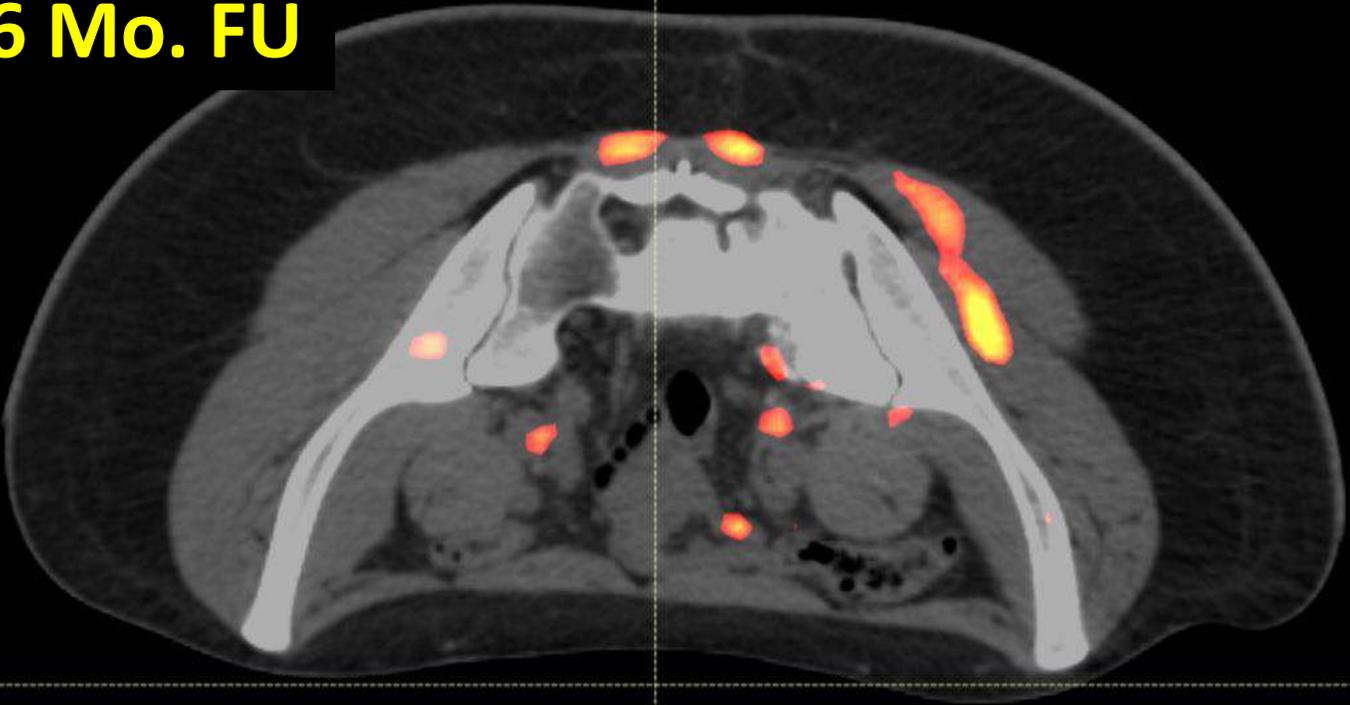
6 Mo. FU



PRE CIRT



6 Mo. FU



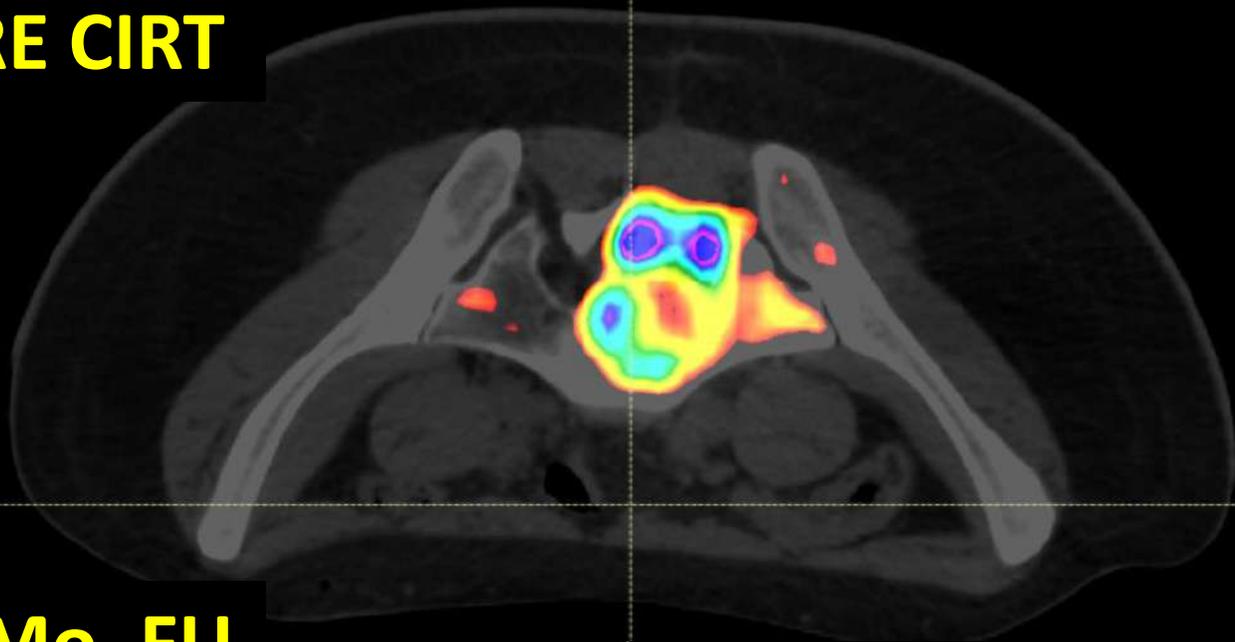
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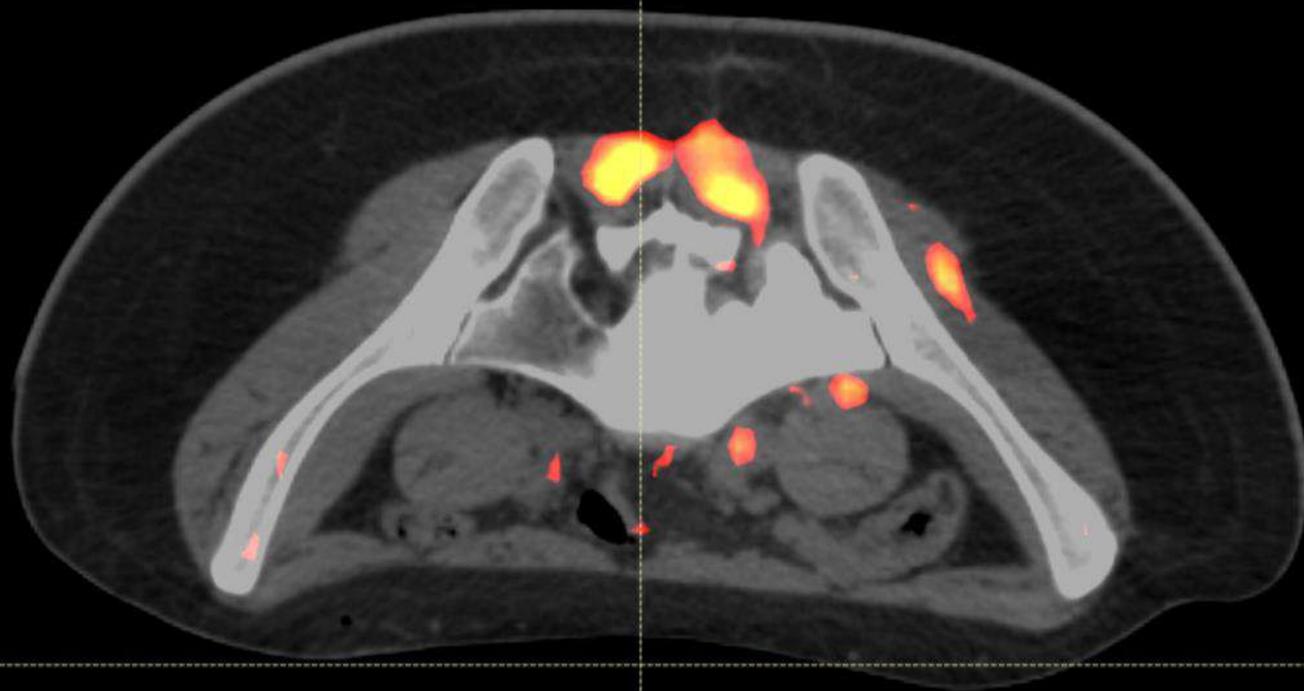
6 Mo. FU



PRE CIRT



6 Mo. FU



At 12 months NED

Late radiation induced severe neuropathy is a rare event that may reduce quality of life

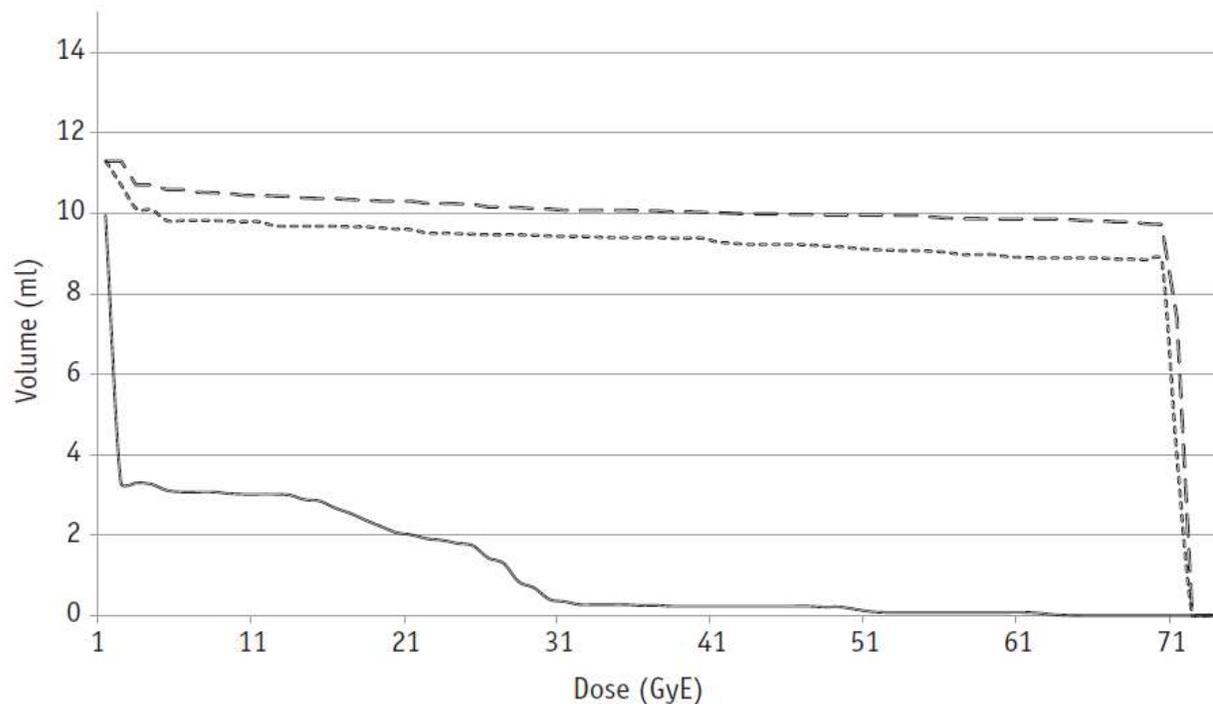
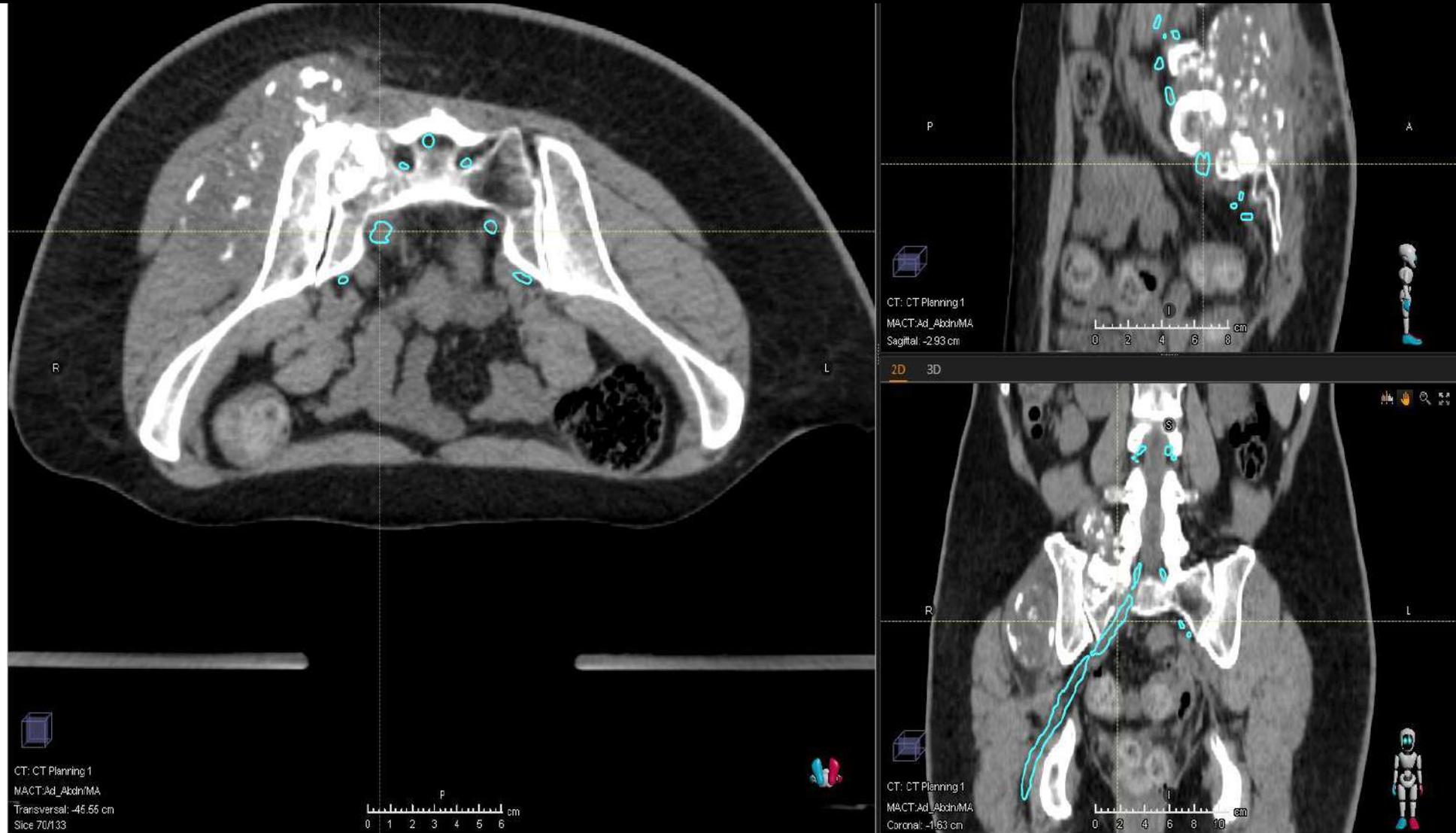


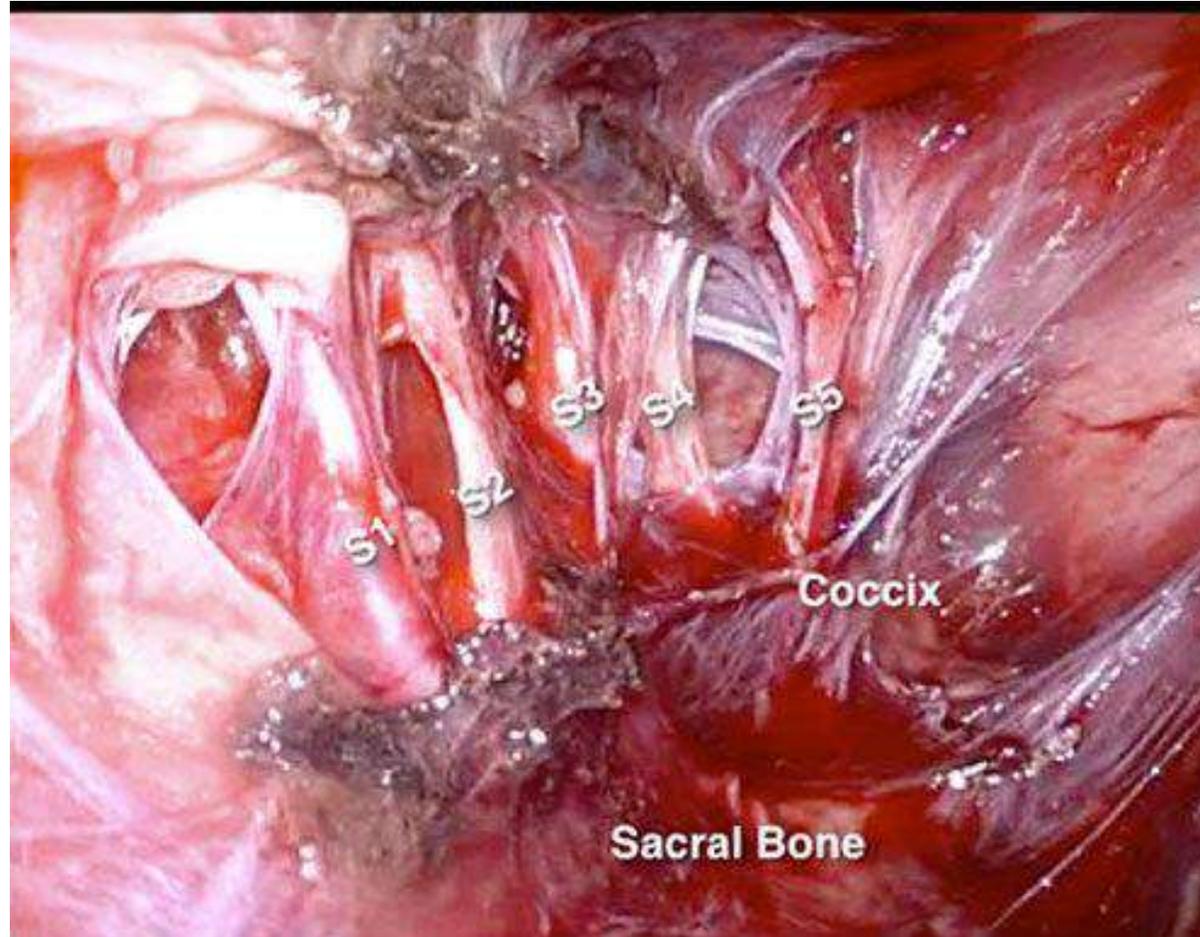
Fig. 3. Representative dose–volume histograms of sciatic nerves with grade 3 toxicity (dotted and dashed lines) that received a total dose of 70.4 gray equivalents/16 fractions. Compared with the grade 0 dose–volume histogram (solid line), a higher dose was applied to a long distance of the sciatic nerves.

At MedAustron we are
trying to reduce the risk of
severe neuropathy
by :

1) Contouring the single nerve roots until they merge in the ischial nerve



...they are not so small



2) Reducing the dose in the nerve roots



With a prescription dose of 70.4-76.8
Gy RBE in 16 fractions of 4.4-4.8 Gy
RBE we keep nerve roots outside of
GTV to

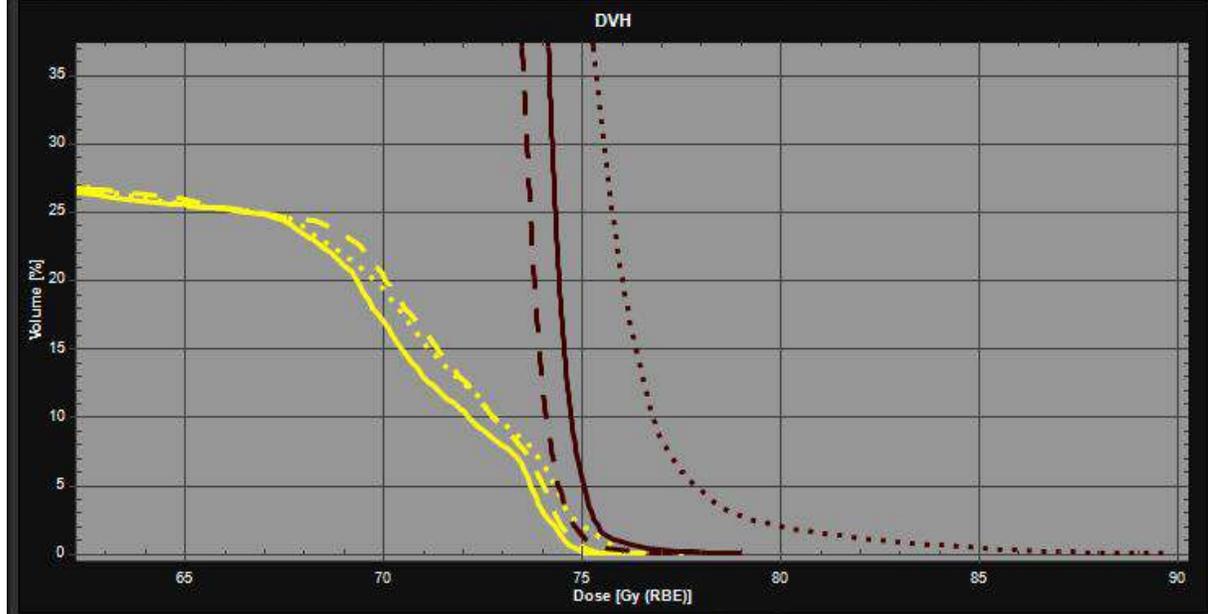
D1% < 69 Gy RBE

and we avoid hot spots for nerve
roots inside GTV



DVH Dose Statistics Clinical Goals Biological Response Plan Fraction Schedule Line Dose

Summed dose (RBE): 7B... Summed dose (RBE): 7 B... Summed dose (RBE): BS...



Dose Statistics Clinical Goals Biological Response

ROI statistics POI statistics

3) Trying to be robust against range and set-up uncertainties

% outside grid
0%
0%
0%
0%
0%

Does it work ?

Japanese experience

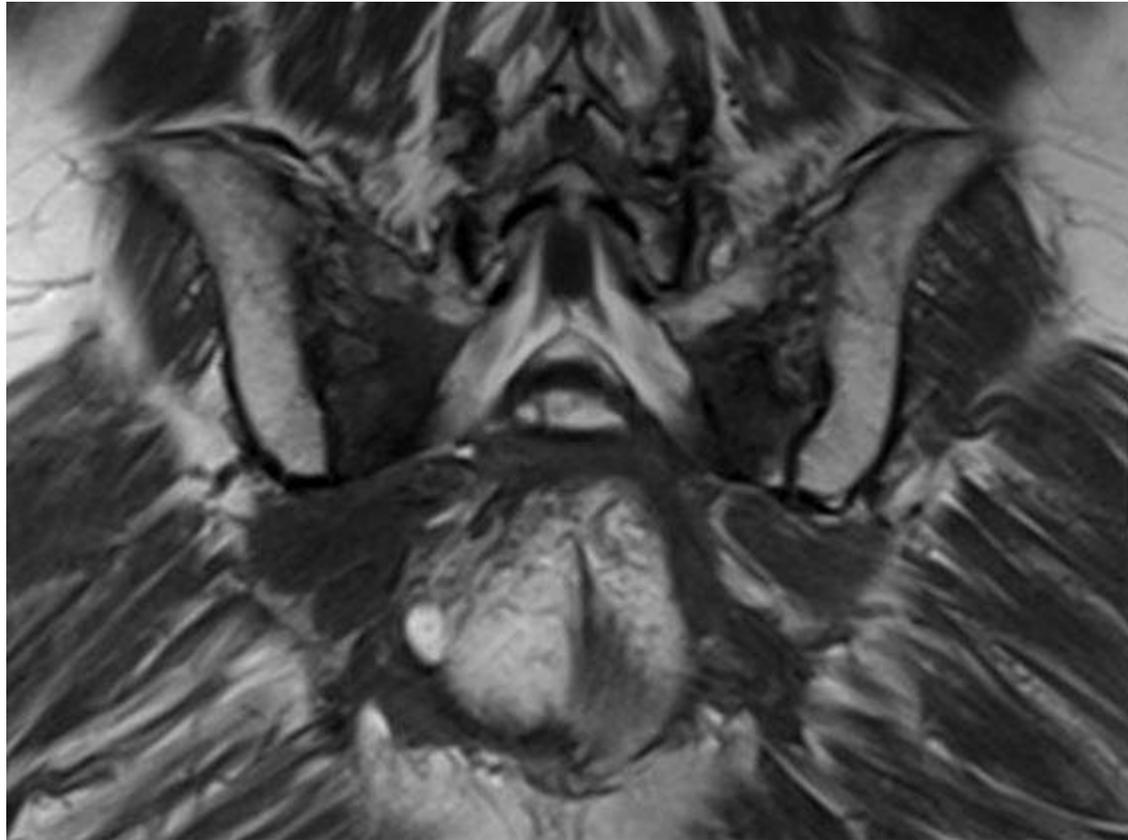
- 188 patients
- Median FU 10 Months
- 3% severe neuropathy

Austron experience

- 25 patients
- Median FU 10 Months (range 1-26)
- **0% severe neuropathy** (2 cases after COVID vaccination, 1 resolved after 6 weeks , the other is ongoing)

We need longer Follow up

Not only the nerves...



Constraints for rectum at MedAustron

• :

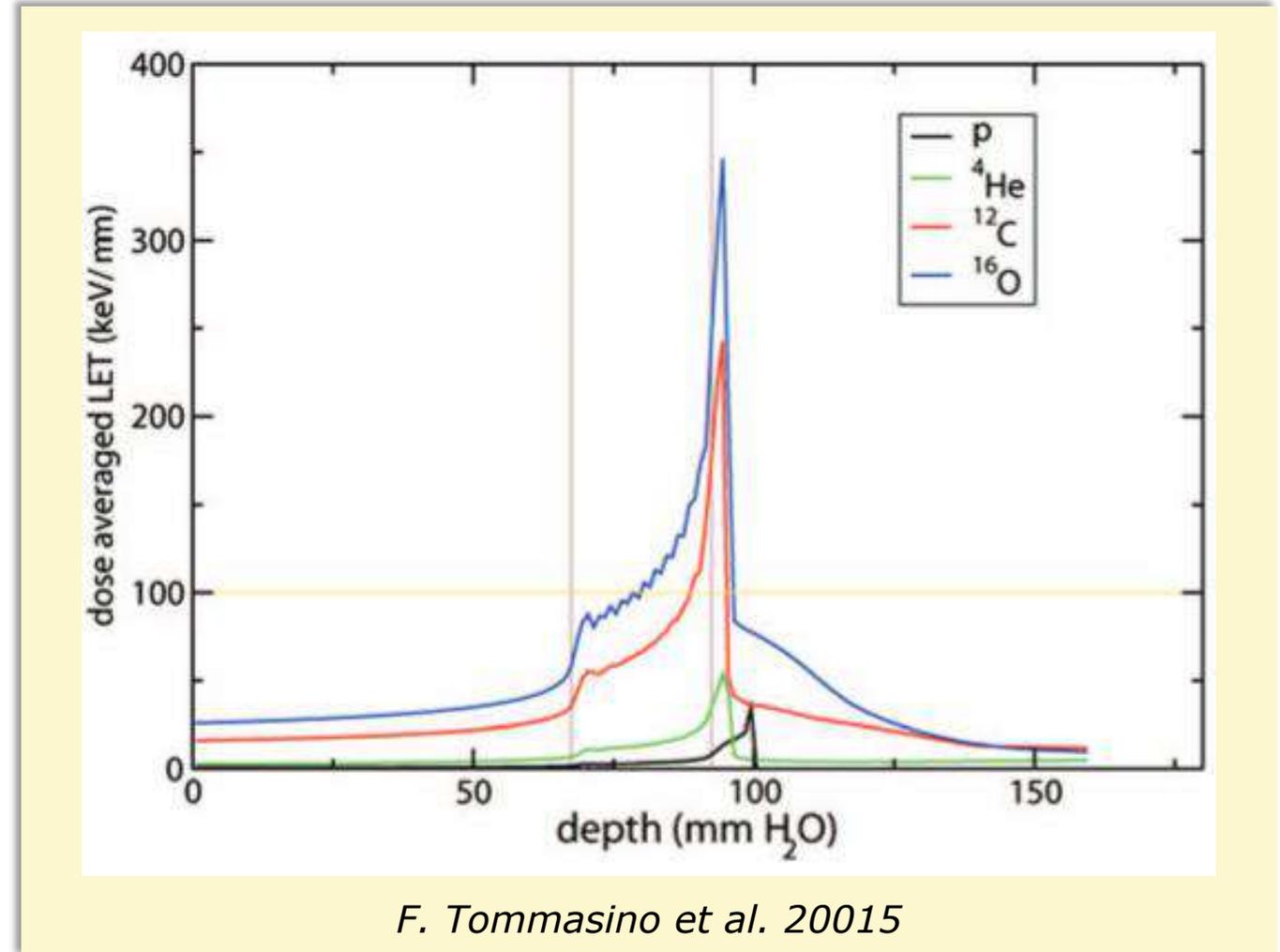
- **D (RBE, 1 cc) < 66 Gy RBE**
- **D (RBE, 5 cc) < 63 Gy RBE**
- **D (RBE, 10 cc) < 55 Gy RBE**

Constraints for rectum at MedAustron

- **69 out of 200 patients treated with CIRT were irradiated in the Pelvic region**
- Median FU is only 10 Months, however cumulative rectal toxicity is minimal
- G3 = 0%
- G2 = 0%

Room for improvement in the current clinical practice

- Mixed irradiation field
 - High and low LET
- Large targets receive mainly low LET
- Optimization process only in terms of RBE weighted dose
 - In-vitro survival data of a given cell line
 - Other parameters like LET or physical dose above a certain LET threshold are not considered
 - Hypoxia not considered



Inferior clinical outcomes in large tumors

- A. Matsunobu et al. 2012

- Y. Demizu et al. 2017

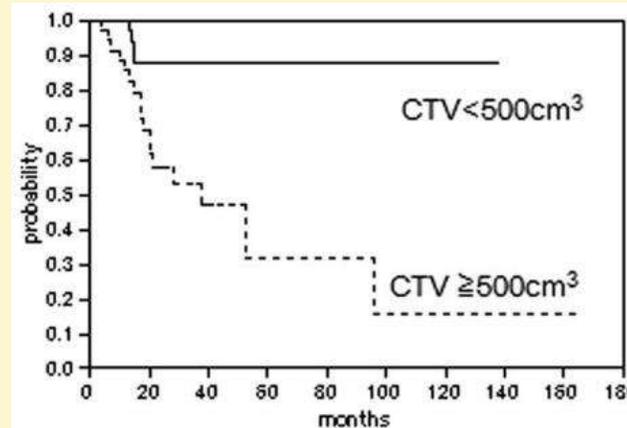
- M. Osama et al. 2018

- T. Bostel et al. 2020

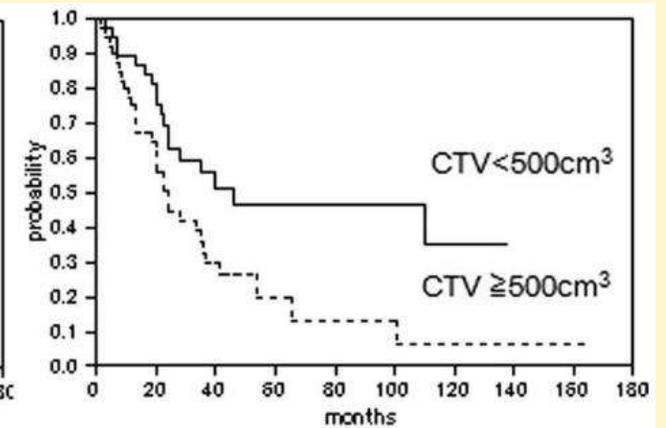
Unresectable Osteosarcoma of the trunk treated with CIRT

Clinical target volume ($<500 \text{ cm}^3$ vs. $\geq 500 \text{ cm}^3$):

- Significantly associated with 5-year LC
 - 88% vs 31%
- Significantly associated with 5-year OS:
 - 46% vs 19%



5-year LC

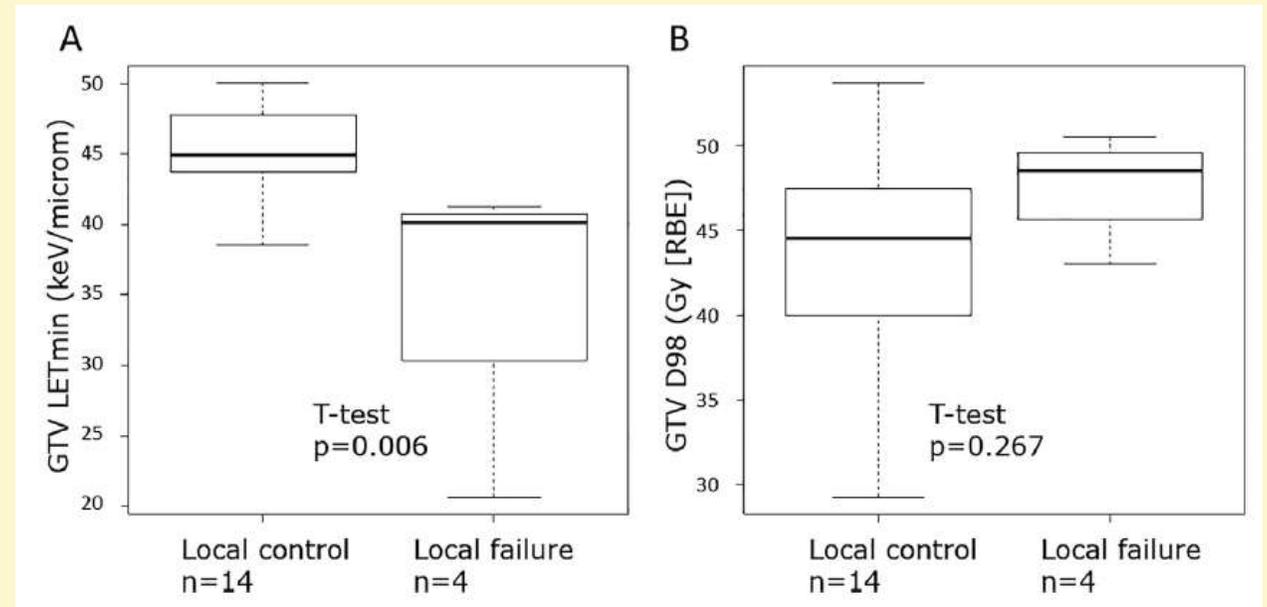


5-year OS

Recent studies

- Y. Hagiwara et al. 2020
 - Influence of dose-averaged linear energy transfer on tumour control after carbon-ion radiation therapy for pancreatic cancer
- S. Matsumoto et al. 2020
 - Unresectable chondrosarcomas treated with carbon ion radiotherapy: Relationship between dose-averaged linear energy transfer and local recurrence
- S. Molinelli et al. 2021
 - How LEM-based RBE and dose-averaged LET affected clinical outcomes of sacral chordoma patients treated with carbon ion radiotherapy

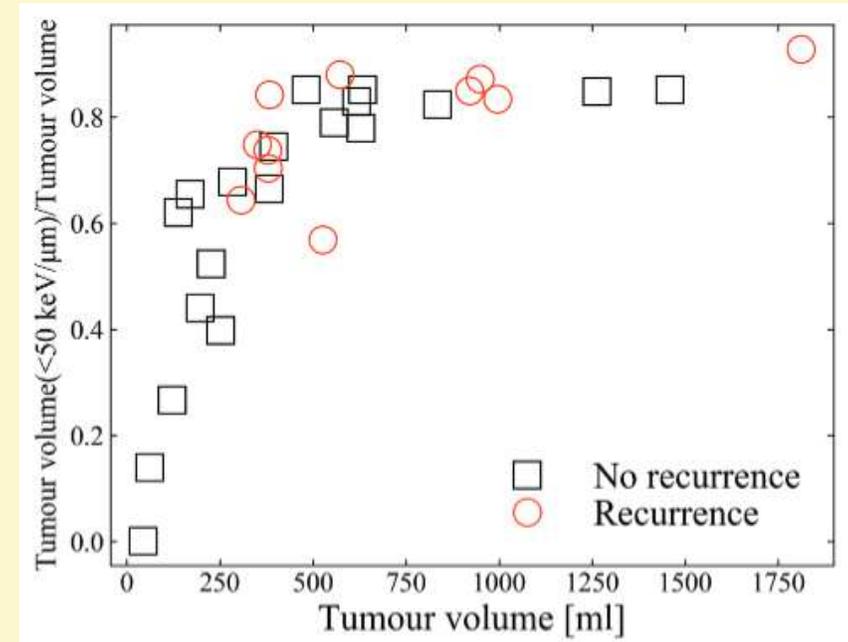
- Influence of LET_d on tumor control
- Significant association of high $LET_{d,min} (\geq 44 \text{ keV}/\mu\text{m})$ in the GTV with better 18-month LC
 - 100% vs. 34.3%



Recent studies

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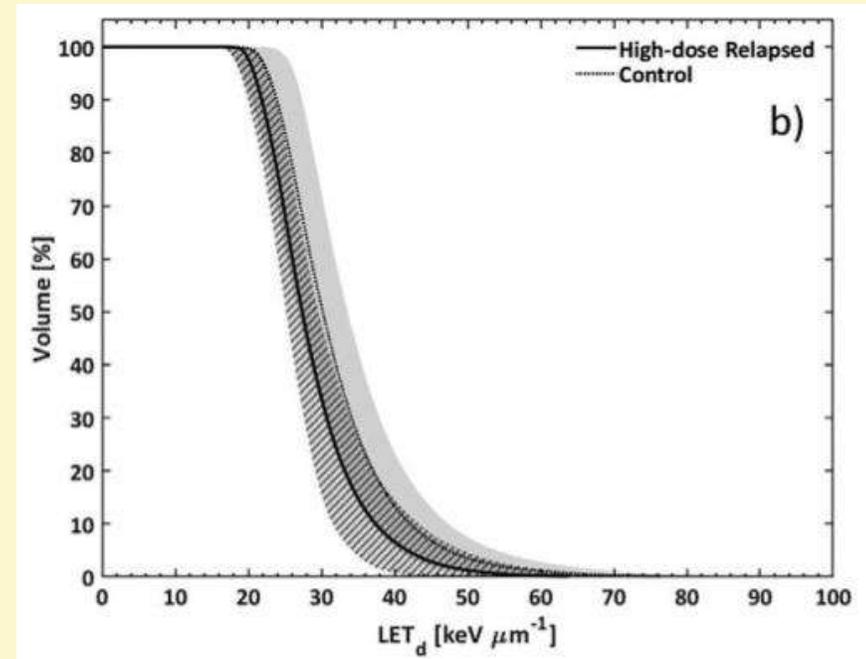
- Significant correlation of $V_{50 \text{ keV}/\mu\text{m}}$ with tumor volume
 - $V_{50 \text{ keV}/\mu\text{m}}$: The ratio of the volume in the PTV receiving less than $50 \text{ keV}/\mu\text{m}$ to the entire volume of the PTV



Recent studies

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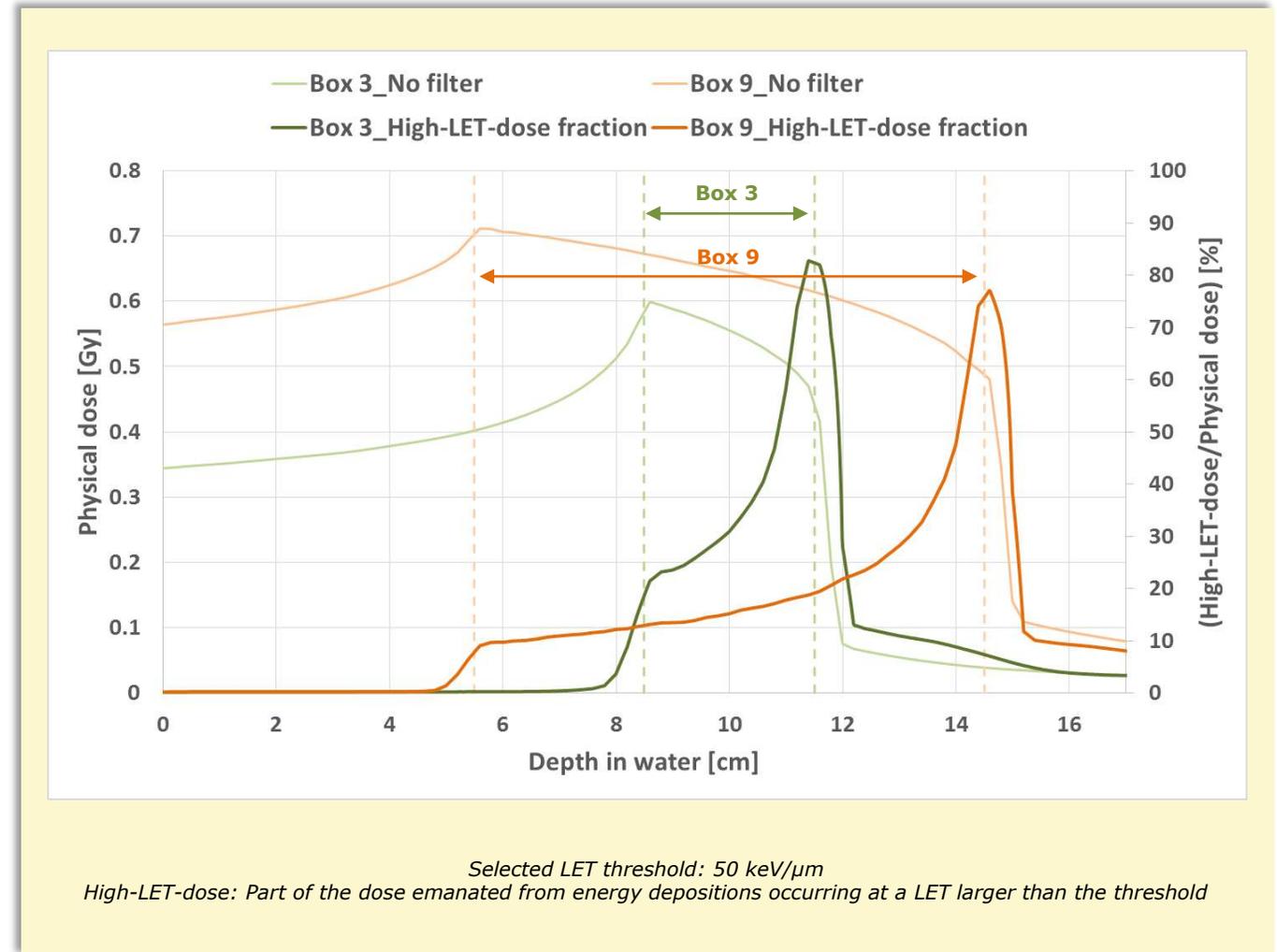
- All LET_d evaluators obtained from the CTV_{HD} (boost) were higher than the CTV_{LD}
- $LET_{d|50\%}$ of the CTV_{HD} was significantly higher for the control group



LET_d & high-LET-dose distribution in a plan - 1

Target volume

- Setup (1 beam):
 - Box 3, centered at 10 cm in water
 - Box 9, centered at 10 cm in water
- Outcome
 - The longer the SOBP extension:
 - The larger the target portion covered by low LET
 - The lower the fraction of high-LET-dose



LET_d & high-LET-dose distribution in a plan - 1

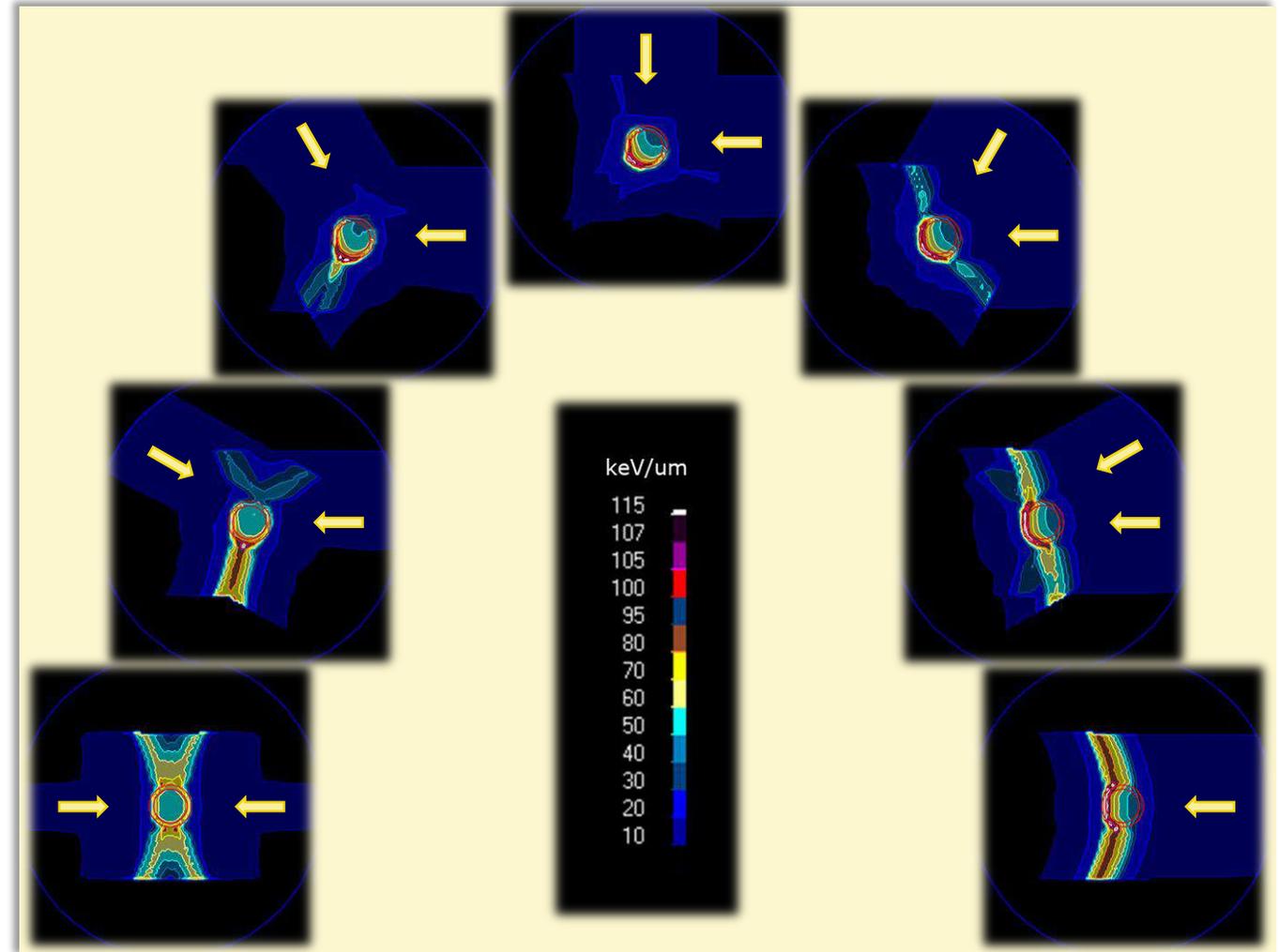
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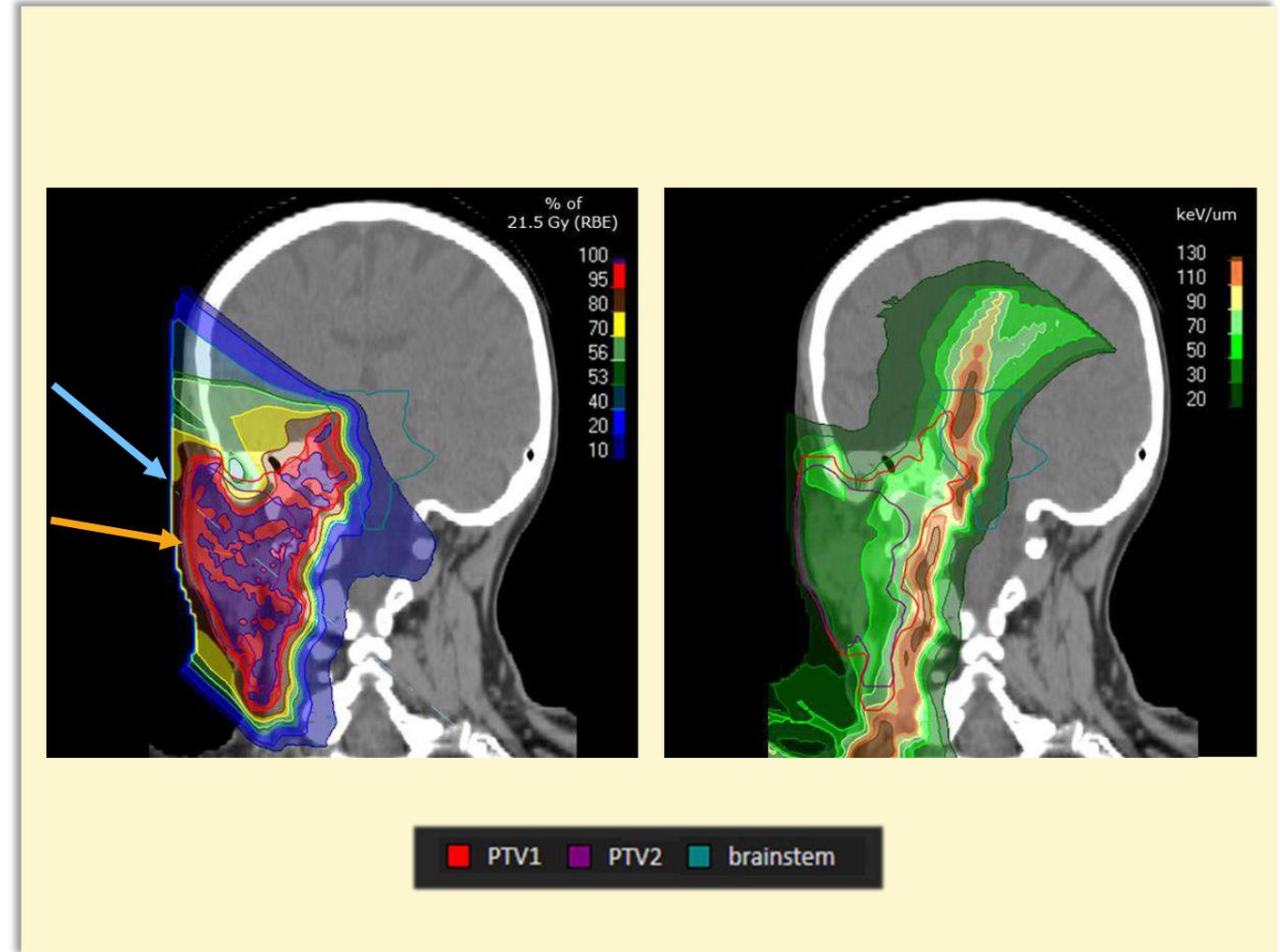
Beam arrangement dependency

- Setup:
 - Target:
 - Sphere; radius=2 cm
 - Shell:
 - Target extended by 0.5 cm
 - 2 beams
 - One fixed
 - The other was rotated by 30° each time
- Outcome:
 - By increasing the beam angle difference:
 - The near min LET_d increases in the target
 - The near max LET_d decreases in the shell



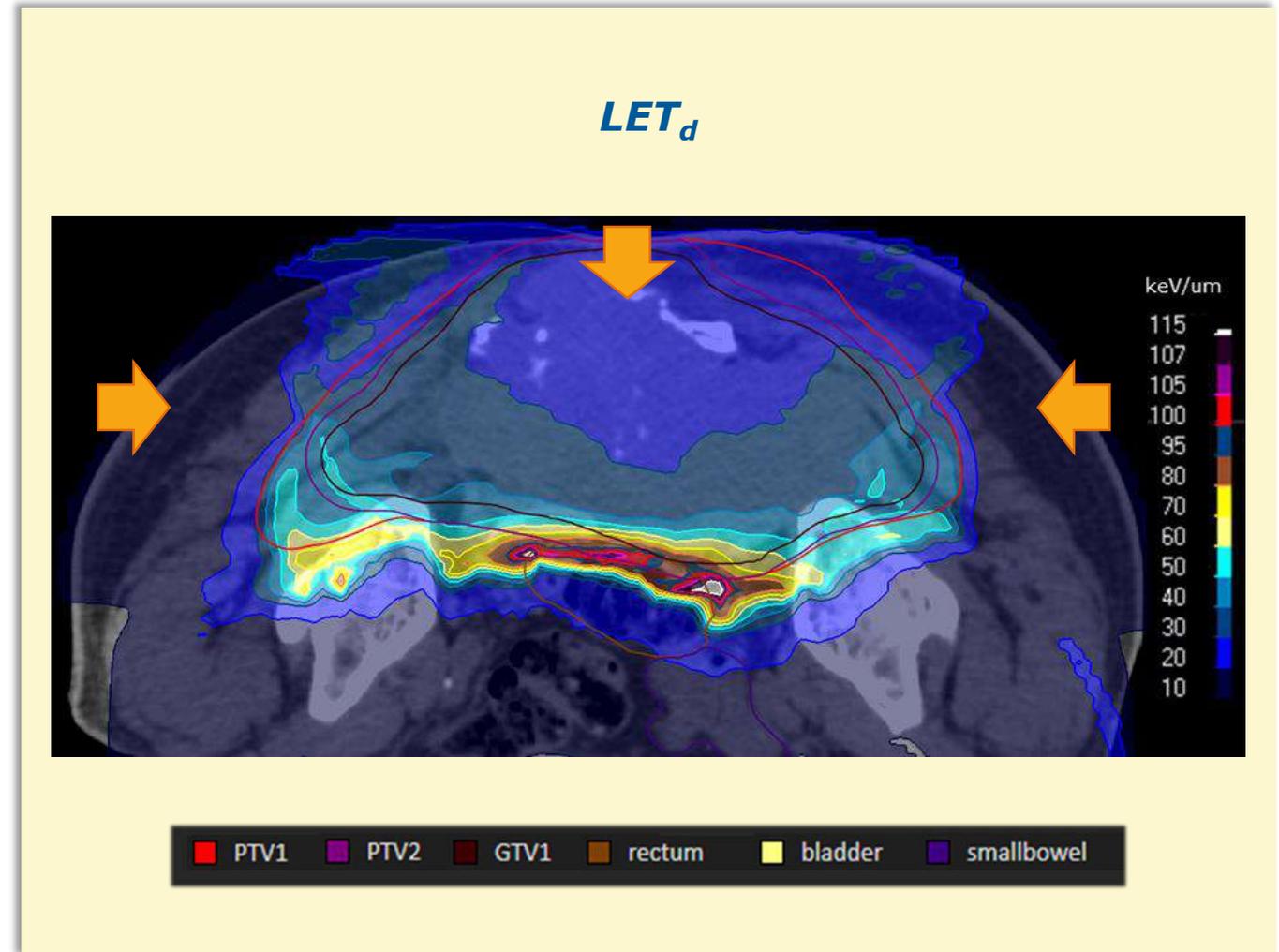
High LET_d in the OAR

- Adenoid Cystic Carcinoma
 - PTV1: 232.6 cm³
 - PTV2: 128.7 cm³
- Sequential boost
 - RBE-weighted dose per fraction:
 - PTV1: 9 fx; 4.3 Gy (RBE)/fx
 - PTV2: 7 fx; 4.3 Gy (RBE)/fx
- Setup:
 - CTs:
 - HFS, 30° clockwise
 - HFS, 30° counterclockwise rotation
- Major part of brainstem dose was delivered by one beamset aiming at PTV1
 - Angles: 190° and 220°
 - High LET area directly within brainstem



LET_d/High-LET-dose in large targets

- Sacral chordoma
 - PTV1: 1954.5 cm³
 - PTV2: 1305.7 cm³
- Sequential dose prescription
 - RBE-weighted dose per fraction:
 - PTV1: 9 fx; 4.6 Gy (RBE)/fx
 - PTV2: 7 fx; 4.6 Gy (RBE)/fx
- Beam arrangement:
 - T-shape (2 horizontal + 1 vertical)

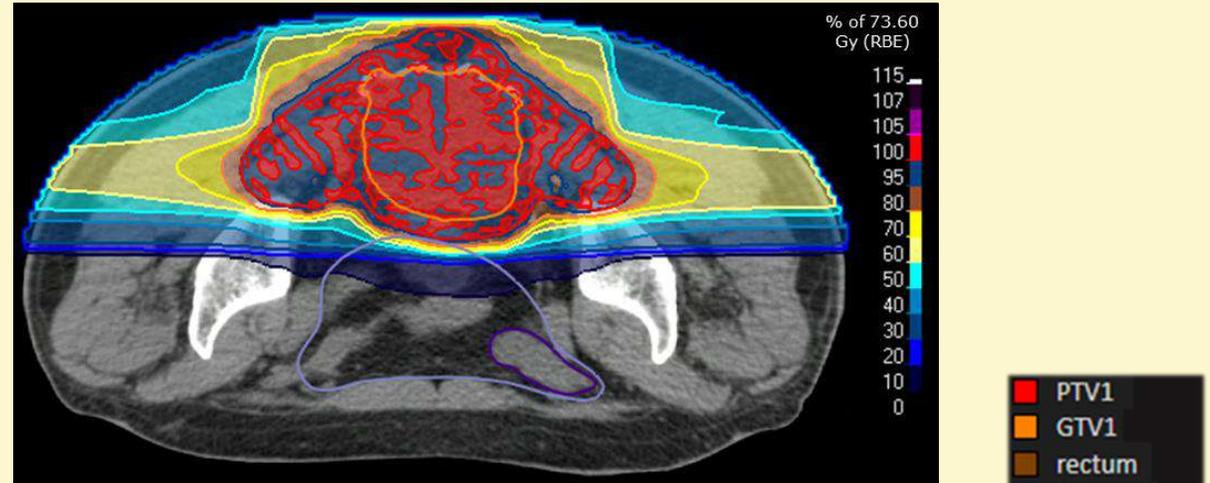


PTV: Planning Target Volume; RBE: Relative Biological Effectiveness; fx: Fraction

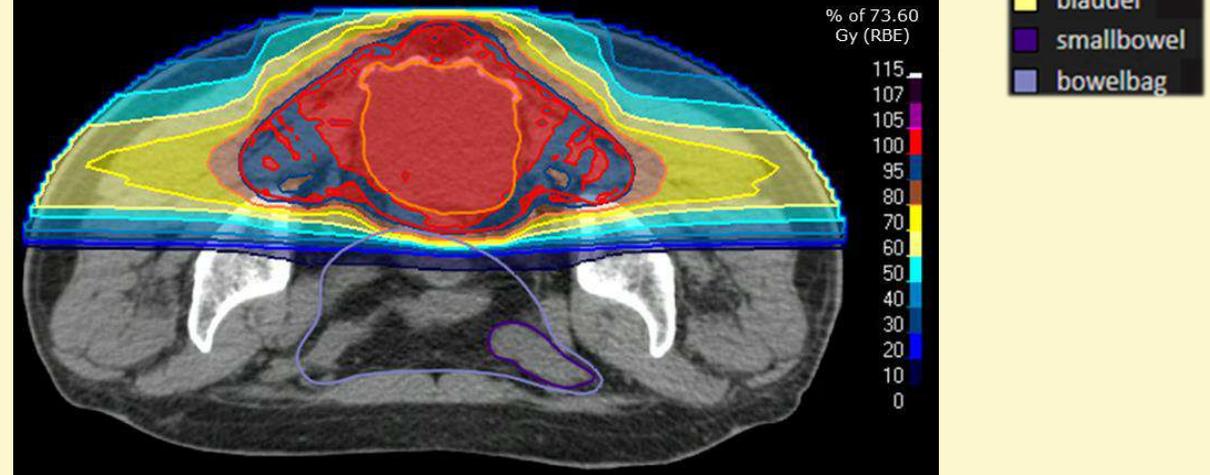
LET-based optimization

- Sacral chordoma
 - PTV1: 1244.3 cm³
 - PTV2: 656.7 cm³
- Sequential dose prescription
 - RBE-weighted dose per fraction:
 - PTV1: 9 fx; 4.6 Gy (RBE)/fx
 - PTV2: 7 fx; 4.6 Gy (RBE)/fx
- Beam arrangement:
 - T-shape (2 horizontal + 1 vertical)
- Comparing the:
 - RBE-weighted dose distribution
 - LET_d distribution
 - DVHs & LVHs

Original plan



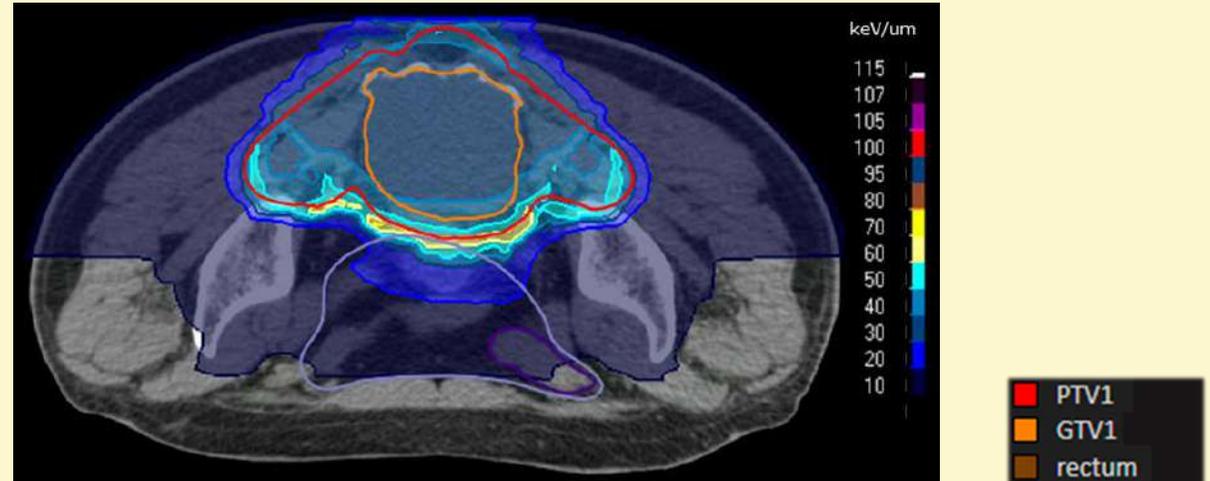
Optimized plan



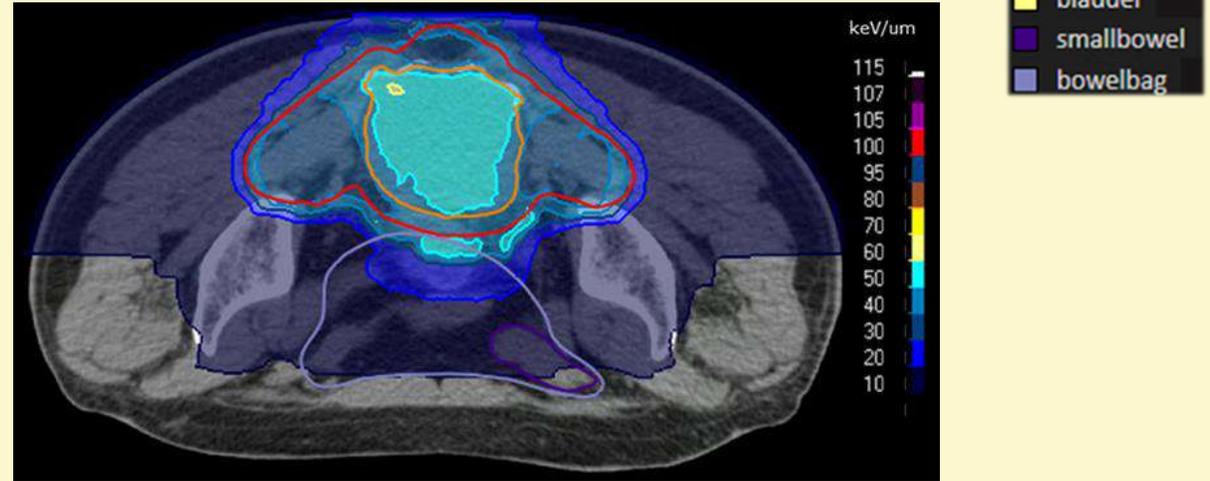
LET-based optimization

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 - PTV1: 1244.3 cm³
 - PTV2: 656.7 cm³
- Sequential dose prescription
 - RBE-weighted dose per fraction:
 - PTV1: 9 fx; 4.6 Gy (RBE)/fx
 - PTV2: 7 fx; 4.6 Gy (RBE)/fx
- Beam arrangement:
 - T-shape (2 horizontal + 1 vertical)
- Comparing the:
 - RBE-weighted dose distribution
 - LET_d distribution
 - DVHs & LVHs

Original plan

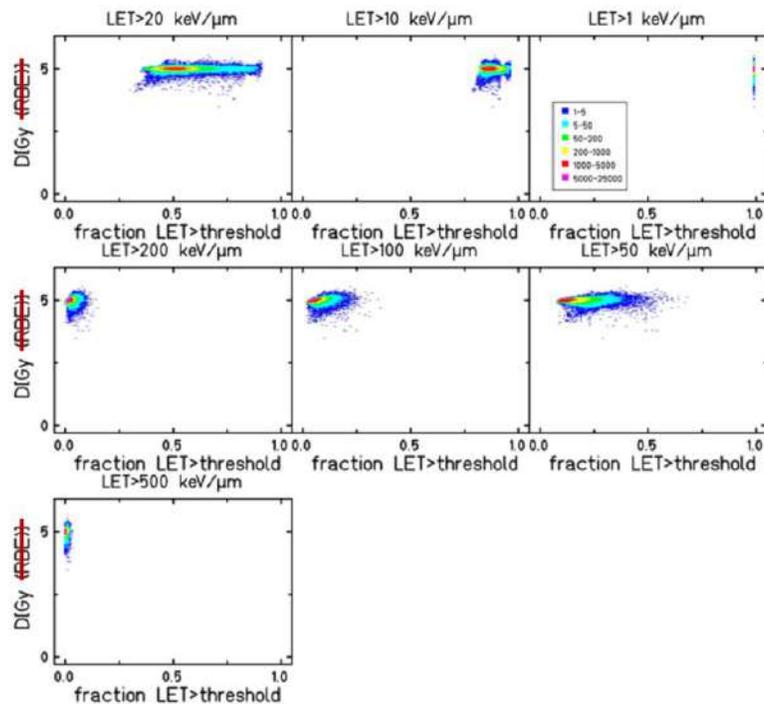


Optimized plan



RBE WEIGHTED DOSE DOES NOT GIVE US THE FULL PICTURE

“In order to achieve a good LC probability, most tumor voxels must receive enough dose with high LET.”

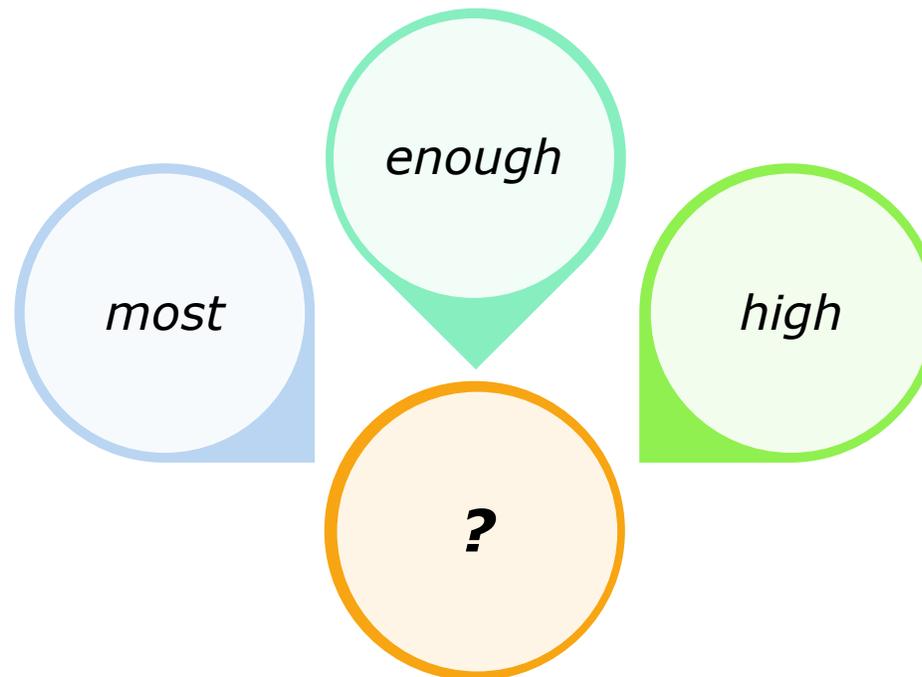


At MedAustron we are carrying out a research project to determine quantitatively what does “most” “enough” and “high” mean.

The physical parameter we are considering is: % of physical dose delivered by *LET* higher than a given threshold (known as “dirty dose” in the proton world)

Research question

*“In order to achieve a good clinical outcome, **most** tumor voxels must receive besides prescribed dose, **enough** dose with **high** LET”*



SKULL BASE CHORDOMA

Patient & Sx:

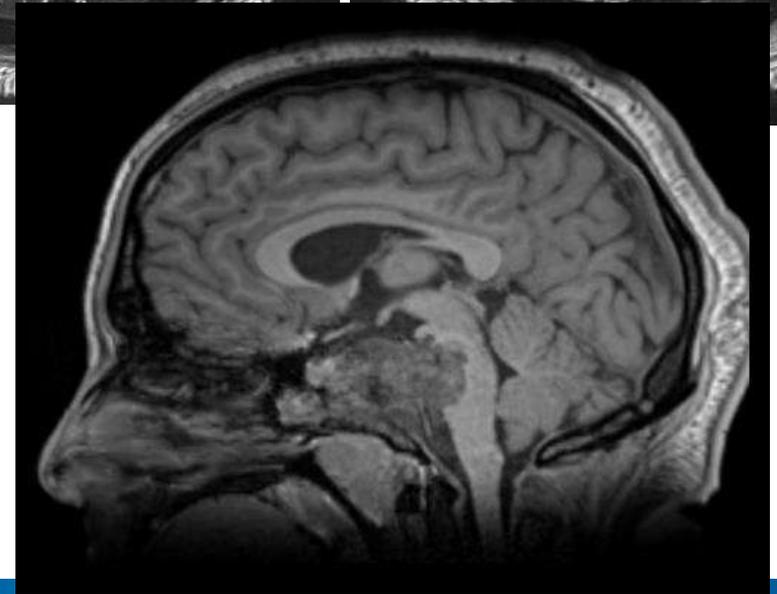
27 year old female,
April 2019 cranial nerves deficit: hypoglossus-paresis with laterodeviation of the tongue to the right, dysarthria, ptosis right, dyplopia, hypoesthesia V2 right

Dx:

Skull base chordoma

Initial Tx:

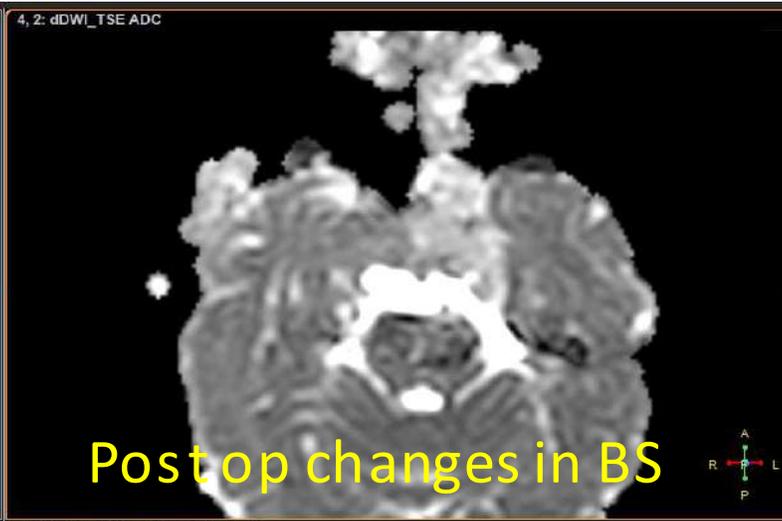
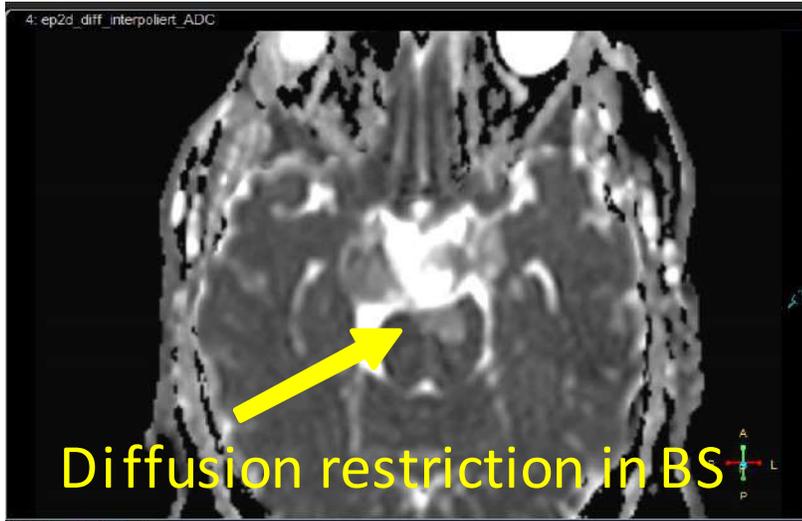
- 04/2019 neurosurgical tumor debulking with open craniotomy and pterional approach



SKULL BASE CHORDOMA

Surgical debulking could achieve an excellent brainstem decompression - prerequisite for curative particle therapy

Pre OP



Post OP



SKULL BASE CHORDOMA

Volume & Contour Definition:

- CTV 1: macroscopic tumor + surgical cavity in the brainstem + prepontine cistem + sinus cavernosus bilaterally+ whole clivus + tip of os petrosum bilaterally + petroclival junction bilaterally + retropharyngeal space extending caudally to C2
- CTV 2: macroscopic tumor + prepontine cistem + sinus cavernosus bilaterally+ whole clivus + petroclival junction bilaterally
- PTVs 3 mm

Prescription Dose / Fractionation:

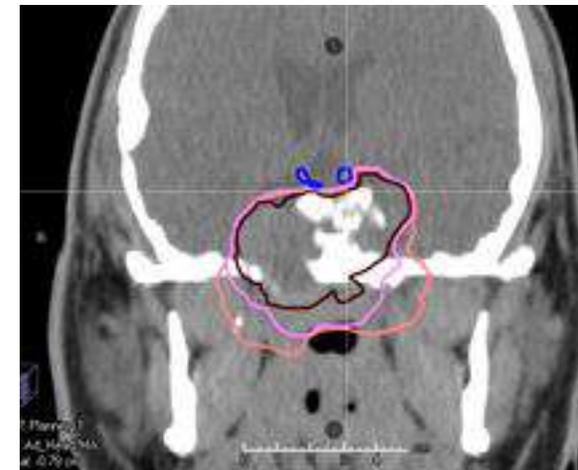
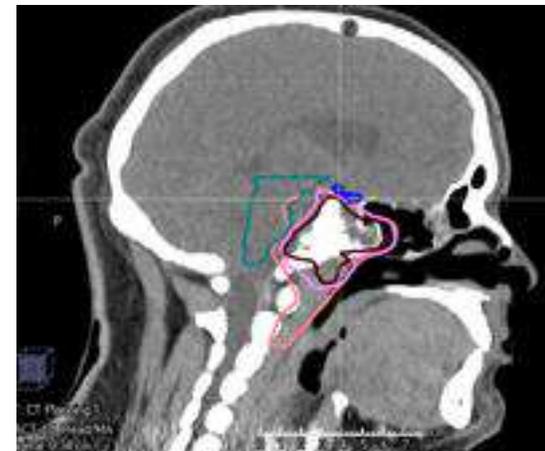
- 66 Gy RBE in 22 Fr of 3 Gy RBE
- CTV1 15 fr 45 Gy RBE , CTV2 7 fr 21 Gy RBE

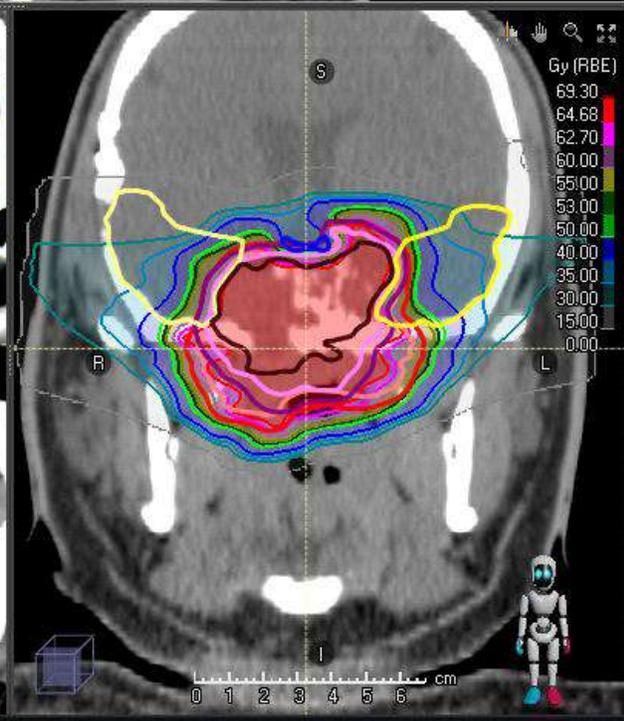
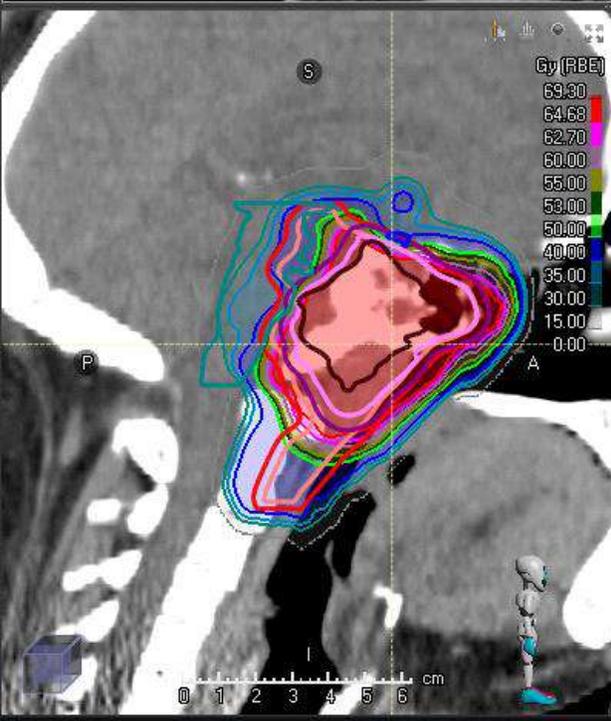
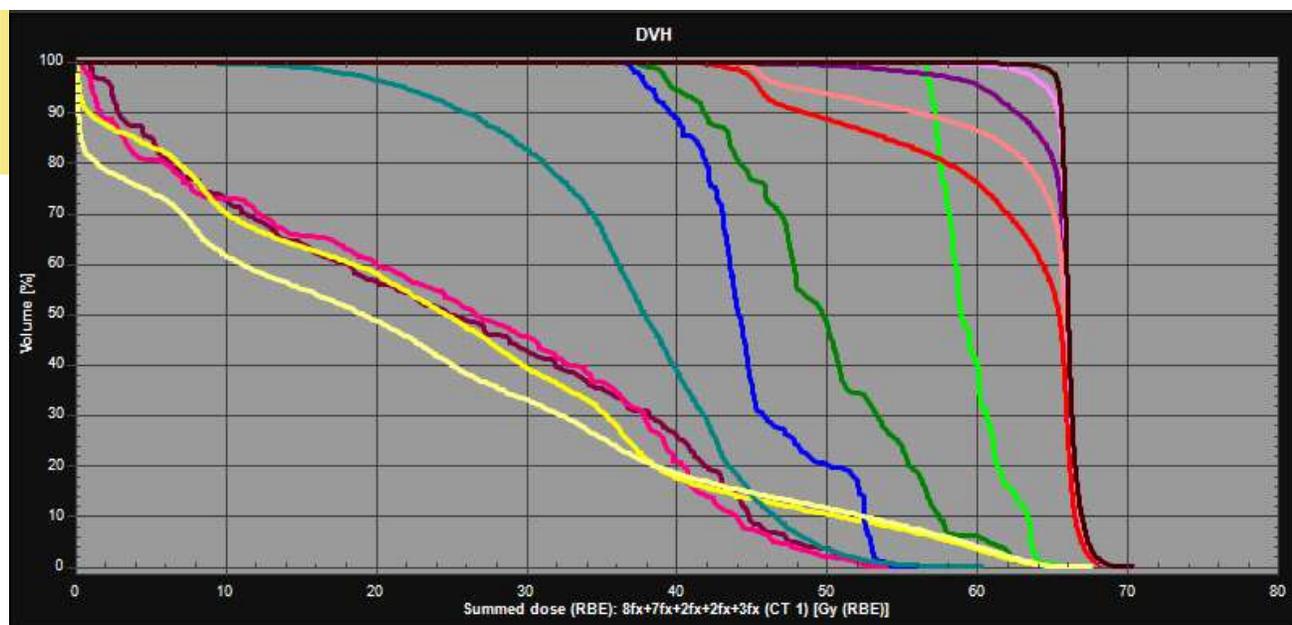
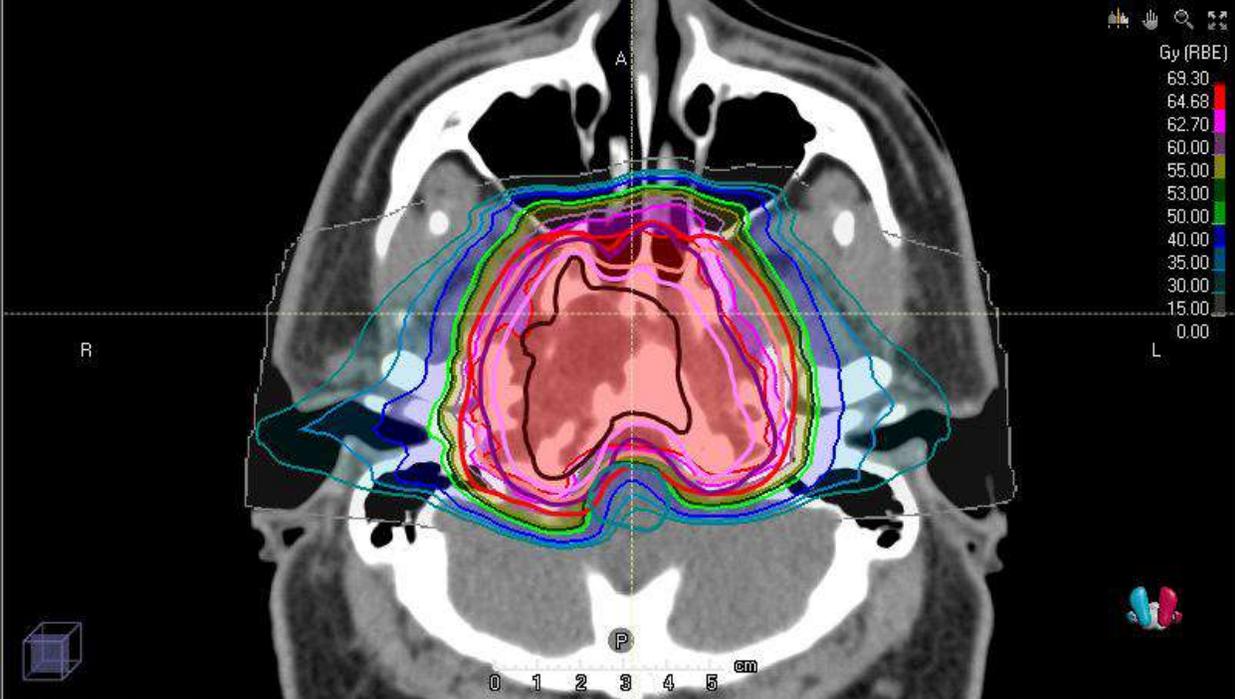
OAR Constraints:

- Brainstem: D0.01cc < 54 Gy (RBE)
- Chiasm, opticus R&L: D0.01cc < 50 Gy (RBE)
- Temporal lobe left: D1cc < 59 Gy (RBE)
- Cochlea: Dmean < 43 Gy (RBE)

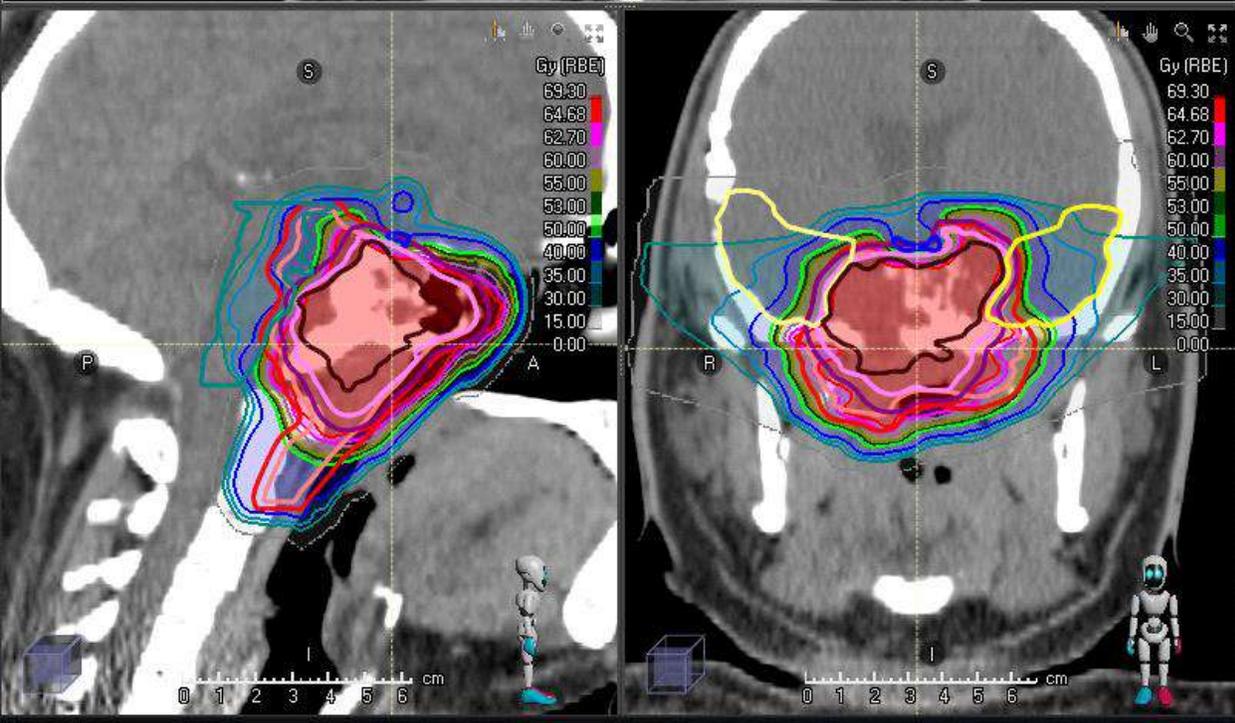
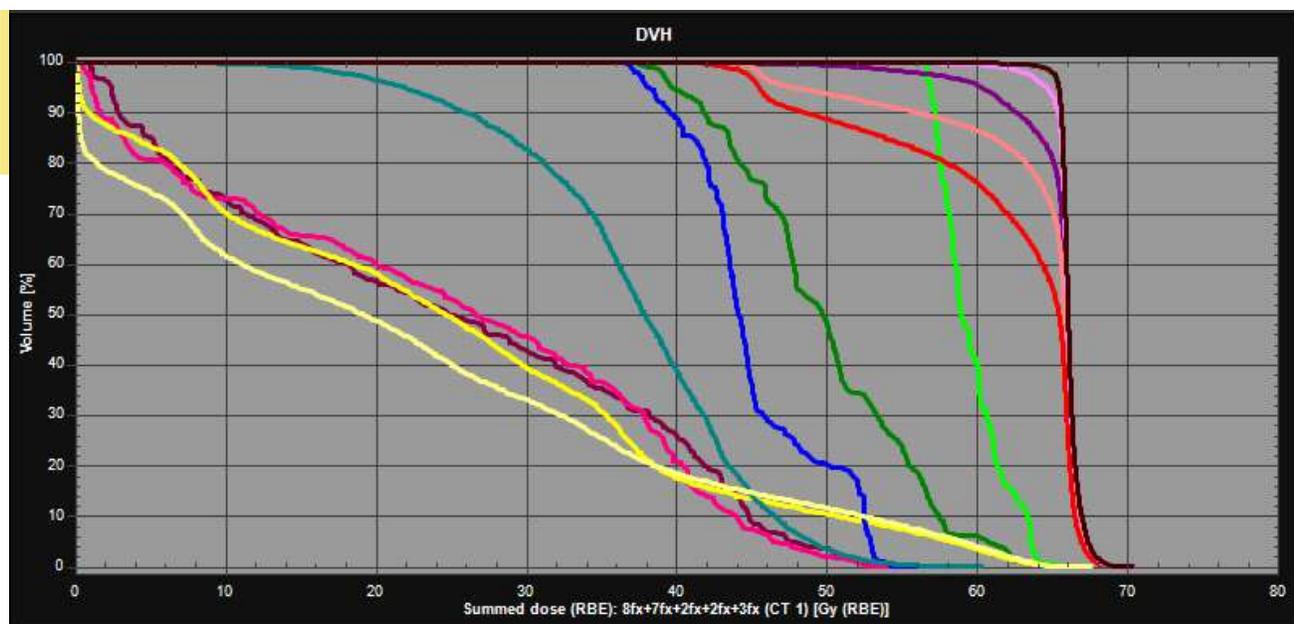
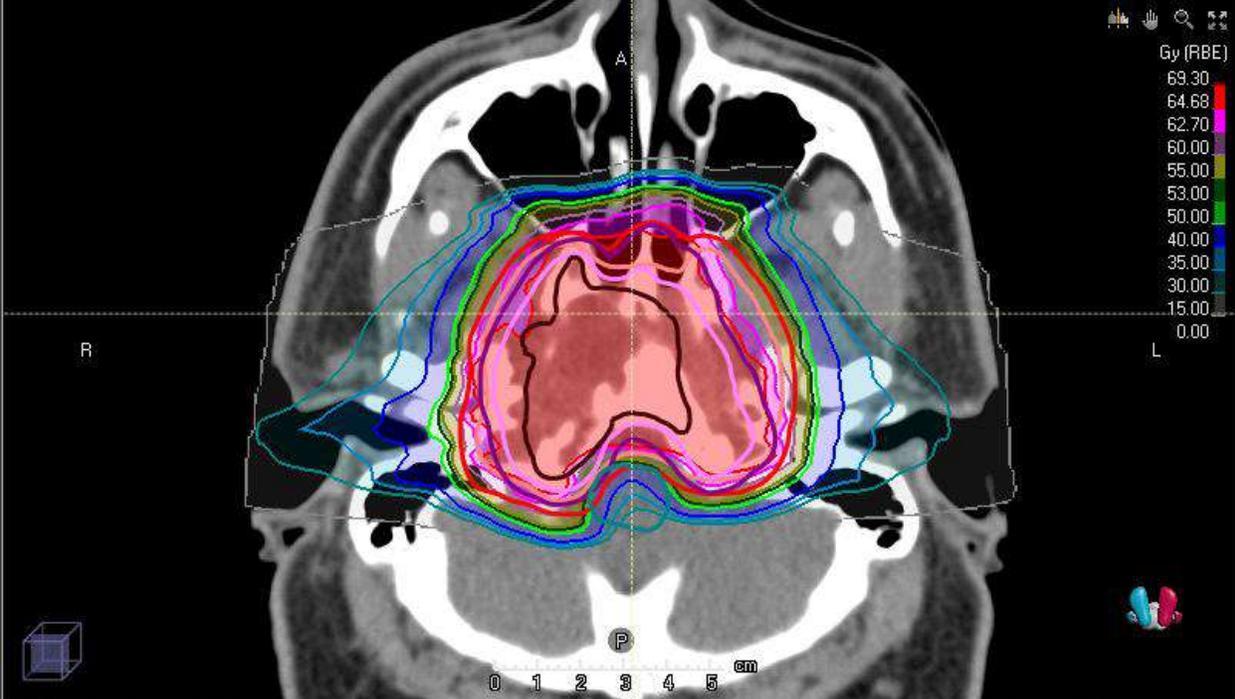
Comments:

- Prescription dose according to HIT protocol

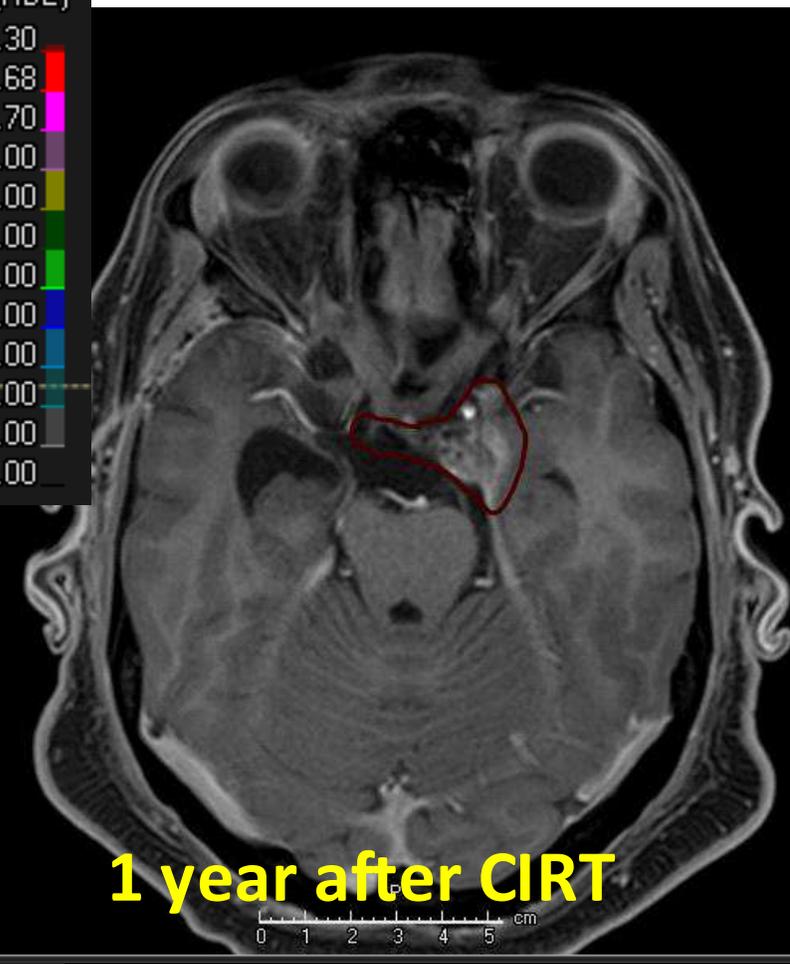
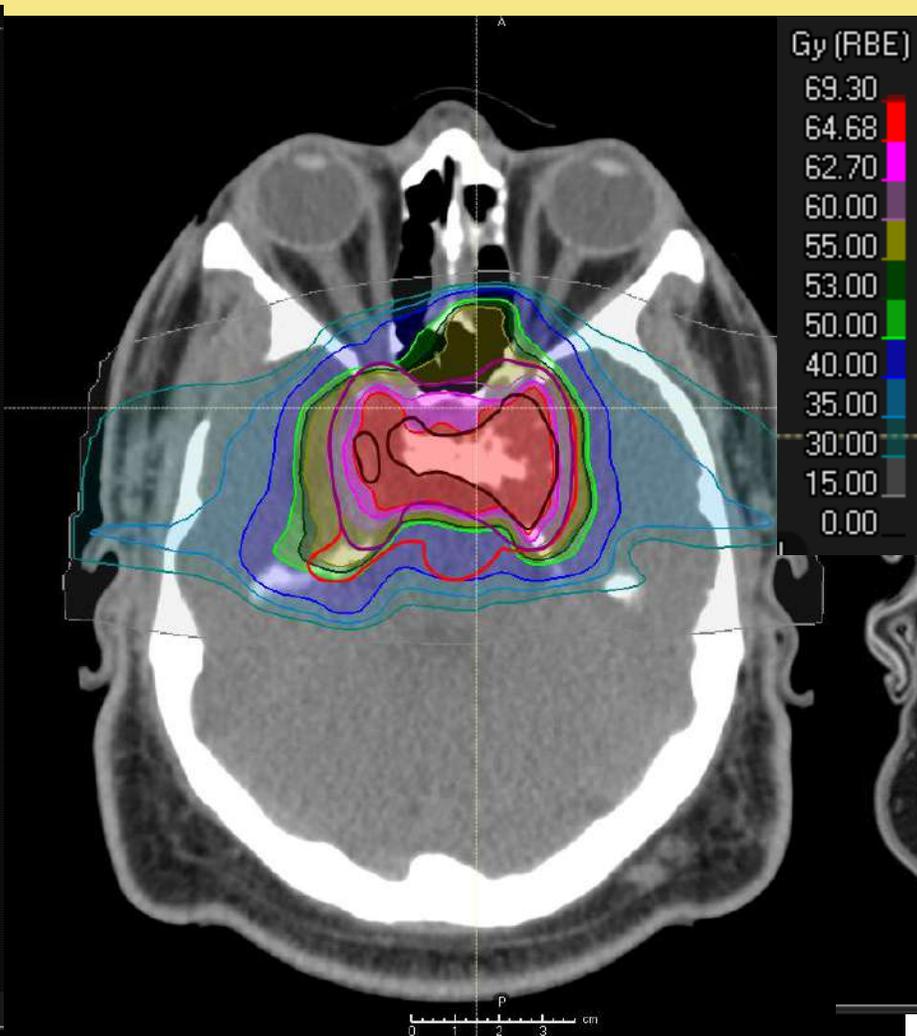


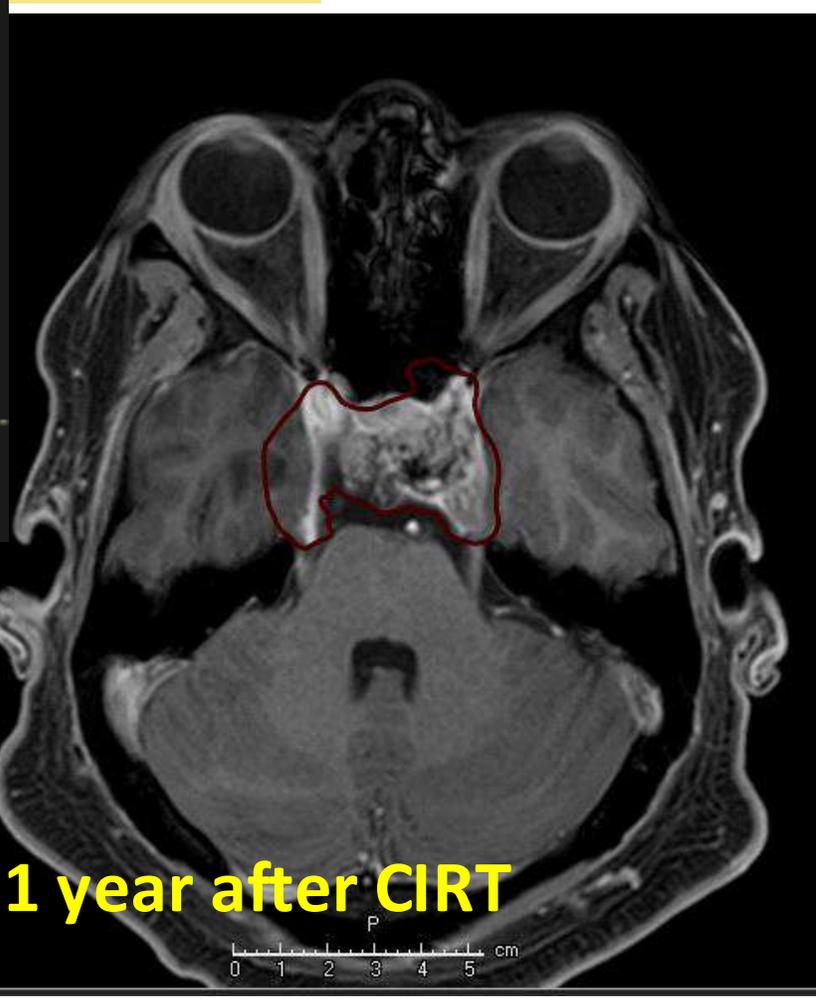
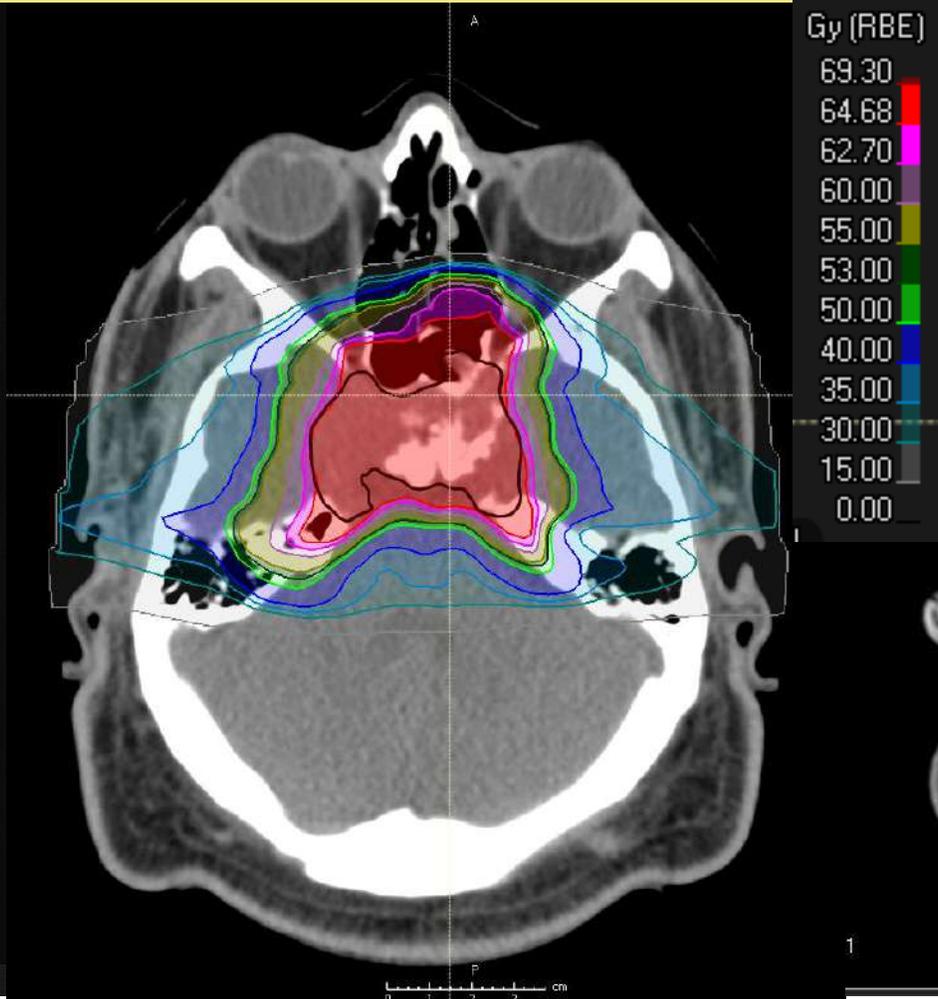


ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]						
		D99	D98	D95	Average	D50	D2	D1
brainstem	23.33	14.69	17.44	21.97	37.15	37.86	51.53	52.92
chiasm	0.47	36.94	37.25	38.11	45.11	44.11	53.10	53.74
cochleaLEFT	0.12	38.21	38.99	39.69	49.81	49.72	62.12	62.70
cochleaRIGHT	0.16	56.64	56.64	56.92	59.59	58.93	63.90	63.99
CTV1	134.13	45.07	45.46	47.71	63.66	65.81	67.65	68.04
CTV2	79.61	61.61	63.10	64.61	65.98	66.02	67.82	68.22
GTV1	46.87	64.32	64.96	65.43	66.14	66.05	67.85	68.26
opticusLEFT	0.63	1.04	1.16	2.42	24.71	24.87	51.19	52.15
opticusRIGHT	0.96	0.56	0.74	1.12	24.65	26.62	50.11	51.82
PTV1	189.67	43.18	44.47	45.47	61.85	65.44	67.47	67.84
PTV2	117.02	52.06	55.71	60.27	65.19	65.92	67.71	68.14
templobeLEFT	81.86	0.13	0.17	0.27	24.66	24.66	61.56	62.84
templobeRIGHT	99.34	0.07	0.10	0.15	21.88	19.08	62.14	63.42



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cochleaLEFT	0.12	38.21	38.99	39.69	49.81	49.72	62.12	62.70
cochleaRIGHT	0.16	56.64	56.64	56.92	59.59	58.93	63.90	63.99
CTV1	134.13	45.07	45.46	47.71	63.66	65.81	67.65	68.04
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GTV1	46.87	64.32	64.96	65.43	66.14	66.05	67.85	68.26
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SKULL BASE CHORDOMA

Treatment Tolerance:

last F/U: 13 Months after end of CIRT

- Skin G0
 - Mucosa: G0
 - CNS G0
 - Vision G0
 - Hearing G0
 - The only symptom is mild dysarthria evoked by alcohol consumption
-

CLINICAL INVESTIGATION

Kidney

**CARBON ION RADIATION THERAPY FOR PRIMARY RENAL CELL CARCINOMA:
 INITIAL CLINICAL EXPERIENCE**

TAKUMA NOMIYA, M.D., PH.D.,* HIROSHI TSUJI, M.D., PH.D.,* NAOKI HIRASAWA, M.D., PH.D.,*
 HIROYUKI KATO, M.D.,* TADASHI KAMADA, M.D., PH.D.,* JUNETSU MIZOE, M.D., PH.D.,*
 HIROHISA KISHI, M.D., PH.D.,† KOICHI KAMURA, M.D., PH.D.,† HITOSHI WADA, M.D., PH.D.,‡
 IEMOTO, M.D., PH.D.,§ AND HIROHIKO TSUJII, M.D., PH.D.*

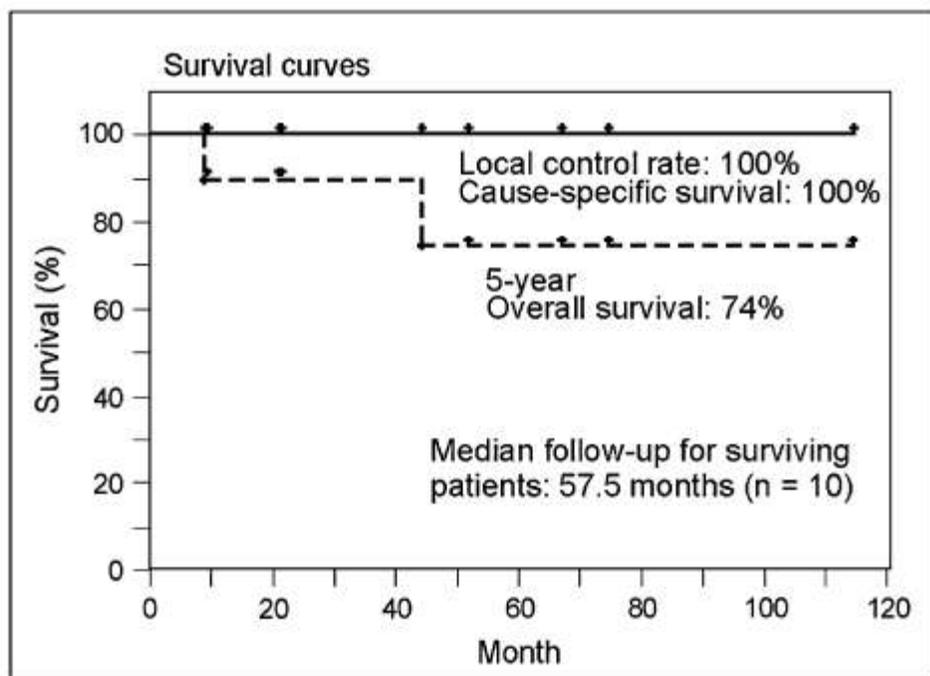


Fig. 2. Local control rate, progression-free survival rate, cause-specific survival rate, and overall survival rate in the 10 patients studied. No local failure, distant metastasis, or disease-specific death was observed in a median follow-up of 57.5 months for the surviving patients.

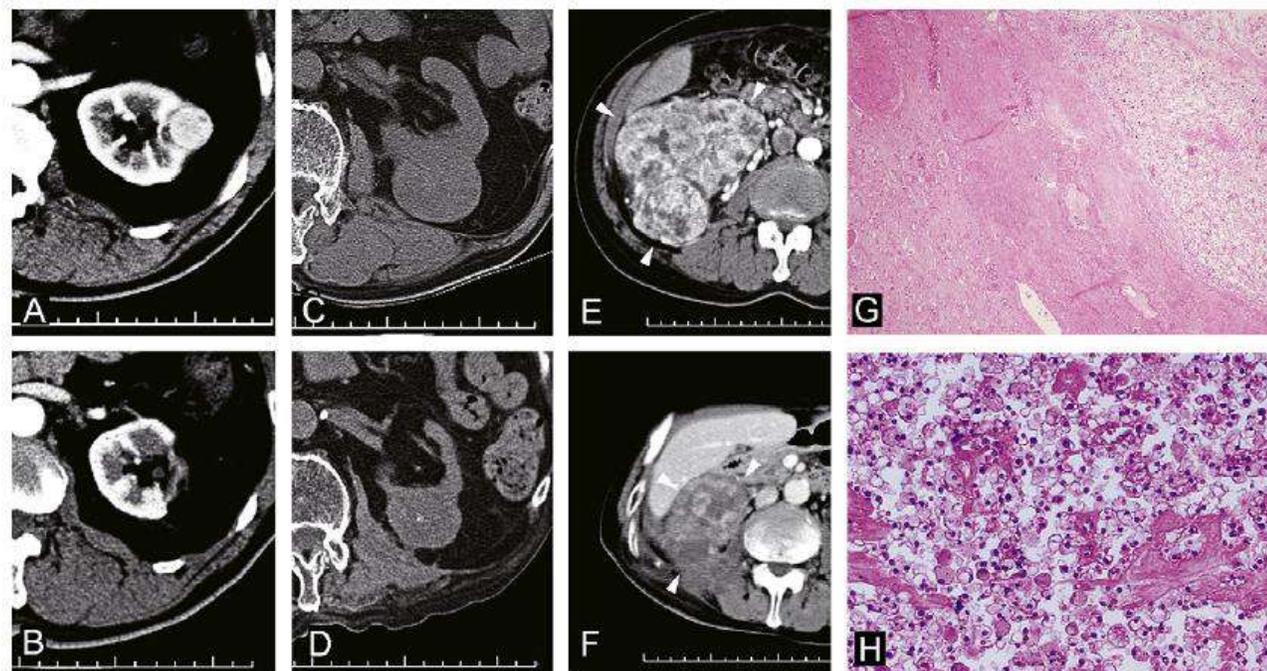


Fig. 4. (A, B) Computed tomography (CT) images before carbon ion radiotherapy (CIRT) (A) in 1 patient, and 5 years after CIRT (B) in the same patient, showing that the tumor has disappeared. (C, D) CT images before CIRT (C) and 9 years after CIRT (D) in another patient, showing that the tumor had been shrinking. Nonenhanced CT was performed because of diabetic nephropathy; this nephropathy seems to have caused renal atrophy. (E, F) CT images before CIRT (E) and 4 years after CIRT (F). This tumor, although large (white arrowheads), had been shrinking without metastasis. (G) Specimen of renal cell carcinoma (RCC) 8 months after CIRT, at low-magnification ($\times 40$). (H) Specimen of RCC 8 months after CIRT, at high magnification ($\times 200$). The specimen of treated RCC shows degenerative cancer cells with clear cytoplasm, loss of nucleus, hyaline degeneration, macrophage/lymphatic invasion, and vascular invasion.

ORIGINAL ARTICLE**Updated long-term outcomes after carbon-ion radiotherapy for primary renal cell carcinoma**

Goro Kasuya¹  | Hiroshi Tsuji¹ | Takuma Nomiya² | Hirokazu Makishima¹ | Yasuo Haruyama³ | Gen Kobashi³ | Daniel K. Ebner^{1,4} | Kazuhiko Hayashi¹  | Tokuhiko Omatsu¹ | Riwa Kishimoto¹ | Shigeo Yasuda^{1,5} | Tatsuo Igarashi^{6,7} | Mototsugu Oya⁸ | Koichiro Akakura⁹ | Hiroyoshi Suzuki¹⁰ | Tomohiko Ichikawa⁶ | Jun Shimazaki⁶ | Tadashi Kamada¹ | the Working Group for Genitourinary Tumors

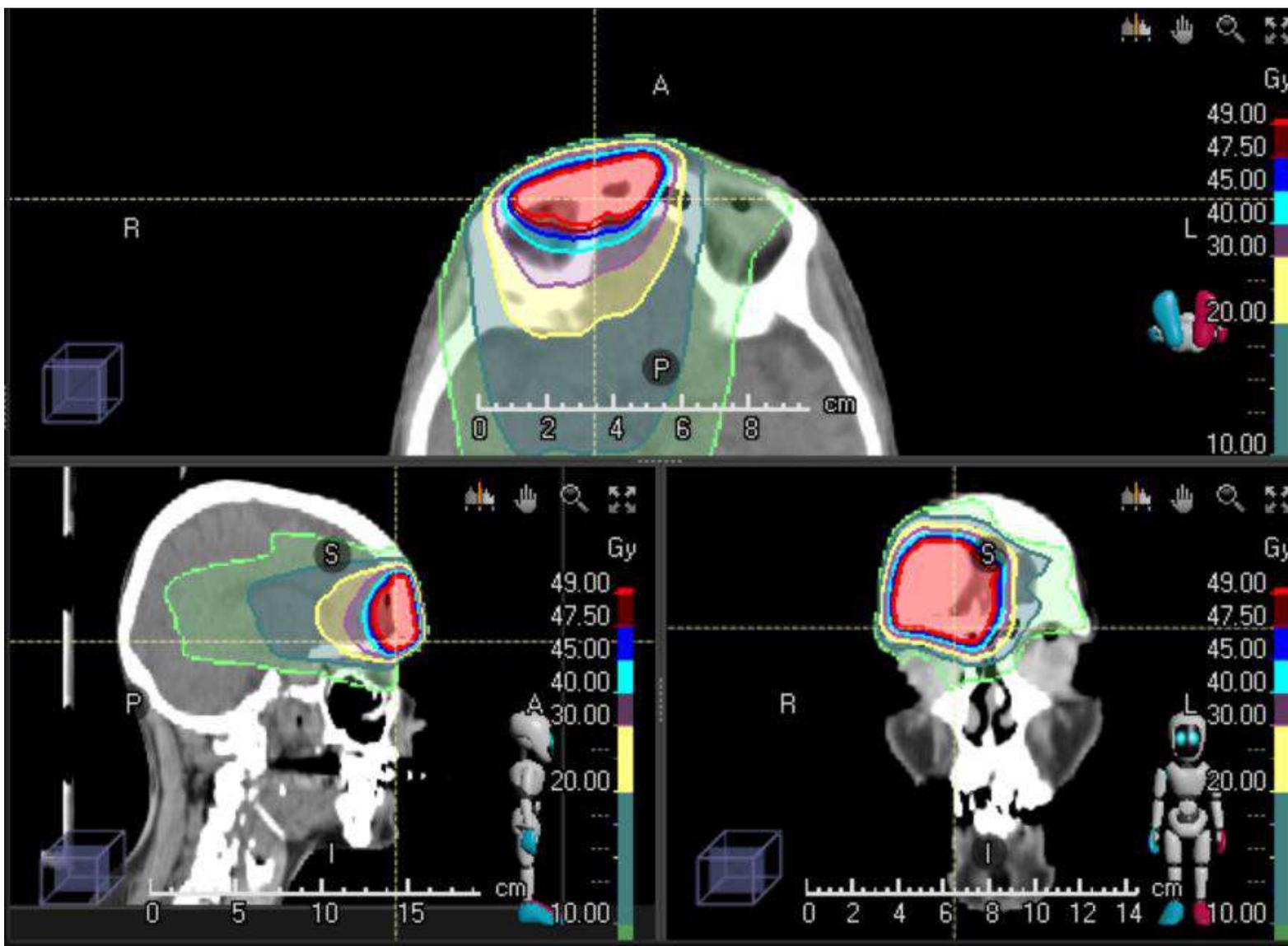
TABLE 5 Acute and late adverse events (excluding renal function) in 19 patients

	Grade					
	0	1	2	3	4	5
Acute, n						
Dermatitis	7	11	1	0	0	0
Gastrointestinal disorder	19	0	0	0	0	0
Lower urinary tract	17	2	0	0	0	0
Abdominal or flank/dorsal pain	19	0	0	0	0	0
Late, n						
Dermatitis	13	5	0	0	1	0
Gastrointestinal disorder	19	0	0	0	0	0
Lower urinary tract	19	0	0	0	0	0
Abdominal or flank/dorsal pain	17	0	2	0	0	0

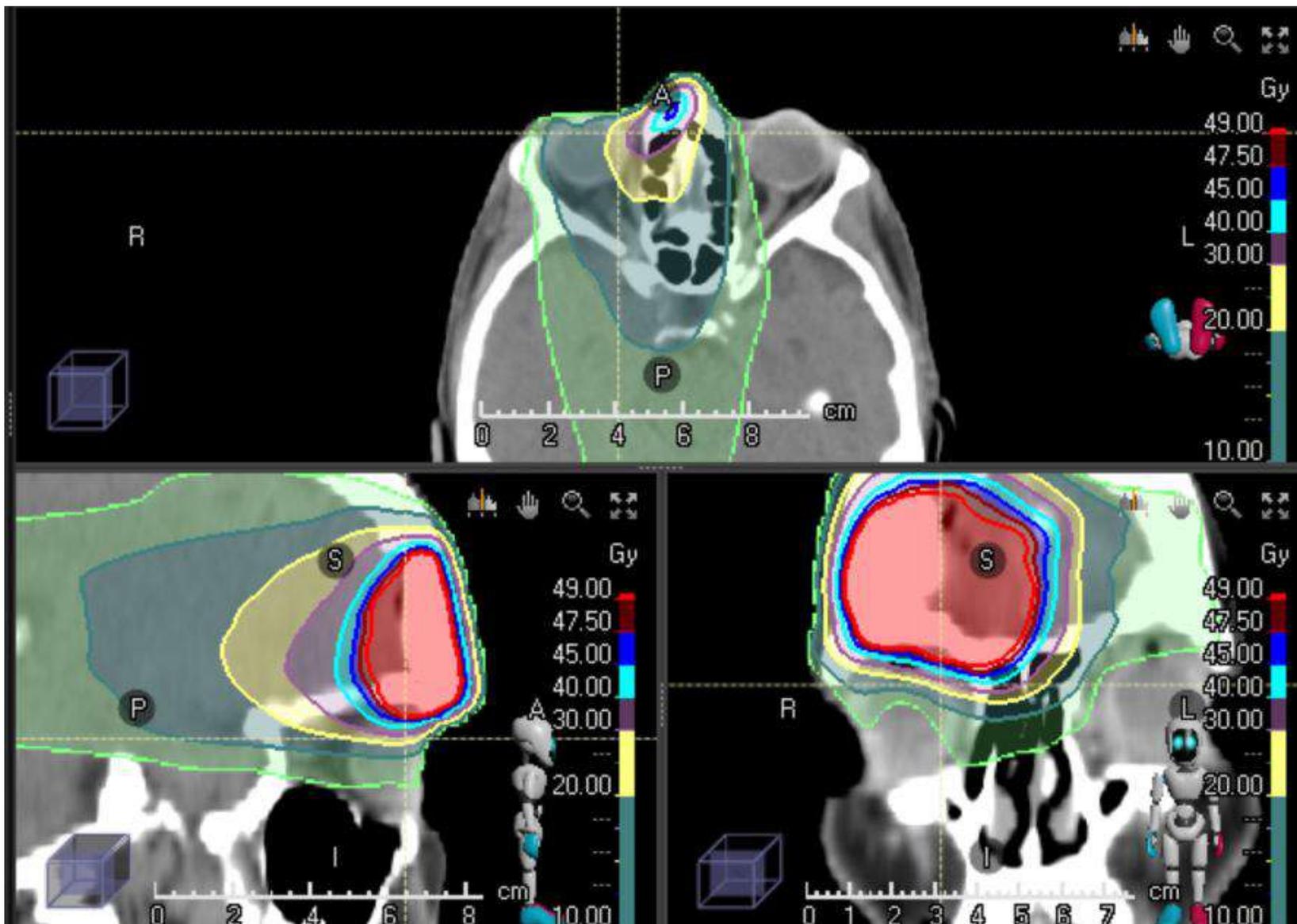
Concerning the appropriate total dose, local recurrence was observed in patients treated with BED ≤ 72 Gy (RBE)/16 fractions, but in none of the patients treated with 80 Gy (RBE) in the present

- Female 80 YO
- 2018 diagnosis of RCC with M+ in the skull
- 2018 right nephrectomy, resection of skull metastasis RT 50 Gy to the skull
- 2019 systemic therapy with Pembrolizumab +Axitinib,
- 2020 systemic therapy with Pembrolizumab and Ipilimumab
- July 2020 PD in the skull photons re-RT excluded

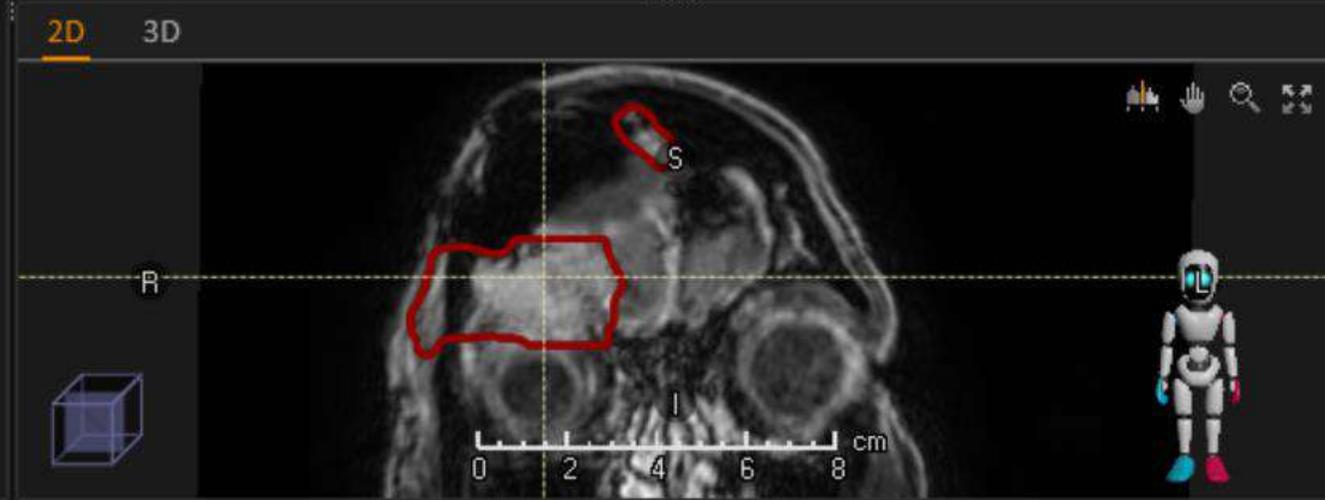
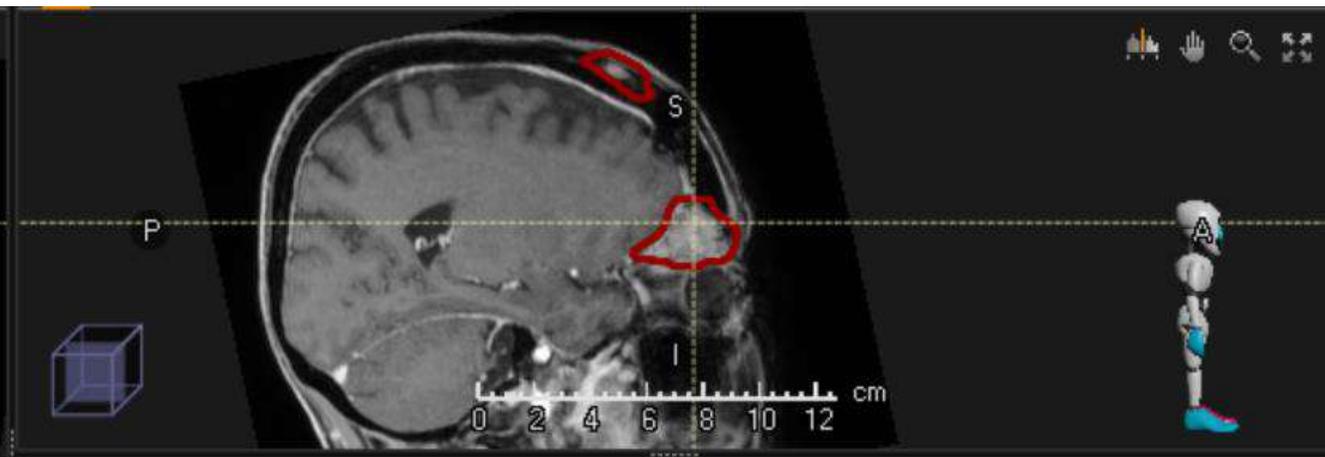
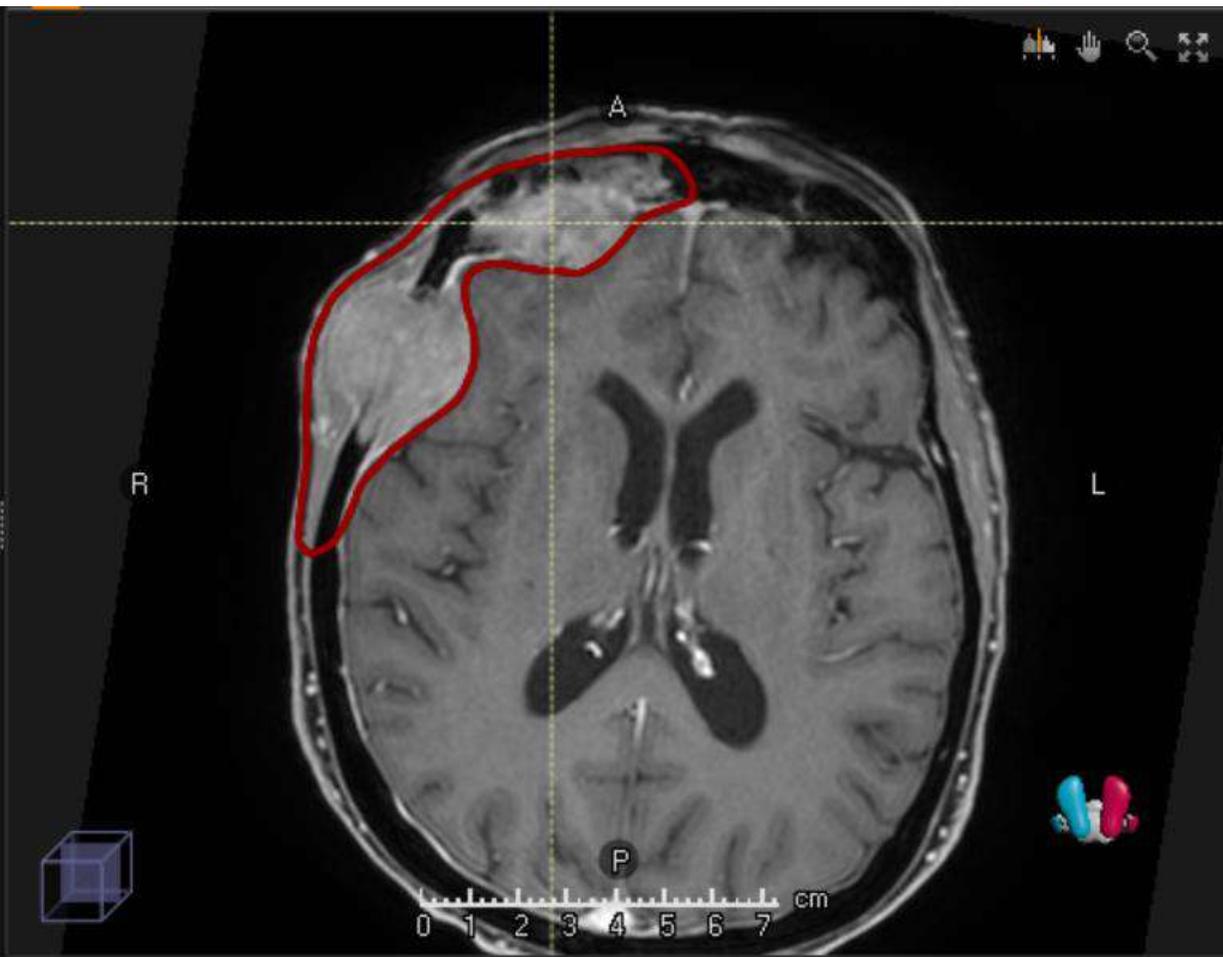
Previous RT

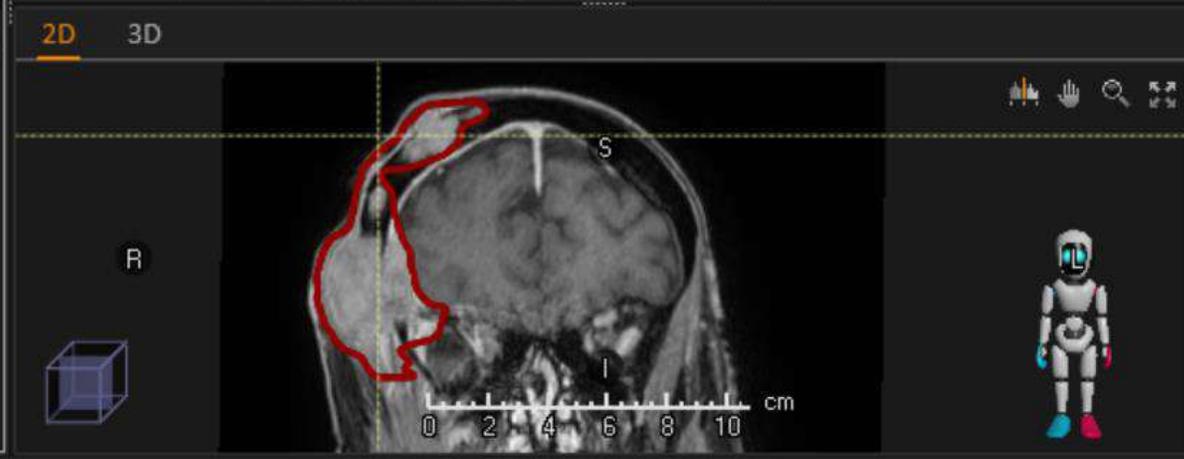
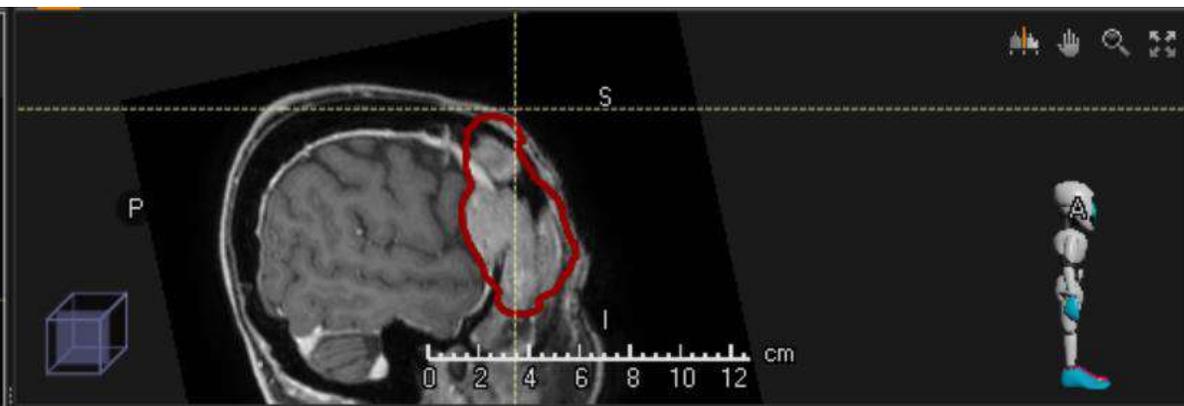
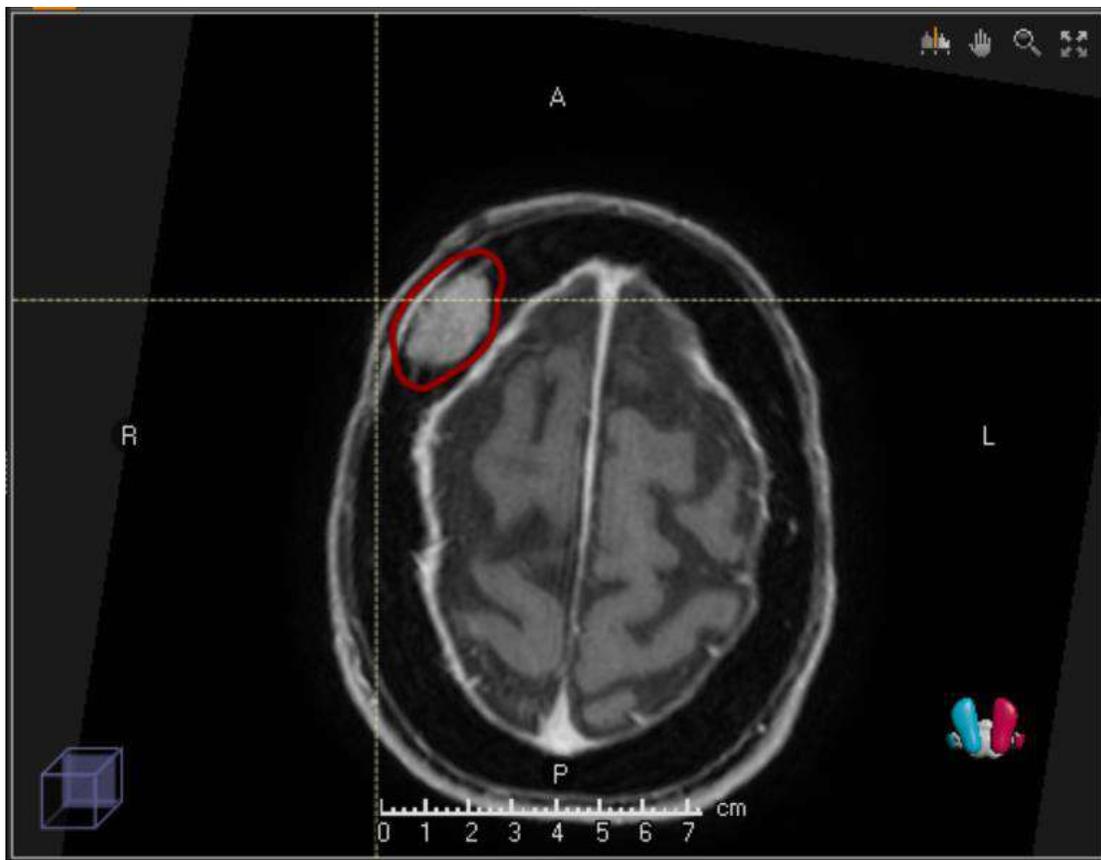


The orbit was in the gradient



Recurrence in the skull and in the orbit

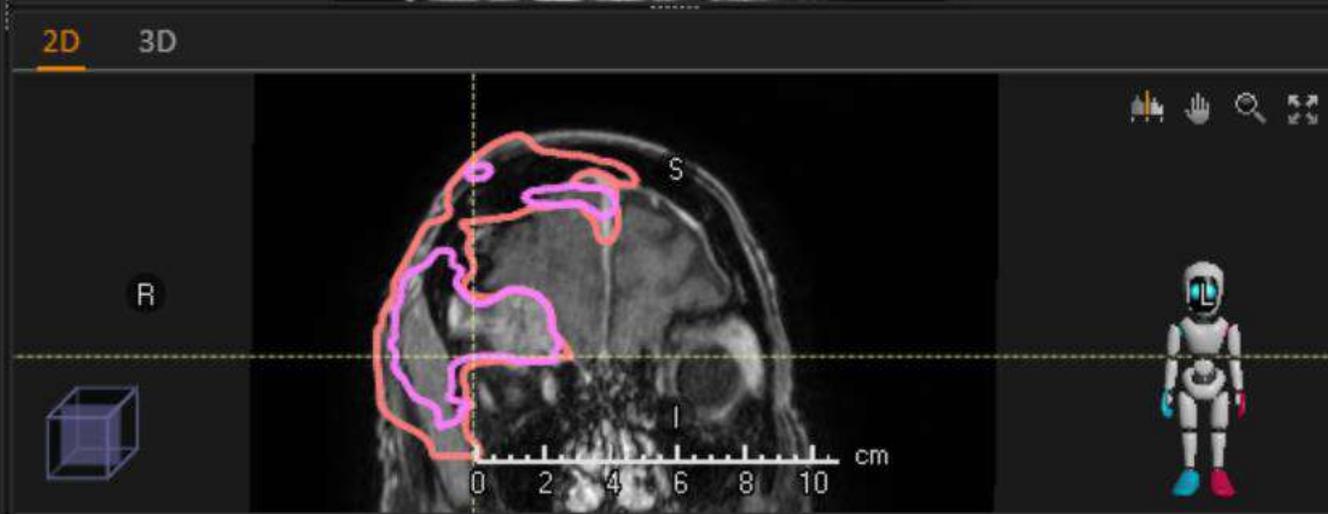
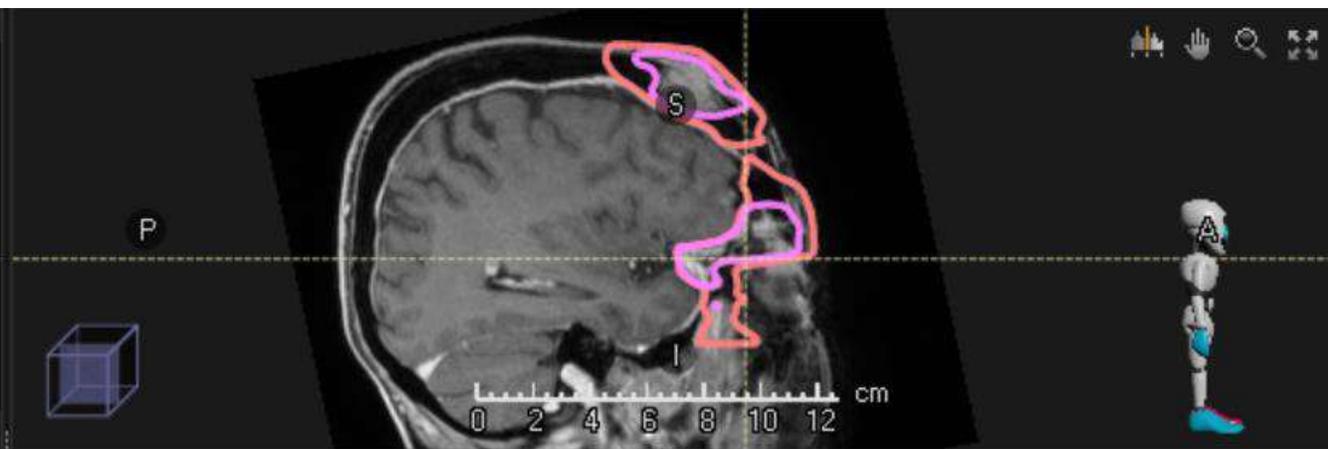
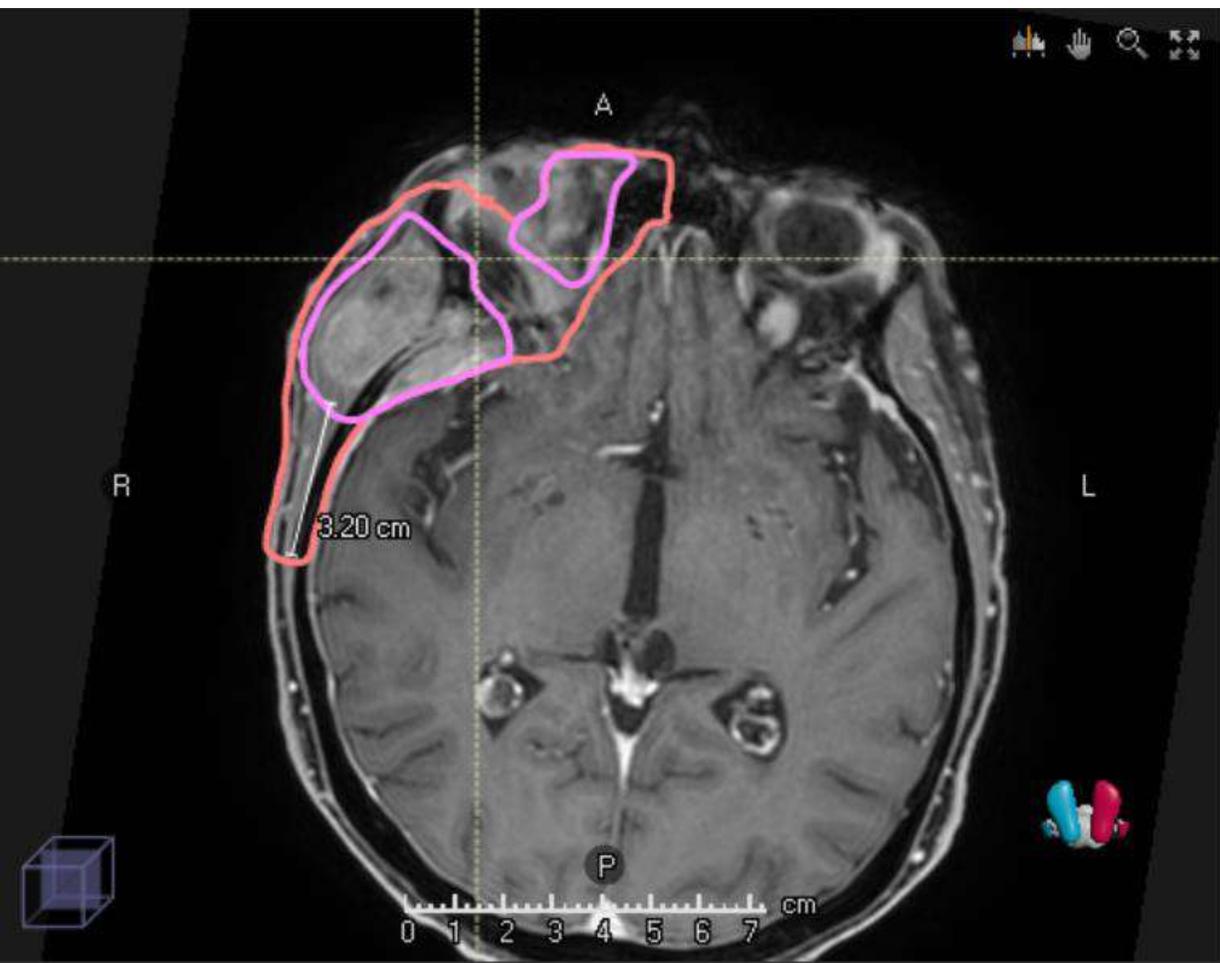




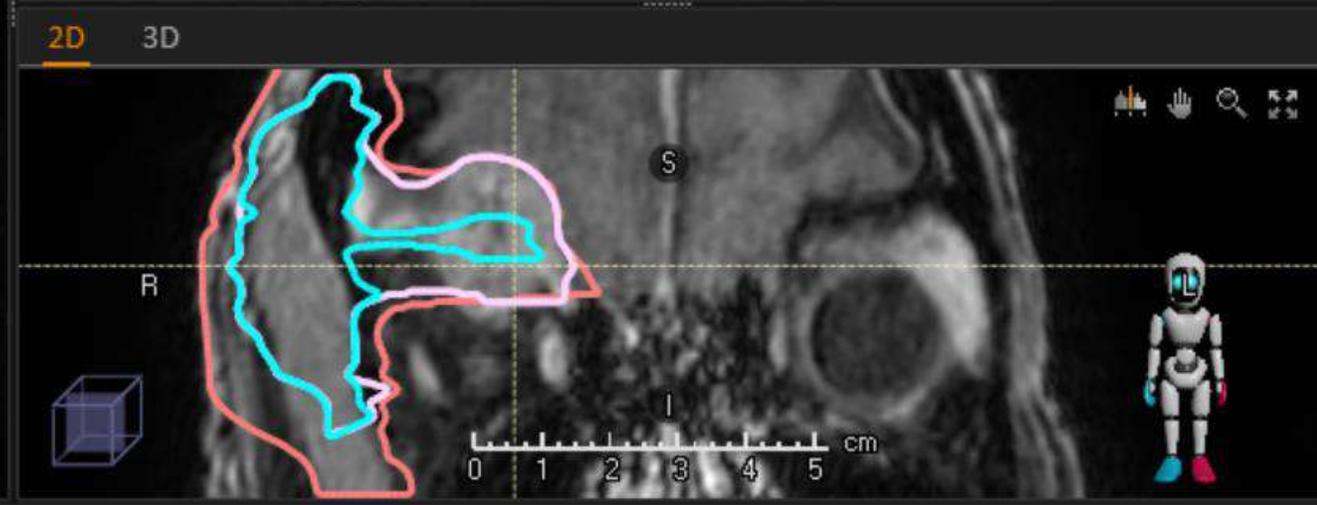
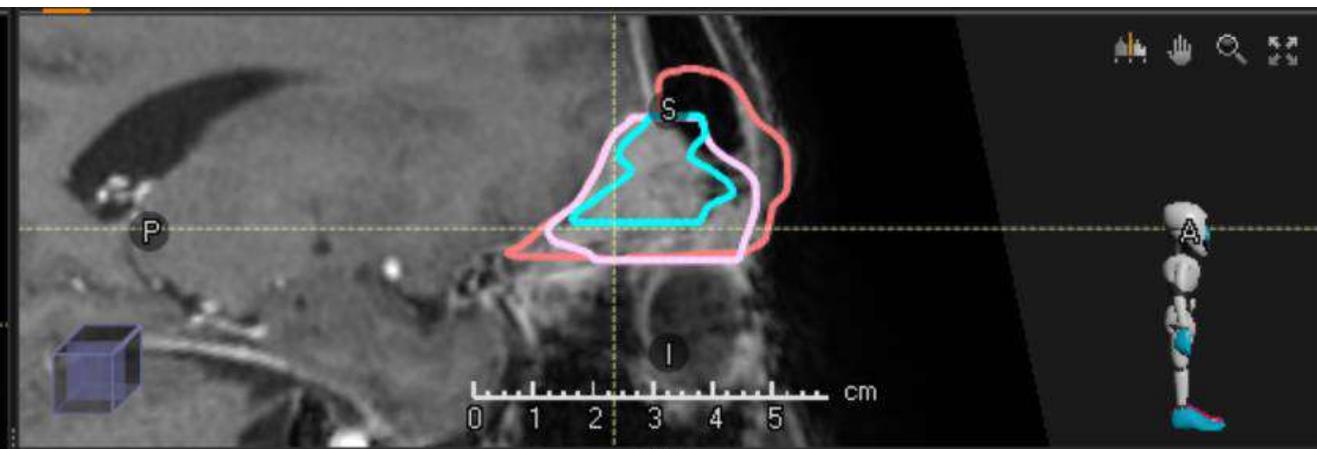
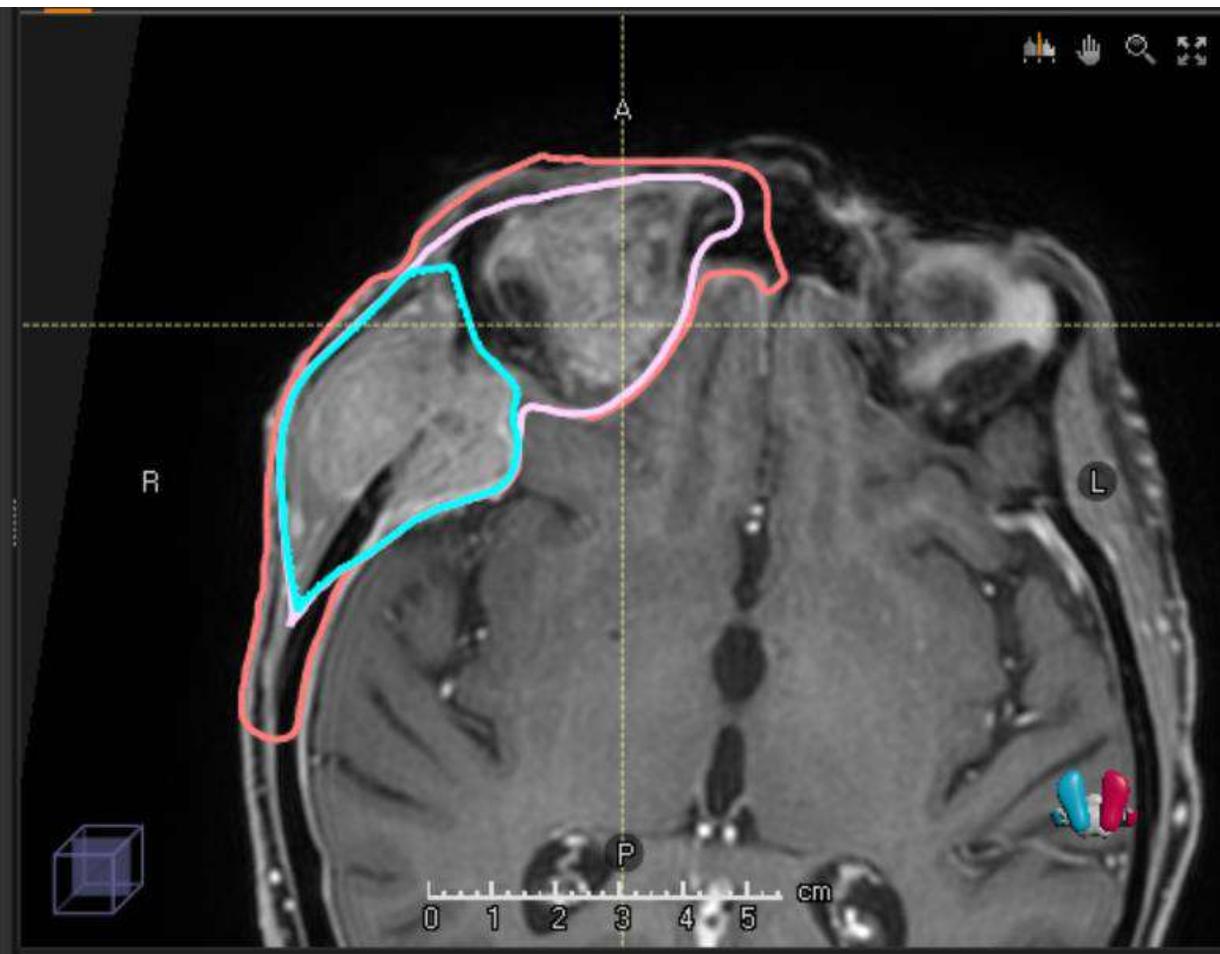
prescription

- 73.6 Gy RBE in 16 fractions of 4.6 Gy RBE over 4 weeks (4fr per week)
- PTV1 9 fr to 41.4 Gy RBE
- Sequential Boost to PTV2 with additional 3 fr to 55.2 Gy RBE
- Orbit sparing boost to PTV3 for 4 fr to 73.6 Gy RBE
- GTV = visible tumor in CT and MRI
- CTV1 = GTV + areas at risk
- CTV2 = GTV
- CTV3 = GTV minus heavily pretreated intraorbital component

CTV1 and CTV2



CTV3

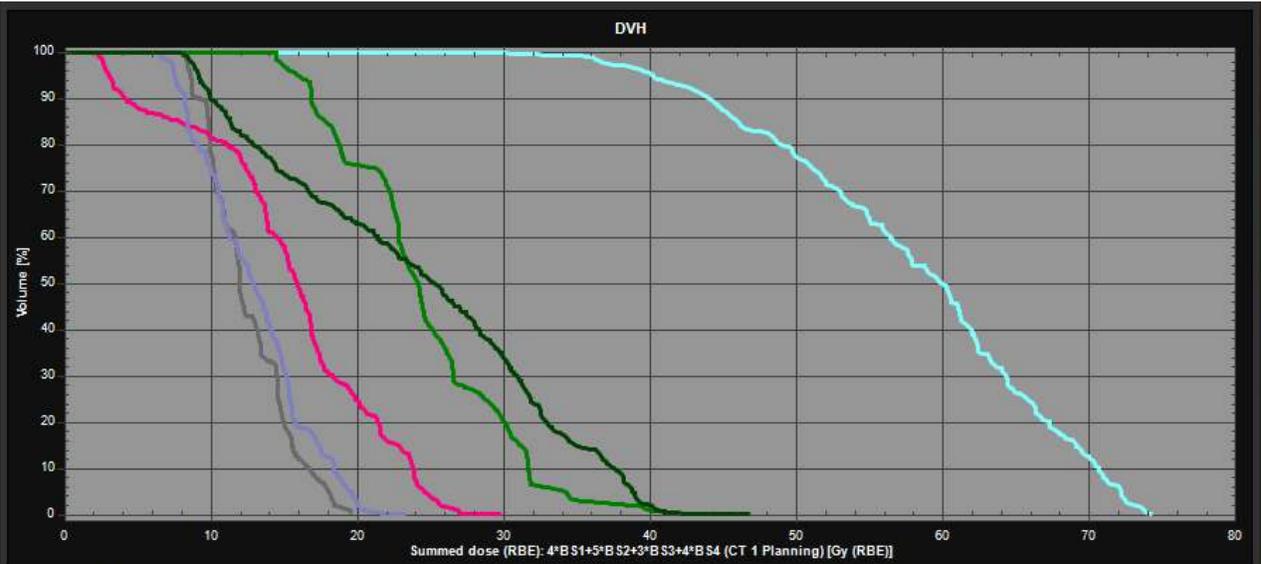
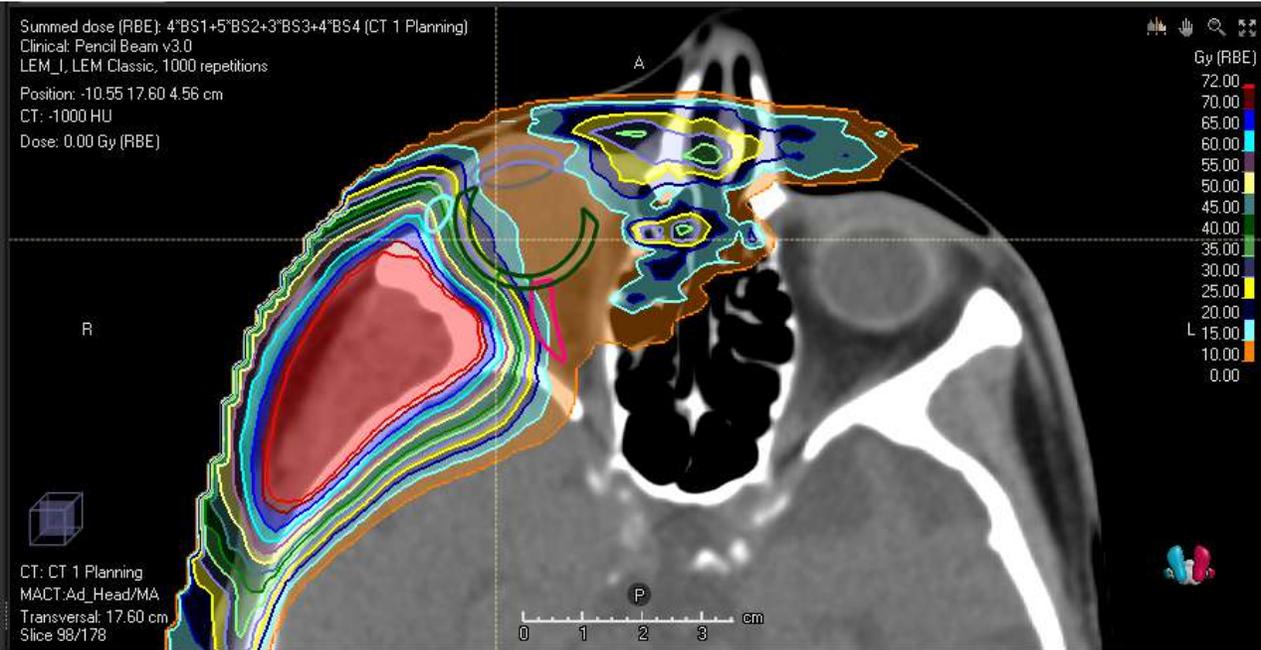


OARs constraint

- Based on previous dose

Priorisation and constraints for the whole plan

No.	Organ/target and clinical constraint	Soft	Hard	Alternative constraint/comments
1	Right optic nerve	<input type="checkbox"/>	<input type="checkbox"/>	D2% < 28 Gy RBE
1	Right eye bulb	<input type="checkbox"/>	<input type="checkbox"/>	D2% < 40 Gy RBE
1	Right cornea	<input type="checkbox"/>	<input type="checkbox"/>	D2% < 25 Gy RBE
3	brain	<input type="checkbox"/>	<input type="checkbox"/>	D1cc < 40 Gy RBE, D5cc < 35 Gy RBE
3	Frontal lobe to spare	<input type="checkbox"/>	<input type="checkbox"/>	D1cc < 30 Gy RBE, D 5 cc < 25 Gy RBE
2	GTV	<input type="checkbox"/>	<input type="checkbox"/>	D90% > 70 Gy RBE D95% > 66 Gy RBE D98% > 60 Gy RBE
4	CTV	<input type="checkbox"/>	<input type="checkbox"/>	Klicken Sie hier, um Text einzugeben.
4	PTV	<input type="checkbox"/>	<input type="checkbox"/>	Klicken Sie hier, um Text einzugeben.
1	Skin	<input type="checkbox"/>	<input type="checkbox"/>	D0,5cc(2,5sqcm) < 71 Gy RBE
3	Skin	<input type="checkbox"/>	<input type="checkbox"/>	D2cc (10 sqcm) < 66 Gy RBE D4cc (20 sqcm) < 60 GyRBE
1	eyebulbleft	<input type="checkbox"/>	<input type="checkbox"/>	D0.1% < 9 Gy RBE D3% < 5 Gy RBE

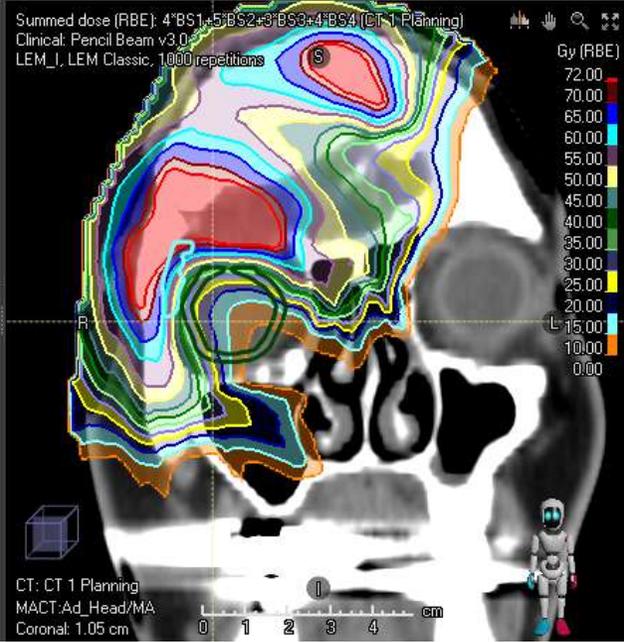
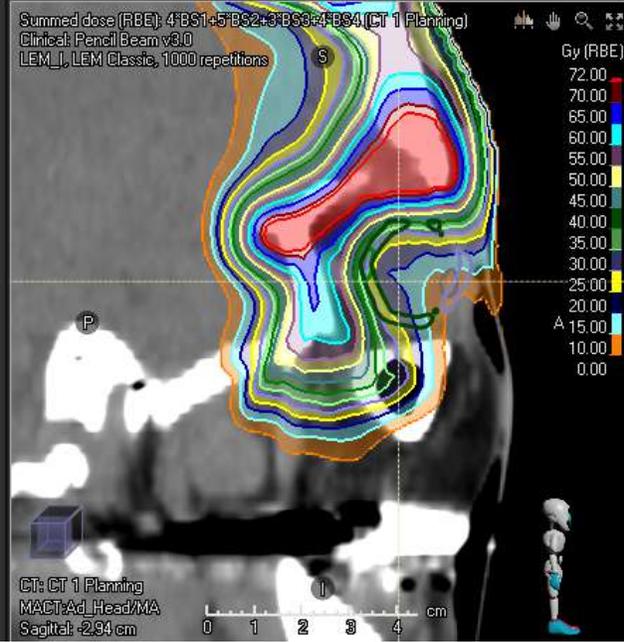


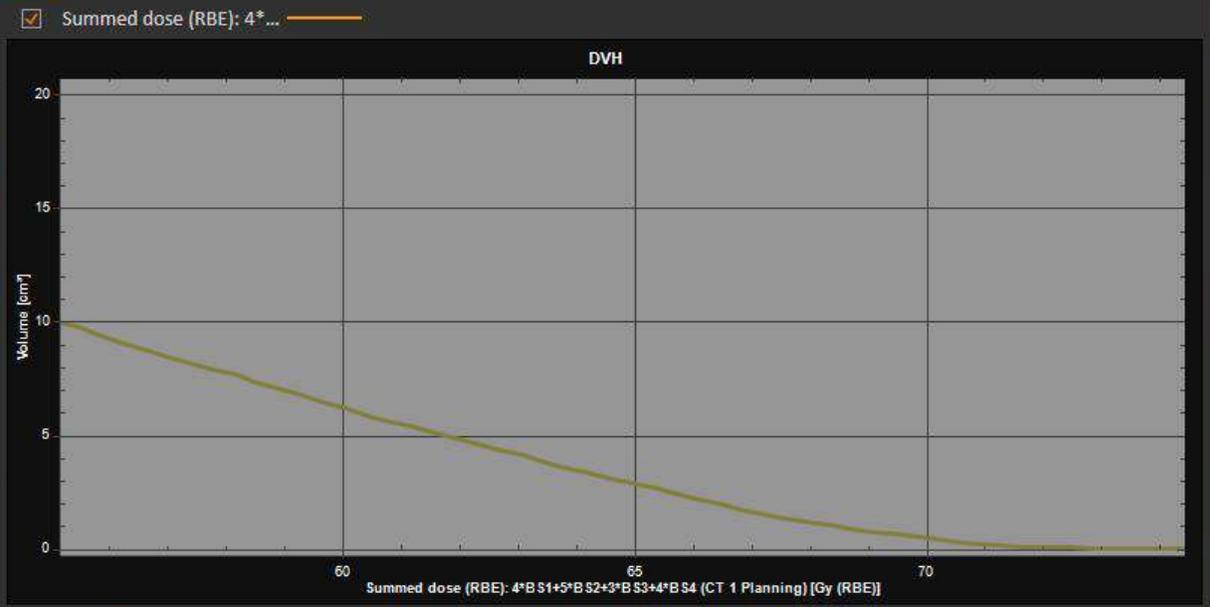
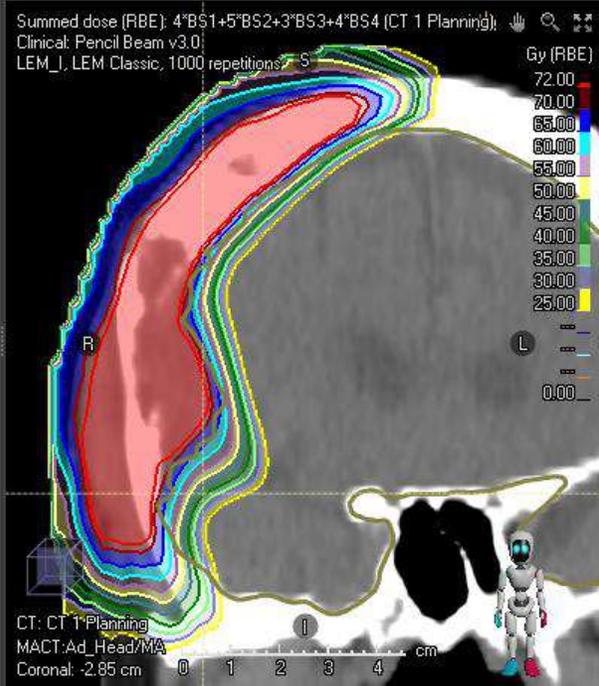
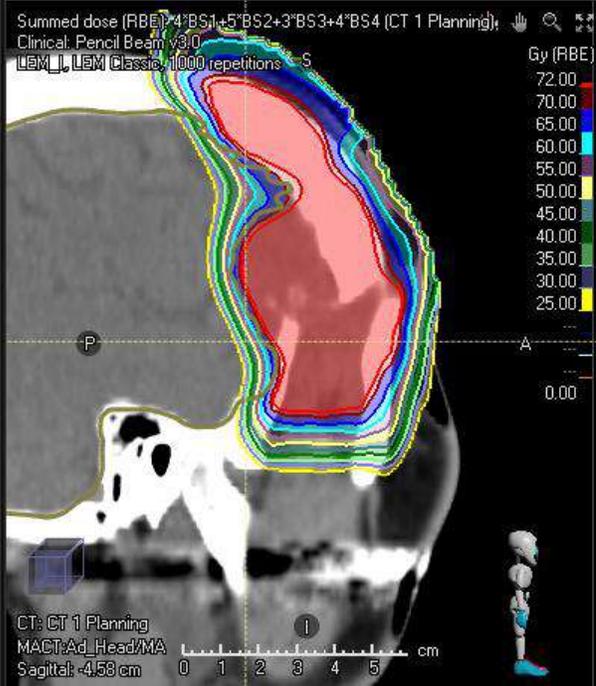
Dose axis: Absolute Relative max Relative dose [Gy (RBE)]: Volume axis: Relative Absolute

[Dose Statistics](#) [Clinical Goals](#) [Biological Response](#) [Plan Fraction Schedule](#) [Beams \(Current\)](#) [Control Points \(Current\)](#) [BEV \(Current\)](#)

ROI statistics POI statistics

Dose	ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]							% outside gr
			D99	D98	D95	Average	D50	D2	D1	
Summed dose (RBE): 4...	corneaRIGHT	0.39	6.69	7.25	7.54	12.97	12.90	20.07	20.26	0 %
Summed dose (RBE): 4...	lacrglandRIGHT	0.75	35.87	36.56	40.20	58.04	59.91	73.22	73.76	0 %
Summed dose (RBE): 4...	lensRIGHT	0.23	8.34	8.42	8.67	12.59	11.99	18.46	19.41	0 %
Summed dose (RBE): 4...	maculaRIGHT	0.10	14.53	14.68	15.97	24.47	24.20	38.38	39.90	0 %
Summed dose (RBE): 4...	opticusRIGHT	0.98	2.44	2.63	3.04	15.35	15.91	25.70	26.77	0 %
Summed dose (RBE): 4...	retinacrucialRIGHT	1.93	8.41	8.65	9.17	24.04	25.29	40.03	40.48	0 %





Beams (Current) Control Points (Current) BEV (Current)

Dose Statistics Clinical Goals Biological Response Plan Fraction Schedule

ROI statistics POI statistics

Dose	ROI	ROI vol. [cm³]	Dose [Gy (RBE)]						
			D99	D98	D95	Average	D50	D2	D1
Summed dose (RBE): 4*...	■ brain new	1312.94	0.00	0.00	0.00	3.00	0.14	39.94	51.77

ROI Matl RBE

Doses
 Eye Left
 Eye Right
 Whole Brain
 Optic Nerve
 Hippocamp
 Optic Nerve
 Hippocamp
 Lens Left
 Optic Tract I
 Ventricles
 PTV1-Brain
 PTV1-OARs
 40gy
 spare Brain
 helpBrain
 PTV2-Optic
 PTV2-OARs
 GTVuSkin
 PTV1-Brain
 PTV2-Brain
 SPARE_SKIN
 fov
 old10gy
 15gy
 20gy
 25gy
 30gy
 35gy
 45gy
 old40Gy
 PTV3-brain
 PTV3-OAR
 PTV3-OARs
 77Gy BS4

Current
 Select dose: Summed dose (RBE): 4*BS1+5*BS2+3*BS3+4*BS4 (CT 1 Planning)

Summed dose (RBE): 4*BS1+5*BS2+3*BS3+4*BS4 (CT 1 Planning)
 Clinical: Pencil Beam v3.0
 LEM_J, LEM Classic, 1000 repetitions

CT: CT 1 Planning
 MACT:Ad_Head/MA
 Transversal: 20.60 cm
 Slice 113/178

CT: CT 1 Planning
 MACT:Ad_Head/MA
 Sagittal: -3.21 cm

CT: CT 1 Planning
 MACT:Ad_Head/MA
 Coronal: -0.45 cm

DVH Dose Statistics Clinical Goals Biological Response Plan Fraction Schedule Line Dose

Summed dose (RBE): 4*...

Dose axis: Absolute Relative max Relative dose [Gy (RBE)]:

Volume axis: Relative Absolute

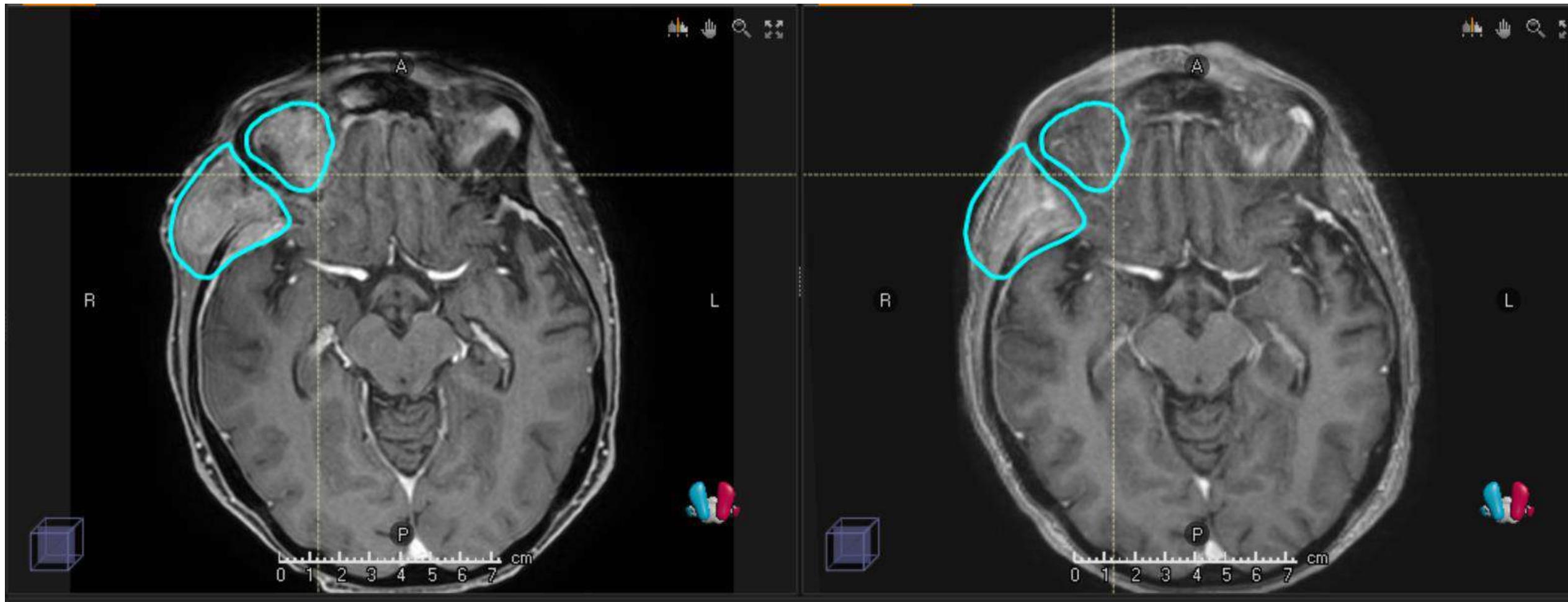
Beams (Current) Control Points (Current) BEV (Current)

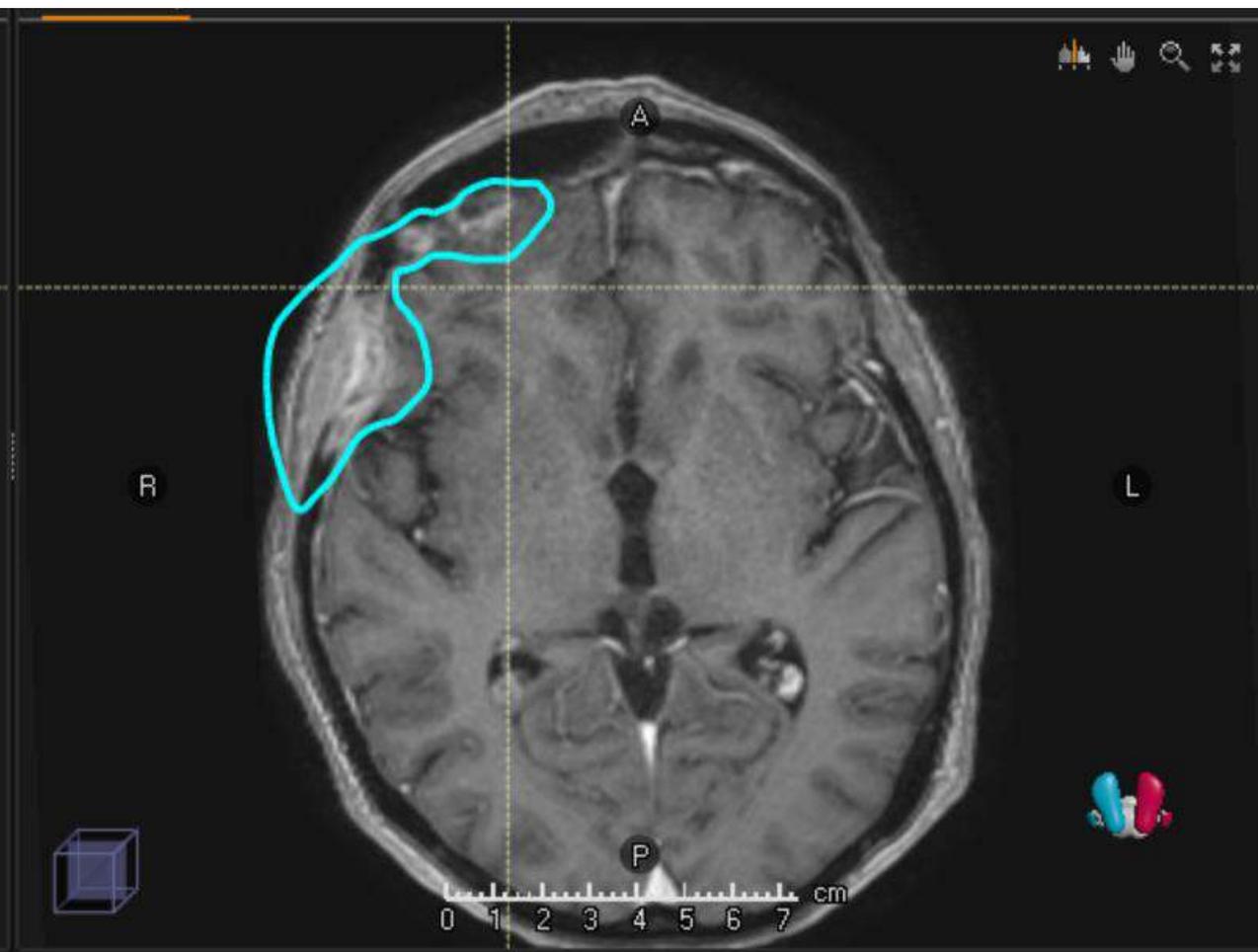
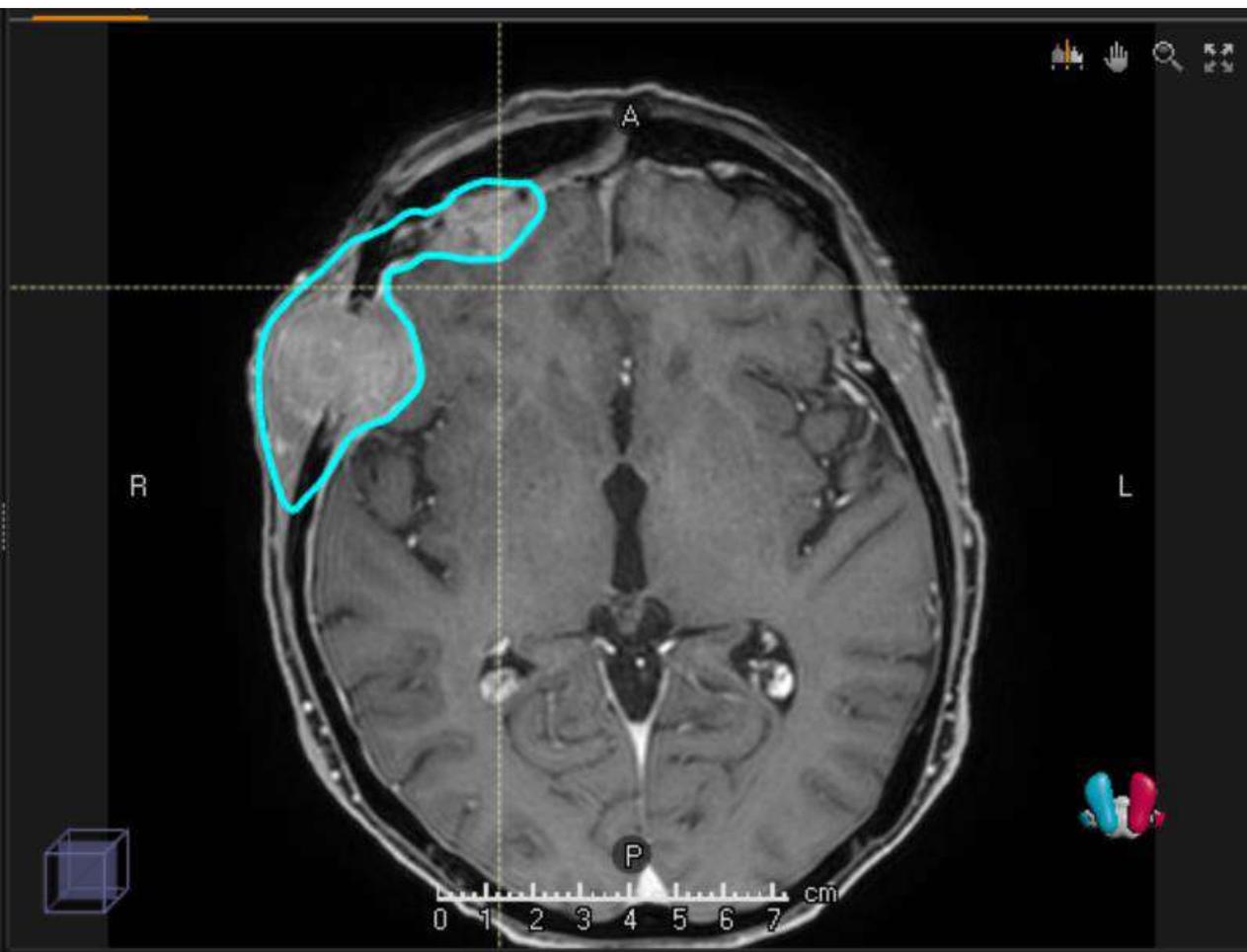
Dose Statistics Clinical Goals Biological Response Plan Fraction Schedule

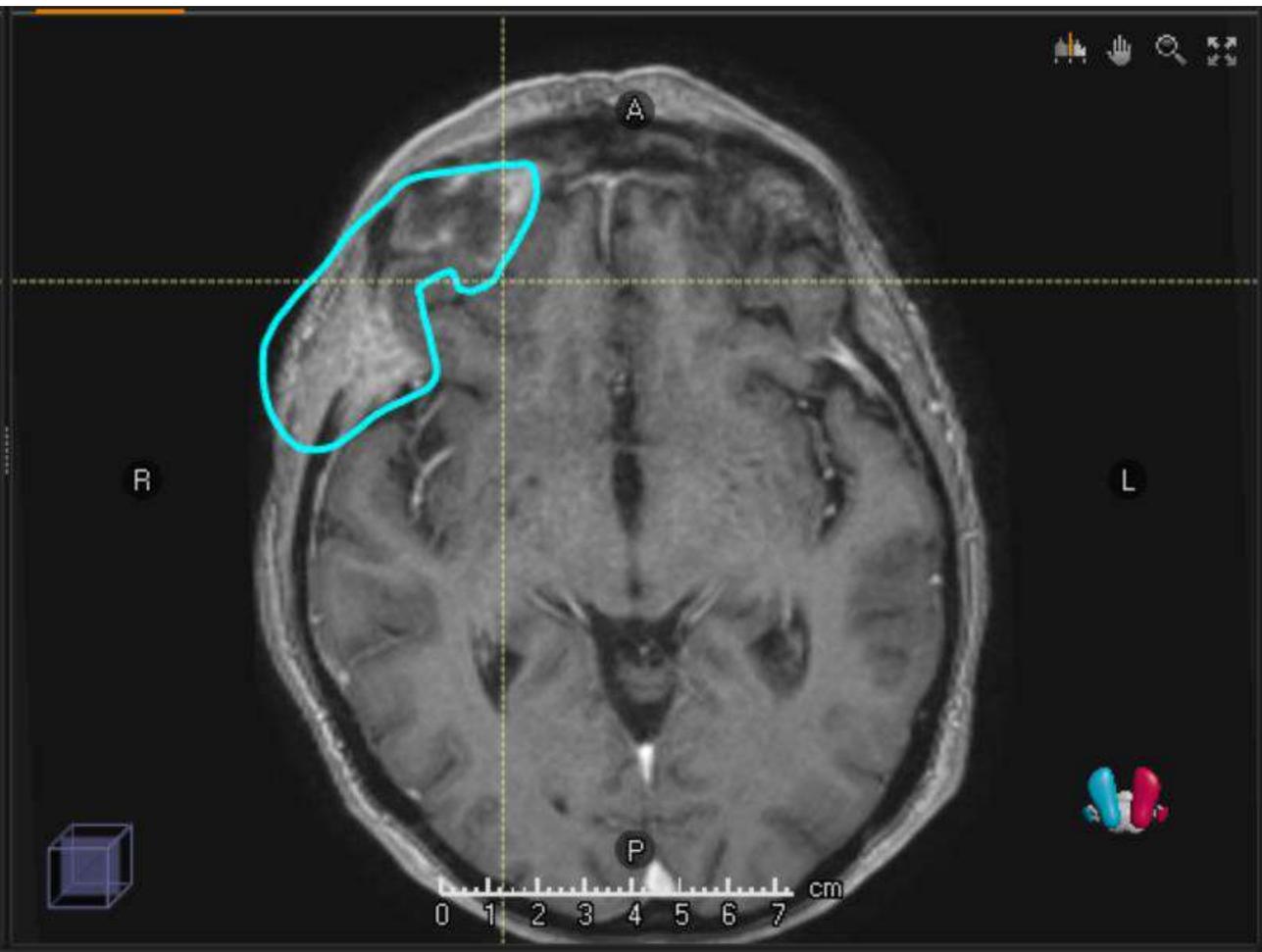
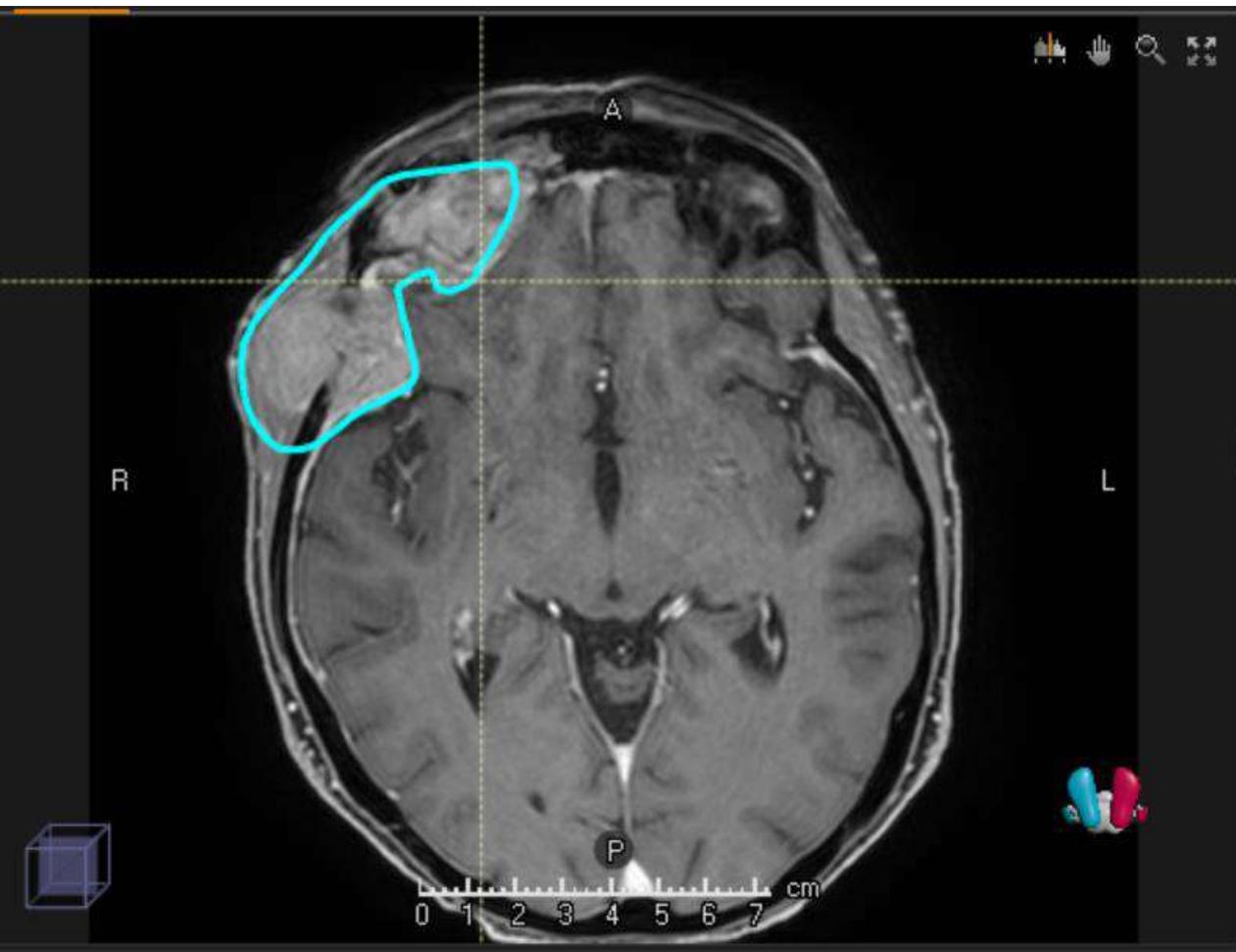
ROI statistics POI statistics

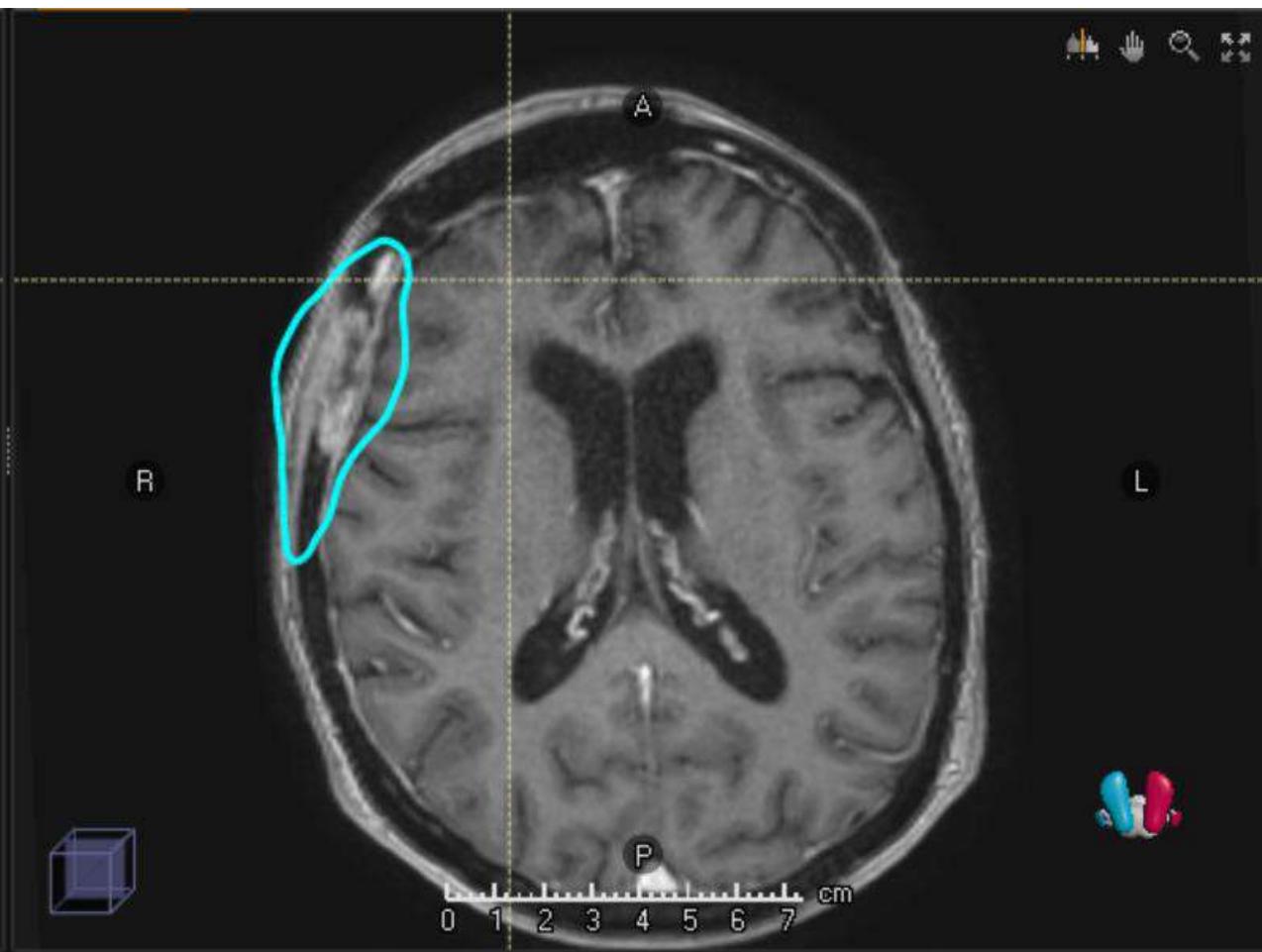
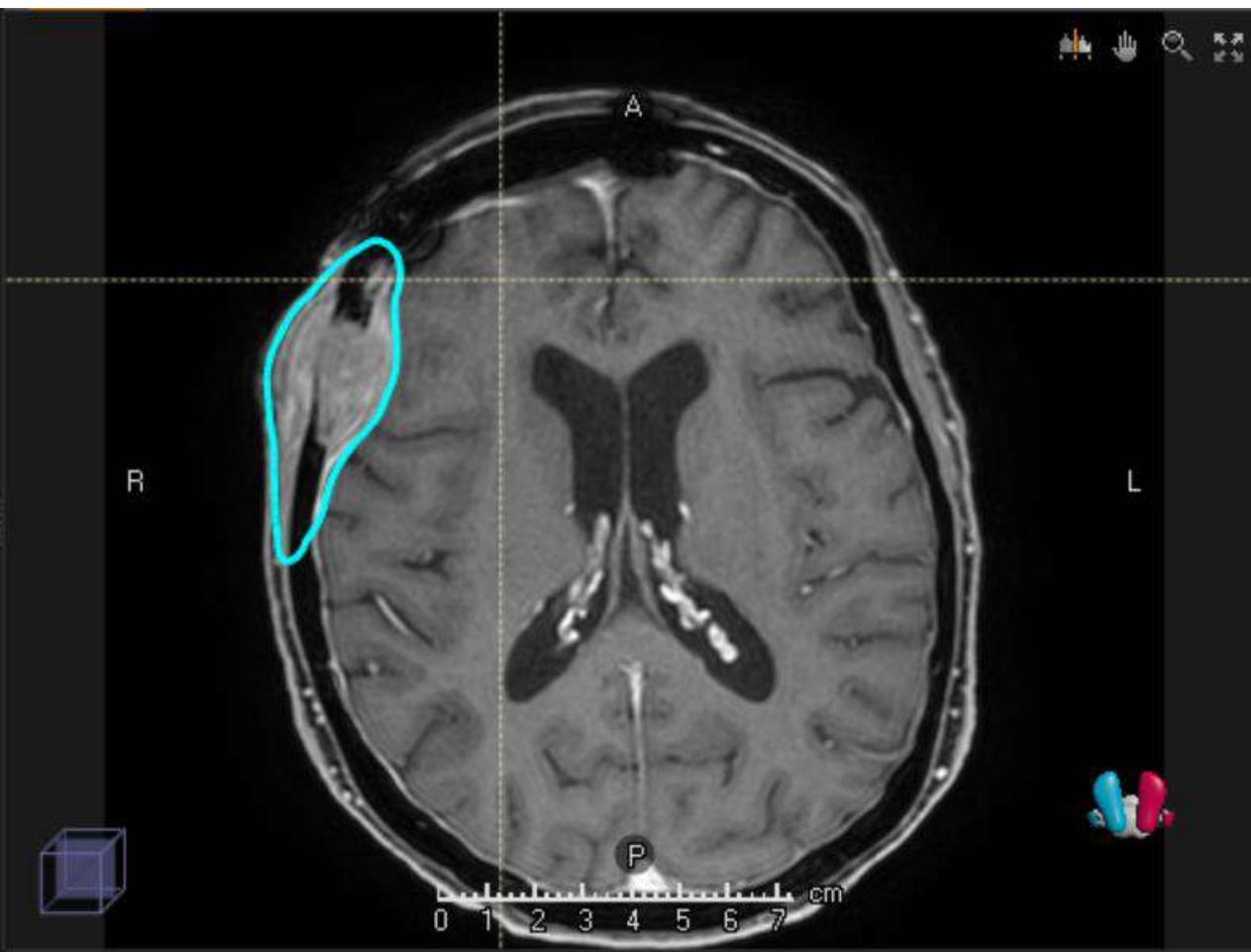
Dose	ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]						
			D99	D98	D95	Average	D50	D2	D1
Summed dose (RBE): 4...	20gy	139.87	3.56	3.89	4.67	41.25	47.64	74.64	75.02
Summed dose (RBE): 4...	25gy	105.39	4.80	5.31	6.72	45.43	52.69	74.73	75.12
Summed dose (RBE): 4...	30gy	66.52	8.09	9.49	13.71	51.60	56.33	74.82	75.15
Summed dose (RBE): 4...	35gy	42.25	12.18	14.48	20.94	55.22	57.63	74.89	75.19
Summed dose (RBE): 4...	brain new	1312.94	0.00	0.00	0.00	3.00	0.14	39.94	51.77

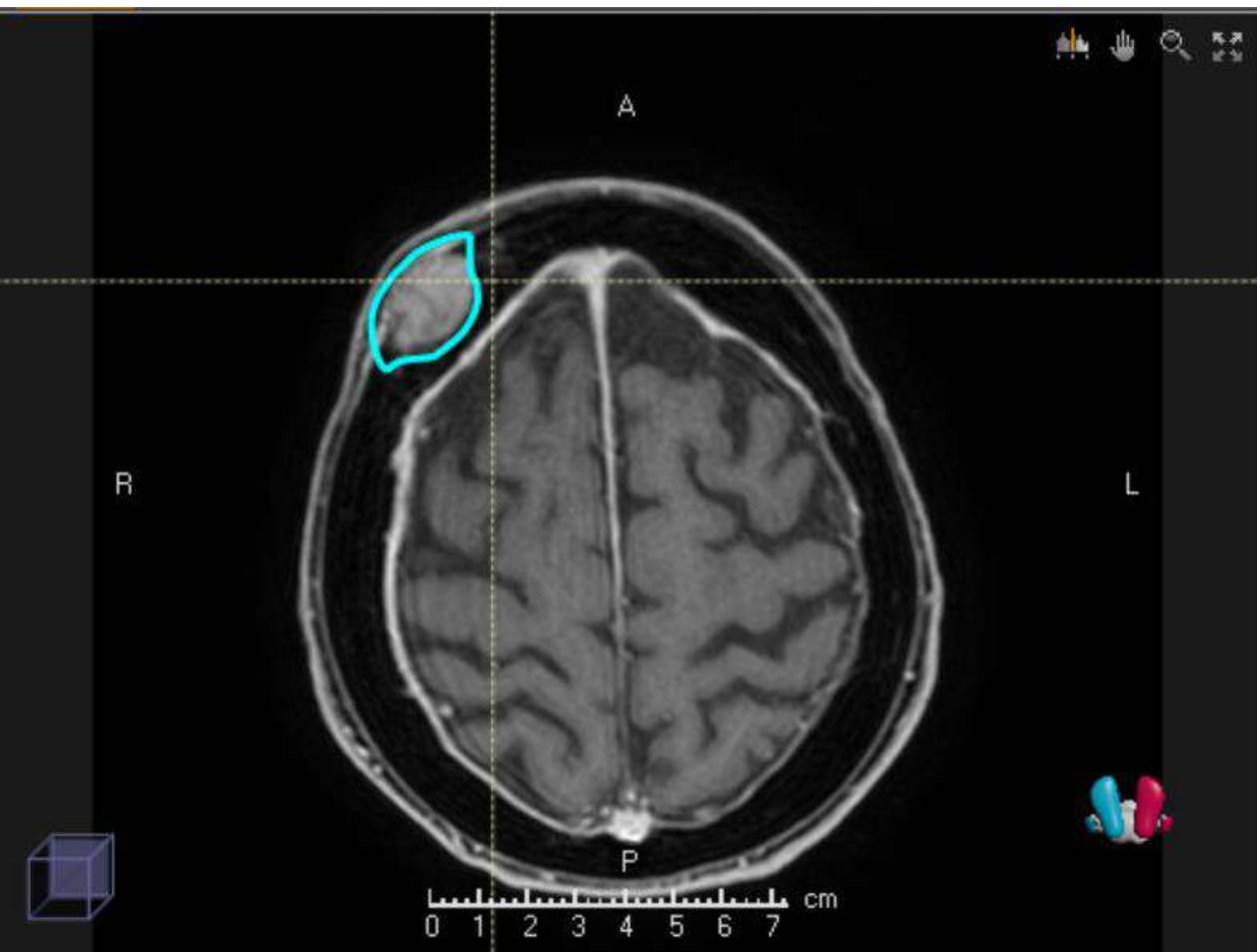
Response at 6 months (Tox G0)











Dose constraints in H&N: Optic Pathways

Fractionation	Safe constraint	Low-to-medium risk (used only for one optic nerve sparing chiasm and contralateral nerve)	Medium-to-high risk (used only for one optic nerve sparing chiasm and contralateral nerve)
Japanese fractionation	D1% < 50 Gy RBE (LEM)	D1% < 54 Gy RBE (LEM)	D1% < 57 Gy RBE (LEM)
	D20% < 40 Gy RBE (LEM)	D20% < 40 Gy RBE (LEM)	D20% < 40 Gy RBE (LEM)
German Fractionation	D1% < 54 Gy RBE (LEM)	D1% < 57 Gy RBE (LEM)	D1% < 60 Gy RBE (LEM)

Dose constraints in H&N: Brainstem

Fractionation	Safe constraint
Japanese fractionation	D0.1cc < 46 Gy RBE (LEM)
	D0.7cc < 38 Gy RBE (LEM)
German Fractionation	D2% < 50 Gy RBE (LEM)
	Dmax < 54 Gy RBE (LEM)

- RBE in carbon ions varies with different factors
 - Sophisticated mathematical models needed for biological dose estimations
- Two models are applied worldwide
 - Microdosimetric kinetic model (MKM)
 - Local effect model (LEM)
- MedAustron
 - Planning based on LEM RBE model
 - Combined with information from clinical evidence collected in MKM

WHY DO WE NEED TRANSLATIONS?

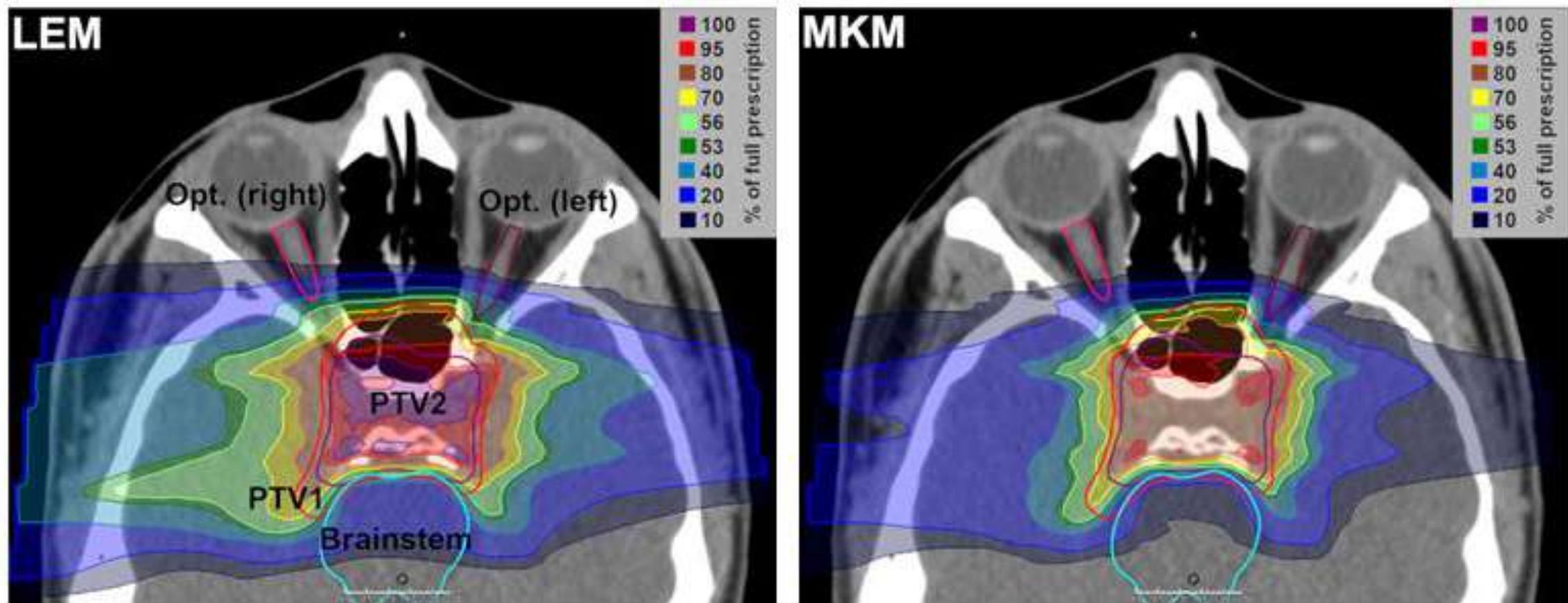


Figure: Comparison of a LEM-optimized treatment plan and its recalculation to MKM. PTV1 was prescribed to 56% of full dose.

- Ratio LEM/MKM approaches 1 with increasing LEM dose
- For low doses, LEM clearly exceeds MKM
 - Also increased variation
- Relevant area for investigated OARs was 30-50 Gy
 - Some data points have ratio which is almost 1/below 1

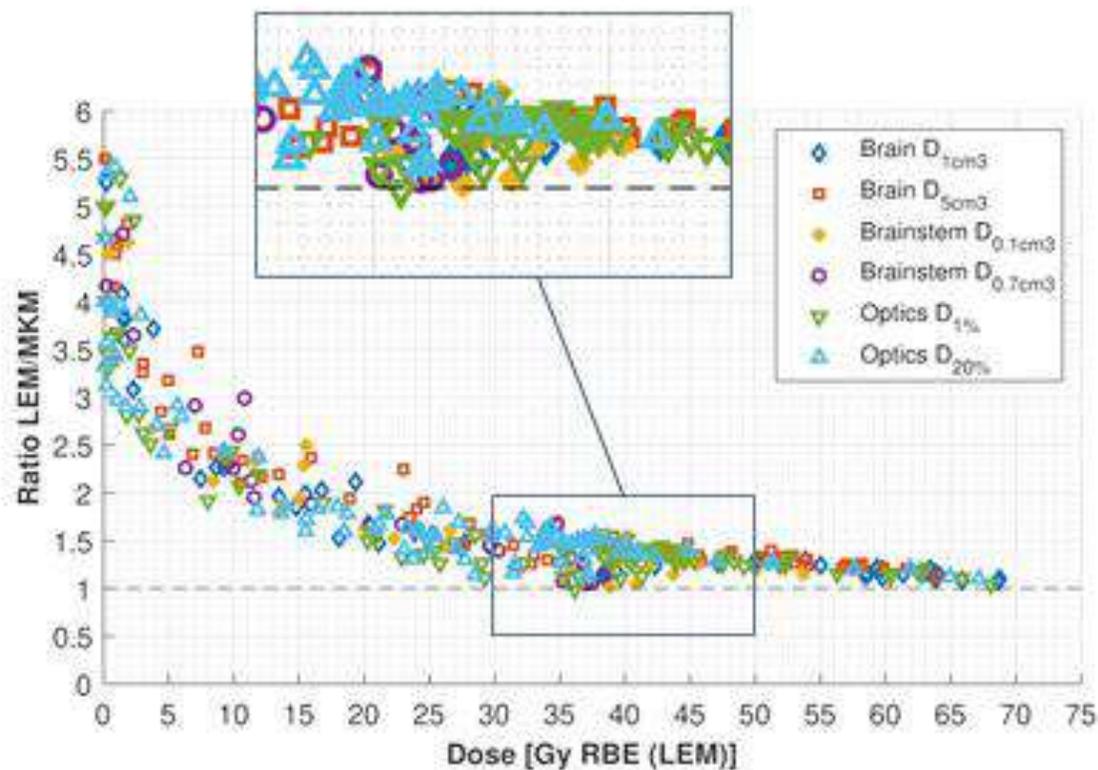


Figure: Ratio LEM/MKM for all extracted dose points.

RESULTS

- Brainstem: increased spread for data points in the dose area around 40 Gy RBE (LEM)
 - Comparably large 95% CI = higher uncertainty
- Points are located directly at or outside upper 95% CI
 - LEM constraint fulfilled ($D_{0.7\text{cm}^3} < 38$ Gy RBE)
 - MKM constraint exceeded ($D_{0.7\text{cm}^3} < 30$ Gy RBE)

Patient		$D_{0.1\text{cm}^3}$	$D_{0.7\text{cm}^3}$
Pat1	LEM	37.51	35.23
	MKM	35.22	32.79
Pat9	LEM	38.78	36.97
	MKM	38.06	35.25
Pat142	LEM	40.83	37.43
	MKM	38.84	35.43

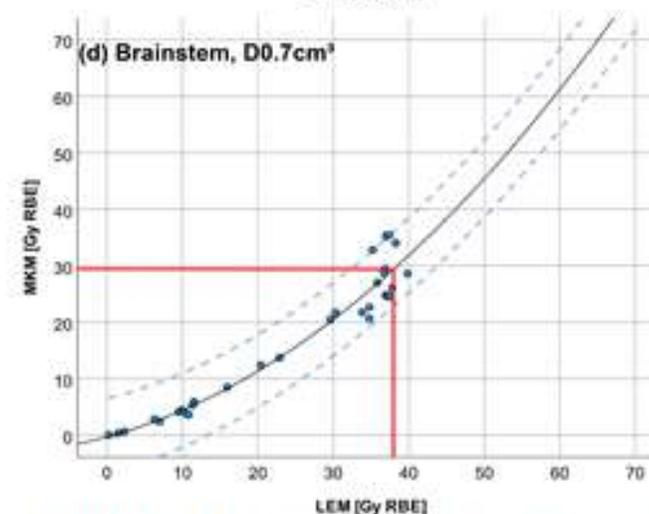
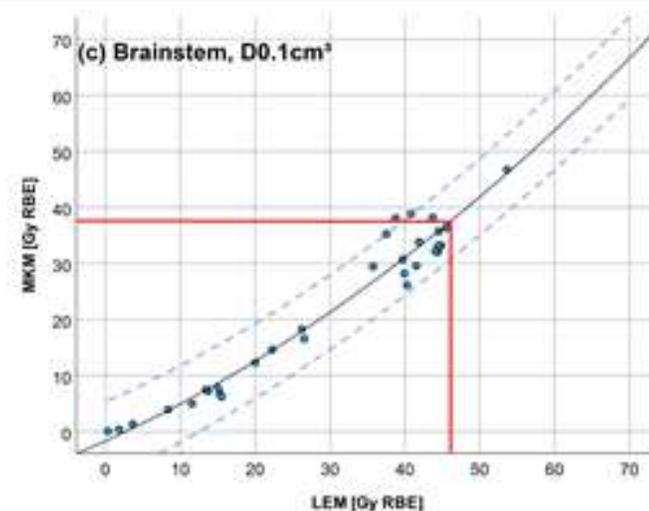


Figure: LEM vs. MKM translation curves for the brainstem

OUTLIER ANALYSIS: PAT9

- Brainstem dose statistics
 - $D_{0.1\text{cm}^3}$: 38.78 LEM vs. 38.06 MKM
 - $D_{0.7\text{cm}^3}$: 36.96 LEM vs. **35.25 MKM**
- LEM constraints are met, but MKM is exceeded
- Overlap between brainstem and PTV1
 - Areas exist where LEM and MKM are almost equal = critical regions

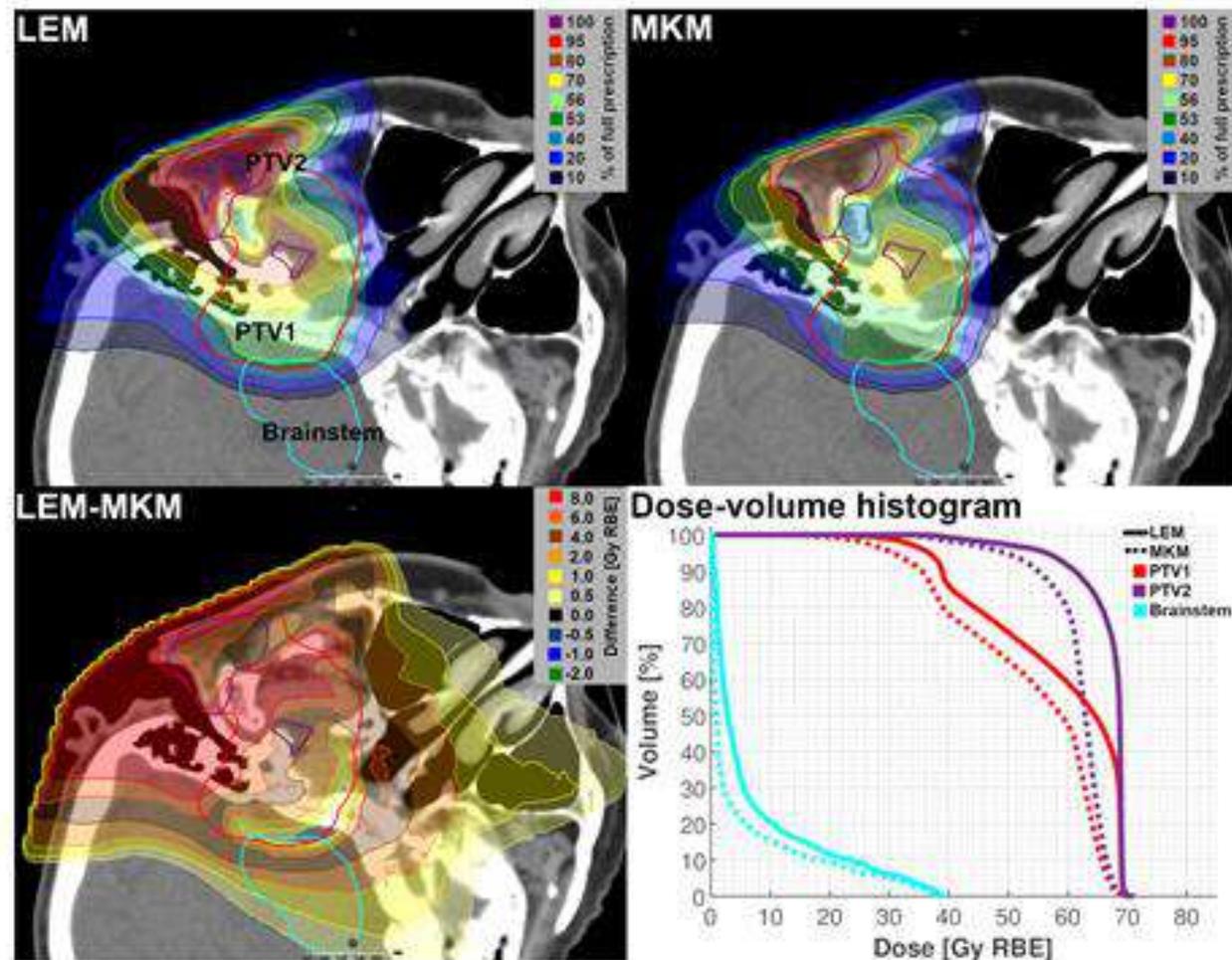


Figure: Screenshots of LEM/MKM/difference and DVH for pat9

COMPARISON STANDARD VS. OUTLIER

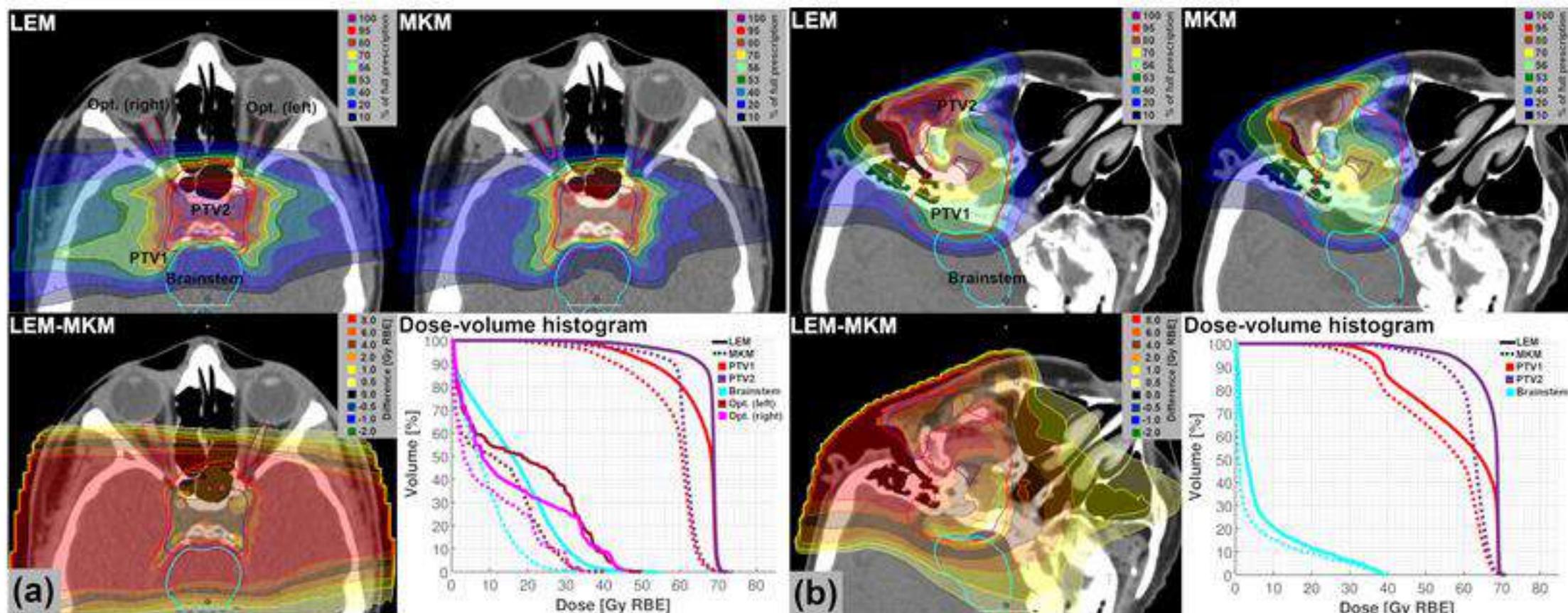


Figure: Standard case for behaviour of LEM and MKM distribution (a, pat167) compared to outlier case (b, pat9).

BLOCKING VS. CONSTRAINTS

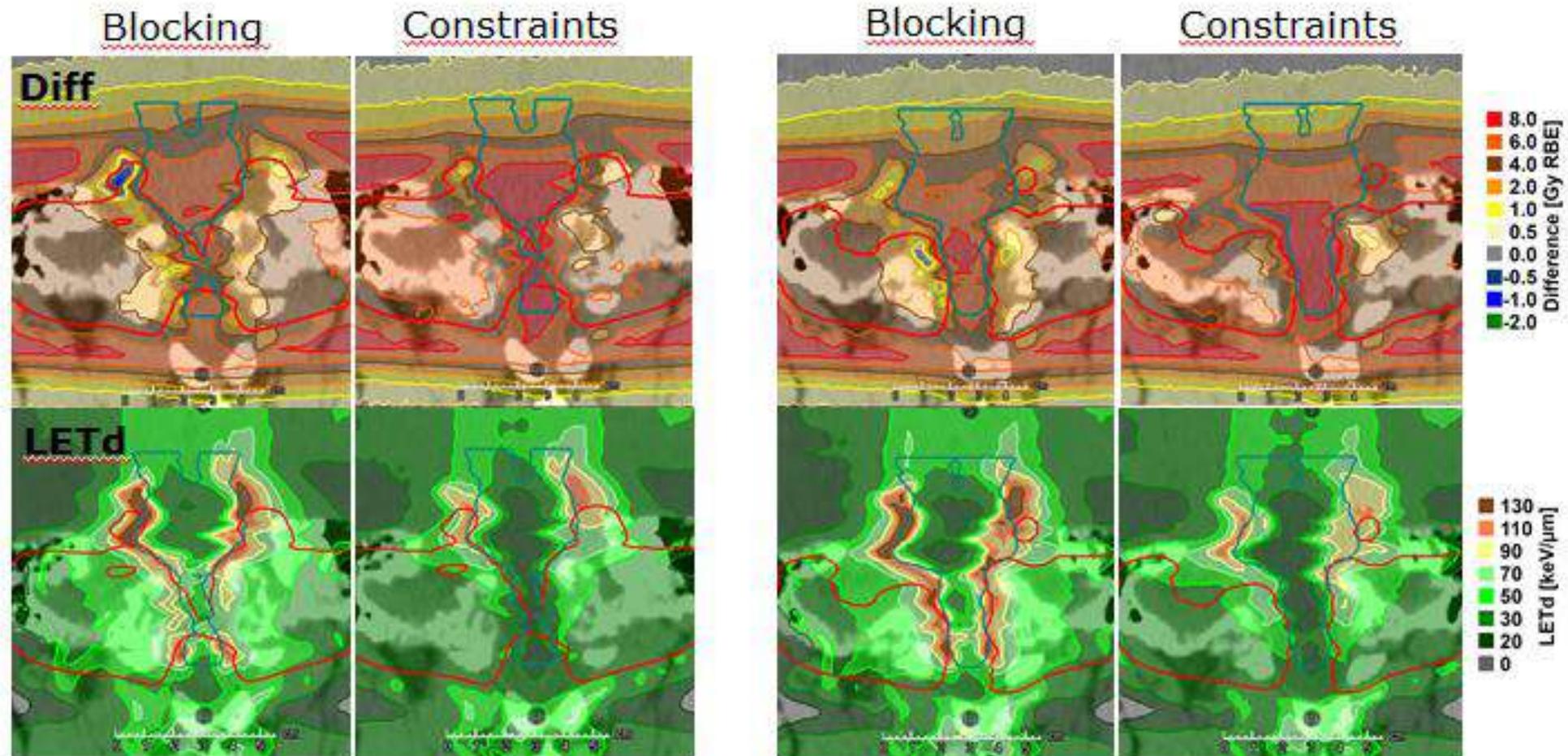


Figure: Blocking vs. constraints in terms of differences LEM-MKM and LETd distribution for two different slices of the CT.

BLOCKING VS. CONSTRAINTS

- Same setting as before, but now emphasis on the bulbus left
 - $180^{\circ}+360^{\circ}$ beam
 - Either blocked by bulbus or several constraints on bulbus to achieve same DVH

Figure: LEM, MKM, difference LEM-MKM and LETd for equivalent plans with blocking or constraints on the left bulbus for two individual slices.

