Clinical considerations for hadron therapy

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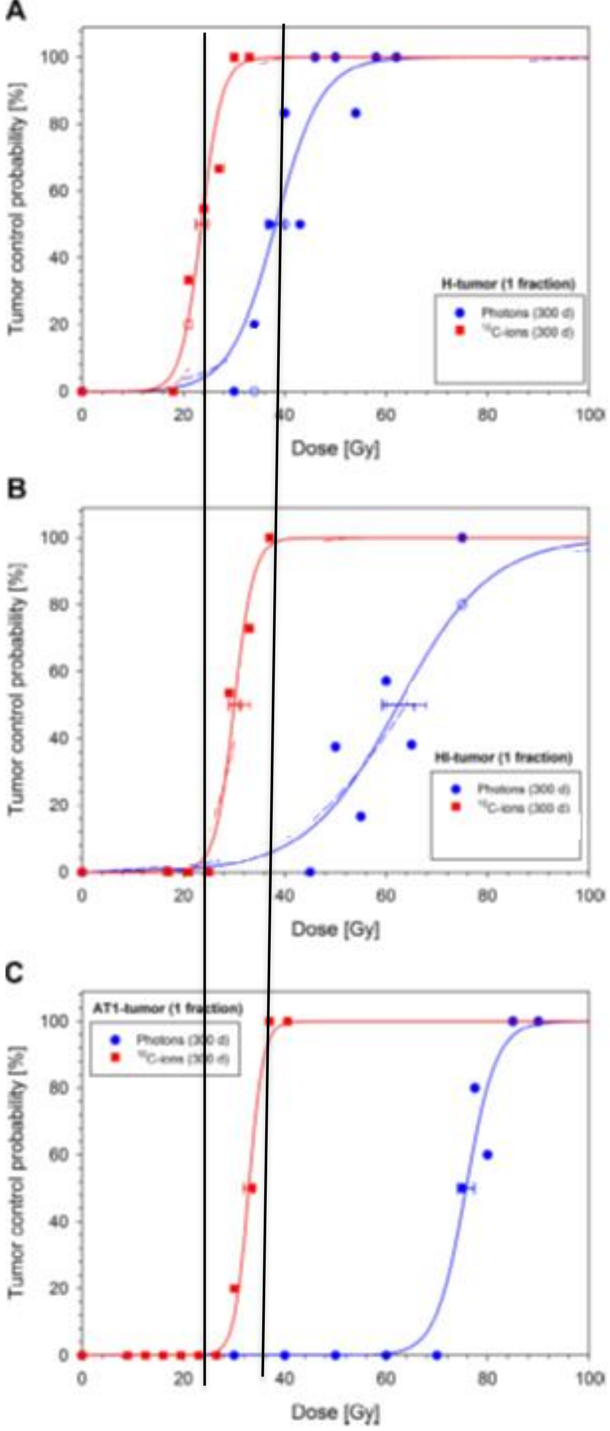
No Conflict of Interest to disclose

Carbon ions: where do we go next



Well diferentiated prostate cancer

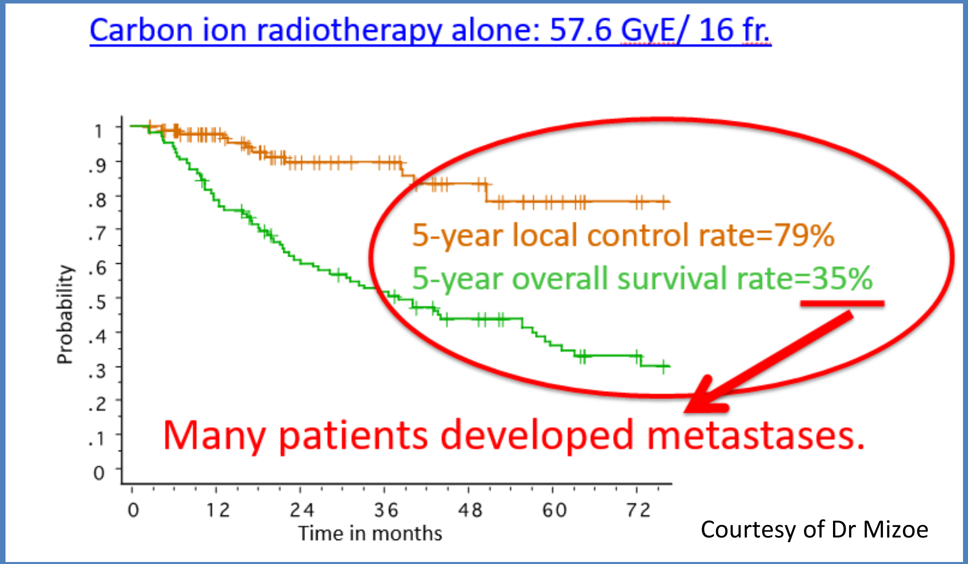
Moderately diferentiated prostate cancer

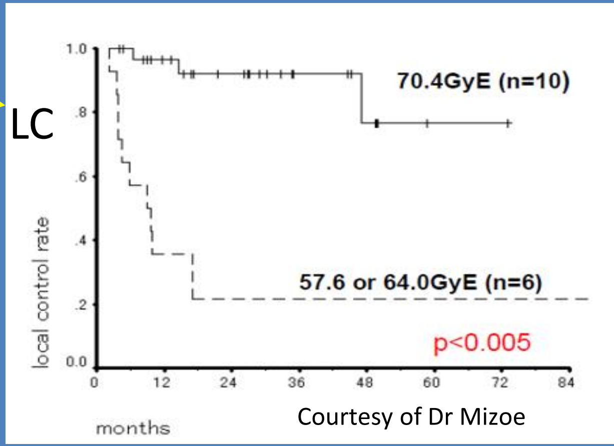
poorly diferentiated prostate cancer

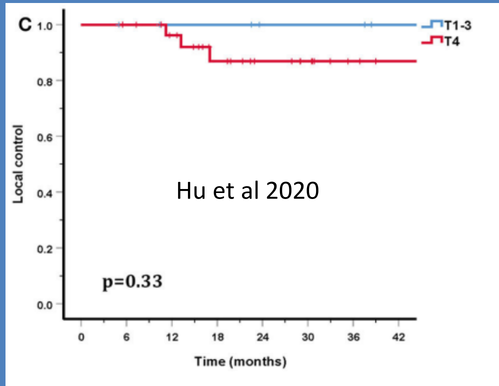
Modified from C. Glowa et al. / Cancer Letters 378 (2016) 97–103

CIRT in H&N

- Mucosal Melanoma
- B&STS
- Paranasal sinuses



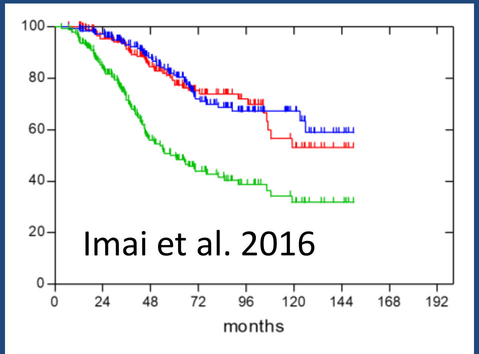


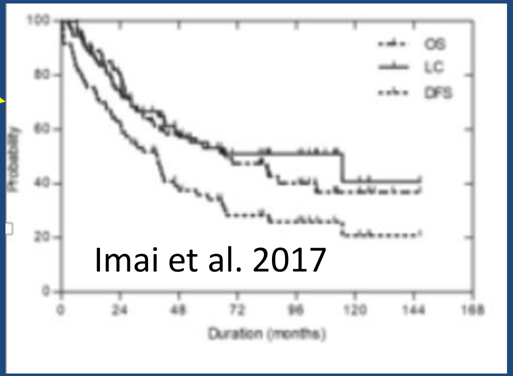


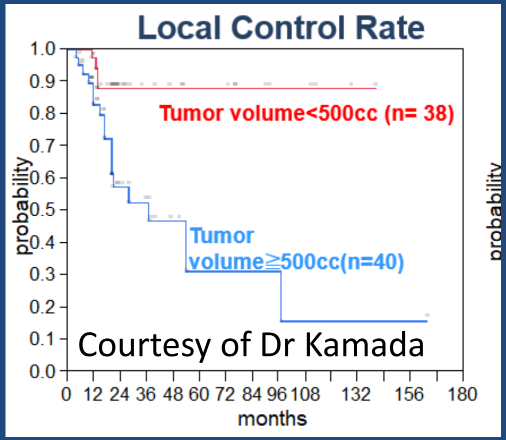
CIRT for sarcoma

CIRT has been used with curative intent in many non operated sarcoma such as:

- Chordoma
- Chondrosarcoma
- Osteosarcoma







Potential advantages

- Non SCC H&N
- Sarcoma
- Rectal cancer re-RT
- High risk prostate cancer
- Pancreatic cancer

We need more centers to produce the evidence
We need more evidence to build the centers

The path forward

Prove that good results are tru

- Clinical trials
- Cooperation
- Innovative methodology

Explore new potential use

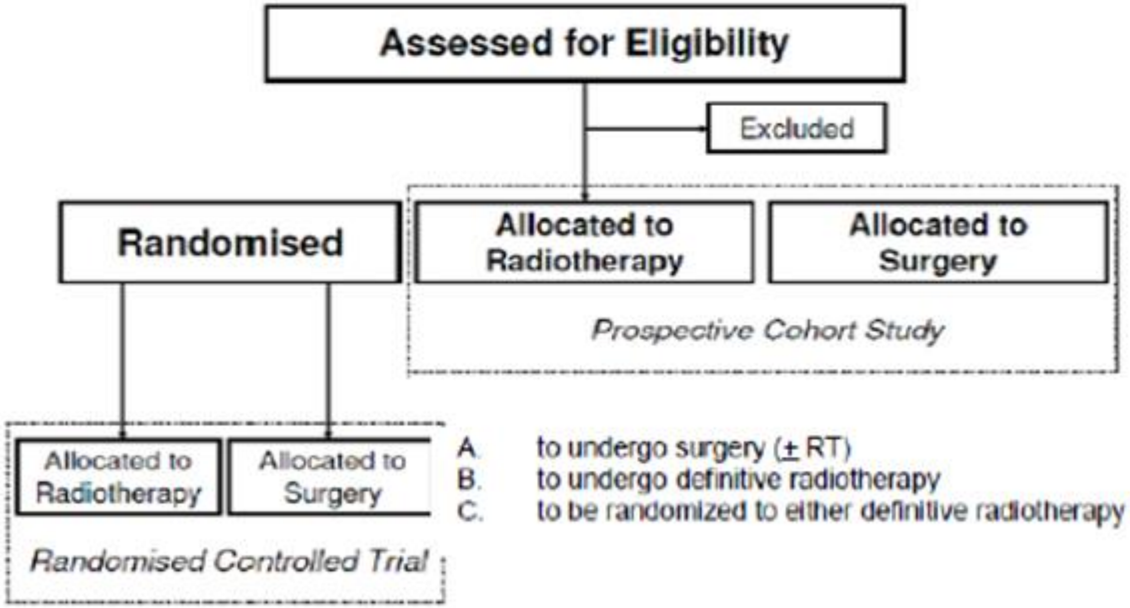
- Hypoxia/reoxygenation
- LET painting
- Immune response

Showcase: sacral chordoma

- **Can we propose carbon ions as an alternative to surgery?**
- **How much should we insist before accepting patient refusal ?**
- **Are the Japanese data reproducible ?**
- **Is long term toxicity profile really better with carbon ions?**
- **What are the salvage treatment options?**
- **Can we do the same with protons?**

SAcral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)

Schematic flow-chart



A. to undergo surgery (± RT)
B. to undergo definitive radiotherapy
C. to be randomized to either definitive radiotherapy or surgery (± RT).

2.1 Primary objective

This study is aimed at estimating the effectiveness of definitive radiotherapy as compared to standard surgical treatment for patients with primary sacral chordoma who are candidates to a complete en-bloc resection, in term of relapse-free-survival (RFS)

2.2 Secondary objectives

- To estimate the efficacy, activity, safety, QoL of definitive radiotherapy as compared to standard surgical treatment for patients with primary sacral chordoma who are candidates to a complete en-bloc resection.
- To identify patients, radiological and pathological characteristics that might be used as predictors of relapse-free survival (RFS)/ progression free survival (PFS), overall survival (OS)
- To identify patients, radiological and pathological characteristics that might be used as predictors of treatment effects

Open sites

2016	2017	2018	2019	2020	2021	Total
1	7	2	7	4	2	**23**

23 active sites in 7 countries and more are joining

Courtesy of S. Radaelli

Courtesy of S. Radaelli

Accrual-Institution

Site	Registered/Rand. pts	Treated pts
INT Milan (Surg)	23	11
CNAO Pavia (RT)	25	41
IFO Rome (Surg)	9	4
IOR Onco-Spine (Surg)	7	4
Galeazzi Milan (Surg)	0	6
Trento (RT)	0	1
Seville (Surg)	4	2
Oslo (RT)	4	2
Graz (Surg)	3	2
MedAustron (RT)	6	7
Saitama (Surg)	2	2
Essen (RT)	3	3
Essen (Surg)	1	1
IOR-Onco Surg (Surg)	1	1
Hospital Vall d'Hebrón (Surg)	1	1
Hospital Gregorio Maranon (Surg)	1	1
Humanitas (Surg)	2	1
Heidelberg (RT)	0	2
Total enrolled	92*	92*

05 Oct 21

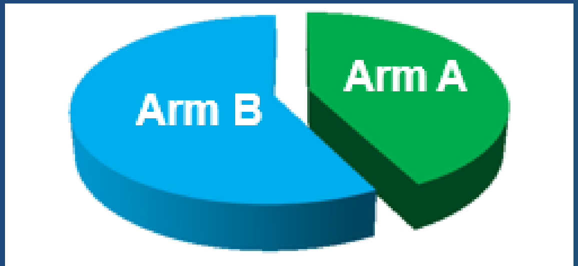
* 93 registered in web platform: 1 pt registered twice

Courtesy of S. Radaelli

Study Cohorts & Treatment

PCS	RCT
89 (100%)	0 (0%)

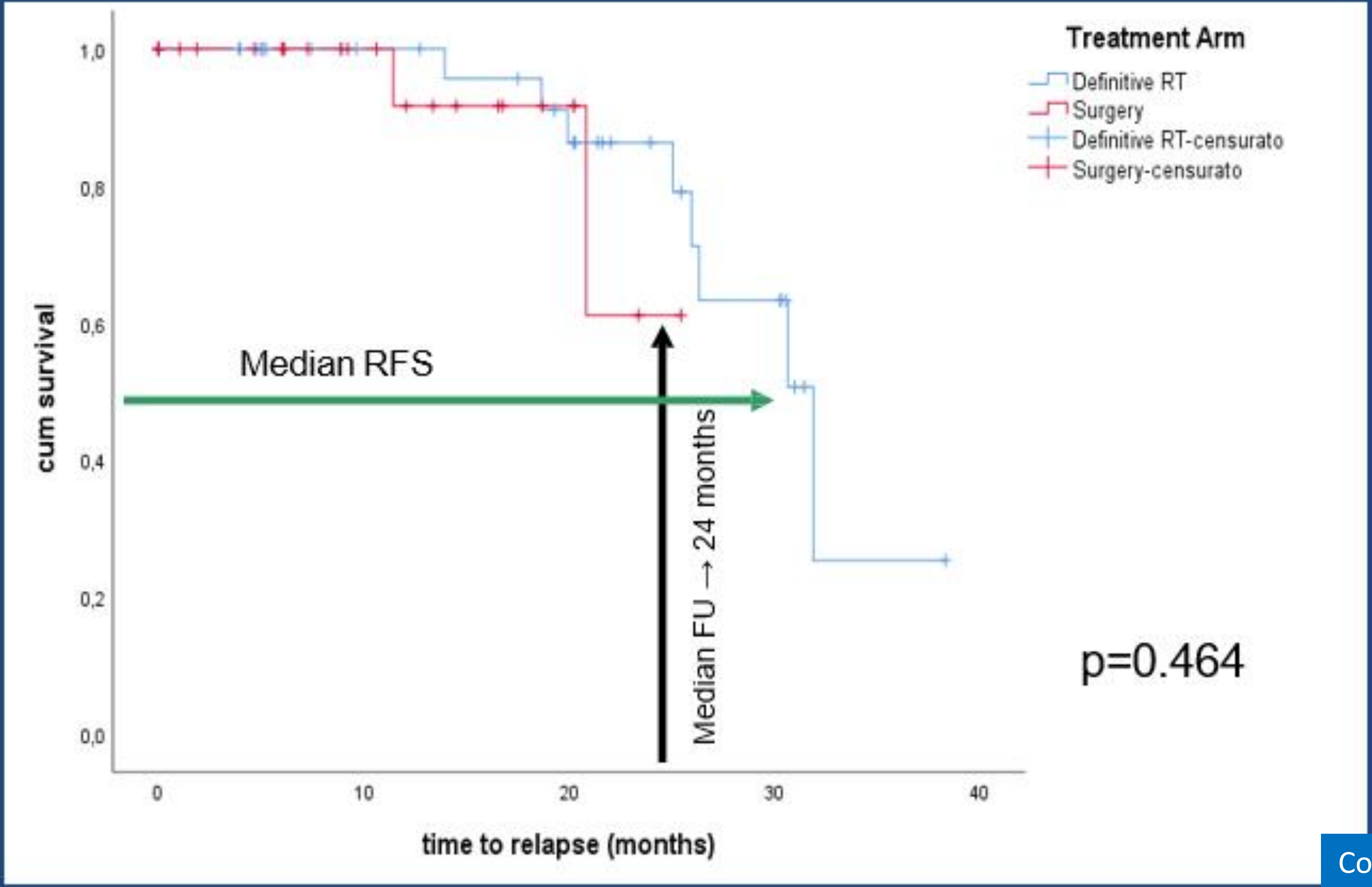
Arm A (Surgery +/-RT)	Arm B (Definitive RT)
37 (42%)	52 (58%)*



Carbon IONS	Protons
50 (96%)	2 (4%)

Courtesy of S. Radaelli

Relapse-Free Survival



Courtesy of S. Radaelli

NED		AWD		DOD		Dead for Complication	Dead for other cause
37% (32)		57% (50)		3% (3)		1% (1)	1% (1)
97%(31) (Arm A)	3%(1) (Arm B)	6%(3) (Arm A)	94%(47) (Arm B)	33%(1) (Arm A)	67%(2) (Arm B)	100%(1) (Arm A)	100%(1) (Arm B)

Courtesy of S. Radaelli

RT toxicity

33 pts (87%) experienced RT related toxicity

AE Term	Total	G1	G2	G3	G4
Radiodermatitis	27	52,6% (20)	13,2% (5)	5,3% (2)	0,0% (0)
Peripheral sensory neuropathy	25	26,3% (10)	26,3% (10)	13,2% (5)	0,0% (0)
Peripheral motor neuropathy	22	21,1% (8)	21,1% (8)	15,8% (6)	0,0% (0)
Skin induration	20	26,3% (10)	23,7% (9)	2,6% (1)	0,0% (0)
Rectal toxicity (Constipation)	15	31,6% (12)	2,6%	5,3% (2)	0,0% (0)
Bone fracture	12	28,9% (11)	0,0% (0)	2,6% (1)	0,0% (0)
Sacral/extremities Pain	11	5,3% (2)	13,2% (5)	10,5% (4)	0,0% (0)
Neuralgia	8	0,0% (0)	13,2% (5)	7,9% (3)	0,0% (0)
Urinary toxicity (retention)	8	21,1% (8)	0,0% (0)	0,0% (0)	0,0% (0)
Urinary toxicity (incontinence)	5	5,3% (2)	5,3% (2)	2,6% (1)	0,0% (0)
Skin hyperpigmentation	4	7,9% (3)	2,6% (1)	0,0% (0)	0,0% (0)
Rectal toxicity (Incontinence)	3	5,3% (2)	0,0% (0)	2,6% (1)	0,0% (0)

Data from Interim Analysis (on 33 pts)

Courtesy of S. Radaelli

Surgery post-operative Complications ≥ 3 according to Clavien-Dindofill grade

Pts with surgical complication
41%(13/32*)

5 missi ng pts (14%)

Nr of post-operative Complications ≥ 3 according to Clavien-Dindofill grade
63%(20/32*)

Infection	Wound dehiscence	Hemorrhage (SAE)	Seroma (SAE)	CSF leak
40% (8/20)	35% (7/20)	15% (3/20)	5% (1/20)	5% (1/17)

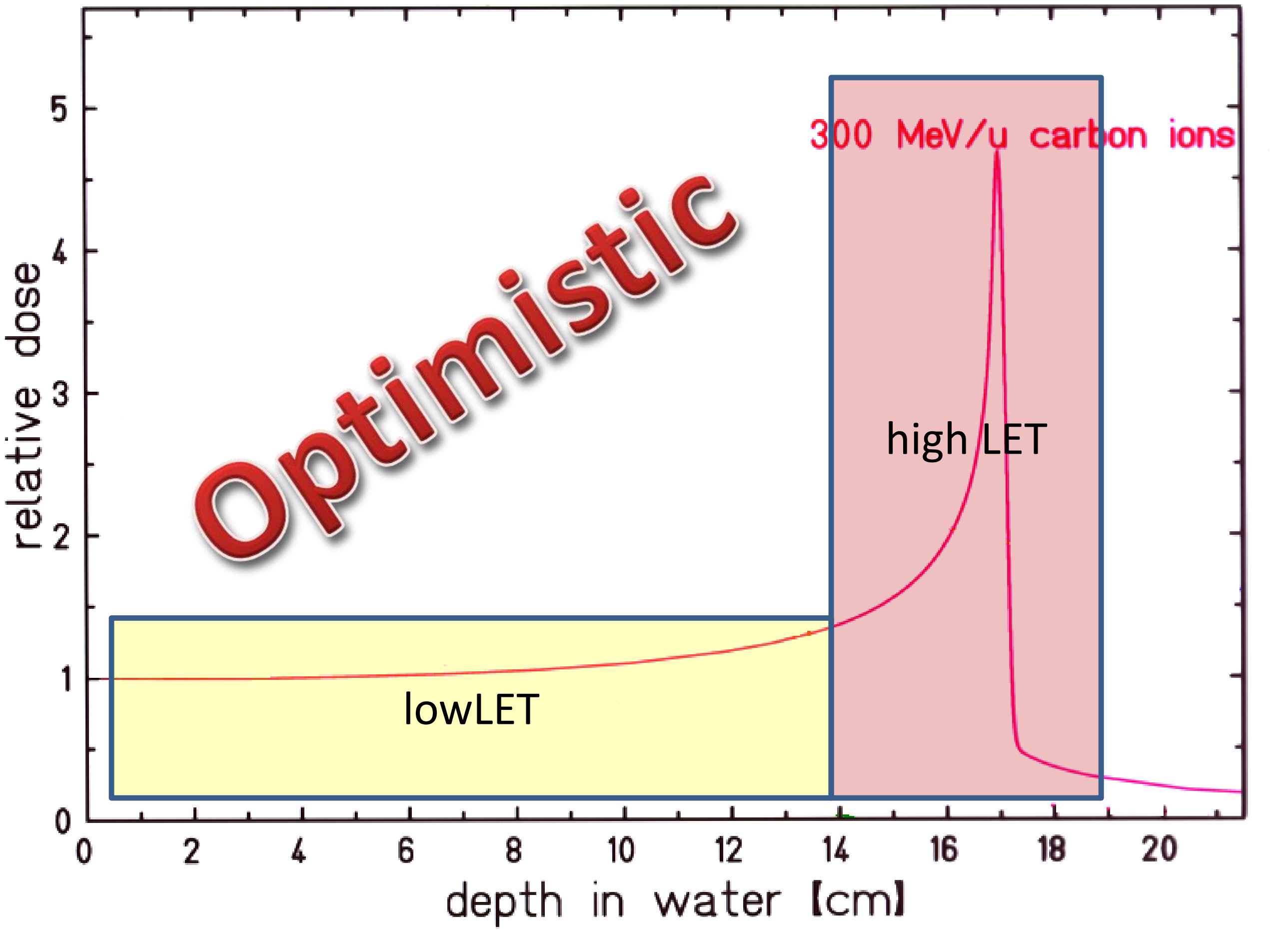
1 pt had hemorrhagic shock after on 30th pod and died

Courtesy of S. Radaelli

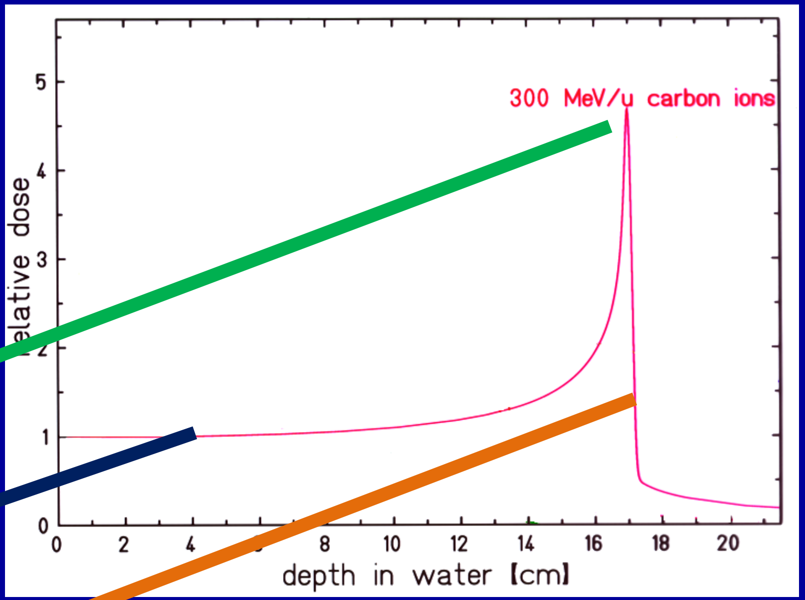
LET painting

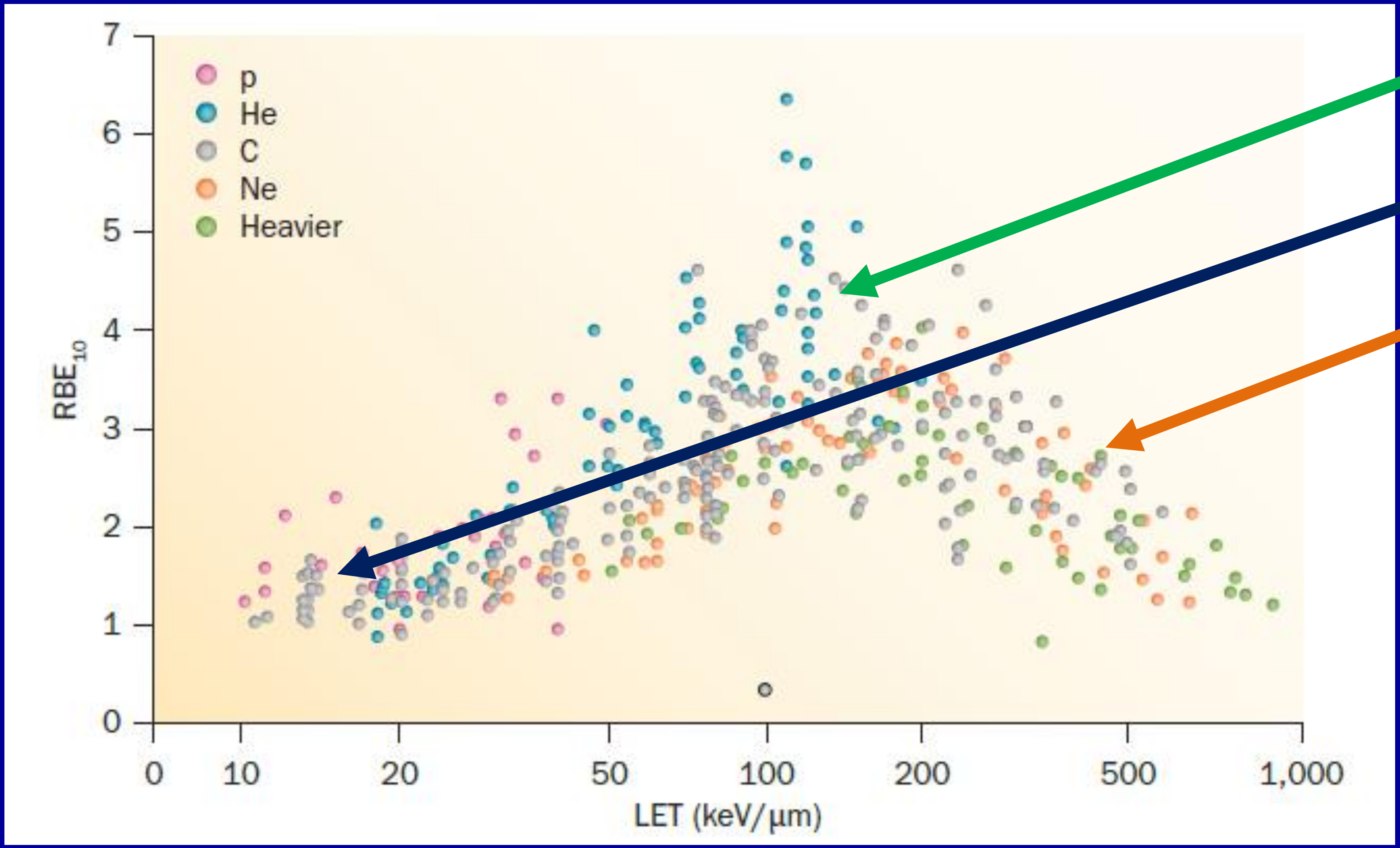
Carbon ion is not a high LET RT

Carbon ions
High LET RT ?(only where you need it)



RBE





Does RBE tell the truth,
all the truth,
nothing but the truth?

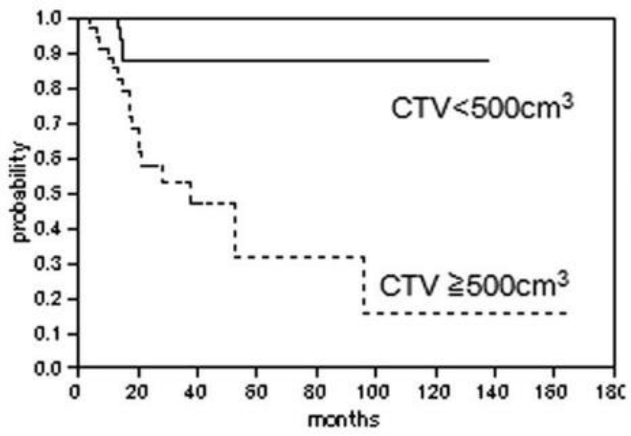
Inferior clinical outcomes in large tumors

- A. Matsunobu et al. 2012

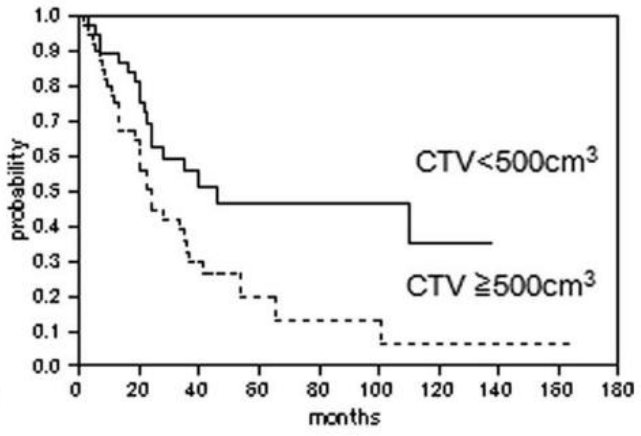
Unresectable Osteosarcoma of the trunk treated with CIRT

Clinical target volume (<500 cm³ vs. ≥500 cm³):

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



5-year LC



5-year OS

CIRT: Carbon Ion Radiotherapy; LC: Local Control; OS: Overall Survival

Recent studies

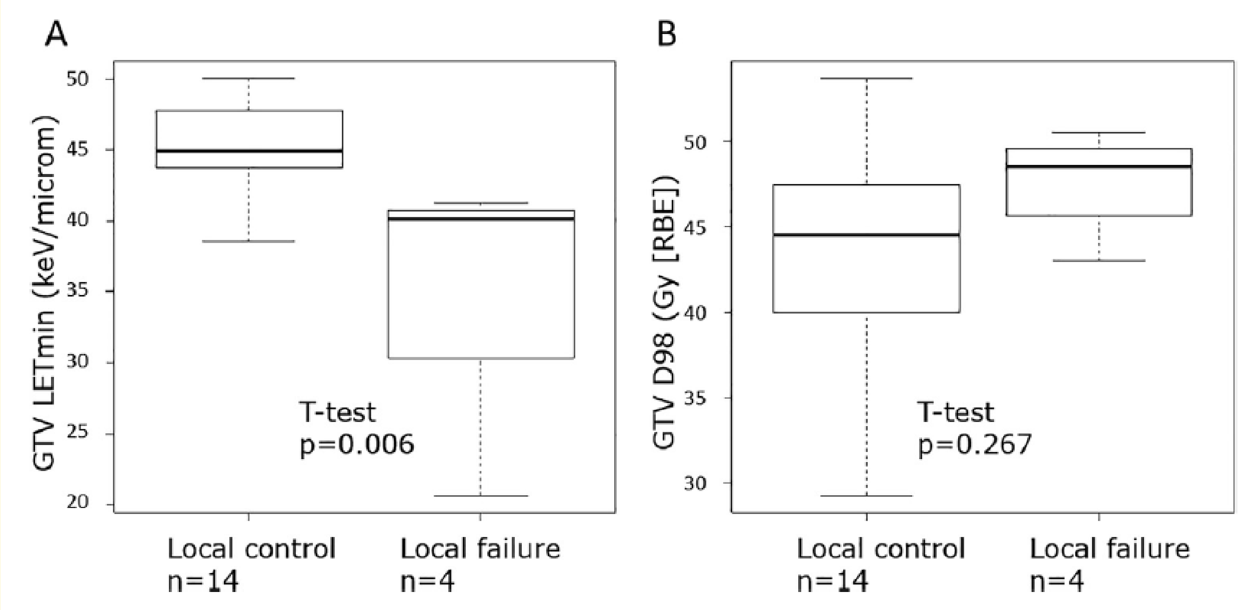
- Y. Hagiwara et al. 2020
  - Influence of dose-averaged linear energy transfer on tumour control after carbon-ion radiation therapy for pancreatic cancer

- 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 keV/µm) in the GTV with better 18-month LC
  - 100% vs. 34.3%



LET_d: Dose averaged Linear Energy Transfer; $LET_{d,\ min}$: Minimum dose averaged Linear Energy Transfer; LC: Local Control

Recent studies

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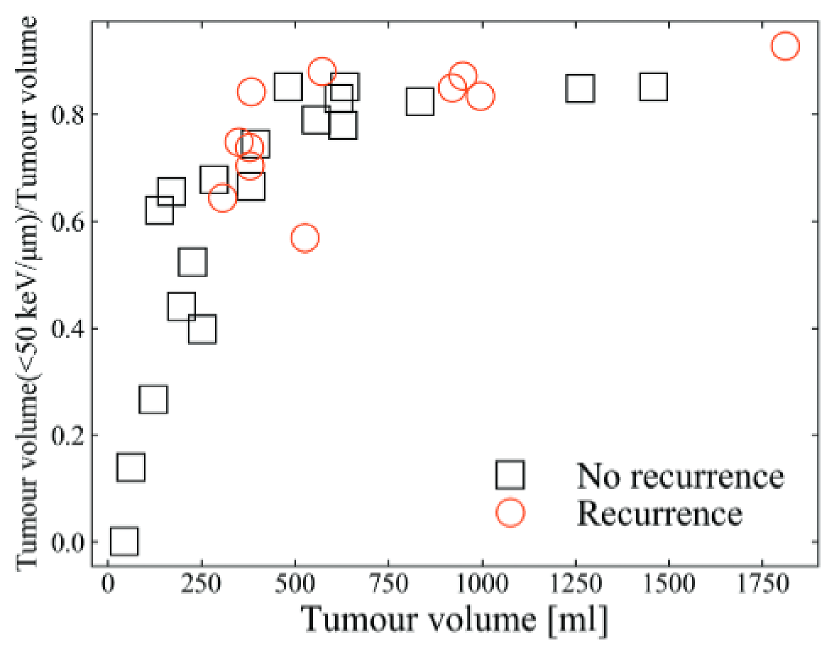
  - Influence of dose-averaged linear energy transfer on tumour control after carbon-ion radiation therapy for pancreatic cancer
- S. Matsumoto et al. 2020
  - Unresectable chondrosarcomas treated with carbon ion radiotherapy: Relationship between dose-averaged linear energy transfer and local recurrence
- 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

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



PTV: Planning Target Volume

Recent studies

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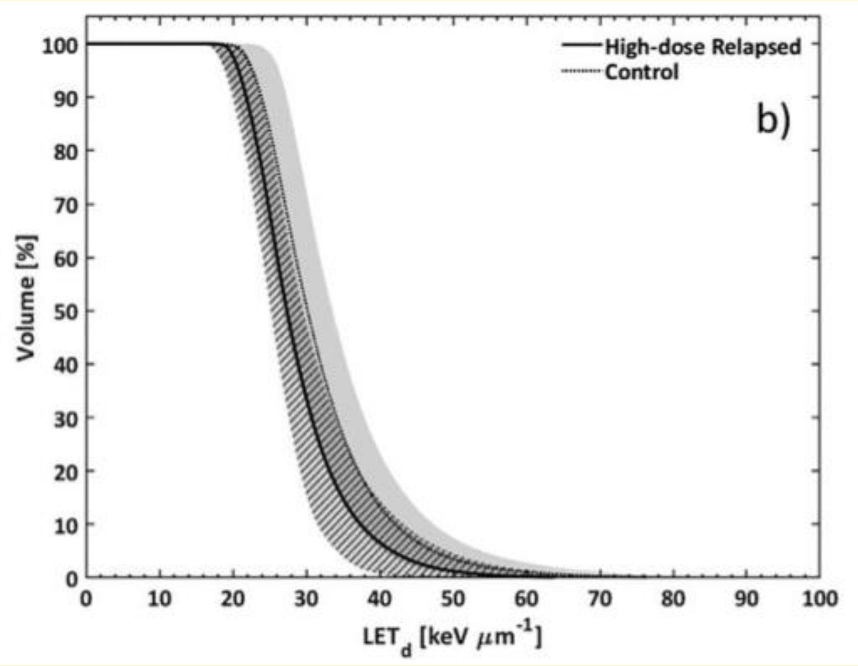
  - Unresectable chondrosarcomas treated with carbon ion radiotherapy: Relationship between dose-averaged linear energy transfer and local recurrence
- S. Molinelli et al. 2021
  - How LEM-based RBE and dose-averaged LET affected clinical outcomes of sacral chordoma patients treated with carbon ion radiotherapy

- 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: dose averaged Linear Energy Transfer; $LET_{d|50\%}$: Median LET_d; CTV_{HD}: Clinical Target Volume high dose; CTV_{LD}: Clinical Target Volume low dose

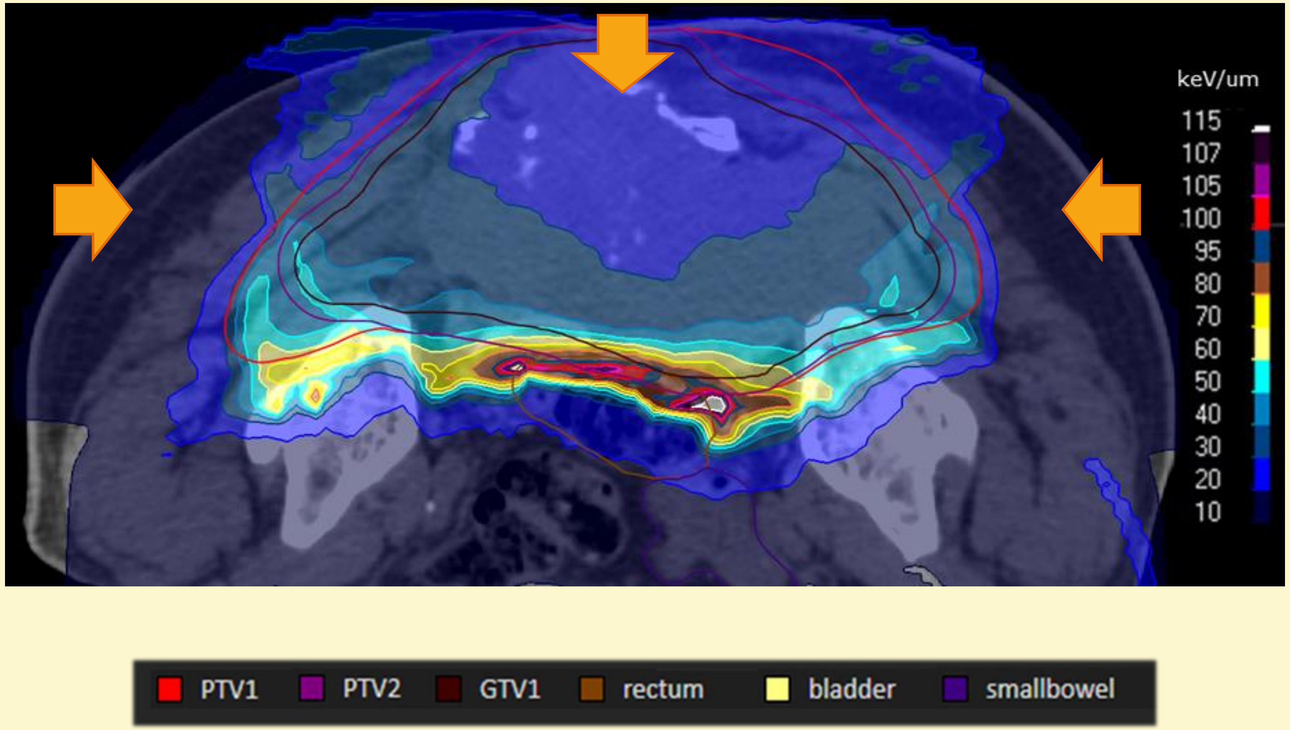
LET_d/High-LET-dose in large targets

- Sacral chordoma
  - PTV1: 1954.5 cm^3
  - PTV2: 1305.7 cm^3

- 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)

LET_d



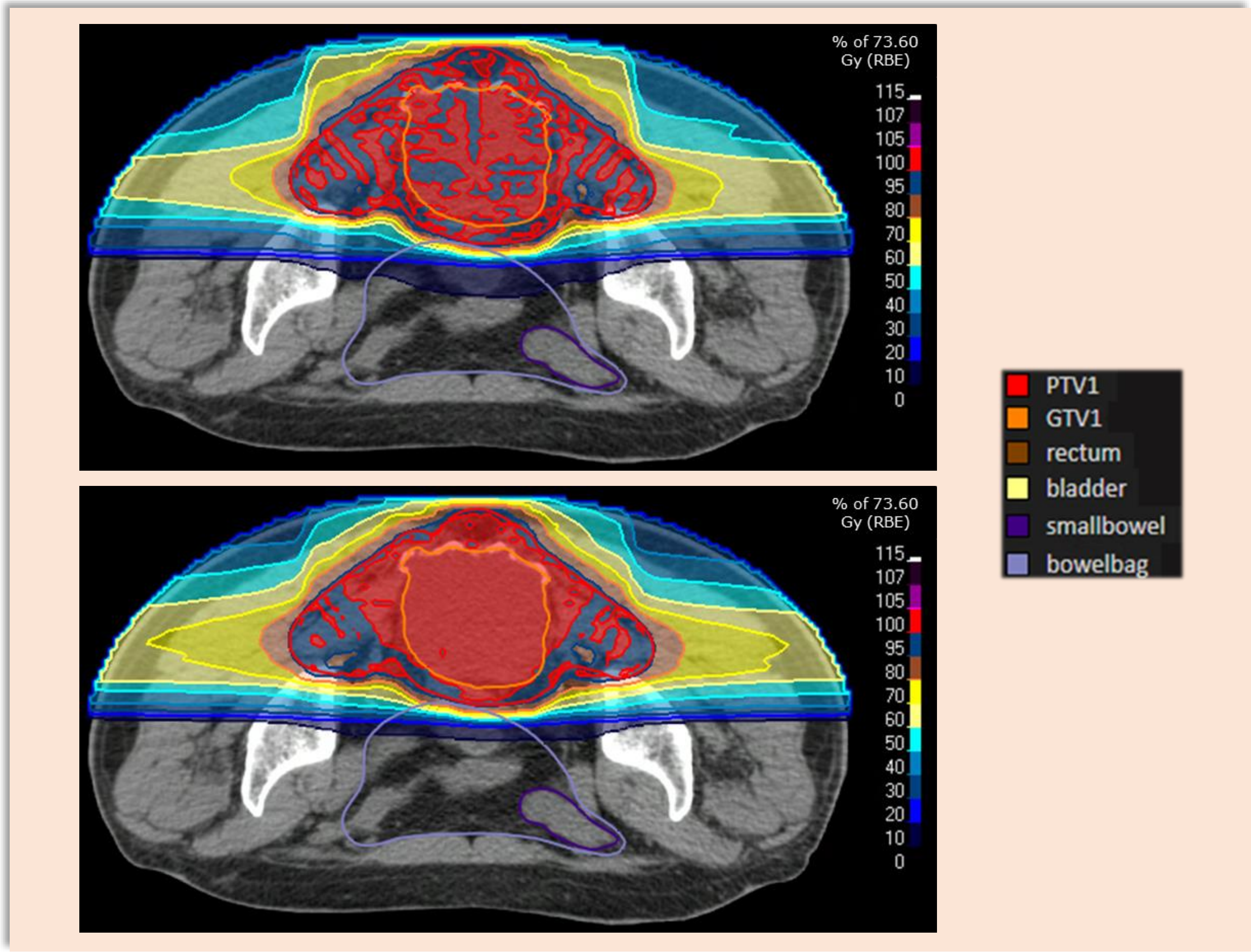
PTV: Planning Target Volume; RBE: Relative Biological Effectiveness; fx: Fraction

LET-based optimization

- Sacral chordoma
  - PTV1: 1244.3 cm^3
  - PTV2: 656.7 cm^3
- 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



PTV: Planning Target Volume; GTV: Gross Tumor Volume; RBE: Relative Biological Effectiveness; fx: Fraction; DVH: Dose Volume Histogram; LVH: LET_d Volume Histogram

LET-based optimization

- Sacral chordoma
  - PTV1: 1244.3 cm^3
  - PTV2: 656.7 cm^3
- Sequential dose prescription
  - RBE-weighted dose per fraction:
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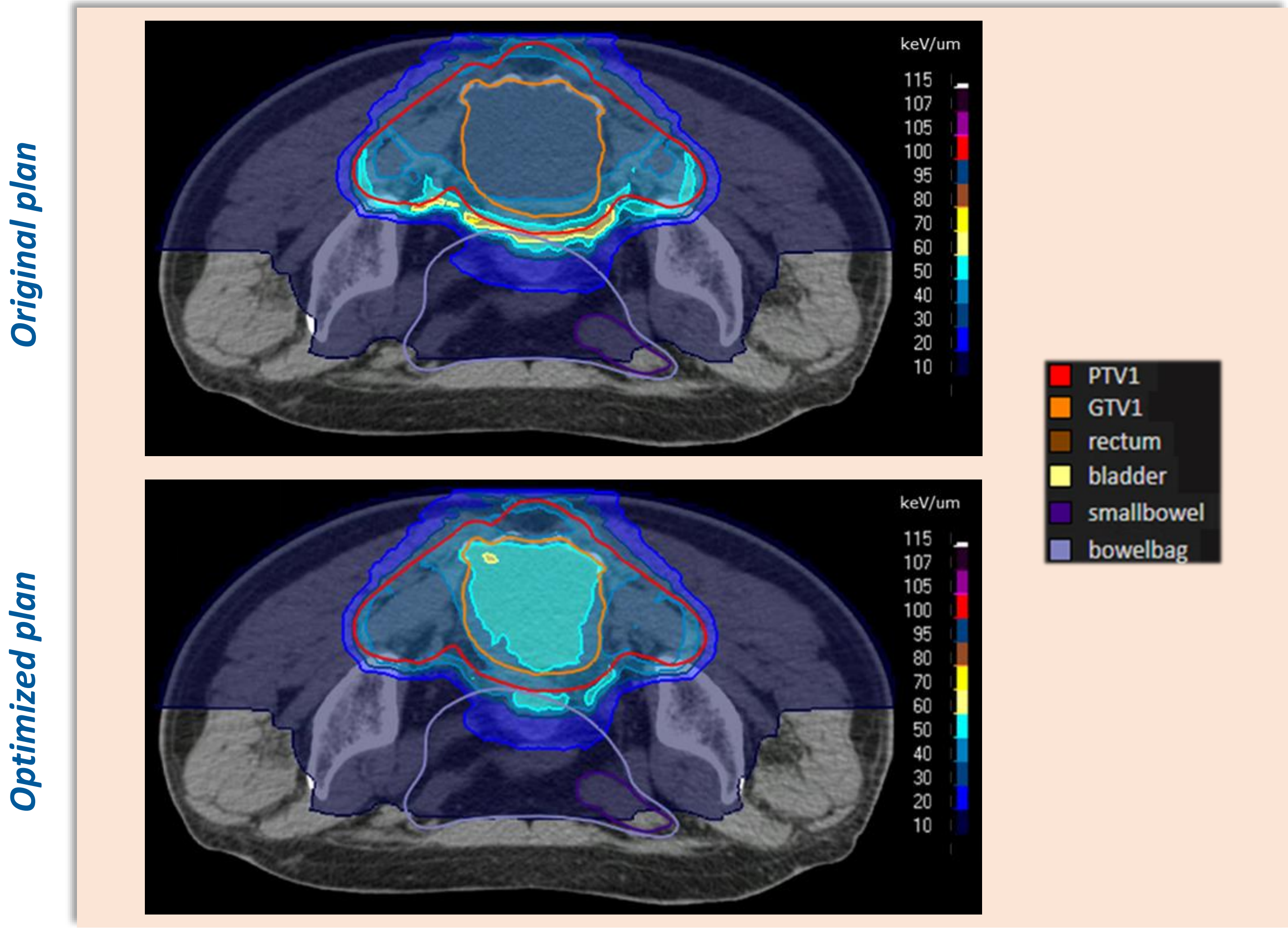
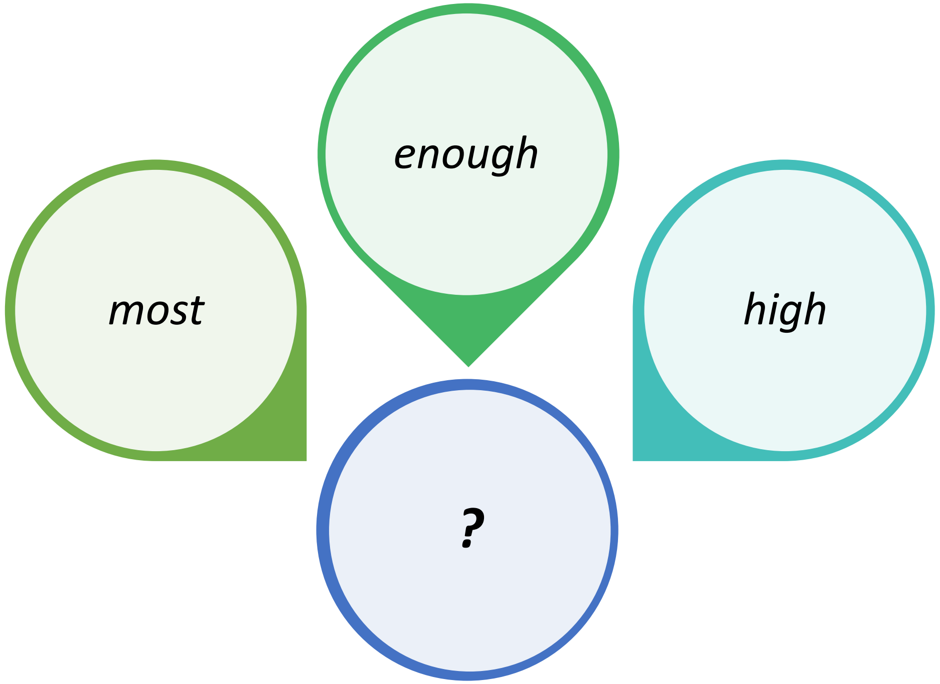


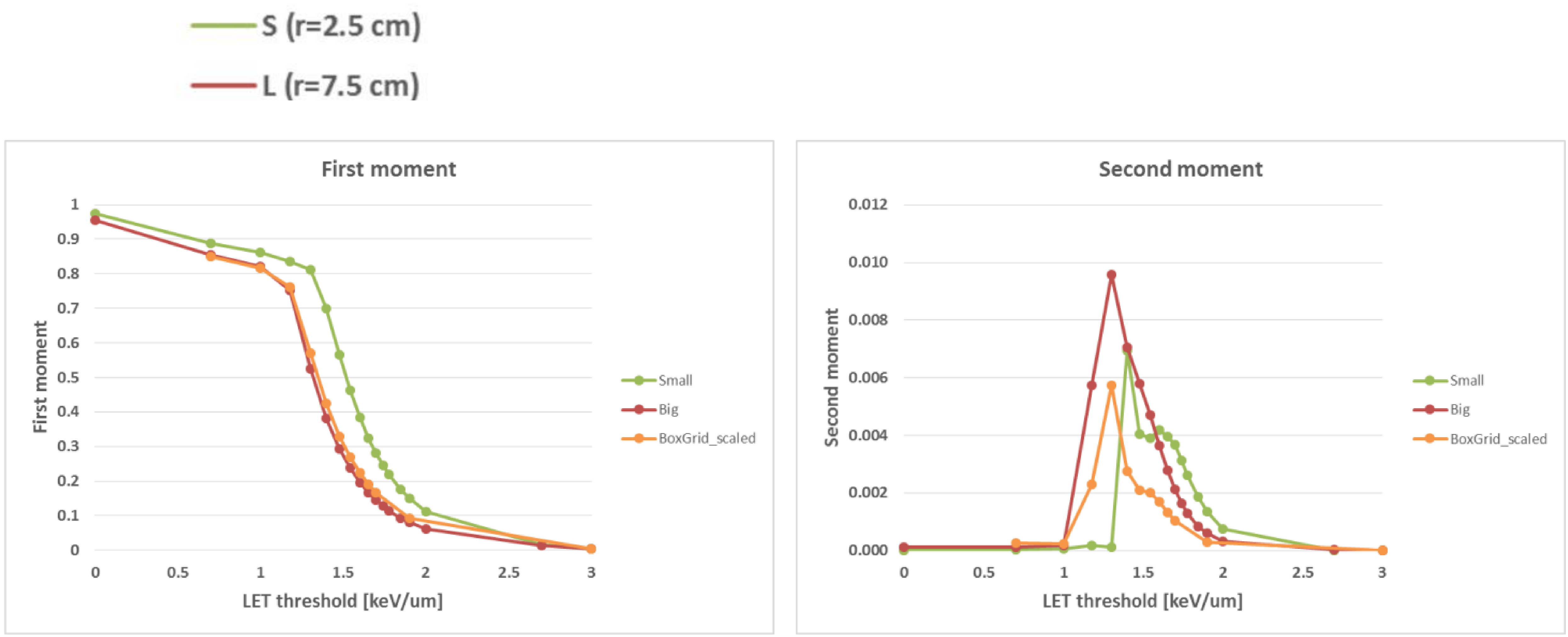
PTV: Planning Target Volume; GTV: Gross Tumor Volume; RBE: Relative Biological Effectiveness; fx: Fraction; DVH: Dose Volume Histogram; LVH: LET_d Volume Histogram

Research question

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



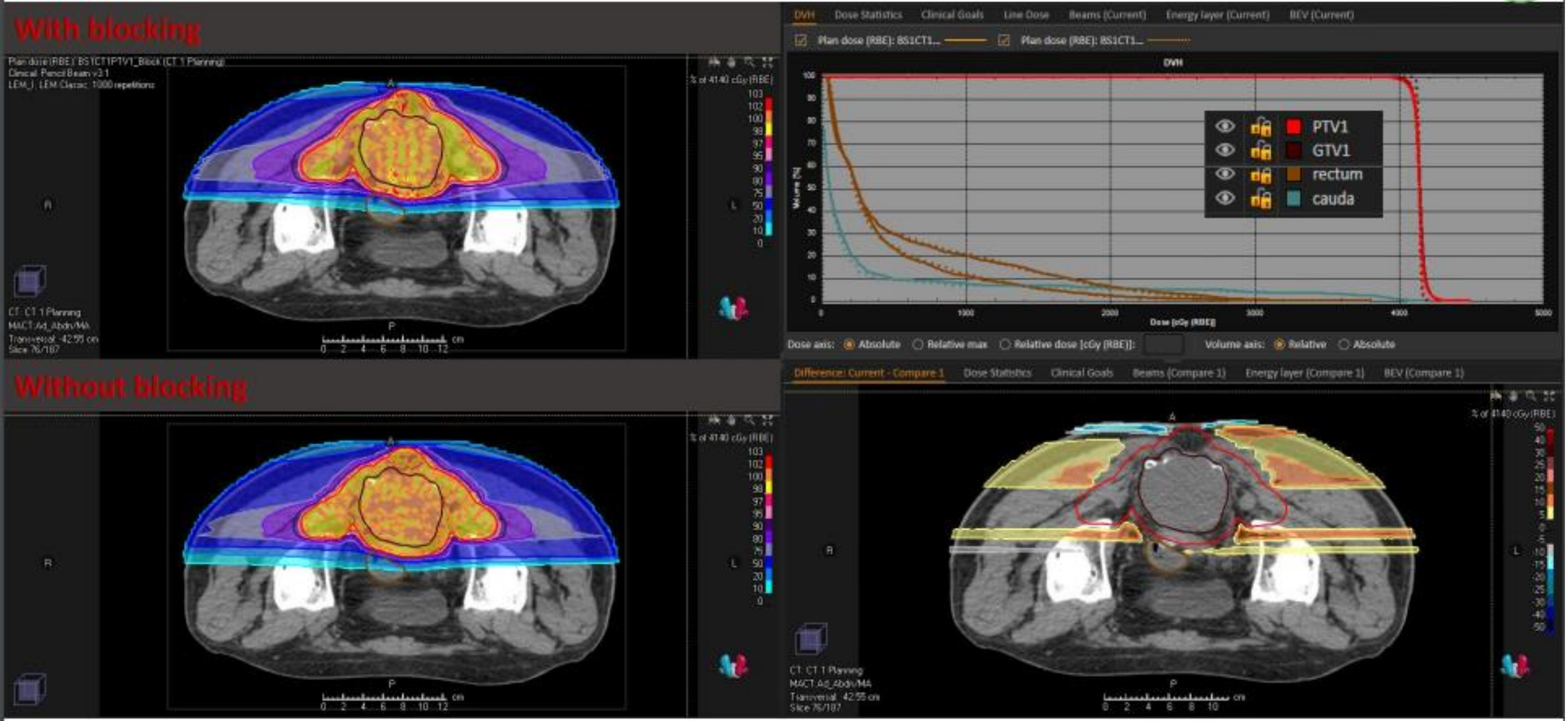
LET: Linear Energy Transfer


S (r=2.5 cm)
L (r=7.5 cm)
First moment
First moment
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
LET threshold [keV/um]
Small
Big
BoxGrid_scaled
Second moment
Second moment
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
0.5
1
1.5
2
2.5
3
LET threshold [keV/um]
Small
Big
BoxGrid_scaled


LET threshold [keV/um]

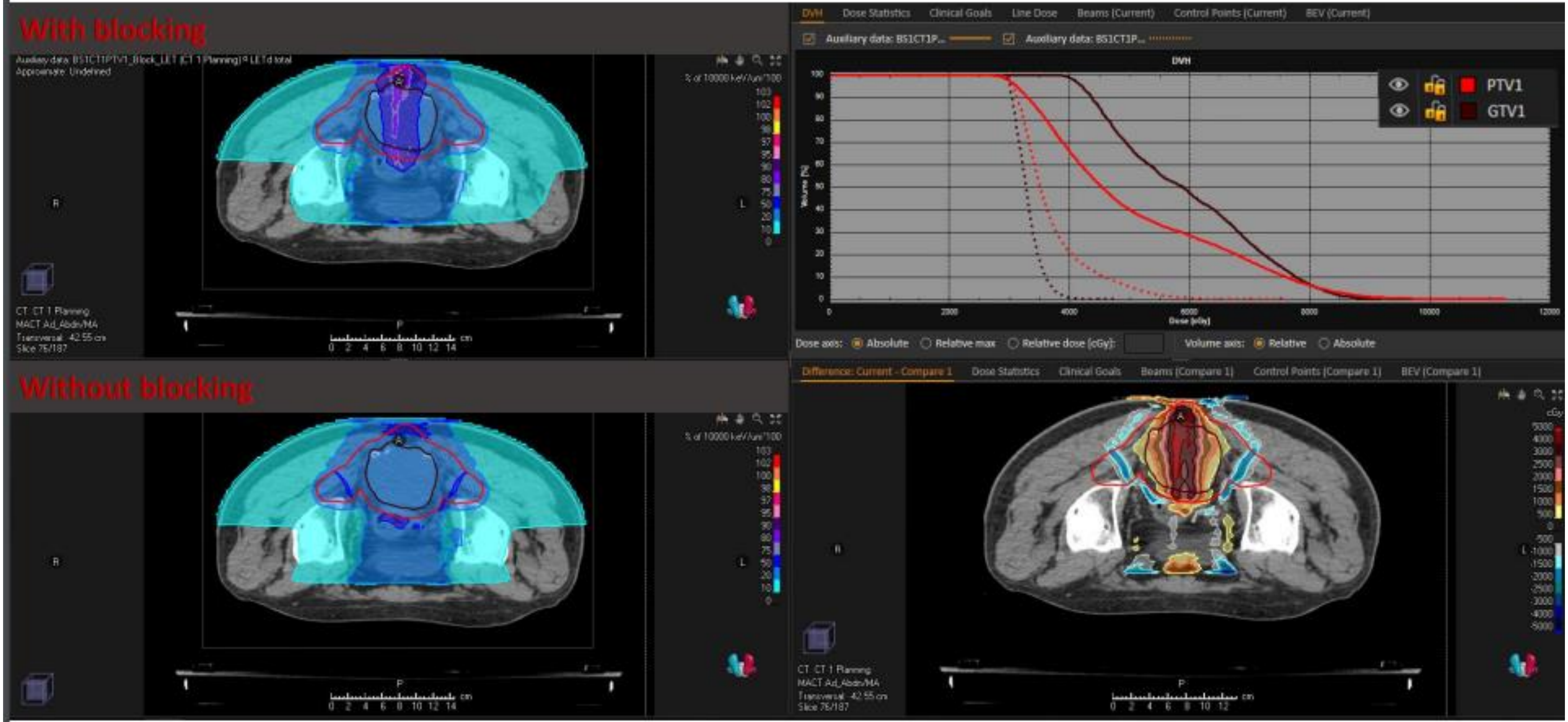
And in the meanwhile…

RBE|LEM dose



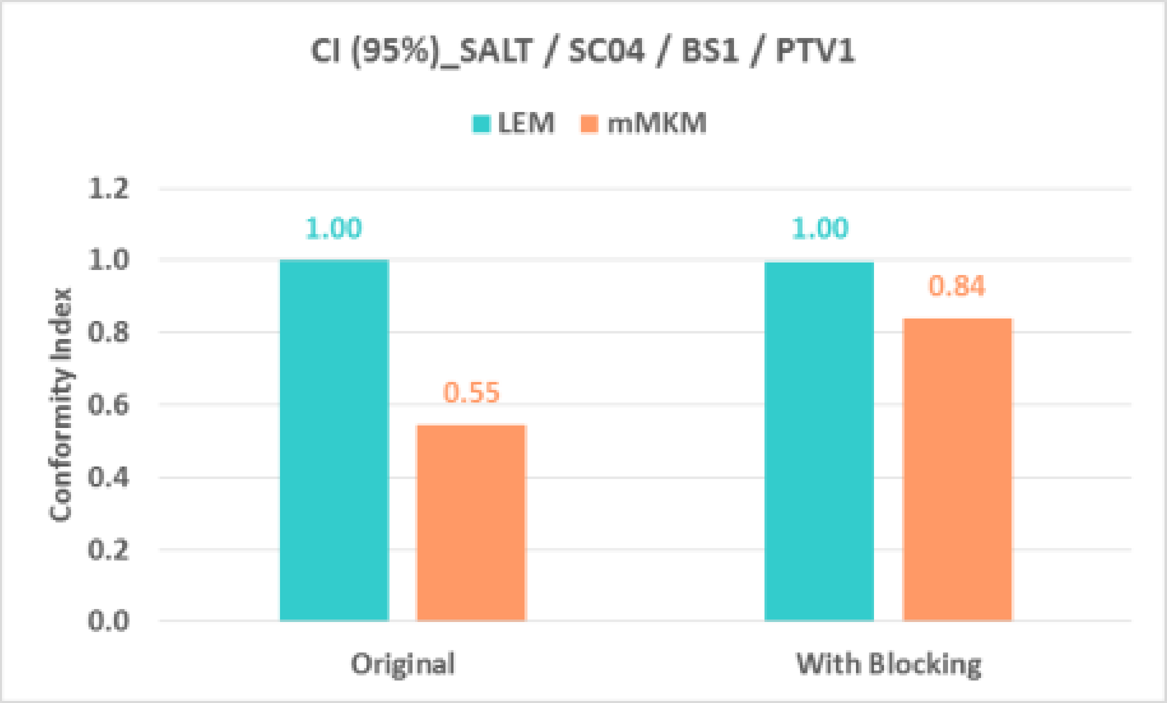
With blocking
Without blocking
DVH
Dose Statistics
Clinical Goals
Line Dose
Beams (Current)
Energy layer (Current)
BEV (Current)
PTV1
GTV1
rectum
cauda
Dose axis: Absolute
Relative max
Volume axis: Relative
Absolute
Difference: Current - Compare 1
Beams (Compare 1)
Energy layer (Compare 1)
BEV (Compare 1)

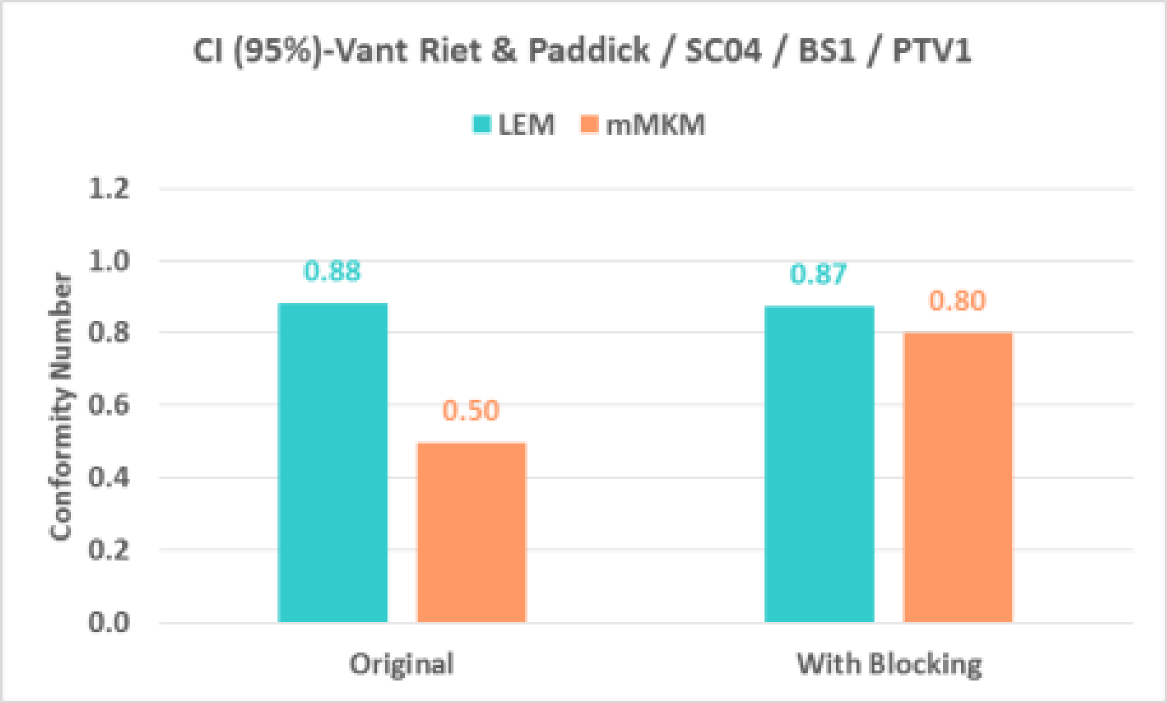
LETd



With blocking
Without blocking
DVH
Dose Statistics
Clinical Goals
Line Dose
Beams (Current)
Control Points (Current)
BEV (Current)
Auxiliary data: BS1CT1P...
PTV1
GTV1
Dose axis: Absolute
Relative max
Relative dose (cGy):
Volume axis: Relative
Absolute
Difference: Current - Compare 1
Beams (Compare 1)
Control Points (Compare 1)
BEV (Compare 1)

Conformity index → Only for the blocked BS

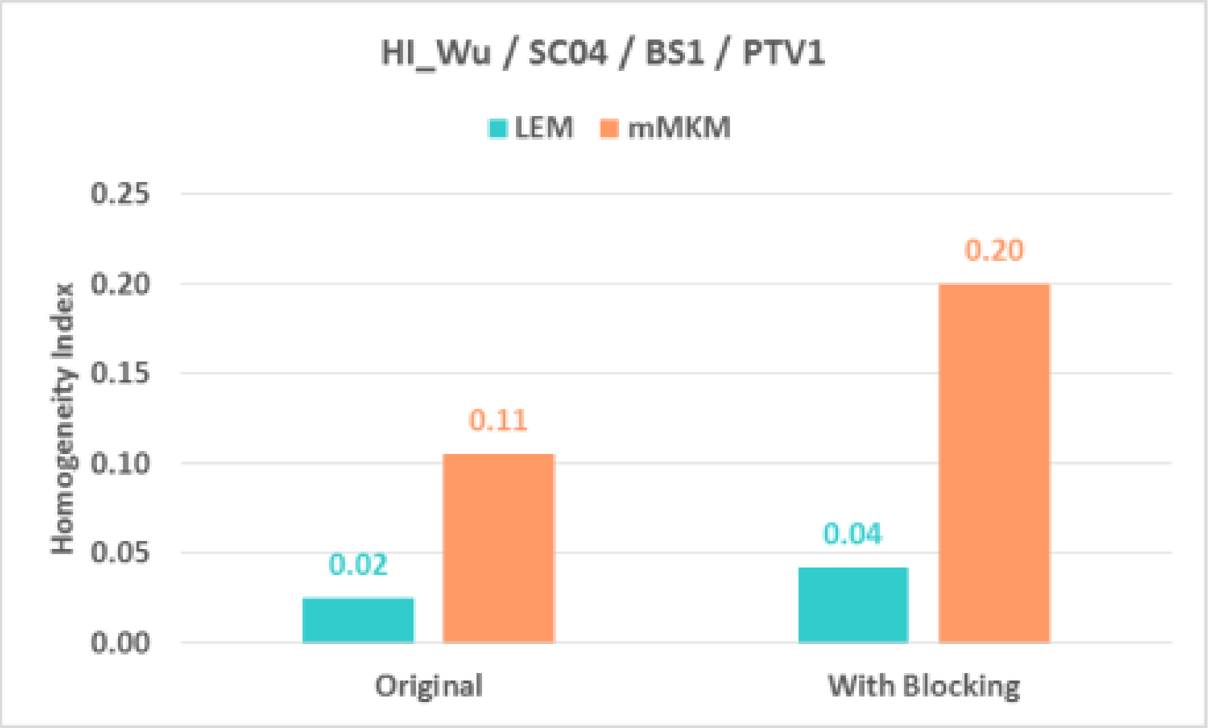


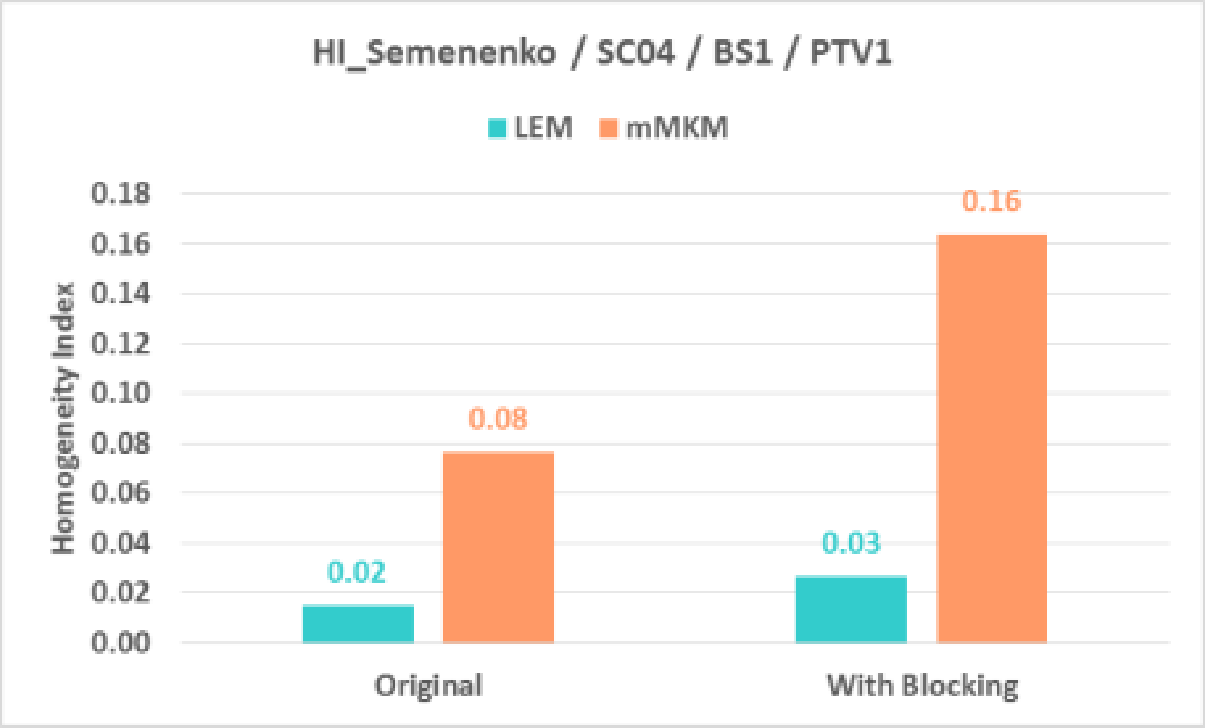


$$CI_{SALT} = \frac{V_{target,\, covered\ by\ 95\%\ of\ prescribed\ dose}}{V_{target}}$$

$$CI_{Vant\&Paddickck} = \frac{V_{target,\, covered\ by\ 95\%\ of\ prescribed\ dose}}{V_{target}} \cdot \frac{V_{target,\, covered\ by\ 95\%\ of\ prescribed\ dose}}{V_{covered\ by\ 95\%\ prescribed\ dose}}$$

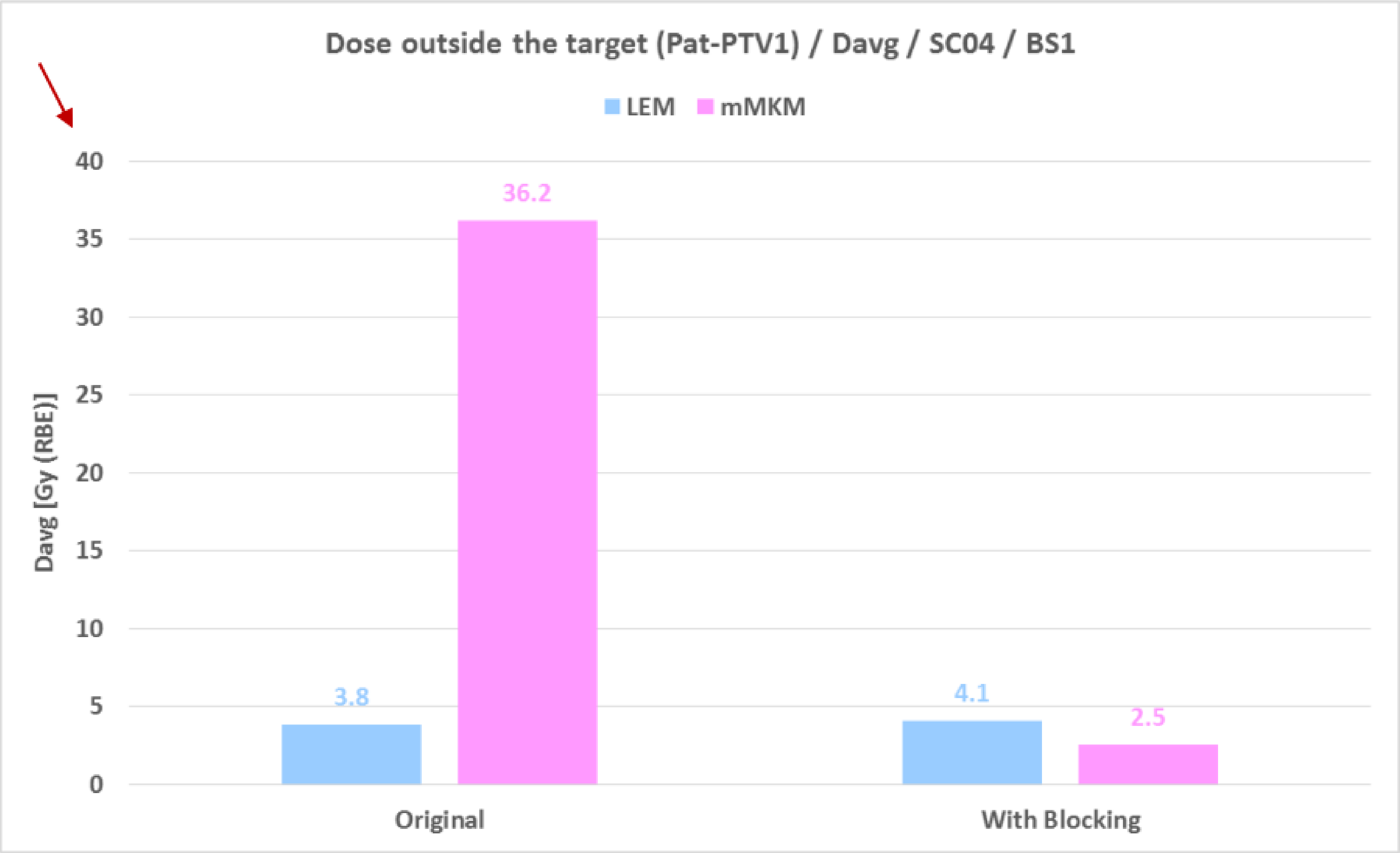
Homogeneity index → Only for the blocked BS



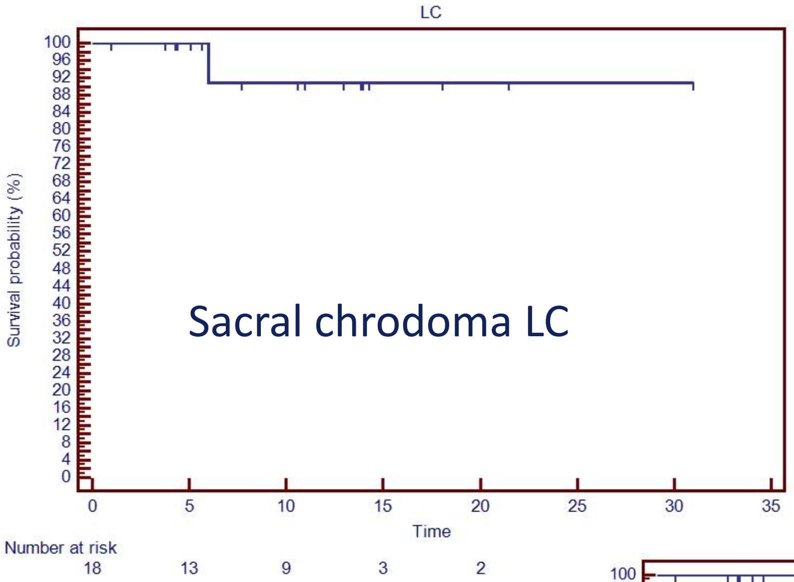


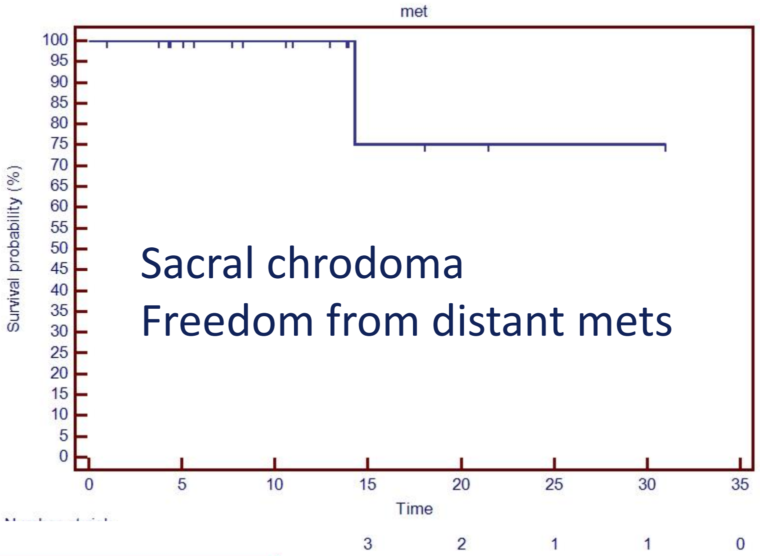
$$HI_{Wu} = \frac{D_{2\%} - D_{98\%}}{D_{prescribed}}$$

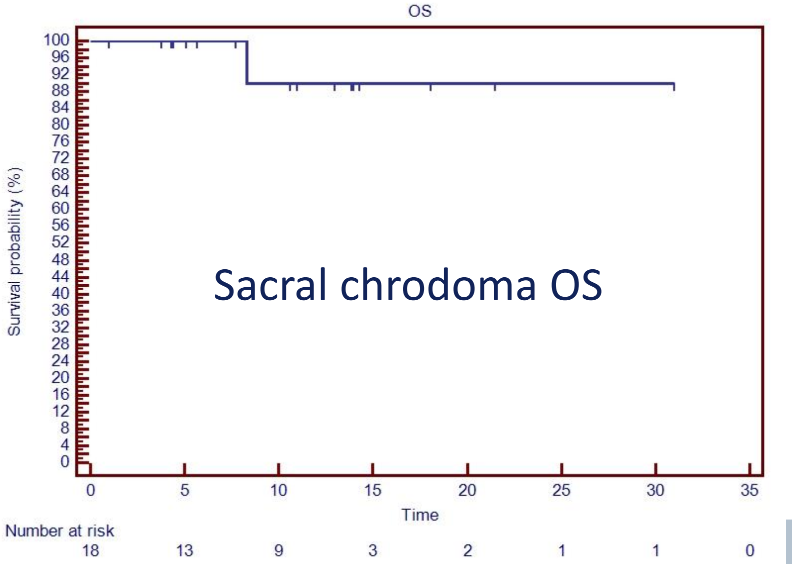
$$HI_{Semenenko} = \frac{D_{5\%} - D_{95\%}}{D_{prescribed}}$$

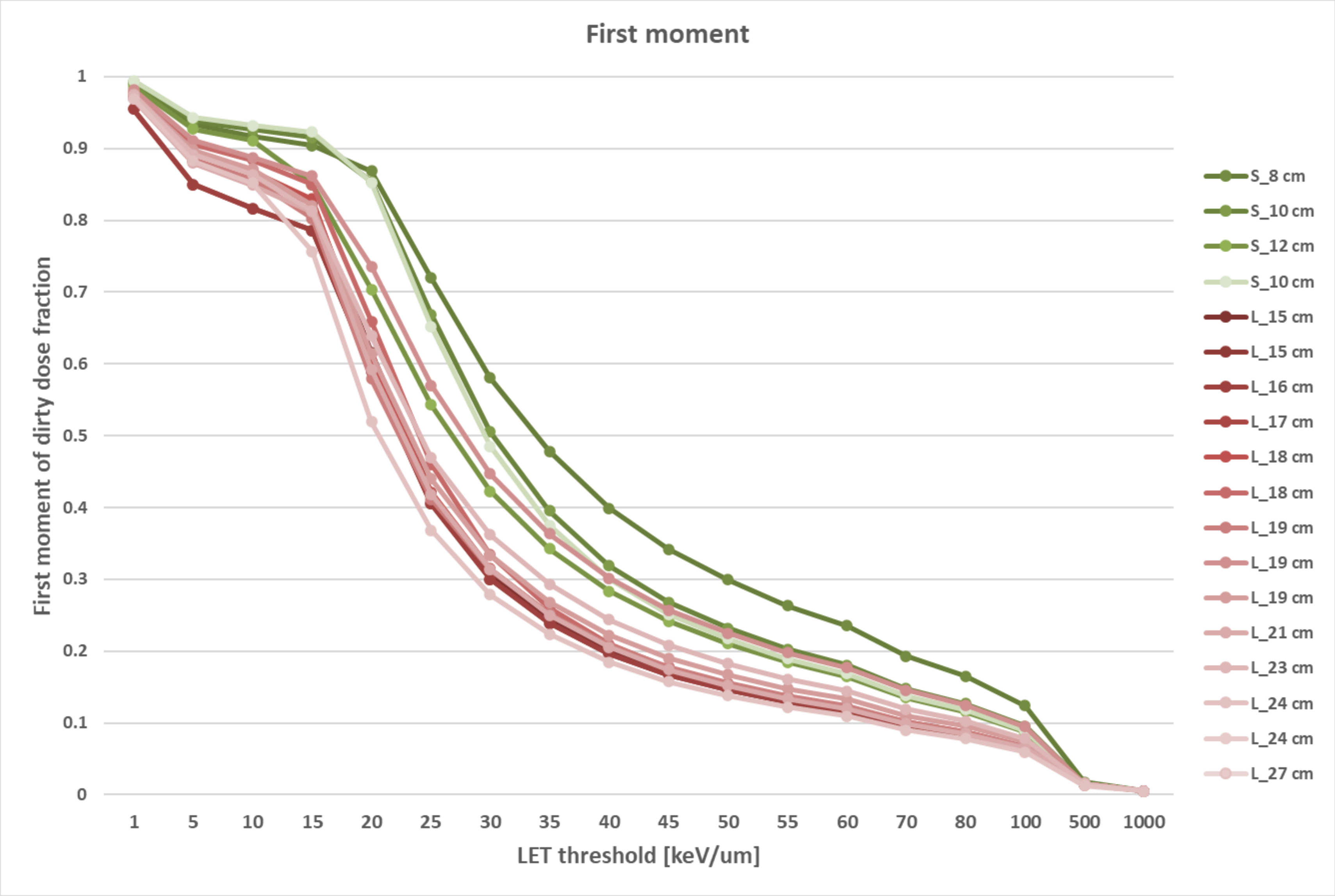

Dose outside the target (Pat-PTV1) / Davg / SC04 / BS1
LEM
mMKM
Davg [Gy (RBE)]
40
35
30
25
20
15
10
5
0
36.2
3.8
4.1
2.5
Original
With Blocking

SACRAL CHORDOMA AT MEDAUSTRON

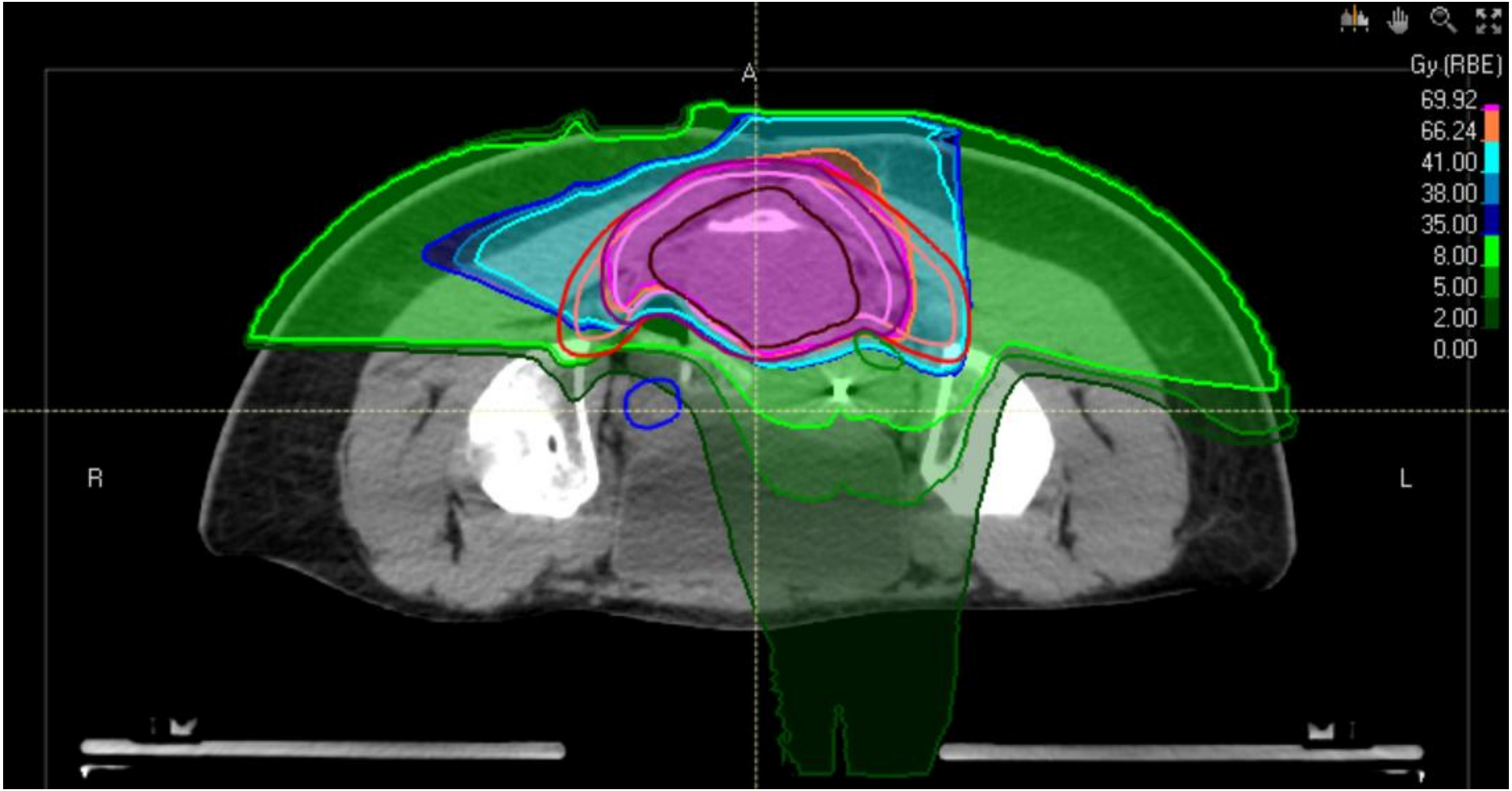


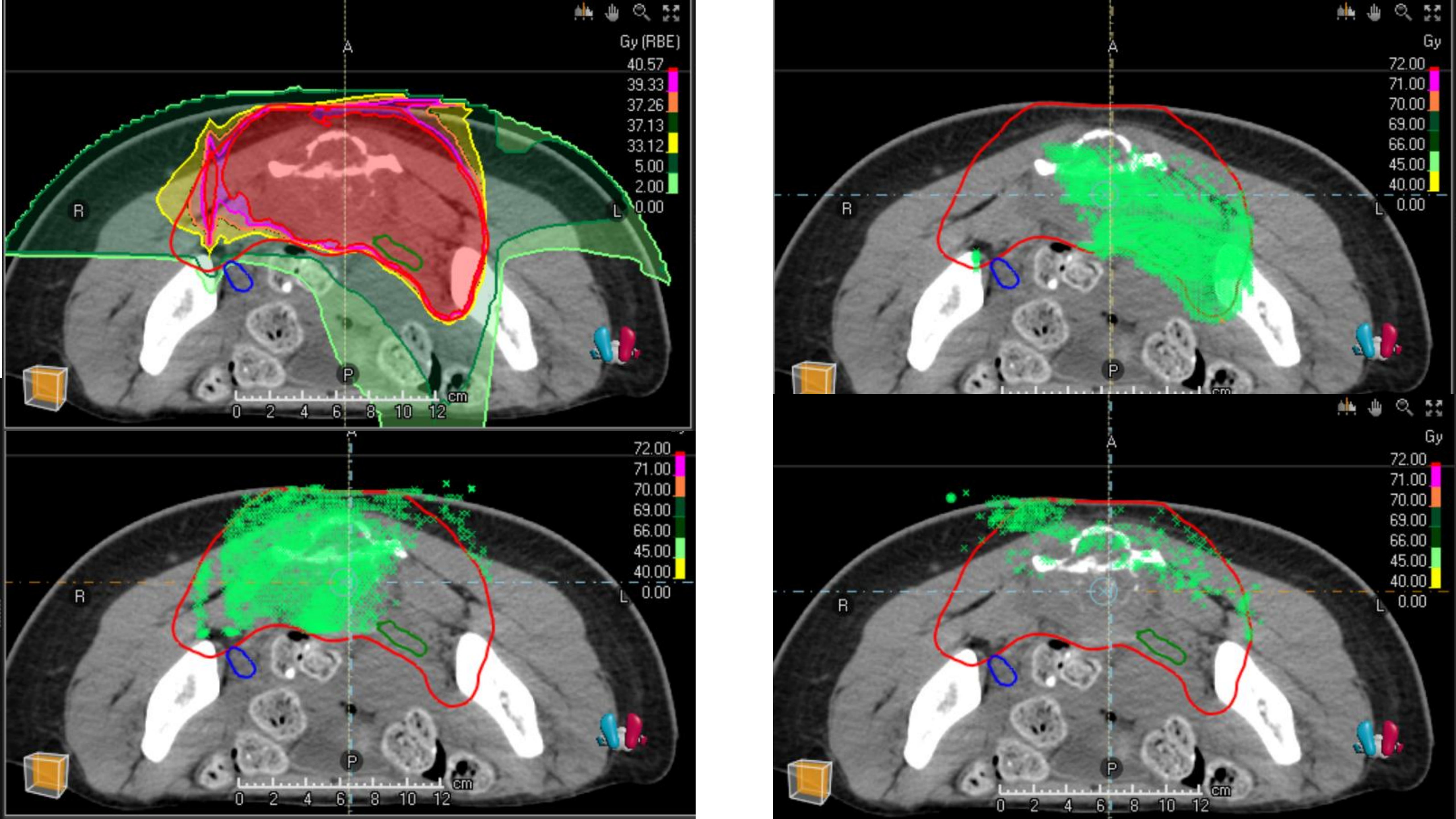




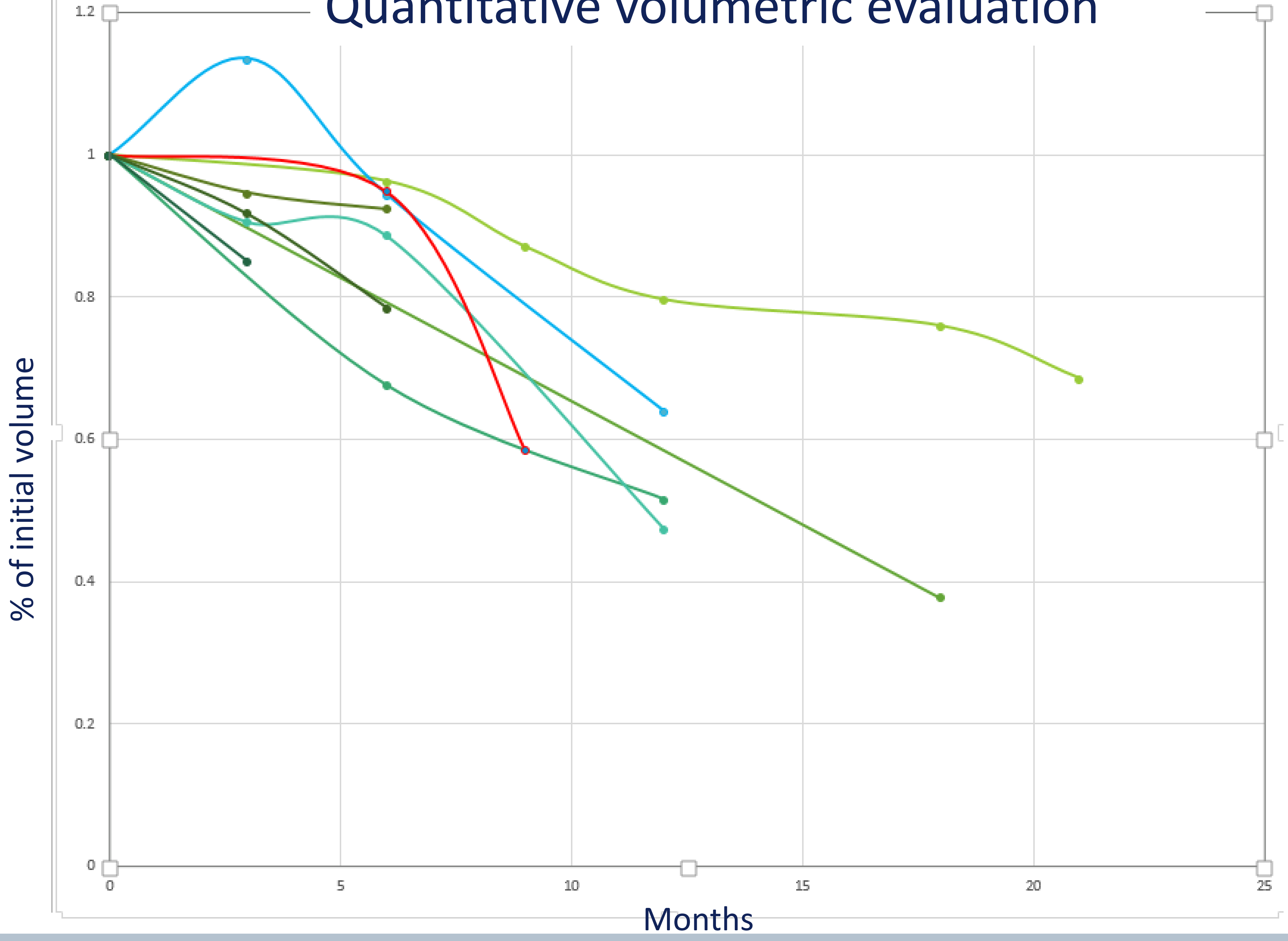


First moment
First moment of dirty dose fraction
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
5
10
15
20
25
30
35
40
45
50
55
60
70
80
100
500
1000
LET threshold [keV/um]
S_8 cm
S_10 cm
S_12 cm
S_10 cm
L_15 cm
L_15 cm
L_16 cm
L_17 cm
L_18 cm
L_18 cm
L_19 cm
L_19 cm
L_19 cm
L_21 cm
L_23 cm
L_24 cm
L_24 cm
L_27 cm

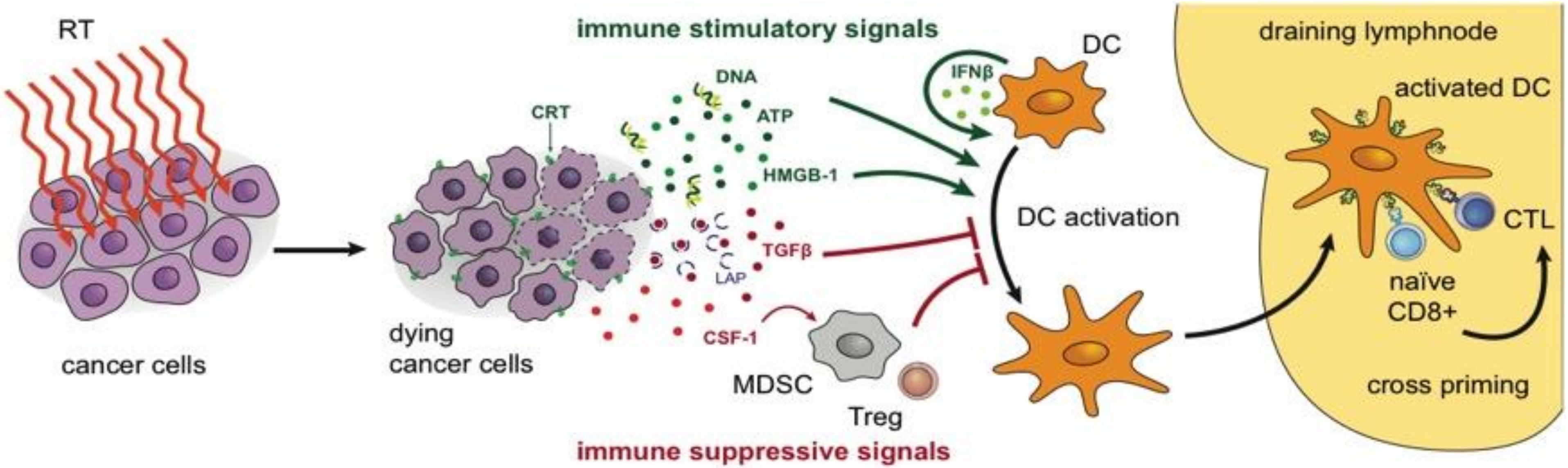

A
Gy (RBE)
69.92
66.24
41.00
38.00
35.00
8.00
5.00
2.00
0.00
R
L


Gy (RBE)
40.57
39.33
37.26
37.13
33.12
5.00
2.00
0.00
A
R
L
P
0 2 4 6 8 10 12 cm
Gy
72.00
71.00
70.00
69.00
66.00
45.00
40.00
0.00

Quantitative volumetric evaluation



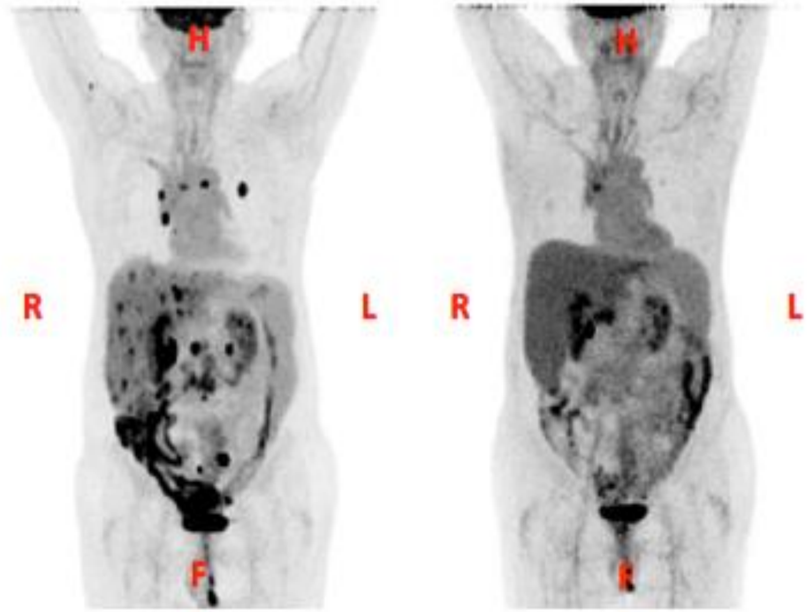
CIRT + immune response



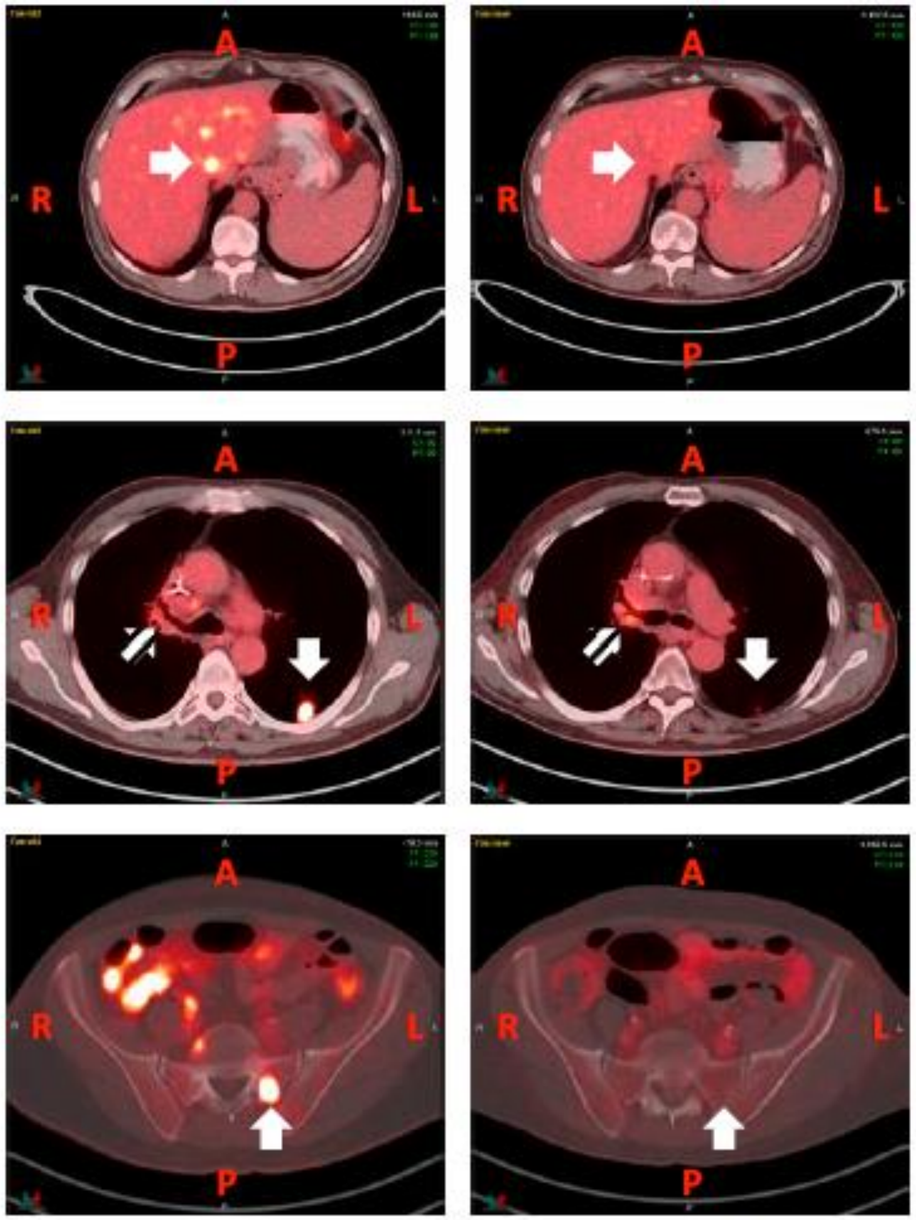
Formenti & Demaria, *Lancet Oncol*. 2009

Courtesy of dr. M Durante

NSCLC progressing after 3 lines of chemo
and chest RT: Multiple lung, bone
and liver metastasis



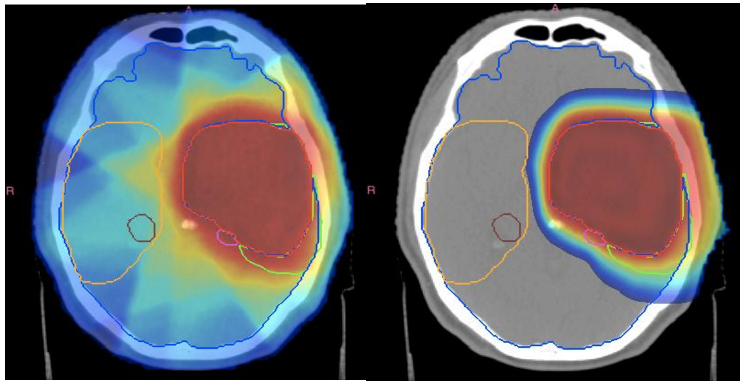
August 2012 PET/CT January 2013 PET/CT



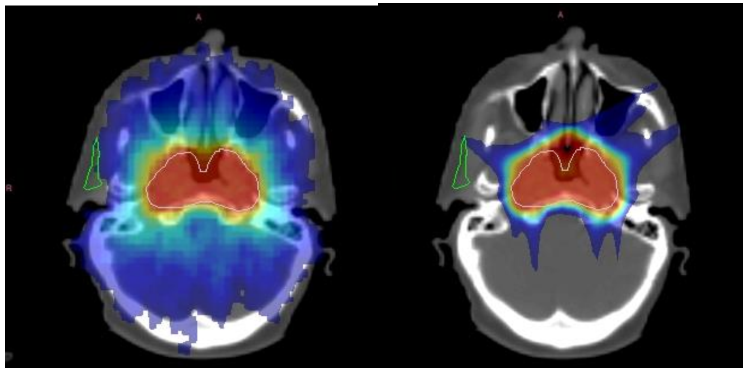
August 2012 PET/CT January 2013 PET/CT

RT to one liver met 6 Gy X 5 (TD 30 GY)
Ipilimumab, 3 mg/Kg, after first RT q3 weeks, X 4

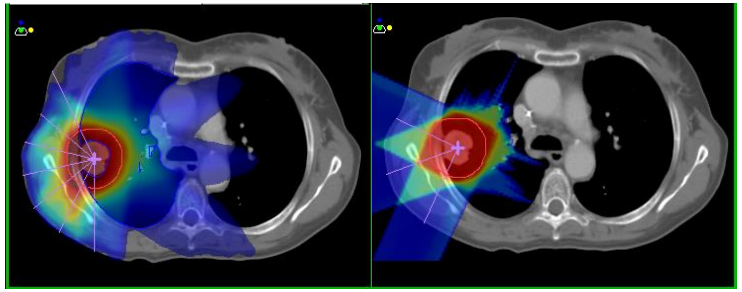
The physical advantages of CPT



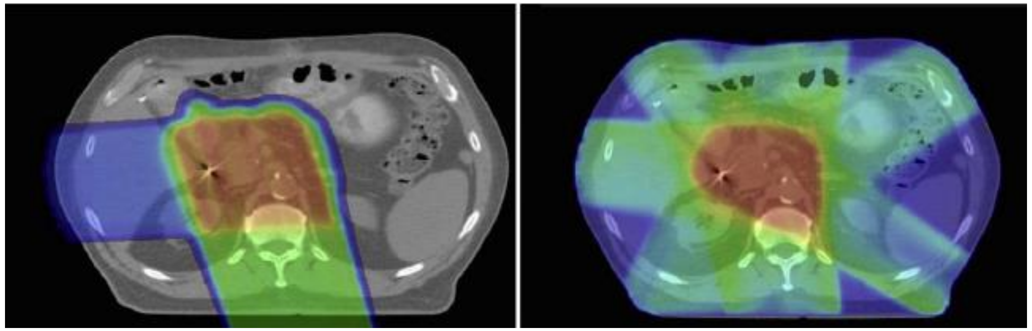
CNS



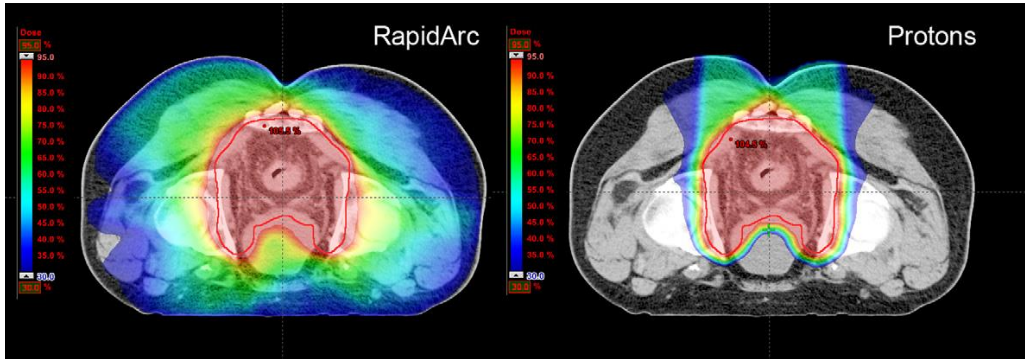
H & N



LUNG

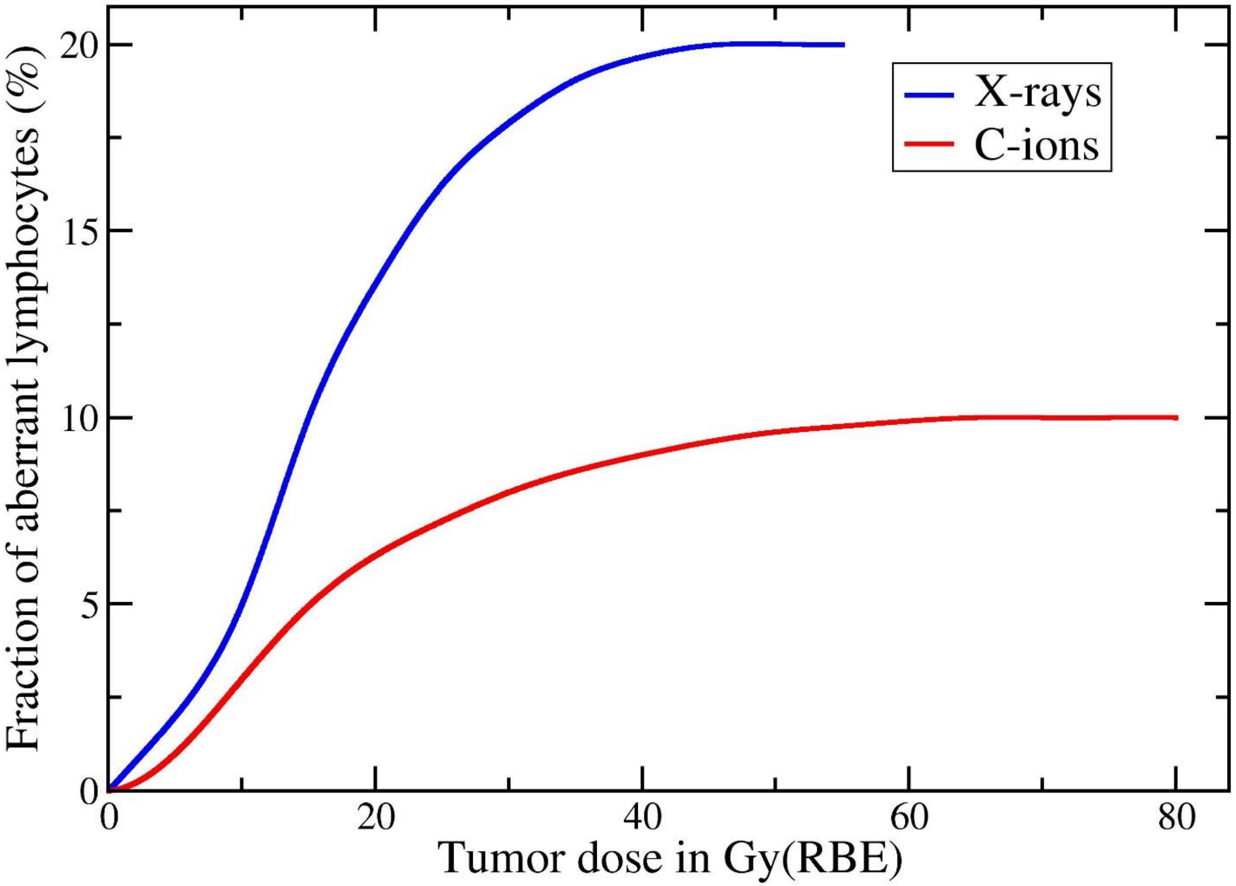


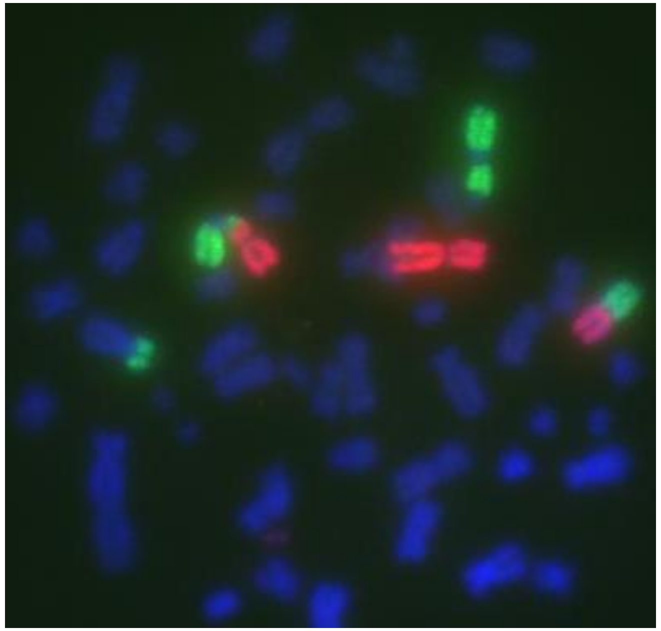
ABDOMEN



PELVIS

Courtesy of Marco Schwarz, TIFPA, Trento





Durante *et al., Int. J. Radiat. Oncol. Biol. Phys*. 2000

High LET Helium (160 keV/mm) killed cells producing more ICD markesr as compared to X rays:

ATP 4.12 times

HMGB1 1.97 times

CRT 2.74 times

1075

High Linear Energy Transfer Particle Irradiation Leads to Increased Expression of In Vitro Markers of Immunogenic Cell Death

J. Ng,[1] E.B. Golden,[2] J. Khani,[1] M. Buonanno,[3] M. Ouyeng,[2] D. Stuff,[2] J. Khani,[2] W.H. Shen,[2] V. Grilj,[4] A. Harken,[4] I. Shuryak,[4] D.J. Brenner,[5] and S.C. Formenti[6]; *[1]Weill Cornell Medicine, New York, NY, [2]Weill Cornell Medical College, New York, NY, [3]Columbia University Medical Center, New York, NY, [4]Columbia University Medical Center, New York, NY, [5]Center for Radiological Research, Columbia University Medical Center, New York, NY, [6]Department of Radiation Oncology, Weill Cornell Medicine, New York, NY*

Journal of Radiation Research, Vol. 59, No. 5, 2018, pp. 541–546
doi: 10.1093/jrr/rry049
Advance Access Publication: 27 June 2018

High linear energy transfer carbon-ion irradiation increases the release of the immune mediator high mobility group box 1 from human cancer cells

Masahiro Onishi[1,2], Noriyuki Okonogi[1,*], Takahiro Oike[2], Yuya Yoshimoto[2], Hiro Sato[2], Yoshiyuki Suzuki[3], Tadashi Kamada[1] and Takashi Nakano[2]

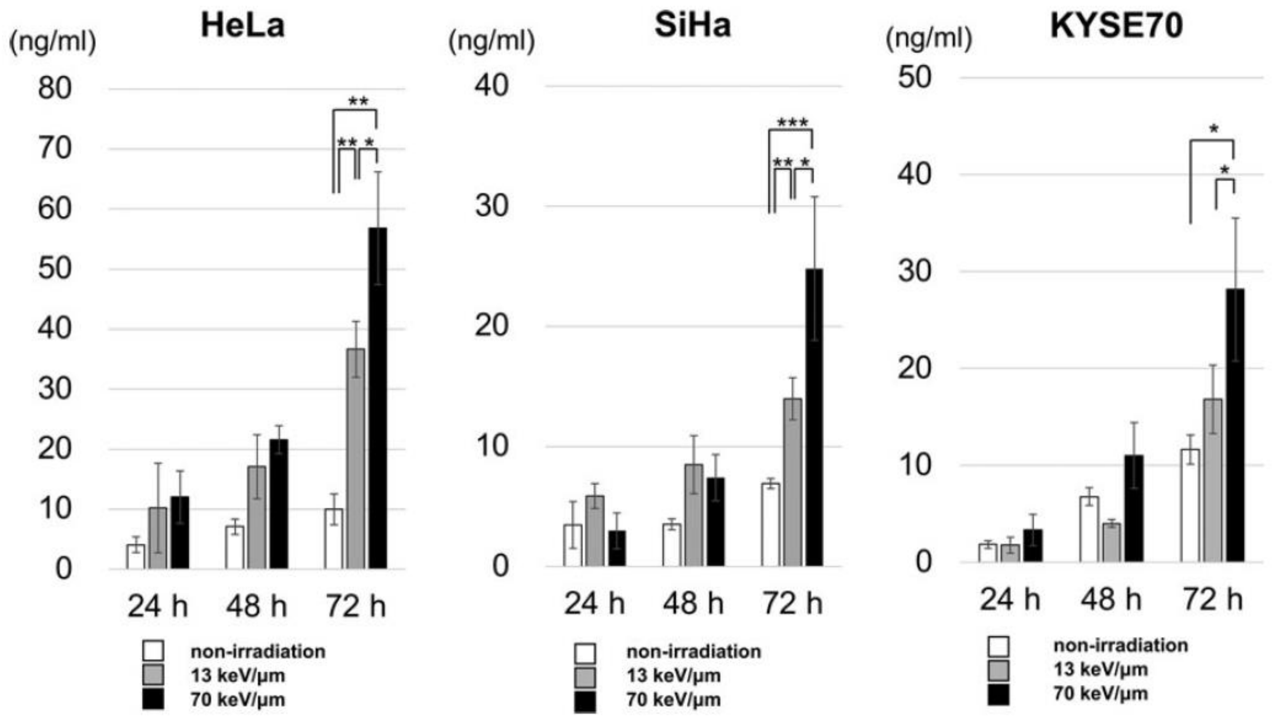


Fig. 3. HMGB1 release from irradiated cancer cells. Three human cancer cell lines were treated with a D_{10} dose of 13 or 70 keV/μm C-ion beams and cultured for the indicated times. ELISA was used to measure the HMGB1 concentrations in the culture supernatants. The results are expressed as the mean ± SD of four independent experiments. *, $P < 0.05$;**, $P < 0.01$; ***, $P < 0.001$.

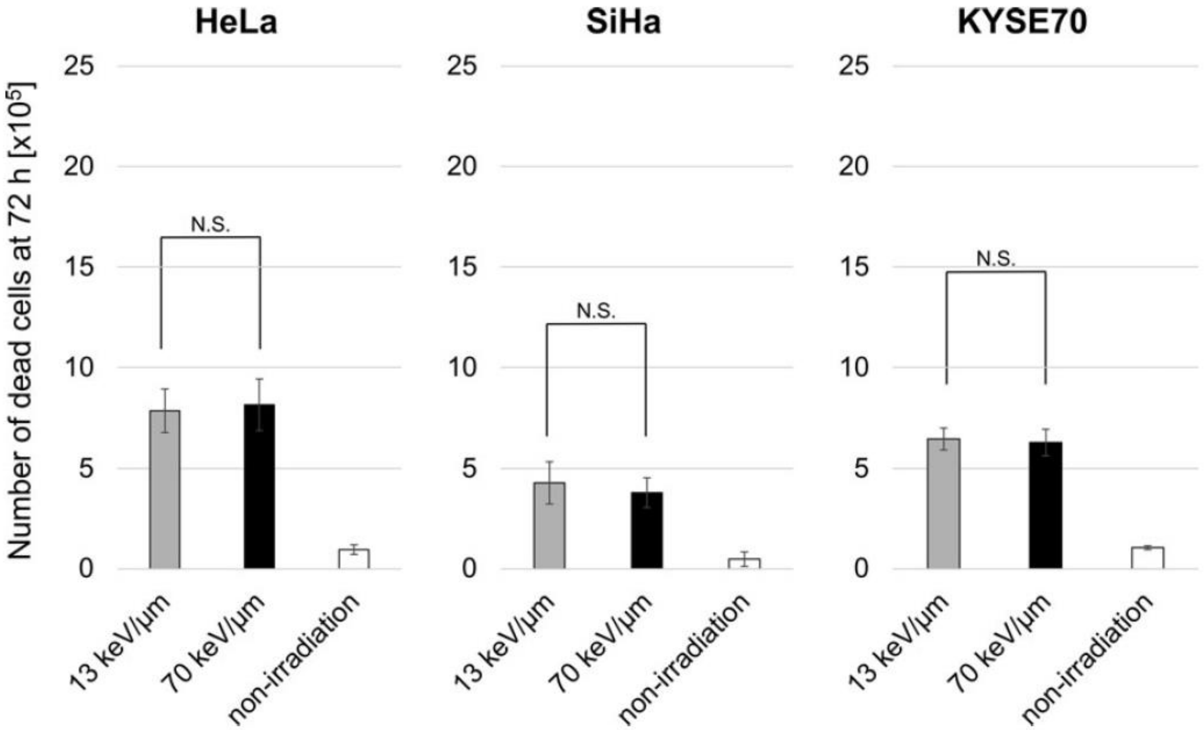
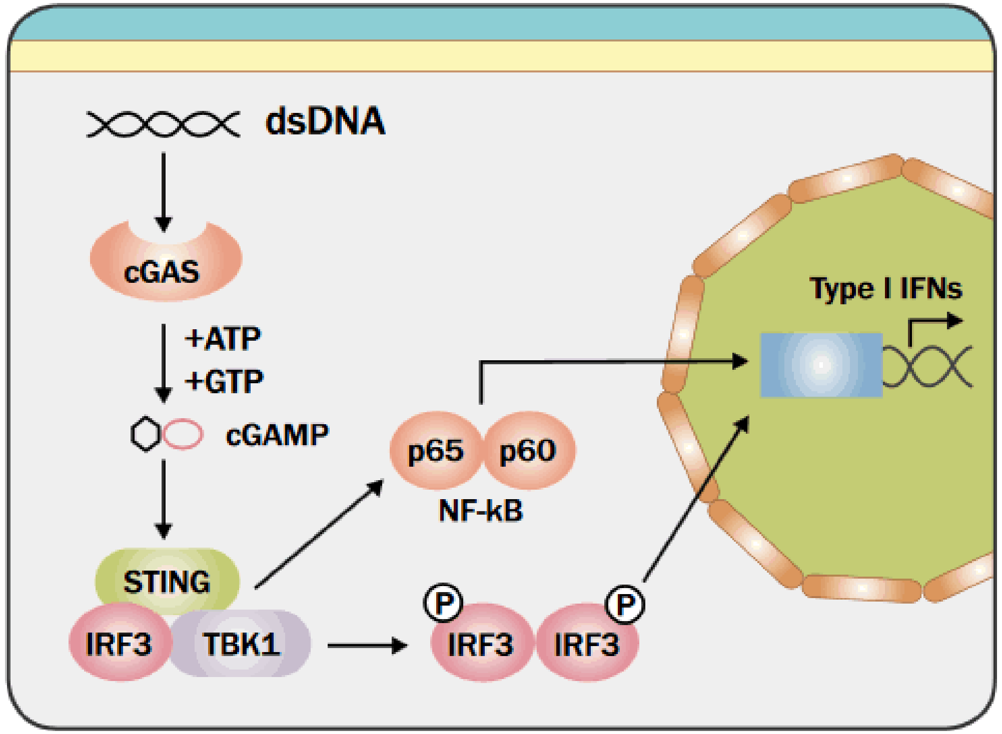
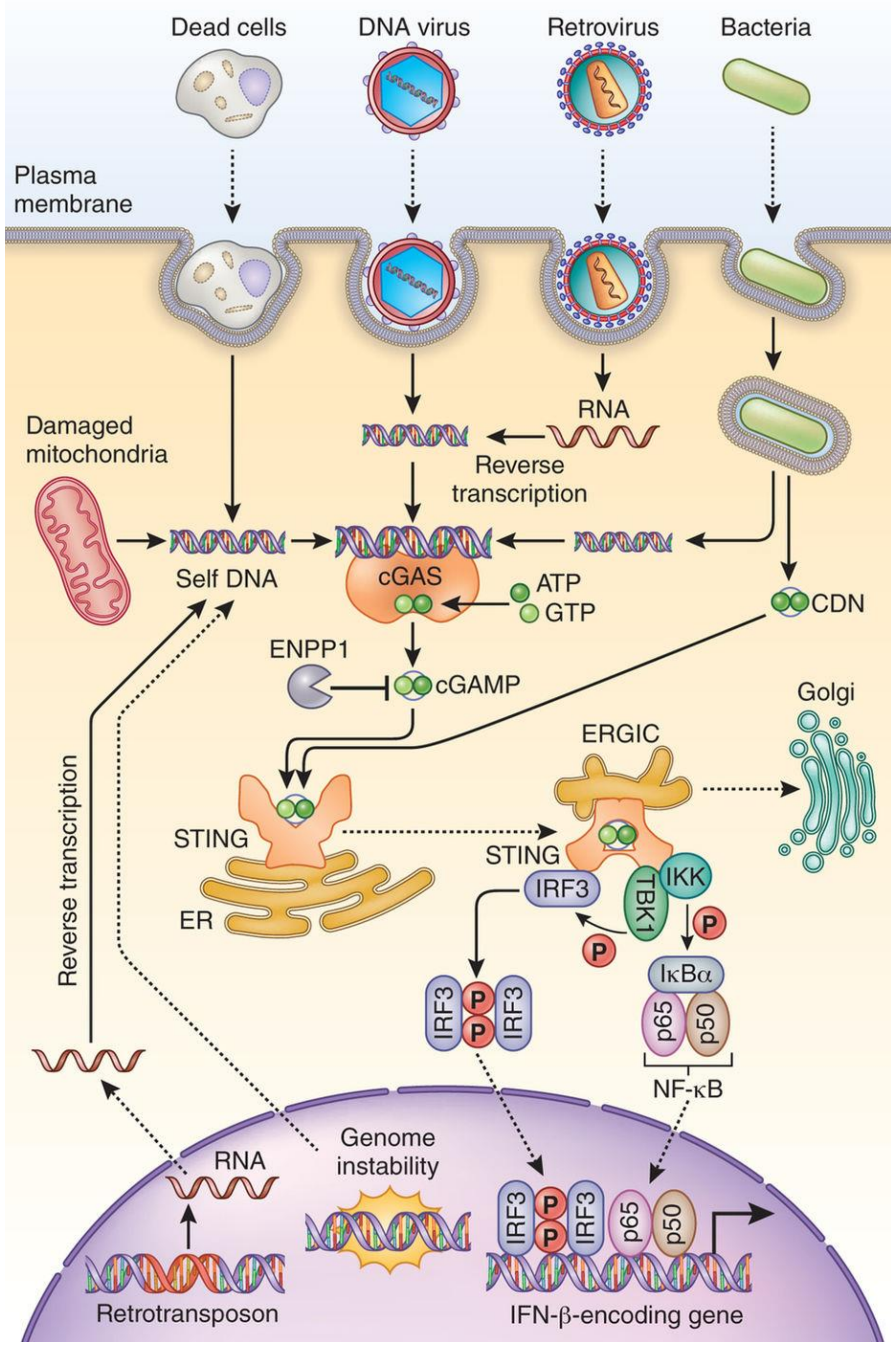


Fig. 4. Number of dead cancer cells 72 h after irradiation. Three human cancer cell lines were treated with a D_{10} dose of C-ion beams and then cultured for 72 h. The numbers shown are dead cells expressed as the mean ± SD of four independent experiments. N.S., not significant.

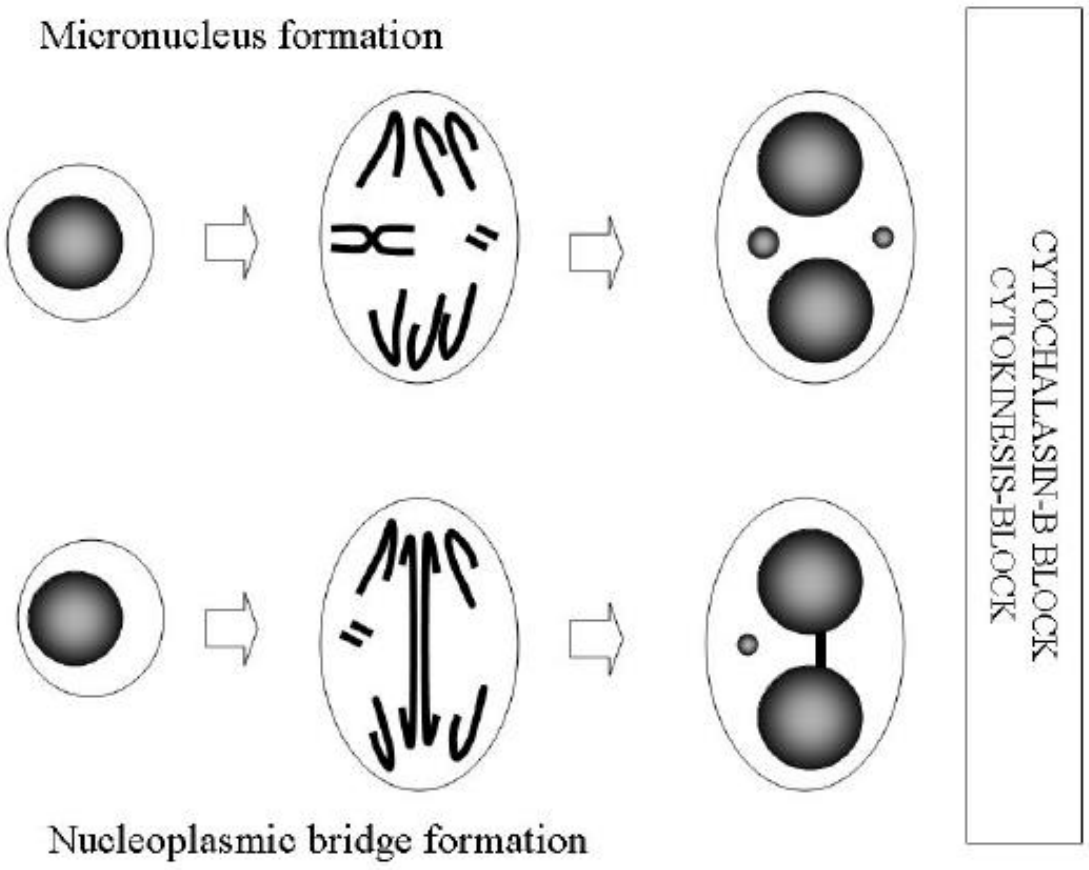
cGAS/STING pathway



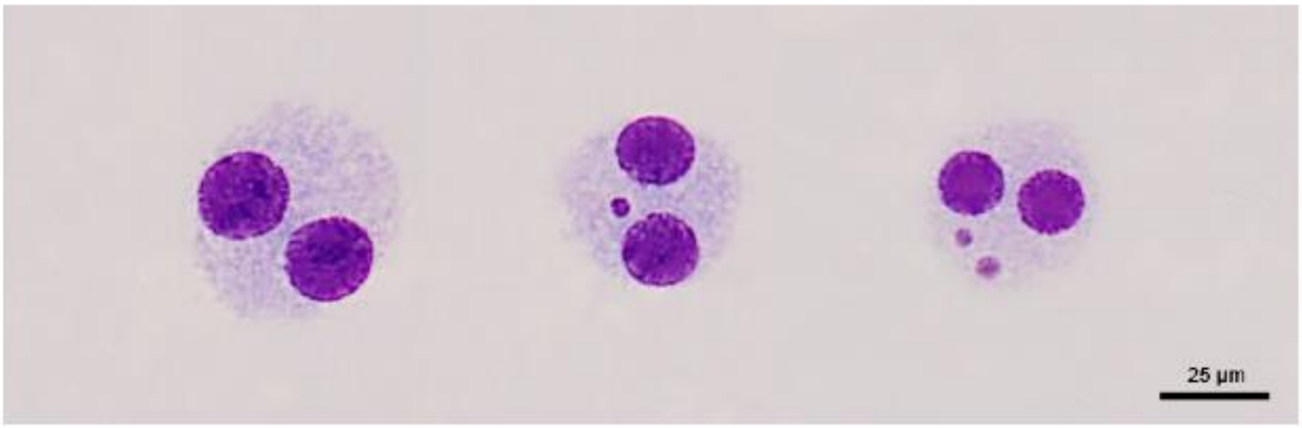


Chen *et al., Nat. Immunol*. 2016

Micronuclei can trigger the cGAS/STING pathway



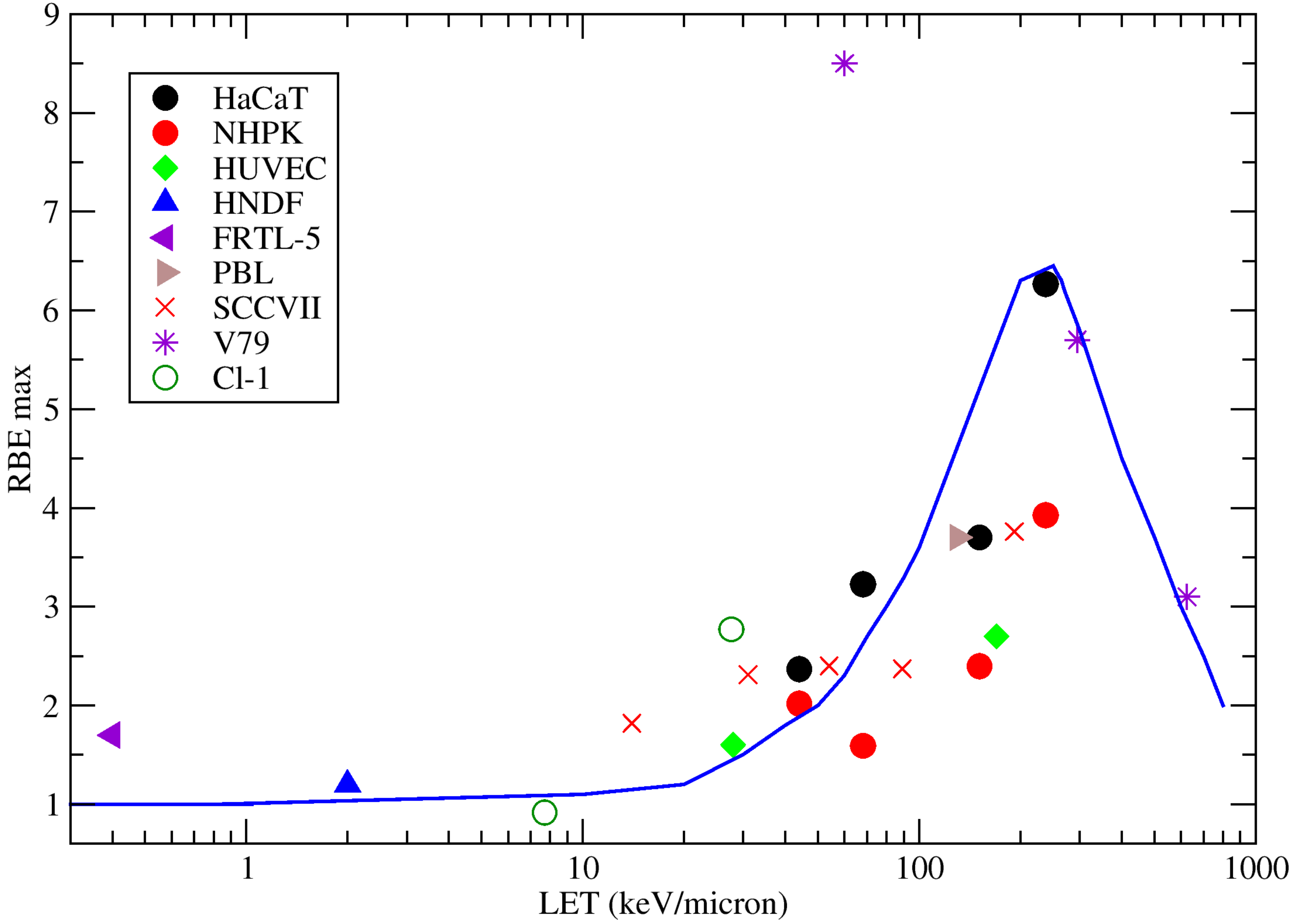
A



Mackenzie et al., *Nature* 2017

Harding et al., *Nature* 2017

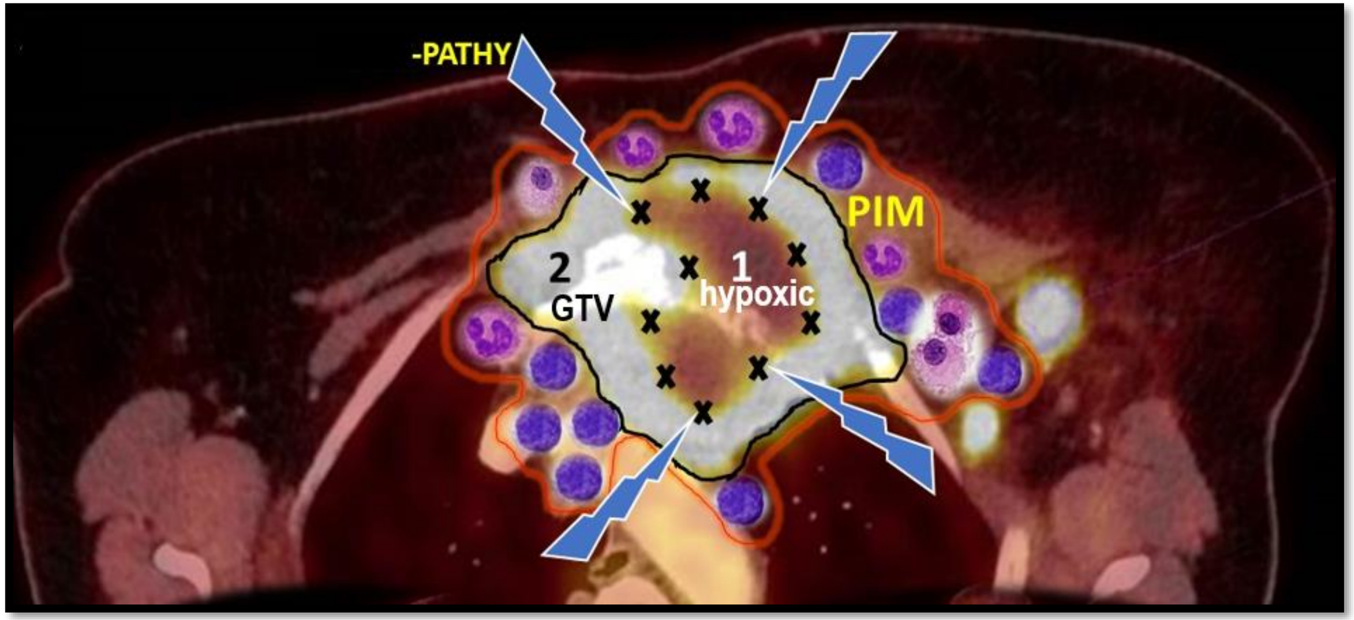
Courtesy of dr. M Durante

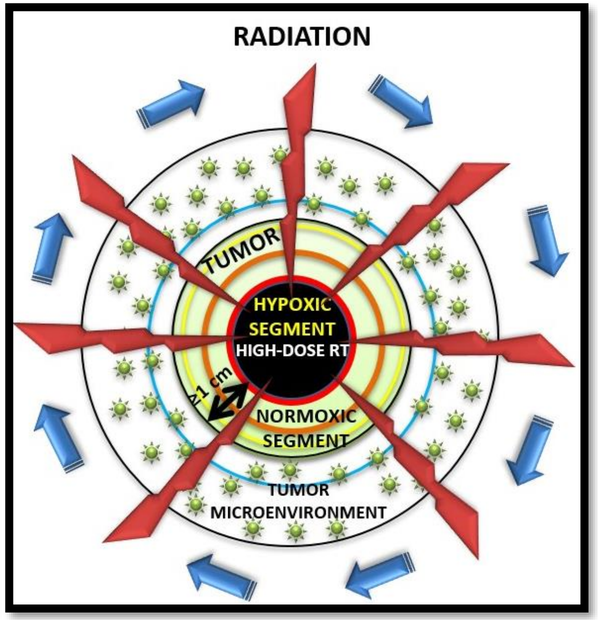


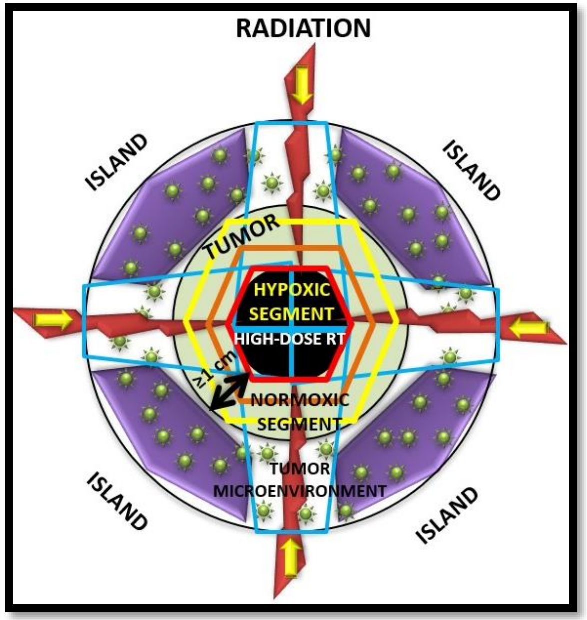
Durante & Formenti, *Front. Oncol. 2018*

PATHY concept

- ***PATHY – PArtial Tumor irradiation targeting HYpoxic segment***: a novel approach for exploitation of bystander and abscopal effects.
- Developed in 2015 aiming to improve RT-therapeutic ratio by maximizing the radiation-induced immune response (local and distant).
- –**PATHY** consists of 3 components:
  1.) HIGH-DOSE PARTIAL TUMOR IRRADIATION TARGETING HYPOXIC SEGMENT (more abscopal tumor part(preclinical findings)),
  2.) SPARING OF PERITUMORAL IMMUNE MICROENVIRONMENT (PIM) as a NEW OAR,
  3.) TIME-SYNCHRONIZED IMMUNE-GUIDED IRRADIATION.







- TARGET POPULATION: patients with unresectable bulky unsuitable for conventional RT-CHT.

PATIENTS TREATED WITH -PATHY APPROACH: OUTCOMES

cancers
2021

Review

Shifting the Immune-Suppressive to Predominant Immune-Stimulatory Radiation Effects by SBRT-PArtial Tumor Irradiation Targeting HYpoxic Segment (SBRT-PATHY)

Slavisa Tubin [1,*], Seema Gupta [2], Michael Grusch [3], Helmuth H. Popper [4], Luka Brcic [4], Martin L. Ashdown [5], Samir N. Khleif [2], Barbara Peter-Vörösmarty [3], Martin Hyden [6], Simone Negrini [7], Piero Fossati [1] and Eugen Hug [1]

Table 1. Treatment characteristics of the selected studies.

Authors (year of publication) [reference]	Tubin et al. (2017) [21]	Tubin et al. (2019) [37]	Massaccesi* et al. (2019) [38]	Tubin et al. (2019) [39]	Tubin** et al. (2020) [40]	Tubin et al. (2019) [41]	Tubin** et al. (2020) [42]
Type of study	Retrospective	Retrospective phase II	Retrospective case series (re-irradiation)	Retrospective	Retrospective	Prospective	Prospective phase I
Number of patients underwent SBRT-PATHY	7	20	8	23	3	8	20
Median follow up (months)	6 (2–9)	13 (4-27)	7 (1-15)	9.4 (4-20)	5.3 (3-7)	11.8 (4-22)	9 (4-12)
Local control (bystander effect)	100%	95%	83%	96%	67%	75%	73%
Abscopal response	28.6%	45%	Not evaluable	52%	Not evaluable	50%	47%
Symptom relief	100%	80%	100%	96%	67%	88%	82%
Treated symptoms	Dyspnea, pain.	Dyspnea, pain, cough, hemoptysis.	Pain, bleeding	Dyspnea, pain, cough.	Pain, Dysphagia.	Dyspnea, pain, cough.	Dyspnea, pain, cough, haemoptysis, edema-extremities, dysphonia.
Toxicity	none	Fatigue G1 (15%)	none	none	none	none	Fatigue G1 (20%)
Hematological toxicity/leucopenia	none	none	none	none	none	none	none
Median total dose/ dose-fraction (Gy)	10/10	10-30/10	10/10	10-30/10	36/12	30/10	30/10

Apr 2022

cancers

Novel Carbon Ion and Proton Partial Irradiation of Recurrent Unresectable Bulky Tumors (Particle-PATHY): Early Indication of Effectiveness and Safety

by Slavisa Tubin *, Piero Fossati, Antonio Carlino, Giovanna Martino, Joanna Gora, Markus Stock and Eugen Hug

Follow Up (Median/Range)	**6.3/3–16**
BULKY-TUMOR CONTROL at 3 months:	**8/73%**
PR	8/73%
PD	3/27%
OVERALL BULKY-TUMOR CONTROL	5/46%
CR	1/9%
PR	4/37%
PD	6/54%
DOWNSIZING (neoadjuvant effect):	
achieved	8/73%
not achieved	3/27%
OVERALL SURVIVAL	
alive	7/64%
dead	4/36%
Median survival	6.73 months (range 3–16)
PROGRESSION-FREE SURVIVAL	
progression-free	5/46%
progressed	6/54%
Median progression-free survival	5.16 months (range 2–16)
SYMPTOM(s) RELIEF:	
yes	10/91%
no	1/9%
KPS IMPROVEMENT after PATHY (median/range)	**91% (20%/10–60%)**
SIDE EFFECTS:	**3/27%**
fatigue	3/27%
others	0/0%
PAIN KILLERS REDUCTION	**10/91%**
ABSCOPAL EFFECT (5 Pts with assessable N+/M+)	**3/60%**
TUMOR-VOLUME REGRESSION avg (cc/%)	**890.4/61%**
DURATION OF LOCAL CONTROL (avg/range) (months)	**5.4/2–16**

Particle-based Partial Tumor Irradiation of Unresectable Bulky Tumors (PARTICLE-PATHY)

ClinicalTrials.gov Identifier: NCT04875871

Protocol approved by the local ethic committee on 25th of February 2021

Estimated Study Start Date: June 2021

PURPOSE:

to explore the effectiveness of the **CARBON**-ions-based **PA**rtial **T**umor irradiation targeting **HY**poxic segment (**CARBO-PATHY**)

Primary endpoint:

Bystander (non-targeted local) bulky tumor response rate.

Secondary endpoints:

1. Abscopal (non-targeted distant) metastatic tumor response rate.
2. Overall survival,
3. Time to local tumor progression,
4. Time to distant tumor progression,
5. Symptoms relief,
6. Radiation related toxicity,
7. Patient reported quality of life,
8. Timing of PARTICLE-PATHY in relation to clinical outcomes.

PATIENT SELECTION/clinical scenarios:

- unresectable, bulky central nervous system (CNS)/body cT3-T4 tumors,
- bulky disease defined as tumor mass with the diameter ≥6 cm,
- largely hypoxic tumors,
- large in-field/marginal recurrence after prior radiotherapy.

SAMPLE SIZE: 22 patients

ARM I HIGH-DOSE GROUP:

Patients with one or more adverse clinical conditions described

RADIATION DOSE:
12-15 Gy RBE x 3

ARM II LOWER-DOSE GROUP:

Patients with no any of adverse conditions

RADIATION DOSE:
8-10 Gy RBE x 3

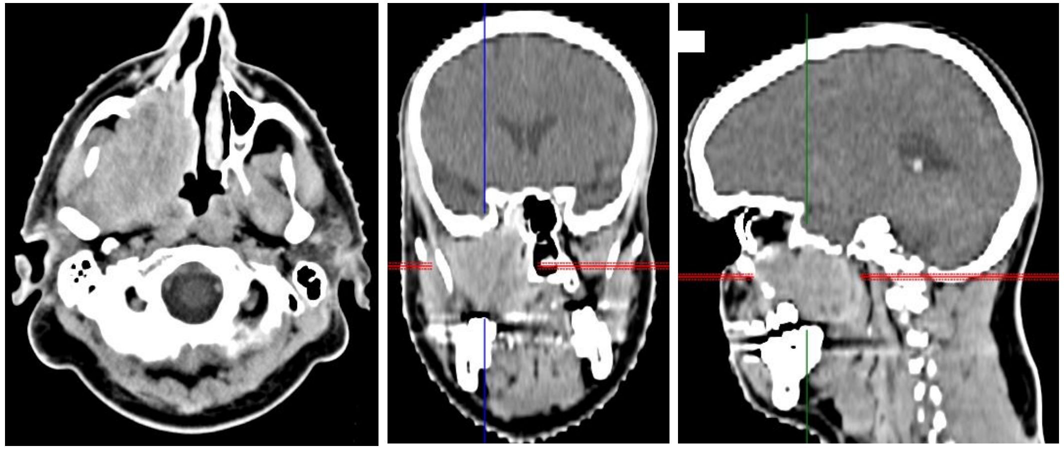
Case presentation

46 years old male

1977: St.p. Retinoblastoma right, Enucleation, external radiotherapy und Ruthenium applicator.

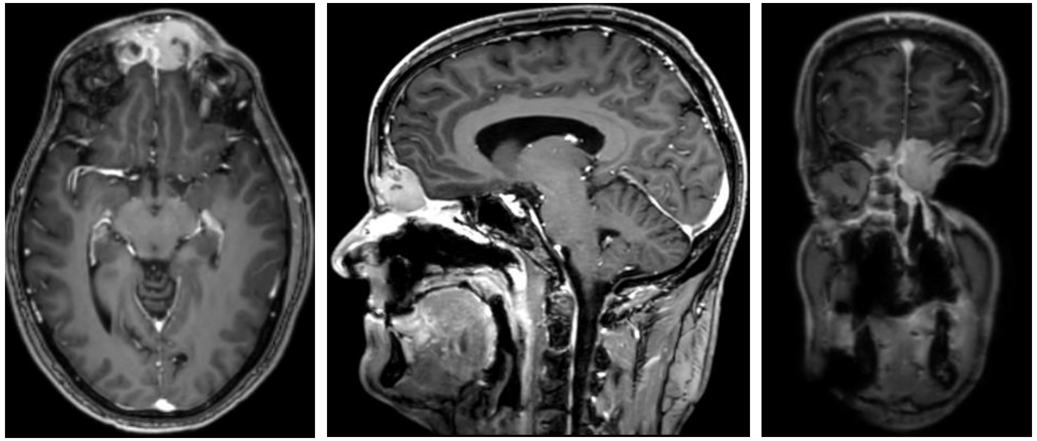
1994: St.p. Retinoblastoma left, Enucleation.

2011: Radiation-induced (secondary) leiomyosarcoma of the skull base/sinus maxillaris/nasal cavity/ base of tounge:



Treatment:
- Chemotherapy (Epirubicin/Ifosfamid),
- EBRT 70Gy/2Gy,
- Macroscopic radical tumor resection.

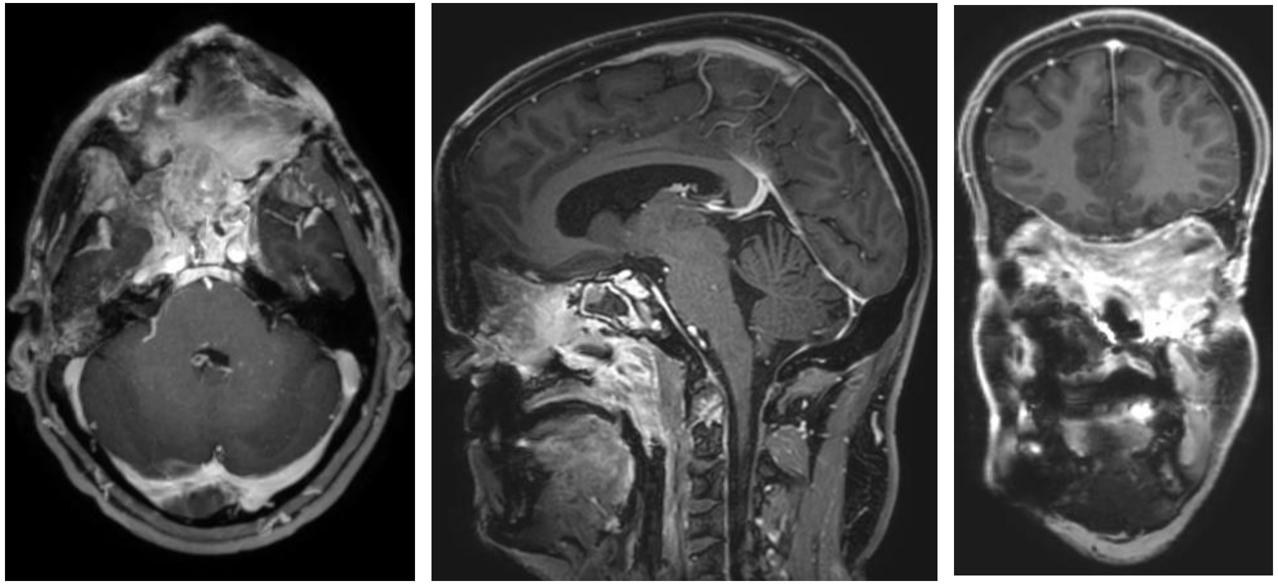
OCTOBER 2019: Local recidiv of leiomyosarcoma right frontal base:



Treatment NOVEMBER 2019:
- Macroscopic radical tumor resection.

Evaluation of further radiotherapy: PATHY planning

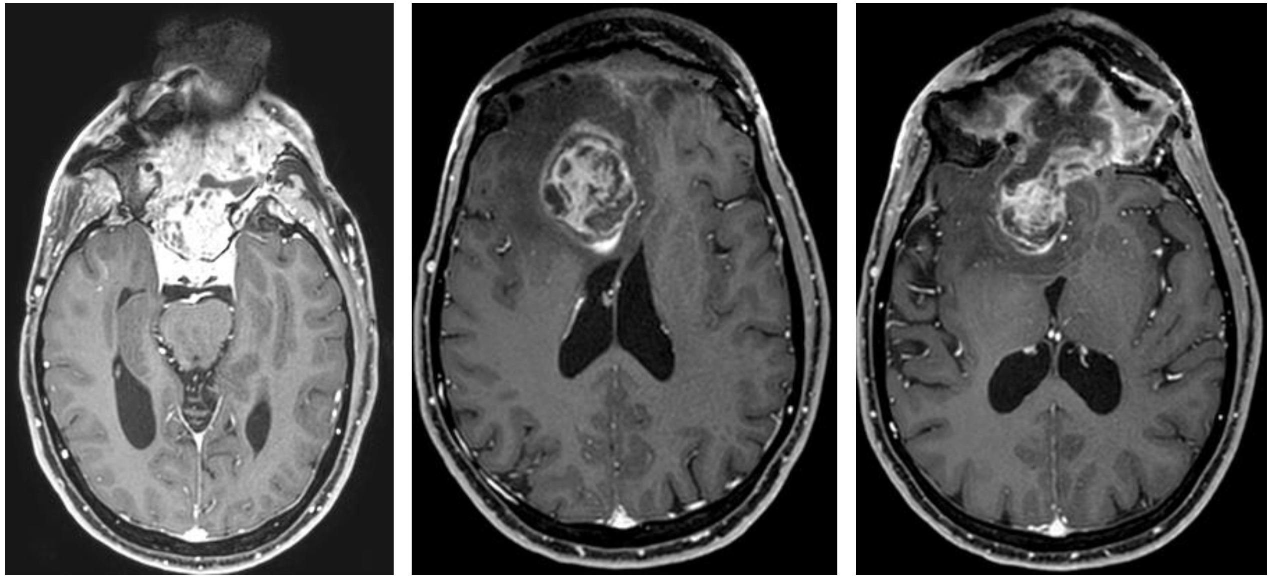
February 2020: fast growing recurrence.



Symptoms: headaches, epistaxis, dysphagia.

Fairly good general condition, KPS 80%.

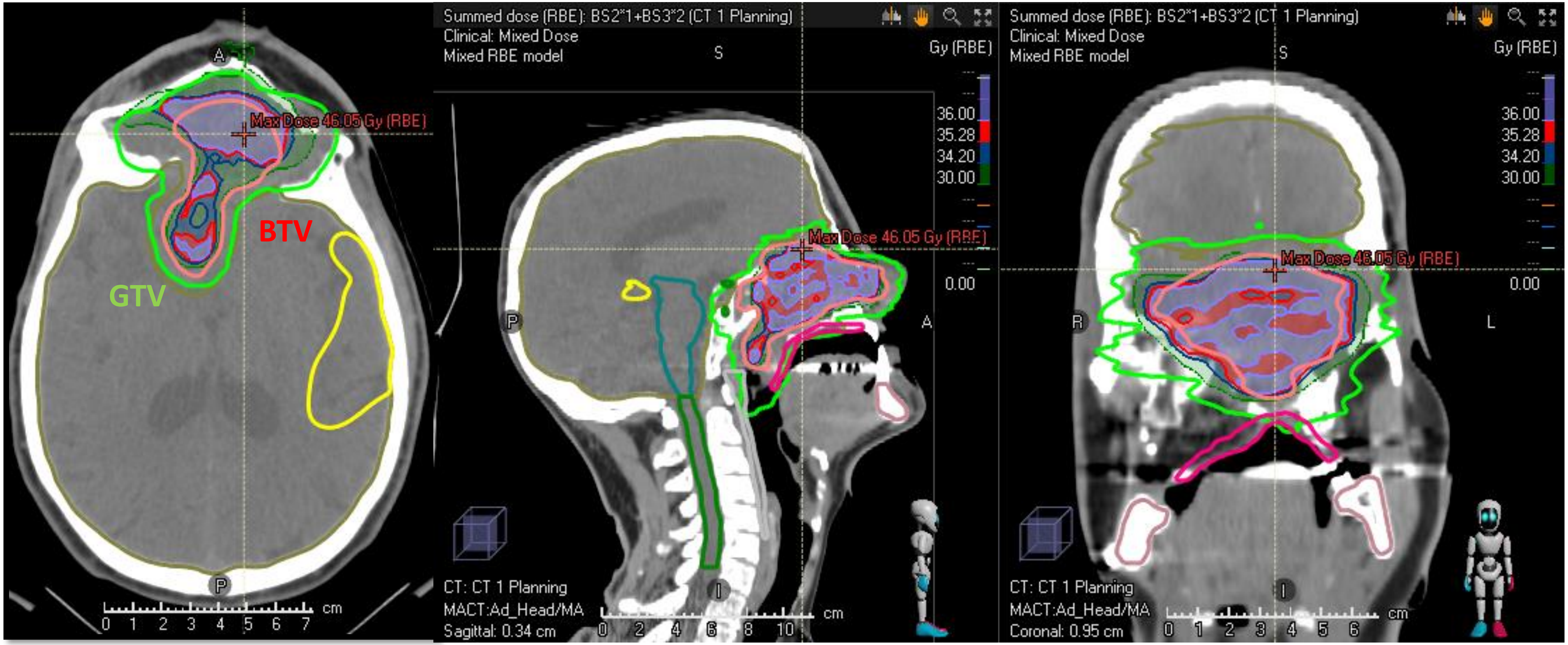
March 2020: fast local progression.

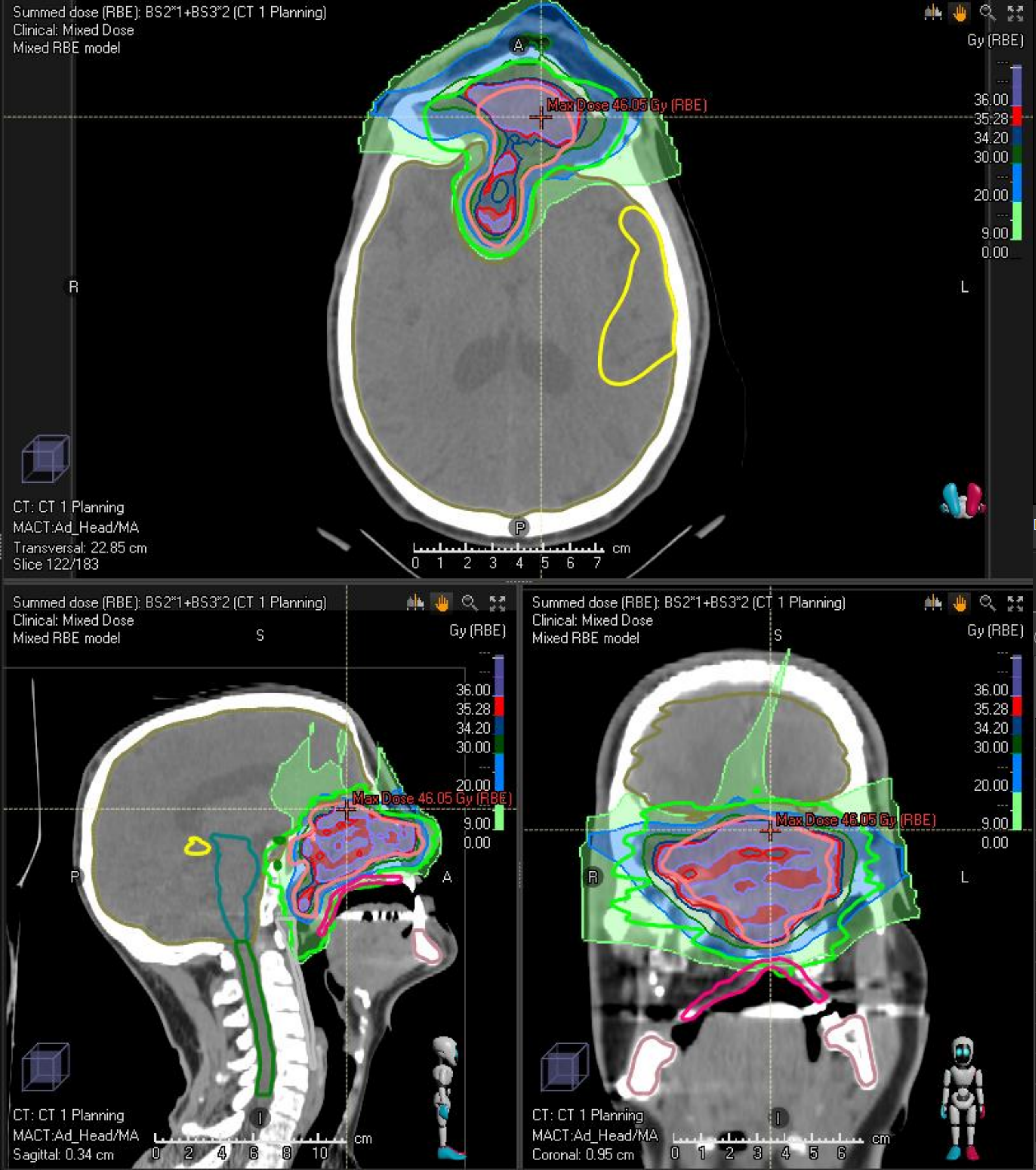


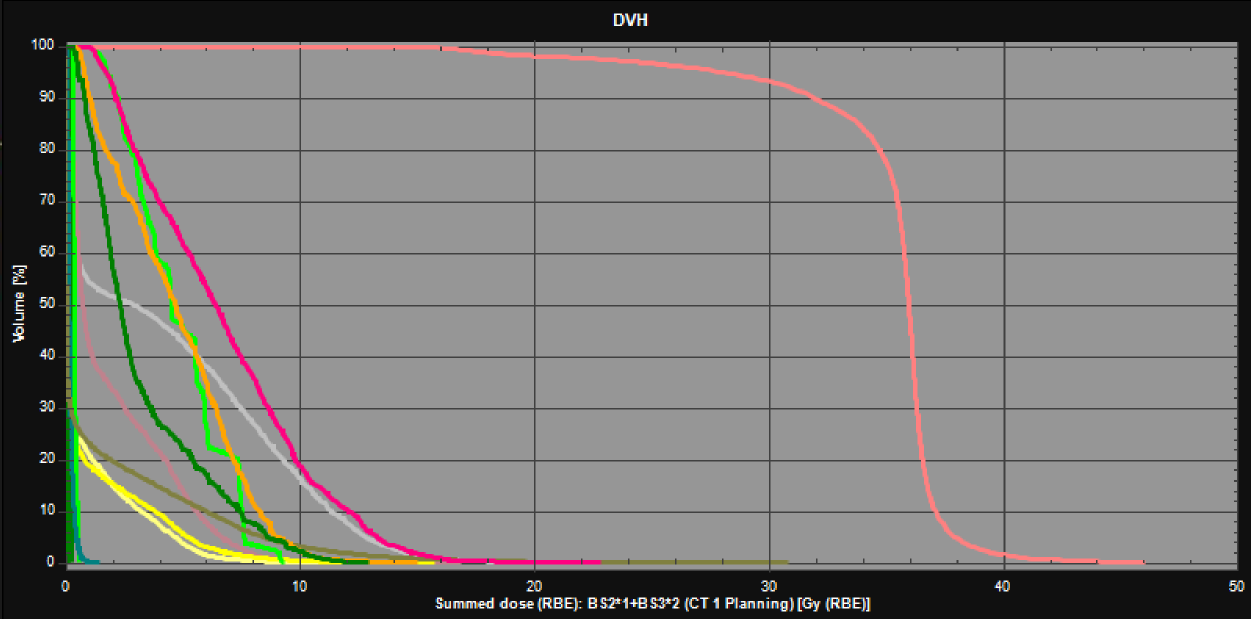
Fast symptom- and general conditions-deterioration,
KPS 40%.

No indication to further surgery, photons X-ray, CIRT, systemic therapy.

CARBO-PATHY: 12Gy RBE x 3 to 70% (Dmax 46Gy RBE in 3 fractions)







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

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

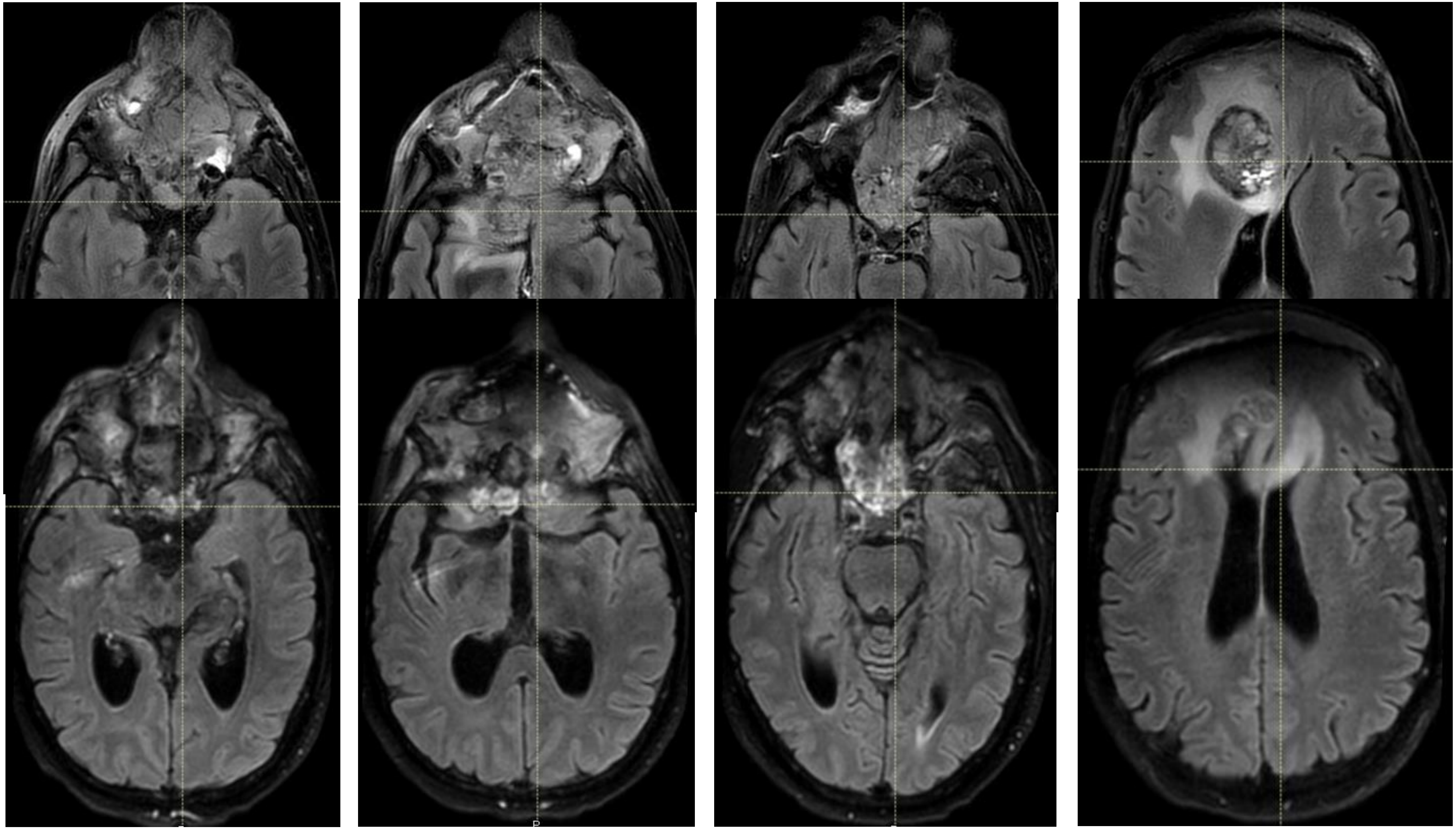
Dose Statistics Clinical Goals Biological Response Plan Fraction Schedule

ROI statistics POI statistics

Dose	ROI	ROI vol. [cm³]	Dose [Gy (RBE)] D99	D98	D95	Average	D50	D2	D1
Summed dose (RBE): B...	brain	1495.72	0.00	0.00	0.00	1.43	0.03	11.65	14.10
Summed dose (RBE): B...	brainstem	30.10	0.05	0.06	0.07	0.19	0.15	0.61	0.68
Summed dose (RBE): B...	carotid left	2.44	0.36	0.48	0.54	3.24	2.33	10.18	10.66
Summed dose (RBE): B...	carotid right	3.10	0.59	0.67	0.81	4.69	4.67	10.12	10.77
Summed dose (RBE): B...	cochleaLEFT	0.18	0.11	0.12	0.13	0.18	0.18	0.26	0.27
Summed dose (RBE): B...	cochleaRIGHT	0.15	0.26	0.27	0.31	0.40	0.41	0.56	0.57
Summed dose (RBE): B...	CTV1	101.70	17.71	21.24	28.13	35.09	35.98	39.47	40.78
Summed dose (RBE): B...	mandible	46.84	0.13	0.15	0.20	1.99	0.73	7.79	8.52
Summed dose (RBE): B...	palate	11.28	1.25	1.32	1.73	6.70	6.37	14.75	15.84
Summed dose (RBE): B...	pharynx	15.21	0.07	0.08	0.10	4.49	2.86	14.46	15.30
Summed dose (RBE): B...	pituitary	0.25	1.31	1.53	1.73	4.76	4.52	9.08	9.16
Summed dose (RBE): B...	spinalcord	10.26	0.01	0.01	0.01	0.05	0.03	0.13	0.14
Summed dose (RBE): B...	templobeLEFT	101.88	0.00	0.00	0.00	0.85	0.04	6.83	8.17
Summed dose (RBE): B...	templobeRIGHT	95.47	0.00	0.00	0.00	0.80	0.07	5.72	6.52

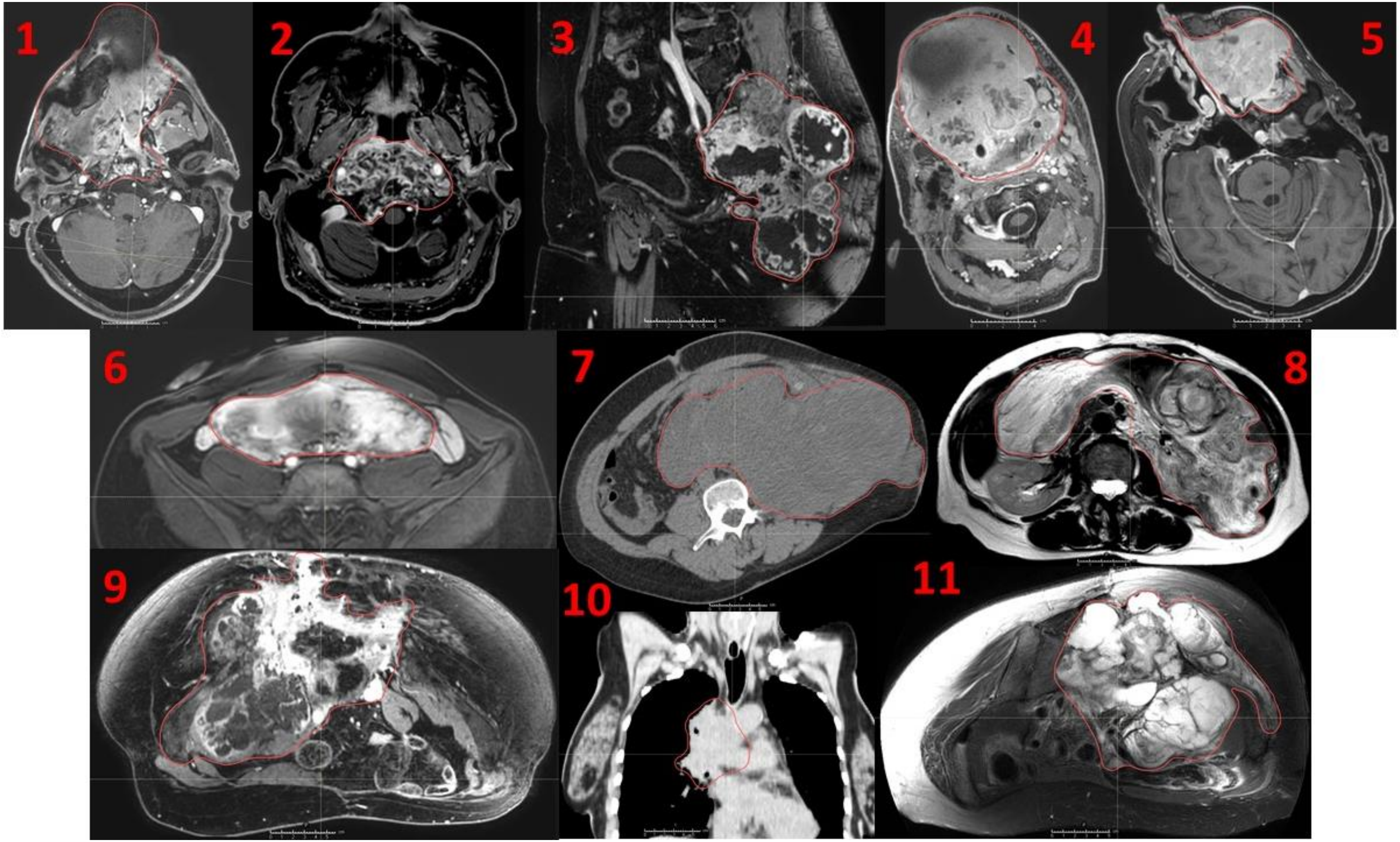
Before CARBO-PATHY

2 months after

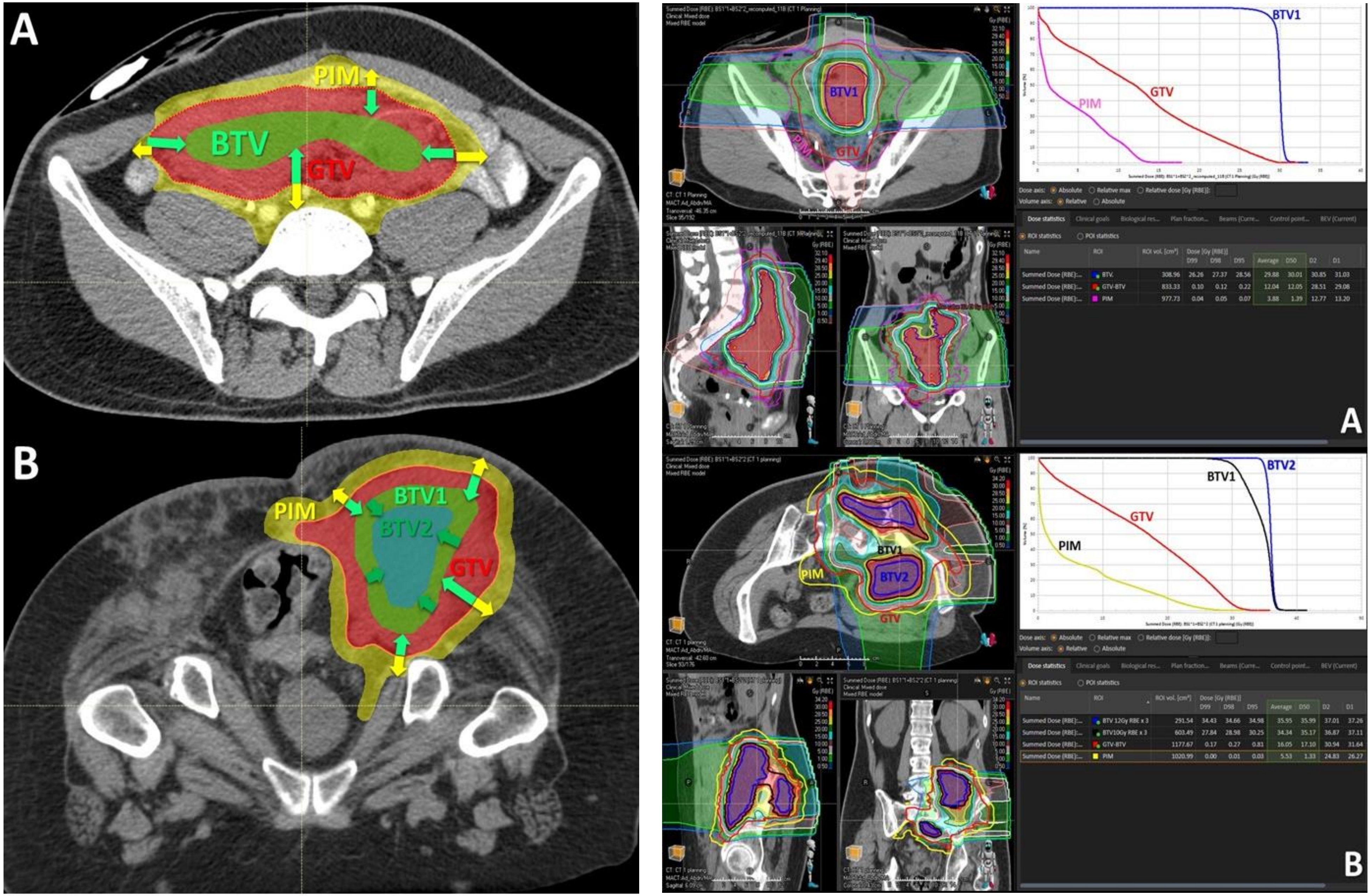


Side effects: none. KPS improved to 90%. The patient got out of bed and rode a bicycle with his wife.
He died 3 months after the treatment due to another recurrence.

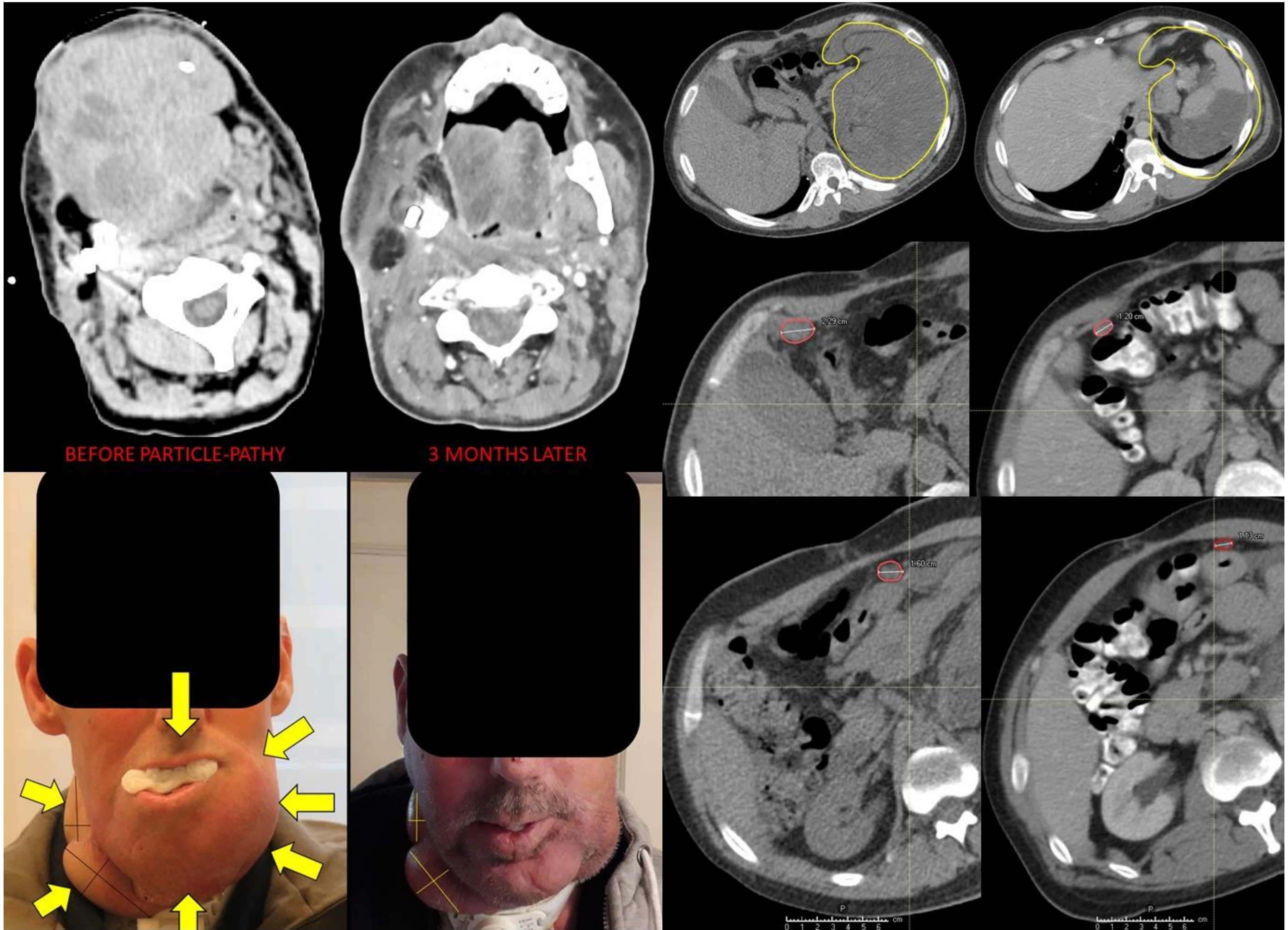
MORE IMAGES: patient population



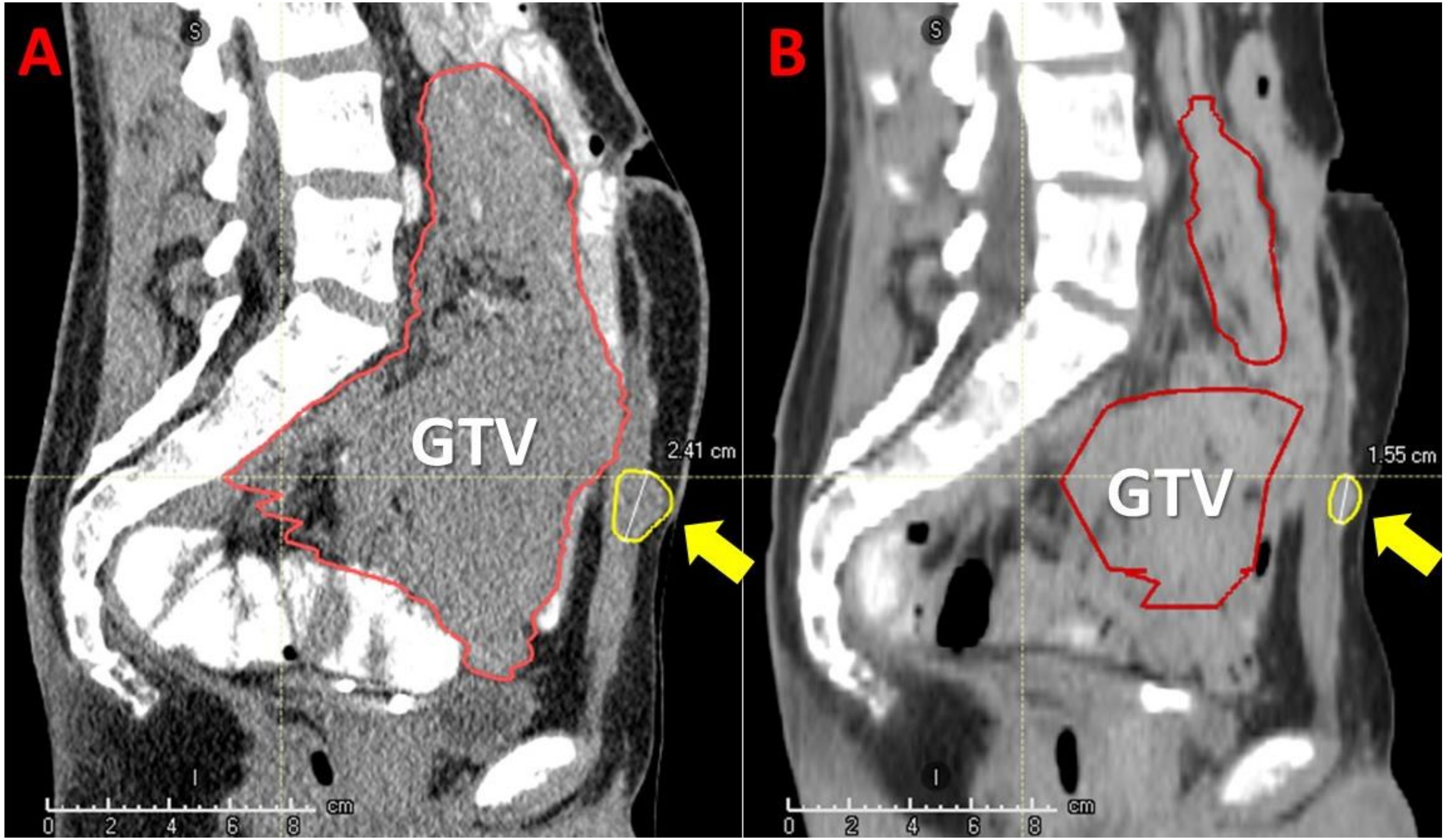
Treatment planning



Outcomes: bystander and abscopal effects



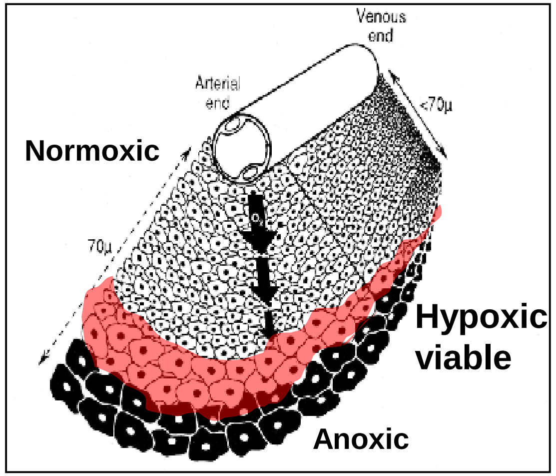
Outcomes: bystander and abscopal effects



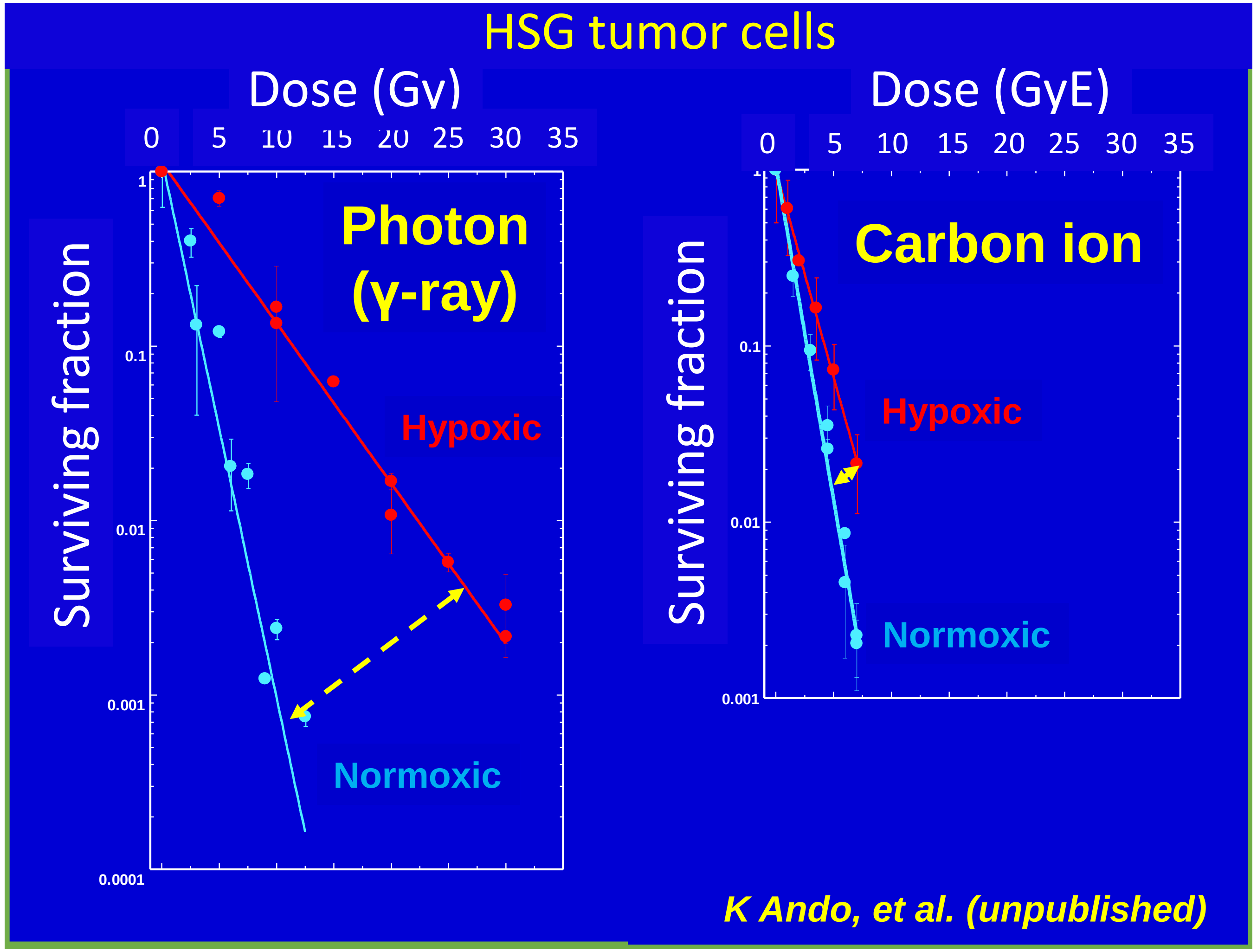
Hyopxia / reoxygenation

Carbon ion for OPC ?

Carbon ion beam have significantly smaller OER than photons



Courtesy of dr. Sato



K Ando, et al. (unpublished)

Radiotherapy and Oncology 105 (2012) 21–28
Contents lists available at SciVerse ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

PET imaging of hypoxia

Exploratory prospective trial of hypoxia-specific PET imaging during radiochemotherapy in patients with locally advanced head-and-neck cancer

Daniel Zips [b,1], Klaus Zöphel [b,1], Nasreddin Abolmaali [b], Rosalind Perrin [a,*], Andrij Abramyuk [b], Robert Haase [a], Steffen Appold [b], Jörg Steinbach [c], Jörg Kotzerke [b,2], Michael Baumann [b,c,2]

[a] OncoRay National Center for Radiation Research in Oncology, Medical Faculty, Dresden University of Technology, Germany; [b] Medical Faculty and University Hospital Carl Gustav Carus, Dresden, Germany; [c] Helmholtz Research Center Dresden-Rossendorf, Germany

Published OnlineFirst January 11, 2016; DOI: 10.1158/1078-0432.CCR-15-1990
Cancer Therapy: Clinical
Clinical Cancer Research

Low Cancer Stem Cell Marker Expression and Low Hypoxia Identify Good Prognosis Subgroups in HPV(−) HNSCC after Postoperative Radiochemotherapy: A Multicenter Study of the DKTK-ROG

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Prospective clinical trial

Residual tumour hypoxia in head-and-neck cancer patients undergoing primary radiochemotherapy, final results of a prospective trial on repeat FMISO-PET imaging

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Robustness of quantitative hypoxia PET image analysis for predicting local tumor control

David Mönnich, Stefan Welz, Daniela Thorwarth, Christina Pfannenberg, Gerald Reischl, Paul-Stefan Mauz, Konstantin Nikolaou, Christian la Fougère & Daniel Zips

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Spatial distribution of FMISO in head and neck squamous cell carcinomas during radio-chemotherapy and its correlation to pattern of failure

Sebastian Zschaeck, Robert Haase, Nasreddin Abolmaali, Rosalind Perrin, Kristin Stützer, Steffen Appold, Jörg Steinbach, Jörg Kotzerke, Daniel Zips, Christian Richter, Volker Gudziol, Mechthild Krause, Klaus Zöphel & Michael Baumann

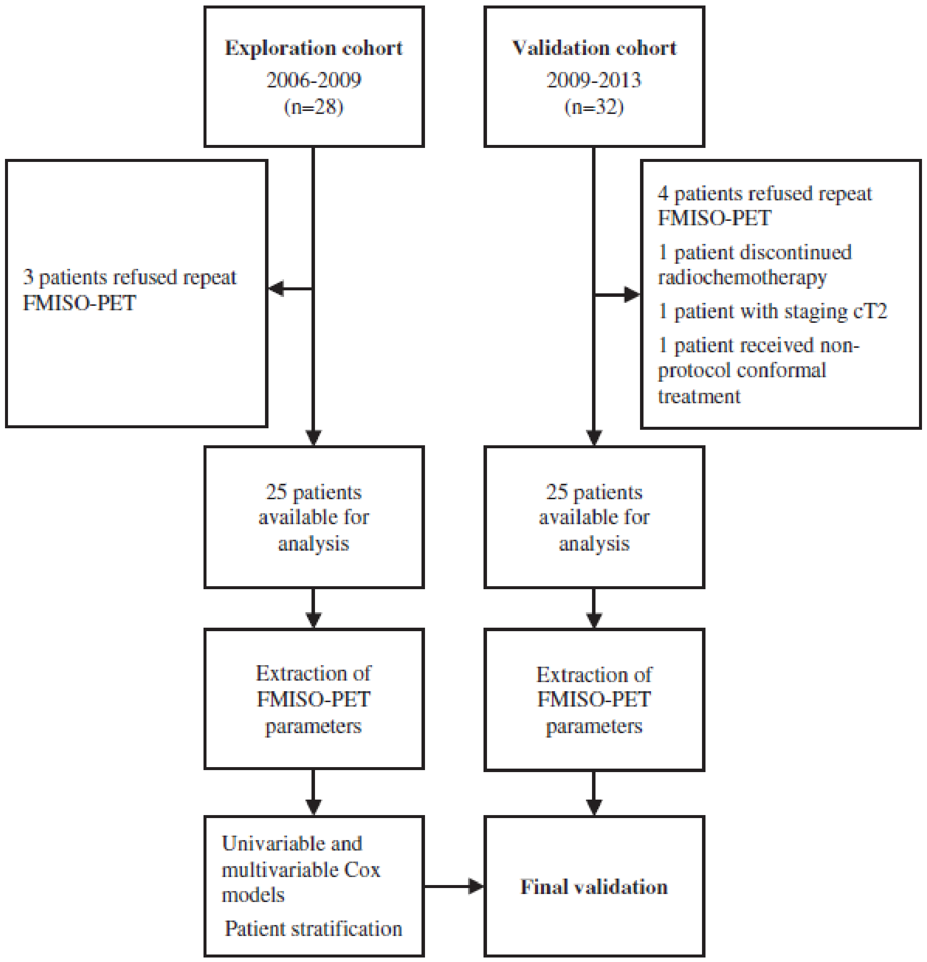
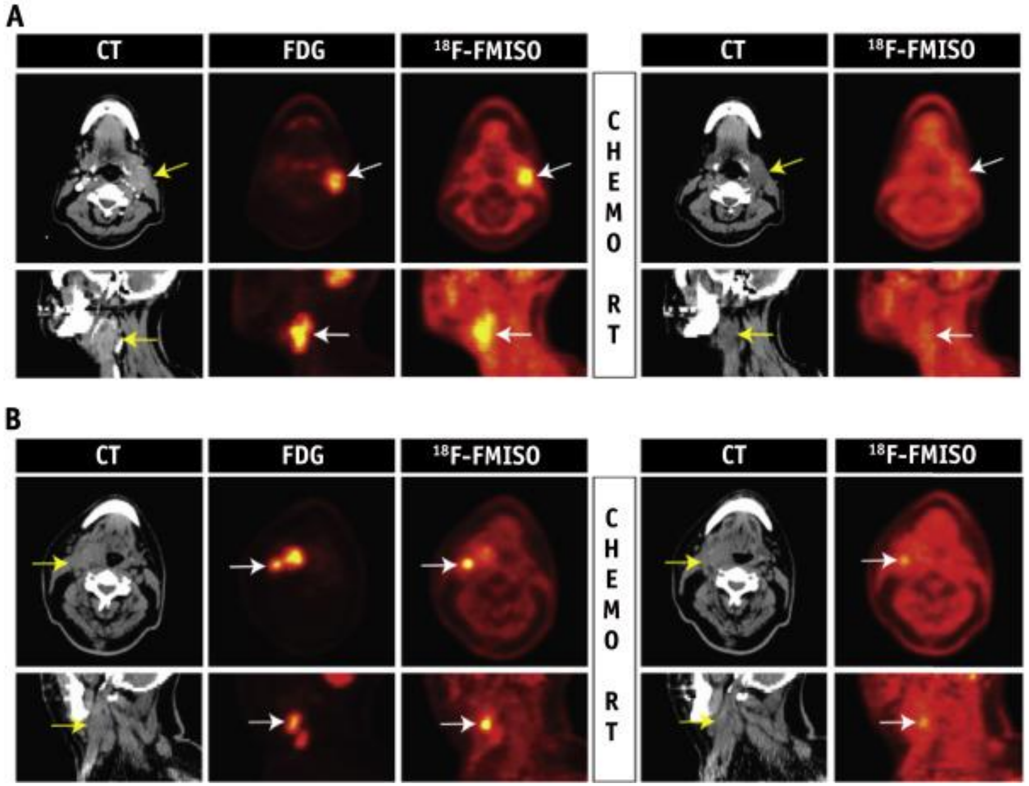


Fig. 1. Study design.

Lack of re-oxygenation at 2 weeks is the key



Loco regional control of HPV- locally advanced OPC

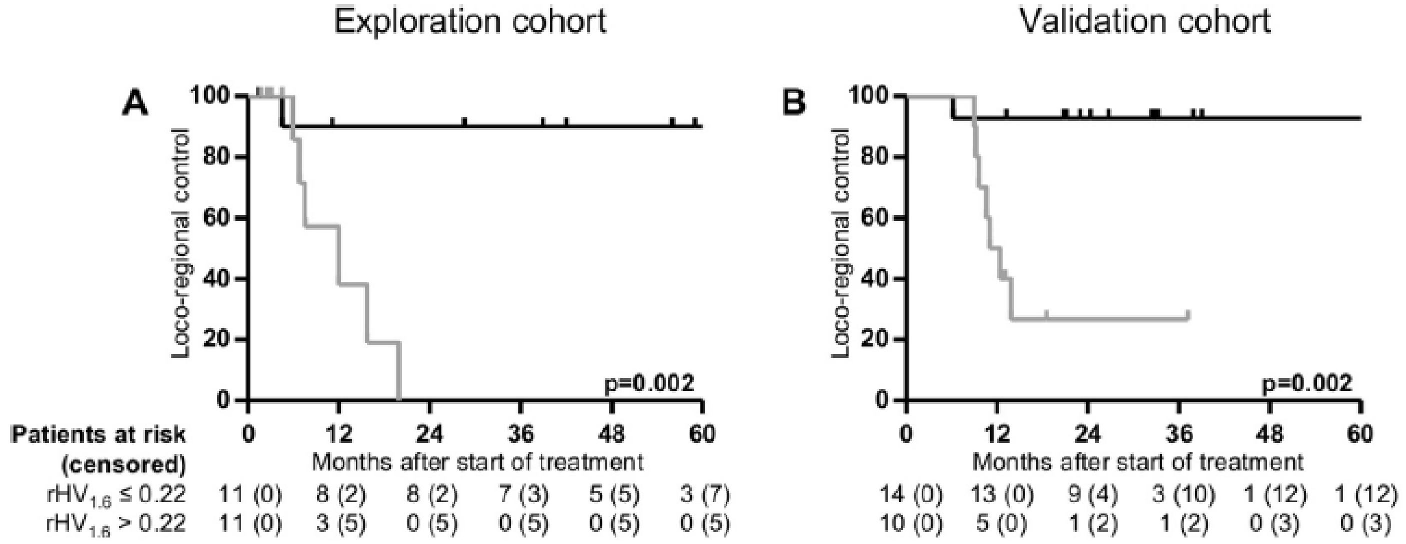


Fig. 2. Patient stratification by residual tumour hypoxia after second week of treatment: loco-regional tumour control of patients in the exploration cohort (A) and the validation cohort (B), stratified by the median individual residual tumour hypoxia determined after the second week of treatment in the exploration cohort. Residual tumour hypoxia was defined as ratio of $HV_{1.6}$ after the second week of treatment and the corresponding pre-treatment HV.

Hypoxia and reoxygenation

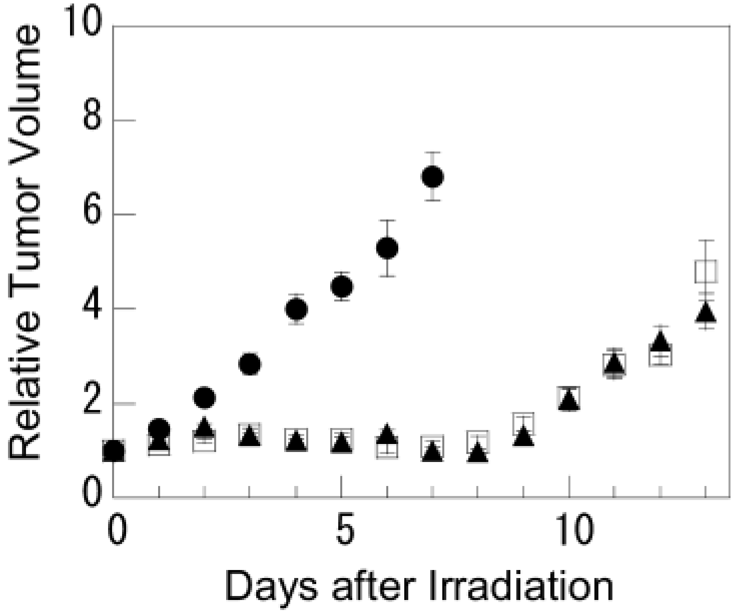


Fig. 1. Volume changes of the NFSa fibrosarcomas after irradiation. Closed circles, closed triangles, and open squares are untreated, X-ray, and carbon-ion irradiated tumors, respectively. The symbols and bars are the mean and SEM calculated from five mice each.

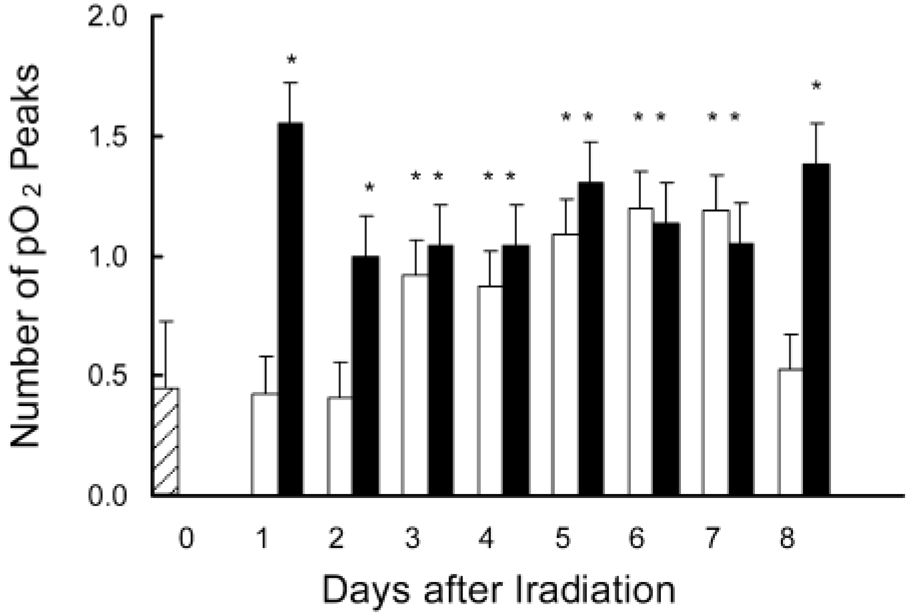


Fig. 3. Time course of the number of pO$_2$ peaks after irradiation. The average number of pO$_2$ peaks was calculated from 20–25 pO$_2$ profiles per day for each group. The striped, white, and black bars are untreated, X-ray, or carbon-ion irradiated tumors, respectively. The error bars indicate SEM. The statistical significance (*$p < 0.05$) was obtained between untreated and irradiated tumors.

Fukawa et al. 2004

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