HITRIplus
Heavy Ion Therapy Research Integration

Linear Energy Transfer Painting

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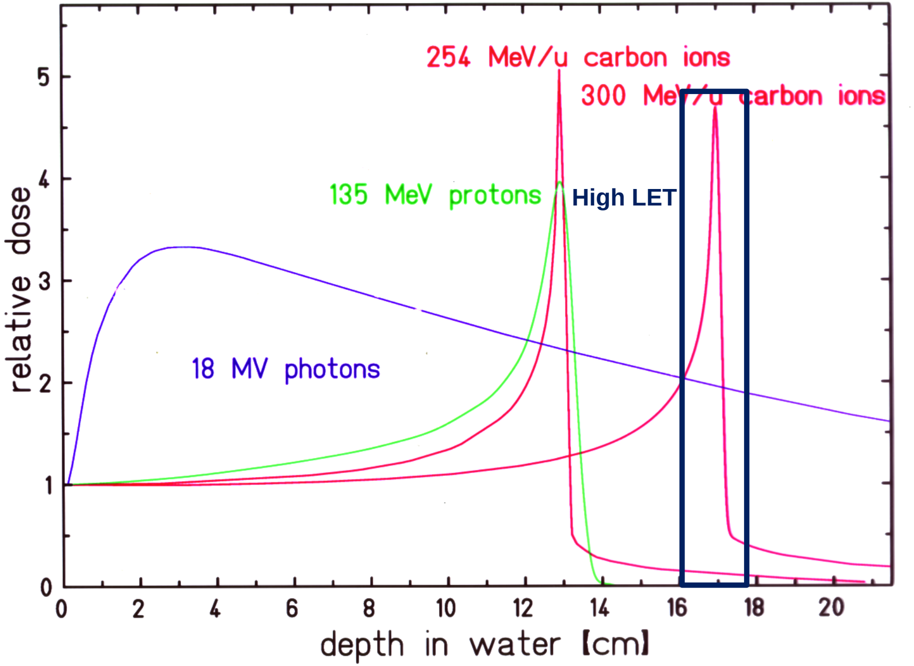
Carbon ions: Unique Physical and biological properties



U. Weber et al.

Courtsey – Dr. Fossati

Technical concepts: LET based optimization

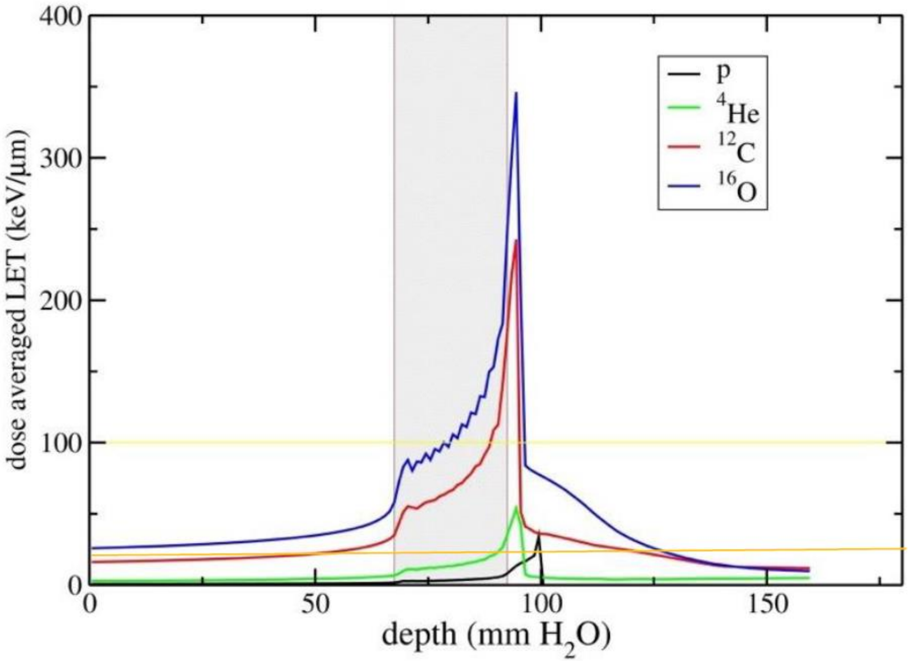
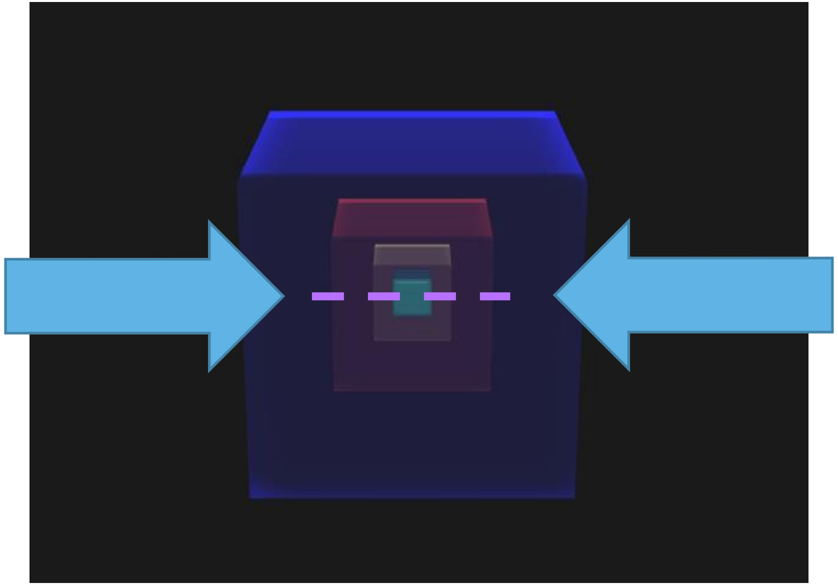
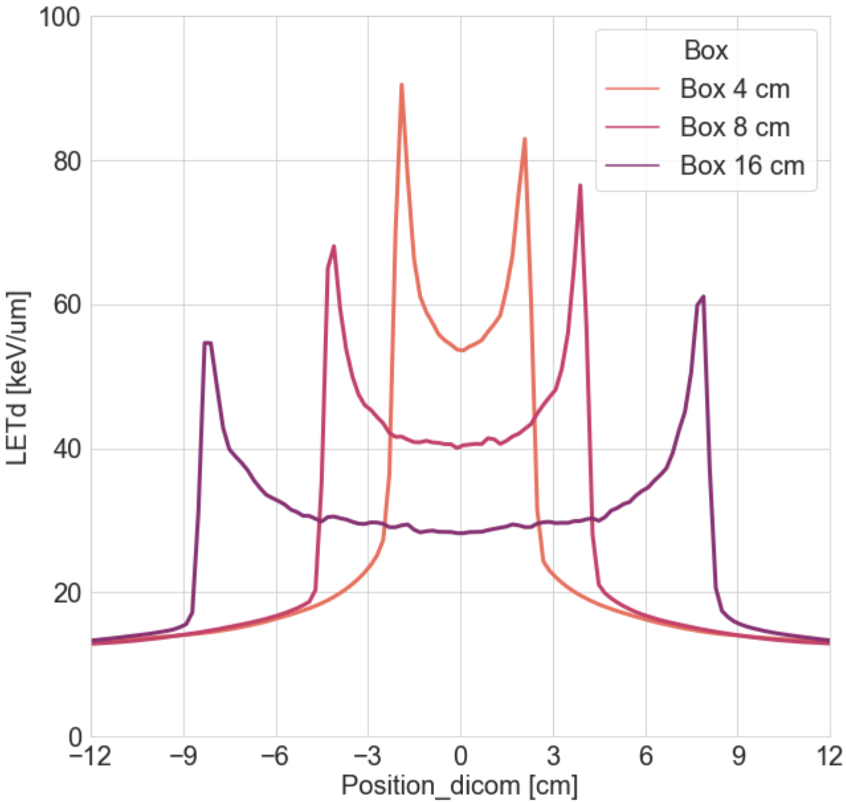


Figure 3. LET versus depth in tissue for a single SOBP of p, He, C, and O providing a uniform physical dose (2 Gy). The grey area represents the tumor region, a 2.5 × 2.5 × 2.5 cm^3 volume centered at 8 cm in water. The yellow and orange lines are 100 and 20 keV/μm level, respectively. Figure from [15], distributed under Creative Commons CC-BY.

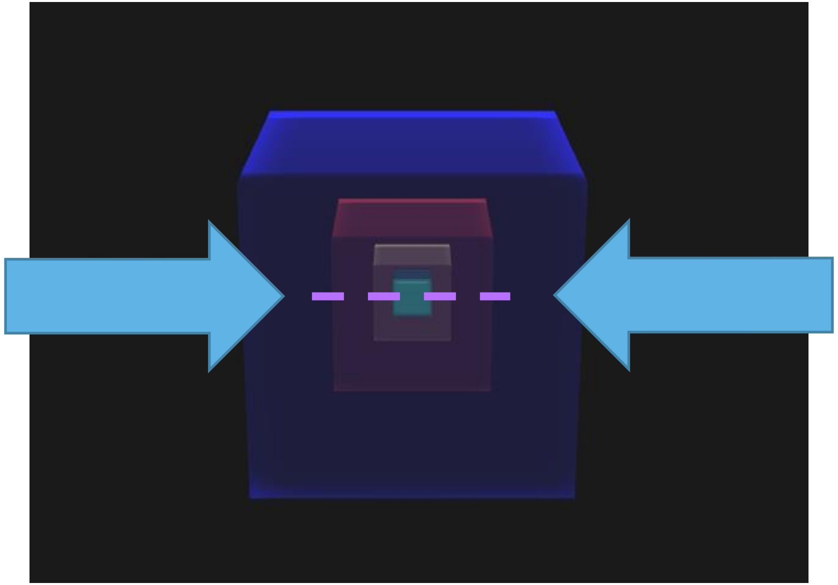
Tommasino, F, et al Int. J. Part. Ther. 2015.

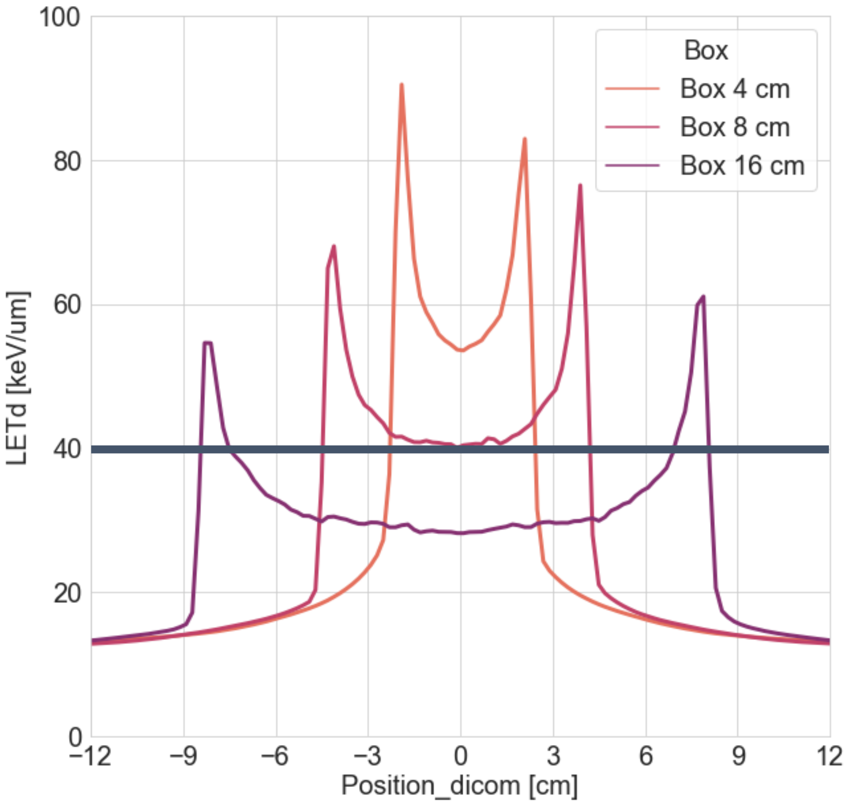
Is CIRT a high LET_d radiation?





Is CIRT dealing with high LET_d?





Local control of large pelvic sarcoma is unsatisfactory

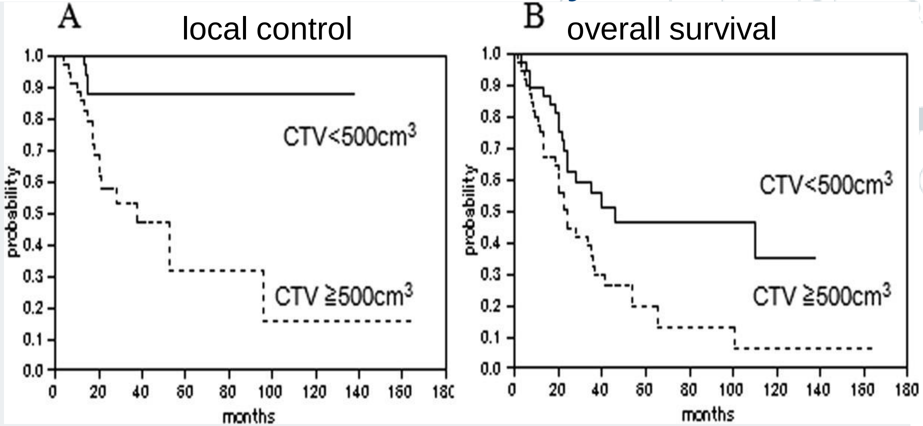
Matsunobu A. et al., Cancer, 2012

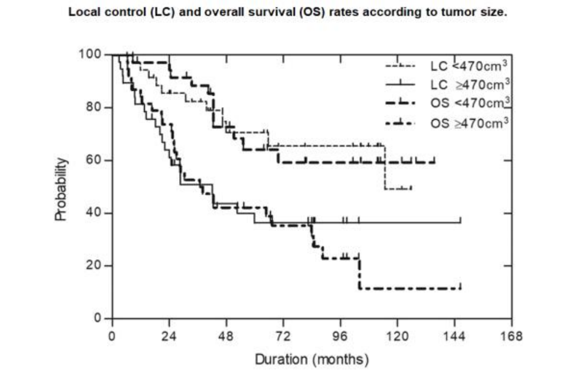
Demizu Y. et al. IJROBP, 2017

Mohamad O, et al. Oncotarget, 2018

Imai R, et al. Anticancer research. 2017

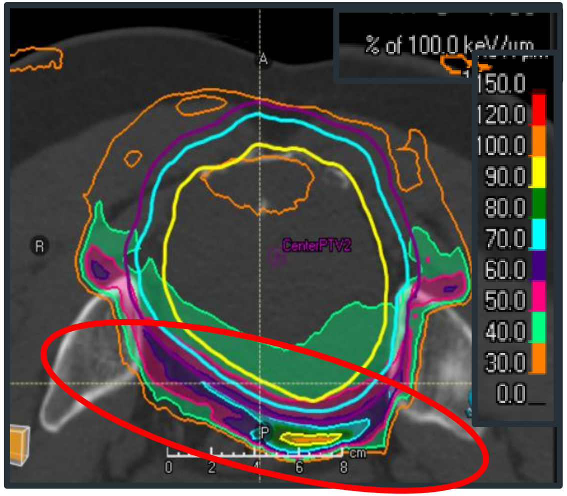
- **Large tumor volume inversely correlate with 5yr LC and 5yr OS**
- Most studies defined CTV/PTV volume of **500cc as cutoff** for large tumors
- For larger tumors apart from high dose coverage several other factors like **LET distribution** may be important **for tumor control**
- Some reports suggest **increase RBE modeling uncertainties for larger targets.**

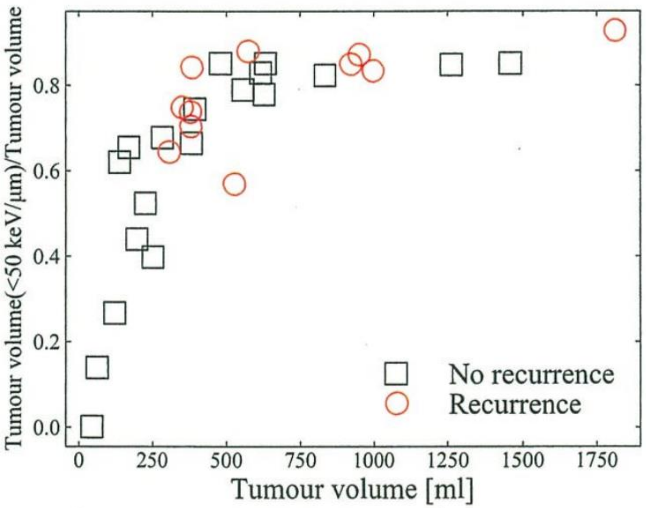




Background | D_{RBE} + ? LETd

Besides D_{RBE}, quantities such as LETd can play a relevant role in Tumor control”





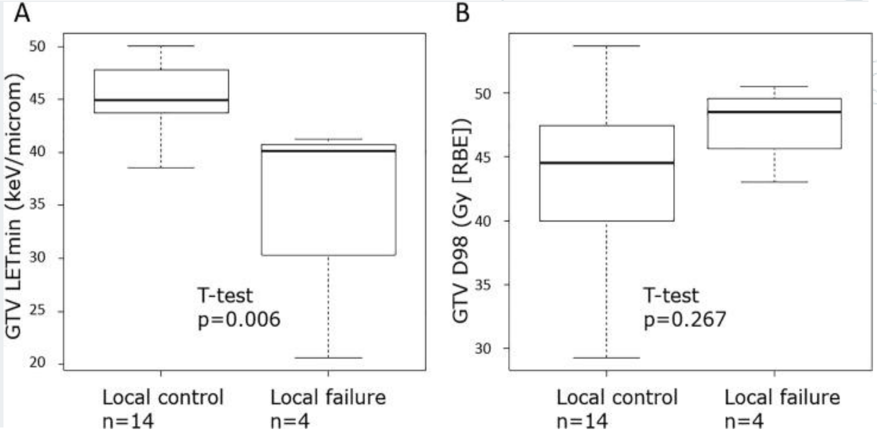
Most of the relapsed tumors are located region of tumor receiving significantly lower LETd

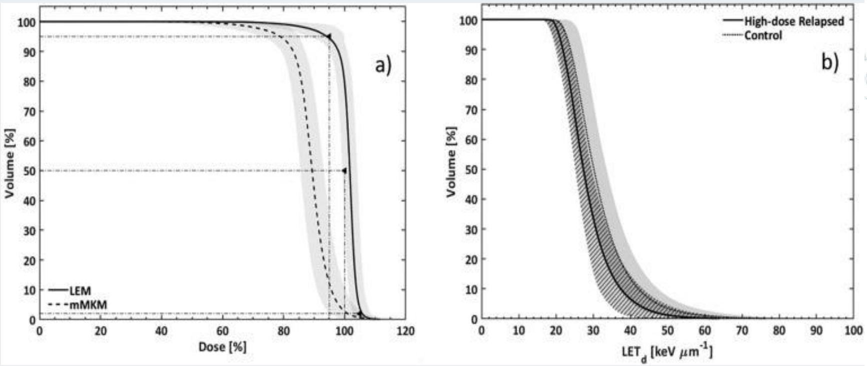
-*S. Matsumoto et al. 2020*

Key points

- As tumor size increases LETd distribution varies widely in target
- Low LETd distribution in tumor associated with increased local failure

S. Matsumoto et al. 2020, Y. Hagiwara et al. 2020, S. Molinelli et al. 2021

Citation	Key results	Plots
Hagiwara Y. et al. Clin. Transl. Radiat. Oncol, 2020	Within GTV, if **LETmin ≥44 keV/µm** (pancreas) 18-months LC 100.0% vs 34.3%, $p = 0.0366$	

Citation	Key results	Plots
Molinelli S, et al, Radiother Oncol, 2021	Large size - increase RBE modeling uncertainties **Half of the relapse volumes were located in a well-covered high dose region** (Sacral Chordomas) **LETd|50% - significantly higher for the controlled patients compared to relapsed** Proposed role of **multi model RBE- and LET-based optimization**	

"Mounting evidence besides RBE weighted dose, quantities such as local distribution of ***linear energy transfer (LET)*** can play a relevant role"

State of the art of LET based optimization

- LET painting
- Kill painting
- Multi modal therapy

Restricting the high LET radiation to hypoxic compartments of the tumor volume

- Using functional imaging techniques to generate patient specific hypoxia maps
- Desired LET distribution is achieved based on selected beam arrangement
- Dealing with small volumes

N. Bassler et al. 2014
N. Bassler et al. 2010

State of the art of LET based optimization

- LET painting
- Kill painting
- Multi modal therapy

Prescribe uniform cell killing across volumes with heterogeneous radiosensitivity

- Using directly the surviving fraction as optimization quantity rather than using the RBE-weighted dose

W. Tinganelli et al. 2015

State of the art of LET based optimization

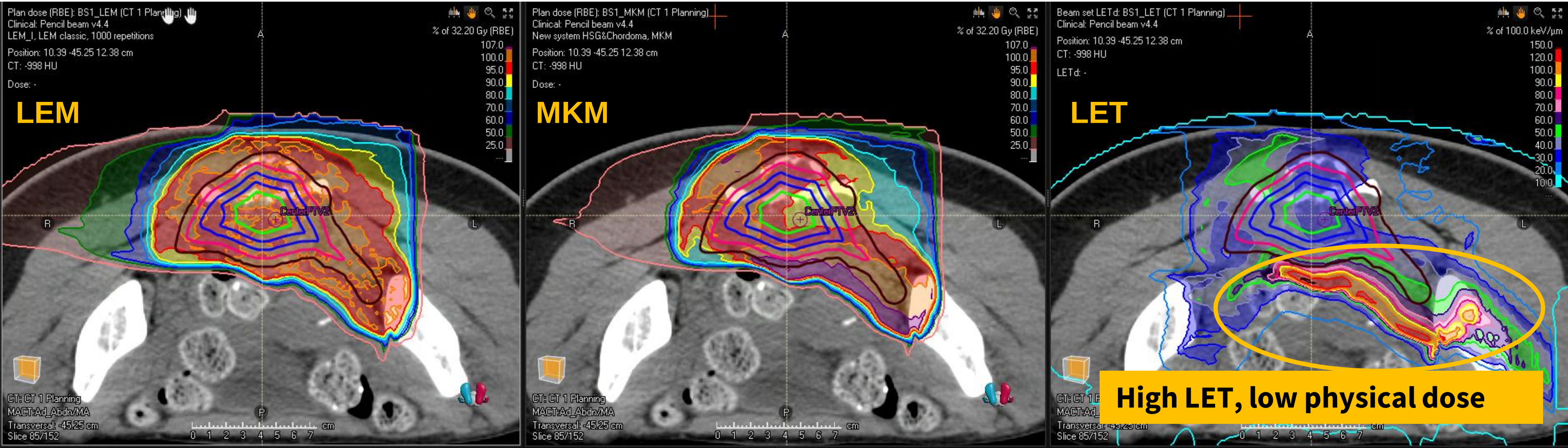
- LET painting
- Kill painting
- Multi modal therapy

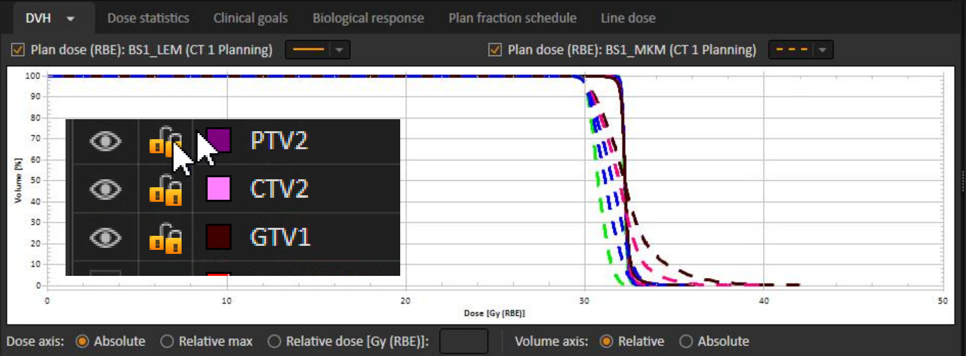
- Particles as a boost
- Intensity modulated composite particle therapy (IMPACT)
  - Two or more species in one treatment session

BIG CONCEPT

“To achieve good clinical outcome,
most tumor voxels must receive
besides **prescribed RBE weighted dose**,
enough dose with high LET”

RBE weighted dose/LET distribution | LEM vs MKM vs LET





DVH | Dose statistics | Clinical goals | Biological response

ROI statistics | POI statistics

Name	ROI	ROI vol. [cm³]	Dose [Gy (RBE)], LETd [keV/µm] D99	D98	D95	Average	D50	D2	D1	% outside grid
Plan dose (RBE): BS1_...	GTV-0.5cm rim	154.49	29.82	29.97	30.18	31.96	31.93	35.07	35.64	0 %
Beam set LETd: BS1_L...	GTV-0.5cm rim	154.49	27.5	28.3	29.8	41.8	41.7	60.8	66.0	0 %
Plan dose (RBE): BS1_...	GTV1	274.50	31.55	31.74	31.92	32.29	32.27	33.24	33.63	0 %
Plan dose (RBE): BS1_...	GTV1	274.50	29.76	29.96	30.24	32.44	32.21	37.23	38.15	0 %
Beam set LETd: BS1_L...	GTV1	274.50	26.9	28.0	29.9	45.1	43.5	79.5	88.7	0 %
Plan dose (RBE): BS1_...	GTV-1.5cm rim	39.66	31.92	31.96	32.03	32.27	32.26	32.67	32.75	0 %
Plan dose (RBE): BS1_...	GTV-1.5cm rim	39.66	29.80	29.90	30.08	31.18	31.15	32.67	32.85	0 %
Beam set LETd: BS1_L...	GTV-1.5cm rim	39.66	28.4	28.9	29.8	37.0	36.5	47.4	47.8	0 %
Plan dose (RBE): BS1_...	GTV-1cm rim	82.89	31.80	31.90	31.99	32.26	32.26	32.68	32.77	0 %

Purpose

Evaluating the ***feasibility*** and ***efficiency*** of ***LET$_d$-based optimization*** strategies for carbon ion treatment plans with a ***large sacral chordoma tumor***

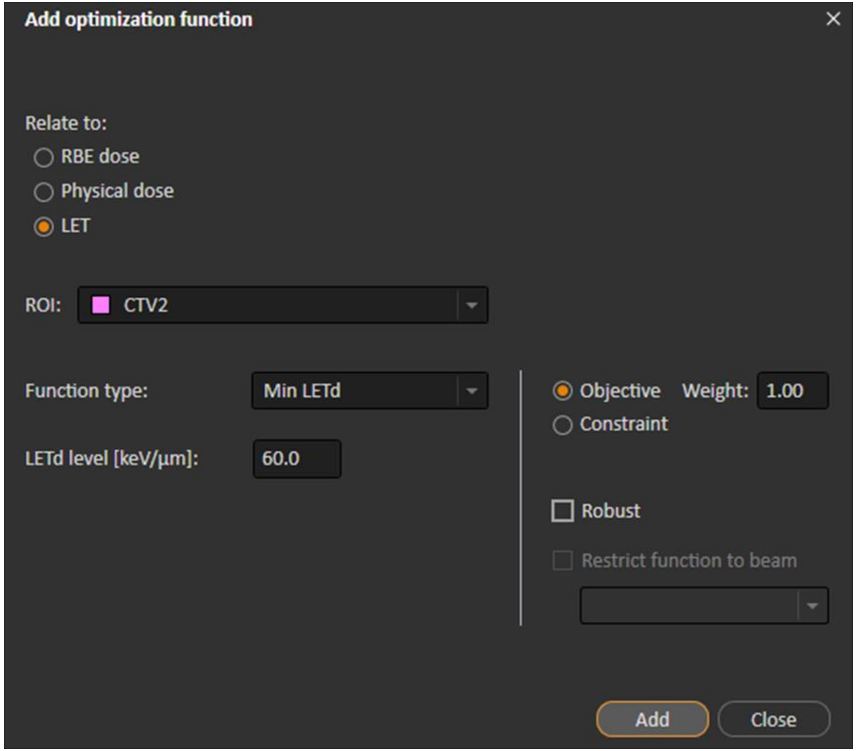
STRATEGY 1

LETd optimization

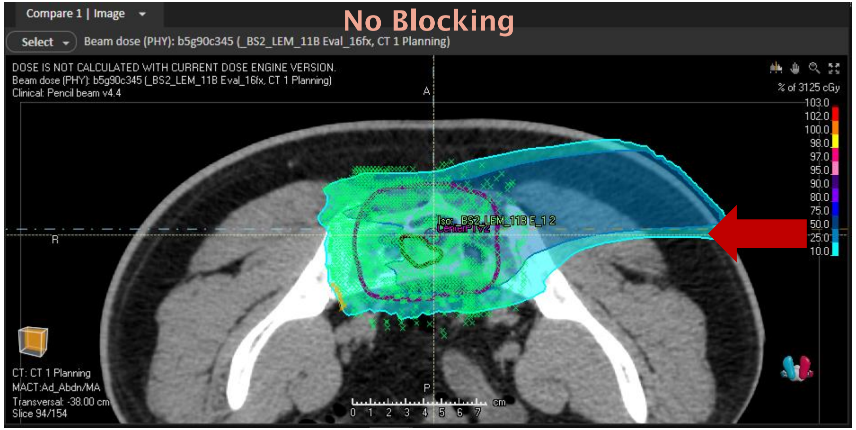
STRATEGY 2

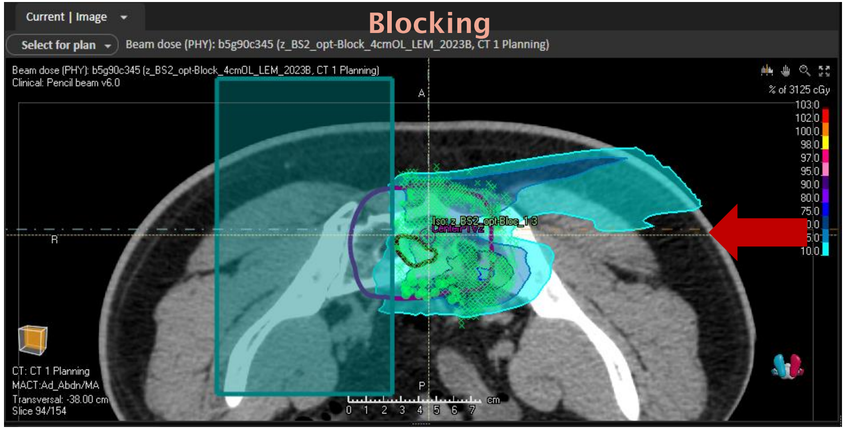
Blocking

Strategy 1: LETd optimization



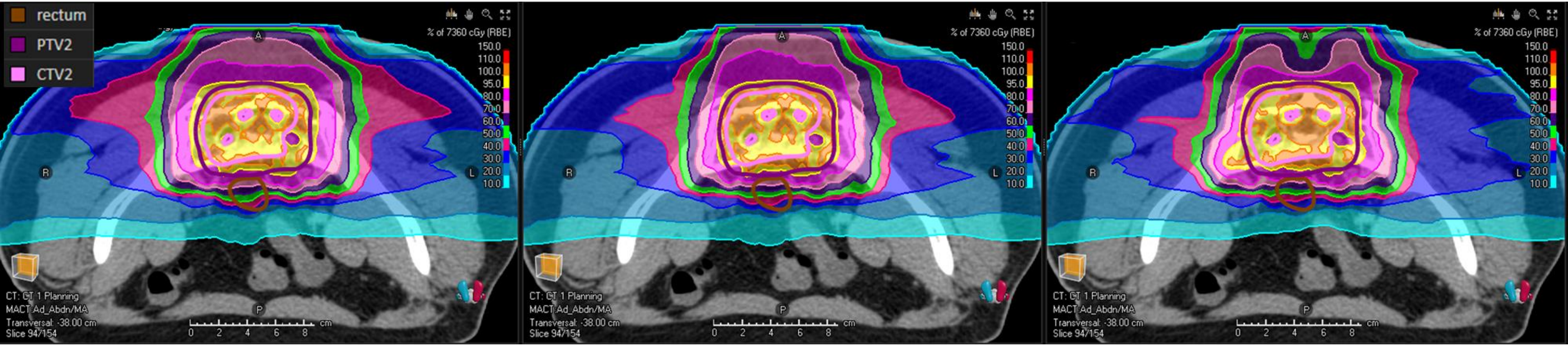
Strategy 2: Blocking





Results / Dose$_{LEM}$ distribution

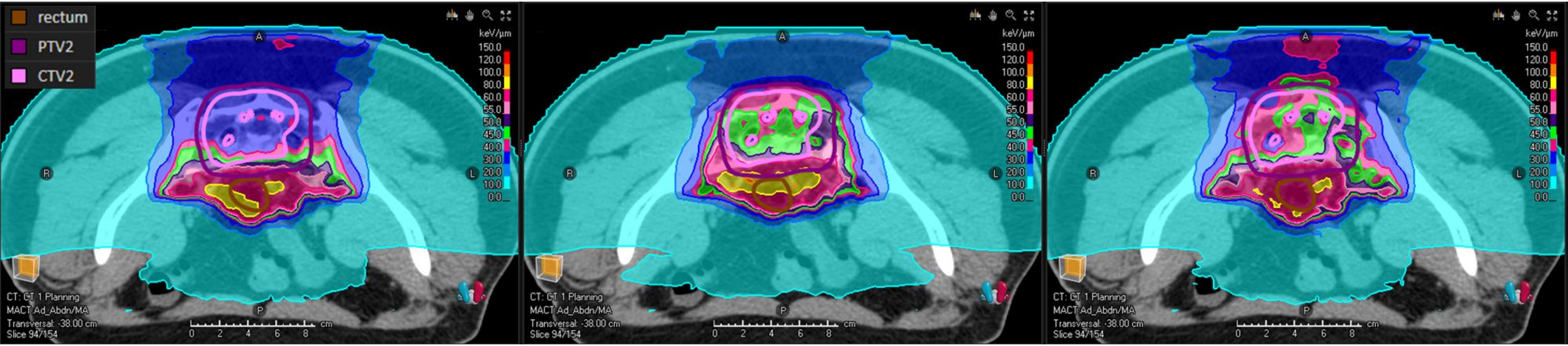
No LETd-optimization | **LETd-optimization** | **Blocking**



Similar dose distribution with and without LET$_d$ optimization

Results / LET_d distribution

- No LETd-optimization
- LETd-optimization
- Blocking



"LETd-optimization" and "Blocking" resulted in higher LET_d

Patient Characteristics

Registry Study, SACRO Trial

Patient Characteristics

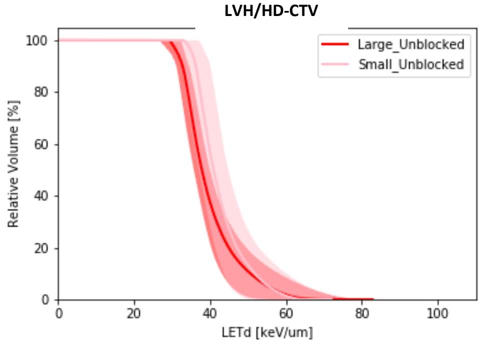
- N= 22 (Non-metastatic Pelvic chordoma/ sarcoma)
- Age = 64 yr (range, 43- 77)
- Chordoma (21), Synovial sarcoma (1)
- Small : HD-PTV < 400 cc, HD-CTV < 250 cc
- Large: HD-PTV >/= 400 cc, HD-CTV >/= 250 cc
- Dose prescription-HD-PTV, doses, LETd evaluation -HD-CTV

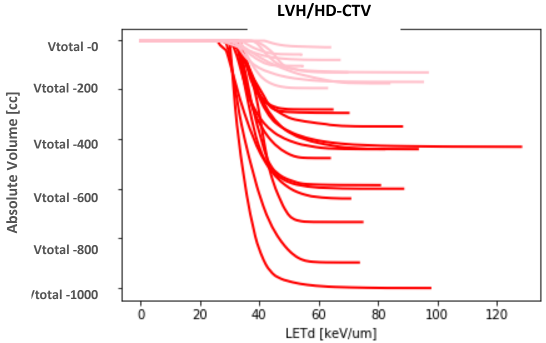
Tumor Characteristics		Small (n = 9)	Large (n = 13)	p - value Small vs Large
GTV	Mean ± SD (cc)	55.94 ± 39.8	300.95 ± 243.5	0.004
HD-CTV	Mean ± SD (cc)	116.26 ± 52.57	551.72 ± 211.3	<0.001
HD-PTV	Mean ± SD (cc)	195.13 ± 76.8	776.66 ± 257.7	<0.001
Maximum Tumor diameter along the beam path	(cm)	5.6 ± 2.1	8.3 ± 3.8	0.01
CIRT dose	Median [Gy RBE]	73.6	73.6	NS
	Range [Gy RBE]	70.4 - 73.6	70.4 - 73.6	

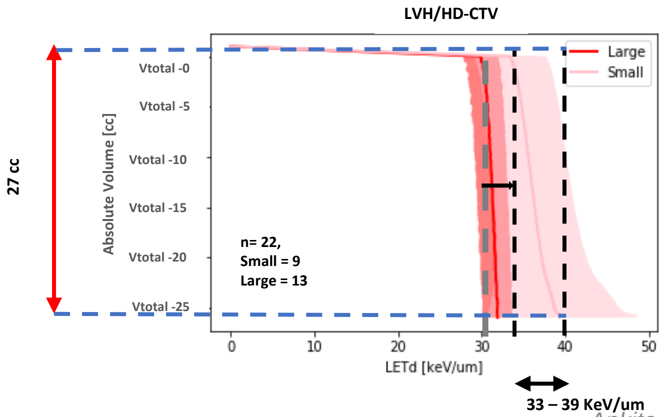
Dose prescription: LD-PTV: 4.4-4.6Gy RBE x 9 fr followed by HD-PTV: 4.4-4.6Gy RBE x 7 fr

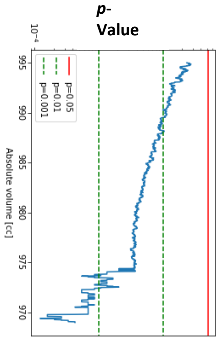
Clinical planning: clinical TPS RayStation 8B, 11A and 11B, LETd evaluation /optimization-Blocking: Research TPS RayStation 11B

Results | LETd | small vs large tumors





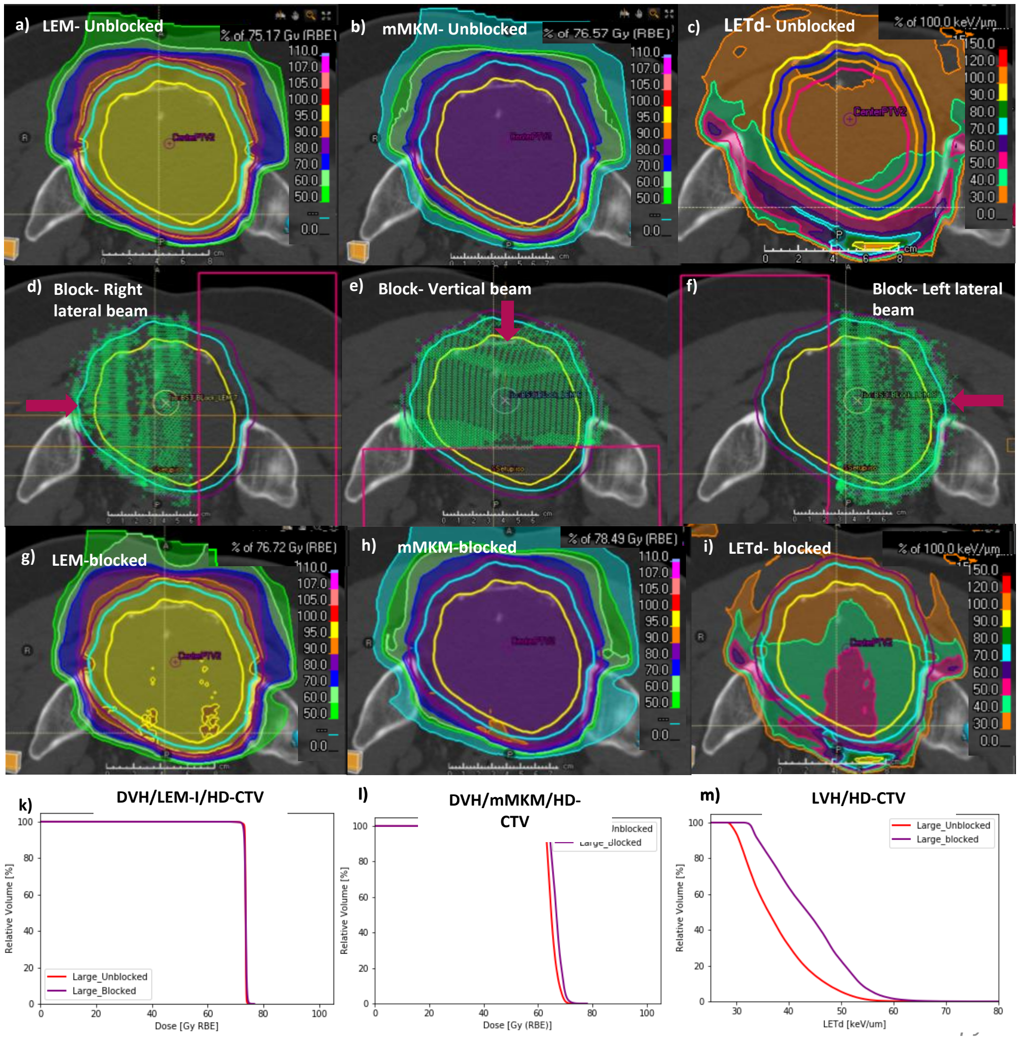




Key Results

- LETd-cold portion of the HD-CTV in large tumors in received LETd of 28 – 32keV/µm,
- To convert LETd behaviour of large similar to small tumors, the LETd cold portion of HD-CTV should receive atleast 33-40keV/µm, or more.

Methods | Blocking



Original Clinical plans :
D_{RBE}, LEM-I | D_{RBE}, mMKM | LETd

Blocking structures
Only boost volume (HD-PTV) i.e.6-7 fractions of treatment were blocked) for ***Large tumors***

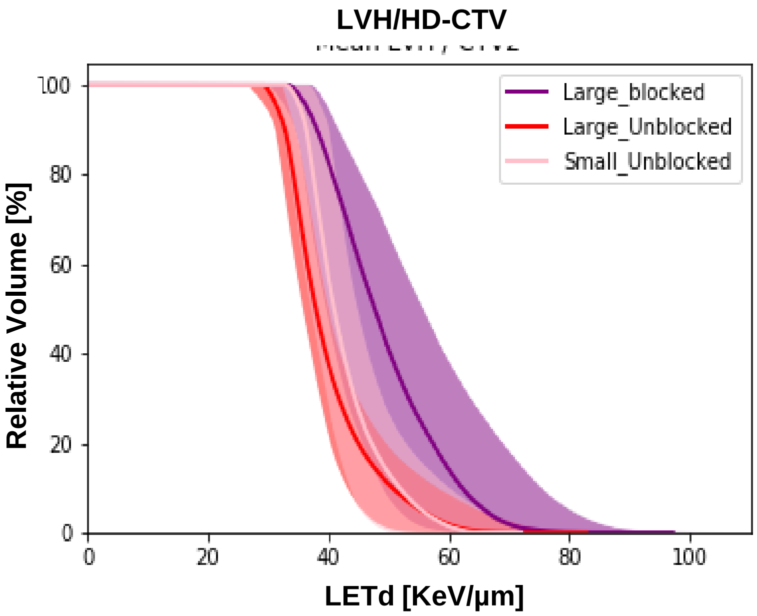
D_{RBE} and LETd distribution with **Blocking**

D-/ L-VH

unpublished data do

Results | Cumulative LVH | Small vs Large vs Large Blocked

BLOCKING → Improvement in high LETd component, median LETd in HD-CTV of large tumors increased from 38 ± 3.4 KeV/µm (unblocked) to 47 ± 8.1 KeV/µm (blocked)



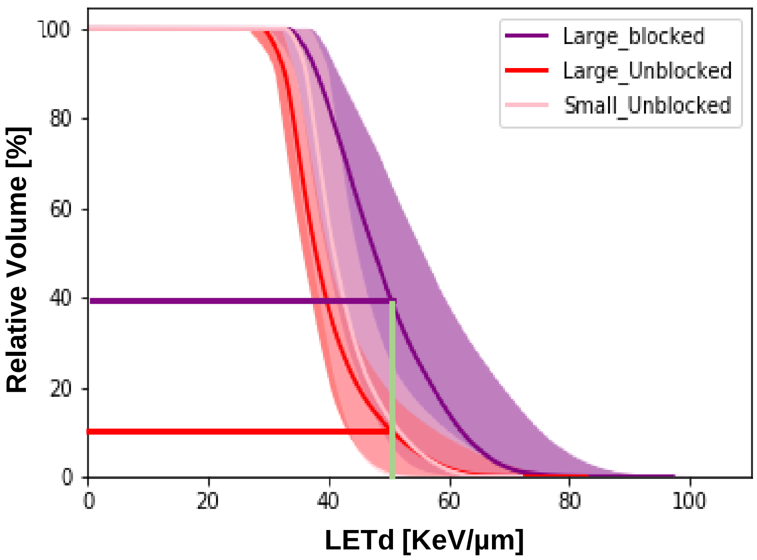
N = 22

- Small = 9
- Large_Unblocked = 13
- Large_Blocked = 13

Results | Cumulative LVH | Small vs Large vs Large Blocked

BLOCKING → Improvement in high LETd component, median LETd in HD-CTV of large tumors increased from 38 ± 3.4 KeV/μm (unblocked) to 47 ± 8.1 KeV/μm (blocked), fraction of HD-CTV receiving > 50 KeV/μm improved from <10% in

LVH/HD-CTV



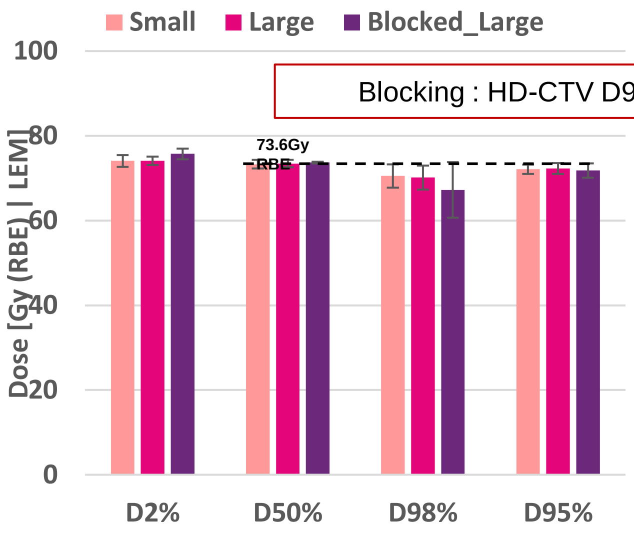
N = 22

- Small = 9
- Large_Unblocked = 13
- Large_Blocked = 13

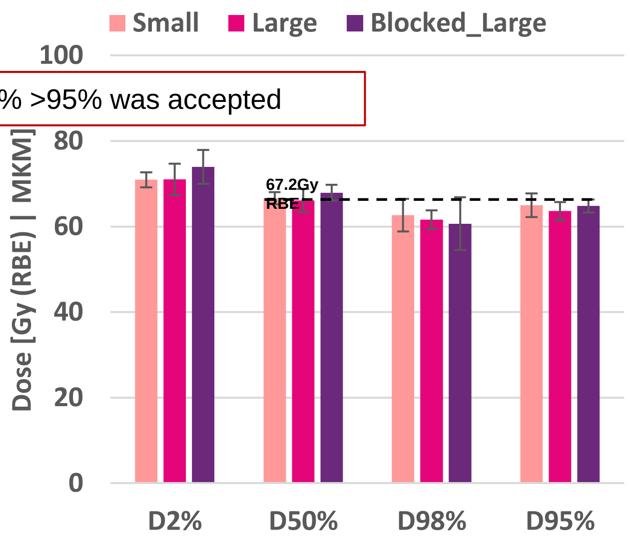
Ankita Nachankar

D_{RBE} , LETd :2%, 50%, 98%, 95%| HD-CTV | Small vs Large vs Large Blocked

LEM-I

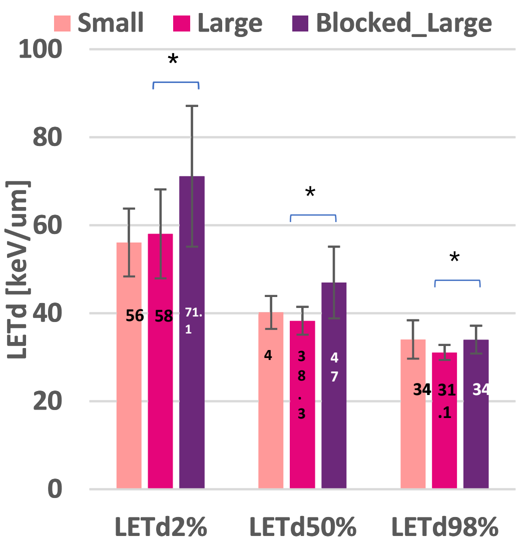


mMKM



Blocking : HD-CTV D95% >95% was accepted

LETd



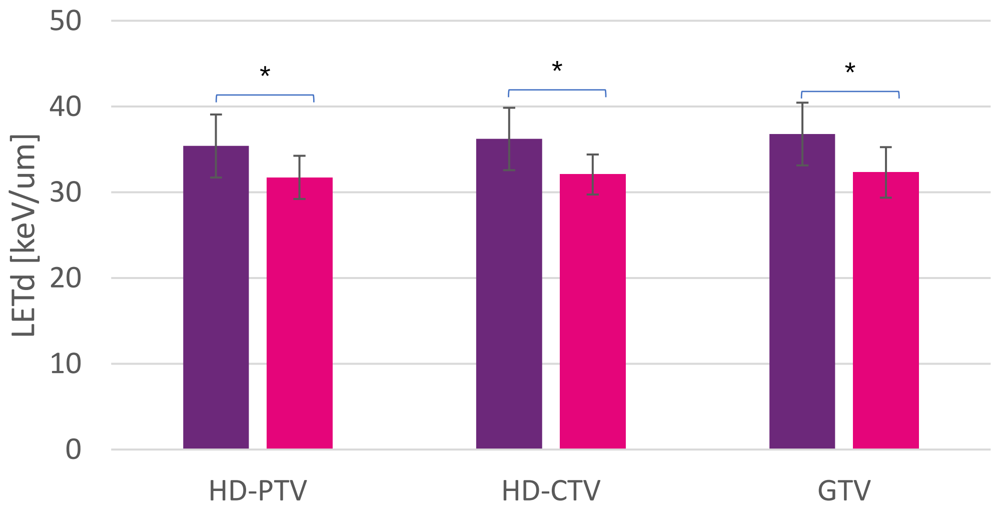
*p- value : T test * < 0.05*

N = 22

- Small = 9
- Large_Unblocked = 13
- Large_Blocked = 13

LETd-cold portion | HD-CTV

BLOCKING → **Significant improvement in LETd distribution in the critical volume that must be treated with high LETd i.e. LETd-cold portion (for HD-CTV)**



N = 22

- Large_Unblocked = 13
- Large_Blocked = 13

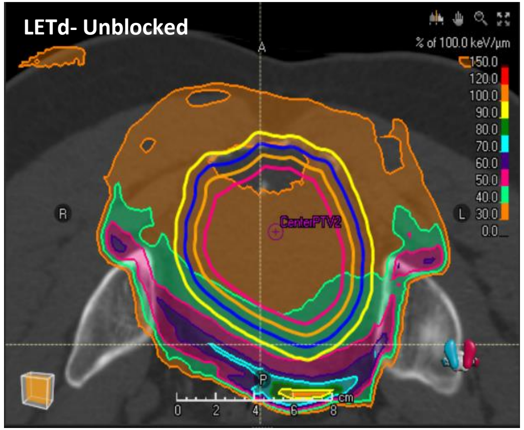
p- value : T test
* < 0.001

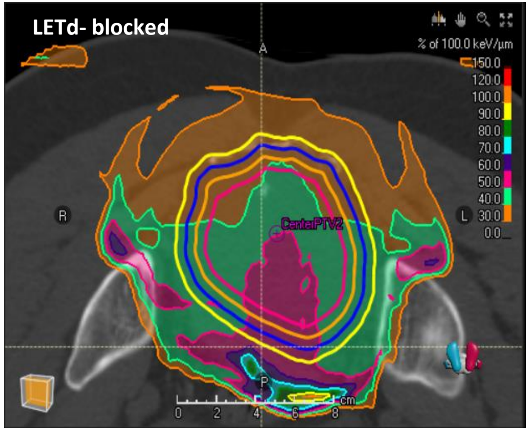
Key Results

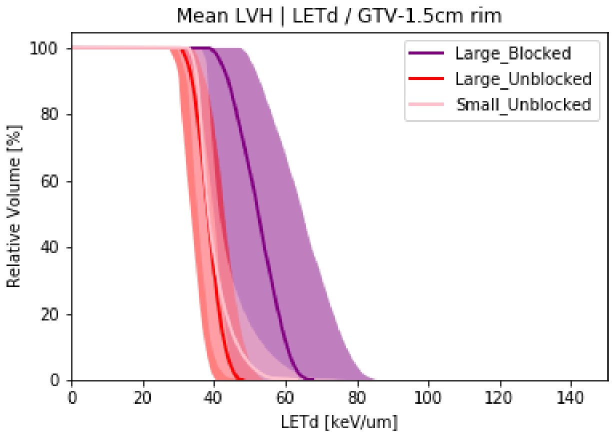
- **LETd-cold portion for HD-PTV** improved from **31.7 +/- 2.5 KeV/µm to 35.4 +/-3.6 KeV/µm**.
- **LETd-cold portion for HD-CTV** improved from **32 +/-2.3 KeV/µm to 36.2 +/- 3.6 KeV/µm**.
- **LETd-cold portion for GTV** improved from **32.3 +/-3 KeV/µm to 36.8 +/- 3.7 KeV/µm**.

LETd Spatial Redistribution | central portion of GTV

BLOCKING → Redistribution of high LETd component from distal region of PTV & between PTV & OARs to the center of GTV , median LETd in central region of GTV in large tumors > 55 keV/µm







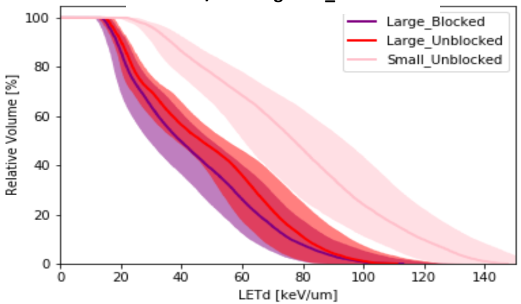
N = 22

- Large_Unblocked = 13
- Large_Blocked = 13

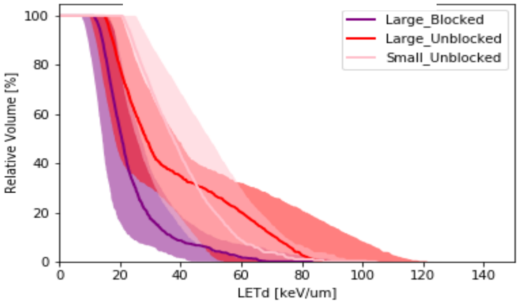
LVH | OARs

BLOCKING → No Significant improvement difference in LETd on OARs especially dose filtered LETd in Rectum and small intestines

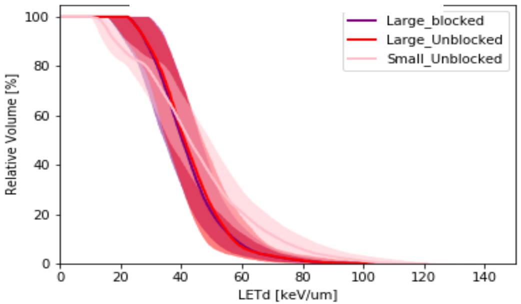
LVH/Rectosigmoid_10%PD



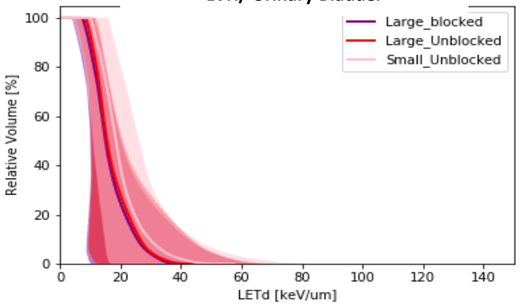
LVH/Bowelloops_10%PD



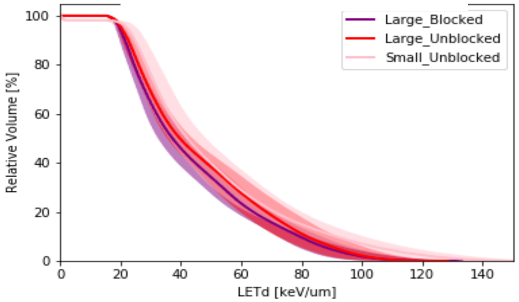
LVH/Nerveroots



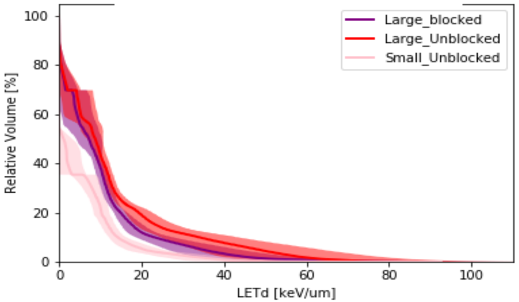
LVH/ Urinary Bladder



LVH/ 1cm rim beyond LD-PTV

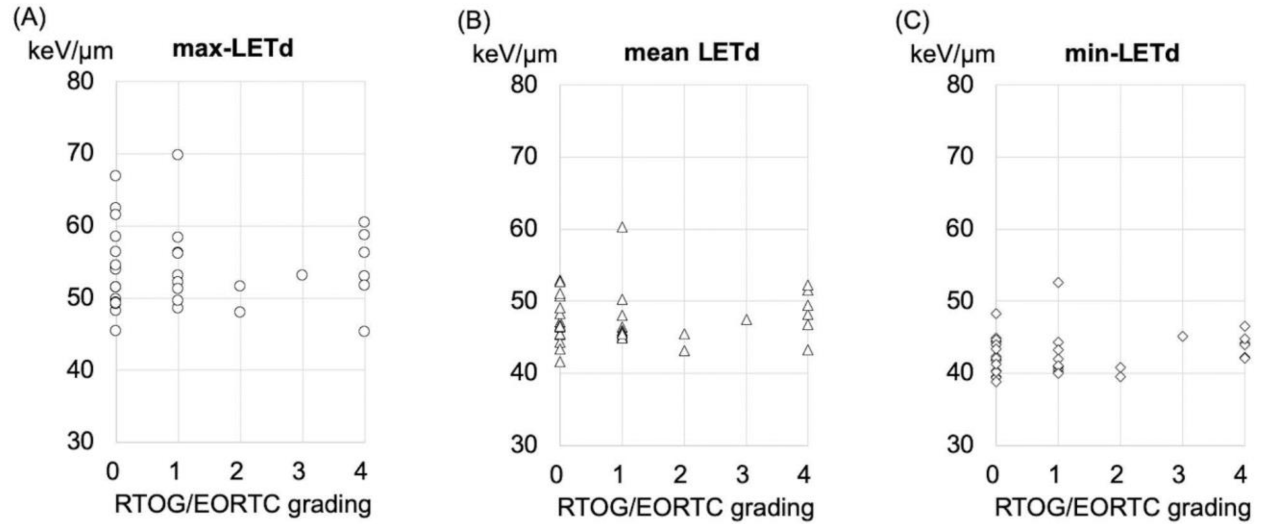


LVH/ Skin



Rectosigmoid| LET Literature

Supplementary figure 3.



(keV/μm)	Grade 0-2 (n = 28)	Grade 3-4 (n = 7)
Avg. ± SD	53.8 ± 5.9	54.0 ± 5.0
p value	0.937	

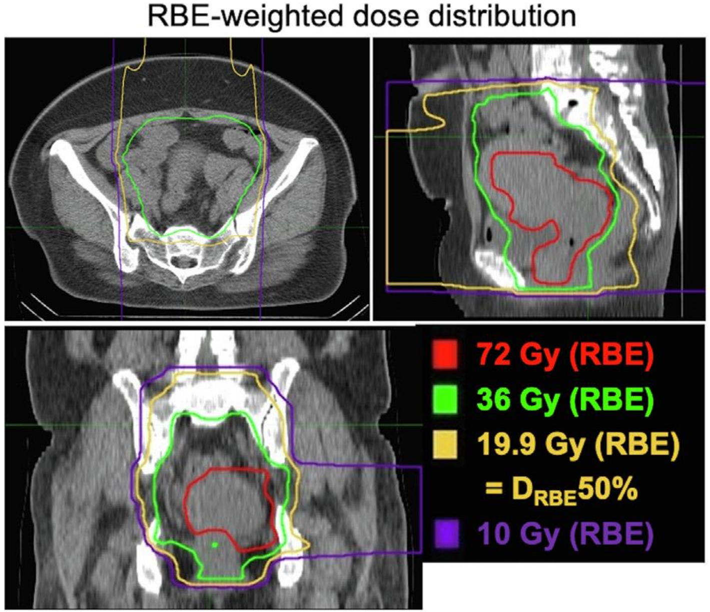
(keV/μm)	Grade 0-2 (n = 28)	Grade 3-4 (n = 7)
Avg. ± SD	47.3 ± 3.7	48.4 ± 3.0
p value	0.484	

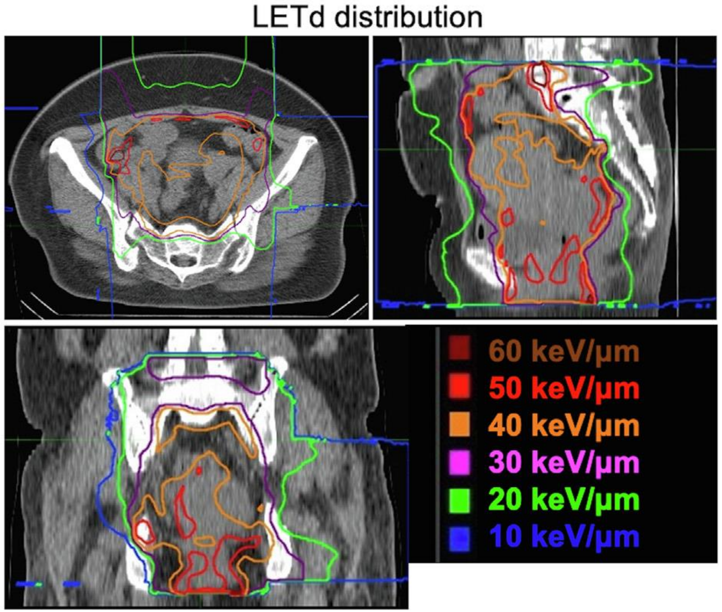
(keV/μm)	Grade 0-2 (n = 28)	Grade 3-4 (n = 7)
Avg. ± SD	42.3 ± 3.0	44.1 ± 1.6
p value	0.146	

No correlations were found between severe rectal toxicities and **LETd** alone or physical dose

Okonogi N, et al Radiotherapy and Oncology. 2020

Sacral insufficiency fracture





Univariate analyses of risk factors for sacrum insufficiency fracture in 51 patients whose $D_{RBE}50\%$ was above the median in the relative biological effectiveness-weighted dose.

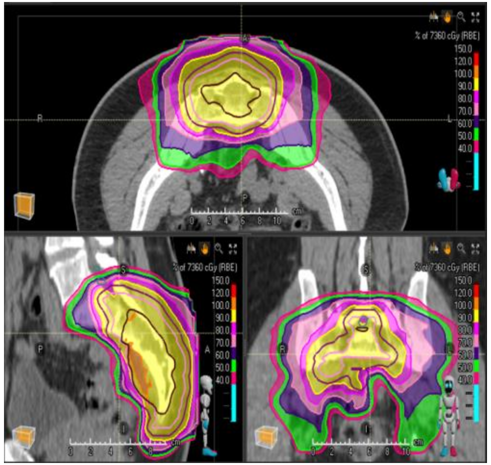
Sacrum	Subgroup	Number of patients	Number of patient with SIF	*p*-value
LETd				
V_L10 keV/μm (mean ± SD, cc)	< 192.7 / ≥ 192.7	25 / 26	5 / 12	0.034
V_L20 keV/μm (mean ± SD, cc)	< 161.3 / ≥ 161.3	25 / 26	6 / 11	0.139
V_L30 keV/μm (mean ± SD, cc)	< 104.5 / ≥ 104.5	25 / 26	6 / 11	0.415
V_L40 keV/μm (mean ± SD, cc)	< 29.5 / ≥ 29.5	25 / 26	6 / 11	0.174

On Cox regression analysis LETd was not associated with SIF.

Mori, Y., Okonogi, N., Radiotherapy and Oncology, 177, pp.33-39.

Carbon ion therapy for Pelvic sarcomas

Carbon ion therapy is a potentially curative treatment for unresectable Pelvic sarcomas



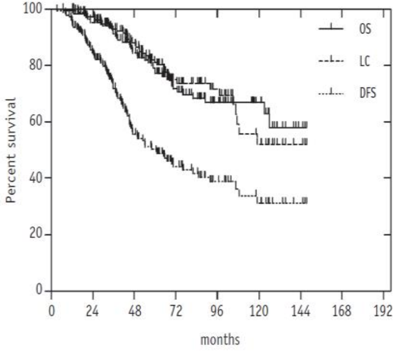


Fig. 2. Local control (LC, dashed line), overall survival (OS, solid line), and disease-free survival (DFS, dotted line) curves of the 188 patients.

- Imai R IJROBP 2016, Mohamad, O. Oncotarget 2018, Shiba S Cancers 2021

Late Radiation induced Lumbo-sacral neuropathy (RILSN) is a debilitating morbidity associated with CIRT treatment for pelvic malignancies!

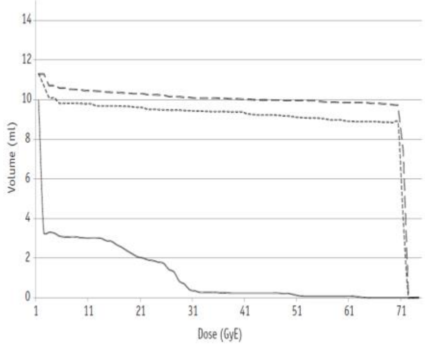


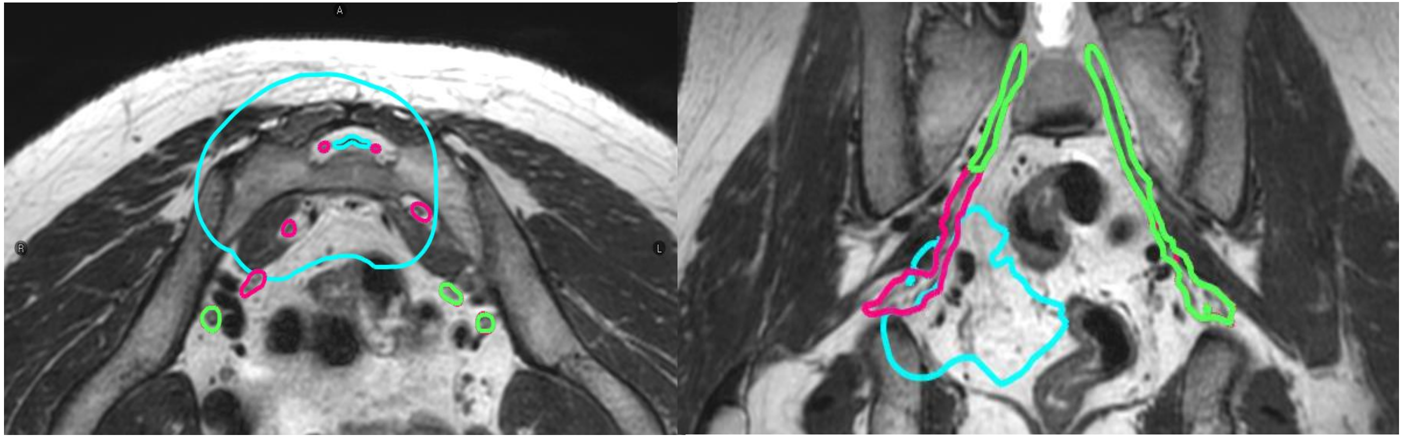
Fig. 3. Representative dose–volume histograms of sciatic nerves with grade 3 toxicity (dotted and dashed lines) that received a total dose of 70.4 gray equivalents/16 fractions. Compared with the grade 0 dose–volume histogram (solid line), a higher dose was applied to a long distance of the sciatic nerves.

- Imai R BJR 2011, Imai R IJROBP 2016, Takenaka S, Cancer. 2020

Sacral nerve sparing optimization | SNSO-CIRT Strategy

Contouring

Contouring the individual sacral nerveroots between L5–S3 levels until sciatic nerves



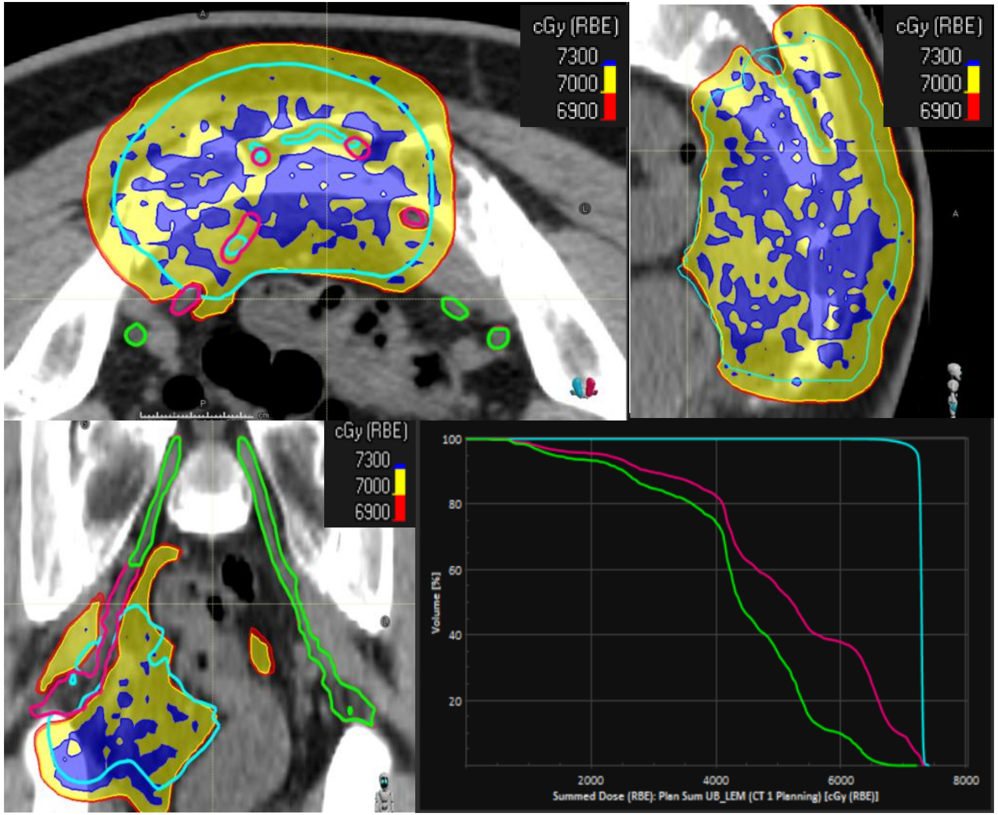
Sacral nerve sparing optimization | SNSO-CIRT Strategy

Dose Constraints

D(RBE) LEM-I: 73.6-76.8 Gy RBE/16 fractions @ 4.6-4.8 Gy RBE /fr (PBS)

Sacral nerves outside HD-CTV i.e. “S. nerves to spare” : D5% <69 Gy RBE

Sacral nerves inside of HD-CTV: D2% <73Gy RBE, avoid hot spots



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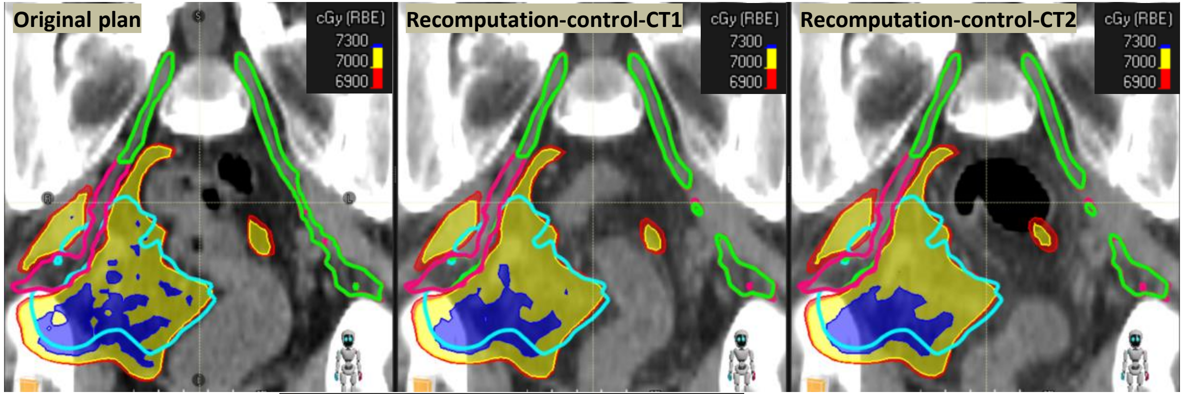
Sacral nerve sparing optimization | SNSO-CIRT Strategy

Robustness

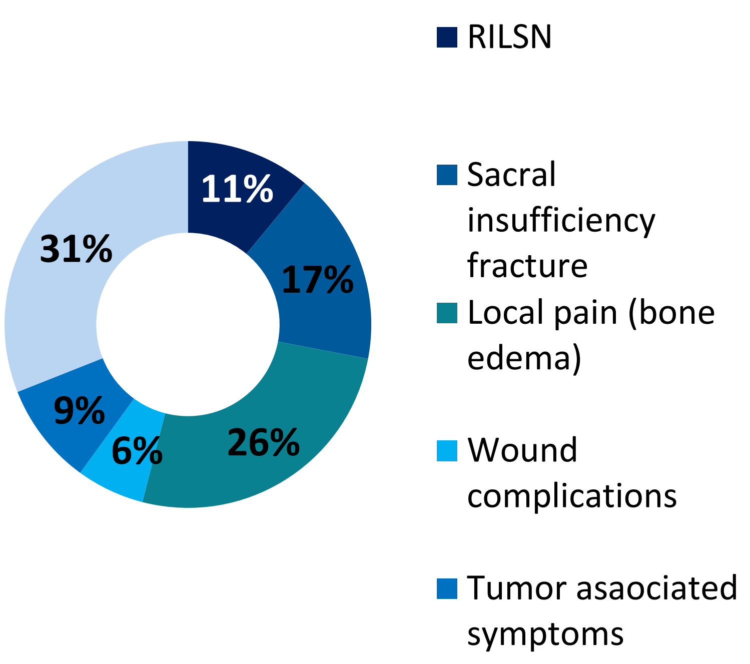
Ensure robustness against range and set-up uncertainties



Clinical Results | SNSO-CIRT Strategy

Patient / Tumor Characteristics		No RILSN (n = 31)	RILSN (n = 4)	p - value No RILSN vs RILSN
Age	Median (years)	51.8	56.1	NS
	Range (years)	30.8-75.8	54-66	
Gender	Male	19	3	NS
	Female	12	1	NS
Follow up	Median (months)	15.2	14.3	NS
	Range (months)	3-42.8	6-28	
Histology	Chordoma	24	4	NS
	Chondrosarcoma	3	0	NS
	Leiomyosarcoma	2	0	NS
	Others	2	0	NS
Comorbidities	Surgery	8	1	NS
	Chemotherapy	5	1	NS
	Diabetes	1	1	NS
	Neurodegenerative disease	0	0	NS
CIRT dose	Median [Gy RBE]	73.6	73.6	NS
	Range [Gy RBE]	70.4 - 73.6	70.4 - 73.6	

Post CIRT Toxicity profile (> /= grade 2CTCAE v5.0)



RILSN Results | SNSO-CIRT Strategy

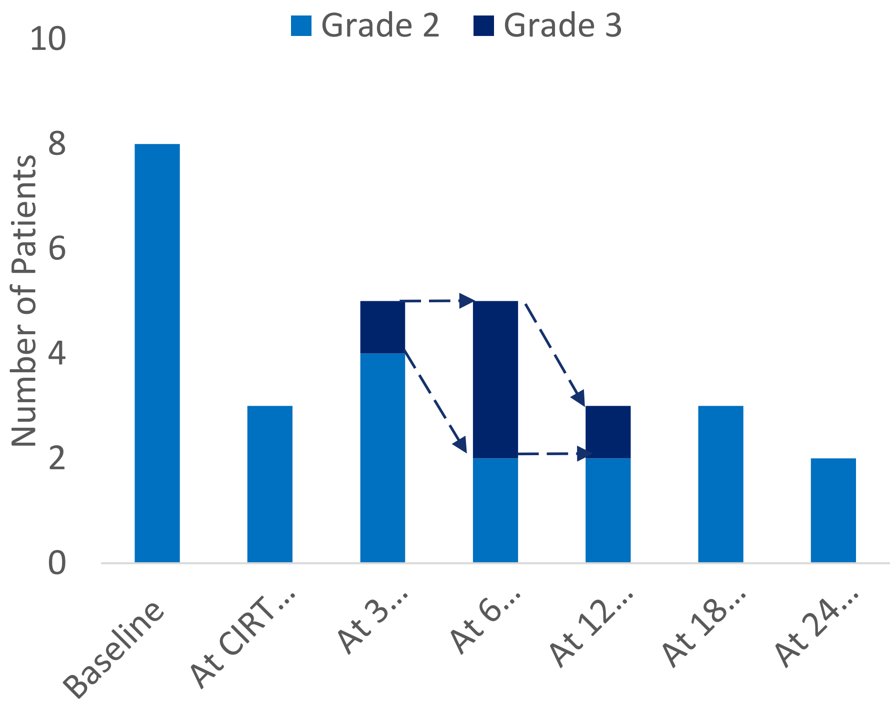
Neuropathy Results

- Median Time to RILSN: 7 months (range, 4 - 11)
- RILSN free survival @ 1 & 2-yrs is 92.46% (CI -79-98) & 82.78% (CI -57-95)
- On UVA : Age, gender, H/O Diabetes Mellitus, local oncologic surgery, chemotherapy or tumor Volume not significant predictors for RILSN

Key takeaways

- 100% patients remained ambulatory
- Local pain = Gr 3 : 3 (8.6%)
- Neuralgia = Gr 3 : 3 (8.6%)
- Paraesthesia = Gr 3 : 0
- Only one patient developed transient motor deficit with neuropathy
- Two patients with RILSN developed grade 2 urinary dysfunction
- One patient developed grade 3 radiation dermatitis

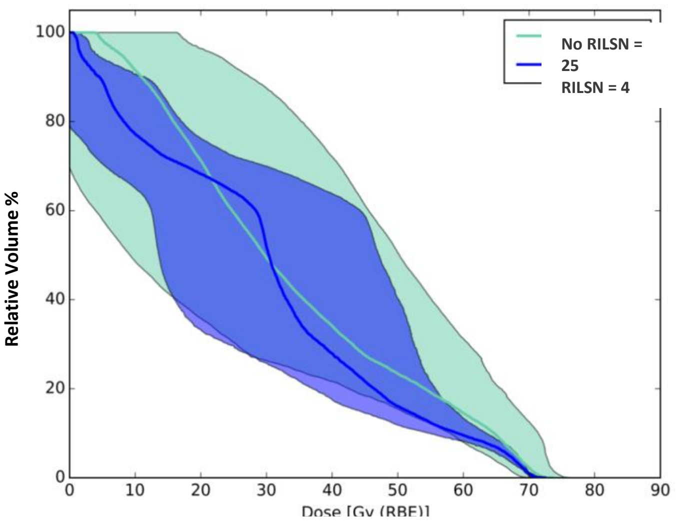
Neuropathic symptom progression CTCAE v5.0



D_{RBE} analysis for Sacral nerves | LEM- I/mMKM

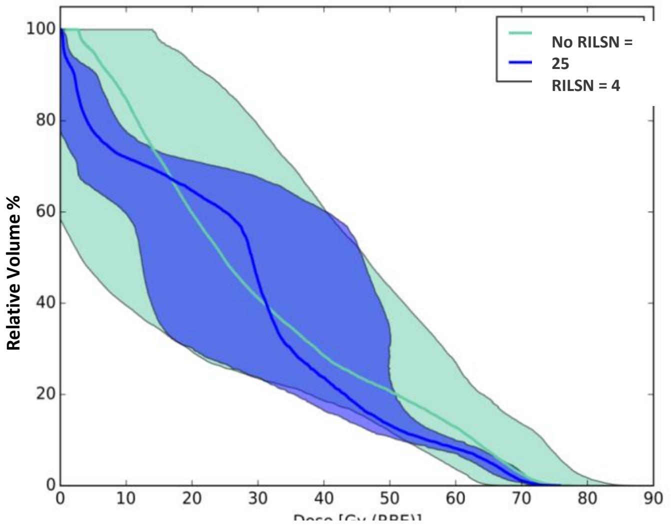
Dose calculation by both biological models did not show any significant difference between those with or without neuropathy RBE weighted Dosimetric parameters and DVH

LEM-I (local effect model –I: European)



Dose [Gy RBE]

mMKM (modified microdosimetric kinetic model: Japanese)

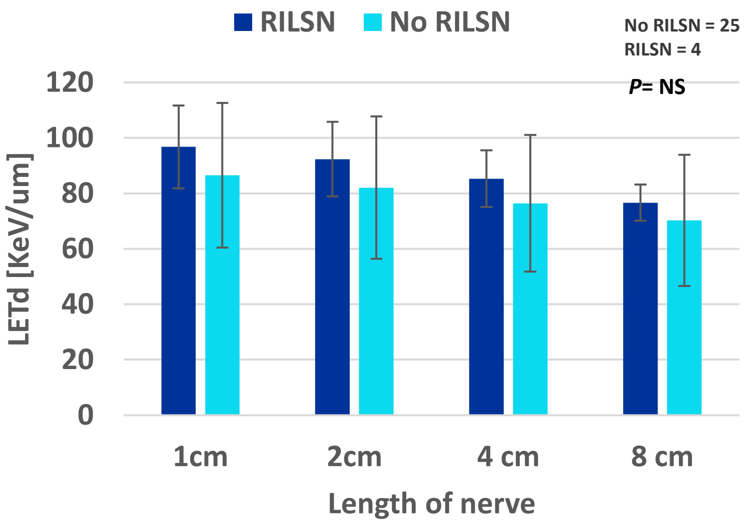


Dose [Gy RBE]

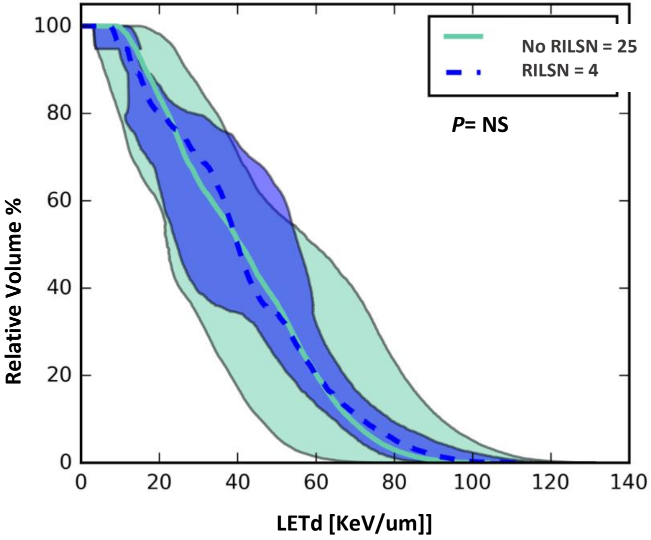
LETd analysis for Sacral nerves

LETd in sacral nerves with RILSN was higher but no significant difference in both groups.

LETd

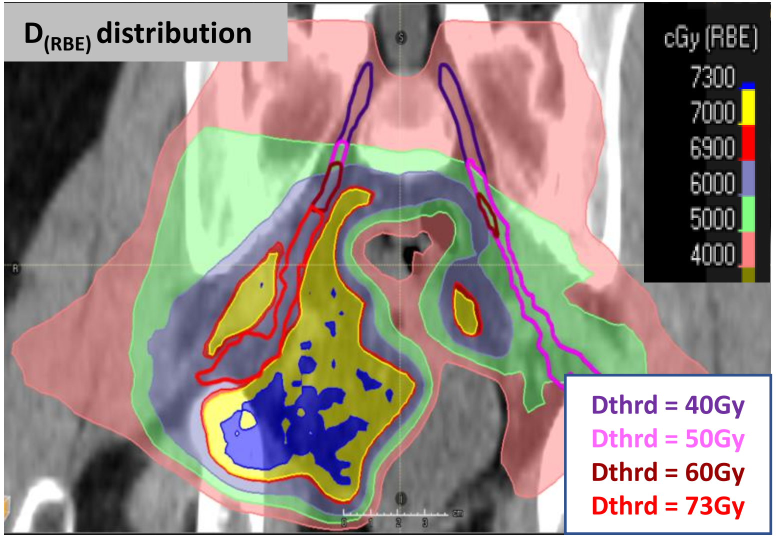


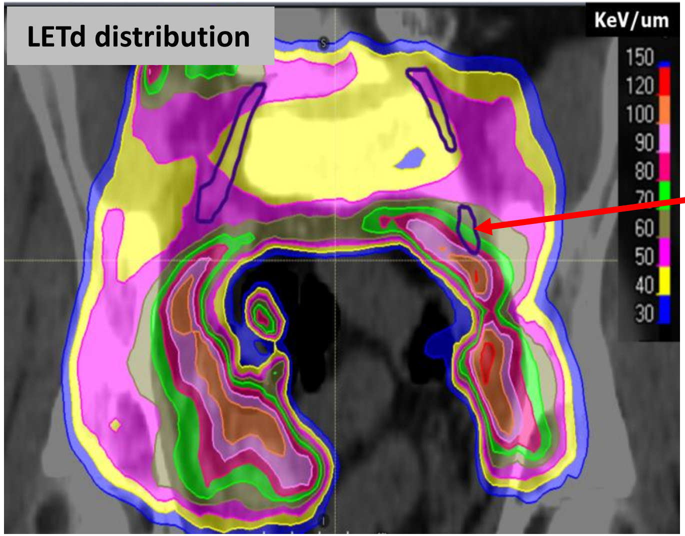
LETd volume histogram (LVH)



D_{RBE} filtered LETd analysis | Hypothesis

But LETd alone may not be reliable ……….

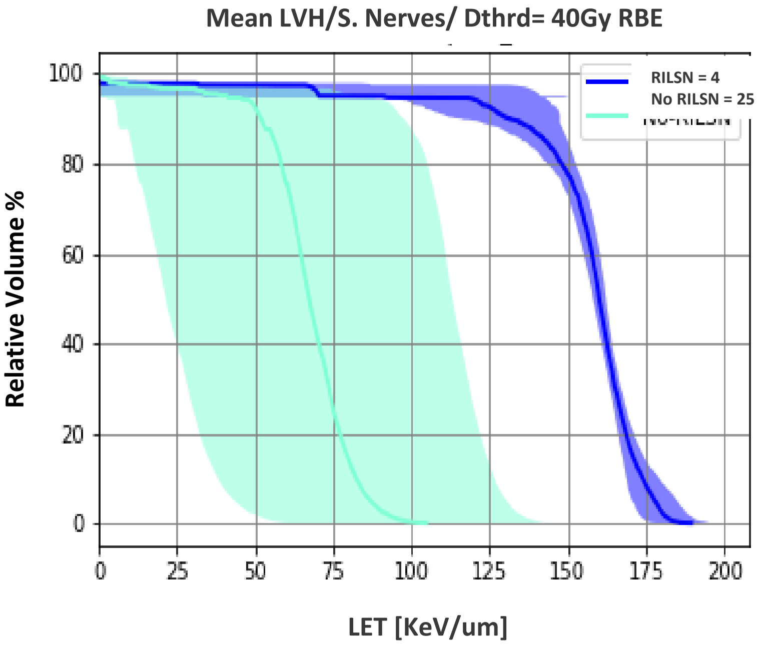




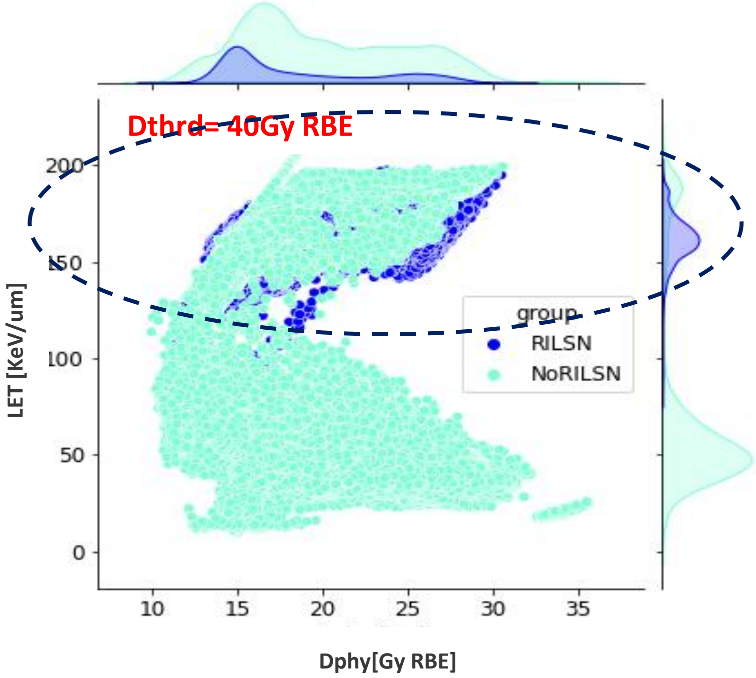
Region of the sacral nerves receiving moderate to high **D_{RBE} and high LETd may trigger an event**

D_{RBE} filtered LETd analysis

Dthrd LVH Eval



Voxel by voxel analysis



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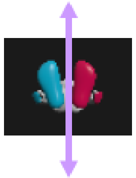
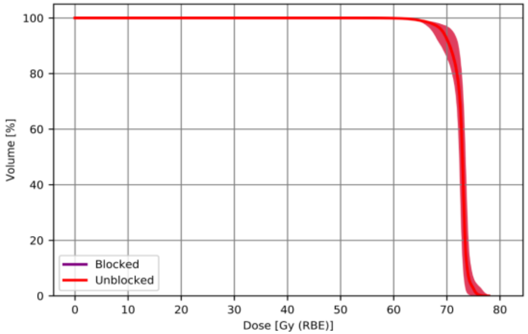
Robustness | HD-CTV | LEM-I

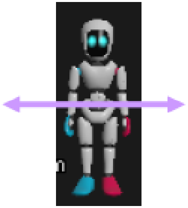
BLOCKING → No significant compromise in Robustness in terms of LEM-I

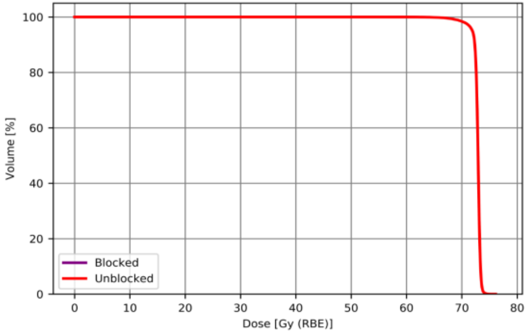
AP
+/- 5 mm



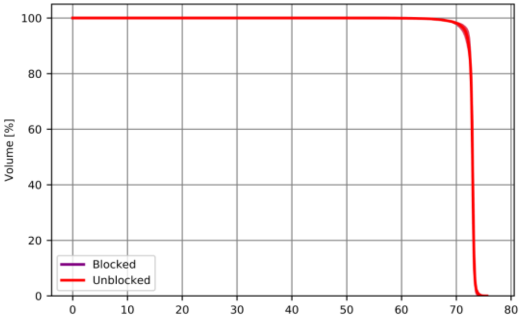


RL
+/- 5 mm

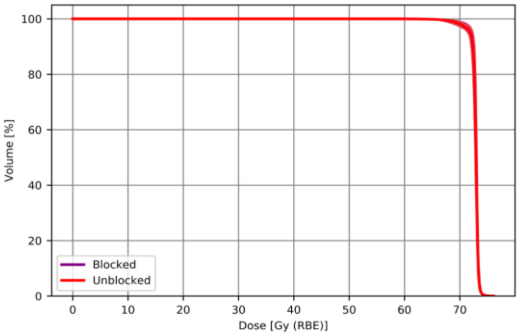




SI
+/- 5 mm



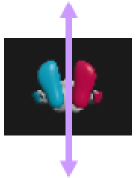
Density
+/- 3.5%

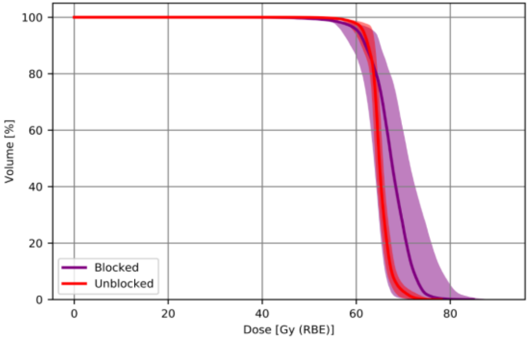


Robustness | HD-CTV | mMKM

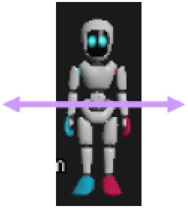
BLOCKING → Hotspot increases for mMKM

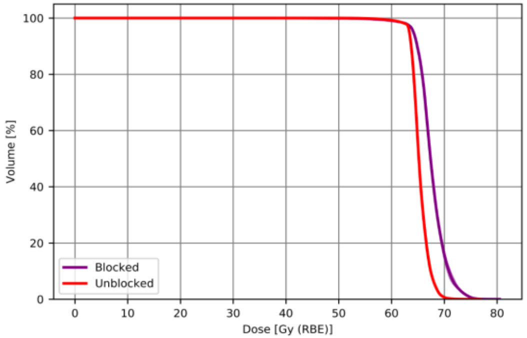
AP
+/- 5 mm



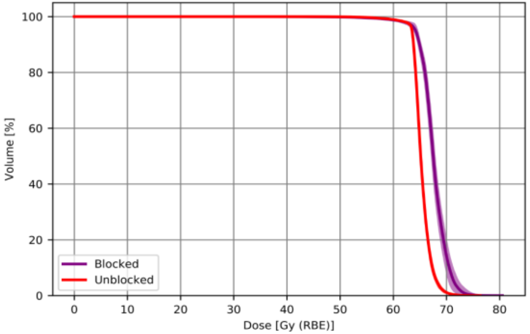


RL
+/- 5 mm





SI
+/- 5 mm



Density
+/- 3.5%