

# WP3 Clinical networking

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**WP3: Clinical networking**

|  |                            |         |                 |          |  |  |
|--|----------------------------|---------|-----------------|----------|--|--|
| <b>WP NA3</b>  | <b>Start Date</b>          | Month 1 | <b>End Date</b> | Month 48 |  |  |
| <b>WP Title:</b>   | <b>Clinical Networking</b> |         |                 |          |  |  |
| <b>Participant no.</b>   |                            |         |                 |          |  |  |
| <b>Participant</b>   | <b>MEDA</b>                | HIT     | CNAO            | MIT      |  |  |
| <b>Person months</b>   | 19                         | 25      | 33              | 17       |  |  |
| <b>Objectives</b>  |                            |         |                 |          |  |  |
| <p>Task 3.1: Trial design for innovative use of heavy ion therapy</p> <ul style="list-style-type: none"> <li>Review preclinical data to identify promising novel approaches to exploit heavy ion therapy advantage</li> <li>Design one trial as a template for bringing innovative heavy ion therapy approaches in the clinics</li> </ul> <p>Task 3.2: European registry of heavy ion therapy patients</p> <ul style="list-style-type: none"> <li>Set up a European registry to collect data on rare cancers treated with heavy ion therapy</li> </ul> <p>Task 3.3: European agreement for OARs dose constraints with heavy ion therapy</p> <ul style="list-style-type: none"> <li>Review existing data on OARs dose constraints in use in the clinical facilities</li> <li>Perform pooled data analysis to validate constraints on critical OARs</li> </ul> |                            |         |                 |          |  |  |

## Task 3.1

- 1: Hypoxia and reoxygenation**
- 2: Synergistic effect of CIRT and immunotherapy**
- 3: LET based optimization**

# LETd evaluation for targets

| No | Citation             | Purpose  | Population   | Tumor Volume (TV)<br>(cc)   | RBE Model   | Dose prescription                  | Results   | Drawback / limitations  |
|----|----------------------|--|--|---|---|------------------------------------|---|---|
| 1  | Matsumoto et al [26] | Role of LET in Chondrosarcomas recurrence                            | N = 45, Unresectable chondrosarcoma June 2000 -February 2012 at NIRS-QST | PTV= 50- 1750cc (median 400 cc)   | Non - LEM RBE model ( RBE profile was taken from measurements in HSG cells- Kanai et al 1999) | 70.4 Gy (RBE) / 16 fractions       | LETdmax (PTV) = 124 keV/μm,<br>LETdmin (PTV) = 37 keV/μm (@ isocenter),<br>LETd50% (w. r.)= 37.8 to 46.8 keV/μm,<br>LETd50% (wo r.) = 38.5 to 70.6 keV/μm,<br>LETd50% (No recurrence) > 46.8 keV/μm,<br>LETd <sub>mean</sub> (w. r.)= 38.7 to 52.2 keV/μm,<br>LETd <sub>mean</sub> (wo r.) = 41.4 to 72.3 keV/μm,<br>PTV <sub>(L1 ml)</sub> (w. r.)= 24.7 to 54.9 keV/μm,<br>PTV <sub>(L1 ml)</sub> (wo r.) = 22.4 to 36.3 keV/μm,<br>PTV <sub>(L1 ml)</sub> (No recurrence) > 36.3 keV/μm,<br>correlation - PTV(L1 ml) vs TV (r=-0.90, p<0.01),<br>V <sub>50 keV/μm</sub> (w. r.)= 0.56-0.92,<br>V50 keV/μm (wo r.) = 0 - 0.85,<br>correlation - V50 keV/μm vs TV (r=0.86, p<0.01) | LETd evaluation only  |
| 2  | Molineli et al [28]  | To D <sub>RBE</sub> and LETd parameters of CIRT for sacral chordomas | N = 52, Sacral Chordoma March 2013 -August 2018 at CNAO                  | Relapsed:<br>GTV = 337 (2–1738) cc,<br>HD-CTV = 844 (104–2397) cc, LD-CTV = 1621 (286–3411) cc,<br>Controlled:<br>GTV = 466 (22–2678) cc,<br>HD-CTV = 1145 (89–4351) cc,<br>LD-CTV = 1883 (182–4714) cc | LEM-I optimization, mMKM recomputation  | 70.4 -73.6 Gy (RBE) / 16 fractions | D <sub>RBE</sub> :<br>Delta [D <sub>mMKM 50%</sub> ] = 10% (wrt mMKM PD),<br>Delta [D <sub>mMKM 95%</sub> ] = 18% (wrt mMKM PD)<br>LETd:<br>GTV<br>LETd50% (w. r.)= 25.0 ± 2.3 keV/μm<br>LETd50% (wo r.) = 28.6 ± 4.0 keV/μm,<br>PTV(L1 ml) (w. r.)= 18.7 ± 2.1 keV/μm,<br>PTV(L1 ml) (wo r.) = 20.2 ± 6.0 keV/μm,<br>LETd50 keV/μm (w. r.)= 0.7 ± 1.0 (%),<br>LETd50 keV/μm (wo r.) = 2.7 ± 2.8 (%),<br>HD-CTV<br>LETd50% (w. r.)= 27.4 ± 2.1 keV/μm<br>LETd50% (wo r.) = 30.2 ± 3.3 keV/μm,<br>PTV(L1 ml) (w. r.)= 18.5 ± 1.9 keV/μm,<br>PTV(L1 ml) (wo r.) = 19.0 ± 5.6 keV/μm,<br>LETd50 keV/μm (w. r.)= 2.2 ± 2.6 (%),<br>LETd50 keV/μm (wo r.) = 7.6 ± 5.4 (%)                | Severely compromised D <sub>mMKM</sub> and LETd distribution in the nominal CIRT plans compared to other series . Limitations with dose and LETd computation with Syngo TPS |

# LETd evaluation for targets

|   |                     |   |   |                          |  |                                    |   |   |
|---|---------------------|---|---|--------------------------|--|------------------------------------|---|---|
| 3 | Hagiwara et al [27] | Evaluation of how LET contributes to a therapeutic effect in pancreatic cancers   | N = 18, Pancreatic adenocarcinoma April 2013 -November 2013 at NIRS-QST | GTV = 28.7 (5.9–62.8) cc | Non - LEM RBE model                    | 55.2 Gy (RBE) / 12 fractions       | GTV DMKM 98%, GTV $D_{MKM min}$ = No difference those with or without local relapse<br>LETdmin (w. r.)= 40.1 keV/μm (median),<br>LETdmin (wo r.) = 45 keV/μm (median),<br>LETd98% < 45 keV/μm 18 m LC = 43.8 mo, >= 45 keV/μm, 18 m LC = 100 mo ( p< 0.05),<br>LETdmin < 44 keV/μm 18 m LC = 34.3 mo, >= 44 keV/μm, 18 m LC = 100 mo ( p< 0.05) | LETd50 keV/μm lower in spite of low tumor volumes |
| 4 | Moreli et al [50]   | To investigate prognostic biomarkers : survival models fed with Dosimetrics features and conventional DVH metrics ( $D_{RBE}$ ) and (LETd) maps | N = 50 Sacral Chordoma March 2013 -August 2018 at CNAO                  |                          | LEM-I optimization, mMKM recomputation | 70.4 -73.6 Gy (RBE) / 16 fractions |   |   |

# LETd optimization for targets

| No | Citation             | Population  | Tumor Volume (TV) (cc)   | RBE Model                              | Dose prescription                   | LETd optimization goals  | Results  | Drawback / limitations   |
|----|----------------------|---|--|--|-------------------------------------|--|--|--|
| 1  | Kohno et al [30]     | N = 13<br>Head and neck cancer<br>March 2013 - August 2018 at NIRS-QST          | GTV = 5.9 - 143.1 cc, PTV= 29.41 - 287.97 cc   | mMKM                                   | 60.8 - 70.4 Gy (RBE) / 16 fractions | LP beam design similar to nominal IMIT plans.<br>LETd constraints GTV: LETdmin= L-5, LETd goal = L, LETdmax= L + 10 [ here L = L= 45, 55, 65, 75, 85, 95, and 105 keV/μm for PTV<br>D <sub>mMKM 90%</sub> , D <sub>mMKM 50%</sub>  | PTV<br>D <sub>MKM 90%</sub> deteriorated for L = > 75 keV/μm,<br>GTV<br>LETdmin = 45.9 ± 6.0 keV/μm (IMIT),<br>LETdmin = 59.2 ± 7.9 keV/μm [LP --> increased mean 13.2 ( 8 - 24) keV/μm],<br>LETdmean = 69.2 ± 7.0 keV/μm (LP),<br>LETdmean = 58.5 ± 5.7 keV/μm (IMIT),<br>LETdmax = 90.0 ± 6.1 keV/μm (LP),<br>LETdmax = 94.9 ± 14.5 keV/μm (IMIT)  | Total optimization time for the LP took 1.5 times longer than that for the IMIT<br>Planning comparison with IMIT and LETd painting (No clinical evaluation)  |
| 2  | Nachankar et al [33] | N = 22<br>Pelvic sarcomas/ Chordoma<br>September 2020 - June 2022 at MedAustron | small : GTV = 55.9 ± 39.8 cc, HD-CTV = 116.3 ± 52.6 cc, LD-CTV = 195.1 ± 76.8 cc,<br>Large: GTV = 301 ± 243.5 cc, HD-CTV = 551.7 ± 211.3 cc, LD-CTV = 776.7 ± 257.7 cc | LEM-I optimization, mMKM recomputation | 70.4-73.6 Gy (RBE) / 16 fractions   | 1. LETd optimization using 'distal patching': Distal-patching structures were created to stop beams 1–2 cm beyond the HD-PTV-midplane.<br>2. LETd goals for evaluation only (LETd goals for evaluation<br>a. HD-CTV: V <sub>-27 cm<sup>3</sup></sub> ≥ 33 - 39 keV/μm,<br>b. GTV: V <sub>-9 cm<sup>3</sup></sub> ≥ 33 - 39 keV/μm,<br>c. HD-PTV: V <sub>-56 cm<sup>3</sup></sub> ≥ 33 - 42 keV/μm<br>d. GTV: V <sub>[LETd50keV/μm]</sub> > 50% | 1. D <sub>RBE LEM-I</sub> , D <sub>RBE mMKM</sub> statistics (D98%, D95%, D50%, and D2%) for distally patched plans for HD-CTV and for HD-PTV and GTV were (goal ±3%, compared to unpatched plans)<br>Distal patching increased LETd50% in HD-CTV (from 38 ± 3.4 keV/μm to 47 ± 8.1 keV/μm) (24% increase),<br>2. LETdmean in low-LETd regions of the HD-CTV (from 40.1 ± 3.5 keV/μm to 48.6 ± 8 keV/μm) (21% increase),<br>3. LETdmin in low-LETd regions of the HD-CTV (from 32 ± 2.3 keV/μm to 36.2 ± 3.6 keV/μm),<br>LETdmean in GTV fraction receiving LETd of > 50 keV/μm, (from <10% to >50%)<br>high-LETd component in the central region of the GTV. by 7.1 ± 6.5 keV/μm, HD-CTV by 8.5 ± 7.3 keV/μm, GTV by 10 ± 8.8 keV/μm. | Distal patching is sensitive to setup/range uncertainties, there is always a tradeoff between target coverage with D <sub>RBE</sub> and LETd and CIRT plan robustness.<br>Retrospective evaluation and LETd optimization planning study (No clinical evaluation) |

# LETd optimization for targets

|   |                         |  |                     |  |                                 |   |   |  |
|---|-------------------------|--|---------------------|--|---------------------------------|---|---|--|
| 3 | Schafasand et al. [51 ] | N = 10<br>Pelvic sarcomas/<br>Chordoma<br>at MedAustron                        |                     | LEM-I optimization,<br>mMKM<br>recomputation | 73.6 Gy (RBE) / 16<br>fractions | LETd goals<br>HD-CTV: V-27 cm <sup>3</sup> ≥ 40 keV/μm<br>GTV V-9 cm <sup>3</sup> ≥ 42 keV/μm | LETd<br>optimization method with LETdmin = 60 keV/μm<br>HD-CTV, LETd98% increased by 8.9±1.5 keV/μm (27%)<br>HD-CTV, LETd50% increased by 6.9±1.3 keV/μm (17%)<br>By compromising target prescription by ±5%<br>HD-CTV, LETd98% increased by 11.3±1.2 keV/μm (34%)<br>HD-CTV, LETd50% increased by 11.7±3.4 keV/μm(29%)<br>robustness evaluation, the pass rate of the LETdmin = 60 keV/μm optimized plans in achieving the OAR goals was in the same level as the reference plans in all scenarios | With mixed field CIRT LETd optimization (Single ion) LETdmin ≥ 80-100 keV/μm goal cannot be reached without compromising target coverage and homogeneity.<br>LETd optimization planning study (No clinical evaluation) |
| 4 | Koto et al. [2024]      | N = 12<br>Head and neck cancer<br>October 2021-<br>October 2023 at<br>NIRS-QST | SCC, ACC, AD,DC, ME | mMKM,<br>LEM-I optimization                  | 64 Gy (RBE) / 16<br>fractions   | LETd goals<br>GTV: LETdmin ≤ 70 keV/μm  | GTV<br>LETdmin = increased from 52 keV/μm ( No LETd optimization) to 63 keV/μm (LETd optimization)<br>LETdmean = increased from 64 keV/μm (No LETd optimization) to 73 keV/μm (LETd optimization)<br><br>Clinical result:<br>No acute / late toxicity ≥ G3 at 180 days except G4 optic nerve toxicity.<br>Treatment response rate (CR + PR) 67% (Koto et al IJROBP 2024) vs 56% ( previously reported by Mizoe et al Radiother Oncol 2012) at 180 days.   | Longer follow up period is required for validation of clinical benefits.<br>Dosimetric correlation with G4 optic nerve toxicity is not reported.   |

# LETd evaluation for OARs

| No | Citation              | Aim   | Population  | Tumor Volume (TV)           | RBE Model  | Dose prescription                                    | Results   | Drawback / limitations  |
|----|-----------------------|---|---|-----------------------------|--|--|---|---|
| 1  | Okonogi et al [42]    | To assess predictive factors for late morbidities in the rectum and bladder after carbon-ion C-ion RT for uterus carcinomas   | N = 134<br>uterus carcinomas<br>June 1995 - January 2010, at NIRS-QST             |                             | Non - LEM RBE model (RBE profile was taken from measurements in HSG cells- Kanai et al 1999) | 52.8 Gy (RBE)–<br>74.4 Gy (RBE) /<br>20-24 fractions | 1. D2cc > 60.2 Gy (RBE) grade 3 late rectal complications (p = 0.012).<br>2. No trends between grading of late rectal complications and these LETd histograms   | Studies LETd as a sole parameter without studying the dose in in same voxel |
| 2  | Mori et al [43 ]      | To investigate the effects of LETd and dose on pelvic insufficiency fractures after CIRT  | N = 134<br>uterus carcinomas<br>June 1995 and January 2010 - NIRS-QST             |                             | mMKM model   | 52.8 Gy (RBE)–<br>74.4 Gy (RBE) /<br>20-24 fractions | 1. D50% RBE-weighted dose was a valuable predictor of SIF.<br>2. patients over 50 years of age validated that current smoking habit were risk factors for SIF   | Studies LETd as a sole parameter without studying the dose in in same voxel |
| 3  | Nachankar et al [48 ] | To evaluate results of sacral nerve sparing strategy (SNSo-CIRT) and investigate the effects of LETd and $D_{RBE}$ on Radiation induced lumbosacral neuropathy after CIRT | N = 35<br>Pelvic sarcomas/<br>Chordoma<br>August 2019 - August 2022 at MedAustron | HD-CTV:<br>503.3 ± 402.1 cc | LEM-I optimization,<br>mMKM recomputation  | 70.4 Gy (RBE)-<br>73.6 Gy (RBE) / 16<br>fractions    | 1. No difference in sole $D_{RBE}$ or LETd distribution on sacral nerves in patient with or without neuropathy.<br>2. RILSN-free survival at $D_{RBE LEM-I}$ cutoff = 65 Gy (RBE) and LETd < 55 keV/μm for sacral-nerves-to-spare was 100% and those with LETd ≥ 55 keV/μm was 70% (CI, 47-100) (p = 0.03). |   |



# LETd evaluation for OARs

|   |                       |  |   |  |  |  |  |        |
|---|-----------------------|--|---|--|--|--|--|--------|
| 4 | Nachankar et al [49 ] | To evaluate results of mucosa-sparing-strategy (MSS-CIRT) and investigate the effects of LETd and $D_{RBE}$ on G3 late mucosal toxicity after CIRT | N = 55<br>Non-squamous Head and neck cancer<br>August 2019 - October 2023 at MedAustron |  | LEM-I optimization, mMKM recomputation | 65.6 Gy (RBE)-<br>73.6 Gy (RBE)/16 fractions | <p>1. Average <math>D_{RBE}</math> LETd after filtering-out RBE-weighted doses (<math>D_{RBE}</math>-filtered LETd) for mucosa were higher in patients with LMT3 (without MSS-CIRT) compared to those treated with MSS-CIRT, [<math>D_{RBE LEM-I 0.1cc}</math> =73.2 vs 66.8 Gy (RBE) and <math>D_{RBE mMKM 0.1cc}</math> =74.2 vs 64.4 Gy (RBE) (Figure 2, n: MSS-CIRT=25, LMT3=2)] respectively.</p> <p>2. Limiting <math>D_{RBE}</math>-filtered LETd for MTS substructure receiving <math>D_{RBE mMKM 0.1cc}</math> &gt;69 and &gt;70 Gy (RBE) appears critically important.</p> | .....? |
|---|-----------------------|--|---|--|--|--|--|--------|

# Two possible strategy for LET painting

- Blocking
- Let optimization in TPS

# DVH | LEM | Small vs Large vs Large Blocked

PTV2

CTV2

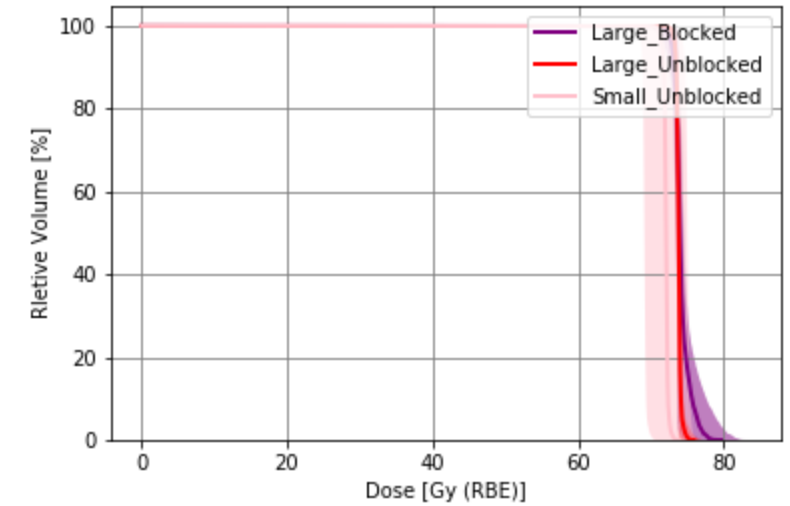
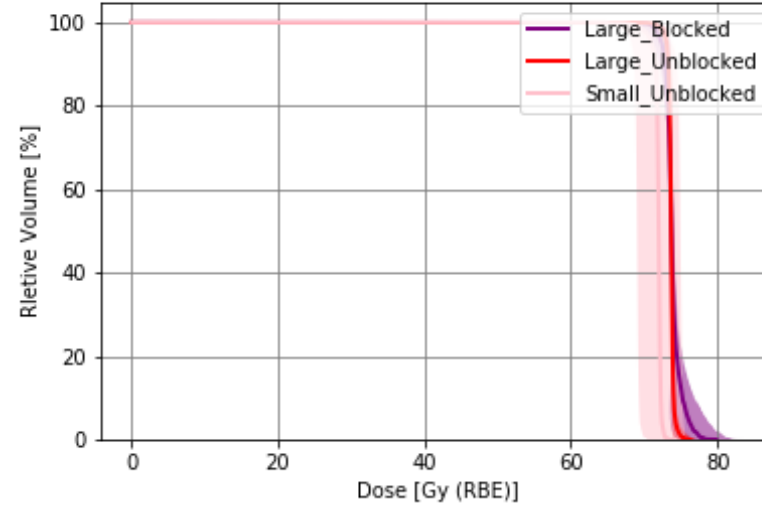
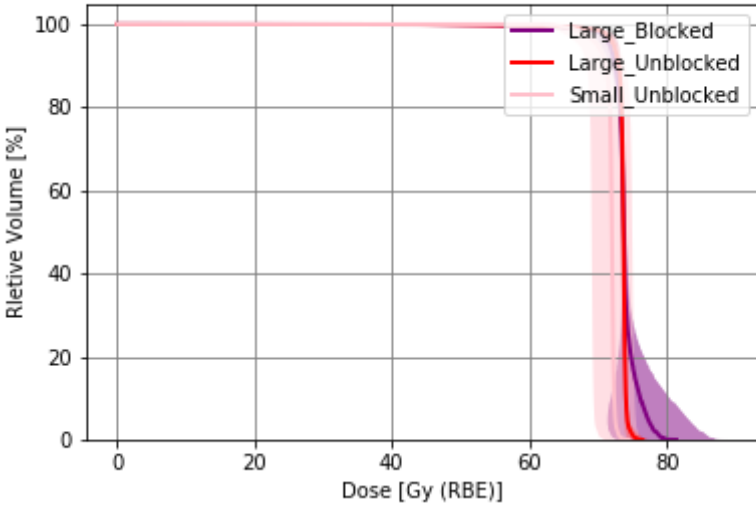
GTV

n= 20,  
Small = 10  
Large = 10  
Large\_Blocked = 10

Mean DVH / PTV2

Mean DVH / CTV2

Mean DVH / GTV1



Satisfactory LEM: For blocked cases: Satisfactory coverage in terms of LEM RBE weighted dose

# DVH | MKM | Small vs Large vs Large Blocked

PTV2

CTV2

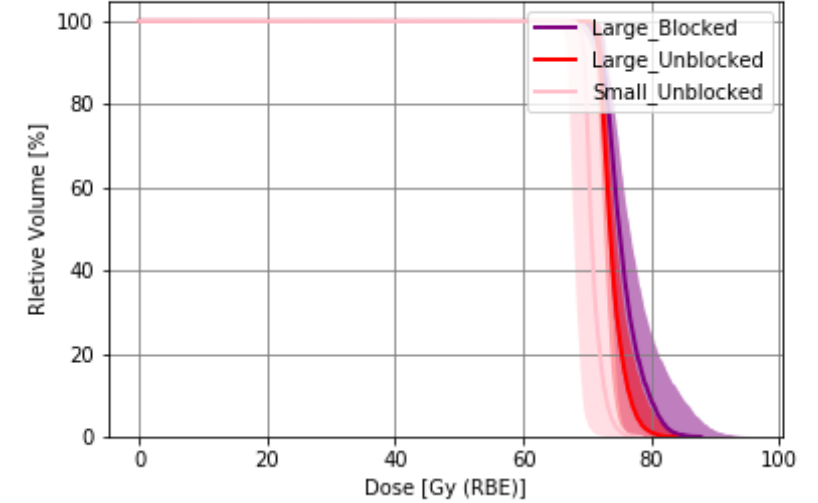
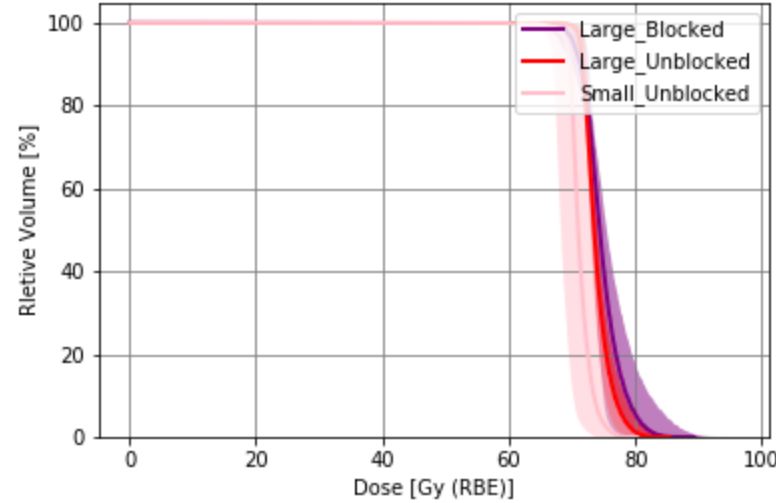
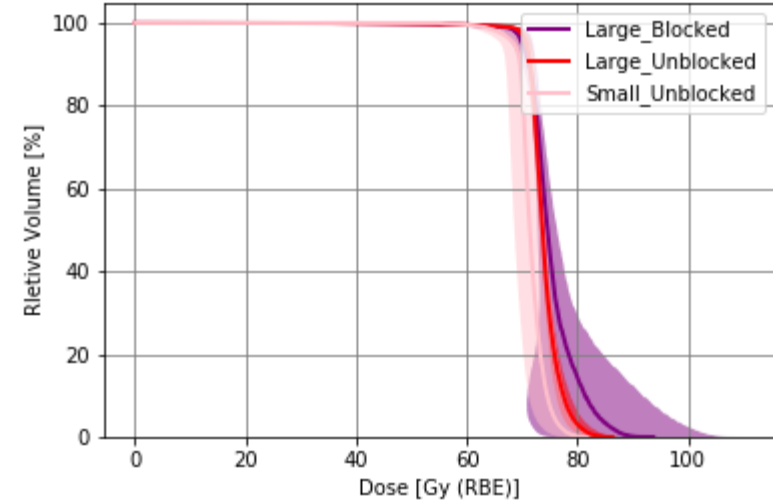
GTV

n= 20,  
Small = 10  
Large = 10  
Large\_Blocked = 10

Mean DVH / PTV2

Mean DVH / CTV2

Mean DVH / GTV1



MKM: FOR BLOCKED CASES: SATISFACTORY COVERAGE, BUT HOTSPOT ESPECIALLY FOR PTV2

# LVH | LET | Small vs Large vs Large Blocked

PTV2

CTV2

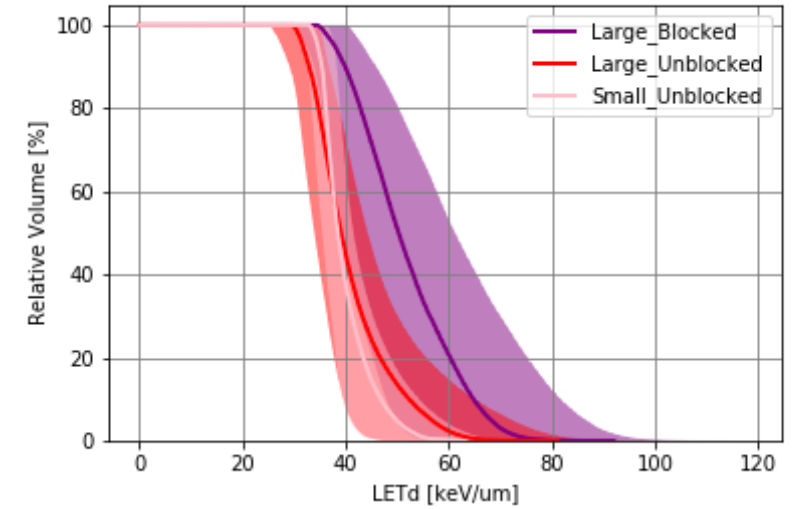
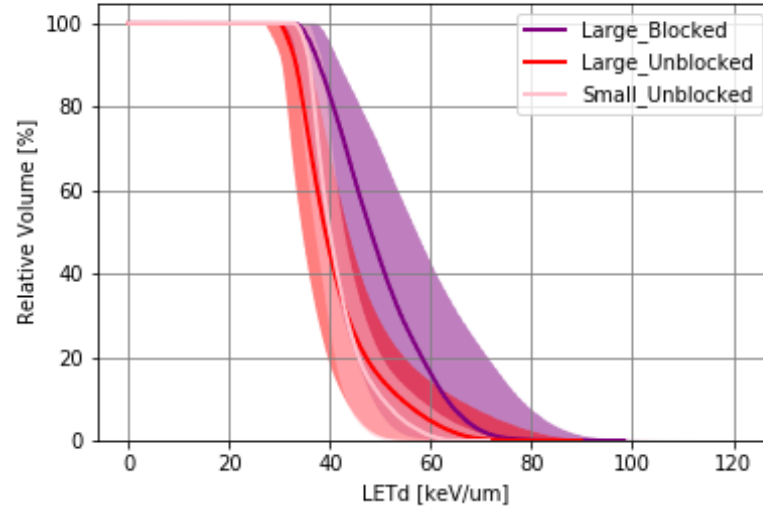
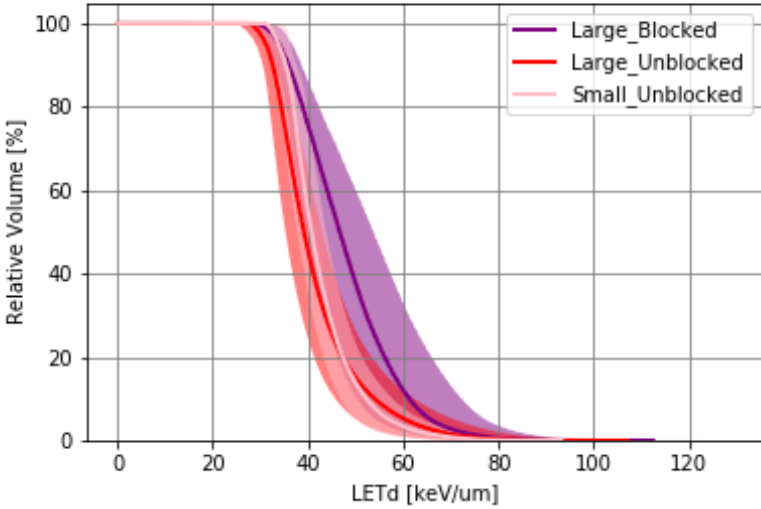
GTV

n= 20,  
Small = 10  
Large = 10  
Large\_Blocked = 10

Mean LVH / PTV2

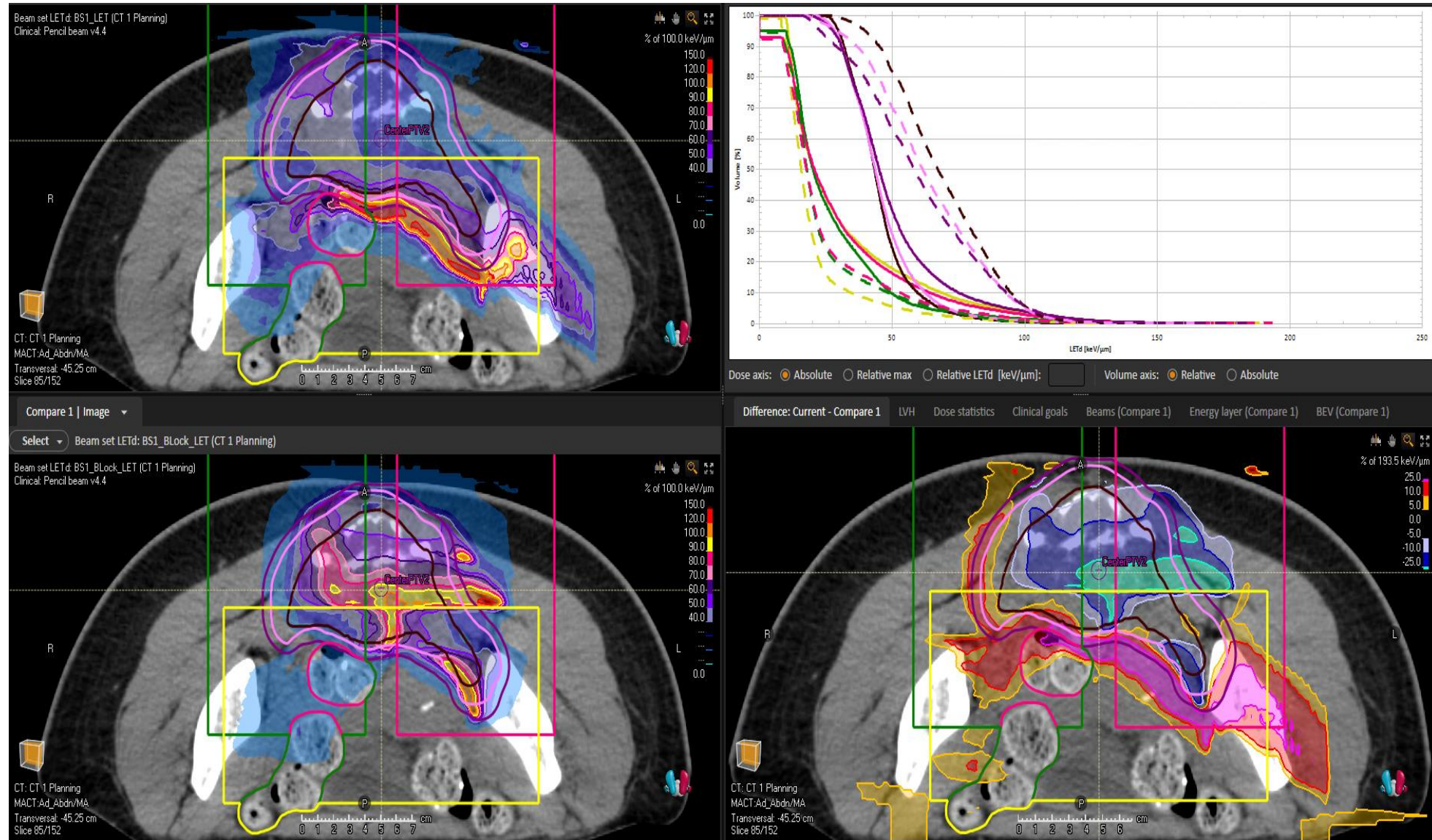
Mean LVH / CTV2

Mean LVH / GTV1



Satisfactory LET: For blocked cases: Significantly better LET Distribution most benefit with GTVc

# LET in central portion of GTV | Small vs Large vs Large Blocked



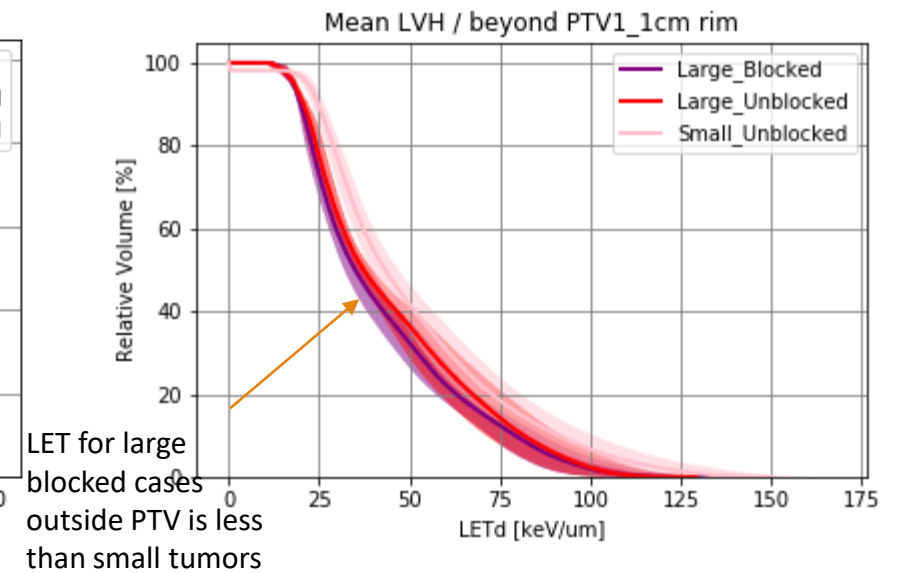
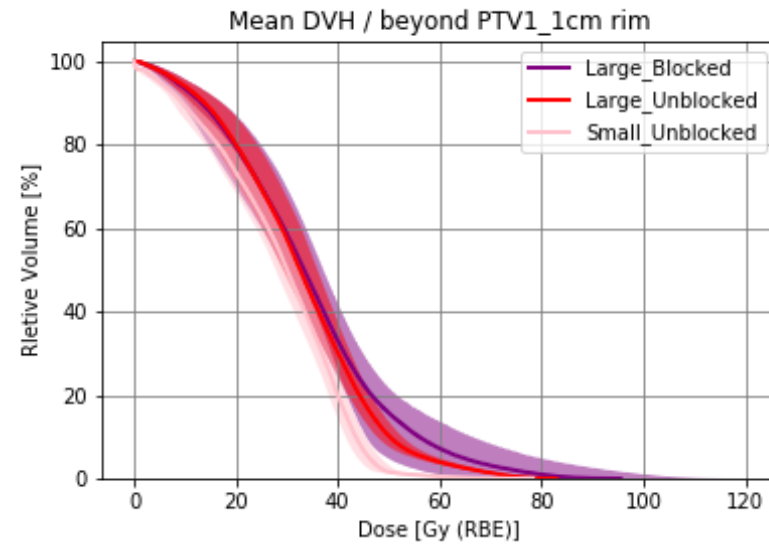
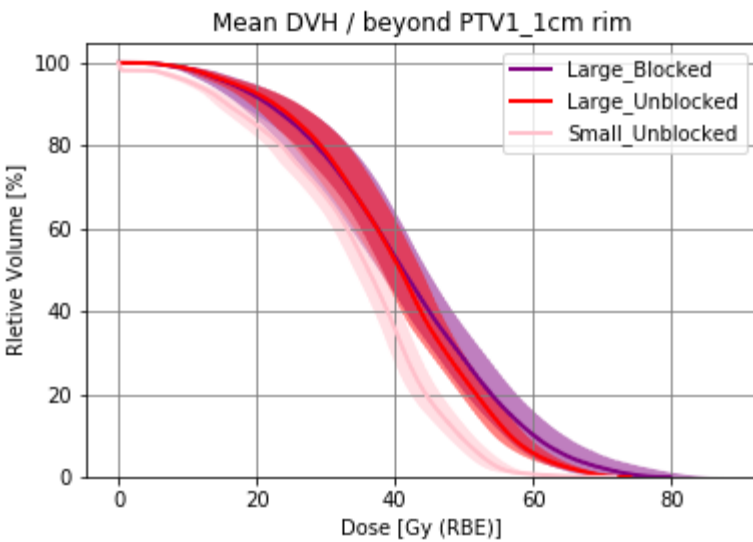
# Dose, LET outside PTV | Small vs Large vs Large Blocked

LEM

MKM

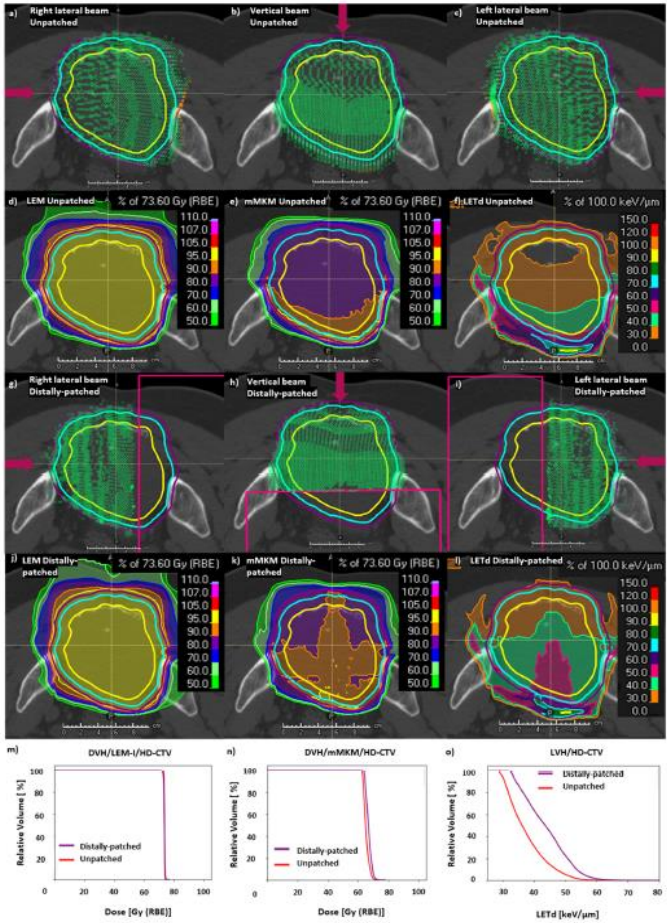
LET

n = 20,  
Small = 10  
Large = 10  
Large\_Blocked = 10



LET LET: For blocked cases: LET DISTRIBUTION OUTSIDE PTV1 IS ALSO IMPROVED DUE TO SPATIAL REDISTRIBUTION OF LET IN THE CENTER OF GTV/PTV

# First Patient experience sin MedAustron





Parameters used in clinical cases  
in MA

# Acceptable clinical goals for targets

| Target                         | Internally (MedAustron) validated LETd Constraints   | Constraints extrapolated form other series                      | Priority        |
|--------------------------------|--|---|-----------------|
| HD-CTV                         | CTV - 27 cc > 40 keV/μm (Chordomas/sarcomas)   |   | Moderate        |
| GTV                            | GTV - 9 cc > 40 keV/μm (Chordomas/sarcomas)  |   | High            |
|                                | V[LETd50 keV/μm] > 50% (Chordomas/sarcomas)  |   | High            |
|                                |  | LETdmin > 59 keV/μm (Bulky, non-squamous Head and neck cancers) | High            |
|                                |  | LETdmin > 80 keV/μm (Pancreatic cancers, renal cell carcinoma)  | High            |
| HD-PTV                         | PTV - 56 cc > 42 keV/μm  |   | Moderate to low |
| Sacral-nerves (outside HD-CTV) | at $D_{RBE LEM-I}$ cutoff = 64 Gy (RBE), <12% of volume should receive > LETd < 55 keV/μm (Dose filtered LETd) |   | Moderate        |
|                                | at $D_{RBE LEM-I}$ cutoff = 63 Gy (RBE), <10% of volume should receive > LETd < 50 keV/μm (Dose filtered LETd) |   | Moderate        |

# Draft of the protocol is being finalised

The image displays a grid of 30 thumbnail images, each representing a different section of a research protocol draft. The thumbnails are arranged in a 3x10 grid. The top row contains 10 thumbnails, the middle row contains 10, and the bottom row contains 10. The thumbnails show various elements of a protocol, including text, tables, diagrams, and figures. Some thumbnails show text with red and blue highlights, indicating changes or specific sections. One thumbnail in the middle row shows a diagram of a human head and neck with colored regions. Another thumbnail in the bottom row shows a grid of small images, possibly representing experimental results or data. The thumbnails are arranged in a grid that is roughly 3 rows by 10 columns, with the bottom row containing 10 thumbnails and the top two rows containing 10 each.



# Task 3.2

| Patient ID | Sex | Date of birth | Age | Type of diagnosis   | Comorbidity   | Previous cancer | Specify cancer | Year of diagnosis | Radiotherapy treatment | Year of radiotherapy | Specify energy  | Total dose | Chemotherapy treatment? | Year |  |  |  |  |  |  |  |  |  |  |  |  |  |
|------------|-----|---------------|-----|---|---|-----------------|----------------|-------------------|------------------------|----------------------|---|------------|-------------------------|------|--|--|--|--|--|--|--|--|--|--|--|--|--|
|            |     |               |     | <b>Campo Chiara:</b> <ul style="list-style-type: none"> <li>- Primary Tumor</li> <li>- Relapsed Tumor - Local (T)</li> <li>- Relapsed Tumor - Regional (N)</li> <li>- Relapsed Tumor - Metastatic (M)</li> <li>- Radiation-induced Tumor</li> </ul> | <b>Campo Chiara:</b> <ul style="list-style-type: none"> <li>- Yes</li> <li>- No</li> <li>- Unknown</li> </ul> |                 |                |                   |                        |                      | <b>Campo Chiara:</b> <ul style="list-style-type: none"> <li>- Carbon ions</li> <li>- Protons</li> <li>- Photons</li> <li>- Unknown</li> </ul> |            |                         |      |  |  |  |  |  |  |  |  |  |  |  |  |  |
|            |     |               |     |   | <b>Campo Chiara:</b><br>According to MedDRA   |                 |                |                   |                        |                      |   |            |                         |      |  |  |  |  |  |  |  |  |  |  |  |  |  |

# The database has so far been used only by CNAO

In the last phase of the project the database will be used to support the activity of task 3.3.

### Task 3.3

| A                                | B MedAustron * red constraints must be respected in the LEM optimized plan and in the MKM recalculated plan                                      |   |  |   |  |  | G |
|----------------------------------|--|---|--|---|--|--|---|
|                                  | japanese fractionation (> 4 Gy RBE LEM per fraction)   |   |  | german fractionation (3 Gy RBE LEM per fraction)            |  |  |   |
|                                  | optimal  | acceptable  | high risk ( to be used only on one side)   | optimal   | acceptable                             | high risk ( to be used only on one side) |   |
| optic nerve                      | <b>D1% &lt; 45 Gy RBE LEM<br/>D20% &lt; 40 Gy RBE LEM<br/>D1% &lt; 40 Gy RBE MKM<br/>D20% &lt; 30 Gy RBE MKM</b>                                 | <b>D1% &lt; 50Gy RBE LEM<br/>D20% &lt; 40 Gy RBE LEM<br/>D1% &lt; 40 Gy RBE MKM<br/>D20% &lt; 30 Gy RBE MKM</b> | <b>D1% &lt; 54 Gy RBE LEM<br/>D20% &lt; 40 Gy RBE LEM<br/>D1% &lt; 40 Gy RBE MKM</b> | D (RBE, 2%) < 50 Gy RBE                                     | D (RBE, 2%) < 54 Gy RBE                | D (RBE, 2%) < 56 Gy RBE                  |   |
| optic chiasm                     | <b>D1% &lt; 45 Gy RBE LEM<br/>D20% &lt; 40 Gy RBE LEM<br/>D1% &lt; 40 Gy RBE MKM<br/>D0.1cc &lt; 46 Gy RBE LEM<br/>D0.7cc &lt; 38 Gy RBE LEM</b> | na  | na   | D (RBE, 2%) < 50 Gy RBE                                     | D (RBE, 2%) < 54 Gy RBE                | na                                       |   |
| brainstem                        | <b>D0.1cc &lt; 46 Gy RBE LEM<br/>D0.7cc &lt; 38 Gy RBE LEM<br/>D0.1cc &lt; 40 Gy RBE MKM<br/>D0.7cc &lt; 30 Gy RBE MKM</b>                       | na  | na   | D (RBE, 0,01 ccm) < 54 Gy (RBE),<br>D (RBE, 2%) < 50 Gy RBE | na                                     | na                                       |   |
| spinal cord                      | <b>D0.1cc &lt; 46 Gy RBE LEM<br/>D0.7cc &lt; 38 Gy RBE LEM<br/>D0.1cc &lt; 40 Gy RBE</b>   | na  | na   | D (RBE, 0,01 ccm) < 54 Gy (RBE),<br>D (RBE, 2%) < 50 Gy RBE | na                                     | na                                       |   |
| brain parenchyma                 | D1cc < 60 Gy RBE<br>D5cc < 54 Gy RBE L   | D1cc < 64 Gy RBE<br>D5cc < 60 Gy RBE L  | na   | D1cc < 65 Gy RBE  | D1cc < 69 Gy RBE                       | na                                       |   |
| parotid gland                    | Dmean < 20 Gy RBE  | na  | Dmean < 26 Gy RBE  | Dmean < 20 Gy RBE   | na                                     | Dmean < 26 Gy RBE                        |   |
| mandible (teeth bearing)         |  |   |  | D (RBE, 2%) < 50 Gy RBE                                     | na                                     | na                                       |   |
| mandible ( ramus)                | D (RBE,1cc) < 53 Gy RBE,<br>D (RBE,3cc) < 50 Gy RBE ,<br>D (RBE,5cc) < 38 Gy RBE   | D (RBE,3cc) < 60 Gy RBE,<br>D (RBE,5cc) < 50 Gy RBE,<br>D (RBE 8cc) < 38 Gy RBE                                 | na   | D (RBE, 2%) < 50 Gy RBE                                     | na                                     | na                                       |   |
| cornea                           | D2% < 30 Gy RBE  | D2% < 40 Gy (RBE),<br>D10% < 30 Gy RBE  | na   | D2% < 30 Gy RBE   | D2% < 40 Gy (RBE),<br>D10% < 30 Gy RBE | na                                       |   |
| retina                           | D (RBE, 2%) < 40 Gy (RBE)  | D (RBE, 2%) < 45 Gy   | na   | D (RBE, 2%) < 40 Gy (RBE)                                   | D (RBE, 2%) < 45 Gy (RBE)              | na                                       |   |
| cochlea                          | Dmean < 30 Gy RBE  | Dmean < 43 Gy RBE   | na   | Dmean < 30 Gy RBE   | Dmean < 43 Gy RBE                      | na                                       |   |
| skin                             | D5sqcm < 60 Gy RBE   | na  | na   | none  | none                                   | none                                     |   |
| duodenum                         | D (RBE, 0.1 ccm) < 46 Gy RBE,<br>D (RBE, 5 ccm) < 36 Gy RBE,<br>D (RBE, 25 ccm) < 25 Gy RBE  | D (RBE, 0.1 ccm) < 48 Gy RBE  | na   | not used  | not used                               | not used                                 |   |
| Stomach                          | D (RBE, 0.1 ccm) < 46 Gy RBE,<br>D (RBE, 5 ccm) < 36 Gy RBE,<br>D (RBE, 25 ccm) < 25 Gy RBE  | D (RBE, 0.1 ccm) < 48 Gy RBE  | na   | not used  | not used                               | not used                                 |   |
| small bowel                      | D (RBE, 0.1 ccm) < 45 Gy RBE,<br>D (RBE, 2 ccm) < 40 Gy RBE  | D (RBE, 0.1 ccm) < 50 Gy RBE,<br>D (RBE, 1 ccm) < 66 Gy RBE   | na   | not used  | not used                               | not used                                 |   |
| rectum/sigmoid colon             | D (RBE, 1 ccm) < 66 Gy RBE,<br>D (RBE, 5 ccm) < 60 Gy RBE,<br>D (RBE, 10 ccm) < 47 Gy RBE  | RBE, D (RBE, 5 ccm) < 63 Gy RBE,<br>D (RBE, 10 ccm) < 55 Gy   | na   | not used  | not used                               | not used                                 |   |
| urinary bowel                    | D (RBE, 1 ccm) < 66 Gy RBE,<br>D (RBE, 50 ccm) < 50 Gy RBE   | na  | na   | not used  | not used                               | not used                                 |   |
| kidney                           | D (RBE, mean) < 10 Gy RBE;   | D (RBE, mean) < 18 Gy   | na   | D (RBE, mean) < 10 Gy RBE;                                  | D (RBE, mean) < 18 Gy                  | na                                       |   |
| cauda equina                     | D (RBE, 0.1%) < 66 Gy RBE  | D (RBE, 0.1%) < 70 Gy RBE   | na   | not used  | not used                               | not used                                 |   |
| nerveroots outside high dose CTV | D1% < 69 Gy RBE  | D1% < 71 Gy RBE   | na   | not used  | not used                               | not used                                 |   |
| nerveroots inside high dose CTV  | D1% < 71 Gy RBE  | D1% < 73 Gy RBE   | na   | not used  | not used                               | not used                                 |   |

# Brain has been selected as organ at risk for pooled analysis





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CLINICAL INVESTIGATION

## Prospective Analysis of Radiation-Induced Contrast Enhancement and Health-Related Quality of Life After Proton Therapy for Central Nervous System and Skull Base Tumors

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ELSEVIER

Original Article

Radiation induced contrast enhancement after proton beam therapy in patients with low grade glioma – How safe are protons?

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## Radiation-induced contrast enhancement following proton radiotherapy for low-grade glioma depends on tumor characteristics and is rarer in children than adults

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Article

## Patterns of Temporal Lobe Reaction and Radiation Necrosis after Particle Radiotherapy in Patients with Skull Base Chordoma and Chondrosarcoma—A Single-Center Experience

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# Happy to answer your questions

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