LET and RBE investigation of various structures for a cohort of proton patients with brain tumors

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**Full Title:** LET and RBE investigation of various structures for a cohort of proton patients with brain tumors

**Short Running Title:** LET and RBE for neuro cohort

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Abstract

Background and purpose: The current knowledge on biological effects associated with proton therapy is limited. Therefore, we investigated the distributions of dose, dose-averaged linear energy transfer \( (\text{LET}_d) \) and the product between dose and \( \text{LET}_d \) (\( \text{DLET}_d \)) for a patient cohort treated with proton therapy. Different treatment planning system (TPS) features and visualization tools were explored.

Material and methods: For a cohort of 24 patients with brain tumors, the \( \text{LET}_d \), \( \text{DLET}_d \) and dose was calculated for a fixed relative biological effectiveness (RBE) value and two variable models: a plan-based and a phenomenological one. Dose threshold levels of 0, 5 and 20 Gy were imposed for \( \text{LET}_d \) visualization. The relationship between physical dose and \( \text{LET}_d \) and the frequency of the \( \text{LET}_d \) hotspots were investigated.

Results: The phenomenological RBE model presented consistently higher dose values. For lower dose thresholds, the \( \text{LET}_d \) distribution was steered towards higher values, related to low treatment doses. Differences up to 26.0% were found, according to the threshold. Maximum \( \text{LET}_d \) values were identified in the brain, periventricular space (PVS) and ventricles. An inverse relationship between \( \text{LET}_d \) and dose was observed. Frequency information to the domain of dose and \( \text{LET}_d \) allowed the identification of the clusters which steer the mean \( \text{LET}_d \) values and the identification of the higher but sparse \( \text{LET}_d \) values.

Conclusions: It is necessary to identify, quantify and record \( \text{LET} \) distributions, in a standardized fashion, as concern exists over a link between toxicity and \( \text{LET} \) hotspots. Visualizing \( \text{DLET}_d \) or dose \times \( \text{LET}_d \) during treatment planning could allow clinicians to take informed decisions.

Introduction
The decreased integral dose of ion therapy with respect to photon therapy combined with recent technological advances contributed to the significant growth of particle treatments in the last decades. Physically, the finite range of protons and the Bragg peak, with a sharp dose fall-off after the target volume, enables better organ-at-risk (OAR) sparing and conformal dose around the target. Biologically, protons cause cellular damage more effectively than photons. Therefore, a conversion factor, the relative biological effectiveness (RBE), is used for treatment and comparison between modalities\(^1\). However, biological effects of proton therapy (PT), in particular those associated with the RBE, are less understood than those of photons, triggering discussions on its intrinsic uncertainty\(^2\)–\(^4\).

Current clinical practice bases treatments on physical dose and assumes a spatially invariant average RBE value of 1.1\(^1\). Extensive experimental evidence shows that the RBE is in fact variable, dependent on the tissue, dose, radiation quality, among other parameters\(^5\)–\(^7\). For the clinical energy range, RBE and the linear energy transfer (LET), a non-stochastic quantity used to characterize the quality of a beam, present a monotonic correlation, which increases toward the distal edge of the Bragg peak reaching a maximum at the falloff region: as energy decreases, energy deposition occurs more densely around the protons' tracks, which causes more confined and complex damage\(^4\),\(^8\). Several phenomenological RBE models exist but present high uncertainties and large variability when compared against each other\(^6\),\(^9\)–\(^11\). While a constant average value allows for ubiquitous treatment standardization and disregards RBE uncertainties, neglecting RBE variation might lead to underestimation of normal tissue complication probability as highly modulated fields may result in inhomogeneous linear energy transfer (LET) distributions\(^12\),\(^13\). Some studies have also suggested a correlation between late normal tissue toxicity and LET hotspots\(^14\)–\(^18\).

LET is defined at a point and describes the average energy transfer from electronic interactions per unit length travelled by charged primary particles\(^19\),\(^20\). The unrestricted LET is equivalent
to the electronic stopping power, representing energy loss(19). Dose-averaged LET (LET$_d$) is a frequently used quantity that considers the stopping power of each individual particle weighted by its contribution to the local dose\(^{21,22}\). LET$_d$ combines different beam qualities contributing to damage in a single value and can be used as a predictor for RBE\(^{22}\), considering a suggested LET-RBE linear dependence\(^{24-27}\). To avoid RBE uncertainty while reducing biological variability in treatment planning, metrics based on computable physical parameters e.g. dose and the LET-RBE dependence (as a proxy for response) have been suggested, e.g. the product between dose and LET$_d$ (DLET$_d$) \(^{25,26,28}\).

In this retrospective study, we investigated the distributions of LET$_d$, dose (with different RBE models) and DLET$_d$ in a cohort of patients with brain tumors treated between 2019 and 2020 in our institute. The distributions were quantified and analyzed focusing on hotspots adjacent to the clinical target volumes (CTV) and inside the OARs. The Monte Carlo (MC) engine from our treatment planning system (TPS) was used for all calculations. Although judging physical dose might be common practice, it is less intuitive for LET$_d$ distributions. The lack of knowledge and experience with this quantity (and its units) pose an additional challenge. To interpret these results, we propose various visualization tools to improve the perception and acquaintance regarding the relationship between treatment planning dose and LET$_d$ distribution.
Materials & methods

Cohort of neurological patients

A cohort of 24 patients with brain tumors, which received proton therapy between September 2019 and July 2020, was selected for this study. Institutional review board approval (XXXXXXX) was obtained for retrospective analysis. Table 1 presents characteristics of the cohort and treatment planning parameters.

The MC algorithm of Raystation (Raysearch, Sweden) was used for dose calculations with uncertainty set to 1%. All plans were robustly optimized (voxel-wise-min-max)(29) with range uncertainty set to 3% and universal uncertainty to 1 mm. The TPS optimization for our Mevion S250i Hyperscan PT system (Mevion, Littleton, MA, USA) allows setting a number of proximal and distal energy layers. CTV coverage was evaluated on the voxel-wise-min and -max doses to OAR and on the voxel-wise-max and mean doses on the nominal plan, considering constraints according to Lambrecht et al. (30).

Contouring

Target volumes were delineated by experienced radiation oncologists according to national guidelines and OARs according to the European Particle Therapy Network (EPTN) neuro contouring atlas(31). The periventricular space (PVS) and the brain ventricles were also included in this analysis, although not yet contoured in our clinical practice. Besides the CTV, a selection of critical OARs for dosimetric analysis included: brain, brainstem, chiasm, pituitary, left and right (LR) optic nerve, (LR) cochlea, (LR) cornea, (LR) hippocampus, (LR) lacrimal gland, (LR) lens and (LR) retina. The OAR contours, dose, RBE and LET distributions were extracted from the TPS for further statistical analysis.

LET and RBE Calculations
LET_d, DLET_d and RBE were calculated using the Raystation-9AR-IONPG-Research with the MC engine commissioned for our Mevion system and in-house developed scripts. LET_d, the unrestricted mass stopping power scored in the medium and normalized to unity density, was calculated according to \(1\)

\[
LET_d(z) = \frac{\sum_i \int_0^\infty S_{el}^i(E) D^i(E,z) dE}{\sum_i \int_0^\infty D^i(E,z) dE}
\]

where \(S_{el}^i\) is the unrestricted electronic stopping power, \(D^i\) is the dose of the ion type \(i\), \(E\) is the kinetic energy of the ion, \(z\) is the position of the ion and \(i\) is the ion type. LET_d was computed for primary and secondary protons with its maximum displayed value set to 50 keV/\(\mu\)m. It was calculated for all dose levels within the voxelized geometry and, as high LET_d at low planning doses is not clinically relevant, three dose threshold levels were defined: 0, 5 and 20 Gy. Here LET_d was calculated for the voxels with a dose value above the threshold, otherwise LET_d was set to zero. DLET_d was computed through the voxel-wise product between the planning dose and LET_d distribution through scripting within the TPS.

For the RBE calculation, two models were investigated, the Unkelbach (UNK)(26) and McNamara (MCN)(7) models, with the \((\alpha/\beta)_x\) set to 2Gy, and fixed to all voxels. While UNK is a dose-scaling, non-tissue dependent model, MCN is a phenomenological model, which considers all published RBE experimental measurements up to 2014.

**Visualizing distributions**

For each patient, the 3D distributions of physical dose with RBE of 1.1 (RBE_{1.1}), UNK and MCN RBE maps and weighted dose, LET_d (dose threshold of 0, 5 and 20 Gy) and DLET_d were generated. They were displayed as auxiliary doses or additional plans within the TPS and further exported and processed through scripting. To visualize and compare distributions of similar quantities, raincloud plots were chosen as they provide a transparent visualization of raw
distributions combined with probability density and statistics (32). Bivariate histograms were used to map the relationship between physical dose and LET_d and to highlight the frequency of the hotspots.

**Results**

RBE, LET_d and DLET_d were calculated for all patients considered in the cohort.

**RBE models**

Considering the entire population, MCN presented the highest dose values for OARs followed by UNK and RBE_{1.1}, Figure 1. For small structures, e.g. chiasm and pituitary gland, an average increase of 19.3% and 25.5% for MCN and 5.2% and 7.3% for UNK, respectively, was identified with respect to RBE_{1.1}. For larger structures and the CTV, the difference was less pronounced, e.g. Brain and PVS, 2.9% and 18.3% for MCN and 1.0% and 4.8% for UNK. The mean RBE_{1.1}, MCN and UNK CTV doses were 52.1Gy (±2.5, range 41.8–63.5), 52.1Gy (±2.7, range 42.4–67.6) and 57.2Gy (±3.1, range 46.5–75.7).

**LET_d calculations**

The choice of a clinically meaningful dose threshold caused a substantial impact on LET_d results. The avoidance of voxels with lower doses greatly affected the LET_d distribution in OARs. When no dose limit was imposed, the distribution was steered towards higher LET_d values, which arose from very low treatment doses, red plots (LET0) of Figure 2. LET5 and LET20 showed that the threshold magnitude affects the mean LET values. Differences were found up to 26.0% (for the retina). Although the largest average values were found for the chiasm (LET20: 3.1±1.8, LET5: 3.5±1.8, LET0: 4.4±2.1 keV/µm) and the pituitary (LET20: 3.0±2.2, LET5: 4.0±2.0, LET0: 4.8±1.7 keV/µm), the maximum LET_d values were identified in the brain, PVS and ventricles (LET20: 8.6±1.0, LET5: 10.5±1.5 keV/µm). For LET0, maximum values coincided with the maximum displayed setting of 50 keV/µm for most structures. Besides
the skin, brain, CTV, PVS and ventricles, when a dose threshold was imposed most patients exhibited zero LET distributions for all other structures, e.g. for the left lacrimal gland, retina and cochlea, only 2 patients presented LET distributions higher than zero, and for the spinal cord, lenses and corneas the whole cohort presented a zero LET distribution. Considering all the OARs, a mean organ-wise LET\textsubscript{d} of 0.8 (±0.9, range: 0.0–3.1), 1.26 (±1.11, range: 0.0–4.0) and 4.12 keV/µm (±0.72, range: 2.9–5.6) was found for the highest to lowest dose threshold and a consistent value of 2.51 keV/µm (±0.4, range: 1.2–6.0) for the CTV, independent of the threshold.

Dose-LET\textsubscript{d} relationships

Different dose cutoffs affected DLET\textsubscript{d} distributions to a lesser extent as this quantity prevents high LET spikes in low dose regions, Figure 3. Considering DLET\textsubscript{d} values higher than zero (Figure 3), for the 20 Gy threshold, mean DLED\textsubscript{d} results ranged from 74 (±27, range: 32-143) to 174 Gy·keV/µm (±28, range: 69-267) for the right lacrimal gland and the brainstem, respectively. The maximum values were found in the PVS, ventricles, brain, skin and CTV (306±28 – 354±45 Gy·keV/µm).

Throughout the population, an inverse relationship between LET\textsubscript{d} and dose was observed. For some structures, e.g. chiasm and pituitary, this relationship was more evident, Figure 4. As these structures abut the CTV and several distal layers are used for treatment optimization, higher LET\textsubscript{d} regions may arise beyond the OARs, in regions not considered during optimization, such as the PVS.

Figure 4b presents an overview of the relationship between LET\textsubscript{d} and dose. Additional frequency information was visualized using the dose and LET\textsubscript{d}, on a structure- (Figure 5) or patient-basis (Figure 6). Such enhanced visualization allows the identification and interpretation of the clusters, which steer the mean LET\textsubscript{d} values and the identification of the higher but sparse
LET_d values. For this cohort (Figure 5), LET_d values exceeding 6keV/µm were only present for half of the investigated OARs and always below 5% of the structure’s voxels (1.2% on average). While the pituitary presented 4.2% of its voxels above 6keV/µm (mean: 6.3±0.2, range: 6.0-6.9, corresponding to a mean dose of 27.2±3.5 keV/µm), the PVS and the brain presented 0.7% (mean: 6.5±0.5, 6.0–8.6, mean dose: 29.2±5.3 keV/µm) and 0.2% (mean: 6.5±0.4, 6.0–8.6, mean dose: 28.4±5.1 keV/µm).

As a patient-based approach, planning quality for individual anatomies, promoted organ-based visualization of LET gradients, see Figure 6. Similar histograms associated with each OAR, e.g. PVS, promoted the identification of variation within the cohort and the identification of outliers and higher LET_d distributions.

**Discussion**

An approach was presented for visualization and explorative investigations of RBE-weighted doses, LET_d and DLET_d for multiple OARs of patients with tumors in different regions of the brain. For the considered RBE models, MCN values were consistently higher than UNK, which has been shown in other studies(6,16). For brain structures associated with cognition, the average RBE values found for MCN and UNK of 1.54(0.13) and 1.09(0.02) agree with reported values of 1.21 and 1.09(16). While UNK performs LET optimization based on objective functions evaluated for DLET_d (scaled down by a factor and considered as a measure of the additional biological dose caused by high LET), MCN is a variable phenomenological model. For simplicity and consistency (α/β) was defined as 2Gy. This assumption possibly affected MCN results, which predict the highest RBE for low (α/β) values. Moreover, it is also likely that brain tumors have high (α/β) values(34) and variable models(7,35,36) predict large RBE differences when the difference in (α/β) is large between adjacent structures. A recent review reported (α/β)_x target values between 3.1–12.5 Gy for glioma, 3.3–3.8 Gy for meningioma, and for OAR endpoints between 2–3 for chiasm (loss of vision), optic nerve (neuropathy) and brain (necrosis)(33).
Besides the investigated models, many others exist with various levels of complexity, regression techniques and experimental datasets. However, the correlation between RBE variation and outcome data is still impaired by a lack of current in-vivo data with up-to-date fractionation schedules, modulation techniques and evidence from randomized clinical trials(2). Recent reviews highlight considerable variability among models, predominantly in normal tissues(6,24,33). Moreover, RBE is intrinsically a quantity conceived for comparing radiation qualities. Thus, the conservative clinical recommendation of using the 1.1 constant factor still simplifies clinical routine, ensures tumor control, promotes clinical consistency and shared experience across the PT field(5).

Although the invariant factor is clinically reasonable, experimental evidence indicates increased RBE towards the distal edge of the treatment field(1,2,14,34). In this region, as proton energies decrease, denser energy deposition clusters and more complex DNA damage are expected(21). Therefore, higher LET values and an extension of the treatment range beyond target are also possible(35). A thorough RBE review presented average values of 1.1, 1.15, 1.35 and 1.7 at the entrance, center, distal edge and distal fall-off of the SOBP(24). This consideration is relevant for neurological cases as increased tissue homogeneity, positioning accuracy, less range straggling and shallower tumors promote sharper dose distributions, thus OARs close to the target could be affected(2,36).

Preliminary analysis showed that the majority of patients presented here reported little or no acute toxicity and normal performance during and up to 2 years after treatment. However, two years could be too early for detection of any observable toxicities. Although PT radiation-induced brain lesions have been associated with increased RBE and LET values(17,34,37), comparable results have been observed for photon treatments, where the LET effect is much less pronounced(38-40). Further outcome investigation e.g. periodic functional imaging to track changes in brain anatomy, along with cognitive tests for protons, photons and correlation with
LETd distributions for large patient cohorts selected with specific criteria could improve the current knowledge. The full analysis of the current visualization techniques related to treatment side effects is however outside the scope of the current study and subject to further analysis. Additionally, there is a lack of consensus or guidelines on what configures LET hotspots. LET values of typical beam arrangements have been reported of ≈2–4 keV/µm in the center of the beam, from proximal to distal target regions, and >10 keV/µm at the distal fall-off (24,36). However, IMPT delivers highly inhomogeneous dose distributions outside of the target volume and dose-response data has been reported for a broad range of LET values, which may not consider dose threshold and incorporate low-energy protons with increased LET (41).

Although high LET values in low dose regions are reported not to be clinically relevant (24,42), to our best knowledge, no agreement exists on cutoff doses below which no LET should be evaluated. Monte Carlo methods unavoidably result in a number of voxels with few interactions and high statistical uncertainty. The choice of a 0Gy threshold, exemplifies this effect in low dose and out-of-field regions. In this study, different thresholds were evaluated (Figure 2) and, considering prescription dose and OAR constraints, the highest threshold (20Gy) is likely to be more clinically relevant. Individual OAR radiosensitivity could also be considered for specifying a constraint, as 20 Gy can be prohibiting for some OARs, e.g. eye lenses. On the other hand, as we also consider the stochastic nature radiation effects and a general unfamiliarity with the underlying causes of late effects, a threshold becomes relevant for instant visualization but the full data should be preserved for future outcome analyses.

The chiasm (3.1±1.8 keV/µm) and the pituitary (3.0±2.2 keV/µm) presented the largest averaged LETd values. For these and other small structures, e.g. optic nerve and cochlea, decreasing LETd values with increasing dose were observed. Due to limitations of this study, e.g. cohort size and heterogeneous tumor sites and beam orientations, different OARs, especially the smaller ones, have received little or no dose. This aspect was considered in the
statistical analysis and it does not explain the larger differences found for smaller structures when compared to the larger structures. As multiple distal layers are used during treatment optimization, it is possible that high LET values fall beyond critical structures when they adjoin the CTV. It is likely that these regions coincide with the ventricles and PVS, for which no clinical dose constraints are considered during optimization and where the maximum global LET\(_d\) values were identified (8.6±1.0). Different studies have associated late radiation-induced brain lesions in regions of increased LET\(_d\), RBE and radiosensitivity at the PVS\((14,15,43)\). Our study also aims to highlight this structure, considering that treatment planning strategies to neutralize increased RBE (or LET) focus on placing the distal edge outside OARs, which coincide with the periventricular region. A recent survey showed that even though all European PT centers use a constant RBE factor of 1.1, they also apply measures to counteract variable RBE effects, i.e. avoiding beams stopping inside or in front of an OAR\((44)\) – disregarding the PVS.

Considering the uncertainties on RBE models and the difficult interpretation of LET alone, the LET-RBE dependence has been used as a proxy for biological response, e.g. as in the product between dose and LET\((2,6,14,25,26,45)\). Logically, a dose cutoff is not so relevant when the product itself attends the effect of LET spikes in low dose regions. To avoid LET overestimation, McMahon and added a factor to LET-weighted doses, which performed well compared to several RBE models\((25)\). Although a thorough analysis of this factor might still be necessary, it represents a simple approach to readily identify high-LET without the influence of low dose values. Additional tools to promote a better visualization of the relationship between LET and dose are also helpful to estimate its magnitude, identify hotspots, compare and characterize treatment planning quality considering inter- and intra-patient LET distributions.

The heat maps presented in this study showed a low frequency of higher LET values in regions restricted to lower doses, below known tolerances. This effect should become less pronounced when different treatment uncertainties are also considered such as range straggling, imaging
uncertainty, treatment variation in anatomy, positioning, motion, setup, dose distribution, tissue heterogeneity, etc. (13,34,46). Nevertheless, LET-guided robust optimization is a growing field, which focuses on maximizing LET to the target while minimizing it in OARs, minimally affecting the clinical goals of the treatment plan (15,42,47-50). This approach is supported by the TG-256, which suggests LET assessment and LET-based optimization (1). Besides optimization, adaptation of treatment techniques (e.g. splitting the target) have also been reported (51,52).

Since the effect of high LET in normal tissue is not fully understood, there is growing concern over its management, as LET visualization and optimization tools are not yet fully implemented in clinical TPSs. This study presented visualization strategies to quantify OAR and patient treatment quality based on the relationship between dose and LET. It is necessary to invest such visualization tools and standardization of LET reporting (41). This could assist clinicians to identify and characterize hotspots in regions susceptible to damage and to examine LET distributions for new techniques e.g. proton arc.

**Conclusion**

From the analysis of RBE models, LET$_d$ and DLET$_d$ derived from our TPS for patients with brain tumors, strategies were proposed to assess treatment quality considering regions with increased LET$_d$. For clinical practice it is important to identify, quantify and record LET distributions as concern exists over a link between normal tissue toxicity and LET hotspots. LET calculation and reporting requires standardization. The lack of a uniform approach was exemplified by the effect of establishing dose thresholds, which modifies LET reporting and should be considered with a clinical rationale. Visualizing the dose, LET$_d$ space during treatment planning can provide a prompt check of high-LET regions and allow the clinician to decide if changes in the planning technique are necessary. Finally, it is necessary to systematically acquire clinically relevant data for treatment and outcome for robust clinical analysis and
comparison with photon treatments and to provide guidance how to incorporate this information in clinical decision-making.

References


45. McMahon SJ, Prise KM. A mechanistic DNA repair and survival model (medras): Applications to intrinsic radiosensitivity, relative biological effectiveness and dose-rate. *Front Oncol* 2021;11:689112.


Table 1 – Cohort description including number of patients, treatment parameters, tumor type and location. The values were calculated considering the whole population. The performance status grades from the World Health Organization (WHO) Eastern Cooperative Oncology Group (ECOG) correspond to (0) fully active, normal; (1) symptomatic and ambulatory, cares for self; and 2 ambulatory >50% of the time; occasional assistance needed.

<table>
<thead>
<tr>
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<tr>
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</tr>
<tr>
<td></td>
<td></td>
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<tr>
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<td>54.2%</td>
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<tr>
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<td>Average age and range [years]</td>
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<tr>
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<th>WHO (ECOG) Performance Status</th>
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Figure 1 – RBE dose distributions, for a selection of OARs, calculated using the constant clinical factor of 1.1 (red), McNamara’s model (green, α/β of 2Gy), and Unkelbach’s model (blue). Both histograms and bars present the frequency distribution – the differential dose, the number of voxels per unit of RBE dose. The boxplots show the interquartile range, median and outliers.
Figure 2 – LET$_d$ distributions, for a selection of OARs, calculated using dose thresholds of 0 Gy (red), 5 Gy (blue) and 20 Gy (green). Both histograms and bars present the frequency distribution, or the number of voxels per unit of LET$_d$ value. The boxplots show the interquartile range, median and outliers according to the individual distribution.
Figure 3 – DLET_d distributions, for a selection of OARs, calculated using 0 Gy (red), 5 Gy (blue) and 20 Gy (green) RBE dose threshold. Both histograms and bars present the frequency distribution, or the number of voxels per unit of DLET_d value. The boxplots show the interquartile range, median and outliers according to the individual distribution.
Figure 4 – a) Example patient with the planning dose, LET_d and D\LET_d distributions with the optic chiasm contoured in yellow. b) Distribution of dose and LET_d values for the chiasm (orange) and pituitary (blue) for all patients (N=24) included in the study. c,d) Relationship between mean values of dose, LET_d and D\LET_d (for a dose threshold of 20Gy) for the chiasm and the pituitary gland. Dose, LET_d and D\LET_d are represented by the blue, red and green axes.
Figure 5 – Dose and LET\textsubscript{d} histograms of a selection of the investigated structures for a single patient. Dose and LET\textsubscript{d} values are represented on the x- and y-axis, respectively, for each subplot. Next to each structure name, it is indicated the percentage of voxels higher than zero, used for the graph. The color bar on the right indicates the frequency, in the same scale for all plots.
Figure 6 – a) CTV (gray color map) and PVS (multiple colors) LET\textsubscript{d} distribution spatial representation. b) Dose, LET\textsubscript{d} histograms of the PVS for different patients. Dose and LET\textsubscript{d} values are represented on the x- and y-axis, respectively, for each subplot. The color bar on the right indicates the frequency, in the same scale for all plots.