Retrospective Estimation of Linear Energy Transfer Distributions within Pediatric Patients Treated with Passive Scattering Proton Therapy

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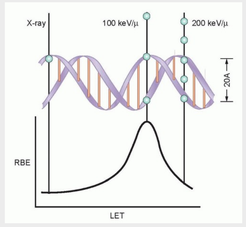
Purpose

- The **NCI Pediatric Proton and Photon Therapy Comparison Cohort** aims to compare the risk of second cancer after proton vs. photon radiotherapy.
- Prior work estimated absorbed radiation dose to normal tissues using Monte Carlo simulations for passive scattering proton therapy patients.
- However, biological effects depend not only on radiation dose, but also on radiation quality.
- **Dose-averaged linear energy transfer (LET_d)** describes how densely radiation deposits energy in tissue. For each voxel, LET_d is calculated by averaging the LET of particles passing through that voxel, with particles that contribute more dose receiving more weight.
- Higher LET_d reflects denser ionization patterns, which may increase complex DNA damage, including double-strand breaks.



Linear energy transfer and DNA damage. Ionizing radiation deposits energy along the track (linear energy transfer [LET]), which causes DNA damage and cell killing. The most biologically potent (highest relative biologic effectiveness [RBE]) LET is 100 keV per µm because the separation between ionizing events is the same as the diameter of the DNA double helix (2 nm). (From Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist*. Philadelphia: Lippioncott Williams & Williams; 2012, with permission.) [1]

Aim: Develop a workflow to retrospectively estimate dose-averaged LET in pediatric patients treated with passive scattering proton therapy.

Methods

- Pilot study sample included **30 pediatric patients (ages 1–21)** treated with passive scattering proton therapy (2007–2022) using:
  - Intracranial Irradiation (n=15)
  - Craniospinal Irradiation (CSI) (n=15)
- **Key Steps:**
  - Radiotherapy treatment records were used to guide **Monte Carlo (MC) simulations** of each patient's therapy
  - The patient's computed tomography (CT) image set was used to represent anatomy within the MC simulation
    - For intracranial treatments, in-house tools were used to generate a whole-body CT image set from the available head CT
  - MC simulations were performed using the **TOPAS** simulation package:
    - Physical dose distribution
    - ProtonLET scorer, used to compute the distribution of LET_d

References

[1] Jairam V, Roberts KB, Yu JB. Historical trends in the use of radiation therapy for pediatric cancers: 1973-2008. *Int J Radiat Oncol Biol Phys*. 2013;85(3):e151-e155. doi:10.1016/j.ijrobp.2012.10.007

Results

Intracranial Irradiation

Craniospinal Irradiation

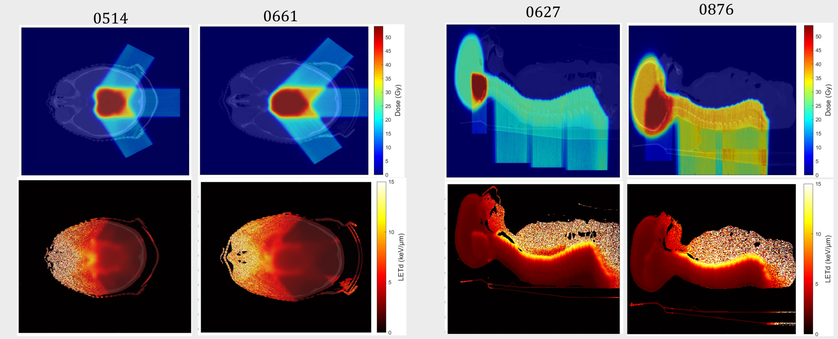
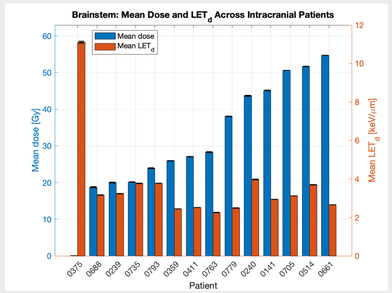


Fig 1. Patient-specific absorbed dose and LET_d overlays for intracranial and craniospinal proton therapy cases. Elevated LET_d is observed near distal field edges and similar dose distributions can correspond to different LET_d patterns across patients.



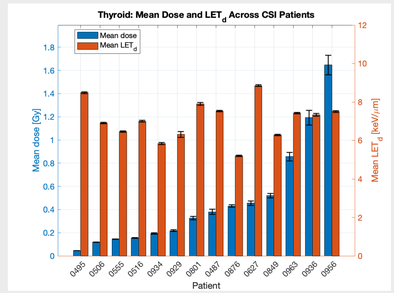
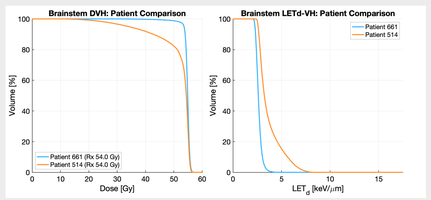


Fig 2. Comparison of mean absorbed dose (Gy) and mean dose-averaged LET (keV/µm) for the brainstem and thyroid across intracranial and craniospinal irradiation (CSI) patients.



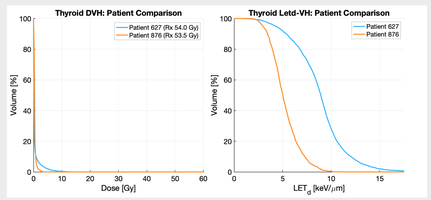


Fig. 3. Comparison of dose-volume histograms (DVH) and LET_d-volume histograms for the brainstem (left) and thyroid (right) between two representative patients treated with intracranial (left) and craniospinal irradiation (right) techniques.

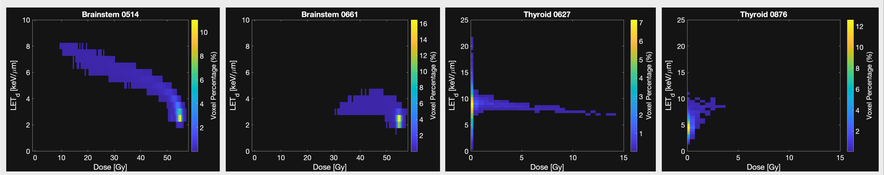


Figure 4. Comparison of absorbed dose (Gy) and dose-averaged LET (keV/µm) values within organ voxels, with color indicating voxel percentage.

Discussion

Voxel-level LET_d and absorbed dose were evaluated to characterize patient radiation exposure in the organs at risk and out-of-field organs.

Elevated LET_d was observed:

- Near the distal edge of the proton treatment field, reflecting increased energy deposition density as protons approach the end of their range
- Outside the treatment field, reflecting contributions from secondary particles

Intracranial Irradiation

In the example comparison shown in the results for one organ at risk, the brainstem of patient 0514 was not completely in-field, and thus had both lower dose and higher LET_d:

- Patient 0514: mean dose - **5162.15 cGy** ; mean LET_d - **4.09 keV/µm**
- Patient 0661: mean dose - **5473.57 cGy** ; mean LET_d - **2.91 keV/µm**
- Mean LET_d values ranged from 6.19 to 25.16 keV/µm for out of field tissues.

Craniospinal Irradiation

Despite similar mean absorbed thyroid doses, LET_d values differed in the two example patients due to the variation in thyroid position relative to the distal edge of the spinal treatment field:

- Patient 0627: mean dose - **45.35 cGy ;** mean LET_d - **10.09 keV/µm**
- Patient 0876: mean dose - **42.92 cGy;** mean LET_d - **5.96 keV/µm**
- Mean LET_d values ranged from 7.16 to 13.30 keV/µm for out-of-field tissues.

The combination of these voxel-level data enables identification of hotspots with elevated biological damage where both high dose and high LET_d occur in patients.

Overall, these results demonstrate that LET provides information beyond absorbed dose and may help identify organs at increased risk for treatment-related late effects.

Conclusion

- By calculating LET_d in our exposure assessment methods, we have demonstrated an ability to quantify the radiation quality of the dose received by patients.
- Elevated LET_d values were consistently observed at or near the distal edge of the treatment field across both intracranial and craniospinal irradiation techniques.
- These methods will support the integration of radiation quality metrics (such as LET_d) into future cohort analyses and risk modeling of treatment-related toxicities.

Acknowledgments

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