Quantifying the impact of irradiation dose on normal white matter volume development in children

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Purpose: Brain tumors are the second most common form of cancer in children, with medulloblastoma and ependymoma being the two of the most common forms. Therapy for both tumors consists primarily of surgery combined with radiation therapy (RT) with chemotherapy reserved for patients with medulloblastoma. While the current therapies are effective and many patients achieve long term survival, children who survive are at risk for serious neurocognitive sequelae. Neurocognitive deficits are associated with a younger age at treatment, time following treatment and dose of radiation. Our current research builds on the hypotheses that white matter damage resulting from RT spans a continuum of severity that can be reliably probed using MR and that changes in white matter have functional significance and impact quality of life.[1-7] This project combines quantitative longitudinal MR imaging of children treated for medulloblastoma and ependymoma with digital radiation dosimetry fused with the initial MR examination to establish the response of normal-appearing white matter (NAWM) to varying doses of therapeutic radiation. This project adds to our previous work by expanding the number of subjects and adding a group with ependymoma treated without craniospinal irradiation.

Methods: Pediatric patients with medulloblastoma (n=42) and ependymoma (n=19) with a mean age of 7.7 years (± 4.1 years) at the time of irradiation were included in the study. The mean follow-up was 3.2 years (± 1.4 years) and a total of 640 MR examinations contributed to the analysis. Treatment and imaging protocols were approved by the hospital's Institutional Review Board, and written informed consent was obtained from the patient, parent, or guardian, as appropriate.

Medulloblastoma patients received post-operative risk-adapted craniospinal irradiation (CSI) to 23.4 Gy for average-risk and 36 Gy for high-risk presentations. The primary site in the posterior fossa was irradiated to a cumulative dose of 55.8 Gy using a conformal approach. Beginning six weeks after completion of RT, all patients received adjuvant chemotherapy comprising four cycles of high-dose cyclophosphamide, cisplatin, and vincristine. Ependymoma patients received post-operative irradiation to the primary site (54-59.4 Gy) using a clinical target volume margin of 1cm surrounding the tumor bed.

MR imaging was performed on a 1.5T whole-body system using the standard circular polarized volume head coil (Siemens Medical Systems, Iselin, NJ). Nineteen 5 mm thick axial T1-weighted FLASH images (TR/TE = 266/6 ms, 90° flip) and T2/PD-weighted TurboSE images (TR/TE1/TE2 = 3500/19/93 ms, 2 echoes) were collected with a 1 mm gap. All volumetric measurements were calculated for five transverse sections centered on an index section at the level of the basal ganglia. Imaging sets were registered, RF corrected, and then analyzed with a hybrid neural network segmentation and classification algorithm to identify normal-appearing brain parenchyma.[1,7]

Radiation dosimetry, generated on a CT reference examination used for RT planning, was fused with the initial MR examination. The median dose was determined for the NAWM across the five sections using the registered dosimetry (Figure 1). Change in NAWM volume as a function of time after irradiation was correlated with the median dose.

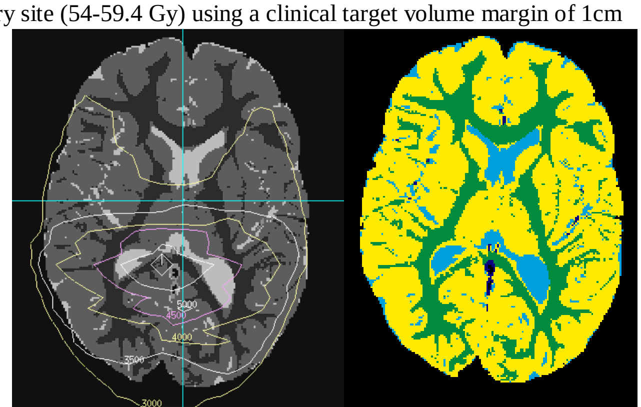

Figure 1 – Gray scale representation of segmented image with overlay of radiation isodose (left) and pseudo-color map of segmented image at same position (right).

Results and Discussions: Regression analysis (Figure 2) demonstrated a significant relationship (F=9.168; p=0.0036) between the rate of change in NAWM volume and median dose. Positive growth in volumes were observed at low median doses and declines were observes at higher doses. Considering the average young age of these patients, the increases seen in NAWM at lower dose levels is consistent with normally expected maturation. Increasing dose levels corresponded to a slower rate of growth, complete lack of growth and even volume loss at the highest dose level. Combining this information with the previously demonstrated relationship between NAWM volume and neurocognitive function emphasizes the importance of these findings for future therapy and radiation therapy planning optimization.

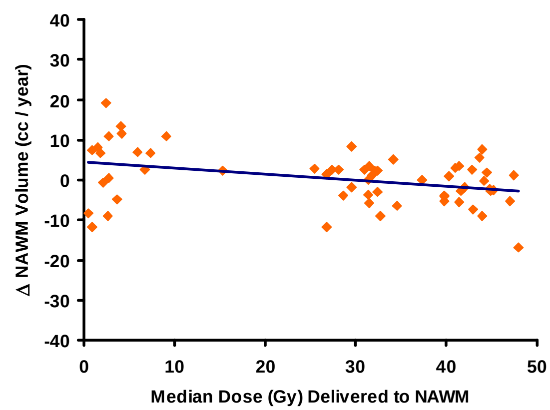

Figure 2 – Change in white matter volume (volume per year) as a function of median radiation dose (F=9.16; p=0.0036).

Conclusion: This study establishes a relationship between radiation dose and change in NAWM volume after therapeutic irradiation. Similar changes in volume have been previously associated with deficits in neurocognitive function.

References:

1. Reddick WE, IEEE-TMI, 16:911, 1997.
2. Reddick WE, Mag Reson Imaging, 16(4):413, 1998.
3. Mulhern RK, Annals of Neurology 46(6):834, 1999.
4. Reddick WE, Mag Reson Imaging 18(7):787, 2000.
5. Mulhern RK, et al., J Clin Onc 19(2):472, 2001.
6. Palmer SL, J Clin Onc 19(8):2302, 2001.
7. Reddick WE, Mag Reson Med 47(5):912, 2002.