RONC-04. RELATIONSHIP BETWEEN PROTON THERAPY AND THE DEVELOPMENT OF THE LIMBIC SYSTEM IN PEDIATRIC POSTERIOR FOSSA TUMORS

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BACKGROUND: Pediatric brain tumor survivors may develop neuropsychological impairments after treatment. The first months after treatment could be a crucial time-window where the development of the brain may be affected by different types of treatments. For example, deficits in memory and learning related to hippocampal damage have resulted in radiotherapy dose constraints to the hippocampus. However, other limbic system substructures, important for cognition or behavior, may suffer from collateral doses. Therefore, we investigated the early effect of treatment on limbic structure volume. We hypothesized that radiotherapy (vs. no radiotherapy) would contribute to a decrease in volume of the limbic structures. METHODS AND MATERIALS: Thirty-eight patients with a tumor in the posterior fossa region (medulloblastoma n=12; pilocytic astrocytoma n=24; other=2) who were diagnosed between June 2018 and September 2020 and were alive ≥1 year diagnosis were included. Patients receiving neurosurgery only (n=26) were compared to patients treated with neurosurgery, proton therapy and chemotherapy (n=12). Limbic structures were automatically segmented in 111 MRI scans. These structures were amygdala, hippocampus (CA1+CA2/3), subiculum, dentate gyrus, parahippocampal gyrus, fornix, mammillary bodies, nucleus accumbens and thalamo-anteroventral nucleus of thalamus. RESULTS: Analyses revealed a significant negative effect of time on the amygdala ($p<0.01$), hippocampus (CA1) ($p<0.001$), and dentate gyrus ($p<0.01$). This indicates that these structures decreased in volume within the first year after diagnosis, independent of radiation treatment. Furthermore, an interaction effect was found between time and radiation in the subiculum ($p=0.02$) and fornix ($p=0.052$). CONCLUSION: These results indicate that the volumetric decline were stronger for the patients that received proton radiation. Future comparisons will test how results relate to the volumes in healthy children of the same age. Also, we will investigate whether this abnormal development is associated to the radiation dose and how it relates to the neuropsychological outcomes of the child over time.

RONC-05. PERI-TRANSPLANT RADIATION THERAPY FOR YOUNG CHILDREN TREATED WITH HIGH-DOSE CHEMOTHERAPY FOR PRIMARY BRAIN TUMORS

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PURPOSE: The role of peri-transplant radiation therapy (RT) in young children with primary brain tumors is unclear. We characterized our institutional practice patterns and patient outcomes. MATERIALS AND METHODS: The cohort included all patients treated with high-dose chemotherapy for primary brain tumors at our institution from 2011-2017. Rates of local control (LC), progression-free survival (PFS), overall survival (OS), and radiation-associated injury were assessed. RESULTS: Of 37 eligible patients, 29 (78%) received peri-transplant RT at a median age of 4 years. Patients treated with RT were more likely to have metastatic ($p=0.0121$) and incompletely resected ($p=0.056$) disease, and to have high-risk histologies including atypical teratoid rhabdoid tumor, nongerminomatous germ cell tumor, pineoblastoma, primitive neuroectodermal tumor, glioneuronal tumor and group 3 medulloblastoma. Of those treated with RT, 13 (45%) received craniospinal irradiation (CSI) and 16 (55%) received focal RT. The median CSI dose was 23.4 Gy (IQR: 18-36; boost median 54 Gy [IQR: 53.7-55.8]) and focal RT dose was 50.4 Gy (IQR: 50.4-54.5). Compared to the focal RT group, patients treated with CSI were older ($p=0.0499$) and more likely to have metastatic disease ($p=0.0004$). For the complete cohort, at a median follow-up of 3.8 years, the 2-year rate of LC was 82% (95% CI: 70-96%), PFS was 63% (95% CI: 49-81%), and OS was 65% (95% CI: 51-82%). These rates did not differ significantly between patients treated with and without peri-transplant RT. Two cases of fatal myelopathy were observed after spinal cord doses within the highest tertile (41.4 CGE and 36 Gy); both cases occurred in patients who received RT before high-dose chemotherapy. CONCLUSION: Peri-transplant RT was used for high-risk disease. Oncologic outcomes after RT were encouraging. However, 2 cases of grade 5 myelopathy were observed. If used cautiously, RT may contribute to durable remission in patients at high risk of relapse.

RONC-06. STEREOTACTIC RADIOSURGERY AND STEREOTACTIC RADIOTHERAPY FOR PEDIATRIC BRAIN METASTASES OR RECURRENCES

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BACKGROUND/PURPOSE: Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) deliver highly conformal, ablative doses of radiation over 1–5 treatments, while minimizing dose to surrounding normal tissues. To document toxicities and outcomes of these treatments in children, our updated institutional experience with SRS or SRT for intracranial targets in pediatric patients was reviewed. METHODS: On an IRB approved study, institutional databases were reviewed to identify pediatric patients with intracranial lesions treated with SRS or SRT from October 2009 to July 2021. Medical records were retrospectively reviewed for patient and treatment characteristics. Outcomes were analyzed for symptomatic radionecrosis and CNS progression. RESULTS: Thirty SRS or SRT treatment courses in 26 patients age 3.2 to 17.8y (median, 15.6y) at the time of SRS or SRT were identified. Twenty-two patients had one treatment and four had two treatments. Sixteen patients had brain metastases from extracranial primary disease; 10 had recurrence of a primary CNS tumor. Fifteen patients had prior fractionated radiation to the brain. Nineteen treatments used Gamma Knife (GK) with Leksell frame, three used GK ICON with mask, and eight used linear accelerator with volumetric modulated arc therapy with thermoplastic mask. All patients (10 treatments in nine patients) treated since July 2016 received mask-based radiation. Twelve of 26 (46%) patients were treated with anesthesia. With 9.6-month median follow up (range, 0.1-96.2m), five patients had progression of treated lesions, eight had distant CNS failure, and one had both local and distant failure, for a crude local failure rate of 6/26 (23%) and a crude distant failure rate of 9/26 (35%). There were no skull fractures or other complications from Leksell frame placement. One patient developed symptomatic radionecrosis requiring surgery. CONCLUSION: SRS and SRT can be safely performed in pediatric patients with intracranial lesions. Mask-based immobilization provides an alternative to frame-based treatments.

RONC-07. FRACTIONATED RADIOTHERAPY IS REQUIRED TO ACCURATELY MIMIC NEUROSTRUCTURAL LATE EFFECTS IN PRECLINICAL MODELS

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Pediatric brain cancer patients treated with fractionated radiotherapy commonly develop long-term late side-effects including cognitive deficits. Many preclinical models of late effects have been developed that use a single, high dose of radiotherapy, which does not mimic the fractionated schedule children receive clinically. This study aimed to create a mouse model of late effects using clinically-relevant fractionated radiotherapy, and to measure the effects on the developing brain. Juvenile mice were treated at postnatal day 16 with a single dose of 8Gy whole brain radiation, or a mathematically-equivalent fractionated dose of 18Gy (9 x 2Gy daily fractions). Sham control mice received a CT scan, or 9 x sham CT scans. Mice were allowed to grow to young adulthood (63 days). Ex vivo anatomical MRI scans were performed along with diffusion tensor imaging (DTI) and histology. Mice receiving a single 8Gy radiation dose exhibited significantly decreased volumes in areas including the olfactory bulbs (-19%), hippocampus (-7%), corpus callosum (-9%) and motor cortex (-9%). In contrast, mice receiving fractionated radiotherapy showed fewer significantly decreased regions, although olfactory bulbs were reduced (-12%). Furthermore, doublecortin-positive cells were significantly reduced in the dentate gyrus indicating profound effects of radiotherapy on murine neural stem cells. Few radiotherapy-induced differences were observed by DTI, and immunohistochemistry revealed no changes in myelin basic protein, suggesting that white matter is minimally altered in mice. These results show that preclinical models exhibit treatment-induced late effects, and that commonly-used experimental approaches of single dose radiotherapy induce more neurological changes than an equivalent fractionated dose, thus may over-estimate radiotherapy-induced late effects. We have developed a clinically-relevant fractionated dosing protocol in mice, which replicates late effects experienced by children, and can be used to measure long-term effects of novel chemo/radiotherapy treatment combinations, ensuring children with brain cancer receive treatment both effective and safe treatment.