### Title

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### Journal

Journal of Pediatric Hematology/Oncology, 45(7)



### Authors

Unnikrishnan, Soumya
Yip, Anthony
Qian, Alexander
et al.



### Publication Date

2023-10-01

### DOI

10.1097/MPH.0000000000002724

Peer reviewed

HHS Public Access

Author manuscript

*J Pediatr Hematol Oncol*. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

*J Pediatr Hematol Oncol*. 2023 October 01; 45(7): e837–e846. doi:10.1097/MPH.0000000000002724.

# Neurocognitive Outcomes in Multiethnic Pediatric Brain Tumor Patients Treated with Proton vs Photon Radiation

**Soumya Unnikrishnan, MD, MS**[*,1,2], **Anthony T. Yip, MD, MAS**[*,1,2], **Alexander S. Qian, MD**[1,2], **Mia A. Salans, MD, MAS**[1,2], **Justin D. Yu, MAS**[2], **Minh-Phuong Huynh-Le, MD, MAS**[3], **Anny Reyes, PhD**[4], **Alena Stasenko, PhD**[4], **Carrie McDonald, PhD**[2,4], **Ryan Kaner, PsyD**[5], **John R. Crawford, MD**[6], **Jona Hattangadi-Gluth, MD**[2]

[1]University of California San Diego School of Medicine, La Jolla, CA

[2]Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA

[3]Radiation Oncology, The Brooklyn Cancer Center, Brooklyn, NY

[4]Department of Psychiatry, University of California San Diego, La Jolla, CA

[5]Rady Children's Hospital, San Diego, CA

[6]Department of Neurosciences and Pediatrics University of California San Diego, La Jolla, CA

## Abstract

**Background—**We analyzed post-radiation (RT) neurocognitive outcomes in an ethnically diverse pediatric brain tumor population undergoing photon (XRT) and proton RT (PRT).

**Procedure—**Post-RT neurocognitive outcomes from 49 pediatric patients (37% Hispanic/Latino) with primary brain tumors were analyzed. Tests included cognitive outcomes, behavioral outcomes, and overall intelligence. For each outcome, proportion of patients with cognitive impairment (scores <1.5 SD) was calculated. Fisher's exact tests compared proportion of patients with impairment and t-tests compared T-scores between XRT (n=32) and PRT (n=17) groups. Linear regression assessed associations between radiation modality and outcomes.

**Results—**Median follow-up was 3.2 and 1.8 years in the XRT and PRT groups, respectively. Median RT dose was 54.0Gy. We found impairment in 16%−42% of patients across most neurocognitive domains except executive function. There was no difference in scores between XRT and PRT groups. Regression analyses revealed no association of neurocognitive outcomes with radiation modality. Non-Hispanic patients had better Verbal Comprehension Index (VCI) and General Ability Index (GAI) scores than Hispanic patients ($p < 0.05$).

**Conclusions—**Among pediatric patients with brain tumors receiving RT, all cognitive domains were affected except executive function. Radiation modality was not associated with

Corresponding Author: Jona A. Hattangadi-Gluth, MD, Department of Radiation Medicine and Applied Sciences, University of California, San Diego, 9500 Gilman Dr. Mail Code 0861, La Jolla, CA 92093-0861, USA (jhattangadi@health.ucsd.edu; jhattangadi@ucsd.edu).

*Co-first authors

neurocognitive outcomes. Hispanic patients may be more vulnerable to post-treatment cognitive effects that warrants further study.

### Keywords

pediatric; brain tumor; neurocognition; radiation therapy

## Introduction

Primary brain tumors are one of the most common childhood cancers[1], treated with radiotherapy (RT), surgery and/or chemotherapy. Despite clear benefits, cranial RT is associated with long-term neurocognitive deficits[2] which can affect quality of life including global health status and physical functioning[3]. Pediatric patients exposed to brain RT perform worse than their peers[4], placing them at risk of decreased academic success, issues with future employment, and failure to live independently as adults[2,5–7]. The degree and scope of post-RT impairments in pediatric patients across multiple cognitive domains (ie language, executive functioning, processing speed, etc) are unclear as most studies examine only intelligence quotient (IQ) or a limited number of neurocognitive outcomes[8–10].

Compared to photon radiotherapy (XRT), proton radiotherapy (PRT) offers greater dosimetric control in terms of normal tissues, which can be advantageous for the treatment of pediatric brain tumors[11–14]. By minimizing surrounding tissue toxicity, PRT may reduce post-RT neurocognitive sequelae. Among patients receiving craniospinal irradiation (CSI), dosimetric comparisons suggest that protons may minimize long-term side-effects including cognitive decline[15]. Within pediatric brain tumor cohorts, several studies have described no significant post-radiation IQ decline following PRT[11,13,16–19]. There are no randomized trials of PRT versus XRT for pediatric brain tumor patients. Few retrospective studies have compared neurocognitive outcomes following XRT versus PRT in pediatric brain tumor patients; these suggest proton superiority for overall IQ, though the results for specific neurocognitive domains are conflicting[8–10,20]. We sought to perform a multi-domain analysis of post-treatment neurocognitive outcomes in a cohort of pediatric patients with brain tumors treated with either XRT or PRT, including a sub-analysis of patients receiving CSI.

Few studies have examined neurocognitive outcomes in ethnically diverse pediatric brain tumor cohorts which is critical given the increasing diversity in United States demographics. Since our study was performed at a large pediatric hospital which is a catchment area for an ethnically diverse population, we also sought to explore the impact of Hispanic ethnicity on neurocognitive outcomes in our cohort.

## Materials and Methods

### Patients

This study was approved by the Institutional Review Board at University of California, San Diego. Using a prospectively maintained pediatric brain tumor database of 432 patients diagnosed with a brain tumor from Rady Children’s Hospital, we selected 49 pediatric

patients with primary brain tumors treated from 1999–2019. Inclusion criteria were: diagnosis of primary brain tumor, treatment with XRT or PRT, age <21 years at time of RT, follow-up ≥ 6 months (time from RT completion to last documented visit), documentation of RT treatment plan, and at least one post-treatment neuropsychological evaluation ≥ 6 months from RT. Patient, tumor, treatment characteristics as well as primary outcomes were collected via retrospective chart review using coded search queries whenever possible to minimize bias. Ethnicity (Hispanic vs. non-Hispanic) was documented in the electronic medical record but race (Caucasian, Black, etc.) was not. Covariates included patient sex, ethnicity, tumor histology, type of surgical resection, treatment with craniospinal irradiation (CSI), hydrocephalus treated with ventriculoperitoneal (VP) shunt, baseline performance status (Lansky/Karnofsky), systemic therapy, age at RT, total RT dose, time between radiation and neurocognitive exam, and socioeconomic status (SES). SES is represented by percent poverty and median income, derived from patients' residential zip codes using 2018 census data[21,22]; results were categorized as binary variables with cutoffs (13% poverty, median income of $75,000) based on average results within California[15,21]. Additionally, we created a separate cohort of patients receiving CSI, all diagnosed with medulloblastoma, for sub-analyses given the different radiation fields in this population.

## Neuropsychological Outcomes

Neurocognitive test scores ≥ six months post-RT were available for 49 patients resulting in a total of 530 individual test scores. Each patient in the cohort underwent one comprehensive neurocognitive testing session at least 6 months post-RT. Six months was determined as a reference point to represent potential for long-term irreversible sequelae[23]. Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JPHO/A630 summarizes the neurocognitive domains, associated tests and versions, and scoring scales.

Cognitive outcomes were measured using the following standardized neuropsychological exams administered by licensed neuropsychologists: Wechsler Intelligence Scales for Children (WISC), Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) and California Verbal Learning Test (CVLT). Behavioral outcomes were measured with Adaptive Behavior Assessment System (ABAS), and the Behavior Rating Inventory of Executive Function (BRIEF). ABAS is a parent-report measure of adaptive emotional and social functioning and BRIEF is a parent-report that measures behavioral components of executive functioning. Scores extracted from Wechsler, ABAS and BRIEF are detailed in Supplemental Table 1 (see Table, Supplemental Digital Content 1, http://links.lww.com/JPHO/A630 which summarizes all neurocognitive domains tested and associated scores/scales). These tests have all been previously validated and are commonly used to assess neurocognitive function in children[24–30]. At the time of neurocognitive testing, if the preferred/dominant language was Spanish, the assessment was performed by a bilingual tester or with an in-person Spanish interpreter.

We grouped all 17 scores into seven neurocognitive domains. Six domains are defined by neuropsychologic criteria and include complex attention, social cognition, learning/memory, language, perceptual-motor function, and executive function[31]. We included an additional "other" category for scores representing overall intelligence (IQ and general ability) or

adaptive functions. Age-adjusted scores (standard, scaled, or T-scores) were derived from the most recent standardization sample associated with each test. We converted standard and scaled scores to corresponding T-scores for consistency. Higher scores represent better performance across all exams except BRIEF. Impairment was defined as T-score >1.5 standard deviations (SD) on BRIEF and T-score of <1.5 SD on all other tests.

### Statistical Analysis

Patient, tumor, and treatment characteristics were compared between XRT and PRT cohorts. Categorical and continuous covariates were examined with Fisher's exact and Wilcoxon rank sum tests, respectively. Significant covariates ($p < 0.05$) between cohorts were included as potential confounders in multivariable analyses.

For each neurocognitive outcome, we calculated the proportion of patients that were impaired in the whole cohort, XRT group and PRT group. We used Fischer's exact tests to determine if the proportion of impairment was different between the XRT and PRT groups. We next performed independent samples t-tests between T-scores of XRT and PRT patients to determine if scores were significantly different. We performed univariable linear regression to assess correlation of each neurocognitive outcome with each covariate mentioned above. We then constructed multivariable models by including radiation modality, baseline confounders, and covariates significant on univariable analysis. Multivariable models also controlled for time from RT to neurocognitive test, given association of time with post-radiation neurocognitive decline[32]. Coefficients with $p < 0.05$ were deemed significant. False discovery rate (FDR) correction was applied to adjust for multiple comparisons. All analyses were also performed in the CSI subgroup.

## Results

### Baseline cohort characteristics

Patient, tumor, and treatment characteristics by radiation modality are shown in Table 1. XRT and PRT cohorts were similar across ethnicity, age at RT, baseline performance, and SES. Tumor histology between cohorts was similar, the most common being medulloblastoma (47% XRT, 59% PRT). Median prescription RT dose was 54Gy in both groups with about half of patients receiving CSI (50% XRT, 59% PRT). The two cohorts statistically differed only by sex: 81.3% males in XRT cohort compared to 47.1% in the PRT cohort ($p = 0.02$).

Within the CSI sub-cohort (n=26 patients; 15 XRT and 10 PRT), all had medulloblastoma (one patient with non-germinomatous germ cell tumor was excluded to maintain cohort homogeneity). Patients were similar in age at RT, gender, ethnicity, baseline performance status, RT dose, and SES.

### Time from radiation treatment to neurocognitive testing

The XRT and PRT groups differed in time from RT completion to neurocognitive testing: median duration was 3.2 years in XRT patients and 1.8 years in PRT patients ($p < 0.001$). Comparing radiation group differences in time from RT for each individual test, group

differences were only significant for Verbal Comprehension Index (VCI) ($p = 0.04$) and Global Executive Composite (GEC) tests ($p < 0.01$).

In the CSI sub-cohort as well, groups differed by radiation modality in median duration from RT to exam (3.8 years XRT and 2.1 years PRT, $p=0.04$). In comparing group differences in time from RT for individual neurocognitive tests, no differences in time were noted between radiation groups (all $p > 0.05$).

### Post-treatment neurocognitive outcomes

The cohort showed impairment among 16–42% of patients on most neurocognitive tests, Table 2. Processing Speed Index (PSI) showed the most impairment at 42%. Tests for executive function were least affected with the Global Executive Composite (GEC) score showing 24% impairment. Remaining outcomes for executive function, namely Adaptive, Externalizing, and Internalizing ABAS scores showed 6%, 3% and 11% impairment, respectively.

In the CSI sub-cohort, Full Scale IQ and ABAS Practical showed the most impairment at 47% each, Table 2. Among outcomes assessing executive function, the GEC showed 27% impairment while Adaptive (11%), Externalizing (5%), and Internalizing (16%) ABAS scores showed the least impairment.

### Comparison of neurocognitive outcomes between XRT and PRT patients

Compared to XRT, PRT patients had numerically higher scores across most cognitive domains. However, Fischer's exact tests showed no significant difference in proportion of patients with impairment between the two groups, Table 2. Similarly, independent sample t-tests showed no significant difference between T-scores of XRT and PRT patients on any of the neurocognitive tests in the full cohort or the CSI sub-cohort as noted in Table 3. Fig. 1 summarizes all the neurocognitive outcomes grouped by cognitive domain and stratified by radiation modality.

### Association of radiation modality with neurocognitive outcomes

On univariable and multivariable regression models performed on the full cohort and the CSI-sub-cohort, radiation modality was not significantly associated with any of the neurocognitive outcomes (all p-values $>0.05$). Table 4 shows detailed results from the regression models.

### Association of ethnicity with neurocognitive outcomes

As shown in Table 5, Hispanic patients performed worse than non-Hispanic patients on several neurocognitive tests. On univariable analyses, non-Hispanic patients had higher FDS, WMI, VCI, PRI, full-scale IQ and GAI (all $p \leq 0.01$) scores compared to Hispanic patients. On multivariable analysis with FDR correction, these findings remained significant for VCI ($p = 0.001$) and GAI ($p = 0.009$).

Ethnicity remained associated with neurocognitive outcomes on multivariable models in the CSI sub-cohort as well even after FDR correction. As shown in Table 5, compared to

Hispanic patients, non-Hispanic patients had greater FDS (p = 0.003), VCI (p = 0.025), and GAI (p = 0.009) scores.

## Discussion

Pediatric patients with brain tumors are especially vulnerable to post-radiation neurocognitive changes[2], and these effects can negatively impact children's day-to-day functioning, educational prospects, or future employment[33]. We examined neurocognitive and behavioral outcomes across several domains and multiple tests in a cohort of pediatric patients with primary brain tumors following XRT or PRT radiation. We found a considerable proportion of patients with impairment across almost all cognitive domains, but no significant differences in proportion of impaired patients between XRT and PRT groups.

Our study is unique in that we examined 17 post-treatment neurocognitive and behavioral outcomes over 7 different domains, Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JPHO/A630. As shown in Table 2, this cohort demonstrated impairment across multiple tests/domains including complex attention and processing speed, learning and memory, language, perceptual motor function, full-scale IQ, and social cognition. The proportion of patients with impairment ranged between 16% to 42% compared with approximately 7% in the normative population (using 1.5 SD as threshold as T-scores are normally distributed). These findings indicate which domains could potentially be affected in a child following brain irradiation and can help guide pre-treatment counseling. Social cognition encompasses the recognition of emotions as well as insight into social interactions[34], with deficits commonly associated with frontotemporal neurocognitive disorders[34]. We found poorer social cognition scores in the cohort compared with normative populations, which can be associated with worse quality of life[35]. Our findings are consistent with other studies showing suppressed IQ, memory, and attention in survivors of pediatric brain tumors[36], and a smaller study in 18 pediatric patients with brain tumors which found similar deficits over time after treatment[37]. Yet, another study in 39 survivors of pediatric brain tumors after PRT found no differences compared with population norms in attention/processing speed or executive function, though did find areas of weakness in processing speed in patients who underwent proton CSI[18]. Indeed, our cohort showed the least impairment in executive function, suggesting this domain may be relatively spared compared with others. Additionally, because executive functioning is largely regulated by the prefrontal cortex[23], benefits of PRT may become more pronounced in cohorts receiving focal radiation for tumors near the frontal lobe. However, since executive function was measured on the BRIEF assessment, which is based on parent report, it is less objective and can be skewed by the parents' perception of their child's behavior. Future comprehensive studies exploring neurocognitive outcomes across several domains and over time are necessary to shed more light on the selective vulnerability of certain domains to radiation, which would be beneficial in educating pediatric patients and their parents about the long-term effects of radiation on their function.

Prior studies comparing neurocognitive outcomes following XRT versus PRT in pediatric patients with brain tumors[8–10,20] suggest proton superiority in terms of overall IQ, though

effects on other domains are conflicting. We found no statistically significant difference between neurocognitive scores from the two treatment groups, and the proportion of children with impairment between the two groups was not significantly different. All analyses performed in the CSI sub-cohort produced similar results. In contrast to our findings, two cohort studies found higher full-scale IQ[10,20,38] and processing speed[20] in patients who received PRT versus XRT. Another study in pediatric patients with medulloblastoma found that those receiving PRT exhibited superior long-term outcomes in IQ, perceptual reasoning and working memory compared with those receiving XRT[9]. A recent prospective cohort study showed significantly higher scores in Full Scale IQ, verbal comprehension and perceptual reasoning with PRT versus XRT treatment but found no differences in processing speed and working memory[10]. Our study may have been relatively underpowered to show statistically significant differences between groups given modest sample size. Also, post-treatment neurocognitive outcomes reflect a complex interplay between patient related factors, tumor type and location and other treatment factors like surgery, systemic therapy, and medical complications. While proton therapy has advantages from a dose fall-off perspective, it is likely one of many influencing variables.

Notably, we found that ethnicity was a consistent predictor of lower neurocognitive scores, with non-Hispanic patients scoring higher in FDS, VCI, and GAI compared to Hispanic patients. To our knowledge, the impact of ethnicity on post-treatment neurocognitive outcomes has not been well-explored in previous studies among pediatric patients with brain tumors. Since we did not have data on race, it is possible that non-Hispanic patients could be from diverse racial backgrounds which may confound these results. FDS, VCI and GAI scores are derived from tasks that require patients to listen and verbalize their responses. As such, language barriers for non-native Hispanic patients may partially account for the discrepancies between Hispanic and non-Hispanic groups. While we do not have information on the number of patients that were bilingual or Spanish dominant, all neurocognitive assessments were performed by a bilingual tester or with an in-person Spanish interpreter when the patient's preferred or dominant language was Spanish. However, it is notable that some verbal tasks do not translate well to other languages, require some language formulation from the patient, and are not very culturally sensitive. Our results demonstrate a need for a *well-validated battery of neurocognitive tests for linguistically diverse populations*. Such tests would minimize the effect of language barriers and further clarify the association between ethnicity and neurocognitive changes following radiation. Our findings suggest that it is critical to carefully interpret results from cognitive assessments administered in English in this patient population, so patients are not implicitly discriminated against during school placement or future employment opportunities.

Socioeconomic factors influencing neurocognitive outcomes include cultural biases in neurocognitive assessments[39,40] in addition to other unmeasured factors such as quality of schooling or parent education levels. We looked for correlation between patient's ethnicity and two measures of socioeconomic status (SES)- percent poverty and median family income based on patients' zip codes. We found no association between these variables; however, it is important to note that these are crude rather than direct measures of SES. Hence it is difficult to make a conclusion regarding the interplay of ethnicity, SES, and cognition; this is an important dimension that could be explored further in future studies.

Indeed, one study showed that adaptive functioning in pediatric brain tumor survivors did not differ by patient ethnicity after accounting for primary caregiver education and family income[41].

Limitations of this study include its retrospective nature and modest sample size, though our cohort is similar or larger in size than several retrospective pediatric brain tumor studies[4,6–7,11,14,16,18]. Given that our inclusion criteria required documentation of radiation treatment plan, adequate follow up, and comprehensive neuropsychological evaludation >6 months from treatment completion, there may be inherent selection bias within this cohort. We did not have pre-RT baseline neurocognitive scores, nor serial or longitudinal testing over time, as these are not routinely assessed outside of a clinical trial setting. Thus, our analyses focus on cross-sectional post-treatment outcomes to explore specific domains affected and severity of impairments in comparison to gender and age matched normative populations. Our approach is similar to other studies in this space[4,5,14]. While tumor type was heterogenous in the present cohort, we also performed a subset analysis of patients with medulloblastoma receiving CSI to explore a more homogenous group[20]. We had different follow-up time between the two groups, as proton radiation is a relatively newer treatment option. Thus, we accounted for follow up time in all analyses. Referral bias, especially for protons, is a concern in all studies which compare outcomes by treatment modality and likely influenced by various confounders including insurance status. Presence of hearing impairments following cisplatin treatments, visual or motor impairments, parent education, and quality of schooling are some of several other confounders which may influence neurocognition.

In conclusion, radiation therapy is associated with global cognitive impairment affecting multiple domains in pediatric patients with brain tumors, with the potential for less vulnerability to executive function changes. We found no significant differences in neurocognitive outcomes by radiation modality, PRT compared with XRT, though we were likely underpowered to detect a statistical difference. Our study also brings forth the need for appropriate instruments to assess neurocognitive outcomes in minority ethnic groups. Our results underscore the importance of future work to assess neurocognitive performance longitudinally over time to better understand the trajectory of late effects on survivorship in pediatric brain tumor patients. Future comparative studies, especially with larger collaborative registries like the Pediatric Proton/Photon Consortium Registry[42], are needed to fully understand the impact of radiation on cognitive function, and to assess whether use of PRT versus XRT would lead to better cognitive preservation for pediatric patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Conflicts of Interest and Source of Funding:

This work was supported by the National Institutes of Health (F31 NS111883-01 (AR); F32NS119285-01A1 (AS); 1TL1TR001443 (MS, AY); 1KL2TR001444, R01 CA238783-01 to JAH-G); and American Cancer Society (RSG-15-229-01-CCE to CRM). For the remaining authors, none were declared.

## References


1. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008–2012. Neuro Oncol. 2015; 17 Suppl 4:iv1–iv62. [PubMed: 26511214]
2. Nathan PC, Patel SK, Dilley K, et al. Guidelines for Identification of, Advocacy for, and Intervention in Neurocognitive Problems in Survivors of Childhood Cancer. Arch Pediatr Adolesc Med 2002; 161(8):798–806.
3. Dutz A, Agolli L, Bütof R, et al. Neurocognitive function and quality of life after proton beam therapy for brain tumour patients. Radiother Oncol. 2020; 143:108–116. [PubMed: 32044170]
4. Liu F, Scantlebury N, Tabori U, et al. White matter compromise predicts poor intellectual outcome in survivors of pediatric low-grade glioma. Neuro Oncol. 2015; 17(4):604–613. [PubMed: 25395463]
5. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst 2009; 101(13):946–958. [PubMed: 19535780]
6. Edelstein K, Spiegler BJ, Fung S, et al. Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes. Neuro Oncol. 2011; 13(5):536–545. [PubMed: 21367970]
7. Maddrey AM, Bergeron JA, Lombardo ER, et al. Neuropsychological performance and quality of life of 10 year survivors of childhood medulloblastoma. J Neurooncol. 2005; 72(3):245–253. [PubMed: 15937648]
8. Kahalley LS, Ris MD, Grosshans DR, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. J Clin Oncol. 2016; 34(10):1043–1049. [PubMed: 26811522]
9. Kahalley LS, Peterson R, Ris MD, et al. Superior Intellectual Outcomes After Proton Radiotherapy Compared With Photon Radiotherapy for Pediatric Medulloblastoma. J Clin Oncol. 2019; JCO.19.01706.
10. Eaton BR, Fong GW, Ingerski LM, et al. Intellectual functionaing among case-matched cohorts of children treated with proton or photon radiation for standard-risk medulloblastoma. Cancer. 2021; 127(20):3840–3846. [PubMed: 34255345]
11. Jimenez RB, Sethi R, Depauw N, et al. Proton Radiation Therapy for Pediatric Medulloblastoma and Supratentorial Primitive Neuroectodermal Tumors: Outcomes for Very Young Children Treated With Upfront Chemotherapy. Int J Radiat Oncol. 2013; 87(1):120–126.
12. Rieken S, Habermehl D, Haberer T, Jaekel O, Debus J, Combs SE. Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts. Radiat Oncol. 2012; 7(1):41. [PubMed: 22436135]
13. Mac Donald SM, Sethi R, Lavally B, et al. Proton radiotherapy for pediatric central nervous system ependymoma: Clinical outcomes for 70 patients. Neuro Oncol. 2013; 15(11):1552–1559. [PubMed: 24101739]
14. Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of Intellectual Development Among Survivors of Pediatric Medulloblastoma: A Longitudinal Analysis. J Clin Oncol. 2001; 19(8):2302–2308. [PubMed: 11304784]
15. Bernier V, Klein O. Late effects of craniospatial irradiation for medulloblastomas in paediatric patients. Neurochirurgie. 2021; 67(1):83–86. [PubMed: 30149928]
16. Greenberger BA, Pulsifer MB, Ebb DH, et al. Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys. 2014; 89(5):1060–1068. [PubMed: 25035209]
17. Pulsifer MB, Sethi RV, Kuhlthau KA, MacDonald SM, Tarbell NJ, Yock TI. Early Cognitive Outcomes Following Proton Radiation in Pediatric Patients With Brain and Central Nervous System Tumors. Int J Radiat Oncol Biol Phys. 2015; 93(2):400–407. [PubMed: 26254679]

18. Antonini TN, Ris MD, Grosshans DR, et al. Attention, processing speed, and executive functioning in pediatric brain tumor survivors treated with proton beam radiation therapy. Radiother Oncol. 2017; 124(1):89–97. [PubMed: 28655455]
19. Pulsifer MB, Duncanson H, Grieco J, et al. Cognitive and Adaptive Outcomes After Proton Radiation for Pediatric Patients With Brain Tumors. Int J Radiat Oncol Biol Phys.. 2018; 102(2).
20. Gross JP, Powell S, Zelko F, et al. Improved neuropsychological outcomes following proton therapy relative to X-ray therapy for pediatric brain tumor patients. Neuro Oncol. 2019; 21(7):934–943. [PubMed: 30997512]
21. United States Census Bureau. American Community Survey: Poverty. American Community Survey 5-year estimates. https://data.census.gov/cedsci/. Published 2018. Accessed February 26, 2020.
22. United States Census Bureau. American Community Survey: Median Income. American Community Survey 5-year estimates. https://data.census.gov/cedsci/. Published 2018. Accessed February 26, 2020.
23. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol. 2017; 13(1):52–64. [PubMed: 27982041]
24. Peterson RK, Tabori U, Bouffet E, et al. Predictors of neuropsychological late effects and white matter correlates in children treated for a brain tumor without radiation therapy. Pediatr Blood Cancer. 2019; 66(10):e27924.
25. Szentes A, Erős N, Kekecs Z, et al. Cognitive deficits and psychopathological symptoms among children with medulloblastoma. Eur J Cancer Care (Engl). 2018; 27(6):e12912.
26. Khalil J, Chaabi S, Oberlin O, Sialiti S, Hessissen L, Benjaafar N. Medulloblastoma in childhood: What effects on neurocognitive functions? Cancer/Radiothérapie. 2019; 23(5):370–377. [PubMed: 31331843]
27. Newby RF, Epping A, Geiger JA, Miller MS, Scott JP. Visual Motor Integration in Children With Sickle Cell Disease. J Pediatr Hematol Oncol. 2018; 40(7):495–498. [PubMed: 30044354]
28. Fournier-Goodnight AS, Ashford JM, Merchant TE, et al. Neurocognitive functioning in pediatric craniopharyngioma: performance before treatment with proton therapy. J Neurooncol. 2017; 134(1).
29. Eby NS, Griffith JL, Gutmann DH, Morris SM Adaptive functioning in children with neurofibromatosis type 1: relationship to cognition, behavior, and magnetic resonance imaging. Dev Med Child Neurol. 2019; 61(8):972–978. [PubMed: 30659594]
30. Viola A, Balsamo L, Neglia JP, Brouwers P, Ma X, Kadan-Lottick NS The Behavior Rating Inventory of Executive Function (BRIEF) to Identify Pediatric Acute Lymphoblastic Leukemia (ALL) Survivors At Risk for Neurocognitive Impairment. J Pediatr Hematol Oncol. 2017; 39(3):174–178. [PubMed: 28085741]
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association. Published 2013.
32. Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ. Change in Neurocognitive Functioning After Treatment With Cranial Radiation in Childhood. J Clin Oncol. 2004; 22(4):706–713. [PubMed: 14966095]
33. Turner CD, Rey-Casserly C, Liptak CC, Chordas C. Late effects of therapy for pediatric brain tumor survivors. J Child Neurol. 2009; 24(11):1455–1463. [PubMed: 19841433]
34. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol. 2014; 10(11):634–642. [PubMed: 25266297]
35. Hasson-Ohayon I, Mashiach-Eizenberg M, Arnon-Ribenfeld N, Kravetz S, Roe D Neuro-cognition and social cognition elements of social functioning and social quality of life. Psychiatry Res. 2017; 258:538–543. [PubMed: 28916297]
36. Tonning Olsson I, Perrin S, Lundgren J, Hjorth L, Johanson A. Long-term cognitive sequelae after pediatric brain tumor related to medical risk factors, age, and sex. Pediatr Neurol. 2014; 51(4):515–521. [PubMed: 25266614]

37. Brière ME, Scott JG, McNall-Knapp RY, Adams RL. Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. Pediatr Blood Cancer. 2008; 50(2):337–340. [PubMed: 17458873]

38. Kahalley LS, Douglas Ris M, Mahajan A, et al. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. Neuro Oncol. 2019; 21(6):809–818. [PubMed: 30753584]

39. Statucka M, Cohn M. Origins Matter: Culture Impacts Cognitive Testing in Parkinson's Disease. Front Hum Neurosci. 2019; 13:269. [PubMed: 31440150]

40. López E, Steiner AJ, Hardy DJ, IsHak WW, Anderson WB. Discrepancies between bilinguals' performance on the Spanish and English versions of the WAIS Digit Span task: Cross-cultural implications. Appl Neuropsychol Adult. 2016; 23(5):343–352. [PubMed: 26786894]

41. Raghubar KP, Orobio J, Ris MD, et al. Adaptive functioning in pediatric brain tumor survivors: An examination of ethnicity and socioeconomic status. Pediatr Blood Cancer. 2019; 66(9):e27800.

42. Lawell MP, Indelicato DJ, Paulino AC, et al. Proton therapy special feature : Full paper An open invitation to join the Pediatric Proton / Photon Consortium Registry to standardize data collection in pediatric radiation oncology. Br J Radiol. 2019; 93(1107):20190673.

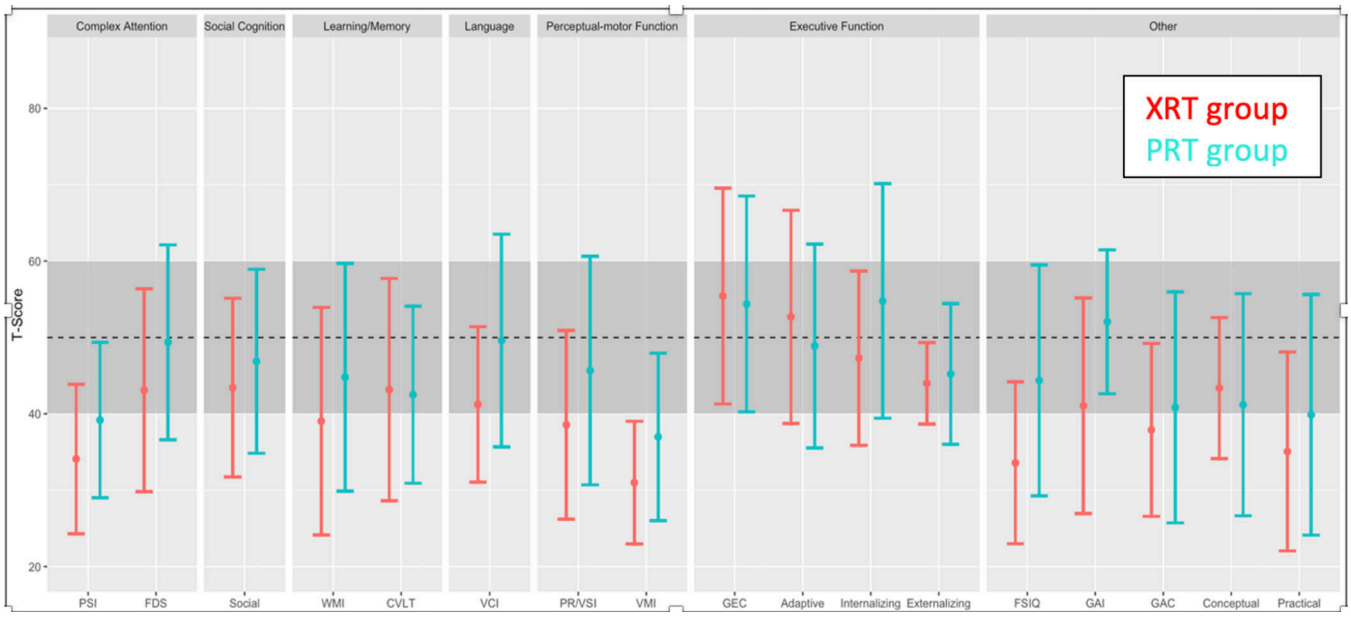


**Figure1.**

Summary of Neurocognitive Outcomes grouped by domains and stratified by radiation modality Abbreviations: PSI, processing speed index; WMI, working memory index; VCI, verbal comprehension index; PRI, perceptual reasoning index; VMI, visual-motor integration; FSIQ, full-scale IQ; GAI, general ability index; GAC, general adaptive composite; FDS, forward digit span; CVLT, California Verbal Learning Test Trials 1–5 List A; GEC, global executive composite

X-axis depicts test name

Y-axis depicts T-score

Solid dot= mean

Error bars= standard deviation

Horizontal dashed line = population mean (T-score= 50)

Dark grey shading = one standard deviation above and below the population mean

The y-axis for executive functioning is inverted because higher scores are associated with worse performance

**Table 1:**

Cohort Characteristics

| Covariate | Radiation Type | | p-value[a] |
|---|---|---|---|
| | XRT (N=32) | PRT (N=17) | |
| Sex | | | 0.022 |
| Female | 6 (18.8%) | 9 (52.9%) | |
| Male | 26 (81.3%) | 8 (47.1%) | |
| Ethnicity | | | 0.541 |
| Hispanic/Latino | 13 (40.6%) | 5 (29.4%) | |
| Non-Hispanic | 19 (59.4%) | 12 (70.6%) | |
| Tumor Histology | | | 0.551 |
| Medulloblastoma | 15 (46.9%) | 10 (58.8%) | |
| Other[b] | 17 (53.1%) | 7 (41.2%) | |
| Resection Type[c] | | | >0.9 |
| GTR | 19 (70.4%) | 12 (75.0%) | |
| Other | 8 (29.6%) | 4 (25.0%) | |
| Craniospinal Irradiation | | | 0.764 |
| Yes | 16 (50.0%) | 10 (58.8%) | |
| No | 16 (50.0%) | 7 (41.2%) | |
| VP Shunt | | | 0.135 |
| Yes | 15 (46.9%) | 4 (23.5%) | |
| No | 17 (53.1%) | 13 (76.5%) | |
| Baseline Karnofsky Performance Status | | | 0.688 |
| <70 | 5 (41.7%) | 4 (30.8%) | |
| ≥70 | 7 (58.3%) | 9(69.2%) | |
| Systemic Therapy | | | 0.467 |
| Yes | 25 (78.1%) | 15 (88.2%) | |
| No | 7 (21.9%) | 2 (11.8%) | |
| Age at RT (years) | | | 0.231 |
| Median | 7.76 (2.43 – 16.99) | 5.38 (1.39 – 17.41) | |
| Total RT Dose, Tumor (Gy) | | | 0.494 |

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| Covariate | Radiation Type | | p-value[a] |
|---|---|---|---|
| | XRT (N=32) | PRT (N=17) | |
| Median | 54.0 (20.0 – 56.4) | 54.0 (37.8 – 59.4) | |
| Time from RT to neurocognitive exam (years)[d] | | | <0.001* |
| Median | 3.2 (0.11 – 13.4) | 1.8 (0.46 – 10.6) | |
| Percent Poverty[e] | | | >0.9 |
| <13% | 5 (15.6%) | 3 (17.6%) | |
| ≥13% | 27 (84.4%) | 14 (82.4%) | |
| Median Income[e] | | | 0.331 |
| <$75,000 | 25 (78.1%) | 11 (64.7%) | |
| ≥$75,000 | 7 (21.9%) | 6 (35.3%) | |

Footer:

Abbreviations: XRT: photon radiotherapy; PRT, proton radiotherapy; GTR, gross tumor resection; VP, ventriculoperitoneal; RT, radiotherapy; Gy, gray

[a]Categorical and continuous data were respectively analyzed using Fisher's exact and Wilcoxan rank-sum tests

[b]Other tumor histology: astrocytoma (6), ependymoma (4), germinoma (4), craniopharyngioma (3), glioma (2), meningioma (1), ATRT (1), germ cell (1), pineoblastoma (1), NF-2 associated vestibular schwannoma (1)

[c]GTR was determined by direct verbiage in chart review. Other includes near/sub-total resection, biopsies, and unspecified resection.

[d]Shows overall time from RT to all 17 neurocognitive exams (530 observations)

[e]Calculated from patient zip codes via US census data from 2018. Cutoff levels of 13% poverty and median income of $75,000 were determined based on average results within California.

*p-value <0.05

**Table 2:**

Percentage of patients with cognitive impairment

| Neurocognitive Domain[a] | Test | Full Cohort (n=49) | | | | CSI sub-cohort (n=26) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Total[g] % impaired patients[h] | XRT % impaired patients[h] | PRT % impaired patients[h] | p-value | Total[g] % impaired patients[h] | XRT % impaired patients[h] | PRT % impaired patients[h] | p-value |
| Complex Attention | Processing Speed Index[b] | 41.7 | 45.8 | 33.3 | 0.721 | 40.0 | 50.0 | 25.0 | 0.373 |
| | Forward Digit Span[b] | 18.9 | 20.0 | 16.7 | >0.9 | 26.3 | 27.3 | 25.0 | >0.9 |
| Social Cognition | Social[c] | 18.5 | 25.0 | 9.1 | 0.619 | 20.0 | 22.2 | 16.7 | >0.9 |
| Learning/Memory | Working Memory Index[b] | 26.3 | 30.8 | 16.7 | 0.453 | 35.0 | 41.7 | 25.0 | 0.642 |
| | Verbal Learning[d] | 27.5 | 25.0 | 33.3 | 0.704 | 33.3 | 38.5 | 25.0 | 0.656 |
| Language | Verbal Comprehension Index[b] | 17.5 | 22.2 | 7.7 | 0.393 | 30.0 | 41.7 | 12.5 | 0.325 |
| Perceptual-motor Function | Perceptual Reasoning Index[b] | 18.9 | 20.0 | 16.7 | >0.9 | 28.6 | 30.8 | 25.0 | >0.9 |
| | Visual-Motor Integration[e] | 33.3 | 28.6 | 36.4 | >0.9 | 41.6 | 40.0 | 42.9 | >0.9 |
| Executive Function | Global Executive Composite[f] | 24.0 | 27.3 | 21.4 | >0.9 | 26.7 | 28.6 | 25.0 | >0.9 |
| | Adaptive[f] | 6.1 | 11.1 | 0.0 | 0.489 | 10.5 | 20.0 | 0.0 | 0.474 |
| | Externalizing[f] | 3.0 | 0.0 | 6.7 | 0.455 | 5.3 | 0.0 | 11.1 | 0.474 |
| | Internalizing[f] | 11.4 | 10.0 | 13.3 | >0.9 | 15.8 | 10.0 | 22.2 | 0.582 |
| Other | Full Scale Intelligence Quotient[b] | 27.8 | 33.3 | 16.7 | 0.438 | 47.4 | 63.6 | 25.0 | 0.170 |
| | General Ability Index[b] | 15.8 | 15.4 | 16.7 | >0.9 | 20.0 | 28.6 | 0.0 | >0.9 |
| | General Adaptive Composite[c] | 34.6 | 40.0 | 27.3 | 0.683 | 42.9 | 50.0 | 33.3 | 0.627 |
| | Conceptual[c] | 26.1 | 25.0 | 27.3 | >0.9 | 23.1 | 14.3 | 33.3 | 0.559 |
| | Practical[c] | 33.3 | 43.6 | 18.2 | 0.231 | 46.7 | 55.6 | 33.3 | 0.608 |

Footer:

Abbreviations:

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[a] Major neurocognitive domains as described in the DSM-5 (reference). “Other” domain encompasses tests that span multiple domains or are not adequately represented by a single domain.

[b] via Wechsler exams

[c] via parent-rated Adaptive Behavior Assessment System

[d] via California Verbal Learning Test Trials 1–5 List A

[e] From Beery Buktenica Developmental Test of Visual Motor Integration

[f] via parent-rated Behavior Rating Inventory of Executive Function. Higher scores indicate worse executive functioning

[g] total number of patients that received either type of radiation

[h] impairment defined as 1.5 standard deviations below mean T-score of 50

**Table 3:**

Comparison of Neurocognitive Outcomes between XRT and PRT patients by domain and test

| Neurocognitive Domain[a] | Test | Entire Cohort n = 49 | | | CSI Sub-cohort n = 26 | | |
|---|---|---|---|---|---|---|---|
| | | XRT Mean Score[g] (Percentile) | PRT Mean Score[g] (Percentile) | p-value | XRT Mean Score[g] (Percentile) | PRT Mean Score[g] (Percentile) | p-value |
| Complex Attention | Processing Speed Index[b] | 35.9(7.9) | 37.3(10.2) | p=0.696 | 35.1(6.8) | 39.2(13.8) | p=0.382 |
| | Forward Digit Span[b] | 43.3(25.1) | 47.7(40.9) | p=0.262 | 44.4 (28.8) | 49.4(47.6) | p=0.421 |
| Social Cognition | Social[c] | 41.5(19.8) | 47.0 (38.2) | p=0.197 | 43.4(25.5) | 46.9(37.8) | p=0.590 |
| Learning/Memory | Working Memory Index[b] | 41.1(18.7) | 44.8(30.2) | p=0.388 | 40.3(16.6) | 44.8(30.2) | p=0.519 |
| | Verbal Learning[d] | 45.6(33.0) | 39.2(14.0) | p=0.163 | 44.8(30.2) | 42.5(22.7) | p=0.713 |
| Language | Verbal Comprehension Index[b] | 44.1(27.8) | 47.5(40.1) | p=0.325 | 41.8(20.6) | 49.6(48.4) | p=0.159 |
| Perceptual-motor Function | Perceptual Reasoning Index[b] | 42.2(21.8) | 46.1(34.8) | p=0.314 | 39.4(14.5) | 45.7(33.4) | p=0.311 |
| | Visual-Motor Integration[e] | 34.5(6.06) | 40.1(16.1) | p=0.266 | 31.0(2.87) | 37.0(9.68) | p=0.325 |
| Executive Function | Global Executive Composite[f] | 58.17(79.3) | 53.5(63.7) | p=0.354 | 55.4(70.5) | 54.4(67.0) | p=0.888 |
| | Adaptive[f] | 49.0(46.0) | 49.1(46.4) | p=0.987 | 52.7(60.6) | 48.8(45.2) | p=0.552 |
| | Externalizing[f] | 45.3(31.9) | 44.7(29.8) | p=0.806 | 44.0(27.4) | 45.2(31.56) | p=0.724 |
| | Internalizing[f] | 49.4(47.6) | 51.7(56.8) | p=0.558 | 47.3(9.2) | 54.8(68.4) | p=0.242 |
| Other | Full Scale Intelligence Quotient[b] | 39.4(14.5) | 44.1(27.8) | p=0.235 | 35.2(6.9) | 44.4(28.8) | p=0.147 |
| | General Ability Index[b] | 42.9(23.9) | 48.2(42.9) | p=0.311 | 42.3(22.1) | 52.1(58.3) | p=0.291 |
| | General Adaptive Composite[c] | 38.5(12.5) | 42.1(21.5) | p=0.419 | 37.9(11.3) | 40.8(17.9) | p=0.684 |
| | Conceptual[c] | 42.1(21.5) | 42.5(22.7) | p=0.922 | 43.4(25.5) | 41.2(18.9) | p=0.748 |
| | Practical[c] | 36.9(9.5) | 41.3(19.22) | p=0.378 | 35.1(6.8) | 39.9(15.6) | p=0.530 |

Footer:

Abbreviations:

[a]Major neurocognitive domains as described in the DSM-5 (reference). “Other” domain encompasses tests that span multiple domains or are not adequately represented by a single domain.

[b]via Wechsler exams

[c]via parent-rated Adaptive Behavior Assessment System

[d] via California Verbal Learning Test Trials 1–5 List A

[e] From Beery Buktenica Developmental Test of Visual Motor Integration

[f] via parent-rated Behavior Rating Inventory of Executive Function. Higher scores indicate worse executive functioning

[g] T-scores

**Table 4:**

Treatment Modality as a Predictor of Neurocognitive Outcomes by Domain and Test

| Neurocognitive Domain[a] | Test | Entire Cohort n = 49 | | CSI Sub-cohort n = 26 | |
|---|---|---|---|---|---|
| | | Univariate | Multivariate | Univariate | Multivariate |
| | | p-value[g] | p-value[g] | p-value[g] | p-value[g] |
| Complex Attention | Processing Speed Index[b]† | 0.650 | 0.617 | 0.352 | 0.908 |
| | Forward Digit Span[b]§ | 0.238 | 0.991 | 0.389 | 0.726 |
| Social Cognition | Social[c]† | 0.192 | 0.461 | 0.595 | 0.223 |
| Learning/ Memory | Working Memory Index[b]† | 0.410 | 0.960 | 0.540 | 0.522 |
| | Verbal Learning[d]‖ | 0.163 | 0.581 | 0.713 | 0.544 |
| Language | Verbal Comprehension Index[b]† | 0.331 | 0.898 | 0.168 | 0.745 |
| Perceptual-motor Function | Perceptual Reasoning Index[b]† | 0.368 | 0.989 | 0.372 | 0.879 |
| | Visual-Motor Integration[e]† | 0.231 | 0.852 | 0.288 | 0.758 |
| Executive Function | Global Executive Composite[f]‖ | 0.354 | 0.978 | 0.888 | 0.703 |
| | Adaptive[f]‖ | 0.987 | 0.974 | 0.552 | 0.581 |
| | Externalizing[f]‖ | 0.806 | 0.992 | 0.724 | 0.537 |
| | Internalizing[f]‖ | 0.558 | 0.557 | 0.242 | 0.246 |
| Other | Full Scale Intelligence Quotient[b]† | 0.293 | 0.996 | 0.194 | 0.852 |
| | General Ability Index[b]† | 0.305 | 0.286 | 0.287 | 0.851 |
| | General Adaptive Composite[c]† | 0.407 | 0.700 | 0.668 | 0.900 |
| | Conceptual[c]† | 0.944 | 0.843 | 0.745 | 0.511 |
| | Practical[c]† | 0.351 | 0.604 | 0.515 | 0.690 |

Footer:

Abbreviations:

[a]Major neurocognitive domains as described in the DSM-5 (reference). “Other” domain encompasses tests that span multiple domains or are not adequately represented by a single domain.

[b]via Wechsler exams

[c]via parent-rated Adaptive Behavior Assessment System

[d] via California Verbal Learning Test Trials 1–5 List A

[e] From Beery Buktenica Developmental Test of Visual Motor Integration

[f] via parent-rated Behavior Rating Inventory of Executive Function. Higher scores indicate worse executive functioning

[g] p-values from regression models with treatment modality (photon versus proton) as the predictor

**Table 5:**

Effects of Ethnicity on Neurocognitive Outcomes

| Neurocognitive Domain[a] | Test | Full cohort | | | | CSI sub-cohort | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariable | | Multivariable | | Univariable | | Multivariable | |
| | | Non-Hispanic vs Hispanic Beta | p-value | Non-Hispanic vs Hispanic Beta | p-value | Non-Hispanic vs Hispanic Beta | p-value | Non-Hispanic vs Hispanic Beta | p-value |
| Complex Attention | Forward Digit Span[b§] | 3.41 | 0.001** | 2.33 | 0.027* | 5.67 | 0.001** | 4.62 | 0.003** |
| Learning/Memory | Working Memory Index[b†] | 16.56 | 0.006** | 12.02 | 0.057 | 28.21 | 0.008** | 21.41 | 0.055 |
| Language | Verbal Comprehension Index[b†] | 17.21 | <0.001** | 16.27 | 0.001** | 22.69 | 0.005** | 20.18 | 0.025** |
| Perceptual-motor Function | Perceptual Reasoning Index[b†] | 13.47 | 0.013** | 10.47 | 0.076 | 18.90 | 0.051 | --- | --- |
| Other | Full Scale IQ[b†] | 16.29 | 0.004** | 12.62 | 0.034* | 21.94 | 0.031* | --- | --- |
| | General Ability Index[b†] | 20.69 | 0.001** | 20.92 | 0.009** | 35.00 | 0.002** | 35.93 | 0.009** |

Footer:

Abbreviations: IQ, intelligence quotient;

[a]Major neurocognitive domains as described in the DSM-5 (reference). “Other” domain encompasses tests that span multiple domains or are not adequately represented by a single domain.

[b]via Wechsler exams

[†]Measured via standard score (average 100, standard deviation 15)

[§]Measured via scaled score (average 10, standard deviation 3)

*P < 0.05

**p-value remained statistically significant after false discovery rate correction

--- Multivariate analyses not performed as univariate analyses not significant post FDR correction

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