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PENTEC ORGAN SYSTEM REVIEW

Neurocognitive Effects and Necrosis in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: A PENTEC review of childhood cancer survivors who received brain radiation therapy (RT) was performed to develop models that aid in developing dose constraints for RT-associated central nervous system (CNS) morbidities.

Methods and Materials: A comprehensive literature search, through the PENTEC initiative, was performed to identify published data pertaining to 6 specific CNS toxicities in children treated with brain RT. Treatment and outcome data on survivors were extracted and used to generate normal tissue complication probability (NTCP) models.

Results: The search identified investigations pertaining to 2 of the 6 predefined CNS outcomes: neurocognition and brain necrosis. For neurocognition, models for 2 post-RT outcomes were developed to (1) calculate the risk for a below-average intelligence quotient (IQ) (IQ <85) and (2) estimate the expected IQ value. The models suggest that there is a 5% risk of a subsequent IQ <85 when 10%, 20%, 50%, or 100% of the brain is irradiated to 35.7, 29.1, 22.2, or 18.1 Gy, respectively (all at 2 Gy/fraction and without methotrexate). Methotrexate (MTX) increased the risk for an IQ <85 similar to a generalized

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uniform brain dose of 5.9 Gy. The model for predicting expected IQ also includes the effect of dose, age, and MTX. Each of these factors has an independent, but probably cumulative effect on IQ. The necrosis model estimates a 5% risk of necrosis for children after 59.8 Gy or 63.6 Gy (2 Gy/fraction) to any part of the brain if delivered as primary RT or reirradiation, respectively.

Conclusions: This PENTEC comprehensive review establishes objective relationships between patient age, RT dose, RT volume, and MTX to subsequent risks of neurocognitive injury and necrosis. A lack of consistent RT data and outcome reporting in the published literature hindered investigation of the other predefined CNS morbidity endpoints.

Introduction

The definitive management of many pediatric malignancies requires radiation therapy (RT) to the central nervous system (CNS) that may predispose survivors to neurologic complications. A detailed understanding of radiation dose-volume effects is required to maximize the therapeutic ratio of brain irradiation. This understanding will facilitate thoughtful use of advanced RT modalities such as intensity modulated RT (IMRT), with x-rays or proton therapy (IMPT). This comprehensive PENTEC review of cancer survivors who received brain RT aims to describe the risks of 2 RT-related CNS toxicities: neurocognition and brain necrosis. Data on survivors were used to generate normal tissue complication probability (NTCP) models specific to the 2 toxicity endpoints.

Clinical Significance

A child may receive whole or partial brain irradiation for various reasons including: (1) primary CNS tumors, (2) non-CNS tumors near the skull base, and (3) treatment of known or suspected CNS hematologic malignancy, such as leukemia. More specifically, approximately 3300 new benign or malignant primary CNS tumors are diagnosed annually in patients younger than age 16 years in the United States, and in this age group, brain tumors are the most common solid tumor indication for RT. Many of these patients require large-field radiation such as craniospinal irradiation (CSI) and/or focal RT (45-60 Gy).

The main neurocognitive deficit noted in many childhood survivors appears to be a difficulty in acquiring new abilities at a rate similar to their peers, rather than a progressive loss of skill or knowledge already gained before cranial RT exposure; this observation partially explains the age dependence of the effect seen with treatment.[1-4] The consequences, therefore, have considerable repercussions on the functional outcomes and quality of life for childhood cancer survivors. Such cognitive effects may lead to poor social skills, difficulty adjusting to new environments, problems with peers, social withdrawal, and mild deficits in academic functioning; however, severe deficits in intellectual ability and language also occur.[5-7] Unlike survivors of most other pediatric cancer types, brain tumor survivors are less likely to live independently, marry, or attain degrees in higher levels of education.[8-10] These morbidities affect independence and psychosocial quality of life extending into adulthood and can even affect survival.[11]

Patients receiving RT to larger volumes and higher doses report increasing frequency and intensity of cognitive deficits over time. Young children treated with full-dose CSI (36 Gy) are observed to have lower full-scale IQ (FSIQ) scores and decreased school performance compared with their peer groups.[12-14] There is also a dose-response relationship for decline in intelligence quotient (IQ): a higher cumulative cranial dose predisposes survivors to worse IQ scores.[14-16] Indeed, follow-up studies of children treated on contemporary protocols using lower cranial doses and smaller treatment volumes have demonstrated a reduction in late cognitive deficits, spurring the development of prospective clinical trials to evaluate neurocognitive outcomes associated with reductions in RT field and dose.[17-19] Proton RT (PRT) has a dosimetric advantage compared with x-ray −based RT (XRT) that reduces the exposure of normal tissues to low doses owing to the abrupt dose fall-off (Bragg peak) of protons versus photons.[20] Preliminary evidence suggests that PRT, by reducing normal brain exposure, is associated with lower acute and late toxicity rate compared with historical and contemporary photon-RT cohorts.[20,21] In a recent report, PRT was associated with more favorable outcomes (compared with XRT) in most neurocognitive domains in children with medulloblastoma.[22,23]

In addition to the dose and volume dependence previously noted, RT doses to specific regions of the brain, particularly the temporal lobes and hippocampi, may disproportionally affect long-term IQ and academic performance.[16,24,25] RT-induced injury of the brain's white matter may partially explain these cognitive changes as magnetic resonance imaging (MRI) studies have correlated a decline in cognitive ability with white matter loss.[17,26,27] The impact of irradiated volume on cognitive subdomains such as executive function or processing speed (PS) (that broadly includes cognitive speed and efficiency of output) is not as well studied.

Of note, late cognitive changes in childhood cancer survivors are also affected by the tumor itself, and by other therapeutic interventions. Tumors in the cerebral hemispheres can be associated with difficulty in performance IQ (but generally not verbal IQ), academic achievement, memory, motor skills, and attention. Midline tumors have been associated with difficulties in memory, motor skills, and

attention. Children with posterior fossa tumors often develop difficulties in memory and motor abilities, and those with brain stem tumors are often within the average range in tested abilities.[28,29] Systemic therapies such as high-dose methotrexate (MTX), widely used for acute lymphoblastic leukemia (ALL), or intrathecal chemotherapy independently contribute to CNS toxicity, and can compound the effects of radiation.[30] A meta-analysis reported that children treated for ALL without RT scored 7.8 points lower FSIQ than the control group of children without ALL.[31] Concomitant chemotherapy and radiation appears to result in greater cognitive decline and educational burdens compared with RT alone in children treated for medulloblastoma.[32] To complicate matters, other early and late clinical events occurring at increased rates among childhood brain tumor survivors, such as hydrocephalus, postsurgical cerebellar mutism, stroke, seizure, and visual or auditory deficiencies, can also contribute to cognitive decline, independent of the direct therapy effects.[18,33-37]

In addition to functional injury, direct RT-induced brain injury that causes cell injury and death, or necrosis, has been reported in childhood cancer survivors. Follow-up MRI may identify necrosis that is characterized by increased heterogeneous contrast enhancement with surrounding edema within the irradiated volume in the absence of tumor progression. The functional severity of this damage depends on the extent and location of the injury, and can include headaches, seizures, motor or sensory loss, or cranial nerve palsies. Brain stem necrosis can be particularly debilitating, or even fatal. The risk of brain necrosis is low with the typical RT doses for childhood brain tumors; however, synergistic effects of chemotherapy and surgery may influence RT tolerance. Medical management for necrosis, typically corticosteroids, can be effective but is often transient or of limited use for some patients. More recently, bevacizumab and hyperbaric oxygen therapy have been shown to have some benefit.[38] Some patients with refractory symptomatic necrosis may require resection of affected tissue.

Other, less studied, but common areas of concern for patients undergoing brain RT are subacute somnolence syndrome, chronic headache, brain atrophy, and leukoencephalopathy.[39-43] These morbidities can be self-limited or progressive and can affect quality of life, physical function, and neurocognitive outcomes; however, guidelines for objective assessments, incidence, and relationship with RT are all limited.

Owing to the elevated risk of neurologic morbidities, there has been a continued effort to reduce the intensity or omit RT whenever possible. Elective cranial RT has been eliminated in the majority of treatment protocols for ALL.[44-46] There has been a transition to lower CSI doses and an increased reliance on chemotherapy in the management of medulloblastoma.[47,48] Similarly, RT to smaller target volumes, such as postsurgical tumor beds versus the entire posterior fossa, has become the standard of care for medulloblastoma.[16] Nevertheless, RT continues to play a critical role in many patients. For example, despite reluctance to expose children younger than 3 years of age to any cranial RT, optimal disease control and survival for children as young as 18 months with ependymoma, medulloblastoma, or atypical teratoid rhabdoid tumors appear to justify RT.[49-52] Reirradiation is being increasingly used as definitive management of locally recurrent disease despite the increased risk of brain necrosis; however, specific reirradiation guidelines are lacking.[53-56]

Endpoints and Toxicity Scoring

For this review, the endpoints of potential interest were neurocognitive impairment, brain/brain stem necrosis, subacute somnolence syndrome, chronic headache, brain atrophy, and leukoencephalopathy. Objective information on the relationship between each of these endpoints and RT exposure would be valuable. The literature review methodology is summarized in "Review of Dose-Volume Response Data and Risk Factors." Sufficient data were available for the analysis of only neurocognitive impairment and necrosis. Only sparse data were available for the other 4 areas of interest (Appendix A).

Ideally, neurocognitive functioning would be determined by formal testing at baseline and after RT at multiple time points. A variety of cognitive domains can be assessed, and multiple validated tests are available to measure individual or broad functional domains. Interpretation of these test results can be challenging because tests are routinely updated and refined; different test versions could be administered depending on the date ranges of assessments. Furthermore, tests are only appropriate for specific age groups and the appropriate testing can change over time. Although scoring of many tests is standardized such that scores and/or percentiles relative to the general population may be comparable, there is no single or uniformly accepted composite assessment that captures the multidimensional aspects of neurocognitive functioning. In addition, in an individual, neurocognitive dysfunction can evolve over time, such that increasing deficits may be observed for patients with longer post-treatment follow-up intervals. For the purpose of this review, global IQ and PS were considered because these 2 indices were most consistently reported and related to RT use. Thus, all studies that reported some component of neurocognitive evaluation for childhood brain tumor survivors who had received brain RT were included in this review, and measurements of global IQ and PS were extracted from these studies. The specific testing varied between reports and there are no good means to adjust for possible interstudy variations or absence of baseline pre-RT testing.

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https//ctep.cancer.gov) scores both cognitive disturbance and concentration impairment as mild, moderate, or severe by the degree of interference with work or school for cognition, or ability to perform activities of daily living. Most reports did not use a specific toxicity

scoring system for neurocognitive toxicity. Similarly, CTCAE version 5.0 defines CNS necrosis as a disorder characterized by a necrotic process in the brain or spinal or cord. Most studies diagnosed RT-induced necrosis with imaging, associated symptoms, and on occasion, by histopathology and scored with alternative scoring systems (eg, Radiation Therapy Oncology Group [RTOG], European Organisation for Research and Therapy for Cancer [EORTC] and CTCAE).[57,58]

Anatomy and Developmental Dynamics

Brain development is complex and starts during the third gestational week and continues well into adolescence and even adulthood. A programmed process of cell proliferation, migration, differentiation, axonal growth, and connection modification occurs throughout this time.[59] In parallel, cognitive functions develop from infancy through adulthood, with more rapid cognitive growth occurring during earlier stages of development. Thus, younger patients are more vulnerable to any insult from tumor infiltration, mass effect, surgery, radiation therapy, or chemotherapy, which could affect neurocognitive development. Fortunately, some of the negative impact of therapy may be attenuated by the increased neuro-plasticity that occurs in young children.[60] The negative impact of cranial irradiation on cognition commonly occurs within the first 5 years from treatment and is typically permanent. There is potential additional deterioration over time, though there are few studies beyond 10 to 20 years of follow-up to evaluate any potential of long-term functional recovery after RT.

The mechanism of radiation-induced neurocognitive effects is not completely understood but neurogenesis, the process by which neural stem cells differentiate into mature cells in multiple brain structures, is thought to be affected. Neurogenesis is promoted and regulated by the microenvironment of neuronal stem cells, astrocytes, and endothelial cells.[61] It is likely that radiation reduces neurogenesis by direct and indirect damage and apoptosis of neuronal stem cells, oligodendrocytes, and endothelial cells. Radiation injury to endothelial cells and activated microglia is thought to mediate chronic neuroinflammation that negatively affects neurogenesis and also leads to ischemic axonal and oligodendrocyte death.[11,62,63] In adults, neural stem cells are located in the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus. The hippocampi are especially sensitive to RT-induced decline in neurogenesis and are associated with cognitive deficits, specifically declines in IQ and poor neurocognitive performance.[64-66] Structural changes including a reduction in hippocampal volume may mediate this decline and are associated with lower cognitive performance.[27,67]

Neurocognitive decline also occurs through damage to cortical and subcortical white matter.[4] Irradiated childhood brain tumor survivors have decreased white matter volume compared with healthy controls and to unirradiated cancer survivors.[68-70] Reduction in white matter volume after RT appears to be responsible for most of the subsequent cognitive decline. Diffusion tensor imaging (DTI) demonstrates subtle changes in white matter microstructure that can be described using diffusion metrics such as fractional anisotropy (FA). FA is a quantitative index that is thought to reflect axonal degeneration or decreased myelin integrity and has been used to investigate radiation injury.[71] Previous studies have found a reduction in FA after RT in the corpus callosum and frontal lobes.[72,73] In support of these findings, a reduction in FA is correlated with decline in school performance, PS, and IQ.[17,68,72,74-76]

This observation of decreasing white matter volume over time may be due to direct damage and loss of white matter and/or failure to undergo maturation. However, it is notable that myelination is completed last in the frontal and prefrontal lobes, which are implicated in many of the areas of deficit seen in survivors: executive function and working memory, as well as planning and attention.[77-80] This correlation suggests that failure to complete normal developmental myelination or maturation may represent an important mechanism underlying the development of radiation-induced late cognitive decline.

Cranial irradiation can also cause injury to the existing neural structures that can lead to transient or permanent loss of function through inflammation, vascular changes, gliosis, and cell death leading to necrosis. Brain radionecrosis may be caused by injury to glial cells, creating demyelination in the white matter or by direct primary injury to the blood vessels, with brain parenchymal injury as secondary damage.[81] The risk for brain necrosis is chiefly influenced by RT dose and fractionation, RT volume, prior/subsequent surgery, and chemotherapy. There are limited data regarding the incidence of radiation necrosis in pediatric patients or any association with age. One example by Plimpton et al reports an incidence of radiation necrosis of 5% in 101 pediatric patients, after an average prescribed dose of 54.6 Gy, which is higher than what is noted in the adult literature.[82,83]

Defining Volumes: Pediatric Imaging Issues

Anatomic structures, such as the whole brain, cerebellum, brain stem, supratentorial brain, specific lobes, hippocampi, hypothalamus, and pituitary gland can be delineated on the planning CT scan, though image registration with MRI scans usually enables more accurate delineation, in particular for more challenging structures such as the hippocampi. Few of the studies used in this report provided DVH information for these specific structures. The functional subunits of the hippocampi can also be identified, but there is less agreement on the importance of such segmentation.[84] Similarly, functional components of the brain (eg, memory centers, speech centers, and fasciculi) are challenging to identify on conventional imaging. Finally, the functional dependence of structures on each other, ie, their connectivity, is

incompletely understood and not possible to delineate. As more knowledge accumulates, the CNS maturation and age-specific vulnerability of structures may become better understood and be incorporated in RT planning (see "Anatomy and Developmental Dynamics").

Review of Dose-Volume Response Data and Risk Factors

Methodology

Comprehensive literature search criteria terms were developed to locate all studies that evaluated radiation dose-volume effects on the risk of the neurocognitive toxicities, brain/brain stem necrosis, subacute somnolence syndrome, chronic headache, brain atrophy, and leukoencephalopathy among survivors of childhood cancer. This comprehensive review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[85] PubMed and Cochrane Library searches of peer-reviewed manuscripts written in English and published from January 1, 1995, to October 2, 2017, were conducted. Appendix A and B provide further details of the search strategy and data collection.

Twelve investigators independently reviewed titles and abstracts and, subsequently, full texts of any article that any reviewer considered potentially eligible. For eligible studies, the same investigators independently extracted the information on study design, source of data, population characteristics, and outcomes of interests using an electronic data extraction form. Eligibility assessment of the included studies, risk of bias assessment, and data extraction were performed independently and in duplicate. Studies were included if they had quantitative or adequate qualitative data describing neurocognitive or brain necrosis outcomes for patients younger than age 21 years that constituted at least 50% of the study cohort. Outcomes were not limited to a specific follow-up duration. In addition, information about treated volumes (whole brain versus partial brain) and dose information as a group or individual (prescribed dose, fractionation) were required. Additional information, if available, for technique, dose distribution, and other therapies was recorded.

A total of 4028 unique references at title and abstract screening were identified. After review by task force members, 160 studies with potentially relevant information were selected: 108 IQ/PS, 51 necrosis, and 1 both endpoints. Of those, 43 studies with pertinent information were analyzed and are reported here: 31 IQ/PS, 11 necrosis, and 1 both endpoints. Figure 1 summarizes the selection and elimination process used to identify the eligible studies. The selected studies represent 2844 data sets (1817 and 1027 for IQ/PS and necrosis, respectively) from patients younger than age 21 at initial treatment. The prescribed doses ranged from 18 Gy to more than 60 Gy. Tables 1 and 2 summarize these studies.

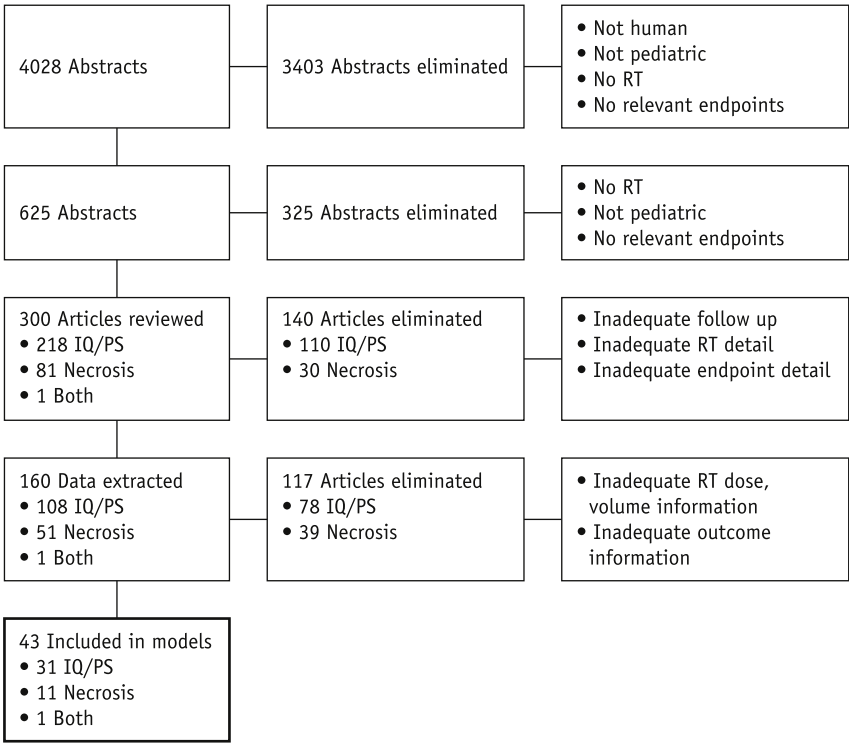

Fig. 1. Consort diagram summarizing process of selection and elimination of published data used in evaluation for this project. Of note, 1 paper was used for both cognitive and necrosis outcome analysis. *Abbreviations:* PS = processing speed; RT = radiation therapy.

Table 1 Data used for modeling risk of neurocognitive impairment

Author	Year	Patient no.	Dx	MTX (Y/N)	WB/ CS dose (Gy)	PF dose (Gy)	TB dose (Gy)	RT age (y)	Median FU (y)	FU IQ	Impairment incidence
Hertzberg[86]	1997	115	ALL	Y	11.3	-	-	5.8	9	99	0.16*
Anderson[87]	2000	35	ALL	Y	18	-	-	3	2	93	0.27*
									3	91	0.32*
Waber[88]	2001	61	ALL	Y	18	-	-	4.6	7	100	0.14*
Iuvone[30]	2002	21	ALL	Y	19.7	-	-	3.7	4.4	97	0.20*
Waber[89]	2004	71	ALL	Y	18	-	-	3.9	8.1	101	0.13*
		54				-	-	5	8.1	101	0.13*
Waber[90]	2007	39	ALL	Y	18	-	-	3	6	97	0.18*
Edelstein[91]	2011	12	ALL	Y	18	-	-	4.5	15.7	-	0.20
		12	ALL	Y	18	-	-	10.2	15.7	-	0.02
Krull[92]	2013	167	ALL	Y	18	-	-	6.6	24.9	-	0.0‡
		186				-	-	6.3	32.8	-	0.01‡
Kim[93]	2015	18	ALL	Y	18	-	-	4	6.5	102	0.17*
Kramer[94]	1997	25	BMT—TBI non-CNS tumors	N	11.58	-	-	3.8	1	97	0.23*
Schuitema[95]	2015	29	Lymphoid malignancy	Y	20.9	-	-	5.4	26.7	94	0.34*
		7		Y	25.5	-	-	7.2	24.3	104	0.16*
Jalali et al[13]	2010	28	LGG, benign	N	-	-	54	13	2	-	0.33
Greenberger[96]	2014	4	LGG	N	-	-	52.2	5.2	7.6	107	0.073*
		7		N	-	-	7	109	0.018*		
Vern-Gross[97]	2014	4	HGG	N	-	-	56.7	6.3	9.1	87	0.4†
Merchant[98]	2004	88	PF Epend	N	-	-	58.5	2.9	15	100	0‡
Merchant[99]	2005	49	PF Epend	N	-	-	59.0	2.8	14.7	96	0.23
Merchant[16]	2014	76	PF Epend	N	-	-	56.7	3.3	5	97	0.20*
Fouladi[100]	2003	17	Primary BT	N	-	-	52.2	7.9	6	86	0‡
Howarth[101]	2013	50	Primary BT	N	-	-	56.7	6.4	6.7	98	0.17*
Conklin[102]	2012	50	Primary BT	N	-	-	56.7	8.5	7.2	98	0*
Fouladi[103]	2005	14	Primary BT	N	-	-	54	3.1	7.6	-	0.23‡
		38		N	27.5+	-	51.9+	3.1	7.6	-	0.74‡
Pulsifer[104]	2015	60	Primary BT	N	10.9	-	53.0	12.3	2.5	104	0.06*
O'Neil[105]	2011	20	Germinoma	N	-	-	30	14.4	3	100§	0‡
Merchant[106]	2000	12	Germinoma	N	25.6	-	50.8	12	5.75	97	0.17†
Jakacki[107]	2004	38	MB	N	18	54	-	3.5	4.7	82	0.5‡
Moxon-Emre[108]	2014	27	MB	N	19.2	-	50.2	6.5	6.8	84	0.66*
		7		N	19.2	50.2	-	8.4	3.2	85	0.50*
		19	N		29.4	36	55.8	7.5	3.26	92	0.05*
		49		N	35	-	50.2	7.3	7.28	83	0.85*
Camara-Costa[109]	2015	66	MB	N	23.4	54	-	9.5	5.4	86	0.47*
		71		N	36	52	60	9.1	5.2	90	0.39*

(*Continued*)

Table 1 (*Continued*)

Author	Year	Patient no.	Dx	MTX (Y/N)	WB/ CS dose (Gy)	PF dose (Gy)	TB dose (Gy)	RT age (y)	Median FU (y)	FU IQ	Impairment incidence
Mulhern et al[110]	1998	5	MB	N	23.4	54	-	6.3	7	84◇	0.4*
		4		N	23.4	54	-	14.3	9	92◇	0.25*
		6		N	36	54	-	5.8	10	74◇	0.83*
		7		N	36	54	-	11.6	9	87◇	0.57*
Wahba[111]	2013	28	MB	N	24	54.6	-	5.5	5	87.6	0.45*
Christopherson[112]	2014	39	MB	N	28.8	54	-	7.1	15.4	_	0.49‡
Merchant[113]	2014	58	MB	N	29.4	36	55.8	8.1	5	89	0.39‖
Dufour[114]	2014	24	MB/PNET	N	31.9	-	53.8	8.9	4.4	81	0.62*

All data are average values in the patient population as reported in each study or calculated from the reported data.

Abbreviations: ALL = acute lymphoblastic leukemia; BMT = bone marrow transplant; LGG = low grade glioma, BT = brain tumor; CS = average prescribed dose craniospinal; Dx = diagnosis; Epend = posterior fossa ependymoma; FU = follow-up; HGG = high-grade glioma; MB = medulloblastoma; MTX = methotrexate; MTX Y/N = all/none patients had MTX; PF = posterior fossa; PNET = primitive neuro-ectodermal tumor; TB = average prescribed tumor bed dose; TBI = total body irradiation; WB = average prescribed dose whole brain.

* Estimated as risk for IQ <85 calculated from average and standard error of IQ + weighted average in patient cohort ‖interpolated from reported TD50 and TD5 for IQ <85 †calculated from table data in each paper. §Assumed normal IQ (= 100 ± 15), as no cognitive impairment was found in the study. Studies ordered by clinical indication for radiation therapy and year of publication.

‡ Incidence of neurocognitive impairment as reported in the study.

Table 2 Data used for modeling the risk of necrosis

Author	Pub year	Patient no.	Dx	Nec Dx primary method	Grading system	Avg D (Gy)	Med age at Dx /RT (y)	Med FU (y)	% Surgery	% Chemo	ReRT	PRT	No. Nec and Sx (%)
Merchant[118]	2009	153	PF Epend	MRI clinical	None	54	2.9	5.3	100%	23%	N	N	3 (2.5%)
Murphy[119]	2012	236	MB	MRI	None	55.8	3-21	4.3	100%	100%	N	N	7 (3%)
Christopherson[112]	2014	39	MB	Medical record	CTCAE 4.0	54	7.1	15.4	100%	40%	N	N	2 (5.1%)
Plimpton[82]	2015	101	Primary BT	MRI clinical	None	56.2	9.3	1.1	NM	74%	N	N	4 (4%)
Benk[120]	1995	18	Chordoma	CT	None	69	13	6	100%	NM	N	Y	1 (5%)
Indelicato[121]	2014	313	Primary BT, BOS	MRI clinical	CTCAE 4.0	54	5.9	2	100%	50 %	N	Y	10 (3.8%)
McGovern[51]	2014	31	AT/RT	MRI	RTOG	52	1.6	2	100%	100%	N	Y	5 (16%)
Mizumoto[122]	2015	6	PF Epend	MRI clinical	RTOG	54.7	5	2	100%	100%	N	Y	0 (0%)
Kralik[123]	2015	52	Primary BT	MRI clinical	CTCAE 4.0	59.4	7.2	1.5	“	69%	N	Y	4 (7.7%)
Bauman[124]	1996	34	Primary BT	CT/MRI clinical	None	79.7	19.8	0.7 survival	32%	35% pre-RT 44% post-RT	Y	N	3 (8.3%)
Russo[125]	1999	21	PNET	MRI	None	72	14	3.3	100%	58%	Y	N	1 (4.8%)
Waxweiler[129]	2017	23	Rec BT	MRI clinical	Not defined	102	1-24	12.8	61%	78%	Y	N	5/28 lesions (18%)

Abbreviations: AT/RT = atypical teratoid/rhabdoid tumor; Avg D = average prescribed dose; BOS = base of skull; BT = brain tumor; Clin = clinical evaluation; CTCAE = Common Terminology Criteria for Adverse Events; Dx = diagnosis; FU = follow-up; Nec = necrosis; MB = medulloblastoma; MRI = magnetic resonance imaging; N = no; PF Epend = posterior fossa ependymoma; PNET = primitive neuro-ectodermal tumor; PRT = proton RT; ReRT = reirradiation; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; Sx = symptoms; Y = yes.

Review of dose-volume data

Mathematical models

Neurocognitive effects. Models for the following 2 post-RT neurocognitive outcomes were developed: (1) the risk for a below-average IQ (IQ <85), and (2) to predict the expected IQ value. To estimate the risk for a below-average IQ, the incidence of neurocognitive impairment at last follow-up, commonly manifested as below-average IQ and/or working memory (<85 or 2 standard deviations from the mean), or a history of special education service, as a surrogate for below-average IQ, was extracted from each selected study (see Table 1).[13,16,30,86-114] For those studies lacking reports of complication rates in comparison to a normal population, rates were calculated as percentage of patients with IQ <85, estimated from IQ and its standard deviation, assuming normal distribution of values of IQ. Prescribed doses were converted into equivalent dose with 2 Gy per fraction (EQD2), previously termed normalized total dose (NTD) using the LQ model and an α/β ratio of 3 Gy, to compare studies with different doses per fraction.

The reported incidences of neurocognitive effects were fitted using a model including dose, dose per fraction, irradiated volume, and administration of MTX. These variables were preferred because they have been correlated with neurocognitive effects in many studies.[13,99,108,110] In addition, these variables were the most consistently reported in the selected studies (Table 1). Attempts were made to also include the time post-RT and age at RT that are thought to be pertinent factors.[13,92,99,104] The model, however, did not converge to a solution when it included more than 4 variables, and therefore the model included only the most consistently reported and relevant variables of dose, irradiated volume, age at RT, and MTX. In addition, due to the limitations of the reported data as previously noted, incorporation of other important factors including prior surgery or location of tumor was not possible, which is a potentially significant limitation due to the strong effects of either of these factors.

The Lyman-Kutcher-Burman (LKB) model with generalized equivalent uniform dose[115] (gEUD) was used to analyze neurocognitive outcome risks. In gEUD, the volume parameter, *a,* describes the volume effect of the irradiated organ or tissue. Serial organs (low effect of irradiated volume) have large *a* values for the volume effect parameter (approximating maximum dose effect), and parallel organs have a value close to 1 (approximating mean dose). $gEUD_{50}$ is the gEUD that produces a probability of the endpoint of 50%, and *m* is the slope of the dose response curve. The gEUD was calculated categorizing (with assumptions) the fraction of the whole brain that received the prescribed dose using the following: 1 with whole brain/craniospinal treatments; 1/4 with posterior cranial fossa treatment; and 1/8 with tumor bed treatment. It was also assumed that each of these target volumes received a homogeneous distribution of the prescribed dose. Age dependence was studied by separately fitting the data with median age at diagnosis older and younger than age 5 years. Confidence intervals for the parameters of the NTCP models were determined using the Jacobian matrix of the delta method (Fig. 2).[116]

The results demonstrate that RT is associated with the risk of neurocognitive impairment (ie, IQ <85) in a dose-, volume-, and MTX-dependent manner (Figs. 2 and 3).

Estimating the IQ after RT at a long follow-up time is

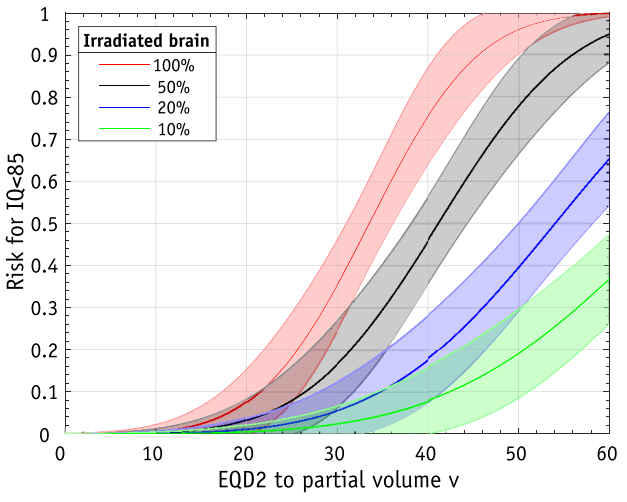

Fig. 2. Risk of IQ <85 for different volumes of the brain irradiated as determined from the model for normal tissue complication probability of neurocognitive impairment. *Abbreviations:* EQD2 = equivalent dose with 2 Gy per fraction; volume v = volume of irradiated brain.

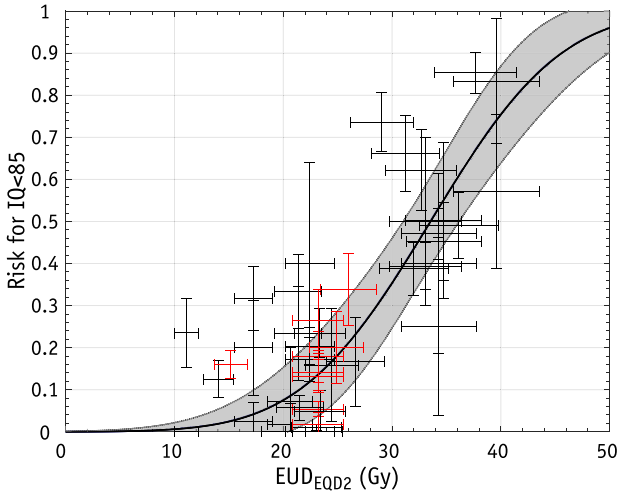

Fig. 3. Risk of IQ <85 for children irradiated described using normal tissue complication probability models with 95% confidence intervals (*dashed lines*) and incidence of neurocognitive impairment reported in studies used for fitting (Table 1). The data points of studies in which patients also received methotrexate (MTX) are shown in red. *Abbreviation:* EUD = equivalent uniform dose; EQD2 = equivalent dose with 2 Gy per fraction.

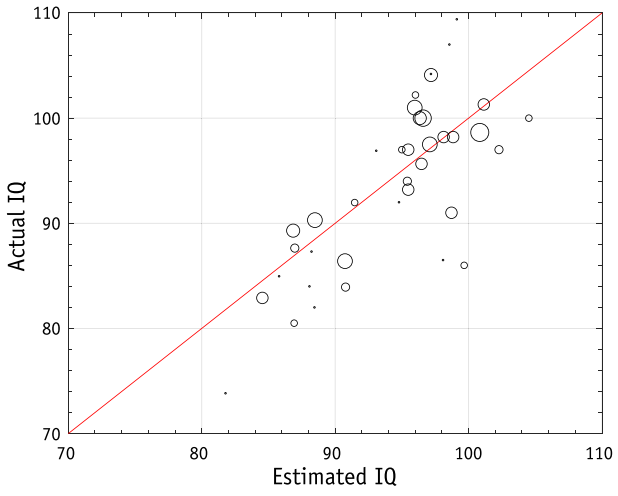

Fig. 4. Calibration of model (see Equation 1) to estimate predicted IQ from the prescribed dose to the craniospinal irradiation or whole brain, prescribed dose to the tumor bed or posterior fossa, methotrexate, and age at radiation therapy. The IQ predicted by the model is depicted versus IQ in the studies in Table 1. Marker sizes are proportional to patient number in the study.

described using the formula:

$$IQ(WBD, MTX, FD, A) = 108.15 - (WBD + MTX) \times (0.61593 - 0.02328 \times Age) - FD \times (0.22357 - 0.0061758 \times Age)$$

Where:

- WBD is the prescribed dose to the CSI or whole brain, in Gy, at 2 Gy per fraction.
- MTX is 5.9 Gy if the patient received MTX, zero otherwise (see subsequent explanation regarding how this value was derived)
- FD accounts for irradiation to the posterior fossa or tumor bed: it is zero if no focal dose is administered; otherwise, it is the sum of all the prescribed doses to the tumor bed or posterior fossa, including whole brain dose if there is a boost dose after whole brain irradiation
- Age represents age at RT (years).

The prediction model for a nominal IQ after irradiation in children is dependent on dose, volume, age, and MTX (Fig. 4). It was not possible to incorporate time after RT in this model. Nomograms (Figs. 5A, 5B) based on this model predict IQ (y-axis-1) or reduction in IQ (y-axis-2) compared with unirradiated cohorts and probably apply only to patients who have a baseline IQ in the range of 85 to 115. The differential effect of whole brain and partial brain RT with their dependence on RT dose and age at RT with and without MTX is demonstrated through the varying slopes.

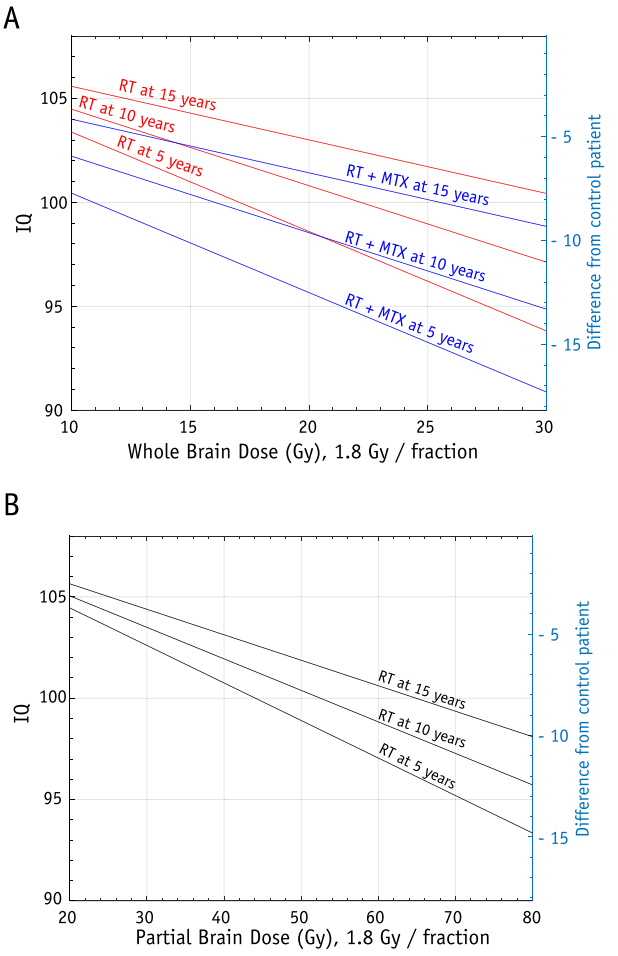

Fig. 5. Nomograms to predict IQ (y-axis-1) and decrease from baseline IQ (y-axis-2) for patients receiving radiation therapy (RT) at 5, 10, or 15 years of age after: (A) Whole brain RT with and without methotrexate (MTX). (B) Partial brain RT, ie, treatment of either the posterior fossa or tumor bed.

Effect of chemotherapy on neurocognition. The lack of direct comparisons of chemoradiotherapy and RT alone and the inability to separate various tumor types or surgical extent make it difficult to estimate the effect of individual therapeutic interventions, including chemotherapy. We analyzed the effect of MTX on RT dose because the total risk of damage from chemotherapy and RT can be modeled as a summed effect.[117] By fitting the model for IQ <85 we derived that MTX produces the same decline in IQ as adding gEUD of 5.9 Gy, which is equivalent to whole brain irradiation of 5.9 Gy (Table 3).

Risk factors

As noted in "Anatomy and Developmental Dynamics," neurocognitive injury is affected by the tumor itself and other therapeutic interventions, such as surgery. Systemic or

Table 3 Parameters of NTCP models for different endpoints with 95% confidence intervals

Best-fitting parameters (95% confidence interval)			
Endpoint	**Neurocognitive impairment, IQ <85**	**Necrosis primary RT**	**Necrosis reirradiation**
Dose corresponding to 50% risk	$gEUD_{50}$ = 33.5 (31.1 - 36.0) Gy	$EQD2_{50}$ = 108.9 (62.0-155.7) Gy	$EQD2_{50}$ = 149.9 (128.8-171.1) Gy
Slope of dose response	m = 0.28 (0.18-0.38)	0.27 (0.15-0.40)	0.35 (0.31-0.39)
Volume parameter, a	a = 3.39 (2.63-4.76)	N/A	N/A
MTX effect (Gy)	gEUD = 5.9 Gy (0.5-11.3) Gy	N/A	N/A

intrathecal chemotherapies given concurrently or sequentially can independently contribute to CNS toxicity and can compound the effects of radiation. Other clinical events such as hydrocephalus, postsurgical cerebellar mutism, stroke, seizure, and visual or auditory deficiencies can also contribute to cognitive decline in childhood brain tumors survivors.[18,33-37]

Necrosis

The incidence of necrosis, reported as imaging changes with or without clinical symptoms, in the absence of tumor progression, was extracted from each selected study (see Table 2).[51,82,118-126] The risk for symptomatic necrosis was modeled using the LKB model of normal tissue complication probability (NTCP), after converting doses into their EQD2 assuming a generic α/β = 3 Gy.[127,128] The model fitting was done using a weighted least squares method, with weighting of data sets according to the number of patients in the study as shown in Table 3. For studies on proton therapy, the prescribed dose was corrected for proton RBE (assumed at 1.1), if not already done so in the original study. Figure 6A depicts the risk of necrosis with escalating doses of RT from 1 RT course, ie, without reirradiation.

The analysis was also performed using studies that included patients treated with reirradiation. The estimated cumulative RT dose computed as a simple sum of EQD2 of prescribed doses was associated with risk of necrosis as shown in Figure 6B. Because the time interval between the primary RT and reirradiation was not consistently stated, it was not possible to include this parameter in the analysis; therefore, the contribution of radiation injury repair between radiation courses was not quantifiable, though it likely exists.

In the QUANTEC group review, adults at 5 years post-RT have an approximate 5% risk of necrosis after 72 Gy at 2 Gy per fraction delivered to any part of the brain.[83,129] In contrast, children receiving 72 Gy to the brain, including reirradiation as a cumulative dose with the assumption of an appropriate interval between courses, have an 8.4% (95% CI 5.5%-11.3%) risk of necrosis according to the models derived here. These results suggest that pediatric patients

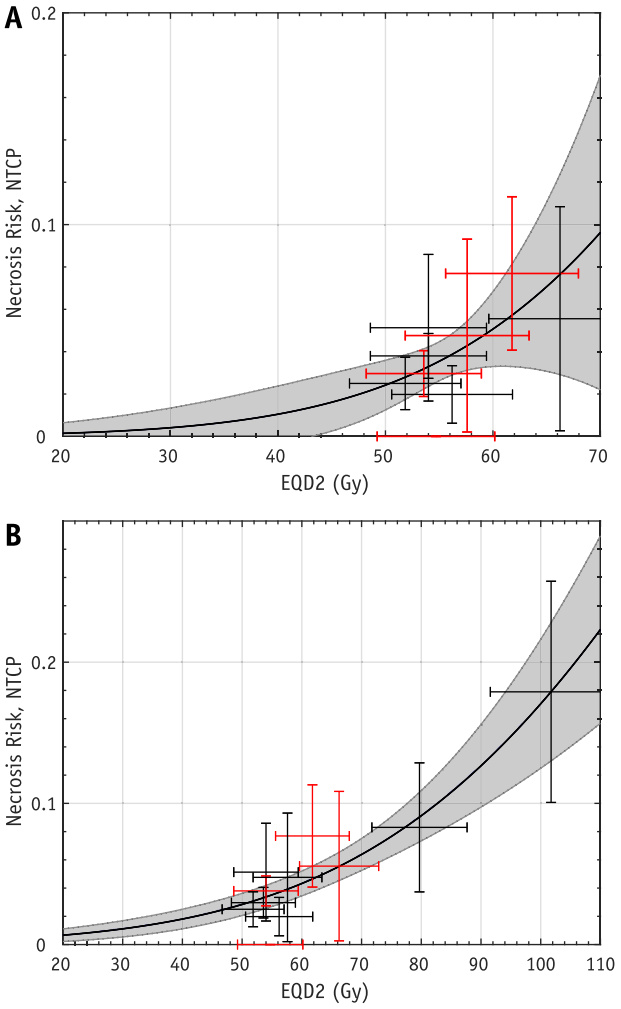

Fig. 6. Normal tissue complication probability (NTCP) model for necrosis (*solid line*) without (A) and with (B) retreatment studies with dose noted as a cumulative dose from all treatment courses assuming a sufficient time between courses. Dashed lines indicate 95% confidence intervals on NTCP. Markers indicate rates of necrosis from clinical studies (see Table 2) used in analysis. The data point of studies that included proton therapy are shown in red. *Abbreviation:* EQD2 = equivalent dose with 2 Gy per fraction.

Table 4 Doses corresponding to 5% risk for IQ <85 for different volumes of irradiated brain derived using the parameters in Table 3

% Brain irradiated	Doses* corresponding to a 5% risk of neurocognitive effects (Gy) with 95% CI
10	35.7 (27.0-47.1)
20	29.1 (22.0-38.4)
50	22.2 (16.8-29.3)
100	18.1 (13.7-23.8)

* 2 Gy/fraction, without use of methotrexate.

are similar, or possibly slightly more sensitive, to RT-induced necrosis than adults.[82]

Dose-Volume/Outcome Associations

Dose-volume recommendations

Neurocognitive function

Dose levels at 2 Gy per fraction associated with a 5% risk for neurocognitive impairment (IQ <85) were derived using NTCP models for 10%, 20%, 50%, and 100% volume of the brain irradiated (Figs. 2A, 2B and Table 4. Younger age, MTX, whole brain RT, and higher dose independently affect predicted IQ (Figs. 5A, 5B).

Brain necrosis

Our analysis suggests children receiving a cumulative RT dose of 59.8 Gy or 63.6 Gy at 2 Gy per fraction to any part of the brain, including the brain stem, as primary RT or reirradiation, respectively, have an approximate 5% risk of necrosis (Fig. 6).

Limitations

The most consistently reported variables in the selected studies were included in this analysis. A summary of the quality of data and risk of biases of the selected papers are noted in Appendix C. Baseline testing for preexisting neurocognitive problems was not uniformly reported and generally will affect interpretation of subsequent tests. Neurocognitive outcome assessment was limited to conventionally fractionated RT schema, and these results may not be applicable to children who receive alternative RT dose fractionation schedules. The necrosis outcome evaluation was limited to prescribed dose owing to the dearth of target volume data. This analysis may not be applicable to very small or large treatment volumes.

The task force medical physicist performed a dose accuracy evaluation for each investigation analyzed for dose-response modeling that included a categorization of the reported doses as well as an estimate, when possible, of the accuracy of those doses (Appendix D, E, and F). The uncertainty score for each report also assessed the accuracy of the assumption of 1/4 or 1/8 brain irradiation for those patients receiving less than whole brain. Most investigations reported prescribed dose rather than organ of interest dose. The prescribed dose for whole brain radiation using 2 opposing fields may underestimate actual brain dose owing to dose heterogeneity. Large areas of the brain may receive 5% to 10% more than the prescribed dose, which results in an up to 6% underestimation of gEUD.

In focal treatments, we assumed a simple dose distribution in which the target volume receives 100% dose and the low/intermediate doses out of the treatment volume were not considered. Because of these approximations, the gEUD is underestimated by a maximum of 14% in the worst case of all the out-of-target brain receiving 50% of prescribed dose from scatter, penumbra, and exit dose.

Dose binning was uncommon in CNS publications. However, for some publications outcomes were binned according to different treated sites (eg, boost to the tumor bed vs boost to posterior fossa) or doses (eg presence or not of boost after CSI). Our dose-response model uses average prescribed doses in each cohort when available or the midpoint of prescribed doses in each cohort.

Caveats

Despite the known risks associated with radiation to the brain in the management of childhood brain tumors, RT remains an essential component in the definitive management of the majority of cases. When treating this vulnerable population, potential morbidities should be considered and discussed with the family and the treating team. Patients will benefit from monitoring and early detection for rehabilitation and educational accommodations to mitigate some of the known risks.

Toxicity Scoring Recommendations

The following methods for toxicity scoring are recommended:

- CTCAE version 5.0 criteria for scoring toxicity for brain necrosis, cognitive deficits, somnolence, and headache based on imaging and clinical symptoms
- CTCAE version 5.0 criteria for leukoencephalopathy based on MRI imaging
- Formal neurocognitive testing:
  1. Overall cognitive ability (IQ), as measured by the age-appropriate Wechsler Intelligence Scale, which comprises verbal and nonverbal cognitive abilities and represents these as separate cognitive factors
  2. Cognitive speed and efficiency of task performance, as that measured by the age-appropriate Wechsler Processing Speed Index

3. Working memory, which is the short-term storage and manipulation of information, such as measured by the age-appropriate Wechsler Working Memory Index
4. Testing should be performed ideally before, or very soon after, the start of RT. Subsequent testing should be performed every year or 2 at the clinician's discretion.

Data Reporting Standards Specific to the Brain

Systematic dosimetric analyses based on published data on brain injury are limited for several reasons, for example: (1) minimal radiation dose and/or volume information, (2) neurocognitive testing is not performed uniformly, and (3) pooling of incomplete data from combined large inhomogeneous patient cohorts. Consequently, it is vital that published data sets conform to rigorous reporting standards to facilitate data pooling. Thus, we propose reporting the following information in future studies:

- Patient sex and race
- Pre-existing medical diagnoses, genetic syndromes, learning disabilities, intellectual developmental disorders, or delay
- Clinical indication for RT (ie, cancer diagnosis)
- Age when treated with RT
- Attained age at last follow-up
- Prescribed RT dose and dose fractionation
- RT technique and modality (ie, photon-based 2-dimensional, 3-dimensional, IMRT, or volumetric-modulated arc therapy (VMAT), tomotherapy, etc; proton therapy —passive scatter, spot scanning, IMPT)
- Dosimetric data for patients with and without toxicity:

1. Organ radiation exposure, described by relevant normal organ DVHs with 0.1 Gy dose resolution. Include brain substructures such as the hippocampi, temporal lobes, supratentorial brain, brain stem, and other functional subunits.
2. Other metrics that were used in the modeling for this report also should be included such as:

- Mean dose
- Volume of whole brain receiving >10, 20, 30, 50, and 60 Gy
- Chemotherapy, immunotherapy, or steroid use (if yes, timing with respect to radiation therapy and agents used)
- Neurosurgical interventions: type/location and date(s) of surgery. Postoperative complications: yes/no, dates, symptoms and grade
- Frequency of clinical follow-up including laboratory and imaging follow-up for late complications using long-term follow-up guidelines such as COG Long-Term Follow-Up Guidelines (http://www.survivorshipguidelines.org)
- Number of patients in the study and the number of those with or without toxicity.

1. Toxicity endpoint, yes/no
2. Description of the toxicity endpoint including how it is measured
3. Description of which toxicity scoring system was used.
4. Grade or severity of endpoint in patients
5. Timing of toxicity onset and resolution.

Future Investigations

Additional studies are needed to better understand the following:

1. Predictors of toxicity for the endpoints of subacute somnolence syndrome, chronic headache, brain atrophy, and leukoencephalopathy
2. Associations between the various neurocognitive dimensions that comprise a patient's functional cognitive performance
3. Standardization of follow-up evaluations and optimal timing of regular surveillance to have consistent objective measurements to facilitate understanding of RT-related toxicities and better opportunities for interventions
4. The impact of post-RT time interval on different neurocognitive domains and whether abnormalities plateau, continue to increase, or recover
5. The impact of area(s) of the brain irradiated (eg, laterality, hippocampal doses) and patient-specific genetic susceptibility on toxicity
6. Evaluation of association of chemotherapy, vascular injury, fractionation, and irradiated volume with risk of radionecrosis
7. The impact of the tumor type and surgery on toxicity
8. Influence of pre-RT cognitive status on post-RT dose-volume effects

References

1. Briere ME, Scott JG, McNall-Knapp RY, et al. Cognitive outcome in pediatric brain tumor survivors: Delayed attention deficit at long-term follow-up. *Pediatr Blood Cancer* 2008;50:337-340.
2. 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;13:536-545.
3. Mabbott DJ, Spiegler BJ, Greenberg ML, et al. Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *J Clin Oncol* 2005;23:2256-2263.
4. Mulhern RK, Merchant TE, Gajjar A, et al. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol* 2004;5:399-408.
5. Palmer SL, Reddick WE, Gajjar A. Understanding the cognitive impact on children who are treated for medulloblastoma. *J Pediatr Psychol* 2007;32:1040-1049.

6. Brinkman TM, Palmer SL, Chen S, et al. Parent-reported social outcomes after treatment for pediatric embryonal tumors: A prospective longitudinal study. *J Clin Oncol* 2012;30:4134-4140.
7. Moyer KH, Willard VW, Gross AM, et al. The impact of attention on social functioning in survivors of pediatric acute lymphoblastic leukemia and brain tumors. *Pediatr Blood Cancer* 2012;59:1290-1295.
8. Janson C, Leisenring W, Cox C, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: A report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev* 2009;18:2626-2635.
9. Kunin-Batson A, Kadan-Lottick N, Zhu L, et al. Predictors of independent living status in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer* 2011;57:1197-1203.
10. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer* 2003;97:1115-1126.
11. Roddy E, Mueller S. Late effects of treatment of pediatric central nervous system tumors. *J Child Neurol* 2016;31:237-254.
12. Carrie C, Grill J, Figarella-Branger D, et al. Online quality control, hyperfractionated radiotherapy alone and reduced boost volume for standard risk medulloblastoma: Long-term results of MSFOP 98. *J Clin Oncol* 2009;27:1879-1883.
13. Jalali R, Mallick I, Dutta D, et al. Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;77:974-979.
14. Fuss M, Poljanc K, Hug EB. Full scale IQ (FSIQ) changes in children treated with whole brain and partial brain irradiation. A review and analysis. *Strahlenther Onkol* 2000;176:573-581.
15. Silber JH, Radcliffe J, Peckham V, et al. Whole-brain irradiation and decline in intelligence: The influence of dose and age on IQ score. *J Clin Oncol* 1992;10:1390-1396.
16. Merchant TE, Schreiber JE, Wu S, et al. Critical combinations of radiation dose and volume predict intelligence quotient and academic achievement scores after craniospinal irradiation in children with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2014;90:554-561.
17. Brinkman TM, Reddick WE, Luxton J, et al. Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma. *Neuro Oncol* 2012;14(Suppl 4):iv25-iv36.
18. Di Pinto M, Conklin HM, Li C, et al. Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma. *Int J Radiat Oncol Biol Phys* 2012;84:e363-e369.
19. Ris MD, Packer R, Goldwein J, et al. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: A Children's Cancer Group study. *J Clin Oncol* 2001;19:3470-3476.
20. 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;34:1043-1049.
21. 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;124:89-97.
22. Roth AK, Ris MD, Orobio J, et al. Cognitive mediators of adaptive functioning outcomes in survivors of pediatric brain tumors treated with proton radiotherapy. *Pediatr Blood Cancer* 2020;67 e28064.
23. Kahalley LS, Peterson R, Ris MD, et al. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *J Clin Oncol* 2020;38:454-461.
24. Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. *J Clin Oncol* 2001;19:2302-2308.
25. Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Med Pediatr Oncol* 2003;40:26-34.
26. Jacola LM, Ashford JM, Reddick WE, et al. The relationship between working memory and cerebral white matter volume in survivors of childhood brain tumors treated with conformal radiation therapy. *J Neurooncol* 2014;119:197-205.
27. Reddick WE, White HA, Glass JO, et al. Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. *Cancer* 2003;97:2512-2519.
28. Moore 3rd. BD. Neurocognitive outcomes in survivors of childhood cancer. *J Pediatr Psychol* 2005;30:51-63.
29. Ater JL, Moore 3rd BD, Francis DJ, et al. Correlation of medical and neurosurgical events with neuropsychological status in children at diagnosis of astrocytoma: Utilization of a neurological severity score. *J Child Neurol* 1996;11:462-469.
30. Iuvone L, Mariotti P, Colosimo C, et al. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. *Cancer* 2002;95:2562-2570.
31. Iyer NS, Balsamo LM, Bracken MB, et al. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: A review and meta-analysis. *Blood* 2015;126:346-353.
32. Bull KS, Spoudeas HA, Yadegarfar G, et al. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: A follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). *J Clin Oncol* 2007;25:4239-4245.
33. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol* 2011;13:223-234.
34. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: A report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2006;24:5277-5282.
35. Nassar SL, Conklin HM, Zhou Y, et al. Neurocognitive outcomes among children who experienced seizures during treatment for acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2017;64. https://doi.org/10.1002/pbc.26436.
36. Orgel E, O'Neil SH, Kayser K, et al. Effect of sensorineural hearing loss on neurocognitive functioning in pediatric brain tumor survivors. *Pediatr Blood Cancer* 2016;63:527-534.
37. Ris MD, Walsh K, Wallace D, et al. Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. *Pediatr Blood Cancer* 2013;60:1350-1357.
38. Drezner N, Hardy KK, Wells E, et al. Treatment of pediatric cerebral radiation necrosis: A systematic review. *J Neurooncol* 2016;130:141-148.
39. Harjani RR, Gururajachar JM, Krishnaswamy U. Comprehensive assessment of somnolence syndrome in patients undergoing radiation to the brain. *Rep Pract Oncol Radiother* 2016;21:560-566.
40. Ryan J. Radiation somnolence syndrome. *J Pediatr Oncol Nurs* 2000;17:50-53.
41. Kelsey CR, Marks LB. Somnolence syndrome after focal radiation therapy to the pineal region: Case report and review of the literature. *J Neurooncol* 2006;78:153-156.
42. Tanguturi SK, Alexander BM. Neurologic complications of radiation therapy. *Neurol Clin* 2018;36:599-625.
43. Ailion AS, King TZ, Wang L, et al. Cerebellar atrophy in adult survivors of childhood cerebellar tumor. *J Int Neuropsychol Soc* 2016;22:501-511.
44. Sison EA, Silverman LB. CNS prophylaxis in pediatric acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2014;2014:198-201.
45. Wilejto M, Di Giuseppe G, Hitzler J, et al. Treatment of young children with CNS-positive acute lymphoblastic leukemia without cranial radiotherapy. *Pediatr Blood Cancer* 2015;62:1881-1885.
46. Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. *J Clin Oncol* 1996;14:911-918.

47. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol* 2006;24:4202-4208.
48. Massimino M, Biassoni V, Gandola L, et al. Childhood medulloblastoma. *Crit Rev Oncol Hematol* 2016;105:35-51.
49. Dhall G, O'Neil SH, Ji L, et al. Excellent outcome of young children with nodular desmoplastic medulloblastoma treated on "Head Start" III: A multi-institutional, prospective clinical trial. *Neuro Oncol* 2020;22:1862-1872.
50. Merchant TE, Bendel AE, Sabin ND, et al. Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. *J Clin Oncol* 2019;37:974-983.
51. McGovern SL, Okcu MF, Munsell MF, et al. Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system. *Int J Radiat Oncol Biol Phys* 2014;90:1143-1152.
52. Isikay I, Hanalioglu S, Basar I, et al. Survival benefit with gross total resection and adjuvant radiotherapy in childhood atypical teratoid/rhabdoid tumors: Results of a single-center cohort of 27 cases. *Turk Neurosurg* 2019;29:689-697.
53. Tsang DS, Burghen E, Klimo Jr. P, et al. Outcomes after reirradiation for recurrent pediatric intracranial ependymoma. *Int J Radiat Oncol Biol Phys* 2018;100:507-515.
54. Farnia B, Philip N, Georges RH, et al. Reirradiation of recurrent pediatric brain tumors after initial proton therapy. *Int J Part Ther* 2016;3:1-12.
55. Regnier E, Laprie A, Ducassou A, et al. Re-irradiation of locally recurrent pediatric intracranial ependymoma: Experience of the French Society of Children's Cancer. *Radiother Oncol* 2019;132:1-7.
56. Lu VM, Welby JP, Mahajan A, et al. Reirradiation for diffuse intrinsic pontine glioma: A systematic review and meta-analysis. *Childs Nerv Syst* 2019;35:739-746.
57. Corn BW, Yousem DM, Scott CB, et al. White matter changes are correlated significantly with radiation dose. Observations from a randomized dose-escalation trial for malignant glioma (Radiation Therapy Oncology Group 83-02). *Cancer* 1994;74:2828-2835.
58. Huang RY, Wen PY. Response assessment in neuro-oncology criteria and clinical endpoints. *Magn Reson Imaging Clin N Am* 2016;24:705-718.
59. Stiles J, Jernigan TL. The basics of brain development. *Neuropsychol Rev* 2010;20:327-348.
60. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain* 2011;134(Pt 8):2197-2221.
61. Greene-Schloesser D, Robbins ME. Radiation-induced cognitive impairment—From bench to bedside. *Neuro Oncol* 2012;14(Suppl 4):iv37-iv44.
62. Michaelidesova A, Konirova J, Bartunek P, et al. Effects of radiation therapy on neural stem cells. *Genes (Basel)* 2019;10:640.
63. Gibson E, Monje M. Effect of cancer therapy on neural stem cells: Implications for cognitive function. *Curr Opin Oncol* 2012;24:672-678.
64. Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol* 2010;97:370-376.
65. Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res* 2004;162:39-47.
66. Redmond KJ, Mahone EM, Terezakis S, et al. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: A prospective study. *Neuro Oncol* 2013;15:360-369.
67. Riggs L, Bouffet E, Laughlin S, et al. Changes to memory structures in children treated for posterior fossa tumors. *J Int Neuropsychol Soc* 2014;20:168-180.
68. Khong PL, Kwong DL, Chan GC, et al. Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: A pilot study. *AJNR Am J Neuroradiol* 2003;24:734-740.
69. Reddick WE, Russell JM, Glass JO, et al. Subtle white matter volume differences in children treated for medulloblastoma with conventional or reduced dose craniospinal irradiation. *Magn Reson Imaging* 2000;18:787-793.
70. Rueckriegel SM, Driever PH, Blankenburg F, et al. Differences in supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging. *Int J Radiat Oncol Biol Phys* 2010;76:859-866.
71. Beaulieu C. The basis of anisotropic water diffusion in the nervous system—A technical review. *NMR Biomed* 2002;15:435-455.
72. Khong PL, Leung LH, Fung AS, et al. White matter anisotropy in post-treatment childhood cancer survivors: Preliminary evidence of association with neurocognitive function. *J Clin Oncol* 2006;24:884-890.
73. Mabbott DJ, Noseworthy MD, Bouffet E, et al. Diffusion tensor imaging of white matter after cranial radiation in children for medulloblastoma: Correlation with IQ. *Neuro Oncol* 2006;8:244-252.
74. Qiu D, Kwong DL, Chan GC, et al. Diffusion tensor magnetic resonance imaging finding of discrepant fractional anisotropy between the frontal and parietal lobes after whole-brain irradiation in childhood medulloblastoma survivors: Reflection of regional white matter radiosensitivity? *Int J Radiat Oncol Biol Phys* 2007;69:846-851.
75. Aukema EJ, Caan MW, Oudhuis N, et al. White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. *Int J Radiat Oncol Biol Phys* 2009;74:837-843.
76. Palmer SL, Glass JO, Li Y, et al. White matter integrity is associated with cognitive processing in patients treated for a posterior fossa brain tumor. *Neuro Oncol* 2012;14:1185-1193.
77. Bunge SA, Wright SB. Neurodevelopmental changes in working memory and cognitive control. *Curr Opin Neurobiol* 2007;17:243-250.
78. Klingberg T, Vaidya CJ, Gabrieli JD, et al. Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. *Neuroreport* 1999;10:2817-2821.
79. Nagy Z, Westerberg H, Klingberg T. Maturation of white matter is associated with the development of cognitive functions during childhood. *J Cogn Neurosci* 2004;16:1227-1233.
80. Paus T, Zijdenbos A, Worsley K, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science* 1999;283:1908-1911.
81. Miyatake S, Nonoguchi N, Furuse M, et al. Pathophysiology, diagnosis, and treatment of radiation necrosis in the brain. *Neurol Med Chir (Tokyo)* 2015;55:50-59.
82. Plimpton SR, Stence N, Hemenway M, et al. Cerebral radiation necrosis in pediatric patients. *Pediatr Hematol Oncol* 2015;32:78-83.
83. Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 2010;76(Suppl 3):S20-S27.
84. Gondi V, Tolakanahalli R, Mehta MP, et al. Hippocampal-sparing whole-brain radiotherapy: A "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;78:1244-1252.
85. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009;6 e1000097.
86. Hertzberg H, Huk WJ, Ueberall MA, et al. CNS late effects after ALL therapy in childhood. Part I: Neuroradiological findings in long-term survivors of childhood ALL—An evaluation of the interferences between morphology and neuropsychological performance. The German Late Effects Working Group. *Med Pediatr Oncol* 1997;28:387-400.

87. Anderson VA, Godber T, Smibert E, et al. Cognitive and academic outcome following cranial irradiation and chemotherapy in children: A longitudinal study. *Br J Cancer* 2000;82:255-262.
88. Waber DP, Shapiro BL, Carpentieri SC, et al. Excellent therapeutic efficacy and minimal late neurotoxicity in children treated with 18 grays of cranial radiation therapy for high-risk acute lymphoblastic leukemia: A 7-year follow-up study of the Dana-Farber Cancer Institute Consortium Protocol 87-01. *Cancer* 2001;92:15-22.
89. Waber DP, Silverman LB, Catania L, et al. Outcomes of a randomized trial of hyperfractionated cranial radiation therapy for treatment of high-risk acute lymphoblastic leukemia: Therapeutic efficacy and neurotoxicity. *J Clin Oncol* 2004;22:2701-2707.
90. Waber DP, Turek J, Catania L, et al. Neuropsychological outcomes from a randomized trial of triple intrathecal chemotherapy compared with 18 Gy cranial radiation as CNS treatment in acute lymphoblastic leukemia: Findings from Dana-Farber Cancer Institute ALL Consortium Protocol 95-01. *J Clin Oncol* 2007;25:4914-4921.
91. Edelstein K, D'Agostino N, Bernstein LJ, et al. Long-term neurocognitive outcomes in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2011;33:450-458.
92. Krull KR, Brinkman TM, Li C, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St Jude lifetime cohort study. *J Clin Oncol* 2013;31:4407-4415.
93. Kim SJ, Park MH, Lee JW, et al. Neurocognitive outcome in survivors of childhood acute lymphoblastic leukemia: Experience at a tertiary care hospital in Korea. *J Korean Med Sci* 2015;30:463-469.
94. Kramer JH, Crittenden MR, DeSantes K, et al. Cognitive and adaptive behavior 1 and 3 years following bone marrow transplantation. *Bone Marrow Transplant* 1997;19:607-613.
95. Schuitema I, de Sonneville L, Kaspers G, et al. Executive dysfunction 25 years after treatment with cranial radiotherapy for pediatric lymphoid malignancies. *J Int Neuropsychol Soc* 2015;21:657-669.
96. 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;89:1060-1068.
97. Vern-Gross TZ, Schreiber JE, Broniscer A, et al. Prospective evaluation of local control and late effects of conformal radiation therapy in children, adolescents, and young adults with high-grade glioma. *Neuro Oncol* 2014;16:1652-1660.
98. Merchant TE, Mulhern RK, Krasin MJ, et al. Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. *J Clin Oncol* 2004;22:3156-3162.
99. Merchant TE, Kiehna EN, Li C, et al. Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with localized ependymoma. *Int J Radiat Oncol Biol Phys* 2005;63:1546-1554.
100. Fouladi M, Wallace D, Langston JW, et al. Survival and functional outcome of children with hypothalamic/chiasmatic tumors. *Cancer* 2003;97:1084-1092.
101. Howarth RA, Ashford JM, Merchant TE, et al. The utility of parent report in the assessment of working memory among childhood brain tumor survivors. *J Int Neuropsychol Soc* 2013;19:380-389.
102. Conklin HM, Ashford JM, Howarth RA, et al. Working memory performance among childhood brain tumor survivors. *J Int Neuropsychol Soc* 2012;18:996-1005.
103. Fouladi M, Gilger E, Kocak M, et al. Intellectual and functional outcome of children 3 years old or younger who have CNS malignancies. *J Clin Oncol* 2005;23:7152-7160.
104. Pulsifer MB, Sethi RV, Kuhlthau KA, et al. Early cognitive outcomes following proton radiation in pediatric patients with brain and central nervous system tumors. *Int J Radiat Oncol Biol Phys* 2015;93:400-407.
105. O'Neil S, Ji L, Buranahirun C, et al. Neurocognitive outcomes in pediatric and adolescent patients with central nervous system germinoma treated with a strategy of chemotherapy followed by reduced-dose and volume irradiation. *Pediatr Blood Cancer* 2011;57:669-673.
106. Merchant TE, Sherwood SH, Mulhern RK, et al. CNS germinoma: Disease control and long-term functional outcome for 12 children treated with craniospinal irradiation. *Int J Radiat Oncol Biol Phys* 2000;46:1171-1176.
107. Jakacki RI, Feldman H, Jamison C, et al. A pilot study of preirradiation chemotherapy and 1800 cGy craniospinal irradiation in young children with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004;60:531-536.
108. Moxon-Emre I, Bouffet E, Taylor MD, et al. Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. *J Clin Oncol* 2014;32:1760-1768.
109. Camara-Costa H, Resch A, Kieffer V, et al. Neuropsychological outcome of children treated for standard risk medulloblastoma in the PNET4 European randomized controlled trial of hyperfractionated versus standard radiation therapy and maintenance chemotherapy. *Int J Radiat Oncol Biol Phys* 2015;92:978-985.
110. Mulhern RK, Kepner JL, Thomas PR, et al. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: A Pediatric Oncology Group study. *J Clin Oncol* 1998;16:1723-1728.
111. Wahba HA, Abu-Hegazy M, Wasel Y, et al. Adjuvant chemotherapy after reduced craniospinal irradiation dose in children with average-risk medulloblastoma: A 5-year follow-up study. *J BUON* 2013;18:425-429.
112. Christopherson KM, Rotondo RL, Bradley JA, et al. Late toxicity following craniospinal radiation for early-stage medulloblastoma. *Acta Oncol* 2014;53:471-480.
113. Merchant TE, Sharma S, Xiong X, et al. Effect of cerebellum radiation dosimetry on cognitive outcomes in children with infratentorial ependymoma. *Int J Radiat Oncol Biol Phys* 2014;90:547-553.
114. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermic tumors. *Pediatr Blood Cancer* 2014;61:1398-1402.
115. Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. *Med Phys* 1997;24:103-110.
116. Seber GAF, Wild CJ. *Estimation methods. Nonlinear Regression*. Hoboken, NJ: John Wiley & Sons; 2005:21-89.
117. Jones B, Dale RG. The potential for mathematical modelling in the assessment of the radiation dose equivalent of cytotoxic chemotherapy given concomitantly with radiotherapy. *Br J Radiol* 2005;78:939-944.
118. Merchant TE, Li C, Xiong X, et al. Conformal radiotherapy after surgery for paediatric ependymoma: A prospective study. *Lancet Oncol* 2009;10:258-266.
119. Murphy ES, Merchant TE, Wu S, et al. Necrosis after craniospinal irradiation: Results from a prospective series of children with central nervous system embryonal tumors. *Int J Radiat Oncol Biol Phys* 2012;83:e655-e660.
120. Benk V, Liebsch NJ, Munzenrider JE, et al. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. *Int J Radiat Oncol Biol Phys* 1995;31:577-581.
121. Indelicato DJ, Flampouri S, Rotondo RL, et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. *Acta Oncol* 2014;53:1298-1304.
122. Mizumoto M, Oshiro Y, Takizawa D, et al. Proton beam therapy for pediatric ependymoma. *Pediatr Int* 2015;57:567-571.
123. Kralik SF, Ho CY, Finke W, et al. Radiation necrosis in pediatric patients with brain tumors treated with proton radiotherapy. *AJNR Am J Neuroradiol* 2015;36:1572-1578.
124. Bauman GS, Sneed PK, Wara WM, et al. Reirradiation of primary CNS tumors. *Int J Radiat Oncol Biol Phys* 1996;36:433-441.

125. Russo C, Fischbein N, Grant E, et al. Late radiation injury following hyperfractionated craniospinal radiotherapy for primitive neuroectodermal tumor. *Int J Radiat Oncol Biol Phys* 1999; 44:85-90.
126. Waxweiler TV, Amini A, Vinogradskiy Y, et al. Hypofractionated re-irradiation to the brainstem in children with recurrent brain tumors. *Pediatr Blood Cancer* 2017;64.
127. Lyman JT. Complication probability as assessed from dose-volume histograms. *Radiat Res Suppl* 1985;8:S13-S19.
128. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys* 1982;8:1981-1997.
129. Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. *Int J Radiat Oncol Biol Phys* 2010;76(Suppl 3):S36-S41.