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Late effects in survivors of childhood CNS tumors treated on Head Start I and II protocols

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Abstract

Background—Due to the devastating late effects associated with cranial irradiation in young children with CNS tumors, treatment for these patients has evolved to include the use of intensive chemotherapy to either avoid or postpone irradiation. While survival outcomes have improved, late effects data in survivors treated on such regimens are needed.

Objective—This multi-institutional study comprehensively describes late effects in survivors treated on the Head Start I/II protocols.

Methods—Survivors of CNS tumors treated on Head Start I/II protocols were enrolled. Late effects data were collected using a validated parent-report questionnaire. Social, emotional, and behavioral functioning and quality of life were assessed using parent-report on the BASC-2 and CHQ-PF50 questionnaires.

Results—Twenty one survivors (medulloblastoma=13, sPNET=4, ATRT=1, ependymoma=3) were enrolled. Ten (48%) were irradiation-free. Late effects (frequency; median time of onset since diagnosis) included grade III hearing loss (67%; 3.9 years), vision (67%; 4.1 years), hypothyroidism (33%; 4 years), growth hormone (GH) deficiency (48%; 4.7 years) and dental (52%; 7.1 years) and no cases of secondary leukemia. Irradiation-free (versus irradiated) survivors reported low rates of hypothyroidism (0/10 vs 7/11; $p=0.004$) and GH deficiency (2/10 vs 8/11; $p=0.03$). The BASC-2 and CHQPF-50 mean composite scores were within average ranges relative to healthy comparison norms. Neither age at diagnosis nor irradiation were associated with these scores.

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CONFLICTS OF INTEREST: Nothing to declare

Conclusions—Irradiation-free Head Start survivors have lower risk of hypothyroidism and GH deficiency. Secondary leukemias are not reported. With extended follow up, survivors demonstrate quality of life, social, emotional, and behavioral functioning within average ranges.

Keywords

Head Start; CNS tumors; CNS tumor survivors; late effects; quality of life

INTRODUCTION

Central nervous system (CNS) tumors are the second most common malignancy of childhood with over 3,500 cases diagnosed each year in the US [1]. Despite being the biggest contributor to mortality from pediatric cancer, modern treatment approaches have resulted in >70% of children with CNS tumors becoming long-term survivors [2]. As of 2005, it is estimated that there are >50,000 survivors of pediatric CNS tumors in the US [3].

Survivors of pediatric CNS tumors are at risk for late effects. The Childhood Cancer Survivor Study (CCSS) and others have published reports characterizing a wide range of late effects in CNS tumor survivors [4–24]. Survivors may be inherently predisposed to late effects [25]; however, the primary diagnosis and treatment modalities are important determinants of specific outcomes. Irradiation and young age at diagnosis are two consistent risk factors for developing severe late effects in CNS tumor survivors.

In the past few decades, cooperative groups have explored irradiation sparing/delaying approaches to treat very young children with CNS tumors to avoid the devastating effects of irradiation [26–28]. Head Start (HS) I and II were two such protocols, open from 1991–97 and 1997–2003, respectively, that treated children with newly diagnosed CNS tumors with multiple cycles of induction chemotherapy consolidated by myeloablative chemotherapy and autologous stem cell transplantation (ASCT) [29–38]. Other studies have also used irradiation sparing/delaying approaches [26–28]. Building on these pioneering studies, the Children's Oncology Group (COG) is incorporating this approach into their current protocols (ACNS0333/0334).

Prior publications have reported on neuropsychological and psychosocial outcomes of patients treated on HS I/II. Sands et al. completed baseline (T1) and follow-up (T2, median follow-up: 2.7 years) neuropsychological testing with HS patients [35]. At T2, patient's mean performance was within the low average range for intelligence, academic achievement, receptive language and visual-motor integration, while social-emotional and behavioral functioning were within average ranges. There were no statistically significant changes in intelligence scores from T1-T2. Time since diagnosis was inversely associated with T2 Full Scale IQ scores. A follow-up study of psychosocial outcomes of HS I survivors at 5.7 years (T1) and 11.6 years (T2) post-treatment demonstrated that survivors were reported by parents to be within the average range for internalizing problems, externalizing problems and adaptive skills at both time points. At T1, the Parental Emotional Impact fell outside the average range, and at T2, survivors' General Health fell outside the average range. Auditory outcomes in survivors treated using similar protocols have been published [30,34–36,38–40]. However, late effects data regarding physical outcomes from other initial

irradiation sparing/delaying studies are sparse [26–38]. Current studies have focused on those treated with conventional treatments [4–24].

There is a need for late effects data in this unique and expanding cohort of survivors being treated with newer irradiation sparing/delaying approaches. Follow-up quality of life data to previous reports from the HS group are needed. The primary aim of this study was to characterize late effects in survivors of childhood CNS tumors treated on HS I and II protocols. This study is the first, to our knowledge, to report comprehensive late effects findings and extended long-term data on quality of life in a cohort of survivors treated on protocols that aimed to spare irradiation in very young patients with CNS tumors.

METHODS

Patients

Survivors were eligible to enroll if they met all criteria: 1. Diagnosis of malignant CNS tumor (embryonal, ependymal, choroid plexus tumors, per 2007 WHO Classification); 2. Enrolled and completed treatment on HS I/II protocols; 3. Off-treatment for primary diagnosis; 4. 5 years from primary diagnosis.

Tools

Late effects data were collected using a self or parent-report ‘patient questionnaire’ modeled after the CCSS. The responder was chosen as described below in the ‘Consent’ section. We obtained permission from Dr. Leslie Robison, Study Chair, CCSS, to use CCSS questionnaires for this study. The ‘original cohort’ baseline questionnaires for the survivors (<18 and 18 years of age) were used [41]. The format of the questions and page format were modified slightly (Appendix A).

Consistent with prior reports on HS survivors, two parent-report questionnaires assessed the social, emotional, and behavioral health and quality of life: Behavior Assessment System for Children, 2nd Edition (BASC-2) and Children’s Health Questionnaire, Parent Form (CHQ-PF50). The BASC-2 is a standardized, parent-report measure and assesses any at risk or clinically significant areas of concern regarding social, emotional and behavioral functioning in individuals <21 years old [42]. Data were evaluated using standardized, age adjusted T-scores [Mean (M)=50, Standard deviation (SD)=10]. For the clinical scales (Externalizing Problems, Internalizing Problems, and Behavioral Symptoms), a T-score of 41–59 is “average,” 60–69 is “at-risk,” and 70 is “clinically significant.” For the adaptive scales (Adaptability, Social Skills, Leadership, Activities of Daily Living, and Functional Communication), a T-score of 41–59 is “average,” 31–40 is considered “at-risk”, and 30 is “clinically significant.” The CHQ-PF50 is a parent-report, multidimensional measure of physical and psychosocial quality of life of children (5–18 years) [43]. Ten subscale scores are generated based on population norms (M=50; SD=10). Higher scores represent better functioning. Both measures are validated, used in medically ill populations and previously administered to HS survivors [35,36]. Three children were >18 years and not included in CHQ-PF50 analyses.

Consent

Parents of minors provided informed consent to complete the CCSS questionnaire. When appropriate, assent was obtained from the minor. Adult survivors provided consent and completed the questionnaire.

Involved institutions

Participating institutions included British Columbia Children's Hospital (Vancouver, Canada), Nationwide Children's Hospital (Columbus, Ohio) and New York University Langone Medical Center (New York, NY).

Regulatory issues

Institutional/FDA/NCI requirements for human studies were fulfilled. IRB approval was obtained at all institutions.

Statistical Methods

Data analysis was conducted after all data were collected. Late effect outcomes were recorded as dichotomous variables. In anticipation of a small study size, composite variables were used for aggregate assessments of each late effect. For example, a survivor with an ocular late effect could have strabismus, amblyopia, blindness, cataracts, glaucoma, double vision, etc. Timing of onset was recorded. The proportion of patients with each late effect was summarized for the entire cohort and presented separately as appearing within 5 years from diagnosis and after. To identify factors associated with late effects, we classified patients by irradiation treatment any time, age at diagnosis, extent of resection and tumor type. For each factor, we evaluated its association with late effects using 2-sided Fisher's exact test. These analyses are descriptive. Given the small sample size, non-parametric two-tailed Mann-Whitney U-tests were used to compare group differences in BASC-2 and CHQ-PF50 scores for children in relation to methotrexate and irradiation exposure.

RESULTS

Demographics

Among participating institutions, 22 eligible patients were identified. Twenty one patients enrolled and completed the study. Demographic characteristics are summarized in Table I. The median age at diagnosis was 1.7 years (range: 0.2–7 years; male: 15/21) and median age at time of study was 15.3 years (range: 11.4–22.5 years). Most were Caucasian (n=13, 62%). Primary diagnoses included medulloblastoma (n=13, 62%), sPNET (n=4, 19%), AT/RT (n=1, 5%) and ependymoma (n=3, 14%).

Treatment

Four patients were treated on HS I and 17 on HS II. The treatment schema is illustrated in Figure 1. All patients underwent surgical resection at diagnosis: 14 (67%) had gross total resection and 7 (33%) had partial resection. All patients underwent chemotherapy on their respective HS protocol. The cumulative doses and roadmap for the protocols have been described [46–54]. Six patients (29%) received high dose methotrexate during induction as

per protocol requirements. One patient (diagnosis: medulloblastoma) delayed treatment due to bacterial meningitis following induction and completed therapy on HS II. For the primary diagnosis, 6 patients received irradiation per protocol. Five additional survivors were irradiated for recurrence; 10 patients (48%) were irradiation-free survivors at the time of this study. Radiation fields and doses were varied and depended on the specific tumor; this has been previously described [46–54].

Late effects

Median time from diagnosis to follow up was 12.6 years (range: 9.6–20.8 years). The proportion of patients reporting various late effects outcomes are summarized in Table II.

Hearing, Ocular, Speech and Taste—Fourteen patients (percent of responders, median time of onset after diagnosis: 67%, 3.9 years) had grade III hearing loss (per CTCAE version 4; hearing loss requiring therapeutic intervention). Fourteen patients (67%, 4.1 years) reported ocular late effects (cataracts, blindness, strabismus, amblyopia, double vision, dry eyes). Some survivors reported multiple late effects related to their ocular system. Nine patients (43%, 1.3 years) had speech-related late effects and most reported concomitant auditory late effects. One reported taste-related problems.

Endocrine—Hypothyroidism was reported in 7 survivors (33%, 4 years). Ten survivors reported GH deficiency (48%, 4.7 years). Five of 6 female survivors reported menarche-related issues. Fertility was not assessed in this study. No survivor reported other endocrine-related late effects such as diabetes, osteoporosis or osteopenia.

Body Mass Index (BMI)—We used a tool from the Center for Disease Control (CDC) to make BMI assessments in our cohort [44]. This tool calculates BMI and the corresponding BMI-for-age percentile based on CDC data. None were underweight (<5th-ile), 67% had normal BMI (5–85th-ile), 33% were overweight/obese (>85th-ile) and 19% were obese (>95th-ile).

CNS—As an aggregate measure, 14 survivors had CNS late effects (67%, 1.8 years). CNS-specific late effects included sensory, balance, weakness, memory, seizures, headaches and paralysis. Several patients had multiple issues; however, due to the small study size we did not stratify the specific CNS late effects.

Cardiovascular, pulmonary, gastrointestinal, and renal—Aggregate measures of cardiovascular, pulmonary, gastrointestinal and renal late effects were determined. Three patients (14%, 15.2 years) reported cardiovascular late effects (deep vein thrombosis, hypercholesterolemia requiring medications, hypertension requiring medications with history of CNS stroke). Four patients (19%, 4.9 years) had respiratory late effects (asthma, cough, pneumonia, chronic oxygen requirement). Two patients (10%, 10.2 years) reported gastrointestinal problems and one reported urinary incontinence.

Dental—Dental late effects were commonly reported with 11 (52%, 7.1 years) survivors having at least one dental late effect (microdontia, hypodontia, root abnormalities, cavities and gingivitis). One patient with Gorlin syndrome was being treated for odontogenic cysts;

this was not classified as a late effect as this is a clinical feature of the patient's underlying syndrome.

Secondary Malignancies—No secondary leukemia or CNS tumors were reported. One survivor has basal cell nevus/Gorlin syndrome. A second survivor (not irradiated for primary disease) was diagnosed with synovial sarcoma of the cheek 8.7 years after diagnosis, treated with surgery alone and is in remission. For this survivor, it is unclear if the synovial sarcoma is a late effect or a second primary neoplasm.

Prognostic factors

Irradiation exposure—Ten survivors were irradiation-free. These patients were <6 years old at diagnosis and, as per protocol, not irradiated. The indications for irradiation were specifically dictated by the protocol. While admittedly examining two distinct subgroups within the HS protocols, we wished to determine if irradiation exposure was associated with late effects. Hypothyroidism, cardiovascular, pulmonary and gastrointestinal late effects were exclusive to the irradiated group. Hypothyroidism (7/11 vs 0/10; $p=0.004$) and GH deficiency (8/11 vs 2/10; $p=0.03$) differed between the irradiated and non-irradiated survivors. While dental late effects were more commonly reported in the non-irradiated group (7/10) compared to the irradiated survivors (4/11), this was not statistically significant (Table III).

Age at diagnosis—The median age at diagnosis was 1.7 years (range: 0.2–7 years). The late effects profile did not differ statistically between the two groups when dichotomized at median age of diagnosis. However, certain trends were noted. Speech late effects and dental late effects tended to occur in those that were younger at diagnosis (Table III).

Surgical resection—The extent of surgical resection was not associated with the late effects (Table III).

Diagnosis—Patients with medulloblastoma ($n=13$) versus those without ($n=8$) were compared with respect to occurrence of late effects. There were no differences between the two groups (Table III).

Quality of life and social, emotional, and behavioral functioning

Standardized T-scores ($M=50$; $SD=10$) and 95% confidence intervals (CI) of parent-reported BASC-2 and CHQ-PF50 are presented in Tables IV and V. The interpretation of the scores has been described in detail in the 'Methods' section. The mean scores were within 'average range' on the four composite scores generated by the BASC-2, including Externalizing ($M=48.18$, 95% CI [44.00, 50.10]), Internalizing ($M=55.06$, 95% CI [48.55, 60.25]), Behavioral Symptoms Index ($M=53.41$, 95% CI [48.19, 56.41]), Adaptive Skills ($M=45.82$, 95% CI [41.96, 50.94]). The higher end of the CI for the composite Internalizing score was in the 'at risk' range. The BASC-2 subscale score means were within the 'average range' as well, but the CI fell in the 'at risk' range for a few of the subscales including anxiety, depression, withdrawal and functional communication.

Survivors' mean scores were within the 'average range' on the CHQ-PF50 Physical Summary Score ($M=45.00$, 95%CI [38.97, 51.02]) and Psychosocial Summary Score ($M=45.20$, 95%CI [39.82, 50.57]), but the CI did indicate that the scores would fall in the 'at risk' range. The mean and CI Parental Impact-Emotional subscale was outside the 'average range' ($M=38.80$, 95%CI [32.05, 45.55]). The CI was outside the 'average range' for several CHQ-PF50 sub-scales despite the means being in the 'average range.' There were no statistically significant correlations between age at diagnosis and any BASC-2 or CHQ-PF50 composite scores or subscales (data not included).

We evaluated group differences in functioning with respect to irradiation and methotrexate exposure using non-parametric Mann-Whitney U-test (Tables IV and V). The BASC-2 Social Skills subscale score in irradiated survivors ($Mdn=57.50$) was significantly higher than non-irradiated survivors ($Mdn=44.50$, $U=20.50$, $z=-2.24$, $p=0.03$). The CHQ-PF50 Self-Esteem subscale score was higher in irradiated survivors ($Mdn = 52.29$) versus non-irradiated survivors ($Mdn=45.28$, $U=14.55$, $z=-2.09$, $p=0.04$). There were no other differences between these groups.

DISCUSSION

We present comprehensive data regarding late effects in a cohort of survivors treated using an approach that sought to avoid or delay irradiation in very young patients newly diagnosed with malignant CNS tumors and extended follow-up data on emotional and behavioral functioning, and physical and psychosocial health of the survivors.

In our cohort, 48% were irradiation-free and 5 patients had delayed irradiation (median of 1.7 years after primary diagnosis). As a whole group, survivors reported a wide range of late effects; irradiation-free survivors, however, had lower rates of several outcomes including ocular, speech, hypothyroidism, GH deficiency, CNS, cardiovascular and pulmonary.

Among the irradiation-free survivors, none reported hypothyroidism, cardiovascular or pulmonary late effects. The lack of hypothyroidism in this group spares the survivor the life-long replacement therapy. The cardio-pulmonary findings may be attributed to the scatter irradiation to the heart and lungs, but due to the small sample size, this cannot be confirmed.

The incidence of hypothyroidism and GH deficiency in our study cohort was similar (33% and 48%, respectively) compared to reported historical data on those treated with chemotherapy, surgery and irradiation. Also, no non-irradiated survivor had hypothyroidism and only 20% reported GH deficiency. A CCSS study reported among 244 patients with medulloblastoma, PNET and ependymoma treated with surgery, chemotherapy and irradiation, the incidence of hypothyroidism and GH deficiency was 28% and 47% [10]. The CCSS cohort, however, has a much longer follow-up than ours. Continued follow-up of our cohort of patients is needed to determine the incidence of long-term endocrine outcomes.

Other potential associated factors (age, extent of surgical resection and tumor type) had no statistically significant effects on reported late effects. Some trends were noted, however. Consistent with a CCSS report, in our cohort, younger patients had higher rates of dental problems [13]. The negative effects of alkylating chemotherapy in young patients' dental

development are known. Our results support that finding. The irradiation-free group, comprising of patients <6 years old had higher incidence of dental problems (70%). Consistent with CCSS, older patients had lower rates of dental problems (30%) despite irradiation and alkylators. Since speech development tends to occur at a very early age, it may explain why these issues were more frequently reported in younger patients. However, age at diagnosis and irradiation are strongly confounded. Our small study size cannot account for the effect these factors on outcomes.

In our cohort, two-thirds reported grade III hearing loss and ocular late effects, consistent with previous reports (including irradiation-free survivors) [4,23,24,39,40]. Risk factors for these late effects include irradiation, cisplatin and glucocorticoid exposure [4,23,24]. Despite platinum therapy, irradiation did not have an additive effect on auditory outcomes in our cohort. This is likely due to the ceiling effect of very high doses of platinum exposure in HS (Figure 1).

In 940 adult survivors of childhood CNS tumors, Meacham et al reported that 5.6% were underweight, 47.3% had normal weight and 47% were overweight/obese [16]. We cannot compare our cohort to the adult survivors' BMI due to age differences. However, in the 1999–2000 NHANES report of children in the US between the ages 12–19 (similar to most patients in our study), the prevalence of overweight/obesity was 30.4% [45]. This is similar to our cohort, where 33% of the survivors were overweight. Encouragingly, none were underweight and the majority had a normal BMI.

Despite exposure to alkylators and epipodophyllotoxins, and irradiation in a select group of survivors, secondary malignancies are not reported with extended follow-up. One patient had synovial sarcoma several years following treatment with chemotherapy only. It is unclear if this was a secondary or second primary neoplasm. We are unaware of chemotherapy causing a secondary synovial sarcoma.

Prior reports indicate that children treated for CNS tumors are at increased risk for difficulties in areas of social, emotional, and behavioral functioning and at greater risk than children treated for non-CNS cancers [46,47]. In this study, extended follow-up data shows that the outcomes in these areas are mixed. This is likely related to the small sample size and the resulting wider CI of the scores. For example, while survivors were within 'average range' for the BASC-2 and CHQ-PF50 mean composite and subscale scores, the CI for the composite and subscale scale scores for a few of the measures were in the 'at risk' range (Tables IV and V). Mostly, however, scores were within 'average ranges' with a few falling in the 'at risk' ranges. These data are similar to what has been reported in prior HS and other studies, which concluded that survivors continue to require surveillance and supportive interventions long after treatment [35,36,48].

On the majority of subscales, survivors who received irradiation or methotrexate were rated no differently from those who did not. Surprisingly, however, irradiated survivors were reported by their parents to have stronger social skills and better self-esteem than non-irradiated survivors. This is contrary to prior reports indicating that irradiated children are at increased risk for late effects including neurocognitive, internalizing and social difficulties

[49,50]. Unfortunately, due to limits in sample size and power, we were unable to explore explanations for these findings. This may represent a spurious finding. Notably, survivors in both groups fell within the ‘average range’ with regard to social skills and self-esteem suggesting that despite irradiation, they are functioning similarly to healthy peers in these areas.

The small number of concerns identified by parent-report on these standardized measures, is promising given the evidence documenting long-term neurocognitive and psychosocial sequelae typically reported for children and adolescents following treatment for CNS tumors [22]. Specifically, some literature notes that survivors’ functioning can continue to decline over time following treatment and lead to detrimental social consequences during adulthood. Remarkably, the median time since diagnosis to this study was 12.6 years and, per parent-report, the survivors were functioning well overall.

Our study has some limitations. The sample size is small and it is not possible to extricate all confounding effects. While 21 of 22 eligible patients completed the study at participating institutions, we did not conduct this study in all HS treatment institutions; this limits the interpretation and generalizability of the results. The small study population also limits the capturing of some outcomes. Recall bias is a potential bias due to the study design. To address this, we used validated questionnaires to collect data. The small study size allowed us to address potential discrepancies and clarify data with regards to the medical late effects. We only included parent-report psychosocial measures and did not present standardized psychological/psychosocial testing data on the survivors subjects. Thus, potential discrepancies of parent and survivor’s perspectives on psychosocial outcomes are not presented.

Our study population is heterogeneous with respect to diagnosis, location, age, irradiation, relapse, extent of surgery and treatment-related complications. We did not have the power to stratify patients with these individual characteristics. We describe the association of these characteristics with late effects to generate hypotheses for further study in similar groups of patients. Age and irradiation are strongly confounded. Non-survivors are not included due to sensitive issues; we did not wish to contact the parents of non-survivors. Some late effects may appear <5 years from diagnosis. Patients with these late effects who did not survive >5 years were not included leading to selection bias. Despite the long period of follow-up, certain late effects (secondary malignancies, renal, cardiopulmonary issues) may appear later than our follow-up period. We did not collect data on posterior fossa syndrome; this has been associated with certain late effects. The HS protocols were not randomized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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<u>Induction (5 cycles)</u>							
Day	0	1	2	3	7	14	21/0
	CDDP	CPM	CPM				
		VP 16	VP 16	MTX [#]			
	VCR*					VCR	VCR
<i>*VCR: only cycles 1-3.</i>							
<i>[#]MTX: on HS II only for patients with AT/RT or metastatic disease</i>							
<u>Consolidation</u>							
Day	-8	-7	-6	-5	-4	-3	0
	Carboplatin	Carboplatin	Carboplatin				
				Thiotepa	Thiotepa	Thiotepa	
				VP 16	VP 16	VP 16	
							Re-infusion
Cumulative Doses							
CDDP: 17.5 mg/kg							
CPM: 650 mg/kg							
VP 16: 40 mg/kg (induction) + 25 mg/kg (consolidation)							
VCR: 0.45 mg/kg							
MTX: 400 mg/kg							
Thiotepa: 30 mg/kg							
Carboplatin: AUC 7 (not higher than 16.7 mg/kg)							

Figure 1.

TABLE I**Patient Characteristics**

Total patients enrolled		N=21	
Age		Years	Range
Median age at diagnosis		1.7	0.2 – 7
Median age at time of follow up		15.3	11.4 – 22.5
Median time since diagnosis to current study		12.6	9.6 – 20.8
Sex		N	%
Female		6	29
Male		15	71
Diagnosis			
Medulloblastoma		13	62
sPNET		4	19
AT/RT		1	5
Ependymoma		3	14
Treatment Information			
Protocol			
Head Start I		4	19
Head Start II		17	81
Surgical resection			
Gross Total		14	67
Partial		7	33
Radiation (at any point--primary or relapse)			
Yes		11	52
No		10	48
Chemotherapy with ASCT		21	100

Range, in years; N, number; %, percentage; sPNET, supratentorial primitive neuroectodermal tumor; AT/RT, atypical teratoid/rhabdoid tumor; ASCT, autologous stem cell transplant

TABLE II

Summary of medical late effects

Late Effects	Onset <5 yrs	Onset >5 yrs	N	%	Median	Range
Grade III Hearing loss	10	4	14	67	3.8	0–7.8
Vision	10	4	14	67	4.1	0–14.6
Speech	8	1	9	43	1.3	0–5.2
Taste	1	0	1	5		
Hypothyroidism	5	2	7	33	4	1.6–7.7
Growth hormone deficiency	6	4	10	48	4.7	1–11.8
CNS	10	4	14	67	1.3	0–9.6
Cardiovascular	0	3	3	14	15.2	10.6–18.7
Pulmonary	2	2	4	19	4.9	2.6–6.7
Gastrointestinal	0	2	2	10	10.2	9.6–10.8
Renal	1	0	1	5		
Dental	3	8	11	52	7.3	0.8–10.3
Secondary malignancy						
Recurrence/Relapse	4	1	5	24	1.7	1.6–11.5
Other malignancy			2			

Onset <5 yrs, Number of patients reporting late effect within 5 years from diagnosis; Onset >5 yrs, Number of patients reporting late effect after 5 years from diagnosis; N, Total number of patients reporting late effect; %, percentage; Median, median time of onset since diagnosis in years; Range, in years; CNS, central nervous system

TABLE III

Association of late effects with potential risk factors

Late effect	Age at diagnosis			
	1.7 years (N=11)		>1.7 years (N=10)	
	N	%	N	%
Grade III hearing loss	8	73	6	60
Vision	8	73	6	60
Speech *	7	64	2	20
Hypothyroidism	4	36	3	30
GH deficiency	6	55	4	40
CNS	8	73	6	60
Cardiac	2	18	1	10
Pulmonary	2	18	2	20
GI	1	9	1	10
Dental *	8	73	3	30
Late effect	Irradiation exposure			
	Irradiated (N=11)		Non-Irradiated (N=10)	
	N	%	N	%
Grade III hearing loss	8	73	6	60
Vision	9	82	5	50
Speech	7	64	2	20
Hypothyroidism **	7	64	0	0
GH deficiency **	8	73	2	20
CNS	9	82	5	50
Cardiac	3	27	0	0
Pulmonary	4	36	0	0
GI	2	18	0	0
Dental	4	36	7	70
Late effect	Surgical Resection			
	GTR (N=14)		PR (N=7)	
	N	%	N	%
Grade III hearing loss	10	72	4	57
Vision	9	64	5	71
Speech	5	36	4	57
Hypothyroidism	5	36	2	29
GH deficiency	6	43	4	57

	Age at diagnosis			
Late effect	1.7 years (N=11)		>1.7 years (N=10)	
	N	%	N	%
CNS	9	64	5	71
Cardiac	2	14	1	14
Pulmonary	4	29	0	0
GI	2	14	0	0
Dental	7	50	4	57
	Tumor Type			
Late effect	Medulloblastoma (N=13)		Non-MB (N=8)	
	N	%	N	%
Grade III hearing loss	9	69	5	63
Vision	8	62	6	75
Speech	6	46	3	38
Hypothyroidism	5	39	2	25
GH deficiency	7	54	3	38
CNS	8	62	6	75
Cardiac	2	15	1	13
Pulmonary	4	31	0	0
GI	1	8	1	13
Dental	7	54	4	50

N, number; %, percentage; p value, determined using two tailed Fisher's exact test; GH, growth hormone; CNS, central nervous system; GI, gastrointestinal; GTR, gross total resection; PR, partial resection; non-MB, non-medulloblastoma;

* p=0.08;

** p<0.05; the remainder of the comparisons were not statistically significant.

Table IV

Social, Emotional, and Behavioral Functioning: Means, Standard Deviations and 95% Confidence Intervals^a

Measure	Treatment									
	Total Sample (N = 20)		Irradiated (N = 10)		Non-Irradiated (N = 10)		Received Methotrexate (N = 6)		No Methotrexate (N = 14)	
	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval
Hyperactivity	48.85 ± 7.66	[45.27, 52.43]	48.80 ± 6.89	[43.87, 53.73]	48.90 ± 8.74	[42.65, 55.15]	49.17 ± 9.41	[39.29, 59.04]	48.71 ± 7.18	[44.57, 52.86]
Aggression	47.70 ± 8.05	[43.93, 51.47]	45.90 ± 5.99	[41.62, 50.18]	49.50 ± 9.68	[42.58, 56.42]	46.00 ± 6.90	[38.76, 53.24]	48.43 ± 8.63	[43.45, 53.41]
Conduct Problems	45.80 ± 4.99	[43.46, 48.14]	45.30 ± 5.77	[41.17, 49.43]	46.30 ± 4.32	[43.21, 49.39]	47.33 ± 6.15	[40.88, 53.79]	45.14 ± 4.50	[42.54, 47.74]
Anxiety	55.90 ± 12.40	[49.86, 61.94]	58.30 ± 12.62	[49.27, 67.33]	53.50 ± 13.39	[43.92, 63.08]	56.00 ± 6.54	[49.13, 62.87]	55.86 ± 15.06	[47.16, 64.55]
Depression	54.50 ± 13.00	[48.42, 60.58]	55.20 ± 15.95	[43.79, 66.61]	53.80 ± 10.05	[46.61, 60.99]	52.83 ± 5.74	[46.81, 58.86]	55.21 ± 15.24	[46.41, 64.02]
Somatization	50.25 ± 9.62	[45.75, 54.75]	53.90 ± 11.70	[45.53, 62.27]	46.60 ± 5.36	[42.77, 50.43]	47.00 ± 5.48	[41.25, 52.75]	51.64 ± 10.80	[45.41, 57.88]
Atypicality	52.55 ± 11.15	[47.33, 57.78]	52.20 ± 13.89	[42.27, 62.13]	52.90 ± 8.33	[46.94, 58.86]	50.83 ± 8.86	[41.53, 60.14]	53.29 ± 12.23	[46.22, 60.35]
Withdrawal	55.80 ± 10.25	[51.00, 60.60]	53.30 ± 8.14	[47.48, 59.12]	58.30 ± 11.90	[49.79, 66.81]	55.33 ± 15.67	[38.89, 71.78]	56.00 ± 7.68	[51.57, 60.43]
Attention Problems	51.20 ± 8.79	[47.08, 55.32]	49.80 ± 7.93	[44.13, 55.47]	52.60 ± 9.80	[45.59, 59.61]	49.50 ± 10.01	[38.99, 60.01]	51.93 ± 8.52	[47.01, 56.85]
Adaptability	49.00 ± 7.96	[45.27, 52.73]	51.50 ± 8.70	[45.28, 57.72]	46.50 ± 6.65	[41.74, 51.26]	49.50 ± 7.66	[41.46, 57.54]	48.79 ± 8.36	[43.96, 53.61]
Social Skills	49.70 ± 10.87	[44.61, 54.79]	54.70 ± 9.27 *	[48.07, 61.33]	44.70 ± 10.38 *	[37.27, 52.13]	49.17 ± 14.50	[33.95, 64.38]	49.93 ± 9.57	[44.40, 55.45]
Leadership	44.85 ± 9.26	[40.51, 49.19]	45.80 ± 8.53	[36.69, 51.91]	43.90 ± 10.31	[36.52, 51.28]	41.67 ± 11.99	[29.08, 54.25]	46.21 ± 7.96	[41.62, 50.81]
Activities of Daily Living	46.95 ± 12.36	[41.16, 52.74]	48.40 ± 10.02	[41.23, 55.57]	45.50 ± 14.75	[34.95, 56.05]	46.17 ± 18.48	[26.78, 65.56]	47.29 ± 9.58	[41.75, 51.75]
Functional Communication	43.45 ± 11.61	[38.02, 48.88]	41.60 ± 11.47	[33.39, 49.81]	45.30 ± 12.05	[36.68, 53.92]	44.67 ± 14.87	[29.06, 60.27]	42.93 ± 10.53	[36.85, 49.01]

^aMeans and standard deviations for standardized scores from the Behavior Assessment Scale for Children – 2nd Edition (BASC-2); Expected mean and SD are 50 and +/-10

* p<0.05

Table V

Quality of Life: Means, Standard Deviations and 95% Confidence Intervals ^a

Measure	Treatment							
	Total Sample ^b (N = 17)		Irradiated (N = 8)		Non-Irradiated (N = 9)		Received Methotrexate (N = 6)	
	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval	Mean ± SD	95% Confidence Interval
Physical Functioning	46.01 ± 12.36	[39.66, 52.36]	43.29 ± 11.31	[33.83, 52.75]	48.42 ± 13.40	[38.13, 58.72]	45.98 ± 11.82	[33.56, 58.39]
Role/Social limitations due to emotional or behavioral difficulties	43.86 ± 18.51	[34.35, 53.38]	48.51 ± 13.76	[37.01, 60.02]	39.73 ± 21.88	[22.92, 56.55]	44.48 ± 20.19	[23.29, 65.67]
Role/Social limitations due to physical difficulties	46.72 ± 13.90	[39.58, 53.87]	46.79 ± 12.85	[36.02, 57.53]	46.66 ± 15.55	[34.71, 58.61]	48.62 ± 14.39	[33.52, 63.73]
Bodily Pain/Discomfort	51.77 ± 9.27	[47.01, 56.53]	48.83 ± 11.22	[39.45, 58.20]	54.39 ± 6.72	[49.22, 59.56]	53.05 ± 8.49	[44.14, 61.96]
General Behavior	51.06 ± 8.88	[46.69, 55.62]	54.12 ± 8.74	[46.81, 61.43]	48.32 ± 8.56	[41.75, 54.91]	55.46 ± 7.06	[48.05, 62.87]
Mental Health	46.84 ± 11.70	[40.83, 52.86]	48.35 ± 15.13	[35.70, 60.99]	45.51 ± 8.33	[39.11, 51.91]	53.22 ± 9.43	[43.32, 63.12]
Self-Esteem	45.69 ± 13.73	[38.63, 52.75]	51.70 ± 11.63 [*]	[41.98, 61.43]	40.34 ± 13.80 [*]	[29.74, 50.95]	50.34 ± 7.00	[43.00, 57.68]
General Health	41.68 ± 10.04	[36.52, 46.84]	40.73 ± 10.94	[31.58, 49.87]	42.52 ± 9.76	[35.02, 50.03]	39.22 ± 10.76	[27.93, 50.52]
Parental Impact-Time	46.03 ± 13.99	[38.83, 53.22]	43.57 ± 13.07	[32.64, 54.50]	48.21 ± 15.19	[36.53, 59.99]	50.64 ± 12.80	[37.21, 64.08]
Parental Impact-Emotional	38.80 ± 13.13	[32.05, 45.55]	39.77 ± 14.82	[27.38, 52.16]	37.93 ± 12.28	[28.50, 47.37]	42.69 ± 17.92	[23.88, 61.50]
							36.67 ± 10.06	[29.92, 43.43]

^a Means and standard deviations are standardized scores from the Children’s Health Questionnaire (CHQ-PF50); Expected mean and SD are 50 and +/-10

^b Three participating survivors were greater than 18-years of age at the time of data collection and therefore those CHQ-PF50 scores were not included in analyses

^{*} p<0.05