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Long-Term Survival of Children Less than Six Years of Age Enrolled on the CCG-945 Phase III Trial for Newly-Diagnosed High-Grade Glioma: A Report from the Children's Oncology Group

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Abstract

Background—We analyzed the long-term survival of children under six years of age (<6 yo) enrolled upon the Children's Cancer Group (CCG)-945 high-grade glioma (HGG) study to determine the impact of intrinsic biological characteristics as well as treatment upon both survival and quality of life (QOL) in this younger age population.

Procedure—Analyses were undertaken on patients <6 yo with institutionally diagnosed HGG enrolled on the CCG-945 trial. Comparisons of survival were performed for patients less than three years of age (<3 yo) (treated with intent to avoid irradiation) *versus* those between three to six years of age (3–6 yo) (treated with irradiation and chemotherapy) at diagnosis. Discordance between the institutional diagnoses of HGG and consensus-reviewed diagnoses led us to perform

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further survival analyses for both groups. We compared the two groups of patients for biological markers, and evaluated the neuropsychological and QOL outcomes of long-term survivors.

Results—Patients <3 yo (n=49, 19.5% of all enrolled patients) at diagnosis had a 10-year EFS and OS of $29 \pm 6.5\%$ and $37.5 \pm 7\%$ respectively while for patients 3–6 yo (n=34, 13.5% of all enrolled patients) 10-year EFS and OS were $35 \pm 8\%$ and $36 \pm 8\%$ respectively. Molecular marker analysis showed that a smaller proportion of patients <3 yo harbored *TP53* mutations ($p=0.05$). Analysis of QOL outcomes with a median length of follow up of 15.1 years (9.5–19.2) showed comparable results.

Conclusions—QOL and survival data were similar for the two groups. A larger prospective study is justified to study the efficacy of chemotherapy only regimens in younger children.

Keywords

High grade glioma; irradiation

Introduction

High-grade gliomas (anaplastic astrocytoma, AA, and glioblastoma multiforme, GBM) represent approximately 6.5% of all newly diagnosed childhood intracranial tumors. Radical surgical resection and aggressive multimodality interventions have contributed to a modest improvement in survival (1–9).

Children with high-grade gliomas (HGG) continue to present a therapeutic challenge, especially in sustaining quality of life and improving long-term survival. The serious and irreversible sequelae of irradiation therapy on neurocognitive function, especially in young children, have been well described (10–17). Strategies to avoid or delay irradiation in young children in order to minimize these ominous effects are being sought in several ongoing treatment strategies (4, 5, 18).

We have analyzed long-term survival in children <6 yo enrolled upon the CCG-945 trial, to determine the impact of chemotherapy with avoidance of irradiation upon outcome in those children <3 yo so treated, in comparison with those children between 3–6 yo who all received irradiation in addition to the chemotherapy. We also established whether any differences in outcome between the youngest children and the older cohort might reflect clinical or intrinsic pathological or biological characteristics between the two groups. Additionally, we followed the survivors of both age group populations almost twenty years after the closure of the study and assessed the neuropsychological and quality of life (QOL) outcome measures.

Methods

The CCG-945 trial for children with HGG was opened to patient accrual on April 1st, 1985 and closed on May 31st, 1992. The randomized component closed in 1990 after patient accrual to the randomized component was completed. The sample size was projected to provide 80% power of detecting a 50% reduction in the estimated hazards ratio of 0.458 per

year for the control arm (two-sided Mantel-Haenszel test with $\alpha = 0.10$). The non-randomized component was continued until 1992.

The study design, treatment and assessments have been described previously (4). Briefly, eligibility for the CCG-945 study mandated institutional histopathological confirmation of HGG. Prior chemotherapy or irradiation therapies were considered exclusion criteria. Surgical resection was performed with the recommendation to attempt as radical a resection as feasible without jeopardizing the patient (1–3).

Patients with intracranial HGG older than 36 months of age at diagnosis were randomly assigned to either the standard pCV (adjuvant prednisone, lomustine (CCNU) and vincristine) or the “eight-drugs-in-one-day” (“8-in-1”) regimen, including lomustine, vincristine, hydroxyurea, procarbazine, cisplatin, cytosine arabinoside and dacarbazine.

There was an additional non-randomized component, which accrued younger patients and those with primary spinal cord tumors. These patients were non-randomly assigned to the more intensive chemotherapy “8-in-1” chemotherapy arm, with intent to avoid or at least delay irradiation. The treatment schema for the CCG-945 study has been described previously (4).

It was left to the investigators’ discretion to treat children younger than 24 months of age with radiotherapy after initial treatment with chemotherapy with the intent of minimizing irradiation exposure in this age group. This age limit was increased to 36 months on May 31st 1990. The decision to increase the age from 18 to 24 and then to 36 months was based upon the Study Committee concerns that such young children would otherwise not be enrolled on the irradiation-containing randomized component of the study.

Patients assigned to the non-randomized arm had the option of receiving involved field radiotherapy after two cycles of chemotherapy or after completion of all ten cycles of chemotherapy. None were to receive craniospinal irradiation except children with primary spinal cord tumors.

Histopathological Assessment

Study eligibility was determined by the institutional neuropathologists’ determination of the diagnosis of HGG. Central review of pathology was performed initially by the single study neuropathologist (AY). Subsequently, he and four additional experienced neuro-pathologists provided a second central review of all the pathological material. They reclassified patients as having AA, GBM, other eligible HGG (e.g. anaplastic mixed gliomas) and discordant diagnoses (i.e., diagnoses other than HGG, such as low-grade glioma or ependymoma). A consensus diagnosis based on the five independent reviews of the pathological material was finally provided. The following analyses were performed on the basis of the both the institutional diagnoses and the reviewed consensus diagnoses.

Assessment of *TP53* Mutations and Other Molecular Alterations

Detailed methodology has been described and published previously (19–21) and the purpose of the present work was to determine associations for the two groups of patients (<3 yo

versus 3–6 yo). The evaluations done in the context of the CCG biology study CCG-B975 included immuno-histochemical analysis of p53 and mutational analysis of *TP53*. Expression of p53 was evaluated on the basis of percentage of p53 staining cells in the tumor (semi-quantitative). MIB-1 labeling was determined quantitatively as previously described (22). MGMT expression status was assessed semi-quantitatively based upon immunoreactivity, with categorization of tumors into subgroups exhibiting overexpression or normal expression, as previously reported (23). Chromosome 1p and 19q deletions were evaluated by loss of heterozygosity analysis as previously described (24).

Statistical Analyses

The primary endpoints for analysis were event-free survival (EFS) and overall survival (OS). OS was calculated from the date of enrollment on the study to the date of death, with censoring on the date of the most recent contact. EFS was calculated from the time of study enrollment to the date of first occurrence of the following events, death from any cause, relapse, progressive disease or development of a second malignancy. Kaplan Meier (KM) analyses were performed on the two groups of patients (<3 yo *versus* 3–6 yo) to determine 10 year OS and EFS. KM analyses were also performed on patients with eligible reviewed HGG pathology and those with discordant pathology. Fisher's exact tests were used to test if the patient characteristics and the distribution of molecular markers were different for children <3 yo and those between 3–6 yo. A comparison was also made between the neuropsychological measures between the two groups using Independent sample t-tests.

Comparison of the two groups of patients (<3 yo *versus* 3–6 yo) was not an original objective of the study. With the small number of patients presented in this paper, the study was not powered to make the comparison attempted. For example, a retrospective power calculation shows that with a baseline long term EFS of 29% and a total of 83 patients, based on a two-sided logrank test and a long-term follow up of 12 years on the last patient enrolled, there will be approximately 15% power to detect a 10% improvement in long-term EFS (29% to 39%) and 45% power to detect a 20% improvement in long-term EFS. Hence the results presented in this paper are primarily descriptive.

Results

Patient Characteristics

Eighty-three eligible children < 6 yo (33.1% of all patients entered on the CCG-945 study) were enrolled with institutional reviewed consensus diagnoses of HGG. Table 1 details the characteristics of the two groups of patients: those <3 yo (n=49) *versus* those between 3–6 yo (n=34); the p-values from Fisher's exact test are included. Both groups had comparable sex, race, location of tumor and extent of resection. Extent of resection (less than 90% resection *versus* greater than 90%) was one of the most powerful predictors of outcome on the CCG-945 study (2). An equivalent percentage of children in each group (43% in the younger group and 41% in the older group) underwent a resection greater than 90% at diagnosis.

Table 1 also indicates that no significant difference was found between the two groups (<3 yo *versus* 3–6 yo) with respect to institutional or review diagnosis. Upon consensus panel review of pathology, 39% of children <3 yo and 38% of children aged 3–6 yo had diagnoses other than HGG. This reflected the high discordance rate between the institutional diagnoses and the consensus review diagnoses (GBM institutional *versus* GBM central and AA institutional *versus* AA central); the discordance rate did not differ between the younger and the older children. However, consensus panel reviewed diagnoses of AA and GBM suggested possible differences between the two groups; of those <3 yo, 12% were diagnosed with GBM and 41% were diagnosed with AA compared to 27% of the 3–6 yo who were diagnosed with AA and 27% with GBM.

Biologic Markers

Table 2 summarizes the differences in molecular markers between the two groups of patients (<3 yo *versus* 3–6 yo). A high proliferation index (MIB-1 proliferation index greater than 18%) has been associated with a less than favorable outcome on the CCG-945 study (22).

Fifty-five of 83 (66%) children <6 yo had MIB-1 proliferation index analyses performed centrally on the original tumor tissue. No difference between the two groups could be demonstrated ($p=0.87$).

p53 over-expression has been shown to be an adverse prognostic factor on the CCG-945 study (19, 20). Fifty-seven percent (47 of 83) of children <6 yo underwent centralized p53 expression analyses. p53 over-expression was noted in 25% (seven of 28) in children <3 yo while 26% (five of 19) of the older cohort had p53 over-expression ($p=1.0$).

Fifty-five percent (46 of 83) children <6 yo underwent centralized *TP53* mutation analyses. Among children <3 yo, 28% showed *TP53* mutations while among children 3–6 yo, 53% had *TP53* mutations. No statistically significant difference in *TP53* mutations could be demonstrated between the two groups ($p=0.12$). Deletions in the short arm of chromosome 1p and long arm of 19q have not been found to show any survival advantage in pediatric patients with HGG (24). These characteristics were not significantly different for children <3 yo and those who were between 3–6 yo; the p-value was $p=0.72$ for 1p loss and $p=0.27$ for 19q loss.

It has been shown that over-expression of MGMT in childhood HGG is strongly associated with an adverse outcome in children treated with alkylator-based chemotherapy, independently of clinical prognostic factors (23). Among children <3 yo, 24% showed MGMT over-expression while among children 3–6 yo, 14% showed MGMT over-expression ($p=0.69$). It is important to note that MGMT expression was described rather than MGMT promoter methylation as has been undertaken in several studies (25, 26).

Similar sets of analyses were performed after excluding 32 discordant cases. MIB-1 proliferation index, p53 expression, 1p loss, 19q loss and MGMT expression were not significantly different between children <3 yo and those who were 3–6 yo. Table 2 indicates that the frequency of *TP53* mutations (after excluding discordant diagnoses) was the only molecular feature that differed significantly between the two age groups (<3 yo *versus* 3–6

yo) ($p=0.05$). The incidence of *TP53* mutations in the younger age group was much lower (28%) compared to the older cohort 3–6 yo (70%) ($p=0.05$). Given the small numbers of patients in individual groups and the potential influence of biological factors on outcome, it is not possible in this small sample set to conclude that a single indicator, such as *TP53* mutations, is definitively associated with a more aggressive tumor subset.

Kaplan Meier Analyses of EFS and OS

For the 49 children <3 yo at diagnosis, the 10-year EFS and OS were $29 \pm 6.5\%$ and $37.5 \pm 7\%$ respectively. For the 34 patients 3–6 years of age at diagnosis, the 10-year EFS and OS were $35 \pm 8\%$ and $36 \pm 8\%$ respectively. No statistically significant difference between the two age groups with respect to EFS ($p=0.70$) or OS ($p=0.83$) could be demonstrated. Figures 1 and 2 show the EFS and OS plots comparing the two age groups.

The consensus review diagnosis was discordant (predominantly low-grade glioma) for nineteen patients <3 yo and for thirteen patients between 3–6 yo. Table 3 tabulates the 10-year EFS and OS rates for the patients with discordant review diagnosis ($p=0.47$ (EFS) and $p=0.94$ (OS)) and for those with an eligible, reviewed HGG diagnosis ($p=0.72$ (EFS) and $p=0.62$ (OS)). No significant difference between the two age groups could be demonstrated.

Irradiation

Irradiation was given to 100% of 3–6 yo children, while 13 of 49 (26.5%) of children <3 yo received irradiation at some point during their treatment. Of the 13 patients younger than three years of age who received irradiation, eight received irradiation to the brain before relapse, three received irradiation only to the spinal cord (two of these three were irradiated at tumor progression) and the two remaining were irradiated at progression. All thirteen patients were between 13 and 36 months at irradiation. There was no survival advantage for children <3 yo who received irradiation. The 10-year EFS and OS for the 13 patients who received irradiation was $31 \pm 13\%$ compared to $28 \pm 8\%$ for the 36 without irradiation ($p=0.94$). The 10-year OS for the 13 patients who received irradiation was $31 \pm 13\%$ compared to $40 \pm 8\%$ for the 36 without irradiation ($p=0.73$).

Neuropsychological outcomes and Quality of Life measures

Neuropsychological outcomes of current survivors from the category of patients <3 yo ($n=10$) at diagnosis were compared to the survivors from the category between 3–6 yo ($n=14$) at diagnosis. Ninety percent of survivors in the <3 yo category were not treated with irradiation while 100% ($n=14$) of those between 3–6 yo were treated with irradiation. These results are summarized in Table IV.

While the small numbers of survivors who were assessed precludes statistical analyses, the less than 3 year old cohort performed below the mean of the 3–6 year old cohort on measures of Intelligence, Visual-Motor Integration, Visual Memory and Processing Speed, while the outperforming the older cohort on a measure of verbal learning and memory. In marked contrast, primarily self-report Quality of Life (QoL) measures were completed which identified similar Physical and Mental QoL profiles, with slightly lowered Physical QoL for both groups. It is interesting to note that the younger cohort tested were

predominantly female (70%) with cerebral hemispheric tumors (80%), in contrast to the older group who were 21% female with 36% cerebral hemispheric tumors, which may have influenced the outcomes for these two groups and warrants further inquiry on a larger cohort. Additionally, it is important to note that the mean Full Scale IQ for both groups is within the borderline range and underscores the potential risk factor of young age at treatment for pediatric brain tumors, regardless of whether or not they receive radiotherapy.

Discussion

Patients with HGG, including AA and GBM, continue to exhibit a poor prognosis both in the adult and pediatric age groups. Extensive work has been undertaken in trying to define both outcome variables and optimal combinations of adjuvant chemotherapy to improve OS. This report is unique; it includes the largest ever cohort of children with centrally reviewed diagnoses of HGG enrolled on a prospective national cooperative group trial, with the longest follow-up of such children ever reported, and with follow-up information on neuropsychological functioning and quality of life of the long-term survivors. Although study enrollment was completed some 20 years ago, a similar report has never been published. The pioneer study in these attempts in children was the first randomized phase III trial for children with HGG (the CCG-943 trial) conducted between 1976 and 1981 (9). The study showed that extent of resection was the single most important predictor of outcome, and reported an EFS of 46% in children treated with combined radiotherapy and chemotherapy as opposed to 18% treated with radiotherapy alone. The largest randomized phase III trial (CCG-945) in HGG performed between 1985 and 1992 was designed to improve survival by combining the “8-in-1” chemotherapy regimen (4, 5). An important finding was the significant discordance between institutional and central consensus panel review of diagnoses of HGG, which has led to reassessment of the outcomes of these children based upon institutional *versus* centralized pathologic diagnoses (27, 28). These observations have also led to the incorporation of prospective central review on more recent studies of the Children’s Oncology Group (COG).

The deleterious effects of cranial irradiation have been described (10–17), and include damage to visual motor integration, visual memory, verbal fluency and executive functioning in addition to endocrine and skeletal late effects. The CCG-945 study included a cohort of younger patients (<3 yo) who largely avoided irradiation. This group provided the opportunity to study the OS and EFS and analyze and compare outcomes with the older group. However, it must be emphasized that such retrospective sub-set analyses implicitly contain significant problems. Such comparisons were neither primary nor secondary aims of the original protocol, so that the study was not powered to make the comparisons attempted. In comparing the outcome between the two groups in the CCG-945 study, our limited data show comparable survival in the two groups of children studied; larger prospective studies will be needed to confirm this. This outcome is true for all enrolled patients as well as for patients with consensus pathology reviewed and confirmed diagnosis of HGG.

A statistically significant difference in neuropsychological measures was not observed. This was because the CCG-945 study was not adequately powered to make the comparisons attempted. However, our limited data showed comparable physical and mental QOL could

be seen between the two categories in the long-term survivors. Importantly, these data reflect survival almost twenty years after closure of the study.

The finding that OS and EFS in children with HGG tend to be better than in adults with HGG, has led to extensive research in order to identify the distinguishing molecular markers. Notably, EGFR amplification or PTEN deletion commonly encountered in adult HGG are lacking in childhood HGG (29). We do not have enough data to irrefutably conclude that the survival advantage in the younger cohort is due to biologic differences but there is enough evidence presented that this is an important area of distinction that needs to be carefully investigated. Prolonged postoperative chemotherapy and delayed irradiation with improved survival in much younger HGG infants has been shown by Duffner *et al.* emphasizing the presence of intrinsic biologic differences in this cohort, which need to be better defined (30).

Genotyping and molecular studies carried out on the histopathological material archived from the CCG-945 studies have shown that over-expression of p53 protein in HGG has been linked to adverse outcome. However mutations in the *TP53* gene have not been shown to have a statistically significant correlation with outcome measures. A strong association has been found between the MIB - 1 proliferation index and outcome as well as with histological characterization.

1p and 19q alterations have not been shown to have an impact on survival in pediatric malignant gliomas, even those with oligodendroglial morphology (24). No prognostic association was shown with deletions involving chromosomes 1p or 19q. The numbers in this cohort were too small to obtain a meaningful association with outcome. Finally, a strong adverse correlation between O (6)-methyl guanine-DNA methyl transferase expression and outcome has been shown in children with HGG treated with alkylator-based chemotherapy, (23) based upon archival histopathological material derived from the CCG-945 study. The numbers were too small to obtain a meaningful association with outcome in our study.

In our analyses, no statistically significant differences could be demonstrated between the two age groups in terms of expression of p53 and MIB-1 proliferation index. However, a less frequent incidence of *TP53* mutation (but not over-expression) was noted in the younger children. This could contribute towards a favorable biology and similar outcome to the older children despite the avoidance of irradiation in this group.

The present analysis from the CCG-945 study suggests comparable survival in the two cohorts that were studied; a larger prospective study will be required to confirm this observation. The patients with a diagnosis of definitive HGG did poorly as a group and the long-term survival for both groups (HGG and AA) was less than 20%. While our small patient numbers appear to indicate that there was no survival advantage to receiving irradiation in children < 3 years of age, outcome would likely have been influenced by several confounding factors, including lack of tumor resectability at recurrence for children then receiving irradiation, and the likely palliative nature of irradiation in patients with recurrent disease. Thus, any improvement in survival through creative use of conventional chemotherapy or innovative biological strategies as are currently under evaluation should be

undertaken with careful consideration for minimization of radiotherapy. Perhaps strategic administration of radiotherapy in patients with residual disease after surgery and initial chemotherapy should be administered in the context of a clinical trial.

Differences in the proportion of children with GBM *versus* AA between the younger and older groups, as well as less frequent *TP53* mutation in the younger group, might suggest that the younger group has an intrinsically more favorable tumor pathology and biology and thus an outcome equal to the older children but with avoidance or at least delay of irradiation. The assumption that biological indicators may define a more aggressive group is based on data in the larger group of HGG in the CCG-945 and ACNS0126 cohorts. Given the recent molecular observations in these tumors (31,32), it is likely that over time additional markers may be identified that will help to better characterize tumor behavior based on intrinsic biological features.

A large multi-center prospective study, powered to further answer the questions raised from the current retrospective study, is required to firmly demonstrate whether young children with HGG can benefit from radical changes in treatment strategies. Studies such as the Head Start regimen (intensive consolidative marrow-ablative chemotherapy with autologous stem cell rescue, following initial induction chemotherapy) as well as other chemotherapy only regimens should be explored with the intent of avoidance of radiotherapy in very young children to improve their quality of life (33).

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Figure 1.
Event-Free Survival by age group for all patients.

Figure 2.
Overall Survival by age group for all patients.

Table I

Characteristics of Childhood High-Grade Glioma Patients.

Patient Characteristic		Patients <3yo (n=49)		Patients 3-6 yo (n=34)		p-value
		No.	%	No.	%	
Sex	Male	21	43	19	56	0.27
	Female	28	57	15	44	
Race	White	34	69	22	65	0.81
	Non-White	15	31	12	35	
Location of tumor	Cerebral/Hemisphere	21	43	14	41	1.00
	Posterior fossa	10	20	7	21	
	Midline	13	27	10	29	
	Spinal/Other	5	10	3	9	
Extent of resection	Total (>90%)	21	43	14	41	0.99
	Subtotal	11	22	9	27	
	Partial	8	16	5	15	
	Biopsy	9	18	6	18	
Institutional diagnosis	Glioblastoma	9	18	10	29	0.28
	Anaplastic Astrocytoma	29	59	14	41	
	Other Eligible	11	52	10	29	
	Glioblastoma	6	12	9	27	
Reviewed consensus diagnosis	Anaplastic Astrocytoma	20	41	9	27	0.34
	Other Eligible	4	8	3	9	
	Discordant	19	39	13	38	

Comparison between patients less than 3 years of age and those between 3 and 6 years of age.

Table II

Biological Markers of Childhood High-Grade Glioma Patients.

Biologic markers	Criterion	Patients <3 No. (%)	Patients 3–6 No. (%)	Total	p-value
MIB-1	<18%	19 (58%)	12 (55%)	31	0.87
	18–36%	7 (21%)	4 (18%)	11	
	>36%	7 (21%)	6 (27%)	13	
	Total	33	22	55	
p53 over-expression	Absent	21 (75%)	14 (74%)	35	1.00
	Present	7 (25%)	5 (26%)	12	
	Total	28	19	47	
p53 mutation	Present	8 (28%)	9 (53%)	17	0.12
	Not present	21 (72%)	8 (47%)	29	
	Total	29	17	46	
1p Loss	Present	6 (24%)	3 (18%)	9	0.72
	Not present	19 (76%)	14 (82%)	33	
	Total	25	17	42	
19q Loss	Present	7 (30%)	2 (13%)	9	0.27
	Not present	16 (70%)	13 (87%)	29	
	Total	23	15	38	
MGMT over-expression	Over-expression	6 (24%)	2 (14%)	7	0.69
	No over-expression	19 (76%)	12 (86%)	31	
	Total	25	14	39	
p53 mutation (without discordants)	Present	5 (28%)	7 (70%)	12	0.05
	Not present	13 (72%)	3 (30%)	16	
	Total	18	10	28	

Comparison between patients less than 3 years of age and those between 3 and 6 years of age.

Table III

10-year EFS and OS Rates by Consensus Review Pathology.

Survival	Review Path	Patients <3yo		Patients 3–6 yo		p-value
		No.	10-yr rate	No.	10-yr rate	
Event-Free Survival	Eligible	30	20 ± 7%	21	24 ± 9%	0.72
	Discordant	19	42 ± 11%	13	54 ± 14%	0.47
Overall Survival	Eligible	30	24 ± 8%	21	25 ± 10%	0.62
	Discordant	19	58 ± 11%	13	54 ± 14%	0.94

Neuropsychological outcome measures in patients less than 3 years of age and between 3–6 years of age.

Table IV

	Age group less than 3 yo			Age group between 3–6 yo		
	N	Mean	Standard deviation	N	Mean	Standard deviation
Full Scale IQ	9	70.00	22.42	13	79.73	29.22
Verbal IQ	9	72.00	25.54	11	80.15	24.37
Performance IQ	9	71.44	20.85	11	81.82	27.71
Rey Complex figure Copy	7	17.67	11.97	7	18.5	11.94
Rey Delayed recall	7	31.57	16.10	7	32.29	12.39
CVLT Trials 1–5 total	9	41.22	17.44	10	34.50	17.44
Symbol digit	8	–2.02	1.45	8	–1.56	1.95
Overall Physical QOL	7	42.87	14.63	9	45.84	16.27
Overall Mental QOL	7	47.68	10.95	9	50.49	7.40

N=Number, yo=years, CVLT=California verbal learning test. Survivors less than 3 years of age (n=10) had a mean age of 10.51 months. Total number of males in this group was 30% while females were 70%. Majority of the survivors (90%) did not receive radiotherapy. Location of tumors: 80% of the tumors were in the cerebral hemispheres while 20% were in the posterior fossa. Survivors between 3–6 years of age [n=14] had mean age of 58.24 months. Total number of males was 78.6% while females were 21.4%. All the survivors in this group received radiotherapy. Location of tumors: 35.7% of tumors were in the cerebral hemisphere, 35.7% in the posterior fossa, 14.3% in the spine and 14.3% in the midline.