Title: Outcome of Young Children with High-Grade Glioma Treated with Irradiation-Avoiding Intensive Chemotherapy Regimens: Final report of the Head Start II and III Trials.

Authors: Juan C Espinoza MD¹, Kelley Haley RN¹, Neha Patel MD², Girish Dhall MD¹, Sharon Gardner MD³, Jeffrey Allen MD³, Joseph Torkildson MD⁴, Albert Cornelius MD⁵, Rod Rassekh MD⁶, Antranik Bedros MD⁷, Morris Etzl MD⁸, James Garvin MD⁹, Kamnesh Pradhan MD¹⁰, Robin Corbett MD¹¹, Michael Sullivan MD¹¹, Geoffrey McGowage¹², Dagmar Stein MD¹³, Rama Jasty MBBS¹⁴, Stephen A. Sands PsyD¹⁵, Lingyun Ji MS¹⁶, Richard Sposto PhD¹, and Jonathan L. Finlay MB, ChB¹⁷

Affiliations:

¹Children's Hospital Los Angeles, Los Angeles, CA

²University of Wisconsin, Madison, WI

³New York University Medical Center, New York, NY

⁴Children's Hospital of Oakland, Oakland, CA

⁵DeVos Children's Hospital, Grand Rapids, MI

⁶British Columbia Children's Hospital, Vancouver, BC, Canada

⁷Loma Linda University Medical Center, Loma Linda, CA

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/pbc.26118](#).

This article is protected by copyright. All rights reserved.

⁸Phoenix Children's Hospital, Phoenix, AZ

⁹Columbia Children's Hospital, New York, NY

¹⁰Riley Children's Hospital, Indianapolis, IN

¹¹University of Otago, Christchurch, New Zealand

¹²Children's Hospital at Westmead, Sydney, Australia

¹³Promedica Children's Hospital of Toledo, OH

¹⁴Mercy Children's Hospital, Toledo, OH

¹⁵Columbia University Medical Center, New York, NY

¹⁶USC Norris Comprehensive Cancer Center, Los Angeles, CA

¹⁷Nationwide Children's Hospital and The Ohio State University, Columbus, OH

Corresponding author's contact information:

Jonathan L. Finlay MB ChB FRCP,

Nationwide Children's Hospital

Division of Hematology, Oncology and BMT

700 Children's Drive, Room ED544,

Columbus, OH 43205

neuronc514@aol.com

PH: (614) 722-3550

FX: (614) 722-8826

Abstract Word Count: 247

Main Text Word Count: 3,015

Number of Tables: 3, 1 supplemental

Number of Figures: 3

Running Title: Head Start protocol for pediatric high-grade glioma

Keywords: pediatrics, gliomas, Head Start, irradiation-avoiding strategies

Abbreviation Key

AA	Anaplastic Astrocytoma
GBM	Glioblastoma Multiforme
EFS	Event-Free Survival
OS	Overall Survival
HGG	High Grade Gliomas
CNS	Central Nervous System

HS	Head Start
WHO	World Health Organization
auHPCR	Autologous Hematopoietic Progenitor Cell Rescue
MRI	Magnetic Resonance Imaging
CSF	Cerebrospinal Fluid
DIPG	Diffuse Intrinsic Pontine Glioma
GTR	Gross Total Resection
NTR	Near Total Resection
STR	Subtotal Resection
PR	Partial Resection
AUC	Area Under the Curve
G-CSF	Granulocyte colony-stimulating factor
WBC	White Blood Cell Count
IV	Intravenous
CHLA	Children's Hospital Los Angeles
IRB	Institutional Review Board
CCR	Clinical Complete Response

CR	Complete Response
PR	Partial Response
MR	Minimal Response
SD	Stable Disease
PD	Progressive Disease
RT	Radiation Therapy

ABSTRACT

PURPOSE: To report the final analysis of survival outcomes for children with newly diagnosed HGG treated on the “Head Start” II and III protocols with chemotherapy and intent to avoid irradiation in children less than 6 years old.

PATIENTS AND METHODS: Between 1997 and 2009, 32 eligible children were enrolled in Head Start II and III with anaplastic astrocytoma (AA, n=19), glioblastoma multiforme (GBM, n=11), or other HGG (n=2). Central pathology review was completed on 78% of patients. Patients with predominantly brainstem tumors were excluded. Patients were to be treated with single induction chemotherapy Regimen C, comprising 4 cycles of vincristine, carboplatin and temozolomide. Following induction, patients underwent marrow-ablative chemotherapy and autologous hematopoietic cell rescue. Irradiation was to be used for patients with residual tumor after consolidation or >6 years old or at time of tumor progression.

RESULTS: The 5 year event-free (EFS) and overall survival (OS) for all HGG patients were 25±8% and 36±9% respectively. The EFS at 5 years for patients with AA and GBM were 24±11% and 30±16%, respectively (p=0.65). The OS at 5 years for patients with AA and GBM were 34±12% and 35±16%, respectively (p=0.83). Children < 36 months old experienced improved 5 year EFS and OS of 44±17% and 63±17%, compared with children 36-71 months old (31±13% and 38±14%) and children >72 months old (0% and 13±12%).

CONCLUSIONS: Irradiation-avoiding treatment strategies should be evaluated further in young children with HGG given similar survival rates to older children receiving standard irradiation-containing therapies.

INTRODUCTION

CNS tumors are the second most common childhood malignancy and the leading cause of cancer-related death in children [1]. High-grade gliomas (HGG) are a heterogeneous group of tumors that include World Health Organization (WHO) grade III (anaplastic Astrocytoma, AA) and IV (glioblastoma multiforme, GBM) neoplasms. HGGs account for approximately 10% of pediatric brain tumors and are the second commonest malignant central nervous system (CNS) tumor after medulloblastoma [2]. Current therapies include surgical resection, radiotherapy and chemotherapy, administered both concomitant with and following irradiation [2-6]. Despite aggressive multimodality therapy, historically the long-term survival has been poor, ranging from 10-30% [2]. In addition, young children treated with cranial irradiation experience significant and irreversible neurocognitive sequelae, a phenomenon now well described in the literature [7-9]. As a result, several clinical trials have attempted to delay or eliminate radiotherapy in the treated of intracranial malignancies, particularly in very young children [10-12]. Over the last two decades, marrow-ablative chemotherapy with autologous hematopoietic cell rescue has gained a role in the treatment of children with CNS tumors [13, 14]. Since 1991, the “Head Start” (HS) trials have focused on avoiding radiotherapy in young children and preserving neurocognitive function by incorporating high-dose, marrow-ablative chemotherapy and autologous hematopoietic progenitor cell rescue (AuHPCR) in the treatment of malignant CNS tumors. The success of this effort in the overall preservation of neuropsychological functioning and quality of life for patients treated on the HS protocols has been extensively discussed in other publications [7, 8]. Here we present the analysis of survival outcomes for children with HGG treated with a uniform induction and consolidation chemotherapy strategy (Regimen C) on the HS II and III protocols

PATIENTS AND METHODS

Patient Selection

Children less than 10 years old with newly diagnosed HGG without prior chemotherapy or irradiation were enrolled in two sequential, prospective, non-randomized international multi-institution studies, HS II (1997 – 2003) and “Head Start” III (2003 – 2009). Patients with diffuse intrinsic pontine gliomas (DIPG) were excluded. Gadolinium-enhanced magnetic resonance imaging (MRI) of the head and complete spine, as well as lumbar CSF cytology, was required at the time of study enrollment. Chemotherapy was required to begin within 42 days of the most recent definitive surgical procedure. With respect to HGG, The primary aim of the HS II and III protocols was to determine the event-free survival (EFS) and overall survival (OS) from the time of study enrollment of children treated with Regimen C followed by consolidation with marrow-ablative chemotherapy and AuHPCR after maximal surgical resection.

Surgery

All patients were to undergo maximal possible surgical resection, consistent with preservation of neurologic function, prior to enrollment in the studies. The extent of surgical resection was defined as follows: gross total resection (GTR) if no residual tumor was present, near total resection (NTR) when less than GTR but more than 90% resection was achieved, subtotal resection (STR) when less than 90% but more than 50% resection was achieved, and partial resection (PR) if less than 50% of the tumor was resected. A small

number of patients had biopsies only, where 10% or less of the tumor volume was resected. The degree of surgical resection was determined by central review of operative reports and of the pre-operative and post-operative MRI reports; where these differed, the extent of resection was based on the imaging studies.

Pathology Review

Patients were eligible to start therapy based on the institutional pathologic diagnosis. Every effort was made to obtain samples for central pathology review by leading neuropathologists in key centers in the United States and by the HS study committee neuropathologists at Children's Hospital Los Angeles. Two of 5 patients from HS II underwent central pathology review, with no discordant cases. For HS III patients, 23 of 27 (85%) underwent central review, with 2 discordant cases. Both cases were originally classified as GBM, and later revised to AA after central review. Histology was classified according to the most recent WHO criteria. Of the 13 long-term survivors (>3 years), 0 of 3 HS II patients had central review, and 9 of 10 HS III patients had central review. Two of those 9 cases were discordant; both were read at the institution as GBM and later revised to AA by the central reviewer.

Chemotherapy Regimen

All patients were to be treated with Regimen C, which consisted of 4 cycles of induction chemotherapy at 28 day intervals with vincristine (0.05 mg/Kg IV on days 0, 7 and 14), carboplatin (560 mg/m² or 20 mg/Kg IV, whichever was less, on days 0 and 1), and temozolomide (6.5 mg/Kg PO on days 0 through 4) followed by a consolidation phase with

one cycle of marrow-ablative chemotherapy consisting of thiotepa (300 mg/ m² IV on days -5 through -3) and carboplatin (calculated using the Calvert formula for a desired AUC of 7mg/mL/min, given IV, on days -8 through -6), with AuHPCR. Granulocyte colony-stimulating factor (G-CSF) 5µg/kg/day was to be administered subcutaneously commencing 24 hours after the last dose of chemotherapy in each induction cycle and continued until the post-nadir WBC was greater than 10,000/microliter. Chemotherapy was to be discontinued if disease progression or unacceptable toxicity occurred. Autologous hematopoietic progenitor cell leukopheresis was to be undertaken upon recovery from cycles 1 or 2.

Radiotherapy

Patients were to receive radiotherapy *only* if they were older than 6 years old at the time of diagnosis and/or had residual tumor at entry into consolidation chemotherapy. Radiotherapy was to be initiated following recovery from consolidation chemotherapy. Per protocol, children with localized residual tumor were to receive 54Gy local field RT. RT doses and volumes for rare patients with metastatic disease was left to treating investigators.

Quality of Life, Behavioral Functioning and Neuropsychologic Assessment

Data were collected using methodology similar to studies published from HS I and II [7,8]. All subjects enrolled on the Head Start III study were expected to undergo a neuropsychological assessment prior to transplant and every two years thereafter. Unfortunately, given the small number of high-grade glioma subjects and limited follow-up data, the available neuropsychological data will be reported as descriptive.

Informed Consent

Parents or legal guardians for each child signed an informed consent approved by the treating center's Institutional Review Board or equivalent committee. No patient was permitted to be enrolled from a participating center before the local institutional IRB approval letter and consent form were further reviewed and approved by the Operating office (CHLA) IRB.

Statistical Considerations

Primary endpoints for analysis were: EFS – time from date of diagnosis to progression, relapse or death from any cause; OS – time from date of diagnosis to death; and irradiation-free survival – time from date of diagnosis to death or to the initiation of radiotherapy for any reason. These were estimated using product-limit estimates with Greenwood standard errors. Comparisons between groups were based on the log-rank test.

RESULTS

From May 2001 to December 2009, 32 children less than 10 years old newly-diagnosed with and previously untreated for high-grade glioma were enrolled on the HS II and III protocols. Patient characteristics, tumor characteristics and surgical outcomes are described in detail in **Table I.**

Response to Induction and Consolidation Chemotherapy

Twenty of 32 children completed induction chemotherapy. Of the other 12 patients, 9 had progressive disease, 1 patient discontinued therapy per parent request, 1 patient died of sepsis during induction, and 1 patient had progressive disease prior to starting induction and elected to start XRT right away. **Table II** details the radiographic responses to the induction chemotherapy.

Nineteen patients (59.4%) proceeded to consolidation chemotherapy. A single patient that completed induction had SD at the end of induction, but the family opted not to proceed to consolidation. Radiographic response was assessed on day +42 following consolidation.

Radiation Therapy

Sixteen patients (50%) received radiation therapy at some point during their management. Nine patients received XRT for recurrence after BMT, 4 patients had disease progression during induction therapy, 2 patients had residual disease after consolidation, and 1 patient discontinued chemotherapy on day 2 of cycle 1 due to significant progression prior to starting therapy, and proceeded directly radiotherapy. Figure 1 diagrams patient outcomes based on response to induction, AuHPCR, and XRT.

Toxicity

One patient enrolled on HS III died of toxicity due to sepsis during induction; this patient was steroid-dependent and arrived at the ER in septic shock, rapidly developed ARDS and expired due to respiratory failure. Bronchoalveolar lavage demonstrated *Candida glabrata* and *Candida krusei*. There were no toxicity-related deaths during consolidation. Other non-fatal toxicity data are similar to those published for other patients enrolled on HS II and III on Regimens A, A2 or D, consisting primarily of cytopenias, mucositis, and anorexia, and are described in prior publications [10, 11].

Recurrent Disease and Relapses

Eleven patients experienced relapse after AuHPCR, and 1 patient who had stable disease after induction but declined AuHPCR had disease progression 2 years after stopping therapy. Of these 12 patients, eight relapsed within 12 months of AuHPCR (1, 1, 3, 3, 3, 5, 7, and 8 months after AuHPCR) and 4 patients relapsed at least 12 months after AuHPCR (17 months, 2, 4, and 5 years). One patient had metastatic recurrence in the paranasal sinus; the other 11 were local recurrences. Three families declined radiotherapy at recurrence; these patients died at 3, 5, and 9 months after recurrence. Nine patients received radiotherapy at the time of recurrence; 4 patients are still alive (3+, 42+ and 47+ months from date of recurrence) and 5 patients died at 11, 12, 15, 19, and 44 months after recurrence.

EFS, OS and Irradiation-Free Survival

Among patients who were still alive, the median follow-up time was 5.2 years (range 1.1 ~ 8 years). For those patients that passed away, their time to death ranged from 22 days to 4.4 years after starting on study. The 5-year Kaplan-Meier analyses of EFS and OS for the 32 patients with HGG treated on HS II and III with Regimen C were $25 \pm 8\%$ and $36 \pm 9\%$, respectively (Figure 2). Age-stratified EFS and OS are shown in Figure 3. 5-year irradiation-free survival was $31 \pm 10\%$ (Supplemental Figure 1). Overall, 11 of 32 patients survive. Nine of those 11 underwent BMT, 6 of whom survive without XRT. One additional surviving patient, who did not undergo BMT, had a second surgery and declined XRT, bringing the total number of patients who survive without XRT to 7.

Neuropsychological Assessment Results

Five patients underwent at least 3 serial neuropsychological evaluations that consisted of either an age appropriate Wechsler Full Scale IQ score, Verbal IQ and Performance IQ score, and/or the parent-report Adaptive Behavior Assessment Scale – 2nd edition. Four of the five subjects were assessed prior to transplant, (age range 5-49 month), with the most recent follow-up between 89 to 133 months, while the fifth subject was assessed at 79 months post transplant. As the data available in the Supplemental Table I illustrates, the IQ and adaptive functioning scores between subjects varied between the high average to impaired ranges; however, it is notable that the predominance of scores within subjects were generally consistent between pre-transplant and most recent follow-up, which is suggestive of similar stable findings from other HS subjects [7,8].

Analysis of Prognostic Factors

Supplemental Table II shows the analysis of prognostic factors. There was no statistically significant difference in EFS or OS by pathology, age at diagnosis, or extent of resection. Patient sex was the only factor that had statistical significance, with males having better OS than females ($65 \pm 12\%$ vs. $29 \pm 12\%$, $p=0.02$).

DISCUSSION

Patients with HGGs have historically experienced very poor prognosis and limited treatment options. Due to their relative rarity in children, there is a dearth of large randomized clinical trials. Many treatment options for children are therefore based on standard adult therapies with poor outcomes [19, 20]. Several publications have noted that pediatric and adult HGGs are molecularly different diseases, which may explain in part the lack of efficacy of adult-originated therapies in children [12, 20-29].

The first trial to evaluate the use of chemotherapy in the treatment of pediatric HGGs was the CCG-943 trial initiated in 1976, in which patients were randomized to receive regional field irradiation with or without adjuvant chemotherapy [30]. Two important conclusions arose from this study: that extent of resection was the single most important prognostic factor, and that adjunctive chemotherapy improves outcomes in pediatric patients (EFS of 46% for children receiving radiation plus chemotherapy *versus* 18% for those treated with radiotherapy alone) [30,31]. In contrast, adult trials using adjunct chemotherapy have had little success. In 2005, Stupp et al. demonstrated statistically significant improvement in survival for patient with GBM treated with adjunct temozolomide, reporting a 2 year OS of 27% for the irradiation plus temozolomide arm, compared to 10% for the irradiation only arm, or an absolute improvement in survival of 2.5 months [32].

Since the results of CCG-943, a limited number of studies, including the seminal CCG-945 and “Baby POG” trials, have continued to demonstrate an important role for chemotherapy in the treatment of pediatric HGG [12, 15-18, 35]. **Table III** summarizes the results of the most relevant of these trials. One commonality to all these studies is that the youngest children seem to have better outcomes than older children. Although no single explanation fully accounts for this observation, some studies have suggested that the gliomas of very young children are molecularly different from those of older children. For example, P53 gene mutations are associated with poor outcomes in high grade gliomas [27]. CCG-945 reported that among children less than 3 years old, 28% had p53 mutations, as compared to 70% of children three to six years old ($p=0.5$) [12]. Several other molecular genetic targets have been or are being investigated for their roles in the differences between adult and pediatric HGG, including phosphatase and tensin homolog (*PTEN*) deletions, epidermal growth factor receptor gene (*EGFR*) amplification, Alpha-type platelet-derived growth factor receptor (PDGFR α), and Akt pathway activation [22-26,28]. These biomarkers and others will need further research to establish their role as prognostic indicators and/or potential therapeutic targets in pediatric HGG.

The survival outcomes of the current study, although not statistically significant, show a trend that supports the theory of a biological difference between the HGG of younger *versus* older children. Our study included 9 patients under the age of 3 years, with 3 of those patients being 6 months or younger, and 7 of them less than 24 months of age at time of diagnosis. Three patients died (2 developed PD during induction therapy, one had relapse 3 months post AuHPCR), one patient left the study and was lost to follow up after 2 years and 5 patients survive 28+ to 72+ months after diagnosis. Four of these patients underwent AuHPCR and one family refused. One of these patients relapsed 6 months post-AuHPCR,

but was successfully treated with radiotherapy. Overall, for our patient under 3 years of age, the 5 year EFS and OS were $44\pm 17\%$ and $63\pm 17\%$, respectively, compared to children 36-71 months old ($31\pm 13\%$ and $38\pm 13\%$) and children >72 months old (0% and $13\pm 12\%$), $p=0.36$ for EFS and $p=0.32$ for OS. The small number of patients likely contributed to the lack of statistical significance, but the overall trend of this and other reported studies suggests that these youngest of patients have relatively more favorable survival rates with irradiation-avoiding strategies than their older counterparts with irradiation and chemotherapy.

The psychological and neurological burden of cranial radiation in children has been well documented [7-9]. The HS protocols were designed to eliminate or delay irradiation in the youngest children with the goal of preserving neuropsychological function and quality of life. The positive impact of the HS protocols on both of these metrics has been published previously [7,8,10]. Unfortunately, we have an insufficient number of subjects and follow-up testing data to report on the neurocognitive outcomes for these particular 32 patients. However, the limited outcomes for the high-grade glioma patients treated with the HS II and III protocols display a relative consistency of neurocognitive and adaptive functioning over time.

In terms of survival, the results of HS protocols have been mixed depending on the type of CNS tumor. For medulloblastomas, the survival compares favorably to other treatment protocols [10], while treating patients with DIPGs showed no survival benefit [28, 34]. Few data have been previously available for patients with HGG, and this is largest analysis of patients with HGG treated on a HS protocol, showing response rate, EFS and OS that are comparable to other irradiation-avoiding protocols.

There are several limitations to the current study. The lack of neurocognitive data does not allow us to make direct comments about the potential benefits of regimen C in HGG with regards to preservation of neurocognitive function. There was no collection or analysis of biological markers to further differentiate tumors on a molecular basis, such as in CCG-945. The relatively small number of patients makes it difficult to make generalizations about our data. Our analysis of prognostic factors such as diagnosis, age, and extent of resection failed to find any statistically significant differences where other studies have done so. The difference in OS between males and females may be an idiosyncrasy of our small patient sample and likely does not reflect a biologic difference between the sexes. Other studies have shown no difference in survival, and one study showed improved OS for females [15].

CONCLUSIONS

The survival for young children treated with this irradiation-avoiding strategy is similar to that of older children with standard irradiation-containing therapies. This outcome may reflect biological differences between HGG in young children versus older children. These relatively favorable EFS and OS are likely achieved with relative preservation of quality of life and intellectual functioning as compared to regimens using upfront irradiation; while our surviving patient numbers are too few to document this within this specific patient population, it is quite reasonable to extrapolate from other well-published reports on long-term outcomes on larger numbers of young children treated with the "Head Start" strategy for medulloblastoma and other malignant CNS embryonal tumors. These data suggest that, while improved outcomes with BMT remain unproven, irradiation-avoiding treatment strategies such as HS deserve

further development and evaluation in young children with HGG, and would best be tested in a multicenter trial comparing conventional with marrow-ablative chemotherapy.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the Michael Hoefflin Foundation, Soccer for Hope Foundation, Maddi's Closet, Alex's Lemonade Stand and the pediatric Cancer Research Foundation of Southern California for financial support provided for the conduct of these studies, and the Children's Hospital of Los Angeles Pediatric Residency program for supporting this research.

CONFLICT OF INTEREST STATEMENT

Dr. Espinoza is a clinical advisor to Birich Technologies, a small biotechnology firm with no products related to the diagnosis or treatment of CNS malignancies, or related research applications.

Research Support: funding provided by the Michael Hoefflin Foundation, Soccer for Hope Foundation, Maddi's Closet, Alex's Lemonade Stand, and the Pediatric Cancer Research Foundation of Southern California

REFERENCES

1. CBTRUS (2012). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2008 (March 23, 2012 Revision). Source: Central Brain Tumor Registry of the United States.
2. Broniscer A, Gajjar A. Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist. *Oncologist* , 2004 9: 197–206.
3. Friedman HS, Dolan ME, Pegg AE, Marcelli S, Keir S, Catino JJ, Bigner DD, Schold SCJ. Activity of temozolomide in the treatment of central nervous system tumor xenografts. *Cancer Res* , 1995 55: 2853–2857.
4. Nicholson HS, Krailo M, Ames MM, Seibel NL, Reid JM, Liu-Mares W, Vezina LG, Ettinger AG, Reaman GH. Phase I study of temozolomide in children and adolescents with recurrent solid tumors: a report from the Children's Cancer Group. *J Clin Oncol* , 1998 16: 3037–3043.
5. Estlin EJ, Lashford L, Ablett S, Price L, Gowing R, Gholkar A, Kohler J, Lewis IJ, Morland B, Pinkerton CR, Stevens MC, Mott M, Stevens R, Newell DR, Walker D, Dicks-Mireaux C, McDowell H, Reidenberg P, Statkevich P, Marco A, Batra V, Dugan M, Pearson AD. Phase I study of temozolomide in paediatric patients with advanced cancer. United Kingdom Children's Cancer Study Group. *Br J Cancer* , 1998 78: 652–661.
6. Friedman HS, McLendon RE, Kerby T, Dugan M, Bigner SH, Henry AJ, Ashley DM, Krischer J, Lovell S, Rasheed K, Marchev F, Seman AJ, Cokgor I, Rich J, Stewart E, Colvin OM, Provenzale JM, Bigner DD, Haglund MM, Friedman AH, Modrich PL. DNA

mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. *J Clin Oncol* , 1998 16: 3851–3857.

7. Sands SA, Oberg JA, Gardner SL, Whiteley JA, Glade-Bender JL, Finlay JL. Neuropsychological functioning of children treated with intensive chemotherapy followed by myeloablative consolidation chemotherapy and autologous hematopoietic cell rescue for newly diagnosed CNS tumors: an analysis of the Head Start II survivors. *Pediatr Blood Cancer* , 2010 54: 429–436.
8. Sands SA, Pasichow KP, Weiss R, Garvin J, Gardner S, Dunkel IJ, Finlay JL. Quality of life and behavioral follow-up study of Head Start I pediatric brain tumor survivors. *J Neurooncol* , 2011 101: 287–295.
9. Sands SA, Zhou T, O'Neil SH, Patel SK, Allen J, McGuire Cullen P, Kaleita TA, Noll R, Sklar C, Finlay JL. Long-term follow-up of children treated for high-grade gliomas: children's oncology group L991 final study report. *J Clin Oncol* , 2012 30: 943–949.
10. Dhall G, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ, McCowage GB, Diez B, Allen JC, Gopalan A, Cornelius AS, Termuhlen A, Abromowitch M, Sposto R, Finlay JL. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. *Pediatr Blood Cancer* , 2008 50: 1169–1175.
11. Mason WP, Grovas A, Halpern S, Dunkel IJ, Garvin J, Heller G, Rosenblum M, Gardner S, Lyden D, Sands S, Puccetti D, Lindsley K, Merchant TE, O'Malley B, Bayer L, Petriccione MM, Allen J, Finlay JL. Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. *J Clin Oncol* , 1998 16: 210–221.

12. Batra V, Sands SA, Holmes E, Geyer JR, Yates A, Becker L, Burger P, Gilles F, Wisoff J, Allen JC, Pollack IF, Finlay JL. 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. *Pediatr Blood Cancer* , 2014 61: 151–157.
13. Finlay JL, Massimino M. A consensus and state-of-the-art workshop: marrow ablative chemotherapy with hematopoietic cell rescue for malignant brain tumors of childhood and adolescence. *Pediatr Blood Cancer* , 2010 54: 634.
14. Massimino M, Cohen KJ, Finlay JL. Is there a role for myeloablative chemotherapy with autologous hematopoietic cell rescue in the management of childhood high-grade astrocytomas? *Pediatr Blood Cancer* , 2010 54: 641–643.
15. Wolff JEA, Gnekow AK, Kortmann R-D, Pietsch T, Urban C, Graf N, Kuhl J. Preradiation chemotherapy for pediatric patients with high-grade glioma. *Cancer* , 2002 94: 264–271.
16. Sanders RP, Kocak M, Burger PC, Merchant TE, Gajjar A, Broniscer A. High-grade astrocytoma in very young children. *Pediatr Blood Cancer* , 2007 49: 888–893.
17. Dufour C, Grill J, Lellouch-Tubiana A, Puget S, Chastagner P, Frappaz D, Doz F, Pichon F, Plantaz D, Gentet JC, Raquin MA, Kalifa C. High-grade glioma in children under 5 years of age: a chemotherapy only approach with the BBSFOP protocol. *Eur J Cancer* , 2006 42: 2939–2945.
18. Duffner PK, Horowitz ME, Krischer JP, Burger PC, Cohen ME, Sanford RA, Friedman HS, Kun LE. The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. *Neuro Oncol* , 1999 1: 152–161.

19. Khatua S, Sadighi ZS, Pearlman ML, Bocharé S, Vats TS. Brain tumors in children--current therapies and newer directions. *Indian J Pediatr* , 2012 79: 922–927.
20. Rood BR, MacDonald TJ. Pediatric high-grade glioma: molecular genetic clues for innovative therapeutic approaches. *J Neurooncol* , 2005 75: 267–272.
21. MacDonald TJ, Aguilera D, Kramm CM. Treatment of high-grade glioma in children and adolescents. *Neuro Oncol* , 2011 13: 1049–1058.
22. Pollack IF, Hamilton RL, James CD, Finkelstein SD, Burnham J, Yates AJ, Holmes EJ, Zhou T, Finlay JL. Rarity of PTEN deletions and EGFR amplification in malignant gliomas of childhood: results from the Children's Cancer Group 945 cohort. *J Neurosurg* , 2006 105: 418–424.
23. Paugh BS, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, Bax DA, Coyle B, Barrow J, Hargrave D, Lowe J, Gajjar A, Zhao W, Broniscer A, Ellison DW, Grundy RG, Baker SJ. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol* , 2010 28: 3061–3068.
24. Haas-Kogan D, Shalev N, Wong M, Mills G, Yount G, Stokoe D. Protein kinase B (PKB/Akt) activity is elevated in glioblastoma cells due to mutation of the tumor suppressor PTEN/MMAC. *Curr Biol* , 1998 8: 1195–1198.
25. Pollack IF, Hamilton RL, Burger PC, Brat DJ, Rosenblum MK, Murdoch GH, Nikiforova MN, Holmes EJ, Zhou T, Cohen KJ, Jakacki RI. Akt activation is a common event in pediatric malignant gliomas and a potential adverse prognostic marker: a report from the Children's Oncology Group. *J Neurooncol* , 2010 99: 155–163.

26. Faury D, Nantel A, Dunn SE, Guiot M-C, Haque T, Hauser P, Garami M, Bogнар L, Hanzely Z, Liberski PP, Lopez-Aguilar E, Valera ET, Tone LG, Carret A-S, Del Maestro RF, Gleave M, Montes J-L, Pietsch T, Albrecht S, Jabado N. Molecular profiling identifies prognostic subgroups of pediatric glioblastoma and shows increased YB-1 expression in tumors. *J Clin Oncol* , 2007 25: 1196–1208.
27. Pollack IF, Hamilton RL, Finkelstein SD, Campbell JW, Martinez AJ, Sherwin RN, Bozik ME, Gollin SM. The relationship between TP53 mutations and overexpression of p53 and prognosis in malignant gliomas of childhood. *Cancer Res* , 1997 57: 304–309.
28. Di Sapio A, Morra I, Pradotto L, Guido M, Schiffer D, Mauro A. Molecular genetic changes in a series of neuroepithelial tumors of childhood. *J Neurooncol* , 2002 59: 117–122.
29. Knobbe CB, Reifenberger G. Genetic alterations and aberrant expression of genes related to the phosphatidyl-inositol-3'-kinase/protein kinase B (Akt) signal transduction pathway in glioblastomas. *Brain Pathol* , 2003 13: 507–518.
30. Spoto R, Ertel IJ, Jenkin RD, Boesel CP, Venes JL, Ortega JA, Evans AE, Wara W, Hammond D. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group. *J Neurooncol* , 1989 7: 165–177.
31. Finlay JL, Zacharoulis S. The treatment of high grade gliomas and diffuse intrinsic pontine tumors of childhood and adolescence: a historical - and futuristic - perspective. *J Neurooncol* , 2005 75: 253–266.

32. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* , 2005 352: 987–996.
33. Duffner PK, Krischer JP, Burger PC, Cohen ME, Backstrom JW, Horowitz ME, Sanford RA, Friedman HS, Kun LE. Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. *J Neurooncol* , 1996 28: 245–256.
34. Fangusaro JR, Jubran RF, Allen J, Gardner S, Dunkel IJ, Rosenblum M, Atlas MP, Gonzalez-Gomez I, Miller D, Finlay JL. Brainstem primitive neuroectodermal tumors (bstPNET): results of treatment with intensive induction chemotherapy followed by consolidative chemotherapy with autologous hematopoietic cell rescue. *Pediatr Blood Cancer* , 2008 50: 715–717.
35. Strother DR, Lafay-Cousin L, Boyett JM, Burger P, Aronin P, Constine L, Duffner P, Kocak M, Kun LE, Horowitz ME, Gajjar A. Benefit from prolonged dose-intensive chemotherapy for infants with malignant brain tumors is restricted to patients with ependymoma: a report of the Pediatric Oncology Group randomized controlled trial 9233/34. *Neuro Oncol* , 2014 16: 457–465.

FIGURE LEGENDS

Figure 1: Diagram of Patient Outcomes

Figure 2: EFS and OS for All 32 Patients

Figure 3: A) EFS by Age at Diagnosis, B) OS by Age at Diagnosis

Table I. Patient Demographics and Tumor Characteristics

Characteristic	No.	%	Characteristic	
Gender			Diagnosis	
Female	18	56.3	AA	
Male	14	43.8	GBM	
			Malignant Glioma NOS	
			Malignant Glioneuronal tumor	
Age			Location	
Mean	4.6 years			
Median	4.1 years			
Range	0 - 9.8 years		Supratentorial	
0-6 months	3	9.4	Infratentorial	
All <3 years	9	28.1	Both	
3 - <6 years	13	40.6		
6 - 10 years	10	31.3	M Stage	
			M0	
			M1	
Race			M2	
Asian	1	3.1	M3	
Black	1	3.1		

Hispanic	6	18.8	Not evaluated
Maori	2	6.3	
Pacific Islander	1	3.1	Extent of Resection
White	21	65.6	No surgery
			Biopsy
			Partial Resection
			Sub-total resection
			Near total resection
			Gross total resection

AA= Anaplastic Astrocytoma, GBM= Glioblastoma Multiforme

Table II. Response to Induction Therapy

Response	Extent of resection		Total
	>90%	<90%	
CCR	2	0	2
CR	2	1	3
PR	2	1	3
MR	0	1	1
SD	2	9	11
PD	3	7	10
Not evaluated	0	0	2
Total	11	19	32
Response rate	44%	16%	25%
PD rate	27%	37%	33%

Response to Consolidation Therapy

Response	No.
CCR	5
CR	3
PR	2
MR	1
SD	6
PD	2
Total	19
Response rate	43%
PD rate	10.5%

Response Rate = CR + PR + MR/Total (excluding CCR), Progressive Disease (PD) Rate = PD/Total (including CCR), CCR= clinical complete response, CR= complete response, PR= partial response, MR= minimal response, SD= stable disease, PD= Progressive Disease

Table III. Summary of Clinical Studies

Table III. Summary of Clinical Studies

Study/year published	Age	No. of patients	% GBM	EFS	OS
Baby POG 8633 (1999) [18]	< 3 years	18	33	43% at 5 years	50% at 5 years
Wolff HIT-91 (2002) [15]	3- 17 years	52	52	not reported	15% at 5 years (maintenance Cx) 60% at 5 years (sandv Cx)

Baby POG 9234 (2014) [35]	< 3 years	9	100	not reported	55% at 5 years
Dufour BBSFOP (2006) [17]	< 5 years	21	38	35% at 5 years	59% at 5 years
Sanders (2007) [16]	< 3 years	16	31	28.6% at 5 years	66% at 5 years
CCG-945 (2013) [12]	0 -3 years	30	18	20% at 10 years	24% at 10 years
	3 - 6 years	21	29	24 % at 10 years	25% at 10 years
Head Start (2014 current study)	0 -3 years	9	22	44±17% at 5 years	63±17% at 5 years
	3 - 6 years	13	46	31±13% at 5 years	38±13% at 5 years
	> 6 years	10	30	0% at 5 years	13±12% at 5 years
	All patients	32	34	25±8% at 5 years	36±9% at 5 years

EFS= Event-Free Survival, OS= Overall Survival, GBM= Glioblastoma Multiforme, XRT= Radiation Therapy

Supplemental Figure 1: Irradiation-free Event-Free Survival

Supplemental Table I. Neuropsychologic Assessments

Supplemental Table II. Prognostic Factors

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Espinoza, JC;Haley, K;Patel, N;Dhall, G;Gardner, S;Allen, J;Torkildson, J;Cornelius, A;Rassekh, R;Bedros, A;Etzl, M;Garvin, J;Pradhan, K;Corbett, R;Sullivan, M;McGowage, G;Stein, D;Jasty, R;Sands, SA;Ji, L;Spoto, R;Finlay, JL

Title:

Outcome of young children with high-grade glioma treated with irradiation-avoiding intensive chemotherapy regimens: Final report of the Head Start II and III trials

Date:

2016-10-01

Citation:

Espinoza, J. C., Haley, K., Patel, N., Dhall, G., Gardner, S., Allen, J., Torkildson, J., Cornelius, A., Rassekh, R., Bedros, A., Etzl, M., Garvin, J., Pradhan, K., Corbett, R., Sullivan, M., McGowage, G., Stein, D., Jasty, R., Sands, S. A. ,... Finlay, J. L. (2016). Outcome of young children with high-grade glioma treated with irradiation-avoiding intensive chemotherapy regimens: Final report of the Head Start II and III trials. PEDIATRIC BLOOD & CANCER, 63 (10), pp.1806-1813. <https://doi.org/10.1002/pbc.26118>.

Persistent Link:

<http://hdl.handle.net/11343/291440>