



Subgroup-specific outcomes of children with malignant childhood brain tumors treated with an irradiation-sparing protocol

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Abstract

Purpose Molecular subgroups of pediatric brain tumors associated with divergent biological, clinical, and prognostic features have been identified. However, data regarding the impact of subgroup affiliation on the outcome of children with malignant brain tumors treated with radiation-sparing protocol is limited. We report long-term clinical outcomes and the molecular subgroups of malignant brain tumors in young children whose first-line treatment was high-dose chemotherapy without irradiation.

Methods Tumor subclassification was performed using the Illumina HumanMethylation450 BeadChip (450k) genome-wide methylation array profiling platform. Clinical information was obtained from chart review.

Results Methylation array profiling yielded information on molecular subgroups in 22 children. Median age at surgery was 26 months (range 1–119 months). Among medulloblastomas (MB), all 6 children in the infant sonic hedgehog (SHH) subgroup were long-term survivors, whereas all 4 children in subgroup 3 MB died. There was one long-term survivor in subgroup 4 MB. One out of five children with ependymoma was a long-term survivor (RELPOS). Both children with primitive neuroectodermal tumors died. One child with ATRT TYR and one child with choroid plexus carcinoma were long-term survivors.

Conclusions The efficacy of high-dose chemotherapy radiation-sparing treatment appears to be confined to favorable molecular subgroups of pediatric brain tumors, such as infant SHH MB. Identification of molecular subgroups that benefit from radiation-sparing therapy will aid in the design of prospective, “precision medicine”-driven clinical trials.

Keywords Pediatric brain tumor · Clinical outcome · Molecular subgroups

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Introduction

With continued development of technology, we are now able to determine the molecular subgroups within histological groups of pediatric brain tumors. These subgroups could differ from each other in their clinical trajectory, prognosis, and response to treatment despite similar histology. For many of these subgroups, the optimal treatment strategy is yet to be determined. It has long been accepted that craniospinal irradiation has deleterious long-term effects in the pediatric population, resulting in a decline in both intellectual quotient (IQ) and cognitive dysfunction, especially in the youngest children [1, 2]. When treated with radiation therapy (RT), children with medulloblastoma (MB) and primitive neuroectodermal tumors (PNET) had a 17.4-point drop in Full Scale IQ 4 years after treatment [3]. As a result, there have been efforts since the 1990s to develop chemotherapy regimens that could delay or prevent the use of RT in young children [4–7].

One of the more commonly used radiation-sparing chemotherapy regimens for young children newly diagnosed with malignant brain tumors is the Head Start approach [8–10]. There have been three successive Head Start protocols completed to date. The Head Start protocols include five cycles of induction chemotherapy followed by a single cycle of marrow-ablative chemotherapy with autologous hematopoietic cell rescue and no irradiation for the very youngest children [7, 11]. Children with progressive or recurrent disease after chemotherapy can receive irradiation at the discretion of their physician.

With radiation-sparing protocols being more widely used, it has been noted that subsets of young children with malignant brain tumors are being successfully treated with chemotherapy even without the use of high-dose myeloablative chemotherapy or irradiation. In a study by Rutkoski et al., children with MB without metastasis had a 5-year overall survival (OS) rate of 93% without the use of RT [12]. There is substantial variation even within the MB classification: children with desmoplastic MB had 93% lower risk of relapse or death than children with classic MB [12]. Supratentorial ependymomas have also been successfully treated with chemotherapy alone, yet children with infratentorial ependymomas have a higher risk of recurrence or death without RT [13].

While some patients with these tumors can be treated without RT, others continue to have a poor prognosis with or without the use of irradiation. Atypical teratoid/rhaboid tumors (ATRT) have a 3-year event-free survival (EFS) of 21% when using the Head Start III protocol [14]. It is clear that for certain tumor groups, there is a need for better treatment protocols. The impact of subgroup affiliation on the outcomes of children with high-grade brain tumors treated with a radiation-sparing protocol is unknown. The goal of this study is to report progression-free survival (PFS) and overall survival (OS) in the molecular subgroups of high-grade tumors treated with a high-dose chemotherapy approach without irradiation.

Methods

Clinical data

We performed a retrospective chart review of all children who underwent surgery for a malignant brain tumor between 1996 and 2014 and were subsequently treated at NYU Langone Health using a radiation-sparing approach. The study was approved by the NYU Institutional Review Board (IRB no. S14-00948).

Independent variables included age, sex, clinical presentation, associated disease, imaging features (localization, enhancement), pathology, staging, indication of surgery, age at surgery, extent of resection, shunt placement, complications,

recurrence (local or distant), and adjuvant therapies. Radiological and clinical outcomes were assessed.

All children were treated initially with surgery and chemotherapy. Gross total resection (GTR) was performed as part of the treatment in 20 cases. In 2 cases, only a diagnostic biopsy was performed, due to the size and location of the tumor or presence of metastatic disease.

Three Head Start protocols have been completed to date [8, 15]. The details of the Head Start treatment have been previously published and are summarized as follows. Head Start I was open from 1991 to 1996; Head Start II was open from 1996 to 2003; Head Start III was open from 2003 to 2009. Each of the Head Start protocols included 5 cycles of induction chemotherapy followed by a single course of high-dose chemotherapy with autologous stem cell rescue. Head Start I induction included cisplatin 3.5 mg/kg on day 1, cyclophosphamide 65 mg/kg/day and etoposide 3 mg/kg/day on days 2 and 3 for all 5 cycles, and vincristine 0.05 mg/kg on days 1, 8, and 15 for the first 3 cycles. Head Start II induction was the same as Head Start I except for the addition of methotrexate 12 g/m² on day 4 of each of the 5 cycles for children with metastatic MB, PNET, and ATRT. Induction for Head Start III included the same induction regimen as Head Start II with methotrexate for cycles 1, 3, and 5. Cycles 2 and 4 included temozolomide 150 mg/m²/day on days 1–5, oral etoposide 50 mg/m²/day on days 1–10, and cyclophosphamide 55 mg/kg/day on days 9 and 10; and vincristine 0.05 mg/kg on days 1, 8, and 15 for cycles 1–3. The consolidation course for each of the Head Start protocols was the same and included carboplatin daily for 3 days at a dose of 16.7 mg/kg/day (or 500 mg/m²/day, the lower of the two), followed by 3 days of thiotepa 10 mg/kg/day (300 mg/m²/day) and etoposide 8.3 mg/kg/day (250 mg/m²/day) with autologous stem cell rescue 3 days following completion of the chemotherapy. Irradiation at consolidation was only considered for children under the age of 6 years if there was residual tumor preconsolidation [15]. Each Head Start protocol investigates the efficacy of new chemotherapeutic agents in providing event-free survival after irradiation-free treatment as evidenced by the stepwise addition of chemotherapeutic agents at each protocol.

At progression, the physician and the family decided on the best treatment course. For some children, this included RT at this time.

For children who had surgery at an outside institution with histopathological review of the tissue and molecular subclassification, these findings were reviewed and included in the study.

Pathology and DNA methylation analysis

To confirm diagnosis and WHO grade, all tumors were reviewed by two neuropathologists (MS and CT), and the best

block of formalin-fixed paraffin-embedded (FFPE) tissue was selected for molecular studies. In 11 cases where FFPE tissue was not available, previously collected frozen tissue was obtained from the New York University Center for Biospecimen Research and Development (NYU CBRD).

Genomic DNA was extracted from FFPE tissue specimens using a Maxwell Promega DNA extraction kit. The DNA was bisulfite-converted using the EZ-96 DNA Methylation Kit from Zymo Research. FFPE samples underwent DNA restoration using the Illumina Infinium HD FFPE DNA Restore Kit. Samples were profiled using the Illumina Human Methylation 450 BeadChip Array for hybridization.

To establish the molecular subclassification of each tumor, tumors were analyzed using the whole-genome DNA methylation brain tumor classifier [16].

Illumina Infinium HumanMethylation450 BeadChip arrays were further analyzed using R package RnBeads version 1.0.0 [17]. Briefly, probes overlapping single nucleotide polymorphisms ($n = 4713$) were removed. The remaining probes were background-corrected using the “noob” method of the methylumi package [18], and beta values were normalized using the beta-mixture quantile method [19]. Subsequent beta values were used for principal component, exploratory hierarchical clustering, and differential methylation analyses. For unsupervised hierarchical clustering, the top 5000 probes with the greatest variance were selected for analysis. Statistics of differential sites were calculated using hierarchical linear models employed in the limma package.

Statistical analyses were run on GraphPad Prism 8 for Mac OS X. Data were compared using Fisher’s exact tests and Kaplan-Meier curves. Statistical significance was considered as probability of less than 0.05.

Results

The retrospective review yielded 57 consecutive children with high-grade tumors treated on a radiation-sparing protocol at our institution. Of those 57 children, 40 children had surgery at NYU or tissue deposited at our Institutional Tissue Bank. Tissue was available and methylation profiling was performed on tissue from 24 children. Methylation array profiling yielded information on molecular subgroups in 20 children. In addition, two children were included in the study in whom the subgroup classification was done at an outside institution as part of their diagnostic clinical plan. Age at surgery of children included in the study is shown in Fig. 1.

Pathology and treatment

Following the neuropathological review, our cohort included subjects with MB ($n = 11$), EPN ($n = 6$), ATRT ($n = 2$), pineal PNET ($n = 1$), supratentorial PNET ($n = 1$), and choroid

plexus carcinoma (CPC) ($n = 1$). The methylation array confirmed the diagnosis in 17 out of 20 cases. One child diagnosed with an anaplastic ependymoma in the histological review was classified as an ETMR in the 450k methylation array, one child diagnosed with supratentorial PNET was classified as an ETANTR, and one child diagnosed with pineal PNET was classified as pineoblastoma.

The overall survival of children with respect to their tumor type and molecular subgroup is shown in Fig. 2.

The methylation array-based subclassification was performed on children operated and treated at NYU (20/22, 91% children). Concordant with the previously published data, methylation profiling of the FFPE-derived DNA enables robust molecular subclassification of brain tumors (Fig. 3) [20–26].

The demographics, treatment, and outcome of the children in this study are shown in Tables 1 and 2.

Medulloblastoma

Medulloblastomas were classified into three out of the known four molecular subgroups using 450k methylation array [23]: sonic hedgehog (SHH), group 3 (G3), and group 4 (G4) were present, but there were no children with tumors in the Wnt subgroup. One histopathologically defined pineoblastoma in our study clustered together with group 3/4 medulloblastoma samples.

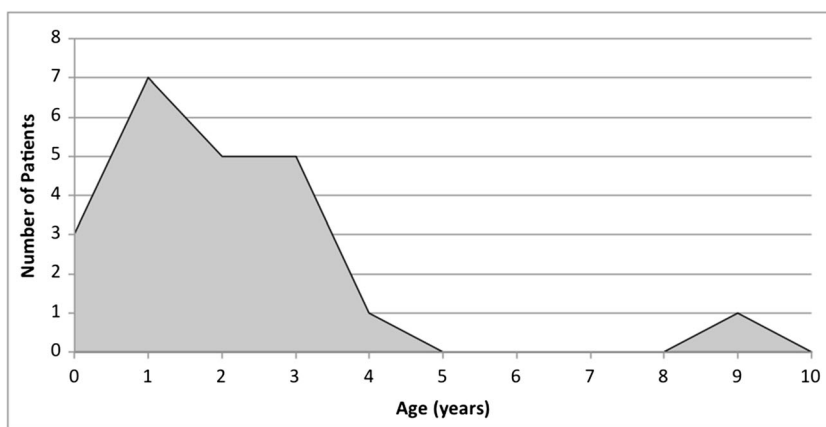
SHH

For children with MB-SHH tumors, the median age at surgery was 27 months (range 11–47 months), and the initial staging was a local disease in all cases except in child 5. All were long-term survivors and the 5-year PFS was 67%. The median length of follow-up was 13 years (range 4–16 years).

Group 3

There were 4 MB-G3 children with a median age of 31 months (range 15–56 months) at surgery. All of the children recurred at a median of 8 months after surgery (range 3–11 months) except for child 8. Both child 7 and child 8 were found to have diffusely metastatic disease at presentation. Child 7 underwent maximal safe resection of a large pineal mass but was also noted to have leptomeningeal spread in the brain and spine. Child 8 had extensive disease in the brain and spine, including a 4th ventricular mass, and biopsy of one of the spine lesions was performed prior to treatment with the Head Start protocol. There were no survivors and the MB-G3 children had a median OS of 5.5 months (range 2–37 months), including child 8 who died of infection.

Fig. 1 Age distribution at surgery of children included in the study



Ependymoma

In our study, children with EPN tumors had the following distribution: three posterior fossa group A (PFA) and two EPNs with C11orf95-RELA translocations (RELPOS). No posterior fossa group B (PFB) or Yap-positive ependymomas were present in our cohort [21]. There was one long-term survivor (child 16) in this group.

PFA

The median age at surgery was 23 months (range 19–119 months) for the three children with EPN-PFA tumors.

All three children recurred at a median of 16 months (range 4–25 months) after surgery. The survivors in this subgroup had a median OS of 71 months (range 62–91 months).

Age-related outcome

Of the 22 children in this group, 14 children (64%) were under the age of 3 years at diagnosis. Of those 14 children, 7 (50%) were survivors. In the 8 children over 3 years old, 3 children (38%) were survivors. There was no difference in progression-free or overall survival between those who had surgery before the age of 3 years or at older than 3 years ($p = 0.1$; $p = 0.5$).

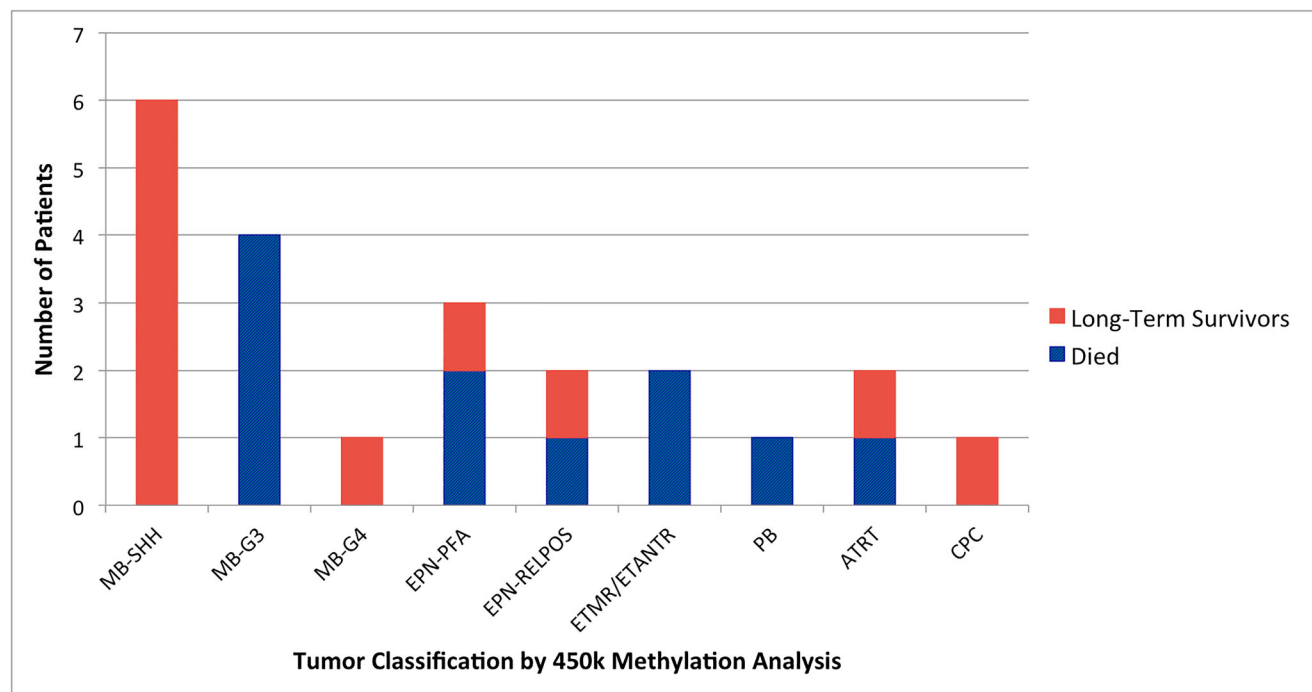


Fig. 2 Proportion of children in each tumor subgroup who are long-term survivors

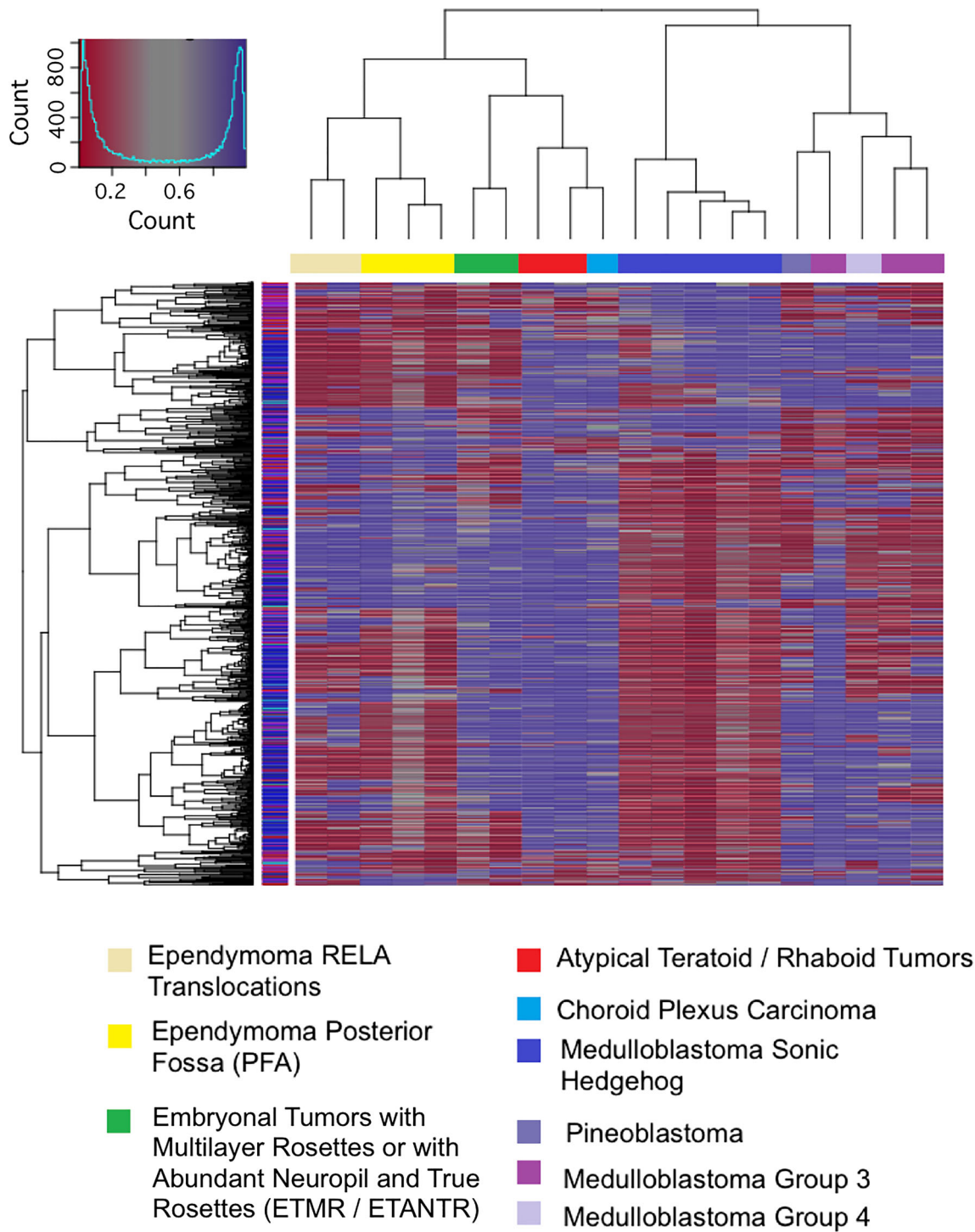


Fig. 3 Molecular subclassification of Head Start samples based on their DNA methylation profiles. Samples are classified using unsupervised hierarchical clustering using X (how many on the Y axis) differentially methylated probes. Neuroblastic tumors such as medulloblastoma and

pineoblastoma cluster together, while ATRT, choroid plexus carcinoma, and ETMR form a relatively separate cluster. Ependymomas form the third cluster and their signatures matched subclassification in PFA- and RELA-positive tumors

Table 1 Clinical characteristics and outcomes of 11 children with medulloblastoma

	Histological diagnosis	450k tumor subgroup	Age at surgery (months)	Metastatic disease	Clinical risk group	Resection	Chemotherapy	Progression-free survival (months)	Treatment at progression	Survival (months)	Length of follow-up (years)
1	MB—desmoplastic/nodular	MB-SHH	26	No	High	GTR	CCG protocol 99703				16
2	MB	MB-SHH	27	No	High	GTR	HS II + MTX				16
3	MB—desmoplastic/nodular	MB-SHH	24	No	High	GTR	HS II	25	RT		14
4	MB—desmoplastic/nodular	MB-SHH	47	No	Standard	GTR	HS III	35	Surgery/Chemo/RT		4
5	MB—desmoplastic/nodular	MB-SHH	11	Yes	High	GTR	HS III				11
6	MB—desmoplastic/nodular	MB-SHH	18	No	High	GTR	HS III				12
7	MB	MB-G3	15	Yes	High	Biopsy	HS II + MTX	8	None	10	
8	MB—anaplastic	MB-G3	25	Yes	High	Biopsy	HS III	1	None	2	
9	MB—anaplastic	MB-G3	56	Yes	High	GTR	HS III	3	None	3	
10	MB	MB-G3	36	No	High	GTR	HS II + MTX	11	Surgery/Chemo/RT	37	
11	MB—anaplastic	MB-G4	40	No	Standard	GTR	HS II + MTX	19	Surgery/Chemo/RT		16

Chemo chemotherapy, *G3* group 3, *G4* group 4, *GTR* gross total resection, *HS* Head Start, *MB* medulloblastoma, *MTX* methotrexate, *RT* radiation therapy, *SHH* sonic hedgehog

Functional outcomes of survivors

Ten children from this study were survivors and functional outcome at last follow-up is summarized in Table 3. Three of the children recurred and all had RT at the time of recurrence. Of these children, 8 were mainstreamed in school.

Discussion

This study shows that select children with high-grade tumors have favorable outcomes with high-intensity chemotherapy without radiation. A very promising response was seen in the group of children with MB-SHH tumors. Additionally, we report the results of radiation-sparing treatments in molecular subgroups of malignant pediatric CNS tumors. While it is important to continue looking at large cohorts for tumor-specific outcomes, a broader investigation of all pediatric CNS tumors, as in this study, is also necessary.

Prior to the incorporation of high-dose chemotherapy with autologous stem cell reinfusion, the prognosis for children diagnosed at a young age treated with surgery and chemotherapy with or without radiation therapy was dismal. In one review, the 12-month survival of patients with medulloblastoma or ependymoma who were less than 2 years of age at diagnosis was less than 32% and 5-year survival was less than 12% [27]. Similarly, Farwell and her colleagues reported a 23% survival at 1 year in patients of similar age and diagnosis [28]. The reported 5-year survival for children less than 4 years of age with medulloblastoma treated with either irradiation alone or irradiation and chemotherapy on the CCG-942 study was 32% [29].

Medulloblastomas

The Head Start protocols have continued to evolve to produce better clinical outcomes. In Head Start I, patients with desmoplastic and classical medulloblastomas had 5-year event-free and overall survival rates of 67% and 78%, and 29% and 57%, respectively. Patients with metastatic medulloblastoma fared worse [8]. Therefore, in Head Start II, patients with metastatic medulloblastoma received methotrexate during each of the 5 cycles of induction chemotherapy in addition to the cisplatin, vincristine, cyclophosphamide, and etoposide. Patients with standard-risk medulloblastoma received the same therapy in Head Start II as Head Start I. With the addition of methotrexate to the patients with high-risk medulloblastoma, 3-year event-free and overall survival rates improved to 49% and 60%, respectively. However, there was significant gastrointestinal toxicity and infections associated with methotrexate [10]. In Head Start III, the treatment was the same for patients with standard- and high-risk medulloblastoma. Induction cycles 1, 3, and 5 contained methotrexate with

Table 2 Clinical characteristics and outcomes of 11 children with different tumor classifications

Histological diagnosis	450k tumor subgroup	Age at surgery (months)	Metastatic disease	Resection	Chemotherapy	Progression-free survival (months)	Treatment at progression	Survival (months)	Length of follow-up (years)
12 EPN	EPN-PFA	119	No	GTR		16	Chemo/RT	71	
13 EPN—anaplastic	EPN-PFA	23	Yes	GTR	HS I	4	Surgery/Chemo/RT	91	
14 EPN	EPN-PFA	19	No	GTR		26	Surgery/Chemo/RT	62	
15 EPN	EPN-RELPOS	40	No	GTR	HS II + MTX	33	Gamma knife/RT	81	
16 EPN—anaplastic	EPN-RELPOS	19	No	GTR	HS III			10	5
17 EPN—anaplastic	ETMR	1	Yes	GTR	HS III	7	Chemo	17	
18 Supratentorial PNET	ETANTR	27	No	GTR	HS III	5	Surgery/Chemo/RT		
19 Pineal PNET	Pineoblastoma	48	Yes	GTR	HS II			11	
20 ATRT	ATRT other	11	Yes	GTR	HS III			2	
21 ATRT	ATRT TYR	24	No	GTR	HS II + MTX				15
22 GPC	GPC	37	No	GTR	HS III	2	Surgery/RT		5

ATRT atypical teratoid/rhabdoid tumor, Chemo chemotherapy, EPN ependymoma, GTR gross total resection, HS Head Start, MTX methotrexate, PNET primitive neuroectodermal tumor, RT radiation therapy

the goal of maintaining the encouraging results found in patients with high-risk disease in Head Start II. Induction cycles 2 and 4 were less intensive with oral temodar, etoposide, and intravenous cyclophosphamide with the goal of decreasing the toxicity associated with Head Start II.

In our study, all 6 MB-SHH children are survivors with a median follow-up of 12 years. This study supports recent data that show that infants with MB-SHH have an excellent outcome and may not need combined radio- and chemotherapy in all cases [30]. Our cohort of children with MB-SHH had a 5-year PFS of 67% and 33% required RT at recurrence. These results are similar to a report by Lafay-Cousin et al. in which clinical outcomes of a cohort of 53 subjects with MB who underwent a radiation-sparing, high-dose chemotherapy protocol are described [30]. The study used a different chemotherapy protocol and performed methylation profiling using a different technique. In their MB-SHH cohort, a PFS of up to 86% was observed, and ultimately, only 8% of the subjects required RT. A study by Robinson et al. investigating irradiation-sparing treatments for pediatric MB found that children with MB-SHH tumors have a 5-year PFS of 52%; 5-year PFS rates for children with tumors classified as MB-G3 and MB-G4 were 8% and 13%, respectively [31]. This is also similar to our cohort showing that MB-SHH patients had better outcomes than the other two molecular subgroups represented in our cohort.

While it is the standard of care for children under the age of 3 to have irradiation-sparing treatment, many children ≥ 3 years old are treated with craniospinal irradiation at diagnosis. The 5-year EFS for treatment of children ages 3–21 with average-risk MB with RT and adjuvant chemotherapy was found to be 81% [32]. However, a 10-year cumulative likelihood of developing a secondary malignancy at the site of radiation is estimated at 4% [33]. While RT is a very effective treatment for MB, the long-term effects on the quality of life and possible secondary malignancy behooves the improvement of irradiation-sparing treatments available to these children.

It is important to note that even within the MB-SHH subgroup, there is variability in the observed histology and genetic mutations [34]. The 5-year PFS rates with irradiation-sparing treatment are reported as 28% in the molecular subtype known as iSHH-I and 75% for iSHH-II [31]. New technology allows for more sophisticated risk stratification with molecular analysis compared with the classic stratification by clinicopathologic information. Ramaswamy et al. have described a risk stratification for children over the age of 3 years that takes into account specific genetic mutations within molecular subgroups [35]. In this stratification method, TP53 mutation, MYC mutation, and identified metastases can all alter the risk level of an MBB-SHH tumor. For the youngest children, Robinson et al. described the use of risk stratification

Table 3 Functional outcomes at last follow-up of the 10 children who were long-term survivors

Patient	Pathology	Age at surgery (months)	Recurrence (with RT)	Follow-up (years)	Functional outcome
1	MB-SHH	26	No	16	Mainstreamed in high school with individual assistance; ADHD
2	MB-SHH	27	No	16	Mainstreamed in high school, applied to colleges
3	MB-SHH	24	Yes (yes)	14	Matriculated in college, active runner
4	MB-SHH	47	Yes (yes)	4	Entered kindergarten
5	MB-SHH	11	No	11	Nonambulatory, nonverbal with developmental delay; attends school for severely handicapped children
6	MB-SHH	18	No	12	Mainstreamed high school; plays flag football and participates in extracurriculars
11	MB-G4	40	No	16	Mainstreamed in high school and maintains summer job stocking supplies; hypothyroid and growth hormone deficient, blind
16	EPN-RELPOS	19	No	5	Mainstreamed for first grade
21	ATRT	24	No	15	Attends high school with individual learning plan; is a black belt in karate
22	CPC	37	Yes (yes)	5	Mainstreamed for first grade

for treatment; most notably, the classification of SHH could be further subdivided into two groups in which the second group had increased survival [31]. One limitation of this study is the lack of identification of the p53 mutation in these tumors. By clinical risk stratification, the two children with standard-risk tumors were survivors. However, more advanced risk stratification—informed by molecular data—could provide more insight into defining treatment for these children.

This study follows 11 children with MB, but we had no representation of the MB-WNT subgroup which typically comprises 15–20% of MB tumors. The small cohort size and lack of representation of all molecular subgroups are limitations of this study. While we were able to comment on the survival of MB-SHH children in comparison with data in the literature, more studies with larger cohorts are necessary to include MB-WNT in the analysis.

Ependymomas

Only one of the children with ependymoma (anaplastic) achieved long-term survival. This outcome was achieved without any RT. This finding was expected, given the results of the Head Start protocols, in which ependymomas did poorly with the radiation-sparing approach [36]. As a result of this observation, radiation therapy is established as standard treatment in children with ependymoma, with recommended proton treatment in children < 3 years of age [37–39]; 3-year and 5-year PFS of children with EPN treated with RT have been reported as 76% and 66%, respectively [37, 39]. Children with grade III EPN treated with RT and adjuvant chemotherapy had a 5-year PFS of 57% and OS of 73% [37]. Considering this data, all children in this study with EPN who recurred were treated with RT at the time of recurrence.

In ependymomas, the extent of resection has been shown to correlate with PFS and OS regardless of subgroup [40]. Recent studies further suggest that EPN-PFBs can be treated with surgery alone, while EPN-PFAs need adjuvant radiation as part of the initial treatment [40]. EPN-PFAs occur mostly in younger children, while EPN-PFBs are mostly seen in older children, which may also be a factor in how the different subgroups respond to treatment.

ATRT

Children with ATRT tend to have lower survival rates compared with other tumor types. With the Head Start III protocol, children with ATRT had an OS of 26%, with a significant mortality from toxic death from high-dose chemotherapy treatment [14]. One of the children in our study with ATRT died of toxicity. However, child 21 (subgroup ATRT TYR) never recurred and was followed for 12 years following surgery and chemotherapy without irradiation. Such a long survival of a child with ATRT is an atypical outcome. This is an

example of how children with distinct molecular subgroups may have vastly different outcomes. Prospective studies comparing survival in the different molecular subgroups are needed.

Age at treatment and long-term quality of life

Long-term quality of life in survivors of pediatric CNS cancers has been assessed in several studies [41–44]. Although the combination of chemotherapy and irradiation can result in durable survival, the majority of children with malignant brain tumors treated with irradiation at a young age are left severely handicapped. Irradiation of the craniospinal axis will result in severe intellectual impairment, growth delay, and endocrine deficits [45]. It was identified early that young children who had irradiation-sparing treatment had better long-term outcomes in terms of general intelligence and motor skills among other factors [41]. The incidence and severity of these sequelae are inversely proportional to the age of the child at the time of irradiation [46]. Packer and his colleagues have demonstrated in a prospective study of children with medulloblastoma that the median decline in IQ for children less than 5 years of age at the time of irradiation was 25 points by 2 years from irradiation [47].

This was the impetus to develop effective irradiation-sparing protocols for children with CNS malignancies. There have been a number of studies looking at the quality of life of children who were treated using Head Start I/II protocols for both MB and non-MB tumors using validated questionnaires [42, 43]. These studies found that quality of life and behavioral/emotional functioning are within normal limits for survivors. One limitation of this study is the lack of analysis of measures of long-term quality of life of the surviving children. In all the studies looking at quality of life, specific data points on quality of life need to be collected through surveys filled out by the parents or patients. Since no contact with the patients was made for this pilot study, limited functional outcome data was collected from chart review.

Differences between histopathological diagnosis and molecular classification

Recent studies have shown how molecular classifications, especially through methylation arrays, can be used to more accurately diagnose and prognosticate CNS tumors [24, 48–50]. Methylation arrays can be used as a tool alongside histologic analysis to identify the appropriate diagnosis and can therefore inform treatment [25]. Two of the children in our cohort were found to have different tumors on methylation array than had been diagnosed with histological review. It has been estimated that up to 12% of children could have a change in diagnosis after DNA methylation analysis of their tissue [16]. Accurate diagnosis with the use of molecular tools can be important for

clinical decision-making and appropriate treatment of children.

Molecular analysis of tissue can also be used in risk stratification, which can inform the prognosis for a child [49, 50]. Larger studies are needed to improve our understanding on how molecular subgrouping can be used to predict treatment response and clinical outcomes of children.

This is a pilot study showing the feasibility of using methylation array to correlate molecular subgroups of malignant CNS tumors with outcome for young children treated with a radiation-sparing approach. However, this study is limited by the size of the cohort investigated, which was in part limited due to lack of tissue samples. Considering the small sample size, we were unable to come to any significant statistical conclusions about how age or extent of resection may have impacted clinical outcomes. Additionally, bigger cohorts and survey administration are needed to better assess long-term functional outcome of survivors. This study was also limited due to its retrospective nature; thus, we were unable to control for which children were chosen to be treated with the radiation-sparing protocol.

Conclusion

We conclude that the efficacy of radiation-sparing treatment approaches appears to be largely confined to favorable molecular subgroups of pediatric brain tumors, such as infant SHH MB. Identification of molecular subgroups that benefit from radiation-sparing therapy will aid in the design of future prospective, “precision medicine”-driven clinical trials using this treatment approach.

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Compliance with ethical standards

The study was approved by the NYU Institutional Review Board (IRB no. S14-00948).

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Formal consent is not required for this type of study.

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