Salvage therapies for first relapse of SHH medulloblastoma in early childhood

Craig Erker, MD[1*^]; Martin Mynarek, MD[2,3*]; Marie Simbozel, MD[4]; Brandon T. Craig, PhD[5]; Virginia L. Harrod, MD[6]; Andrea M. Cappellano, MD[7]; Kenneth J. Cohen, MD[8]; Vicente Santa-Maria Lopez, MD[9]; Andres Morales-La Madrid, MD[9]; Chantel Cacciotti, MD[10]; Lorena Baroni, MD[11]; Ralph Salloum, MD[12]; Ashley S. Margol, MD, MS[13]; George Michaiel, MD[14]; Dolly Aguilera, MD[15]; Claire M. Mazewski, MD[15]; Cassie N. Kline, MD[16]; Jonathan L. Finlay, MBChB[17]; Mohamed S. Abdelbaki, MD[18]; Jeffrey C. Murray, MD[19]; Kathleen Dorris, MD[20]; Bruce Crooks, MBChB[1]; Kevin F. Ginn, MD[21]; Nisreen Amayiri, MD[22]; Stephan Tippelt, MD[23]; Gudrun Fleischhack, MD[23]; Svenja Tonn, MD[2]; Nicolas U Gerber, MD[24]; Alvaro Lassaletta, MD[25]; Jordan R. Hansford, MBBS[26,27]; Sara Khan, MD[12]; Stephen W. Gilheeney, MD[28]; Lindsey M. Hoffman, DO[29]; Michal Zapotocky, MD[30]; Valérie Larouche, MD[31]; Shafqat Shah, MD[32]; Vijay Ramaswamy, MD[33]; Amar Gajjar, MD[34]; Sébastien Perreault, MD[35]; Sabine Mueller, MD [36,37]; Juliette Hukin, MB[38]; Sylvia Cheng, MD[14]; Zhihong J. Wang, MD[39]; Kara Matheson, MSc[40]; Simon Bailey, MBChB[41]; Eric Bouffet, MD[33]; Steven C. Clifford, PhD[41]; Giles Robinson, MD[34]; Christelle Dufour, MD[4#]; Stefan Rutkowski, MD[2#]; and Lucie Lafay-Cousin, MD[42#]

*Co-first author

#Co-last author

^Corresponding author: Craig Erker, Department of Pediatrics, Dalhousie University, 5850/5980 University Avenue, Halifax, Nova Scotia, Canada. E-mail: craig.erker@iwk.nshealth.ca . Phone: 902-470-3743

1) Division of Hematology/Oncology, Department of Paediatrics, IWK Health Centre and Dalhousie University, Halifax, NS, Canada
2) Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3) Mildred Scheel Cancer Career Center HaTriCS4, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
4) Department of Child and Adolescent Oncology, Gustave Roussy, Paris-Saclay University, Villejuif, France
5) Department of Pediatrics, University of Calgary and Alberta Children's Hospital Research Institute (ACHRI), Calgary, AB, Canada
6) Departments of Pediatric Hematology and Oncology, Dell Children's Medical Center of Central Texas and University of Texas, Austin, TX, USA
7) Division of Pediatric Oncology/BMT, Instituto de Oncologia Pedi´ atrica-GRAACC-UNIFESP, São Paulo, Brazil
8) Pediatric Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA
9) Pediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain
10) Children's Hospital London Health Sciences, Division of Pediatric Hematology/Oncology, Western University, London, ON, Canada
11) Hospital of Pediatrics SAMIC Prof. Dr Juan P. Garrahan, Buenos Aires, Argentina
12) Division of Hematology, Oncology and Blood and Marrow Transplant, Nationwide Children's Hospital and The Ohio State University, Columbus, OH, USA

13) Departments of Pediatrics and Radiation Oncology, The Ohio State University College of Medicine, Columbus, OH, USA

14) Cancer and Blood Disease Institute, Children's Hospital Los Angeles, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA

15) Division of Hematology, Oncology/ Bone Marrow Transplant, Department of Pediatrics, British Columbia Children's Hospital and University of British Columbia, Vancouver, BC, Canada

16) Aflac Cancer and Blood Disorder Center, Children's Healthcare of Atlanta & Emory University, Atlanta, GA, USA

17) Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

18) Division of Pediatric Hematology, Oncology, and Bone Marrow Transplant, Washington University School of Medicine in St Louis, St Louis, MO, USA

19) Division of Pediatric Hematology/Oncology, Cook Children's Medical Center, Fort Worth, TX, USA

20) Children's Hospital of Colorado & University of Colorado School of Medicine, Denver, CO, USA

21) Division of Pediatric Hematology and Oncology, Children's Mercy Hospital, Kansas City, MO, USA

22) Department of Pediatric Hematology/Oncology, King Hussein Cancer Center, Amman, Jordan

23) Pediatrics III, Pediatric Oncology and Hematology, University Hospital Essen, Essen, Germany

24) Department of Oncology, University Children's Hospital, Zurich, Switzerland

25) Department of Pediatric Hematology and Oncology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

26) Children's Cancer Centre, The Royal Children's Hospital; Murdoch Children's Research Institute; University of Melbourne, Melbourne, VIC, Australia

27) Michael Rice Centre for Hematology and Oncology, The Women's and Children's Hospital; South Australia Health and Medical Research Institute, South Australian immunoGENomics Cancer Institute; University of Adelaide, Adelaide, Australia

28) Department of Pediatrics and Division of Hematology and Oncology, Mount Sinai, New York, NY, USA

29) Center for Cancer and Blood Disorders, Phoenix Children's Hospital, Phoenix, AZ, USA

30) Department of Paediatric Haematology and Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

31) Department of Pediatrics, Centre Mère-enfant Soleil du CHU de Quèbec-Université Laval, Quebec City, QC, Canada

32) The University of Texas Health Science Center, Department of Pediatric Hematology-Oncology, San Antonio, TX, USA

33) Division of Haematology/Oncology, Department of Paediatrics, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada

34) Department of Oncology, St Jude Children's Research Hospital, Memphis, TN, USA

35) Centre Hospitalier Universitaire Sainte Justine, Université de Montreal, Montreal, QC, Canada

36) Department of Neurology, Neurosurgery and Pediatrics, University of California San Francisco, San Francisco, CA, USA

37) Department of Pediatrics, University of Zurich, Switzerland

38) Divisions of Neurology and Hematology, Oncology/ Bone Marrow Transplant, Department of Pediatrics, British Columbia Children's Hospital and University of British Columbia, Vancouver, BC, Canada

39) Division of Hematology and Oncology, Children's Hospital of Richmond and Virginia Commonwealth University, Richmond, VA, USA

40) Research Methods Unit, Nova Scotia Health Authority, Halifax, NS, Canada

41) Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle-upon-Tyne, United Kingdom

42) Section of Pediatric Hematology and Bone Marrow Transplantation, Alberta Children's Hospital, Calgary, AB, Canada

**ABSTRACT**

*Background:* Sonic hedgehog (SHH) medulloblastoma is the most common molecular group of infant and early childhood medulloblastoma (iMB) and has no standard of care at relapse. This work aimed to evaluate the post-relapse survival (PRS) and explore prognostic factors of patients with nodular desmoplastic (ND) and/or SHH iMB.

*Methods:* This international retrospective study included 147 subjects diagnosed with relapsed Nodular Desmoplastic/SHH iMB between 1995 and 2017, < 6 years old at original diagnosis, and treated without initial craniospinal irradiation (CSI). Univariable and multivariable Cox models with propensity score analyses were used to assess PRS for those in the curative intent cohort.

*Results:* The 3-year PRS was 61.6% (95% CI, 52.2 to 69.6). The median age at relapse was 3.4 years (IQR, 2.6-4.1). Those with local relapse (40.8%) more often received salvage surgery ($p$ <0.001), low-dose CSI (≤ 24 Gy; $p$ < 0.001), or focal radiotherapy ($p$ = 0.008). Patients not receiving CSI (40.5%) more often received salvage marrow-ablative chemotherapy (HDC+AuHCR [$p$ <0.001]). On multivariable analysis, CSI was associated with improved survival (Hazard Ratio [HR] 0.33 [95% CI, 0.13 to 0.86], $p$ =0.04). Salvage HDC+AuHCR, while clinically important, did not reach statistical significance (HR 0.24 [95% CI, 0.0054 to 1.025], $p$ =0.065).

*Conclusions:* Survival of patients with relapsed SHH iMB is not satisfactory and relies on treatments associated with toxicities including CSI and/or HDC+AuHCR. Upfront cure to avoid relapse is crucial. For patients with localized relapse undergoing resection, alternative salvage regimens that avoid high-dose CSI (> 24 Gy) can be considered.

**KEYWORDS:** SHH, Medulloblastoma, relapse, infant and early childhood

**IMPORTANCE OF THE STUDY:** ND/SHH is the most common molecular group of iMB. Upfront HDC+AuHCR or intrathecal/intraventricular (IT/IV) methotrexate given with conventional chemotherapy have achieved improved outcomes, yet management for patients with recurrence remains poorly described. This international study describes and analyzes current salvage practices, post-relapse survival, and variables that influence prognosis. This study shows the use of salvage CSI is associated with improved survival. Although clinically meaningful improvement in survival is seen with salvage HDC+AuHCR, it does not reach statistical significance. Patients with recurrent ND/SHH iMB remain young at the time of relapse (median age 3.4 years), highlighting the importance of maximizing first-line treatment for cure to minimize toxic therapies at relapse. We also report patients with local relapses can be successfully treated with surgical resection and either non-CSI approaches or low-dose CSI (≤ 24 Gy) without significant differences in outcome compared to those with distant relapses who are often treated with high-dose CSI.

**KEY POINTS:**

- The survival of relapsed SHH iMB patients is just above 60% and relies on treatment mainly with CSI and/or HDC+AuHCR
- Pattern of relapse informs salvage treatment where local recurrence may be considered for treatment that avoids high-dose CSI (> 24 Gy)

## INTRODUCTION

Infant and early childhood medulloblastoma (iMB) therapy is based on the avoidance of craniospinal irradiation (CSI) often using marrow-ablative high-dose chemotherapy and autologous hematopoietic cell rescue (HDC+AuHCR) regimens or with conventional chemotherapy (CT) and intrathecal/intraventricular (IT/IV) chemotherapy to maximize survival and minimize neurocognitive late effects.[1-6] Young patients with nodular desmoplastic medulloblastoma (ND)/Sonic Hedgehog (SHH) have favorable prognosis with these strategies.[5,7,8] However, conventional chemotherapy alone results in relapse in up to 50% of patients.[5,8-10]

In a prior report, we described SHH iMB group often presented with early (< 12 months from diagnosis) and localized relapses.[11] Although SHH iMB patients commonly received CSI-based salvage therapy, 40% underwent non-CSI salvage treatments.[11] Following salvage therapy their 3-year post-relapse survival (PRS) was 60%.[11] In the current study, we evaluate outcomes of relapsed ND and/or SHH iMB based on salvage treatment modalities, relapse patterns, and explore prognostic factors.

## PATIENTS AND METHODS

### Study population

Considering the near complete overlap between ND histology and the SHH molecular group in iMB,[5] the presented cohort was assembled using all patients with ND and/or SHH medulloblastoma from our previously reported cohort[11] and two new cohorts from France and Germany. All patients were age < 6 years at initial diagnosis[11] with either SHH molecularly defined or ND/MBEN histology, and presented with relapse following frontline CSI-sparing therapy.

Patients treated with focal radiotherapy (fRT) before relapse were eligible. All patients were initially diagnosed between 1995 and 2017.

**Clinical data collection**

Following ethics approval at participating centers, standardized forms were used to collect clinical and outcome data as previously defined and described.[11] Data was collected as a convenience sample from patients involved in previous clinical trials (SJYC07 [NCT00602667], ACNS1221 [NCT02017964], and HIT-2000-BIS4 [NCT00303810]), patient trial registries (HIT [NCT02238899 and NCT02417324]), and individual treating centers. For patients enrolled previously in upfront clinical trials, data was collected through existing databases, and when data was not available then through individual centers or a patient registry. Metastatic status was defined according to the Chang classification.[12] The cohort was categorized as molecularly defined iMB SHH or ND/MBEN non-molecularly defined iMB, according to local institutional reports. Tumor histology was determined by the institutional pathologist via the patient's pathology report while SHH molecular classification was determined by institutionally assessed immunohistochemistry or molecular platform. As methylation characterization of SHH iMB was obtained through different platforms, the data from the SHH1 and SHH β were merged, as were SHH2 and SHH γ.[13,14] Information on constitutional genetic predisposition was not collected. CSI dosing was dichotomized to reflect the bimodal dose distribution seen in clinical practice and in our cohort. We used 24 Gy as a cutoff with ≤24 Gy being called low-dose CSI and >24 Gy called higher-dose CSI to reflect clinical practice and historical data that doses of 23.4 Gy result in less severe neuropsychological toxicity than higher CSI doses.[6,15]

**Statistical analysis**

Non-parametric analyses were used to assess for differences between the ND non-molecularly defined group and SHH-defined cohorts. PRS, defined as the time from the first relapse to death or last follow-up, was examined using patients in the curative intent cohort. PRS was performed using Kaplan-Meier analysis and significance testing ($\alpha = 0.05$) based on log-rank testing. Univariable and multivariable Cox proportional hazard models were used to estimate the hazard ratio to death. The Kaplan-Meier curves and proportional hazard models were adjusted using an inverse probability of treatment weight. The propensity score weight was stabilized using standardized mean weight to compensate for imbalances in treatment prior to relapse.[16] The propensity score weight was generated by fitting a logistic regression model with CSI treatment as the outcome adjusting for confounders believed to be related to CSI treatment after relapse and the study outcome, mortality. Variables included in the propensity score model included diagnosis era, molecular group and subgroup, frontline fRT, age at relapse, pattern of relapse, upfront chemotherapy type (CT alone *versus* HDC+AuHCR), time from diagnosis to relapse, and sex. Salvage CSI and HDC+AuHCR variables were assessed as time-dependent variables accounting for the time from initial relapse until a patient received CSI and/or HDC+AuHCR to account for the possibility of immortal time bias. Variables for the multivariable analysis were chosen *post hoc*, based on clinical relevance and/or univariable survival analysis results ($P < 0.1$). SAS 9.4 (Cary, NC) was used for all statistical analyses.

## RESULTS

### Patient characteristics and treatments prior to relapse

A total of 147 patients were included in the study, 129 received curative intent salvage therapy while 18 underwent palliative treatment. Forty-one were not previously reported.[11] One-hundred and thirteen of the 147 patients had molecularly-defined SHH MB with the remainder having ND MB. Fifty percent (n = 74) were originally enrolled in prospective clinical trials for upfront disease and suffered relapse or were part of registries: 19 from SJYC07, 10 from ACNS1221, 30 from the HIT trials and registry, and 15 from the United Kingdom Children's Cancer Leukemia Group (UK-CCLG). The remaining patients were collected from 20 individual international institutions.

The patient characteristics and treatment modalities at initial diagnosis are described in *table 1*. The median age at initial diagnosis of MB was 27 months (range 1-70 months). Localized disease was present in 74.3%. Gross total resection (GTR) of the primary mass was achieved in 72.8%. Regarding the 113 (76.9%) patients with molecularly-defined SHH MB, 13 (11.5%) had non-ND/MBEN histology (9 classic iMB and 4 large-cell anaplastic iMB). Defining SHH medulloblastoma molecularly was conducted via institutional standard testing (*supplemental table 1*). Methylation subtyping was available in 37.2% of the SHH MB cohort, segregating into SHH1/β and SHH2/γ for 61.9% and 38.1% respectively (*supplemental table 2*).

After initial surgical resection, patients primarily received adjuvant CT. The most commonly used regimens were the HIT SKK regimen[17] followed by Head Start induction treatment[8] in 39.2% and 20% respectively (*supplemental figure 1*). IT/IV chemotherapy was administered in 26.2% of the cases. Twenty-one patients (14.3%) underwent maintenance therapy, with 12 (57.1%) receiving

maintenance according to the SJYC07 protocol.[9] HDC+AUHCR strategies were used in 17.7% predominantly with one cycle (69.2%) or three sequential cycles (30.8%). Only eight patients (5.4%) received fRT. At completion of initial therapy, 51% achieved complete response, 7.5% incomplete response, 36.7% progressive disease, and 4.8% had unknown response status.

**Pattern of relapse**

The median time to relapse/progression from initial diagnosis was 14.7 months (IQR 9.0-18.4) or 4 months (IQR 0-9) from treatment completion. Relapse on therapy occurred in 38.1% while only four patients relapsed beyond 30 months from diagnosis (31, 41, 56, and 140 months). The median age at the time of relapse was 3.4 years (IQR 2.6-4.1). Only 17.0% of the patients presented with symptomatic relapse whereas the majority were detected during routine surveillance. Local relapse accounted for 40.8%, while combined or disseminated relapse was reported in 57.1% (unknown 2%; *figure 1a*).

**Salvage therapy for the curative intent cohort**

The 18 patients who underwent palliative management were younger at the time of diagnosis ($p$ = 0.02) and at relapse ($p$ = 0.045), and more likely to present with clinically symptomatic ($p$ = 0.003) and disseminated relapse ($p$ = 0.03).

Of the 129 patients treated with curative intent, 99 (76.7%) were molecularly defined SHH and 30 (23.3%) were histologically defined ND iMB. Of the 99 patients with molecularly defined SHH, 92% were diagnosed via various molecular platforms with DNA methylation being the most common (n=71) and the remaining 8% diagnosed by IHC. The characteristics of patients with molecularly defined SHH iMB and histologically defined ND iMB were not significantly different

(*table 2*). Given the similarity, the two cohorts were combined (n = 129) to describe salvage modalities and outcomes for the curative intent cohort.

Surgery

Half of the patients underwent surgical resection at the time of relapse. Among them, 63.3% achieved GTR. Surgery was more likely to be attempted in local relapse than in metastatic dissemination, 74.6% *versus* 36.7%, respectively ($p < 0.0001$).

Radiotherapy

RT was a core modality of salvage, used in 96 patients (74.4 %). Salvage RT was given most often as CSI in 78 patients (81.3 %). CSI dose was available in 69 (88.5%) patients with the median dose and boost delivered being 35.2 Gy [IQR 23.4-36] and 54.9 Gy [54-55.9], respectively. Thirty-two percent of the patients received CSI without chemotherapy [median dose 36.0 Gy IQR 31.7-36.0]. Twenty-three (33.3%) patients received low-dose CSI (≤ 24 Gy; *figure 1b*). Patients with localized relapses were more likely to receive low-dose salvage CSI ($p < 0.001$). Age at relapse was not statistically different ($p=0.58$) for those receiving ≤24 Gy compared to those who received higher-dose CSI (> 24 Gy). For the 30 patients with local relapse receiving CSI, the median dose was 23.4Gy [IQR 23.4-36 Gy; *supplemental figure 2*].

Children who received salvage CSI were older at the time of relapse than those who did not (44.4 months *versus* 34.8 months; $p <0.0001$) and were more likely to have later relapse from initial diagnosis (15.6 months *versus* 11 months; $p = 0.006$). Children who received salvage CSI were less likely to have received HDC+AuHCR as part of their salvage therapy compared to children who did not receive salvage CSI (16.7% *vs* 45.1%; $p = 0.0004$).

Of the 18 children receiving non-CSI-based salvage irradiation, 16 underwent salvage fRT at a median dose of 54 Gy [IQR 50.4-54] and the 2 remaining patients received systemic radio-isotope. Thirteen of 16 (81.3%) patients who received salvage fRT had a localized relapse.

Chemotherapy and targeted treatments

Chemotherapy was given to 76.9% of patients including 47.2% receiving conventional CT, 36.2% using HDC+AuHCR, and the remainder receiving maintenance chemotherapy alone. Patients who underwent HDC+AuHCR predominantly received one cycle of consolidation (47.2%) most commonly with carboplatin, etoposide, and thiotepa (58.8%). Sequential consolidation with 3 cycles was reported in 33.3%, mainly using carboplatin and thiotepa (83.3%). Other combinations of agents including busulfan/thiotepa and melphalan/carboplatin among others, accounted for the remaining third of the marrow-ablative regimens. None of the children who underwent salvage HDC+AuHCR had previously received HDC+AuHCR at initial diagnosis. Twenty patients also received IT/IV chemotherapy as a part of salvage therapy. Eleven of them previously had IT/IV during upfront treatment. Eleven patients (8.5%) received SHH inhibitors during salvage treatment (eight patients received vismodegib and three sonidegib)

Treatment combinations

For the 78 patients who underwent salvage CSI, most also received either CT (51.3%) or HDC+AuHCR (16.7%). In those receiving CT in combination with CSI, CT was used pre-, post, or both pre- and post-RT in 31.6%, 42.1%, and 26.3% respectively. The median dose of CSI used in combination with CT or HDC+AuHCR was not significantly different compared to CSI alone ($p$ = 0.09). Patients who received salvage CSI ≤ 24 Gy (82.6% (n=19) vs 37.2% (n=16)) were more likely to have undergone salvage surgery (p =0.0004).

Thirteen of the 36 patients who received HDC+AuHCR also underwent CSI. Five of 23 patients treated with CSI ≤24Gy also underwent salvage HDC. In all cases, the CSI followed HDC+AuHCR at a median time of 1 month (range 0-14 months). For those who received both salvage HDC+AuHCR and CSI, there was no difference in the frequency of low-dose *versus* higher-dose CSI (p=0.5005). The remaining 23 patients did not receive CSI after HDC+AuHCR, although 7 received focal FT and 2 had systemic radioisotope.

Overall, 72 patients (55.8%) either received no RT (n=33) or underwent CSI at a dose ≤ 24 Gy (n=23) or fRT only (n=16). Treatment combinations for the patients who received CSI ≤24Gy are illustrated in *supplemental figure 3.* Of the 33 patients who did not receive any radiotherapy, 14 (42.4%) underwent surgery with additional chemotherapy (seven HDC+AuHCR and seven conventional CT). The remaining 19 patients were treated without surgery and received HDC+AuHDC (36.8%), CT (42.1%), and IT/IV chemotherapy (15.7%) with one patient missing chemotherapy details. Patients treated without RT were more likely to receive salvage HDC than those treated with RT. Fourteen (42.4%) patients treated without RT had local relapse.

**Causes of death**

Forty-two patients (33.1%) died of disease and 11 (8.7%) died of other causes including three from acute treatment toxicity (1 sepsis during HDC+AuHDC with thiotepa, etoposide and carboplatin, 1 hemorrhage with conventional chemotherapy and 1 unknown), two from late treatment-related complications (irradiation-related chronic lung disease and acute subdural hemorrhage), five (3.9%) of subsequent malignancies (including one hip osteosarcoma, one bithalamic glioma, one glioblastoma, one leukemia, and one unknown subsequent malignancy), and one of unknown cause. For the 5 patients who died of subsequent malignancy, all had

ND/MBEN histology and were < 3 years of age at original diagnosis (range 0-2.8 years). The onset of subsequent malignancy from relapse was at a mean of 8.9 years (range 7.2 – 12.5).

**Post-relapse survival and associated prognostic factors**

At a median follow-up of 32.3 months (IQR 14-72), the 3-year PRS was 61.6% (95% 52.2-69.6; *figure 1c*). Patients treated with salvage RT (CSI or fRT) had a 3-year PRS of 74.8% (95% CI 60.7%-83.6 %) compared to 38.5 % (16.9%-59.9%) for those who did not ($p$=0.006; *figure 2a*). However, no statistical difference was detected when comparing CSI with fRT only ($p$=0.53; *figure 2b*). Of interest, the 3-year PRS for the 23 patients who received salvage CSI ≤ 24 Gy was 87.8% (95% CI 53.5, 97.3) compared with 68.2% (95% CI 51.1, 80.4) for those with CSI > 24 Gy, ($p$ = 0.1005; *figure 2c*). Similarly, the 3-year PFS for those who received fRT was 65.6 % (29.6-86.4). Patients with localized relapse were more likely to receive CSI dose ≤24Gy ($p$ < 0.0001), focal irradiation, and undergo surgical resection ($p$ < 0.0001). The PRS for patients treated with CSI in combination with CT or HDC+AuHCR as compared to salvage CSI only (81.2% [61.8-91.3] *versus* 62.0% [38.4-78.7, $p$=0.059; *figure 2d*). PRS for patients with localized relapse *versus* those with disseminated relapse is shown in *figure 2e* ($p$ = 0.35).

In univariate Cox Proportional-Hazard analysis, younger age at relapse (<36 months old) and early relapse (<12 months from diagnosis) were associated with worse PRS, while the use of salvage CSI was associated with better PRS (*table 3*). Although salvage HDC+AuHCR and surgery at relapse were not significant in improving PRS (p = 0.083 and 0.06, respectively), they were included in multivariable testing. In post-hoc analysis, there was a statistically significant interaction between salvage HDC+AuHCR without CSI *versus* salvage CSI without HDC+AuHCR with crossing of survival curves. Patients who received both CSI and HDC+AuHCR appeared to do best

(*supplemental figure 4*), followed by patients treated without either CSI or HDC+AuHCR had the lowest 3-year PRS at 31.6% (95% CI 10.7-55.3%). The upfront metastatic status, the use of HDC+AuHCR or CT at initial diagnosis, the initial histology subtype, and the pattern of relapse were not associated with PRS. The use of upfront fRT also did not impact PRS ($p$ = 0.18), although only 6 patients had upfront fRT.

Multivariable analysis with propensity scoring analyzed the use of surgery at relapse, age at relapse, CSI (time-dependent), and salvage HDC+AuHCR (time-dependent). The median time to CSI receipt from relapse was 2.5 months (IQR 1.0 to 6.0 months), and the median time to HDC+AuHCR was 3.0 months (IQR 1.0 to 4.0 months). An interaction term (HDC+AuHCR + CSI) was placed in the model to adjust for the relationship between HDC+AuHCR and CSI. Time from diagnosis to relapse was highly correlated with age at relapse and therefore was not included in the model due to multicollinearity. The age at relapse (< 36 *versus* ≥ 36 months) was deemed more clinically significant so was preferentially included in the model. A second model was run adding in the molecularly defined *versus* non-molecularly defined MB, which did not influence the model outcome. On the final multivariable model (n = 117) CSI was a significant predictor of PRS with an HR of 0.33 (95% CI 0.13 to 0.86, $p$ = 0.044) while HDC+AuHCR at relapse showed an HR of 0.24 (95% CI 0.005 to 1.03, $p$ = 0.065; *figure 3*).

**DISCUSSION**

We show that most patients with relapsed SHH medulloblastoma can be retrieved with a 3-year PRS of 61.6% (95% CI 52.2-69.6). We also corroborate other reports indicating that 40% of patients with relapsed SHH/ND iMB treated without upfront CSI are localized.[9-11] Similar to

patients with other iMB subgroups, salvage therapy for SHH/ND iMB relies heavily on radiotherapy, used in 74.4% of the patients. Salvage CSI was associated with significant survival benefits in both univariate and multivariable analyses. Previous studies showed the role of salvage CSI as a potentially successful strategy in CSI naive relapsed iMB.[18-20] However, unique to our cohort are the characteristics of various salvage strategies employed including over half of the cohort (55.8%) that received either no RT (25.6%), fRT only (12.4%), or low-dose CSI (17.8%). Although the PRS for patients who received RT was better than those who did not, no significant difference in PRS was detected between salvage CSI and salvage fRT, possibly related to small fRT numbers and their predominance of local relapse.

The median dose of salvage CSI delivered for the entire cohort was 35.2 Gy which is not unexpected as a dose of 36 Gy CSI is a well-accepted dose for upfront therapy in older children with high-risk MB. Importantly, our cohort had CSI doses that were largely dichotomized and did not include any patients with salvage therapy between > 24Gy and <30.6Gy making assessment of this intermediate dose range unfeasible. We previously reported a tendency for some patients with relapsed SHH/ND iMB to receive salvage therapy without CSI.[11] Here we describe one-third of patients who received salvage CSI did so with low-dose CSI (≤24 Gy). Similar to those treated with salvage fRT, patients who underwent low-dose CSI presented more frequently with local relapse (78%). Our data shows that physicians are managing patients with local relapse differently compared to patients with disseminated or combined relapse. Patients with localized disease were more likely to undergo disease resection at relapse and/or to receive fRT or low-dose CSI, suggesting a bias in the allocation of irradiation modalities according to pattern of relapse. With this allocation of low-dose CSI preferentially to those with localized relapse, there

were only 4 events reported for the 23 patients who received CSI ≤24Gy. With the limitation of the retrospective nature of this cohort, our data suggest that some patients with localized relapsed SHH/ND iMB can be successfully salvaged with strategies that avoid high-dose CSI, principally when salvage surgical resection is undertaken. This finding also highlights the importance of obtaining a state of minimal gross residual prior to radiation or chemotherapy for those with localized relapse.

We show that PRS for patients salvaged with chemotherapy and CSI, compared to those who received CSI alone survival was 81.2% *vs* 62.0%, and although not statistically significant (p=0.059) is an area deserving further investigation. The median dose of CSI was not statistically different when used alone or in conjunction with conventional CT or HDC+AuHCR. Whether salvage CT and safely allow for lower doses of CSI for relapsed SHH/ND iMB is also worth additional study. Our data caution against the use of a CSI-alone approach in children with relapsed SHH iMB. Although, the timing of CSI after relapse was accounted for through time-dependent analyses, the relevance of the precise timing of salvage conventional chemotherapy whether before or after salvage CSI remains unknown.

The use of salvage HDC+AuHCR was not statistically significant in univariate (HR 0.55 [0.28 to 1.08], p = 0.08) or multivariable analyses (HR 0.24 [95% CI, 0.0054 to 1.025], p = 0.06). However, these results with salvage HDC+AuHCR appear clinically meaningful as patients who received salvage HDC+AuHCR without CSI fared better than those who received neither CSI nor HDC+AuHCR ($p$ = 0.03). Ultimately, salvage CSI outperformed HDC in multivariate modeling. It is important to recognize the limitation of this model even with propensity scoring, as these patients were not randomly allocated and the number of patients receiving HDC+AuHCR (n= 36)

was smaller compared to that of CSI (n = 78). There were no patients who underwent HDC+AuHCR upfront and then again at salvage, which questions the applicability of such an approach although further investigation may be needed.[8-10,21] We suggest that for patients treated with conventional chemotherapy as used in the HIT -2000 or as currently investigated in the SJiMB21 clinical trial *(NCI-2022-07099),* salvage HDC+AuHCR with or without low-dose CSI represents an important salvage strategy.[5,22] However, if CSI is given as part of salvage with HDC+AuHCR, the current practice has been to give CSI after completion of HDC+AuHCR as a consolidation approach. This is especially important if there is consideration of methotrexate as part of the treatment regimen which should be given prior to CSI to avoid increased risk of leukoencephalopathy. While international collaboration is underway through SIOPE and the CONNECT consortium to compare upfront treatment modalities for SHH/ND iMB, a large international effort will also be needed to assess patients who will fail these strategies.

These children remain young at the time of relapse and therefore vulnerable to treatment-related toxicities, raising the importance of considering the associated harms of salvage therapies and highlighting the priority of achieving upfront cure. Likely underestimated due to the lack of data completeness, we report that nearly one-third of these young patients required hearing support. Additional analyses of long-term toxicities such as neurocognitive and ototoxicity data for these patients are needed to assess the post-relapse intellectual profile of survivors.

At a median follow-up of 32.3 months from relapse, subsequent malignancies were reported in five (3.9%) patients. The cumulative incidence of subsequent malignancies in older children treated for MB with CSI and chemotherapy has been estimated at 4.2% (1.9-6.5%) at 10 years.[23] The true frequency of second malignancy in our cohort is likely underestimated, as only those

leading to death were captured, but the number we report is sizeable. Radiotherapy's impact on patients with SHH iMB is important to consider as young children with SHH have a high rate of underlying germline mutation (up to 20%) notably *SUFU* and *PTCH1* mutation predisposing them to multiple cancers and may be further exacerbated by radiotherapy.[24,25] Therefore the pros and cons of omitting CSI in this population should be considered especially if HDC+AuHCR is a salvage option. Interestingly, none of the described subsequent malignancies in our cohort were ones commonly associated with *SUFU* or *PTCH1* germline alterations.[24] If not undertaken at initial diagnosis, a genetic referral at the time of relapse is critical to integrate the risk of basal cell carcinoma or meningioma associated with Gorlin syndrome and radiation exposure.[26-28]

This study combined patients originally enrolled in clinical trials prior to relapse, and those from national and institutional databases. Combining these groups of clinical data will result in added data heterogeneity leading to variability in data completeness and accuracy increasing caution in the application of our results. Also, our cohort of relapsed SHH MB did not undergo central review of imaging. It is possible that some patients with relapsed disease may have had a second de novo tumor rather than relapsed disease and is important to consider given the common occurrence of constitutional genetic predisposition in those with SHH MB.

A significant limitation of this work is the lack of constitutional genetic data. Specifically, in our cohort, information on germline *ELP1* mutation was not collected limited by the retrospective nature of the study. Its occurrence should be low given the median age of this *ELP1* germline mutation is 7.3 years old and is restricted to the SHH3/α subgroup.[29,30] Also, we did not capture the prevalence of TP53 mutations in our patient population which is known to be a poor predictor in older children with SHH medulloblastoma generally 8-17 years old, generally clustering with

SHH3, although testing is recommended in SHH MB for those with LCA histology who are 4 or more years old.[31,32] Eleven percent of our patients were aged 4 or above at diagnosis although none of these had LCA histology. Otherwise, TP53 mutation is not prognostic in SHH1/β and SHH2/γ subgroups which given the age of our cohort would be the vast majority.[33] Similarly, we did not capture *MYCN* or *GLI* amplification in our cohort. However again it is the SHH3/α subgroup that is enriched for this alteration and its presence is not prognostic in SHH1/β and SHH2/γ subgroups.[33,34] Due to the limitations of available biology details, we are not able to exclude the possibility of a rare patient with an SHH3/α subgroup iMB in our cohort.

Heterogenous methods were used to confirm the diagnosis of the SHH MB subgroup which limits data uniformity steming from use of retrospective data. Some methods are less precise than others which may give variability in misclassification depending on the platform used. There were also a limited number of patients with methylation status (28%) prevented us from assessing the possible impact of methylation subgrouping and salvage outcomes so we cannot infer outcomes of relapse SHH iMB based upon SHH1/β and SHH2/γ subgroup. The increasing integration of methylation status with copy number variations in the most recent clinical trials may contribute to delineating varying risk groups for relapsed SHH iMB.[22,35]

The comprehensive description of this large cohort of patients with relapsed SHH/ND iMB provides useful information for parents and treating physicians for counseling at the time of relapse. Importantly, successful salvage is not guaranteed and CSI, the modality initially desired to be avoided, is often the best chance of cure after relapse. This emphasizes the need to maximize upfront cure and to be highly cautious when attempting to reduce therapies with proven efficacy. The pattern of relapse, prior therapies, and age at relapse should guide salvage

management. Further efforts to characterize tumor biology in this cohort of patients may further help stratify SHH iMB in the relapse setting. Therapies that avoid high-dose salvage CSI may be considered for patients with localized relapse after surgical resection. Further characterization of these patients will benefit from prospective international collaboration.

## REFERENCES


1. Ottensmeier H, Schlegel PG, Eyrich M, et al. Treatment of children under 4 years of age with medulloblastoma and ependymoma in the HIT2000/HIT-REZ 2005 trials: neuropsychological outcome 5 years after treatment. *PLoS One.* 2020; 15(1):e0227693.
2. Merlin M-S, Schmitt E, Mezloy-Destracque M, et al. Neurocognitive and radiological follow-up of children under 5 years of age treated for medulloblastoma according to the HIT-SKK protocol. *Journal of Neuro-Oncology.* 2023; 163(1):195-205.
3. O'Neil SH, Whitaker AM, Kayser K, et al. Neuropsychological outcomes on Head Start III: A prospective, multi-institutional clinical trial for young children diagnosed with malignant brain tumors. *Neuro-Oncology Practice.* 2020; 7(3):329-337.
4. Levitch CF, Malkin B, Latella L, et al. Long-term neuropsychological outcomes of survivors of young childhood brain tumors treated on the Head Start II protocol. *Neuro-Oncology Practice.* 2021; 8(5):609-619.
5. Mynarek M, von Hoff K, Pietsch T, et al. Nonmetastatic medulloblastoma of early childhood: results from the prospective clinical trial HIT-2000 and an extended validation cohort. *Journal of clinical oncology.* 2020; 38(18):2028-2040.
6. Mulhern RK, Palmer SL, Merchant TE, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *Journal of Clinical Oncology.* 2005; 23(24):5511-5519.
7. Lafay-Cousin L, Smith A, Chi SN, et al. Clinical, pathological, and molecular characterization of infant medulloblastomas treated with sequential high-dose chemotherapy. *Pediatric blood & cancer.* 2016; 63(9):1527-1534.
8. Dhall G, O'Neil SH, Ji L, et al. Excellent outcome of young children with nodular desmoplastic medulloblastoma treated on "Head Start" III: a multi-institutional, prospective clinical trial. *Neuro-oncology.* 2020; 22(12):1862-1872.

**9.** Robinson GW, Rudneva VA, Buchhalter I, et al. Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. *The Lancet Oncology.* 2018; 19(6):768-784.

**10.** Lafay-Cousin L, Bouffet E, Strother D, et al. Phase II study of nonmetastatic desmoplastic medulloblastoma in children younger than 4 years of age: a report of the Children's Oncology Group (ACNS1221). *Journal of Clinical Oncology.* 2020; 38(3):223.

**11.** Erker C, Mynarek M, Bailey S, et al. Outcomes of Infants and Young Children With Relapsed Medulloblastoma After Initial Craniospinal Irradiation–Sparing Approaches: An International Cohort Study. *Journal of Clinical Oncology.* 2023; 41(10):1921-1932.

**12.** Chang CH, Housepian EM, Herbert C. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. *Radiology.* 1969; 93(6):1351-1359.

**13.** Garcia-Lopez J, Kumar R, Smith KS, Northcott PA. Deconstructing sonic hedgehog medulloblastoma: molecular subtypes, drivers, and beyond. *Trends in Genetics.* 2021; 37(3):235-250.

**14.** Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro-Oncology.* 2021; 23(8):1231-1251.

**15.** Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. *Journal of Clinical Oncology.* 1998; 16(5):1723-1728.

**16.** Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Statistics in medicine.* 2015; 34(28):3661-3679.

**17.** Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. *New England Journal of Medicine.* 2005; 352(10):978-986.

**18.** Hill RM, Richardson S, Schwalbe EC, et al. Time, pattern, and outcome of medulloblastoma relapse and their association with tumour biology at diagnosis and therapy: a multicentre cohort study. *The Lancet Child & Adolescent Health.* 2020; 4(12):865-874.

**19.** Huybrechts S, Le Teuff G, Tauziède-Espariat A, et al. Prognostic clinical and biologic features for overall survival after relapse in childhood medulloblastoma. *Cancers.* 2020; 13(1):53.

**20.** Müller K, Mynarek M, Zwiener I, et al. Postponed is not canceled: role of craniospinal radiation therapy in the management of recurrent infant medulloblastoma—an experience from the HIT-REZ 1997 & 2005 studies. *International Journal of Radiation Oncology* Biology* Physics.* 2014; 88(5):1019-1024.

**21.** Mazewski C, Kang G, Kellie S, et al. MBCL-34. Efficacy of methotrexate (MTX) according to molecular sub-type in young children with medulloblastoma (MB): a report from Children's Oncology Group phase III trial ACNS0334. *Neuro-Oncology.* 2020; 22(Supplement_3):iii396-iii396.

**22.** Bagchi A, Dhanda SK, Dunphy P, Sioson E, Robinson GW. Molecular classification improves therapeutic options for infants and young children with medulloblastoma. *Journal of the National Comprehensive Cancer Network.* 2023; 21(10):1097-1105.

**23.** Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro Oncol.* 2013; 15(1):97-103.

**24.** Guerrini-Rousseau L, Dufour C, Varlet P, et al. Germline SUFU mutation carriers and medulloblastoma: clinical characteristics, cancer risk, and prognosis. *Neuro-oncology.* 2018; 20(8):1122-1132.

**25.** Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. *The Lancet Oncology.* 2018; 19(6):785-798.

**26.** Foulkes WD, Kamihara J, Evans DGR, et al. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome. *Clinical Cancer Research.* 2017; 23(12):e62-e67.

**27.** Hansford JR, Das A, McGee RB, et al. Update on cancer predisposition syndromes and surveillance guidelines for childhood brain tumors. *Clinical Cancer Research.* 2024:OF1-OF9.

**28.** Lee SG, Evans G, Stephen M, Goren R, Bondy M, Goodman S. Medulloblastoma and other neoplasms in patients with heterozygous germline SUFU variants: A scoping review. *American Journal of Medical Genetics Part A.* 2024.

**29.** Waszak SM, Robinson GW, Gudenas BL, et al. Germline elongator mutations in sonic hedgehog medulloblastoma. *Nature.* 2020; 580(7803):396-401.

**30.** Guerrini-Rousseau L, Masliah-Planchon J, Filser M, et al. Medulloblastomas with ELP1 pathogenic variants: a weakly penetrant syndrome with a restricted spectrum in a limited age window. *Neuro-Oncology Advances.* 2024:vdae075.

**31.** Kool M, Jones DT, Jäger N, et al. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer cell.* 2014; 25(3):393-405.

**32.** Kolodziejczak AS, Guerrini-Rousseau L, Planchon JM, et al. Clinical outcome of pediatric medulloblastoma patients with Li–Fraumeni syndrome. *Neuro-oncology.* 2023; 25(12):2273-2286.

**33.** Cavalli FM, Remke M, Rampasek L, et al. Intertumoral heterogeneity within medulloblastoma subgroups. *Cancer cell.* 2017; 31(6):737-754. e736.

**34.** Hicks D, Rafiee G, Schwalbe EC, et al. The molecular landscape and associated clinical experience in infant medulloblastoma: prognostic significance of second-generation subtypes. *Neuropathology and Applied Neurobiology.* 2021; 47(2):236-250.

**35.** Tonn S, Korshunov A, Obrecht D, et al. Risk prediction in early childhood sonic hedgehog medulloblastoma treated with radiation-avoiding chemotherapy: Evidence for more than 2 subgroups. *Neuro-oncology.* 2023; 25(8):1518-1529.

**FUNDING:** Funded through a grant from the IWK Health oncology division

**CONFLICTS OF INTEREST:**

- Craig Erker is a DSMC member for CONNECT
- Martin Mynarek was supported for data collection by the German Childhood Cancer Foundation. He has grants supported by the German Cancer Aid (Deutsche Krebshilfe)
- Bruce Crooks is a DSMC member for Re-irradiation of progressive or recurrent DIPG, NCT03126266. Member of the Medical Advisory Committee and NS Chapter Advisory Board, and Make-A-Wish Canada.
- Jordan R. Hansford receives consulting fees from Alexion Pharmaceuticals and Bayer Pharmaceuticals. Receives funding for travel or meetings from Alexion Pharmaceuticals. Institution receives payment from Servier Pharmaceuticals for work on Scientific Advisory Board. He is the director of ANZHOG.
- Valérie Larouche receives payment for presentations on pediatric neurofibromatosis and from Alexion. DSMC member for Re-irradiation of progressive or recurrent DIPG, NCT03126266.
- Jonathan Finlay has received consulting fee payments from Nkore Biotherapeutics Inc and the Department of Defense. He has received payment from Nationwide Children's Hospital Research Institute. He has received payment for expert review from Muro & Lampe Law Firm Consultation.
- Steve Clifford has received funding from Cancer Research UK.
- Amar Gajjar is a member of the Day One Therapeutics Advisory Board.
- Andréa M. Cappellano serves as president of both the Latin American Society of Pediatric Oncology and the International Society of Pediatric Oncology Continental President for Latin America.

- Claire Mazewski is the co-chair for the Children's Oncology Group protocol ACNS0334: A randomized phase 3 trial of intensified chemotherapy with or without methotrexate for high-risk embryonal brain tumors in young children which is unpaid.
- Alvaro Lassaletta has received payment from Alexion and Eli Lilly. He also serves on advisory boards for Alexion and Servier.
- Lindsey Hoffman has received payment for membership in the following DSMBs: Children's Oncology Group, Pediatric Brain Tumour Consortium, Georgia Cancer Center.
- Cassie Kline holds grant funds with Cannonball Kids' Cancer Foundations, Kortney Rose Foundation, Bristol-Myers Squibb Foundations. She has contracts related to clinical trial work with Curis Inc, Regeneron Pharmaceuticals, Day One Biotherapeutics, Midatech, Ipsen, Chimerix, Kazia, Bristol-Myers Squibb. She also has leadership roles on scientific advisory board for Cannonball Kids' Cancer Foundation, Raymond A. Wood Foundation, Children's Brain Tumor Network, and the Neev Kolte & Brave Ronil Foundation.
- Kathleen Dorris was a member of the advisory board for RAF inhibitors for Day One Bio. Kathleen has CRSP stock and is currently employed by Cogent Biosciences.
- Gudrun Fleischhack has a research grant from German Children Cancer Foundation. Gudrun is a member of the DSMB for the clinical trial, NCT04738162.
- Stephan Tippelt has grant funding with Deutsche Kinderkrebsstiftung (DKKS)
- Vijay Ramaswamy has received consulting fees from Alexion and Servier
- Stefan Rutkowski has received funding from the German Children's Cancer Foundation and BMBF. He has received consulting fees from FennecPharma and Norgine GmbH.

**DECLARATIONS OF AUTHOR CONTRIBUTIONS:**

Experimental design— Craig Erker, Martin Mynarek, Eric Bouffet, Lucie Lafay-Cousin

Experimental implementation (by providing cases, data, and/or clinical annotation)—all authors.

Analysis and interpretation of the data— Craig Erker, Kara Matheson, Lucie Lafay-Cousin

All authors were involved in the writing of the manuscript at draft and any revision stages and have read and approved the final version.

**DATA AVAILABILITY:** Data via statistical analysis will be made available upon reasonable request to the corresponding author.

## FIGURE LEGENDS

**Figure 1.** (A) Pie chart of pattern of relapse for curative intent cohort; (B) Bar graph for salvage CSI dosing for curative intent cohort; (C) Kaplan-Meier Plot showing the overall survival of curative intent cohort with the gray zone representing the 95% confidence interval.

**Figure 2.** Kaplan-Meier Plot showing post-relapse survival for curative intent cohort with the shaded red and blue zones representing the 95% confidence intervals for (A) those treated with and without salvage radiation therapy; (B) treatment with salvage CSI compared to those treated with salvage focal radiation therapy; (C) treatment with salvage CSI at ≤ 24 Gy compared to > 24 Gy; (D) treatment with salvage CSI alone compared to salvage CSI with systemic chemotherapy; (E) those with localized compared to disseminated pattern of relapse

**Figure 3.** Post-relapse survival forest plot of exploratory multivariable analysis of curative intent cohort. The wiskers represents the 95% confidence interval of the hazard ratio (HR) which is represented by the small square.

TABLE 1. Description of Intent-to-Cure and Overall Cohort

| | Curative Intent (n = 129) | Palliative Intent (n = 18) | Overall Cohort (n = 147) |
|---|---|---|---|
| UPFRONT | | | |
| Gender (male) | 78 (61%) | 8 (44%) | 86 (59%) |
| Diagnosis Era | | | |
| 1995-2006 | 38 (30%) | 5 (28%) | 43 (29%) |
| 2007-2017 | 91 (70%) | 13 (72%) | 104 (71%) |
| Age at diagnosis | | | |
| < 24 months | 49 (38%) | 12 (67%) | 61 (42%) |
| Metastatic status | | | |
| M0 | 96 (76%) | 11 (61%) | 107 (74%) |
| Histology | | | |
| Classic | 9 (7%) | 0 | 9 (6%) |
| ND/MBEN | 117 (91%) | 17 (94%) | 134 (91%) |
| LCA | 3 (2%) | 1 (6%) | 4 (3%) |
| Molecular subgroup | | | |
| SHH1/β | 22 (60%) | 4 (80%) | 26 (62%) |
| SHH2/γ | 15 (40%) | 1 (20%) | 16 (38%) |
| HDC (Yes) | 24 (19%) | 2 (11%) | 26 (18%) |
| IT/IV chemotherapy | 34 (26%) | 4 (25%) | 38 (26%) |
| Focal RT | 6 (5%) | 2 (11%) | 8 (5%) |
| RELAPSE | | | |
| Relapse timepoint | | | |
| On therapy | 45 (35%) | 11 (65%) | 56 (38%) |
| Off therapy | 79 (61%) | 6 (35%) | 85 (58%) |
| Time from diagnosis to relapse < 12 months | 49 (38%) | 9 (50%) | 58 (40%) |
| Detection of Relapse | | | |
| Routine imaging or CSF | 86 (67%) | 6 (43%) | 92 (63%) |
| Symptomatic relapse | 17 (13%) | 8 (57%) | 25 (17%) |
| Relapse pattern | | | |
| Local | 57 (44%) | 3 (18%) | 60 (41%) |
| Disseminated ± Local | 70 (54%) | 14 (82%) | 84 (57%) |
| Surgery (Yes) | 65 (50%) | 3 (17%) | 68 (46%) |
| HDC (Yes) | 36 (28%) | 0 | 36 (25%) |
| Alive (Yes) | 76 (59%) | 1 (6%) | 77 (52%) |

Abbreviations: ND/MBEN, nodular desmoplastic/medulloblastoma with extensive nodularity; LCA, large-cell/anaplastic; HDC, high-dose chemotherapy; IT/IV, intrathecal/intraventricular; RT, radiation therapy; CSF, cerebrospinal fluid.

TABLE 2. Curative Intent Cohort Comparing Molecularly SHH iMB and ND Non-Molecularly Defined iMB

| | SHH (n = 99) | ND (n = 30) | p-value |
|---|---|---|---|
| UPFRONT | | | |
| Gender (male) | 63 (63%) | 15 (50%) | 0.18 |
| Diagnosis Era | | | 0.06 |
| 1995-2006 | 25 (25%) | 13 (43%) | |
| 2007-2017 | 74 (75%) | 17 (57%) | |
| Age original diagnosis | | | 0.80 |
| < 24 months | 37 (37%) | 12 (40%) | |
| Metastatic status | | | 0.57 |
| M0 | 72 (75%) | 24 (80%) | |
| M+ | 24 (25%) | 6 (20%) | |
| Histology | | | 0.13 |
| Classic | 9 (9%) | 0 | |
| ND/MBEN | 87 (88%) | 30 (100%) | |
| LCA | 3 (3%) | 0 | |
| HDC (Yes) | 15 (15%) | 9 (30%) | 0.07 |
| RELAPSE | | | |
| Relapse timepoint | | | 0.21 |
| On therapy | 37 (39%) | 8 (27%) | |
| Off therapy | 57 (61%) | 22 (73%) | |
| Time from diagnosis to relapse < 12 months | 40 (40%) | 9 (30%) | 0.30 |
| Relapse pattern | | | 0.25 |
| Local | 47 (48%) | 10 (33%) | |
| Disseminated ± Local | 50 (51%) | 20 (67%) | |
| Surgery (Yes) | 52 (53%) | 13 (43%) | 0.14 |
| Radiation type | | | 0.10 |
| No RT | 28 (28%) | 5 (17%) | |
| CSI | 55 (56%) | 23 (77%) | |
| Focal RT only | 15 (15%) | 1 (3%) | |
| Systemic radioisotope | 1 (1%) | 1 (3%) | |
| HDC (Yes) | 29 (29%) | 7 (23%) | 0.52 |
| Relapse Treatment Combo | | | 0.33 |
| CSI alone | 16 (16%) | 9 (30%) | |
| CSI + conventional chemo | 30 (30%) | 10 (33%) | |
| CSI + HDC | 20 (20%) | 3 (10%) | |
| HDC without CSI | 9 (9%) | 4 (13%) | |
| Non-HDC only | 21 (21%) | 4 (13%) | |
| Other non-CSI approach | 3 (3%) | 0 | |
| Alive (Yes) | 59 (60%) | 17 (57%) | 0.78 |

Abbreviations: SHH, Sonic Hedgehog; ND, nodular desmoplastic; ND/MBEN, nodular desmoplastic/medulloblastoma with extensive nodularity; LCA, large-cell/anaplastic; HDC, high-dose chemotherapy; RT, radiation therapy; CSI, craniospinal irradiation; combo, combination; chemo, chemotherapy.

TABLE 3. Univariate Analysis for PRS for the Curative Intent Cohort

| Variable | 3-Year PRS (95% CI) | Overall Log-Rank *P* | Point Estimate HR (95% CI) | HR *P* |
|---|---|---|---|---|
| UPFRONT | | | | |
| Sub-cohort | | 0.87 | | 0.84 |
| SHH (ref) | 62.7 (48 to 73) | | | |
| ND | 68.3 (42 to 84) | | 0.94 (0.49 to 1.80) | |
| Metastatic status | | 0.18 | | 0.14 |
| M0 (ref) | 68.5 (54 to 79) | | | |
| M+ | 43.2 (23 to 62) | | 1.56 (0.86 to 2.83) | |
| Upfront HDC | | 0.40 | | 0.34 |
| No HDC (ref) | 61.3 (48 to 72) | | | |
| HDC | 77.8 (45 to 92) | | 0.62 (0.23 to 1.68) | |
| Upfront focal RT | | 0.18 | | 0.16 |
| Yes | 26.6 (3 to 62) | | 2.07 (0.75 to 5.71) | |
| No (ref) | 65.4 (53 to 75) | | | |
| Upfront IT/IV therapy | | 0.69 | | 0.63 |
| Yes | 56.8 (35 to 74) | | 1.15 (0.65 to 2.06) | |
| No (ref) | 65.9 (51 to 77) | | | |
| RELAPSE | | | | |
| Time, diagnosis to relapse | | 0.007 | | 0.0006 |
| ≥ 12 months (ref) | 73.1 (58 to 83) | | | |
| < 12 months | 48.3 (28 to 65) | | 2.67 (1.52 to 4.67) | |
| Age at relapse | | 0.056 | | 0.009 |
| ≥ 36 months | 70.7 (57 to 81) | | 0.48 (0.28 to 0.83) | |
| < 36 months (ref) | 50.6 (27 to 70) | | | |
| Pattern of Relapse | | 0.35 | | 0.24 |
| Local (ref) | 70.5 (51 to 83) | | | |
| Disseminated ± Local | 58.8 (43 to 71) | | 1.40 (0.80 to 2.46) | |
| Surgery | | 0.13 | | 0.06 |
| No | 56.7 (37 to 72) | | 1.71 (0.97 to 3.02) | |
| Yes (ref) | 73.7 (58 to 84) | | | |
| CSI (time-dependent) | | | | 0.037 |
| Yes vs No | N/A | | 0.54 (0.30 to 0.96) | |
| HDC (time-dependent) | | | | 0.08 |
| Yes | | | 0.55 (0.28 to 1.08) | |
| No (ref) | N/A | | | |
| Relapse therapy combo | | 0.0034 | N/A | |
| CSI + HDC | 95.3 (34 – 100) | | | |
| CSI + non-HDC | 76.2 (51 – 90) | | | |
| CSI alone | 62.0 (38 – 79) | | | |
| HDC +/- non-HDC | 69.2 (39 – 87) | | | |
| Non-HDC only | 27.2 (8 – 51) | | | |
| Other therapy | 55.4 (1 – 93) | | | |

Abbreviations: PRS, post-relapse survival; HR, hazard ratio; SHH, Sonic Hedgehog; ND, nodular desmoplastic; HDC, high-dose chemotherapy RT, radiation therapy; IT/IV, intrathecal/intraventricular; CSI, craniospinal irradiation.

Figure 1

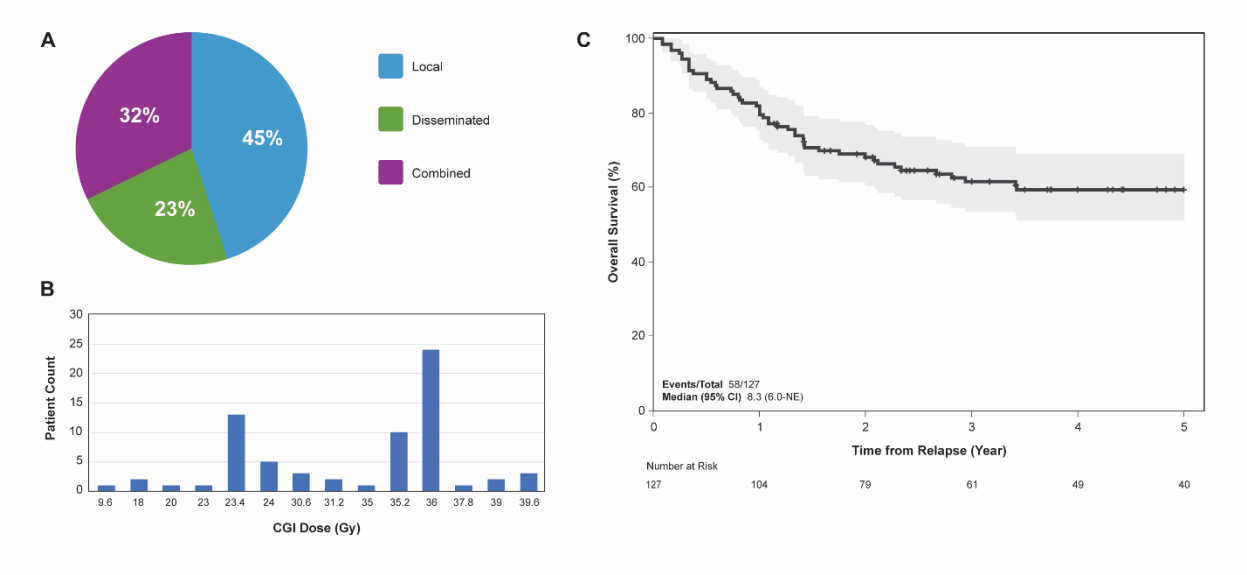

Figure 2

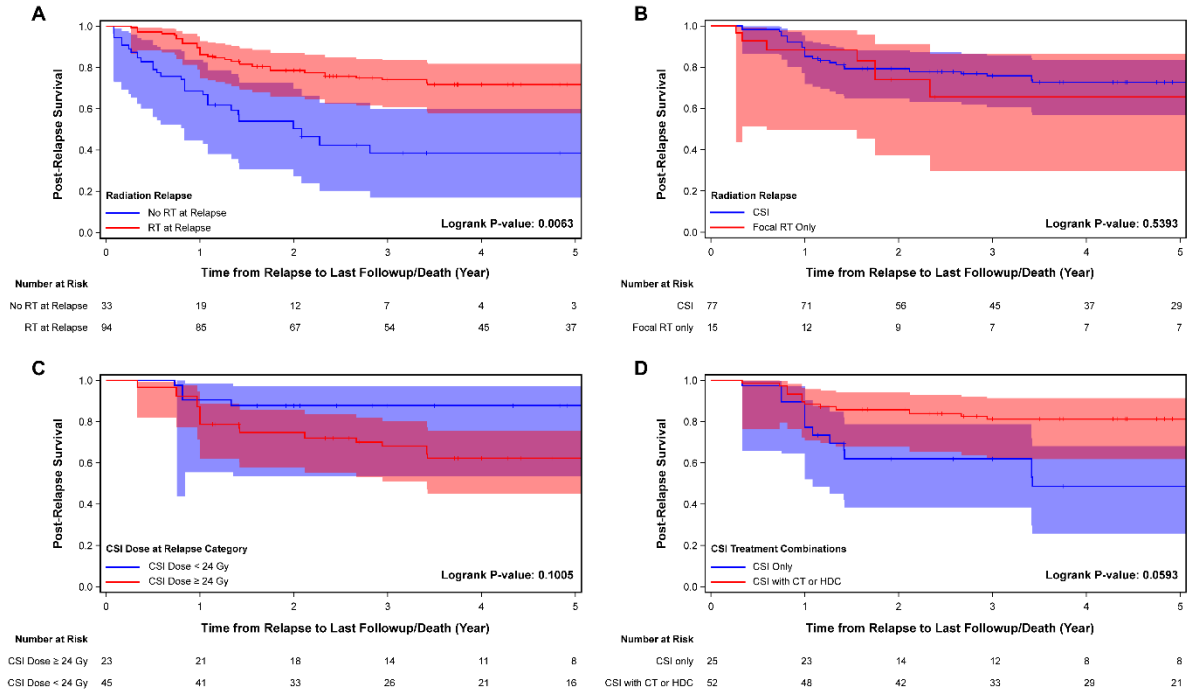

Figure 3