Malignant brainstem tumors in children, excluding diffuse intrinsic pontine gliomas

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OBJECTIVE Malignant tumors of the brainstem, excluding classic diffuse intrinsic pontine gliomas (DIPGs), are a very rare, heterogeneous group of neoplasms that have been infrequently described in the literature. In this paper, the authors present their experiences with treating these unique cancers.

METHODS A retrospective chart review was conducted to identify eligible cases over a 15-year period. All tumors involving the pons were, by consensus, felt not to be DIPGs based on their neuroimaging features. Demographic information, pathological specimens, neuroimaging characteristics, surgical and nonsurgical management plans, and survival data were gathered for analysis.

RESULTS Between January 2000 and December 2014, 29 patients were identified. The mean age at diagnosis was 8.4 years (range 2 months to 25 years), and 17 (59%) patients were male. The most common presenting signs and symptoms were cranial neuropathies (n = 24; 83%), hemiparesis (n = 12; 41%), and ataxia or gait disturbance (n = 10; 34%). There were 18 glial and 11 embryonal tumors. Of the glial tumors, 5 were radiation-induced and 1 was a malignant transformation of a previously known low-grade tumor. Surgical intervention consisted of biopsy alone in 12 patients and some degree of resection in another 15 patients. Two tumors were diagnosed postmortem. The median overall survival for all patients was 196 days (range 15 to 3999 days). There are currently 5 (17%) patients who are still alive: 1 with an anaplastic astrocytoma and the remaining with embryonal tumors.

CONCLUSIONS In general, malignant non-DIPG tumors of the brainstem carry a poor prognosis. However, maximal cytoreductive surgery may be an option for select patients with focal tumors. Long-term survival is possible in patients with nonmetastatic embryonal tumors after multimodal treatment, most importantly maximal resection.

http://thejns.org/doi/abs/10.3171/2015.6.PEDS15166

KEY WORDS brainstem tumor; malignant; glioma; embryonal; outcomes; resection; oncology

Brainstem tumors account for 10% of pediatric brain tumors with a peak incidence between 5 and 10 years of age.11 There are several well-recognized groups of tumors. The first group is known as diffuse intrinsic pontine gliomas (DIPGs). Children with DIPGs are typically young, have a relatively short time course of symptoms, and present with a combination of cranial neuropathies and long tract signs. On MRI, the pons is markedly enlarged and engulfs the basilar artery, infiltrates rather than displaces the brainstem tracts and nuclei, demonstrates heterogeneous enhancement, and may have an exophytic component. For “typical” DIPGs, surgery is relegated to the management of obstructive hydrocephalus, although some clinicians still believe that all require a biopsy.11,19 However, for children with an “atypical” DIPG based on clinical—but, more importantly, radiographic—features, biopsy is indicated.34,36 DIPG progression is often rapid with a brief pause induced by radiation followed by near-universal progression and, inevitably, death. Many chemotherapeutic agents have been tested, but none to date have made a clear improvement in prognosis.11,19,21,22

Conversely, children with low-grade brainstem tumors—

ABBREVIATIONS AA = anaplastic astrocytoma; ADC = apparent diffusion coefficient; ATRT = atypical teratoid rhabdoid tumor; DIPG = diffuse intrinsic pontine glioma; DWI = diffusion-weighted imaging; ETANTR = embryonal tumor with abundant neuropil and true rosettes; GBM = glioblastoma multiforme; GTR = gross-total resection; HGG = high-grade glioma; NTR = near-total resection; OS = overall survival; PNET = primitive neuroectodermal tumor; STR = subtotal resection.


INCLUDE WHEN CITING Published online October 16, 2015; DOI: 10.3171/2015.6.PEDS15166.
the second group of tumors—have a much different clinical course. Patients with these tumors usually have more protracted symptoms and are older, and their tumor is typically focal rather than infiltrative but can have an exophytic component. Tumors may arise anywhere within the brainstem. With the exception of tectal gliomas, tissue diagnosis is necessary and resection is often a treatment option along with chemotherapy or radiation therapy.\textsuperscript{25,30} Although tumor progression may occur, these children have an excellent chance of enjoying a long and functional life.\textsuperscript{25,30}

Non-DIPG malignant brainstem tumors represent the third group of tumors that are exceedingly rare, can be focal or diffuse, exophytic or wholly intrinsic, and represent a spectrum of pathologies. There are but a few case reports or small case series in the literature of embryonal tumors, with the most commonly described example of this group being a primitive neuroectodermal tumor (PNET).\textsuperscript{1,4,12–14,38,40,44} We present our experience with these unusual and challenging neoplasms.

**Methods**

**Study Population**

The institutional review boards of St. Jude Children’s Research Hospital and Le Bonheur Children’s Hospital approved this study. We retrospectively identified patients with malignant non-DIPG brainstem tumors diagnosed between January 2000 and December 2014. Patients were enrolled in the study if they had pathological confirmation of their tumor type by biopsy or resection at Le Bonheur Children’s Hospital or an outside institution with at least 6 months of follow-up. There were 2 patients whose tumors were diagnosed postmortem (see details below). Patients who died of tumor progression were also included. Each patient’s imaging and pathology were reviewed, and treatment options were deliberated during a weekly multidisciplinary pediatric neurooncology conference.

**Definitions**

A malignant non-DIPG brainstem tumor was defined as a tumor whose origin was in the midbrain, pons, or medulla with or without extension into the cerebellar peduncles. Tumors that were centered within the pons were deemed markedly different on MRI than a DIPG with uniform or near-uniform, multidisciplinary agreement during our tumor board. The characteristic features of a DIPG include uniform expansile hypertrophy, diffuse infiltration of the basis pontis with the tumor folding around the basilar artery, hypointense on T1-weighted and hyperintense on T2-weighted MRI with indistinct margins, with or without areas of necrosis, and relatively little or patchy enhancement. Decussating pontocerebellar fiber bundles within the basis pontis are often well outlined on T2-weighted images.

Tumor histopathology was defined according to the current WHO classification system.\textsuperscript{29} All tumors were intrinsic to the brainstem but may have had 1 or more exophytic component, which was defined as a breach of the pial boundary. The extent of resection was based on postoperative MR images as gross-total resection (GTR), near-total resection (NTR), or subtotal resection (STR), which were defined as no evidence of residual tumor, greater than 90% excision, and less than 90% excision, respectively. Overall survival (OS) was defined as number of days from the date of diagnosis to the date of last clinical follow-up or death. At the last follow-up, we classified patients as either having stable disease or progressive disease based on their most recent MRI results. Patients who had a GTR with no evidence of regrowth at the last follow-up were still labeled as stable disease rather than disease free.

**Data Collection and Outcomes**

Age, sex, time to death or last follow-up, clinical history, tumor appearance on imaging (i.e., location, exophytic vs intrinsic), treatment modalities, surgical notes, and final histopathological diagnosis were gathered for each patient. In cases for which the original pathological specimens were available for review, the initial pathological diagnosis was independently verified by a board-certified neuropathologist (B.A.O.). Overall survival was calculated, and Kaplan-Meier curves were generated using SPSS (version 22; IBM).

**Results**

**Presentation and Pathology**

We identified 29 patients (17 male and 12 female) with malignant non-DIPG brainstem tumors (Table 1). The mean age at diagnosis was 8.4 years (range 2 months to 25.9 years), and 26 (90%) patients were younger than 18 years of age. The most common presenting signs and symptoms were cranial neuropathy (n = 24; 83%), hemiparesis (n = 12; 41%), and ataxia or gait disturbance (n = 10; 34%). Seventeen patients (59%) presented with symptoms lasting less than 1 month, and 2 patients (7%) were asymptomatic at the time of diagnosis. The tumor origin was the midbrain in 4 (14%) patients, pons or pons/middle cerebellar peduncle junction in 19 (66%) patients, and the medulla or pontomedullary junction in 6 (21%) patients. Fifteen tumors (52%) had an exophytic component on initial imaging. Twenty-four tumors (83%) were diagnosed de novo, including a malignant transformation of a previously identified low-grade neoplasm, and 5 tumors (17%) were radiation induced, including in 2 patients who were asymptomatic at the time of diagnosis.

The histopathology of non-DIPG brainstem tumors was diverse, but could be categorized as either glial (n = 18; 62%) or embryonal (n = 11; 38%). The 18 glial tumors included 11 WHO Grade IV glioblastomas (GBM), 6 WHO Grade III anaplastic astrocytomas (AA), and 1 high-grade glioma (HGG) not otherwise specified. The 11 embryonal tumors consisted of 4 atypical teratoid rhabdoid tumors (ATRTs), 4 embryonal tumors with abundant neuropil and true rosettes (ETANTRs), 2 PNETs, and 1 Wnt-subtype medulloblastoma. Of the 20 tumors that were entirely or partially located within the pons, 7 (35%) were embryonal tumors and the rest were HGGs.

The characteristics of the 5 radiation-induced high-grade glial tumors are shown in Table 2. The mean patient age at diagnosis of the original tumor was 8.0 years (range 8 months to 16 years). The original tumors were 2...
TABLE 1. Clinicopathological features of the non-DIPG brainstem tumors in this study (n = 29)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.4 yrs</td>
</tr>
<tr>
<td>Median</td>
<td>6.3 yrs</td>
</tr>
<tr>
<td>Range</td>
<td>2 mos–26 yrs</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (59)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (41)</td>
</tr>
<tr>
<td>Presenting signs and symptoms, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Ataxia or impaired balance</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>12 (41)</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>24 (83)</td>
</tr>
<tr>
<td>Pain &amp;/or numbness</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Duration of preoperative symptoms, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 wk</td>
<td>3 (10)</td>
</tr>
<tr>
<td>1 wk–1 mo</td>
<td>14 (48)</td>
</tr>
<tr>
<td>&gt;1 mo</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Medulla</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Pontomedullary</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pons</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Pons/middle cerebellar peduncle</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Tumor appearance, n (%)</td>
<td></td>
</tr>
<tr>
<td>Intrinsic</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Exophytic component</td>
<td>15 (52)</td>
</tr>
<tr>
<td>CSF shunt required, n (%)</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Pathology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma (GBM)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>AA</td>
<td>6 (21)</td>
</tr>
<tr>
<td>HGG-NOS</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Embryonal</td>
<td>11 (38)</td>
</tr>
<tr>
<td>ATRT</td>
<td>4 (14)</td>
</tr>
<tr>
<td>ETANTR</td>
<td>4 (14)</td>
</tr>
<tr>
<td>PNET</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Wnt-medulloblastoma</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

NOS = not otherwise specific.

ependymomas, 1 pilocytic astrocytoma, 1 hypothalamic/suprasellar germinoma, and 1 medulloblastoma. All radiation was fractionated, and 1 patient underwent radiotherapy for recurrent anaplastic ependymoma 4 years after her initial treatment. The mean time from completion of initial radiotherapy to the diagnosis of radiation-induced brainstem tumor was 8.64 years (range 4.9 to 14.1 years).

**Treatment**

Twenty-seven (93%) patients included in this study successfully underwent a surgical procedure for either biopsy or resection as part of the initial management plan (Table 3). Two tumors were diagnosed postmortem; 1 of these tumors initially underwent an attempted needle biopsy that was aborted due to significant hemorrhage. Sixteen patients (60%) initially underwent a biopsy (open or stereotactic needle), 4 of whom later underwent a second operation for tumor resection. A total of 15 patients ultimately had some degree of tumor resection: GTR in 5 patients, NTR in 1 patient, and STR in 9 patients.

Our patients received a variety of treatments relating to the specific tumor type and input from the family (Table 3). The most common combination was surgery followed by radiotherapy and chemotherapy (8 patients; 30%). Resection was the sole form of therapy in only 2 patients (7%), both of whom experienced short-onset symptoms (1 week) and aggressive, rapid tumor progression postoperatively.

**Survival**

The median duration of follow-up from the time of diagnosis was 1.7 years (range 1.2–10.9 years) for those patients who are still alive. At the time of this writing (March 2015), 24 patients (83%) have died. Of the 5 surviving patients, there were 2 PNETs, 1 ETANTR, 1 Wnt-medulloblastoma, and 1 AA. All children except the 1 patient with the AA have stable disease; this child exhibited progressive disease 6 months after completing radiation. In terms of their surgical procedures, the patients with the PNETs underwent needle biopsies followed by NTR (n = 1) or GTR (n = 1); the patient with an ETANTR had 1 GTR, the patient with an AA had 2 STRs, and the patient with a Wnt-medulloblastoma had an open biopsy. The median OS for all patients and those with glial and embryonal tumors are 196 days (range 15–3999 days), 205 days (range 15–1018 days), and 181 days (range 51–3999 days), respectively. The Kaplan-Meier survival curves for these 3 groups are shown in Fig. 1.

**Discussion**

**Our Results**

Malignant neoplasms of the brainstem—excluding DIPGs—are exceedingly rare. Even with our unique referral network, we were able to identify only 29 patients over a 15-year period. Unlike focal, low-grade brainstem tumors, the patients in this study more often presented with progressive neurological symptoms of short duration. Pathologically, these tumors can be dichotomously classified as glial or embryonal. Survival, in general, is dismal for the group as a whole. The median OS following diagnosis was 6.4 months, and only 9 patients (31%) survived more than 1 year.

The HGGs (n = 18) in our study were clearly distinct from DIPGs on imaging and included 5 radiation-induced malignancies and 1 child with a known low-grade infiltrative tumor that underwent malignant transformation (Figs. 2–4). The tumor origin was the midbrain in 4 (14%) patients, pons or pons/middle cerebellar peduncle junction in
19 (66%) patients, and medulla or pontomedullary junction in 6 (21%) patients. The radiation-induced patients had a particularly dismal survival with a median OS of 124 days (range 15–599 days). Our longest survivor with a HGG to date is a 5-year-old girl with a GBM of the medulla who was diagnosed by open biopsy followed by radiation: she survived 1018 days (2.79 years). The median survival of our HGG patients—6 months—is worse than the 9 to 12 months commonly seen for DIPG patients.

Our understanding of the genetic and biological basis of HGG in the brainstem has expanded significantly. For example, a large proportion of DIPGs are characterized by missense mutations in the histone genes $H3F3A$ and $HIST1H3B$. These mutations inhibit the PRC2 complex and regulate gene expression via the global reduction in dimethylation and trimethylation of lysine residue 27 of histone subunit 3 (H3K27me2 and H3K27me3).7, 28 Relative to other mutations in high-grade gliomas, $H3F3A$ mutations are associated with a poor prognosis.23 However, considerably less is known about the molecular characteristics of non-DIPG HGG in the brainstem. In our cohort, several tumors were induced by radiation. Camacho et al. recently explored a cohort of radiation-induced murine gliomas and found amplification of the $MET$ proto-oncogene to be an important recurrent event.6 While validation in an expanded cohort is necessary, $MET$ amplification...
Malignant non-DIPG brainstem tumors

The remaining tumors in our series were embryonal tumors (n = 11): PNET, ETANTR, ATRT, and Wnt-medulloblastoma (Figs. 5–7). All of these tumors have distinct histopathological and molecular features. ATRTs are clinically aggressive and histologically primitive tumors that typically contain cells with rhabdoid morphology. They often have a sizeable exophytic component. ATRTs have mutations in the tumor suppressor gene SMARCB1, which codes for a protein involved in the SWI/SNF chromatin-remodeling pathway. Mutant tumors demonstrate loss of immunoreactivity for the BAF47/INI-1 protein and can be readily detected clinically. CNS-PNETs likely represent a heterogeneous group of tumors with multiple molecular subgroups. Typically, PNETs demonstrate a small-cell phenotype and express neural lineage markers such as synapsin and synaptophysin. While the specific molecular underpinnings of CNS-PNET remain to be elucidated, a small proportion demonstrates amplification of MYCN. ETANTR is an aggressive variant of CNS-PNET characterized by the presence of primitive tumor cells with a small-cell phenotype, abundant neuropil, and ependymoblastic rosettes. The tumor is characterized by a specific amplicon of a microRNA locus on chromosome 19 (C19MC). Interestingly, we also identified a patient with a Wnt-medulloblastoma in the brainstem, which is distinct from fourth ventricular medulloblastomas with brainstem invasion (Fig. 5). While medulloblastomas are typically considered fourth ventricular or cerebellar hemispheric tumors, data suggest that tumors in the WNT molecular subgroup arise from cells located in the lower rhombic lip of the dorsal brainstem. In some instances, all 4 embryonal tumors identified in our cohort can present with overlapping histomorphology, particularly when material for review is limited. Distinction between these entities may be of prognostic significance, particularly in the case of WNT medulloblastoma, which has been shown to have a significantly better prognosis compared with other embryonal neoplasms.

Although the OS for the group is still poor, there is some glimmer of hope for these patients. Four of the 5 current survivors have embryonal tumors, including 2 patients with PNETs, who continue to be disease free at 3.8 and 10.9 years after diagnosis, respectively, and 1 patient with ETANTR who has been disease free for almost 2 years (Figs. 6 and 7). In our opinion, the best hope for
long-term disease remission in patients with embryonal tumors is to have no leptomeningeal disease on presentation and GTR followed shortly thereafter with adjuvant therapy. Our results with PNETs and our surviving patients with ETANTR are in contrast to the recent report by Friedrich et al. They reported 6 children with brainstem PNETs and 2 with “ependymoblastomas” collected over an almost 20-year period from 8 centers within Germany. No patient had GTR: 3 had partial resection, 3 had STR, and 2 had biopsies. All patients developed local failures and eventually succumbed to their disease with a median survival of only 2 months (range 0.5–12.2 months). Similarly, Zagzag et al. reported 7 tissue-proven brainstem PNETs collected over a 10-year period at a single institution. Two patients had a biopsy only, and the rest had partial resections but the degree of the resection was not provided. Despite therapy, all 7 patients died within 17 months of diagnosis with a mean survival of 8 months (range 4–17 months).

Evaluation and Surgical Treatment

The first step involves obtaining high-quality MRI. The important features that need to be determined include whether the tumor has infiltrative features or more focal, well-delineated margins; its location with respect to cranial nuclei and the corticospinal tracts; and whether there is an exophytic component. MRI can often provide information that can differentiate an HGG from an embryonal tumor, as HGGs tend to be infiltrating with indistinct margins and embryonal tumors are more likely to have discrete margins. While both can have solid and cystic components and variable enhancement, HGGs more often have distinct areas of lower apparent diffusion coefficient (ADC) values (i.e., suggesting areas with a higher nuclear/cytoplasmic ratio) within a heterogeneous background, while embryonal tumors tend to have less heterogeneity of their solid components and fewer solid areas that may look low grade. Diffusion tensor imaging may be able to play a role in evaluating the relationship of tumor margins to fiber tracts in the brainstem, possibly being able to guide biopsy and/or resection similar to recent work in spinal cord tumors.

FIG. 4. HGG Patient 3. An 11-year-old girl with a radiation-induced AA diagnosed 10 years after completing treatment for a posterior fossa ependymoma. Axial T2-weighted images show chronic right cerebellar volume loss with an intrinsic lesion in the right aspect of the brainstem with a ventrolateral exophytic cystic component. This lesion was detected on a routine surveillance MRI and was asymptomatic at the time of detection. The patient underwent GTR via the Kawase subtemporal approach.

FIG. 5. Embryonal Patient 1. A 19-year-old male patient with Wnt-medulloblastoma. Left: Axial T1-weighted image with contrast at the level of the cerebellum showing focal thickening of the medial aspect of the left middle cerebellar peduncle with involvement of the left facial colliculus and partial effacement of the fourth ventricle. Right: Axial diffusion-weighted image showing that the lesion has a hyperintense signal, which was confirmed to be related to reduced water diffusion on the ADC maps. The lesion was found to be a Wnt-medulloblastoma with an open biopsy.

FIG. 6. Embryonal Patient 2. A 2-year-old with ETANTR. A: Axial T2-weighted image demonstrating a circumscribed lesion in the left aspect of the pons. B: Axial T2-weighted image of the brainstem obtained 1.5 years after resection showing a stable focal area of nodularity along the anterior aspect of the resection cavity. C: Sagittal T2-weighted image showing the pontine resection cavity and otherwise normal morphology of the pons.
While the surgical management of DIPG is limited to the management of hydrocephalus, there are 2 added roles in non-DIPG malignant tumors: obtaining tissue for diagnosis and resection. For tumors that are clearly infiltrative (i.e., tumors with borders that are ill-defined) or with leptomeningeal metastases, there is no role for resection and thus the tissue needs to be obtained via an open (i.e., craniotomy) approach or stereotactically with a needle. For those patients with nonmetastatic tumors—glial or embryonal—that have well-defined margins, are accessible through one of the described brainstem surgical corridors or via the exophytic portion, and can be removed with acceptable neurological deficit(s), surgery with the goal of achieving GTR should be considered. Admittedly controversial, this opinion has been voiced by others.32,39 Thorough preoperative counseling with the patients and/or their families is required so that they understand and are accepting of the neurological deficit(s) that may occur with resection. In our experience, 1 or more new neurological deficits or findings develop postoperatively in virtually all patients who undergo an aggressive resection within an eloquent area, but some may improve with time. For all types of focal, non-DIPG, malignant brainstem tumors, we feel that maximal resection, when technically possible, affords the patient the best chance of maximizing survival. As depicted in Fig. 7, intraoperative MRI is an invaluable asset that helps guide the resection of such discrete brainstem lesions.8 Due to the rarity of these tumors, our surgical philosophy is admittedly based on our limited experience and extrapolation of the known beneficial impact that radical resection has on survival in children with malignant glial and embryonal tumors located elsewhere in the brain.2,43 Postoperative adjuvant therapy—radiation therapy and/or chemotherapy—is essential and dependent upon the type of tumor and the age of the patient. In cases where the tumor is focal but the pathology is unknown, it is also reasonable to start with a biopsy (stereotactic needle or open), which then allows a more thorough discussion with the family before pursuing resection.

Conclusions

Malignant brainstem tumors are remarkably rare and pathologically diverse, but can be classified as glial or embryonal and as a group may have a worse prognosis than DIPG. However, we have demonstrated that survival of a year or longer is possible, particularly for patients with embryonal tumors without leptomeningeal disease at presentation who undergo GTR. High-quality imaging is critical for surgical planning.

Acknowledgment

We thank Andrew J. Gienapp, BA (Department of Medical
Education, Methodist University Hospital, Memphis, TN, and Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN), for technical editing and copyediting, preparation of the manuscript and figures for publishing, and publication assistance with this manuscript.

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**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Klimo. Acquisition of data: Klimo, Broniscer, Orr. Analysis and interpretation of data: Klimo, Nesvick, Broniscer. Drafting the article: Klimo, Nesvick. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Klimo. Study supervision: Klimo.

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