Current Clinical Challenges in Childhood Ependymoma: A Focused Review

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ABSTRACT

Ependymoma is a locally aggressive tumor with metastatic potential that arises in diverse locations throughout the brain and spine in children. Tumor and treatment may result in significant morbidity. Cure remains elusive for many patients owing to diverse biology and resistance to conventional therapy. The implementation of systematic postoperative irradiation in clinical trials during the past 20 years has increased the proportion of patients achieving durable disease control with excellent results, as measured by objective functional outcome measures. Clinical, pathologic, and molecular risk stratification should be used to refine treatment regimens for children with ependymoma to reduce the risk of complications associated with therapy and increase the rate of disease control in the setting of combined modality or more intensive therapy. This review covers standards of care and current clinical trials for children with ependymoma, emphasizing the history and evolution of treatment regimens during the past 20 years and the clinical questions they hoped to address.

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INTRODUCTION

Ependymoma is a devastating pediatric disease. Children with ependymoma have significant morbidity from the events leading to diagnosis as well as the treatments required for its cure. They also have high rates of mortality because ependymoma challenges all forms of conventional therapy. Challenges in treating ependymoma include the need for specialized resources, variability in extent and location of tumor, rarity and diverse biology of the tumor, and patient age. These factors are affected by the health-care provider’s experience, introduce bias in the overall treatment plan, and add uncertainty to current treatments.

The standard of care for ependymoma varies by geographic location and treatment center. Despite differing opinions about potential indications and clinical scenarios of ependymoma, experts worldwide generally agree that surgery and radiation therapy (RT) are mainstays of treatment. Surgery and RT form the backbone for Children’s Oncology Group (COG) and International Society for Pediatric Oncology (SIOP) trials on ependymoma. Outcomes of children with ependymoma have markedly improved over the last 20 years as a result of advances in surgery and RT through new technologies, increased participation in clinical trials, more centers with pediatric neuro-oncology expertise, improved care, and better communication among caregivers and investigators.

CLINICAL TRIALS ON PEDIATRIC EPENDYMOMA

Surgery and RT were established as the gold standard for intracranial ependymoma, as outlined in a benchmark study at St Jude Children’s Research Hospital (St Jude) from 1997 to 2007. This study was the most extensive follow-up of patients (n = 153) treated with aggressive surgery followed by immediate postoperative high-dose photon irradiation, and included children as young as 12 months at the time of irradiation. Children with intracranial tumors and those previously receiving chemotherapy were included, and those with spinal cord tumors and metastatic disease were excluded from analysis.

The high rate of gross total resection (GTR; defined as resection of all macroscopically visible residual tumor) was key to excellent patient outcomes. Greater than 81% of patients achieved GTR before irradiation, and > 92% achieved near-total resection (< 5 mm residual tumor). Sixty-six patients underwent second resection before irradiation.
During the early phase of the trial, chemotherapy was administered to children younger than 3 years at the time of diagnosis. In a separate analysis, patients treated with chemotherapy (22.9%) or those starting irradiation > 4.4 months after diagnosis (8.1%) were excluded from analysis. Strikingly, the resulting group of patients had the highest 7-year progression-free survival (PFS; 76.9%) and overall survival (OS; 85%) rates. Extent of resection, tumor grade, pre-irradiation chemotherapy, age, and race were significant predictors of PFS and OS. Notably, there was an association between extent of resection and local failure, as well as between tumor grade and distant failure. The 7-year cumulative incidence was 12.59% for local failure and 8.56% for distant failure.

The St Jude study prompted subsequent trials and current standards of care. The COG trial ACNS0121 from 2003 to 2007 enrolled 378 children and young adults (ages 1 to 22 years). Final results of the trial were presented at the American Society for Radiation Oncology Annual Meeting in 2015. Patients were stratified as follows:

- **Stratum 1:** Observation for completely resected (microscopic GTR) differentiated, supratentorial ependymoma
- **Stratum 2:** Chemotherapy, second surgery, and RT for incompletely resected ependymoma
- **Stratum 3:** Conformal RT after near-total or macroscopic GTR, regardless of tumor grade or location
- **Stratum 4:** Conformal RT after microscopic GTR, regardless of tumor grade or location, excluding supratentorial, differentiated tumors

The 5-year (± standard error) PFS rates of patients in strata 1, 2, 3, and 4 were 61% ± 14%, 39% ± 7%, 67% ± 5%, and 70% ± 4%, respectively. Primary mode of failure was local for patients in strata 3 and 4, and one-third of failures included a component of metastatic failure. ACNS0121 completed enrollment in 4 years and set the stage for the subsequent COG study ACNS0831.

ACNS0831 is a randomized phase III trial (ClinicalTrials.gov identifier: NCT01096368) with treatment strata similar to those for ACNS0121. It opened in March 2010 and plans to enroll 400 patients ages 1 to 21 years with newly diagnosed ependymoma. Currently, the trial is open in the United States, Australia, Canada, and New Zealand. The primary aim is to compare the 5-year event-free survival (EFS) for patients randomly assigned to adjuvant chemotherapy or observation after irradiation. Patients were stratified as follows:

- **Stratum 1:** Observation for microscopic completely resected supratentorial, differentiated ependymoma
- **Stratum 2:** Chemotherapy, second surgery, and conformal RT for patients initially treated with subtotal resection
- **Stratum 3:** Immediate postoperative irradiation for all patients randomly assigned to observation or maintenance chemotherapy. Maintenance chemotherapy begins within 30 days of RT completion and consists of four 21-day cycles of vincristine, cisplatin, etoposide, and cyclophosphamide. Vincristine is not included in cycle 4.

SIOP-EP-II (ClinicalTrials.gov identifier: NCT02265770) is a multi-arm phase II and III trial involving 15 European countries. It opened in September 2014 and plans to enroll children ages 1 to 22 years for treatment according to age, tumor location, and initial extent of resection. This trial was also initiated based on early results of the St Jude study, lack of cognitive effects observed during serial testing in the first 5 years after irradiation, and the need to test novel agents as frontline treatment. Patients receive conventional chemotherapy with or without a histone deacetylase (HDAC) inhibitor. HDAC inhibitors and epigenetic modifiers are considered potential treatment because of identification of hypermethylated phenotypes in ependymoma, potential epigenetic targets, and easy availability of novel agents as frontline treatment. Patients were stratified as follows:

- **Stratum 1:** Resection with no evidence of residual tumor, followed by conformal RT and randomization to 16 weeks of multiagent chemotherapy (vincristine, etoposide, cyclophosphamide, cisplatin) or observation.
- **Stratum 2:** Resection with evidence of residual tumor, followed by randomization to 7 (vincristine, etoposide, cyclophosphamide) or 9 (vincristine, etoposide, cyclophosphamide, methotrexate) weeks of chemotherapy, followed by second surgery, conformal RT, and 16 weeks of chemotherapy (all patients), similar to that for stratum 1. Patients with residual disease after second surgery receive 8 GY (4 Gy two times) of supplemental RT.
- **Stratum 3:** Postoperative dose-intensive chemotherapy (methotrexate, vincristine, etoposide, cyclophosphamide, cisplatin, carboplatin) administered for 1 year with or without the HDAC inhibitor valproate to patients ≤ 12 months old at enrollment or those not eligible to receive RT.

The RT regimen for SIOP-EP-II is novel and based on results of the second AIEOP study. The AIEOP study (2002 to 2014) enrolled 160 patients and was designed to guide future trials. Patients with WHO grade II tumors and no evidence of disease (NED) after initial surgery were treated with fractionated irradiation of 59.4 Gy. Children younger than 3 years of age and with NED were treated with six chemotherapy cycles (vincristine, etoposide, and cyclophosphamide). Patients with WHO grade III tumors and NED received adjuvant postirradiation chemotherapy. Patients with residual disease received up to four chemotherapy courses, second-look surgery, and irradiation of 59.4 Gy, followed by irradiation of 8 Gy in two fractions if measurable residual tumor was present. For 24 of 40 patients receiving an 8-Gy RT boost, 5-year PFS and OS were 58.1% and 68.7%, respectively. For the entire cohort, PFS and OS were 65.4% and 81.1%, respectively. Tumor grade was associated with PFS, whereas tumor grade and extent of resection were associated with OS.

Ependymoma recurrence after prior surgery and irradiation was once considered fatal, but currently there are several options for patients with recurrent disease to prolong survival or achieve cure. The most recommended option is additional surgery and RT. Patients with locally recurrent tumors can undergo salvage treatment with further surgery and focal or craniospinal irradiation (CSI). The decision to administer focal RT or CSI is largely empirical and based on the patient’s age. Barring some exceptions, patients with local recurrence evaluated at St Jude undergo surgery and focal reirradiation. In a recent study in Toronto, all patients...
with local recurrence were offered surgery and CSI, although the number of patients studied was small.\textsuperscript{18}

Patients receiving focal reirradiation are at risk for local recurrence and metastatic tumor progression; the latter tends to be more frequent in patients with gains in chromosome 1q (unpublished data). In a study of patients with posterior fossa primary tumors having local recurrence and treated with CSI, none experienced distant-only failure.\textsuperscript{17} However, when patients treated focally at the time of recurrence were considered, distant-only failure occurred in four of 14 (29%) with no gains in 1q versus four of five (80%) patients with gains in 1q (unpublished data).

Recent findings suggest that compared with patients without gains of 1q, those with gains of 1q have a higher risk of distant failure after initial treatment. In a study of newly diagnosed patients at St Jude receiving focal irradiation, 1q gain was a marker for neuraxis metastatic tumor progression (unpublished data). Of 29 patients with primary infratentorial tumors and 1q gains, 17 (58.6%) had distant or combined failure after initial irradiation.\textsuperscript{21}

Investigators continue to explore chemotherapy use in very young patients to avoid irradiation and in children with residual disease after initial resection. From 1994 to 2003, 41 children younger than 3 years of age were treated with multiagent chemotherapy including vincristine, methotrexate, and cyclophosphamide alternating with cisplatin and etoposide for 14 months, followed by vincristine, etoposide, and cyclophosphamide for 6 months. The 5-year PFS, EFS, and OS rates were 27%, 26%, and 37%, respectively. Among survivors, there were no significant differences in cognitive outcomes for those receiving or not receiving RT.\textsuperscript{28}

The UKCCSG/SIOP CNS 9204 trial (1993 to 2003) included 89 children ≤ 3 years old who received chemotherapy for 1 year.\textsuperscript{29} Of these, 59 had disease progression, including nine with metastatic disease at presentation. Median time to disease progression was 1.6 years. The 3-year and 5-year EFS were 47.6% and 41.8%, respectively. Irradiation was delayed or avoided in a substantial proportion of patients.\textsuperscript{29}

In a French Society of Pediatric Oncology study (1990 to 1998), 73 patients were treated with conventional chemotherapy with seven cycles of alternating procarbazine and carboplatin, etoposide and cisplatin, and vincristine and cyclophosphamide. Systematic irradiation was not given at relapse. The 4-year PFS was 22%, which slightly differed from that reported in very early studies.\textsuperscript{30}

**NOVEL THERAPEUTIC OPTIONS FOR RECURRENT EPENDYMOMA**

There are several novel options for children with recurrent ependymoma after prior surgery and irradiation. Tumor-associated antigens can be overexpressed in ependymoma;\textsuperscript{22} this triggered studies on vaccine therapy for patients with recurrent tumors after prior conventional therapy. A study using HLA-A2–restricted tumor antigen peptides in combination with imiquimod, an immune response modifier, is underway for patients 1 to 21 years of age with recurrent ependymoma.\textsuperscript{23} A phase 1 trial is testing the heat shock protein peptide complex-96 vaccine in patients 3 to 21 years old with recurrent ependymoma.\textsuperscript{24} A novel pilot study using a hypomethylating agent is currently underway (ClinicalTrials.gov identifier: NCT02940483). The study involves the infusion of 5-azacytidine into the fourth ventricle via Ommaya reservoir in children with recurrent posterior fossa ependymoma. The aim is to establish direct administration of the study agent into the resection cavity. A total of 12 infusions are planned for a limited number of patients.

**Chemotherapy**

Extent of resection is the most important predictor of disease control outcomes, regardless of series or treatment approach. Use of irradiation remains debatable because it achieves tumor control but carries risks when used in young children. The nonmetastatic presentation of most tumors as determined by conventional magnetic resonance imaging and CSF cytology, advent of conformal RT, and poor outcomes when irradiation is delayed or avoided led to RT being used as frontline treatment of all children with ependymoma. This was followed by systematic attempts to optimize patients for RT and consider second surgery. The Children’s Cancer Group study reported poor outcomes for young patients with ependymoma who were randomly assigned to chemotherapy or observation after surgery and CSI.\textsuperscript{25} In infant brain tumor studies by the Pediatric Oncology Group, conventional or intensive chemotherapy was given to delay irradiation in children ≤ 3 years old.\textsuperscript{26,27}

**Integrating Chemotherapy and Radiation Therapy**

Several recent studies in which chemotherapy was administered to young children used integrated strategies that include irradiation or focus on improving outcomes for patients with residual disease.

A German trial (2001 to 2005) on 296 patients treated at 63 centers used a risk-adapted approach for nonmetastatic ependymoma.\textsuperscript{31} The study initially had two regimens: (1) 10 months of chemotherapy and local RT (54 Gy, 1 × 1.8 Gy/d) for children 18 to 48 months old (regimen A), or (2) hyperfractionated RT (68 Gy, 2 × 1 Gy/d) followed by modified chemotherapy for children ≥ 4 years old with WHO grade III tumors (regimen B). From 2006 to 2011, regimen C was added for patients with residual disease, which included 3 months of chemotherapy followed by risk-adapted RT and adjuvant chemotherapy. There was no difference in 3-year PFS of completely resected patients receiving regimen A or B (73% ± 4% vs 75% ± 4%). For patients with residual disease, 3-year PFS was similar for regimens A, B, and C (50% ± 10% vs 58% ± 11% vs 41% ± 8%). Investigators concluded that delay of irradiation for 10 months of chemotherapy was safe and those with residual disease did not benefit from a brief course of chemotherapy.\textsuperscript{31}

St Jude trial SJYC07 also used a risk-adapted approach to test a 4-month course of postoperative chemotherapy, focal irradiation.
(54 Gy), and maintenance chemotherapy in children younger than 3 years of age with WHO grade II or III intracranial ependymoma. Chemotherapy included intravenous methotrexate, vincristine, cisplatin, and cyclophosphamide before irradiation and oral maintenance chemotherapy postirradiation, which consisted of six total 28-day cycles of oral cyclophosphamide and topotecan alternating with oral erlotinib. The 5-year EFS and OS rates were 74% ± 10% and 84% ± 8%, respectively, with no significant differences by genomic subgroup or tumor grade.32

**Proton Therapy**

A major advance in ependymoma treatment has been the introduction of conformal RT using photons for frontline management of young children. Photon RT was introduced owing to results from a St Jude study and confirmed by COG ACNS0121, which enrolled 378 patients from 115 institutions. COG ACNS0121 included 111 children younger than age 3 years and more than 204 children younger than 6 years of age at enrollment.4 Understanding the importance of irradiation and the ability of its most advanced forms to spare normal tissues and reduce the risk of complications, parents and caregivers now prioritize RT over participation in cooperative group trials for patients. Proton therapy is considered the newest form of RT for pediatric ependymoma.33 Although ependymoma is commonly diagnosed among children referred for proton therapy, few are treated with this modality on protocol.35 Because of limited access to proton therapy and proton therapy centers not being closely associated with pediatric hospitals, adhering to cooperative protocol guidelines can be difficult, especially in cases of nonstandard-care target volumes, target volume doses, normal tissue dose constraints, or combined modality therapy. These challenges can lead to compliance problems, making enrollment or continued participation in protocols difficult. In the United States, compliance with cooperative group guidelines is overseen by the enrolling institution; thus, a patient may be enrolled in a protocol and undergo irradiation at a distant, cooperative group-approved proton therapy center. Although a proton therapy center may be credentialed to treat patients in cooperative group trials, credentialing for most tumor types and protocols is not specific. If physicians at the proton therapy center are not satisfied with the guidelines for irradiation or the overall treatment plan, they can request that the enrolling institution remove the patient from the study.

**Challenges With Proton Therapy**

Given the limited number of enrollments in pediatric cooperative group trials, established procedures cannot be applied to report disease control and toxicity to regulatory agencies. Reporting of outcomes and the reliability of published information is further compromised by referral of patients to remote centers that cannot follow patients after treatment. Reports citing unexpected clinical findings or toxicity related to proton therapy in children with brain tumors, including those with ependymoma, raise concerns about the guidelines for proton therapy use in children and highlight uncertainties in proton therapy physics and relative biologic effectiveness.36-38

Some radiation oncologists are reluctant to treat patients with infratentorial tumors with total doses > 54 Gy, even though target volume margins established for the COG and SIOP trials were smaller (clinical target volume [CTV] = 0.5 cm and planning target volume [(PTV] = 0.3 cm) than for an earlier COG trial (CTV = 1.0 cm and PTV = 0.5 cm). In the current COG study, there is a mandated volume reduction for treatment with 54 to 59.4 Gy, and normal tissue dose constraints can be prioritized over PTV2 coverage.3 The SIOP study recommends that for patients with infratentorial tumors, the spinal cord be excluded at a cumulative dose of 54 Gy and dose to the brainstem be minimized.4 The trial does not specify a dose constraint for the brainstem. Patients with residual disease selected to receive an 8-Gy boost after a dose of 59.4 Gy should be given intensity-modulated treatment to spare the brainstem. The current COG study mandates a volume reduction and suggests treatment to a minimum dose of 54 Gy and allowance for supplemental irradiation to 59.4 Gy for the volume at highest risk for local tumor recurrence.

**Why 59.4 Gy for Ependymoma?**

Failure is predominantly local in children treated with postoperative RT. Beginning with POG-9132 (1991 to 1994), the primary site dose was escalated to 69.6 Gy using a hyperfractionated approach (1.2 Gy twice per day) and later to 59.4 Gy (1.8 Gy per day), which is consistent with doses used to treat other aggressive or high-grade brain tumors.39 In a St Jude study in which the GTR rate was > 80%, the cumulative incidence of local failure was 16.3% (95% CI, 9.6% to 23.0%) at 5 to 7 years.5

Table 1 lists photon and proton therapy trials for pediatric ependymoma.2,3,39-43 The number of children treated with a dose of 54 Gy is low for trials in North America. In European trials, tumor control rates are superior in patients treated with high-dose regimens.

**Future Trends**

The design and interpretation of future trials will rely on assessing biologic differences among ependymoma subtypes and their association with outcome after conventional treatment. Distinct entities of ependymoma have been defined by molecular profiling. There are substantial differences between adult and pediatric tumors,4 as well as by tumor location in pediatric tumors.45 Important considerations in future trials include identifying novel targets and therapeutic agents, using more aggressive treatment regimens for high-risk patients,46,47 and prioritizing patients for de-escalation of therapy.48

None of the current frontline trials on pediatric ependymoma use clinicobiologic risk stratification, although this has been proposed and supported by consensus review.4 The simplest stratification for children is based on disease risk, according to which low-, intermediate-, and high-risk patients receive observation (surgery only), standard of care (surgery and irradiation), and intensive combined modality therapy (surgery and concurrent radiation and chemotherapy), respectively.49

Identifying low-risk patients for observation studies is reasonable and is being considered for children with supratentorial differentiated tumors who underwent complete resection by an operating microscope. This factor was not addressed in ACNS0121 because of few low-risk patients in the study. The strategy is being used in ACNS0831 and can be potentially successful. It can be
argued that this strategy be used for all patients with supratentorial tumors, given anecdotal evidence that anaplastic tumors may be observed, controversies associated with assessing tumor grade, and potential risks associated with supratentorial irradiation. Arguments against using this strategy for all patients include excellent concordance between institutional and expert pathology assessment in ACNS0121 and evidence that in patients who undergo irradiation (mixed tumor grades), disease control rates after RT are 80% at best, suggesting that intensive therapy beyond irradiation is required for patients with supratentorial tumors.2 Conformal RT has been used for children with ependymoma for the last 20 years. Future trials should focus on achieving excellent functional outcomes in long-term survivors of ependymoma.

Table 1. Photon and Proton Therapy Trials for Pediatric Ependymoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Period</th>
<th>Age Restriction (months)</th>
<th>Target Volume</th>
<th>CTV Margin (cm)</th>
<th>Dose (cGy/CcGE)</th>
<th>Total (IT/ST)</th>
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<td>Photon-proton</td>
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Abbreviations: BiD, twice per day; cGy/CcGE, centigray/centigray equivalent; CTV, clinical target volume; IT/ST, infratentorial/supratentorial; PBS, pencil beam scanning; PSI, Paul Scherrer Institute; TBD, to be decided.

Disclosures provided by the authors are available with this article at jco.org.
32. Robinson GW, Orr B: Molecular subgrouping and outcomes for young children with newly diagnosed ependymoma treated on the multi-institutional SJYC07 trial. ASPHO 2017, Montreal, Quebec, Canada, April 26-29, 2017 (abstract 4026)

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AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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