

# Advances in Management of Pediatric Ependymomas

Frank Y. Lin<sup>1,2,3</sup> · Murali Chintagumpala<sup>1,2,3</sup>

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**Abstract** Ependymomas are a heterogeneous group of neuroepithelial tumors of children and adults. In pediatric cases, the standard of care has long consisted of neurosurgical resection to the greatest extent acceptable followed by adjuvant involved field irradiation. Complete macroscopic surgical resection has remained the only consistent clinical variable known to improve survival. Adjuvant chemotherapy has yet to predictably affect outcome, possibly due to the molecular heterogeneity of histologically similar tumors. The administration of chemotherapy subsequently remains limited to clinical trials. However, recent comprehensive genomic, transcriptomic, and epigenetic interrogations of ependymomas have uncovered unique molecular characteristics and subtypes that correlated with clinical features such as age, neuroanatomical location, and prognosis. These findings represent a potential paradigm shift and provide a biologic rationale for targeted therapeutic strategies and risk-adapted administration of conventional treatment modalities. In this review, we focus on intracranial WHO grade II and III ependymoma of children and discuss conventional management strategies, followed by recent biologic findings and novel therapeutics currently under investigation.

**Keywords** Pediatric ependymoma · Radiation therapy for ependymoma · Molecular subtypes of ependymoma · Prognostic factors in ependymoma

## Introduction

Ependymomas comprise a heterogeneous group of neuroepithelial tumors that affect children and adults. Approximately 170 new pediatric cases occur each year in the USA, accounting for 6–10 % of primary pediatric central nervous system (CNS) tumors [1–5]. The majority are seen in children under 7 years of age, with 25–51 % of all cases occurring in children under 3 years of age. A second peak is observed in adults in the third to fifth decades; however, the prevalent histologic subtypes differ from that seen in the pediatric population [5–8]. While ependymomas can occur across the neuraxis, nearly 90 % occur intracranially, one third of which are supratentorial and two thirds are located in the posterior fossa [3]. Neuroanatomic location as well as histologic type vary between age groups; for example, a higher incidence of posterior fossa ependymoma occurs in younger children, whereas spinal cord tumors (particularly World Health Organization (WHO) grade I subependymoma and myxopapillary variants) are more frequently seen in adolescents and adults [9]. Among children, the approach to management has remained strikingly similar over the past two decades: surgical resection to the greatest extent possible without unacceptable neurologic sequelae, followed by postoperative involved field irradiation. The role of chemotherapy remains under further investigation, as clinical trials have yet to demonstrate definitive survival benefit. Five-year event-free survival (EFS) and overall survival (OS) is an unsatisfactory 23–57 % and 50–71 %, respectively [1, 2, 6, 10, 11], with modest improvements largely attributed to improvements in neurosurgical

✉ Frank Y. Lin  
fylin@txch.org

<sup>1</sup> Section of Hematology-Oncology, Department of Pediatrics, Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA

<sup>2</sup> Brain Tumor Program, Texas Children's Cancer Center, 6701 Fannin St, Ste 1510, Houston, TX 77030, USA

<sup>3</sup> Dan L. Duncan Cancer Center, Houston, TX, USA

and radiotherapy technique. However, this long-standing management paradigm may soon be challenged by recent genomic/epigenomic breakthroughs that may potentially provide a biologic basis for novel diagnostics and therapeutics.

This article will focus on the most common variants in children, intracranial WHO grade II and III ependymoma, first reviewing conventional management strategies, followed by recent biologic findings and novel therapeutics currently under investigation.

## Extent of Surgical Resection

Local control for pediatric ependymoma is of critical importance, as these tumors are locally invasive with low metastatic potential. Leptomeningeal dissemination is seen at diagnosis in 7–12 % of cases, and recurrent disease most frequently occurs at the primary tumor site [12–14]. The most significant clinical intervention for local control remains neurosurgical resection, and the extent of macroscopic tumor removal as the most consistent independent prognostic variable. Survival of patients who received a gross total resection (GTR) range from 66 to 80 %, compared with 0–47 % among patients with a sub-total resection (STR). Unfortunately, GTR historically was achieved in only 42–66 % of patients due to tumor location and the risk of unacceptable neurovascular injury [10, 12, 15, 16]. For example, supratentorial tumors arise within or adjacent to the lateral ventricles and are technically more amenable to GTR. In contrast, posterior fossa ependymomas develop in the fourth ventricle and have the potential to extend laterally and ventrally to involve eloquent structures, cranial nerves, and blood vessels along the brain stem.

The survival advantage conferred by GTR has prompted consideration for pre-irradiation neo-/adjuvant chemotherapy in patients with incompletely resected ependymoma, in an attempt to reduce residual tumor size and allow for a second-look surgery and GTR [17]. While adjuvant chemotherapy alone has not been demonstrated across multiple trials to benefit survival [18], subsets of patients achieve an objective response in tumor size that may allow for subsequent complete neurosurgical resection [2]. This approach was included as a study question in the two latest ependymoma trials conducted by the Children's Oncology Group (COG), ACNS 0121 and ACNS 0831. One of the objectives in ACNS 0121, a completed phase II trial, was to evaluate the rate that second-look GTR can be achieved in patients with an initial STR followed by chemotherapy consisting of vincristine, carboplatin, and cyclophosphamide, alternating with vincristine, carboplatin, and etoposide. This data is yet to be published. ACNS 0831 currently includes a similar treatment arm with an option for second surgery. However, pending more definitive results, the administration of pre-irradiation

chemotherapy has not been a standard practice outside the context of a clinical trial.

## Adjuvant Radiotherapy

Postoperative involved field radiotherapy dosed at 54–59.4 cGy is considered the standard of care for patients with non-disseminated ependymoma to lower the risk of local recurrence [19]. Although adjuvant radiotherapy has never been compared to surgical resection alone in a randomized trial, multiple studies have demonstrated improved outcomes versus historical data. A study of 22 children who received postoperative intensity-modulated radiation therapy (IMRT) had a 3-year EFS and OS of 68 and 87 %, respectively [20], and in another study of 153 patients, including 78 children under the age of 3 years, children treated with adjuvant 3D-conformal radiotherapy or IMRT attained a 7-year EFS and OS of 69.1 and 81 %, respectively [7]. This study also highlighted several unique clinical challenges involved in treating very young children. Historically, patients under 3 years of age were considered particularly poor candidates to receive radiation therapy due to the greater susceptibility of devastating neurocognitive, endocrinologic, and neurologic adverse effects [21]. However, attempts to defer radiotherapy by administering chemotherapy as a bridge to irradiation resulted in unacceptably higher mortality (see section “[Uncertain Role of Chemotherapy](#)”), and general practice currently extends the utilization of adjuvant radiation therapy to children greater than 12 months of age [2, 15, 22, 23].

Efforts to mitigate the risk for radiation-related adverse effects are critical but require longitudinal study [21]. An active area of interest is the utilization of proton beam irradiation, which generates a significantly reduced exit dose compared with photons, theoretically decreasing the amount of radiation exposure outside the treatment target. Potential clinical benefits of proton beam have been reported in other pediatric CNS tumors [24, 25]; however, long-term studies are needed to demonstrate equivalent tumor control and the actual risk for radiation necrosis, in addition to long-term benefits for survivors of pediatric ependymoma. At this time, proton beam irradiation is not widely available and may cause a logistical burden for some patients.

A subset of patients who attained a GTR for WHO grade II ependymoma with well-differentiated histology were reported in several small series to have a 5-year mortality without adjuvant radiotherapy to be as low as 3.3 % [26, 27] but needs further study. For these patients, radiotherapy is held as a salvage option if needed for treatment of recurrent tumor. This “observation only” strategy is being prospectively evaluated for patients with GTR of well-differentiated supratentorial tumors in ACNS 0831. A similar approach was used in the prior COG study ACNS 0121. Future studies will need to refine the

criteria for identification of patients that will benefit the most with observation only.

### Re-irradiation of Relapsed Ependymoma

Relapsed ependymoma carries an extremely poor prognosis, with 5-year OS reported at 27.6 % [28]. The median time to recurrence or progression is widely distributed at 18–45 months, and approximately 9–10 % of patients develop leptomeningeal dissemination [29]. Surgical resection/palliative debulking is often performed when possible, but re-irradiation has emerged as a potential strategy. One study reported 18 patients who were treated with an additional >10.8 cGy at the time of tumor recurrence and attained a 3-year OS of 81 versus 7 % among 16 patients who did not receive re-irradiation [30]. Several other publications have reported the feasibility of stereotactic radiosurgery, involved field radiation, or cranial-spinal radiation [13, 30, 31]; however, additional follow-up is necessary.

### Uncertain Role of Chemotherapy

The role of chemotherapy in the management of ependymoma has been extensively studied but remains controversial and is not routinely recommended outside the context of a clinical trial. In 1975, the Children's Cancer Group (CCG) trial CCG942 randomized 36 children with intracranial ependymoma to PCV (procarbazine, CCNU, vincristine) versus no adjuvant chemotherapy after irradiation [32], and CCG921 randomized 32 children from 1986 to 1992 to treatment with PCV versus "8-in-1" (vincristine, hydroxyurea, procarbazine, CCNU, cisplatin, cytarabine, methylprednisolone, and cyclophosphamide) [33]. Neither study demonstrated survival benefit from the addition of chemotherapy. However, a Children's Cancer and Leukemia Group (UKCCSG) and International Society of Paediatric Oncology (SIOP) trial, CNS 9204, investigated 89 children under 3 years of age who were treated with up to 4 cycles of postoperative chemotherapy consisting of myelosuppressive carboplatin and cyclophosphamide alternating with cisplatin and cyclophosphamide. In children who did not receive radiotherapy, 5-year OS of patients without metastatic disease was surprisingly high at 63.4 %, and 5-year EFS was 41.8 %. However, a similar protocol conducted by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) reported a 5-year OS of 37 % [34]. The reason for the discordant survival between chemotherapy protocols is unclear.

In the 1995 Children's Cancer Group study, CCG 9942, 41 patients with incomplete surgical resection received 4 cycles of vincristine, etoposide, cisplatin, and cyclophosphamide prior to radiation therapy. Children with greater than 90 %

resection of tumor and treated with pre-irradiation chemotherapy experienced a similar 5-year EFS as those with GTR and adjuvant radiation therapy alone. The 5-year EFS of children with less than 90 % tumor resected was 29 % [2]. The French Society of Pediatric Oncology conducted a trial of pre-irradiation chemotherapy with a 16-month regimen of alternating cycles of procarbazine and carboplatin, etoposide and cisplatin, and vincristine and cyclophosphamide, but a 4-year OS was only 23 % [22].

Despite disappointing survival outcomes from chemotherapy-based clinical trials, a subset of patients demonstrated radiologic response of tumor to chemotherapy, raising the possibility of a GTR with a second-look surgery. In CCG 9942, 57 % of patients treated with chemotherapy had significant tumor response (40 % complete and 17 % partial response) [2]. The feasibility of neoadjuvant chemotherapy and second-look surgery was prospectively examined in one arm of the COG trial ACNS 0121 and will be assessed in ACNS 0831 with a chemotherapy regimen of vincristine, cisplatin, etoposide, and cyclophosphamide.

### Prognostic Value of Histologic Classification

Ependymomas are categorized by the WHO classification system into three grades and four histologic variants: grade I subependymoma and grade I myxopapillary ependymoma, grade II classic ependymoma (further subdivided into histopathologic variants including cellular, papillary, clear cell, and tanycytic), and grade III anaplastic ependymoma. Subependymoma and myxopapillary ependymoma are both very rare in children, in whom WHO grade II and grade III ependymomas predominate [35]. Grade II or III histology does not alter the current clinical approach of maximum feasible surgical resection and adjuvant radiotherapy. Additionally, the prognostic value of tumor grade is a subject of continued debate as it has not consistently predicted survival outcomes across multiple clinical trials [2, 7, 29, 33, 36]. This may be due in part to the relatively subjective nature of the criteria distinguishing classic versus anaplastic ependymomas, and the subsequent inter-observer variability between neuropathologists [37, 38]. The incorporation of additional molecular variables to histopathologic criteria will be important considerations for future clinical protocols.

### Molecular Characterization of Ependymal Tumors

Researchers have previously demonstrated that the cell of origin and signaling pathways driving tumorigenesis differed among tumors arising from different neuroanatomical locations, providing a biologic basis for variations in survival outcomes. For example, gene expression profiling and copy

number analysis demonstrated upregulation of EPHB-EPHRIN and NOTCH signaling as well as deletion of *Ink4a/ARF* in subsets of supratentorial tumors [39–41]. Very recently, large collaborative genome-scale research efforts uncovered not only landmark findings in ependymoma, revealing molecularly distinct subtypes, but also a surprisingly quiet genome with absence of recurrent gene alterations and a low mutation rate per tumor [42•, 43•]. Molecular profiling of 500 cases suggested that ependymal tumors represent a heterogeneous collection of at least nine distinct entities that correlate well with certain clinical features including neuroanatomical location, patient age, and outcome [44•]. Utilizing DNA methylation profiling, researchers identified three subgroups in each of the three anatomic locations, labeled supratentorial (ST-subependymoma, ST-EPN-YAP1, ST-EPN-RELA), posterior fossa (PF-subependymoma, PF-EPN-A, PF-EPN-B), and spine (SP-subependymoma, SP-myxopapillary, SP-EPN) [44•]. Three subtypes, ST-EPN-YAP1, ST-EPN-RELA, and PF-EPN-A, were seen most frequently in the pediatric population, and the biology of each subtype was consistent with the current understanding of genomic, transcriptomic, and histopathologic characteristics of ependymomas. While these findings have uncovered significant insight into the biology of these tumors, its impact still needs to be strategically translated into patient care. Strategies under consideration include the incorporation of molecular variables into histologic diagnosis, risk-adjusted therapy for tumor subtypes, and testing novel therapeutic agents.

### Supratentorial Ependymoma Subtypes

The supratentorial subtypes, ST-EPN-RELA and ST-EPN-YAP1, are characterized by recurrent gene fusions initially discovered by whole genome and RNA sequencing techniques [43•, 44•]. Recurrent gene fusions between *C11orf95* and *RELA* were identified in 70 % of supratentorial ependymomas, distinguishing the ST-EPN-RELA subtype. The resultant *RELA*-fusion protein upregulates NF- $\kappa$ B signaling, a central mediator of inflammation, and was demonstrated to be sufficient to drive tumorigenesis in a mouse model [43•]. The *RELA*-fusion protein subsequently provides an enticing and novel focus to potentially target therapeutically but requires further study. Interestingly, ST-EPN-RELA tumors exhibit extensive chromosome aberrations consistent with chromothripsis, in contrast to the relatively quiet genome of ST-EPN-YAP1 subtypes. While the prognostic utility of molecular classification requires further investigation, the majority of patients in the ST-EPN-RELA cohort were preschool/school-age children and exhibited an inferior survival outcome. ST-EPN-YAP1 ependymoma were less frequently identified but were uniquely marked by YAP1 fusion proteins. Children with the ST-EPN-YAP1 subtype tended to be very

young (62 % less than 4 years in the referenced study) and appeared to have a favorable survival outcome but require further follow-up [44•]. Functional studies of YAP1 fusion products are also needed to further uncover its role in tumorigenesis and potential as a therapeutic target.

### Posterior Fossa Ependymoma Subtypes

Two clinical and molecular subtypes of posterior fossa ependymoma (among grade II and III tumors) have been consistently delineated by transcriptional, genomic, and epigenetic analysis, recently labeled PF-EPN-A and PF-EPN-B [41, 42•, 45, 46]. As mentioned above, PF-EPN-A tumors almost exclusively affected younger pediatric patients (median age of 2.5 years) and were associated with an inferior prognosis (5-year PFS 47 % and OS 69 %). These tumors demonstrated a greater propensity to recur and a higher likelihood to extend laterally towards the cerebellopontine angle [42•, 45]. Notably, whole genome sequencing of this subtype did not reveal recurrent gene alterations, but epigenetic analysis by the same investigators identified increased DNA methylation (and subsequent transcriptional silencing) in a set of genes involved in cell differentiation, which they termed the CpG island methylator phenotype (CIMP). These same genes are similarly silenced by the Polycomb repressive complex 2 (PRC2) in embryonic stem cells, which researchers have proposed as a biologic mechanism for maintaining PF-EPN-A tumors in a primitive state [42•]. Additionally, a member of the PRC2 complex, the histone modifier enhancer of zeste homolog 2 (*EZH2*), has generated interest as a potential therapeutic target and also as a prognostic marker detectable by immunohistochemistry [47, 48]. Although the PF-EPN-A genome is known to be relatively stable, chromosome 1q gain was reported in 25 % of tumors in this subgroup, correlating with previous studies that identified 1q gain as a negative prognostic factor [41, 42•, 44•, 49–51].

While PF-EPN-B ependymomas were more commonly seen in adult patients, approximately 20 % of cases occur in older children [44•]. In contrast to PF-EPN-A tumors, the PF-EPN-B subgroup was associated with superior outcomes (5-year PFS 73 % and OS 100 %) [42•, 44•] and demonstrated greater copy number variation including 6q and 22q loss and 9q, 15q, and 18q gain, markers which have been previously associated with an improved prognosis [41, 45, 51, 52].

### Future Directions

The improved biologic understanding of pediatric ependymoma has generated significant clinical and translational research needs to refine conventional management strategies and develop novel approaches. For example, questions

remain as to whether a chemotherapy-responsive subset can be selected to receive adjuvant chemotherapy and improve surgical outcome, or alternatively, if lower-risk patients can be rationally selected to receive reduced or no radiation therapy [48]. The investigation of biologic prognostic factors in a prospective fashion, such as in a secondary objective of the current COG protocol ACNS 0831, may provide important data correlating molecular and clinical variables.

### Clinical Trials for Novel Therapeutic Targets

Targeted agents have been actively investigated by several collaborative early phase clinical trials, but challenges remain. Based on earlier data identifying ERBB2 and ERBB4 co-expression in a majority of ependymoma [53], the Pediatric Brain Tumor Consortium (PBTC) and the Collaborative Ependymoma Research Network (CERN) each investigated lapatinib, an ERBB1 and ERBB2 small molecule inhibitor, in separate phase II studies, but did not demonstrate tumor response [54–56] nor sufficient intratumoral drug levels to elicit target inhibition [56]. A recent phase II study of sunitinib, a promiscuous tyrosine kinase inhibitor, was conducted by the COG (ACNS 1021), with results yet to be published. Immunotherapeutic approaches are yet to be regularly investigated in pediatric ependymoma, but distinct perturbations in cellular and signaling pathways associated with immunologic function have been reported among ependymoma subtypes [57, 58]. A recent study identified IL6/STAT3 pathway activation in a posterior fossa subtype (equivalent to PF-EPN-A) that contributed to tumor survival and may emerge as a target of interest [58]. Molecular characterization of ependymoma has uncovered a number of potential targets but will require the development of effective targeted agents, pre-clinical studies, and appropriate selection of suitable agents. Biologically faithful pre-clinical model systems of ependymoma are lacking, and continued support for the generation of additional cell lines and animal models are necessary [59, 60].

### Conclusions

The standard of care for pediatric ependymoma has long consisted of surgical resection to the greatest extent acceptable followed by adjuvant local irradiation. Complete macroscopic resection has remained the only consistent clinical intervention known to improve survival. Use of chemotherapy has thus far been unable to predictably affect outcome, possibly due to the molecularly heterogeneous signatures of histologically indistinguishable subtypes of ependymal tumors in children and is an important clinical question currently investigated by a prospective, randomized trial. The incorporation of molecular characteristics of ependymoma subtypes has the

potential to refine the prognostic value of histologic grading and also provide a biologic rationale for the consideration of novel therapeutic agents. While management implications of these data are not yet known, bridging recent breakthroughs in ependymoma tumor biology with known clinical variables represents the most significant opportunity to challenge the therapeutic paradigm of this cancer and should be a high priority for future clinical research.

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### Compliance with Ethics Guidelines

**Conflict of Interest** Frank Y. Lin and Murali Chintagumpala declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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