REVIEW

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Multidisciplinary management of pediatric intracranial ependymoma

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Practice Points

- The current WHO classification of ependymoma includes grade I (myxopapillary and subependymoma subtypes), II (ependymoma) and III (anaplastic ependymoma) tumors.
- Treatment with surgery is the cornerstone of ependymoma management, and gross total resection is consistently associated with improved outcomes.
- A work-up including complete neuraxis imaging and cerebrospinal fluid cytology should be completed in all patients with grade II and III tumors because up to 20% of patients present with disseminated disease.
- Based on retrospective data, postoperative localized radiation therapy is used routinely in the treatment of grade II and III tumors without evidence of dissemination.
- Patients with disseminated disease require craniospinal radiation therapy.
- Limited data on the use of stereotactic radiosurgery indicate this modality may be better utilized as upfront therapy rather than as a treatment for recurrent disease.
- Recurrent ependymoma has a poor prognosis and is a therapeutic challenge. The limited data indicate that re-operation followed by fractionated re-irradiation may give the best outcome.
- Chemotherapy has been used in different settings, but the role of this modality remains undefined. It is currently being investigated in a national clinical trial conducted by the Children's Oncology Group.

SUMMARY Pediatric intracranial ependymoma is a rare disease representing approximately 7% of brain tumors in children aged 15 years or younger. Due to the relative rarity of these tumors, a clear standard therapy has been difficult to establish. The mainstay of treatment is surgical resection and the majority of data demonstrate improved outcome with gross total resection. The standard of care also includes postoperative radiation therapy for most patients with grade II and III tumors. Chemotherapy has been used in many capacities in this disease; however, its optimal role is yet to be defined. Current controversies such as treatment with surgery alone in completely resected tumors, use of chemotherapy for subtotally resected tumors and use of adjuvant postradiation chemotherapy are incorporated into the design of the current Children's Oncology Group clinical trial.

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Ependymomas are relatively uncommon neoplasms representing approximately 2% of CNS tumors. However, they occur at a proportionally higher rate in younger patients. In persons younger than 15 years of age, ependymomas represent approximately 7% of CNS tumors [1]. These tumors have been recognized as distinct from other types of gliomas since the time of Bailey [2], but their relative scarcity has resulted in controversy with regard to their optimal treatment. This article will review outcomes for pediatric intracranial ependymoma and current multidisciplinary treatment recommendations.

Histology, classification & radiographic appearance

The current WHO classification of ependymomas is presented in [Table 1](#) [3]. Myxopapillary tumors occur almost exclusively in the cauda equina region of the spinal canal. Their management is primarily surgical; however, recent studies have demonstrated improved outcome with the addition of postoperative radiation therapy (RT) [4,5]. Subependymoma is typically an intracranial tumor associated with the ventricles and gross total resection (GTR) and is generally curative. The remainder of this article will focus on the management of grade II and III intracranial ependymomas. Note that no ependymomas are classified as grade IV.

The histologic features of ependymoma include the perivascular pseudorosette and the true ependymal rosette ([Figure 1](#)). The latter can be thought of as neoplastic attempts at recapitulating normal ependymal structures. Grade III tumors must include at least two of the following features: endothelial proliferation; a mitotic rate >10 per high-power field; palisading necrosis; or hypercellularity with nuclear pleomorphism and/or hyperchromasia [6]. However, the influence of grade on prognosis is inconsistent in the literature. Some reports describe worse outcomes with grade III tumors [7–9], while others do not [10–16]. This inconsistent effect of tumor

grade on outcome is probably due, in part, to discordant grading between institutions and individuals. This is illustrated by a recent retrospective study conducted by members of the Children’s Oncology Group (COG). In this review, 96 cases of ependymoma treated on prior Pediatric Oncology Group (POG) protocols had slides reviewed by three expert neuropathologists to examine the prognostic value of the modern WHO grading system [6]. There was not agreement in grading in 26 (27%) of the cases. Once a consensus diagnosis was achieved, the influence of grade on outcome was statistically significant for progression-free survival (PFS), but not overall survival (OS). This discordance among experts and the lack of OS differences makes treatment decisions based on grade problematic in ependymomas. Unlike the differences in management of grade II and III astrocytomas, which are quite significant, the management of both grade II and III ependymomas is similar.

The radiographic appearance of intracranial ependymoma is illustrated in [Figure 2](#). No consistent differences in imaging characteristics distinguish grade II from III tumors, which are often complex masses displaying brisk gadolinium enhancement. While the classic presentation of these tumors is that of a fourth ventricular mass, approximately a third of cases occur in the supratentorial brain where they are more likely to have a cystic component. Note the inferior extension of tumor through the foramen magnum in [Figure 2A](#). Attention must be paid to this region in both surgical resection and RT planning.

General management

The optimal management of all pediatric brain tumors requires a multidisciplinary approach. Close communication between surgeons, radiologists, radiation oncologists and pediatric oncologists is critical in the therapeutic decision-making process. Pediatric sedation specialists or anesthesiologists are routinely involved for younger patients to facilitate delivery of RT. Finally, involvement of endocrinologists, neuropsychologists, school liaisons and social workers are invaluable during the many years of follow-up care necessary for any child after treatment of a brain tumor.

Surgical management & work-up

The management of pediatric intracranial ependymoma begins with maximal safe surgical resection. The majority of series have demonstrated

Table 1. Classification of ependymoma.			
Histology	WHO grade	Relative location	
		Brain	Spine
Myxopapillary ependymoma	I	Very rare	Very common
Subependymoma	I	Common	Rare
Ependymoma: cellular, papillary, clear cell and tanycytic	II	Common	Uncommon
Anaplastic ependymoma	III	Common	Uncommon

Figure 1. Histological features of an ependymoma. (A) Perivascular pseudorosettes and **(B)** true ependymal rosettes.

Images courtesy of Arie Perry, University of California San Francisco, CA, USA.

improved outcome following GTR of grade II and III intracranial ependymomas [6,8,10,13–15,17–21]. The extent of resection should be determined by discussion with the neurosurgeon and immediate postoperative imaging. Brain MRI should be carried out within 48 h of surgery, which is before postoperative effects begin to enhance with gadolinium. Postoperative imaging after this window of time will make distinguishing between postoperative changes and residual enhancing tumor nearly impossible. Representative pre- and post-operative changes observed on MRI are illustrated in [Figure 3](#). Following maximal safe resection, the patient must be carefully

evaluated for disseminated disease, since both grade II and III tumors have a small but well-recognized tendency to spread throughout the craniospinal axis. The published rates of disseminated disease at diagnosis range from 0 to 21%, and appear to be independent of tumor grade and location [8,13,14,17,18,22]. The presence of disseminated disease greatly impacts radiotherapeutic recommendations. Therefore, it is critical to determine the extent of disease at diagnosis. While postoperative imaging of the resection site should be carried out within 48 h, imaging of the spine should be carried out either preoperatively or delayed approximately 10–14 days after

Figure 2. Radiographic appearance of an ependymoma. (A) Fourth ventricular mass with extensive tumor extension through the foramen magnum. **(B)** Supratentorial tumors are more likely to have a cystic component.

Figure 3. Pre- and post-operative MRI of an ependymoma patient. (A) Preoperative MRI of an ependymoma. **(B)** Immediate postoperative images demonstrate gross total resection. **(C)** Imaging at 3 weeks, however, demonstrates how the resection bed will briskly enhance.

resection to avoid debris and blood products in the immediate postoperative setting from being misinterpreted as drop metastases. Unless the spinal MRI demonstrates unambiguous drop metastases, a lumbar puncture for cerebrospinal fluid cytology should be performed in all patients to rule out microscopic dissemination. Ideally this would be carried out following the MRI of the spine, at least 10–14 days after resection. The presence of disseminated disease not only impacts prognosis, but also subsequent treatment recommendations. Patients with localized disease are candidates for adjuvant focal RT to the resection cavity, while those with disseminated disease, whether gross seeding observed on MRI or positive cytology, or both, require craniospinal RT.

Surgical resection is usually followed by postoperative RT. Exceptions include very young children who are often treated with systemic chemotherapy in an attempt to delay RT and the associated adverse neurocognitive effects on the developing brain. No randomized data exist comparing surgery only with surgery and postoperative RT. Some retrospective comparisons in adults demonstrate no clear benefit to postoperative RT [23]. The majority of comparisons in children, however, demonstrate improved PFS [18,24] and OS [13,20,22,25] after planned postoperative RT. These data have established postoperative RT as the standard of care for most patients.

There are several reports in the literature describing small cohorts treated with surgery alone [26–29]. These studies demonstrate a PFS

ranging from 50 to 71%. This raises the possibility of omitting RT in ependymoma following GTR. However, the small number of patients and limited follow-up in these studies means firm conclusions about the efficacy of surgery alone in this disease are difficult to make. This approach is best limited to prospective clinical trials. The COG has incorporated a surgery-only arm for completely resected grade II supratentorial tumors in the recently closed ACNS 0121 and current ACNS 0831 trials.

External-beam RT

Following maximal safe surgical resection the standard of care remains postoperative RT for most patients with grade II and III ependymomas. As stated above, in the absence of prospective randomized trials, the existing retrospective data demonstrate improved outcome with postoperative RT compared with surgery alone.

The radiotherapeutic management of intracranial ependymoma has evolved over the past few decades. While postoperative RT has been the standard of care in these tumors, controversy has historically centered on the volume of RT required. In the past, many of these patients were treated prophylactically with large fields, including craniospinal RT [12,30–32]. However, numerous modern reports have demonstrated the efficacy of local-field RT in the management of localized ependymoma [8,9,13,15,16,21,22,33,34]. After treatment with local RT fields, the rate of isolated out-of-field recurrence ranges from 0 to 12.5% in the literature [13,15,16,21,22,33,35]. Given the well-recognized neurocognitive, endocrine

and musculoskeletal complications associated with the use of craniospinal RT in children, the low out-of-field relapse rates do not warrant its routine prophylactic use. Therefore, current recommendations for RT in patients without disseminated disease are for conformal RT to the residual tumor and/or resection cavity with a 1–2 cm margin. Patients with documented disseminated disease either by spinal MRI or cerebrospinal fluid cytology have a poor prognosis with a PFS of approximately 30% [36]. These patients require craniospinal RT followed by a boost to the primary tumor or resection cavity.

There are limited and conflicting RT dose response data for ependymoma; some authors have demonstrated a dose response [12,15,31,37], while others have not [22,33]. Results of hyperfractionated RT have been reported from Europe. Regimens using 1.0 Gy twice-daily to a total dose of 60–66 Gy [38] and 1.1 Gy twice-daily to a total dose of 70.4 Gy [39] have been used. Since outcomes with this approach are similar to historic results with conventional fractionation, the use of hyperfractionated RT has not been widely adopted. The most commonly recommended RT dose is 54.0–59.4 Gy to conformal fields. Recent COG protocols use 59.4 Gy for children older than 18 months and 54.0 Gy for younger children. In the setting of disseminated disease, an initial dose of 36 Gy to the craniospinal axis should be followed by a conformal boost to residual tumor and/or resection cavity to 54.0–59.4 Gy.

Outcome data with surgery and postoperative RT have improved over the years. Historically, PFS rates of 46–70% and OS rates of 57–88% have been reported [8,13,14,17,18]. The most encouraging outcome data to date in the management of pediatric ependymomas have been reported from St Jude Children's Research Hospital (TN, USA) [21]. Their prospective trial of 153 children utilized conformal RT consisting of tumor and/or tumor bed with a 1 cm clinical planning volume expansion and a prescribed dose of 59.4 Gy (54 Gy in children younger than 18 months). Children as young as 12 months of age were included. With a median follow-up of 5.3 years, local tumor control was 87%, with an event-free survival of 70% and OS of 81%. Brainstem necrosis occurred in two patients (1.6%) and was fatal in one patient. Despite the high dose of RT used in this study, the neurocognitive effects were acceptable with

only a modest decline in reading function noted at the 60-month median follow-up [40]. These data demonstrate that high doses of RT can be used safely, even in young children, provided conformal techniques are used and the target volume is limited to the resection cavity with a small margin. These encouraging results are from a single institution. Whether or not these outcomes can be duplicated in the broader national approach and cooperative group setting remains to be demonstrated.

The current standard RT technique is either 3D conformal RT, or intensity-modulated RT with treatment volumes including the tumor cavity and/or residual disease with a clinical planning volume expansion of 1–2 cm. An example of standard treatment volumes is presented in **Figure 4**. Even smaller volumes utilizing a clinical planning volume expansion of 0.5 cm are being investigated in the current COG prospective trial ACNS 0831. The lack of exit dose of a proton beam results in significant advantages for the treatment of childhood brain tumors by reducing low doses to uninvolved normal brain tissue [41]. A comparison of a five-beam intensity-modulated RT plan and a single-beam proton plan is presented in **Figure 5**. It is hoped that with the increasing numbers of proton facilities more children will be offered this modality.

Figure 4. Treatment volumes for radiation therapy following gross total resection for grade II or III ependymoma. Yellow: resection cavity; red: clinical target volume is a 1-cm expansion; and blue: planning target volume is an additional 0.5-cm expansion.

Figure 5. Dosimetric comparison of a five-beam intensity-modulated radiation therapy plan and a single-proton beam plan. (A) A five-beam intensity-modulated radiation therapy plan and **(B)** a single proton beam plan. Note the similar conformality of the high-dose region, but there is much less low dose to the uninvolved brain with the proton plan.

Images courtesy of Beth Pierburg, Barnes-Jewish Hospital, St Louis, MO, USA.

Stereotactic radiosurgery

The use of stereotactic radiosurgery (SRS) for intracranial ependymoma is not routine. Published results with this modality are shown in **Table 2**. The PFS ranges from 22 to 80% and OS ranges from 23 to 80% [42–49]. Symptomatic complications occur in up to 26% of patients and include radionecrosis and cranial nerve palsies. These patients usually respond to treatment with corticosteroids and fatal complications are rare. The wide range of outcomes with SRS probably reflects the limited numbers and heterogeneity of patients and limited follow-up in these reports. In addition, most patients were treated with SRS as a salvage therapy for recurrent disease. There is a trend in these data for improved outcome in patients treated with planned SRS as part of their initial management compared with those treated to salvage recurrent disease. Mansur *et al.* report a PFS of 100% in four patients treated with SRS as a component of the initial management, but PFS of only 20% for five patients treated to salvage an external-beam failure [46]. Similar improved outcomes for those treated with upfront SRS have been reported by others [42,47]. While these data are limited, they raise the interesting possibility of using SRS as

a component of upfront therapy for patients with unresectable disease. Such an approach could utilize SRS as a highly conformal boost to residual disease following external-beam RT.

Chemotherapy

The role of systemic chemotherapy in the management of pediatric intracranial ependymoma is not fully defined. It has been used together with postoperative RT, either as induction therapy or adjuvant therapy, as an upfront treatment in very young children in an attempt to delay or omit RT, and as a high-dose chemotherapy with stem cell rescue.

The Children's Cancer Group (CCG) protocol 942 randomized ependymoma patients to either craniospinal RT alone or craniospinal RT with weekly vincristine and eight cycles of adjuvant vincristine, CCNU and prednisone. After the 10-year follow-up, the OS for all patients was 39%. No differences were observed between the two arms [50]. The CCG protocol 921 randomized ependymoma patients to craniospinal RT plus the above chemotherapy or to craniospinal RT and the eight-in-one chemotherapy regimen [14]. With a median follow-up of 6.5 years, no differences between these two combined modality

treatment arms were observed. These early randomized studies for chemotherapy in ependymoma were conducted before the modern imaging era, used outdated RT volumes and included very few patients, so definitive conclusions as to the efficacy of these chemotherapy approaches cannot be made. More recently, CCG-9942 investigated the use of induction chemotherapy with vincristine, etoposide, cisplatin and cyclophosphamide for four cycles in patients older than 3 years with subtotally resected intracranial ependymoma [51]. They report an encouraging overall response rate of 57%. In addition, those patients with near-total resection (>90% resection) had outcomes equivalent to those patients with GTR treated with RT alone. This indicates that the induction chemotherapy may make up for a lack of GTR in those patients with minimal postoperative residual tumor. The use of chemotherapy prior to external-beam RT in patients with subtotal resection has been incorporated into recent COG trials ACNS 0121 and 0831.

Initial chemotherapy used as definitive postoperative treatment in an attempt to delay or avoid RT has been investigated by multiple groups in Europe and the USA [10,11,19,35,52,53]. These results are summarized in **Table 3**. PFS rates range from 22 to 42%, and OS rates range from 37 to 63%. Compared with data using planned postoperative RT, these results using chemotherapy as initial definitive treatment are inferior. This is especially true with regard to PFS, which is poor in the majority of these studies. It is true that these patients were very young and part of the poor outcome may be related to age, which has been reported to be a negative

prognostic factor in many studies. Proponents of this approach also note that OS tends to be improved compared with PFS, indicating that deferred RT is an effective salvage strategy. While the treatment of very young children and babies must be individualized, given the suboptimal outcomes with initial chemotherapy and deferred RT, this approach remains investigational and is best applied in clinical trials.

Currently, there are limited data on high-dose chemotherapy and stem cell rescue for children with ependymomas. The largest study to date involved 29 patients aged 3–10 years treated with induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell rescue. The 5-year outcome was disappointing, with a treatment-related mortality of 10%, an event-free survival of 12% and an OS of 38% [54]. By contrast, after a 3.75-year median follow-up, Sung *et al.* reported an event-free survival of 80% and OS of 100% in five patients younger than 3 years treated with tandem high-dose chemotherapy and autologous stem cell transplant [55].

Despite multiple studies investigating its use in ependymomas, the role of chemotherapy remains undefined and is best limited to prospective clinical trials. The COG has incorporated select use of chemotherapy in its most recent multi-institutional trials. In the recently closed ACNS 0121, carboplatin, vincristine, cyclophosphamide and etoposide were used following subtotal resection to help facilitate respectability on second-look surgery prior to planned conformal RT to 59.4 Gy. The current COG study, ACNS 0831, utilizes a similar approach, but also

Table 2. Results with stereotactic radiosurgery for intracranial ependymoma.

Study (year)	Patients (n)	Age range (years)	Grade III (%)	Median dose (Gy)	Median follow-up (months)	PFS (%)	OS (%)	Symptomatic complications (%)	Ref.
Hodgson <i>et al.</i> (2001)	25 salvage 3 initial	1.4–21.4	–	12.5	24	22	–	26	[42]
Jawahar <i>et al.</i> (1999)	22 salvage	1.5–65	100	16.1	21	32	50	4.5	[43]
Stafford <i>et al.</i> (2000)	12 salvage	5–56	–	18	22	68	–	17	[44]
Aggarwal <i>et al.</i> (1997)	4 salvage [†] 1 initial	1.3–12.4	20	10	24	80	80	20	[45]
Mansur <i>et al.</i> (2004)	5 salvage 4 initial	3–72	22	16	28	56	71	22	[46]
Lo <i>et al.</i> (2006)	5 salvage 3 initial	1.3–34.9	12.5	14	30	50	–	25	[47]
Kano <i>et al.</i> (2010)	21 salvage	2.9–17.2	43	15	28	42	23	4	[48]
Stauder <i>et al.</i> (2012)	26 salvage	1.4–69.6	34	18	37	66	69	8	[49]

[†]Four patients progressed on chemotherapy and were treated with planned external-beam and stereotactic radiosurgery boost.
OS: Overall survival; PFS: Progression-free survival.

Table 3. Studies utilizing systemic chemotherapy in very young ependymoma patients in order to delay or omit radiation therapy.

Study (year)	Patients (n)	Age (years)	GTR (%)	Grade III (%)	Agents	Response rate (%)	PFS (%)	OS (%)	Role of RT	Ref.
Massimino <i>et al.</i> (2011)	41	<3	54	39	VCR/HD MTX Cyclophosphamide Cisplatin/etoposide	–	27	37	Planned if residual disease after chemotherapy or to salvage progressive disease	[52]
Grill <i>et al.</i> (2001)	73	<5	60	88	Procarbazine carboplatin Cisplatin/etoposide VCR/cyclophosphamide	0	22	59	None planned. To salvage progressive disease only	[19]
Grundy <i>et al.</i> (2007)	80	<3	50	33	Carboplatin/VCR MTX/cyclophosphamide/ cisplatin	–	42	63	None planned. To salvage progressive disease only	[11]
Timmermann <i>et al.</i> (2005)	34	<3	53	100	Procarbazine/MTX VCR/ ifosfamide etoposide/ cisplatin cytarabine/ cyclophosphamide IV MTX/carboplatin	–	27	56	Planned at age 3 years or to salvage progressive disease	[35]
Duffner <i>et al.</i> (1998)	48	<3	40	29	VCR/cyclophosphamide Cisplatin/etoposide	–	27	41	Planned after 1 year if >2 years old, and after 2 years if <2 years old, or as salvage for progression	[10]
Geyer <i>et al.</i> (2005)	74	<3	81 (>90 resected)	–	VCR/etoposide Cisplatin/cyclophosphamide Carboplatin/ifosfamide	44	32	59	None planned if no residual or metastatic disease. Only to salvage progressive disease	[53]

GTR: Gross total resection; HD: High dose; IV: Intraventricular; MTX: Methotrexate; OS: Overall survival; PFS: Progression-free survival; RT: Radiation therapy; VCR: Vincristine.

includes a randomization to maintenance chemotherapy or no further therapy following conformal RT. Results of these two trials are eagerly awaited and should help to better establish the role of chemotherapy in these patients.

Treatment of recurrent disease

Recurrent ependymoma poses difficult management challenges and no clear standard of care has been established. Treatment, therefore, must be individualized. As with initial management, the mainstay of treatment in the recurrent setting is surgery. This provides histopathological confirmation of recurrence and is therapeutic, especially if the recurrence is suspected to be local only. Recent retrospective studies demonstrate the importance of surgical extent on survival following relapse of ependymoma [56–58], and show a subset of relapsed patients can be cured with surgical salvage. Following maximal safe surgical resection, restaging of the patient is important and should include full neuraxis imaging and lumbar puncture for cerebrospinal fluid cytology. The pattern of disease recurrence will help guide decisions regarding possible salvage therapies.

Isolated local recurrences can be treated with additional local therapies but disseminated disease requires a more systemic approach.

Re-irradiation has been utilized at several centers in an attempt to improve the outcome of relapsed patients following re-operation. The radiation approach in these patients has included SRS [42–44,46–49], hypofractionated RT [59] and repeat fractionated RT [60,61]. With a relatively short follow-up and low patient numbers, results with re-irradiation are encouraging. The best results to date involve repeat fractionated RT, with PFS rates ranging from 56 to 100%. The fully fractionated RT regimens appear to be associated with a lower risk of radiation necrosis than either the single fraction (SRS) or hypofractionated regimens.

The role of systemic chemotherapy in relapsed ependymoma is not well established. Agents such as temozolomide [62] and bevacizumab with irinotecan [63] have not demonstrated efficacy in pediatric recurrent ependymoma. Newer approaches with low-dose or metronomic chemotherapy have encouraging preliminary results and deserve additional investigation [64].

Conclusion & future perspective

Many questions remain regarding the optimal treatment of pediatric intracranial ependymoma. While some patients are cured after surgery alone, many will relapse despite GTR and post-operative RT. There exists a need to better stratify risk of relapse in this disease which would help in tailoring more aggressive therapies to those at higher risk. Existing clinicopathologic factors do not provide adequate stratification of patients' risk. As we have seen, even tumor grade does not reliably predict survival [6].

Newer attempts to stratify patients have centered on molecular markers. Telomere stability has been hypothesized to lead to more aggressive and resistant pediatric tumors. hTERT is the catalytic subunit of the telomerase complex. Its expression has been strongly correlated with poor PFS and OS in pediatric ependymoma [65]. In another report utilizing ependymoma tissue microarrays, Korshunov *et al.* described three distinct cytogenetic subgroups with highly variable outcomes [66]. In this study, gain of 1q and deletion of *CDKN2A* were associated with very poor PFS and OS, while gain of chromosome 9, 15q and 18, and loss of chromosome 6 was correlated with excellent PFS and OS. The poor prognosis associated with gain of 1q has also been demonstrated in children with posterior fossa tumors by other investigators [67].

Several other reports have also identified possible important molecular markers. Nestin is a biomarker of neural stem cells and its expression

in paraffin-fixed tissue detected by immunohistochemistry has been shown to predict worse PFS and OS in a large cohort of adult and pediatric intracranial ependymomas [68]. Investigators from the Collaborative Ependymoma Research Network (CERN) have correlated PFS with specific genetic signatures in 56 posterior fossa ependymomas in both adults and children [69]. Yet another report utilizing transcriptional profiling identifies two molecularly distinct subgroups of posterior fossa ependymoma in cohorts containing both adult and pediatric patients. This molecular distinction predicts outcome for both PFS, and OS [70].

These various examples of molecular staging demonstrate the heterogeneity of intracranial ependymoma. Which of these are most clinically useful remains to be determined. Utilization of these molecular markers should be a priority for future clinical trials and may ultimately allow better patient stratification and selection of therapies.

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