TITLE:

Current and Emerging Methods of Management of Ependymoma

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## Abstract

*Purpose of review:* This review discusses the evidence base behind current and emerging strategies of management of intracranial and spinal ependymoma in children, with a particular focus on aspects of surgical techniques, challenges and complications.

*Recent findings:* The cornerstone of management remains maximal safe resective surgery, which has repeatedly been shown to correlate with improved survival. This is followed by focal conformal radiotherapy, although good results using proton beam therapy, with the potential for diminished side effects, are emerging. The role of chemotherapy remains largely unproven for paediatric ependymoma. Despite optimal management strategies, many children with ependymoma suffer from tumour recurrence.

*Summary:* The standard of care for paediatric ependymoma comprises surgery and radiotherapy. Results of ongoing clinical trials will help shape its management in order to leverage our increasingly sophisticated understanding of the genetic drivers behind these tumours into survival benefit for this challenging group of patients.


## Introduction

Ependymoma is a central nervous system (CNS) tumour arising from the ependymal cells lining the spinal canal and the ventricles of the brain. They can arise anywhere in the neuraxis, and in any age group, although they are more common in the paediatric population – constituting 6-10% of all paediatric CNS tumours – and more common in males(1,2). In children, 70% of ependymomas arise within the posterior fossa, 25% in the supratentorial compartment, and the remainder in the spine(3). The cornerstone of management of paediatric ependymoma is maximal safe surgical resection, followed by radiotherapy. This article reviews the evidence behind current and emerging strategies of management of ependymoma in children.

## Pathology

### *Histology*

Ependymomas are neoplasms of glial origin, which are described histologically according to the WHO grading system, reflecting their degree of mitotic activity. Grade I include the entities subependymoma and myxopapillary ependymoma (MPE), both seen more commonly in adults than children, in the ventricles of the brain and conus medullaris respectively. Grade II, the most commonly encountered histology in children, corresponds to 'classic' ependymoma. This is characterised by perivascular pseudorosettes (tumour cells radially encircling blood vessels) and, in around one quarter of cases, ependymal rosettes (neoplastic ependymal cells arranged around a central lumen). Papillary, clear cell and tanycytic histological variants also exist but these lack any clear clinicopathological or prognostic relevance. Grade III corresponds to anaplastic ependymoma, a malignant tumour characterised by a high nuclear-to-cytoplasmic ratio and a high mitotic count. However, distinguishing

between Grades II and III on histological grounds alone is challenging(4,5) due to intratumoural heterogeneity, and the utility of tumour grade in predicting prognosis remains unclear.

### *Molecular profiling*

Advances in immunohistochemical, transcriptome and methylome profiling have, in recent years, redefined the biological landscape of ependymoma. A seminal study of a large international cohort of over 500 ependymomas stratified nine distinct epigenetic subtypes of ependymal neoplasms(2). Posterior fossa (PF), supratentorial (ST) and spinal (SP) ependymomas were each subdivided into three subtypes, with demographic, clinical, genetic and prognostic differences.

PF ependymoma comprise subependymoma (PF-EPN-SE), a WHO Grade I neoplasm which arises in adults more often than in children; and the PF-EPN-A and PF-EPN-B subtypes, distinguished on transcriptional profiling in two large independent cohorts, subsequently confirmed in a third non-overlapping cohort(6). PF-EPN-A are found to occur more commonly in young children, are often located laterally within the posterior fossa, and have a high recurrence rate, although an underlying genetic driver has yet to be definitively identified(3). PF-EPN-A have a poor prognosis, with 10-year PFS of 37.1%, although this has shown an upward trend over time(7). In contrast to this, a multicentre retrospective analysis demonstrated that children with PF-EPN-B subgroup treated with GTR have an excellent 10-year OS of 85%(8).

ST ependymomas include subependymoma (ST-EPN-SE), and two distinct subtypes with recognised genetic drivers on Chromosome 11. The ST-EPN-RELA sub-group comprises around 70% of ST-EPN, and are characterised by fusion of the obscure gene *C11orf95* with *RELA*. The resultant protein activates NF-κB signalling involved in immune regulation; this pathway may show potential for therapeutic intervention. ST-EPN-YAP1 tumours have a better prognosis, and are caused by a recurrent fusion involving the oncogene YAP1.

SP ependymoma are more common in adults, and include subependymoma (SP-EPN-SE), myxopapillary ependymoma (SP-EPN-MPE) and SP-EPN, which correspond to histologically Grade II/III ependymoma. SP-EPN subgroup has a known genetic association with mutations in the NF2 gene, either sporadically or as part of Neurofibromatosis Type 2 syndrome, the recognition of which predates the current subgrouping paradigm(9).

Survival analysis of 388 patients within this large international cohort found better correlations within these nine subgroups than with WHO histopathological grading. Multivariate analysis of the entire cohort showed that only extent of resection (EoR) and chromosome 1q gain, in addition to molecular subtyping, were independent prognostic markers. Two subgroups with the poorest prognosis, PF-EPN-A and ST-EPN-RELA, comprised 65% of this cohort and accounted for most of the mortality.

The 2016 update of the WHO Classification of CNS tumours(10) partially reflects this major advance in ependymoma diagnostics by including ST-EPN-RELA as a clinicopathological entity, in addition to the aforementioned subependymoma, MPE, classic and anaplastic ependymoma. Furthermore, a recent consensus statement proposes that "outside of clinical trials, treatment decisions should not be based on grading (II or III)" but instead on the molecular profile of the tumour(11).

## Clinical presentation

The clinical features of ependymoma depend on site of the tumour. Children with posterior fossa ependymoma present with symptoms of raised intracranial pressure (ICP) due to obstructive hydrocephalus from tumour compression of CSF circulating pathways – headache, vomiting, and visual disturbance. Ataxia, hemiparesis and cranial neuropathies can be caused by involvement of cerebellar or brainstem structures. Supratentorial ependymoma often cause seizures, focal weakness, headache, and signs of raised ICP. In infants, intracranial tumours may present non-specifically with vomiting, failure to thrive, developmental delay and insidious macrocephaly(12). Spinal ependymoma can present with back pain, sphincter or focal sensorimotor disturbance.

## Management of newly diagnosed paediatric intracranial ependymoma

Resective surgery plays a critical role in the management of children with ependymoma. Gross total resection (GTR) has repeatedly been shown to be the most important prognostic factor in paediatric ependymoma(13–21). A post-operative MRI scan at no more than 72h after surgery is indicated to determine EoR. A lumbar puncture for cerebrospinal fluid (CSF) cytology, performed at least 14 days post-operatively to rule out false positive results, will determine metastatic status and guide further therapy. The mainstay of management after this point is focal radiotherapy, with chemotherapy having a less clear role.

### *Diagnostic imaging*

Children suspected of harbouring an intracranial tumour often undergo computed tomography (CT) scans in the first instance. Ependymoma may show coarse calcifications on CT in around half of cases. It is recommended that all children should then undergo magnetic resonance imaging (MRI) of the entire neuraxis to rule of metastatic disease, which is seen in around 10% of ependymoma(22). This can be seen as leptomeningeal thickening on contrast-enhanced T1-weighted sequences. Typically, ependymoma appear hypointense to white matter on T1-weighted sequences, and hyperintense to white matter on T2-weighted sequences (see Figure 1). They may show cystic or necrotic components (particularly in supratentorial tumours), and typically enhance heterogeneously after contrast administration. Heterogeneously restricted diffusion patterns may be seen on diffusion-weighted imaging, particularly in anaplastic ependymoma. Ependymoma of the posterior fossa can display protrusion through the foramina of Luschka, Magendie and foramen magnum (so-called

"plastic" ependymoma); in this situation the differential diagnosis on imaging grounds is primarily of medulloblastoma.

### *Surgery*

Resective surgery is the critical first step in management of children with ependymoma. The objectives of surgical resection are to obtain tumour tissue for diagnosis, to open CSF pathways to relieve hydrocephalus, remove compression of delicate neural structures, and to achieve maximal safe resection. The presence of symptomatic hydrocephalus pre-operatively will determine the use of CSF diversion, either in the form of endoscopic or external ventriculostomy or permanent ventriculo-peritoneal shunt, prior to definitive surgical management of the tumour. In our institution, many patients with tumours of the posterior fossa (including ependymoma) can be temporised with glucocorticoid administration prior to definitive surgery within a couple of days.

In our institution surgery for midline fourth ventricular ependymoma is carried out through a suboccipital craniotomy in the prone position. The tumour is accessed through a telovelar approach, attempting to spare the cerebellar vermis as much as possible. A caudal tumour extension can almost always be resected without removing the posterior arch of C1. The cavitron aspirator is avoided as the periphery of the tumour adjacent to the cerebellar peduncles and dentate nuclei is approached. At the end of the procedure, the tumour cavity is inspected under high magnification to ensure complete resection. Sometimes tumour may be adherent or invasive at the floor of the fourth ventricle; this is carefully shaved down to the level of the rest of the floor, taking care not to disturb this eloquent surface.

It has long been recognised that EoR is strongly correlated with prognosis in ependymoma. In a historical series of 80 children treated between 1975 and 1989, 5-year PFS and OS of 51% and 75% for GTR, and 26% and 41% for subtotal resection (STR) were reported(23). In another series of 92 patients treated over a similar time period, ten-year PFS and OS of 57.2% and 69.8% were reported for GTR cases; and 11.1% and 35.2% where resection was incomplete(21). More recently, in the paradigm-defining St Jude trial of conformal radiation therapy in 153 children with ependymoma(13), 5-year PFS and OS were 81.5% and 93% respectively, in the 125 participants who underwent GTR.

### *Cerebellopontine angle ependymoma*

Despite the overwhelming evidence that GTR confers survival benefit, certain situations can make this a very challenging proposition. One such example can be seen in ependymomas of the cerebellopontine angle (CPA). These arise from ependymal cells of the foramen of Luschka, and grow extra-axially, encasing the lower cranial nerves (though rarely causing palsy at presentation), basilar and posterior inferior cerebellar arteries along the way, before occluding the fourth ventricle to cause symptoms by way of obstructive hydrocephalus. They often occur in children under three years of

age, often display anaplastic histology and are likely to have a PF-EPN-A molecular subtype(6). The surgical challenges are compounded by the large tumour size at presentation, hydrocephalus, pathological rotation of the brainstem, and the low circulating blood volume in these young children. A lateral retrosigmoid extension to the midline suboccipital craniotomy is essential to allow maximal appreciation of the stretched and distorted cranial nerves.

The largest reported series of CPA ependymoma describes 45 children in whom GTR was achieved in 43 (24). The authors report a mean age at diagnosis of 2.9 years; 15 children had undergone surgery previously, of whom five had also received radiotherapy. Median surgical time was 5 hours. Longer procedures were associated with younger children and a tendency towards more complications, reflecting surgical difficulty. Major complications occurred after 13 procedures, including cranial nerve palsy (11 patients), gastrostomy (9 patients) and tracheostomy (7 patients) placement. In all but one patient with tracheostomy, decannulation occurred within 1 year of surgery. Unilateral hearing loss occurred in almost all children with large tumours. There was no surgical mortality. Surgery was most challenging in children who had undergone previous surgery and radiotherapy or where thick scarring rendered safe tumour dissection difficult; this however was not reflected in poorer outcomes.

In those patients who underwent definitive surgery for their CPA ependymoma at the authors' institution(24), within three months of diagnosis of their tumour, PFS and OS were 53.8% and 64% respectively; this compared well with the non-CPA ependymomas in the authors' series. The importance of operative experience and volume with these difficult tumours is underlined; comparison with ten patients whose surgery was carried out before this series in the same institution showed a significant improvement in resection and complication rates in the later cohort.

*Surgical complications*

Complications arising from surgery include those common to all surgical procedures such as haematomas and infections, both of which are rare in the modern micro-neurosurgical era involving electrocautery and perioperative antibiotics. Aseptic meningitis may manifest around 5 days after surgery, typically upon glucocorticoid weaning(25). This can only be confirmed following CSF sampling to rule out bacterial infection. Post-operative alterations in flow of CSF can lead to pseudomeningocoele and CSF leak. This risk can be mitigated by careful operative site closure techniques, including dural 'hitch' stitches and suturing of the nuchal muscles to the replaced bone flap(24). Pseudomeningocoele can be treated initially by repeated lumbar puncture, and, if persistent, permanent CSF diversion.

Following resective surgery for ependymoma, a major determinant of quality of life in survivors is the burden of neurological morbidity. A series of 96 patients with posterior fossa ependymoma were closely monitored up to 120 months following maximal safe resection and radiotherapy, at 6-monthly

intervals(26). The commonest neurological deficits seen in the cohort included abducens and facial cranial nerve palsies, limb dysmetria or paresis, dysphagia and truncal ataxia. Deficits were maximal in the early post-operative period and generally did not worsen during subsequent radiotherapy.

The prevention of respiratory distress and aspiration pneumonia is an important consideration after surgery for ependymoma, particularly in the region of the CPA, where bulbar function can be compromised post-operatively. A protocolised approach to this situation has been described(27), involving a multi-disciplinary team, with fibreoptic nasendoscopy to assess vocal cord function prior to extubation, and tracheostomy placement as required.

*Intraoperative neurosurgical adjuncts*

Neuromonitoring, or the ongoing activation of the neural pathways with evaluation of their responses as resection progresses, is an established adjunct for surgery of the posterior fossa in children(28). It allows continuous assessment of the integrity of neural structures, providing real-time feedback to the operating surgeon to alter surgical strategy in order to prevent neurological injury. Evidence from the adult glioma literature attests to the benefits of neuromonitoring in reducing neurological deficit and maximising EoR (29).

Corticobulbar monitoring of the V to XII nerves, as well as motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs), covering the brainstem, including the fourth ventricle floor, cranial nerves and spinal cord, and represents an adequate level of monitoring required for infratentorial ependymoma surgery.

Intraoperative MRI (iMRI) is an increasingly widely used surgical adjunct, and several groups report extensive experience in the paediatric setting(30–33), although de-aggregated data on ependymoma are not available. The benefits of iMRI include correction for brain shift during an operation, enabling accurate navigation. This is particularly useful to identify residual tumour margins after initial resection, thus avoiding the necessity of a return to theatre for further surgery.

*Role of 'Second-look' surgery*

As complete surgical resection has such a significant value in the long-term prognosis of ependymoma, it is not surprising that the value of 'second-look' surgery has been evaluated by a number of groups(13,34–38). This is particularly relevant if tumour has been inadvertently overlooked or the resection was discontinued as a result of blood loss. Residual tumour related to brain stem, basilar artery, basal ganglia or cranial nerve infiltration, or causing haemodynamic instability or bradycardia on attempted resection, is clearly less amenable to 'second-look' surgery. In the first

report describing its value for ependymoma, five patients underwent 'second-look' surgery, one at diagnosis and four after chemotherapy; four became tumour-free without additional morbidity(34).

Indeed, multiple surgical resections can be carried out in certain patients, whilst limiting cumulative morbidity(36). This aggressive surgical strategy was seen in the seminal St. Jude study referred to above(13), in which 43% of patients underwent multiple resections. Although outcome was better for children who underwent fewer resections, this did not reach statistical significance which may be related to delays in administration of radiotherapy.

Italian investigators reviewed 38 out of 173 children who underwent second look surgery across two protocols(35). 20 of these children became tumour-free after further surgery. Only one child demonstrated new neurological deterioration. The longer-term outcomes were similar to the rest of the cohort who underwent only one operation; over a median four-year follow up, the three-year local control rate was 84.7% and 90% in the children undergoing a single surgical procedure and those having second look surgery, respectively. Three-year OS rates were 85.6 and 87.5% respectively. The authors suggest that central post-operative radiology review of ependymoma, with referral for 'second-look' surgery to larger and more experienced centres is likely to result in better outcomes. In the UK, centralised review by experienced neuroradiologists and neurosurgeons at the Ependymoma Multidisciplinary Advisory Group (39) is a key part of the management of these patients, and forms part of the ongoing SIOP Ependymoma II trial(40).

### *Radiotherapy*

The standard of care for children with intracranial ependymoma of WHO Grade II or III is to receive focal conformal radiotherapy after tumour resection, with doses up to 59.4Gy(1). This is commonly administered in 33 daily fractions of 1.8Gy each in children above 3 years of age(13), leading to excellent 7-year OS rates of 85%. In younger children, concerns regarding long-term cognitive effects of radiotherapy mandates a lower dose of 54Gy(41). Indeed, despite indications that modern radiotherapy treatment paradigms improve survival in paediatric ependymoma, this comes at the cost of worsened neurocognitive outcomes, as shown in a cohort of 72 patients with PF-EPN from a single centre studied across a 30-year time period(7). A recent Italian prospective trial indicates a survival benefit in patients with evidence of residual disease treated with an additional 8Gy radiotherapy boost delivered in 2 fractions(42), with a 5-year PFS of 58.1%, compared to 43.0% in those who did not receive boost therapy.

Craniospinal irradiation can be used to treat newly diagnosed metastatic disease. Commonly a dose of 36Gy in 20 fractions is administered, with a treatment boost of 59.4Gy to the tumour bed and metastases(43). As presentation with metastatic disease in paediatric ependymoma is less common(22), these doses are not supported by evidence from the literature, but are a 'Good Practice Point' in the recently published EANO guidelines(1).

## *Proton beam therapy*

Intracranial ependymoma is one of the foremost indications for proton beam therapy (PBT) in children. PBT is capable of reducing the dose of ionising radiation deposited to uninvolved CNS tissue, primarily by way of an abrupt dose fall off, dramatically lowering the exit dose. This allows treating physicians to potentially avoid harmful late toxicities with respect to endocrine, hearing and cognitive function. A retrospective series of paediatric intracranial ependymoma found 3-year PFS rates in children treated with PBT were broadly equivalent to those treated with conformal radiotherapy(44). These results have also been confirmed in larger prospective series(45,46). However, there have been sporadic reports of brainstem necrosis following PBT to infratentorial tumours(47), and, although rare, the prevalence of this complication should be definitively established by ongoing prospective trials.

## *Chemotherapy*

Chemotherapy has a less clear role in the management of paediatric ependymoma(1). Infants and younger children are particularly susceptible to delayed neurotoxicity related to radiotherapy(7,48,49). Several studies have therefore attempted to deploy frontline chemotherapy immediately post-operatively in this cohort of patients, in order to delay or avoid radiotherapy(50–53), whilst maintaining tumour control. Various regimens have been trialled, including platinum derivatives, etoposide, cyclophosphamide, vincristine and methotrexate. The most promising results of chemotherapy in ependymoma thus far are from a prospective UK study of 89 children under the age of 3, with 5-year OS of 76%(50). Similar results were demonstrated in other European studies with 3-year OS of 55.9%(54) and 4-year OS of 59%(52). The “Head Start” III trial of intensive induction and consolidation chemotherapy following maximally resective surgery, demonstrated 3-year OS of 100% in supratentorial ependymoma, and 73% in infratentorial ependymoma, of whom 8/11 suffered relapse, with 6 of those 8 dying of relapsed disease(17).

However, no studies of chemotherapy in paediatric ependymoma have so far been able to supersede those of conformal radiotherapy, whose 7-year OS in children under 3 is 77%(13). Since its original suggestion over 20 years ago(34), the use of neo-adjuvant chemotherapy prior to second-look surgery shows some promise(42,53,55), and this treatment strategy will be studied further in ongoing clinical trials in North America(56) and Europe(40). Other clinical trials are investigating intraventricular infusions of chemotherapeutic agents 5-azacytidine (57)and autologous *ex vivo* expanded natural killer cells(58).

**Commented [TS1]:** These references clarified.

## Management of recurrent paediatric intracranial ependymoma

Despite advances in the standard of care owing to neurosurgical and oncological developments, up to one half (59) of children with intracranial ependymoma will suffer relapse. This mostly occurs early, often before 2 years, and is usually at the primary site of tumour(60). In the majority of cases, relapsed ependymoma carries a poor prognosis, with 5-year survival rates of merely 25% (60).

This group of children remain a therapeutic challenge. Surgery (see section “Role of ‘second-look’ surgery”) to resect local and metastatic disease is often combined with reirradiation in various formats: stereotactic radiosurgery(61,62), PBT(63), craniospinal irradiation(64) or focal fractionated radiotherapy(37,65). The St Jude team reported on a series of 38 children with ependymoma recurring after surgery and primary radiotherapy(37). Recurrence was local in 21, metastatic in 13 and synchronous in four. GTR was achieved in 12 patients with local recurrence only; 12 of 13 patients with metastatic failure underwent resection of the metastatic lesions (up to three sites per patient) followed by craniospinal irradiation; their four-year event free survival was 53% ± 20%. Six patients underwent stereotactic radiosurgery with poor long-term disease control and morbidity related to radiation necrosis, concerns which have been noted by other authors(62,66). More recently, a larger cohort of 101 patients from the same institution undergoing reirradiation at ependymoma recurrence demonstrated a 5-year OS and PFS of 57.3% and 36.7%, respectively(65). Reirradiation was well-tolerated by most patients, with a 10-year cumulative incidence of radiation necrosis of 7.9%.

A wide variety of chemotherapeutic agents have been trialled in this context, but response rates are low with either single (12.9%) or multiple agents (17.4%)(67), and the strategy does not show any definitive survival benefit in the paediatric population(38). Etoposide and cisplatin showed some early promise in single-agent studies, with response seen in 10/29 and 8/25 patients, respectively, collated over several studies(67). A recent study of temozolomide in 18 chemo-naïve adult patients with recurrent ependymoma showed no disease progression in 39% of patients after a median of 8 cycles, and median OS of 30.6 months(68). However, TMZ showed very limited benefit in the paediatric setting(69). On the basis of current evidence, firm recommendations cannot be made regarding the use of chemotherapy in recurrent paediatric intracranial ependymoma.

## Management of paediatric spinal ependymoma

Ependymomas of the spinal cord are less common in children compared to adults, and often present at a slightly later age than intracranial ependymoma(70). Owing to their rarity, much of the literature on paediatric spinal ependymoma is comprised of single-centre, retrospective reports(71). As with intracranial ependymoma, prognosis is optimised by early surgery aiming at GTR. In one retrospective study of 29 paediatric spinal ependymomas, 5-year PFS was 84.4% in those who underwent GTR, compared with 57.1% in those who did not(72). Nuances of surgical technique will depend on whether the tumour is intra- or extra-medullary, as well as its rostrocaudal location in the spinal cord. GTR may be more difficult to achieve in tumours arising in the upper spinal cord(73), and for MPE, there is some evidence that preserving capsular integrity leads to a reduction in recurrence

rates(74). The adjunctive use of intra-operative neurophysiological monitoring is crucial in the resection of spinal cord ependymomas.

The use of adjuvant radiotherapy, which has been shown to prolong PFS after STR in adult spinal ependymoma(75), is dependent on the histological grading. MPE, which most commonly occur in the caudal spinal cord, have a high recurrence rate which belies their WHO Grade I classification(76). Post-operative radiotherapy has been recommended for MPE (particularly in the case of STR)(1), following evidence that this improves local control in combination with surgical resection(77), although this remains contentious. For WHO Grade II spinal ependymoma, a watch-and-wait strategy is appropriate(71), whilst anaplastic ependymoma should receive adjuvant radiotherapy.

## Conclusions

Significant advances have been made in understanding the biological landscape of ependymomas. The cornerstone of management remains maximal safe neurosurgical resection followed by irradiation, and proton beam therapy has emerged as a viable alternative delivery. The role of chemotherapy remains unclear. Results of ongoing clinical trials will help shape the management of paediatric ependymoma in order to leverage our increasingly sophisticated understanding of the genetic drivers behind these tumours into survival benefit for this challenging group of patients.

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Figure

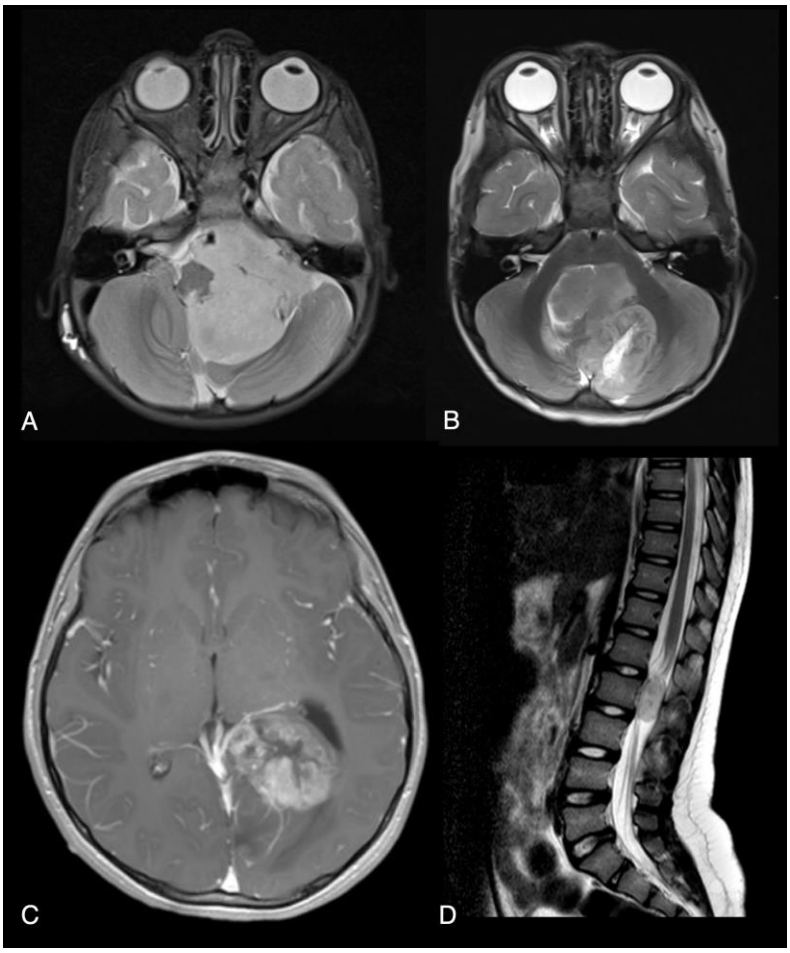


Figure 1. Imaging examples of paediatric ependymoma. A, axial T2-weighted sequence showing a large left cerebellopontine angle ependymoma with encasement of the lower cranial nerves and basilar trunk, and displacement and rotation of the brainstem. B, axial T2-weighted sequences showing a midline posterior fossa anaplastic ependymoma (PF-EPN-A) obliterating the fourth ventricle. C, Axial T1-weighted post-Gadolinium sequence showing a heterogeneously enhancing supratentorial anaplastic ependymoma (ST-EPN-RELA). D, Mid-sagittal T2-weighted sequence showing an intradural extramedullary myxopapillary ependymoma at the L2 level compressing the cauda equina.