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Review

# Current therapy and the evolving molecular landscape of paediatric ependymoma

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**Abstract** Ependymomas are the third commonest paediatric central nervous system (CNS) tumour, accounting for 6–12% of brain tumours in children. The management of these tumours has seen considerable changes over the last two decades, leading to a significant improvement in outcomes. However, despite advances in neurosurgical, neuroimaging and postoperative adjuvant therapy, management of these tumours remain challenging, and recurrence occurs in over 50% of cases, particularly when complete resection is not achieved prior to conformal radiotherapy. To-date no chemotherapeutic regimen has proven to be of significant clinical benefit. Predicting tumour behaviour and defining robust correlates of disease outcome based on histopathology and clinical characteristics remains suboptimal. Paucity of cell lines, failure to develop ideal animal models of these tumours, have precluded better understanding of the oncogenic drivers, undermining development of targeted therapies. Over the last few years breakthrough in the understanding of the molecular biology, are now providing clues to therapeutic insights. It is clear that even with histopathological similarities, these are genetically heterogeneous tumours with diverse clinical outcomes. Rapid evolution of data based on genome-wide DNA methylation patterns, have now identified nine molecular subgroups in these tumours, across three anatomic compartments which include supratentorial (ST), posterior fossa (PF) and the spinal locations. More recently based on transcriptome profiling, two subgroups (group A and B) of PF ependymoma have been identified with distinct molecular, clinical characteristics and specific chromosomal aberrations. This review includes current management, evolving molecular biology and the shifting paradigm of treatment profile that targets molecular alterations in paediatric ependymoma.


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## 1. Introduction

Ependymomas are the third most common paediatric tumour of the central nervous system (CNS), accounting for 6–12% of brain tumours in children [1]. These tumours can occur anywhere in the neuraxis, arise from the ependymal lining of the ventricles and the central canal. In children over 90% of these malignancies are intracranial, of which two-thirds arise in the infratentorial (IT) region and one-third are located in the supratentorial (ST) area. The ST tumours occur more frequently in older children and adolescents and IT tumours predominate in the younger age group. Unlike adults where most ependymomas occur in the spine, in children it constitutes less than 10%. More than half of paediatric ependymomas occur in children less than 5 years and are prevalent twice as common in males [2–4]. The aetiology of these tumours remains obscure, and no robust correlations with environmental or infectious aetiology is defined. Few non-specific data show the SV40 virus is capable of inducing brain tumours including ependymoma [5]. Neurofibromatosis type 2 (NF2) is the only known genetic defect with a predisposition to develop these tumours, with nearly 25–70% of sporadic intraspinal ependymomas harbouring NF2 mutations [6].

Currently these tumours are classified into three grades by the World Health Organization (WHO) 2016, Grade I subependymomas and myxopapillary (MPE), Grade II (classic ependymomas) and Grade III as anaplastic type [7]. These tumours when treated identically based on similar histological grading, has shown diverse clinical outcomes. This is suggestive of genetic heterogeneity amongst these malignancies. Current principle of management of these tumours has remained the same over the last two decades, with surgery followed by radiation therapy as an adjuvant strategy. However a major change in the management has been the progressive abandonment of so called baby brain strategies since the early 2000, with an increasing number of infants and young children managed with postoperative conformal radiation. The role of chemotherapy has remained uncertain and controversial, although chemotherapy is still nowadays largely used in the management of this condition. Considered as a surgical disease, gross total resection (GTR) has been the most favourable consistent prognostic factor [8]. GTR is possible more frequently when tumours are located in surgically accessible areas such as the ST region. Still a large number of children proceed to radiation after incomplete resection, more so when these tumours are infiltrating into vital structures or located in eloquent areas of the brain. Incomplete surgical resection is a main factor influencing outcome in children with ependymoma. In this context, recurrences will develop in over 50% of patients [9]. There is still a reluctance to accept potential morbidity associated with aggressive surgery despite increasing evidence that postoperative radiation cannot compensate for incompleteness of resection.

## 2. Histopathological characteristics

The most common histopathological subtypes occurring in children are classic and anaplastic ependymoma. Classic variant exhibits perivascular pseudorosettes of glial tumour cells. These tumours are less cellular, do not have vascular proliferation, necrosis or significant elevation of mitosis as seen in the anaplastic types. Four subtypes are noted in this grade which includes papillary, cellular, clear-cell variant and tanycytic. Papillary ependymomas have papillary structures surrounding vascular elements. Clear-cell ependymomas frequently have cystic components and feature oligodendroglioma-like cells [10,11]. Tanycytic variant have long eosinophilic fibrillary processes but lack the Rosenthal fibres distinguishing them from the fibrillary variant of astrocytoma [12]. These tumours have been shown to have the highest MIB-1 and p53 expression amongst grade II ependymomas [13]. Anaplastic variants have higher cellularity, nuclear atypia and frequent mitosis and variable degrees of vascular proliferation. The distinction between the two grades (cellular and anaplastic) is often difficult and lack reproducibility, with discordance between neuropathologists being as high as 69% [14]. The WHO 2016 classification has incorporated changes, by deleting the cellular variant of these tumours and incorporating the *RELA* fusion-positive subtype as a distinct entity [7]. Grade I subtypes are more common in adults. MPE are slow growing tumours and occur almost exclusively in the cauda equina, originating from the filum terminale, with a predisposition to spread in other parts of the CNS in children [15]. Subependymoma is a rarer variant of grade I ependymoma, located mostly in the lateral and fourth ventricle. They are seen in less than 1% of children, and have a low proliferation index (MIB-1) and have an excellent prognosis following surgical resection [16].

## 3. Treatment

Current therapeutic strategy for paediatric ependymomas includes maximal safe surgical resection, followed by adjuvant therapy. This includes in most cases radiation with or without chemotherapy.

### 3.1. Surgery

Local control is most important to prevent recurrence as these tumours are locally invasive with low metastatic potential and leptomeningeal dissemination, seen in a