Ependymoma in pediatric patients

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Article information

Abstract

Pediatric ependymomas encompass distinct tumor types characterized by variations in epigenetics, age distribution, localization, and prognosis. Histopathological features continue to hold relevance in risk stratification within these defined tumor types. The primary treatment approach involves achieving complete surgical removal, whenever feasible, utilizing intraoperative monitoring and neuronavigation. In cases where mandatory, a second surgery may be performed, ensued by adjuvant radiation therapy. Nevertheless, emerging proof suggests that certain ependymal tumors can be successfully treated with surgery only, whilst others may experience relapse despite adjuvant therapy. The function of chemotherapy remains unclear at present. Current therapeutic strategies yield affordable survival rates for most patients with ependymoma. The next hurdle is to surpass initial tumor control by employing risk-adapted therapy, aiming to minimize secondary effects and therapy-induced morbidity for low-risk individuals, while intensifying treatment for high-risk individuals. The recognition of specific variations may pave the way for targeted therapy, enabling personalized treatment approaches in the future.

1. Introduction

Ependymomas are the third most prevalent fatal brain tumor in pediatric. They can develop in any part of the central nervous system. The most prevalebt site is the posterior fossa, ensued by locations above the tentorium, while spinal tumors are relatively uncommon. There is a slight overall male predominance in cases (1). Historically, ependymomas were regarded as a single entity based on their similar appearance under a microscope but were assigned different tumor grades. This grading system was utilized for risk assessment along with treatment decisions, assuming that certain histopathological features like mitotic activity, necrosis, and vascular proliferation predict outcomes regardless of patient age or tumor location. However, the usefulness of grading for risk assessment has been a subject of controversy, primarily due to inconsistencies in interpretation among different observers (2, 3). Over the past decade, there has been extensive research focused on posterior fossa ependymoma, which is a major contributor to morbidity and mortality among children. Furthermore, during this period, a uniform treatment approach has emerged for all pediatric patients with posterior fossa ependymoma, where conformal radiation has become the established standard of care. However, despite efforts to minimize the radiation field, there remains a notable risk of adverse effects on the developing brain due to radiation exposure. (4, 5).

2.Origins and Epidemiology of Ependymoma

Ependymomas basically originate from ependymal cells that line ventricles in the brain or the central canal in spinal cord. Although they are near the leptomeninges and cerebrospinal fluid (CSF), the spread of ependymomas to the leptomeninges is rare, occurring in only 2.2 percent of children diagnosed with intracranial ependymoma (6).

Ependymomas account for approximately 5% of all intracranial neoplasms in children under 20 years old. However, estimates can vary between 5 percent and 10 percent depending on different sources and databases (7, 8). Based on the latest data from the Central Brain Tumor Registry of the U.S. (CBTRUS), there were around 185 cases of ependymoma diagnosed in children aged 0-14 between 2015 and 2019, with an additional 237 cases in children aged 0-19. The incidence of ependymoma can vary based on its specific location. According to a review of the SEER registry from 1973 to 2003, it was discovered that a majority of pediatric ependymomas (54.4%) were found to originate in the posterior fossa. Another significant portion (32.5%) was located in the supratentorial compartment, while a smaller percentage (13.1%) was found in the spine (5). On the other hand, when it comes to adults, a significant majority of 64.1% of ependymomas originate in the spinal cord. Children with infratentorial tumors had an average age of 5 years, while those with supratentorial tumors had an average age of 7.8 years. Children with spinal cord lesions had the highest average age at 12.2 years.

3.Types of Childhood Ependymoma

Ependymomas exhibit distinct subtypes based on their specific locations within the body. Among children, three primary variants of ependymoma are commonly observed:

○   **Posterior fossa (infratentorial) ependymomas** originate in the lower region of the brain, near the central back of the head. In children, the majority of ependymomas arise in this specific area, impacting the cerebellum and brain stem.

When observed through magnetic resonance imaging (MRI), posterior fossa ependymomas may exhibit homogeneous and well-defined tumors. Additionally, there may be signs of hemorrhage and potential calcification spots, along with varying contrast enhancement because of necrosis and the formation of cysts. These neoplasms can be found within fourth ventricle, and they could extend laterally through foramina of Luschka or foramen of Magendie (1).

o **Supratentorial ependymomas**: Supratentorial ependymomas, which happen at the upper part of the head and affect the cerebrum, are more commonly diagnosed in young individuals, and display a declining prevalence with age. In children, ependymomas in this brain region are less prevalent. The cerebrum is responsible for various cognitive functions such as voluntary movement, thinking, speech, learning, writing, problem-solving, emotions, and reading (4). When observed through MRI, supratentorial ependymomas manifest as large tumors with heterogeneous contrast enhancement. They often exhibit cystic areas and, calcifications, less frequently, hemorrhage, and necrosis. It is worth noting that supratentorial ependymomas in childhood are generally associated with a more favorable prognosis related to those in the posterior fossa, probably due to a higher possibility of achieving complete neoplasm removal in the former group (9).

o **Spinal cord ependymomas:** Ependymomas originating in the spinal cord are infrequent among children. Moreover, pediatric patients diagnosed with ependymomas in this area are generally older than those with supratentorial or infratentorial tumors (4, 5). Histologically, spinal ependymomas can be categorized into different types, including myxopapillary ependymoma (WHO grade I), classic ependymoma (WHO grade II), and the rare anaplastic ependymoma (WHO grade III) (10, 11). (See Figure 1).

Figure(1): A detailed illustration showcases the intricate internal structure of the brain, highlighting the various ventricles and the interconnected pathways that facilitate the flow of CSF, represented by a soothing blue color. In addition, the illustration also showcases various other parts of the brain, including the cerebrum, cerebellum, spinal cord, and brain stem, which includes the pons and medulla.
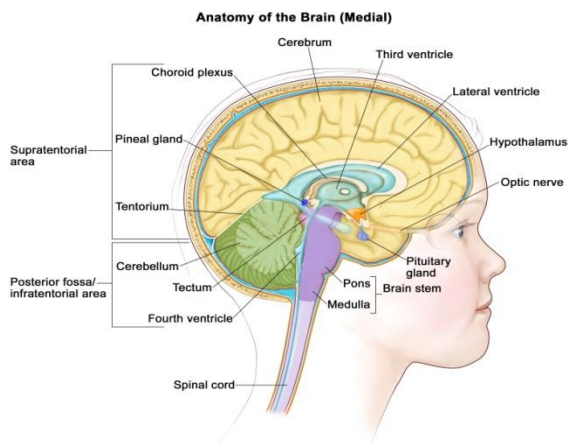
4. Clinical presentation

Children diagnosed with posterior fossa ependymomas usually exhibit signs indicative of obstructive hydrocephalus and compression in the posterior fossa, namely severe headaches, persistent vomiting, and impaired coordination. Additionally, children with posterior fossa ependymomas often display torticollis resulting from the tumor's growth through the foramen of Magendie, a distinguishing feature that sets it apart from other neoplasms located in the posterior fossa like medulloblastoma. It is worth mentioning that the incidence of familial malignancies is seldom observed during the initial presentation of this condition (12).

The initial assessment of patients typically involves the use of neuroimaging techniques, typically starting with a CT scan, followed by MRI. On CT scans, posterior fossa ependymomas typically appear isodense, often exhibiting small calcifications and the formation of cysts (13). However, differentiating between ependymomas and medulloblastomas solely based on CT images can be challenging. During the MRI examination, posterior fossa ependymomas can often be recognized from embryonal tumors like medulloblastomas owing to their specific location, particularly their invasion into the foramina of Luschka and Magendie (14). Furthermore, posterior fossa ependymomas frequently extend into the cerebellopontine angle as well as the upper cervical canal. While leptomeningeal dissemination is a possible occurrence in ependymomas, it is rare during the initial diagnosis. However, if it is observed, it is important to consider the morphological diagnosis of ependymoma (15, 16).

Pediatric patients with supratentorial tumors may exhibit symptoms such as headaches, seizures, and focal neurological shortages, which vary depending on tumor's location within the brain. In respect to spinal cord ependymomas, children often experience persistent back pain, along with possible deficits in the lower extremities and dysfunction of the bowel and bladder. Infants, on the other hand, may present with less specific symptoms, including irritability, developmental delays or plateaus, and a bulging fontanelle. While these malignancies are not benign, their growth tends to be slow and gradual, with signs emerging gradually over several months before reaching a level of significance that prompts medical attention and evaluation. Therefore, it is crucial to not only consider the symptoms present during a particular evaluation but also to monitor the child's symptoms over time (17).

5. Diagnostic Assessment

Every individual speculated of having an ependymoma undergoes a comprehensive diagnostic imaging assessment of entire brain and spinal cord. To accurately evaluate subarachnoid metastasis in the spinal cord, the most effective method available is the utilization of spinal MRI with gadolinium. It is recommended that this imaging be conducted prior to any surgical intervention to prevent potential confusion arising from postoperative blood. When MRI is employed, the spinal cord is typically imaged in multiple planes, with contiguous MRI slices taken after gadolinium enhancement. Whenever conceivable, a cytological evaluation of the CSF is performed (18). Although disseminated disease is often detected during recurrence, the presence of metastatic disease upon the initial presentation of ependymoma is rare (6).

6. Pathology

Since the early days when ependymoma was first described by Cushing and Bailey, pathologists have played a crucial role in understanding this condition. Their job is not just to observe and describe what they see under the microscope, but also to connect those outcomes with both prognosis and treatment. Over time, it has become clear that ependymomas in different parts of the body can have distinct characteristics and behaviors. Take, for instance, the case of a myxopapillary ependymoma or spinal ependymoma. A thorough removal of these tumors typically led to a complete cure. However, when it came to a posterior fossa ependymoma, achieving complete resection rarely resulted in the same level of success (19). As mentioned, initial descriptions of ependymoma classified the tumors based on cellularity and anaplasia, with three general categories assigned regardless of their anatomical location. With the advent of immunohistochemical staining, various types of ependymoma have been identified, such as clear cell ependymomas and tanycytic ependymomas. In addition, there were several tumors that were easier to distinguish from ependymomas. These types of tumors are angiocentric gliomas, central neurocytomas, papillary glioneuronal tumors, and papillary tumors of the pineal region (19).

Through advancements in molecular diagnostics, it became clear in the early 2000s that ependymomas in different parts of the nervous system may appear similar when examined under a microscope, but they are actually unique entities at the molecular level (20). Subsequent research has shown that the presumed cancer stem cell responsible for ependymomas is most probably a radial glial cell, indicating that ependymomas are essentially a subtype of glioma (21).

Recent research has raised doubts about the predictive importance of cellularity and anaplasia in comparison to molecular profiling since it is related to the outcome of ependymoma. In the 2021 WHO CNS Tumor Classification System, tumor location and molecular profiling are considered more significant than the typing of ependymomas as Grade II versus Grade III. However, the typing still serves as a descriptive histopathological feature (22). By gaining a deeper understanding of the genetic changes occurring in different cellular compartments, researchers were able to introduce specific driver mutations found in humans into animals. This allowed them to create animal models of neoplasms that closely resembled the human condition in terms of both histology and molecularly (23).

Posterior fossa ependymomas are frequently observed in children, accounting for approximately 60-70% of all pediatric ependymomas. There are two distinct tumor types found in posterior fossa ependymomas, known as PF-A and PF-B. These tumor types have specific demographics and biological characteristics (24). PF-A tumors are recognized for their well-balanced genome along with some changes in the 1q and 6q genes (25, 26).

Discovering chromosome 1q gain has been linked to a particularly unfavorable prognosis, with high relapse rates observed in infants with posterior fossa ependymoma (25, 27). Understanding the methylation profile is crucial for customizing more effective treatment for this subgroup. At present, it is understood that PF-A exhibits a widespread decrease in H3K27me3 and the corresponding presence of EZHIP (Enhancer of Zeste homolog inhibitory protein) (28). PF-B, on the other hand, exhibits a significantly more positive outcome. The genetic, chromosomal changes, and demographic in this subgroup vary from PF-A. Unlike PF-A, this group is recognized for exhibiting a more common chromosomal instability. It has been demonstrated in other tumor types that this is linked to a favorable prognosis. There are certain alterations observed in PF-B, such as increased expression of H3K27me3, loss of chromosome 2, and the acquisition of 1q and chromosome 5. While the significance of 1q gain has been established for the prognosis of patients with PF-A, it does not appear to have the same impact on PF-B (28).

The prevailing agreement is to classify ependymomas into nine distinct variants, regarding factors such as molecular discoveries, histology, and clinical significance. This recognition stems from the realization that the previous classification, which was based on cellularity and the extent of anaplasia, was not as precise or predictive (29). It is important to mention that there are further divisions within these subtypes based on consensus clustering analysis. For example, Ellison et al. described nine subtypes of posterior fossa type A tumors (30). However, the current classification has become so detailed that conducting clinical trials becomes challenging, as it becomes difficult to gather enough patients in any one subgroup to make the results meaningful (31). While it offers valuable insights into the developmental aspects, this highly detailed grading system has yet to demonstrate clinical relevance.

Supratentorial ependymomas have primarily been classified into two subtypes: RELA-fused and Yap1. Among these, RELA-fused tumors are more prevalent and frequently observed in infants. However, studies have presented varying perspectives on the clinical significance of this subtype. According to Pages et al., RELA-fused tumors exhibited more aggressive behavior and a poorer prognosis compared to Yap tumors (32). Nonetheless, these findings were not consistently confirmed in other studies, prompting a collaborative analysis of outcomes across multiple institutions. As a result, this specific subtype of supratentorial ependymoma was renamed "ZFTAfus ST-EPN." It was discovered that the expression of RELA fusion alone is insufficient to initiate tumorigenesis, which led to an expanded investigation into the role of ZFTA. The currently accepted terminology for these tumors is "ZFTA-RELA gene fusion tumors. The RELA fusion subtype of ependymoma constitutes over 70% of supratentorial ependymomas. Recent studies have highlighted the crucial role of ZFTA in various animal models, underscoring its significance in tumorigenesis (33). Although the combined data has not confirmed a worse prognosis for this tumor, it has once again emphasized the importance of maximal surgical resection in achieving optimal outcomes, as seen in multiple other ependymoma trials. Future investigations are likely to explore associated driver mutations present in this subgroup of supratentorial ependymomas, such as CDKN2A. Loss of CDKN2A is observed in approximately one-third of RELA fusion ependymomas (33).

Spinal ependymomas typically manifest within the age range spanning from adolescence to early adulthood. This anatomically distinct category is further divided into subependymomas, myxopapillary ependymomas, ependymomas

(SP-EPN), and MYCN ependymomas (SP-MYCN). The SP-MYCN group, which is a relatively newly recognized subgroup, exhibits a significantly worse prognosis. This type of ependymoma is often characterized by an aggressive presentation, including the presence of diffuse leptomeningeal disease. It is important to note that, based on recent clinical data, the 2021 WHO CNS tumor classification system has reclassified myxopapillary ependymomas from Grade I to Grade II tumors (22).

7.Treatment Strategies

7.1.Surgical intervention

In the past, surgical resection has remained the primary treatment approach for all types of ependymomas. It may seem perplexing how surgery can provide a cure for tumors that possess intrinsic genetic alterations leading to tumorigenesis. However, complete surgical resection continues to be linked with the highest likelihood of achieving a cure. The significance of GTR or near-total resection (NTR) as the most crucial prognostic factor for ependymomas has been consistently demonstrated across various studies conducted worldwide, irrespective of the specific pathological subgroup (34).

Determining the acceptable amount of residual tumor that does not compromise survival has been a subject of debate. Previous studies have demonstrated the advantages of surgical resection, highlighting the benefits not only of achieving a GTR but also of maximizing the extent of resection (EOR) (35). However, the benefit of anything less than a GTR did not reach statistical significance but displayed a trend towards prolonged survival. One consistent finding across various publications is that radiation therapy plays a definitive role in improving PFS, even in cases where a GTR has been achieved. When considering historical publications on PFS and OS for all intracranial ependymomas recent studies continue to demonstrate better long-term outcomes with the addition of focal radiation following a maximal safe resection (36). The challenge in comparing different publications regarding the benefits of a greater extent of resection lies in the lack of consistent stratification with regard to residual tumor volume. Therefore, we, along with others, advocate for pursuing a maximal safe resection with the intention of achieving a GTR whenever feasible. In contrast to supratentorial ependymomas, posterior fossa ependymomas present a formidable challenge in achieving a GTR due to involvement of critical neurovascular structures (37).

A recent publication by Malhotra et al. revealed that achieving a GTR not only led to significantly improved survival in cases of primary resection at initial presentation but also in cases of recurrent disease (38). Based on their findings, it can be inferred that striving for GTR as the treatment goal should be pursued. It is important to note that achieving GTR may require more than one surgical procedure in many cases. Massimino et al. demonstrated that the overall survival and event-free survival of patients who underwent multiple surgeries to achieve GTR were comparable to those who achieved GTR in a single surgery (39). Therefore, it is recommended that surgeons approach newly diagnosed ependymoma patients with the intention of accomplishing a gross total resection, while also informing the family in advance that it may require more than one operation to yield the best possible outcome.

An additional factor to consider pertains to highly vascularized tumors. In these cases, there is compelling evidence supporting the use of neoadjuvant chemotherapy prior to definitive resection. This approach aims to devitalize the tumor, thereby facilitating complete removal during subsequent surgery. In such instances, it is reasonable, though not mandatory, to conduct a biopsy before initiating neoadjuvant treatment (40).

In a recent publication by the German multi-center E-HIT-REZ-2005, it was demonstrated that patients with relapsed or recurrent ependymoma who underwent GTR/NTR experienced improved OS compared to those who underwent a lesser extent of resection (41). However, despite numerous publications supporting the significance of extent of resection (EOR) for relapsed disease, there are other studies that question these findings (42). Considering the current wealth of knowledge regarding EOR in patients with recurrent disease, what is evident is that adjuvant therapy alone does not eradicate ependymomas but is most effective in preventing their recurrence following maximal resection, as confirmed by post-operative MRI. Therefore, whenever feasible, resection of recurrent disease should be considered.

7.2.Radiation therapy

As previously mentioned, the inclusion of radiation therapy (RT) following surgical resection of ependymoma is a well-established practice. Numerous previous publications have provided evidence of the survival benefits associated with (GTR) followed by adjuvant radiation therapy, resulting in estimated OS rates ranging from 63% to 93%. Conversely, patients who underwent surgery with a lesser extent of resection and subsequent radiation therapy achieved OS rates between 22% and 56% (43). It is worth considering the utility of post-operative radiation therapy in light of the distinct subtypes of ependymoma. Currently, the necessity of radiation therapy following complete resection of myxopapillary ependymomas, intramedullary spinal ependymomas, and posterior fossa Type B (PF-B) ependymomas is under question.

Pediatric ependymoma exhibits its highest incidence during the infancy to toddler age range (0-3 years), which unfortunately poses a considerable challenge when considering the use of radiation therapy. In this age group, chemotherapy has been employed as a temporary measure to postpone the administration of radiation therapy. However, the effectiveness of chemotherapy in improving survival outcomes for ependymomas has not been demonstrated. Consequently, various research groups have investigated the efficacy and long-term safety of radiation therapy for patients aged 0-3 years (19, 44-46). The findings have indicated an OS rate of approximately 80% within this age bracket following GTR and focal radiation therapy, with favorable cognitive outcomes observed during long-term follow-up. Ongoing advancements in radiation therapy delivery, utilizing more precise conformal techniques or proton therapy, have resulted in reduced treatment failures while minimizing radiation exposure to surrounding healthy tissues. In 2019, Merchant et al. published their findings from the ACNS0121 study (47).

This study encompassed a substantial cohort of newly diagnosed ependymoma patients who underwent surgery, radiation therapy, and chemotherapy. For patients younger than 18 months, a reduced radiation dose of 54 Gy was administered. The authors effectively demonstrated that radiation therapy should remain the primary treatment approach following maximal safe resection for nearly all ependymoma subtypes (47). Considering all factors, particularly the discouraging outcomes associated with delaying radiation therapy in the younger age group, it is advisable to recommend focal radiation therapy even for patients younger than 3 years old (43). In a recent trial involving the administration of chemotherapy to infants under 3 years old followed by radiation therapy, no significant survival benefit was observed compared to infants who solely received radiation therapy as reported by Merchant et al. (43, 48).

In cases of recurrent disease following prior resection and irradiation, it is advisable to consider a second look surgical resection before contemplating re-irradiation, as discussed earlier. Surgical resection has demonstrated a positive impact on survival even in the context of recurrent disease. Re-irradiation, particularly craniospinal irradiation, has been associated with the most favorable survival outcomes in children with relapsed disease (49). Previous studies have indicated that the best results are observed when the relapse occurs at a distance from the initial resection cavity, where the initial radiation therapy encompassed focal radiation. However, the use of stereotactic radiosurgery (SRS) in children with recurrent ependymoma has not yielded comparable outcomes (50, 51). Merchant et al. documented their findings in a publication where they compared various radiation modalities for recurrent ependymomas. Their results revealed that the utilization of stereotactic radiosurgery (SRS) led to notably inadequate long-term disease control and a high incidence of morbidity among the patients. Conversely, the implementation of fractionated therapy demonstrated exceptional rates of disease control, particularly when administered after complete resection of the patient's local recurrence. Craniospinal radiation emerged as the approach that achieved the most favorable disease control outcomes with an acceptable level of toxicity (52).

7.3. Chemotherapy

The use of chemotherapy for ependymoma treatment has sparked significant controversy. It was primarily seen as an approach to maintain non GTR cases or to treat patients under 3 years old, with the goal of avoiding the potential harm of radiation therapy. Recently, there has been a lot of research conducted on the effectiveness of chemotherapy after surgery in various age groups. Upadhyaya et al. published the results of the multi-institutional SJYC07 trial, which demonstrated the advantages of using chemotherapy to allow additional surgical resection before starting radiation therapy. This approach aims to achieve complete or near-complete tumor removal before radiation therapy begins (48). However, a recent study examining the outcomes of radiation therapy in patients under the age of 3 revealed that there was no notable disparity in survival rates between those who underwent bridging chemotherapy followed by delayed radiation and those who solely received radiation therapy. This raises significant concern regarding the effectiveness of chemotherapy in younger patients, as it puts them at risk of developing leukemia and

other blood-related cancers without any proven benefits (43). Hopefully, ongoing studies like ACNS-0831 and SIOP EPII will provide more conclusive evidence to settle this debate. According to the latest research, the findings do not provide enough evidence to recommend the regular use of chemotherapy in infants with ependymoma.

8. Conclusion

Ependymoma continues to present itself as one of the most formidable brain tumors we encounter in our medical practice. In highly skilled medical centers, these tumors are identified before surgery through a combination of clinical presentation and MRI assessment. In the past, prognostic factors relied upon age, gender, tumor location, tumor grade, extent of surgical removal, and the timing of adjuvant therapies. At present, neurosurgeons are in a crucial stage where the extent of tumor removal plays a vital role in determining the survival of these patients. It is crucial for neurosurgeons to consistently conduct early post-operative MRI imaging after surgery for patients with ependymoma.

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