International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 10 October 2023

Page No: 2526-2531

DOI: https://doi.org/10.47191/ijmscrs/v3-i10-75, Impact Factor: 6.597

An In-Depth Analysis of Ependymoma: Neuropathological Insights, Therapeutic Strategies, and Prognostic Implications in Intracranial Ependymal Tumors

Alejandro Arias Mendoza[1], Daniela Itzel Moreno Falcón[2], Maria Guadalupe Campos Canelo[3], Jessica Arlene Avalos[2], Teresa Jannete Ortega Valls[2], Hector Manuel Valdez Jimenez[2]

[1]Hospital General de Zona 1-A Dr. Rodolfo Antonio de Mucha Macías. Hospital de Especialidades Dr. Bernardo Sepúlveda Gutiérrez. Centro Médico Nacional Siglo XXI. IMSS.

[2]Universidad Autónoma De Guadalajara, Guadalajara, Jalisco. México.

[3]Universidad de Guanajuato, Guanajuato. México

ABSTRACT

Ependymomas are primary central nervous system (CNS) neoplasms arising from ependymal cells lining the ventricular system and spinal cord. They represent a heterogeneous group of tumors with distinct histological and molecular subtypes, making their diagnosis, management, and prognosis a complex and evolving challenge in the field of neuro-oncology.

This comprehensive review delves into the intricate landscape of ependymomas, elucidating their pathogenesis, classification, and molecular underpinnings. Histologically, they can manifest as myxopapillary, subependymoma, and anaplastic ependymomas, each carrying distinct clinical implications and therapeutic strategies. Moreover, recent advancements in molecular profiling have unveiled significant genetic alterations such as amplifications in RELA, YAP1, and C11orf95-MAML2 fusion, which have profound implications for prognosis and therapeutic decision-making.

We explore the intricacies of clinical management, encompassing surgical resection, radiation therapy, and chemotherapy regimens tailored to the tumor's location, grade, and molecular profile. Despite their location within the CNS, ependymomas are notorious for their diverse clinical presentations, including headache, neurological deficits, and intracranial hypertension, necessitating multidisciplinary care and vigilant surveillance.

Additionally, this article investigates the latest developments in targeted therapies, immunotherapeutic approaches, and ongoing clinical trials in an attempt to provide a glimpse into the future of ependymoma treatment, as precision medicine begins to play a more significant role in guiding therapeutic decisions.

Furthermore, the abstract examines the critical issue of ependymoma prognosis, emphasizing the importance of integrating histopathological and molecular data in order to stratify patients into risk categories more accurately. The role of genetic markers, such as chromosome 1q gain and chromosome 6q loss, in predicting outcomes is thoroughly explored.

In summary, this article aims to offer a comprehensive perspective on ependymomas, from their cellular origins to the latest breakthroughs in their management, offering insights into their clinical course, and underscoring the critical role of multidisciplinary collaboration in advancing the understanding and treatment of these complex intracranial tumors.

KEYWORDS: ependymomas, brain, tumor, nervous.

ARTICLE DETAILS

Published On:
30 October 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Ependymomas, a rare but formidable category of primary central nervous system (CNS) tumors, have long captivated the interest of neuro-oncologists, neurosurgeons, and neuropathologists. These neoplasms, arising from the ependymal cells lining the cerebral ventricles and spinal canal, present a unique and complex challenge within the landscape of intracranial tumors.1,2

Ependymomas encompass a spectrum of histological subtypes, with myxopapillary, subependymoma, and anaplastic ependymomas standing out as key representatives, each characterized by distinct cellular features and clinical behavior. The intricate histopathological classification, coupled with the evolving understanding of molecular heterogeneity, has revolutionized the diagnosis and therapeutic strategies in recent years.1,2

At the molecular level, ependymomas have revealed their intricate secrets, uncovering genetic alterations that guide not only diagnosis but also treatment decisions. The discovery of key molecular markers such as amplifications in the RELA, YAP1 genes, and the C11orf95-MAML2 fusion has offered fresh insights into the pathogenesis and the potential for targeted therapies.1,2

The management of ependymomas is inherently complex, demanding a multidisciplinary approach that combines the skills of neurosurgeons, radiation oncologists, medical oncologists, and pathologists. The intricate location of these tumors within the CNS, their propensity for infiltration, and the varied clinical presentations, ranging from headaches and neurological deficits to intracranial hypertension, underscore the importance of precise surgical resection, tailored radiation therapy, and evolving chemotherapy regimens.1,2

This article embarks on a comprehensive journey through the multifaceted world of ependymomas, exploring their clinical challenges, molecular intricacies, and the evolving landscape of therapeutic interventions. It delves into the latest advancements in precision medicine and immunotherapeutic strategies that are promising to transform the treatment paradigm for these enigmatic tumors.1,2

Moreover, a critical aspect of the ependymoma puzzle lies in the accurate prognostication of these neoplasms, as their clinical course can vary dramatically. Incorporating both histopathological and molecular data into risk stratification becomes increasingly vital. Genetic markers like chromosome 1q gain and chromosome 6q loss have emerged as potential predictors of outcomes, opening the door to more personalized therapeutic approaches.2,3

In summary, this article seeks to provide a comprehensive overview of ependymomas, from their cellular origins to the forefront of modern diagnostic and therapeutic approaches. It underscores the intricate interplay between histopathology, molecular profiling, and clinical management, all underpinning the quest to enhance our understanding of and ability to combat these complex intracranial tumors.2,3

EPIDEMIOLOGY

Ependymomas represent a subset of primary central nervous system (CNS) tumors characterized by their distinct cellular origin within the ependymal lining of the cerebral ventricles and spinal cord. The epidemiological landscape of ependymomas is a multifaceted domain that warrants in-depth exploration, as understanding the incidence, prevalence, demographic patterns, and associated risk factors is pivotal in the pursuit of improved clinical management and prognosis for individuals afflicted by these rare intracranial neoplasms.3,4

INCIDENCE AND PREVALENCE

Ependymomas are generally considered rare, accounting for approximately 2-5% of all pediatric CNS tumors and 2-3% of adult CNS tumors. Nevertheless, within the pediatric population, they represent the third most common malignant brain tumor, highlighting their particular relevance in this age group. The annual incidence of ependymomas exhibits variation between pediatric and adult populations, further underscoring the unique epidemiological dynamics surrounding these tumors.3,4

AGE DISTRIBUTION

Epidemiological studies have consistently shown a bimodal age distribution in ependymoma cases, with one peak occurring in early childhood (typically between the ages of 3 and 7) and a second peak in adulthood, often between the ages of 35 and 45. This bimodal distribution suggests that the biological mechanisms and potentially associated risk factors underlying ependymoma development may differ between pediatric and adult cases.3,4

SEX DISPARITIES

Regarding gender differences, ependymomas display a slight male predominance in pediatric cases, with a male-to-female ratio of approximately 1.3:1. In contrast, adult ependymomas exhibit a more balanced gender distribution, suggesting potential differences in hormonal influences and etiological factors.3,4

GEOGRAPHICAL AND RACIAL DISPARITIES

The epidemiology of ependymomas also manifests geographical and racial variations. Studies have reported regional differences in ependymoma incidence, possibly related to environmental factors, genetic predisposition, or variations in diagnostic practices. Furthermore, there is evidence to suggest disparities in ependymoma incidence among different racial and ethnic groups, though the underlying causes of these disparities remain a subject of ongoing investigation.3,4

RISK FACTORS

Identifying definitive risk factors for ependymoma development remains a challenge, given the rarity of these tumors. However, some potential associations have been proposed, including genetic predisposition, exposure to ionizing radiation, and certain hereditary syndromes, such as neurofibromatosis type 2 (NF2). Nevertheless, these associations are not fully understood and are still subjects of ongoing research.3,4

The epidemiological landscape of ependymomas is a dynamic and evolving field, characterized by the rarity and complexity of these intracranial tumors. Continued efforts to enhance our understanding of the incidence, prevalence, and associated risk factors are imperative in the quest for improved diagnostic and therapeutic strategies, ultimately offering better outcomes and quality of life for individuals affected by ependymoma. As research in neuro-oncology advances, it is anticipated that the epidemiological insights provided herein will further refine our approach to these intriguing and challenging CNS neoplasms.3,4

CLINICAL MANIFESTATIONS

Ependymomas, as primary intracranial tumors, often present with a spectrum of clinical manifestations that arise from their location, growth patterns, and the compression or infiltration of adjacent neurological structures. The complexity of clinical symptoms associated with ependymoma reflects the intricate nature of these neoplasms and underscores the importance of early recognition and management.4,5

HEADACHE

One of the most common clinical presentations of ependymoma, particularly in the pediatric population, is recurrent and severe headaches. These headaches can be attributed to increased intracranial pressure resulting from the tumor's mass effect on cerebrospinal fluid (CSF) circulation within the ventricular system.4,5

NEUROLOGICAL DEFICITS

Ependymomas often exert pressure on surrounding brain structures, leading to a myriad of neurological deficits. These deficits may include motor disturbances, sensory deficits, and coordination problems. In the pediatric population, signs of increased intracranial pressure such as papilledema (optic disc swelling) can manifest as well.4,5

CRANIAL NERVE DYSFUNCTION

Given their location near cranial nerves, particularly in the posterior fossa, ependymomas may lead to cranial nerve deficits. This can result in symptoms like diplopia (double vision), facial weakness, hearing loss, swallowing difficulties, and vocal cord paralysis.4,5

SEIZURES

Seizures can occur in patients with ependymoma, especially when the tumor involves or irritates the surrounding cortical tissue. Seizures are more common in adults with ependymoma and can be focal or generalized.4,5

VOMITING AND NAUSEA

Ependymomas can obstruct the normal flow of CSF, leading to hydrocephalus and subsequent nausea and vomiting. This occurs as a consequence of elevated intracranial pressure, a phenomenon that often necessitates the placement of ventricular shunts to relieve the pressure.4,5

GAIT DISTURBANCES AND ATAXIA

Due to the potential compression of the cerebellum and adjacent structures, ependymomas may cause ataxia, characterized by uncoordinated or unsteady gait. This can affect both pediatric and adult patients and contributes to a decline in their overall quality of life.4,5

COGNITIVE AND BEHAVIORAL CHANGES:

In cases where ependymomas affect the frontal or parietal lobes, cognitive and behavioral alterations may be observed. Patients may experience changes in personality, mood disturbances, and difficulties with memory and concentration.4,5

SPINAL CORD MANIFESTATIONS

Intramedullary ependymomas, which occur within the spinal cord, present with symptoms that often include back pain, extremity weakness, sensory deficits, and bladder or bowel dysfunction. These symptoms can vary depending on the level and extent of the spinal cord involvement.4,5

ENDOCRINE DISTURBANCES

In rare instances, ependymomas situated in the vicinity of the pituitary gland may lead to endocrine dysfunction, resulting in hormonal imbalances and associated clinical manifestations.4,5

The clinical manifestations of ependymomas are diverse and multifaceted, reflecting the intricate interactions between tumor location, growth patterns, and their influence on adjacent neurological structures. An awareness of these various presentations is paramount for prompt diagnosis, appropriate management, and the optimization of patient outcomes. Early recognition of ependymoma-related symptoms allows for timely intervention and an improved prognosis, underscoring the significance of continued research in neuro-oncology to better understand and manage these complex intracranial tumors.4,5

DIAGNOSIS

Ependymomas, intracranial neoplasms arising from ependymal cells lining the cerebral ventricles and spinal cord, present a diagnostic challenge due to their histological heterogeneity and variable clinical manifestations. Achieving a timely and accurate diagnosis is imperative for optimal patient care, guiding treatment decisions, and estimating prognosis. 6,7

CLINICAL EVALUATION

The diagnostic journey often commences with a comprehensive clinical assessment. Patients may present

with a constellation of symptoms, such as severe headaches, neurological deficits, seizures, or behavioral changes. A thorough neurological examination is typically performed to assess motor and sensory function, cranial nerve deficits, coordination, and cognitive status. Specific attention is paid to signs of increased intracranial pressure, including papilledema, vomiting, and altered consciousness.6,7

IMAGING STUDIES

Neuroimaging, primarily through magnetic resonance imaging (MRI), plays a pivotal role in diagnosing ependymomas. These tumors typically present as intraventricular or intraparenchymal lesions, exhibiting various degrees of contrast enhancement and irregular borders. Their location and associated features on MRI, such as the degree of hydrocephalus and local mass effect, aid in characterizing the tumor and planning subsequent management.6,7

HISTOPATHOLOGICAL EVALUATION

The gold standard for confirming ependymoma diagnosis remains histopathological examination of the tumor tissue. Surgical resection, when feasible, allows for the collection of tissue samples, which are then subjected to detailed analysis by a neuropathologist. Ependymomas exhibit diverse histological subtypes, including myxopapillary, subependymoma, and anaplastic ependymoma, each necessitating distinct diagnostic criteria.6,7

IMMUNOHISTOCHEMISTRY

Immunohistochemical staining of tumor specimens is often employed to further classify ependymomas and confirm the diagnosis. Specific markers, such as glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA), help differentiate ependymomas from other intracranial tumors. Furthermore, the evaluation of Ki-67 labeling index may provide insights into the tumor's proliferative potential and, in the case of anaplastic ependymomas, its aggressiveness. 6,7

MOLECULAR PROFILING

Recent advancements in the field of molecular diagnostics have revealed a growing understanding of the genetic underpinnings of ependymomas. Genetic markers such as RELA amplifications, YAP1 fusions, and C11orf95-MAML2 fusions are being increasingly utilized for both diagnostic and prognostic purposes, with specific genetic alterations often associated with certain histological subtypes.6,7

CEREBROSPINAL FLUID EXAMINATION

In cases where ependymoma involvement of the ventricular system is suspected, cerebrospinal fluid (CSF) analysis may be warranted. Examination of CSF for tumor cells or molecular markers can provide crucial diagnostic information, although it is often less sensitive than tissue-based approaches.6,7

GENETIC TESTING

In light of the growing recognition of the significance of genetic markers, molecular testing, such as fluorescent in situ hybridization (FISH) and next-generation sequencing (NGS), is increasingly being integrated into the diagnostic process. These tests can assist in confirming the presence of specific genetic alterations that aid in both classification and therapeutic decision-making.6,7

The diagnosis of ependymoma is a multidisciplinary endeavor that necessitates a combination of clinical assessment, neuroimaging, histopathological evaluation, immunohistochemistry, and, increasingly, molecular profiling. Advancements in diagnostic tools and molecular techniques are reshaping our understanding of these complex intracranial tumors, facilitating more precise classification and therapeutic strategies. The continued evolution of diagnostic approaches holds the promise of further improving patient outcomes and refining our ability to confront the diverse challenges posed by ependymomas.6,7

TREATMENT

Ependymomas, intricate and diverse intracranial tumors, pose a therapeutic challenge due to their unique anatomical locations, histological subtypes, and potential for aggressive behavior. Effective management requires a multidisciplinary approach, combining surgical intervention, radiation therapy, chemotherapy, and, more recently, targeted therapies tailored to the tumor's molecular profile.8,9

SURGICAL RESECTION

Surgical resection of ependymomas is often the cornerstone of treatment. The extent of resection, whether gross total resection (GTR) or subtotal resection (STR), greatly influences patient outcomes. The goal is to safely maximize tumor removal while preserving neurological function. Neurosurgeons employ various techniques, such as microsurgery and intraoperative imaging, to achieve the best possible surgical outcome.8,9

RADIATION THERAPY

Radiation therapy, including external beam radiation and, in some cases, brachytherapy, is an integral component of ependymoma treatment. It is typically employed following surgery, especially for cases of STR or when tumors exhibit aggressive histological features. Techniques like conformal radiation therapy and proton therapy are utilized to minimize damage to healthy surrounding tissues.8,9

CHEMOTHERAPY

Chemotherapy has a limited role in the treatment of ependymoma, particularly in the pediatric population. Agents like vincristine, cisplatin, etoposide, and cyclophosphamide may be considered, often in the context of clinical trials. While the efficacy of chemotherapy in ependymoma is modest, it remains an option, particularly for recurrent or high-risk cases.8,9

MOLECULARLY TARGETED THERAPIES

The emergence of molecular profiling has opened new avenues for targeted therapies in ependymoma. Specific genetic alterations, such as RELA amplifications or YAP1 fusions, are now guiding therapeutic decisions. Experimental treatments that target these genetic alterations are under investigation, with potential for more tailored and effective interventions.8,9

IMMUNOTHERAPY

Immunotherapeutic approaches are also being explored in ependymoma treatment. Immune checkpoint inhibitors and vaccines are being investigated as potential options, aiming to harness the immune system's power to target and destroy tumor cells. Clinical trials are underway to evaluate the safety and efficacy of these therapies.8,9

NOVEL AGENTS AND EMERGING STRATEGIES

Ongoing research is continuously uncovering novel therapeutic avenues. Innovative agents and strategies, such as epigenetic modifiers, targeted small molecules, and gene therapies, are under investigation in preclinical and clinical settings. These experimental therapies hold promise for revolutionizing the management of ependymomas.8,9

PEDIATRIC VS. ADULT TREATMENT PARADIGMS

It's worth noting that the treatment approach can vary between pediatric and adult ependymoma cases. Pediatric ependymomas, often located in the posterior fossa, are frequently managed with the aim of preserving neurocognitive development. In contrast, adult ependymomas, which tend to be supratentorial, may require more aggressive therapy.8,9

PROGNOSTICATION AND SURVEILLANCE

The risk stratification of ependymoma patients is crucial for tailoring treatment regimens and estimating prognosis. Integrating histopathological and molecular data, along with clinical parameters, enables a more accurate assessment of disease course. Long-term surveillance is necessary to monitor for recurrence and late treatment-related complications.8,9

The management of ependymoma is a multifaceted and evolving process, incorporating surgery, radiation therapy, chemotherapy, and increasingly targeted and immunotherapeutic approaches. Emerging insights into the molecular underpinnings of these tumors are paving the way for more precise and effective interventions. As research in neuro-oncology advances, the prognosis for individuals with ependymoma is likely to improve, offering hope for enhanced outcomes and quality of life for those affected by these complex intracranial tumors.8,9

CONCLUSION

In the realm of neuro-oncology, the intricate and often enigmatic landscape of ependymoma has been a subject of both fascination and frustration for clinicians, researchers, and, most importantly, patients and their families. This complex intracranial tumor, originating from ependymal cells lining the cerebral ventricles and spinal cord, has continued to challenge our diagnostic, therapeutic, and prognostic capabilities.

Ependymoma, a neoplasm with a diverse histological spectrum, biologically distinct molecular subtypes, and a variable clinical course, underscores the importance of a multidisciplinary approach to diagnosis and management. The journey begins with clinical evaluation, where an array of symptoms, from headaches and neurological deficits to seizures and cognitive changes, may alert clinicians to the possibility of ependymoma.

While the clinical picture provides essential insights, it is neuroimaging, particularly magnetic resonance imaging (MRI), that offers a critical window into the tumor's anatomy and location. This guides surgical planning, where the delicate balance between tumor removal and preservation of neurological function is paramount. Histopathological assessment, supported by immunohistochemistry and molecular profiling, remains the cornerstone of definitive diagnosis, enabling a precise classification of ependymoma subtypes and, increasingly, guiding targeted therapies.

Treatment paradigms encompass a triad of modalities: surgical resection, radiation therapy, and chemotherapy. Surgical intervention, when feasible, aims at achieving maximal resection while respecting neurological function. Radiation therapy, often following surgery, targets residual disease and helps prevent recurrence. Chemotherapy, though modest in its efficacy, still plays a role, particularly in pediatric cases and high-risk situations. Emerging strategies, including targeted therapies, immunotherapeutic approaches, and experimental agents, are expanding the treatment landscape, offering hope for more tailored and effective interventions.

The distinction between pediatric and adult ependymoma cases further underscores the complexity of these tumors. Pediatric ependymomas, often situated in the posterior fossa, demand a treatment approach that preserves neurocognitive development. Adult ependymomas, more frequently

supratentorial, may require a more aggressive therapeutic stance.

Furthermore, advances in risk stratification, incorporating both histopathological and molecular data, enable more accurate prognosis and individualized treatment plans. Long-term surveillance remains vital to monitor for recurrence and late complications associated with treatment.

As research in the field of ependymoma continues to unfold, the future is filled with promise. Molecular profiling and the emergence of targeted therapies are reshaping our understanding and approach to these neoplasms. Immunotherapeutic strategies hold the potential to harness the immune system's power against ependymoma. Novel agents and experimental therapies are paving the way for innovative treatments.

In conclusion, the management of ependymoma is a dynamic and evolving journey, marked by the collaboration of medical professionals, researchers, and the resilience of patients. Our efforts are increasingly guided by the molecular intricacies of these tumors, allowing for more precise, less invasive, and more effective interventions. As we navigate the intricacies of ependymoma, we remain committed to improving patient outcomes, offering hope for a future where these complex intracranial tumors can be not just treated, but conquered.

REFERENCES

I. Zacharoulis S, Ashley S, Moreno L, et al.: Treatment and outcome of children with relapsed ependymoma: a multi-institutional retrospective analysis. Childs Nerv Syst 26 (7): 905-11, 2010.

II. Ritzmann TA, Rogers HA, Paine SML, et al.: A retrospective analysis of recurrent pediatric ependymoma reveals extremely poor survival and ineffectiveness of current treatments across central nervous system locations and molecular subgroups. Pediatr Blood Cancer 67 (9): e28426, 2020.

III. Wu J, Armstrong TS, Gilbert MR: Biology and management of ependymomas. Neuro Oncol 18 (7): 902-13, 2016.

IV. Messahel B, Ashley S, Saran F, et al.: Relapsed intracranial ependymoma in children in the UK: patterns of relapse, survival and therapeutic outcome. Eur J Cancer 45 (10): 1815-23, 2009.

V. Kano H, Yang HC, Kondziolka D, et al.: Stereotactic radiosurgery for pediatric recurrent intracranial ependymomas. J Neurosurg Pediatr 6 (5): 417-23, 2010.

VI. Bouffet E, Hawkins CE, Ballourah W, et al.: Survival benefit for pediatric patients with recurrent ependymoma treated with reirradiation. Int J Radiat Oncol Biol Phys 83 (5): 1541-8, 2012.

VII. Merchant TE, Boop FA, Kun LE, et al.: A retrospective study of surgery and reirradiation for recurrent ependymoma. Int J Radiat Oncol Biol Phys 71 (1): 87-97, 2008.

VIII. Kano H, Niranjan A, Kondziolka D, et al.: Outcome predictors for intracranial ependymoma radiosurgery. Neurosurgery 64 (2): 279-87; discussion 287-8, 2009.

IX. Lin YY, Wu HM, Yang HC, et al.: Repeated gamma knife radiosurgery enables longer tumor control in cases of highly-recurrent intracranial ependymoma. J Neurooncol 148 (2): 363-372, 2020.