NARRATIVE REVIEW

Consensus guidelines for the management of intracranial ependymoma for low- and middle-income countries

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Abstract

This paper presents comprehensive consensus guidelines for the management of intracranial ependymoma, neoplasms arising from ependymal cells in the central nervous system's ventricular system, in low- and middle-income countries (LMICs). Acknowledging the distinct epidemiological patterns of ependymomas, notably their higher incidence in paediatric patients, and variable survival rates, these guidelines emphasize tailored management approaches for different age groups. An expert panel, comprising specialists in neuro-oncology, convened to address gaps in diagnosis and management within LMICs, considering the varying clinical presentation based on tumour size and location. Emphasizing surgical intervention as the cornerstone of treatment, the guidelines also address challenges such as intraoperative bleeding and tumour location impacting complete resection. The role of molecular subgrouping in stratifying treatment and predicting prognosis is highlighted, alongside a careful consideration of radiotherapy timing, dose, and volume based on risk factors. Chemotherapy's role, especially in paediatric cases, is explored. The paper synthesizes current research and expert opinions, including the need for standardisation, genetic testing, and exploration of less invasive treatment modalities, to address the unique healthcare infrastructure challenges in LMICs. The guidelines also emphasize multidisciplinary teams, aiming to bridge the care gap between high-income countries and LMICs, and improve survival rates and quality of life for patients with intracranial ependymoma. This article serves as a valuable resource for clinicians, researchers, and policymakers in Pakistan and beyond, facilitating the development of evidence-based strategies in diverse healthcare settings.

Keywords: Nervous system, genetic, ependymoma, prognosis, ependymoma, surgery, radiotherapy.

DOI: https://doi.org/10.47391/JPMA.S3.GNO-17

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Introduction

Ependymomas originate from the ependymal cells lining the ventricular system in the central nervous system.[1] Ependymomas are more common in children, comprising 5.2% of all CNS tumours compared to 1.9% of adult CNS tumours.[2] Ependymomas in children are commonly found intracranially especially in the posterior fossa, whereas in adults they mainly affect the spinal cord.[1-3] Overall survival (OS) rate is significantly higher in adults compared to children with a 79% 10-year OS in adults, but it decreases in older adults 75 years and older with a 28% 10-year OS.[1, 2]

Methodology

The literature search of the high-quality data on intracranial ependymomas was done in March 2023 on different databases including PubMed, Google Scholar, Scopus, and Embase. The most relevant and high-quality studies were analyzed to develop the evidence-based recommendations. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in diagnosis and management of intracranial ependymomas within Pakistan. This group was tasked with identifying best-practice recommendations and their application within the context of Pakistan as one of the low- and middle-income countries (LMICs). Recommendations were collated and reviewed for utility and evidence-based practices in LMICs.[4]

Clinical presentation and evaluation

Clinical presentation of intracranial ependymomas varies depending on tumour location and size with global neurological symptoms in cases of obstructive hydrocephalus or focal symptoms due to local mass effect.[5] These mainly present with symptoms of headache,

gait disturbance along with hemiparesis and vomiting in children.[4] Ependymomas present with local growth, but their metastasis rate is low. Factors influencing survival in ependymoma patients include age, gain of chromosomal arm 1q, tumour location, gender, telomerase reactivation and molecular subgrouping.[5, 6]

Diagnostic workup

Diagnostic workup of ependymomas should be done through MRI with contrast enhancement of the entire neuroaxis and cerebrospinal fluid (CSF) cytology to identify disseminated disease.[1, 5]

The modality of choice for ependymoma diagnosis is MRI, which appears as a well-circumscribed mass lesion. To differentiate between other neoplasms and ependymomas in the posterior fossa, diffusion-weighted imaging is advised.[1] Ependymomas exhibit elevated choline and reduced N-acetylaspartate in MR spectroscopy and elevated cerebral blood volume in perfusion MRI.[1] An enhancing mass lesion with T1 hypointensity and T2 hyperintensity is indicative of ependymomas.[5] T2 hypointenstiy is also seen on cyst walls if there is cyst formation. CT scans can be useful in diagnosing subependymomas due to their calcification.[1]

Surgical management

Surgical management of ependymomas is the first-choice treatment of ependymomas. Gross total resection is linked with higher progression-free survival as well as overall survival compared to sub-total resection. [7] Surgical management with radiotherapy is advised for PF-EPN-A ependymomas for patients above 12 months of age. Follow-up surgery may be required for incomplete resection in the first procedure. 5 However, intraoperative bleeding and invasion into the basal ganglia and thalamus hinders total resection in surgical management. [8] Deep rooted and microinvasive ependymomas may require neuro-navigation and maximal safe resection should be the goal if the tumour cannot be resected completely. [8]

Surgical technique applied is dependent on tumour size and location. For the majority of ependymomas, gross total resection is preferred due to its greater prognostic value. Subtotal resection may be employed for ependymomas involving cranial nerves and the brainstem.[1] However, patients with subtotal resection have a higher chance of developing progressive disease.[9] Second-look surgery can be used for subtotally resected ependymomas.[8]

Histopathology

The 2022 WHO classification of CNS tumours classifies EPN according to a combination of histopathological and molecular features and anatomical site.[10, 11] The current classification lists EPN by anatomic site into supratentorial, posterior fossa and spinal. Supratentorial EPN can be further divided into those with ZFTA fusion, those with YAP1 fusion, or a "not otherwise specified [NOS]" group without any of these features. Similarly posterior fossa (PF) EPN is divided into group A (PFA) or PFB. Spinal tumours can feature MYCN amplification. Immunohistochemical surrogate of ZFTA fusion is L1CAM and that for PFA is loss of immunoreactivity for H3K27me[3]. If molecular subclassification is unfeasible or unsuccessful, the EPN should be classified by the anatomic site and is designated "not otherwise specified [NOS]". Histologically distinct types include myxopapillary ependymoma and subependymoma.[11]

Classic histologic features of EPN include true ependymal rosettes which are characterized by arrangement of tumour cells around a central canal with a lumen and an intervening 'nuclear-free zone'. More often, however, the tumour shows pseudo-rosettes which are marked by arrangement of tumour cells around blood vessels.[6, 10-12]

Myxopapillary ependymomas (MPE), are characterised by papillary structures encompassing areas that show myxoid degeneration and hyalinized blood vessels.[10, 13]MPE previously designated as WHO grade 1 are now considered grade 2 based on the presence of frequent recurrences in this entity. These most commonly arise in the spinal cord, predominantly in the region of the conus medullaris, the cauda equina or filum terminale.[14] Myxopapillary ependymoma WHO grade I is histologically characterised by cuboidal or elongated tumour cells forming fibrillary processes toward fibrovascular cores typically showing perivascular mucoid degeneration. Mitotic activity is low.[1, 13]

Other histologically distinct EPN variants such as papillary, clear cell or tanycytic ependymoma are no longer listed as discrete entities in CNS5. Mitotic activity is low while non-palisading necrosis may be present in a fraction of cases.[1]

Subependymoma is given a WHO grade 1, subependymoma, grade 2, while other EPN can be grade 2 or 3 based on histologic criteria. EPN can be assigned WHO grade 3 based upon the presence of anaplastic features including hypercellularity, increased proliferative activity including increased mitotic rate and/ or higher MIB1, and the presence of necrosis or microvascular proliferation. The current WHO classification does not specify a discrete criteria for grading of EPN and the utility of grading in EPN has been challenged.[10, 11]

Molecular pathology

Recent advances show that genetic markers play a major role in stratifying treatment and predicting survival in EPN.[7] Hence, where possible, molecular subgrouping should be performed as part of the routine histologic workup for EPN.

Two molecular subtypes of ependymomas that have been shown to have poor prognosis are PF-EPN-A ependymomas and ependymomas with fusions involving ZFTA/ RELA.[1, 15] The PF-EPN-A subtype mostly occurs in the cerebellum of young children, and although it does not exhibit recurrent genomic alterations, it is readily identified by a characteristic hypermethylation signature and/or an absence of H3K27me3 immunostaining in tumour cell nuclei.[16] Chromosome 1q gain has been associated with worse prognosis in PFA EPN. ZFTA fusion positive EPN are characterised by the presence of gene fusions involving the ZFTA gene (formerly known as C11orf95) causing increased NF-κB signalling. The most common fusion partner of ZFTA is RELA gene, hence this tumour was formerly called RELA fusion positive EPN. ZFTA EPN can be identified by the presence of positive staining for L1CAM. PF-EPN-B, ST-EPN-YAP1, molecular SE (PF-SE/ST-SE/SP-SE), and spinal molecular groups (SP-MPE, SP-EPN) are mainly associated with favourable prognosis.[5, 6, 11, 15, 17, 18]

Over 75% of ependymomas was reported to demonstrate ErbB 2 (Her2) and ErbB 4 co-expression; in addition, ligand-dependent activation of the ErbB receptor was found to trigger cellular proliferation in cultured ependymoma cells; therefore, the ErbB protein family would also be investigated as a therapeutic target in intramedullary ependymoma.[19]

DNA methylation profiling has emerged as a robust source for the reliable distinction of different brain tumour entities or the identification of clinically relevant subgroups within a specific tumour entity.[20, 21]

Radiotherapy

Surgery with maximum safe resection remains the mainstay of curative treatment for all children with Ependymoma. As a standard of care, postoperative radiotherapy is the standard of care in patients with high-grade ependymomas, patients who are unable to tolerate gross total resection, after incomplete resection and recurrence of tumour. Radiotherapy should follow surgical removal in patients with intracranial ependymoma WHO grades 2 or 3, regardless of the fact whether gross total resection is done or not.[1, 9, 15, 22, 23] This has been shown to locally control the tumour as well as increase the overall survival. The irradiation field depends upon neuroaxis findings, if CSF or MRI shows neural axis dissemination of disease then craniospinal irradiation is recommended otherwise localised radiation to operative /disease site is indicated.[7]

The timing, dose and volume of radiotherapy may affect overall survival, as well.[24] Current studies have suggested radiotherapy doses of 54-59.[4] Gy in 30-33 fractions @ 1.8Gy/fraction, five days a week in 6-6.5 weeks period as per risk of local tumour recurrence. Radiotherapy can be given to patients starting from 1 year of age. Patient who requires craniospinal irradiation usually receive radiation dose of 36 Gy /20 fractions @ 1.8 Gy/fraction followed by focal boost to postoperative bed/residual/gross disease up to 59.4Gy.[2, 7, 9, 14, 22] Recommended units of post operative radiotherapy with respect to age are shown below Shown in Table 1

RT is given to children with grade 2 in anaplastic spinal ependymomas, even if gross total resection has been achieved. 5 Adjuvant RT is also administered in myxopapillary ependymomas, without which the rate of recurrence has been shown to be high.

Role of radiosurgery is evolving and can provide benefit in term of local control in highly selected patients, however, it is not recommended as upfront treatment after surgery.[5, 17] Similarly, proton therapy is also emerging as new radiation treatment modality because of its reduced toxicity outcome due to its characteristic beam profile.[25, 26] All efforts should be made to deliver a useful dose to the target area and spare the normal CNS structures of these children. Peer review of radiation treatment planning and delivery remains crucial for maintaining quality of treatment.[27]

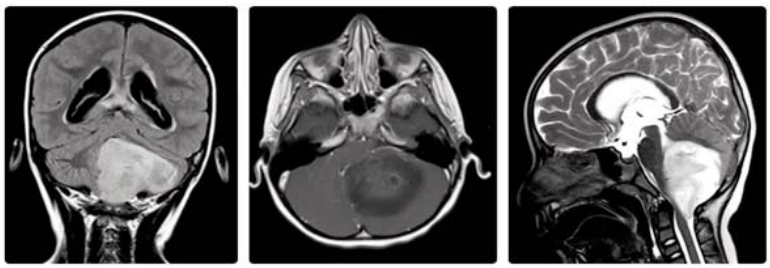
It is appropriate to conclude that Multidisciplinary approach involving all stakeholders including paediatric neurosurgeon, medical and radiation oncologist is essential component of comprehensive cancer care and peer review is crucial step in this critical process hence translating into maximum clinical benefit with minimal toxicity.[28]

Chemotherapy

Surgery and radiotherapy (RT) are the current therapeutic

Table-1: Units of post operative radiotherapy.

Age	Dose of Radiotherapy administered
12-18 months	54 Gy (1.8 Gy/fraction)
18 months or altered neurological status	54 Gy (1.8 Gy/fraction)
> 18 months	59.4Gy (1.8 Gy/fraction)



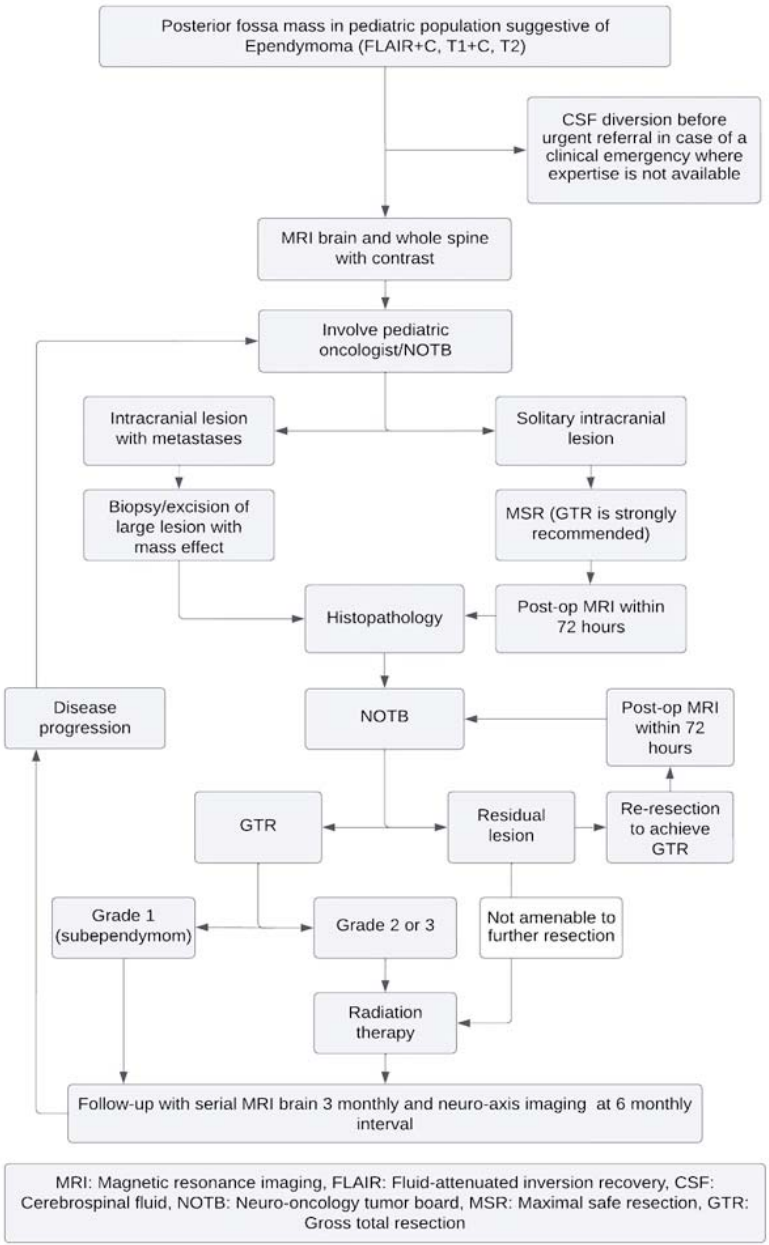


Figure-1: Management of intracranial ependymoma algorithm

mainstays for ependymomas, and the role of chemotherapy alone is not proven.[5] The role of chemotherapy in the management of ependymomas in young population is being investigated whereas its efficacy in adults is minimal7 In paediatric population, preoperative chemotherapy can sometimes be administered in adjunct to reduce the volume and vascularity of tumour.[8] Chemotherapy when used, is in patients with subtotally removed tumours, in already irradiated patients with inoperable recurrences and in children <12 months with ependymomas, due to the possible side effects of the chemotherapy due to the immature brain which can result in neurocognitive deficits over time.1, 2 Different regimens of chemotherapy include vincristine, cyclophosphamide, etoposide, platinum derivatives and methotrexate, but none of these have showed outcomes better than adjuvant radiotherapy.[7, 9, 24, 29]

Post-operative management and follow-up

Main therapeutic treatments are surgery and RT. Frequent neuroimaging along with clinical assessments is recommended.[5] For the first two years after treatment, MRI should be repeated after 3 months and from third to sixth year, it should be repeated every 6 months to monitor the progress and recurrence of tumour. This is also summarized in Table 2.

Table-2: Post-operative management and follow-up.

Year of tumour resection	Imaging (MRI)
First 2 years	Every 3 months
3rd-6th years	Every 6 months

Before resorting to radiotherapy, early second-look surgery can be proposed to achieve total removal in selected cases where an accessible tumour remnant is disclosed on postoperative MRI. A repeat MRI may be appropriate to confirm the diagnosis of tumour remnant before proposing second-look surgery.

The regular assessment of neurocognitive function, as well as monitoring quality of life, is also deemed necessary as part of the protocol. In cases where there is tumour recurrence after irradiation, histomolecular reassessment can be performed in order to rule out the formation of novel tumours, e.g., glioblastoma.[5] Recurrent STE is an indication of choice for reoperation. [8] Even when treated with additional radiation therapy, patients with subtotal resection remain at higher risk for disease progression. [7, 8] For spinal ependymomas, there can be tumour recurrence even after a decade, thus follow up

Table-3: Summary of Recommendations for Ependymoma.

Radiology	• Complete MRI brain and spine study is needed. • 'Minimum required' MRI brain protocol: o Imaging on at least 0.5T. o Sequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast enhanced T1. • Tumour location, tumour margins, enhancement pattern, tumour size, involvement of brainstem, and presence of hemorrhage/mineralisation. • Postoperative MRI is recommended in the first 48 hours after surgery. If delayed by 72 hours, then MRI should be delayed by 3 weeks but not more than 4 weeks. o To identify the extent of resection. o To have a baseline to compare successive imaging. o Not required after biopsy.
Neurosurgery	• Surgical goals: Resection of tumour and opening of the CSF pathway. • Gross total resection should be attempted where possible. However, in case of tumour adherence to the surrounding critical structures i.e. obex or floor of the fourth ventricle, maximum safe resection should be performed. • Abstain from VP shunt as a temporising procedure unless there is a significant risk of deterioration due to hydrocephalus. Consider referring the patient to a facility where surgical resection can be done along with CSF diversion if needed. • In case of delay in surgical intervention, CSF drainage (VPS or ETV) is recommended. • Redo surgery can be considered in case of recurrence/disease progression after risk stratification in NOTB.
Neuropathology	• Haematoxylin and Eosin (H&E) for histological typing. • The role of histologic grading is limited in EPN but should be rendered according to the degree of cellularity, proliferative activity (mitoses and Ki-67/MIB1 rate), the presence or absence of necrosis, and microvascular proliferation. • Immunostain L-1CAM to identify ZFTA fusion-positive supratentorial EPN and H3K27me to differentiate Posterior fossa A and B subtypes. Both stains are to be used as surrogates for molecular studies.
Medical Oncology	• Chemotherapy is not a mainstay of therapy and is not currently recommended.

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Radiation oncology	• Radiotherapy is recommended after STR, and in grade 2/3 tumours irrespective of extent of resection and after recurrence. • Recommended dose is 59.4 Gy @ 1.8 Gy/ fraction per day five days a week over 6.5 weeks. For children <18 months, the total dose will be restricted to 54 Gy.
Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology, and NOTB recommendations. • Serial MRI brain at 3 months, and Neuro-axis MRI at 6 months for two years then every 6 months for 3 years.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CSF: Cerebrospinal fluid, VPS: Ventriculoperitoneal shunt, ETV: endoscopic third ventriculostomy, NOTB: Neuro-oncology tumour board, EPN: Ependymoma, MIB1: Mindbomb Homolog-1, ZFTA: Zinc Finger Translocation Associated, STR: Subtotal resection, Gy: Gray.

can be done life-long.[4] Multi-disciplinary tumour board discussion are vital in decision making.

Miscellaneous/prognosis/quality of life

Overall, ependymomas have a generally decent outcome if resected completely 67 to 85% five-year survival rate versus the one with incomplete resection 30 to 50%. Progression free survival for five years is 43 to 64% and 24 to 53% for ten years.[1] With improvements in management of ependymomas, the survival rates have been increasing in the last decade. [24] Prognosis depends on multiple factors such as age, resection of tumour, and molecular subgrouping. Infants usually have a worse prognosis for ependymomas.[2] Extent of surgical resection is still the best depicter of prognosis with significantly better survival rate in gross total resection as compared to sub-total resection. [17]

Gaps in knowledge

There is still a need for standardisation of ependymoma management along with the utility of new and emerging techniques in molecular genetics. New research involving genetic testing and prognosis of ependymoma treatment is vitally important in assessing new treatment modalities in the future. Less invasive and procedures requiring less radiation especially in the children population is of immense importance to improve quality of life in patients with ependymomas.

Conclusion

Developed to support healthcare professionals working in resource-constrained settings, these recommendations provide a practical framework based on valuable expertise (see Table 3 and Figure 1). Implementing these guidelines has the potential to significantly improve specific outcomes and promote increased emphasis on teamwork in healthcare within low- and middle-income countries (LMICs) such as Pakistan.

Disclaimer: None.

Conflict of Interest: None.

Funding Disclosure: None.

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