NARRATIVE REVIEW

Consensus guidelines for the management of brain stem and diffuse midline glioma for low and middle-income countries

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Abstract

The understanding of brainstem gliomas and diffuse midline gliomas has significantly increased in the last decade. However, the management paradigm remains a dilemma. The critical location is the foremost factor dictating the outcome. Recent advancements in the field of neuro-oncology are pushing the boundaries of optimal care in the developed world nevertheless, the strategies in low- and middle-income countries (LMICs) need to be tailored according to the resources to improve outcome. The objective of these guidelines is to provide an algorithm-based management plan to cater challenges for healthcare providers in LMICs.

Keywords: Algorithms, brain stem, glioma.

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Introduction

Brainstem gliomas are glial tumours, divided anatomically and clinically into diffuse intrinsic pontine (DIPG), exophytic medullary, tectal, cervicomedullary, and focal gliomas. Genomic studies show that these tumours can broadly be divided into 3 molecular groups, namely: 1) histone mutant tumours with H3K27M mutation, 2) IDH mutant tumours, and 3) H3 wild-type and IDH wild-type tumours. Up to 2/3rd of all DIPG and non-pontine diffuse midline gliomas (DMGs) harbour a mutation in histone H3 genes wherein lysine 27 is substituted with methionine (H3K27M). Their aggressive behaviour, poorer prognosis, and a common mutation was the justified reason for grouping them as a separate entity.[1,2] Infratentorial/ brainstem IDH mutant gliomas are less common but likely under-reported due to the difficulty in diagnosis as most have non-canonical IDH mutations (which are not identified by IDH immunostain).

Brainstem gliomas make up only about 1-2% of adult malignant CNS neoplasms, however, they are more frequent in children.[3] DMGs are mainly found in pons, however, they can occur among any of the midline structures, including the brainstem, spinal cord, cerebellum, and thalamus.

Histologically, brainstem gliomas can be categorized into grades1-4, however recent studies show that molecular group (H3K27M, IDH mutant or H3-wildtype/ IDH-wild type) is a stronger predictor of clinical behaviour. Grade 1 is restricted to localized tumours without histologic or radiologic evidence of invasion into the surrounding brain. The signs and symptoms might range from cranial nerve impairments to long tract signs, as well as limb and trunk ataxia, depending on the location and degree of spread.[1, 4] DMGs are classified as WHO Grade 4 with even less than a year's survival.[1]

Factors predicting prognosis comprise poorly differentiated architecture, large size, tumour duration of more than 3 months, age 40 years or more, and low Karnofsky Performance Scale (KPS ≤ 70) are associated with a poorer prognosis.[4] Treatment options mainly include maximal safe resection, chemotherapy, and/or radiotherapy[4, 5,] however, we still find room in the literature for discussions on the best ways to treat these tumours, particularly in adults. Most of the literature on brainstem lesions comes from high-income countries and hence the treatment paradigm, cannot be applied to low-income countries (LMICs), where limited resources need to be aligned with the outcome. Here we formulated guidelines for brainstem and diffuse midline gliomas, supported by the evidence and working dynamics in LMICs

Methodology

The literature search of the high-quality data on brain stem and midline gliomas was done in March 2023 on different databases including PubMed, Google Scholar, Scopus, and Embase. The most relevant and high-quality

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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 brain stem and midline gliomas within Pakistan. This group was tasked with identifying best-practice recommendations and their application within the context of Pakistan as an LMIC. Recommendations were collated, reviewed and debated regarding utility and evidence-based practices, in a process that has been previously detailed.[6]

Epidemiology

The majority of cancer registries focus on histopathology, and the true incidence is unknown as biopsy is not usually recommended for the diagnosis of these tumours.[7] Even when recommended (to distinguish DMGs from DIPGs), it is rarely performed due to the critical location.[1]

Most LMICs lack well-established brain tumour registries. According to the most recent Central Brain Tumour Registry of the United States (CBTRUS) data from 2019, 4.4% of all gliomas are found in the brainstem.[8] The majority of paediatric brain tumour deaths are caused by diffuse pontine gliomas. [7]

Classification

Brainstem gliomas are classified into pontine, medullary, and midbrain gliomas based on the anatomical location, based on imaging features into diffuse and focal (less than 2cm, with no edema) tumours. The direction and size of the tumour, magnitude of brainstem involvement, growth pattern (intrinsic or exophytic), and presence of haemorrhage, necrosis, or hydrocephalus can be used to further categorise these tumours.[8]

Choux et al classified them as (1) diffuse intrinsic or exophytic; (2) focal intrinsic or exophytic, (cystic or solid); (3) dorsal or lateral exophytic, arising in the subependymal zone and growing into the fourth ventricle; and (4) cervicomedullary, excluding cervical cord tumours that respect the border of the medulla. [9]

In 2021, the DMG classification was further updated from 'DMG, H3K27M-mutant' to 'DMG, H3K27M-altered' to ensure that other alterations such as EZHIP protein overexpression are included as well which can better explain this entity, in addition to the previously recognized H3K27 mutations.[10]

Initial evaluation

Screening and prevention

Although gliomas are typically sporadic, they can be linked to a few familial diseases, including Turcot, Li-Fraumeni, Lynch syndromes, and neurofibromatosis type I. Neuroimaging is only performed during the early diagnostic work-up for screening. Unless new symptoms favouring an intracranial pathology emerge, repeat imaging is not advised. When counselling and testing unaffected relatives of glioma patients who are found to be carriers of germline mutations linked to gliomagenesis, clinical geneticists should be consulted. However, glioma growth cannot be halted in any known way.[11] It is important to use caution when having costly screening imaging for gliomas in LMICs.

Clinical presentation

A history and examination of patients help establish localizing signs and symptoms along with recognition of warning signs of neurological deterioration. In general, the progression of neurological signs and symptoms serves as an estimate of glioma growth, with fast-growing tumours causing symptoms merely weeks before detection and slow-growing tumours requiring years before diagnosis.[11] Duration of symptoms is more determinant of prognosis than symptoms themselves.[12,13]

The symptomatology depends on the location and extent of the tumour. Non-specific manifestations include fatigue and headache.[11] Diffuse gliomas, commonly called Diffuse Intrinsic Pontine Gliomas (DIPG) are aggressive tumours that produce widespread brainstem oedema. They frequently appear with brainstem syndromes that include cranial nerve deficits, ataxia, and long tract signs, isolated or combined. [12] Hydrocephalus and intra-tumoural bleeding have also been seen at presentation in some patients.[14] Diffuse midline gliomas H3K27M mutant is the most aggressive subtype. Symptoms correlate with compression of adjacent structures i.e. midbrain, pons, or thalamus.[1,15]

Focal tumours are typically low-grade, and have a protracted course before diagnosis. Oculomotor dysfunction or cerebellar signs are mainly seen with upper brainstem tumours, while the lower ones mainly present with lower cranial nerve deficits and long tract findings. Tectal tumours can expand and compress the aqueduct of Sylvius, which is when they produce neurological symptoms secondary to obstructive hydrocephalus. Tegmental ones can present with hydrocephalus and oculomotor paresis with or without associated long tract findings. In cases of medullary involvement, the patient may present with lower cranial nerve dysfunction (hoarseness of voice, dysphagia, or recurrent chest infections due to micro-aspirations and ataxia).

Cervicomedullary brainstem gliomas progress slowly. Two main syndromes, a medullary and a cervical cord syndrome, have been described. Medullary dysfunction may manifest as failure to thrive due to nausea, vomiting, or dysphagia, upper respiratory tract infection, dysarthria, and sleep apnoea. Chronic neck pain, cervical myelopathy with weakness and spasticity are the symptoms of cervical cord dysfunction.[16]

The Neurological Assessment in Neuro-Oncology (NANO) Scale can be used to document the neurological examination and Mini-Mental State Examination (MMSE) can be used to document the neurocognitive status of adult patients.[11]

Delayed diagnosis has been shown to drastically impact outcomes.[17] Limited access to healthcare, delayed referral to imaging, higher costs, and far-off hospitals all contribute to delay in diagnosis, however, the most important variable delaying diagnosis is delayed parental and physician recognition of symptoms. Another important delay occurs in the correct and early referral of patients to neurological specialists. Tumour characteristics and symptoms, like behavioural changes which are not very commonly found, are often overlooked. Low-grade tumours with subtle signs are frequently disregarded and not investigated. Therefore, it's crucial to raise awareness among patients, parents as well as physicians regarding the symptomology and the necessity to investigate accordingly.[18]

Confounding pathologies within the brainstem regions can be mistaken for brainstem glioma – adult patients with unclear radiological characteristics may benefit from further workup. CSF analysis and systemic imaging may be useful in ruling out metastasis to the CNS or demyelinating pathology. Global neuro-oncology collaborations can help low-volume centers in pre-operatively discussing cases with a neuroradiologist or experts with experience in CNS imaging for optimizing the clinical approach.

Diagnostic workup

The preferred diagnostic method is magnetic resonance imaging (MRI) both with and without contrast. An infiltrative T2/fluid-attenuated inversion recovery (FLAIR) high-signal lesion that occupies at least two thirds of the pons and frequently extends laterally into the cerebellum as well as vertically into the midbrain and medulla is the classic MRI picture. Contrast enhancement typically only accounts for 0–25 % of the tumour volume on average. Cysts are uncommon, however, necrosis can be present.[19]

Based on the MRI and location of the tumour, Choux et al classified brainstem gliomas into four main categories, and Yin L. et al further modified it as shown in Table.1 [9, 16]

CT is more frequently employed in developing nations because of its greater accessibility and lower costs; however, tissue differentiation and delineating tumour involvement require MR imaging. Diffuse brainstem gliomas are often seen as diffuse enlargements iso-dense to the brain parenchyma or have a lower density and may exhibit partial enhancement. Focal gliomas may present as an exophytic or expansile lesion with heterogeneous density and prominent enhancement. Early diagnosis can be done if displacement of the fourth ventricle and compression of the cisterns is appreciated.[20] Compared

Table-1: Classification of brainstem gliomas.

Diffuse	Intrinsic	Enhancing (T1- Hypointense, contrast-enhancing, T2- hyperintense)
		Non-enhancing(T1- Hypointense, non- contrast enhancing, T2- hyperintense)
	Exophytic	Enhancing (T1- Hypointense invading surrounding structures, contrast-enhancing, T2- hyperintense)
		Non-enhancing T1- Hypointense not invading surrounding structures, contrast-enhancing, T2- hyperintense)
Focal (Midbrain, Pons, or Medulla Oblongata (solid or cystic)	Intrinsic	Enhancing (T1- Focal hypointense, contrast enhancing, T2- Focal hyperintense)
		Non-enhancing (T1- Focal Hypointense, non- contrast enhancing, T2- Focal hyperintense)
	Exophytic	Enhancing (T1- Focal hypointense not confined to the brainstem, contrast-enhancing, T2- Focal hyperintense)
		Non-enhancing (T1- Focal hypointense not totally confined to brainstem, non- contrast enhancing, T2- Focal hyperintense)

Dorsal or lateral exophytic, Cervicomedullary.

to MRI, CT has a substantially poor sensitivity for detecting and planning surgical intervention. As repeat MRIs significantly increase costs, patients frequently donot get them done at regular intervals, which might result in missed diagnoses or missed relapses after intervention.[17] CT scans are not indicated for follow-up as it has poor sensitivity and can miss small recurrence.

Management of brainstem gliomas

Management of brainstem glioma requires a multidisciplinary approach that involves expertise from neurosurgery, medical oncology, radiation oncology, neuroradiology, and neuropathology, along with nursing and supportive care services to exchange ideas and define an optimal treatment plan. Studies have shown that it improves clinical outcomes and patient satisfaction hence it is highly recommended to discuss each case in a multidisciplinary neuro-oncology tumour board meeting before embarking on any treatment plan.

Surgical management of brainstem gliomas

Careful patient selection is key to the successful management of brainstem gliomas. The main aims of surgery are: controlling raised intracranial pressure, providing tissue for histopathology, and decreasing the maximum possible tumour burden to improve neurological outcomes.[21] For diffuse brainstem gliomas, surgical intervention is not recommended. Tumours arising in the ventral midline pons are a common hallmark of diffuse, inoperable brainstem gliomas .T1-T2 inequality (T1 abnormality is volumetrically inequivalent/differing from the T2 signal), visibility of crossing pontine fibers, and symmetric encasement of the basilar artery are distinguishing radiological findings. [5]

For other brainstem gliomas like focal brainstem gliomas, the role of surgery and the surgical entrance point remains controversial. Usually, early surgery before the development of neurological complications, with maximal safe resection using intra-operative neuromonitoring is indicated. Tumours are most commonly approached via the posterior fossa in the prone position.[16] Since focal midbrain tumours are often indolent, they are typically treated conservatively; in the event of hydrocephalus, an endoscopic third ventriculostomy (ETV) should be performed. In LMICs, where access to specialized centres for multidisciplinary team and surgical expertise to perform specialized procedures like ETV are limited, CSF diversion such as ventriculoperitoneal (VP) shunt and then urgent referral should be considered. Implementing a one-on-one approach between referring and referred physicians significantly minimizes the risk of delayed care. Personal and individualized strategy is also appropriate to link specialised physicians for a multidisciplinary team, especially in LMICs where a structured team approach is lacking.

Resection is necessary if the tumour increases in size, or if it occupies a significant portion of the midbrain and pineal region. A biopsy is advised at the point of tumour progression to best determine treatment for tumour recurrence. Serum concentrations of α fetoprotein, β human chorionic gonadotrophin, and placental alkaline phosphatase can be used to identify the few non-germinomatous germ cell tumours. Biopsy may also be done in such cases while doing ETV. Focal tumours of the tegmentum also may be amenable to resection.[16, 21] Maximum safe resection of focal or exophytic pontine, medullary, and upper cervical spine tumours can considered for symptomatic, extra-axial components. Intrinsic brainstem lesions are generally non-operable and considered the significant postoperative morbidity, except focal, benign gliomas where surgical intervention needs careful consideration.[16]

Surgical management of diffuse midline gliomas

The brainstem, thalamus, and spinal cord are crucial structures and surgical resection here can lead to neurological problems that may be irreversible. Resection is not a viable option, with biopsy only considered in cases where the radiological diagnosis is unclear.[1]

For pontine and extrapontine DMGs, different recommendations and patient counselling may apply. Thalamic tumours have been shown to have improved survival outcomes following maximum safe resection when treated with superior facilities like MRI, neuronavigation, and/ or intra-operative neuromonitoring.[22] For spinal cord DMGs, the aim should be to achieve maximal safe resection. Thalamic and spinal cord DMGs have better prognoses than pontine DMGs, thus MSR is recommended.[23] Surgery is contraindicated for diffuse midline pontine gliomas [5]

Second surgery

Second surgery can be offered if there is delayed, recurrent growth of the tumour with new neurological symptoms, or if the resection had to be stopped prematurely on the initial attempt because of the transient intra-operative deficit.[16] These should be discussed in a multi-disciplinary tumour board weighing pre-operative functional status and goals of care for the patient.

Pathologic sssessment

DMG can be broadly classified into H3K27 altered, IDH mutant, and histone-wt, IDH-wt astrocytomas. DMG is usually reserved for astrocytic tumours with diffuse histology and should be distinguished from circumscribed gliomas such as pilocytic astrocytoma, and glineuronal tumours such as gangliogliomas amongst other tumours. Histologically these tumours can be graded from 1-4 with grade 1 reserved for circumscribed/ non-diffuse tumours. The role of histologic grading remains controversial as molecular features such as the presence of histone mutations often trump histologic grading.[9]

Grade 1 lesions (such as pilocytic astrocytoma and ganglioglioma) are uncommon, are histone and IDH wildtype and show better outcomes than diffuse tumours with these alterations. These tumours can be seen to occur throughout the brainstem, including the tectum of the midbrain, focally within the pons, or at the cervicomedullary junction where they are frequently exophytic. Diffuse tumours can be graded grade 2-4 depending upon the presence of proliferative index, i.e. mitoses and Ki67/ MIB1 count (grade 2 vs. 3), necrosis, and microvascular proliferation (grade 3 vs. 4)[24, 25]

Surrogate immunohistochemical markers can be used to identify H3K27M, BRAF V600E, and IDH1 R132H mutations. Tumours without these alterations require more molecular testing[26,] which remains expensive and difficult to perform and therefore largely out of reach of LMICs. Depending upon clinical need, selected cases may be sent to HIC centers with molecular analysis capacity.

Radiotherapy

The aims of radiation therapy (RT) range from the relief of neurological symptoms in diffuse intrinsic gliomas to the complete removal of any remaining tumour after subtotal resection of focal tumours. Since surgery cannot be done for diffuse intrinsic pontine gliomas, radiotherapy is the mainstay of treatment, as chemotherapy has not yet demonstrated a substantial benefit. Although there may be some neurological improvement, there hasn't been any discernible difference in the patient's prognosis and survival. [7] The conventional median dose of radiotherapy is 50–55 Gy, using fractions of 1.8–2 Gy continuously for five days a week.[27] Ideally, the RT should begin within 1 week of diagnosis, and steroids may be used to manage life-threatening symptoms while waiting for RT to begin especially in LMICs where it might take longer. As a general rule, the treatment volume of the radiation field should enclose all the disease sites, called gross total volume (GTV) plus a margin of 1-2 cm (1 cm for low-grade and 2 cm for high-grade tumours) to incorporate microscopic disease.[21] For high-grade gliomas, GTV typically includes contrast-enhancing areas visible on the T1 contrast sequence of MRI and for low-grade gliomas, GTV is represented by hyperintense signal areas lesions seen on T2-weighted, FLAIR sequence of MRI.[1] It is important to remember that the majority of the time both patterns have been found on MRI due to heterogeneity of tumour population, hence, a careful review by a neuro-radiologist is crucial to delineate target volume adequately. In addition, a margin of 3-5mm is needed to incorporate daily setup variation according to individual institute data. Conventionally, fractionated RT is typically administered over 6 weeks with a total dose of 54-60 Gy at 1.8 – 2 Gy fraction with 3D conformal or IMRT/ VMAT techniques. In addition, peer review of radiation treatment plans at every level is an integral and essential tool of quality assurance programs and literature has shown its direct impact on clinical outcomes and patient care therefore it is highly recommended to be a part of every radiation therapy service.[28] Numerous clinical trials have compared conventional radiotherapy to altered fractionation schedules such as hyper- and hypofractionated radiation therapy however they failed to show any advantage as compared to the conventional radiation treatment. However, in a patient with poor performance status, a hypofractionated schedule emerges as an alternative approach with comparable clinical outcomes without significant toxicity.[29] The guidelines of RT are the same for diffuse midline gliomas as for diffuse brainstem gliomas. Re-irradiation in the case of tumour recurrence or progression is a highly challenging situation that requires careful patient selection and rigorous peer review of radiation treatment planning and should be considered in a center having expertise and supportive care services available. The role of stereotactic radiosurgery in the management of brainstem gliomas is evolving and should be only considered in the context of clinical trials as we do not have a good amount of literature on the side effects of RT.[30]

Chemotherapy

As per most of the studies, chemotherapy hasn't been proven to be very effective in brainstem gliomas. Most of these tumours do not contain MGMT promoter methylation, making temozolomide and other chemotherapeutic agents ineffective.[26, 27]

Post-operative management

Based on the tumour location, the degree of the resection, and the surgical technique, post-operative neurological impairments (temporary or irreparable) may

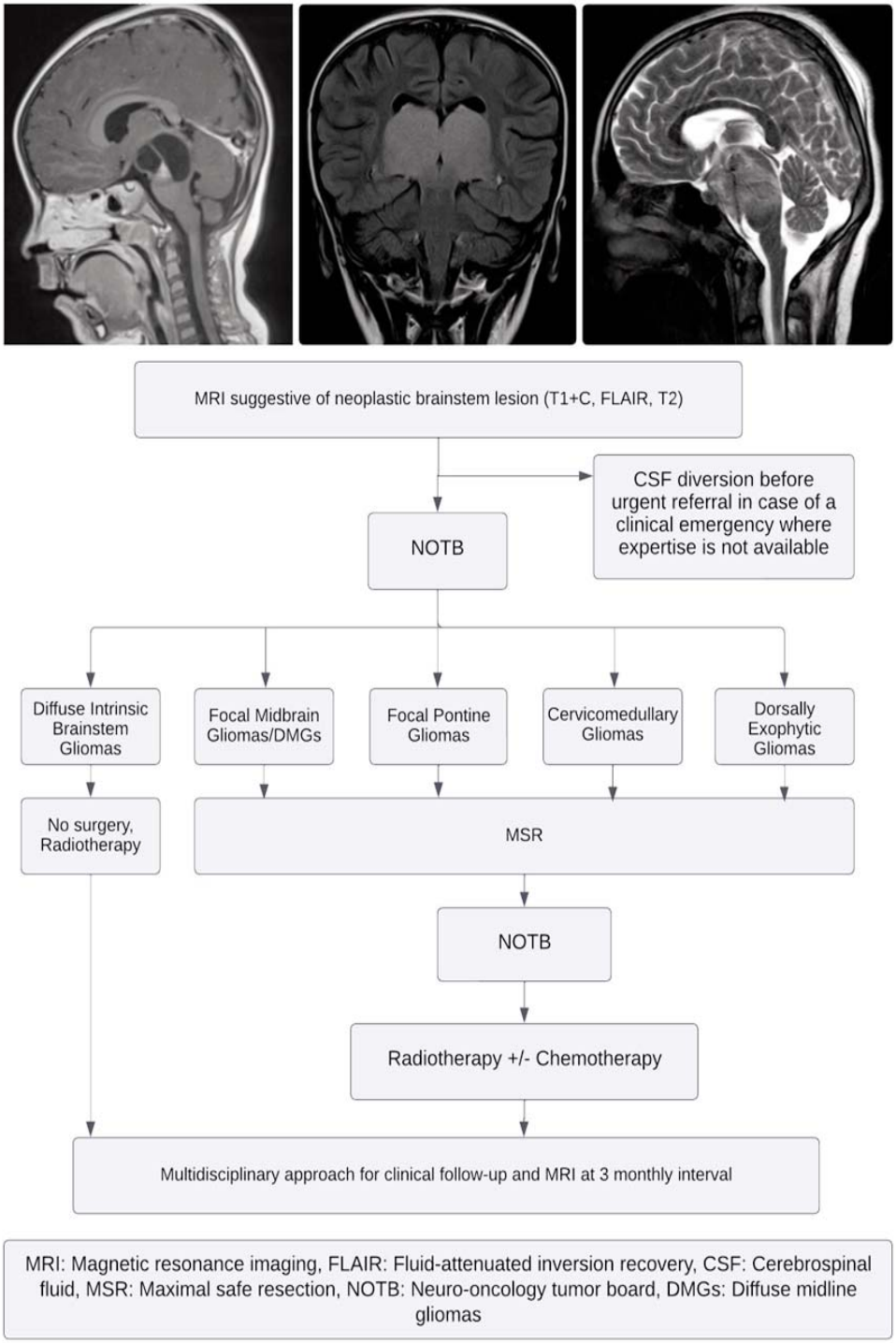

Figure-1: Management of Brain stem and diffuse midline glioma algorithm.

Table-2: Summary of Recommendations for Brainstem and Diffuse Midline Glioma.

Radiology	• MRI brain with and without contrast. • 'Minimum required' MRI protocol: • Imaging on at least 0.5T. • Sequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast enhanced T1. • Tumour location, tumour margins, enhancement pattern, tumour size, relation with critical neurovascular structure, and presence of haemorrhage/mineralization must be included. • Postoperative MRI is recommended within 72 hours of surgery. If delayed, then MRI should be performed after 6 weeks. o To identify the extent of resection. o To have a baseline to compare successive imaging. o Not required after biopsy.
Neurosurgery	• The main aims of surgery are: controlling raised intracranial pressure, providing tissue for histopathology, and decreasing the maximum possible tumour burden to improve neurological outcomes. • The extent of resection depends on the tumour location and cranial nerve involvement within the brainstem. • Surgery is contraindicated in diffuse intrinsic brainstem gliomas. • Maximum safe resection with intra-operative neuromonitoring should be achieved wherever possible. • Maximum Safe Resection is preferred for DMGs, or at least biopsy is preferred where surgical resection is not possible.
Neuropathology	• Haematoxylin and Eosin (H&E) slides for histological typing. • Immunohistochemical stains GFAP, Olig-2, p-53, IDH1 R132H, Ki-67 (proliferative marker), H3K27M to possible definite characterization.
Medical & Radiation Oncology	• Radiation is the therapy of choice in diffuse intrinsic brainstem gliomas and diffuse midline gliomas. • Dose: 54 Gy in 30 fractions at 1.8 Gy per fraction or 39 Gy in 13 fractions at 3 Gy per fraction depending upon the availability of radiation service and the patient's performance status. • Radiation treatment shall be started urgently after a decision for radiation therapy has been taken in the neuro-oncology tumour board. • Chemotherapy can be considered after discussing in NOTB.

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Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology, and NOTB recommendations. • Clinical follow-up with MRI every 3 months.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, DMGs: Diffuse midline gliomas, GFAP: Glial fibrillary acidic protein, TP53: Tumour protein 53, IDH: Isocitrate dehydrogenase, Gy: Gray, NOTB: Neuro-oncology tumour board.

manifest. Cranial nerve deficits vary with the tumour location. Transient diplopia due to internuclear ophthalmoplegia can occur if surgery is done within the pons. Ophthalmologic therapy with specialized eyeglass prisms may be required for persistent diplopia. Facial nerve injury can cause facial palsy and corneal abrasions due to problems with eye closure. Lower cranial nerve damage can lead to severe dysphagia, vocal cord paralysis, and loss of gag and cough reflexes. Aspiration and recurrent pneumonia can occur because of this. Thus, proper post-op swallowing evaluation is mandatory. In case of medullary involvement of the tumour, the patient is left intubated for at least 48-72 hours and is only weaned off after 24 hours of stable respiratory drive. Due to these reasons, tracheostomy and feeding tube placements are often planned in these patients.[16] Limited access to resources like speech therapist, occupational therapist, nursing care, and rehabilitation care in low- and middle-income countries can significantly hinder post-op patient care. Therefore, Emphasizing the significance of safe surgery and preservation of neurological functions cannot be overstated in resource-limited settings for better quality of life.

The cornerstone of the management of brainstem and diffuse midline gliomas is a multidisciplinary approach, as it is with all brain tumours. To correctly diagnose and effectively manage these illnesses neurosurgeons, medical and radiation oncologists, paediatric oncologists, histopathologists, and radiologists collaborate on tumour boards.[17] Virtual tumour board meetings have been adopted at a few centres and can help manage complex interdisciplinary cases in centers with lower volume or limited resources. This might help to significantly decrease mismanagement and treatment delays. In LMICs, virtual tumour boards can potentially revolutionise the management paradigm for these complex cases without adding a significant financial burden.

Prognosis and follow-up

The prognosis is poorer in children than in adults. Children mostly have high-grade gliomas while adults have low-grade disease. The mean survival of diffuse

intrinsic low-grade gliomas ranges between 4.9 to 7.3 years, and they are slow and progressive. High-grade gliomas, especially the diffuse intrinsic forms, have an extremely dismal prognosis and have an average lifespan of under 2 years. Following ventriculoperitoneal shunting and, in some cases, focussed radiation, focal tectal gliomas have been linked to extended overall life (over 10 years). Other brainstem gliomas also have good outcomes. DMGs of the thalamus and spine have a much better prognosis with longer survival than pontine gliomas.[23]

In addition to the tumour's prognosis, the lack of a clear treatment protocol, limited funding, delayed referrals, financial constraints, and poor accessibility to healthcare in low- and middle-income countries further contribute to overall worse outcomes than in developed nations.[31] Unfortunately, these delayed diagnoses and referrals have a major negative impact on immediate post-operative outcomes. Progress has been made to reduce surgical morbidity with neuro-navigation and stereotactic biopsy techniques. An appraisal of local and patient-specific financial constraints is needed before recommending treatment protocols, considering the need for further follow-ups, investigations, and supportive care.[32]

Regular follow-ups in 3-6 months shall be done for observation, and to look for the development of any post-op neurological deficits. Follow-up with a repeat MRI brain with contrast must be done in case of the development of new neurological symptoms.[16, 27]

Patients with neurological morbidity significantly benefit from rehabilitation care which is significantly lacking in many LMICs. Postoperative cranial nerve dysfunction, ataxia, incoordination, and other neurological deficits limit patients' functionality. For these patients, motor learning through repetitive practice of focussed tasks is a beneficial strategy for promoting plasticity and obtaining optimal performance.[33]

Gaps in knowledge

Surgical management has significantly improved with stereotactic access to the midbrain for decreased morbidity for biopsy. The utility of diffusion tensor imaging (DTI) for white matter tracts is still debatable within the midbrain and requires greater analysis of complex connections within the region.[34] Mutational analysis of the H3 histone gene provides greater insight into biological and morphological differentiation of paediatric brainstem gliomas from classical adult glioma. Global hypomethylation of H3K27 is posited to be a significant epigenetic driver for DIPG gliomagenesis. H3.3 and H3.1 variants of this gene may be oncogenic drivers for brainstem gliomas, however, the origins are still unknown. Other somatic mutations such as ACVR1, PDGFRA, ATRX, and TP53 are being studied to look for any role in their development and proliferation.[35] Potential therapies to restore baseline levels of methylation of H3K27 may be a solution; the demethylase inhibitor GSKJ1 has been shown to increase cancer cell apoptosis in pre-clinical models. Similarly, immune checkpoint inhibition is being investigated as a solution. Anti-PD1 drugs have yet to show a significant benefit in retrospective analysis with ongoing clinical trials for anti-PD1 monoclonal antibodies.[36] Pre-clinical and efficacy trials are also looking into CAR-T cell therapy for brainstem gliomas.[37]

Despite significant strides in treatment opportunities for brainstem gliomas in high-income countries (HICs), these benefits will not easily translate to countries with limited resources for neuro-oncology services. Greater uptake of newer therapies may lead to price reduction and cost-effective solutions, however, it is difficult to ascertain future impact at this time.

Conclusion

These guidelines serve as a practical roadmap based on valuable experience (Table 2 and Figure 1) and are designed for physicians working in resource-limited settings. Their implementation has significant potential to improve focused outcomes and aims to nurture a stronger emphasis on multidisciplinary care within LMICs, such as Pakistan.

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