NARRATIVE REVIEW

Consensus guidelines for the management of adult high-grade gliomas for low- and middle-income countries

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Abstract

High-grade glioma (HGG), a formidable and often incurable disease, presents an even greater challenge in low- and middle-income countries (LMICs) where resources and medical expertise are scarce. This scarcity not only exacerbates the suffering of patients but also contributes to poorer clinical outcomes. Particularly in LMICs, the underrepresentation of the population in clinical trials and the additional hurdles posed by financial constraints underscore an urgent need for context-specific management strategies. In response, we have rigorously evaluated recent guidelines from leading medical societies, adapting them to suit the specific needs and limitations of the local context in Pakistan. This effort, undertaken in collaboration with local physicians, aims to provide a comprehensive, standardised approach to diagnose, treat, and follow-up with HGG patients. By focussing on the best available clinical evidence and judicious use of limited resources, we strive to improve patient care and outcomes in these challenging settings.

Keywords: Patient care, societies, medical, physicians, glioma, brain tumour,

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Introduction

Gliomas account for about 80% of all central nervous system (CNS) and malignant brain tumours.[1] These tumours are further divided into astrocytoma and oligodendroglioma. The grade attributes clinical prognosis. Histologically, an increased proliferative index, anaplasia, necrosis, and microvascular proliferation delineate high (3 or 4) from low (1 or 2) grade glioma as per WHO 2021 classification.[2] Molecular analysis for isocitrate dehydrogenase (IDH), TERT promoter mutations, EGFR gene amplification, and combined gain of entire chromosome 7 and loss of entire chromosome 10 have recently been incorporated for the grading system. [3]

High-grade glioma (HGG) is the most common primary CNS tumour, with an annual incidence ranging from 5-10 per 100 000 populations.[4-5] Incidence increases with age; the mean age for grade 3 gliomas is 40 to 64 years, while grade 4 is more common in the elderly aged 75 to 84 years.[5-6] Over the last decade, the understanding of HGG, primarily due to the widespread use of next-generation sequencing, has lead to the evolution of diagnostic and therapeutic recommendations.[7] Although minuscule but progressively increased survival is attributed to the implementation of the Stupp regimen that serves to be the current standard of care.[8,9]

The survival outcome of HGG in low to middle-income countries (LMICs) is comparable to those in high-income countries (HICs).[10] However, the limited literature, absence of clinical trials, and high treatment costs highlight the health care disparities that exist on practical grounds. A significant number of individuals forgo seeking medical care at various stages, including before seeking care, during treatment and after treatment, which contributes to a substantial proportion of dropouts, skewing the reported outcome. It is ascribed to a lack of awareness, delayed medical attention, prolonged waiting time, lack of specialised facilities, and financial constraints.[11–15] These limitations, along with a lack of consensus among physicians regarding the treatment algorithm, potentiate the fallout.

The dire need for practical guidelines that could include LMICs' limitations without significantly compromising the outcome, is the way forward for managing HGG. We proposed these guidelines by incorporating the most up-to-date evidence-based practices and reflecting the unique challenges faced by patients and healthcare providers.

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Methodology

The literature search of the high-quality data on high-grade gliomas was done 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 HGG 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.[16]

Initial evaluation

Clinical presentation of brain tumours varies, with symptoms ranging from headache to neurological deficits, depending on tumour location, size, and disease extent. The most common symptoms include headache (50-60%), seizures (20-50%), and focal neurological deficits (20-40%) such as memory dysfunction, motor weakness, visual impairment, speech deficit, and cognitive or personality changes.[1,17-19] A comprehensive physical, neurological, and systemic examination is crucial. Factors like being elderly, rapid disease progression, short disease history, and complicating conditions such as an immunocompromised state or a history of cancer are important in differential diagnosis, potentially indicating conditions like metastasis, lymphoma, or bacterial and fungal abscesses. In LMICs, where cost is a major concern, thorough history-taking and clinical examination are key in guiding diagnostic investigations.

MRI is the gold standard for diagnosing HGG. The standard MRI protocol for brain tumours includes T1 and T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences, with and without gadolinium-based contrast.[20] HGGs are hypointense on T1 and show heterogeneous post-contrast enhancement, while being hyperintense on T2 and FLAIR sequences, regardless of histological grade. Glioblastomas typically exhibit central necrosis with irregular rim enhancement, while oligodendrogliomas may have internal calcification. HGGs often cross the midline, especially glioblastomas. Advanced imaging techniques like diffusion-weighted imaging (DWI), Apparent diffusion coefficient (ADC), perfusion scans, and MR spectroscopy provide additional information but usually don't alter management plans significantly, making them optional for cost containment. These features are crucial in challenging diagnoses, such as differentiating recurrence from radiation necrosis or distinguishing HGGs from abscesses or lymphomas.

In cases of suspected HGG, a multidisciplinary approach is essential for management. In LMICs, however, such multidisciplinary teams and tumour boards are often lacking. Surgeons typically receive initial referrals. Relevant history and imaging usually help rule out other differentials like metastatic lesions, making surgical excision the primary intervention. For complex cases, consultation with a Neuro-Oncology Tumour Board (NOTB) is advised before surgery. Post-surgery, cases should be discussed in the NOTB, involving a team of neurosurgeons, neuroradiologists, oncologists, and palliative care physicians. This multidisciplinary discussion is vital for a holistic approach to improve patient outcomes.

Management

Quality of life, overall survival, and progression-free survival are key outcomes in HGG treatment. In LMICs, the quality of life is especially critical due to financial constraints and limited healthcare resources, impacting both patients and the wider community. Treatment strategies in LMICs need to address these challenges when dealing with incurable diseases.

The typical treatment for HGGs involves maximal safe tumour resection followed by chemoradiotherapy. However, in LMICs, factors like low literacy, underdeveloped healthcare systems, and economic issues often lead to delayed medical intervention. Many patients present at advanced disease stages where effective surgery is not feasible, or they have comorbidities complicating treatment. While age is a known predictor of poor outcomes[21], recent surgical advancements are improving prospects for older patients, though these are less evident in LMICs.[22] Here, a conservative approach focussing on quality of life is often preferred over treatments offering minimal survival benefit. For such patients, alternative or palliative care may be more suitable.

Surgical intervention decisions for HGG patients should be based on a multifactorial assessment. Important considerations include Karnofsky Performance Status/Eastern Cooperative Oncology Group (ECOG) performance score, tumour location and extent, and patient frailty. This approach aims to balance survival extension with quality of life maintenance, a crucial consideration in resource-limited settings.

Surgical adjuncts

The field of glioma surgery has advanced significantly in

recent years with the development of surgical adjuncts and microsurgical techniques. These advancements have allowed for the maximal safe resection of tumours while minimizing morbidity by preserving eloquent areas. Neuronavigation, functional MRI, tractography, intraoperative MRI and ultrasound, somatosensory evoked potentials, electrocorticography, and fluorescence-guided resections, are readily available in specialized Centers and, when combined with awake craniotomy, have added a new milestone in glioma surgery. However, the availability of these advanced surgical tools remains limited in LMICs, primarily due to their high cost. Therefore, it is strongly recommended that centres catering to neuro-oncology cases in LMICs equip themselves with at least any affordable magnification (preferably a microscope), intraoperative ultrasound, and an anaesthesia team capable of performing an awake craniotomy. The implementation of these tools in LMICs could lead to several benefits, including reduced hospital stays and overall costs.[23-24] Additionally, the use of these surgical adjuncts and microsurgical techniques, in conjunction with awake craniotomy, allows for early postoperative neurological evaluation, speedy recovery, and minimized hospital stay, making it particularly beneficial in developing countries.[23, 25, 26] By broadening the extent of maximal safe resection while minimizing morbidity, these tools have the potential to significantly improve outcomes for patients with gliomas in LMICs

Surgical objective

The objectives of surgical intervention are:

1. Cytoreduction

2. Relieving of mass effect and reduction of ICP

3. Obtain adequate tissue for histopathological and molecular analysis

Overall survival (OS) and progression-free survival (PFS) of the patients with HGG correlate with the extent of resection.[27] Resection of at least 97% of the lesion or more tends to increase the overall survival.[28] The concept of supra-marginal resection (SMR) has recently been popularized over gross total resection in low-grade glioma, however, in HGG the evidence is still evolving.[29] However, the importance of preserving eloquent areas and hence the functional capacity of an individual dictates the extent of resection.

With the use of basic surgical adjuncts like navigation systems and ultrasound, along with deep anatomical knowledge and capacity for awake craniotomy, outcomes are comparable in terms of the extent of resection, quality of life, and overall survival.[30, 31] A neurosurgeon working in an LMIC must be trained enough to predict the extent of resection considering the location of the lesion and hence the goal of surgery. Immediate post-op MRI is obligatory to document the extent of resection, and intra-operative assessment is often overestimated and should not be considered. We recommend maximum safe resection of the lesion.

Supra marginal resection (SMR)

Gross total resection of enhancing lesions along with any resection of non-contrast-enhanced disease is referred to as SMR.[32] SMR may be considered in cases where the lesion is small and situated in non-eloquent areas of the brain. Right frontal and right anterior temporal lesions are identified as non-eloquent areas amenable to SMR.[31] A number of methods have been identified such as resection of FLAIR signals beyond enhancing areas, anatomical resection through normal white matter, and fluorescence-guided resection beyond gross tumour visualization.[32] SMR for glioblastoma GBM has been established as a crucial approach that provides a significant overall and progression-free survival advantage to eligible patients.[29, 33, 34]

Gross total resection (GTR)

It is defined as the complete excision of a contrast-enhancing lesion. GTR is an ideal extent of resection in a significant number of patients. The literature highlights the crucial role of GTR as a favourable prognostic factor, independent of other factors that can affect the patient's outcome. This finding has been consistently reported in several other series in the relevant literature.[35]

Partial resection (PR)

Any resection more than a biopsy but not achieving GTR is considered PR. GTR is not advised in lesions involving eloquent areas, major white matter tracts, and deep brain nuclei, hence maximum safe resection is an ideal approach for such lesions. Partial resection, irrespective of the size of the residual lesion, does increase overall survival.[36] This effect is subtle, only adding a few months in HGG compared to LGG. With molecular advancement and their role in glioma outcome, partial resection is linked with better overall survival in patients with MGMT-unmethylated IDH-wild type glioblastoma compared to biopsy alone.[37]

Biopsy

In patients with extensive, multicentric, or multifocal disease, advanced age, poor functional status, and high surgical risk, a biopsy is a recommended course of action. However, it is crucial to minimize potential sampling

errors. Typically, a biopsy is planned for contrast enhancing areas. Extent of resection, presenting KPS, age, MGMT methylation status all play a significant role in the outcome of multifocal glioblastoma.[38]

Post-operative follow-up

First post-op MRI with and without contrast is recommended within 72 hours of surgery for any extent of intra-op resection.[39] This is meant to distinguish post-surgical contrast enhancement from residual tumour and serves as a baseline for future disease progression and response to adjuvant therapy. Lesions where only a biopsy was taken, do not require immediate post-op MRI. The extent of resection on post-op MRI in high-grade glioma is distinguished with contrast enhancement. However, tumour cells are infiltrated beyond contrast-enhancing boundaries and FLAIR hyperintensities are as important and need to be followed.[40, 41] The cost of MRI is a potential factor and its significance has frequently been overshadowed in comparison to the cost. The potential of low filed MRI can be explored as a cost cutting strategy specially in LMICs.[42]

Lost-to-follow-up; is one of the major dilemmas in the management of tumour patients in LMICs. Surgeons, as the first in line for patients' care, need to take responsibility till the oncologist takes over. All patients must be presented to the NOTB within a week of surgery.

Histopathology

Histopathology is essential in oncology diagnostics and management, including determining chemo and radiotherapy strategies. Surgeons must correctly handle biopsy or resection specimens, typically placing them in 10% formalin and promptly sending them to the pathology lab at room temperature. These specimens, ideally no less than 0.5 cubic cm, undergo various processing steps like dehydration, de-rigidification, and staining with Haematoxylin and Eosin (H&E) preparation. A separate fresh specimen can be sent for intraoperative consultation. Pathologists provide rapid assessments within 20-30 minutes, identifying specimen adequacy and characterizing the tumour type, aiding in immediate surgical decision-making.

Tumour grading involves evaluating mitotic rate, necrosis, and microvascular proliferation. Specific criteria vary by tumour type; for instance, oligodendroglioma needs over 5 mitoses per 10 High-Power Fields (HPFs) for a grade 3 designation, unlike astrocytoma which requires fewer mitoses. Following morphological analysis, immunohistochemical stains are used to determine lineage (like astrocytoma vs. oligodendroglioma using ATRX and P53 stains), proliferation rate (using Ki67/MIB1 stain), and oncogenic drivers (IDH1,2, H3 K27M, BRAF V600E, etc.). These biomarkers are crucial in diagnosis and prognosis determination.

While next-generation sequencing and DNA methylation analysis are gold standards in molecular tumour analysis, they remain expensive and less accessible, particularly in low- and middle-income countries (LMICs). Immunohistochemical surrogates for molecular alterations, such as IDH1 R132H, BRAF V600E, H3 K27M, and H3 G34R/V, are used instead, boasting over 90% sensitivity and specificity and utilizing existing lab infrastructure.[43] Additionally, markers for mismatch repair (MMR) genes can identify MMR in over 80% of cases of Lynch syndrome and constitutional mismatch repair defect.[44] The adoption of these surrogate markers is recommended until more affordable molecular techniques are widely available.

Adjuvant treatment

Concurrent chemoradiotherapy (CCRT) is essential in managing high-grade gliomas (HGG). To mitigate the risk of residual disease and recurrence, it's recommended to start chemoradiotherapy within 6 weeks post-surgery. Initiating treatment earlier than 3 weeks may be harmful. Thus, a 6-week delay is advised.[45, 46]

The standard protocol involves administering radiotherapy (XRT) with concurrent Temozolomide (TMZ), followed by monthly TMZ cycles from day 1 to 5 every 28 days, continuing until disease progression or the onset of unacceptable toxicities. Post-gross total resection (GTR), adjuvant TMZ for 6 months is advised for glioblastoma, as per the Stupp trial. For Grade III Oligodendroglioma or Astrocytoma, adjuvant monthly TMZ is recommended for 12 months.[47] Alternatively, a PCV (Procarbazine, Lomustine, and Vincristine) regimen can be used, though it's associated with recurrent cytopenia and increased hospital visits, adding financial strain. TMZ is generally easier to administer and better tolerated.

In low- and middle-income countries (LMICs), the choice of regimen should prioritize the availability and cost-effectiveness of chemotherapeutic agents. Physicians must also be vigilant about drug quality due to often inadequate drug regulation. During CCRT with TMZ, the risk of pneumocystis pneumonia is increased due to selective lymphopenia; therefore, antimicrobial prophylaxis with Septran DS is recommended. Patient compliance and baseline health are also important considerations. Prerequisites for therapy include[48]:

- ANC > 1.5 x 10^9/L
- PLT > 100 x 10^9/L

Table-1: Summary of Recommendations for High-Grade Gliomas

Radiology	• 'Minimum required' MRI 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. • Tumor location, tumor margins, enhancement pattern, tumor size, edema and presence of hemorrhage/mineralization. • ADC and DWI: Helpful to rule out differential diagnoses such as abscess, if needed. • Postoperative MRI is recommended within 72 hours of surgery. If delayed, then an 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. • Systemic workup if suspecting a metastatic lesion. • Based on radiological features, early coordination with the radiation oncologist for registration can potentially reduce delays in post-op radiation therapy in high-volume centers.
Surgery	• SMR: Excision beyond contrast enhancement; achievable in localized lesions in non-eloquent areas, with potential survival benefit. • GTR: Excision of all contrast-enhancing parts; a benchmark for the extent of resection. • STR/debulking: In eloquent areas where GTR is not possible. • Biopsy: Extensive disease or locations with high surgical risks. • Awake resection is advised if expertise is available.
Neuropathology	• Hematoxylin and eosin (H&E) preparation for o Establish astrocytic or oligodendroglia lineage. o Distinguish low-grade glioma from high-grade gliomas based on evaluation of cytological atypia, cellularity, mitotic count, presence/ absence of necrosis and vascular proliferation. • Immunohistochemical stains GFAP, Olig2, IDH1 R132H, ATRX, o p-53, stains stratify these tumors. • For diffuse glioma with morphological features of Oligodendroglioma, 1p/19q co-deletion is to be tested by FISH or refer to reference labs for the same, if not available at the same centre. • Consider IDH1 and IDH2 PCR testing if IHC is inconclusive for the same.
Medical and Radiation Oncology	• Focal brain irradiation therapy with concomitant chemotherapy TMZ (75mg/m2) within six weeks after surgery is recommended, followed by monthly TMZ (150-200mg/m2). • Conformal radiation techniques, such as 3DCRT or IMRT/VMAT, are recommended for focal brain irradiation. • The recommended radiation dosage is 59.4-60 Gy in 30-33 fractions given at 1.8-2 Gy per fraction for five days a week for 6-6.5 weeks. • Peer review of radiation treatment plans by site-specific specialists is an integral and essential component of quality assurance and should be a part of radiation therapy services to improve patient care. • In case of GTR: o Glioblastoma: Adjuvant monthly TMZ for 6 months. o Oligodendroglioma GIII/ Astrocytoma GIII/ /Astrocytoma GIV: Adjuvant monthly TMZ for 12 months. • In case of STR or biopsy: • Monthly TMZ will be continued until disease progression or unacceptable toxicities. • PCV can be considered in Oligodendroglioma, but TMZ is easy to administer and has better patient tolerance.
Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology and NOTB recommendations. • The neurosurgeon needs to connect the patient with radiation and medical oncologists. • Lifelong follow-up with MRI 3 monthly with medical oncologist/neurosurgeon. • Redo surgery can be considered in case of recurrence/disease progression after risk stratification in NOTB.

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MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, ADC: Apparent diffusion coefficient, DWI: Diffusion-weighted imaging, SMR: Supra marginal resection, GTR: Gross total resection, STR: Subtotal resection, GFAP: Glial fibrillary acidic protein, IDH: Isocitrate dehydrogenase, ATRX: α thalassemia/mental retardation syndrome X-linked, FISH: fluorescence in situ hybridization, PCR: Polymerase chain reaction, IHC: Immunohistochemistry, TMZ: Temozolomide, 3DCRT: 3-dimensional conformal radiation therapy, IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric modulated arc therapy, Gy: Gray, PCV: Procarbazine, Lomustine, and Vincristine, NOTB: Neuro-oncology tumor board

- Serum creatinine ≤1.5 times the upper limit of normal
- Total bilirubin ≤1.5 times the upper limit of normal
- AST/ALT <3 times the upper limit of normal

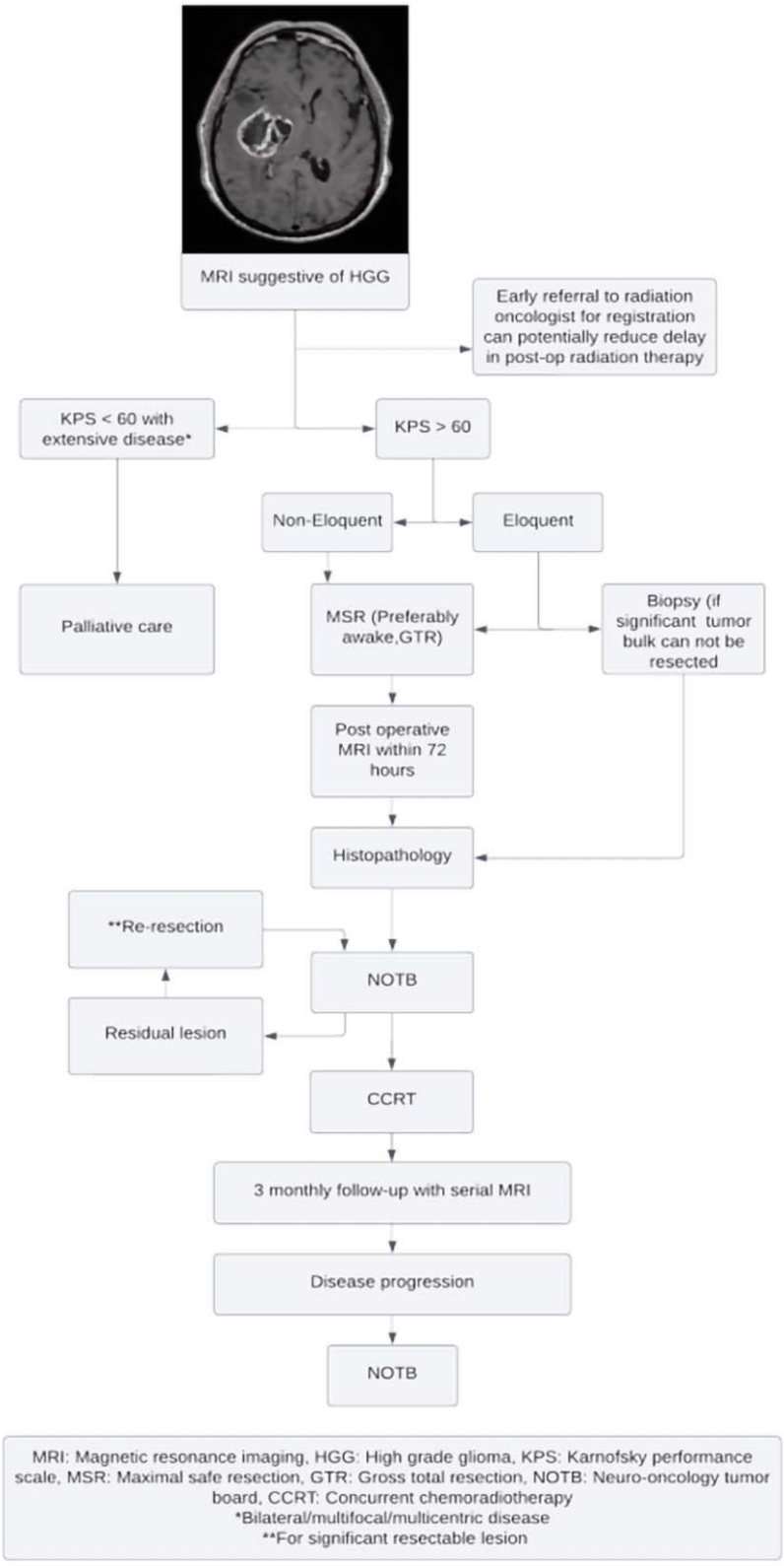

Figure-1: Management of HGG algorithm.

TMZ should be administered at 75 mg/m^2/day from the start of XRT until its last day. 8 After 4 weeks of CCRT, monthly TMZ cycles should begin, and for PCV, each cycle should be repeated every 6-8 weeks. TMZ dosage is 150-200 mg/m^2/day for 1-5 days every 28 days.[8]

The regimens are as follows[49]:

- Glioblastoma with GTR: 6 cycles of monthly TMZ
- Grade 3 Oligodendroglioma with GTR: 12 cycles of monthly TMZ
- High-grade Oligodendroglioma with PCV: 6 cycles

Due to their vascular nature, HGGs are sometimes treated with bevacizumab alongside radiation and TMZ. This improves progression-free survival but doesn't significantly impact overall survival and carries increased toxicity risks, limiting its routine use in newly diagnosed glioblastoma patients.[50]

Monitoring during treatment should include[51]:

- MRI brain with contrast 6-8 weeks post-CCRT, then every 3 months during monthly TMZ or earlier if symptomatic.
- CBC with differentials and serum creatinine every two weeks during CCRT and before each monthly cycle.
- Liver Function Tests before each monthly TMZ cycle.
- Weekly neurological exams.

For all HGGs, conformal radiation therapy at 1.8-2 Gy/fraction/day, 5 days a week to a total dose of 59.4-60 Gy over 30-33 fractions in 6-6.5 weeks is recommended.8 In elderly patients or those with low performance status, hypo-fractionated radiation regimens may be considered.[8]

Recurrent high-grade gliomau

HGG carries a poor prognosis, despite optimal standard treatment; nearly all cases of high-grade glioma progress.

Repeat surgery, alternate chemotherapeutic agents and in certain cases re-radiation can be considered in a select subset of patients. Surgery remains the mainstay treatment in recurrent HGG.[52-53] However, our experience does not align with existing literature and carries guarded prognosis.

Second-line chemotherapy Includes: Bevacizumab, Temozolomide re-challenge, PCV. High-Grade gliomas are highly vascular tumours with noteworthy angiogenesis, an anti-angiogenetic agent such as bevacizumab can be used in recurrent disease. Bevacizumab can be used alone or in combination with irinotecan.[8] This therapy has been shown to increase overall survival and progression-free survival in various phase II and phase III trials. The usual dosage is 10mg/kg every 14 days for every 28 days' cycle.[51] The available options with doses are as follows;

1. TMZ: The recommended dose for TMZ is 150-200 mg/m2/day, from day 1 till day 5, for every 28 days until disease progression or unacceptable toxicity.[8,54]

2. Bevacizumab: BVC can be given alone or in combination with irinotecan.[51, 55] The recommended dose of BVC is 10 mg/kg every 2 or 3 weeks until disease progression. Irinotecan can be administered at a dose of 125 mg/m^2 every 2 or 3 weeks.[51] If the patient is on enzyme-inducing antiepileptics drugs dose of irinotecan should be increased to 340mg/m^2

3. PCV combination regimen can be used if a patient progress on TMZ and Bevacizumab combination.

The role of re-irradiation in the management of recurrent HGG is evolving. A multidisciplinary approach is mandatory for appropriate patient selection considering disease-free intervals from previous treatment, performance status, and the biological nature of the tumour. Peer review treatment planning, and previous radiation treatment details including but not limited to dose to the surrounding normal structures, mode of delivery, patient tolerance and current disease volume are essential components required for the re-irradiation decision-making process.[56] The optimal dose fractionation regimen remains unclear and further research is needed to strategize the management of this patient.

The recurrence sets in with the financial and emotional exhaustion of the patient as well as family. Added survival of a few months must calculate the risk based on several poor prognostic factors such as age, performance status, ependymal involvement and last but not the least indispensable use of limited finance.

Conclusion

Formulated for physicians working in resource-limited settings, these guidelines serve as a practical roadmap based on valuable experience (Table 1 and Figure 1). 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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