NARRATIVE REVIEW

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

Ahsan Ali Khan[1], Ayesha Akbar Waheed[2], Ali Azan Ahmed[3], Asim Hafiz[4], Adeeba Zaki[5], Ahmed Gilani[6], Faiza Urooj[7], Mohammad Hamza Bajwa[8]

Pakistan Brain Tumour Consortium: (Authors list at the end of the supplement), Syed Ather Enam

Abstract

Low-grade gliomas (LGG) are brain tumors of glial cells origin. They are grade 1 and grade 2 tumors according to the WHO classification. Diagnosis of LGG is made through imaging, histopathological analysis, and use of molecular markers. Imaging alone does not establish the grade of the tumor and thus a histopathological examination of tissue is crucial in establishing the definite histopathological diagnosis. Clinical presentation varies according to the location and size of the tumor. Surgical resection is strongly recommended in LGG over observation to improve overall survival as surgery leads to greater benefit due to progression-free survival. Radiation has shown benefits in LGG patients in randomized controlled trials and chemotherapy with temozolomide has also shown good results. This paper covers the principles of low-grade gliomas management and summarizes the recommendations for the LMICs.

Keywords: Temozolomide, survival, brain Neoplasms, glioma, neuroglia

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Introduction

Brain tumors are defined upon their histopathological features and their cells of origin. Tumors arising from the glial cells of the nervous system are defined as gliomas. These tumors are further divided into astrocytoma and oligodendroglioma. The grade attributes clinical prognosis. Histological appearance and molecular markers such as isocitrate dehydrogenase (IDH), ATRX, tumor protein (TP53), 1p19q co-deletion attributes to the final diagnosis LGG in parenthensis as per WHO classification 2021.[1] However, recently another term ´lower-grade gliomas have been used to include grade 3 also, but we have discussed only grade 2 in this paper.

[1,8,9]Department of Neurosurgery, The Aga Khan University, Karachi, [2,3,7]The Aga Khan Medical College and University, Karachi, .[4]Department of Radiation Oncology, The Aga Khan University, Karachi, Pakistan.[5]Department of Oncology, Aga Khan University Hospital, Pakistan.[6]Department of Pathology, University of Colorado, Children's Hospital Colorado, USA.

Correspondence: Syed Ather Enam **Email: a**ther.enam@aku.edu

LGGs are glial tumors with slow growth rates and their occurrence is usually between the third and fourth decades of life. Seizures are present as the primary complaint in majority of the patients while focal neurological deficits and headaches are also common. [2] In most cases, LGGs exist in the high-functioning regions of the brain, in the eloquent cortical, subcortical, and the secondary functional areas of the insula and the supplemental motor areas.[3]

The low-grade gliomas are not necessarily benign tumors, they have the potential for malignant transformation over time, but this process is not uniform and can vary significantly from case to case. The mean time for malignant transformation of low-grade glial tumors to high-grade varies and depends on several factors, including the type of tumor, its location, genetic factors, and the patient's overall health. The timeframe of malignant transformation can range from a few years to over a decade.

The median time for this transformation is often cited in various studies, but it's essential to note that these are average figures and individual cases can vary widely. Approximately 72% of grade 2 tumors may show malignant transformation over time and hence, we recommend early surgical resection of the low-grade gliomas over “wait and see” approach. This paper covers the principles of low-grade gliomas management and summarizes the recommendations for the low-middle income countries (LMICs).[4,5]

Methods

The literature search of the high-quality data on low-grade gliomas was done in March 2023 on different databases including PubMed, Google Scholar, Scopus, and Embase in March 2023. 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 low-grade gliomas within Pakistan. This group was tasked with identifying best-practice recommendations and their application within the

context of Pakistan as a (LMIC). Recommendations were collated and reviewed for utility and evidence-based practices.[6]

Initial evaluation

Initial diagnosis of LGGs is made through imaging, histopathological analysis and use of molecular markers. Imaging alone does not establish the grade of the tumor and thus a histopathological examination of tissue is crucial in establishing the definite histopathological diagnosis.[7] In Computed Tomography (CT) scans, LGGs appear as regions of low attenuation that may or may not enhance.[8] Meanwhile, Magnetic Resonance Imaging (MRI), both T1 and T2, are non-enhancing and sometimes minimal or subtle enhancement with calcifications appearing on high T1 and low T2 signals.[9] FLAIR sequence plays an important role in defining the extent and boundaries of the LGGs.

LGGs management involves factors such as the extent of surgical resection, the timing of intervention, risks associated with chemotherapy, the timing of radiotherapy, and the long-term consequences of all treatments. Therefore, the purpose of this study is to outline the difficulties faced in the provision of these aforementioned treatments and their applicability in low- and middle-income countries (LMICs), ascertaining the recent developments in the diagnostic workup of LGGs in order to establish refined treatment methods that are suitable for LMICs.

Clinical symptoms for LGGs are not consistent. Mostly symptoms are associated with mass effect from invasion into obstructive hydrocephalus or surrounding parenchyma. While some patients with LGGs may be asymptomatic, many patients present with seizures, signs of increased intracranial pressure through headache and papilledema, and cognitive changes.[3, 10]

Surgical management

The main goal involved with surgery is to obtain a maximal safe resection or form a pathological diagnosis through biopsy. Developments such as tractography, preoperative functional MRIs, and intraoperative neurophysiological monitoring allow surgeons to maximize the objectives of the surgery. Moreover, in cases where safe resection is not a possibility, image guided biopsy is conducted using preoperative and intraoperative imaging to gather tissue for histopathological examination.[2, 10] In comparison to a needle biopsy, which has an over 50% misdiagnosis rate, surgical resection provides a far feasible avenue for characterization, grading, proper diagnosis, and treatment of LGGs. [11]

Recent studies have strongly suggested surgery over observation to improve overall survival as surgery leads to greater benefit due to progression-free survival. [12, 13] Moreover, surgical resection has also shown substantial benefits in reducing seizure [14] It is important to consider two factors when proceeding to a surgery, the impact on patients' quality of life (QoL) and the overall survival in comparison to monitored waiting. With the latest developments in surgical techniques, it has now become more efficient for surgeons to conduct surgeries in cases of patients with LGGs while also not affecting the eloquent brain. Through magnetic source imaging and functional MRI, surgeons can map the vital regions of the brain such as language and motor cortices.[15] Intraoperative MRI and MRS enable the evaluation of the degree of tumor resection, further clarifying the residual tumor whereas Diffusion Tensor Imaging allows improved surgical planning, reducing risks and deficits involved. [6, 16] Intra-operative ultrasonography (IOUS) has also shown benefits during surgical resection. It provides real-time guidance which plays an important role in the extent of tumor resection. In limited resources, ultrasound can be an extremely effective adjunct. [17, 18]

Pathological assessment

Histopathological diagnosis is crucial in the definite management of the LGGs. The molecular pathology of low-grade gliomas involves deletion on chromosomes 1p and 19q, with significant association with oligodendrogliomas. Deletion of the 19q13.3 region is responsible for 73% of oligodendrogliomas and 38% of astrocytomas, the deletion of 1p36 region is involved in 18% of astrocytomas and 73% of oligodendrogliomas and finally, both 1p36 and 19q13.3 regions are codeleted in 64% of oligodendrogliomas, and 11% of astrocytomas. [19]

Moreover, overexpression and mutation of tumor protein 53 (TP53), involved in the p53 pathway, leads to diffuse astrocytomas.[20] Decreased MGMT activity is also found in correlation to low grade gliomas. MGMT is a DNA repair enzyme that removes alkyl groups from the O6 position of guanine. [21]

However, methylation of the MGMT promoter leads to increased sensitivity of gliomas to the effects of alkylating agents- most likely due to reduced activity of MGMT. [22]

In addition, mutations in the gene BRAF of chromosome 7 (7q34), also contribute to low grade gliomas. The BRAF gene is involved in production of a protein that activates the mitogen-activated protein kinase (MAPK) pathway. [23]

Finally, isocitrate dehydrogenase mutations, IDH1 and IDH2, are also found in pathogenesis of low-grade

gliomas. IDH1 and IDH1 are NADP dependent enzymes that catalyze the conversion of isocitrate to α-ketoglutarate. [24] Mutation of IDH1 results in reduced enzymatic activity due to impaired isocitrate binding that leads to production of D-2-hydroxyglutarate (d-2HG), which then acts as an oncogenic metabolite. [25, 26]

When looking closely into the histopathological end of the diagnosis, stains such as eosin and hematoxylin are employed for identification. Oligodendrogliomas are infiltrating cells with perinuclear clearing following a honeycomb pattern, meanwhile, astrocytomas have fibrillary neoplastic astrocytes, and oligoastrocytomas contain both types of tumor cell types.

Adjuvant treatment radiotherapy

Radiation is one of the few intervention methods that has shown benefit in LGG patients in a randomized controlled trial. [27] Numerous clinical trials have been set up to discern the differences between high-dose and low-dose radiation and early postoperative radiation vs. delayed radiation at time of disease recurrence or progression. Regarding timing of RT, studies have shown better progression free survival when radiation had incorporated early after surgery as compared to delayed radiation in the management of LGG however it failed to show any benefit in term of survival.[27] Similarly, dose response study failed to show significant difference in both the progression-free survival and overall survival in LGG through radiation dose escalation beyond 54 Gy instead lead to more toxicity.[28]

Radiotherapy is put forward for management of recently diagnosed LGG in adults, to improve progression free survival regardless of the level of surgical resection (Level I recommendation). Radiotherapy is suggested for management of recently diagnosed LGG as a substitute to observation in maintaining cognitive function (Level II recommendation). Radiotherapy suggested for management of recently diagnosed LGG that involves ameliorating seizure control and prolonging progression free survival in patients with subtotal resection and epilepsy (Level III recommendation).

In case of progression free survival, it was noted that a more aggressive approach towards surgical resection combined with radiotherapy led to significantly higher levels of 5-year progression free survival rates.[29] Moreover, radiotherapy also showed substantial improvements in controlling seizures. [30]

Recent advances in radiotherapy techniques such as intensity-modulated radiation therapy (IMRT)/ Volume modulated arc therapy (VMAT) and stereotactic radiation therapy have allowed targeting the tumor with high precision during treatment, without damaging the surrounding healthy brain tissue and hence addressing the concerned related with radiation toxicity. [2, 31]

Chemotherapy

Neuro-oncologists have found renewed interest in chemotherapy with specific focus on temozolomide, with its ability to cross the blood-brain barrier, heightened activity against glioblastomas and favorable toxicity profile in comparison to other available agents- leading to an improved quality of life. [32]

The major concern in the application of chemotherapy is should all LGG patients be provided adjuvant chemotherapy involving Procarbazine, CCNU, and Vincristine (PCV) or rather it should be specified to high-risk patients solely.[33] However, to follow this path, better analysis upon the differentiation of high-risk LGG must be more probed into to ensure that the cognitive decline induced by chemotherapy is minimized and limited to patients where it is of greater benefit and increased quality of life.[34] Therefore, a molecular analysis study was conducted to determine the benefits of adjuvant chemotherapy involving PCV chemotherapy in 1p/19q co-deleted tumors as well as in CpG Island Methylated Phenotype (CIMP) positive tumors, IDH mutations, and MGMT promoter methylation. [35, 36]

Recent years have seen PCV being gradually replaced by temozolomide that has improved tolerance levels and is easier to administer. Even though RTOG studies have yielded similar treatment results in temozolomide, and CCNU, the latter had to be eventually discontinued due to its extreme levels of toxicity that led to a decreased survival rate.[37] However, a new chemotherapeutic drug vorasidenib has shown to increase progression-free survival in patients with grade 2 IDH mutant glioma. [38]

While decline in cognition and defining the correct set of patients to provide chemotherapy remain as the focal challenges, developments such as temozolomide remain to be proponents of chemotherapy in LGG management.

Post-operative management and follow-up

Post-op MRI brain with and without contrast should be done within 72 hours. Clinically speaking, the extent of surgical resection is the major determinant of post-operative management and eventually the quality of life. The accurate analysis of the extent of surgical excision is reported on post-op MRI brain. Looking into the follow up aspect of LGG management, we find key metrics such as (i) physical activity, (ii) social function, (iii) cognitive function, (iv) emotions function, and (v) fatigue with

Table-1: Summary of Recommendations for Low-Grade Glioma.

Radiology	•MRI brain with and without contrast. •'Minimum required' MRI protocol: oImaging on at least 0.5T. oSequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast enhanced T1. • Tumor location, size, margins, enhancement pattern, and presence of hemorrhage/mineralization. • 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.
Neurosurgery	• Surgical goals: Maximal safe resection of the tumor, preferably GTR. • SMR should be attempted where possible with potential survival benefit. • Biopsy/debulking is recommended where maximal safe resection is not possible. • Awake resection is advised if the expertise is available.
Neuropathology	• Hematoxylin and eosin (H&E) preparation to establish astrocytic or oligodendroglia lineage. • 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, 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	• **Low risk patients:** (GTR & Age < 40 years): Observation. • **High-risk patients:** (STR or Age > 40 years): o Radiation followed by Adjuvant PCV x 6 cycles. o CCRT with TMZ followed by monthly TMZ. • Focal brain radiation with advanced conformal techniques such as 3DCRT/IMRT/VMAT is recommended. • The common radiation dose is 54 Gy in 30 fractions given at 1.8 Gy per fraction for five days a week for 6 weeks. • **Recurrent disease:** o Temozolomide, PCV, Avastin.

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	• Case needs to be discussed in a radiation oncology facility having peer review practice by site-specific specialists for consideration of re-irradiation with highly conformal techniques such as IMRT/VMAT or stereotactic radiation SRS/f-SRT
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 if needed. • Lifelong follow-up with MRI every 3 months for 1 year and then 6 monthly with neurosurgeon/medical oncologist. • Redo surgery can be considered in case of recurrence/disease progression after risk stratification in NOTB.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, GTR: Gross total resection, SMR: Supra marginal 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, STR: Subtotal resection, CCRT: Concurrent chemoradiotherapy, TMZ: Temozolomide, 3DCRT: Three-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric modulated arc therapy, Gy: Gray, PCV: Procarbazine, Lomustine, and Vincristine, SRS/f-SRT: Stereotactic radiosurgery/fractionated stereotactic radiation therapy, NOTB: Neuro-Oncology tumor board.

respect to time after the surgery or other treatment method.

Prognosis

Close follow-up is advised, preferably with MRI every 3 to 6 months post-operatively. Redo surgery can be offered in case of recurrence. Several prognostic factors allude to the risk of death in patients with LGG. The size of tumor diameter being > 5cm, presence of tumor in eloquent regions of the brain, patients with preoperative KPS, and IDH non mutated/wild type tumors are the important markers of risk of death.[39] In addition, seizures, volume of residual tumor, delayed post-operative radiotherapy, Age, and the respective pathology (astrocytoma, oligodendroglioma/mixed) are other prognostic factors related to the 5-year and 10-year progression free rates.[40]

Factors affecting optimal care

Although treatment options have expanded, as well as

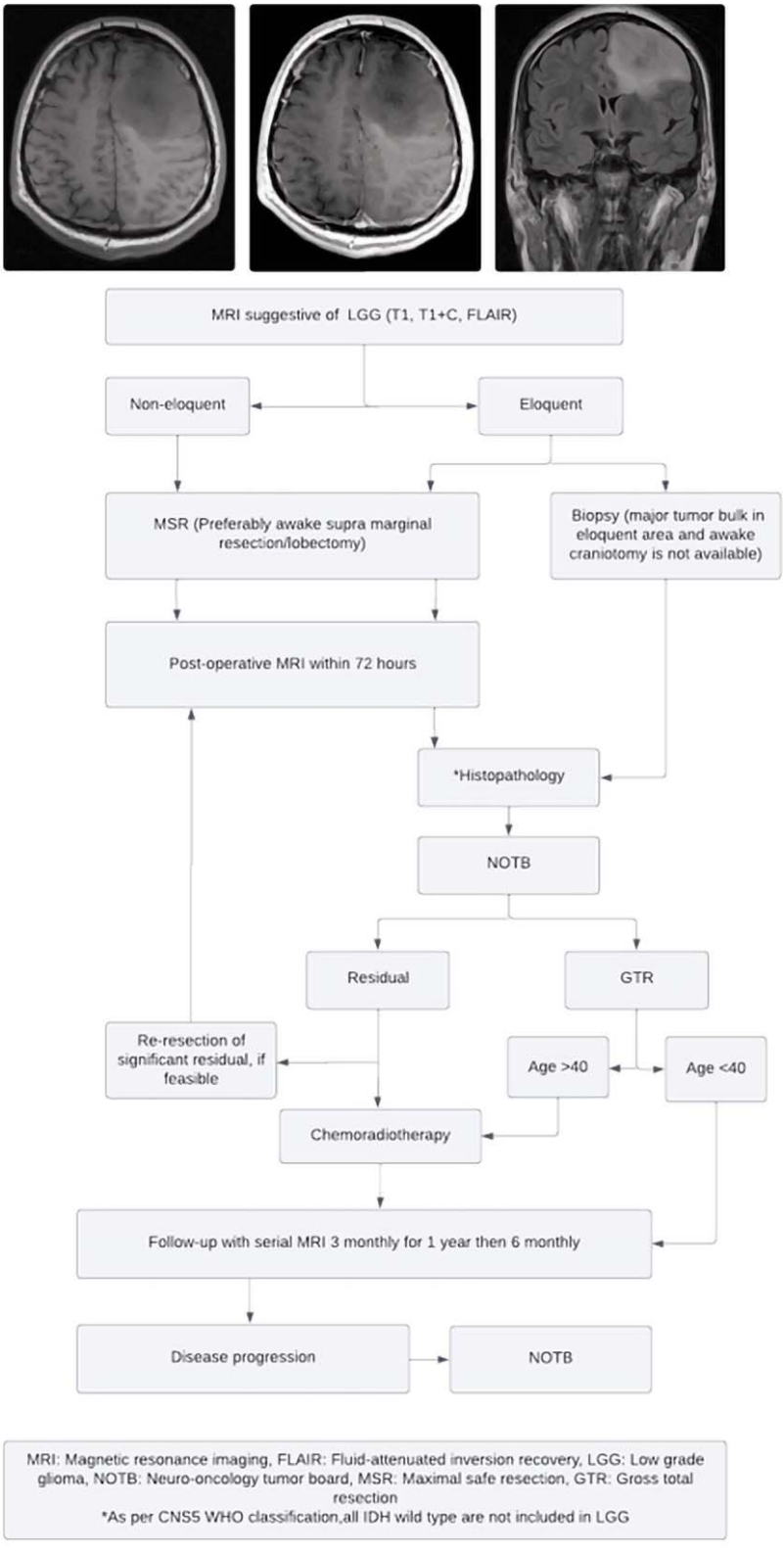

Figure-1: Management of LGG algorithm.

efforts to improve existing treatment regimes, a serious limiting factor remains in the lack of clinical follow-up. This serves as an obstacle in assessing the efficacy and effectiveness of chosen treatment plans, narrowing the pool of viable data. Many reasons behind this poor rate of follow-up are mostly situational and apply more so in the case of LMIC settings. For example, there is a dearth of tertiary care health care centers in Pakistan. In addition to coming from less affording households, patients must travel large distances to seek treatment. It is barely possible to access treatment, let alone follow-up. Moreover, treatment can be suboptimal owing to the burden of patients on a single center. The most appropriate treatment plan may not be an option for each patient. Hence, the effort in treating LGGs should not only be directed at finding the best treatment, but also eliminating the factors that affect care.

Gaps in knowledge

With new advancements in imaging, radiotherapy, chemotherapy, and surgical techniques, the management of LGG keeps varying and it is more apt to identify the risks associated with the "wait-and-see" approach. Current data is in strong favor of surgical resection to maximize benefits, but further trials and investigations are necessary to unlock the complete potential of novel imaging techniques and molecular marker pathogenesis. However, the presence of cognitive decline, epilepsy, and insufficient health-related Quality of Life remain important issues that have to be addressed to ensure a sustainable management procedure.[39] [40] Finally, implications concerning stereotactic biopsy and Perfusion weighted MR imaging still require further exploration to introduce them into the mainstream treatment modalities.

Conclusion

These guidelines serve as a practical roadmap based on valuable experience

and are formulated for physicians working in resource-limited settings, (Table 1 and Figure 1). Their implementation has significant potential to improve outcomes and aims to nurture a stronger emphasis on multidisciplinary care within LMICs, such as Pakistan.

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