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REVIEW ARTICLE

First Mexican consensus guideline for the management of IDH-mutant low-grade gliomas: Mexican guidelines for IDH-mutant gliomas

*Mónica Serrano-Murillo[1], Enrique Caballe-Pérez[1], Alberto González-Aguilar[2], Talia Wegman-Ostrosky[1], Marco A. Rodríguez-Florido[3], Alejandro Rodríguez-Camacho[4], Sergio Moreno-Jiménez[2,5], Federico Maldonado-Magos[6], Alan O. Chávez-Martínez[1], Pedro R. Corona-Cedillo[7], Héctor A. Montenegro-Rosales[8], Guillermo A. Gutiérrez-Aceves[9], Alexandra Diaz-Alba[10], Norma C. Aréchiga-Ramos[11,12], Oscar Arrieta[1], Alipio Gonzalez-Vazquez[1], and Bernardo Cacho-Díaz[1]**

[1]Unidad Funcional de Neuro-Oncología, Instituto Nacional de Cancerología, Mexico City; [2]Unidad de Radiocirugía, Instituto Nacional de Neurología y Neurocirgía Manuel Velasco Suárez, Mexico City; [3]Anatomía Patológica, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City; [4]Subdirección de Radioterapia, Instituto Nacional de Cancerología, Mexico City; [5]Neurocirugía, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City; [6]Subdirección de Radioterapia, Instituto Nacional de Cancerología, Mexico City; [7]Neuroimagen, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City; [8]Neuroradiología intervencionista, Fundación Médica Sur, Mexico City; [9]Servicio de Radioneurocirugia, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City; [10]Neuro-Oncology Unit, Instituto Jaliscience de Cancerología, Guadalajara; [11]Grupo de estudio de Neuro-Oncología, Academia Mexicana de Neurología, Mexico City; [12]Unidad de Neuro-oncología, Centro Médico ABC, Mexico City. Mexico*

Abstract

The objective of the study is to propose a diagnostic and therapeutic algorithm for patients with mIDH-LGG tailored to our country's healthcare setting. Patients with isocitrate dehydrogenase-mutant (mIDH) low-grade gliomas (LGGs) demand a multidisciplinary approach. Individualized management should consider local resources, patient preferences, clinical features, imaging results, and tumor pathological characteristics. We use a multidisciplinary team of neuro-oncologists, medical oncologists, neurosurgeons, radiation oncologists, neuroimaging specialists, geneticists, and neuropathologists collaborated to develop a manuscript through a Delphi consensus method. Diagnosis includes a complete clinical examination, neuroimaging, histopathological tissue examination, and molecular analysis. Treatment options include (a) surgery as the first-line approach, aiming for maximal safe resection; (b) radiation therapy, administered postoperatively or as a primary treatment in selected cases; (c) systemic therapy; and (d) palliative care for patients with advanced disease or limited therapeutic options. For asymptomatic, slow-growing tumors or elderly patients, an appropriate strategy of active surveillance might be considered. We present custom-made diagnostic and therapeutic algorithms for Mexican patients with mIDH-LGG. To optimize treatment outcomes, participation in clinical trials and early referral to specialized centers are encouraged.

Keywords: *Isocitrate dehydrogenase. Low-grade glioma. Adult-type diffuse glioma.*

Correspondece:
Bernardo Cacho-Díaz
E-mail: bernardocacho@doctor.com

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Primera guía de consenso mexicana para el manejo de gliomas de bajo grado con mutación IDH: guías mexicanas para gliomas con mutación IDH

Resumen

El objetivo es proponer un algoritmo diagnostico y terapeutico para pacientes con gliomas de bajo grado IDHm adaptado al contexto del Sistema de salud Mexicano. Los pacientes con gliomas de bajo grado con mutación en la isocitrato deshidrogenasa (IDHm) requieren un enfoque multidicilinario. El manejo individualizado debe considerar los recursos locales, las preferencias del paciente, las caracteristicas clinicas, los hallazgos por imagen y las caracteristicass patologicas del tumor. Se usó un equipo multidisciplinario conformado por neurooncologos, oncólogos médicos, neurocirujanos, radiooncólogos, especialistas en neuroimagen, genetistas y neuropatólogos elaboró el presente documento mediante una metodología de consenso Delphi. El diagnóstico incluye una evaluación clínica, estudios de neuroimagen, análisis histopatológico y evaluación molecular. Las opciones terapéuticas comprenden: a) Cirugía como primera línea, con el objetivo de lograr una resección máxima segura; b) Radioterapia en el periodo postoperatorio o como tratamiento primario en casos seleccionados; c) Terapia sistémica; y d) Cuidados paliativos. En casos de tumores asintomáticos, de crecimiento lento, o en pacientes de edad avanzada, puede considerarse vigilancia activa. Se presentan algoritmos diagnósticos y terapéuticos personalizados para pacientes mexicanos con GBG-mIDH. Para optimizar los resultados del tratamiento, se recomienda la participación en ensayos clínicos y la referencia temprana a centros especializados.

Palabras clave: *Isocitrato deshidrogenasa. Glioma de bajo grado. Glioma difuso del adulto.*

Introduction

Primary central nervous system (CNS) tumors originate from neural and oligodendroglial cells, with gliomas being the most common type. These CNS tumors develop from cells with genetic variants that lead to tumor initiation mechanisms and are a significant cause of brain cancer-related deaths.

CNS tumors are divided according to their histological features and molecular markers as described in the 2021 World Health Organization (WHO) classification of CNS tumors[1]. Primary CNS tumors are divided into six major groups: adult-type diffuse gliomas (AtDGs), pediatric-type diffuse low-grade gliomas (LGGs), pediatric-type diffuse high-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors, and ependymal tumors. AtDGs account for most gliomas, which comprise three main distinctive types: isocitrate dehydrogenase (*IDH*)-mutated astrocytoma (mIDH astrocytoma), mIDH and 1p/19q-deleted oligodendroglioma, and *IDH* wild type (wtIDH) glioblastoma. In the WHO 2021 classification, mIDH CNS tumors fall into two main types: mIDH and 1p/19q codeleted oligodendrogliomas or mIDH astrocytomas; both are referred to in this manuscript as mIDH LGGs. Therefore, the present consensus aims to provide evidence on the epidemiology, clinical presentation, diagnosis, treatment, and prognosis of patients with mIDH LGG personalized to the current assets accessible in our country.

Methods

A multidisciplinary team of neuro-oncologists, medical oncologists, neurosurgeons, radiation oncologists, neuroimaging specialists, geneticists, and neuropathologists collaborated to develop a manuscript through a Delphi consensus method (Fig. 1), by gathering published information from our country and local accessible resources.

Epidemiology

In Mexico, a study by Hernández et al.[2] reported information on a cohort of 9,615 patients with CNS tumors treated at a single center for a sex proportion of 51% females and 49% males, being the neuroepithelial tumors the most prevalent (42%), followed by meningeal tumors (24%), and tumors of the sellar region (22%). Neuroepithelial tumors were supratentorial in most cases (79%). A nationwide study[3] from Mexico reported that the mortality rates increased from 1.9 to 2.1/100,000 people from the years 2000 to 2017, with a male-to-female ratio of 1:2, and the age group with the highest number of deaths was in those aged 65-69 years.

Clinical presentation

In a study with information on 193 Mexican patients with CNS tumors[4], the most common clinical presentations were headache (49%), altered mental status (32%), visual complaints (25%), seizures (21%), focal

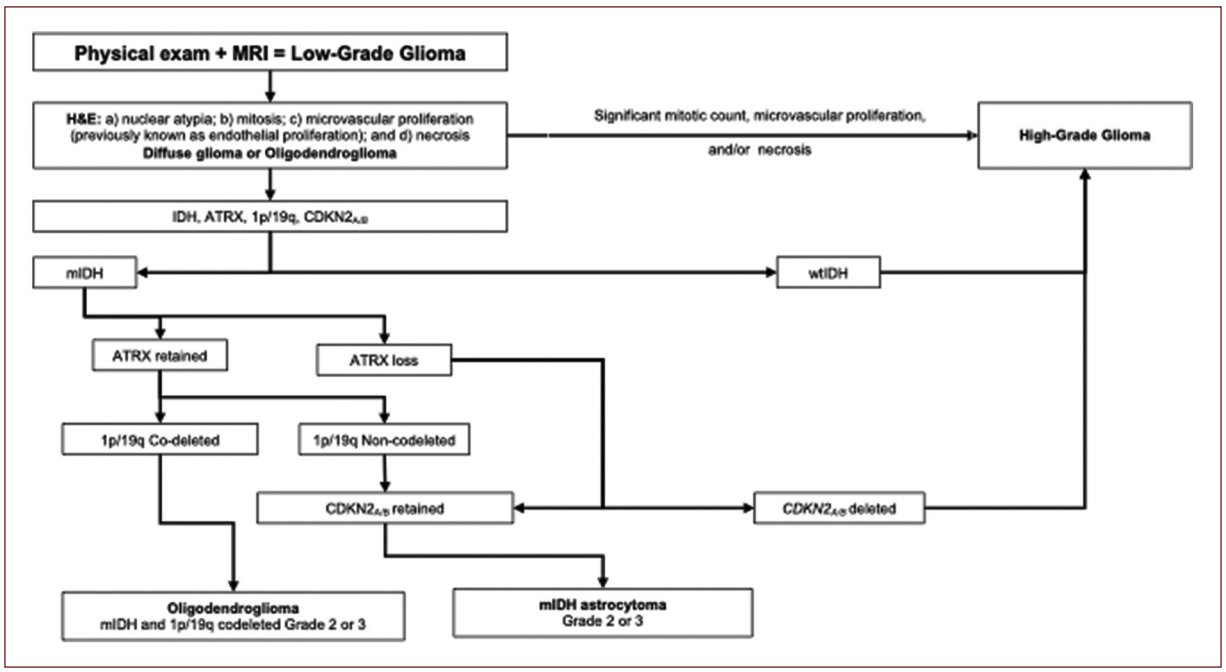

Figure 1. Diagnostic algorithm for adult patients with a suspected primary brain tumor. ATRX: X-linked mental retardation syndrome gene; CDKN: cyclin-dependent kinase inhibitor; H&E: hematoxylin and eosin; IDH: isocitrate dehydrogenase; mIDH: IDH mutated; MRI: magnetic resonance imaging; wt: wild type.

motor weakness (18%), ataxia (15%), focal sensitive complaint (8%), cognitive complaint (8%), vertigo (7%), cranial neuropathy (6%), speech disorder (5%), and abnormal movement disorder (2%).

In 30-50% of patients with CNS tumors, an epileptic seizure is the presenting clinical manifestation, and 10-30% will develop seizures later in the course of their disease[5]. LGGs with a supratentorial location have been associated with a higher risk for seizures[6].

Clinical markers

In patients from Mexico, authors have reported that the age at presentation is significantly younger in those with gliomas and glioblastomas, with a male-to-female incidence ratio of 1.39[7]. In this population, recognized prognostic factors associated with overall survival (OS) are histological grade, Karnofsky Performance Score (KPS), resection type, chemotherapy, radiation therapy (RT), alcohol consumption, familial history of cancer, and clinical presentation[8].

Histologic grade

The four primary histological markers traditionally used to evaluate malignancy in primary CNS tumors are (a) nuclear atypia, (b) mitosis, (c) microvascular proliferation, and (d) necrosis. A significant mitotic count, anaplasia, high cellularity, cellular pleomorphism, and increased nuclear atypia are required to diagnose Grade 3 tumors; the presence of microvascular proliferation or necrosis is required for a CNS tumor to be considered as Grade 4[9]. According to the 2021 WHO guidelines, the histological grade should not be based solely on histological aspects and compels the use of molecular markers[1].

Molecular diagnostic markers

The main molecular markers required to classify a CNS tumor as LGG are *IDH* and 1p/19q [chromosome loss in the short arm of chromosome 1 (1p), in the large arm of chromosome 19 (19q), or both (1p/19q)].

The *IDH* biomarker should be considered the first step in the molecular classification of gliomas, followed by the 1p/19q status. A pooled analysis[10] reported that patients with Grade 2 oligodendroglial tumors (mIDH and 1p/19q codeleted) had an OS of > 20 years and those with Grade 3 > 14 years. In the same study[10], patients with mIDH astrocytomas classified as Grade 2 had an OS > 14 years, Grade 3 had an OS of 5-10 years, and Grade 4 around 3 years. Over 40% of Grade 2 or

3 astrocytomas and around 2% of Grade 4 astrocytomas are mIDH[11].

The most common *IDH* variant (mutation) in gliomas is R132H (> 70%) and can be detected by immunohistochemistry (iCH)[12]; if this IDH1 R132H is negative by iCH, sequencing of *IDH1* codon 132 and *IDH2* codon 172 should be conducted in all WHO Grade 2 and 3 diffuse astrocytic and oligodendroglial tumors, and in all patients diagnosed with glioblastoma aged < 55 years[13].

The 1p/19q co-deletion has been associated with an improved survival rate irrespective of tumor morphology or histological Grade; it is a marker of treatment response, and its presence has also been associated with progression-free survival[14].

Homozygous deletion of the cyclin-dependent kinase inhibitor 2A ($CDKN2_A$) or the cyclin-dependent kinase inhibitor 2B ($CDKN_{2B}$) locus on 9p21 is associated with poor outcome and indicates a WHO Grade 4 disease[1]. Therefore, the detection of $CDKN2_{A/B}$ is a marker of poor prognosis and excludes the diagnosis of a LGG; in other words, Grades 2, 3, or 4 gliomas should no longer be based entirely on the histological characteristics, for the presence of $CDKN_{2A/B}$ homozygous deletion results in the diagnosis of CNS WHO Grade 4, even in the absence of microvascular proliferation or necrosis.

Mutation/loss of alpha-thalassemia/mental retardation syndrome X-linked (*ATRX*) expression[15] can be detected by iCH or *ATRX* sequencing. If a glioma is ATRX positive (mutation/loss present), it is diagnostic of an mIDH astrocytoma[1]; in other words, astrocytomas are either mIDH, *ATRX* altered, and *TP53* mutated, or they are wtIDH astrocytomas.

The *BRAF* gene encodes the B-Raf protein; targetable genetic variants in *BRAF* have been detected in 15 to 20% of LGGs, and their prognostic and therapeutic significance is under study[16-18]. Finally, the WHO has never implemented the use of Ki-67 antibodies to assess the degree of malignancy, so we do not endorse using this marker to establish a diagnosis or guide therapeutic interventions.

Molecular tests – Summary

- Detection of mIDH and ATRX by iCH tests should be performed routinely for all gliomas. If negative, IDH1 codon 132 and IDH2 codon 172 sequencing should be determined in all WHO Grade 2 or 3 gliomas and patients with glioblastoma if the age at diagnosis was < 55 years. A 1p/19 codeletion status should be determined in all mIDH gliomas. $CDKN_{2A/B}$ deletions should be investigated in all mIDH astrocytomas.
- The suffix NOS is used when insufficient DNA is found, and the suffix NEC when molecular studies are done but the results do not fit the WHO diagnostic criteria.

Diagnosis

The diagnosis of a CNS tumor is often made in a previously healthy patient who presents with focal neurological deficits such as focal motor weakness, new-onset seizures, and headache. Patients may also be diagnosed incidentally through neuroimaging findings. If a glioma is suspected, we recommend a diagnostic algorithm described in figure 2.

Magnetic resonance imaging (MRI)

The proposed imaging protocol includes the following[19]:

- Axial fluid attenuation inversion recovery (FLAIR) with canthomeatal alignment: 3-5 mm sections, 1 mm interslice gaps, slice registration preserved as much as possible between sequential studies.
- Axial T2: 5 mm sections, 1 mm interslice gap.
- Coronal T1: 5 mm sections, 1 mm interslice gap.
- Post-gadolinium chelate (contrast agent as per local clinical practice): coronal T1, axial T1.
- Alternatively, pre-gadolinium and post-gadolinium volumetric T1 may replace axial and coronal T1-weighted sequences.
- Supplementary imaging methods that can be done at some specialized centers include two-dimensional or three-dimensional spectroscopic imaging (MR spectroscopy), perfusion imaging (DSC-MRI), and diffusion-weighted imaging (–B = 0, B = 1000).

Positron emission tomography (PET) imaging

^{11}C-methionine (^{11}C-MET) and ^{18}F-fluoroethyltyrosine (^{18}F-FET) tracer PET might be used by intravenous administration; ideally 6 mm or better special resolution is recommended. Glucose metabolism in LGGs is decreased compared to that of a normal brain; ergo, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET is currently considered to be of limited use. Compared with ^{18}F-FDG, the uptake of amino acids (^{11}C-MET and ^{18}F-FET) is less affected by inflammatory processes, although tumor specificity is not perfect[20]. The addition of

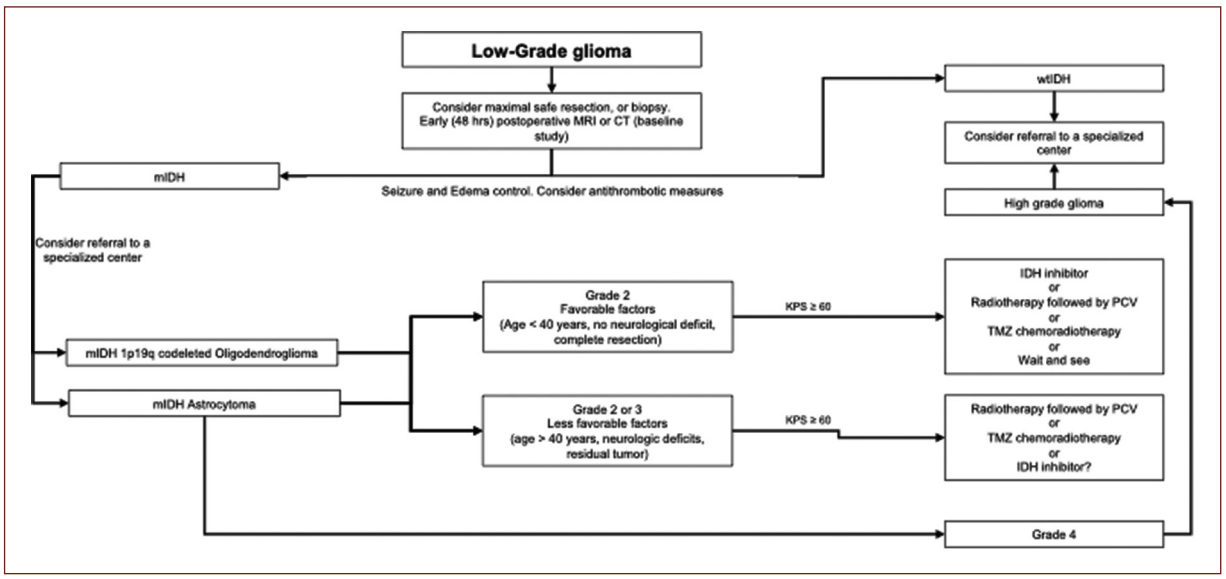

Figure 2. Therapeutic algorithm for adult patients with mIDH low-grade glioma. IDH: isocitrate dehydrogenase; mIDH: IDH mutated; KPS: Karnofsky performance status; MRI: magnetic resonance imaging; PCV: procarbazine, lomustine (CCNU), and vincristine; TMZ: temozolomide; wtIDH: IDH wild type.

^{18}F-FET PET to MRI has been shown to improve the diagnosis of active gliomas by increasing the specificity from 53% to 94%, with unchanged sensitivity (93-96%) in one study[21]. ^{11}C-MET PET is well suited to follow the effects of RT, and it enables the differentiation of recurrent tumors from radiation necrosis[22-24].

Treatment

The CNS WHO grade[1] has traditionally been used to guide therapeutic interventions. Younger age and better performance status at diagnosis are the major prognostic factors associated with longer survival[25].

Surgical therapy

The first line of treatment in patients with LGGs is to consider a maximal safe resection (MSR), which means resecting as much of the tumor as possible. An MSR is associated with longer OS and progression-free survival (PFS) and helps achieve an onco-functional balance and improve the quality of life (QoL). Several techniques and tools have been used to achieve this onco-functional balance, including navigation, functional MRI, intraoperative MRI, ultrasonography, fluorescence-based visualization with 5-aminolevulinic acid (5-ALA)[26], and functional monitoring, all of which are encouraged in the operating room[27]. Surgical resection must be personalized, for no "standard" surgical approach exists[28].

Gross total resection (GTR) has been defined as the absence of residual lesion, based on T1-weighted contrast enhancement (CE) images; subtotal resection (STR) was considered when tumoral tissue was left in the surgical field, even if no tumor is seen in the post-operative MRI, STR was also considered in the presence of residual tumor after an extent of resection (EOR) of > 90%; partial resection (PR) was defined as the presence of > 10% but < 90% EOR[29]; finally, a supratotal resection (SpTR) was considered when the resection involved the removal of more than 100% of the visible tumor tissue, true SpTR was defined as excision past all discernible and visible MRI abnormalities, including fluid-attenuated inversion recovery (FLAIR) borders[30,31]. In 2023, the Response Assessment in Neuro-Oncology (RANO) resect group[32] stratified the EOR into four categories as presented in table 1. The EOR is a prognostic factor; thus, efforts to obtain a Class 1 or 2 resection are recommended.

After surgery, a watch-and-wait approach is advised for younger patients (< 40 years) who have achieved maximal CE resection and for those younger patients with submaximal CE resection if there is no neurologic deficit beyond symptomatic epilepsy[33]; with this approach, studies have estimated OS rates of 99% at 2 years and 93% at 5 years; and PFS rates of 82% at 2 years and 48% at 5 years[29].

Table 1. RANO resect group categories for the extent of resection

Class 1 Supramaximal CE resection	Class 2 Maximal CE resection		Class 3 Submaximal CE resection		Class 4 Biopsy
0 cm^3 CE + ≤ 5cm^3 nCE	Class 2A Complete CE resection	Class 2B Near-total CE resection	Class 3A Subtotal CE resection	Class 3B Subtotal CE resection	No reduction of tumor volumen
	0 cm3 CE + < 5cm^3 nCE	≤ 1 cm^3 CE	≤ 5cm^3 CE	> 5cm^3 CE	

Supramaximal resection of CE tumor = beyond CE tumor borders (cut-off values remain to be defined); *complete resection* of CE tumor = removal of all CE tumor; *near total resection* of CE tumor: 95-99.9% CE tumor reduction + ≤ 1 cm^3 residual CE tumor; *subtotal resection* of CE tumor = 80-94.9% CE tumor reduction + ≤ 5 cm^3 residual CE tumor; *partial resection* of CE tumor = 5 cm^3 residual CE tumor (administered for mass effect-related symptoms); or *biopsy* = no tumor reduction (intervention done for tissue-based diagnosis only).
CE: contrast enhanced; nCE: non-contrast enhanced.

Radiotherapy

RT aims to improve local control, increase OS, prevent or delay malignant transformation, minimize treatment-associated adverse events, and maintain or improve patients´ QoL. A radiation oncology specialist should always supervise the dose, timing, and scheduling of RT.

Early administration of RT has been demonstrated to prolong PFS and improve seizure control[34]. Deferring RT until disease progression can be considered for those with LGGs, aged < 40 years, and GTR[29]. In patients without these conditions or symptomatic LGGs (i.e., seizures), post-operative (3-6 weeks after surgery)[35,36] RT should be considered, with an optimal dose of 50-60 Gy in 1.8-2.0 Gy per fraction[37,38]. Hypofractionated radiotherapy with a higher dose per fraction and a lower total dose might be appropriate for older (> 65 years of age) and those with poor performance status (KPS < 70).

Systemic treatment

Before considering any systemic treatment, a complete blood count and hepatic/renal function tests should be determined. The addition of adjuvant PCV (procarbazine, lomustine [CCNU], and vincristine) to post-operative RT in patients with high-risk LGGs (pre-operative tumor diameter ≥ 4 cm or greater, astrocytoma/oligoastrocytoma histologic type, and/or residual tumor ≥ 1 cm) resulted in an increased OS (13.3 years vs. 7.8 years) and longer PFS (4.0 years vs. 10.4 years, p < 0.001)[39].

At present, the standard of care for patients with LGGs considered candidates for post-operative therapy is RT, followed by PCV chemotherapy[39]. Studies have shown the benefit of adding PCV chemotherapy in patients with oligodendrogliomas[33]. The median OS (MOS) times varied significantly, being 1.9 years for those with wtIDH tumors, 6.9 years for mIDH/1p19q non-codeleted tumors, and 13.9 years for mIDH/1p19q co-deleted tumors. Interestingly, the mIDH subgroups (1p19q co-deleted or non-codeleted) demonstrated longer survival with the addition of PCV; mIDH/1p19q non-codeleted tumors improved their MOS from 4.3 years to 11.4 years (hazard ratio [HR] = 0.38, p = 0.01), and those with mIDH/1p19q codeleted tumors from 13.9 years to still not reached (HR = 0.21, p = 0.04). In contrast, the wtIDH group did not experience a survival benefit from receiving PCV.

Promising outcomes have been observed with combined temozolomide (TMZ) and RT for patients with high-risk LGG. The phase II single-arm study, RTOG 0424, enrolled 136 patients diagnosed with WHO Grade 2 gliomas. Eligibility criteria included at least three unfavorable factors: age ≥ 40 years, pre-operative tumor diameter ≥ 6 cm, bi-hemispheric tumor, astrocytoma histology, and/or pre-operative neurological function status > 1. Patients received 54 Gy in 1.8 Gy fractions with concurrent and adjuvant TMZ for up to 12 cycles. The observed 3-year OS rate of 73.5% significantly exceeded prespecified historical control values (p < 0.001)[40].

Adjuvant TMZ has also been shown to improve survival compared to RT alone for patients with non-1p/19q codeleted WHO Grade 3 gliomas. The CATNON (EORTC 26053-22054) phase III trial randomized 745 patients with non-codeleted WHO Grade 3 gliomas to receive RT (total 59.4 Gy in 1.8 Gy per fraction) with or without adjuvant TMZ (12 4-week cycles) or to receive RT plus concurrent TMZ with or without adjuvant TMZ. With a median follow-up of 55.7 months, adjuvant TMZ improved survival compared with no

adjuvant treatment (MOS 82.3 months vs. 46.9 months; HR = 0.64, p < 0.001).

Exploratory analysis revealed that patients with mIDH, 1p/19q non-codeleted tumors had a longer PFS when treated with RT alone compared to TMZ alone (HR = 1.86, p = 0.004)[41]. Considering this data, TMZ as monotherapy could be considered if RT cannot be administered[42].

Temozolomide (TMZ)

TMZ is an oral DNA alkylating agent that penetrates the blood-brain barrier and is the most common agent used in glioma treatment[36]. The chemoradiation therapy, also known as the Stupp regimen, consists of concurrent and adjuvant TMZ. Concomitant chemotherapy consists of TMZ at a dose of 75 mg per square meter per day (mg/m^2/d), given 7 days per week from the 1st day of radiotherapy until the last day, but not longer than 49 days. After a 4-week break, patients are then to receive up to six to twelve cycles of adjuvant TMZ at a dose of 150 to 200 mg/m^2/d for 5 days scheduled every 28 days (days 1-5 with TMZ and days 6-28 without TMZ = 1 cycle). Hematologic toxic effects should be followed, and TMZ might cause lymphopenia and thrombocytopenia. Pneumocystis jirovecii pneumonia prophylaxis should be considered. A retrospective study of antiemetic therapy with ondansetron, ondansetron + domperidone, and ondansetron + olanzapine showed that the latter is the better option[43].

Procarbazine, lomustine (CCNU), and vincristine [PCV]

The first clinical trial to demonstrate an increase in OS with the addition of adjuvant chemotherapy (post-radiation chemotherapy) in 251 patients with high-risk LGGs, defined as age > 40 years or subtotal resection/biopsy, was the RTOG 9802[39]. Chemotherapy consisted of 6 cycles of procarbazine (at a dose of 60 mg per square meter of body-surface area orally per day on days 8 through 21 of each cycle), CCNU (at a dose of 110 mg per square meter orally on day 1 of each cycle), and vincristine (at a dose of 1.4 mg per square meter [maximum dose, 2.0 mg] administered intravenously on days 8 and 29 of each cycle). The cycle length was 8 weeks. Patients who received RT plus PCV had a longer median OS than those who received RT alone (13.3 vs. 7.8 years); the HR for death was 0.59 (p = 0.003). The ten-year PFS was 51% in the PCV and radiation group vs. 21% in the RT alone group; the OS rates at 10 years were 60% and 40%, respectively. A *post hoc* analysis[33] determined that treatment with post-radiation chemotherapy with PCV was associated with longer PFS [HR = 0.22 (95% confidence interval [CI]: 0.11-0.40), p = 0.003] and OS [HR = 0.18 (0.09-0.40). In contrast, no significant difference in either PFS or OS was observed with the addition of PCV in patients in the wtIDH group. Unfortunately, the access to PCV in Mexico is limited.

Vorasidenib

In a double-blind, randomized, placebo-controlled, phase 3 trial, 331 patients with Grade 2 mIDH oligodendroglioma or astrocytoma, with confirmed *IDH1* and *IDH2* mutations, received 40 mg of vorasidenib or placebo, once daily, orally in continuous 28-day cycles[44]. The median PFS in the vorasidenib group was 27.7 vs. 11.1 months; the HR for disease progression or death was 0.39 (95%CI 0.27-0.56), p < 0.0001. A Grade 3 or higher adverse event occurred in 9.6% of the treatment group vs. 0 in the placebo group. Vorasidenib has now been approved for patients with mIDH LGGs.

Palliative care

It is essential to consider palliative care for patients with poor performance (KPS < 60). Palliative care offers a comprehensive approach to improving a patient's quality of life by addressing their physical, psychological, and emotional needs and can provide additional support that complements medical treatment. Integrating palliative care into the care plan can help optimize a patient's well-being and provide support throughout their illness[45].

Monitoring and follow-up

Watch-and-wait strategies might be appropriate in patients with Grade 2 tumors, especially if asymptomatic or with a GTR. In addition to clinical examination, MRI is the standard diagnostic measure for evaluating disease status or response; using the RANO criteria, clinicians should be able to assess every 3 months if the patient has a complete response, partial response, stable disease, or progression[19,46]. A brain MRI should be performed every 3-6 months for five years, then at least every 6 months.

The following definitions described in table 2 should be universally included in each MRI report essential

Table 2. The Response Assessment in Neuro-Oncology (RANO) for gliomas

Complete response	Partial response	Stable disease	Progression
Disappearance of all measurable and non-measurable disease in T1 + GAD	≥ 50% decrease in sustained injury over 4 weeks at T1 + GAD	Not eligible for complete, partial response, or progression in T1 + GAD	≥ 25% increase in T1 + GAD enhanced lesions or any new lesions
Lesions that do not enhance in T2/FLAIR	Stable or non-enhancing lesions in T2/FLAIR	Stable lesions that do not enhance in T2/FLAIR	Significant increase in T2/FLAIR injury
No use of corticosteroids	With the same or lower dose of corticosteroids	With the same or lower dose of corticosteroids	Increased dose of corticosteroids
Clinically stable or improving	Clinically stable or improving	Clinically stable or with new symptoms	Clear clinical deterioration
Patients with non-measurable disease cannot have a complete response	Patients with non-measurable disease cannot have a partial response	Better response in patients with non-measurable disease	Clear progression of the disease not measurable

GAD: gadolinium; FLAIR: fluid-attenuated inversion recovery.

factors to ensure that the recommendations are both practical and achievable.

Conclusion

mIDH LGGs represent a significant proportion of primary CNS tumors. We have reviewed their clinical implications and management and presented recommendations based on the available resources. We emphasize a multidisciplinary approach when managing every patient with a LGG.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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