# Management of glioblastoma: a perspective from Mexico

**Sergio Moreno-Jiménez[1], Marco A. Alegría-Loyola[2], Adam M. Sonabend[3], Sofia K. Romano[4], Carlos G. Romo[5,6]**

[1]Centro Neurológico, Centro Médico American British Cowdray, Ciudad de Mexico, Mexico; [2]Centro Neurológico y Comité de Neuro-oncología, Centro Médico ABC, Ciudad de Mexico, Mexico; [3]Department of Neurosurgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [4]Johns Hopkins University, Baltimore, Maryland, USA; [5]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [6]Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA

*Contributions:* (I) Conception and design: MA Alegría-Loyola, S Moreno-Jiménez, AM Sonabend, CG Romo; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: MA Alegría-Loyola, S Moreno-Jiménez, CG Romo; (V) Data analysis and interpretation: S Moreno-Jiménez, CG Romo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Carlos G. Romo. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
Email: cromo1@jhmi.edu.

**Abstract:** Access to healthcare in Mexico is available to its population via publicly and privately funded institutions. The public sector, administered by both the local and federal government under the jurisdiction of the Department of Health, provides healthcare to the majority of the country's population. Privately funded institutions vary in size and scope of practice, ranging from small clinics focused on family practice, to large tertiary hospitals with capacity for treating patients with complex conditions and performing clinical research. The evaluation and treatment of patients with cancer in Mexico is also available through both sectors. In the country's capital, Mexico City, patients with glioblastoma are primarily treated at the National Institute of Neurology and Neurosurgery and the National Institute of Oncology. Epidemiological data is incomplete due to the lack of a national cancer registry. In the case of neoplasms of the central nervous system, the available information suggests that gliomas represent 33% of all intracranial tumors. The treatment of patients in Mexico diagnosed with glioblastoma has not been standardized owing to the lack of resources in some communities and the expense of antineoplastic agents. Current options range from a biopsy only to maximal safe resection followed by adjuvant treatment with radiation and chemotherapy. Currently, basic science and clinical research is being conducted in academic institutions associated with universities and in private hospitals. Studies include the evaluation of tumor biology, neuroimaging biomarkers and new treatment options such as the use of chloroquine.

**Keywords:** Glioblastoma; Mexico; international perspective

Submitted Mar 29, 2020. Accepted for publication May 13, 2020.
doi: 10.21037/cco-20-129
**View this article at:** http://dx.doi.org/10.21037/cco-20-129

## Introduction

The diagnosis and treatment of patients with cancer in Mexico is available to its population via publicly and privately administered institutions. According to the Organization for Economic Cooperation and Development (OECD), Mexico has the highest ratio of public to private sector facilities at 11.4 public hospitals and 28.6 private hospitals per 1 million inhabitants (1). The majority of public institutions are overseen by the Department of Health at both the federal and local levels, with a smaller portion administered by other branches of government. These institutions provide healthcare to the vast majority of Mexicans (76.9%) (2). Within the public sector three systems provide most of the available services: the Mexican Institute of Social Security (IMSS), the Institute for Social Security and Services for State Workers (ISSSTE), and community hospitals operated by local governments.

Medical expenses in these hospitals are covered by government-sponsored programs with a fraction paid by the patient as out-of-pocket fees, or by the employers.

Private institutions in Mexico, which are primarily located in urban areas, provide healthcare to a smaller percentage of the population and accept payment through insurance or out of pocket fees. These hospitals and clinics vary in size and scope of practice. They may be affiliated with academic centers and aid in the education of healthcare professionals. In addition, some private institutions conduct preclinical and clinical research. Patients with neoplasms affecting the central nervous system are treated by a multidisciplinary team of physicians which includes, when available, a neurosurgeon, and medical and radiation oncologists. Recently two formal neuro-oncology training programs were established.

## Epidemiology of glioblastoma in Mexico

Statistical data regarding the incidence of cancer in Mexico, including glioblastoma, is largely unavailable due to the lack of a national tumor registry. The National Institute of Neurology and Neurosurgery (NINN) conducted a retrospective analysis using records of all cases of intracranial neoplasms between 1988 and 1994 in order to evaluate the overall frequency of intracranial tumors and prognostic factors for glioblastoma in Mexican patients. Within that 7-year period, 1,776 patients with intracranial neoplasms were treated at the NINN. The distribution of patients included 586 (33%) with gliomas, 165 of which were glioblastomas (WHO grade IV). Sixty two percent of the patients were male, 38% female with 52% of them living in rural areas. Forty-one percent of patients survived less than 1 year, 39% between 1 and 2 years, 12% between 2 and 3 years and 8% more than 3 years (3).

In a more comprehensive study, also conducted at the NINN, patients treated between 1964 and 2016 (a 52-year period) were evaluated. A total of 9,615 cases of primary brain tumors or brain metastases were recorded, with 3,346 gliomas distributed as follows: 1,220 (12.6%) astrocytomas I–III, 1,586 (16.4%) glioblastoma, 154 (1.6%) ependymomas, 121 (1.2%) oligodendrogliomas, and 265 (2.7%) oligoastrocytomas. The mean age at diagnosis was 46.4 years in patients with glioblastoma (4).

The Spanish Hospital of Mexico, a private institution, performed an analysis of their patient population seen between 1993 and 2013 (a 20-year period). This cohort included 511 patients with intracranial tumors, 57% of whom were female and 43% male, with a median age at diagnosis of 49.3 years. In this report glioblastoma represented 24% of the diagnosed neuroepithelial tumors (5). One of the major limitations of all of these studies is that they report on the experience of single institutions in Mexico City, which might not be representative of the country's population and incidence.

## Current management of glioblastoma in Mexico

In 2015, the first consensus regarding the treatment of patients with glioblastoma was published by the Mexican Interdisciplinary Group on Neuro-oncology Research (GIMINO) (6). It recommended taking into consideration patients' age, clinical and functional status, as well as the size and location of their tumor in order to determine an appropriate course of action. It also recommended discussing the potential risks and benefits of treatment with the patient before committing to a plan. For patients under 70 years of age with a Karnofsky performance status (KPS) greater than 70, the recommended frontline therapy included maximal safe resection followed by concurrent radiation and chemotherapy using temozolomide and six cycles of adjuvant temozolomide. In addition, the authors suggested administering bevacizumab as part of this regimen, despite a lack of overall survival benefits in clinical trials (7,8). For patients older than 70 years, but with a KPS >70, the recommendation was to decrease the dose of radiotherapy to 50 Gy and omit concurrent temozolomide. This recommendation is based on clinical trials evaluating different radiation regimens, although unfortunately, the evidence is weak as none of these studies compared their population to standard therapy which includes concurrent chemoradiation followed by 6 cycles of adjuvant TMZ (9-11). For patients older than 70 who have poor performance status, the authors suggest using temozolomide as monotherapy or offering palliative care options.

Other options discussed in their recommendations include a regimen with procarbazine, lomustine and vincristine. It is important to note that access to lomustine, the most critical component of this combination in the treatment of gliomas, is very limited in Mexico. As a less effective option, carboplatin was mentioned with the only attractive feature being its low cost.

Due to the lack of standardization of care and to the limited available data on clinical practices across the country, it is challenging to describe in a granular fashion the current

management for glioblastoma that any given patient might receive. Unpublished data from the NINN suggests that the diagnosis of glioblastoma is confirmed in the majority of patients based on a histopathological analysis from a biopsy or resection tissue sample by a neuropathologist. At the NINN the evaluation of *IDH1* mutational status is infrequently performed and when it is, it is determined by immunohistochemistry techniques. The determination of MGMT promoter methylation at this institution is not currently feasible and therefore does not influence decisions regarding therapy with an alkylating agent. In contrast, patients covered by medical insurance who seek treatment at private institutions or some large academic centers are more likely to have additional testing and resources available to them, including molecular sequencing and determination of the MGMT promoter methylation status. In smaller community hospitals, pathology slides may be reviewed by a general pathologist without access to genomic testing.

Surgical treatment involves maximal safe resection. The location and extension of the tumor dictates the surgical approach, which ranges from a stereotactic biopsy in the case of deep-seated lesions to gross total resection when the tumor is located in a non-eloquent area of the brain through the use of neuro-navigation. Awake craniotomies are performed in patients with masses affecting language function and electric stimulation when involvement of motor areas is suspected. Fluorescence with 5-aminolevulinic acid is also occasionally used to visualize tumor extension.

The implantation of carmustine wafers and the prescription of tumor treating fields are not standard practices as they are not readily available due to their high costs.

## Preclinical and clinical research

Research in the field of glioblastoma is mainly conducted by academic institutions, which occasionally collaborate with large private healthcare systems in their efforts to better understand the pathophysiology of gliomas and to improve diagnostics and treatment of patients affected by these tumors. The aim of this paper is not to be a comprehensive account of the body of research performed in Mexico; the following examples of research represent a small fraction of studies performed to date in the country and is only meant to convey a broad sense of recent investigations.

### *Molecular and neuroimaging biomarkers in glioblastoma*

A novel approach using diffusion tensor imaging (DTI)-derived biomarkers to evaluate the brain of patients with glioblastoma was studied in a phase 2 clinical trial to better define areas affected by tumor when compared to standard imaging techniques. The results suggest that using a predictive model composed of three metrics including axial diffusivity, spherical tensor, and linear tensor can differentiate between glioblastoma and normal brains through a discriminant analysis (12). Additionally, a case-control study was conducted using eleven DTI-derived metrics from magnetic resonance imaging to globally evaluate the brains of 27 patients and 34 controls. The results suggest that this technology is able to detect significant differences between healthy brains and those affected by glioblastoma. The authors conclude that an advantage of using a global approach is that it allows for monitoring not only of the contrast-enhanced regions, but also the less evident tumor infiltration (13).

In another attempt at evaluating the prognostic value of imaging characteristics, Roldan-Valadez *et al.* investigated the contribution of several MRI biomarkers in glioblastoma. Their results suggest that a higher preoperative Choline-to-N-acetyl acetate aspartate (Cho/Naa) ratio and a lower lipid-lactate-to-creatine ratio have predictive potential of survival which might be more relevant than the classic T2 weighted pre-gadolinium and T1 weighted post-gadolinium volumetric standards (14).

The renin-angiotensin system (RAS) was evaluated for its potential role in the development and behavior of astrocytomas in a cohort of 48 patients by Perdomo-Pantoja and other investigators. They prospectively collected blood samples prior to surgery and analyzed the DNA using Ion Torrent next-generation sequencing. Their findings suggest that an AGT rs5050 GG-genotype is associated with poor prognosis in this population, making it a potential prognostic biomarker (15).

### *Pathophysiology of glioblastoma*

A multidisciplinary team from different institutions led by Orozco-Morales investigated the ability of tumor cells to evade the immune system by obtaining three transformed glioma cell lines ($Rb^{-/-}$, $Ras^{V12}$, and $Rb^{-/-}/Ras^{V12}$) by *in vitro* retroviral transformation of astrocytes. The researchers also injected $Ras^{V12}$ and $Rb^{-/-}/Ras^{V12}$ transformed cells into immunodeficient mice and allowed tumor growth to occur. They then collected two stable glioma cell lines, which were characterized by evaluating their gene expression of Rb and Ras, morphology, proliferative

capacity, expression of MHC I, and their susceptibility to natural killer (NK) cell-mediated cytotoxicity. The results demonstrated that the transformation of astrocytes (via RB loss, Ras overexpression, or both) induces phenotypical and functional changes associated with resistance to NK cell-mediated cytotoxicity (16).

Given that progesterone is produced in minute amounts by neurons and glial cells as a neurosteroid in certain regions of the brain, a team of researchers from the Autonomous National University of Mexico studied the effects of Org OD 02-0, a progesterone membrane receptor agonist, on human glioblastoma cell lines. The researchers evaluated the changes in cell number, proliferation, migration, invasion, and intracellular signaling after treating the cells *in vitro* and by conducting *in vivo* experiments. Their results suggest that progesterone may have a role, through various mechanisms, in the tumorigenesis of glioblastoma (17,18).

### *Clinical studies*

The treatment of patients with glioblastoma within a clinical trial is recommended as the preferred frontline therapy for eligible patients with this condition, especially those with MGMT-unmethylated glioblastoma (19,20). Unfortunately, the availability of clinical studies for this patient population in Mexico is very limited. At the time of publication of this review, there were no clinical trials open for accrual to the best of our knowledge. In the past, investigator-initiated trials have been conducted as well as studies performed in collaboration with institutions in the United States and other countries.

Chloroquine was evaluated in a phase 2 clinical study due to its DNA-intercalating properties by administering in addition to conventional treatment for patients with glioblastoma in a randomized, double blind, placebo-controlled trial. Thirty patients with histologically confirmed glioblastoma were accrued and overall survival was studied as the primary outcome. All participants received conventional chemoradiation and were randomized to concurrently receive either chloroquine (150 mg/d for 12 months starting on postoperative day 5) or placebo. The median survival was 24 months for chloroquine-treated patients and 11 months for controls, although this was not a statistically significant difference, likely due to the small sample size they studied (21).

## Conclusions

Epidemiological data of glioblastoma in the Mexican population is largely unknown in great measure due to the lack of a national tumor registry for neoplasms of the nervous system and to the disparity in resources available throughout the country. The limited data available regarding treatment practices and outcomes does not allow for a comprehensive account of the state of neuro-oncology in the country. Anecdotal experience suggests that there is much need for the standardization of diagnostic evaluation, treatment, and monitoring of patients with glioblastoma. The development and execution of clinical trials should also be a priority in order to improve the quality of care and treatment options for these patients. To this end, additional funding and resources must be procured. Fortunately, some efforts are being done to contribute to basic glioblastoma research.

## Acknowledgments

The authors would like to thank B. Nettel and Alvaro Barbosa Quintana, MD for contributing with information presented in this publication.

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Rimas V Lukas) for the series "The evolving landscape of the management of glioblastoma" published in *Chinese Clinical Oncology*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cco-20-129). The series "The evolving landscape of the management of glioblastoma" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## References


1. Gomez Frode C. El Sistema de Salud en México. Revista CONAMED 2017;22:129.
2. Instituto Nacional de Estadistica y Geografia. Mexico – Encuesta Intercensal 2015. Available online: https://www.inegi.org.mx/temas/derechohabiencia. Accessed March 10, 2020.
3. Lopez-Gonzalez MA, Sotelo J. Brain tumors in Mexico: characteristics and prognosis of glioblastoma. Surg Neurol 2000;53:157-62.
4. Hernández-Hernández A, Reyes-Moreno I, Gutiérrez-Aceves A, et al. Primary tumors of the central nervous system. Clinical experience at a third level center. Rev Invest Clin 2018;70:177-83.
5. Anaya-Delgadillo G, de Juambelz-Cisneros PP, Fernández-Alvarado B, et al. Prevalencia de tumores del sistema nervioso central y su identificación histológica en pacientes operados: 20 años de experiencia. Cir Cir 2016;84:447-53.
6. Celis MA, Alegría-Loyola MA, González-Aguilar A, et al. Primer consenso mexicano sobre recomendaciones de la atencion multidiciplinaria del paciente con glioblastoma multiforme (GBM). Grupo Interdisciplimnar Mexicano de Investigación en Neuroon-cología (GIMINO). Gaceta Med Mex 2015;151:403-15.
7. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
8. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709-22.
9. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527-35.
10. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial.J Clin Oncol 2004;22:1583-1588.
11. Malmström A, Grønberg BH, Marosi C, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. Lancet Oncol 2012;13:916-26.
12. Roldan-Valadez E, Rios C, Cortez-Conradis D, et al. Global diffusion tensor imaging derived metrics differentiate glioblastoma multiforme vs. normal brains by using dis-criminant analysis: introduction of a novel whole-brain approach. Radiol Oncol 2014;48:127-36.
13. Cortez-Conradis D, Rios C, Moreno-Jimenez S, et al. Partial correlation analyses of global diffusion tensor imaging-derived metrics in glioblastoma multiforme: Pilot study. World J Radiol 2015;7:405-14.
14. Roldan-Valadez E, Rios C, Motola-Kuba D, et al. Choline-to-N-acetyl aspartate and lipids-lactate-to-creatine ratios together with age assemble a significant Cox's survival in high-grade gliomas. Br J Radiol 2016;89;20150502.
15. Perdomo-Pantoja A, Mejia-Perez SI, Reynoso-Noveron N, et al. Angiotensinogen rs5050 germline genetidc variant as potential biomarker of poor prognosis in astrocytoma. PLoS One 2018;13:e0206590.
16. Orozco-Morales M, Sánchez-García FJ, Golán-Cancela I, et al. RB mutation and RAS overexpression induce resistance to NK cell-mediated cytotoxicity in glioma cells. Cancer Cell International 2015;15:57.
17. González-Orozco JC, Hansberg-Pastor V, Valadez-Cosmes P, et al. Activation of membrane progesterone receptor-alpha increases proliferation, migration, and invasion of human glioblastoma cells. Mol Cell Endocrinol 2018;477:81-9.
18. González-Agüero G, Gutierrez D, Gonzalez-Espinoza JD, et al. Progesterone effects on cell growth of U373 and D54 human astrocytoma cell lines. Endocrine 2007;32:129-35.
19. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 1.2020). Available online: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed March 10, 2020.
20. Stupp R, Brada M, van de Bent MJ, et al. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Supp 3:iii93-101.
21. Sotelo J, Briceño E, López-González MA. Adding Chloroquine to Conventional Treatment for Glioblastoma Multiforme. Ann Int Med 2006;144:337-43.


**Cite this article as:** Moreno-Jiménez S, Alegría-Loyola MA, Sonabend AM, Romano SK, Romo CG. Management of glioblastoma: a perspective from Mexico. Chin Clin Oncol 2021;10(4):44. doi: 10.21037/cco-20-129