



A 10-Year Survival-Trend Analysis of Low-Grade Glioma and Treatment Patterns from an LMIC

Mohammad Hamza Bajwa¹ Saad Bin Anis² Irfan Yousaf² Mashal Shah¹

¹Department of Surgery, The Aga Khan University, Karachi, Pakistan

²Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan

Address for correspondence Saad Bin Anis, FRCS-SN, FRCSEd, FCPS Neurosurgery, Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Center, 7 A Khayaban-e-Firdousi, Block R3 Block R 3 M.A Johar Town, Lahore, Punjab 54000, Pakistan (e-mail: saadanis@skm.org.pk).

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Abstract

Objectives The 2021 WHO Classification of Central Nervous System Tumors taxonomy laid further stress on molecular classification and prognostication of glial tumors in comparison to histopathological grading. Research shows that low-grade gliomas (LGGs) can go through malignant differentiation and lead to severe disability and death. Data from various populations will be necessary to ascertain the exact interplay between genotypic predictors of LGG and outcomes.

Materials and Methods To assess the molecular pathology for glial tumors in the Pakistani population, the Shaukat Khanum Memorial Cancer Hospital carried out a retrospective chart review of electronic health records from 2008 to 2018, with immunohistochemistry analysis findings from 2010 to 2018. Patients with a pathological diagnosis of a glioma were included.

Statistical Analysis Analysis was performed using IBM SPSS Statistics Version 23 and STATA Version 16. A *p*-value of less than 0.05 was considered statistically significant with 95% confidence intervals reported.

Results In all, 281 operable tumors were recorded. The most common procedure was a subtotal resection, and astrocytomas (64.77%) were the most common tumors. Radiation therapy and PCV (procarbazine, CCNU, and vincristine) was received by 85 patients, while radiation therapy and temozolomide were administered to 15 patients.

Conclusions Isocitrate dehydrogenase (IDH) wild-type LGG had a lower survival time, while improved survival times were seen for alpha-thalassemia X-linked intellectual disability syndrome (ATRX) retained and 1p19q co-deleted LGGs. Further studies are required to gain a better understanding of lower-grade glial tumor treatment and survival in Pakistan.

Keywords

- ▶ brain tumor
- ▶ epidemiology
- ▶ glioma
- ▶ LMIC
- ▶ low-grade glioma

Introduction

The 2021 WHO Classification of Central Nervous System Tumors taxonomy laid further stress on molecular classification and prognostication of glial tumors in comparison to

histopathological grading. Low-grade gliomas (LGGs) in particular are understood to have a prolonged and indolent course. Research shows that LGG can go through malignant differentiation and lead to severe disability and death.¹ While the standard of care is to achieve gross total resection

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without functional deterioration, the extent of resection is predicated on eloquent versus noneloquent location of tumor, adjuncts to surgery like neuronavigation, cavitron ultrasonic aspirator (CUSA), awake craniotomy, brain mapping and monitoring, and surgeons' expertise and decision-making. Recent evidence suggests that combining chemotherapy and radiation therapy is beneficial, and that early surgeries positively impact survival.² In terms of chemotherapy, both temozolomide and PCV (procarbazine, CCNU, and vincristine) are widely used, with their individual efficacies being the subject of comparison in much of the global literature. Awake craniotomies have shown to promote a better extent of resection, a lower risk of new deficits, and improved progression-free survival among patients.³

Histologically, astrocytomas and oligodendrogliomas are the two most common subtypes of LGGs, and can be further characterized by molecular genotypes and growth patterns.⁴ Oligodendrogliomas are characterized by both an isocitrate dehydrogenase (IDH) mutation and chromosomal 1p and 19q co-deletions, and have an encouraging prognosis. Diffuse astrocytomas are further divided into those with an IDH mutation, which carry a moderate prognosis, and those lacking an IDH mutation (IDH wild type), which have a poor prognosis, similar to glioblastoma. In IDH-mutant oligodendrogliomas, a clear survival benefit with gross total resection in retrospective studies has not been seen when compared to subtotal resections. A study found that IDH-mutant 1p/19q co-deleted tumors had longer progression-free survival if treated with radiotherapy along with TMZ, compared with TMZ chemotherapy only.⁵

Data from various populations will be necessary to ascertain the exact interplay between genotypic predictors of LGG and outcomes. In particular, data from our region with regard to surgical outcomes and molecular markers are currently missing. This study intends to establish a baseline for understanding LGG outcomes in our population in light of the most recent updates to the WHO Classification of central nervous system (CNS) tumors.

Methods

To assess the molecular pathology for glial tumors in the Pakistani population, the Shaukat Khanum Memorial Cancer Hospital (SKCMH) carried out a retrospective chart review of electronic health records from 2008 to 2018. Patients with a pathological diagnosis of a glioma were included. From 2010 onward, all glioma tissue samples at the hospital were processed with hematoxylin and eosin (H&E) staining, followed by a detailed immunohistochemistry analysis. Samples taken prior to 2010 had not been processed in this way. Telephonic follow-up with the patients was carried out as and when required to determine morbidity and mortality.

Data Analysis

Survival time after diagnosis and surgery is shown by Kaplan-Meier curves stratified according to molecular markers. Primary endpoints of this study were survival

Table 1 Adjuvant treatment outcomes for isocitrate dehydrogenase (IDH) mutations versus IDH wild-type tumors

	IDH mutation					IDH wild type			p	
	Radiation therapy	Without radiation therapy	p	Chemotherapy	Without chemotherapy	Radiation therapy	Without radiation therapy	Chemotherapy		Without chemotherapy
Mean survival (mo)	33.2	11.75	0.03	35.6	25.4	24.5	55	32.7	25.5	0.59
Mean progression (mo)	31.1	-	N/A	26.8	46.8	18.67	-	25.5	5	-

and progress-free survival (as ascertained by follow-up magnetic resonance imaging [MRI] scans), quantified in months, and substratified according to the histopathological categories, extent of surgical resection, and specific molecular mutations. Analysis was performed using IBM SPSS Statistics Version 23 and STATA Version 16. A *p*-value of less than 0.05 was considered statistically significant, with 95% confidence intervals reported.

Results

Between 2008 and 2018, SKCMH operated on 281 patients with LGG, of which 196 (69.8%) were males and 85 (30.2%) were females. Surgeries included biopsies (16.73%), subtotal resections (58.01%), and gross total resections (25.27%) for astrocytic tumors (64.77%), oligodendrogliomas (20.64%), gangliogliomas (1.78%), ependymomas (3.20%), and other (9.61%) low-grade glial tumors. Adjuvant treatment included radiation therapy and chemotherapy (both PCV and temozolomide).

Chemoradiotherapy for all patients was carried out as adjuvant treatment postsurgery. Radiation therapy and PCV was received by 85 patients, while radiation therapy and temozolomide were administered to 15 patients. Only radiation therapy was received by 143 patients, and chemotherapy without specification was given to 40 patients.

Astrocytic Mutations

Of the astrocytic 182 tumors included in our study, 47 patients underwent biopsies, 110 underwent subtotal resections, and gross total resection was achieved for 25 patients. Genetic analysis was carried out for 64 tumors, of which 93.7% had IDH mutations and 6.25% were IDH wild-type tumors. The mean survival in months for tumors with IDH mutations was 32.2 months, whereas the mean survival in months for IDH wild-type tumors was 31.3 months (*p* > 0.05). The mean time to progression in months for tumors with IDH mutations was 27.9 months and the mean survival in months for IDH wild-type tumors was 18.7 months, again a difference that was insignificant. Chemotherapy had a significant effect on the mean survival of tumors with IDH mutations; as can be seen in ►Table 1, the mean survival for patients who underwent chemotherapy was 35.6 months, whereas the mean survival for patients who did not undergo chemotherapy was 25.4 months

(*p* < 0.05). The effects of the extent of resection on tumors with IDH mutations versus IDH wild-type tumors can be found in ►Table 2.

Chromosomal Deletions in Oligodendrogliomas

Of the 58 oligodendrogliomas present in our study, 11 underwent biopsies, 38 underwent subtotal resections, and 9 underwent gross total resections. Genetic analysis was carried out for 45 tumors, of which 88.9% had a 1p19q co-deletion and 11.1% did not have a deletion. The mean survival for tumors that had a 1p19q co-deletion was 54.2 months, whereas the mean survival for 1p19q nondeletions was 41.2 months, which was insignificant. However, the mean time to progression for 1p19q co-deletions and 1p19q nondeletions was 55.5 and 32 months, respectively, which was statistically significant (*p* < 0.05). 1p19q co-deleted tumors also demonstrated a longer time to progression when treated with chemotherapy, with the mean time to progression for patients undergoing chemotherapy and not undergoing chemotherapy being 63.5 and 34.5 months, respectively (*p* < 0.05), as shown in ►Table 3. The effects of the extent of resection on tumors with 1p19q co-deletions can be found in ►Table 4.

Survival

The Kaplan–Meier curves used to analyze survival according to the specific characteristics are the following: IDH mutation status, alpha-thalassemia X-linked intellectual disability syndrome (ATRX) retention, 1p19q co-deletion, and histopathological subtype. Survival trends can be seen in ►Figs. 1–3.

Discussion

Our data suggest a longer overall survival time for low-grade oligodendrogliomas in comparison to astrocytomas, on an average of 10 months. Gross total resection of the tumor yielded significantly improved survival times as well for all LGGs within our population. On subanalysis according to the molecular markers, IDH wild-type LGG had a lower survival time, as depicted in the Kaplan–Meier curves. Similarly, improved survival times were seen for ATRX-retained and 1p19q co-deleted LGGs.

The study provided insight into the interplay between intratumoral mutations and treatment response. The overall

Table 2 Extent of resection outcomes for isocitrate dehydrogenase (IDH) mutations versus IDH wild-type tumors

	IDH mutation				IDH wild type			
	Biopsy	Subtotal resection	Gross total resection	<i>p</i>	Biopsy	Subtotal resection	Gross total resection	<i>p</i>
Mean survival (mo)	26.2	33.2	41	0.38	27.8	28	N/A	0.99 (between biopsy and subtotal resection)
Mean progression (mo)	49.3	24	29	0.22	22.5	11	N/A	N/A

Table 3 Adjuvant treatment outcomes for 1p19q co-deleted tumors versus 1p19q nondeleted tumors

	1p19q Co-deletion				1p19q Nondeletion				p
	Radiation therapy	Without radiation therapy	Chemotherapy	Without chemotherapy	Radiation therapy	Without radiation therapy	Chemotherapy	Without chemotherapy	
Mean survival (mo)	51.8	N/A	57.6	56.5	42.2	67	44.3	36.5	0.7
Mean progression (mo)	59.6	N/A	63.5	34.5	32.9	-	32	-	-

mean survival in months between IDH-mutant tumors and IDH wild-type tumors in astrocytomas is not significant, nor is the mean progression time significant between a mutant and a wild-type tumor. However, evidence suggests that there is, in fact, a difference in survival outcomes between IDH mutants and IDH wild-type tumors, as the latter is more genetically similar to more aggressive glioblastomas. The difference between our findings and global literature may be a result of our study using a small sample size. However, our study does explore the effects of various treatments on IDH mutations, and here we have found similarities between our results and existing work. When treated with chemotherapy, IDH-mutant astrocytomas have significantly longer overall survival times (but not progression-free survival times) when compared with IDH-mutant astrocytomas that are not treated with chemotherapy. This is supported in the literature, including a 2010 study that states that IDH mutations appear to be an important marker suggesting a promising prognosis in LGGs, while untreated IDH-mutant astrocytomas have a poorer prognosis.⁶ There was no significant difference in the mean overall or progression-free survival between IDH-mutant and IDH wild-type tumors treated with chemotherapy.

Further, treatment with chemotherapy on IDH wild-type tumors does not impact survival time when compared with IDH wild-type tumors that did not receive chemotherapy. The impact of chemotherapy on the progression time of IDH wild-type tumors could not be assessed due to lack of available data. Radiation therapy is also shown to benefit IDH-mutant tumors; however, since there was only one case of an IDH wild-type tumor that was not treated with radiation, survival outcomes could not be ascertained. Extent of resection did not impact the overall or progression-free survival in either IDH-mutant or IDH wild-type astrocytomas. These findings differ from those of glioma studies in high-income countries, and therefore further studies are warranted. With a larger sample size, our findings may reflect those established in literature. However, the differences in our results may also indicate that LGGs present distinctively in low- and middle-income countries and may therefore have different prognoses and survival outcomes depending on the mutation status and extent of resection.

In oligodendrogliomas, the mean survival and progression between 1p and 19q co-deletion and nondeletion are both statistically significant, suggesting that chromosomal co-deletions have a better prognosis. The effect of radiation therapy on 1p and 19q co-deletions could not be assessed due to the nontreatment groups only having one data point.

While tumors with either co-deletions or nondeletions did not appear to respond differently to chemotherapy in terms of survival, chemotherapy did have an impact on progression-free survival in 1p/19q co-deleted oligodendrogliomas. The impact of chemotherapy on 1p and 19q co-deletions versus nondeletions proposed that overall survival was not impacted by chemotherapy, but chemotherapy did significantly affect progression-free survival, indicating that 1p and 19q co-deleted tumor types have a delayed progression when treated with chemotherapeutic agents. This is

Table 4 Extent of resection outcomes for 1p19q co-deleted tumors versus 1p19q nondeleted tumors

	1p19q Co-deletion				1p19q Nondeletion		
	Biopsy	Subtotal resection	Gross total resection	<i>p</i>	Biopsy	Subtotal resection	Gross total resection
Mean survival (mo)	39.2	53.7	91.7	0.03	34.5	44.7	67
Mean progression (mo)	56.3	53	70.8	0.7	40.5	30.4	–

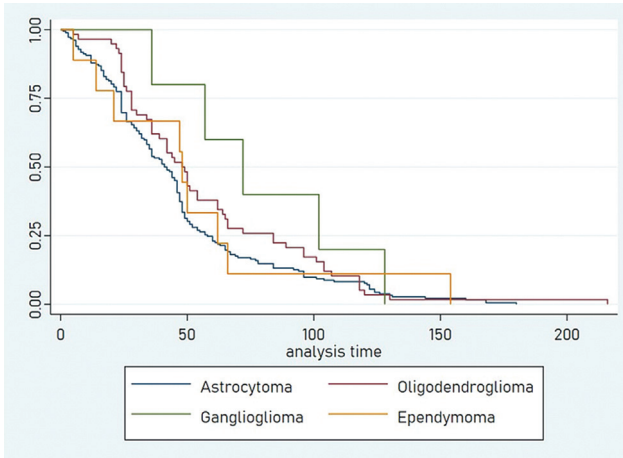


Fig. 1 Survival by low-grade glioma (LGG) subtype.

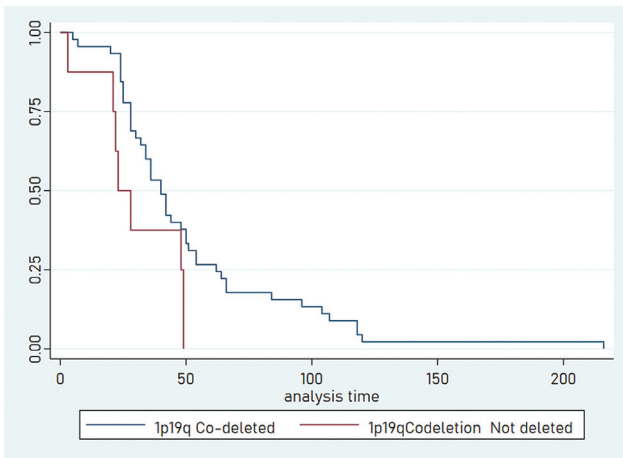
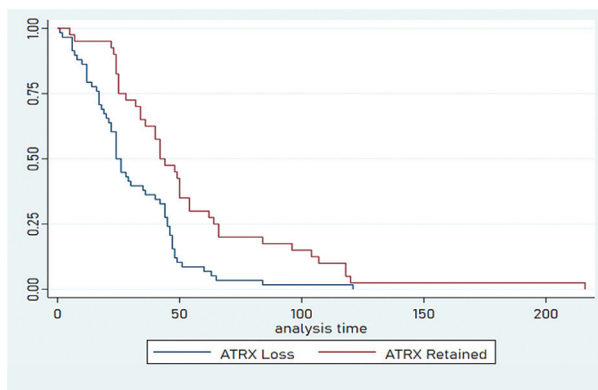


Fig. 2 Survival by 1p19q co-deleted status.



only partially corroborated by Iwadate et al's conclusions that 1p/19q co-deleted oligodendrogliomas can be treated solely with chemotherapy without jeopardizing overall survival.⁷ While both this study and Iwadate et al's study assessed patients at a single center, this difference may be explained by small sample sizes in both studies ($n = 48$ in Iwadate et al's study and $n = 37$ in our study). Further studies conducted with larger sample sizes are required to further determine the effects of chromosomal co-deletions on response to treatment, overall survival, and progression-free survival. Within our data set, we were able to show a significant ($p = 0.03$) benefit with gross resection of the tumor in comparison with suboptimal resection or biopsy followed by adjuvant treatment. Volumetric analyses of resection of LGG show that reducing the tumor burden has a significant impact on overall survival.⁸ A U.S.-based study also showed that the extent of resection improved survival of those with 1p/19q co-deletions in oligodendrogliomas.⁹ While Kinslow et al found that gross total resections improved overall survival in low-grade oligodendroglioma subtypes, subtotal resections did not significantly improve outcomes in the United States. However, our findings have shown that, while gross total resections do have the longest overall survival, subtotal resections for oligodendrogliomas with a 1p/19q co-deletion still have better prognoses than those who only underwent biopsies. In the United States, gross total resections revealed a 61-month survival time, while our study found a 91.8-month survival time. Our study holds true to the average LGG survival average between 4.7 and 9.8 years.² For overall LGG within our study, improved survival was seen in IDH-mutated and ATRX-retained tumors, with conflicting results regarding the role of 1p19q co-deletions.

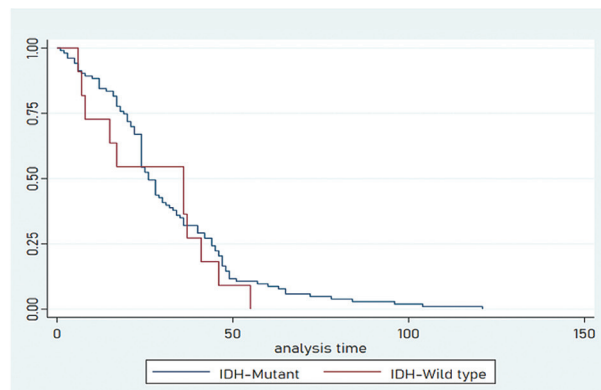


Fig. 3 Survival for isocitrate dehydrogenase (IDH) mutations and alpha-thalassemia X-linked intellectual disability syndrome (ATRX) loss.

Interestingly, a comparison can be made between IDH-mutant astrocytomas in our cohort with 1p19q non-co-deleted oligodendrogliomas; this is primarily due to the updates within the WHO 2021 Classification of CNS Tumors where non-co-deleted oligodendrogliomas are reclassified as IDH-mutant astrocytomas. As seen in the data, similar months to progression are seen (27.9 for IDH-mutant astrocytomas and 32 for non-co-deleted oligodendrogliomas). However, survival data in our cohort show longer survival for non-co-deleted oligodendrogliomas (41.2 months). Response to chemotherapy was equivocal in both groups, with trends showing good response to treatment in terms of overall survival. However, response to radiotherapy is observed to be diametrically opposed in our cohort; IDH-mutant astrocytomas are shown to have statistically significant ($p = 0.03$) improved survival after completing cycles of radiotherapy. Non-co-deleted oligodendrogliomas had no significant improvement in overall survival with similar treatment.

Conclusion

Our study found that in Pakistan, lower-grade gliomas with IDH, 1p19q, and ATRX mutations respond differently to treatment than wild-type gliomas. While IDH-mutated tumors do not impact survival, their response to chemoradiotherapy is in line with global findings. 1p19q co-deletions indicate better survival outcomes; however, chemotherapy only impacted progression-free survival and not overall survival. The differences between our findings and global data can be explained by the small sample size in our study. Further studies with larger sample sizes are required to gain a better understanding of lower-grade glial tumor treatment and survival in Pakistan and South Asia.

Author Contribution

All authors contributed to the study conception and design. Material preparation and data collection were performed by SBA and IY. Analysis was done by MHB, MS, and SBA. The first draft of the manuscript was written by MHB, MS, and SBA, and all the authors commented on

previous versions of the manuscript. All the authors read and approved the final manuscript.

Ethical Approval

Prior to initiation of this study, ethical approval, and exemption was granted by the IRB (Institutional Review Board) at the Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan.

Funding

None.

Conflict of Interest

None declared.

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