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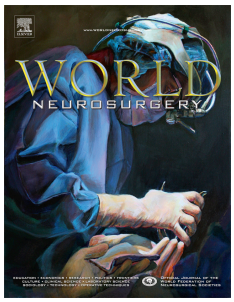

Analytical Insights into the Epidemiology of Glioma and Treatment Modalities

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Abstract

Background. Glioma is a common malignant intracranial tumor. This study investigated different treatment strategies and multiple epidemiological characteristics—including age, sex, ethnicity, and income—on the risk of developing glioblastoma and patient survival outcomes.

Methods. We obtained data from 44,778 patients treated for gliomas (1980–2019) from the Surveillance, Epidemiology, and End Results (SEER) database. The survival curve was plotted using the Kaplan-Meier method, and Cox regression analysis was employed for prognostic factor analysis.

Results. This study analyzed the incidence and survival trends of glioma based on population data from the SEER database. The overall incidence rate exhibited a downward trend, with a higher incidence rate among Whites, men, and people aged >60 years. The survival rate of each subgroup gradually increased. Surgical treatment yields the best survival rates in grade 1–2 gliomas. In grade 3–4 gliomas, survival outcomes are better when treated with surgery, followed by chemotherapy. Cox regression analysis of the prognosis of patients undergoing postoperative radiotherapy revealed that chemotherapy (HR, 0.386; 95% CI, 0.272-0.549) and IDH mutations (HR, 0.181; 95% CI, 0.097-0.335) were protective factors, whereas grade 3–4 tumors (HR, 2.179; 95% CI, 1.303-3.645) and age ≥50 years (HR, 1.746; 95% CI, 1.239-2.461) were risk factors. For patients with IDH mutations and/or 1p/19q codeletion, surgery combined with chemoradiotherapy offers the best therapeutic efficacy.

Conclusion. These findings reveal the dynamic changes in the incidence pattern of glioma, the continuous improvement in survival rates, and the prognostic value of molecular characteristics and

socioeconomic factors, deepening the understanding of the effects of different treatment modalities and providing a basis for clinical diagnosis and treatment strategies.

Keywords: glioma; surveillance, epidemiology, and end Results; survival; isocitrate dehydrogenase; chromosome 1p/19q deletion;

Introduction

Gliomas are the most common primary central nervous system (CNS) tumors, accounting for over 40% of all CNS tumors[1]. Originating from glial cells or precursor cells, gliomas include astrocytomas, oligodendrogliomas, glioblastomas (GBMs), ventricular meningiomas, and other rare tumors. Common glioma symptoms include rapid growth or destruction of brain structures, with neurological symptoms that include focal neurological signs, altered mental status, and elevated intracranial pressure. In addition, the incidence and survival of these patients vary significantly by histological type, age at diagnosis, sex, race, ethnicity, and geographic location[2, 3].

Despite remarkable breakthroughs in molecular targeted therapies and immunotherapies for various cancer types, their therapeutic value in glioma remains limited, potentially because of the selective permeability of the blood–brain barrier, which severely restricts most therapeutic drugs from entering the CNS and accumulate in effective therapeutic concentrations in brain tumor regions[4]. Furthermore, glioma cells exhibit highly invasive growth characteristics, allowing them to invade diffusely into normal brain tissue and complicating complete surgical resection. These core therapeutic bottlenecks for glioma necessitate in-depth characterization to advance precision medicine and improve patient outcomes[5].

The current standard of care for glioma is a comprehensive, multimodal approach that combines surgery with radiotherapy, chemotherapy, targeted agents, and tumor-treating fields (TTFields)[6]. Treatment strategies require rigorous individualization according to specific tumor molecular and clinicopathological profiles. To this end, we examined glioma incidence and survival patterns stratified by age, sex, race, and income status. Furthermore, we assessed and compared the therapeutic efficacy of various treatment modalities over a 40-year period for gliomas of different grades and genetic backgrounds. These insights will enhance the understanding of glioma heterogeneity and contribute to evidence-based clinical decision-making.

Patients and methods

The analyzed data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database, a population-based cancer registry maintained by the National Cancer Institute. We identified 44,778 patients treated for gliomas (classified per the World Health Organization International Classification of Diseases of Oncology, Third Edition [ICD-O-3] codes C71.0–C71.9) between 1980 and 2019 from eight SEER registries on incidence, survival, and treatment for patients with gliomas. We analyzed incidence and survival rates based on tumor grade (grades 1–4) and genetic profiles, including chromosome 1p/19q deletion (data available from 2010 onward) and Isocitrate Dehydrogenase (IDH) mutation status (data available from 2018 onward). To adjust for differences in distribution by ethnicity, incidence rates were normalized to the 2000 U.S. population and reported per 100,000 population. Survival rate were evaluated using period analysis. Rank-sum ratios (RSR) were derived by comparing the absolute survival rate of patients with gliomas with the expected survival rate for individuals of the same age, sex, and ethnicity to determine the survival rate associated with gliomas.

Because the SEER database has been tracking median household income inflation since 1990, income data collected from patients in 1980–1989 were excluded. From 1990 to 2019, income level was categorized as low (<$35,000–$49,999), middle ($50,000–$69,999), or high (>$70,000). Sex was classified as male or female, and ethnicity was classified as White, Black, or other ethnic groups (American Indian/Alaskan Native or Asian/Pacific Islander). Age at diagnosis was stratified into five groups: 0–19, 20–39, 40–59, and ≥60 years. RSR estimates were calculated using the Ederer II method and expressed as percentages. Standard statistical techniques were performed with SEER*Stat software.

Herein, R Studio (version 4.1.0) and GraphPad Prism (version 10.1.2) software were used for statistical analysis and chart drawing. The Kaplan–Meier method was used to compare the differences in survival rates among groups with different clinicopathological characteristics and treatment methods and to plot the survival curve. The log-rank test was used to compare between groups. We applied the Cox proportional hazards regression model to analyze the characteristics of patients undergoing postoperative radiotherapy. Initially, potential prognostic variables were screened through univariate analysis. Then, variables with $P < 0.05$ were included in the multivariate model for stepwise regression analysis to correct for influencing confounding factors and determining independent prognostic predictors. The results were expressed with hazard ratios (HR) and its 95% confidence intervals (CI).

Results

Incidence of gliomas in 1980–2019

Gliomas increased every decade from 1980–2019, with GBM comprising the highest percentage. The incidence estimates for GBM (48.9% in 1980–1989, 56.5% in 1990–1999, 62.4% in 2000–2009, and 67.1% in 2010–2019), astrocytoma (32.5%, 15.2%, 8.2%, and 7.0%, respectively), astrocytoma anaplastic (6.2%, 8.1%, 7.1%, and 9.5%, respectively), oligodendroglioma (4.5%, 8.4%, 7.6%, and 4.6%, respectively), Oligodendroglioma anaplastic (0.3%, 1.6%, 3.0%, and 2.5%, respectively), Pilocytic astrocytoma (2.3%, 5.3%, 7.4%, and 6.6%, respectively), fibrillary astrocytoma (2.7%, 2.6%, 2.2%, and 0.8%, respectively) and Gemistocytic astrocytoma (1.7%, 1.2%, 0.7%, and 0.4%, respectively) and other tumors (1.1%, 1.1%, 1.4%, and 1.6%, respectively) showed different patterns of increases and decreases over the period (Supplement Table 1 and Figure 1).

Trends in incidence of grade 1 gliomas

From 1980–2019, the incidence of grade 1 glioma cases registered in the SEER database was 0.1/100,000, 0.2/100,000, 0.1/100,000, and 0.1/100,000, respectively. Overall, the incidence of grade 1 gliomas was stable and did not differ significantly by ethnicity, sex, age, or income (Supplement Table 2 and Figure 2 A1–A4).

Trends in incidence of grade 2 gliomas

From 1980–2019, the incidence of grade 2 glioma cases registered in the SEER database showed a decreasing trend, to 0.5/100,000, 0.5/100,000, 0.3/100,000, 0.2/100,000. Patients identifying as White had a slightly higher incidence than other ethnicity; the incidence was lower in patients younger than 19 (Supplement Table 3 and Figure 2 B1–B4).

Trends in incidence of grade 3 gliomas

From 1980–2019, the incidence of grade 3 glioma cases registered in the SEER database showed a decreasing trend to 0.7/100,000, 0.4/100,000, 0.2/100,000, 0.1/100,000. Males demonstrated a higher incidence than females; this trend increased with age (Supplement Table 4 and Figure 2 C1–C4).

Trends in incidence of grade 4 gliomas

From 1980–2019, the incidence of grade 4 glioma cases registered in the SEER database remained

stable at 1.6/100 000, 1.9/100 000, 1.7/100 000, 1.8/100,000. Whites had a higher incidence than other ethnic groups; males had a higher incidence than females. Glioma incidence increased across the board with age; middle-income patients had the highest incidence (Supplement Table 5 and Figure 2 D1–D4).

Relative survival estimates of grade 1 gliomas

For 1980–1989, 1990–1999, 2000–2009, and 2010–2019, the 12-month (90.4%, 93.4%, 95.2%, and 95.8%, respectively), 36-month (79.1%, 88.1%, 90.7%, and 91.6% respectively), and 60-month (71.1%, 84.7%, 85.2%, and 90.8%, respectively) survival rates for each subgroup steadily increased. Women demonstrated slightly better survival than men; older patients consistently demonstrated lower survival (Supplement Table 6 and Figure 3–5).

Relative survival estimates of grade 2 gliomas

For 1980–1989, 1990–1999, 2000–2009, and 2010–2019, the 12-month (78.4%, 84.9%, 92.4%, and 93.2%), 36-month (63.9%, 72.6%, 81.8%, and 82.1%), and 60-month (55.1%, 65.1%, 72.4%, and 79.3%) overall survival (OS) and survival rates mostly improved for each subgroup mostly improved. Older patients with grade 2 gliomas demonstrated worse survival than their younger counterparts (Supplement Table 7 and Figure 3–5).

Relative survival estimates of grade 3 gliomas

For 1980–1989, 1990–1999, 2000–2009, and 2010–2019, the 12-month (44.6%, 43.5%, 48.5%, and 57.1%), 36-month (21.4%, 20.6%, 27.1%, and 30.6%), and 60-month (15.0%, 16.7%, 21.3%, and 21.8%) survival rates for each subgroup mostly improved. The higher the age, the lower the survival rate and it decreased significantly for patients aged 60 years and older. The survival rate of patients aged 20–39 years at 36 months increased significantly after 2000 (Supplement Table 8 and Figure 3–5).

Relative survival estimates of grade 4 gliomas

The survival rate was lowest for patients with grade 4 gliomas. The 12-month (41.5%, 40.5%, 47.4%, and 61.4%, respectively), 36-month (18.6%, 16.3%, 21.2%, and 31.1%, respectively), and 60-month (14.8%, 12.2%, 16.5%, and 24.3%, respectively) survival rates for each subgroup showed upward trends in 1980–1989, 1990–1999, 2000–2009, and 2010–2019. The survival rate for other ethnicities was higher than that of patients who identified as Black or White. The survival rate decreased with age, and 20–39-year-olds had the highest survival rate among all groups. The higher the income, the better the survival rate (Supplement Table 9 and Figure 3–5).

Relative survival of gliomas by age, sex, ethnicity, and income

There was no significant difference between ethnicity in grade 1–3 glioma, but the survival rate of other ethnicity and the survival rate of black race were higher than that of White race in grade 4 glioma ($P < 0.05$). The survival rate of women in grade 1 and grade 2 gliomas was higher than that of men ($P < 0.05$). The survival rate decreased with age, but the survival rate was highest in grade 4 gliomas aged 20–39 years ($P < 0.05$). Income-related differences were evident for patients with grade 1, 2, and 4 gliomas ($P < 0.05$). Higher-income patients had better survival; however, there was no significant difference in grade 3 gliomas (Table 6–9 and Figure 6).

Survival analysis of treatment patterns for gliomas

For grade 1 and 2 gliomas, surgery alone can significantly improve the survival rate. Furthermore, surgery plus chemotherapy (SCT) also yielded very good outcomes. Particularly, the survival rate for postoperative radiotherapy (PORT) was significantly higher than that for preoperative radiotherapy between 1990 and 1999. No significant trend existed between treatment modalities in grade 3 gliomas from 1980–1999. From 2000–2019, SCT was most effective at improving survival. In grade 4 gliomas, SCT showed the best improvement in survival among all treatments, followed by SCRT. The effects of

RT or surgery alone were the worst (Figure 7).

Univariate analysis was conducted on various clinical and molecular characteristics of patients with glioma who received PORT. The variables investigated were sex, ethnicity, age, tumor location, chemotherapy use, IDH mutation status, 1p/19q codeletion status, income, and tumor grade and size. Reportedly, the differences in variables, such as age, chemotherapy, IDH status, 1p/19q codeletion status, and tumor grade were all statistically significant ($P < 0.05$). Stepwise analysis performed using the multivariate Cox proportional hazards regression model indicated that age ≥50 years (HR, 1.746; 95% CI, 1.239–2.461), grade 3-4 gliomas (HR, 2.179; 95% CI, 1.303–3.645) are independent risk factors for patient mortality and significantly increased mortality risk ($P < 0.05$). Conversely, chemotherapy (HR, 0.386; 95% CI, 0.272–0.549) and the presence of IDH mutations (HR, 0.181; 95% CI, 0.097-0.335) were protective factors that could significantly reduce mortality risk (Supplement Table 10 and Figure 8).

Survival analysis of glioma with IDH mutations and chromosome 1p/19q deletion

Patients with IDH mutant glioma accounted for 13.3% of all patients, including 167 grade 2 gliomas and 178 grade 3 gliomas. The patients with 1p/19q deletion accounted for 5.1% of all patients (n = 110 grade 2, n = 70 grade 3, and n = 165 grade 4 cases). Of the patients with IDH mutation and chromosome 1p/19q codeletion glioma, 76 were grade 2, and 66 were grade 3.

Survival analysis showed that in grade 2 gliomas, the survival rate of patients with IDH mutations was higher than that of patients with IDH mutations combined with 1p/19q codeletion. Among grade 3 patients, although the survival rate of the 1p/19q codeletion was higher than that of the simple IDH mutation type, the difference was not significant ($P = 0.125$). In terms of treatment, the IDH-mutant type is more suitable for SCRT, while the 1p/19q deletion type has a better therapeutic effect with SCT. For patients with IDH mutations combined with 1p/19q codeletion, SCRT is recommended as the first choice (Figure 9).

Discussion

Glioma is one of the most common malignant CNS tumors. Analysis of the data collected between 1980 and 2019 revealed that the overall incidence of gliomas showed a decreasing trend, along with a continuous improvement in patient survival. Surgical treatment alone yielded the best therapeutic efficacy for grade 1–2 gliomas, whereas SCT is more effective for grade 3–4. Notably, although the overall benefit of combined CRT in grade 1–2 gliomas is limited, this treatment regimen still significantly improved survival in patients with specific molecular subtypes with IDH mutations and/or 1p/19q deletions. Furthermore, IDH-mutant status and chemotherapy are associated with prolonged survival in patients with PORT gliomas. These findings provide an important rationale for precision treatment strategies for gliomas.

This study demonstrates a clear sex dimorphism in glioma, characterized by a significantly higher incidence of grade 2–4 gliomas in men than in women but a more favorable survival prognosis in women. This gender dimorphism may be multifactorial; genetic analysis revealed that female patients with low-grade gliomas (LGG) had significantly higher X-chromosome mutations loads than males, which is consistent with previous findings on sex differences in GBM (male-to-female incidence ratio, 1.61:1)[7-9]. Notably, the male incidence advantage persists, even in IDH-mutant gliomas[10, 11]. These findings provide crucial clues for understanding sex-specific mechanisms in glioma development.

Consistent with the results of other studies[12-14], the incidence of gliomas was significantly higher in White than other ethnic populations; however, the survival prognosis was relatively poorer. This epidemiological difference may be attributed to population-specific differences in susceptibility allele

frequencies and genetic pathways of tumorigenesis in different racial groups[15]. Reportedly, non-White patients with glioma have higher p53 mutation loads, a molecular feature that may partially explain the higher incidence in White groups[16]. Notably, non-Hispanic White patients have the worst clinical prognosis of all racial groups[15]. Several factors must be considered while interpreting these results. First, the SEER database used herein suffers from overrepresentation of the non-Hispanic White population, which may affect the external validity of the study conclusions[17]. Second, the higher morbidity in the White population may be associated with a better healthcare coverage system, which may facilitate higher disease detection rates and diagnostic accuracy[18, 19].

Herein, no significant difference was found in morbidity between income subgroups, although the survival rate of high-income patients was significantly higher than that of the low-income group. This finding is consistent with evidence from previous studies that patients with high socioeconomic status usually show a better survival prognosis[20, 21]. Possible explanations include low levels of exposure to environmentally harmful factors in high-income groups[22] and better access to quality, comprehensive healthcare resources, which are protective factors that effectively reduce the mortality risk in this population[23].

This study confirms significant age differences in the incidence and prognosis of gliomas. Older patients show a higher incidence and worse survival prognosis, which is consistent with Ladomersky's findings of 3.4- and 7-fold increases in the incidence and mortality rates, respectively, for GBM in people aged >65 years compared with other age groups[24]. *IDH1/2* mutations (primarily *IDH1* R132H) occur in 5%–10% of primary GBM in adults, whereas the mutation rate in secondary GBM can reach >80%. This mutation inhibits α-ketoglutarate-dependent dioxygenase through 2-hydroxyglutarate accumulation, affects epigenetic regulation, and is often accompanied by methylation of the methylguanine methyltransferase (MGMT) promoter methylation, which may enhance temozolomide (TMZ) sensitivity. In contrast, although the IDH mutation rate is <5% in pediatric patients, *H3F3A* mutations are more common[25], inducing RT resistance by activating the ATM/ATR repair pathway, which may be a key mechanism of the poor prognosis in children[26].

Surgery has always been the primary treatment method in patients with grade 1 glioma. Between 1980 and 1999, OS was significantly higher than that of other treatment regimens. Sequence volume measurement by fluid-attenuated inversion recovery confirmed that the 5-year OS of patients with glioma decreased with the extent of resection: gross total resection (GTR) 95%, near-total resection (NTR) 80%, and subtotal resection (STR) 70%[27]. Thus, GTR was established as a key prognostic factor for long-term survival. However, in 2000–2019, the survival benefit of SCT exceeded that of stereotactic radiotherapy (SRT). This is consistent with earlier research findings. The Southwest Oncology Group trial on partially resected[28]. LGG in 1993 found that the objective response rate (ORR) of RT alone (79%) was significantly higher than that of RT combined with lomustine chemotherapy (CCNU; 54%). Furthermore, chemoradiotherapy (CRT) did not improve survival rates[29]. This may be because RT technology was still imperfect, and chemotherapeutic drugs were in the exploratory stage. The survival trends following treatment were similar between grade 1 and 2 gliomas. In 1980–1999, the survival benefit of SRT was significantly superior, whereas the clinical efficacy of SCT gradually improved after 2000. In 2010–2019, the OS of patients undergoing SRT, SCT, and SCRT were comparable. The single-arm phase II trial by Wahl et al. (2017) found that TMZ monotherapy in 120 patients with WHO grade II gliomas (57 oligodendrogliomas, 20 oligodendroglioma-astrocytomas, and 43 astrocytomas) achieved a median OS of 9.7 years, indicating efficacy in high-risk LGG (IDH-mutant non-1p/19q codeletion and 1p/19q codeletion). Thus, TMZ monotherapy could serve as a

transitional strategy for delaying or omitting RT[28]. The RTOG 0424 Phase II trial confirmed that RT combined with concurrent/adjuvant TMZ treatment for high-risk LGG achieved a 3-year OS rate of 73.1%[30]. In a prospective trial conducted in 2016, LGG was stratified based on age and GTR status. The low-risk group (<40 years old and GTR) was observed and followed up. In the high-risk group (≥40 years old and/or STR/NTR), RT combined with PCV significantly prolonged median survival compared with radiotherapy alone (13.3 vs 7.8 years)[31]. The abovementioned study demonstrates the therapeutic significance of chemotherapy in grade 1–2 gliomas. Furthermore, RT may be suitable for patients with high-risk factors. Herein, surgery alone yields the best therapeutic efficacy, followed by SCT. This result may have several explanations. The SEER database lacks detailed data on surgical resection margins, and it only recently began incorporating molecular typing data into the grading system. Furthermore, our study did not perform risk stratification for grade 1–2 gliomas. Therefore, simple surgical treatment may have been more suitable for some patients classified as lower risk.

Notably, because of technological advancement in surgical techniques, the survival outcomes of patients with all grades of glioma who undergo surgery alone have gradually improved. However, for grade 3–4 gliomas, the efficacy of simple surgery remains limited, and the role of chemotherapy is becoming increasingly important. The 2012 RTOG 9402 trial established procarbazine (PCV) combined with RT as the standard treatment regimen for anaplastic oligodendroglioma with 1p/19q codeletion[32]. In addition, IDH mutation status predicts benefit from PCV chemotherapy independent from 1p/19q codeletion. The long-term follow-up results of the EORTC 26951 and RTOG 9402 studies were published in 2022[33]. The EORTC 26951 study demonstrated that PORT combined with six cycles of PCV adjuvant chemotherapy significantly improved patient survival compared with RT alone. The median OS was 3.5 years in the combination group and 2.6 years in the RT group, with 14-year OS rates of 25.1% and 13.4%, respectively, and 20-year OS rates of 16.8% and 10.1%, respectively. The benefit was even more pronounced in the 1p/19q codeletion subgroup, with a median OS of 14.2 vs. 9.3 years; 14-year OS rate of 51.0% vs. 26.2%; and 20-year OS rate of 37.1% vs. 13.6%. The RTOG 9402 study demonstrated that four cycles of neoadjuvant PCV followed by RT doubled the 20-year OS rate compared with RT alone (24.6% vs. 11.2%); however, no significant difference was found in median OS between the two groups. In the 1p/19q codeletion subgroup, combined therapy also demonstrated a clear survival advantage, with a median OS of 13.2 vs. 7.3 years; 14-year OS rate of 46.1% vs. 25.0%; and 20-year OS rate of 37% vs. 14.9%. Herein, the survival rate of SCRT after 2000 was indeed higher than that of SRT; however, both were lower than that of SCT. The CATNON trial published in 2017 demonstrated that for patients with IDH-mutant and 1p/19q non-codeletion anaplastic glioma, adjuvant TMZ after RT significantly improved survival, with a 5-year OS of 55.9%[34]. This finding theoretically supports the phenomenon observed herein—the introduction of TMZ adjuvant chemotherapy after 2,000 significantly prolonged OS following SCT. However, the therapeutic effect of RT alone was poor in gliomas of any grade, whereas the survival rate of PORT was lower than that of SCT. Because of the scarcity of clinical studies on these two treatment methods, the patients who can benefit from PORT could not be determined. Cox regression analysis revealed that IDH mutations and chemotherapy were associated with increased survival in patients undergoing PORT. In an RTOG trial, combination chemotherapy improved progression-free survival (PFS) in LGG compared with PORT (4.0 vs. 10.4 years)[31]. Patients with IDH mutations who received radiotherapy achieved a median survival of 10.1 years, whereas patients without mutations undergoing radiotherapy had a median survival of only 7.8 years[35].

In the treatment of grade 4 gliomas, although the short-term survival benefit of SCT is comparable with other combination regimens, its long-term survival benefit is more pronounced. The Stupp regimen, proposed in 2005, established the standard treatment for GBM, involving concurrent RT and TMZ followed by six cycles of adjuvant TMZ therapy[36]. This regimen significantly improved patient survival, with median OS increasing from 12.1 to 14.6 months, and the 2-year OS improving from 10.4% to 26.5%. Currently, various novel treatment strategies for grade 4 gliomas have emerged. *MGMT* and *TERT* promoter mutations provide important prognostic value in WHO grade 4 IDH-mutant astrocytomas. The methylation status of the MGMT promoter is a key predictive marker for the efficacy of TMZ therapy. In patients with GBM and MGMT promoter methylation, CCNU and TMZ combination therapy significantly prolonged median OS compared with TMZ monotherapy (median OS: 48.1 vs. 31.4 months), potentially establishing it as the new therapeutic standard for this subgroup[37]. Targeted therapy has also demonstrated significant efficacy. In 2009, the FDA approved bevacizumab for treating recurrent GBM, providing an imaging response rate of 63% and a 6-month PFS of 38%[38]. However, it did not improve OS. The 2019 INDIGO trial demonstrated that vorasidenib extended PFS to 27.7 months in patients with IDH-mutant gliomas and delayed indications for subsequent RT and chemotherapy. Considerably, the FDA has approved vorasidenib for treating patients aged ≥12 years with IDH*1/2* mutations who have undergone surgery for grade II astrocytoma or oligodendroglioma. Furthermore, IDH-mutant tumors may be more sensitive to immune checkpoint inhibitors, with an ORR of 36.1%, compared with 22.6% in the control group[39]. This sensitivity may be associated with higher tumor mutational burden. Reportedly, a genetically modified oncolytic adenovirus with enhanced antitumor activity demonstrated adequate safety and tolerability in patients with high-grade glioma, with a median PFS and OS of 9.1 and 18.4 months, respectively[40]. TTFields have also demonstrated significant efficacy. The EF-14 trial published in 2015 showed that in patients with newly diagnosed GBM, TTFields combined with TMZ treatment extended the median OS to 20.9 months and increased the 5-year survival rate to 13%, compared with only 5% in the control group[41].

Limitations

Although the SEER database is one of the most comprehensive data sources for assessing cancer incidence and survival patterns, it has certain limitations. The WHO classification system for gliomas has evolved from an early emphasis on histopathology (1st and 2nd Editions) to incorporating molecular markers as supplementary criteria (3rd and 4th Editions). In the 2021 5th Edition guidelines, an integrated diagnostic approach has been completely adopted, with IDH mutations and 1p/19q codeletion serving as core classification criteria; this implies that changes in classification standards may affect the probability of different grades occurring within the same tumor. For example, lesions previously classified as grade II astrocytomas must now be differentiated from IDH-mutant and wild-type variants. Oligodendroglioma diagnosis requires a concurrent IDH mutation and 1p/19q codeletion; if only IDH mutation is present, it is classified as astrocytoma; if IDH is wild-type, further evaluation is required to determine whether it is IDH wild-type GBM or another subtype. These changes may introduce bias by assigning different grades to the same glioma type. Although this study analyzed patients based on IDH status and 1p/19q deletion, the number of patients with IDH mutations registered in the SEER database was insufficient, which prevented more detailed stratified studies. In our study, SCT was associated with the most substantial survival benefit among patients with grade 3–4 gliomas. These findings suggest that besides surgery and chemotherapy, other treatments—like radiotherapy, targeted therapy, TTFields, and immunotherapy—may be more effective for certain

patient groups or those with specific molecular features. However, the SEER database does not include data on many of these treatments. In addition, the limited availability of genetic mutation data makes it difficult to perform detailed analyses of how treatments interact with molecular subtypes. Future work will focus on collecting more data to test these hypotheses and identify which patients benefit most from each treatment.

Conclusion

From 1980 to 2019, the incidence of grade 2–3 gliomas declined, and survival rates for all grades continued to improve. The results varied according to race, sex, age, and income. Surgery alone is the best treatment for grade 1–2 gliomas; however, SCT is superior for treating grade 3–4 gliomas. For glioma patients with PORT, chemotherapy and IDH mutations can significantly improve their survival prognosis. Overall, patients with IDH mutations and/or chromosome 1p/19q codeletion derive the greatest benefit from SCRT. The increasing precision of glioma molecular typing is expected to more accurate incidence and survival statistics. This improved classification will also guide the selection of more personalized treatment plans.

DATA AVAILABILITY STATEMENT Publicly available datasets were analyzed in this study. These data were derived from the following resources available in the public domain: Surveillance, Epidemiology, and End Results (SEER) (http://seer.cancer.gov/).

Ethics declaration

Review and/or approval by an ethics committee was not needed for this study because it only included analyses of secondary and publicly available data. Informed consent was not required for this study because it only included analyses of secondary and publicly available data.

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AUTHOR CONTRIBUTIONS Conception and design: Meichen Ji and Haiqing Ma. Collection and assembly of data: Meichen Ji and Qing Qi. Data analysis and interpretation: Liwei Zhao, Peixu Lin, Qing Li and Jian Wu. Manuscript writing: Yue Cheng and Yanzhen Lai. Critical review of the manuscript: Meichen Ji and Haiqing Ma. Final approval of manuscript: all authors.

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397
398 **Compliance with ethical standards**
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400 **Conflict of interest** The authors report no confict of interest concerning the materials or methods used
401 in this study or the fndings specifed in this paper.
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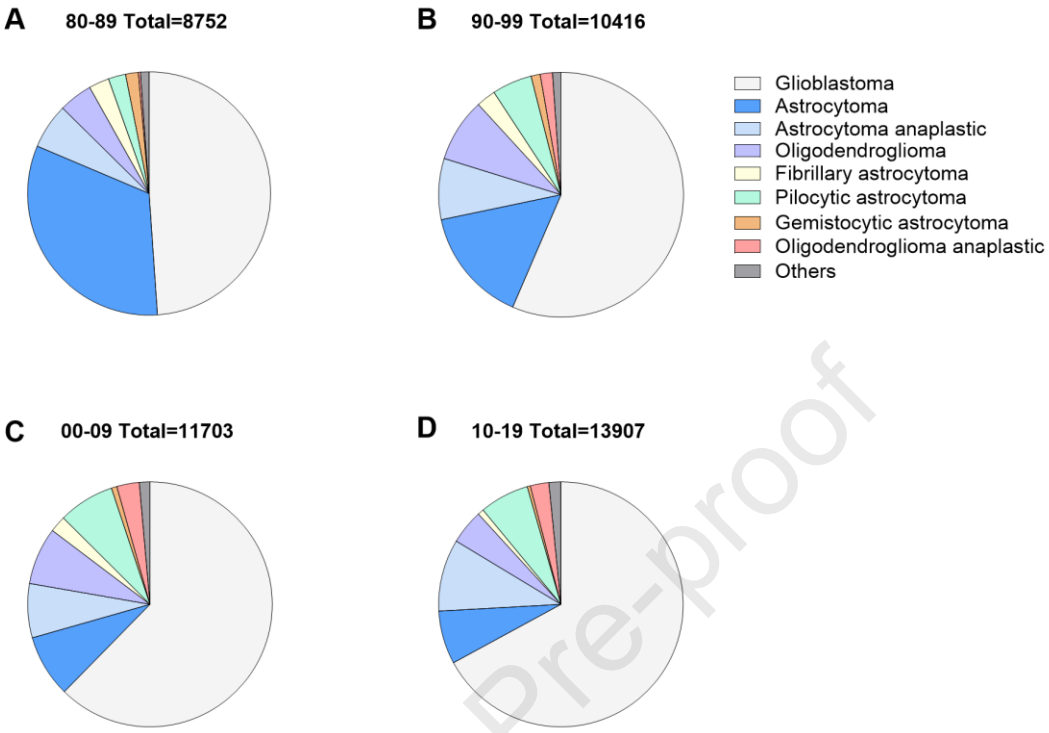


Figure 1. Distribution of different pathological types of tumors in gliomas, 1980-2019.

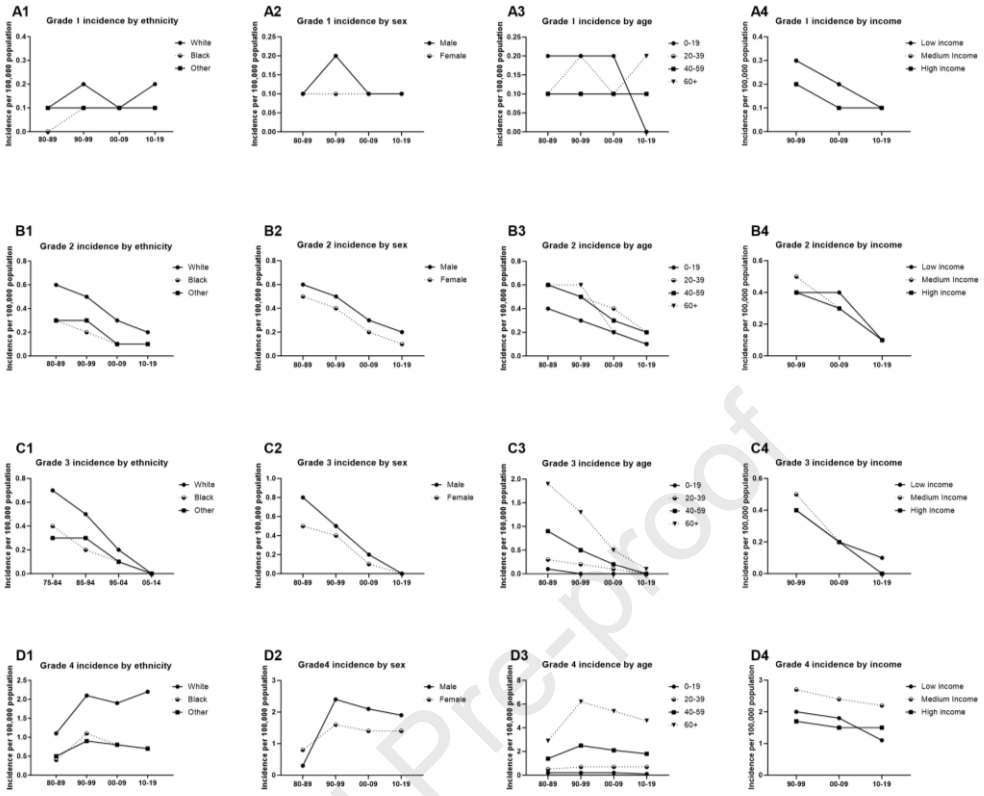
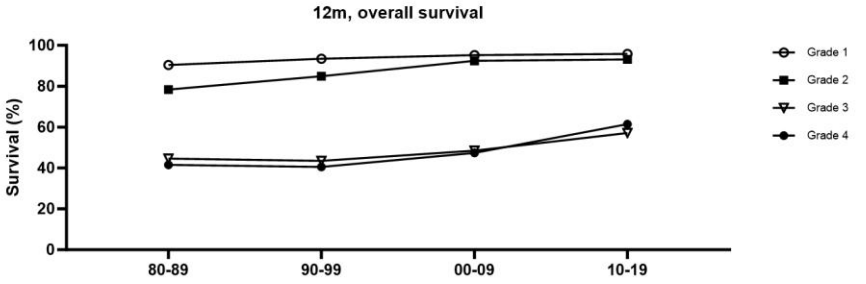
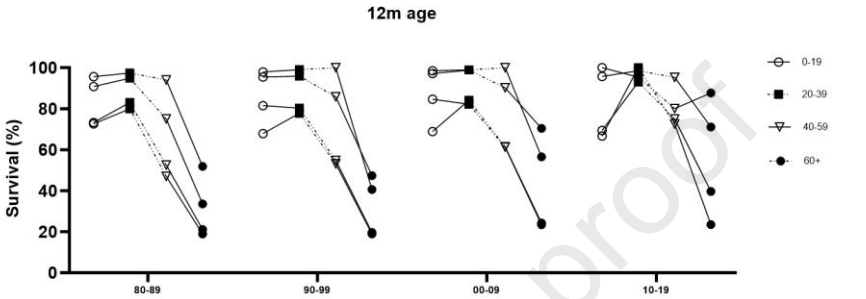
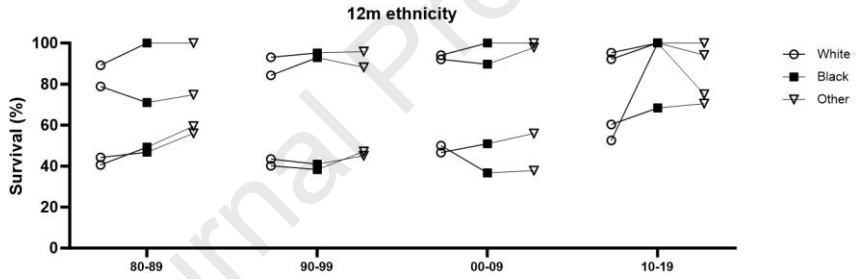
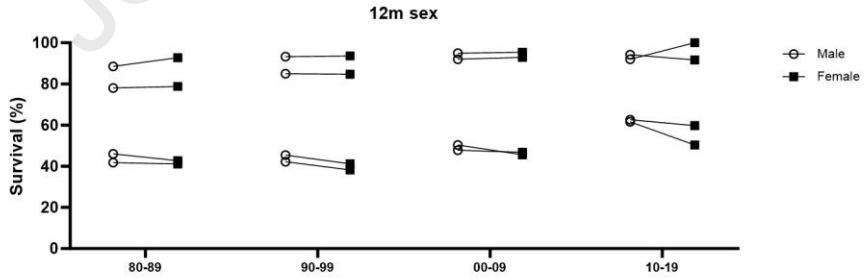


Figure 2. Trends in grade 1–4 gliomas incidence according to ethnicity, sex, age, and income, 1980-2019.









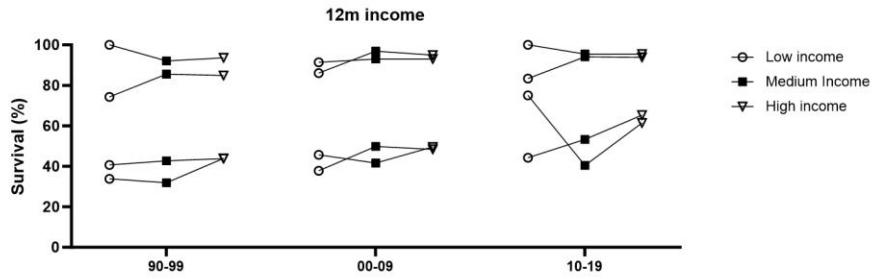
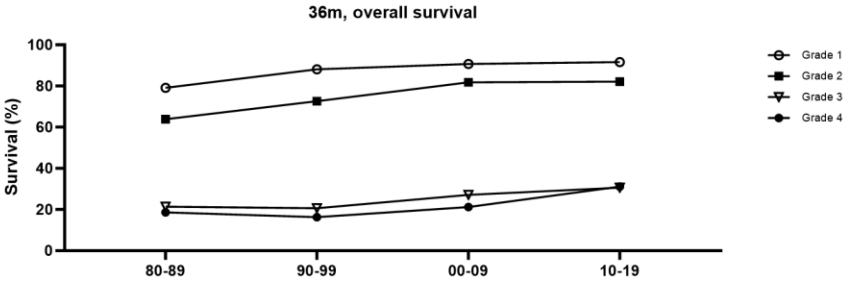
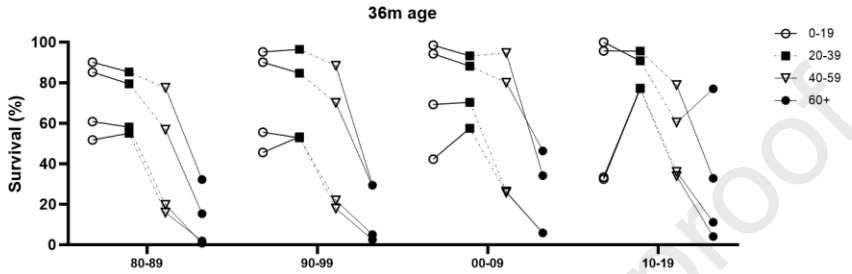
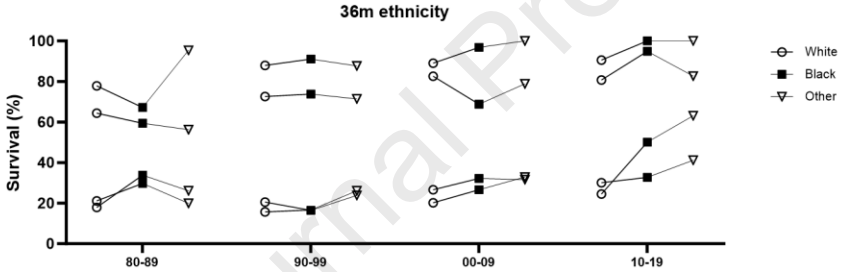
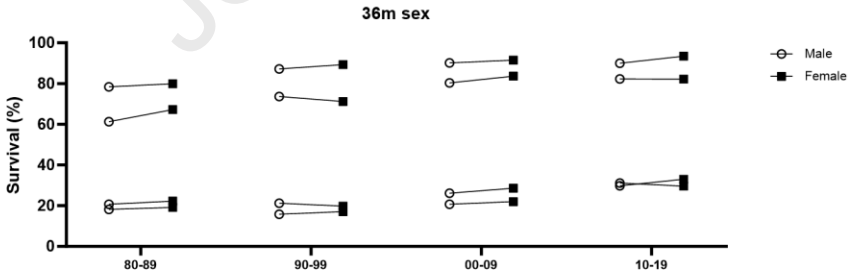


Figure 3. The12-month overall survival rates for glioma patients from 1980 to 2019, stratified by age, race, sex, and income level. Data from top to bottom represent WHO grades 1–4 gliomas.









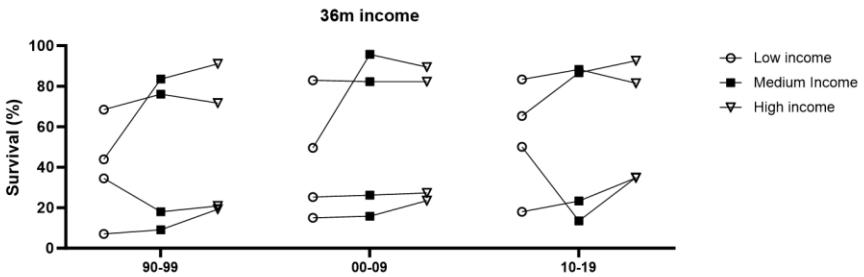
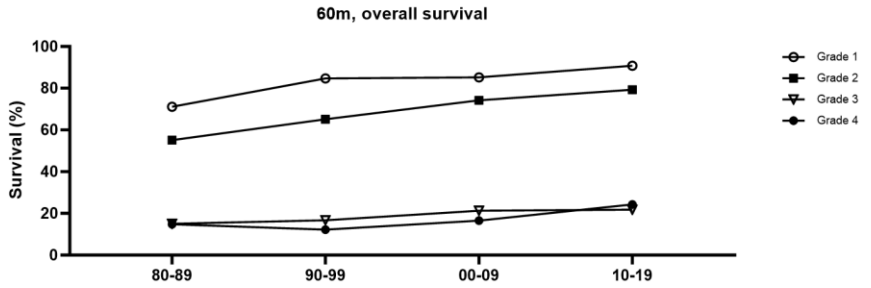
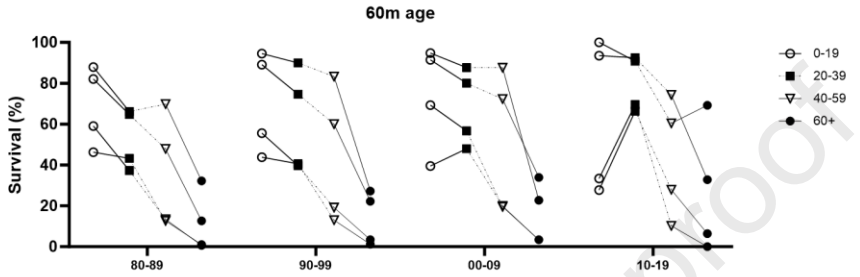
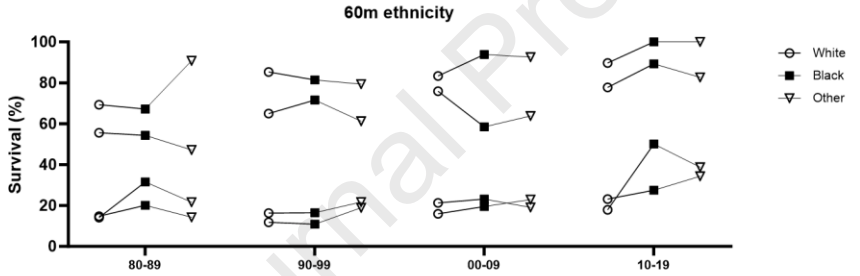
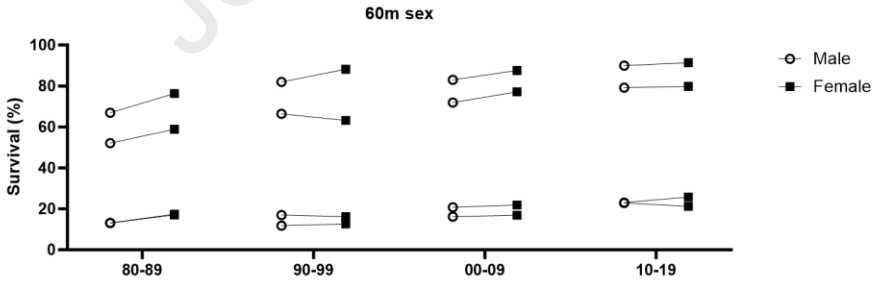


Figure 4. The 36-month overall survival rates for glioma patients from 1980 to 2019, stratified by age, race, sex, and income level. Data from top to bottom represent WHO grades 1–4 gliomas.









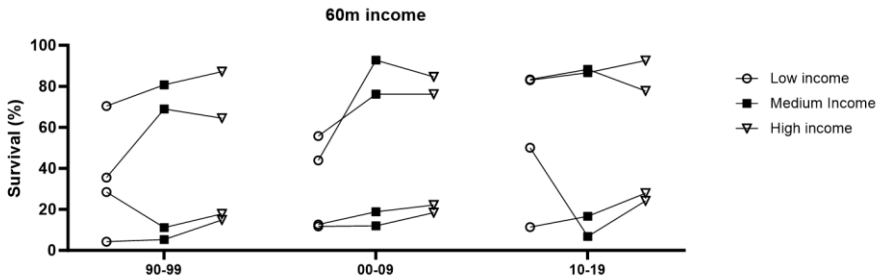


Figure 5. The 60-month overall survival rates for glioma patients from 1980 to 2019, stratified by age, race, sex, and income level. Data from top to bottom represent WHO grades 1–4 gliomas.

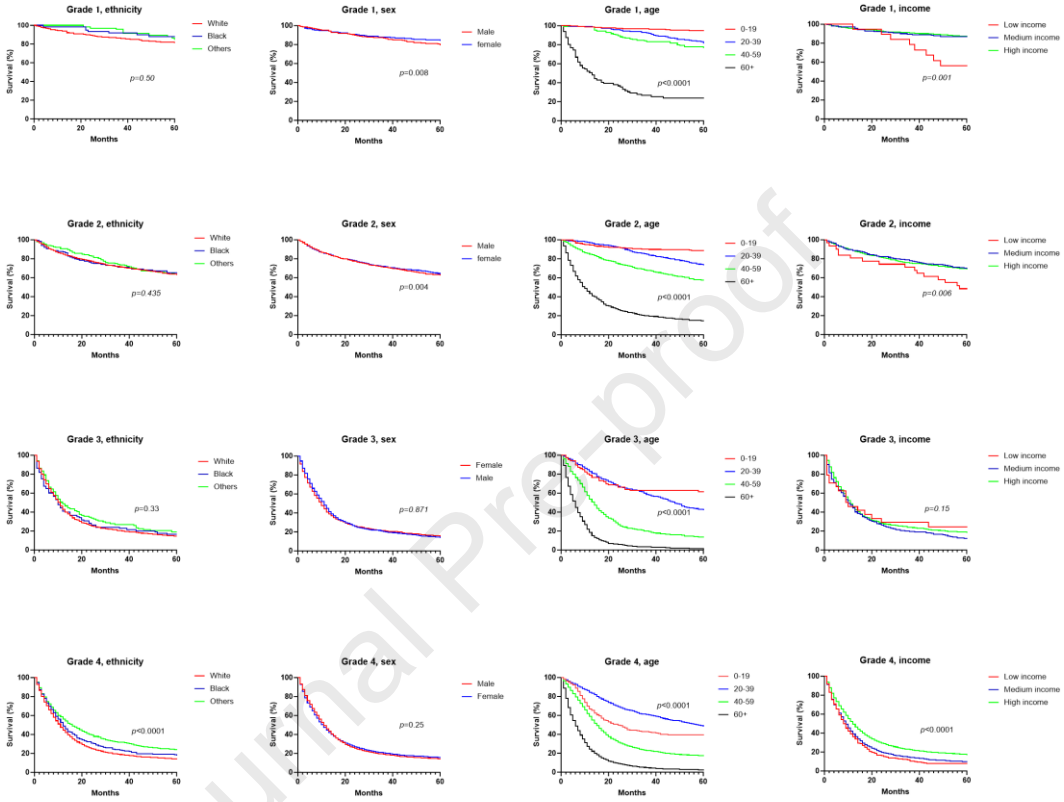


Figure 6. Kaplan-Meier survival analysis according to age, sex, ethnicity, and income, 1980-2019.

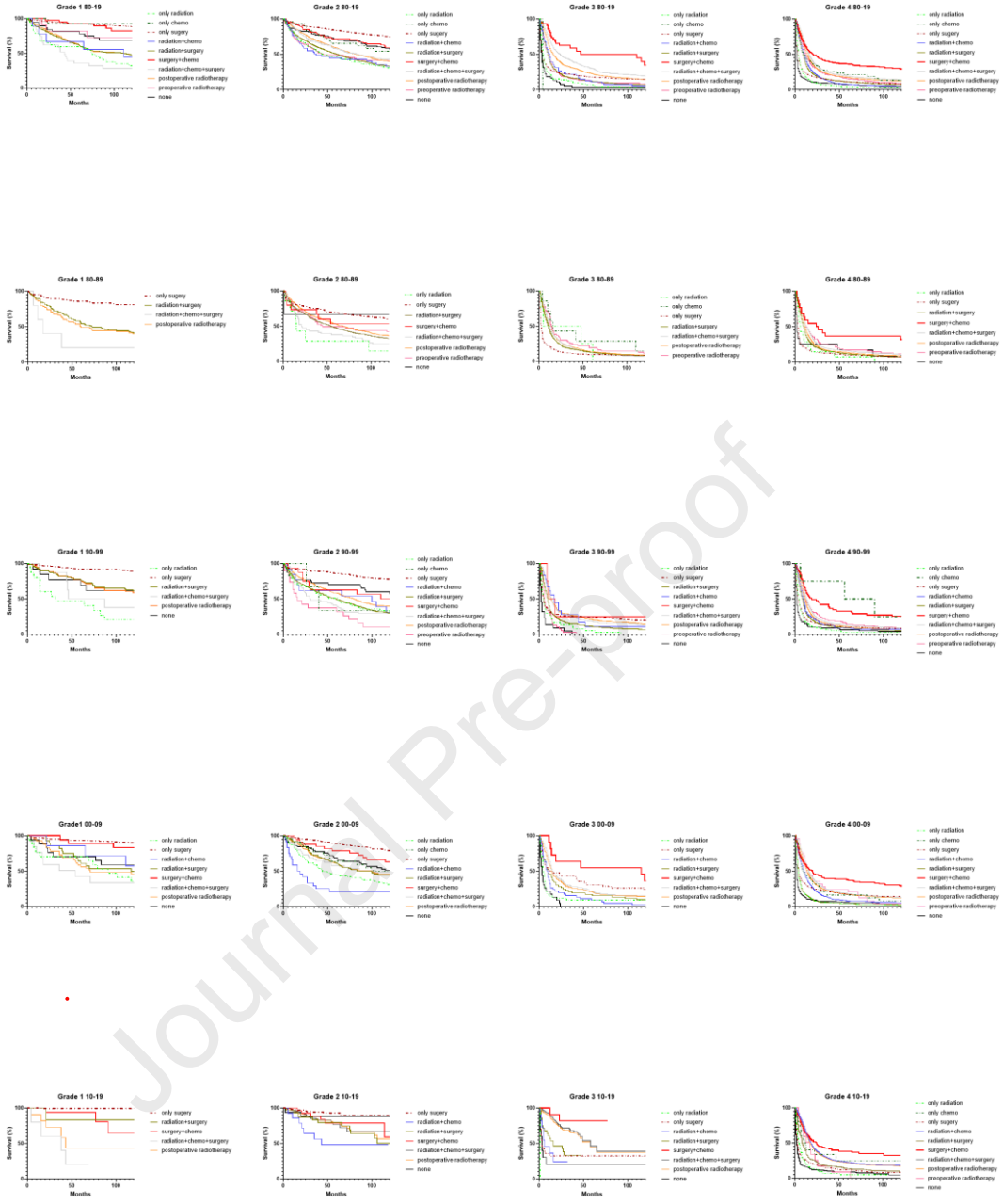


Figure 7. Analysis of Kaplan-Meyer survival rates for grades 1-4 gliomas by different treatment patterns, 1980-2019. The monotherapy is indicated by dashed lines, while combination therapy is indicated by solid lines.

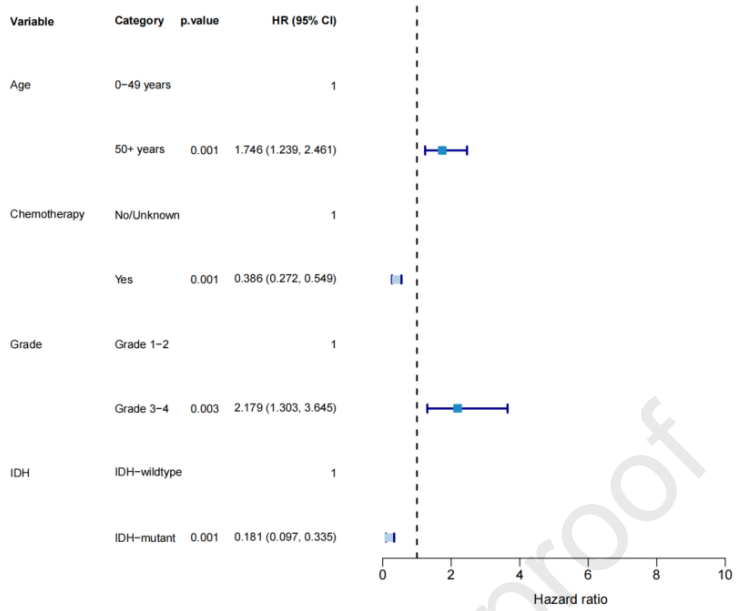


Figure 8. Multivariate COX Regression Analysis Results for Postoperative Radiotherapy in Gliomas.

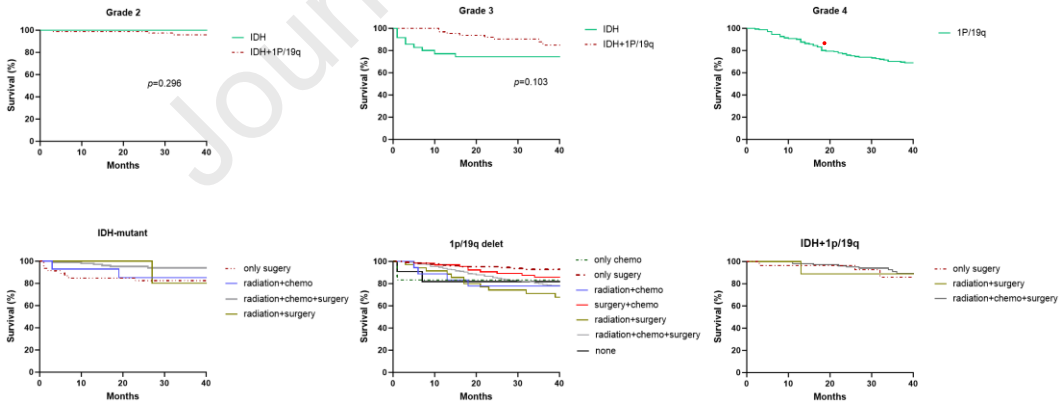
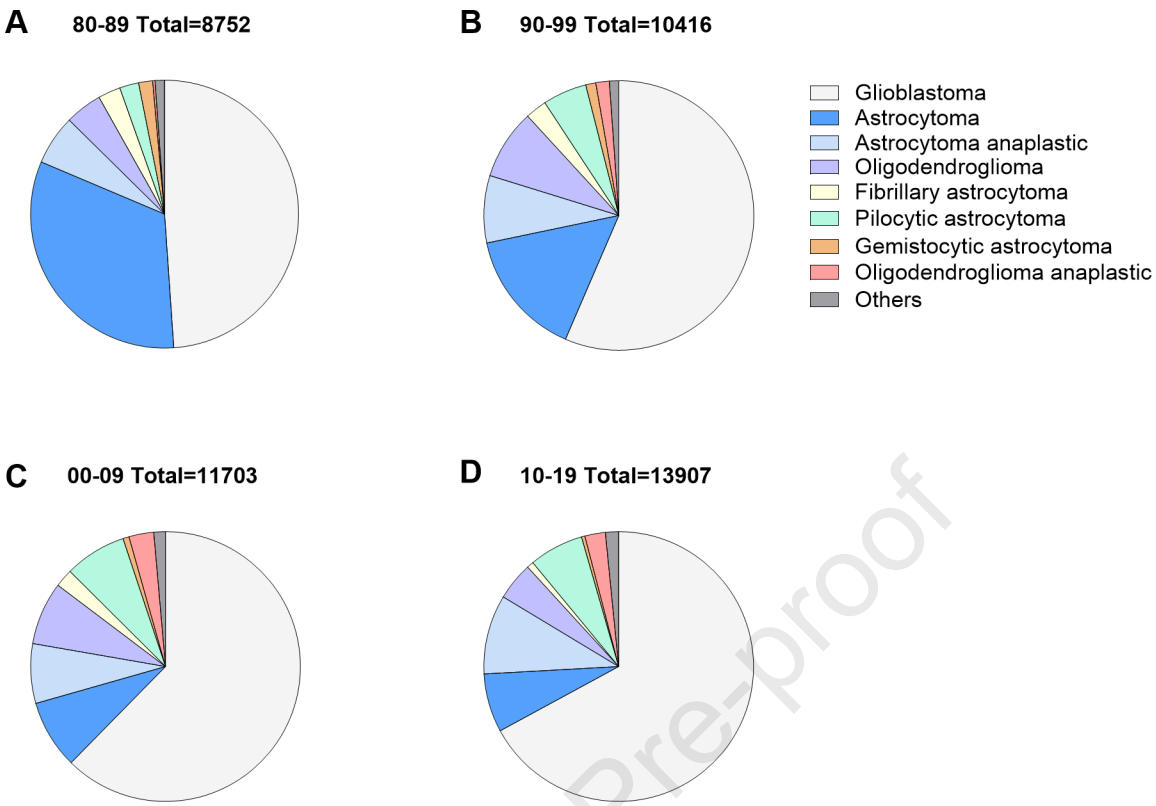
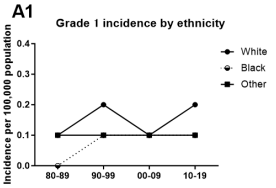
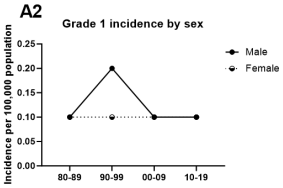
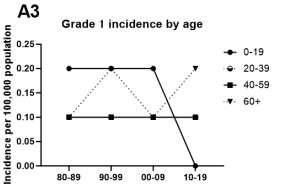


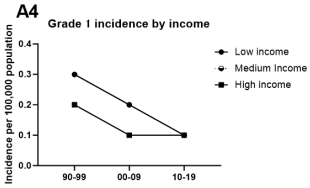
Figure 9. Kaplan-Meier survival analysis of gliomas with IDH and chromosome 1p/19q deletion in different grades and treatment patterns.

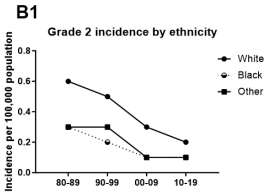


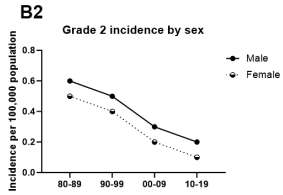


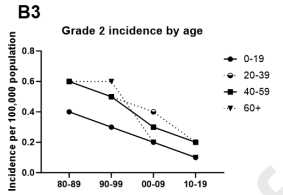


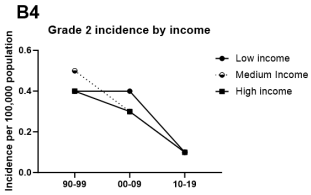


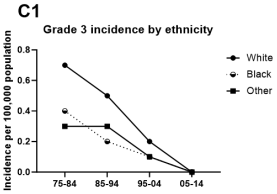


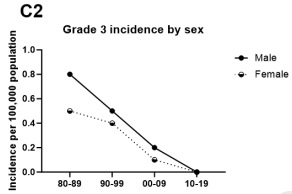


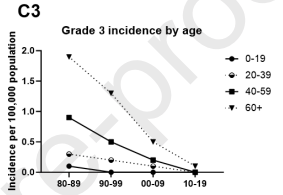


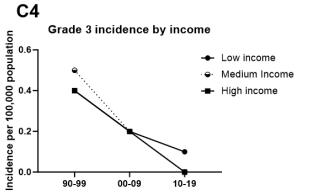


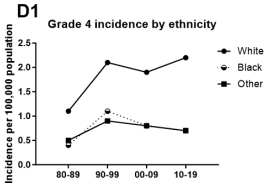


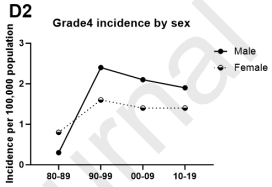


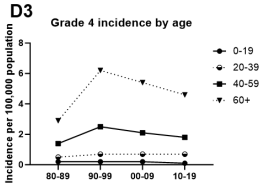


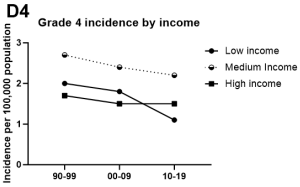


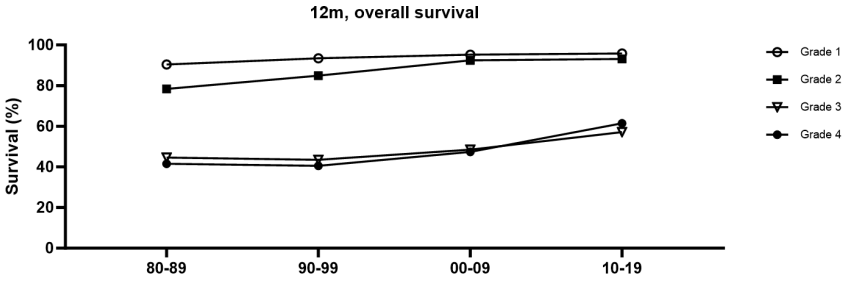


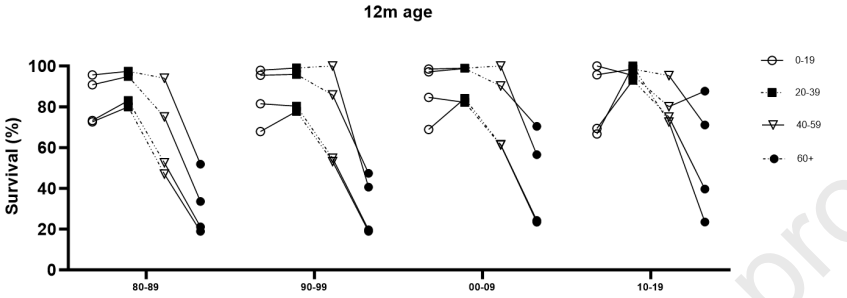


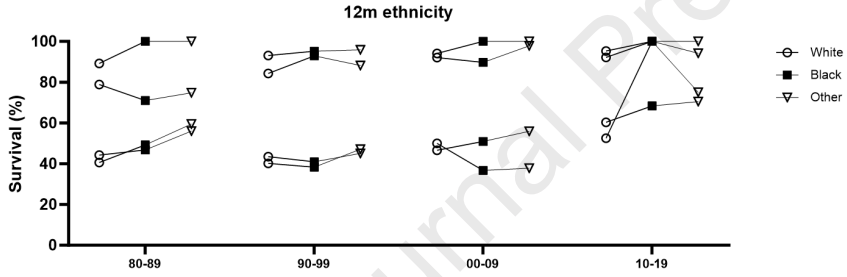


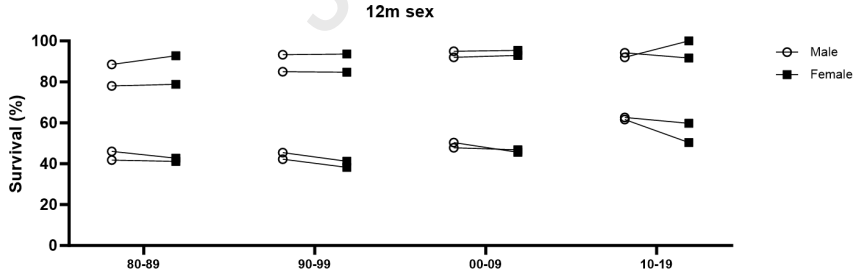


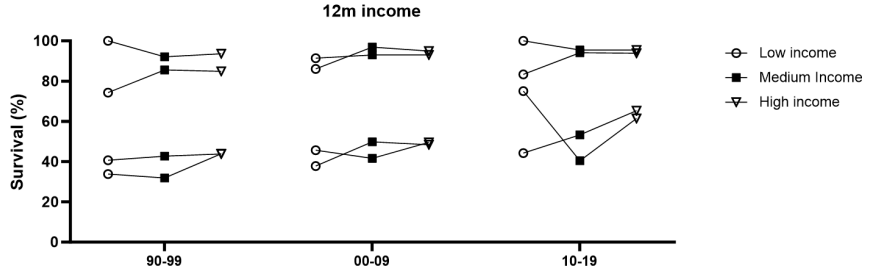


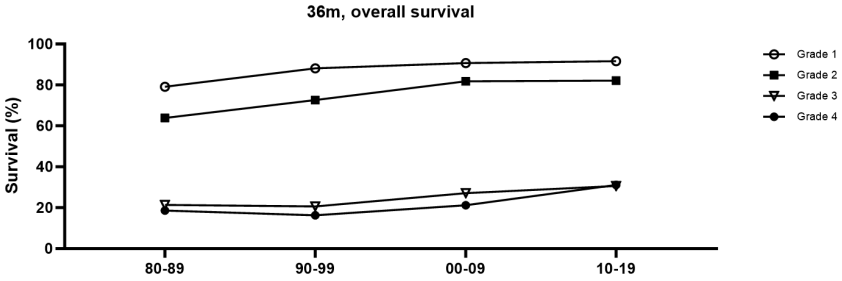


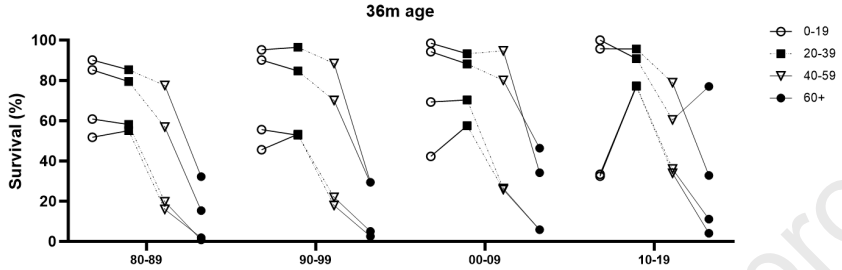


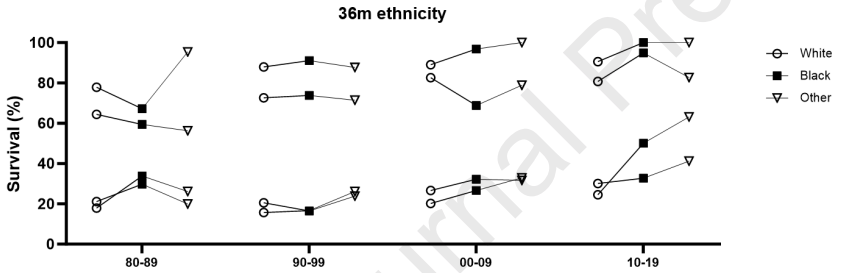


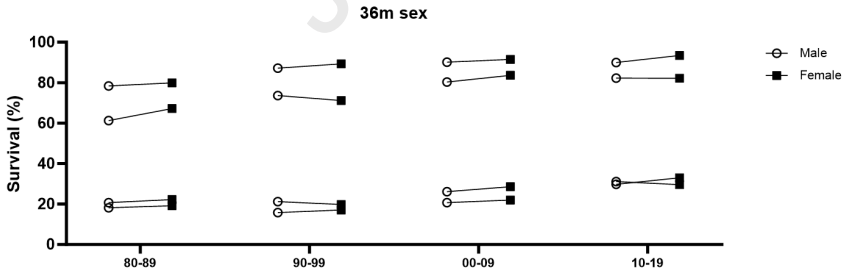


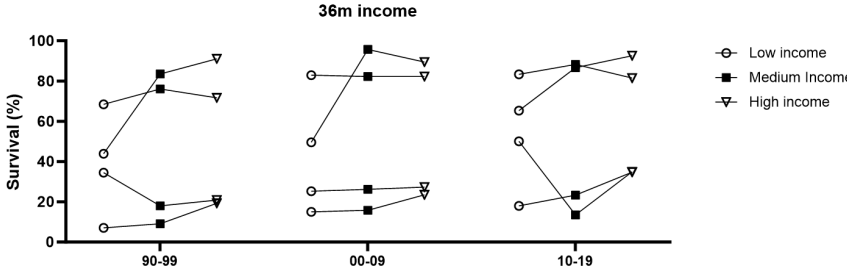


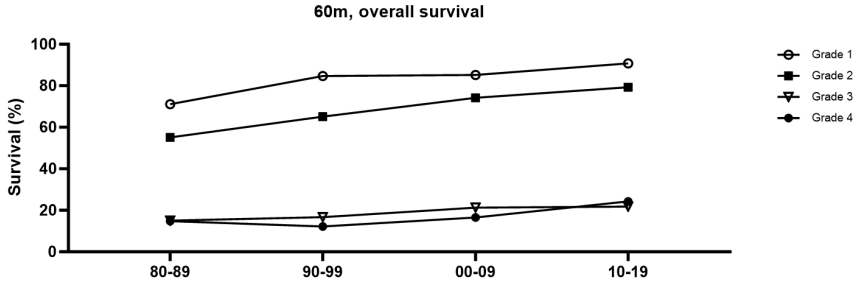


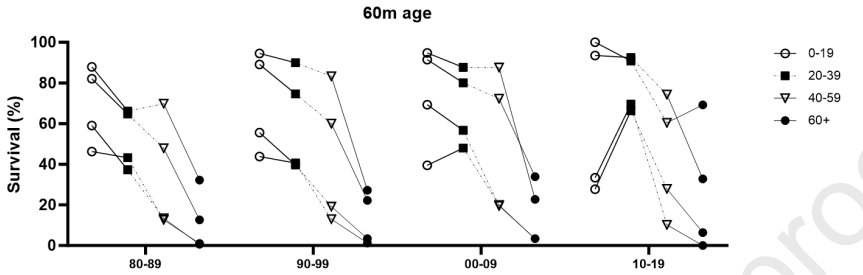


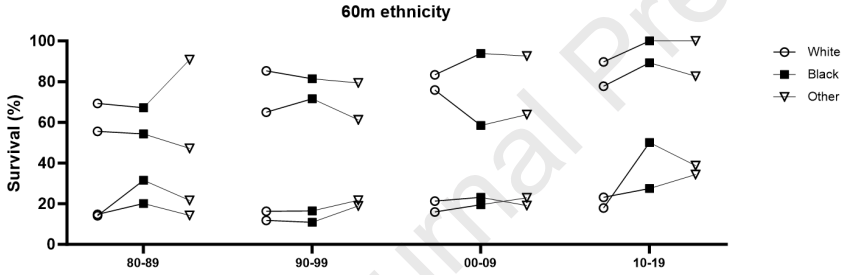


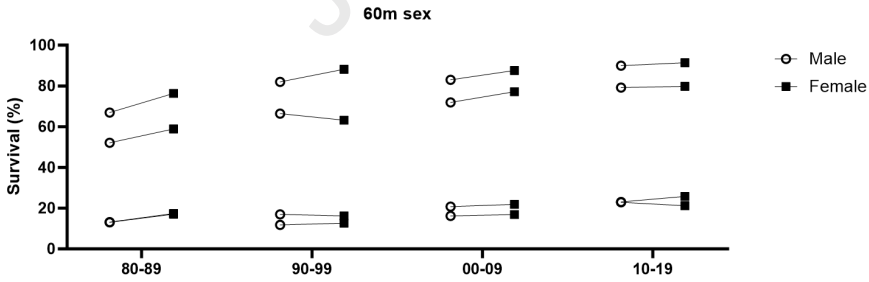


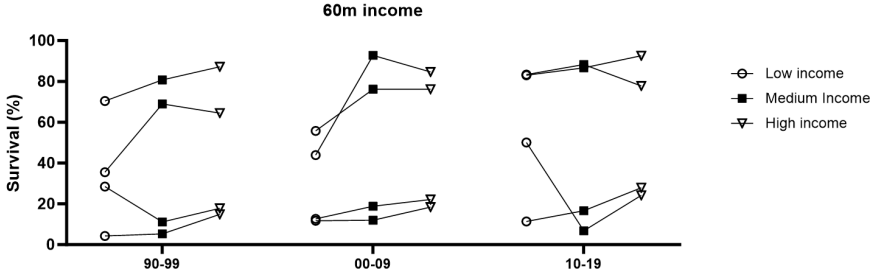


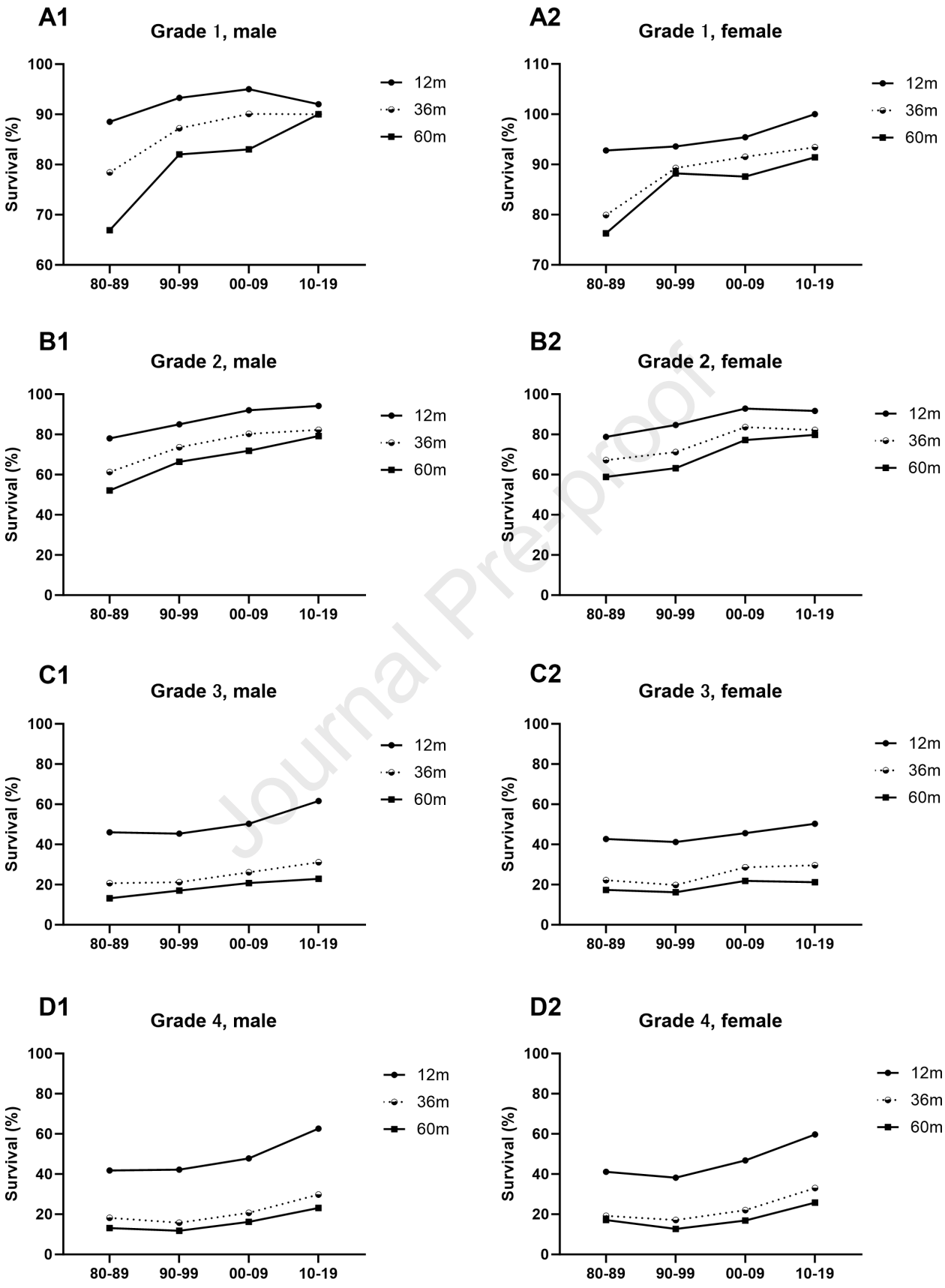


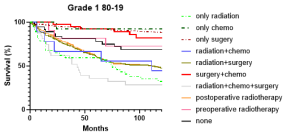


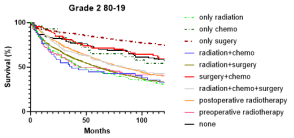


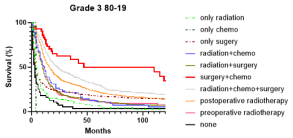


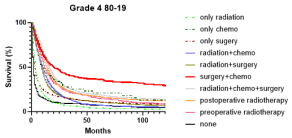


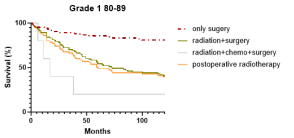


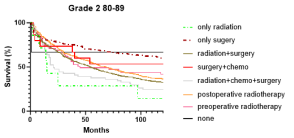


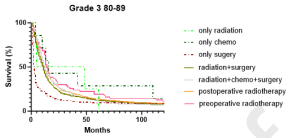


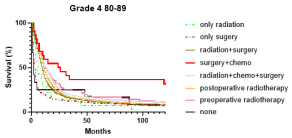


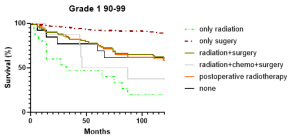


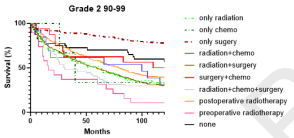


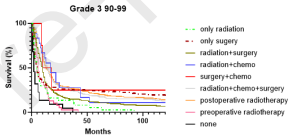


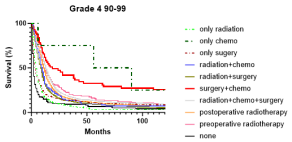


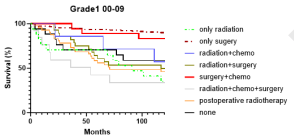


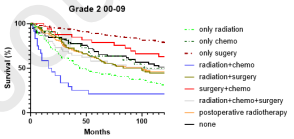


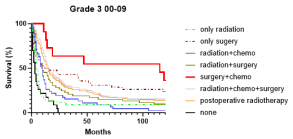


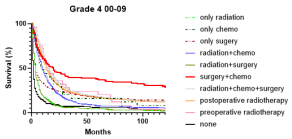


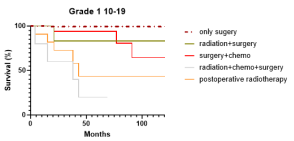


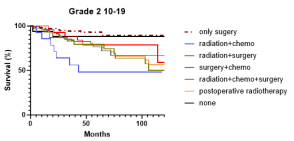


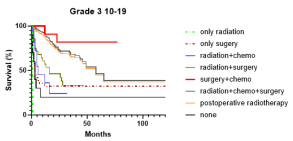


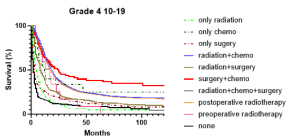




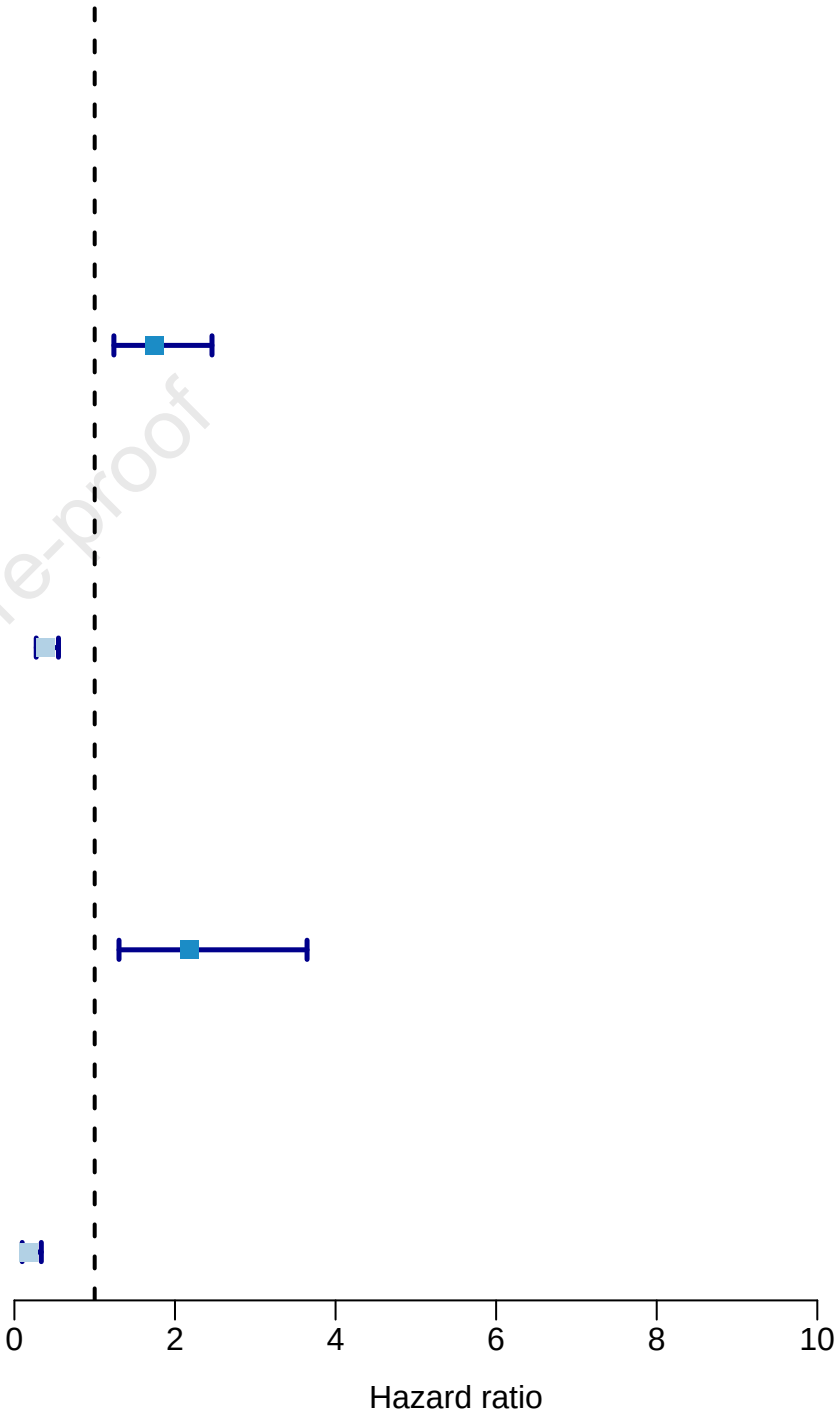


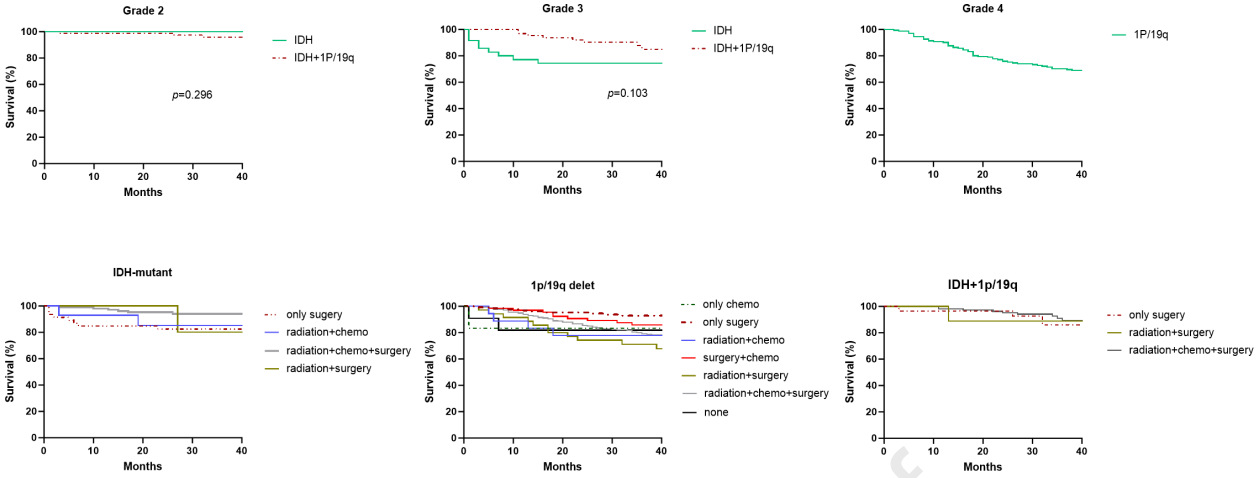






Variable	Category	p.value	HR (95% CI)
Age	0−49 years		1
	50+ years	0.001	1.746 (1.239, 2.461)
Chemotherapy	No/Unknown		1
	Yes	0.001	0.386 (0.272, 0.549)
Grade	Grade 1−2		1
	Grade 3−4	0.003	2.179 (1.303, 3.645)
IDH	IDH−wildtype		1
	IDH−mutant	0.001	0.181 (0.097, 0.335)





SEER database: Surveillance, Epidemiology, and End Results database
CRT: chemoradiotherapy
IDH: isocitrate dehydrogenase
CNS: central nervous system
RT: radiotherapy
RSRs: Rank sum ratios
SCT: surgery combined with chemotherapy
PORT: postoperative radiotherapy
IDH: Isocitrate Dehydrogenase
SCRT: surgery combined with chemoradiotherapy
GBM: glioblastoma
TTFields: tumor-treating fields
WHO: World Health Organization
ICD-O-3: International Classification of Diseases of Oncology, Third Edition
HR: Hazard Ratio
CI: Confidence Interval
LGG: low-grade gliomas
MGMT: methylguanine methyltransferase
GTR: gross total resection
NTR: near total resection
STR: subtotal resection
mOS: median overall survival
TERT: telomerase reverse transcriptase
ICIs: immune checkpoint inhibitors

Conflict of Interest Disclosure Statement

Manuscript Title:

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Authors:
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We, the authors of this manuscript, hereby disclose any potential conflicts of interest that might be perceived to influence the results or interpretation of our work.

Financial Interests

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No personal or institutional relationships with third parties could influence this work.

Intellectual Property

No intellectual property conflicts are declared.

Ethical Compliance

No Ethical Compliance

Final Declaration:

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.