

Analysis of Effectiveness of Therapeutic Approaches in the Treatment of Recurrent Malignant Gliomas of the Brain

Karimova Nargiza Sunnatillayevna^{1,*}, Nishanov Daniyar Anarbayevich²,
Mamadaliyeva Yashnar Mamasaliyevna³

¹Oncology, Medical Radiology, Tashkent State Medical University, Uzbekistan, Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology of the Republic of Uzbekistan

²Pathomorphology, Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology of the Republic of Uzbekistan

³Medical Radiology, Center for the Development of Professional Qualification of Medical Workers, Uzbekistan

Abstract Objective: The aim of this study was to evaluate the overall survival (OS) of patients with recurrent malignant gliomas of the brain (MGGB) based on prognostic factors and treatment modalities. **Materials and Methods:** The treatment outcomes of 39 patients diagnosed with recurrent grade III-IV gliomas (G3-G4) were analyzed. These patients were admitted to the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology of the Republic of Uzbekistan (RSSPMCOandR) between 2018 and 2021. The mean age of the patients was 47 ± 4.7 years, with a male-to-female ratio of 2:1. The average time to recurrence was 11.4 months. Among the patients, 32 had a single recurrence, while 7 experienced two consecutive recurrences. The treatment of high-grade glioma recurrences included repeat surgical resection in 5 patients, re-irradiation in various regimens in 22 patients, monochemotherapy with temozolomide in 5 patients, and combined therapy in 9 patients. **Results:** The OS of patients with recurrent malignant gliomas in the study was 27 months. The 1-year OS rate was 47.2%, and the 3-year OS rate was 27%. The median overall survival after recurrence treatment was 18 months. Age and gender did not significantly affect survival outcomes. The best OS outcomes for first-line recurrence treatment were observed in groups undergoing radiotherapy and reoperation, with a median OS of 18 months. In second-line recurrence treatment, the 1-year OS rate for patients receiving chemotherapy was 38%, compared to 31% for those undergoing re-irradiation ($p=0.372$). **Conclusion:** The OS of patients with recurrent malignant gliomas was 26.5 months, with a 1-year OS rate of 47.2%. No significant differences in survival outcomes were identified based on age or gender. Histological tumor type influenced prognosis: the median OS was 11 months for glioblastomas and 21 months for astrocytomas. Radiotherapy was identified as the most effective treatment for recurrence, achieving the highest survival outcomes.

Keywords Glioma recurrence, Recurrence treatment method, Radiotherapy

1. Introduction

Malignant glial tumors of the brain are among the most aggressive primary neuroepithelial neoplasms, characterized by high mortality rates and frequent local and distant recurrences [7]. These tumors exhibit diffuse infiltrative growth, which complicates complete surgical resection and contributes to their high recurrence rates [1, 8]. Glioblastoma is the most aggressive type of glioma, representing nearly 49% of all malignant brain tumors diagnosed in adults (JAMA, 2023) [2].

The classification of glial tumors is based on their histological structure and degree of malignancy. According to the classification of the World Health Organization (WHO), gliomas are categorized into four grades (I-IV). Tumors classified as grades I-II are considered low-grade malignancies, whereas those in grades III-IV exhibit high-grade malignancy characteristics. High-grade gliomas, such as anaplastic astrocytoma (grade III) and glioblastoma (grade IV), are distinguished by rapid growth and a high propensity for recurrence [1,6].

Prognostic factors for recurrence include patient age, tumor localization, and molecular-genetic characteristics. Younger age and superficial tumor localization are associated with a more favorable prognosis [7]. Mutations in the IDH1/2 genes, MGMT promoter methylation, and 1p/19q codeletion are critical molecular markers influencing prognosis and recurrence rates [7].

* Corresponding author:

dnargizakarimova@gmail.com (Karimova Nargiza Sunnatillayevna)

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Several molecular predictors are associated with the recurrence of malignant glial brain tumors. Mutations in the IDH gene have been linked to shorter time to recurrence [4,9].

Ransohoff [3] determined that surgical intervention for tumor recurrence does not significantly impact survival rates, particularly in patients experiencing further disease progression. These findings suggest that surgical management of recurrence should be considered only in cases of confirmed clinical progression. In such instances, reoperation contributes to a more precise morphological diagnosis by taking into account the tumor's specific characteristics, thereby enabling a more accurate prediction of its future course [11].

The role of chemotherapy in the treatment of recurrent malignant gliomas remains a subject of debate. Temozolomide is the standard chemotherapeutic agent for the treatment of recurrent high-grade malignant gliomas (Grade III and IV). Studies have shown that different dosing regimens of temozolomide can affect its efficacy and tolerability. A meta-analysis including 33 studies with 1,760 participants demonstrated that the 7-day on/7-day off regimen outperforms the standard schedule in terms of 6-month progression-free survival (34.8%) and 12-month progression-free survival (15.5%) in patients with Grade IV gliomas [12].

Van den Bent *et al.* [5] documented a 63% objective response rate, along with an enhancement in overall survival, among patients undergoing PCV therapy. Nonetheless, the clinical efficacy and safety of alternative chemotherapeutic agents, including nitrosoureas, hydroxyurea in combination with imatinib, irinotecan, and paclitaxel, in the context of recurrent gliomas, have not been extensively investigated, limiting their adoption in standard clinical practice [1,5].

Objective: The aim of this study was to evaluate the overall survival (OS) of patients with recurrent malignant

gliomas of the brain (MGGB) based on prognostic factors and treatment modalities.

2. Materials and Methods

A retrospective analysis of medical records was conducted for 39 patients with confirmed recurrences of high-grade malignant gliomas (G3-G4) who underwent treatment at the RSSPMCOandR from 2018 to 2021.

Morphological examination identified anaplastic oligodendroglioma (G3) in 8 patients, anaplastic astrocytoma (G3) in 22 patients, and glioblastoma (G4) in 9 patients (Table 1). The mean age of the patients was 47 ± 4.7 years, with a male-to-female ratio of 2:1.

The analysis of primary therapy revealed that combined treatment, including surgical intervention, radiotherapy, and chemotherapy, was administered to 30 patients. Exclusive surgical treatment was performed in 6 patients, while isolated radiotherapy was applied in 3 patients. In the adjuvant setting, 4 patients underwent a polychemotherapy regimen using the PCV protocol, which consisted of 4 cycles.

The mean time to recurrence was 46.4 months. A single recurrence was observed in 32 patients, whereas 7 patients experienced two consecutive recurrences.

In the first-line treatment of recurrence, reoperation was performed in 5 patients. Repeat radiotherapy with a cumulative focal dose of 60 Gy was administered to 31 patients. Of these, volumetric modulated arc therapy (VMAT) was applied in 17 cases, intensity-modulated radiotherapy (IMRT) in 10 cases, and conventional conformal radiotherapy in 4 cases. Monochemotherapy with temozolomide (at a dose of 200 mg/m² from days 1 to 5 every 28 days) was performed in 5 patients. Combined treatment for recurrence was provided to 9 patients.

Table 1. Characteristics of Patients with Recurrent Malignant Gliomas of the Brain

Category	Subcategory	Number of Patients (n)	Percentage (%)
Gender	Women	14	36
	Men	25	64
Histological Tumor Type	Anaplastic Oligodendroglioma (G3)	8	21
	Anaplastic Astrocytoma (G3)	22	56
	Glioblastoma (G4)	9	23
Primary Treatment	Surgical	6	15
	Combined	30	77
	Radiotherapy	3	8
Treatment of First Recurrence (n=32)	Surgical	5	15.6
	Radiotherapy	22	68.7
	Combined	9	28.1
	Chemotherapy	5	15.6
Treatment of Subsequent Recurrences (n=7)	Radiotherapy	2	28
	Monochemotherapy with Temozolomide	5	72

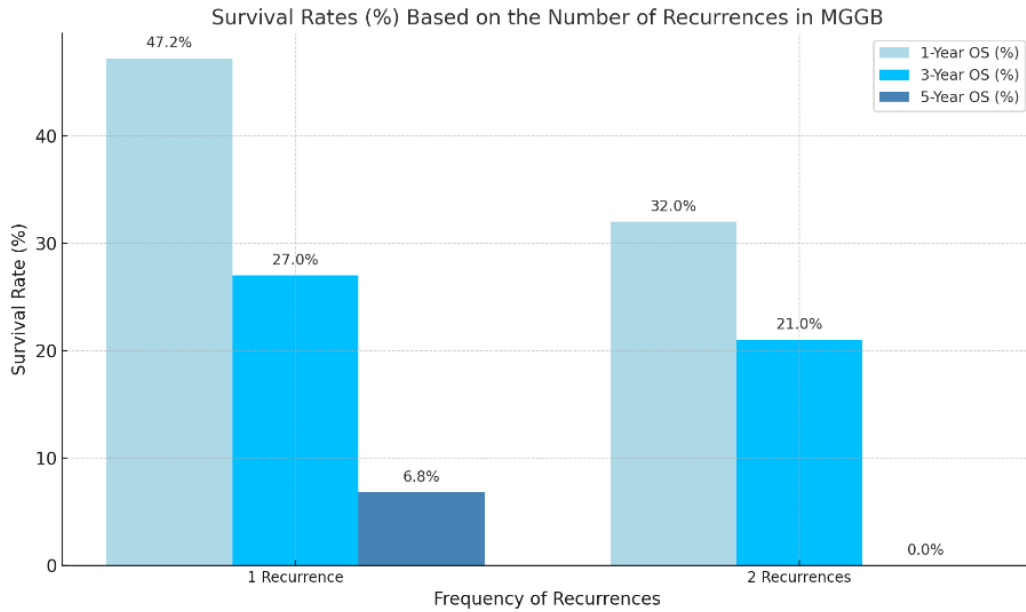


Figure 1. Comparison of Survival Rates (%) Based on the Number of Recurrences in MGGB

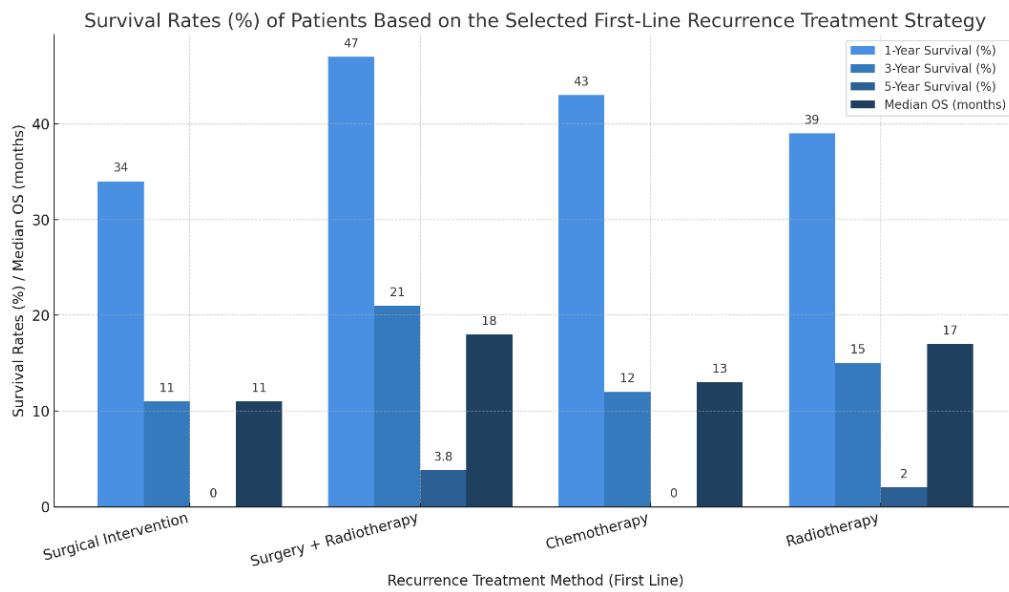


Figure 2. Survival Rates (%) of Patients Based on the Selected First-Line Recurrence Treatment Strategy

Second-line treatment for recurrence was administered to 7 patients, of whom 5 received monochemotherapy with temozolomide, and 2 underwent radiotherapy. A detailed clinical characterization of the patients is presented in Table 1.

The pathological process was localized to the left hemisphere in 16 patients and to the right hemisphere in 23 patients. Among cases of isolated involvement of specific brain lobes, frontal (9 patients) and temporal (11 patients) lobes were the most frequently affected. Tumor infiltration of the midline structures was observed in 14 patients, while in 8 patients, the tumor extended to the contralateral hemisphere, which was more commonly associated with a diffuse growth pattern of the primary tumor.

An analysis of the neurological status in the preoperative period identified motor deficits as the predominant focal

symptoms: paresis, plegia, epileptiform seizures, various forms of speech disorders, motor aphasia, sensory and amnesic aphasia.

3. Results

The OS with recurrent MGGB was 26.5 months. The one-year OS rate was 47.2%, while the three-year OS rate was 27.0%. The median OS following recurrence treatment was 27 months.

An analysis of OS considering age demonstrated that elderly patients have a less favorable prognosis due to challenges in administering intensive treatment, whereas younger patients tend to exhibit a more aggressive disease course. However, no statistically significant differences

between age groups were identified ($p=0.46$). Similarly, OS analysis by gender did not reveal statistically significant differences ($p=0.89$), although women exhibited a slightly higher OS rate (27.0%) compared to men (18.8%).

When OS was analyzed by histological tumor type, it was found that patients with glioblastomas had a poorer prognosis compared to those with astrocytomas, with median OS of 11 and 21 months, respectively, although the differences did not reach statistical significance ($p=0.578$).

The analysis of survival based on the number of recurrences demonstrated a trend toward reduced survival rates in cases with two recurrences (Figure 1.). The impact of treatment modalities on OS showed that the best outcomes were achieved in groups receiving radiotherapy or reoperation, with median OS of 18 and 17 months, respectively ($p=0.26$) (Figure 2.).

An evaluation of the effectiveness of second-line chemotherapy in treating recurrent malignant gliomas demonstrated its prominent role: the 1-year OS rate with chemotherapy was 38%, compared to 31% for repeat radiotherapy ($p=0.372$), indicating no statistically significant difference between the two approaches.

The assessment of OS based on radiotherapy techniques revealed superior outcomes with VMAT, achieving a 3-year OS rate of 27%, while IMRT resulted in a 3-year OS rate of 22.3%. The median OS was 17 months for VMAT and 14 months for IMRT.

Regarding the neurological status of patients, specialized treatment resulted in the regression of motor deficits in 6 patients and improvement in speech functions in 7 patients. However, the frequency and duration of epileptic seizures remained unchanged. Neurological deterioration was observed in 11 patients (28.2%), correlating with tumor progression during treatment.

4. Conclusions

The OS of patients with recurrent malignant gliomas of the brain was 26.5 months, with a 1-year OS rate of 47.2% and a 3-year OS rate of 27.0%. No statistically significant differences in survival outcomes were observed based on age or gender ($p>0.05$), although women demonstrated slightly higher 1-year OS rates compared to men. The histological tumor type had a notable impact on prognosis, with glioblastoma patients exhibiting worse survival outcomes than those with astrocytomas (median OS of 11 months and 21 months, respectively, $p=0.578$).

The most effective treatment for recurrences was radiotherapy. At the same time, second-line chemotherapy demonstrated better one-year overall survival (OS) rates (38%) compared to repeat radiotherapy (31%). Despite the treatment efforts, neurological deterioration was observed in 11 patients, indicating tumor progression.

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