

Survival Outcomes in Recurrent Glioma Following Second Surgery, Systemic Chemotherapy, and Radiotherapy – A Single-Center Experience

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Abstract

Background:

Gliomas account for approximately 81% of all malignant brain tumors. Standard treatment typically consists of surgical resection, radiotherapy, and chemotherapy. Despite these interventions, tumor recurrence is nearly inevitable. The prognostic value of repeat surgical resection remains controversial. In this retrospective study, we reviewed data from patients with recurrent glioma and compared survival outcomes between different patient treatment groups.

Methods:

We retrospectively reviewed the files of adult patients diagnosed with glioma and treated at our center, King Hussein Cancer Center, between 2017 and 2024; patients with medulloblastoma or other non-glioma histology were excluded. The primary endpoint was overall survival (OS) from radiologically confirmed recurrence to death or last follow-up. We compared survival between patients who underwent repeat resection and those managed without resection. Chemotherapy and radiotherapy after recurrence were included as covariates rather than treated as mutually exclusive alternatives to surgery. Prespecified subgroup analyses were performed for WHO grade 4 and WHO grade 1–3 tumors. Kaplan–Meier survival analysis and Cox proportional hazards regression were used.

Results:

Out of 327 patients included in this study, 122 (37.3%) underwent second resection at recurrence, while 205 (62.7%) were managed without further surgery; 226 deaths were observed. Median overall survival from recurrence was significantly longer in the second surgery group at 25.8 months (95% CI: 18.3–56.8), compared with 9.6 months (95% CI: 8.7–11.2) in the non-surgical group (log-rank $p < 0.0001$; univariable HR for absence of repeat resection 2.67, 95% CI 1.99–3.59, $p < 0.001$). On multivariable analysis, absence of repeat resection was independently associated with a higher risk of death (adjusted HR 1.97, 95% CI 1.40–2.79, $p < 0.001$), as was WHO grade 4 histology (adjusted HR 2.04, 95% CI 1.43–2.90, $p < 0.001$). In the WHO grade 4 subgroup ($n = 215$), median overall survival was 14.4 months (95% CI: 10.2–19.7) versus 8.7 months (95% CI: 7.7–10.2) (adjusted HR for absence of repeat resection 2.14, 95% CI 1.37–3.34, $p = 0.001$), and receipt of chemotherapy after recurrence was also independently associated with improved survival (adjusted HR 0.21, 95% CI 0.09–0.48, $p < 0.001$). In the WHO grade 1–3 subgroup ($n = 112$), median overall survival was 59.6 months (95% CI: 46.3 – not reached) versus 13.4 months (95% CI: 10.6–25.7) (univariable HR 3.14, 95% CI 1.84–5.37, $p < 0.001$), although this association was attenuated on multivariable analysis from recurrence (HR 1.94, 95% CI 0.96–3.93, $p = 0.064$).

Conclusions:

To our knowledge, this is the largest single-institution series reported from a middle-income country, and the largest from the Middle East region, to examine repeat surgical resection across the full spectrum of WHO grade 1–4 recurrent glioma. Repeat surgical resection was associated with longer survival in selected patients with recurrent glioma, particularly those with WHO grade 4 tumors. These findings support consideration of repeat resection within multidisciplinary salvage management; however, they do not demonstrate a causal survival benefit, given the retrospective study design and the potential for selection bias related to performance status, tumor location and volume, and molecular characteristics.

1. Background:

Gliomas are the most common type of primary intracranial tumor, accounting for approximately 81% of malignant brain tumors. Among them, Glioblastoma is the most prevalent histologic subtype around 45% and is associated with poor prognosis, with a 5-year relative survival of about 5%. [1]

Treatment for gliomas typically includes a combination of surgery, radiotherapy, and chemotherapy. Patient survival outcomes vary widely depending on the glioma type and prognostic factors. [2]

Molecular genetic markers, especially IDH mutation and 1p/19q codeletion, have a critical prognostic role in glioma classification and are now considered disease-defining factors in the updated WHO classification. The methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter is an important prognostic indicator, associated with improved survival and a better response to alkylating agent-based chemotherapy. [3]

Surgical intervention remains the cornerstone of management of all grades of gliomas, with the primary aim being maximal safe resection of tumors. It represents a balance between maximizing the extent of resection and the need to preserve neurological function and quality of life. Increasing evidence indicates that a greater extent of surgical resection is associated with improved survival in both high-grade and low-grade gliomas. [4] [5]

Following surgery, postoperative radiotherapy and chemotherapy should be administered in accordance with the glioma type, grade, and molecular characteristics (including 1p/19q status, IDH status, and MGMT promoter methylation status), as part of the standard treatment protocol. [6]

Recurrence in Glioblastoma (GBM) is almost inevitable. Recurrent GBM is associated with a poor prognosis, with a median OS of less than 1 year, and there is currently no established standard of care in this clinical situation. [7]

Treatment options for recurrent gliomas are generally non-curative, and only a limited number of randomized trials have evaluated the optimal approach. Most available evidence is derived from retrospective or non-randomized trials; therefore, treatment decisions should be individualized and take into account the risks and benefits, while considering quality of life in the setting of a non-curative

disease. [9] Management of these tumors depends on several factors including age, performance status, neurological deficit, tumor diameter and molecular markers. [8]

In recurrent low-grade glioma, the role of surgical resection has not been well studied. This is particularly important as these tumors frequently recur, often with progression to higher-grade tumors after initial treatment, resulting in substantial morbidity and mortality. [9]

Various treatment strategies may be considered, including locoregional approaches such as surgery, radiotherapy (RT), as well as devices like the Novo TTF-100A. Systemic treatments have also been explored in the setting of recurrent disease. [10] The role of repeat surgery in patients with progressive or recurrent glioblastoma remains controversial, with some retrospective studies suggesting a survival benefit following reoperation, while others have not shown an advantage.

At KHCC, different treatment modalities have been offered to patients with recurrent glioma following individualized case review, including surgery, radiotherapy, and systemic chemotherapy.

In this retrospective study, we aimed to evaluate survival outcomes in patients with recurrent glioma based on whether they underwent repeat surgical resection, while adjusting for systemic therapy, radiotherapy, tumor grade, and other clinical factors. We will also compare our results with published international data.

2. Materials and methods

We retrospectively reviewed the files of adult patients diagnosed with glioma and treated at our center, King Hussein Cancer Center, between 2017 and 2024; A total of 327 patients with recurrent glioma were included in the analysis. A further 12 patients with non-glioma histology (10 with medulloblastoma and 2 with other rare histology) were identified during case review and excluded.

The primary endpoint was overall survival (OS) from radiologically confirmed recurrence to death or last follow-up. We compared survival between patients who underwent repeat resection and those managed without resection. Chemotherapy and radiotherapy after recurrence were included as covariates rather than treated as mutually exclusive alternatives to surgery. Prespecified subgroup analyses were performed for WHO grade 4 and WHO grade 1–3 tumors. Kaplan–Meier survival analysis and Cox proportional hazards regression were used.

3. Result:

3.1. Overall Cohort

A total of 327 patients with recurrent glioma were included in the analysis. A further 12 patients with non-glioma histology (10 with medulloblastoma and 2 with other rare histology) were identified during

case review and excluded. The mean age at diagnosis was 46.1 years (SD 13.2, range 18.0–76.0), and the majority were male (223/327, 68.2%). Baseline and treatment characteristics are shown in Table 1.

WHO grade 4 tumors were the most prevalent, comprising 215 patients (65.7%), followed by grade 3 tumors in 63 patients (19.3%) and grade 1–2 tumors in 49 patients (15.0%).

After initial surgical resection, 197 patients (60.2%) received concurrent chemoradiotherapy, 81 patients (24.8%) received sequential radiotherapy, and 49 patients (15.0%) received no radiotherapy. Temozolomide-based chemotherapy was given to 241 patients (73.7%), while 84 patients (25.7%) received other regimens and 2 patients (0.6%) received PCV. The mean time to recurrence was 19.3 months (SD 22.1).

At recurrence, 122/327 patients (37.3%) underwent second resection, while 205/327 (62.7%) were managed without further surgery; a total of 226 events (deaths) were observed. After recurrence, 302 patients (92.4%) received systemic therapy (PCV in 145 patients (44.3%), temozolomide in 131 patients (40.1%), and other regimens in 26 patients (8.0%)), while 25 patients (7.6%) received no chemotherapy. Radiotherapy after recurrence was administered to 78 patients (23.9%), comprising concurrent chemoradiotherapy in 36 patients (11.0%), sequential radiotherapy in 39 patients (11.9%), and stereotactic radiosurgery in 3 patients (0.9%).

Table 1

Baseline demographic, tumour and treatment characteristics of the study cohort, overall and by WHO grade.

Characteristic	Overall (N = 327)	WHO grade 4 (n = 215)	WHO grade 1–3 (n = 112)
Sex			
Female	104 (31.8)	69 (32.1)	35 (31.2)
Male	223 (68.2)	146 (67.9)	77 (68.8)
Extent of first surgery			
Biopsy only	30 (9.2)	18 (8.4)	12 (10.7)
Gross total resection	294 (89.9)	196 (91.2)	98 (87.5)
Not done	1 (0.3)	1 (0.5)	0
Total resection	2 (0.6)	0	2 (1.8)
Age at diagnosis, years			
Mean (SD)	46.1 (13.2)	50.3 (12.8)	37.6 (10.5)
Range	18.0–76.0	–1.8–76.0	18.2–68.0
Histology			
WHO grade 4	215 (65.7)	215 (100.0)	0
WHO grade 3	63 (19.3)	0	63 (56.2)
WHO grade 1–2	49 (15.0)	0	49 (43.8)
Radiotherapy after first surgery			
Concurrent	197 (60.2)	179 (83.3)	18 (16.1)
Sequential	81 (24.8)	32 (14.9)	49 (43.8)
Not done	49 (15.0)	4 (1.9)	45 (40.2)
Chemotherapy after first surgery			
Temozolomide	241 (73.7)	207 (96.3)	34 (30.4)
PCV	2 (0.6)	0	2 (1.8)
Other	84 (25.7)	8 (3.7)	76 (67.9)
Time to recurrence, months			
Mean (SD)	19.3 (22.1)	13.3 (15.0)	30.7 (28.3)

Characteristic	Overall (N = 327)	WHO grade 4 (n = 215)	WHO grade 1–3 (n = 112)
Sex			
Range	0.1–168.1	0.1–113.8	1.7–168.1
Second surgery at recurrence			
Yes	122 (37.3)	63 (29.3)	59 (52.7)
No	205 (62.7)	152 (70.7)	53 (47.3)
Systemic therapy after recurrence			
Yes	302 (92.4)	204 (94.9)	98 (87.5)
No	25 (7.6)	11 (5.1)	14 (12.5)
Regimen after recurrence			
PCV	145 (44.3)	114 (53.0)	31 (27.7)
Temozolomide	131 (40.1)	68 (31.6)	63 (56.2)
Other	26 (8.0)	22 (10.2)	4 (3.6)
Not given	25 (7.6)	11 (5.1)	14 (12.5)
Radiotherapy after recurrence			
Concurrent	36 (11.0)	20 (9.3)	16 (14.3)
Sequential	39 (11.9)	9 (4.2)	30 (26.8)
Stereotactic radiosurgery	3 (0.9)	2 (0.9)	1 (0.9)
Not done	249 (76.1)	184 (85.6)	65 (58.0)
Deaths			
Yes	226 (69.1)	166 (77.2)	60 (53.6)
No	101 (30.9)	49 (22.8)	52 (46.4)
Overall survival from recurrence, months			
Mean (SD)	17.4 (23.3)	11.4 (11.1)	28.9 (34.0)
Range	0.2–287.2	0.2–82.9	0.8–287.2

.SD, standard deviation; PCV, procarbazine-lomustine-vincristine.

Median overall survival from recurrence was significantly longer in patients who underwent second surgery than in those who did not, 25.8 months (95% CI: 18.3–56.8) versus 9.6 months (95% CI: 8.7–11.2), log-rank $p < 0.0001$.

Estimated survival from recurrence in patients who underwent second surgery versus those who did not was 71.2% versus 37.7% at 1 year, 42.1% versus 13.5% at 3 years, and 27.8% versus 5.4% at 5 years (Fig. 1).

In univariable Cox regression analysis, the absence of second surgery was significantly associated with inferior overall survival, with HR of 2.67 (95% CI: 1.99–3.59, $p < 0.001$).

The variables included in multivariable Cox regression analysis were second surgery, WHO grade (grade 4 versus grade 1–3), gender, age at diagnosis, chemotherapy and radiotherapy following recurrence. Absence of second surgery was independently associated with an increased risk of death, adjusted HR 1.97 (95% CI 1.40–2.79, $p < 0.001$). Similarly, WHO grade 4 histology was independently associated with increased risk of death compared with grade 1–3 tumors, adjusted HR 2.04 (95% CI 1.43–2.90, $p < 0.001$). Older age at diagnosis was also independently associated with increased mortality, adjusted HR 1.02 per year (95% CI 1.00–1.03, $p = 0.011$). Using concurrent chemoradiotherapy as reference category, sequential radiotherapy after recurrence was associated with a non-significant trend towards lower risk of death, adjusted HR 0.53 (95% CI 0.27–1.03, $p = 0.060$). The absence of further radiotherapy was not significantly associated with survival, adjusted HR 1.33 (95% CI 0.81–2.20, $p = 0.257$). Likewise, neither gender, adjusted HR 1.18 (95% CI 0.88–1.58, $p = 0.269$), nor receipt of chemotherapy after recurrence, adjusted HR 0.76 (95% CI 0.39–1.46, $p = 0.407$), demonstrated an independent association with survival. Full univariable and multivariable results for the whole cohort are shown in Table 2.

Table 2

Univariable and multivariable Cox proportional hazards models for overall survival from recurrence in the whole cohort (n = 327; 226 events).

Variable	n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Second surgery at recurrence			
Yes	122 (37.3)	Reference	Reference
No	205 (62.7)	2.67 (1.99–3.59); p < 0.001	1.97 (1.40–2.79); p < 0.001
WHO grade			
Grade 1–3	112 (34.3)	Reference	Reference
Grade 4	215 (65.7)	3.02 (2.22–4.11); p < 0.001	2.04 (1.43–2.90); p < 0.001
Systemic therapy after recurrence			
No	25 (7.6)	Reference	Reference
Yes	302 (92.4)	1.51 (0.86–2.64); p = 0.154	0.76 (0.39–1.46); p = 0.407
Radiotherapy after recurrence			
Concurrent	36 (11.0)	Reference	Reference
Sequential	39 (11.9)	0.50 (0.26–0.97); p = 0.040	0.53 (0.27–1.03); p = 0.060
Stereotactic radiosurgery	3 (0.9)	0.35 (0.05–2.63); p = 0.310	0.21 (0.03–1.57); p = 0.127
Not done	249 (76.1)	2.07 (1.30–3.29); p = 0.002	1.33 (0.81–2.20); p = 0.257
Sex			
Female	104 (31.8)	Reference	Reference
Male	223 (68.2)	1.24 (0.93–1.66); p = 0.142	1.18 (0.88–1.58); p = 0.269
Age at diagnosis, per year	46.1 (13.2)*	1.03 (1.02–1.04); p < 0.001	1.02 (1.00–1.03); p = 0.011

HR, hazard ratio; CI, confidence interval.

3.2. WHO Grade 4

A predefined subgroup analysis was performed in patients with WHO grade 4 glioma (n = 215). The mean age at diagnosis in this subgroup was 50.3 years (SD 12.8), 146 patients (67.9%) were male, and the mean time to recurrence was 13.3 months (SD 15.0). At recurrence, 63 patients (29.3%) underwent second resection and 152 (70.7%) did not; 166 events were observed. Systemic therapy after recurrence was given to 204 patients (94.9%), comprising PCV in 114 (53.0%), temozolomide in 68 (31.6%), and other regimens in 22 (10.2%), while radiotherapy after recurrence was administered to 31 patients (14.4%) and 184 (85.6%) received none.

Median overall survival from recurrence was 14.4 months (95% CI 10.2–19.7) in patients who underwent second surgery, compared with 8.7 months (95% CI 7.7–10.2) in those who did not (log-rank $p < 0.001$), with estimated survival of 56.1% versus 29.1% at 1 year, 19.4% versus 6.6% at 3 years, and 12.9% versus 2.2% at 5 years.

On univariable analysis, absence of second surgery was associated with worse overall survival from recurrence (HR 1.88, 95% CI 1.32–2.68, $p < 0.001$). (Fig. 2A)

In multivariable analysis, absence of second surgery remained independently associated with a higher risk of death compared with patients who underwent second resection, adjusted HR 2.14 (95% CI 1.37–3.34, $p = 0.001$). (Supplementary Table S1)

Receipt of chemotherapy after recurrence was independently associated with improved survival (adjusted HR 0.21, 95% CI 0.09–0.48, $p < 0.001$). Gender, radiotherapy after recurrence, and age at diagnosis were not independently associated with survival in this subgroup. (Fig. 3)

3.3. WHO Grade 1–3

A corresponding subgroup analysis was performed among patients with WHO grade 1–3 tumors (n = 112); patients with medulloblastoma and other rare histologies were excluded. Of these patients, 63 (56.2%) had grade 3 tumors and 49 (43.8%) had grade 1–2 tumors. The mean age at diagnosis was 37.6 years (SD 10.5), 77 patients (68.8%) were male, the mean time to recurrence was 30.7 months (SD 28.3), with 60 events observed.

At recurrence, 59 patients (52.7%) underwent second resection, whereas 53 (47.3%) did not. Systemic therapy following recurrence was given to 98 patients (87.5%), most commonly Temozolomide in 63 patients (56.2%) and PCV in 31 (27.7%). Radiotherapy after recurrence was administered to 47 patients (42.0%), including sequential radiotherapy in 30 (26.8%), concurrent chemoradiotherapy in 16 (14.3%), and stereotactic radiosurgery in 1 (0.9%); the remaining 65 patients (58.0%) did not receive radiotherapy.

Median overall survival from recurrence was 59.6 months (95% CI 46.3 – not reached) in patients who underwent second surgery, compared with 13.4 months (95% CI 10.6–25.7) in those who did not (log-rank $p < 0.0001$). The estimated overall rates at 1, 3, and 5 years were 87.3%, 63.1%, and 41.2%,

respectively, in the second-surgery group, compared with 59.6%, 31.7%, and 14.1% in the non-surgical group.

On univariable analysis, absence of second surgery was associated with worse overall survival from recurrence (HR 3.14, 95% CI 1.84–5.37, $p < 0.001$). In multivariable analysis measured from recurrence, which was the prespecified primary endpoint, the hazard ratio for absence of second surgery was 1.94 (95% CI 0.96–3.93, $p = 0.064$), and no covariate reached statistical significance in this model, likely reflecting the limited number of events in this subgroup. (Fig. 2B; Supplementary Table S1)

Discussion:

Our results showed improved survival among patients who underwent second surgery at recurrence, with this association observed in both WHO grade 4 and WHO grade 1–3 tumors. The association was most robust in the grade 4 subgroup and remained significant on multivariable analysis measured from the time of recurrence. Whereas, in the grade 1–3 subgroup, the multivariable estimate from recurrence did not reach statistical significance. Nevertheless, repeat resection was associated with higher 1-, 3-, and 5-year survival rates in both subgroups.

In a retrospective study of patients treated between 1997 and 2007, Chaichana et al. identified 578 patients with primary glioblastoma. Of these, 354, 168, 41, and 15 patients underwent 1, 2, 3, or 4 resections, respectively. Multivariate analysis demonstrated a significant association between the number of resections and overall survival. The median survival was 6.8, 15.5, 22.4, and 26.6 months, respectively, with statistical significance. These results suggest that repeat surgical resection is associated with prolonged survival. Furthermore, the risk of postoperative infections or new neurological deficits did not increase with repeat resections in this group ($p > 0.05$). [11]

Another retrospective study, done by Djamel-Eddine et al., evaluated the impact of repeat surgical resection on survival in patients with recurrent glioblastoma. The study included 132 patients who underwent two or three surgical resections. The results demonstrated that patients who underwent repeat surgery for recurrent glioblastoma had significantly longer survival compared with patients who did not undergo a second surgery. However, there was no difference in survival between patients who underwent two resections and those who underwent three resections. [12]

The optimal timing of second surgery has not yet been well defined. Nevertheless, as emphasized by Martino et al., it is better to “over-indicate” an early second surgery rather than performing a delayed surgery when the tumor has progressed into high-grade gliomas, particularly given the relatively low morbidity profile associated with reoperation. [13]

In our WHO grade 4 subgroup ($n = 215$), 63 patients (29.3%) underwent second resection after recurrence. Median overall survival from recurrence was 14.4 months in patients who underwent second surgery compared with 8.7 months among those who did not (HR 1.88, 95% CI 1.32–2.68, $p < 0.001$). In

multivariable analysis, absence of second surgery remained independently associated with worse survival (HR 2.14, 95% CI 1.37–3.34, $p = 0.001$).

In a retrospective trial conducted by Gonzales et al, 214 patients were included between 2005 and 2019. Among these, 33 patients underwent second surgical resection, while 84 patients received chemotherapy alone. The study showed no survival advantage for patients who underwent surgical resection compared with those treated with chemotherapy alone. These findings suggest that the survival benefit reported in studies supporting repeat surgical intervention may be influenced by selection bias, as patients selected for surgery are often those with more favorable clinical characteristics and a better overall prognosis. [14]

In contrast, a retrospective study by De Bonis et al., conducted between 2002 and 2008, reported different findings. The study included 76 patients with recurrent GBM. The results showed that patients treated with chemotherapy alone had a longer OS than those treated with second surgery alone.[15]

Several studies have examined systemic treatment regimens in recurrent glioblastoma. In 2013, a Korean study evaluated the role of low-dose metronomic Temozolomide (TMZ) in recurrent GBM patients. Data from 125 patients were presented at the ESMO congress. Patients received continuous dose-intense TMZ at 50 mg/m² daily. This metronomic dose was associated with low toxicity and demonstrated that it may represent a feasible treatment option in recurrent GBM patients. [16] More recently, Bosio et al. published data in 2023 from a retrospective cohort of 120 heavily pretreated patients with recurrent GBM treated between 2013 and 2021. Patients received continuous metronomic TMZ at a dose of 50mg/m² daily; the study demonstrated a survival benefit with a favorable safety profile, supporting the selection of this protocol in this group of patients. [17]

In our WHO grade 4 cohort, 204 of 215 patients (94.9%) received systemic therapy following recurrence. PCV was administered to 114 patients (53.0%), Temozolomide to 68 (31.6%), and other regimens to 22 (10.2%), while 11 patients (5.1%) received no chemotherapy. Notably, PCV was the most common regimen in our practice, rather than temozolomide, in contrast to the metronomic Temozolomide protocols described above. Receipt of chemotherapy after recurrence was independently associated with improved survival (adjusted HR 0.21, 95% CI 0.09–0.48, $p < 0.001$). However, our study was not powered to compare individual chemotherapy regimens, and the small number of patients who did not receive chemotherapy limits the precision of this estimate. Therefore, our findings do not allow conclusions regarding the optimal salvage regimen.

Regarding radiotherapy for recurrent glioblastoma, available evidence remains limited. Results published in 2025 from a single-center retrospective study suggested a potential PFS benefit in carefully selected patients. The emergence of Bevacizumab in the treatment protocol has shown promising results, both in radiation necrosis and in enhancing treatment efficacy. [18]

Several factors have been suggested to explain the variability in reported outcomes, but it may be concluded that patients who tended to have significantly longer PFS may have been carefully selected.

[19] Another study similarly demonstrated that carefully selected patients with recurrent GBM who underwent surgery due to raised ICP or worsening neurological symptoms experienced improvement in OS. [20]

In our WHO grade 4 cohort, re-irradiation was administered to a minority of patients, with 20 (9.3%) receiving concurrent chemoradiotherapy, 9 (4.2%) sequential radiotherapy, and 2 (0.9%) stereotactic radiosurgery; the remaining 184 patients (85.6%) received no additional radiotherapy. On multivariable analysis, none of the radiotherapy categories were independently associated with survival, although sequential radiotherapy demonstrated a non-significant trend toward improved survival (HR 0.39, 95% CI 0.13–1.14, $p = 0.085$). Given the small number of patients within each treatment category, these findings should be considered exploratory and are consistent with the highly selective use of re-irradiation described in the published literature.

With regard to low-grade glioma (LGG), several studies over the past two decades have shown that the extent of resection of the primary tumor has a major impact on overall survival. [21]

In a study by Ramakrishna et al. involving 52 patients with recurrent LGG treated at the University of Washington, variable prognostic factors were found to be associated with improved survival. Among these, repeat surgery was associated with a significant survival benefit; in addition, the extent of surgical resection was the strongest predictor of OS among these variables. [22]

In our WHO grade 1–3 cohort ($n = 112$), 59 patients (52.7%) underwent second resection at recurrence. Median overall survival from recurrence was 59.6 months in patients who underwent second surgery versus 13.4 months in those who did not (HR 3.14, 95% CI 1.84–5.37, $p < 0.001$). The estimated overall survival at 1 and 5 years was 87.3% and 41.2%, respectively, in the second surgery group, compared with 59.6% and 14.1% among those who did not undergo second surgery. In multivariable analysis measured from the time of recurrence, the hazard ratio for absence of second surgery was 1.94 (95% CI 0.96–3.93, $p = 0.064$).

The impact of re-irradiation in recurrent low-grade glioma remains incompletely understood. [23] Several prognostic factors have been associated with improvement in OS, including younger age, good performance status, lower histological grade at both initial diagnosis and recurrence, longer interval between prior radiotherapy and re-irradiation, higher dose of re-irradiation, smaller tumor volume at the time of re-irradiation, and MGMT methylation status. [24]

The optimal dose-fractionation for re-irradiation has not yet been well established. In a retrospective study by Lee et al., 36 patients with recurrent glioma, including 17 patients with WHO grade I/II tumors, who received re-irradiation between 1996 and 2011 were evaluated; they concluded that re-irradiation of approximately 40–45 Gy was feasible in selected patients with recurrent glioma who had previously received 60 Gy, with an acceptable rate of complications. Furthermore, re-irradiation combined with surgical resection may serve as an effective salvage treatment for selected patients with good performance status and prolonged interval between initial radiotherapy and tumor recurrence. [25]

Regarding chemotherapy in recurrent low-grade gliomas, a Canadian study reported a series of eight consecutive patients with recurrent oligodendroglioma who showed favorable responses to chemotherapy. Six patients received PCV, and all patients responded, including one complete response, although the disease subsequently recurred. [26]

In our WHO grade 1–3 cohort, 47 patients (42.0%) received radiotherapy following recurrence, including sequential radiotherapy in 30 (26.8%), concurrent chemoradiotherapy in 16 (14.3%), and stereotactic radiosurgery in 1 (0.9%); the remaining 65 patients (58.0%) received no further radiotherapy. Systemic therapy after recurrence was administered to 98 patients (87.5%), most commonly Temozolomide in 63 (56.2%) and PCV in 31 (27.7%). In multivariable analysis, neither radiotherapy nor chemotherapy post-recurrence was independently associated with survival. Sequential radiotherapy showed a non-significant trend toward improved survival (HR 0.57, 95% CI 0.23–1.46, $p = 0.244$), whereas the estimate for systemic chemotherapy was imprecise (HR 2.11, 95% CI 0.64–6.99, $p = 0.221$), likely reflecting the small number of patients who did not receive systemic therapy. Thus, in our cohort, second surgery was the treatment-related variable most consistently associated with outcome in lower-grade tumors.

This study has several limitations, including its retrospective nature, single-center design, non-standardized treatment selection, and limited sample sizes within some subgroups. Treatment decisions were based on physician discretion and individual patient characteristics, creating substantial potential for selection bias and residual confounding. Prospective multicenter studies with standardized treatment protocols are needed to validate these findings and better define the role of repeat surgery in recurrent glioma.

Conclusion:

To our knowledge, this is the largest single-institution series reported from a middle-income country, and the largest from the Middle East region, to evaluate the survival impact of repeat surgical resection across the full spectrum of WHO grade 1–4 recurrent glioma. In this cohort, second surgery at recurrence was associated with a clinically meaningful survival advantage that was evident in the cohort as a whole and in both grades. The association remained independent after multivariable adjustment in WHO grade 4 disease. Systemic therapy after recurrence emerged as a second independent determinant of survival in grade 4 tumors, indicating that the benefit of salvage treatment is multimodal rather than surgical alone.

Two important implications can be drawn from these findings. First, repeat surgery should be actively considered during multidisciplinary discussion rather than reserved as a last-resort option. In carefully selected patients with good performance status and surgically accessible tumors, repeat surgery may be integrated with systemic therapy as part of a multimodal treatment strategy rather than as an alternative. Second, the current evidence in recurrent glioma is largely based on Western populations and mainly focuses on glioblastoma. Our study contributes real-world data from the region while also providing evidence on recurrent lower-grade gliomas, for which the available evidence remains limited.

Declarations

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Institutional Review Board Statement:

The studies involving humans were approved by King Hussein Cancer Center institutional review board. Approval number No. 25 KHCC 085

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics approval and informed consent

The study was conducted in accordance with the Declaration of Helsinki. All patient data will be handled with strict confidentiality.

The study was approved by the Office of Scientific Affairs and Research at King Hussein Cancer Center.

In this retrospective study, the IRB previously granted a waiver of the requirement to obtain informed consent.

Author Contributions: T.A. wrote the main manuscript, R.K. collected data, A.A. collected data, M.H. reviewed data, H.J. revised the tables, R.A. revised the manuscript, B.M. reviewed the pathology results, A.A. wrote and reviewed the manuscript, A.E. reviewed and edited the manuscript, A.I. reviewed data, N.S. reviewed figures and tables, M.O. collected data, A.A. reviewed data, M.A. reviewed the manuscript, H.M. collected data, H.M. collected data, O.E. did the analysis.

Clinical trial number: not applicable

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Figures

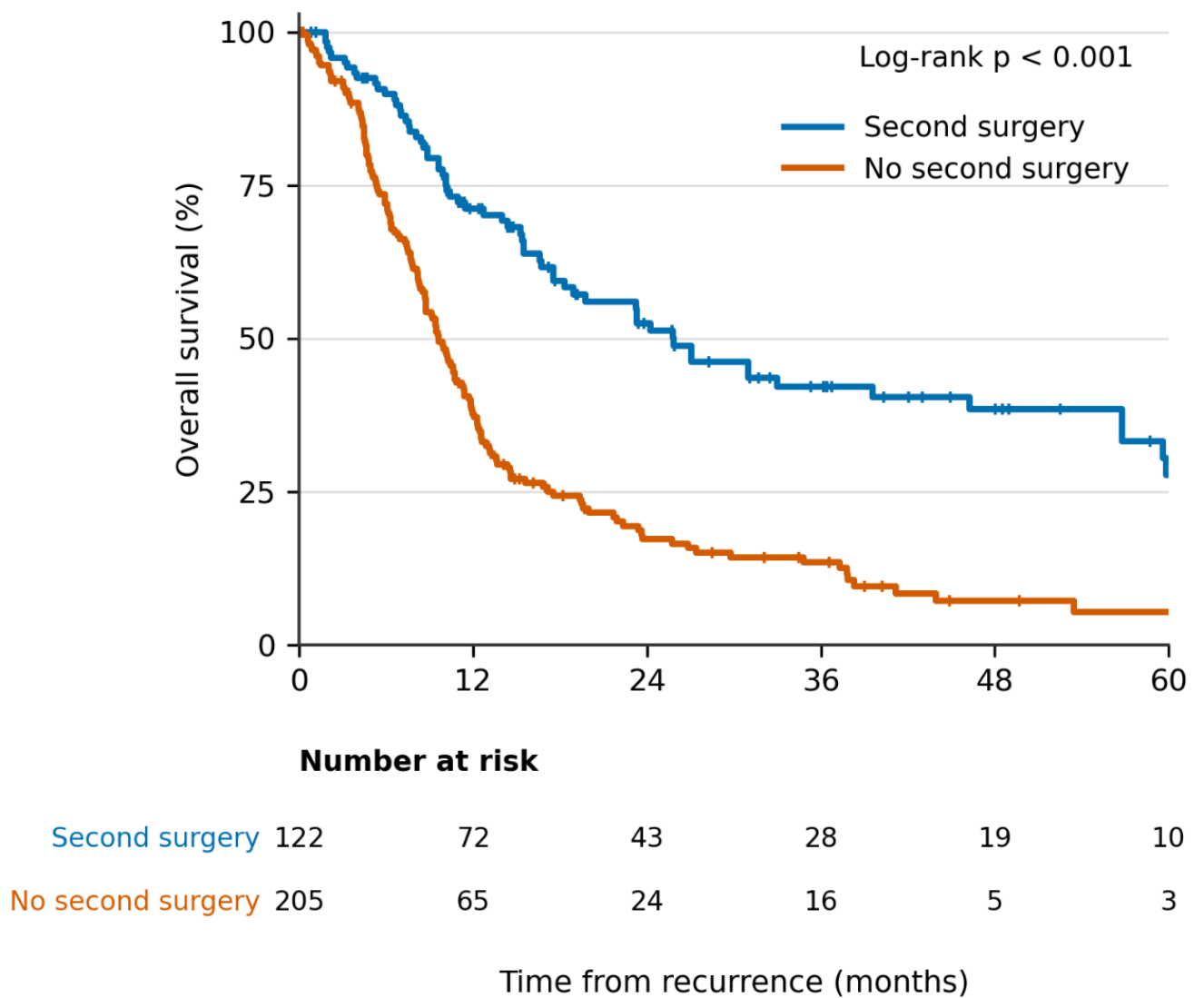


Figure 1

Kaplan-Meier estimates of overall survival from recurrence in the whole cohort ($n = 327$).

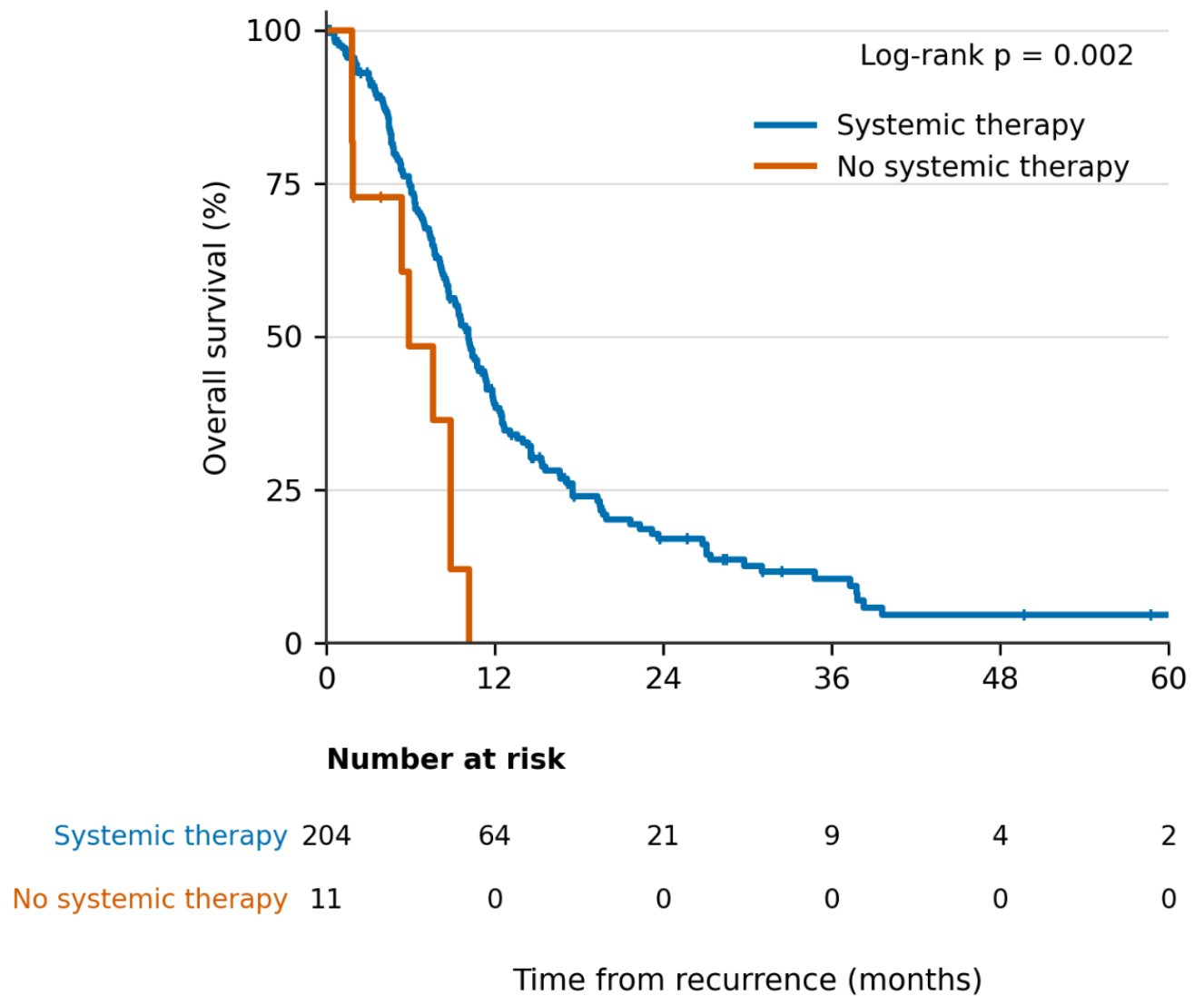


Figure 2

Kaplan-Meier estimates of overall survival from recurrence in the WHO grade 4 subgroup ($n = 215$).

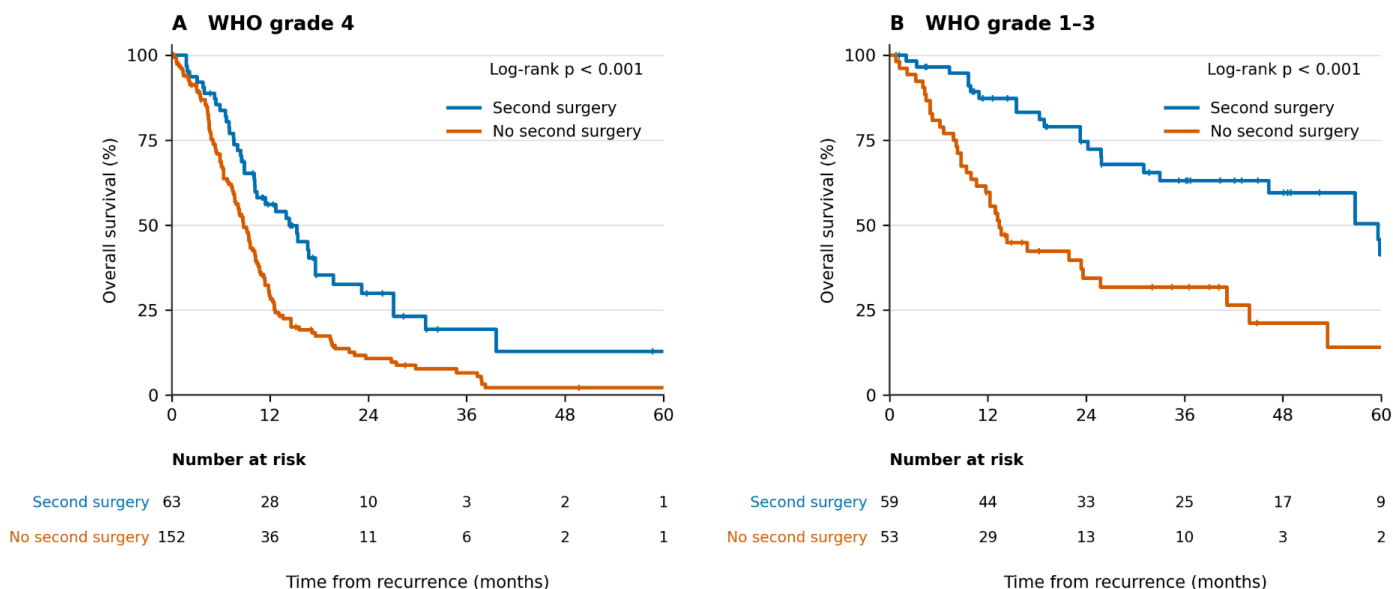


Figure 3

Kaplan-Meier estimates of overall survival from recurrence by second surgical resection, within WHO grade. (A) WHO grade 4 ($n = 215$). (B) WHO grade 1-3 ($n = 112$).

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