DOI: 10.2478/romneu-2018-0033

Surgery for recurrent high-grade gliomas: the dilemma of debate

Wael Musa, Ahmed N. Taha

Department of Neurosurgery, Mansoura Medical School, EGYPT

Abstract: *Background*: Treating recurrent gliomas is a big dilemma in the literature and no uniform protocol is approved to treat such disappointing problem. Although improvement in the RT techniques, new CTX techniques and new techniques including targeted therapy and gene therapy; all fail to dramatically improve the outcome and solve the problem of significant mass effect when the recurrent tumor is big So resurgery play a role in treating such challenging problem. *The aim of the study*: to assess the goal and outcome of surgery in treatment of recurrent malignant glioma. *Methods*: We retrospectively analyzed the data of 56 patients who were operated upon for recurrent or progressed high grade gliomas in the Mansoura neurosurgery department allover 2007 to 2016. We have excluded patients with recurrent thalamic gliomas and patients with Kps score less than 70. *Results*: 12 patient underwent sterotactic biopsy for their tumor and were sent for adjuvant radiotherapy, 29 patients underwent partial tumor resection and gross total resection was done in 15 patients. The median time to progression was 5 months. All patients were sent after surgery for poster radiotherapy and chemotherapy. The median overall survival was 4 months. *Conclusion*: Recurrent high grade glioma is one of unsolved problem and optimal management is no longer available. Redo surgery is quiet challenging with higher minorities and no add to overall survival. Surgery is indicated to relieve significant mass effect. Outcome of surgery is better for those who did aggressive surgical resection at initial surgery than those who did only partial resection.

Key words: RT radiotherapy, CTX chemotherapeutic, kps karnofsky performance status

Introduction

High grade gliomas are the most common primary brain tumor and the most challenging regarding the treatment opportunities.[1–2–3] Safe gross total resection followed by adjuvant treatment including radiotherapy and chemotherapy (temozolomide) is the standard treatment that could be offered to such dismal tumors.[4] Despite advancement in the treatment modalities; the outcome is improved mostly in the functional status but

the potential survival has not significantly improved and recurrence is mostly inevitable. Treating recurrent gliomas is a big dilemma and no uniform protocol is approved to treat such disappointing problem. Although improvement in the radiotherapeutic techniques making re-irradiation for recurrent gliomas is potentially safe and new chemotherapeutic techniques and the development of new techniques including targeted therapy and gene therapy; all fail to dramatically improve the outcome and solve the problem of significant mass effect when the recurrent tumor is big making redo surgery play a role in treating such challenging problem. [5–6]

Surgery for recurrent high-grade glioma should be tailored and individualized based on the patient's age, clinical status, Karnofsky Performance Status score. The extent of resection and numbers of redo surgeries played an important role regarding the quality of life and expected survival for recurrent grade III or IV gliomas.[6] The aim of this retrospective study is to assess the goal and outcome of surgery in treatment of recurrent malignant glioma.

Patients and methods

We retrospectively analyzed the data of 56 patients who were operated up on for recurrent or progressed high grade gliomas in the neurosurgery department, Mansoura University during the period from 2007 to 2016. Previous treatment for those cases was surgery followed by adjuvant treatment in the form of radiotherapy with or without chemotherapy. We have excluded patients with recurrent thalamic gliomas and patients with Karnofsky Performance Status score less than 70.

Results

Patient characteristics are shown in Table 1. Median age was 47.79 years. Thirty-three patients were male, and 23 were female. Histology was WHO Grade 4 in 44 patients and Grade 3 in 12 patients. At last follow-up, 32 of 56 patients had died. Median follow-up from the date of reoperation was 7 months (range, 0–94 months) for all patients and 11 months (range, 0–94 months) for surviving patients.

Predictors of survival

We chose certain factors to predict the survival of our patient from diagnosis and from reoperation to be included in this study, and these factors are; age, size of 2ry tumor, interval between operation, pathology of 2ry tumor and treatment offered after reoperation.

As regard age of patients, median survival rate from diagnosis for patients less than 50 years was 11.00 and 9.00 for patients more than 50 years(p value 0.034) figure 1-A; median survival rate from reoperation for patients less than 50 years was 5.00 and 4.00 for patients more than 50 years(p value 0.060) figure 1-B

TABLE 1

Patient characteristics

AGE	**Mean ± SD**		**47.79**	**9.81**
Size of 1ry_tumor (CM)	**Median**	**Min – Max**	**5.00**	**3-7**
Time to recurrence (m)	**Median**	**Min – Max**	**5.00**	**2-15**
Size of recurrence (CM)	**Median**	**Min – Max**	**4.00**	**2.5-7**
Survival time (m)	**Median**	**Min – Max**	**5.00**	**1-13**
Sex	**Male**		**33**	**58.9%**
	Female		**23**	**41.1%**
Tumor location	**RT frontal**		**8**	**14.3%**
	RT T/P		**4**	**7.1%**
	LF F/T/P		**3**	**5.4%**
	LF F/T		**5**	**8.9%**
	LF TEMPORAL		**4**	**7.1%**
	RT TEMPORAL		**4**	**7.1%**
	RT P/O		**2**	**3.6%**
	LF F/P		**2**	**3.6%**
	RT F/T/P		**5**	**8.9%**
	CORPUS CALLOSUM		**9**	**16.1%**
	LF P/O		**2**	**3.6%**
	LF P		**3**	**5.4%**
	LF T/P		**2**	**3.6%**
	LF F		**1**	**1.8%**
	RT F/P		**1**	**1.8%**
	RT P		**1**	**1.8%**
Pathology of 1ry tumor	**GBM**		**39**	**69.6%%**
	G3		**8**	**14.3%**
Primary TTT	**GTR RT**		**19**	**33.9%**
	PTR RT CH		**7**	**12.5%**
	GTR RT CH		**10**	**17.9%**
	PTR RT		**9**	**16.1%**
	STB RT CH		**3**	**5.4%**
	STB RT		**8**	**14.3%**
Pathology of 2dry T	**GBM**		**44**	**78.6%**
	G3		**12**	**21.4%**
Surgery complication	**NO**		**22**	**39.3%**
	Lt hemiparesis		**7**	**12.5%**
	Coma		**6**	**10.7%**
	Aphasia		**2**	**3.6%**
	Rt hemiparesis		**9**	**16.1%**
	Seizures		**9**	**16.1%**
	CSF leakage		**1**	**1.8%**

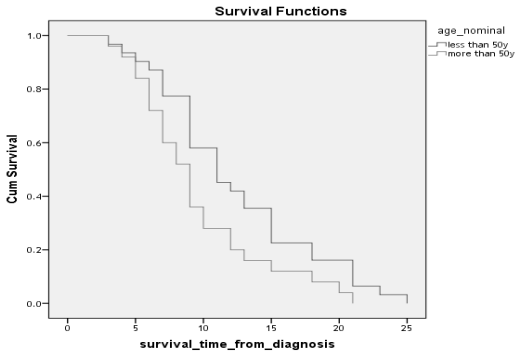

Figure 1-A - median survival rate from diagnosis according patients age

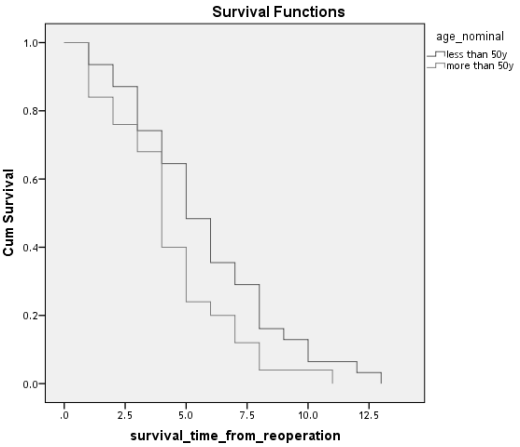

Figure 1-B - median survival rate from reoperation according patients age

Survival from diagnosis and from reoperation acording to size of 2ry tumor is shown in figure 2-A,B. Median survival rate from diagnosis for 2ry tumor less than 5cm in size was 11.00 and for more than 5 cm was 7.00 with p value 0.004,while it was from reoperation for tumor less than 5cm 5.00 and 3.00 for larger tumor size with p value < 0.001.

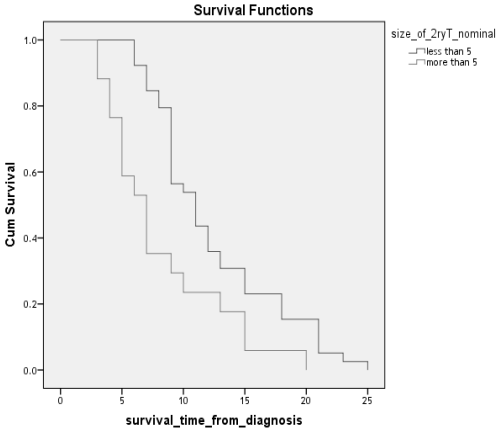

Figure 2-A - Survival from diagnosis according to size of 2ry tumor

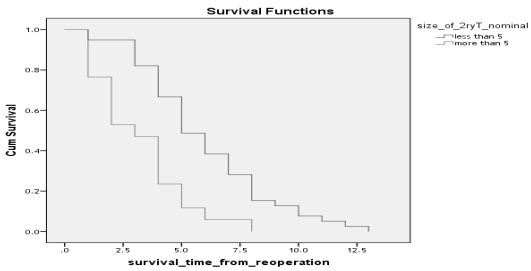

Figure 2-B - Survival from reoperation according to size of 2ry tumor

On the other hand, if we are looking for Survival from diagnosis and from reoperation according to interval between operation as shown in figure 3-A, B.

We found that the median survival rate from diagnosis for patients whom underwent another surgery for the tumors in less than 6 months from the primary surgery was 8.00 and its increase to 18.00 for patients did 2nd surgery in period more than 6 months from first tumor attacking with p value 0.001.

While median survival rate from reoperation for patients whom underwent

another surgery for the tumors in less than 6 months from the primary surgery was 4.00 and its increase to 7.00 for patients did 2nd surgery in period more than 6 months from first tumor attacking with p value < 0.001.

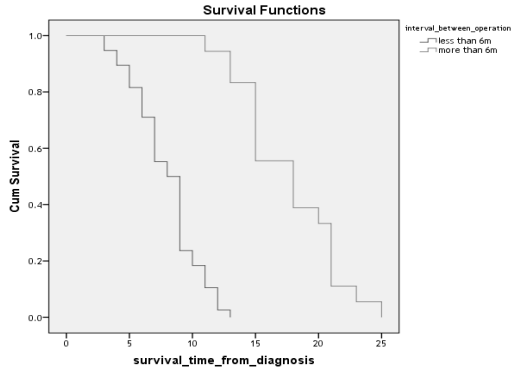

Figure 3-A - Survival from diagnosis according to interval between operation

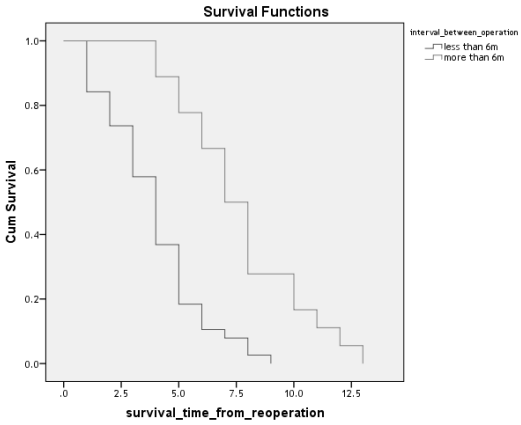

Figure 3-B - Survival from reoperation according to interval between operation

According to pathology of 2ry tumor, Survival from diagnosis and from reoperation shown figure 4-A, B.

We found that the median survival rate from diagnosis for patients whom 2ry tumor pathology was GBM was 9.00 and its 15.00 for patients whom 2ry tumor pathology was grade 3 with p value 0.003.While median survival rate from reoperation for patients whom 2ry tumor pathology was GBM was 4.00 and its 7.00 for patients whom 2ry tumor pathology was grade 3 with p value 0.011.

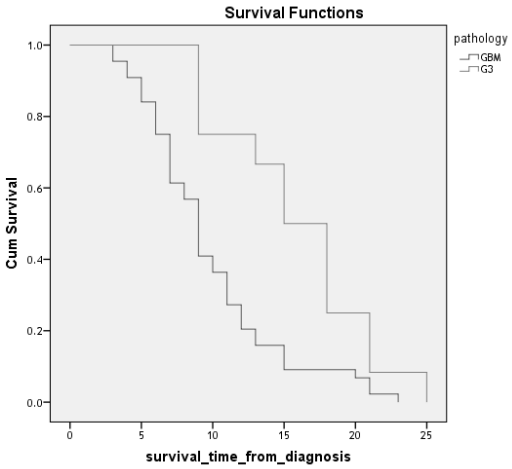

Figure 4-A - Survival from diagnosis according to pathology of 2ry tumor

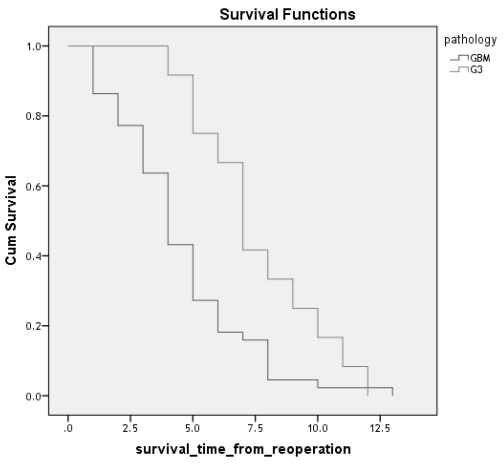

Figure 4-B - Survival from reoperation according to pathology of 2ry tumor

Finally, According to treatment offered after reoperation, Survival from diagnosis (Table 2, figure 5-A) and from reoperation (Table 3, figure 5-B).

TABLE 2

Survival from diagnosis according to treatment offered after reoperation

TTT_offered	Total N	N of Events	Censored		Median survival time	P
			N	Percent		
GTR_RT_CHT	6	6	0	0.0%	12.000	<0.001
PTR	2	2	0	0.0%	6.000	
GTR_CHT	15	15	0	0.0%	18.000	
PTR_RT	1	1	0	0.0%	11.000	
PTR_CHT	18	18	0	0.0%	9.000	
PTR_RT_CHT	8	8	0	0.0%	9.000	
PTR_DC	6	6	0	0.0%	4.000	
Overall	56	56	0	0.0%	9.000	

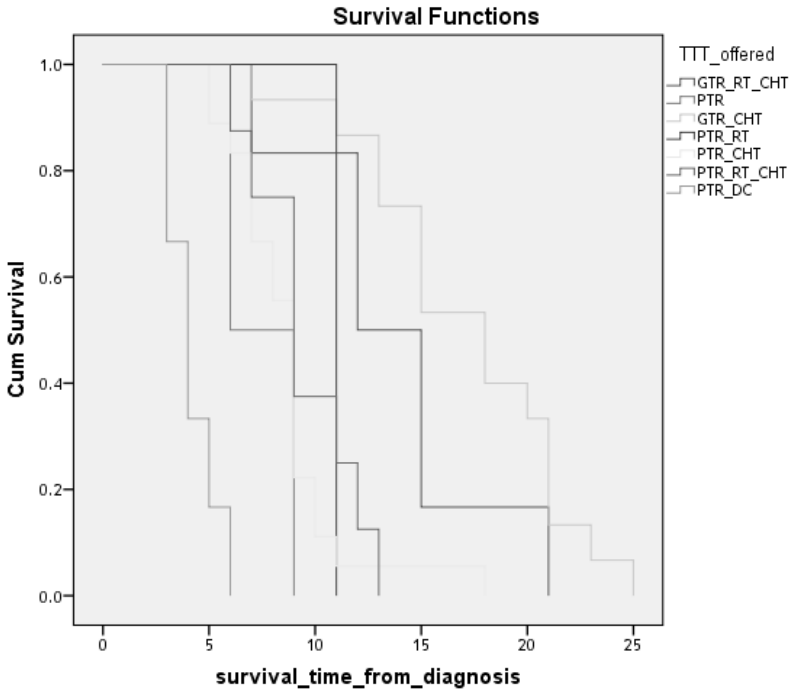

Figure 5-A - Survival from diagnosis according to treatment offered after reoperation

TABLE 3

Survival from reoperation according to treatment offered after reoperation

TTT_offered	Total N	N of Events	Censored		Median survival time	P
			N	Percent		
GTR_RT_CHT	6	6	0	0.0%	7.000	<0.001
PTR	2	2	0	0.0%	1.000	
GTR_CHT	15	15	0	0.0%	8.000	
PTR_RT	1	1	0	0.0%	6.000	
PTR_CHT	18	18	0	0.0%	4.000	
PTR_RT_CHT	8	8	0	0.0%	3.000	
PTR_DC	6	6	0	0.0%	1.000	
Overall	56	56	0	0.0%	5.000	

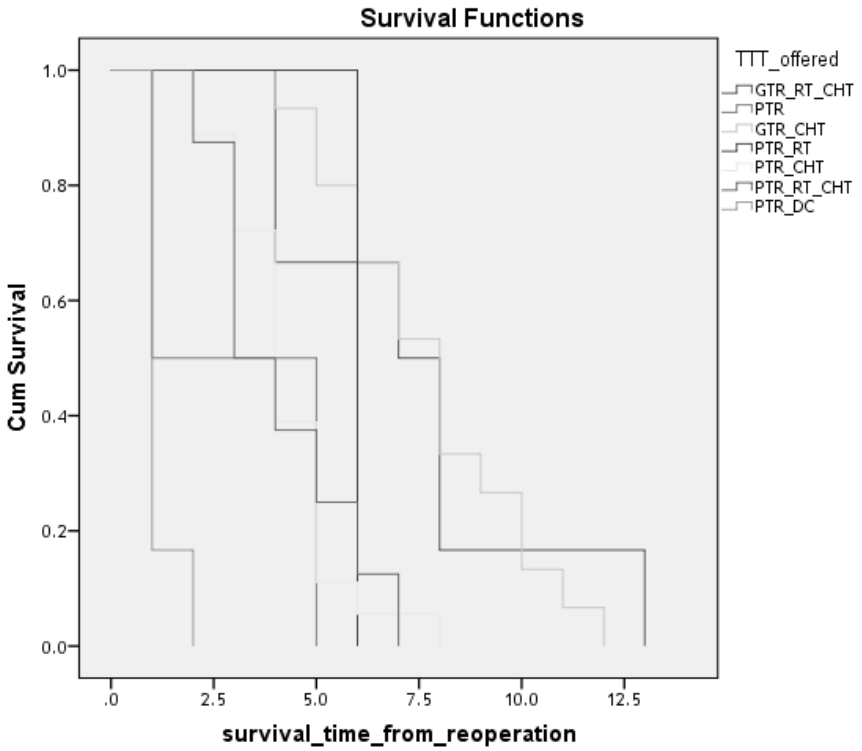

Figure 5-B - Survival from reoperation according to treatment offered after reoperation

In our current study we have different patient complications varied from hemiparesis, coma, CSF leakage, and aphasia (Table 4)

TABLE 4

Patient complications

			Sex	
			Male	Female
Surgery complication	NO	Count	14	8
		%	63.6%	36.4%
	Lt hemiparesis	Count	6	1
		%	85.7%	14.3%
	Coma	Count	4	2
		%	66.7%	33.3%
	Aphasia	Count	1	1
		%	50.0%	50.0%
	Rt hemiparesis	Count	5	4
		%	55.6%	44.4%
	Seizures	Count	3	6
		%	33.3%	66.7%
	CSF leakage	Count	0	1
		%	0.0%	100.0%

Treating recurrent high-grade gliomas is a big dilemma and debate still exist in the literature about the value of redo surgery in improving the overall prognosis of such dismal tumors. Patient age and Karnofsky Performance Status (KPS) are very important detectors for the quality and duration of survival after reoperation. Patients with recurrent high-grade glioma with KPS more than 70 have better outcome than those less than 70. Age and preoperative KPS score had a significant effect on duration of high-quality survival after reoperation.[8–12–13–14–15–16–17–19–20–21]

Some studies compared the quality of survival and duration of survival for patients with recurrent high-grade gliomas who offered re-operation to those who not operated up on. One study found a 9-month survival (operated group) compared with 5.75 months (Non-operated group). [9–22–25–26–27] Many published data showed 5-50%

improvement in KPS after re-operation for recurrent high-grade gliomas.

Improvement in the adjuvant treatment protocols with the use of conformal fractionated radiotherapy with the use of temozolomide chemotherapy helped to improve the clinical outcome and overall survival for high-grade glioma. Despite such improvement; the chance of tumor progression or recurrence still exist and still there is a big debate if adjuvant treatment alone is enough for recurrence or there is a role for re-operation.[4] In a one retrospective study done by on 65 patients who underwent re-operation for progressing high grade gliomas. Median time to second surgery was 7.1 months. The indications to reoperation were increase in the tumor size on magnetic resonance imaging, new neurological deficit, manifestation of increased intracranial pressure and epilepsy. The authors found better overall survival for those who did re-operation the those who did not.[9] Many other reports addressed such controversial problem and they found that outcome of re-operation for recurring high-grade gliomas is multifactorial and more favorable outcome was found for those patients with age 50 years or less, time interval more than 9 months between operations, achieving gross total resection (GTR), and KPS scores 70 at reoperation.[9–22–25]

Some studies addressed the role of either radiotherapy plus temozolimide or temozolimide alone for treating progressing high-grade gliomas and despite initial good results; the found less capabilities of achieving good tumor control and overall survival compared to re-operation with adjuvant treatment. However; there was no difference in outcome of the patient functional status.[11]

Improvement in neurosurgical techniques, neuro-anesthesia, and post-operative ICU care minimized procedure related morbidities and mortalities. However, proper patient selection is very important to choose the case who might get benefit from re-operation. Beside the patient age, KPS, the time to recurrence; other factors may play an important role be considering the outcome.[5–7–8–10–12–13–15–18–21–23–28]

The tumor size and the degree of central necrosis play an important role regarding the outcome and it was found in some studies that the prognosis was favorable with patients having tumor necrosis rather than tumor recurrence. Smaller tumor volume had a more favorable outcome compared with bigger tumor volume at time of re-operation. The extent of tumor removal is another prognostic indicator for the outcome which is also dependent on the tumor size and location with more favorable outcome occur with achieving adequate gross total resection at both the time of primary and re-operations. It was found the re-operation for recurrent tumor after initial gross total resection has a better outcome than after partial resection or just biopsy.[24] Gross total resection (GTR) is recognized by many studies as an independent predictor of improved survival in patients with recurrent high-grade glioma. It was found that the residual tumor volume has its impact on outcome of temozolomide chemotherapy after re-operation.[2] One study on recurrent high-grade gliomas reported a median survival of

11months after GTR compared to 5 months after only partial resection disregarding patient age and performance status.[23] In another study; authors analyzed a series of 107 patients with re-operation for recurring high-grade glioma. They addressed the value of the extent of tumor resection at the initial and subsequent surgery. The found the best survival outcome with subtotal resection at the initial surgery and GTR at re-operation with median overall survival of 16.7-month and the worst outcome with partial resection at both surgery with 7.4 median overall survival.[5]

Patients age play an important role in overall prognosis for recurrent high-grade gliomas and the younger the age the better the prognosis. Although some centers did not offer surgery for elderly with recurrent high-grade gliomas; some studies concluded that surgery should be considered for all patients with favorable KPS disregarding the age of the patient.[29]

The goal of surgery for recurrent high-grade gliomas is to do safe adequate resection with limited morbidities. The potential morbidities for re-operation was studied in many case series. Some studies showed no difference in the incidence of morbidities while others showed higher chance of surgery related morbidities. In one study; 18% patients had neurological deterioration for surgery of recurrent cases compared to 8% neurological deterioration after the initial surgery. [7]

Conclusion: Although advancement in neurosurgical techniques; recurrent high grade glioma is one of unsolved problem for neurosurgical practice and optimal management is no longer available. Redo surgery is quiet challenging with higher minorities and no add to overall survival. Surgery is indicated to relieve significant mass effect. Outcome of surgery is better for those who did aggressive surgical resection at initial surgery than those who did only partial resection. But if resurgery is indicated due to mass effect of the tumor may help to improve survival and should be considered in patients with a favorable KPS score at time resugery.

References

1. DeAngelis LM. Brain tumors.N Engl J Med.2001;344(2):114-123.

2. Deorah S, Lynch CF, Sibenaller ZA, Ryken TC. Trends in brain cancer incidence and survival in the United States: Surveillance, Epidemiology, and End Results Program, 1973 to 2001.Neurosurg Focus.2006;20(4):E1.

3. Surawicz TS, Davis F, Freels S, Laws ER Jr, Menck HR. Brain tumor survival: results from the National Cancer Data Base. J Neurooncol. 1998;40(2):151-160.

4. Stupp R, Dietrich PY, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide.J Clin Oncol.2002;20(5): 1375-1382.

5. Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012;117 (6):1032-1038.

6. Chaichana KL, Zadnik P, Weingart JD, et al. Multiple resections for patients with glioblastoma: prolonging survival.J Neurosurg. 2013;118(4):812-820.

7. Chang SM, Parney IF, McDermott M, et al. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg. 2003;98(6):1175-1181.

8. Harsh GR, Levin VA, Gutin PH, Seager M, Silver P, Wilson CB. Reoperation for recurrent glioblastoma and anaplastic astrocytoma. Neurosurgery. 1987;21(5): 615-621.

9. Helseth R, Helseth E, Johannesen TB, et al. Overall survival, prognostic factors, and repeated surgery in a

consecutive series of 516 patients with glioblastoma multiforme.Acta Neurol Scand.2010;122(3):159-167.
10. Rusthoven KE, Olsen C, Franklin W, et al. Favorable prognosis in patients with high-grade glioma with radiation necrosis: the University of Colorado reoperation series. Int J Radiat Oncol Biol Phys.2011;81(1):211-217.
11. Terasaki M, Ogo E, Fukushima S, et al. Impact of combination therapy with repeat surgery and temozolomide for recurrent or progressive glioblastoma multiforme: a prospective trial.Surg Neurol.2007;68(3):250-254.
12. Young B, Oldfield EH, Markesbery WR, et al. Reoperation for glioblastoma. J Neurosurg. 1981;55(6):917-921.
13. Ammirati M, Galicich JH, Arbit E, Liao Y. Reoperation in the treatment of recurrent intracranial malignant gliomas. Neurosurgery. 1987;21(5):607-614.
14. Azizi A, Black P, Miyamoto C, Croul SE. Treatment of malignant astrocytomas with repetitive resections: a longitudinal study.Isr Med Assoc J. 2001;3(4):254-257.
15. Barker FG II, Chang SM, Gutin PH, et al. Survival and functional status after resection of recurrent glioblastoma multiforme.Neurosurgery. 1998;42(4):709-720.
16. Clark AJ, Butowski NA, Chang SM, et al. Impact of bevacizumab chemotherapy on craniotomy wound healing.J Neurosurg. 2011;114(6):1609-1616.
17. Clark AJ, Lamborn KR, Butowski NA, et al. Neurosurgical management and prognosis of patients with glioblastoma that progresses during bevacizumab treatment. Neurosurgery. 2012;70(2):361-370.
18. Dirks P, Bernstein M, Muller PJ, Tucker WS. The value of reoperation for recurrent glioblastoma. Can J Surg.1993;36(3):271-275.
19. Durmaz R, Erken S, Arslantas A, Atasoy MA, Bal C, Tel E. Management of glioblastoma multiforme: with special reference to recurrence. Clin Neurol Neurosurg.1997;99(2):117-123.
20. Keles GE, Lamborn KR, Chang SM, Prados MD, Berger MS. Volume of residual disease as a predictor of outcome in adult patients with recurrent supratentorial glioblastomas multiforme who are undergoing chemotherapy.J Neurosurg.2004; 100(1):41-46.
21. Landy HJ, Feun L, Schwade JG, Snodgrass S, Lu Y, Gutman F. Retreatment of intracranial gliomas. South Med J.1994;87(2):211-214.
22. Mandl ES, Dirven CM, Buis DR, Postma TJ, Vandertop WP. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy.Surg Neurol.2008;69(5):506-509.
23. McGirt MJ, Chaichana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma.J Neurosurg. 2009;110(1):156-162.
24. Park JK, Hodges T, Arko L, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol.2010;28(24):3838-3843.
25. Pinsker M, Lumenta C. Experiences with reoperation on recurrent glioblastoma multiforme. Zentralbl Neurochir.2001;62(2):43-47.
26. Rostomily RC, Spence AM, Duong D, McCormick K, Bland M, Berger MS. Multimodality management of recurrent adult malignant gliomas: results of a phase II multiagent chemotherapy study and analysis of cytoreductive surgery. Neurosurgery. 1994;35(3):378-388.
27. Salcman M, Kaplan RS, Ducker TB, Abdo H, Montgomery E. Effect of age and reoperation on survival in the combined modality treatment of malignant astrocytoma.Neurosurgery. 1982;10(4):454-463.
28. Sipos L, Afra D. Re-operations of supratentorial anaplastic astrocytomas.Acta Neurochir (Wien).1997;139(2):99-104.
29. Stark AM, Hedderich J, Held-Feindt J, Mehdorn HM. Glioblastoma: the consequences of advanced patient age on treatment and survival.Neurosurg Rev. 2007;30(1):56-61.