Initial surgical resection and long time to occurrence from initial diagnosis are independent prognostic factors in resected recurrent IDH wild-type glioblastoma

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Keywords

Keywords: IDH wild-type, overall survival, progression-free survival, recurrent glioblastoma, reoperation

Highlights

- IDH-wildtype glioblastoma is the most common and aggressive primary brain cancer in adults.
- At tumor recurrence, treatment decision-making is not standardized with several option including second surgery, reirradiation and/or second line of chemotherapy.
- We conducted a retrospective monocentric study to analyzed the clinical benefit of second surgery at recurrence and the prognostic factors in resected recurrent glioblastoma patients in a well-defined patient population at the era of WHO 2016 classification.
- We enrolled 229 IDH-wildtype newly glioblastoma patients meeting the inclusion criteria.
- 25% of patients were reoperated and these patients had longer post-progression median overall survival compared to their non-reoperated couterparts (14 versus 9 months, $p < .05$).
- Initial surgical resection and long time to first recurrence from initial diagnosis were independent prognostic factors of good outcome in resected recurrent IDH-wildtype glioblastoma patients while tumor size before and after surgery does not impact post-surgical survival.
- Further prospective and larger studies are warranted to validate our findings.

Abstract

Objective

IDH-wildtype glioblastoma is the most common and aggressive primary brain cancer in adults. At tumor recurrence, treatment decision-making is not standardized with several options including second surgery, reirradiation and/or second line of chemotherapy. In this retrospective monocentric study conducted at the era of WHO 2016 classification, we investigated in IDH-wildtype glioblastoma patients, aged below 70, in good clinical conditions and treated according to first line SOC: (i) the clinical benefit of second surgery at recurrence and (ii) the prognostic factors in resected recurrent glioblastoma patients.

Methods

229 IDH-wildtype newly diagnosed glioblastoma patients aged below 70, treated with the SOC, were enrolled in the current study and stratified into two subgroups according to treatment at recurrence: re-resection and no re-resection groups.

Results

All experienced tumor recurrence with a median progression free survival of 11 months. 25% of patients were reoperated. Patients reoperated at recurrence had longer post-progression median overall survival compared to their non-reoperated counterparts (14 versus 9 months, $p < .05$). Initial surgical resection and long time to first recurrence from initial diagnosis were independent prognostic factors of good outcome in resected recurrent IDH-wildtype glioblastoma patients while tumor size before and after surgery does not impact post-surgical survival.

Conclusion

Our study supports surgical resection at recurrence as one therapeutic in IDH-wildtype glioblastoma patients aged below 70 and in good clinical conditions, regardless preoperative tumor size; particularly in patients with longer time to first recurrence and surgery at initial diagnosis. Further prospective and larger studies are warranted to validate our findings.

Introduction

Glioblastoma exhibiting Isocitrate DeHydrogenase wildtype (IDH-wildtype) status is the most common and the most aggressive primary malignancy of central nervous system (CNS) in adults. The incidence rate is estimated to approximately 3 new cases per year per 100 000 population [1,2].

Since 2005, the standard of care (SOC) of newly diagnosed glioblastoma patients includes maximal safe surgical resection followed by external beam radiotherapy with concomitant and adjuvant temozolomide-based chemotherapy [3]. Despite this intensive therapeutic regimen, the median overall survival remains below 18 months [4,5].

Virtually all glioblastoma patients experience tumor recurrence after the first-line SOC treatment. At first tumor recurrence, treatment options are not standardized and limited [6] : reresection, reirradiation and second line of chemotherapy including Lomustine or Lomustine plus Bevacizumab [7].

At initial diagnosis, many studies have shown the positive impact of surgical resection on overall survival and progression-free survival [8–10]. However, its benefit in terms of survival is matter of controversies with patients exposed to surgical morbimortality [11–13]. Mortality after first resection is estimated at 36.2 for 1000 cases [14]; the morbimortality after reoperation at recurrence is not well established but is higher than at initial diagnosis [12]. Extent of resection (EOR) and Karnofsky performance status (KPS) at recurrence have been shown as the most important prognostic factors in recurrent glioblastoma patients [12,15–17]. In 2010, Park and al. had proposed a preoperative scale including poor prognostic factors in recurrent glioblastoma patients : involvement of eloquent or critical brain areas, low KPS ($\leq 80\%$) and tumor volume ≥ 50 cm^3 [3, 18].

The aim of this retrospective study was to interrogate the impact of second surgical resection and to identify prognostic factors in an homogeneous group of recurrent glioblastoma patients, aged below 70 years, in good clinical conditions (i.e. KPS $\geq 70\%$ at initial diagnosis and recurrence) and, treated according the SOC first line treatment, at the era of the 2016 World Health Organization classification of primary brain tumors [19].

Methods

Patients and tumors

We retrospectively reviewed all patients diagnosed and treated for IDH-wildtype newly diagnosed glioblastoma at our institution between 2005 and 2018. The neuropathological diagnosis was performed according to World Health Organization 2016 criteria.

Our study was based on concurrent eligibility criteria at initial diagnosis of glioblastoma and at first recurrence.

At initial diagnosis inclusion criteria were: (i) age ≥ 18 years, (ii) KPS ≥ 70%, (iii) IDH-wildtype glioblastoma, (iv) treatment with the SOC and, (v) available follow-up data. At first recurrence: (i) KPS ≥ 70%, (ii) available follow-up data.

For each patient, the following parameters were recorded at initial diagnosis: (i) gender, (ii) age, (iii) tumor lateralization (right, left or bilateral), (iv) date of initial surgery, (v) EOR according to the post-operative report - gross total resection of contrast enhancement, GTR, subtotal resection, STR, biopsy- and, (vi) KPS. The following parameters were recorded for first recurrence: (i) date second surgery, (ii) tumor lateralization (right, left or bilateral) and tumor site, (iii) KPS. For the second surgery, we collected: (i) date of surgery, (ii) EOR (GTR or STR according to the post-operative report), (iii) tumor size on both contrast T1-weighted images and on T2-weighted Fluid Attenuated Inversion Recovery images on MRI before and after second surgery according to RANO criteria (product of maximal diameter and maximal perpendicular diameter) and, (iv) pathological examination.

Progression free survival was defined between initial surgery and first tumor recurrence (PFS1) and between the date of first progression and the date of second progression (PFS2). Overall survival was calculated from date of initial surgery and last follow-up or death (OS1) and post-progression overall survival between the date of first recurrence and the date of last follow up or death (OS2).

Written consent obtained from the patients for data collection and molecular analysis. Tumor tissue was stored in the certified OncoNeuroTek tumor tissue bank linked to a clinical database. The IDH1 Arg132His (IDH1R132H) mutation was investigated by immunohistochemistry on paraffin (paraffin-embedded tissue sections or FFPE) [20]. For patients under 55 years of age with negative IDH1R132H immunohistochemistry, the mutational status of IDH1 and IDH2 was determined by Sanger technique as previously described [19]. Promoter methylation status of O6-methylguanine DNA-methyltransferase gene (MGMT) was determined on DNA from FFPE tumor samples using methylation-specific polymerase chain reaction, as previously described [21].

Statistical analysis

Statistical analyses were performed using SPSS 23.0. Categorical variables were presented as frequencies and percentages, and continuous variables as medians and range. To evaluate the normality of the quantitative data distributions, the Kolmogorov-Smirnov was performed. Assessment of the qualitative variables was performed using chi-square test or Fischer exact test. For the quantitative variables, t-test or Wilcoxon test (two-tailed) was used. Patients lost to follow-up were censored for survival at the last date of follow-up. We used a Kaplan-Meier method to estimate overall survival and progression free-survival and log-rank tests for comparisons of subgroups. For multivariate analyses, we used a Cox proportional hazard ratio model. Variables with p-value<0.2 in univariate

analysis were included as covariates in the multivariate analysis. All statistical tests were 2-sided with a significance level of 0.05.

Results

Patients population and tumors at initial diagnosis

229 patients met the inclusion criteria at both time points of the disease. The characteristics of patients and tumors are reported in Table 1. The median age at first surgery was 56 years (range 24-70). 146 were male (64%) and 83 were female (36%). All patients had KPS ≥ 70%. The first surgery was GTR in 62 patients (27%), STR in 133 patients (58%) and biopsy was performed in 34 patients (15%). 120 (52%) had a tumor in the left hemisphere, 107 (47%) in the right hemisphere and 2 (1%) in both hemispheres. All the patients had an IDH-wildtype glioblastoma. *MGMT* promoter status was available in 119 patients (52%) including 47% MGMT-methylated glioblastoma patients. After initial surgery, all the patients were treated with the first line SOC. Of these 229 patients, all relapsed. The median PFS and OS from initial diagnosis (i.e. PFS1 and OS1) were 11 and 27 months respectively (Table 1).
Patients with MGMT methylated tumor had a better outcome compared to their unmethylated counterparts for OS1 and OS2 (41 vs. 23 months, $p < .05$; 14 vs. 11 months, $p <.05$, respectively).

Patients population and tumors at first recurrence

At first relapse, median age of patients was 57 years (range 24-75). KPS was above 70% in all patients in line with inclusion criteria. The recurrence was in tumor initial site in all patients.
60 (26%) underwent a second surgery (re-resection group) and 169 (74%) were treated with second medical treatment (no re-resection group). Age, gender, KPS, tumor lateralization and location were well-balanced between both groups (i.e. re-resection versus no re-resection). In the re-resection group, a limited number of patients underwent a biopsy at initial diagnosis (10 vs. 17%, $p < 0.05$). The median PFS1 was similar in each group (11 vs. 11 months, $p = 0.9$).
In the re-resection group, 15 (25%) had gross GTR and 45 (75%) STR. Before surgery, the median tumor size on contrast-T1 MRI and FLAIR-MRI were 38 and 62 mm2 respectively. After surgery, the median tumor size on contrast-T1 MRI and FLAIR-MRI were 23 and 71 mm2 respectively. Neuropathological examination showed 58 IDH-wildtype glioblastomas and 2 gliosarcomas. MGMT status at recurrence was available for 10 patients only with 5 methylated and 5 unmethylated MGMT glioblastoma. Chemotherapy was the main adjuvant treatment used in each group.

Clinical impact of re-resection

In univariate analysis, OS1 were 29 and 25 months in the re-resection and the no re-resection group, respectively. Although a trend is observed, no significant statistical difference was observed ($p = 0.3$). The survival rates at 2 years after diagnosis were 48% and 39% in the re-resection and the no re-resection group, respectively ($p = 0.2$).
Post-progression median overall survival or median overall survival after first recurrence (OS2) was significantly longer in the re-resection group patients, 14 months vs 9 months in no re-resection group ($p < 0.05$).
The median time between first and second recurrences (PFS2) was longer in the re-resection group than in the non-reresection group (6 vs. 4 months respectively, p-value = 0.002).

Prognostic factors in resected recurrent glioblastoma patients

Multivariate analysis identified biopsy at initial diagnosis and short PFS1 as independent poor prognostic factors for OS2 in the reresected group ($p<.05$) (Table 2). In contrast, gender, age at recurrence, KPS at diagnosis and KPS at recurrence, tumor size on both contast-T1 and FLAIR weighted MRI before and after reresection did not add independent prognostic information for OS2 (Table 2).

Discussion

Our retrospective study included a homogeneous cohort of glioblastoma patients in good performance status and initially treated with the SOC first line treatment. Indeed, all patients fulfilled the selection criteria of the phase III clinical trial that has established the SOC [22]. In addition, pathological diagnosis was established according to the last classification of primary brain tumors published by the WHO and requiring IDH status for most glioblastoma patients [19].

As expected and demonstrated in multiple studies, in our population, MGMT promoter methylation is associated with better prognosis for both OS1 and OS2. The number of patients analyzed for MGMT status is limited in our study and does not allow robust statistical analysis in the subgroup of patients (i.e. reoperated and non-reoperated at recurrence).

The prognosis of patients with newly diagnosed IDH-wildtype glioblastoma remains poor. The median OS1 is 14 months and the median OS2 is 5.8 to 8.1 months in literature [6]. Second line of treatment after first tumor progression is not standardized. Chemotherapies such as alkylating agents [23] and platinum-derivative agents [24] have limited efficacy on PFS and OS. Bevacizumab, an anti-angiogenic agent, has shown an effect on PFS but not on OS in recurrent glioblastoma patients [7,23]. Many trials are underway to develop new therapies for recurrence, including immunotherapies [25] and molecular targeted therapies [26,27]. The role of surgery in first recurrence glioblastoma patients is debated. Many studies are retrospective and the results remain conflicting with some studies showing a benefit on survival while others were negative [5,12,16,28–32]. Meta-analyses have been conducted and pinpoint a trend towards increased overall survival in young patients with good performance status and long time to first recurrence [33–35]. The most robust factor for increased survival after re-operation in recurrent glioblastoma patients is EOR at diagnosis and at recurrence [15,36,37].

In the literature, about 20-30% of glioblastoma patients are eligible for second surgery at tumor recurrence [3]. Our data are in line with these data in a patient population with a good clinical condition. Indeed, 25% of our patients were reoperated at first recurrence.

Although reoperation has been shown to relieve neurological symptoms related to tumor first recurrence in glioblastoma patients [38,39], its impact on survival benefit has been poorly documented. In our study, post-progression progression free survival (PFS2) and overall survival (OS2) were increased in patients who undergone second surgery at first recurrence (6 vs 4 months for PFS2 and 14 vs. 9 months for OS2, $p < 0.05$).

Among reoperated patients, the multivariate analysis showed two independent prognostic factors associated with outcome: EOR at diagnosis and PFS1. Indeed, first surgical resection and longer PFS1 are associated with longer PFS2 and OS2 in reoperated glioblastoma patients. Tumor size on both contast-T1 and FLAIR weighted MRI before and after reresection do not appear as a prognostic factor (Table 2).

There are no guidelines for surgical indications at first recurrence in glioblastoma patients. Our study assessing the clinical impact of surgical resection in recurrent glioblastoma patients is the first including the diagnostic criteria of the integrated classification of primary brain tumor published by the WHO in 2016 (i.e. IDH status) [19]. Our study is in line with the literature for: (i) proportion of glioblastoma patients reoperated at recurrence, (ii) prognostic value of MGMT promoter methylation in newly diagnosed glioblastoma patients and, (iii) clinical benefit of surgical

resection at recurrence. Interestingly, our study suggests that patients with surgical resection (i.e. STR or GTR) at initial diagnosis and long PFS1 (*i.e* $\geq$ 11 months) would get greater clinical benefit from a new surgical procedure at recurrence. Indeed, both criteria have independent positive prognostic value in reoperated patients. Surgery at recurrence therefore has multiple interests: to facilitate a new anatomopathological examination to explore targeted therapies or radiosurgery, to improve symptoms and to be a treatment option for a better survival of the patients.

However, our study has the limitations of retrospective studies. The definition of EOR at diagnosis and recurrence was specified in the post-operative report only. MGMT status at recurrence was available for few patients and could not be tested in univariate. Further prospective studies are warranted to interrogate our findings.

References

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. *Neuro-Oncol*. 2019;21(Supplement_5):v1-v100. doi:10.1093/neuonc/noz150

2. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults: a "state of the science" review. *Neuro-Oncol*. 2014;16(7):896-913. doi:10.1093/neuonc/nou087

3. Weller M, van den Bent M, Hopkins K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. *Lancet Oncol*. 2014;15(9):e395-403. doi:10.1016/S1470-2045(14)70011-7

4. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459-466. doi:10.1016/s1470-2045(09)70025-7

5. Nava F, Tramacere I, Fittipaldo A, et al. Survival effect of first- and second-line treatments for patients with primary glioblastoma: a cohort study from a prospective registry, 1997-2010. *Neuro-Oncol*. 2014;16(5):719-727. doi:10.1093/neuonc/not316

6. Weller M, Cloughesy T, Perry JR, Wick W. Standards of care for treatment of recurrent glioblastoma--are we there yet? *Neuro-Oncol*. 2013;15(1):4-27. doi:10.1093/neuonc/nos273

7. Wick W, Gorlia T, Bendszus M, et al. Lomustine and Bevacizumab in Progressive Glioblastoma. *N Engl J Med*. 2017;377(20):1954-1963. doi:10.1056/NEJMoa1707358

8. Kreth F-W, Thon N, Simon M, et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. *Ann Oncol Off J Eur Soc Med Oncol*. 2013;24(12):3117-3123. doi:10.1093/annonc/mdt388

9. Stummer W, Reulen H-J, Meinel T, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery*. 2008;62(3):564-576; discussion 564-576. doi:10.1227/01.neu.0000317304.31579.17

10. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. *Lancet Oncol*. 2011;12(11):997-1003. doi:10.1016/S1470-2045(11)70196-6

11. Hervey-Jumper SL, Berger MS. Reoperation for recurrent high-grade glioma: a current perspective of the literature. *Neurosurgery*. 2014;75(5):491-499; discussion 498-499. doi:10.1227/NEU.0000000000000486

12. Oppenlander ME, Wolf AB, Snyder LA, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. *J Neurosurg*. 2014;120(4):846-853. doi:10.3171/2013.12.JNS13184

13. Zhao Y-H, Wang Z-F, Pan Z-Y, et al. A Meta-Analysis of Survival Outcomes Following Reoperation in Recurrent Glioblastoma: Time to Consider the Timing of Reoperation. *Front Neurol*. 2019;10:286. doi:10.3389/fneur.2019.00286

14. De la Garza-Ramos R, Kerezoudis P, Tamargo RJ, Brem H, Huang J, Bydon M. Surgical complications following malignant brain tumor surgery: An analysis of 2002–2011 data. *Clin Neurol Neurosurg*. 2016;140:6-10. doi:10.1016/j.clineuro.2015.11.005

15. 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. doi:10.3171/2012.9.JNS12504

16. Ringel F, Pape H, Sabel M, et al. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. *Neuro-Oncol*. 2016;18(1):96-104. doi:10.1093/neuonc/nov145

17. Woodroffe RW, Zanaty M, Soni N, et al. Survival after reoperation for recurrent glioblastoma. *J Clin Neurosci Off J Neurosurg Soc Australas*. Published online January 24, 2020. doi:10.1016/j.jocn.2020.01.009

18. Park JK, Hodges T, Arko L, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010;28(24):3838-3843. doi:10.1200/JCO.2010.30.0582

19. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol (Berl)*. 2016;131(6):803-820. doi:10.1007/s00401-016-1545-1

20. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *J Clin Oncol Off J Am Soc Clin Oncol*. 2009;27(25):4150-4154. doi:10.1200/JCO.2009.21.9832

21. Everhard S, Kaloshi G, Crinière E, et al. MGMT methylation: a marker of response to temozolomide in low-grade gliomas. *Ann Neurol*. 2006;60(6):740-743. doi:10.1002/ana.21044

22. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996. doi:10.1056/NEJMoa043330

23. Song J, Xue Y-Q, Zhao M-M, Xu P. Effectiveness of lomustine and bevacizumab in progressive glioblastoma: a meta-analysis. *OncoTargets Ther*. 2018;11:3435-3439. doi:10.2147/OTT.S160685

24. Field KM, Simes J, Nowak AK, et al. Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. *Neuro-Oncol*. 2015;17(11):1504-1513. doi:10.1093/neuonc/nov104

25. Filley AC, Henriquez M, Dey M. Recurrent glioma clinical trial, CheckMate-143: the game is not over yet. *Oncotarget*. 2017;8(53):91779-91794. doi:10.18632/oncotarget.21586

26. Lombardi G, Salvo GLD, Brandes AA, et al. Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet Oncol*. 2019;20(1):110-119. doi:10.1016/S1470-2045(18)30675-2

27. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol*. 2017;18(10):1373-1385. doi:10.1016/S1470-2045(17)30517-X

28. Franceschi E, Bartolotti M, Tosoni A, et al. The effect of re-operation on survival in patients with recurrent glioblastoma. *Anticancer Res*. 2015;35(3):1743-1748.

29. Ening G, Huynh MT, Schmieder K, Brenke C. Repeat-surgery at Glioblastoma recurrence, when and why to operate? *Clin Neurol Neurosurg*. 2015;136:89-94. doi:10.1016/j.clineuro.2015.05.024

30. Sastry RA, Shankar GM, Gerstner ER, Curry WT. The impact of surgery on survival after progression of glioblastoma: A retrospective cohort analysis of a contemporary patient population. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2018;53:41-47. doi:10.1016/j.jocn.2018.04.004

31. 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. doi:10.1111/j.1600-0404.2010.01350.x

32. van Linde ME, Brahm CG, de Witt Hamer PC, et al. Treatment outcome of patients with recurrent glioblastoma multiforme: a retrospective multicenter analysis. *J Neurooncol*. 2017;135(1):183-192. doi:10.1007/s11060-017-2564-z

33. Montemurro N, Perrini P, Blanco MO, Vannozzi R. Second surgery for recurrent glioblastoma: A concise overview of the current literature. *Clin Neurol Neurosurg*. 2016;142:60-64. doi:10.1016/j.clineuro.2016.01.010

34. Lu VM, Goyal A, Graffeo CS, et al. Survival Benefit of Maximal Resection for Glioblastoma Reoperation in the Temozolomide Era: A Meta-Analysis. *World Neurosurg*. 2019;127:31-37. doi:10.1016/j.wneu.2019.03.250

35. Lu VM, Jue TR, McDonald KL, Rovin RA. The Survival Effect of Repeat Surgery at Glioblastoma Recurrence and its Trend: A Systematic Review and Meta-Analysis. *World Neurosurg*. 2018;115:453-459.e3. doi:10.1016/j.wneu.2018.04.016

36. Perrini P, Gambacciani C, Weiss A, et al. Survival outcomes following repeat surgery for recurrent glioblastoma: a single-center retrospective analysis. *J Neurooncol*. 2017;131(3):585-591. doi:10.1007/s11060-016-2330-7

37. Suchorska B, Weller M, Tabatabai G, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma—results from the DIRECTOR trial. *Neuro-Oncol*. 2015;18(4):549-556. doi:10.1093/neuonc/nov326

38. Wann A, Tully PA, Barnes EH, et al. Outcomes after second surgery for recurrent glioblastoma: a retrospective case-control study. *J Neurooncol*. 2018;137(2):409-415. doi:10.1007/s11060-017-2731-2

39. Easaw JC, Mason WP, Perry J, et al. Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme. *Curr Oncol*. 2011;18(3):e126-e136.

Table 1. Characteristics of patient population and tumors at initial diagnosis

		Total	No re-resection at first recurrence	Re-resection at first recurrence	
N,%		229 (100%)	169 (74%)	60 (26%)	
Gender (N,%)	Male Female	146 (64%) 83 (36%)	103 (61%) 66 (39%)	43 (72%) 17 (28%)	p = .14
Age (years)	Median (range)	56 (24-70)	56 (24-70)	55 (24-70)	p = .35
KPS at initial diagnosis (N,%)	70-80% 90- 100%	132 (58%) 97 (42%)	103 (61%) 66 (39%)	29 (48%) 31 (52%)	p = .09
Tumor location (N,%)	Left Hemisph. Right Hemisph. Both Hemisph.	120 (52%) 107 (47%) 2 (1%)	85 (50%) 82 (49%) 2 (1%)	35 (58%) 25 (42%) 0 (0%)	p = .43
Primary surgery (N,%)	GTR STR Biopsy	62 (27%) 133 (58%) 34 (15%)	35 (20%) 106 (63%) 28 (17%)	27 (45%) 27 (45%) 6 (10%)	p < .05
MGMT at diagnosis (N,%)	Unmethylated Methylated Unknown	63 (27%) 56 (25%) 110 (48%)	38 (23%) 33 (20%) 98 (58%)	25 (42%) 23 (38%) 12 (20%)	p < .05
PFS1 (months)	Median (range)	11 (3-70)	11 (3-70)	11 (4-46)	p = .99*
KPS at first recurrence (N,%)	70 – 80% (%) 90 – 100% (%)	153 (67%) 76 (33%)	116 (69%) 53 (31%)	37 (62%) 23 (38%)	p = .33
Surgery at recurrence (N,%)	GTR STR	NA	NA	15 (25%) 45 (75%)	
Diagnosis at recurrence (N,%)	Glioblastoma Gliosarcoma	NA	NA	58 (97%) 2 (3%)	
Adjuvant oncologic treatment (N,%)	CT Reirradiation + CT Surgery alone	214 (93%) 6 (3%) 9 (4%)	166 (98%) 3 (2%) 0 (0%)	48 (80%) 3 (5%) 9 (15%)	p < .05
OS1 (months)	Median (range)	27 (5-146)	25 (5-127)	29 (12-146)	p = .27*
OS2	Median	11	9	14	p < .05*

(months)	(range)	(0-128)	(0-114)	(0-128)	
PFS2 (months)	Median (range)	4 (0-66)	4 (0-66)	6 (1-20)	$p < .05$*

Legend : N, number; KPS, Karnofsky Performance Status; MGMT, MGMT promoter status; PFS1, progression free survival from initial diagnosis to first recurrence; Hemisph, brain hemisphere; GTR, gross total resection; STR, subtotal resection; CT, chemotherapy; OS1, overall survival from initial diagnosis to last follow-up; OS2, overall survival from first recurrence to last follow-up; PFS2, progression free survival from first recurrence to second recurrence; * log-rank test

Table 2. Prognostic analysis in reresected recurrent glioblastoma

Variable	Categories	n	14-months OS2 (%)	P-value	HR [CI 95%]	P-value2
Gender	Male	43	33	.88		
	Female	17	35			
Age	≤50	16	31	.83		
	>50	44	34			
Primary surgery	Biopsy	6	0	.16	3.492 [1.115-10.936]	< .05
	STR	27	33			
	GTR	27	41			
PFS1	>11 months	29	48	.02	.965 [.035-.997]	< .05
	≤11 months	31	19			
KPS at first recurrence	70-80%	37	27	.22		
	90-100%	23	44			
Tumor lateralization	Left Hemisph.	35	34	.85		
	Right Hemisph.	25	32			
Tumor location	Parietal lobe	8	25	.38		
	Frontal lobe	11	36			
	Occipital lobe	10	40			
	Temporal lobe	17	47			
Tumor size on contrast-T1 MRI before re-resection	≤38mm2	19	47	.27		
	>38mm2	17	29			
Tumor size on contrast-T1 MRI after re-resection	≤23mm2	21	38	.85		
	>23mm2	17	35			
Tumor size on FLAIR MRI before re-resection	≤62mm2	16	44	.46		
	>62mm2	16	31			
Tumor size on FLAIR MRI after re-resection	≤71mm2	20	40	.58		
	>71mm2	19	32			
MGMT status	Methylated	23	39	.82		
	Unmethylated	25	36			
Surgery at recurrence	STR	45	31	.52		
	GTR	15	40			
Adjuvant oncologic treatment	CT	48	29	.31		
	Reirradiation + CT	3	67			
	No adjuvant treatment	9	44			

Legend : N, number; KPS, Karnofsky Performance Status; MGMT, MGMT promoter status; PFS1, progression free survival from initial diagnosis to first recurrence; Hemisph, brain hemisphere; GTR, gross total resection; STR, subtotal resection; CT, chemotherapy; RT, radiotherapy; FLAIR, Fluid Attenuated Inversion Recovery; OS2, overall survival from first recurrence to last follow-up; HR, hazard-ratio; CI 95%, confidence interval 95%; p-value2, cox-proportional hazard-ratio p-value