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Reoperation for recurrent glioblastomas: What to expect?

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ABSTRACT

Background: The current standard treatment for glioblastoma (GBM) is maximal safe surgical resection followed by radiation and chemotherapy. Unfortunately, the disease will invariably recur even with the best treatment. Although the literature suggests some advantages in reoperating patients harboring GBM, controversy remains. Here, we asked whether reoperation is an efficacious treatment strategy for GBM, and under which circumstances, it confers a better prognosis.

Methods: We retrospectively reviewed 286 consecutive cases of newly diagnosed GBM in a single university hospital from 2008 to 2015. We evaluated clinical and epidemiological parameters possibly influencing overall survival (OS) by multivariate Cox regression analysis. OS was calculated using the Kaplan–Meier method in patients submitted to one or two surgical procedures. Finally, the survival curves were fitted with the Weibull model, and survival rates at 6, 12, and 24 months were estimated.

Results: The reoperated group survived significantly longer (n = 63, OS = 20.0 ± 2.3 vs. 11.4 ± 1.0 months, $P < 0.0001$). Second, the multivariate analysis revealed an association between survival and number of surgeries, initial Karnofsky Performance Status, and age (all $P < 0.001$). Survival estimates according to the Weibull regression model revealed higher survival probabilities for reoperation compared with one operation at 6 months (83.74 ± 3.42 vs. 63.56 ± 3.59, respectively), 12 months (64.00 ± 4.85 vs. 37.53 ± 3.52), and 24 months (32.53 ± 4.78 vs. 12.02 ± 2.36).

Conclusion: Our data support the indication of reoperation for GBM, especially for younger patients with good functional status. Under these circumstances, survival can be doubled at 12 and 24 months.

Keywords: Brain tumor, Glioblastoma, Reoperation

INTRODUCTION

Glioblastomas (GBMs) account for 14.6% of all primary central nervous system tumors and 48.3% of all malignant tumors. The incidence of GBM is greater in males (1.58 M:1.0 F) and Caucasians (1.95 times greater than in Afro-descendants) and increases with age (median age at diagnosis = 65). Standard of care for patients younger than 70 years old and with a Karnofsky Performance Status (KPS) > 70 is surgical resection, adjuvant radiotherapy plus temozolomide, followed by six cycles of temozolomide, which confers a median progression-free survival (PFS) of 4.4–8.4 months.[15,18,27]

Almost inevitably recurrent, the rate of survival after 1 year of diagnosis is 40.8%, declining to 18.5% after 2 years and to 6.8% in 5 years, with a median overall survival (OS) of 12–15 months.[12] There is still no consensus about the standard of care for GBM recurrence. Indeed, rechallenge of temozolomide may benefit patients with methylguanine methyltransferase (MGMT) promoter methylated tumors.[6]

Reoperation for recurrent GBM is indicated for 3–30% of cases and remains controversial due to the lack of high-level evidence (randomized double-blind trials). Furthermore, the survival benefit reported by some case series may be associated with confounding factors, such as adjuvant therapies, patients' performance status, tumor location and volume, and genetic profile.[30]

Here, we asked whether reoperation is an efficacious treatment strategy for GBM, and under which circumstances, it should be indicated.

MATERIALS AND METHODS

Case series

This retrospective study reviewed 286 consecutive cases of newly diagnosed GBM at a single institution (Instituto do Cancer do Estado de São Paulo – Universidade de São Paulo), from 2008 to 2015. All patients were between 18 years old and 82 years old. Patients were divided into two groups: the one surgery group, including patients who underwent surgical resection once during GBM treatment, and the reoperation group, including patients who were reoperated during follow-up, undergoing two or more interventions. Patients submitted to stereotactic biopsy, for whom surgical resection was judged risky or not indicated, were excluded from the comparative survival analyses.

Management

Brain tumor diagnosis was performed based on clinical history, preoperative magnetic resonance imaging (MRI), and histopathologic study, as per the latest World Health Organization Classification of Tumors of the Central Nervous System.[8] Surgical resection aimed to achieve maximum safe resection, guided by Neuronavigation (BrainLab system), 3D tractography, fMRI, preoperative transcranial magnetic stimulation, and intraoperative electrophysiological monitoring when necessary. Patients were referred to adjuvant chemo- and radiotherapy. All clinical data were collected retrospectively and handled anonymously, following the institution's and Brazil's ethics guidelines. Patients were followed up routinely by a multidisciplinary team, and functional status based on KPS and Eastern Cooperative Oncology Group (ECOG) was measured and recorded at each clinical presentation. MRI scans were performed every 2 months. We obtained T1 native images and with gadolinium, as well as FLAIR, diffusion-weighted images, perfusion-weighted images, and spectroscopy. Tumor volume was estimated based on the three large diameters (d_1, d_2, and d_3), according to the formula $V = 4/3 \times \pi \times (d_1/2 \times d_2/2 \times d_3/2)$. Candidates for reoperation met the following criteria: (i) tumor volume between 3 cm^3 and 50 cm^3 (smaller and larger tumors were excluded), (ii) KPS > 70, and (iii) noncritical/eloquent brain area (cases with tumors in the basal ganglia, thalamus, brainstem, and eloquent/visual cortex were excluded). We included only patients with tumor volume between 3 mL and 50 mL because they represent the group of cases in which there is no consensus concerning reoperation. Tumors larger than 50 mL usually cause mass effects symptoms. In these cases, reoperation can improve patients' quality of life. Finally, individuals presenting lesions of <3 mL are frequently asymptomatic or oligosymptomatic. They do not have a clear benefit that is worth a new surgical procedure. Instead, tumor growth was followed up. Patients who had surgery and did not meet these criteria were excluded from this retrospective analysis. We excluded patients with KPS lower than 70 because they usually are not candidates for reoperation. Nevertheless, in these cases, treatment was according to the standard of care of our institution, which included second-line chemotherapy and reradiation, and the indication of reoperation is under the discretion of the attending surgeon. We compared the OS of patients submitted to one surgery versus patients submitted to two or more interventions [Figure 1].

Statistical analyses

For statistical computations, we used JMP 14.2 (SAS Institute, CA, USA). We evaluated clinical and epidemiological parameters possibly influencing OS by multivariate analysis, REML estimation method (restricted maximal likelihood). The variables included were age, gender, initial KPS, number of surgeries, treatment strategy, and chemotherapy regimen. Next, OS from the time of diagnosis was calculated using the Kaplan–Meier method in patients submitted to one or two or more surgical procedures. Finally, the survival curves were fitted with the Weibull model, and survival probabilities at 6, 12, and 24 months were estimated. Significance was set at $P < 0.01$.

RESULTS

Patients' mean age was 56.2 ± 13.9, and 60.5% were male. The mean preoperative KPS and ECOG scores were 73.5 ± 20.1 and 1.6 ± 1.4, respectively. Mean OS for the whole series (286 cases) was 8.5 (3–16) months. One hundred and twenty-three patients (43.0%) received standard of care treatment, composed of surgery, radiation, and chemotherapy. Fifty-three patients (18.5%) were submitted only to surgery, while

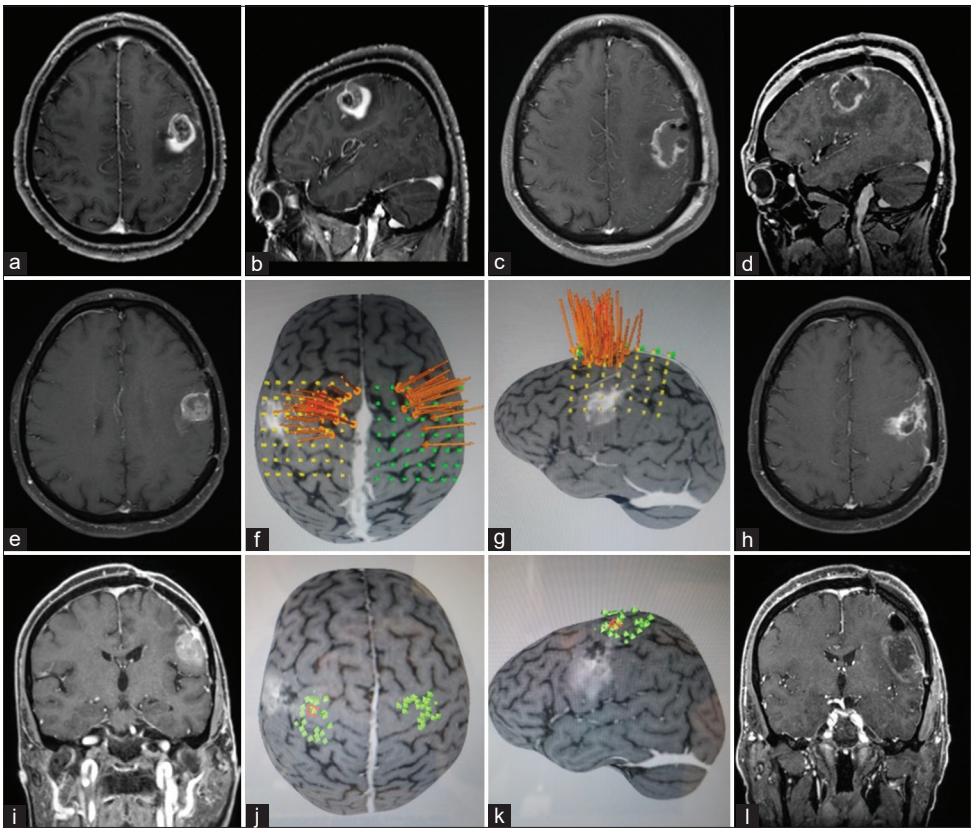

Figure 1: This patient presented a wild-type isocitrate dehydrogenase glioblastoma on the left frontal lobe and underwent three resections. Preoperative postgadolinium T1 magnetic resonance imaging (MRI) axial (a), sagittal (b), early postoperative MRI axial (c), sagittal (d), second resection preoperative postgadolinium T1 MRI axial (e), preoperative motor cortex mapping using navigated transcranial magnetic stimulation (TMS): long arrows point location of M1 activation using nTMS (f and g), late postoperative axial (h), third resection preoperative postgadolinium T1 MRI coronal (i), preoperative motor cortex mapping using navigated TMS (j and k), early postoperative coronal (l).

11 patients (3.8%) received radiotherapy and chemotherapy, and 4 patients (1.4%) only chemotherapy. The median time from surgery to radiation therapy was 70 days (45–104 days). Carmustine was the chemotherapy of choice for patients who were recruited between 2008 and 2010, while patients recruited later (84.6%) received temozolomide as the first-line drug. In line with previous findings, temozolomide was associated with longer OS compared with carmustine (19.36 ± 11.74 months vs. 12.95 ± 7.51, respectively, $P < 0.05$, Chi-square). Thirty-three patients (11.5%) received second-line chemotherapy. The OS survival of patients submitted to surgical resection was 14.2 ± 1.0 months.

Next, we analyzed 190 patients submitted to surgical resection (excluding those submitted to stereotactic biopsies and those who were not operated on). Patients were divided into two groups: those who underwent one single surgery and those who underwent two or more surgeries (one surgery group vs. reoperation group, respectively). The median time from the index surgery to the second surgery was 156 days (77–337 days). Patients in the reoperation group were slightly younger than patients in the one surgery group (50.5 ± 13.2 vs. 57.9 ± 12.8, respectively, $P < 0.001$), groups did not differ in terms of gender composition, and patients in the reoperation group presented slightly higher KPS compared with the one surgery group (82.2 ± 14.8 vs. 75.2 ± 18.8, $P = 0.008$, Table 1).

The Kaplan–Meier curves for OS (from the time of diagnosis) differed consistently between groups (one surgery: $n = 127$, OS = 11.4 ± 1.0 months vs. reoperation: $n = 63$, OS = 20.0 ± 2.3 months, Wilcoxon W = 21,30, $P < 0.0001$) [Figure 2]. Furthermore, the univariate analysis showed that better OS was significantly associated with younger age, higher performance status (KPS and ECOG), three modalities of treatment (surgery + radiotherapy + chemotherapy), chemotherapy with temozolomide, and reoperation. The multivariate analysis revealed a significant association between survival and number of surgeries, initial KPS, and age (all $P < 0.001$, Table 2).

A mathematical regression for survival estimates was performed according to Weibull, which revealed that OS at 6, 12, and 24 months was significantly greater for the reoperation group [Figure 3 and Table 3]. [Figure 4] and [Table 4] depict OS according to treatment modality,

Table 1: General sample characterization.

Variable	Mean±SD or *n* (%)
Age	56.2±13.9
Male sex	169 (60.6)
Initial KPS	73.5±20.1
Initial ECOG	1.6±1.4
OS (months)	8.5 (3.0–16.0)
Treatment	
Only surgery	53 (18.5)
Only radiotherapy	11 (3.8)
Only chemotherapy	4 (1.4)
Surgery + radiotherapy	46 (16.1)
Surgery + chemotherapy	3 (1.0)
Radiotherapy + chemotherapy	11 (3.8)
Surgery + radiotherapy + chemotherapy	123 (43.0)
No treatment	35 (12.2)
Number of surgeries	
0	62 (21.7)
1	155 (54.2)
2	60 (21.0)
3	8 (2.8)
4	1 (0.3)
Chemotherapy	
Carmustine	19 (13.3)
Temozolomide	121 (84.6)
Lomustine	1 (0.7)
Irinotecan	1 (0.7)
Procarbazine + Lomustine + Vincristine	1 (0.7)

	One surgery group (*n*=155)	Reoperation group (*n*=69)	*P*
Age	57.9±12.8	50.5±13.2	<0.001
Male sex	88 (57.5)	41 (61.2)	0.612
Initial KPS	75.2±18.8	82.2±14.8	0.008
Initial ECOG	1.5±1.3	1.0±1.1	0.006

KPS: Karnofsky Performance Status, ECOG: Eastern Cooperative Oncology Group, OS: Overall survival

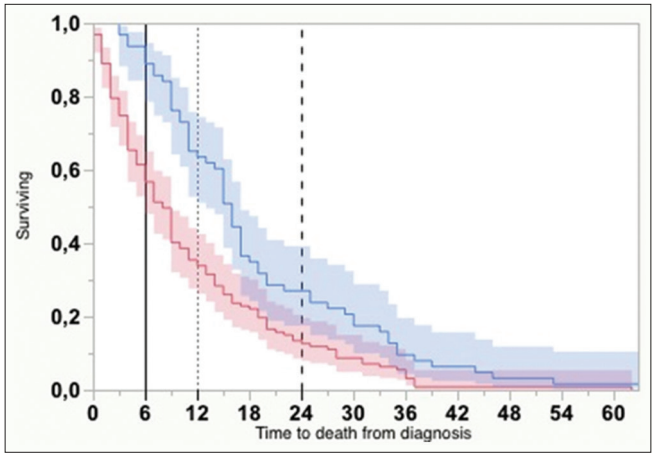

Figure 2: Kaplan–Meier curves with 95% confidential interval showing overall survival from the time of diagnosis, for cases submitted to one surgical intervention (darker gray), and two or more (lighter gray) (P < 0.0001, Wilcoxon). Vertical lines indicate the absolute times for survival estimate calculations (6, 12, and 24 months).

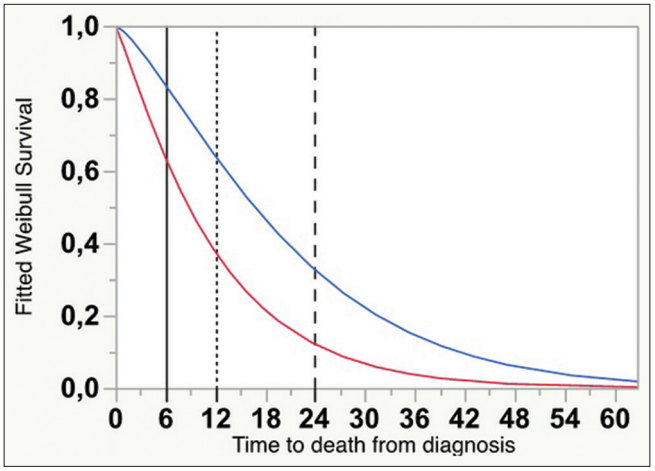

Figure 3: Linear regression model according to the Weibull method, constructed from the data shown in Figure 2, for estimates of survival probability at 6, 12, and 24 months, for one surgery (lower curve) and reoperation (upper curve) groups.

Table 2: Univariate and multivariate analysis of the factors associated with overall survival.

	Univariate		Multivariate	
	P	**HR (95% CI)**	***P***	**HR (95% CI)**
Age	<0.001	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)
Male sex	0.184	1.19 (0.92–1.56)	-	-
Initial KPS	<0.001	0.97 (0.97–0.98)	<0.001	0.98 (0.97–0.99)
Initial ECOG	<0.001	1.31 (1.18–1.44)	-	-
Number of surgeries	<0.001	0.52 (0.43–0.63)	<0.001	0.67 (0.54–0.83)
Treatment (Surgery + RT + CT)	<0.001	0.05 (0.03–0.08)	-	-
Type of chemotherapy	0.019	0.538 (0.32–0.90)	-	-
Reoperation	<0.001	0.57 (0.42–0.78)	-	-

KPS: Karnofsky Performance Status, ECOG: Eastern Cooperative Oncology Group, RT: Radiotherapy, CT: Chemotherapy

Table 3: Overall survival estimates.

	One surgery	Two or more surgeries
	Survival probability±SD	Survival probability±SD
6 months	63.56±3.59	83.74±3.42
12 months	37.53±3.52	64.00±4.85
24 months	12.02±2.36	32.53±4.78

Table 4: Overall survival according to treatment modality.

Treatment modality	Number of cases	Mean OS (months)	Std. error
Palliative treatment	33	1.82	0.30
Rt	10	5.80	0.84
Cht	4	9.25	2.69
Rt + Cht	8	12.25	2.74
Surg	45	3.29	0.50
Surg + Cht	2	19.00	5.00
Surg + Rt	40	14.20	3.39
Surg + Rt + Cht	104	18.67	1.13
Combined	246	11.99	0.86

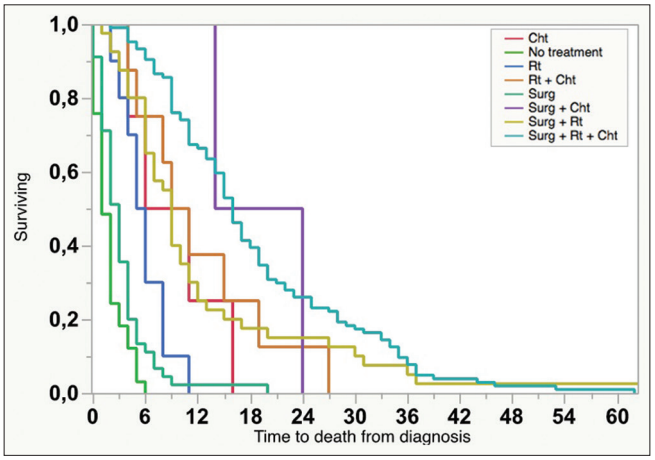

Figure 4: Kaplan–Meier curves showing overall survival according to treatment modality.

showing increased survival in patients who received surgery, radiotherapy, and chemotherapy.

DISCUSSION

Despite recent advances in the genetic profile of GBMs, an improved classification system, better neuroimaging techniques (which allow the early recognition of recurrence and the differential diagnosis of pseudoprogression and radionecrosis), and new technologies available in the operation theater (including better intraoperative mapping techniques, intraoperative imaging, and better neuro-anesthesiological protocols), these patients continue to face very disappointing long-term survival rates. In fact, disease progression is virtually inevitable and occurs at a median of 6.9 months.[19] At recurrence, patients fail even after maximal resection, alkylating chemotherapy with temozolomide, and radiotherapy. No high-level evidence for treatments exists at this phase of the disease.[11] Indeed, reoperation for GBM remains controversial, and clinical decision-making is usually influenced by age, KPS, previous treatment, and radiological progression pattern. Reoperation is indicated in clinical practice for 20–30% of patients[27] and may be more effective in patients for whom a second intervention allows gross total resection.[20] Importantly, no therapeutic option seems optimal; for instance, although it has acceptable toxicity, the efficacy of reirradiation remains controversial.[16] Lomustine has recently been considered a viable alternative, yet it is associated with only 15–25% of PFS rates at 6 months.[1] Dose-intensified temozolomide yielded similar results, which were limited to patients with MGMT promoter methylation.[14] On the other hand, bevacizumab, when added to lomustine, was initially associated with better OS at 9 months;[22] nevertheless, the EORTC 26101 Phase III trial did not confirm the superiority of bevacizumab + lomustine over lomustine alone.[28]

Based on the paucity of efficacious alternatives, reoperation is often considered. In a recent review about the effectiveness

of reoperation in GBM in the post temozolomide era, Robin *et al*. observed a median OS of 9.9 months after reintervention. Some predictors of improved survival after reoperation were as follows: (i) performance status, (ii) age, (iii) focal versus multifocal disease, (iv) favorable disease location, (v) lower preoperative tumor size, and (vi) greater likelihood of complete resection and safe surgery.[15]

In favor of reoperation, van Linde *et al*. performed a multicenter retrospective analysis comparing four groups of patients with recurrent GBMs according to treatment: systemic treatment (SYST), reresection followed by systemic treatment and/or reirradiation (SURG), reirradiation (RT), and best supportive care. After *post hoc* corrections, the SYST, SURG, and RT subgroups did not differ significantly in terms of age, gender, time of recurrence, performance status (KPS and ECOG), or OS. However, patients in the SURG group had greater PFS compared with patients in the SYST group, even after correcting for potential confounders. No differences were found between the SURG and RT groups.[26]

In contrast, Sastry *et al*. observed that reresection at the time of recurrence was not significantly associated with increased postprogression survival (PPS), which was only influenced by three variables: good performance status (KPS > 70), treatment with bevacizumab, and cytotoxic chemotherapy (all at first progression).[17] A meta-analysis by Zhao *et al*. concluded that improved OS and PPS were only observed if reoperation was considered a fixed covariate. When reoperation timing was taken into account, similar survival rates were observed between patients submitted to a new surgery and patients without reoperation, which the authors called estimate bias.[30] Similarly, Mukherjee *et al*. performed a prospective comparative cohort analysis and observed slightly better survival after recurrence (10.8 vs. 6.9 months, log-rank 0.04) and OS (24.1 vs. 20.4 months, log-rank 0.03) in the reoperated patient group.[10] This last study reports surprisingly long survival rates relative to other studies in the literature.

It is important to note that in many studies, patients who underwent a new surgical procedure were usually younger (<65), had a better performance status (KPS > 80, ECOG < 2), and a lower degree of necrosis and enhancement on preoperative MRI, factors that are independently associated with increased survival.[3,4,7,24] Tumor morphology at diagnosis (location, uni/multifocal lesions, initial/residual volume, isocitrate dehydrogenase [IDH] mutation, and MGMT methylation) and the presence of adjuvant therapies, such as radiation, temozolomide, bevacizumab, and carmustine wafers, have also been associated with higher OS.[2,5,9,21,25]

Another confounding factor in some retrospective analyses is that the nonoperated group usually includes a subgroup of patients whose clinical profile would never render them potential candidates for surgery. Tully *et al*. addressed this potential bias by analyzing two cohorts of patients with recurrent GBM. At first glance, the reoperation group seemed to have better OS than the nonoperated group. However, this effect vanished after excluding a subgroup of patients with infest prognostic factors (aged over 70 years, posterior fossa location, multicentric manifestation, ECOG >2).[23] For this reason, in the current study, we excluded 40 patients from the comparative analysis for whom surgery had never been considered since the beginning of follow-up. Our data show a clear advantage of reoperation for OS. Accordingly, survival estimates using the Weibull fitting method revealed almost twice the survival rates at 12 and 24 months in the reoperated group. The univariate analysis revealed that age, functional status as measured by KPS and ECOG, temozolomide use, combined therapy (surgery, chemotherapy, and radiotherapy), and the number of surgeries were important predictors of survival. Among these, age, initial KPS, and the number of surgeries remained significant in the multivariate analysis.

Robin *et al*. previously reported some potential bias associated with those positive results.[15] First, patients who underwent a new surgical procedure are usually younger (<65), with a better performance status (KPS > 80, ECOG < 2), and a lower degree of necrosis and enhancement on preoperative MRI, factors independently associated with increased survival.[3] Tumor morphology at diagnosis (location, uni/multifocal lesions, initial/residual volume, IDH mutation, and MGMT methylation) and the presence of adjuvant therapies, such as radiation, temozolomide, bevacizumab, and carmustine wafers, also are determinants for a higher OS. In this series, the retrospective design of this study did not allow the stratification of patients before reoperation, according to their performance status and age.

This retrospective case series has some limitations. First, patients submitted to reoperation were mostly younger with good performance status, highlighting a potential selection bias. Second, at the time data were collected, IDH1 and MGMT promoter methylation status were not available at our institution (as the largest public University Hospital in Brazil, budget limitations have always been a major concern). However, the effect of this limitation on external validation is small, as only 5–12% of GBMs have IDH-1 mutations.[13,29] Furthermore, IDH-1 and MGMT status play a lesser role at the time of recurrence. Finally, this study included patients who underwent different types of chemotherapy, and patients who received temozolomide presented significantly better OS compared with patients who received carmustine. Considering 84% of our cases treated with chemotherapy received temozolomide, we believe that this limitation does not impact the main conclusion about the role of reoperation in the management of GBM.

The decision to reoperate a patient with recurrent GBM is often made on an individual basis, taking into account the criteria listed above, as well as the benefits of potentially achieving gross total resection, alleviation of mass effect, the possibility of further biomolecular analysis, and enrollment in ongoing clinical trials. The results presented here clearly support reintervention, especially for younger patients with a good functional status. Thus, strict and regular clinical and radiological follow-up is critical for detecting radiological recurrence before any relevant clinical deterioration is observed.

CONCLUSION

Reoperation for recurrent glioblastoma is an option to be considered when the functional status is not compromised, and our data indicate that this subgroup of patients may profit in terms of overall survival.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Batchelor TT, Mulholland P, Neyns B, Nabors LB, Campone M, Wick A, *et al*. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol 2013;31:3212-8.
2. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, *et al*. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The polymer-brain tumor treatment group. Lancet 1995;345:1008-12.
3. Fatehi M, Hunt C, Ma R, Toyota BD. Persistent disparities in survival for patients with glioblastoma. World Neurosurg 2018;120:e511-6.
4. Gately L, Collins A, Murphy M, Dowling A. Age alone is not a predictor for survival in glioblastoma. J Neurooncol 2016;129:479-85.
5. Hata N, Mizoguchi M, Kuga D, Hatae R, Akagi Y, Sangatsuda Y, *et al*. First-line bevacizumab contributes to survival improvement in glioblastoma patients complementary to temozolomide. J Neurooncol 2020;146:451-8.
6. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, *et al*. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997-1003.
7. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, *et al*. A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. J Neurosurg 2001;95:190-8.
8. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol 2016;131:803-20.
9. Marenco-Hillembrand L, Wijesekera O, Suarez-Meade P, Mampre D, Jackson C, Peterson J, *et al*. Trends in glioblastoma: Outcomes over time and type of intervention: A systematic evidence based analysis. J Neurooncol 2020;147:297-307.
10. Mukherjee S, Wood J, Liaquat I, Stapleton SR, Martin AJ. Craniotomy for recurrent glioblastoma: Is it justified? A comparative cohort study with outcomes over 10 years. Clin Neurol Neurosurg 2020;188:105568.
11. NCCN: National Comprehensive Cancer Network Guidelines Version 2.2020, Central Nervous System Cancers; 2020.
12. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, *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:v1-v100.
13. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, *et al*. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807-12.
14. Perry JR, Bélanger K, Mason WP, Fulton D, Kavan P, Easaw J, *et al*. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. J Clin Oncol 2010;28:2051-7.
15. Robin AM, Lee I, Kalkanis SN. Reoperation for recurrent glioblastoma multiforme. Neurosurg Clin N Am 2017;28:407-28.
16. Ryu S, Buatti JM, Morris A, Kalkanis SN, Ryken TC, Olson JJ, *et al*. The role of radiotherapy in the management of progressive glioblastoma: A systematic review and evidence-based clinical practice guideline. J Neurooncol 2014;118:489-99.
17. 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 2018;53:41-7.
18. Skardelly M, Dangel E, Gohde J, Noell S, Behling F, Lepski G, *et al*. Prolonged temozolomide maintenance therapy in newly diagnosed glioblastoma. Oncologist 2017;22:570-5.
19. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
20. Suchorska B, Weller M, Tabatabai G, Senft C, Hau P, Sabel MC, *et al*. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. Neuro Oncol 2016;18:549-56.
21. Sung KS, Roh TH, Moon JH, Kim EH, Kang SG, Kim SH, *et al*. Treatment results for recurrent glioblastoma and alteration of programmed death-ligand 1 expression after recurrence. World Neurosurg 2020;135:e459-67.
22. Taal W, Oosterkamp HM, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, *et al*. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus

lomustine in patients with recurrent glioblastoma (BELOB trial): A randomised controlled phase 2 trial. Lancet Oncol 2014;15:943-53.
23. Tully PA, Gogos AJ, Love C, Liew D, Drummond KJ, Morokoff AP. Reoperation for recurrent glioblastoma and its association with survival benefit. Neurosurgery 2016;79:678-89.
24. Tykocki T, Eltayeb M. Ten-year survival in glioblastoma. A systematic review. J Clin Neurosci 2018;54:7-13.
25. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, *et al*. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: A randomized double-blind study. Neurosurgery 1997;41:44-8; discussion 48-9.
26. van Linde ME, Brahm CG, de Witt Hamer PC, Reijneveld JC, Bruynzeel AM, Vandertop WP, *et al*. Treatment outcome of patients with recurrent glioblastoma multiforme: A retrospective multicenter analysis. J Neurooncol 2017;135:183-92.
27. Weller M, van den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-Jonathan-Moyal E, *et al*. European association for neuro-oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol 2017;18:e315-29.
28. Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, *et al*. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 2017;377:1954-63.
29. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, *et al*. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-73.
30. Zhao YH, Wang ZF, Pan ZY, Péus D, Delgado-Fernandez J, Pallud J, *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.

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