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ORIGINAL ARTICLE

Impact of recurrence pattern in patients undergoing a second surgery for recurrent glioblastoma

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Abstract
The impact of different patterns of glioblastoma (GBM) recurrence has not yet been fully established in patients suitable for a second surgery. Through the present observational study carried out at Pisa University Hospital, we aimed to investigate how different patterns of GBM failure influence second surgery outcomes. Overall survival (OS) and post-recurrence survival (PRS) were assessed according to clinical characteristics, including pattern of recurrence, in a prospective cohort of recurrent GBM patients. Survival curves were calculated using the Kaplan–Meier method and the log-rank test was applied to evaluate the differences between curves. Patients with local recurrence had better OS than patients with non-local one, 24.1 versus 18.2 months, respectively [$P = 0.015$, HR = 1.856 (1.130–3.050)]. The second surgery conferred an advantage in OS respect to non-operated patients, however, this advantage was more evident in patients with local recurrence [$P = 0.002$ with HR 0.212 (95% CI 0.081–0.552) and $P = 0.029$ with HR = 0.522 (95% CI 0.291–0.936), respectively]. The recurrence pattern can influence the outcome of patients with recurrent GBM suitable for a second surgery.

Keywords Glioblastoma · Recurrent glioblastoma · Second surgery · Pattern of failure

Introduction

Glioblastoma (GBM) is the most aggressive primary brain tumor and it is characterised by a poor prognosis [1–3]. Despite technical–scientific developments in surgery and post-operative therapies recorded in the last decade, median progression-free survival (PFS) and overall survival (OS) remained constantly at 7 and 16 months, respectively [4].

Post-operative combined radio-chemotherapy with temozolomide, according to Stupp regimen, represents the standard post-operative therapy. Following the diagnosis of GBM recurrence, some patients may benefit from the second surgery, second-line chemotherapy or re-irradiation; however, there is currently no standard therapy for GBM recurrence, and the clinical decision-making process lacks default guidelines [2, 5–9].

Recent studies reported different OS times after disease recurrence according to patterns of failure, suggesting a potential correlation between clinical behaviors and underlying differences in tumor biology. For instance, patients experiencing in-site local recurrence show a better prognosis than patients with a widespread disease due to multicentric or multifocal regrowth [10]. At present, the literature on this topic is still limited, and the impact of different patterns of recurrence has not yet been investigated in patients suitable for a second surgery. This study aimed to assess the impact

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of different patterns of recurrence on second surgery outcomes in patients with recurrent GBM.

Materials and methods

This prospective observational study was carried out at Pisa University Hospital (Pisa, Italy) and approved by the local Ethics Committee [Comitato Etico di Area Vasta Nord Ovest (CEAVNO); protocol 560/2015]. Clinical data were collected starting from 2015, without affecting the clinical decision making.

To make our analysis as homogeneous as possible, all patients included in the present analysis had histopathological diagnosis of IDH1/2 wild-type GBM obtained through a gross-total or sub-total tumor excision. They were treated with concomitant radio-chemotherapy and subsequent chemotherapy with temozolomide (TMZ), had a Karnofsky Performance Score at the time of disease recurrence greater than 80, and radiological imaging available in Pisa University dataset. Considering the small simple size, to make the study population as standardized as possible, we decided to include in the present analysis only patients with KPS greater than 80. Patients unable to carry on normal activity or to do active work (KPS 70 or lesser) often experience a rapid decay after the diagnosis of recurrence, therefore, they could not benefit from a salvage treatment. Patients with unresected (i.e., stereotactic biopsy) or multicentric disease (lesions representing separate synchronous tumors which have multiple discrete areas of contrast-enhancing tumor without connecting T2/FLAIR signal abnormality [11]), or history of low-grade glioma at first surgery were excluded. Assessment of O-6-methylguanine-DNA methyltransferase (MGMT) methylation was optional. After the end of Stupp Regimen, patients were followed-up with MRI performed at 4–6 weeks, and then, every 3 months.

Date of disease progression was defined as the date of MRI showing recurrent disease (RANO criteria were adopted [12]). The diagnosis of tumor progression was made by a multidisciplinary team (MDT) composed by the following professional figures: neuroradiologists, neurosurgeons, medical oncologists, radiation oncologists and neuropathologists. Radiotherapy was delivered to surgical bed or, in case of partial tumor excision, to surgical bed plus residual disease with a 2 cm margin. A total dose of 60 Gy was administered in 30 fractions (the entire PTV was covered using 95% of reference dose). TMZ was administered daily (7 days a week) at the dose of 75 mg/m^2/day during radio-chemotherapy, and for 5 days every 4 weeks at the dose of 150–200 mg/m^2/day for up to 12 cycles as maintenance treatment, until disease progression or toxicity occurrence [1]. Once the disease reappeared, all patients evaluated in this study received salvage chemotherapy treatment with temozolomide or fotemustine with or without bevacizumab (in patients suitable for a second surgery, chemotherapy was administered as soon as they recovered). Overall survival (OS) and post-recurrence survival (PRS) were calculated from GBM diagnosis to death and from the time of recurrent disease to death, respectively.

Assessment of pattern of failure

Radiological assessment of the recurrence pattern was performed by MDT members who were unaware of clinical data. T1 contrast enhancement imaging was used to assess the presence of multifocal (lesions considered to be part of the same tumor which have multiple discrete areas of contrast-enhancing tumor connected by T2/FLAIR signal abnormality) or multicentric spread, meningeal involvement and direct contact with the ventricle system. Two recurrence patterns were identified. We considered as local recurrence tumors with no multifocal, multicentric or meningeal spread. Otherwise, when one of these features was present, the recurrence was defined as non-local.

Statistical analysis

We considered as endpoints OS and PRS

Categorical data were described by absolute and relative frequency, continuous data by median and range. Survival curves were calculated using the Kaplan–Meier method and the log-rank test was applied to evaluate the differences between curves. A multivariate Cox model based on the step-wise method was performed to assess the predictive factors' influence on the endpoints, and hazard ratio with its 95% CI was expressed. Significance was fixed at 0.05. SPSS v.27 technology carried out all analyses.

Results

From July 2015 to September 2020, 156 patients were referred to the Radiotherapy Unit of Pisa University Hospital for recurrent GBM and were subsequently included in the present study. In December 2020, at the time of data analysis, 90 patients within this cohort met the inclusion criteria: Table 1 reports patients' characteristics. After a median follow-up of 34 months (range 18–127 months), median OS was 20.1 months (95% CI = 18.7–21.9) and median PRS was 6.7 months (95% CI = 4.9–8.6). MTMG methylation was tested in 63 patients, 39 (61.9%) had the promoter methylated, whereas 24 (37.1%) did not (OS in methylated and unmethylated patients was not statistically different, $P = 0.59$, HR = 1.175 (0.672–2.052). Among clinical features considered at the time of recurrence, the second

Table 1 Patients' characteristics at the time of disease recurrence

Clinical characteristics	
Gender M/F	51/39
Median age (years)	58 (range 24–81)
Second surgery	39 (43.3%)
Pattern of recurrence	
Local	59 (65.5%)
Non-local	31 (34.5%)
C.V.	62 (68.8%)
M.I.	19 (21.1%)

C.V. Contact with ventriculi, *M.I.* Meningeal invasion, *KPS* Karnofsky Performance Score, *M* Male, *F* Female, *pts* Patients

surgery and meningeal spread had a statistically significant impact on PRS ($P=0.032$ and $P=0.019$, respectively). Moreover, the second surgery were significantly correlated with OS ($P=0.031$) (Table 2).

Fifty-nine (65.6%) and 31 (34.4%) patients experienced local and non-local recurrence, respectively. Patients with local recurrence had a better OS (24.1 months) compared with patients with non-local recurrence (18.2 months) ($P=0.015$, HR = 1.856 (1.130–3.050) Fig. 1.

Second surgery was performed in 39 patients (43.3%); 18 (46.2%) and 21 (53.8%) presented with local and non-local recurrence, respectively. Among patients underwent second surgery, there was not statistically difference between PRS of patients with local and non-local recurrence, 13.4 months (95% CI 6–20) and 11.0 months (95% CI 3.4–18.7), respectively ($P=0.554$).

The advantage of the second surgery resulted more evident in the subset of patients with local recurrence. In this group, OS was 19.8 months (95% CI 17.4–22.4) and

Table 2 Multivariate analyses of the survival factors

Multivariate analysis of the survival factors by step-wise method					
	RC	HR	95% CI lower	95% CI upper	*P* value
OS					
Contact with ventriculi	0.539	1.714	1.051	2.797	0.031
Second surgery	−0.917	0.400	0.245	0.651	<0.001
Multicentric recurrence					0.331
Multifocal recurrence					0.738
Meningeal invasion					0.428
Survival from the diagnosis of GBM recurrence					
Contact with ventriculi	0.536	1.710	1.049	2.787	0.032
Meningeal invasion	0.679	1.972	1.116	3.484	0.019
Second surgery	−0.993	0.371	0.226	0.608	<0.001
Multicentric recurrence					0.668
Multifocal recurrence					0.998

HR Hazard Ratio, *RC* Regression Statistics

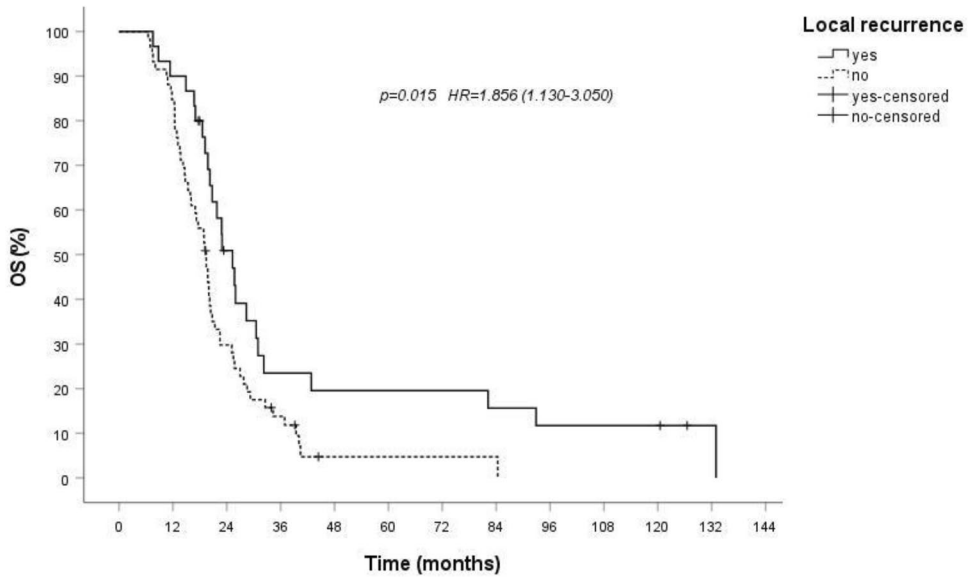

Fig. 1 Overall survival in patients with local and non-local pattern of failure

31 months (95% CI 23.1–38.9%), for non-operated and operated patients, respectively ($P = 0.002$, with Hazard Ratio (HR 0.212; 95% CI 0.081–0.552). In patients who experienced non-local recurrence, OS was 17.6 months (95% CI 11.9–23.3) and 19.8 months (95% CI 17.5–33%) for non-operated and operated patients, respectively ($P = 0.029$ with HR = 0.522; 95% CI 0.291–0.936) (Fig. 2a, b).

PRS was also improved by second surgery, both in local and non-local recurrence patterns. In patients who experienced non-local recurrence, PRS for operated and non-operated patients were 19.8 and 17.6 months, respectively [$P = 0.002$, HR = 0.360 (95% CI 0.191–0.682)]. In patients who experienced local recurrence, PRS for operated and non-operated patients were 13.4 months and 7 months, respectively [$P = 0.054$, HR = 0.449 (95% CI 0.199–1.015)] (Table 3).

Discussion

This study reported a prospective observational analysis carried out in patients with recurrent GBM referred to Pisa University Hospital. In our analysis, before assessing the impact of the second surgery, we observed that different failure patterns were associated to different OS. Maybe due to less aggressive disease, in our series, patients with local failure showed better OS than patients with non-local one, OS were 24.1 versus 18.2 months, respectively ($P = 0.015$). Interesting that the OS of 24.1 months recorded in patients with local recurrence was even better than the OS reported in several series of patients underwent to second surgery [13–15], making this clinical parameter a prognostic factor to be considered in clinical decision making of recurrent GBM.

Several studies in patients with recurrent GBM have reported promising results after the second surgery, however,

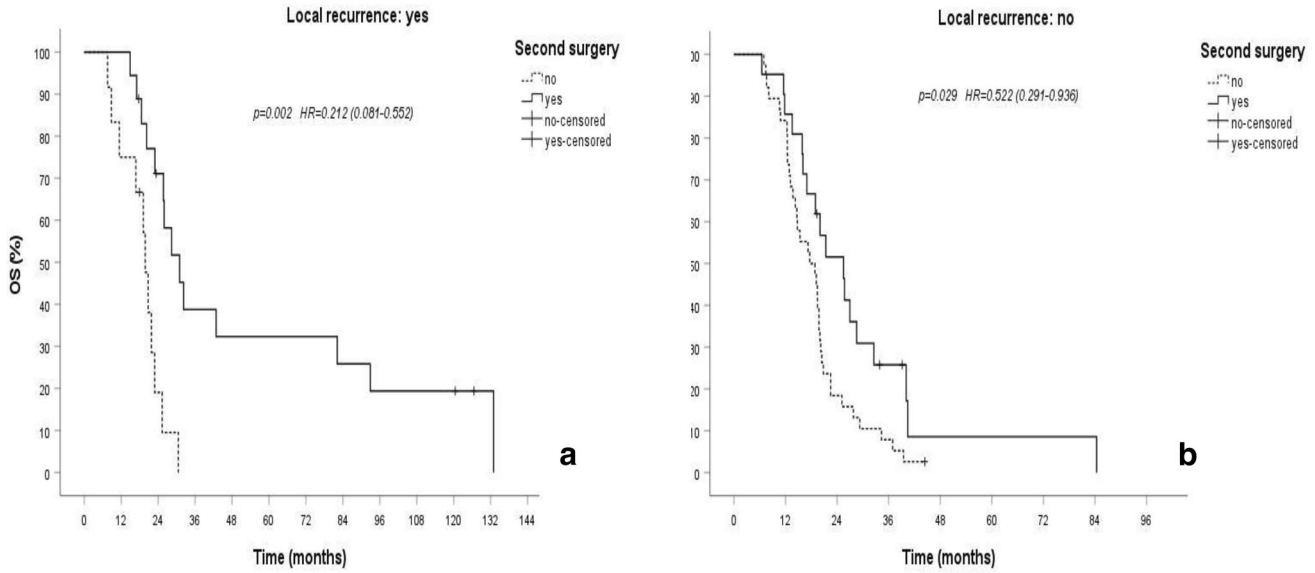

Fig. 2 **a** Overall survival in patients with local recurrence undergoing second surgery. **b** Overall survival in patients with non-local recurrence undergoing second surgery

Table 3 Impact of second surgery in patients with local and non-local recurrence

Pattern of recurrence	Overall survival	Post-recurrence survival (months)
Local	Surgery Y:31.0	Surgery Y: 13.4 months
	Surgery N: 19.8	Surgery N: 7
	$P = 0.002$, HR 0.212; 95% CI 0.081–0.552	$P = 0.05$ HR = 0.499 (95% CI 0.199–1.015)
Non-local	Surgery Y:19.8 months	Surgery Y:19.8
	Surgery N: 17.6	Surgery N: 17.6
	$P = 0.029$, HR = 0.522; 95% CI 0.291–0.936	$P = 0.002$, HR = 0.360 (95% CI 0.191–0.682)

Y yes, *N* not, *HR* Hazard Ratio, *CI* Confidence Interval

without addressing the risk of running into selection bias. Generally, among patients diagnosed with recurrent GBM, those who underwent second surgery showed a better prognosis [14, 16–19]. In our study, the impact of second surgery on OS was greater in patients with local recurrence, but that advantage was in part lost when we considered PRS ($P=0.002$ and $P=0.54$, respectively). The selection of patients suitable for second surgery, therefore, with better clinical features, can in part had helped second surgery to prolong OS.

Currently, literature on second surgery reports long OS, but these retrospective studies could under-estimate the risk of patient selection. In 2019, Zhao et al. performed a meta-analysis carried out in 8630 patients and investigated the outcome of reoperation after GBM recurrence [20]. Both OS and PRS were improved by the second surgery, suggesting the important role of surgery and the benefit of surgical management in recurrent GBM patients. Nevertheless, among clinical features considered to select patients who can achieve the best benefit from the second surgery, only the recurrence timing correlated favorably with survival, suggesting that a longer disease-free interval from primary treatment was associated with improved survival after a second/multiple disease diagnosis. Tully et al. reported a retrospective analysis of 204 GBMs with 49 patients (24%) undergoing a second surgery [21]. The study showed a significant advantage in terms of OS (measured from the diagnosis of GBM) in patients treated with second surgery as compared to other patients (20.1 months versus 9.0, $P=0.001$). However, even in this study, the limiting bias was represented by the lack of criteria used to consider patients suitable for the second surgery. In 2013, Chaichana et al. reported their results on 578 patients receiving repeated surgery at Johns Hopkins Hospital for recurrent GBM [22]. They concluded that repeated resections improve OS; however, even that retrospective study may have been influenced by the selection of patients. In 2017, Azoulay et al. reported their General Hospital's experience assessing the benefit of reoperation and salvage therapies for recurrent GBM [23]. They compared the outcome of re-operated patients with patients treated at the same Institution with other salvage approaches. They reported a better OS after the diagnosis of GBM recurrences in re-operated patients, 9.8 versus 5 months, respectively ($P<0.0001$). However, analyzing the impact of the different patterns of tumor failure, 67 out of 69 patients in the surgery arm (97%) had a unifocal disease recurrence, whereas 60 out of 68 (88.2%) in the non-surgical one ($P=0.051$). In that study, patients with local failure and a more favorable prognosis were slightly over-represented in the operated arm; therefore, this imbalance could have contributed to a better OS. The differences in OS related to a distinct type of recurrence were confirmed by Bette et al. in 2019 [10]. They reported results of a retrospective study attempting to assess GBM recurrence patterns and their association with survival, finding that patients with isolated local recurrence had more prolonged survival after the diagnosis of relapsed GBM ($P=0.019$, HR 1.75).

In our series, the benefit of second surgery in terms of PRS was greater in non-local recurrence (Fig. 2). A possible explanation could be that many patients referred to second surgery did not experience a true disease recurrence, but just a pseudo progression or radionecrosis; therefore, it can also give a contribution to explain the longer OS. Before introducing RANO criteria, diagnosis of disease recurrence was based on the onset of any new enhancing lesions following RT-CT [1, 12, 24]. The criteria used to assess GBM recurrence in our series (RANO criteria) have reduced but not eliminated the risk to consider a pseudoprogression as a recurrence [12].

The present experience had some limitations, the most important was represented by the small sample size that limited the statistical power of some clinical and molecular profiling (extent of surgery, age, IDH1/2 mutation and MGMT methylation, for example). Therefore, it could be considered as a proof of concept to be reproduced in more extensive series aiming to confirm our results.

Conclusion

In patients with recurrent GBM, the pattern of failure can have an impact in patients suitable for a second surgery.

Authors' contributions All authors whose names appear on the submission made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; drafted the work or revised it critically for important intellectual content; approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or.

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Code availability Not applicable.

Declarations

Conflict of interest All authors agreed with the content of the present paper, gave explicit consent to submit and obtained consent from the responsible authorities at the institute/organization where the work has been carried out before the work is submitted.

Ethics approval Comitato Etico di Area Vasta Nord Ovest CEAVNO; protocol #560/2015.

Consent to participate Not applicable.

Consent for publication Not applicable.

Research involving humans and animal participate This article does not contain any studies involving animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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