Impact of Recurrence Pattern in Patients Undergoing a Second Surgery for Recurrent Glioblastoma

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Abstract

Background. 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 examine the impact of different patterns of GBM failure on patients' survival and second surgery outcomes.

Methods. Overall survival was 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.

Results. Contact with ventricles, a second surgery and meningeal spread had a statistically impact on patient survival after the diagnosis of GBM recurrence (P=0.032, P=0.019 and P<0.01, respectively). Patients with local recurrence had better survival than patients with non-local ones, 24.1 versus 18.2 months, respectively (P=0.015, HR=1.856 (1.130 -3.050). Considering the cohort as a whole, the second surgery conferred an advantage in recurrent survival 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).

Conclusions. The local recurrence pattern could be a promising field of interest for patients with recurrent GBM suitable for a second surgery.

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, the median progression-free survival (PFS) and overall survival (OS) are plateauing at 7 and 16 months, respectively [4].

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

Recent studies reported different overall survival (OS) time after disease recurrence according to patterns of failure, suggesting a possible correlation between clinical behaviour 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 the different patterns of recurrence has not yet been investigated in patients suitable for a second surgery.

This study aimed to assess the impact of different pattern of recurrence on OS and 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).

All patients included in the present analysis had a histopathological diagnosis of IDH1/2 wild type GBM obtained through a gross-total or sub-total tumor excision, were treated with concomitant radio-chemotherapy and sequential chemotherapy with temozolomide (TMZ), had a Karnofsky Performance Score at the time of disease recurrence greater than 80 and radiological imaging available on Pisa University dataset. Patients with unresected (i.e., stereotactic biopsy) or multicentric disease, or history of low-grade glioma at first surgery were excluded. 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 [11]). The diagnosis of tumor progression was made by a multidisciplinary team (MDT) composed by the following professional figures: neuroradiologists, neurosurgeons, clinical oncologist 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. 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 following the end of radiation, until disease progression or toxicity occurrence [1].

OS and Post Recurrence Survival (PRS) were calculated from GBM diagnosis 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 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. Pattern of recurrence was also correlated with primary radiation treatment and defined as follows: in-field recurrence, consisting of a tumour growth inside or marginal to the prescription isodose-line, out-of-field recurrence consisting of a relapse with at least a 1cm distance from the prescription isodose line.

Statistical analysis.

We considered as endpoints OS and the survival interval after the diagnosis of recurrence.

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 stepwise 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 of this study: 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). Fifty-nine (65.6%) and 31 (34.4%) patients experienced local and non-local recurrence, respectively. In 31 out of 59 patients, progression occurred inside the radiotherapy field. Second surgery was performed in 39 patients (43.3%); among these 39 reoperated patients, 18 (46.2%) and 21 (53.8%) presented with 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.

Among clinical features considered at the time of recurrence, the direct contact with ventricles, a second surgery and meningeal spread had a statistically significant impact on PRS (P=0.032, P=0.019 and P<0.01, respectively). Moreover, the contact with ventricles and the second surgery were significantly correlated with OS (P=0.031 and P>0.01, respectively) (tab 2).

Considering the cohort as a whole, the second surgery conferred an advantage in PRS as compared to non-surgical management. However, this advantage is more evident in the subset of patients with local recurrence (P=0.002, with Hazard Ratio (HR) 0.212; 95% CI 0.081-0.552) when compared with non-local recurrence pattern (P=0.029 with HR=0.522; 95% CI 0.291-0.936) (fig. 2a and 2b).

Discussion

This study reported a prospective observational analysis carried out in patients with recurrent glioblastoma 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. Secondly, our study was designed to evaluate the improvement in OS due to the second surgery by minimising the different prognosis related to recurrence patterns. Maybe due to less aggressive disease, in our series, patients with local failure showed better survival than patients with non-local one, OS were 24.1 versus 18.2 months, respectively (P = 0.015). Interesting, 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

[12, 13], making this clinical parameter a prognostic factor to be considered in clinical decision making of recurrent GBM.

Several studies in patients with recurrent GBM reported promising outcomes following second surgery; generally, among patients diagnosed with recurrent GBM, those who underwent second surgery showed a better prognosis [13–17]. In 2019, Zhao et al. performed a meta-analysis carried out in 8630 patients and investigated the outcome of reoperation after GBM recurrence [18]. Both OS and PRS were improved by the second surgery, and their results strongly supported 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 favourably with survival, suggesting that a longer disease-free interval from primary treatment was correlated with improved survival after the diagnosis of disease recurrence. However, possible selection bias favouring fitter patients deemed suitable for second surgery represents a significant issue.

More recently, Tully et al. reported a retrospective analysis of 204 GBMs with 49 patients (24%) undergoing a second surgery [19]. 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). Anyhow, 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 [20]. They concluded that repeated resections improve OS. However, even the results of that retrospective study may strongly be influenced by the selection of patients.

Considering all patients evaluated in our study, second surgery confers an advantage in recurrent survival compared to non-operated patients. However, this advantage is more evident in patients with locally recurrence than in patients with non-locally recurrent GBM (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).

In 2017, Azoulay et al. reported their General Hospital's experience assessing the benefit of reoperation and salvage therapies for recurrent glioblastoma [21]. They compared the outcome of re-operated patients with patients treated at the same Institution with other salvage approaches. They reported a better survival after the diagnosis of GBM recurrences in re-operated patients, 9.8 versus 5 months, respectively (P < 0.0001). However, analysing 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). Therefore, in that study, patients with local failure and a more favourable prognosis were slightly over-represented in the operated arm. 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 study 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).

One more question must be addressed about patients underwent a second surgery for local failure. Before introducing RANO criteria, diagnosis of disease recurrence was based on the onset of any new enhancing lesions following RT-CT [1, 11, 22]. Therefore, many patients referred to second surgery did not experience a true disease recurrence, but just a pseudoprogression or radionecrosis. The possibility that a subset of re-operated patients did not have a GBM progression, but rather a phenomenon related to radiotherapy, might result in a possible confounding effect. The criteria used to assess GBM recurrence in our series (RANO criteria) reduced the risk to consider a pseudoprogression as a recurrence [11].

In the light of our data, the present analysis confirmed that the most active local salvage treatment for recurrent GBM, represented by a second surgery, confers an OS advantage OS advantage in our patient population. However, this benefit was more pronounced in patients whose recurrence were defined as local.

The present experience had some limitations, such as sample size and lack of molecular profiling. However, this study could be considered as a proof of concept to be reproduced in more extensive series in order to confirm our results.

Conclusion

Based on our results, we can consider pattern of failure as a valuable predictor of survival benefit from second surgery in patients with recurrent GBM that could be implemented in clinical practice to identify candidates eligible for this approach.

Declarations

Conflicts of interest/Competing interests: 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.

Availability of data and material: not applicable

Code availability: not applicable

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

Conflicts of interest/Competing interests: none

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

Consent to participate not applicable

Consent for publication: not applicable

Statements on compliance with ethical standards and standards of research involving humans and anim:

- **Conflict of Interest**: The authors declare that they have no conflicts of interest.
- 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.
- The authors did not receive support from any organization for the submitted work.

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Tables

Tab. 1 Patients’ characteristics

Feature	Number
Gender M/F	51/39
Median age (years)	58 (range 24 – 81)
Second surgery	39 (43.3%)
Median KPS	90
Pattern of recurrence:	
Local	59 (65.5%)
Non-local	31 (34.5%)
C.V.	62 (68.8%)
M.I.	19 (21.1%)
In field.	31 (34.4%)
MGMT meth.	39/63 (61.9%)

C.V. Contact with ventriculi, **M.I.** Meningeal invasion, **KPS** Karnofsky Performance Score, **MGMT** O(6)-Methylguanine-DNA methyltransferase, **M** Male, **F** Female

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
Meningi invasion:					0,428
Survival from the diagnosis of GBM recurrence					
Contact with ventriculi:	0,536	1,710	1,049	2,787	0,032
Meningi 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

Figures

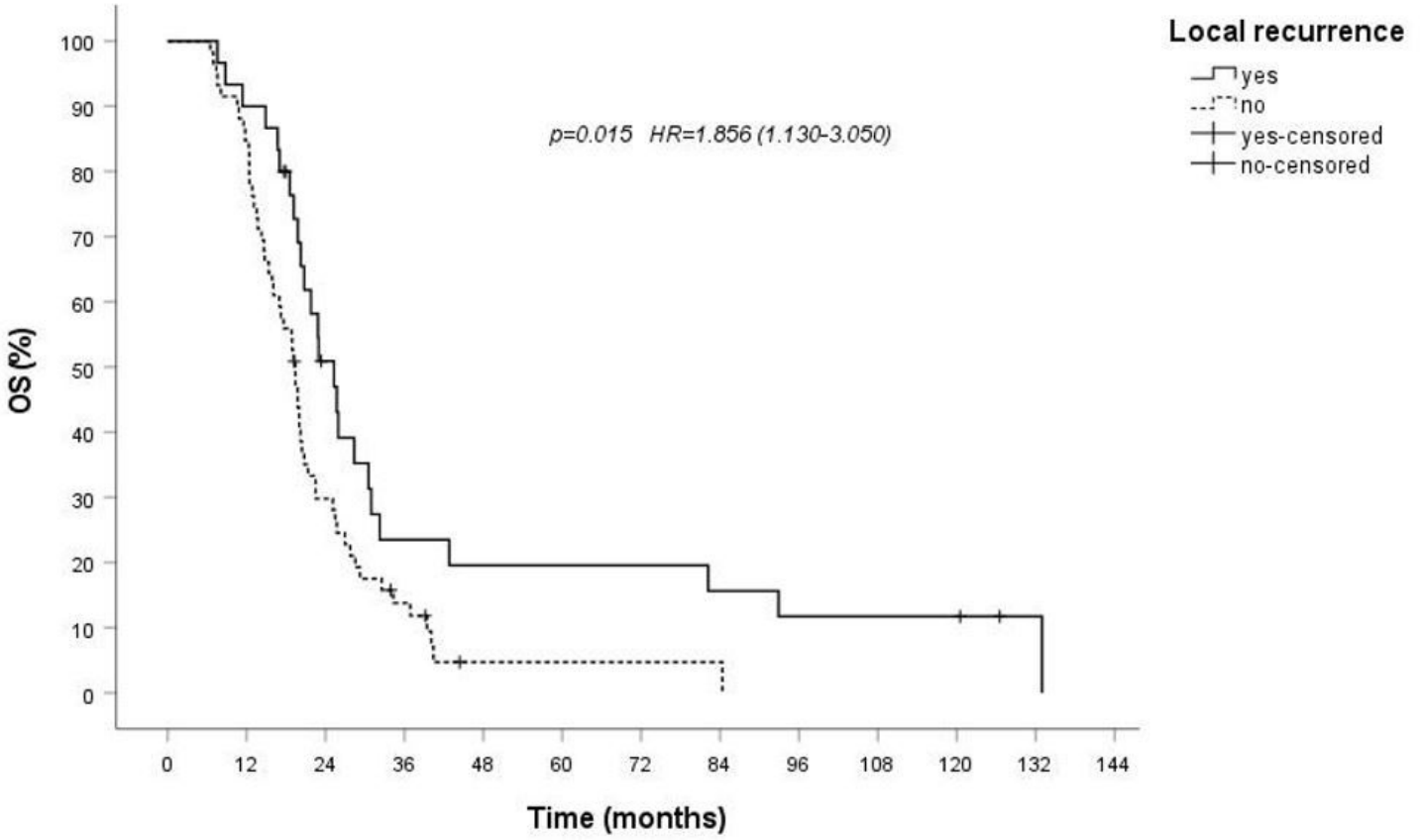

Figure 1

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

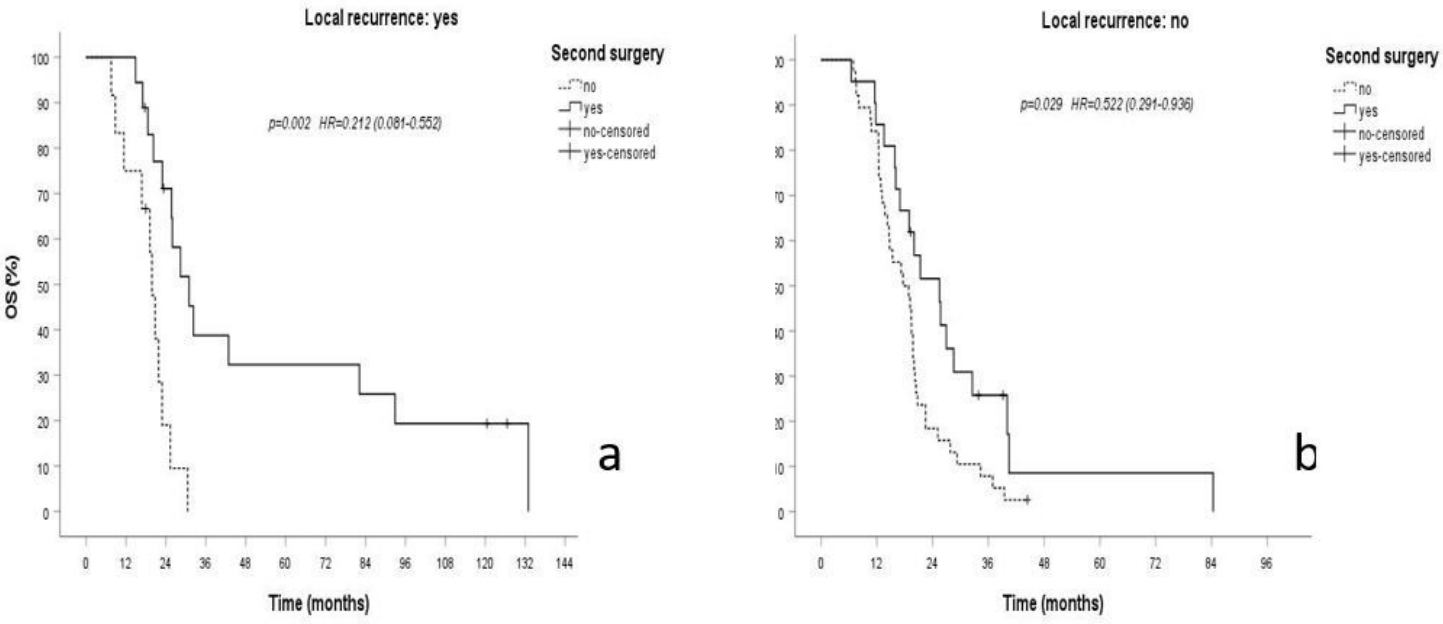

Figure 2

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