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The impact of repeated surgery and adjuvant therapy on survival for patients with recurrent glioblastoma

Pasquale De Bonis[a,*], Alba Fiorentino[b], Carmelo Anile[a], Mario Balducci[b], Angelo Pompucci[a], Silvia Chiesa[b], Gigliola Sica[c], Gina Lama[c], Giulio Maira[a], Annunziato Mangiola[a]

[a] Institute of Neurosurgery, Catholic University School of Medicine, l.go F. Vito, 1 00168 Rome, Italy
[b] Institute of Radiation Therapy, Catholic University School of Medicine, l.go F. Vito, 1 00168 Rome, Italy
[c] Institute of Histology and Embryology, Catholic University School of Medicine, l.go F. Vito, 1 00168 Rome, Italy

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ABSTRACT

Objective: Treatment of glioblastoma recurrence can have a palliative aim, after considering risks and potential benefits. The aim of this study is to verify the impact of surgery and of palliative adjuvant treatments on survival after recurrence.
Methods: From January 2002 to June 2008, we treated 76 consecutive patients with recurrent glioblastoma. Treatment was: 1-surgery alone – 17 patients; 2-adjuvant-therapy alone – 24 patients; 3-surgery and adjuvant therapy – 16 patients; no treatment – 19 patients. The impact on median overall-survival (OS-time between recurrence and death/last follow-up) of age, Karnofsky performance scale (KPS), resection extent and adjuvant treatment scheme (Temozolomide alone vs low-dose fractionated radiotherapy vs others) was determined. Survival curves were obtained through the Kaplan–Meier method. Cox proportional-hazards was used for multivariate analyses. Significance was set at $p < 0.05$.
Results: Median OS was 7 months. At univariate analysis, patients with a KPS $\geq$ 70 had a longer OS (9 months vs 5 months – $p < 0.0001$). OS was 6 months for patients treated with surgery alone, 5 months for patients that received no treatment, 8 months for patients treated with chemotherapy alone, 14 months for patients treated with surgery and adjuvant therapy-$p = 0.01$. Patients with a KPS < 70 were significantly at risk for death – HR 2.8 – $p = 0.001$.

Subgroup analysis showed no significant differences between patients receiving gross total or partial tumor resection and among patients receiving different adjuvant therapy schemes. Major surgical morbidity at tumor recurrence occurred in 16 out of 33 patients (48%).
Conclusion: It is fundamental, before deciding to operate patients for recurrence, to carefully consider the impact of surgical morbidity on outcome.

1. Introduction

The unfavorable prognosis of patients with glioblastoma (GBM) is mainly due to the high propensity for tumor recurrence. Present therapies seldom obtain tumor control: in most cases recurrence occurs within 7–9 months [1–4]. Treatment of tumor recurrence can have a palliative aim, after considering risks and potential benefits, in particular on quality of life. Surgery can play a role in providing symptom relief. However, before surgical intervention, it is essential to clearly define treatment goals and the expected impact on prognosis and the patient's quality of life [5]. In fact, surgical and adjuvant therapies after recurrence have a much greater morbidity and mortality [4]. Selection of patients that can be treated after recurrence is mainly based on age and clinical conditions – Karnofsky performance scale (KPS) – Table 1 [6].

The aim of this study is to verify the impact of surgery and of palliative adjuvant treatments on survival after GBM recurrence.

2. Materials and methods

2.1. Patient selection

From January 2002 to June 2008, 76 consecutive patients with recurrent glioblastoma were treated at Neurosurgery Department and Radiation Therapy Department of Catholic University, Rome. All these patients were previously treated at our institution and had undergone surgery (gross total resection) followed by concomitant chemotherapy to Radiotherapy – RT (60 gray – Gy) with Temozolomide (TMZ) at a daily dose of 75 mg/m^2 per day and adjuvant TMZ at a dose from 150 to 200 mg/m^2 per day on the standard schedule

* Corresponding author. Tel.: +39 06 3015 4120.
E-mail address: debonisvox@gmail.com (P. De Bonis).

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Table 1
Karnofsky performance scale.

100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Table 2
Patients demographics and treatment.

	Groups	No. of patients
Sex	M	43
	F	33
Mean age (years)		59 (range 29–81)
Age cut-off	≥65	49
	<65	27
Pre-operative mean KPS		70 (range 40–90)
Post-operative mean KPS		50 (range 0–90)
Treatment of recurrence	Surgery alone	17
	Adjuvant therapy alone	24
	Surgery + chemotherapy	16
	Supportive care	19*

Median overall survival (time between recurrence and death/last follow-up) in months (CI 95%): 7 months (CI 95% 5–9 months).

* 17 patients with a KPS < 50 at recurrence and 2 patients who refused treatment.

of 5 days per week every 28 days. All these patients had no residual tumor after initial combined treatment.

None of these patients was lost at follow-up. Follow-up data were obtained by the outpatients department of Radiation Therapy, where patients were followed-up initially once a week until adjuvant therapy completion and then every three months. Patient demographics are shown in Table 2. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to their inclusion in the study.

2.2. Treatment at recurrence

Pre-operative magnetic resonance imaging (MRI) with Gadolinium was used to assess tumor limits. Tumor borders were defined as the contrast-enhanced peripheral areas of tumors. For 1 nonenhancing tumor, tumor volume was defined as the region of T2-w signal abnormality corresponding to the mass seen on both T1- and T2-weighted images (excluding the ill-defined hyperintense signal abnormality surrounding the mass on T2-weighted images), in accordance with Lacroix et al. [7]

Indication for surgery at tumor recurrence was based on: patient clinical condition (i.e. KPS ≥ 60), lesion location (one surgically resectable, not deep-seated lesion – corpus callosum, basal ganglia/thalamus/insula, brainstem) and spread of disease (patients with multifocal spread of disease were excluded). These patients underwent tumor removal with the aid of intra-operative ultrasounds, neuronavigation (Medtronic Stealth Station) and/or 5-aminolevulinic acid, in order to identify tumor borders with greater accuracy. The extent of tumor resection was determined on the basis of early postsurgical imaging (contrast enhanced MRI/CT studies were obtained within 72 h after surgery). Gross total tumor resection was defined as 100% macroscopic removal of the tumor mass.

Palliative adjuvant therapy was administered if patients had a KPS ≥ 60. Most patients received TMZ (dose from 150 to 200 mg/m^2 per day on the standard schedule of 5 days per week every 28 days). Different chemotherapy schemes with Cisplatin, Fotemustine, Carmustine, Irinotecan and low-dose fractionated radiotherapy were also used [8]. For patients who underwent surgery alone, adjuvant therapy was not administered due to: poor clinical condition after surgery (8 cases), subgaleal collection/hydrocephalus/wound dehiscence (8 cases), patient will (1 case). For cases who did not undergo surgery, radionecrosis was excluded by MRI through spectroscopy, perfusion, and diffusion.

2.3. Statistical analysis

Statistical software used for analyses was Statistical Package for the Social Sciences (SPSS) 11.0 for Windows. Median Overall-survival (OS-time between recurrence and death/last follow-up) was determined. The impact on OS of age at recurrence (≥65 vs <65), KPS at recurrence (≥70 vs <70) and treatment received (surgery alone vs adjuvant therapy alone vs surgery + adjuvant therapy vs supportive care) was analyzed. Subgroup analysis was also performed, in order to analyze the impact of extent of resection (gross total vs partial) and of adjuvant treatment scheme used (TMZ alone vs low-dose fractionated radiotherapy vs others) on OS. Survival curves were obtained through the Kaplan–Meier method and were compared by using the log-rank test and the Breslow test. Cox proportional-hazards was used for multivariate analyses. The Fisher's exact test was used to compare proportions. Significance was set at $p < 0.05$.

3. Results

Treatment of recurrence was: surgery alone (17 patients); adjuvant therapy alone (24 cases); surgery and adjuvant therapy (16 patients); the remaining 19 patients only received supportive care (corticosteroids and anticonvulsant agents), due to poor clinical conditions or patient/relative will – Table 2. Patients belonging to this last group were followed-up as outpatients or were given hospice care. Gross total resection was achieved in 11 out of 33 patients who underwent surgery (33%), partial resection was achieved in the remaining 22 patients (67%). Overall, 40 patients received palliative adjuvant treatment. All but six patients received TMZ (dose from 150 to 200 mg/m^2 per day on the standard schedule of 5 days per week every 28 days). Seven patients received low-dose fractionated radiotherapy (0.4 gray – Gy twice daily) with TMZ-four patients – or low-dose fractionated radiotherapy (0.3 Gy twice daily) with Cisplatin (30 mg/m^2) and Fotemustine (40 mg/m^2) if progressing on TMZ-three patients. Five patients showing progressing on TMZ received Irinotecan (75 mg/m^2) and Carmustine (100 mg/m^2)-three patients-or Fotemustine-two patients.

Median OS for all 76 patients was 7 months (confidence interval – CI 95% 5–9 months).

At univariate analysis, KPS and treatment received were significantly associated with survival. In particular, patients with a higher KPS at tumor recurrence (≥70) had a longer OS (9 months, CI 95% 7–11 months, vs 5 months, CI 95% 3–7 months) – Breslow $p < 0.0001$, Log Rank $p < 0.0001$ – Fig. 1.

OS was 6 months (CI 95% 3–9) for patients (17 cases) treated with surgery alone and 5 months (CI 95% 3–7) for patients (19 cases) that received no treatment. Patients treated with chemotherapy alone (24 cases) had an OS of 8 months (CI 95% 5–10). Patients treated with surgery and adjuvant therapy (16 cases) had an OS of 14 months (CI 95% 10–18) – log-rank $p = 0.01$, Breslow $p = 0.004$ – Fig. 2.