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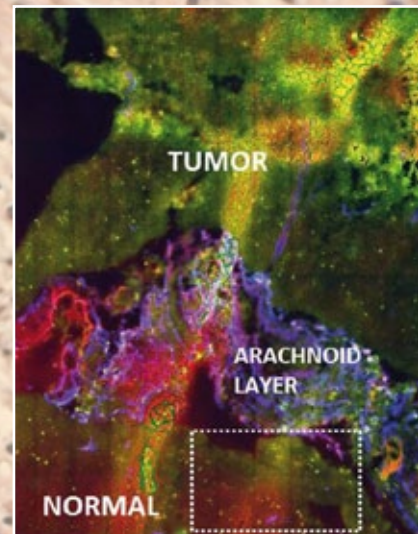
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Reoperation for Recurrent Glioblastoma: Outcome Analysis and Correlation with MGMT Status

Alba A Brandes, Enrico Franceschi

Abstract: The treatment of recurrent glioblastoma remains a challenge. Although second surgery may provide effective palliation, it has yet to be established whether it has a role at all. The few studies investigating this issue are small, retrospective, and characterized by inhomogeneous datasets.

Moreover, the role of MGMT at the time of relapse remains controversial, since MGMT status may vary across the disease's natural history and its impact on post-progression survival is unclear.

The aim of this study was therefore to analyze predictors of outcome in patients with recurrent glioblastoma and to compile a review of

data in the literature with a view to comparing the effect on outcome of second surgery against well-known prognostic determinants. **Eur Assoc NeuroOncol Mag 2014; 4 (1): 16–9.**

Key words: glioblastoma, recurrence, second surgery, prognostic factors, MGMT methylation

■ Introduction

Although we have improved our understanding of glioblastoma biology and achieved an improvement in survival thanks to the use of combined radio- and chemotherapies [1], many treated patients relapse and their prognosis is extremely poor. Following standard treatment, the 5-year survival rate amounts to approximately 10 % [2]. The therapeutic options available for patients with disease progression are compromised because the efficacy of chemotherapy is limited and neurologic deterioration is often severe; approaches for those with recurrence include second surgery, usually considered indicated since it can relieve symptoms. Few retrospective studies have been conducted to ascertain the outcome of recurrent glioma patients who undergo second surgery for relapse.

■ Prognostic Factors and Second Surgery

The only prospective data regarding outcome of patients who have undergone surgery for recurrent disease comes from the phase-III trial that randomized patients with gliomas (65 % glioblastomas) to receive surgery with carmustine implants or surgery with placebo at relapse [3]. In this trial, patients who underwent surgical resection with placebo showed a median survival of about 5 months. Factors that were significant predictors of outcome in patients with glioblastoma included age ($p = 0.004$), interval from previous surgery ($p < 0.001$), Karnofsky Performance Status (KPS; $p = 0.02$), race ($p = 0.06$), and previous nitrosourea chemotherapy ($p = 0.03$).

Retrospective Studies

Moreover, many retrospective data are available (Table 1). The first important reports [4, 8, 14] on this issue appeared in 1987, when Ammirati studied 55 cases of recurrent anaplastic astrocytoma and glioblastoma (20 and 35, respectively); in all cases, second surgery was performed; 41 of the 55 patients (75 %) underwent postoperative chemotherapy and/or radio-

therapy. Overall median survival was 92 weeks, whereas median survival time after re-surgery was 36 weeks. Outcome was better in patients with low-grade recurrence at histology and a good KPS (> 70) who underwent radical resection. At multivariate analysis, the most powerful variables were KPS and extent of resection. However, the reliability of the data reported in this study, one of the first to suggest a correlation between reoperation and survival, was undermined by the fact that it was conducted on a small series of patients with different histologies. Landy [5] analyzed 33 recurrent glioma patients, all of whom had second surgery. After surgery, 9 patients had re-irradiation and 24 received chemotherapy. Median survival after reoperation was 8 months, 13 months, 22 months, and 47 months for glioblastoma, anaplastic astrocytoma, astrocytoma, and oligodendroglioma/mixed group, respectively. Despite a trend toward improvement in survival depending on the tumour grades, the difference did not attain statistical significance; a significant correlation was found between age/KPS and prognosis, with younger patients with a better KPS having a longer survival. According to the authors, 11 patients benefited from second surgery and any consideration of aggressive treatment for recurrent gliomas should be balanced against the predicted outcome since symptoms of pressure, unlike those of infiltration, are usually ameliorated by surgery. The small series precluded any sound conclusion: patients with a better histological diagnosis would probably have enjoyed a better outcome irrespective of the surgical approach.

Keles reported on a series of 92 patients with hemispheric glioblastoma who underwent a total of 107 operations [6]; 52 were undertaken on patients who had undergone previous surgery or biopsy; the percentage of resection (POR) and volume of residual disease (VRD) were calculated using volumetric image technique analysis. Preoperative KPS, chemotherapy, POR, and VRD have a statistically significant effect on time to tumour progression: improvement in outcome was proportionate to residual disease reduction.

Pinsker reported on 38 patients who underwent repeat surgery for recurrent glioblastoma [6], survival was longer in patients in whom total resection was achieved than in subtotal resection (21 and 18 weeks, respectively), although the difference was not of statistical significance. Moreover, on eval-

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Table 1. Studies.

Author, year [Ref]	n	Setting (newly/recurrent)	Histology	Role of surgery
Ammirati, 1987 [4]	55	Recurrent	GBM, AA	Positive
Landy, 1994 [5]	33	Recurrent	GBM, AA, WHO grade II	ns
Keles, 1999 [6]	92	Mixed (48 % second surgeries)	GBM	Positive
Pinsker, 2002 [7]	38	Recurrent	GBM	ns
Mandl, 2008 [8]	32	Recurrent	GBM	Negative
McGirt, 2009 [9]	949	Mixed (73 % second surgeries)	GBM, WHO grade III	Positive
Clarke, 2011 [10]	758	Recurrent	GBM	ns
Carson, 2007 [11]	333	Recurrent	GBM, WHO grade III	ns
Gorlia, 2012 [12]	300	Recurrent	GBM	ns
De Bonis, 2012 [13]	76	Recurrent	GBM	Positive

ns: not significant; GBM: glioblastoma; AA: anaplastic astrocytoma

uating the effect of conventional variables (age < 50 years, time between first and second resection > 26 weeks, KPS > 90 at second resection, total primary resection) they found a correlation with longer survival; for postoperative survival, extent of resection, unlike age and recurrence-free interval, KPS was predictive of outcome improvement. This data suggests that second surgery enhances efficacy of treatment in patients with a good KPS. Although this study is valuable because it was performed on a homogeneous, well-defined, and stratified cohort, the size of the series compromises the value of the evidence provided.

In Mandl's retrospective analysis of 32 patients with recurrent glioblastoma [8], the inclusion criteria were good clinical condition (KPS at least 60), local recurrence without multifocality, and the feasibility of debulking. The cohort was split into 3 subgroups: 9 patients received only surgical resection as salvage therapy (4 had > 1 resection), 11 had surgery plus chemotherapy or stereotactic radiosurgery (SRS), and 12 were given chemotherapy alone or SRS. Median overall survival was 34 weeks in patients who had chemotherapy or SRS plus surgery, 28 weeks for those given chemotherapy alone or SRS, and 13 weeks for those resected without further treatment. The authors therefore advised that patients with severe mass effect symptoms be considered candidates for resection followed by further salvage therapy but that patients with mild symptoms could be spared surgery since a similar survival advantage can be gained by means of other approaches. Importantly, in 40 % of re-operated patients, the performance status deteriorated; this suggests that second surgery may be detrimental.

McGirt [9] made a retrospective analysis on a large series of patients with malignant astrocytoma; altogether 949 patients were considered: 700 were WHO grade IV and 249 WHO grade III; 549 had primary resection and 400 second surgery; 294 of the latter had glioblastoma. Resection was considered gross-total (GTR) in the absence of contrast enhancement at postoperative MRI, near-total (NTR) if a rim enhancement of the resection cavity was evidenced, and sub-total (STR) if nodular enhancement was found. In patients given second surgery, median survival after GTR, NTR, and STR was 11, 9, and 5 months, respectively. At adjustment for variables independent at multivariate analysis (ie, age, KPS, and temozolomide adjuvant therapy), GTR and NTR were associated with improved survival; GTR provided a 10-% greater reduction

of the risk of death than NTR, which provided a further 37-% greater decrease than STR. The time interval between 2 subsequent surgeries and the tumour site was not a significant factor. The author concluded that extensive resection, even at the time of recurrence, may provide better outcome and patients receiving optimal surgery are more likely to benefit from subsequent therapy. This study is significant because the series was large and any bias obviated by precautions such as a blind review of the neuro-radiological images.

Park [15] evaluated 34 consecutive patients with recurrent supratentorial hemispheric glioblastoma to identify a prognostic model predictive of outcome. Patients had radical resection for recurrence in a single institution with all procedures being performed by the same surgeon. At survival analysis, significant variables for survival were KPS < 80, tumour mass > 50 cm³, and a motor-speech-middle (MSM; a scale to assess the involvement of 3 eloquent/critical brain areas) cerebral artery score > 2. The findings from these parameters were used to determine the overall score for each case and patients were subsequently divided into 3 prognostic groups; median survival was 10.8 months for patients with null scores and 1 month for those with 3.

Commenting on this study, Xu et al [16] argued that since the number of patients believed to have the worst prognosis was only 10 % there might have been a selection bias precluding a reliable conclusion; moreover, they stated that the performance status alone cannot be considered an independent prognostic factor because it is frequently influenced by tumour location; finally they pointed out that although all patients underwent surgery some might have benefited from upfront chemotherapy without any adverse effect on the final outcome.

Clarke [10] analyzed 758 patients with recurrence from glioblastoma; of the cohort enrolled in the North American Brain Tumor Consortium (NABTC) phase-II clinical trials, 208 underwent second surgery at the time of disease progression/relapse. Patients who underwent surgery were compared with those who did not for progression-free survival at 6 months (PFS6) and overall survival. No difference was found between the surgical and non-surgical groups, either for progression-free and overall survival, which ranged from 8–19 weeks and from 24–34 weeks, respectively. Chamberlain and Silbergeld [17] questioned the methodological approach used in this

study, arguing that it did not report data on tumour volume or extent of resection; nor did the authors evaluate whether there was any correlation between surgery and improvement of symptoms – this would have strengthened their assumption that second surgery does not affect outcome.

De Bonis [13] made a retrospective evaluation of 76 recurrent glioma patients, 17 of whom had second surgery alone, 24 chemotherapy alone, 16 surgery and chemotherapy, and 19 no treatment; it was found that patients undergoing surgery and chemotherapy lived longer than patients who had alternative treatment. Moreover, unlike age and extent of resection, performance status was a significant independent prognostic factor.

Carson et al [11] reported the results of a recursive partitioning analysis (RPA) conducted on 333 recurrent glioma patients in phase-I and -II trials in order to investigate systemic or local chemotherapy and brachytherapy in the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Glioblastoma patients made up 67.4 % of the study population; 44.5 % (n = 146) underwent second surgery. The RPA selected different prognostic factors for the glioblastoma and non-glioblastoma groups. The former was split on the basis of the Karnofsky Performance Status (60–70 vs 80–100), age (≥ 50 vs < 50), and tumour location (outside frontal lobe versus confined to frontal lobe) while the latter was split on the basis of the Karnofsky Performance Status (60–80 vs 90–100), age (≥ 50 vs < 50), and corticosteroid use. Seven classes were identified during analysis. Survival ranged from 3.8 months for patients with a histology other than glioblastoma and a low KPS via 10.4 months for glioblastoma patients < 50 years and a high KPS to 25.7 months for non-glioblastoma patients with a frontal tumour and good performance status. The number of surgical procedures performed was not significant at multivariate analysis being ruled out by RPA.

To investigate prognostic factors in recurrent glioma patients Gorlia [12] considered 300 patients recruited in phase-I or -II trials conducted by the EORTC Brain Tumor Group: 138 had received temozolomide concomitant with and adjuvant to radiotherapy, 158 radiotherapy alone or combined with another chemotherapy regimen, and 4 chemotherapy without previous radiotherapy. Post-progression survival and the progression-free survival were 6.2 months and 1.8 months, respectively. The prognostic variables that proved significant were PS, neurological deficit, time since primary diagnosis, baseline administration of steroids, number of target lesions, tumour size, frontal tumour location, and prior chemotherapy with temozolomide; at multivariate analysis, variables impacting on overall survival were performance status, baseline steroids, number of target lesions, frontal location, and tumour diameter; age and second surgery at recurrence did not affect survival. It should be pointed out that only 8 % of patients underwent second surgery.

■ MGMT Methylation

The value of tissue in recurrence from glioblastoma is questionable; however, it is probably advisable to achieve the best possible definition of the biological signature at recurrence,

although predictive markers for decision-making after reoperation are lacking. MGMT methylation status at the time of first surgery has been shown to be a potent prognostic factor for patients treated with either RT followed by temozolomide or temozolomide concurrent with and adjuvant to RT [18]. However, it is unclear whether this epigenetic feature is consistent also at the time of disease recurrence after postsurgical radiotherapy (RT) followed by temozolomide and whether its prognostic role is retained. In a consecutive and prospectively recorded database of glioblastoma cases, Brandes et al [19] evaluated data from tumour specimens obtained during first and second surgery. Concordance between MGMT methylation status at the time of first and second surgeries was relatively low (63 %). Moreover, MGMT status changed more frequently in patients with MGMT-methylated (61.5 %) than in patients with unmethylated (24 %) status at first surgery ($p = 0.03$). Interestingly, patients treated with concurrent chemotherapy/RT were characterized by a substantially high percentage of MGMT shifts from methylated status at the time of first surgery to unmethylated status at the time of second surgery ($p = 0.03$).

On the contrary, another retrospective series [20] showed concordance between first and second evaluation of the MGMT methylation status in 89 % of glioblastoma patients. In this study, MGMT methylation was associated with longer progression-free survival, overall survival, and post-progression survival.

■ Discussion

Age and KPS are valid prognostic factors. Furthermore, the majority of studies suggested tumour size as a valuable predictor of outcome. Conflicting data are available regarding the role of tumour site as a factor affecting survival since in some studies tumour involvement of eloquent brain areas is associated with poorer outcome. However, surgery did not prove significant in the study by Clarke, who provided a valuable analysis conducted on a large series.

The role of MGMT methylation status as a prognostic factor for post-progression survival remains unclear and warrants further studies.

As yet, there is little consensus regarding the role of surgery for recurrent glioblastoma, common limitations are the small patient series and heterogeneity in samples; treatment options at recurrence can vary, often depending on the urgent need to alleviate symptoms, and taking previous treatment and performance status into account. Finally, age and KPS were the only true predictors of survival, proving significant in all the studies reviewed. Since a trial randomizing patients to surgery versus chemotherapy is not feasible from an ethical standpoint, an analysis on a large series of patients using prospectively collected data would be welcome since it would provide a more reliable insight on the value of second operation for patients with recurrent glioblastoma.

■ Conflict of Interest

The authors declare that they have no conflict of interest.

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