ORIGINAL ARTICLE

# Does Extent of Resection Impact Survival in Patients Bearing Glioblastoma?

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**ABSTRACT:** ***Background:*** The impact of malignant glioma resection on survival is still a matter of controversy. The lack of well-designed prospective studies as well as control of all factors in retrospective studies plays an important role in this debate. Amongst some of these uncontrolled factors, are the inclusion of different histological grades, the lack of objective methods to estimate the extent of resection and unspecified delays in post-operative imaging. ***Methods:*** We retrospectively reviewed 126 consecutive patients with glioblastoma, operated on by the senior authors at the Centre Hospitalier Universitaire de Sherbrooke, who met the following criteria: >18 years of age, newly diagnosed glioblastoma, pre-operative magnetic resonance imaging (MRI) within 2 weeks prior to surgery, and a post-operative MRI within 72 hours after surgery. Extent of tumour resection was calculated using pre and post-operative tumour delimitation on gadolinium-enhanced T1 MRI in a volumetric analysis. ***Results:*** Applying stringent specific inclusion criteria, 126 patients were retained in the analysis. The median overall survival was 271 days and the median extent of resection was 65%. Patients with more than 90% of tumour resection had a significantly better outcome, improving median survival from 225 to 519 days (P=0.006). Other factors that significantly improved survival were the use of radiotherapy, the number of regimens and type of chemotherapy used. ***Conclusion:*** A more aggressive approach combining maximal safe resection and use of salvage chemotherapy seems to confer a survival advantage for glioblastoma patients.

**RÉSUMÉ: L'étendue de la résection influence-t-elle la survie des patients atteints de glioblastomes?** ***Contexte :*** L'impact de la résection d'un gliome malin sur la survie demeure controversé. L'absence d'études prospectives bien conçues ainsi que de contrôle de tous les facteurs dans les études rétrospectives joue un rôle important dans ce débat. Mentionnons l'inclusion de tumeurs de grades anatomopathologiques différents, le manque de méthodes objectives pour estimer l'étendue de la résection et des retards non spécifiés à procéder à une imagerie postopératoire sont quelques uns de ces facteurs non controlés. ***Méthode :*** Nous avons revu rétrospectivement les cas de 126 patients consécutifs atteints d'un glioblastome et ayant été opérés par les auteurs seniors au Centre hospitalier universitaire de Sherbrooke. Ils rencontraient tous les critères suivants : être âgés de plus de 18 ans, un diagnostic de glioblastome qui vient d'être posé, une IRM préopératoire dans les 2 semaines précédant la chirurgie et une IRM postopératoire dans les 72 heures suivant la chirurgie. L'étendue de la résection de la tumeur était calculée sur l'IRM pondérée en T1 après gadolinium par analyse volumétrique des limites de la tumeur avant et après la chirurgie. ***Résultats :*** Cent vingt-six patients rencontraient les critères d'inclusion spécifiques rigoureux préétablis. La survie globale médiane était de 271 jours et l'étendue médiane de la résection était de 65%. Les patients dont plus de 90% de la tumeur avait été enlevée avaient un meilleur résultat et leur survie médiane passait de 225 à 519 jours (p = 0,006). Les autres facteurs qui amélioraient significativement la survie étaient la radiothérapie, le nombre de traitements et le type de chimiothérapie qu'ils avaient reçu. ***Conclusion :*** Une approche plus agressive combinée à une résection sécuritaire maximale et l'utilisation de la chimiothérapie de rattrapage semblent améliorer la survie chez les patients atteints d'un glioblastome.

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Malignant glial tumours, in particular glioblastoma multiforme (GBM), are the most frequent primary brain tumours encountered in neurosurgical practice. Despite recent advances in therapeutic modalities, the prognosis for patients remains poor, with a median survival of 12 to 16 months. Since the advent of the Stupp[1] protocol as a first-line treatment, concomitant chemotherapy and radiotherapy have become integral in the therapeutic regimen for these aggressive tumours. Surgery as a single treatment modality has no curative benefit, given the highly invasive behavior of this cancer, as was first hinted at by Dandy in 1933[2]. Malignant astrocytomas are infiltrative tumours with no cleavage plane, thus prohibiting a complete microscopic surgical resection. Individual tumour cells have even been found outside of the T2 anomaly on MRI, thus depicting the highly infiltrative nature of these lesions[3]. This is in contrast to many solid tumours in which a gross total resection with clear margins clearly impacts survival.

There is, nevertheless, a role for surgery in the management paradigm of these tumours[4], even if many uncertainties persist. Surgery remains mandatory for tissue analysis, and this role will

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likely increase in the future as the need for molecular characterization of tumours should take a greater part in the study of individual tumour samples and the eventual design of tailored therapies. More so, there is no denying that reduction of intracranial hypertension is of unquestionable benefit to the patient by alleviating the mass effect and thus allowing a decrease in the consequent doses of required steroids. However, the impact of the surgical extent of resection on the survival of patients bearing a glioblastoma remains a matter of controversy. A recent meta-analysis by Sanai and Berger[5] concluded that more extensive surgical resection is associated with longer life expectancy. However, these authors also recognized that the lack of uniformity in the methodology of extent of resection studies could raise concerns about the validity of these conclusions. More specifically, the inclusion of different histologies and grades, thus producing inhomogeneous samples, the non-objective radiological measurement of residual tumour volumes and undue delay in post-operative imaging are just a few of the methodological biases that could limit the conclusions of some of these reports.

Even though recent studies seem to lean toward a significant role of surgery in prolonging survival of malignant glioma patients, several authors feel that the contribution of surgery to survival has yet to be convincingly shown, and the only way to do so would be through a randomized phase III study. Some even argue that a difference between stereotactic biopsy and open surgery has not been demonstrated convincingly, suggesting a randomized study design to settle the question[6]. However, such a study is highly unlikely to take place, as a significant component of the neurosurgical community remains by and large convinced that resection is superior to biopsy, when safely feasible.

In the past years, newer and more sophisticated technologies have become available to assist the surgeon in maximizing the extent of resection. These technologies are expensive and increase the length of surgery; thus their use should be supported not only by evidence that they increase the extent of resection, but also by evidence that this increase really impacts the median survival of patients, as well as their quality of life.

The present study was designed to retrospectively analyze the impact of the extent of resection on survival of patients diagnosed with glioblastoma, trying to limit some of the aforementioned biases.

## Materials and Methods

The charts of patients diagnosed with glioblastoma multiforme at the Centre Hospitalier Universitaire de Sherbrooke between 2004 and 2008 were retrospectively reviewed. The analysis included only adult patients (18 years of age or older) with newly diagnosed supratentorial glioblastoma according to the World Health Organization (WHO) histological criteria who were operated on by the two senior authors of the study (DF, DM). Patients were required to have had a pre-operative magnetic resonance imaging (MRI) within two weeks prior to surgery, and a post-operative MRI within 72 hours after surgery. One hundred twenty six patients met these inclusion criteria. Ninety-six patients were not included in the analysis because the post-op MRI took place after the 72 hours prescribed interval for this study, who otherwise met the inclusion criteria.

**Table 1: Patient and tumor characteristics**

| | | n (%) |
|---|---|---|
| Sex | Male | 80 (63,5) |
| | Female | 46 (36,5) |
| Localization | Frontal | 48 (38,1) |
| | Parietal | 49 (38,9) |
| | Temporal | 43 (34,1) |
| | Occipital | 13 (10,3) |
| | Corpus callosum | 19 (15,1) |
| | Thalamus | 3 (2,4) |
| | Deep nuclei | 4 (3,2) |
| Lateralization | Left | 57 (45,2) |
| | Right | 55 (43,7) |
| | Median | 14 (11,1) |
| No of surgery | Unique | 95 (75,4) |
| | Multiple | 31 (24,6) |
| Radiotherapy | Yes | 97 (77) |
| | No | 29 (23) |
| Stupp | Yes | 39 (31) |
| | No | 87 (69) |
| Chemotherapy | None | 53 (42,1) |
| | Temozolomide | 47 (37,3) |
| | Salvage IA chemo | 24 (19) |
| Ki-67 | Median: 16 % (1-62) | |

The primary outcome of this study was the correlation of the extent of resection and patient survival. As secondary outcomes, the impact of several other factors on survival were also studied. The different factors analyzed are listed in Table 1. The evaluation of MGMT methylation status was not performed, as this biomarker was not routinely assessed in our center at the time of accrual for this study.

To evaluate the extent of resection, a standard procedure was designed as follows: pre and post-operative MRI scans images were initially imported in Metamorph 4.0 software (MTS Analytical Technologies ®). Multiple contiguous thin slices (1 mm) covering the totality of the tumour volume were used. Analysis of each slice was achieved in such a way to allow manual delimitation of the pre-operative surface area (PRE) and the post-operative surface area (POST) (Figure 1). All enhancing tumour components on axial T1 contrast-enhanced images were included, as well as the central hypointense signal (Figure 1). The peri-tumoural T2 changes were not considered in this analysis. To decrease a potential source of contamination of the



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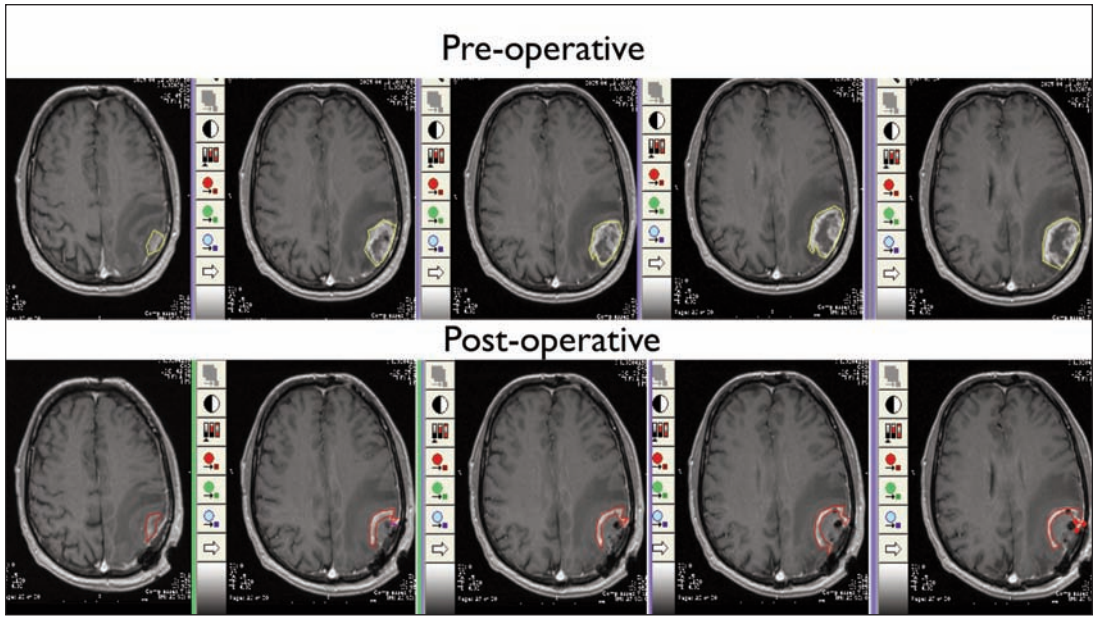


***Figure 1:*** *Example of tumour delimitation using Metamorph 4.0 software.*

data, a comparative analysis of the post-op T1 enhanced slice with the corresponding non-enhanced T1 slice was conducted in all samples, so that spontaneous T1 signal on the non-enhanced image (blood) was subtracted from the enhanced image. The generation of an area-pixel ratio (POST/PRE) for each slice as well as the calculation of tumour volume (as summation of all slices) was performed using Metamorph 4.0. Two evaluators, including the senior author of this study, reviewed all sections of tumour delineation. Aside from minor discrepancies in post-op images in seven patients, both evaluators agreed on tumour delineations. An estimate of the post-operative residual volume was calculated by summation of all post-operative slices areas scored against pre-operative areas, and globally expressed as a volume ration (POST/PRE). This lent a global %, considered as the residual post-operative disease. All patients who were only submitted to a stereotactic biopsy were arbitrarily attributed 1% as the extent of resection value.

Statistical analysis was performed with SPSS 13.0 software (SPSS inc., Chicago, Il). Kaplan-Meier survival curves were generated. Cox regression models with all covariates were used for univariate and multivariate analysis. The covariates used for Cox regression were as follows: sex, age, KPS, localization and lateralization of the tumour, extent of resection, number of surgical resections, Ki-67 immunoassaying, radiotherapy and chemotherapy treatments. Extent of resection was also studied as a continuous variable against survival using Cox regression.

## Results

Patients and tumour characteristics are shown in Table 1. The mean age at diagnosis was 60.5 years (range, 24.7-88.7). The median overall survival was 271 days for the whole cohort, and the median extent of resection was 65%. This result includes 41 patients who were only submitted to biopsy (extent of resection of 1%) thereby severely negatively biasing this estimate (Table 2). The actuarial survival rate was 61% at 6 months, 40% at one year and 7.2% at two years. The distribution of patients with regards to the extent of tumour resection and respective survival is shown in Table 2.

Studied as a continuous variable in Cox regression, extent of resection was found to significantly impact survival (p=0.001). Looking for a cut-off value in the multivariate analysis, we observed that resection of more than 90% of the tumour volume

**Table 2: Survival by extent of resection categories**

| Extent of resection | N | Median Survival (days) |
|---|---|---|
| 1% (biopsy) | 41 | 121 |
| 2-50% | 11 | 292 |
| 51-75% | 24 | 290 |
| 76-90% | 19 | 312 |
| 91-100% | 27 | 519 |



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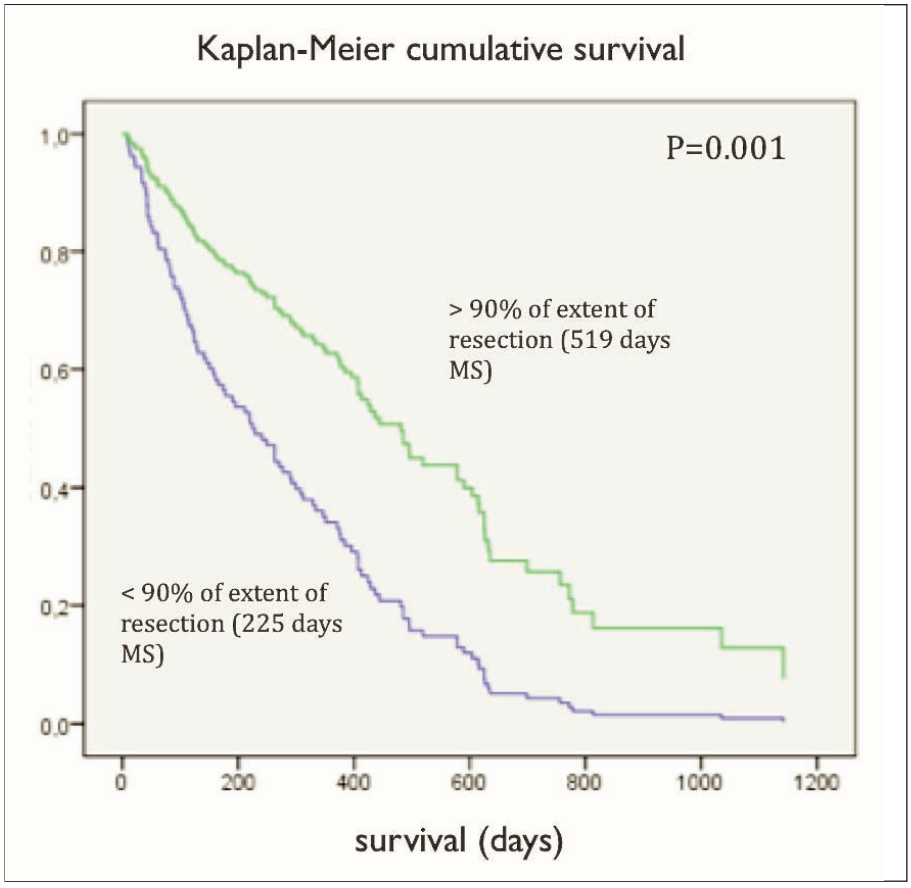


***Figure 2:*** *Kaplan-Meier curves comparing the survival of patients (in days) according to the extent of resection.*

was found to significantly improve survival (p=0.006). Figure 2 demonstrates the Kaplan-Meier survival curve estimates comparing patients with >90% tumour resection to those with <90% tumour resection. The 90% cutoff for extent of resection was the only significant one in the multiple multivariate models used in the analysis. Other variables that were identified as significant factors influencing survival in multivariate Cox models were radiotherapy (p<0.001), number of chemotherapy regimens (p<0.001) as well as the use of intra-arterial carboplatin chemotherapy (p=0.05). Corpus callosum localization (p=0.008) was also identified as adversely impacting survival. Interestingly, proliferative activity of the tumour as measured by Ki-67 immunoassaying did not predict survival.

This study accrued some patients that were treated prior to the establishment of the Stupp protocol as a first-line standard of treatment, as only 31% of patients were exposed to the combined temozolomide-radiation treatment. Radiation was administered according to the Stupp protocol parameters for the patients accrued after the instauration of this approach as a standard of care. Patients accrued prior to Stupp were typically treated with radiotherapy-only as a first line of treatment, at the usual dose of 60 gy over 30 fractions. Forty-two percent of patients in this cohort did not receive chemotherapy. The median survival of patients who did not receive any chemotherapy was 84 days, whereas survival of those who received only a single temozolomide regimen was 351 days. Patients treated initially with temozolomide followed by a salvage carboplatin IA chemotherapy regimen presented a median survival of 578 days. Patients who underwent first-line concomitant radiotherapy and chemotherapy (Stupp protocol)[1] had a median survival of 485 days. This last group, however, also includes patients who received additional second-line chemotherapy (intra-arterial carboplatin) at tumour recurrence.

## Discussion

Management of glioblastoma patients always includes a form of surgery, as pathological analysis is the only reliable way to obtain a diagnosis. With the increasing demand for molecular analysis of samples to direct therapy and derive prognosis, and with the continued search for predictive biomarkers, new molecular targets as well as the design of tailored therapies, surgery will remain at the forefront of malignant glioma management[7]. Thus, notwithstanding the controversy on the impact of the extent of resection on survival, surgery remains desirable and should be considered in all patients suspected of



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bearing malignant gliomas. In our view, the question is not whether surgery should be performed (as opposed to biopsy), but to what extent and to what degree should the patient be put at risk to produce optimal resection. As surgery is not curative, preservation of neurological function should remain an absolute priority. With recent advances in microsurgical techniques, monitoring during awake craniotomies, access to refined technologies such as neuro-navigation and sono-neuro-navigation, and integration of more sophisticated imaging sequences such as diffusion tensor imaging, it is now increasingly possible to achieve gross total resection with functional preservation in a considerable number of patients. It remains to be seen whether intra-operative MRI will also permit a greater and safer extent of resection, and whether this extent of resection will be beneficial to the patient[8]. Despite numerous studies investigating this interesting topic, controversy still remains regarding the impact of the extent of tumour resection on survival. Our study demonstrates that a resection of 90% or more of the tumour volume is associated with improved survival in a consecutive cohort of GBM patients. By comparison, a frequently cited study by Lacroix and al[9], concluded that a resection of 98% of the tumour was necessary to improve survival. Although that study accrued significantly more patients than the present work, it was also affected by several limitations related to the methodology of analysis. Specifically, patients undergoing reoperation were included, as well as patients treated at other institution (44%). The authors also neglected to include in the analysis the impact of adjuvant treatments, an omission greatly reducing the reach of the author's conclusion.

In many studies, non-objective criteria are often used to measure the extent of resection[5]. The method described in this work is reproducible and offers a good estimate of residual tumour volume while being objective. Post-operative imaging time interval is also an important issue in this type of analysis. Inflammatory changes on contrast-enhanced MRI can be misinterpreted as residual tumour and can appear as early as within 24 hours of surgery[10,11]. Actually, the so-called "diagnostic window" of 72 hours to perform the post-op MRI has been questioned by observations that post-op enhancement actually appears as early as during surgery, and is already installed in 90% of patients within 24 hours[12]. In nonvolumetric studies, there seems to be no consensus on how to classify the extent of resection, and many such studies relied on the surgeon's subjective impression of tumour resection as being either gross total, subtotal, partial resection or biopsy. We would argue that this is methodologically unsound, as it is common knowledge that surgeons tend to overestimate resection; this is obviously not the most objective method of assessing tumour resection.

To further increase the study population homogeneity and limit confounding variables, only patients with proven newly-diagnosed WHO grade 4 astrocytoma were included in this series. Malignant glioma studies often include grade 3 tumours, which undoubtedly create biases due to the different natural history of these tumours[5]. In a meta-analysis by Sanai and Berger, reviewing all articles on the extent of glioma resection since 1990[5], only four papers considering high grade gliomas used volumetric tumour analysis[9,13,14,15]. Of these, two reached significance in multi-variate models showing an increase in survival with more extensive resection[9,13]. Moreover, these two studies included only glioblastomas in the analysis. The study by Lacroix et al[9], obtained statistical significance at a resection cut off of 98%, improving survival from 8.8 to 13.0 months. The other study, by Keles et al[13], demonstrated a benefit on survival by stratifying their population into five groups according to resection percentage as such: <25%, 25-49%, 50-74%, 75-99% and 100% resection. The mean survival time ranged from 8 months for those with less than 25% of resection to 23.3 months for those with complete resection. An interesting aspect of this study was the demonstration of an increased time to tumour progression with a more extensive resection. A 90% extent of resection, as found in our study, may be a more achievable outcome compared to the 98% reported by Lacroix et al[9]. Moreover, as shown in Table 2, it appears that survival may be improved with partial resection compared to biopsy alone, thus supporting the use of surgery even in conditions where a complete resection is out of reach; this is in keeping with the results by Keles et al[13].

Another recent study by McGirt et al. reviewed an impressive number of patients [949 cases) using MRI[16]. The conclusions were strongly in favor of a relationship between the extent of surgery and median survival. However, this study used an objective qualitative assessment (gross total, near total vs partial) to stratify the patients, and excluded from the series deep-seated lesions requiring biopsy. More so, different histopathological diagnosis and grade were pooled for the analysis, decreasing the reach of these conclusions.

Interestingly, as part of a Cochrane review, Hart et al[6] concluded that there was no high quality evidence supporting the use of surgery in favor of stereotactic biopsy in the management of high grade gliomas. These authors thus pleaded for randomized controlled trials to settle once and for all this conundrum of neuro-oncology. Such a study is unlikely to ever take place, however, as there is a strong bias in the neuro-oncological community in favor of surgery. Commenting on this perspective, Gutin formulated the following comment: "Randomized studies that would eliminate the confounding selection of retrospective studies are not likely to be conducted. I do not think we will ever know the impact of surgical resection on the survival of patients with gliomas"[17]. In response to this reflection, and to our inability as a community to produce definitive proof supporting surgery and optimal resection, we have to wonder whether no firm proof is obtainable because of the inadequacy of current adjuvant therapy to take full advantage of cytoreduction[3,18,19,20]?

This study was not specifically designed to assess the impact of other treatment modalities, but some general observations are nonetheless worthwhile. As was already recognized in the literature, results from this study acknowledge the role of radiotherapy in extending survival[20]. However, such a relationship has not always been clear for chemotherapy[3]. In the present study, chemotherapy was found to significantly influence survival of the patients in a very clear fashion. Only 31% of patients in this series were exposed to the Stupp protocol as the study started to accrue prior to its establishment as a standard of care, and 42% of patients were actually not exposed to chemotherapy, thus producing a fairly heterogeneous population of patients. The multivariate analysis showed that patients who

received a second line intra-arterial chemotherapy regimen (carboplatin, etoposide) after failing the first course of chemotherapy depicted the best survival of the entire cohort. It is current practice at our center to offer this treatment when patients fail first line chemotherapy. Data supporting intra-arterial chemotherapy have previously been published by our team[18,19]. We are aware that the survival advantage measured in this study might be due to a selection bias whereas we tend to offer more aggressive salvage therapy to patients in better clinical conditions. We can nevertheless claim that an aggressive approach on all accounts (surgery and chemotherapy) is not detrimental to patients and appears to offer a survival advantage.

## Conclusion

In this retrospective study, resection of more than 90% of the enhancing tumour mass at the time of diagnosis conferred a significant survival advantage for patients with glioblastoma multiforme. A more aggressive approach combining maximal tumour removal with chemoradiotherapy and salvage chemotherapy at recurrence seems to confer an advantage in the management of this aggressive tumour type, and benefit patients.

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