

# Cytoreductive surgery of glioblastoma as the key to successful adjuvant therapies: new arguments in an old discussion

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## Abstract

**Background** This article discusses data from 3 randomized phase 3 trials, supporting a role for surgery in glioblastoma. **Methods** Data were reviewed by extent of resection during primary surgery from the ALA-Glioma Study (fluorescence-guided versus conventional resection), the BCNU wafer study (BCNU wafer versus placebo), and the EORTC Study 26981–22981 (radiotherapy versus chemoradiotherapy with temozolomide). **Results** For glioblastoma patients in the ALA study, median survival was 16.7 and 11.8 months for complete versus partial resection, respectively ( $P < 0.0001$ ). Survival effects were maintained after correction for differences in age and tumor location. For glioblastoma patients who received  $\geq 90\%$  resection in the BCNU wafer study, median survival increased for BCNU wafer versus placebo (14.5 versus 12.4 months, respectively;  $P = 0.02$ ), but no survival increase was found for  $< 90\%$  resection (11.7 versus 10.6 months, respectively;  $P = 0.98$ ). In the EORTC study, absolute median gain in survival with chemoradiotherapy versus radiotherapy was greatest for complete resections (+4.1 months;  $P = 0.0001$ ), compared with partial resections

(+1.8 months;  $P = 0.0001$ ), or biopsies (+1.5 months;  $P = 0.088$ ), suggesting surgery enhanced adjuvant treatment. **Conclusion** Complete resection appears to improve survival and may increase the efficacy of adjunct/adjuvant therapies. If safely achievable, complete resection should be the surgical goal for glioblastoma.

**Keywords** 5-aminolevulinic acid · BCNU wafer · Glioblastoma · Surgery · Temozolomide

## Introduction

Cytoreductive surgery for glioblastomas (GBM) has been performed for decades, initially with radical procedures including lobectomies and even hemispherectomies. While it has been acknowledged that surgery cannot cure GBM because of the diffuse nature of the disease, it has often been assumed that surgery provides some survival benefit. Surgery provides a rapid reduction of tumor bulk and mass effect, leading to symptom palliation, and provides tissue for histopathological diagnosis [22]. Thus, the neurosurgery community has invested great efforts to improve the safety of maximal tumor resection, including costly intraoperative imaging modalities. Nevertheless, the value of extensive surgery for improving survival has repeatedly been challenged, with emphasis on risks of craniotomy and cost [16, 24–26, 30, 48].

There is no Class I evidence from well designed and adequately powered trials that conclusively demonstrates a survival benefit with surgery. In fact, some studies suggest that if there is a survival benefit it is modest and may be limited to select patients [2, 24, 35, 45]. The perception of resection as beneficial is largely based on a collection of data from retrospective and observational studies that

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assessed survival or disease progression by extent of resection [5, 6, 10, 19, 20, 27, 29, 37, 49]. It has been debated whether the cohorts analyzed in these studies were adequately balanced by known prognostic factors such as age and Karnofsky Performance Status (KPS) [16]. In fact, studies in which the distribution of such factors was assessed demonstrated that younger patients or patients with high KPS scores received more extensive resections [1, 9, 41]. Moreover, small and superficially located tumors are more likely to undergo extensive resections, and such tumors may intrinsically have a better prognosis [18, 37, 41]. Such biased data may influence the postulated effect of resection and thus confound conclusions regarding the prognostic role of resection as estimated by multivariate analysis.

Recently, 3 prospective, randomized phase 3 studies were conducted that employed surgical resection in addition to investigational agents in patients with newly diagnosed malignant glioma. The first of these studies investigated the support of resection by intraoperative fluorescent guidance with 5-aminolevulinic acid (5-ALA, Gliolan®, Medac GmbH, Hamburg, Germany) in malignant glioma patients [40]. The second study investigated the efficacy and safety of intracavitary chemotherapy with carmustine (BCNU) wafers (Gliadel® Wafer, Eisai Corporation North America, Woodcliff Lake, NJ) in malignant glioma patients [46], and the third study investigated the efficacy and safety of concomitant radiochemotherapy with temozolomide followed by sequential temozolomide (Temodar®, Schering Corp., Kenilworth, NJ) in glioblastoma patients [42]. The results of each of these studies led to the approval of the investigational agent for the treatment of patients with malignant gliomas (ALA study, BCNU wafer study) and glioblastomas (temozolomide study). Within all three trials, extent of resection and other prognostic factors were collected prospectively. Post-hoc analyses of these data provide similar results with respect to the impact of extent of resection on survival and its potential influence on the efficacy of adjunct/adjuvant therapies.

#### Influence of resection on survival

##### *5-ALA fluorescence-guided resection and radiotherapy*

In the 5-ALA study, patients with resectable, newly diagnosed malignant glioma were randomized to receive 5-ALA fluorescence-guided resection (n=139) or conventional non-enhanced microsurgery (n=131) [40]. Resection was followed by a standard course of fractionated radiotherapy (60 Gy). The primary study endpoints were the rate of complete resection—removal of all contrast-enhancing tumor on early (within 72 hours of surgery) magnetic resonance imaging (MRI)—and the 6-month progression-

free survival (PFS) rate. The complete resection rate was 65% and 36% in the 5-ALA and conventional surgery groups, respectively. In logistic-regression models, the use of 5-ALA had the most important effect on the probability of complete resection (odds ratio=3.41; 95% CI, 2.03–5.71;  $P<0.0001$ ), followed by age and tumor location, while performance status did not reach statistical significance. The 29% difference in the frequency of complete resections translated into a significantly improved 6-month PFS rate (41.0% versus 21.0%, respectively;  $P=0.0003$ ). Analysis of overall survival also favored surgery with 5-ALA over conventional surgery (15.2 versus 13.5 months; hazard ratio [HR]=0.82; 95% CI, 0.62–1.07;  $P=0.1$ ). Although this difference was not statistically significant, it should be realized that the study was not powered to show differences in overall survival. A significant survival difference was observed in the whole study cohort between patients who received complete resection compared with partial resection: 17.9 months (95% CI, 14.3–19.4) versus 12.9 months (95% CI, 10.6–14.0), respectively ( $P<0.0001$ ).

To investigate the impact of resection in glioblastomas only, a post-hoc analysis of these data re-stratified the per-protocol cohort of patients by extent of resection, ie, complete versus partial, excluding all patients with grade III gliomas [41]. The resulting groups were balanced regarding a number of possible prognostic factors (eg, neurological function, preoperative tumor characteristics, additional treatments received), with the exception of age and tumor location (eloquent versus noneloquent), the latter of which was assessed by surgeons. The survival benefit associated with complete versus partial resection in the intent-to-treat (ITT) population was maintained in the per-protocol cohort (median survival, 16.7 versus 11.8 months, respectively;  $P<0.0001$ ), and the 2-year survival rate was significantly greater for complete versus partial resections (26.2% [95% CI, 18.5–34.6%] versus 7.0% [95% CI, 3.8–13.1%]). The survival advantage with complete resection was maintained when patients were substratified by age <60 years versus >60 years (Table 1), and the differences in age distributions in the substrata were no longer detectable. Median age was 52 and 54 years for complete and partial resection, respectively, in the subgroup <60 years of age, and 65 and 66 years, respectively, in the subgroup >60 years of age. The survival advantage also was maintained after substratification of patients by tumor location. Thus, both age and tumor location could be eliminated as confounding factors. In multivariate analysis, resection status had the strongest prognostic effect (HR for residual tumor=1.752; 95% CI, 1.258–2.438;  $P=0.0009$ ).

In a subsequent analysis that evaluated survival by the Radiation Therapy Oncology Group recursive partitioning analysis (RPA), the survival advantage associated with complete versus partial resection was maintained in RPA

**Table 1** 5-ALA study: survival by extent of resection<sup>a</sup> for the per-protocol collective<sup>b</sup> [41]

	Overall N=243	Age, years <sup>c</sup>		Tumor location <sup>c</sup>	
		<60 n=123	>60 n=120	Eloquent n=137	Non-eloquent n=106
2-year survival rate (95% CI), %					
Complete resection	26.2 (18.5–34.6)	NA	NA	NA	NA
Partial resection	7.0 (3.8–13.1)	NA	NA	NA	NA
Median survival (95% CI), months					
Complete resection	16.7 (14.3–19.0)	19.4 (15.2–21.0)	13.8 (10.0–17.4)	15.1 (12.3–20.1)	17.4 (13.7–19.7)
Partial resection	11.8 (10.4–13.7)	14.0 (11.3–16.6)	11.0 (7.9–12.9)	11.5 (10.2–13.4)	13.2 (9.7–15.3)
Hazard ratio (95% CI), complete versus partial	0.54 (0.41–0.71) <i>P</i> <0.0001	0.61 (0.41–0.91) <i>P</i> =0.0146	0.55 (0.36–0.82) <i>P</i> =0.0028	0.49 (0.33–0.72) <i>P</i> =0.0003	0.63 (0.42–0.96) <i>P</i> =0.0306

<sup>a</sup> Complete resection was removal of all contrast-enhancing tumor on postoperative MRI (centralized review)

<sup>b</sup> Patients with grade IV gliomas; n=122 for complete resection and n=121 for partial resection

<sup>c</sup> Age and tumor location differed in the complete versus partial resection groups; other factors tested included neurological condition (NIH score), KPS, ependymal infiltration, extent of edema, preoperative tumor size, hemisphere, sex, histological subtype, midline shift

NA, not available

class IV and V subgroups [33]. Complete resection was also favored for the RPA class III subgroup, but this did not reach statistical significance, likely because of the small sample size.

#### *Surgery, BCNU wafers, and radiotherapy*

In a randomized, double-blind, placebo-controlled, phase 3 trial by Westphal et al [46], 240 patients with newly diagnosed malignant glioma were randomized to receive resection with BCNU wafer or placebo wafer implantation (120 patients in each arm). Following resection and wafer implantation, patients received a standard course of fractionated radiotherapy (total dose, 55–60 Gy). Implantation of BCNU wafer resulted in significantly longer survival compared with placebo in the ITT population (13.9 versus 11.6 months; HR=0.71, 95% CI, 0.52–0.96; *P*=0.03) [25] with a tail of stable long-term survivors. The 2-year survival rate was 15.8% for BCNU wafer versus 8.3% for placebo (not significant), and the 3-year survival rate was 9.2% versus 1.7% (*P*=0.01), respectively [47]. In the subgroup with GBM, there was a trend of improved survival for BCNU wafer versus placebo, although the difference was not statistically significant (13.5 versus 11.4 months; HR=0.76, 95% CI, 0.55–1.05; *P*=0.10) [46].

During the BCNU study, data on extent of resection were captured by the investigators prospectively at participating institutions from the reports made by the local neuroradiologists on radiographs mandated to be taken 24 to 48 hours postoperatively. The preferred radiographic method was tumor volume on MRI, but tumor area and CT scans were also used. There was no centralized radiographic

review. Complete resection was defined as removal of  $\geq 90\%$  of tumor tissue as measured on postoperative radiographs compared with preoperative scans. When these data were analyzed, 48% and 44% of patients in the BCNU wafer and placebo groups, respectively, received complete resections in the ITT population as documented in case report forms (Table 2). In the complete resection subgroup, median survival was significantly greater for BCNU wafer than for placebo (14.8 versus 12.6 months; *P*=0.01). In the partial resection subgroup, median survival was 12.1 and 11.2 months, respectively (*P*=0.39).

For patients with GBM, the results were very similar, with a median survival of 14.5 months for BCNU wafer versus 12.4 months for placebo (*P*=0.02) in the complete resection subgroup, and 11.7 and 10.6 months, respectively (*P*=0.98), in the partial resection subgroup.

These data suggest that survival improved in patients receiving complete resection compared with partial resection in both the BCNU and placebo wafer arms [25]. The survival advantage of BCNU wafers compared with placebo was significant in the complete resection subgroup but did not reach statistical significance in the partial resection subgroup. For the ITT population, the absolute median gain in survival time with BCNU wafer versus placebo was +2.2 months for complete resection and +0.9 months for partial resection.

#### *Concomitant radiochemotherapy followed by adjuvant temozolomide*

The EORTC-NCIC trial (EORTC 26981–22981; NCIC CE.3) study was a randomized, multicenter trial in 573

**Table 2** BCNU Wafer Data: Survival by Treatment Group and Extent of Resection<sup>a</sup>

	BCNU Wafer	Placebo
Intent-to-treat population	n=120 <sup>b</sup>	n=120 <sup>c</sup>
2-year survival rate (95% CI), %		
Complete resection	20.7 (11.4–31.8)	7.6 (2.4–16.6)
Partial resection	11.3 (5.0–20.5)	9.1 (3.7–17.5)
Median survival (95% CI), months		
Complete resection	14.8 (13.5–18.4)	12.6 (10.2–14.8)
Partial resection	12.1 (9.3–14.4)	11.2 (9.6–12.4)
Hazard ratio (95% CI), BCNU wafer vs placebo		
Complete resection	0.58 (0.39–0.86); <i>P</i> =0.01	
Partial resection	0.85 (0.60–1.22); <i>P</i> =0.39	
GBM patients	n=101 <sup>d</sup>	n=106 <sup>e</sup>
2-year survival rate (95% CI), %		
Complete resection	18.0 (8.8–29.7)	6.0 (1.6–14.9)
Partial resection	3.9 (0.7–11.9)	5.5 (1.4–13.6)
Median survival (95% CI), months		
Complete resection	14.5 (12.7–18.1)	12.4 (10.2–14.8)
Partial resection	11.7 (9.0–13.8)	10.6 (9.5–12.1)
Hazard ratio (95% CI), BCNU wafer vs placebo		
Complete resection	0.62 (0.41–0.93); <i>P</i> =0.02	
Partial resection	1.00 (0.68–1.48); <i>P</i> =0.98	

<sup>a</sup> Complete and partial resections defined as  $\geq 90\%$  and  $< 90\%$ , respectively, of tumor removed on postoperative CT/MRI scans (non-centralized review)

<sup>b</sup> n=58 for complete resection, n=62 for partial resection

<sup>c</sup> n=53 for complete resection, n=67 for partial resection

<sup>d</sup> n=50 for complete resection, n=51 for partial resection

<sup>e</sup> n=50 for complete resection, n=56 for partial resection

patients with newly diagnosed malignant glioma [42]. Patients were randomized to receive radiotherapy alone (2 Gy/day for 5 days a week over a course of 6 weeks) or radiotherapy with continuous daily temozolomide (75 mg/m<sup>2</sup>/day, 7 days a week) followed by 6 cycles of temozolomide (150–200 mg/m<sup>2</sup> for 5 days during each 28-day cycle). In the primary report, Stupp et al. observed a significant survival benefit with temozolomide [42]. Median survival was 14.6 months in the radiochemotherapy group versus 12.1 months in the radiotherapy only group (HR=0.63; 95% CI, 0.52–0.75; *P*<0.001), and the 2-year survival rate was 26.5% (95% CI, 21.2–31.7) versus 10.4% (95% CI, 6.8–14.1), respectively. Long-term follow-up demonstrated that the survival benefit with temozolomide was maintained at 3 years (16.7% versus 4.3%, respectively; *P*<0.0001) [31].

During this study, extent of resection was reported per surgeon assessment on clinical and/or radiological grounds. The study did not mandate postoperative imaging (although it

**Table 3** EORTC-NCIC 26981–22981 Data: Survival by Treatment Group and Extent of Resection<sup>a</sup> [43]

	RT+TMZ (n=287) <sup>b</sup>	RT (n=286) <sup>c</sup>
2-year survival rate (95% CI), %		
Complete resection	37.1 (28.0–46.3)	14.5 (7.8–21.2)
Partial resection	23.2 (15.5–30.9)	8.9 (3.9–14.0)
Biopsy	10.0 (1.3–18.7)	4.6 (0.0–10.8)
Median survival (95% CI), months		
Complete resection	18.3 (15.7–22.5)	14.2 (12.7–16.2)
Partial resection	13.5 (11.9–16.3)	11.7 (9.7–13.1)
Biopsy	9.4 (7.5–13.2)	7.9 (5.4–10.6)
Hazard ratio (95% CI), RT+TMZ vs RT		
Complete resection	0.57 (0.43–0.76); <i>P</i> =0.0001	
Partial resection	0.65 (0.50–0.84); <i>P</i> =0.0001	
Biopsy	0.69 (0.46–1.06); <i>P</i> =0.088	

<sup>a</sup> Clinical or radiographic assessment of the surgeon

<sup>b</sup> n=113 for complete resection, n=126 for partial resection, n=48 for biopsy

<sup>c</sup> n=113 for complete resection, n=128 for partial resection, n=45 for biopsy

RT, radiotherapy; TMZ, temozolomide

was recommended) nor centrally review imaging. Ninety-three patients (16%) had a diagnostic biopsy only, 254 patients (44%) had partial resections, and 226 patients (39%) had complete resections. A Cox analysis adjusting for age and performance status demonstrated that the treatment effect remained significant in the resected group (HR=0.63; 95% CI, 0.51–0.76; *P*<0.0001) but not in the biopsied group (HR=0.69; 95% CI, 0.45–1.05; *P*=0.084).

The clinical impact of resection was examined further in a post-hoc analysis of survival by extent of resection [43]. While this study was not designed to assess survival by extent of resection and assessment of the surgeon is less accurate than radiographic assessment [1], the data indicate that the more complete the resection, the more prolonged the survival (Table 3). Absolute median gain in survival time with radiochemotherapy versus radiotherapy alone was greatest in patients with complete resections (+4.1 months) compared with those with incomplete resections (+1.8 months) or biopsies (+1.5 months), although this increase did not meet statistical significance in tests for interaction (test for heterogeneity, *P*=0.24). The Kaplan-Meier survival data corresponded to a risk reduction for radiochemotherapy versus radiotherapy alone of 43% in patients who received complete resection (*P*=0.0001), 35% for partial resection (*P*=0.0001), and a nonsignificant decrease of 31% for biopsy (*P*=0.088). Adjuvant temozolomide appeared to have the greatest survival impact in patients who received complete resection, suggesting that

the effectiveness of temozolomide may be related to the extent of resection.

## Discussion

The controversy surrounding the value of surgery in malignant glioma has not been investigated in well-controlled and adequately powered prospective trials and likely never will be. Historically, the relationship between extent of resection and survival has been primarily described in retrospective, observational studies [1, 4, 27, 39, 44]. Because of their retrospective and uncontrolled design, these studies have been criticized for potentially confounded results. Biased distribution of patients may have caused differences between study groups for known prognostic factors, such as age, tumor location, and KPS [8, 34, 38]. For example, patients recommended for aggressive surgical resection are often younger than those recommended for biopsy [29]. Biased distribution of prognostic factors may have concurrently influenced survival and extent of resection [16]. Also, there was no centralized review for neuropathology in these studies [36].

To our knowledge, there is only 1 randomized, prospective study that examined the effectiveness of resection in malignant glioma [45]. In this small study, 30 patients over the age of 65 years were randomized to receive biopsy or resection. Histological diagnosis confirmed malignant glioma in 13 biopsy patients and 10 resection patients. All patients received radiotherapy. There was a significant but modest improvement in median survival for resection versus biopsy (171 days versus 85 days, respectively;  $P=0.035$ ), but no significant difference in time to deterioration (105 days versus 72 days, respectively;  $P=0.057$ ). When adjusted for tumor grade, resection was more favorable than biopsy for both survival (HR=2.621; 95% CI, 1.035–6.641;  $P=0.0422$ ) and time to deterioration (HR=2.757; 95% CI, 1.004–7.568;  $P=0.0491$ ). Unfortunately, this study was not adequately powered to draw definitive conclusions (the trial is subject to chance findings) and excluded younger patients who have been shown to benefit from resection more than older patients [29].

There is a substantial collection of prospective and retrospective data supporting resection over biopsy in malignant glioma (summarized in Laws et al.) [29]. Unfortunately, data on extent of resection were not captured in the majority of studies for about 40 years, as most centers did not have the infrastructure to accurately assess extent of resection. When it became included in phase 3 trials, resection was frequently used for stratification, but these trials were not specifically designed or powered to examine the relationship between survival and extent of resection, which was often based on local neuroradiology

evaluations without uniform protocols. While almost all meaningful glioma trials of the last decade have had centralized neuropathological evaluation [36] centralized radiographic review of resection has been the exception, although it has been performed in more recent trials, including the 5-ALA trial [40]. Despite this limitation, the availability and quality of resection data have improved in recent studies to a standard that allows an attempt at correlative analyses.

The 3 clinical trials reviewed here further support the use of resection in glioblastoma and maximal tumor resection [40–43, 46]. These 3 studies were well-controlled, prospective, randomized trials that assessed various treatment options for malignant glioma, and each study prospectively collected resection data. Most of the patients in the 5-ALA and BCNU wafer trials were glioblastoma patients, as were all patients in the temozolomide study. Thus, these studies provide evidence on the relationship between resection and survival and between resection and the efficacy of adjuvant therapies. More extensive resection was associated with improved outcome, and in the temozolomide and BCNU wafer studies the survival benefit of the study treatment appeared to be most favorable in patients who received extensive resection.

It is important to recognize caveats to the results reported here. Because of the patient selection process, there are limitations to the generalizability of the results as the cohorts of patients from these 3 studies represent a more narrow population than that observed in the community setting. These studies excluded patients with low KPS. Resection was mandatory in the 5-ALA and BCNU wafer studies with a goal of maximal tumor resection in both. Patients with tumors deemed only partially resectable were excluded in the 5-ALA study.

Furthermore, the 3 studies were not designed or powered to assess the relationship between resection and survival. The data were post-hoc subgroup analyses of glioblastoma patients and are subject to confounding influences. Resection data were centrally reviewed only in the 5-ALA study. In the temozolomide study, extent of resection was captured by the surgeon and was based on clinical or radiographic assessment [1]. In the BCNU wafer study, radiographic assessment of resection was not centralized. It is unclear whether the surgical subgroups were balanced with respect to known and unknown prognostic factors. In the temozolomide and BCNU studies, the surgical subgroups are likely to differ as surgical decisions are affected by tumor characteristics (eg, size and location) and the status of the patient (eg, age). It will be important to determine whether the relationship between complete resection and temozolomide or BCNU wafer is maintained with more rigorous statistical analyses that adjust for other known prognostic factors. A smaller randomized phase 2 study in

newly diagnosed GBM patients (N=110) with a similar protocol as the EORTC-NCIC trial did not find an association between the extent of surgery and survival [3]. However, only 17% of patients received complete resection and the small sample size limits the power of subgroup analyses. Since the number of grade III gliomas in the 5-ALA and BCNU wafer studies was small (no grade III tumors were included in the temozolomide study), our conclusions cannot be conferred to grade III glioma patients based on the present data.

Despite the limitations of these analyses, the data reviewed here support the value of maximal resection in the multimodality treatment of glioblastoma. The concept that resection may also enhance the efficacy of adjuvant therapies is novel and expands the benefits of surgical intervention beyond immediate relief of symptoms due to mass effect and a rapid and logarithmic kill of tumor cells. The question remains about the underlying mechanisms. One mechanism may be the beneficial effect on hypoxia-related phenomena. On MRI, a central core of contrast-enhancing tumor with necrosis is surrounded by a wide margin of invading cells. This enhancing region is known to be hypoxic. Hypoxia influences the behavior of tumor cells by activating genes involved in the adaptation to hypoxic stress (eg, angiogenesis), representing an important indicator of cancer prognosis [7, 11, 21, 50]. Hypoxia is associated with aggressive growth, metastasis, and poor response to treatment [23, 28]. Central GBM cells appear to proliferate more readily than they invade [14] which may affect short-term prognosis. The marginal region of the tumor has more angiogenesis [17] and tumor cells in this region may be less proliferative, more migratory, and more resistant to apoptosis, which likely contributes to treatment resistance [14].

Hypotheses also suggest that interstitial fluid pressure (IFP) may affect the penetration and residence time of chemotherapy agents. Increased IFP in glioma tumors with increased permeability may produce a pressure gradient that distributes chemotherapy agents into necrotic areas or into surrounding brain tissue where it is absorbed and cleared, thus limiting the residence time of the cytotoxic agents in the marginal region [32]. Following resection, there is an initial increase in IFP in the immediate postoperative period because of cerebral edema. Once edema is resolved, IFP decreases and the direction of fluid flow reverses toward the resection cavity [14]. With intracavitary chemotherapy, the increase in IFP in the immediate postoperative period because of edema, particularly with BCNU wafer, [15] may improve the limited penetration of antitumor agents into the infiltrating zone [12, 13]. Systemic chemotherapy, on the other hand, is generally delivered a few weeks after resection when edema has been resolved and there is a decrease in IFP, particularly in the marginal zone, and

permeability is limited from cytokine production of tumor cells within that zone. Thus, decreasing IFP may prolong the drug residence time in the marginal zone [32]. Regardless of the potential mechanism for improving the effectiveness of adjuvant treatments with complete resection, the problem remains that undetectable infiltrative tumor stem-like cells or tumor repopulating cells persist and eventually develop into detectable recurrence.

## Conclusion

Treatment of patients with malignant glioma demands multimodal approaches that deliver highly effective anti-tumor agents. Rapid, local tumor control afforded by surgery sets the stage for other treatments to become more efficacious. The collection of clinical data currently available supports the use of surgery for the management of glioblastoma. Surgery improves survival and may enhance the efficacy of adjunct/adjuvant therapies. The 3 prospective, randomized trials reported here support this view. Future treatment studies should continue to collect resection data prospectively, preferably by centralized radiographic review, so that results can be analyzed by the extent of resection to determine the relationship between resection, other treatment modalities, and survival.

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