Neuro-Oncology Advance Access published August 2, 2011
Neuro-Oncology
doi:10.1093/neuonc/nor110
NEURO-ONCOLOGY

Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma?

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Historically, the North American Brain Tumor Consortium used 6-month progression-free survival (PFS6) as the primary outcome for recurrent glioma phase II clinical trials. In some trials, a subset of patients received the trial treatment before surgery to assess tumor uptake and biological activity. We compared PFS6 and overall survival (OS) for patients with glioblastoma undergoing surgery at progression to results for those without surgery to evaluate the impact of surgical intervention on these outcomes. Two data sets were analyzed. The first included 511 patients enrolled during the period 1998–2005, 105 of whom had surgery (excluding biopsies) during the study or ≤30 days prior to registration. Analysis was stratified on the basis of whether temozolomide was part of the protocol treatment regimen. The second data set included 247 patients enrolled during 2005–2008, 103 of whom underwent surgery during the clinical trial or immediately prior to study registration. A combined data set consisting of all patients who did not receive temozolomide was also compiled. No statistically significant difference in PFS6 or OS was found between the surgery and nonsurgery groups in either data set alone or in the combined data set ($P > .45$). We conclude that PFS6 and OS results for patients with and without surgical intervention at the time of progression are similar, allowing data from these patients to be combined in assessing the benefit of new treatments without the need for stratification or other statistical adjustment.

Keywords: glioblastoma, PFS6, prognosis, recurrence, surgery.

Received May 12, 2011; accepted June 8, 2011.

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Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and remains a challenge to treat. The standard primary

outcome in therapeutic phase II trials in recurrent GBM is 6-month progression-free survival (PFS6), which represents a clinically meaningful outcome in this patient population and has been shown to be a strong predictor of overall survival (OS).[1] Age has been the strongest prognostic factor for survival in patients with recurrent GBM.[2–4]

Many patients undergo repeat resection of tumor at the time of recurrence, both for confirmation of recurrent disease as well as for debulking, prior to enrolling in a therapeutic trial. Moreover, many trials testing targeted agents include a brief period of treatment with the drug of interest, followed by surgical resection, to simultaneously debulk and allow for assessment of biological activity and tumor uptake of the drug. As a result of these practices, a substantial fraction of patients undergo surgical resection at recurrence. It is possible and even plausible that undergoing surgical resection at recurrence could be a positive prognostic factor independent of any subsequent drug treatment. If true, the design of future phase II trials would need to be adjusted on the basis of whether surgery was undertaken. This possibility led to the retrospective analysis presented here, in which patients from a large number of phase II trials by the North American Brain Tumor Consortium (NABTC) were stratified by surgery at recurrence, either before study enrollment or as part of a study, and both PFS6 and OS were compared between the 2 subsets.

Materials and Methods

All patients treated in NABTC phase II trials for recurrent disease during the period February 1998 through November 2008 were included in this study (Table 1). Because of differences in the types of patient data that were collected, data for patients treated before January 2005 were analyzed as one data set (older studies), and patients treated more recently were analyzed as a second data set (newer studies). Some of the older studies included temozolomide (TMZ) as one of the treatment agents. Because this is now recognized as an effective agent, data from the older studies were stratified on the basis of whether TMZ was part of the treatment regimen. None of the newer studies included TMZ, so this stratification was not necessary. Some studies included both a phase I and a phase II component; for the purposes of this analysis, all patients treated with the recommended phase II dose and who met the phase II eligibility criteria were included even if they were enrolled in the phase I portion of the study. Patients treated with the other phase I doses (lower or higher than the recommended phase II dose) were excluded.

Standard trial entry criteria included confirmed high-grade glioma (grades III and IV) and a Karnofsky performance status score (KPS) ≥ 60. All protocols required central pathology review; in the few cases in which tissue samples were not available for central review, local pathology designation was accepted. Diagnosis was based on the most recent surgery for which data were available at the time of protocol registration, and only those patients with a diagnosis of GBM were included in this analysis. Patients could have been enrolled in >1 protocol and, if so, were included for each protocol in which they were enrolled. In total, 49 patients enrolled in >1 protocol, accounting for a total of 100 observations. Analyses were repeated including these patients only once, either for the first or the last protocol in which they were enrolled; because the results were substantially the same, only results from the primary analysis are presented (ie, with patients included for each protocol in which they were enrolled).

For all studies, progression was defined using the criteria of Macdonald et al.[5] Because the primary end point for these studies was PFS6, either evaluable disease (unidimensionally measurable lesions or margins not clearly defined) or measurable disease (bidimensionally measurable lesions with clearly defined margins) was allowed for patients not undergoing surgery at recurrence. For patients who underwent surgery, there was no requirement for the presence of residual tumor postoperatively. Progression was determined by the local institutional investigator and was defined as a new lesion or an increase in tumor size of $\geq 25\%$ for measurable disease and clear worsening for evaluable disease. Failure to return for evaluation due to death or deteriorating condition was considered to represent progression. In this case, the date that the patient was declared off-treatment due to progression was used as the progression date.

For assignment to the surgery versus nonsurgery groups for this study, patients were initially categorized on the basis of whether they were on the surgery arm of a trial that included a subset of patients treated with the experimental therapy prior to surgery. For those not on the surgery arm of a trial, the time of the most recent surgery was determined. For the older studies, the date of the progression that qualified the patient for the study was not known; it was assumed that if the surgery occurred within 30 days of registration, it was for the most recent progression, and the patient was included in the surgery group. For the newer studies, the date of the qualifying progression was known, and patients were placed in the surgery group if the date of surgery was later than the date of progression. Eighteen patients met the criteria for being in the surgery group but only underwent a biopsy; these patients were excluded from the analysis. Seventeen patients on the surgery arm were not able to receive treatment after surgery; these patients were excluded because they received no treatment with therapeutic intent.

PFS and OS were measured from time of study registration for patients who did not undergo surgery on protocol and for those who underwent surgery prior to study enrollment. For patients who did undergo surgery as part of a study, the date of first postoperative treatment was used as the baseline date. Because of the retrospective nature of this analysis, the date of the start of postoperative chemotherapy

Table 1. Numbers of patients undergoing resection on North American Brain Tumor Consortium phase II trials

Trial	Treatment	No. of patients		
		Surgery during study	Surgery ≤30 days before study enrollment	No surgery
Older studies				
00-01	ZD1839	10	9	29
01-01	Temsirolimus	6	6	32
01-03	Erlotinib	7	2	29
97-01	TMZ + BCNU	0	3	32
97-05	Thymidine + carbo	0	3	30
98-01	CPT-11	0	2	44
98-03	TMZ + cis-RA	0	13	27
99-01	Tipifarnib	19	8	53
99-04	TMZ + thalidomide	0	5	39
99-05	Fenretinide	0	1	23
99-07	TMZ + CPT-11	0	6	40
99-08	Imatinib	0	5	28
Older Subtotals		42	63	406
Newer studies				
03-02	EMD0121974	26	0	0
03-03	Desipeptide	3	8	22
04-01	GW572016	36	0	0
04-02	Erlotinib + temsirolimus	3	9	28
05-02	Sorafenib + others[a]	0	3	32
06-01	Aflibercept	0	7	35
06-02	Pazopanib	0	8	27
Newer Subtotals		68	35	144
Total		110	98	550

BCNU indicates lomustine; carbo indicates carboplatin; cis-RA indicates cis-retinoic acid; TMZ indicates temozolomide.
[a]Three-arm study: sorafenib + erlotinib, sorafenib + temsirolimus, and sorafenib + tipifarnib.

was not available for 17 patients. In those patients, we imputed the date using the latest of date of first response assessment minus 8 weeks (12 cases), surgery date (2 cases), and registration date (when surgery date was not known; 3 cases). Surgery date (or registration date) represented conservative estimates, because postoperative chemotherapy would have to have been started after these dates. The median time from earliest possible chemotherapy start date to imputed start date for those where response assessment minus 8 weeks was used was 16.5 days (range, 1–29 days). This is consistent with the expected time from surgery and is not sufficiently long to substantially affect results. Therefore, no additional sensitivity analyses were conducted.

Patients not known to have died were censored for survival as of the last date known alive. In absence of a progression date, death ≤30 days after the end of treatment was considered date of progression. If a patient was removed from treatment for a reason other than progression, that patient was censored for further evaluation of progression as of the date of starting other therapy (if that was known); if not, the date of removal from treatment was used. In cases in which follow-up for progression was not consistent once off-treatment, the off-treatment date was used.

Studies typically required repeated imaging every 8 weeks. Because the actual timing of the scans could vary, rules were developed to determine whether there was sufficient information to declare that a patient met the criteria for success for PFS6. Specifically, if the PFS duration was ≤26 weeks, then treatment was considered a failure; if the duration of PFS was >30 weeks, then treatment was considered a success. For those patients who progressed between 26 and 30 weeks, we looked for an indication of when the last stable scan was documented. Documentation of progression-free status at the 24-week scan was sufficient to declare success. If the information was not available and PFS was <28 weeks, then we assumed the treatment failed before week 26. For the 3 patients remaining, information on the last progression-free scan was not available, and PFS6 was considered to be unknown.

Both PFS and OS were estimated using the Kaplan-Meier method. To allow for some variability in timing of the scans, we summarized PFS status at 9, 18, and 26 weeks. Survival curves comparing outcome based on surgical status were created. For those analyses including patients in studies involving TMZ, the data were stratified on the basis of whether TMZ was part of the treatment. For the primary end point of PFS6, comparison between the surgery and nonsurgery

Table 2. Patient characteristics

Characteristic	Older studies		Newer studies		Combined[a]	
	Surgery	No surgery	Surgery	No surgery	Surgery	No surgery
No. of patients	105	406	103	144	181	412
KPS						
60	1	5	1	6	1%	5
70	25	19	10	11	15%	17
80	33	33	29	23	30%	29
90	29	33	47	44	40%	38
100	12	11	14	15	14%	11
Age, years						
Median	50	52	52	55	52	53
Range	26–78	21–84	26–69	20–78	26–78	20–78
Sex, % male/% female	61/39	66/34	57/43	65/35	60/40	65/35
Race, % white/% other	93/7	95/5	94/6	89/11	94/6	93/7
No. of prior chemotherapy regimens						
0	22	29	7	6	9	9
1	50	48	66	58	60	58
2	22	21	20	26	23	28
3	7	3	7	9	8	6

Data are percentage of patients, unless otherwise indicated. KPS, Karnofsky performance status score.
[a]includes older studies, no temozolomide subset only, and newer studies.

Table 3. Six-month progression-free survival (PFS6) and overall survival (OS) as a function of surgical subset

Outcome	Older studies		Newer studies		Combined[a]	
	OR or HR (95% CI)	*P*	OR or HR (95% CI)	*P*	OR or HR (95% CI)	*P*
PFS6	0.97 (0.46–2.08)	.94	0.80 (0.27–2.32)	.68	0.77 (0.37–1.60)	.48
OS	1.04 (0.84–1.30)	.71	1.01 (0.77–1.32)	.95	1.05 (0.87–1.27)	.59

Data are odds ratio (OR) for PFS6 and hazard ratio (HR) for OS. ORs, HRs, and *P* values are for no surgery versus surgery from a multivariate model including age and Karnofsky performance status score. For older studies, temozolomide (TMZ) during the study was also included in the model. For the combined data, data source (newer vs older) was included. Odds are odds of PFS6.
[a]Includes older studies, no TMZ subset only, and newer studies.

groups was based on logistic regression. Time-to-event analyses were conducted using the Cox proportional hazards model. All models included adjustment for age, KPS, and TMZ, when appropriate. All *P* values presented in this article are 2-tailed.

Results

Patient Characteristics

The older studies cohort included 511 patients, 105 of whom underwent surgery and 406 of whom did not. The newer studies cohort included 247 patients, 103 of whom underwent surgery and 144 of whom did not. The combined cohort, comprised of all newer studies plus the older studies that did not include TMZ, included 593 patients, 181 of whom underwent surgery and 412 of whom did not. Age, KPS, sex, race, and number of prior chemotherapeutic regimens are described for each group in Table 2 and were comparable across all cohorts.

PFS

Our primary outcome for this analysis was PFS6, and as shown in Table 3, there was no difference in outcome between the surgical and nonsurgical groups in the combined cohort ($P = .48$), the newer cohort ($P = .68$), or the older cohort ($P = .94$) when adjusted for age, KPS, and (in the older cohort) inclusion of TMZ in the study regimen. Moreover, no difference was seen even in the setting of an effective chemotherapeutic regimen (eg, in the TMZ subset of the older cohort, PFS6 was 14.8% in the surgical group versus 18.8% in the nonsurgical group).

PFS rates at 9 weeks, 18 weeks, and 26 weeks were 44%, 19%, and 10%, respectively, for the surgical group and 33%, 15%, and 8%, respectively, for the nonsurgical group of the combined data set (Table 4).

Table 4. Patient outcomes

Outcome	Older studies				Newer studies		Combined[a]	
(surgery vs no surgery)	Including TMZ		No TMZ					
	Surgery	No surgery	Surgery	No surgery	Surgery	No surgery	Surgery	No surgery
PFS								
No. of patients (no. censored)	27 (4)	138 (25)	78 (11)	268 (27)	103 (7)	144 (17)	181 (18)	412 (44)
PFS6, %[b]	14.8	18.8	7.7	5.2	6.8	5.6	7.2	5.3
PFS, %[c]								
9 weeks	73	61	37	33	50	34	44	33
18 weeks	50	39	16	15	21	17	19	15
26 weeks	26	31	10	8	10	8	10	8
Median PFS duration, weeks	18.9 (12.0–24.0)	13.0 (10.0–16.1)	8.0 (7.9–8.7)	7.3 (6.7–7.9)	9.3 (8.0–13.3)	8.0 (7.7–8.4)	8.3 (8.0–9.6)	7.9 (7.3–8.0)
Survival								
No. Of patients (no. censored)	27 (0)	138 (12)	78 (5)	268 (15)	103 (10)	144 (8)	181 (15)	412 (23)
OS, %[b]								
26 weeks	81	69	53	47	58	59	56	51
52 weeks	33	42	18	18	32	29	26	22
78 weeks	22	22	8	7	16	17	12	11
Median OS duration, weeks	33.7 (30.9–66.9)	44.6 (34.7–50.7)	27.7 (24.0–34.9)	24.6 (22.4–28.6)	33.1 (24.0–40.6)	33.2 (28.0–39.0)	31.4 (25.3–35.9)	27.6 (24.3–31.4)

OS indicates overall survival; PFS indicates progression-free survival; PFS6 indicates 6-month progression-free survival; TMZ indicates temozolomide.
[a]Includes older studies, no TMZ subset only, and newer studies.
[b]On the basis of the protocol-defined end point.
[c]On the basis of Kaplan-Meier estimates.

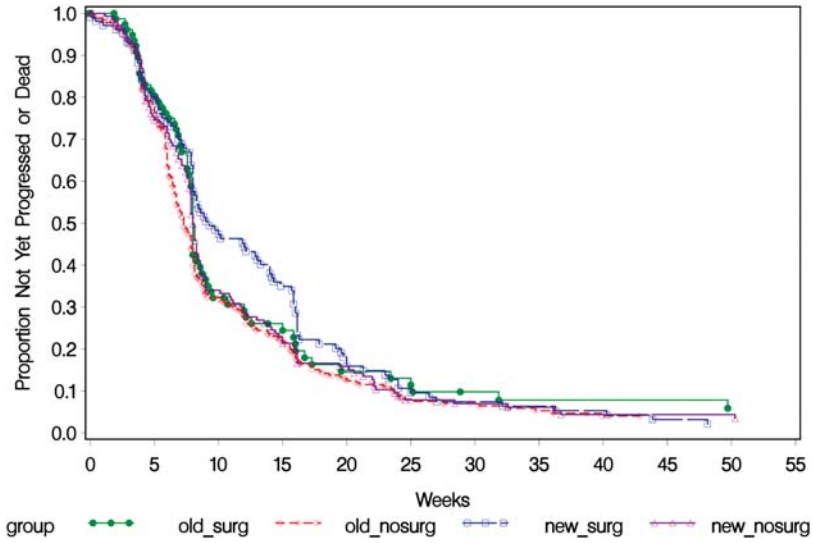

Fig. 1. Kaplan-Meier curve for progression-free survival, combined* cohort, truncated at 52 weeks. "Old_surg" refers to patients in older studies who underwent surgery; "Old_nosurg" refers to patients in older studies who did not receive surgery; "New_surg" refers to patients in newer studies who received surgery; "New_nosurg" refers to patients in newer studies who did not receive surgery. *Includes older studies, no temozolomide subset only, and newer studies.

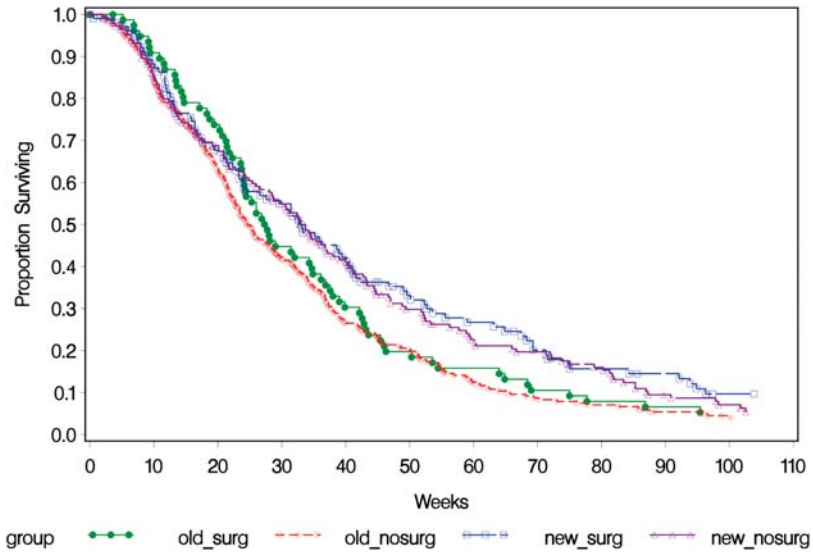

Fig. 2. Kaplan-Meier curve for overall survival, combined* cohort, truncated at 104 weeks. "Old_surg" refers to patients in older studies who underwent surgery; "Old_nosurg" refers to patients in older studies who did not receive surgery; "New_surg" refers to patients in newer studies who received surgery; "New_nosurg" refers to patients in newer studies who did not receive surgery. *Includes older studies, no temozolomide subset only, and newer studies.

As such, the 9-week PFS rate favored the surgical group, but that difference had diminished by 18 weeks and was no longer present by 26 weeks. This pattern was also consistent in each of the smaller patient cohorts (older and newer). The Kaplan-Meier curve for PFS for the combined group by cohort and surgical group is shown in Fig. 1.

OS

OS also did not differ between the surgery and nonsurgery groups in any of the 3 patient cohorts when adjusted for age, KPS, and (within the older cohort) inclusion of TMZ in the study regimen (Table 3). Specifically, the hazard ratio (HR) for survival for the surgery versus nonsurgery groups was 1.04 for the older studies cohort, 1.01 for the newer studies cohort, and 1.05 for the combined cohort; *P* values ranged from .59 to .95. The Kaplan-Meier curve for OS for the combined data set by cohort and surgical group is shown in Fig. 2. Interestingly, although there is no difference between the surgery and nonsurgery groups in any cohort, both groups in the newer studies cohort had better survival rates than the corresponding group in

the older studies. This difference came close to statistical significance when tested as part of the combined group analysis of all patients who did not receive TMZ as part of their treatment regimen (HR, 0.85; 95% confidence interval, 0.71–1.01).

Discussion

We report a retrospective analysis of patients who participated in 19 NABTC phase II studies of various treatments for recurrent GBM. Our primary goal was to determine whether surgery at the time of recurrence was an independent positive prognostic factor for outcome in these patients. In total, our results demonstrate clearly that there is no difference in either PFS6 or OS between patients who do versus do not undergo surgery for tumor recurrence. This was true in 2 separate data sets from different time intervals, as well as in the combined data set. It also held true for the subset of patients who received TMZ, an effective therapy at recurrence, as part of their study treatment.

Perhaps the most important implication of these results is the fact that data from surgical and nonsurgical patients in the same study can be combined without requiring adjustments in methods of statistical analysis (and hence in sample size) when designing studies to assess the potential benefit of new treatments for GBM at recurrence. Similarly, it eliminates concerns about the need to stratify patients enrolling in trials for recurrence according to whether they have had surgical resection immediately before enrollment. Finally, it allows for the possibility of pooling data from multiple trials to serve as a historical reference, regardless of whether the trials contain surgery patients. Although our analysis is retrospective in nature, the large sample size and high quality of prospectively collected data allow for confidence in the significance of the results.

Of note, our results do not imply a lack of utility to surgical debulking at the time of tumor recurrence. Because neuro-oncologists have increasingly recognized the pitfalls of using magnetic resonance imaging to distinguish between treatment effects and tumor regrowth, pathologic sampling has remained an important method by which to confirm true tumor progression. Moreover, surgical debulking continues to be an important mechanism to provide relief of symptoms of increased intracranial pressure and sometimes of focal neurologic symptoms, allowing patients to better tolerate subsequent therapy. As such, we would interpret our results to indicate that surgery at recurrence "balances the scales," permitting patients who would otherwise do worse due to bulky tumor to do as well as patients who do not require surgery.

Interestingly, although there was no difference in PFS6, we did incidentally note that there appeared to be an improvement in OS in the newer cohort relative to the subset of the older cohort that did not receive TMZ in both the surgery and nonsurgery groups. This improvement may be attributable to the introduction of bevacizumab into more common use, which occurred around 2005, or may simply be due to more aggressive overall treatment of patients with tumor at recurrence, including improvements over time in supportive care practices.

Acknowledgments

We acknowledge the expert editorial assistance of Ms. Ilona Garner. The data in this study were presented in partial form as an abstract at the 2010 Society for Neuro-Oncology Annual Meeting.

Conflict of interest statement. None declared.

Funding

This work was supported by the North American Brain Tumor Consortium [CA62399].

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