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Independent association of extent of resection with survival in patients with malignant brain astrocytoma

Clinical article

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Object. With recent advances in the adjuvant treatment of malignant brain astrocytomas, it is increasingly debated whether extent of resection affects survival. In this study, the authors investigate this issue after primary and revision resection of these lesions.

Methods. The authors retrospectively reviewed the cases of 1215 patients who underwent surgery for malignant brain astrocytomas (World Health Organization [WHO] Grade III or IV) at a single institution from 1996 to 2006. Patients with deep-seated or unresectable lesions were excluded. Based on MR imaging results obtained < 48 hours after surgery, gross-total resection (GTR) was defined as no residual enhancement, near-total resection (NTR) as having thin rim enhancement of the resection cavity only, and subtotal resection (STR) as having residual nodular enhancement. The independent association of extent of resection and subsequent survival was assessed via a multivariate proportional hazards regression analysis.

Results. Magnetic resonance imaging studies were available for review in 949 cases. The mean age and mean Karnofsky Performance Scale (KPS) score at time of surgery were 51 ± 16 years and 80 ± 10, respectively. Surgery consisted of primary resection in 549 patients (58%) and revision resection for tumor recurrence in 400 patients (42%). The lesion was WHO Grade IV in 700 patients (74%) and Grade III in 249 (26%); there were 167 astrocytomas and 82 mixed oligoastrocytoma. Among patients who underwent resection, GTR, NTR, and STR were achieved in 330 (35%), 388 (41%), and 231 cases (24%), respectively. Adjusting for factors associated with survival (for example, age, KPS score, Gliadel and/or temozolomide use, and subsequent resection), GTR versus NTR ($p < 0.05$) and NTR versus STR ($p < 0.05$) were independently associated with improved survival after both primary and revision resection of glioblastoma multiforme (GBM). For primary GBM resection, the median survival after GTR, NTR, and STR was 13, 11, and 8 months, respectively. After revision resection, the median survival after GTR, NTR, and STR was 11, 9, and 5 months, respectively. Adjusting for factors associated with survival for WHO Grade III astrocytoma (age, KPS score, and revision resection), GTR versus STR ($p < 0.05$) was associated with improved survival. Gross-total resection versus NTR was not associated with an independent survival benefit in patients with WHO Grade III astrocytomas. The median survival after primary resection of WHO Grade III (mixed oligoastrocytomas excluded) for GTR, NTR, and STR was 58, 46, and 34 months, respectively.

Conclusions. In the authors' experience with both primary and secondary resection of malignant brain astrocytomas, increasing extent of resection was associated with improved survival independent of age, degree of disability, WHO grade, or subsequent treatment modalities used. The maximum extent of resection should be safely attempted while minimizing the risk of surgically induced neurological injury. *(DOI: 10.3171/2008.4.17536)*

Key Words • extent of resection • glioblastoma multiforme • malignant glioma • survival

Malignant astrocytomas, which include AAs (WHO Grade III) and GBMs (WHO Grade IV), are the most common malignant primary central nervous system tumors in adults.[10] Despite advances in medical and surgical therapy, the median survival remains < 2 years.[4,8,10] Although mean survival for patients with GBMs remains short, individual patient survival is heterogeneous.[36] As a result, there has been an emphasis on studying factors that are prognostic of improved survival in patients with malignant astrocytomas.[19]

For many solid organ malignant tumors, GTR with clear margins is associated with extended survival.[15,41]

Abbreviations used in this paper: AA = anaplastic astrocytoma; CI = confidence interval; GBM = glioblastoma multiforme; GTR = gross-total resection; KPS = Karnofsky Performance Scale; NTR = near-total resection; RR = relative risk; STR = subtotal resection; WHO = World Health Organization.

However, the effects of extensive resection on prolonging survival in patients with malignant astrocytomas is less clear.[1,11,27,29,32,37] Extensive resection of malignant astrocytomas is made difficult because these tumors are frequently invasive and widely infiltrative, and often involve eloquent areas.[7] Improvements in surgical adjuncts including functional MR imaging,[2,28] cortical mapping,[12,31,38] and intraoperative MR imaging[24] have made it possible to achieve extensive resection of these lesions. However, the infiltrative nature of malignant astrocytomas precludes total tumor removal. It therefore remains unclear whether more extensive resection of malignant astrocytomas is associated with prolonged survival. We set out to determine if the extent of resection was associated with survival in our institutional experience with malignant astrocytomas.

Methods

We retrospectively identified all patients who had undergone resection of malignant astrocytomas (WHO Grade III or IV)[22] at our academic institution from 1996–2007. Deep-seated or eloquent lesions not amenable to complete resection were excluded from the study. Presenting clinical, radiological, operative, and hospital course records were retrospectively reviewed. Outpatient clinic notes from both neurosurgical and neurooncological follow-up visits were reviewed. Demographics, presenting symptoms and signs, degree of resection, operative course, perioperative complications, adjuvant radiotherapy and chemotherapy regimens, and date of death were recorded according to the public Social Security Death Index database (http://www.ancestry.com). A reviewed operative case was defined as primary resection if the resection was a first-time resection for that patient. If the reviewed operative case was a revision resection of progressive tumor, it was classified as revision resection. Tumor grade was histologically confirmed as WHO Grade III or IV. For WHO Grade III astrocytomas, mixed oligoastrocytomas were identified and assessed as a prognostic variable.

Tumor characteristics on pre- and postoperative MR images (obtained < 48 hours postoperatively) were assessed at the time of surgery by a neuroradiologist. Degree of resection was retrospectively classified by a blinded reviewer based on the neuroradiologist's dictations as GTR if no residual enhancement was noted on postoperative MR imaging, NTR if only rim enhancement of the resection cavity was noted on postoperative MR imaging, or STR if residual nodular enhancement was noted on postoperative MR imaging. In the small subset of WHO Grade III astrocytomas that did not demonstrate enhancement on preoperative MR imaging, FLAIR abnormalities were used to determine the preoperative extent of tumor (similar to assessing low-grade gliomas). In these few cases, the postoperative presence of residual nodular FLAIR signal that corresponded to tumor on preoperative MR imaging was classified as STR.

During the review period, all patients underwent postoperative radiotherapy consisting of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily 5 days per week over a period of 6 weeks, for a total dose of 60 Gy. Given the reported survival benefit observed with Gliadel wafer implantation (2.87% 1,3-bis-(2-chloroethyl)-1-nitrosourea; MGI Pharma)[21,39,40] and postoperative temozolomide therapy,[35] we recorded whether patients received Gliadel wafer implantation or adjuvant postoperative temozolomide therapy at any point after surgery in addition to radiotherapy. It was also recorded whether patients underwent a subsequent resection for tumor progression at a later date. Because the time frame in which subsequent resection was performed may have prognostic consequence, we classified subsequent resection as early if performed < 12 months after resection and late if performed > 12 months after surgery.

Statistical Analysis

Parametric data were expressed as means ± standard deviations and compared via the Student t-test. Nonparametric data were expressed as median values (interquartile range) and compared via the Mann–Whitney U-test. Percentages were compared via the chi-square test or Fisher exact test based on sample size. Survival as a function of time after resection was expressed as estimated Kaplan–Meier plots. Three separate models (Cox models) were established to assess the independent association of GTR or NTR versus STR with overall survival for: 1) primary GBM resection, 2) revision GBM resection, and 3) resection of WHO Grade III astrocytoma. Variables associated with survival in univariate analysis (proportional hazards regression analysis) were included in the multivariate Cox model if $p < 0.10$. Variables with probability values > 0.05 were then removed from the multivariate model in a stepwise fashion.

Results

Patient Population

We reviewed 1215 consecutive surgical procedures for this study. Tumors were deep seated or in eloquent locations precluding complete resection in 211 cases; these were excluded from the study. Among the 1004 remaining cases, postoperative MR images were not obtained in 55 cases (5.6%) due to MR imaging incompatibility or patient refusal, resulting in the total inclusion of 949 cases. Primary resection was performed in 549 patients (58%) and secondary resection in 400 (42%). Tumor grades were WHO Grade IV in 700 cases (74%) and WHO Grade III in 249 cases (26%). Of the WHO Grade III tumors, 167 were astrocytomas and 82 were mixed oligoastrocytoma. Gross-total resection, NTR, and STR were achieved in 330 (35%), 388 (41%), and 231 (24%) cases, respectively. Patient demographics, clinical characteristics, and treatment modalities stratified by extent of resection are listed in Table 1. Surgical site infection and meningitis occurred in 22 (2%) and 8 (0.8%) patients. Perioperative deep vein thrombosis and pulmonary embolism occurred in 40 (4%) and 23 (2%) patients, respectively. Surgical morbidity did not differ as a function of extent of resection.

All patients who underwent primary resection received adjuvant radiotherapy, 279 patients (29%) received Gliadel wafer implantation at the time of surgery, and 258 patients (27%) received postoperative temozolomide. Te-

Table 1: Summary of patient characteristics stratified by resection type for malignant astrocytoma*

Variable	GTR (330 patients)	NTR (388 patients)	STR (231 patients)
age (yrs)	49 ± 16	51 ± 15	51 ± 16
KPS score	80 ± 10	80 ± 10	80 ± 10
male sex	189 (57)	236 (61)	139 (60)
Caucasian	225 (68)	280 (72)	134 (58)
hypertension	36 (11)	35 (9)	27 (12)
coronary artery disease	2 (1)	4 (1)	8 (3)
preop motor deficit	48 (15)	95 (24)	67 (29)
preop language deficit	39 (12)	64 (16)	40 (17)
preop epilepsy	57 (17)	70 (18)	96 (42)
frontal lesion	164 (49)	189 (49)	116 (50)
parietal lesion	65 (20)	88 (22)	38 (16)
temporal lesion	80 (24)	87 (22)	64 (28)
occipital lesion	21 (6)	24 (6)	13 (5)
WHO Grade III	91 (27)	68 (18)	90 (38)
astrocytoma	75 (22)	49 (13)	43 (18)
oligo or mixed astro-oligo	16 (5)	19 (5)	47 (20)
revision resection	115 (35)	168 (43)	117 (50)
Gliadel wafers	132 (40)	108 (28)	39 (17)
postop TMZ†	106 (32)	103 (27)	49 (21)
2nd op <12 mos after 1st	37 (11)	36 (9)	8 (3)
2nd op >24 mos after 1st	22 (7)	16 (4)	5 (2)
new postop motor deficit	19 (6)	28 (6)	16 (6)
new postop language deficit	9 (3)	26 (6)	13 (6)
postop ICH	2 (1)	8 (2)	1 (0.5)
surgical site infection	5 (2)	14 (4)	3 (1)
LOS (days)	4 ± 2	5 ± 1.5	5 ± 2

* Data are given as number of patients (%) unless otherwise indicated. Abbreviations: ICH = intracerebral hemorrhage; LOS = length of stay; TMZ = temozolomide.

† Includes TMZ administered concomitantly with radiotherapy or as delayed adjuvant treatment.

mozolomide was administered concomitantly with radiotherapy in 102 patients via the protocol described by Stupp et al.,[35] and as a delayed adjuvant therapy in 172 patients. Median survival after resection of malignant astrocytoma (WHO Grade III or IV) was 12 months. Six hundred and seventy patients (71%) died after tumor resection during the 10-year review period. The mean follow-up period in the surviving patients was 18 months.

Extent of Resection for Primary GBM

Primary resection was performed in 451 patients with GBMs. The median survival after GTR, NTR, and STR was 13, 11, and 8 months, respectively (Fig. 1 *upper*). Adjusting for all variables independently associated with survival in this series (age, KPS, Gliadel wafer implantation, adjuvant temozolomide therapy, and subsequent resection > 12 months after primary resection), both NTR ($p = 0.002$) and GTR ($p = 0.001$) were independently associated with increased survival compared with STR (Table 2). Near-total resection versus STR (RR 0.61, 95% CI 0.46–0.89; $p = 0.002$) was independently associated with a 39% reduction in relative risk of overall mortality (Table 1). Gross-total resection versus NTR (RR 0.85, 95% CI 0.69–0.96; $p = 0.040$) was independently associated with a further 15% risk reduction in overall mortality rate.

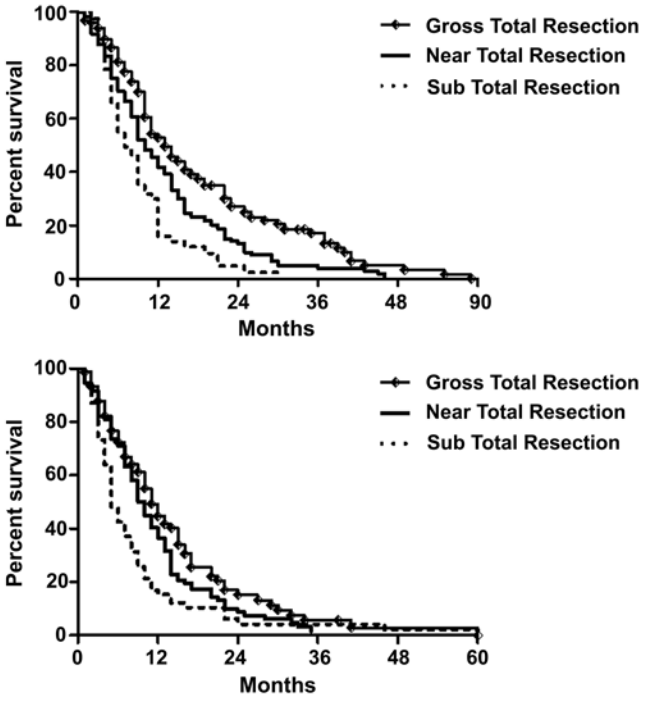

FIG. 1. Estimated Kaplan–Meier plot of survival after primary *(upper)* and revision resection *(lower)* of GBM. In both primary and secondary resection, patients who underwent NTR experienced an independent survival benefit compared with patients who underwent STR ($p < 0.002$). Patients who received GTR experienced an independent survival benefit compared with patients receiving NTR ($p < 0.05$). After primary GBM resection, the median survival after GTR, NTR, or STR was 13, 11, and 8 months, respectively. For revision surgery, median survival after GTR, NTR, and STR was 11, 9, and 5 months, respectively, from time of revision surgery. (GTR = no residual enhancement on MR; NTR = rim enhancement of resection cavity on MR imaging; STR = residual nodular enhancement).

Extent of Resection for Revision GBM

Two hundred and ninety-four patients underwent revision resection after progression of a previously resected GBM. The median survival after GTR, NTR, and STR was 11, 9, and 5 months, respectively (Fig. 1 *lower*). Adjusting for all variables independently associated with survival in this series (age, KPS, and adjuvant temozolomide therapy), both NTR ($p = 0.004$) and GTR ($p = 0.002$) were independently associated with increased survival compared with STR. Near-total resection versus STR (RR 0.63, 95% CI 0.56–0.92; $p = 0.002$) was independently associated with a 37% reduction in relative risk of overall mortality (Table

Table 2: Variables associated with overall survival after primary resection of GBM in univariate and multivariate proportional hazards regression analysis (Cox model)*

Variable	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	p Value	Hazard Ratio	p Value
age (yrs)†	1.029	0.001	1.023	0.001
KPS score†	0.983	0.001	0.988	0.018
male sex	0.923	0.396	NA	NA
Caucasian	1.078	0.534	NA	NA
hypertension	1.713	0.007	1.342	0.124
coronary artery disease	1.752	0.101	NA	NA
preop motor deficit	1.482	0.002	1.412	0.156
preop language deficit	1.351	0.044	1.213	0.212
preop epilepsy	0.898	0.536	NA	NA
frontal lesion	0.989	0.954	NA	NA
parietal lesion	1.102	0.449	NA	NA
temporal lesion	0.963	0.743	NA	NA
occipital lesion	0.895	0.608	NA	NA
hemorrhagic lesion	1.067	0.722	NA	NA
GTR	0.377	0.001	0.449	0.001
NTR	0.567	0.001	0.614	0.002
Gliadel wafers	0.811	0.050	0.793	0.056
postop TMZ‡	0.476	0.001	0.546	0.001
2nd op <12 mos after 1st	0.814	0.167	NA	NA
2nd op >12 mos after 1st	0.349	0.001	0.403	0.003

* Variables associated with survival in univariate analysis ($p < 0.10$) were included in the multivariate model. Decreasing age, increasing KPS, increasing extent of resection, Gliadel wafer, temozolomide, and subsequent resection of late recurrence were independently associated with improved overall survival. Patients who received either GTR or NTR experienced an independent survival benefit compared with patients who received STR, independent of disability or subsequent treatments. Abbreviation: NA = not applicable.

† Increasing variable.

‡ Includes TMZ administered concomitantly with radiotherapy or as delayed adjuvant treatment.

Table 3: Univariate and multivariate proportional hazards analysis of variables associated with overall survival after revision resection of GBM*

Variable	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	p Value	Hazard Ratio	p Value
age (yrs)†	1.019	0.001	1.015	0.004
KPS score†	0.989	0.008	0.990	0.009
male sex	0.910	0.439	NA	NA
Caucasian	1.082	0.548	NA	NA
hypertension	1.149	0.571	NA	NA
coronary artery disease	1.26	0.742	NA	NA
preop motor deficit	1.372	0.032	1.121	0.529
preop language deficit	1.046	0.813	NA	NA
preop epilepsy	2.542	0.234	NA	NA
frontal lesion	0.871	0.283	NA	NA
parietal lesion	0.989	0.992	NA	NA
temporal lesion	1.315	0.131	NA	NA
occipital lesion	0.971	0.918	NA	NA
hemorrhagic lesion	1.001	0.997	NA	NA
GTR	0.535	0.001	0.566	0.002
NTR	0.617	0.002	0.630	0.004
Gliadel wafers	0.840	0.119	NA	NA
postop TMZ	0.587	0.002	0.586	0.003
subsequent resection <12 mos after 1st	0.573	0.109	0.535	0.081

* Variables associated with survival in univariate analysis ($p < 0.10$) were included in the multivariate model. Patients receiving either GTR or NTR experienced an independent survival benefit compared with patients receiving STR independent of disability or subsequent treatment modalities.

† Increasing variable.

3). Gross-total resection versus NTR (RR 0.90, 95% CI 0.69–0.99; $p = 0.048$) was independently associated with a further 10% risk reduction in the overall mortality rate.

Extent of Resection for AA

Two hundred forty-nine patients underwent resection of WHO Grade III astrocytomas (167 astrocytomas and 82 mixed oligoastrocytomas). The median survival period after primary resection of AA (mixed oligoastrocytomas excluded) for GTR, NTR, and STR was 58, 46, and 34 months, respectively (Fig. 2). Adjusting for all variables independently associated with survival in this series (age, KPS score, and revision resection), GTR was independently associated with increased survival over STR ($p = 0.048$), and NTR was associated with a trend of increased survival compared with STR ($p = 0.070$; Table 4). Gross-total resection was not associated with a survival benefit ($p = 0.348$) compared with NTR (Fig. 2).

Discussion

In our experience of nearly 1000 craniotomies for malignant astrocytoma resection, we observed survival benefits with both GTR and NTR, independent of age, degree of disability, or subsequent treatment modalities. Although patients with no evidence of postoperative residual enhancement demonstrated the greatest survival benefit, an independent survival benefit was also observed in patients with residual linear enhancement of the resection cavity (NTR). In fact, NTR and STR were associated with a 3- and 4-month survival benefit after primary and secondary resection, respectively. These observations suggest that an increasing extent of tumor resection may be associated with prolonged survival in patients with malignant astrocytomas.

Malignant astrocytomas are characterized by their invasive and infiltrative nature, making curative resection unlikely.[7] In fact, in the 1930s, Walter Dandy performed

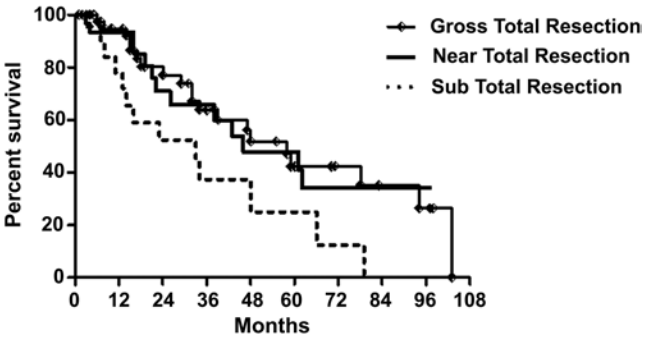

FIG. 2. Estimated Kaplan–Meier plot of survival after primary resection of AAs (mixed oligoastrocytoma excluded). Both GTR and NTR were associated with a survival benefit versus STR. Gross-total resection versus NTR was not associated with improved survival. After GTR, NTR, or STR, median survival was 58, 46, and 34 months, respectively. The 5-year survival for patients undergoing GTR, NTR, and STR was 42, 41, and 12%, respectively.

hemispherectomies, and survival was still < 2 years.[9] However, given the primitive imaging available at the time, it is uncertain whether these tumors were fully resected. Stupp and colleagues[35] reported a median survival of 14.6 months in patients with GBMs after resection, radiotherapy, and temozolomide chemotherapy. Brem et al.[3] found that the use of biodegradable carmustine polymers increased survival in patients with recurrent malignant gliomas from 23 to 31 weeks after revision resection. However, it remains unclear whether the extent of resection of these lesions was associated with improved survival.[14,25,27] Intuitively, one would predict that extensive resection should prolong survival, as it has with other solid organ malignant tumors.[15,41] Tumor recurrence for malignant astrocytomas commonly occurs close to the tumor margin, where there is increased tumor cell density at the periphery of the tumor, and a sharp drop off in cell numbers as the distance from the resection cavity increases.[33] Extensive resection theoretically decreases the number of remaining cells, making the decreased tumor burden more responsive to adjuvant therapy and potentially prolonging patient survival.[1,5,6,11,17,29,32,37]

Recent advances in surgical adjuncts include intraoperative image-guided stereotactic surgery, functional MR imaging,[2,28] cortical mapping,[13,31,38] and intraoperative MR imaging.[24] Although these additions are intended to assist in increasing the extent of tumor resection, it remains unclear whether the extent of resection is associated with improved survival. To date, there have been 4 systematic reviews of the literature.[14,23,25,30] These reviews were limited in that they did not control for confounding variables, were often underpowered, included biopsies in their analyses, and often included studies conducted before 1990.[14,23,25,30] In fact, these reviews stated that the lack of good scientific evidence precluded any definitive statement on the effects of extensive resection and survival in patients with malignant astrocytomas.[14,23,25,30]

More recent studies have also been limited. Lacroix et al.[18] found that after analyzing 416 consecutive cases of GBM, resections greater than 98% of the tumor were significantly associated with improved survival. The limitation of that study was that 44% of the patients in it had been treated previously at other institutions and adjuvant therapy was not included in the survival analysis, which may hinder accurate survival analyses. Buckner[4] and Laws and colleagues[20] also concluded that patients who underwent resection had improved survival times compared with patients who underwent biopsy sampling. The effects of GTR, NTR, and STR on survival therefore remain unclear.

By adjusting for factors that may impact survival, we found that the extent of resection is associated with prolonged survival, and both GTR and NTR were independently associated with prolonged survival. This was observed for primary and revision resection of GBM, independent of age, KPS score, subsequent resection, and the 2 adjuvant therapies proven to influence survival (Gliadel and temozolomide). Furthermore, GTR was associated with increased survival compared with NTR in both primary and revision GBM resection. Although GTR was

Table 4: Variables associated with overall survival after resection of WHO Grade III astrocytomas in univariate and multivariate proportional hazards regression analysis*

	Univariate Analysis		Multivariate Analysis	
Variable	Hazard Ratio	p Value	Hazard Ratio	p Value
age (yrs)†	1.029	0.002	1.033	0.001
KPS score†	0.980	0.036	0.977	0.012
male sex	0.950	0.811	NA	NA
Caucasian	1.254	0.337	NA	NA
hypertension	1.143	0.283	NA	NA
preop motor deficit	2.131	0.005	1.521	0.208
preop language deficit	2.178	0.006	1.982	0.075
preop epilepsy	1.235	0.546	NA	NA
frontal lesion	0.915	0.675	NA	NA
parietal lesion	0.606	0.178	NA	NA
temporal lesion	1.273	0.308	NA	NA
occipital lesion	2.431	0.113	NA	NA
hemorrhagic lesion	0.553	0.405	NA	NA
mixed oligo-astro	0.508	0.028	0.704	0.188
revision resection	1.851	0.004	1.575	0.031
GTR	0.587	0.038	0.589	0.048
NTR	0.600	0.049	0.653	0.070
Gliadel wafers	1.213	0.506	NA	NA
postop TMZ	0.835	0.402	NA	NA
2nd resection <12 mos after 1st	0.884	0.791	NA	NA
2nd resection >12 mos after 1st	0.549	0.067	0.554	0.116

* Variables associated with survival in univariate analysis ($p < 0.10$) were included in the multivariate model. Decreasing age, increasing KPS score, revision versus primary resection, and GTR were independently associated with improved overall survival. Patients receiving NTR experienced a trend toward a survival benefit compared with patients receiving STR. Mixed astro-oligodendroglioma was not associated with an independent survival advantage for this WHO Grade III series.
† Increasing variable.

associated with a further survival advantage over NTR in the surgical treatment of GBM, GTR and NTR demonstrated similar survival benefits compared with STR in the treatment of AAs. The presence of residual nodular enhancement on postoperative MR images (STR) was associated with a 1-year survival disadvantage in patients who underwent primary resection of AA.

This disadvantage may be due to the fact that extensive resection may decrease the tumor burden to a point that radiotherapy and chemotherapy are more effective. A lower tumor load has been shown to increase the efficacy of adjuvant chemotherapy and radiotherapy in killing remaining tumor cells and increasing patient survival.[26,34] Besides increasing survival, safe and extensive resection may be associated with other secondary benefits. Extensive resection may provide increased symptomatic relief and neurological improvement,[13] a more accurate diagnosis,[16] and more tissue for scientific research. Advances in surgical adjuncts including functional MR imaging,[2,28] cortical mapping,[12,31,38] and intraoperative MR imaging[24] have made it safer to achieve extensive resection of these malignant lesions. It should be realized that the effects of extensive resection on survival might be partially affected by tumor location, where deeper tumors are often times less resectable and therefore more prone to poorer outcomes. However, the decreased survival seen in patients with a thin rim-enhancement pattern (NTR) versus no residual enhancement (GTR) suggests a true relationship between the degree of postoperative tumor burden and subsequent survival. Our philosophy has been to resect high-grade astrocytomas as much as possible without causing new neurological deficits to maximize quality functional survival.

This study is inherently limited by its retrospective design, and as a result, no direct causal relationships can be inferred from our observations. Prospective studies or randomized controlled trials examining extent of resection, although not pragmatically feasible, would provide better data to guide clinical decision making. Furthermore, volumetric measurement of postoperative tumor volume was not assessed as a continuous variable. Rather, we stratified degree of resection based on 3 clinically applicable categories. We attempted to limit the bias associated with this approach by strictly defining the extent of resection and controlling for each variable known to have an effect on survival. Furthermore, tumors amenable to GTR may also have been biologically more favorable even though all tumors were infiltrating high-grade astrocytomas. Given this large patient series, statistical control, and a relatively precise outcome measure, we believe our findings offer useful insights into the prognostic value of postoperative MR images and help justify taking measures to increasing the extent of resection in patients with malignant astrocytomas.

Conclusions

In our experience, an increased extent of resection of primary or recurrent malignant astrocytoma was associated with improved survival independent of age, degree of disability, or subsequent treatment modalities used. Maximum extent of resection should be safely attempted while minimizing the risk of surgically induced neurological injury.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

1. Barker FG II, Prados MD, Chang SM, Gutin PH, Lamborn KR, Larson DA, et al: Radiation response and survival time in patients with glioblastoma multiforme. **J Neurosurg 84:**442–448, 1996
2. Berman JI, Berger MS, Chung SW, Nagarajan SS, Henry RG: Accuracy of diffusion tensor magnetic resonance imaging tractography assessed using intraoperative subcortical stimulation mapping and magnetic source imaging. **J Neurosurg 107:**488–494, 2007
3. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, et al: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-Brain Tumor Treatment Group. **Lancet 345:**1008–1012, 1995
4. Buckner JC: Factors influencing survival in high-grade gliomas. **Semin Oncol 30:**10–14, 2003
5. Butowski N, Lamborn KR, Berger MS, Prados MD, Chang SM: Historical controls for phase II surgically based trials requiring gross total resection of glioblastoma multiforme. **J Neurooncol 85:**87–94, 2007
6. Chang SM, Parney IF, Huang W, Anderson FA Jr, Asher AL, Bernstein M, et al: Patterns of care for adults with newly diagnosed malignant glioma. **JAMA 293:**557–564, 2005
7. Claes A, Idema AJ, Wesseling P: Diffuse glioma growth: a guerilla war. **Acta Neuropathol 114:**443–458, 2007
8. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. **J Natl Cancer Inst 85:**704–710, 1993
9. Dandy WE: Removal of right cerebral hemisphere for certain tumors with hemiplegia. **JAMA 90:**823–825, 1928
10. DeAngelis LM: Brain tumors. **N Engl J Med 344:**114–123, 2001
11. Dinapoli RP, Brown LD, Arusell RM, Earle JD, O'Fallon JR, Buckner JC, et al: Phase III comparative evaluation of PCNU and carmustine combined with radiation therapy for high-grade glioma. **J Clin Oncol 11:**1316–1321, 1993
12. Guggisberg AG, Honma SM, Findlay AM, Dalal SS, Kirsch HE, Berger MS, et al: Mapping functional connectivity in patients with brain lesions. **Ann Neurol 63:**193-203, 2007
13. Hentschel SJ, Lang FF: Current surgical management of glioblastoma. **Cancer J 9:**113–125, 2003
14. Hess KR: Extent of resection as a prognostic variable in the treatment of gliomas. **J Neurooncol 42:**227–231, 1999
15. House MG, Gonen M, Jarnagin WR, D'Angelica M, Dematteo RP, Fong Y, et al: Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. **J Gastrointest Surg 11:**1549–1555, 2007
16. Jackson RJ, Fuller GN, Abi-Said D, Lang FF, Gokaslan ZL, Shi WM, et al: Limitations of stereotactic biopsy in the initial management of gliomas. **Neuro-oncol 3:**193–200, 2001
17. Keles GE, Chang EF, Lamborn KR, Tihan T, Chang CJ, Chang SM, et al: Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. **J Neurosurg 105:**34–40, 2006
18. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al: A multivariate analysis of 416 patients with

glioblastoma multiforme: prognosis, extent of resection, and survival. **J Neurosurg 95:**190–198, 2001
19. Lamborn KR, Chang SM, Prados MD: Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. **Neuro-oncol 6:**227–235, 2004
20. Laws ER, Parney IF, Huang W, Anderson F, Morris AM, Asher A, et al: Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. **J Neurosurg 99:**467–473, 2003
21. Lawson HC, Sampath P, Bohan E, Park MC, Hussain N, Olivi A, et al: Interstitial chemotherapy for malignant gliomas: the Johns Hopkins experience. **J Neurooncol 83:**61–70, 2007
22. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al: The 2007 WHO Classification of Tumours of the Central Nervous System. **Acta Neuropathol 114:**97–109, 2007
23. Metcalfe SE, Grant R: Biopsy versus resection for malignant glioma. **Cochrane Database Syst Rev 3:**CD002034, 2005
24. Muragaki Y, Iseki H, Maruyama T, Kawamata T, Yamane F, Nakamura R, et al: Usefulness of intraoperative magnetic resonance imaging for glioma surgery. **Acta Neurochir Suppl 98:** 67–75, 2006
25. Nazzaro JM, Neuwelt EA: The role of surgery in the management of supratentorial intermediate and high-grade astrocytomas in adults. **J Neurosurg 73:**331–344, 1990
26. Ng WH, Wan GQ, Too HP: Higher glioblastoma tumour burden reduces efficacy of chemotherapeutic agents: in vitro evidence. **J Clin Neurosci 14:**261–266, 2007
27. Pang BC, Wan WH, Lee CK, Khu KJ, Ng WH: The role of surgery in high-grade glioma–is surgical resection justified? A review of the current knowledge. **Ann Acad Med Singapore 36:**358–363, 2007
28. Pirzkall A, Li X, Oh J, Chang S, Berger MS, Larson DA, et al: 3D MRSI for resected high-grade gliomas before RT: tumor extent according to metabolic activity in relation to MRI. **Int J Radiat Oncol Biol Phys 59:**126–137, 2004
29. Pope WB, Sayre J, Perlina A, Villablanca JP, Mischel PS, Cloughesy TF: MR imaging correlates of survival in patients with high-grade gliomas. **AJNR Am J Neuroradiol 26:** 2466–2474, 2005
30. Quigley MR, Maroon JC: The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. **Neurosurgery 29:**385–389, 1991
31. Schiffbauer H, Berger MS, Ferrari P, Freudenstein D, Rowley HA, Roberts TP: Preoperative magnetic source imaging for brain tumor surgery: a quantitative comparison with intraoperative sensory and motor mapping. **J Neurosurg 97:**1333–1342, 2002
32. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, et al: Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. **Int J Radiat Oncol Biol Phys 26:** 239–244, 1993
33. Sneed PK, Gutin PH, Larson DA, Malec MK, Phillips TL, Prados MD, et al: Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. **Int J Radiat Oncol Biol Phys 29:**719–727, 1994
34. Stewart LA: Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. **Lancet 359:**1011–1018, 2002
35. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. **N Engl J Med 352:**987–996, 2005
36. Tait MJ, Petrik V, Loosemore A, Bell BA, Papadopoulos MC: Survival of patients with glioblastoma multiforme has not improved between 1993 and 2004: analysis of 625 cases. **Br J Neurosurg 21:**496–500, 2007
37. Vecht CJ, Avezaat CJ, van Putten WL, Eijkenboom WM, Stefanko SZ: The influence of the extent of surgery on the neurological function and survival in malignant glioma. A retrospective analysis in 243 patients. **J Neurol Neurosurg Psychiatry 53:**466–471, 1990
38. Walker JA, Quinones-Hinojosa A, Berger MS: Intraoperative speech mapping in 17 bilingual patients undergoing resection of a mass lesion. **Neurosurgery 54:**113–118, 2004
39. Westphal M, Ram Z, Riddle V, Hilt D, Bortey E: Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. **Acta Neurochir (Wien) 148:**269–275, 2006
40. Whittle IR, Lyles S, Walker M: Gliadel therapy given for first resection of malignant glioma: a single centre study of the potential use of Gliadel. **Br J Neurosurg 17:**352–354, 2003
41. Yoshimoto M, Tada K, Nishimura S, Makita M, Iwase T, Kasumi F, et al: Favourable long-term results after surgical removal of lung metastases of breast cancer. **Breast Cancer Res Treat** [epub ahead of print], 2007

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