Treatment of Malignant Astrocytomas with Repetitive Resections: A Longitudinal Study

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Abstract

Background: The impact of repeated surgical resection on the survivorship of patients with malignant astrocytomas is an issue of some controversy in the medical literature.

Objectives: To clarify this issue through a retrospective analysis of treatment outcomes in a brain tumor clinic.

Methods: The patient records from the Brain Tumor Clinic at Hahnemann University Hospital for the period 1988 to 2000 were reviewed. From these, 112 cases of glioblastoma multiforme and 50 cases of anaplastic astrocytoma were chosen for analysis.

Results: The group of patients with glioblastomas showed a median survival of 415 days. When analyzed as subgroups based on the number of surgical resections, the median survival was 393 days in the group with biopsy only, 380 days in the group with one surgical resection, and 548 days in the group with two or three resections. Using the Kaplan-Meier method to generate survival plots and the log rank test to compare groups, repeat debulking was found to be a significant predictor of survival ($P = 0.173$). The group of patients with anaplastic astrocytomas showed a median survival of 1,311 days. When analyzed by subgroups, the patients with biopsy only had a median survival of 544 days, those with one debulking 1,589 days and those with two or three debulkings 1,421 days. There was a trend toward increased survival with debulking and the log rank test again showed statistical significance ($P = 0.1998$).

Conclusions: This study indicates that repeated surgical resections offer increased survival for both glioblastomas and anaplastic astrocytomas.

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The last two decades have seen the advent of several new therapeutic options in the treatment of malignant gliomas. These include the surgical modalities of stereotactic biopsy and computer image-guided resections [1,2]; the radiotherapeutic options of partial brain irradiation, altered fractionation schedules, conformal therapy and brachytherapy [3]; and the chemotherapeutic options of new systemic agents and combinations, depot administration of agents directly to the tumor bed, and novel systemic biologic and molecular agents [4]. As a result, numerous trials have been instituted to test the efficacy of these options as monotherapies or combination therapies for the treatment of these tumors. Despite this, considerable debate still remains regarding some basic aspects of the treatment, in particular with regard to the efficacy of tumor resection as opposed to biopsy. While there is little question that aggressive tumor resection alleviates intracranial pressure and focal neurological deficits due to mass effect, the degree to which it influences the long-term patient outcome is less clear.

In our brain tumor clinic, patients with malignant astrocytomas are routinely offered aggressive tumor resection at the time of initial diagnosis, in addition to standard and conformal radiotherapies and standard chemotherapy. Since 1987, patients have been offered additional systemic therapy with ^{125}I-labeled monoclonal antibody to the epidermal growth factor receptor (EGFr-425) which is commonly expressed in high levels on the plasma membrane of gliomas. The results of this therapeutic option have been reported previously [5].

In addition, we have routinely offered these patients repeated aggressive surgical resection to manage intracranial hypertension and the associated deficits due to recurrent disease. The aim of this study was to assess retrospectively the degree to which the treatment option of repeated aggressive resection affected longevity in our patients with anaplastic astrocytoma and glioblastomas multiforme.

Materials and Methods

Records dating from 1988 to 2000 were selected from the data bank of the Hahnemann University Hospital Brain Tumor Clinic. Patients presenting to the Brain Tumor Clinic with central nervous system neoplasms received a preoperative workup that included history, physical examination, standard laboratory studies, computed tomography and/or magnetic resonance imaging of the brain. At the initial surgery a tumor biopsy was usually performed, and whenever possible this was followed by aggressive surgical debulking at the initial sitting or shortly thereafter. All patients with malignant astrocytomas received definitive postoperative radiation therapy. Following that, when tumor recurrences resulted in deterioration in patient function due to mass effect that was not easily manageable with medical therapy, surgery was offered to the patient and family

as an alternative. All patients were also treated with intravenous iodine-125 labeled antibody directed against EGFr-425 as reported previously [5]. Selected patients also received chemotherapy.

For the purposes of this study, the biopsy or initial resection materials of all patients with diagnoses of anaplastic astrocytoma, malignant astrocytoma, astrocytoma grade 2, 3, 4, or glioblastoma were reviewed. These were restratified as either anaplastic astrocytoma or glioblastoma according to WHO criteria. These methods allowed us to select 50 cases of anaplastic astrocytoma and 112 cases of glioblastoma managed in the Brain Tumor Clinic that were appropriate for further analysis. The clinical details of these cases including survival following initial surgery, radiotherapy, chemotherapy and monoclonal antibody therapy are summarized in Table 1 for glioblastomas and Table 2 for anaplastic astrocytomas.

Survival plots were generated using the Kaplan-Meier method. The log rank test was used to compare groups.

Results

Glioblastoma multiforme

We analyzed 109 patients, 64 men and 45 women with a median age of 54 years, who presented to the Brain Tumor Clinic with a median Karnofsky Performance Scale of 80. All patients analyzed succumbed to their disease. These data are referenced in Table 1. Median survival for the group as a whole was 415 days while the mean survival was 570 days [Table 2]. Figure 1 shows the survival data as a Kaplan-Meier plot.

The group that was not surgically debulked consisted of 17 patients – 10 men and 7 women with a median age of 52 years and median KPS of 80. Median survival for this group was 393 days, mean survival 510 days. Fifty-seven patients with glioblastoma received one debulking. Of these, 31 were men and 26 were women, median age 54 years and median KPS 70. Median survival was 380 days and the mean was 446. Two or three debulkings were performed on 33 patients, 21 of them men and 12 women with a median age of 48 and median KPS 80. The median survival was 548 days and the mean survival 813 days. Again, the patient data are referenced in Table 1, survival data in Table 2 and Kaplan-Meier plots of the data are shown in Figure 1.

Inspection of the 95% confidence intervals of both the median and mean survivals ($\pm$ standard error) reveals no clear difference between the group of patients who received only one resection when compared to the group that received no resection and all glioblastoma patients. However, inspection of the group that received multiple (two or three) debulkings shows 95% confidence intervals for median survival of 484–612 days and for mean survival of 492–1,134 days. The log rank test revealed debulking to be significant with a P value of 0.173 assuming 2 degrees of freedom.

EGFr-425 = epidermal growth factor receptor
KPS = Karnofsky Performance Scale

Table 1. Patient data

Tumor histology	No. of tumor resections	No. of patients	Male/female (numbers and ratio)	Median age of patients at presentation (yr)	Median KPS at presentation
Glioblastoma	0	17	10/7 : 1.4	52	80
	1	57	31/26 : 1.2	54	70
	2-3	33	33/21 : 1.6	48	80
	Total	107	63/44 : 1.4	54	80
Anaplastic astrocytoma	0	16	14/2 : 7	42	70
	1	24	18/6 : 3	42	80
	2-3	10	5/5 : 1	37	80
	Total	50	37/13 : 2.8	42	80

Table 2. Median survival after diagnosis

Tumor histology	No. of tumor resections	Median survival (days $\pm$ SE)	Mean survival (days $\pm$ SE)	P value for debulking
Glioblastoma	0	393 +/– 72	510 +/– 110	
	1	380 +/– 22	446 +/– 36	
	2–3	548 +/– 33	813 +/– 164	
	Total	425 +/– 24	570 +/– 57	0.173
Anaplastic astroctytoma	0	544 +/– 167	1,113 +/– 306	
	1	1,589 +/– 202	1,797 +/– 259	
	2-3	1,421 +/– 89	2,022 +/– 500	
	Total	1,311 +/– 336	1,737 +/– 239	0.1998

Anaplastic astrocytoma

Fifty patients, 37 men and 13 women with a median age of 42 years, who presented to the Brain Tumor Clinic with a median Karnofsky Performance Scale of 80 were analyzed. Eight of these patients are still followed by the Clinic at this time; 42 have since died [Table 1]. The survival data are shown in Table 2 and Figure 2. Median survival for the group as a whole was 1,311 days and mean survival 1,737 days.

Sixteen of these patients (14 men and 2 women) received no surgical debulking. The median age of this group was 42 and median KPS 70. Median survival for this group was 544 days, mean survival 1,113 days. Twenty-four patients (18 men and 6 women) underwent one surgical debulking. Median age in this group was 42 and median KPS 80. Median survival was 1,589 days, mean 1,797. The group that underwent two to three resections of tumor consisted of 10 patients (5 men and 5 women) with a median age of 37 and median KPS of 80. Median survival was 1,421 and mean survival 2,022 days.

There is a clear trend toward increasing survival in both the median and mean values between 0 and 1 debulkings. This trend continues in the mean values between one and two or three debulkings. The 95% confidence intervals for the median survival following 0 debulkings (217–871 days) does not overlap with the single debulking group (1,291–2,304 days). Nonetheless, there is clear overlap between the one debulking and the two to three debulking groups (1,246–1,596). The log rank test reveals debulking to be significant with a *P* value of 0.1998 assuming 2 degrees of freedom.

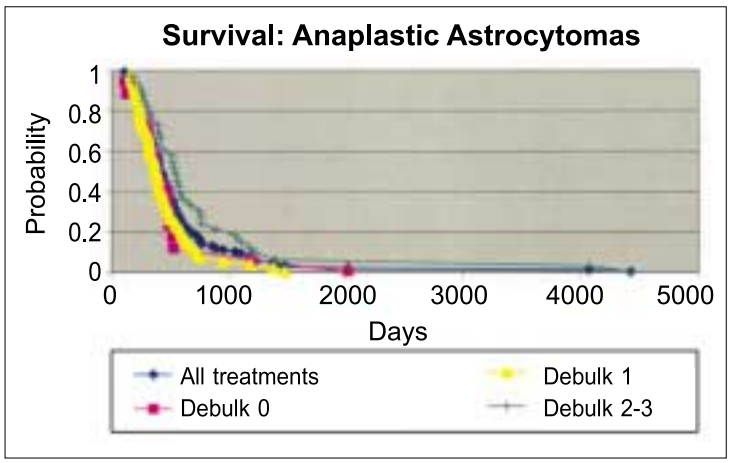

Figure 1. Graph demonstrating cumulative survival rates of patients with glioblastoma multiforme. The entire set of patients is shown in blue diamonds. The set is further broken down into those who did not receive debulking (pink squares), those who received one debulking (yellow triangles) and those who were debulked two to three times (green x's). The log rank test revealed debulking to be significant with a *P* value of 0.173 assuming 2 degrees of freedom.

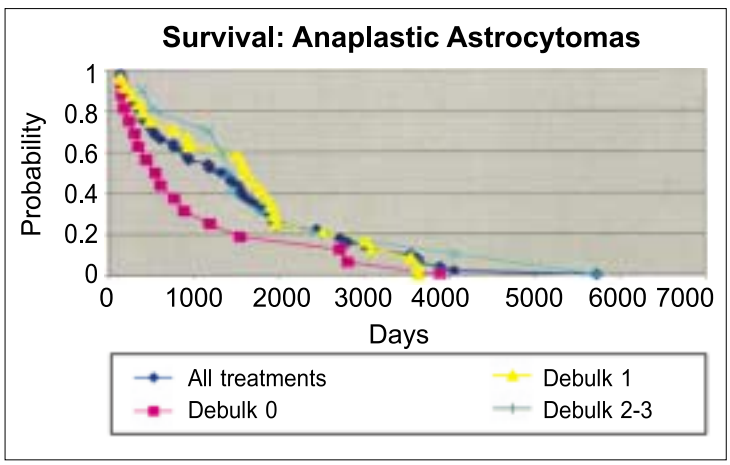

Figure 2. Graph demonstrating cumulative survival rates of patients with anaplastic astrocytomas. The entire set of patients is shown in blue diamonds. The set is further broken down into those who did not receive debulking (pink squares), those who received one debulking (yellow triangles) and those who were debulked two to three times (green x's). The log rank test revealed debulking to be significant with a *P* value of 0.1998 assuming 2 degrees of freedom.

Discussion

The standard of care for both anaplastic astrocytomas and glioblastoma has long consisted of surgery followed by radiotherapy. The median survival for anaplastic astrocytomas treated in this fashion has been reported as 720 days for anaplastic astrocytomas and 270 days for glioblastomas [6–9]. The addition of chemotherapy has increased median survival to approximately 330 days for glioblastoma [6–8]. Some debate continues as to the degree to which surgical excision prolongs survival. A few authors argue that aggressive cytoreduction of malignant astrocytic tumors confers no significant benefit [10–12]. A growing number of studies finds distinct benefit to aggressive resections in either all or a selected group of anaplastic astrocytomas and glioblastomas [13–15]. Despite this, median survival following resection varies widely in the reports recommending that therapy. The reasons for this variability are clearly multiple. Probably the most significant factor involves the estimate of the extent of tumor resection, whether adjudged by the surgeon at the time of operation or through assessment of postoperative enhanced CT and/or MRI scans [16].

The issue of reoperation for recurrent astrocytomas has been examined by few previous studies. The introduction of peri-operative steroid use for intracranial surgeries in the 1960s decreased the mortality for initial malignant glioma resections to less than 3% [17]. Prior to that, despite Cushing's reported mortality of 11% for the last 3 years of his experience, operative mortality for malignant gliomas ranged from 8 to 38% [18–20] until the 1960s. Due to perceptions of the poor peri-operative risk, until recently re-resection of gliomas was performed in 10% or less of patients. However, in the last 20 years several studies have established that reoperation can be performed safely [13,21–23]. In addition, these studies suggest that repetitive resections prolong survival in patients with malignant gliomas, particularly in those whose KPS is higher than 60 or 70.

In the case of glioblastomas, the data from the present study demonstrate a statistically significant increase in patient survival following multiple resections. For anaplastic astrocytomas, a single debulking clearly improved survival. A trend toward more prolonged survival is shown for multiple resections although it does not reach the level of statistical significance.

The practice guidelines in the Brain Tumor Clinic at our center have not in the past preselected groups of patients for single resections of malignant gliomas versus multiple resections of these tumors using criteria other than mass effect, neurological symptoms, surgical accessibility of the tumor, and patient consent to operation. Based on this set of data and reports from other centers, it seems reasonable to conclude that a subset of patients accrues significant benefit from this

aggressive surgical management and represents the long-term survivors in this data set best appreciated by the Kaplan-Meier survivor curves in Figures 1 and 2. Further analyses of our data and others may help us understand how those patients can be identified prospectively and treated appropriately with our surgical resources.

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Capsule

Primate genetic engineering

The ability to genetically engineer non-human primates would facilitate the development of animal models of human diseases. Chan et al. transferred the gene encoding green fluorescent protein (GFP) to rhesus macaque oocytes by injecting a pseudotyped retroviral vector. After intracytoplasmic sperm injection and transfer of the embryos to surrogate mothers, one live animal and one stillborn set of twins were observed to be transgenic by polymerase chain reaction analysis and by fluorescence of toenails, hair, and placenta.

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