

## Repeated operations for infiltrative low-grade gliomas without intervening therapy

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**Object.** Progression of infiltrative low-grade gliomas (LGGs) has been reported previously. The limitations of such studies include diverse histological grading systems, intervening therapy, and the lack of histological confirmation of malignant tumor progression. The aim of this study was to determine tumor progression in adult patients with an initial diagnosis of infiltrative LGG who subsequently underwent a repeated operation, but no other intervening therapy. The authors examined factors that may be associated with tumor progression.

**Methods.** The authors retrospectively reviewed a database of 300 patients with the initial diagnosis of LGG and who had been treated at their institution between 1990 and 2000. One hundred four of these patients had undergone a second surgery. Patients with infiltrative LGGs who had undergone two surgical procedures at least 3 months apart without intervening therapy were selected; the authors identified 40 patients who fit these criteria. Clinical, neuroimaging, and pathological data were centrally reviewed.

There were 29 men and 11 women in the study, whose median age was 35.5 years (range 23–48 years). At the time of the second surgery, 50% of patients had experienced tumor progression. Patients whose tumors had progressed had a longer median time to repeated operation (49 compared with 22.5 months). Patients who had undergone gross-total resection, as demonstrated on postoperative magnetic resonance images, had a median time to repeated operation of 49 compared with 25 and 24 months in patients who underwent subtotal resection and biopsy, respectively ( $p = 0.02$ ). The extent of resection did not influence the likelihood of tumor progression ( $p > 0.3$ ).

**Conclusions.** Fifty percent of patients with initially diagnosed infiltrative LGGs had tumor progression at the time of a repeated operation. A gross-total resection was associated with an increased time to repeated surgery. There was no statistically significant effect of gross-total resection as a predictor of tumor progression.

**KEY WORDS** • low-grade glioma • tumor recurrence • natural history • tumor

Low-grade gliomas are a heterogeneous group of brain tumors with variable biological behaviors. Every year, 1500 new cases of LGGs are diagnosed and the majority of these occur within the supratentorial hemispheres in adults.<sup>4,7</sup> Compared with patients harboring malignant gliomas, those with LGGs are usually younger when diagnosed. Approximately one half of patients present with seizures and are otherwise neurologically intact. Magnetic resonance imaging typically demonstrates a low-signal lesion that does not enhance on T<sub>1</sub>-weighted images with Gd and a high signal without mass effect on T<sub>2</sub>-weighted images.

The histological characteristics of LGGs are diverse, and approximately 31.1% of these lesions consist of low-grade astrocytomas, oligodendrogliomas, and ependymomas. There are also LGGs of mixed histological characteristics of which oligoastrocytoma occurs most commonly. Although some LGGs such as pilocytic astrocytomas and ependymomas show limited infiltrative growth, most of these lesions diffusely invade brain tissue. The prognosis

and treatment for these infiltrating LGGs have been the subject of much controversy in the literature. Patient age, presence of neurological deficit, tumor size and extension across the midline, and histological subtype (in particular, the presence of an oligodendroglioma component) appear to be the most important prognostic factors.<sup>2,17</sup> Overall median survival in patients with infiltrative LGGs is between 3 and 9 years.<sup>17,18</sup>

Infiltrative LGGs are known to dedifferentiate to more aggressive histological characteristics. The incidence of malignant tumor transformation in various clinical series has ranged from 13 to 86%.<sup>1,10,12,13,15,16</sup> In many of these studies, however, malignant transformation is not well documented. Deficiencies in histological data from repeated surgeries and substantial differences in tumor grading systems that define permissible anaplastic features for the diagnosis of an LGG may account for the wide range of transformation rates. In addition, many of these patients received radiation therapy and/or chemotherapy, which may have interfered with histological interpretation and confounded the natural progression of the LGG.

The aim of this study was to determine the rate of and factors influencing tumor progression as well as to analyze malignant transformation in a well-defined cohort of adult

*Abbreviations used in this paper:* GBM = glioblastoma multiforme; LGG = low-grade glioma; MR = magnetic resonance; WHO = World Health Organization.

TABLE 1

Summary of tumor characteristics and progression in 40 patients\*

Variable	Tumor Grade at 1st Op			
	Astrocytoma II	Oligoastrocytoma II	Oligodendroglioma II	LGG II
no. of patients	10	11	14	5
age (yrs)				
median	36.5	31	35.5	41
range	29–47	24–47	23–48	26–45
time to 2nd op (mos)				
median	11.5	46	35	33
range	5–57	12–86	3–125	18–65
no. of patients w/ symptoms				
before 1st op				
seizure	9	5	11	3
headache	1	2	2	0
incidental finding	0	2	1	2
neurological deficit	0	2	0	0
before 2nd op				
increasing seizures	6	6	5	4
increasing headaches	0	2	0	1
stable	2	2	5	0
neurological deficit	2	1	4	0
MRI results before 1st op				
no enhancement	10	11	13	4
min enhancement	0	0	1	1
MRI results before 2nd op				
new enhancement	3	5	6	3
no enhancement	7	6	8	2
tumor grade at 2nd op				
astrocytoma				
II	2	0	0	0
III	0	1	0	0
oligoastrocytoma				
II	4	5	0	1
III	2	3	1	0
AA III	2	0	0	1
oligodendroglioma				
II	0	0	7	1
III	0	2	4	0
GBM	0	0	2	2
tumor progression (%)	40	55	50	60
extent of resection after 1st op†				
subtotal	4	5	8	2
gross total	0	5	3	2

\* AA = anaplastic astrocytoma.

† All other patients underwent biopsy only.

patients who had undergone repeated operations without confounding therapy by using a uniform histological grading system in the era of MR imaging.

## Clinical Material and Methods

### Study Characteristics

The Neurosurgery and Neuro-Oncology database was searched for patients treated for LGGs at the University of California at San Francisco between 1990 and 2000; 300 such patients were identified. One hundred four patients had undergone two operations during the course of their illness. In 11 patients diagnostic biopsy was performed less than 3 months prior to the second (and final) operation; these patients were excluded from further analysis. Forty patients met all inclusion criteria and were eligible for the

study. Inclusion criteria consisted of the following: 1) patient age older than 17 years; 2) histological confirmation of an infiltrative LGG at the initial surgery; 3) a second surgical procedure at least 3 months after the initial surgery; 4) no intervening therapy between surgeries; 5) MR images obtained at initial diagnosis and at the time of repeated surgery; and 6) central pathological review of all specimens.

The following information was coded for computer analysis for each patient: demographics, date of first and second surgery, signs and symptoms at diagnosis and tumor progression, MR imaging findings prior to operation, tumor histological characteristics at both surgeries, and location and extent of resection. In this analysis, the definition of the extent of resection was based on the surgeon's operative notes and postoperative imaging studies. Subtotal resection was characterized as up to 90% excision and gross-total resection as greater than 90% removal.

This study was conducted with approval from both the Committee on Human Research and the Institutional Review Board at the University of California at San Francisco.

### Neuropathological Analysis

All tumor samples obtained during the first and second surgeries were interpreted by a team of neuropathologists at the University of California at San Francisco. The WHO classification system was uniformly used to identify low-grade histological characteristics.<sup>9</sup> To be considered WHO Grade II, the tumor sample had no evidence of increased mitosis, endothelial proliferation, or necrosis.

### Statistical Analysis

Because the length of follow up from the time of first surgery varied, we analyzed the predictors of the likelihood of tumor progression by using a Cox proportional-hazards model. If data obtained during the second surgery indicated there was no progression, the time to tumor progression was considered to be censored. Predictors of the time to second surgery were analyzed using the Wilcoxon rank-sum test.

## Results

### Patient Characteristics

There were 29 men and 11 women. Tumors were located on the left side in 21 cases and on the right in 19. The predominantly involved cerebral lobe was the frontal in 20 patients, temporal in 11, parietal in eight, and occipital in one patient. All biopsies were performed with the aid of image guidance. Patient characteristics, MR imaging findings, and tumor pathological characteristics at the time of first and second surgeries are summarized in Table 1. Patients most often presented with the new onset of seizures. None suffered chronic epilepsy prior to diagnosis. On neuroimaging for head trauma or migraine evaluation an incidental intracranial mass was demonstrated in five patients. In only two patients was minimal diffuse enhancement exhibited on diagnostic MR images. Given the retrospective nature of this study, MR imaging reports were available; initial scans were not reviewed, however, and so tumor diameters and volumes are unavailable in these cases. The initial pathological analysis revealed 10 WHO Grade II astrocytomas, 14 Grade II oligodendrogliomas, and 11 Grade II mixed oligoastrocytomas. Five infiltrative LGGs could not be further

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classified despite the use of special histological stains and central review.

At the time of the second surgery most patients presented with increasing seizures. In nine patients with stable symptoms at second surgery tumor progression was demonstrated on MR images (Table 2). In 17 patients evidence of new enhancement was exhibited on MR images. Neuroimaging studies in 20 patients revealed no enhancement but increasing abnormalities on T<sub>2</sub>-weighted images. All tumor recurrences were local. Three patients whose residual abnormality had stabilized according to T<sub>2</sub>-weighted images underwent a second surgery as part of their therapy for medically refractory seizures. Pathological characteristics found at the time of second surgery are shown in Table 2. Overall, in 20 patients the tumor remained at Grade II and in the other 20 the tumor progressed to Grade III or IV. Thus, 50% of patients had experienced tumor progression at the time of repeated surgery.

A comparison of patient characteristics based on initial low-grade tumor pathological characteristics and subsequent progression is summarized in Table 1. Forty percent of astrocytomas, 55% of oligoastrocytomas, 50% of oligodendrogliomas, and 60% of LGGs progressed.

### Analysis of the Results of Second Surgery

To find differences between patients whose tumors remained histologically stable and those whose tumors were upgraded, we considered several factors (Table 2). There was a tendency toward tumor progression in patients who were older (32 years in patients without tumor progression compared with 42 years in patients with progression), but this did not reach statistical significance ( $> 0.5$ ). Four (35%) of 13 biopsies, six (38%) of 17 subtotal resections, and 10 (100%) of 10 gross-total resections were associated with tumor progression. Patients who harbored tumors that had progressed had a longer median time to second surgery (47 months) compared with patients who harbored histologically stable tumors (22.5 months). The most important factor in determining the time to repeated operation was the extent of initial resection. Patients who had undergone a gross-total resection, as demonstrated on postoperative MR images, had a median time to repeated surgery of 49 months, compared with 25 months in those who had subtotal resection and 24 months in those who had undergone biopsy ( $p = 0.02$ , comparing gross-total resection with subtotal resection and biopsy). When the extent of resection as a predictor of tumor progression was adjusted for the time between initial and second surgery in a Cox model, there was no indication that the extent of resection influenced the likelihood of progression ( $p > 0.3$ ). New enhancement demonstrated on MR images prior to the second surgery was more common in patients with upgraded tumors (13 patients compared with four), but seven patients whose images revealed nonenhancing progression had tumors that had progressed to Grade III. New enhancement on MR images had a sensitivity of 65% and a specificity of 80%. Tumor progression was similar in all histological subgroups.

### Discussion

Infiltrative LGGs are tumors found in young adults,

TABLE 2

*Patient characteristics and tumor findings at the second surgery*

Variable	Tumor Grade at 2nd Op	
	II	III/IV
no. of patients	20	20
age (yrs)		
median	32	42
range	24–45	28–51
time to 2nd op (mos)		
median	22.5	47
range	3–45	6–86
no. of patients w/ symptoms		
before 1st op		
seizure	12	16
headache	3	0
incidental finding	4	0
neurological deficit	1	0
before 2nd op		
increasing seizures	11	10
increasing headaches	2	3
stable	4	5
neurological deficit	3	4
MRI results before 1st op		
no enhancement	19	19
min enhancement	1	1
MRI results before 2nd op		
new enhancement	4	13
no enhancement	13	7
stable	3	0
initial tumor type		
astrocytoma II	6	4
oligodendroglioma II	7	7
oligoastrocytoma II	5	6
LGG	2	3
tumor type at 2nd op		
astrocytoma	2 Grade II	4 Grade III
oligodendroglioma	8 Grade II	6 Grade III
oligoastrocytoma	10 Grade II	6 Grade III
GBM	0	4
extent of resection after 1st op*		
subtotal	11	6
gross total	0	10

\* All other patients underwent biopsy only.

which may transform into more malignant lesions. Most investigators think that the death of patients with LGGs is primarily due to malignant recurrence. The incidence of malignant tumor transformation varies in published reports and ranges from 13 to 86%.<sup>10–13,15,16,20,22,23</sup> This large range may be due to the use of diverse histological grading systems, intervening therapies, low rates of repeated surgeries, and a definition of malignant transformation that was based on an aggressive clinical course at the time of recurrence and limited follow-up time. Many of these reports involved patients treated during the pre-MR imaging era.

Muller, et al.,<sup>12,13</sup> published two large reports on patients with supratentorial recurrences of astrocytomas and oligodendrogliomas. The modified Ringertz classification system,<sup>12,13</sup> which allowed for some mitoses, vascular changes and minor areas of necrosis even in low-grade tumors, was used. Many of the 137 patients with astrocytomas and the 52 patients with oligodendrogliomas had undergone intervening radiation. Nevertheless, there were 47 patients with astrocytomas and 16 patients with oligodendrogliomas who were considered to have low-grade tumors and had under-

gone repeated operations after clinical progression without intervening radiation. Of the 47 astrocytomas, seven remained at Grade II and 40 progressed (15 GBMs). Of the 16 oligodendrogliomas, five remained stable and 11 progressed. Excluding patients who had undergone radiation therapy, there were malignant transformation rates of 85.1 and 69% in those harboring astrocytomas and oligodendrogliomas, respectively. The median age of the patients in this study was 42 years and the median time to repeated surgery was 24 months.

Laws, et al.,<sup>10</sup> reviewed data in 461 patients with low-grade astrocytomas as defined by the Kernohan histological grading system. These patients underwent surgery and radiation therapy. Seventy-nine patients had recurrent tumor documented on repeated operation or autopsy. In this series, 39 (49%) of 79 patients had tumors that progressed.

Piepmeyer<sup>16</sup> reported one of the lowest malignant transformation rates (13.3%). Sixty patients with astrocytomas, including seven mixed and three pleomorphic xanthoastrocytoma, were included in this study. Fifty-one percent of patients received radiation therapy. In eight patients a malignant change in the tumor was noted. Six patients were diagnosed based on biopsy results and two by computerized tomography scanning findings. Only 14 patients had undergone repeated operations at the time of the report. The rate of malignant transformation in patients who underwent a second surgery was approximately 42.8% (six of 14 patients).

The rate of malignant transformation in our study was 50%. This confirms that malignant progression of infiltrative LGGs occurs in a significant number of patients at the time of a second surgery. We tried to minimize the degree of histological variability by using centralized pathological review and a uniform grading scheme. In addition, patients who had undergone intervening therapy with radiation therapy or chemotherapy were excluded to decrease the histological artifacts that may have resembled tumor dedifferentiation. Limitations of this study were its retrospective nature and the lack of a uniform follow-up evaluation between the two surgical procedures. Despite these limitations and the fact that this was a small cohort, there are some important implications in the fact that 50% of patients experienced tumor progression at the time of the second surgery.

Age in this group of patients did not predict the occurrence of malignant transformation at the time of second surgery. Patients older than 40 years of age are considered at risk for malignant tumor transformation. The median age of patients at the time of repeated operation in this study was only 37.5 years. Five patients older than 40 years harbored tumors that remained stable at the time of the repeated operation and seven patients harbored tumors that progressed.

The influence of the extent of resection on malignant transformation is controversial. In most studies researchers did not document the extent of resection based on MR images obtained 24 to 72 hours postoperatively. In 1994 Berger, et al.,<sup>3</sup> used MR images and computerized tomography scans to evaluate the effect of the extent of resection. This study was based on 53 patients with low-grade astrocytomas and mixed oligoastrocytomas. In addition to having undergone surgery, 75% of patients received postoperative radiation therapy. Ten of 53 patients underwent a second surgery for recurrent tumors, three had lesions that remained stable, and seven had lesions that progressed (two

anaplastic astrocytomas and five GBMs). All seven patients with a malignant recurrence also had a preoperative tumor volume of 30 cm<sup>3</sup>. Further, the recurrence rate depended on the postoperative tumor volume. A recurrence rate of 46.2% occurred in patients with postoperative tumor volumes greater than 10 cm<sup>3</sup>; 14.3% of recurrences occurred in patients with postoperative tumor volumes less than 10 cm<sup>3</sup>. In this study all patients who had undergone 100% resections remained recurrence free during the follow-up period (mean 54 months). These patients also tended to have smaller tumors and were younger.

One limitation of the current study is its lack of data regarding the initial tumor size or volumetric analysis of residual tumor following initial resection. It may well be that these factors influence the timing or degree of tumor progression. Pignatti, et al.,<sup>17</sup> demonstrated that a tumor size larger than 6 cm was an important prognostic factor for patient survival and that the influence of this factor with respect to tumor dedifferentiation must be studied in a prospective manner. The Radiation Therapy Oncology Group study<sup>18</sup> of good risk patients with infiltrative LGGs (age < 40 years and gross-total resection of tumor) who are being followed up with neuroimaging studies but no intervening therapy may be an ideal subset of patients to provide this information. In our study, although 10 patients with prior gross-total resection harbored tumors that had progressed at the time of second surgery, the number is too small for any conclusions regarding the effect of such resections on malignant transformation.

The effect of therapeutic modalities such as radiation therapy and chemotherapy on the natural progression of an infiltrative LGG is unclear. We plan to review a similar cohort of matched patients harboring such tumors who had undergone repeated operations following therapy in an attempt to compare the results of frequency and timing of tumor progression.

The influence of malignant transformation on patient survival is also controversial. Data from some studies have shown that most patients die of malignant transformation. Our data indicate that malignant changes occur most frequently within the first 5 years after the initial procedure, although tumor progression and histological upgrade also occurred beyond 5 years. Outcome data in these patients in terms of their survival following repeated surgery continue to be assessed, and at the time of this report most patients are alive. In those in whom GBM was subsequently diagnosed, it will be interesting to assess patient outcome because these lesions would be considered the classic secondary glioblastoma as opposed to the de novo glioblastoma.<sup>9</sup> Expected survival in patients harboring these two types of tumors has not been described separately in studies focused on glioblastomas.

The implications of data in this report are extremely relevant to investigators planning prospective therapeutic studies in patients with recurrent glioma. If the initial histological subtype of a tumor is low grade and the diagnosis of progression is based purely on clinical and radiographic criteria, the histological diagnosis in this group could vary from Grades II to IV, thereby making it difficult to determine the true effect of therapy on patient outcome. One cannot assume that the grade of a recurrent infiltrative LGG has remained stable regardless of patient age, clinical signs and symptoms, or neuroradiographic features, thus emphasizing

the importance of histological confirmation prior to enrollment into clinical trials.

Perhaps the most relevant implication of this study is the demonstration of heterogeneity among infiltrative LGGs and the need for better predictors of tumor behavior and malignant transformation other than accepted clinical and histological factors. Molecular and cytogenetic analyses may yield better insights into the multistep process of malignant tumor progression, especially in a unique cohort such as in this study in which inpatient sampling was available at two different time points in the individual's illness. The development of tissue arrays and patterns of gene expression relevant to gliomagenesis can, we hope, advance our understanding of the malignant phenotype and allow for appropriate interventions that may delay or abrogate tumor progression.<sup>5,6,8,14,19,21,24</sup> We are currently assessing as many tissue samples as possible in this cohort of patients, with plans to evaluate at the time of initial diagnosis potential markers that may predict tumor progression. We also plan to look at changes that occur on a molecular and cytogenetic basis during malignant transformation.

### Conclusions

Data from this study demonstrate that tumor progression occurs in 50% of a select group of infiltrative LGGs subjected to second surgeries. Patient age was not a significant factor in predicting tumor progression in this study. Gross-total resection without postoperative adjuvant therapy was associated with increased time to second surgery. Future studies ought to be directed at the molecular and cytogenetic profiles of the tissue samples obtained as well as the evaluation of patients who underwent repeated operations following therapeutic intervention.

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