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Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial

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Abstract

Object—In 1998, the Radiation Therapy Oncology Group initiated a Phase II study of observation for adults < 40 years old with cerebral low-grade glioma who underwent a neurosurgeon-determined gross-total resection (GTR).

Methods—Patient eligibility criteria included the presence of a World Health Organization Grade II astrocytoma, oligodendroglioma, or mixed oligoastrocytoma confirmed histologically; age 18–39 years; Karnofsky Performance Scale score ≥ 60; Neurologic Function Scale score ≥ 3; supratentorial tumor location; neurosurgeon-determined GTR; and pre- and postoperative MR imaging with contrast enhancement available for central review by the principal investigator. Patients were observed following GTR and underwent MR imaging every 6 months. Prognostic factors analyzed for their contribution to patient overall survival, progression-free survival (PFS), and tumor recurrence included age, sex, Karnofsky Performance Scale score, Neurologic Function Scale score, histological type, contrast enhancement on preoperative MR imaging, preoperative

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tumor diameter, residual disease based on postoperative MR imaging, and baseline Mini-Mental State Examination score.

Results—Between 1998 and 2002, 111 eligible patients were entered into the study. In these 111 patients, the overall survival rates at 2 and 5 years were 99 and 93%, respectively. The PFS rates in these 111 patients at 2 and 5 years were 82 and 48%, respectively. Three prognostic factors predicted significantly poorer PFS in univariate and multivariate analyses: 1) preoperative tumor diameter ≥ 4 cm; 2) astrocytoma/oligoastrocytoma histological type; and 3) residual tumor ≥ 1 cm according to MR imaging. Review of the postoperative MR imaging results revealed that 59% of patients had < 1 cm residual disease (with a subsequent 26% recurrence rate), 32% had 1–2 cm residual disease (with a subsequent 68% recurrence rate), and 9% had > 2 cm residual disease (with a subsequent 89% recurrence rate).

Conclusions—These data suggest that young adult patients with low-grade glioma who undergo a neurosurgeon-determined GTR have a $> 50\%$ risk of tumor progression 5-years postoperatively, warranting close follow-up and consideration for adjuvant treatment.

Keywords

gross-total resection; low-grade glioma; progression-free survival; surgery

Low-grade gliomas are primary brain tumors classified as Grade I and II by the WHO grading system¹⁴ and occur primarily in children and young adults. The most common LGGs are the WHO Grade I pilocytic astrocytomas and the WHO Grade II diffuse astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Based on data from the American Cancer Society and Central Brain Tumor Registry of the US, ~ 1800 LGGs were diagnosed in 2006, thus representing $\sim 10\%$ of all newly diagnosed primary brain tumors.^{6,10} Although WHO Grade I and II tumors are grouped together under the category of LGG, they are an extremely heterogeneous group of tumors. Pilocytic astrocytomas, which are generally well circumscribed histologically and radiographically, are amenable to complete resection using GTR. In contrast, the diffuse astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are infiltrative and thus less likely to be completely resected.⁴

In adults there are numerous prognostic factors reported in various prospective studies that have been shown to affect survival in patients with LGG, the most consistent of which are histological type, patient age, extent of resection (as defined by the neurosurgeon at the time of surgery, or more recently, using imaging), and tumor size. Pilocytic astrocytomas, regardless of site (cerebral hemispheres, cerebellum, or spinal cord), are associated with a 10-year patient survival rate of $\sim 80\%$,^{3,9,15,22} but the rate is 100% in the subset of patients with brain tumors who undergo GTR.^{3,22} Within the diffuse LGG group there is a significant difference in patient outcome based on histological tumor type. In the NCCTG intergroup study comparing low- and high-dose radiation therapy, patients with oligodendrogliomas or oligodominant mixed oligoastrocytomas had a 5-year survival rate of $\sim 75\%$, compared with 55% for astrocytomas or astrodominant mixed oligoastrocytomas.²¹ In the previously referenced NCCTG study, the 5-year survival rate of adults < 40 years of age was 77 versus 60% for those ≥ 40 years of age. In an EORTC study comparing early versus delayed radiation therapy for LGG, the 5-year survival rate was $\sim 75\%$ in patients who underwent GTR, 60% in patients with STR, and 50% in patients with a biopsy procedure.^{12,25} Regarding LGG tumor size, patients with larger tumors have worse outcomes than those with smaller tumors. In another EORTC study of patients with LGG comparing low- versus high-dose radiation therapy, the 5-year patient survival rate was $\sim 78\%$ for tumors ≤ 3 cm, 58% for tumors > 3 to ≤ 5 cm, and 44% for tumors > 5 to ≤ 10 cm.¹³ The NCCTG intergroup study found a 5-year patient survival rate of 81% for those with tumors < 5 cm compared with 61% for those with tumors ≥ 5 cm.²¹ A subset analysis

from that study found that patients whose tumors had codeletion of chromosomes 1p and 19q, and/or the 1;19 translocation, had significantly better survival rates.¹¹

Perhaps the most controversial issue in the management of adult patients with supratentorial LGG is whether to administer immediate (that is, postoperative) radiation therapy, or delay this therapy until the time of tumor recurrence. The EORTC prospective randomized trial of immediate versus delayed radiation therapy did show a significant (but not overall) PFS benefit for immediate radiation therapy, but most patients participating in that study had adverse prognostic factors.^{12,25} In 1998 the RTOG began Protocol 9802 for adults with supratentorial diffuse LGG. An underlying assumption in the study design was that patients could be dichotomized into 2 risk groups, favorable and unfavorable LGG, based on the prognostic factors of patient age and extent of resection. By definition, patients with favorable LGG had to be both < 40 years of age and have undergone a neurosurgeon-determined GTR, whereas those with unfavorable LGG were ≥ 40 years old or had to have undergone less than a GTR (STR or biopsy procedure). Two studies were embedded within Protocol 9802. Patients with favorable LGG were observed postoperatively (no adjuvant therapy was given), whereas patients with unfavorable LGG were randomized to receive radiation therapy alone or radiation therapy followed by PCV chemotherapy. The hypothesis of the study was that patients with favorable LGG would have better PFS and OS rates than patients with unfavorable LGG and thus could be observed postoperatively without adjuvant treatment and with a low risk of tumor recurrence and death. This report will focus on the results of the study in adult patients with favorable supratentorial LGG.

Methods

Eligibility Criteria

Patient eligibility criteria included the following: unifocal or multifocal WHO Grade II astrocytoma, oligodendroglioma, or mixed oligoastrocytoma confirmed histologically, based on central pathology review by the neuropathology coprincipal investigator of the study (S.W.C.); patient age between 18 and 39 years; KPS score ≥ 60; NFS score ≤ 3 (range 0 [asymptomatic] to 4 [life-threatening]); supratentorial tumor location; GTR based on the operative report (determined by the neurosurgeon); pre- and postoperative MR imaging with contrast enhancement available for central review by the overall principal investigator (E.G.S.) to verify tumor location, size, and presence/absence of contrast enhancement (timing of postoperative scan not specified); and a signed consent form. Patients were required to be entered into the study within 12 weeks of surgery.

Ineligibility Criteria

Patient ineligibility criteria included the following: LGG histological types including pilocytic astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, or dysneuroembryoplastic epithelial tumor; presence of WHO Grade III or IV glioma including anaplastic astrocytoma, glioblastoma multiforme, anaplastic oligodendroglioma, or anaplastic mixed oligoastrocytoma; nonsupratentorial tumor location including optic chiasm, optic nerve(s), pons, medulla, cerebellum, or spinal cord; evidence of tumor spread to noncontiguous cranial leptomeninges or spinal leptomeninges; gliomatosis cerebri; synchronous malignancy excluding carcinoma of the cervix in situ or nonmelanomatous skin cancer; prior malignancy unless disease free ≥ 5 years; and prior radiation therapy or chemotherapy.

Patient Evaluation and Follow-Up

Baseline assessment required before patient registration in the study included a medical history and physical examination (including a neurological examination), documentation of

neurological symptoms and signs, medication history such as steroids and anticonvulsants, KPS score, NFS score, and MMSE score. Preoperative and postoperative MR images, including T1-weighted images with and without contrast enhancement as well as T2-weighted images (and FLAIR images when available), were required. The maximum preoperative tumor diameter, based on the axial and/or coronal T2-weighted or FLAIR MR images, was measured and recorded at the time of study entry, as was the presence or absence of contrast enhancement, based on the T1-weighted MR images with contrast enhancement. An imaging-based assessment of the extent of resection was also made for each patient by the overall principal investigator of the study. The pre- and postoperative MR images were compared to quantify the amount of residual imaging abnormality, a surrogate marker for residual disease, on the postoperative MR images. Specifically, a measurement was made of the maximum dimension of residual T2-weighted or FLAIR abnormality from the edge of the surgical cavity laterally, anteroposteriorly, and superoinferiorly based on axial and coronal images. The measurements were categorized as follows: < 1 cm (Fig. 1A and B), 1–2 cm (Fig. 1C and D), or > 2 cm. Peripheral blood and paraffin-embedded tumor tissue from each patient were collected and stored at baseline for future study. Following study registration, patients were followed up using serial clinical evaluations and MR imaging every 6 months. The MR imaging at the time of tumor progression (based on a clear increase in the T2-weighted or FLAIR abnormality and/or new contrast enhancement) was compared with the postoperative MR imaging to describe the site or sites of failure. These sites were coded as follows: 1) within 2 cm of the resection cavity; 2) > 2 cm from the resection cavity but in the same region of the brain (contiguous white matter and/or cortex); and 3) in a different (discontiguous) region of the brain.

Statistical Analysis

This Phase II study of observation in patients with favorable LGG did not have an a priori estimate of monthly or total accrual. The plan was to keep the study open for the same length of time as the Phase III trial of radiation therapy $\pm$ PCV chemotherapy in patients with unfavorable LGG. Prognostic factors analyzed for their effect on patient OS, PFS, and tumor recurrence using univariate and multivariate analysis included: age (< 30 vs $\geq$ 30 years old); sex (male or female); KPS score (< 90 vs $\geq$ 90); NFS score (0 vs 1–3); histological type (pure astrocytoma or mixed oligoastrocytoma vs pure oligodendroglioma); contrast enhancement on preoperative MR imaging (present or absent); preoperative tumor diameter (< 4 vs $\geq$ 4 cm); baseline MMSE score (< 30 vs $\geq$ 30); and maximum dimension of residual T2-weighted or FLAIR abnormality on postoperative MR imaging (< 1 cm vs 1–2 cm vs $\geq$ 2 cm).

Results

Between October 1998 and June 2002, 116 patients with favorable LGG were entered in this study. Five patients were retrospectively deemed ineligible due to age $\geq$ 40, incomplete tumor resection based on review of the neurosurgeon's operative report, or prior use of chemotherapy, leaving 111 patients to be analyzed. Patient characteristics are shown in Table 1. At the time of this analysis, the median follow-up duration was 4.4 years for all patients (range 0.3–7.1 years); there were 8 deaths (all due to disease progression) and 49 tumor recurrences. The OS rates at 2 and 5 years were 99 and 93%, respectively. The PFS rates at 2 and 5 years were 82 and 48%, respectively. In contrast, for the 251 patients with unfavorable LGG, the 2- and 5-year OS rates were 87 and 66%, significantly lower in comparison with the patients with favorable LGG ($p < 0.0001$), whereas the 2- and 5-year PFS rates in these 251 patients (73 and 50%, respectively; $p = 0.13$) were similar to those of the patients with favorable LGG (Fig. 2). The median PFS time was 4.9 years for patients with favorable LGG versus 5.5 years for patients with unfavorable LGG.

Given the high OS rates and low number of deaths, there were no factors predictive of significantly poorer OS. Three factors predicted a significantly poorer PFS in univariate and multivariate analyses: preoperative tumor diameter ≥ 4 cm (HR = 1.98, 95% CI 1.01–3.89; $p = 0.05$; Fig. 3), astrocytoma/oligoastrocytoma histological type (HR = 2.09, 95% CI 1.11–3.96; $p = 0.02$; Fig. 4), and imaging residual tumor ≥ 1 cm (HR = 3.54, 95% CI 1.83–6.84; $p = 0.0002$; Fig. 5).

Ninety-eight of the 111 study patients (88%) had postoperative MR images of sufficient quality to quantify the amount of residual disease. Fifty-nine percent (58 of 98) of patients had < 1 cm residual disease (Fig. 1A and B), 31 (32%) had 1–2 cm residual disease (Fig. 1C and D), and 9 (9%) had > 2 cm residual disease. The crude incidence of tumor recurrence was 26% (15 of 58 patients) in patients with < 1 cm residual disease according to imaging results, 68% (21 of 31 patients) in those with 1–2 cm of residual tumor, and 89% (8 of 9 patients) if > 2 cm residual disease was present. For the other prognostic factors that significantly predicted poorer PFS, the crude incidence of tumor recurrence was 54% (33 of 61 patients) for astrocytomas and mixed oligoastrocytomas, 32% (16 of 50 patients) for oligodendrogliomas, 27% (15 of 55 patients) for tumors < 4 cm, and 63% (34 of 54 patients) for tumors ≥ 4 cm. The crude incidence of tumor recurrence in the 61 astrocytomas and mixed oligoastrocytomas was 28% (9 of 32 patients) in those with < 1 cm residual disease, 88% (15 of 17 patients) in patients with 1–2 cm residual disease, 100% (5 of 5 patients) in those with > 2 cm residual disease, and 57% (4 of 7 patients) in those whose postoperative MR images were not able to be evaluated. In the 50 oligodendrogliomas, the incidence of tumor recurrence was 23% (6 of 26 patients) in those with < 1 cm residual tumor, 43% (6 of 14 patients) in patients with 1–2 cm residual disease, 75% (3 of 4 patients) in those with > 2 cm residual disease, and 17% (1 of 6 patients) for those who were unable to be evaluated. In those patients with all 3 unfavorable prognostic factors for PFS (≥ 1 cm residual disease according to imaging results, preoperative tumor diameter ≥ 4 cm, and astrocytoma/oligoastrocytoma histological type), the 2- and 5-year PFS rates were 60 and 13%, respectively (Fig. 6). If all 3 favorable prognostic factors were present (< 1 cm residual tumor, tumor diameter < 4 cm, and oligodendroglioma histological type), the 2- and 5-year PFS rates were 100 and 70%, respectively (Fig. 6). Patients with a mixture of prognostic factors had an intermediate outcome.

Of the 49 patients with recurrence, 23 (47%) had further surgery, 31 (63%) underwent radiation therapy, and 21 (43%) had chemotherapy. Of the 23 patients who underwent reresection, pathological results (not centrally reviewed) were available in 8, half of which revealed LGG and half malignant glioma (1 anaplastic astrocytoma and 3 glioblastoma multiforme).

Magnetic resonance images were available for 37 (76%) of the 49 patients with tumor progression. Most relapses (82%) were within 2 cm of the resection cavity, but 16% extended beyond 2 cm of the resection cavity and 1 patient (2%) had a discontinuous relapse in a different region of the brain.

Discussion

The underlying hypothesis that favorable and unfavorable LGG could be defined based on patient age and extent of resection proved correct for OS but not for PFS. The 93% 5-year OS rate for the patients with favorable LGG was significantly better than the 66% rate for patients with unfavorable LGG in RTOG Protocol 9802, as well as the 64–68% 5-year OS rates in several other recent randomized trials that largely included patients with unfavorable LGG.^{13,21,25} Patients with favorable LGG (those patients < 40 years of age who underwent a neurosurgeon-determined GTR) had a much poorer PFS than anticipated. Their 5-year PFS

rate of 48% was similar to the 50% 5-year PFS rate observed in unfavorable patients in RTOG Protocol 9802 (patients $\geq$ 40 years old, regardless of the extent of resection, or those $<$ 40 who had STR or a biopsy procedure, treated with postoperative radiation therapy with or without PCV chemotherapy), similar to the 52–55% 5-year PFS rate reported in several recent randomized trials of unfavorable LGG patients who underwent radiation therapy,^{13,21,25} and similar to the 50% recurrence rate recently reported in a large retrospective series from the University of California San Francisco.²⁰

The reason for entering patients with a neurosurgeon-determined GTR into the study was 2-fold. First, this has been the “standard” definition of GTR dating back to the pre-CT and pre-MR imaging eras. Second, we wanted to systematically collect postoperative MR images to quantify the degree of imaging-based residual disease on the T2-weighted or FLAIR images, an approach supported by the neuroradiology literature.^{5,24} A shortcoming of this methodology is the possibility that imaging changes assumed to be residual disease could be postoperative edema or ischemia. Thus, our quantitative assessment of the amount of residual imaging abnormality (increased T2/FLAIR signal measured in cm from the edge of the resection cavity) represents a surrogate marker of postoperative residual tumor. With this in mind, we found that only 59% of patients had a GTR ($<$ 1 cm residual tumor) based on the postoperative MR image. These patients had a 26% recurrence rate. Of the 41% of patients who had a STR according to MR imaging ($\geq$ 1 cm residual tumor), the recurrence rate was 68% in those with 1–2 cm residual disease and 89% (8 of 9 patients) in those with $>$ 2 cm residual disease. These data have several implications. First, they support the diffusely infiltrative nature of LGGs. Pallud and colleagues¹⁸ recently reported that isolated tumor cells in patients with low-grade oligodendroglioma are present even beyond the MR imaging abnormalities, an observation that has importance for the neurosurgeon and radiation oncologist, both of whom use imaging guidance to direct their respective treatment modalities. Second, they suggest that in general, the neurosurgeon is unable to accurately predict whether GTR of an infiltrative tumor has been accomplished intra-operatively.

The first report of outcome based on an MR imaging-based assessment of surgical resection for LGG was reported by Berger et al.¹ in a series of 53 patients from the University of Washington. The extent of resection (based on the volume of residual disease) and tumor size were inversely correlated with the likelihood of tumor recurrence, time to recurrence, and tumor grade at the time of recurrence (no survival data reported). No patients with 100% resection experienced tumor recurrence. The incidence of recurrence and time to tumor progression were 46% and 30 months, respectively, in patients with $>$ 10 cm³ residual disease, compared with 15% and 50 months in those with $<$ 1 cm³ residual tumor. In addition, 46% of those with $>$ 10 cm³ residual disease had higher grade tumors at recurrence, compared with 4% of patients with $<$ 10 cm³ residual tumor. Claus and associates⁸ recently reported an HR of 1.4 for recurrence and 4.9 for death in 156 patients with LGG who underwent an intraoperative MR imaging-guided STR compared with GTR. Intraoperative MR imaging for anatomical imaging guidance, as well as functional mapping, MR spectroscopy, diffusion tensor imaging, and fluorescence-guided resection^{2,7,16,17,19,23} are all contemporary neurosurgical techniques that were likely not used for patients in the present study, but may contribute to a higher percentage of patients undergoing a safe, image-guided GTR of an LGG, although even currently these techniques are not universally used, even for malignant gliomas.⁷

The inability to differentiate favorable from unfavorable subsets of patients with LGG with regard to PFS has several important implications for clinical trial design. For clinical trials of adult patients with LGG utilizing PFS as the primary end point, all patients, regardless of age and extent of resection, can be included from an eligibility standpoint. It may be possible to exclude the most favorable subset of patients with LGG from therapeutic trials ($<$

1 cm residual tumor, tumor diameter < 4 cm, and oligodendroglioma histological type), because their 2- and 5-year PFS rates were 100 and 70%. However, all other subsets are reasonable candidates for adjuvant treatment approaches that attempt to reduce the likelihood of tumor progression.

Conclusions

The data presented in this study suggest that young adult patients with LGG who undergo a neurosurgeon-determined GTR have a 52% risk of tumor progression 5-years after surgery, warranting close follow-up and consideration for adjuvant treatment.

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Disclosure

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Abbreviations used in this paper

CI	confidence interval
EORTC	European Organization for the Research and Treatment of Cancer
GTR	gross-total resection
HR	hazard ratio
KPS	Karnofsky Performance Scale
LGG	low-grade glioma
MMSE	Mini-Mental State Examination
NCCTG	North Central Cancer Treatment Group
NFS	Neurological Function Scale
OS	overall survival
PCV	procarbazine, CCNU, and vincristine
PFS	progression-free survival
RTOG	Radiation Therapy Oncology Group
STR	subtotal resection
WHO	World Health Organization

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Fig. 1. Preoperative (A and C) and postoperative (B and D) MR images of patients who underwent a neurosurgeon-determined GTR and were found to have < 1 cm of imaging-based residual disease (A and B) or 1–2 cm residual disease (C and D).

Fig. 2.

Line graph showing the overall survival and PFS curves for the 111 patients with favorable (low risk) LGG and the 251 patients with unfavorable (high risk) LGG.

Fig. 3.
Line graph showing patient PFS according to 2 different tumor diameters (< 4 cm vs ≥ 4 cm).

Fig. 4.
Line graph showing patient PFS according to histological type (pure oligodendroglioma vs astrocytoma and mixed oligoastrocytoma).

Fig. 5.
Line graph of patient PFS according to surgical residual tumor (< 1 cm vs ≥ 1 cm).

Fig. 6.

Line graph showing patient PFS according to 3 different prognostic factor groups: the favorable group (< 1 cm residual tumor, tumor diameter < 4 cm, and oligodendroglioma histological type); the unfavorable group (> 1 cm residual tumor according to imaging, preoperative tumor diameter ≥ 4 cm, and astrocytoma histological type); and the group of patients with tumors with a mix of favorable and unfavorable characteristics.

TABLE 1

Summary of patient preoperative characteristics*

Characteristic	Value
age in yrs	
median (range)	30 (18–39)
sex	
male	57 (51)
female	54 (49)
KPS score	
60–80	14 (13)
90–100	97 (87)
NFS score	
0	65 (59)
1	39 (35)
2–3	7 (6)
histological type	
pure astrocytoma or oligoastrocytoma	61 (55)
pure oligodendroglioma	50 (45)
preop MR contrast enhancement	
present	53 (48)
absent	58 (52)
preop tumor diameter in cm	
median (range)	3.8 (1.1–8.0)
MMSE score	
median (range)	30 (24–30)

* Values given are number of patients (%) unless otherwise indicated.