Low-grade Gliomas

Volker W. Stieber, MD

Address
Department of Radiation Oncology, Wake Forest University Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC 27157-1030, USA.
E-mail: vstieber@wfubmc.edu

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Opinion statement

Low-grade gliomas are uncommon primary brain tumors classified as histologic grades I or II in the World Health Organization (WHO) classification. The most common variants are pilocytic and low-grade astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas located in the cerebral hemispheres. Prognostic factors that predict progression-free and overall survival include young age, pilocytic histology, good Karnofsky performance status, gross total resection, lack of enhancement on imaging, and small preoperative tumor volumes. Edema and vasogenic effects are typically managed with corticosteroids. Dexamethasone is given at an initial dosage of 4 mg given four times daily. Anticonvulsants are given prophylactically after resection and for patients who present with seizures. The rationale for open craniotomy depends on the need for immediate palliation of symptoms by reduction of intracranial pressure or focal mass effect, and/or improved oncologic control. Gross total resection of tumor is generally defined as the absence of residual enhancement on contrast-enhanced postoperative MRI scan. Most retrospective studies suggest that patients who have undergone a gross total resection of tumor have improved survival. Depending upon the proximity of the tumor to eloquent brain, gross total resection may or may not be possible. In these cases a stereotactic biopsy is required to provide the histologic diagnosis. Adjuvant radiotherapy is recommended for patients with incompletely resected grade II tumors or for patients older than age 40 regardless of extent of resection. It may be considered for any pilocytic astrocytoma from which a biopsy has been performed. Phase III randomized prospective trials have shown statistically significantly improved progression-free survival at 5 years with the addition of radiotherapy, though overall survival does not appear different. Based on prospective randomized phase III trials, 50.4 Gy to 54 Gy of conventionally fractionated radiotherapy appears to be a safe and effective regimen with minimal neurotoxicity; 45 Gy may be adequate for biopsied pilocytic astrocytomas. Currently, RTOG trial 98-02 is investigating the efficacy of postradiation PCV chemotherapy (procarbazine, CCNU, and vincristine) in the treatment of newly diagnosed unfavorable low-grade gliomas. Other areas of investigation include Temozolomide chemotherapy and the association of 1p and 19q chromosomal deletions with prolonged survival in oligodendrogliomas and sensitivity to PCV chemotherapy. Radiosurgery and/or experimental chemotherapy may provide some measure of local control in the recurrent disease setting.

Introduction

According to the Central Brain Tumor Registry of the United States (CBTRUS), which collects data from fourteen state cancer registries [1•], the incidence rate of all primary benign and malignant brain tumors is 11.3 cases per 100,000 person years. Based on these numbers, there should be an expected 35,519 new cases of primary benign and malignant brain tumors diagnosed in 2001 in the United States. Data from the American Cancer Society suggest that approximately 16,500 of these will be malignant in origin [2•]. The prevalence of malignant primary brain tumors, however, is approximately 81,000 in 2000 [3].

Low-grade gliomas are primary brain tumors classified as histologic grades I or II in the World Health Organization (WHO) classification (Table 1) [4••]. There are several clinicopathologic entities that are glial in origin or that contain glial components. Although the annual incidence of malignant primary brain tumors has remained steady during the years, there have been relative shifts in the incidences of some of the histological subgroups, likely due to improvements in the skills of pathologists at making accurate histopathological diagnoses [5]. Relative incidences of the most common low-grade gliomas, when known, have been published by the CBTRUS [1•] and are reproduced in Table 2. This article discusses the treatment of the most common variants of low-grade gliomas: pilocytic and low-grade astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas. In addition, this article will focus on adults with tumors located in the cerebral hemispheres. Discussion of treatment options for the other less common variants is beyond the scope of this article; readers may gain an overview from recent textbooks [4••, 6–9]. An excellent overview of the multidisciplinary management of low-grade gliomas also has been published recently [10•].

Several papers have been published that examine various prognostic factors that predict progression-free and overall survival in patients with low-grade gliomas. Laws *et al* [11] have reviewed 461 patients treated at the Mayo Clinic who had supratentorial lesion. These patients survived at least 30 days postoperatively, and had follow up data available. Young age (<20 years) had a positive correlation with long-term survival. Shaw *et al* [12••] have shown that patients with low-grade gliomas have statistically significantly better 5-year survival if they are younger than 40 years of age (83% versus 58% for patients aged 40 or older) and if their tumors are oligo-dominant in composition (76% versus 58% for patients with tumors that are predominantly astrocytic). This has subsequently been confirmed by multiple other studies and the current randomized RTOG trial (see below) uses young age as a stratification parameter.

Lote *et al*. [13] have shown that patient age, performance status, and contrast enhancement are significant pretreatment prognostic factors. Pilocytic histology also has been shown by Shaw *et al*. [14] to be associated with improved survival (79% at 10 years versus 23% for patients with astrocytomas or mixed oligo-astrocytomas). If completely resected, this group of patients enjoys long-term survival rates of 100%, as opposed to the 10-year survival rate of 21% for the other histologic subtypes. Berger *et al* [15] have shown that patients with small pre-operative tumor volumes (*ie*, those less than 10 cm^3) have a zero rate of recurrence after resection, with a median follow up of 41 months. In contrast, patients with preoperative tumor volumes of 10 cm^3 to 30 cm^3 have a 13.6% incidence of recurrence with 58 months to progression although patients with larger preoperative volumes of disease have a 41.2% incidence of recurrence with 30 months to progression. These differences are statistically significant. Finally, a multigroup recursive partitioning analysis evaluating pretreatment factors for overall survival has been published recently [16•]. The databases of patients with low-grade gliomas treated at the London Regional Cancer Centre, The Norwegian Radium Hospital, and the University of California, San Francisco were merged. Inclusion criteria for the pooled analysis included age ≥ 18 years with histologically confirmed WHO grade II tumors (supratentorial fibrillary astrocytoma, oligodendroglioma, or mixed oligo-astrocytoma). Recursive partitioning analysis yielded four prognostic groups with statistically different median survival rates that ranged from 12 months to 128 months (Table 3).

Table 1. World Health Organization (WHO) classification of low-grade primary glial tumors

WHO Grade I	WHO Grade II
Pilocytic astrocytoma	Low-grade astrocytoma
Subependymoma	Oligodendroglioma
Desmoplastic infantile	Mixed oligo-astrocytoma
Astrocytoma/ganglioglioma	
Dysembryoplastic neuroepithelial tumors	Ependymoma
Gangliogliomas	Gangliogliomas
Myxopapillary ependymoma	Pleomorphic xantho-astrocytoma
	Choroid gliomas of the third ventricle

Table 2. Relative incidence of low-grade gliomas from the CBTRUS report

Histology	All reported brain tumors (%)	Average age at diagnosis (yr)	Adjusted Incidence Rate	Relative 2-yr SR	Relative 5-yr SR	Relative 10-yr SR
Pilocytic Astrocytoma	1.9	17	0.23	91.4	87.6	84.3
Oligodendroglioma	2.7	42	0.34	79.1	64.3	47
Mixed gliomas	1	40	0.12	73.7	57.7	40.5
Astrocytoma, NOS	6.1	47	0.76	34.1	27.2	23

SR=survival rate.

Table 3. Pretreatment factors determined by recursive partitioning analysis, predicting overall survival for patients with low-grade gliomas

Group	KPS	Age (*yr*)	Enhancement on CT or MRI	MS (*mo*)
I	<70	>40		12
II	≥ 70	0.4	Present	46
III	<70	18–40	None	87
	≥ 70	>40		
IV	≥ 70	18–40		128

KPS=Karnofsky performance status; MS=median survival.

Treatment

Diet and lifestyle

There are no clear dietary [17] and/or lifestyle [18] factors associated with the prevention or treatment of primary low-grade gliomas [19].

Pharmacologic treatment

- In general, low-grade gliomas tend to have markedly less edema and vasogenic effects than the higher-grade invasive anaplastic astrocytomas or glioblastoma multiformes [20•].
- The mainstay of symptomatic management is corticosteroids. Their effects appear within 24 hours to 48 hours after their initial administration and usually peak within a week. They produce a significant reduction in brain tumor volume and an even greater reduction in the peritumoral edema [21]. Although the exact mechanisms are not completely clear, hypotheses include reversal of increases in permeability of the capillary-endothelial cell junctions of the blood brain barrier and stabilization of lysosomal membranes [22].
- Dexamethasone is the most commonly used agent, typically given at a dosage of 16 mg divided into four daily doses [23], with a subsequent taper that lasts a few weeks to several months (usually a dose reduction of 2 mg every 3 days to 7 days), as tolerated by the patient [24•].
- If radiotherapy is delivered, additional swelling may occur. Thus, if patients are still on corticosteroids by the time radiotherapy begins, it may be prudent to keep them on a low dose of 2 mg to 8 mg daily. Patients not on corticosteroids at the beginning of radiation may be observed and dexamethasone may be added if patients become symptomatic.

- Side effects of intermediate– to long-term steroid use include hyperglycemia, insomnia, emotional lability, steroid induced proximal muscle wasting, weight gain, and adiposity (moon facies, buffalo hump, centripetal obesity), osteoporotic compression fractures, and aseptic necrosis of the hip joints [25].
- Nonsteroidal anti-inflammatory agents (NSAIDs) have been investigated as alternatives, but are not in widespread use at this time. They include ibuprofen [26] and more recently the newer class of COX-2 inhibitors [27]. Mannitol given as a bolus (0.25 to 1 g/kg every 4 hours to 6 hours) also can acutely reduce symptoms associated with peritumoral edema [24•]. Anticonvulsants are given prophylactically after resection and for patients who present with seizures.

Dexamethasone

Standard dosage	Initially, dexamethasone 4 mg orally four times daily, then slow taper, reducing dose by 2 mg every 3 days to 7 days.
Contraindications	No clear benefit to prophylactic use without clinical evidence of vasogenic edema or mass effect.
Main side effects	Hyperglycemia, insomnia, emotional lability, steroid induced proximal muscle wasting, weight gain and adiposity, osteoporotic compression fractures, and aseptic necrosis of the hip joints.
Special points	Too rapid a taper may result in significant, possibly life-threatening morbidity.
Cost effectiveness	Inexpensive, rapid symptomatic therapy.

Surgery

- Traditionally, many authors have advocated gross total resection of tumor, which is generally defined as the absence of residual enhancement on contrast-enhanced postoperative MRI scan. The rationale for open craniotomy depends on the need for immediate palliation of symptoms by reduction of intracranial pressure or focal mass effect, and/or improved oncologic control.
- Most retrospective studies have indicated that patients who have undergone a gross total resection of their lesion have enjoyed a longer survival than those who have not. Berger *et al* [15] have shown that patients with 100% resection of their tumor had no recurrence during a mean follow up time of 54 months. Patients with residual tumor that measured < 10 cm^3 had a 14.8% incidence of recurrence with time to tumor progression that lasted 50 months, a statistically significant improvement over the 46.2% incidence and 30 months seen in patients with larger residuals. Interestingly, the group of patients with large volume residuals also had a significantly higher incidence of recurrences at a higher histologic grade (46% versus 3.6%). In the pediatric population, the natural history of low-grade gliomas after radical resection (defined as >90% resection with <1.5 cm^3 of residual tumor) is currently being evaluated in a joint prospective trial by the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG). CCG9891/POG 9130 (also referred to as Intergroup [INT] 0128) now has more than 700 children enrolled who have been preliminarily evaluated [28]. Seventy-six percent of cases have been juvenile pilocytic astrocytomas, followed by low-grade diffuse (fibrillary) astrocytoma (8%), ganglioglioma (6%), oligodendroglioma (5%) and small numbers of other histologic subtypes. So far there does not appear to be a significant difference in progression-free survival between pilocytic and diffuse astrocytomas after radical resection. When

breaking these tumors down by location, cerebellar hemisphere gliomas make up 32% of all tumors, cerebellar vermis 18% and cerebral hemisphere gliomas 28%. All of these have a similar 5-year progression-free survival (approximately 80%) after radical resection. Midline and chiasmatic-hypothalamic tumors, which make up 19% and 4% of tumors, respectively, have higher relapse rates (approximately 67% and 40%, respectively) than those in the other locations mentioned. However, these tumors also are less frequently resected, due to their sensitive locations. Overall, it would appear that gross total resection, when safely achievable, is desirable.

- Depending upon the proximity of the tumor to eloquent brain, gross total resection may or may not be possible. Brain mapping during removal of the tumor may be required to achieve this goal safely. In patients with low-grade gliomas and intractable seizures, intraoperative electrocorticography also is desirable to achieve the best postoperative seizure control [29, 30].
- When the benefits of surgical resection or debulking are uncertain or outweighed by the risks of the procedure, at minimum a stereotactic biopsy is required to provide a histological diagnosis. This is because currently it is impossible to determine the pathology of an intracranial lesion by diagnostic imaging alone. Furthermore, many asymptomatic patients with imaging evidence of a small lesion associated with little or no mass effect potentially are excellent candidates for MRI-guided stereotactic biopsy and thus may avoid the risks, though relatively small, of a standard craniotomy.
- If only a biopsy is performed or if the resection is incomplete, adjuvant treatment is usually required. Lunsford *et al* [31] have suggested that biopsy alone followed by adjuvant radiotherapy is an appropriate initial management strategy. This argument is strengthened by data from prospective randomized studies that evaluate the addition of adjuvant radiotherapy to biopsy or subtotal resection (discussed below in the section on radiotherapy). Thus, it would appear reasonable to attempt a gross total removal of the tumor if this can be done without producing a postoperative neurological deficit. In all other patients, biopsy followed by adjuvant radiotherapy can be expected to provide an optimum of local control without unnecessary neurological deficits.

Standard procedure Gross total resection by open craniotomy.

Contraindications Location of tumor such that resection is associated with excessive morbidity.

Complications Bleeding, infection, CSF leak, neurologic impairment, death.

Special points If gross total resection is not achievable, biopsy alone may be adequate if adjuvant radiotherapy is given. All patients should be seen in a multidisciplinary fashion before surgery. Referral to a major medical center with open trials should be considered, especially for pediatric patients.

Cost effectiveness Cost effective if gross total resection achieved; otherwise, stereotactic biopsy is more cost-effective, because the patient also will incur cost of necessary adjuvant radiotherapy.

Table 4. Dose-response of unfavorable low-grade gliomas to radiation in randomized trials

Dose	OS_5 (%)	PFS_5 (%)	Study
45 Gy	58	47	$EORTC_{36}$
50.4 Gy	73	N/A	$NCCTG_{12}$
54 Gy	66	44	$EORTC_{33}$
59.4 Gy	59	50	$EORTC_{36}$
64.8 Gy	68	N/A	$NCCTG_{12}$
Observation	63	37	$EORTC_{33}$

OS_5=Overall survival at 5 years; PFS_5=progression-free survival at 5 years.

Radiotherapy

- Radiotherapeutic management of low-grade gliomas has traditionally been based on retrospective series from large institutions, largely due to the low incidence of these tumors (*vide infra*). However, in the last several years, the publication of several large national Phase III randomized trials has helped to define the optimum management of these lesions. A review of some of the most important recent retrospective reports is illustrative in showing how these trials came about. The results of the randomized trials are summarized in Table 4.
- The review by Laws *et al* [11] of patients treated at the Mayo Clinic revealed that gross total resection alone was determined to be adequate treatment in young patients. Adjuvant radiotherapy appeared to benefit patients with adverse prognostic factors. Lunsford *et al* [31] have reported their experience with adult patients with nonpilocytic, nonanaplastic astrocytomas who underwent stereotactic biopsy and radiotherapy to a median dose of 56 Gy. Median survival was 9.8 years after completion of treatment and 12.3 years from the time of onset of neurologic symptoms. Wallner *et al* [32] also have shown a benefit with postoperative radiotherapy for oligodendrogliomas, with 10-year survival rates of 56% versus 18% with and without radiotherapy, respectively.
- To determine the need for adjuvant radiotherapy in patients with unfavorable low-grade gliomas, the European Organization for the Research and Treatment of Cancer (EORTC) mounted a phase III randomized prospective trial. Patients with incompletely resected pilocytic astrocytomas and grade II astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas were randomized to observation versus localized radiotherapy to a total of 54 Gy in 30 fractions [33••, 34]. For patients in the observation arm who showed evidence of disease progression, the trial recommended the same radiotherapy for salvage as in the treatment arm. Sixty-two percent of patients underwent bulk removal and 38 % had only a biopsy performed. Sixty-five percent of patients were found to have astrocytomas and 25% had oligodendrogliomas, with the remainder being mixed histologies. At 4.6 years median follow-up the 5-year progression-free survival was statistically significantly in favor of the radiotherapy arm at 44% versus 37%, although overall survival was not statistically different (66% versus 63%). Sixty-five percent of the patients in the observation arm received radiotherapy for salvage. Although a more detailed analysis of the data is still pending, it appears convincing that radiotherapy does prevent local recurrence in unfavorable low-grade gliomas. Accordingly, the current RTOG phase III trial 98-02 has immediate radiotherapy as the standard arm (to be compared to immediate radiotherapy followed by PCV chemotherapy) for unfavorable patients

(age 40 and older or 18 and older with subtotal resection of a grade II lesion); favorable patients (patients younger than 40 with gross total resection of grade II tumors) are stratified to the Phase II arm, which is observation alone.

- Another area of controversy is the dose required to control low-grade lesions. Lote *et al* [13] reviewed 379 patients with low-grade gliomas who received adjuvant radiotherapy. They were unable to show a significant difference in survival between patients who received 45 Gy to 50 Gy, 51 Gy to 55 Gy, and greater than or equal to 56 Gy (up to 70.4 Gy). Lindegaard *et al* [35] retrospectively have suggested that doses of 40 Gy to 50 Gy are as effective as doses of 50Gy to 60 Gy in achieving local control. However, Shaw *et al* [14] also evaluated the Mayo Clinic experience for data regarding optimum radiotherapy dose. They demonstrated that 5-year survival for patients receiving >53 Gy was 68% as opposed to 48% for those receiving <53 Gy; at 10 years this difference was maintained at 39% and 11%, respectively.
- Subsequently, two prospective phase III randomized trials have attempted to answer the question of what the optimum radiation dose is. The EORTC randomized completely or incompletely resected WHO grade II astrocytoma, oligo-astrocytoma, or oligodendroglioma, and incompletely resected grade I pilocytic astrocytoma to either 45 Gy in 25 fractions or 59.4 Gy in 33 fractions delivered locally [36••]. Sixty percent of patients had grade 2 astrocytomas, 22% had oligodendrogliomas, with mixed and pilocytic tumors equally divided among the rest. Forty-five percent of patients underwent only biopsy or minimal resection, although gross total resection was performed in 25% of patients. With a median follow-up time of 74 months, overall survival (58% versus 59%, low-dose versus high-dose) and progression-free survival (47% versus 50%, low-dose versus high-dose) were not statistically significantly different at 5 years. Young age, the extent of resection, and pilocytic histology were again found to be statistically significant, favorable prognostic factors; all three predicted overall survival, although extent of resection and pilocytic histology but not age were predictive of progression-free survival.
- The second Phase III trial to evaluate dose was conducted jointly by the North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (NCCTG/RTOG/ECOG) [12••]. Patients with completely or incompletely resected Grade II astrocytoma, oligo-astrocytoma or oligodendroglioma were randomized to local radiotherapy, either 50.4 Gy versus 64.8 Gy. Eighty-five percent of patients had either biopsy or subtotal resection and median follow-up was 4.25 years. Multivariate analysis identified age and histologic subtype as the only significant prognostic factors. Five-year survival was not statistically different between the two dose arms: 73% for the low-dose versus 68% for the high-dose group.
- Regarding the safety of adjuvant radiotherapy, North *et al* [37] reviewed a series of patients treated at Johns Hopkins with doses of 50 Gy to 55 Gy and found that 67 % of long-term survivors were intellectually and physically intact without major neurologic deficits. Marks and Wong [38] reviewed many patients treated with radiotherapy for brain tumors and found a correlation between dose and radiation necrosis: 1.5% at 55 Gy, 4% at 60 Gy, and higher rates above 60 Gy. Shaw *et al* [12••]have demonstrated a 1% incidence of grade 3 to 5 radiation necrosis at 2 years in patients with low-grade gliomas treated with 50.4 Gy versus 4.5% necrosis when treated with 64.8 Gy. Also, a subset of the patients entered on NCCTG dose response trial 86-72-51 have been prospectively evaluated

regarding neurocognitive function (*ie*, with pre- and post-treatment testing and long-term follow-up [39•]. No difference has been demonstrated between the two arms regarding loss of intellectual function, new learning, or memory. Long-term follow-up data have been presented and at 5 years, radiotherapy has not been shown to be a predictor for cognitive deterioration [40•]. Thus, doses in the range of 50 Gy to 55 Gy given to patients with unfavorable prognostic factors appear to provide good overall and progression-free survival with an acceptable safety profile.

Standard procedure 50.4 Gy to 54 Gy conventionally fractioned.

Contraindications Patients younger than 40 years of age with gross total resection of grade II tumors may be observed; patients with pilocytic astrocytomas could be considered for observation.

Complications Cognitive sequelae uncommon at the above doses; neurocognitive delay in young children a potential consideration. Focal alopecia, mild skin irritation, and edema are easily managed. Hypothalamic-pituitary axis dysfunction, and visual deficits.

Special points Referral to a major medical center with open trials should be considered, especially for pediatric patients.

Cost effectiveness Adjuvant radiotherapy is considered standard of care in most instances; price is determined by regional and national reimbursement issues.

Chemotherapy

- Data for the use of chemotherapy in the management of low-grade gliomas have been mostly retrospective. Lote *et al* [13] reviewed a series of 379 patients with low-grade gliomas, 40% of whom received CCNU chemotherapy. On retrospective analysis, chemotherapy was not found to be associated with an increase in survival.
- Only a single prospective randomized trial that evaluated adjuvant chemotherapy in patients with low-grade gliomas has been completed. Mounted by the Southwestern Oncology Group (SWOG), it randomized patients with low-grade gliomas (gemistocytic astrocytomas, pilocytic astrocytomas, mildly anaplastic astrocytomas, oligodendrogliomas, mixed gliomas, and gangliogliomas) to receive radiation therapy alone or with CCNU after gross total resection. This trial demonstrated that the addition of CCNU to radiotherapy did not improve response rate (79% RT versus 54 % CCNU + RT) or median survival (4.45 years) [41•].
- Multi-agent chemotherapy appears somewhat more promising based on retrospective data (initially in the setting of recurrent disease), and is now being evaluated prospectively. The Dutch Neuro-Oncology Group has published its experience with procarbazine, CCNU, and vincristine (PCV) given for recurrent oligodendrogliomas and mixed oligo-astrocytomas initially treated with surgery and adjuvant radiation [42]. Forty-five percent of patients with initial diagnosis of low-grade oligodendroglioma and 33% of patients with mixed tumors responded. However, histologic confirmation of grade at the time of recurrence was not mandated. The NCCTG has published preliminary results of PCV chemotherapy given as initial therapy to patients with newly diagnosed low-grade oligodendrogliomas or mixed oligo-astrocytomas [43]. Of the evaluable patients, 33 % responded, 56% had stable disease, and 11% had disease progression based on post-chemotherapy, pre-irradiation MRI scans when compared to baseline imaging studies. However, 33% did not complete chemotherapy as planned because of toxicity. Thoron *et al.* [44] have reported preliminary results in 10 adult patients with low-grade oligodendrogliomas treated

with PCV chemotherapy after subtotal resection. Excessive toxicity led to only 20% of patients being able to complete more than 4 cycles of chemotherapy without complication.

- The current RTOG Phase III trial 98-02 hopes to answer the question of the efficacy of PCV in the use of newly diagnosed unfavorable low-grade gliomas. It randomizes unfavorable patients (age 40 and older or 18 and older with subtotal resection of a grade II lesion) to immediate radio therapy versus immediate radiotherapy followed by PCV chemotherapy. Favorable patients (patients younger than 40 with gross total resection of grade II tumors) are stratified to the Phase II arm, which is observation alone.

Standard procedure PCV currently most effective agent for recurrent tumors.

Contraindications Cannot yet be considered standard of care in the setting of newly diagnosed tumors.

Complications Hematologic toxicity, especially low platelet counts.

Special points Referral to a major medical center with open trials should be considered, especially for pediatric patients.

Cost effectiveness No clear data available.

Emerging therapies

Radiosurgery

- Currently, radiosurgery, whether by Gamma Knife [45•] or linear accelerator [46], is not considered first-line treatment for low-grade gliomas. In the setting of a well-circumscribed recurrence after standard irradiation, radiosurgery may provide local control. Shaw *et al* [47••] have published the results of a landmark radiosurgery dose seeking trial conducted by the RTOG. They report maximum tolerated doses of 24 Gy, 18 Gy, and 15 Gy for tumor diameters less than or equal to 20 mm, 21 mm to 30 mm and 31mm to 40 mm, respectively.

Future directions

- Temozolomide is an oral second generation alkylating agent currently approved for use in recurrent anaplastic astrocytomas. Its efficacy in the setting of low-grade gliomas currently is under investigation and appears promising in cell lines [48] and in phase II testing. Initial data have come from the use of the drug in the second line setting. The EORTC has shown that recurrent oligodendrogliomas previously treated with PCV have a modest but real response to temozolomide [49]. Friedman *et al* [50] evaluated the activity of temozolomide in a phase II study, giving the drug every 4 weeks to patients with progressive low-grade glioma. Sixty-five percent of patients have shown radiographic responses, with 20% of patients awaiting evaluation. Viviers *et al* assessed temozolomide in patients with stable and progressive low-grade gliomas who had had no therapy other than surgery [51, 52]. The drug was given every 4 weeks up to 12 cycles or until tumor progression. Objective radiological responses were seen in 21% of patients at 6 months and 37% of patients at 12 months. The efficacy of temozolomide remains to be proven in a phase III setting.
- Progress also is being made in the mapping of genetic alterations and in determining their relation to chemosensitivity. Loss of heterozygosity (LOH) at 19q and deletion of chromosome 1p is found in 40% to 80% of oligodendroglial tumors [53, 54]. These 1p and 19q deletions are

independently associated with prolonged survival in oligodendrogliomas and are predictive of sensitivity to PCV chemotherapy in anaplastic oligodendrogliomas [55, 56]. Buckner *et al* [43] in their trial of PCV as initial therapy in patients with low-grade oligodendroglioma or oligoastrocytoma, found that no 1p or 19q alterations were seen in patients with oligoastroctyomas, but were present on 69% of patients with pure oligodendrogliomas. In addition, deletions of one or both genes occurred in 46% of those patients who showed stable disease [43]. Data by Smith *et al*. [56] have shown statistically significant correlation between loss of 1p and/or 19q and the oligodendroglial phenotype. The combined loss of both also was a statistically significant predictor for prolonged overall survival, even after adjusting for the effects of patient age and tumor grade. Alternatively, loss of chromosome 9p and the P16 gene are associated with tumor progression and shorter survival [55,57]. Conceivably, chromosome testing may be used in future trials to stratify patients to predict chemotherapy response.

Standard procedure No clear standard. Radiosurgery reasonable for small, well-circumscribed unifocal recurrences. Temozolomide appears promising. Genetic susceptibility testing for PCV chemotherapy may become standard some years in the future.

Contraindications Radiosurgery is not optimum therapy for diffusely infiltrative lesions. Chemotherapy response often transient with recurrent disease.

Complications Tumor necrosis that requires steroids and/or operation with radiosurgery. Chemotherapy side effects depend on individual therapy; beyond scope of this discussion.

Special points Referral to a major medical center with open trials should be considered for all recurrences.

Cost effectiveness Most are potentially expensive, but benefit to individual patient (and to society if patient is enrolled on a trial) may outweigh cost issues.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Statistical Report: **primary brain tumors in the United States, 1992–1997.** *Central Brain Tumor Registry of the United States* 2000,

Current epidemiological data.

2.• Woolam G: **Cancer Statistics, 2000: a benchmark for the new century.** *CA Cancer J Clin* 2000, **50:**7–33.

Current epidemiological data.

3. Davis FG, Kupelian V, Freels S, *et al.*: **Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups.** *Neuro-Oncol* 2001, **3:**152–158.

4.•• World Health Organization. *Classification of Tumours, Pathology and Genetics of Tumours of the Nervous System.* Edited by Kleihues P, Cavence WK. Lyon, France: IARC Press; 2000.

This is the international standard of pathologic classification of primary brain tumors, recently updated.

5. Jukich PJ, McCarthy BJ, Surawicz TS, *et al.*: **Trend in incidence of primary brain tumors in the United States, 1985–1994.** *Neuro-Oncol* 2001, **3:**141–151.

6. Brain Tumors: *An Encyclopedic Approach,* edn. 2. Edited by Kaye AH, Laws ER. London, UK: Churchill Livingstone; 2001.

7. *Cancer of the Nervous System,* edn. 1. Edited by Black PM, Loeffler JS. Boston: Blackwell Science; 1997.

8. *The Gliomas.* Edited by Berger M, Wilson C. Philadelphia: WB Saunders; 1999.

9. *The Practical Management of Low-Grade Primary Brain Tumors.* Edited by Rock JP, Rosenblum M, Shaw E, Cairncross J. Philadelphia: Lippincott Williams & Wilkins; 1999.

10.• Shaw E: **Low Grade Gliomas.** *Sem Radiat Oncol* 2001, 2:93–180.

Comprehensive recent overview of the management of low-grade gliomas.

11. Laws ER Jr, Taylor WF, Clifton MB, *et al.*: **Neurosurgical management of low-grade astrocytomas of the cerebral hemispheres.** *J Neurosurg* 1984, **61:**665–673.

12.•• Shaw E, Arusell R, Scheithauer B, *et al.*: **A prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade gliomas: initial report of a NCCTG-RTOG-ECOG study abstract].** *Proc ASCO* 1998, **17:**401a.

Phase III trial that examines the question of radiotherapy dose.

13. Lote K, Egeland T, Hagar B, *et al.*: **Survival, prognostic factors, and therapeutic efficacy in low-grade gliomas: a retrospective study in 379 patients.** *J Clin Oncol* 1997, **15:**3129–3140.

14. Shaw EG, Daumas-Duport C, Scheithauer BW, *et al.*: **Radiation therapy in the management of low-grade supratentorial astrocytomas.** *J Neurosurg* 1989, **70:**853–861.

15. Berger M, Deliganis A, Dobbins J, *et al.*: **The effect of extent of resection on recurrence in patients with low-grade cerebral hemisphere gliomas.** *Cancer* 1994, **74:**1784–1791.

16.• Bauman G, Lote K, Larso D, *et al.*: **Pretreatment factors predict overall survival for patients with low-grade gliomas:a recursive partitioning analysis.** *Int J Radiat Oncol Biol Phys* 1999, **45:**923–9239.

Recent recursive partitioning analysis of prognostic factors.

17. Brown J, Byers T, Thompson K, *et al.*: **Nutrition during and after cancer treatment: a guide for informed choices by cancer survivors.** *CA Cancer J Clin* 2001, **51:**153–187.

18. National Radiological Protection Board: **Electromagnetic fields and the risk of cancer. National Radiological Protection Board, Report of an advisory group on non-ionising radiation.** *Doc NRBP* 1992, **3:**1–138.

19. Giles GG, Gonzales MF: Epidemiology of brain tumors and factors in prognosis. In *Brain Tumors: An Encyclopedic Approach,* edn. 2. Edited by Kaye AH, Laws ER. London, UK: Churchill Livingstone, 2001:189–215.

20.• Ricci PE, Dungan DH: **Imaging of low- and intermediate-grade gliomas.** *Sem Radiat Oncol* 2001, **11:**103–112.

Useful summary of diagnostic imaging criteria.

21. Leiguarda R, Sierra J, Pardal C, *et al.*: **Effect of large doses of methylprednisolone on supratentorial intracranial tumors. A clinical and CAT scan evaluation.** *Eur Neurol* 1985, **24:**23–32.

22. Yamada K, Ushio Y, Hayakawa T: Effects of steroid on the blood brain barrier. In *Implications of the Blood-brain Barrier and its Manipulation.* Edited by Neuwelt EA. New York: Plenum Press, 1989;**1:**53–76.

23. Thapar K, Taylor MD, Laws ER, *et al.*: Brain edema, increased intracranial pressure, and vascular effects of human brain tumors. In *Brain Tumors: An Encyclopedic Approach* edn. 2. Edited by Kaye AH, Laws ER. London, UK: Churchill Livingstone, 2001:189–215.

24.• Tatter SB: **Neurosurgical management of low- and intermediate-grade gliomas.** *Semin Radiat Oncol* 2001, **11:**113–123.

Comprehensive overview of surgical management of low-grade gliomas.

25. Bilsky M, Posner JB: Intensive and postoperative care of intracranial tumors. In *Neurological and Neurosurgical Intensive Care,* edn. 3. Edited by Ropper AH. New York: Raven Press, 1993:309–329.

26. Del Maestro RF, Megyesi JF, Farrell CL: **Mechanisms of tumor-associated edema: a review.** *Can J Neurol Sci* 1990, **17:**177–183.

27. Grossman SA, Suleman S, Eller S, *et al.*: **Novel COX-2 inhibitor is equal to dexamethasone in prolonging survival in rats with 9L gliomas.** *Proc ASCO* 2001, **20:**53a.

28. Watson GA, Kadota RP, Wisoff JH: **Multidisciplinary management of pediatric low-grade gliomas.** *Semin Radiat Oncol* 2000, **11:**152–162.

29. Berger M, Rostomily R: **Low-grade gliomas: functional mapping resection strategies, extent of resection, and outcome.** *J Neurooncol* 1997, **34:**85–101.

30. Berger M, Wilson C: Extent of resection and outcome for cerebral hemispheric gliomas. In *The Gliomas.* Edited by Berger M, Wilson C. London, UK: WB Saunders, 1999:660–679.

31. Lunsford LD, Somaza S, Kondziolka D, Flickinger JC: **Survival after stereotactic biopsy and irradiation of cerebral nonanaplastic, nonpilocytic astrocytoma.** *J Neurosurg* 1995, **82:**523–529.

32. Wallner KE, Gonzales M, Sheline GE. **Treatment of oligodendrogliomas with or without postoperative irradiation.** *J Neurosurg* 1988, **68:**684–688.

33.•• Karim AB, Cornu N, Bleheem D, *et al.*: **Immediate postoperative radiotherapy in low-grade gliomas improves progression free survival, but not overall survival: preliminary results of an EORTC/MRC randomized phase III study.** *Proc ASCO* 1998, **17:**400a.

Phase III trial that examines the need for adjuvant radiotherapy.

34. Bolla M. **EORTC trials: a bridge between two millennia abstract].** *Radiother Oncol* 2001, **58:**S58.

35. Lindegaard KF, Mork SJ, Eide GE, *et al.*: **Statistical analysis of clinicopathological features, radiotherapy, and survival in 170 cases of oligodendroglioma.** *J Neurosurg* 1987, **67:**224–230.

36.•• Karim A, Maat B, Hatlevoll R, *et al.*: **A randomized trial of dose-response in radiation therapy of low-grade gliomas: EORTC Study 22844.** *Int J Radiat Oncol Biol Phys* 1996, **36:**549–556.

This phase III trial examines the question of radiotherapy dose.

37. North CA, North RB, Epstein JA, *et al.*: **Low-grade cerebral astrocytomas: survival and quality of life after radiation therapy.** *Cancer* 1990, **66:**6–14.

38. Marks JE, Wong I: **The risk of cerebral radionecrosis in relation to dose, time and fractionation: a follow-up study.** *Prog Exp Tumor Res* 1985, **29:**210–218.

39.• Hammack J, Shaw E, Ivnik R, *et al.*: **Neurocognitive function in patients receiving radiation therapy for supratentorial low-grade gliomas: a North Central Cancer Treatment Group prospective study abstract].** *Proc ASCO* 1995, **14:**151.

Examines a subgroup of patients from a phase II randomized prospective trial for cognitive deficits from radiotherapy.

40.• Brown PD, Buckner JC, Brown CA, *et al.*: **The effects of radiation on cognitive function in patients with low-grade gliomas.** *Proc ASCO* 2001, **20:**58a.

Examines a subgroup of patients from a phase II randomized prospective trial for cognitive deficits from radiotherapy.

41.• Eyre HJ, Eltringham JR, Crowley J, *et al.*: **A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: Southwest Oncology Group Study.** *J Neurosurg* 1993, **78:**909–914.
Phase III trial that demonstrates the lack of efficacy of single-agent chemotherapy.

42. Van den Bent MJ, Kros JM, Heimans JJ, *et al.*: **Response rate and prognostic factors of recurrent oligodendroglioma treated with procarbazine, CCNU, and vincristine chemotherapy.** *Neurol* 1998, **51:**1140–1145.

43. Buckner JC, Smith JS, Nelson DF, *et al.*: **Phase II trial of procarbazine, CCNU, and vincristine (PCV) as initial therapy in patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy results and associations with chromosome 1p and 19q loss abstract].** *Proc ASCO* 1999, **18:**140.

44. Thoron L, Colinskas C, McDevitt K, et al.: **Adjuvant I-PCV chemotherapy for treatment of low-grade oligodendroglioma.** *Proc Am Soc Clin Oncol* 1997, **16:**410.

45.• Leksell L. **The stereotaxic method and radiosurgery of the brain.** *Acta Chir Scand* 1951, **102:**316–319.
Seminal paper from the inventor of the Elekta Gamma Knife and modern radiosurgery.

46. Friedman WA, Bova FJ: **The University of Florida radiosurgery system.** *Surg Neurol* 1989, **32:**334–342.

47.••Shaw E, Scott C, Souhami L, *et al.*: **Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05.** *Int J Radiat Oncol Biol Phys* 2000, **47:**291–298.
Landmark radiosurgery dose-escalation trial.

48. van Rijn J, Heimans JJ, van den Berg J, *et al.*: **Survival of human glioma cells treated with various combination of temozolomide and x-rays.** *Int J Radiat Oncol Biol Phys* 2000, **47:**779–784.

49. van den Bent MJ, Chinot O, Boogerd W, *et al.*: **EORTC study 26972: second line temozolomide chemotherapy in recurrent oligodendroglial tumors after PCV chemotherapy.** *Proc ASCO* 2001, **20:**52a.

50. Friedman AH, Cokgor I, Edward S, *et al.*: **Phase II treatment of anaplastic oligodendroglioma and low-grade gliomas with temozolomide. abstract].** *Proc ASCO* 2000, **19:**169.

51. Viviers L, Brada M, Hines F, *et al.*: **A phase II trial of primary chemotherapy with temozolomide in patients with low-grade cerebral gliomas abstract].** *Proc ASCO* 2000, **19:**167.

52. Viviers L, Murphy P, Britton J, *et al.*: **A phase II trial of primary chemotherapy with temozolomide in patients with low-grade cerebral gliomas.** *Radiother Oncol* 2001, **58:**S58.

53. Smith JS, Alderet B, Minn T, *et al.*: **Localization of common deletion regions on 1p and 19q in human gliomas and their association with histological subtype.** *Oncogene* 1999, **18:**4144–4152.

54. Reifenberger J, Reifenberger G, Liu L, *et al.*: **Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p.** *Am J Pathol* 1994, **145:**1175–1190.

55. Cairncross JG, Ueki K, Zlatescu MC, *et al.*: **Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendroglioma.** *J Natl Cancer Inst* 1998, **90:**1473–1479.

56. Smith JS, Perry A, Borell TJ, *et al.*: **Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas.** *J Clin Oncol* 2000, **18:**636–645.

57. Bigner SH, Matthews MR, Rasheed BK, *et al.*: **Molecular genetic aspects of oligodendrogliomas including analysis of comparative genomic hybridization.** *Am J Pathol* 1999, **155:**375–386.