

LOW-GRADE ASTROCYTOMAS AND OLIGODENDROGLIOMAS

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The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

By the end of 2009, it is estimated that 2600 new cases of central nervous system (CNS) tumours will be diagnosed in Canada, and 1750 deaths from CNS tumours will occur during the same period.¹ Primary brain tumours are a heterogeneous group of neoplasms with varied treatment strategies and outcomes. The Alberta Provincial CNS Tumour Team uses the classification system of the World Health Organization (WHO) to describe CNS tumours, which is based on histologic features of the tumour.² Table 1 outlines the grades and histologic characteristics:

Table 1. World Health Organization Grading of Central Nervous System Tumours²

WHO Grade	Histologic Characteristics
Grade I	Includes lesions with low proliferative potential and a frequently discrete nature; surgical resection is the main treatment.
Grade II	Includes lesions that are generally infiltrating and low in mitotic activity but recur. Some tumour types tend to progress to higher grades of malignancy.
Grade III	Includes lesions with histologic evidence of malignancy, generally in the form of mitotic activity, clearly expressed infiltrative capabilities, and anaplasia.
Grade IV	Includes lesions that are mitotically active with vascular proliferation, necrosis-prone, and generally associated with a rapid preoperative and postoperative evolution of disease.

Low-grade gliomas consist of both WHO grades I and II astrocytic, oligodendroglial, mixed or ependymal origin tumours.³⁻⁴ The present guideline will address only low-grade astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas; ependymomas are addressed in a separate guideline (CNS-004).

Patients with low-grade gliomas tend to be young, between the second and fourth decades of life, and present with seizures in up to 90 percent of the cases.³⁻⁴ Because these patients are usually otherwise healthy individuals with no neurological deficits, the timing of interventions such as radiotherapy and chemotherapy, extent of surgical resection, and long-term benefits and risks of therapy, are often controversial. Survival and response rates are usually related to histology type, size of tumour, age of the patient, and mental status.³⁻⁴

GUIDELINE GOALS AND OBJECTIVES

- To develop an evidence-based guideline for the management of low-grade astrocytomas and oligodendrogliomas.

GUIDELINE QUESTIONS

- What is the role of surgery in the management of low-grade gliomas?
- Which are the recommendations for radiotherapy in the management of low-grade gliomas?
- What is the role of chemotherapy in the management of low-grade gliomas?
- What treatment options are recommended for high risk patients with low-grade gliomas?

DEVELOPMENT PANEL

This updated **guideline** was reviewed and endorsed by the Alberta Provincial CNS Tumour Team. Members of the Alberta Provincial CNS Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, neurosurgeons, nurses, neuropathologists, and pharmacists. Updated **evidence** was

selected and reviewed by a working group comprised of members from the Alberta Provincial CNS Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

SEARCH STRATEGY

Medical journal articles were searched using the Medline (1950 to November Week 4, 2009), EMBASE (1980 to November Week 4), Cochrane Database of Systematic Reviews (3rd Quarter, 2009), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Glioma [MeSH heading], Brain Neoplasms [MeSH heading], Astrocytoma [MeSH heading], Oligodendroglioma [MeSH heading], low-grade glioma, practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Articles were excluded from the review if they: had a non-English abstract, were not available through the library system, were case studies involving less than 5 patients, involved pediatric patients, or were published prior to the year 2000. All retrieved articles were graded using the criteria outlined by *Lau et al.*⁵ A review of the relevant existing practice guidelines for low-grade gliomas, astrocytomas, and oligodendrogliomas was also conducted by accessing the practice guidelines on the websites of the British Columbia Cancer Agency (BCCA), National Comprehensive Cancer Network (NCCN), the Australian Cancer Network, and the National Institute for Health and Clinical Excellence (NICE).

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

RECOMMENDATIONS

1. In patients with a low-grade glioma and controlled epilepsy as the single symptom, surgery may be deferred until clinical or radiological progression.
2. Whenever possible, maximal surgical resection should be attempted in patients who have increased intracranial pressure, neurological deficits, uncontrollable seizures, or in those who have clinical or radiological progression.
3. For patients who undergo a complete surgical resection, radiotherapy may be deferred until clinical or radiological disease progression; in such cases, regular follow-up is essential.
4. Post-surgical radiotherapy may be administered to patients who undergo an incomplete surgical resection or biopsy only. When radiotherapy is indicated, the dose should be between 45 and 54 Gy, delivered in 1.8 to 2.0 Gy fractions.
5. Chemotherapy should not be routinely added to radiation therapy for first line treatment following surgery, since the combination shows limited benefit in comparison to radiotherapy alone following surgery, and may increase toxicity.
6. At disease progression or recurrence, the standard treatment is repeat surgical resection followed by radiotherapy. Temozolomide may also be considered for the treatment of disease recurrence, particularly for patients that harbour a combined chromosome 1p/19q loss of heterozygosity.
7. For high risk patients, inclusion in a clinical trial is recommended. In the absence of a clinical trial adjuvant chemotherapy and radiation therapy may be considered on an individual basis.

DISCUSSION

The treatment of low-grade gliomas is a challenging task, and requires a multidisciplinary approach which can include surgery, radiotherapy, and/or chemotherapy. Survival times and response rates are related to tumour type (oligodendrogliomas or oligo-dominant mixed histology are associated with better survival), size (smaller size is associated with better survival), age of the patient (younger is better), and mental status.⁶ WHO grade I gliomas, which consist primarily of pilocytic astrocytomas, are generally treated with surgery alone, and radiotherapy is only used in circumstances where surgery is not possible. Therefore, throughout this guideline, the term “low-grade glioma” will be used to describe WHO grade II astrocytomas, oligodendrogliomas, and mixed oligodendrogliomas.

Surgery

Tumour location is the principal factor determining resectability in low-grade gliomas. Although biopsy remains necessary for pathological diagnosis of a suspected low-grade glioma⁶, there are currently no published randomized clinical trials to determine the benefit of early versus late surgery or the effect of the extension of the resection in these tumours; thus current management is based on retrospective studies only. In one retrospective study by *van Veelen et al.*, patients with low-grade astrocytomas and controlled seizures as the single symptom had a better prognosis than those with more symptoms (5-year overall survival = 63% versus 27%), and the prognosis was not influenced by the timing of the surgery.⁷ The authors concluded that it was safe to defer surgery until clinical or radiological progression in patients with low-grade astrocytomas who experienced controlled epilepsy as their only symptom. Members of the Alberta Provincial CNS Tumour Team agree that in patients with a low-grade glioma and controlled epilepsy as the only symptom, surgery may be deferred until clinical or radiological progression (recommendation #1).

In 1994, *Berger et al.* analyzed the effect of extent of surgical resection on recurrence in patients with low-grade gliomas.⁸ They reported that for tumours larger than 10 cm³, a greater percent of resection and a smaller volume of residual disease conveyed a significant advantage in terms of recurrence, compared to those that had a less aggressive resection or biopsy. For tumours smaller than 10 cm³, no recurrence was detected over three to four years, regardless of the degree of resection. A critical review of 30 studies was performed by *Keles et al.* in 2001 in order to evaluate the extent of resection as a prognostic factor influencing outcome.⁹ Ten of the 30 studies they reviewed included five-year survival data, and the authors reported that the five-year survival rates were higher for patients who had undergone gross total resection compared to patients in whom lesser degrees of resection were achieved. They also determined that the extent of surgical resection at the time of the initial diagnosis was a statistically significant prognostic indicator of overall survival. Members of the Alberta Provincial CNS Tumour Team agree that for patients with low-grade astrocytomas and oligodendrogliomas who show disease progression, an increase in intracranial pressure, neurological deficits related to mass effect, or uncontrollable seizures, surgical debulking of the tumour is the standard approach (recommendation #2). In these cases, a gross total resection, when safe, should be the goal of surgery as there is a trend for better outcome based on the extent of resection.^{9,10}

Radiotherapy

Postoperative radiotherapy is a standard of therapy for low-grade gliomas to treat residual disease. Controversies exist, however, with regards to the optimal timing and doses of radiotherapy, as well as the ideal balance between tumour control and potential toxicities from radiotherapy. To date, three prospective randomized clinical trials have addressed these questions, the results of which are summarized in Table 2.¹¹⁻¹³

Table 2. Randomized Phase III Clinical Trials Addressing Radiotherapy for Low-Grade Gliomas

Author/ Study	N	Treatment Allocation	Survival Rate	p-Value
<i>van den Bent et al.</i> , 2005 ¹¹	154	early RT (54 Gy/ 30 fractions)	68.4% at 5 yrs	0.872
EORTC 22845	157	deferred RT (54 Gy/ 30 fractions)	65.7% at 5 yrs	
<i>Shaw et al.</i> , 2002 ¹²	101	low-dose RT (50.4 Gy/ 28 fractions)	85% at 2 yrs; 72% at 5 yrs	0.48
NCCTG/RTOG/ECOG	102	high-dose RT (64.8 Gy/ 36 fractions)	94% at 2 yrs; 65% at 5 yrs	
<i>Karim et al.</i> , 1996 ¹³	171	low-dose RT (45 Gy/ 25 fractions)	58% at 5 yrs	0.73
EORTC 22844	172	high-dose RT (59.4 Gy/ 33 fractions)	59 % at 5 yrs	

Timing of Radiotherapy: The EORTC 22845 clinical trial, published in 2005, compared immediate radiotherapy given after surgery versus radiotherapy after tumour recurrence.¹¹ At a median follow-up of eight years, the progression-free survival was 5.3 years for the immediate radiotherapy group versus 3.4 years for the deferred radiotherapy group, and the seizures were better controlled in the immediate radiotherapy group. However, there was no difference in five-year survival (68.4% versus 65.7%) or overall survival for the two groups in this study (7.4 years versus 7.2 years). The results of this study suggest that using the “wait and see” approach in which radiation is delayed until disease progression may be beneficial in postponing or avoiding potential radiation-associated toxicity in patients with low-grade gliomas. In a case-series involving 97 consecutive patients with WHO grade II astrocytomas, *Hanzély et al.* compared patients who received early postoperative radiotherapy (N=36) to those who received delayed postoperative radiotherapy (N=61).¹⁴ In the patients who underwent a subtotal resection, early postoperative radiotherapy was significantly associated with improved five-year progression-free survival (60.0% versus 12.4%, $p=0.0036$) and disease-specific survival (66.7% versus 49.8%, $p=0.0389$). However, in patients who underwent a gross total resection, the timing of postoperative radiotherapy had no effect on progression-free or disease-specific survival rates. The authors concluded that early postoperative radiotherapy was not of benefit for patients who underwent extensive surgical resections, and for these patients, radiotherapy should be withheld until disease progression.¹⁴

Dose of Radiotherapy: The EORTC 22844 clinical trial, published in 1996, showed no difference in overall survival or progression-free survival between low dose and high dose radiotherapy; however low dose radiotherapy resulted in less neurotoxicity and provided a better quality of life than the higher dose.¹³ The results of the EORTC 22844 trial were partially confirmed by a second study published in 2002 by *Shaw et al.*¹² Although the doses of radiotherapy differed from those used in the EORTC 22844 study, Shaw and colleagues also did not find an advantage for high- over low-dose radiotherapy in adults with supratentorial low-grade gliomas with regards to overall survival or time to tumour progression.¹²

Based on these data, the Alberta Provincial CNS Tumour Team members agree that, for patients who undergo a complete surgical resection, it is appropriate to defer the post-surgical radiotherapy until progression of disease; in such cases, regular follow-up is essential (recommendation # 3). Post-surgical radiotherapy may be administered to patients who undergo an incomplete surgical resection or biopsy only. When radiotherapy is indicated, the dose should be between 45 and 54 Gy, delivered in 1.8 to 2.0 Gy fractions (recommendation #4).

Chemotherapy

The role of chemotherapy in the management of low-grade gliomas is poorly defined. However the unique chemosensitivity of aggressive and anaplastic oligodendrogliomas to chemotherapeutic regimens such as procarbazine, lomustine and vincristine (PCV) has prompted recent investigations into the potential for the use of such regimens in the initial treatment of low-grade gliomas. To date, only two prospective randomized clinical trials addressing the addition of chemotherapy to radiotherapy have been published, and they are described below in Table 3.¹⁵⁻¹⁶ The RTOG study by *Shaw et al.* reported that in the short-term, patients who received radiotherapy followed by six cycles of PCV had a better progression-free survival compared to those without PCV. However, neither study demonstrated a benefit in overall survival with the addition of chemotherapy to radiotherapy, and both studies reported higher toxicity in the chemotherapy arm. Based on the results from these two trials, the Alberta Provincial CNS Tumour Team members recommend that chemotherapy should not be routinely added to radiation therapy for first-line treatment following surgery, since the combination shows limited benefit in comparison to radiotherapy alone following surgery, and may increase toxicity (recommendation #5).

Table 3. Randomized Clinical Trials Addressing Radiotherapy plus Chemotherapy for Low-Grade Gliomas

Author/Study	N	Treatment Allocation	Response Rate	Overall Survival	Progression-Free Survival
<i>Shaw et al.</i> , 2006 ¹⁵	126	RT alone (54 Gy/ 30 fractions)	not reported	63% at 5 yrs; mean=7.5 yrs	46% at 5 yrs; mean=4.4 yrs
RTOG-9802	125	RT + adjuvant PCV	not reported	72% at 5 yrs; mean=NR (HR=0.72, <i>p</i> =0.33)	63% at 5 yrs; mean=NR (HR=0.6, <i>p</i> =0.06)
<i>Eyre et al.</i> , 1993 ¹⁶	19	RT alone	79%	40% at 5 yrs	not reported
SWOG	35	RT + CCNU	54%	50% at 5 yrs (<i>p</i> =0.7)	

Abbreviations: RT=radiotherapy, PCV=procarbazine + CCNU + vincristine, CCNU=lomustine, NR=not reached, HR=hazard ratio.

Several phase II studies, both retrospective and prospective, have examined the role of chemotherapy in the treatment of newly diagnosed and progressive low-grade gliomas, and the results of these studies are summarized in Table 4. As shown in Table 4, irrespective of tumour histology, varying degrees of responses have been reported in these trials.^{17-24, 26-30} The largest study to date was performed by *Kaloshi et al.*, and involved a retrospective review of 149 patients with progressive low-grade gliomas who received temozolomide as their initial treatment after surgery.¹⁹ The treatment was well tolerated, and 53 percent of the patients had objective response (partial or minimal response); the median progression-free survival was 28 months, and the three-year survival was 69.8%. In this study, a combined 1p/19q chromosome deletion was significantly associated with a higher rate (*p*=0.02) and longer objective response to chemotherapy (*p*=0.0017), as well as longer progression-free survival (*p*=0.00041) and overall survival (*p*=0.04).¹⁹ Genetic alterations, specifically loss of heterozygosity (LOH) of chromosomes 1p and 19q, have been shown to be powerful predictors of response to chemotherapy and overall survival in several phase III trials of anaplastic gliomas.³¹⁻³² Although limited by their lack of control groups and retrospective designs, the results of several phase II studies add evidence that low-grade gliomas respond to temozolomide, and that, similar to the findings in anaplastic gliomas, 1p/19q LOH is associated with chemosensitivity and improved outcomes in progressive low grade gliomas.^{17-19, 22, 24, 25} The standard treatment at disease progression or recurrence is repeat surgical resection followed by radiotherapy. However, members of the Alberta Provincial CNS Tumour Team agree that chemotherapy with temozolomide may be considered on an individual basis for the treatment of disease progression or recurrence, particularly for patients that harbour a combined chromosome 1p/19q loss of heterozygosity (recommendation #6).

Table 4. Phase II Observational Studies of First Line Chemotherapy for Low-Grade Gliomas: 2000 to 2009

Author/Study	Indication for Chemotherapy	N	Histology	Regimen	Overall Response	Progression-Free Survival
<i>Kesari et al., 2009</i> ¹⁷	Initial and progression	44	O/ OA	TMZ: 75 mg/m ² /day 7 wks on/ 4 wks off x 6 cycles	20% PR 75% SD	median = 28 mos
<i>Tosoni et al., 2008</i> ¹⁸	Progression	30	O/ OA/ A	TMZ: 75 mg/m ² /day for 21 days every 28 days x 12 cycles max	30% PR 56.7% SD	median = 21.8 mos
<i>Kaloshi et al., 2007</i> ¹⁹	Progression	149	O/ OA/ A	TMZ: 200 mg/m ² /day on days 1-5 every 28 days	15% PR 38% MR 37% SD	79.5% at 12 mos 55.8% at 24 mos median = 28 mos
<i>Lebrun et al., 2007</i> ²⁰	Initial	33	O	PCV: Lomustine 110 mg/m ² day 1 + procarbazine 60 mg/m ² days 8-21 + vincristine 1.4 mg/m ² days 8 and 29 over 6 weeks x 6 cycles	3% CR 24.2% PR 54.5% SD	mean = 24.4 mos
<i>Pouratian et al., 2007</i> ²¹	Initial and progression	25	O/ OA/ A	TMZ: 75 mg/m ² /day for 21 days every 28 days x 16 cycles max	24% PR 28% MR 32% SD	92% at 6 mos 74% at 12 mos
<i>Levin et al., 2006</i> ²²	Progression	28	O	TMZ: 200 mg/m ² /day on days 1-5 every 28 days	35.7% PR 25% MR 35.7% SD	89% at 12 mos 70% at 24 mos median = 31 mos
<i>Biemond-ter Stege et al., 2005</i> ²³	Initial and progression	21	O/ OA	PCV : Lomustine 110 mg/m ² day 1 + procarbazine 60 mg/m ² days 8-21 + vincristine 1.4 mg/m ² days 8 and 29 over 6 weeks x 6 cycles	19.1% PR 57.1% MR 14.3% SD	median = > 24 mos
<i>Hoang-Xuan et al., 2004</i> ²⁴	Progression	60	O/ OA	TMZ: 200 mg/m ² /day on days 1-5 every 28 days x 12-24 cycles	17% PR 14% MR 61% SD	73.4% at 12 mos
<i>Pace et al., 2003</i> ²⁶	Progression	43	O/ OA/ A	First line TMZ : 200 mg/m ² /day on days 1-5 every 28 days Second line TMZ: 150 mg/m ² /day on days 1-5 every 28 days if pre-treated with PCV	9.3% CR 37.2% PR 39.5% SD	76% at 6 mos 39% at 12 mos median = 10 mos
<i>van den Bent et al., 2003</i> ²⁷	Progression	38	O/OA	TMZ: 200 mg/m ² /day on days 1-5 every 28 days x 12 cycles max	26.3% CR 26.3% PR 31.6% SD	71% at 6 mos 40% at 12 mos median = 10.4 mos
<i>Quinn et al., 2003</i> ²⁸	Progression	46	O/ OA/ A	TMZ: 200 mg/m ² /day on days 1-5 every 28 days x 12 cycles max	24% CR 37% PR 35% SD	98% at 6 mos 76% at 12 mos median = 22 mos
<i>Brada et al., 2003</i> ²⁹	Initial and progression	29	O/ OA/ A	TMZ: 200 mg/m ² /day on days 1-5 every 28 days x 12 cycles max	10.3% PR 48.3% MR 37.9% SD	76% at 24 mos 66% at 36 mos
<i>Buckner et al., 2003</i> ³⁰	Progression	28	O/ OA	PCV: Lomustine 130 mg/m ² day 1 + procarbazine 75 mg/m ² days 8-21 + vincristine 1.4 mg/m ² days 8 and 29 over 8 weeks x 6 cycles pre-radiotherapy	Pre-RT: 29% PR 61% SD Post -RT: 44% PR 44% SD	Kaplan-Meier estimates of recurrence-free at 1 and 2 years = 91% and 62% respectively

Abbreviations: O=oligodendroglioma, OA=oligoastrocytoma, A=astrocytoma, TMZ=temozolomide, PCV = procarbazine + lomustine + vincristine, CR=complete response, PR=partial response, MR=minimal response, SD=stable disease, RT=radiotherapy.

Comparison studies of temozolomide versus other chemotherapeutic agents or radiotherapy have not been published to date, but the question of whether upfront chemotherapy with temozolomide can replace initial radiotherapy is being addressed by an ongoing, large, multi-centre phase III clinical trial.³³ In the EORTC 22033-26033 trial, patients with low-grade gliomas are being randomized to receive either

radiotherapy (once daily, 5 days/week, for a total of 28 fractions) or temozolomide (75 mg/m²/day for 21 days every 28-days, to a maximum of 12 cycles).

High Risk Patients

In an analysis of the results from the two phase III EORTC trials of radiotherapy for low-grade gliomas (EORTC 22844¹³ and EORTC 22845¹¹), *Pignatti et al.* identified several criteria which are important prognostic factors for overall survival.³⁴ Based on these factors, patients with low-grade gliomas can be divided into two groups: low-risk patients are those who meet two or less of the following criteria, while high-risk patients are defined as those who meet at least three of the following criteria:

- Age ≥40 years
- Largest preoperative tumour diameter ≥6 cm
- Tumour crossing midline
- Tumour of astrocytoma histology
- Preoperative neurologic deficits (Neurologic Function Score >1)

Alternatively, the RTOG defines a “high risk” patient as one who is aged 40 years or older and has had a subtotal resection/biopsy, while a “low risk” patient is one who is younger than 40 years of age and has had a gross total resection. The RTOG is currently conducting a phase II non-randomized, multicentre study, the RTOG 0424, addressing the use of concurrent temozolomide and radiotherapy followed by 12 cycles of 4-weekly temozolomide chemotherapy for high-risk patients with low-grade gliomas.³⁵ Members of the Alberta Provincial CNS Tumour Team recommend that all high-risk patients should be encouraged to participate in appropriate clinical trials (recommendation #7). In the absence of a clinical trial, adjuvant chemotherapy and radiation therapy may be considered on an individual basis.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
A	astrocytoma
CCNU	lomustine
CNS	central nervous system
CR	complete response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
HR	hazard ratio
LOH	loss of heterozygosity
MR	minimal response
NCCTG	North Central Cancer Treatment Group
O	oligodendroglioma
OA	oligoastrocytoma
PCV	procarbazine + CCNU + vincristine
PR	partial response
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SD	stable disease
SWOG	Southwest Oncology Group
TMZ	temozolomide
WHO	World Health Organization

IMPLEMENTATION STRATEGY

- Present and review the guideline at local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in January 2011, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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