

ANAPLASTIC 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. |

Among adults, more than half of all gliomas are high-grade malignant neoplasms. These include anaplastic astrocytomas (WHO grade III), anaplastic oligodendrogliomas (WHO grade III), anaplastic oligoastrocytomas (WHO grade III), anaplastic ependymomas (WHO grade III) and glioblastoma (WHO grade IV).² For the remainder of this guideline, the term “anaplastic gliomas” will refer only to WHO grade III astrocytomas and oligodendrogliomas. Ependymomas and glioblastoma will each be addressed in separate reports (CNS-001 and CNS-004).

Anaplastic astrocytomas and oligodendrogliomas share several histopathological features:

- moderate hypercellularity
- moderate cellular and nuclear pleomorphism
- variable mitotic activity
- microvascular proliferation

In addition, several important prognostic indicators of survival have been identified and must be taken into account when evaluating the benefit of any therapeutic intervention.³⁻⁴

- age at diagnosis
- Karnofsky Performance Score (KPS)
- histological type (oligodendroglial, mixed or astrocytic)
- tumour grade (WHO grade III or IV)

GUIDELINE GOALS AND OBJECTIVES

- To develop evidence-based guidelines for the management of WHO grade III gliomas.

GUIDELINE QUESTIONS

- Is resection better than biopsy in the management of WHO grade III gliomas?
- What is the optimal radiation therapy plan for WHO grade III gliomas?
- What is the role of radiation and chemotherapy in the adjuvant treatment of WHO grade III 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, neuro-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 journals were searched using the Medline (1950 to December Week 2, 2009), Embase (1980 to December Week 2, 2009), Cochrane Database of Systematic Reviews (3rd Quarter, 2009), and PubMed databases. The search terms included Glioma [MeSH heading], Brain Neoplasms [MeSH heading], Astrocytoma [MeSH heading], Oligodendroglioma [MeSH heading], high-grade gliomas, anaplastic gliomas, practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. The references and bibliographies of articles identified through these searches were scanned for additional sources. 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 10 patients, involved pediatric patients, involved glioblastoma as the only high-grade glioma, or were published prior to the year 2000. All retrieved articles were graded using the criteria outlined by *Lau et al.*⁵

A search for new or updated clinical practice guidelines published from January 2000 to December 2009 was also conducted, and yielded eight published guidelines by the following organizations: Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia (CCNS), the National Comprehensive Cancer Network (NCCN), the National Cancer Institute (NCI), the National Institute for Health and Clinical Excellence (NICE), the Australian Cancer Network, and the European Society for Medical Oncology (ESMO).

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. Surgery is the initial recommended approach in patients with radiographically suspected anaplastic gliomas for debulking, clinical improvement and pathologic diagnosis/ tumour banking. Whenever possible, safe, maximal resection is preferred in the management of anaplastic gliomas. In some cases, a second resection may be indicated after initial biopsy.

2. Adjuvant radiation therapy is the standard of care for anaplastic gliomas following surgery. External beam radiation therapy should be given in standard fractionation to a maximum total dose of 59.4 to 60 Gy using 3D conformal planning techniques. The volume treated should be partial brain irradiation and not whole brain irradiation. There is no strong evidence to recommend a total dose greater than 60 Gy in standard fractionation, and alternative fractionation schedules have not proven to be more beneficial.
3. Whenever possible, patients with anaplastic gliomas should be considered for participation in ongoing clinical trials of postoperative adjuvant chemotherapy.
4. In the absence of a clinical trial, postoperative treatment with temozolomide combined with radiotherapy, followed by monthly temozolomide to a maximum of six cycles, may be considered.
5. Whenever possible, genetic testing for loss of heterozygosity on chromosomes 1p and 19q should be obtained for all patients with tumours that have oligodendroglial features, in order to improve diagnostic accuracy and prognostic prediction.
6. For elderly patients with a poor performance status, consideration may be given to adjuvant radiotherapy alone.

DISCUSSION

Surgery

Members of the Alberta Provincial CNS Tumour Team recommend surgery as the initial therapeutic approach in patients with anaplastic gliomas for tumour debulking, obtaining tissue for diagnosis, and clinical improvement (recommendation #1). Considerable debate exists in the literature, however, as to whether biopsy alone versus aggressive resection is the best surgical approach for these patients. This is because in most published studies evaluating surgical management of high-grade gliomas, patients with anaplastic gliomas usually represent the minority of patients included, while patients with glioblastoma (GBM) make up the majority. In addition, many of the published clinical practice guidelines extrapolate recommendations from the results of studies involving WHO grade IV tumours.

Hart et al. recently conducted a comprehensive and systematic search of the literature to address whether surgical resection was superior to biopsy for anaplastic gliomas.⁶ They identified only one randomized phase III trial, published by *Vuorinen et al.* in 2003, which met their search criteria. Although many of the other studies they identified did report a survival advantage for resection over biopsy, *Hart et al.* suggested that these studies be interpreted with caution as most were not designed to answer this question, were underpowered, and had methodological flaws.⁶ In another recent review of the published literature on surgery for malignant gliomas, *Proescholdt et al.* analyzed the methodological aspects and level of evidence of studies addressing the extent and impact of surgical resection on outcomes.⁷ The authors identified 120 publications, the majority of which were retrospective studies with an individual case-control design, and none of the studies were rated as having a high level of evidence. Although 72.5 percent of the identified studies *did* report some positive effect of radical resection on various outcomes, the authors identified methodological limitations to many of the reviewed studies. The most recent systematic review, published by *Tsitlakidis et al.* in 2009, included a meta-analysis of five studies addressing biopsy versus surgical resection for malignant gliomas.⁸ The results of the meta-analysis demonstrated a significant increase in overall survival for patients treated with resection instead of biopsy (HR 0.61, 95% CI 0.52-

0.71; $p < 0.0001$). In addition, the authors reported that quality of life appeared to be improved in patients treated with resection rather than biopsy.

Table 3 contains a summary of one randomized clinical trial and four observational studies which report survival outcomes for patients with anaplastic gliomas who underwent surgical resection versus biopsy alone. While the potential for selection bias should not be overlooked, specifically the variations in age and pre-surgery prognosis among patients who undergo surgical resection and patients who only undergo biopsy, the results of these studies do suggest that patients with anaplastic gliomas have significantly better survival outcomes when they undergo surgical resection compared to biopsy alone.

Table 3. Studies of Surgical Resection versus Biopsy for High-Grade Gliomas: 1995 to 2010

| Author | Study Design | Tumour Histology | Treatment Allocation | N | Median Survival | p-Value |
|---|---------------|------------------------------|---------------------------------|----------------|------------------------------|--|
| <i>Nomiya et al., 2007</i> ⁹ | Retrospective | anaplastic astrocytoma | Partial or biopsy GTR or STR | 94 76 | 22.9 mos 62.6 mos | <0.0001 |
| <i>Vuorinen et al., 2003</i> ¹⁰ | RCT | GBM/ anaplastic gliomas | Biopsy Resection | 13 10 | 171 days 85 days | 0.0346 |
| <i>Laws et al., 2003</i> ¹¹ | Prospective | Anaplastic gliomas | Biopsy Resection | 41 106 | 52.1 days 87.0 days | < 0.0001 |
| <i>Kowalczyk et al., 1997</i> ¹² | Retrospective | GBM/ anaplastic astrocytomas | Biopsy STR GTR | 13 33 29 | 56 wks 116 wks 143 wks | 0.039 (biopsy vs. STR + GTR) |
| <i>Kiwit et al., 1996</i> ¹³ | Retrospective | GBM/ anaplastic gliomas | Biopsy Resection | 40 40 | 184 days 292 days | <0.05 |
| <i>Quigley et al., 1995</i> ¹⁴ | Retrospective | GBM/ anaplastic astrocytoma | Biopsy STR GTR | 23 31 9 | 10 mos 11 mos 27 mos | Biopsy versus: • GTR <0.001 • STR = 0.35 |

Abbreviations: GTR=gross total resection, STR=sub-total resection, RCT=randomized controlled trial, GBM=glioblastoma multiforme.

Radiotherapy

Radiation therapy is the standard of care for anaplastic gliomas following surgery (recommendation #2). Most of the randomized clinical trials involving whole brain radiotherapy (WBRT) following surgery were performed in the late 1970s and early 1980s, and in many cases, little distinction was made between the different histologies of malignant gliomas. Therefore, the recommendations for the use of radiotherapy are based on trials that included both WHO Grade III and IV gliomas. A meta-analysis of six of these early randomized clinical trials was conducted by Cancer Care Ontario (CCO); five of the six studies demonstrated a statistically significant survival benefit of postoperative radiotherapy compared to supportive care or chemotherapy.¹⁵⁻²¹ The authors of the CCO publication reported an overall risk ratio of 0.81 (95% CI, 0.74 to 0.88; $p < 0.00001$) favouring post-operative radiotherapy compared to no radiotherapy in the management of high-grade gliomas.²¹ More recent trials of radiotherapy in anaplastic gliomas have focused on comparisons between post-operative radiotherapy alone and in combination with chemotherapy, as well as on varying techniques and dosing of radiation following surgical resection.

Radiotherapy Volume. The original randomized trials assessing the impact of radiotherapy on survival involved treating patients with WBRT.¹⁵⁻²⁰ More recent publications have focused on techniques that maximize treatment to the tumour while minimizing radiation to surrounding brain tissue. The rationale for limiting the radiation field is based on results from several large reviews which reported that recurrent malignant gliomas following WBRT develop within two centimetres of the original tumour site in 80 to 90

percent of cases; therefore, localized external beam radiotherapy has now replaced WBRT as the standard approach.²² The introduction and widespread use of computerized tomography (CT) and magnetic resonance imaging (MRI) techniques has further contributed to improving the accuracy of target volumes for external beam radiotherapy.²³

One recently published randomized trial and several smaller trials have demonstrated that while there is no statistically significant benefit in overall survival associated with localized external beam radiotherapy, the use of this technique leads to a decrease in excessive radiation to normal brain tissue, and therefore may lead to improvements in quality of life. In a prospective trial of 68 patients with anaplastic astrocytomas and GBM, *Phillips et al.* randomized patients to receive 60 Gy of localized radiotherapy in 30 fractions or 35 Gy of WBRT in 10 fractions.²⁴ The authors reported a small, non-significant increase in median survival for patients treated with the localized radiotherapy (10.3 months vs. 8.7 months, $p=0.37$). Similarly, *Sharma et al.* randomized 50 patients with anaplastic gliomas and GBM to receive either 50 Gy of localized external beam radiotherapy in 25 fractions with a boost of 10 Gy in 5 fractions, or 40 Gy of WBRT delivered in 20 fractions with a boost of 20 Gy in 10 fractions.²⁵ The authors reported a small, non-significant six-month overall survival benefit in the localized radiotherapy group (66.7% vs. 50.7%, $p > 0.1$), as well as a statistically significant improvement in the Karnofsky Performance Status (KPS) of the patients treated with localized radiotherapy (80% vs. 56% improved, $p < 0.01$).

Radiotherapy Dosing. In a key trial addressing radiotherapy dosing, *Bleehen and Stenning* randomized 474 patients with anaplastic gliomas or GBM to receive either 45 Gy of post-operative radiation in 20 fractions over 4 weeks or 60 Gy in 30 fractions over 6 weeks.²⁶ The authors reported a statistically significant difference in median survival of the higher dose group versus the lower dose group (12 months vs. 9 months; HR=0.75, $p=0.007$). In addition, when the authors performed a subgroup analysis based on prognostic indicators, the effect of the higher dose on overall survival was still evident in even the poorest prognostic group. To date, doses higher than 60 Gy have not convincingly demonstrated a meaningful improvement in overall survival. In a recent trial addressing dose-escalation to 90 Gy for high-grade gliomas, *Chan et al.* reported no significant improvement in survival for patients treated with 70, 80, or 90 Gy using a 3D conformal intensity-modulated radiotherapy (IMRT) technique.²⁷

Hyperfractionation. Hyperfractionation refers to the delivery of two smaller doses of radiation per day, separated by 4 to 8 hours, and allows for an increase in the maximal safe dose that can be given. In an analysis of the RTOG 8302 trial, *Nelson et al.* identified the experimental arm of 72.0 Gy in 1.2 Gy twice daily fractions as having the best outcome compared to the other three arms of a hyperfractionated radiotherapy schedule.²⁸ However, subsequent studies of hyperfractionated radiotherapy doses reported by *Fulton et al.* and *Scott et al.* have not shown significant improvements in median survival when compared to conventional fractionation.²⁹⁻³⁰ In a thorough review of 21 phase II and III altered fractionation studies published during a 5-year period, *Neider et al.* concluded that while altered fractionation shortens the overall treatment time for adult patients with high-grade gliomas, it does not result in a significant improvement in overall survival.³¹ Similarly, in a pooled analysis of seven randomized trials of hyperfractionated radiation dosing for anaplastic gliomas and GBM, the CCO reported no statistically significant survival benefit for hyperfractionated radiotherapy compared with conventional radiotherapy (RR=0.89; 95% CI 0.73 – 1.09; $p=0.27$).²¹

Radiotherapy Timing. In a recent retrospective analysis of 172 patients with anaplastic astrocytoma or GBM, *Irwin et al.* reported clinically significant reductions in survival associated with delay in receiving radiotherapy.³² When they adjusted for age and tumour grade, the authors reported that every additional week of delay until the start of radiotherapy was associated with an increased likelihood for death

(HR=1.089, 95% CI 1.020 – 1.161; $p=0.010$). They concluded that, for a typical patient with a high-grade glioma, a delay of six weeks in starting radiotherapy post-surgery was associated with an 11 week decrease in median survival. The results of the study by *Irwin et al.* confirmed a previous report by *Do et al.*, published in 2000.³³ In their retrospective analysis of 182 patients with anaplastic gliomas and GBM, *Do et al.* reported that older age, reduced dose, and prolonged waiting time from presentation were all significantly associated with worse survival, and the risk of death increased by 2% for each day of waiting for radiotherapy.

Based on the published results of radiotherapy for patients with anaplastic astrocytomas to date, the Alberta Provincial CNS Tumour Team members recommend that external beam radiation therapy should be given in standard fractionation to a maximum total dose of 59.4 to 60 Gy using 3D conformal planning techniques. The volume treated should be partial brain irradiation and **not** whole brain irradiation. There is no strong evidence to recommend a total dose greater than 60 Gy in standard fractionation, and alternative fractionation schedules have not proven to be more beneficial (recommendation #2).

Adjuvant Chemotherapy

The Alberta Provincial CNS Tumour Team members recommend that whenever possible, patients with anaplastic gliomas should be considered for participation in ongoing clinical trials of postoperative adjuvant chemotherapy (recommendation #3). There is no clear consensus in the literature and published clinical practice guidelines on the value of adjuvant chemotherapy in patients with newly diagnosed anaplastic gliomas. Traditionally, trials of chemotherapy for high-grade gliomas have made little distinction between different high-grade histologies; so while several early randomized controlled trials and meta-analyses have demonstrated that adjuvant chemotherapy is beneficial for patients with high-grade gliomas, there is only limited evidence available specifically for the anaplastic gliomas. Moreover, oligodendrogliomas, particularly those with a combined 1p19q chromosome deletion, have been reported to be particularly chemo-sensitive, and patients with anaplastic oligodendroglial tumours have been shown to have a better prognosis than those with anaplastic astrocytomas.

Anaplastic Astrocytomas. The treatment of anaplastic astrocytomas with adjuvant chemotherapy is based largely on the results of clinical trials which have addressed high-grade gliomas as a group, as well as several smaller retrospective analyses specifically addressing anaplastic astrocytomas. Earlier research focused on nitrosourea-based chemotherapy, such as the procarbazine, lomustine, and vincristine (PCV) regimen, while more recent research has focused on temozolomide, a chemotherapeutic agent which is the standard of care for patients with GBM.

Only one small clinical trial, published by the Northern California Oncology Group (NCOG) in 1990, has reported an improvement in patients with anaplastic astrocytomas treated with PCV.³⁴ In that trial, patients were randomized to receive either single-agent carmustine (BCNU) (200 mg/m² IV every 6 to 8 weeks, starting 2 weeks after radiotherapy) or PCV (lomustine 110 mg/m² on day 1, procarbazine 60 mg/m² on days 8 to 21, and vincristine 1.4 mg/m² IV on days 8 and 29). The authors reported that all patients treated with PCV had a longer time to tumour-progression and overall survival, but these improvements were only statistically significant in the subgroup of patients with anaplastic astrocytomas.³⁴ In a thorough systematic review and meta-analysis published by the Glioma Meta-analysis Trialists Group in 2002, individual patient data from 12 randomized controlled trials that compared radiotherapy alone with radiotherapy plus chemotherapy over a 30 year period were analyzed.³⁵ In total, data from 3004 patients, 706 of which were patients with anaplastic astrocytomas, were included in the analysis, and the majority of the trials involved nitrosourea-based chemotherapy regimens. The group reported a small but statistically significant

improvement in overall survival associated with the administration of adjuvant chemotherapy (HR=0.85, 95% CI 0.78 – 0.91; $p<0.0001$). Unlike the NCOG study, however, the authors reported that there was no evidence that chemotherapy was differentially effective in patients with anaplastic astrocytomas compared to GBM.³⁵

In a large multi-centre phase III clinical trial of adjuvant chemotherapy for high-grade astrocytomas (anaplastic astrocytoma and GBM), conducted by the Medical Research Council (MRC) Brain Tumour Working Party, 674 patients were randomized to receive either radiotherapy alone or radiotherapy plus PCV chemotherapy following surgery.³⁶ The data from this study were not included in the analysis performed by the Glioma Meta-analysis Trialists Group. The median survival was 9.5 months in the radiotherapy group versus 10.0 months in the radiotherapy plus PCV group (HR=0.95, 95% CI 0.81 – 1.11; $p=0.50$), and the authors reported that there was no evidence of a differential treatment effect for patients with anaplastic astrocytomas compared to GBM.³⁶ The results of a retrospective analysis of data from four separate RTOG trials further confirmed the results of the MRC study. In their analysis of 257 patients treated with BCNU versus 175 patients treated with the PCV regimen, *Prados et al.* also reported that there was no statistically significant survival benefit to PCV chemotherapy for patients with anaplastic astrocytomas.³⁷

A growing body of recent literature suggests that temozolomide, an oral alkylating agent, may now be the preferred agent for adjuvant chemotherapy in patients with malignant gliomas, due to a more acceptable toxicity profile than PCV chemotherapy. The strongest data to date has come from phase III trials in patients with GBM,³⁸⁻⁴⁰ as well as limited data from nonrandomized studies of patients with anaplastic astrocytomas. In a retrospective examination of patients with a newly diagnosed anaplastic astrocytoma, *Brandes et al.* compared 49 patients treated with adjuvant PCV chemotherapy to 60 patients treated with temozolomide post-radiation.⁴¹ While the type of adjuvant chemotherapy was not found to influence progression-free or overall survival, there were fewer incidences of hematological toxicities and premature discontinuation of treatment in the temozolomide group compared to the PCV group. The authors concluded that temozolomide should be considered first-line therapy for anaplastic astrocytomas due to ease of administration and better tolerability. The Alberta Provincial CNS Tumour Team members recommend that postoperative adjuvant treatment with temozolomide or combined chemoradiation, followed by monthly temozolomide to a maximum of six cycles, may be considered in all patients with anaplastic astrocytomas (recommendation #4).

Oligodendroglial Tumours. Anaplastic oligodendroglial tumours are markedly more chemo- and radio-sensitive than anaplastic astrocytomas, and are also associated with a better prognosis.⁴²⁻⁴³ The presence of a combined loss of chromosomes 1p and 19q is emerging as the most important factor associated with improved survival in patients with anaplastic oligodendroglial tumours.⁴⁴

Two important randomized clinical trials focused specifically on patients with anaplastic oligodendroglial tumours have been published in recent years.⁴⁵⁻⁴⁶ In the intergroup RTOG trial, *Cairncross et al.* randomized 289 patients to either PCV followed by radiotherapy or radiotherapy alone following surgical resection.⁴⁵ PCV chemotherapy was associated with longer progression-free survival, but 65 percent of the patients in the PCV group experienced grade 3 or 4 toxicities, and one patient died. In addition, adjuvant PCV chemotherapy was not associated with an improved overall survival. In a trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC), *van den Bent et al.* randomized patients to either immediate radiotherapy following surgery (N=183), or postoperative radiotherapy followed by PCV chemotherapy (N=185).⁴⁶ Similar to the RTOG trial, PCV chemotherapy was associated with better progression-free survival but not better overall survival. In addition, 38 percent of the patients in

the PCV arm of the trial discontinued chemotherapy because of toxicity. In both studies, patients with tumours demonstrating a combined 1p/19q chromosome deletion lived longer than patients whose tumours did not have the deletion, regardless of the treatment arm they were randomized to. This difference was only statistically significant in the RTOG trial, however (7.0 years versus 2.8 years, $p \leq 0.001$). Table 4 summarizes the results of the three randomized trials of radiotherapy and adjuvant chemotherapy for the treatment of anaplastic gliomas published to date.

Table 4. Randomized Clinical Trials of Radiotherapy and Adjuvant Chemotherapy for Anaplastic Gliomas

| Authors | Histology | Treatment Allocation | N | Median OS | Grade 3/4 Toxicity* |
|---|-----------|--|------------|--|-------------------------------------|
| <i>Cairncross et al., 2006</i> ⁴⁵ | AO, AOA | 1. Radiotherapy alone 2. Intensive PCV (lomustine 130 mg/m ² day 1, procarbazine 75 mg/m ² days 8-21, vincristine 1.4 mg/m ² days 8,29) → Radiotherapy | 142 147 | 4.7 years 4.9 years ($p=0.26$, NS) | hematologic: 56% neurologic: 19% |
| <i>Van den Bent et al., 2006</i> ⁴⁶ | AO, AOA | 1. Radiotherapy alone 2. Radiotherapy → standard PCV (lomustine 110 mg/m ² day 1, procarbazine 60 mg/m ² days 8-21, vincristine 1.4 mg/m ² days 8,29) | 183 185 | 30.6 months 40.3 months ($p=0.23$, NS) | hematologic: 46% |
| <i>MRC Brain Tumour Working Party, 2001</i> ³⁶ | AA | 1. Radiotherapy alone 2. Radiotherapy → PCV (lomustine 100 mg/m ² day 1, procarbazine 100 mg/m ² days 1-10, vincristine 1.5 mg/m ² day 1) | 60 53 | 11.5 months 12.5 months ($p=NS$) | hematologic: 15% neurologic: 0% |

*Grade 3 or 4 toxicities associated with chemotherapy treatment.

Abbreviations: OS=overall survival, AO=anaplastic oligodendroglioma, AOA=anaplastic oligoastrocytoma, PCV= procarbazine + lomustine + vincristine, NS=not statistically significant, MRCBT=Medical Research Council, AA= anaplastic astrocytoma.

In recent years, the PCV-based regimen has been replaced by temozolomide due to the significant toxicity of the former regimen. While these treatments have yet to be compared in a published randomized trial, several smaller phase II studies suggest that temozolomide is a safe and effective alternative to PCV. In a prospective, non-randomized, multicentre trial of temozolomide, *van den Bent et al.* treated 38 chemotherapy-naïve patients with temozolomide following surgery and radiotherapy at tumour recurrence.⁴⁷ A complete response was observed in ten patients, and a partial response was observed in ten additional patients; the median time-to-progression was 13.2 months in the responding patients. In a similar study published in 2006 by *Brandes et al.*, 67 patients were treated with temozolomide at tumour recurrence.⁴⁸ The overall response rate was 46.3 percent, with 17 complete responses and 14 partial responses. Multivariate analysis showed that 1p19q loss of heterozygosity and histology of anaplastic oligodendroglioma were independently and significantly related to response. In the most recent phase II trial, published in 2009 by *Vogelbaum et al.*, 39 patients with newly diagnosed anaplastic oligodendrogliomas or mixed anaplastic oligoastrocytomas received high doses of pre-radiotherapy temozolomide followed by concurrent temozolomide and radiotherapy.⁴⁹ The overall response rate was 32 percent and the rate of disease progression during the pre-radiotherapy temozolomide treatment was ten percent. The authors also reported that 17 of 28 evaluable patients had tumours with a 1p19q co deletion, and all 17 were free from disease progression at six months.

Taken together, these trials suggest that temozolomide is an effective alternative to PCV chemotherapy for anaplastic oligodendrogliomas. Members of the Alberta Provincial CNS Tumour Team agree that, in the absence of a clinical trial, postoperative adjuvant treatment with temozolomide or combined chemoradiation followed by monthly temozolomide to a maximum of six cycles, may be considered (recommendation #4). In addition, genetic testing for loss of heterozygosity on chromosomes 1p and 19q

should be obtained, whenever possible, for all patients with tumours that have oligodendroglial features, in order to improve diagnostic accuracy and prognostic prediction (recommendation #5).

Older Patients with Poor Performance Status. Older patients with high-grade gliomas present unique challenges, and the optimal treatment strategy for this group has yet to be determined. Advanced age has been repeatedly identified as one of the most powerful predictors of a poor prognosis in patients with high-grade gliomas, and therefore becomes an important factor in planning treatment strategies.⁵⁰⁻⁵³ However, the causal relationship between age and poor prognosis is not fully understood; since survival time and quality of life are often poor in older patients, many are offered only supportive care with no further interventions, and this itself may have a negative impact on disease outcome.^{51,54} Small prospective trials and retrospective reviews of older patients with high-grade gliomas have shown that initial clinical status (i.e. KPS) is an important parameter in treatment planning, and radiotherapy, either in a shortened lower-dose course or the conventional 60 Gy in 30 fractions, is effective in improving survival time for patients over the age of 60 with a low KPS.^{50,53,55,56} The response of patients with high-grade gliomas to chemotherapy has been reported to be inversely proportional to the age of the patient, and is generally limited to patients with a good KPS (i.e. > 70).^{50,57} At the present time, members of the Alberta Provincial CNS Tumour Team recommend that for older patients who are in good clinical condition, the treatment strategy should not differ from that of younger patients: surgery followed by radiotherapy and adjuvant chemotherapy with temozolomide where appropriate. For older patients with a KPS of less than 70, consideration may be given to surgery and adjuvant radiotherapy alone (recommendation #6).

GLOSSARY OF ABBREVIATIONS

| Acronym | Description |
|---------|--|
| BCNU | carmustine |
| CCO | Cancer Care Ontario |
| CI | confidence interval |
| CNS | central nervous system |
| CT | computerized tomography |
| EORTC | European Organisation for Research and Treatment of Cancer |
| GBM | glioblastoma |
| GTR | gross total resection |
| HR | hazard ratio |
| IMRT | intensity-modulated radiotherapy |
| KPS | Karnofsky performance status |
| MRC | Medical Research Council |
| MRI | magnetic resonance imaging |
| NCOG | Northern California Oncology Group |
| PCV | procarbazine + lomustine + vincristine |
| RCT | randomized controlled trial |
| RR | risk ratio |
| RTOG | Radiation Therapy Oncology Group |
| STR | sub-total resection |
| WBRT | whole brain radiotherapy |
| 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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