MANAGEMENT OF RECURRENT HIGH-GRADE GLIOMAS

Effective Date: July, 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Central Nervous System 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

High-grade gliomas account for the large majority of malignant primary brain tumours diagnosed in adults, with an annual incidence of approximately 5 cases per 100,000 people. Glioblastomas (GBMs) account for approximately 60 to 70 percent of high-grade gliomas; anaplastic astrocytomas, anaplastic oligodendrogliomas and anaplastic oligoastrocytoma account for the rest. The prognosis for patients diagnosed with a high-grade glioma remains poor. The median survival is only 12 to 15 months for patients with GBMs and 2 to 5 years for patients with anaplastic gliomas, regardless of the salvage therapy offered for progression/recurrence. However, a recent phase III trial of chemoradiotherapy for anaplastic oligodendrogliomas found that patients with codeleted tumours for 1p/19q lived significantly longer than those with noncodeleted tumours (14.7 years versus 2.6 years). A recent retrospective study evaluated the role of patient and clinical characteristics on overall survival (OS) for anaplastic glioma patients and found that first-course radiotherapy (RT), younger age, female sex, treatment in recent years, and surgery were associated with improved survival in anaplastic astrocytoma patients; age was the most prominent predictor of survival in anaplastic oligodendroglioma patients.

High-grade gliomas are challenging to treat effectively for a number of reasons. The biology of these types of tumours resist standard therapeutic approaches, their infiltrative properties make resection with truly negative margins in the brain impossible, there are limits to the amount of radiation that can be safely given, and there is limited penetrance of systematically administered drugs due to the blood-brain barrier. Despite aggressive use of surgery, RT, and chemotherapy, nearly all high-grade gliomas recur.

GUIDELINE QUESTIONS

- What is the definition of recurrence/progression in high-grade gliomas?
- What is the appropriate role of surgery in treating adult patients with recurrent high-grade gliomas?
- What is the appropriate role of chemotherapy in treating adult patients with recurrent high-grade gliomas?
- What is the appropriate role and standard of care for the use of re-irradiation in treating adult patients with recurrent high-grade gliomas?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Central Nervous System (CNS) Tumour Team. Members of the Alberta Provincial CNS Tumour Team include medical oncologists, pediatric oncologists, neuro-oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. 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. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in July, 2014.

SEARCH STRATEGY

Three separate searches were conducted to identify scientific literature related specifically to grade III gliomas, grade IV gliomas, and re-irradiation.
To identify grade III glioma literature, PubMed (1946 to December Week 3, 2012) electronic database was searched using the search terms high grade glioma AND neoplasm recurrence, local [MeSH heading] NOT glioblastoma [MeSH heading]. Results were limited to English, humans, clinical trial phase I–IV, controlled clinical trial, meta analysis, randomized controlled trial and guideline.

To identify grade IV glioma literature, PubMed (1946 to May Week 4, 2012), MEDLINE (1946 to May Week 4, 2012), EMBASE (1946 to May Week 4, 2012), and the Cochrane Database of Systematic Reviews electronic databases were searched using the search terms glioblastoma AND neoplasm recurrence, local [MeSH heading]. Results were limited to English, humans, clinical trial phase I–IV, controlled clinical trial, meta analysis, randomized controlled trial and guideline.

To identify re-irradiation literature, MEDLINE (1999 to February Week 4, 2012) electronic database was searched using the search terms glioma [MeSH heading], radiotherapy [subheading] AND recurrence. Results were limited to English, humans, clinical trial phase III–IV, controlled clinical trial, meta analysis and randomized controlled trial. PubMed (1999 to February Week 4, 2012) electronic database was searched using the search terms high grade glioma AND recurrence AND radiotherapy. Articles that did not address external beam radiotherapy were excluded. Only retrospective, prospective and clinical trials were included in the literature review.

The literature review was updated in October 2013. MEDLINE (2012 to October Week 2, 2013) and EMBASE (2012 to October Week 2, 2013) electronic databases were searched using the search terms glioma [MeSH heading] AND neoplasm recurrence, local [MeSH heading]. Results were limited to English, humans, adult (19+), clinical trial phase III–IV, guideline, meta analysis, randomized controlled trial and systematic reviews. PubMed (2012 to October Week 2, 2013) electronic database was searched using the search terms glioma [MeSH heading] AND recurrent. Results were limited to English, clinical trial phase III–IV, guideline, meta analysis, randomized controlled trial and systematic reviews. The Cochrane Database of Systematic Reviews was also searched using the search terms glioma AND recurrent; no limits were applied to the results. Small case series (<50 patients) were excluded from the review. Reference lists were scanned for relevant literature.

A review of the relevant existing practice guidelines for recurrent high-grade gliomas was also conducted by accessing the practice guidelines on the websites of the British Columbia Cancer Agency (BCCA), the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Clinical Excellence (NICE), the National Cancer Institute (NCI), 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 with recurrent high-grade gliomas. This includes grade III anaplastic astrocytomas, anaplastic oligodendrogliomas, anaplastic oligoastrocytomas and grade IV GBMs. Different principles may apply to pediatric patients.

RECOMMENDATIONS

The Alberta Provincial CNS Tumour Team has adopted the recommendations developed by the Canadian Glioblastoma Recommendations Committee and the NCCN, with modifications to fit the Alberta context.
1. All patients should be assessed for tumour recurrence using the Macdonald Criteria (Appendix A). According to the Macdonald Criteria, tumour progression is defined by any of the following:
   - ≥ 25% increase in size of enhancing tumour, or
   - any new tumour on CT or MRI scans, or
   - stable or increased corticosteroids, or
   - neurological deterioration
   Note: Patients receiving antiangiogenic therapies (e.g., bevacizumab)* or any form of chemoRT may be assessed according to the Response Assessment in Neuro-Oncology (RANO) Criteria (Appendix B).
2. Patient’s Goals of Care Designation (i.e., resuscitative care, medical care, or comfort care) should be re-evaluated, if previously defined.
3. Management of patients should be individualized and involve a multidisciplinary team of neurosurgeons, neuropathologists, radiation oncologists, neuro-oncologists and allied health professionals.
4. Patient participation in clinical trials is encouraged, where available, and only in the presence of radiologic evidence of tumour progression.
5. For local or diffuse/multiple recurrent tumours, treatment options include the following:
   a. If the tumour is resectable, conduct maximal safe resection followed by:
      i. Systemic chemotherapy using one or more of the following and at the discretion of the treating oncologist:
         • bevacizumab*, or
         • oral etoposide, or
         • lomustine, or
         • tamoxifen, or
         • temozolomide, or
         • other agents at the discretion of the treating oncologist
      ii. Palliative/best supportive care if poor performance status
   b. If the tumour is unresectable, treatment options include:
      i. Systemic chemotherapy using one or more of the following and at the discretion of the treating oncologist:
         • bevacizumab*, or
         • oral etoposide, or
         • lomustine, or
         • tamoxifen, or
         • temozolomide, or
         • other agents at the discretion of the treating oncologist
      ii. Palliative/best supportive care if poor performance status
   c. Discussion of re-irradiation should take place at a multidisciplinary Tumour Board for patients with a long interval since prior RT, for recurrence outside the prior RT field, and/or if there was a good response to prior RT. Systemic chemotherapy may be considered after re-irradiation.
6. Palliative/best supportive care should follow all treatment.

*Bevacizumab is currently not funded by the Alberta Health Services Cancer Drug Benefit Program for the treatment of neuro-oncologic cancer patients.
DISCUSSION

Diagnosing Recurrence

A systematic review by Shah et al. found that the average time from the end of treatment to the onset of a recurrent enhancing lesion was 13.2 months. It is challenging to differentiate between tumour recurrence and radiation-induced necrosis. Standard treatment for newly diagnosed high-grade gliomas involves surgery followed by RT with or without concurrent and adjuvant chemotherapy, depending on tumour histology. Unfortunately, a potential complication of RT is radiation necrosis (RN), which is a focal structural lesion that usually occurs at the original tumour site as a result of increased permeability (enhanced by temozolomide) of the tumour vasculature from irradiation and characterized by demyelination and vasogenic edema. Approximately 5–25 percent of patients receiving standard RT will present with RN.

With conventional MRI, RN typically presents as an increase in the size of contrast-enhancing lesions, which mimics tumour progression or recurrence after remission. As a result, after the completion of primary RT treatment, early MRI scans may appear worse during the first 3 months, even though there is no actual tumour progression or recurrence. In this case of pseudo-progression, stabilization or improvement typically occurs within 3 months post-treatment and therefore, within this timeframe, a diagnosis of recurrence can only be confirmed if the majority of the new enhancement is outside of the radiation field, or if there is histopathologic evidence of recurrence. The NCCN suggest that MR spectroscopy, MR perfusion, or brain PET be used to rule out RN. Shah et al. suggest that SPECT imaging has the highest combined specificity to distinguish RN from tumour progression or recurrence; however, they note that each imaging modality should be tailored to fit specific patient circumstances. After 3 months, tumour recurrence should be confirmed using the Macdonald Criteria (Appendix A); patients receiving antiangiogenic therapies or any form of chemoRT may be assessed according to the RANO Criteria (Appendix B). If there is uncertainty regarding tumour recurrence, the patient should remain under close clinical observation and be re-evaluated at 4-week intervals.

A questionnaire-based study of patients with recurring high-grade gliomas found that patients self-reported the following signs and symptoms: fatigue, uncertainty about the future, motor difficulties, drowsiness, communication difficulties, headaches, pain and visual deficits.

Treatment

Due to the lack of randomized trials in this patient population, standard therapies have not been defined and there is debate about the potential benefits of treatment after tumour recurrence; palliative/best supportive care may be a better option for patients with a poor performance status (PS) and should follow all treatment regardless of PS. Management of recurrent high-grade glioma tumours is complex and depends on the extent of disease and the patient’s condition. Patients with a previously established Goals of Care Designation should have it reviewed to validate its sustained relevance. The Goals of Care Designation Order can be found here: http://www.albertahealthservices.ca/frm-103547.pdf Management of patients should be individualized and involve a multidisciplinary team of neurosurgeons, neuropathologists, radiation oncologists, neuro-oncologists and allied health professionals. The following factors should be considered when determining treatment: patient’s age, PS, histology, extent of initial resection, response to initial therapy, time since diagnosis, and whether the recurrence is local or diffuse. In addition, it is important to define individual treatment goals and their...
effect on prognosis and quality of life for the patient. Unfortunately, patients with recurrent brain tumours are rarely curable and should be encouraged to enroll in a clinical trial, if available.

**Surgery.** Re-resection of recurrent high-grade glioma tumours is indicated in patients with limited recurrence, a good PS (KPS >70), and with a tumour in a resectable location; all surgically treated patients should receive systemic chemotherapy after re-resection. A recent retrospective review of 578 GBM patients found that repeated resections improved survival after controlling for age, functional status, periventricular location, extent of resection, and adjuvant therapy. Specifically, the median survival for patients who underwent 1, 2, or, 3 resections was 4.5, 16.2, and 24.4 months (p<0.05), respectively. Furthermore, the authors found that repeat resections can be achieved without a significant increase in post-operative deficits or wound infections. However, the authors of the study note that these findings may be limited by an intrinsic patient selection bias, for which they attempted to minimize by using strict inclusion criteria, multivariate analyses, and case-control evaluation. Unfortunately, the majority of studies are confounded by the inherent selection bias to perform surgery in patients with a good PS, a favourable anatomical tumour location, and lack of medical contraindications.

In addition to survival benefits, repeat surgery may also help to confirm tumour pathology, reduce neurological symptoms due to mass effect, edema, or hydrocephalus, and debulk the tumour. Although there are multiple benefits, the majority of patients do not qualify for a re-resection because of a deteriorating condition or a technically inoperable tumour.

**Chemotherapy.** Chemotherapy is the most common treatment option for patients with recurrent high-grade gliomas, especially if the tumour is unresectable. The Alberta Provincial CNS Tumour Team also recommends chemotherapy after tumour re-resection. Despite the wide use of chemotherapy in this patient population, optimal drug combinations and sequences have not yet been established, especially for patients who have received prior chemotherapy.

Temozolomide (TMZ) is the most studied agent in recurrent GBM. Chen et al. conducted a meta analysis of clinical trials to assess the overall efficacy of TMZ in the treatment of recurrent GBM. The overall 6-month PFS rate was 27.8 percent (95 percent CI, 22.7–33.5 percent); the study authors found a significant difference between metronomic and standard schedules at 33.1 percent versus 20.1 percent (p<0.001). Furthermore, a significant difference in 6-month PFS was found between high (average daily dose >100 mg/m²) and low (average daily dose ≤100 mg/m²) dose metronomic schedules (RR=1.57, 95 percent CI, 1.17–2.09 percent, p=0.002). The 6-month and 12-month OS rates were 65.0 percent (95 percent CI, 57.4–71.9 percent) and 36.4 percent (95 percent CI, 26.9–47.1 percent), respectively. The authors concluded that TMZ is effective for recurrent GBMs and its efficacy may be increased with metronomic schedule and high average daily dose. A recent systematic review of randomized controlled trials investigating recurrent high-grade glioma found that TMZ did not increase OS compared to nitrosourea-based chemotherapy (HR 0.9, 95 percent CI, 0.76–1.06, p=0.2) but it did increase PFS in a subgroup analysis of grade IV GBM tumours (HR 0.68, 95 percent CI, 0.51–0.90, p=0.008).

Anaplastic gliomas are also highly responsive to repeat TMZ therapy. The RESCUE study stratified 120 high-grade glioma patients by tumour type and found that continuous dose-intense TMZ 50 mg/m²/d was very effective in the anaplastic glioma subgroup with 6-month PFS and 1-year OS rates of 35.7 percent and 60.7 percent, respectively. The RESCUE study also found differences in prognosis depending on the duration of adjuvant treatment and treatment-free interval at the time of recurrence. Best responses were seen in patients with early progression (i.e., before completion of six cycles of adjuvant TMZ) and in previous responders who progressed more than two months after completing adjuvant treatment. These
findings suggests that recurrent high-grade glioma patients are not a homogenous group and that treatment should take into consideration the different subgroups of patients (i.e., anaplastic gliomas, early GBM progression while receiving adjuvant TMZ, GBM progression while receiving extended adjuvant TMZ, and GBM progression after completion of adjuvant treatment). Easaw et al. suggest that other agents should be considered in patients who progress after receiving adjuvant TMZ for more than one year.5

In 2009, the Food and Drug Administration approved bevacizumab for the treatment of recurrent GBM. This decision was based on the results of a phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumour progression in recurrent GBM. Kreisl et al. found that median PFS was 16 weeks (95 percent CI, 12–26 weeks); 6-month PFS was 29 percent (95 percent CI, 18–48 percent); median OS was 31 weeks (95 percent CI, 21–54 weeks); and 6-month OS was 57 percent (95 percent CI, 44–75 percent). The study authors concluded that single-agent bevacizumab has significant biologic and antiglioma activity in patients with recurrent GBM. In a recent systematic review of phase II studies, Koukourakis found that the drug combination of bevacizumab and irinotecan might improve OS and response rate in patients with recurrent high-grade gliomas. It should be noted that bevacizumab is currently not funded by the Alberta Health Services Cancer Drug Benefit Program for the treatment of neuro-oncologic cancer patients.

Before the advent of TMZ, adjuvant nitrosourea-based regimens (e.g., carmustine, lomustine, and PCV regimen [procarbazine, lomustine, and vincristine]) were commonly used to treat recurrent high-grade gliomas. The BC Cancer Agency recommends nitrosourea chemotherapy for recurrent astrocytomas patients who have not received prior chemotherapy and who have a KPS PS >50. Brem et al. conducted a placebo-controlled trial of surgically-implanted chemotherapeutic wafers in 222 recurrent high-grade glioma patients. Patients were randomly assigned to receive biodegradable polymer discs with or without 3.85 percent carmustine. Median survival was 31 weeks versus 23 weeks (HR=0.67, p=0.006), for intervention versus placebo, respectively. Despite these positive results, a systematic review of randomized controlled trials investigating chemotherapeutic wafers in recurrent patients concluded that this treatment does not appear to confer any additional benefits. Therefore, the Alberta Provincial CNS Tumour Team does not recommend the use of chemotherapeutic wafers at this time.

Given that there is no established chemotherapy regimen for recurrent high-grade glioma patients, patients are best treated within clinical trial protocols.

Re-irradiation. There are no randomized trials that have investigated the role of repeat radiation after tumour recurrence and therefore, it is seldom recommended. In carefully selected cases, re-irradiation may be considered; treatment should be discussed at a multidisciplinary Tumour Board and take into consideration the risk of neurocognitive deficits and RN. According to Easaw et al., the choice to re-irradiate depends on the size and location of the tumour, prior RT dose, time since last radiation, and target volume. Specifically, the Alberta Provincial CNS Tumour Team recommends that re-irradiation may be considered for patients with a long interval since prior RT, for recurrence outside the prior RT field, and/or if there was a good response to prior RT.

A recent systematic review reported class III evidence for re-irradiation for progressive glioblastoma, especially in the form of stereotactic radiosurgery or fractionated stereotactic radiosurgery, in select
patients. The study authors found that re-irradiation can maintain or improve neurological status and reduce steroid use, as well as possibly improve quality of life.

Some studies have found that repeat RT using modern high-precision techniques (e.g., fractionated stereotactic RT) may be a palliative option for select patients that have a good PS and small recurrent tumours. Nieder et al. synthesized data from over 300 GBM patients and found that re-irradiation yields 6-month PFS of 28 to 39 percent and 1-year OS of 18 to 48 percent, without additional chemotherapy; clinical improvement was observed in 24 to 45 percent of patients. The study authors noted that patients with a Karnofsky PS <70 were at higher risk of early progression and appeared to have less benefit from re-irradiation. Serious late toxicities were uncommon, especially for patients treated with conventional therapy and fractionated stereotactic RT, as long as the total dose is limited to 30–35 Gy. The authors of the review did note that quality of life assessments in their selected studies were suboptimal. They conclude that further, prospective and randomized studies are warranted given the fatal outcome after progression for these patients (expected 1-year survival at 14 percent), compared with the 26 percent median rate that they found in their review. Similarly, another review article by Combs et al. concluded that re-irradiation using high precision RT offers significant benefit, at least for a subgroup of patients.

A number of invasive and non-invasive RT techniques are available to treat recurrent high-grade glioma patients. The choice of modality should be decided on a case-by-case basis, taking into consideration other treatment options, potential benefits and potential side effects. For all RT modalities, close vicinity to sensitive risk structures (e.g., optic pathway, basal ganglia, motor or speech areas, and the brain stem) is a major obstacle for a second course of RT since the risk for severe side effects, limiting quality of life or jeopardizing vital organ functions are high due to the limited tolerance dose. Fortunately, modern highly conformal RT techniques exist that make it possible to non-invasively give doses to a defined target volume while sparing the surrounding normal tissue. For example, stereotactic radiosurgery (SRS) has been shown to offer a median survival of 8 to 16 months; hypofractionated SRS has similar survival outcomes in the range of 9 to 12 months. Although newer approaches such as intensity-modulated RT are able to deliver highly conformal radiation doses with a reduced dose to areas adjacent to critical tissues, compared to SRS, it is more costly and does not seem to improve patient outcomes.

The Alberta Provincial CNS Tumour Team suggests that systemic chemotherapy may be considered after re-irradiation to further optimize treatment results obtained by re-irradiation; however, very little data exists to support this treatment. Arcicasa et al. conducted a study in 24 high-grade glioma patients that received re-irradiation and lomustine. Patients received a total dose of 34.5 Gy delivered in 23 fractions over 4.5 weeks; oral administration of lomustine was administered concomitantly at 130 mg/m² and repeated every 6 weeks until disease progression or up to 12 courses. The range interval between RT courses was 6 to 73 months. The study authors reported a median time to progression of 8.4 months and OS of 13.7 months and conclude that overall acute toxicity was moderate and re-irradiation was associated with modest response rates. A more recent study conducted by Wurm et al. found that the median OS was 14.5 months for 25 patients treated with hypofractionated stereotactic RT (maximal dose 30 Gy delivered in 5–6 fractions) with concurrent topotecan (1.1 mg/m²/day). In this study, 12 percent of patients developed adverse group 2 RT effects; no topotecan-related grade 4 toxicity was observed. The study authors conclude that hypofractionated stereotactic RT with topotecan is well tolerated and results in similar survival compared to other recurrent treatment modalities.
TREATMENT ALGORITHM

Management of patients should be individualized and involve discussion at a multidisciplinary Tumour Board

Tumour recurrence?

Macdonald Criteria
- ≥25% increase in size of enhancing tumour?
- Any new tumour on CT or MRI scans?
- Stable or increased corticosteroids?
- Neurological deterioration?

Patients receiving antiangiogenic therapies or any form of chemoRT may be assessed using the RANO criteria

Yes

Patient participation in clinical trials is encouraged

Re-evaluate patient's Goals of Care Designation, if previously defined

No

Radiation Necrosis
Re-evaluate patient at 4-week intervals

Re-irradiation
May be considered for patients with:
- A long interval since prior RT, and/or
- Recurrence outside the prior RT field, and/or
- Good response to prior RT

Systemic Chemotherapy
- Bevacizumab, or
- Oral etoposide, or
- Lomustine, or
- Tamoxifen, or
- Temozolomide, or
- Other agents at the discretion of the treating oncologist

Systemic Chemotherapy
- Bevacizumab, or
- Oral etoposide, or
- Lomustine, or
- Tamoxifen, or
- Temozolomide, or
- Other agents at the discretion of the treating oncologist

Yes

Resectable?

Surgery

No

Poor PS

Palliative/best supportive care

Systemic Chemotherapy
- Bevacizumab, or
- Oral etoposide, or
- Lomustine, or
- Tamoxifen, or
- Temozolomide, or
- Other agents at the discretion of the treating oncologist
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>BCCA</td>
<td>British Columbia Cancer Agency</td>
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<tr>
<td>ChemoRT</td>
<td>Chemoradiotherapy</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<td>FLAIR</td>
<td>Fluid-attenuated inversion recovery</td>
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<td>GBM</td>
<td>Glioblastoma</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
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<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<td>PFS</td>
<td>Progression-free survival</td>
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<td>PS</td>
<td>Performance status</td>
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<td>RN</td>
<td>Radiation necrosis</td>
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<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SRS</td>
<td>Stereotactic radiosurgery</td>
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<td>TMZ</td>
<td>Temozolomide</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial CNS Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial CNS Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


APPENDIX A: Macdonald Criteria for Malignant Gliomas

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
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<tr>
<td>Complete response</td>
<td>Requires all of the following:</td>
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<td>• disappearance of all enhancing tumour on consecutive CT or MRI scans at least 1 month apart,</td>
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<td>• off corticosteroids, and</td>
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<td></td>
<td>• neurologically stable or improved</td>
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<td>Partial response</td>
<td>Requires all of the following:</td>
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<td>• (\geq 50%) reduction in size of enhancing tumour on consecutive CT or MRI scans at least 1 month apart,</td>
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<td></td>
<td>• stable or reduced corticosteroid dose, and</td>
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<td></td>
<td>• neurologically stable or improved</td>
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<td>Progression</td>
<td>Defined by any of the following:</td>
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<td>• (\geq 25%) increase in size of enhancing tumour,</td>
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<td>or</td>
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<td></td>
<td>• any new tumour on CT or MRI scans, or</td>
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<td></td>
<td>• stable or increased corticosteroids, or</td>
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<td>• neurological deterioration</td>
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<td>Stable disease</td>
<td>Requires all of the following:</td>
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<td>• does not qualify for complete response</td>
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<td></td>
<td>• does not qualify for partial response</td>
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<td></td>
<td>• does not qualify for progression</td>
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<td></td>
<td>• neurologically stable</td>
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### APPENDIX B: RANO Criteria for Determining First Progression Depending on Time from Initial ChemoRT

<table>
<thead>
<tr>
<th>First Progression</th>
<th>Definition</th>
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| **Progressive disease < 12 weeks after completion of chemoRT** | - Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor).  
- Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoRT. |
| **Progressive disease > or equal to 12 weeks after completion of chemoRT** | - New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.  
- Increase by > or equal to 25% in the sum of the products of perpendicular diameters between the first post-radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.  
- Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence.  
- For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). |