GLIOBLASTOMA

Effective Date: September, 2012

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 2012, it is estimated that approximately 2800 Canadian adults will be diagnosed with primary brain tumours, and 1850 will die from their disease.¹ Primary brain tumours are a heterogeneous group of neoplasms with varied treatment strategies and outcomes. The Alberta Provincial Central Nervous System (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

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

Glioblastoma (GBM), a WHO grade IV tumour, is the most common and aggressive of the primary brain tumours, accounting for approximately 40 percent of all CNS malignancies. In patients over the age of 60, the rate of GBM greatly increases, and thus accounts for the majority of primary brain tumours in this population.³ Despite recent advances in treatment, the prognosis for patients with GBM is dismal. The overall survival rates after diagnosis have been reported to range between 5 and 12 months; long-term survivors are usually young, in good health, and able to undergo multimodality treatment for their disease.

GUIDELINE QUESTIONS

- Is resection better than biopsy for patients with glioblastoma?
- Is adjuvant chemotherapy beneficial for patients with glioblastoma?
- Is adjuvant chemotherapy of benefit to elderly patients with glioblastoma?
- What is the optimal radiation therapy plan for patients with glioblastoma?
- Is adjuvant radiation of benefit to elderly patients with glioblastoma?

DEVELOPMENT AND REVISION HISTORY

This 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, neurosurgeons, neurologists, nurses, neuropathologists, 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 April, 2008. This guideline was revised in February, 2010 and September, 2012.
SEARCH STRATEGY

Medical journals were searched using the Medline (1950 to July Week 4, 2012), Embase (1980 to July Week 4, 2012) Cochrane Database of Systematic Reviews (2nd Quarter, 2012), and Pubmed databases. The search terms included: Glioblastoma [MeSH heading], Glioma [MeSH heading], Brain Neoplasms [MeSH heading], Astrocytoma [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 anaplastic astrocytomas or anaplastic oligodendrogliomas as the only high-grade gliomas, or were published prior to the year 2000. All retrieved articles were graded using the criteria outlined by Lau et al.4

A search for new or updated clinical practice guidelines published from January 2000 to July 2012 was also conducted, and yielded nine 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, the European Society for Medical Oncology (ESMO), and the Canadian GBM Recommendations Committee.

TARGET POPULATION

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

RECOMMENDATION

1. Surgery is the initial recommended approach for both debulking and obtaining of tissue for diagnosis. Whenever possible, safe, maximal resection is preferred in the management of GBM. A larger resection after initial biopsy is left to the discretion of the surgeon depending on the location of tumour and other factors.

2. Adjuvant chemo-radiation therapy is considered the standard of care following surgery for patients with newly diagnosed GBM. Whenever possible, surgery should be followed by radiotherapy and concurrent temozolomide chemotherapy, followed by six cycles of adjuvant temozolomide. For patients who show improvement on therapy, additional cycles of temozolomide may be considered.

3. External beam radiation therapy should be given in standard fractionation to a maximum total dose of 60Gy 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.

4. Determination of MGMT promoter methylation status may assist in determination of prognosis.
5. The course of radiotherapy may be abbreviated to 40 Gy in 15 fractions in elderly patients (≥60 years old). For elderly patients with a poor performance status, consideration may be given to adjuvant radiation therapy alone.

6. Concurrent and/or adjuvant treatment with temozolomide may be considered in patients older than 60 years of age with a good performance status (KPS ≥70).

**DISCUSSION**

**Surgery**

**Biopsy versus Surgical Resection.** Although prospective, randomized trials addressing surgery for GBM are lacking, there is a consensus among the published clinical practice guidelines that surgical resection is the main treatment for alleviation of symptoms and prolongation of life in patients with GBM. Members of the Alberta Provincial CNS Tumour Team therefore recommend surgery as the initial approach for both debulking and obtaining of tissue for diagnosis (recommendation #1).

Over the past fifteen years, several small studies and retrospective analyses have addressed the impact of biopsy versus surgical resection on overall survival in patients with high grade gliomas, and the results of these studies are summarized in Table 2. Hart et al. recently conducted a comprehensive and systematic search of the literature to address whether surgical resection was superior to biopsy for high-grade gliomas. 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. In another recent systematic review, Tsitlakidis et al. reported the results of a meta-analysis of five studies addressing biopsy versus surgical resection for malignant gliomas. The results suggested a significant survival benefit 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 2. Studies of Surgical Resection versus Biopsy for Glioblastoma: 1995 to 2012 |
|-----------------|--------|--------|--------|--------|----------|--------|
| Author          | Study Design | Treatment Allocation | N | Patient Age | Median Survival | p-Value |
| *Vuorinen et al., 2003* | RCT | Resection Biopsy | 10 | 66-80 yrs | 171 days | 0.0346 |
| Laws et al., 2003 | Prospective | Biopsy Resection | 84 | 58 yrs | 21.0 wks | <0.0001 |
| Kreth et al., 1999 | Retrospective | Resection Biopsy | 126 | Mean 58 yrs | 37 wks | 0.09 |
| *Kowalczuk et al., 1997* | Retrospective | Biopsy STR GTR | 13 | Mean 63 yrs | 56 wks | 0.039 (biopsy vs. STR + GTR) |
| *Kiwit et al., 1996* | Retrospective | Biopsy Resection | 40 | Mean 58 yrs | 184 days | <0.05 |
| *Quigley et al., 1995* | Retrospective | Biopsy STR GTR | 23 | Overall mean 57.6 yrs | 10 mos | Biopsy versus: |
|                 |         |         | 31 | 56 yrs | 11 mos | |
|                 |         |         | 9  | 60 yrs | 27 mos | |

*Includes anaplastic astrocytomas (grade III) and glioblastoma (grade IV) tumours

**Abbreviations:** RCT=randomized controlled trial, STR=subtotal resection, GTR=gross total resection.
Extent of Surgical Resection. There remains considerable debate in the literature regarding the impact of the extent of resection on overall survival in patients with GBM. While some studies have failed to show a benefit with more complete tumour resection, others have demonstrated an increase in overall survival for patients with GBM who undergo more complete resections of their tumours. Further, the extent of resection, in addition to important factors such as the age of the patient, Karnofsky Performance Status (KPS) score, and the location and volume of the tumour, has been identified as a prognostic indicator of overall survival in patients with GBM.\textsuperscript{13,16-20}

Several recent systematic reviews have addressed the issue of survival benefit for gross total resection versus partial resection in patients with GBM. In a thorough systematic review of the literature up to 2004, \textit{Taylor et al.}, along with the Neuro-oncology Disease Site Group of Cancer Care Ontario reviewed five retrospective studies and five prospective studies comparing gross total resection (GTR) to subtotal resection (STR) in terms of survival.\textsuperscript{8} Apart from one preliminary prospective analysis published in 1990, all of the studies included in their review reported a significant improvement in survival for patients undergoing GTR compared to STR (\(p<0.05\)).\textsuperscript{8} However, the authors identified several confounding factors, including the trend for more aggressive surgery in younger patients with a better KPS score, and therefore recommended that the results be interpreted with caution.

In 2005, \textit{Proescholdt et al.} analyzed the methodological aspects and level of evidence of studies addressing the extent and impact of surgical resection on outcomes in patients with grade III and grade IV malignant gliomas.\textsuperscript{21} 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 \textit{did} report some positive effect of radical resection on various outcomes, the authors identified methodological limitations to many of the reviewed studies.\textsuperscript{21} In a 2008 review of 28 high-grade glioma studies, \textit{Sanai et al.} also identified persistent limitations in the quality of the available data, but estimated an overall improvement in survival time of 2.9 months for patients who undergo a GTR versus a STR.\textsuperscript{22}

Table 3 includes summaries of the trials conducted from 1995 to the present which have compared GTR with STR in patients with newly diagnosed GBM. The strongest data to date come from a European multicentre phase III trial conducted by the ALA Glioma Study Group, in which fluorescence-guided resection with 5-aminolevulinic acid (ALA) was studied as a way to improve the extent of resection in patients with high-grade gliomas.\textsuperscript{23,24} In the original analysis, the authors reported that the use of 5-aminolevulinic acid resulted in a higher rate of complete resections compared to conventional microsurgery with white light (65% versus 36%), and a better 6-month progression-free survival rate (41.0% versus 21.1%, \(p=0.0003\)) in patients with high-grade gliomas.\textsuperscript{23} In a subsequent analysis of the ALA trial, \textit{Stummer et al.} stratified the 243 patients from the ALA trial who specifically had a diagnosis of GBM into those who underwent complete versus incomplete resections, irrespective of their original study arm.\textsuperscript{23} The median overall survival from the time of surgery was 11.8 months in patients with incomplete resections and 16.9 months in patients with complete resections, and this difference was highly significant in univariate analysis (\(p<0.0001\)). In multivariate analysis, when they accounted for factors which could influence survival (age, KPS, post-operative therapies, eloquent location of tumour), the authors reported an independent and overwhelming prognostic impact of complete resection on survival (HR=1.752, 95% CI 1.258 - 2.438; \(p< 0.0004\)).
Table 3. Studies of Gross Total Resection versus Subtotal Resection for Glioblastoma: 1995 to 2012

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Treatment Allocation</th>
<th>N</th>
<th>Patient Age</th>
<th>Median Survival</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stummer et al., 2008²⁴</td>
<td>RCT</td>
<td>Partial resection</td>
<td>121</td>
<td>51 &lt;60 yrs, 51 &gt;60 yrs</td>
<td>11.8 mos</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete resection</td>
<td>122</td>
<td>72 &lt;60 yrs, 50 &gt;60 yrs</td>
<td>16.9 mos</td>
<td></td>
</tr>
<tr>
<td>Lacroix et al., 2001²⁵</td>
<td>Retrospective</td>
<td>&lt; 98% resection</td>
<td>219</td>
<td>Overall mean 53 yrs</td>
<td>8.8 mos</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 98% resection</td>
<td>197</td>
<td></td>
<td>13.0 mos</td>
<td></td>
</tr>
<tr>
<td>Keles et al., 1999²⁶</td>
<td>Retrospective</td>
<td>&lt; 25% resection</td>
<td>25</td>
<td>Median 53.5 yrs</td>
<td>32 weeks</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25-49% resection</td>
<td>21</td>
<td>Median 48.5 yrs</td>
<td>57 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-74% resection</td>
<td>18</td>
<td>Median 50.5 yrs</td>
<td>63 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>75-99% resection</td>
<td>20</td>
<td>Median 45 yrs</td>
<td>89 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GTR</td>
<td>23</td>
<td>Median 53 yrs</td>
<td>93 weeks</td>
<td></td>
</tr>
<tr>
<td>Mohan et al., 1998²⁷</td>
<td>Retrospective</td>
<td>Biopsy</td>
<td>53</td>
<td>Overall mean 74.5 yrs</td>
<td>3.4 mos</td>
<td>GTR vs. STR: &lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STR</td>
<td>42</td>
<td></td>
<td>7.2 mos</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GTR</td>
<td>7</td>
<td></td>
<td>17.3 mos</td>
<td></td>
</tr>
<tr>
<td>Slotman et al., 1996²⁸</td>
<td>Prospective</td>
<td>&lt; 75% resection</td>
<td>8</td>
<td>Overall mean 56 yrs</td>
<td>31 weeks</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 75% resection</td>
<td>20</td>
<td></td>
<td>42 weeks</td>
<td></td>
</tr>
<tr>
<td>Nitta et al., 1995²⁹</td>
<td>Prospective</td>
<td>Partial resection</td>
<td>39</td>
<td>Overall mean 55.4 yrs</td>
<td>11 mos</td>
<td>GTR vs. STR + PR: &lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STR</td>
<td>26</td>
<td></td>
<td>12 mos</td>
<td>STR vs. PR: 0.123</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GTR</td>
<td>36</td>
<td></td>
<td>20 mos</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RCT=randomized controlled trial, STR=subtotal resection, GTR=gross total resection.

Based on the results of the trials published to date, as well as findings from systematic reviews and published clinical practice guidelines consensus statements, the members of the Alberta Provincial CNS Tumour Team currently recommend maximal tumour resection for patients with GBM whenever possible. A larger resection after initial biopsy should be left to the discretion of the surgeon, depending on the location of tumour and other factors (recommendation #1).

**Adjuvant Treatment**

Adjuvant chemo-radiation therapy is considered the standard of care following surgery for patients with newly diagnosed GBM (recommendation #2).

**Radiotherapy.** The use of external-beam radiotherapy is a well-established recommendation for patients with newly diagnosed GBM following surgical resection. Most of the randomized clinical trials involving whole brain radiotherapy (WBRT) following surgery were performed in the 1970s, 1980s, and early 1990s, 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 based on six of these early randomized clinical trials, published by Cancer Care Ontario (CCO), reported an overall risk ratio of 0.81 (95% CI 0.74 - 0.88; p<0.00001) favouring post-operative conformal radiotherapy compared to no post-operative radiotherapy.³⁰ More recent trials of radiotherapy in GBM have focused on varying techniques and dosing of radiation following surgical resection, as well as on comparisons between post-operative radiotherapy alone and in combination with chemotherapy.

The issue of radiation volume was addressed by several early studies which reported that recurrent malignant gliomas following WBRT develop within 2 cm of the original tumour site in 80 to 90 percent of cases.³¹,³² 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. The authors reported a small, non-significant increase in median survival for patients treated with the localized radiotherapy (10.3 months versus 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. 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 KPS of the patients treated with localized radiotherapy (80% versus 56% improved, \( p<0.01 \)). 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.

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 four weeks or 60 Gy in 30 fractions over six weeks. The authors reported a statistically significant difference in median survival of the higher dose group versus the lower dose group (12 months versus 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.

Alternative fractionation schedules, particularly hyperfractionation, have not demonstrated a statistically significant survival advantage for patients with newly diagnosed GBM. In a thorough review of 21 phase II and III altered fractionation studies published during a five-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. 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; \( p=0.27 \)).

With regards to radiotherapy timing, a recent retrospective analysis of 172 patients with anaplastic astrocytoma or GBM demonstrated clinically significant reductions in survival associated with delay in receiving radiotherapy. 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. Similarly, 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 two percent for each day of waiting for radiotherapy.

Based on the published results of radiotherapy for patients with newly diagnosed GBM 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 #3).

**Chemotherapy.** For patients with a good KPS, a high level of evidence supports the use of daily temozolomide administered with postoperative radiotherapy and followed by six cycles of adjuvant temozolomide.\(^{43-47}\) Three phase II clinical trials conducted by Stupp et al., Lanzetta et al., and Athanassiou et al. all reported better one-year survival rates with the addition of temozolomide compared to radiotherapy alone (58%, 58%, 56.3%, respectively).\(^{43,45,46}\) In 2005, Stupp et al. published the results of a large, randomized, multicentre phase III trial that included 573 patients with newly diagnosed GBM from 85 European and Canadian centres.\(^{47}\) Following surgical resection, patients were randomized to receive radiotherapy alone or in combination with chemotherapy. In the chemotherapy arm, patients received radiotherapy with concurrent low dose temozolomide (75 mg/m\(^2\)) for six weeks, followed by a four week break and then six cycles of temozolomide (150 – 200 mg/m\(^2\)/day on days 1-5 of a 28 day cycle). The median overall survival was 14.6 months (95% CI 13.2 – 16.8) for the radiotherapy plus temozolomide group versus 12.1 months (95% CI 11.2 – 13.0) for the radiotherapy alone group. In addition, the two-year survival rate was 26.4 percent for the radiotherapy plus temozolomide group versus 10.4 percent for the radiotherapy alone group (\(p<0.001\)).\(^{47}\) The results of the five-year analysis from this trial were recently published. At five years, the overall survival was 9.8 percent for the group treated with temozolomide versus 1.9 percent for the group treated with radiotherapy alone (HR 0.6, 95% CI 0.5 – 0.7; \(p<0.0001\)).\(^{44}\)

The Canadian GBM Recommendations Committee recommends that for patients with stable symptoms during combined radiotherapy and temozolomide, completion of at least three cycles of adjuvant therapy is advised before a decision is made about whether or not to continue treatment.\(^{48}\) This is because, in the first few weeks or months following radiotherapy, MRI changes alone are not reliable to determine true disease progression. In a recent retrospective analysis, Roldán et al. reported on the incidence of radiographic pseudo-progression in a population-based cohort of 43 patients with GBM.\(^{49}\) Twenty-five of the patients (58%) exhibited radiographic progression on the first MRI scan after concurrent treatment, and of the twenty patients who went on to receive adjuvant treatment with temozolomide, ten demonstrated pseudo-progression (50%). The results of the Roldán et al. study confirm previously published observations by Brandes et al., and Taal et al., in which pseudo-progression was reported in 58 and 50 percent of the cases, respectively.\(^{30,51}\)

Based on the results of trials published to date, the Alberta Provincial CNS Tumour Team recommends that, whenever possible, surgery should be followed by radiotherapy and concurrent temozolomide chemotherapy, followed by six cycles of adjuvant temozolomide. For patients who show improvement on therapy, additional cycles of adjuvant temozolomide may be considered (recommendation #2).

**MGMT Promoter Methylation Status**

In a companion to the 2005 Stupp et al. publication, Hegi et al. reported an analysis of 206 patients who were treated as part of the clinical trial.\(^{52}\) The authors examined the relationship between occurrence of epigenetic silencing of the O\(^{6}\)-methylguanine – DNA methyltransferase (MGMT) gene by promoter methylation and overall survival. Among the patients with MGMT promoter methylation, the median survival was 21.7 months for those treated with temozolomide versus 15.3 months for those treated with radiotherapy alone (\(p=0.007\)). In patients with tumours without a methylated MGMT promoter, the administration of concurrent and monthly temozolomide only marginally improved median survival when
compared to radiotherapy alone (12.7 months versus 11.8 months, \( p=0.06 \)). The authors also reported that, irrespective of treatment, MGMT promoter methylation was an independent favourable prognostic factor for patients with GBM (HR=0.45, 95% CI 0.32 – 0.61; \( p<0.001 \)).

The Canadian GBM Recommendations Committee states that since MGMT status appears to be a prognostic factor for increased survival and possibly for better response to temozolomide treatment, sufficient tissue should be obtained during surgery for cytogenetic analysis and tumour banking. On the basis of this recommendation, the members of the Alberta Provincial CNS Tumour Team agree that, whenever possible, determination of MGMT promoter methylation status should be conducted, as it may assist in determination of prognosis (recommendation #4).

Management of GBM in Older Patients

The incidence of GBM greatly increases in patients over the age of sixty, and thus accounts for the majority of primary brain tumours in this population. Advanced age has also 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. 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.

**Radiotherapy.** The Alberta Provincial CNS Tumour Team members recommend that the course of radiotherapy may be abbreviated to 40 Gy in 15 fractions in elderly patients. For those with a poor performance status, consideration may be given to adjuvant radiation therapy alone (recommendation #5). These recommendations are based on the results from two key studies. In the first trial, Roa et al. randomized 100 patients over the age of 60 to receive either standard radiotherapy (60 Gy in 30 fractions) or an abbreviated course (40 Gy in 15 fractions) within six weeks of surgery. The authors reported similar median survival times for the two groups of patients (5.1 months standard versus 5.6 months abbreviated, \( p=0.57 \)). In addition, they did not report any significant differences in KPS over time between the two groups. They concluded that a shorter course of radiotherapy is a reasonable treatment option for older patients with GBM, and may be considered particularly appropriate in patients with a poor performance status where survival after a standard six-week course of radiotherapy is short.

In the second trial, Keime-Guibert et al. randomized 81 patients over the age of 70 with a good KPS (\( \geq 70 \)) to receive either supportive care alone or supportive care in combination with radiotherapy (50 Gy in 1.8 fractions/day x 5 days/week). The authors reported a median survival of 29.1 weeks in the patients receiving radiotherapy compared to 16.9 weeks for those receiving only supportive care (HR=0.47, 95% CI 0.29 – 0.76; \( p=0.002 \)). In addition, quality of life and cognitive evaluations did not differ significantly between the two treatment groups.

**Chemotherapy.** The response of patients with high-grade gliomas to chemotherapy is inversely proportional to the age of the patient, and is generally limited to patients with a good KPS (i.e. \( \geq 70 \)). The Alberta Provincial CNS Tumour Team members recommend that concurrent and/or adjuvant treatment with temozolomide may be considered in patients older than 60 with good performance status (recommendation #6). This recommendation is based on results from several small prospective trials. In 2003, Brandes et al. reported the results of a study involving 79 patients over the age of 65 who were treated with either radiotherapy alone, radiotherapy and adjuvant chemotherapy with procarbazine, lomustine, and vincristine (PCV), or radiotherapy and adjuvant temozolomide. The authors reported that,
for elderly patients with a KPS score greater than 70, aggressive management with radiation therapy and adjuvant temozolomide offered a significant survival advantage over radiotherapy alone (14.9 months versus 11.2 months, \( p=0.002 \)). In addition, while there was no significant difference in overall survival for patients treated with adjuvant temozolomide compared to adjuvant PCV chemotherapy (14.9 months versus 12.7 months), the temozolomide was better tolerated, with a lower rate of grade 3-4 hematologic toxicity. In 2008, Combs et al. reported the results of a study involving 43 patients over the age of 65 treated with postoperative radiotherapy plus temozolomide.\(^6^1\) Thirty-five patients received concurrent temozolomide at a dose of 50 mg/m\(^2\) and eight patients received concurrent temozolomide at a dose of 75 mg/m\(^2\). Only five patients were prescribed adjuvant doses of temozolomide in this study. The median overall survival for all patients was 11 months, and the actuarial overall survival rate was 48 percent at one year and eight percent at two years. Similar results were published in 2008 by Minniti et al., who reported an overall survival of 10.6 months in 32 patients older than 70 years with GBM treated with standard radiotherapy plus concurrent and adjuvant temozolomide.\(^6^2\)

In 2009, Minniti et al. published the results of a prospective trial examining hypofractionated radiotherapy followed by adjuvant temozolomide.\(^6^3\) In this study, 43 patients over the age of 70 with a KPS of 60 or more received 30 Gy of radiotherapy (6 fractions of 5 Gy each over 2 weeks) followed by up to 12 cycles of adjuvant temozolomide (150 – 200 mg/m\(^2\)). The median overall and progression-free survival was 9.3 months and 6.3 months, respectively. The authors suggested that hypofractionated radiotherapy with adjuvant temozolomide may be a reasonable therapeutic approach for patients with less favourable prognostic factors. A further phase II study, also by Minniti et al., addressed short-course radiotherapy (40 Gy in 15 fractions over 3 weeks) plus concomitant and adjuvant temozolomide in patients \( \geq 70 \) years with a KPS of 60 or more. The investigators reported a median overall survival of 12.4 months, and a median progression free survival of 6 months.\(^6^4\)

Taken together, this data suggest that treatment with concurrent and adjuvant temozolomide in elderly patients with a good performance status is well tolerated and may increase the length of both overall and progression-free survival. At the present time, however, several questions regarding the optimal combination of temozolomide and radiotherapy in elderly patients, many of which will hopefully be answered by the findings from several ongoing clinical trials.\(^6^5\)

The management of GBM in elderly patients with poor performance status is not well established. Gallego Perez-Larraya et al. conducted a non-randomized phase II trial of temozolomide alone (150-200 mg/m\(^2\) per day for 5 days, every 4 weeks until disease progression) in patients 70 years or older with a median KPS of 60. The median overall survival was 25 weeks, and the median progression free survival was 16 weeks. In the 31 tumours evaluated for MGMT promoter methylation, a methylated status was associated with longer progression free survival (26 versus 11 weeks, \( p=0.03 \)) and overall survival (31 versus 19 weeks, \( p=0.03 \)).\(^6^6\)
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALA</td>
<td>5-aminolevulinic acid</td>
</tr>
<tr>
<td>CCO</td>
<td>Cancer Care Ontario</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>GBM</td>
<td>glioblastoma</td>
</tr>
<tr>
<td>GTR</td>
<td>gross total resection</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IMRT</td>
<td>intensity-modulated radiotherapy</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky performance status</td>
</tr>
<tr>
<td>MGMT</td>
<td>O\textsuperscript{6} - methylguanine – DNA methyltransferase</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PCV</td>
<td>procarbazine + lomustine + vincristine</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>STR</td>
<td>subtotal resection</td>
</tr>
<tr>
<td>WBRT</td>
<td>whole brain radiotherapy</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

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 2013. 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


