MEDULLOBLASTOMA

Effective Date: March, 2014

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

Medulloblastoma is the most common brain tumour in children, accounting for 15 to 30 percent of all pediatric cancers of the central nervous system (CNS); in adults, however, the tumour is quite rare, accounting for only one to three percent of all primary brain tumours.1-3 Because of its rarity in the adult population, most published reports in adults with medulloblastoma involve limited and select populations, and are retrospective analyses conducted over several decades with varying diagnostic procedures and treatment protocols. Based on the assumption that adult tumours have the same properties as those in children, adult patients with medulloblastoma are often given treatment protocols according to therapies developed for children with similarly staged disease at diagnosis.4,5 However, important histologic and phenotypic differences have been identified between pediatric and adult medulloblastoma patients. In addition, radiologic differences have also been identified: adult tumours involve the lateral cerebellar hemispheres, while pediatric tumours most often occur in the vermis.6,7 Further, late relapse, which occurs only rarely in pediatric tumours, occurs more frequently among adult patients with medulloblastoma.

Reported survival rates for adult medulloblastoma vary in the literature. In a recent large, multicentre study, Padovani et al. retrospectively reviewed the outcomes of 253 adult patients treated for medulloblastoma between 1975 and 2004, and reported five- and ten-year overall survival rates of 72 and 55 percent, respectively.6 When low- and high-risk patients were compared, the ten-year overall survival rates were 62 and 49 percent ($p=0.03$). Lower five-year survival rates were reported in an unselected, population-based study published by Roldán et al.8 In this study, the Alberta Cancer Registry database was used to identify all cases of medulloblastoma occurring in Southern Alberta during a 21 year period, and five-year survival rates were reported to be 44.1 percent for patients over the age of sixteen, and 55.7 percent for those under the age of sixteen.8 The authors reported that these rates were more in line with those of other population-based studies. In addition, the survival curves in this analysis did not “level off”, suggesting that the patients had a lifetime risk of recurrence.8 A recent analysis of 454 patients in the Surveillance, Epidemiology, and End Results (SEER) database in the United States reported five- and ten-years survival rates of 64.9 and 52.1 percent, respectively, for adult patients diagnosed with medulloblastoma between 1973 and 2004.9 Multivariate analysis identified that diagnosis after the 1980s, age of diagnosis before 20 years, gross total resection, and treatment with radiotherapy were all associated with better survival.9

The most commonly reported symptoms of medulloblastoma at initial diagnosis are associated with increased intracranial pressure and cerebellar dysfunction. In the Roldán et al. study, headache (80%), nausea and vomiting (78%), and ataxia (73%) were most commonly identified;8 similar symptoms and rates have been reported in retrospective series from France, India, and the MD Anderson Cancer Center in the United States.4,10,11

GUIDELINE QUESTIONS

1. What are the recommended management strategies for adult patients with newly diagnosed medulloblastoma?
2. What are the recommended management strategies for adult patients with relapsed or recurrent medulloblastoma?
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 August, 2010, and was revised in February, 2013 and March, 2014.

SEARCH STRATEGY

Medical journal articles were searched using the Medline (1950 to November Week 4, 2012), EMBASE (1980 to November Week 4, 2012), Cochrane Database of Systematic Reviews (3rd Quarter, 2012), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The MeSH heading Medulloblastoma was combined with the search terms “Surgery”, “Radiotherapy”, “Drug Therapy”, “Therapy”, and “Follow-up Studies”. The results were limited to adults, practice guidelines, systematic reviews, meta-analyses, comparative studies, multicentre studies, randomized controlled trials, and clinical trials. Articles were excluded from the review if they: addressed medulloblastoma in pediatric or adolescent patients, had a non-English abstract, or were not available through the library system. A review of the relevant existing practice guidelines for medulloblastoma was also conducted by searching the websites of the American Society of Clinical Oncology (ASCO), Australian Cancer Network, British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia, Cancer Care Ontario (CCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network National Guidelines Clearinghouse, National Institute for Health and Clinical Excellence (NICE), National Cancer Institute (NCI), and the Scottish Intercollegiate Guidelines Network (SIGN).

An updated literature search was conducted in January, 2014 following the same search strategy as described above.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 16 years diagnosed with medulloblastoma. Different principles may apply to pediatric patients.

RECOMMENDATIONS

Evaluation and Workup:

1. Evaluation and management of adult patients with medulloblastoma should be discussed and planned within a multidisciplinary tumour team. Whenever possible, participation in clinical trials is encouraged.

2. Prior to initiating therapy, an MRI of the brain and total spine should be performed within 72 hours postoperatively, given the risk of seeding throughout the craniospinal axis. Lumbar cerebrospinal fluid (CSF) cytology should also be performed, either pre-operatively if safe or 2-3 weeks post-operatively;
the MRI should precede lumbar CSF sampling to avoid false positive interpretations of imaging data.

3. Adult patients with T1, T2, T3a and M0 disease who undergo a total or near-total resection (< 1.5 cm²) are classified as having average-risk disease. In contrast, adult patients with T3b or T4 plus M1 to M3 disease plus postoperative residual tumours are classified as having high-risk disease.

**Treatment for Newly Diagnosed Patients:**

4. Maximal safe surgical resection followed by postoperative radiotherapy and possibly concurrent and/or adjuvant chemotherapy is the recommended treatment algorithm for adult patients with medulloblastoma. An attempt should be made to excise as much as possible of the grossly visible tumour.

5. Postoperative radiotherapy to the entire craniospinal axis to a dose of 36-40Gy, followed by a posterior fossa boost to 54-55.8Gy should be administered. Sites of gross disease elsewhere in the craniospinal axis should be boosted to at least 40Gy. Adjuvant chemotherapy may allow for use of lower craniospinal radiation doses of 23.4Gy.

6. In contrast to childhood medulloblastoma, the role of chemotherapy in adult patients with medulloblastoma is less clear. Based on extrapolation from the pediatric literature, however, concurrent and/or adjuvant chemotherapy may be considered for select adults with high-risk disease, and also for the treatment of recurrence. There is currently no strong evidence to support a specific chemotherapy regimen in adults. Decisions should be made on an individual basis for each patient, and should be discussed and planned at multidisciplinary Tumour Board meetings.

**Follow-up:**

7. Long term follow-up (5 to 10 years) is recommended following completion of therapy, due to the potential for late recurrence, as well as neurocognitive, neuroendocrine, thyroid, pulmonary, cardiac, gastrointestinal, renal, and reproductive late effects.

**Treatment for Recurrent Patients:**

8. Patients with disseminated disease should be managed with chemotherapy, focal radiation where indicated, and best supportive care. Fit patients with localized recurrence should undergo maximum safe re-resection, and may be offered re-irradiation or high-dose chemotherapy with autologous stem cell transplantation. Decisions should be made on an individual basis for each patient, and should be discussed and planned at multidisciplinary Tumour Board meetings.

**DISCUSSION**

**Evaluation and Workup**

Combined modality therapy, including surgery, radiotherapy, and possibly chemotherapy is the standard of care for both children and adult patients with medulloblastoma. Therefore, evaluation and management should be discussed and planned with a multidisciplinary team of clinicians. Whenever possible, patient participation in clinical trials is encouraged (recommendation #1).
Prior to initiating therapy, an MRI of the brain and total spine is recommended, as this is an important tool
for accurate staging of the tumour, particularly when the tumour extends beyond the posterior fossa and
into the spinal spaces. Postoperative neuro-imaging with MRI will help to quantify residual disease,
and is recommended within 72 hours following surgical resection. Medulloblastoma tumours in adult
patients are associated with a high likelihood for craniospinal seeding and spread through the
cerebrospinal fluid (CSF). Therefore, when safe to do so, the workup of adult patients should include
lumbar CSF cytology, either pre-operatively if safe, or two to three weeks post-operatively
(recommendation #2). Because the use of either spinal MRI or lumbar CSF alone has been associated
with a rate of false negatives as high as 20 percent, both spinal MRI and lumbar CSF are ideal. A
lumbar puncture may introduce imaging artifacts, therefore the MRI should precede lumbar CSF.

Staging and Classification

Historically, adult medulloblastoma has been clinically staged according to the Chang staging definitions
for tumour and metastases parameters; a modified Chang Staging System, is described in Table 1.

<table>
<thead>
<tr>
<th>Tumour Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>T1</td>
<td>greatest tumour dimension &lt;3cm</td>
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<tr>
<td>T2</td>
<td>greatest tumour dimension &gt;3cm</td>
</tr>
<tr>
<td>T3a</td>
<td>greatest tumour dimension &gt;3cm with spread into the aqueduct of Sylvius and/or foramen of Luschka, cerebral subarachnoid space, third or lateral ventricles</td>
</tr>
<tr>
<td>T3b</td>
<td>greatest tumour dimension &gt;3cm with unequivocal spread into the brainstem; for T3b, surgical staging may be used in the absence of involvement at imaging</td>
</tr>
<tr>
<td>T4</td>
<td>greatest tumour dimension &gt;3cm with spread beyond the aqueduct of Sylvius and/or the foramen magnum</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>M0</td>
<td>no evidence of gross subarachnoid or hematogenous metastasis</td>
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<tr>
<td>M1</td>
<td>microscopic tumour cells in cerebrospinal fluid</td>
</tr>
<tr>
<td>M2</td>
<td>gross nodular seeding in cerebellum</td>
</tr>
<tr>
<td>M3</td>
<td>gross nodular seeding in spinal subarachnoid space</td>
</tr>
<tr>
<td>M4</td>
<td>metastasis beyond cerebrospinal axis</td>
</tr>
</tbody>
</table>

While the “T” component of this classification system has little prognostic value, the “M” component
remains vital for determining the appropriate risk-adapted treatment protocols for adult patients. More
recently, average- and high-risk classification has been identified to be an important factor in treatment
decisions as well as a prognostic indicator in several studies, although the definition of average- and high-
risk is variable. According to the Chang criteria, average-risk patients are those that have T1, T2, T3a
and M0 disease, and have totally or near totally resected disease (≤ 1.5 cm²) following surgery. In
contrast, high-risk patients are those that have T3b or T4 plus M1 to M3 disease, and do have
postoperative residual tumours (recommendation #3). In their retrospective study of adult patients with
medulloblastoma, Padovani and colleagues defined high-risk patients as those with metastatic disease
and/or CSF involvement and/or macroscopic residual tumour after surgery, while the standard-risk
patients had none of these risk factors. In comparison, the Children’s Oncology Group defines average-
risk patients as those with any T-stage who have totally or near totally resected disease (≤ 1.5 cm²)
following surgery and no metastases, while high-risk patients have greater than 1.5 cm² residual disease
following surgery and/or metastatic disease.
Histology and Molecular Classification

Medulloblastoma is described as malignant and invasive, and is classified by the World Health Organization (WHO) as a grade IV tumour. In addition to the classic type of medulloblastoma, four histologic subtypes have also been identified (desmoplastic/nodular type, medulloblastoma with extensive nodularity, anaplastic medulloblastoma, large-cell medulloblastoma), and recent publications stress the importance of these histologic subtypes in the prognosis of medulloblastoma. In general, the large-cell and anaplastic subtypes appear to be associated with the worst prognosis.

A recent consensus statement published by Taylor and colleagues proposed nomenclature for four molecular subgroups of medulloblastoma: Wnt, Sonic Hedgehog (SHH), Group 3, and Group 4. This statement was supplemented by an international meta-analysis of 550 patients from seven studies, and described distinct differences with respect to transcriptome, DNA copy-number aberrations, demographics, and survival of patients in each of the four subtypes. A recently published comprehensive review of adult medulloblastoma suggests that SHH tumours are most common in adult patients, comprising about two-thirds of adult medulloblastoma cases.

Standard histologic reporting for medulloblastoma includes documentation of tumour nodularity, necrosis, mitoses, apoptosis, cell size, nuclear wrapping, and large cell and anaplastic distribution. Immunohistochemical tests, such as those for expression or mutation of p53, INI-1, Her2/neu, and β-catenin, may also be required for determining prognosis and ruling out medulloblastoma mimics. Other specialized molecular tests, including those for MYC-C and MYC-N amplification, and loss of chromosome 17p, may allow a more accurate prediction of disease prognosis, but are not considered standard tests in Alberta at the present time.

Treatment for Newly Diagnosed Patients

**Surgery.** Maximal safe surgical resection followed by postoperative radiotherapy and possibly adjuvant chemotherapy is the recommended treatment strategy for adult patients with medulloblastoma (recommendation #4). An attempt should be made to excise as much as possible of grossly visible tumour, as several studies have correlated outcome with the extent of resection and the amount of residual tumour. In a retrospective review of 32 adult patients with medulloblastoma confined to the craniospinal axis, Chan et al. reported that the five year disease-free survival rate was significantly better for patients who underwent complete total resection versus a less than complete resection (89% vs. 27%; RR=10.9, 95% CI 2.73-80.8; p<0.01). In addition, only one of 17 patients who underwent complete total resection experienced failure in the posterior fossa, whereas ten of 15 patients who underwent a less than complete resection experienced failure in the posterior fossa. Similarly, in a retrospective review of 53 adult patients with medulloblastoma, del Charco et al. reported that absolute survival rates at five years after biopsy alone, subtotal excision, and gross total excision were 43, 67, and 78 percent, respectively (p=0.04), and posterior fossa control rates were 27, 89, and 83 percent, respectively (p=0.004).

**Radiotherapy.** Postoperative radiotherapy is the standard of care for the treatment of adult patients with medulloblastoma. The reported five-year overall survival rates for adult patients with medulloblastoma treated with craniospinal irradiation range from 58 to 84 percent. In the pediatric setting, there has been a recent shift to a reduction in the craniospinal radiation dose, in an effort to prevent or reduce the negative neurocognitive effects of radiation on the developing brain. However, a dose of 36-40 Gy to the spinal axis appears to be well tolerated in adults, with no major acute or late effects reported in the literature to date. In their retrospective review of 156 adult patients, Carrie et al. reported that 36 Gy to
the craniospinal axis was well tolerated and had a statistically significant positive effect on prognosis ($p=0.003$). The authors also reported a trend to longer event-free survival for doses higher than 50Gy to the posterior fossa ($p=0.09$). In the series reported by Padovani et al., a craniospinal radiation dose greater than 30Gy and a posterior fossa radiation dose greater than 50Gy both correlated significantly with overall survival ($p=0.0054$ and $p<0.0001$, respectively). In multivariate analysis, a radiotherapy dose less than 50Gy to the posterior fossa was negatively associated with overall survival (RR=2.7, 95% CI 3.0-5.8; $p=0.009$). In a recent retrospective analysis, Balducci and colleagues presented the long-term outcomes of 13 adult patients treated with postoperative radiotherapy over a 20 year period. The median dose to the brain was 40 Gy (range 34.5-44) and to the posterior fossa was 55 Gy (range 50.4-55.8); eleven patients also received a dose of 30 Gy on the spinal cord. The ten-year rates of local control, overall survival, and disease-free survival were 91%, 76%, and 84%, respectively. A recent retrospective review of 40 adult medulloblastoma patients compared proton craniospinal irradiation (CSI) with conventional photon CSI and found that patients treated with proton CSI experienced less treatment-related morbidity, including less acute gastrointestinal and hematologic toxicities. Members of the Alberta Provincial CNS Tumour Team recommend that postoperative radiotherapy to the entire craniospinal axis at a total dose of 36-40Gy/20 fractions, followed by a posterior fossa boost to 54-55.8Gy should be administered to all adult patients with medulloblastoma. Sites of gross disease elsewhere in the craniospinal axis should be boosted to at least 40Gy. Concurrent chemotherapy, as described below, may allow for use of lower craniospinal radiation doses of 23.4Gy, but only for adult patients with average risk disease (recommendation #5).

Chemotherapy. Beginning in the early 1990’s, several randomized clinical trials reported that treatment with chemotherapy resulted in improved survival for children with high-risk medulloblastoma, and these children demonstrated better survival when compared to their low-risk counterparts who were not treated with chemotherapy. As a result, it became standard to treat all children with medulloblastoma with chemotherapy in addition to radiotherapy. In contrast to childhood medulloblastoma, the role of chemotherapy in adult patients with medulloblastoma is less clear. Recent publications suggest that the biology of adult medulloblastoma might closely resemble the Sonic Hedgehog (SHH) pediatric subtype of medulloblastoma; thus, based on extrapolation from the pediatric literature, adjuvant chemotherapy may be considered for adults with high-risk disease, and also for the treatment of recurrence (recommendation #6). Although there is currently no strong evidence to support a specific chemotherapy regimen for adults, treatment toxicity may be an important factor to take into consideration in this population. In a retrospective review of toxicities for 56 adolescents treated for medulloblastoma, Tabori and colleagues reported significant grade 2 or higher neurotoxicity and ototoxicity in 71% and 45% of patients treated with chemotherapy, respectively. Apart from two recent prospective trials, most of the published reports addressing chemotherapy in the adult population are small, retrospective, involve patients diagnosed and treated more than 30 years ago, involve a variety of chemotherapy drugs or regimens, and include both low-risk and high-risk populations. Table 2 summarizes the results from a selection of the largest of these published trials of adjuvant chemotherapy in adult patients with medulloblastoma.
Table 2. Review of Select Studies of Adults with Medulloblastoma Treated with Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age</th>
<th>Adjuvant Chemotherapy Regimen(s)</th>
<th>Radiation Doses</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Rao, 2014\(^{44}\)    | 363   | not reported | Regimen A:  
Day 0=CCNU (75 mg/m\(^2\))  
Day 0=cisplatin (75 mg/m\(^2\))  
Day 0, 7, 14=VCR (1.5 mg/m\(^2\); max. 2 mg)  
Regimen B:  
Day 0=cisplatin (75 mg/m\(^2\))  
Day 0, 7, 14=VCR (1.5 mg/m\(^2\); max. 2 mg)  
Day 21, 22=cyclophosphamide (1 mg/m\(^2\)) | Craniospinal: 2,340 cGy  
Posterior fossa boost: 3,240 cGy  
Total: 5,580 cGy  
180 cGy/day; 5 days/week | 8-yr EFS=78.2 ± 2.6%  
8-year OS=83.9 ± 2.4% |
| Friedrich, 2013\(^{45}\) | 70    | 28.5 yrs   | lomustine orally (75 mg/m\(^2\)) + vincristine intravenous (1.5 mg/m\(^2\); max. 2 mg) + cisplatin infusion over 6 h after CSI (70 mg/m\(^2\)) | Craniospinal: 35.2 Gy  
Posterior fossa boost: 55.2 Gy | 4-year EFS=68 ± 7%  
4-year OS=89 ± 5%  
Peripheral neuropathy (74%) and haematotoxicity (55%) appear to be more common in adults than children  
Histological subtype and tumour location identified as risk factors |
| Silvani, 2012\(^{43}\) | 28    | 27 yrs     | cisplatin (45 mg/m\(^2\) days 1-3) + etoposide (120 mg/m\(^2\), days 1-3) every 4 wks x 3 cycles | Craniospinal: 36 Gy  
Posterior fossa boost: 53.2–60 Gy (median=54 Gy) | 5-yr OS rate=80%  
10-yr OS rate=55.8%  
5-yr OS rates for standard- vs. high-risk patients=69.8% vs. 50% (p=0.0063)  
extent of surgery and desmoplastic vs. classic variant were not predictive of survival  
5-yr PFS rate=57.6%  
18/28 patients developed recurrence |
| Ang, 2008\(^{46}\)    | 25    | 30 yrs     | N=1: vincristine + CCNU + prednisone  
N=6: cisplatin/etoposide alternating with vincristine/ cyclophosphamide  
N=1: vincristine + CCNU  
N=4: other protocols | Craniospinal: 23.4 – 28.8 Gy (n=3) or 35 – 39.6 Gy (n=16)  
Posterior fossa boost: 50–56 Gy | 5-yr OS rate=78%  
10-yr OS rate=30%  
adjuvant therapy did not significantly impact survival |
| Ertas, 2008\(^{47}\)   | 29    | not reported | N=11: procarbazine + CCNU + vincristine | Whole brain: 40 Gy  
Spine: 36 Gy  
Posterior fossa boost: 10–14 Gy | Mean OS=59.8 months CT-treated vs. 41.4 months no CT (p=0.15) |
| Brandes, 2007\(^{48}\) | 36    | 26 yrs     | N=10 standard-risk patients: treated with RT alone  
N=26 high-risk patients: treated with RT + CT  
- pre-1995: nitrogen mustard + vincristine + prednisone + procarbazine  
- post-1995: cisplatin + etoposide + cyclophosphamide | Craniospinal: 36 Gy (20 fractions of 1.8 Gy/5 fractions/week)  
Posterior fossa boost: 18.8 Gy (in 10 fractions up to total of 54.8 Gy) | 5-yr OS rates=80% standard-risk patients vs. 73% high-risk patients (p=NS) |
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
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<tbody>
<tr>
<td>Padovani, 2007&lt;sup&gt;6&lt;/sup&gt;</td>
<td>253</td>
<td>29 yrs</td>
<td>N=146: heterogeneous adjuvant CT regimens (8 drugs in 1 day regimen; carboplatin + etoposide)</td>
<td>Brain: 35 Gy</td>
<td>• 5-yr OS rate=71% CT vs. 73% no CT</td>
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<td>Spine: 35 Gy</td>
<td>• 10-yr OS =58% CT vs. 53% no CT (p=NS)</td>
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<td>Posterior fossa boost: 54 Gy</td>
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<tr>
<td>Herrlinger, 2005&lt;sup&gt;48&lt;/sup&gt;</td>
<td>34</td>
<td>24.5 yrs</td>
<td>N=8: vincristine + CCNU + cisplatin or carboplatin N=7: methotrexate alone or methotrexate + vincristine based protocols N=5: other protocols</td>
<td>Brain: 35 Gy</td>
<td>• 5-yr OS rate=84% CT vs. 75% no CT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Spine: 35 Gy</td>
<td>• 10-yr OS rate=84% CT vs. 41% no CT</td>
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<td></td>
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<td></td>
<td></td>
<td>Posterior fossa boost: 55 Gy</td>
<td>• Median survival=NR for CT patients vs. 101 mos for patients not treated with CT (RR=1.89, 95% CI 0.95-4.86; p=0.068)</td>
</tr>
<tr>
<td>Abacioglu, 2002&lt;sup&gt;49&lt;/sup&gt;</td>
<td>30</td>
<td>27 yrs</td>
<td>N=10 high-risk patients: varying combinations of procarbazine + CCNU + vincristine</td>
<td>Brain: 40 Gy (1.8–2 Gy fractions/day) Spine: 36 Gy (1.4–1.8 Gy fractions/day) Posterior fossa boost: 54 Gy</td>
<td>• 5-yr OS rate=65%</td>
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<td></td>
<td>• 8-yr OS rate=51%</td>
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<td>• 5-yr DFS rate=69% CT vs. 60% no CT (p=NS)</td>
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</table>
| Greenberg, 2001<sup>50</sup> | 17  | 23 yrs     | N=10: weekly vincristine followed by cisplatin + CCNU + vincristine (Packer protocol) N=7: cisplatin/etoposide alternating with vincristine/cyclophosphamide (POG protocol) | Craniospinal: 36 Gy Posterior fossa boost: 53.2–60 Gy | • Median OS=36 mos
|                       |     |            |                                                   |                                  | Packer protocol vs. 57 mos POG protocol (p=0.058)                      |
|                       |     |            |                                                   |                                  | • Toxicity moderately severe with Packer protocol                      |
| Kunschner, 2001<sup>4</sup> | 28  | 30.5 yrs   | N=1: thioguanine + procarbazine + dibromodulcitol + CCNU + vincristine N=4: cyclophosphamide + etoposide + cisplatin N=1: methotrexate + nitrogen mustard + vincristine + prednisone + procarbazine | NA                               | • No significant difference in OS demonstrated between the patients treated with CT vs. no CT |
| Chan, 2000<sup>26</sup>   | 32  | 25.5 yrs   | N=16: cisplatin + vincristine N=4: cisplatin + vincristine + cyclophosphamide + etoposide N=1: cisplatin + vincristine + cyclophosphamide N=1: cisplatin + vincristine + etoposide N=1: vincristine + CCNU | Craniospinal: 36 Gy Posterior fossa boost: 55 Gy | • 5-yr OS rate=83%                                                  |
|                       |     |            |                                                   |                                  | • 8-yr OS rate=45%                                                   |
|                       |     |            |                                                   |                                  | • CT adversely associated with rate of posterior fossa control (p=0.03) |
|                       |     |            |                                                   |                                  | • Patients treated with CT presented with more advanced M-stage than patients treated with RT alone |
| Le, 1997<sup>37</sup>    | 34  | 23 yrs     | N=12: procarbazine + hydroxyurea N=5: cisplatin + CCNU + vincristine N=2: CCNU + vincristine + procarbazine + hydroxyurea N=2: thioguanine + procarbazine + dibromodulcitol + CCNU + vincristine N=1: CCNU + hydroxyurea N=1: cytarabine | Brain: 39.6 Gy Spine: 38.4 Gy Posterior fossa boost: 55.8 Gy | • 5-yr OS rate=58%                                                  |
|                       |     |            |                                                   |                                  | • No effect of CT on survival or posterior fossa control               |
| Prados, 1995<sup>18</sup> | 47  | 28 yrs     | N=11 standard-risk patients: procarbazine + hydroxyurea (+ CCNU in | Brain: 33.9 Gy Spine: 31.1 Gy | • 5-yr OS rate=81% standard-risk patients |
|                       |     |            | Brain: 33.9 Gy Spine: 31.1 Gy Posterior fossa boost: 55.8 Gy |                                  |                                                                           |
The use of concurrent chemotherapy and radiotherapy followed by adjuvant chemotherapy has also been described in the literature. Douglas et al. treated 33 pediatric and adults patients with average risk disease using concurrent vincristine and reduced-dose cranial spinal irradiation (23.4 Gy) plus a conformal tumour bed boost, followed by eight cycles of adjuvant chemotherapy (vincristine, cisplatin, and lomustine or cyclophosphamide). They reported an estimated 5-year disease free survival rate of 86 percent, as well as estimated 5-year disease free posterior fossa control and primary tumour bed control rates of 94 percent.

A recent randomized trial of medulloblastoma patients aged 3 to 21 years evaluated EFS after receiving chemotherapy before radiation (n=112) or after radiation (n=112). Patients received either 7-weeks of cisplatin and VP-16 followed by chemoRT then 28 weeks of vincristine/cyclophosphamide (arm 1) or chemoRT followed by 7-weeks of cisplatin and VP-16 then 28 weeks of vincristine/cyclophosphamide (arm 2). The study authors reported a 5-year EFS of 66 percent in the arm 1 group and 70 percent in the arm 2 group (p=0.54); 5-year OS in the two groups was 73.1 percent and 76.1 percent, respectively (p=0.47). Five-year EFS did not differ significantly between the two groups in this study. These results do not support the use of neoadjuvant chemotherapy for medulloblastoma in children.

The use of temozolomide as an alternative to some of the older chemotherapy regimens has recently shown favourable results with improved efficacy and reduced adverse effects in adult patients with both newly diagnosed and recurrent medulloblastoma.

Prospective randomized studies are required to more definitively address whether the combination of concurrent and adjuvant chemotherapy is an effective treatment for adults with medulloblastoma, and if so, which chemotherapy regimens are most effective. At the present time, it is reasonable to treat select

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<tr>
<td>Carrie, 1994</td>
<td>156</td>
<td>28 yrs</td>
<td>N=31: vincristine + BCNU + procarbazine + hydroxyurea + cisplatin + cytarabine + methotrexate N=29: vincristine + CCNU or BCNU N=9: ifosfamide + cisplatin + vincristine N=6: other protocols</td>
<td>Brain: 35 Gy Spine: 35 Gy Posterior fossa boost: 55 Gy</td>
<td>vs. 54% high-risk patients (p=0.03) • Adjuvant CT associated with longer survival (p=0.03) • Lack of adjuvant CT associated with shorter time to tumour progression (p=0.05)</td>
</tr>
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</table>
high-risk adult patients with the chemotherapy protocols which have been shown to be effective through randomized clinical trials in the pediatric population. Decisions should be made on an individual basis for each patient, and should be discussed and planned at multidisciplinary Tumour Board meetings.

Follow-up

In their population-based review of adult patients with medulloblastoma in Alberta, Roldán et al. reported a 50 percent survival rate at five years, and noted that the estimated survival curves did not level off, suggesting that these patients have a lifetime risk of tumour recurrence, and should not be considered cured.8 Late relapses in adult patients with medulloblastoma have also been documented in several other studies. Chan et al. reported that 59 percent of all recurrences in their series occurred more than two years after completion of treatment, and 29 percent occurred more than five years after the completion of treatment.28 Riffaud et al. reported a recurrence rate of 41 percent, with a median time to first recurrence of 4.2 years (range 0.7–18 years).10 Similarly, in one of the only prospective studies published to date, Brandes et al. reported that the risk of recurrence increased markedly after seven years of follow-up for low-risk adult patients, and after ten years for high-risk adult patients.5 In a review of 23 patients aged 2 to 40 years with extra-CNS medulloblastoma metastases, Eberhart and colleagues reported that only four cases were identified at diagnosis, while the remaining cases of recurrence or metastasis appeared up to 11 years after the initial diagnosis.57

Due to the potential for late recurrences, the Alberta CNS Tumour Team members recommend a minimum of five to ten years of follow-up for adult patients with medulloblastoma (recommendation #7). In particular, monitoring and surveillance should be focused on neurocognitive, neuroendocrine, thyroid, pulmonary, cardiac, gastrointestinal, renal, and reproductive system late effects.14 An MRI of the brain and full spine with gadolinium enhancement should be obtained every three to six months for the first two years of follow-up, and every year thereafter. The final discharge of the patient to their family physician will be at the discretion of the treating oncologist.

Treatment for Recurrent Patients

Published trials addressing the treatment of disease recurrence in adult patients with medulloblastoma are limited mostly to small case series and retrospective reviews. Treatments described in the literature most often involve re-resection combined with chemotherapy and re-irradiation,28,48,53,58-60 but re-irradiation alone4 and chemotherapy alone5 have also been reported. It is difficult to compare treatment responses at the time of recurrence across these studies however, due to the wide variety of chemotherapeutic agents and treatment schedules reported. In their published guidance, the National Comprehensive Cancer Network (NCCN) recommends that patients with disseminated disease should be managed with chemotherapy or best supportive care including focal radiation, where indicated, while patients with localized brain recurrences should be treated with maximum safe re-resection, followed by chemotherapy and/or additional radiotherapy.51 For patients who have not previously received chemotherapy, the NCCN recommends the use of high-dose cyclophosphamide/etoposide, carboplatin/etoposide/ cyclophosphamide, or cisplatin/etoposide/ cyclophosphamide. For patients previously treated with chemotherapy, they recommend the use of high-dose cyclophosphamide/ etoposide, oral etoposide, or temozolomide.61

The NCCN also lists high-dose chemotherapy followed by autologous stem cell transplantation as an option following re-resection.61 To date, there have been 12 publications involving 61 adults patients with recurrent medulloblastoma treated with high-dose chemotherapy followed by stem-cell transplantation.52-74
The majority of these studies have been case reports, case series, or retrospective reviews, and patient characteristics such as the degree of disease progression at recurrence, first versus later recurrence, and the fitness of the patients varies across studies. In addition, both high-dose and salvage chemotherapy regimens have varied across studies, limiting the comparability of the results. In the only publication to include a comparison group, Gill et al. reported that patients treated with high-dose chemotherapy and autologous stem cell transplantation at recurrence had a better overall survival than a group of historical controls treated with conventional chemotherapy at recurrence (3.47 years vs. 2 years, \( p = 0.04 \)). A recent systematic review on the management of recurrent medulloblastoma in the adult population found similar results.

Based on our interpretation of the existing literature combined with our expert opinion, the Alberta Provincial CNS Tumour Team members recommend that patients with disseminated disease should be managed with chemotherapy, focal radiation where indicated, and best supportive care. Fit patients with localized recurrence should undergo maximum safe re-resection, and may be offered re-irradiation or high-dose chemotherapy with autologous stem cell transplantation. Decisions should be made on an individual basis for each patient, and should be discussed and planned at multidisciplinary Tumour Board meetings (recommendation #8).
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASCT</td>
<td>autologous stem cell transplantation</td>
</tr>
<tr>
<td>BCNU</td>
<td>carmustine</td>
</tr>
<tr>
<td>CCNU</td>
<td>lomustine</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CSI</td>
<td>craniospinal irradiation</td>
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<tr>
<td>CT</td>
<td>chemotherapy</td>
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<tr>
<td>DFS</td>
<td>disease-free survival</td>
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<tr>
<td>EFS</td>
<td>event-free survival</td>
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<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>OS</td>
<td>overall survival</td>
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<tr>
<td>POG</td>
<td>Pediatric Oncology Group</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>RT</td>
<td>radiotherapy</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results database</td>
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<tr>
<td>SHH</td>
<td>sonic hedgehog</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</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 2015. 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


