EPENDYMOMAS

Effective Date: May, 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 2800 new cases of central nervous system (CNS) tumours will be diagnosed in Canada, and 1850 deaths from CNS tumours will occur during the same period.1 Ependymomas are a rare group of CNS cancers that develop from either the ependymal cells lining the cerebral ventricles or in the central canal of the spinal cord. In adults, ependymomas account for between two and eight percent of all primary brain tumours,2-4 with supratentorial ependymomas being less common and associated with lower survival rates than their infratentorial counterparts.2,5 Ependymomas also represent approximately fifteen percent of all spinal tumours in adults, and approximately 60 percent of all spinal cord gliomas; spinal cord ependymomas most commonly occur in younger adults, are less prevalent than intracranial ependymomas, are most often low-grade lesions, and are associated with a better prognosis.2,4,6-9

Given the relative rarity of ependymomas in adults, a lack of well-controlled studies has resulted in a wide range of prognostic factors, reported treatment outcomes, and consequently, varying survival rates. Reported five-year survival rates for intracranial ependymomas range from 62 to 84.8 percent; ten-year survival rates have been reported to be between 43 and 76.5 percent.3,5,10 For spinal ependymomas, data from small case series studies suggest that five-year survival rates are over 80 percent for completely resected tumours.7-9

The Alberta Provincial CNS Tumour Team uses the classification system of the World Health Organization (WHO) to describe CNS tumours, which is based on histologic features of the tumour.11 Table 1 outlines the grades and histologic characteristics:

Table 1. World Health Organization Grading of Central Nervous System Tumours11

<table>
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<tr>
<th>WHO Grade</th>
<th>Histologic Characteristics</th>
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<tr>
<td>Grade I</td>
<td>Includes lesions with low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone.</td>
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<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>
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<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>
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<tr>
<td>Grade IV</td>
<td>Includes lesions that are mitotically active, necrosis-prone, and generally associated with a rapid preoperative and postoperative evolution of disease.</td>
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Low-grade ependymomas include subependymomas and myxopapillary ependymomas (WHO grade I) and ependymal tumours (WHO grade II); these tumours are generally associated with a good prognosis and favourable outcomes. Anaplastic ependymomas (WHO grade III) account for approximately 30 percent of all intracranial ependymomas, and have a more variable prognosis, depending on the location of the tumour and the extent of the disease.2

GUIDELINE QUESTIONS

- What are the optimal treatment strategies for adult patients with WHO grades II and III (anaplastic) ependymomas?
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 November, 2009, and was revised in May, 2012.

SEARCH STRATEGY

For the development of the original guideline, medical journal articles were searched using the Medline (1950 to August Week 3, 2009), EMBASE (1980 to August Week 3, 2009), Cochrane Database of Systematic Reviews (3rd Quarter, 2009), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Ependymoma [MeSH heading], low-grade ependymoma, subependymoma, myxopapillary ependymoma, practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Articles were excluded from the review if they: had a non-English abstract, were not available through the library system, were case studies involving less than 5 patients, or were published prior to the year 2000.

For the 2012 update of this guideline, Medline, EMBASE, Cochrane and PubMed were searched using the terms Ependymoma [MeSH heading], low-grade ependymoma, subependymoma, and myxopapillary ependymoma, limited to clinical trials, clinical trials phase I-IV, controlled clinical trials, randomized controlled trials, published from September 2009- present (May 25, 2012). Articles were excluded if they had a non-English abstract, were case studies involving less than 5 patients, did not include survival outcomes or were over 50% patients under 18 years old with a median age of less than 18 years. A review of the relevant existing practice guidelines for ependymomas was also conducted by accessing the practice guidelines on the websites of the British Columbia Cancer Agency (BCCA), Cancer Care Ontario (CCO), the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and the National Cancer Institute (NCI).

TARGET POPULATION

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

**WHO Grade II Ependymomas:**

1. Surgery represents the standard initial treatment. Maximal surgical resection is important whenever possible.
2. Postoperative MRI within 72 hours allows assessment of residual tumour and guides further management.
3. Postoperative radiotherapy may be considered for a known or suspected residual intracranial tumour, in order to increase local disease control. If administered, a standard dose of 45-54 Gy may be administered in 1.8-2.0 Gy per fraction.
4. Currently, there is no evidence that the addition of chemotherapy to surgery or radiotherapy improves outcome.

**WHO Grade III (Anaplastic) Ependymomas:**

5. Surgery plus radiotherapy represents the standard treatment.
6. Postoperative radiotherapy doses of 54-60 Gy should be administered in 1.8-2.0 Gy per fraction whenever possible. The dose to the optic chiasm, optic nerves, and spinal cord should be limited as appropriate.
7. Craniospinal irradiation in patients with evidence of craniospinal spread should be considered. A palliative approach, using limited doses and volumes of radiotherapy or other approaches may be used.
8. Chemotherapy is a treatment option being evaluated; recurrent patients should be considered as candidates for chemotherapy or clinical trials.

**Follow-up:**

9. Close observation and long-term follow-up is recommended for all patients with ependymomas, due to late effects of radiotherapy in long-term survivors.

DISCUSSION

**Treatment of WHO Grade II Ependymomas**

Surgery represents the standard initial treatment for grade II ependymomas (recommendation #1). The extent of surgical resection has emerged as the most significant predictor of progression-free and overall survival for patients with intracranial ependymomas, and the results of several recent studies suggest that this is true for spinal cord ependymomas as well. Results from the Surveillance, Epidemiology, and End Results (SEER) database, which is a cancer registry of 2408 malignant ependymomas, and is the largest series of ependymoma cases published to date, were recently published, and solidify the findings of previous smaller studies. The authors confirmed that surgery was associated with a significantly improved median survival time (237 months versus 215 months, p<.001), and that patients who underwent gross total resection (GTR) had better ten-year overall survival rates than those with subtotal resections (STR) (75% versus 60%, p<.05).

GTR can be hindered by anatomical factors such as adherence of the tumour to surrounding structures, particularly for tumours in the fourth ventricle, brain stem, lower cranial nerves, or major vascular structures. Thus, consideration must be given to the balance between improved survival with GTR and postoperative morbidity related to high-risk surgery.
The Alberta Provincial CNS Tumour Team recommends the use of postoperative MRI in patients with low-grade ependymomas (recommendation #2). For intracranial ependymomas, an MRI scan should be conducted within 72 hours of surgery. Regular surveillance with MRI allows for improved accuracy in the assessment of residual tumours, may lead to the discovery of asymptomatic recurrences, and guides further management of the disease.\textsuperscript{2,4} For spinal cord ependymomas, the MRI should occur at least two to three weeks postoperatively in order to avoid post-surgical artefacts.\textsuperscript{18,19}

Debate exists as to what role radiotherapy plays in the management of patients with grade II intracranial ependymomas, especially when complete tumour resection can be achieved. In one retrospective analysis of 45 patients with low-grade intracranial ependymomas, Rogers et al. reported that the use of adjuvant radiotherapy was statistically significantly associated with improved ten-year actuarial local tumour control rates in patients who underwent GTR and radiotherapy compared to GRT alone (p=0.018).\textsuperscript{15} Ten-year overall survival rates were 83 percent for patients who underwent GTR plus radiotherapy, 67 percent for those who underwent GTR alone, and 43 percent in those who had an incomplete resection plus radiotherapy, although these results were not statistically significant. The authors concluded that, regardless of the extent of tumour resection, adjuvant radiotherapy is recommended.\textsuperscript{15,20} In another recent multi-institutional retrospective analysis of 152 patients with intracranial ependymomas, Metellus et al. reported a statistically significant difference in progression-free survival between patients with incomplete total resections who received post-operative radiotherapy compared to those without adjuvant treatment (p=.05).\textsuperscript{10} In addition, the authors reported a trend towards better overall survival for these patients. There were no significant differences found in progression-free or overall survival for patients with GTR plus adjuvant radiotherapy compared to those without adjuvant radiotherapy. The authors of this study concluded that there was not yet enough conclusive evidence to support the use of adjuvant radiotherapy in completely resected low-grade intracranial ependymomas.\textsuperscript{10} Patients from the SEER database who underwent partial tumour resection and received radiotherapy had a significantly improved ten-year progression-free survival rate compared to those who did not receive adjuvant radiotherapy (65% versus 56%, p<.05).\textsuperscript{17} In addition, multivariate analysis of the cases involving STR revealed that lack of adjuvant radiotherapy was associated with poorer prognoses (HR=1.748, p=.024).\textsuperscript{17} At the present time, the Alberta Provincial CNS Tumour Team recommends the use of postoperative limited-field radiotherapy to a known or suspected residual tumour, when appropriate, to increase the local control rate (recommendation #3). Tumour Team members agree that, if administered, a standard dose of 45 to 54 Gy should be used in 1.8 to 2.0 Gy per fraction.

Currently, there is very limited data available regarding the use of chemotherapy as an adjuvant to surgery or radiotherapy for the treatment of low-grade ependymomas. In a limited number of case study reports, chemotherapy with etoposide, temozolomide, nitrosourea, or platinum-based agents has been employed as a salvage treatment; however, there is no conclusive evidence that chemotherapy improves time to progression or overall survival.\textsuperscript{21} Therefore, the Alberta Provincial CNS Tumour Team does not recommend the use of chemotherapy as an adjuvant to surgery or radiotherapy for the treatment of low-grade ependymomas (recommendation #4).

**Treatment of WHO Grade III (Anaplastic) Ependymomas**

Surgery plus postoperative radiotherapy represents the standard treatment for patients with grade III (anaplastic) ependymomas (recommendation #5). As previously described, surgery is associated with significant improvements in overall survival time for patients with all stages of ependymal tumours;\textsuperscript{3,7-10,10-16} however, a total resection is not achieved in all cases. For anaplastic ependymomas, there is a general consensus in the literature and published cancer care guidelines that postoperative radiotherapy improves
outcomes. In a study examining treatment outcomes according to the histologic grade of the ependymoma, Korshunov et al. found that when the 127 patients with anaplastic ependymomas were examined separately from the lower-grade tumours, the receipt of adjuvant radiotherapy was associated with a lengthening of the five-year progression-free survival (38% versus 12%, p=.01) and the five-year overall survival times (70% versus 32%, p=.01). In addition, patients who had undergone GTR followed by radiotherapy demonstrated five-year overall survival rates that were comparable to those for patients with low-grade tumours.

There is some debate as to how much normal tissue should be included in the radiotherapy treatment volume in patients with localized anaplastic ependymomas. In earlier published studies, whole-brain radiotherapy (WBRT) or craniospinal irradiation were often employed, but more recent publications have suggested that there is no significant improvement in outcomes associated with these regimens for patients with localized tumours. The Alberta Provincial CNS Tumour Team recommends postoperative radiotherapy doses of 54 to 60 Gy, administered in 1.8-2.0 Gy per fraction (recommendation #6). Whenever possible, the dose to the optic chiasm, optic nerves, and spinal cord should be limited. Craniospinal irradiation should be considered for cases where there is evidence of craniospinal spread, or where there is a high potential to spread to the ventricular system and spinal subarachnoid space (recommendation #7). A palliative approach, using limited doses and volumes of radiotherapy or other approaches may be used. The Alberta Provincial CNS Tumour Team has adopted the recommendations of the NCCN for anaplastic ependymomas. These guidelines state that if the spinal MRI scan is positive, the whole brain and spine (to the bottom of the thecal sac) should receive 36 Gy in 1.8 fractions, followed by limited-field to the spine lesions to 45 Gy.

As previously described, information regarding the role of chemotherapy for treatment of ependymomas in adults is very limited. In recent years, however, there have been some data published which support the use of chemotherapy for the treatment of recurrences, specifically in adults. In a retrospective analysis of 28 adult patients with progressive or recurrent ependymoma, Brandes et al. found that patients treated with cisplatin-based chemotherapy did have more complete responses than those treated with non-platinum regimens, although this did not translate into improved progression-free or overall survival rates. In the study by Korshunov et al., of the 127 patients with anaplastic ependymomas, 44 received chemotherapy with cisplatin, lomustine, and vincristine. The investigators reported a significant improvement in five-year overall survival rates when compared to patients with anaplastic ependymomas who did not receive chemotherapy (78% versus 48%, p=.01). The Alberta Provincial CNS Tumour Team recommends that patients with anaplastic ependymoma who experience recurrences of their disease should be considered for participation in chemotherapy clinical trials (recommendation #8); these patients may provide an important opportunity for prospective investigation of potentially effective chemotherapeutic agents.

Follow-Up

The Alberta Provincial CNS Tumour Team recommends close observation and long-term follow-up for all patients with ependymomas, due to late effects of radiotherapy in long-term survivors (recommendation #9). Follow-up of ependymoma depends on the extent and location of the disease. The Alberta Provincial CNS Tumour Team has adopted the recommendations of the NCCN which state that follow-up of ependymal tumours using contrast-enhanced brain and spine MRI should be done two to three weeks postoperatively and then every three to four months for one year. For year two, the interval can be expanded to every four to six months, and then every six to twelve months after year two, depending on
the preference of the treating physician, the extent of disease, and other relevant factors such as patient travel.

**GLOSSARY OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>GTR</td>
<td>gross total resection</td>
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<td>HR</td>
<td>hazard ratio</td>
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<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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<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results database</td>
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<td>STR</td>
<td>subtotal resection</td>
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<td>WBRT</td>
<td>whole brain radiotherapy</td>
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<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 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**


