MENINGIOMAS

Effective Date: June, 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 Meningiomas arise from the dural covering of the brain, and are estimated to account for 13 to 26 percent of all primary brain tumours, making them the second most common intracranial tumours reported in adults.²⁻⁴ These typically slow-growing tumours occur most frequently after the fifth decade of life, and affect women almost twice as often as men.⁵ Clinically, meningiomas present with symptoms causing focal or generalized seizure disorders, focal neurological deficits, or neuropsychological decline; though many asymptomatic meningiomas are only discovered incidentally during a CT or MRI scan for unrelated symptoms.⁵,⁶

The World Health Organization (WHO) classification system divides meningiomas into three grades based on histological and pathological characteristics:⁷ grade I meningiomas account for as many as 90 percent of all cases, and are typically benign, grade II or atypical meningiomas account for 5 to 7 percent of cases, and grade III or anaplastic meningiomas account for 1 to 3 percent of cases.³,⁵,⁷ The development of high-grade meningiomas has been correlated with exposure to ionizing radiation: the majority of patients with radiation-induced meningiomas either have a history of low-dose radiation to the scalp for tinea capitis, or received high-dose radiation for primary brain tumours between 20 and 35 years previous.⁸,⁹

The management of a patient with a meningioma will depend on the signs and symptoms produced by the tumour, the age of the patient, and location and size of the tumour.⁵

GUIDELINE QUESTIONS

• What is the optimal treatment for adult patients with low-grade (WHO grade I) meningiomas?
• What are the optimal treatment strategies for adult patients with atypical (WHO grade II) and anaplastic (WHO grade III) meningiomas?

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 updated in June, 2012.

SEARCH STRATEGY

For the 2012 update of this guideline, medical journal articles were searched using the Medline (2009 to June 18, 2012), EMBASE (2009 to June 18, 2012), the Cochrane Database of Systematic Reviews (2nd Quarter, 2012), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Meningioma [MeSH heading], Meningeal Neoplasms [MeSH heading], 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 2009. A review of the relevant existing practice guidelines for meningiomas was also conducted by accessing the practice guidelines on the websites of the British Columbia Cancer Agency (BCCA), the National Institute for Health and Clinical Excellence (NICE) and the National Comprehensive Cancer Network (NCCN).

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 I Meningioma:**

1. Surgery is the primary treatment for patients who are not candidates for management by watch-and-wait. Complete tumour resection is associated with high rates of disease-free survival.
2. Radiotherapy may be considered in the cases of a tumour location not amenable to surgery (such as a cavernous sinus meningioma), an unresectable tumour, symptomatic residual disease, or a recurrent tumour. Radiological diagnosis may be sufficient in these cases.

**WHO Grades II and III Meningiomas:**

3. Standard treatment is surgery plus radiotherapy. Radiotherapy is usually delivered at a dose of 54 to 60 Gy, in 1.8 to 2.0 Gy per fraction.
4. Patients with select tumours may be candidates for stereotactic radiosurgery.
5. Other systemic therapies may be considered for unresectable or recurrent tumours on a clinical trial basis.

DISCUSSION

**WHO Grade I Meningioma**

The Alberta Provincial CNS Tumour Team has adopted the recommendations of NICE which state that surgery is the primary therapy for patients who are not candidates for management by a watch-and-wait approach (recommendation #1). Small, asymptomatic, benign-appearing meningiomas that are found during a radiographic evaluation are often followed without therapy, using CT and/or MRI imaging at regular intervals. Yano et al. recently published a large retrospective series involving 603 patients with asymptomatic meningiomas and 831 patients with symptomatic ones who were seen between 1989 and 2003 in Japan. Among the 67 asymptomatic patients who were followed for the entire five year follow-up period, 63 percent did not exhibit tumour growth. Morbidity rates for the asymptomatic patients who were treated surgically were 4.4 percent for patients younger than 70 years of age and 9.4 percent in patients over the age of 70. The authors concluded that, since a large proportion of asymptomatic patients will not become symptomatic in the short-term, active surveillance is an acceptable and recommended approach for asymptomatic patients with low-grade meningiomas.

For patients with surgically accessible tumours, surgical intervention is recommended when the tumour begins to cause symptoms, or when it displays significant growth on consecutive CT or MRI images. The completeness of surgical removal is the most important prognostic factor for grade I meningiomas. In a
classic study of 145 patients with meningiomas who underwent gross total resection, Miramanoff et al. reported disease-free survival rates of 93 percent at five years, 80 percent at ten years, and 68 percent at fifteen years. Patients who underwent partial resection had significantly lower disease-free survival rates in this study: 63 percent at five years, 45 percent at ten years, and only 9 percent at fifteen years. Similarly, in a more recent large series involving 581 patients with grade I meningiomas seen at the Mayo Clinic between 1978 and 1988, Stafford et al. reported disease-free survival rates of 88 percent at five years and 75 percent at ten years for completed resected patients, while those rates decreased to 61 percent at five years and 39 percent at ten years for the partially resected patients.

Gross total resection should always be the goal of surgery, and offers the best possibility of a cure for low-grade meningiomas. However, some meningeal tumours, particularly those involving the cavernous sinus, petroclival region, posterior aspect of the superior sagittal sinus, or optic nerve sheath, cannot be completely removed due to their relationship to vital neural or vascular structures. For incompletely resected or recurrent symptomatic grade I meningiomas, the Alberta Provincial CNS Tumour Team recommends the use of radiotherapy (recommendation #2). In observational studies, external beam radiotherapy (EBRT) has been shown to decrease recurrence rates in patients with incompletely resected low-grade meningiomas. Rogers et al. recently conducted a comprehensive review of 23 studies published during a 24 year period involving 2971 patients treated with either gross total resection alone, partial resection alone, or partial resection plus adjuvant EBRT. Five-year progression-free survival rates ranged from 77 to 98 percent for the completely resected patients, 43 to 63 percent for the partially resected patients who did not receive EBRT, and 80 to 100 percent for the partially resected patients who received adjuvant EBRT. The Alberta Provincial CNS Tumour Team recommends doses of adjuvant EBRT in the range of 50 to 55 Gy in fractions of 1.8 to 2.0 Gy.

**WHO Grades II and III Meningiomas**

Because high-grade meningiomas are associated with high rates of postsurgical recurrence, the standard treatment for patients with WHO grades II or III meningiomas is surgery followed by post-operative radiotherapy (recommendation #3). Although there are no data available from randomized clinical trials, several retrospective analyses suggest that post-operative radiotherapy is effective in decreasing recurrence rates for high-grade meningiomas. In a recent review of 119 patients with high-grade meningiomas who had either complete or incomplete resections and were treated post-operatively with EBRT, Pasquier et al. reported five- and ten-year disease-free survival rates of 58 and 48 percent, respectively. Similar progression- and disease-free survival rates have been reported in earlier published series as well, lending support to the consensus that favours administering EBRT early after surgery for patients with both completely- and partially-resected high-grade meningiomas. For patients with high-grade meningiomas, the Alberta Provincial CNS Tumour Team recommends that post-operative radiotherapy be delivered at a dose of 54 to 60 Gy, in 1.8 to 2.0 Gy per fraction.

Patients with select tumours may be eligible for stereotactic radiosurgery (SRS), a procedure that utilizes multiple convergent beams to deliver a single dose of radiation to a discrete treatment area, thereby minimizing injury to surrounding structures (recommendation #4). This technique is most often used for patients who have small-to-medium sized meningiomas, have tumours that are surgically inaccessible, are not candidates for surgery, or have residual or recurrent tumours following surgery. In a retrospective analysis of 127 patients with meningiomas, Hakim et al. reported one-year overall survival rates of 91.7 percent for the 26 patients with grade II tumours treated with SRS, and 92.3 percent for the 18 patients with grade III tumours treated with SRS. At four years, the overall survival rates were 83.3 percent for grade II and 21.5 percent for grade III tumours. The median marginal tumour dose in this study
was 15 Gy (range 9-20 Gy). In a more recent study involving retrospective analysis of 18 patients with grade II and 12 patients with grade III meningiomas, Harris et al. reported five-year progression-free survival rates of 83 and 72 percent for grades II and III, respectively.\textsuperscript{23} The median marginal tumour dose for the grade II meningiomas was 14.9 Gy, with a median maximal dose of 29.4 Gy; for grade III meningiomas, the median marginal tumour dose was 15.7 Gy, with a median maximal dose of 31.4 Gy. In both the Hakim et al. study and the Harris et al. study, minimal adverse events were reported.

In cases where the tumour is unresectable or all other therapies have failed to prevent a recurrence, systemic treatment may be considered on a clinical trial basis (recommendation #5). There is only limited data available on the use of systemic agents in the treatment of meningiomas, and to date, no randomized controlled studies have been published. The anti-progesterone agent mifepristone has been linked to the treatment of meningiomas because of epidemiological and biochemical data suggesting that meningioma growth is hormone-dependent.\textsuperscript{24} To date, limited data suggest only moderate improvements in tumour size.\textsuperscript{25-27} The use of hydroxyurea, which is an oral chemotherapeutic agent, has also been associated with moderate tumour volume reduction and periods of stable disease in studies involving a limited number of patients.\textsuperscript{28-31}

**GLOSSARY OF ABBREVIATIONS**

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<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>CT</td>
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<td>EBRT</td>
<td>external beam radiotherapy</td>
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<td>NICE</td>
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<td>SRS</td>
<td>stereotactic radiosurgery</td>
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<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


