Disseminated ependymomas of the central nervous system

Ali R. Rezai, M.D., Henry H. Woo, M.D., Mark Lee, M.D., Ph.D., Henry Cohen, M.P.H., David Zaggag, M.D., Ph.D., and Fred J. Epstein, M.D.

Department of Neurosurgery, Division of Neuropathology, Department of Pathology, Microvascular and Molecular Neurooncology Laboratory, and Department of Environmental Medicine, New York University Medical Center, New York, New York

Ependymomas are rare central nervous system (CNS) neoplasms that occasionally disseminate along the neuraxis or to extraneural sites. Definitive criteria predictive of dissemination have yet to be determined. One hundred forty patients with CNS ependymoma (88 primary spinal and 52 primary intracranial tumors) were surgically treated by the senior author (F.J.E.) between 1986 and 1994. Sixteen patients (11.4%) demonstrated tumor dissemination. The disseminated group consisted of 11 (12.5%) of 88 primary spinal and five (9.6%) of 52 primary intracranial ependymomas. The authors retrospectively reviewed the patients with CNS ependymoma and have identified several characteristics associated with dissemination from the primary tumor site. The mean time from diagnosis to dissemination was 6.8 years. The patients with disseminated disease were younger (16.8 vs. 28.3 years old, p = 0.02), had fewer gross-total resections (29% vs. 68%, p = 0.015), and had tumors with higher proliferative indices (MIB-1 staining, 13.14% vs. 2.06%, p = 0.02). High-grade tumors had a mean proliferation index of 21%, versus 2.4% and 1.6% for myxopapillary and low-grade tumors, respectively (p = 0.0003). In contrast to previous studies, tumor histology was the most significant variable for time to dissemination as determined by multivariate analysis (p = 0.008). Myxopapillary and high-grade tumors were 3.6 and 5.6 times more likely to have a shorter time to dissemination than low-grade tumors. In addition, dissemination is associated with a worse prognosis. At follow-up review, 31% of patients with disseminated disease had died compared to 7% of patients without dissemination (p = 0.04). It is concluded that younger patients with subtotal resections, myxopapillary or high-grade histology, and tumors with high proliferative indices are at substantial risk for the development of disseminated disease during their clinical course.

Key Words • brain tumor • dissemination • ependymoma • metastasis • myxopapillary tumor • proliferation index • spinal cord tumor

Clinical Material and Methods

Patient Population

Between 1986 and 1994, 140 patients with ependymomas of the CNS were surgically treated at the New York University Medical Center by the senior author (F.J.E.). The tumors consisted of 88 primary spinal cord ependymomas and 52 primary intracranial ependymomas. Sixteen patients (11.4%) demonstrated subsequent dissemination along the neuraxis. We considered dissemination to be the spread of tumor along the neuraxis to a location separate from the primary site. The group with disseminated disease consisted of 11 patients with primary spinal cord tumors (four intramedullary and seven cauda equina/filum terminale tumors) and five patients with primary intracranial tumors. In addition, there was one patient with extraneural metastases. The mean time from initial diagnosis to discovery of dissemination was 6.7 years. Of the 124 patients without dissemination, 35 were selected randomly for analysis. Seven of these were excluded because of incomplete medical records or the lack of tumor tissue for immunohistochemical analysis. The 28...
remaining patients without dissemination were used as the control group. This number provided adequate statistical power for analysis. Our series was limited to 16 cases of disseminated lesions. As the control/case ratio increases from 2:1 to 3:1 or greater, the information that the additional number of controls provides is limited. We compared the control population analyzed in this report to the remainder of nondisseminated cases and found no difference in age, sex, or histology. The group with nondisseminated lesions consisted of 23 patients with primary spinal cord tumors and five patients with primary intracranial tumors.

A retrospective review of the medical records was performed to determine the patient’s age, gender, duration of symptoms prior to diagnosis, time interval from diagnosis to dissemination, the extent and number of surgical resections, and the use of adjuvant therapy.

Pathological Evaluation

All histological slides were graded by a single neuropathologist (D.Z.) as low-grade, high-grade, or myxopapillary ependymoma. The sections were evaluated for the presence of mitotic figures, vascular hyperplasia, and necrosis. Only when all three of these characteristics were present was a tumor designated as high grade. All tumor specimens were analyzed by immunohistochemistry for a nuclear activation antigen (Ki-67) to determine the cellular proliferation index. This was accomplished using the mouse monoclonal antibody MIB-1 (Immunotech, Westbrook, ME), which recognizes the Ki-67 antigen in formalin-fixed, paraffin-embedded tissues. The Ki-67 nuclear antigen is expressed in each phase of the cell cycle except the Go phase and serves as a marker for cellular proliferation.1,2,14,17 For each specimen, 4 µm-thick sections were cut from paraffin blocks, deparaffinized, rehydrated, and stained by standard methods using the avidin-biotin-horseradish peroxidase complex to localize the antibody bound to antigen (Fig. 1).

The MIB-1 nuclear staining was automated and quantitated on an image analysis system (SAMBA 4000 Immuno Software Program; Imaging Products International, Chantilly, VA). For each specimen, 10 fields were analyzed at 40 magnification and stained tumor cells were counted. The percentage of stained cells was then determined.

Statistical Analysis

Statistical associations were assessed using a two-tailed test. A probability value of 0.05 was considered statistically significant. All statistical computations were performed using a statistical analysis program (JMP Version 3.0; SAS Institute, Inc., Cary, NC).

The statistical procedure used for evaluating the difference between the medians was the nonparametric Mann–
Chi-square tests were performed to compare categorical variables. A chi-square analysis was used to evaluate the association between extent of resection and tumor dissemination. Multivariate analysis was performed using the Cox proportional hazards model. To simplify the multivariate model, we used the univariate methods to reduce the number of variables that were ultimately tested in the multivariate model. Only those variables that were significant in the univariate models were included in the multivariate analysis. The multivariate model subsequently determined which of these variables had the most profound effect on the endpoint, whether that was time to dissemination or survival. Risk ratios were calculated for each of the various clinical and pathological criteria with respect to the time to dissemination. Kaplan–Meier survival analysis was used to evaluate time to dissemination for extent of resection and histology.

### Results

#### Clinical and Surgical Characteristics

A summary of the patients’ clinical and surgical characteristics is shown in Table 1. The groups with disseminated and nondisseminated disease did not differ in regard to gender. The group with disseminated lesions was significantly younger than the group with nondisseminated lesions. The mean age for the group with disseminated lesions was 16.8 years, compared to 28.3 years for the nondisseminated group. The group with disseminated lesions was also significantly younger than the group with nondisseminated lesions, with a mean age of 16.8 years compared to 28.3 years.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Disseminated* (16 patients)</th>
<th>Nondisseminated* (28 patients)</th>
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<tr>
<td><strong>age†</strong></td>
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<tr>
<td>mean (yrs)</td>
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<td>range (yrs)</td>
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<tr>
<td><strong>location (%)‡</strong></td>
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<td>conus medullaris</td>
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<td>9</td>
</tr>
<tr>
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<td>17</td>
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<tr>
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<td></td>
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<tr>
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* There were five intracranial and 11 spinal ependymomas in the disseminated group and five intracranial and 23 spinal ependymomas in the nondisseminated group.
† Statistical significance at $p \leq 0.05$.
‡ The radiographic location of the primary lesion at the initial presentation.
§ The mean and range in months of the duration of symptoms prior to the initial diagnosis.
‖ The extent of resection of the initial surgery. This is divided into three categories based on the surgeon’s operative estimates and the postoperative magnetic resonance image.

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**Fig. 2.** Graphs showing times to dissemination for various ependymomas and resection methods. **Upper:** Comparison of time to dissemination in patients with subtotal resection and biopsy versus gross-total resection ($p = 0.03$). **Center:** Comparison of time to dissemination in patients with myxopapillary and high-grade tumors versus low-grade tumors ($p = 0.01$). **Lower:** Comparison of time to dissemination in patients with high-grade versus myxopapillary tumors ($p = 0.03$).
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disease was 16.8 years, whereas that for the group with nondisseminated disease was 28.3 years (p = 0.02). There was a strong suggestion that the group with dissemination had a shorter duration of symptoms prior to initial presentation. The group with dissemination had a mean duration of symptoms of 10 months whereas in the group without dissemination the duration was 18 months (p = 0.09). In addition, the mean duration of symptoms for disseminated intracranial ependymomas was 1 month, versus 14 months for disseminated spinal tumors (p = 0.003, Mann–Whitney). Clinical symptoms included headaches, nausea and vomiting, motor deficits, sensory loss, and gait difficulties. There was no difference between the groups with regard to primary tumor location (p = 0.3, chi-square test).

All patients underwent operation at the time of or very close to the time of diagnosis. The two groups differed significantly with regard to the extent of initial surgical resection. There were two patients who presented with dissemination at the time of diagnosis and were excluded from the analysis concerning extent of initial resection; however, they were included in all other analyses. The extent of resection was determined by the operative estimate of resection and by the postoperative magnetic resonance image. The group with disseminated disease included 29% of patients with gross-total tumor resections, whereas the group without dissemination included 68% of patients with gross-total resections (p = 0.015, chi-square). Kaplan–Meier analysis was used to compare the time to dissemination in patients with and without total tumor resections (Fig. 2 upper). At 5-year follow-up review, only 4% of the patients with gross-total resections suffered dissemination compared to 44% of patients without gross-total resections (log-rank p = 0.03). The Kaplan–Meier analysis was limited to 6 years because the small sample size beyond that time period made the analysis unstable statistically.

The mean number of reoperations in the group with disseminated disease was greater than that for nondisseminated tumors (1.15 vs. 0.6, p = 0.0001). However, the mean number of reoperations was significantly associated with the extent of the initial resection, and therefore seemed related to dissemination of the primary tumor.

Similarly, the use of adjuvant therapy after the initial surgical procedure appeared to have a significant association with dissemination (p = 0.024, chi-square). However, adjuvant therapy was more likely to be used in the setting of subtotal resection, and therefore was not independently related to disseminated disease. For example, 87% of patients undergoing gross-total resection did not receive subsequent adjuvant therapy, whereas 74% of patients with subtotal resections did receive adjuvant therapy (p = 0.0002, chi-square).

Tumor Histology and Proliferation Index

The groups differed significantly with regard to tumor histology. The histological data is summarized in Table 2. Kaplan–Meier analysis was used to compare the time to dissemination for histological subtypes of ependymomas (Fig. 2 center). At 5-year follow-up review, 66% of the high-grade tumors and 33% of the myxopapillary tumors had become disseminated, as opposed to only 8% of the low-grade tumors (log-rank p = 0.002). In addition, the high-grade lesions disseminated earlier than the myxopapillary tumors (Fig. 2 lower). All high-grade tumors had disseminated by 3 years, whereas the myxopapillary tumors did not disseminate until at least 4 years. In the nondisseminated population, 82% of tumors were low grade on histological review.

As a whole, high-grade tumors exhibited a proliferation index of 21%, versus 2.4% and 1.6% for myxopapillary and low-grade tumors, respectively. There was no statistical difference between the myxopapillary and low-grade tumors; however, high-grade tumors exhibited a higher proliferation index than the other groups (p = 0.0003, chi-square). The overall mean proliferation index of the group without dissemination was 13.14%, whereas that for the group without dissemination was 2.06% (p = 0.02, Wilcoxon). The mean proliferation index for the group with disseminated intracranial disease (31%) was significantly higher when compared to the nondisseminated intracranial tumors (4.8%) (p = 0.014, Wilcoxon). In addition, there was a strong suggestion of a higher MIB-1 in the disseminated spinal ependymomas (5.19%) when compared to the nondisseminated spinal lesions (1.47%) (p = 0.106, Wilcoxon).

Multivariate Analysis

The Cox proportional hazards regression model was used to evaluate age, extent of resection, histology, and proliferation index simultaneously with respect to time to dissemination. Pathological grading had the most profound effect on the time to dissemination (p = 0.02, chi-square). Myxopapillary and high-grade ependymomas had hazards ratios of 3.6 and 5.6 for dissemination when compared to low-grade tumors (p = 0.008 for each chi-square). The extent of resection was strongly associated with dissemination; however, due to the small sample size, statistical significance was approached but not achieved (p = 0.07, chi-square). The proliferation index was not found to be significant in the multivariate analysis (p = 0.9, chi-square).

### Table 2

<table>
<thead>
<tr>
<th>Feature</th>
<th>Disseminated* (16 patients)</th>
<th>Nondisseminated* (28 patients)</th>
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<tr>
<td></td>
<td>Intracranial</td>
<td>Spinal</td>
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<tr>
<td>spinal</td>
<td>5.2</td>
<td>1.5</td>
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</tbody>
</table>

* There were five intracranial and 11 spinal ependymomas in the disseminated group and five intracranial and 23 spinal ependymomas in the nondisseminated group.
† The percentage of nuclei staining positive (proliferation index) after immunohistochemical analysis with MIB-1 monoclonal antibody directed against the nuclear activation marker (see Methods). Intracranial and spinal refer to the primary location of the ependymoma.
Discussion

Ependymomas are rare neoplasms accounting for less than 10% of primary CNS tumors. Ependymomas are potentially curable tumors because they are amenable to complete surgical resection. Dissemination in the CNS and systemic metastasis have been reported previously in case studies and in large series in which they comprise a small fraction of cases. These studies have analyzed patient survival as their outcome and have not specifically addressed the question of dissemination. The rarity of disseminated ependymomas has precluded an adequate risk analysis.

Between 1986 and 1994, the senior author (F.J.E.) surgically treated 140 patients with CNS ependymoma. Of these, 16 patients have suffered from dissemination of their primary disease (11.4%). The incidence of dissemination for primary spinal disease was 12.5% and that for primary intracranial disease was 9.6%. This is similar to rates reported in previous studies in which the incidence of dissemination ranged from three to 11%. The extent of the initial surgical resection was highly significant with respect to dissemination. Of particular interest is the fact that 83% of the patients with gross-total tumor resections never developed disseminated disease, whereas 71% of the patients with subtotal resections demonstrated dissemination. The importance of total resection at the initial surgical attempt must be emphasized because a patient with residual tumor is 5.3 times more likely to suffer from disseminated disease eventually (p = 0.02, chi-square).

The prognosis of aggressive surgical resection for patient survival has been emphasized frequently. There is a lower incidence of recurrence and a more favorable outcome with gross-total resection. Higher recurrence rates have been shown with incomplete resection of intramedullary spinal cord ependymomas, and long-term disease-free survival is best achieved with a total resection at the initial setting. However, dissemination potential was not specifically addressed in previous studies.

Ependymomas, in particular the spinal cord and supratentorial tumors, are amenable to complete surgical resection. These tumors are generally well circumscribed and tend to displace rather than infiltrate the surrounding neural tissue. There is usually a distinct tumor margin that allows for the development of a well-defined surgical plane. This is not necessarily the case for posterior fossa ependymomas, which are more hazardous to resect. Gross-total or en bloc resection is the desired goal of surgery. However, factors such as location, tumor infiltration, and the experience of the surgeon may preclude a gross-total removal.

Encapsulated tumors involving the cauda equina or filum terminale are potential candidates for en bloc resection. Sonneland, et al., have reported that encapsulated myxopapillary tumors involving the filum terminale that are removed en bloc exhibit a lower proportion of dissemination (10%) than tumors that are removed piecemeal (19%). Thus, violation of the tumor capsule may lead to subsequent cerebrospinal fluid seeding and dissemination. This may be the mechanism of dissemination for some histologically benign tumors located in this region. In our disseminated population, none of the seven tumors involving the filum terminale or the cauda equina was resected en bloc.

Other aspects of patient treatment such as the number of reoperations on the primary tumor and the use of adjuvant therapy were not independently related to tumor dissemination, but were related to the extent of tumor resection. Hence, it was difficult to assess the role of the number of resections and adjuvant therapy with respect to dissemination due to the significant association of these variables with extent of surgical resection.

Tumor Histology

In contrast to other primary CNS tumors in which histological anaplasia usually corresponds to a greater degree of clinical malignancy, conflicting results have been found when correlating ependymoma histology with clinical prognosis. Waldron, et al., reported on 59 cases of spinal ependymomas and found that tumor grade was important with respect to recurrence and survival. Nazar, et al., in their study of infratentorial ependymomas in children, suggested that histological criteria, in particular mitotic index, are influential prognostic criteria for outcome. However, they also note that other factors including subtotal resection or tumor invasion into the brainstem may be responsible for the poor outcome in tumors with a benign histological picture. On the other hand, Kricheff, et al., found no correlation between histology and biological behavior in their review of 65 cases of intracranial ependymomas. Ross and Rubinstein only found no correlation between pathology and survival in 15 patients with malignant ependymomas. Fokes and Earle also did not observe an association between histological grading and survival time in their review of 133 ependymomas. Similarly, Mørk and Løken found histological classification to be of limited prognostic value in their study of 101 patients with ependymomas. Even myxopapillary ependymomas, which are benign histologically, have been known to recur and disseminate. In particular, there may be a tendency for late recurrence, especially with subtotal resection.

In this report, the histological subtypes significantly associated with dissemination were high-grade and myxo-
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Markers of proliferative activity are being used increasingly to gauge the malignant potential of tumors. Proliferation index analysis supplements conventional histological information and may provide a more thorough prognostic picture. Until recently, analysis of proliferation capacity was difficult and cumbersome because it required radioisotope injection, fresh or frozen tissue for bromodeoxyuridine analysis, and tedious cell counting. However, the advent of immunohistochemical techniques and the development of antibodies against cellular proliferation markers such as Ki-67 and the proliferating cell nuclear antigen have revolutionized cellular proliferation analysis. These markers now appear to have a strong correlation with tumor grading and clinical outcome in patients with brain tumors.

The group with disseminated disease had a higher proliferation index than the group without disseminated disease ($p = 0.02$). This difference was most pronounced for the intracranial tumors and an association was suggested in the spinal tumors. In addition, there was a significant association between MIB-1 and tumor histology. High-grade tumors exhibited higher proliferation indices as well as an increased probability of dissemination. It is possible that MIB-1 is simply a reflection of pathology and may not have an independent effect on dissemination. The multivariate analysis demonstrated that pathology was the most significant factor related to dissemination, whereas proliferation index was not. The significance of proliferation indices and their relationship to tumor histology requires further clarification.

It is of interest that the disseminated intracranial ependymomas were all high grade on histological review, exhibited the highest proliferation indices, produced the shortest duration of symptoms prior to diagnosis, and disseminated earlier. Thus, disseminated intracranial ependymomas may be inherently more aggressive tumors.

The significance of dissemination and its association with survival has not been specifically addressed previously. In our series, 31% of patients with disseminated tumors died compared to 7% with nondisseminated tumors ($p = 0.04$). Thus, risk factors that are predictive for dissemination may also reflect a worse prognosis.

**Conclusions**

In this report, we have attempted to define prognostic criteria for dissemination in ependymomas. Tumor dissemination occurred in 11.4% of our patients with CNS ependymomas and was significantly associated with increased mortality. The comparison between patients with disseminated and nondisseminated ependymomas revealed that patients at risk for dissemination of tumor during the course of their disease were relatively younger, did not undergo gross-total tumor resections, had high-grade or myxopapillary tumors, and may exhibit high proliferation indices. We recommend that patients fitting these criteria receive follow-up care with a heightened sense of suspicion for disseminated disease. The importance of total resection at the initial surgical attempt must again be emphasized because a patient with residual tumor is 5.3 times more likely to eventually suffer from disseminated disease. Therefore, we believe strongly that ependymomas must be treated aggressively and all possible attempts should be made to achieve gross-total resections.

**References**


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