Infratentorial ependymomas in childhood: prognostic factors and treatment

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The prognostic factors and survival data were analyzed for 35 children (aged under 16 years at diagnosis) with childhood infratentorial ependymomas treated surgically at The Hospital for Sick Children in Toronto during the years 1970 to 1987. Tumor histology was reviewed individually and grouped into three categories (Categories I to III) for survival analysis. An overall 5-year survival rate of 44.6% was obtained after the exclusion of perioperative mortality. Factors associated with an improved 5-year survival rate were: total tumor removal, noninvasive tumors, Category I histology, age greater than 6 years, and absent physical signs of parenchymal invasion or lower cranial nerve involvement. The 5-year survival rate was lower when associated with Category II histology, brain-stem or cranial nerve signs, age less than 2 years, tumor invasion and/or cranial nerve involvement, and subtotal tumor removal. Clinical evidence of spinal metastases was found to be uncommon (3.1%). Surgical excision followed by radiation therapy was the primary mode of treatment for these tumors. Different approaches regarding the volume of radiotherapy to be delivered and the use of adjuvant chemotherapy are discussed.

KEY WORDS • ependymoma • infratentorial tumor • posterior fossa • radiotherapy • chemotherapy • children
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TABLE 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Category I</th>
<th>Category II</th>
<th>Category III</th>
</tr>
</thead>
<tbody>
<tr>
<td>mitotic index</td>
<td>low</td>
<td>low</td>
<td>moderate</td>
</tr>
<tr>
<td>dense cellularity</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>necrosis</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Mitotic index: low = 0 or 1 mitosis/10 high-power fields (HPF); moderate = 2 or 3 mitoses/10 HPF; high = > 3 mitoses/10 HPF. - = feature absent; + = feature present.

Examined by two of the authors (L.E.B. and G.B.N.) who were unaware of the patients' outcome. Based on actuarial survival methods, a number of histological features were examined individually including the presence and/or amount of: mitoses (low: 0 or 1 mitosis/10 high-power fields (HPF); moderate: 2 or 3 mitoses/10 HPF; or high: > 3 mitoses/10 HPF); cellularity; pleomorphism; necrosis; differentiation; calcium; and ependymal cell or pseudorosette formation. From the analysis of these features, three tumor categories (Categories I to III) were formulated to simplify survival data (Table 1). Primitive neuroectodermal tumors with ependymal cells (ependymoblastoma) were excluded from analysis.49

Results

Age and Clinical Presentation

There were 18 males and 17 females in the study group. The mean age at diagnosis was 70.5 months (range 3 to 189 months) and 49% of patients were less than 4 years of age (Fig. 1). The mean duration of symptoms was 100.7 days (range 4 to 450 days). The presenting clinical symptoms and signs are listed in Table 2. Children less than 2 years of age presented differently from older children, reflecting the presence of their open sutures and fontanels and their neurological immaturity.59 Fourteen patients presented with focal cerebellar (unilateral limb ataxia) and/or brain-stem or lower cranial nerve signs (diminished gag reflex, diminished corneal reflex, internuclear ophthalmoplegia, gaze paresis, and facial weakness). Patients with a sixth nerve paresis were excluded from the latter category. In 10 of these 14 patients tumor invasion into adjacent parenchyma was documented at surgery.

Operative Data

All patients had surgical excision of their tumor. There were no deaths within a 30-day period following surgery but a 14.3% incidence (five cases) of major morbidity was noted in the initial perioperative period. Three of these latter patients improved substantially over time and later received a full course of radiotherapy. The two remaining patients were not irradiated and suffered relentless progression of their tumors; they died 2 and 3 months postoperatively. Of the 35 patients undergoing surgical excision, gross total removal was performed in 10 (28.6%).

Tumor invasion into the brain stem and/or cerebellum was found in 54.3% of the 35 patients (19 cases), not specified in 14.3% (five cases), and not present in 31.4% (11 cases). Extension of the tumor over the upper cervical spinal cord was present in 65.7% (23 cases). In only one of these patients did the tumor invade the dorsal aspect of the spinal cord. In 25.7% (nine cases) the tumor extended into the cerebellopontine angle (CPA). Four of these cases were “plastic” ependymomas as described by Courville and Broussalian.11 Only five tumors were localized solely within the fourth ventricle.

Pathological Findings

Histological sections were available for analysis in all patients. Cases were grouped according to their mitotic indices (Table 1) as being either low (51.4%), moderate (25.7%), or high (22.9%); mitotic indices were based on areas of tumor containing the greatest cell densities. The 5-year actuarial survival rates (after exclusion of perioperative deaths) in relation to mitotic index were 69.3%, 41.8%, and 0%, respectively. The presence of focal areas of dense cellularity amid a low-to-moderate cellular background also had prognostic importance. These areas were present in 34.3% of the tumor specimens and were associated with a 5-year survival estimate of 19.1%. The absence of these areas (65.7%) was associated with a 5-year survival rate of 62.3%. The presence of calcium, cellular pleomorphism, or ependymal or pseudorosettes had no impact on the overall

Fig. 1. Age distribution among the 35 patients in this series.
Fig. 2. Photomicrographs of a tumor from each histological category. **Upper Left:** Category I histology with low mitotic index and no areas of dense cellularity or necrosis. Perivascular pseudorosettes are prominent. H & E, × 112. **Upper Right:** Category II histology with focal areas of dense cellularity and perivascular pseudorosettes, absence of necrosis, but moderate mitotic activity. H & E, × 45. **Lower Left:** Category III histology with dense cellularity, focal necrosis (lower right), and a moderate-to-high mitotic index. Perivascular pseudorosetting is also present. H & E, × 112.

prognosis. The patients with tumors that had focal areas of necrosis had a worse outcome (15 cases: 23.3% 5-year survival rate) than those who did not (20 cases: 54.7% 5-year survival rate). Six patients had tumors with diffuse dense cellularity and high mitotic rates; five of these patients have died. The three histological categories were formulated based on the above histological data (Table 1 and Fig. 2). There were 12 patients (34.3%) with Category I histology, 12 (34.3%) with Category II histology, and 11 (31.4%) with Category III histology. The correlation of these data with tumor invasion and tumor removal is noted in Table 3; the correlation of age and histology is noted in Table 4.

**Spinal Metastasis**

Clinical evidence of spinal metastasis was observed only in one patient. He was a 61-month-old child who had a left seventh nerve palsy on clinical presentation. At surgery, a Category I tumor was subtotally removed and local radiotherapy was given. Forty-seven months posttreatment, he became symptomatic for spinal metastasis which was treated by surgical excision and spinal irradiation. A computerized tomography scan at this time showed residual tumor in the posterior fossa which became symptomatic 31 months later. The patient survived an additional 18 months.

Lumbar cerebrospinal fluid (CSF) analysis was performed at the time of diagnosis in seven patients, and the fluid was negative for cytology in all cases. Delayed CSF surveillance was performed in four cases at the time of local recurrence and was positive in only one. Excluding patients who did not survive 2 months after primary treatment, the incidence of clinical metastases was 3.1% (one of 32 patients).

**Survival Data**

There were 20 deaths, 95% of which were related to tumor recurrence or progression at the primary site. Only two of these patients survived longer than 5 years, although neither was recurrence-free longer than 4 years. Fifteen patients remain alive, of whom seven have been recurrence-free for longer than 5 years. Eight patients remain at risk, of whom seven have been recurrence-free for longer than 5 years. Eight patients remain at risk and have a mean follow-up period of 23.6 months; in two of these patients recurrence has been documented. One survivor has been lost to follow-up review at 25 months posttreatment. The overall 5-year actuarial survival rate was 40.7%.

In an analysis of the relationship of prognostic factors and treatment modalities to survival, three patients were excluded. Two died within 2 months of completing treatment and one succumbed to a disseminated varicella infection during postoperative chemotherapy. The 5-year survival rate among the remaining 32 patients was 44.6%. The actuarial survival curves of different age groups are shown in Fig. 3. Children aged 24 months or over had a better survival rate than children less than 2 years old. Children aged over 6 years had the best outcome, with a 5-year survival rate of 61.4%. This was significantly better than the survival rate of children less than 2 years old (p < 0.05).
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Patients with gross total tumor removal or with noninvasive tumors had a significantly better 5-year survival rate than those with either subtotal tumor removal or invasive lesions (p < 0.01 and p < 0.05, respectively). Analyzed together, all six patients with a totally removed noninvasive tumor are alive, and four have survived longer than 5 years. The 14 patients with subtotaltially removed invasive tumors had a 5-year survival rate of 26.7%. The poorest outcome (5-year survival rate of 10%) was noted in the 10 patients with positive focal cerebellar and brain-stem and/or cranial nerve signs associated with tumor invasion documented at surgery.

Of the nine totally removed tumors, six (66.7%) were noninvasive; all six patients were alive at 5 years after diagnosis. Two totally removed tumors (22%) invaded the cerebellum; one of these patients is alive more than 5 years after diagnosis. One patient had a small nubbin of tumor invading the floor of the fourth ventricle. A gross total removal of the tumor mass was performed. This patient had significant postoperative morbidity, but was doing well enough to complete a full course of radiotherapy. She is alive without recurrence 14 months after diagnosis. Prognostically, brain-stem invasion implies a subtotal removal and has the worst prognosis. Total tumor removal is possible primarily in noninvasive tumors and in those tumors invading the cerebellum.

Tumors extending into the CPA presented unique problems due to their intimate relationship to the cranial nerves. Four of these cases were “plastic” ependymomas11 and involved both CPA’s. Of these tumors, two were totally removed and were not invasive. Both of these patients had Category I histology and have survived longer than 5 years; neither received postoperative radiotherapy (Fig. 4). Five patients had tumors extending unilaterally into the CPA. In all five the tumors were invasive into the adjacent parenchyma and only one had a gross total removal. Only one of these five patients is alive, now 20 months postsurgery.

Clinical signs at the time of diagnosis weighed heavily as a prognostic factor in our series. All patients with brain-stem or cranial nerve signs had significantly

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**TABLE 2**

<table>
<thead>
<tr>
<th>Symptoms &amp; Signs</th>
<th>Age &lt; 2 Yrs</th>
<th>Age ≥ 2 Yrs</th>
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<tbody>
<tr>
<td>no. of cases</td>
<td>10</td>
<td>25</td>
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<tr>
<td>vomiting</td>
<td>80%</td>
<td>80%</td>
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<tr>
<td>irritability</td>
<td>60%</td>
<td>0</td>
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<tr>
<td>headache</td>
<td>0</td>
<td>68%</td>
</tr>
<tr>
<td>lethargy</td>
<td>50%</td>
<td>0</td>
</tr>
<tr>
<td>gait disturbance</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>weight loss/feeding problem</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>increased head circumference/bulging fontanel</td>
<td>50%</td>
<td>0</td>
</tr>
<tr>
<td>papilledema</td>
<td>40%</td>
<td>72%</td>
</tr>
<tr>
<td>stiff neck</td>
<td>50%</td>
<td>0</td>
</tr>
<tr>
<td>truncal ataxia</td>
<td>20%</td>
<td>53%</td>
</tr>
<tr>
<td>limb ataxia</td>
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<td>32%</td>
</tr>
<tr>
<td>sixth nerve palsy</td>
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<td>36%</td>
</tr>
<tr>
<td>nystagmus</td>
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<td>44%</td>
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<tr>
<td>brain-stem signs</td>
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<td>28%</td>
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**TABLE 3**

<table>
<thead>
<tr>
<th>Histological Category*</th>
<th>No. of Cases</th>
<th>Tumor Invasion†</th>
<th>No Tumor Invasion†</th>
<th>Tumor Removal</th>
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<tr>
<td>I</td>
<td>12</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
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<td>II</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>total cases</td>
<td>35</td>
<td>19</td>
<td>11</td>
<td>24</td>
</tr>
</tbody>
</table>

* See Table 1 for description of each category.
† Tumor invasion could not be assessed in five patients at the time of surgery due to limited tumor resections.

**TABLE 4**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>No. of Cases</th>
<th>Histological Category*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>10</td>
<td>II</td>
</tr>
<tr>
<td>2-6</td>
<td>11</td>
<td>I</td>
</tr>
<tr>
<td>&gt;6</td>
<td>14</td>
<td>II</td>
</tr>
<tr>
<td>total</td>
<td>35</td>
<td>II</td>
</tr>
</tbody>
</table>

* See Table 1 for description of each category.

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![Fig. 3. Influence of age on survival rates in patients with infratentorial ependymoma.](image-url)
FIG. 4. Axial enhanced computerized tomography scans in a 4-year-old child. Left: Preoperative scan showing a large "plastic" ependymoma filling the fourth ventricle. Right: Postoperative scan confirming total resection of the ependymoma. This patient remains free of tumor 9 years after surgery. He received no radiotherapy or chemotherapy.

poorer survival rates, which were unrelated to the treatment modalities employed (Fig. 5).

The formulated histological categories (Table 1) also had an impact on survival times (Table 5). Five-year survival rates of 70.5%, 49.5%, and 12.1% were observed for Categories I (11 cases), II (11 cases), and III (10 cases), respectively (Fig. 6). Only the difference in survival rates associated with Category I and III tumors reached statistical significance at 5 years (p < 0.02). Category I tumors had the lowest incidence of invasion (22.2%), comprised 71% of all noninvasive totally removed tumors, and had the lowest incidence of patients presenting with focal cerebellar, brain-stem, or cranial nerve signs (25%). Differences in the 5-year survival rate between patients in Categories I and II were primarily related to the lower incidence of invasion and a greater number of Category I patients with total tumor removal. The 5-year survival rates of patients with invasive and/or subtotally removed tumors were similar (52.6% for seven cases with Category I tumors and 41.6% for 10 cases with Category II tumors). Patients with Category III lesions had a high percentage of invasive (66.7%) and subtotally removed (90%) tumors, and included 60.0% of the children under 2 years of age. The 5-year survival rate in this group of 10 patients was 12.1%.

Treatment Analysis

Analysis of treatment responses was made by comparing actuarial estimates derived from the time of diagnosis to the development of a clinical local recurrence. Twenty patients (62.5%) had local recurrences; all except one occurred within 3 years of diagnosis; the exception was in a patient who developed spinal metastasis at 47 months and then a symptomatic local recurrence at 78 months postdiagnosis. The actuarial estimate of 5-year survival for patients who were recurrence-free at 3 years was 31.4%.

Six patients (18.8%) were treated initially by surgery alone. Two of these patients have survived without recurrence 90 and 157 months, respectively. Both had noninvasive totally removed Category I "plastic" ependymomas. A third patient with a Category II noninvasive totally removed tumor had a recurrence at 25 months; this tumor was also totally removed and craniospinal axis irradiation was given. He has now survived recurrence-free for 68 months. The remaining three patients had invasive tumors, which were subtotally removed in two patients and totally removed in one. An example from each histological category was represented. Irradiation had been withheld in two patients due to their young age and was declined by the third. All three had local recurrences; two have subsequently died and one has survived 13 months despite tumor progression. The 26 remaining patients received radiotherapy postoperatively; 30% of these were recurrence-free at 3 years. A statistical comparison between local and craniospinal axis therapy could not be made due to the small number of patients (six cases) treated with local irradiation. The 3-year recurrence-free estimates were 25% for locally treated patients and 31.2% for those receiving craniospinal axis irradiation.

The highest percentage of patients who received radiation treatment and were recurrence-free at 3 years was observed in the groups with: total tumor removal (100%, five cases); a noninvasive tumor (51%, seven cases); and tumors in Categories I (46.0%, eight cases) and II (52.1%, nine cases). The lowest percentages were found in the groups with: Category III tumors (0%, nine cases), subtotal tumor removal (19.3%, 21 cases), and invasive tumors (23.4%, 14 cases).

The 20 patients who suffered a documented recurrence did poorly, with a 5-year survival rate of 21.1% from the time of diagnosis and 10.0% from the time of...
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TABLE 5
Prognostic factors influencing survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>5-Year Survival Rate</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>best outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total tumor removal</td>
<td>86.7%</td>
<td>9</td>
</tr>
<tr>
<td>noninvasive tumor</td>
<td>79.4%</td>
<td>10</td>
</tr>
<tr>
<td>Category I histology</td>
<td>70.5%</td>
<td>11</td>
</tr>
<tr>
<td>patient's age &gt; 6 yrs</td>
<td>61.4%</td>
<td>14</td>
</tr>
<tr>
<td>no neurological signs</td>
<td>57.2%</td>
<td>19</td>
</tr>
<tr>
<td>worst outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>subtotal tumor removal</td>
<td>29.5%</td>
<td>23</td>
</tr>
<tr>
<td>invasion by tumor</td>
<td>31.2%</td>
<td>17</td>
</tr>
<tr>
<td>Category III histology</td>
<td>12.1%</td>
<td>10</td>
</tr>
<tr>
<td>patient's age &lt; 2 yrs</td>
<td>18.8%</td>
<td>9</td>
</tr>
<tr>
<td>brain-stem/cranial nerve signs</td>
<td>14.3%</td>
<td>7</td>
</tr>
</tbody>
</table>

* See Table 1 for description of histological categories.

Fig. 6. Influence of histology on survival data in this series. NR = not reached.

Recurrence. Of the nine recurrences that were treated surgically, invasion was noted in all and total tumor removal was performed in only one. This latter patient was the only patient to survive longer than 5 years. Recurrences were treated by a number of different methods, usually in combination. Nine patients underwent further surgery, following which two had implantation of $^{125}$I radioactive seeds. One patient died shortly after implantation due to progressive bulbar paralysis and aspiration; the other remained well for 24 months posttreatment but then developed progressive bulbar paralysis from tumor recurrence and died 3 years after brachytherapy. Seven patients received radiotherapy; four of these belonged to the surgical failure group and received radiation therapy for the first time. Two of these patients are alive at 9 and 68 months after recurrence; the remaining two died 1 year postirradiation. Three patients received additional radiotherapy to the posterior fossa; their mean survival time posttreatment was 9$\frac{1}{2}$ months.

Chemotherapy was administered to six patients at the time of recurrence and to five patients as part of their primary treatment. Due to the small numbers, the different protocols used, and the varied responses, information obtained was anecdotal. Among the five patients receiving chemotherapy initially, there were four deaths, one secondary to a varicella infection. One patient who received "8 in 1" chemotherapy is still alive 19 months following a subtotal excision of an invasive Category II tumor without recurrence. In the six patients treated for recurrence, three had no clinical response to a variety of drugs including the "8 in 1" protocol, vincristine, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), intrathecal methotrexate, and cis-platinum. Only one of these six patients remains alive 1 year after starting his course of "8 in 1" chemotherapy.

Discussion

Analysis of survival data and an understanding of prognostic factors concerning infratentorial ependymomas in children have been difficult to obtain among the many published reports. The 5-year survival rate of children with infratentorial ependymomas in our series was 44.6%. Other series have reported 5-year survival rates of 17.1% (17 cases, 1935–1973) and 26.2% (30 cases, 1955–1973) for a similar population profile. Series of children with both supratentorial and infratentorial ependymomas have had 5-year survival rates of: 51% (32 cases, 1969–1979); 47% (30 cases, 1952–1971); 44% (20 cases, 1959–1979); and 27% (104 cases, 1968–1979).

Further analysis of age-related factors has revealed that children less than 2 years of age have not done as well as older children. In our series, an 18.8% 5-year survival rate was observed in children less than 2 years old, versus 52.3% in children aged 2 years or older (Fig. 3). In our study, a higher incidence of Category III histology (60.0%) was found in children less than 2 years old, a finding supported by other authors. Consideration must also be given to the influence of smaller radiation doses and perhaps other unidentified biological factors unique to young children with immature brains and developing nervous systems.

Although the majority of these tumors are slow-growing and have low mitotic indices, the recurrence of such "low grade" lesions has been associated with very poor outcomes in most cases. The diversity of histological features between tumors and within different areas of the same specimen makes it difficult and often controversial to group these tumors into more rigid grading schemes. Despite histological variability, many authors contend that tumor histology remains a useful, if not the best, prognostic indicator. However, many instances have arisen where histology had a poor correlation.
FIG. 7. Contrast-enhanced computerized tomography scans in an 18-month-old child. Left: Preoperative scan. Center: Immediate postoperative scan showing residual invasive tumor. Right: Scan obtained after completion of "8 in 1" chemotherapy and radiotherapy demonstrating disappearance of tumor.

40, 48, 56 or even had no association 2, 26, 44, 50 with outcome. A few attempts have been made to isolate which histological features may be of prognostic importance. 7, 24, 25, 29, 44, 48, 56 Histological Categories I to III in our study were structured on the analysis of the relationship between different histological features and survival data and were used to simplify outcome analysis. Results showed the mitotic index to be the most influential. Also associated with a poor outcome were focal areas of hypercellularity amid a low-to-moderate cellular background, necrosis, and diffusely highly cellular tumors. However, as previously implied, the absence of these features (Category I) did not necessarily equate to a good outcome, as a substantial proportion (54.5%) of Category I patients have died or are alive with clinical recurrences. All of these patients, however, had tumors that were associated with either brain-stem invasion or subtotal tumor removal.

Tumor invasion into the brain stem or cerebellum is common, 42 and has also been considered an important prognostic criterion 2, 31 irrespective of the histology or the treatment modalities used. In our series, patients with invasive tumors had one of the poorest 5-year survival estimates (31.2%), whereas noninvasive tumors were associated with an excellent outcome (79.4%, p < 0.05). A lower incidence for invasion was noted in Category I tumors (Table 3).

Radical removal for infratentorial ependymomas has been advocated by several authors to decrease the tumor burden prior to radiotherapy and because of the associated better prognosis 2, 9, 10, 12, 30, 33, 36, 40, 45, 59 In our series, gross total tumor removal was possible in 28.6% of patients. These patients had an 86.7% 5-year survival rate versus 29.5% for those with subtotally removed tumors (p > 0.01). Furthermore, all of the patients with totally removed noninvasive tumors are alive without recurrence, two-thirds of them longer than 5 years after diagnosis. Two of these patients did not receive postoperative radiotherapy.

In the past, the risk of developing spinal metastases has played an important role in the formulation of radiation therapy protocols, particularly with regard to the volume of tissue irradiated. Data collected from combined series of supra- and infratentorial tumors in both adults and children have revealed an overall average seeding in 10% to 13% of cases 4, 42 (range 0% to 64% 2, 5, 7, 10, 12, 14, 21, 29, 31, 33, 36, 37, 39, 42, 45, 52, 54, 59, 60, 63). A higher incidence has been noted for infratentorial ependymomas and malignant tumors; 5, 23, 29, 32, 40, 42, 46, 52, 54, 60, 61 however, seeding has also been observed in low-grade tumors. 4, 7, 44, 57, 63 Autopsy series of patients with infratentorial ependymomas have yielded an incidence of metastases in approximately 30% of cases (range 6% to 50%) 2, 30, 33, 59, 60 however, patients examined post mortem represent a highly select group with most patients dying of a local recurrence and the majority of implants being asymptomatic. 31 More specifically and more important therapeutically, most series report an average clinical (symptomatic) incidence of 3.9% spinal metastases for infratentorial tumors 2, 7, 12, 21, 29, 31, 36, 44, 45, 53, 59 Overall, it appears that only a few patients will develop symptomatic spinal metastases from infratentorial tumors over the course of their disease. Most of these clinical cases are delayed, and metastases are usually found in association with tumor recurrence at the primary site 2, 7, 29, 46, 57, 62 suggesting that the local recurrence was responsible for tumor seeding. 7, 36, 46, 57 This association is supported by the not-infrequent occur-
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Fig. 8. Suggested treatment protocol for children with infratentorial ependymoma. 
Upper: Children aged 2 years or older. Lower: Children less than 2 years of age. IT = infratentorial, CSA = craniospinal axis.

The recurrence of spinal seeding following prophylactic spinal irradiation is of concern. Diffusely cellular tumors with a high mitotic rate potentially have elevated rates of seeding similar to other poorly differentiated tumors. These tumors should therefore receive craniospinal irradiation, particularly in the presence of positive CSF cytology, myelography, or magnetic resonance (MR) imaging. These tumors account for 17.0% of cases in our series and for 50% of the Category III tumors.

The current standard treatment for infratentorial ependymomas has been surgical excision (with or without local radiotherapy) followed by radiation therapy. Permanent cures following total removal of histologically benign noninvasive lesions have been reported, and include two patients in our series (both with plastic ependymomas). The response of infratentorial ependymomas to radiation has been difficult to define as most series are small, are collected over long periods of time, and lack control randomization for the various protocols employed. Tumor shrinkage following irradiation has not been documented in previous reports, although cases of prolonged stabilization have been reported. In our series, three patients with subtotally removed tumors have shown definite regression of their tumor mass following radiation therapy (Fig. 7). However, two other tumors continued to grow during radiotherapy and a further three rapidly progressed after radiotherapy to produce clinical symptoms within 6 months of radiation treatment. Salazar, et al., noted four similar cases of rapid tumor growth following radiation. Thus, opinion as to the sensitivity of infratentorial ependymomas to radiation therapy varies: some authors consider them to be the most radiosensitive type of glioma, some believe their response to be variable (with radiotherapy increasing life expectancy in some patients but not in others), and others have found that the tumors are minimally radiosensitive, particularly if they are benign and the patients older. Decisions as to radiation treatment should balance local control with radiation toxicity, and the use of adjuvant treatment should be considered in patients with tumor characteristics suggesting a high recurrence rate (Table 5).

Accepting that radiotherapy can be successful, the most important controversy is the volume of tissue that should be irradiated. Radiotherapy to the whole brain in young children is toxic. Thus, the main issues are whether or not to electively irradiate the brain and spinal cord, and what dose to select for local therapy in young children (aged less than 4 years). Several authors have observed higher survival rates in uncontrolled retrospective studies using full craniospinal irradiation for intracranial ependymomas (both supra- and infratentorial), which cannot be solely attributed to the prevention of metastases. Others have emphasized the need for craniospinal axis irradiation only in cases of histological "malignancy." Yet others support craniospinal axis irradiation only when positive CSF cytology and/or spinal metastases (myelography) have been demonstrated and deny that there is a significant difference in outcome between groups with local craniospinal axis irradiation. These issues have been emphasized that the main problem with infratentorial ependymomas is achieving and sustaining local control. Only a small number of cases in our series received local radiotherapy. However, actuarial recurrence estimates between patients treated with craniospinal axis irradiation (20 cases), those in the overall treatment group (32 cases), and those receiving local treatment (six cases) were not significantly different.

Information regarding the use of chemotherapy in these cases has been anecdotal due to the few cases being treated in most series. A wide variety of agents have been tried, but survival data have not been improved. One difficulty arises because of the low mitotic index in many of these tumors. Recently, adjuvant chemotherapy has not been recommended for primary treatment. However, consideration should be given for its use in special situations such as for poorly differentiated tumors, in young children receiving lower radiation doses or no radiation, in children with positive CSF cytology at diagnosis, and in those patients having factors predicting a high chance of recurrence (Table 5).
Conclusions

The treatment of infratentorial ependymomas must be individualized particularly with respect to age and other prognostic variables. A suggested protocol for children aged less than 2 years and for those aged 2 years or over is presented in Fig. 8. Surgery alone should be considered for patients with total removal of non-invasive Category I tumors, providing that there is negative cytology and myelography (or possibly negative gadolinium-enhanced MR imaging of the spine). Local radiotherapy generously incorporating the tumor boundaries should be given to patients with subtotally removed Category I tumors, to all patients with Category II tumors, and to patients with noninvasive, well-differentiated, totally removed Category III tumors. Cytology and myelography must be negative in patients receiving only local radiotherapy. Craniospinal axis radiotherapy and chemotherapy should be used following surgery in patients with invasive subtotally removed Category III tumors, particularly if there is positive cytology or myelography, as long as the patients are older than 2 years of age. For patients who are less than 2 years old, a policy of chemotherapy and delayed radiotherapy is attractive, but is as yet of uncertain value.

References

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