Outcomes in treatment for primary spinal anaplastic ependymomas: a retrospective series of 20 patients

Clinical article

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Object. Little is known regarding the anaplastic variant of primary ependymomas that involve the spinal cord. The aim of this study was to evaluate the clinical characteristics and treatment outcomes of primary spinal anaplastic ependymomas (PSAEs).

Methods. Medical records were reviewed in 20 patients with pathologically proven PSAEs who underwent surgical treatment at the Department of Neurosurgery in Huashan Hospital between 1999 and 2008.

Results. This series included 7 women and 13 men between the ages of 2 and 67 years (mean 31.9 years). The mean preoperative course was 9.3 months (range 20 days to 48 months). The most common PSAE locations were the cervical and thoracic spinal cords. The most common presenting symptom was weakness, followed by numbness, bowel or bladder dysfunction, and pain. Gross-total resection (GTR) was achieved in 17 patients, and a subtotal removal was performed in 3 patients. Nine patients received radiation therapy and/or chemotherapy. The mean follow-up duration was 83.5 months. Functional assessment of the 10 patients available at the latest follow-up evaluation showed that 2 had worsened and 8 remained unchanged from their preoperative status. There were 2 local recurrences and 1 lung metastasis.

Conclusions. Patients with PSAEs presented with a much shorter preoperative course than patients with Grade II ependymomas in previous studies. Patients with tumors that involved the cervical spinal cord experienced a worse outcome. Surgical removal of PSAEs, with the goal of GTR, is beneficial to patients. The role of radiation therapy and chemotherapy in PSAEs remains to be determined in further studies.

* Drs. Liu and Sun contributed equally to this work.

Abbreviations used in this paper: AIS = American Spinal Injury Association Impairment Scale; GTR = gross-total resection; PSAE = primary spinal anaplastic ependymoma; STR = subtotal resection.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
we analyzed 26 patients with anaplastic ependymomas with spinal cord involvement who were treated at Huashan Hospital between January 1999 and December 2008. In these 26 cases, 2 patients who developed spinal seeding after an operation for intracranial anaplastic ependymomas were excluded. Four patients who developed spinal recurrences or remote disseminations were also excluded from further analysis. Thus, a total of 20 patients with PSAEs were included, and their medical records were reviewed. Pathological specimens of all patients were available and classified as anaplastic ependymomas (WHO Grade III) according to the WHO classification of 2000 and 2007; typical examples are shown in Fig. 1. All patients were uniformly evaluated with preoperative MRI.

Operation and Follow-Up

In all patients, a posterior midline approach was performed; the surgical technique has been previously described. After the operation patients were followed up by clinical examinations or telephone interviews. Neurological function was evaluated using the AIS (http://www.asia-spinalinjury.org) and the McCormick classification system. Grades were assigned retrospectively on the basis of documented preoperative and postoperative examinations. All patients underwent follow-up imaging studies.

Results

Epidemiological Characteristics

During the study period, 273 patients with spinal ependymal tumors underwent surgery, 20 of which were for PSAEs (Fig. 2). There were 13 men and 7 women, ranging in age from 2 to 67 years old (mean 31.9 years old; Table 1). Two patients had tumors localized in the medullocervical cord, 6 were in the cervical cord, 4 were in the cervicothoracic cord, 6 were in the thoracic cord, and 2 were in the thoracic cord-conus medullaris. The tumors spanned 2 vertebral levels in 2 patients, 3 vertebral levels in 5 patients, 4 vertebral levels in 7 patients, and 5 or more vertebral levels in 6 patients.

Clinical and Radiographic Features

The average duration of the clinical history was 9.3 months, with a range of 20 days to 48 months. Table 1 summarizes clinical features in the patients with PSAE. The most common symptom was limb weakness in 18 patients (90%), followed by limb numbness in 15 patients (75%), bowel or bladder dysfunction in 12 patients (60%), and pain in the neck or back or radiating to the extremities in 10 patients (50%). Objective neurological signs were detected in only 14 patients (70%) at the time of diagnosis. These signs included motor dysfunction in 14 (70%), hypesthesia in 11 patients (55%), ataxia in 7 (35%), lower cranial nerve paralysis in 2 (10%), and muscular atrophy in 2 (10%).

Twelve patients had neuroimaging or radiology reports available for review. The T1-weighted images were hypointense to isointense in 10 cases, with 2 tumors exhibiting minimal hyperintense signaling. All tumors were heterogeneously hyperintense on T2-weighted images. Five patients presented with tumor-associated cysts. Administration of contrast medium resulted in more or less marked enhancement in all ependymomas, with 6 exhibiting a heterogeneous pattern (irregular or patchy enhancement; Fig. 3), 5 a homogeneous pattern, and 1 with a heterogeneous pattern and cyst wall rim enhancement (Fig. 4).

Fig. 1. A–C: Hematoxylin and eosin–stained photomicrographs of PSAEs. Hypercellularity, nuclear atypia, and mitotic activity are present (A). Microvascular proliferation (B) and pseudopalisading necrosis (C) may be features of PSAEs. D–F: Immunohistochemistry revealed positive glial fibrillary acidic protein expression (D) and dot-like intracytoplasmic immunoreactivity for epithelial membrane antigen in a few cells (E). The Ki-67 labeling index was very high (15%) in the highly cellular areas (F). Original magnification ×400 (A, B, E, and F), ×200 (C and D).
Primary spinal anaplastic ependymomas

the center of the spinal cord, 1 in the intramedullary cord with an exophytic component (Fig. 5), and 1 entirely in the intradural-extradural space.

Surgical Outcome

All patients underwent an initial surgical procedure. A GTR was achieved in 17 patients (85%) according to the surgical reports and postoperative MR images. An STR was achieved in 3 patients (15%) because of a poorly defined cleavage plane between the tumor and spinal cord. Surgical outcome summaries are provided in Table 2.

Postoperatively, 3 patients with a cervicothoracic or medullocervical tumor required a tracheostomy, and 2 patients developed ventilator-associated pneumonia necessitating intravenous antibiotics. One patient developed a urinary tract infection. There were no recorded complications of CSF leakage, deep venous thrombosis, or pulmonary embolism in any of the patients. The length of stay was prolonged in the patients with sustained complications. No patient had evidence of instability, neurological morbidity, or other significant complications.

Of the 20 patients, 2 developed a local recurrence and 1 developed a distant recurrence. Specifically, Case 13, who received GTR and adjuvant radiotherapy, developed lung metastasis; Case 6, who only received STR, developed a local recurrence; and Case 20, who received STR followed by adjuvant radiotherapy, also developed a local recurrence in the radiation field.

TABLE 1: Summary of clinical features in the 20 patients with PSAEs*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Duration of Symptoms (mos)</th>
<th>Chief Signs &amp; Symptoms at Presentation</th>
<th>Tumor Location</th>
<th>Tumor Size (cm)</th>
<th>AIS Grade at Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48, F</td>
<td>48</td>
<td>numbness, weakness, pain, BBD, ataxia</td>
<td>med–C5</td>
<td>7</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>31, F</td>
<td>24</td>
<td>numbness, weakness, pain, BBD, ataxia</td>
<td>T4–6</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>2, M</td>
<td>3</td>
<td>weakness, ataxia</td>
<td>C1–2</td>
<td>2.5</td>
<td>D</td>
</tr>
<tr>
<td>4</td>
<td>38, M</td>
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<td>C5–7</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
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<td>T3–6</td>
<td>6</td>
<td>D</td>
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<tr>
<td>6</td>
<td>15, M</td>
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<td>weakness, pain, BBD</td>
<td>C5–T5</td>
<td>9</td>
<td>D</td>
</tr>
<tr>
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<td>30, M</td>
<td>2</td>
<td>numbness, weakness, BBD</td>
<td>T11–L2</td>
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<td>D</td>
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<td>numbness, weakness, BBD</td>
<td>C3–T2</td>
<td>11</td>
<td>C</td>
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<tr>
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<td>37, M</td>
<td>12</td>
<td>numbness, weakness, BBD, ataxia</td>
<td>C7–T8</td>
<td>16</td>
<td>D</td>
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<td>6</td>
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<td>T7–9†</td>
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<td>D</td>
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<tr>
<td>11</td>
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<td>T11–L2</td>
<td>14</td>
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<td>D</td>
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<td>E</td>
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<td>D</td>
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<tr>
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<td>C2–5</td>
<td>6</td>
<td>D</td>
</tr>
<tr>
<td>17</td>
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<td>0.7</td>
<td>pain</td>
<td>T4–6†</td>
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<td>E</td>
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<tr>
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<td>6</td>
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<td>T4–7</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>19</td>
<td>14, F</td>
<td>0.7</td>
<td>numbness, weakness, pain, ataxia</td>
<td>C4–5</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>20</td>
<td>37, F</td>
<td>16</td>
<td>numbness, weakness</td>
<td>med–C3</td>
<td>6.5</td>
<td>D</td>
</tr>
</tbody>
</table>

* BBD = bowel or bladder dysfunction; med = medulla oblongata.
† Exogenous.
‡ Extramedullary.
At the time of admission, neurological function was scored according to the AIS (Table 1) and the McCormick classification system (Table 2). Three patients (15%) scored C, 15 (75%) scored D, and 2 (10%) scored E on the AIS. Twelve patients (60%) were classified as Grade I, 4 (20%) as Grade II, and 4 (20%) as Grade III on the McCormick scale.

Immediately after surgery, 12 patients (60%) had un-
changed neurological function; the condition of 8 patients deteriorated, but 3 of these 8 patients (15%) experienced only transient deterioration and later recovered to the preoperative status in follow-up.

Ten patients who were still alive were recently followed up. Two patients (20%) scored C, 6 (60%) scored D, and 2 (20%) scored E on the AIS. In terms of the McCormick scale, 8 patients (80%) scored Grade I, 1 (10%) scored Grade II, and 1 (10%) had a moderate to severe deficit and required assistance to ambulate (Grade III).

Adjuvant Therapy

Radiation therapy to the tumor bed and surrounding spinal cord was used postoperatively in 9 patients, and 6 were also treated with chemotherapy as adjuvant treatment. Documented regimens included a single agent (temozolomide) or a combination of teniposide and semustine. There were 5 patients in this cohort who never received radiation therapy and chemotherapy at any time during their treatment. One was unknown.

Follow-Up

The length of follow-up was calculated from the date of surgery at our department to the patient’s latest clinic visit or telephone interview. Case 9, with a cervicothoracic tumor, died of respiratory dysfunction 6 days after the operation. Case 8, with a cervicothoracic tumor, died of severe pneumonia related to his neurological condition 5 months after the operation. Case 13, with a cervicothoracic tumor, died of lung metastasis from the initial site after the operation. Cases 6 and 20, with a cervicothoracic and medullocervical tumor, respectively, developed residual tumor progression after STR and died 23 and 24 months later, respectively. Five patients were lost to follow-up. Ten living patients were followed up from 51 to 129 months (mean 83.5 months). The 5- and 10-year overall survival

Fig. 5. Case 12. Sagittal (A–D) and axial (E–G) MR images of an exogenous PSAE extending from T-4 to T-7. Preoperative T1-weighted images (A and E) demonstrated the thoracic spinal cord tumor. A T2-weighted image (B) demonstrated a mixed signal lesion involving both the intradural-extramedullary (white asterisk) and intramedullary (black asterisk) compartments. There was a sharp border (arrows) between the spinal cord and the exophytic part of the tumor. A preoperative contrast-enhanced T1-weighted image (C) showed an enhancing lesion intrinsic to an expanded spinal cord with an anterior exophytic component, and an axial image (F) showed an enhancing lesion involving both the intramedullary (white arrow) and intradural-extramedullary (arrowheads) components. The latter displaced the spinal cord (black arrows) to the right and in an anterior direction. Postoperative contrast-enhanced T1-weighted images (D and G) obtained 78 months after surgery showed no recurrence.
rates of patients were both 67.9%, based on Kaplan-Meier estimates (Fig. 6).

**Discussion**

Spinal cord ependymomas are the most common intramedullary spinal neoplasms in adults, and many studies of them have been conducted. However, compared with classical ependymomas, little is known regarding PSAEs, which are clinical entities distinct from anaplastic ependymomas disseminated from intracranial space, anaplastic tumors that arise from infratentorial space and extend into the spinal canal, and recurrent or metastatic spinal anaplastic ependymomas. We report a series of 20 consecutive cases of PSAE that underwent surgical treatment at our department in the past 10 years. These PSAEs accounted for 7.3% of spinal ependymomas and 1.2% of spinal cord tumors in our series. Primary spinal anaplastic ependymomas developed most commonly in middle-aged men, and tended to have a male predominance, with a male to female ratio of 1.86:1. Symptoms and signs developed slightly more rapidly when compared with the data reported for classic spinal cord ependymomas. The mean preoperative course was 9.3 months in our series as opposed to a 32.3–35 month course in patients with Grade II ependymomas. These PSAEs developed most frequently in cervical and thoracic spinal cords, and were centrally located like classic ependymomas. Less commonly, they presented as exophytic tumors arising from the intramedullary portion or as intradural-extradural tumors arising from heterotopic ependymal cells of the spinal canal. Clinical presentation was nonspecific, and symptoms and signs varied according to the size and location of the tumor, and were related to nerve root irritation and mass effect. In our series, most of them generally demonstrated low T1 and high T2 signal intensity that was often heterogeneous, and contrast enhancement was homogeneous or heterogeneous. It appeared that the tumors shared similar MRI characteristics with classic spinal cord ependymomas and are difficult to differentiate from the classic type. However, a sharply defined and enhanced border on contrast MR images may be a feature of classic ependymomas.

It is widely accepted that the first-line therapy for spinal cord ependymoma is surgery. Modern microsurgical techniques have resulted in a greater percentage of GTRs. Although anaplastic ependymomas are more aggressive than classic ependymomas, Prayson et al. found that anaplastic ependymomas, like

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Resection</th>
<th>Complications</th>
<th>Radiation Therapy/Chemotherapy</th>
<th>Recurrence/Dissemination</th>
<th>Follow-Up (mos), Alive/Dead</th>
<th>Clinical Grade† (Preop/Discharge/Late Postop)</th>
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<tbody>
<tr>
<td>1</td>
<td>GTR tracheostomy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>III / IV / NA</td>
<td></td>
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<td>2</td>
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<td>yes/yes</td>
<td>no</td>
<td>129, alive</td>
<td>I / I / I</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>GTR no</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I / II / NA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>GTR no</td>
<td>unknown</td>
<td>no</td>
<td>128, alive</td>
<td>I / I / I</td>
<td></td>
</tr>
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<td>5</td>
<td>GTR no</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I / I / NA</td>
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<tr>
<td>6</td>
<td>STR no</td>
<td>no/no</td>
<td>local recurrence</td>
<td>23, dead</td>
<td>II / III / NA</td>
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<tr>
<td>7</td>
<td>STR no</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>III / III / NA</td>
<td></td>
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<td>8</td>
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<td>no</td>
<td>5, dead</td>
<td>III / III / NA</td>
<td></td>
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<tr>
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<td>GTR respiratory dysfunction</td>
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<td>no</td>
<td>6 days, dead</td>
<td>II / IV / NA</td>
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<td>GTR no</td>
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<td>NA</td>
<td>NA</td>
<td>I / II / NA</td>
<td></td>
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<td>yes/yes</td>
<td>no</td>
<td>94, alive</td>
<td>I / I / I</td>
<td></td>
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<td>12</td>
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<td>yes/yes</td>
<td>no</td>
<td>78, alive</td>
<td>I / I / I</td>
<td></td>
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<tr>
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<td>remote (lung)</td>
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<td></td>
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<tr>
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<td>no</td>
<td>78, alive</td>
<td>I / I / I</td>
<td></td>
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<tr>
<td>15</td>
<td>GTR urinary tract infections</td>
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<td>no</td>
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<td>no</td>
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<td>17</td>
<td>GTR no</td>
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<td>no/no</td>
<td>no</td>
<td>64, alive</td>
<td>II / III / III</td>
<td></td>
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<tr>
<td>19</td>
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<td>yes/no</td>
<td>no</td>
<td>51, alive</td>
<td>I / I / I</td>
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<td>20</td>
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<td>local recurrence</td>
<td>24, dead</td>
<td>I / III / NA</td>
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</table>

* NA = not available.
† Clinical grade based on the classification scheme of McCormick et al.: I = normal to mild focal deficit; II = moderate deficit, significant motor or sensory loss but able to function independently; III = moderate to severe deficit, requires assistance to ambulate; IV = severe deficit, unable to function independently or to ambulate.
Primary spinal anaplastic ependymomas

In this study, we report a series of 20 consecutive patients with PSAEs. Our data show PSAEs exhibit a more rapid growth pattern and are occasionally invasive. Therefore, adjuvant radiation therapy should be considered for these high-grade tumors. Some authors regarded radiation therapy for spinal anaplastic ependymomas as the gold standard in treatment, and recommended postoperative radiation therapy regardless of resection grade. Local field radiation is the common choice, whereas some authors suggested that craniospinal radiation could be considered. Several investigators reported that patients with PSAEs had a good survival rate (50%), or even 100% after GTR and radiation therapy. However, recurrence at its primary site or dissemination of the tumor with seeding along the subarachnoid spaces may occur despite GTR and postoperative irradiation. Of our 9 patients who received postoperative radiation therapy, 1 died due to a local recurrence after an STR, and 1 died of lung metastasis in the absence of a local recurrence following GTR. It is difficult to assess the role of adjuvant radiation therapy with respect to recurrence or dissemination due to the significant association of these variables with the extent of resection.

Chemotherapy could lead to a decrease in tumor size to facilitate surgery, and may have an impact on survival or quality of life. In our series, chemotherapy with single-agent temozolomide or a combination of teniposide and semustine was used in 5 patients who underwent GTR and radiation therapy and in 1 patient who underwent STR and radiation therapy. Only the patient who underwent STR died. However, there was no evidence that the addition of chemotherapy to radiation therapy in PSAEs improves outcome. There is a lack of literature on the role of chemotherapy in PSAEs, and only a few studies have been published on the role of chemotherapy in spinal ependymomas. Thus, the benefit of adjuvant chemotherapy in PSAE remains to be defined. In particular, we have yet to determine if a more aggressive chemotherapy treatment might be more advantageous in terms of patient survival rates in comparison with traditional schemes. However, chemotherapy is sometimes considered as a salvage option if a patient is unable to receive surgical treatment or radiation therapy.

Limitations of our study include the small sample size of our series as well as the retrospective nature of the analysis. Prospective studies will be necessary for future guidance of clinical decision making. This study has not analyzed the molecular markers and genotypes that may be linked to patient outcomes. In addition, because the histological assessment of anaplasia (defined as hypercellularity, cellular and nuclear pleomorphism, frequent mitosis, pseudopalisading necrosis, and microvascular proliferation) can be difficult and subjective, further molecular and cytogenetic analyses should be conducted to distinguish anaplastic from classic ependymomas. Nonetheless, we have presented useful insights into the management of patients with PSAEs in this study.

Conclusions

In this study, we report a series of 20 consecutive patients with PSAEs. Our data show PSAEs exhibit a more rapid growth pattern and are occasionally invasive.
In particular, patients with tumors involving the cervical spinal cord have a poor outcome. Our results suggest good survival rates in patients with PSAEs who have received GTR; nevertheless, the small sample size of our series limits firm statistical results. The role of adjuvant radiation therapy and chemotherapy for PSAEs should be further defined in the future.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Che. Acquisition of data: Liu, Sun. Analysis and interpretation of data: Che, Liu, Gu, Shou. Drafting the article: Liu, Sun. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Che. Study supervision: Xu.

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