Prognostic factors in pediatric brain-stem gliomas

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The clinical, computerized tomography (CT), and histological findings from 84 children with brain-stem gliomas were reviewed to determine whether any of these features correlated with outcome. Clinical data were available from all children, CT data from 62 children, and biopsy data from 54 children. Actuarial life tables were constructed for each clinical, CT, and histological feature and the differences between these were analyzed. The period of survival was significantly shorter in children who presented with cranial nerve palsies (p < 0.0001), and such children were more likely to have malignant tumors. Two CT features correlated with a significantly decreased survival time: a hypodense tumor prior to contrast administration and a tumor that involved the entire brain stem. Tumor enhancement was not associated with any alteration in survival times. Children with tumor biopsies that were histologically benign survived significantly longer than those whose tumors were malignant (p < 0.0001). The histological feature associated with the poorest survival time was the presence of mitoses; features associated with the best prognosis were Rosenthal fibers and calcification. The data indicate that brain-stem gliomas are not a homogeneous group of tumors as far as their clinical, CT, and pathological features are concerned. These features may be useful in assessing prognosis and in developing future treatment protocols.

KEY WORDS • astrocytoma • brain tumor • brain-stem tumor • glioblastoma • children

Children with brain-stem gliomas generally have a poor prognosis. Most die within 2 years after diagnosis; however, 20% to 35% of these patients are reported to survive several years and may be cured of their tumors.1,2 The present study was carried out to identify prognostic factors that might distinguish long-term from short-term survivors.

A few prognostic factors have already been identified for children with brain-stem gliomas. In 1980, Hoffman, et al.,6 reported that infants with exophytic brain-stem gliomas survived substantially longer than children with the usual endophytic tumors. In 1983, we reported that the survival period was significantly reduced in children whose clinical manifestations began with cranial nerve palsies and whose tumor biopsies contained mitoses; survival times were significantly longer in children with exophytic tumors and in those who received more than 4000 rads.1 Those prognostic factors were identified in a study of 53 children, 27 of whom underwent biopsy, from the Children's Hospital of Pittsburgh.

The present study was conducted in order to determine whether the factors studied previously would remain significant in a larger series of patients emanating from more than one institution. We therefore combined brain-stem glioma data from the Children's Hospitals of Pittsburgh and Philadelphia to reevaluate the conclusions of the first study and to determine whether any computerized tomography (CT) features correlate with outcome.

Clinical Material and Methods

Patient Population

The records of all children with biopsy-proven brain-stem gliomas treated at the Children's Hospital of Pittsburgh between 1960 and 1985, and of all children with brain-stem gliomas treated at the Children's Hospital of Philadelphia between 1975 and 1985, were examined. For this study, we defined the brain stem as the mesencephalon, pons, and medulla. We excluded patients with tumors of the thalamus and hypothalamus,
and with lesions originating from the cerebellar peduncles or upper cervical spinal cord. Patients with neither CT nor pathological verification were also excluded.

The database was assembled retrospectively from the records of 37 children from the Children’s Hospital of Pittsburgh, all of whom underwent biopsy, and those of 47 children from the Children’s Hospital of Philadelphia, 17 of whom had biopsies. We analyzed the following clinical information: age at diagnosis, duration of symptoms before diagnosis, and the presence or absence of cranial nerve palsies at the time of diagnosis. The latter feature was the only symptom entered into the database since the previous study, which had shown that, of a considerable number of signs and symptoms examined, no other feature even approached a significant level of association with length of survival.

Computerized Tomography Studies

Computerized tomography scans were available in 62 children. The following CT variables were reviewed: extent of the tumor (whether it was confined to the midbrain or to the pontomedullary region or extended throughout the brain stem at the time of the first CT examination); the presence or absence of an exophytic component; the relative density (whether hypodense, isodense, or hyperdense) of the lesion in the unenhanced scan; and whether the tumor enhanced, and if so whether the enhancement was diffuse or ring-shaped.

Pathological Examination

Pathology records, tissue blocks, and slices of the biopsy specimens were examined by neuropathologists (R.A.P. and L.B.R.) who had no knowledge of the patients’ clinical status. The data were examined for 11 histological characteristics: pleomorphism, hyperchromatism, mitoses, necrosis, endothelial proliferation, calcification, Rosenthal fibers, perivascular rosettes, leptomeningeal spread, microcysts, and tumor-cell density (low, medium, or high). Last, an overall judgment as to whether the tumor should be considered low grade (benign) or high grade (malignant) was recorded.

Statistical Analysis

The survival time of those children with and without each clinical, CT, and histological feature was calculated using Kaplan-Meier methods and the BMDP1L computer software program. Curves were compared using both the generalized Wilcoxon (Breslow) and the log-rank (Mantel-Cox) tests. To test for the effect of several covariants simultaneously, Cox’s proportional hazards model was fitted using the BMDP2L program.

Results

Clinical Features

There was no significant difference between the patterns of survival of the Pittsburgh and Philadelphia cases (p = 0.30, Breslow; p = 0.69, Mantel-Cox), nor did the children’s age at the time of appearance of the first symptom (mean 7.34 ± 3.64 years (standard deviation)) significantly affect the length of survival (χ² = 0.33; p = 0.57). Addition of the Philadelphia cases to the Pittsburgh series reaffirmed our previous impression of the prognostic importance of the early appearance of cranial nerve palsies (Fig. 1). For the 55 patients who presented with this feature, the actuarial predicted—survival rates were: to 1 year 43.22%, to 2 years 20.3%, and to 6 years 9.5%. For the 29 patients with other presenting symptoms the chances for a similar length of survival were 83.7%, 71.3%, and 60.7%, respectively. The differences are significant (p = 0.0001, Breslow; p < 0.0001, Mantel-Cox).

Computerized Tomography Findings

Two CT variables were significantly associated with length of survival: the extent of the tumor and the presence of a hypodense area in the brain stem prior to contrast enhancement. For 43 children in whom the tumor was localized to either the midbrain or the pontomedullary region, the survival hazard to 2.1 years was 40.4%, whereas for 19 children in whom the whole brain stem was involved it was 14.0% (p = 0.048, Breslow; p = 0.014, Mantel-Cox). For 44 children whose pre-enhancement CT scans showed a hypodense tumor, the likelihood of survival to 2.1 years was 18.3%, otherwise it was 60.1% (p = 0.008, Breslow; p = 0.002, Mantel-Cox) (Fig. 2). Neither diffuse nor ring-like enhancement of the tumor following the injection of contrast material was associated with any significant alteration in length of survival.

Ten patients showed CT or other neuroradiological evidence of ventriculomegaly, which was treated in eight cases by the insertion of a ventriculoperitoneal shunt. The survival pattern of these patients did not differ from that of the remainder.
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**Pathology**

Diagnosis of the biopsy specimen correlated significantly with survival times. When the pathologist reported the tumor to be a high-grade (malignant) lesion, the child’s chance of surviving 2.1 years was only 14.1%, but when biopsies showed a low-grade (benign) tumor, the chance was 65.8%. The difference in survival times was highly significant (p < 0.0001, Breslow and Mantel-Cox) (Fig. 3). The proportions of tumors judged to be malignant in the two series were almost identical (Pittsburgh: 15 of 36 (41.7%); Philadelphia: seven of 18 (38.9%)). The only statistically significant difference in the frequencies with which the various histological variables were recorded at each center was that microcysts were more commonly reported from Philadelphia (five of 18 cases or 27.8%) than from Pittsburgh (one of 36 cases or 2.8%) (χ² = 4.062, p ~ 0.04 with Yates’ correction). We do not regard this difference as important.

Table 1 shows the histological variables which, when entered singly as covariants, attained or approached a statistically significant level in predicting length of survival. Entering all the histological variables into the regression equation in a stepwise manner, we found that the presence of mitoses was the most significant variable (p < 0.0001) from the point of view of survival time (Fig. 4). All 18 patients in whom mitoses were observed have died, 15 of them within 6 months of the onset of their symptoms; the longest survival time was 2.4 years. On the other hand, of 36 patients whose biopsies exhibited no mitoses, 50% lived 4 years or more, and their survival pattern was further significantly (p = 0.003) improved if calcification and/or Rosenthal fibers were present. No other variables contributed significantly to the estimation of the survival hazard.

**Assessment Using All Variables Studied**

Of the 23 biopsied patients without early cranial nerve palsies, 19 had benign tumors and four had malignant tumors. Of the 31 biopsied patients who did have early cranial nerve palsies, 13 had benign tumors and 18 had malignant tumors. Thus, children with early cranial nerve palsies are significantly more likely to have malignant tumors than are those who do not (χ² = 9.047; p ~ 0.002).

Of the 34 patients for whom biopsy data and CT scans were available, 25 had hypodense tumors; in 14 the lesions were considered to be benign and in 11 they were malignant. Of the nine non-hypodense tumors, eight were benign and one was malignant. This difference is not statistically significant (p = 0.1135 by Fisher’s exact two-tailed test). Unfortunately, CT scans were not available for any of the four patients who did not have early cranial nerve palsies but did have malignant tumors; scans were available for 12 patients without early palsies, and all had benign tumors. An area of low density was observed in six of them but not in the other six. The numbers are too small for formal

![Fig. 2](image1.png) **Actuarial life table for children whose pre-enhancement computerized tomography scan revealed a hypodense brain-stem glioma versus an iso- or hyperdense glioma. The curves are significantly different (p = 0.003).**

![Fig. 3](image2.png) **Actuarial life table for children whose biopsies revealed low-grade (benign) and high-grade (malignant) brain-stem gliomas. The curves are significantly different (p < 0.0001).**

**Table 1**

<table>
<thead>
<tr>
<th>Influence on Survival Time</th>
<th>Histological Feature</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>favorable</td>
<td>Rosenthal fibers</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>calcification</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>microcysts</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>unfavorable</td>
<td>mitosis</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>hyperchromatism</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>necrosis</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>pleomorphism</td>
<td>0.065</td>
<td></td>
</tr>
</tbody>
</table>

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From our data, it was not possible to judge the effectiveness of radiation therapy, since all but four children received this; of those who did not, two were judged too ill to benefit from it, while in the other two children therapy was withheld because of the absence of any sign of tumor progression. In this series there was no significant correlation \((p = 0.25)\) between the level of radiation dosage, which lay between 4500 and 6000 rads in all cases, and length of survival.

**Discussion**

These results indicate that the prognosis of children with brain-stem gliomas is significantly worse in those whose first symptoms include loss of function in one or more cranial nerves, in those whose pre-enhancement CT scans show a hypodense or diffuse tumor, and in those whose tumor biopsy material contains mitoses or is regarded as histologically malignant. Conversely, the prognosis is much better for patients in whom the above features are absent, particularly if the biopsy specimen contains calcification or Rosenthal fibers. We do not know why the prognosis is poor for children with early cranial nerve palsies. The presence of an early, highly focal neurological deficit may reflect the invasive and destructive nature of a rapidly growing neoplasm.

In regard to CT appearances, our findings were unexpected. We had thought that the prognosis of enhancing tumors might be worse, but in fact it was not. The association of CT hypodensity with poor survival times probably indicates infiltration of brain-stem structures by neoplasm; biopsies of such tumors have not shown edema. The correlation between extent of tumor and outcome was also observed by Epstein and McCleary\(^8\) in recurrent brain-stem gliomas and underlines the importance of including the entire tumor volume within the radiotherapy fields. The boundaries of those fields should ideally be based on magnetic resonance imaging (MRI), since the extent of pediatric brain-stem gliomas on MRI exceeds that visible on CT scans in 50% of cases.\(^9\)

Brain-stem gliomas can now be safely biopsied stereotactically. Coffey and Lunsford\(^8\) obtained diagnostic tissue from 12 patients with pontine and mesencephalic masses, with no morbidity or mortality, using a CT-guided stereotactic technique that can be used in children. However, because MRI appears to delineate the tumor extent better than CT, and reveal areas of inhomogeneity not seen on CT, MRI-guided stereotactic biopsies may be even more representative of the tumor histology since CT scans often show relatively little heterogeneity.

Addition of the Philadelphia data to the Pittsburgh data further substantiates the correlation of cranial nerve palsies and mitoses with outcome, and clarifies the value of biopsy. In the initial study,\(^1\) the difference in survival times between low-grade and high-grade tumors approached statistical significance; in this study, that difference became highly significant. Although Littman, et al.,\(^8\) indicated the prognostic value of brain-stem biopsies in 32 patients and found that none of their 18 biopsied patients with malignant tumors lived...
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more than 16 months, whereas half of their 14 children with well-differentiated astrocytomas had an actuarial survival time of 5 years, the role of biopsy in children with brain-stem gliomas remains controversial.

One may ask whether biopsy provides additional prognostic information relating to children with both cranial nerve palsies and a hypodense nonenhancing tumor, two features associated with a poor prognosis. Only 19 of the 62 children with CT scans had both cranial nerve palsies and hypodense nonenhancing tumors. Eight tumors were histologically benign and 11 were malignant. These numbers are too small for such a comparison, although the p value (0.101) for the difference in their survival times suggests that additional prognostic information may be gained by biopsy.

Epstein has written that “there is no useful information to be obtained from biopsy” and that “the overwhelming majority of brain stem neoplasms are malignant.” Results of this study and others do not support that opinion. We are well aware of the heterogeneous appearance of brain-stem neoplasms on MRI, heterogeneity that might result in sampling error. It might be assumed that multiple biopsies would be required to diagnose the lesion. Our results do not contradict that assumption but show that information obtained from single-site biopsy is of value for estimating prognosis and for planning treatment; stereotaxic biopsies should provide even greater information.

Children with CT-enhancing low-grade astrocytomas that contain calcification or Rosenthal fibers are effectively treated by conventional radiotherapy. However, for children whose biopsies reveal anaplastic gliomas, conventional radiotherapy is inadequate, with survival rates of less than 20%. For those children, more aggressive therapy such as hyperfractionation radiotherapy or multidrug chemotherapy (although potentially neurotoxic) is justified.

The value of extensive removal of brain-stem gliomas is becoming clearer. We agree with Epstein and McCleary that extensive removal is not indicated in diffuse brain-stem tumors. However, the 10% to 15% of brain-stem tumors that are focal and enhancing can often be subtotally removed, with low morbidity and no mortality, using adjuncts such as the laser, the Cavitron ultrasonic surgical aspirator, and evoked potential monitoring. This approach may perhaps improve survival. Children with focal low-grade tumors are probably benefited by extensive tumor removal; children with anaplastic gliomas may be helped by this treatment, but those with glioblastomas are almost certainly not improved.

We conclude from this study that brain-stem gliomas comprise a unique group of central nervous system tumors that is by no means homogeneous in clinical, CT, or histopathological characteristics. Furthermore, it is precisely this heterogeneity that offers the opportunity to identify high- and low-risk groups and to develop different treatment strategies.

References


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