Prognostic Factors and Therapeutic Options of Radiotherapy in Pediatric Brain Stem Gliomas

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Background: A retrospective analysis was made to clarify the relationship between prognosis, radiation dose and survival of brain stem gliomas.

Methods: From 1983 to 1995, 22 children with brain stem tumors were treated by radiotherapy in the Veterans General Hospital–Taipei. Twelve patients had pathology proof and the remainder were diagnosed by computerized tomography and/or magnetic resonance imaging. Seven patients had postoperative radiotherapy. Fifteen patients had radiotherapy as primary management, five of whom had adjuvant chemotherapy. All patients received 4000–7060 cGy, either in conventional daily or hyperfractionated twice daily radiotherapy. Survival from date of diagnosis was calculated by the Kaplan–Meier method. Univariate analyses and multivariate analyses were calculated by the log rank test and the Cox proportional hazard model, respectively.

Results: Most patients showed improvement following treatment. The overall 2-year survival rate was 55.5% with a median survival of 27.1 months. Two-year survival for patients with primary management of operation and radiotherapy (n = 7), radiotherapy alone (n = 10) and radiotherapy with adjuvant chemotherapy (n = 5) were 66.7, 50 and 53.3%, respectively. In univariate analysis, the study revealed that the growth pattern of tumors and the simultaneous presence of cranial neuropathy and long tract sign were significant prognostic factors (P = 0.017 and 0.036). A trend of better outcome with radiation dose >6600 cGy and the hyperfractionation scheme was also noted in our study (P = 0.0573 and 0.0615). However, only the hyperfractionation scheme showed significance in multivariate analyses (P = 0.0355). Survival was not significantly affected by age, gender or method of diagnosis.

Conclusion: Radiotherapy appears to be an effective treatment modality of brain stem tumors. Patients with both cranial neuropathy and long tract signs had a poorer outcome. Hyperfractionated radiotherapy may give better local control and lead to better survival.

Key words: brain stem – gliomas – radiotherapy – survival – hyperfractionation

INTRODUCTION

Brain tumors are the most common solid tumors and the second most common malignancy in children after leukemia. Brain stem tumors account for 10–20% of all brain tumors in children (1–4). Radiotherapy is the primary modality of management for brain stem tumors. Complete surgical removal of the tumors is usually not possible because of their critical locations except in the more exophytic type. Although the histology types of brain tumors are important prognostic factors, brain stem tumors are often treated without histological confirmation. Local failure is the major obstacle to cure. Since subarachnoid seeding is seldom reported, whole brain or neuroaxis irradiation is not necessary.

About 35–41% of 3- and 5-year survival rate had been reported for patients with brain stem tumors with or without pathological proof (5). Several factors had been reported as being of prognostic importance, such as presenting symptoms and signs, histopathology grade (6), location of tumors in the brain stem, radiographic appearance in computerized tomography (CT) and/or magnetic resonance imaging (MRI) and growth pattern of the tumors. This study retrospectively evaluated the outcome of pediatric patients.
with brain stem gliomas treated at the Veterans General Hospital-Taipei (VGH-TP).

MATERIALS AND METHODS

PATIENT POPULATION

From 1983 to 1995, 44 children with brain stem glioma registered at the VGH-TP were reviewed. Six patients received surgical treatment alone, three of whom received salvage radiotherapy for local recurrence of tumors. Seven patients had chemotherapy alone as their primary treatment. Another six patients had either palliative ventriculoperitoneal shunting (V-P shunting) or supportive care only. The remaining 25 patients received radiotherapy as part of their primary treatments. Three of these 25 patients had incomplete radiotherapy with dose <4000 cGy and were excluded from the study. Only the 22 patients receiving complete radiotherapy were included in this retrospective analysis. There were 12 boys and 10 girls. The median age at presentation was 9 years with a range of 3–13 years. Karnofsky performance status (KPS) data were collected from the medical records of all 22 patients. The median value of KPS was 70 with a range of 40–90. Ten patients were still alive at the time of this analysis. The follow-up of patients still alive at the time of this analysis ranged from 1.5 to 146 months with a median of 9.5 months.

METHODS OF DIAGNOSIS

Twelve patients had pathology proof of gliomas, five by stereotactic biopsy and seven by craniotomy. Six of these 12 patients had low-grade astrocytoma (6,7) (WHO grade 1 and 2, well differentiated, WDA). Of the remaining six patients with high-grade astrocytoma, there were four anaplastic astrocytoma (WHO grade 3, moderate pleomorphism and hypercellularity, AA) and two glioblastoma multiforme (WHO grade 4, with zone of necrosis, GBM). Ten patients without tissue proof were diagnosed on the basis of CT and/or MRI images.

Table 1. Symptoms and signs at presentation

<table>
<thead>
<tr>
<th>Symptoms/signs</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve signs</td>
<td>15 (68)</td>
</tr>
<tr>
<td>Gait disorder</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Limb weakness/paralysis</td>
<td>13 (59)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Incoordination</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Mental state change</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

PRESENTING SYMPTOMS AND SIGNS

Cranial nerve deficits, most commonly involving nerves III–VII, occurred in 68% of the patients. Abnormal cerebellar testing occurred in 41% of patients. Other less common signs included papilledema, head tilting and long tract signs. The presenting symptoms and signs of the patients in this study are shown in Table 1. One child had no full documentation of presentation problems.

The duration of symptoms prior to diagnosis was highly variable. More than 36% of the patients had duration of symptoms less than 1 month before diagnosis. The median duration of symptoms/signs prior to diagnosis was 2 months.

LOCATION AND PATTERNS OF TUMOR INVOLVEMENT

Based on the finding of CT scan or MRI, there were 12 patients with pons/medulla lesions, three with thalamus/midbrain lesions and seven with multiple site involvement. The pontine region of the brain stem was the most commonly affected site, representing 54% of all patients.

A brain stem lesion was considered diffuse if it intrinsically involved more than one geographic area of the brain stem. Focal lesions were single, contrast enhancing and localized to one area such as pons or had a focal brain stem component and an exophytic component into the fourth ventricle or cistern surrounding the brain stem. Of the 22 patients analyzed in this study, 12 had focal diseases and 10 had multiple or diffuse lesions.

MANAGEMENT

Of the 22 patients in the study, 15 received definitive radiotherapy without prior surgery. Five of these 15 patients received additional chemotherapy. Another seven patients received postoperative radiotherapy after surgical removal of the tumors.

All radiotherapy was delivered via 10 MV linear accelerators. The radiotherapy fields encompassed the tumor volume plus a 2–3 cm margin. Thirteen patients received twice daily hyperfractionated radiotherapy (HFRT) with a dose range from 5200 to 7100 cGy (median 6600 cGy) given in 110–120 cGy per fraction. Eight patients received HFRT as definitive management and five patients as postoperative management. Nine patients received conventional daily radiotherapy with a dose range of 4400–6200 cGy (median 6000 cGy) in fraction sizes of 200 cGy. Seven patients received conventional daily radiotherapy as definitive management and two patients as postoperative management.

Five of the 15 patients receiving definitive radiotherapy also received chemotherapy, two adjuvant and three neoadjuvant. The chemotherapy regimen was vinblastine on day 1, VP-16 on days 1–4 and cisplatin on day 2. Most of the patients had more than three courses of chemotherapy with an interval of 3 weeks between each course.

STATISTICAL METHODS

Because of the retrospective nature of the study, there were no predetermined standardized response criteria. Survival was the
end-point for statistical evaluation. Survival was calculated using the Kaplan–Meier product limited method (8). All deaths were counted regardless of cause. Survival was measured from the date of diagnosis to the date of last follow-up. Differences and trends in survival between groups were tested using the log rank test. The stratified Cox proportional hazard model was used in multivariate analyses.

RESULTS

The 2-year survival rate of all patients in this study was 55.5% with a 95% confidence interval (CI) ranging from 26.5 to 77.1%. The median survival time (MST) was 27.1 months. Owing to the small number of patients in this study, the lower end of the 95% CI was only 9.5 months while the upper end of the 95% CI was not reached.

Table 2. Analysis of variables influencing survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median survival (months)</th>
<th>2-year survival rate (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 12)</td>
<td>14.2</td>
<td>45.8</td>
<td>NS</td>
</tr>
<tr>
<td>Female (n = 10)</td>
<td>27.1</td>
<td>66.6</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤9 (n = 13)</td>
<td>27.1</td>
<td>73.3</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;9 (n = 9)</td>
<td>16.2</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single (n = 10)</td>
<td>–*</td>
<td>75</td>
<td>0.036</td>
</tr>
<tr>
<td>Both (n = 11)</td>
<td>–*</td>
<td>51.4†</td>
<td></td>
</tr>
<tr>
<td>Karnofsky scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS ≥70 (n = 12)</td>
<td>16.2</td>
<td>36.3</td>
<td>NS</td>
</tr>
<tr>
<td>KPS &lt;70 (n = 10)</td>
<td>–*</td>
<td>76.1</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus/midbrain (n = 3)</td>
<td>–*</td>
<td>66.7</td>
<td>NS</td>
</tr>
<tr>
<td>Pons/medulla (n = 12)</td>
<td>16.2</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal (n = 12)</td>
<td>14.2</td>
<td>33</td>
<td>0.017</td>
</tr>
<tr>
<td>Diffuse (n = 10)</td>
<td>–*</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 months (n = 10)</td>
<td>9.5</td>
<td>33.3</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;2 months (n = 12)</td>
<td>43</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>Low grade (n = 6)</td>
<td>–*</td>
<td>60</td>
<td>NS‡</td>
</tr>
<tr>
<td>High grade (n = 6)</td>
<td>–*</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>No pathology (n = 10)</td>
<td>27.1</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 5)</td>
<td>146</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>No (n = 17)</td>
<td>27.1</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

NS, no statistical significance. *Median survival not reached. †1-Year survival rate only, follow-up too short to achieve 2-year survival. ‡For pathologically proved low- and high-grade tumors only.

PRETREATMENT CHARACTERISTICS AND SURVIVAL

Factors affecting survival are summarized in Table 2. Eleven patients with both cranial neuropathy and long tract sign had a 1-year survival rate of 51.4%. The remaining 10 patients with either symptoms/signs of cranial neuropathy or long tract sign were all alive 12 months after diagnosis.

One of the three patients with thalamus/midbrain lesions died 14.2 months after diagnosis. Another two patients were alive with survival of 41.5 and 77.1 months. The median survival and 2-year survival rate of patients with pons/medulla lesions were 16.2 months and 33.7%, respectively. Seven patients with multiple focus were all alive at the last follow-up time (5.5–115 months).

TREATMENT MODALITY

Of the 10 patients treated with definitive radiotherapy without chemotherapy, four had improvement of the symptoms and signs
after radiotherapy, five had disease progression after 6 months (4-7 months) and one had tumor seeding over the cervical spine 4 months later. The estimated actuarial median survival was 16.2 months (1.5-115 months) and the 2-year survival rate was 50%.

Five patients received definitive radiotherapy and chemotherapy, two adjuvant and three neoadjuvant. Two patients receiving adjuvant chemotherapy died at 5.1 and 146 months after diagnosis, respectively. Two of the three patients receiving neoadjuvant chemotherapy died at 14.2 and 27.1 months, respectively. The remaining one patient with neoadjuvant chemotherapy was alive 10.3 months after diagnosis. The estimated actuarial median survival was 27.1 months (5.1-146 months) and the 2-year survival rate was 53.3%.

Seven patients had postoperative radiotherapy with 4400–7000 cGy after surgical removal of tumor, two by conventional fractionation and five by twice daily HFRT. One patient had disease progression with loss of consciousness and tumor seeding over craniospinal fluid. He died 6.8 months after diagnosis. The remaining patients all had improvement of symptoms and signs after radiotherapy. Of patients who completed postoperative radiotherapy, two died at 6.9 and 8.7 months and three lost to follow-up at 5.5, 10 and 10.2 months. The actuarial two-year survival was 66.7%.

**Survival**

There was no significant statistical difference in survival between the patients who received radiotherapy alone and those who received postoperative adjuvant radiotherapy, although the latter group showed a better 2-year survival (50 vs 66.7%). In patients receiving definitive radiotherapy, there was no significant difference in survival between those receiving radiotherapy alone and those receiving radiotherapy and chemotherapy.

**Univariate Analyses of Factors Associated With Survival**

The following categorical parameters were analyzed by the log rank test for associations with survival: gender, age, patterns of tumor growth, presentation of cranial neuropathy and long tract sign, duration of pretreatment symptoms and signs, KPS, fractionation scheme and irradiation dosage. Patterns of tumor growth and simultaneous presentation of both cranial neuropathy and long tract sign were found to be significant factors ($P < 0.05$). A trend of better results with high radiation dose ($P = 0.0573$, Fig. 1) and hyperfractionation scheme ($P = 0.0615$, Fig. 2) were shown in our study.

**Multivariate Analyses of Factors Associated With Survival**

Stepwise Cox analysis, stratified by histology, location of tumors and treatment modalities, was used to perform multivariate analyses. Fractionations and irradiation dosage were analyzed separately. The parameter of irradiation dosage was dropped in the analysis because of high collinearity with fractionation. Fractionation scheme was the only parameter found to be significant ($P = 0.0355$).
DISCUSSION

EFFECT OF PRETREATMENT CHARACTERISTICS ON PROGNOSIS

Chang et al. (9) and Byar et al. (10) reported a better prognosis for patients with younger age in malignant glioma. In our study, younger children (<9 years) showed better median survival (27.1 months) and 2-year survival rate (48.9%). The results were not statistically significant.

Kretschmar et al. (3) and Shrieve et al. (11) reported a better prognosis in children with tumor location of thalamus or midbrain. Our study showed a similar result. However, no significant survival difference was noted.

Approximately 80-90% of patients with brain stem gliomas have diffuse infiltrating lesions (12). Survival was significantly longer for children with tumors appearing as focal brain stem lesions on MRI compared with those with diffuse tumors (1,11,13). Packer et al. (14), however, reported no statistically significant difference. In our study, there was a different result with a better outcome for patients with diffuse lesions (P = 0.017, log rank) (Fig. 3). However, the prognostic value of growth pattern, diffuse vs focal, was not confirmed by multivariate analysis. In this study, eight of the 10 patients with diffuse brain stem lesion received hyperfractionated radiotherapy whereas only five of the 12 patients with focal brain stem lesion received hyperfractionated radiotherapy (P = 0.063, chi-squared). Because the multivariate analyses found that the hyperfractionation scheme was the most important prognostic factor, this may account for the superior survival in patients with diffuse lesions. No obvious difference in pathology and pretreatment duration was noted between patients with different growth patterns.

Many studies have reported that tumor histology is of prognostic significance for pediatric brain stem gliomas (15). Shrieve et al. (11) showed that patients with moderately anaplastic astrocytoma had a significantly better outcome than patients with glioblastoma multiforme, whereas Berger et al. (16,17), Epstein and McCleary (18), Edwards and Prados (19) and Tetsuo et al. (15) doubted its prognostic reliability. Twelve patients who had tissue proof by either stereotactic biopsy or surgical operation were included in this study. Patients with low-grade gliomas had a better median survival and a better 2-year survival rate than patients with high-grade gliomas (AA and GBM). However, the results were not statistically significant. Ten patients without pathology proof had a poorer outcome than patients with low-grade tumors. In our study, most of the patients with high-grade tumors received HPRT with a higher radiation dose than patients with low-grade tumors.

In this study, children with symptoms for ≤2 months prior to treatment had a poorer outcome (median survival 9.5 months and 2-year survival 33.3%) compared with those who had had symptoms for >2 months (median survival 43 months and 2-year survival 59%). Similar results were reported by Shrieve et al. (11), Packer et al. (14), Prados et al. (20) and Edwards et al. (1). A duration of 4 months was reported by Leibel et al. (13), 6 months by Kretschmar et al. (3) and 9 months by Guiney et al. (5).

The presence of long tract sign and cranial nerve deficits at diagnosis was consistent with pontine involvement; both signs have been reported as unfavorable factors (11,21). Most patients in our study had either complaint or both. A significantly better outcome was noted in patients with single complaint only compared with patients with both complaints of cranial neuropathy and long tract sign (P = 0.036) (Fig. 4).

Higher KPS is associated with a better outcome for malignant cerebral gliomas treated with radiotherapy (22). However, its prognostic value has not been confirmed in brain stem gliomas. Tetsuo et al. (15) reported no difference in survival of patients with different KPS at the time of diagnosis. No significant survival difference was noted in our study with a cut-off KPS at 70.

Although pathological proof by biopsy is not popular because of excessive neurological morbidity of hemorrhage and swelling, the use of biopsy for diagnosis had been reported as one of the prognostic factors at a dose level of 7020 cGy (P = 0.04) (16). Better median survival for patients with biopsy was reported by Edwards et al. (1). Different results were also reported by Guiney et al. (5). In our study, use of biopsy is not a prognostic factor.

MANAGEMENT

The role of surgery in the treatment of brain stem glioma has changed in recent years. Before the era of MRI, most patients were diagnosed clinically together with a CT scan and seldom had biopsy. Now, following MRI, surgery is considered to be the treatment of choice for focal lesions such as dorsally exophytic tumors and tumors arising at the cervicomedullary junction (2,12,16,23,24). Surgery may also be used to determine pathological grade and drain cyst and/or relieve hydrocephalic obstruction. The addition of postoperative radiotherapy also confers a significant survival improvement over surgery alone in malignant brain glioma (13). Although not statistically significant, our study showed a better 2-year survival for patients who had received surgical removal of tumor and postoperative radiotherapy compared with patients who had received radiotherapy alone (66.7 vs 50%).

Even though patients with brain stem gliomas showed little or no response to chemotherapy (1,3,12,15,22), chemotherapy appears to be an effective postoperative treatment for many malignant brain tumors in young children. Disease control for 1–2 years in a large majority of patients permitted a delay in the delivery of radiation and resulted in a reduction in radiation-induced neurotoxicity (6,13,25,26,27). Pre-irradiation chemotherapy can also be successfully added to the treatment of patients with brain stem tumors, but the apparent development of drug resistance should be considered (3). In our study, five patients receiving radiotherapy and chemotherapy had a better result of a 53.3% 2-year survival rate and 27.1 months median survival. The results were not statistically significant.

Historically, the treatment of choice for brain stem tumors has been radiotherapy (5,11,28). The tolerance of normal glial and vascular tissues limits the amount of radiation that can be safely delivered to brain tumors (13). A total dose of 5500–6000 cGy to the normal brain in conventional fractions is generally considered a safe dose (11,15). Further dose escalation using standard fractionated irradiation was associated with a higher risk of radiation myelitis. It has been attempted to improve the duration of response by using higher doses of radiotherapy delivered with hyperfractionated regimens. This is based on the theory that radiotherapy given...
in smaller individual fractions will be less toxic than the same total
dose of radiotherapy given in larger fractions. In addition, tumor
tissue, dividing at a more rapid rate than the surrounding brain, will
be more sensitive to multiple fractions of radiation therapy
(1,2,11,12,21,28). Since 1984, large numbers of children with brain
stem tumors have been entered in a series of studies by the Pediatric
Oncology Group (POG), the Children’s Cancer Group (CCG), the
Children’s Hospital of Philadelphia (CHOP) and the Brain Tumor
Research Center at the University of California at San Francisco
(UCSF). Each of these groups undertook dose escalations with the
result that there is now a large, well documented, experience of
HFRT with doses ranging from 6480 to 7800 cGy. At dose levels of
6480 cGy (100 cGy, twice daily, CHOP) and 6600 cGy (110 cGy,
twice daily, POG), no toxicity was noted. At dose levels of 7020 cGy
(110 cGy, twice daily, POG) and 7200 cGy (100 cGy, twice daily, UCSF and CCG), there was a suggestion of increased efficacy when
compared with the lower dose of HFRT and with conventional
radiotherapy at a dose of 5400 cGy (2). No further gains were seen at
the high dose levels of 7560 cGy (126 cGy, twice daily, POG) and
7800 cGy (100 cGy, twice daily, CCG). Moreover, at the 7560 cGy
dose level in the POG study, there appeared to be increased acute and
subacute toxicity that consisted primarily of steroid dependence and
intralesional necrosis (2,11,13,14,20,21,23). In our study, 22
patients completed radiotherapy. Eight patients receiving higher dose
levels of 6600 cGy showed better results than patients receiving
lower doses. However, their follow-up was relatively short and this
may explain why statistical significance had not been reached. In our
study, patients who received radiation doses higher than 6600 cGy
were all alive at the time of analysis. Patients receiving twice daily
HFRT had a better 2-year survival than those on conventional daily
radiotherapy (68.2 vs 25%, P = 0.0615, log rank; Fig. 2). Generally,
patients with HFRT had higher dose levels. No patient received a
dose level higher than 7200 cGy.

CONCLUSION

Radiotherapy is an effective treatment for brain stem gliomas in
pediatric patients. Compared with the seven excluded patients
receiving supportive care only, patients with curative intent
radiotherapy showed a better outcome, median survival (27.1 vs
3.1 months) and 2-year survival rate (55.5 vs 0%) (P < 0.0001,
Fig. 1). Simultaneous presentation of pretreatment cranial neuropathy and long tract signs was found to be one of the significant prognostic factors in our study. Patients with a duration of symptoms of <2 months had a poorer outcome. Hyperfractionated irradiation with a higher tumor dose may yield higher tumor local control with acceptable side effects. Although multivariate analysis showed that HFRT was the only significant prognostic factor, further studies should be performed because of the small number of cases and the short follow-up time here.

References


