Diffuse brainstem glioma: prognostic factors

Clinical article

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Object. Brainstem gliomas were regarded as a single entity prior to the advent of MRI; however, several studies investigating MRI have recognized that these lesions are a heterogeneous group, and certain subgroups have a better prognosis for long-term survival. The aim of this study was to conduct a retrospective analysis of prognostic factors of patients with brainstem gliomas confirmed by histopathological diagnosis, particularly regarding assessment of whether histological grade, age, and MRI findings are prognostic factors for patient survival.

Methods. The study evaluated 100 patients diagnosed with brainstem glioma. There were 63 adults (40 men and 23 women; age range 18–75 years, mean 41 years) and 37 children (19 boys and 18 girls; age range 2–12 years, mean 6.9 years).

Results. The mean overall survival of this population, measured from the date of biopsy, was 57 months for diffuse low-grade glioma and 13.8 months for diffuse high-grade glioma (p < 0.001). The mean survival among patients with nonenhancing contrast lesions on MRI was 54.2 months, whereas for patients with enhancing lesions, it was 21.7 months (p < 0.001). Comparisons between the Kaplan-Meier survival curves of adults and children revealed similar median survival periods of 25 and 16 months, respectively (p > 0.05). The multivariate analysis (Cox proportional hazards regression) revealed that only histological grade was a significant prognostic factor (p < 0.001).

Conclusions. The study revealed that histological grade and MRI features were significant prognostic factors for survival in these patients, but in multivariate analysis, only histological grade remained a significant factor.

Key Words • brainstem tumor • diffuse glioma • prognostic factor • diagnostic and operative techniques

Prior to the advent of MRI, brainstem gliomas were regarded as a single entity; however, several studies investigating MRI have recognized that these lesions are a heterogeneous group, with certain subgroups having better prognoses for long-term survival. Essentially, brainstem gliomas are now divided into 2 categories; 20% are considered to be low grade, arising in the midbrain, medulla, or dorsal pons, and are often focal, dorsally exophytic, and amenable to resection with a relatively good prognosis. The remaining 80% of tumors arise and occupy the majority of the pons and are diffuse in nature with poor prognosis. This latter group, termed diffuse intrinsic brainstem glioma, remains one of the most challenging tumor types, with multiple clinical trials failing to improve survival.

The aim of this study was a retrospective analysis to determine whether histological grade, age, and MRI findings are prognostic factors for survival of patients with brainstem gliomas confirmed by histopathological diagnosis.

Methods

The study involved a retrospective evaluation of medical records of 142 patients with brainstem lesions who underwent stereotactic biopsy between February 1984 and August 2007 at the Roger Salengro Hospital (Lille, France). Institutional review board approval was obtained for this study.

The procedures were performed under general anesthesia; 109 patients underwent stereotactic biopsy procedures using a Talairach halo, and 33 underwent the procedures using the robotic system (neuramate systems, Renishaw plc). Target location was determined using MRI in all cases. The target was the center of the lesion and/or area of contrast enhancement. The transfrontal approach...
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was used in 123 patients, and the suboccipital transcer-
beellar approach was used in the remaining 19. All biopsy
specimens were formalin-fixed and analyzed after stain-
ing with H & E, Masson trichrome, and immunostains.
The procedure was considered successful in cases in
which a definitive diagnosis was obtained and confirmed
by the clinical course of the tumor.

The overall diagnosis rate of the biopsy procedure
was 93.7%, and in 9 patients the biopsy results were nega-
tive. Diffuse brainstem glioma was diagnosed in 100
patients. Other neoplastic diseases were diagnosed in 23
patients. Moreover, histological evaluation revealed non-
neoplastic lesions in 10 patients (Table 1). The tumors
were graded according to WHO classification; low-grade
gliomas were classified as Grade II and high-grade gli-
omas as Grades III and IV.10

Of the patients with diffuse brainstem glioma, 63
were adults, including 40 men and 23 women who ranged
in age from 18 to 75 years (mean 41 years). Thirty-seven
patients were children, including 19 boys and 18 girls who
ranged in age from 2 to 12 years (mean 6.9 years). Patient
follow-up occurred from 4 days to 278 months after the
biopsy (mean 40.4 months).

Eighty-four patients received conventional focal ra-
diotherapy; 9 patients were not treated because they pre-
SENTed with minor symptoms, nonprogressive tumors,
and a histological diagnosis of low-grade glioma; and 7
patients died before radiotherapy was performed. Chem-
otherapy was administered to 40 patients at the time of relapse
or when radiotherapy failed.

Regarding complications in the current series, 1 death
occurred due to the procedure and 13 patients (9.8%) pre-
SENTed with definitive complications.

Statistical Analysis

Data analysis was performed using Epi info (version
6.02, Centers for Disease Control) and MedCalc (ver-
sion 9.3.0.9, bvba). Univariate analysis of the following
variables was performed: characteristics of T1-weighted
MRI studies after infusion of Gd, histological grade, and
patient age.

Survival time was measured from the time of the bi-
yop procedure to the date of the patient’s last follow-up
or death due to diffuse glioma. Survival was estimated
using the Kaplan-Meier method with 95% confidence
intervals. Comparison of Kaplan-Meier curves between
histological grades (low-grade vs high-grade glioma),
characteristics of T1-weighted MRI after infusion of Gd
(enhancing vs nonenhancing tumors), and age (adults vs
children) were performed using the log-rank test. The
Cox proportional hazards model was used to test prog-
nostic factors in multivariate analysis. Parameters were
considered statistically significant at a value of p < 0.05.

Results

The histological grade of the diffuse high-grade gli-
omas was determined in 51 patients (51%; 32 adults and 19
children). Diffuse low-grade gliomas were diagnosed in
49 patients (31 adults and 18 children). At the time of the
last follow-up in August 2007, 55 patients (55%) had died.

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high-grade glioma</td>
<td>51 (36)</td>
</tr>
<tr>
<td>low-grade glioma</td>
<td>49 (34.6)</td>
</tr>
<tr>
<td>lymphoma</td>
<td>7 (4.9)</td>
</tr>
<tr>
<td>pilocytic astrocytoma</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>metastasis</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>inflammatory disease</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>ischemic lesion</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>fungal abscess</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>ganglioglioma</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>cranioopharyngioma</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>gliosis</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>ependymoma</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>inconclusive</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>total</td>
<td>142 (100)</td>
</tr>
</tbody>
</table>

The mean overall survival of this population, mea-
sured from the date of biopsy, was 57 months for diffuse
low-grade glioma and 13.8 months for diffuse high-grade
glioma (p < 0.001). A comparison between the Kaplan-
Meier survival curves for adults and children revealed
a similar median survival period of 25 and 16 months,
respectively (p > 0.05). The 1-year actuarial survival for
adults was 64% ± 0.6% and for children it was 66% ±
0.08% (p > 0.05) (Fig. 1).

Figure 2 shows the comparison of Kaplan-Meier sur-
vival of the 2 subgroups of diffuse glioma. The 1-year
actuarial survival rates for patients classified with low-
grade and high-grade gliomas were 87.6% ± 0.04% and
34.9% ± 0.8%, respectively (Fig. 3).

In the patients with low-grade glioma, the 1-year sur-
vival rates were 92.9% for adults and 79.4% for children
(p = 0.07). In the high-grade glioma group, the 1-year sur-
vival rates were 29.1% for adults and 44.9% for children
(p = 0.34). These differences were not statically signifi-
cant.

In the group of adults, the comparison of Kaplan-
Meier curve survival showed higher survival in patients
with low-grade glioma. The 1-year actuarial survival
rates for adult patients were 92.9% for low-grade gliomas
and 29.1% for high-grade gliomas. This difference was
statistically significant (p = 0.0001) (Fig. 4). However, in
the group of children, the 1-year actuarial survival rates
for patients classified as harboring low- and high-grade
gliomas were 80.4% ± 0.08% and 48.6% ± 0.14%, respec-
tively. This difference was not statistically significant (p
= 0.0755) (Fig. 5).

Regarding MRI characteristics, 51 patients (29 adults
and 22 children) presented with contrast-enhancing le-
sions. Nonenhancing lesions were observed in 48 patients
(34 adults and 14 children). One patient had a T1-weight-
ed image without Gd infusion.

The mean survival among patients with nonenhanc-
ing lesions on MRI was 54.2 months, whereas that for pa-

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tients with enhancing lesions was 21.7 months (p < 0.001). The Kaplan-Meier curve also revealed greater survival for patients with nonenhancing tumors (Fig. 6); moreover, the 1-year actuarial survival rate for patients with nonenhancing tumors was 88.6% ± 0.04%, while for enhancing tumors, it was 44.9% ± 0.07% (Fig. 7).

Multivariate analysis (Cox proportional hazards regression) revealed that only histological grade (p = 0.001) was a significant prognostic factor. The variables MRI findings (p = 0.053) and age (p = 0.27) had no statistically significant relation to patient survival in this analysis.

Discussion

In most studies, treatment decisions for brainstem glioma are based on MRI features alone and do not include histopathological diagnosis. Most authors regard biopsy procedures for intrinsic brainstem tumors as being too dangerous and consider imaging methods as sufficiently reliable.1,5 Thus, the impact of MRI findings on treatment decisions for brainstem tumors is very high, but the accuracy of MRI-based diagnosis of diffuse brainstem gliomas has not been fully verified by histopathological findings.8 Thus, some authors have reported that all diffuse brainstem gliomas located above the medulla behave as high-grade astrocytomas, and histological grade is not a significant factor for the survival of these patients.1,4,5,18,20

Few studies have been conducted concerning prognosis and prognostic factors in brainstem gliomas.7 This may be due to the low incidence of these tumors and the fact that histopathological diagnosis is rarely confirmed.

The present study showed that of the 3 factors studied, in univariate analysis, contrast enhancement and histological grade were significant prognostic factors, but age was not. In multivariate analysis, only histological grade remained a significant prognostic factor. However, the histological grade was a significant prognostic factor only in the group of adults. In children, despite the longer survival of patients with low-grade glioma, the difference was not statistically significant (p = 0.088).

These data are similar to those published by Selvapandian et al.,17 who demonstrated that the tumor grade was a significant factor in predicting survival in adults.
but in children it did not correlate with outcome. However, Broniscer et al.3 showed improved outcome in children who are younger than 3 years.

Rachinger et al.14 recently reported that adult patients with diffuse low-grade gliomas showed a 1-year survival rate of 93%, while this rate was 42% in patients with diffuse high-grade gliomas, also demonstrating the impact of histological grade on the survival of these patients.

Using univariate analysis, Guillamo et al.6 showed in adults with diffuse glioma that histological grade and MRI “necrosis” were significant prognostic factors but that contrast enhancement not. When histological grade and MRI necrosis were included in multivariate analysis, the relative risks of these factors were similar, but only MRI necrosis was considered significant.

It is highly probable that conventional fractionated radiotherapy will not remain the only efficient treatment in diffuse brainstem glioma over the next few decades. In addition, for patients with low-grade gliomas, an initial observational policy is being adopted, followed by treatment when the patient’s disease progresses clinically.17 Indeed, new chemotherapies, gene therapies, or immunotherapies, alone or in combination, will certainly succeed in improving the outcome of these patients.6,16,19 These therapies will undoubtedly require tissue sampling for diagnostic confirmation and histological grade, for molecular marker studies, or for immunological purposes prior to adopting target therapies.16 Therefore, Pollack et al.13 found that overexpression of p53 in malignant gliomas during childhood is strongly associated with adverse outcome, independent of clinical prognostic and histological findings.

**Conclusions**

This study revealed that histological grade and MRI features were significant prognostic factors for survival in these patients, but in multivariate analysis only histological grade remained a significant factor. Further studies should be conducted to determine whether histological
T1-weighted MRI after infusion of Gd. The solid line represents the contrast-enhancing lesion, and the dotted line represents the nonenhancing contrast lesion. \( p < 0.001 \), log-rank test.

grade has a greater impact than MRI alone on the treatment of these patients.

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: Dellaretti. Acquisition of data: Dellaretti, Dubois. Analysis and interpretation of data: Dellaretti, Reyns, Touzet, Dubois. Drafting the article: Dellaretti, Pereira. 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: Dellaretti. Study supervision: Gusmão, Blond.

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