Prognostic Limitations of the Daumas-Duport Grading Scheme in Childhood Supratentorial Astroglial Tumors

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Abstract. The Daumas-Duport grading scheme (DDGS) is a commonly used method for determining the grade of a tumor. It scores 4 histologic features and is used as a prognostic tool in adult astroglial tumors. This system of assigning children to prognostically homogeneous groups has not been evaluated. The Childhood Brain Tumor Consortium (CBTC) database includes 327 children with a CBTC assigned World Health Organization (WHO) diagnosis of supratentorial astroglial tumor and histologic features necessary for Daumas-Duport grading. We compared survival estimates for tumors within and between DDGS grades using a slightly broadened definition of endothelial prominence. The DDGS yielded only 3 histologic groups in children and only 2 prognostically differing groups. Subgroups within DDGS grades had significantly different survival distributions. The summing of 4 disparate histologic features in the DDGS is inadequate for the assessment of childhood supratentorial astroglial tumors. A classification system more fully summarizing the complete histologic content of tumors is most likely to provide diagnoses useful for clinical purposes.

Key Words: Astroglial tumors; Child; Grading; Survival.

INTRODUCTION

The assignment of names and grades to astrocytic tumors has been controversial ever since Bailey and Cushing first proposed a classification scheme for these tumors in 1926 (1). Multiple separate schemes (2–15) described since then have posed new methodologic and operational problems. The broad correlation of "diagnostic" names such as astrocytoma, anaplastic astrocytoma, and glioblastoma with increasingly greater mortality and a "higher grade" has caused considerable confusion as clinicians and pathologists have found significant numbers of cases that do not conform to this association. Most pediatric supratentorial astroglial tumors are histologically heterogeneous, posing additional classification problems (16–21).

In 1981, Daumas-Duport (10) proposed a reproducible and standardized method of grading astrocytic tumors (12, 14) based upon the presence or absence of 4 histologic features: endothelial proliferation, necrosis, mitosis, and nuclear atypia. The conceptual advantages of this simple standardized grading system were that it did not require subjective interpretation of histologic features or correlation of these features with conflicting nosologies. The observer merely records the presence (score = 1) or absence (score = 0) of the 4 features and adds up the total score. Grade depends upon the sum: grade 1 = total score of 0, grade 2 = score of 1, grade 3 = score of 2, and grade 4 = score of 3 or 4. The Daumas-Duport Grading System (DDGS) is reproducible in adults with supratentorial astrocytic tumors (22, 23), but its applicability to children has not been evaluated.

The rationale for numeric summation of disparate histologic features has not been presented. For example, does the combination of nuclear atypia and endothelial proliferation (grade 3) have the same effect on survival as the combination mitoses and necrosis (also grade 3)? In this study we evaluated the effectiveness of the DDGS in predicting survival of children with a supratentorial astrocytoma, anaplastic astrocytoma, or glioblastoma in the Childhood Brain Tumor Consortium (CBTC) database (24).

MATERIALS AND METHODS

The CBTC, described previously (24), consists of 10 hospitals in the United States and Canada recognized for their care of children with brain tumors (Appendix 1). The database includes 3,291 patients under the age of 21 years at their first brain tumor surgical procedures between 1930 and 1979. Tissue specimens from the original surgical procedure were available for all cases as was survival information. With a tumor incidence of approximately 3/100,000 children per year, this sample represents approximately 100,000,000 children-years of observation. For this study, all 340 patients with a CBTC assigned WHO (1979) consensus diagnosis of any WHO diagnosis astrocytoma (WHO 1.1.1) subset: supratentorial protoplasmic,
fibrillary, gemistocytic, subependymal giant cell astrocytoma, or plain astrocytoma (WHO 1.1.2) and glioblastoma (WHO 1.1.3) were selected for analysis. Patients with spinal or infratentorial tumors and pilocytic astrocytomas were excluded from analysis.

The presence or absence of 144 operationally defined histologic features, recorded for each case by separate teams of neuropathologists using consensus reading, constitutes the histologic section of this database. Among the features recorded were the 4 needed for assignment of a Daumas-Dupont score. The database contains clinical, surgical, treatment, and survival data. We restricted our survival analyses to the cases that survived at least 1 month after their first surgical procedure, thus excluding those cases whose death might have been due to complications of surgery.

The 18 pathologists and neuropathologists constituting the slide review portion of the CBTC agreed upon operational definitions for each of the histologic features to be used in the study (25) including those required for tumor grading under Daumas-Dupont (10, 12, 14). Complete information was available for all but 13 tumors, leaving 327 for assignment of a DDGS score. The definitions for each feature included: (a) endothelial prominence (EP), any prominence of endothelial cells greater than that which is usual in capillaries in nonneoplastic tissue. The characterization included those cases with multiple layers of endothelial cells. The occurrence of endothelial cushions and glomeruloid capillaries were recorded separately (25). This definition is somewhat more inclusive than the term "endothelial proliferation" in the original description by Daumas-Dupont; (b) necrosis (NEC), a region of tissue that may contain "ghosts" of cells or a loss of nuclear or cytoplasmic characteristics with a background of eosinophilic amorphous or granular material; (c) mitosis (MIT), mitosis in nonendothelial cells, whether bizarre or not; and (d) nuclear atypia (NA), nuclei with any of the following: a twofold variation of size or variation in shape except for multinucleation; greater than a twofold difference in major and minor axes including spindle and fusiform nuclei; or neoplastic cells with lobulated, notched, or indented nuclei.

Statistical analyses were performed using the SAS/STAT statistical software, version 6, 1991, (SAS Institute, Inc. Box 8000 Cary, NC 27511-8000). Using the LIFETEST procedure, survival function estimates were calculated for each scheme. Survival curves were compared using Log-Rank, Wilcoxon, and −2Log (LR) statistics.

RESULTS

Less than 2% of the tumors in our study received a Daumas-Dupont grade of 1 (DD1). The remainder of the tumors were rather evenly distributed among the remaining grades DD2, DD3, and DD4 (Table 1). All tumors in DD3 and DD4, and nearly all in DD2 had NA and most tumors graded as DD3 and DD4 contained either NEC or EP (Table 2). Since NA occurred in almost all of our pediatric supratentorial astroglial tumors, it is not an effective discriminating histologic feature. In contrast, the other features in the DDGS (mitosis, necrosis, and endothelial prominence) were more useful discriminating variables.

We found an overall difference (p < 0.0001) between the survival curves in the DDGS (Fig. 1). Evaluation of DD1 could not be performed due to the low number of cases with this grade. There were statistically significant differences between DD2 and DD4 (p < 0.0001), and between DD3 and DD4 (p < 0.0001), but not between DD2 and DD3 (p = 0.325), which had similar survival distributions.

In our study, NA was present in nearly all pediatric supratentorial astrocytic tumors with DD grades of 2–4 (Table 2), a figure comparable with previously reported figures of 100.0% and 99.4% (14, 23). Mitotic activity was present in 76.3% of DD4, but only 10.8% of DD3. MIT in DD2 tumors (0.9%) were rare. Daumas-Dupont, in contrast, found MIT in virtually all (97%) of DD3 tumors (14). In our series, EP was present in 82.9% of supratentorial tumors with DD3 and in 89.7% with DD4, but in only 2.6% of DD2 tumors. NEC was common (77.3%) in DD4 tumors, but rare in DD3, and nonexistent in DD2 tumors. NEC and EP never appeared together except in DD4 tumors, an observation made previously (14). NEC or EP were rare in DD2, but frequent in DD3

| TABLE 1 |
| Distribution of DDGS Grades in CBTC Database |
| DDGS grade | n | (%) |
| DD 1 | 5 | (01.5) |
| DD 2 | 114 | (33.5) |
| DD 3 | 111 | (32.6) |
| DD 4 | 97 | (28.5) |
| Insufficient data | 13 | (03.8) |

| TABLE 2 |
| Distribution of Histologic Features Within DDGS |
| Histologic features | Nuclear atypia | Endothelial prominence | Necrosis | Mitosis | Frequency | Grade total |
| DD2 | + | + | | | 110 | 3 |
| | | | | | 0 | 0 |
| | | | | | 114 | 1 |
| DD3 | + | + | + | | 92 | 7 |
| | | | | | 7 | 1 |
| | | | | | 111 | 2 |
| DD 4 | + | + | + | | 9 | 9 |
| | | | | | 22 | 12 |
| | | | | | 21 | 11 |
| | | | | | 42 | 3 |

* = features present, but one missing observation for each case.
Fig. 1. Daumas-Dupont Grading. The survival distributions for DD2 and DD4, and of DD3 and DD4 are statistically different (p < 0.0001). There is no difference between DD2 and DD3.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Histologic features</th>
<th>Probability of survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FreQUENCY 1 year 5 year</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td></td>
</tr>
<tr>
<td>Endothelial prominence</td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td></td>
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<tr>
<td>Mitosis</td>
<td></td>
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<tr>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>86*</td>
<td>0.87 0.67</td>
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<tr>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>11*</td>
<td>0.36 0.09</td>
</tr>
</tbody>
</table>

* = cases not surviving one month removed.

The survival distributions between these two subgroups were significantly different (p < 0.0001).

(89.2%) and omnipresent in DD4 tumors. NEC appeared without EP infrequently (<10%) in DD3. EP occurred without NEC in most DD3 tumors (82.9%), but occurred in only 22.7% of DD4.

The DDGS assumes that tumors within a grade have the same prognosis. Of the 111 DD3 tumors, NA and EP was present in 92 cases, 86 of whom survived at least 1 month after first surgery. This subgroup had 1 and 5 year survival estimates of 0.87 and 0.67 respectively (Table 3). In comparison, 11 cases had the features of NA and MIT and 1 and 5 year survival estimates of 0.36 and 0.09, respectively. The survival distributions between these 2 subgroups of DD3 were significantly different (p < 0.0001) (Fig. 2). The majority of DD4 tumors that survived at least 1 month contained 2 subgroups (Table 4). Tumors with all 4 features present had a significantly worse prognosis than tumors with NA, EP, NEC, and without MIT (p < 0.015).

**DISCUSSION**

Our dataset included 2 diagnoses that might have influenced the survival distributions. We included the 31 subependymal giant cell astrocytomas for several reasons: 1) The WHO classification uses it as a subset; 2) about 16% have anaplastic features, significantly more than for pilocytic astrocytomas; 3) our results were unchanged by their presence or absence in the dataset; and 4) because they are part of 1 of the neurocutaneous syndromes, tuberous sclerosis, similar to some astrocytic neoplasms encountered in neurofibromatosis. The other diagnosis, desmoplastic cerebral astrocytoma of infancy (WHO 1.7.3), was described during the analysis phase of this study. However, there was only 1 case of supratentorial astrocytoma with any desmoplasia.

The DDGS is reproducible for astrocytic supratentorial tumors in adults (22, 23). Yet, like the Kernohan grading system, it results in some grades with survival curves that are not statistically separable (14, 26–31). In children, only 2 significantly separable survival curves resulted.
Fig. 2. DD Grade 3. Within DD grade 3, children with nuclear atypia and endothelial prominence have a significantly (p < 0.0001) better estimated survival probability than do children with nuclear atypia and mitosis.

Moreover, within Daumas-Duport grades 3 and 4 there are significant subsets of tumors, defined by differing combinations of the requisite histologic features. These subsets have disparate survival distributions, suggesting that the underlying assumption of the Daumas-Duport scheme, that any of the 4 disparate histologic features have equal weight and may be summed, is not valid. The effects of treatment on tumors within each grade are difficult to evaluate for 2 reasons: 1) the underlying assumption that tumors with the same grade have the same behavior may not be correct; and 2) these children were not enrolled in a standardized protocol and did not receive the same therapies.

The observation that different histologic features of glioma are related to survival is an old one, attributed to Tooth over 80 years ago (32). Several studies (13, 31, 33, 34) have attempted to associate specific histologic features and tumor behavior, but with contradictory results. Necrosis, for example, is either highly (13), or not at all (31, 33) correlated with survival in either anaplastic astrocytoma or glioblastoma. Even an easily recognizable feature such as mitosis has yielded conflicting results, being correlated (34) or uncorrelated (31, 33) with shorter survival in glioblastoma. Setting aside the obvious problem of sample bias in these studies, additional problems are the lack of operationally defined criteria for the assignment of a tissue diagnosis to astrocytic tumors and unreliable identification of histologic features.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Survival Probability Relation to Histologic Feature Prevalence Within DD Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic features</td>
<td>Frequency</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>Endothelial prominence</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
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<tr>
<td>+</td>
<td>+</td>
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<td>+* = cases not surviving one month removed.</td>
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<td>The survival distributions between these two subgroups were significantly different (p &lt; 0.015).</td>
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</table>

Only 1.5% of the supratentorial tumors in our study population received a DDGS grade of 1; this is consistent with previous adult studies that show that DD1 tumors are "rare" (14, 22, 23). We identified a greater percentage of tumors with DD2 and DD3, and far fewer with DD4 designations, reflecting the lower incidence of glioblastomas in children than in adults. Daumas-Duport (14) was able to demonstrate statistically different survival curves for DD1, DD2, and tumors with designations DD3 or DD4, but not between DD3 and DD4. We could not show significant differences between DD2 and DD3 in our population, but statistically separable survival curves existed between DD2 and DD3 grades and DD4 (22). Thus, since grade 1 tumors were so rare in children, the DDGS yielded only 2 distinct tumor classes, DD4 and DD2-3.
LIMITATIONS OF DAUMAS-DUPORT GRADING

Criteria used for assigning diagnosis should first be defined before slide review (operational criteria) and second, be reliably identified (14). Both Daumas-Dupont and the CBTC defined necrosis, nuclear atypia, and mitosis similarly. Daumas-Dupont’s criterion “endothelial proliferation” (14) uses the subjective terms “haphazard” and “piled up”; such endothelial cushions are not reliably identified by pathologists (25) and therefore should not be used as a criterion for grading. Vascular proliferation, endothelial proliferation, and endothelial prominence are used in different, but overlapping, ways in the WHO manual (17), leading to further operational difficulties. The common denominator to the Daumas-Dupont and WHO schemes and the standard text of Russell and Rubinstein (6) is “prominence” of endothelial cells. The CBTC operational criterion “endothelial prominence” was defined inclusively so that such conflicts could be resolved in favor of inclusion; it was also reliably identified by pathologists (25) and limits confounding effects of topology when endothelial cells are cut obliquely.

The successful application of present or absent criteria for only 4 histologic features to a grading scheme seems excessively simplistic. Preferably, a diagnostic scheme needs specific histologic features that should be present for that tumor to be placed in a specific diagnostic class, additional criteria to separate that diagnostic class from similar or neighboring diagnoses, and a way to incorporate the many remaining histologic features into the diagnosis. Such a system is available for pediatric supratentorial and infratentorial neuroglial tumors (35, 36).

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APPENDIX 1

The Childhood Brain Tumor Consortium (Floyd H. Gilles, Principal Investigator) is Composed of the Following:

Institutions
- Barnes and St. Louis Children's Hospital, St. Louis
- Cardinal Glennon Memorial Hospital, St. Louis
- Children's Hospital, Boston
- Children's Hospital of Denver
- Children's Hospital of Los Angeles
- Children's Hospital of Philadelphia
- Children's Hospital of Pittsburgh
- Hospital for Sick Children, Toronto
- Los Angeles County-University of Southern California Medical Center
- St. Christopher's Hospital for Children, Philadelphia

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