Survival status of children with cerebellar gliomas

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The goals of this study were: 1) to determine how well a multivariate analytic procedure shortly after surgery would have classified children with cerebellar glioma according to expected survival status (alive or dead) 5 years later, and 2) to identify histological, clinical, and other features that contributed most to the classification. Fifteen of the 76 (20%) children in this study died before the end of the fifth postoperative year. The linear discriminant function (LDF) constructed with the four histological features of microcysts, high cell density, oligodendroglia, and endothelial proliferation, misclassified outcome in only eight children and discriminated as well as the LDF constructed with 12 additional histological features. The LDF constructed with eight symptoms and 12 signs had a misclassification rate of 9.2%, and was no more successful than the LDF constructed with the single symptom of lethargy. The LDF constructed with all 42 variables misclassified only three children. The variables that contributed most to successful analysis were altered consciousness, microcysts, oligodendroglia, high cell density, endothelial proliferation, and perivascular desmoplasia. Multivariate analysis of histological features, symptoms, and signs appears to classify children with cerebellar glioma according to survival status with an acceptably low error.

KEY WORDS • childhood brain tumor • cerebellar glioma • multivariate analysis

Information about prognosis of a disease can be useful in several ways. It can aid in guiding the physician's discussion with the patient and the patient's family, in identifying situations where treatment may be beneficial, in providing a basis for evaluating the effects of treatment, and in allocating resources.

Little attention has been directed to the formal study of prognosis of children with brain tumors. The small amount of prognostic information available about children with brain tumors is based on anecdotal data. We have recently developed a simple classification of cerebellar gliomas in children that conveys information about prognosis. Although this classification holds promise of predicting survival better than previously devised schemes, an even lower rate of error may be possible with a multivariate analysis.

The following investigation was a feasibility study to see how accurately a multivariate analysis of histological features and clinical symptoms and signs (specifically, a linear discriminant function) would have classified children at the time of surgery into...
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those who would be alive or dead 5 years later. In addition, those histological and clinical features that contributed most to the discrimination were identified.

The step-up linear discriminant function (LDF) first identifies the feature that best discriminates between two populations, in this case between children who would be alive and those who would be dead 5 years after operation. Then it removes this feature from consideration and identifies the next best discriminator, and so forth. Features that are highly associated with an identified discriminator are suppressed to a degree proportional to the strength of the association.

Materials and Methods

Population

This study is based on all 76 children who had a glioma of the cerebellum surgically removed at The Children’s Hospital Medical Center of Boston between 1951 and 1968. These children were included in the latter portion of the sample reported by Winston, et al.3 The year 1951 was chosen as the starting date because no operative fatalities occurred thereafter. Fifteen of the 76 children (20%) died between 1 month and 5 years after operation.

Data Collected

The dependent variable was whether or not the child was alive 5 years after operation. The 16 histological features of cerebellar gliomas in children described by Gilles, et al.,5 constituted one set of independent variables (the “histology” set). The eight symptoms and 12 signs of cerebellar gliomas recorded routinely on the data-collection sheet for the children described by Winston, et al.19 constituted a second set of independent variables (the “clinical” set). The third (“total”) set consisted of these two sets plus age, sex, year of operation, duration of symptoms, presence or absence of a gross cyst, and extent (total or subtotal) of surgical removal of the tumor.

Data Analysis

The independent variables were incorporated into the linear discriminant function to classify children into two groups (alive or dead 5 years after surgery) as might have been done shortly after surgery. The results of this analysis were then compared to what actually happened 5 years after surgery.

The reader who wants to gain an understanding of LDF’s or who wants to use packaged programs to discriminate between two populations is referred to the text by Afifi and Azen.1 Linear discriminant functions were constructed by both a step-up procedure included in the Biomedical Computer Program package BMD 07M1,4 and a step-down procedure using the COPS-4 program prepared by Raymond Neff10 of the Health Sciences Computing Facility of the Harvard School of Public Health. The results of the two procedures were similar.

The F test for additional discrimination11 was calculated to determine at what point in the step-up procedure additional variables no longer contributed “significantly” to the discrimination.

Results

One of the goals of this study was to identify which histological and clinical features contributed most to discriminating, shortly after tumor resection, which children would be alive 5 years later. The LDF procedure identifies those variables that discriminate best, while minimizing the contribution of variables that discriminate almost as well, but are closely related to the best discriminators. This in no way diminishes the importance of the closely related features. Because of the known association between histological and clinical features,13 separate LDF’s were constructed from histological and clinical variables to identify which variables in each of these sets best discriminated survival status.

The best discriminators are associated with other features that provide minimal additional information. Within the “histology” set of variables, microcysts discriminated best (Table 1); therefore, features closely associated with microcysts12 contributed insignificantly to better discrimination. Thus, Rosenthal fibers and leptomeningeal deposits were not included among the four “best discriminators.” Similarly, most of the histological features (namely, necrosis, mitosis, and perivascular pseudorosettes) that clustered with the second best discriminator, high cell density, were also not among the four “best discriminators.” Because each of

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Survival status of children with cerebellar gliomas

TABLE 1

<table>
<thead>
<tr>
<th>Set of Variables</th>
<th>Total No. Variables in Set</th>
<th>Minimum No. Significant Variables</th>
<th>Best Discriminators</th>
<th>Misclassification Rate (%)</th>
<th>Misclassification Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>histology set</td>
<td>16</td>
<td>4</td>
<td>microcysts</td>
<td>10.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>high cell density</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>oligodendroglioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>endothelial proliferation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinical set</td>
<td>20</td>
<td>1</td>
<td>lethargy</td>
<td>9.2</td>
<td>6</td>
</tr>
<tr>
<td>total set</td>
<td>42</td>
<td>6</td>
<td>altered consciousness</td>
<td>6.6</td>
<td>3</td>
</tr>
</tbody>
</table>

The best discriminating features encompasses the contributions of many other variables, the misclassification rate (10.5%) achieved with the four best histology discriminators (microcysts, high cell density, oligodendroglioma, and endothelial proliferation) was not improved by adding the remaining 12 histological features.

As with the histology set of features, some of the 20 clinical features measure the same effect measured by other clinical features. Since some of the signs are objective measures of symptoms, the number of clinical features that can be expected to contribute additional information toward classification of survival is reduced. Cerebellar tumor growth can express itself clinically in a limited number of interrelated ways, such as brain-stem compression, obstruction of cerebrospinal fluid pathways, and cerebellar dysfunction. A very small number of variables, therefore, might be expected to discriminate as well as all 20 variables. Indeed, the LDF that contained only a single variable (lethargy) had a slightly lower misclassification rate (9.2%) than the LDF constructed with all 20 clinical features.

The second and major goal of this study was to achieve the lowest possible error rate of discrimination. The ability to discriminate between two groups with a linear discriminant function is related to the amount of valid information about the two groups. As expected, the LDF constructed with all 42 variables had a lower misclassification rate (4.0%) than did any of the three linear discriminant functions constructed with fewer variables.

The results of the LDF's based on the 76 children with cerebellar glioma are presented in the Appendix in a way that allows an estimate of outcome to be made without the aid of a computer or calculator.

Discussion

The discriminant function derives a specific "weight" for each variable to maximize discrimination (see Appendix). The products of each variable (\(X_1 = 1\) if microcysts are present, and 2 if absent) multiplied by its computer-derived weight are summed to achieve a discriminant score. If the discriminant score exceeds a critical value, the child is classified as having one outcome. If the discriminant score is less than that value, the child is classified as having the alternative outcome.

The LDF's based on data from 76 children with cerebellar glioma first seen at one institution between 1951 and 1968 are presented in the Appendix. We hope that these functions will be of clinical value. For two reasons shortened versions only are presented. First, only the functions that can be calculated most readily are included. Second, the refinement in discrimination achieved by adding features is small compared to the additional...
### TABLE 2
Values for each variable, their weights, and the cutoff points for two discriminant functions that discriminate between death and survival in 76 children with a cerebellar glioma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>Weight</th>
<th>Contribution to Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>histology set*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X1 = microcyst</td>
<td>present = 1, absent = 2</td>
<td>1.05</td>
<td>1.05 (X_1)</td>
</tr>
<tr>
<td>X2 = cell density</td>
<td>low = 1, moderate = 2, high = 3</td>
<td>1.24</td>
<td>1.24 (X_2)</td>
</tr>
<tr>
<td>X3 = oligodendroglial foci</td>
<td>present = 1, absent = 2</td>
<td>1.02</td>
<td>1.02 (X_3)</td>
</tr>
<tr>
<td>X4 = endothelial proliferation</td>
<td>present = 1, absent = 2</td>
<td>0.78</td>
<td>0.78 (X_4)</td>
</tr>
<tr>
<td>total set†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X1 = altered consciousness</td>
<td>absent = 0, present = 2</td>
<td>1.34</td>
<td>1.34 (X_1)</td>
</tr>
<tr>
<td>X2 = microcysts</td>
<td>present = 1, absent = 2</td>
<td>1.28</td>
<td>1.28 (X_2)</td>
</tr>
<tr>
<td>X3 = oligodendroglial foci</td>
<td>present = 1, absent = 2</td>
<td>1.21</td>
<td>1.21 (X_3)</td>
</tr>
<tr>
<td>X4 = cell density</td>
<td>low = 1, moderate = 2, high = 3</td>
<td>1.21</td>
<td>1.21 (X_4)</td>
</tr>
<tr>
<td>X5 = endothelial proliferation</td>
<td>present = 1, absent = 2</td>
<td>1.17</td>
<td>1.17 (X_5)</td>
</tr>
<tr>
<td>X6 = perivascular desmoplasia</td>
<td>present = 1, absent = 2</td>
<td>1.00</td>
<td>1.00 (X_6)</td>
</tr>
</tbody>
</table>

*Total score = 1.05 (microcyst value) + 1.24 (cell density value) + 1.02 (oligodendroglial foci value) + 0.78 (endothelial proliferation value). If total score is less than 7.01, 5-year survival is predicted.
†Total score for this set is calculated in the same fashion as above. If total score is less than 6.77, 5-year survival is predicted.

Calculations necessary. This is especially evident with the “total set” of variables. Adding 36 variables to the six-variable equation reduced the error rate from 6.6% to 4.0%

The low error rates achieved with these discriminant functions are considered an acceptable beginning to the use of multivariate analysis in classifying children with brain tumors. However, these error rates are idealized because they were calculated in the same population in which the linear discriminant functions were prepared. These are, however, the only data available for comparison. Armitage and Gehan believed that “A method of prediction is likely to be less effective on subsequent data than it appears to be when applied retrospectively to the data from which it was derived.”

We have measured classification, however, and not prediction. The only valid way to evaluate the prognostic capability of such a multivariate analytical procedure is through prospective studies. Thus, until the LDF in the Appendix is validated by an appropriate prospective study, we offer the caveat that reliance not be placed on it yet.

Our previous classification of cerebellar gliomas in children into types A, B, and C is supported by the results of this study. With the single exception of endothelial proliferation, the “best discriminators” in each of the three sets of variables have been shown to be characteristic of either glioma type A or B, or associated with one of these glioma types.

Multivariate analyses, such as linear discriminant functions, appear to be valuable in predicting the survival of children with cerebellar gliomas and could perhaps be applied to people with other diseases. Incorporating these procedures in tumor registries, in which new data are incorporated repeatedly, would allow frequent reassessment of the weights assigned by the LDF to each variable. Thus, the variables identified in the children reported here might not be those identified in a different, or more recently collected sample. On the other hand, the best possible multivariate analytical procedure is rarely completely accurate because of unpredictable complications, deaths from competing causes and unmeasured (but nevertheless discriminating) features of disease and host.

How much prognostic information people need or want remains controversial. This has been brought to light most recently in discussions about tests that were thought to predict which offspring of Huntington's chorea patients would later develop the disease, about the risks and benefits of Tay-Sachs screening, and about the way adults who might have a malignant tumor seek and handle information about diagnosis and prognosis. For two reasons, we feel that...
improved ability to predict survival is an asset and not a liability. For many years, neurosurgeons and neuropathologists have been predicting survival with considerable accuracy, and multivariate procedures may improve the accuracy. Clinicians will continue to make decisions for treatment based on their assessment of benefit:risk ratios. Multivariate procedures that improve the ability to predict survival should contribute to a better estimate of these ratios. The improved prognostic capability may be expected to help physicians to identify which patients need a particular therapy (such as radiation or chemotherapy), and to compare different modes of therapy.2

APPENDIX

Examples of Two Discriminant Functions

Clinicians and pathologists may want to compare their own experience with the predictions based on the linear discriminant functions created with the data in this study. Two functions are presented. One is for the histology set, and the other is for the total set (see Table 2). Until additional evidence is available that demonstrates the value of this approach, caution is advised in placing confidence in it.

Histology Set

Information about only four features is necessary for this function. If, for instance, a microcyst is identified then $X_1 = 1$; otherwise $X_1 = 2$. Values are defined similarly for $X_2$ and $X_4$. If oligodendroglia are seen, then $X_3 = 1$; if not, then $X_3 = 2$. The values for cell density ($X_2$) are 1 for low, 2 for moderate, and 3 for high. Each of these four values is multiplied by a weight that has been determined specifically for that variable. If the sum of these four weighted values is less than 7.01, then it is likely that the child will be alive 5 years later. If the sum is equal to or greater than 7.01, then death within the next 5 years is probable.

Total Set

This discriminant function contains the four variables of the histology set plus the two additional variables of altered consciousness and perivascular desmoplasia. In a manner identical to that for the histology set, the value of each variable is multiplied by the weight for that variable. If the sum of these six weighted values equals or exceeds 6.77, death within the next 5 years is predicted. Survival is predicted if the sum is less than 6.77.

References


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