SUMMARY

Variants of a linear logistic model are used to analyze 2-year survival proportions for 246 children treated for neuroblastoma. The analysis shows that age and stage (extent) of disease at diagnosis are both important factors in determining chances for survival, even after adjusting for the effects of the other. Estimation of prognosis is facilitated by curves relating the probability of survival to age (up to 5 years) for each of 5 stages.

INTRODUCTION

The prognosis in childhood neuroblastoma varies markedly with both the age of the patient and the extent of tumor spread at diagnosis (7, 10). Younger children, and especially those with less widespread disease, tend to respond more favorably to treatment. The site of origin and number of circulating lymphocytes present at diagnosis may also have prognostic significance (3, 7, 8).

The purpose of this article is to illustrate the joint effect on chances for survival of the 2 most prominent factors, age and extent of disease, by means of a detailed statistical analysis of a relatively large series of cases. This analysis permits an assessment of the effect of extent of disease, while adjusting for, and at the same time getting at, the effect of age. It is recognized that other factors, some of which already have been mentioned, may also play a role in the determination of prognosis. However, their effects are not considered here. Thus the analysis and presentation of results is made as simple as possible while at the same time accounting for a major portion of the variability in survival.

The clinical staging criteria proposed by Evans et al. (8) are used as a measure of the extent of disease. These criteria were developed specifically as an aid to prognosis and this study confirms their usefulness in this regard. An important feature of the analysis is that age is treated as a continuous variable.

MATERIALS AND METHODS

Clinical records were reviewed of 2 large series of cases: 148 children treated at the Children's Hospital of Philadelphia during the years 1947 to 1967; and 112 children entered into 2 protocol studies by members of CCSGA during the years 1966–1968 (9). Age was recorded as the number of completed months at diagnosis. Clinical staging was performed on the basis of information available in the clinical records according to the criteria of Evans et al. (8). The 5 stages are defined as follows.

Stage I. Tumors are confined to the organ or structure of origin.
Stage II. Tumors extend in continuity beyond the organ or structure of origin but do not cross the midline. Regional lymph nodes on the homolateral side may be involved.
Stage III. Tumors extend in continuity beyond the midline. Regional lymph nodes bilaterally may be involved.
Stage IV. There is remote disease involving skeleton, parenchymatous organs, soft tissues, or distant lymph node groups, etc. (see Stage IV-S).
Stage IV-S (Special Category). In this group are patients who would otherwise be Stage I or II, but who have remote disease confined only to 1 or more of the following sites: liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).

Twelve of the Philadelphia cases were excluded from analysis because there was insufficient information available for staging or because of an autopsy diagnosis of neuroblastoma in situ (2). One patient with severe mental defects and another with rhabdomyosarcoma were also excluded, leaving a final sample of 134 from this series.

All patients were available for a minimum of 2 years of follow-up from diagnosis. Those surviving the 2 years free of disease were counted "alive" while those succumbing prior to 2 years, or showing evidence of recurrent or metastatic disease at the 2-year point, were treated as "dead." Survival at 2 years, free of disease, was considered equivalent to cure with rare exceptions (7). Thirty-six of the Philadelphia "survivors" have been followed 5 or more years (a more conventional measure of survival), and none have succumbed in that time. However, 1 patient in this group died of recurrent disease 12 years from...
diagnosis, while another is surviving 9 years with evidence of
ganglioneuroma. None of the CCSGA patients have yet been
followed for 5 years. Of 9 patients counted as dead because of
evidence of disease at the 2-year point, all have in fact since
died.

RESULTS

For ease in presentation of the data and as a preliminary
means of adjustment, age was broken down into 3 categories:
0 to 11 months, 12 to 23 months, and 24+ months. Crude
survival proportions for the resulting age/stage
cross-classification are given separately for the 2 series in Table
1. The 2 series are reasonably comparable with respect to the
distribution of cases by stage ($\chi^2 = 6.91, 4$ d.f.); however, the
CCSGA children are slightly older with a median age of 29.5
months compared to 25 months for Philadelphia. In view of
the limited numbers of cases, it seemed desirable to undertake
the statistical analysis on the combined data from both series.
For investigation of whether there might be systematic
differences in the survival proportions for the 2 series which
would preclude such pooling, a matched-pairs comparison was
made. Pairs were formed by matching a Philadelphia case with
a CCSGA case from the corresponding cell (Table 1), thus
automatically adjusting for age and stage differences. This
resulted in 98 pairs of which 20 had different outcomes: in 9
pairs, the Philadelphia patient survived while the CCSGA
patient died, and in 11 pairs the CCSGA patient survived while
the Philadelphia patient died. Since the exact test for
comparing proportions in paired samples (6) thus failed to
show a difference between the 2 series, it was deemed feasible
to proceed with the pooled data. With more extensive data, a
separate analysis of each series along the lines developed below
would be indicated, so as to be able to judge more fully the
dependence of the results on the particular series analyzed.

The 1st step in the analysis was to “smooth” the crude
survival proportions of Table 1 (combined data) so that they
would present a more coherent pattern. Results of this process
are presented in Table 2. Note that the predicted survival
proportions decreased uniformly with age for each stage, while
the survival proportions by stage for each age group fall
consistently in the order I, IV-S, II, III, IV.

The smoothing was carried out in terms of a mathematical
model based on the logistic transformation of the survival
probability, $p$, associated with any particular age/stage
category (6). Formally, the model states that

$$\ln \left( \frac{p}{1-p} \right) = \mu + \alpha + \beta$$  \hspace{1cm} (I)

where $\ln$ denotes the natural logarithm, $\mu$ is a constant, and $\alpha$
and $\beta$ are the additive stage and age effects, respectively. These
latter are assumed to sum to 0 over stage and age categories,
respectively. The quantity shown on the left-hand side of
Equation I is known as the logit of $p$ (from which the model
derives its name). Estimates of the parameters in this equation,
obtained by the method of maximum likelihood, are presented
in Table 3 along with large-sample approximations to their
standard errors. These estimates were then entered in the
inverse equation

$$p = \left[ 1 + \exp \left( -\mu - \alpha - \beta \right) \right]^{-1} \hspace{1cm} (II)$$

to yield the estimated survival probabilities of Table 2. As a
check on calculations, Table 2 was also obtained by the
iterative proportional method of Bishop (4).

Equation I specifies that the effects of age and stage on
survival probability are additive in the logistic scale. This
assumption can alternately be expressed as the hypothesis of
no interaction between the 2 factors, meaning that the effects
of age are the same regardless of which stage category is
considered and vice versa. A test of this hypothesis is provided

<table>
<thead>
<tr>
<th>Age (mos.)</th>
<th>I</th>
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<th>III</th>
<th>IV</th>
<th>IV S</th>
<th>All stages</th>
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<tr>
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<td>8/9</td>
<td>10/11</td>
<td>2/4</td>
<td>1/11</td>
<td>8/8</td>
<td>29/43</td>
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<td>2/4</td>
<td>2/3</td>
<td>0/16</td>
<td>1/1</td>
<td>6/26</td>
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<tr>
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<td>2/2</td>
<td>2/5</td>
<td>3/9</td>
<td>1/48</td>
<td>1/1</td>
<td>9/65</td>
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<td>7/16</td>
<td>2/75</td>
<td>9/9</td>
<td>44/134</td>
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<td>CCSGA series</td>
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<td>4/7</td>
<td>10/11</td>
<td>22/26</td>
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<td>1/3</td>
<td>3/5</td>
<td>0/9</td>
<td>1/3</td>
<td>6/21</td>
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<td>2/3</td>
<td>2/7</td>
<td>0/6</td>
<td>2/45</td>
<td>1/4</td>
<td>7/65</td>
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<td>8/15</td>
<td>3/11</td>
<td>6/61</td>
<td>12/18</td>
<td>35/112</td>
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<td>Combined series</td>
<td>11/12</td>
<td>15/16</td>
<td>2/4</td>
<td>5/18</td>
<td>18/19</td>
<td>51/69</td>
</tr>
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<td>3/4</td>
<td>3/7</td>
<td>5/8</td>
<td>0/25</td>
<td>1/3</td>
<td>12/47</td>
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<tr>
<td>24+</td>
<td>4/5</td>
<td>4/12</td>
<td>3/15</td>
<td>3/93</td>
<td>2/5</td>
<td>16/130</td>
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<tr>
<td>All ages</td>
<td>18/21</td>
<td>22/35</td>
<td>10/27</td>
<td>8/136</td>
<td>21/27</td>
<td>79/246</td>
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Table 2
Smoothed survival proportions for the combined series, by age
and stage of disease

<table>
<thead>
<tr>
<th>Age (mos.)</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>IV S</th>
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<tbody>
<tr>
<td>0–11</td>
<td>0.965</td>
<td>0.887</td>
<td>0.824</td>
<td>0.259</td>
<td>0.909</td>
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<tr>
<td>12–23</td>
<td>0.768</td>
<td>0.487</td>
<td>0.360</td>
<td>0.040</td>
<td>0.544</td>
</tr>
<tr>
<td>24+</td>
<td>0.669</td>
<td>0.366</td>
<td>0.255</td>
<td>0.025</td>
<td>0.421</td>
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</table>

Table 1
Crude proportions of children surviving 2 years free of disease
following diagnosis and treatment for neuroblastoma,
by age and stage of disease at diagnosis

Proportions are expressed as number of survivors divided by total
number of cases.
other choices between 1 and 12 give very similar results.

Equation IV represents an improvement over Equation III.

choice of 6 as the constant in the term \( \ln(x + 6) \) is arbitrary; gives just such a formulation (Table 5, Model D). The choice of 6 as the constant in the term \( \ln(x + 6) \) is arbitrary; other choices between 1 and 12 give very similar results. Equation IV represents an improvement over Equation III.

by the chi-square goodness of fit criterion \((\chi^2 = 9.52)\) and also by the likelihood ratio criterion \((-2 \cdot \ln \Lambda = 9.64)\) which compares the maximum \( \ln \) likelihood of the data under the additive model with the unrestricted maximum \( \ln \) likelihood of \(-73.00\). The appropriate degrees of freedom are 8 in each case. Hence both criteria indicate a good fit or an acceptance of the hypothesis of no interaction.

By calculating the corresponding statistics for even more restrictive models, in which the effects of 1 of the 2 factors are assumed to equal 0, tests can be made of the statistical significance of the variation of survival probability with stage and age. These results are presented in Table 4. The large chi-squares and low \( \ln \) likelihoods for the single factor models, compared to those of the 2-factor model, show that age and stage both play highly significant roles in determining prognosis, even after adjustment for the other variable.

The preceding preliminary analysis investigates and adjusts for the effects of age by means of grouping into 3 broad categories. Treating age as a continuous variable \( x \), measured in months, gives a refined analysis which could result in more accurate prognosis. Perhaps the simplest mathematical formulation for such an analysis assumes that the logistic transform of survival probability is linearly related to age, with the slope constant for all 5 stages (6). In symbols,

\[
\ln\left(\frac{p}{1-p}\right) = a_i + bx,
\]

where \( i = I, \ldots, IV,S \) indexes stage. The assumption of constant slope is analogous to the hypothesis of no interaction which was found to hold for the grouped data. These data also indicated that the effect of age is more dramatic for the younger children (note that in Table 3, \( \beta_{12-23} = 2.118 \) while \( \beta_{12-23} = 0.495 \) which means that the assumption of linearity is somewhat in doubt. Formal tests of these assumptions are obtained by fitting more elaborate models and comparing them with the one just described, with the likelihood ratio criterion. While little is gained by allowing the slope to vary with stage (Table 5, Model C: \(-2 \cdot \ln \Lambda = 4.36, 4 \text{ d.f.}\) ), the addition of a quadratic term for the logarithm no longer results in an improved fit (Table 5, Model E: \(-2 \cdot \ln \Lambda = 0.12, 1 \text{ d.f.}\) ). The assumption of constant slope in Equation IV is again accepted by the usual criterion (Table 5, Model F: \(-2 \cdot \ln \Lambda = 3.16, 4 \text{ d.f.}\) ).

Maximum likelihood estimates of the parameters in Models A, D, and F are presented in Table 6. The individually estimated slopes of Model F, with the exception of that for Stage I, and all reasonably close to the common value \(-1.36\) of Model D. While the apparent discrepancy for Stage I may be due to small numbers, as indicated by the formal test for constant slope above, the possibility that age is of lesser or minimal importance for patients with completely localized disease should not be ruled out.

A computationally simpler method of estimation of the parameters in these models could be based on linear discriminant analysis. Although less general than the present approach, this method is widely used for prediction purposes (1, 5, 11). When discriminant analysis was applied to the present data, however, it overestimated survival probabilities in the upper ranges and underestimated them in the lower ranges. This is not surprising since the assumption of multivariate normality underlying discriminant analysis is patently false for
Estimating Prognosis in Neuroblastoma

Table 6
Maximum likelihood estimates of the parameters in Models A, D, and F, with standard errors

<table>
<thead>
<tr>
<th>Stage (i)</th>
<th>( a_i )</th>
<th>( b )</th>
<th>( a_i )</th>
<th>( d )</th>
<th>( a_i )</th>
<th>( d_i )</th>
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<tr>
<td>I</td>
<td>2.73 ± 0.74</td>
<td>6.08 ± 1.15</td>
<td>1.97 ± 2.58</td>
<td>-0.06 ± 0.85</td>
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<td>II</td>
<td>1.41 ± 0.44</td>
<td>4.77 ± 0.97</td>
<td>5.96 ± 2.02</td>
<td>-1.73 ± 0.62</td>
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<tr>
<td>III</td>
<td>0.57 ± 0.49</td>
<td>-0.0383</td>
<td>4.07 ± 1.02</td>
<td>-1.36</td>
<td>3.28 ± 2.35</td>
<td>-1.12 ± 0.70</td>
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<tr>
<td>IV</td>
<td>-1.63 ± 0.43</td>
<td>±0.0098</td>
<td>1.73 ± 0.92</td>
<td>±0.28</td>
<td>2.04 ± 1.54</td>
<td>-1.47 ± 0.50</td>
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<tr>
<td>IV-S</td>
<td>1.94 ± 0.54</td>
<td>5.15 ± 0.99</td>
<td>6.10 ± 2.17</td>
<td>-1.68 ± 0.69</td>
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Table 7
Age-adjusted stage effects (relative to Stage I) on the logistic scale for several models, compared to unadjusted effects

<table>
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<th>Continuous age variable</th>
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<tr>
<th>Stage</th>
<th>Unadjusted effects</th>
<th>Grouped ages</th>
<th>Model A</th>
<th>Model B</th>
<th>Model D</th>
<th>Model E</th>
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<tbody>
<tr>
<td>II</td>
<td>-1.27</td>
<td>-1.25</td>
<td>-1.32</td>
<td>-1.28</td>
<td>-1.31</td>
<td>-1.31</td>
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<td>III</td>
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<td>-1.78</td>
<td>-2.16</td>
<td>-2.07</td>
<td>-2.01</td>
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<td>IV</td>
<td>-4.57</td>
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<tr>
<td>IV-S</td>
<td>-0.54</td>
<td>-1.02</td>
<td>-0.79</td>
<td>-0.78</td>
<td>-0.93</td>
<td>-0.95</td>
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</table>

Chart 1. Probability of survival for 2 years free of disease estimated on the basis of Model D, by stage of disease and age in months at diagnosis.

These data. Nevertheless, the estimates obtained in this way provided a convenient starting point for iterative solution of the likelihood equations.

Models A, B, D, and E, as well as the model for grouped data (Equation I), can all be viewed as alternate routes to the estimation of stage effects while adjusting for age. Since Models C and F allow the stage effects to vary with age, these are not as well suited to age adjustment. By expressing the effects in terms of the difference, on the logistic scale, of the estimated survival probabilities for the other stages relative to those for Stage I, a comparison can be made of the results obtained with the various models. This is presented in Table 7,

which also shows the unadjusted effects calculated directly from the marginal totals of Table 1 (combined data). The adjusted effects are all in relatively good agreement. Adjustment does not alter the Stage II survival probability (relative to Stage I) but increases the Stage III and IV probabilities while decreasing that for Stage IV-S.

The final results are presented in Charts 1 and 2, which show estimated survival probabilities plotted against age for each of the 5 stages. Values on the curves in Chart 1 were determined by substituting estimates from Table 6, Model D in Equation IV; while for Chart 2 estimates from Table 6, Model A, were substituted in Equation III.

DISCUSSION

The plots of survival probability against age presented in Chart 1 offer a convenient means of estimating prognosis in childhood neuroblastoma based on the staging criteria of Evans et al. (8). They represent the best estimates possible from the 2 available series of data. Nevertheless, consideration of their applicability should take account of the various sources of bias and error inherent in their construction. These include the possibility that the 2 series studied are not necessarily representative of all children with neuroblastoma.
and the possibility that the assumed model (Model D) may not entirely represent the true situation. Unfortunately, neither of these 2 difficulties are ever amenable to perfect resolution. Even if they could be discounted completely, a considerable amount of error would remain solely due to sampling fluctuations. For example, an approximate 90% confidence interval for the probability that a Stage II patient aged 36 months at diagnosis will survive for 2 years is (0.27, 0.60); while for a Stage III patient at birth it is (0.65, 0.93).

Some encouragement regarding the representativeness of the data may be taken from the fact that the 2 series seemed comparable with respect to survival, although lack of sufficient numbers in each series prevented a detailed evaluation. This is true in spite of the fact that the treatment used in the 2 groups was dissimilar. Almost all patients entered on the 2 CCSGA protocols had surgical removal of the primary tumor, postoperative radiation therapy, and 94 of 100 received "vigorou" chemotherapy with cyclophosphamide with or without vincristine. The Philadelphia group was seen over 20 years when treatment regimens varied. In general, this group was treated less vigorously. Radiation therapy was used sparingly and chemotherapy was used only in those patients with Stage IV disease. A detailed analysis of these 2 groups of patients suggests that the therapy given had little effect upon their ultimate survival.5

While the choice of model does not seem to matter much in calculating age-adjusted stage effects, it does make a substantial difference in the estimated probabilities of survival. Chart 1 shows a steeper drop in survival probability over the 1st year or 2 of life but a tapering off of the age effect thereafter; consequently, the estimates at birth are considerably higher than those in Chart 2. Since Model D gives a better fit to the observed data, use of Chart 1 for purposes of estimating prognosis should give better overall results than Chart 2. However, the disparity between the 2, as well as the wide confidence intervals, indicates that much more data will have to be collected before the statistical estimation of prognosis becomes even moderately precise.

The analysis of Sutow et al. (10) failed to show that stage of disease, as indicated by presence or absence of metastases, had a statistically significant effect on prognosis among patients 2 years or older at diagnosis. The present study concludes that stage is important regardless of the age of the child at diagnosis. This discrepancy is due mainly to the fact that survival for the group of children with nonmetastatic disease aged 2 years or older was about twice as high in the present study. However, the trend in the data of Sutow et al. (10) was clearly in the direction of improved survival for those without metastatic disease. In view of the small numbers of patients in this category (ca. 40 in each study), the discrepancy may be more apparent than real.

The finding that age and stage both play strong roles in determining prognosis, even after adjustment for the other factor, has implications for the design of protocol studies of neuroblastoma as well as for the comparison of historical series. It suggests that efforts might be directed towards achieving balance of treatment groups with respect to both of these factors simultaneously. (Such a design has been adopted for the most recent CCSGA protocol for nonmetastatic neuroblastoma.) Likewise, it suggests that adjustments be made for both factors jointly in comparison of historical series.

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APPENDIX 1

Participants in Children's Cancer Study Group A

<table>
<thead>
<tr>
<th>Institution</th>
<th>Investigators</th>
<th>Grant no.</th>
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<tr>
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<td>CA 05436</td>
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<td>Hospital for Sick Children, Toronto</td>
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<td>L. Gilbert Thatcher, Samuel P. McCreadie</td>
<td>CA 11075</td>
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<tr>
<td>Strong Memorial Hospital, University of Rochester</td>
<td>Eugene C. Beatty</td>
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<td>Children's Mercy Hospital, Kansas City</td>
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REFERENCES


Statistical Estimation of Prognosis for Children with Neuroblastoma

Norman Breslow and Barbara McCann


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