Multivariate Analysis of Prognostic Factors in Patients with Disseminated Nonseminomatous Testicular Cancer: Results from a European Organization for Research on Treatment of Cancer Multiinstitutional Phase III Study1


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ABSTRACT

Univariate and multivariate linear logistic regression analyses of potential prognostic variables have been performed for 163 patients with disseminated nonseminomatous testicular cancer, treated with cisplatin, vinblastine, and bleomycin in a multicenter study of the European Organization for Research on Treatment of Cancer. A univariate analysis led to the following conclusions: (1) the number of prior courses of chemotherapy was the single most important factor. This model aids the physician in selecting prospectively good risk patients who are candidates for low toxicity chemotherapy and poor risk patients with whom innovative treatment should be attempted.

INTRODUCTION

With standard cisplatin combination chemotherapy, the risk of death from disseminated nonseminomatous testicular cancer is approximately 30%, including a 5% toxic death rate from these regimens (1–5). This underlines the need to define good and poor risk patients prior to treatment in order to decrease the toxicity in the first category and to intensify the treatment in the second group. Several factors have been reported as influencing the prognosis such as extent of disease (3–8), initial serum marker concentrations of BHCG,3 AFP, and LDH (8–11) or their rate of decrease during chemotherapy (12, 13), histology (14, 15), prior treatment (3, 16), treatment protocol, age, time from diagnosis to treatment (8), and performance status (11).

Since many of these variables may be interrelated, a multivariate analysis of various factors has been performed in order to determine their relative prognostic importance.

MATERIALS AND METHODS

Patients Studied. From July 1979 until March 1983, the European Organization for Research on Treatment of Cancer Genito-Urinary Tract Cancer Cooperative Group entered 214 patients with disseminated nonseminomatous testicular cancer in a randomized prospective study. None of these patients had received prior radiotherapy or chemotherapy. The patients received 4 cycles of induction chemotherapy with cisplatin, vinblastine, and bleomycin with a randomization between 100%, 90%, 80%, or 70% vinblastine. One hundred and sixty-three patients were evaluable for response. The treatment results of this study have been reported elsewhere (4).

For this analysis the patients were divided into 2 groups: CRs and those who did not achieve a complete response (no CR). CR is defined as the complete disappearance of all clinical, radiographic, and biochemical evidence of disease, which includes the results of computed tomographic scan of the chest or whole-lung tomography, computed tomographic scan of the abdomen, assays of BHCG and AFP, and debulking surgery for those patients with evidence of residual tumor after 4 cycles of induction chemotherapy in the absence of elevated markers. Patients with fibrosis, necrosis, and mature teratoma in the resected specimen were classified as CR. If there was histological evidence of residual viable cancer cells the patients were classified as partial responders, as were those with persistently elevated markers after 4 cycles. The patients’ data have been externally reviewed by the first author (G. S.) who was also the study coordinator. Histological diagnosis was based on a central review of the orchidectomy specimens by Dr. P. Spaander in 131 of the 163 cases. All cell types present were recorded whereas the diagnosis was made according to the British classification (14). For the remaining 32 patients the diagnosis of the local pathologist was accepted.

Staging of the disease was according to the Royal Marsden Hospital classification (8). However, it was also felt necessary to record the exact number and size of all metastatic lesions.

Serum tumor marker concentrations were measured in each participating institution without a central reference. Radioimmunoassay techniques were used for quantitative determination of BHCG and AFP. Serum concentrations of BHCG ≤4 ng/ml and AFP ≤16 ng/ml were considered to be normal. Serum concentrations of LDH were measured by different methods in different institutions where the upper limits of normal varied significantly. For these reasons LDH has been expressed as a numerical factor multiplied by the upper limit of normal for each institution.

All data pertain to the patient’s status immediately prior to chemotherapy.

Patient Characteristics. Patient characteristics and CR rates with regard to several of the most important prognostic factors are given in Table 1. Sixty-nine patients (42%) had a normal BHCG and 67 patients (41%) had a normal AFP. Only 38 patients (24%) were normal with respect to both markers. Ninety-seven patients (60%) had a high tumor burden (lymph node metastases ≥5 cm or lung metastases >2 cm). Malignant teratoma trophoblastic was found in 15% of the specimens and possible trophoblastic elements were seen in another 7%. Seminomatous components were observed in 16% of the specimens.

Infradiaphragmatic metastases were present in 135 patients (83%), mediastinal metastases in 18 patients (11%), supraclavicular metastases in 35 patients (22%), and lung metastases in 95 patients (58%). Hepatic metastases were observed in 8 patients (5%).

Statistical Techniques. The end point used to assess the prognostic importance of the different factors was the CR rate. The duration of survival was not retained as an end point since only 32 of 163 (20%) of the patients had died at the time of analysis.
The relative importance of the prognostic factors with regard to the CR rate was studied using a linear logistic regression model (18). This model allows many variables to be studied simultaneously (see "Appendix factors (17).

Identical factors (17). However, multivariate techniques that allow all variables to act together are required so that the relative importance of each variable can be determined.

Identification of Prognostic Factors. In order to identify the variables of potential prognostic importance, continuous variables were made discrete and a univariate analysis of each variable was carried out by comparing the CR rate for the different levels of that variable. Table 2 presents those variables which were not related to the rate of CR while those which were statistically significant are listed in Table 3. As can be seen from these tables, variables representing tumor histology, markers, and lung metastases are all highly significant.

Multivariate Analysis. Since some of the variables described above are correlated with each other, for example patients with trophoblastic elements in the primary tumor (poor prognosis) tend to have lower values of AFP (good prognosis), it can be difficult to predict the prognosis of an individual patient. Therefore, multivariate techniques that allow all variables to act together are required so that the relative importance of each variable can be determined.

Hence a linear logistic regression model was fitted using the variables given in Table 4. This includes all the variables which were significant in the univariate analyses (Table 3) and several of the clinically most important variables from Table 2. Using a step-up procedure to add variables one by one to the model, the single most important factor was \( \log_{10} (\text{BHCG}) + 1 \), the logarithm of the BHCG. The final model, using a step-up procedure to add variables one by one to the model, is given in the "Appendix" and was composed of the following variables which were all available in 154 patients. TROPH (trophoblastic elements in primary tumor): 0 = no or possible; 1 = yes/possible; 2 = yes.

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Comparisons of the CR rate for the different levels of a given factor were carried out using the classical chi-squared test for the comparison of proportions. For ordered categoral variables, Kendall's \( \tau \) and \( \beta \) were calculated as a nonparametric measure of correlation or "trend." Kendall and Spearman rank correlation coefficients were also calculated for the different levels of that variable. Table 2 presents those variables which were not related to the rate of CR while those which were statistically significant are listed in Table 3. As can be seen from these tables, variables representing tumor histology, markers, and lung metastases are all highly significant.

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The relative importance of the prognostic factors with regard to the CR rate was studied using a linear logistic regression model (18). This model allows many variables to be studied simultaneously (see "Appendix" for a description of the linear logistic model).

RESULTS

Identification of Prognostic Factors. In order to identify the variables of potential prognostic importance, continuous variables were made discrete and a univariate analysis of each variable was carried out by comparing the CR rate for the different levels of that variable. Table 2 presents those variables which were not related to the rate of CR while those which were statistically significant are listed in Table 3. As can be seen from these tables, variables representing tumor histology, markers, and lung metastases are all highly significant.

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1 = yes. ALPH (serum concentration of AFP): 0 = 0–999 ng/ml; 1 = ≥1000 ng/ml. LUNG (lung metastases): 0 = no; 1 = yes. SIXNB (size and number of lung metastases): 0 = none; 1 = 1–3 and ≤3 cm; 2 = 4–19 and ≤3 cm; 3 = ≥20 or 4–19 and >3 cm. Once these values are known for any patient, the probability of a CR can be estimated using the formulas in the “Appendix.”

Of special note is the fact that the single most important variable, LB = \( \log_{10}(\text{BHCG} + 1) \), was not retained in the final model. This is because it is highly correlated with all the other variables in the model, especially with TROPH and SIXNB. In fact, as shown in Table 5, BHCG is correlated with most of the other important prognostic factors. In contrast, AFP, which is retained in the model, is not correlated with the presence of lung metastases, nor with their size or number, and is only weakly negatively correlated with trophoblastic elements in the primary tumor. Trophoblastic elements are not correlated with the presence or absence of lung metastases, nor with their size and number. Elevated markers, tumor volume, and number of metastatic sites are correlated with AFP and are not retained in the model.

Variables other than the 4 included in the final model do not significantly increase one’s ability to predict the probability of CR.

As noted in Table 1, patients with 1–3 lung metastases and patients with lung metastases ≥2 cm in diameter have a better prognosis than patients with no lung metastases. This may be explained by the fact that 54% of the patients without lung metastases have infradiaphragmatic metastases ≥5 cm as opposed to only 20% of the patients in each of the 2 most favorable lung subgroups mentioned above. Patients with infradiaphragmatic metastases ≥5 cm have a response rate of only 56% as compared to a response rate of 84% for the remaining patients.

Risk Groups. For a given set of patient characteristics TROPH, ALPH, LUNG, and SIXNB, a patient can be assigned to one of 4 risk groups based on the predicted probability of CR calculated by the linear logistic regression model. Table 6 presents the composition of the risk groups according to the possible values of these 4 variables and the observed and predicted probabilities of CR by patient characteristics within each group. Finally the observed CR rate for all patients within each risk group is given in Table 7. It is seen that the observed CR rate ranges from 100% in risk group 1 to only 18% in risk group 4. From a clinical point of view these 4 groups may be divided into 3 risk groups: group I (=1 + 2) with a high probability of CR (89–100%), group II (=3) with an intermediate probability of CR (41%) and group III (=4) with a low probability of CR (18%).

Model Validation. Before a model can be used to assign prospective patients to risk groups based on the predicted probability of CR, it must be validated, preferably using an independent data set, in order to confirm the results and to ensure that only a small proportion of patients assigned to receive a more intensive treatment would have responded to the treatment used in the low risk group. That is, the misallocation rate to the high risk group should be low.

The European Organization for Research on Treatment of Cancer Genito-Urinary Tract Cancer Cooperative Group is currently performing 2 randomized studies of induction chemotherapy for patients with high and low volume metastases. Applying the results of our model to the very preliminary data from these studies, we find the same trend in CR rates between the various risk groups. However, the CR rates in each risk group are higher, especially in the poor prognosis patients. Since the final data are not yet available we do not have an independent data set, so that the following is based on “self-validation.”

If we require a probability of at least 0.80 (\( P \geq 0.80 \)) of predicting CR (i.e., a patient falls in risk group I) (see Table 7), then, using the data from this study, we observe the actual and predicted responses as shown in Table 8. The correct prediction of CR (sensitivity) is \( \frac{109}{110} \) (91%) and the correct prediction of not achieving CR (specificity) is \( \frac{36}{44} \) (82%). The response rate is \( \frac{119}{154} \) (77%) and the misallocation rate is \( \frac{21}{57} \) (37%), which means that 37% of the patients predicted not to achieve CR would have in fact achieved a CR.

If we require a probability of at least 0.40 (\( P \geq 0.40 \)) to predict CR (i.e., a patient falls in either risk group 1 or II) (see Table 7), then the sensitivity is \( \frac{109}{110} \) (98%), while the specificity is \( \frac{36}{44} \) (82%). However, the misallocation rate is only \( \frac{3}{111} \) (18%), which means that in this case just 18% of the patients predicted not to achieve CR would have in fact achieved CR. However, only 11 of 154 patients are predicted to not respond.

DISCUSSION

The main goal of clinical research is to decrease the toxicity of treatment regimens in good risk patients and to intensify the treatment of poor risk patients. For that reason it is of the utmost importance for physicians to be able to estimate prospectively the probability of CR in each one of their patients. The best tool for such an estimation is the linear logistic regression model since it provides an “optimal” subset of variables for use in determining a patient’s prognostic category.

Applied to the data in this study the model yielded 4 prognostic variables: TROPH (trophoblastic elements in the primary tumor, yes or no); ALPH (serum level of AFP below or above 1000 ng/ml); LUNG (lung metastases, yes or no); and SIXNB (size and number of lung metastases). On the basis of these 4 variables we can divide our patient population into 4 risk groups (Table 6), varying from a very high to a very low probability of achieving CR (Table 6). In practice one might define 3 treatments of differing intensity corresponding to the 3 risk groups in Table 7. None of the other variables listed in Table 4, when added to the model, significantly increased the predictive capability of the model.

The requirement that the probability of achieving CR is \( P \geq 0.80 \) (Table 8) yields an acceptable sensitivity (correct prediction of CR) and specificity (correct prediction of no CR); however, the misallocation rate is high (37%).

The results of any multivariate prognostic factor analysis are of course a function of the variables which are analyzed, the way in which they are analyzed, and of the end point of the analysis, i.e. CR rate, disease-free survival, or overall survival. For instance, it has not been possible to analyze the prognostic value of brain metastasis because these patients were excluded.
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Table 6 Composition of risk groups based on patient characteristics and the observed and predicted CR rates

<table>
<thead>
<tr>
<th>Risk group</th>
<th>TROPH</th>
<th>ALPH</th>
<th>LUNG</th>
<th>SIXNB</th>
<th>No. of patients</th>
<th>No. of CR observed</th>
<th>No. of CR predicted</th>
<th>P of CR</th>
</tr>
</thead>
<tbody>
<tr>
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<td>No</td>
<td>&lt;1000</td>
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<td>1</td>
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<td>24</td>
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<td>1.0</td>
</tr>
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Table 7 Response rate by risk group

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Predicted no. of CR</th>
<th>Observed no. of CR</th>
<th>No. of patients</th>
<th>Observed percentage of CR</th>
</tr>
</thead>
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<td>24</td>
<td>24</td>
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<td>41</td>
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<td>4</td>
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<td>2</td>
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<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>110</td>
<td>154</td>
<td>71</td>
</tr>
</tbody>
</table>

Table 8 Predicted and actual response if a predicted P ≥ 0.80 is required (risk group I versus II and III)

Sensitivity, $\frac{9}{10} = 81\%$; specificity, $\frac{9}{10} = 82\%$; response rate, $\frac{9}{10} = 71\%$; misallocation rate, $\frac{9}{10} = 37\%$; correct overall prediction of response, $\frac{9}{10} = 81\%$.

Predicted Actual
<table>
<thead>
<tr>
<th>No CR</th>
<th>CR</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>36</td>
<td>8</td>
<td>44</td>
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<td>21</td>
<td>89</td>
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<tr>
<td>Total</td>
<td>57</td>
<td>97</td>
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by the study protocol. In the initial phase of this analysis, using a step-up procedure, $LB = \log_{10} (BHCG + 1)$ appeared to be the single most important variable, not BETA or NBETA (Table 4). When it was decided to omit the Royal Marsden classification of lung metastases and let them take on a continuum of values with regard to size and number, $LB$ fell out of the model using a step-down procedure and $LUNG$ (lung metastases, yes/no) and SIXNB (lung metastases by size and number) remained in the model, with greater predictive power than $LB$. It became clear that for our patient population the Royal Marsden staging classification of lung metastases should be modified (Table 4, Point 22). This did not hold true for retroperitoneal metastases. When a separate category was provided for patients with infradiaphragmatic metastases larger than 10 cm (Table 4, Point 16), the variable SINFRA, while significant in a univariate analysis, was not retained by the model. However, it is striking to observe that 5 of 12 (42%) patients who relapsed from CR had large infradiaphragmatic metastases >10 cm (2 patients) or >15 cm (3 patients). SINFRA might have been retained if disease-free survival as an end point could have been used.

Investigators in the United States (10, 19) and Europe (8, 11, 20) have performed multivariate analyses with slightly different variables and end points. All models yield tumor markers and/or tumor volume as significant variables, although none of the model results is identical. In contrast to the other models, trophoblastic elements in the primary tumor appear to be a prognostic variable in this model.

The multivariate analysis of prognostic factors becomes an increasingly important method for the prospective determination of a patient’s risk category. However, due to lack of uniformity in the assessment of laboratory measurements, pathology, and tumor burden, the relative merits of the various models proposed in the literature cannot be determined. For this reason we believe that it is of urgent necessity that such techniques be standardized.

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APPENDIX

The Linear Logistic Regression Model

The linear logistic regression model (17) assumes that the relationship between the probability $P$ that a patient achieves a CR and the patient’s characteristics $x_1, x_2, x_m$ at entry into the study is given by

$$P = \frac{e^y}{1 + e^y} \quad \text{or} \quad \ln \frac{P}{1 - P} = y$$

where $y = \sum b_i x_i$ is a linear function of the patient’s characteristics, $x_0 = 1$ and the $b_i$ are the unknown regression coefficients that are estimated from the data by the technique of maximum likelihood.

The variables which were analyzed in the model and their coding are given in Table 4. Both step-up (variables are added to the model one by one) and step-down (variables are deleted from the model one by one, thus allowing a simultaneous analysis of all the variables and their interactions) methods were used.

The following model was obtained using the step-down method

$$\hat{p} = \frac{e^{\hat{y}}}{1 + e^{\hat{y}}}$$

where

$$\hat{y} = 1.9381 - 2.1327 \times TROPH - 2.2723 \times ALPH + 4.878 \times LUNG - 2.3212 \times SIXNB$$

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as an optimal estimate of the CR rate. Once the values of TROPH, ALPH, LUNG, and SIXNB (see Table 6) are known for any given patient, the above formula for \( \tilde{P} \) gives an estimate of the probability that a patient will have a CR. Risk groups can then be formed based on the value of \( \tilde{P} \).

**REFERENCES**

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