Multivariate Analysis of Prognostic Variables in Patients with Metastatic Testicular Cancer

George J. Bosl, Nancy L. Geller, Constance Cirrincione, Nicholas J. Vogelzang, B. J. Kennedy, Willet F. Whitmore, Jr., Davor Vugrin, Howard Scher, Jerome Nisselbaum, and Robert B. Golbey

INTRODUCTION

Recent advances in the therapy of patients with metastatic testicular cancer have resulted in a high proportion of survivors with long disease-free intervals (5, 9, 20). CR of all radiographic, biochemical, and clinical findings of metastatic disease occurs in 60 to 80% of patients treated with regimens in which high doses of cisplatin are used and residual disease is resected. Although this progress has been dramatic, patients who never achieve a complete remission as a result of current treatment programs. However, patients who fail to achieve a complete remission have a very poor prognosis, and nearly all die of their disease. A multivariate logistic regression analysis of several clinical variables associated with prognosis was performed using data from 171 patients treated for metastatic testicular cancer at Memorial Hospital between September 1975 and February 1981. A mathematical model was identified which correctly predicted 94% of complete remissions and 83% of all outcomes. The variables achieving statistical significance were the logarithm of the serum values of lactate dehydrogenase (p < 0.001) and human chorionic gonadotropin (p < 0.001) and the total number of sites of metastasis (p < 0.001). The model was tested against 49 patients with metastatic testicular cancer treated at the University of Minnesota Hospitals, and it correctly predicted 86% of complete remissions and 84% of all outcomes. In a highly curable disease such as testicular cancer, mathematical modeling may enable the clinical investigator to anticipate those patients who are least likely to do well. Alternate treatment strategies would be appropriate for such patients.

ABSTRACT

A majority of patients with metastatic testicular cancer achieve a complete remission as a result of current treatment programs. However, patients who fail to achieve a complete remission have a very poor prognosis, and nearly all die of their disease. A multivariate logistic regression analysis of several clinical variables associated with prognosis was performed using data from 171 patients treated for metastatic testicular cancer at Memorial Hospital between September 1975 and February 1981. A mathematical model was identified which correctly predicted 94% of complete remissions and 83% of all outcomes. The variables achieving statistical significance were the logarithm of the serum values of lactate dehydrogenase (p < 0.001) and human chorionic gonadotropin (p < 0.001) and the total number of sites of metastasis (p < 0.001). The model was tested against 49 patients with metastatic testicular cancer treated at the University of Minnesota Hospitals, and it correctly predicted 86% of complete remissions and 84% of all outcomes. In a highly curable disease such as testicular cancer, mathematical modeling may enable the clinical investigator to anticipate those patients who are least likely to do well. Alternate treatment strategies would be appropriate for such patients.

MATERIALS AND METHODS

Patient Population. Memorial Hospital is a referral center for patients with germ cell tumors. Since 1972, several chemotherapy trials (VAB 1 through 6) have been conducted establishing the drug combination activity of vinblastine, actinomycin D, and bleomycin, with and without cisplatin and cyclophosphamide (8, 15, 19, 20, 22). Regimens containing high doses of cisplatin (VAB 3 through 6) (15, 19, 20) were highly effective treatment for metastatic testicular cancer.

The charts of patients with metastatic testicular cancer treated with regimens containing high doses of cisplatin between September 1975 and January 1981 were reviewed, and clinical data prior to treatment were recorded. These data included HP, prior chemotherapy, individual organ and nodal sites of metastasis, and serum levels of LDH, AFP, and HCG. All data pertained to patient status immediately prior to chemotherapy at Memorial Hospital. Patients were considered for this study only once; i.e., a patient failing one VAB protocol and treated subsequently with another was excluded from the analysis of the second study. Patients with primary extragonadal germ cell tumors and those previously receiving high doses of cisplatin were not included in this study. The VAB 5 regimen was excluded because the majority of patients had either extragonadal germ cell tumors, prior high doses of cisplatin, or no review of HP at Memorial Hospital. Thus, all patients considered for this study were treated with either VAB 3, VAB 4, or VAB 6. A total of 135 patients had complete data sets, and an additional 36 patients had complete data sets except for serum levels of AFP. This latter group was treated between September 1975 and May 1976, a period during which the assay for AFP was not available (see below). These 171 patients constitute the data base for this analysis.

The HP of the orchiectomy specimen was used as the HP of reference, unless only a metastatic site was reviewed. At the time treatment was initiated, the slides were reviewed by members of the Department of Pathology at Memorial Hospital. These reports were reviewed retrospectively, and all cell types noted in these reports were recorded. If a specimen from the orchiectomy or a metastatic site was not reviewed by a pathologist at Memorial Hospital, the patient was excluded from this study. Embryonal carcinoma, teratoma, and choriocarcinoma were the cell types most frequently encountered. "Teratocarcinoma" reflected the presence of both embryonal carcinoma and teratoma in the tumor (13, 14). Since few patients with pure seminoma and metastatic disease
were treated with VAB regimens, seminoma was not considered as a separate variable in this study. Yolk sac tumor was reported inconsistently and also was not considered as a variable in this study.

Serum HCG and AFP levels were assayed by radioimmunoassay techniques beginning in September 1975 and May 1976, respectively. HCG was quantitatively assessed using a modification of the highly sensitive and specific double-antibody radioimmunoassay procedure of Valtukaitis et al. (17). The standard HCG for this assay was obtained from the National Institute of Arthritis, Metabolism, and Digestive Diseases. The antiserum against the purified β-subunit of HCG was prepared in rabbits. A value less than 2 ng/ml was considered normal. The AFP was assayed with reagents kindly provided by Wampole Laboratories, a division of Carter Wallace (Cranbury, N. J.). A specific antiserum to purified AFP from pooled human fetal serum was prepared in rabbits. A serum value of less than 40 ng/ml was considered normal. Carcinoembryonic antigen was measured by the CEA-Roche (Nutley, N. J.) method, and a value of less than 5 ng/ml was considered normal. Normal values for LDH were less than 230 units/liter.

CR was defined as the complete disappearance of all clinical, radiographic, and biochemical findings of testicular cancer after either chemotherapy alone or chemotherapy and surgical resection of residual tumor. All patients not achieving a CR were called incomplete responders; this group included both patients with a partial response and those with no response.

Statistical Analysis. The likelihood, or probability, that a patient with a metastatic germ cell tumor achieves a CR was assessed as a function of certain patient characteristics using the technique of logistic regression (1). The characteristics included were those found significant in univariate analyses as well as others considered by previous investigators (2, 5, 6, 11, 13, 20, 21). Marker values, treatment protocol, HP, prior treatment history, and sites of metastasis were considered in an attempt to improve the logistic regression model. Marker values and prior treatment history each underwent 3 separate analyses; treatment protocol and HP remained constant in each analysis (Table 1). The logarithm (Base 10) of the actual value of an individual marker was considered for this analysis because of the considerably skewed distribution of marker values. The logarithmic function reduces this skew (4). The addition of (+1) before logarithmic transformation eliminates the possibility of log (0) for which no value exists and precludes the generation of negative values for assays between 0 and 1.

Two definitions of extent of disease were used in an attempt to determine if a nodal metastasis in the retroperitoneum was an independent predictor of response in addition to the total number of sites of metastasis outside the retroperitoneum (Table 2). In one analysis, ABDMET was assessed separately from other sites of metastasis (SUMMET); in another analysis, only TOTMET was considered. The organ and nodal metastatic sites included lung, mediastinum, supraclavicular lymph nodes, liver, retroperitoneal lymph nodes, bone, and brain.

Let denote the probability that Patient responds eventually, i.e., achieves a CR either to chemotherapy alone or to chemotherapy plus surgery. We assume:

\[ p_i = \exp h_i(1 + \exp h_i) \]  

where is a linear function of several variables of Patient and \( e = 2.714 \ldots \) (the base of natural logarithms) raised to the power . The coefficients of the linear function are assumed unknown and are estimated from the data for a group of patients. The technique of estimation of the coefficients, known as "maximum likelihood," makes no assumptions about the distribution of the variables used in the expression (1).

Thus, we considered discrete variables, such as presence or absence of choriocarcinoma (0 = absence, 1 = presence), along with variables, such as value of the serum LDH prior to treatment, which could take on a continuum of values (see Tables 1 and 2). The method of logistic regression was chosen since it is better suited to predictor variables which are not normally distributed than is the method of discriminant analysis (1). Spearman rank correlation coefficients between variables were also determined (7).

RESULTS

Multivariate Analysis. Several logistic models were developed using the variables listed in Tables 1 and 2. Models which considered the marker values as either elevated or not and models using the actual marker values had less explanatory power than did models using the logarithmic function of the actual marker values. Log (LDH + 1), log (HCG + 1), and SUMMET were the only significant predictor variables.AFP and retroperitoneal metastases consistently failed to achieve statistical significance as predictor variables as did HP, prior treatment history, and treatment protocol.

The next analysis was performed using only the logarithmic marker functions and TOTMET. Previous chemotherapy, treatment protocol, HP, and the variables separating abdominal and extraabdominal sites of metastasis were excluded since they had repeatedly failed to improve the model. In this analysis of only 4 variables, AFP again failed to achieve statistical significance. Log (LDH + 1), log (HCG + 1), and TOTMET each achieved statistical significance. This model, using TOTMET, was a slight improvement over models using SUMMET and ABDMET.

### Table 1
Prognostic variables considered for multivariate analysis

<table>
<thead>
<tr>
<th>A. Markers (AFP, HCG, LDH, carcinoembryonic antigen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elevated or normal marker value</td>
</tr>
<tr>
<td>2. Actual marker value</td>
</tr>
<tr>
<td>3. Log (marker value + 1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Treatment protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VAB 3</td>
</tr>
<tr>
<td>2. VAB 4</td>
</tr>
<tr>
<td>3. VAB 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presence or absence of choriocarcinoma</td>
</tr>
<tr>
<td>2. Presence or absence of embryonal carcinoma</td>
</tr>
<tr>
<td>3. Presence or absence of teratocarcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Prior treatment history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Some vs. no prior treatment</td>
</tr>
<tr>
<td>2. 0 or 1 drug vs. 2 or more drugs</td>
</tr>
<tr>
<td>3. 0, 1, or 2 drugs vs. 3 or more drugs</td>
</tr>
</tbody>
</table>

| E. Sites of metastasis (see Table 2) |

### Table 2
Analysis of site of metastasis as a predictor of response

1. **ABDMET**
   - Either no retroperitoneal metastasis
   - Or nonpalpable retroperitoneal metastasis
   - Or palpable retroperitoneal metastasis

2. **SUMMET**
   - Either no sites of metastasis, excluding retroperitoneum and elevated markers
   - Or one site of metastasis, excluding retroperitoneum and elevated markers
   - Or 2 or more sites of metastasis, excluding retroperitoneum and elevated markers

3. **TOTMET**
   - Either no sites of metastasis, including retroperitoneal and excluding elevated markers
   - Or one site of metastasis, including retroperitoneal and excluding elevated markers
   - Or 2 or more sites of metastasis, including retroperitoneal and excluding elevated markers

*Note: ABDMET + SUMMET = TOTMET.
Since AFP had not been determined prior to May 1976, an additional 36 patients were available for analysis for whom complete data sets were available except for AFP. These additional patients were treated with the VAB 3 regimen between September 1975 and May 1976, prior to our quantitative AFP method. With this increased data set, a last analysis was performed using only the logarithmic transformations of the actual values of LDH and HCG and TOTMET. Using Equation A, the best single-function \( h_1 \) based on the aforementioned variables was

\[
\begin{align*}
  h_1 &= 8.514 - 1.973 \log (LDH + 1) - 0.530 \log (HCG + 1) - 1.111 \text{TOTMET}
\end{align*}
\]

This model was based upon data on 171 patients for whom data on all 3 variables were available. TOTMET equals 0, 1, or 2, depending on whether there are zero, one, or 2 or more sites of metastasis. The negative coefficients imply an inverse relationship between each variable and the probability of a CR. The variables in Equation B appear in order of their explanatory power; i.e., \( \log (LDH + 1) \), which contributed the most to the likelihood function, is listed first.

Each variable in Equation B contributed to the model in a statistically significant manner (\( p < 0.001 \)) (Table 3). The variables were somewhat dependent as measured by the Spearman rank correlation (Table 4). No other variable contributed at \( p < 0.05 \). This implies that based on these data neither protocol, nor previous chemotherapy (excluding prior cisplatin) were significant predictors for CR. Table 5 shows the probability of CR for previous carcinoembryonic antigen or AFP, nor tumor histology, nor pretreatment HCG and LDH were <3 ng/ml and <330 units/liter, respectively. The actual responses of 49 consecutive previously untreated patients were compared against responses predicted by the model described in Equations A and B using clinical data obtained prior to chemotherapy. Normal values for HCG and LDH were <3 ng/ml and <330 units/liter, respectively. Although these normal values were slightly different from those at Memorial Hospital, the logarithmic function minimized this discrepancy. Our model correctly predicted 36 of 42 (86%) of patients actually achieving a CR and 41 of 49 (84%) of all actual patient responses (Table 8). These results suggest the general applicability of such a model.

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \chi^2 )</th>
<th>d.f.</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log(LDH + 1)</td>
<td>28.7</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log(HCG + 1)</td>
<td>14.7</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOTMET</td>
<td>9.1</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All 3 variables</td>
<td>52.5</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 4

Correlation coefficients between pairs of the 3 variables best predicting CR (Spearman rank correlation)

<table>
<thead>
<tr>
<th>Variable pair</th>
<th>Correlation coefficient</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTMET with LDH</td>
<td>0.3779</td>
<td>0.001</td>
</tr>
<tr>
<td>TOTMET with HCG</td>
<td>0.2443</td>
<td>0.002</td>
</tr>
<tr>
<td>LDH with HCG</td>
<td>0.3639</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Analysis of an Independent Data Set

The value of such a model can also be judged by testing it against an independent data set. Patients treated at the University of Minnesota Hospital for metastatic testicular cancer receive vinblastine, bleomycin, and cisplatin (5). The actual responses of 49 consecutive previously untreated patients were compared against responses predicted by the model described in Equations A and B using clinical data obtained prior to chemotherapy. Normal values for HCG and LDH were <3 ng/ml and <330 units/liter, respectively. Although these normal values were slightly different from those at Memorial Hospital, the logarithmic function minimized this discrepancy. Our model correctly predicted 36 of 42 (86%) of patients actually achieving a CR and 41 of 49 (84%) of all actual patient responses (Table 8). These results suggest the general applicability of such a model.
tases was a predictor variable. Other staging systems attempt to subclassify the extent of disease based on arbitrary determinations of organ tumor bulk (16). Provided that individual metastatic sites are noted (see "Methods"), our data suggest that numerous anatomical substages are not necessary, probably because of the interdependence that exists among the 3 predictor variables. The model accurately predicted the responses of patients with metastatic testicular cancer at the University of Minnesota. This suggests that the patient characteristics, the disease process, and the treatment plan were similar and that the model can be applied at other institutions. The chemotherapy regimens failed to achieve statistical significance. This implies that there were no major differences between regimens using high doses of cisplatin and that factors relating to the bulk of disease are far more important in determining responses than are relatively minor alterations in dose and schedule of drugs common to each regimen. Lastly, LDH values are central to this model, confirming its value as a tumor marker and the need to monitor it closely along with HCG and AFP.

Performance status was not considered as a variable in this study for a variety of reasons. Most patients had a high performance status prior to therapy. The variables considered for analysis were objective; the performance status is a subjective appraisal of a patient's functional status. This subjectivity varies from one physician to another, and at least 8 physicians cared for patients over the years. Intensive therapy is usually given to patients with metastatic testicular cancer despite their performance status because of the highly responsive nature of the disease. The model is not intended to replace clinical judgment. Rather, we feel that it can complement the physician's subjective assessment with an objective measure of the likelihood of a complete remission based on clinical data obtained prior to starting treatment.

We believe that future progress in the management of patients with metastatic testicular cancer will depend on the study of innovative methods of treatment. Studies which attempt to reduce immediate and delayed toxicity are crucial to the management of patients with a good prognosis. Indeed, delayed toxicity is now being recognized (18), and much recent work has been dedicated to dosage reduction and drug elimination (9, 10). However, for the patient with a poor prognosis, the goal must be to design more efficacious therapy. If the patients in this study had been chosen for the investigation of a new treatment plan based on the likelihood that they would or would not eventually achieve a CR, then 35 patients would have received a new treatment strategy. With standard treatment methods, only about 20% of these would have achieved a CR, a percentage no better than that for VAB 1 (22). It would be entirely reasonable to test a new treatment plan in these patients.

The physician-investigator faces 2 problems with a new treatment strategy. The first is to provide the best treatment for a given patient, and the second is to design the study so that a meaningful improvement in response can be detected. In a disease for which therapy is generally successful, mathematical modeling can enable the clinical investigator to address both issues: (a) the testing of a new treatment strategy can be limited to patients least likely to do well. This will spare patients who are likely to respond to standard treatment methods the potential toxicities of new treatment; (b) if new treatment is better than standard therapy, then detection of this improvement is more likely since the result will not be diluted by the responses of

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**DISCUSSION**

The treatment of patients with metastatic germ cell tumors of the testis has improved dramatically over the past decade (2, 5, 9). However, a high response and cure rate tend to obscure the very poor prognosis of patients who do not achieve a CR. Better treatment methods are needed in order to improve the response and ultimately the survival of patients with a poor prognosis. Ideally, a new treatment plan should be evaluated first in those patients with a poor prognosis, and standard therapy should be given to patients with a good prognosis. This consideration led us to multivariate statistical analysis in an attempt to predict response prior to initiating therapy.

Many variables were considered as potential predictors of CR to combined-modality treatment. In a previous report using data on only a subset of patients (those on the VAB 3 and 4 protocols), we found that elevated serum values of AFP, SUMMET, and ABDMET were the best predictors of CR (3). However, in mathematical modeling, the statistically significant variables are a function of the data used to generate the model. Therefore, the additional data on patients from the VAB 6 study and the reduction of the skewed distribution of marker values by logarithmic transformation had the effect of changing the model. In our model with the most explanatory power, log (LDH + 1), log (HCG + 1), and TOTMET were the only statistically significant predictors of CR. Nevertheless, neither the model reported here nor the one reported earlier (3) predict an incomplete response with a sufficient degree of accuracy. Other variables not considered by us, or perhaps variables not yet known, may improve predictability of all responses in this disease.

The data also show that serum values of LDH and HCG and the extent of disease are interrelated. LDH is an ubiquitous enzyme possessed by all cells; thus, a relationship between serum LDH and extent of disease is not surprising and is consistent with previously published data (6). However, when HCG is produced by a germ cell tumor, it is usually the product of a distinct subset of cells; this has been demonstrated clearly by immunoperoxidase studies (12). It may be that cells producing HCG are relatively less sensitive to treatment than are cells that either produce AFP or do not produce any specific known tumor marker substance. It is interesting to note that men with pure choriocarcinoma, fortunately very rare and invariably producers of large amounts of HCG, have a very poor prognosis.

The variables in this model were carefully defined. "Prior chemotherapy" failed to reach statistical significance as a predictor variable, but the definition did not include cisplatin. The model, therefore, most appropriate for patients who are previously untreated. We found that the total number of sites with metastases was a predictor variable. Other staging systems attempt to subclassify the extent of disease based on arbitrary determinations of organ tumor bulk (16). Provided that individual metastatic sites are noted (see "Methods"), our data suggest that numerous anatomical substages are not necessary, probably because of the interdependence that exists among the 3 predictor variables. The model accurately predicted the responses of patients with metastatic testicular cancer at the University of Minnesota. This suggests that the patient characteristics, the disease process, and the treatment plan were similar and that the model can be applied at other institutions. The chemotherapy regimens failed to achieve statistical significance. This implies that there were no major differences between regimens using high doses of cisplatin and that factors relating to the bulk of disease are far more important in determining responses than are relatively minor alterations in dose and schedule of drugs common to each regimen. Lastly, LDH values are central to this model, confirming its value as a tumor marker and the need to monitor it closely along with HCG and AFP.

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**Table 8**

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Does not respond eventually</th>
<th>Responds eventually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Correct prediction</td>
<td>0.84</td>
<td>0.71</td>
</tr>
<tr>
<td>Correct prediction of not responding eventually</td>
<td>0.86</td>
<td>0.66</td>
</tr>
</tbody>
</table>

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*G. J. Bos*
patients with a good prognosis.

We believe that this model will permit accurate stratification of patients with metastatic testicular cancer for future clinical trials.

ACKNOWLEDGMENTS

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REFERENCES


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