Stat 565 **Assignment 4** **Fall 2005**

Reading Assignment: Collett, Chapters 3, 4 and 8

Written Assignment: Due in class October 26

Exam: The first exam will be held on Thursday, October 27 from 7:30-9:30 a.m. in a place to be announced

1. In a study of the effectiveness of two types of bone marrow transplants for non-Hodgkin's lymphoma and Hodgkin's lymphoma patients, times to death or relapse (in days) after transplant were recorded. There were 23 non-Hodgkin's lymphoma (NHL) patients, with 11 patients receiving an allogenic (Allo) transplant from an HLA-matched sibling donor and 12 patients receiving an autologous (Auto) transplant. There were 20 Hodgkin's lymphoma (HOD) patients, with 5 patients receiving an allogenic (Allo) transplant from an HLA-matched sibling donor and 15 patients receiving an autologous (Auto) transplant.

   a) Treating the four combinations of types of lymphoma and types of transplant as four separate groups, describe a proportional hazards model and a coding of covariates that would allow the investigator to test for any difference in survival functions for any of the other three groups against the NHL Allo baseline group,

   b) Specifying the NHL Allo group as the baseline group, describe a proportional hazards model and a coding of covariates that would allow the investigator to test for no interaction between type of transplant and disease type by testing that a particular coefficient is zero.

   c) Suppose we have the following hazard functions for the four groups:

   $h(t|\text{NHL Allo}) = h_0(t)$

   $h(t|\text{HOD Allo}) = h_0(t)\exp(2)$

   $h(t|\text{NHL Auto}) = h_0(t)\exp(1.5)$

   $h(t|\text{HOD Auto}) = h_0(t)\exp(0.5)$

   What are the coefficients, for your model in part (b)?

2. The data in table D.2 on page 365 in Collett's book, gives times to first recurrence of a tumor in bladder cancer patients. These data come from a randomized clinical trial conducted by the Veteran's Administration cooperative Urological Research Group. Patients with superficial bladder tumors first had their tumors removed. They were next randomized to either a placebo or a chemotherapeutic agent called thiotepa. The initial number of tumors and the diameter of the largest tumor in each patient were recorded at the time of randomization to treatment. The response is time to first recurrence of a tumor, in months. Times for patients who had not experienced a recurrence by the end of the follow-up period are right censored.

The data are posted in the file bladder.txt in the assignment section of the course web page. SAS code for reading the file and fitting a particular proportional hazards model is posted in the file bladder1.sas. R-Plus code for reading the data into a data frame and fitting a particular proportional hazards model is posted in the file bladder1.R. You should be able to modify one of files to obtain answers to the following questions. There are 86 lines in the data file, one for each subject, with the values for six variables on each line in the following order.

Patient	Patient identification code (1-86)
Time	Time to first recurrence of a bladder tumor (months)
Status	Censoring Status (0 = censored, 1 = actual time)
Treat	Treatment group (1 = placebo, 2 = thiotepa)
Init	Initial number of tumors
Size	Diameter of largest initial tumor (in cm)

(a) First fit a Cox proportional hazards model using the treatment factor as the only covariate. To do this, create a new variable.

$$x_1 = \begin{cases} 0 & \text{placebo} \\ 1 & \text{treated with thiotepa} \end{cases}$$

Then the hazard function for the i-th individual is $h_i(t) = h_0(t)e^{\beta_1 X_{1i}}$.

(i) Report the partial likelihood estimate of β_1 and its standard error.

(ii) Report an estimate of exp(β_1) and interpret this quantity in the context of this bladder cancer study.

(iii) Report an approximate 95% confidence interval for exp(β_1) and interpret the confidence interval.

(b) Fit the following Cox proportional hazards model:

$$h_i(t) = h_0(t)e^{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}}$$

where X_{2i} is the initial number of tumors and X_{3i} is the diameter of the largest initial tumor for the i-th patient.

(i) Report partial likelihood estimates of β_1, β_2, β_3 and their standard errors.

(ii) Test the null hypothesis $H_0 : \beta_1 = \beta_2 = \beta_3 = 0$. Report p-values for the partial likelihood ratio test, the score test, and the Wald test. Briefly describe how each of those test statistics is evaluated (formulas are not needed to answer this).

(iii) After adjusting for the number of initial tumors and the diameter of the largest initial tumor, is there a significant treatment effect? Use $a = .05$ for your Type I error level.

(iv) Report estimates of $\exp(\beta_1)$, $\exp(\beta_2)$ and $\exp(\beta_3)$ and interpret these quantities in the context of this bladder cancer study.

(v) Construct a 95% confidence interval for $\exp(\beta_1)$) and compare it with the confidence interval in (iii) of part (b). Before seeing the results of the analysis, which confidence interval would you have expected to be wider? Explain.

(c) Plot estimates of the survival functions for time to first recurrence of a tumor in bladder cancer patients for patients treated with placebo and patients treated with thiotepa. Produce one set of curves for bladder cancer patients with one initial tumor of size 2 cm. Produce another set of curves for bladder cancer patients with one initial tumor of size 6 cm. Try to put all four curves on the same plot.

(d) Using the plot from part (c), estimate the median time to tumor recurrence for patients treated with the placebo and patients treated with thiotepa who had one initial tumor of 6 cm in diameter.

(e) Using a Cox proportional hazards model, is there any evidence of interaction between the treatment factor and either the number of initial tumors or the diameter of the largest initial tumor? Explain.

(f) Search for and report results from the model you think best fits these data. Interpret the effects of treatment with thiotepa on time to bladder tumor recurrence for the model you select.