Analysis of Treatment of Carcinoma of the Oropharynx

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1 Introduction

1.1 The Data

The data set used for all of the analysis can be found at http://inside.mines.edu/∼wnavidi/math439439/project/pharynx.dat. Data was collected during a 1980's clinical trial by the Radiation Therapy Oncology Group in the US. The study contained 195 patients (53 of which were censored) who were randomly assigned into one of the two treatment groups, radiation therapy alone or radiation with a chemotherapeutic agent. Also the censoring events are random. All of the variables are as follows:

Case Case number
Inst Participating institutions
Sex: 1 = Male, 2 = Female
Tx: Treatmentents given to patient: 1 = radiation, 2 = radiation and chemotherapy
Grade: The amount of abnormality in cells within the tumor (1=well differentiated, 2=moderately differentiated, 3=poorly differentiated, 9=missing)
Age: Age of patients in study at the time of diagnosis
Cond: Overall condition/health the patient is in when being treated (1=no disability, 2=restricted work, 3=requires assistance with self care, 4=bed confined, 9=missing)
Site: Site in the mouth where the tumor is located (1=faucial arch, 2=tonsillar fossa, 3=posterior pillar, 4=pharyngeal tongue, 5=posterior wall)
t_stage: Tumor size (1=primary tumor measuring 2 cm or less in largest diameter, 2=primary tumor measuring 2 cm to 4 cm in largest diameter with minimal infiltration in depth, 3=primary tumor measuring more than 4 cm, 4=massive invasive tumor)
n_stage: Whether or not tumor exits in the lymph nodes. (0=no clinical evidence of node metastases, 1=single positive node 3 cm or less in diameter, not fixed, 2=single positive node more than 3 cm in diameter, not fixed, 3=multiple positive nodes or fixed positive nodes)
Entry Date: Date patients entered study.

1.2 Question of Interest

The primary question is whether the treatment (radiation therapy with a chemotherapeutic agent) is more effective on the survival time than just radiation therapy. Potential confounders and effect modifiers include participating institution, Sex, Grade, Age, Condition, site, T_stage, and N_stage.

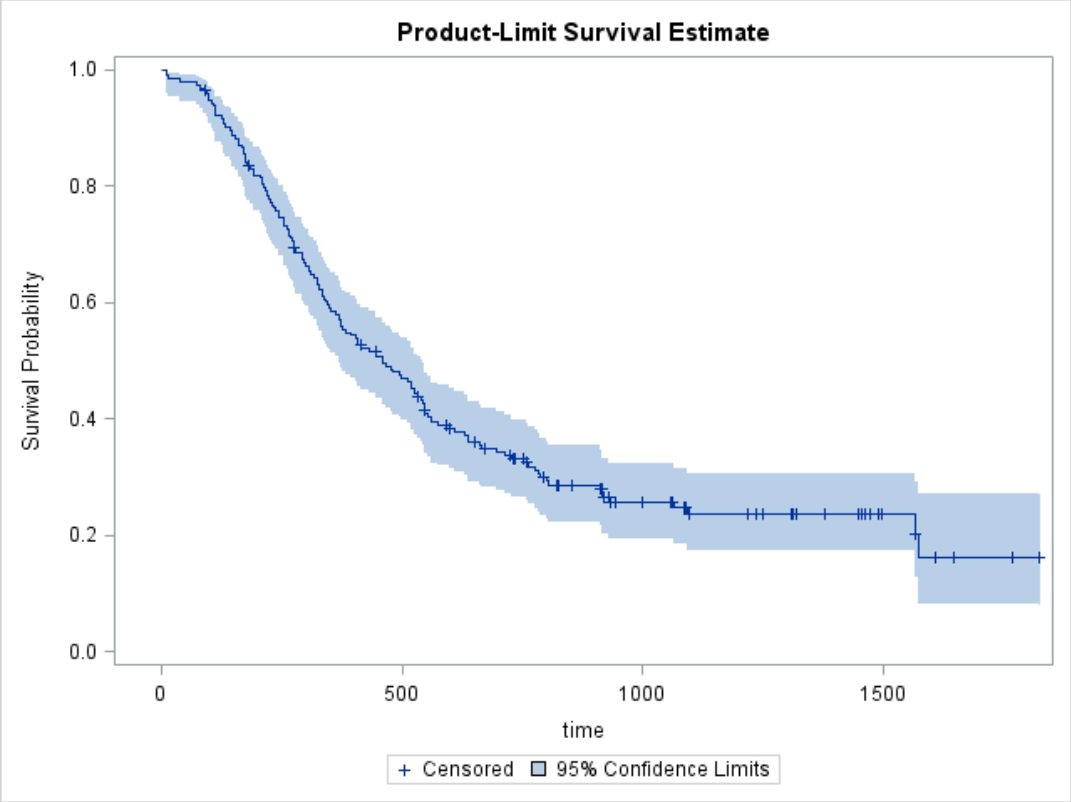
2 Preliminary Steps to Building the Model

2.1 Kaplan-Meier estimator

The Kaplan-Meier estimator is the standard technique to estimate the survival function. It is defined as:

$$\hat{S}(t) = \prod_{t_i \leq t} (1 - \frac{d_i}{Y_i})$$

The ouput below is our estimate for the survival function with a 95% confidence bound (Appendix 1.1):



The output also tells us that the mean survival time was 674.3 days, and the median was 461 days, suggesting that the data is skewed to the right.

2.2 Logrank Test

To test whether the radiation treatment and the radiation with chemotherapy treatment have the same hazards, we will use the two-sample Logrank test which is defined by the following hypothesis test:

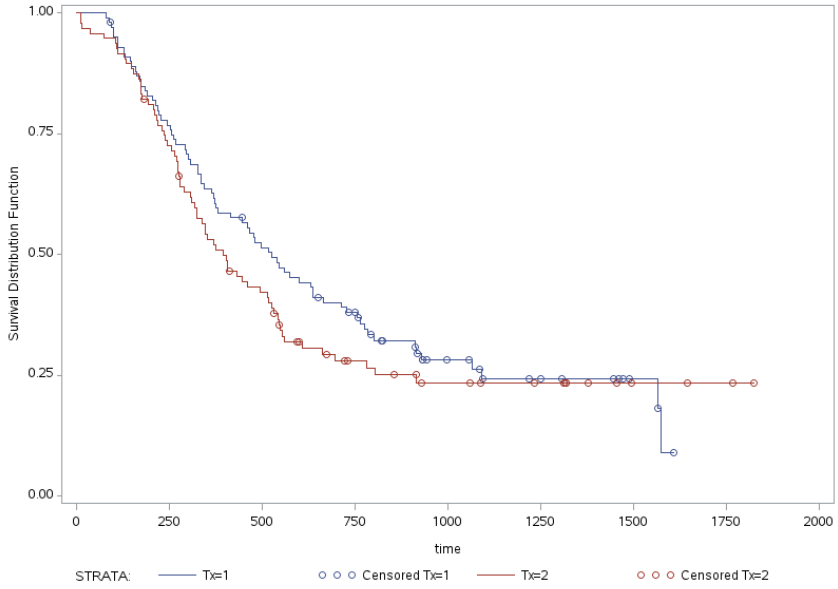
$$H_0 : \lambda_0(t) = \lambda_1(t)$$

$$H_1 : \lambda_0(t) \neq \lambda_1(t)$$

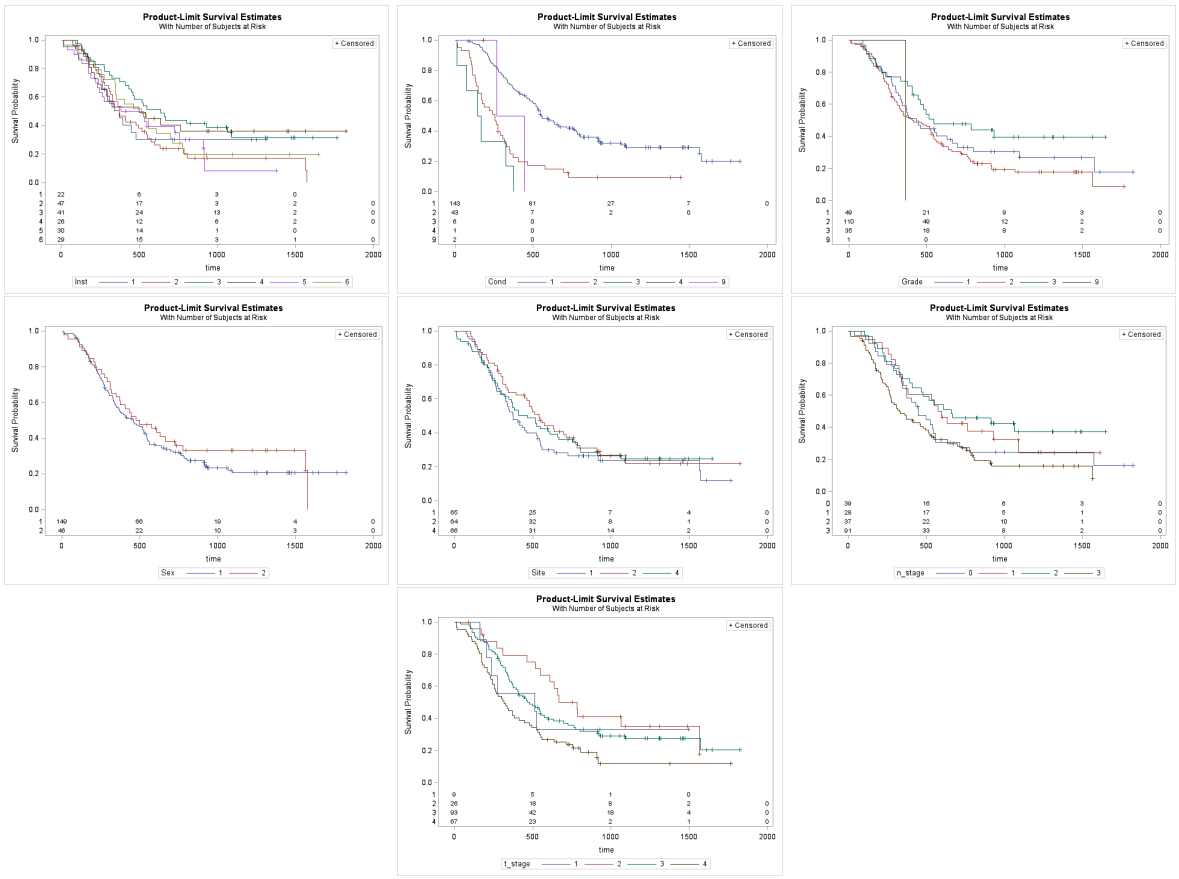
The Logrank test is often used to test an assumption that the proportional hazards, meaning that the hazard for one group is scaled by a constant, i.e.

$$H_0 : \lambda_0(t) = \beta\lambda_1(t)$$

Preforming this test in SAS, gives us a p-value of 0.3358, indicating that we fail to reject our null hypothesis that the hazards are different. This is an indication that we can assume the hazards are proportional. Also this shows us that the difference in the effects of the treatments are likely insignificant. (Appendix 1.2)



We will now preform the same Log-rank test on each parameter individually.



The variables that gave us significant p-values when the Logrank test was preformed were Condition ($p \leq 0.001$), t_stage ($p = 0.0125$), and n_stage ($p = 0.0122$) (Appendix 1.2). This indicates that these are variables we can expect to be significant when we do a multivariate model.

3 Cox Proportional Hazards Model

3.1 Introduction

In order to take into account all of the variables and see what kind of affect this would have on survival, we will first check the Cox proportional hazards model. The model is defined as:

$$\lambda_z(t) = \lambda_0(t)e^{z^T\beta}$$

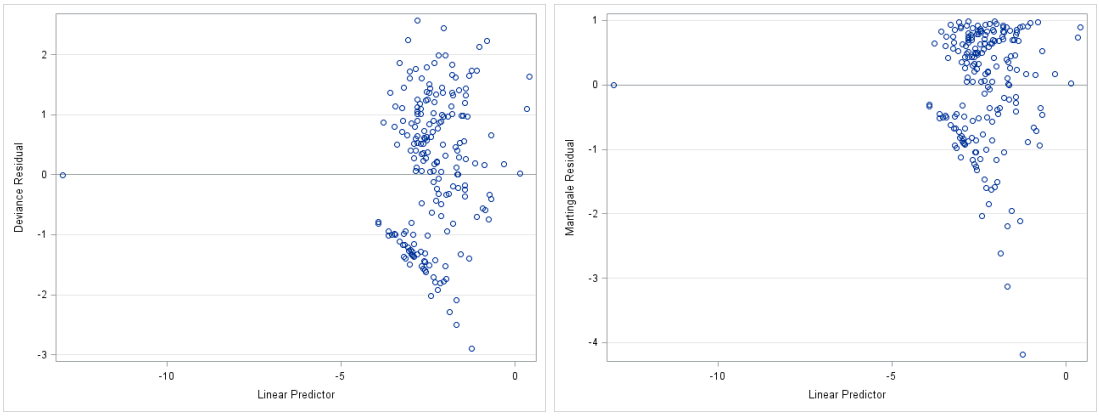
where $\lambda_0(t)$ is called the baseline hazard. z is the value of the different covariates. And β represents vector of the different parameters.

A main assumption of the model is that the hazard functions are proportional over time. For example, if smokers have twice the risk of heart disease than non-smokers at the age of 40, then they have the same risk at any other age. The Logrank test we preformed earlier shows us that it is satisfactory to make this assumption.

3.2 Other Model Assumptions

As a first step we wanted to test the treatment variable by itself to see if it was significant because our question is based upon the two treatments. We found that treament had a p-value=0.3366, which is insignificant (Appendix 2.3). Which we will investigate further in the follwing sections.

Now we want to check for outliers using the deviance residuals and the martingale residuals. The plot for these is shown below (code refrenced in Appendix 1.3)



We see that all the data is within 3 standard deviations, so we can conlcude there are no outliers.

We will also assume that the functional form of the continuous and the covariates have a linear form. The only continuous variable we have is age, and we can assume that this is linear.

Moving forward, we will construct our model using both backward and forward selection and look for possible interactions.

3.3 Stepwise Selection-Backward method

The first step was to run the model with all the variables in it, and then taking out the variables that are insignificant. After running the full model we found that institution was highly insignificant with p-values ranging from 0.2195-0.9988, along with site with p-values ranging from 0.6945-0.9246. Also, the institutions shouldn't have an effect on they type of treatment as the treatment methos were held constant throughout the study. We re-ran the model without those two variables and found treatment became slightly more significant but other variable such as condition that had p-values ranging from 0.0971 to 0.9824. Treatment once again became slightly more significant, giving a p-value of 0.2609. Grade became insignificant with p-values ranging from 0.4218-0.6998. So we removed grade, which decreased the treatment significance and made sex more insignificant thus we took it out. In the next step we took out age since it had a large p-value as well (reference appendix 2.1). Thus with the remaining variables we determined our model would be as follows:

$$\lambda_1(t) = \lambda_0(t)\exp(\text{treatment} * x_1 + \text{n-stage} * x_2 + \text{t-stage} * x_3)$$

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Tx	1	1	-0.13892	0.17069	0.6624	0.4157	0.870	Tx 1
n_stage	0	1	-0.31274	0.22878	1.8687	0.1716	0.731	n_stage 0
n_stage	1	1	-0.56101	0.26292	4.5530	0.0329	0.571	n_stage 1
n_stage	2	1	-0.48855	0.26551	3.3858	0.0658	0.614	n_stage 2
t_stage	1	1	-0.39182	0.45202	0.7514	0.3860	0.676	t_stage 1
t_stage	2	1	-0.70033	0.31137	5.0588	0.0245	0.496	t_stage 2
t_stage	3	1	-0.36377	0.19107	3.6248	0.0569	0.695	t_stage 3

3.4 Checking for Interactions

Now that we have an idea what should be included in our final model, we will test to see if there are any interactions between our final two parameters. We tested the interaction between treatment and n_stage, and between treatment and t_stage. We found that there were no significant interactions, therefore we will not include any in our final model.

3.5 Stepwise Selection-Forward method

After constructing our model using the Backward method, we decided to compare this model to the Forward selection method. We began with the sample size testing, where we tested treatment against all categorical variables. We wanted to make sure there was a large enough sample size in each of the categorical variables(refer to Appendix 2.2). We found Treatment with Grade 9, Treatment with Condition 3, 4, and 9, were small with less than three people. The rest of the groups were large enough so we continued and begun construction the model, keeping the small sample sizes in mind, using stepwise selection. Here we began with treatment as our base for the model, then compared it individually to each variable. We found that only n_stage and t_stage were significant after we ran though all the other variables. Then we compared compared them together within the same model and found that they were still significant. This confirms our result from the backward method. Thus from here we concluded our final model was the same as in the backward method.

4 Accelerated Failure Time Model

4.1 Introduction

The accelerated failure time model is used when the assumption for the hazards ratio being proportional is not met. This model is used when the survival time accelerates by a constant factor when comparing the different covariates. There are many different distributions that can be used within this model such as the Exponential, Weibull, Lognormal, log-logistic, etc. We chose to use the accelerated failure time model with the Weibull distribution to compare this to our Cox Proportional Hazards model.

4.2 Implementation

Here we implemented the Accelerated failure time model by including all of the covariates and then using the backwards stepwise selection to reduce the model (see Appendix 3.1). We removed site first, then institution, grade, age, sex, condition individually based on their high level of p-values. This left us with treatment, t_stage, and n_stage, which was the exact same as our Cox model.

Type III Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
Tx	1	0.5182	0.4716
t_stage	3	8.6382	0.0345
n_stage	3	7.3121	0.0626

Analysis of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	6.0528	0.1492	5.7604	6.3453	1645.42	<.0001
Tx	1	1	0.1071	0.1488	-0.1845	0.3987	0.52	0.4716
Tx	2	0	0.0000	.	.	.	.	.
t_stage	1	1	0.3900	0.3964	-0.3869	1.1670	0.97	0.3251
t_stage	2	1	0.6970	0.2699	0.1681	1.2259	6.67	0.0098
t_stage	3	1	0.3783	0.1667	0.0515	0.7050	5.15	0.0233
t_stage	4	0	0.0000	.	.	.	.	.
n_stage	0	1	0.3050	0.1974	-0.0820	0.6920	2.39	0.1224
n_stage	1	1	0.4672	0.2299	0.0166	0.9177	4.13	0.0421
n_stage	2	1	0.4545	0.2316	0.0006	0.9084	3.85	0.0497
n_stage	3	0	0.0000	.	.	.	.	.
Scale		1	0.8720	0.0594	0.7630	0.9965		
Weibull Shape		1	1.1468	0.0781	1.0035	1.3106		

When we compare this with our Cox model, we see that the treatment became slightly more insignificant with the other covariates having similar levels of significance.

5 Final Model and Conclusion

After analysis of all the different covariates, our final model takes the form of the Cox proportional hazards model

$$\lambda_1(t) = \lambda_0(t)\exp(\text{treatment} * x_1 + \text{n-stage} * x_2 + \text{t-stage} * x_3)$$

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Tx	1	1	-0.13892	0.17069	0.6624	0.4157	0.870	Tx 1
n_stage	0	1	-0.31274	0.22878	1.8687	0.1716	0.731	n_stage 0
n_stage	1	1	-0.56101	0.26292	4.5530	0.0329	0.571	n_stage 1
n_stage	2	1	-0.48855	0.26551	3.3858	0.0658	0.614	n_stage 2
t_stage	1	1	-0.39182	0.45202	0.7514	0.3860	0.676	t_stage 1
t_stage	2	1	-0.70033	0.31137	5.0588	0.0245	0.496	t_stage 2
t_stage	3	1	-0.36377	0.19107	3.6248	0.0569	0.695	t_stage 3

The main question we wanted to answer was if there was a difference in survival times for two different treatments (radiation therapy, and radiation with chemotherapy). We started off by getting an estimate for each covariate's affect on the survival function with the Kaplan-Meier estimate. We saw that treatment was insignificant, while t_stage, n_stage, and the condition were significant. This gave us a reasonable hypothesis of what would be significant when we did a multivariate model.

The two types of models we considered were the Cox Proportional Hazards model and the Accelerated Failure Time model. We were able to verify the assumption that the hazards are proportional (through the Logrank test), therefore the Cox model was satisfactory. Through stepwise selection, the final covariates in our model were the treatment, n_stage, and t_stage. We had to leave the type of treatment in the model because it was our main focus, even though it was insignificant through the entire process. When we ran a stepwise regression model in SAS we found that treatment was left out of the final model do to it's insignificance.

Therefore it is reasonable that there is not a significant difference between the two treatments. Which makes sense as the chemotherapy drug was taken in correlation with the radiation treatment. The chemotherapy drug did not seem to make a difference in the survival times of those patients who received it. Thus the main factors that contribute to the patients survival time is the size of the tumor and whether the tumor is in the lymph nodes.

Appendices

```
1.0
#-----Data entry and read-in-----#
data pharynx;
infile "pharynx.dat" firstobs=2;
input Case Inst Sex Tx Grade Age Cond Site t_stage n_stage entrydt status time;
run;

1.1
#-----95% Confidence Interval for Kaplan-Meier-----#
proc lifetest method=km plots=s(cl) outsurv=cidat;
time time*status(0);
run;
proc print data = cidat;
run;
ods graphics off;

1.2
#-----Logrank Testing-----#
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata Tx;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata Inst;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata Cond;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata Sex;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata Grade;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata Site;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata n_stage;
run;
proc lifetest data=pharynx plots=(survival(atrisk) logsurv);
time time*status(0);
strata t_stage;
run;
```

```
1.3
#-----Residual Plots Martingale & Deviance-----#
proc sgplot data=Outp;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=Mart x=Xb;
   run;
proc sgplot data=Outp;
   yaxis grid;
   refline 0 / axis=y;
   scatter y=Dev x=Xb;
   run;

 2.0 Stepwise Selection
 2.1 Backward Selection
#-----Testing all variables in model taking them out one by one-----#
proc phreg data = pharynx;
class Inst Sex Tx Grade Cond Site t_stage n_stage;
model time*status(0) = Inst Sex Site Tx Grade Cond t_stage n_stage Age;
run;
#-----Taking out Institution-----#
proc phreg data = pharynx;
class Sex Tx Grade Cond t_stage n_stage;
model time*status(0) = Sex Tx Grade Cond t_stage n_stage Age;
run;
#-----Taking out Condition-----#
proc phreg data = pharynx;
class Sex Tx Grade t_stage n_stage;
model time*status(0) = Sex Tx Grade t_stage n_stage Age;
run;
#-----Taking out Grade-----#
proc phreg data = pharynx;
class Sex Tx t_stage n_stage;
model time*status(0) = Sex Tx t_stage n_stage Age;
run;
#-----Taking out Sex-----#
proc phreg data = pharynx;
class Tx t_stage n_stage;
model time*status(0) = Tx t_stage n_stage Age;
run;
#-----Taking out Age-----#
proc phreg data = pharynx;
class Tx t_stage n_stage;
model time*status(0) = Tx t_stage n_stage;
run;

2.2
#-----Checking interactions-----#
proc phreg data = pharynx;
class Tx t_stage n_stage;
model time*status(0) = Tx t_stage n_stage Tx*t_stage;
run;
```

```
proc phreg data = pharynx;
class Tx t_stage n_stage;
model time*status(0) = Tx n_stage Tx*n_stage;
run;
proc phreg data = pharynx;
class Tx t_stage n_stage;
model time*status(0) = Tx n_stage t_stage Tx*n_stage Tx*t_stage;
run;

2.3
#-----Testing Treatment by itself-----#
proc phreg data = pharynx;
class Tx;
model time*status(0) = Tx;
run;

2.4
#-----Sample size of categorical variables-----#
proc freq;
tables Tx*Inst / nocol nocum nopercent norow;
tables Tx*Sex / nocol nocum nopercent norow;
tables Tx*Grade / nocol nocum nopercent norow;
tables Tx*Cond / nocol nocum nopercent norow;
tables Tx*Site / nocol nocum nopercent norow;
tables Tx*t_stage / nocol nocum nopercent norow;
tables Tx*n_stage / nocol nocum nopercent norow;

2.5
#-----Treatment vs. all other variables-----#
#-----Treatment vs. Institution-----#
proc phreg data = pharynx;
class Tx Inst;
model time*status(0) = Tx Inst;
run;
#-----Treatment vs. Sex-----#
proc phreg data = pharynx;
class Tx Sex;
model time*status(0) = Tx Sex;
run;
#-----Treatment vs. Grade-----#
proc phreg data = pharynx;
class Tx Grade;
model time*status(0) = Tx Grade;
run;
#-----Treatment vs. Age-----#
proc phreg data = pharynx;
class Tx;
model time*status(0) = Tx Age;
run;
#-----Treatment vs. Condition-----#
proc phreg data = pharynx;
class Tx Cond;
model time*status(0) = Tx Cond;
run;
```

```
#-----Treatment vs. Site-----#
proc phreg data = pharynx;
class Tx Site;
model time*status(0) = Tx Site;
run;
#-----Treatment vs. Institution-----#
proc phreg data = pharynx;
class Tx;
class t_stage;
model time*status(0) = Tx t_stage;
run;
#-----Treatment vs. n_stage-----#
proc phreg data = pharynx;
class Tx n_stage;
model time*status(0) = Tx n_stage;
run;

3.0 SAS Stepwise model building
proc phreg data = pharynx;
class Inst Sex Tx Grade Cond Site t_stage n_stage;
model time*status(0) = Inst Sex Tx Grade Age Cond Site t_stage n_stage
/ selection = stepwise slentry = 0.26 slstay = 0.25;
run;

3.1 Accelerated Failure time Model
proc lifereg data = pharynx;
class Inst Sex Tx Grade Cond Site t_stage n_stage;
model time*status(0) = Inst Sex Tx Grade Age Cond Site t_stage n_stage
/ distribution=weibull;
/ selection = stepwise slentry = 0.26 slstay = 0.25;
run;
```