Survival Analysis: Glioblastoma

Background

The glioma dataset can be found in the coin package in R. The glioma dataset is taken from tables 1 and 2 of Grana et al. (2002) Pretargeted adjuvant radioimmunotherapy with Yttrium-90-biotin in malignant glioma patients: A pilot study. British Journal of Cancer 86(2), 207-212.

The pilot study's aim was to further study the promising results obtained in phase I-II study where a three step avidin-biotin pretargeting approach was used to target Yittrium-90-biotin in patients with recurrent high grade gliomas.

The pilot study applied the same apprach as the phase I-II studies in an adjuvant setting and evaluated patient survival times. This was a controlled open non-randomized study with 37 high grade glioma patients: 17 with grade III glioma and 20 with glioblastoma(GBM-grade IV).

Each patient received surgery and radiotherapy and susbsequently was shown to be disease free by neuroradiological exams before adjuvant treatment with radioimmunotherapy. There were 19 patients in the radioimmunotherapy(RIT) treatment group and 18 in the control group who did not undergo RIT treatment.

Dataset structure

The data from the glioma pilot study is in a dataframe with 37 observations and 7 variables.

- no. - Indicates the patient number in study(1-19) in RIT treatment and (1-18) are in the control group
- age - Denotes the enrolled patient's age
- sex - Coded as a factor with 2 levels for Female and Male.
- histology - A factor with 2 levels for GBM and Grade III
- group - A factor with 2 levels for Control and RIT treatment group
- event - Status indicator for time to event where FALSE indicates a right censored observation and TRUE indicates the event was uncensored
- time - Time is the survival time in months

Censoring Status

This study only deals with right censoring data, that is at the conclusion of the study there were patients who had still not experienced the event under study. In this case the time to event being studied is death from malignant tumor recurrence in glioma patients.

Patients were enrolled in the study under the prespecifiied inclusion criteria from December 1994 to August 1997.

Methods and Data Analysis

Structure

```r
library(survival)
library(coin)
data('glioma')
head(glioma)
```

```
##   no. age    sex histology group event time
## 1   1  41 Female    Grade3   RIT  TRUE   53
## 2   2  45 Female    Grade3   RIT FALSE   28
## 3   3  48   Male    Grade3   RIT FALSE   69
## 4   4  54   Male    Grade3   RIT FALSE   58
## 5   5  40 Female    Grade3   RIT FALSE   54
## 6   6  31   Male    Grade3   RIT  TRUE   25
```

```r
#added an id Column to make the following plot
#1-19 are part of RIT and 20-27 are part of Control group

id = c(1:37)
glioma = cbind(id, glioma)
str(glioma)
```

```
## 'data.frame':    37 obs. of  8 variables:
##  $ id       : int  1 2 3 4 5 6 7 8 9 10 ...
##  $ no.      : int  1 2 3 4 5 6 7 8 9 10 ...
##  $ age      : int  41 45 48 54 40 31 53 49 36 52 ...
##  $ sex      : Factor w/ 2 levels "Female","Male": 1 1 2 2 1 2 2 2 2 2 ...
##  $ histology: Factor w/ 2 levels "GBM","Grade3": 2 2 2 2 2 2 2 2 2 2 ...
##  $ group    : Factor w/ 2 levels "Control","RIT": 2 2 2 2 2 2 2 2 2 2 ...
##  $ event    : logi  TRUE FALSE FALSE FALSE FALSE TRUE ...
##  $ time     : int  53 28 69 58 54 25 51 61 57 57 ...
```

After adding a column to the data frame to number patients from 1-37, creating 8 variables, a table was generated to see how many Censored and Uncensored observations were in the data set. Where False indicates the observation is censored and TRUE indicates the observation is uncensored.

```r
#False is right censored data
#True indicates the event was observed
table(glioma$event)
```

```
##
## FALSE  TRUE
##    14    23
```

```r
#For future analysis created subsets by group
RIT_group = subset(glioma, group=='RIT')
Control_group = subset(glioma, group=='Control')
```

```r
library(plotly)
library(webshot)

ggplotly(
  glioma %>%
    mutate(
      text = paste("Subject ID = ", id, "<br>", "Time = ", time, "<br>", "Event = ",
                   event, "<br>", "Age = ", round(age, 2), "<br>", "Histology = ", histology, "<br>", '(
    ) %>%
  ggplot(aes(x = id, y = time, text = text)) +
```

```
    geom_linerange(aes(ymin = 0, ymax = time)) +
    geom_point(aes(shape = event, color = event), stroke = 1, cex = 2) +
    scale_shape_manual(values = c(1, 3, 4)) +
    labs(y = "Time (months)", x = "Subject ID") + coord_flip() + theme_classic(),
  tooltip = "text"
)
```

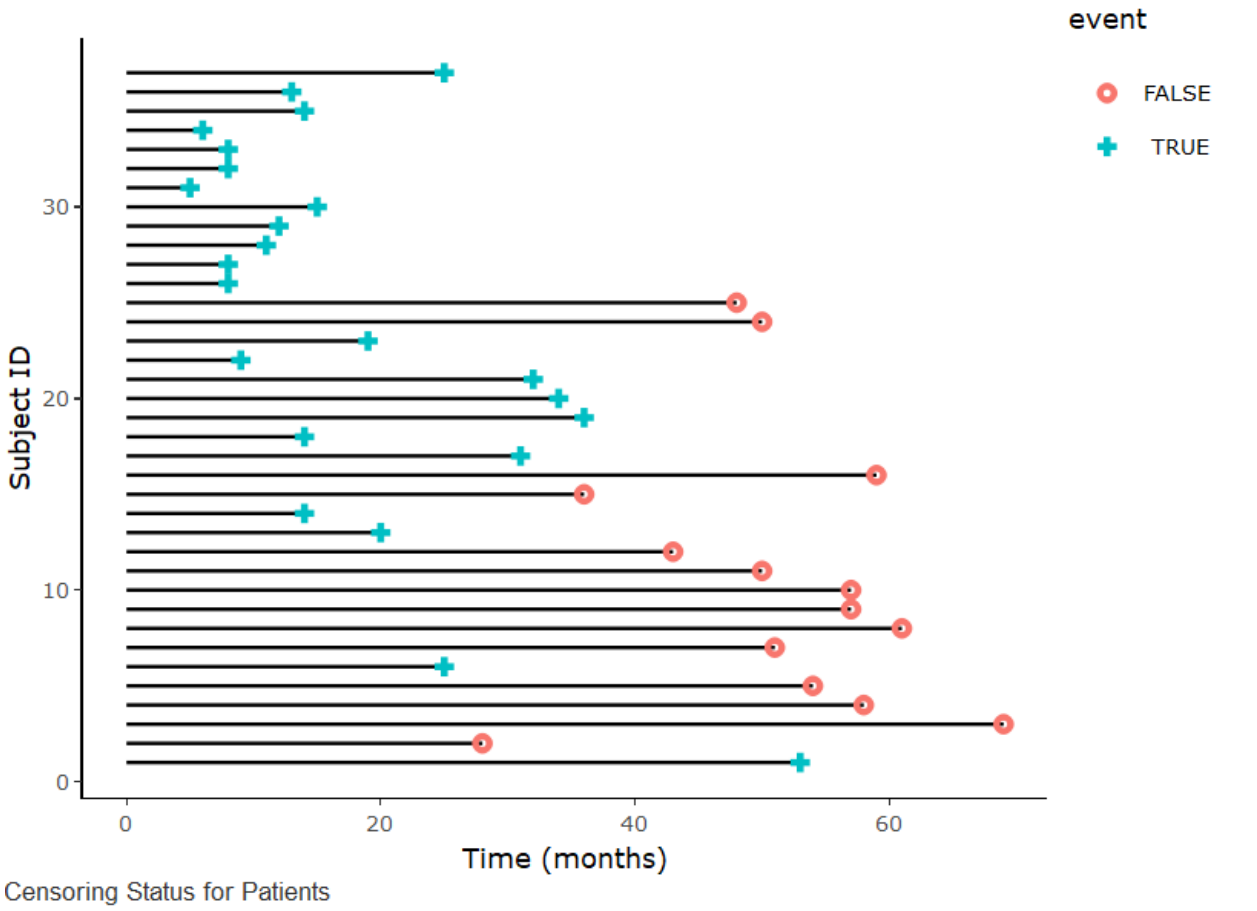


Figure 1: Horizontal Plot of Censoring Status for Patients
Plot showing each patients survival time from initial treatment. Showing 14 censored(False) patients who are right censored and 23 uncensored patients. False meaning, patient had not yet died from tumor recurrence at conclusion of the study.

Kaplain-Meir Survival Estimates

The survival library in R was used to carry out survival analysis on the glioma dataset.
A survival object was created with the Surv() function which takes as arguments the time to event data collected and censoring status to create an object that has the right censoring times taken into account.
The survival function estimates were then calculated with the survfit() function and the created surv.object to calculate Kaplan-Meir Estimators for the glioma dataset.

```
#Create PL estimates
surv.object = Surv(glioma$time, glioma$event)
```

```r
#KM - PL estimates
PL_fit = survfit(surv.object ~ 1)

head(surv.object)
```

```
## [1] 53  28+ 69+ 58+ 54+ 25
```

Survival Probability S(t) is the probability an individual survives from the the start of the study to a specified future time t.
The Survival probablity is estimated nonparametrically from the data collected in the trial as time(months) and these times are used to calculate the survival probability using the product-limit method(KM).

$$\hat{S}_{PL} = \prod_{t_i \leq t} [1 - \frac{d_i}{Y_i}]$$

The hazard function h(t) is the probability that an individual under observation has an event occur at that time. Whereas the survivor function focuses on the event not occuring, the hazard function is concerned with the event occuring.
Hazard function h(t):

$$h(t) = -\frac{d}{dt}[logS(t)]$$

Using the summary(PL_fit) feature of the survival package to generate the individual product limit estimators for the glioma dataset: $\hat{S}_{PL}(t_1 = 5) = 0.9729730$ where the number at risk is indicated by $Y_1 = 37$ and the number of events is denoted by $d_1 = 1$. Therefore we can say that the probability of a patient in the trial surviving for 5 months is 0.972.
The median survival time for both groups is the survival time when S(t) = 0.5. Patients in the trial have a median survival time of 31.5 months.

```r
library(ggfortify)
library(survminer)

PL_est = fortify(PL_fit)

head(PL_est)
```

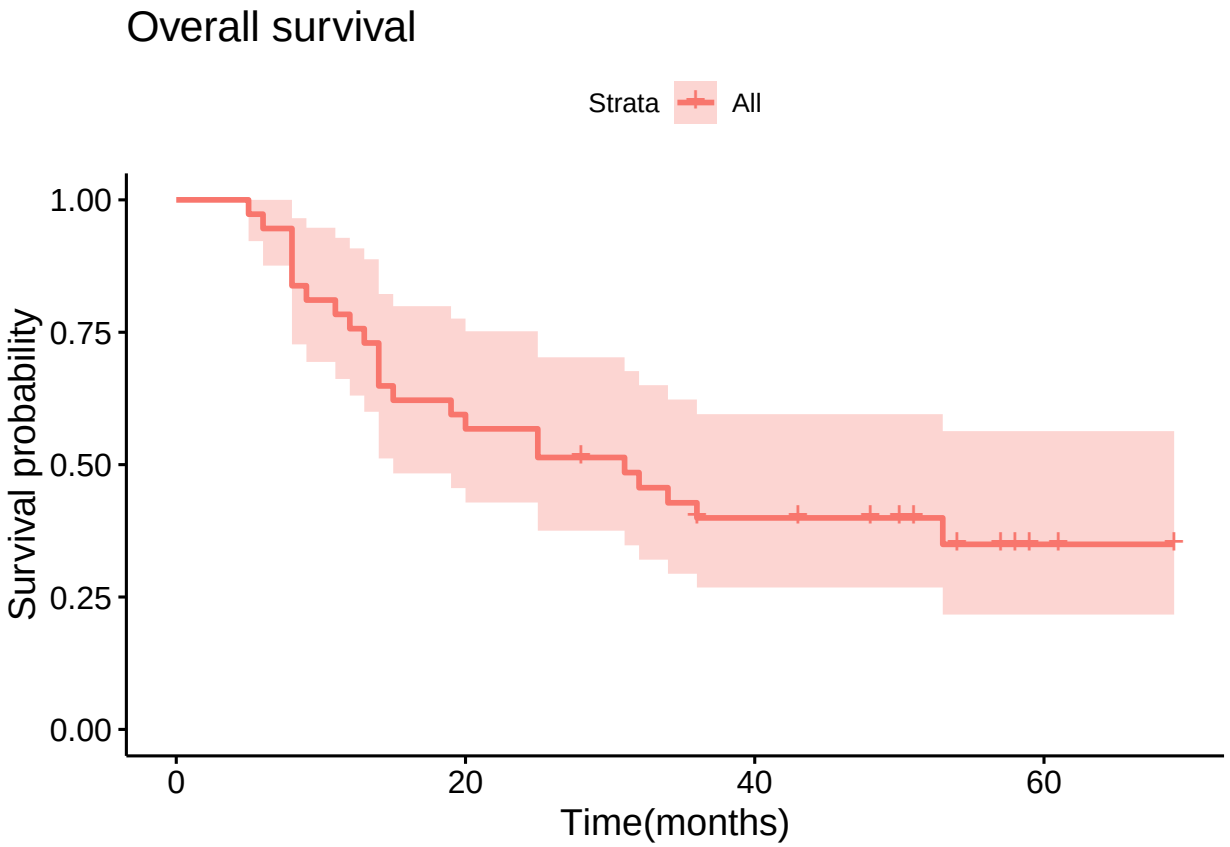
```
##   time n.risk n.event n.censor      surv    std.err     upper     lower
## 1    5     37       1        0 0.9729730 0.02739983 1.0000000 0.9220999
## 2    6     36       1        0 0.9459459 0.03929887 1.0000000 0.8758204
## 3    8     35       4        0 0.8378378 0.07232591 0.9654369 0.7271032
## 4    9     31       1        0 0.8108108 0.07941226 0.9473607 0.6939428
## 5   11     30       1        0 0.7837838 0.08634658 0.9283134 0.6617561
## 6   12     29       1        0 0.7567568 0.09320546 0.9084331 0.6304050
```

```r
summary(PL_est$time)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##    5.00   13.75   31.50   32.89   51.50   69.00
```

The KM survival curve for the overall glioma dataset is shown below. Notice the steep decline in the early months indicating that there is a poor chance of survival for those diagnosed with a glioma even after surgery and being neurologically cleared, i.e. there is a high recurrence rate with a significant mortality rate.

```r
ggsurvplot(PL_est, risk.table = TRUE, xlab = 'Time(months)', censor = T, conf.int = T, title = 'Overall
```

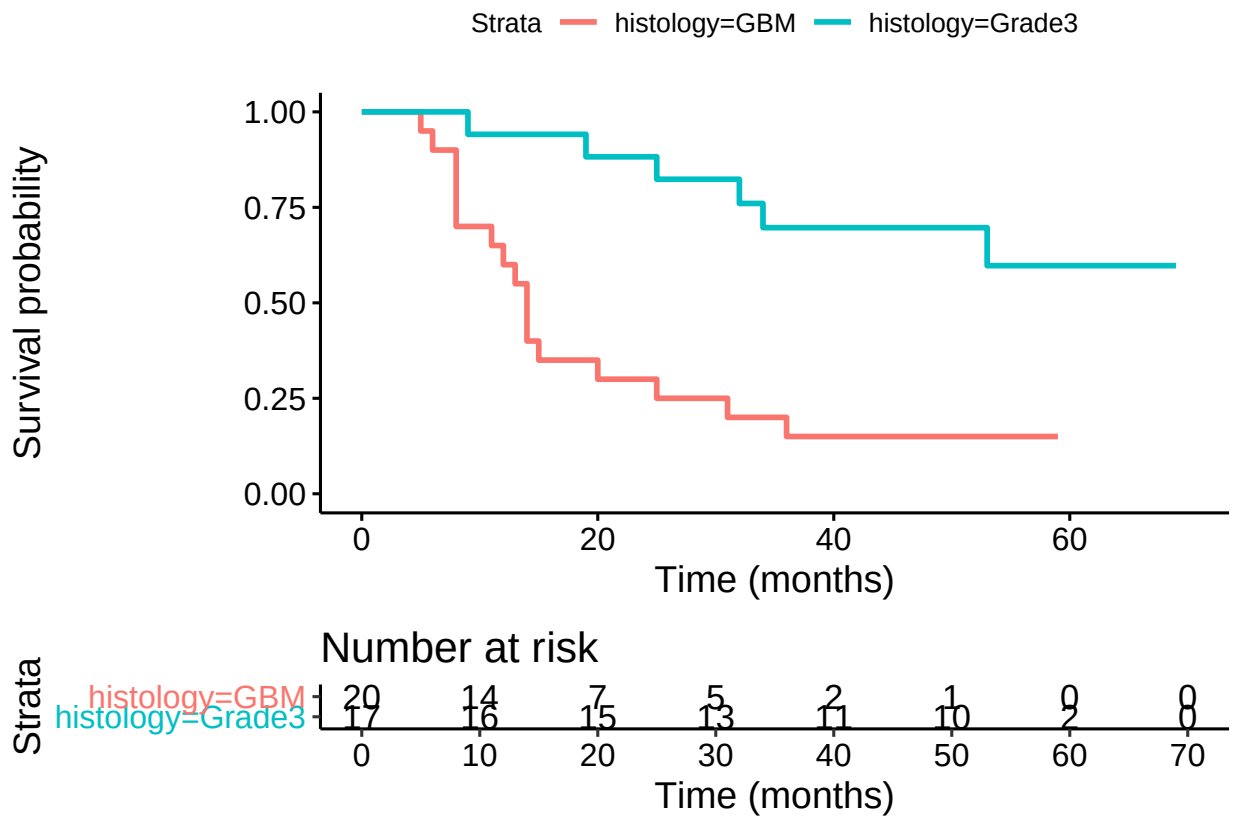


Shown above in the highlighted region is the 95% confidence interval for the KM survival curve and as the study's time progresses the survival probability's confidence region grows wider. This is due to the loss of patients as the study goes on, in this study due to death as there is no missing data, and makes interpretations of the curve less reliable at the end of the study.

Comparing Survival Curves

After creating a survival curve grouped by the patient's histology it is clear that GBM has a signficantly worse prognosis than the grade III patients and as such the two groups of patients were subsequently analyzed separately.

```
surv_hist = survfit(surv.object ~ glioma$histology, data = glioma)

ggsurvplot(surv_hist, risk.table = T,  censor = F, xlab = "Time (months)")
```



Grade III Survival Curve

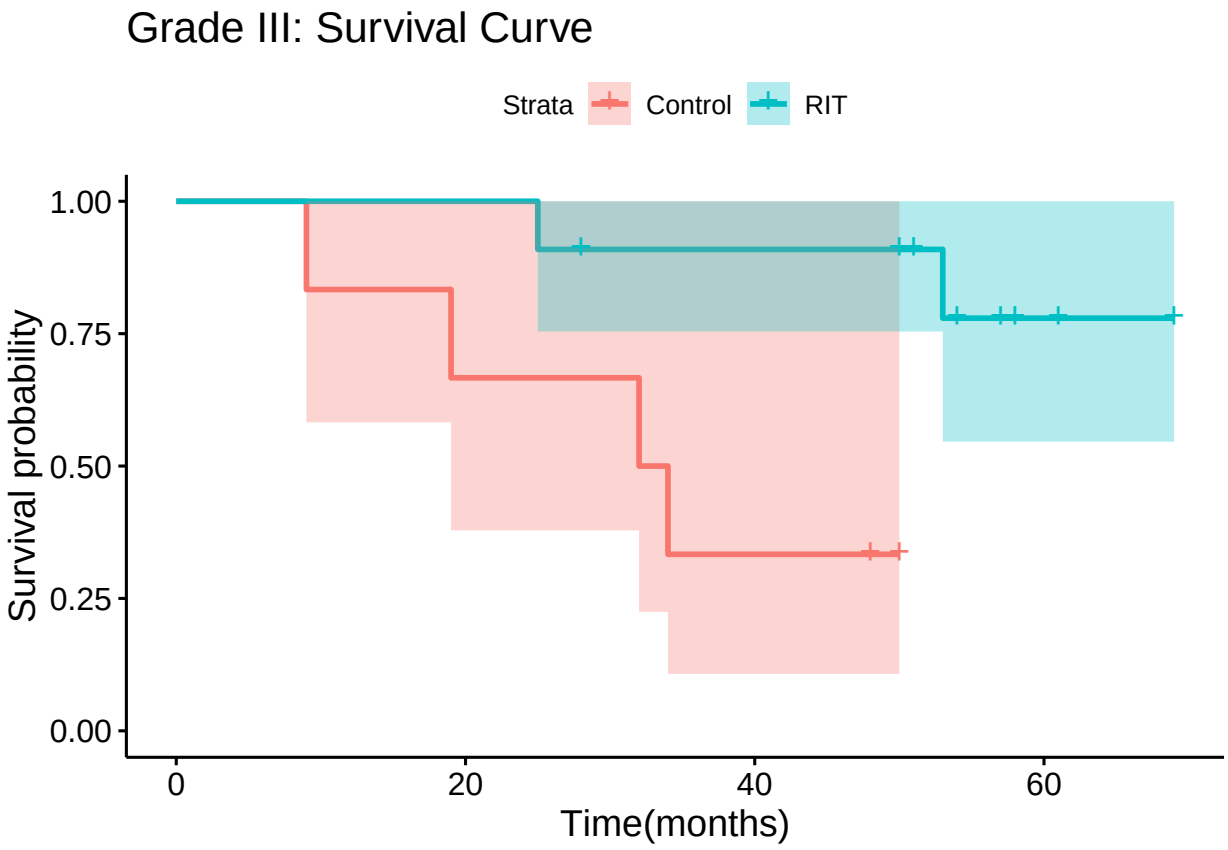
After noticing the differing prognoses for Grade 3 versus GBM, separate survival curves were created where patients were grouped by either the control or the treatment(RIT).

```
Grade3 = subset(glioma, glioma$histology == 'Grade3')

#Create PL estimates
surv.object.Grade3 = Surv(Grade3$time, Grade3$event)

#KM - PL estimates
PL_fit_Grade3 = survfit(surv.object.Grade3 ~ Grade3$group)


#############
library(ggfortify)

PL_est_Grade3 = fortify(PL_fit_Grade3)

head(PL_est_Grade3)
```

```
##   time n.risk n.event n.censor      surv   std.err upper     lower  strata
## 1    9      6       1        0 0.8333333 0.1825742     1 0.5826548 Control
## 2   19      5       1        0 0.6666667 0.2886751     1 0.3786065 Control
## 3   32      4       1        0 0.5000000 0.4082483     1 0.2246303 Control
## 4   34      3       1        0 0.3333333 0.5773503     1 0.1075071 Control
## 5   48      2       0        1 0.3333333 0.5773503     1 0.1075071 Control
```

```
## 6   50      1        0         1 0.3333333 0.5773503      1 0.1075071 Control
```

```
 ############
library(survminer)

ggsurvplot(PL_est_Grade3, risk.table = TRUE, xlab = 'Time(months)', censor = T, conf.int = T, title = '
```



Median:

```
print(PL_fit_Grade3, show.rmean= TRUE)
```

```
## Call: survfit(formula = surv.object.Grade3 ~ Grade3$group)
##
##                         n events median 0.95LCL 0.95UCL
## Grade3$group=Control  6      4     33      19      NA
## Grade3$group=RIT     11      2     NA      NA      NA
```

Grade III glioma control patients were found to have a median survival time of 33 months and the RIT group's median could not be calculated as only 2 of the 11 treated patients died over the course of the study.

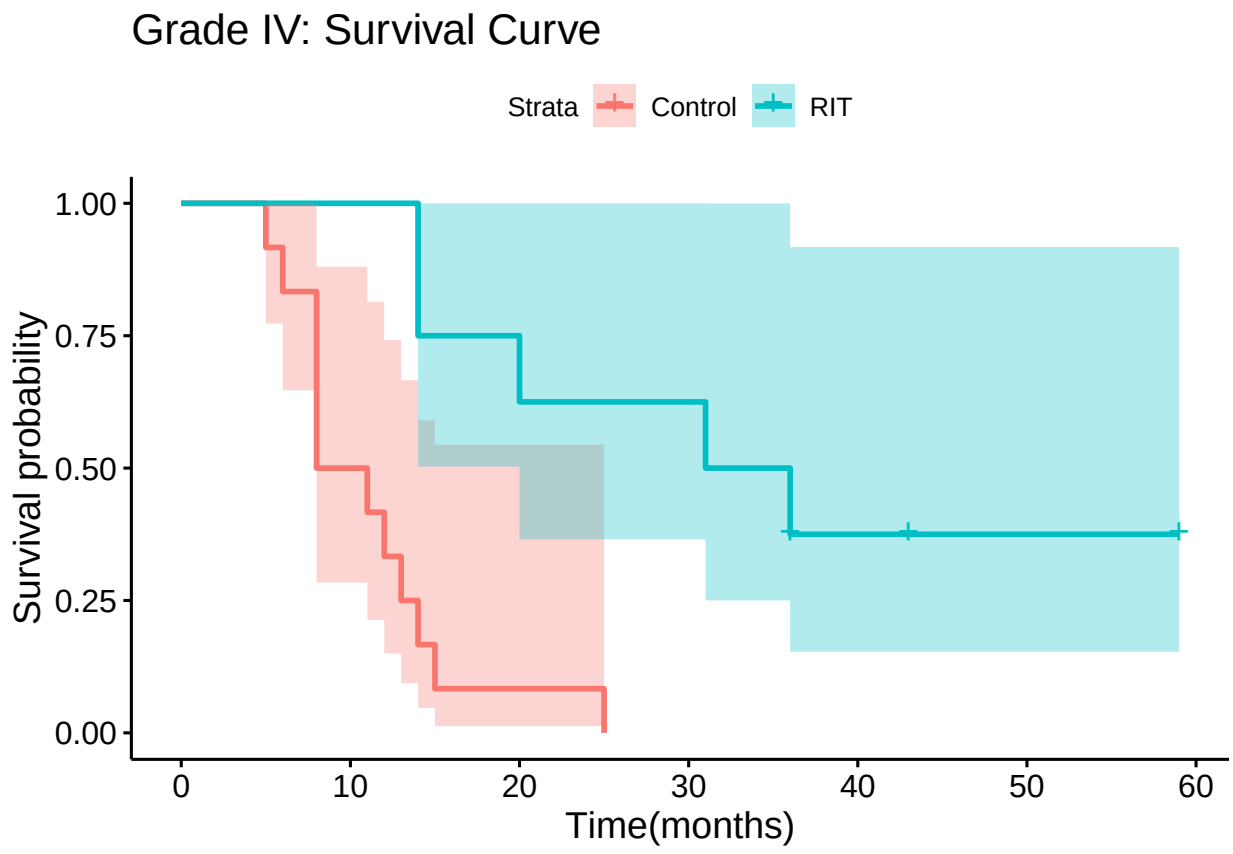
Grade IV(GBM) Survival Curve

```
GBM = subset(glioma, glioma$histology == 'GBM')


#Create PL estimates
surv.object.GBM = Surv(GBM$time, GBM$event)

#KM - PL estimates
PL_fit_GBM = survfit(surv.object.GBM ~ GBM$group)
```

```
############
library(ggfortify)

PL_est_GBM = fortify(PL_fit_GBM)

head(PL_est_GBM)
```

```
##   time n.risk n.event n.censor      surv    std.err     upper      lower
## 1    5     12       1        0 0.9166667 0.08703883 1.0000000 0.77290097
## 2    6     11       1        0 0.8333333 0.12909944 1.0000000 0.64703699
## 3    8     10       4        0 0.5000000 0.28867513 0.8804217 0.28395485
## 4   11      6       1        0 0.4166667 0.34156503 0.8138220 0.21332811
## 5   12      5       1        0 0.3333333 0.40824829 0.7419597 0.14975357
## 6   13      4       1        0 0.2500000 0.50000000 0.6661021 0.09382946
##    strata
## 1 Control
## 2 Control
## 3 Control
## 4 Control
## 5 Control
## 6 Control
```

```
 ############
library(survminer)

ggsurvplot(PL_est_GBM, risk.table = TRUE, xlab = 'Time(months)', censor = T, conf.int = T, title = "Gra
```



Median:

```r
print(PL_fit_GBM, show.rmean= TRUE)
```

```
## Call: survfit(formula = surv.object.GBM ~ GBM$group)
##
##                     n events median 0.95LCL 0.95UCL
## GBM$group=Control 12     12    9.5       8      NA
## GBM$group=RIT      8      5   33.5      20      NA
```

After plotting a survival curve for those with a GBM histology, Control patients were found to have a median survial time of 9.5 months and the treatment patients were found to have a a median survival time of 33.5 months.

Log Rank Test

Log Rank Test is a nonparametric test,that is it makes no assumptions about the survival distributions, and is used to test the null hypothesis: that there is no difference in survival between the two groups.
$H_0 : S_1(t) = S_2(t)$ or $h_1(t) = h_2(t)$ etc..
$H_1 : S_1(t) \neq S_2(t)$
Test Statisic is

$$X^2 = \sum_{i=1}^{k} \frac{O_i - E_i}{E_i}$$

or Z~N(0,1) where k is the number of groups and X^2 follows a Chi-square distribution with k-1 degrees of freedom.
A p-value can then be found to determine the statistical significance regarding the differences between the two survival curves.
The log rank test was chosen over the Wilcoxon Test since log rank is more sensitve to the later differences in the data. The test statistic is comparing the O_i observed events of the treatment group i to the expected number of events for the Control and RIT group.

Log rank test for Grade III Treatment versus No Treatment

```r
#PL_fit_Grade3 = survfit(surv.object.Grade3 ~ Grade3$group)


survdiff(surv.object.Grade3 ~ Grade3$group, rho=0)
```

```
## Call:
## survdiff(formula = surv.object.Grade3 ~ Grade3$group, rho = 0)
##
##                          N Observed Expected (O-E)^2/E (O-E)^2/V
## Grade3$group=Control  6        4     1.49      4.23      6.06
## Grade3$group=RIT     11        2     4.51      1.40      6.06
##
##  Chisq= 6.1  on 1 degrees of freedom, p= 0.01
```

$H_0 : S_{Treatment}(t) = S_{Control}(t)$
$H_1 : S_{Treatment}(t) \neq S_{Control}(t)$
After performing a log rank test comparing the grade III patients control group versus treatment group a test statistic of $X^2 = 6.1$ $\chi^2_{df=1}$ was calculated with a p-value of 0.01. Therfore we can reject the null hypothesis at $\alpha = .05$ and claim that there is a statistically signifcant difference between the survival functions for the Grade III treatment and Control groups.

Log Rank Test for GBM Treatment versus no Treatment

```
survdiff(surv.object.GBM ~ GBM$group, rho = 0)
```

```
## Call:
## survdiff(formula = surv.object.GBM ~ GBM$group, rho = 0)
##
##                       N Observed Expected (O-E)^2/E (O-E)^2/V
## GBM$group=Control 12       12     5.93      6.23      12.6
## GBM$group=RIT      8        5    11.07      3.33      12.6
##
##  Chisq= 12.6  on 1 degrees of freedom, p= 4e-04
```

$H_0 : S_{Treatment}(t) = S_{Control}(t)$
$H_1 : S_{Treatment}(t) \neq S_{Control}(t)$
After performing a log rank test comparing the GBM patients control group versus treatment group a test statistic of $X^2 = 12.6$ $\chi^2_{df=1}$ was calculated with a p-value of 4e-04. Therfore we can reject the null hypothesis at $\alpha = .05$ and claim that there is a statistically signifcant difference between the survival functions for the GBM treatment and Control groups.

Semi-Parametric Cox Model

The logrank test only signifies there is a difference between the treatment and control in both Grade III and GBM, it does not help with estimation of the effect size. Employment of a statistical model can allow for the survival to be assesed in relation to several factors and offer estimates of the corresponding effect.
A semi-parametric Cox model was tested on the glioma dataset as a whole, patients were not separated by Histology level as they were in the previous section comparing survival curves. The cox model estimates hazard ratios with respect to multiple covariates.
The Cox model format:

$$h(t) = h_0(t) * exp[\beta_i * X_i + ... + \beta_p * X_p]$$

Where the hazard is a function of the baseline hazard $h_0(t)$, hazard function when all coefficents are zero, and the p covariates employed in the model. As we estimate hazard nonparametrically we can say this model is semiparametric and there are no assumption about the shape of the baseline hazard function. It is assumed that covariates have proportional hazards regardless of time.
The main goal of the original study is to determine whether RIT prolongs patients survival and should be further studied, as such it is the main factor that is under investigation. Here we'll choose a model with RIT, but also look at how other factors affect a patients survival.
Stepwise Selection
Covariates were chosen based on step-wise selection utilizing a function from the MASS library. StepAIC() is a function that selects models based on the AIC value for the model. Starting from a null model with no covariates, models were selected based on the which covariate led to the smaller AIC value using both forward and backward selection.
Akaike Information Criterion(AIC):

$$AIC(M) = -2loglikelihood(M) + 2 * k(M)$$

Where the M is the model and the partial log likelihood term represents the deviance of the model and k(M) is the number of free parameters in the model. Models with smaller AIC are preferred as we want a model that is not too complex yet still has a good fit or high likelihood. All of the categorical variables in the model are binary and therfore have 1 degree of freedom and the continuous covariates also get 1 degree of freedom allocated to the k(M) term.

```
library(MASS)
#no covariates
null_model = coxph(surv.object~1, data = glioma)
#all covariates
full_model = coxph(surv.object~ age + histology + group + sex, data = glioma)
```

```
fit= stepAIC(null_model, scope= formula(full_model), direction = 'both', k=2)
```

```
## Start:  AIC=146.55
## surv.object ~ 1
##
##             Df    AIC
## + group      1 132.35
## + histology  1 135.31
## + age        1 142.42
## <none>         146.55
## + sex        1 148.53
##
## Step:  AIC=132.35
## surv.object ~ group
##
##             Df    AIC
## + histology  1 118.13
## + age        1 119.77
## <none>         132.35
## + sex        1 134.20
## - group      1 146.55
##
## Step:  AIC=118.13
## surv.object ~ group + histology
##
##             Df    AIC
## + age        1 115.17
## <none>         118.13
## + sex        1 119.37
## - histology  1 132.35
## - group      1 135.31
##
## Step:  AIC=115.17
## surv.object ~ group + histology + age
##
##             Df    AIC
## <none>         115.17
## + sex        1 117.16
## - age        1 118.13
## - histology  1 119.77
## - group      1 135.14
```

After running stepwise selection based on AIC values the model selected is surv.object ~ group + histology + age with an AIC = 115.17.

Final Cox Model

$$h(t) = h_0(t) * exp[\beta_{group} * X_{group} + \beta_{histology} * X_{histology} + \beta_{age} * X_{age}]$$

```
cox_reg1 = coxph(surv.object~ age + histology + group , data = glioma)
summary(cox_reg1)
```

```
## Call:
## coxph(formula = surv.object ~ age + histology + group, data = glioma)
##
##   n= 37, number of events= 23
##
```

```
##                      coef exp(coef) se(coef)      z Pr(>|z|)
## age               0.04441   1.04542  0.02019  2.200   0.0278 *
## histologyGrade3 -1.45879   0.23252  0.58373 -2.499   0.0125 *
## groupRIT        -2.44551   0.08668  0.58013 -4.215 2.49e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                 exp(coef) exp(-coef) lower .95 upper .95
## age               1.04542     0.9566   1.00485    1.0876
## histologyGrade3   0.23252     4.3008   0.07406    0.7300
## groupRIT          0.08668    11.5364   0.02780    0.2702
##
## Concordance= 0.851  (se = 0.068 )
## Rsquare= 0.636   (max possible= 0.981 )
## Likelihood ratio test= 37.37  on 3 df,   p=4e-08
## Wald test            = 27.49  on 3 df,   p=5e-06
## Score (logrank) test = 40.28  on 3 df,   p=9e-09
```

The p-value for all of the tests(Likelihood,Wald,Score) are significant for the final model, therfore the final model can be said to be signifcant. The Wald test has a null hypothesis of:

$$H_0 : \beta_{age} = \beta_{histology} = \beta_{group} = 0$$

H_1 : At least one $\beta_i \neq 0$

From above, all of the covariates are statistically significant:Age has a univariate test statistic of Z = 2.200 with a p-value of 0.0278, Histology has a test statistic of Z = -2.499 and p-value of 0.0125 and finally group has a test statistic of Z =-4.215 and p-value of 2.49e-05.

A hazard ratio greater than 1 indicates that when holding all other covariates constant, increasing the given covariate leads to the event hazard also increasing and as such survival decreases.

The hazard ratio defined as

$$HR(RIT, Control) = e^{\hat{\beta}}_{group} = exp(-2.44551) = 0.08668 == h(RIT)/h(Control)$$

The 95% Confidence interval for $HR = e^{\hat{\beta}}$ is found with the formula:

$$exp(\hat{\beta} \pm Z_{\alpha/2} * (\hat{SE}(\hat{\beta})))$$

The point estimate for the group covariate HR(RIT, Control)= 0.08668 and has a 95% Confidence Interval of [0.02780, 0.2702] when controllong for nusiance factors age and histology in the final cox model. Therfore from the given data, patients in the RIT treatment group will have their hazard reudced by a factor of 0.08668 or 91.32%. In essence RIT treatment have 0.08668 the risk(hazard) that the control patients have and will have a 91.32% lower risk of death than those who do not receive the treatment.

The hazard ratios for age and histology are respectively 1.04542, and 0.23252. The HR for age is close 1 and as such does not affect the overall survival. Histology's HR of 0.23252 indicates that grade III patients have decreased hazard by a factor of 0.23252 when compared to the GBM histology group.

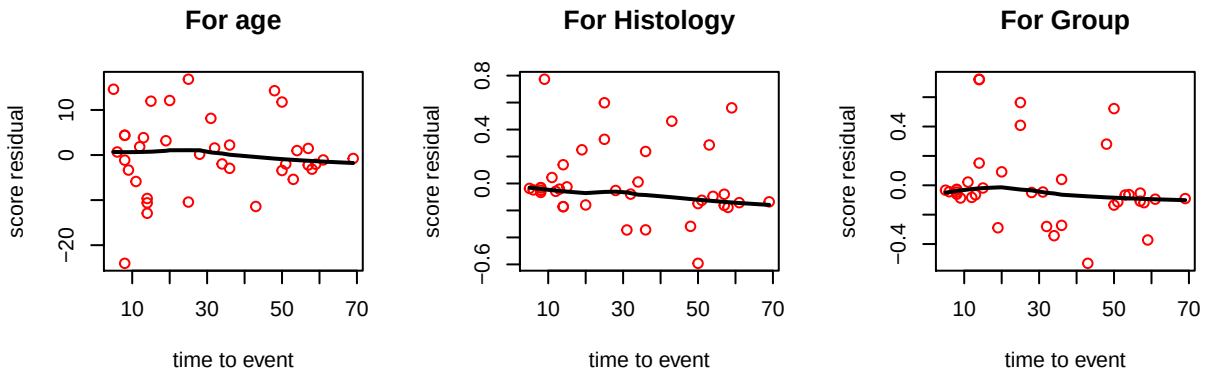
Residuals

To evaluate how the final model fit represents the given data residuals were calculated and plotted. A survival model should be able to represent the survival data and provide an acceptable goodness of fit. From a cursory look the model should show that those in the treatment group live longer and have a lower hazard, as was seen in the HR(RIT, Control)= 0.08668. It is also expected that those with GBM histology should have a higher hazard than those with Grade III histology and this was seen to be true in the model with a HR of 0.23252.

Residuals can be said to be the difference between observed data and the model's predictions based on the data given. If the difference is large this indicates a poor model.

Residual plots, based on the Score residual for each covariate were created. Score residuals approximate the full likelihood and take into acccount all of the samples, whereas Schoenfeld is used on the uncensored samples only and uses partial likelihood.
Score residuals Plots:

```
#residuals w/ final model

#score residuals

Residual_2 = residuals(cox_reg1, type = 'score')


#plot score residuals
par(mfrow=c(2,3))

plot(glioma$time, Residual_2[,1], ch=19, col="red", xlab="time to event", ylab="score residual",main="Fo
lines(lowess(cbind(glioma$time, Residual_2[,1])),lwd=2)


plot(glioma$time, Residual_2[,2], ch=19, col="red", xlab="time to event", ylab="score residual",main="Fo
lines(lowess(cbind(glioma$time, Residual_2[,2])),lwd=2)

plot(glioma$time, Residual_2[,3], ch=19, col="red", xlab="time to event", ylab="score residual",main="Fo
lines(lowess(cbind(glioma$time, Residual_2[,3])),lwd=2)
```



The three graphs above show the score residuals plotted against the time to event for the covariates:Age,Histology, and Group. If the covariates have been modeled incorrectly the figures will show a trend that is not a strictly horizontal line. A loess line was plotted for each covariate and shows that there is

a general horizontal trend centered around 0, indicating an adequate model fit for the given covariates.

Proportional Hazards Assumptions

As the Cox model is a proportional hazards model, meaning the hazard of each group is a multiple of the hazard of other groups in model, hazards for the groups should not cross.
The function cox.zph() was used on the model to test whether the hazards for the covariates are proportional over time, i.e. are the covariates hazard functions nonoverlapping.
The cox.zph() function uses the Schoenfeld residuals from the final cox regression model to test for independece between the residuals and time.

```
#Test Proportional Hazards

test.ph = cox.zph(cox_reg1)

test.ph
```

```
##                       rho   chisq     p
## age              -0.13893 0.61201 0.434
## histologyGrade3 -0.00585 0.00074 0.978
## groupRIT         0.05207 0.07578 0.783
## GLOBAL                NA 0.68901 0.876
```

Proportional hazards assumption is a central assumption of the Cox model and in this case it Does Not Fail. If the p-values had been significant it would mean that there are time dependent covariates in the model and transformations would need to be done to accomodate their time dependent nature.
Here all p-values are shown to be greater than the defined alpha of 5%, so the proportional hazards assumption is satisfied and no further transformations need to be done.

Discussion

Selection of covariates via stepwise selection purely based on statistical significance does not always lead to a model with clinical significance. In this case the covariates chosen make clinical sense(Age,Group,Histolgy) as they are all likely to impact a glioma patient's survival.
A cox model was used in this case as it is the most widely used model in the medical literature in studies pertaining to survival analysis, and as such makes the results easily interpretable in relation to other glioma treatment protocols. Of further interest would be the fitting of parametric survival models to see how they compare with the final cox model chosen in this scenario.
Unique to this study, patients overall survival was evaluated after being actively selected and shown to be macroscopically disease free. This aids in discerning the effect of the RIT treatment in relation to other clinical trials with different treatment protocols. Even though patients were shown to be macroscopically disease free upon their enrollment this does not preclude them from having a tumor recurrence, as glioblastoma's have a very high rate of recurrence. It could be argued that patients in this study have a more favorable prognosis given that they have been neurologically cleared via MRI upon admission into the study and could have led to some bias in the results.
A limitation is the fact that the entire sample is of only 37 patients, 19 in the treatment group and 18 in the control group, and is not representative of the population as a whole. With such a small trial it is hard to draw definite conclusions as to the true effectiveness of the 3 step RIT treatment's actual effect on survival, but it does appear to show promising results.
Another limitation is the analysis done with the log rank test to determine the statistical significance of the treatment in the GBM and Grade III groups. The treatment was deemed statistically significant, but with such a small sample this may need further analysis. A permutation test could be done to determine if the treatment is truly effective in this trial.
This trial does warrant further study of the RIT treatment and in the future a larger more representative randomized trial should be conducted to discern the true effectiveness of RIT in glioma patients.

Conclusions

The Grade III control patients were shown to have a median survival time of 33 months and a median was not able to be calculated for the Grade III RIT patients. A log rank test showed that the difference between these groups was statistically signifcant with a chi-squared test statistic of 6.1 with 1 degree of freedom and p=0.01.

The GBM control patients had a median survival time of 9.5 months versus the GBM RIT patients whose median survival time was 33.5 months. This difference was shown to be statistically significant with the log rank test with a test statistic of Chisq=12.6 on 1 degree of freedom and a p-value of 4e-04.

The log rank test shows that the RIT treatment is a statistically signifcant treatment protocol and led to longer survival times in the treatment group overall. This indicates that the RIT treatment protocol warrants further study.

A final Cox model selected by stepwise AIC selection with covariates: Age, Group, and Histology was shown to be statisically signifcant with a Wald Test =27.49 on 3 df with p=5e-06. Each covariate was deemed individually statistically significant at a value of $\alpha = .05$

The point estimate for the group covariate HR(RIT, Control)= 0.08668 and has a 95% Confidence Interval of [0.02780, 0.2702] when controllong for nusiance factors age and histology in the Cox model. Therfore from the given data, patients in the RIT treatment group will have their hazard reudced by a factor of 0.08668 or 91.32% reduction in risk.

The results of this study indicate that RIT is an effective treatment protocol for patients with glioblastoma, a cancer that is rare and notoriously difficult to treat, offering a significant improvement in survival time over traditional treatment alone.