Exercise: Veteran Data

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A study was conducted to compare the effects of two chemotherapy treatments in survival times for lung cancer patients. A total of 137 patients were randomly assigned to one of standard or test treatment group. The data include a number of covariates including tumor cell types, a Karnofsky performance score, the age of patient and time in months from diagnosis to randomization.

Table 1: Description of Variables in Veteran Lung Cancer Data.

Variable	Description
trt	1 = standard 2 = test
celltype	1 = squamous, 2 = smallcell, 3 = adeno, 4 = large
time	survival time
status	event status
karno	Karnofsky performance score. A scale of 10.
diagtime	the months from diagnosis of lung cancer to entry into the study
age	the age of the patient in years
prior	0 = no prior therapy 10 = prior therapy

```r
library(survival)
attach(veteran)
?veteran
head(veteran)
```

```
##   trt celltype time status karno diagtime age prior
## 1   1 squamous   72      1    60        7  69     0
## 2   1 squamous  411      1    70        5  64    10
## 3   1 squamous  228      1    60        3  38     0
## 4   1 squamous  126      1    60        9  63    10
## 5   1 squamous  118      1    70       11  65    10
## 6   1 squamous   10      1    20        5  49     0
```

1. The Kaplan-Meier estimator

Now we calculate the Kaplan-Meier estimates of the survival function for each group using the survfit function in library(survival).

survfit uses the Greenwood's formula ($\tilde{\tau}^2(t)$ in Lecture note) for the variance calculation by default, which is $Var(\widehat{S}(t)) = \widehat{S}(t)^2 \sum_{j:t_j \le t} \frac{d_j}{n_j(n_j - d_j)}$, where $\widehat{S}(t) = \prod_{j:t_j \le t} \left(1 - \frac{d_j}{n_j}\right)$.

Confidence limits for $S(t)$

Here we consider $100(1-\alpha)\%$ pointwise confidence intervals for $S(t)$ for a particular specified time t.

survfit has several options for types of confidence intervals.

1. conf.type="plain"
$$\widehat{S}(t) \pm z_{1-\alpha/2}\ se(\widehat{S}(t))$$
2. conf.type="log" (default)
$$\widehat{S}(t)\exp(\pm z_{1-\alpha/2}\ se(\log\widehat{S}(t)),$$
where
$$Var(\log\widehat{S}(t)) = \sum_{j:t_j\le t}\frac{d_j}{n_j(n_j-d_j)}.$$
3. conf.type="log-log"
$$\{\widehat{S}(t)\}^{\exp[\pm z_{1-\alpha/2}\ se(\log[-\log\{\widehat{S}(t)\}])]},$$
where
$$Var[\log\{-\log\widehat{S}(t)\}] = \frac{1}{\{\log\widehat{S}(t)\}^2}\sum_{j:t_j\le t}\frac{d_j}{n_j(n_j-d_j)}.$$

```r
library(survival)
library(knitr)

# Kaplan-Meier curve for standard treatment
fit0.km <- survfit(Surv(time, status) ~ 1, data=veteran, subset=(trt==1))
summary(fit0.km)
```

```
## Call: survfit(formula = Surv(time, status) ~ 1, data = veteran, subset = (trt ==
##     1))
##
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##     3     69       1   0.9855  0.0144      0.95771        1.000
##     4     68       1   0.9710  0.0202      0.93223        1.000
##     7     67       1   0.9565  0.0246      0.90959        1.000
##     8     66       2   0.9275  0.0312      0.86834        0.991
##    10     64       2   0.8986  0.0363      0.83006        0.973
##    11     62       1   0.8841  0.0385      0.81165        0.963
##    12     61       2   0.8551  0.0424      0.77592        0.942
##    13     59       1   0.8406  0.0441      0.75849        0.932
##    16     58       1   0.8261  0.0456      0.74132        0.921
##    18     57       2   0.7971  0.0484      0.70764        0.898
##    20     55       1   0.7826  0.0497      0.69109        0.886
##    21     54       1   0.7681  0.0508      0.67472        0.874
##    22     53       1   0.7536  0.0519      0.65851        0.862
##    27     51       1   0.7388  0.0529      0.64208        0.850
##    30     50       1   0.7241  0.0539      0.62580        0.838
##    31     49       1   0.7093  0.0548      0.60967        0.825
##    35     48       1   0.6945  0.0556      0.59368        0.812
##    42     47       1   0.6797  0.0563      0.57782        0.800
##    51     46       1   0.6650  0.0570      0.56209        0.787
##    52     45       1   0.6502  0.0576      0.54649        0.774
##    54     44       2   0.6206  0.0587      0.51565        0.747
##    56     42       1   0.6059  0.0591      0.50040        0.734
##    59     41       1   0.5911  0.0595      0.48526        0.720
##    63     40       1   0.5763  0.0598      0.47023        0.706
##    72     39       1   0.5615  0.0601      0.45530        0.693
```

```
##    82      38        1   0.5467  0.0603       0.44049        0.679
##    92      37        1   0.5320  0.0604       0.42577        0.665
##    95      36        1   0.5172  0.0605       0.41116        0.651
##   100      34        1   0.5020  0.0606       0.39615        0.636
##   103      32        1   0.4863  0.0607       0.38070        0.621
##   105      31        1   0.4706  0.0608       0.36537        0.606
##   110      30        1   0.4549  0.0607       0.35018        0.591
##   117      29        2   0.4235  0.0605       0.32017        0.560
##   118      27        1   0.4079  0.0602       0.30537        0.545
##   122      26        1   0.3922  0.0599       0.29069        0.529
##   126      24        1   0.3758  0.0596       0.27542        0.513
##   132      23        1   0.3595  0.0592       0.26031        0.496
##   139      22        1   0.3432  0.0587       0.24535        0.480
##   143      21        1   0.3268  0.0582       0.23057        0.463
##   144      20        1   0.3105  0.0575       0.21595        0.446
##   151      19        1   0.2941  0.0568       0.20151        0.429
##   153      18        1   0.2778  0.0559       0.18725        0.412
##   156      17        1   0.2614  0.0550       0.17317        0.395
##   162      16        2   0.2288  0.0527       0.14563        0.359
##   177      14        1   0.2124  0.0514       0.13218        0.341
##   200      12        1   0.1947  0.0501       0.11761        0.322
##   216      11        1   0.1770  0.0486       0.10340        0.303
##   228      10        1   0.1593  0.0468       0.08956        0.283
##   250       9        1   0.1416  0.0448       0.07614        0.263
##   260       8        1   0.1239  0.0426       0.06318        0.243
##   278       7        1   0.1062  0.0400       0.05076        0.222
##   287       6        1   0.0885  0.0371       0.03896        0.201
##   314       5        1   0.0708  0.0336       0.02793        0.180
##   384       4        1   0.0531  0.0295       0.01788        0.158
##   392       3        1   0.0354  0.0244       0.00917        0.137
##   411       2        1   0.0177  0.0175       0.00256        0.123
##   553       1        1   0.0000     NaN            NA           NA
```

```r
fit0.km$surv   # est of S(t)
```

```
##  [1] 0.98550725 0.97101449 0.95652174 0.92753623 0.89855072 0.88405797
##  [7] 0.85507246 0.84057971 0.82608696 0.79710145 0.78260870 0.76811594
## [13] 0.75362319 0.75362319 0.73884626 0.72406934 0.70929241 0.69451549
## [19] 0.67973856 0.66496164 0.65018471 0.62063086 0.60585394 0.59107701
## [25] 0.57630009 0.56152316 0.54674623 0.53196931 0.51719238 0.51719238
## [31] 0.50198084 0.48629394 0.47060704 0.45492014 0.42354634 0.40785944
## [37] 0.39217253 0.39217253 0.37583201 0.35949149 0.34315097 0.32681044
## [43] 0.31046992 0.29412940 0.27778888 0.26144836 0.22876731 0.21242679
## [49] 0.21242679 0.19472456 0.17702232 0.15932009 0.14161786 0.12391563
## [55] 0.10621339 0.08851116 0.07080893 0.05310670 0.03540446 0.01770223
## [61] 0.00000000
```

```r
fit0.km$std.err   # se of H(t) or -log(S(t))
```

```
##  [1] 0.01459893 0.02079951 0.02566635 0.03364887 0.04045094 0.04359689
##  [7] 0.04956207 0.05242734 0.05523682 0.06073767 0.06344892 0.06614507
## [13] 0.06883324 0.06883324 0.07162522 0.07442000 0.07722374 0.08004229
## [19] 0.08288126 0.08574611 0.08864223 0.09454997 0.09757262 0.10064876
## [25] 0.10378438 0.10698580 0.11025969 0.11361316 0.11705384 0.11705384
## [31] 0.12080094 0.12490369 0.12913636 0.13351264 0.14275820 0.14766315
```

```
## [37] 0.15278373 0.15278373 0.15860158 0.16471413 0.17115855 0.17797809
## [43] 0.18522359 0.19295532 0.20124545 0.21018135 0.23044473 0.24207288
## [49] 0.24207288 0.25724509 0.27434639 0.29389974 0.31664798 0.34369039
## [55] 0.37673945 0.41864776 0.47462190 0.55551713 0.68939535 0.98755554
## [61]        Inf
```

```r
fit0.km$lower # lower 95% CI for S(t)
```

```
##  [1] 0.957708167 0.932225845 0.909594044 0.868338214 0.830062311 0.811654129
##  [7] 0.775917611 0.758494913 0.741324068 0.707641998 0.691093573 0.674720630
## [13] 0.658511386 0.658511386 0.642076214 0.625797382 0.609666523 0.593676439
## [19] 0.577820910 0.562094548 0.546492680 0.515646755 0.500396160 0.485256867
## [25] 0.470226669 0.455303714 0.440486479 0.425773747 0.411164597 0.411164597
## [31] 0.396151404 0.380698046 0.365373756 0.350178113 0.320173165 0.305365110
## [37] 0.290688219 0.290688219 0.275417708 0.260305707 0.245354942 0.230568888
## [43] 0.215951849 0.201509057 0.187246807 0.173172619 0.145626048 0.132177179
## [49] 0.132177179 0.117612453 0.103396054 0.089557640 0.076135425 0.063179515
## [55] 0.050757251 0.038962286 0.027931171 0.017876902 0.009167347 0.002555167
## [61]          NA
```

```r
fit0.km$upper # upper 95% CI for S(t)
```

```
##  [1] 1.0000000 1.0000000 1.0000000 0.9907700 0.9726901 0.9629206 0.9423023
##  [8] 0.9315478 0.9205416 0.8978703 0.8862423 0.8744391 0.8624724 0.8624724
## [15] 0.8502009 0.8377734 0.8251982 0.8124826 0.7996327 0.7866541 0.7735514
## [22] 0.7469894 0.7335368 0.7199734 0.7063015 0.6925229 0.6786393 0.6646519
## [29] 0.6505618 0.6505618 0.6360820 0.6211794 0.6061491 0.5909916 0.5602952
## [36] 0.5447555 0.5290868 0.5290868 0.5128563 0.4964706 0.4799275 0.4632241
## [43] 0.4463568 0.4293212 0.4121120 0.3947232 0.3593758 0.3413989 0.3413989
## [50] 0.3223949 0.3030764 0.2834252 0.2634203 0.2430389 0.2222596 0.2010720
## [57] 0.1795093 0.1577634 0.1367327 0.1226413        NA
```

```r
# Kaplan-Meier curve for test treatment
fit1.km <- survfit(Surv(time, status) ~ 1, data=veteran, subset=(trt==2))
summary(fit1.km)
```

```
## Call: survfit(formula = Surv(time, status) ~ 1, data = veteran, subset = (trt ==
##     2))
##
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##     1     68       2   0.9706  0.0205      0.93125        1.000
##     2     66       1   0.9559  0.0249      0.90830        1.000
##     7     65       2   0.9265  0.0317      0.86647        0.991
##     8     63       2   0.8971  0.0369      0.82766        0.972
##    13     61       1   0.8824  0.0391      0.80900        0.962
##    15     60       2   0.8529  0.0429      0.77278        0.941
##    18     58       1   0.8382  0.0447      0.75513        0.930
##    19     57       2   0.8088  0.0477      0.72056        0.908
##    20     55       1   0.7941  0.0490      0.70360        0.896
##    21     54       1   0.7794  0.0503      0.68684        0.884
##    24     53       2   0.7500  0.0525      0.65383        0.860
##    25     51       3   0.7059  0.0553      0.60548        0.823
##    29     48       1   0.6912  0.0560      0.58964        0.810
##    30     47       1   0.6765  0.0567      0.57394        0.797
##    31     46       1   0.6618  0.0574      0.55835        0.784
##    33     45       1   0.6471  0.0580      0.54289        0.771
```

```
##    36     44       1  0.6324  0.0585      0.52754        0.758
##    43     43       1  0.6176  0.0589      0.51230        0.745
##    44     42       1  0.6029  0.0593      0.49717        0.731
##    45     41       1  0.5882  0.0597      0.48216        0.718
##    48     40       1  0.5735  0.0600      0.46724        0.704
##    49     39       1  0.5588  0.0602      0.45244        0.690
##    51     38       2  0.5294  0.0605      0.42313        0.662
##    52     36       2  0.5000  0.0606      0.39423        0.634
##    53     34       1  0.4853  0.0606      0.37993        0.620
##    61     33       1  0.4706  0.0605      0.36573        0.606
##    73     32       1  0.4559  0.0604      0.35163        0.591
##    80     31       2  0.4265  0.0600      0.32373        0.562
##    84     28       1  0.4112  0.0597      0.30935        0.547
##    87     27       1  0.3960  0.0594      0.29509        0.531
##    90     25       1  0.3802  0.0591      0.28028        0.516
##    95     24       1  0.3643  0.0587      0.26560        0.500
##    99     23       2  0.3326  0.0578      0.23670        0.467
##   111     20       2  0.2994  0.0566      0.20673        0.434
##   112     18       1  0.2827  0.0558      0.19203        0.416
##   133     17       1  0.2661  0.0550      0.17754        0.399
##   140     16       1  0.2495  0.0540      0.16326        0.381
##   164     15       1  0.2329  0.0529      0.14920        0.363
##   186     14       1  0.2162  0.0517      0.13538        0.345
##   201     13       1  0.1996  0.0503      0.12181        0.327
##   231     12       1  0.1830  0.0488      0.10851        0.308
##   242     10       1  0.1647  0.0472      0.09389        0.289
##   283      9       1  0.1464  0.0454      0.07973        0.269
##   340      8       1  0.1281  0.0432      0.06609        0.248
##   357      7       1  0.1098  0.0407      0.05304        0.227
##   378      6       1  0.0915  0.0378      0.04067        0.206
##   389      5       1  0.0732  0.0344      0.02912        0.184
##   467      4       1  0.0549  0.0303      0.01861        0.162
##   587      3       1  0.0366  0.0251      0.00953        0.140
##   991      2       1  0.0183  0.0180      0.00265        0.126
##   999      1       1  0.0000     NaN           NA           NA
```

```r
fit1.km$surv   # est of S(t)
```

```
##  [1] 0.97058824 0.95588235 0.92647059 0.89705882 0.88235294 0.85294118
##  [7] 0.83823529 0.80882353 0.79411765 0.77941176 0.75000000 0.70588235
## [13] 0.69117647 0.67647059 0.66176471 0.64705882 0.63235294 0.61764706
## [19] 0.60294118 0.58823529 0.57352941 0.55882353 0.52941176 0.50000000
## [25] 0.48529412 0.47058824 0.45588235 0.42647059 0.42647059 0.41123950
## [31] 0.39600840 0.38016807 0.36432773 0.33264706 0.33264706 0.29938235
## [37] 0.28275000 0.26611765 0.24948529 0.23285294 0.21622059 0.19958824
## [43] 0.18295588 0.16466029 0.14636471 0.12806912 0.10977353 0.09147794
## [49] 0.07318235 0.05488676 0.03659118 0.01829559 0.00000000
```

```r
fit1.km$std.err  # se of H(t) or -log(S(t))
```

```
##  [1] 0.02111002 0.02605251 0.03416334 0.04107993 0.04428074 0.05035372
##  [7] 0.05327267 0.05895707 0.06174655 0.06451389 0.07001400 0.07827804
## [13] 0.08105994 0.08386446 0.08669683 0.08956222 0.09246584 0.09541300
## [19] 0.09840915 0.10145993 0.10457124 0.10774928 0.11433239 0.12126781
## [25] 0.12488854 0.12862394 0.13248465 0.14063028 0.14063028 0.14525711
```

```
## [31] 0.15008041 0.15553391 0.16125257 0.17361790 0.17361790 0.18894108
## [37] 0.19739986 0.20650224 0.21635583 0.22709414 0.23888544 0.25194545
## [43] 0.26655631 0.28664155 0.30992300 0.33750468 0.37110502 0.41358466
## [49] 0.47016196 0.55171152 0.68633248 0.98541984        Inf
```

```r
fit1.km$lower # lower 95% CI for S(t)
```

```
##  [1] 0.931249696 0.908298321 0.866466452 0.827663163 0.809003685 0.772783638
##  [7] 0.755127288 0.720558806 0.703600421 0.686835340 0.653830589 0.605482979
## [13] 0.589644975 0.573935858 0.558350781 0.542885532 0.527536456 0.512300383
## [19] 0.497174586 0.482156725 0.467244822 0.452437226 0.423129867 0.394227263
## [25] 0.379926606 0.365726282 0.351626537 0.323731062 0.323731062 0.309351156
## [31] 0.295090839 0.280275370 0.265603502 0.236700873 0.236700873 0.206727978
## [37] 0.192032858 0.177540994 0.163261032 0.149203443 0.135380898 0.121808777
## [43] 0.108505870 0.093885637 0.079731407 0.066093677 0.053041093 0.040669842
## [49] 0.029120832 0.018614438 0.009531672 0.002651890          NA
```

```r
fit1.km$upper # upper 95% CI for S(t)
```

```
##  [1] 1.0000000 1.0000000 0.9906301 0.9722730 0.9623525 0.9414131 0.9304900
##  [8] 0.9079002 0.8962798 0.8844663 0.8603146 0.8229296 0.8101908 0.7973233
## [15] 0.7843323 0.7712217 0.7579955 0.7446567 0.7312081 0.7176520 0.7039907
## [22] 0.6902256 0.6623896 0.6341520 0.6198839 0.6055165 0.5910496 0.5618156
## [29] 0.5618156 0.5466859 0.5314386 0.5156634 0.4997475 0.4674848 0.4674848
## [36] 0.4335639 0.4163223 0.3988859 0.3812478 0.3633997 0.3453319 0.3270328
## [43] 0.3084889 0.2887877 0.2686849 0.2481584 0.2271866 0.2057597 0.1839115
## [50] 0.1618398 0.1404700 0.1262226        NA
```

```r
par(mfrow=c(1,2))
plot(fit0.km, xlab="TIME(DAYS) SINCE RANDOMIZATION",
     ylab="ESTIMATED  PROBABILITY  OF  SURVIVAL", cex.lab=.7, cex.axis=0.5)
mtext("STANDARD TREATMENT", side=3, line=0.5,  cex=.8)
plot(fit1.km, xlab="TIME(DAYS) SINCE RANDOMIZATION",
     ylab="ESTIMATED  PROBABILITY  OF  SURVIVAL", cex.lab=.7, cex.axis=0.5)
mtext("TEST TREATMENT", side=3, line=0.5,  cex=.8)
```

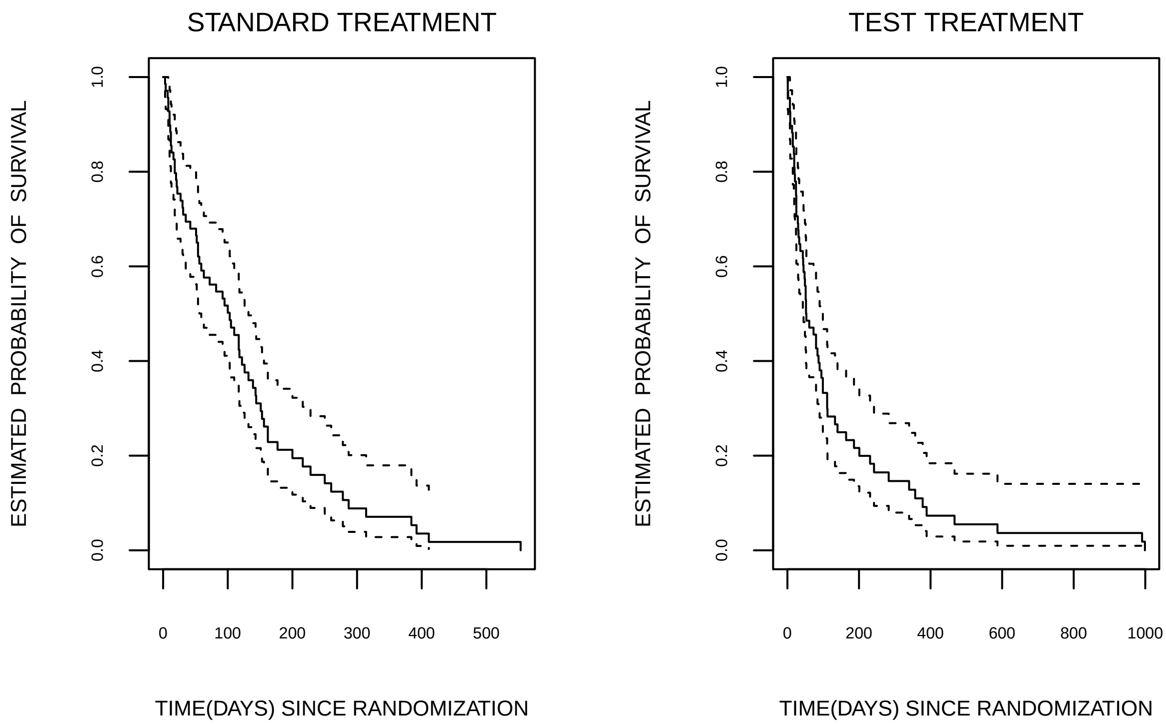


Figure 1: Pointwise 95% interval estimates for S(t)

```r
library(ggsurvfit)
```

```
## Loading required package: ggplot2
```

```r
library(ggplot2)
library(ggsci)

veteran$trt2 <- factor(veteran$trt, 1:2, c("Standard", "Test"))

p1 <- survfit2(Surv(time, status) ~ trt2, data = veteran) %>%
  ggsurvfit(type="survival",
    theme = theme_classic() +
             theme(legend.position = "top") +
             theme(panel.grid.major.y = element_line(color = "gray90", size = 0.3))) +
  scale_x_continuous(breaks=c(0, 200, 400, 600, 800, 1000), expand=c(0,0))+
  scale_y_continuous(limits=c(0, 1), expand=c(0,0)) +
  labs(x = "TIME(DAYS) SINCE RANDOMIZATION", y = "SURVIVAL PROBABILITY",
      title = "MORTALITY") +
  theme(axis.title.y = element_text(vjust = -0.1),
       axis.title.x = element_text(vjust = -0.1),
       plot.title = element_text(hjust = -0.08, vjust=-3, size=10))+
  scale_color_jama()+
  add_risktable(times = c(0, 200, 400, 600, 800, 1000),
                risktable_stats = c("n.risk"),
                risktable_group = c("risktable_stats"),
                risktable_height = 0.2, # Adjusts the height of the risk table (default is 0.25),
                stats_label = "No. at risk",
                size =3, hjust= 0)
```

```
## Warning: The `size` argument of `element_line()` is deprecated as of ggplot2 3.4.0.
## i Please use the `linewidth` argument instead.
```

```r
p1
```

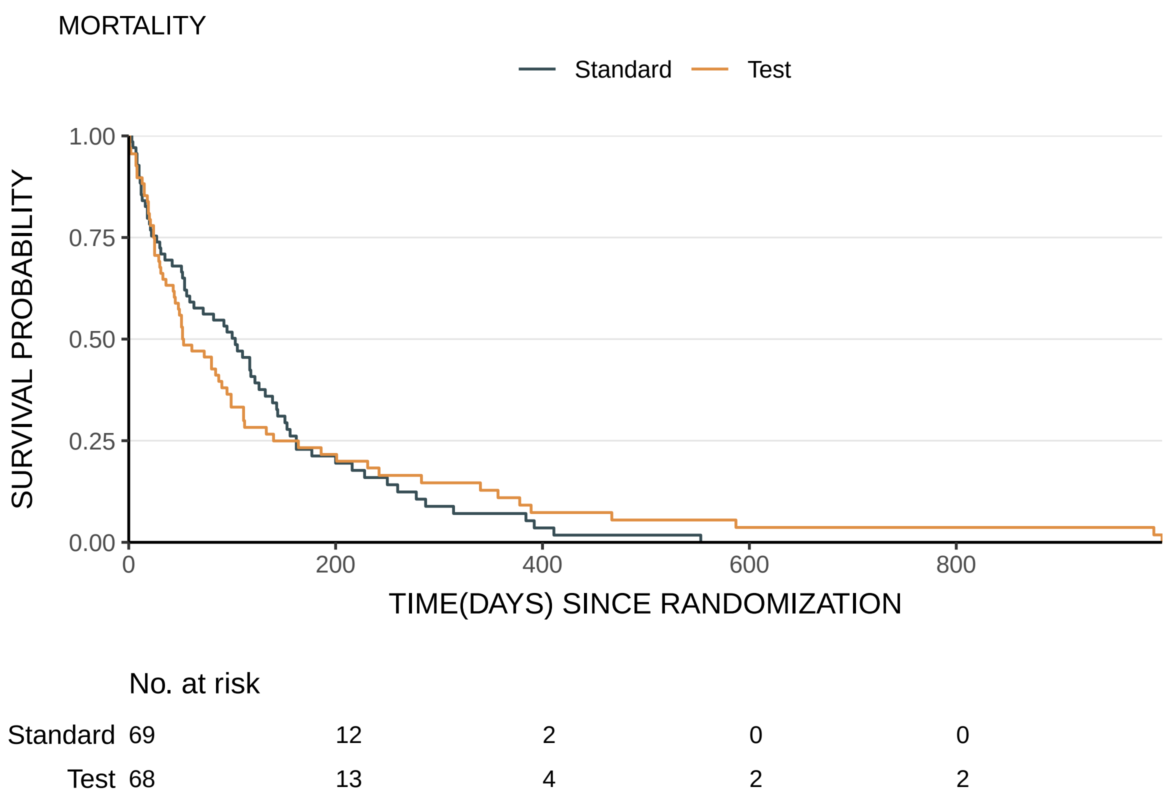


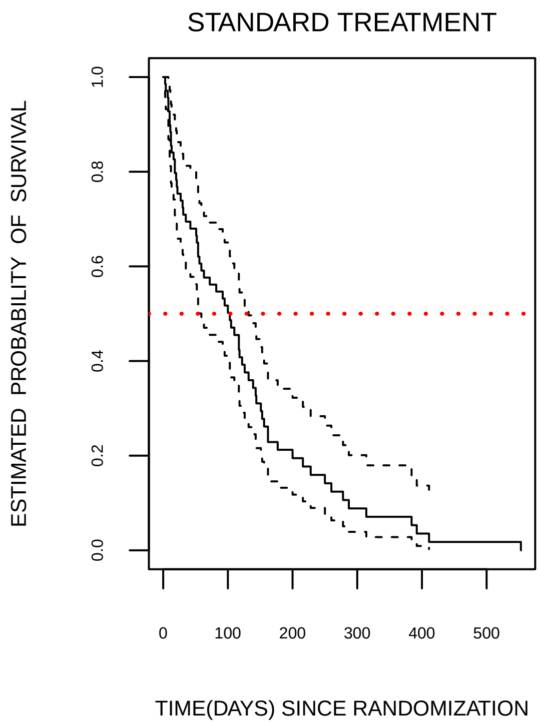
Figure 2: Esimated survival function stratified by treatment group

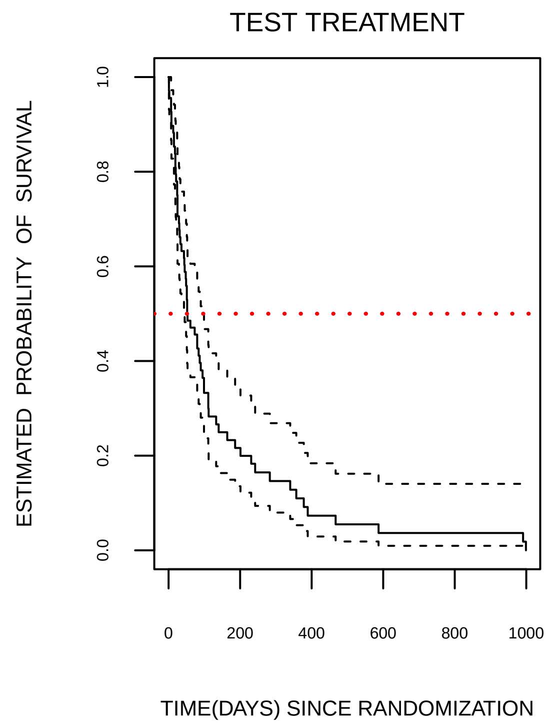
Median Survival Time

Suppose we construct the confidence limit of $S(t)$ based on the log-transformation. From the graphical method, the median survival time for the standard treatment group is 103 days and the corresponding 95% confidence intervals are (59, 132). In addition, the median survival time for the test treatment group is 52 days and the corresponding 95% confidence intervals are (44, 95).

```r
par(mfrow=c(1,2))
plot(fit0.km, xlab="TIME(DAYS) SINCE RANDOMIZATION",
     ylab="ESTIMATED  PROBABILITY  OF  SURVIVAL", cex.lab=0.7, cex.axis=0.5)
abline(h=0.5, lty=3, lwd=2, col="red")
mtext("STANDARD TREATMENT", side=3, line=0.5,  cex=.8)

plot(fit1.km, xlab="TIME(DAYS) SINCE RANDOMIZATION",
     ylab="ESTIMATED  PROBABILITY  OF  SURVIVAL", cex.lab=0.7, cex.axis=0.5)
abline(h=0.5, lty=3, lwd=2, col="red")
mtext("TEST TREATMENT", side=3, line=0.5,  cex=.8)
```





3. Log-rank test

Now, we want to test $H_0 : S_1(t) = S_2(t)$ for all t.

```
library(KMsurv)
survdiff(Surv(time, status)~factor(trt), data = veteran)
```

```
## Call:
## survdiff(formula = Surv(time, status) ~ factor(trt), data = veteran)
##
##                N Observed Expected (O-E)^2/E (O-E)^2/V
## factor(trt)=1 69       64     64.5   0.00388   0.00823
## factor(trt)=2 68       64     63.5   0.00394   0.00823
##
##  Chisq= 0  on 1 degrees of freedom, p= 0.9
```

```
1-pchisq(0.00823, 1)
```

```
## [1] 0.9277156
```

The test statistic is

$$\frac{(O-E)^2}{V} \sim \chi^2_1 \quad \text{under } H_0$$

The p-values is $P(\chi^2_1 > 0.00823) = 0.9277156$. Therefore we do not reject the null hypothesis, therefore, the survival function is not different between the standard treatment group and the test treatment group.

Cox Proportional Hazard Regression Model

Estimation

We fit a Cox regression model including the treatment indicator (trt), cell types (celltype), performance status (karno), the months from diagnosis of lung cancer to entry into the study (diagtime), prior therapy (prior), and age(age).

```r
library(survival)
attach(veteran)
```

```
## The following objects are masked from veteran (pos = 8):
##
##     age, celltype, diagtime, karno, prior, status, time, trt
```

```r
veteran$celltypef. <- factor(veteran$celltype, levels=c("large", "squamous",
                                                        "smallcell", "adeno"))
fit1 <- coxph(Surv(time, status)~ factor(trt) + celltypef. + karno + diagtime
              + factor(prior) + age , data=veteran, method="breslow")
summary(fit1)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ factor(trt) + celltypef. +
##     karno + diagtime + factor(prior) + age, data = veteran, method = "breslow")
##
##   n= 137, number of events= 128
##
##                          coef exp(coef)  se(coef)      z Pr(>|z|)
## factor(trt)2         0.289936  1.336342  0.207210  1.399  0.16174
## celltypef.squamous  -0.399628  0.670570  0.282663 -1.414  0.15742
## celltypef.smallcell  0.456859  1.579106  0.266273  1.716  0.08621 .
## celltypef.adeno      0.788672  2.200471  0.302668  2.606  0.00917 **
## karno               -0.032622  0.967905  0.005505 -5.926 3.11e-09 ***
## diagtime            -0.000092  0.999908  0.009125 -0.010  0.99196
## factor(prior)10      0.072327  1.075006  0.232133  0.312  0.75536
## age                 -0.008549  0.991487  0.009304 -0.919  0.35816
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                     exp(coef) exp(-coef) lower .95 upper .95
## factor(trt)2           1.3363     0.7483    0.8903    2.0058
## celltypef.squamous     0.6706     1.4913    0.3853    1.1669
## celltypef.smallcell    1.5791     0.6333    0.9370    2.6611
## celltypef.adeno        2.2005     0.4544    1.2159    3.9824
## karno                  0.9679     1.0332    0.9575    0.9784
## diagtime               0.9999     1.0001    0.9822    1.0180
## factor(prior)10        1.0750     0.9302    0.6821    1.6943
## age                    0.9915     1.0086    0.9736    1.0097
##
## Concordance= 0.736  (se = 0.021 )
## Likelihood ratio test= 61.41  on 8 df,   p=2e-10
## Wald test            = 61.65  on 8 df,   p=2e-10
## Score (logrank) test = 65.92  on 8 df,   p=3e-11
```

```r
library(knitr)
xname <- c("Treatment", "Cell Type", "", "", "performance status",
           "Time from Diagnosis to entry", "Prior Therapy", "Age")
compare <- c("Test vs. Standard", "Squamous vs. Large", "Small vs. Large",
             "Adeno vs. Large", "1 unit increase", "1 month increase",
             "Yes vs. No", "1 year increase")
res <- data.frame(xname, compare, summary(fit1)$coef[,2],
                  paste("(", round(exp(confint(fit1))[,1], 3), ", ",
                        round(exp(confint(fit1))[,2], 3), ")", sep=""), summary(fit1)$coef[,c(4,5)])
```

```r
colnames(res) <- c("Covariates", "Comparison",  "RR", "95% CI", "z", "p-value")
rownames(res) <- NULL

kable(res,
digits = c(3, 3, 3, 4),
caption="The results of Cox regression modeling for lung cancer patient survival")
```

Table 2: The results of Cox regression modeling for lung cancer patient survival

Covariates	Comparison	RR	95% CI	z	p-value
Treatment	Test vs. Standard	1.336	(0.89, 2.006)	1.399	0.162
Cell Type	Squamous vs. Large	0.671	(0.385, 1.167)	-1.414	0.157
	Small vs. Large	1.579	(0.937, 2.661)	1.716	0.086
	Adeno vs. Large	2.200	(1.216, 3.982)	2.606	0.009
performance status	1 unit increase	0.968	(0.958, 0.978)	-5.926	0.000
Time from Diagnosis to entry	1 month increase	1.000	(0.982, 1.018)	-0.010	0.992
Prior Therapy	Yes vs. No	1.075	(0.682, 1.694)	0.312	0.755
Age	1 year increase	0.991	(0.974, 1.01)	-0.919	0.358

```r
# drop treatment
fit5 <- coxph(Surv(time, status)~  celltypef. + karno, data=veteran, method="breslow")
summary(fit5)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ celltypef. + karno, data = veteran,
##     method = "breslow")
##
##   n= 137, number of events= 128
##
##                           coef exp(coef)  se(coef)      z Pr(>|z|)
## celltypef.squamous  -0.325143  0.722424  0.276694 -1.175  0.23996
## celltypef.smallcell  0.387005  1.472565  0.261005  1.483  0.13814
## celltypef.adeno      0.825659  2.283384  0.293329  2.815  0.00488 **
## karno               -0.030904  0.969569  0.005179 -5.968 2.41e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                     exp(coef) exp(-coef) lower .95 upper .95
## celltypef.squamous     0.7224     1.3842    0.4200    1.2426
## celltypef.smallcell    1.4726     0.6791    0.8829    2.4561
## celltypef.adeno        2.2834     0.4379    1.2850    4.0575
## karno                  0.9696     1.0314    0.9598    0.9795
##
## Concordance= 0.734  (se = 0.023 )
## Likelihood ratio test= 58.77  on 4 df,   p=5e-12
## Wald test            = 60.58  on 4 df,   p=2e-12
## Score (logrank) test = 63.22  on 4 df,   p=6e-13
```

We drop non-significant variables by backward elimination, which leads to the model including only cell type and performance status variables with the form of

$$\begin{aligned} h(t|\mathbf{z}_i) &= h_0(t)\exp(\mathbf{z}_i'\boldsymbol{\beta}) \\ &= h_0(t)\exp(z_{i1}\beta_1 + z_{i2}\beta_2 + z_{i3}\beta_3 + z_{i4}\beta_4), \end{aligned}$$

where $\mathbf{z}_i = (I(\text{cell-type} = \text{Squamous}), I(\text{cell-type} = \text{Small cell}), I(\text{cell-type} = \text{Adeno cell}), \text{performance status})'$, $\boldsymbol{\beta} = (\beta_1, \beta_2, \beta_3, \beta_4)'$.

```
xname <- c("Cell Type", "", "", "performance status")
compare <- c("Squamous vs. Large", "Small vs. Large", "Adeno vs. Large", "1 unit increase")
res <- data.frame(xname, compare, summary(fit5)$coef[,2],
                  paste("(", round(exp(confint(fit5))[,1], 3), ", ",
                  round(exp(confint(fit5))[,2], 3), ")", sep=""), summary(fit5)$coef[,c(4,5)])
colnames(res) <- c("Covariates", "Comparison",  "RR", "95% CI", "z", "p-value")
rownames(res) <- NULL

kable(res,
digits = c(3, 3, 3, 4),
caption="The results of the final model using a Cox regression for lung cancer patient survival")
```

Table 3: The results of the final model using a Cox regression for lung cancer patient survival

Covariates	Comparison	RR	95% CI	z	p-value
Cell Type	Squamous vs. Large	0.722	(0.42, 1.243)	-1.175	0.240
	Small vs. Large	1.473	(0.883, 2.456)	1.483	0.138
	Adeno vs. Large	2.283	(1.285, 4.058)	2.815	0.005
performance status	1 unit increase	0.970	(0.96, 0.979)	-5.968	0.000

Here we have $\hat{\beta}_1 = -0.325$, $s.e.(\hat{\beta}_1) = 0.276$ and the 95% CI for β_1 is $-0.325 \pm 1.96 \cdot 0.276 = (-0.867, 0.217)$. The estimated relative risk (RR) is $\exp(\hat{\beta}_1) = 0.722$ and the 95% CI for RR is $\exp(-0.325 \pm 1.96 \cdot 0.276) = (0.420, 1.243)$, which is interpreted as the relative risk of death for individuals with squamous cell type versus large cell type given a fixed value of performance status.

Since the performance status increase by 10 units, we now estimate the effect of 10-unit change in performance status on the risk of death, controlling for cell type, which is $10\hat{\beta}_4$.

$10\hat{\beta}_4 = -0.309$, $s.e.(10\hat{\beta}_4) = 10 * s.e.(\hat{\beta}_4) = 0.052$ and the 95% CI for $10\beta_4$ is $-0.309 \pm 1.96 \cdot 0.052 = (-0.411, -0.208)$. Then, the estimated RR associated with a 10 unit increase in performance status is 0.734 and its 95% CI is $\exp(-0.309 \pm 1.96 \cdot 0.052) = (0.663, 0.813)$.

We now plot the estimated cumulative hazard function and the survival function. In R, these estimators are calculated for a hypothesis person with the average covariates. Therefore, it is strongly recommended to use `newdata` to specify covariate values. For example, we are interested in estimating the cumulative hazard function and the survival function for the individuals with squamous cell type and performance status of 50.

```
# The breslow estimates
H0 <- basehaz(fit5)

# The cumulative hazard and survival function for the individual with specified covariates
mydata <- with(veteran, data.frame(celltypef.="squamous", karno=50))
H <- survfit(fit5, newdata=mydata, type="aalen")

par(mfrow=c(1,2))
plot(H, fun="cumhaz", main="Estimated Cumulative Hazard")
plot(H, main="Estimated Survival Function")
```

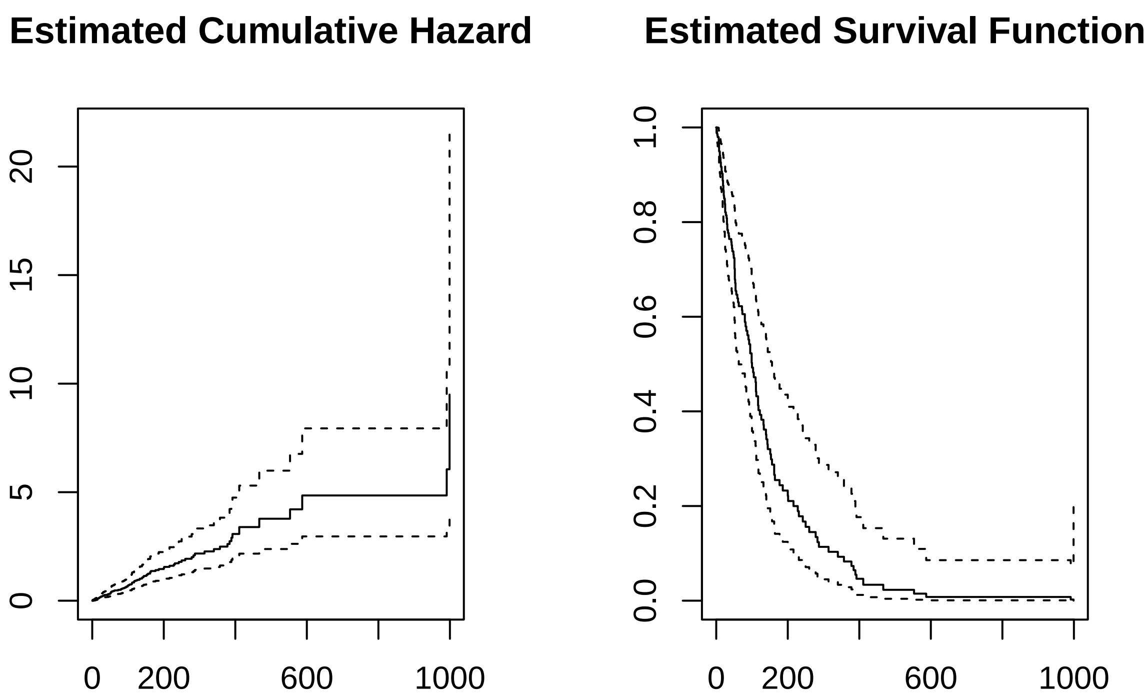


Figure 3: The estimated cumulative hazard function and the survival function for the individulas with cell type of squamous and performance status of 50.

Model diagnostics

Here, we check the proportional hazard assumptions.

```
# Cox-Snell Residuals
coxsnell <- veteran$status - resid(fit5, type="martingale")
fit.coxsnell <- survfit(Surv(coxsnell, veteran$status)~1)

plot(log(fit.coxsnell$time), log(fit.coxsnell$cumhaz), ylab="log Cumulative Hazard of Cox-snell Residua
abline(0, 1, lty=2, lwd=1.5)
```

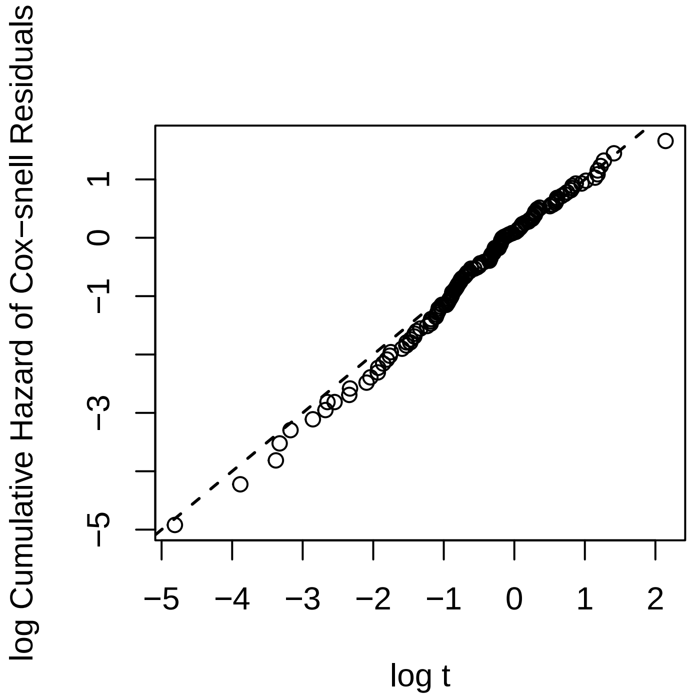


Figure 4: The Cox-Snell residual plots

Although the Cox-Snell residual plots in Figure 2 show no evidence for the misspecified model, we will conduct the formal test for the PH assumption. Note that the Cox-snell residual plots are not very informative.

cox.zph function is used for checking the PH assumptions with the argument transform for a functional form of $g(t)$. transform = "identity" corresponds to the identity transform $g(t) = t$, transform = "log" to $\log(t)$, transform = "rank" to the rank of the event times and transform = "km" to the Kaplan-Meier estimates $\hat{S}(t)$. In the output of cox.zph, chisq gives the test statistics with df, degrees of freedom and p gives the p-value. The last row of GLOBAL gives the global test of proportional hazards over all p Covariates.

```
zph.id.fit5 <- cox.zph(fit5, transform  = 'identity') # g(t) = t
zph.log.fit5 <- cox.zph(fit5, transform  = 'log') # g(t) = log
zph.km.fit5 <- cox.zph(fit5, transform  = 'km') # g(t) = S(t) from the Kaplan-Meier - default

zph.id.fit5
```

```
##             chisq df       p
## celltypef.  17.8  3 0.00048
## karno        7.0  1 0.00814
## GLOBAL      20.7  4 0.00037
```

```
zph.log.fit5
```

```
##             chisq df       p
## celltypef.  12.6  3 0.00554
## karno       11.2  1 0.00081
## GLOBAL      21.4  4 0.00026
```

```
zph.km.fit5
```

```
##             chisq df       p
## celltypef.  13.9  3 0.00305
## karno       14.1  1 0.00017
```

```
## GLOBAL      23.3  4 0.00011
```

```r
plot(zph.id.fit5[1])
```

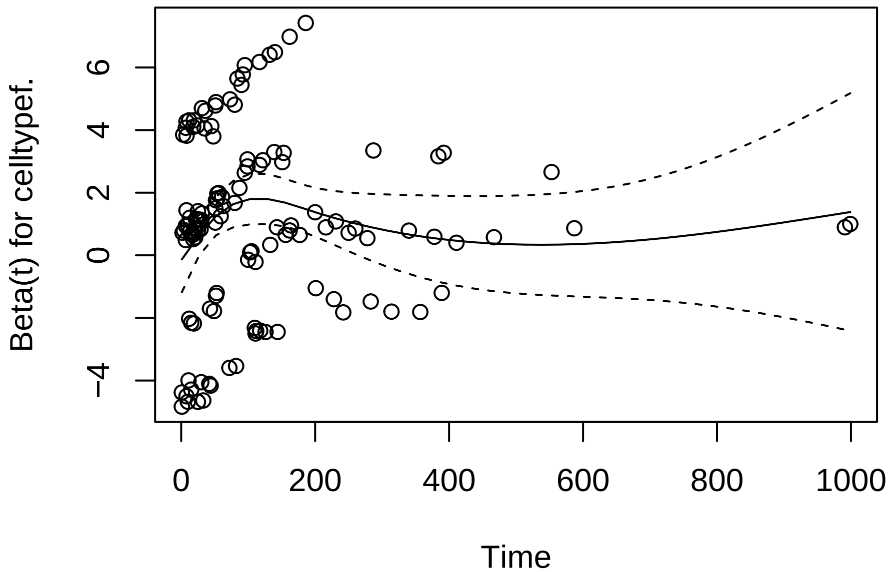


Figure 5: The scaled Schoenfeld residual plot of the cell types in the model with the Kaplan-Meier transformation (i.e. $\hat{\beta}_l + r^*_{lj}(\hat{\boldsymbol{\beta}})$ versus t_j, j=1,2.)

```r
plot(zph.id.fit5[2])
```

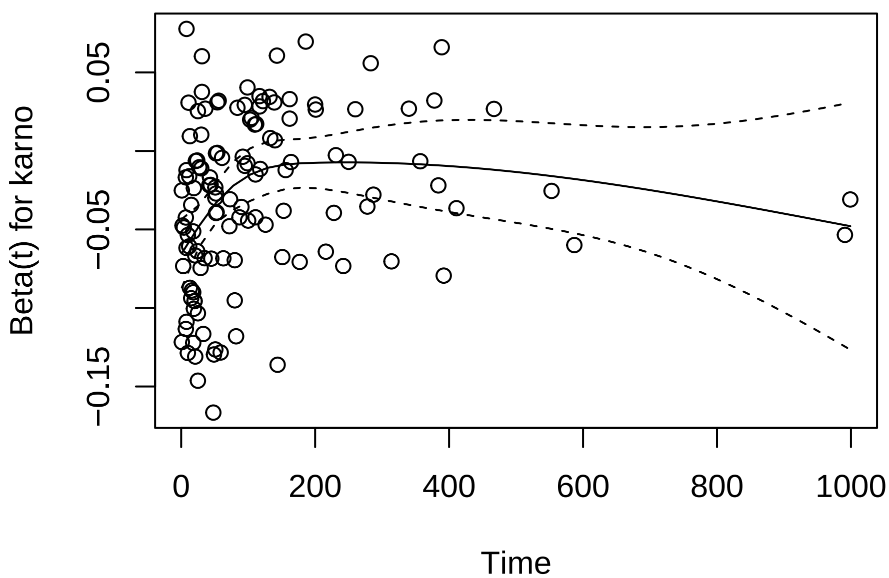


Figure 6: The scaled Schoenfeld residual plot of the performance status in the model with the Kaplan-Meier transformation (i.e. $\hat{\beta}_l + r^*_{lj}(\hat{\boldsymbol{\beta}})$ versus t_j, l=1,2.)

Based on the identity, log, and the Kaplan-Meier scale, there is some evidence for nonproportionality for the cell types and performance status, which are the significant predictor in the Cox model. In particular, the left penal of Figure 4 shows that the upward trend ends around 100 days for the scaled Schoenfeld residual plot of the performance status, $\hat{\beta}_l + r^*_{lj}(\hat{\boldsymbol{\beta}})$ versus t_j, which identifies 100 days as a point to allow the hazard ratio to change.

Stratification

To remove the problem of non-proportionality, first we use a cell-type variable as a stratifying variable. Then, a new model has the form of

$$h_k(t|\mathbf{z}_{ki}) = h_{k0}(t)\exp(z_{ki4}\beta_1), \quad k = 1, 2, 3, 4,$$

which allows the cell-type specific baseline hazard functions.

strata is used to specify a stratifying variable in coxph.

```
fit5.str <- coxph(Surv(time, status) ~ karno + strata(celltypef.), data=veteran, method="breslow")
km <- survfit(fit5.str)
km
```

```
## Call: survfit(formula = fit5.str)
##
##            n events median 0.95LCL 0.95UCL
## large     27     26    111     100     200
## squamous  35     31    118      82     283
## smallcell 48     45     54      30      95
## adeno     27     26     52      36      92
```

```
#summary(km) # gives the Kaplan-Meier estimates with 95% CI

library(survminer)
```

```
## Loading required package: ggpubr
```

```
##
## Attaching package: 'survminer'
```

```
## The following object is masked from 'package:survival':
##
##     myeloma
```

```
## Survival function versus time stratified by cell types
ggsurvplot(km, data = veteran, risk.table = TRUE, conf.int=FALSE, risk.table.height = 0.3)
```

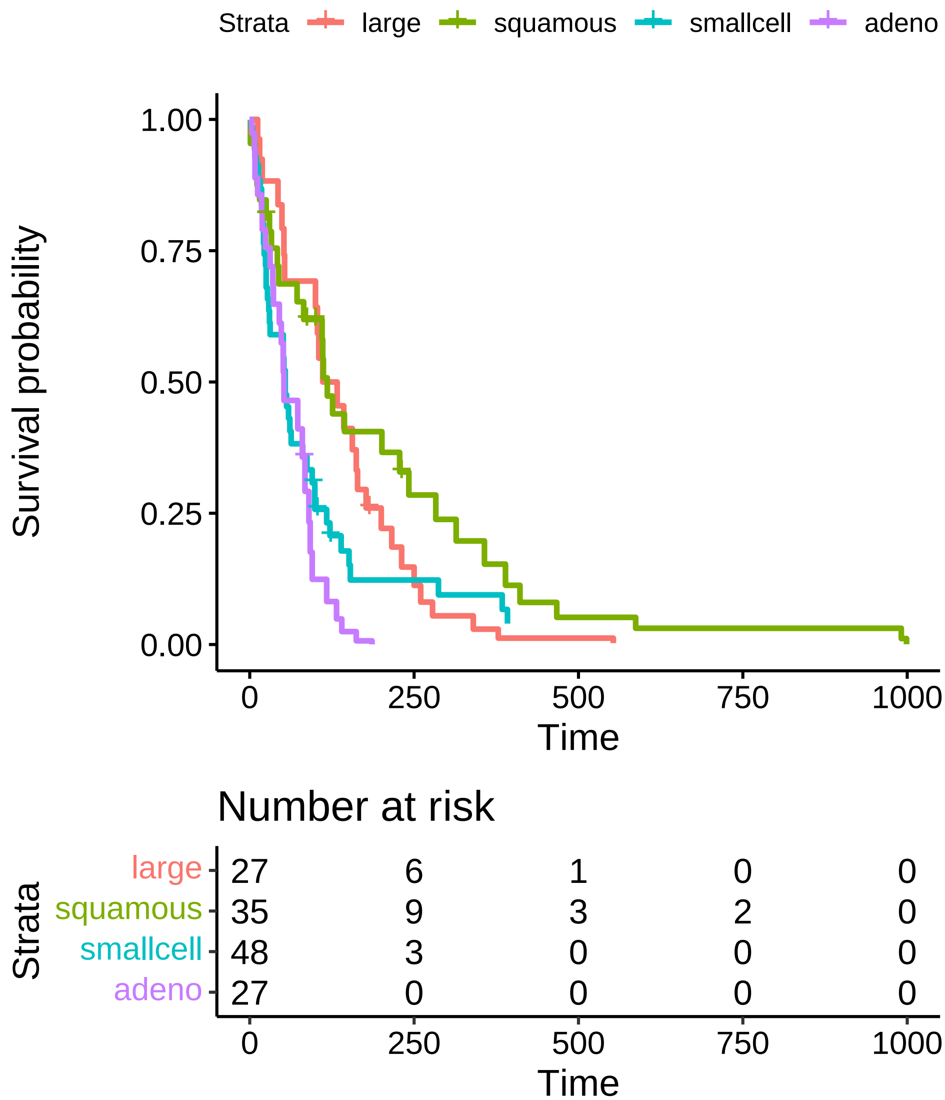


Figure 7: Survival functions versus time stratified by cell types for the individual with performance status of the mean of the performance status

Time-dependent Covariate

Second, we create a time-dependent covariate to allow the effect of performance status to depend on time through the interaction term with time. Here, we let $g(t) = I(t > 100)$.

Then, our model has the form of

$$h_k(t|\mathbf{z}_{ki}) = h_{k0}(t)\exp(z_{ki4}\beta_1 + z_{ki4} * I(t > 100)\beta_2), \quad k = 1, 2, 3, 4 \tag{1}$$

The interpretation of regression coefficients is give in the following table.

```
# Code to create a dataframe with a time-dependent covariate, It,
# where It = 0 if time <= 100 days; 1 if > 100 days months
timedepeff.f <- function(indata, cutpoint) {
        outdata <- NULL
        for (i in 1:nrow(indata)) {
          time    <- indata$time[i]
```

Period	Cell type	performance status	Hazard	Relative Risk
$(0, 100]$	k	$10 + c$	$h_{k0}(t)\exp((10 + c)\beta_1)$	$\exp(10\beta_1)$
	k	c	$h_{k0}(t)\exp(c\beta_1)$	
$(100, \infty]$	k	$10 + c$	$h_{k0}(t)\exp((10 + c)(\beta_1 + \beta_2))$	$\exp(10(\beta_1 + \beta_2))$
	k	c	$h_{k0}(t)\exp(c(\beta_1 + \beta_2))$	

```
        status <- indata$status[i]
        if ( time <= cutpoint) {
          estart  <- 0
          estop   <- time
          estatus <- status
          It <- 0
         } else{
          estart  <- c(0, cutpoint)
          estop   <- c(cutpoint,  time)
          estatus <- c(0, status)
          It      <- c(0, 1)
        }
      nlen <- length(estart)
      karno <- rep(indata$karno[i], nlen)
      id  <- rep(i, nlen)
      celltypef. <- rep(indata$celltypef[i], nlen)
      outdata <- rbind(outdata, data.frame(id, estart, estop, estatus, It, karno, celltypef.))
    }
    outdata <- data.frame(outdata, row.names=c(1:nrow(outdata)))
    return(outdata)
}


# adding a time-dependent covariate
veteran.tdeff <- timedepeff.f(indata=veteran, cutpoint=100)
dimnames(veteran.tdeff)[[2]] <- c("id","estart","estop","estatus","timecut","karno", "celltypef.")

# adding interaction with karno*timecut and stratify by celltype
final.fit <- coxph(Surv(estart, estop, estatus) ~ karno + karno:factor(timecut)
                + strata(celltypef.), data=veteran.tdeff, method="breslow")
summary(final.fit)
```

```
## Call:
## coxph(formula = Surv(estart, estop, estatus) ~ karno + karno:factor(timecut) +
##     strata(celltypef.), data = veteran.tdeff, method = "breslow")
##
##   n= 190, number of events= 128
##
##                             coef exp(coef)  se(coef)      z Pr(>|z|)
## karno                  -0.044308  0.956660  0.006305 -7.028  2.1e-12 ***
## karno:factor(timecut)1  0.043203  1.044150  0.013867  3.116  0.00184 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                        exp(coef) exp(-coef) lower .95 upper .95
## karno                     0.9567     1.0453    0.9449    0.9686
```

```
## karno:factor(timecut)1    1.0441     0.9577    1.0162    1.0729
##
## Concordance= 0.695  (se = 0.027 )
## Likelihood ratio test= 50.43  on 2 df,   p=1e-11
## Wald test            = 49.4  on 2 df,   p=2e-11
## Score (logrank) test = 55.39  on 2 df,   p=9e-13
```

```
zph.id.final.fit <- cox.zph(final.fit, transform="identity")
zph.log.final.fit <- cox.zph(final.fit, transform="log")
zph.km.final.fit <- cox.zph(final.fit, transform="km")
zph.id.final.fit
```

```
##                         chisq df    p
## karno                   0.875  1 0.35
## karno:factor(timecut) 1.509  1 0.22
## GLOBAL                  2.099  2 0.35
```

```
zph.log.final.fit
```

```
##                         chisq df    p
## karno                   0.094  1 0.76
## karno:factor(timecut) 1.798  1 0.18
## GLOBAL                  2.243  2 0.33
```

```
zph.km.final.fit
```

```
##                          chisq df    p
## karno                   0.0982  1 0.75
## karno:factor(timecut) 1.9684  1 0.16
## GLOBAL                  2.7463  2 0.25
```

```
plot(zph.id.final.fit[1])
```

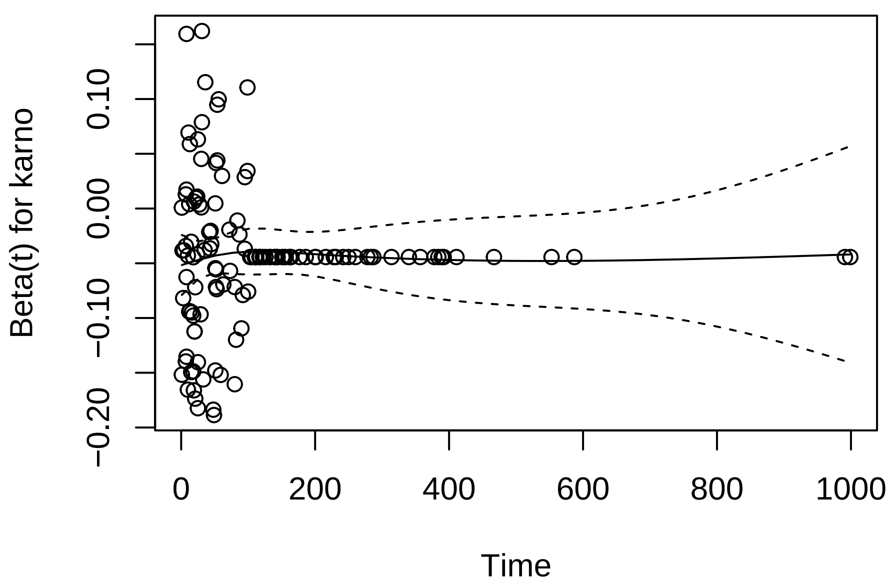


Figure 8: The scaled Schoenfeld residual plot of the performance status in the model with the Kaplan-Meier transformation (i.e. $\hat{\beta}_1 + r^*_{1j}(\hat{\boldsymbol{\beta}})$ versus t_j.)

The p-values from the marginal and global tests do not give evidence against the PH assumption and the plot of the scaled Schoenfeld residuals do not suggest any time trend in the coefficients. Therefore, we choose the model (1) as our final model.

```
# Relative risk for a 10 unit increase for the first 100 days
rr1 <- exp(10*final.fit$coefficients[1])
rr.CI.1 <- exp(10*(final.fit$coefficients[1] + c(-1.96, 1.96)*sqrt(final.fit$var[1,1])))
rr1
```

```
##     karno
## 0.6420584
```

```
rr.CI.1
```

```
## [1] 0.5674259 0.7265073
```

```
# Relative risk for a 10 unit increase for after 100 days
est2<- final.fit$coefficients[1] + final.fit$coefficients[2]
sd2 <- sqrt(final.fit$var[1,1] + 2*final.fit$var[1,2] + final.fit$var[2,2])

rr2 <- exp(10*est2)
rr.CI.2 <- exp(10*(est2 + c(-1.96, 1.96)*sd2))
rr2
```

```
##     karno
## 0.9890129
```

```
rr.CI.2
```

```
## [1] 0.7763699 1.2598975
```

```
z <- est2/sd2 # z-value; H_0: beta1 + beta2 = 0
2*(1-pnorm(abs(z))) # p-value
```

```
##     karno
## 0.9287244
```

For the first 100 days, the estimated RR associated with a 10 unit increase in performance status is 0.642 and its 95% CI is $(0.567, 0.727)$ with p-value = 0.002. However, there is only 1.1% reduction in the risk of death for a 10 unit increase in performance status after 100 days (RR=0.989, 95% CI = $(0.776, 1.260)$; $p = 0.929$. This suggests that performance status is more beneficial to reducing the risk of death of a lung cancer patient during the early days after the randomization.