A Handbook of Statistical Analyses Using R — 2nd Edition

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CHAPTER 11

Survival Analysis: Glioma Treatment and Breast Cancer Survival

11.1 Introduction

11.2 Survival Analysis

11.3 Analysis Using R

11.3.1 Glioma Radioimmunotherapy

Figure~11.1 leads to the impression that patients treated with the novel radioimmunotherapy survive longer, regardless of the tumour type. In order to assess if this informal finding is reliable, we may perform a log-rank test via

```
R> survdiff(Surv(time, event) ~ group, data = g3)

Call:
survdiff(formula = Surv(time, event) ~ group, data = g3)

               N Observed Expected (O-E)^2/E (O-E)^2/V
group=Control  6        4     1.49      4.23      6.06
group=RIT     11        2     4.51      1.40      6.06

 Chisq= 6.1  on 1 degrees of freedom, p= 0.0138
```

which indicates that the survival times are indeed different in both groups. However, the number of patients is rather limited and so it might be dangerous to rely on asymptotic tests. As shown in Chapter~4, conditioning on the data and computing the distribution of the test statistics without additional assumptions are one alternative. The function `surv_test` from package **coin** (Hothorn et~al., 2006, 2008) can be used to compute an exact conditional test answering the question whether the survival times differ for grade III patients. For all possible permutations of the groups on the censored response variable, the test statistic is computed and the fraction of whose being greater than the observed statistic defines the exact p-value:

```
R> library("coin")
R> surv_test(Surv(time, event) ~ group, data = g3,
+            distribution = "exact")

        Exact Logrank Test
```

```
R> data("glioma", package = "coin")
R> library("survival")
R> layout(matrix(1:2, ncol = 2))
R> g3 <- subset(glioma, histology == "Grade3")
R> plot(survfit(Surv(time, event) ~ group, data = g3),
+       main = "Grade III Glioma", lty = c(2, 1),
+       ylab = "Probability", xlab = "Survival Time in Month",
+       legend.text = c("Control", "Treated"),
+       legend.bty = "n")
R> g4 <- subset(glioma, histology == "GBM")
R> plot(survfit(Surv(time, event) ~ group, data = g4),
+       main = "Grade IV Glioma", ylab = "Probability",
+       lty = c(2, 1), xlab = "Survival Time in Month",
+       xlim = c(0, max(glioma$time) * 1.05))
```

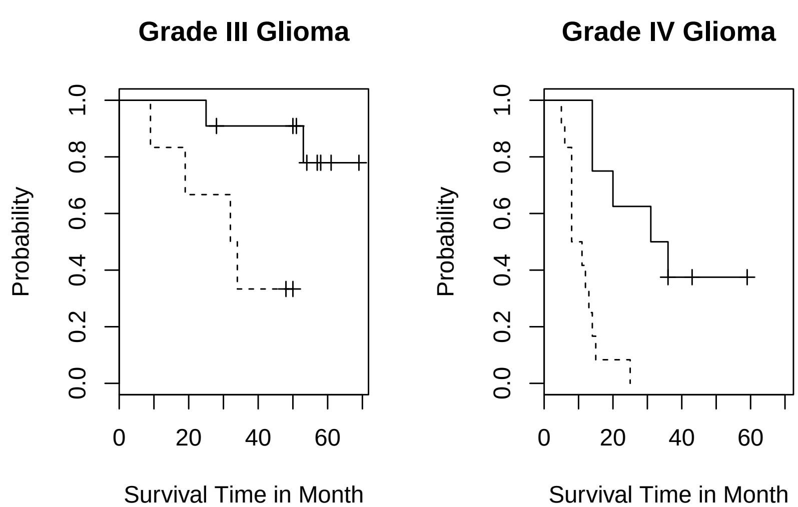

Figure 11.1 Survival times comparing treated and control patients.

```
data:  Surv(time, event) by group (Control, RIT)
Z = 2.17, p-value = 0.02877
alternative hypothesis: two.sided
```

which, in this case, confirms the above results. The same exercise can be performed for patients with grade IV glioma

```
R> surv_test(Surv(time, event) ~ group, data = g4,
+            distribution = "exact")

        Exact Logrank Test
```

```
data:  Surv(time, event) by group (Control, RIT)
Z = 3.22, p-value = 0.0001588
alternative hypothesis: two.sided
```

which shows a difference as well. However, it might be more appropriate to answer the question whether the novel therapy is superior for both groups of tumours simultaneously. This can be implemented by *stratifying*, or *blocking*, with respect to tumour grading:

```
R> surv_test(Surv(time, event) ~ group | histology,
+      data = glioma, distribution = approximate(B = 10000))

        Approximative Logrank Test

data:  Surv(time, event) by
         group (Control, RIT)
         stratified by histology
Z = 3.67, p-value = 1e-04
alternative hypothesis: two.sided
```

Here, we need to approximate the exact conditional distribution since the exact distribution is hard to compute. The result supports the initial impression implied by Figure~11.1.

11.3.2 Breast Cancer Survival

Before fitting a Cox model to the GBSG2 data, we again derive a Kaplan-Meier estimate of the survival function of the data, here stratified with respect to whether a patient received a hormonal therapy or not (see Figure~11.2).

Fitting a Cox model follows roughly the same rules as shown for linear models in Chapter~6 with the exception that the response variable is again coded as a *Surv* object. For the GBSG2 data, the model is fitted via

```
R> GBSG2_coxph <- coxph(Surv(time, cens) ~ ., data = GBSG2)
```

and the results as given by the `summary` method are given in Figure~11.3. Since we are especially interested in the relative risk for patients who underwent a hormonal therapy, we can compute an estimate of the relative risk and a corresponding confidence interval via

```
R> ci <- confint(GBSG2_coxph)
R> exp(cbind(coef(GBSG2_coxph), ci))["horThyes",]

        2.5 % 97.5 %
 0.707  0.549  0.911
```

This result implies that patients treated with a hormonal therapy had a lower risk and thus survived longer compared to women who were not treated this way.

Model checking and model selection for proportional hazards models are complicated by the fact that easy-to-use residuals, such as those discussed in

```
R> data("GBSG2", package = "TH.data")
R> plot(survfit(Surv(time, cens) ~ horTh, data = GBSG2),
+       lty = 1:2, mark.time = FALSE,  ylab = "Probability",
+       xlab = "Survival Time in Days")
R> legend(250, 0.2, legend = c("yes", "no"), lty = c(2, 1),
+         title = "Hormonal Therapy", bty = "n")
```

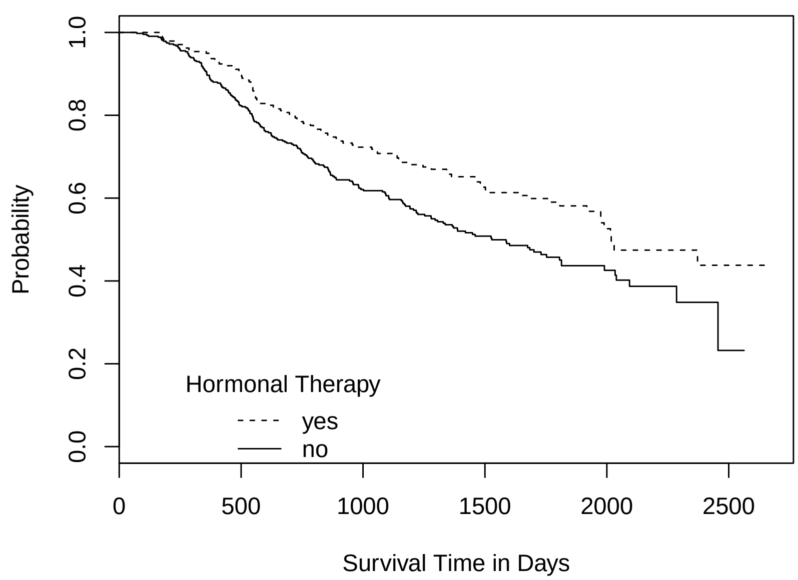

Figure 11.2 Kaplan-Meier estimates for breast cancer patients who either received a hormonal therapy or not.

Chapter˜6 for linear regression models, are not available, but several possibilities do exist. A check of the proportional hazards assumption can be done by looking at the parameter estimates $\beta_1, \dots, \beta_q$ over time. We can safely assume proportional hazards when the estimates don't vary much over time. The null hypothesis of constant regression coefficients can be tested, both globally as well as for each covariate, by using the `cox.zph` function

```
R> GBSG2_zph <- cox.zph(GBSG2_coxph)
R> GBSG2_zph

                  rho    chisq       p
horThyes     -2.54e-02 1.96e-01 0.65778
age           9.40e-02 2.96e+00 0.08552
menostatPost -1.19e-05 3.75e-08 0.99985
```

```
R> summary(GBSG2_coxph)

Call:
coxph(formula = Surv(time, cens) ~ ., data = GBSG2)

  n= 686, number of events= 299

                  coef exp(coef)  se(coef)      z Pr(>|z|)
horThyes     -0.346278  0.707316  0.129075 -2.68  0.00730
age          -0.009459  0.990585  0.009301 -1.02  0.30913
menostatPost  0.258445  1.294915  0.183476  1.41  0.15895
tsize         0.007796  1.007827  0.003939  1.98  0.04779
tgrade.L      0.551299  1.735506  0.189844  2.90  0.00368
tgrade.Q     -0.201091  0.817838  0.121965 -1.65  0.09920
pnodes        0.048789  1.049998  0.007447  6.55  5.7e-11
progrec      -0.002217  0.997785  0.000574 -3.87  0.00011
estrec        0.000197  1.000197  0.000450  0.44  0.66131

             exp(coef) exp(-coef) lower .95 upper .95
horThyes         0.707      1.414     0.549     0.911
age              0.991      1.010     0.973     1.009
menostatPost     1.295      0.772     0.904     1.855
tsize            1.008      0.992     1.000     1.016
tgrade.L         1.736      0.576     1.196     2.518
tgrade.Q         0.818      1.223     0.644     1.039
pnodes           1.050      0.952     1.035     1.065
progrec          0.998      1.002     0.997     0.999
estrec           1.000      1.000     0.999     1.001

Concordance= 0.692  (se = 0.018 )
Rsquare= 0.142   (max possible= 0.995 )
Likelihood ratio test= 105  on 9 df,   p=0
Wald test            = 115  on 9 df,   p=0
Score (logrank) test = 121  on 9 df,   p=0
```

Figure 11.3 R output of the `summary` method for `GBSG2_coxph`.

```
tsize        -2.50e-02 1.88e-01 0.66436
tgrade.L     -1.30e-01 4.85e+00 0.02772
tgrade.Q      3.22e-03 3.14e-03 0.95530
pnodes        5.84e-02 5.98e-01 0.43941
progrec       5.65e-02 1.20e+00 0.27351
estrec        5.46e-02 1.03e+00 0.30967
GLOBAL              NA 2.27e+01 0.00695
```

There seems to be some evidence of time-varying effects, especially for age and tumour grading. A graphical representation of the estimated regression coeffi-

```
R> plot(GBSG2_zph, var = "age")
```

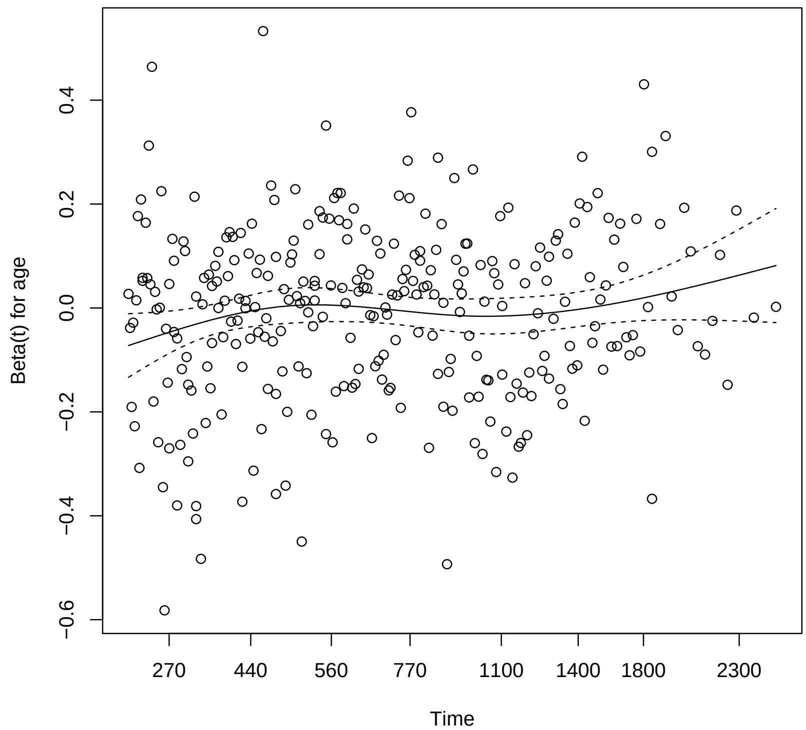

Figure 11.4 Estimated regression coefficient for age depending on time for the GBSG2 data.

cient over time is shown in Figure˜11.4. We refer to Therneau and Grambsch (2000) for a detailed theoretical description of these topics.

The tree-structured regression models applied to continuous and binary responses in Chapter˜9 are applicable to censored responses in survival analysis as well. Such a simple prognostic model with only a few terminal nodes might be helpful for relating the risk to certain subgroups of patients. Both rpart and the ctree function from package **party** can be applied to the GBSG2 data, where the conditional trees of the latter select cutpoints based on log-rank statistics

```
R> GBSG2_ctree <- ctree(Surv(time, cens) ~ ., data = GBSG2)
```

```
sweights 686.000000
swx 440.000000, f1 1.001460, f2 0.001460
```

```
R> layout(matrix(1:3, ncol = 3))
R> res <- residuals(GBSG2_coxph)
R> plot(res ~ age, data = GBSG2, ylim = c(-2.5, 1.5),
+       pch = ".", ylab = "Martingale Residuals")
R> abline(h = 0, lty = 3)
R> plot(res ~ pnodes, data = GBSG2, ylim = c(-2.5, 1.5),
+       pch = ".", ylab = "")
R> abline(h = 0, lty = 3)
R> plot(res ~ log(progrec), data = GBSG2, ylim = c(-2.5, 1.5),
+       pch = ".", ylab = "")
R> abline(h = 0, lty = 3)
```

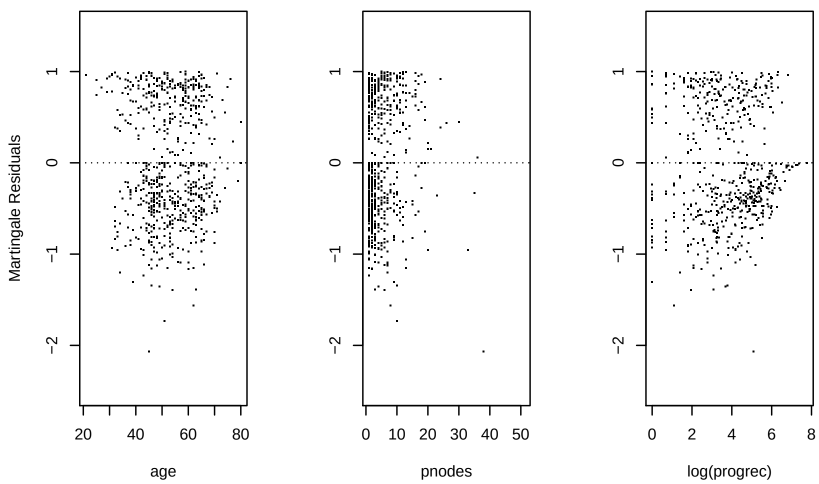

Figure 11.5 Martingale residuals for the GBSG2 data.

```
Exp 0.000000 Cov 68.596491
1: LS 24.656917 Exp 0.000000 Cov 68.596491
LS 24.656917 Exp 0.000000 Cov 68.596491
teststat 8.862896
var 1 teststat 8.862896
sweights 686.000000
swx 440.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 68.596491
1: LS 24.656917 Exp 0.000000 Cov 68.596491
sweights 686.000000
swx 36394.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 30503.751879
1: LS -129.292095 Exp 0.000000 Cov 30503.751879
```

```
LS -129.292095 Exp 0.000000 Cov 30503.751879
teststat 0.548013
var 2 teststat 0.548013
sweights 686.000000
swx 36394.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 30503.751879
1: LS -129.292095 Exp 0.000000 Cov 30503.751879
sweights 686.000000
swx 290.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 72.779204
1: LS -4.502019 Exp 0.000000 Cov 72.779204
LS -4.502019 Exp 0.000000 Cov 72.779204
teststat 0.278489
var 3 teststat 0.278489
sweights 686.000000
swx 290.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 72.779204
1: LS -4.502019 Exp 0.000000 Cov 72.779204
sweights 686.000000
swx 20120.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 60865.481643
1: LS 992.076455 Exp 0.000000 Cov 60865.481643
LS 992.076455 Exp 0.000000 Cov 60865.481643
teststat 16.170343
var 4 teststat 16.170343
sweights 686.000000
swx 20120.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 60865.481643
1: LS 992.076455 Exp 0.000000 Cov 60865.481643
sweights 686.000000
swx 1452.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 101.153207
1: LS 44.534218 Exp 0.000000 Cov 101.153207
LS 44.534218 Exp 0.000000 Cov 101.153207
teststat 19.606858
var 5 teststat 19.606858
sweights 686.000000
swx 1452.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 101.153207
1: LS 44.534218 Exp 0.000000 Cov 101.153207
sweights 686.000000
swx 3437.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 8928.401806
1: LS 708.083160 Exp 0.000000 Cov 8928.401806
LS 708.083160 Exp 0.000000 Cov 8928.401806
teststat 56.155824
var 6 teststat 56.155824
sweights 686.000000
swx 3437.000000, f1 1.001460, f2 0.001460
```

```
Exp 0.000000 Cov 8928.401806
1: LS 708.083160 Exp 0.000000 Cov 8928.401806
sweights 686.000000
swx 75457.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 12191468.784045
1: LS -15837.006814 Exp 0.000000 Cov 12191468.784045
LS -15837.006814 Exp 0.000000 Cov 12191468.784045
teststat 20.572647
var 7 teststat 20.572647
sweights 686.000000
swx 75457.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 12191468.784045
1: LS -15837.006814 Exp 0.000000 Cov 12191468.784045
sweights 686.000000
swx 66029.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 6978919.684012
1: LS -5282.139573 Exp 0.000000 Cov 6978919.684012
LS -5282.139573 Exp 0.000000 Cov 6978919.684012
teststat 3.997896
var 8 teststat 3.997896
sweights 686.000000
swx 66029.000000, f1 1.001460, f2 0.001460
Exp 0.000000 Cov 6978919.684012
1: LS -5282.139573 Exp 0.000000 Cov 6978919.684012
sweights 376.000000
swx 248.000000, f1 1.002667, f2 0.002667
Exp -45.187149 Cov 31.400095
1: LS -29.226276 Exp -45.187149 Cov 31.400095
LS -29.226276 Exp -45.187149 Cov 31.400095
teststat 8.113015
var 1 teststat 8.113015
sweights 376.000000
swx 248.000000, f1 1.002667, f2 0.002667
Exp -45.187149 Cov 31.400095
1: LS -29.226276 Exp -45.187149 Cov 31.400095
sweights 376.000000
swx 19997.000000, f1 1.002667, f2 0.002667
Exp -3643.578274 Cov 14107.299045
1: LS -3712.191460 Exp -3643.578274 Cov 14107.299045
LS -3712.191460 Exp -3643.578274 Cov 14107.299045
teststat 0.333712
var 2 teststat 0.333712
sweights 376.000000
swx 19997.000000, f1 1.002667, f2 0.002667
Exp -3643.578274 Cov 14107.299045
1: LS -3712.191460 Exp -3643.578274 Cov 14107.299045
sweights 376.000000
swx 162.000000, f1 1.002667, f2 0.002667
Exp -29.517412 Cov 34.292418
```

```
1: LS -37.310787 Exp -29.517412 Cov 34.292418
LS -37.310787 Exp -29.517412 Cov 34.292418
teststat 1.771141
var 3 teststat 1.771141
sweights 376.000000
swx 162.000000, f1 1.002667, f2 0.002667
Exp -29.517412 Cov 34.292418
1: LS -37.310787 Exp -29.517412 Cov 34.292418
sweights 376.000000
swx 9741.000000, f1 1.002667, f2 0.002667
Exp -1774.871029 Cov 15648.341027
1: LS -1596.014829 Exp -1774.871029 Cov 15648.341027
LS -1596.014829 Exp -1774.871029 Cov 15648.341027
teststat 2.044277
var 4 teststat 2.044277
sweights 376.000000
swx 9741.000000, f1 1.002667, f2 0.002667
Exp -1774.871029 Cov 15648.341027
1: LS -1596.014829 Exp -1774.871029 Cov 15648.341027
sweights 376.000000
swx 771.000000, f1 1.002667, f2 0.002667
Exp -140.481015 Cov 47.621434
1: LS -126.617214 Exp -140.481015 Cov 47.621434
LS -126.617214 Exp -140.481015 Cov 47.621434
teststat 4.036102
var 5 teststat 4.036102
sweights 376.000000
swx 771.000000, f1 1.002667, f2 0.002667
Exp -140.481015 Cov 47.621434
1: LS -126.617214 Exp -140.481015 Cov 47.621434
sweights 376.000000
swx 644.000000, f1 1.002667, f2 0.002667
Exp -117.340822 Cov 87.394822
1: LS -118.522587 Exp -117.340822 Cov 87.394822
LS -118.522587 Exp -117.340822 Cov 87.394822
teststat 0.015980
var 6 teststat 0.015980
sweights 376.000000
swx 644.000000, f1 1.002667, f2 0.002667
Exp -117.340822 Cov 87.394822
1: LS -118.522587 Exp -117.340822 Cov 87.394822
sweights 376.000000
swx 43124.000000, f1 1.002667, f2 0.002667
Exp -7857.462094 Cov 5450090.998741
1: LS -13790.021910 Exp -7857.462094 Cov 5450090.998741
LS -13790.021910 Exp -7857.462094 Cov 5450090.998741
teststat 6.457739
var 7 teststat 6.457739
sweights 376.000000
```

```
swx 43124.000000, f1 1.002667, f2 0.002667
Exp -7857.462094 Cov 5450090.998741
1: LS -13790.021910 Exp -7857.462094 Cov 5450090.998741
sweights 376.000000
swx 39668.000000, f1 1.002667, f2 0.002667
Exp -7227.757313 Cov 3601478.434652
1: LS -6780.340467 Exp -7227.757313 Cov 3601478.434652
LS -6780.340467 Exp -7227.757313 Cov 3601478.434652
teststat 0.055583
var 8 teststat 0.055583
sweights 376.000000
swx 39668.000000, f1 1.002667, f2 0.002667
Exp -7227.757313 Cov 3601478.434652
1: LS -6780.340467 Exp -7227.757313 Cov 3601478.434652
sweights 248.000000
swx 248.000000, f1 1.004049, f2 0.004049
Exp -29.226276 Cov 0.000000
1: LS -29.226276 Exp -29.226276 Cov 0.000000
LS -29.226276 Exp -29.226276 Cov 0.000000
teststat 0.000000
var 1 teststat 0.000000
sweights 248.000000
swx 248.000000, f1 1.004049, f2 0.004049
Exp -29.226276 Cov 0.000000
1: LS -29.226276 Exp -29.226276 Cov 0.000000
sweights 248.000000
swx 12620.000000, f1 1.004049, f2 0.004049
Exp -1487.240336 Cov 9149.936960
1: LS -1462.514329 Exp -1487.240336 Cov 9149.936960
LS -1462.514329 Exp -1487.240336 Cov 9149.936960
teststat 0.066817
var 2 teststat 0.066817
sweights 248.000000
swx 12620.000000, f1 1.004049, f2 0.004049
Exp -1487.240336 Cov 9149.936960
1: LS -1462.514329 Exp -1487.240336 Cov 9149.936960
sweights 248.000000
swx 136.000000, f1 1.004049, f2 0.004049
Exp -16.027313 Cov 23.761662
1: LS -27.168861 Exp -16.027313 Cov 23.761662
LS -27.168861 Exp -16.027313 Cov 23.761662
teststat 5.224134
var 3 teststat 5.224134
sweights 248.000000
swx 136.000000, f1 1.004049, f2 0.004049
Exp -16.027313 Cov 23.761662
1: LS -27.168861 Exp -16.027313 Cov 23.761662
sweights 248.000000
swx 6448.000000, f1 1.004049, f2 0.004049
```

```
Exp -759.883176 Cov 10097.458174
1: LS -663.508655 Exp -759.883176 Cov 10097.458174
LS -663.508655 Exp -759.883176 Cov 10097.458174
teststat 0.919840
var 4 teststat 0.919840
sweights 248.000000
swx 6448.000000, f1 1.004049, f2 0.004049
Exp -759.883176 Cov 10097.458174
1: LS -663.508655 Exp -759.883176 Cov 10097.458174
sweights 248.000000
swx 517.000000, f1 1.004049, f2 0.004049
Exp -60.927358 Cov 32.970241
1: LS -52.856642 Exp -60.927358 Cov 32.970241
LS -52.856642 Exp -60.927358 Cov 32.970241
teststat 1.975613
var 5 teststat 1.975613
sweights 248.000000
swx 517.000000, f1 1.004049, f2 0.004049
Exp -60.927358 Cov 32.970241
1: LS -52.856642 Exp -60.927358 Cov 32.970241
sweights 248.000000
swx 424.000000, f1 1.004049, f2 0.004049
Exp -49.967504 Cov 57.681933
1: LS -56.912836 Exp -49.967504 Cov 57.681933
LS -56.912836 Exp -49.967504 Cov 57.681933
teststat 0.836269
var 6 teststat 0.836269
sweights 248.000000
swx 424.000000, f1 1.004049, f2 0.004049
Exp -49.967504 Cov 57.681933
1: LS -56.912836 Exp -49.967504 Cov 57.681933
sweights 248.000000
swx 27138.000000, f1 1.004049, f2 0.004049
Exp -3198.155961 Cov 3134313.185618
1: LS -5633.338540 Exp -3198.155961 Cov 3134313.185618
LS -5633.338540 Exp -3198.155961 Cov 3134313.185618
teststat 1.891998
var 7 teststat 1.891998
sweights 248.000000
swx 27138.000000, f1 1.004049, f2 0.004049
Exp -3198.155961 Cov 3134313.185618
1: LS -5633.338540 Exp -3198.155961 Cov 3134313.185618
sweights 248.000000
swx 22811.000000, f1 1.004049, f2 0.004049
Exp -2688.228153 Cov 1888513.635734
1: LS -2310.764935 Exp -2688.228153 Cov 1888513.635734
LS -2310.764935 Exp -2688.228153 Cov 1888513.635734
teststat 0.075445
var 8 teststat 0.075445
```

```
sweights 248.000000
swx 22811.000000, f1 1.004049, f2 0.004049
Exp -2688.228153 Cov 1888513.635734
1: LS -2310.764935 Exp -2688.228153 Cov 1888513.635734
sweights 128.000000
swx 0.000000, f1 1.007874, f2 0.007874
Exp -0.000000 Cov 0.000000
1: LS 0.000000 Exp -0.000000 Cov 0.000000
LS 0.000000 Exp -0.000000 Cov 0.000000
teststat 0.000000
var 1 teststat 0.000000
sweights 128.000000
swx 0.000000, f1 1.007874, f2 0.007874
Exp -0.000000 Cov 0.000000
1: LS 0.000000 Exp -0.000000 Cov 0.000000
sweights 128.000000
swx 7377.000000, f1 1.007874, f2 0.007874
Exp -2264.005448 Cov 3361.173557
1: LS -2249.677131 Exp -2264.005448 Cov 3361.173557
LS -2249.677131 Exp -2264.005448 Cov 3361.173557
teststat 0.061080
var 2 teststat 0.061080
sweights 128.000000
swx 7377.000000, f1 1.007874, f2 0.007874
Exp -2264.005448 Cov 3361.173557
1: LS -2249.677131 Exp -2264.005448 Cov 3361.173557
sweights 128.000000
swx 26.000000, f1 1.007874, f2 0.007874
Exp -7.979415 Cov 6.671875
1: LS -10.141925 Exp -7.979415 Cov 6.671875
LS -10.141925 Exp -7.979415 Cov 6.671875
teststat 0.700920
var 3 teststat 0.700920
sweights 128.000000
swx 26.000000, f1 1.007874, f2 0.007874
Exp -7.979415 Cov 6.671875
1: LS -10.141925 Exp -7.979415 Cov 6.671875
sweights 128.000000
swx 3293.000000, f1 1.007874, f2 0.007874
Exp -1010.623552 Cov 5141.849786
1: LS -932.506175 Exp -1010.623552 Cov 5141.849786
LS -932.506175 Exp -1010.623552 Cov 5141.849786
teststat 1.186796
var 4 teststat 1.186796
sweights 128.000000
swx 3293.000000, f1 1.007874, f2 0.007874
Exp -1010.623552 Cov 5141.849786
1: LS -932.506175 Exp -1010.623552 Cov 5141.849786
sweights 128.000000
```

```
swx 254.000000, f1 1.007874, f2 0.007874
Exp -77.952743 Cov 13.514824
1: LS -73.760572 Exp -77.952743 Cov 13.514824
LS -73.760572 Exp -77.952743 Cov 13.514824
teststat 1.300372
var 5 teststat 1.300372
sweights 128.000000
swx 254.000000, f1 1.007874, f2 0.007874
Exp -77.952743 Cov 13.514824
1: LS -73.760572 Exp -77.952743 Cov 13.514824
sweights 128.000000
swx 220.000000, f1 1.007874, f2 0.007874
Exp -67.518124 Cov 27.653565
1: LS -61.609751 Exp -67.518124 Cov 27.653565
LS -61.609751 Exp -67.518124 Cov 27.653565
teststat 1.262364
var 6 teststat 1.262364
sweights 128.000000
swx 220.000000, f1 1.007874, f2 0.007874
Exp -67.518124 Cov 27.653565
1: LS -61.609751 Exp -67.518124 Cov 27.653565
sweights 128.000000
swx 15986.000000, f1 1.007874, f2 0.007874
Exp -4906.112390 Cov 2103406.119912
1: LS -8156.683370 Exp -4906.112390 Cov 2103406.119912
LS -8156.683370 Exp -4906.112390 Cov 2103406.119912
teststat 5.023382
var 7 teststat 5.023382
sweights 128.000000
swx 15986.000000, f1 1.007874, f2 0.007874
Exp -4906.112390 Cov 2103406.119912
1: LS -8156.683370 Exp -4906.112390 Cov 2103406.119912
sweights 128.000000
swx 16857.000000, f1 1.007874, f2 0.007874
Exp -5173.422780 Cov 1503417.843349
1: LS -4469.575532 Exp -5173.422780 Cov 1503417.843349
LS -4469.575532 Exp -5173.422780 Cov 1503417.843349
teststat 0.329516
var 8 teststat 0.329516
sweights 128.000000
swx 16857.000000, f1 1.007874, f2 0.007874
Exp -5173.422780 Cov 1503417.843349
1: LS -4469.575532 Exp -5173.422780 Cov 1503417.843349
sweights 310.000000
swx 192.000000, f1 1.003236, f2 0.003236
Exp 42.431720 Cov 30.914476
1: LS 53.883193 Exp 42.431720 Cov 30.914476
LS 53.883193 Exp 42.431720 Cov 30.914476
teststat 4.241904
```

```
var 1 teststat 4.241904
sweights 310.000000
swx 192.000000, f1 1.003236, f2 0.003236
Exp 42.431720 Cov 30.914476
1: LS 53.883193 Exp 42.431720 Cov 30.914476
sweights 310.000000
swx 16397.000000, f1 1.003236, f2 0.003236
Exp 3623.713092 Cov 13628.842203
1: LS 3582.899364 Exp 3623.713092 Cov 13628.842203
LS 3582.899364 Exp 3623.713092 Cov 13628.842203
teststat 0.122223
var 2 teststat 0.122223
sweights 310.000000
swx 16397.000000, f1 1.003236, f2 0.003236
Exp 3623.713092 Cov 13628.842203
1: LS 3582.899364 Exp 3623.713092 Cov 13628.842203
sweights 310.000000
swx 128.000000, f1 1.003236, f2 0.003236
Exp 28.287813 Cov 31.787766
1: LS 32.808767 Exp 28.287813 Cov 31.787766
LS 32.808767 Exp 28.287813 Cov 31.787766
teststat 0.642984
var 3 teststat 0.642984
sweights 310.000000
swx 128.000000, f1 1.003236, f2 0.003236
Exp 28.287813 Cov 31.787766
1: LS 32.808767 Exp 28.287813 Cov 31.787766
sweights 310.000000
swx 10379.000000, f1 1.003236, f2 0.003236
Exp 2293.743866 Cov 37300.723082
1: LS 2588.091284 Exp 2293.743866 Cov 37300.723082
LS 2588.091284 Exp 2293.743866 Cov 37300.723082
teststat 2.322754
var 4 teststat 2.322754
sweights 310.000000
swx 10379.000000, f1 1.003236, f2 0.003236
Exp 2293.743866 Cov 37300.723082
1: LS 2588.091284 Exp 2293.743866 Cov 37300.723082
sweights 310.000000
swx 681.000000, f1 1.003236, f2 0.003236
Exp 150.500007 Cov 42.721633
1: LS 171.151432 Exp 150.500007 Cov 42.721633
LS 171.151432 Exp 150.500007 Cov 42.721633
teststat 9.982797
var 5 teststat 9.982797
sweights 310.000000
swx 681.000000, f1 1.003236, f2 0.003236
Exp 150.500007 Cov 42.721633
1: LS 171.151432 Exp 150.500007 Cov 42.721633
```

```
sweights 310.000000
swx 2793.000000, f1 1.003236, f2 0.003236
Exp 617.248928 Cov 4760.852426
1: LS 826.605748 Exp 617.248928 Cov 4760.852426
LS 826.605748 Exp 617.248928 Cov 4760.852426
teststat 9.206393
var 6 teststat 9.206393
sweights 310.000000
swx 2793.000000, f1 1.003236, f2 0.003236
Exp 617.248928 Cov 4760.852426
1: LS 826.605748 Exp 617.248928 Cov 4760.852426
sweights 310.000000
swx 32333.000000, f1 1.003236, f2 0.003236
Exp 7145.545855 Cov 5655740.229202
1: LS -2046.984904 Exp 7145.545855 Cov 5655740.229202
LS -2046.984904 Exp 7145.545855 Cov 5655740.229202
teststat 14.941037
var 7 teststat 14.941037
sweights 310.000000
swx 32333.000000, f1 1.003236, f2 0.003236
Exp 7145.545855 Cov 5655740.229202
1: LS -2046.984904 Exp 7145.545855 Cov 5655740.229202
sweights 310.000000
swx 26361.000000, f1 1.003236, f2 0.003236
Exp 5825.742563 Cov 2664182.685919
1: LS 1498.200894 Exp 5825.742563 Cov 2664182.685919
LS 1498.200894 Exp 5825.742563 Cov 2664182.685919
teststat 7.029404
var 8 teststat 7.029404
sweights 310.000000
swx 26361.000000, f1 1.003236, f2 0.003236
Exp 5825.742563 Cov 2664182.685919
1: LS 1498.200894 Exp 5825.742563 Cov 2664182.685919
sweights 144.000000
swx 91.000000, f1 1.006993, f2 0.006993
Exp 40.064921 Cov 11.759640
1: LS 41.713652 Exp 40.064921 Cov 11.759640
LS 41.713652 Exp 40.064921 Cov 11.759640
teststat 0.231156
var 1 teststat 0.231156
sweights 144.000000
swx 91.000000, f1 1.006993, f2 0.006993
Exp 40.064921 Cov 11.759640
1: LS 41.713652 Exp 40.064921 Cov 11.759640
sweights 144.000000
swx 7628.000000, f1 1.006993, f2 0.006993
Exp 3358.408945 Cov 5253.221124
1: LS 3346.411478 Exp 3358.408945 Cov 5253.221124
LS 3346.411478 Exp 3358.408945 Cov 5253.221124
```

```
teststat 0.027400
var 2 teststat 0.027400
sweights 144.000000
swx 7628.000000, f1 1.006993, f2 0.006993
Exp 3358.408945 Cov 5253.221124
1: LS 3346.411478 Exp 3358.408945 Cov 5253.221124
sweights 144.000000
swx 59.000000, f1 1.006993, f2 0.006993
Exp 25.976157 Cov 12.227782
1: LS 30.098291 Exp 25.976157 Cov 12.227782
LS 30.098291 Exp 25.976157 Cov 12.227782
teststat 1.389621
var 3 teststat 1.389621
sweights 144.000000
swx 59.000000, f1 1.006993, f2 0.006993
Exp 25.976157 Cov 12.227782
1: LS 30.098291 Exp 25.976157 Cov 12.227782
sweights 144.000000
swx 4878.000000, f1 1.006993, f2 0.006993
Exp 2147.655851 Cov 14634.746401
1: LS 2234.055197 Exp 2147.655851 Cov 14634.746401
LS 2234.055197 Exp 2147.655851 Cov 14634.746401
teststat 0.510077
var 4 teststat 0.510077
sweights 144.000000
swx 4878.000000, f1 1.006993, f2 0.006993
Exp 2147.655851 Cov 14634.746401
1: LS 2234.055197 Exp 2147.655851 Cov 14634.746401
sweights 144.000000
swx 347.000000, f1 1.006993, f2 0.006993
Exp 152.775027 Cov 13.632210
1: LS 157.299162 Exp 152.775027 Cov 13.632210
LS 157.299162 Exp 152.775027 Cov 13.632210
teststat 1.501429
var 5 teststat 1.501429
sweights 144.000000
swx 347.000000, f1 1.006993, f2 0.006993
Exp 152.775027 Cov 13.632210
1: LS 157.299162 Exp 152.775027 Cov 13.632210
sweights 144.000000
swx 1388.000000, f1 1.006993, f2 0.006993
Exp 611.100107 Cov 1606.391693
1: LS 715.772801 Exp 611.100107 Cov 1606.391693
LS 715.772801 Exp 611.100107 Cov 1606.391693
teststat 6.820487
var 6 teststat 6.820487
sweights 144.000000
swx 1388.000000, f1 1.006993, f2 0.006993
Exp 611.100107 Cov 1606.391693
```

```
1: LS 715.772801 Exp 611.100107 Cov 1606.391693
sweights 144.000000
swx 800.000000, f1 1.006993, f2 0.006993
Exp 352.219082 Cov 1857.901207
1: LS 357.371475 Exp 352.219082 Cov 1857.901207
LS 357.371475 Exp 352.219082 Cov 1857.901207
teststat 0.014289
var 7 teststat 0.014289
sweights 144.000000
swx 800.000000, f1 1.006993, f2 0.006993
Exp 352.219082 Cov 1857.901207
1: LS 357.371475 Exp 352.219082 Cov 1857.901207
sweights 144.000000
swx 4861.000000, f1 1.006993, f2 0.006993
Exp 2140.171196 Cov 610527.872538
1: LS 2798.615547 Exp 2140.171196 Cov 610527.872538
LS 2798.615547 Exp 2140.171196 Cov 610527.872538
teststat 0.710121
var 8 teststat 0.710121
sweights 144.000000
swx 4861.000000, f1 1.006993, f2 0.006993
Exp 2140.171196 Cov 610527.872538
1: LS 2798.615547 Exp 2140.171196 Cov 610527.872538
sweights 166.000000
swx 101.000000, f1 1.006061, f2 0.006061
Exp 3.109165 Cov 16.195298
1: LS 12.169541 Exp 3.109165 Cov 16.195298
LS 12.169541 Exp 3.109165 Cov 16.195298
teststat 5.068780
var 1 teststat 5.068780
sweights 166.000000
swx 101.000000, f1 1.006061, f2 0.006061
Exp 3.109165 Cov 16.195298
1: LS 12.169541 Exp 3.109165 Cov 16.195298
sweights 166.000000
swx 8769.000000, f1 1.006061, f2 0.006061
Exp 269.943273 Cov 7066.441425
1: LS 236.487886 Exp 269.943273 Cov 7066.441425
LS 236.487886 Exp 269.943273 Cov 7066.441425
teststat 0.158391
var 2 teststat 0.158391
sweights 166.000000
swx 8769.000000, f1 1.006061, f2 0.006061
Exp 269.943273 Cov 7066.441425
1: LS 236.487886 Exp 269.943273 Cov 7066.441425
sweights 166.000000
swx 69.000000, f1 1.006061, f2 0.006061
Exp 2.124083 Cov 16.511063
1: LS 2.710476 Exp 2.124083 Cov 16.511063
```

```
LS 2.710476 Exp 2.124083 Cov 16.511063
teststat 0.020826
var 3 teststat 0.020826
sweights 166.000000
swx 69.000000, f1 1.006061, f2 0.006061
Exp 2.124083 Cov 16.511063
1: LS 2.710476 Exp 2.124083 Cov 16.511063
sweights 166.000000
swx 5501.000000, f1 1.006061, f2 0.006061
Exp 169.341766 Cov 19024.842186
1: LS 354.036087 Exp 169.341766 Cov 19024.842186
LS 354.036087 Exp 169.341766 Cov 19024.842186
teststat 1.793024
var 4 teststat 1.793024
sweights 166.000000
swx 5501.000000, f1 1.006061, f2 0.006061
Exp 169.341766 Cov 19024.842186
1: LS 354.036087 Exp 169.341766 Cov 19024.842186
sweights 166.000000
swx 334.000000, f1 1.006061, f2 0.006061
Exp 10.281794 Cov 20.465528
1: LS 13.852271 Exp 10.281794 Cov 20.465528
LS 13.852271 Exp 10.281794 Cov 20.465528
teststat 0.622916
var 5 teststat 0.622916
sweights 166.000000
swx 334.000000, f1 1.006061, f2 0.006061
Exp 10.281794 Cov 20.465528
1: LS 13.852271 Exp 10.281794 Cov 20.465528
sweights 166.000000
swx 1405.000000, f1 1.006061, f2 0.006061
Exp 43.251260 Cov 2691.811462
1: LS 110.832947 Exp 43.251260 Cov 2691.811462
LS 110.832947 Exp 43.251260 Cov 2691.811462
teststat 1.696733
var 6 teststat 1.696733
sweights 166.000000
swx 1405.000000, f1 1.006061, f2 0.006061
Exp 43.251260 Cov 2691.811462
1: LS 110.832947 Exp 43.251260 Cov 2691.811462
sweights 166.000000
swx 31533.000000, f1 1.006061, f2 0.006061
Exp 970.706034 Cov 4399425.708293
1: LS -2404.356379 Exp 970.706034 Cov 4399425.708293
LS -2404.356379 Exp 970.706034 Cov 4399425.708293
teststat 2.589212
var 7 teststat 2.589212
sweights 166.000000
swx 31533.000000, f1 1.006061, f2 0.006061
```

```
Exp 970.706034 Cov 4399425.708293
1: LS -2404.356379 Exp 970.706034 Cov 4399425.708293
sweights 166.000000
swx 21500.000000, f1 1.006061, f2 0.006061
Exp 661.852020 Cov 1577558.575643
1: LS -1300.414654 Exp 661.852020 Cov 1577558.575643
LS -1300.414654 Exp 661.852020 Cov 1577558.575643
teststat 2.440791
var 8 teststat 2.440791
sweights 166.000000
swx 21500.000000, f1 1.006061, f2 0.006061
Exp 661.852020 Cov 1577558.575643
1: LS -1300.414654 Exp 661.852020 Cov 1577558.575643
```

and the `plot` method applied to this tree produces the graphical representation in Figure~11.6. The number of positive lymph nodes (`pnodes`) is the most important variable in the tree, corresponding to the *p*-value associated with this variable in Cox's regression; see Figure~11.3. Women with not more than three positive lymph nodes who have undergone a hormonal therapy seem to have the best prognosis whereas a large number of positive lymph nodes and a small value of the progesterone receptor indicates a bad prognosis.

```
R> plot(GBSG2_ctree)
```

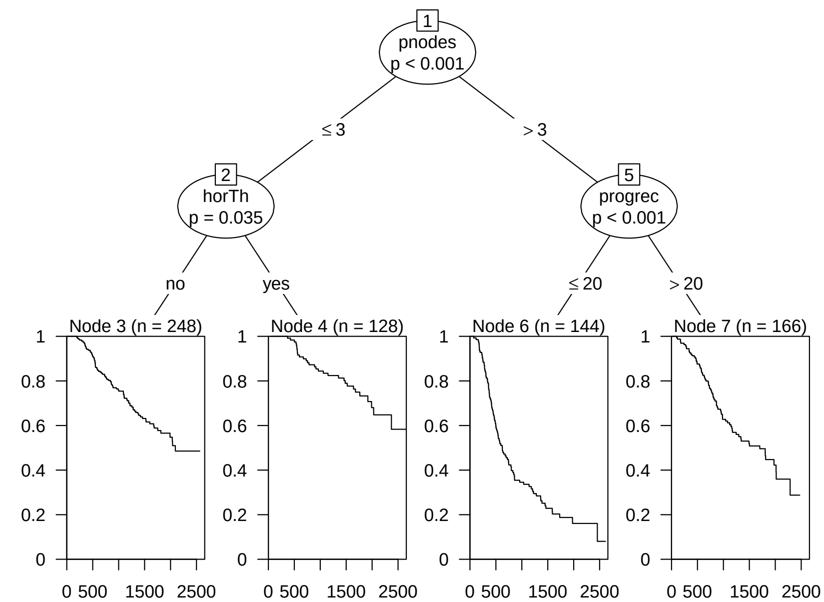

Figure 11.6 Conditional inference tree for the `GBSG2` data with the survival function, estimated by Kaplan-Meier, shown for every subgroup of patients identified by the tree.

Bibliography

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Hothorn, T., Hornik, K., van~de Wiel, M.~A., and Zeileis, A. (2006), "A Lego system for conditional inference," *The American Statistician*, 60, 257–263.

Therneau, T.~M. and Grambsch, P.~M. (2000), *Modeling Survival Data: Extending the Cox Model*, New York, USA: Springer-Verlag.