

Additional survival analyses of the data set from
Wichmann et al. (Int. J. Canc. 2015). Head and neck
tumor patients. Progression-free survival.

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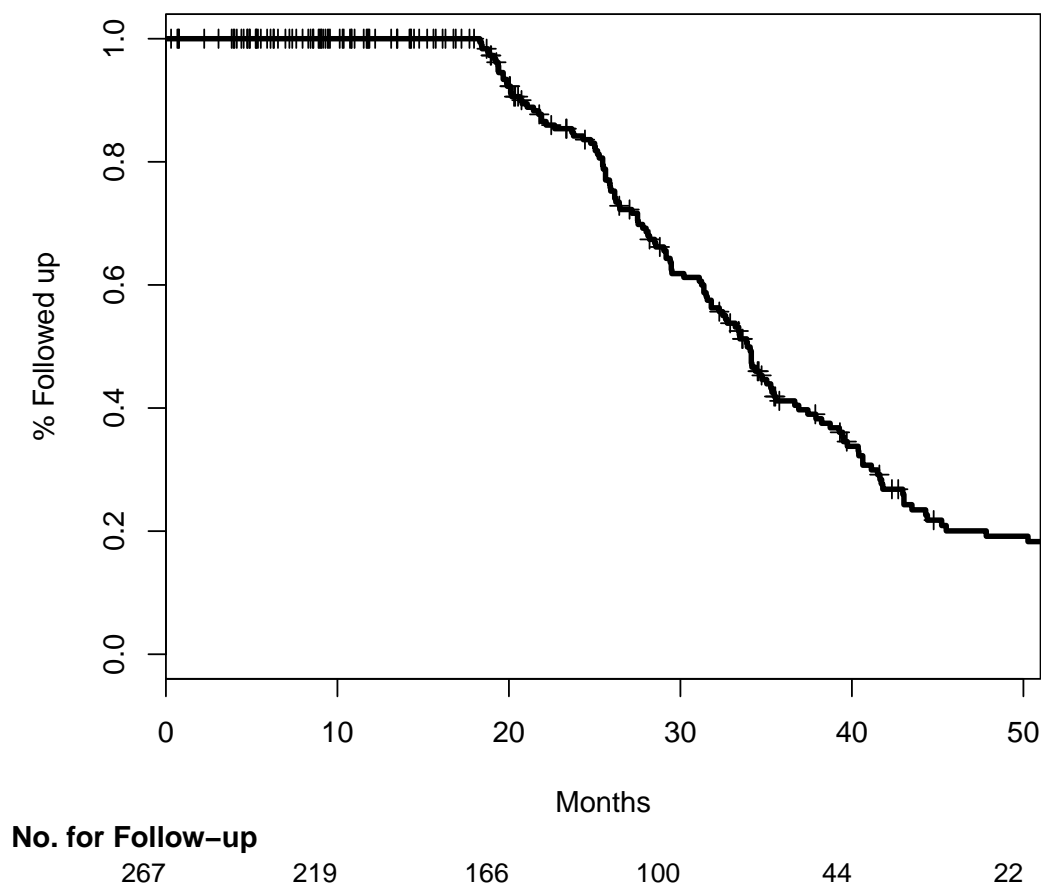
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PLEASE NOTE: For historical reasons, the Immune Response Cluster (one of the Consensus Clusters determined by gene expression) is sometimes called *Atypical* Cluster in this document.

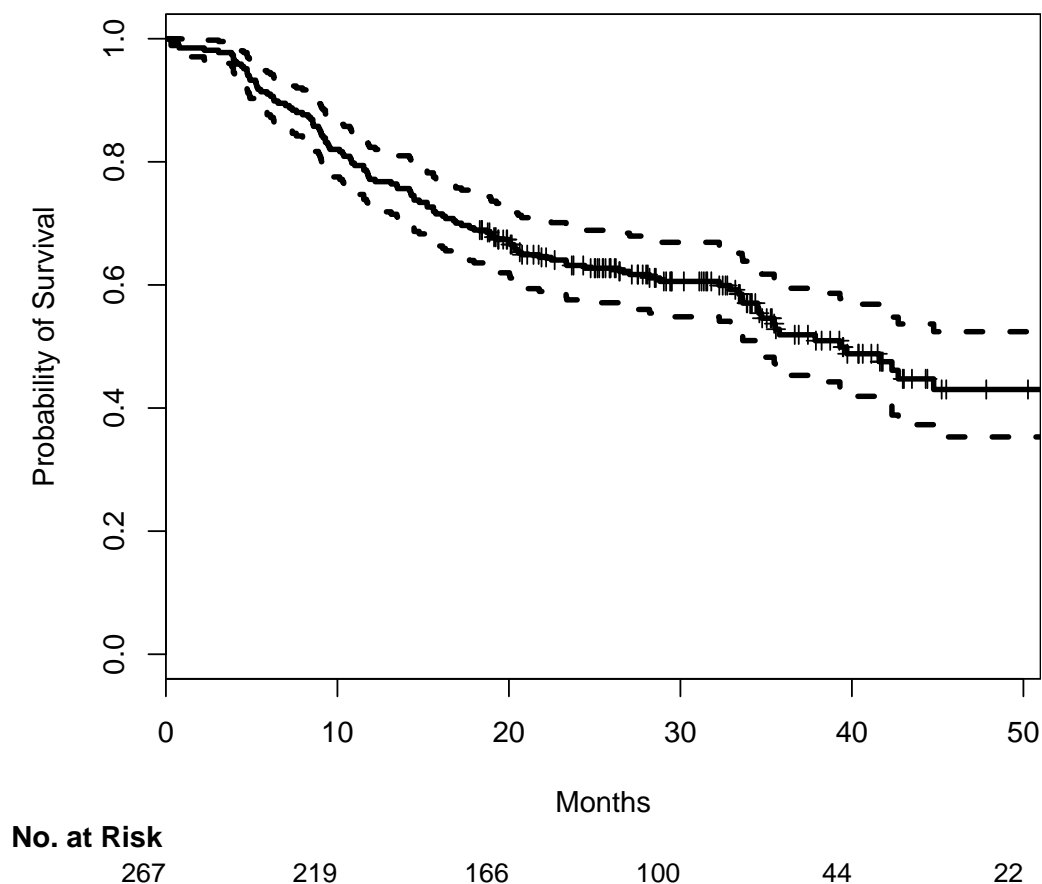
1 Follow-up

```
##
## Median follow-up =
## [1] 34.1
```



2 Survival of all patients

```
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## records    n.max n.start  events  median 0.95LCL 0.95UCL
##    267.0    267.0   267.0   126.0   39.3    34.6    59.0
```



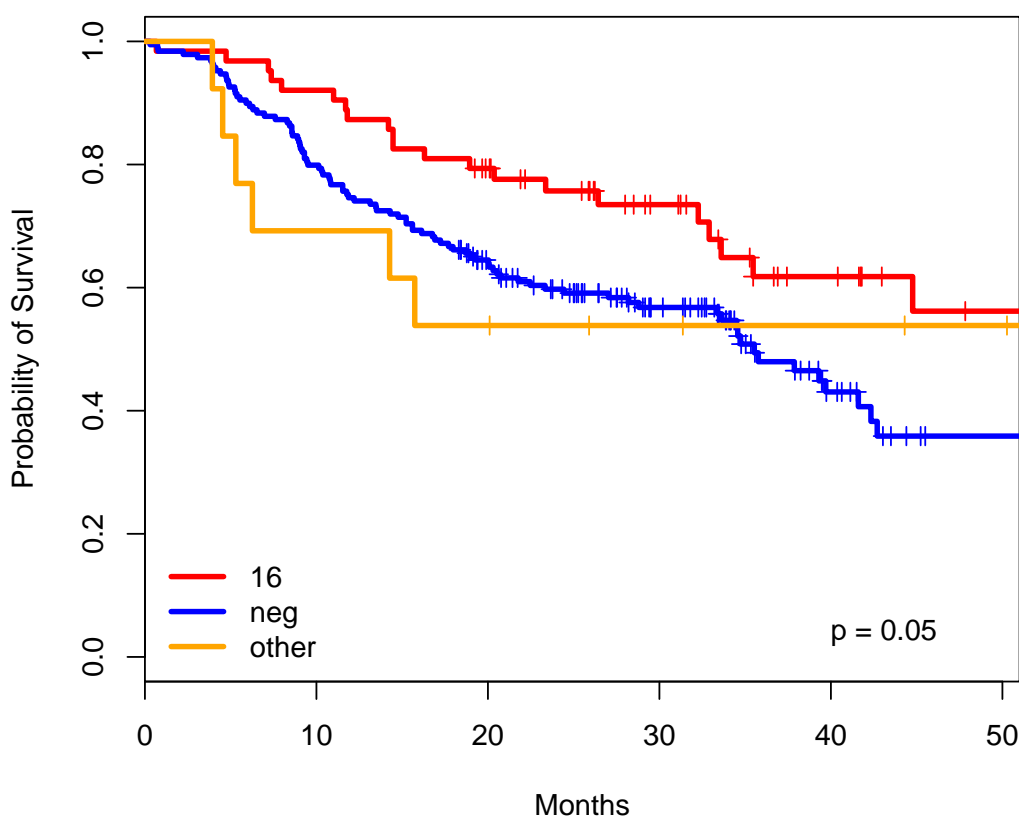
3 Exploration of single variables

3.1 HPV DNA

Legend: 16 denotes HPV16+, neg denotes HPV-, other denotes HPV DNA+ patients having HPV other than HPV16.

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 265, number of events= 125
##    (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]neg  0.563    1.755   0.235  2.39   0.017 *
```

```
## split[cur.subset]other 0.596      1.815      0.434 1.37      0.169
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]neg      1.76      0.570      1.107      2.78
## split[cur.subset]other      1.82      0.551      0.776      4.25
##
## Concordance= 0.557 (se = 0.023 )
## Rsquare= 0.024 (max possible= 0.991 )
## Likelihood ratio test= 6.56 on 2 df,  p=0.0377
## Wald test              = 5.87 on 2 df,  p=0.053
## Score (logrank) test = 6.02 on 2 df,  p=0.0492
```



No. at Risk

16	63	58	47	29	16	9
neg	189	151	111	65	23	9
other	13	9	7	5	4	3

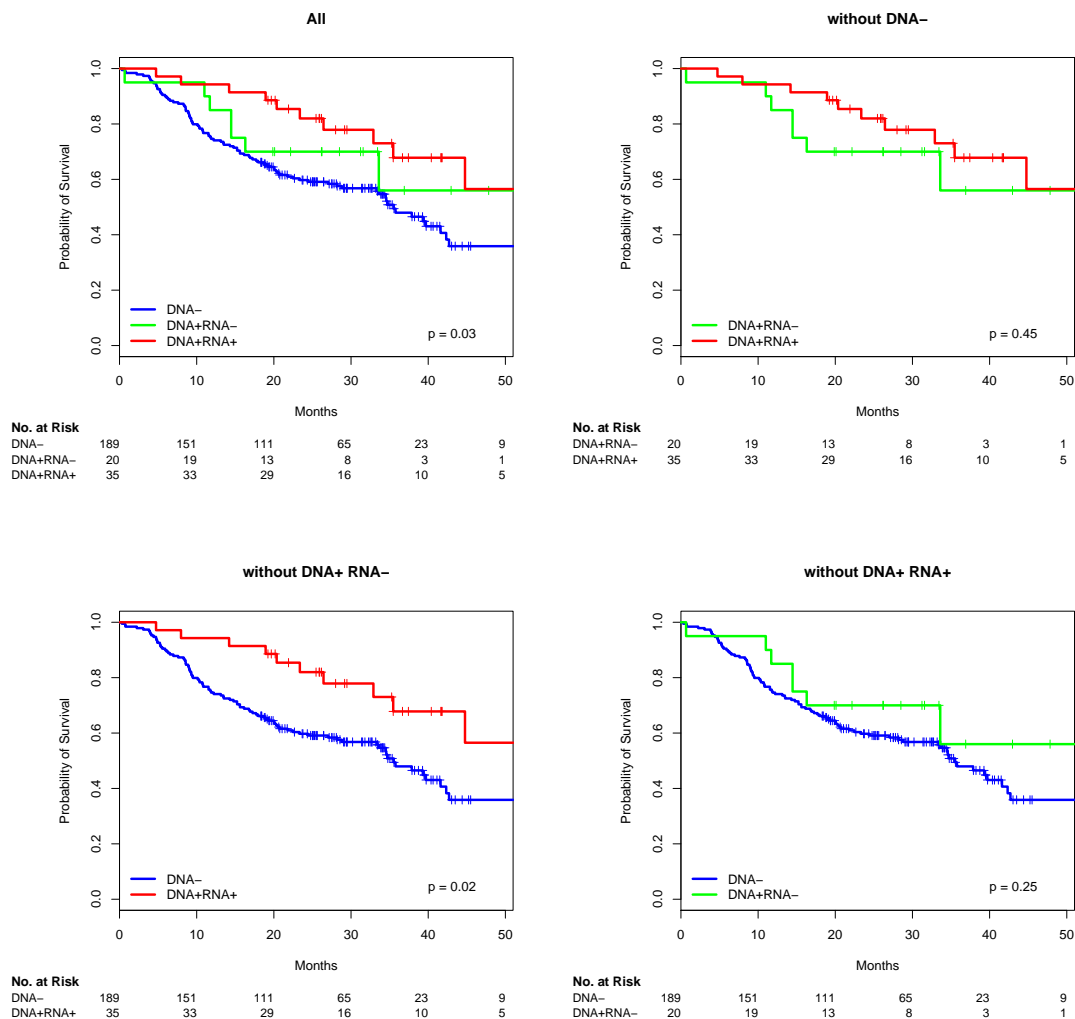
3.2 HPV DNA RNA

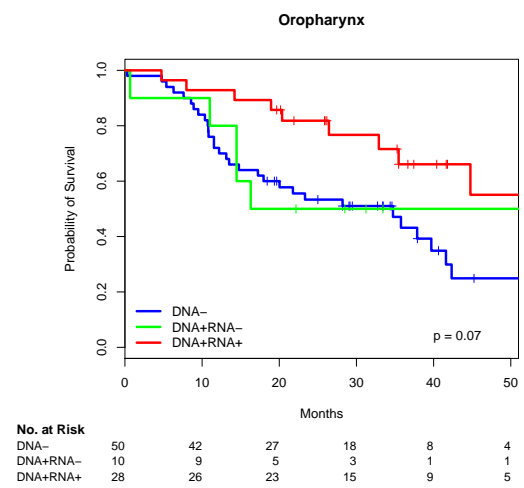
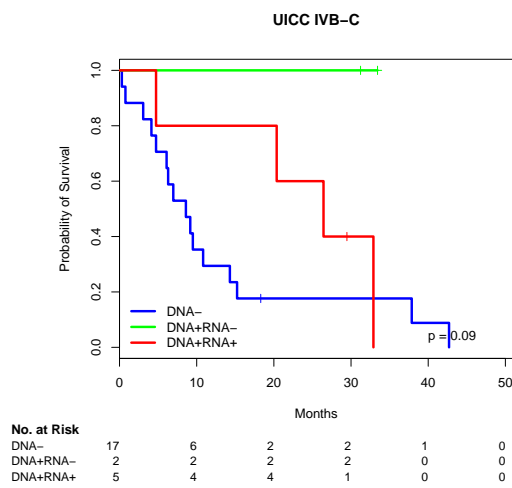
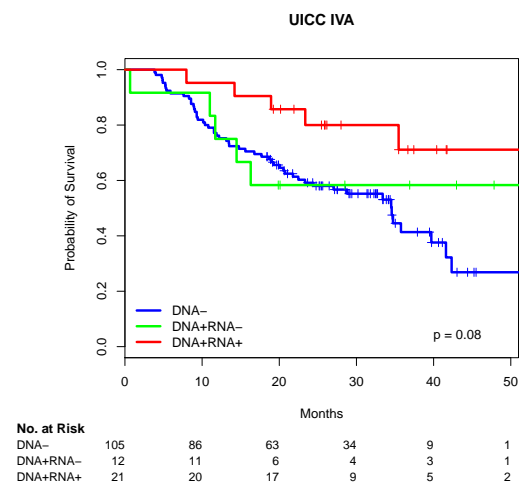
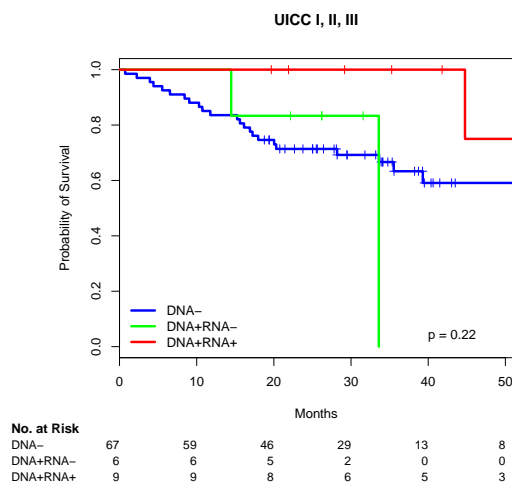
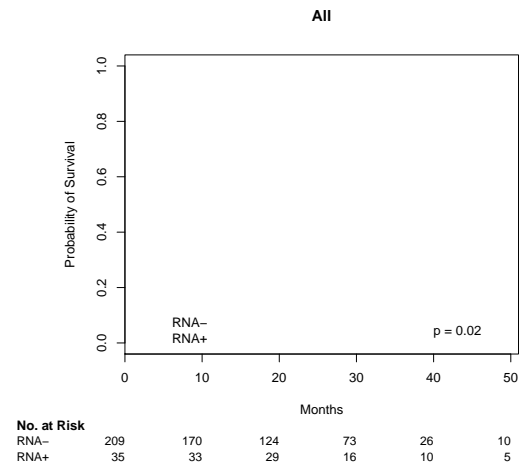
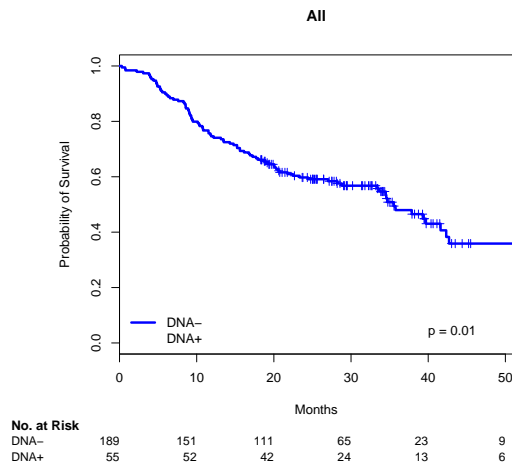
```
##
## 3-Year survival rates for all patients:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 23 observations deleted due to missingness
##           split[cur.subset]=DNA-
##      time      n.risk      n.event      survival      std.err
##    36.0000      33.0000      86.0000      0.4796      0.0442
## lower 95% CI upper 95% CI
##    0.4004      0.5745
##
##           split[cur.subset]=DNA+RNA-
##      time      n.risk      n.event      survival      std.err
##    36.000      4.000      7.000      0.560      0.150
## lower 95% CI upper 95% CI
##    0.332      0.946
##
##           split[cur.subset]=DNA+RNA+
##      time      n.risk      n.event      survival      std.err
##    36.0000     12.0000      9.0000      0.6781      0.0934
## lower 95% CI upper 95% CI
##    0.5177      0.8882
## Call: survfit(formula = surv.obj[cur.subset] ~ 1)
##
##   time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    36     57    113    0.519   0.036     0.453     0.595
##
## 3-Year survival rates in Oropharynx patients:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 19 observations deleted due to missingness
##           split[cur.subset]=DNA-
##      time      n.risk      n.event      survival      std.err
##    36.0000     11.0000     26.0000      0.4317      0.0795
## lower 95% CI upper 95% CI
##    0.3009      0.6193
##
##           split[cur.subset]=DNA+RNA-
##      time      n.risk      n.event      survival      std.err
##    36.000      1.000      5.000      0.500      0.158
## lower 95% CI upper 95% CI
##    0.269      0.929
##
##           split[cur.subset]=DNA+RNA+
##      time      n.risk      n.event      survival      std.err
##    36.000     11.000      8.000      0.661      0.101
## lower 95% CI upper 95% CI
##    0.489      0.892
```

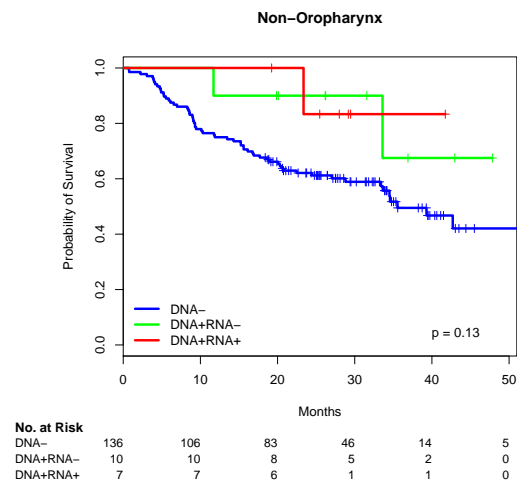


```
## Call: survfit(formula = surv.obj[cur.subset] ~ 1)
##
##   time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    36     30     47     0.52  0.0534      0.425      0.636
##
##
## #####
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 244, number of events= 112
##   (23 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]DNA+RNA- -0.452    0.637   0.392 -1.15   0.249
## split[cur.subset]DNA+RNA+ -0.756    0.469   0.320 -2.36   0.018 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]DNA+RNA-    0.637    1.57    0.295    1.373
## split[cur.subset]DNA+RNA+    0.469    2.13    0.251    0.879
##
## Concordance= 0.56 (se = 0.022 )
## Rsquare= 0.031 (max possible= 0.989 )
## Likelihood ratio test= 7.63 on 2 df,  p=0.0221
## Wald test               = 6.5 on 2 df,  p=0.0389
## Score (logrank) test = 6.77 on 2 df,  p=0.034
##
##
## #####
## Cox model in Oropharynx patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 88, number of events= 45
##   (19 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]DNA+RNA- -0.114    0.893   0.484 -0.23   0.814
## split[cur.subset]DNA+RNA+ -0.831    0.436   0.367 -2.26   0.024 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]DNA+RNA-    0.893    1.12    0.345    2.306
```

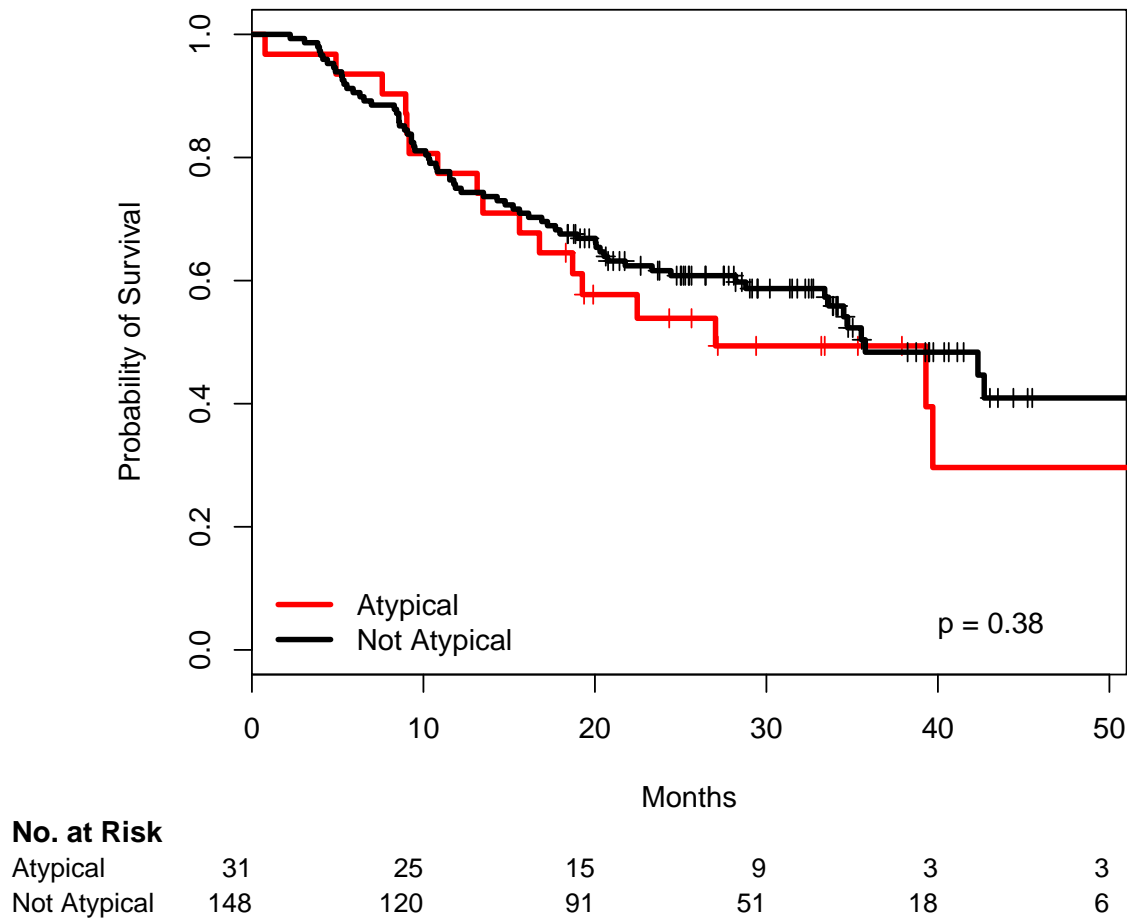
```
## split[cur.subset]DNA+RNA+      0.436      2.30      0.212      0.894
##
## Concordance= 0.597 (se = 0.042 )
## Rsquare= 0.065 (max possible= 0.982 )
## Likelihood ratio test= 5.87 on 2 df, p=0.0532
## Wald test = 5.16 on 2 df, p=0.0756
## Score (logrank) test = 5.45 on 2 df, p=0.0656
```





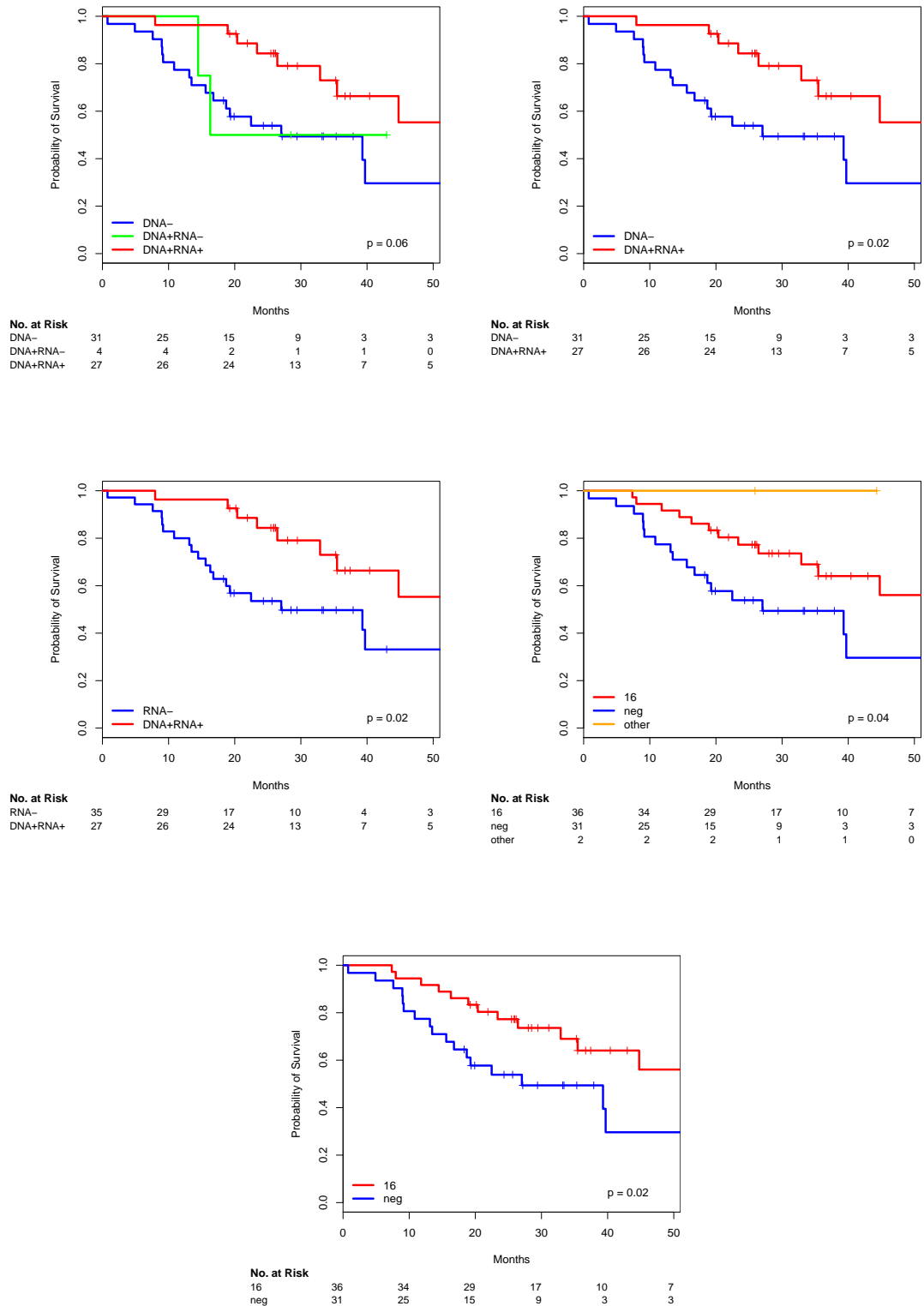


3.2.1 Consensus Cluster in HPV DNA-: Immune Response (IR) Cluster (also called Atypical here) vs. other Clusters



3.2.2 HPV-groups in the Atypical Consensus Cluster

The HPV groups are created by the HPV DNA and RNA status or by the DNA status (HPV16 positive and negative).



3.3 Consensus Clusters, Atypical cluster split by HPV status (DNA, RNA)

```

##
##
## #####
##
## Cox model. Covariates: HPV16 DNA RNA status, all Consensus Clusters, no interaction
## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + CONSENSUS_CLUSTER,
##       data = ds[cur.subset, ])
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA-    -0.2898    0.7484   0.3957 -0.73   0.464
## HPV16_DNA_RNADNA+RNA+    -0.8761    0.4164   0.3548 -2.47   0.014 *
## CONSENSUS_CLUSTERBasal    -0.2888    0.7491   0.2802 -1.03   0.303
## CONSENSUS_CLUSTERClassical -0.6153    0.5405   0.4156 -1.48   0.139
## CONSENSUS_CLUSTERMesenchymal -0.0475    0.9536   0.2689 -0.18   0.860
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.748      1.34    0.345    1.625
## HPV16_DNA_RNADNA+RNA+    0.416      2.40    0.208    0.835
## CONSENSUS_CLUSTERBasal    0.749      1.33    0.433    1.297
## CONSENSUS_CLUSTERClassical 0.540      1.85    0.239    1.220
## CONSENSUS_CLUSTERMesenchymal 0.954      1.05    0.563    1.615
##
## Concordance= 0.594 (se = 0.03 )
## Rsquare= 0.04 (max possible= 0.988 )
## Likelihood ratio test= 9.42 on 5 df,  p=0.0935
## Wald test = 8.5 on 5 df,  p=0.131
## Score (logrank) test = 8.8 on 5 df,  p=0.117
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##               Df Chisq Pr(>Chisq)
## HPV16_DNA_RNA    2  6.34   0.042 *
## CONSENSUS_CLUSTER 3  3.14   0.370
## Residuals       228
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## #####
##
## Cox model. Covariates: HPV16 DNA RNA status, Atypical vs. other Consensus Clusters
## Call:

```

```
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + I(CONSENSUS_CLUSTER ==
## "Atypical"), data = ds[cur.subset, ])
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z
## HPV16_DNA_RNADNA+RNA- -0.288    0.750   0.394 -0.73
## HPV16_DNA_RNADNA+RNA+ -0.850    0.427   0.356 -2.39
## I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.218    1.244   0.243  0.90
##               Pr(>|z|)
## HPV16_DNA_RNADNA+RNA-    0.464
## HPV16_DNA_RNADNA+RNA+    0.017 *
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    0.370
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95
## HPV16_DNA_RNADNA+RNA-    0.750    1.334    0.346
## HPV16_DNA_RNADNA+RNA+    0.427    2.341    0.212
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    1.244    0.804    0.772
##               upper .95
## HPV16_DNA_RNADNA+RNA-    1.622
## HPV16_DNA_RNADNA+RNA+    0.859
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    2.004
##
## Concordance= 0.565 (se = 0.027 )
## Rsquare= 0.029 (max possible= 0.988 )
## Likelihood ratio test= 6.83 on 3 df, p=0.0774
## Wald test = 5.97 on 3 df, p=0.113
## Score (logrank) test = 6.16 on 3 df, p=0.104
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##               Df Chisq Pr(>Chisq)
## HPV16_DNA_RNA    2  5.95    0.051 .
## I(CONSENSUS_CLUSTER == "Atypical")    1  0.80    0.370
## Residuals      230
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## #####
##
## Cox model. Covariates: HPV16 DNA RNA status, Atypical vs. other Consensus Clusters
## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_RNA * I(CONSENSUS_CLUSTER ==
## "Atypical"), data = ds[cur.subset, ])
```



```

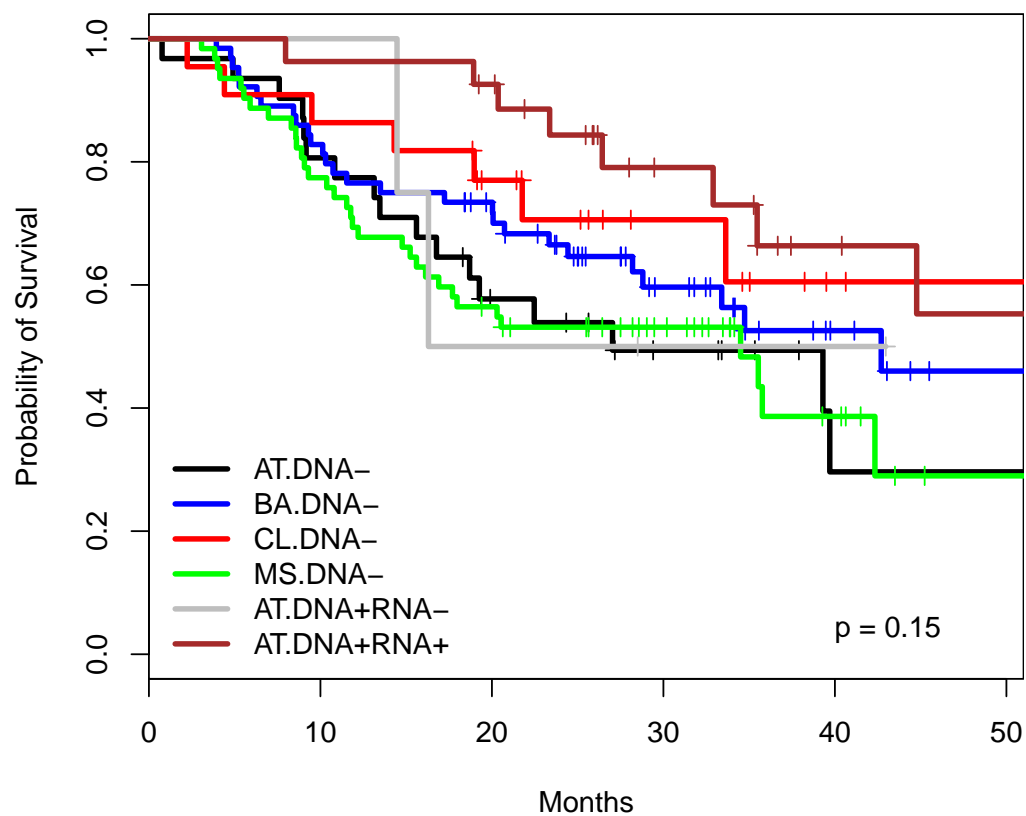
##
##   n= 214, number of events= 97
##   (33 observations deleted due to missingness)
##
##                                     coef exp(coef)
## HPV16_RNARNA+                      -0.692    0.500
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.228    1.257
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE -0.199    0.820
##                                     se(coef)      z
## HPV16_RNARNA+                      0.718 -0.96
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.266  0.86
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.827 -0.24
##                                     Pr(>|z|)
## HPV16_RNARNA+                      0.34
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.39
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.81
##
##                                     exp(coef) exp(-coef)
## HPV16_RNARNA+                      0.50    1.998
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      1.26    0.796
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.82    1.220
##                                     lower .95 upper .95
## HPV16_RNARNA+                      0.122    2.05
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.747    2.11
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.162    4.14
##
## Concordance= 0.562 (se = 0.026 )
## Rsquare= 0.03 (max possible= 0.987 )
## Likelihood ratio test= 6.58 on 3 df, p=0.0866
## Wald test = 5.71 on 3 df, p=0.127
## Score (logrank) test = 5.95 on 3 df, p=0.114
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##                                     Df Chisq Pr(>Chisq)
## HPV16_RNA                          1  5.61    0.018 *
## I(CONSENSUS_CLUSTER == "Atypical")  1  0.68    0.409
## HPV16_RNA:I(CONSENSUS_CLUSTER == "Atypical")  1  0.06    0.810
## Residuals                          211
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
## #####
##
## Cox modell. Covariates: HPV16 RNA status, Atypical vs. other Consensus Clusters,
## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_RNA * I(CONSENSUS_CLUSTER ==

```

```

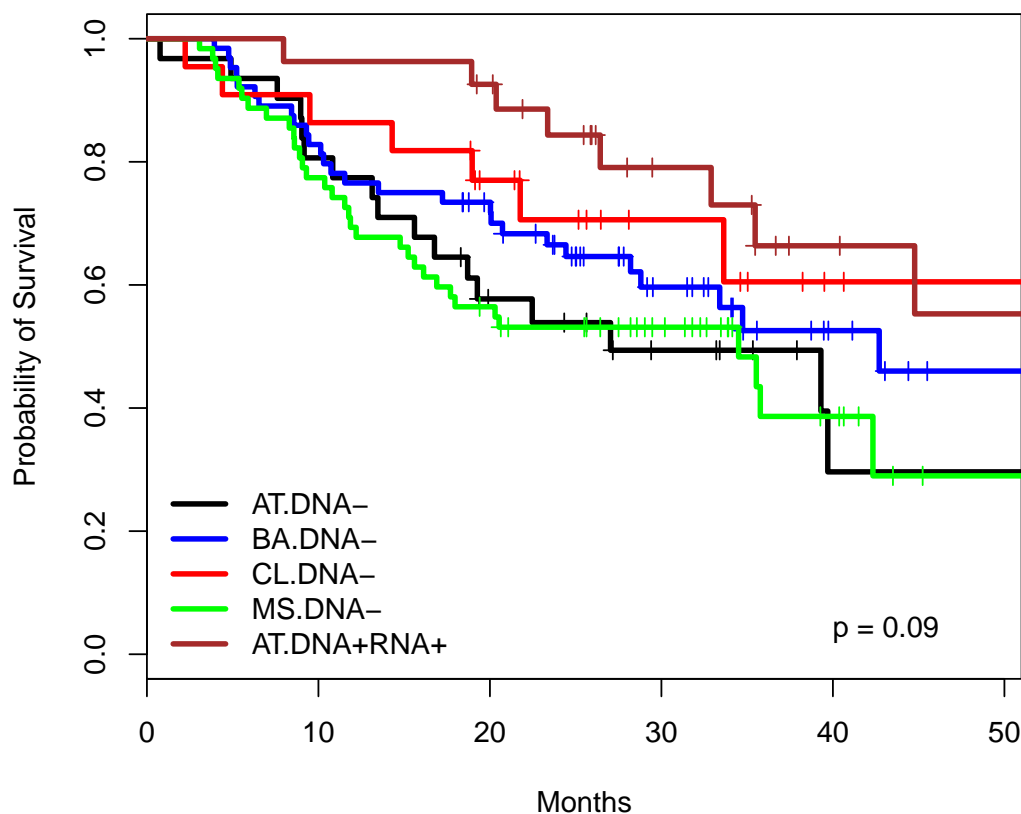
##      "Atypical"), data = ds[cur.subset, ])
##
##      n= 214, number of events= 97
##      (33 observations deleted due to missingness)
##
##                                     coef exp(coef)
## HPV16_RNARNA+                      -0.692    0.500
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.228    1.257
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE -0.199    0.820
##                                     se(coef)      z
## HPV16_RNARNA+                      0.718 -0.96
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.266  0.86
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.827 -0.24
##                                     Pr(>|z|)
## HPV16_RNARNA+                      0.34
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.39
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.81
##
##                                     exp(coef) exp(-coef)
## HPV16_RNARNA+                      0.50    1.998
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      1.26    0.796
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.82    1.220
##                                     lower .95 upper .95
## HPV16_RNARNA+                      0.122    2.05
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.747    2.11
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE  0.162    4.14
##
## Concordance= 0.562 (se = 0.026 )
## Rsquare= 0.03 (max possible= 0.987 )
## Likelihood ratio test= 6.58 on 3 df, p=0.0866
## Wald test = 5.71 on 3 df, p=0.127
## Score (logrank) test = 5.95 on 3 df, p=0.114
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##                                     Df Chisq Pr(>Chisq)
## HPV16_RNA                          1  5.61    0.018 *
## I(CONSENSUS_CLUSTER == "Atypical")  1  0.68    0.409
## HPV16_RNA:I(CONSENSUS_CLUSTER == "Atypical")  1  0.06    0.810
## Residuals                          211
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```



No. at Risk

	0	10	20	30	40	50
AT.DNA-	31	25	15	9	3	3
BA.DNA-	64	53	43	22	9	4
CL.DNA-	22	19	14	7	2	1
MS.DNA-	62	48	34	22	7	1
AT.DNA+RNA-	4	4	2	1	1	0
AT.DNA+RNA+	27	26	24	13	7	5



No. at Risk						
AT.DNA-	31	25	15	9	3	3
BA.DNA-	64	53	43	22	9	4
CL.DNA-	22	19	14	7	2	1
MS.DNA-	62	48	34	22	7	1
AT.DNA+RNA+	27	26	24	13	7	5

3.4 Consensus Cluster

```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 253, number of events= 117
## (14 observations deleted due to missingness)
##
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
--	------	-----------	----------	---	----------

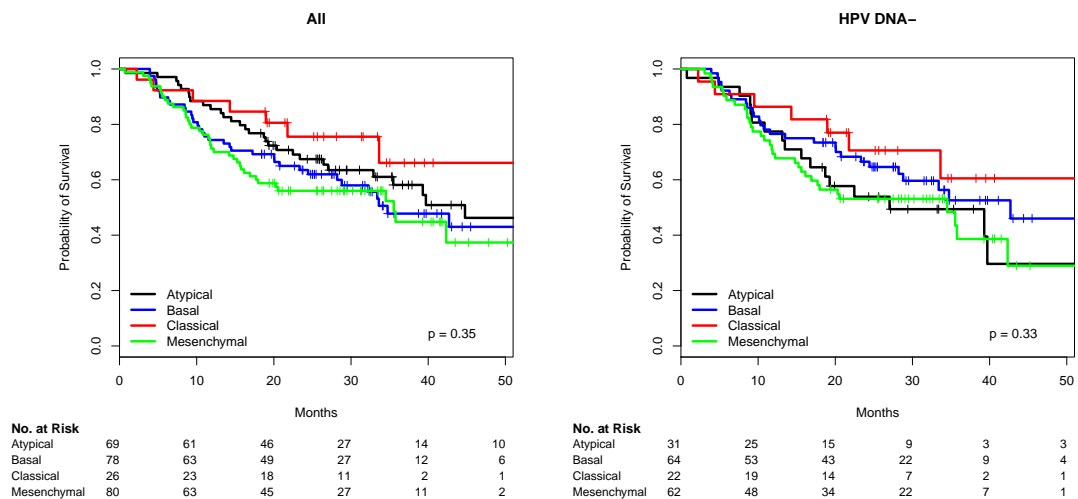
```

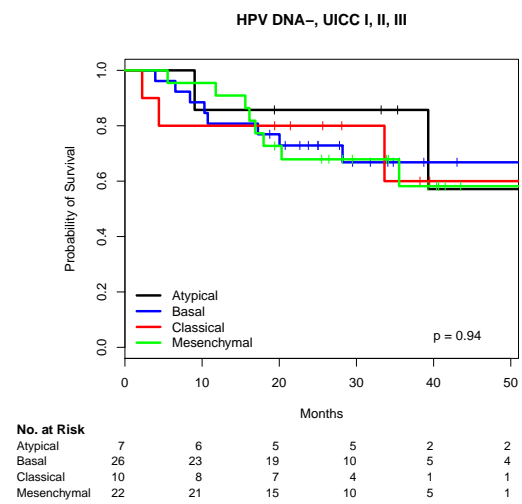
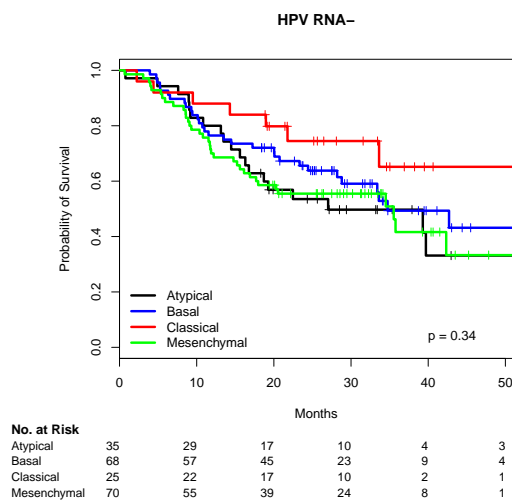
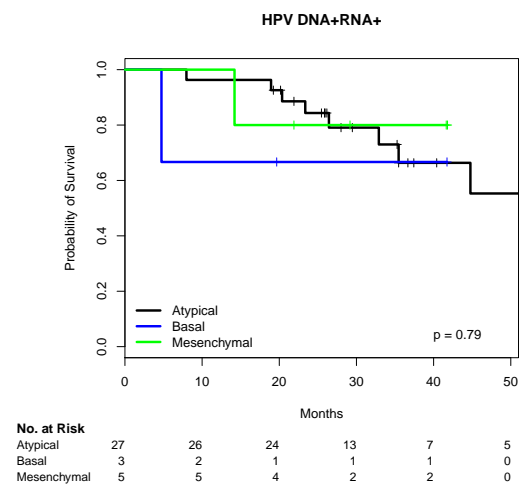
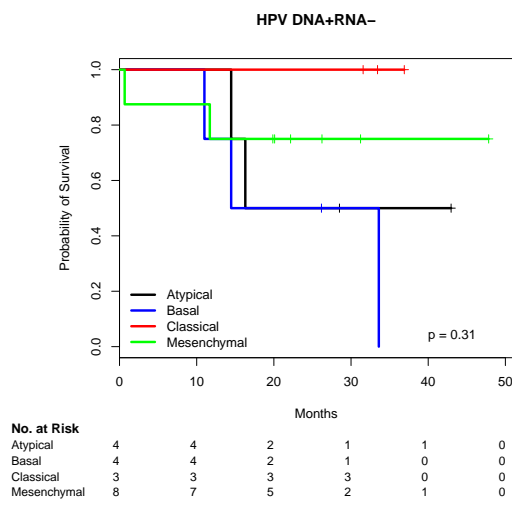
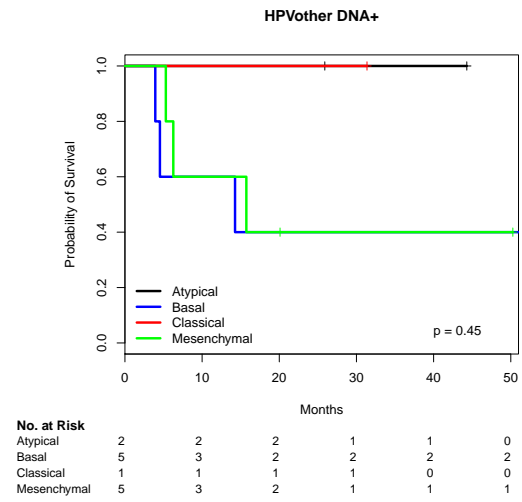
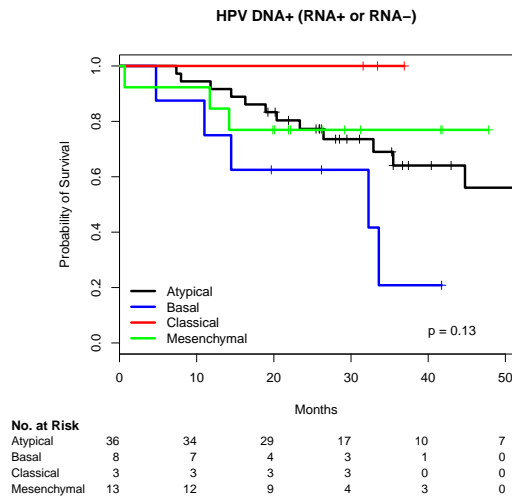
## split[cur.subset]Basal      0.179      1.196      0.242  0.74      0.46
## split[cur.subset]Classical -0.274      0.760      0.398 -0.69      0.49
## split[cur.subset]Mesenchymal 0.316      1.372      0.241  1.31      0.19
##
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      1.20      0.836      0.744      1.92
## split[cur.subset]Classical  0.76      1.315      0.349      1.66
## split[cur.subset]Mesenchymal 1.37      0.729      0.855      2.20
##
## Concordance= 0.562  (se = 0.028 )
## Rsquare= 0.013  (max possible= 0.99 )
## Likelihood ratio test= 3.41  on 3 df,  p=0.332
## Wald test = 3.25  on 3 df,  p=0.355
## Score (logrank) test = 3.29  on 3 df,  p=0.348
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 14 observations deleted due to missingness
##
##              split[cur.subset]=Atypical
##      time      n.risk      n.event      survival      std.err
## 36.0000      19.0000      26.0000      0.5814      0.0662
## lower 95% CI upper 95% CI
## 0.4651      0.7267
##
##              split[cur.subset]=Basal
##      time      n.risk      n.event      survival      std.err
## 36.0000      15.0000      35.0000      0.4778      0.0674
## lower 95% CI upper 95% CI
## 0.3625      0.6298
##
##              split[cur.subset]=Classical
##      time      n.risk      n.event      survival      std.err
## 36.000      5.000      7.000      0.661      0.117
## lower 95% CI upper 95% CI
## 0.467      0.936
##
##              split[cur.subset]=Mesenchymal
##      time      n.risk      n.event      survival      std.err
## 36.0000      12.0000      38.0000      0.4481      0.0731
## lower 95% CI upper 95% CI
## 0.3256      0.6169
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])

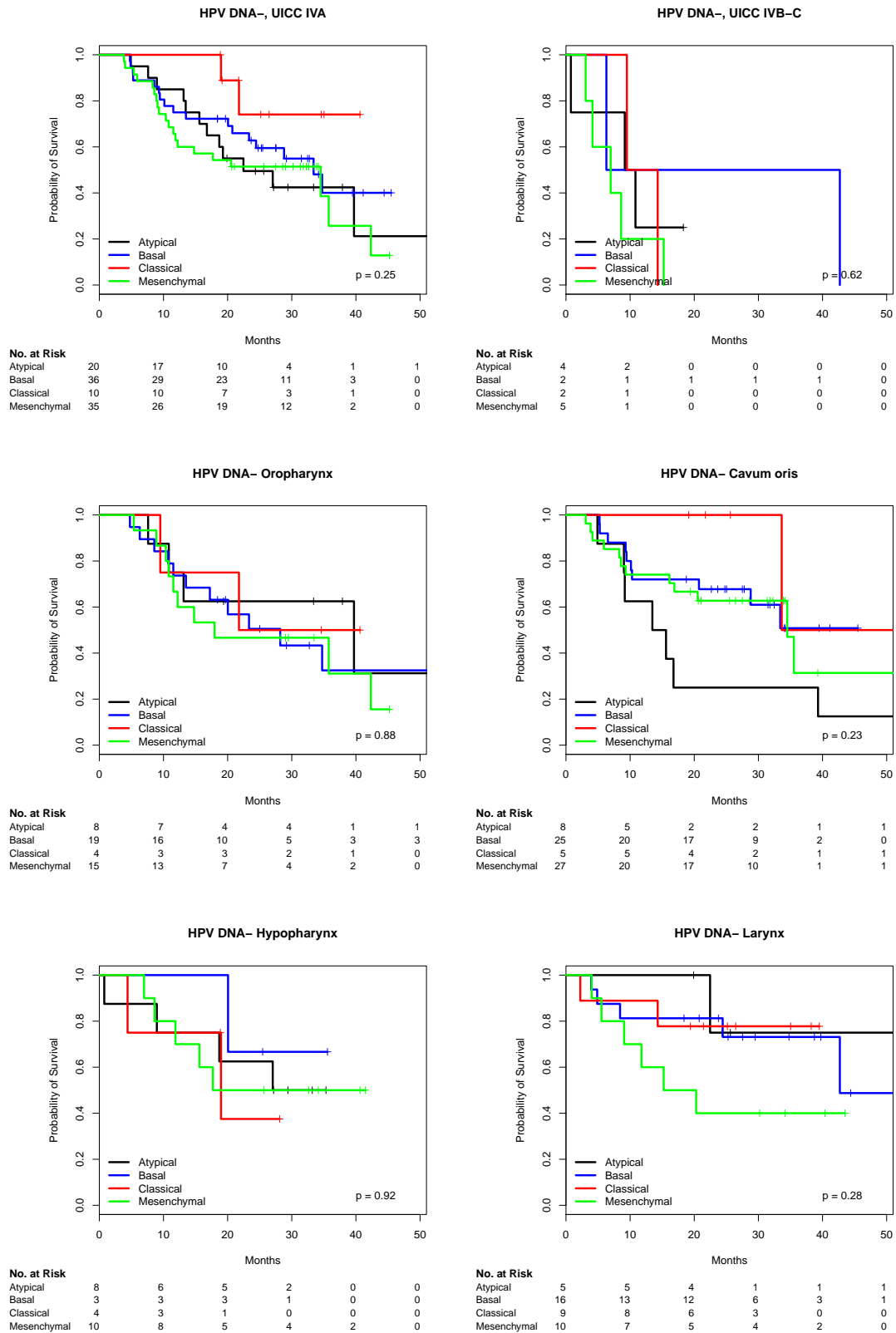
```

```
##
## n= 179, number of events= 86
## (12 observations deleted due to missingness)
##
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      -0.37739    0.68565  0.30462 -1.24    0.22
## split[cur.subset]Classical -0.50239    0.60508  0.42576 -1.18    0.24
## split[cur.subset]Mesenchymal -0.00994    0.99011  0.29400 -0.03    0.97
##
##      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      0.686      1.46    0.377    1.25
## split[cur.subset]Classical  0.605      1.65    0.263    1.39
## split[cur.subset]Mesenchymal 0.990      1.01    0.556    1.76
##
## Concordance= 0.552 (se = 0.032 )
## Rsquare= 0.019 (max possible= 0.989 )
## Likelihood ratio test= 3.49 on 3 df, p=0.322
## Wald test = 3.4 on 3 df, p=0.333
## Score (logrank) test = 3.45 on 3 df, p=0.327
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 198, number of events= 93
## (11 observations deleted due to missingness)
##
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      -0.2915    0.7471  0.2889 -1.01    0.31
## split[cur.subset]Classical -0.6359    0.5295  0.4192 -1.52    0.13
## split[cur.subset]Mesenchymal -0.0472    0.9539  0.2812 -0.17    0.87
##
##      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      0.747      1.34    0.424    1.32
## split[cur.subset]Classical  0.529      1.89    0.233    1.20
## split[cur.subset]Mesenchymal 0.954      1.05    0.550    1.66
##
## Concordance= 0.553 (se = 0.031 )
## Rsquare= 0.018 (max possible= 0.989 )
## Likelihood ratio test= 3.52 on 3 df, p=0.318
## Wald test = 3.28 on 3 df, p=0.351
## Score (logrank) test = 3.34 on 3 df, p=0.342
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
```

```
## 11 observations deleted due to missingness
##
##           split[cur.subset]=Atypical
##           time      n.risk      n.event      survival      std.err
##           36.0000      7.0000      17.0000      0.4970      0.0876
## lower 95% CI upper 95% CI
##           0.3518      0.7021
##
##           split[cur.subset]=Basal
##           time      n.risk      n.event      survival      std.err
##           36.0000      12.0000      29.0000      0.4933      0.0742
## lower 95% CI upper 95% CI
##           0.3674      0.6624
##
##           split[cur.subset]=Classical
##           time      n.risk      n.event      survival      std.err
##           36.000      5.000      7.000      0.652      0.118
## lower 95% CI upper 95% CI
##           0.457      0.930
##
##           split[cur.subset]=Mesenchymal
##           time      n.risk      n.event      survival      std.err
##           36.0000      9.0000      34.0000      0.4162      0.0825
## lower 95% CI upper 95% CI
##           0.2821      0.6139
```







3.5 “Mesenchymal” vs. other Consensus Clusters

```

## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 253, number of events= 117
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.270      1.310      0.198 1.36      0.17
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.31      0.763      0.889      1.93
##
## Concordance= 0.54 (se = 0.023 )
## Rsquare= 0.007 (max possible= 0.99 )
## Likelihood ratio test= 1.81 on 1 df, p=0.179
## Wald test = 1.86 on 1 df, p=0.172
## Score (logrank) test = 1.87 on 1 df, p=0.171
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 14 observations deleted due to missingness
##               split[cur.subset]=Not Mesenchymal
##           time      n.risk      n.event      survival      std.err
##      36.0000      39.0000      68.0000      0.5469      0.0442
## lower 95% CI upper 95% CI
##      0.4668      0.6407
##
##               split[cur.subset]=Mesenchymal
##           time      n.risk      n.event      survival      std.err
##      36.0000      12.0000      38.0000      0.4481      0.0731
## lower 95% CI upper 95% CI
##      0.3256      0.6169
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 179, number of events= 86
## (12 observations deleted due to missingness)

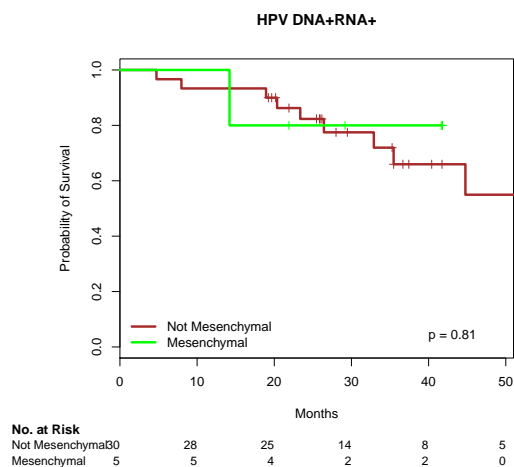
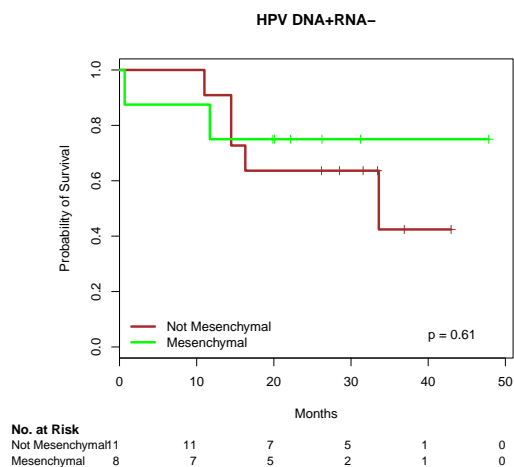
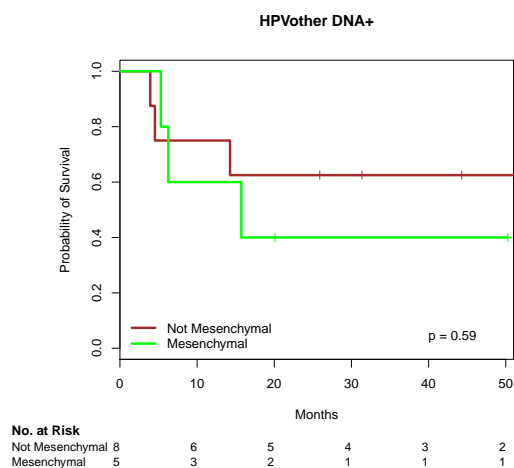
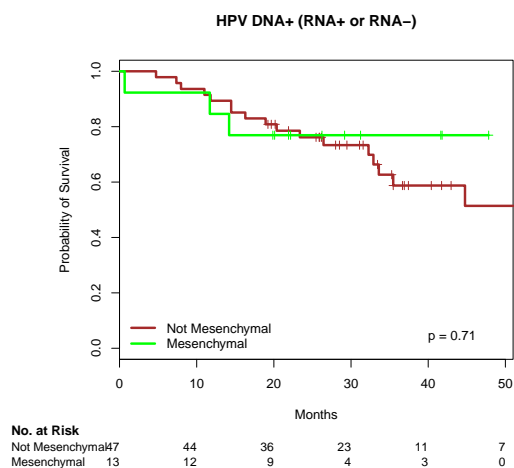
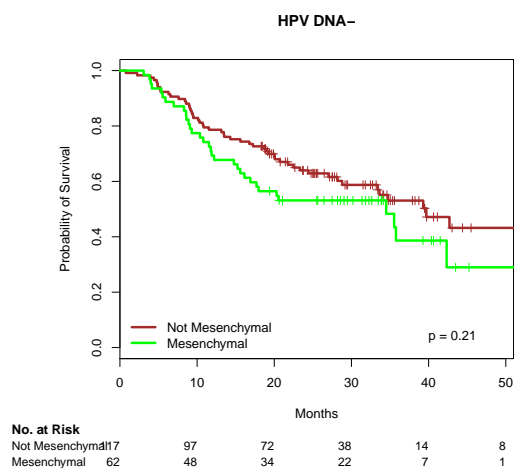
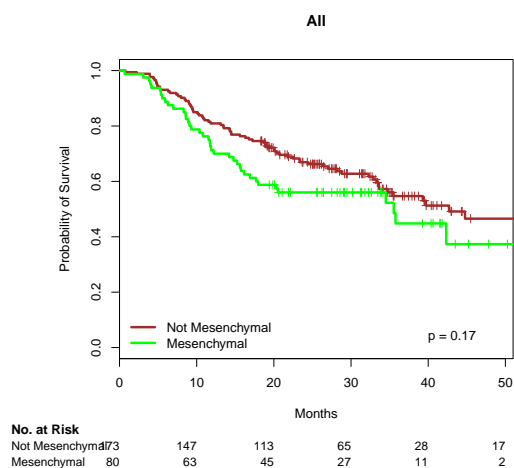
```

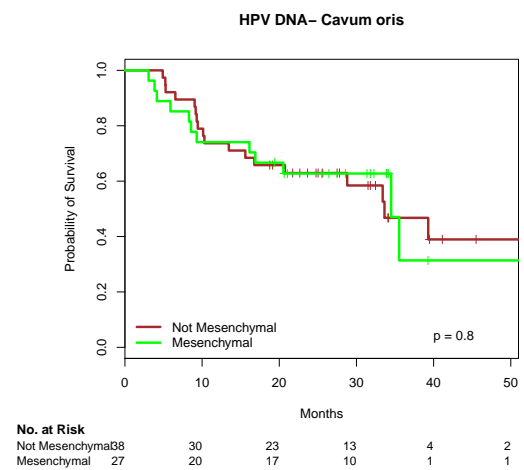
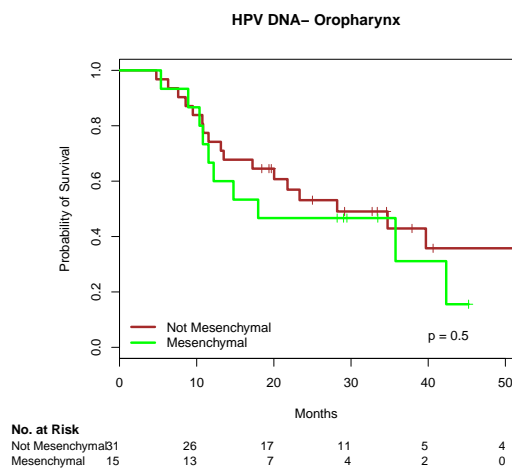
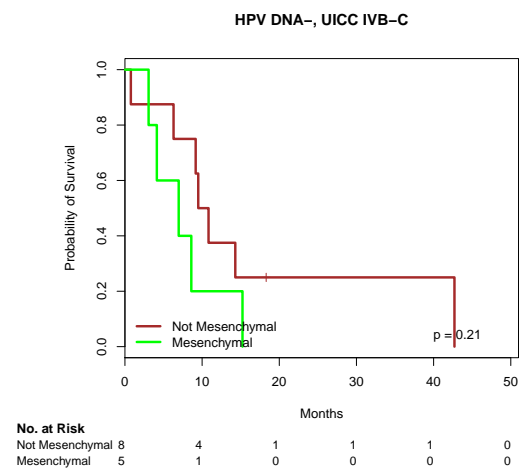
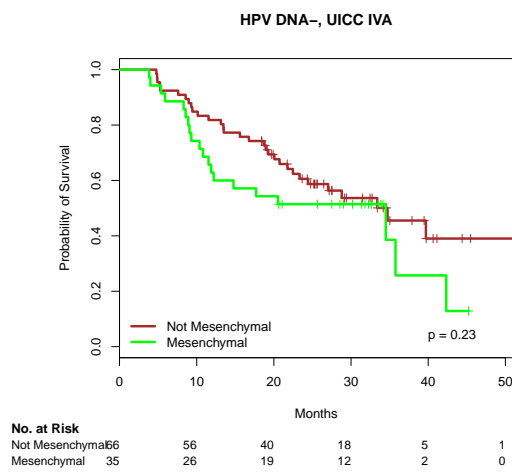
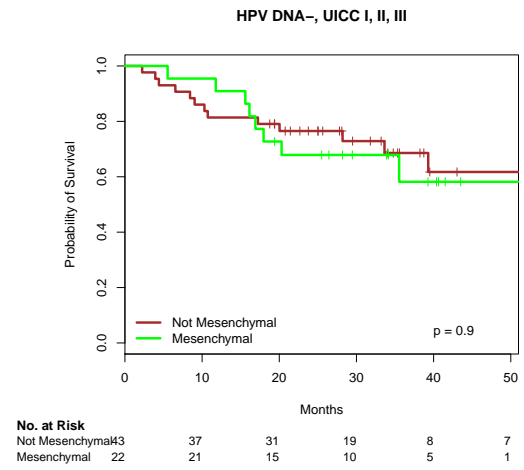
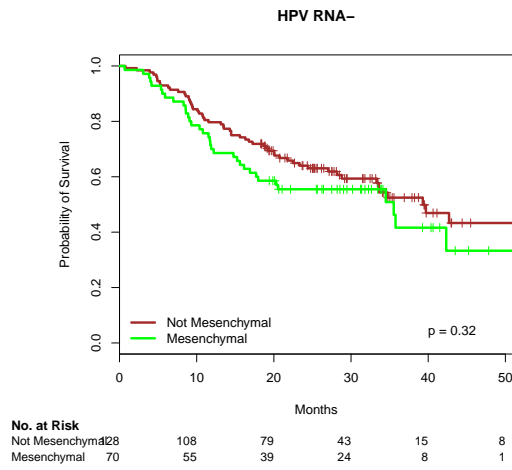
```

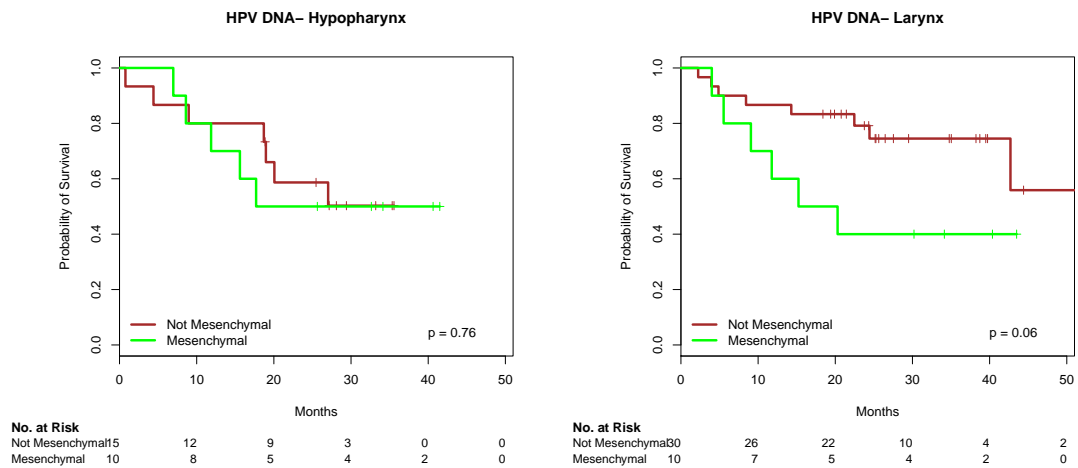
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.277      1.320      0.222 1.25      0.21
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.32      0.758      0.853      2.04
##
## Concordance= 0.539 (se = 0.027 )
## Rsquare= 0.008 (max possible= 0.989 )
## Likelihood ratio test= 1.52 on 1 df,  p=0.218
## Wald test = 1.56 on 1 df,  p=0.212
## Score (logrank) test = 1.57 on 1 df,  p=0.211
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 198, number of events= 93
## (11 observations deleted due to missingness)
##
##               coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.214      1.239      0.215 1      0.32
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.24      0.807      0.814      1.89
##
## Concordance= 0.534 (se = 0.026 )
## Rsquare= 0.005 (max possible= 0.989 )
## Likelihood ratio test= 0.98 on 1 df,  p=0.323
## Wald test = 1 on 1 df,  p=0.318
## Score (logrank) test = 1 on 1 df,  p=0.317
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 11 observations deleted due to missingness
##               split[cur.subset]=Not Mesenchymal
##               time      n.risk      n.event      survival      std.err
##               36.000      24.000      53.000      0.525      0.052
## lower 95% CI upper 95% CI
##               0.432      0.637
##
##               split[cur.subset]=Mesenchymal
##               time      n.risk      n.event      survival      std.err
##               36.0000      9.0000      34.0000      0.4162      0.0825
## lower 95% CI upper 95% CI

```

0.2821 0.6139







3.6 Tumor samples from the LIFE-HNG project vs. obtained prior to the project

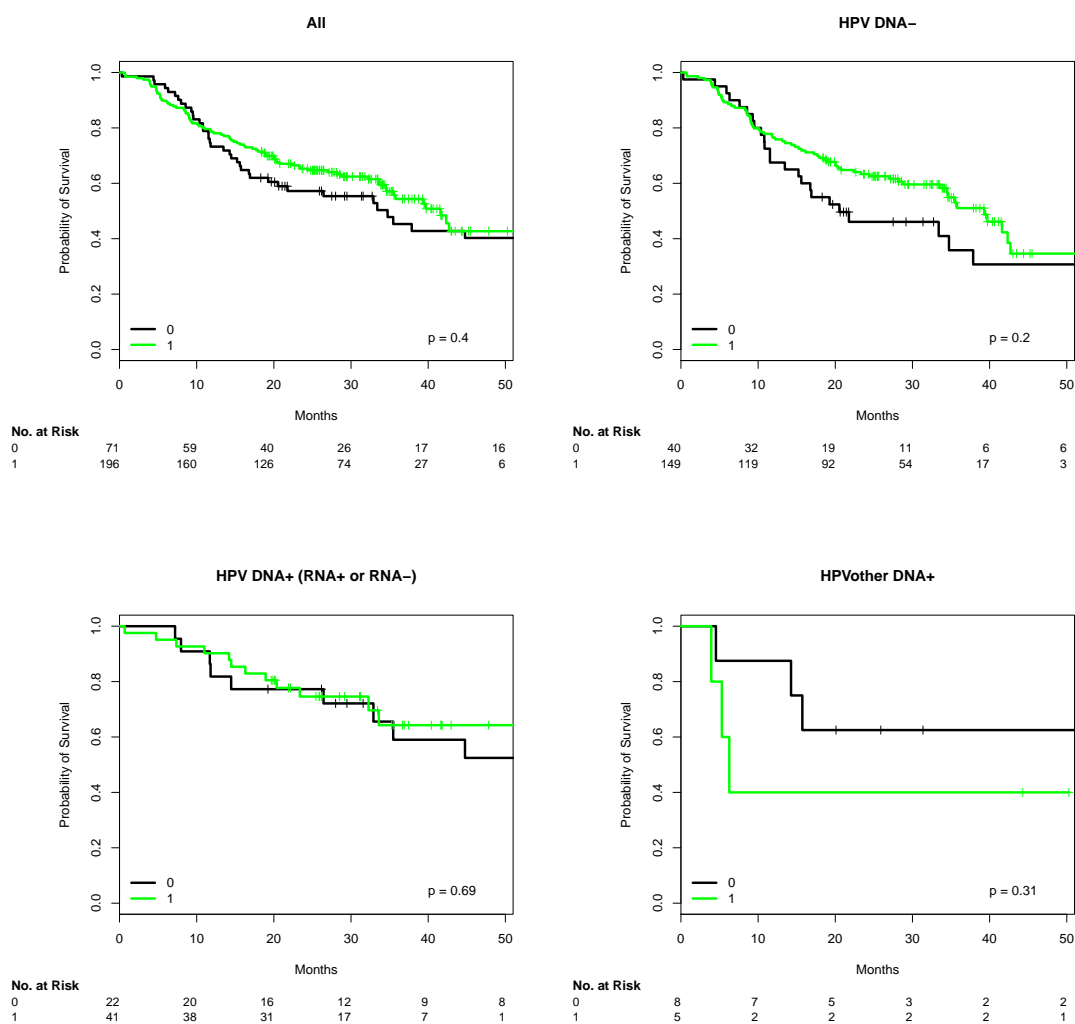
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 267, number of events= 126
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.167      0.846   0.197 -0.85      0.4
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.846      1.18   0.575   1.25
##
## Concordance= 0.52 (se = 0.021 )
## Rsquare= 0.003 (max possible= 0.991 )
## Likelihood ratio test= 0.7 on 1 df,  p=0.402
## Wald test               = 0.72 on 1 df,  p=0.398
## Score (logrank) test = 0.72 on 1 df,  p=0.397
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##              split[cur.subset]=0
##              time      n.risk      n.event      survival      std.err
##              36.0000     18.0000     35.0000     0.4530     0.0671
## lower 95% CI upper 95% CI
##              0.3388     0.6057
##
##              split[cur.subset]=1
```

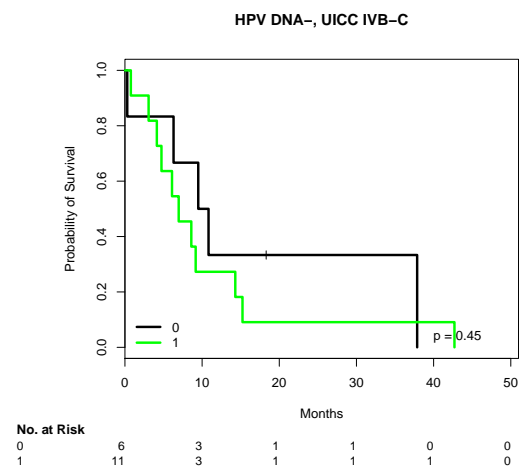
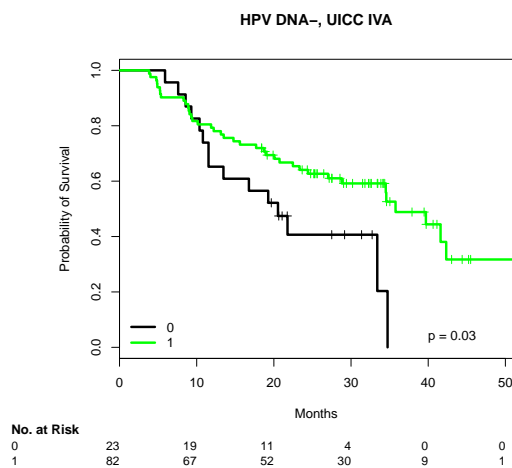
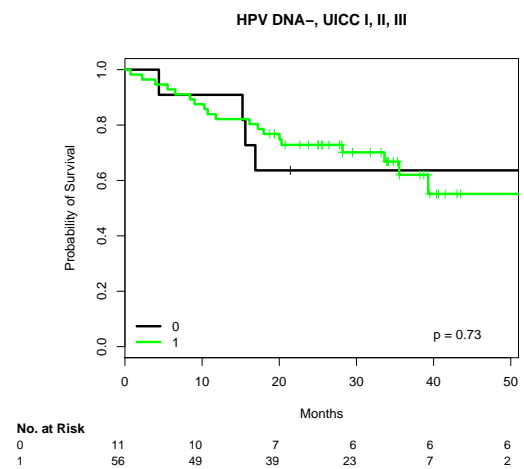
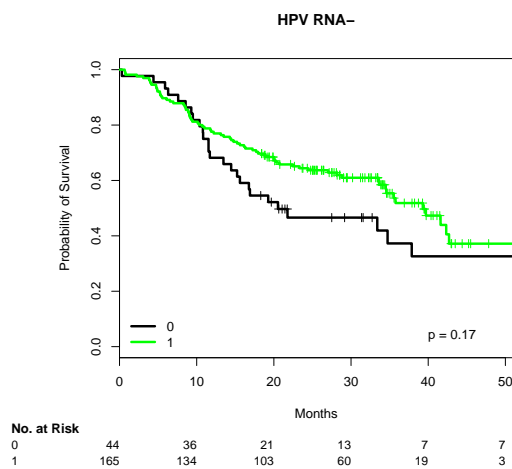
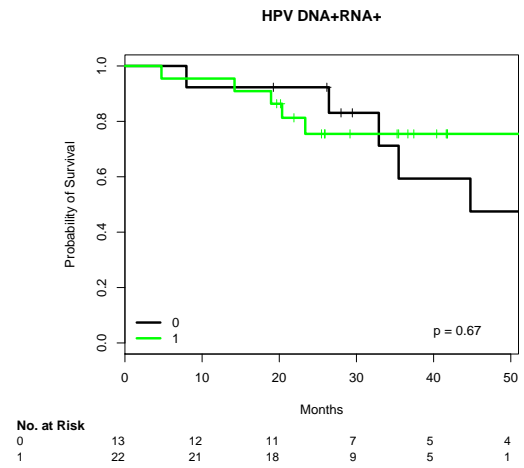
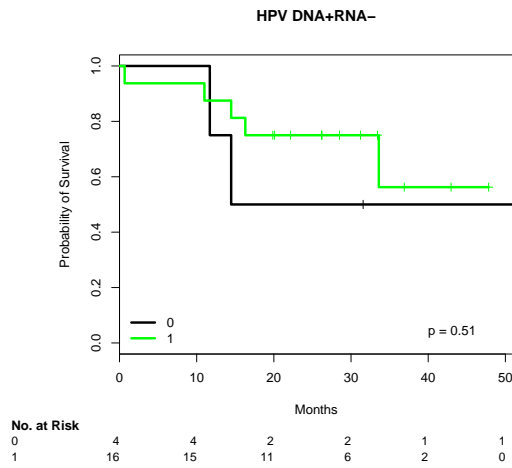
```

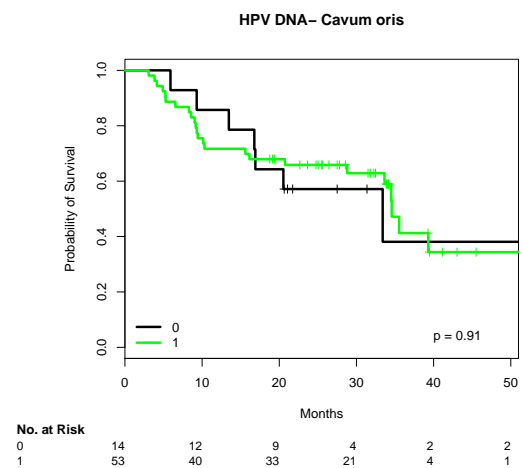
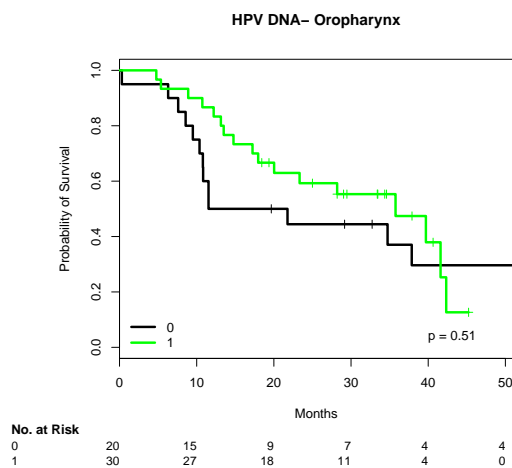
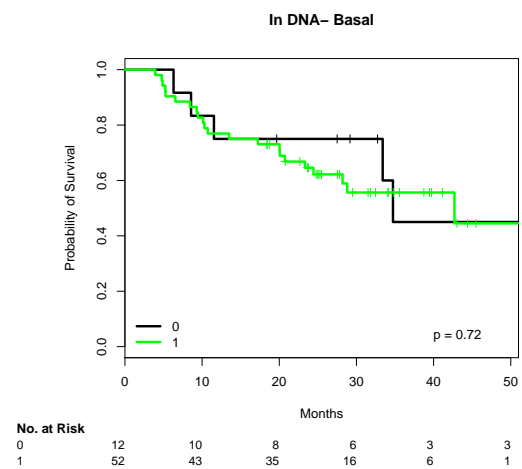
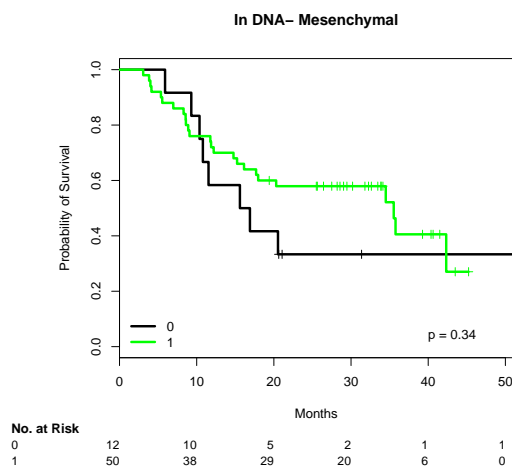
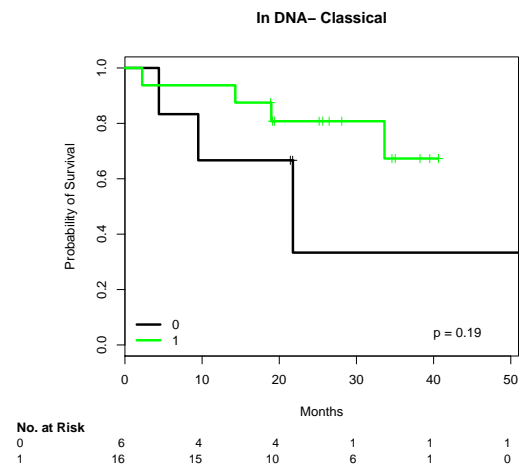
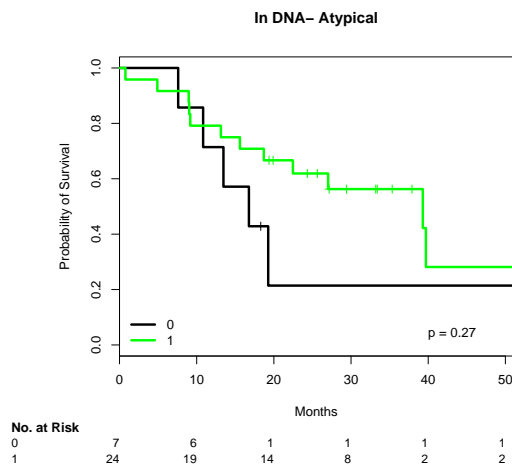
##           time           n.risk           n.event           survival           std.err
##      36.0000           39.0000           78.0000           0.5433           0.0426
## lower 95% CI upper 95% CI
##      0.4659           0.6334
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 94
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.303      0.739      0.238 -1.27      0.2
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.739      1.35      0.464      1.18
##
## Concordance= 0.532 (se = 0.023 )
## Rsquare= 0.008 (max possible= 0.991 )
## Likelihood ratio test= 1.54 on 1 df,  p=0.214
## Wald test = 1.62 on 1 df,  p=0.203
## Score (logrank) test = 1.63 on 1 df,  p=0.201
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 101
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.316      0.729      0.229 -1.38      0.17
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.729      1.37      0.465      1.14
##
## Concordance= 0.534 (se = 0.022 )
## Rsquare= 0.009 (max possible= 0.99 )
## Likelihood ratio test= 1.81 on 1 df,  p=0.179
## Wald test = 1.9 on 1 df,  p=0.168
## Score (logrank) test = 1.92 on 1 df,  p=0.166
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])

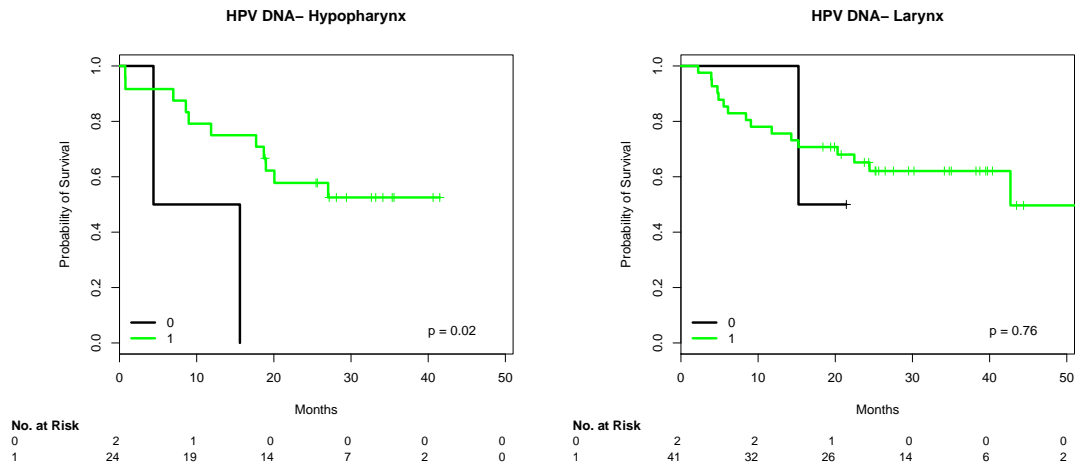
```

```
##
##               split[cur.subset]=0
##           time      n.risk      n.event      survival      std.err
##       36.0000      8.0000     25.0000      0.3727      0.0854
## lower 95% CI upper 95% CI
##       0.2379      0.5838
##
##               split[cur.subset]=1
##           time      n.risk      n.event      survival      std.err
##       36.0000     29.0000     68.0000      0.5184      0.0484
## lower 95% CI upper 95% CI
##       0.4318      0.6224
```









3.7 Therapy, detailed

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##
```

	coef	exp(coef)	se(coef)
split[cur.subset]DeLOS II (IC), Op+PORChT	-1.61e+01	1.02e-07	2.01e+03
split[cur.subset]DeLOS II (IC,RT)	-1.52e+00	2.19e-01	9.15e-01
split[cur.subset]ICHT+OP+RT	2.69e-01	1.31e+00	7.58e-01
split[cur.subset]KRCHT	6.91e-01	2.00e+00	9.14e-01
split[cur.subset]OP	-4.33e-01	6.49e-01	7.35e-01
split[cur.subset]pall CHEMO	-1.76e-01	8.38e-01	1.23e+00
split[cur.subset]PORChT	-4.30e-01	6.50e-01	7.31e-01
split[cur.subset]PORT	-7.82e-01	4.57e-01	7.37e-01
split[cur.subset]RT	1.32e+00	3.74e+00	7.53e-01
split[cur.subset]TISOC 1	-1.24e+00	2.89e-01	9.16e-01

```
##
## z Pr(>|z|)
## split[cur.subset]DeLOS II (IC), Op+PORChT -0.01 0.994
## split[cur.subset]DeLOS II (IC,RT) -1.66 0.097 .
## split[cur.subset]ICHT+OP+RT 0.35 0.723
## split[cur.subset]KRCHT 0.76 0.450
## split[cur.subset]OP -0.59 0.556
## split[cur.subset]pall CHEMO -0.14 0.886
## split[cur.subset]PORChT -0.59 0.556
## split[cur.subset]PORT -1.06 0.288
## split[cur.subset]RT 1.75 0.080 .
## split[cur.subset]TISOC 1 -1.36 0.175
## ---
```

```

## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##                                exp(coef) exp(-coef) lower .95
## split[cur.subset]DeLOS II (IC), Op+PORChT 1.02e-07 9.76e+06 0.0000
## split[cur.subset]DeLOS II (IC,RT)         2.19e-01 4.57e+00 0.0365
## split[cur.subset]ICHT+OP+RT               1.31e+00 7.64e-01 0.2961
## split[cur.subset]KRCHT                    2.00e+00 5.01e-01 0.3328
## split[cur.subset]OP                       6.49e-01 1.54e+00 0.1537
## split[cur.subset]pall CHEMO               8.38e-01 1.19e+00 0.0753
## split[cur.subset]PORChT                   6.50e-01 1.54e+00 0.1553
## split[cur.subset]PORT                     4.57e-01 2.19e+00 0.1079
## split[cur.subset]RT                       3.74e+00 2.68e-01 0.8541
## split[cur.subset]TISOC 1                  2.89e-01 3.46e+00 0.0480
##
##                                upper .95
## split[cur.subset]DeLOS II (IC), Op+PORChT      Inf
## split[cur.subset]DeLOS II (IC,RT)              1.32
## split[cur.subset]ICHT+OP+RT                    5.79
## split[cur.subset]KRCHT                         11.96
## split[cur.subset]OP                            2.74
## split[cur.subset]pall CHEMO                     9.33
## split[cur.subset]PORChT                         2.72
## split[cur.subset]PORT                           1.94
## split[cur.subset]RT                            16.34
## split[cur.subset]TISOC 1                        1.74
##
## Concordance= 0.642 (se = 0.027 )
## Rsquare= 0.172 (max possible= 0.991 )
## Likelihood ratio test= 50.5 on 10 df, p=2.15e-07
## Wald test = 57.5 on 10 df, p=1.08e-08
## Score (logrank) test = 75.9 on 10 df, p=3.13e-12
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##
##               split[cur.subset]=BSC
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##
##               split[cur.subset]=DeLOS II (IC), Op+PORChT
##      time      n.risk      n.event      survival      std.err
##      36             1             0             1             0
## lower 95% CI upper 95% CI
##      1             1
##
##
##               split[cur.subset]=DeLOS II (IC,RT)
##      time      n.risk      n.event      survival      std.err
##      36.000      5.000      3.000      0.808      0.100
## lower 95% CI upper 95% CI
##      0.634      1.000

```

```

##
##           split[cur.subset]=ICHT+OP+RT
##           time           n.risk           n.event           survival           std.err
##           36.0000           2.0000           13.0000           0.2222           0.1171
## lower 95% CI upper 95% CI
##           0.0791           0.6243
##
##           split[cur.subset]=KRCHT
##           time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##           split[cur.subset]=OP
##           time           n.risk           n.event           survival           std.err
##           36.0000           12.0000           23.0000           0.5951           0.0699
## lower 95% CI upper 95% CI
##           0.4727           0.7492
##
##           split[cur.subset]=pall CHEMO
##           time           n.risk           n.event           survival           std.err
##           36           1           0           1           0
## lower 95% CI upper 95% CI
##           1           1
##
##           split[cur.subset]=PORChT
##           time           n.risk           n.event           survival           std.err
##           36.0000           12.0000           28.0000           0.4579           0.0795
## lower 95% CI upper 95% CI
##           0.3258           0.6436
##
##           split[cur.subset]=PORT
##           time           n.risk           n.event           survival           std.err
##           36.0000           18.0000           22.0000           0.6208           0.0694
## lower 95% CI upper 95% CI
##           0.4986           0.7730
##
##           split[cur.subset]=RT
##           time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##           split[cur.subset]=TISOC 1
##           time           n.risk           n.event           survival           std.err
##           36.000           6.000           3.000           0.750           0.125
## lower 95% CI upper 95% CI
##           0.541           1.000
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])

```

```
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## split[cur.subset]DeLOS II (IC), Op+PORChT -1.70e+01 4.18e-08 3.05e+03
## split[cur.subset]DeLOS II (IC,RT) -1.26e+00 2.82e-01 9.15e-01
## split[cur.subset]ICHT+OP+RT 3.85e-01 1.47e+00 7.84e-01
## split[cur.subset]KRCHT 6.65e-01 1.94e+00 9.14e-01
## split[cur.subset]OP -3.09e-01 7.34e-01 7.43e-01
## split[cur.subset]pall CHEMO -2.86e-01 7.51e-01 1.23e+00
## split[cur.subset]PORChT -3.00e-01 7.41e-01 7.42e-01
## split[cur.subset]PORT -6.12e-01 5.42e-01 7.43e-01
## split[cur.subset]RT 1.19e+00 3.27e+00 7.67e-01
## split[cur.subset]TISOC 1 -1.44e+00 2.37e-01 1.01e+00
##
##               z Pr(>|z|)
## split[cur.subset]DeLOS II (IC), Op+PORChT -0.01 1.00
## split[cur.subset]DeLOS II (IC,RT) -1.38 0.17
## split[cur.subset]ICHT+OP+RT 0.49 0.62
## split[cur.subset]KRCHT 0.73 0.47
## split[cur.subset]OP -0.42 0.68
## split[cur.subset]pall CHEMO -0.23 0.82
## split[cur.subset]PORChT -0.40 0.69
## split[cur.subset]PORT -0.82 0.41
## split[cur.subset]RT 1.55 0.12
## split[cur.subset]TISOC 1 -1.43 0.15
##
##               exp(coef) exp(-coef) lower .95
## split[cur.subset]DeLOS II (IC), Op+PORChT 4.18e-08 2.39e+07 0.0000
## split[cur.subset]DeLOS II (IC,RT) 2.82e-01 3.54e+00 0.0470
## split[cur.subset]ICHT+OP+RT 1.47e+00 6.80e-01 0.3162
## split[cur.subset]KRCHT 1.94e+00 5.14e-01 0.3243
## split[cur.subset]OP 7.34e-01 1.36e+00 0.1710
## split[cur.subset]pall CHEMO 7.51e-01 1.33e+00 0.0669
## split[cur.subset]PORChT 7.41e-01 1.35e+00 0.1731
## split[cur.subset]PORT 5.42e-01 1.84e+00 0.1264
## split[cur.subset]RT 3.27e+00 3.05e-01 0.7288
## split[cur.subset]TISOC 1 2.37e-01 4.23e+00 0.0329
##
##               upper .95
## split[cur.subset]DeLOS II (IC), Op+PORChT Inf
## split[cur.subset]DeLOS II (IC,RT) 1.70
## split[cur.subset]ICHT+OP+RT 6.83
## split[cur.subset]KRCHT 11.66
## split[cur.subset]OP 3.15
## split[cur.subset]pall CHEMO 8.43
## split[cur.subset]PORChT 3.17
## split[cur.subset]PORT 2.33
## split[cur.subset]RT 14.71
```

```

## split[cur.subset]TISOC 1 1.70
##
## Concordance= 0.636 (se = 0.032 )
## Rsquare= 0.169 (max possible= 0.991 )
## Likelihood ratio test= 35 on 10 df, p=0.000123
## Wald test = 35.8 on 10 df, p=9.1e-05
## Score (logrank) test = 45.9 on 10 df, p=1.47e-06
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##
## coef exp(coef) se(coef)
## split[cur.subset]DeLOS II (IC), Op+PORChT -1.70e+01 4.07e-08 3.12e+03
## split[cur.subset]DeLOS II (IC,RT) -1.32e+00 2.68e-01 9.15e-01
## split[cur.subset]ICHT+OP+RT 3.64e-01 1.44e+00 7.70e-01
## split[cur.subset]KRCHT 6.62e-01 1.94e+00 9.14e-01
## split[cur.subset]OP -2.69e-01 7.64e-01 7.39e-01
## split[cur.subset]pall CEMO -2.69e-01 7.64e-01 1.23e+00
## split[cur.subset]PORChT -3.93e-01 6.75e-01 7.40e-01
## split[cur.subset]PORT -6.95e-01 4.99e-01 7.43e-01
## split[cur.subset]RT 1.19e+00 3.28e+00 7.66e-01
## split[cur.subset]TISOC 1 -1.42e+00 2.42e-01 1.01e+00
##
## z Pr(>|z|)
## split[cur.subset]DeLOS II (IC), Op+PORChT -0.01 1.00
## split[cur.subset]DeLOS II (IC,RT) -1.44 0.15
## split[cur.subset]ICHT+OP+RT 0.47 0.64
## split[cur.subset]KRCHT 0.72 0.47
## split[cur.subset]OP -0.36 0.72
## split[cur.subset]pall CEMO -0.22 0.83
## split[cur.subset]PORChT -0.53 0.60
## split[cur.subset]PORT -0.94 0.35
## split[cur.subset]RT 1.55 0.12
## split[cur.subset]TISOC 1 -1.41 0.16
##
##
## exp(coef) exp(-coef) lower .95
## split[cur.subset]DeLOS II (IC), Op+PORChT 4.07e-08 2.46e+07 0.0000
## split[cur.subset]DeLOS II (IC,RT) 2.68e-01 3.73e+00 0.0447
## split[cur.subset]ICHT+OP+RT 1.44e+00 6.95e-01 0.3182
## split[cur.subset]KRCHT 1.94e+00 5.16e-01 0.3235
## split[cur.subset]OP 7.64e-01 1.31e+00 0.1797
## split[cur.subset]pall CEMO 7.64e-01 1.31e+00 0.0682
## split[cur.subset]PORChT 6.75e-01 1.48e+00 0.1584
## split[cur.subset]PORT 4.99e-01 2.00e+00 0.1163

```

```

## split[cur.subset]RT                3.28e+00    3.05e-01    0.7308
## split[cur.subset]TISOC 1            2.42e-01    4.13e+00    0.0337
##                                     upper .95
## split[cur.subset]DeLOS II (IC), Op+PORChT    Inf
## split[cur.subset]DeLOS II (IC,RT)            1.61
## split[cur.subset]ICHT+OP+RT                6.51
## split[cur.subset]KRCHT                    11.63
## split[cur.subset]OP                        3.25
## split[cur.subset]pall CHEMO                8.56
## split[cur.subset]PORChT                   2.88
## split[cur.subset]PORT                     2.14
## split[cur.subset]RT                       14.74
## split[cur.subset]TISOC 1                   1.74
##
## Concordance= 0.648 (se = 0.03 )
## Rsquare= 0.163 (max possible= 0.99 )
## Likelihood ratio test= 37.3 on 10 df, p=5.07e-05
## Wald test = 38.7 on 10 df, p=2.83e-05
## Score (logrank) test = 49.5 on 10 df, p=3.31e-07
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=BSC
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##               split[cur.subset]=DeLOS II (IC), Op+PORChT
##      time      n.risk      n.event      survival      std.err
##      36              1              0              1              0
## lower 95% CI upper 95% CI
##      1              1
##
##               split[cur.subset]=DeLOS II (IC,RT)
##      time      n.risk      n.event      survival      std.err
##      36.000      3.000      3.000      0.779      0.113
## lower 95% CI upper 95% CI
##      0.587      1.000
##
##               split[cur.subset]=ICHT+OP+RT
##      time      n.risk      n.event      survival      std.err
##      36.0000      1.0000      11.0000      0.1429      0.1177
## lower 95% CI upper 95% CI
##      0.0284      0.7179
##
##               split[cur.subset]=KRCHT
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##               split[cur.subset]=OP

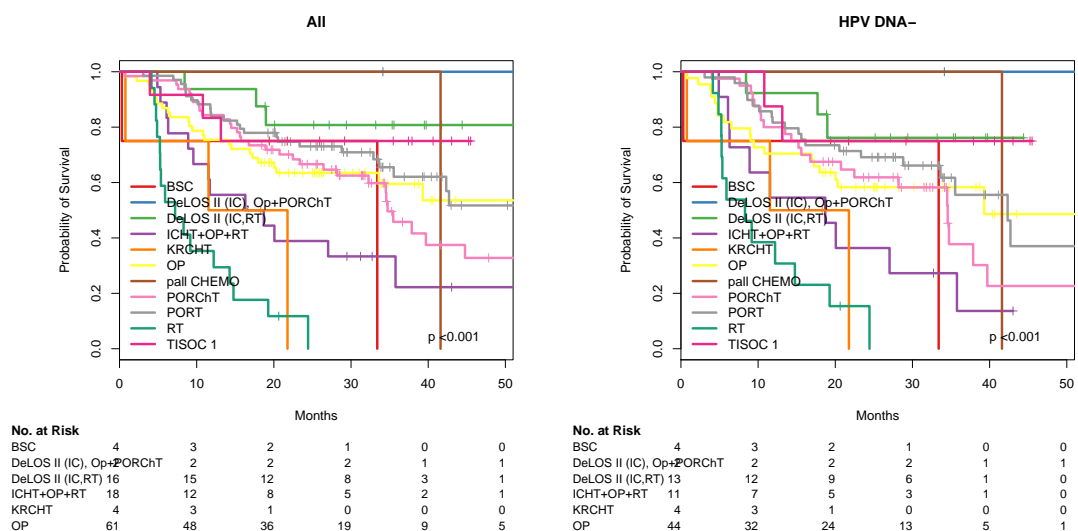
```

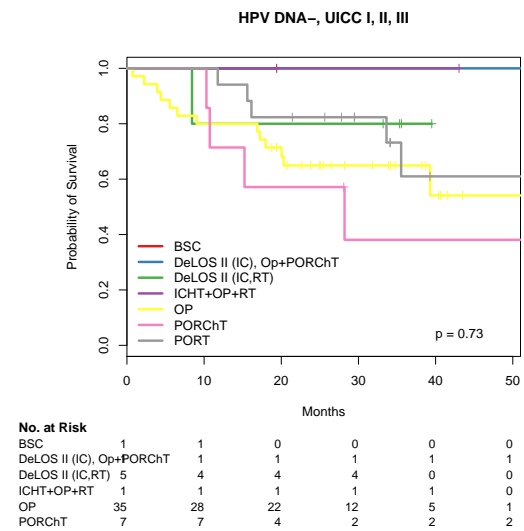
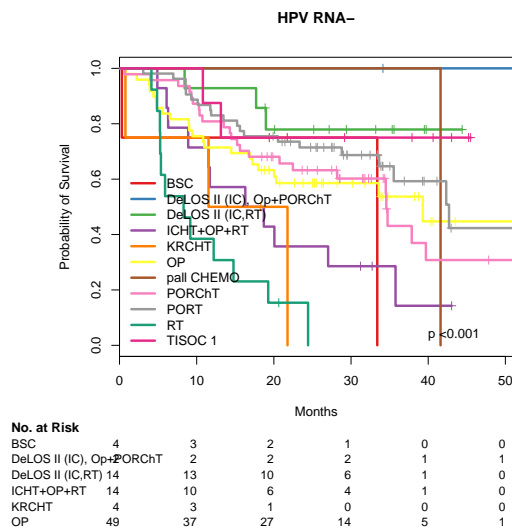
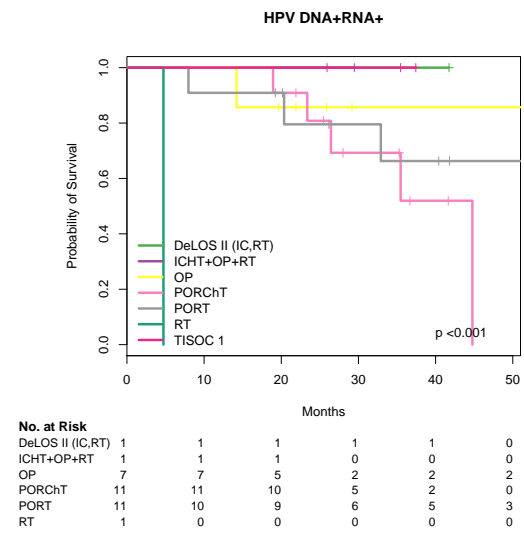
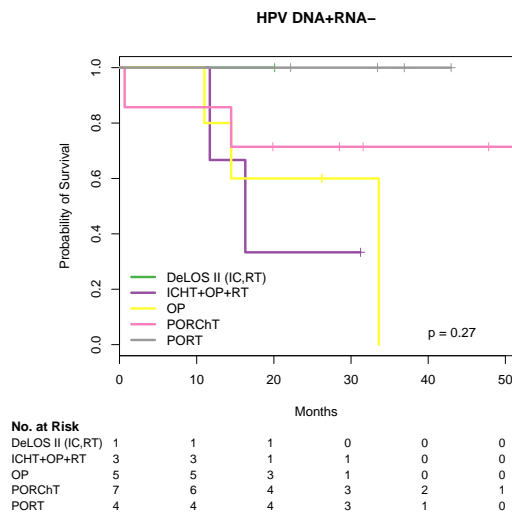
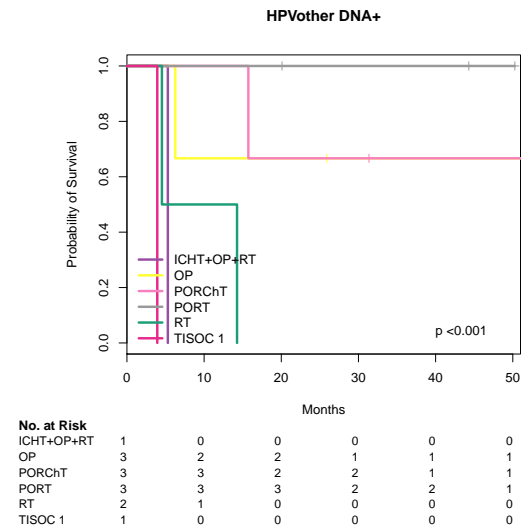
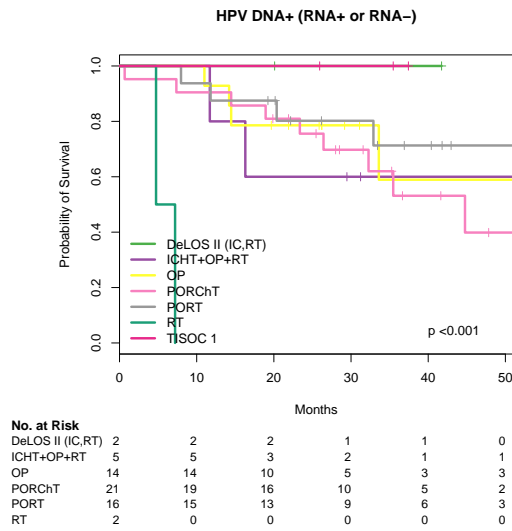


```

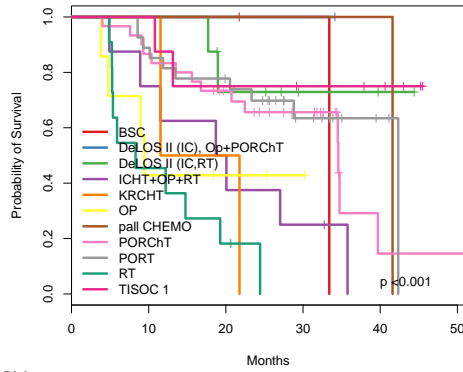
##           time           n.risk           n.event           survival           std.err
##          36.0000           8.0000           21.0000           0.5370           0.0803
## lower 95% CI upper 95% CI
##          0.4005           0.7200
##
##           split[cur.subset]=pall CEMO
##           time           n.risk           n.event           survival           std.err
##            36              1              0              1              0
## lower 95% CI upper 95% CI
##            1              1
##
##           split[cur.subset]=PORChT
##           time           n.risk           n.event           survival           std.err
##          36.0000           7.0000           21.0000           0.4311           0.0994
## lower 95% CI upper 95% CI
##          0.2743           0.6773
##
##           split[cur.subset]=PORT
##           time           n.risk           n.event           survival           std.err
##          36.0000           11.0000           18.0000           0.5926           0.0847
## lower 95% CI upper 95% CI
##          0.4478           0.7842
##
##           split[cur.subset]=RT
##           time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##           split[cur.subset]=TISOC 1
##           time           n.risk           n.event           survival           std.err
##          36.000           5.000           2.000           0.750           0.153
## lower 95% CI upper 95% CI
##          0.503           1.000

```



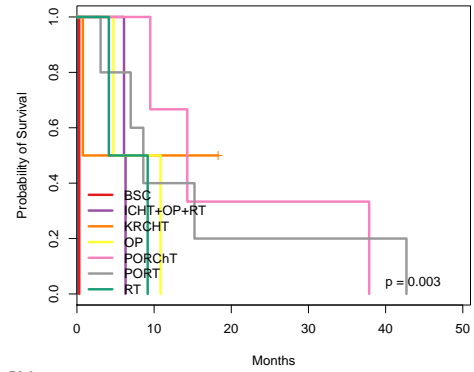


HPV DNA-, UICC IVA



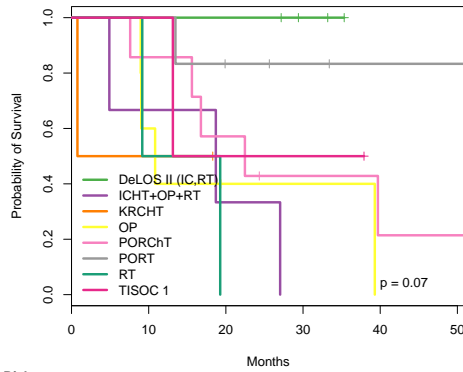
No. at Risk						
BSC	2	2	2	1	0	0
DeLOS II (IC), Op+PORChT	1	1	1	0	0	0
DeLOS II (IC,RT)	8	5	2	1	0	0
ICHT+OP+RT	8	6	4	2	0	0
KRChT	2	2	1	0	0	0
OP	7	3	2	1	0	0

HPV DNA-, UICC IVB-C



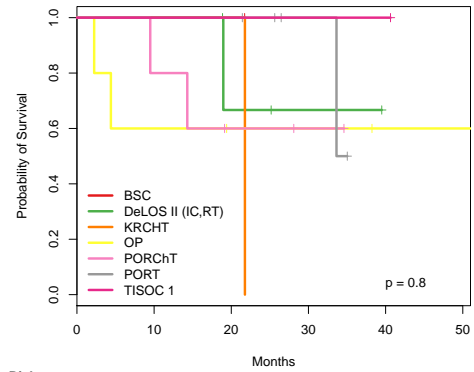
No. at Risk						
BSC	1	0	0	0	0	0
ICHT+OP+RT	2	0	0	0	0	0
KRChT	2	1	0	0	0	0
OP	2	1	0	0	0	0
PORChT	3	2	1	1	0	0
PORT	5	2	1	1	1	0

In DNA- Atypical



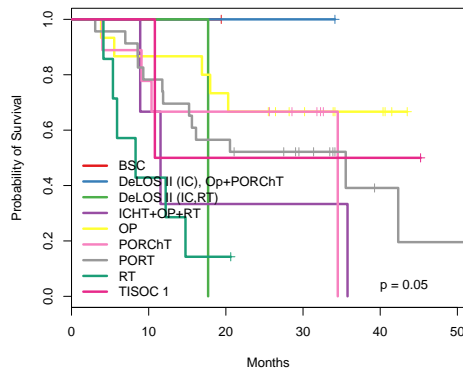
No. at Risk						
DeLOS II (IC,RT)	4	4	4	2	0	0
ICHT+OP+RT	3	2	1	0	0	0
KRChT	2	1	0	0	0	0
OP	5	3	1	1	0	1
PORChT	7	6	4	2	1	1
PORT	6	6	4	3	2	2

In DNA- Classical



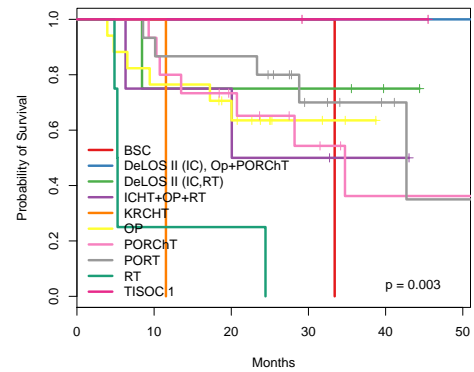
No. at Risk						
BSC	1	1	1	0	0	0
DeLOS II (IC,RT)	4	4	2	1	0	0
KRChT	1	1	1	0	0	0
OP	5	3	2	2	1	1
PORChT	5	4	2	1	0	0
PORT	5	5	5	2	0	0

In DNA- Mesenchymal

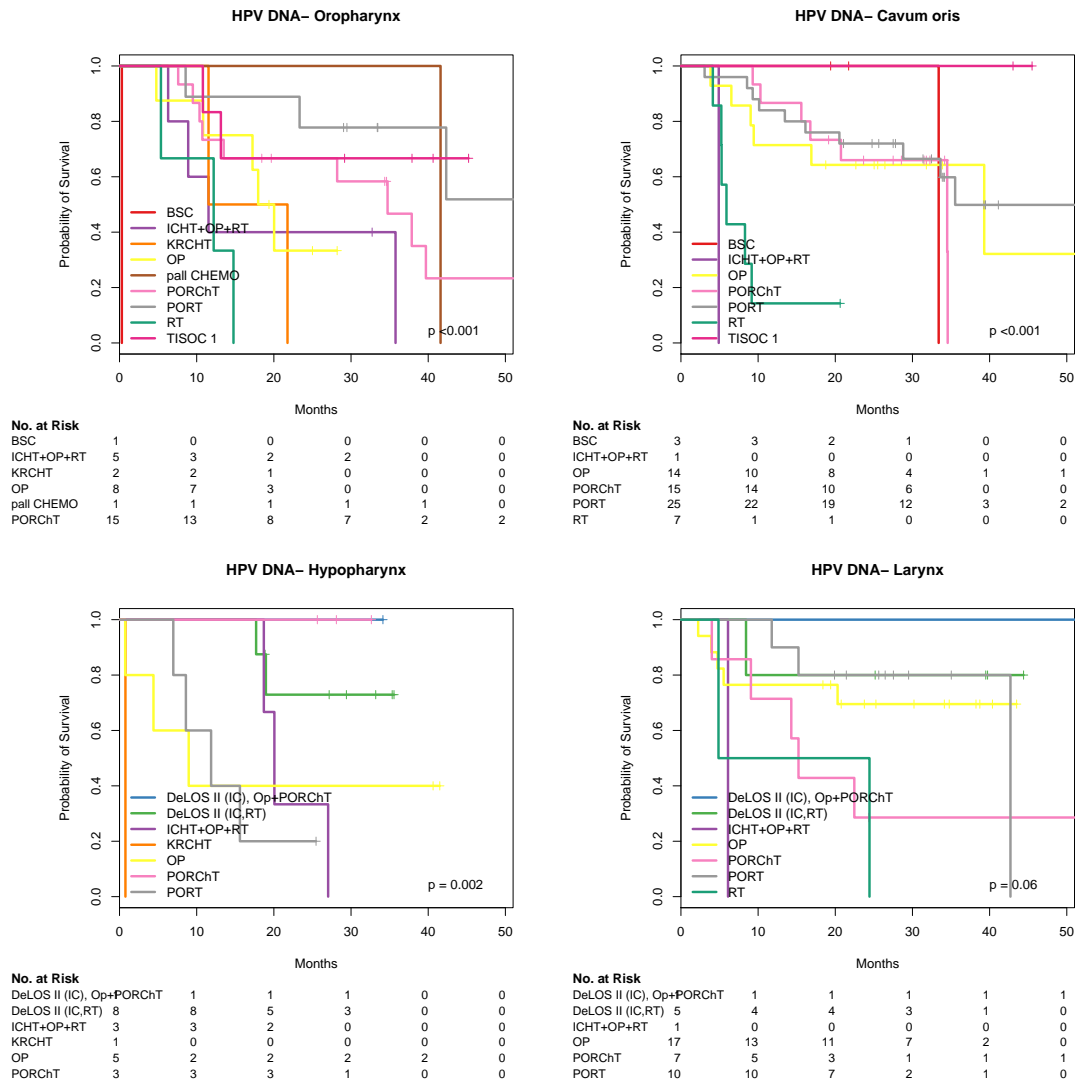


No. at Risk						
BSC	1	1	0	0	0	0
DeLOS II (IC), Op+PORChT	1	1	1	1	0	0
DeLOS II (IC,RT)	1	1	0	0	0	0
ICHT+OP+RT	3	2	1	1	0	0
OP	15	13	11	7	4	0
PORChT	9	7	6	4	0	0

In DNA- Basal



No. at Risk						
BSC	1	1	1	1	0	0
DeLOS II (IC), Op+PORChT	1	1	1	1	1	1
DeLOS II (IC,RT)	4	3	3	3	1	0
ICHT+OP+RT	4	3	3	2	1	0
KRChT	1	1	0	0	0	0
OP	17	13	10	3	0	0



3.8 Therapy

Legend: mono denotes mono modal therapy, multi denotes multi modal therapy. Please see the paper for more information.

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.4965   0.6087  0.1899 -2.61  0.0089 **
## split[cur.subset]palliative 0.0131   1.0132  0.5980  0.02  0.9825
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```

## split[cur.subset]multi          0.609      1.643      0.419      0.883
## split[cur.subset]palliative      1.013      0.987      0.314      3.271
##
## Concordance= 0.565 (se = 0.022 )
## Rsquare= 0.025 (max possible= 0.991 )
## Likelihood ratio test= 6.8 on 2 df, p=0.0334
## Wald test = 7.16 on 2 df, p=0.0278
## Score (logrank) test = 7.31 on 2 df, p=0.0258
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=mono
##      time      n.risk      n.event      survival      std.err
## 36.0000     12.0000     39.0000      0.4733      0.0621
## lower 95% CI upper 95% CI
## 0.3660      0.6120
##
##               split[cur.subset]=multi
##      time      n.risk      n.event      survival      std.err
## 36.0000     44.0000     72.0000      0.5478      0.0433
## lower 95% CI upper 95% CI
## 0.4692      0.6395
##
##               split[cur.subset]=palliative
##      time      n.risk      n.event      survival      std.err
## 36.0000      1.0000      2.0000      0.4000      0.2966
## lower 95% CI upper 95% CI
## 0.0935      1.0000
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi    -0.506    0.603    0.221 -2.28  0.022 *
## split[cur.subset]palliative -0.122    0.885    0.605 -0.20  0.840
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi    0.603      1.66    0.391    0.931
## split[cur.subset]palliative 0.885      1.13    0.271    2.895

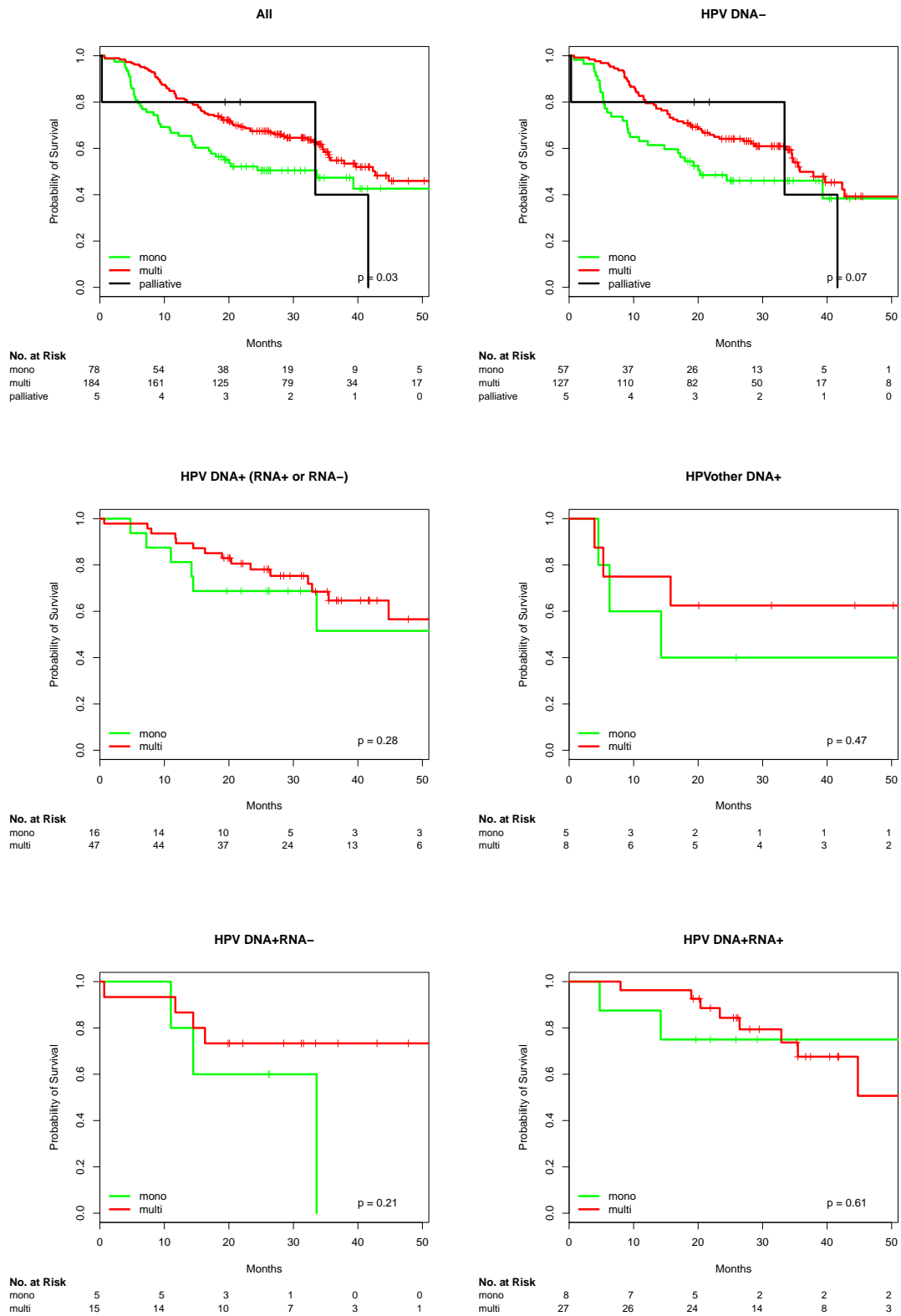
```

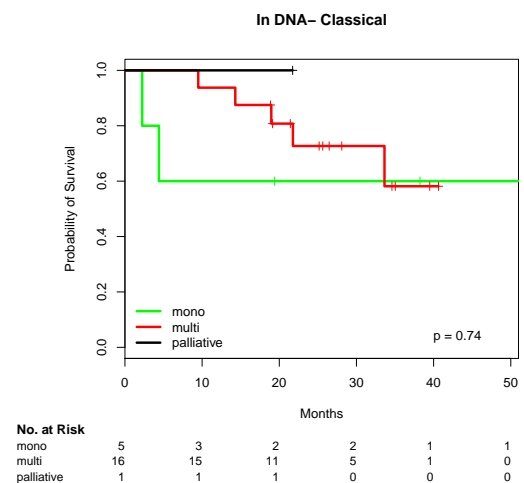
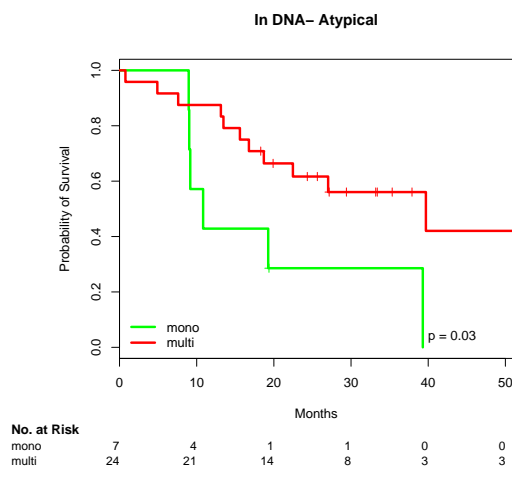
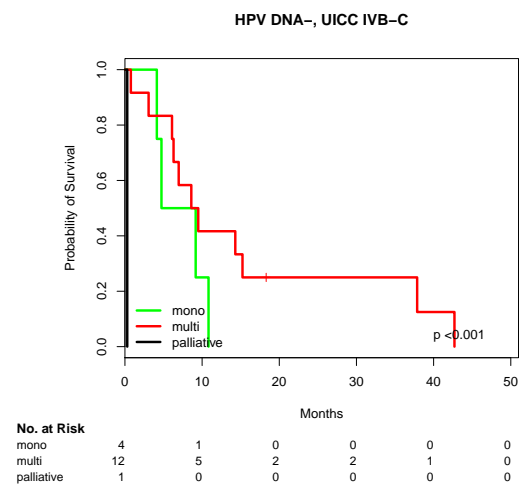
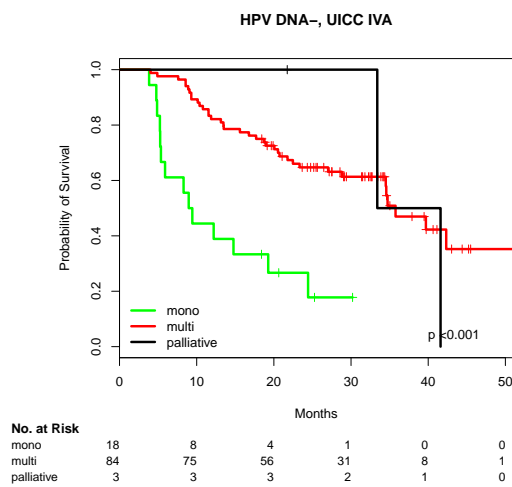
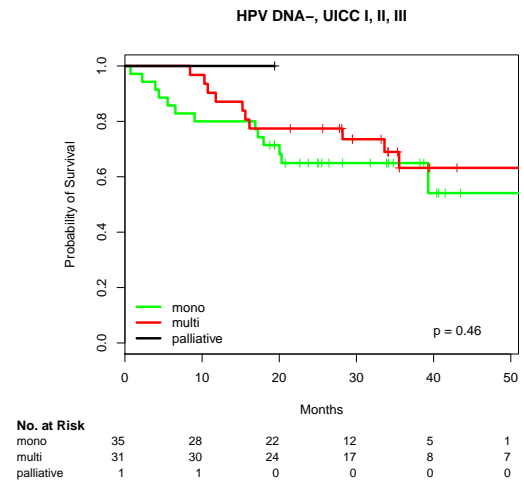
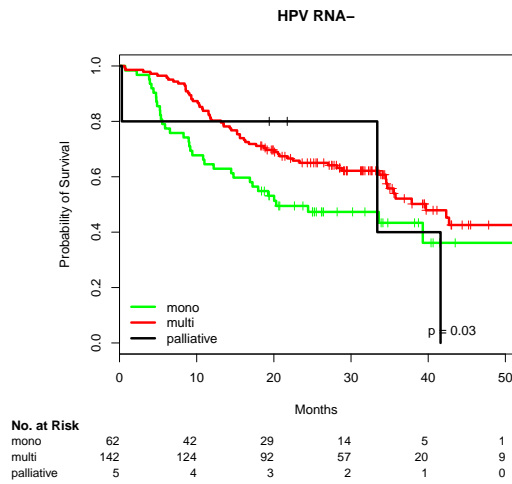
```

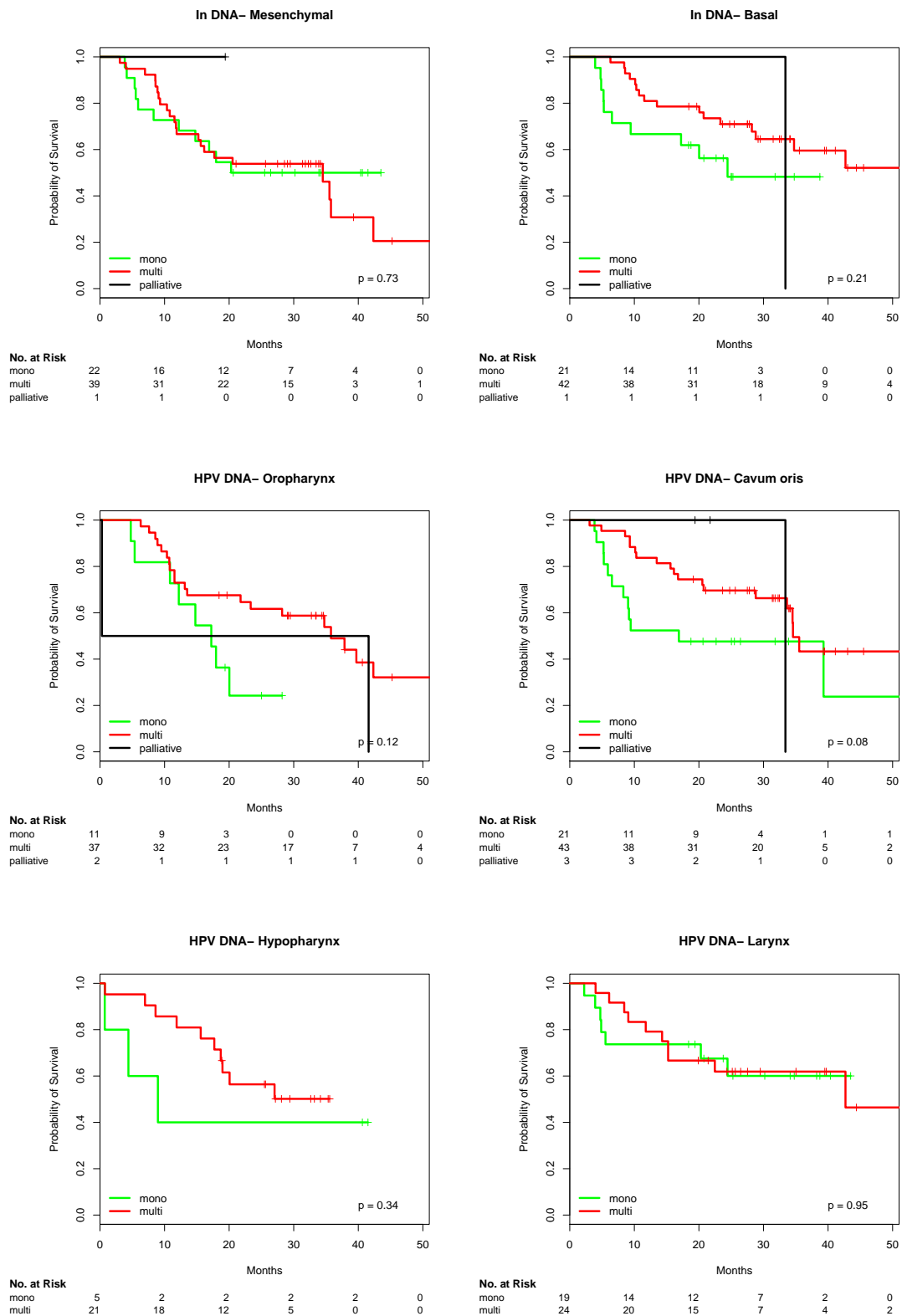
##
## Concordance= 0.569 (se = 0.025 )
## Rsquare= 0.027 (max possible= 0.991 )
## Likelihood ratio test= 5.08 on 2 df, p=0.079
## Wald test = 5.33 on 2 df, p=0.0694
## Score (logrank) test = 5.44 on 2 df, p=0.0657
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.548    0.578    0.213 -2.58    0.01 **
## split[cur.subset]palliative -0.117    0.890    0.602 -0.19    0.85
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi    0.578      1.73    0.381    0.877
## split[cur.subset]palliative 0.890      1.12    0.273    2.898
##
## Concordance= 0.568 (se = 0.024 )
## Rsquare= 0.03 (max possible= 0.99 )
## Likelihood ratio test= 6.45 on 2 df, p=0.0398
## Wald test = 6.8 on 2 df, p=0.0334
## Score (logrank) test = 6.96 on 2 df, p=0.0308
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=mono
##           time      n.risk      n.event      survival      std.err
##           36.0000      8.0000     33.0000      0.4337      0.0705
## lower 95% CI upper 95% CI
##           0.3154      0.5963
##
##               split[cur.subset]=multi
##           time      n.risk      n.event      survival      std.err
##           36.0000     28.0000     58.0000      0.5211      0.0516
## lower 95% CI upper 95% CI
##           0.4291      0.6328
##
##               split[cur.subset]=palliative
##           time      n.risk      n.event      survival      std.err

```

##	36.0000	1.0000	2.0000	0.4000	0.2966
##	lower 95% CI upper 95% CI				
##	0.0935	1.0000			







3.9 Therapy without palliative

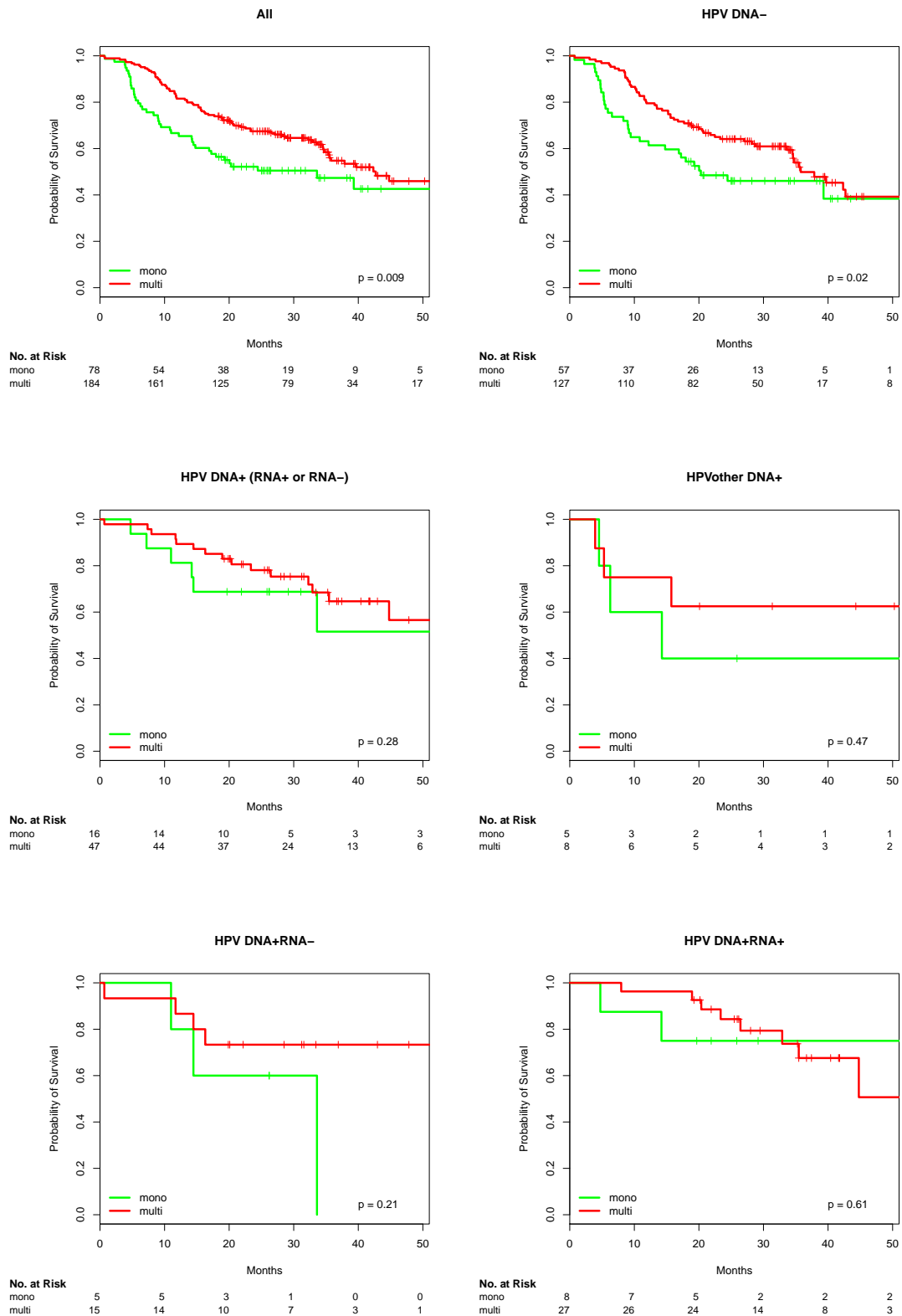
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 262, number of events= 123
## (5 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.493    0.611    0.190 -2.59  0.0095 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi    0.611      1.64    0.421    0.887
##
## Concordance= 0.568 (se = 0.021 )
## Rsquare= 0.024 (max possible= 0.991 )
## Likelihood ratio test= 6.36 on 1 df,  p=0.0117
## Wald test = 6.73 on 1 df,  p=0.00948
## Score (logrank) test = 6.86 on 1 df,  p=0.00879
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 5 observations deleted due to missingness
##
##               split[cur.subset]=mono
##               time      n.risk      n.event      survival      std.err
##               36.0000      12.0000      39.0000      0.4733      0.0621
## lower 95% CI upper 95% CI
##               0.3660      0.6120
##
##               split[cur.subset]=multi
##               time      n.risk      n.event      survival      std.err
##               36.0000      44.0000      72.0000      0.5478      0.0433
## lower 95% CI upper 95% CI
##               0.4692      0.6395
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 184, number of events= 91
## (7 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
```

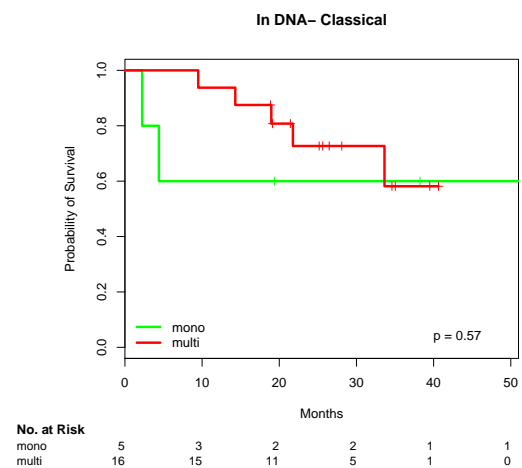
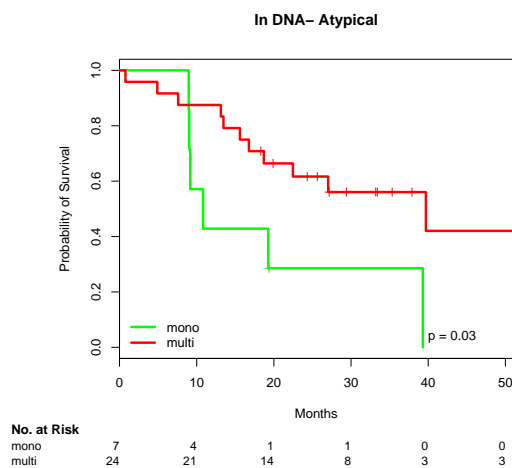
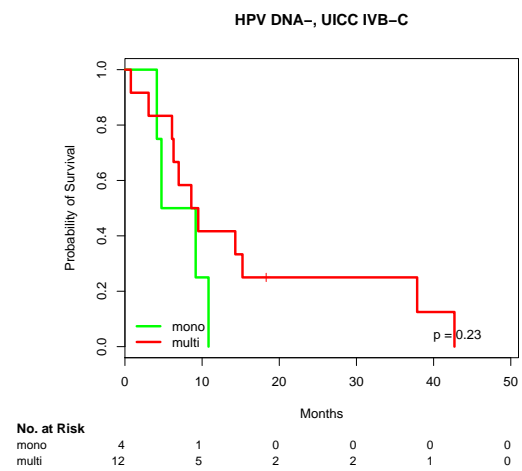
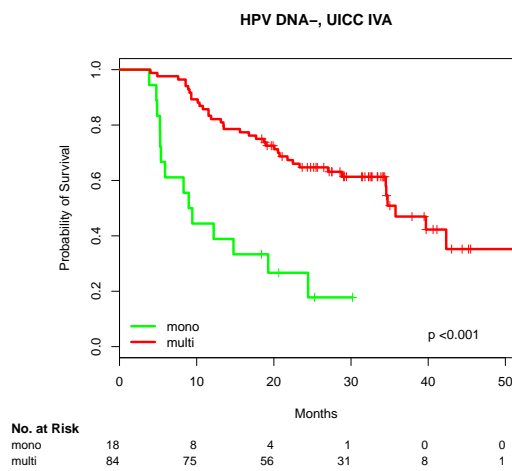
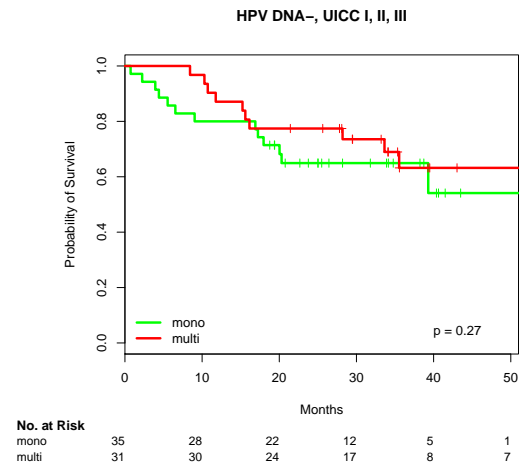
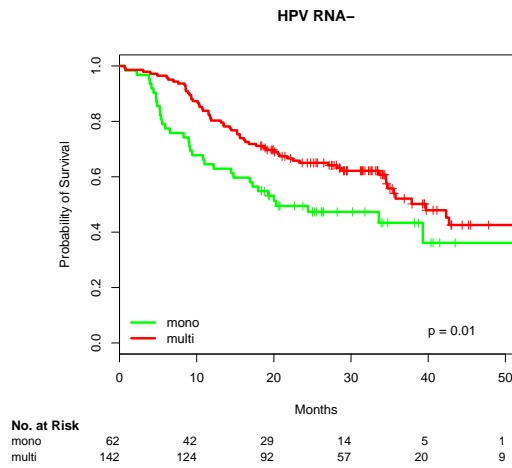
```

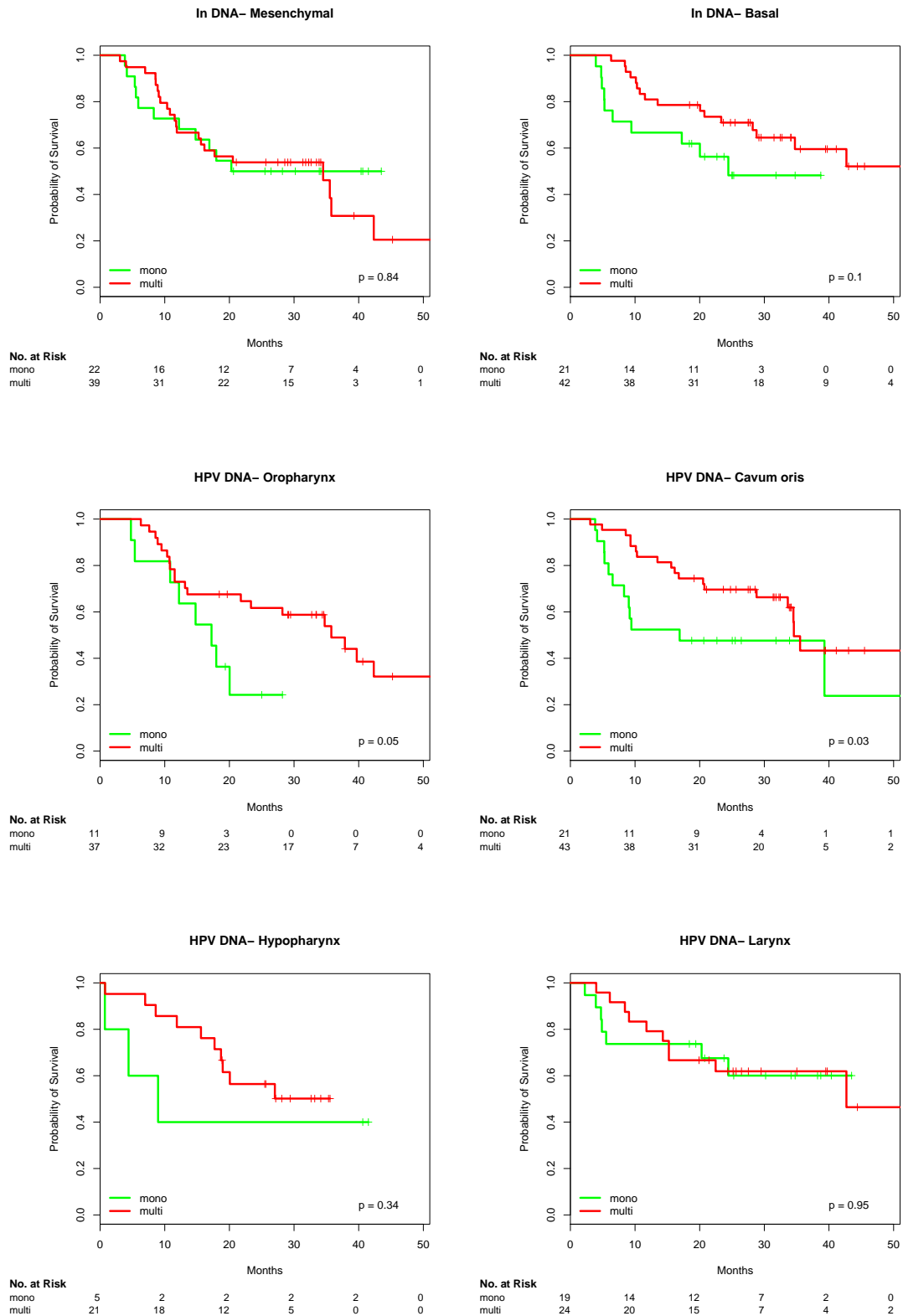
## split[cur.subset]multi -0.498      0.608      0.221 -2.25      0.024 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi      0.608      1.64      0.394      0.938
##
## Concordance= 0.57 (se = 0.025 )
## Rsquare= 0.026 (max possible= 0.99 )
## Likelihood ratio test= 4.79 on 1 df,  p=0.0286
## Wald test              = 5.06 on 1 df,  p=0.0245
## Score (logrank) test = 5.17 on 1 df,  p=0.023
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 204, number of events= 98
## (5 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.540      0.583      0.213 -2.54      0.011 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi      0.583      1.72      0.384      0.884
##
## Concordance= 0.569 (se = 0.024 )
## Rsquare= 0.029 (max possible= 0.99 )
## Likelihood ratio test= 6.08 on 1 df,  p=0.0137
## Wald test              = 6.44 on 1 df,  p=0.0111
## Score (logrank) test = 6.6 on 1 df,  p=0.0102
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 5 observations deleted due to missingness
##
##               split[cur.subset]=mono
##           time      n.risk      n.event      survival      std.err
##           36.0000      8.0000      33.0000      0.4337      0.0705
## lower 95% CI upper 95% CI
##           0.3154      0.5963
##
##               split[cur.subset]=multi
##           time      n.risk      n.event      survival      std.err

```

##	36.0000	28.0000	58.0000	0.5211	0.0516
##	lower 95% CI upper 95% CI				
##	0.4291	0.6328			







3.10 T (TNM staging)

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 267, number of events= 126
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.472    0.624   0.320 -1.47   0.140
## split[cur.subset]3  0.248    1.281   0.312  0.79   0.428
## split[cur.subset]4a 0.399    1.490   0.291  1.37   0.171
## split[cur.subset]4b 0.990    2.690   0.516  1.92   0.055 .
## split[cur.subset]x    NA         NA   0.000   NA     NA
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2    0.624    1.603    0.333    1.17
## split[cur.subset]3    1.281    0.781    0.694    2.36
## split[cur.subset]4a    1.490    0.671    0.842    2.64
## split[cur.subset]4b    2.690    0.372    0.979    7.39
## split[cur.subset]x      NA         NA      NA      NA
##
## Concordance= 0.601 (se = 0.027 )
## Rsquare= 0.064 (max possible= 0.991 )
## Likelihood ratio test= 17.5 on 4 df, p=0.00153
## Wald test = 16.6 on 4 df, p=0.00226
## Score (logrank) test = 17.7 on 4 df, p=0.00141
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##              split[cur.subset]=1
##              time      n.risk      n.event      survival      std.err
##              36.0000      7.0000     13.0000      0.5937      0.0927
## lower 95% CI upper 95% CI
##              0.4371      0.8063
##
##              split[cur.subset]=2
##              time      n.risk      n.event      survival      std.err
##              36.0000     27.0000     19.0000      0.7370      0.0534
## lower 95% CI upper 95% CI
##              0.6395      0.8495
##
##              split[cur.subset]=3
##              time      n.risk      n.event      survival      std.err
##              36.0000     14.0000     29.0000      0.4476      0.0726
## lower 95% CI upper 95% CI
```

```

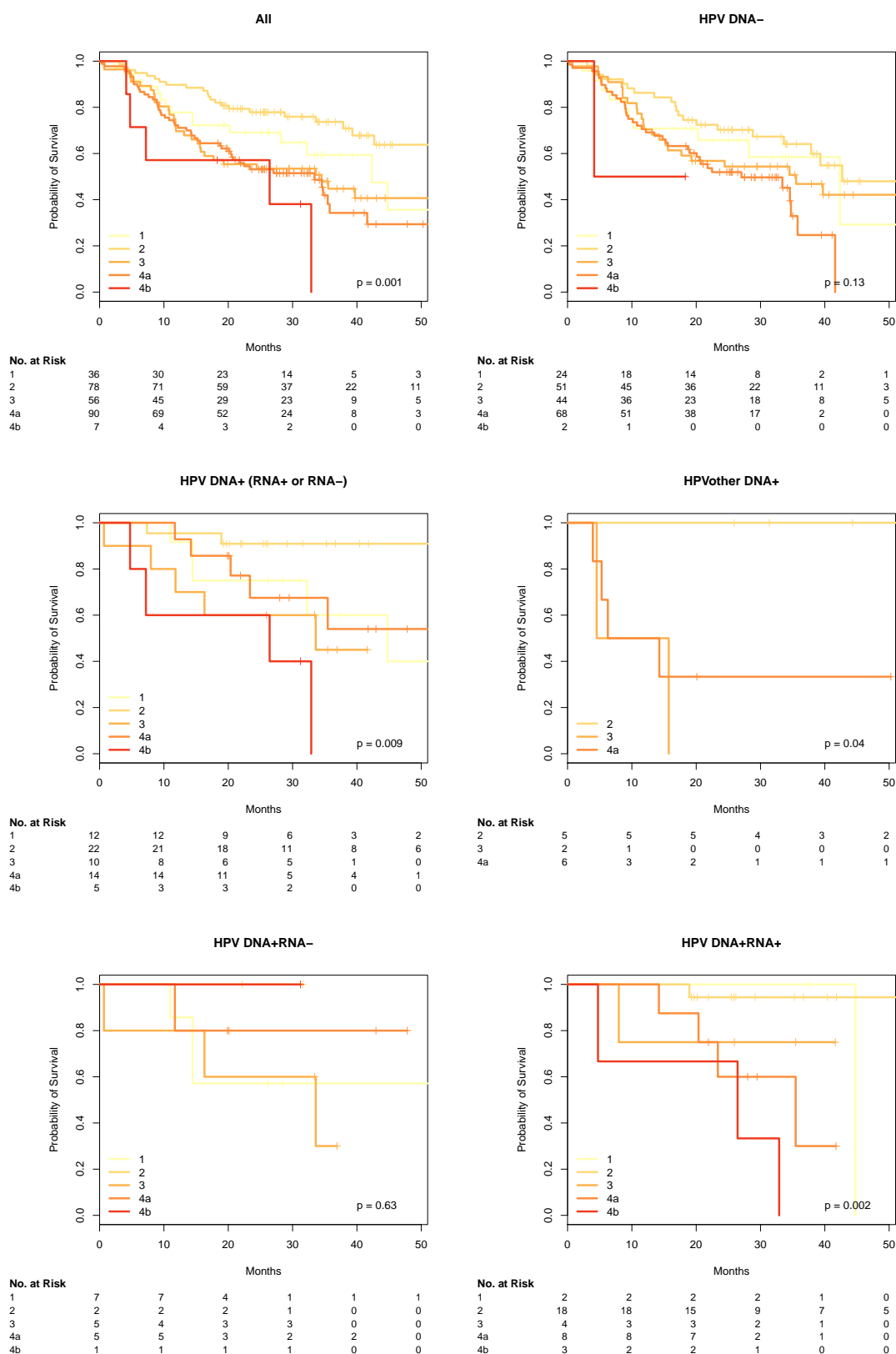
##      0.3257      0.6150
##
##      split[cur.subset]=4a
##      time      n.risk      n.event      survival      std.err
##      36.0000      9.0000      47.0000      0.3428      0.0735
## lower 95% CI upper 95% CI
##      0.2252      0.5218
##
##      split[cur.subset]=4b
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 94
##      (2 observations deleted due to missingness)
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.374      0.688      0.375 -1.00      0.32
## split[cur.subset]3 -0.039      0.962      0.369 -0.11      0.92
## split[cur.subset]4a 0.321      1.378      0.344 0.93      0.35
## split[cur.subset]4b 0.814      2.257      1.047 0.78      0.44
## split[cur.subset]x      NA      NA      0.000      NA      NA
##
##      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.688      1.453      0.330      1.43
## split[cur.subset]3      0.962      1.040      0.467      1.98
## split[cur.subset]4a      1.378      0.726      0.703      2.70
## split[cur.subset]4b      2.257      0.443      0.290     17.58
## split[cur.subset]x      NA      NA      NA      NA
##
## Concordance= 0.566 (se = 0.031 )
## Rsquare= 0.036 (max possible= 0.991 )
## Likelihood ratio test= 7.01 on 4 df, p=0.136
## Wald test = 6.89 on 4 df, p=0.142
## Score (logrank) test = 7.11 on 4 df, p=0.13
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 101
##

```

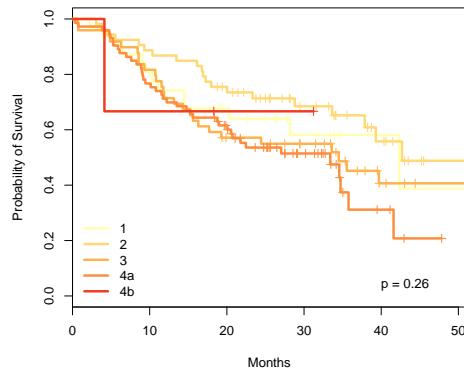


```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.3339   0.7161  0.3459 -0.97   0.33
## split[cur.subset]3  0.0682   1.0705  0.3326  0.20   0.84
## split[cur.subset]4a 0.2883   1.3342  0.3128  0.92   0.36
## split[cur.subset]4b 0.0484   1.0496  1.0362  0.05   0.96
## split[cur.subset]x      NA      NA    0.0000   NA    NA
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.716      1.396      0.364      1.41
## split[cur.subset]3      1.071      0.934      0.558      2.05
## split[cur.subset]4a      1.334      0.750      0.723      2.46
## split[cur.subset]4b      1.050      0.953      0.138      8.00
## split[cur.subset]x      NA      NA      NA      NA
##
## Concordance= 0.562 (se = 0.03 )
## Rsquare= 0.026 (max possible= 0.99 )
## Likelihood ratio test= 5.46 on 4 df, p=0.244
## Wald test = 5.2 on 4 df, p=0.267
## Score (logrank) test = 5.32 on 4 df, p=0.256
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1
##           time      n.risk      n.event      survival      std.err
##      36.0000      4.0000      12.0000      0.5816      0.0968
## lower 95% CI upper 95% CI
##      0.4197      0.8060
##
##               split[cur.subset]=2
##           time      n.risk      n.event      survival      std.err
##      36.0000      15.0000      17.0000      0.6521      0.0708
## lower 95% CI upper 95% CI
##      0.5271      0.8067
##
##               split[cur.subset]=3
##           time      n.risk      n.event      survival      std.err
##      36.0000      13.0000      25.0000      0.4517      0.0779
## lower 95% CI upper 95% CI
##      0.3221      0.6335
##
##               split[cur.subset]=4a
##           time      n.risk      n.event      survival      std.err
##      36.0000      5.0000      38.0000      0.3116      0.0897
## lower 95% CI upper 95% CI
##      0.1773      0.5478
##
##               split[cur.subset]=4b
```

time n.risk n.event survival std.err lower 95% CI upper 95% CI

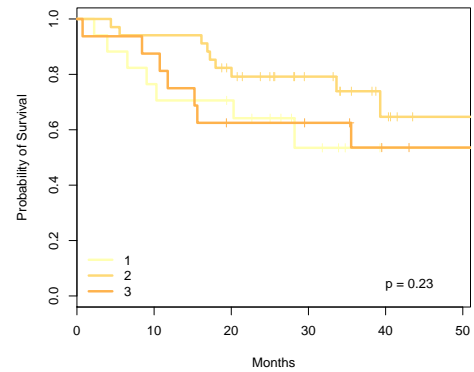


HPV RNA-



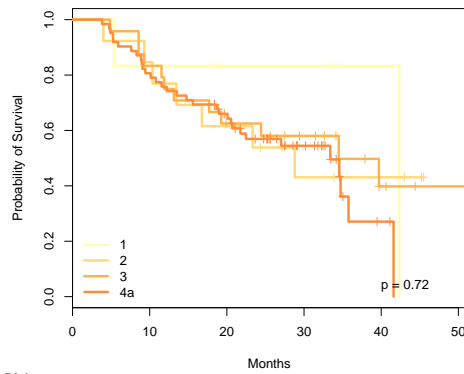
No. at Risk	Months					
1	31	25	18	9	3	2
2	53	47	38	23	11	3
3	49	40	26	21	8	5
4a	73	56	41	19	4	0
4b	3	2	1	1	0	0

HPV DNA-, UICC I, II, III



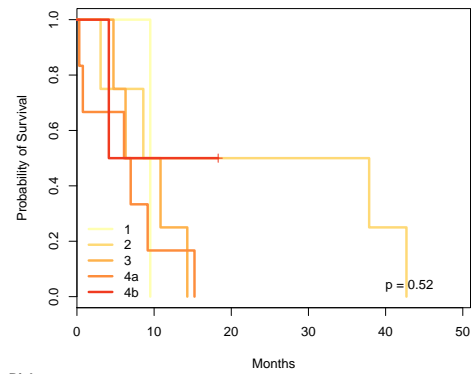
No. at Risk	Months					
1	17	13	11	5	1	1
2	34	32	26	16	7	3
3	16	14	9	8	5	4

HPV DNA-, UICC IVA



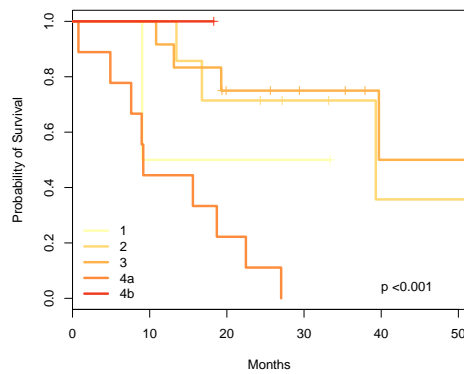
No. at Risk	Months					
1	6	5	3	3	1	0
2	13	11	8	4	3	0
3	24	20	14	10	3	1
4a	62	50	38	17	2	0

HPV DNA-, UICC IVB-C



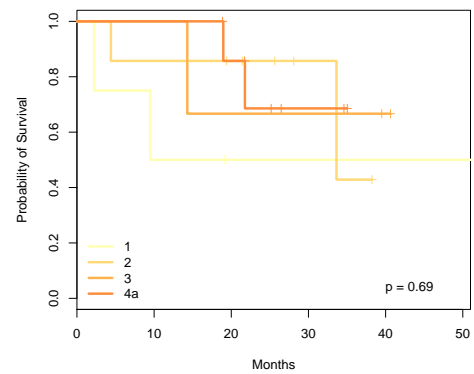
No. at Risk	Months					
1	1	0	0	0	0	0
2	4	2	2	2	1	0
3	4	2	0	0	0	0
4a	6	1	0	0	0	0
4b	2	1	0	0	0	0

In DNA- Atypical

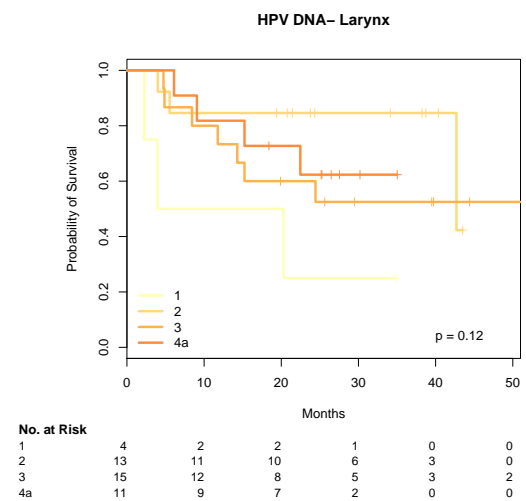
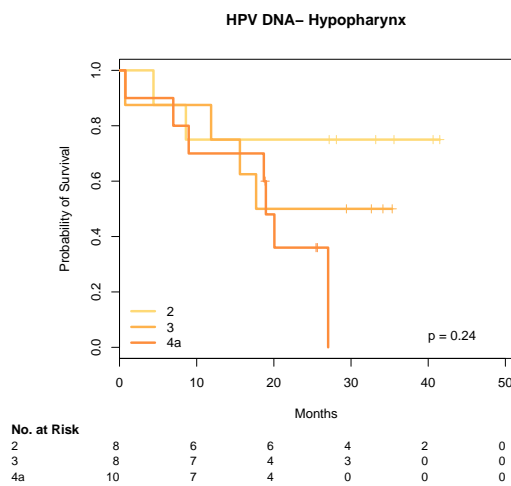
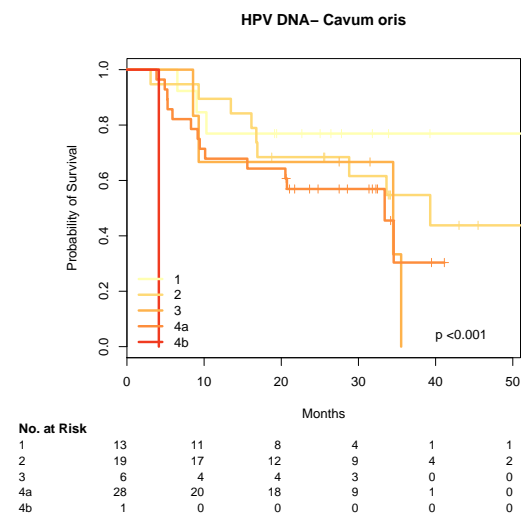
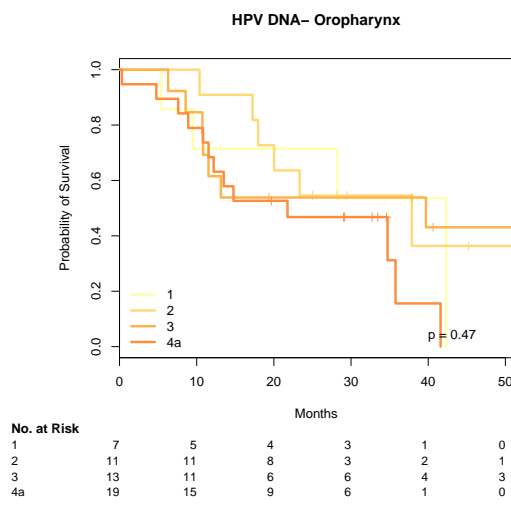
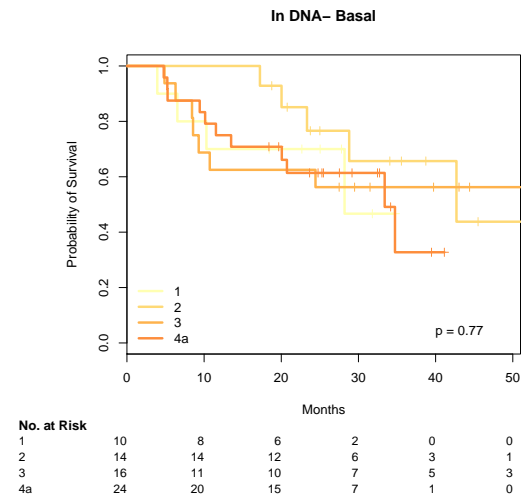
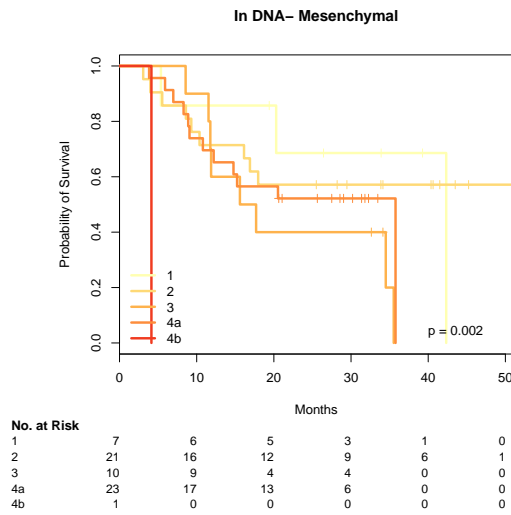


No. at Risk	Months					
1	2	1	1	1	0	0
2	7	7	5	3	1	1
3	12	12	7	5	2	2
4a	9	4	2	0	0	0
4b	1	1	0	0	0	0

In DNA- Classical



No. at Risk	Months					
1	4	2	1	1	1	1
2	7	6	5	2	0	0
3	3	3	2	2	1	0
4a	8	8	6	2	0	0



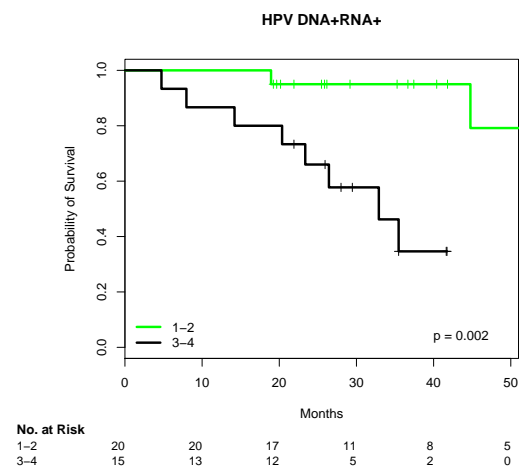
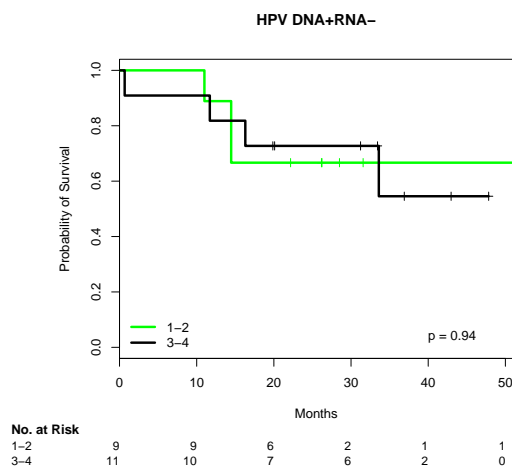
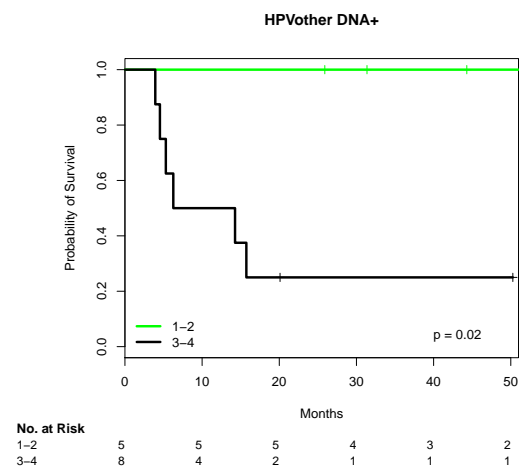
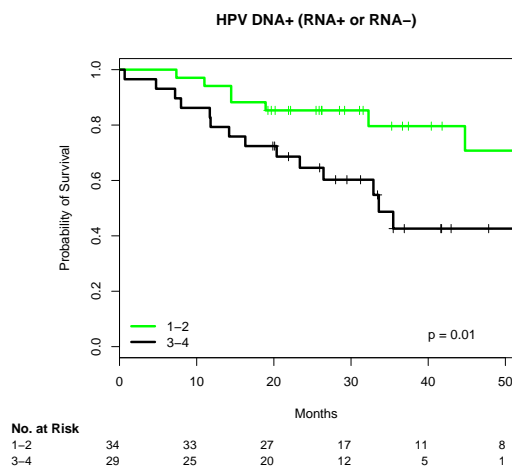
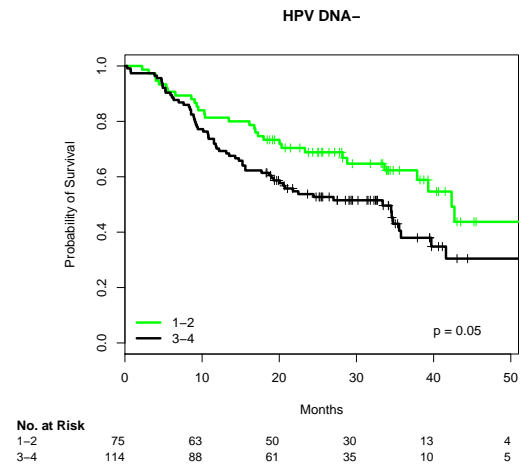
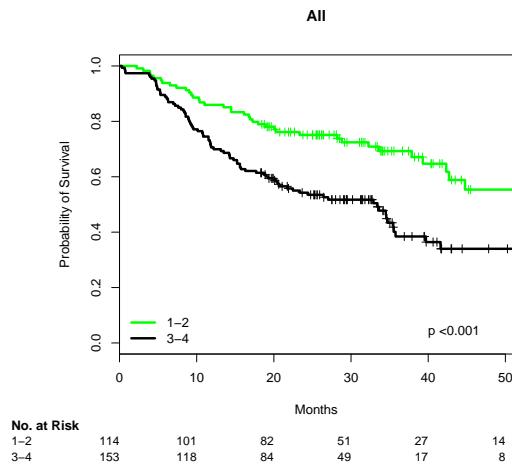
3.11 T stages 1,2 vs. 3,4

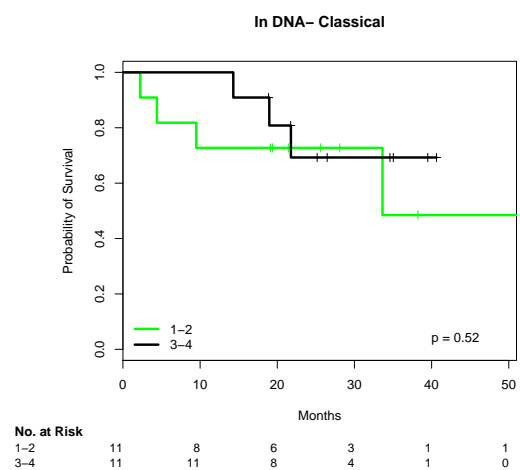
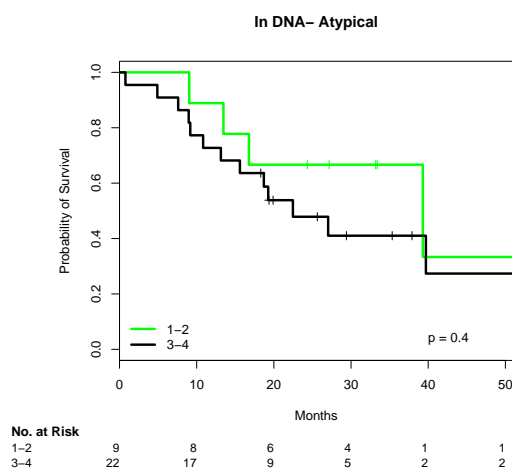
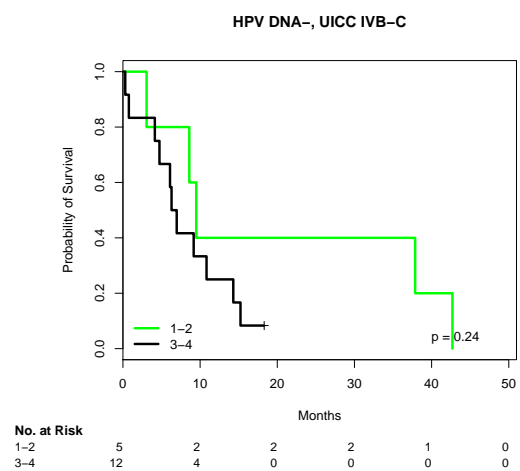
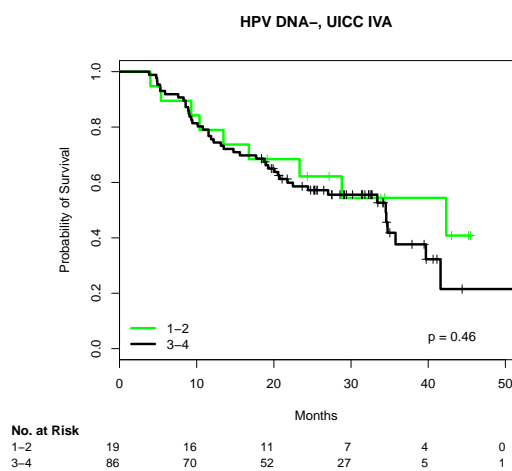
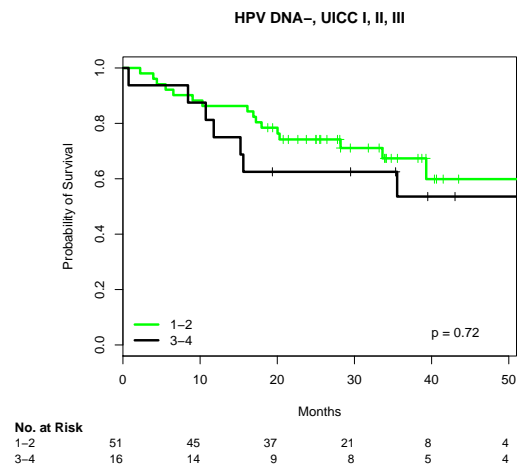
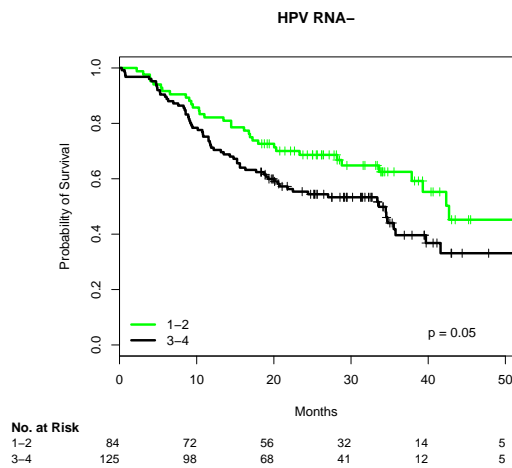
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 0.682      1.977    0.192 3.55  0.00038 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]3-4      1.98      0.506      1.36      2.88
##
## Concordance= 0.588 (se = 0.024 )
## Rsquare= 0.049 (max possible= 0.991 )
## Likelihood ratio test= 13.4 on 1 df,  p=0.000252
## Wald test               = 12.6 on 1 df,  p=0.000382
## Score (logrank) test = 13.1 on 1 df,  p=0.000297
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1-2
##           time      n.risk      n.event      survival      std.err
##           36.0000      34.0000      32.0000      0.6927      0.0471
## lower 95% CI upper 95% CI
##           0.6063      0.7914
##
##               split[cur.subset]=3-4
##           time      n.risk      n.event      survival      std.err
##           36.0000      23.0000      81.0000      0.3844      0.0494
## lower 95% CI upper 95% CI
##           0.2988      0.4946
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 189, number of events= 94
##    (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 0.429      1.536    0.219 1.96  0.05 .
## ---
```

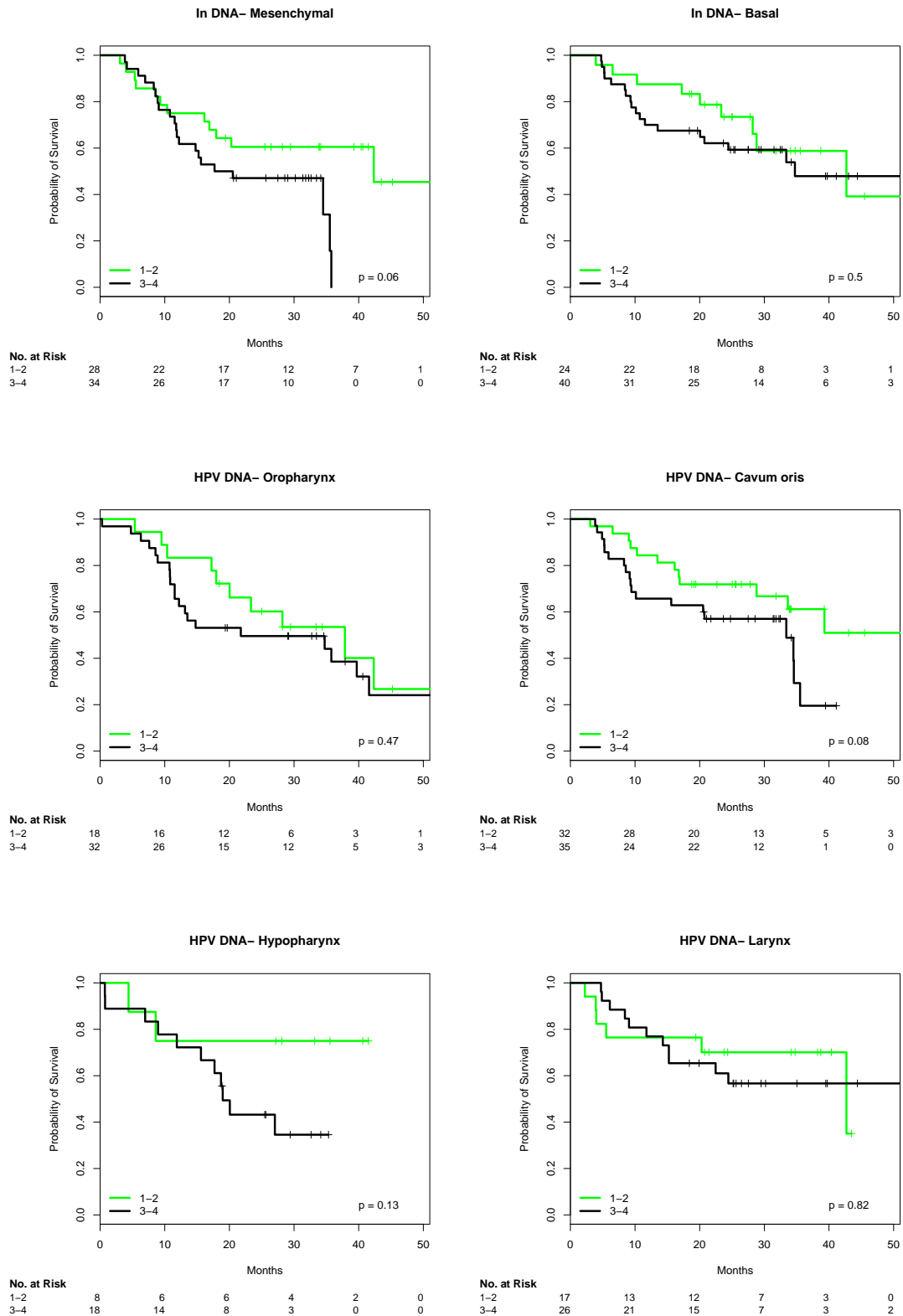
```

## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]3-4      1.54      0.651      1      2.36
##
## Concordance= 0.556  (se = 0.028 )
## Rsquare= 0.021   (max possible= 0.991 )
## Likelihood ratio test= 3.99  on 1 df,   p=0.0458
## Wald test          = 3.84  on 1 df,   p=0.0501
## Score (logrank) test = 3.9   on 1 df,   p=0.0484
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 0.402      1.495    0.210 1.91    0.056 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]3-4      1.5      0.669      0.99      2.26
##
## Concordance= 0.553  (se = 0.027 )
## Rsquare= 0.018   (max possible= 0.99 )
## Likelihood ratio test= 3.8  on 1 df,   p=0.0514
## Wald test          = 3.66  on 1 df,   p=0.0556
## Score (logrank) test = 3.71  on 1 df,   p=0.054
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1-2
##           time      n.risk      n.event      survival      std.err
##           36.0000      19.0000      29.0000          0.6249          0.0577
## lower 95% CI upper 95% CI
##           0.5215          0.7489
##
##               split[cur.subset]=3-4
##           time      n.risk      n.event      survival      std.err
##           36.0000      18.0000      64.0000          0.3963          0.0565
## lower 95% CI upper 95% CI
##           0.2997          0.5240

```







3.12 N (TNM staging)

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.453      0.636   0.382 -1.18  0.2362
## split[cur.subset]2a  0.458      1.580   0.421  1.09  0.2777
## split[cur.subset]2b  0.448      1.565   0.249  1.80  0.0719 .
## split[cur.subset]2c  0.451      1.570   0.255  1.77  0.0773 .
## split[cur.subset]3   1.094      2.986   0.358  3.06  0.0022 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1      0.636      1.573      0.301      1.34
## split[cur.subset]2a      1.580      0.633      0.692      3.61
## split[cur.subset]2b      1.565      0.639      0.961      2.55
## split[cur.subset]2c      1.570      0.637      0.952      2.59
## split[cur.subset]3      2.986      0.335      1.481      6.02
##
## Concordance= 0.589 (se = 0.027 )
## Rsquare= 0.059 (max possible= 0.991 )
## Likelihood ratio test= 16.4 on 5 df, p=0.00585
## Wald test = 16 on 5 df, p=0.00681
## Score (logrank) test = 17.2 on 5 df, p=0.00417
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=0
##           time      n.risk      n.event      survival      std.err
##           36.0000      15.0000      26.0000      0.5970      0.0702
## lower 95% CI upper 95% CI
##           0.4741      0.7519
##
##               split[cur.subset]=1
##           time      n.risk      n.event      survival      std.err
##           36.000      11.000       8.000       0.756      0.075
## lower 95% CI upper 95% CI
##           0.623      0.919
##
##               split[cur.subset]=2a
##           time      n.risk      n.event      survival      std.err
##           36.000       3.000       6.000       0.469      0.150
## lower 95% CI upper 95% CI
```

```

##          0.250          0.879
##
##          split[cur.subset]=2b
##          time          n.risk          n.event          survival          std.err
##          36.0000          13.0000          35.0000          0.4164          0.0719
## lower 95% CI upper 95% CI
##          0.2969          0.5841
##
##          split[cur.subset]=2c
##          time          n.risk          n.event          survival          std.err
##          36.0000          13.0000          29.0000          0.4630          0.0755
## lower 95% CI upper 95% CI
##          0.3363          0.6373
##
##          split[cur.subset]=3
##          time          n.risk          n.event          survival          std.err
##          36.000          2.000          9.000          0.308          0.128
## lower 95% CI upper 95% CI
##          0.136          0.695
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.486    0.615    0.427 -1.14  0.256
## split[cur.subset]2a  0.815    2.259    0.455  1.79  0.073 .
## split[cur.subset]2b  0.622    1.863    0.283  2.20  0.028 *
## split[cur.subset]2c  0.410    1.507    0.295  1.39  0.164
## split[cur.subset]3  1.671    5.317    0.394  4.24 2.3e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1    0.615    1.626    0.266    1.42
## split[cur.subset]2a    2.259    0.443    0.926    5.51
## split[cur.subset]2b    1.863    0.537    1.070    3.24
## split[cur.subset]2c    1.507    0.664    0.845    2.69
## split[cur.subset]3    5.317    0.188    2.455   11.52
##
## Concordance= 0.609 (se = 0.031 )
## Rsquare= 0.113 (max possible= 0.991 )
## Likelihood ratio test= 22.7 on 5 df, p=0.000392

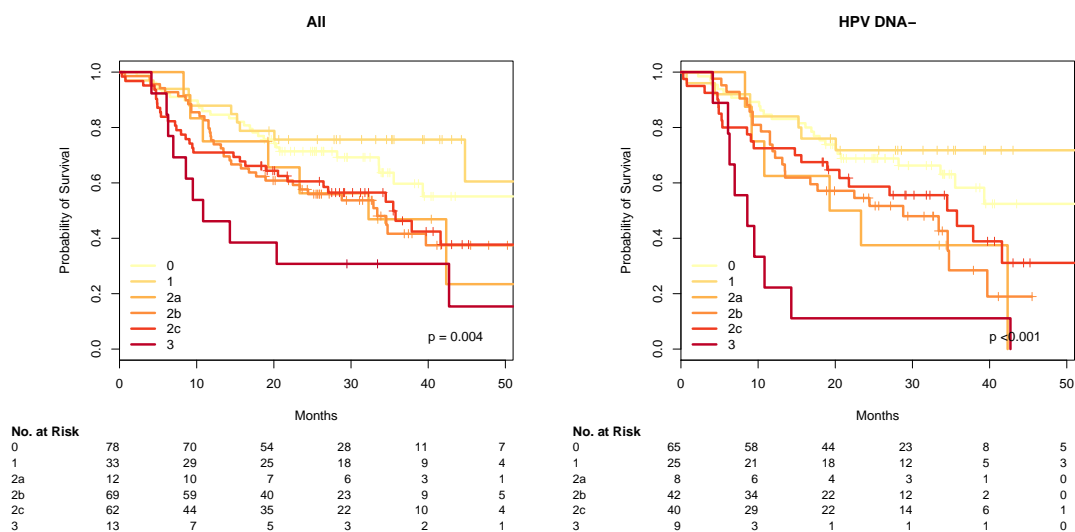
```

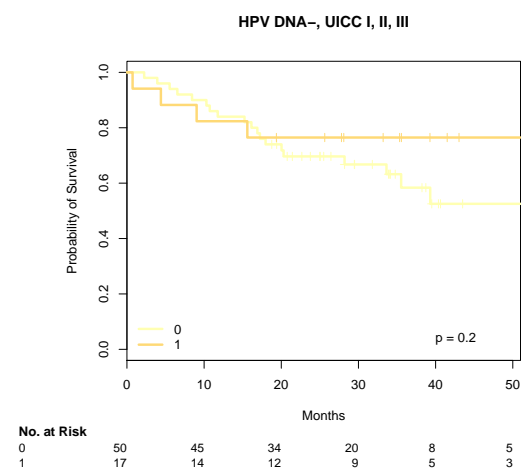
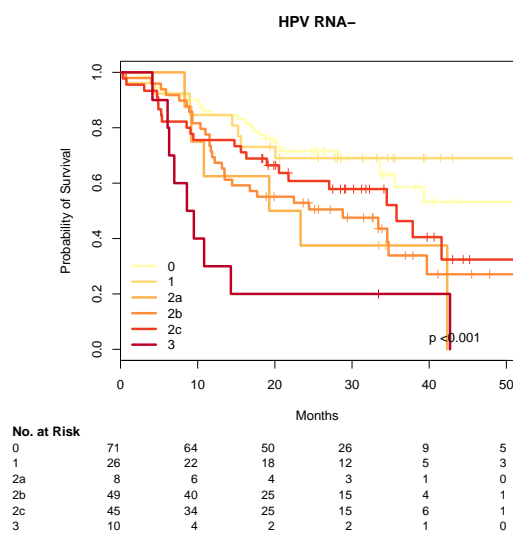
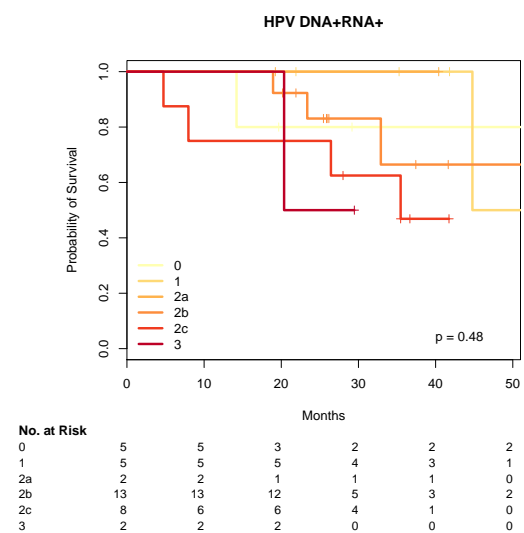
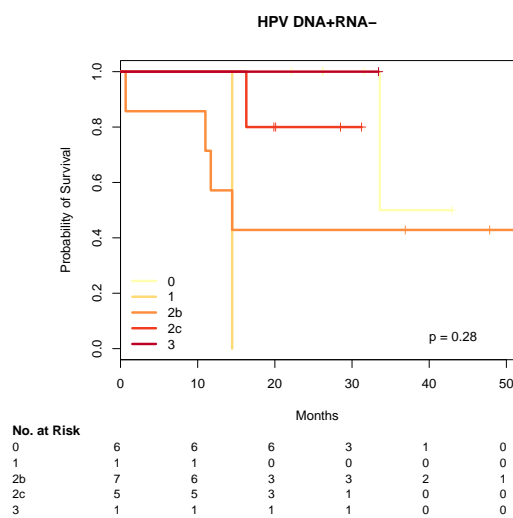
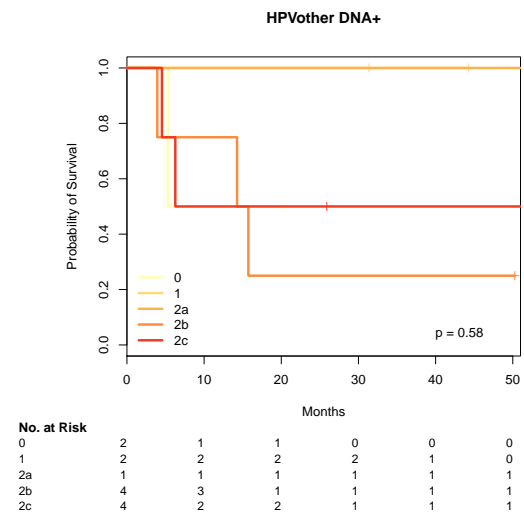
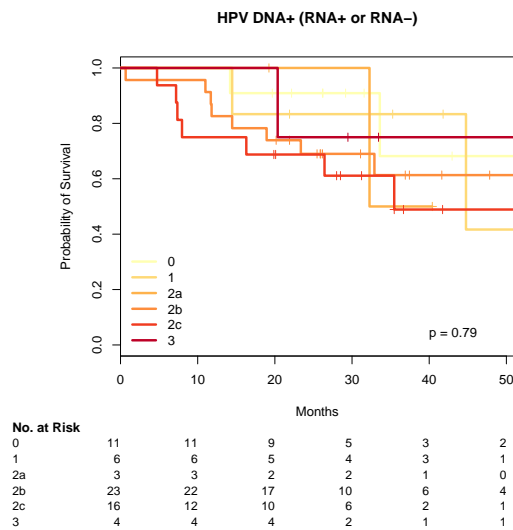
```

## Wald test          = 25.1  on 5 df,    p=0.000132
## Score (logrank) test = 29.2  on 5 df,    p=2.08e-05
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 209, number of events= 101
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.294    0.746   0.404 -0.73   0.467
## split[cur.subset]2a  0.870    2.386   0.452  1.92   0.055 .
## split[cur.subset]2b  0.626    1.870   0.268  2.33   0.020 *
## split[cur.subset]2c  0.392    1.480   0.288  1.36   0.173
## split[cur.subset]3   1.516    4.553   0.389  3.90  9.7e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1    0.746    1.341    0.338    1.64
## split[cur.subset]2a    2.386    0.419    0.983    5.79
## split[cur.subset]2b    1.870    0.535    1.106    3.16
## split[cur.subset]2c    1.480    0.676    0.842    2.60
## split[cur.subset]3    4.553    0.220    2.125    9.76
##
## Concordance= 0.606 (se = 0.03 )
## Rsquare= 0.089 (max possible= 0.99 )
## Likelihood ratio test= 19.5  on 5 df,    p=0.00154
## Wald test          = 21.6  on 5 df,    p=0.000632
## Score (logrank) test = 24.1  on 5 df,    p=0.000206
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##              split[cur.subset]=0
##      time      n.risk      n.event      survival      std.err
## 36.0000    13.0000    24.0000    0.5859    0.0753
## lower 95% CI upper 95% CI
## 0.4555    0.7537
##
##              split[cur.subset]=1
##      time      n.risk      n.event      survival      std.err
## 36.0000    7.0000    8.0000    0.6902    0.0911
## lower 95% CI upper 95% CI
## 0.5328    0.8940
##

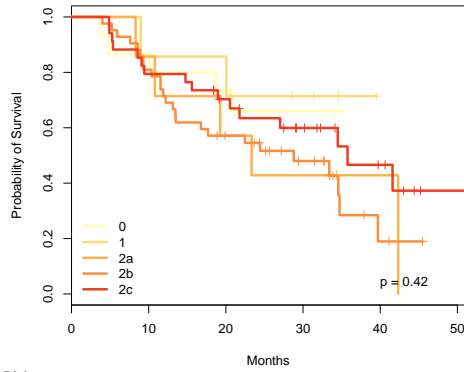
```

```
##                               split[cur.subset]=2a
##           time           n.risk           n.event           survival           std.err
##           36.000           1.000           5.000           0.375           0.171
## lower 95% CI upper 95% CI
##           0.153           0.917
##
##                               split[cur.subset]=2b
##           time           n.risk           n.event           survival           std.err
##           36.0000          7.0000          28.0000          0.3388           0.0854
## lower 95% CI upper 95% CI
##           0.2068           0.5551
##
##                               split[cur.subset]=2c
##           time           n.risk           n.event           survival           std.err
##           36.0000          8.0000          20.0000          0.4630           0.0957
## lower 95% CI upper 95% CI
##           0.3088           0.6942
##
##                               split[cur.subset]=3
##           time           n.risk           n.event           survival           std.err
##           36.0000          1.0000          8.0000          0.2000           0.1265
## lower 95% CI upper 95% CI
##           0.0579           0.6908
```





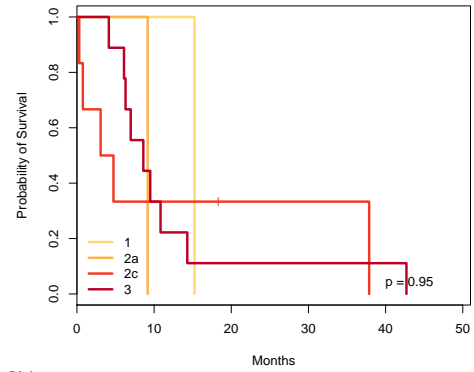
HPV DNA-, UICC IVA



No. at Risk

	0	10	20	30	40	50
0	15	13	10	3	0	0
1	7	6	6	3	0	0
2a	7	6	4	3	1	0
2b	42	34	22	12	2	0
2c	34	27	21	13	6	1

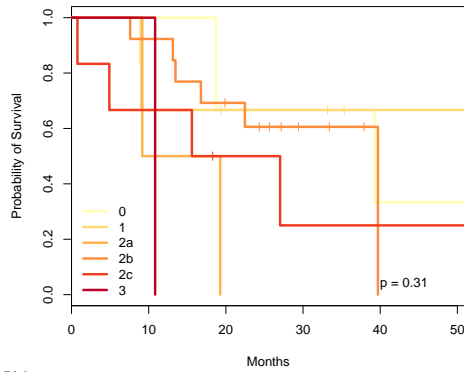
HPV DNA-, UICC IVB-C



No. at Risk

	0	10	20	30	40	50
1	1	1	0	0	0	0
2a	1	0	0	0	0	0
2c	6	2	1	1	0	0
3	9	3	1	1	1	0

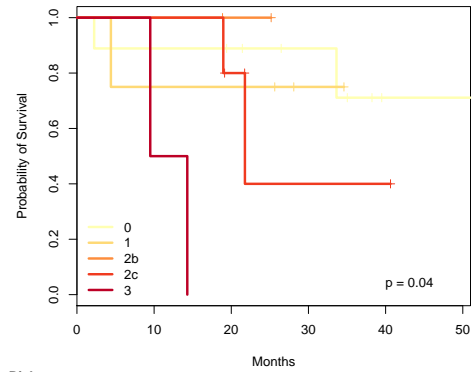
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
0	3	3	2	2	1	1
1	6	4	3	3	1	1
2a	2	1	0	0	0	0
2b	13	12	8	3	0	0
2c	6	4	2	1	1	1
3	1	1	0	0	0	0

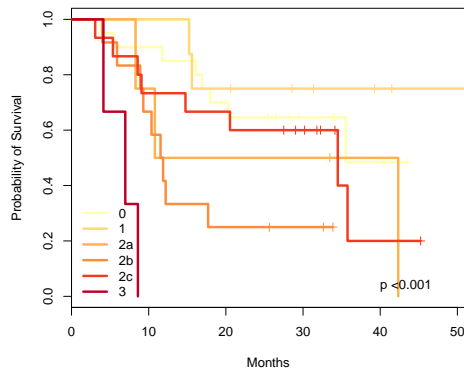
In DNA- Classical



No. at Risk

	0	10	20	30	40	50
0	9	8	7	5	1	1
1	4	3	3	1	0	0
2b	2	2	1	0	0	0
2c	5	5	3	1	1	0
3	2	1	0	0	0	0

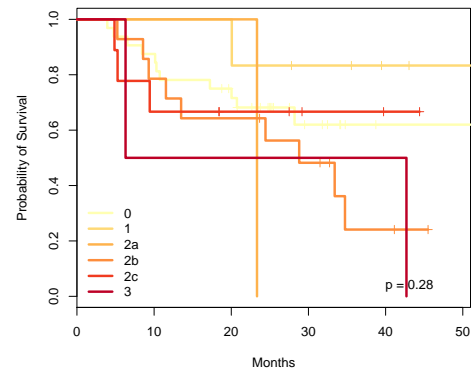
In DNA- Mesenchymal



No. at Risk

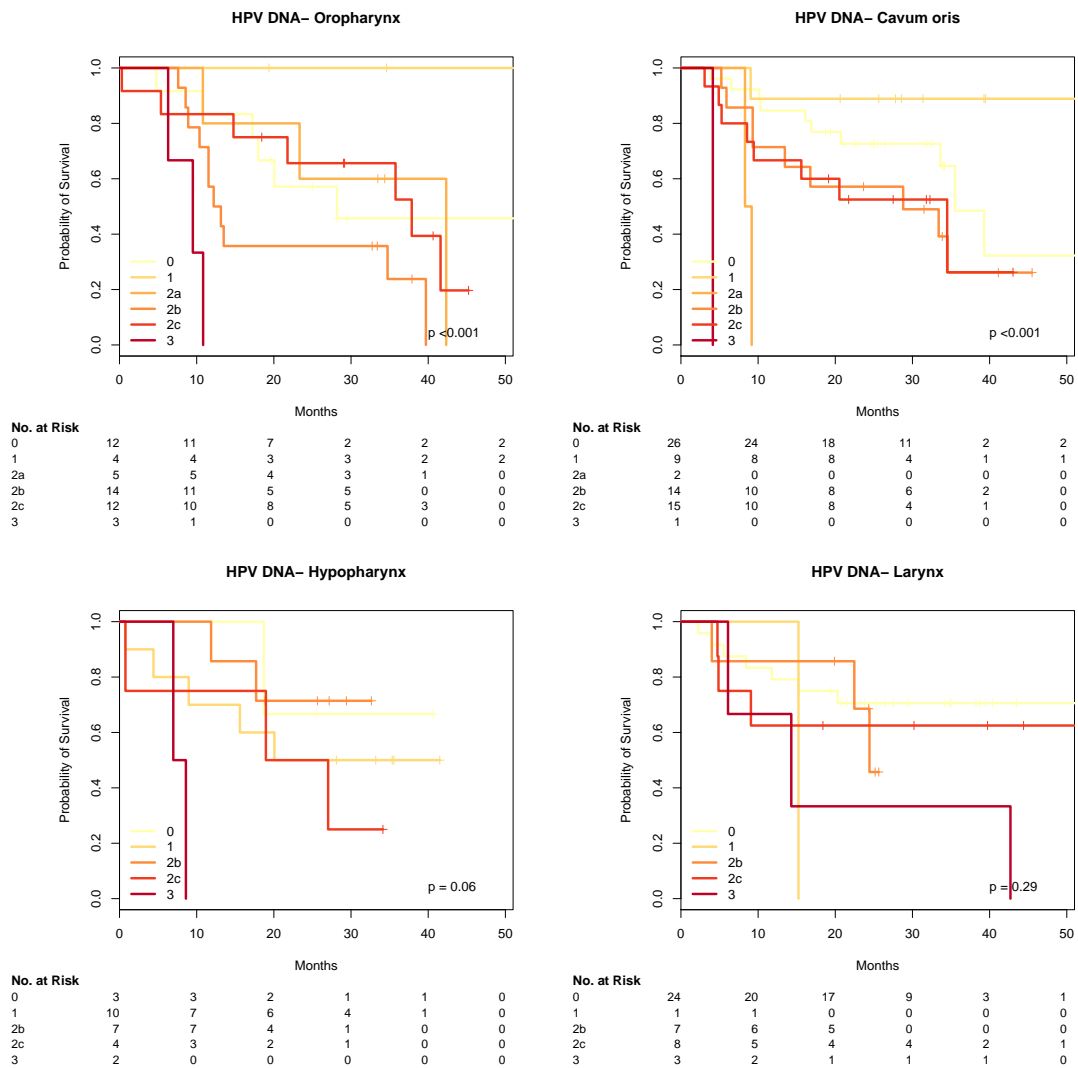
	0	10	20	30	40	50
0	20	18	13	7	3	0
1	8	8	6	4	2	1
2a	4	3	2	2	1	0
2b	12	8	3	2	0	0
2c	15	11	10	7	1	0
3	3	0	0	0	0	0

In DNA- Basal



No. at Risk

	0	10	20	30	40	50
0	32	28	22	9	3	3
1	6	6	6	4	2	1
2a	1	1	1	0	0	0
2b	14	11	9	6	2	0
2c	9	6	4	2	1	0
3	2	1	1	1	1	0



3.13 N0 stage vs. N1-N3

```
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.369      1.446    0.212 1.74   0.082 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3  1.45      0.691    0.954    2.19
##
```

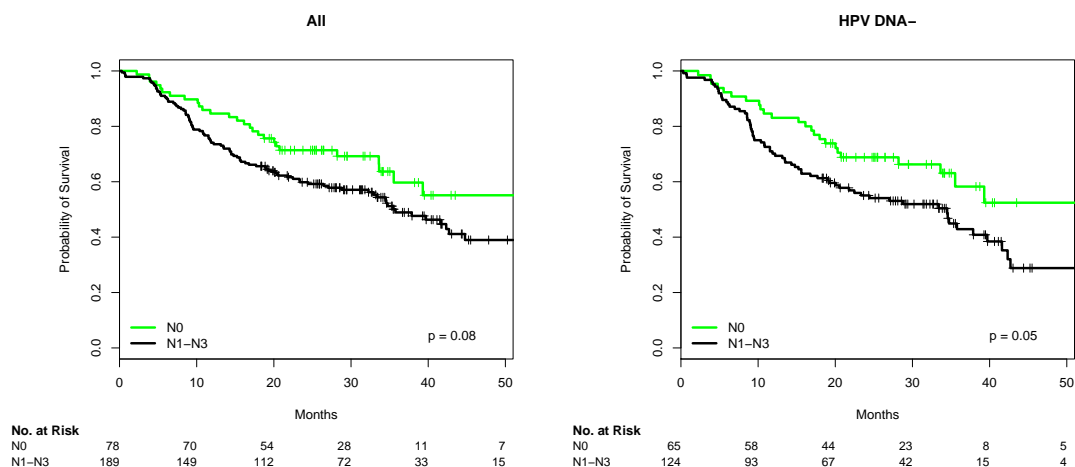


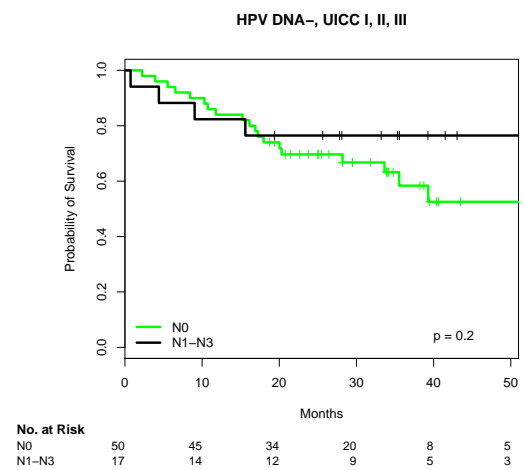
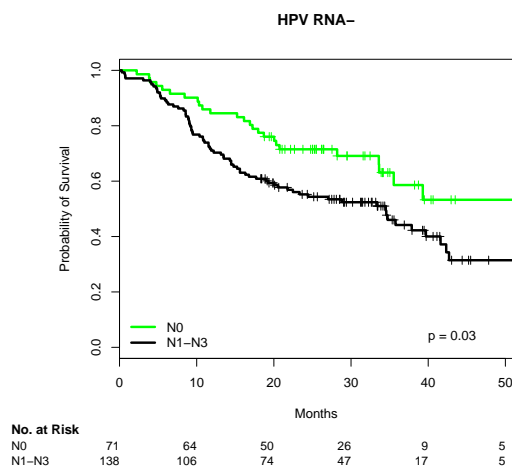
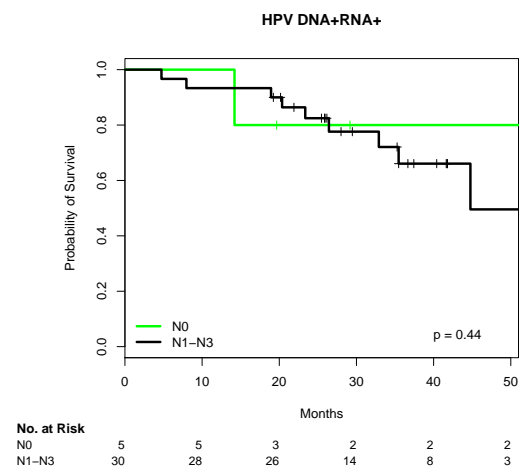
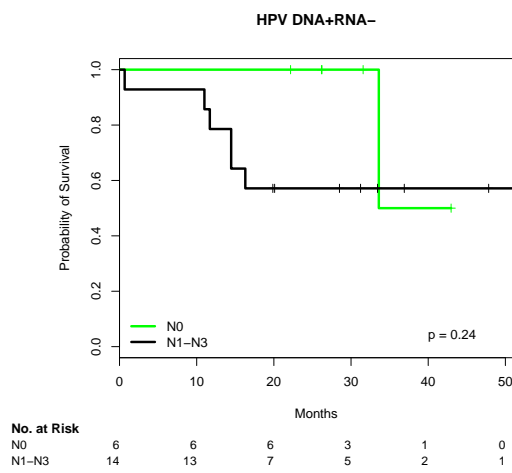
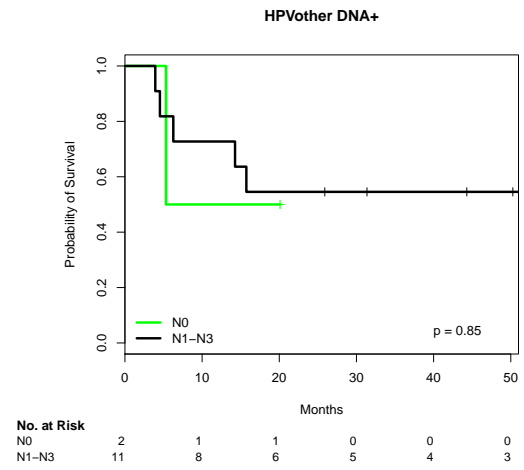
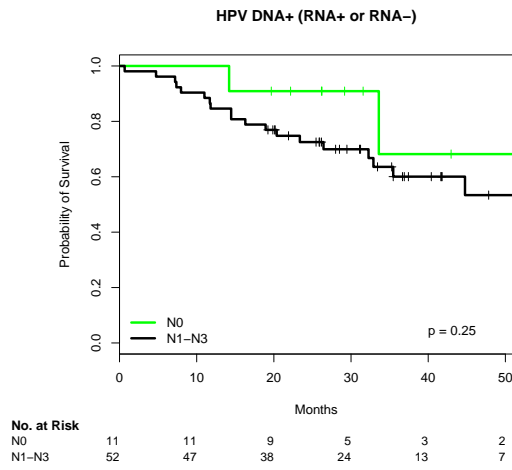
```

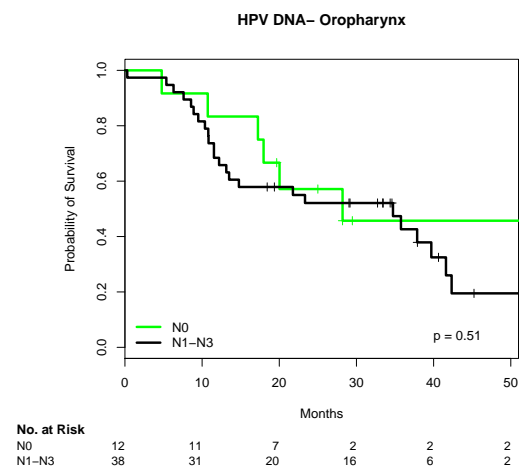
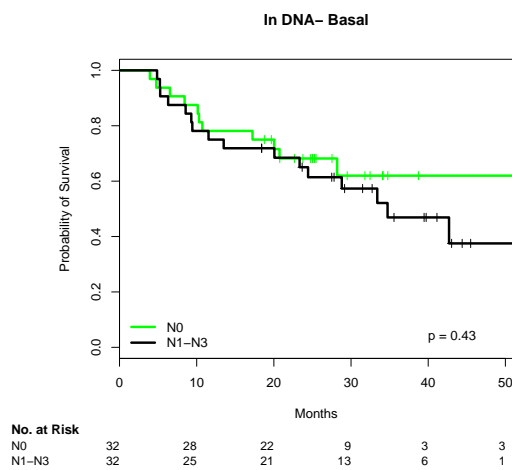
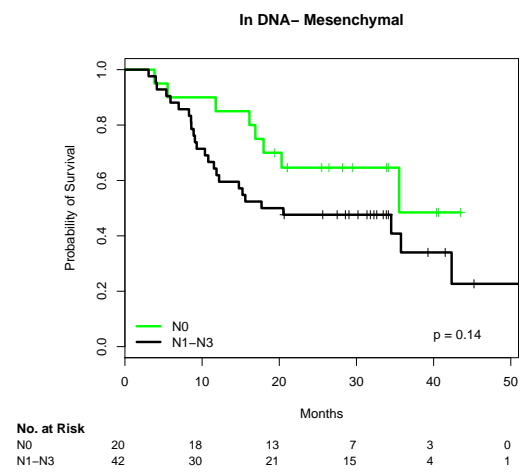
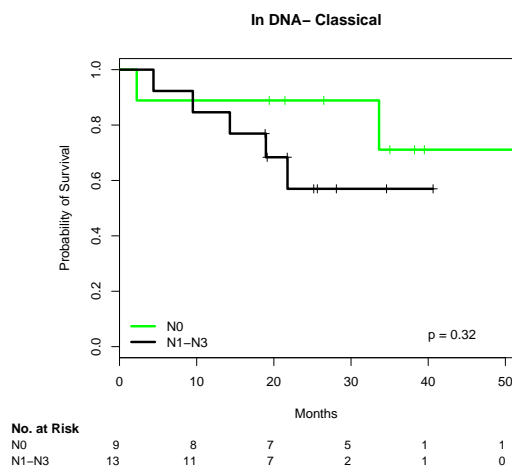
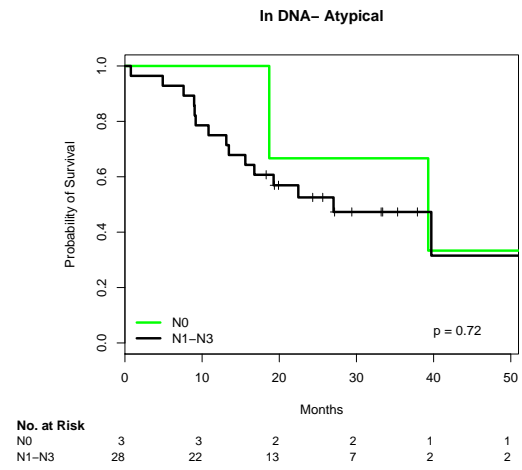
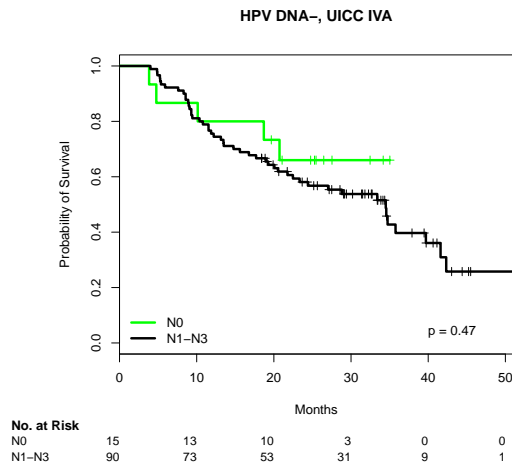
## Concordance= 0.543 (se = 0.022 )
## Rsquare= 0.012 (max possible= 0.991 )
## Likelihood ratio test= 3.21 on 1 df, p=0.0732
## Wald test = 3.02 on 1 df, p=0.0823
## Score (logrank) test = 3.05 on 1 df, p=0.0806
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=N0
##      time      n.risk      n.event      survival      std.err
##    36.0000     15.0000     26.0000         0.5970         0.0702
## lower 95% CI upper 95% CI
##    0.4741         0.7519
##
##               split[cur.subset]=N1-N3
##      time      n.risk      n.event      survival      std.err
##    36.0000     42.0000     87.0000         0.4892         0.0416
## lower 95% CI upper 95% CI
##    0.4142         0.5778
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.446     1.563    0.231 1.93   0.053 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3      1.56      0.64      0.994      2.46
##
## Concordance= 0.556 (se = 0.027 )
## Rsquare= 0.021 (max possible= 0.991 )
## Likelihood ratio test= 3.97 on 1 df, p=0.0464
## Wald test = 3.74 on 1 df, p=0.0533
## Score (logrank) test = 3.8 on 1 df, p=0.0513
##
##
## #####
## Cox model1 in HPV RNA-
## Call:

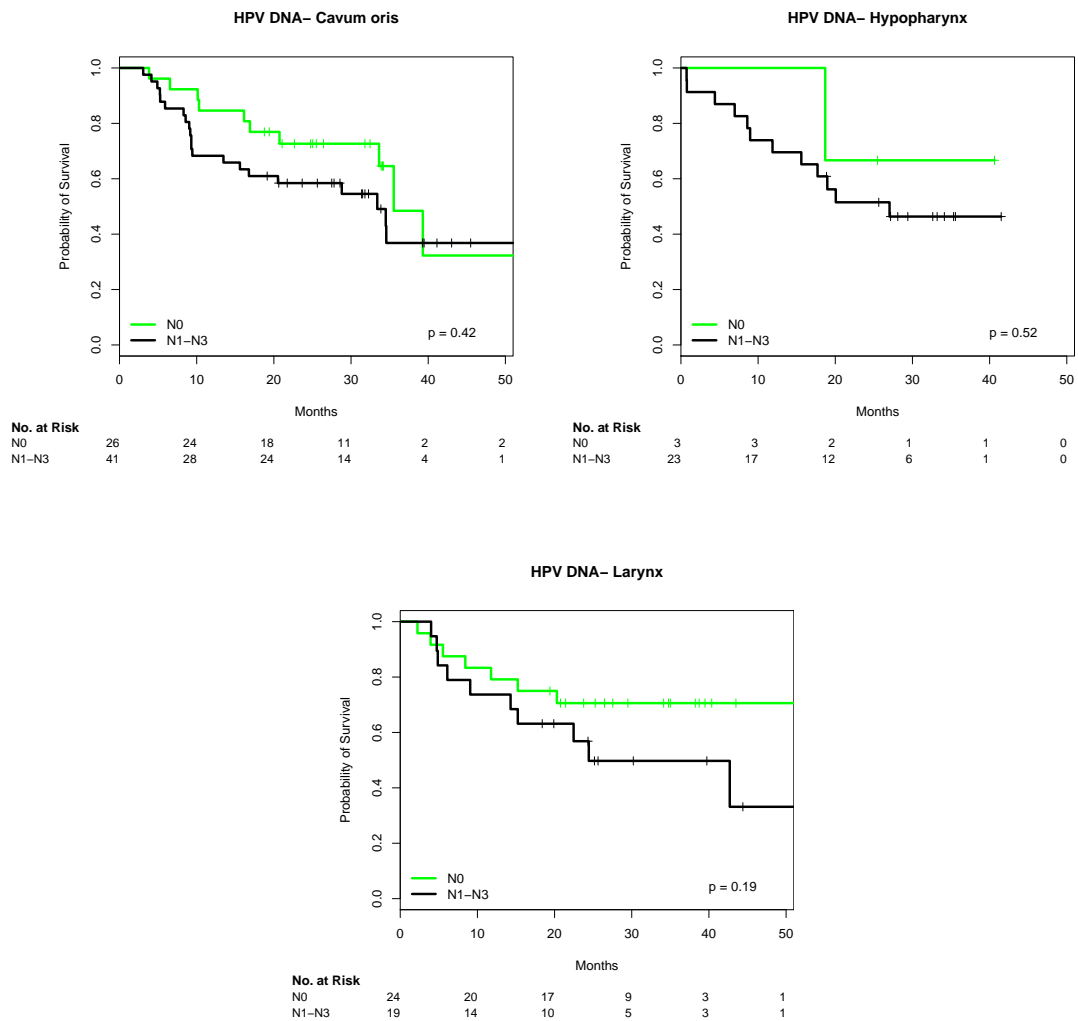
```

```
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.480      1.616    0.225 2.13    0.033 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3      1.62      0.619      1.04      2.51
##
## Concordance= 0.562 (se = 0.026 )
## Rsquare= 0.023 (max possible= 0.99 )
## Likelihood ratio test= 4.87 on 1 df,  p=0.0274
## Wald test               = 4.55 on 1 df,  p=0.0329
## Score (logrank) test = 4.64 on 1 df,  p=0.0313
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=N0
##               time      n.risk      n.event      survival      std.err
##               36.0000      13.0000      24.0000      0.5859      0.0753
## lower 95% CI upper 95% CI
##               0.4555      0.7537
##
##               split[cur.subset]=N1-N3
##               time      n.risk      n.event      survival      std.err
##               36.0000      24.0000      69.0000      0.4417      0.0501
## lower 95% CI upper 95% CI
##               0.3536      0.5517
```









3.14 N0-N1 stages vs. N2-N3

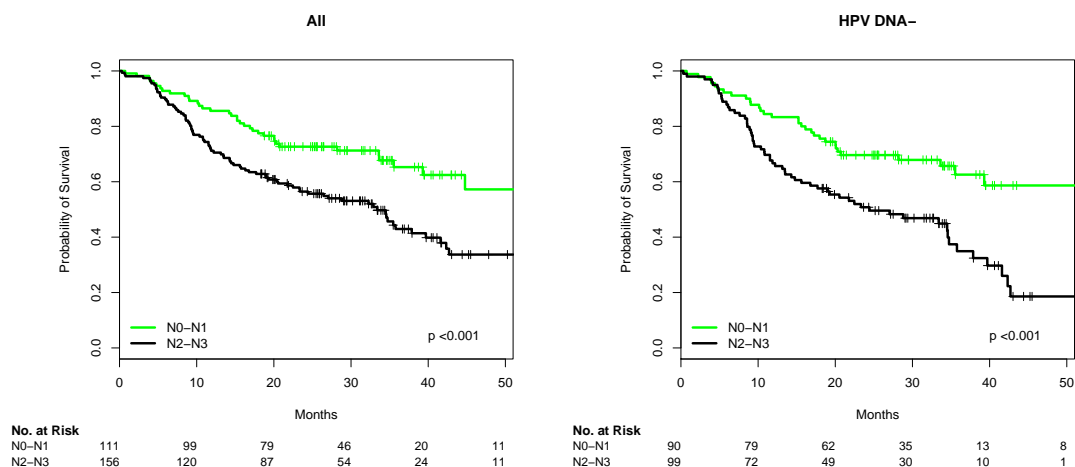
```
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N2-N3 0.638      1.894    0.195 3.28   0.001 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N2-N3    1.89    0.528    1.29    2.77
##
```

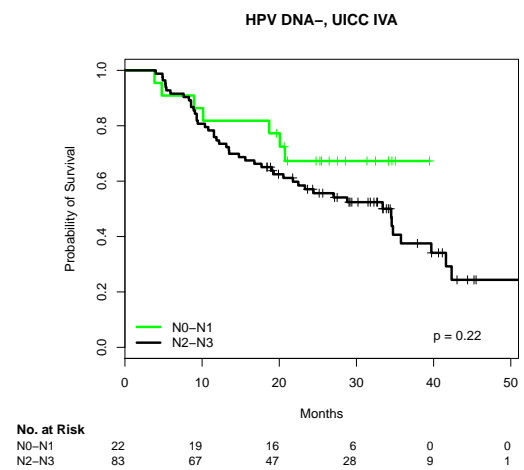
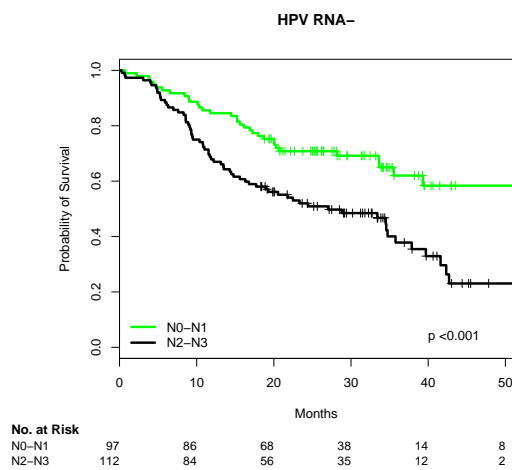
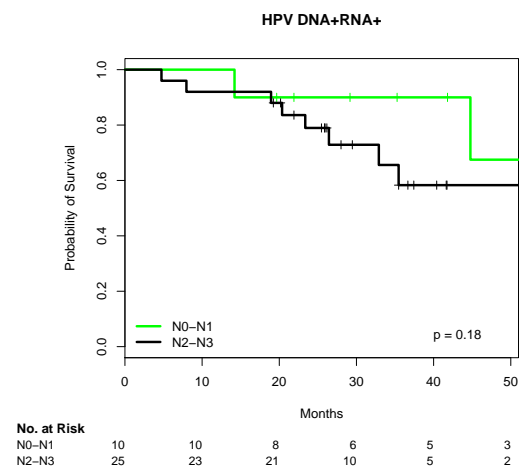
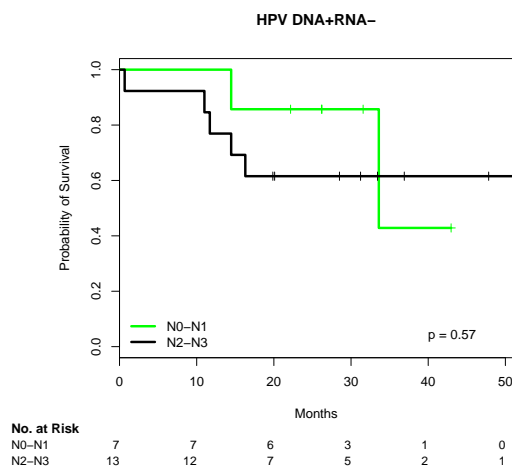
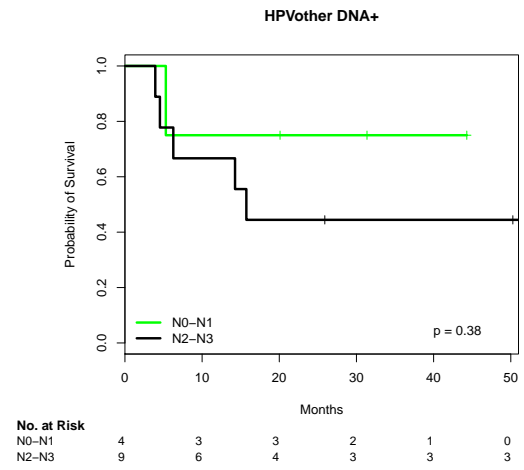
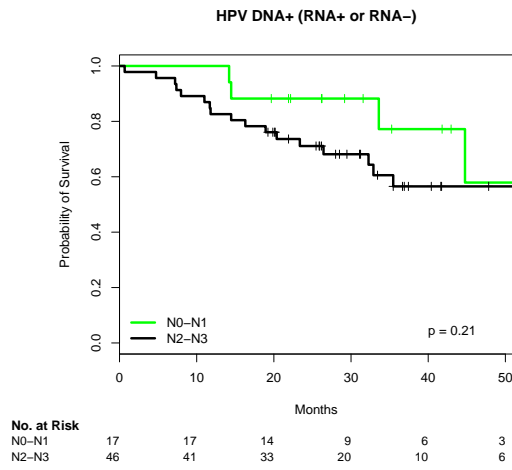
```

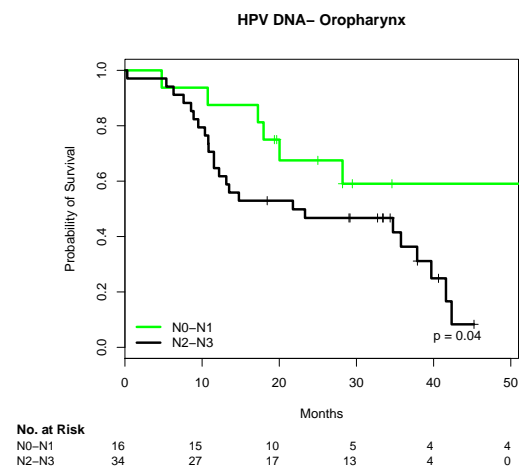
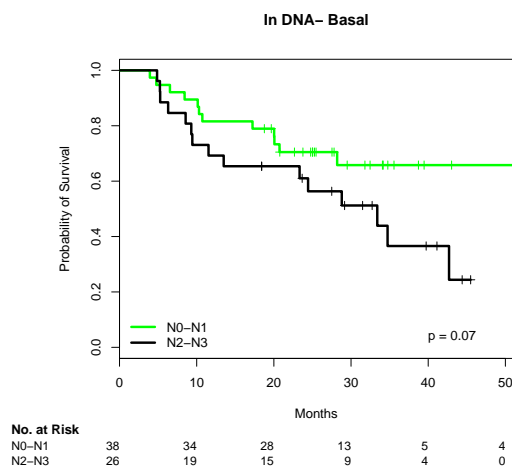
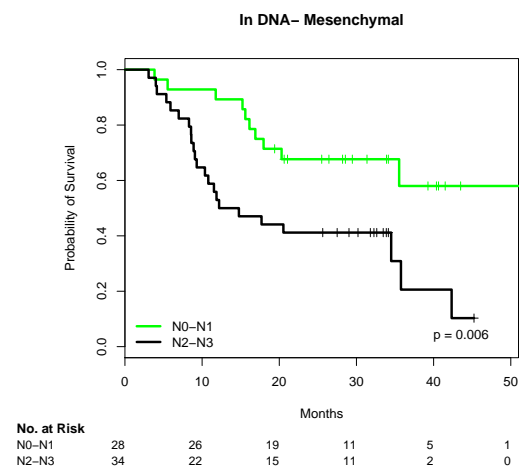
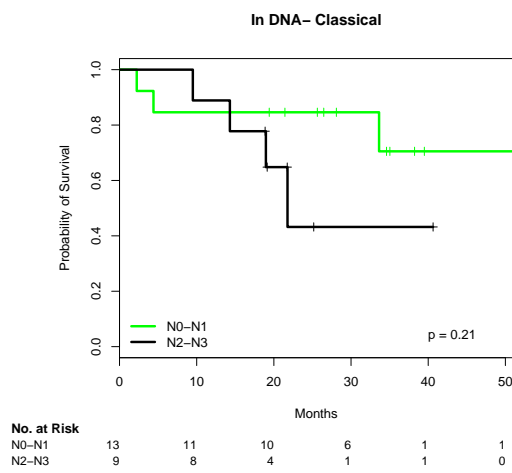
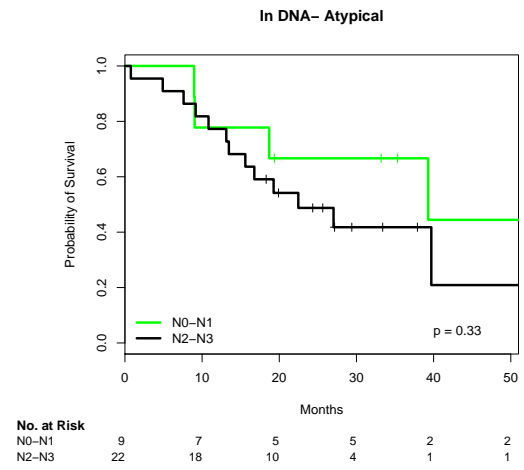
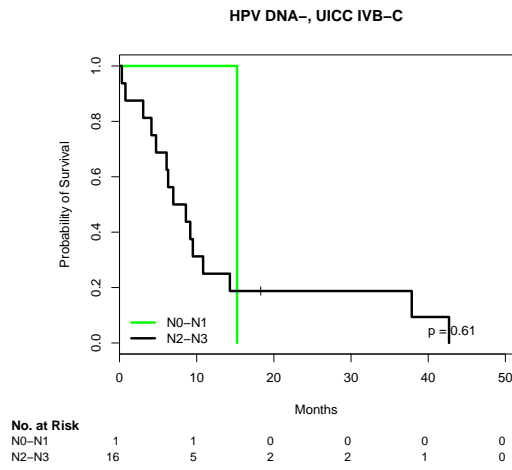
## Concordance= 0.573 (se = 0.024 )
## Rsquare= 0.042 (max possible= 0.991 )
## Likelihood ratio test= 11.5 on 1 df, p=0.000694
## Wald test = 10.7 on 1 df, p=0.00105
## Score (logrank) test = 11.1 on 1 df, p=0.000861
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=N0-N1
##      time      n.risk      n.event      survival      std.err
## 36.0000    26.0000    34.0000      0.6528      0.0525
## lower 95% CI upper 95% CI
## 0.5577      0.7642
##
##               split[cur.subset]=N2-N3
##      time      n.risk      n.event      survival      std.err
## 36.0000    31.0000    79.0000      0.4294      0.0466
## lower 95% CI upper 95% CI
## 0.3472      0.5311
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N2-N3 0.771    2.162    0.220 3.51 0.00045 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N2-N3    2.16    0.463    1.41    3.33
##
## Concordance= 0.584 (se = 0.028 )
## Rsquare= 0.067 (max possible= 0.991 )
## Likelihood ratio test= 13 on 1 df, p=0.000305
## Wald test = 12.3 on 1 df, p=0.000452
## Score (logrank) test = 12.9 on 1 df, p=0.000327
##
##
## #####
## Cox model1 in HPV RNA-
## Call:

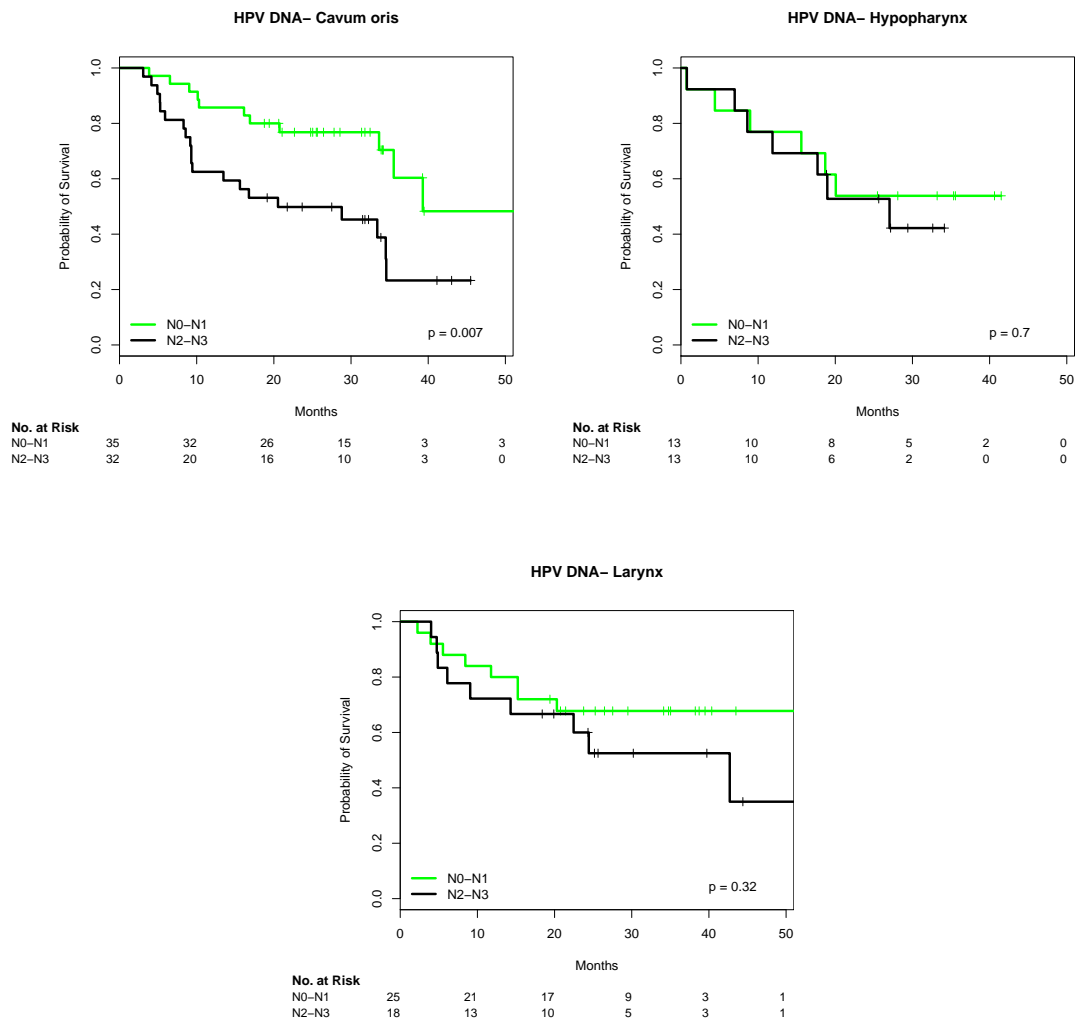
```

```
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N2-N3 0.709      2.033    0.210 3.37  0.00075 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N2-N3      2.03      0.492      1.35      3.07
##
## Concordance= 0.584 (se = 0.027 )
## Rsquare= 0.056 (max possible= 0.99 )
## Likelihood ratio test= 12 on 1 df,  p=0.000535
## Wald test               = 11.4 on 1 df,  p=0.000748
## Score (logrank) test = 11.8 on 1 df,  p=0.000581
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=N0-N1
##               time      n.risk      n.event      survival      std.err
##               36.0000      20.0000      32.0000      0.6202      0.0588
## lower 95% CI upper 95% CI
##               0.5150      0.7469
##
##               split[cur.subset]=N2-N3
##               time      n.risk      n.event      survival      std.err
##               36.000      17.000      61.000      0.378      0.057
## lower 95% CI upper 95% CI
##               0.282      0.508
```







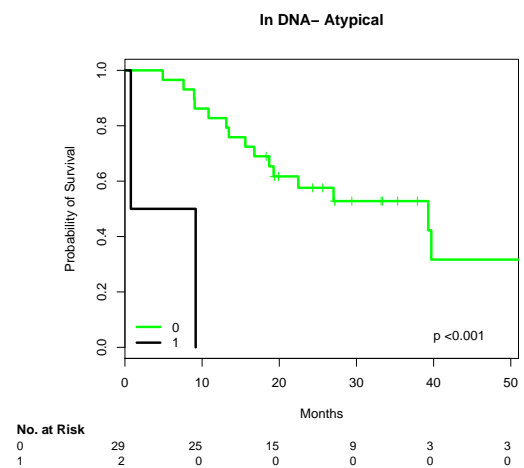
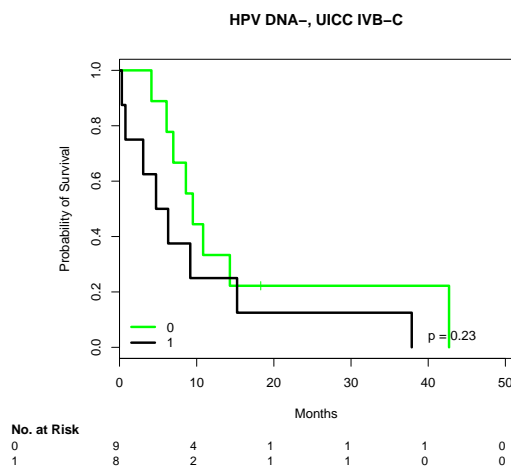
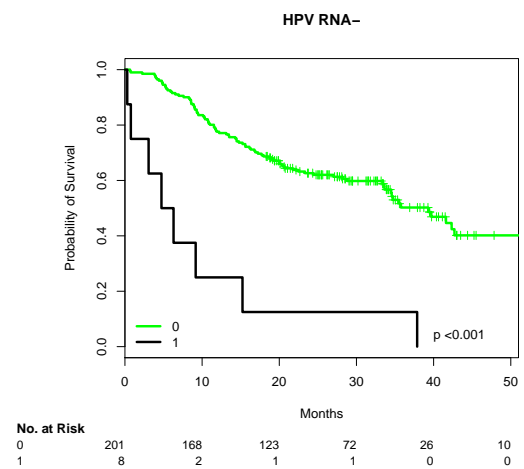
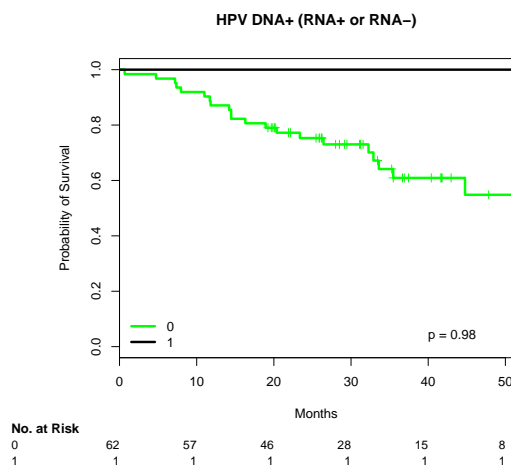
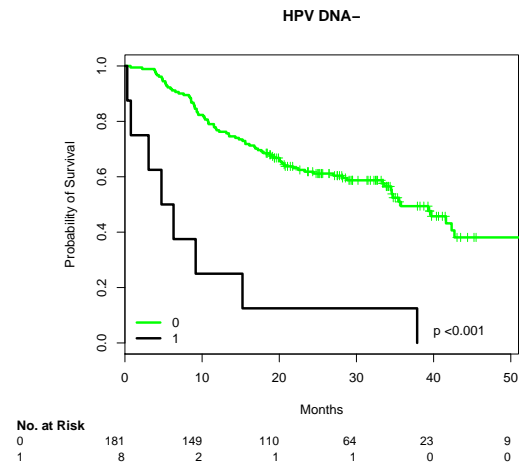
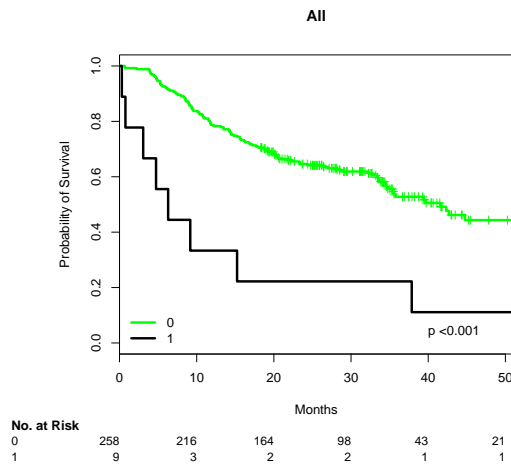


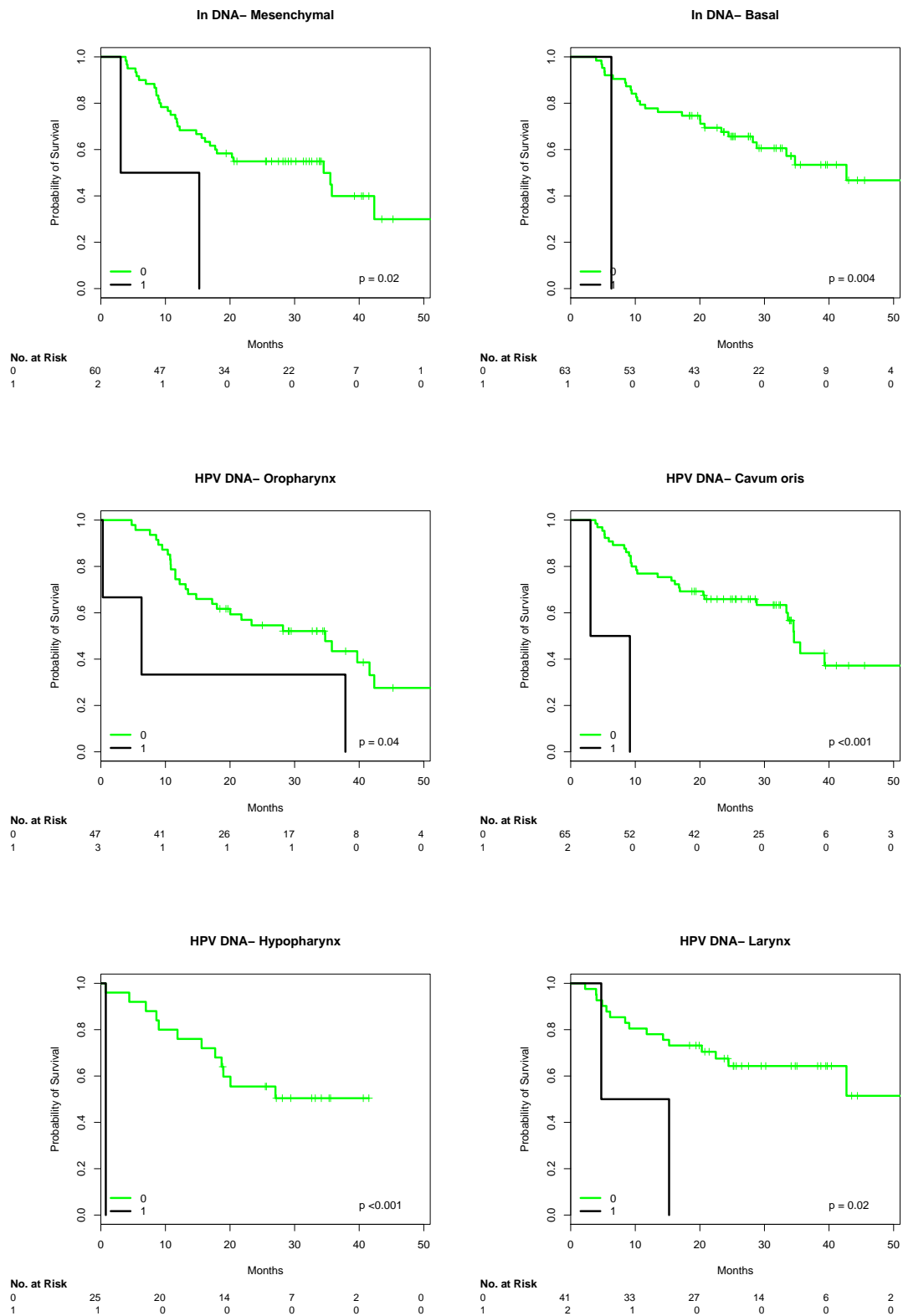
3.15 M (TNM staging)

```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 1.276      3.581    0.355  3.59  0.00033 ***
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      3.58      0.279      1.79      7.18
##
## Concordance= 0.53 (se = 0.006 )
## Rsquare= 0.034 (max possible= 0.991 )
## Likelihood ratio test= 9.34 on 1 df,  p=0.00224
## Wald test = 12.9 on 1 df,  p=0.000327
## Score (logrank) test = 14.6 on 1 df,  p=0.000134
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=0
##      time      n.risk      n.event      survival      std.err
## 36.0000     55.0000     106.0000      0.5279      0.0369
## lower 95% CI upper 95% CI
## 0.4602      0.6055
##
##               split[cur.subset]=1
##      time      n.risk      n.event      survival      std.err
## 36.0000      2.0000      7.0000      0.2222      0.1386
## lower 95% CI upper 95% CI
## 0.0655      0.7544
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 1.748      5.741      0.374 4.67      3e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      5.74      0.174      2.76      12
##
## Concordance= 0.542 (se = 0.008 )
## Rsquare= 0.072 (max possible= 0.991 )
## Likelihood ratio test= 14.1 on 1 df,  p=0.000171
## Wald test = 21.8 on 1 df,  p=2.99e-06
## Score (logrank) test = 27.9 on 1 df,  p=1.25e-07
```

```
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 1.771      5.876    0.373 4.75    2e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      5.88      0.17      2.83      12.2
##
## Concordance= 0.539 (se = 0.007 )
## Rsquare= 0.067 (max possible= 0.99 )
## Likelihood ratio test= 14.5 on 1 df,  p=0.000142
## Wald test              = 22.6 on 1 df,  p=2.01e-06
## Score (logrank) test = 29.1 on 1 df,  p=6.85e-08
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=0
##           time      n.risk      n.event      survival      std.err
##           36.0000      36.0000      86.0000      0.5022      0.0435
## lower 95% CI upper 95% CI
##           0.4239      0.5951
##
##               split[cur.subset]=1
##           time      n.risk      n.event      survival      std.err
##           36.000      1.000      7.000      0.125      0.117
## lower 95% CI upper 95% CI
##           0.020      0.782
```





3.16 UICC staging

```
## Error: There is only 1 group

##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.809    0.445    0.505 -1.60   0.109
## split[cur.subset]III -0.596    0.551    0.478 -1.25   0.213
## split[cur.subset]IVA -0.021    0.979    0.396 -0.05   0.958
## split[cur.subset]IVB  0.814    2.257    0.469  1.73   0.083 .
## split[cur.subset]IVC  1.128    3.090    0.515  2.19   0.028 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.445    2.247    0.165    1.20
## split[cur.subset]III    0.551    1.814    0.216    1.41
## split[cur.subset]IVA    0.979    1.021    0.451    2.13
## split[cur.subset]IVB    2.257    0.443    0.899    5.66
## split[cur.subset]IVC    3.090    0.324    1.127    8.47
##
## Concordance= 0.611 (se = 0.025 )
## Rsquare= 0.096 (max possible= 0.991 )
## Likelihood ratio test= 27 on 5 df, p=5.77e-05
## Wald test = 29.6 on 5 df, p=1.81e-05
## Score (logrank) test = 33.5 on 5 df, p=3.05e-06
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##              split[cur.subset]=I
##      time      n.risk      n.event      survival      std.err
## 36.000      1.000      6.000      0.545      0.154
## lower 95% CI upper 95% CI
## 0.313      0.949
##
##              split[cur.subset]=II
##      time      n.risk      n.event      survival      std.err
## 36.0000     10.0000      7.0000      0.7564      0.0848
## lower 95% CI upper 95% CI
## 0.6071      0.9423
##
##              split[cur.subset]=III
##      time      n.risk      n.event      survival      std.err
## 36.0000     13.0000     11.0000      0.6548      0.0877
```

```

## lower 95% CI upper 95% CI
##      0.5037      0.8513
##
##              split[cur.subset]=IVA
##      time      n.risk      n.event      survival      std.err
##      36.0000      30.0000      70.0000      0.4833      0.0486
## lower 95% CI upper 95% CI
##      0.3969      0.5885
##
##              split[cur.subset]=IVB
##      time      n.risk      n.event      survival      std.err
##      36.000      1.000      12.000      0.224      0.121
## lower 95% CI upper 95% CI
##      0.078      0.644
##
##              split[cur.subset]=IVC
##      time      n.risk      n.event      survival      std.err
##      36.0000      2.0000      7.0000      0.2222      0.1386
## lower 95% CI upper 95% CI
##      0.0655      0.7544
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 94
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.7476  0.4735  0.5079 -1.47  0.1410
## split[cur.subset]III -0.7434  0.4755  0.5101 -1.46  0.1450
## split[cur.subset]IVA -0.0276  0.9728  0.4030 -0.07  0.9454
## split[cur.subset]IVB  1.0251  2.7874  0.5218  1.96  0.0495 *
## split[cur.subset]IVC  1.6008  4.9568  0.5219  3.07  0.0022 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II  0.473  2.112  0.175  1.28
## split[cur.subset]III  0.475  2.103  0.175  1.29
## split[cur.subset]IVA  0.973  1.028  0.442  2.14
## split[cur.subset]IVB  2.787  0.359  1.002  7.75
## split[cur.subset]IVC  4.957  0.202  1.782 13.79
##
## Concordance= 0.624 (se = 0.029 )
## Rsquare= 0.146 (max possible= 0.991 )

```

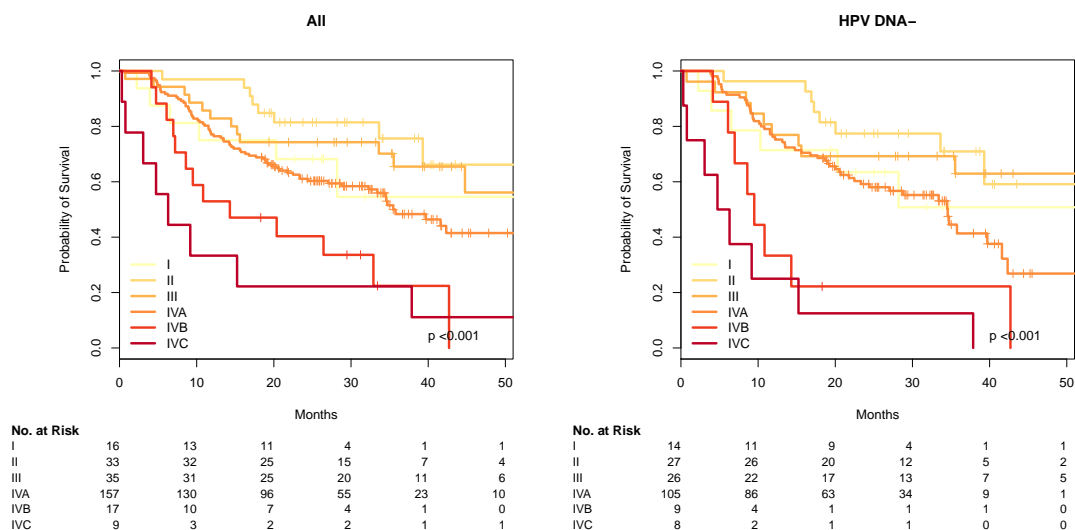


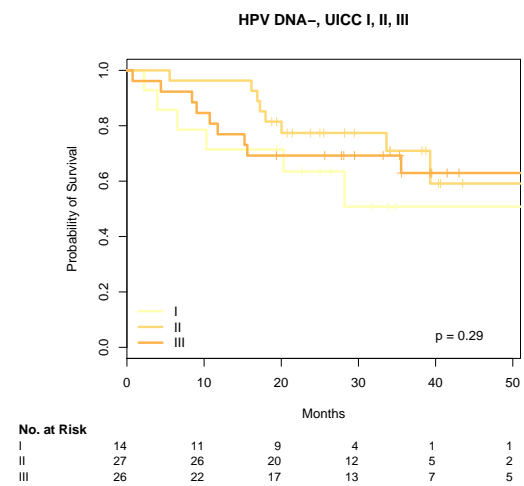
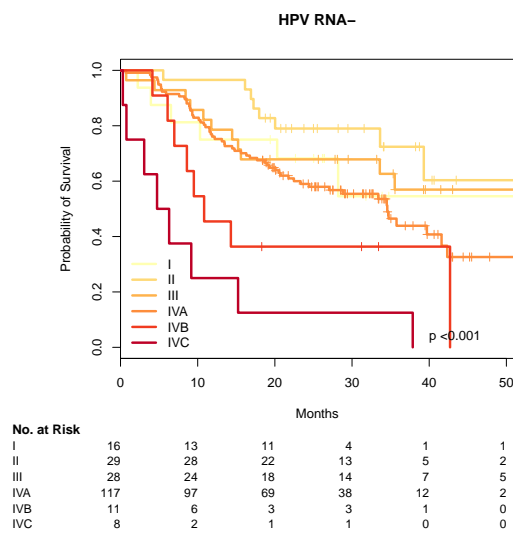
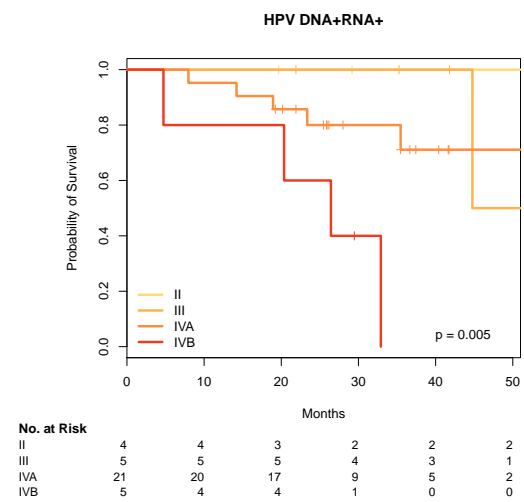
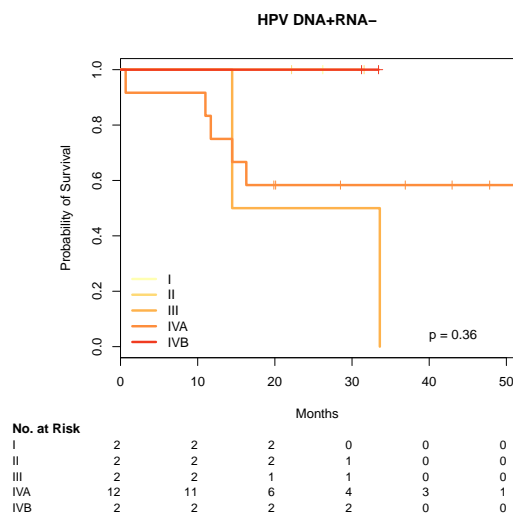
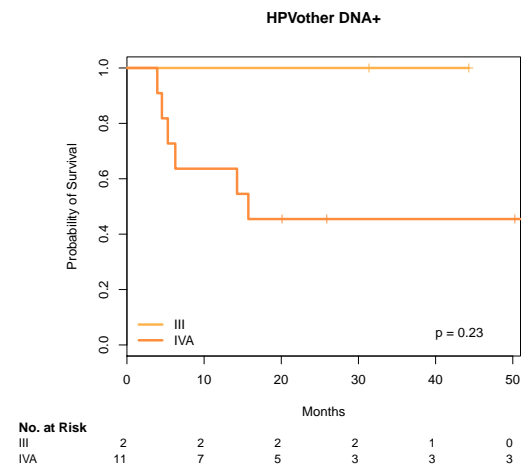
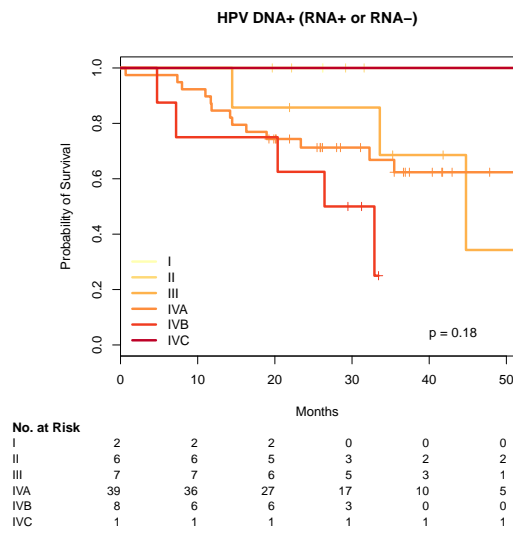
```

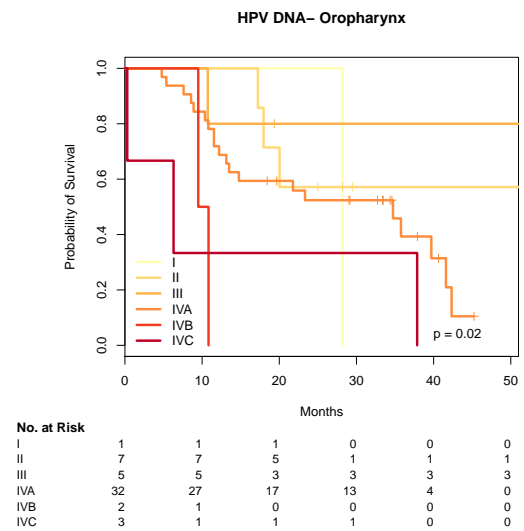
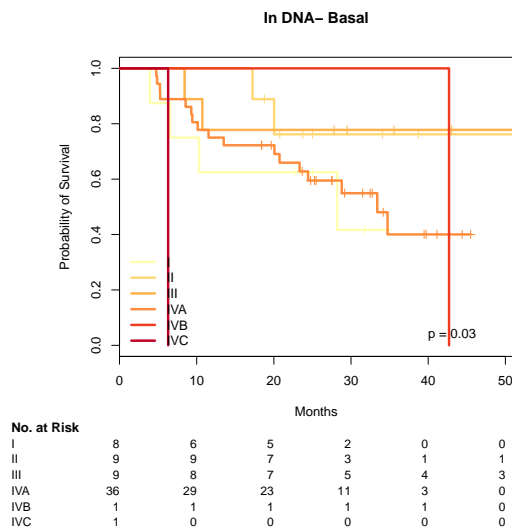
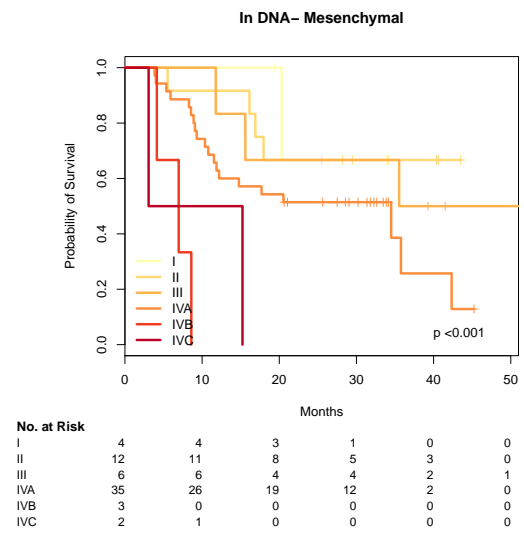
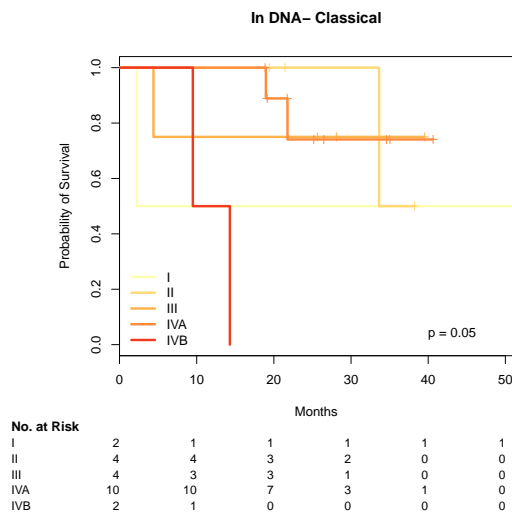
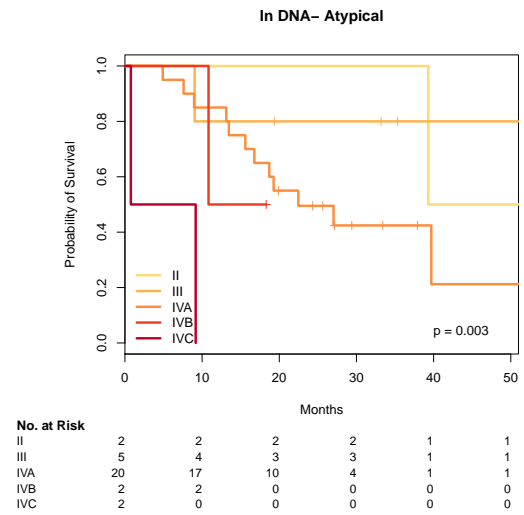
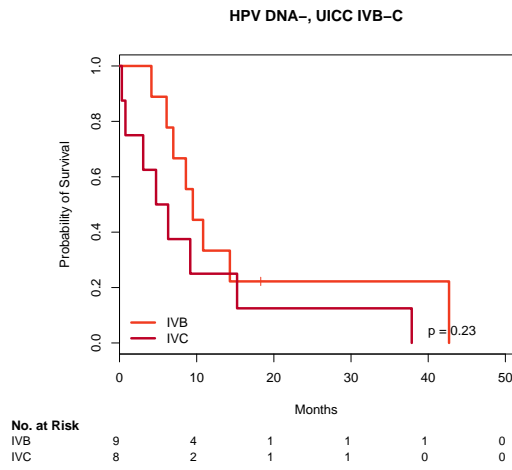
## Likelihood ratio test= 29.8 on 5 df, p=1.59e-05
## Wald test = 36.6 on 5 df, p=7.12e-07
## Score (logrank) test = 45.8 on 5 df, p=1.02e-08
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.6377  0.5285  0.5058 -1.26 0.20739
## split[cur.subset]III -0.4084  0.6647  0.4875 -0.84 0.40214
## split[cur.subset]IVA  0.0812  1.0846  0.4007  0.20 0.83945
## split[cur.subset]IVB  0.8236  2.2788  0.5192  1.59 0.11266
## split[cur.subset]IVC  1.7366  5.6780  0.5214  3.33 0.00087 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.529      1.892    0.196    1.42
## split[cur.subset]III    0.665      1.504    0.256    1.73
## split[cur.subset]IVA    1.085      0.922    0.494    2.38
## split[cur.subset]IVB    2.279      0.439    0.824    6.30
## split[cur.subset]IVC    5.678      0.176    2.044   15.78
##
## Concordance= 0.614 (se = 0.028 )
## Rsquare= 0.114 (max possible= 0.99 )
## Likelihood ratio test= 25.2 on 5 df, p=0.000125
## Wald test = 32.1 on 5 df, p=5.56e-06
## Score (logrank) test = 40.1 on 5 df, p=1.42e-07
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=I
##           time      n.risk      n.event      survival      std.err
##           36.000         1.000         6.000         0.545         0.154
## lower 95% CI upper 95% CI
##           0.313         0.949
##
##               split[cur.subset]=II
##           time      n.risk      n.event      survival      std.err
##           36.0000         8.0000         7.0000         0.7241         0.0942
## lower 95% CI upper 95% CI
##           0.5612         0.9345

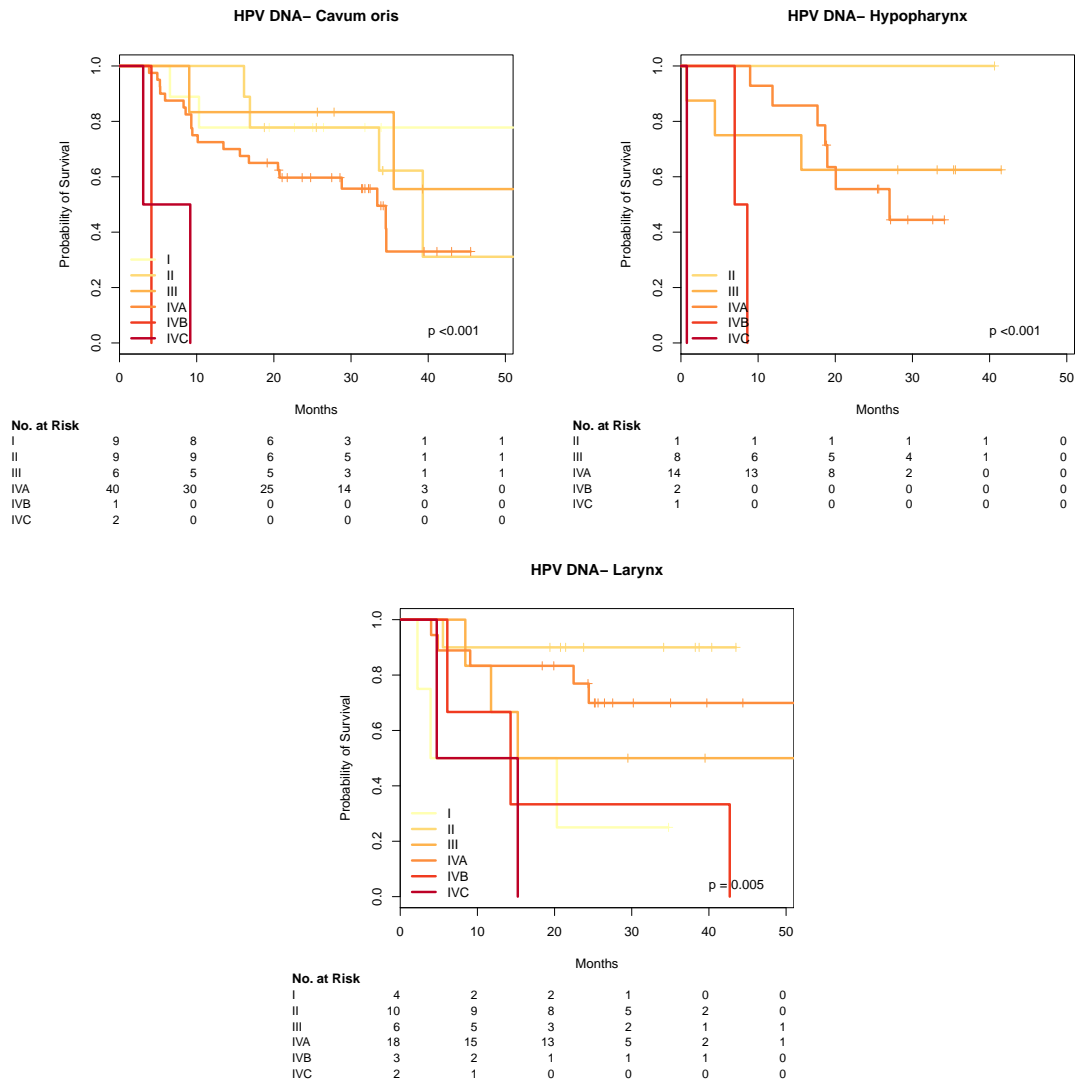
```

```
##
##          split[cur.subset]=III
##      time      n.risk      n.event      survival      std.err
##      36.000      9.000      11.000      0.569      0.103
## lower 95% CI upper 95% CI
##      0.400      0.810
##
##          split[cur.subset]=IVA
##      time      n.risk      n.event      survival      std.err
##      36.000      17.000      55.000      0.439      0.060
## lower 95% CI upper 95% CI
##      0.336      0.574
##
##          split[cur.subset]=IVB
##      time      n.risk      n.event      survival      std.err
##      36.000      1.000      7.000      0.364      0.145
## lower 95% CI upper 95% CI
##      0.166      0.795
##
##          split[cur.subset]=IVC
##      time      n.risk      n.event      survival      std.err
##      36.000      1.000      7.000      0.125      0.117
## lower 95% CI upper 95% CI
##      0.020      0.782
```









3.17 UICC stages, 1,2,3,4a vs. 4b,4c

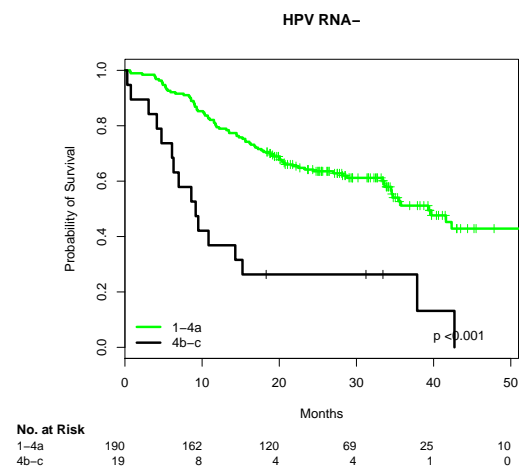
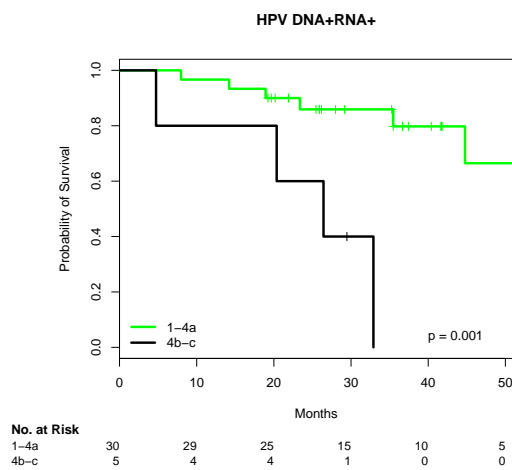
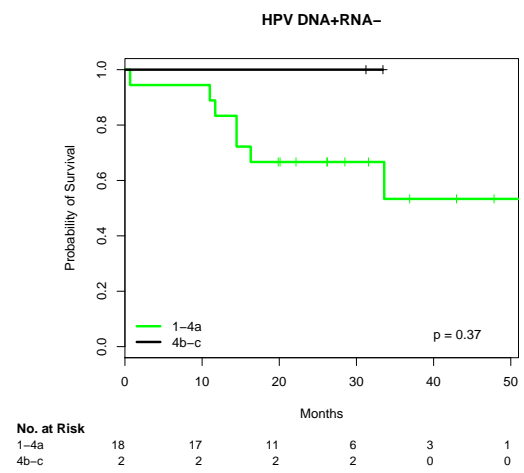
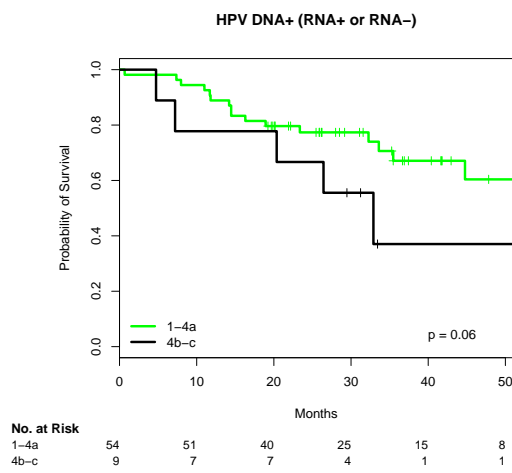
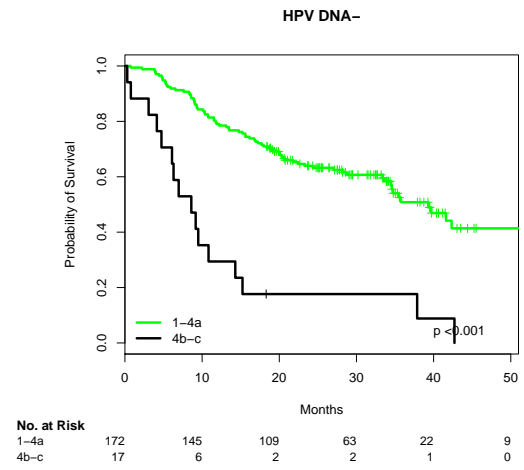
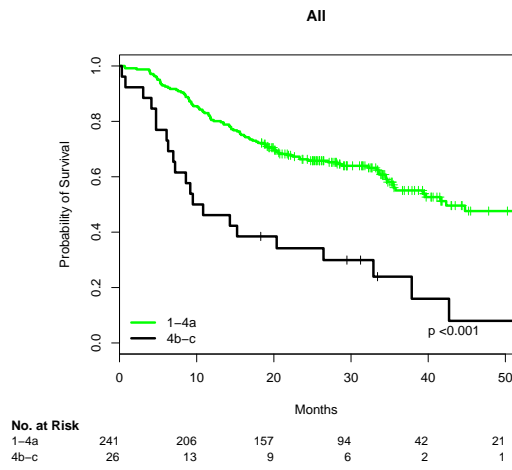
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.125      3.081    0.237 4.76    2e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```

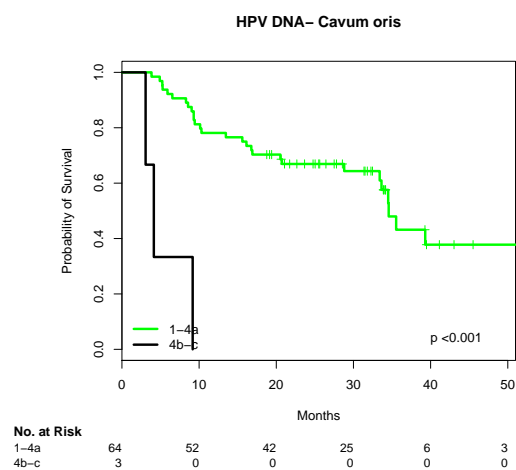
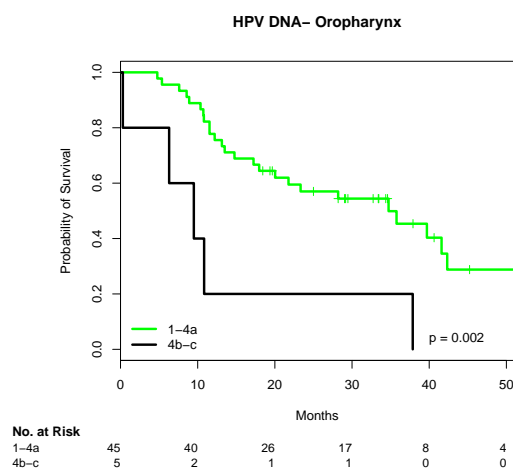
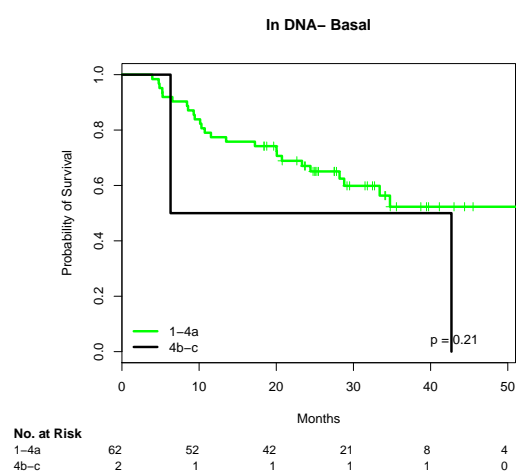
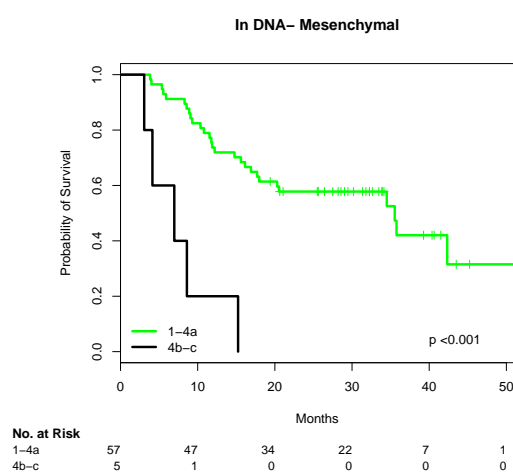
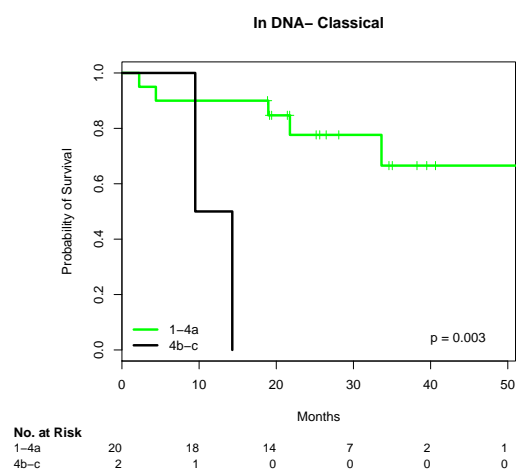
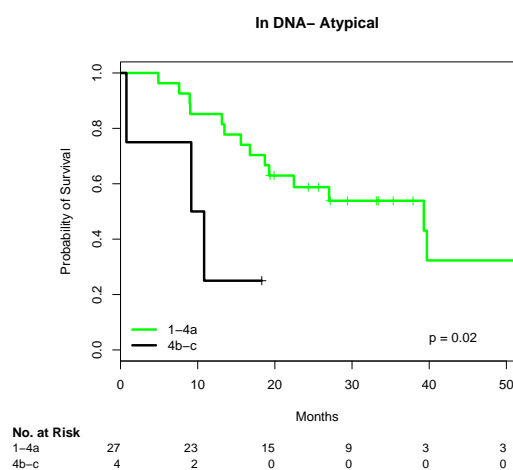
```

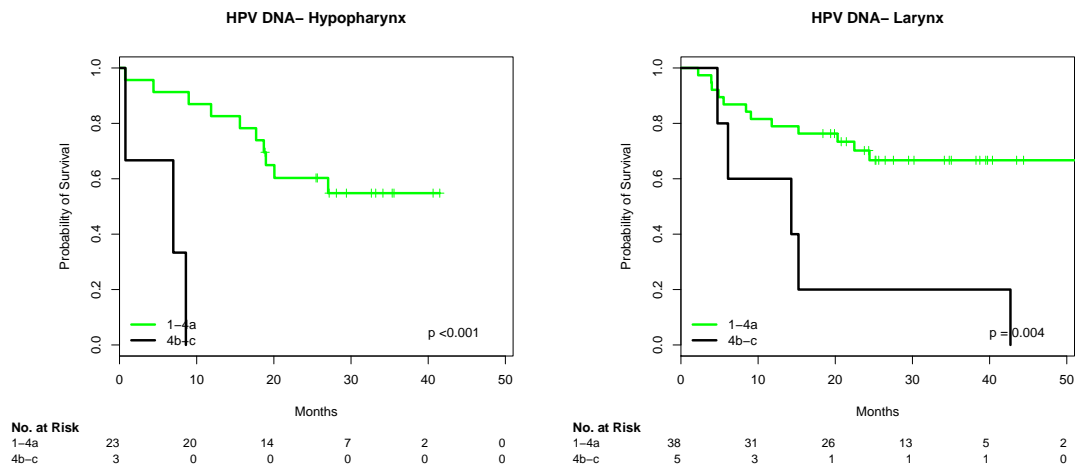
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4b-c      3.08      0.325      1.94      4.9
##
## Concordance= 0.56 (se = 0.012 )
## Rsquare= 0.064 (max possible= 0.991 )
## Likelihood ratio test= 17.7 on 1 df, p=2.58e-05
## Wald test = 22.6 on 1 df, p=1.98e-06
## Score (logrank) test = 25.1 on 1 df, p=5.59e-07
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1-4a
##           time      n.risk      n.event      survival      std.err
##      36.0000      54.0000      94.0000      0.5506      0.0381
## lower 95% CI upper 95% CI
##      0.4808      0.6304
##
##               split[cur.subset]=4b-c
##           time      n.risk      n.event      survival      std.err
##      36.0000      3.0000      19.0000      0.2393      0.0906
## lower 95% CI upper 95% CI
##      0.1140      0.5025
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.502      4.491      0.279 5.38 7.5e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4b-c      4.49      0.223      2.6      7.76
##
## Concordance= 0.574 (se = 0.012 )
## Rsquare= 0.105 (max possible= 0.991 )
## Likelihood ratio test= 21 on 1 df, p=4.55e-06
## Wald test = 28.9 on 1 df, p=7.53e-08
## Score (logrank) test = 34.7 on 1 df, p=3.9e-09
##
##

```

```
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 101
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.270      3.561    0.275 4.62  3.9e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4b-c      3.56      0.281      2.08      6.1
##
## Concordance= 0.564 (se = 0.013 )
## Rsquare= 0.074 (max possible= 0.99 )
## Likelihood ratio test= 16.1 on 1 df,  p=6.18e-05
## Wald test               = 21.3 on 1 df,  p=3.88e-06
## Score (logrank) test = 24.3 on 1 df,  p=8.18e-07
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##              split[cur.subset]=1-4a
##      time      n.risk      n.event      survival      std.err
##      36.0000      35.0000      79.0000      0.5116      0.0449
## lower 95% CI upper 95% CI
##      0.4308      0.6076
##
##              split[cur.subset]=4b-c
##      time      n.risk      n.event      survival      std.err
##      36.000      2.000      14.000      0.263      0.101
## lower 95% CI upper 95% CI
##      0.124      0.558
```







3.18 UICC stages, 1,2,3 vs. 4a vs. 4b,4c

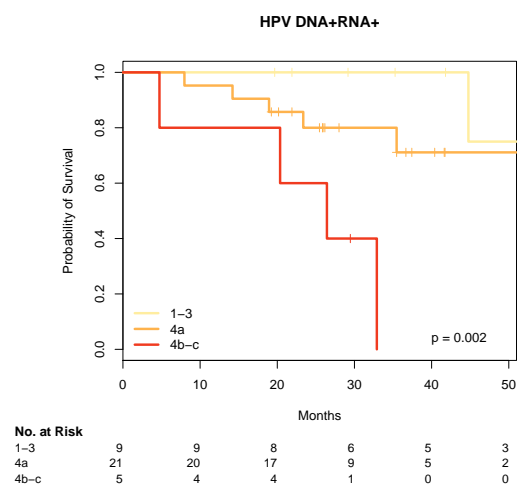
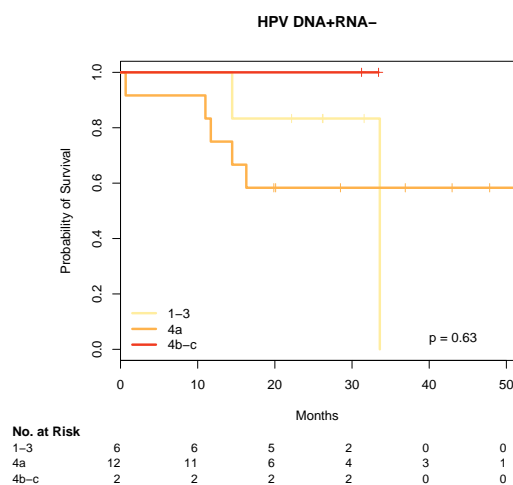
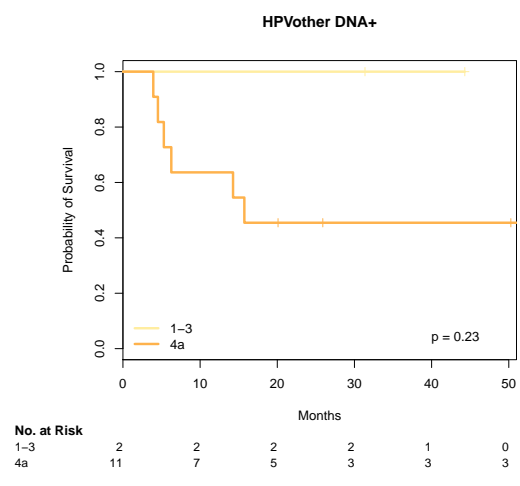
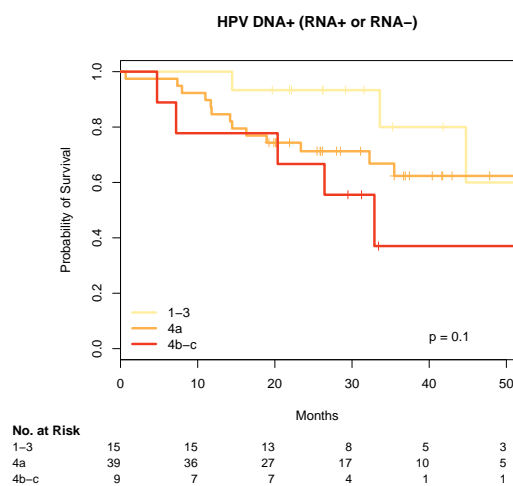
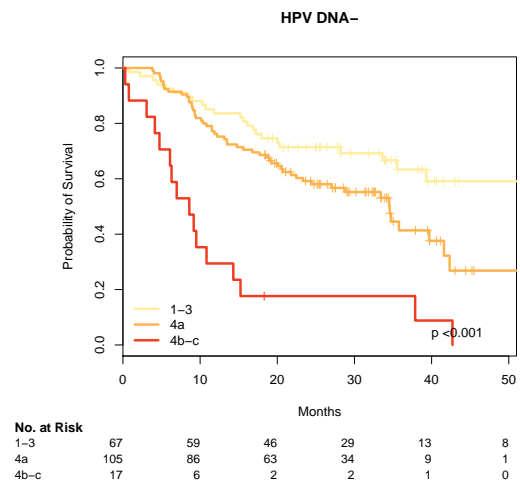
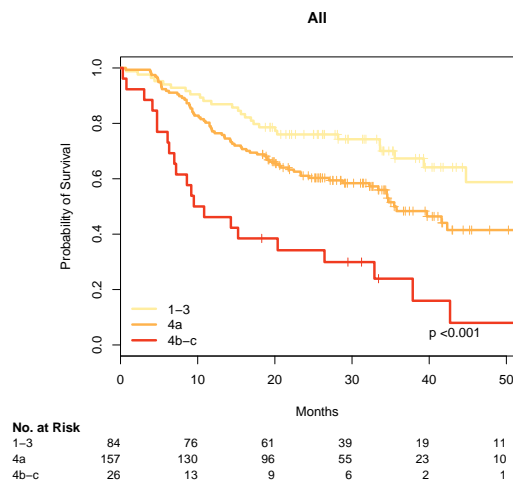
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  0.539    1.714   0.222  2.42   0.015 *
## split[cur.subset]4b-c 1.488    4.429   0.287  5.19  2.1e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      1.71    0.584      1.11      2.65
## split[cur.subset]4b-c      4.43    0.226      2.52      7.77
##
## Concordance= 0.605 (se = 0.024 )
## Rsquare= 0.086 (max possible= 0.991 )
## Likelihood ratio test= 24 on 2 df,  p=6.11e-06
## Wald test               = 27.3 on 2 df,  p=1.18e-06
## Score (logrank) test = 30.4 on 2 df,  p=2.55e-07
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1-3
```

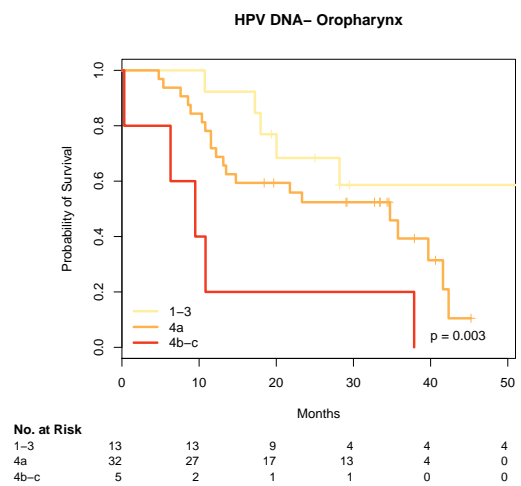
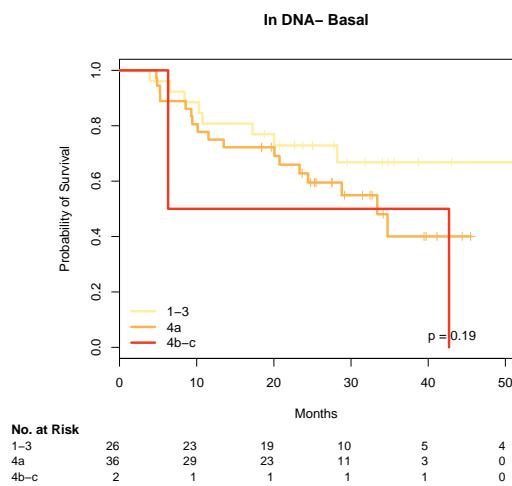
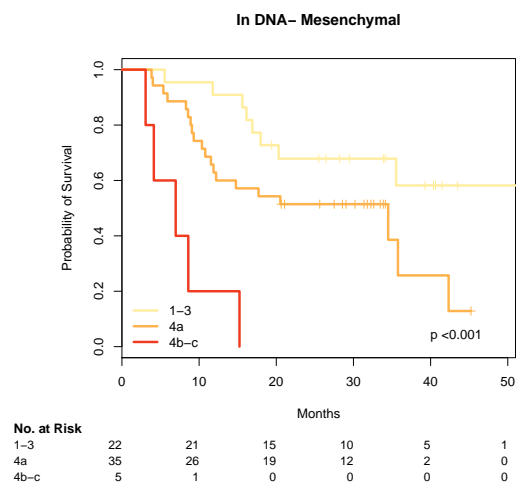
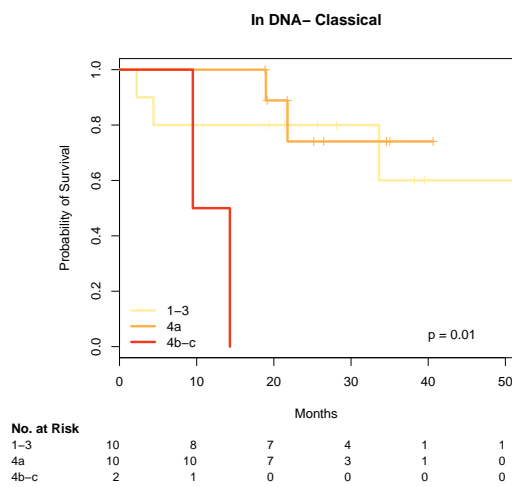
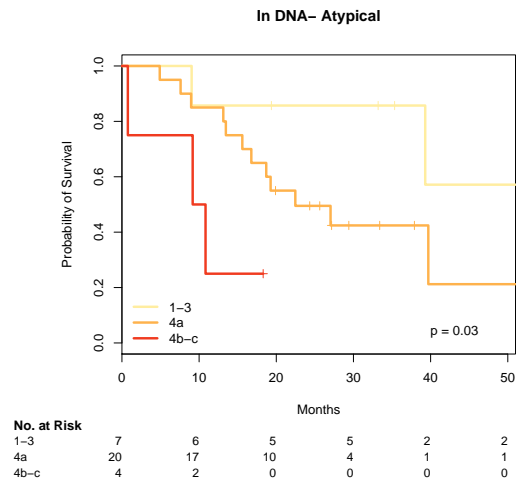
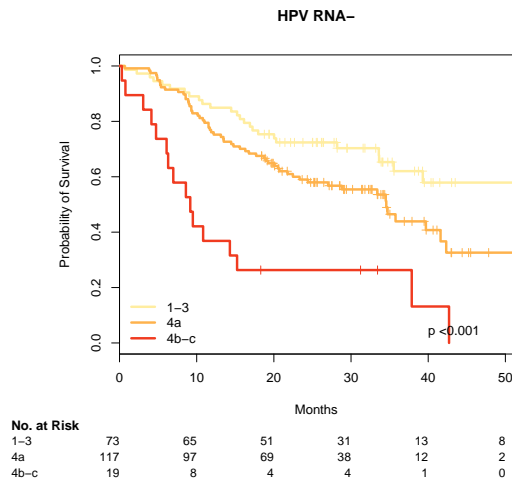
```

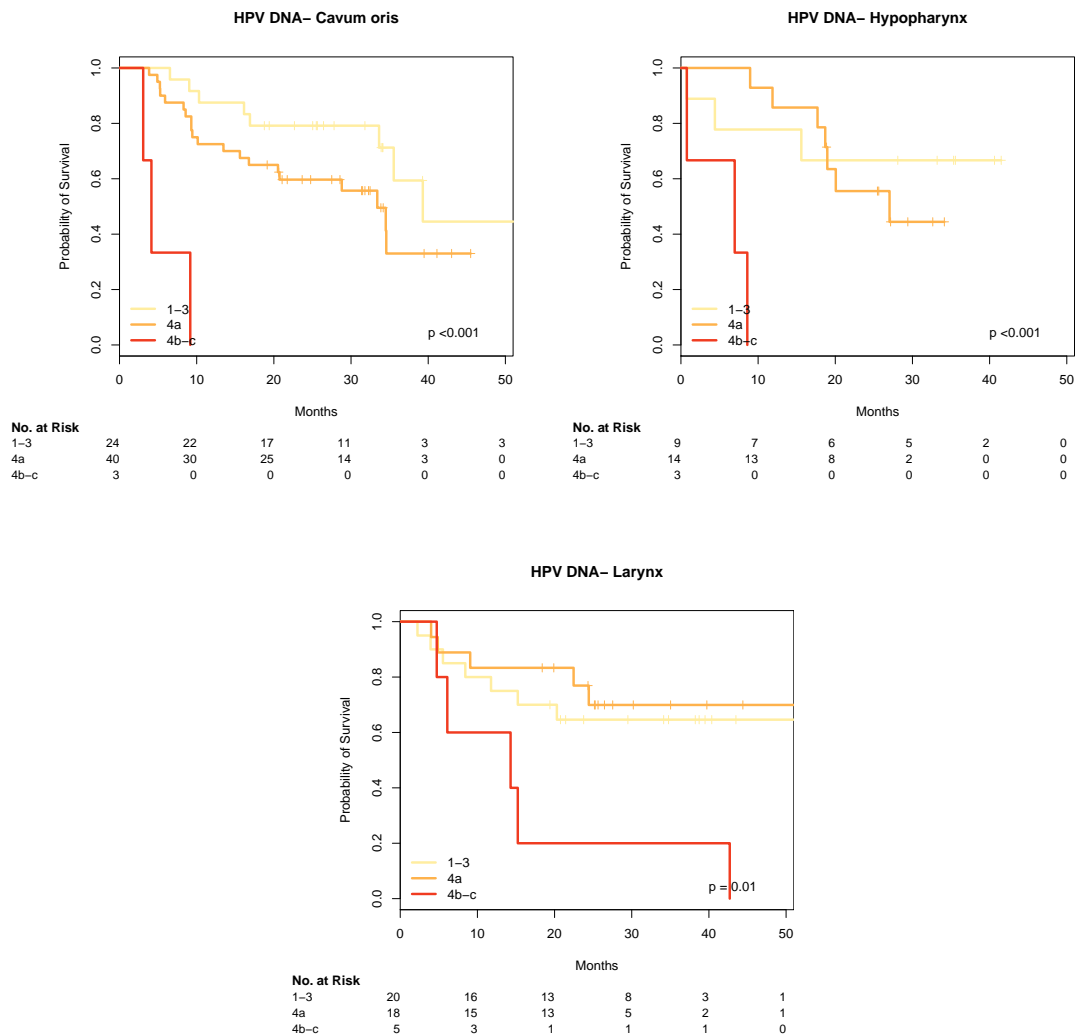
##           time           n.risk           n.event           survival           std.err
##      36.0000           24.0000           24.0000           0.6733           0.0587
## lower 95% CI upper 95% CI
##      0.5675           0.7988
##
##           split[cur.subset]=4a
##           time           n.risk           n.event           survival           std.err
##      36.0000           30.0000           70.0000           0.4833           0.0486
## lower 95% CI upper 95% CI
##      0.3969           0.5885
##
##           split[cur.subset]=4b-c
##           time           n.risk           n.event           survival           std.err
##      36.0000           3.0000           19.0000           0.2393           0.0906
## lower 95% CI upper 95% CI
##      0.1140           0.5025
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 94
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  0.547      1.728   0.249 2.19   0.028 *
## split[cur.subset]4b-c 1.849      6.356   0.329 5.63  1.8e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      1.73      0.579      1.06      2.82
## split[cur.subset]4b-c      6.36      0.157      3.34     12.10
##
## Concordance= 0.612 (se = 0.028 )
## Rsquare= 0.129 (max possible= 0.991 )
## Likelihood ratio test= 26.1 on 2 df,  p=2.14e-06
## Wald test              = 32.5 on 2 df,  p=8.78e-08
## Score (logrank) test = 39 on 2 df,  p=3.47e-09
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##

```

```
## n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  0.486      1.626    0.236 2.06    0.039 *
## split[cur.subset]4b-c 1.582      4.865    0.320 4.94   7.7e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      1.63      0.615      1.02      2.58
## split[cur.subset]4b-c      4.87      0.206      2.60      9.11
##
## Concordance= 0.604 (se = 0.027 )
## Rsquare= 0.094 (max possible= 0.99 )
## Likelihood ratio test= 20.5 on 2 df, p=3.49e-05
## Wald test = 24.7 on 2 df, p=4.27e-06
## Score (logrank) test = 28.2 on 2 df, p=7.64e-07
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1-3
##           time      n.risk      n.event      survival      std.err
##           36.0000      18.0000      24.0000      0.6203      0.0665
## lower 95% CI upper 95% CI
##           0.5027      0.7654
##
##               split[cur.subset]=4a
##           time      n.risk      n.event      survival      std.err
##           36.000      17.000      55.000      0.439      0.060
## lower 95% CI upper 95% CI
##           0.336      0.574
##
##               split[cur.subset]=4b-c
##           time      n.risk      n.event      survival      std.err
##           36.000      2.000      14.000      0.263      0.101
## lower 95% CI upper 95% CI
##           0.124      0.558
```







3.19 Smoking: yes vs. no

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 267, number of events= 126
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein -0.218    0.804    0.250 -0.87    0.38
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein    0.804      1.24    0.493    1.31
##
## Concordance= 0.511 (se = 0.018 )
## Rsquare= 0.003 (max possible= 0.991 )
## Likelihood ratio test= 0.8 on 1 df, p=0.371
```

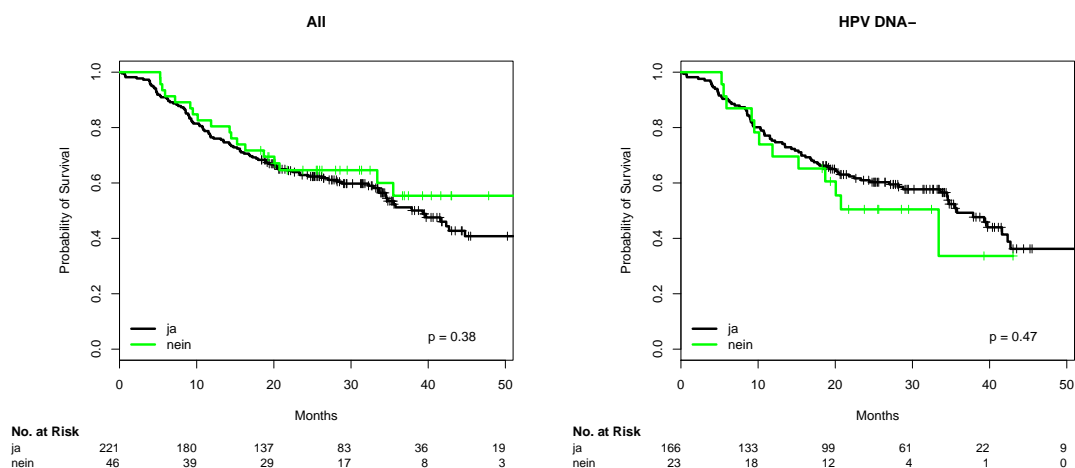
```

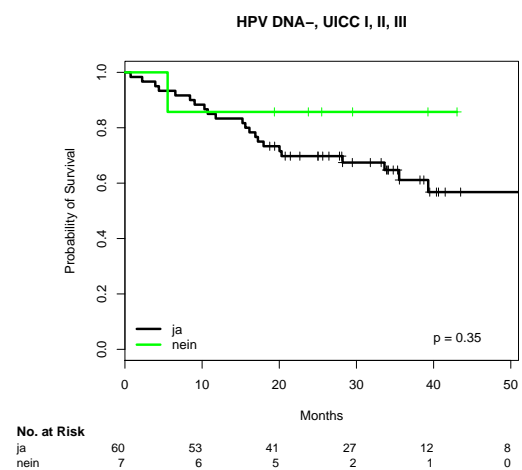
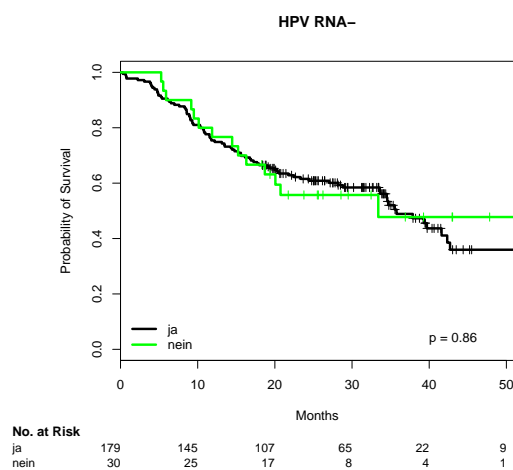
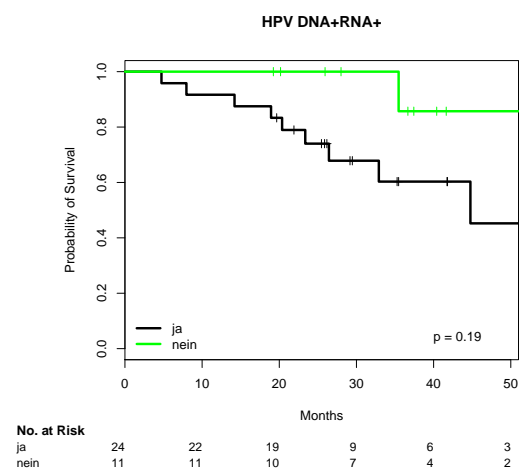
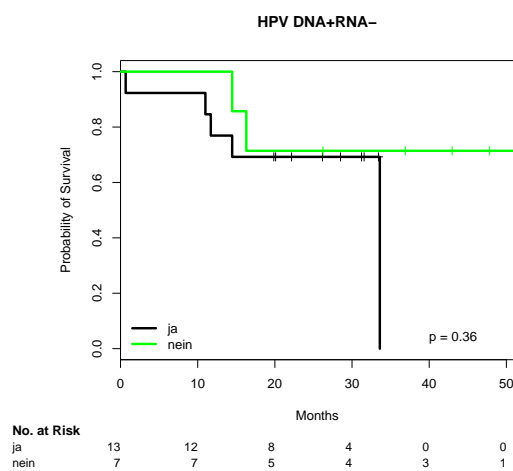
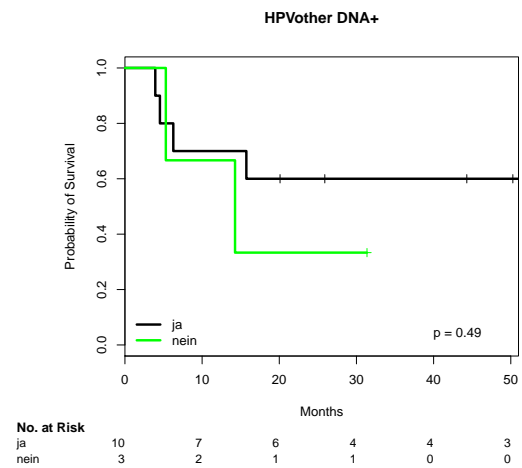
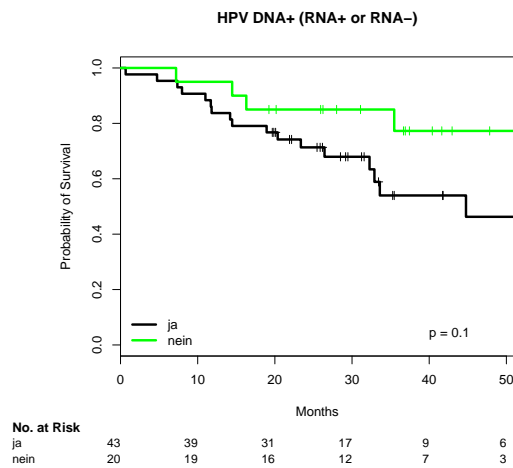
## Wald test          = 0.76  on 1 df,    p=0.383
## Score (logrank) test = 0.76  on 1 df,    p=0.382
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=ja
##      time      n.risk      n.event      survival      std.err
## 36.0000      45.0000      95.0000      0.5119      0.0396
## lower 95% CI upper 95% CI
## 0.4399      0.5957
##
##               split[cur.subset]=nein
##      time      n.risk      n.event      survival      std.err
## 36.000      12.000      18.000      0.554      0.086
## lower 95% CI upper 95% CI
## 0.408      0.751
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein 0.223      1.250      0.311 0.72      0.47
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein      1.25      0.8      0.68      2.3
##
## Concordance= 0.51 (se = 0.018 )
## Rsquare= 0.003 (max possible= 0.991 )
## Likelihood ratio test= 0.49  on 1 df,    p=0.484
## Wald test          = 0.52  on 1 df,    p=0.473
## Score (logrank) test = 0.52  on 1 df,    p=0.472
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)

```

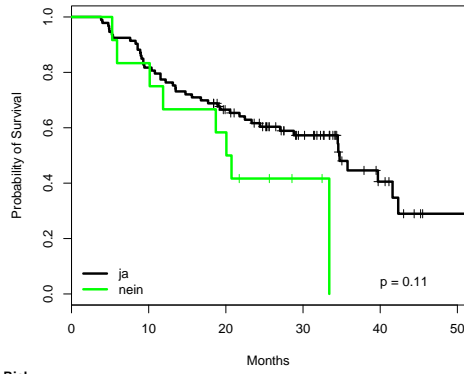


```
## split[cur.subset]nein -0.0493    0.9519    0.2883 -0.17    0.86
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein    0.952      1.05    0.541    1.67
##
## Concordance= 0.499  (se = 0.019 )
## Rsquare= 0      (max possible= 0.99 )
## Likelihood ratio test= 0.03  on 1 df,   p=0.863
## Wald test          = 0.03  on 1 df,   p=0.864
## Score (logrank) test = 0.03  on 1 df,   p=0.864
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##                      split[cur.subset]=ja
##      time      n.risk      n.event      survival      std.err
## 36.0000    31.0000    79.0000    0.4889    0.0461
## lower 95% CI upper 95% CI
## 0.4064    0.5882
##
##                      split[cur.subset]=nein
##      time      n.risk      n.event      survival      std.err
## 36.000    6.000    14.000    0.478    0.108
## lower 95% CI upper 95% CI
## 0.307    0.744
```





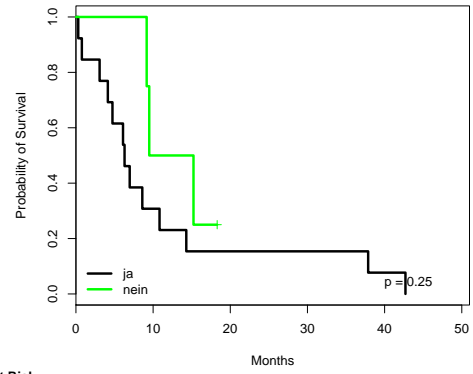
HPV DNA-, UICC IVA



No. at Risk
ja
nein

93 76 56 32 9 1
12 10 7 2 0 0

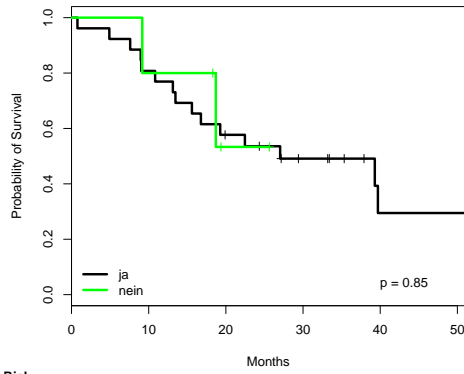
HPV DNA-, UICC IVB-C



No. at Risk
ja
nein

13 4 2 2 1 0
4 2 0 0 0 0

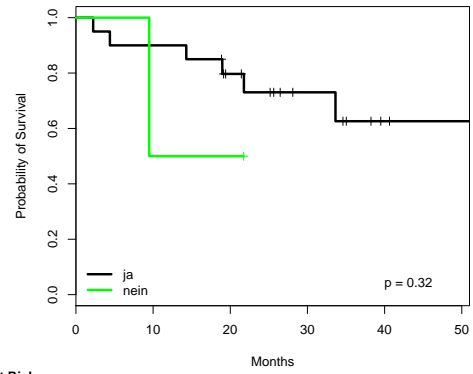
In DNA- Atypical



No. at Risk
ja
nein

26 21 14 9 3 3
5 4 1 0 0 0

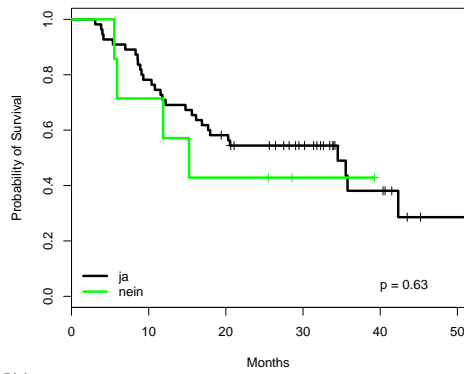
In DNA- Classical



No. at Risk
ja
nein

20 18 13 7 2 1
2 1 1 0 0 0

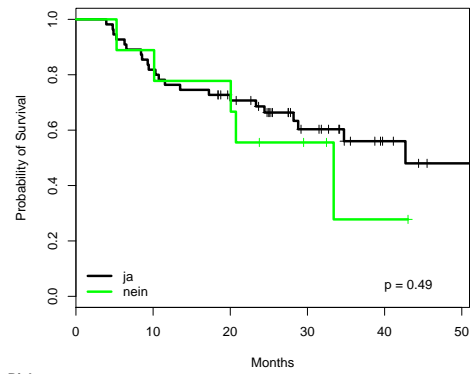
In DNA- Mesenchymal



No. at Risk
ja
nein

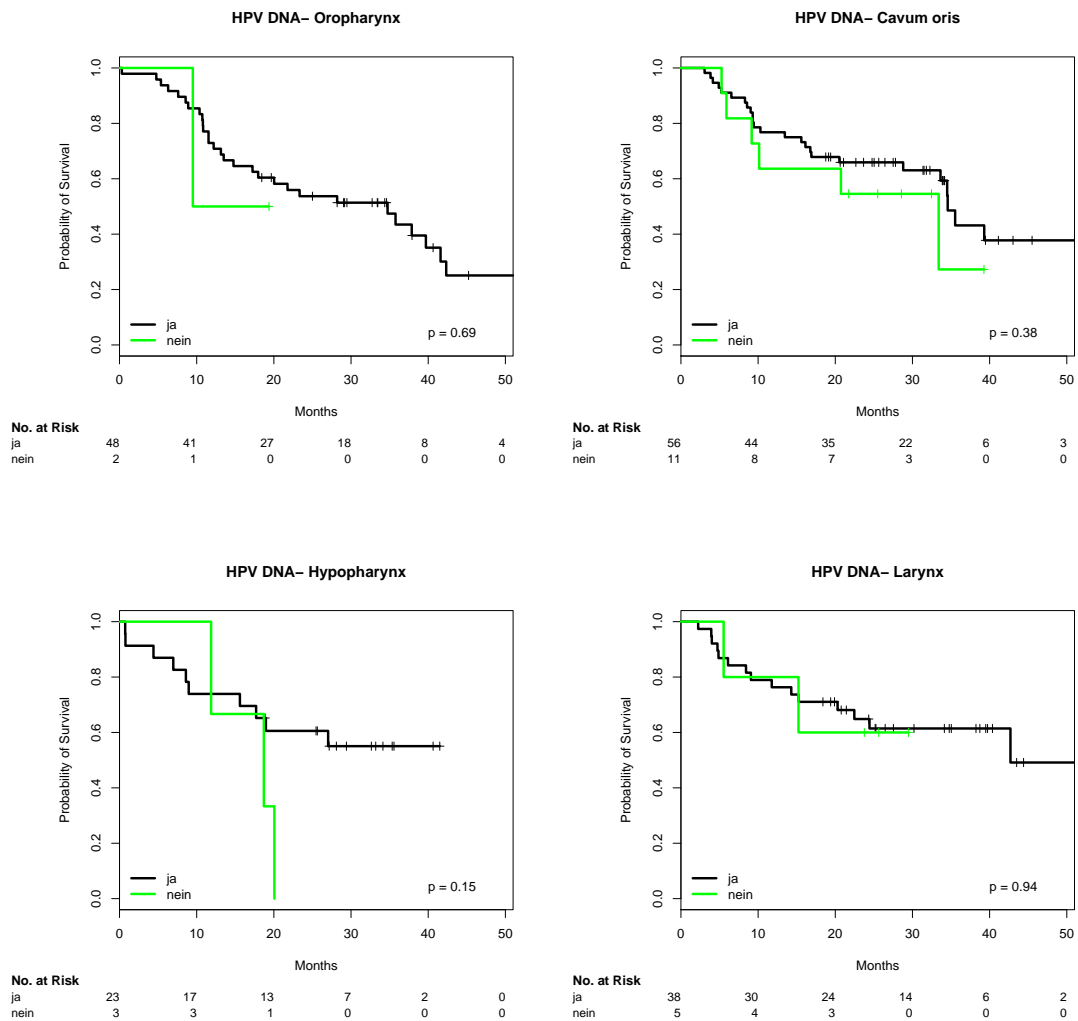
55 43 31 21 7 1
7 5 3 1 0 0

In DNA- Basal



No. at Risk
ja
nein

55 45 36 19 8 4
9 8 7 3 1 0



3.20 Smoking. Pack-years. Quartiles

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 265, number of events= 125
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](10,30) -0.354    0.702   0.277 -1.28   0.201
## split[cur.subset](30,44)  0.527    1.694   0.245  2.15   0.032 *
## split[cur.subset](44,125) 0.132    1.141   0.258  0.51   0.609
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```

## split[cur.subset](10,30]      0.702      1.425      0.408      1.21
## split[cur.subset](30,44]      1.694      0.590      1.047      2.74
## split[cur.subset](44,125]     1.141      0.877      0.688      1.89
##
## Concordance= 0.578 (se = 0.027 )
## Rsquare= 0.045 (max possible= 0.991 )
## Likelihood ratio test= 12.2 on 3 df, p=0.00685
## Wald test = 12.1 on 3 df, p=0.00703
## Score (logrank) test = 12.6 on 3 df, p=0.00561
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##
##           split[cur.subset]=[0,10]
##           time      n.risk      n.event      survival      std.err
##           36.0000      15.0000      28.0000      0.5189      0.0722
## lower 95% CI upper 95% CI
##           0.3950      0.6816
##
##           split[cur.subset]=(10,30]
##           time      n.risk      n.event      survival      std.err
##           36.0000      17.0000      22.0000      0.6174      0.0699
## lower 95% CI upper 95% CI
##           0.4945      0.7709
##
##           split[cur.subset]=(30,44]
##           time      n.risk      n.event      survival      std.err
##           36.0000      11.0000      34.0000      0.4300      0.0708
## lower 95% CI upper 95% CI
##           0.3115      0.5937
##
##           split[cur.subset]=(44,125]
##           time      n.risk      n.event      survival      std.err
##           36.000      14.000      28.000      0.504      0.074
## lower 95% CI upper 95% CI
##           0.378      0.672
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 188, number of events= 93
## (3 observations deleted due to missingness)
##
##
##           coef exp(coef) se(coef)      z Pr(>|z|)

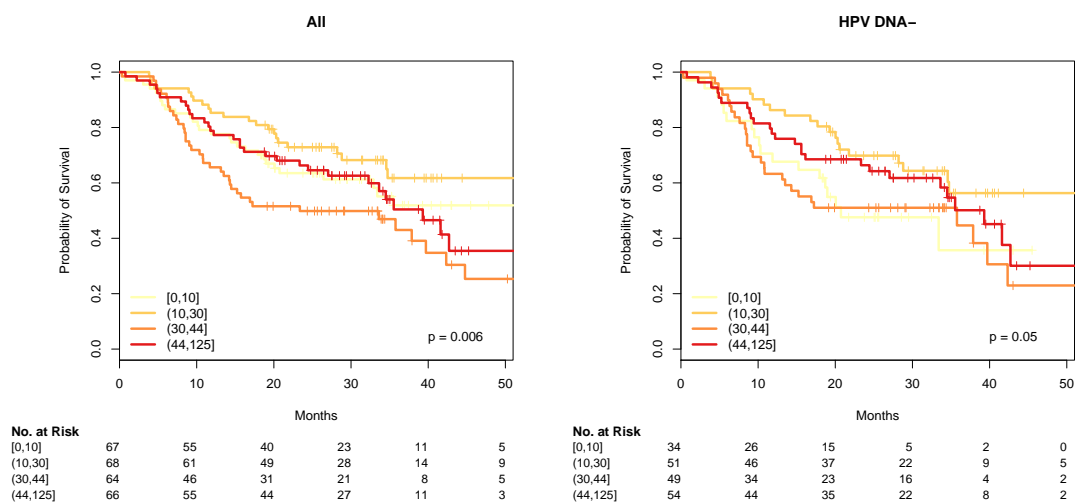
```

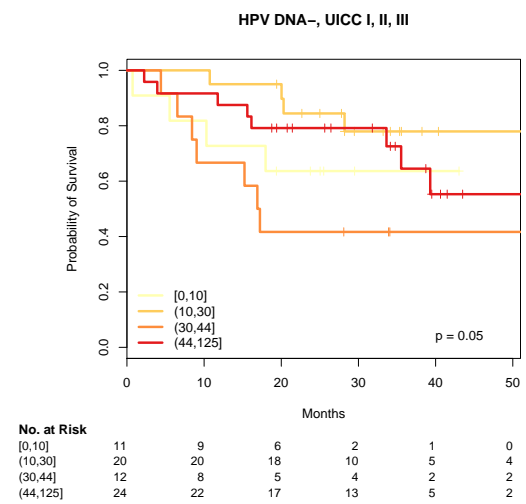
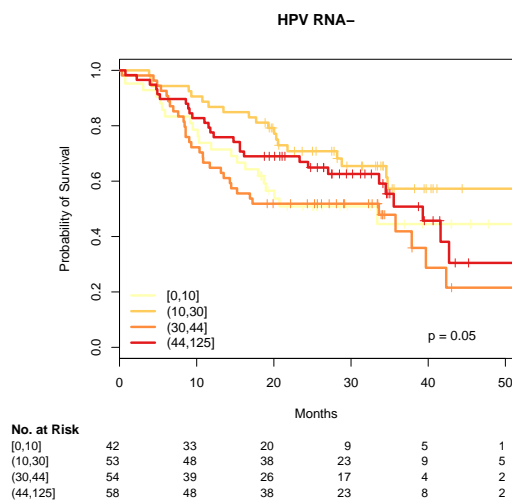
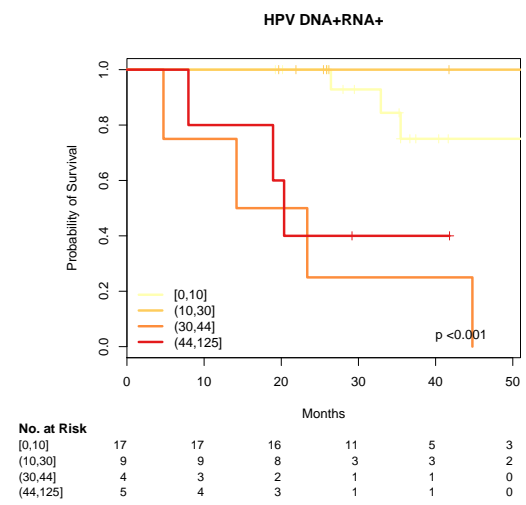
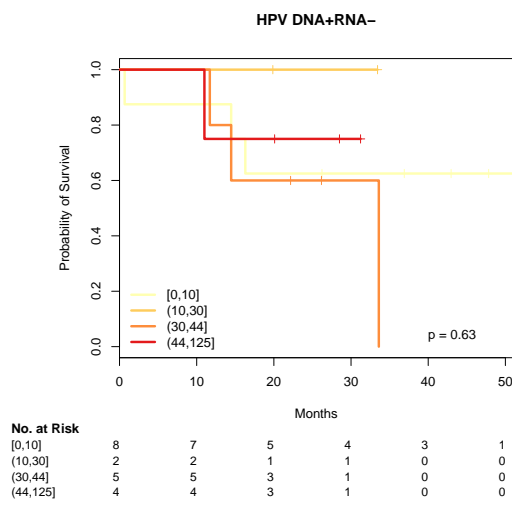
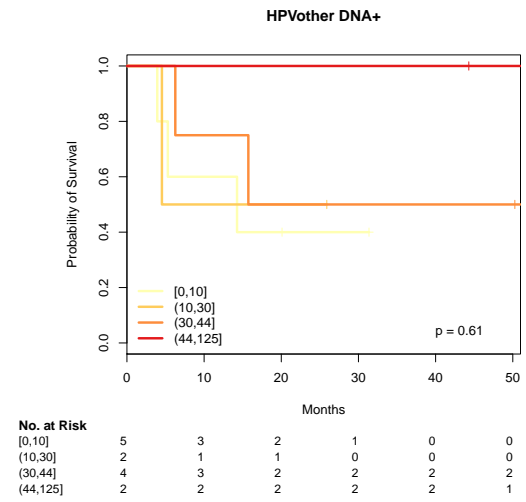
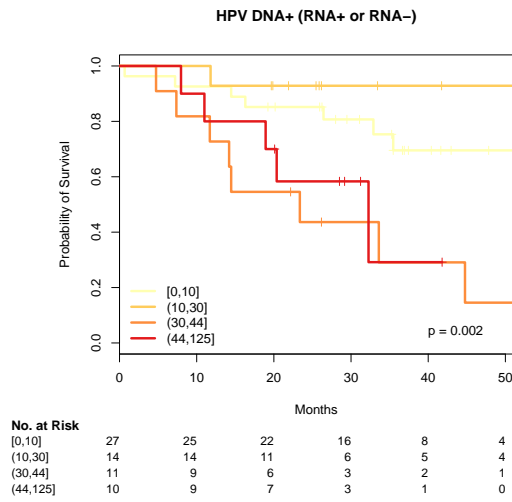
```

## split[cur.subset](10,30] -0.7165    0.4885    0.3319 -2.16    0.031 *
## split[cur.subset](30,44]    0.0364    1.0371    0.3015  0.12    0.904
## split[cur.subset](44,125] -0.3050    0.7371    0.3062 -1.00    0.319
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](10,30]    0.488    2.047    0.255    0.936
## split[cur.subset](30,44]    1.037    0.964    0.574    1.873
## split[cur.subset](44,125]    0.737    1.357    0.405    1.343
##
## Concordance= 0.585 (se = 0.031 )
## Rsquare= 0.042 (max possible= 0.99 )
## Likelihood ratio test= 8.02 on 3 df,  p=0.0456
## Wald test            = 7.57 on 3 df,  p=0.0559
## Score (logrank) test = 7.82 on 3 df,  p=0.0498
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 100
## (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](10,30] -0.571    0.565    0.317 -1.80    0.072 .
## split[cur.subset](30,44]  0.215    1.240    0.281  0.76    0.445
## split[cur.subset](44,125] -0.156    0.856    0.289 -0.54    0.590
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](10,30]    0.565    1.771    0.303    1.05
## split[cur.subset](30,44]    1.240    0.807    0.714    2.15
## split[cur.subset](44,125]    0.856    1.169    0.485    1.51
##
## Concordance= 0.584 (se = 0.03 )
## Rsquare= 0.038 (max possible= 0.99 )
## Likelihood ratio test= 8.02 on 3 df,  p=0.0456
## Wald test            = 7.62 on 3 df,  p=0.0545
## Score (logrank) test = 7.88 on 3 df,  p=0.0486
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness

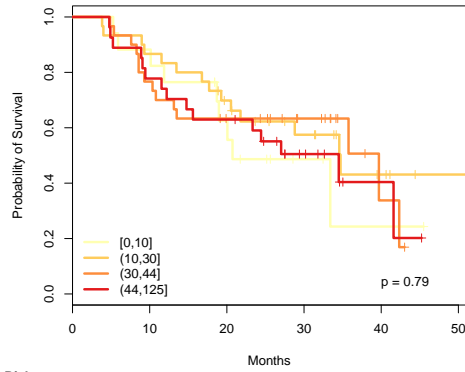
```

```
##                               split[cur.subset]=[0,10]
##           time           n.risk           n.event       survival       std.err
##       36.0000           7.0000           21.0000         0.4451         0.0914
## lower 95% CI upper 95% CI
##       0.2976           0.6658
##
##                               split[cur.subset]=(10,30]
##           time           n.risk           n.event       survival       std.err
##       36.0000          12.0000          19.0000         0.5727         0.0813
## lower 95% CI upper 95% CI
##       0.4337           0.7563
##
##                               split[cur.subset]=(30,44]
##           time           n.risk           n.event       survival       std.err
##       36.0000           7.0000          28.0000         0.4188         0.0853
## lower 95% CI upper 95% CI
##       0.2810           0.6242
##
##                               split[cur.subset]=(44,125]
##           time           n.risk           n.event       survival       std.err
##       36.0000          11.0000          24.0000         0.5080         0.0818
## lower 95% CI upper 95% CI
##       0.3705           0.6965
```

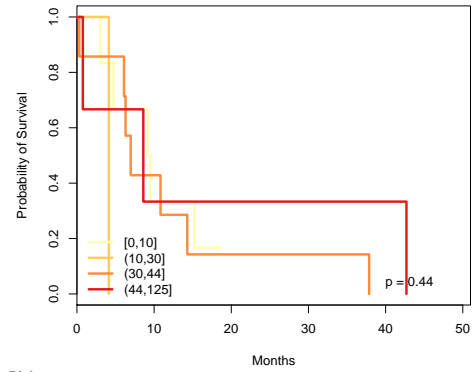




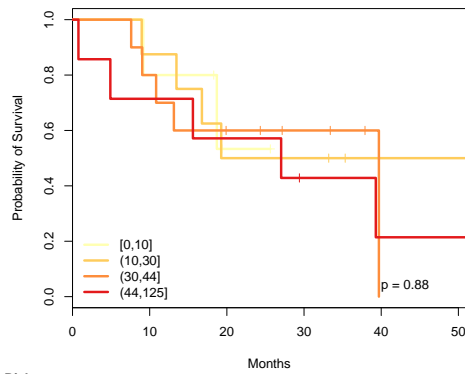
HPV DNA-, UICC IVA



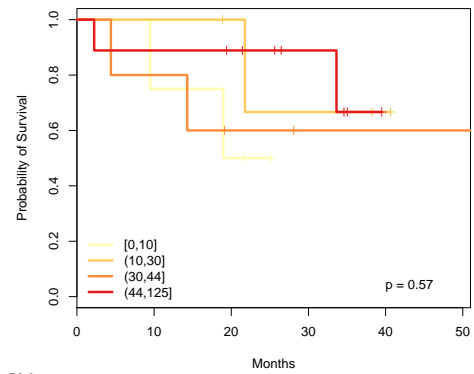
HPV DNA-, UICC IVB-C



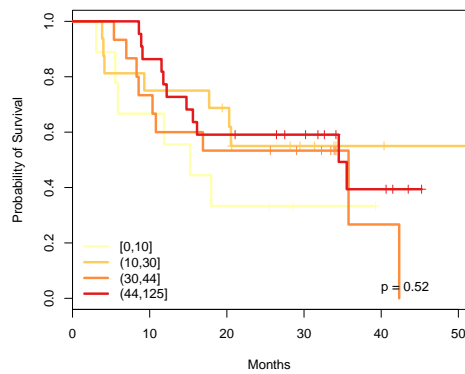
In DNA- Atypical



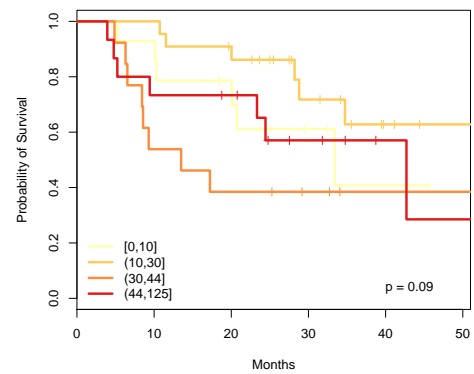
In DNA- Classical

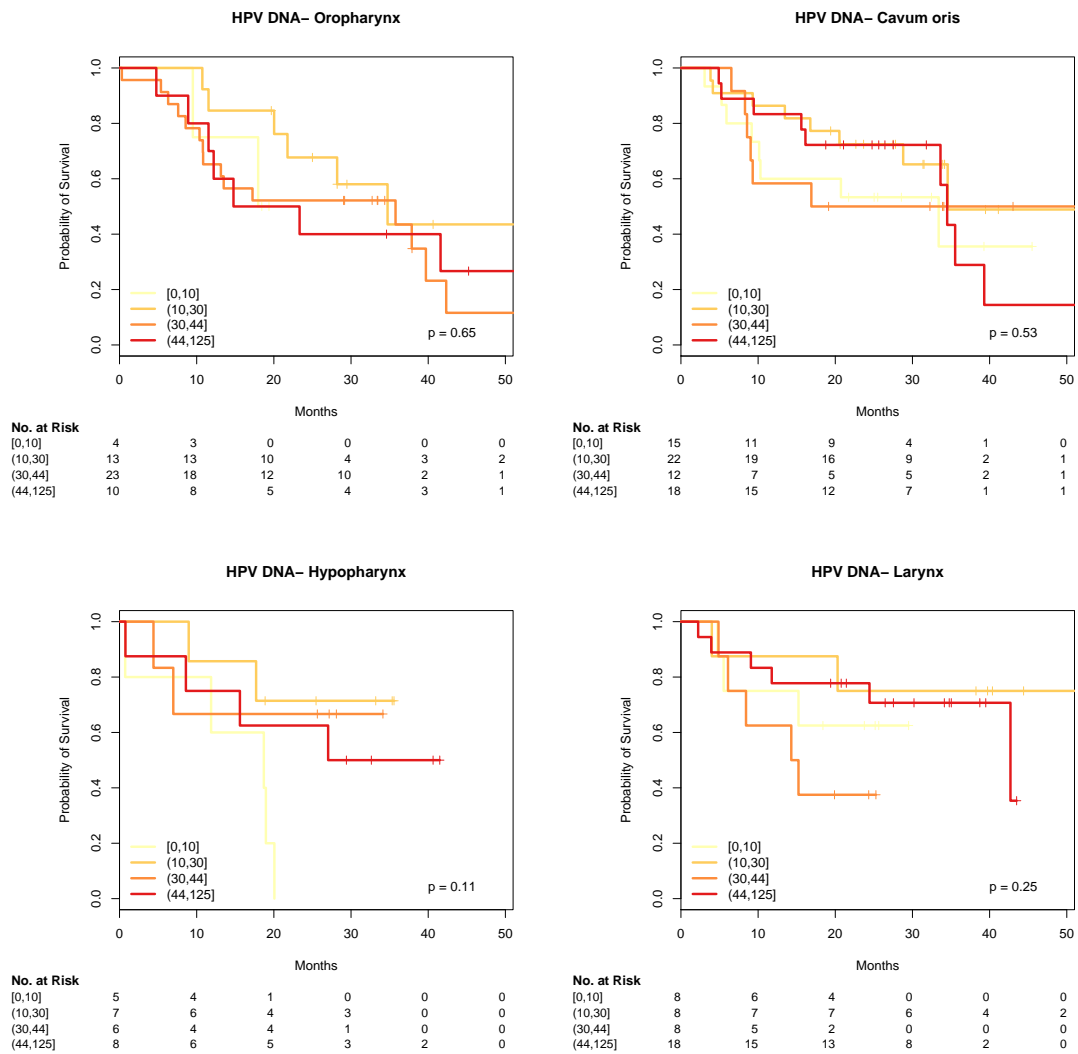


In DNA- Mesenchymal



In DNA- Basal





3.21 Smoking. Pack-years. Cut at 10

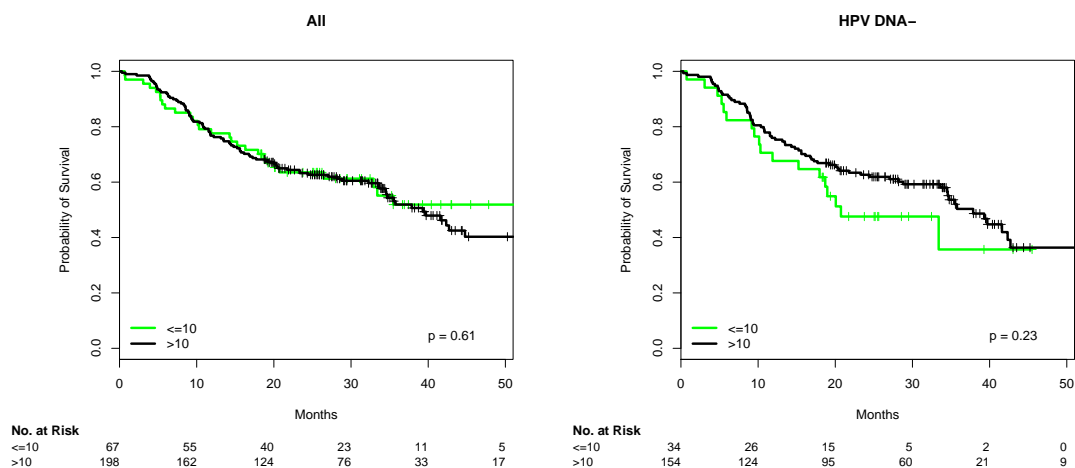
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 265, number of events= 125
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 0.109      1.115    0.212 0.51      0.61
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10      1.11      0.897    0.735    1.69
##
## Concordance= 0.5   (se = 0.021 )
## Rsquare= 0.001    (max possible= 0.991 )
```

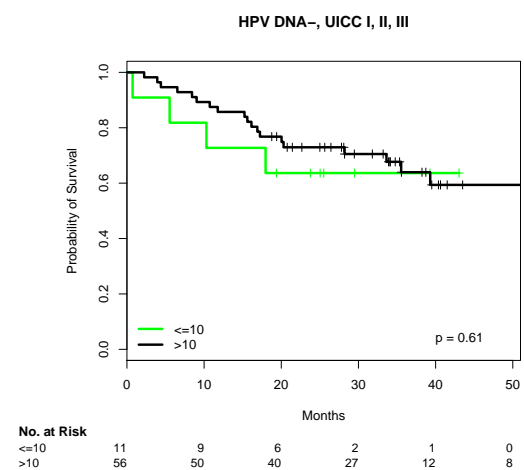
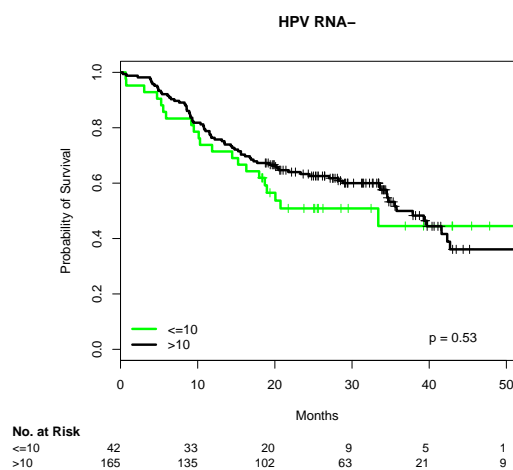
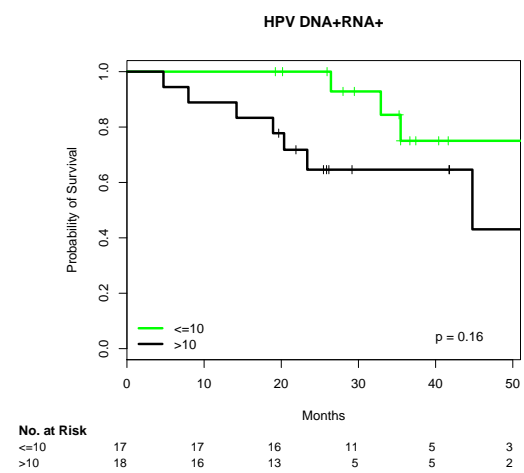
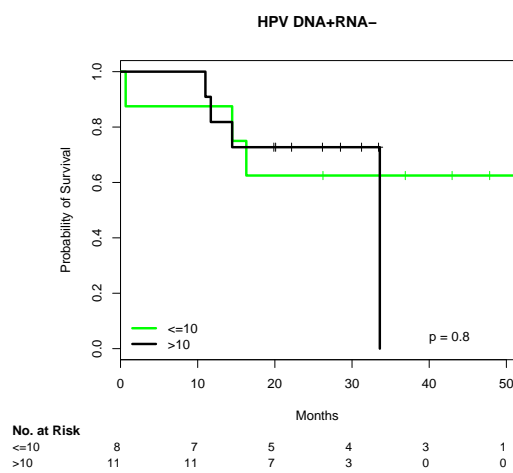
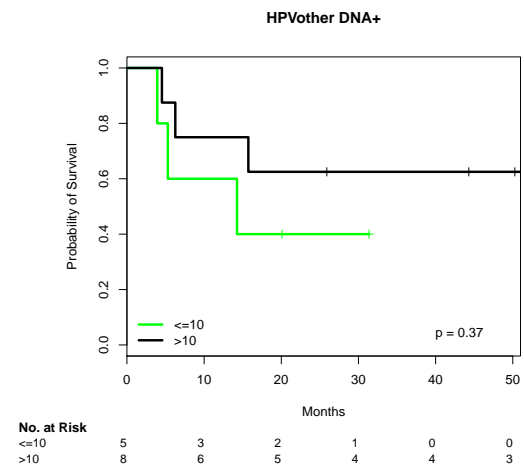
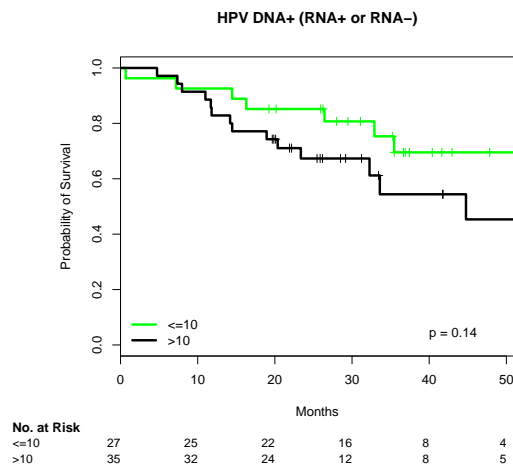
```

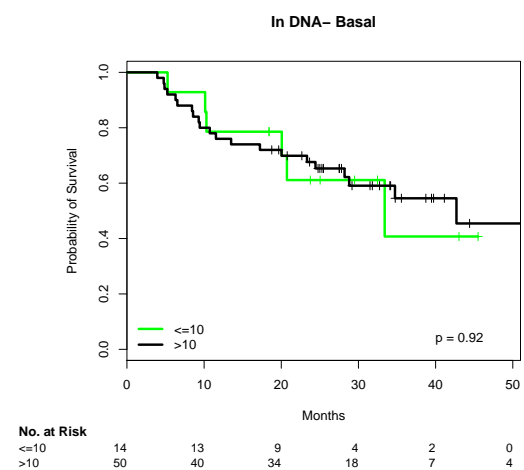
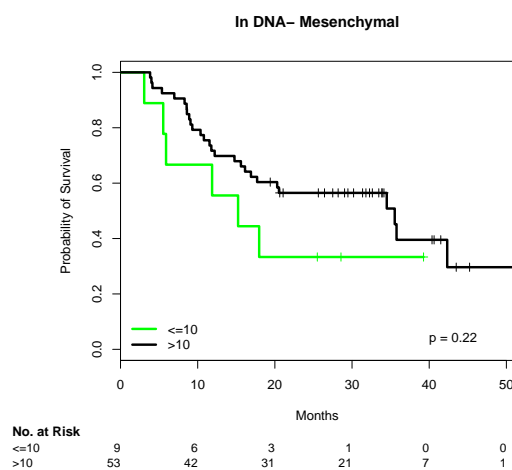
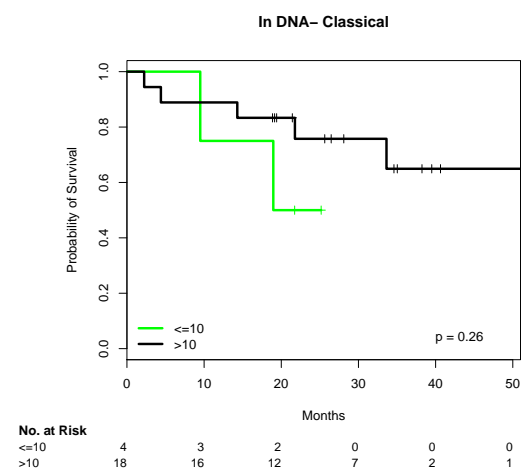
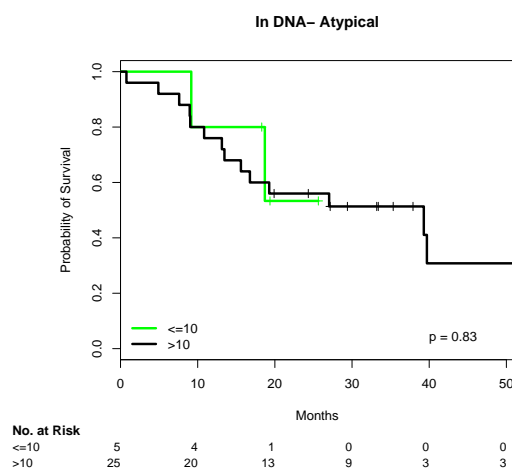
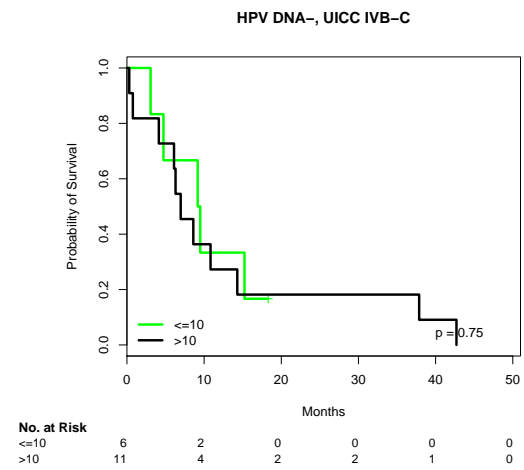
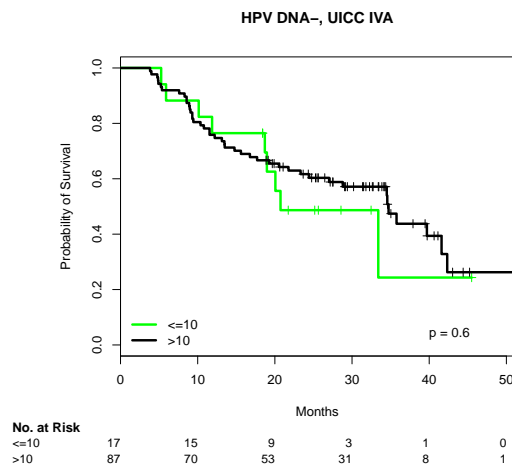
## Likelihood ratio test= 0.27  on 1 df,    p=0.605
## Wald test              = 0.26  on 1 df,    p=0.609
## Score (logrank) test = 0.26  on 1 df,    p=0.609
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##           split[cur.subset]<=10
##           time      n.risk      n.event      survival      std.err
##           36.0000     15.0000     28.0000         0.5189         0.0722
## lower 95% CI upper 95% CI
##           0.3950         0.6816
##
##           split[cur.subset]>=10
##           time      n.risk      n.event      survival      std.err
##           36.0000     42.0000     84.0000         0.5190         0.0418
## lower 95% CI upper 95% CI
##           0.4432         0.6078
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 188, number of events= 93
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.317      0.728    0.265 -1.2    0.23
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.728      1.37    0.433    1.22
##
## Concordance= 0.527 (se = 0.021 )
## Rsquare= 0.007 (max possible= 0.99 )
## Likelihood ratio test= 1.35  on 1 df,    p=0.246
## Wald test              = 1.43  on 1 df,    p=0.231
## Score (logrank) test = 1.45  on 1 df,    p=0.229
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 100

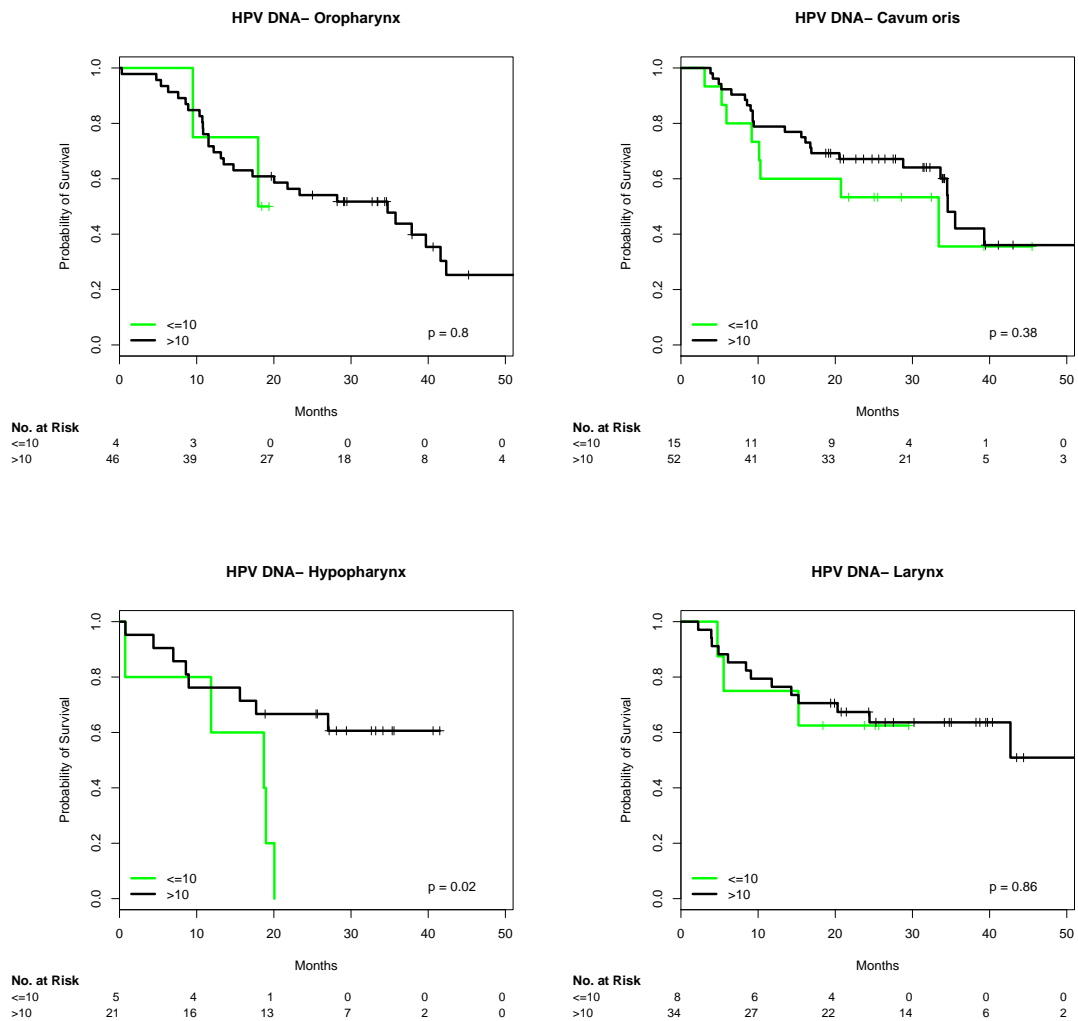
```

```
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.153      0.858    0.246 -0.62    0.53
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.858      1.17    0.53    1.39
##
## Concordance= 0.523  (se = 0.021 )
## Rsquare= 0.002  (max possible= 0.99 )
## Likelihood ratio test= 0.38  on 1 df,   p=0.54
## Wald test               = 0.39  on 1 df,   p=0.534
## Score (logrank) test = 0.39  on 1 df,   p=0.534
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##              split[cur.subset]=<=10
##              time      n.risk      n.event      survival      std.err
##              36.0000      7.0000     21.0000      0.4451      0.0914
## lower 95% CI upper 95% CI
##              0.2976      0.6658
##
##              split[cur.subset]>=10
##              time      n.risk      n.event      survival      std.err
##              36.000      30.000      71.000      0.500      0.048
## lower 95% CI upper 95% CI
##              0.414      0.603
```









3.22 Smoking. Pack-years. Cut at 30

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 265, number of events= 125
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.506      1.658    0.184 2.75  0.0059 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30    1.66      0.603    1.16      2.38
##
```

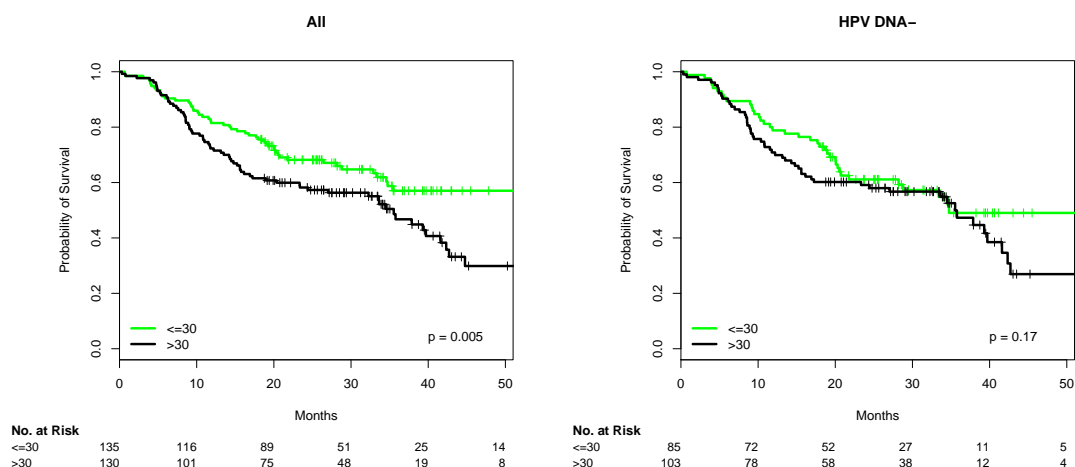
```

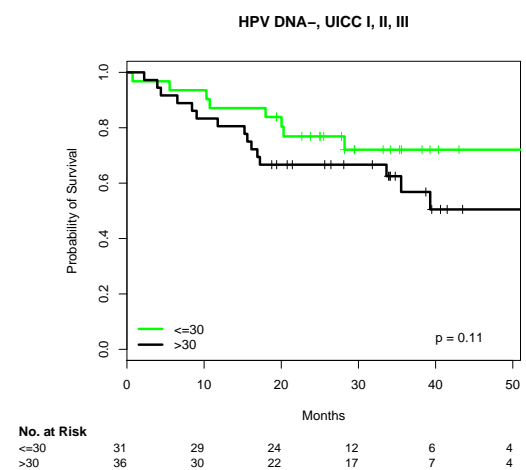
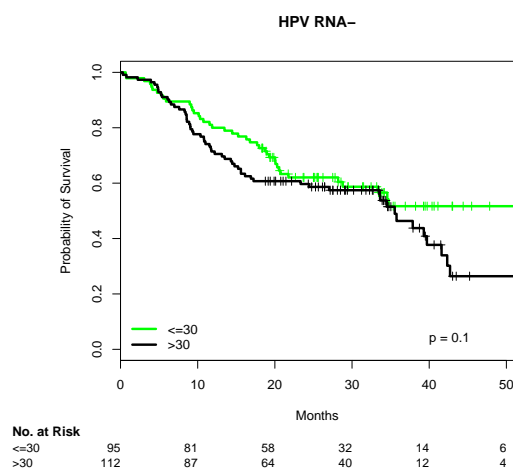
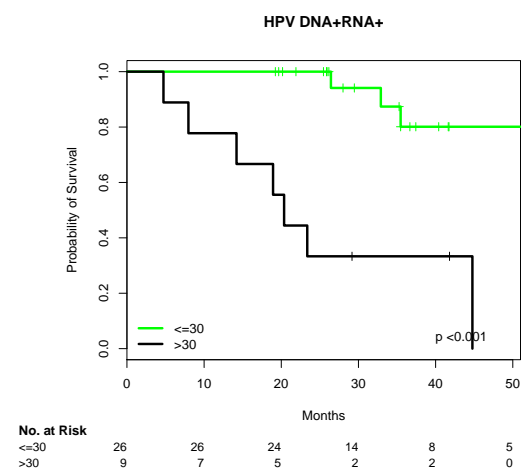
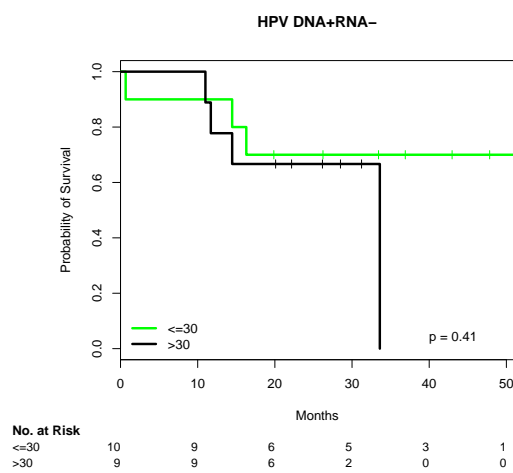
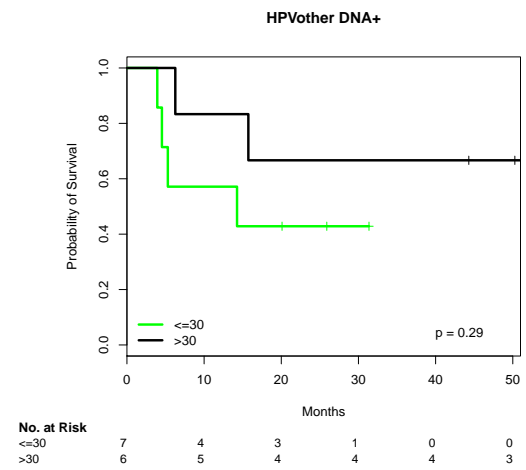
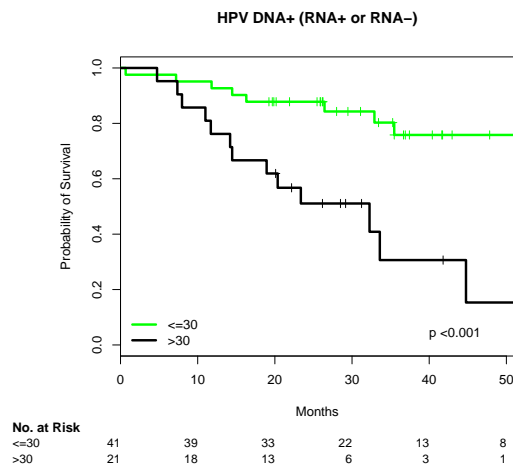
## Concordance= 0.55 (se = 0.024 )
## Rsquare= 0.029 (max possible= 0.991 )
## Likelihood ratio test= 7.73 on 1 df, p=0.00544
## Wald test = 7.59 on 1 df, p=0.00588
## Score (logrank) test = 7.75 on 1 df, p=0.00538
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##
##           split[cur.subset]=<=30
##           time      n.risk      n.event      survival      std.err
##           36.0000      32.0000      50.0000      0.5704      0.0501
## lower 95% CI upper 95% CI
##           0.4802      0.6775
##
##           split[cur.subset]>=30
##           time      n.risk      n.event      survival      std.err
##           36.0000      25.0000      62.0000      0.4673      0.0515
## lower 95% CI upper 95% CI
##           0.3765      0.5800
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 188, number of events= 93
## (3 observations deleted due to missingness)
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.287      1.333      0.212 1.36      0.18
##
##           exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30      1.33      0.75      0.88      2.02
##
## Concordance= 0.529 (se = 0.028 )
## Rsquare= 0.01 (max possible= 0.99 )
## Likelihood ratio test= 1.87 on 1 df, p=0.172
## Wald test = 1.84 on 1 df, p=0.175
## Score (logrank) test = 1.85 on 1 df, p=0.174
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])

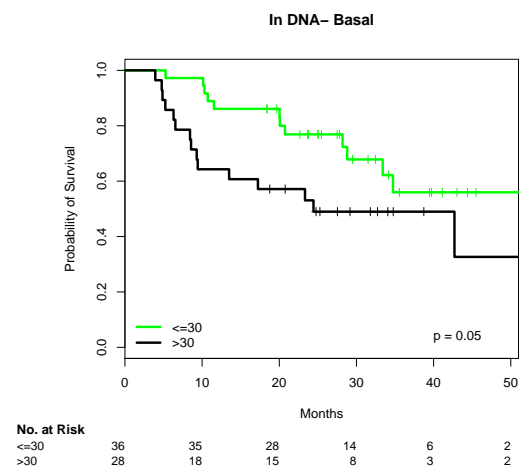
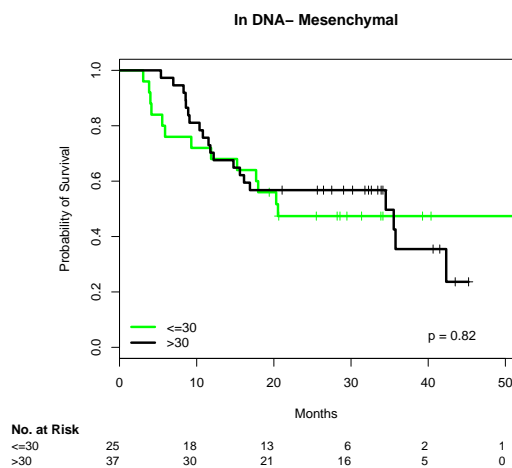
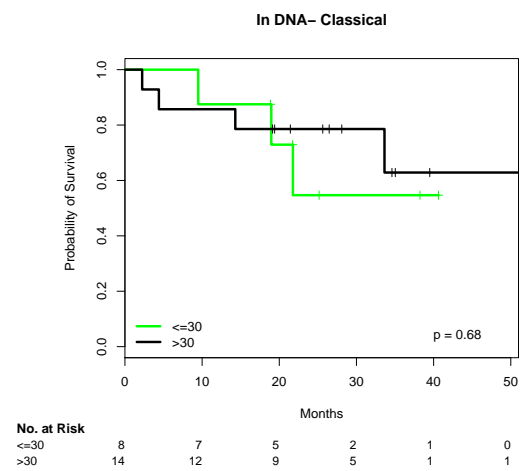
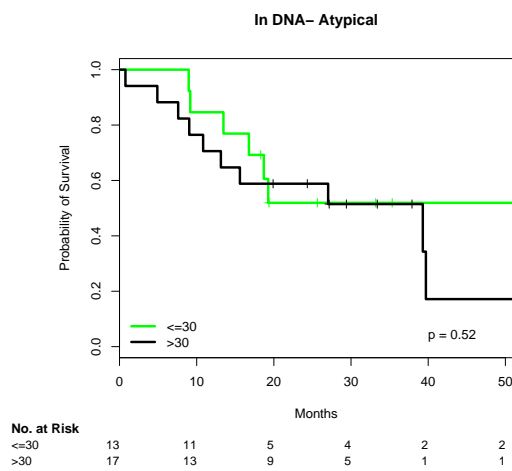
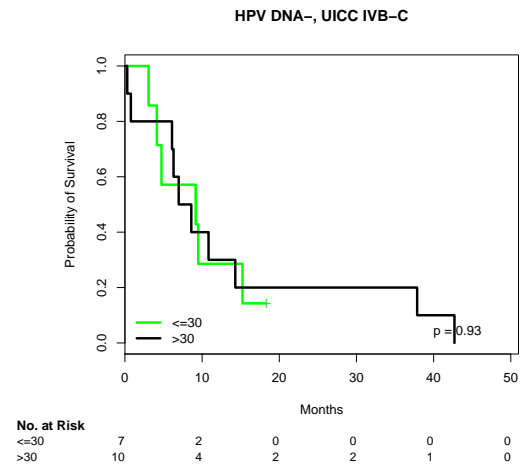
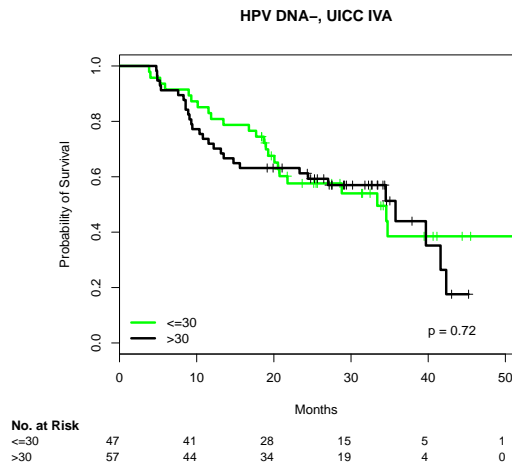
```

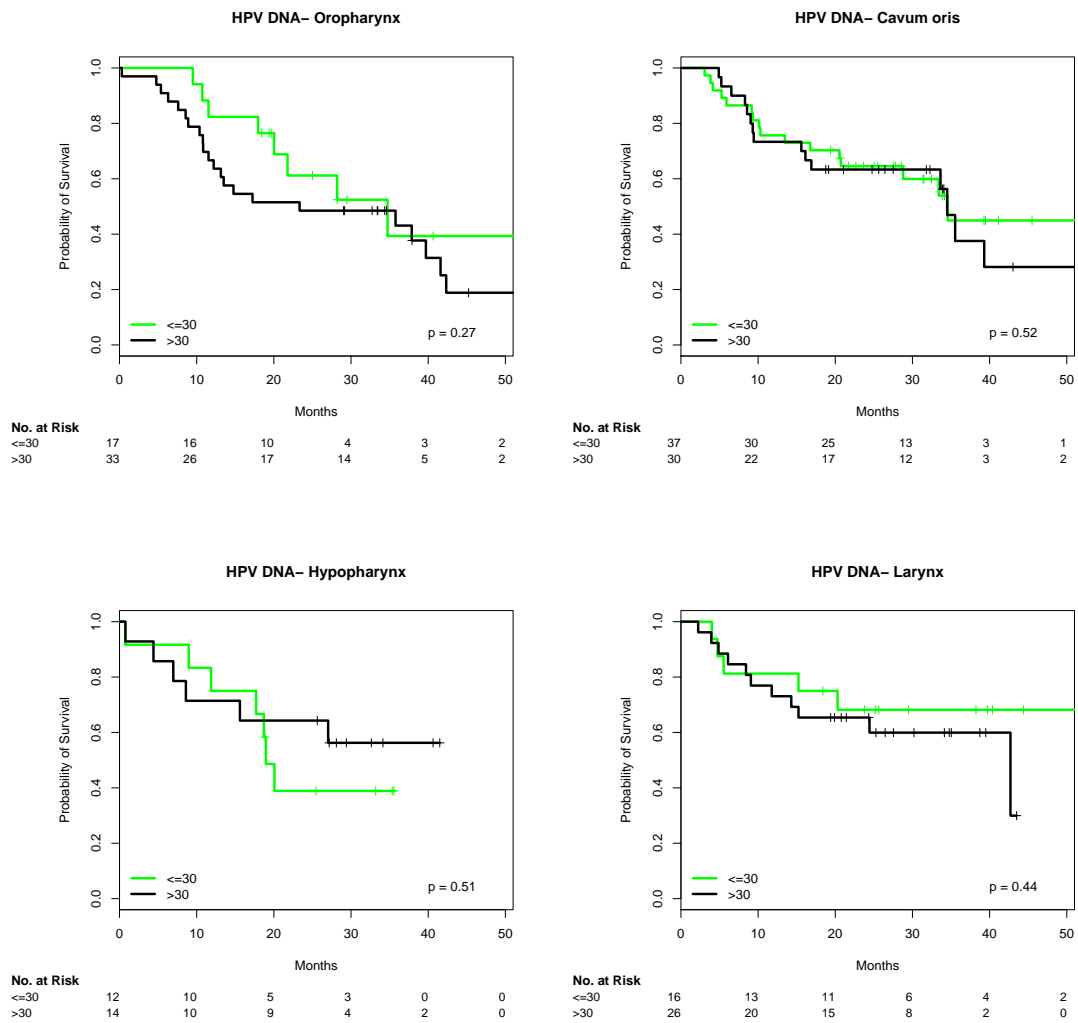


```
##
## n= 207, number of events= 100
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.336      1.399    0.204 1.64      0.1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30      1.4      0.715    0.937    2.09
##
## Concordance= 0.53 (se = 0.027 )
## Rsquare= 0.013 (max possible= 0.99 )
## Likelihood ratio test= 2.75 on 1 df,  p=0.0974
## Wald test = 2.7 on 1 df,  p=0.1
## Score (logrank) test = 2.72 on 1 df,  p=0.0988
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##
##               split[cur.subset]=<=30
##               time      n.risk      n.event      survival      std.err
##               36.0000      19.0000      40.0000      0.5168      0.0606
## lower 95% CI upper 95% CI
##               0.4107      0.6503
##
##               split[cur.subset]>=30
##               time      n.risk      n.event      survival      std.err
##               36.0000      18.0000      52.0000      0.4635      0.0594
## lower 95% CI upper 95% CI
##               0.3606      0.5957
```









3.23 Alcohol consumption

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 267, number of events= 126
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30  0.0534    1.0549   0.3533  0.15   0.880
## split[cur.subset]31 bis 60  0.5205    1.6828   0.3525  1.48   0.140
## split[cur.subset]>60      0.6503    1.9162   0.3337  1.95   0.051 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30      1.05      0.948    0.528    2.11
```

```

## split[cur.subset]31 bis 60      1.68      0.594      0.843      3.36
## split[cur.subset]>60            1.92      0.522      0.996      3.69
##
## Concordance= 0.57 (se = 0.027 )
## Rsquare= 0.035 (max possible= 0.991 )
## Likelihood ratio test= 9.59 on 3 df, p=0.0224
## Wald test = 9.19 on 3 df, p=0.0269
## Score (logrank) test = 9.44 on 3 df, p=0.024
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=nein
##      time      n.risk      n.event      survival      std.err
## 36.000      8.000      10.000      0.578      0.113
## lower 95% CI upper 95% CI
## 0.394      0.848
##
##               split[cur.subset]=1 bis 30
##      time      n.risk      n.event      survival      std.err
## 36.000      23.000      28.000      0.627      0.060
## lower 95% CI upper 95% CI
## 0.520      0.756
##
##               split[cur.subset]=31 bis 60
##      time      n.risk      n.event      survival      std.err
## 36.0000      10.0000      28.0000      0.4912      0.0769
## lower 95% CI upper 95% CI
## 0.3614      0.6675
##
##               split[cur.subset]=>60
##      time      n.risk      n.event      survival      std.err
## 36.0000      16.0000      47.0000      0.4216      0.0606
## lower 95% CI upper 95% CI
## 0.3181      0.5588
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30 0.226      1.253      0.461 0.49      0.62
## split[cur.subset]31 bis 60 0.389      1.476      0.461 0.84      0.40

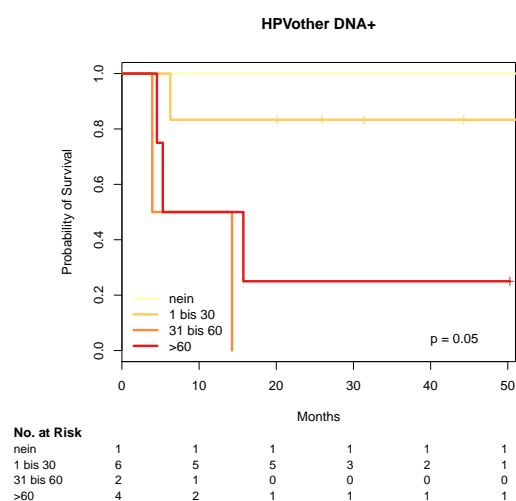
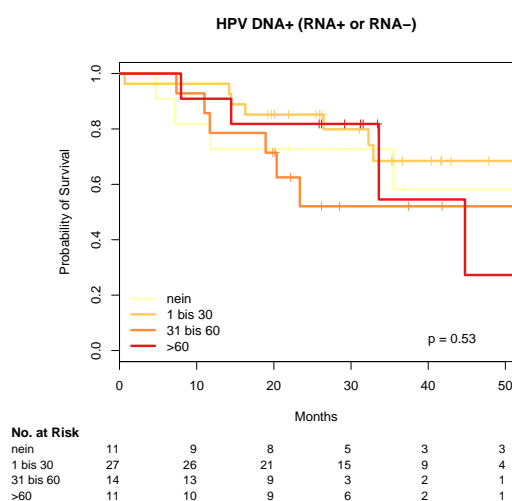
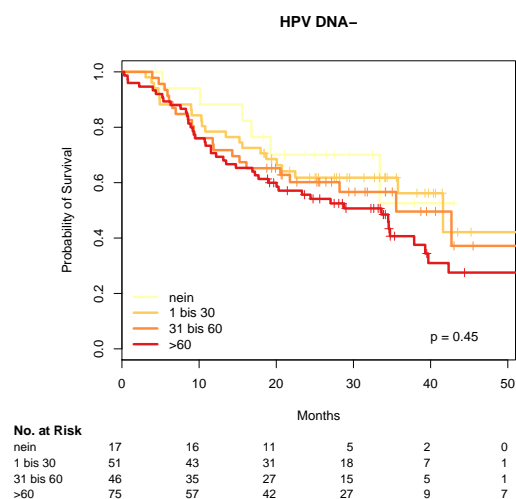
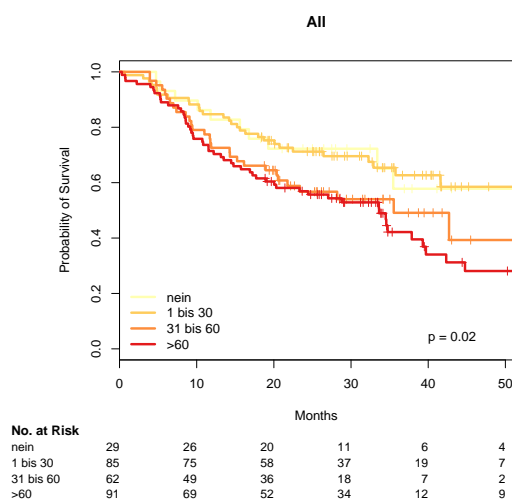
```

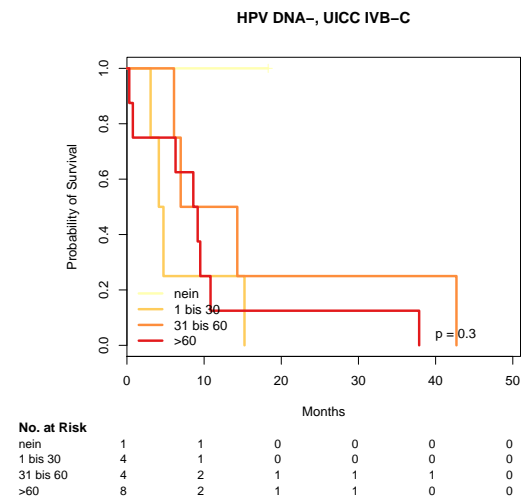
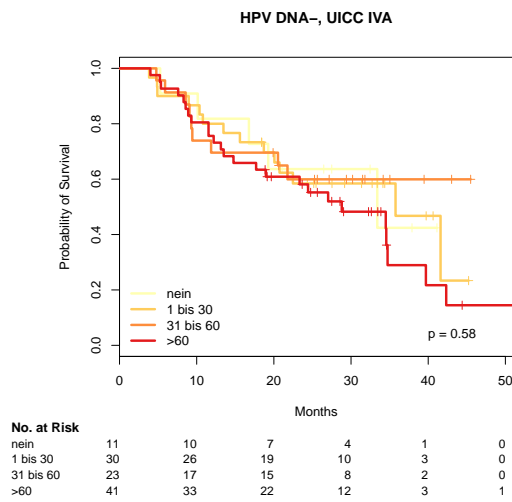
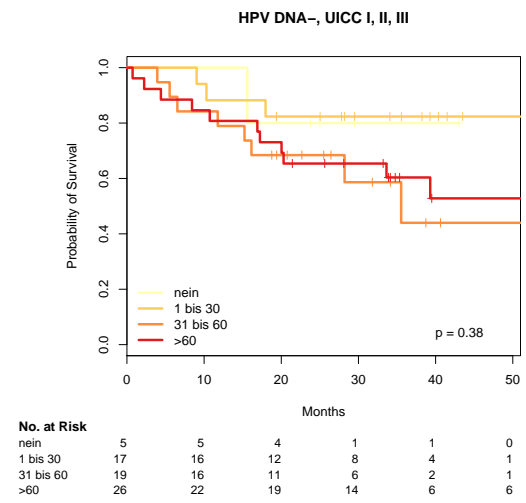
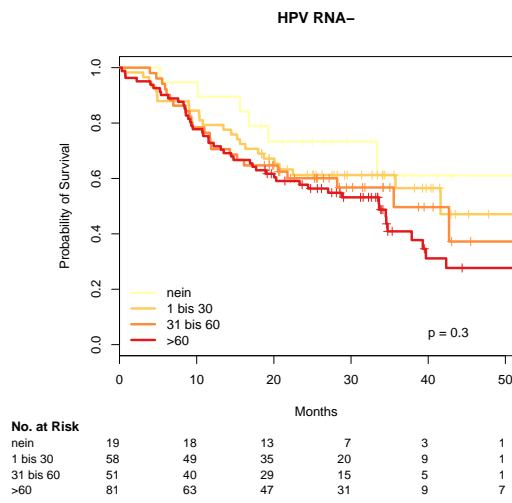
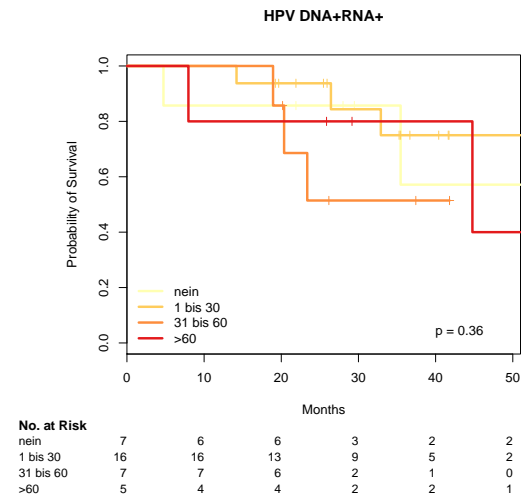
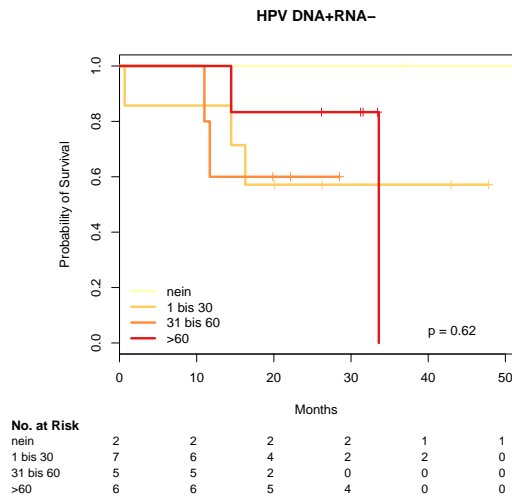
```

## split[cur.subset]>60      0.552      1.737      0.436 1.27      0.21
##
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30      1.25      0.798      0.508      3.09
## split[cur.subset]31 bis 60      1.48      0.678      0.598      3.64
## split[cur.subset]>60      1.74      0.576      0.738      4.09
##
## Concordance= 0.549 (se = 0.031 )
## Rsquare= 0.014 (max possible= 0.991 )
## Likelihood ratio test= 2.74 on 3 df, p=0.434
## Wald test = 2.62 on 3 df, p=0.454
## Score (logrank) test = 2.66 on 3 df, p=0.448
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30  0.427      1.533      0.455 0.94      0.348
## split[cur.subset]31 bis 60 0.597      1.817      0.457 1.31      0.191
## split[cur.subset]>60      0.726      2.067      0.434 1.67      0.095 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30      1.53      0.652      0.628      3.74
## split[cur.subset]31 bis 60      1.82      0.550      0.742      4.45
## split[cur.subset]>60      2.07      0.484      0.882      4.84
##
## Concordance= 0.546 (se = 0.03 )
## Rsquare= 0.019 (max possible= 0.99 )
## Likelihood ratio test= 3.97 on 3 df, p=0.264
## Wald test = 3.58 on 3 df, p=0.31
## Score (logrank) test = 3.67 on 3 df, p=0.299
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##              split[cur.subset]=nein
##              time      n.risk      n.event      survival      std.err
##              36.000      5.000      6.000      0.611      0.140
## lower 95% CI upper 95% CI
##              0.389      0.959
##

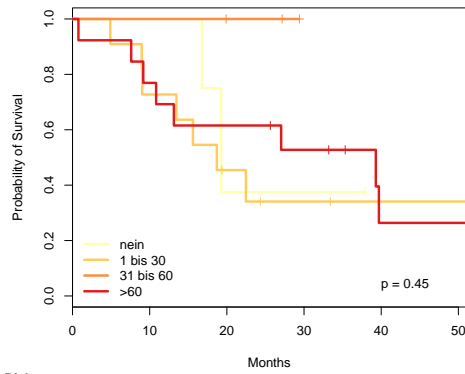
```

```
##                               split[cur.subset]=1 bis 30
##           time           n.risk           n.event           survival           std.err
##           36.0000         12.0000         23.0000           0.5651           0.0753
## lower 95% CI upper 95% CI
##           0.4352           0.7336
##
##                               split[cur.subset]=31 bis 60
##           time           n.risk           n.event           survival           std.err
##           36.0000         7.0000          22.0000           0.4964           0.0923
## lower 95% CI upper 95% CI
##           0.3448           0.7148
##
##                               split[cur.subset]>=60
##           time           n.risk           n.event           survival           std.err
##           36.0000         13.0000         42.0000           0.4089           0.0654
## lower 95% CI upper 95% CI
##           0.2989           0.5594
```





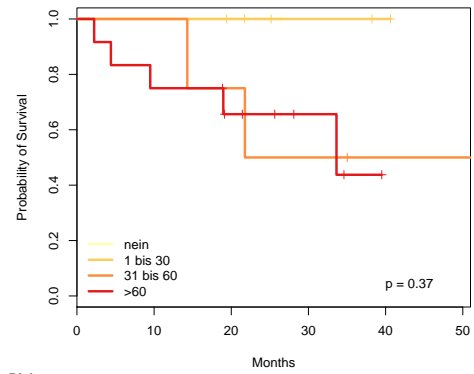
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
nein	4	4	1	1	0	0
1 bis 30	11	8	4	2	1	1
31 bis 60	3	3	2	0	0	0
>60	13	10	8	6	2	2

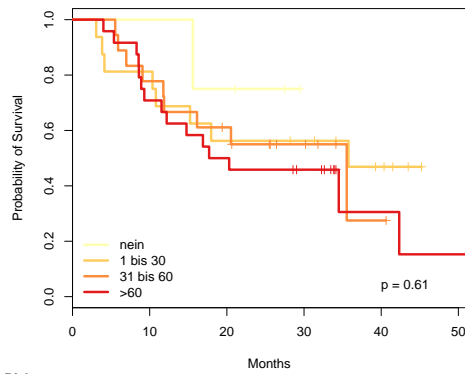
In DNA- Classical



No. at Risk

	0	10	20	30	40	50
nein	1	1	1	0	0	0
1 bis 30	5	5	4	2	1	0
31 bis 60	4	4	3	2	1	1
>60	12	9	6	3	0	0

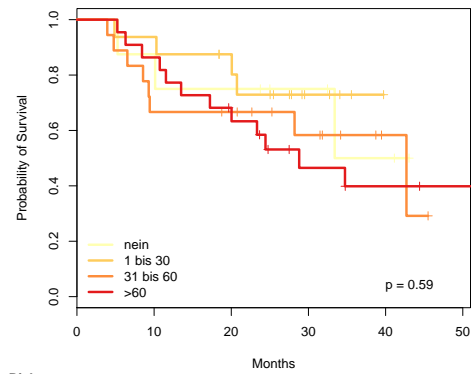
In DNA- Mesenchymal



No. at Risk

	0	10	20	30	40	50
nein	4	4	3	0	0	0
1 bis 30	16	13	9	8	4	0
31 bis 60	18	14	10	5	1	0
>60	24	17	12	9	2	1

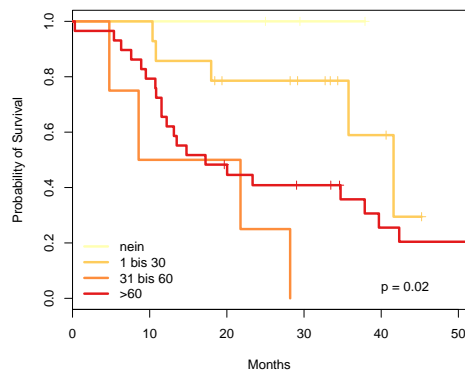
In DNA- Basal



No. at Risk

	0	10	20	30	40	50
nein	8	7	6	4	2	0
1 bis 30	16	15	12	4	0	0
31 bis 60	18	12	11	7	2	0
>60	22	19	14	7	5	4

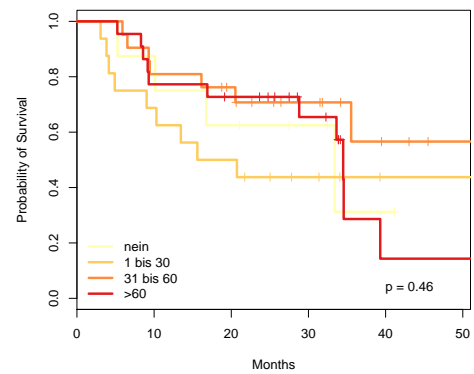
HPV DNA- Oropharynx



No. at Risk

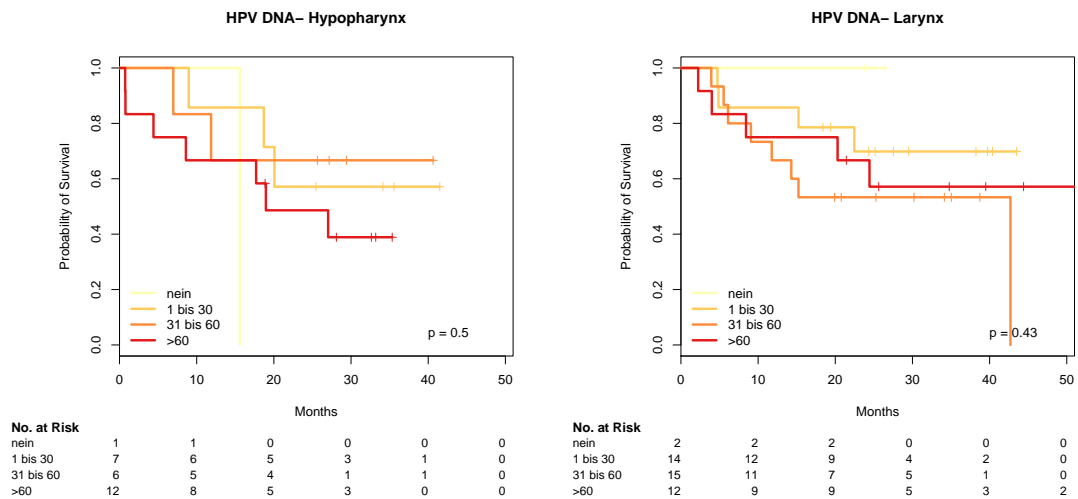
	0	10	20	30	40	50
nein	3	3	3	1	0	0
1 bis 30	14	14	9	7	3	0
31 bis 60	4	2	2	0	0	0
>60	29	23	13	10	5	4

HPV DNA- Cavum oris



No. at Risk

	0	10	20	30	40	50
nein	8	7	5	3	1	0
1 bis 30	16	11	8	4	1	1
31 bis 60	21	17	14	9	3	1
>60	22	17	15	9	1	1



3.24 Localisation

```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 264, number of events= 125
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.0507  0.9506  0.2151 -0.24  0.81
## split[cur.subset]hypopharynx  0.1013  1.1066  0.3140  0.32  0.75
## split[cur.subset]larynx      -0.2022  0.8169  0.2879 -0.70  0.48
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx  0.951  1.052  0.624  1.45
## split[cur.subset]hypopharynx  1.107  0.904  0.598  2.05
## split[cur.subset]larynx      0.817  1.224  0.465  1.44
##
## Concordance= 0.514 (se = 0.027 )
## Rsquare= 0.003 (max possible= 0.991 )
## Likelihood ratio test= 0.83 on 3 df, p=0.843
## Wald test = 0.81 on 3 df, p=0.846
## Score (logrank) test = 0.82 on 3 df, p=0.845
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
```

```

##
## 3 observations deleted due to missingness
##           split[cur.subset]=cavum oris
##           time      n.risk      n.event      survival      std.err
##           36.0000      11.0000      34.0000      0.4327      0.0801
## lower 95% CI upper 95% CI
##           0.3010      0.6220
##
##           split[cur.subset]=oropharynx
##           time      n.risk      n.event      survival      std.err
##           36.0000      30.0000      47.0000      0.5202      0.0534
## lower 95% CI upper 95% CI
##           0.4254      0.6362
##
##           split[cur.subset]=hypopharynx
##           time      n.risk      n.event      survival      std.err
##           36.0000      3.0000      14.0000      0.5140      0.0952
## lower 95% CI upper 95% CI
##           0.3575      0.7390
##
##           split[cur.subset]=larynx
##           time      n.risk      n.event      survival      std.err
##           36.0000      12.0000      17.0000      0.6264      0.0725
## lower 95% CI upper 95% CI
##           0.4992      0.7860
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 186, number of events= 93
##      (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx  0.133    1.142   0.253  0.52   0.60
## split[cur.subset]hypopharynx  0.133    1.142   0.329  0.40   0.69
## split[cur.subset]larynx     -0.258    0.772   0.299 -0.86   0.39
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx    1.142    0.876    0.695    1.88
## split[cur.subset]hypopharynx    1.142    0.876    0.600    2.17
## split[cur.subset]larynx        0.772    1.295    0.429    1.39
##
## Concordance= 0.528 (se = 0.031 )
## Rsquare= 0.01 (max possible= 0.991 )
## Likelihood ratio test= 1.95 on 3 df, p=0.582

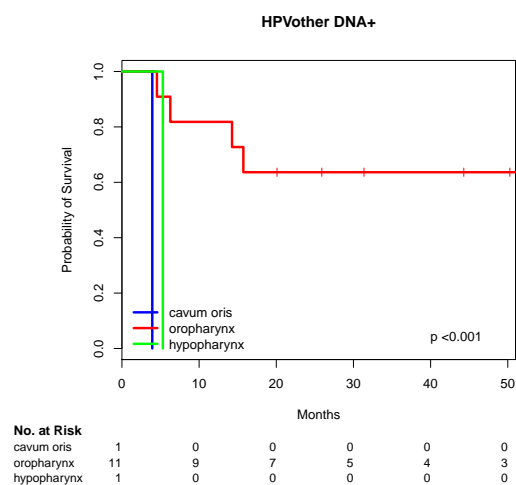
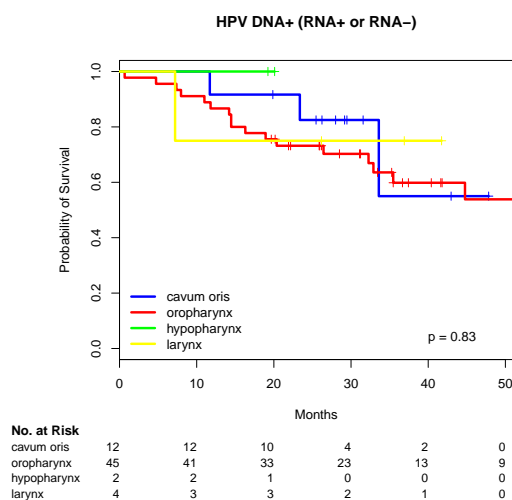
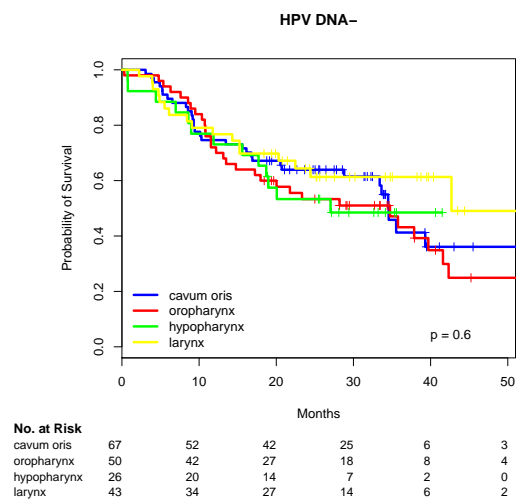
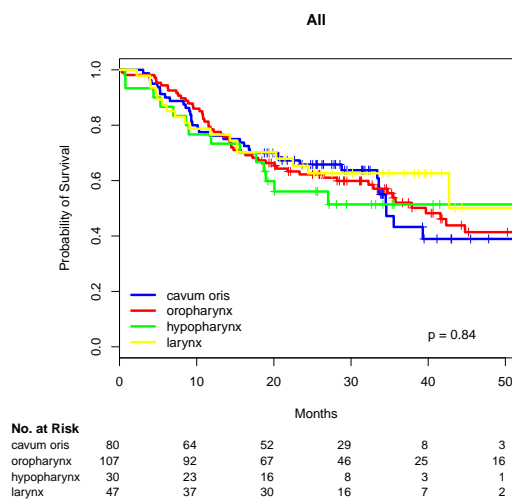
```

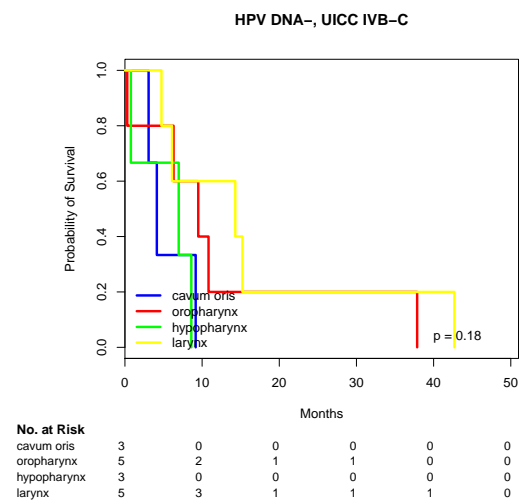
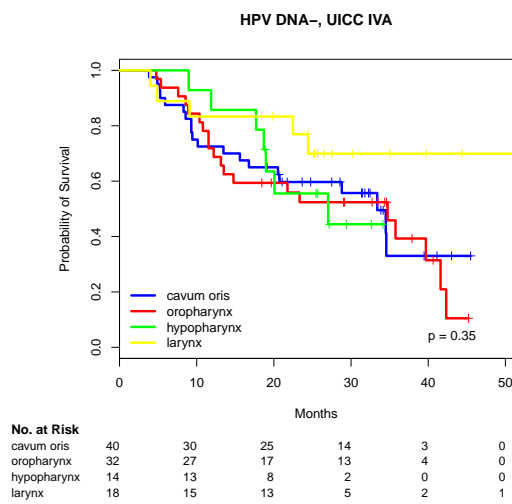
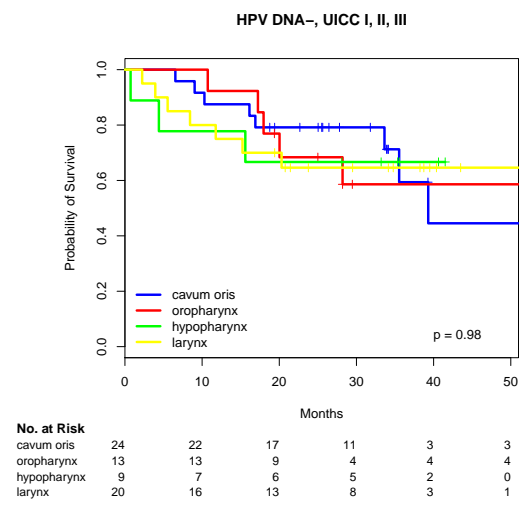
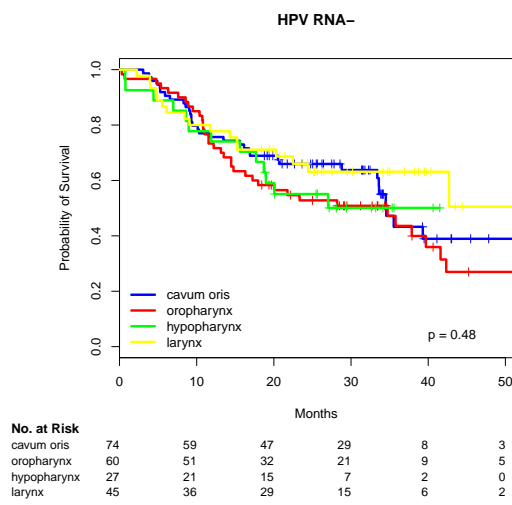
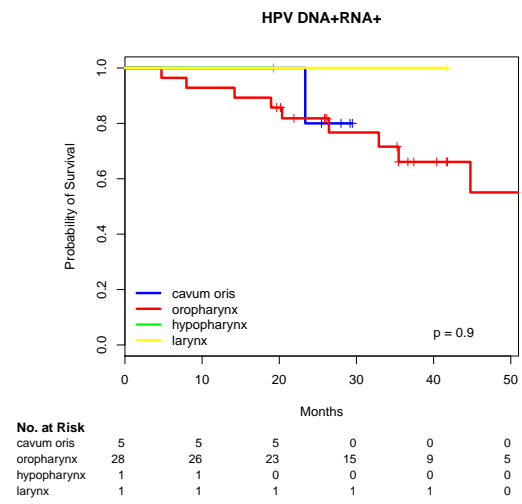
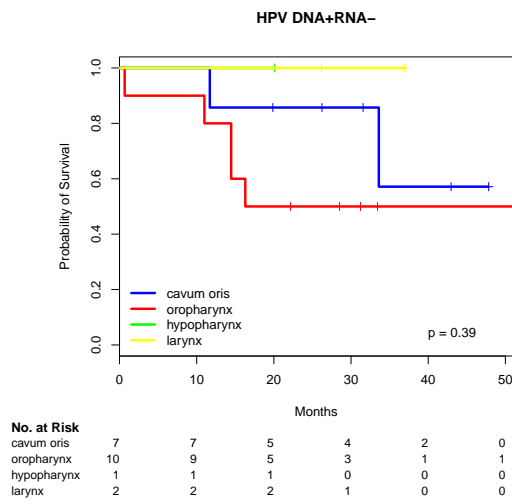
```

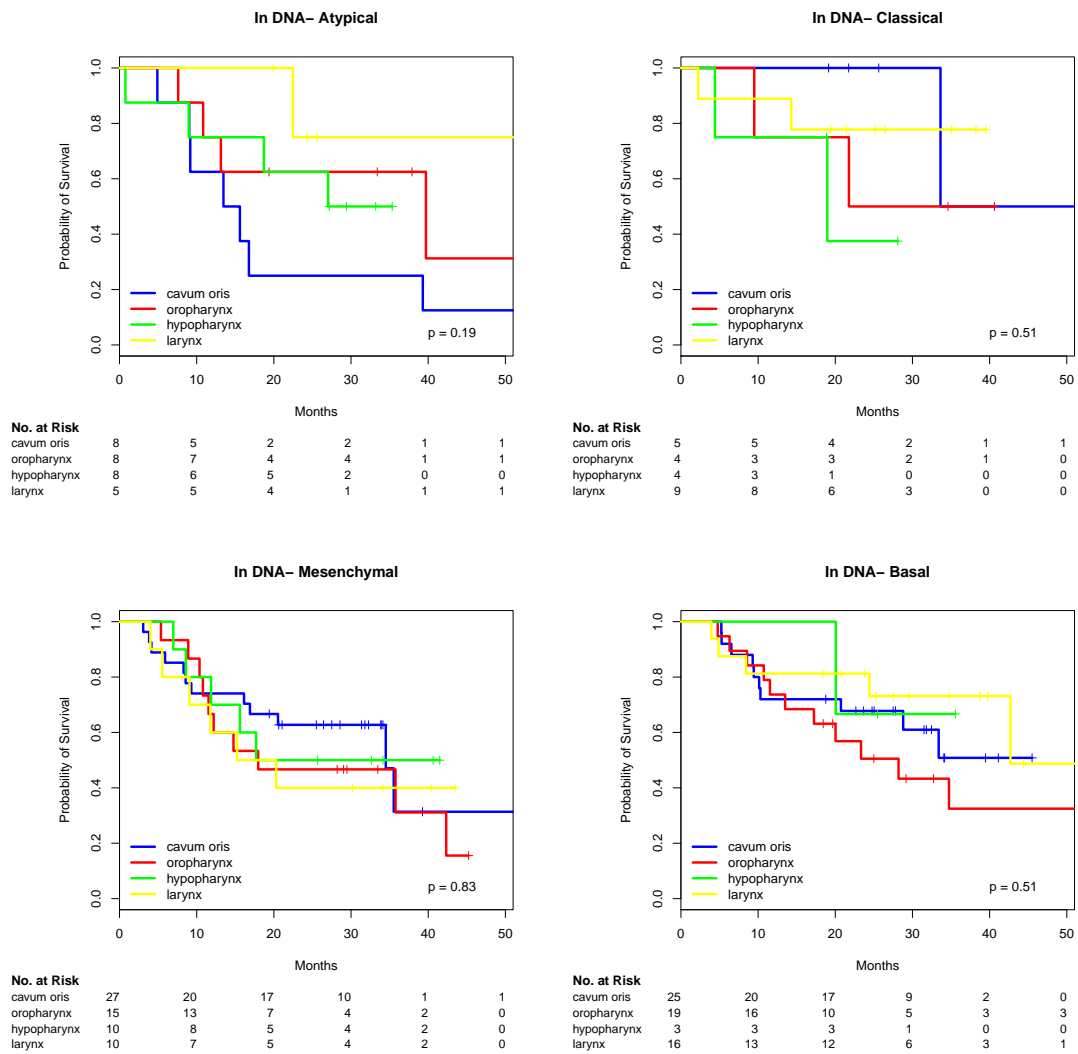
## Wald test          = 1.87  on 3 df,    p=0.601
## Score (logrank) test = 1.88  on 3 df,    p=0.597
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 206, number of events= 100
##    (3 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx  0.192    1.212    0.240  0.80    0.42
## split[cur.subset]hypopharynx 0.151    1.163    0.326  0.46    0.64
## split[cur.subset]larynx     -0.248    0.780    0.296 -0.84    0.40
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx  1.21    0.825    0.757    1.94
## split[cur.subset]hypopharynx  1.16    0.860    0.614    2.20
## split[cur.subset]larynx      0.78    1.281    0.437    1.39
##
## Concordance= 0.536 (se = 0.03 )
## Rsquare= 0.012 (max possible= 0.99 )
## Likelihood ratio test= 2.52  on 3 df,    p=0.472
## Wald test          = 2.42  on 3 df,    p=0.49
## Score (logrank) test = 2.45  on 3 df,    p=0.485
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 3 observations deleted due to missingness
##              split[cur.subset]=cavum oris
##              time      n.risk      n.event      survival      std.err
##              36.0000      11.0000      32.0000      0.4326      0.0808
## lower 95% CI upper 95% CI
##              0.3000      0.6238
##
##              split[cur.subset]=oropharynx
##              time      n.risk      n.event      survival      std.err
##              36.0000      12.0000      31.0000      0.4358      0.0736
## lower 95% CI upper 95% CI
##              0.3130      0.6069
##
##              split[cur.subset]=hypopharynx
##              time      n.risk      n.event      survival      std.err
##              36.0000      2.0000      13.0000      0.5008      0.0999
## lower 95% CI upper 95% CI

```

```
##      0.3387      0.7405
##
##      split[cur.subset]=larynx
##      time      n.risk      n.event      survival      std.err
##      36.0000      11.0000      16.0000      0.6315      0.0741
## lower 95% CI upper 95% CI
##      0.5017      0.7948
```







3.25 Sex

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 267, number of events= 126
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M 0.353    1.423   0.255 1.38    0.17
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M    1.42    0.703   0.863    2.35
##
## Concordance= 0.528 (se = 0.019 )
## Rsquare= 0.008 (max possible= 0.991 )
## Likelihood ratio test= 2.07 on 1 df,  p=0.15
```

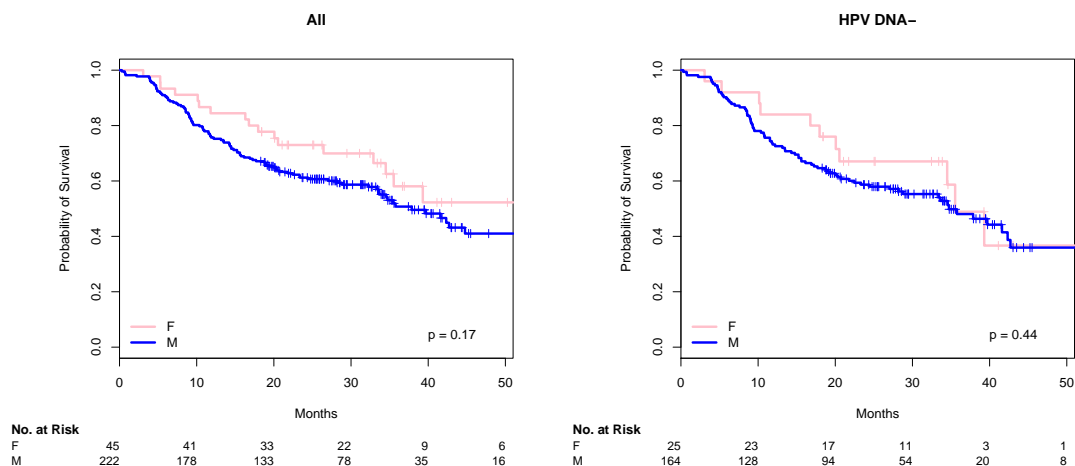
```

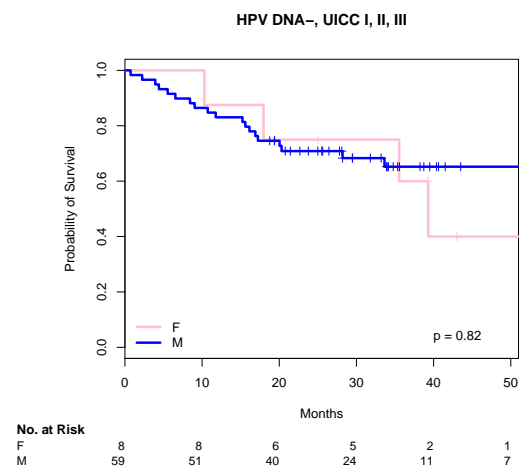
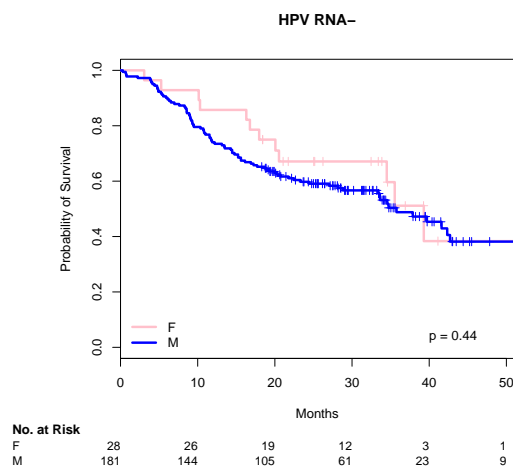
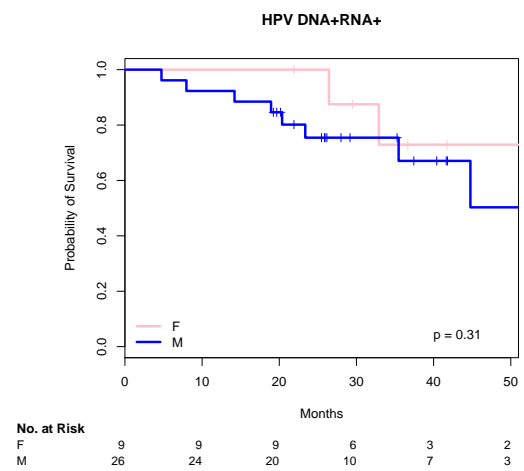
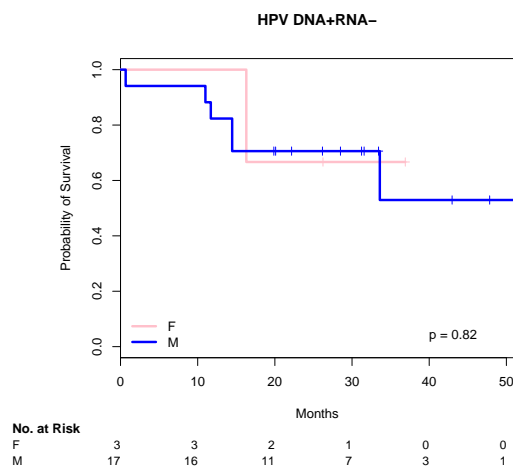
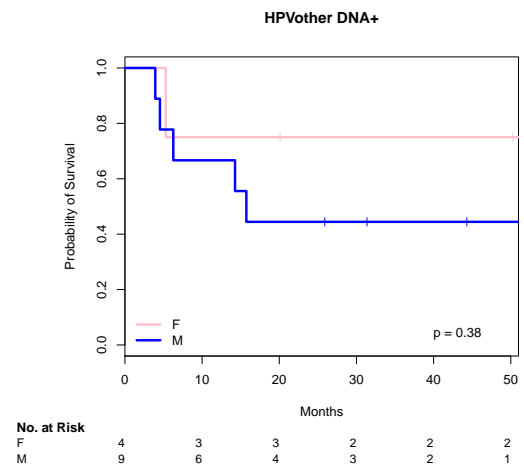
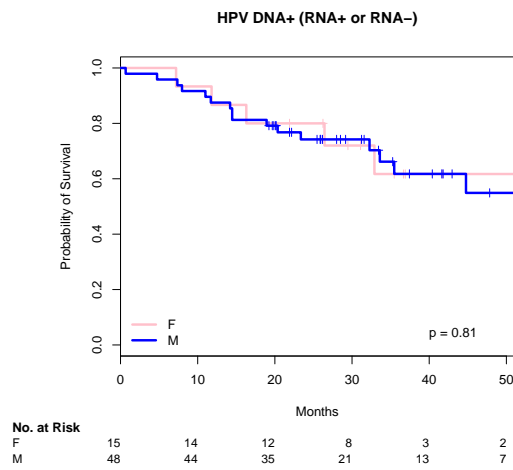
## Wald test          = 1.91  on 1 df,    p=0.167
## Score (logrank) test = 1.93  on 1 df,    p=0.165
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=F
##      time      n.risk      n.event      survival      std.err
## 36.0000      13.0000      16.0000      0.5807      0.0861
## lower 95% CI upper 95% CI
## 0.4343      0.7766
##
##               split[cur.subset]=M
##      time      n.risk      n.event      survival      std.err
## 36.0000      44.0000      97.0000      0.5075      0.0395
## lower 95% CI upper 95% CI
## 0.4357      0.5912
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 94
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M 0.248      1.282      0.321 0.77      0.44
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M      1.28      0.78      0.683      2.41
##
## Concordance= 0.52 (se = 0.02 )
## Rsquare= 0.003 (max possible= 0.991 )
## Likelihood ratio test= 0.64  on 1 df,    p=0.425
## Wald test          = 0.6  on 1 df,    p=0.439
## Score (logrank) test = 0.6  on 1 df,    p=0.438
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)

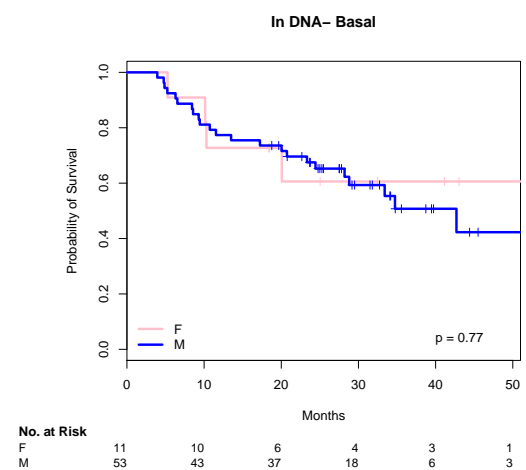
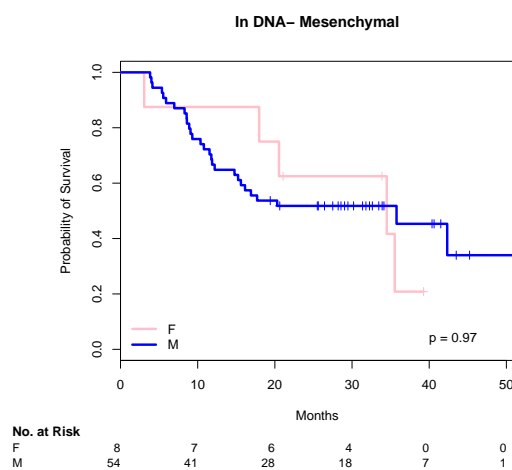
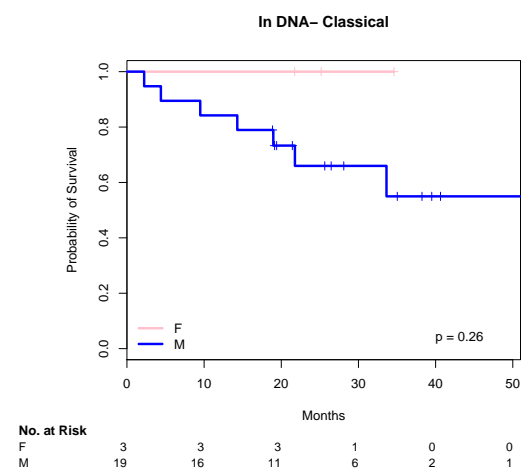
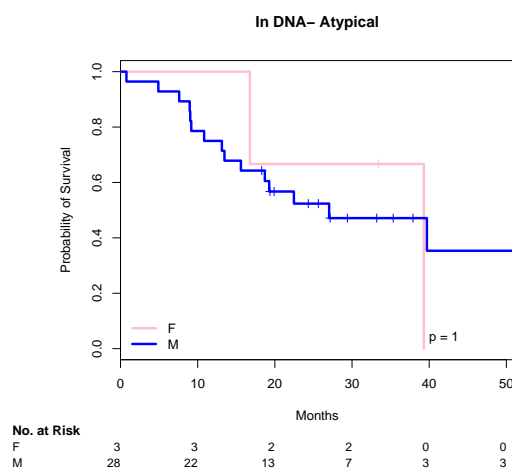
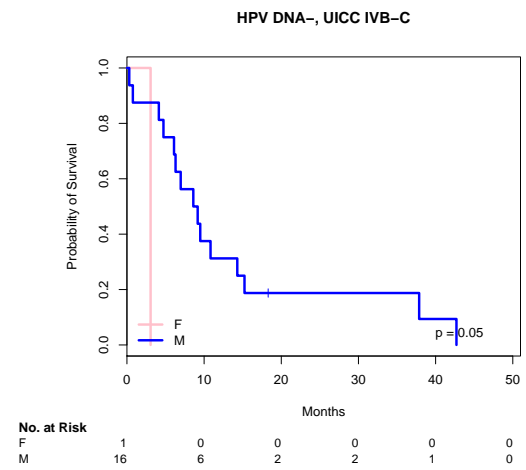
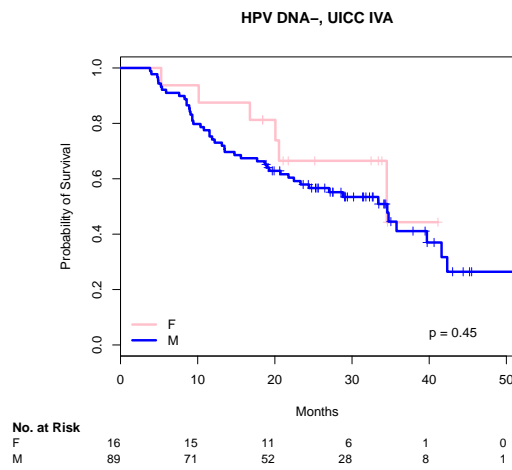
```

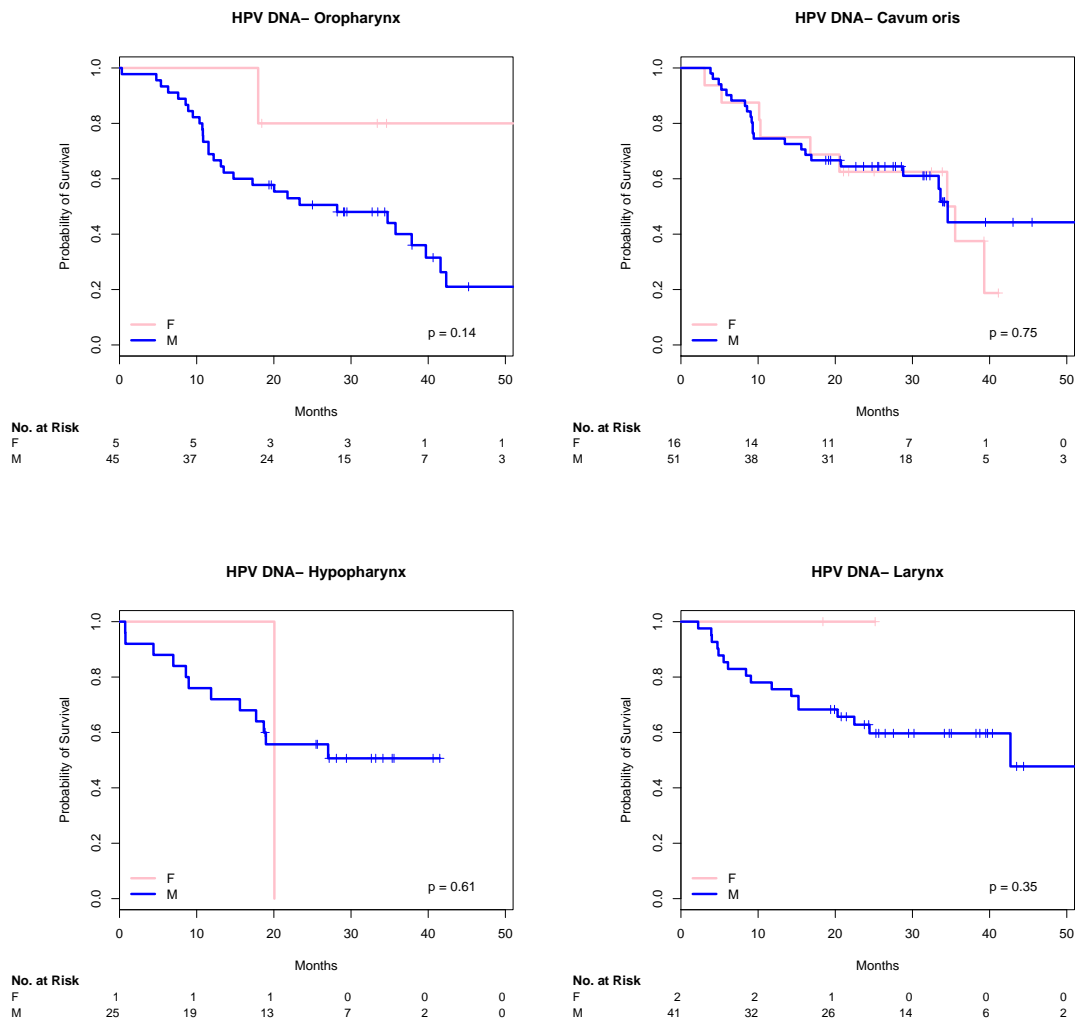


```
## split[cur.subset]M 0.239      1.270      0.308 0.78      0.44
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M      1.27      0.787      0.695      2.32
##
## Concordance= 0.52 (se = 0.019 )
## Rsquare= 0.003 (max possible= 0.99 )
## Likelihood ratio test= 0.64 on 1 df,  p=0.423
## Wald test = 0.6 on 1 df,  p=0.437
## Score (logrank) test = 0.61 on 1 df,  p=0.436
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=F
##      time      n.risk      n.event      survival      std.err
## 36.000      6.000      11.000      0.511      0.121
## lower 95% CI upper 95% CI
## 0.322      0.812
##
##               split[cur.subset]=M
##      time      n.risk      n.event      survival      std.err
## 36.0000     31.0000     82.0000     0.4879      0.0446
## lower 95% CI upper 95% CI
## 0.4079     0.5835
```









3.26 Age, cut at 60

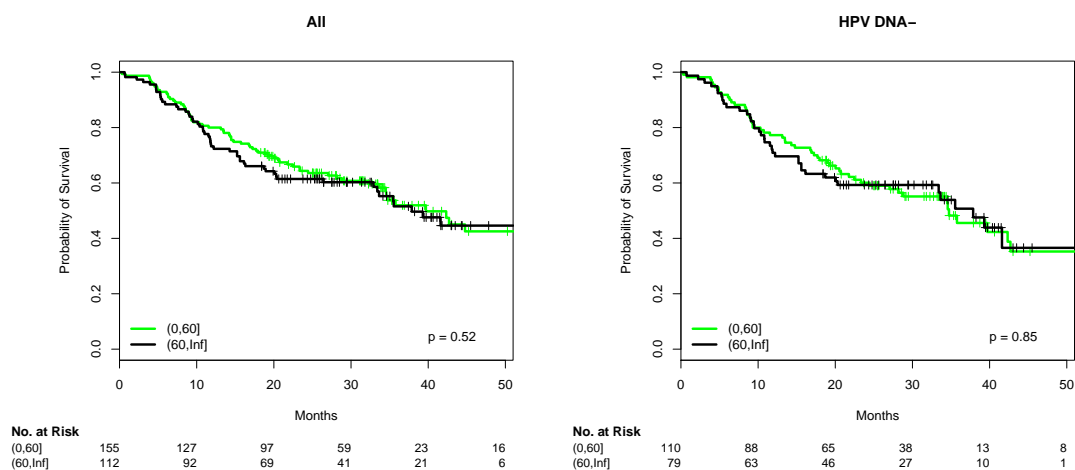
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](60,Inf) 0.116    1.123   0.180 0.65    0.52
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf)    1.12    0.89    0.79    1.6
##
## Concordance= 0.515 (se = 0.024 )
## Rsquare= 0.002 (max possible= 0.991 )
## Likelihood ratio test= 0.42 on 1 df,  p=0.519
```

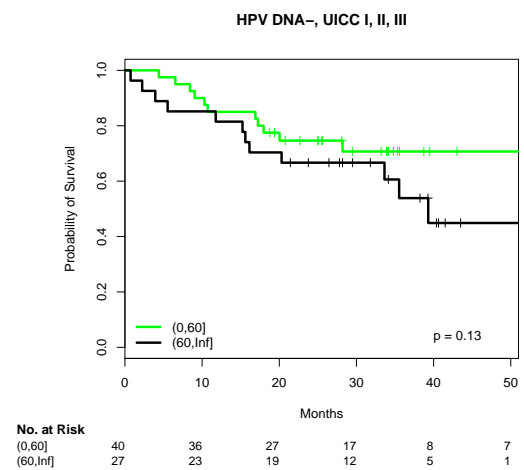
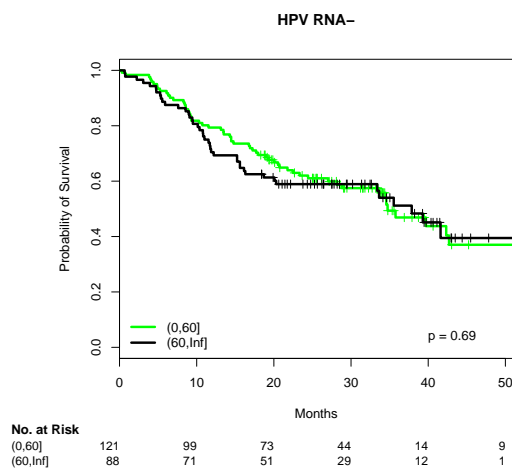
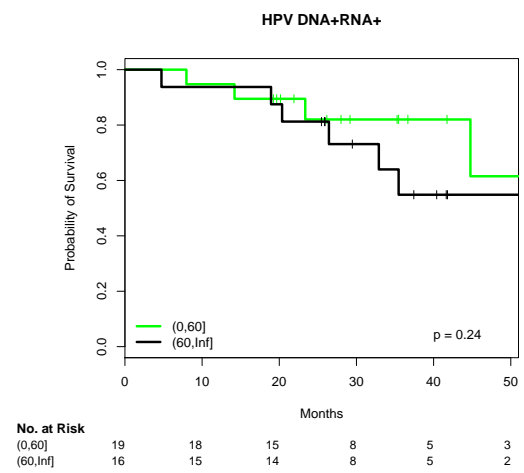
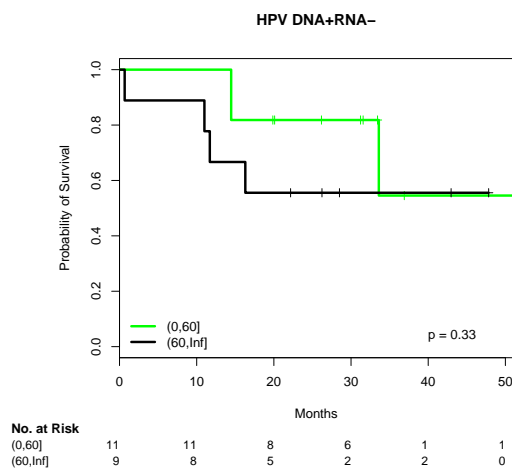
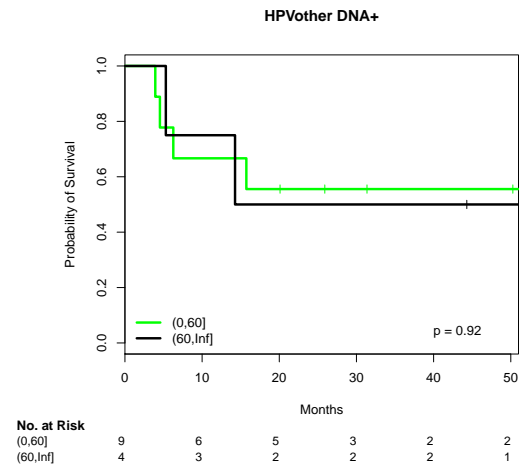
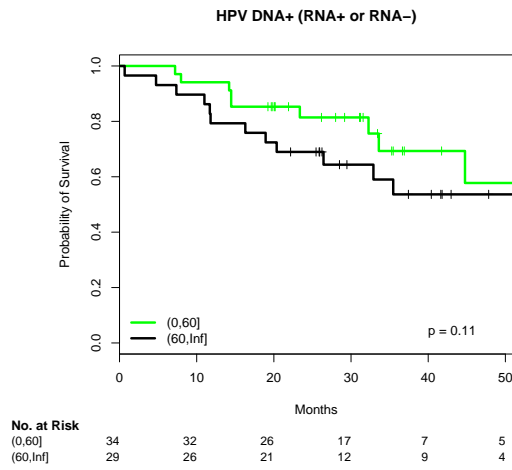
```

## Wald test          = 0.42  on 1 df,    p=0.518
## Score (logrank) test = 0.42  on 1 df,    p=0.517
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=(0,60]
##      time      n.risk      n.event      survival      std.err
##    36.0000      29.0000      64.0000        0.5193        0.0487
## lower 95% CI upper 95% CI
##    0.4321      0.6241
##
##               split[cur.subset]=(60,Inf]
##      time      n.risk      n.event      survival      std.err
##    36.0000      28.0000      49.0000        0.5156        0.0539
## lower 95% CI upper 95% CI
##    0.4201      0.6328
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 94
##      (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](60,Inf] 0.0394    1.0401    0.2101 0.19    0.85
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf]    1.04    0.961    0.689    1.57
##
## Concordance= 0.508 (se = 0.027 )
## Rsquare= 0 (max possible= 0.991 )
## Likelihood ratio test= 0.03  on 1 df,    p=0.852
## Wald test          = 0.04  on 1 df,    p=0.851
## Score (logrank) test = 0.04  on 1 df,    p=0.851
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 101
##
##               coef exp(coef) se(coef)      z Pr(>|z|)

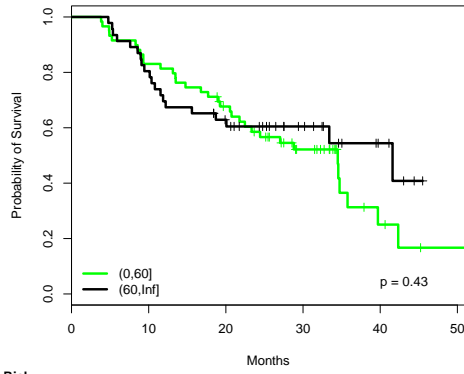
```

```
## split[cur.subset](60,Inf] 0.081      1.084      0.202 0.4      0.69
##
##                               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf]      1.08      0.922      0.73      1.61
##
## Concordance= 0.516  (se = 0.026 )
## Rsquare= 0.001  (max possible= 0.99 )
## Likelihood ratio test= 0.16  on 1 df,  p=0.689
## Wald test               = 0.16  on 1 df,  p=0.688
## Score (logrank) test = 0.16  on 1 df,  p=0.688
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=(0,60]
##      time      n.risk      n.event      survival      std.err
## 36.0000     19.0000     54.0000      0.4688      0.0579
## lower 95% CI upper 95% CI
## 0.3681      0.5971
##
##               split[cur.subset]=(60,Inf]
##      time      n.risk      n.event      survival      std.err
## 36.000     18.000     39.000      0.512      0.062
## lower 95% CI upper 95% CI
## 0.403      0.649
```





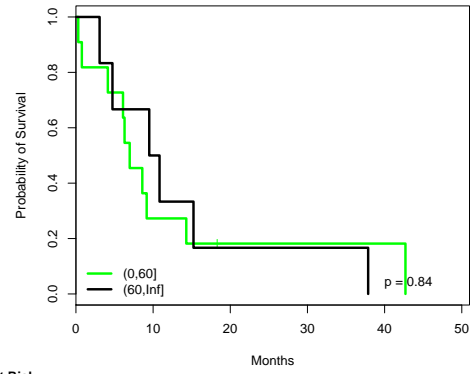
HPV DNA-, UICC IVA



No. at Risk
(0,60]
(60,Inf]

59	49	37	20	4	1
46	37	26	14	5	0

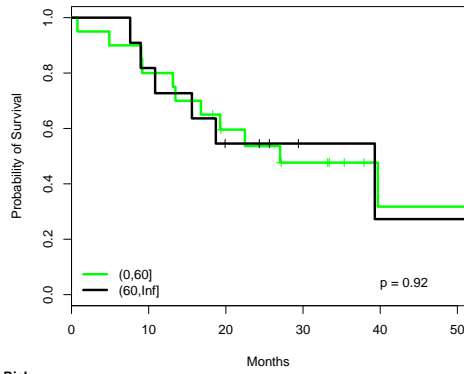
HPV DNA-, UICC IVB-C



No. at Risk
(0,60]
(60,Inf]

11	3	1	1	1	0
6	3	1	1	0	0

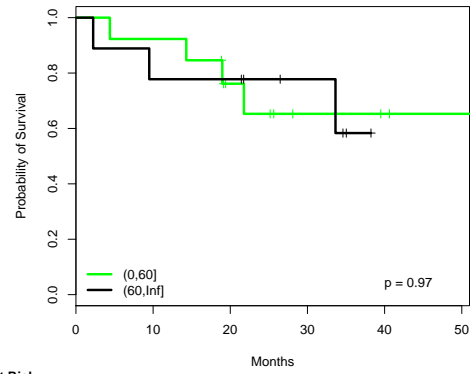
In DNA- Atypical



No. at Risk
(0,60]
(60,Inf]

20	16	10	7	2	2
11	9	5	2	1	1

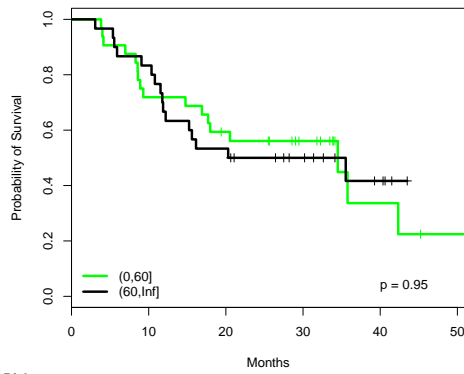
In DNA- Classical



No. at Risk
(0,60]
(60,Inf]

13	12	7	3	2	1
9	7	7	4	0	0

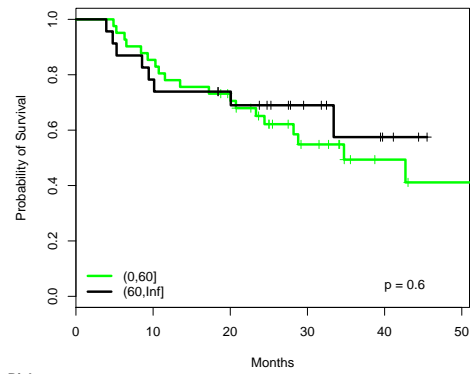
In DNA- Mesenchymal



No. at Risk
(0,60]
(60,Inf]

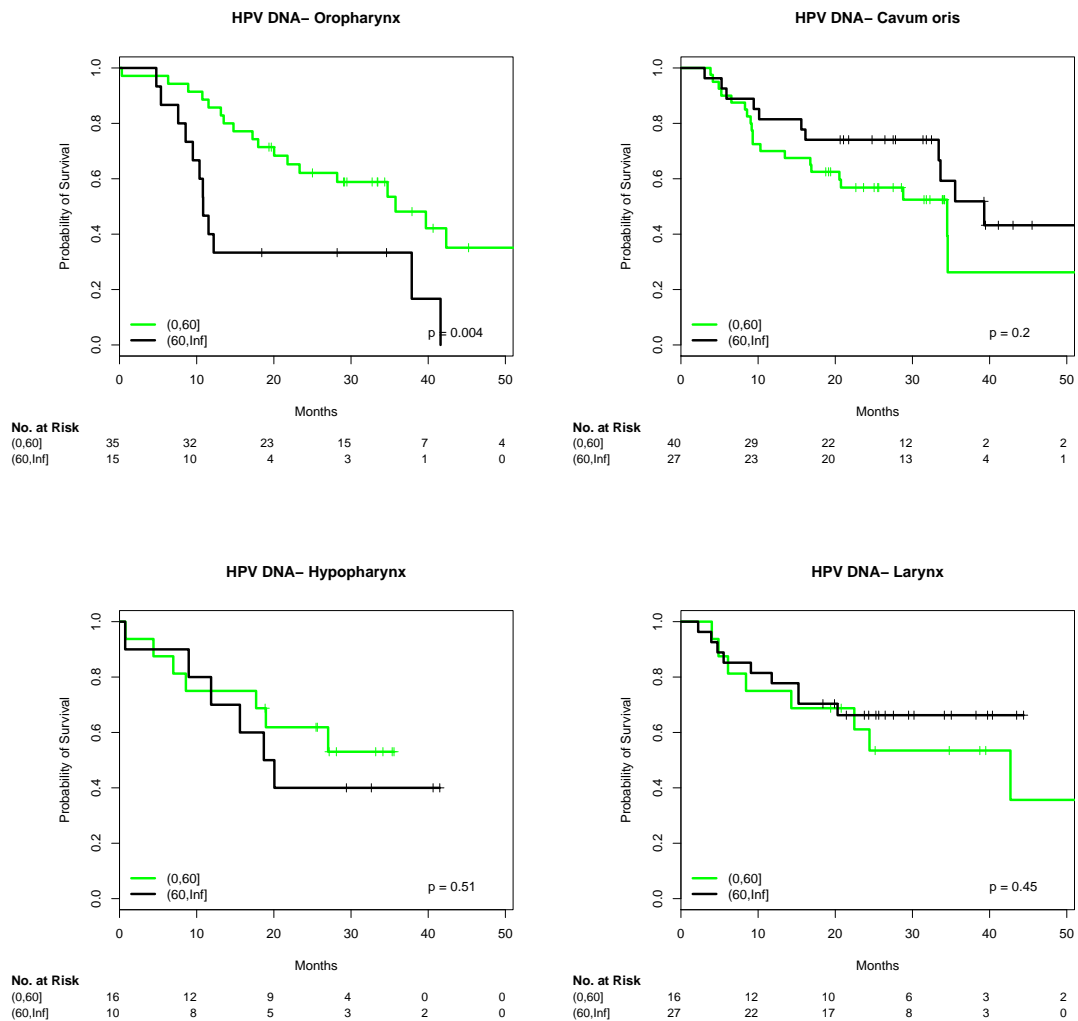
32	23	18	12	3	1
30	25	16	10	4	0

In DNA- Basal



No. at Risk
(0,60]
(60,Inf]

41	35	28	14	6	4
23	18	15	8	3	0



3.27 Age, cut at 50, 70

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 126
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70) -0.440    0.644   0.240 -1.83  0.067 .
## split[cur.subset](70,Inf)  0.011    1.011   0.282  0.04  0.969
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70)    0.644    1.553    0.402    1.03
## split[cur.subset](70,Inf)    1.011    0.989    0.582    1.76
```

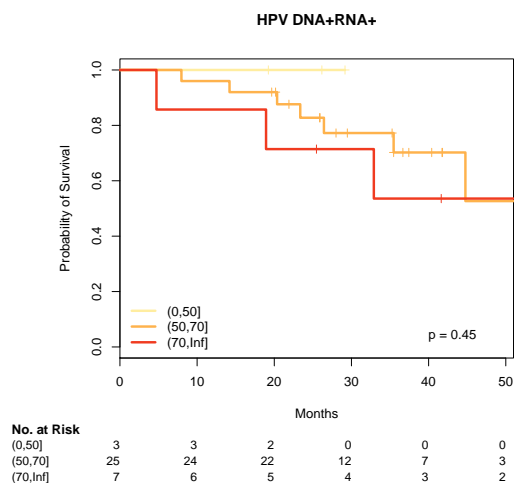
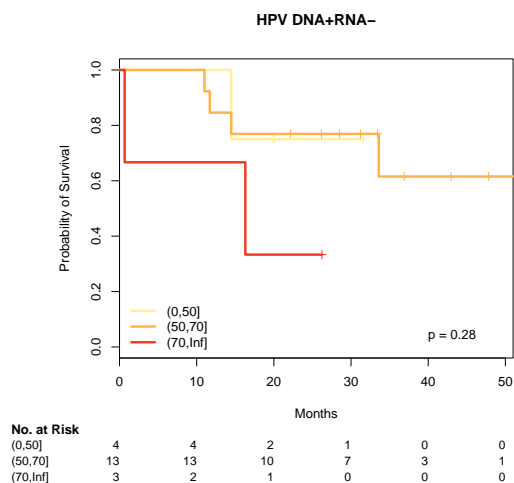
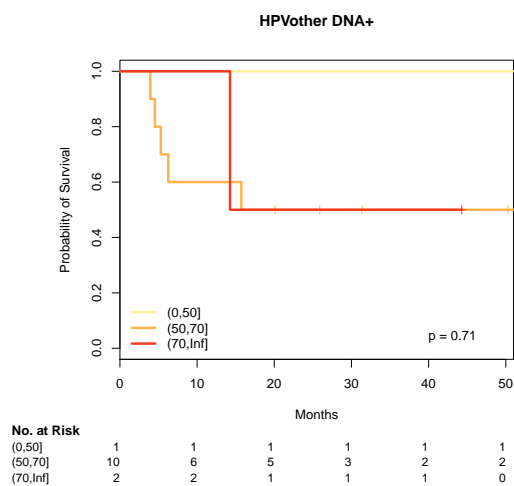
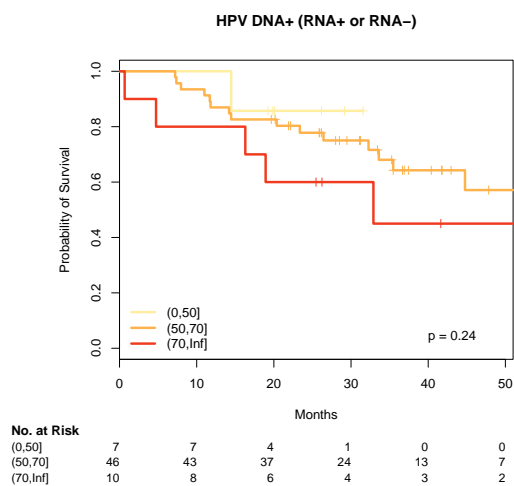
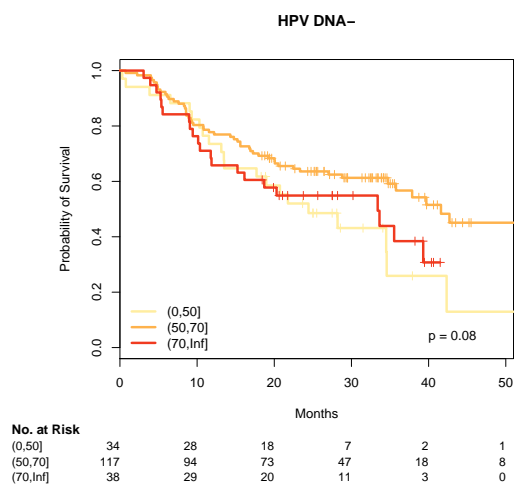
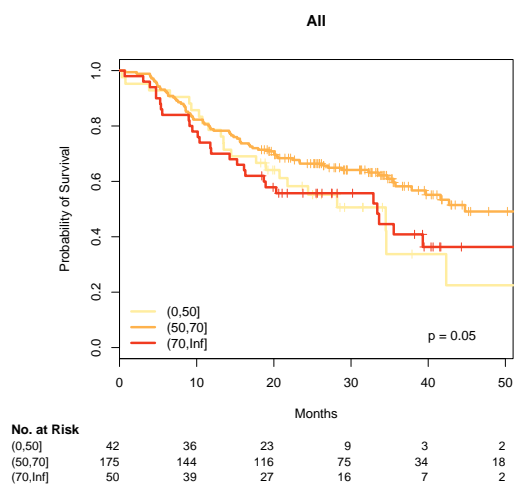
```
##
## Concordance= 0.544 (se = 0.023 )
## Rsquare= 0.021 (max possible= 0.991 )
## Likelihood ratio test= 5.73 on 2 df, p=0.0571
## Wald test = 5.92 on 2 df, p=0.0518
## Score (logrank) test = 6.02 on 2 df, p=0.0494
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=(0,50]
##      time      n.risk      n.event      survival      std.err
##    36.000      4.000      21.000      0.337      0.113
## lower 95% CI upper 95% CI
##    0.175      0.650
##
##               split[cur.subset]=(50,70]
##      time      n.risk      n.event      survival      std.err
##    36.0000     42.0000     66.0000      0.5822      0.0423
## lower 95% CI upper 95% CI
##    0.5049      0.6713
##
##               split[cur.subset]=(70,Inf]
##      time      n.risk      n.event      survival      std.err
##    36.000      11.000      26.000      0.409      0.082
## lower 95% CI upper 95% CI
##    0.276      0.606
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 94
##      (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70] -0.5076  0.6019  0.2604 -1.95  0.051 .
## split[cur.subset](70,Inf] -0.0895  0.9144  0.3101 -0.29  0.773
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70]  0.602      1.66  0.361      1.00
## split[cur.subset](70,Inf]  0.914      1.09  0.498      1.68
##
## Concordance= 0.545 (se = 0.028 )
```

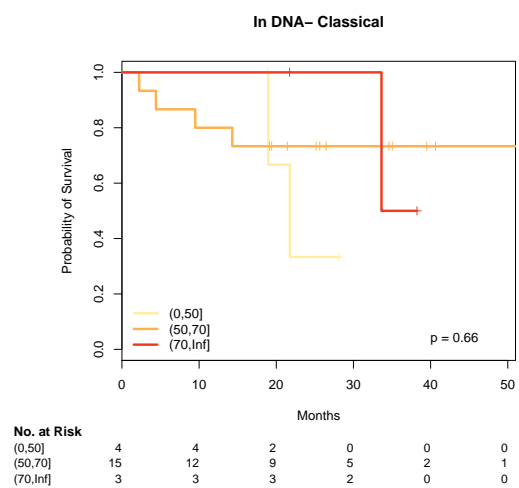
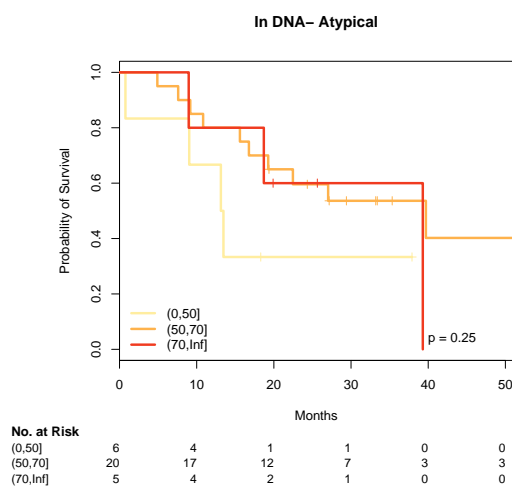
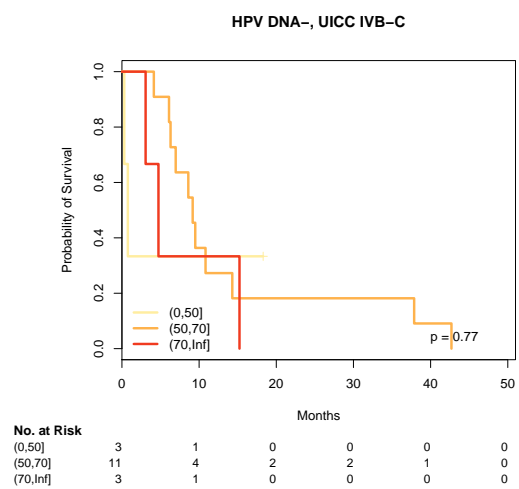
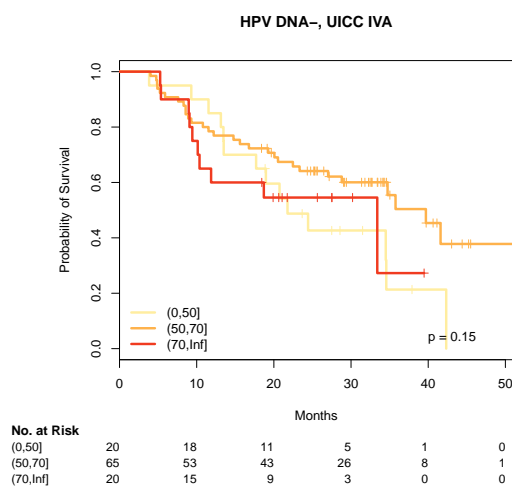
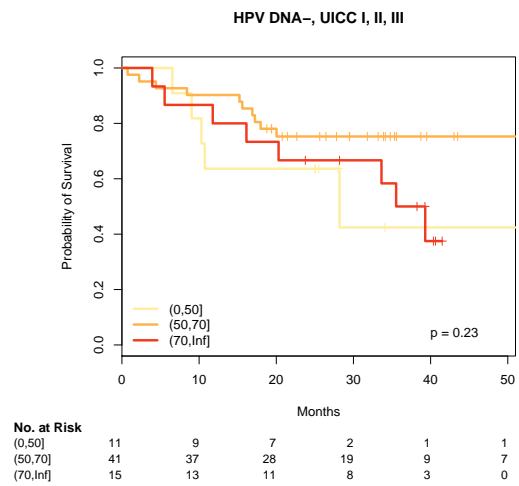
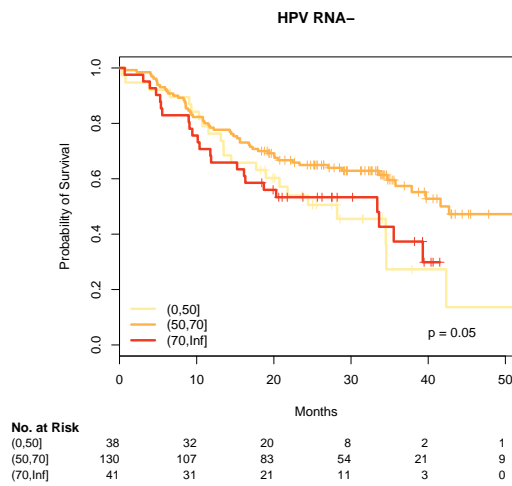
```

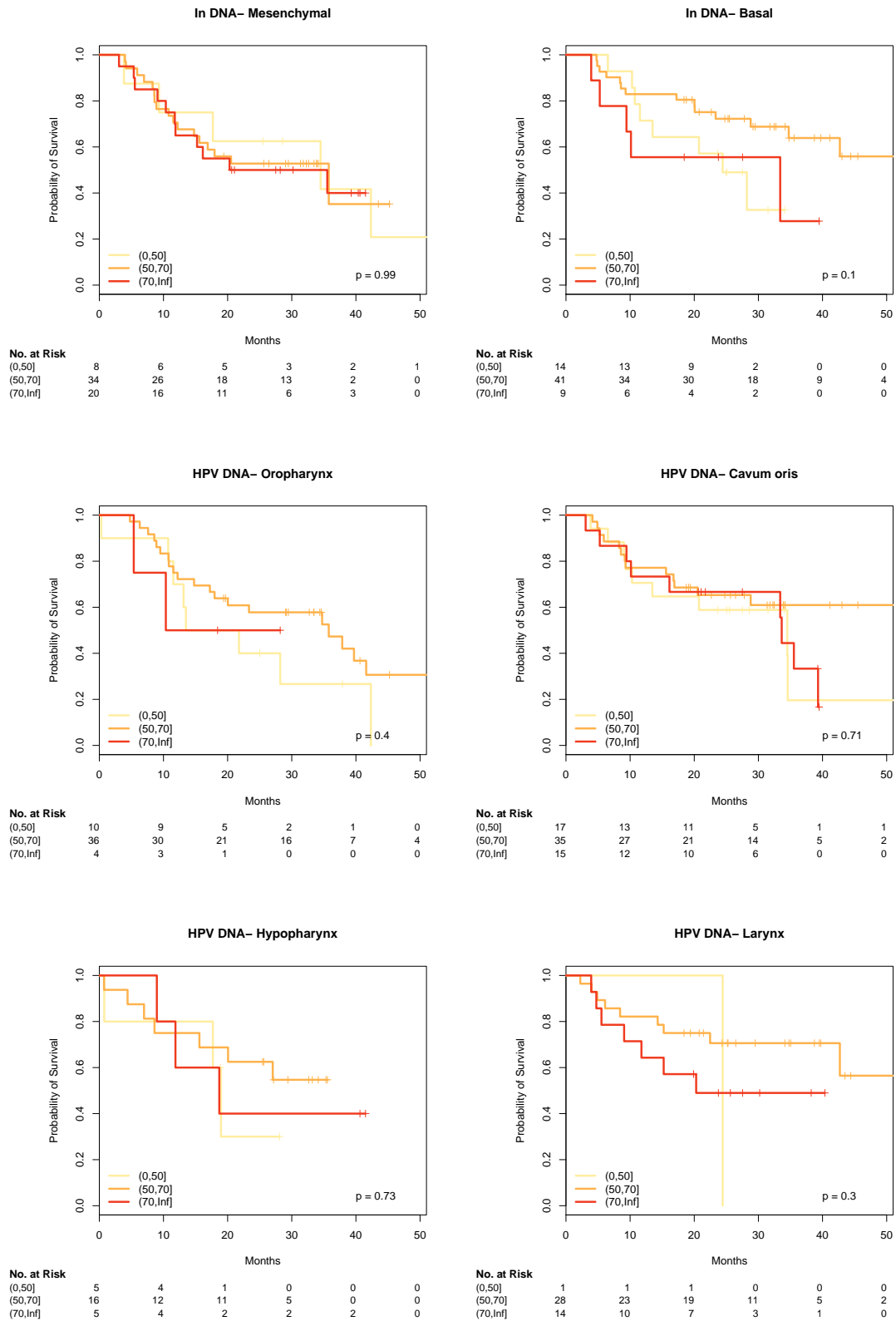
## Rsquare= 0.025 (max possible= 0.991 )
## Likelihood ratio test= 4.83 on 2 df, p=0.0895
## Wald test = 4.96 on 2 df, p=0.0839
## Score (logrank) test = 5.05 on 2 df, p=0.0802
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 101
##
## coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset](50,70) -0.49342 0.61053 0.25370 -1.94 0.052 .
## split[cur.subset](70,Inf] 0.00752 1.00755 0.29933 0.03 0.980
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70) 0.611 1.638 0.371 1.00
## split[cur.subset](70,Inf] 1.008 0.993 0.560 1.81
##
## Concordance= 0.552 (se = 0.026 )
## Rsquare= 0.028 (max possible= 0.99 )
## Likelihood ratio test= 5.87 on 2 df, p=0.0533
## Wald test = 6.01 on 2 df, p=0.0495
## Score (logrank) test = 6.13 on 2 df, p=0.0466
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## split[cur.subset]=(0,50]
## time n.risk n.event survival std.err
## 36.000 3.000 21.000 0.273 0.113
## lower 95% CI upper 95% CI
## 0.121 0.616
##
## split[cur.subset]=(50,70]
## time n.risk n.event survival std.err
## 36.0000 27.0000 50.0000 0.5740 0.0501
## lower 95% CI upper 95% CI
## 0.4837 0.6810
##
## split[cur.subset]=(70,Inf]
## time n.risk n.event survival std.err
## 36.0000 7.0000 22.0000 0.3733 0.0948
## lower 95% CI upper 95% CI

```

0.2269 0.6140







3.28 Age, Pack-years

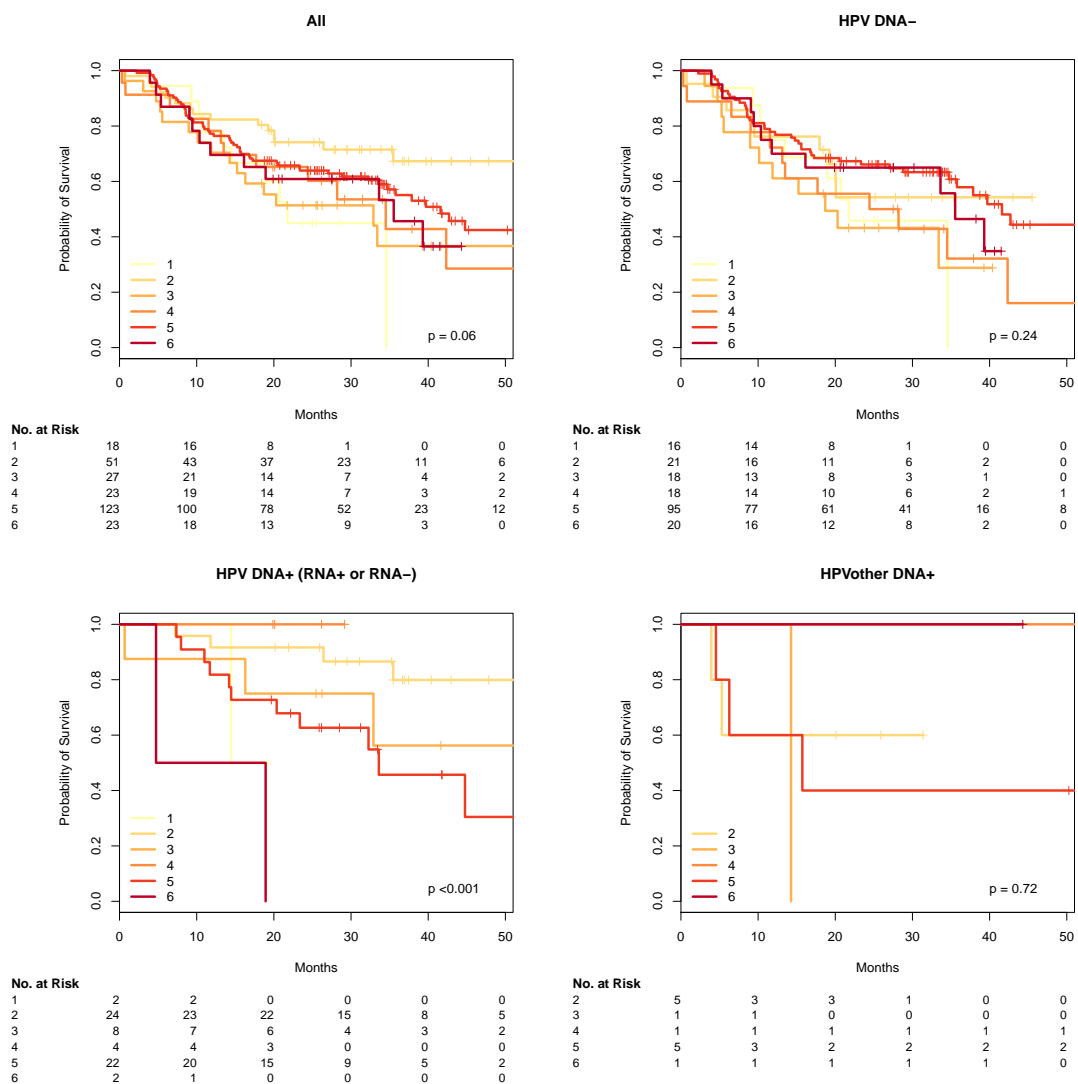
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 265, number of events= 125
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -1.0408    0.3532  0.4131 -2.52   0.012 *
## split[cur.subset]3 -0.0669    0.9353  0.4053 -0.17   0.869
## split[cur.subset]4 -0.2156    0.8061  0.4233 -0.51   0.611
## split[cur.subset]5 -0.4574    0.6329  0.3462 -1.32   0.186
## split[cur.subset]6 -0.2435    0.7839  0.4305 -0.57   0.572
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.353      2.83    0.157    0.794
## split[cur.subset]3      0.935      1.07    0.423    2.070
## split[cur.subset]4      0.806      1.24    0.352    1.848
## split[cur.subset]5      0.633      1.58    0.321    1.247
## split[cur.subset]6      0.784      1.28    0.337    1.823
##
## Concordance= 0.562 (se = 0.026 )
## Rsquare= 0.041 (max possible= 0.991 )
## Likelihood ratio test= 11.2 on 5 df, p=0.0478
## Wald test = 10.3 on 5 df, p=0.0683
## Score (logrank) test = 10.7 on 5 df, p=0.0574
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##               split[cur.subset]=1
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##               split[cur.subset]=2
##      time      n.risk      n.event      survival      std.err
##      36.0000      15.0000      15.0000      0.6729      0.0736
## lower 95% CI upper 95% CI
##      0.5431      0.8338
##
##               split[cur.subset]=3
##      time      n.risk      n.event      survival      std.err
##      36.000      5.000      15.000      0.367      0.112
## lower 95% CI upper 95% CI
##      0.202      0.667
```

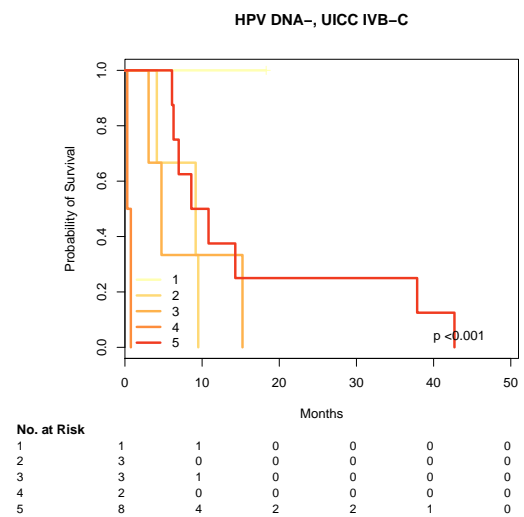
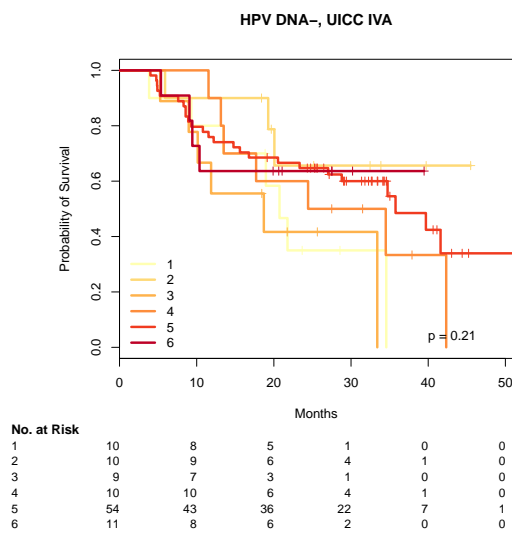
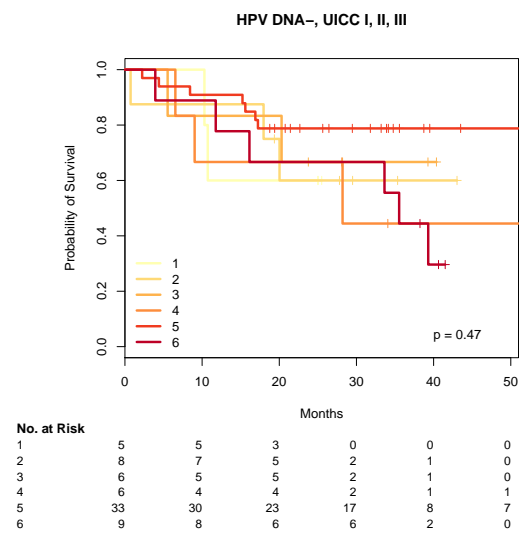
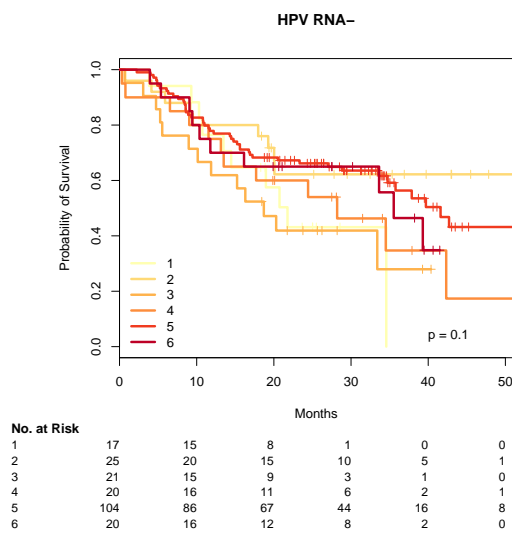
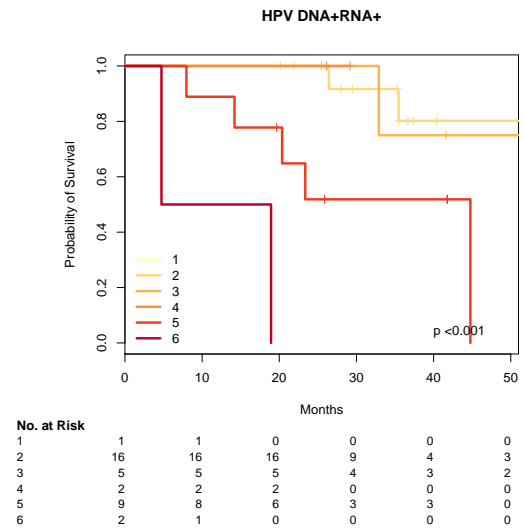
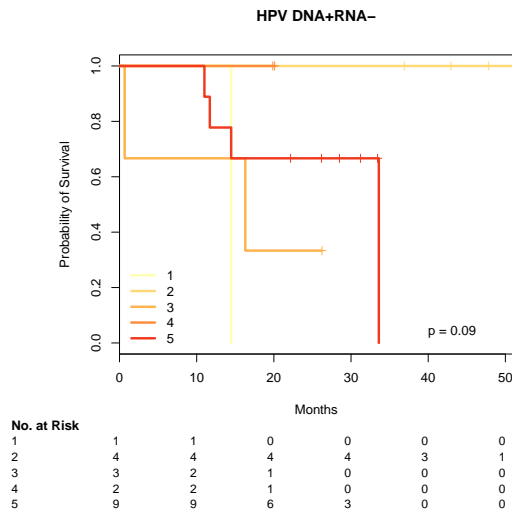
```
##
##               split[cur.subset]=4
##           time      n.risk      n.event      survival      std.err
##           36.000      4.000      11.000      0.428      0.131
## lower 95% CI upper 95% CI
##           0.235      0.779
##
##               split[cur.subset]=5
##           time      n.risk      n.event      survival      std.err
##           36.0000     27.0000     50.0000     0.5507      0.0513
## lower 95% CI upper 95% CI
##           0.4589      0.6610
##
##               split[cur.subset]=6
##           time      n.risk      n.event      survival      std.err
##           36.000      6.000      11.000      0.457      0.120
## lower 95% CI upper 95% CI
##           0.272      0.766
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 188, number of events= 93
##      (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.42945  0.65087  0.47352 -0.91  0.36
## split[cur.subset]3  0.15003  1.16187  0.45019  0.33  0.74
## split[cur.subset]4 -0.00329  0.99671  0.44488 -0.01  0.99
## split[cur.subset]5 -0.54109  0.58211  0.37291 -1.45  0.15
## split[cur.subset]6 -0.30583  0.73651  0.46239 -0.66  0.51
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2    0.651    1.536    0.257    1.65
## split[cur.subset]3    1.162    0.861    0.481    2.81
## split[cur.subset]4    0.997    1.003    0.417    2.38
## split[cur.subset]5    0.582    1.718    0.280    1.21
## split[cur.subset]6    0.737    1.358    0.298    1.82
##
## Concordance= 0.559 (se = 0.03 )
## Rsquare= 0.032 (max possible= 0.99 )
## Likelihood ratio test= 6.17 on 5 df, p=0.29
## Wald test = 6.51 on 5 df, p=0.259
## Score (logrank) test = 6.69 on 5 df, p=0.245
##
```

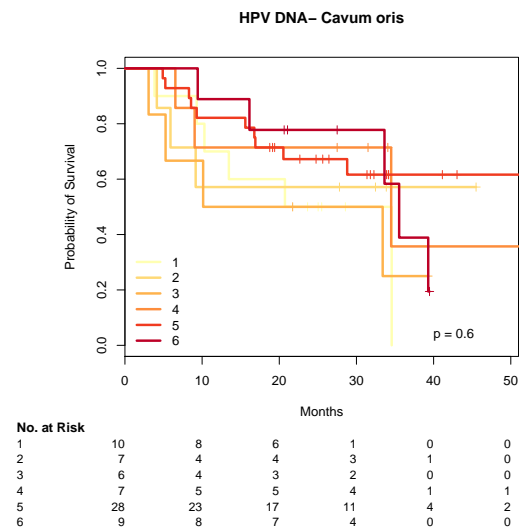
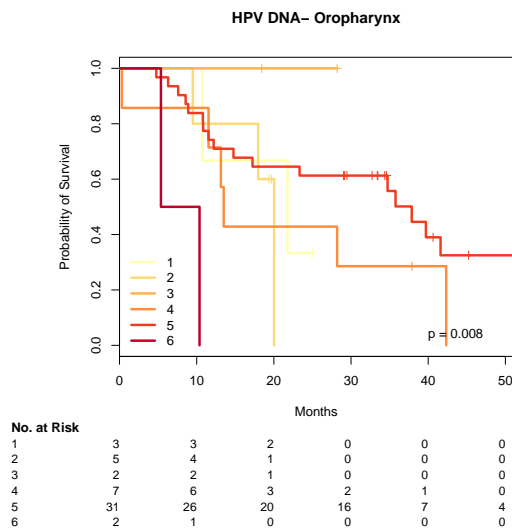
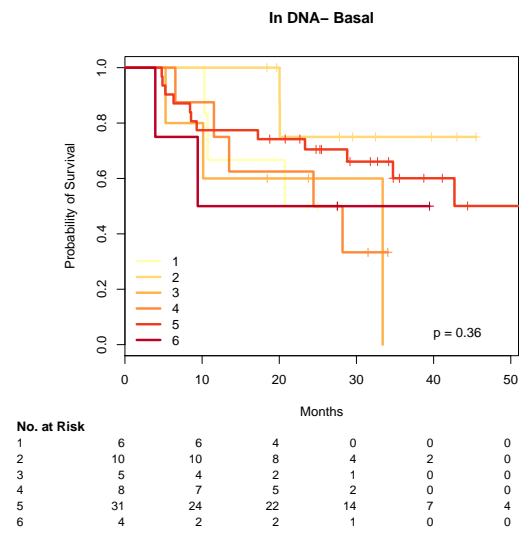
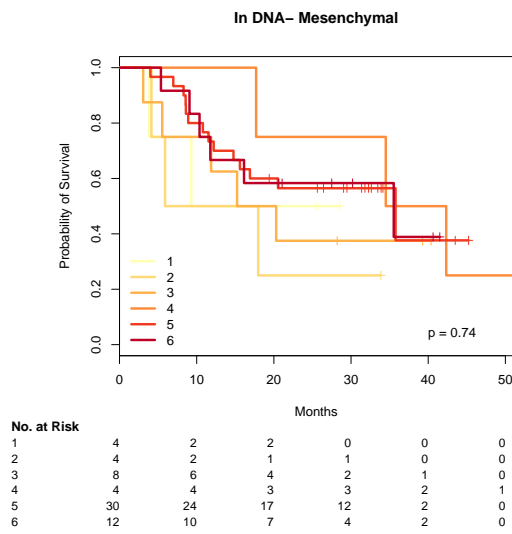
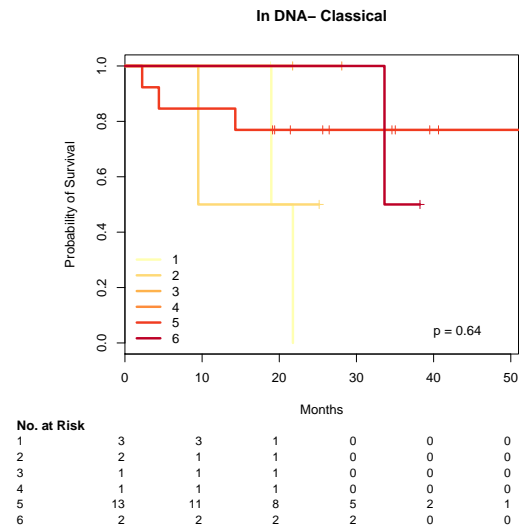
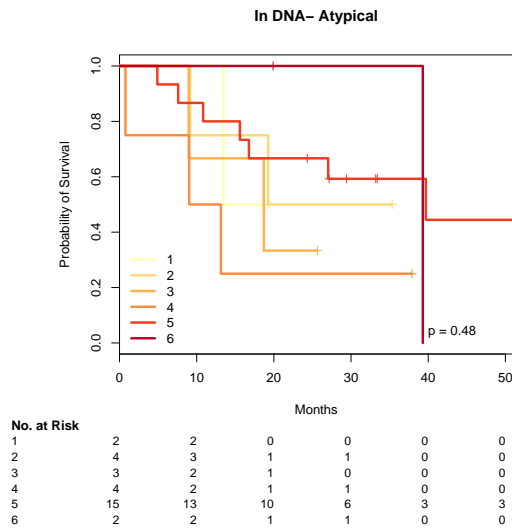


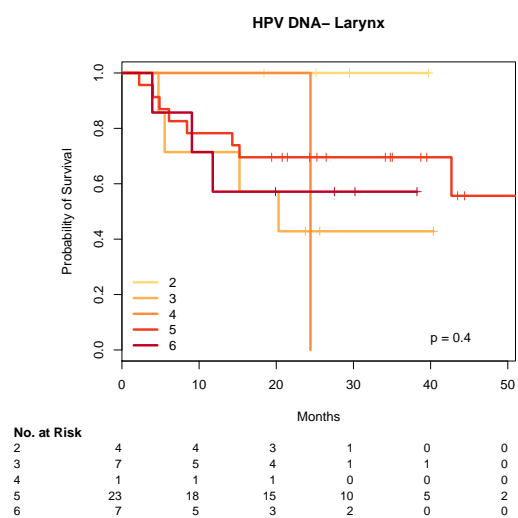
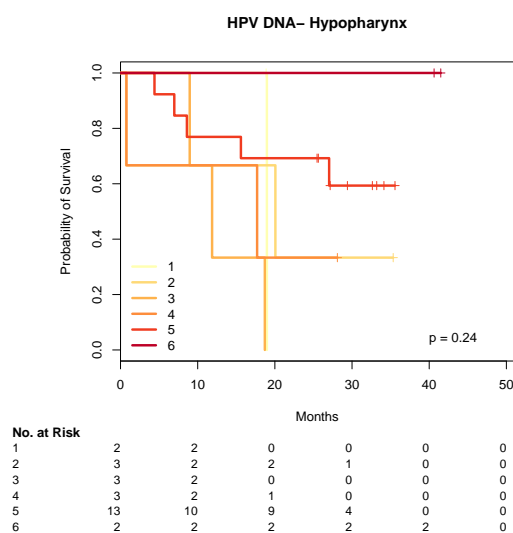
```
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 100
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.840    0.432    0.465 -1.81  0.071 .
## split[cur.subset]3  0.135    1.144    0.421  0.32  0.749
## split[cur.subset]4 -0.153    0.858    0.431 -0.36  0.722
## split[cur.subset]5 -0.580    0.560    0.354 -1.64  0.101
## split[cur.subset]6 -0.366    0.694    0.450 -0.81  0.416
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2    0.432    2.316    0.174    1.07
## split[cur.subset]3    1.144    0.874    0.501    2.61
## split[cur.subset]4    0.858    1.166    0.369    2.00
## split[cur.subset]5    0.560    1.785    0.280    1.12
## split[cur.subset]6    0.694    1.442    0.287    1.68
##
## Concordance= 0.564 (se = 0.029 )
## Rsquare= 0.04 (max possible= 0.99 )
## Likelihood ratio test= 8.52 on 5 df, p=0.13
## Wald test = 8.91 on 5 df, p=0.113
## Score (logrank) test = 9.24 on 5 df, p=0.0999
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##               split[cur.subset]=1
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI
##
##               split[cur.subset]=2
##      time      n.risk      n.event      survival      std.err
##      36.000        7.000        9.000        0.622        0.101
## lower 95% CI upper 95% CI
##      0.453        0.854
##
##               split[cur.subset]=3
##      time      n.risk      n.event      survival      std.err
##      36.000        2.000       13.000        0.279        0.135
## lower 95% CI upper 95% CI
```

```
##      0.108      0.722
##
##      split[cur.subset]=4
##      time      n.risk      n.event      survival      std.err
##      36.000      3.000      11.000      0.347      0.135
## lower 95% CI upper 95% CI
##      0.162      0.745
##
##      split[cur.subset]=5
##      time      n.risk      n.event      survival      std.err
##      36.0000      20.0000      40.0000      0.5636      0.0585
## lower 95% CI upper 95% CI
##      0.4599      0.6906
##
##      split[cur.subset]=6
##      time      n.risk      n.event      survival      std.err
##      36.000      5.000      9.000      0.464      0.135
## lower 95% CI upper 95% CI
##      0.263      0.820
```

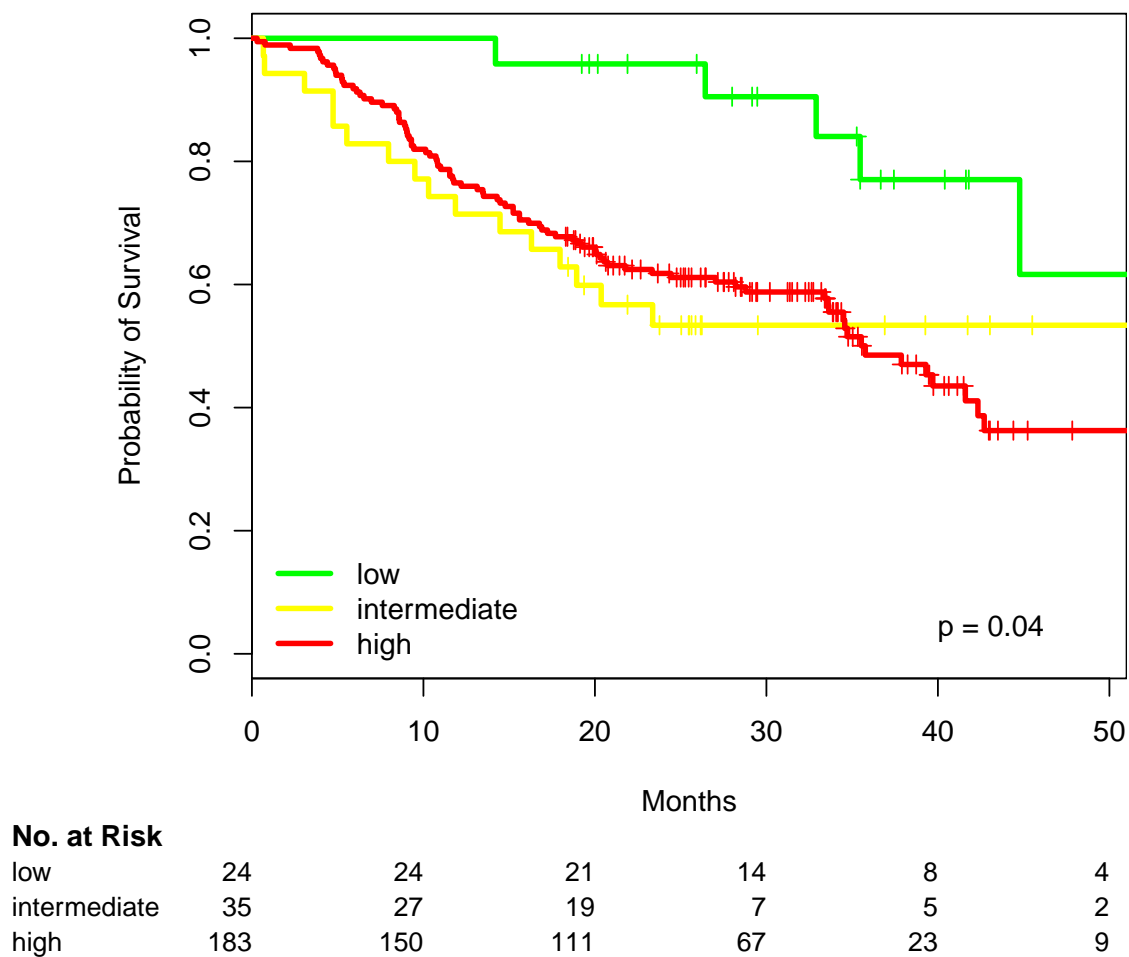


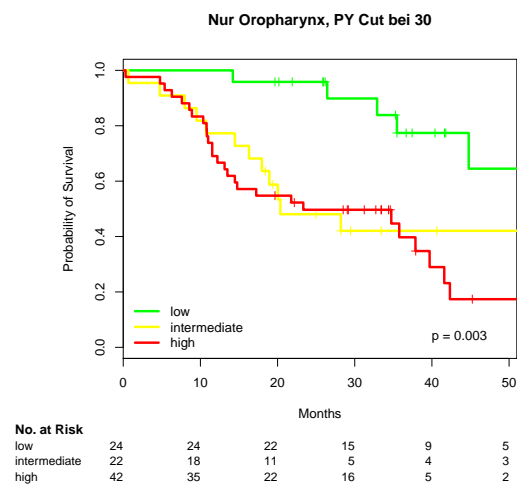
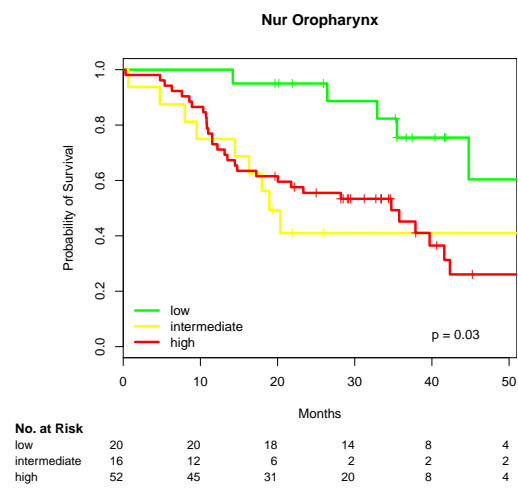
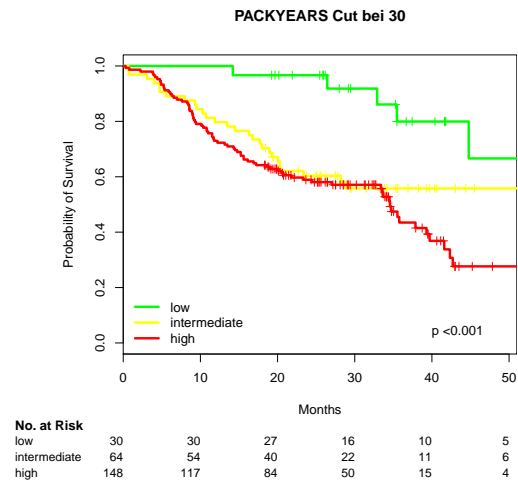






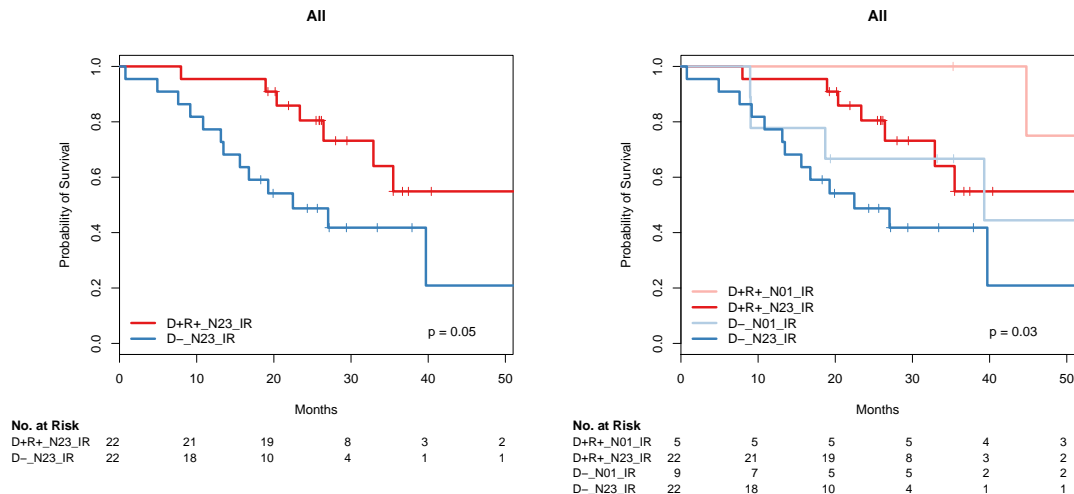
3.29 Risk groups according to Ang et al. Instead of p16+ (immunohisto) HPV16 DNA+RNA+ status is used.





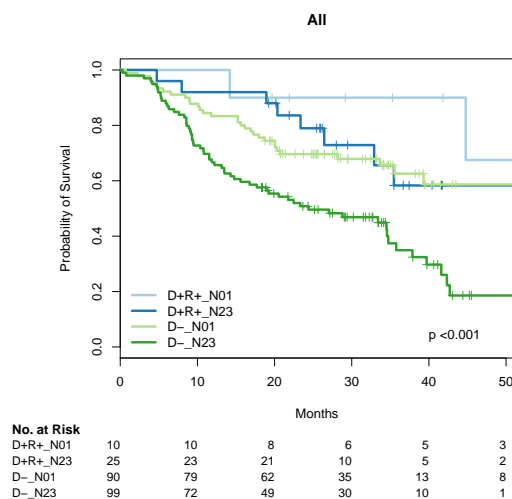
4 Question of whether the lymph node metastases in HPV- and in HPV+ are different.

4.1 2 groups, in which die lymph node metastases co-occur with HPV (DNA+ RNA+) or IR (immune response phenotype).



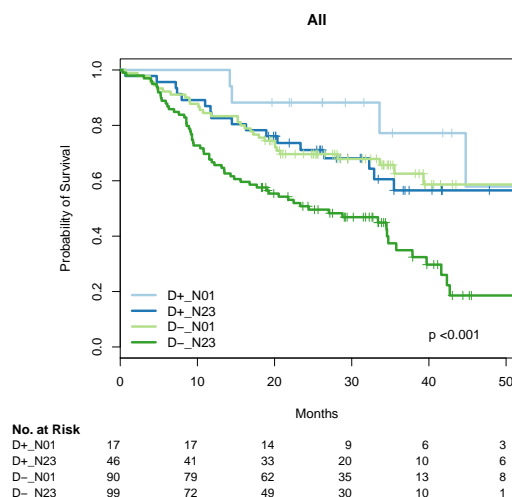
4.2 Interaction of HPV16 DNA RNA status with N0-N1

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 224, number of events= 105
## (43 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+R+_N23 0.953    2.593   0.785 1.21  0.225
## split[cur.subset]D-_N01   1.037    2.821   0.731 1.42  0.156
## split[cur.subset]D-_N23   1.826    6.210   0.725 2.52  0.012 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]D+R+_N23    2.59    0.386    0.556    12.1
## split[cur.subset]D-_N01     2.82    0.355    0.673    11.8
## split[cur.subset]D-_N23     6.21    0.161    1.500    25.7
##
## Concordance= 0.618 (se = 0.028 )
## Rsquare= 0.094 (max possible= 0.989 )
## Likelihood ratio test= 22.2 on 3 df,  p=6.01e-05
## Wald test               = 19.9 on 3 df,  p=0.000182
## Score (logrank) test = 21.8 on 3 df,  p=7.36e-05
```

4.3 Interaction of HPV16 (DNA only) and N0-N1

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 252, number of events= 118
##   (15 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 0.701      2.016   0.552 1.27   0.2039
## split[cur.subset]D-_N01 0.685      1.984   0.530 1.29   0.1964
## split[cur.subset]D-_N23 1.461      4.310   0.519 2.82   0.0049 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]D+_N23      2.02      0.496   0.683   5.95
## split[cur.subset]D-_N01      1.98      0.504   0.702   5.61
## split[cur.subset]D-_N23      4.31      0.232   1.559  11.91
##
## Concordance= 0.606 (se = 0.027 )
## Rsquare= 0.082 (max possible= 0.99 )
## Likelihood ratio test= 21.7 on 3 df, p=7.6e-05
## Wald test               = 20.6 on 3 df, p=0.000128
## Score (logrank) test = 22.2 on 3 df, p=6.06e-05
```



4.3.1 HPV16 DNA RNA (without DNA+RNA-), N0-N1 vs. higher N, Cox model.

```
cur.subset <- is.primary
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_extremes + N_2CAT, data = ds[cur.subset, ])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_extremes + N_2CAT,
##       data = ds[cur.subset, ])
##
##      n= 224, number of events= 105
##      (43 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_extremesDNA+RNA+ -0.907    0.404   0.322 -2.82  0.00485 **
## N_2CATN2-N3           0.801    2.228   0.212  3.78  0.00016 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_extremesDNA+RNA+  0.404      2.476    0.215    0.759
## N_2CATN2-N3            2.228      0.449    1.471    3.375
##
## Concordance= 0.618 (se = 0.028 )
## Rsquare= 0.094 (max possible= 0.989 )
## Likelihood ratio test= 22.1 on 2 df,  p=1.57e-05
## Wald test               = 20.2 on 2 df,  p=4.11e-05
## Score (logrank) test = 21.1 on 2 df,  p=2.65e-05
```

4.3.2 HPV16 DNA RNA (without DNA+RNA-), N0-N1 vs. higher N, Cox model with interaction

```
cur.subset <- is.primary
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_extremes * N_2CAT, data = ds[cur.subset,
])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_extremes * N_2CAT,
##       data = ds[cur.subset, ])
##
##      n= 224, number of events= 105
##      (43 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z
## HPV16_extremesDNA+RNA+      -1.037    0.355    0.731 -1.42
## N_2CATN2-N3                0.789    2.202    0.220  3.59
## HPV16_extremesDNA+RNA+:N_2CATN2-N3  0.164    1.178    0.812  0.20
##
##              Pr(>|z|)
## HPV16_extremesDNA+RNA+      0.15598
## N_2CATN2-N3                0.00033 ***
## HPV16_extremesDNA+RNA+:N_2CATN2-N3  0.84018
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## HPV16_extremesDNA+RNA+      0.355    2.821    0.0846
## N_2CATN2-N3                2.202    0.454    1.4315
## HPV16_extremesDNA+RNA+:N_2CATN2-N3  1.178    0.849    0.2397
##
##              upper .95
## HPV16_extremesDNA+RNA+      1.49
## N_2CATN2-N3                3.39
## HPV16_extremesDNA+RNA+:N_2CATN2-N3  5.79
##
## Concordance= 0.618 (se = 0.028 )
## Rsquare= 0.094 (max possible= 0.989 )
## Likelihood ratio test= 22.2 on 3 df,  p=6.01e-05
## Wald test              = 19.9 on 3 df,  p=0.000182
## Score (logrank) test = 21.8 on 3 df,  p=7.36e-05
```

4.4 IR (Immune Response) Consensus Cluster (also called Atypical here)

```

## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 253, number of events= 117
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical -0.184    0.832    0.210 -0.88    0.38
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical    0.832      1.2    0.551    1.25
##
## Concordance= 0.528 (se = 0.023 )
## Rsquare= 0.003 (max possible= 0.99 )
## Likelihood ratio test= 0.79 on 1 df, p=0.373
## Wald test = 0.77 on 1 df, p=0.379
## Score (logrank) test = 0.78 on 1 df, p=0.379
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 14 observations deleted due to missingness
##               split[cur.subset]=Not Atypical
##           time      n.risk      n.event      survival      std.err
##      36.0000    32.0000    80.0000    0.4931    0.0457
## lower 95% CI upper 95% CI
##      0.4111    0.5914
##
##               split[cur.subset]=Atypical
##           time      n.risk      n.event      survival      std.err
##      36.0000    19.0000    26.0000    0.5814    0.0662
## lower 95% CI upper 95% CI
##      0.4651    0.7267
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 179, number of events= 86
## (12 observations deleted due to missingness)

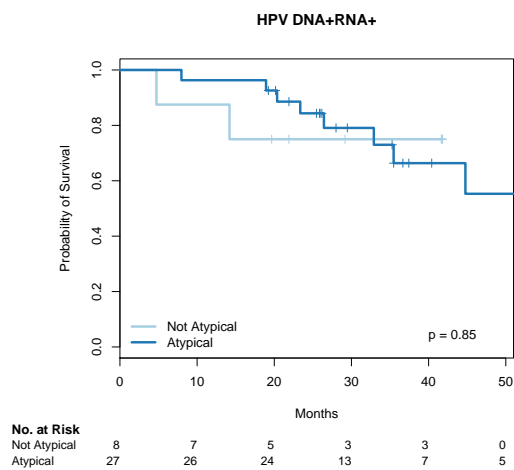
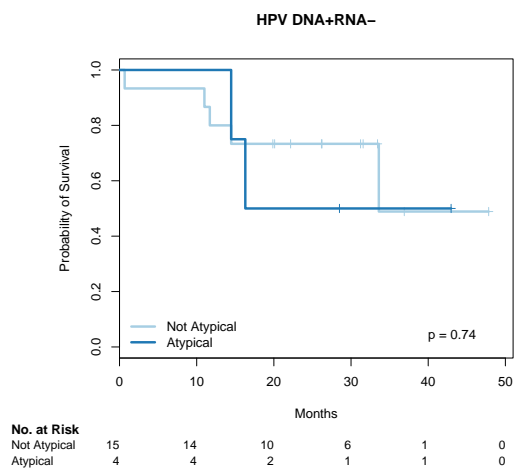
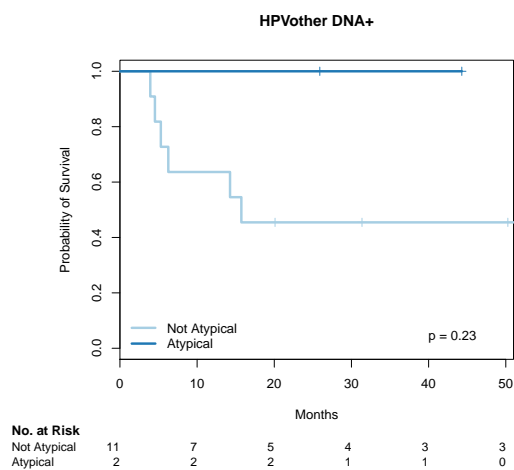
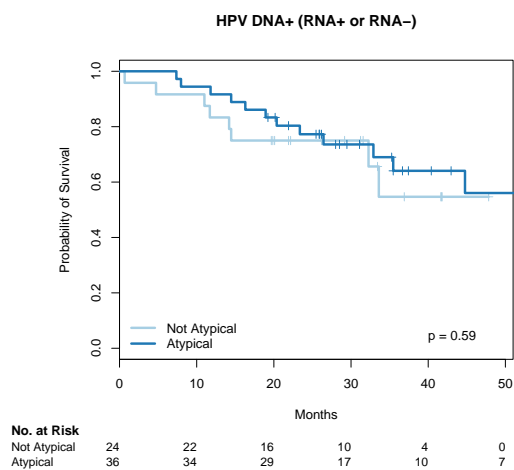
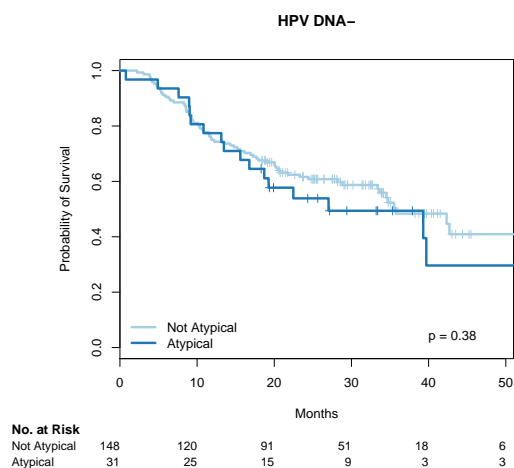
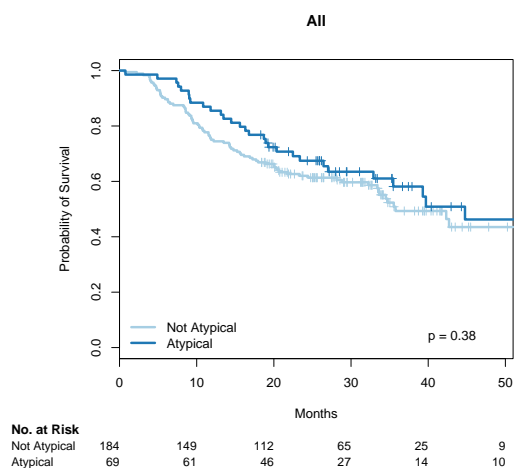
```

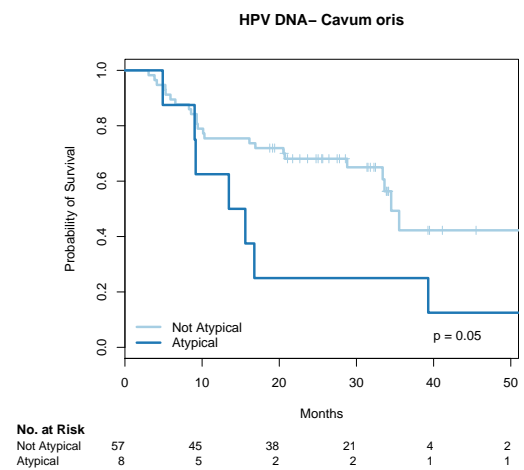
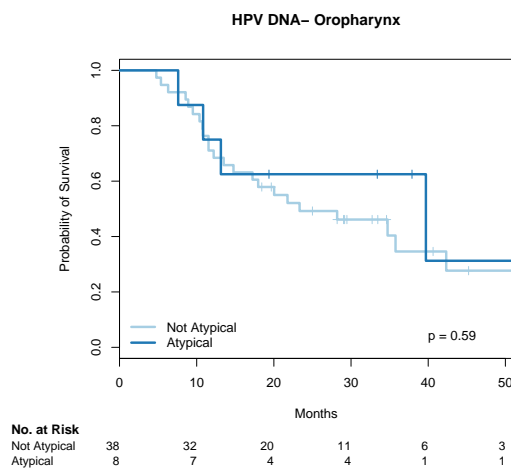
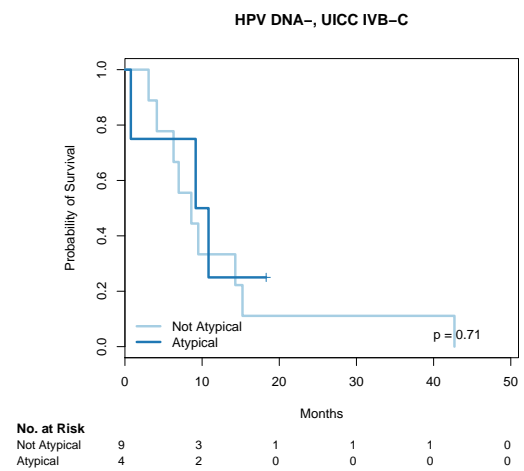
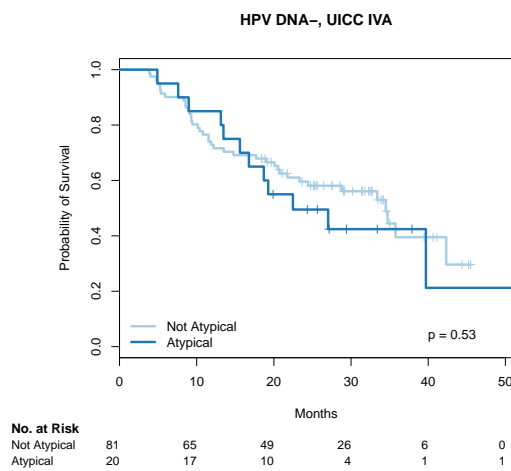
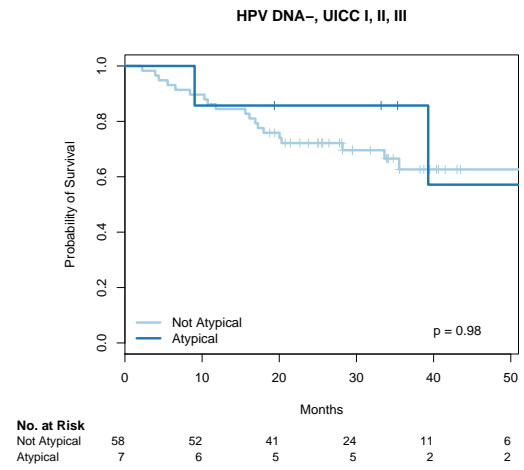
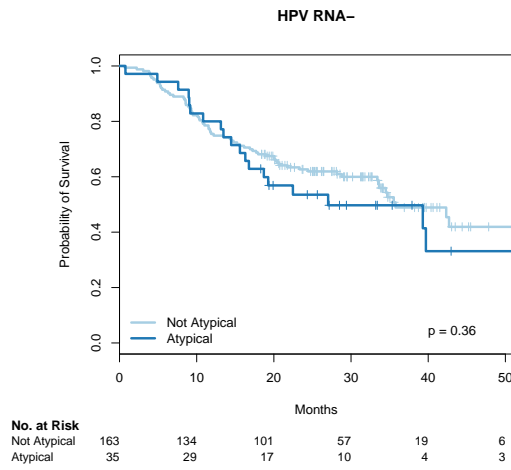
```
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical 0.235      1.265      0.266 0.88      0.38
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical      1.26      0.791      0.751      2.13
##
## Concordance= 0.512 (se = 0.022 )
## Rsquare= 0.004 (max possible= 0.989 )
## Likelihood ratio test= 0.75 on 1 df, p=0.388
## Wald test = 0.78 on 1 df, p=0.377
## Score (logrank) test = 0.79 on 1 df, p=0.375
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 198, number of events= 93
## (11 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical 0.231      1.260      0.253 0.91      0.36
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical      1.26      0.794      0.767      2.07
##
## Concordance= 0.513 (se = 0.021 )
## Rsquare= 0.004 (max possible= 0.989 )
## Likelihood ratio test= 0.8 on 1 df, p=0.372
## Wald test = 0.83 on 1 df, p=0.361
## Score (logrank) test = 0.84 on 1 df, p=0.36
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 11 observations deleted due to missingness
##               split[cur.subset]=Not Atypical
##               time      n.risk      n.event      survival      std.err
##               36.0000      26.0000      70.0000      0.4890      0.0503
## lower 95% CI upper 95% CI
##               0.3998      0.5982
##
##               split[cur.subset]=Atypical
##               time      n.risk      n.event      survival      std.err
##               36.0000      7.0000      17.0000      0.4970      0.0876
## lower 95% CI upper 95% CI
```

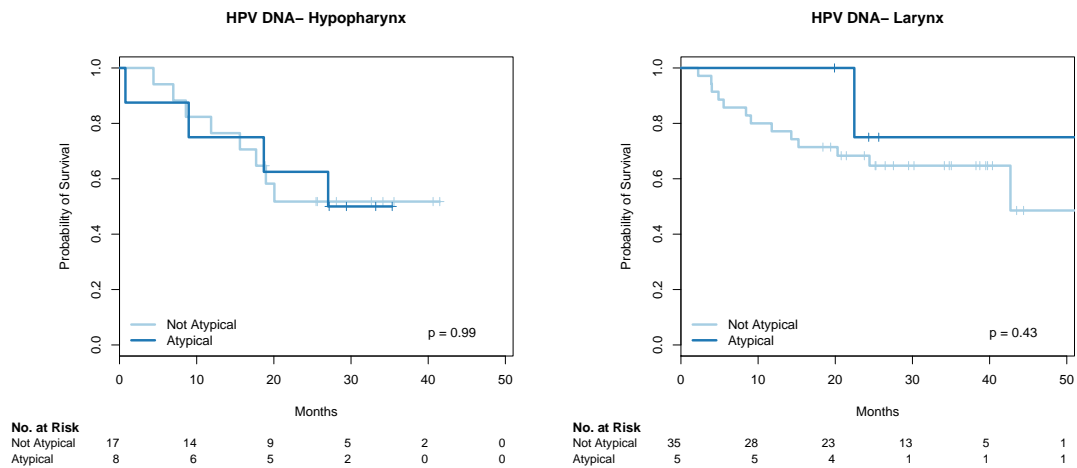
##

0.3518

0.7021







4.5 Interaction of N0-N1 vs. higher N, and IR (Atypical)

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 253, number of events= 117
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N23_  0.8737    2.3959  0.2306  3.79  0.00015 ***
## split[cur.subset]N01_IR -0.0658    0.9363  0.4254 -0.15  0.87712
## split[cur.subset]N23_IR  0.4120    1.5098  0.2740  1.50  0.13271
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N23_    2.396    0.417    1.525    3.76
## split[cur.subset]N01_IR    0.936    1.068    0.407    2.16
## split[cur.subset]N23_IR    1.510    0.662    0.882    2.58
##
## Concordance= 0.608 (se = 0.027 )
## Rsquare= 0.066 (max possible= 0.99 )
## Likelihood ratio test= 17.4 on 3 df,  p=0.000593
## Wald test               = 17 on 3 df,  p=0.000699
## Score (logrank) test = 17.9 on 3 df,  p=0.00045
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 14 observations deleted due to missingness
```



```

##               split[cur.subset]=N01_
##           time      n.risk      n.event      survival      std.err
##       36.0000      17.0000      28.0000          0.6324      0.0636
## lower 95% CI upper 95% CI
##       0.5193      0.7701
##
##               split[cur.subset]=N23_
##           time      n.risk      n.event      survival      std.err
##       36.0000      15.0000      52.0000          0.3667      0.0602
## lower 95% CI upper 95% CI
##       0.2658      0.5060
##
##               split[cur.subset]=N01_IR
##           time      n.risk      n.event      survival      std.err
##       36.000      9.000      4.000          0.765      0.103
## lower 95% CI upper 95% CI
##       0.587      0.995
##
##               split[cur.subset]=N23_IR
##           time      n.risk      n.event      survival      std.err
##       36.0000      10.0000      22.0000          0.4984      0.0844
## lower 95% CI upper 95% CI
##       0.3576      0.6946
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 179, number of events= 86
##      (12 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N23_  0.889      2.434      0.252 3.52 0.00043 ***
## split[cur.subset]N01_IR 0.378      1.459      0.492 0.77 0.44246
## split[cur.subset]N23_IR 0.825      2.282      0.342 2.42 0.01568 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N23_      2.43      0.411      1.484      3.99
## split[cur.subset]N01_IR      1.46      0.685      0.556      3.83
## split[cur.subset]N23_IR      2.28      0.438      1.169      4.46
##
## Concordance= 0.599 (se = 0.031 )
## Rsquare= 0.077 (max possible= 0.989 )
## Likelihood ratio test= 14.3 on 3 df,  p=0.00252

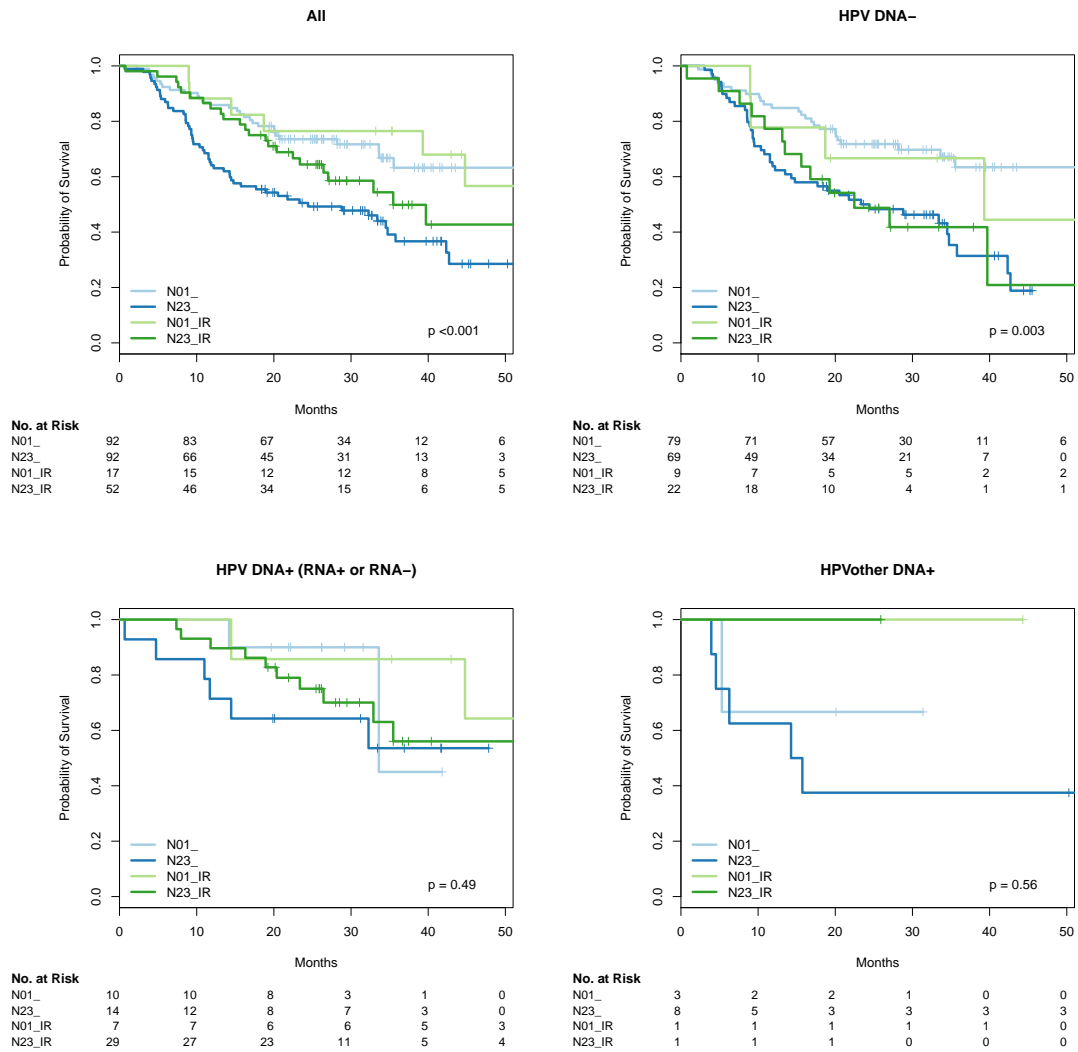
```

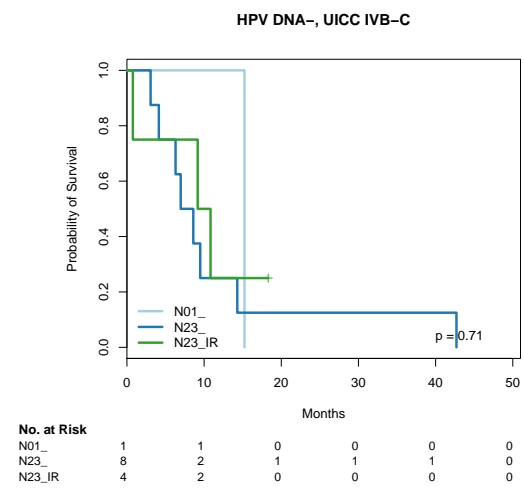
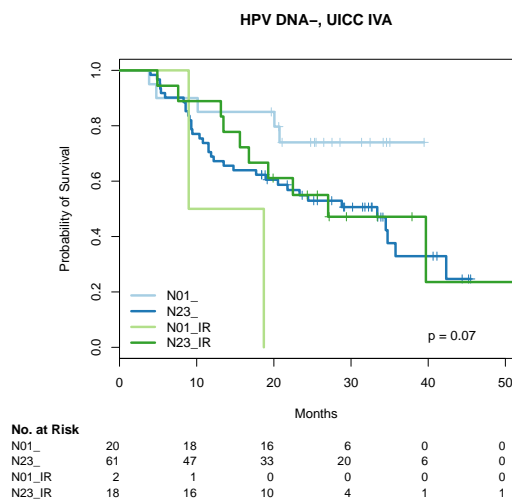
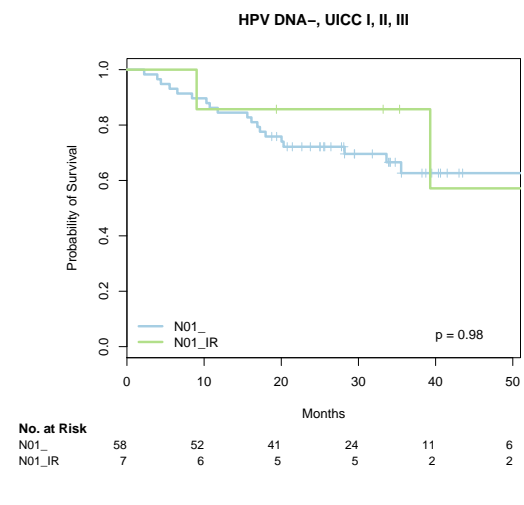
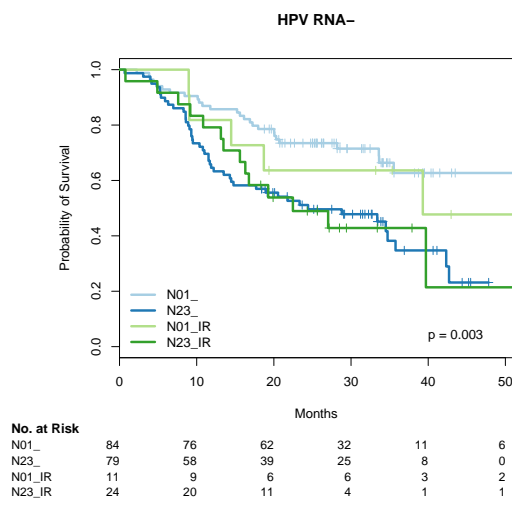
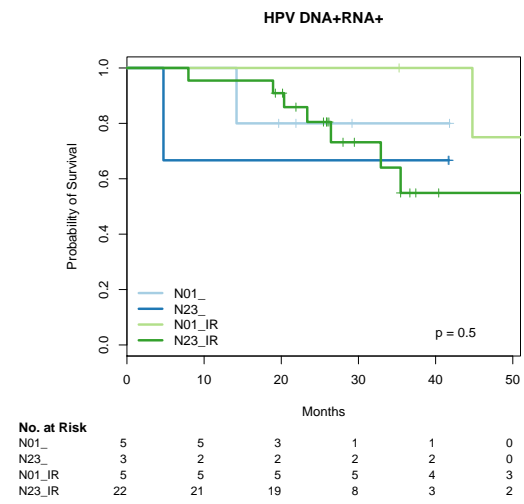
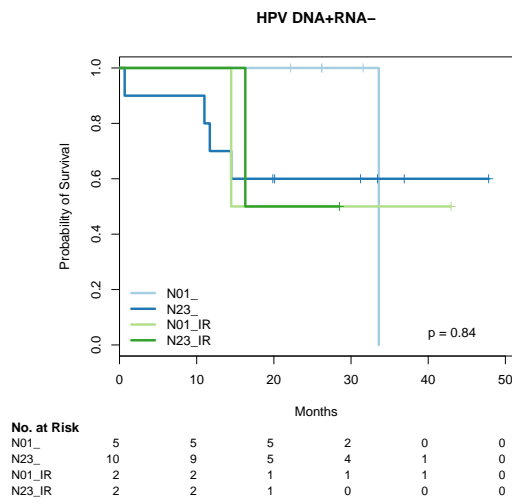
```

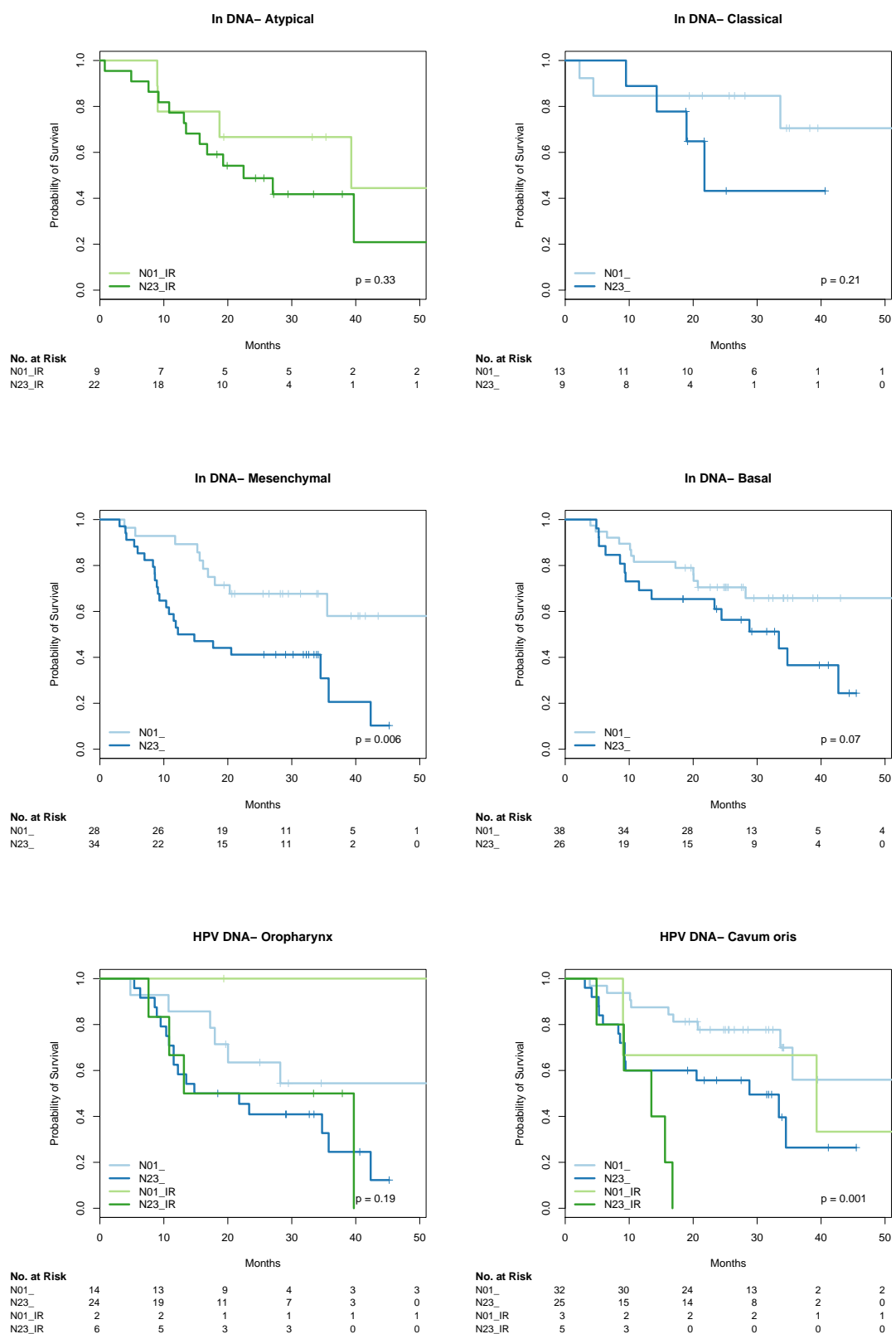
## Wald test          = 13.4  on 3 df,    p=0.00393
## Score (logrank) test = 14.2  on 3 df,    p=0.0027
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 198, number of events= 93
##    (11 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N23_  0.864    2.372    0.245  3.52  0.00043 ***
## split[cur.subset]N01_IR 0.387    1.472    0.454  0.85  0.39452
## split[cur.subset]N23_IR 0.834    2.303    0.331  2.52  0.01177 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N23_    2.37    0.422    1.467    3.84
## split[cur.subset]N01_IR    1.47    0.679    0.604    3.59
## split[cur.subset]N23_IR    2.30    0.434    1.203    4.41
##
## Concordance= 0.601 (se = 0.03 )
## Rsquare= 0.071 (max possible= 0.989 )
## Likelihood ratio test= 14.6  on 3 df,    p=0.00221
## Wald test          = 13.5  on 3 df,    p=0.00361
## Score (logrank) test = 14.3  on 3 df,    p=0.00251
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 11 observations deleted due to missingness
##              split[cur.subset]=N01_
##              time      n.risk      n.event      survival      std.err
##              36.0000      16.0000      26.0000      0.6270      0.0662
## lower 95% CI upper 95% CI
##              0.5098      0.7711
##
##              split[cur.subset]=N23_
##              time      n.risk      n.event      survival      std.err
##              36.0000      10.0000      44.0000      0.3474      0.0704
## lower 95% CI upper 95% CI
##              0.2335      0.5168
##
##              split[cur.subset]=N01_IR
##              time      n.risk      n.event      survival      std.err

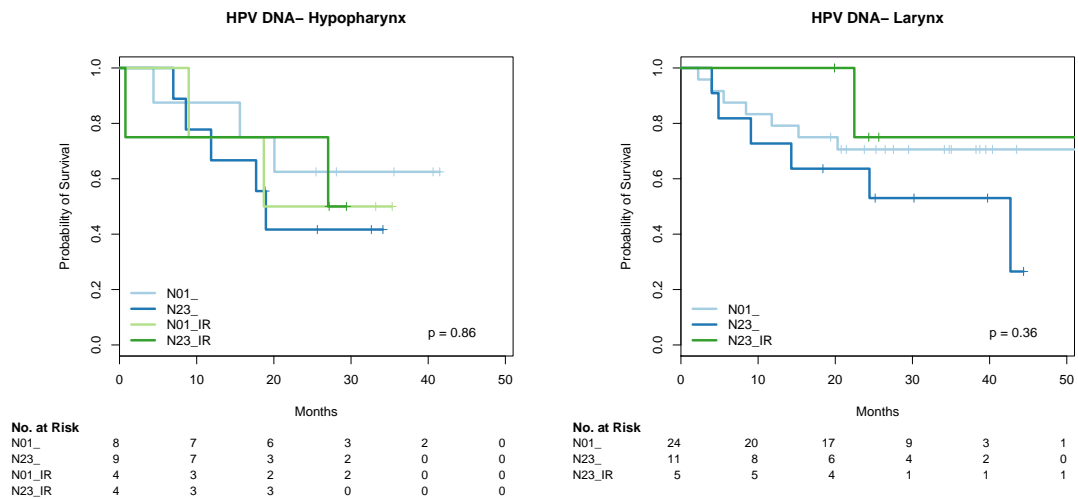
```

```
##          36.000          4.000          4.000          0.636          0.145
## lower 95% CI upper 95% CI
##          0.407          0.995
##
##          split[cur.subset]=N23_IR
##          time          n.risk          n.event          survival          std.err
##          36.000          3.000          13.000          0.428          0.108
## lower 95% CI upper 95% CI
##          0.262          0.701
```









4.5.1 In HPV DNA-. Cox model with IR, N0-N1

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB)
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT + IS_ATYPICAL, data = ds[cur.subset,
])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT + IS_ATYPICAL,
##       data = ds[cur.subset, ])
##
##      n= 179, number of events= 86
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.8172   2.2641  0.2322  3.52  0.00043 ***
## IS_ATYPICALatypical 0.0535   1.0549  0.2696  0.20  0.84279
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3           2.26      0.442    1.436      3.57
## IS_ATYPICALatypical    1.05      0.948    0.622      1.79
##
## Concordance= 0.593 (se = 0.031 )
## Rsquare= 0.074 (max possible= 0.989 )
## Likelihood ratio test= 13.8 on 2 df,  p=0.00103
## Wald test               = 13 on 2 df,  p=0.00148
## Score (logrank) test = 13.8 on 2 df,  p=0.00103
```

4.5.2 In HPV DNA-. Cox model with IR, N0-N1, and interaction

```

cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB)
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT * IS_ATYPICAL, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT * IS_ATYPICAL,
##       data = ds[cur.subset, ])
##
##      n= 179, number of events= 86
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3          0.889    2.434    0.252   3.52  0.00043
## IS_ATYPICALatypical    0.378    1.459    0.492   0.77  0.44246
## N_2CATN2-N3:IS_ATYPICALatypical -0.442    0.643    0.585  -0.76  0.45008
##
## N_2CATN2-N3          ***
## IS_ATYPICALatypical
## N_2CATN2-N3:IS_ATYPICALatypical
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3          2.434    0.411    1.484    3.99
## IS_ATYPICALatypical    1.459    0.685    0.556    3.83
## N_2CATN2-N3:IS_ATYPICALatypical 0.643    1.556    0.204    2.02
##
## Concordance= 0.599 (se = 0.031 )
## Rsquare= 0.077 (max possible= 0.989 )
## Likelihood ratio test= 14.3 on 3 df,  p=0.00252
## Wald test              = 13.4 on 3 df,  p=0.00393
## Score (logrank) test = 14.2 on 3 df,  p=0.0027

```

5 Multivariate models

5.1 In all patients

5.1.1 UICC stages, 1,2,3 vs. 4a vs. 4b,4c

```

cur.subset <- is.primary
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT, data = ds[cur.subset,

```

```
##      ])
```

```
##
```

```
##      n= 267, number of events= 126
```

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
UICC_3CATIVA	0.539	1.714	0.222	2.42	0.015 *
UICC_3CATIVB-C	1.488	4.429	0.287	5.19	2.1e-07 ***

```
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
UICC_3CATIVA	1.71	0.584	1.11	2.65
UICC_3CATIVB-C	4.43	0.226	2.52	7.77

```
##
```

```
## Concordance= 0.605 (se = 0.024 )
```

```
## Rsquare= 0.086 (max possible= 0.991 )
```

```
## Likelihood ratio test= 24 on 2 df, p=6.11e-06
```

```
## Wald test = 27.3 on 2 df, p=1.18e-06
```

```
## Score (logrank) test = 30.4 on 2 df, p=2.55e-07
```

```
cox.zph(surv.res)
```

```
##
```

	rho	chisq	p
UICC_3CATIVA	-0.00302	0.00113	0.973
UICC_3CATIVB-C	-0.06914	0.57784	0.447
GLOBAL	NA	0.80855	0.667

5.1.2 HPV16 DNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA, data = ds[cur.subset, ])
summary(surv.res)
```

```
## Call:
```

```
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA, data = ds[cur.subset,
```

```
##      ])
```

```
##
```

```
##      n= 244, number of events= 112
```

```
##      (23 observations deleted due to missingness)
```

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
HPV16_DNADNA+	-0.648	0.523	0.258	-2.51	0.012 *

```
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
HPV16_DNADNA+	0.523	1.91	0.315	0.868

```
##
```



```
## Concordance= 0.557 (se = 0.022 )
## Rsquare= 0.029 (max possible= 0.989 )
## Likelihood ratio test= 7.24 on 1 df, p=0.00713
## Wald test = 6.3 on 1 df, p=0.0121
## Score (logrank) test = 6.52 on 1 df, p=0.0107

cox.zph(surv.res)

## rho chisq p
## HPV16_DNADNA+ 0.0892 0.873 0.35
```

5.1.3 UICC, HPV16 DNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA,
## data = ds[cur.subset, ])
##
## n= 244, number of events= 112
## (23 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 0.590 1.803 0.232 2.54 0.0110 *
## UICC_3CATIVB-C 1.808 6.100 0.303 5.96 2.5e-09 ***
## HPV16_DNADNA+ -0.841 0.431 0.261 -3.22 0.0013 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 1.803 0.555 1.145 2.84
## UICC_3CATIVB-C 6.100 0.164 3.366 11.06
## HPV16_DNADNA+ 0.431 2.318 0.258 0.72
##
## Concordance= 0.635 (se = 0.028 )
## Rsquare= 0.143 (max possible= 0.989 )
## Likelihood ratio test= 37.6 on 3 df, p=3.39e-08
## Wald test = 41.6 on 3 df, p=4.78e-09
## Score (logrank) test = 45.9 on 3 df, p=6.11e-10

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA 0.0717 0.5747 0.448
## UICC_3CATIVB-C -0.0102 0.0114 0.915
## HPV16_DNADNA+ 0.0967 1.0287 0.310
## GLOBAL NA 1.9516 0.583
```

5.1.4 HPV16 DNA RNA

```
# cur.subset <- is.primary & ds$LOKALISATION_GROB_TEXT %in%
# c('oropharynx')
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA, data = ds[cur.subset,
##      ])
##
##      n= 244, number of events= 112
##      (23 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.452    0.637    0.392 -1.15    0.249
## HPV16_DNA_RNADNA+RNA+ -0.756    0.469    0.320 -2.36    0.018 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.637      1.57    0.295    1.373
## HPV16_DNA_RNADNA+RNA+    0.469      2.13    0.251    0.879
##
## Concordance= 0.56 (se = 0.022 )
## Rsquare= 0.031 (max possible= 0.989 )
## Likelihood ratio test= 7.63 on 2 df,  p=0.0221
## Wald test               = 6.5 on 2 df,  p=0.0389
## Score (logrank) test = 6.77 on 2 df,  p=0.034

cox.zph(surv.res)

##              rho chisq      p
## HPV16_DNA_RNADNA+RNA- -0.0249 0.0694 0.792
## HPV16_DNA_RNADNA+RNA+  0.1449 2.2645 0.132
## GLOBAL                  NA 2.4197 0.298
```

5.1.5 UICC, HPV16 DNA RNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA, data = ds[cur.sub
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA,
##      data = ds[cur.subset, ])
##
```

```
##
## n= 244, number of events= 112
## (23 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.587    1.798    0.232  2.53  0.0113 *
## UICC_3CATIVB-C      1.805    6.079    0.303  5.95  2.7e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.677    0.508    0.395 -1.71  0.0870 .
## HPV16_DNA_RNADNA+RNA+ -0.932    0.394    0.322 -2.90  0.0038 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.798    0.556    1.142    2.83
## UICC_3CATIVB-C      6.079    0.164    3.354   11.02
## HPV16_DNA_RNADNA+RNA-  0.508    1.967    0.234    1.10
## HPV16_DNA_RNADNA+RNA+  0.394    2.540    0.210    0.74
##
## Concordance= 0.637 (se = 0.028 )
## Rsquare= 0.144 (max possible= 0.989 )
## Likelihood ratio test= 37.9 on 4 df, p=1.17e-07
## Wald test = 41.8 on 4 df, p=1.88e-08
## Score (logrank) test = 46 on 4 df, p=2.46e-09

cox.zph(surv.res)

##          rho chisq      p
## UICC_3CATIVA      0.0713 0.5694 0.450
## UICC_3CATIVB-C     -0.0101 0.0114 0.915
## HPV16_DNA_RNADNA+RNA- -0.0421 0.2097 0.647
## HPV16_DNA_RNADNA+RNA+  0.1681 2.9469 0.086
## GLOBAL              NA 4.2211 0.377
```

5.1.6 UICC, HPV16 DNA RNA, PACKYEARS (cut at 30)

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + I(PACKYEARS >
  30), data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       I(PACKYEARS > 30), data = ds[cur.subset, ], model = TRUE)
##
## n= 242, number of events= 111
## (25 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
```

```
## UICC_3CATIVA          0.590      1.805      0.233  2.54      0.011 *
## UICC_3CATIVB-C        1.738      5.687      0.304  5.72      1e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.549      0.578      0.398 -1.38      0.167
## HPV16_DNA_RNADNA+RNA+ -0.741      0.477      0.333 -2.23      0.026 *
## I(PACKYEARS > 30)TRUE  0.450      1.568      0.203  2.21      0.027 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.805      0.554      1.143      2.848
## UICC_3CATIVB-C        5.687      0.176      3.136     10.312
## HPV16_DNA_RNADNA+RNA-  0.578      1.731      0.265      1.259
## HPV16_DNA_RNADNA+RNA+  0.477      2.099      0.248      0.915
## I(PACKYEARS > 30)TRUE  1.568      0.638      1.053      2.334
##
## Concordance= 0.658 (se = 0.029 )
## Rsquare= 0.159 (max possible= 0.989 )
## Likelihood ratio test= 42 on 5 df, p=5.99e-08
## Wald test              = 46.3 on 5 df, p=7.98e-09
## Score (logrank) test = 51 on 5 df, p=8.86e-10

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA      0.0803 0.7138 0.3982
## UICC_3CATIVB-C    -0.0286 0.0920 0.7617
## HPV16_DNA_RNADNA+RNA- -0.0125 0.0187 0.8913
## HPV16_DNA_RNADNA+RNA+  0.1849 4.1686 0.0412
## I(PACKYEARS > 30)TRUE  0.0914 1.1154 0.2909
## GLOBAL            NA  5.7946 0.3267
```

5.1.7 UICC, HPV16 DNA RNA, PACKYEARS (cut at 30), interaction HPV DNA RNA with PACKYEARS

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + I(PACKYEARS >
  30) + HPV16_DNA_RNA:I(PACKYEARS > 30), data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30), data = ds[cur.subset,
##       ], model = TRUE)
##
## n= 242, number of events= 111
## (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)
```

```

## UICC_3CATIVA                0.663      1.940      0.235
## UICC_3CATIVB-C              1.782      5.940      0.305
## HPV16_DNA_RNADNA+RNA-      -0.951      0.386      0.607
## HPV16_DNA_RNADNA+RNA+      -1.631      0.196      0.530
## I(PACKYEARS > 30)TRUE       0.216      1.241      0.214
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.718      2.051      0.802
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 1.942      6.974      0.667
##                               z Pr(>|z|)
## UICC_3CATIVA                2.81    0.0049 **
## UICC_3CATIVB-C              5.85   4.9e-09 ***
## HPV16_DNA_RNADNA+RNA-      -1.57    0.1171
## HPV16_DNA_RNADNA+RNA+      -3.08    0.0021 **
## I(PACKYEARS > 30)TRUE       1.01    0.3124
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.90    0.3707
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.91    0.0036 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                               exp(coef) exp(-coef) lower .95
## UICC_3CATIVA                1.940      0.515      1.2229
## UICC_3CATIVB-C              5.940      0.168      3.2695
## HPV16_DNA_RNADNA+RNA-      0.386      2.589      0.1176
## HPV16_DNA_RNADNA+RNA+      0.196      5.107      0.0694
## I(PACKYEARS > 30)TRUE       1.241      0.806      0.8163
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 2.051      0.488      0.4256
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 6.974      0.143      1.8878
##                               upper .95
## UICC_3CATIVA                3.078
## UICC_3CATIVB-C              10.791
## HPV16_DNA_RNADNA+RNA-      1.269
## HPV16_DNA_RNADNA+RNA+      0.553
## I(PACKYEARS > 30)TRUE       1.886
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 9.881
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 25.763
##
## Concordance= 0.67 (se =0.029 )
## Rsquare= 0.19 (max possible= 0.989 )
## Likelihood ratio test= 51.1 on 7 df,  p=8.78e-09
## Wald test               = 50.4 on 7 df,  p=1.18e-08
## Score (logrank) test = 57 on 7 df,  p=6.06e-10

cox.zph(surv.res)

##                               rho   chisq      p
## UICC_3CATIVA                0.1140  1.4849 0.2230
## UICC_3CATIVB-C              -0.0101  0.0116 0.9143
## HPV16_DNA_RNADNA+RNA-      -0.1207  1.6814 0.1947
## HPV16_DNA_RNADNA+RNA+      0.2258  5.2462 0.0220
## I(PACKYEARS > 30)TRUE       0.0354  0.1439 0.7044

```

```
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.1583 2.8475 0.0915
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0936 0.9347 0.3337
## GLOBAL NA 11.9899 0.1009
```

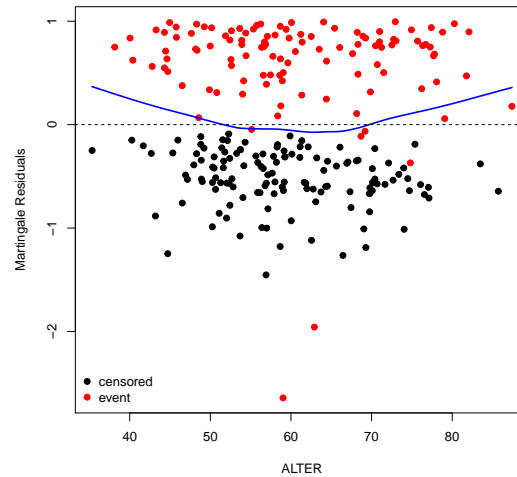
5.1.8 UICC, HPV16 DNA RNA, AGE

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER, data = ds[cur.subset, ], model = TRUE)
##
## n= 244, number of events= 112
## (23 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.58157   1.78884  0.23169  2.51  0.0121 *
## UICC_3CATIVB-C     1.79414   6.01430  0.30375  5.91 3.5e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.63915  0.52774  0.39739 -1.61  0.1077
## HPV16_DNA_RNADNA+RNA+ -0.97427  0.37747  0.32554 -2.99  0.0028 **
## ALTER              0.00904   1.00908  0.00980  0.92  0.3563
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.789      0.559      1.136      2.817
## UICC_3CATIVB-C     6.014      0.166      3.316     10.908
## HPV16_DNA_RNADNA+RNA- 0.528      1.895      0.242      1.150
## HPV16_DNA_RNADNA+RNA+ 0.377      2.649      0.199      0.714
## ALTER              1.009      0.991      0.990      1.029
##
## Concordance= 0.644 (se = 0.03 )
## Rsquare= 0.147 (max possible= 0.989 )
## Likelihood ratio test= 38.7 on 5 df, p=2.67e-07
## Wald test = 42.2 on 5 df, p=5.38e-08
## Score (logrank) test = 46.5 on 5 df, p=7.16e-09

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0704 0.5560 0.456
## UICC_3CATIVB-C    -0.0118 0.0155 0.901
## HPV16_DNA_RNADNA+RNA- -0.0438 0.2343 0.628
## HPV16_DNA_RNADNA+RNA+ 0.1688 2.9296 0.087
## ALTER            -0.0117 0.0199 0.888
## GLOBAL              NA 4.2098 0.520
```



5.1.9 UICC, HPV16 DNA RNA, ALTER (linear and quadratic)

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + poly(ALTER,
  2), data = ds[cur.subset, ])
summary(surv.res)
```

Call:

```
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##     poly(ALTER, 2), data = ds[cur.subset, ])
##
##     n= 244, number of events= 112
##     (23 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.596      1.815   0.232  2.57   0.0102 *
## UICC_3CATIVB-C     1.869      6.482   0.307  6.09  1.2e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.634    0.531   0.398 -1.59   0.1114
## HPV16_DNA_RNADNA+RNA+ -0.941    0.390   0.328 -2.87   0.0041 **
## poly(ALTER, 2)1      0.988      2.685   1.454  0.68   0.4970
## poly(ALTER, 2)2      3.184     24.140   1.303  2.44   0.0146 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.815      0.5510    1.152    2.860
## UICC_3CATIVB-C     6.482      0.1543    3.550   11.833
## HPV16_DNA_RNADNA+RNA- 0.531      1.8843    0.243    1.158
## HPV16_DNA_RNADNA+RNA+ 0.390      2.5614    0.205    0.742
## poly(ALTER, 2)1      2.685      0.3724    0.155   46.432
## poly(ALTER, 2)2     24.140      0.0414    1.876  310.576
##
## Concordance= 0.655 (se = 0.03 )
```

```
## Rsquare= 0.165    (max possible= 0.989 )
## Likelihood ratio test= 44  on 6 df,    p=7.37e-08
## Wald test          = 47.3  on 6 df,    p=1.61e-08
## Score (logrank) test = 52.1  on 6 df,    p=1.8e-09
```

```
cox.zph(surv.res)
```

```
##              rho    chisq      p
## UICC_3CATIVA      0.07888 0.70562 0.4009
## UICC_3CATIVB-C     0.00445 0.00224 0.9623
## HPV16_DNA_RNADNA+RNA- -0.04025 0.19825 0.6561
## HPV16_DNA_RNADNA+RNA+  0.17276 3.09205 0.0787
## poly(ALTER, 2)1      -0.03670 0.16061 0.6886
## poly(ALTER, 2)2       0.13898 1.90490 0.1675
## GLOBAL              NA 6.07960 0.4143
```

5.1.10 UICC, HPV16 DNA RNA, AGE (in categories: up to 50 or over 70 vs. between 50 and 70)

```
ds$ALTER_3CAT <- cut(ds$ALTER, breaks = c(0, 50, 70, Inf))
levels(ds$ALTER_3CAT) <- c("(0,50](70,Inf]", "(50,70]", "(0,50](70,Inf]")
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT,
  data = ds[cur.subset, ])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##     ALTER_3CAT, data = ds[cur.subset, ])
##
##    n= 244, number of events= 112
##    (23 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.609      1.839   0.232  2.62   0.0087 **
## UICC_3CATIVB-C     1.919      6.812   0.307  6.26   4e-10 ***
## HPV16_DNA_RNADNA+RNA- -0.593      0.553   0.396 -1.50   0.1345
## HPV16_DNA_RNADNA+RNA+ -0.941      0.390   0.323 -2.91   0.0036 **
## ALTER_3CAT(50,70]   -0.602      0.548   0.196 -3.08   0.0021 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.839      0.544   1.167   2.899
## UICC_3CATIVB-C     6.812      0.147   3.734  12.425
## HPV16_DNA_RNADNA+RNA-  0.553      1.809   0.254   1.201
## HPV16_DNA_RNADNA+RNA+  0.390      2.562   0.207   0.735
## ALTER_3CAT(50,70]   0.548      1.826   0.373   0.804
```



```
##
## Concordance= 0.661 (se = 0.029 )
## Rsquare= 0.175 (max possible= 0.989 )
## Likelihood ratio test= 47.1 on 5 df, p=5.49e-09
## Wald test = 50.3 on 5 df, p=1.2e-09
## Score (logrank) test = 54.9 on 5 df, p=1.36e-10

cox.zph(surv.res)

##
## rho chisq p
## UICC_3CATIVA 0.08342 0.78181 0.377
## UICC_3CATIVB-C 0.00855 0.00819 0.928
## HPV16_DNA_RNADNA+RNA- -0.03202 0.12110 0.728
## HPV16_DNA_RNADNA+RNA+ 0.14921 2.30696 0.129
## ALTER_3CAT(50,70] -0.07078 0.59134 0.442
## GLOBAL NA 4.26932 0.511
```

5.1.11 UICC, HPV16 DNA RNA, AGE, PACKYEARS (cut at 30)

```
# surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
# poly(ALTER, 2)[,2] + I(PACKYEARS>30), data = ds[cur.subset,])
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
  I(PACKYEARS > 30), data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## ALTER_3CAT + I(PACKYEARS > 30), data = ds[cur.subset, ],
## model = TRUE)
##
## n= 242, number of events= 111
## (25 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 0.619 1.857 0.234 2.65 0.00803 **
## UICC_3CATIVB-C 1.900 6.683 0.308 6.16 7.2e-10 ***
## HPV16_DNA_RNADNA+RNA- -0.404 0.668 0.399 -1.01 0.31174
## HPV16_DNA_RNADNA+RNA+ -0.698 0.498 0.333 -2.10 0.03602 *
## ALTER_3CAT(50,70] -0.770 0.463 0.204 -3.77 0.00016 ***
## I(PACKYEARS > 30)TRUE 0.625 1.868 0.208 3.01 0.00265 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 1.857 0.538 1.175 2.935
## UICC_3CATIVB-C 6.683 0.150 3.652 12.228
## HPV16_DNA_RNADNA+RNA- 0.668 1.497 0.305 1.460
```

```
## HPV16_DNA_RNADNA+RNA+      0.498      2.009      0.259      0.956
## ALTER_3CAT(50,70]          0.463      2.160      0.310      0.691
## I(PACKYEARS > 30)TRUE      1.868      0.535      1.243      2.808
##
## Concordance= 0.677 (se = 0.03 )
## Rsquare= 0.206 (max possible= 0.989 )
## Likelihood ratio test= 55.8 on 6 df, p=3.23e-10
## Wald test = 56.8 on 6 df, p=2.03e-10
## Score (logrank) test = 63.2 on 6 df, p=1e-11

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.09284 0.954333 0.3286
## UICC_3CATIVB-C    -0.00754 0.006369 0.9364
## HPV16_DNA_RNADNA+RNA- 0.00264 0.000834 0.9770
## HPV16_DNA_RNADNA+RNA+ 0.17007 3.446117 0.0634
## ALTER_3CAT(50,70]    -0.07408 0.625459 0.4290
## I(PACKYEARS > 30)TRUE 0.08462 0.901777 0.3423
## GLOBAL              NA 5.587121 0.4710
```

5.1.12 UICC, HPV16 DNA RNA, ALTER, PACKYEARS (cut at 30), interaction HPV DNA RNA with PACKYEARS

```
# surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
# poly(ALTER, 2)[,2] + I(PACKYEARS>30) + HPV16_DNA_RNA:I(PACKYEARS>30),
# data = ds[cur.subset,])
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
  I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30), data = ds[cur.subset,
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##      ALTER_3CAT + I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS >
##      30), data = ds[cur.subset, ])
##
##      n= 242, number of events= 111
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)
## UICC_3CATIVA      0.686      1.985      0.236
## UICC_3CATIVB-C      1.934      6.916      0.309
## HPV16_DNA_RNADNA+RNA- -0.761      0.467      0.608
## HPV16_DNA_RNADNA+RNA+ -1.573      0.207      0.531
## ALTER_3CAT(50,70]    -0.756      0.470      0.205
## I(PACKYEARS > 30)TRUE 0.398      1.488      0.220
```

```

## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 0.624 1.866 0.802
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 1.886 6.590 0.669
##
## z Pr(>|z|)
## UICC_3CATIVA 2.91 0.00366 **
## UICC_3CATIVB-C 6.26 3.8e-10 ***
## HPV16_DNA_RNADNA+RNA- -1.25 0.21058
## HPV16_DNA_RNADNA+RNA+ -2.96 0.00306 **
## ALTER_3CAT(50,70] -3.68 0.00023 ***
## I(PACKYEARS > 30)TRUE 1.81 0.07032 .
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 0.78 0.43652
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 2.82 0.00482 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95
## UICC_3CATIVA 1.985 0.504 1.2501
## UICC_3CATIVB-C 6.916 0.145 3.7762
## HPV16_DNA_RNADNA+RNA- 0.467 2.141 0.1418
## HPV16_DNA_RNADNA+RNA+ 0.207 4.820 0.0733
## ALTER_3CAT(50,70] 0.470 2.129 0.3140
## I(PACKYEARS > 30)TRUE 1.488 0.672 0.9676
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 1.866 0.536 0.3877
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 6.590 0.152 1.7762
## upper .95
## UICC_3CATIVA 3.152
## UICC_3CATIVB-C 12.666
## HPV16_DNA_RNADNA+RNA- 1.538
## HPV16_DNA_RNADNA+RNA+ 0.587
## ALTER_3CAT(50,70] 0.703
## I(PACKYEARS > 30)TRUE 2.289
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 8.979
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 24.448
##
## Concordance= 0.69 (se = 0.03 )
## Rsquare= 0.233 (max possible= 0.989 )
## Likelihood ratio test= 64.2 on 8 df, p=6.8e-11
## Wald test = 61 on 8 df, p=3.02e-10
## Score (logrank) test = 68.6 on 8 df, p=9.2e-12

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA 0.1259 1.8140 0.1780
## UICC_3CATIVB-C 0.0121 0.0165 0.8978
## HPV16_DNA_RNADNA+RNA- -0.1053 1.3076 0.2528
## HPV16_DNA_RNADNA+RNA+ 0.2036 4.2043 0.0403
## ALTER_3CAT(50,70] -0.0902 0.9541 0.3287
## I(PACKYEARS > 30)TRUE 0.0267 0.0811 0.7758
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 0.1506 2.6092 0.1062

```

```
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0650 0.4494 0.5026
## GLOBAL NA 12.1730 0.1437
```

5.1.13 T, N, M, HPV16 DNA RNA, ALTER, PACKYEARS (cut at 30), interaction HPV DNA RNA with PACKYEARS

```
ds$T_2CAT <- ds$T
levels(ds$T_2CAT) <- c(NA, "1-2", "1-2", "3-4", "3-4", "3-4")
ds$N_2CAT <- ds$N
levels(ds$N_2CAT) <- c(rep("N0-N1", 2), rep("N2-N3", 4))
surv.res <- coxph(surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + HPV16_DNA_RNA +
  ALTER_3CAT + I(PACKYEARS > 30) + I(PACKYEARS > 30):HPV16_DNA_RNA, data = ds[cur.s
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M +
## HPV16_DNA_RNA + ALTER_3CAT + I(PACKYEARS > 30) + I(PACKYEARS >
## 30):HPV16_DNA_RNA, data = ds[cur.subset, ])
##
## n= 242, number of events= 111
## (25 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## T_2CAT3-4        0.474      1.606   0.221
## N_2CATN2-N3       0.665      1.944   0.219
## M                1.772      5.885   0.382
## HPV16_DNA_RNADNA+RNA- -0.645    0.525   0.609
## HPV16_DNA_RNADNA+RNA+ -1.335    0.263   0.540
## ALTER_3CAT(50,70] -0.707    0.493   0.201
## I(PACKYEARS > 30)TRUE 0.427    1.533   0.222
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.715    2.044   0.801
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 1.964    7.126   0.673
##
##               z Pr(>|z|)
## T_2CAT3-4      2.15 0.03184 *
## N_2CATN2-N3    3.04 0.00236 **
## M             4.64 3.6e-06 ***
## HPV16_DNA_RNADNA+RNA- -1.06 0.28955
## HPV16_DNA_RNADNA+RNA+ -2.47 0.01346 *
## ALTER_3CAT(50,70] -3.52 0.00043 ***
## I(PACKYEARS > 30)TRUE 1.92 0.05433 .
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.89 0.37186
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.92 0.00352 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95
```

```
## T_2CAT3-4 1.606 0.623 1.0420
## N_2CATN2-N3 1.944 0.514 1.2667
## M 5.885 0.170 2.7816
## HPV16_DNA_RNADNA+RNA- 0.525 1.906 0.1590
## HPV16_DNA_RNADNA+RNA+ 0.263 3.798 0.0914
## ALTER_3CAT(50,70] 0.493 2.028 0.3327
## I(PACKYEARS > 30)TRUE 1.533 0.652 0.9921
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 2.044 0.489 0.4256
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 7.126 0.140 1.9059
## upper .95
## T_2CAT3-4 2.476
## N_2CATN2-N3 2.984
## M 12.453
## HPV16_DNA_RNADNA+RNA- 1.731
## HPV16_DNA_RNADNA+RNA+ 0.759
## ALTER_3CAT(50,70] 0.731
## I(PACKYEARS > 30)TRUE 2.369
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 9.817
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 26.641
##
## Concordance= 0.692 (se = 0.03 )
## Rsquare= 0.238 (max possible= 0.989 )
## Likelihood ratio test= 65.8 on 9 df, p=1e-10
## Wald test = 63.7 on 9 df, p=2.56e-10
## Score (logrank) test = 78.5 on 9 df, p=3.19e-13

cox.zph(surv.res)

## rho chisq p
## T_2CAT3-4 0.0121 0.019 0.8903
## N_2CATN2-N3 0.0854 0.816 0.3662
## M -0.0654 0.464 0.4960
## HPV16_DNA_RNADNA+RNA- -0.1090 1.359 0.2436
## HPV16_DNA_RNADNA+RNA+ 0.1781 3.462 0.0628
## ALTER_3CAT(50,70] -0.1242 1.770 0.1834
## I(PACKYEARS > 30)TRUE 0.0443 0.236 0.6273
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.1441 2.355 0.1249
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0780 0.644 0.4221
## GLOBAL NA 11.205 0.2619
```

5.1.14 T, N, M, HPV16 DNA RNA, ALTER, PACKYEARS (cut at 30), interaction HPV DNA RNA with PACKYEARS, interaction T with PACKYEARS

```
ds$T_2CAT <- ds$T
levels(ds$T_2CAT) <- c(NA, "1-2", "1-2", "3-4", "3-4", "3-4")
ds$N_2CAT <- ds$N
```

```

levels(ds$N_2CAT) <- c(rep("N0-N1", 2), rep("N2-N3", 4))
surv.res <- coxph(surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + HPV16_DNA_RNA +
  ALTER_3CAT + I(PACKYEARS > 30) + T_2CAT:I(PACKYEARS > 30) + I(PACKYEARS >
  30):HPV16_DNA_RNA, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M +
##       HPV16_DNA_RNA + ALTER_3CAT + I(PACKYEARS > 30) + T_2CAT:I(PACKYEARS >
##       30) + I(PACKYEARS > 30):HPV16_DNA_RNA, data = ds[cur.subset,
##       ])
##
##      n= 242, number of events= 111
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)
## T_2CAT3-4          0.0795      1.0827   0.3351
## N_2CATN2-N3         0.6628      1.9403   0.2196
## M                  1.8804      6.5562   0.3907
## HPV16_DNA_RNADNA+RNA- -0.6705      0.5114   0.6110
## HPV16_DNA_RNADNA+RNA+ -1.4617      0.2318   0.5477
## ALTER_3CAT(50,70]    -0.6923      0.5004   0.2009
## I(PACKYEARS > 30)TRUE -0.0236      0.9767   0.3686
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 0.6388      1.8942   0.4282
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.7360      2.0876   0.8022
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.1395      8.4948   0.6839
##
##              z Pr(>|z|)
## T_2CAT3-4          0.24  0.81253
## N_2CATN2-N3         3.02  0.00254 **
## M                  4.81  1.5e-06 ***
## HPV16_DNA_RNADNA+RNA- -1.10  0.27249
## HPV16_DNA_RNADNA+RNA+ -2.67  0.00761 **
## ALTER_3CAT(50,70]    -3.45  0.00057 ***
## I(PACKYEARS > 30)TRUE -0.06  0.94895
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 1.49  0.13574
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.92  0.35886
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 3.13  0.00176 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## T_2CAT3-4          1.083      0.924   0.5614
## N_2CATN2-N3         1.940      0.515   1.2616
## M                  6.556      0.153   3.0484
## HPV16_DNA_RNADNA+RNA- 0.511      1.955   0.1544
## HPV16_DNA_RNADNA+RNA+ 0.232      4.313   0.0793
## ALTER_3CAT(50,70]    0.500      1.998   0.3376
## I(PACKYEARS > 30)TRUE 0.977      1.024   0.4742

```

```
## T_2CAT3-4:I(PACKYEARS > 30)TRUE      1.894      0.528      0.8184
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE      2.088      0.479      0.4334
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE      8.495      0.118      2.2232
##                                     upper .95
## T_2CAT3-4                                     2.088
## N_2CATN2-N3                                     2.984
## M                                              14.100
## HPV16_DNA_RNADNA+RNA-                         1.694
## HPV16_DNA_RNADNA+RNA+                         0.678
## ALTER_3CAT(50,70]                             0.742
## I(PACKYEARS > 30)TRUE                         2.011
## T_2CAT3-4:I(PACKYEARS > 30)TRUE               4.384
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE    10.057
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE    32.459
##
## Concordance= 0.692 (se = 0.03 )
## Rsquare= 0.245 (max possible= 0.989 )
## Likelihood ratio test= 68 on 10 df, p=1.08e-10
## Wald test = 66.8 on 10 df, p=1.8e-10
## Score (logrank) test = 83.1 on 10 df, p=1.22e-13

cox.zph(surv.res)

##                                     rho  chisq      p
## T_2CAT3-4                        0.0886  1.054 0.3046
## N_2CATN2-N3                      0.0864  0.843 0.3584
## M                                -0.0791  0.714 0.3983
## HPV16_DNA_RNADNA+RNA-            -0.1144  1.517 0.2181
## HPV16_DNA_RNADNA+RNA+            0.1786  3.735 0.0533
## ALTER_3CAT(50,70]                -0.1183  1.623 0.2026
## I(PACKYEARS > 30)TRUE              0.1118  1.741 0.1871
## T_2CAT3-4:I(PACKYEARS > 30)TRUE    -0.1077  1.508 0.2194
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.1453  2.410 0.1206
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0843  0.820 0.3651
## GLOBAL                           NA 12.384 0.2602

# best.model <- stepAIC(surv.res) best.model
```

5.1.15 UICC, HPV16 DNA RNA, ALTER, PACKYEARS, Interaktion HPV DNA RNA mit PACKYEARS. Variable selection using stepAIC.

```
# surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
# ALTER_3CAT + poly(ALTER, 2)[,2] + I(PACKYEARS>30) +
# HPV16_DNA_RNA:I(PACKYEARS>30) + GESCHLECHT, data =
# na.omit(ds[cur.subset],
# c('UICC_3CAT', 'HPV16_DNA_RNA', 'ALTER_3CAT', 'PACKYEARS', 'ALTER', 'GESCHLECHT'))))
surv.res <- coxph(as.formula(paste(create.surv.obj, "~ UICC_3CAT + HPV16_DNA_RNA + AL
```



```

data = na.omit(ds[cur.subset, c("UICC_3CAT", "HPV16_DNA_RNA", "ALTER_3CAT",
                                "PACKYEARS", "ALTER", "GESCHLECHT", "OS", "OS_EVENT", "PFS", "PFS_EVENT")]))
best.model <- stepAIC(surv.res)

## Start:  AIC=1054
## Surv(PFS/30, PFS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##      poly(ALTER, 2)[, 2] + I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS >
##      30) + GESCHLECHT
##
##
##              Df  AIC
## - GESCHLECHT      1 1052
## - poly(ALTER, 2)[, 2] 1 1053
## <none>              1054
## - ALTER_3CAT      1 1056
## - HPV16_DNA_RNA:I(PACKYEARS > 30) 2 1058
## - UICC_3CAT       2 1084
##
## Step:  AIC=1052
## Surv(PFS/30, PFS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##      poly(ALTER, 2)[, 2] + I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS >
##      30)
##
##
##              Df  AIC
## - poly(ALTER, 2)[, 2] 1 1051
## <none>              1052
## - ALTER_3CAT      1 1054
## - HPV16_DNA_RNA:I(PACKYEARS > 30) 2 1056
## - UICC_3CAT       2 1082
##
## Step:  AIC=1051
## Surv(PFS/30, PFS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##      I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30)
##
##
##              Df  AIC
## <none>              1051
## - HPV16_DNA_RNA:I(PACKYEARS > 30) 2 1055
## - ALTER_3CAT      1 1062
## - UICC_3CAT       2 1081

best.model

## Call:
## coxph(formula = Surv(PFS/30, PFS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA +
##      ALTER_3CAT + I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS >
##      30), data = na.omit(ds[cur.subset, c("UICC_3CAT", "HPV16_DNA_RNA",
##      "ALTER_3CAT", "PACKYEARS", "ALTER", "GESCHLECHT", "OS", "OS_EVENT",
##      "PFS", "PFS_EVENT")]))
##
##
##

```



```
##
## UICC_3CATIVA      coef exp(coef) se(coef)
## UICC_3CATIVB-C    1.934      6.916   0.309
## HPV16_DNA_RNADNA+RNA- -0.761    0.467   0.608
## HPV16_DNA_RNADNA+RNA+ -1.573    0.207   0.531
## ALTER_3CAT(50,70] -0.756    0.470   0.205
## I(PACKYEARS > 30)TRUE 0.398    1.488   0.220
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.624    1.866   0.802
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 1.886    6.590   0.669
##
##              z      p
## UICC_3CATIVA      2.906 3.7e-03
## UICC_3CATIVB-C    6.264 3.8e-10
## HPV16_DNA_RNADNA+RNA- -1.252 2.1e-01
## HPV16_DNA_RNADNA+RNA+ -2.962 3.1e-03
## ALTER_3CAT(50,70] -3.678 2.3e-04
## I(PACKYEARS > 30)TRUE 1.810 7.0e-02
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.778 4.4e-01
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.819 4.8e-03
##
## Likelihood ratio test=64.2 on 8 df, p=6.8e-11 n= 242, number of events= 111
```

5.1.16 PACKYEARS as a continuous covariate

```
surv.res <- coxph(surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset, ],
  model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset,
## ], model = TRUE)
##
## n= 265, number of events= 125
## (2 observations deleted due to missingness)
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## PACKYEARS 0.00465  1.00466  0.00392 1.19    0.24
##
##      exp(coef) exp(-coef) lower .95 upper .95
## PACKYEARS      1      0.995   0.997   1.01
##
## Concordance= 0.522 (se = 0.028 )
## Rsquare= 0.005 (max possible= 0.991 )
## Likelihood ratio test= 1.37 on 1 df, p=0.241
## Wald test = 1.41 on 1 df, p=0.236
## Score (logrank) test = 1.4 on 1 df, p=0.236

cox.zph(surv.res)
```

```
##          rho chisq      p
## PACKYEARS 0.102  1.28 0.259
```

5.1.17 UICC, HPV16 DNA RNA, PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + PACKYEARS,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       PACKYEARS, data = ds[cur.subset, ], model = TRUE)
##
##      n= 242, number of events= 111
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.57837   1.78313  0.23297   2.48   0.0130 *
## UICC_3CATIVB-C     1.78730   5.97328  0.30417   5.88  4.2e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.64430   0.52503  0.39661  -1.62   0.1043
## HPV16_DNA_RNADNA+RNA+ -0.88608   0.41227  0.33074  -2.68   0.0074 **
## PACKYEARS          0.00212   1.00213  0.00425   0.50   0.6169
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.783      0.561      1.129      2.815
## UICC_3CATIVB-C         5.973      0.167      3.291     10.842
## HPV16_DNA_RNADNA+RNA-   0.525      1.905      0.241      1.142
## HPV16_DNA_RNADNA+RNA+   0.412      2.426      0.216      0.788
## PACKYEARS              1.002      0.998      0.994      1.011
##
## Concordance= 0.638 (se = 0.03 )
## Rsquare= 0.142 (max possible= 0.989 )
## Likelihood ratio test= 37.2 on 5 df,  p=5.5e-07
## Wald test               = 41.1 on 5 df,  p=9e-08
## Score (logrank) test = 45.4 on 5 df,  p=1.23e-08

cox.zph(surv.res)

##          rho chisq      p
## UICC_3CATIVA      0.0707 0.559 0.4545
## UICC_3CATIVB-C    -0.0155 0.027 0.8694
## HPV16_DNA_RNADNA+RNA- -0.0335 0.133 0.7149
## HPV16_DNA_RNADNA+RNA+  0.1672 3.321 0.0684
## PACKYEARS          0.0376 0.181 0.6707
## GLOBAL              NA  4.473 0.4836
```

5.1.18 UICC, HPV16 DNA RNA, ALTER, PACKYEARS continuous

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
  PACKYEARS, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER_3CAT + PACKYEARS, data = ds[cur.subset, ], model = TRUE)
##
##    n= 242, number of events= 111
##    (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.60910   1.83878  0.23378   2.61  0.00917 **
## UICC_3CATIVB-C     1.91869   6.81206  0.30893   6.21  5.3e-10 ***
## HPV16_DNA_RNADNA+RNA- -0.54616   0.57917  0.39928  -1.37  0.17135
## HPV16_DNA_RNADNA+RNA+ -0.84121   0.43119  0.32916  -2.56  0.01060 *
## ALTER_3CAT(50,70]  -0.68725   0.50296  0.20427  -3.36  0.00077 ***
## PACKYEARS          0.00560   1.00562  0.00419   1.34  0.18149
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.839      0.544      1.163      2.908
## UICC_3CATIVB-C         6.812      0.147      3.718     12.481
## HPV16_DNA_RNADNA+RNA-   0.579      1.727      0.265      1.267
## HPV16_DNA_RNADNA+RNA+   0.431      2.319      0.226      0.822
## ALTER_3CAT(50,70]       0.503      1.988      0.337      0.751
## PACKYEARS              1.006      0.994      0.997      1.014
##
## Concordance= 0.668 (se = 0.03 )
## Rsquare= 0.181 (max possible= 0.989 )
## Likelihood ratio test= 48.2 on 6 df,  p=1.08e-08
## Wald test              = 50.2 on 6 df,  p=4.34e-09
## Score (logrank) test = 55.5 on 6 df,  p=3.69e-10

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.085917 8.29e-01 0.3625
## UICC_3CATIVB-C    -0.000223 5.68e-06 0.9981
## HPV16_DNA_RNADNA+RNA- -0.011663 1.66e-02 0.8975
## HPV16_DNA_RNADNA+RNA+  0.160208 2.92e+00 0.0875
## ALTER_3CAT(50,70]   -0.075114 6.68e-01 0.4136
## PACKYEARS          0.040908 1.94e-01 0.6599
## GLOBAL              NA 4.83e+00 0.5661

```

5.1.19 UICC, HPV16 DNA RNA, ALTER, PACKYEARS continuous, interaction HPV16 DNA RNA with PACKYEARS

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
  PACKYEARS + HPV16_DNA_RNA:PACKYEARS, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER_3CAT + PACKYEARS + HPV16_DNA_RNA:PACKYEARS, data = ds[cur.subset,
##       ], model = TRUE)
##
##      n= 242, number of events= 111
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA          0.58876   1.80175  0.23404   2.52   0.0119
## UICC_3CATIVB-C         1.96497   7.13473  0.31032   6.33  2.4e-10
## HPV16_DNA_RNADNA+RNA- -0.25322   0.77630  0.51653  -0.49   0.6240
## HPV16_DNA_RNADNA+RNA+ -1.31414   0.26871  0.45622  -2.88   0.0040
## ALTER_3CAT(50,70]    -0.65083   0.52161  0.20711  -3.14   0.0017
## PACKYEARS             0.00343   1.00344  0.00531   0.65   0.5182
## HPV16_DNA_RNADNA+RNA-:PACKYEARS -0.00989   0.99016  0.01272  -0.78   0.4369
## HPV16_DNA_RNADNA+RNA+:PACKYEARS  0.01694   1.01709  0.00919   1.84   0.0653
##
## UICC_3CATIVA          *
## UICC_3CATIVB-C         ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+  **
## ALTER_3CAT(50,70]     **
## PACKYEARS
## HPV16_DNA_RNADNA+RNA-:PACKYEARS
## HPV16_DNA_RNADNA+RNA+:PACKYEARS .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.802      0.555      1.139      2.850
## UICC_3CATIVB-C         7.135      0.140      3.884     13.107
## HPV16_DNA_RNADNA+RNA-  0.776      1.288      0.282      2.136
## HPV16_DNA_RNADNA+RNA+  0.269      3.722      0.110      0.657
## ALTER_3CAT(50,70]     0.522      1.917      0.348      0.783
## PACKYEARS             1.003      0.997      0.993      1.014
## HPV16_DNA_RNADNA+RNA-:PACKYEARS  0.990      1.010      0.966      1.015
## HPV16_DNA_RNADNA+RNA+:PACKYEARS  1.017      0.983      0.999      1.036
##
## Concordance= 0.678 (se = 0.03 )
## Rsquare= 0.196 (max possible= 0.989 )

```

```
## Likelihood ratio test= 52.9 on 8 df, p=1.13e-08
## Wald test = 55.5 on 8 df, p=3.61e-09
## Score (logrank) test = 60.9 on 8 df, p=3.07e-10
```

```
cox.zph(surv.res)
```

```
##              rho      chisq      p
## UICC_3CATIVA      0.09147 0.939423 0.332
## UICC_3CATIVB-C    -0.01099 0.013629 0.907
## HPV16_DNA_RNADNA+RNA- -0.12300 1.515445 0.218
## HPV16_DNA_RNADNA+RNA+ 0.15647 2.270319 0.132
## ALTER_3CAT(50,70] -0.07358 0.666535 0.414
## PACKYEARS        -0.03917 0.188934 0.664
## HPV16_DNA_RNADNA+RNA-:PACKYEARS 0.17322 1.920928 0.166
## HPV16_DNA_RNADNA+RNA+:PACKYEARS -0.00298 0.000824 0.977
## GLOBAL              NA 8.923634 0.349
```

5.1.20 UICC, HPV16 RNA, ALTER, PACKYEARS continuous, interaction HPV16 RNA with PACKYEARS

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT +
  PACKYEARS + HPV16_RNA:PACKYEARS, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA +
##     ALTER_3CAT + PACKYEARS + HPV16_RNA:PACKYEARS, data = ds[cur.subset,
##     ], model = TRUE)
##
## n= 242, number of events= 111
## (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.56539   1.76013  0.23244   2.43   0.0150 *
## UICC_3CATIVB-C      1.86764   6.47298  0.30553   6.11  9.8e-10 ***
## HPV16_RNARNA+     -1.31388   0.26877  0.44388  -2.96   0.0031 **
## ALTER_3CAT(50,70] -0.66637   0.51357  0.20513  -3.25   0.0012 **
## PACKYEARS          0.00149   1.00149  0.00446   0.33   0.7382
## HPV16_RNARNA+:PACKYEARS 0.01878   1.01895  0.00869   2.16   0.0308 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.760      0.568      1.116      2.776
## UICC_3CATIVB-C          6.473      0.154      3.557     11.781
## HPV16_RNARNA+          0.269      3.721      0.113      0.642
## ALTER_3CAT(50,70]      0.514      1.947      0.344      0.768
```

```

## PACKYEARS                1.001      0.999      0.993      1.010
## HPV16_RNARNA+:PACKYEARS  1.019      0.981      1.002      1.036
##
## Concordance= 0.676 (se = 0.03 )
## Rsquare= 0.187 (max possible= 0.989 )
## Likelihood ratio test= 50.1 on 6 df, p=4.57e-09
## Wald test = 52.3 on 6 df, p=1.65e-09
## Score (logrank) test = 57.8 on 6 df, p=1.25e-10

cox.zph(surv.res)

##                rho      chisq      p
## UICC_3CATIVA      0.07858 0.682856 0.4086
## UICC_3CATIVB-C      0.00277 0.000832 0.9770
## HPV16_RNARNA+      0.19746 3.437028 0.0638
## ALTER_3CAT(50,70] -0.10126 1.223108 0.2688
## PACKYEARS          0.05090 0.248267 0.6183
## HPV16_RNARNA+:PACKYEARS -0.06056 0.295625 0.5866
## GLOBAL              NA 6.690178 0.3505

stepAIC(surv.res)

## Start: AIC=1061
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT + PACKYEARS +
## HPV16_RNA:PACKYEARS
##
##                Df  AIC
## <none>              1061
## - HPV16_RNA:PACKYEARS 1 1063
## - ALTER_3CAT          1 1069
## - UICC_3CAT           2 1089
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA +
## ALTER_3CAT + PACKYEARS + HPV16_RNA:PACKYEARS, data = ds[cur.subset,
## ], model = TRUE)
##
##
##                coef exp(coef) se(coef)      z      p
## UICC_3CATIVA      0.56539      1.760  0.23244  2.432 1.5e-02
## UICC_3CATIVB-C      1.86764      6.473  0.30553  6.113 9.8e-10
## HPV16_RNARNA+     -1.31388      0.269  0.44388 -2.960 3.1e-03
## ALTER_3CAT(50,70] -0.66637      0.514  0.20513 -3.249 1.2e-03
## PACKYEARS          0.00149      1.001  0.00446  0.334 7.4e-01
## HPV16_RNARNA+:PACKYEARS 0.01878      1.019  0.00869  2.160 3.1e-02
##
## Likelihood ratio test=50.1 on 6 df, p=4.57e-09 n= 242, number of events= 111
## (25 observations deleted due to missingness)

```

5.1.21 UICC, HPV16 RNA, ALTER, PACKYEARS > 10, interaction HPV16 RNA with PACKYEARS > 10

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT +
  I(PACKYEARS > 10) + HPV16_RNA:I(PACKYEARS > 10), data = ds[cur.subset, ],
  model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA +
##       ALTER_3CAT + I(PACKYEARS > 10) + HPV16_RNA:I(PACKYEARS >
##       10), data = ds[cur.subset, ], model = TRUE)
##
##      n= 242, number of events= 111
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z
## UICC_3CATIVA      0.579      1.785    0.232  2.49
## UICC_3CATIVB-C     1.927      6.867    0.310  6.22
## HPV16_RNARNA+    -1.376      0.253    0.550 -2.50
## ALTER_3CAT(50,70] -0.703      0.495    0.203 -3.46
## I(PACKYEARS > 10)TRUE      0.113      1.120    0.255  0.44
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE  1.057      2.878    0.677  1.56
##
##              Pr(>|z|)
## UICC_3CATIVA      0.01271 *
## UICC_3CATIVB-C     5e-10 ***
## HPV16_RNARNA+      0.01229 *
## ALTER_3CAT(50,70]  0.00055 ***
## I(PACKYEARS > 10)TRUE      0.65673
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE  0.11815
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## UICC_3CATIVA      1.785      0.560    1.132
## UICC_3CATIVB-C     6.867      0.146    3.741
## HPV16_RNARNA+      0.253      3.958    0.086
## ALTER_3CAT(50,70]  0.495      2.020    0.332
## I(PACKYEARS > 10)TRUE      1.120      0.893    0.680
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE  2.878      0.347    0.764
##
##              upper .95
## UICC_3CATIVA      2.814
## UICC_3CATIVB-C    12.604
## HPV16_RNARNA+      0.742
## ALTER_3CAT(50,70]  0.738
## I(PACKYEARS > 10)TRUE      1.846
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE  10.838
##

```

```

## Concordance= 0.668 (se = 0.029 )
## Rsquare= 0.18 (max possible= 0.989 )
## Likelihood ratio test= 48.1 on 6 df, p=1.13e-08
## Wald test = 50.1 on 6 df, p=4.52e-09
## Score (logrank) test = 55.2 on 6 df, p=4.28e-10

cox.zph(surv.res)

##
## rho chisq p
## UICC_3CATIVA 0.0761 0.6400 0.4237
## UICC_3CATIVB-C 0.0103 0.0117 0.9138
## HPV16_RNARNA+ 0.2305 5.3969 0.0202
## ALTER_3CAT(50,70] -0.1032 1.2459 0.2643
## I(PACKYEARS > 10)TRUE 0.0734 0.5927 0.4414
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE -0.1499 2.3732 0.1234
## GLOBAL NA 7.7296 0.2586

stepAIC(surv.res)

## Start: AIC=1063
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT + I(PACKYEARS >
## 10) + HPV16_RNA:I(PACKYEARS > 10)
##
## Df AIC
## <none> 1063
## - HPV16_RNA:I(PACKYEARS > 10) 1 1063
## - ALTER_3CAT 1 1072
## - UICC_3CAT 2 1092
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA +
## ALTER_3CAT + I(PACKYEARS > 10) + HPV16_RNA:I(PACKYEARS >
## 10), data = ds[cur.subset, ], model = TRUE)
##
##
## coef exp(coef) se(coef) z
## UICC_3CATIVA 0.579 1.785 0.232 2.492
## UICC_3CATIVB-C 1.927 6.867 0.310 6.218
## HPV16_RNARNA+ -1.376 0.253 0.550 -2.504
## ALTER_3CAT(50,70] -0.703 0.495 0.203 -3.457
## I(PACKYEARS > 10)TRUE 0.113 1.120 0.255 0.444
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE 1.057 2.878 0.677 1.563
##
## p
## UICC_3CATIVA 1.3e-02
## UICC_3CATIVB-C 5.0e-10
## HPV16_RNARNA+ 1.2e-02
## ALTER_3CAT(50,70] 5.5e-04
## I(PACKYEARS > 10)TRUE 6.6e-01
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE 1.2e-01
##

```



```
## Likelihood ratio test=48.1 on 6 df, p=1.13e-08 n= 242, number of events= 111
## (25 observations deleted due to missingness)
```

5.1.22 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## ALTER + PACKYEARS, data = ds[cur.subset, ], model = TRUE)
##
## n= 242, number of events= 111
## (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.57499   1.77711  0.23302  2.47   0.0136 *
## UICC_3CATIVB-C     1.77872   5.92228  0.30433  5.84  5.1e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.60810  0.54439  0.39830 -1.53   0.1268
## HPV16_DNA_RNADNA+RNA+ -0.92709  0.39571  0.33399 -2.78   0.0055 **
## ALTER              0.00908   1.00912  0.00993  0.91   0.3607
## PACKYEARS          0.00219   1.00219  0.00422  0.52   0.6034
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.777      0.563    1.126    2.806
## UICC_3CATIVB-C     5.922      0.169    3.262   10.753
## HPV16_DNA_RNADNA+RNA- 0.544      1.837    0.249    1.188
## HPV16_DNA_RNADNA+RNA+ 0.396      2.527    0.206    0.761
## ALTER              1.009      0.991    0.990    1.029
## PACKYEARS          1.002      0.998    0.994    1.011
##
## Concordance= 0.645 (se = 0.03 )
## Rsquare= 0.145 (max possible= 0.989 )
## Likelihood ratio test= 38 on 6 df, p=1.12e-06
## Wald test = 41.5 on 6 df, p=2.31e-07
## Score (logrank) test = 45.9 on 6 df, p=3.17e-08
```

```
cox.zph(surv.res)
```

```
##              rho chisq      p
## UICC_3CATIVA      0.06981 0.5456 0.4601
## UICC_3CATIVB-C    -0.01738 0.0337 0.8543
## HPV16_DNA_RNADNA+RNA- -0.03438 0.1442 0.7042
## HPV16_DNA_RNADNA+RNA+ 0.16825 3.3005 0.0693
```

```
## ALTER -0.00865 0.0112 0.9159
## PACKYEARS 0.03755 0.1776 0.6734
## GLOBAL NA 4.4613 0.6145

# stepAIC(surv.res) prettified table for the paper
coxtable(surv.res)

##          hr 2.5 % 97.5 %      p
## UICC_3CATIVA 1.78 1.13 2.81 0.014
## UICC_3CATIVB-C 5.92 3.26 10.75 0.000
## HPV16_DNA_RNADNA+RNA- 0.54 0.25 1.19 0.127
## HPV16_DNA_RNADNA+RNA+ 0.40 0.21 0.76 0.006
## ALTER 1.01 0.99 1.03 0.361
## PACKYEARS 1.00 0.99 1.01 0.603

# compute SS type II overall p-value for a factor with more than 2
# categories. The function Anova() is in package 'car'. The
# Wald-statistic is chosen so that the p-values are consistent with those
# given in the output of summary(surv.res) SS type II is equivalent to
# type III in this case because there are no interactions in the model.
Anova(surv.res, type = 2, test.statistic = "Wald")

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##          Df Chisq Pr(>Chisq)
## UICC_3CAT 2 35.00 2.5e-08 ***
## HPV16_DNA_RNA 2 9.39 0.0091 **
## ALTER 1 0.84 0.3607
## PACKYEARS 1 0.27 0.6034
## Residuals 236
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.1.23 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, LOCALISATION

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx"), data = ds[cur.subset], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## ALTER + PACKYEARS + relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx"),
## data = ds[cur.subset, ], model = TRUE)
```

```

##
##  n= 239, number of events= 110
##    (28 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                      0.50991
## UICC_3CATIVB-C                    1.89933
## HPV16_DNA_RNADNA+RNA-            -0.72826
## HPV16_DNA_RNADNA+RNA+            -1.10578
## ALTER                            0.01048
## PACKYEARS                         0.00123
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.03111
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.03751
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      -0.61029
##                                     exp(coef)
## UICC_3CATIVA                      1.66514
## UICC_3CATIVB-C                    6.68140
## HPV16_DNA_RNADNA+RNA-            0.48275
## HPV16_DNA_RNADNA+RNA+            0.33095
## ALTER                            1.01053
## PACKYEARS                         1.00123
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.96937
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.03822
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.54319
##                                     se(coef)
## UICC_3CATIVA                      0.23534
## UICC_3CATIVB-C                    0.31700
## HPV16_DNA_RNADNA+RNA-            0.40440
## HPV16_DNA_RNADNA+RNA+            0.35576
## ALTER                            0.01025
## PACKYEARS                         0.00436
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.24165
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.32971
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.30793
##                                     z
## UICC_3CATIVA                      2.17
## UICC_3CATIVB-C                    5.99
## HPV16_DNA_RNADNA+RNA-            -1.80
## HPV16_DNA_RNADNA+RNA+            -3.11
## ALTER                            1.02
## PACKYEARS                         0.28
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.13
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.11
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      -1.98
##                                     Pr(>|z|)
## UICC_3CATIVA                      0.0303
## UICC_3CATIVB-C                    2.1e-09
## HPV16_DNA_RNADNA+RNA-            0.0717

```

```

## HPV16_DNA_RNADNA+RNA+                                0.0019
## ALTER                                                    0.3066
## PACKYEARS                                                0.7779
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.8976
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.9094
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    0.0475
##
## UICC_3CATIVA                                             *
## UICC_3CATIVB-C                                          ***
## HPV16_DNA_RNADNA+RNA-                                  .
## HPV16_DNA_RNADNA+RNA+                                  **
## ALTER
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                                         exp(coef)
## UICC_3CATIVA                                             1.665
## UICC_3CATIVB-C                                           6.681
## HPV16_DNA_RNADNA+RNA-                                    0.483
## HPV16_DNA_RNADNA+RNA+                                    0.331
## ALTER                                                    1.011
## PACKYEARS                                                1.001
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.969
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.038
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    0.543
##                                                         exp(-coef)
## UICC_3CATIVA                                             0.601
## UICC_3CATIVB-C                                           0.150
## HPV16_DNA_RNADNA+RNA-                                    2.071
## HPV16_DNA_RNADNA+RNA+                                    3.022
## ALTER                                                    0.990
## PACKYEARS                                                0.999
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.032
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.963
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    1.841
##                                                         lower .95
## UICC_3CATIVA                                             1.050
## UICC_3CATIVB-C                                           3.590
## HPV16_DNA_RNADNA+RNA-                                    0.219
## HPV16_DNA_RNADNA+RNA+                                    0.165
## ALTER                                                    0.990
## PACKYEARS                                                0.993
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.604
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.544

```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.297
##                                                                upper .95
## UICC_3CATIVA                                                    2.641
## UICC_3CATIVB-C                                                  12.436
## HPV16_DNA_RNADNA+RNA-                                          1.066
## HPV16_DNA_RNADNA+RNA+                                          0.665
## ALTER                                                            1.031
## PACKYEARS                                                       1.010
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.557
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.981
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.993
##
## Concordance= 0.65 (se = 0.03 )
## Rsquare= 0.169 (max possible= 0.989 )
## Likelihood ratio test= 44.1 on 9 df, p=1.34e-06
## Wald test               = 47.5 on 9 df, p=3.24e-07
## Score (logrank) test = 52.7 on 9 df, p=3.33e-08

cox.zph(surv.res)

##                                                                rho
## UICC_3CATIVA                                                    0.07152
## UICC_3CATIVB-C                                                  0.01432
## HPV16_DNA_RNADNA+RNA-                                          -0.04648
## HPV16_DNA_RNADNA+RNA+                                          0.13934
## ALTER                                                            0.01303
## PACKYEARS                                                       0.04819
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.02307
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.00616
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      -0.15603
## GLOBAL                                                            NA
##                                                                chisq
## UICC_3CATIVA                                                    0.5634
## UICC_3CATIVB-C                                                  0.0252
## HPV16_DNA_RNADNA+RNA-                                          0.2602
## HPV16_DNA_RNADNA+RNA+                                          2.2731
## ALTER                                                            0.0263
## PACKYEARS                                                       0.3099
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.0636
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.0041
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      2.5593
## GLOBAL                                                            7.9981
##                                                                p
## UICC_3CATIVA                                                    0.453
## UICC_3CATIVB-C                                                  0.874
## HPV16_DNA_RNADNA+RNA-                                          0.610
## HPV16_DNA_RNADNA+RNA+                                          0.132
## ALTER                                                            0.871
## PACKYEARS                                                       0.578

```

```
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.801
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.949
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.110
## GLOBAL 0.534

# stepAIC(surv.res)
coxtable(surv.res)

##
## UICC_3CATIVA hr 2.5 %
## UICC_3CATIVB-C 1.67 1.05
## HPV16_DNA_RNADNA+RNA- 6.68 3.59
## HPV16_DNA_RNADNA+RNA+ 0.48 0.22
## ALTER 0.33 0.16
## PACKYEARS 1.01 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.00 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.97 0.60
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.04 0.54
## 0.54 0.30
## 97.5 %
## UICC_3CATIVA 2.64
## UICC_3CATIVB-C 12.44
## HPV16_DNA_RNADNA+RNA- 1.07
## HPV16_DNA_RNADNA+RNA+ 0.66
## ALTER 1.03
## PACKYEARS 1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.56
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.98
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.99
## p
## UICC_3CATIVA 0.030
## UICC_3CATIVB-C 0.000
## HPV16_DNA_RNADNA+RNA- 0.072
## HPV16_DNA_RNADNA+RNA+ 0.002
## ALTER 0.307
## PACKYEARS 0.778
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.898
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.909
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.047

Anova(surv.res, type = 2, test.statistic = "Wald")

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##
## Df Chisq Pr(>Chisq)
## UICC_3CAT 2 37.55 7e-09
## HPV16_DNA_RNA 2 11.70 0.0029
## ALTER 1 1.05 0.3066
## PACKYEARS 1 0.08 0.7779
```

```
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")    3  4.64    0.1998
## Residuals                                              230
##
## UICC_3CAT                                              ***
## HPV16_DNA_RNA                                         **
## ALTER
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")
## Residuals
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.1.24 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, LOCALISATION, ALCOHOL consumption, THERAPY

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + ALKOHOL + THERAPIE_GROB + relevel(LOKALISATION_GROB_TEXT, ref = "larynx",
  data = ds[cur.subset, ], model = TRUE)

summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##     ALTER + PACKYEARS + ALKOHOL + THERAPIE_GROB + relevel(LOKALISATION_GROB_TEXT,
##     ref = "larynx"), data = ds[cur.subset, ], model = TRUE)
##
## n= 239, number of events= 110
## (28 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        1.020023
## UICC_3CATIVB-C                      2.354050
## HPV16_DNA_RNADNA+RNA-              -0.651070
## HPV16_DNA_RNADNA+RNA+             -1.014009
## ALTER                             0.001903
## PACKYEARS                          0.000385
## ALKOHOL1 bis 30                     0.341360
## ALKOHOL31 bis 60                    0.459012
## ALKOHOL>60                         0.569232
## THERAPIE_GROBmulti                  -1.151307
## THERAPIE_GROBpalliative             -0.662793
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris  0.648761
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx  0.663918
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.839395
##                                     exp(coef)
## UICC_3CATIVA                        2.773259
## UICC_3CATIVB-C                     10.528123
```

```

## HPV16_DNA_RNADNA+RNA- 0.521488
## HPV16_DNA_RNADNA+RNA+ 0.362762
## ALTER 1.001905
## PACKYEARS 1.000385
## ALKOHOL1 bis 30 1.406859
## ALKOHOL31 bis 60 1.582510
## ALKOHOL>60 1.766910
## THERAPIE_GROBmulti 0.316223
## THERAPIE_GROBpalliative 0.515410
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 1.913169
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.942389
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 2.314966
## se(coef) z
## UICC_3CATIVA 0.264590 3.86
## UICC_3CATIVB-C 0.347365 6.78
## HPV16_DNA_RNADNA+RNA- 0.407123 -1.60
## HPV16_DNA_RNADNA+RNA+ 0.371230 -2.73
## ALTER 0.011202 0.17
## PACKYEARS 0.004707 0.08
## ALKOHOL1 bis 30 0.435520 0.78
## ALKOHOL31 bis 60 0.454637 1.01
## ALKOHOL>60 0.436914 1.30
## THERAPIE_GROBmulti 0.247832 -4.65
## THERAPIE_GROBpalliative 0.652265 -1.02
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.315111 2.06
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.323378 2.05
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.384839 2.18
## Pr(>|z|)
## UICC_3CATIVA 0.00012 ***
## UICC_3CATIVB-C 1.2e-11 ***
## HPV16_DNA_RNADNA+RNA- 0.10978
## HPV16_DNA_RNADNA+RNA+ 0.00631 **
## ALTER 0.86511
## PACKYEARS 0.93486
## ALKOHOL1 bis 30 0.43316
## ALKOHOL31 bis 60 0.31268
## ALKOHOL>60 0.19263
## THERAPIE_GROBmulti 3.4e-06 ***
## THERAPIE_GROBpalliative 0.30956
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.03951 *
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.04007 *
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.02917 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef)
## UICC_3CATIVA 2.773
## UICC_3CATIVB-C 10.528

```


## HPV16_DNA_RNADNA+RNA-	0.521
## HPV16_DNA_RNADNA+RNA+	0.363
## ALTER	1.002
## PACKYEARS	1.000
## ALKOHOL1 bis 30	1.407
## ALKOHOL31 bis 60	1.583
## ALKOHOL>60	1.767
## THERAPIE_GROBmulti	0.316
## THERAPIE_GROBpalliative	0.515
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris	1.913
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx	1.942
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx	2.315
##	exp(-coef)
## UICC_3CATIVA	0.361
## UICC_3CATIVB-C	0.095
## HPV16_DNA_RNADNA+RNA-	1.918
## HPV16_DNA_RNADNA+RNA+	2.757
## ALTER	0.998
## PACKYEARS	1.000
## ALKOHOL1 bis 30	0.711
## ALKOHOL31 bis 60	0.632
## ALKOHOL>60	0.566
## THERAPIE_GROBmulti	3.162
## THERAPIE_GROBpalliative	1.940
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris	0.523
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx	0.515
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx	0.432
##	lower .95
## UICC_3CATIVA	1.651
## UICC_3CATIVB-C	5.329
## HPV16_DNA_RNADNA+RNA-	0.235
## HPV16_DNA_RNADNA+RNA+	0.175
## ALTER	0.980
## PACKYEARS	0.991
## ALKOHOL1 bis 30	0.599
## ALKOHOL31 bis 60	0.649
## ALKOHOL>60	0.750
## THERAPIE_GROBmulti	0.195
## THERAPIE_GROBpalliative	0.144
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris	1.032
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx	1.031
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx	1.089
##	upper .95
## UICC_3CATIVA	4.658
## UICC_3CATIVB-C	20.798
## HPV16_DNA_RNADNA+RNA-	1.158
## HPV16_DNA_RNADNA+RNA+	0.751
## ALTER	1.024

```

## PACKYEARS 1.010
## ALKOHOL1 bis 30 3.303
## ALKOHOL31 bis 60 3.858
## ALKOHOL>60 4.160
## THERAPIE_GROBmulti 0.514
## THERAPIE_GROBpalliative 1.851
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.548
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 3.661
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 4.922
##
## Concordance= 0.694 (se = 0.03 )
## Rsquare= 0.249 (max possible= 0.989 )
## Likelihood ratio test= 68.4 on 14 df, p=3.7e-09
## Wald test = 75.1 on 14 df, p=2.24e-10
## Score (logrank) test = 78.8 on 14 df, p=4.8e-11

cox.zph(surv.res)

## rho
## UICC_3CATIVA 0.00640
## UICC_3CATIVB-C -0.00492
## HPV16_DNA_RNADNA+RNA- -0.04523
## HPV16_DNA_RNADNA+RNA+ 0.10959
## ALTER 0.01885
## PACKYEARS 0.03057
## ALKOHOL1 bis 30 0.06252
## ALKOHOL31 bis 60 0.08810
## ALKOHOL>60 0.10836
## THERAPIE_GROBmulti 0.07651
## THERAPIE_GROBpalliative 0.06458
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.18120
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.15635
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.09236
## GLOBAL NA
## chisq p
## UICC_3CATIVA 0.00559 0.9404
## UICC_3CATIVB-C 0.00355 0.9525
## HPV16_DNA_RNADNA+RNA- 0.24848 0.6181
## HPV16_DNA_RNADNA+RNA+ 1.43287 0.2313
## ALTER 0.05861 0.8087
## PACKYEARS 0.12800 0.7205
## ALKOHOL1 bis 30 0.45238 0.5012
## ALKOHOL31 bis 60 0.89285 0.3447
## ALKOHOL>60 1.23055 0.2673
## THERAPIE_GROBmulti 0.83833 0.3599
## THERAPIE_GROBpalliative 0.49679 0.4809
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.97155 0.0463
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.62738 0.1050
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.97041 0.3246

```

```
## GLOBAL 9.60258 0.7906

# stepAIC(surv.res)
coxtable(surv.res)

## hr 2.5 %
## UICC_3CATIVA 2.77 1.65
## UICC_3CATIVB-C 10.53 5.33
## HPV16_DNA_RNADNA+RNA- 0.52 0.23
## HPV16_DNA_RNADNA+RNA+ 0.36 0.18
## ALTER 1.00 0.98
## PACKYEARS 1.00 0.99
## ALKOHOL1 bis 30 1.41 0.60
## ALKOHOL31 bis 60 1.58 0.65
## ALKOHOL>60 1.77 0.75
## THERAPIE_GROBmulti 0.32 0.19
## THERAPIE_GROBpalliative 0.52 0.14
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 1.91 1.03
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.94 1.03
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 2.31 1.09
## 97.5 % p
## UICC_3CATIVA 4.66 0.000
## UICC_3CATIVB-C 20.80 0.000
## HPV16_DNA_RNADNA+RNA- 1.16 0.110
## HPV16_DNA_RNADNA+RNA+ 0.75 0.006
## ALTER 1.02 0.865
## PACKYEARS 1.01 0.935
## ALKOHOL1 bis 30 3.30 0.433
## ALKOHOL31 bis 60 3.86 0.313
## ALKOHOL>60 4.16 0.193
## THERAPIE_GROBmulti 0.51 0.000
## THERAPIE_GROBpalliative 1.85 0.310
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.55 0.040
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 3.66 0.040
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 4.92 0.029

Anova(surv.res, type = 2, test.statistic = "Wald")

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
## Df Chisq Pr(>Chisq)
## UICC_3CAT 2 46.13 9.6e-11 ***
## HPV16_DNA_RNA 2 9.05 0.011 *
## ALTER 1 0.03 0.865
## PACKYEARS 1 0.01 0.935
## ALKOHOL 3 1.91 0.591
## THERAPIE_GROB 2 21.59 2.0e-05 ***
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx") 3 6.12 0.106
```

```
## Residuals                                225
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.1.25 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, LOCALISATION, ALCOHOL consumption, THERAPY, interaction Therapy with UICC

Palliative Therapy was excluded due to small sample size.

```
ds$THERAPIE_GROB_NOPALLIATIVE <- factor(ds$THERAPIE_GROB, levels = c("multi",
  "mono"))
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + ALCOHOL + THERAPIE_GROB_NOPALLIATIVE + THERAPIE_GROB_NOPALLIATIVE:UICC_3CAT +
  relevel(LOKALISATION_GROB_TEXT, ref = "larynx"), data = ds[cur.subset, ],
  model = TRUE)

summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##     ALTER + PACKYEARS + ALCOHOL + THERAPIE_GROB_NOPALLIATIVE +
##     THERAPIE_GROB_NOPALLIATIVE:UICC_3CAT + relevel(LOKALISATION_GROB_TEXT,
##     ref = "larynx"), data = ds[cur.subset, ], model = TRUE)
##
##      n= 234, number of events= 107
##      (33 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        0.666899
## UICC_3CATIVB-C                      2.070773
## HPV16_DNA_RNADNA+RNA-              -0.616748
## HPV16_DNA_RNADNA+RNA+              -1.084998
## ALTER                             0.002696
## PACKYEARS                          0.000234
## ALCOHOL1 bis 30                     0.428049
## ALCOHOL31 bis 60                    0.476331
## ALCOHOL>60                         0.545295
## THERAPIE_GROB_NOPALLIATIVEmono      0.697725
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.714555
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.679521
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.865007
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.751604
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.351504
##
##                                     exp(coef)
## UICC_3CATIVA                        1.948187
## UICC_3CATIVB-C                      7.930954
## HPV16_DNA_RNADNA+RNA-              0.539697
```

```

## HPV16_DNA_RNADNA+RNA+ 0.337902
## ALTER 1.002700
## PACKYEARS 1.000234
## ALKOHOL1 bis 30 1.534261
## ALKOHOL31 bis 60 1.610156
## ALKOHOL>60 1.725117
## THERAPIE_GROB_NOPALLIATIVEmono 2.009176
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 2.043278
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.972932
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 2.375022
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 2.120399
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 1.421204
## se(coef) z
## UICC_3CATIVA 0.346300 1.93
## UICC_3CATIVB-C 0.436341 4.75
## HPV16_DNA_RNADNA+RNA- 0.412850 -1.49
## HPV16_DNA_RNADNA+RNA+ 0.380590 -2.85
## ALTER 0.011493 0.23
## PACKYEARS 0.004830 0.05
## ALKOHOL1 bis 30 0.462783 0.92
## ALKOHOL31 bis 60 0.478566 1.00
## ALKOHOL>60 0.463321 1.18
## THERAPIE_GROB_NOPALLIATIVEmono 0.403662 1.73
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.322171 2.22
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.328747 2.07
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.389180 2.22
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.516079 1.46
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.698652 0.50
## Pr(>|z|)
## UICC_3CATIVA 0.0541 .
## UICC_3CATIVB-C 2.1e-06 ***
## HPV16_DNA_RNADNA+RNA- 0.1352
## HPV16_DNA_RNADNA+RNA+ 0.0044 **
## ALTER 0.8145
## PACKYEARS 0.9614
## ALKOHOL1 bis 30 0.3550
## ALKOHOL31 bis 60 0.3196
## ALKOHOL>60 0.2392
## THERAPIE_GROB_NOPALLIATIVEmono 0.0839 .
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.0266 *
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.0387 *
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.0262 *
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.1453
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.6149
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef)

```

## UICC_3CATIVA	1.948
## UICC_3CATIVB-C	7.931
## HPV16_DNA_RNADNA+RNA-	0.540
## HPV16_DNA_RNADNA+RNA+	0.338
## ALTER	1.003
## PACKYEARS	1.000
## ALKOHOL1 bis 30	1.534
## ALKOHOL31 bis 60	1.610
## ALKOHOL>60	1.725
## THERAPIE_GROB_NOPALLIATIVEmono	2.009
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris	2.043
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx	1.973
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx	2.375
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono	2.120
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono	1.421
##	exp(-coef)
## UICC_3CATIVA	0.513
## UICC_3CATIVB-C	0.126
## HPV16_DNA_RNADNA+RNA-	1.853
## HPV16_DNA_RNADNA+RNA+	2.959
## ALTER	0.997
## PACKYEARS	1.000
## ALKOHOL1 bis 30	0.652
## ALKOHOL31 bis 60	0.621
## ALKOHOL>60	0.580
## THERAPIE_GROB_NOPALLIATIVEmono	0.498
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris	0.489
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx	0.507
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx	0.421
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono	0.472
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono	0.704
##	lower .95
## UICC_3CATIVA	0.988
## UICC_3CATIVB-C	3.372
## HPV16_DNA_RNADNA+RNA-	0.240
## HPV16_DNA_RNADNA+RNA+	0.160
## ALTER	0.980
## PACKYEARS	0.991
## ALKOHOL1 bis 30	0.619
## ALKOHOL31 bis 60	0.630
## ALKOHOL>60	0.696
## THERAPIE_GROB_NOPALLIATIVEmono	0.911
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris	1.087
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx	1.036
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx	1.108
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono	0.771
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono	0.361
##	upper .95

```

## UICC_3CATIVA 3.841
## UICC_3CATIVB-C 18.653
## HPV16_DNA_RNADNA+RNA- 1.212
## HPV16_DNA_RNADNA+RNA+ 0.712
## ALTER 1.026
## PACKYEARS 1.010
## ALKOHOL1 bis 30 3.800
## ALKOHOL31 bis 60 4.114
## ALKOHOL>60 4.278
## THERAPIE_GROB_NOPALLIATIVEmono 4.432
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.842
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 3.758
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 5.093
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 5.830
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 5.589
##
## Concordance= 0.69 (se = 0.03 )
## Rsquare= 0.247 (max possible= 0.989 )
## Likelihood ratio test= 66.4 on 15 df, p=1.96e-08
## Wald test = 73.9 on 15 df, p=9.01e-10
## Score (logrank) test = 95.4 on 15 df, p=9.67e-14

cox.zph(surv.res)

## rho
## UICC_3CATIVA 0.06758
## UICC_3CATIVB-C 0.02974
## HPV16_DNA_RNADNA+RNA- -0.04175
## HPV16_DNA_RNADNA+RNA+ 0.12371
## ALTER -0.01935
## PACKYEARS 0.03416
## ALKOHOL1 bis 30 0.07941
## ALKOHOL31 bis 60 0.11925
## ALKOHOL>60 0.12227
## THERAPIE_GROB_NOPALLIATIVEmono 0.00403
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.15033
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.14811
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.08142
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono -0.05256
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono -0.00795
## GLOBAL NA
## chisq p
## UICC_3CATIVA 0.53655 0.4639
## UICC_3CATIVB-C 0.12171 0.7272
## HPV16_DNA_RNADNA+RNA- 0.21273 0.6446
## HPV16_DNA_RNADNA+RNA+ 1.92142 0.1657
## ALTER 0.05861 0.8087
## PACKYEARS 0.16139 0.6879
## ALKOHOL1 bis 30 0.71775 0.3969

```

```
## ALKOHOL31 bis 60 1.63616 0.2009
## ALKOHOL>60 1.69520 0.1929
## THERAPIE_GROB_NOPALLIATIVEmono 0.00206 0.9638
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 2.84281 0.0918
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.37522 0.1233
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.76564 0.3816
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.35573 0.5509
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.00841 0.9269
## GLOBAL 10.28148 0.8017
```

```
# stepAIC(surv.res)
coxtable(surv.res)
```

```
## hr 2.5 %
## UICC_3CATIVA 1.95 0.99
## UICC_3CATIVB-C 7.93 3.37
## HPV16_DNA_RNADNA+RNA- 0.54 0.24
## HPV16_DNA_RNADNA+RNA+ 0.34 0.16
## ALTER 1.00 0.98
## PACKYEARS 1.00 0.99
## ALKOHOL1 bis 30 1.53 0.62
## ALKOHOL31 bis 60 1.61 0.63
## ALKOHOL>60 1.73 0.70
## THERAPIE_GROB_NOPALLIATIVEmono 2.01 0.91
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 2.04 1.09
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.97 1.04
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 2.38 1.11
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 2.12 0.77
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 1.42 0.36
## 97.5 % p
## UICC_3CATIVA 3.84 0.054
## UICC_3CATIVB-C 18.65 0.000
## HPV16_DNA_RNADNA+RNA- 1.21 0.135
## HPV16_DNA_RNADNA+RNA+ 0.71 0.004
## ALTER 1.03 0.815
## PACKYEARS 1.01 0.961
## ALKOHOL1 bis 30 3.80 0.355
## ALKOHOL31 bis 60 4.11 0.320
## ALKOHOL>60 4.28 0.239
## THERAPIE_GROB_NOPALLIATIVEmono 4.43 0.084
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.84 0.027
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 3.76 0.039
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 5.09 0.026
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 5.83 0.145
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 5.59 0.615
```

```
Anova(surv.res, type = 2, test.statistic = "Wald")
```

```
## Analysis of Deviance Table (Type II tests)
```



```
##
## Response: surv.obj[cur.subset]
##
## Df Chisq Pr(>Chisq)
## UICC_3CAT 2 42.56 5.7e-10 ***
## HPV16_DNA_RNA 2 9.29 0.0096 **
## ALTER 1 0.06 0.8145
## PACKYEARS 1 0.00 0.9614
## ALKOHOL 3 1.39 0.7068
## THERAPIE_GROB_NOPALLIATIVE 1 21.72 3.2e-06 ***
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx") 3 6.51 0.0894 .
## UICC_3CAT:THERAPIE_GROB_NOPALLIATIVE 2 2.16 0.3401
## Residuals 219
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.1.26 In IR (Atypical): UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous

```
cur.subset <- is.primary & ds$CONSENSUS_CLUSTER == "Atypical"
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA, data = ds[cur.subset,
], model = TRUE)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT, data = ds[cur.subset, ],
model = TRUE)
surv.res <- coxph(surv.obj[cur.subset] ~ ALTER, data = ds[cur.subset, ], model = TRUE)
surv.res <- coxph(surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset, ],
model = TRUE)
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + UICC_3CAT, data = ds[cur.sub
], model = TRUE)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
PACKYEARS, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## ALTER + PACKYEARS, data = ds[cur.subset, ], model = TRUE)
##
## n= 61, number of events= 28
## (22 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 0.91517 2.49719 0.58480 1.56 0.11760
## UICC_3CATIVB-C 2.50391 12.23018 0.73467 3.41 0.00065 ***
## HPV16_DNA_RNADNA+RNA- -0.31665 0.72859 0.78136 -0.41 0.68529
## HPV16_DNA_RNADNA+RNA+ -0.94421 0.38899 0.47143 -2.00 0.04519 *
## ALTER -0.00180 0.99820 0.02433 -0.07 0.94111
## PACKYEARS 0.01797 1.01813 0.00782 2.30 0.02156 *
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      2.497      0.4004      0.794      7.86
## UICC_3CATIVB-C    12.230      0.0818      2.898     51.62
## HPV16_DNA_RNADNA+RNA-  0.729      1.3725      0.158      3.37
## HPV16_DNA_RNADNA+RNA+  0.389      2.5708      0.154      0.98
## ALTER            0.998      1.0018      0.952      1.05
## PACKYEARS         1.018      0.9822      1.003      1.03
##
## Concordance= 0.743 (se = 0.061 )
## Rsquare= 0.286 (max possible= 0.959 )
## Likelihood ratio test= 20.5 on 6 df, p=0.00224
## Wald test = 18.2 on 6 df, p=0.00565
## Score (logrank) test = 21.5 on 6 df, p=0.00151

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA      0.0898 0.2428 0.6222
## UICC_3CATIVB-C      0.0636 0.1098 0.7404
## HPV16_DNA_RNADNA+RNA- -0.0174 0.0105 0.9182
## HPV16_DNA_RNADNA+RNA+  0.2003 1.2721 0.2594
## ALTER            0.2529 3.2428 0.0717
## PACKYEARS        -0.0318 0.0397 0.8421
## GLOBAL            NA 7.7704 0.2554

# stepAIC(surv.res) prettiefied table for the paper
coxtable(surv.res)

##               hr 2.5 % 97.5 %      p
## UICC_3CATIVA      2.50  0.79   7.86 0.118
## UICC_3CATIVB-C    12.23  2.90  51.62 0.001
## HPV16_DNA_RNADNA+RNA-  0.73  0.16   3.37 0.685
## HPV16_DNA_RNADNA+RNA+  0.39  0.15   0.98 0.045
## ALTER            1.00  0.95   1.05 0.941
## PACKYEARS         1.02  1.00   1.03 0.022

# compute SS type II overall p-value for a factor with more than 2
# categories. The function Anova() is in package 'car'. The
# Wald-statistic is chosen so that the p-values are consistent with those
# given in the output of summary(surv.res) SS type II is equivalent to
# type III in this case because there are no interactions in the model.
Anova(surv.res, type = 2, test.statistic = "Wald")

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
```

```
##           Df Chisq Pr(>Chisq)
## UICC_3CAT      2 12.69    0.0018 **
## HPV16_DNA_RNA  2  4.03    0.1336
## ALTER          1  0.01    0.9411
## PACKYEARS      1  5.28    0.0216 *
## Residuals      55
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

# Anova(surv.res, type = 2, test.statistic = 'LR')
```

5.2 Models with Consensus Clusters in all patients

5.2.1 Mesenchymal vs. other Consensus Clusters, univariate

```
cur.subset <- is.primary
surv.res <- coxph(surv.obj[cur.subset] ~ IS_MESENCHYMAL, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ IS_MESENCHYMAL, data = ds[cur.subset,
##      ])
##
##      n= 253, number of events= 117
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## IS_MESENCHYMALMesenchymal 0.270      1.310    0.198 1.36    0.17
##
##              exp(coef) exp(-coef) lower .95 upper .95
## IS_MESENCHYMALMesenchymal      1.31      0.763    0.889    1.93
##
## Concordance= 0.54 (se = 0.023 )
## Rsquare= 0.007 (max possible= 0.99 )
## Likelihood ratio test= 1.81 on 1 df,  p=0.179
## Wald test              = 1.86 on 1 df,  p=0.172
## Score (logrank) test = 1.87 on 1 df,  p=0.171

cox.zph(surv.res)

##              rho chisq      p
## IS_MESENCHYMALMesenchymal -0.0935  1.01 0.314
```

5.2.2 UICC, Mesenchymal vs. other Consensus Clusters

```

cur.subset <- is.primary
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + IS_MESENCHYMAL, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + IS_MESENCHYMAL,
##       data = ds[cur.subset, ])
##
##      n= 253, number of events= 117
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.699      2.011   0.231 3.03   0.0024 **
## UICC_3CATIVB-C     1.487      4.422   0.317 4.69   2.8e-06 ***
## IS_MESENCHYMALMesenchymal 0.367      1.443   0.200 1.84   0.0664 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          2.01      0.497   1.280      3.16
## UICC_3CATIVB-C        4.42      0.226   2.375      8.24
## IS_MESENCHYMALMesenchymal 1.44      0.693   0.975      2.14
##
## Concordance= 0.627 (se = 0.028 )
## Rsquare= 0.088 (max possible= 0.99 )
## Likelihood ratio test= 23.4 on 3 df,  p=3.27e-05
## Wald test              = 24 on 3 df,  p=2.54e-05
## Score (logrank) test = 25.9 on 3 df,  p=1.02e-05

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA    -0.0208 0.0501 0.823
## UICC_3CATIVB-C  -0.0741 0.6310 0.427
## IS_MESENCHYMALMesenchymal -0.0875 0.9089 0.340
## GLOBAL          NA  1.4291 0.699

```

5.2.3 HPV16 DNA, Mesenchymal

```

surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA + IS_MESENCHYMAL, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA + IS_MESENCHYMAL,
##       data = ds[cur.subset, ])

```

```
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNADNA+      -0.539    0.584    0.261 -2.06   0.039 *
## IS_MESENCHYMALMesenchymal  0.214    1.239    0.208  1.03   0.303
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNADNA+      0.584    1.714    0.350    0.973
## IS_MESENCHYMALMesenchymal  1.239    0.807    0.824    1.862
##
## Concordance= 0.58 (se = 0.028 )
## Rsquare= 0.027 (max possible= 0.988 )
## Likelihood ratio test= 6.32 on 2 df,  p=0.0425
## Wald test = 5.78 on 2 df,  p=0.0557
## Score (logrank) test = 5.91 on 2 df,  p=0.052

cox.zph(surv.res)

##               rho chisq      p
## HPV16_DNADNA+      0.108  1.16 0.281
## IS_MESENCHYMALMesenchymal -0.110  1.23 0.267
## GLOBAL              NA   2.64 0.267
```

5.2.4 UICC, HPV16 DNA, Mesenchymal

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA + IS_MESENCHYMAL,
  data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA +
##       IS_MESENCHYMAL, data = ds[cur.subset, ])
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.716    2.046    0.241  2.97   0.0030 **
## UICC_3CATIVB-C    1.906    6.728    0.335  5.68  1.3e-08 ***
## HPV16_DNADNA+    -0.764    0.466    0.267 -2.86   0.0042 **
## IS_MESENCHYMALMesenchymal  0.300    1.350    0.209  1.43   0.1513
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      2.046      0.489      1.275      3.284
## UICC_3CATIVB-C     6.728      0.149      3.486     12.985
## HPV16_DNADNA+     0.466      2.147      0.276      0.786
## IS_MESENCHYMALMesenchymal 1.350      0.741      0.896      2.034
##
## Concordance= 0.648 (se = 0.03 )
## Rsquare= 0.138 (max possible= 0.988 )
## Likelihood ratio test= 34.7 on 4 df, p=5.37e-07
## Wald test          = 36.7 on 4 df, p=2.07e-07
## Score (logrank) test = 39.9 on 4 df, p=4.64e-08

cox.zph(surv.res)

##               rho   chisq    p
## UICC_3CATIVA      0.04419 0.20515 0.651
## UICC_3CATIVB-C    -0.00751 0.00596 0.938
## HPV16_DNADNA+     0.11023 1.24577 0.264
## IS_MESENCHYMALMesenchymal -0.09969 1.03275 0.310
## GLOBAL            NA 2.80730 0.591
```

5.2.5 HPV16 DNA RNA, Mesenchymal

```
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + IS_MESENCHYMAL, data = ds[cur
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + IS_MESENCHYMAL,
##       data = ds[cur.subset, ])
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.288      0.750      0.394 -0.73      0.464
## HPV16_DNA_RNADNA+RNA+ -0.675      0.509      0.324 -2.08      0.037 *
## IS_MESENCHYMALMesenchymal 0.196      1.216      0.209  0.94      0.348
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-      0.750      1.334      0.346      1.622
## HPV16_DNA_RNADNA+RNA+      0.509      1.964      0.270      0.961
## IS_MESENCHYMALMesenchymal 1.216      0.822      0.808      1.832
##
```

```
## Concordance= 0.582 (se = 0.028 )
## Rsquare= 0.029 (max possible= 0.988 )
## Likelihood ratio test= 6.92 on 3 df, p=0.0744
## Wald test = 6.06 on 3 df, p=0.109
## Score (logrank) test = 6.28 on 3 df, p=0.0989
```

```
cox.zph(surv.res)
```

```
##
## rho chisq p
## HPV16_DNA_RNADNA+RNA- 0.0214 0.0481 0.826
## HPV16_DNA_RNADNA+RNA+ 0.1439 2.0425 0.153
## IS_MESENCHYMALMesenchymal -0.1026 1.0873 0.297
## GLOBAL NA 3.5770 0.311
```

5.2.6 UICC, HPV16 DNA RNA, Mesenchymal

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + IS_MESENCHYMAL,
  data = ds[cur.subset, ])
```

```
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## IS_MESENCHYMAL, data = ds[cur.subset, ])
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 0.715 2.045 0.241 2.96 0.003 **
## UICC_3CATIVB-C 1.896 6.662 0.336 5.65 1.6e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.572 0.564 0.401 -1.43 0.154
## HPV16_DNA_RNADNA+RNA+ -0.871 0.418 0.329 -2.65 0.008 **
## IS_MESENCHYMALMesenchymal 0.280 1.323 0.212 1.32 0.186
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 2.045 0.489 1.274 3.282
## UICC_3CATIVB-C 6.662 0.150 3.450 12.867
## HPV16_DNA_RNADNA+RNA- 0.564 1.772 0.257 1.239
## HPV16_DNA_RNADNA+RNA+ 0.418 2.390 0.220 0.797
## IS_MESENCHYMALMesenchymal 1.323 0.756 0.874 2.002
##
## Concordance= 0.653 (se = 0.03 )
## Rsquare= 0.14 (max possible= 0.988 )
## Likelihood ratio test= 35.1 on 5 df, p=1.47e-06
## Wald test = 36.9 on 5 df, p=6.41e-07
```

```
## Score (logrank) test = 40.1 on 5 df, p=1.43e-07

cox.zph(surv.res)

##              rho    chisq    p
## UICC_3CATIVA      0.04350 0.19877 0.656
## UICC_3CATIVB-C    -0.00652 0.00462 0.946
## HPV16_DNA_RNADNA+RNA- 0.00720 0.00604 0.938
## HPV16_DNA_RNADNA+RNA+ 0.15753 2.36267 0.124
## IS_MESENCHYMALMesenchymal -0.08457 0.77110 0.380
## GLOBAL           NA 3.96033 0.555
```

5.2.7 UICC, HPV16 DNA RNA, AGE (in categories: up to 50 or over 70 vs. between 50 and 70)

```
ds$ALTER_3CAT <- cut(ds$ALTER, breaks = c(0, 50, 70, Inf))
levels(ds$ALTER_3CAT) <- c("(0,50](70,Inf]", "(50,70]", "(0,50](70,Inf]")
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
  IS_MESENCHYMAL, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER_3CAT + IS_MESENCHYMAL, data = ds[cur.subset, ])
##
## n= 233, number of events= 104
## (34 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.733      2.081   0.242   3.03  0.0025 **
## UICC_3CATIVB-C    1.967      7.149   0.337   5.84  5.3e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.490      0.613   0.401  -1.22  0.2215
## HPV16_DNA_RNADNA+RNA+ -0.889      0.411   0.330  -2.70  0.0070 **
## ALTER_3CAT(50,70] -0.520      0.594   0.205  -2.54  0.0110 *
## IS_MESENCHYMALMesenchymal 0.189      1.208   0.214   0.88  0.3771
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      2.081      0.481   1.295   3.344
## UICC_3CATIVB-C    7.149      0.140   3.693  13.840
## HPV16_DNA_RNADNA+RNA- 0.613      1.632   0.279   1.344
## HPV16_DNA_RNADNA+RNA+ 0.411      2.432   0.215   0.784
## ALTER_3CAT(50,70] 0.594      1.683   0.398   0.887
## IS_MESENCHYMALMesenchymal 1.208      0.828   0.794   1.839
##
## Concordance= 0.67 (se = 0.03 )
```



```
## Rsquare= 0.163    (max possible= 0.988 )
## Likelihood ratio test= 41.4  on 6 df,    p=2.44e-07
## Wald test          = 42.9  on 6 df,    p=1.21e-07
## Score (logrank) test = 46.2  on 6 df,    p=2.73e-08
```

```
cox.zph(surv.res)
```

```
##              rho    chisq    p
## UICC_3CATIVA      0.05022 0.26607 0.606
## UICC_3CATIVB-C    0.00315 0.00105 0.974
## HPV16_DNA_RNADNA+RNA- 0.02070 0.04956 0.824
## HPV16_DNA_RNADNA+RNA+ 0.13656 1.76445 0.184
## ALTER_3CAT(50,70] -0.09597 1.04572 0.306
## IS_MESENCHYMALMesenchymal -0.12055 1.66051 0.198
## GLOBAL              NA 5.11365 0.529
```

5.2.8 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, Mesenchymal

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + IS_MESENCHYMAL, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)
```

```
## Call:
```

```
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##     ALTER + PACKYEARS + IS_MESENCHYMAL, data = ds[cur.subset,
##     ], model = TRUE)
##
```

```
## n= 231, number of events= 103
## (36 observations deleted due to missingness)
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
## UICC_3CATIVA	0.70458	2.02299	0.24252	2.91	0.0037 **
## UICC_3CATIVB-C	1.86793	6.47486	0.33765	5.53	3.2e-08 ***
## HPV16_DNA_RNADNA+RNA-	-0.51611	0.59684	0.40475	-1.28	0.2023
## HPV16_DNA_RNADNA+RNA+	-0.87401	0.41728	0.34071	-2.57	0.0103 *
## ALTER	0.00927	1.00932	0.01006	0.92	0.3567
## PACKYEARS	0.00201	1.00202	0.00428	0.47	0.6379
## IS_MESENCHYMALMesenchymal	0.26047	1.29754	0.21466	1.21	0.2250

```
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
## UICC_3CATIVA	2.023	0.494	1.258	3.254
## UICC_3CATIVB-C	6.475	0.154	3.341	12.550
## HPV16_DNA_RNADNA+RNA-	0.597	1.675	0.270	1.319
## HPV16_DNA_RNADNA+RNA+	0.417	2.397	0.214	0.814

```
## ALTER 1.009 0.991 0.990 1.029
## PACKYEARS 1.002 0.998 0.994 1.010
## IS_MESENCHYMALMesenchymal 1.298 0.771 0.852 1.976
##
## Concordance= 0.656 (se = 0.031 )
## Rsquare= 0.141 (max possible= 0.988 )
## Likelihood ratio test= 35.1 on 7 df, p=1.07e-05
## Wald test = 36.6 on 7 df, p=5.55e-06
## Score (logrank) test = 39.9 on 7 df, p=1.32e-06
```

```
cox.zph(surv.res)
```

```
## rho chisq p
## UICC_3CATIVA 0.03798 0.15064 0.698
## UICC_3CATIVB-C -0.01367 0.02070 0.886
## HPV16_DNA_RNADNA+RNA- 0.01035 0.01291 0.910
## HPV16_DNA_RNADNA+RNA+ 0.15477 2.50562 0.113
## ALTER -0.00946 0.01185 0.913
## PACKYEARS 0.00841 0.00855 0.926
## IS_MESENCHYMALMesenchymal -0.07041 0.54462 0.461
## GLOBAL NA 3.83507 0.799
```

```
# stepAIC(surv.res)
```

```
coxtable(surv.res)
```

```
## hr 2.5 % 97.5 % p
## UICC_3CATIVA 2.02 1.26 3.25 0.004
## UICC_3CATIVB-C 6.47 3.34 12.55 0.000
## HPV16_DNA_RNADNA+RNA- 0.60 0.27 1.32 0.202
## HPV16_DNA_RNADNA+RNA+ 0.42 0.21 0.81 0.010
## ALTER 1.01 0.99 1.03 0.357
## PACKYEARS 1.00 0.99 1.01 0.638
## IS_MESENCHYMALMesenchymal 1.30 0.85 1.98 0.225
```

```
print(xtable(coxtable(surv.res), digits = c(2, 2, 2, 2, 3)), floating = FALSE)
```

	hr	2.5 %	97.5 %	p
UICC_3CATIVA	2.02	1.26	3.25	0.004
UICC_3CATIVB-C	6.47	3.34	12.55	0.000
HPV16_DNA_RNADNA+RNA-	0.60	0.27	1.32	0.202
HPV16_DNA_RNADNA+RNA+	0.42	0.21	0.81	0.010
ALTER	1.01	0.99	1.03	0.357
PACKYEARS	1.00	0.99	1.01	0.638
IS_MESENCHYMALMesenchymal	1.30	0.85	1.98	0.225

5.2.9 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, CONSENSUS CLUSTER

```

# setting orthogonal contrasts is required for the type III test. Here it
# does not make a difference. One possible reason is that there is no
# interaction in the model. defcontrasts <- options()$contrasts
# options(contrasts=c('contr.sum', 'contr.poly')) make 'Classical' the
# reference level
old.levels <- levels(ds$CONSENSUS_CLUSTER)
ds$CONSENSUS_CLUSTER <- relevel(ds$CONSENSUS_CLUSTER, ref = "Classical")
surv.res.smaller <- coxph(surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)] ~
  UICC_3CAT + HPV16_DNA_RNA + ALTER + PACKYEARS, data = ds[cur.subset & !is.na(ds$C
  ], model = TRUE)
surv.res <- coxph(surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)] ~ UICC_3CAT +
  HPV16_DNA_RNA + ALTER + PACKYEARS + CONSENSUS_CLUSTER, data = ds[cur.subset &
  !is.na(ds$CONSENSUS_CLUSTER), ], model = TRUE)
# restore the original order of the levels
ds$CONSENSUS_CLUSTER <- factor(ds$CONSENSUS_CLUSTER, levels = old.levels)

summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)] ~
##      UICC_3CAT + HPV16_DNA_RNA + ALTER + PACKYEARS + CONSENSUS_CLUSTER,
##      data = ds[cur.subset & !is.na(ds$CONSENSUS_CLUSTER), ], model = TRUE)
##
##      n= 231, number of events= 103
##      (22 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA          0.68476   1.98330  0.24317  2.82  0.0049
## UICC_3CATIVB-C         1.86659   6.46620  0.33767  5.53 3.2e-08
## HPV16_DNA_RNADNA+RNA- -0.48742   0.61421  0.40633 -1.20  0.2303
## HPV16_DNA_RNADNA+RNA+ -1.00209   0.36711  0.37275 -2.69  0.0072
## ALTER                0.00862   1.00866  0.01008  0.86  0.3925
## PACKYEARS            0.00209   1.00209  0.00428  0.49  0.6257
## CONSENSUS_CLUSTERAtypical 0.51055   1.66621  0.42268  1.21  0.2271
## CONSENSUS_CLUSTERBasal   0.37386   1.45334  0.40172  0.93  0.3520
## CONSENSUS_CLUSTERMesenchymal 0.61632   1.85210  0.39500  1.56  0.1187
##
## UICC_3CATIVA          **
## UICC_3CATIVB-C         ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+  **
## ALTER
## PACKYEARS
## CONSENSUS_CLUSTERAtypical
## CONSENSUS_CLUSTERBasal
## CONSENSUS_CLUSTERMesenchymal
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##

```

```
##                                exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA                   1.983      0.504      1.231      3.194
## UICC_3CATIVB-C                 6.466      0.155      3.336     12.534
## HPV16_DNA_RNADNA+RNA-         0.614      1.628      0.277      1.362
## HPV16_DNA_RNADNA+RNA+         0.367      2.724      0.177      0.762
## ALTER                         1.009      0.991      0.989      1.029
## PACKYEARS                     1.002      0.998      0.994      1.011
## CONSENSUS_CLUSTERAtypical     1.666      0.600      0.728      3.815
## CONSENSUS_CLUSTERBasal        1.453      0.688      0.661      3.194
## CONSENSUS_CLUSTERMesenchymal  1.852      0.540      0.854      4.017
##
## Concordance= 0.664 (se = 0.031 )
## Rsquare= 0.147 (max possible= 0.988 )
## Likelihood ratio test= 36.7 on 9 df, p=3e-05
## Wald test = 38.3 on 9 df, p=1.55e-05
## Score (logrank) test = 41.7 on 9 df, p=3.78e-06
```

```
# cox.zph(surv.res) stepAIC(surv.res)
coxtable(surv.res)
```

```
##                                hr 2.5 % 97.5 %      p
## UICC_3CATIVA                   1.98  1.23   3.19 0.005
## UICC_3CATIVB-C                 6.47  3.34  12.53 0.000
## HPV16_DNA_RNADNA+RNA-         0.61  0.28   1.36 0.230
## HPV16_DNA_RNADNA+RNA+         0.37  0.18   0.76 0.007
## ALTER                         1.01  0.99   1.03 0.393
## PACKYEARS                     1.00  0.99   1.01 0.626
## CONSENSUS_CLUSTERAtypical     1.67  0.73   3.82 0.227
## CONSENSUS_CLUSTERBasal        1.45  0.66   3.19 0.352
## CONSENSUS_CLUSTERMesenchymal  1.85  0.85   4.02 0.119
```

```
# compute SS type II overall p-value for a factor with more than 2
# categories. The function Anova() is in package 'car'. The
# Wald-statistic is chosen so that the p-values are consistent with those
# given in the output of summary(surv.res) SS type II is equivalent to
# type III in this case because there are no interactions in the model.
Anova(surv.res, type = 2, test.statistic = "Wald")
```

```
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)]
##              Df Chisq Pr(>Chisq)
## UICC_3CAT      2 30.59   2.3e-07 ***
## HPV16_DNA_RNA  2  8.18    0.017 *
## ALTER          1  0.73    0.393
## PACKYEARS      1  0.24    0.626
## CONSENSUS_CLUSTER 3  2.79    0.426
## Residuals     222
```

```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

# Anova(surv.res, type = 3, test.statistic = 'Wald') these three give the
# same p-value for CONSENSUS_CLUSTER (but a little different from Wald)
# Anova(surv.res, type = 2, test.statistic = 'LR') Anova(surv.res, type =
# 3, test.statistic = 'LR') anova(surv.res.smaller, surv.res)

# options(contrasts = defcontrasts)
```

5.2.10 UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, LOCALISATION, CONSENSUS CLUSTER

```
# setting orthogonal contrasts is required for the type III test. Here it
# does not make a difference. One possible reason is that there is no
# interaction in the model. make 'Classical' the reference level
old.levels <- levels(ds$CONSENSUS_CLUSTER)
ds$CONSENSUS_CLUSTER <- relevel(ds$CONSENSUS_CLUSTER, ref = "Classical")
surv.res.smaller <- coxph(surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)] ~
  UICC_3CAT + HPV16_DNA_RNA + ALTER + PACKYEARS, data = ds[cur.subset & !is.na(ds$C
  ], model = TRUE)
surv.res <- coxph(surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)] ~ UICC_3CAT +
  HPV16_DNA_RNA + ALTER + PACKYEARS + relevel(LOKALISATION_GROB_TEXT, ref = "oropha
  CONSENSUS_CLUSTER, data = ds[cur.subset & !is.na(ds$CONSENSUS_CLUSTER),
  ], model = TRUE)
# restore the original order of the levels
ds$CONSENSUS_CLUSTER <- factor(ds$CONSENSUS_CLUSTER, levels = old.levels)

summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)] ~
##       UICC_3CAT + HPV16_DNA_RNA + ALTER + PACKYEARS + relevel(LOKALISATION_GROB_TEXT
##       ref = "oropharynx") + CONSENSUS_CLUSTER, data = ds[cur.subset &
##       !is.na(ds$CONSENSUS_CLUSTER), ], model = TRUE)
##
##      n= 228, number of events= 102
##      (25 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        0.626450
## UICC_3CATIVB-C                      2.086359
## HPV16_DNA_RNADNA+RNA-              -0.680846
## HPV16_DNA_RNADNA+RNA+             -1.311536
## ALTER                             0.012177
## PACKYEARS                          0.000673
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.140951
```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.196091
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -0.871432
## CONSENSUS_CLUSTERAtypical 0.446055
## CONSENSUS_CLUSTERBasal 0.377207
## CONSENSUS_CLUSTERMesenchymal 0.521105
## exp(coef)
## UICC_3CATIVA 1.870957
## UICC_3CATIVB-C 8.055533
## HPV16_DNA_RNADNA+RNA- 0.506189
## HPV16_DNA_RNADNA+RNA+ 0.269406
## ALTER 1.012251
## PACKYEARS 1.000673
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.868532
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.821937
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.418352
## CONSENSUS_CLUSTERAtypical 1.562137
## CONSENSUS_CLUSTERBasal 1.458206
## CONSENSUS_CLUSTERMesenchymal 1.683887
## se(coef)
## UICC_3CATIVA 0.244616
## UICC_3CATIVB-C 0.355337
## HPV16_DNA_RNADNA+RNA- 0.418283
## HPV16_DNA_RNADNA+RNA+ 0.407772
## ALTER 0.010565
## PACKYEARS 0.004458
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.249448
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.347146
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.345793
## CONSENSUS_CLUSTERAtypical 0.432559
## CONSENSUS_CLUSTERBasal 0.406300
## CONSENSUS_CLUSTERMesenchymal 0.403076
## z
## UICC_3CATIVA 2.56
## UICC_3CATIVB-C 5.87
## HPV16_DNA_RNADNA+RNA- -1.63
## HPV16_DNA_RNADNA+RNA+ -3.22
## ALTER 1.15
## PACKYEARS 0.15
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.57
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.56
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -2.52
## CONSENSUS_CLUSTERAtypical 1.03
## CONSENSUS_CLUSTERBasal 0.93
## CONSENSUS_CLUSTERMesenchymal 1.29
## Pr(>|z|)
## UICC_3CATIVA 0.0104
## UICC_3CATIVB-C 4.3e-09
## HPV16_DNA_RNADNA+RNA- 0.1036

```

```

## HPV16_DNA_RNADNA+RNA+ 0.0013
## ALTER 0.2491
## PACKYEARS 0.8801
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.5720
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.5722
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.0117
## CONSENSUS_CLUSTERAtypical 0.3024
## CONSENSUS_CLUSTERBasal 0.3532
## CONSENSUS_CLUSTERMesenchymal 0.1961
##
## UICC_3CATIVA *
## UICC_3CATIVB-C ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+ **
## ALTER
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx *
## CONSENSUS_CLUSTERAtypical
## CONSENSUS_CLUSTERBasal
## CONSENSUS_CLUSTERMesenchymal
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
## exp(coef)
## UICC_3CATIVA 1.871
## UICC_3CATIVB-C 8.056
## HPV16_DNA_RNADNA+RNA- 0.506
## HPV16_DNA_RNADNA+RNA+ 0.269
## ALTER 1.012
## PACKYEARS 1.001
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.869
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.822
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.418
## CONSENSUS_CLUSTERAtypical 1.562
## CONSENSUS_CLUSTERBasal 1.458
## CONSENSUS_CLUSTERMesenchymal 1.684
##
## exp(-coef)
## UICC_3CATIVA 0.534
## UICC_3CATIVB-C 0.124
## HPV16_DNA_RNADNA+RNA- 1.976
## HPV16_DNA_RNADNA+RNA+ 3.712
## ALTER 0.988
## PACKYEARS 0.999
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.151
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.217
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 2.390

```

```

## CONSENSUS_CLUSTERAtypical 0.640
## CONSENSUS_CLUSTERBasal 0.686
## CONSENSUS_CLUSTERMesenchymal 0.594
## lower .95
## UICC_3CATIVA 1.158
## UICC_3CATIVB-C 4.014
## HPV16_DNA_RNADNA+RNA- 0.223
## HPV16_DNA_RNADNA+RNA+ 0.121
## ALTER 0.992
## PACKYEARS 0.992
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.533
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.416
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.212
## CONSENSUS_CLUSTERAtypical 0.669
## CONSENSUS_CLUSTERBasal 0.658
## CONSENSUS_CLUSTERMesenchymal 0.764
## upper .95
## UICC_3CATIVA 3.022
## UICC_3CATIVB-C 16.164
## HPV16_DNA_RNADNA+RNA- 1.149
## HPV16_DNA_RNADNA+RNA+ 0.599
## ALTER 1.033
## PACKYEARS 1.009
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.416
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.623
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.824
## CONSENSUS_CLUSTERAtypical 3.647
## CONSENSUS_CLUSTERBasal 3.233
## CONSENSUS_CLUSTERMesenchymal 3.710
##
## Concordance= 0.666 (se = 0.031 )
## Rsquare= 0.179 (max possible= 0.988 )
## Likelihood ratio test= 45 on 12 df, p=1.03e-05
## Wald test = 44.5 on 12 df, p=1.26e-05
## Score (logrank) test = 49.2 on 12 df, p=1.92e-06

# cox.zph(surv.res) stepAIC(surv.res)
coxtable(surv.res)

## hr 2.5 %
## UICC_3CATIVA 1.87 1.16
## UICC_3CATIVB-C 8.06 4.01
## HPV16_DNA_RNADNA+RNA- 0.51 0.22
## HPV16_DNA_RNADNA+RNA+ 0.27 0.12
## ALTER 1.01 0.99
## PACKYEARS 1.00 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.87 0.53
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.82 0.42
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.42 0.21

```



```

## CONSENSUS_CLUSTERAtypical 1.56 0.67
## CONSENSUS_CLUSTERBasal 1.46 0.66
## CONSENSUS_CLUSTERMesenchymal 1.68 0.76
## 97.5 %
## UICC_3CATIVA 3.02
## UICC_3CATIVB-C 16.16
## HPV16_DNA_RNADNA+RNA- 1.15
## HPV16_DNA_RNADNA+RNA+ 0.60
## ALTER 1.03
## PACKYEARS 1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.42
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.62
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.82
## CONSENSUS_CLUSTERAtypical 3.65
## CONSENSUS_CLUSTERBasal 3.23
## CONSENSUS_CLUSTERMesenchymal 3.71
## p
## UICC_3CATIVA 0.010
## UICC_3CATIVB-C 0.000
## HPV16_DNA_RNADNA+RNA- 0.104
## HPV16_DNA_RNADNA+RNA+ 0.001
## ALTER 0.249
## PACKYEARS 0.880
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.572
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.572
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.012
## CONSENSUS_CLUSTERAtypical 0.302
## CONSENSUS_CLUSTERBasal 0.353
## CONSENSUS_CLUSTERMesenchymal 0.196

Anova(surv.res, type = 2, test.statistic = "Wald")

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset & !is.na(ds$CONSENSUS_CLUSTER)]
## Df Chisq Pr(>Chisq)
## UICC_3CAT 2 34.77 2.8e-08
## HPV16_DNA_RNA 2 11.77 0.0028
## ALTER 1 1.33 0.2491
## PACKYEARS 1 0.02 0.8801
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") 3 6.50 0.0897
## CONSENSUS_CLUSTER 3 1.72 0.6322
## Residuals 216
##
## UICC_3CAT ***
## HPV16_DNA_RNA **
## ALTER
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") .

```

```
## CONSENSUS_CLUSTER
## Residuals
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.3 In HPV DNA-

5.3.1 UICC stages, 1,2,3 vs. 4a vs. 4b,4c

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT, data = ds[cur.subset, ])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT, data = ds[cur.subset,
##      ])
##
##      n= 189, number of events= 94
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.547      1.728   0.249 2.19   0.028 *
## UICC_3CATIVB-C  1.849      6.356   0.329 5.63  1.8e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.73      0.579      1.06      2.82
## UICC_3CATIVB-C        6.36      0.157      3.34     12.10
##
## Concordance= 0.612 (se = 0.028 )
## Rsquare= 0.129 (max possible= 0.991 )
## Likelihood ratio test= 26.1 on 2 df,  p=2.14e-06
## Wald test              = 32.5 on 2 df,  p=8.78e-08
## Score (logrank) test = 39 on 2 df,  p=3.47e-09
```

```
cox.zph(surv.res)
```

```
##              rho chisq      p
## UICC_3CATIVA    0.1239 1.4617 0.227
## UICC_3CATIVB-C -0.0223 0.0446 0.833
## GLOBAL          NA  2.4590 0.292
```

5.3.2 UICC, AGE

```

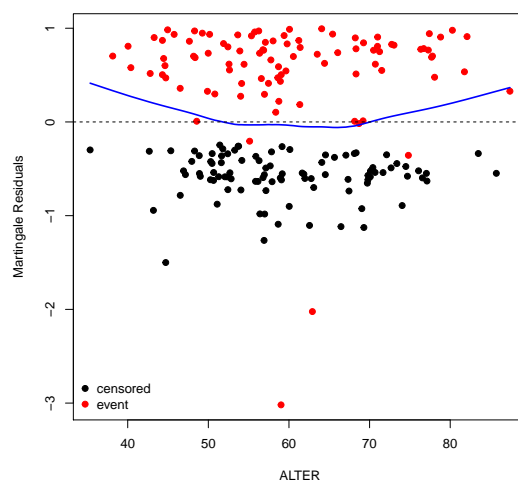
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER, data = ds[cur.subset,
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER, data = ds[cur.subset,
##      ], model = TRUE)
##
##      n= 189, number of events= 94
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.54601   1.72635  0.24944  2.19   0.029 *
## UICC_3CATIVB-C  1.84841   6.34974  0.32866  5.62  1.9e-08 ***
## ALTER          0.00295   1.00296  0.01049  0.28   0.778
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.73      0.579      1.059      2.81
## UICC_3CATIVB-C        6.35      0.157      3.334     12.09
## ALTER                 1.00      0.997      0.983      1.02
##
## Concordance= 0.615 (se = 0.032 )
## Rsquare= 0.129 (max possible= 0.991 )
## Likelihood ratio test= 26.2 on 3 df,  p=8.7e-06
## Wald test              = 32.6 on 3 df,  p=3.98e-07
## Score (logrank) test = 39 on 3 df,  p=1.71e-08

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA    0.1241 1.4695 0.225
## UICC_3CATIVB-C -0.0219 0.0429 0.836
## ALTER          -0.0244 0.0731 0.787
## GLOBAL          NA 2.5293 0.470

```



5.3.3 UICC, AGE (in categories: up to 50 or over 70 vs. between 50 and 70)

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT, data = ds[cur.subset
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT,
##       data = ds[cur.subset, ], model = TRUE)
##
##      n= 189, number of events= 94
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.570      1.768   0.250  2.28  0.0227 *
## UICC_3CATIVB-C     1.961      7.103   0.332  5.90  3.6e-09 ***
## ALTER_3CAT(50,70] -0.578      0.561   0.213 -2.71  0.0066 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.768      0.566      1.08      2.886
## UICC_3CATIVB-C     7.103      0.141      3.70     13.620
## ALTER_3CAT(50,70]  0.561      1.783      0.37      0.852
##
## Concordance= 0.636 (se = 0.031 )
## Rsquare= 0.161 (max possible= 0.991 )
## Likelihood ratio test= 33.3 on 3 df,  p=2.8e-07
## Wald test               = 39.4 on 3 df,  p=1.43e-08
## Score (logrank) test = 46.1 on 3 df,  p=5.31e-10

cox.zph(surv.res)

##              rho      chisq      p

```

```
## UICC_3CATIVA      0.13873 1.83925 0.175
## UICC_3CATIVB-C    0.00441 0.00174 0.967
## ALTER_3CAT(50,70] -0.10371 1.04346 0.307
## GLOBAL            NA 3.66238 0.300
```

5.3.4 UICC, AGE, PACKYEARS

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + I(PACKYEARS >
  30), data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       I(PACKYEARS > 30), data = ds[cur.subset, ], model = TRUE)
##
## n= 188, number of events= 93
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.559      1.750   0.251  2.23  0.0259 *
## UICC_3CATIVB-C    1.940      6.961   0.333  5.82  5.8e-09 ***
## ALTER_3CAT(50,70] -0.692      0.501   0.223 -3.10  0.0019 **
## I(PACKYEARS > 30)TRUE 0.377      1.458   0.222  1.70  0.0888 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.750      0.572   1.070   2.862
## UICC_3CATIVB-C    6.961      0.144   3.622  13.379
## ALTER_3CAT(50,70] 0.501      1.998   0.323   0.775
## I(PACKYEARS > 30)TRUE 1.458      0.686   0.944   2.252
##
## Concordance= 0.652 (se = 0.032 )
## Rsquare= 0.175 (max possible= 0.99 )
## Likelihood ratio test= 36.2 on 4 df,  p=2.63e-07
## Wald test               = 41 on 4 df,  p=2.72e-08
## Score (logrank) test = 48.4 on 4 df,  p=7.9e-10

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA      0.1341 1.6941 0.193
## UICC_3CATIVB-C    -0.0115 0.0118 0.913
## ALTER_3CAT(50,70] -0.0995 0.9497 0.330
## I(PACKYEARS > 30)TRUE 0.0237 0.0537 0.817
## GLOBAL            NA 3.7719 0.438
```

5.3.5 UICC, AGE, ALCOHOL consumption

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + ALKOHOL, data = ds[
  ], model = TRUE)
# surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
# I(ALKOHOL == '>60'), data = ds[cur.subset,], model = TRUE) surv.res <-
# coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + I(ALKOHOL !=
# 'nein'), data = ds[cur.subset,], model = TRUE) surv.res <-
# coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + I(ALKOHOL %in%
# c('1 bis 30', '>60')), data = ds[cur.subset,], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       ALKOHOL, data = ds[cur.subset, ], model = TRUE)
##
##      n= 189, number of events= 94
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.580      1.785   0.250   2.31   0.021 *
## UICC_3CATIVB-C     2.007      7.438   0.337   5.95  2.7e-09 ***
## ALTER_3CAT(50,70] -0.643      0.525   0.217  -2.97   0.003 **
## ALKOHOL1 bis 30    0.490      1.632   0.466   1.05   0.293
## ALKOHOL31 bis 60   0.533      1.704   0.466   1.14   0.253
## ALKOHOL>60         0.768      2.154   0.442   1.73   0.083 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.785      0.560      1.093      2.917
## UICC_3CATIVB-C     7.438      0.134      3.840     14.406
## ALTER_3CAT(50,70]  0.525      1.903      0.344      0.804
## ALKOHOL1 bis 30    1.632      0.613      0.655      4.066
## ALKOHOL31 bis 60   1.704      0.587      0.683      4.251
## ALKOHOL>60         2.154      0.464      0.905      5.127
##
## Concordance= 0.653 (se = 0.032 )
## Rsquare= 0.179 (max possible= 0.991 )
## Likelihood ratio test= 37.3 on 6 df, p=1.55e-06
## Wald test              = 41.9 on 6 df, p=1.93e-07
## Score (logrank) test = 49.4 on 6 df, p=6.23e-09

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.14031 1.889 0.169
## UICC_3CATIVB-C     0.00645 0.004 0.950
## ALTER_3CAT(50,70] -0.07123 0.514 0.474

```

```
## ALKOHOL1 bis 30    -0.03854 0.146 0.702
## ALKOHOL31 bis 60  -0.05764 0.320 0.571
## ALKOHOL>60        -0.06089 0.363 0.547
## GLOBAL              NA 3.837 0.699
```

5.3.6 PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset, ],
  model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset,
##    ], model = TRUE)
##
##    n= 188, number of events= 93
##    (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## PACKYEARS -0.00182   0.99818  0.00529 -0.34    0.73
##
##              exp(coef) exp(-coef) lower .95 upper .95
## PACKYEARS    0.998           1    0.988      1.01
##
## Concordance= 0.513  (se = 0.032 )
## Rsquare= 0.001   (max possible= 0.99 )
## Likelihood ratio test= 0.12  on 1 df,   p=0.731
## Wald test            = 0.12  on 1 df,   p=0.731
## Score (logrank) test = 0.12  on 1 df,   p=0.731

cox.zph(surv.res)

##              rho    chisq      p
## PACKYEARS -0.00261 0.00074 0.978
```

5.3.7 UICC, PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + PACKYEARS, data = ds[cur.subset,
  ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + PACKYEARS,
##    data = ds[cur.subset, ], model = TRUE)
##
```

```
##      n= 188, number of events= 93
##      (1 observation deleted due to missingness)
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.536218  1.709529  0.250223  2.14    0.032 *
## UICC_3CATIVB-C  1.840836  6.301806  0.328928  5.60  2.2e-08 ***
## PACKYEARS      -0.000841  0.999160  0.005196 -0.16    0.871
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.710      0.585      1.047      2.79
## UICC_3CATIVB-C        6.302      0.159      3.307     12.01
## PACKYEARS             0.999      1.001      0.989      1.01
##
## Concordance= 0.61 (se = 0.032 )
## Rsquare= 0.129 (max possible= 0.99 )
## Likelihood ratio test= 25.9 on 3 df,  p=9.87e-06
## Wald test               = 32.3 on 3 df,  p=4.44e-07
## Score (logrank) test = 38.8 on 3 df,  p=1.93e-08

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA    0.1162 1.2698 0.260
## UICC_3CATIVB-C -0.0231 0.0472 0.828
## PACKYEARS      -0.0574 0.3428 0.558
## GLOBAL          NA  2.5247 0.471
```

5.3.8 UICC, AGE continuous, PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS, data = ds[cur
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS,
##       data = ds[cur.subset, ], model = TRUE)
##
##      n= 188, number of events= 93
##      (1 observation deleted due to missingness)
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.535194  1.707779  0.250256  2.14    0.032 *
## UICC_3CATIVB-C  1.839709  6.294709  0.328987  5.59  2.2e-08 ***
## ALTER          0.003051  1.003056  0.010466  0.29    0.771
## PACKYEARS      -0.000884  0.999116  0.005182 -0.17    0.865
```



```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.708      0.586      1.046      2.79
## UICC_3CATIVB-C     6.295      0.159      3.303     12.00
## ALTER             1.003      0.997      0.983      1.02
## PACKYEARS          0.999      1.001      0.989      1.01
##
## Concordance= 0.608 (se = 0.032 )
## Rsquare= 0.129 (max possible= 0.99 )
## Likelihood ratio test= 26 on 4 df,  p=3.14e-05
## Wald test          = 32.4 on 4 df,  p=1.57e-06
## Score (logrank) test = 38.9 on 4 df,  p=7.43e-08

cox.zph(surv.res)

##               rho  chisq    p
## UICC_3CATIVA    0.1162 1.2738 0.259
## UICC_3CATIVB-C -0.0227 0.0454 0.831
## ALTER          -0.0221 0.0590 0.808
## PACKYEARS      -0.0573 0.3401 0.560
## GLOBAL         NA  2.5817 0.630
```

5.3.9 UICC, AGE, PACKYEARS continuous

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + PACKYEARS,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       PACKYEARS, data = ds[cur.subset, ], model = TRUE)
##
## n= 188, number of events= 93
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.56493   1.75932  0.25103   2.25   0.0244 *
## UICC_3CATIVB-C     1.98286   7.26349  0.33499   5.92  3.2e-09 ***
## ALTER_3CAT(50,70] -0.63686   0.52895  0.22584  -2.82   0.0048 **
## PACKYEARS          0.00373   1.00373  0.00535   0.70   0.4861
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```
## UICC_3CATIVA          1.759      0.568      1.076      2.878
## UICC_3CATIVB-C        7.263      0.138      3.767     14.005
## ALTER_3CAT(50,70]     0.529      1.891      0.340      0.823
## PACKYEARS             1.004      0.996      0.993      1.014
##
## Concordance= 0.647 (se = 0.032 )
## Rsquare= 0.164 (max possible= 0.99 )
## Likelihood ratio test= 33.7 on 4 df, p=8.45e-07
## Wald test              = 39.4 on 4 df, p=5.66e-08
## Score (logrank) test = 46.4 on 4 df, p=2.04e-09

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA    0.130 1.5969 0.206
## UICC_3CATIVB-C -0.012 0.0125 0.911
## ALTER_3CAT(50,70] -0.083 0.6873 0.407
## PACKYEARS      -0.047 0.2262 0.634
## GLOBAL         NA 3.8956 0.420
```

5.3.10 UICC, ALTER, PACKYEARS continuous in Oropharynx (HPV-) patients

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB) &
  ds$LOKALISATION_GROB_TEXT == "oropharynx" & !is.na(ds$LOKALISATION_GROB_TEXT)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + PACKYEARS,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##   PACKYEARS, data = ds[cur.subset, ], model = TRUE)
##
## n= 50, number of events= 30
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.6187   1.8565  0.5244   1.18  0.23805
## UICC_3CATIVB-C  2.2421   9.4134  0.6649   3.37  0.00075 ***
## ALTER_3CAT(50,70] -0.9565   0.3842  0.4650  -2.06  0.03970 *
## PACKYEARS       0.0163   1.0165  0.0132   1.24  0.21601
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA    1.857      0.539    0.664    5.189
## UICC_3CATIVB-C  9.413      0.106    2.557   34.649
## ALTER_3CAT(50,70] 0.384      2.603    0.154    0.956
```

```
## PACKYEARS          1.016      0.984      0.991      1.043
##
## Concordance= 0.705 (se = 0.059 )
## Rsquare= 0.234 (max possible= 0.982 )
## Likelihood ratio test= 13.3 on 4 df, p=0.00991
## Wald test = 13.6 on 4 df, p=0.00857
## Score (logrank) test = 15.8 on 4 df, p=0.00324

# cox.zph(surv.res)
```

5.4 Models with Consensus Clusters in HPV-

5.4.1 Mesenchymal vs. other Consensus Clusters, univariate association

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB)
surv.res <- coxph(surv.obj[cur.subset] ~ IS_MESENCHYMAL, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ IS_MESENCHYMAL, data = ds[cur.subset,
##      ])
##
##      n= 179, number of events= 86
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## IS_MESENCHYMALMesenchymal 0.277      1.320      0.222 1.25      0.21
##
##              exp(coef) exp(-coef) lower .95 upper .95
## IS_MESENCHYMALMesenchymal      1.32      0.758      0.853      2.04
##
## Concordance= 0.539 (se = 0.027 )
## Rsquare= 0.008 (max possible= 0.989 )
## Likelihood ratio test= 1.52 on 1 df, p=0.218
## Wald test = 1.56 on 1 df, p=0.212
## Score (logrank) test = 1.57 on 1 df, p=0.211

cox.zph(surv.res)

##              rho chisq      p
## IS_MESENCHYMALMesenchymal -0.0667 0.384 0.536
```

5.4.2 UICC, Mesenchymal vs. other Consensus Clusters

```

cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg"
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + IS_MESENCHYMAL, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + IS_MESENCHYMAL,
##       data = ds[cur.subset, ])
##
##      n= 179, number of events= 86
##      (12 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.662      1.939   0.259  2.55   0.011 *
## UICC_3CATIVB-C     1.995      7.355   0.370  5.39   7e-08 ***
## IS_MESENCHYMALMesenchymal 0.365      1.441   0.224  1.63   0.103
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA           1.94      0.516    1.166    3.22
## UICC_3CATIVB-C          7.36      0.136    3.561   15.19
## IS_MESENCHYMALMesenchymal 1.44      0.694    0.928    2.24
##
## Concordance= 0.632 (se = 0.032 )
## Rsquare= 0.133 (max possible= 0.989 )
## Likelihood ratio test= 25.6 on 3 df,  p=1.17e-05
## Wald test               = 30.2 on 3 df,  p=1.26e-06
## Score (logrank) test = 35.9 on 3 df,  p=8.03e-08

cox.zph(surv.res)

##              rho   chisq    p
## UICC_3CATIVA      0.08284 0.59546 0.440
## UICC_3CATIVB-C    -0.00638 0.00344 0.953
## IS_MESENCHYMALMesenchymal -0.04759 0.20128 0.654
## GLOBAL            NA 1.04349 0.791

```

5.4.3 UICC, AGE, Mesenchymal vs. other Clusters

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER + IS_MESENCHYMAL,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER + IS_MESENCHYMAL,
##       data = ds[cur.subset, ], model = TRUE)

```

```
##
##   n= 179, number of events= 86
##   (12 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.66349   1.94156  0.25959  2.56   0.011 *
## UICC_3CATIVB-C     1.99604   7.35989  0.37009  5.39  6.9e-08 ***
## ALTER             0.00281   1.00282  0.01068  0.26   0.792
## IS_MESENCHYMALMesenchymal 0.36074   1.43439  0.22482  1.60   0.109
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.94         0.515      1.167      3.23
## UICC_3CATIVB-C         7.36         0.136      3.563     15.20
## ALTER                 1.00         0.997      0.982      1.02
## IS_MESENCHYMALMesenchymal 1.43         0.697      0.923      2.23
##
## Concordance= 0.628 (se = 0.034 )
## Rsquare= 0.133 (max possible= 0.989 )
## Likelihood ratio test= 25.6 on 4 df, p=3.74e-05
## Wald test              = 30.3 on 4 df, p=4.33e-06
## Score (logrank) test = 35.9 on 4 df, p=3.03e-07

cox.zph(surv.res)

##               rho   chisq    p
## UICC_3CATIVA      0.08276 0.59285 0.441
## UICC_3CATIVB-C    -0.00576 0.00281 0.958
## ALTER             -0.01558 0.02573 0.873
## IS_MESENCHYMALMesenchymal -0.04338 0.16438 0.685
## GLOBAL            NA 1.04643 0.903
```

5.4.4 UICC, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), Mesenchymal

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + IS_MESENCHYMAL,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       IS_MESENCHYMAL, data = ds[cur.subset, ], model = TRUE)
##
##   n= 179, number of events= 86
##   (12 observations deleted due to missingness)
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.684      1.981    0.260  2.62  0.0087 **
## UICC_3CATIVB-C      2.050      7.767    0.371  5.52  3.3e-08 ***
## ALTER_3CAT(50,70]   -0.472      0.624    0.224 -2.11  0.0348 *
## IS_MESENCHYMALMesenchymal  0.282      1.326    0.227  1.24  0.2142
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.981      0.505    1.189    3.300
## UICC_3CATIVB-C      7.767      0.129    3.754   16.073
## ALTER_3CAT(50,70]    0.624      1.604    0.402    0.967
## IS_MESENCHYMALMesenchymal  1.326      0.754    0.849    2.071
##
## Concordance= 0.645 (se = 0.033 )
## Rsquare= 0.154 (max possible= 0.989 )
## Likelihood ratio test= 29.9 on 4 df,  p=5.01e-06
## Wald test = 34.6 on 4 df,  p=5.55e-07
## Score (logrank) test = 40.3 on 4 df,  p=3.81e-08

cox.zph(surv.res)

##               rho   chisq      p
## UICC_3CATIVA      0.09433 0.77494 0.379
## UICC_3CATIVB-C      0.00521 0.00223 0.962
## ALTER_3CAT(50,70]   -0.12662 1.46751 0.226
## IS_MESENCHYMALMesenchymal -0.08807 0.72907 0.393
## GLOBAL              NA  2.89089 0.576
```

5.4.5 UICC, AGE, PACKYEARS, Mesenchymal

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + I(PACKYEARS >
  30) + IS_MESENCHYMAL, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       I(PACKYEARS > 30) + IS_MESENCHYMAL, data = ds[cur.subset,
##       ], model = TRUE)
##
## n= 178, number of events= 85
## (13 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.665      1.945    0.261  2.55  0.011 *
## UICC_3CATIVB-C      2.037      7.667    0.372  5.48  4.3e-08 ***
## ALTER_3CAT(50,70]   -0.589      0.555    0.234 -2.52  0.012 *
```

```
## I(PACKYEARS > 30)TRUE      0.402      1.495      0.233  1.73      0.084 .
## IS_MESENCHYMALMesenchymal 0.214      1.238      0.232  0.92      0.357
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.945      0.514      1.165      3.245
## UICC_3CATIVB-C     7.667      0.130      3.699     15.891
## ALTER_3CAT(50,70]  0.555      1.802      0.351      0.877
## I(PACKYEARS > 30)TRUE  1.495      0.669      0.948      2.359
## IS_MESENCHYMALMesenchymal 1.238      0.808      0.786      1.952
##
## Concordance= 0.657 (se = 0.034 )
## Rsquare= 0.169 (max possible= 0.988 )
## Likelihood ratio test= 32.9 on 5 df, p=3.89e-06
## Wald test = 36.5 on 5 df, p=7.54e-07
## Score (logrank) test = 42.7 on 5 df, p=4.19e-08

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA      0.0920 0.72556 0.394
## UICC_3CATIVB-C    -0.0116 0.01080 0.917
## ALTER_3CAT(50,70] -0.1222 1.35262 0.245
## I(PACKYEARS > 30)TRUE  0.0103 0.00961 0.922
## IS_MESENCHYMALMesenchymal -0.0860 0.72542 0.394
## GLOBAL              NA  2.97320 0.704
```

5.5 In HPV16 DNA+ RNA+

5.5.1 PACKYEARS

```
# cur.subset <- is.primary & ds$INNO_LIPA_GROB == '16' &
# !is.na(ds$INNO_LIPA_GROB)
cur.subset <- is.primary & ds$HPV16_DNA_RNA == "DNA+RNA+" & !is.na(ds$HPV16_DNA_RNA)
surv.res <- coxph(surv.obj[cur.subset] ~ I(PACKYEARS > 30), data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ I(PACKYEARS > 30), data = ds[cur.subset,
##      ])
##
##      n= 35, number of events= 11
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## I(PACKYEARS > 30)TRUE  2.390     10.912    0.695  3.44  0.00058 ***
```

```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## I(PACKYEARS > 30)TRUE      10.9      0.0916      2.79      42.6
##
## Concordance= 0.808 (se = 0.07 )
## Rsquare= 0.312 (max possible= 0.843 )
## Likelihood ratio test= 13.1 on 1 df,  p=0.000301
## Wald test               = 11.8 on 1 df,  p=0.000584
## Score (logrank) test = 18.3 on 1 df,  p=1.9e-05

cox.zph(surv.res)

##               rho chisq      p
## I(PACKYEARS > 30)TRUE -0.356  1.18 0.277
```

5.5.2 T categorized in 1-2 vs. 3-4

```
ds$T_CAT <- ds$T
ds$T_CAT <- factor(ds$T_CAT, levels = c("1", "2", "3", "4a", "4b"))
levels(ds$T_CAT) <- c("1-2", "1-2", "3-4", "3-4", "3-4")
surv.res <- coxph(surv.obj[cur.subset] ~ T_CAT, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_CAT, data = ds[cur.subset,
##      ])
##
## n= 35, number of events= 11
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4  2.58      13.26      1.06 2.43   0.015 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4      13.3      0.0754      1.65      107
##
## Concordance= 0.736 (se = 0.085 )
## Rsquare= 0.253 (max possible= 0.843 )
## Likelihood ratio test= 10.2 on 1 df,  p=0.00141
## Wald test              = 5.91 on 1 df,  p=0.0151
## Score (logrank) test = 9.9 on 1 df,  p=0.00165

cox.zph(surv.res)

##      rho chisq      p
## T_CAT3-4 0.126 0.177 0.674
```



```

surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_RNA, data = ds[cur.subset, ])
summary(surv.res)
cox.zph(surv.res)

```

5.5.3 AGE continuous

```

surv.res <- coxph(surv.obj[cur.subset] ~ ALTER, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

```

```

## Call:
## coxph(formula = surv.obj[cur.subset] ~ ALTER, data = ds[cur.subset,
##      ], model = TRUE)
##
##      n= 35, number of events= 11
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER 0.0644      1.0666   0.0372 1.73    0.083 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER              1.07         0.938   0.992      1.15
##
## Concordance= 0.633  (se = 0.1 )
## Rsquare= 0.083  (max possible= 0.843 )
## Likelihood ratio test= 3.03  on 1 df,  p=0.0819
## Wald test               = 3  on 1 df,  p=0.0833
## Score (logrank) test = 3.15  on 1 df,  p=0.0758

```

```

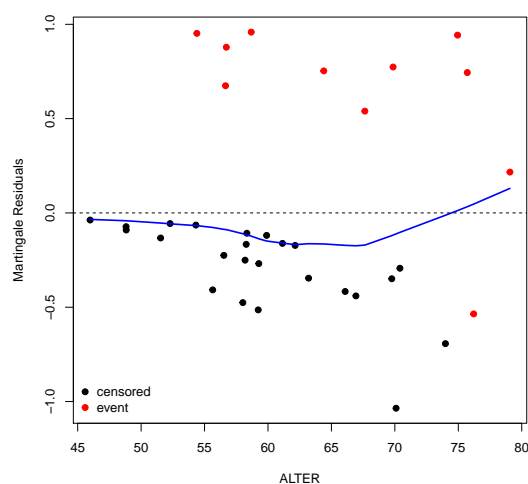
cox.zph(surv.res)

```

```

##              rho chisq      p
## ALTER 0.12 0.167 0.683

```



5.5.4 T categorized in 1-2 vs. 3-4, PACKYEARS

```

surv.res <- coxph(surv.obj[cur.subset] ~ T_CAT + I(PACKYEARS > 30), data = ds[cur.sub
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_CAT + I(PACKYEARS >
##      30), data = ds[cur.subset, ])
##
##      n= 35, number of events= 11
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4          3.86    47.41    1.37 2.81   0.005 **
## I(PACKYEARS > 30)TRUE 3.63    37.61    1.10 3.29   0.001 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4          47.4    0.0211    3.21    700
## I(PACKYEARS > 30)TRUE 37.6    0.0266    4.33    326
##
## Concordance= 0.884 (se = 0.093 )
## Rsquare= 0.562 (max possible= 0.843 )
## Likelihood ratio test= 28.9 on 2 df,  p=5.3e-07
## Wald test            = 12.2 on 2 df,  p=0.00226
## Score (logrank) test = 30.1 on 2 df,  p=2.91e-07

cox.zph(surv.res)

##              rho  chisq      p
## T_CAT3-4          0.2026 0.79997 0.371
## I(PACKYEARS > 30)TRUE 0.0318 0.00568 0.940
## GLOBAL              NA 1.06398 0.587

```

5.5.5 T categorized in 1-2 vs 3-4, PACKYEARS, ALTER (cut at 60)

```

ds$ALTER_60 <- cut(ds$ALTER, breaks = c(0, 60, Inf))
surv.res <- coxph(surv.obj[cur.subset] ~ T_CAT + ALTER_60 + I(PACKYEARS > 30),
  data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_CAT + ALTER_60 + I(PACKYEARS >
##      30), data = ds[cur.subset, ])
##
##      n= 35, number of events= 11

```

```
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4        4.114    61.208    1.437 2.86  0.00420 **
## ALTER_60(60,Inf]  1.265     3.543    0.735 1.72  0.08510 .
## I(PACKYEARS > 30)TRUE 4.073    58.730    1.166 3.49  0.00048 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4          61.21    0.0163    3.66    1024
## ALTER_60(60,Inf]    3.54    0.2822    0.84     15
## I(PACKYEARS > 30)TRUE  58.73    0.0170    5.97    577
##
## Concordance= 0.93 (se = 0.098 )
## Rsquare= 0.602 (max possible= 0.843 )
## Likelihood ratio test= 32.2 on 3 df, p=4.68e-07
## Wald test              = 13.8 on 3 df, p=0.00316
## Score (logrank) test = 31.4 on 3 df, p=7.04e-07

cox.zph(surv.res)

##               rho chisq      p
## T_CAT3-4        0.244 1.298 0.255
## ALTER_60(60,Inf]  0.429 1.124 0.289
## I(PACKYEARS > 30)TRUE 0.176 0.225 0.635
## GLOBAL           NA 2.341 0.505
```

```
ds$ALTER_60 <- cut(ds$ALTER, breaks = c(0, 60, Inf))
surv.res <- coxph(surv.obj[cur.subset] ~ T_CAT + ALTER_60 + I(PACKYEARS > 30) +
  strata(HPV16_RNA), data = ds[cur.subset, ])
summary(surv.res)
cox.zph(surv.res)
```

5.5.6 PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset, ],
  model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ PACKYEARS, data = ds[cur.subset,
##      ], model = TRUE)
##
## n= 35, number of events= 11
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
```

```
## PACKYEARS 0.02962 1.03006 0.00931 3.18 0.0015 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## PACKYEARS 1.03 0.971 1.01 1.05
##
## Concordance= 0.812 (se = 0.098 )
## Rsquare= 0.206 (max possible= 0.843 )
## Likelihood ratio test= 8.09 on 1 df, p=0.00445
## Wald test = 10.1 on 1 df, p=0.00146
## Score (logrank) test = 12.8 on 1 df, p=0.000339

cox.zph(surv.res)

## rho chisq p
## PACKYEARS -0.119 0.102 0.75
```

5.5.7 UICC, PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + PACKYEARS, data = ds[cur.subset,
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + PACKYEARS,
## data = ds[cur.subset, ], model = TRUE)
##
## n= 35, number of events= 11
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 1.9942 7.3463 1.1184 1.78 0.07457 .
## UICC_3CATIVB-C 4.0147 55.4044 1.3166 3.05 0.00229 **
## PACKYEARS 0.0385 1.0392 0.0113 3.41 0.00066 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 7.35 0.136 0.821 65.77
## UICC_3CATIVB-C 55.40 0.018 4.196 731.58
## PACKYEARS 1.04 0.962 1.016 1.06
##
## Concordance= 0.901 (se = 0.099 )
## Rsquare= 0.452 (max possible= 0.843 )
## Likelihood ratio test= 21.1 on 3 df, p=0.000102
## Wald test = 16.1 on 3 df, p=0.0011
## Score (logrank) test = 29.9 on 3 df, p=1.46e-06
```

```
cox.zph(surv.res)

##               rho   chisq     p
## UICC_3CATIVA   -0.1492 0.17048 0.680
## UICC_3CATIVB-C  0.0311 0.00735 0.932
## PACKYEARS      0.1698 0.23867 0.625
## GLOBAL        NA 0.72898 0.866
```

5.5.8 UICC, AGE continuous, PACKYEARS continuous

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS, data = ds[cur
  ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS,
##       data = ds[cur.subset, ], model = TRUE)
##
##      n= 35, number of events= 11
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      2.0737     7.9541  1.1457  1.81  0.0703 .
## UICC_3CATIVB-C    4.2003    66.7054  1.4481  2.90  0.0037 **
## ALTER            -0.0146     0.9855  0.0476 -0.31  0.7598
## PACKYEARS         0.0398     1.0406  0.0123  3.24  0.0012 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      7.954      0.126     0.842     75.13
## UICC_3CATIVB-C    66.705      0.015     3.904    1139.73
## ALTER             0.986      1.015     0.898      1.08
## PACKYEARS         1.041      0.961     1.016      1.07
##
## Concordance= 0.903 (se = 0.1 )
## Rsquare= 0.454 (max possible= 0.843 )
## Likelihood ratio test= 21.2 on 4 df, p=0.000295
## Wald test              = 16.1 on 4 df, p=0.00286
## Score (logrank) test = 30.3 on 4 df, p=4.26e-06

cox.zph(surv.res)

##               rho chisq     p
## UICC_3CATIVA   -0.334 0.736 0.3910
## UICC_3CATIVB-C -0.363 0.595 0.4405
## ALTER          0.555 3.957 0.0467
## PACKYEARS      -0.134 0.137 0.7112
## GLOBAL         NA 4.670 0.3228
```

5.5.9 UICC, AGE continuous, PACKYEARS continuous in Oropharynx (HPV16 DNA+ RNA+)

```

cur.subset <- is.primary & ds$HPV16_DNA_RNA == "DNA+RNA+" & !is.na(ds$HPV16_DNA_RNA) &
  ds$LOKALISATION_GROB_TEXT == "oropharynx" & !is.na(ds$LOKALISATION_GROB_TEXT)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS, data = ds[cur
  ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS,
##       data = ds[cur.subset, ], model = TRUE)
##
##      n= 28, number of events= 10
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.96731   7.15143  1.17234  1.68  0.0933 .
## UICC_3CATIVB-C  4.17535  65.06247  1.46874  2.84  0.0045 **
## ALTER          -0.00982   0.99023  0.04976 -0.20  0.8435
## PACKYEARS       0.03504   1.03566  0.01253  2.80  0.0052 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA         7.15     0.1398     0.719    71.17
## UICC_3CATIVB-C       65.06     0.0154     3.657   1157.51
## ALTER                0.99     1.0099     0.898     1.09
## PACKYEARS            1.04     0.9656     1.011     1.06
##
## Concordance= 0.89 (se = 0.106 )
## Rsquare= 0.502 (max possible= 0.861 )
## Likelihood ratio test= 19.5 on 4 df, p=0.000623
## Wald test              = 13.9 on 4 df, p=0.00759
## Score (logrank) test = 28.1 on 4 df, p=1.2e-05

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA   -0.330 0.6445 0.4221
## UICC_3CATIVB-C -0.245 0.2586 0.6111
## ALTER          0.538 3.1898 0.0741
## PACKYEARS      -0.065 0.0241 0.8767
## GLOBAL         NA 4.0540 0.3987

```

5.5.10 UICC, AGE continuous, PACKYEARS continuous in HPV16 DNA+

```

cur.subset <- is.primary & ds$INNO_LIPA_GROB == "16" & !is.na(ds$INNO_LIPA_GROB)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS, data = ds[cur
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS,
##       data = ds[cur.subset, ], model = TRUE)
##
##      n= 62, number of events= 24
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.62772    1.87333  0.64399  0.97   0.330
## UICC_3CATIVB-C  1.00835    2.74106  0.72913  1.38   0.167
## ALTER          0.04998    1.05125  0.02502  2.00   0.046 *
## PACKYEARS      0.01337    1.01346  0.00598  2.24   0.025 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.87      0.534      0.530      6.62
## UICC_3CATIVB-C        2.74      0.365      0.657     11.44
## ALTER                1.05      0.951      1.001      1.10
## PACKYEARS            1.01      0.987      1.002      1.03
##
## Concordance= 0.7 (se = 0.067 )
## Rsquare= 0.163 (max possible= 0.929 )
## Likelihood ratio test= 11 on 4 df,  p=0.0264
## Wald test              = 12.2 on 4 df,  p=0.0162
## Score (logrank) test = 13.1 on 4 df,  p=0.0108

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA   -0.229  1.118  0.290
## UICC_3CATIVB-C -0.160  0.484  0.487
## ALTER          0.163  0.610  0.435
## PACKYEARS      0.213  0.764  0.382
## GLOBAL         NA   2.341  0.673

```

5.5.11 UICC, AGE continuous, PACKYEARS continuous in Oropharynx (HPV16 DNA+)

```

cur.subset <- is.primary & ds$INNO_LIPA_GROB == "16" & !is.na(ds$INNO_LIPA_GROB) &
  ds$LOKALISATION_GROB_TEXT == "oropharynx" & !is.na(ds$LOKALISATION_GROB_TEXT)
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS, data = ds[cur

```

```

    ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER + PACKYEARS,
##       data = ds[cur.subset, ], model = TRUE)
##
##      n= 45, number of events= 20
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.83882   2.31363  0.77706  1.08   0.280
## UICC_3CATIVB-C  1.03189   2.80636  0.86259  1.20   0.232
## ALTER          0.05907   1.06085  0.02758  2.14   0.032 *
## PACKYEARS      0.01066   1.01071  0.00634  1.68   0.093 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          2.31      0.432      0.504     10.61
## UICC_3CATIVB-C        2.81      0.356      0.517     15.22
## ALTER                 1.06      0.943      1.005      1.12
## PACKYEARS             1.01      0.989      0.998      1.02
##
## Concordance= 0.704 (se = 0.075 )
## Rsquare= 0.198 (max possible= 0.937 )
## Likelihood ratio test= 9.9 on 4 df,  p=0.0421
## Wald test               = 10.1 on 4 df,  p=0.0382
## Score (logrank) test = 10.9 on 4 df,  p=0.0276

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA   -0.1582  0.4457  0.504
## UICC_3CATIVB-C -0.0237  0.0089  0.925
## ALTER          0.1953  0.7746  0.379
## PACKYEARS      0.1740  0.4008  0.527
## GLOBAL         NA  2.1197  0.714

```