

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

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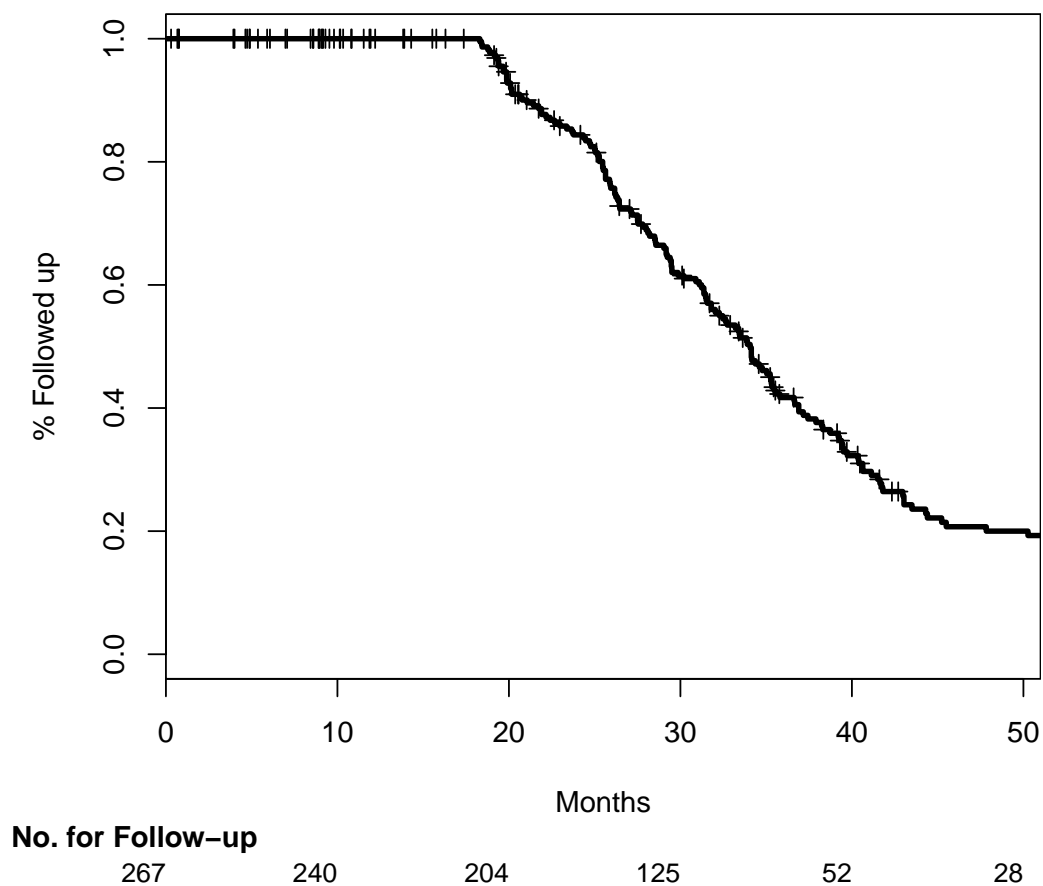
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PLEASE NOTE: For historical reasons, the Immune Response Cluster (one of the Consensus Clusters determined by gene expression) is sometimes called *Atypical* Cluster in this document.

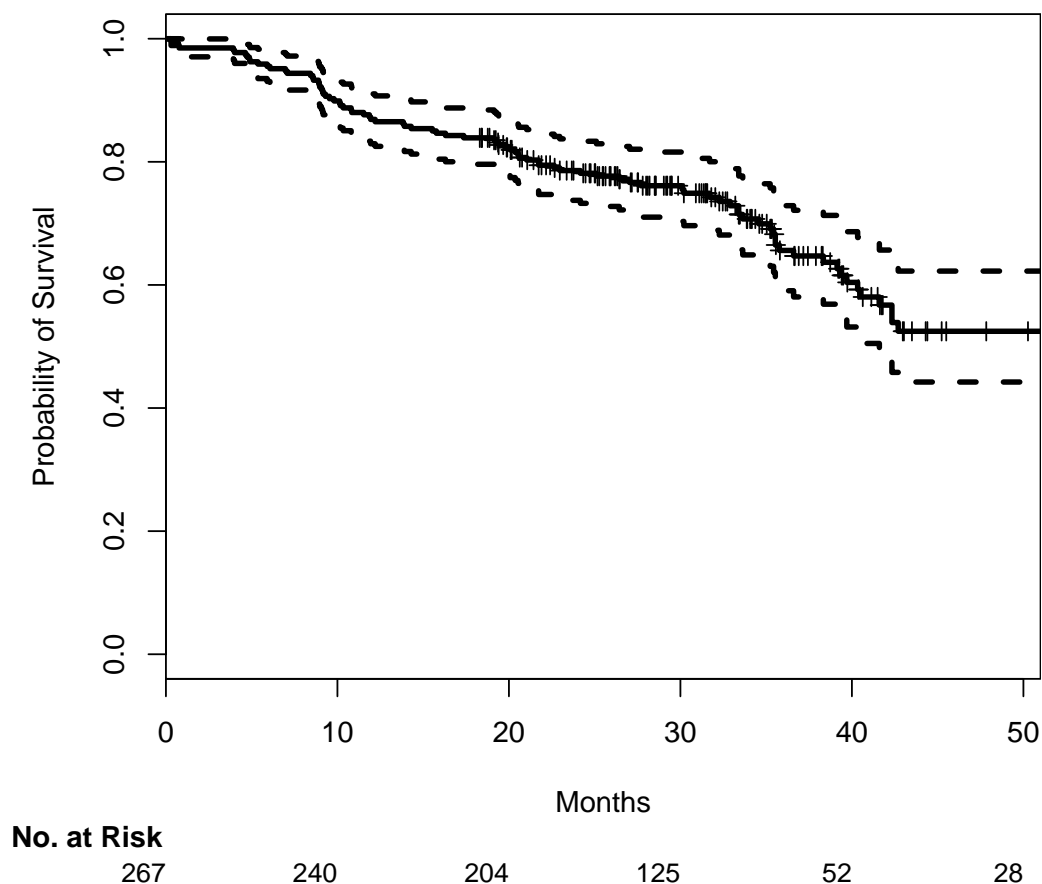
1 Follow-up

```
##
## 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   94.0    60.3    41.6    74.7
```



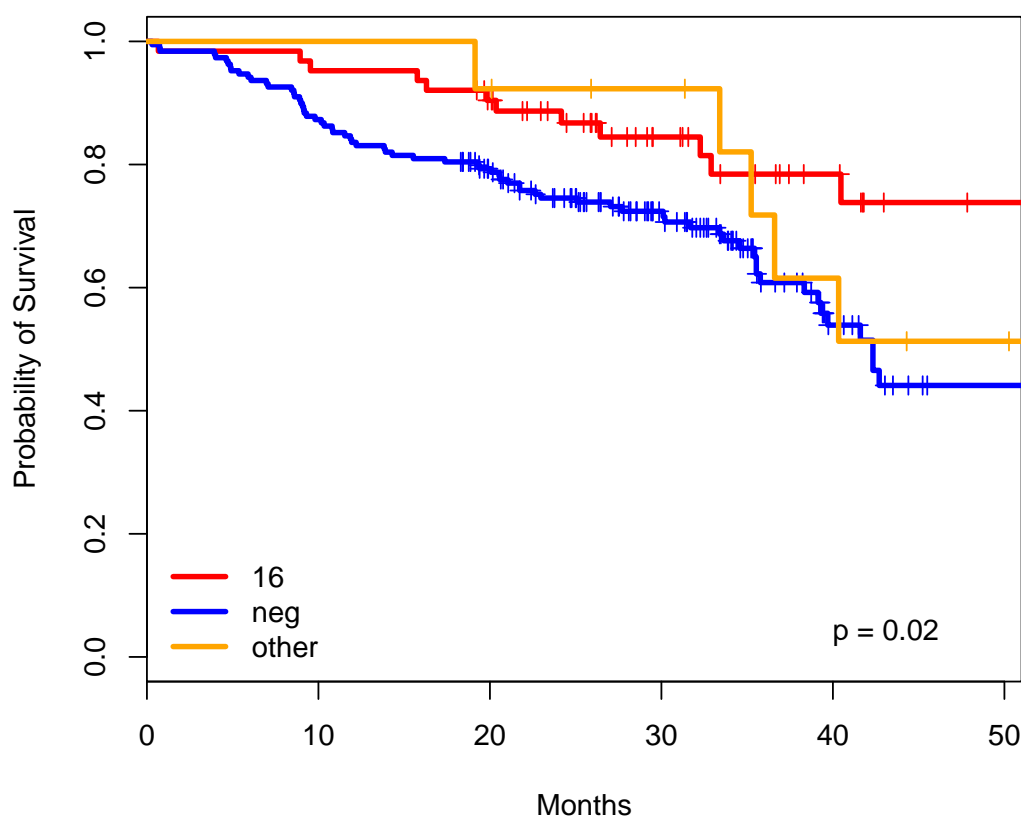
3 Exploration of single variables

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= 93
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]neg  0.801    2.228   0.296  2.71  0.0068 **
```

```
## split[cur.subset]other 0.727      2.069      0.467 1.56      0.1193
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]neg      2.23      0.449      1.247      3.98
## split[cur.subset]other      2.07      0.483      0.829      5.16
##
## Concordance= 0.571  (se = 0.027 )
## Rsquare= 0.032  (max possible= 0.966 )
## Likelihood ratio test= 8.72  on 2 df,   p=0.0128
## Wald test              = 7.35  on 2 df,   p=0.0253
## Score (logrank) test = 7.72  on 2 df,   p=0.021
```



No. at Risk						
16	63	60	54	31	18	11
neg	189	165	137	83	27	12
other	13	13	12	10	6	4

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     42.0000     60.0000     0.6082     0.0445
## lower 95% CI upper 95% CI
##    0.5270     0.7020
##
##           split[cur.subset]=DNA+RNA-
##      time      n.risk      n.event      survival      std.err
##    36.0000     6.0000     3.0000     0.8500     0.0798
## lower 95% CI upper 95% CI
##    0.7071     1.0000
##
##           split[cur.subset]=DNA+RNA+
##      time      n.risk      n.event      survival      std.err
##    36.0000    14.0000     5.0000     0.8133     0.0779
## lower 95% CI upper 95% CI
##    0.6740     0.9813
## Call: survfit(formula = surv.obj[cur.subset] ~ 1)
##
##   time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    36     73     75   0.656  0.0352     0.591     0.729
##
## 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    16.0000    14.0000     0.6861     0.0734
## lower 95% CI upper 95% CI
##    0.5563     0.8461
##
##           split[cur.subset]=DNA+RNA-
##      time      n.risk      n.event      survival      std.err
##    36.000     2.000     2.000     0.800     0.126
## lower 95% CI upper 95% CI
##    0.587     1.000
##
##           split[cur.subset]=DNA+RNA+
##      time      n.risk      n.event      survival      std.err
##    36.000    12.000     5.000     0.774     0.091
## lower 95% CI upper 95% CI
##    0.615     0.975
```

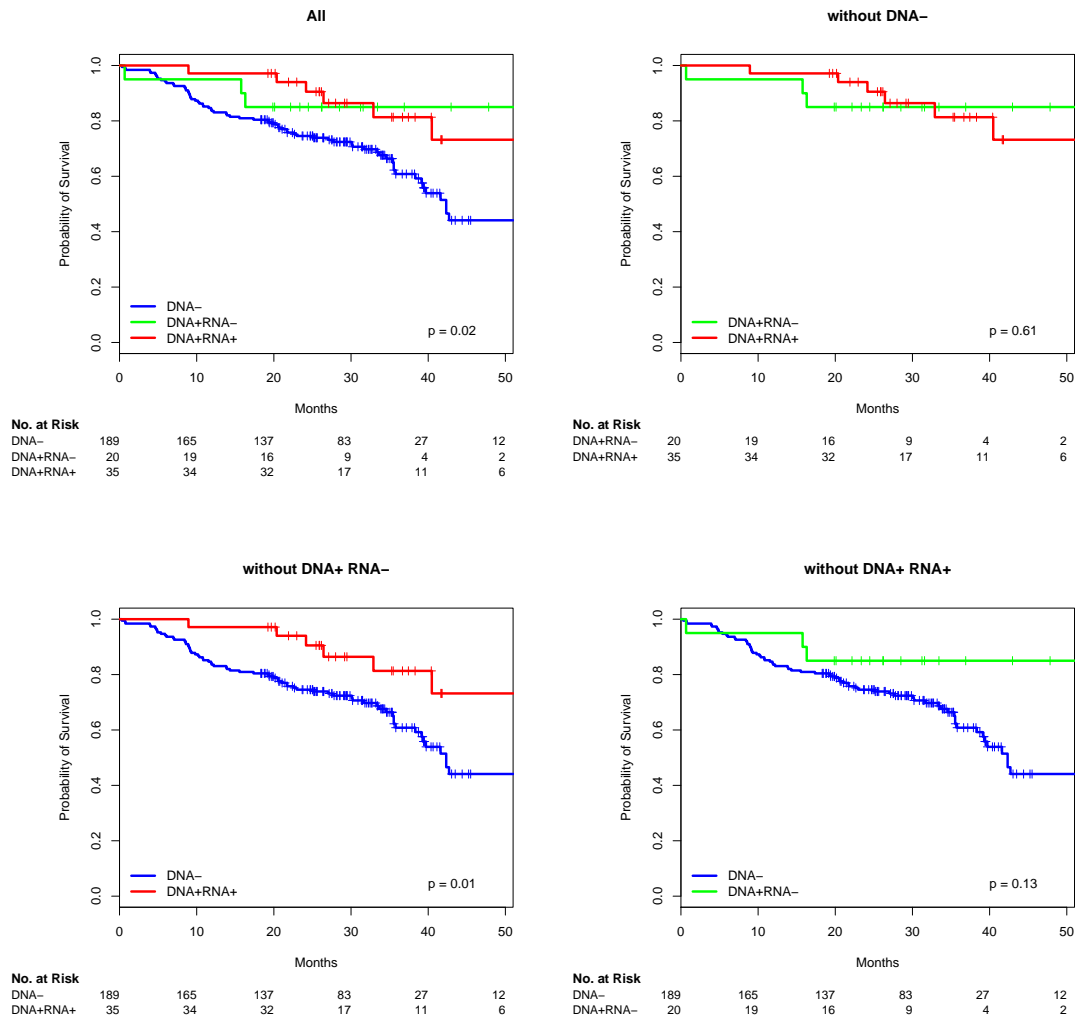


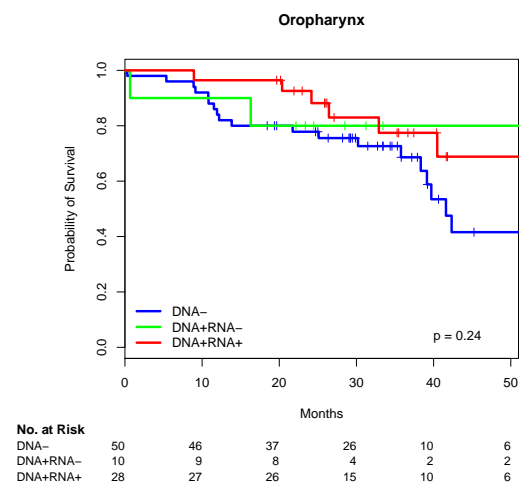
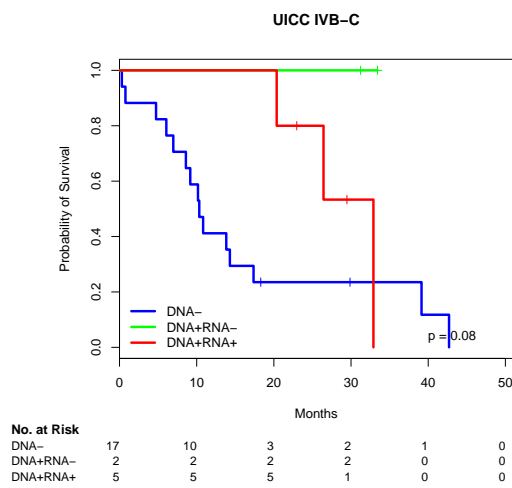
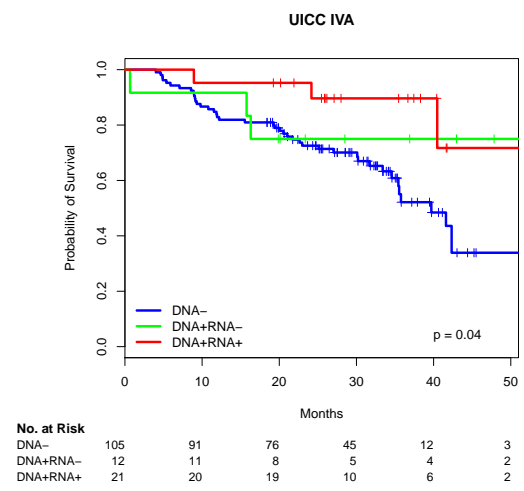
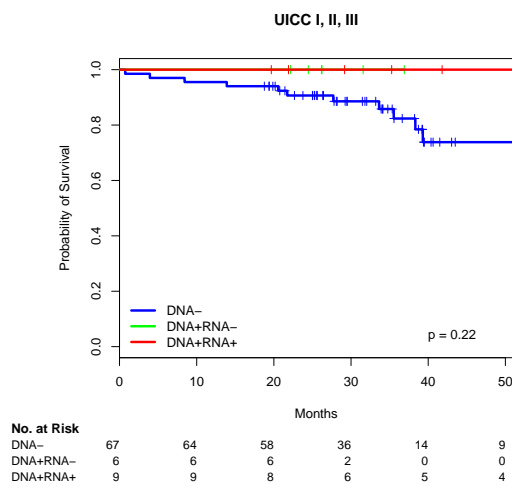
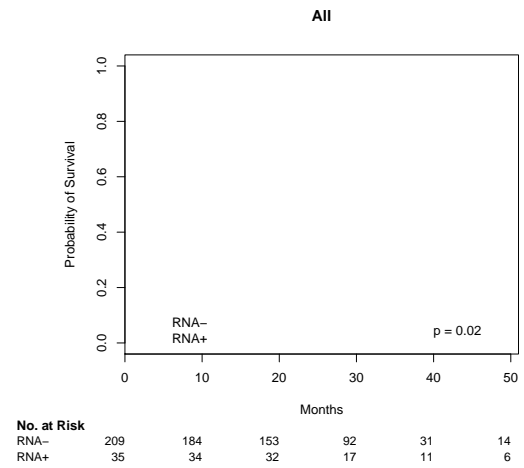
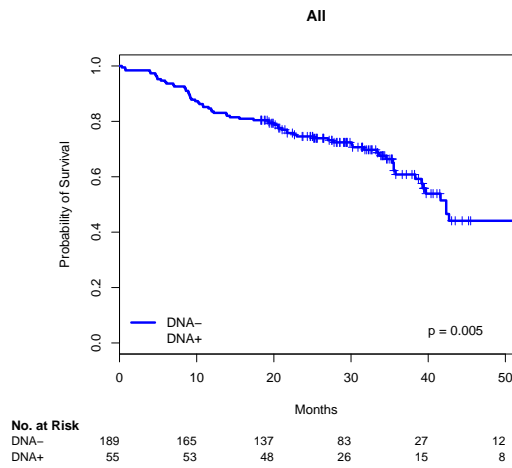
```
## Call: survfit(formula = surv.obj[cur.subset] ~ 1)
##
##   time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    36     38      27   0.703  0.0504      0.611      0.809
##
##
## #####
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 244, number of events= 81
##   (23 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]DNA+RNA- -0.761    0.467    0.515 -1.48    0.139
## split[cur.subset]DNA+RNA+ -1.009    0.364    0.426 -2.37    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-    0.467      2.14    0.170    1.28
## split[cur.subset]DNA+RNA+    0.364      2.74    0.158    0.84
##
## Concordance= 0.568 (se = 0.027 )
## Rsquare= 0.037 (max possible= 0.96 )
## Likelihood ratio test= 9.3 on 2 df,  p=0.00955
## Wald test               = 7.37 on 2 df,  p=0.025
## Score (logrank) test = 7.94 on 2 df,  p=0.0189
##
##
## #####
## Cox model in Oropharynx patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 88, number of events= 29
##   (19 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]DNA+RNA- -0.321    0.725    0.623 -0.52    0.61
## split[cur.subset]DNA+RNA+ -0.764    0.466    0.468 -1.63    0.10
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]DNA+RNA-    0.725      1.38    0.214    2.46
## split[cur.subset]DNA+RNA+    0.466      2.15    0.186    1.17
##
```

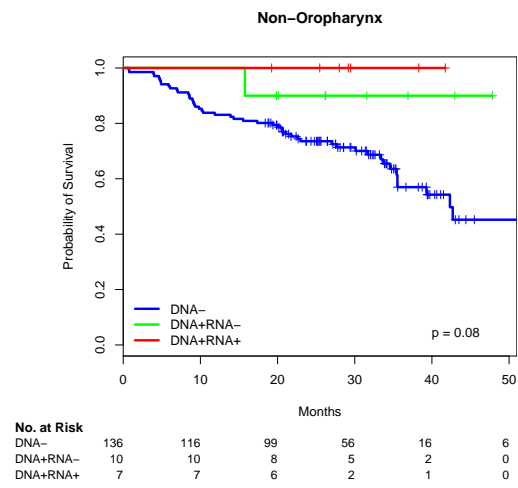
```

## Concordance= 0.58 (se = 0.054 )
## Rsquare= 0.034 (max possible= 0.919 )
## Likelihood ratio test= 3.02 on 2 df, p=0.221
## Wald test = 2.72 on 2 df, p=0.257
## Score (logrank) test = 2.84 on 2 df, p=0.242

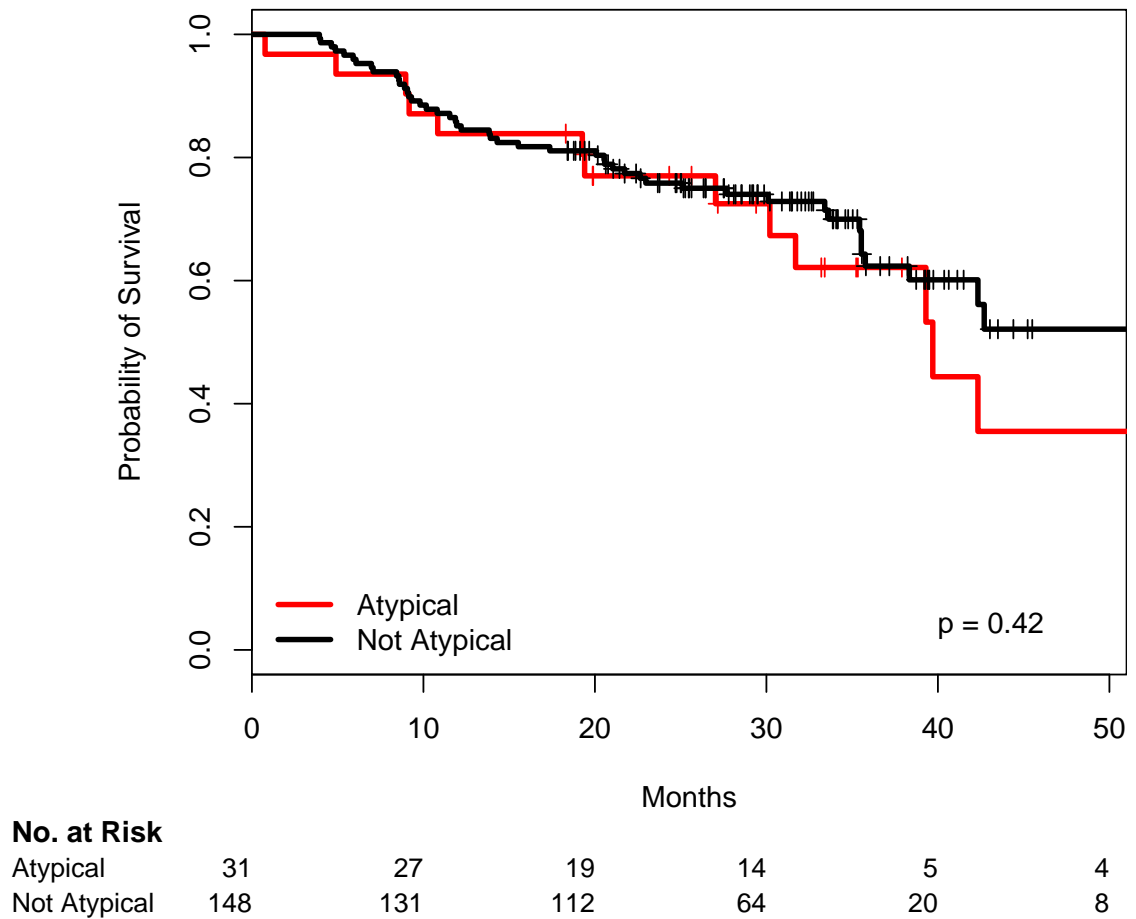
```





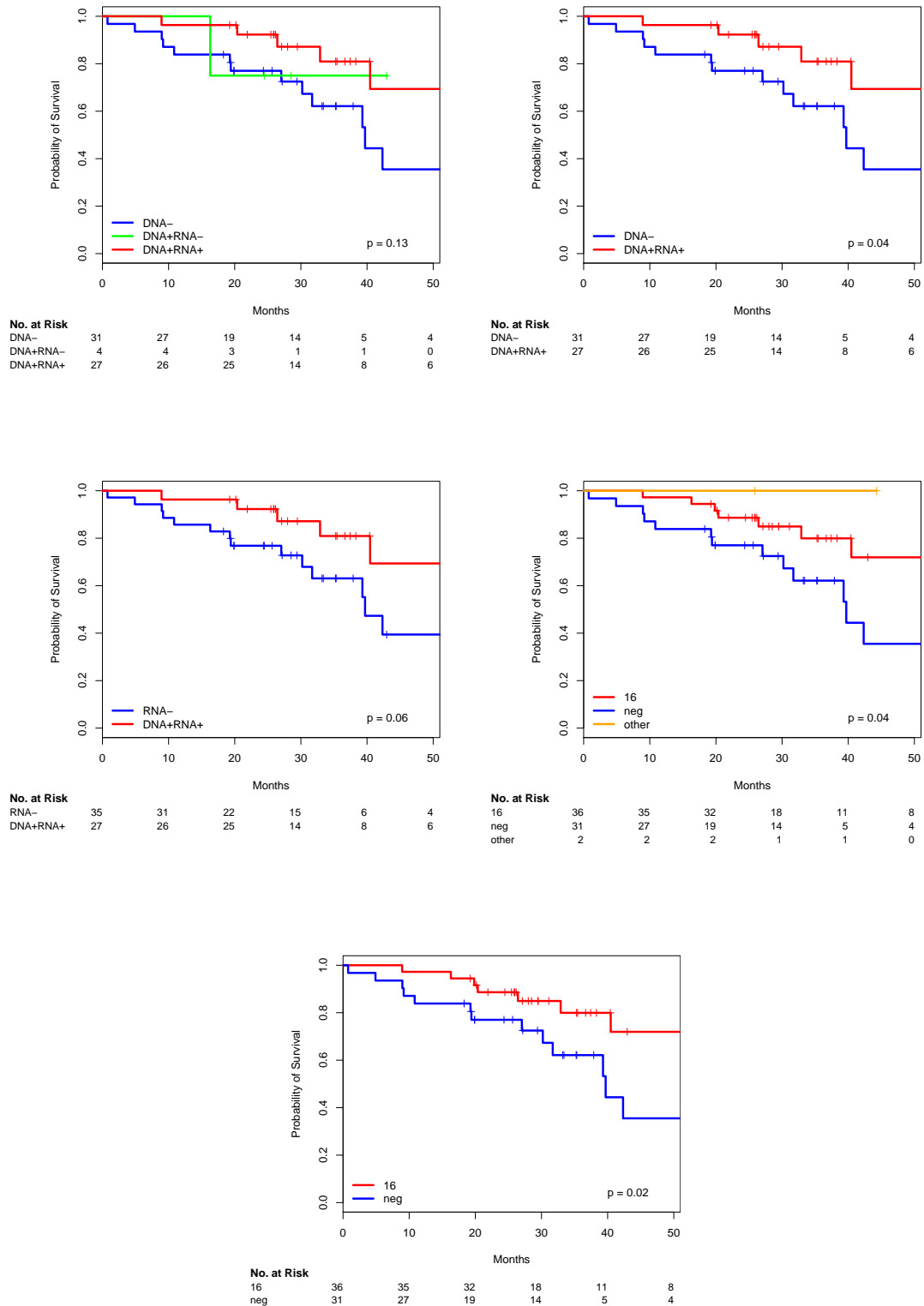


3.2.1 Consensus Cluster in HPV DNA-: Immune Response (IR) Cluster (also called Atypical here) vs. other Clusters



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= 73
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA-    -0.531    0.588    0.517 -1.03    0.304
## HPV16_DNA_RNADNA+RNA+    -1.125    0.325    0.458 -2.45    0.014 *
## CONSENSUS_CLUSTERBasal   -0.588    0.556    0.347 -1.69    0.090 .
## CONSENSUS_CLUSTERClassical -0.968    0.380    0.560 -1.73    0.084 .
## CONSENSUS_CLUSTERMesenchymal 0.194    1.214    0.303  0.64    0.521
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.588    1.701    0.213    1.620
## HPV16_DNA_RNADNA+RNA+    0.325    3.079    0.132    0.798
## CONSENSUS_CLUSTERBasal    0.556    1.800    0.282    1.096
## CONSENSUS_CLUSTERClassical 0.380    2.633    0.127    1.139
## CONSENSUS_CLUSTERMesenchymal 1.214    0.823    0.671    2.199
##
## Concordance= 0.65 (se = 0.037 )
## Rsquare= 0.072 (max possible= 0.951 )
## Likelihood ratio test= 17.5 on 5 df,  p=0.00359
## Wald test = 16 on 5 df,  p=0.00694
## Score (logrank) test = 17.2 on 5 df,  p=0.00415
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##               Df Chisq Pr(>Chisq)
## HPV16_DNA_RNA    2  6.72    0.035 *
## CONSENSUS_CLUSTER 3  9.91    0.019 *
## 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= 73
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z
## HPV16_DNA_RNADNA+RNA- -0.518    0.596    0.517 -1.00
## HPV16_DNA_RNADNA+RNA+ -1.069    0.343    0.462 -2.31
## I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.232    1.261    0.285  0.81
##               Pr(>|z|)
## HPV16_DNA_RNADNA+RNA-    0.316
## HPV16_DNA_RNADNA+RNA+    0.021 *
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    0.416
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95
## HPV16_DNA_RNADNA+RNA-    0.596    1.678    0.216
## HPV16_DNA_RNADNA+RNA+    0.343    2.912    0.139
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    1.261    0.793    0.722
##               upper .95
## HPV16_DNA_RNADNA+RNA-    1.64
## HPV16_DNA_RNADNA+RNA+    0.85
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    2.20
##
## Concordance= 0.571 (se = 0.032 )
## Rsquare= 0.031 (max possible= 0.951 )
## Likelihood ratio test= 7.28 on 3 df, p=0.0636
## Wald test = 6.03 on 3 df, p=0.11
## Score (logrank) test = 6.36 on 3 df, p=0.0953
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##               Df Chisq Pr(>Chisq)
## HPV16_DNA_RNA    2  6.02    0.049 *
## I(CONSENSUS_CLUSTER == "Atypical")    1  0.66    0.416
## 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, ])
```

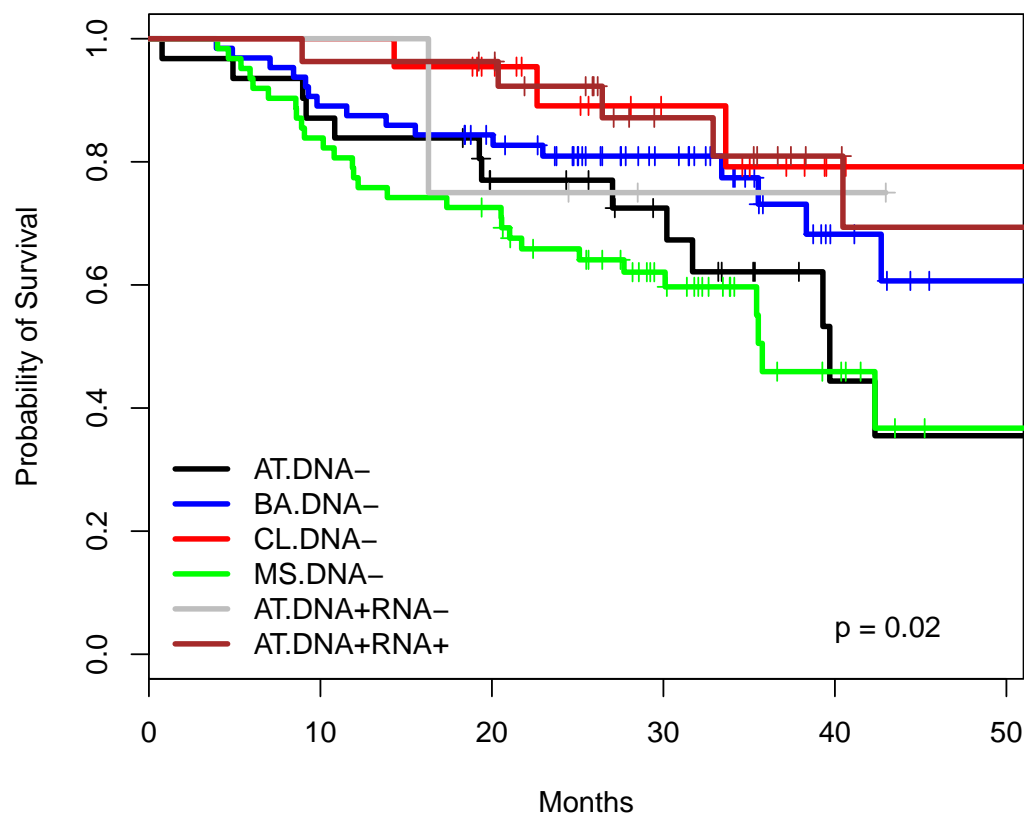


```

##
##   n= 214, number of events= 69
##   (33 observations deleted due to missingness)
##
##                                     coef exp(coef)
## HPV16_RNARNA+                      -1.0782    0.3402
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    0.2475    1.2809
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.0115    1.0116
##                                     se(coef)      z
## HPV16_RNARNA+                      1.0113 -1.07
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    0.3044  0.81
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 1.1376  0.01
##                                     Pr(>|z|)
## HPV16_RNARNA+                      0.29
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    0.42
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.99
##
##                                     exp(coef) exp(-coef)
## HPV16_RNARNA+                      0.34    2.939
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    1.28    0.781
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 1.01    0.989
##                                     lower .95 upper .95
## HPV16_RNARNA+                      0.0469    2.47
## I(CONSENSUS_CLUSTER == "Atypical")TRUE    0.7054    2.33
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.1088    9.41
##
## Concordance= 0.563 (se = 0.032 )
## Rsquare= 0.03 (max possible= 0.953 )
## Likelihood ratio test= 6.58 on 3 df,  p=0.0866
## Wald test = 5.3 on 3 df,  p=0.151
## Score (logrank) test = 5.69 on 3 df,  p=0.128
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##                                     Df Chisq Pr(>Chisq)
## HPV16_RNA                          1  5.30    0.021 *
## I(CONSENSUS_CLUSTER == "Atypical")  1  0.72    0.397
## HPV16_RNA:I(CONSENSUS_CLUSTER == "Atypical") 1  0.00    0.992
## 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 ==

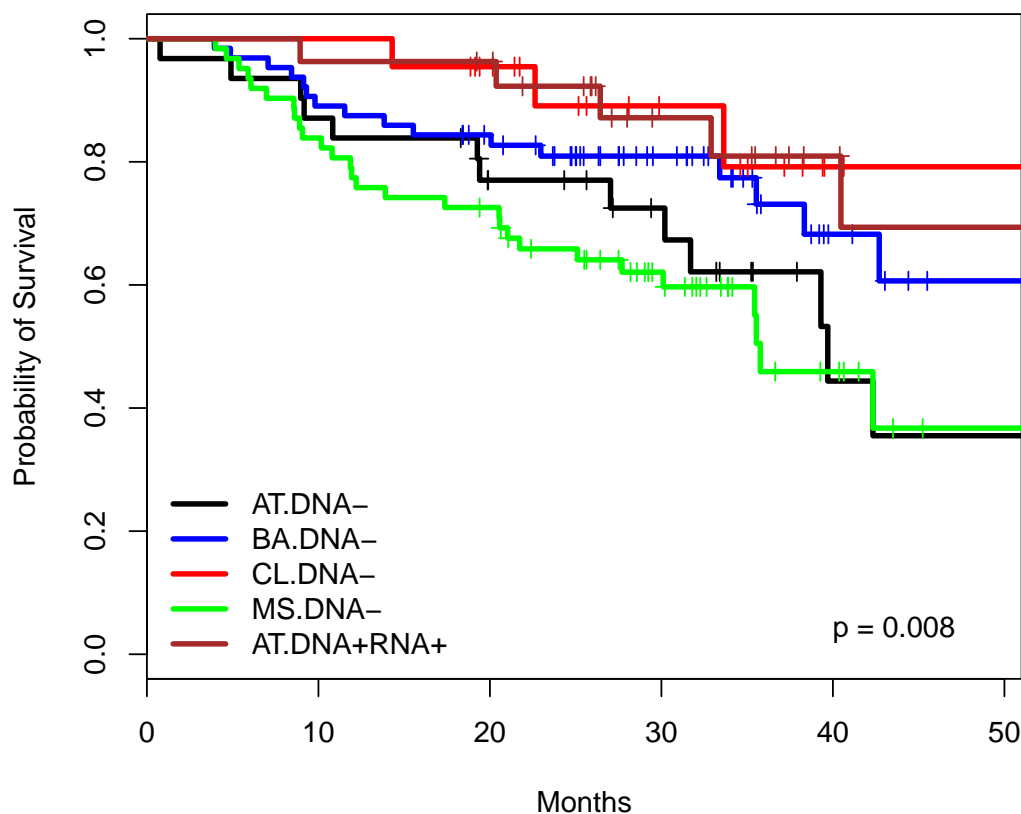
```

```
##      "Atypical"), data = ds[cur.subset, ])
##
##      n= 214, number of events= 69
##      (33 observations deleted due to missingness)
##
##                                     coef exp(coef)
## HPV16_RNARNA+                     -1.0782    0.3402
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.2475    1.2809
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.0115    1.0116
##                                     se(coef)      z
## HPV16_RNARNA+                     1.0113 -1.07
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.3044  0.81
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 1.1376  0.01
##                                     Pr(>|z|)
## HPV16_RNARNA+                     0.29
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.42
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.99
##
##                                     exp(coef) exp(-coef)
## HPV16_RNARNA+                     0.34    2.939
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      1.28    0.781
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 1.01    0.989
##                                     lower .95 upper .95
## HPV16_RNARNA+                     0.0469    2.47
## I(CONSENSUS_CLUSTER == "Atypical")TRUE      0.7054    2.33
## HPV16_RNARNA+:I(CONSENSUS_CLUSTER == "Atypical")TRUE 0.1088    9.41
##
## Concordance= 0.563 (se = 0.032 )
## Rsquare= 0.03 (max possible= 0.953 )
## Likelihood ratio test= 6.58 on 3 df,  p=0.0866
## Wald test = 5.3 on 3 df,  p=0.151
## Score (logrank) test = 5.69 on 3 df,  p=0.128
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##                                     Df Chisq Pr(>Chisq)
## HPV16_RNA                          1  5.30    0.021 *
## I(CONSENSUS_CLUSTER == "Atypical")  1  0.72    0.397
## HPV16_RNA:I(CONSENSUS_CLUSTER == "Atypical") 1  0.00    0.992
## Residuals                          211
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```



No. at Risk

AT.DNA-	31	27	19	14	5	4
BA.DNA-	64	57	50	29	10	5
CL.DNA-	22	22	18	9	2	1
MS.DNA-	62	52	44	26	8	2
AT.DNA+RNA-	4	4	3	1	1	0
AT.DNA+RNA+	27	26	25	14	8	6



No. at Risk						
AT.DNA-	31	27	19	14	5	4
BA.DNA-	64	57	50	29	10	5
CL.DNA-	22	22	18	9	2	1
MS.DNA-	62	52	44	26	8	2
AT.DNA+RNA+	27	26	25	14	8	6

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= 85
## (14 observations deleted due to missingness)
##
##
```

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

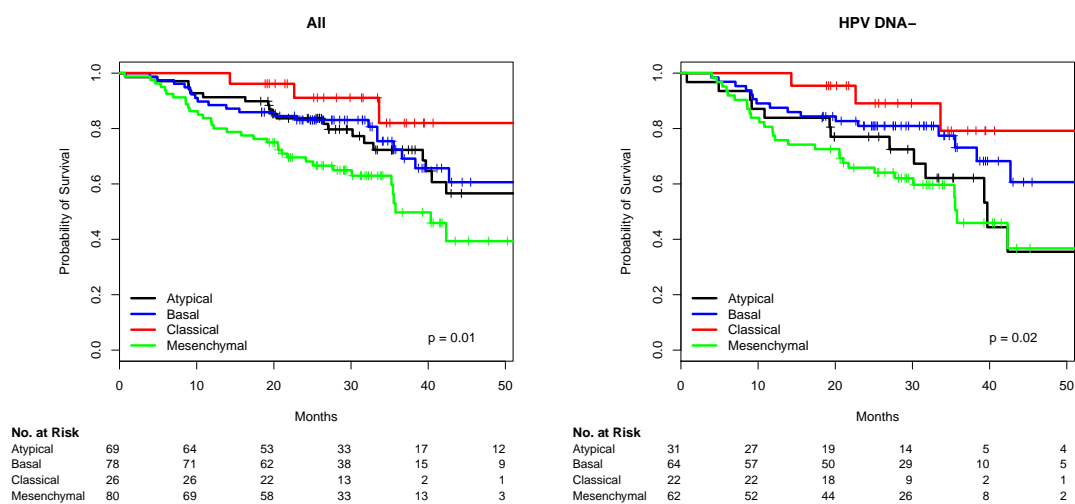
```

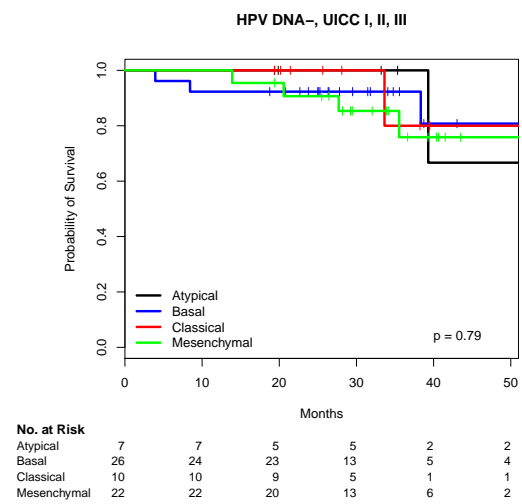
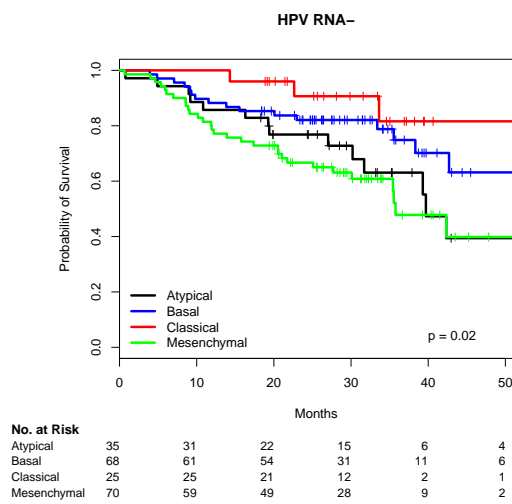
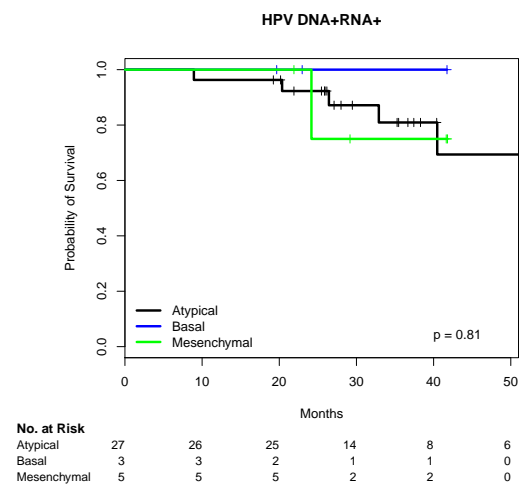
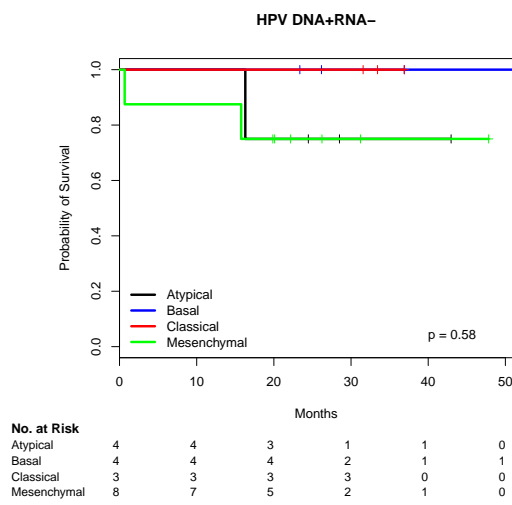
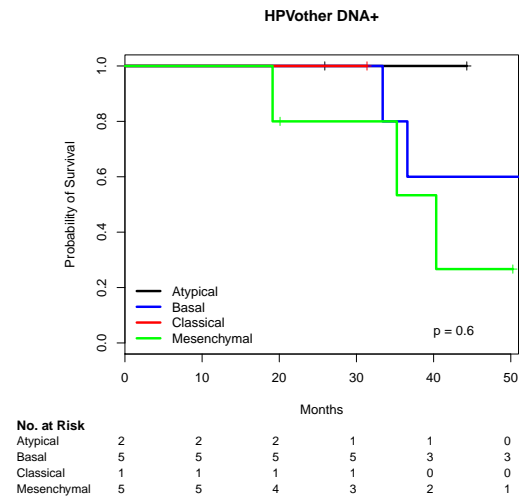
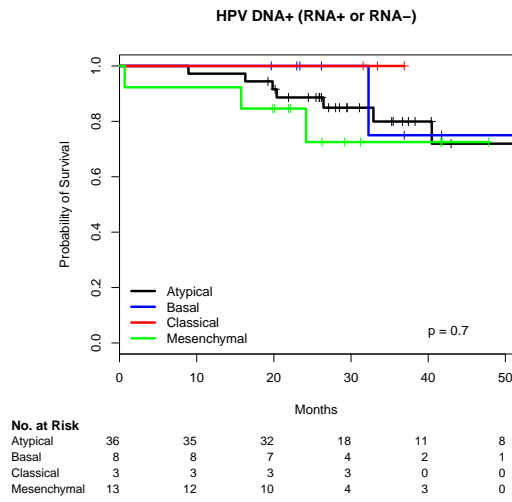
## split[cur.subset]Basal      0.0394    1.0402    0.2997    0.13    0.895
## split[cur.subset]Classical -0.5310    0.5880    0.5465   -0.97    0.331
## split[cur.subset]Mesenchymal 0.6507    1.9169    0.2777    2.34    0.019 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      1.040      0.961      0.578      1.87
## split[cur.subset]Classical    0.588      1.701      0.201      1.72
## split[cur.subset]Mesenchymal  1.917      0.522      1.112      3.30
##
## Concordance= 0.604 (se = 0.034 )
## Rsquare= 0.04 (max possible= 0.959 )
## Likelihood ratio test= 10.3 on 3 df,  p=0.0159
## Wald test = 10.2 on 3 df,  p=0.0167
## Score (logrank) test = 10.8 on 3 df,  p=0.0131
##
## 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      23.0000      16.0000      0.7229      0.0616
## lower 95% CI upper 95% CI
##           0.6116      0.8544
##
##           split[cur.subset]=Basal
##           time      n.risk      n.event      survival      std.err
##           36.0000      22.0000      17.0000      0.7242      0.0625
## lower 95% CI upper 95% CI
##           0.6115      0.8576
##
##           split[cur.subset]=Classical
##           time      n.risk      n.event      survival      std.err
##           36.000      7.000      3.000      0.820      0.102
## lower 95% CI upper 95% CI
##           0.642      1.000
##
##           split[cur.subset]=Mesenchymal
##           time      n.risk      n.event      survival      std.err
##           36.000      15.000      32.000      0.497      0.074
## lower 95% CI upper 95% CI
##           0.371      0.666
##
##
## #####
## Cox model in HPV DNA-

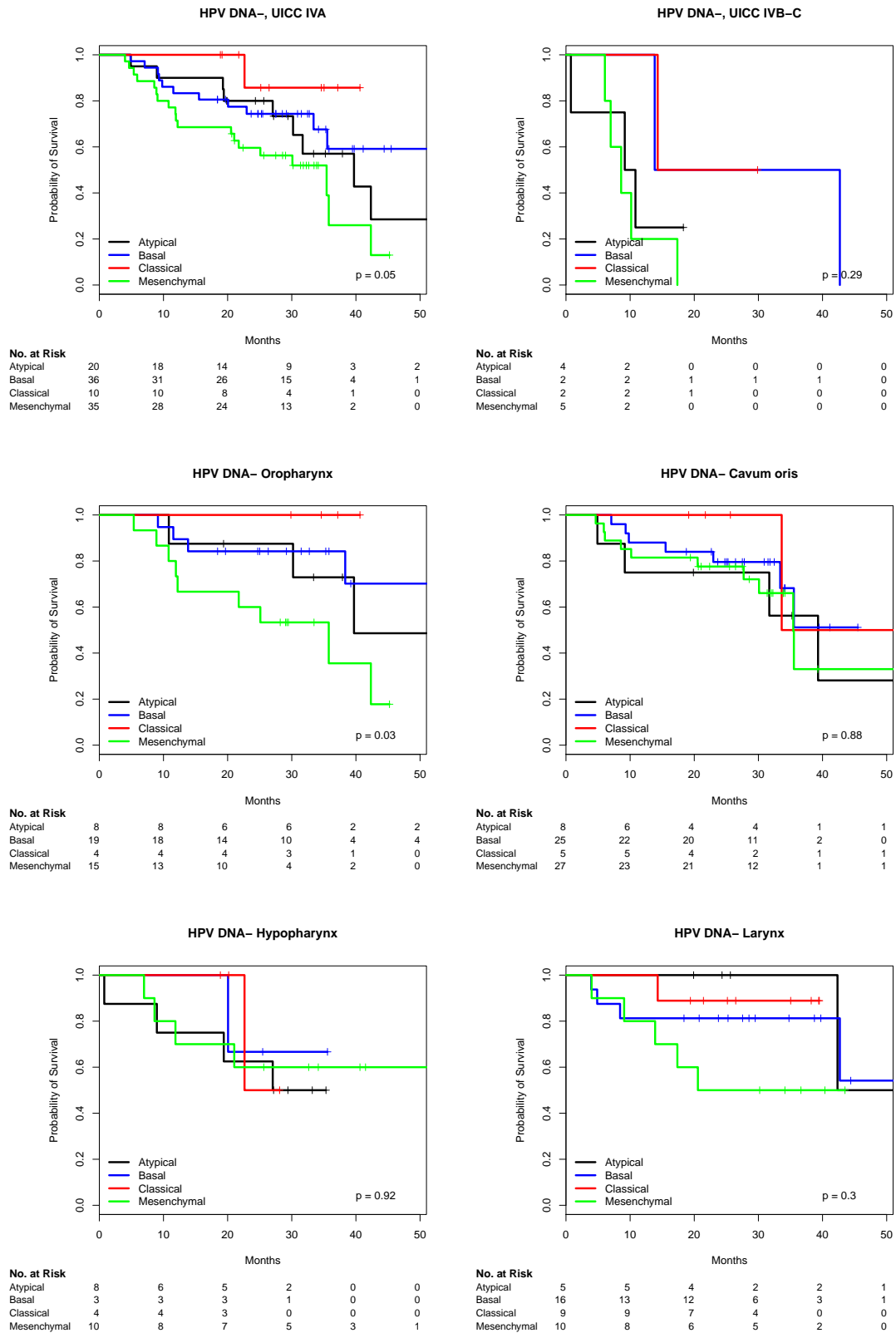
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 179, number of events= 63
##    (12 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      -0.588    0.555   0.367 -1.60    0.11
## split[cur.subset]Classical  -0.883    0.414   0.569 -1.55    0.12
## split[cur.subset]Mesenchymal  0.194    1.214   0.328  0.59    0.55
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      0.555    1.801    0.271    1.14
## split[cur.subset]Classical    0.414    2.418    0.136    1.26
## split[cur.subset]Mesenchymal  1.214    0.824    0.639    2.31
##
## Concordance= 0.615 (se = 0.039 )
## Rsquare= 0.052 (max possible= 0.959 )
## Likelihood ratio test= 9.58 on 3 df, p=0.0225
## Wald test = 8.86 on 3 df, p=0.0312
## Score (logrank) test = 9.39 on 3 df, p=0.0245
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 198, number of events= 67
##    (11 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      -0.539    0.583   0.355 -1.52    0.13
## split[cur.subset]Classical  -0.956    0.384   0.565 -1.69    0.09
## split[cur.subset]Mesenchymal  0.219    1.245   0.317  0.69    0.49
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      0.583    1.714    0.291    1.17
## split[cur.subset]Classical    0.384    2.602    0.127    1.16
## split[cur.subset]Mesenchymal  1.245    0.803    0.669    2.32
##
## Concordance= 0.621 (se = 0.038 )
## Rsquare= 0.051 (max possible= 0.956 )
## Likelihood ratio test= 10.4 on 3 df, p=0.0154
## Wald test = 9.48 on 3 df, p=0.0235
## Score (logrank) test = 10.1 on 3 df, p=0.0177
```

```
##
## 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      9.0000      11.0000      0.6308      0.0935
## lower 95% CI upper 95% CI
##           0.4718      0.8433
##
##           split[cur.subset]=Basal
##           time      n.risk      n.event      survival      std.err
##           36.0000      17.0000      14.0000      0.7485      0.0651
## lower 95% CI upper 95% CI
##           0.6311      0.8877
##
##           split[cur.subset]=Classical
##           time      n.risk      n.event      survival      std.err
##           36.000      7.000      3.000      0.816      0.103
## lower 95% CI upper 95% CI
##           0.637      1.000
##
##           split[cur.subset]=Mesenchymal
##           time      n.risk      n.event      survival      std.err
##           36.0000      11.0000      29.0000      0.4781      0.0823
## lower 95% CI upper 95% CI
##           0.3412      0.6699
```







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= 85
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.692      1.998      0.225 3.08  0.0021 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      2      0.501      1.29      3.1
##
## Concordance= 0.59 (se = 0.028 )
## Rsquare= 0.035 (max possible= 0.959 )
## Likelihood ratio test= 9.03 on 1 df,  p=0.00266
## Wald test = 9.49 on 1 df,  p=0.00206
## Score (logrank) test = 9.86 on 1 df,  p=0.00168
##
## 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      52.0000      36.0000      0.7389      0.0403
## lower 95% CI upper 95% CI
##               0.6641      0.8222
##
##               split[cur.subset]=Mesenchymal
##               time      n.risk      n.event      survival      std.err
##               36.000      15.000      32.000      0.497      0.074
## lower 95% CI upper 95% CI
##               0.371      0.666
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##

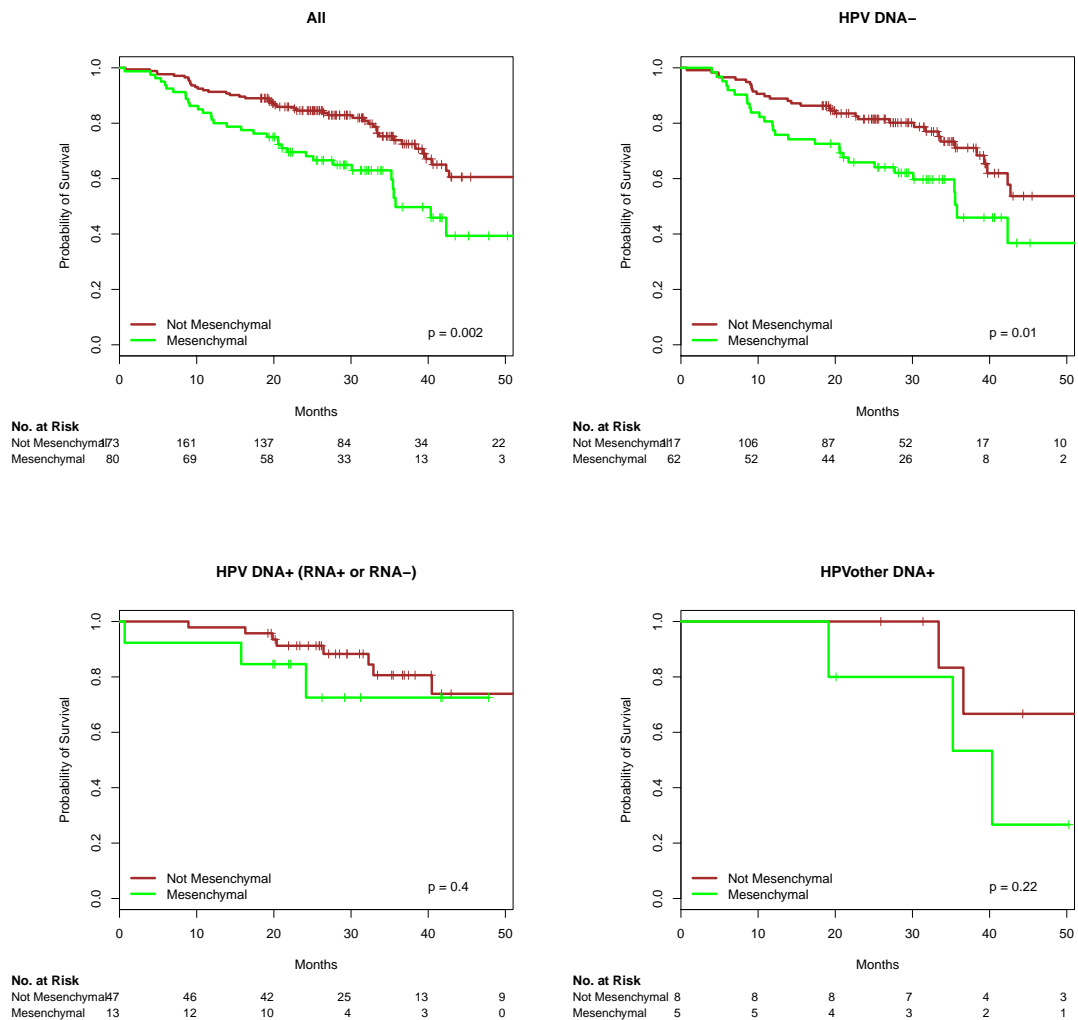
```

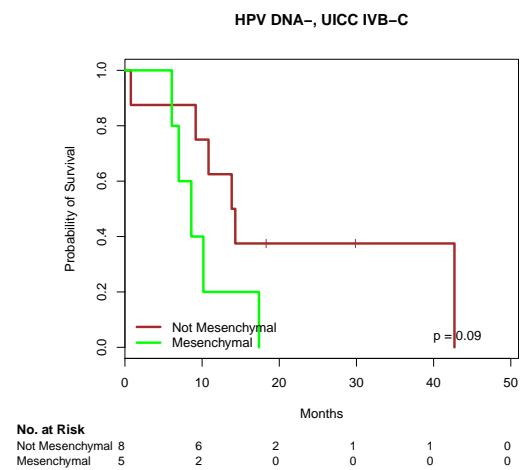
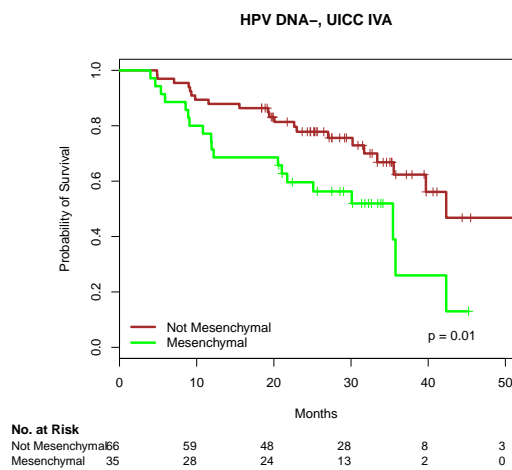
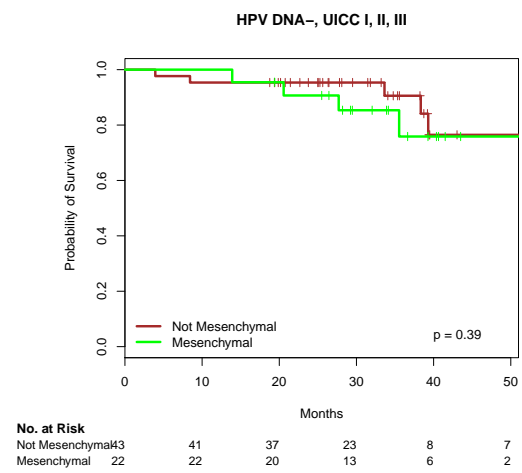
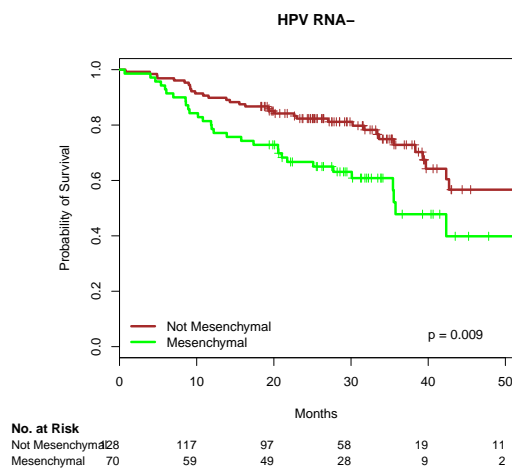
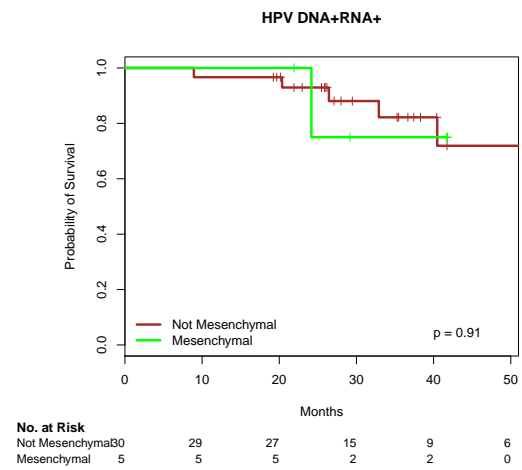
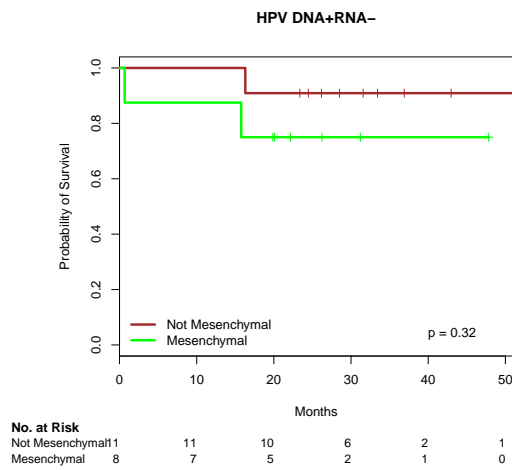
```

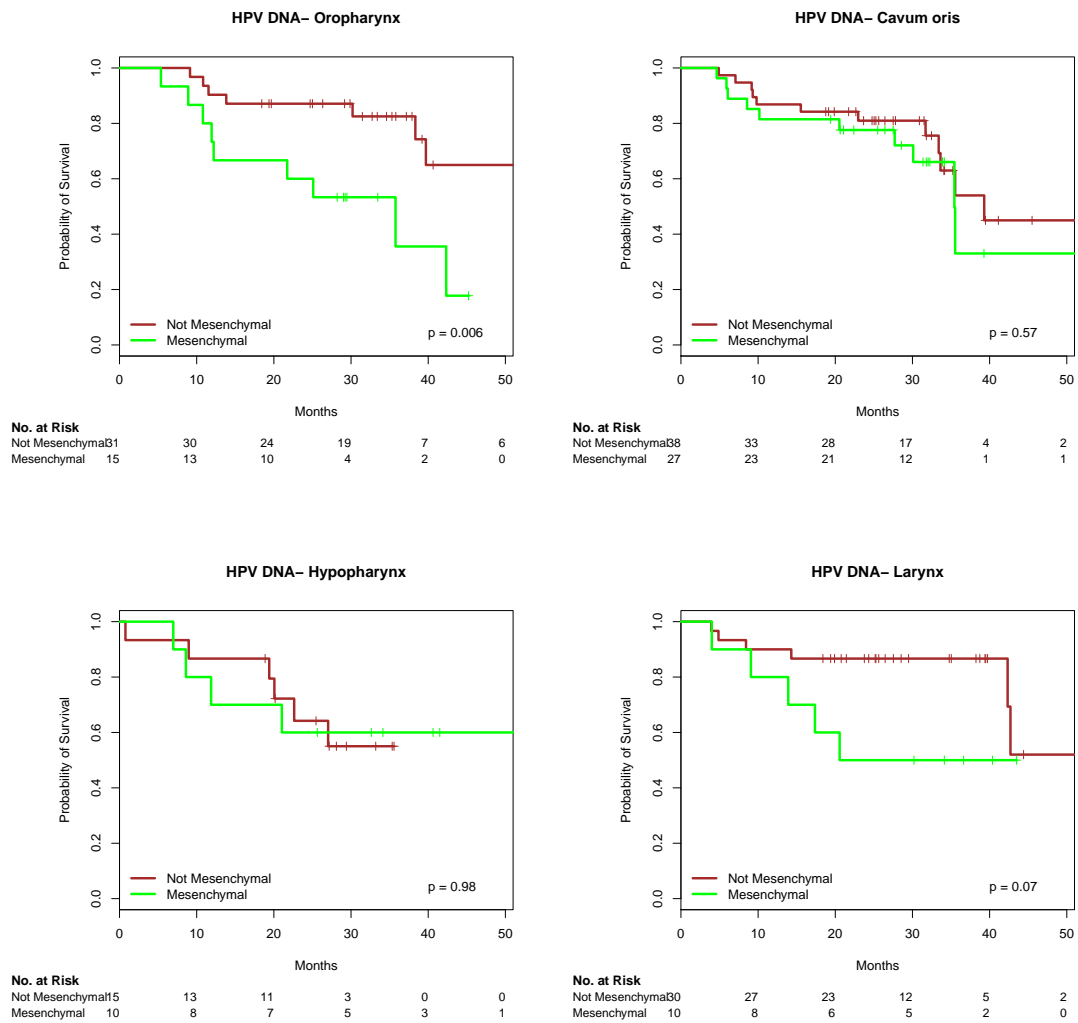
##      n= 179, number of events= 63
##      (12 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.630      1.877      0.254 2.48      0.013 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.88      0.533      1.14      3.09
##
## Concordance= 0.585 (se = 0.033 )
## Rsquare= 0.033 (max possible= 0.959 )
## Likelihood ratio test= 5.97 on 1 df,  p=0.0146
## Wald test = 6.16 on 1 df,  p=0.0131
## Score (logrank) test = 6.36 on 1 df,  p=0.0117
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 198, number of events= 67
##      (11 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.637      1.891      0.246 2.59      0.0096 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.89      0.529      1.17      3.06
##
## Concordance= 0.589 (se = 0.032 )
## Rsquare= 0.032 (max possible= 0.956 )
## Likelihood ratio test= 6.5 on 1 df,  p=0.0108
## Wald test = 6.7 on 1 df,  p=0.00964
## Score (logrank) test = 6.93 on 1 df,  p=0.0085
##
## 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      33.000      28.000      0.728      0.048
## lower 95% CI upper 95% CI

```

```
##          0.640          0.829
##
##          split[cur.subset]=Mesenchymal
##          time          n.risk          n.event          survival          std.err
##          36.0000          11.0000          29.0000          0.4781          0.0823
## lower 95% CI upper 95% CI
##          0.3412          0.6699
```







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

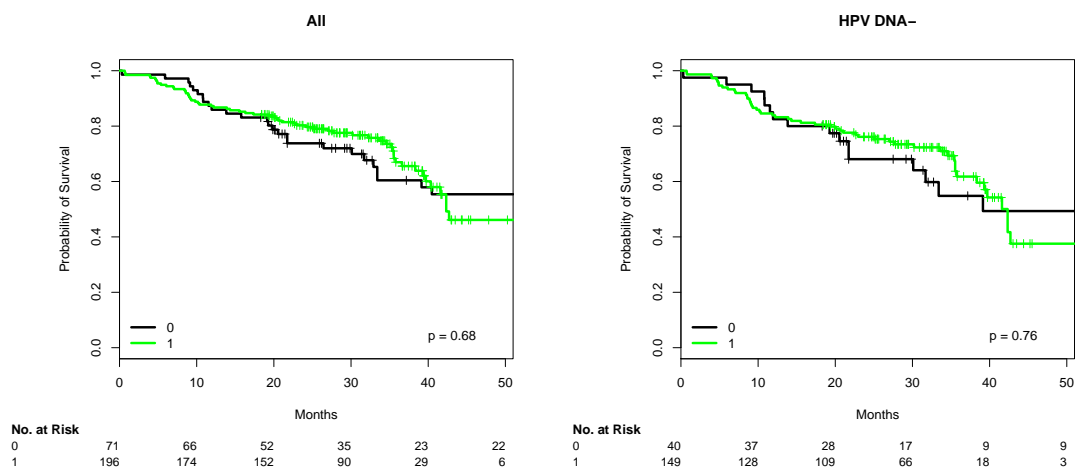
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.0946    0.9097  0.2311 -0.41    0.68
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.91        1.1    0.578    1.43
##
## Concordance= 0.519 (se = 0.026 )
## Rsquare= 0.001 (max possible= 0.967 )
```

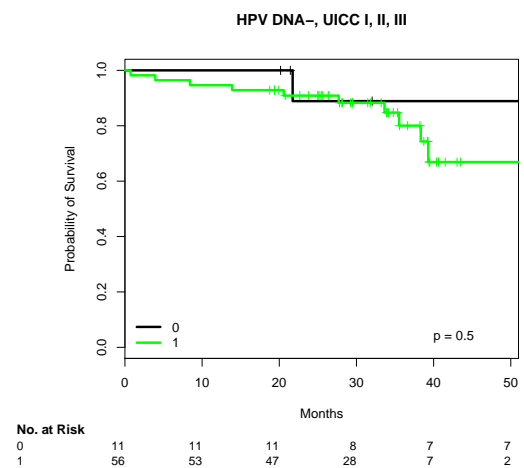
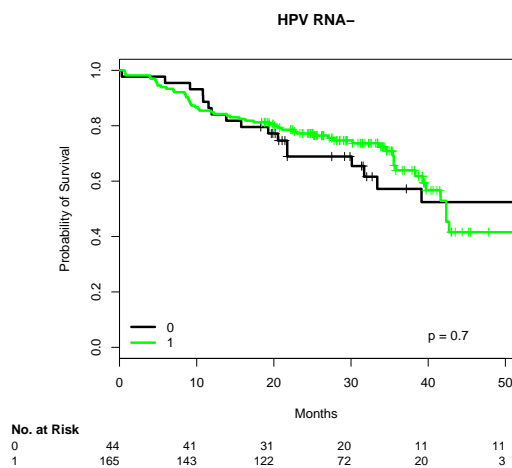
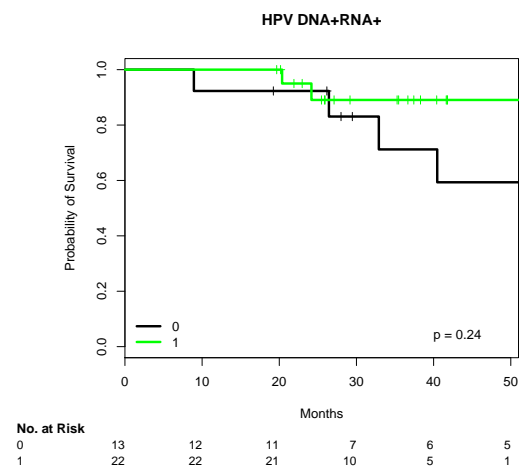
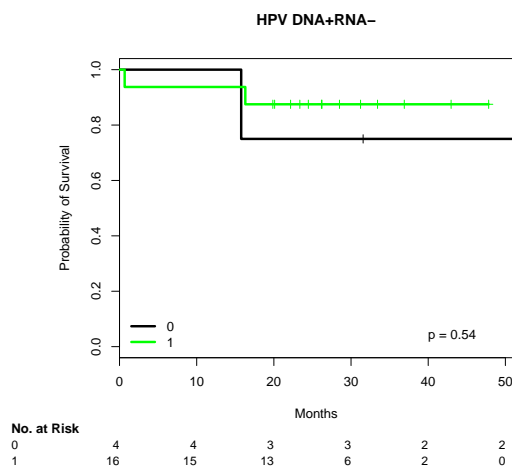
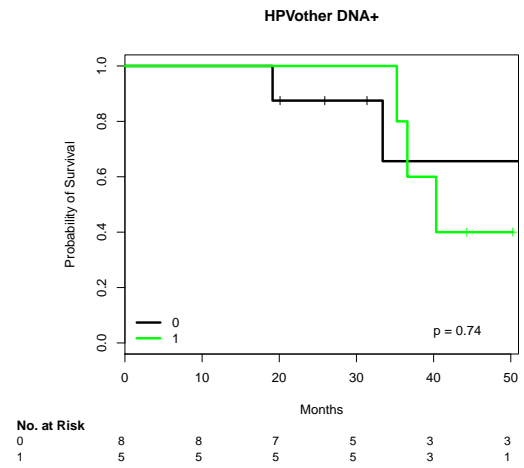
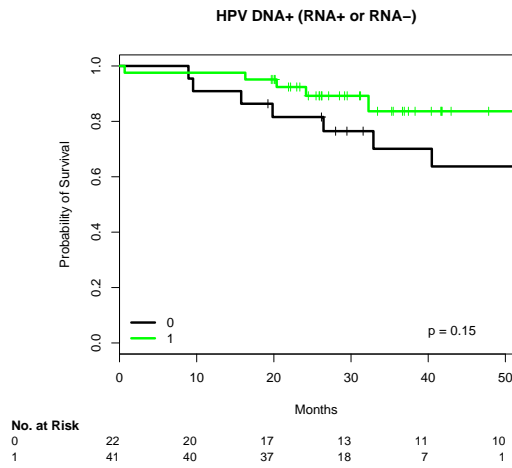
```

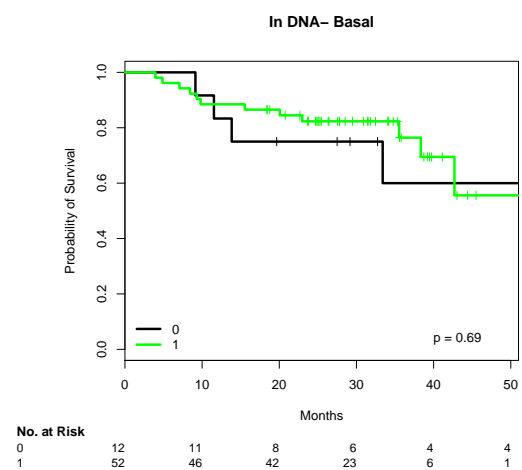
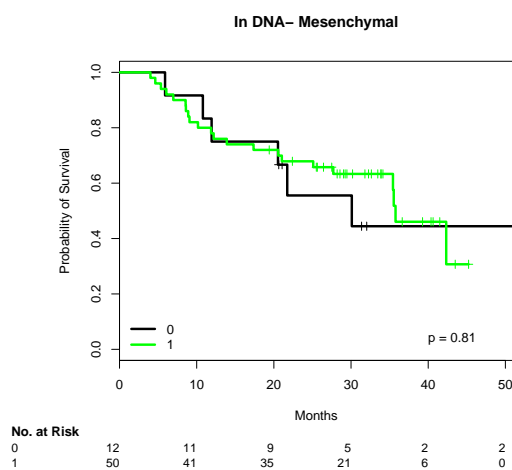
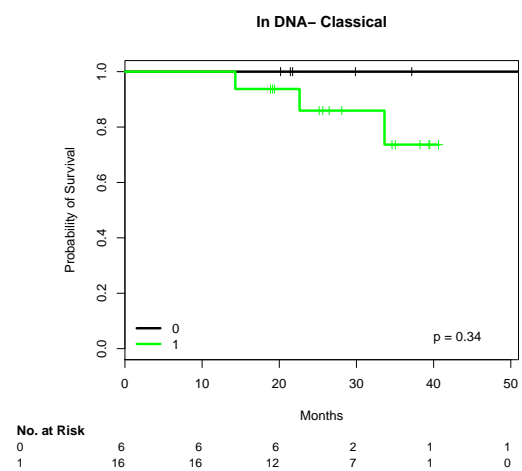
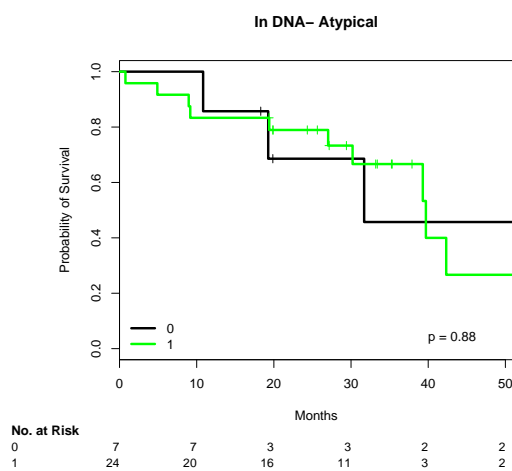
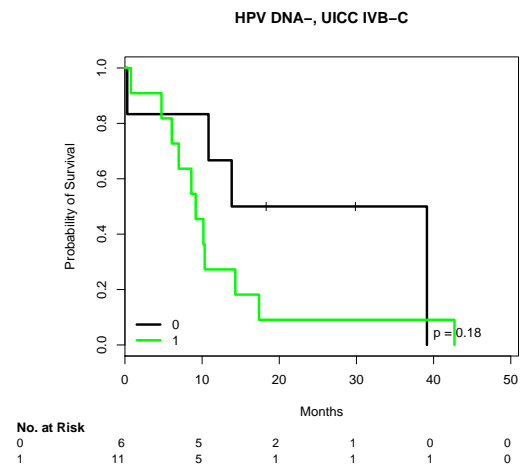
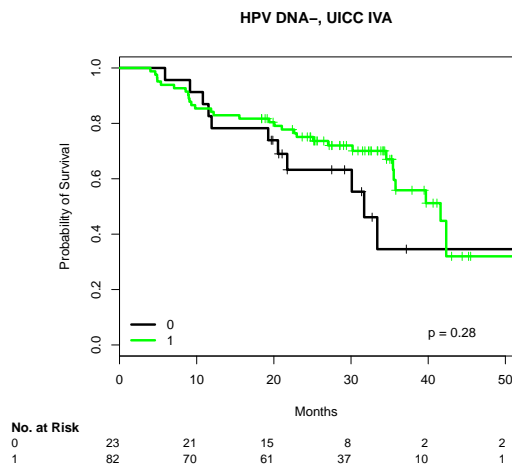
## Likelihood ratio test= 0.17 on 1 df, p=0.684
## Wald test = 0.17 on 1 df, p=0.682
## Score (logrank) test = 0.17 on 1 df, p=0.682
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=0
##      time      n.risk      n.event      survival      std.err
## 36.0000    25.0000    24.0000      0.6043      0.0663
## lower 95% CI upper 95% CI
## 0.4873      0.7493
##
##               split[cur.subset]=1
##      time      n.risk      n.event      survival      std.err
## 36.0000    48.0000    51.0000      0.6696      0.0427
## lower 95% CI upper 95% CI
## 0.5910      0.7588
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.0844    0.9191  0.2823 -0.3    0.76
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]    0.919      1.09    0.529      1.6
##
## Concordance= 0.515 (se = 0.027 )
## Rsquare= 0 (max possible= 0.968 )
## Likelihood ratio test= 0.09 on 1 df, p=0.766
## Wald test = 0.09 on 1 df, p=0.765
## Score (logrank) test = 0.09 on 1 df, p=0.765
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##

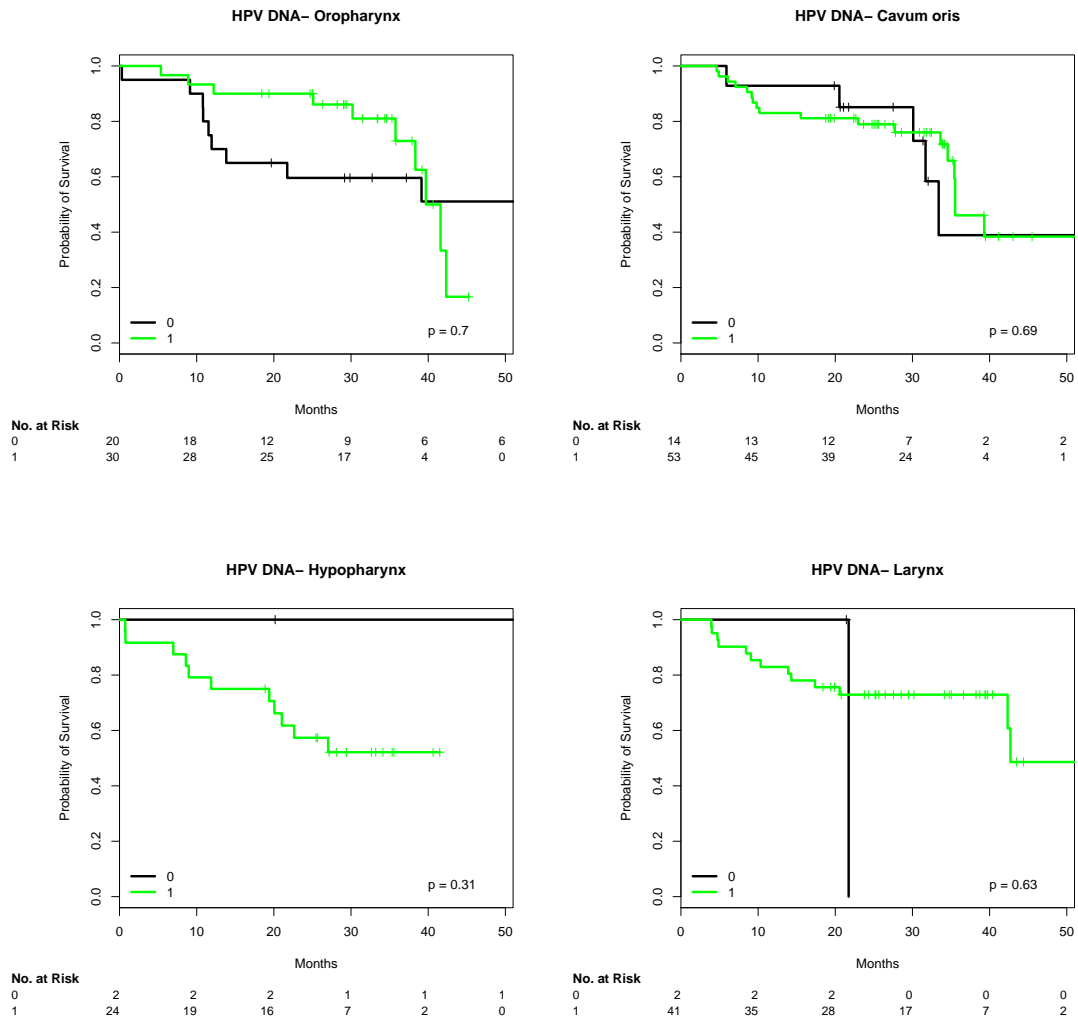
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.104      0.902    0.273 -0.38      0.7
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.902      1.11    0.528    1.54
##
## Concordance= 0.517 (se = 0.026 )
## Rsquare= 0.001 (max possible= 0.965 )
## Likelihood ratio test= 0.14 on 1 df,  p=0.706
## Wald test               = 0.14 on 1 df,  p=0.704
## Score (logrank) test = 0.14 on 1 df,  p=0.704
##
## 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    16.0000      0.5720      0.0865
## lower 95% CI upper 95% CI
## 0.4252      0.7694
##
##               split[cur.subset]=1
##      time      n.risk      n.event      survival      std.err
## 36.0000    35.0000    47.0000      0.6389      0.0488
## lower 95% CI upper 95% CI
## 0.5501      0.7420
```









3.7 Therapy, detailed

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##
```

	coef	exp(coef)	se(coef)
split[cur.subset]DeLOS II (IC), Op+PORChT	-1.68e+01	5.29e-08	2.42e+03
split[cur.subset]DeLOS II (IC,RT)	-1.69e+00	1.85e-01	9.16e-01
split[cur.subset]ICHT+OP+RT	-6.97e-02	9.33e-01	7.61e-01
split[cur.subset]KRChT	-1.75e-02	9.83e-01	1.00e+00
split[cur.subset]OP	-1.49e+00	2.26e-01	7.63e-01
split[cur.subset]pall CHEMO	-4.76e-01	6.21e-01	1.23e+00
split[cur.subset]PORChT	-1.17e+00	3.12e-01	7.43e-01
split[cur.subset]PORT	-1.18e+00	3.06e-01	7.44e-01

```

## split[cur.subset]RT          4.23e-01  1.53e+00  7.62e-01
## split[cur.subset]TISOC 1     -1.56e+00  2.11e-01  9.18e-01
##                               z Pr(>|z|)
## split[cur.subset]DeLOS II (IC), Op+PORChT -0.01    0.994
## split[cur.subset]DeLOS II (IC,RT)        -1.84    0.066 .
## split[cur.subset]ICHT+OP+RT              -0.09    0.927
## split[cur.subset]KRCHT                  -0.02    0.986
## split[cur.subset]OP                     -1.95    0.051 .
## split[cur.subset]pall CHEMO              -0.39    0.699
## split[cur.subset]PORChT                 -1.57    0.117
## split[cur.subset]PORT                   -1.59    0.112
## split[cur.subset]RT                     0.56    0.579
## split[cur.subset]TISOC 1                -1.70    0.090 .
## ---
## 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 5.29e-08  1.89e+07  0.0000
## split[cur.subset]DeLOS II (IC,RT)        1.85e-01  5.40e+00  0.0308
## split[cur.subset]ICHT+OP+RT              9.33e-01  1.07e+00  0.2101
## split[cur.subset]KRCHT                  9.83e-01  1.02e+00  0.1379
## split[cur.subset]OP                     2.26e-01  4.42e+00  0.0507
## split[cur.subset]pall CHEMO              6.21e-01  1.61e+00  0.0555
## split[cur.subset]PORChT                 3.12e-01  3.21e+00  0.0726
## split[cur.subset]PORT                   3.06e-01  3.26e+00  0.0713
## split[cur.subset]RT                     1.53e+00  6.55e-01  0.3432
## split[cur.subset]TISOC 1                2.11e-01  4.75e+00  0.0349
##                               upper .95
## split[cur.subset]DeLOS II (IC), Op+PORChT      Inf
## split[cur.subset]DeLOS II (IC,RT)              1.12
## split[cur.subset]ICHT+OP+RT                    4.14
## split[cur.subset]KRCHT                         7.01
## split[cur.subset]OP                           1.01
## split[cur.subset]pall CHEMO                    6.95
## split[cur.subset]PORChT                       1.34
## split[cur.subset]PORT                         1.32
## split[cur.subset]RT                           6.79
## split[cur.subset]TISOC 1                      1.27
##
## Concordance= 0.651 (se = 0.033 )
## Rsquare= 0.136 (max possible= 0.967 )
## Likelihood ratio test= 39.1 on 10 df, p=2.46e-05
## Wald test = 44.2 on 10 df, p=3e-06
## Score (logrank) test = 55.3 on 10 df, p=2.81e-08
##
## 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      0.793      0.107
## lower 95% CI upper 95% CI
##      0.609      1.000
##
##          split[cur.subset]=ICHT+OP+RT
##      time      n.risk      n.event      survival      std.err
##      36.000      3.000      12.000      0.292      0.120
## lower 95% CI upper 95% CI
##      0.130      0.655
##
##          split[cur.subset]=KRCHT
##      time      n.risk      n.event      survival      std.err
##      36.000      1.000      2.000      0.500      0.250
## lower 95% CI upper 95% CI
##      0.188      1.000
##
##          split[cur.subset]=OP
##      time      n.risk      n.event      survival      std.err
##      36.000      15.000      10.000      0.796      0.066
## lower 95% CI upper 95% CI
##      0.676      0.936
##
##          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      20.0000      14.0000      0.7170      0.0695
## lower 95% CI upper 95% CI
##      0.5929      0.8670
##
##          split[cur.subset]=PORT
##      time      n.risk      n.event      survival      std.err
##      36.0000      19.0000      18.0000      0.6552      0.0726

```

```

## lower 95% CI upper 95% CI
##      0.5273      0.8142
##
##              split[cur.subset]=RT
##      time      n.risk      n.event      survival      std.err
##      36.0000      1.0000      12.0000      0.1544      0.1261
## lower 95% CI upper 95% CI
##      0.0311      0.7657
##
##              split[cur.subset]=TISOC 1
##      time      n.risk      n.event      survival      std.err
##      36.000      7.000      2.000      0.815      0.119
## lower 95% CI upper 95% CI
##      0.611      1.000
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 71
##      (2 observations deleted due to missingness)
##
##
##              coef exp(coef) se(coef)
## split[cur.subset]DeLOS II (IC), Op+PORChT -1.76e+01 2.30e-08 3.56e+03
## split[cur.subset]DeLOS II (IC,RT) -1.40e+00 2.46e-01 9.17e-01
## split[cur.subset]ICHT+OP+RT 1.73e-01 1.19e+00 7.85e-01
## split[cur.subset]KRCHT -3.53e-02 9.65e-01 1.00e+00
## split[cur.subset]OP -1.30e+00 2.72e-01 7.78e-01
## split[cur.subset]pall CHEMO -5.45e-01 5.80e-01 1.24e+00
## split[cur.subset]PORChT -1.05e+00 3.49e-01 7.60e-01
## split[cur.subset]PORT -1.07e+00 3.43e-01 7.54e-01
## split[cur.subset]RT 7.85e-01 2.19e+00 7.77e-01
## split[cur.subset]TISOC 1 -1.72e+00 1.79e-01 1.01e+00
##
##              z Pr(>|z|)
## split[cur.subset]DeLOS II (IC), Op+PORChT 0.00 0.996
## split[cur.subset]DeLOS II (IC,RT) -1.53 0.126
## split[cur.subset]ICHT+OP+RT 0.22 0.825
## split[cur.subset]KRCHT -0.04 0.972
## split[cur.subset]OP -1.67 0.095 .
## split[cur.subset]pall CHEMO -0.44 0.660
## split[cur.subset]PORChT -1.38 0.166
## split[cur.subset]PORT -1.42 0.156
## split[cur.subset]RT 1.01 0.313
## split[cur.subset]TISOC 1 -1.70 0.088 .
## ---
## 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 2.30e-08 4.35e+07 0.0000
## split[cur.subset]DeLOS II (IC,RT)         2.46e-01 4.06e+00 0.0408
## split[cur.subset]ICHT+OP+RT               1.19e+00 8.41e-01 0.2553
## split[cur.subset]KRCHT                    9.65e-01 1.04e+00 0.1351
## split[cur.subset]OP                       2.72e-01 3.67e+00 0.0593
## split[cur.subset]pall CHEMO                5.80e-01 1.72e+00 0.0512
## split[cur.subset]PORChT                   3.49e-01 2.87e+00 0.0786
## split[cur.subset]PORT                     3.43e-01 2.91e+00 0.0783
## split[cur.subset]RT                       2.19e+00 4.56e-01 0.4775
## split[cur.subset]TISOC 1                  1.79e-01 5.60e+00 0.0246
##                                     upper .95
## split[cur.subset]DeLOS II (IC), Op+PORChT      Inf
## split[cur.subset]DeLOS II (IC,RT)              1.48
## split[cur.subset]ICHT+OP+RT                    5.54
## split[cur.subset]KRCHT                         6.90
## split[cur.subset]OP                            1.25
## split[cur.subset]pall CHEMO                     6.56
## split[cur.subset]PORChT                         1.55
## split[cur.subset]PORT                           1.50
## split[cur.subset]RT                             10.06
## split[cur.subset]TISOC 1                        1.29
##
## Concordance= 0.65 (se = 0.037 )
## Rsquare= 0.164 (max possible= 0.968 )
## Likelihood ratio test= 33.9 on 10 df, p=0.000191
## Wald test = 38 on 10 df, p=3.8e-05
## Score (logrank) test = 50 on 10 df, p=2.67e-07
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##                                     coef exp(coef) se(coef)
## split[cur.subset]DeLOS II (IC), Op+PORChT -1.77e+01 2.15e-08 3.60e+03
## split[cur.subset]DeLOS II (IC,RT)         -1.42e+00 2.41e-01 9.16e-01
## split[cur.subset]ICHT+OP+RT                1.89e-01 1.21e+00 7.71e-01
## split[cur.subset]KRCHT                    -2.49e-02 9.75e-01 1.00e+00
## split[cur.subset]OP                       -1.39e+00 2.49e-01 7.78e-01
## split[cur.subset]pall CHEMO                -5.06e-01 6.03e-01 1.24e+00
## split[cur.subset]PORChT                   -1.14e+00 3.20e-01 7.57e-01
## split[cur.subset]PORT                     -1.16e+00 3.15e-01 7.54e-01
## split[cur.subset]RT                       7.82e-01 2.19e+00 7.77e-01

```

```

## split[cur.subset]TISOC 1          -1.68e+00  1.86e-01  1.01e+00
##                                     z Pr(>|z|)
## split[cur.subset]DeLOS II (IC), Op+PORChT  0.00    0.996
## split[cur.subset]DeLOS II (IC,RT)          -1.55    0.120
## split[cur.subset]ICHT+OP+RT                0.24    0.807
## split[cur.subset]KRCHT                    -0.02    0.980
## split[cur.subset]OP                       -1.79    0.074 .
## split[cur.subset]pall CHEMO                -0.41    0.682
## split[cur.subset]PORChT                   -1.50    0.132
## split[cur.subset]PORT                     -1.53    0.125
## split[cur.subset]RT                       1.01    0.314
## split[cur.subset]TISOC 1                  -1.66    0.096 .
## ---
## 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  2.15e-08  4.65e+07    0.0000
## split[cur.subset]DeLOS II (IC,RT)          2.41e-01  4.15e+00    0.0400
## split[cur.subset]ICHT+OP+RT                1.21e+00  8.28e-01    0.2666
## split[cur.subset]KRCHT                     9.75e-01  1.03e+00    0.1366
## split[cur.subset]OP                        2.49e-01  4.02e+00    0.0542
## split[cur.subset]pall CHEMO                 6.03e-01  1.66e+00    0.0534
## split[cur.subset]PORChT                    3.20e-01  3.12e+00    0.0727
## split[cur.subset]PORT                      3.15e-01  3.18e+00    0.0719
## split[cur.subset]RT                        2.19e+00  4.57e-01    0.4766
## split[cur.subset]TISOC 1                   1.86e-01  5.37e+00    0.0258
##                                     upper .95
## split[cur.subset]DeLOS II (IC), Op+PORChT      Inf
## split[cur.subset]DeLOS II (IC,RT)              1.45
## split[cur.subset]ICHT+OP+RT                    5.47
## split[cur.subset]KRCHT                        6.97
## split[cur.subset]OP                           1.14
## split[cur.subset]pall CHEMO                    6.81
## split[cur.subset]PORChT                       1.41
## split[cur.subset]PORT                         1.38
## split[cur.subset]RT                          10.03
## split[cur.subset]TISOC 1                      1.35
##
## Concordance= 0.657 (se = 0.036 )
## Rsquare= 0.165 (max possible= 0.965 )
## Likelihood ratio test= 37.8 on 10 df,  p=4.19e-05
## Wald test              = 42.8 on 10 df,  p=5.33e-06
## Score (logrank) test = 56.7 on 10 df,  p=1.52e-08
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##                                     split[cur.subset]=BSC

```

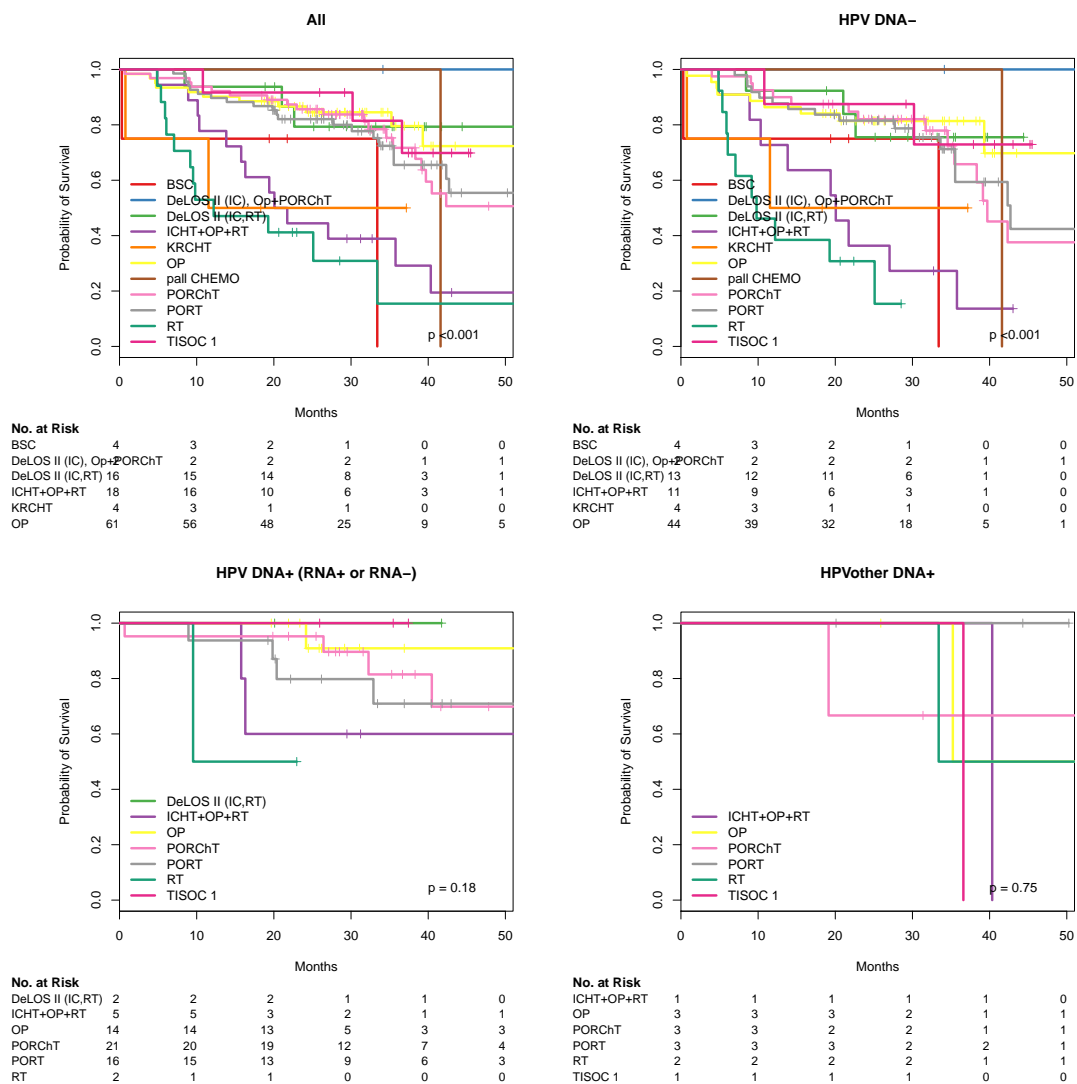


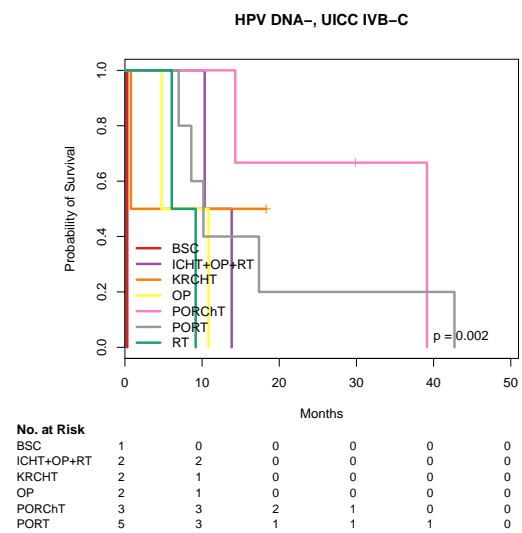
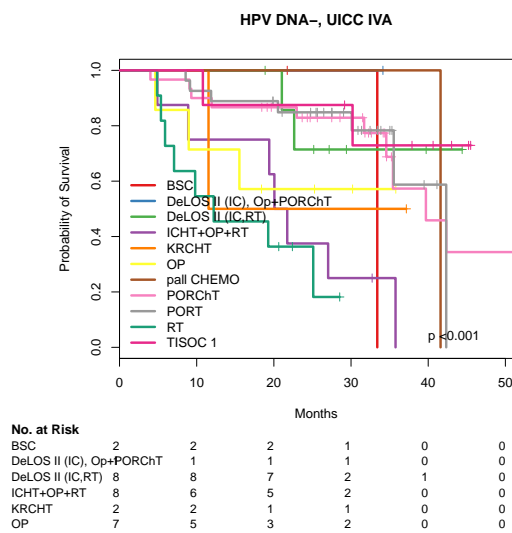
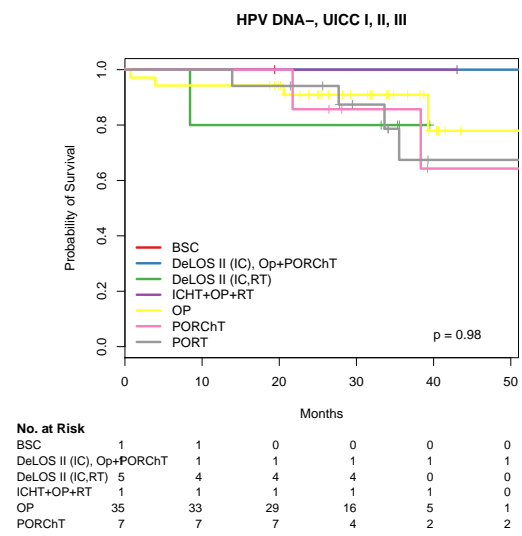
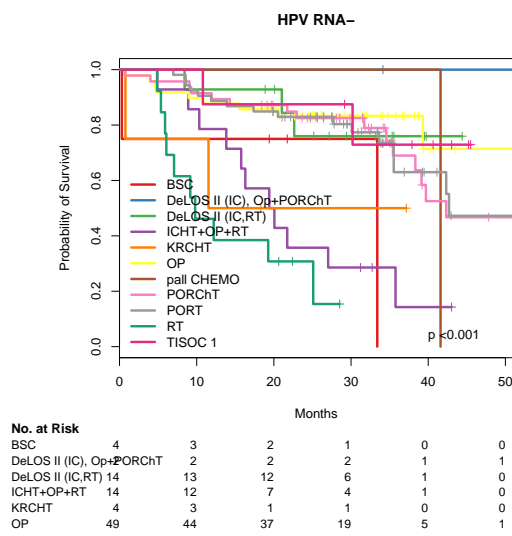
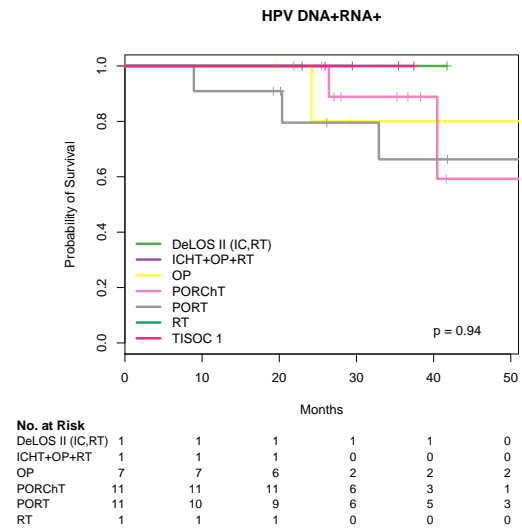
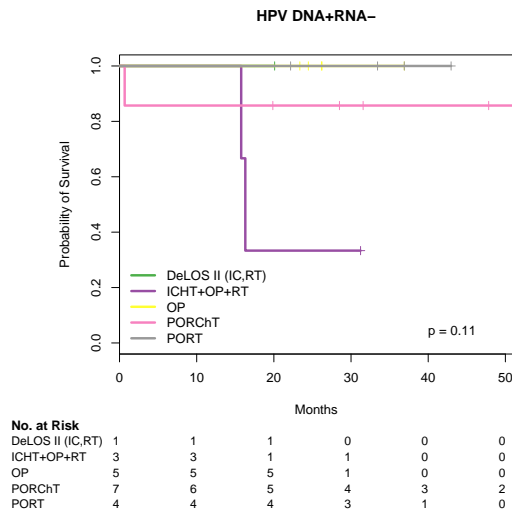
```

##      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      0.760      0.122
## lower 95% CI upper 95% CI
##      0.555      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
##      36.000      1.000      2.000      0.500      0.250
## lower 95% CI upper 95% CI
##      0.188      1.000
##
##      split[cur.subset]=OP
##      time      n.risk      n.event      survival      std.err
##      36.000      11.000      8.000      0.833      0.054
## lower 95% CI upper 95% CI
##      0.734      0.946
##
##      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      13.0000      11.0000      0.6898      0.0867
## lower 95% CI upper 95% CI
##      0.5392      0.8826
##
##      split[cur.subset]=PORT
##      time      n.risk      n.event      survival      std.err
##      36.000      12.000      14.000      0.630      0.091
## lower 95% CI upper 95% CI

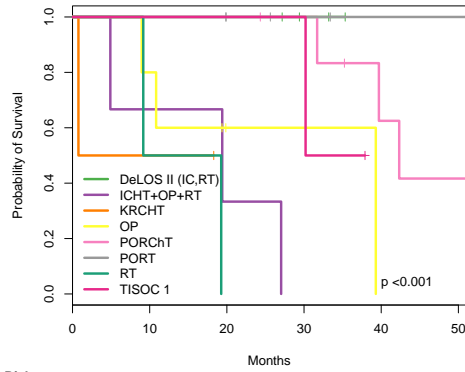
```

```
##          0.475          0.836
##
##          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          0.729          0.165
## lower 95% CI upper 95% CI
##          0.468          1.000
```



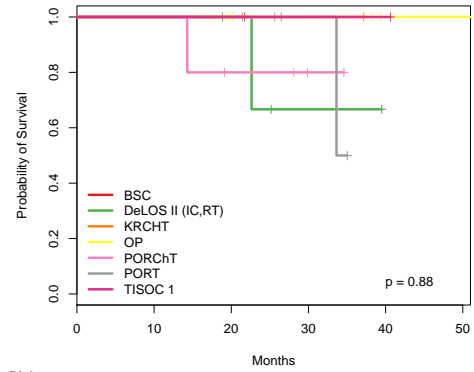


In DNA- Atypical



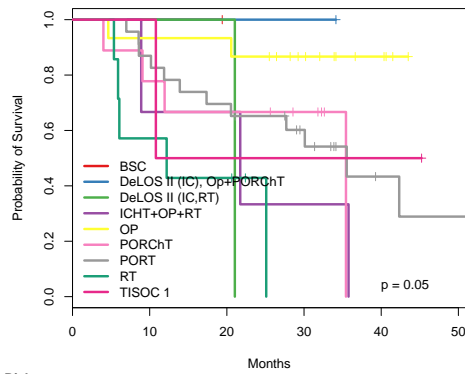
No. at Risk					
DeLOS II (IC,RT)	4	4	4	2	0
ICHT+OP+RT	3	2	1	0	0
KRCHT	2	1	0	0	0
OP	5	4	1	1	0
PORChT	7	7	7	6	3
PORT	6	6	4	3	2

In DNA- Classical



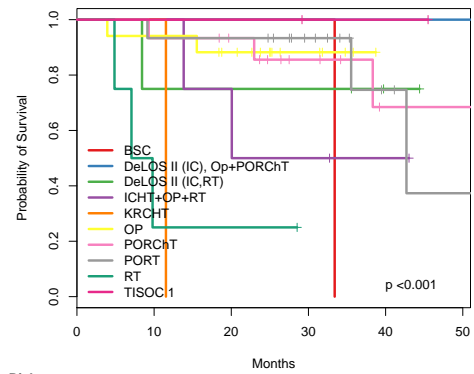
No. at Risk					
BSC	1	1	1	0	0
DeLOS II (IC,RT)	4	4	3	1	0
KRCHT	1	1	1	1	0
OP	5	5	4	3	1
PORChT	5	5	3	1	0
PORT	5	5	5	2	0

In DNA- Mesenchymal



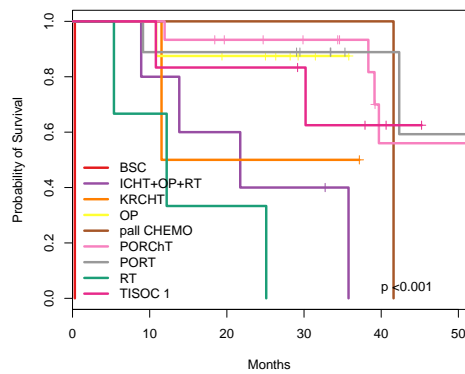
No. at Risk					
BSC	1	1	0	0	0
DeLOS II (IC), Op+PORChT	1	1	1	0	0
DeLOS II (IC,RT)	1	1	1	0	0
ICHT+OP+RT	3	2	2	1	0
OP	15	14	14	9	4
PORChT	9	7	6	4	0

In DNA- Basal



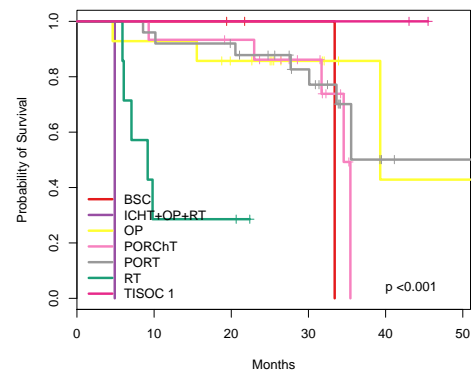
No. at Risk					
BSC	1	1	1	0	0
DeLOS II (IC), Op+PORChT	1	1	1	1	1
DeLOS II (IC,RT)	4	3	3	3	1
ICHT+OP+RT	4	4	3	2	1
KRCHT	1	1	0	0	0
OP	17	16	13	5	0

HPV DNA- Oropharynx

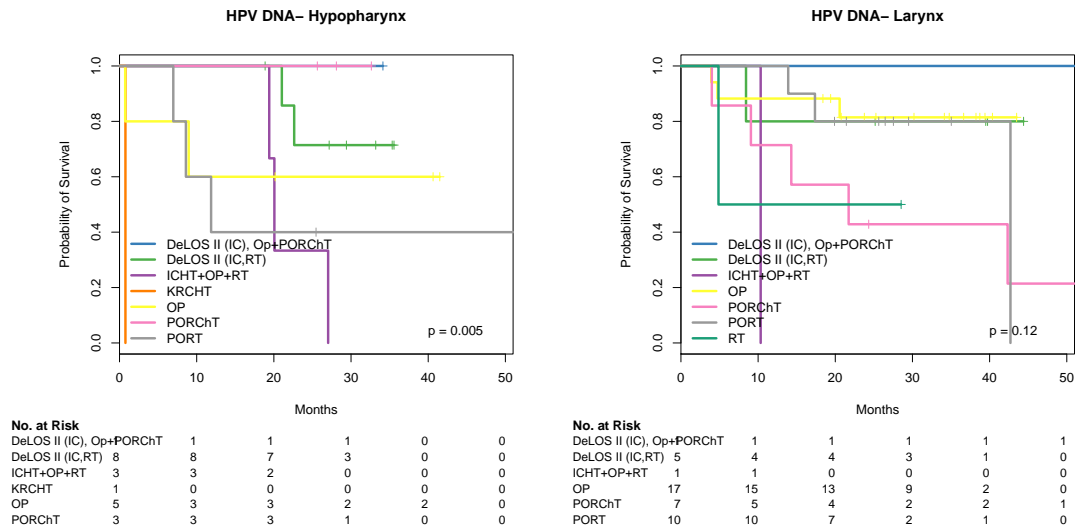


No. at Risk					
BSC	1	0	0	0	0
ICHT+OP+RT	5	4	3	2	0
KRCHT	2	2	1	1	0
OP	8	8	6	2	0
pall CHEMO	1	1	1	1	0
PORChT	15	15	12	10	4

HPV DNA- Cavum oris



No. at Risk					
BSC	3	3	2	1	0
ICHT+OP+RT	1	0	0	0	0
OP	14	13	10	5	1
PORChT	15	14	13	8	0
PORT	25	24	22	15	3
RT	7	2	2	0	0



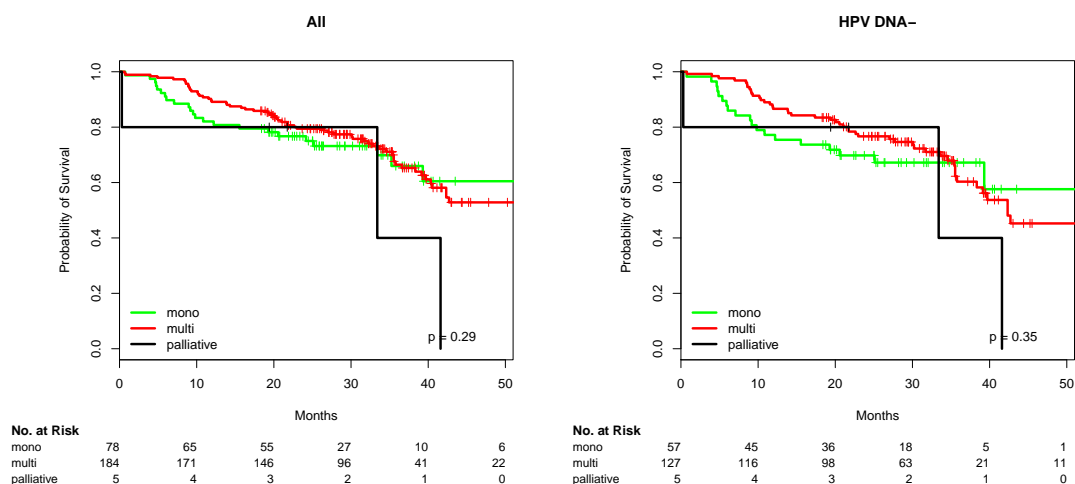
3.8 Therapy

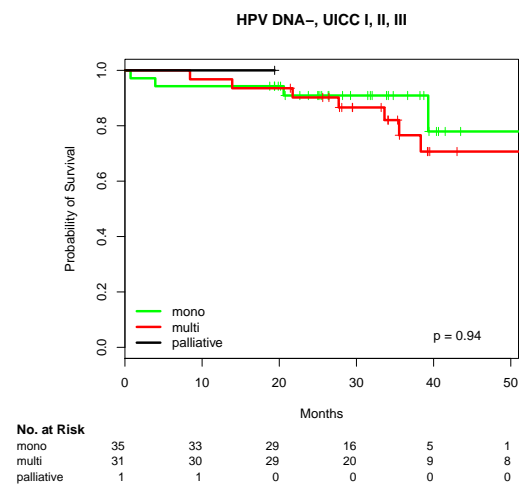
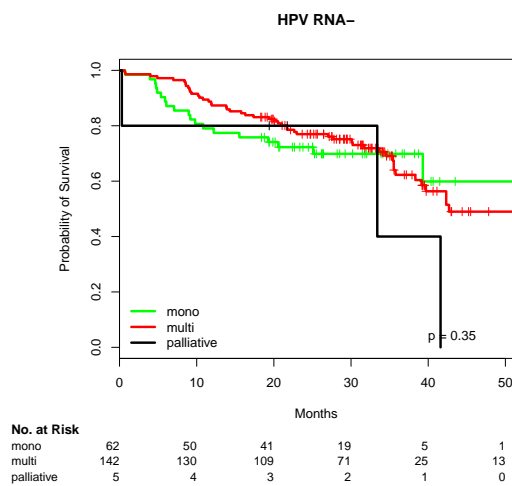
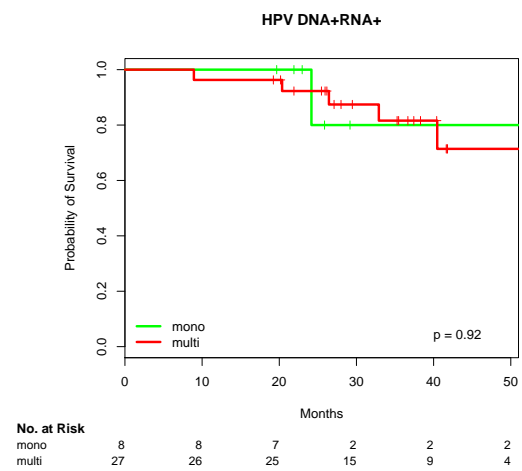
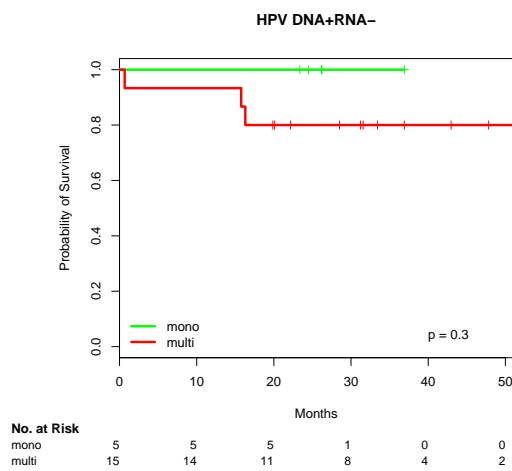
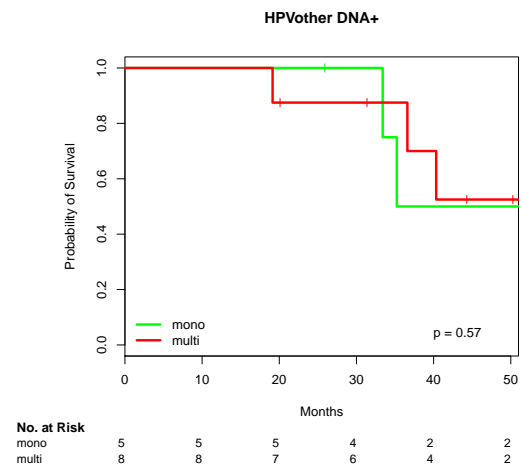
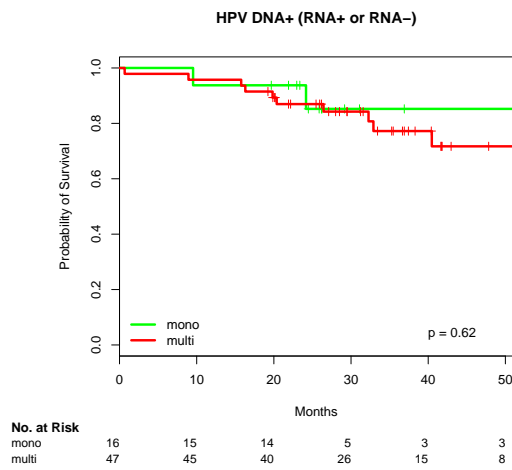
Legend: mono denotes mono modal therapy, multi denotes multi modal therapy. Please see the paper for more information.

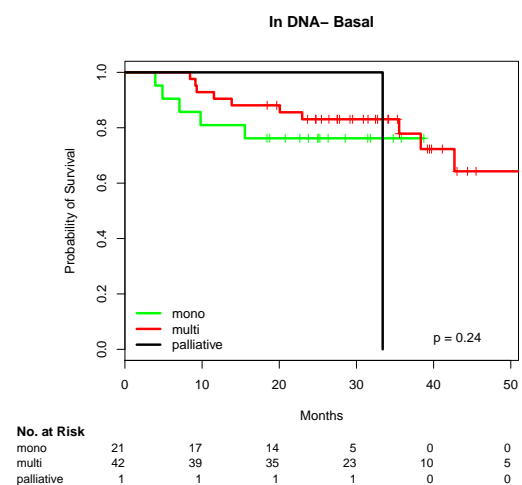
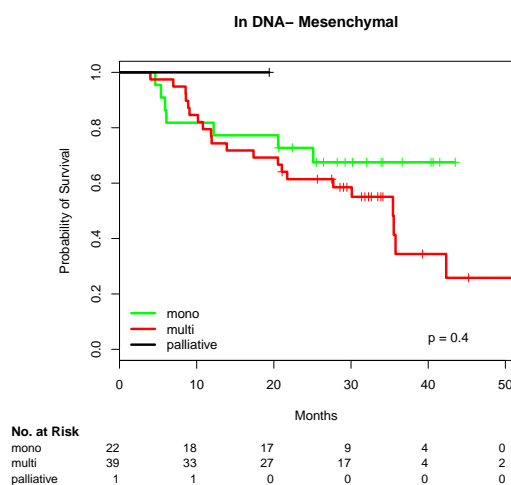
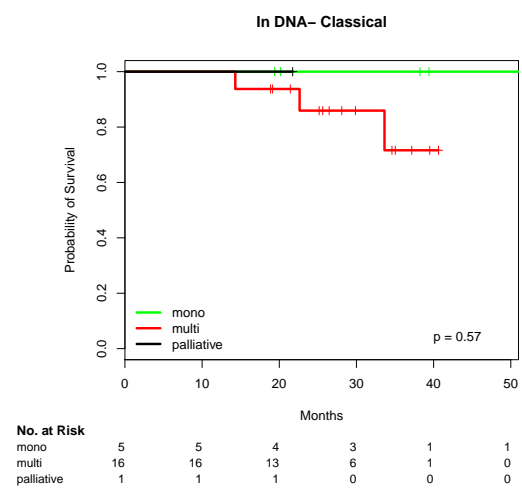
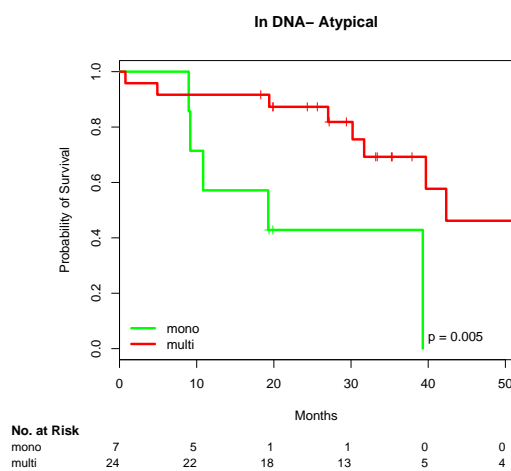
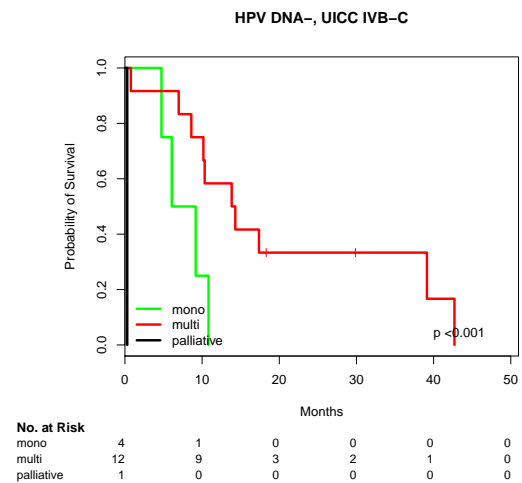
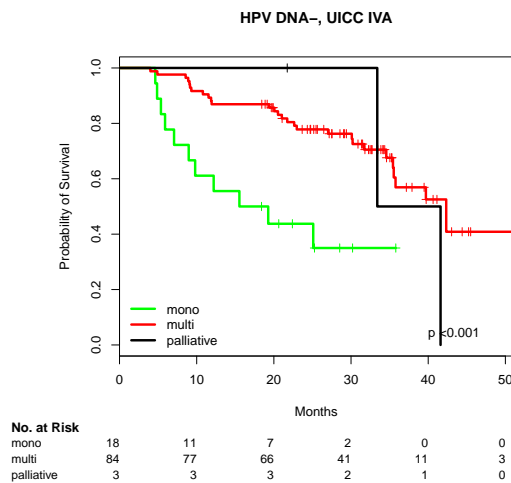
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.136    0.873   0.233 -0.58    0.56
## split[cur.subset]palliative 0.746    2.108   0.611  1.22    0.22
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi    0.873    1.145    0.553    1.38
## split[cur.subset]palliative 2.108    0.474    0.636    6.99
##
## Concordance= 0.53 (se =0.026 )
## Rsquare= 0.007 (max possible= 0.967 )
## Likelihood ratio test= 1.94 on 2 df,  p=0.379
## Wald test               = 2.39 on 2 df,  p=0.303
## Score (logrank) test = 2.52 on 2 df,  p=0.284
##
## 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      16.0000      22.0000      0.6597      0.0676
## lower 95% CI upper 95% CI
```

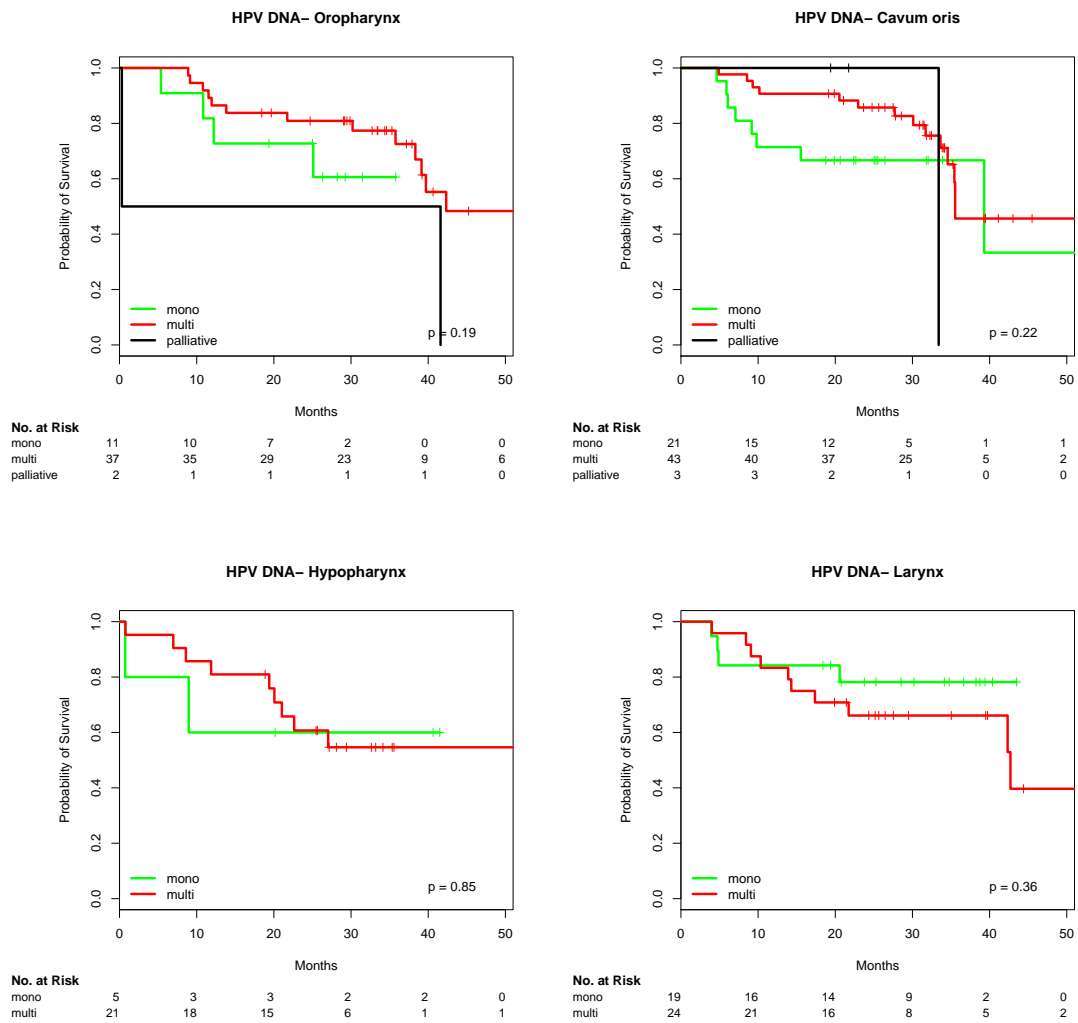
```
##      0.5398      0.8064
##
##      split[cur.subset]=multi
##      time      n.risk      n.event      survival      std.err
##      36.0000      56.0000      51.0000      0.6645      0.0413
## lower 95% CI upper 95% CI
##      0.5883      0.7506
##
##      split[cur.subset]=palliative
##      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= 71
## (2 observations deleted due to missingness)
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi      -0.229      0.795      0.269 -0.85      0.39
## split[cur.subset]palliative  0.523      1.687      0.620  0.84      0.40
##
##      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi      0.795      1.258      0.469      1.35
## split[cur.subset]palliative  1.687      0.593      0.500      5.69
##
## Concordance= 0.543 (se = 0.03 )
## Rsquare= 0.01 (max possible= 0.968 )
## Likelihood ratio test= 1.81 on 2 df, p=0.405
## Wald test = 2.05 on 2 df, p=0.358
## Score (logrank) test = 2.12 on 2 df, p=0.347
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi      -0.176      0.839      0.267 -0.66      0.51
## split[cur.subset]palliative  0.622      1.863      0.620  1.00      0.32
```

```
##
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi          0.839      1.192      0.497      1.42
## split[cur.subset]palliative      1.863      0.537      0.552      6.28
##
## Concordance= 0.534 (se = 0.03 )
## Rsquare= 0.008 (max possible= 0.965 )
## Likelihood ratio test= 1.72 on 2 df, p=0.424
## Wald test = 2.03 on 2 df, p=0.363
## Score (logrank) test = 2.11 on 2 df, p=0.348
##
## 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     11.0000     18.0000      0.6986      0.0603
## lower 95% CI upper 95% CI
## 0.5899      0.8273
##
##                split[cur.subset]=multi
##      time      n.risk      n.event      survival      std.err
## 36.0000     36.0000     43.0000      0.6228      0.0506
## lower 95% CI upper 95% CI
## 0.5311      0.7302
##
##                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

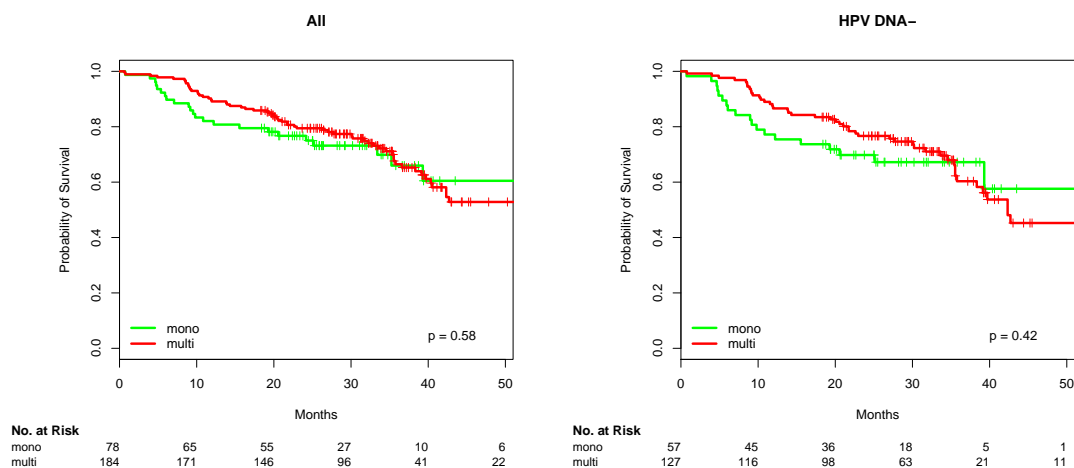
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 262, number of events= 91
##      (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.129      0.879   0.233 -0.56    0.58
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi    0.879      1.14    0.556    1.39
##
## Concordance= 0.526 (se = 0.026 )
## Rsquare= 0.001 (max possible= 0.965 )
```

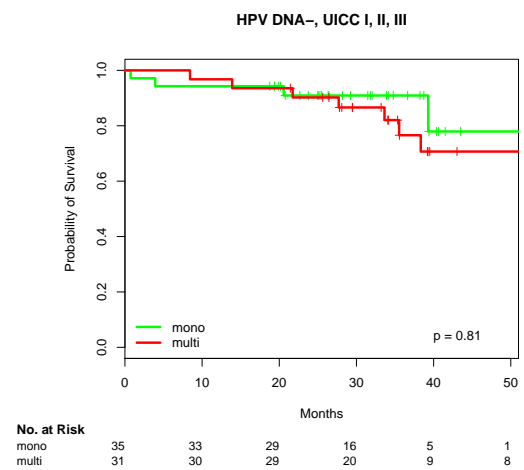
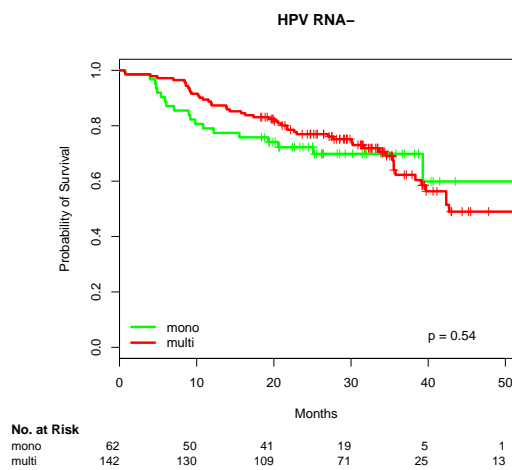
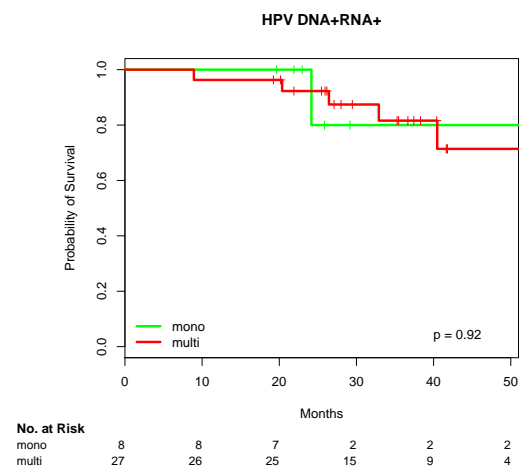
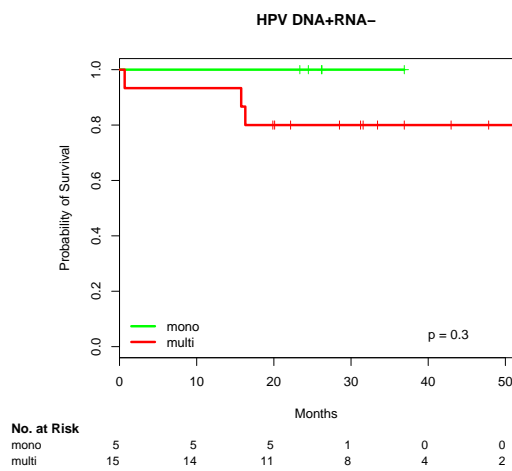
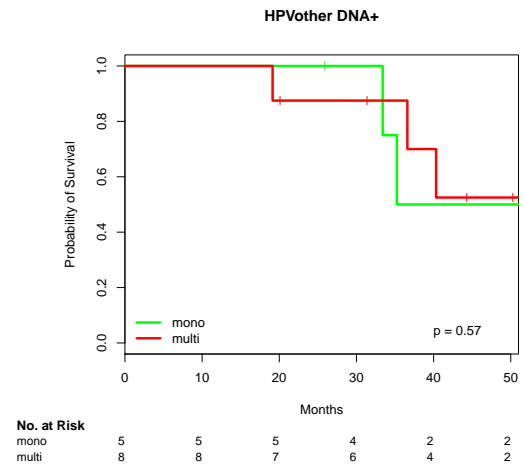
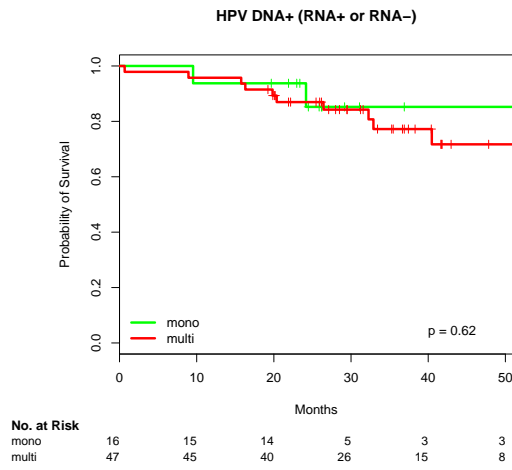
```

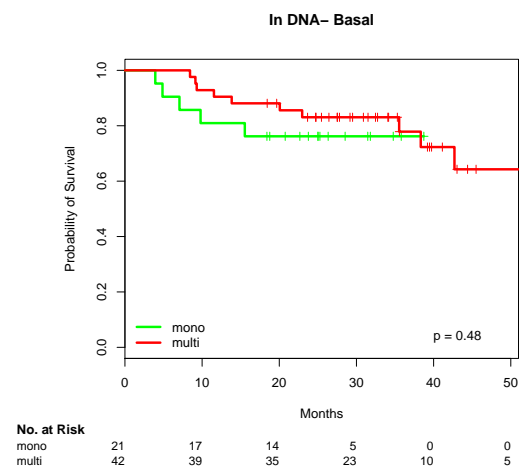
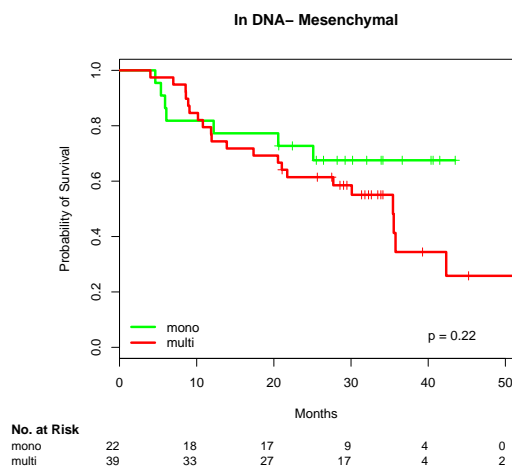
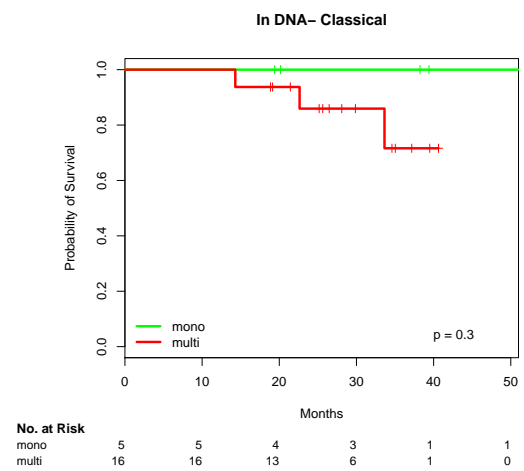
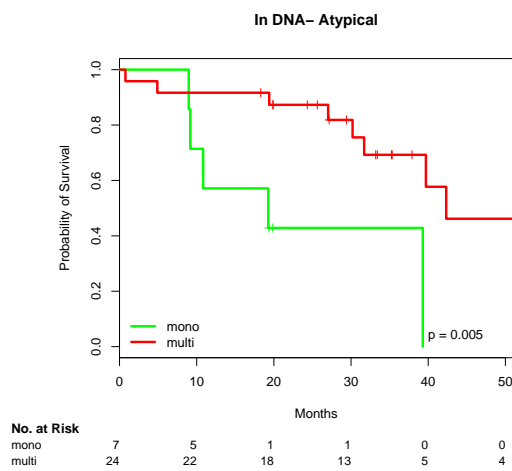
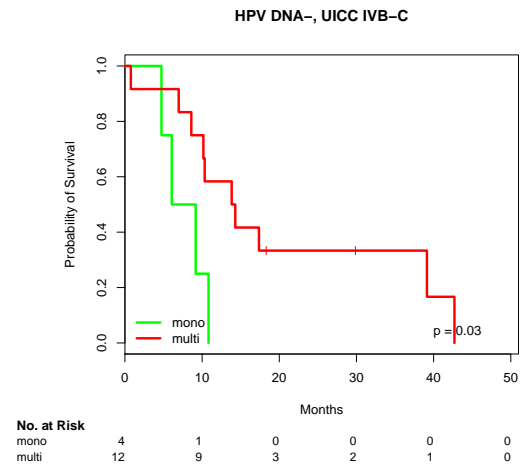
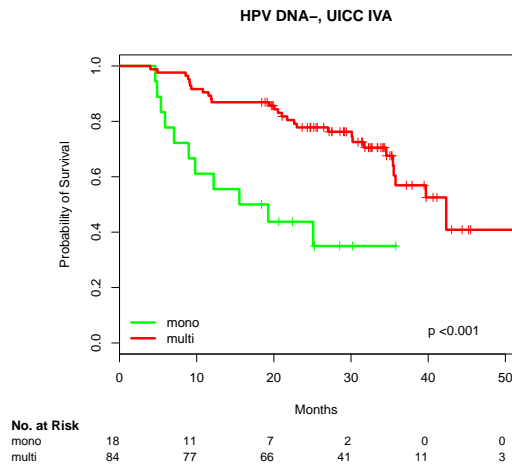
## Likelihood ratio test= 0.3  on 1 df,  p=0.582
## Wald test          = 0.31  on 1 df,  p=0.579
## Score (logrank) test = 0.31  on 1 df,  p=0.579
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 5 observations deleted due to missingness
##           split[cur.subset]=mono
##           time      n.risk      n.event      survival      std.err
##           36.0000      16.0000      22.0000      0.6597      0.0676
## lower 95% CI upper 95% CI
##           0.5398      0.8064
##
##           split[cur.subset]=multi
##           time      n.risk      n.event      survival      std.err
##           36.0000      56.0000      51.0000      0.6645      0.0413
## lower 95% CI upper 95% CI
##           0.5883      0.7506
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 184, number of events= 68
## (7 observations deleted due to missingness)
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.216      0.806      0.269 -0.8      0.42
##
##           exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi      0.806      1.24      0.476      1.37
##
## Concordance= 0.541 (se = 0.03 )
## Rsquare= 0.003 (max possible= 0.966 )
## Likelihood ratio test= 0.63  on 1 df,  p=0.429
## Wald test          = 0.64  on 1 df,  p=0.422
## Score (logrank) test = 0.65  on 1 df,  p=0.422
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 204, number of events= 72

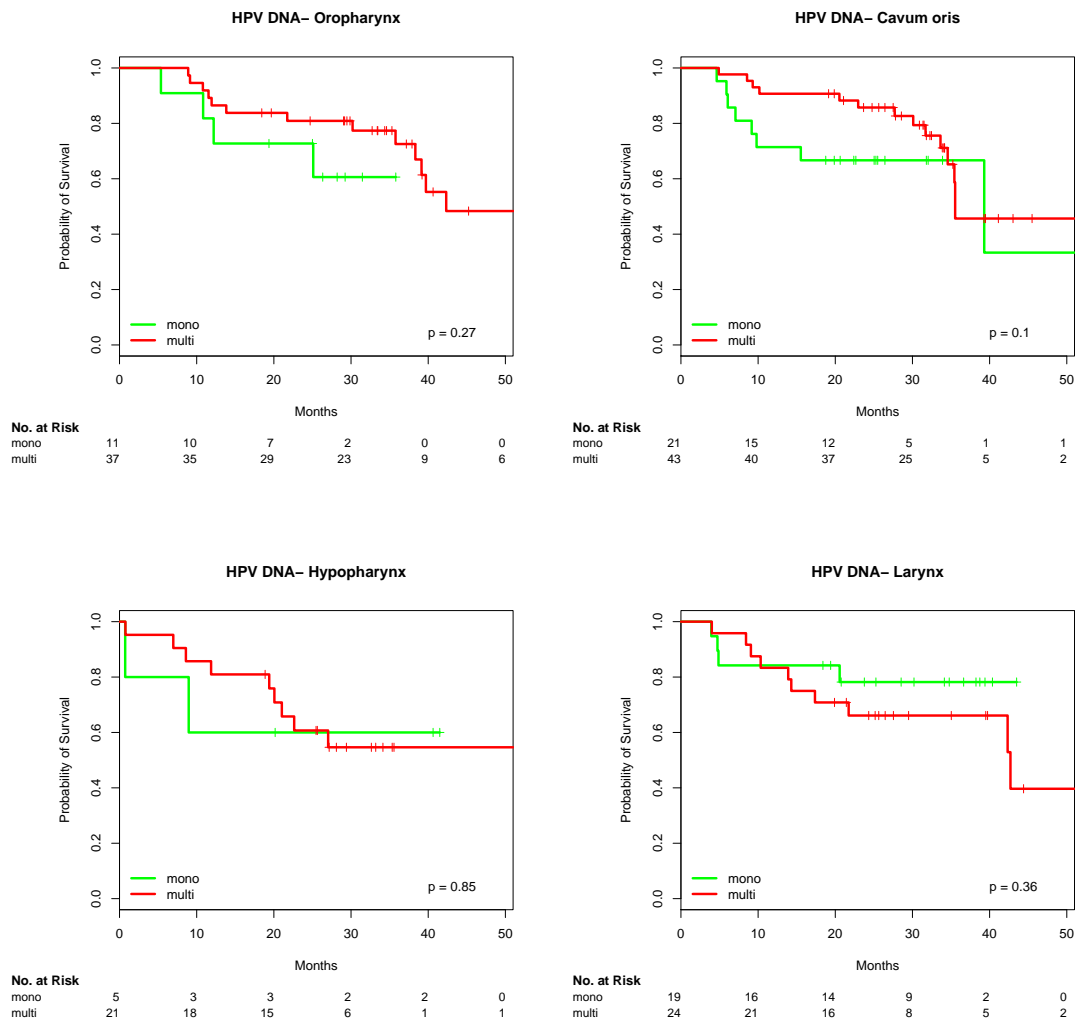
```

```
##      (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]multi -0.161      0.851    0.266 -0.6    0.55
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]multi    0.851      1.17    0.505    1.43
##
## Concordance= 0.531  (se = 0.029 )
## Rsquare= 0.002  (max possible= 0.963 )
## Likelihood ratio test= 0.36  on 1 df,   p=0.55
## Wald test               = 0.37  on 1 df,   p=0.545
## Score (logrank) test = 0.37  on 1 df,   p=0.545
##
## 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     11.0000     18.0000         0.6986         0.0603
## lower 95% CI upper 95% CI
##              0.5899         0.8273
##
##              split[cur.subset]=multi
##              time      n.risk      n.event      survival      std.err
##              36.0000     36.0000     43.0000         0.6228         0.0506
## lower 95% CI upper 95% CI
##              0.5311         0.7302
```









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= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.229    0.795  0.472 -0.49  0.6266
## split[cur.subset]3  1.095    2.991  0.431  2.54  0.0111 *
## split[cur.subset]4a  1.156    3.177  0.417  2.77  0.0056 **
## split[cur.subset]4b  1.786    5.968  0.637  2.80  0.0050 **
## 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      0.795      1.258      0.315      2.00
## split[cur.subset]3      2.991      0.334      1.284      6.96
## split[cur.subset]4a     3.177      0.315      1.403      7.19
## split[cur.subset]4b     5.968      0.168      1.712     20.80
## split[cur.subset]x         NA         NA         NA         NA
##
## Concordance= 0.654  (se = 0.032 )
## Rsquare= 0.118   (max possible= 0.967 )
## Likelihood ratio test= 33.5  on 4 df,   p=9.47e-07
## Wald test          = 27.8  on 4 df,   p=1.37e-05
## Score (logrank) test = 32.3  on 4 df,   p=1.69e-06
##
## 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
##           36.000      10.000       4.000       0.852       0.074
## lower 95% CI upper 95% CI
##           0.719       1.000
##
##               split[cur.subset]=2
##           time      n.risk      n.event      survival      std.err
##           36.0000     28.0000      8.0000      0.8611      0.0478
## lower 95% CI upper 95% CI
##           0.7723      0.9600
##
##               split[cur.subset]=3
##           time      n.risk      n.event      survival      std.err
##           36.000     18.000     24.000      0.540      0.072
## lower 95% CI upper 95% CI
##           0.416      0.701
##
##               split[cur.subset]=4a
##           time      n.risk      n.event      survival      std.err
##           36.0000     17.0000     35.0000      0.5070      0.0683
## lower 95% CI upper 95% CI
##           0.3893      0.6603
##
##               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])

```

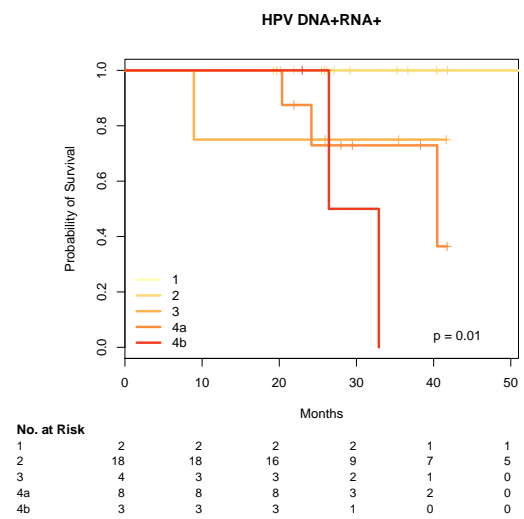
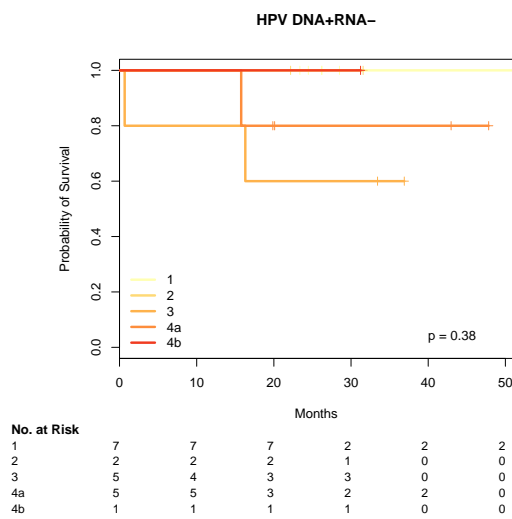
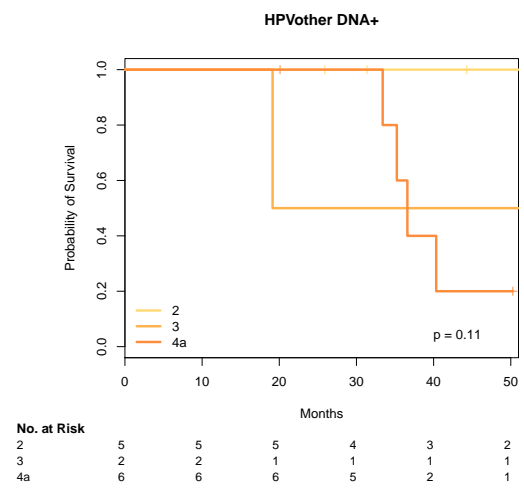
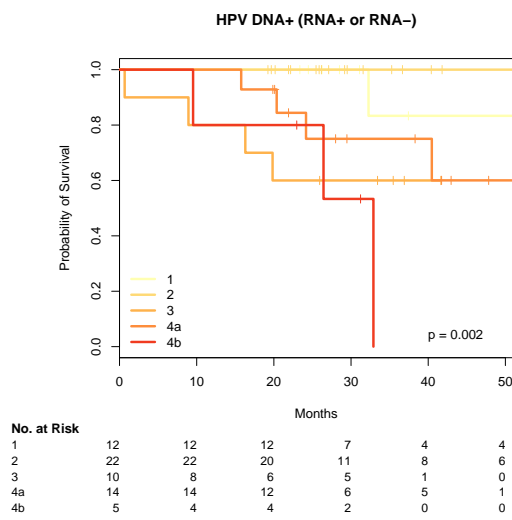
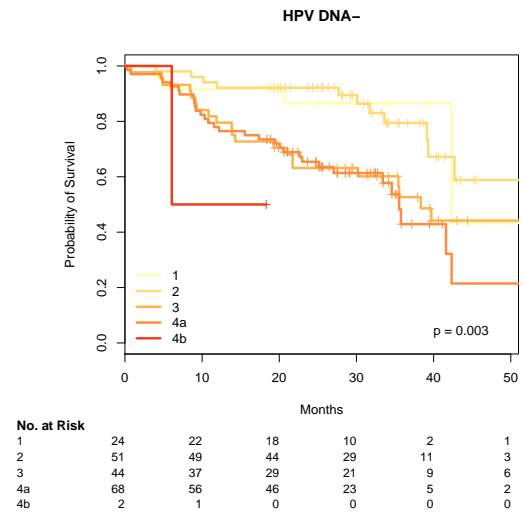
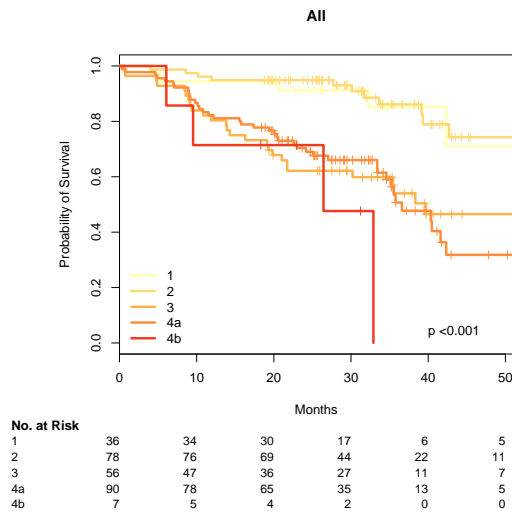


```
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.168      0.845    0.540 -0.31    0.755
## split[cur.subset]3  0.745      2.106    0.498  1.50    0.135
## split[cur.subset]4a 0.982      2.669    0.482  2.04    0.042 *
## split[cur.subset]4b 1.870      6.490    1.103  1.70    0.090 .
## 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      0.845      1.183      0.293      2.44
## split[cur.subset]3      2.106      0.475      0.794      5.59
## split[cur.subset]4a      2.669      0.375      1.038      6.86
## split[cur.subset]4b      6.490      0.154      0.748     56.33
## split[cur.subset]x         NA         NA         NA      NA
##
## Concordance= 0.632 (se = 0.037 )
## Rsquare= 0.081 (max possible= 0.968 )
## Likelihood ratio test= 16.1 on 4 df, p=0.00294
## Wald test = 14.4 on 4 df, p=0.00614
## Score (logrank) test = 15.9 on 4 df, p=0.00319
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.00118    0.99882  0.50800  0.00    0.998
## split[cur.subset]3  0.93547    2.54841  0.45782  2.04    0.041 *
## split[cur.subset]4a 1.09450    2.98770  0.44554  2.46    0.014 *
## split[cur.subset]4b 1.21399    3.36689  1.08373  1.12    0.263
## split[cur.subset]x    NA         NA  0.00000    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      0.999      1.001      0.369      2.70
## split[cur.subset]3      2.548      0.392      1.039      6.25
## split[cur.subset]4a      2.988      0.335      1.248      7.15
## split[cur.subset]4b      3.367      0.297      0.402     28.16
```

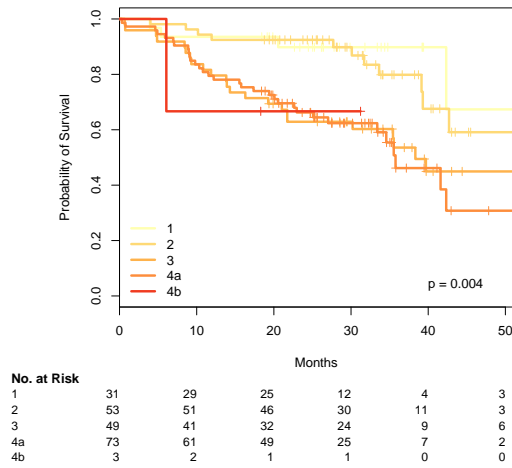
```

## split[cur.subset]x      NA      NA      NA      NA
##
## Concordance= 0.631 (se = 0.036 )
## Rsquare= 0.076 (max possible= 0.965 )
## Likelihood ratio test= 16.5 on 4 df, p=0.00243
## Wald test = 14.2 on 4 df, p=0.0066
## Score (logrank) test = 15.5 on 4 df, p=0.00374
##
## 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
##      36.000      7.000      3.000      0.898      0.056
## lower 95% CI upper 95% CI
##      0.795      1.000
##
##               split[cur.subset]=2
##      time      n.risk      n.event      survival      std.err
##      36.000      16.000      8.000      0.798      0.067
## lower 95% CI upper 95% CI
##      0.677      0.941
##
##               split[cur.subset]=3
##      time      n.risk      n.event      survival      std.err
##      36.0000      16.0000      21.0000      0.5357      0.0776
## lower 95% CI upper 95% CI
##      0.4032      0.7116
##
##               split[cur.subset]=4a
##      time      n.risk      n.event      survival      std.err
##      36.0000      9.0000      30.0000      0.4617      0.0837
## lower 95% CI upper 95% CI
##      0.3236      0.6586
##
##               split[cur.subset]=4b
##      time n.risk n.event survival std.err lower 95% CI upper 95% CI

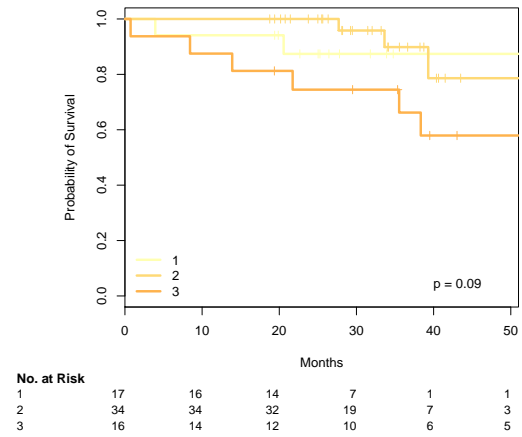
```



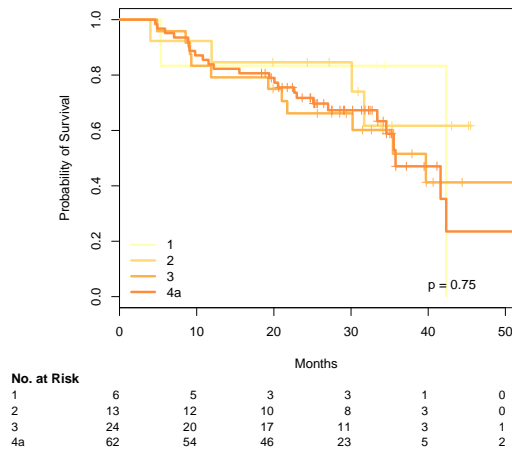
HPV RNA-



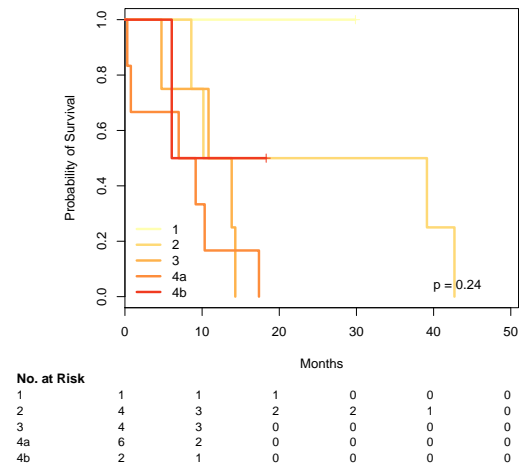
HPV DNA-, UICC I, II, III



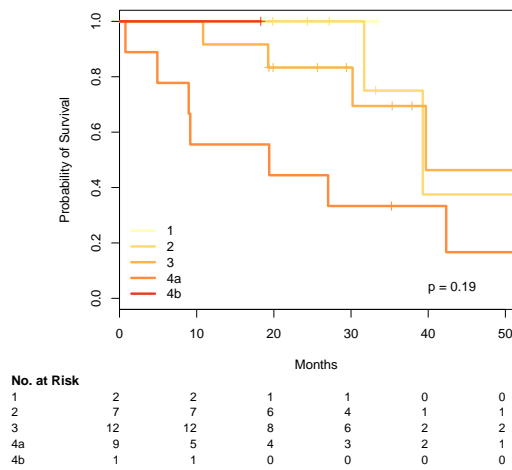
HPV DNA-, UICC IVA



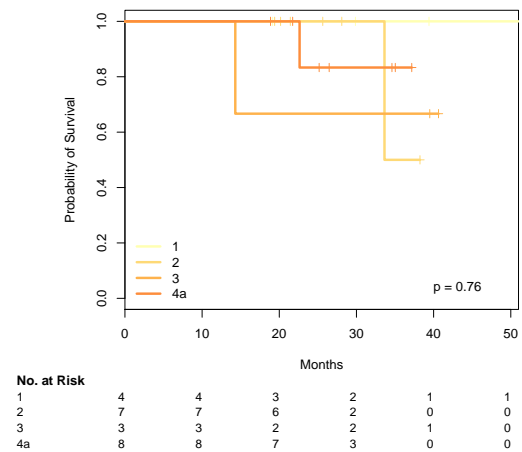
HPV DNA-, UICC IVB-C

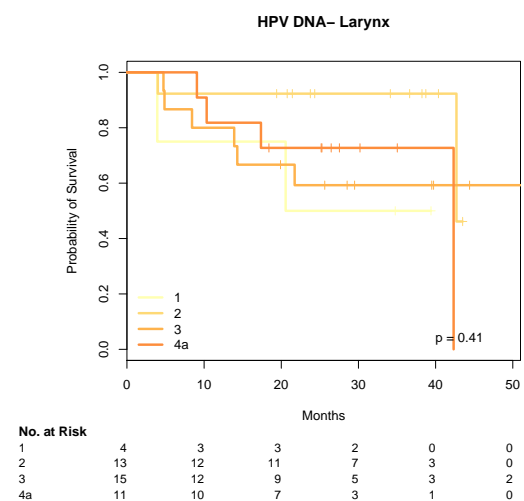
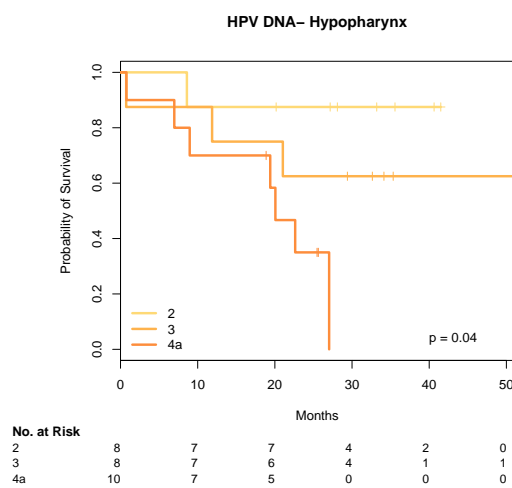
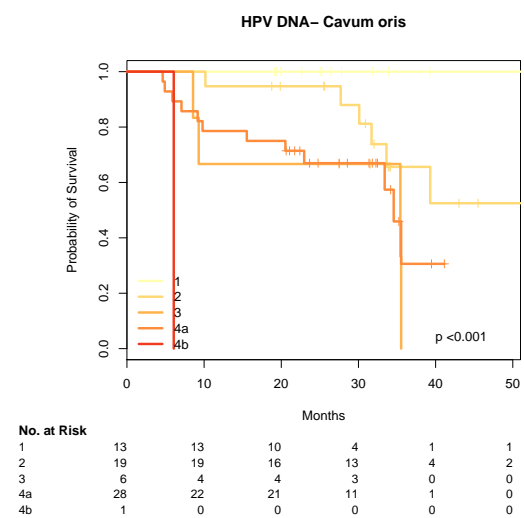
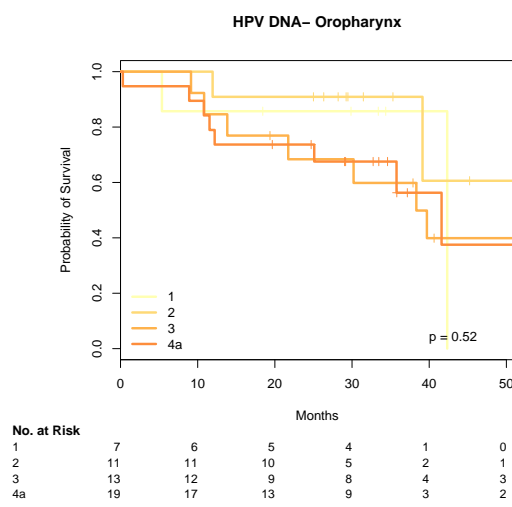
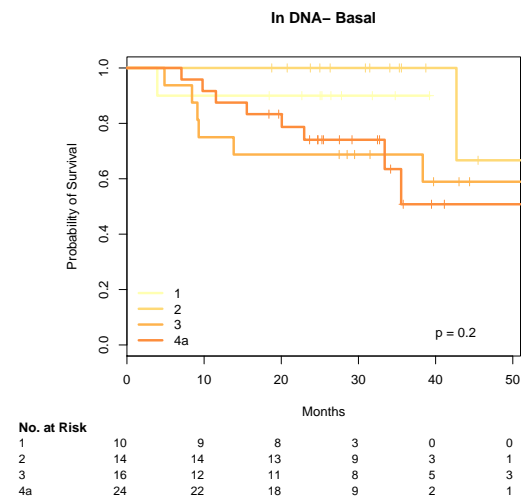
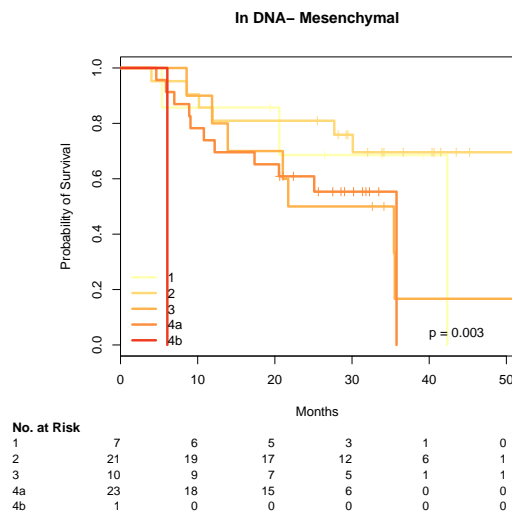


In DNA- Atypical



In DNA- Classical





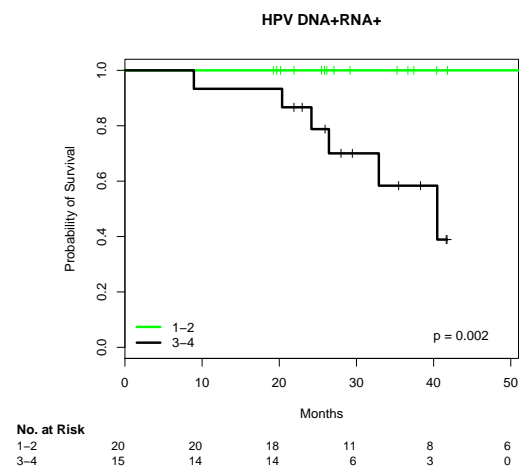
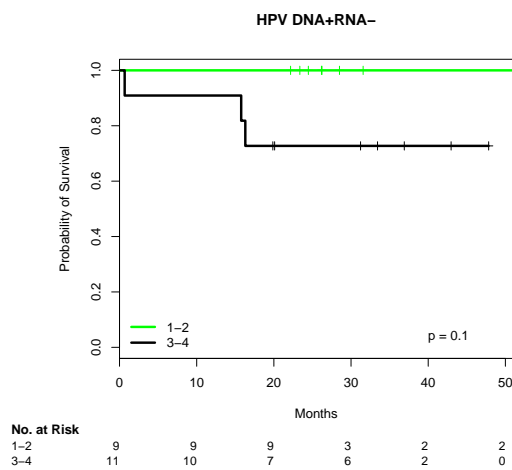
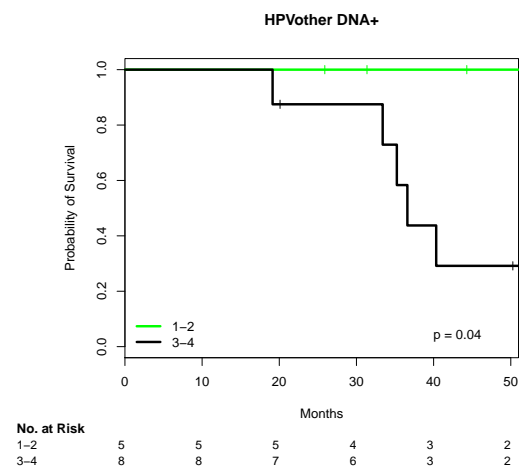
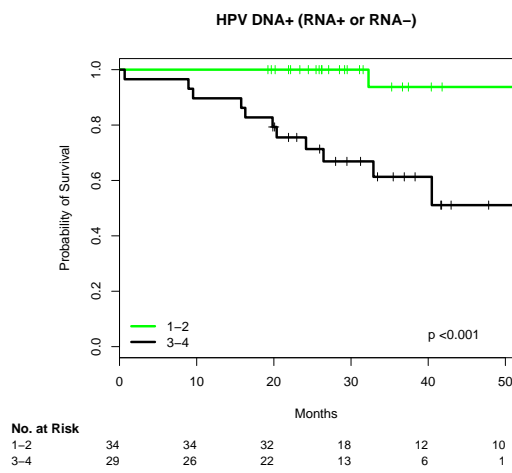
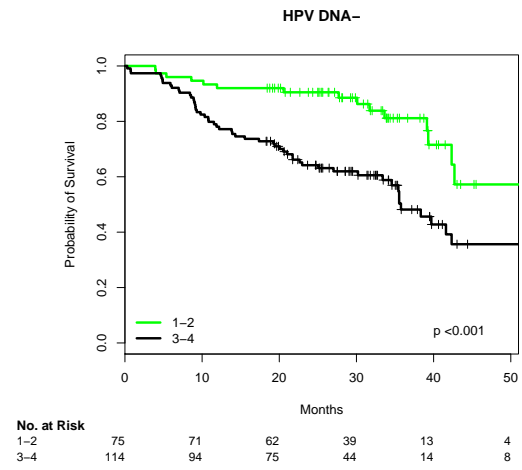
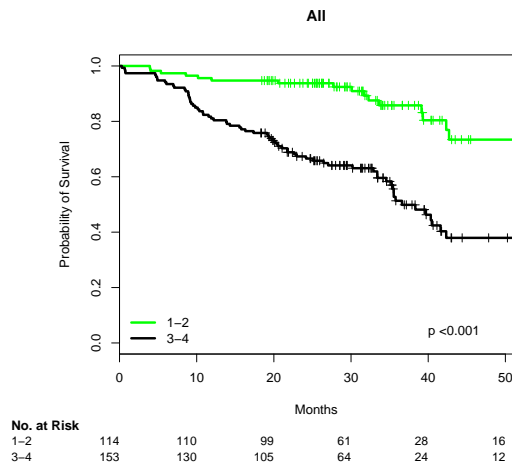
3.11 T stages 1,2 vs. 3,4

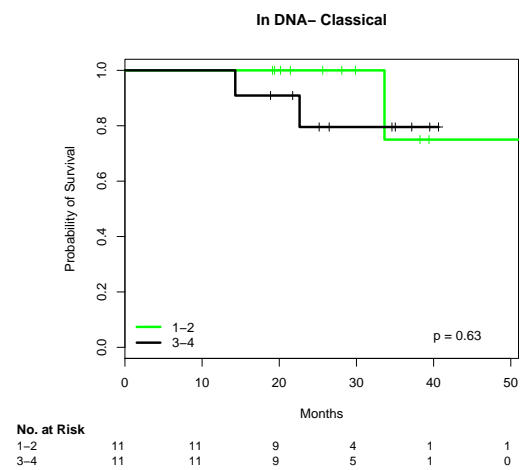
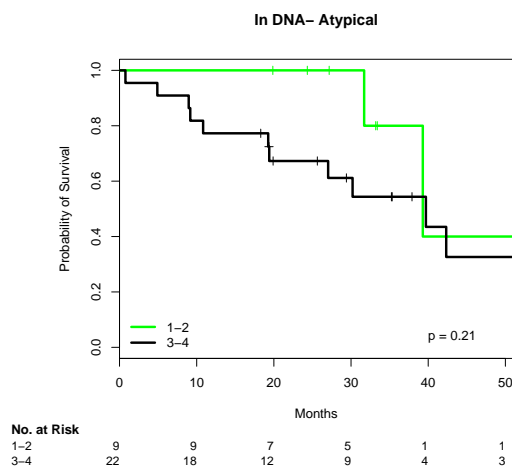
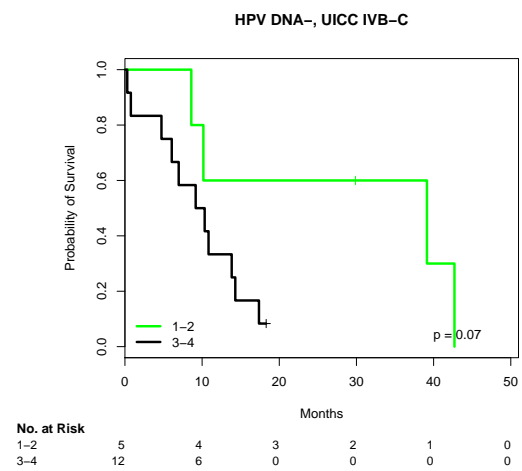
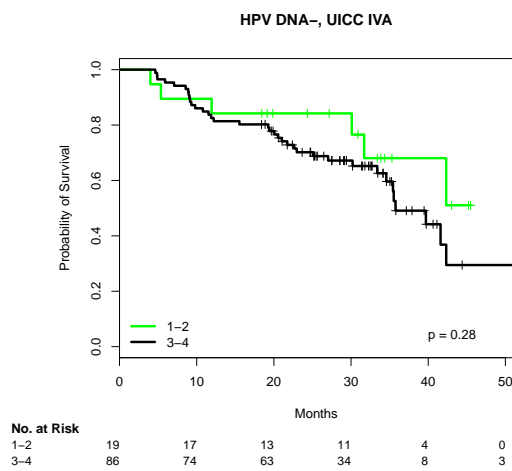
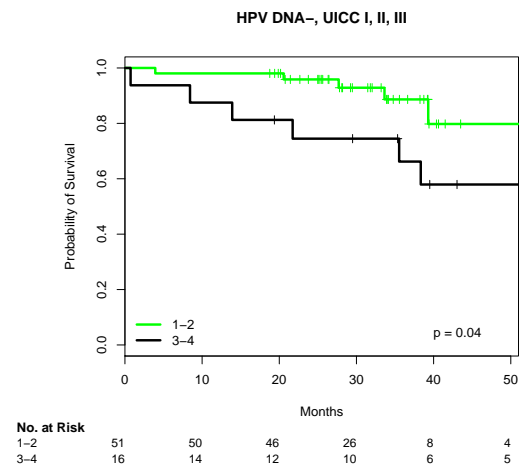
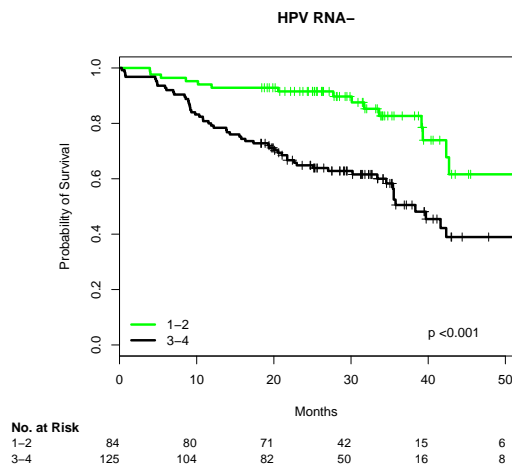
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 1.313      3.716    0.258 5.08  3.7e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]3-4      3.72      0.269      2.24      6.16
##
## Concordance= 0.654 (se = 0.029 )
## Rsquare= 0.113 (max possible= 0.967 )
## Likelihood ratio test= 31.9 on 1 df,  p=1.64e-08
## Wald test               = 25.8 on 1 df,  p=3.71e-07
## Score (logrank) test = 29.7 on 1 df,  p=5.14e-08
##
## 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      38.0000      12.0000      0.8577      0.0403
## lower 95% CI upper 95% CI
##           0.7822      0.9404
##
##               split[cur.subset]=3-4
##           time      n.risk      n.event      survival      std.err
##           36.0000      35.0000      63.0000      0.5132      0.0486
## lower 95% CI upper 95% CI
##           0.4264      0.6178
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 1.006      2.735    0.285 3.53  0.00041 ***
## ---
```

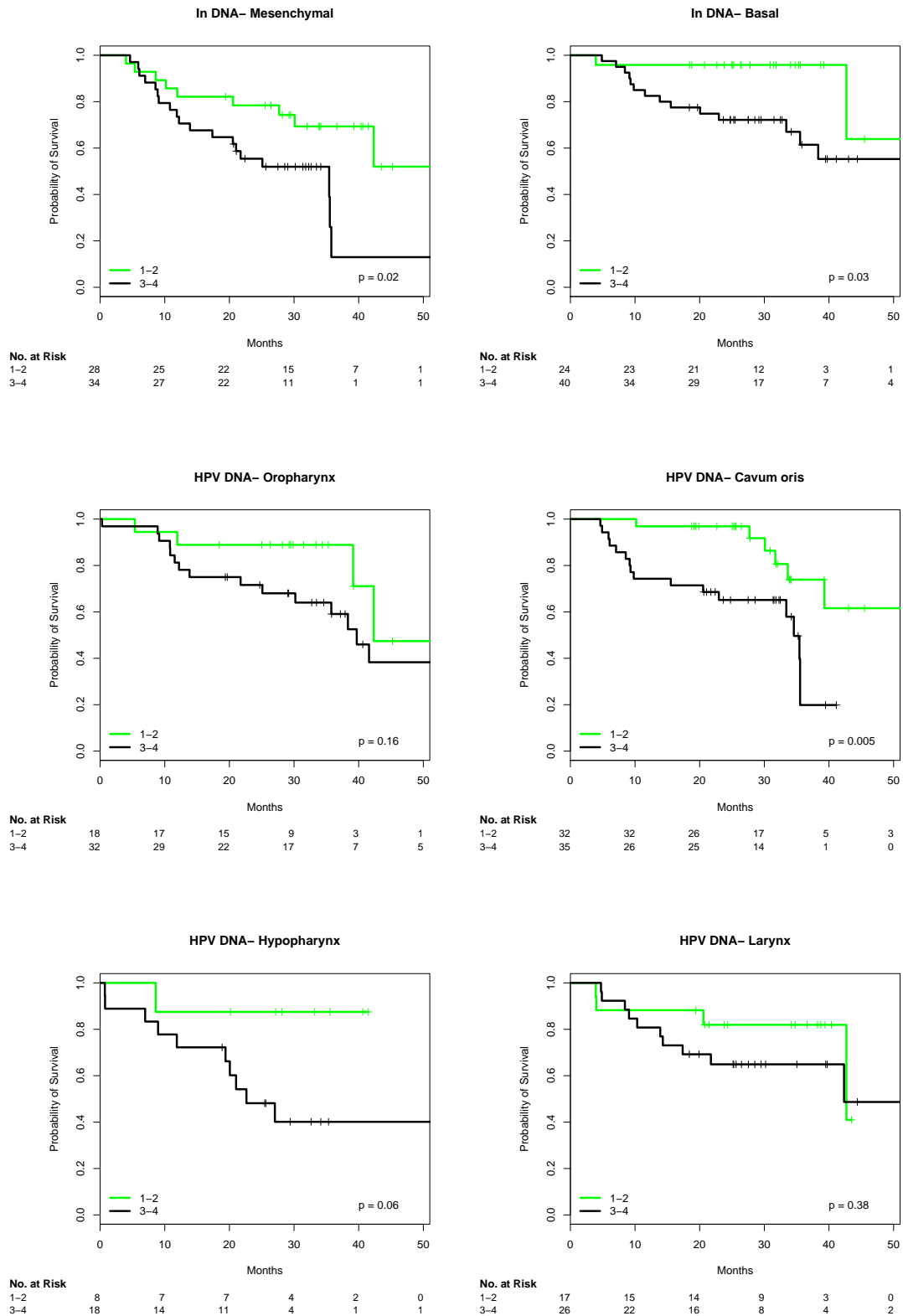
```

## 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      2.74      0.366      1.57      4.78
##
## Concordance= 0.625  (se = 0.033 )
## Rsquare= 0.074  (max possible= 0.968 )
## Likelihood ratio test= 14.6  on 1 df,  p=0.000135
## Wald test               = 12.5  on 1 df,  p=0.000412
## Score (logrank) test = 13.6  on 1 df,  p=0.000233
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 1.027      2.793      0.277 3.71 0.00021 ***
## ---
## 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      2.79      0.358      1.62      4.8
##
## Concordance= 0.632  (se = 0.032 )
## Rsquare= 0.074  (max possible= 0.965 )
## Likelihood ratio test= 16.1  on 1 df,  p=5.96e-05
## Wald test               = 13.8  on 1 df,  p=0.000205
## Score (logrank) test = 15  on 1 df,  p=0.000107
##
## 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      23.0000      11.0000      0.8268      0.0508
## lower 95% CI upper 95% CI
##           0.7330      0.9325
##
##               split[cur.subset]=3-4
##           time      n.risk      n.event      survival      std.err
##           36.0000      25.0000      52.0000      0.5053      0.0554
## lower 95% CI upper 95% CI
##           0.4076      0.6264

```







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= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.522    0.593   0.510 -1.02  0.30626
## split[cur.subset]2a  0.706    2.026   0.510  1.39  0.16595
## split[cur.subset]2b  0.656    1.927   0.309  2.13  0.03358 *
## split[cur.subset]2c  0.838    2.312   0.307  2.73  0.00628 **
## split[cur.subset]3   1.474    4.365   0.405  3.64  0.00027 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1    0.593    1.685    0.218    1.61
## split[cur.subset]2a    2.026    0.494    0.746    5.50
## split[cur.subset]2b    1.927    0.519    1.052    3.53
## split[cur.subset]2c    2.312    0.432    1.268    4.22
## split[cur.subset]3    4.365    0.229    1.974    9.65
##
## Concordance= 0.644 (se = 0.033 )
## Rsquare= 0.083 (max possible= 0.967 )
## Likelihood ratio test= 23.2 on 5 df, p=0.000309
## Wald test = 21.5 on 5 df, p=0.000664
## Score (logrank) test = 24.2 on 5 df, p=2e-04
##
## 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
##           36.000      21.000      13.000      0.760      0.065
## lower 95% CI upper 95% CI
##           0.643      0.899
##
##               split[cur.subset]=1
##           time      n.risk      n.event      survival      std.err
##           36.0000     12.0000      4.0000      0.8766      0.0578
## lower 95% CI upper 95% CI
##           0.7703      0.9976
##
##               split[cur.subset]=2a
##           time      n.risk      n.event      survival      std.err
##           36.000      3.000      4.000      0.635      0.148
## lower 95% CI upper 95% CI
```

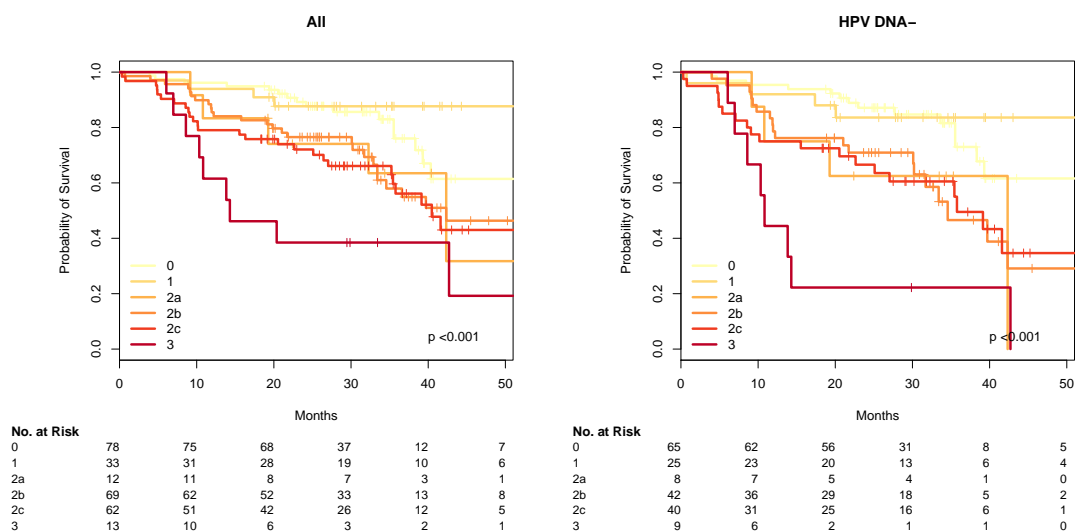
```
##          0.402          1.000
##
##          split[cur.subset]=2b
##          time          n.risk          n.event          survival          std.err
##          36.000          19.000          23.000          0.580          0.073
## lower 95% CI upper 95% CI
##          0.453          0.742
##
##          split[cur.subset]=2c
##          time          n.risk          n.event          survival          std.err
##          36.0000          16.0000          23.0000          0.5614          0.0751
## lower 95% CI upper 95% CI
##          0.4319          0.7297
##
##          split[cur.subset]=3
##          time          n.risk          n.event          survival          std.err
##          36.000          2.000          8.000          0.385          0.135
## lower 95% CI upper 95% CI
##          0.193          0.765
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.334      0.716      0.523 -0.64  0.5231
## split[cur.subset]2a  0.988      2.685      0.565  1.75  0.0804 .
## split[cur.subset]2b  0.876      2.402      0.344  2.55  0.0109 *
## split[cur.subset]2c  0.926      2.523      0.347  2.66  0.0077 **
## split[cur.subset]3   1.961      7.109      0.444  4.42  1e-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      0.716      1.397      0.257      2.00
## split[cur.subset]2a      2.685      0.372      0.887      8.13
## split[cur.subset]2b      2.402      0.416      1.223      4.72
## split[cur.subset]2c      2.523      0.396      1.277      4.99
## split[cur.subset]3      7.109      0.141      2.976     16.98
##
## Concordance= 0.659 (se = 0.037 )
## Rsquare= 0.126 (max possible= 0.968 )
## Likelihood ratio test= 25.5 on 5 df, p=0.00011
```

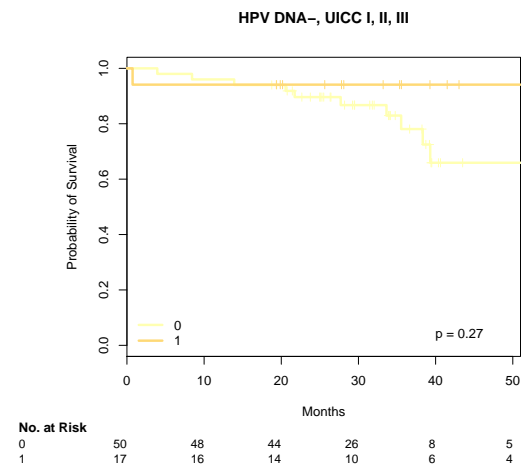
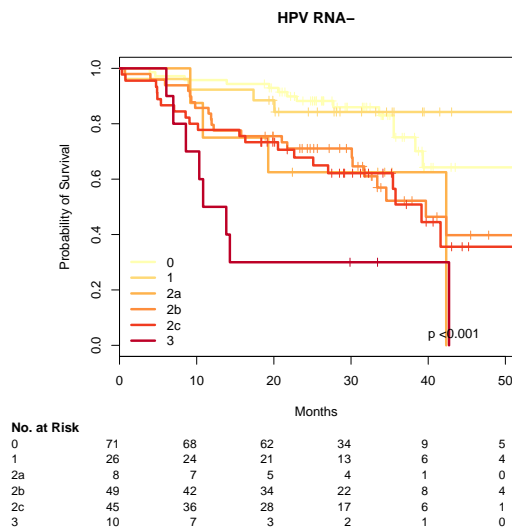
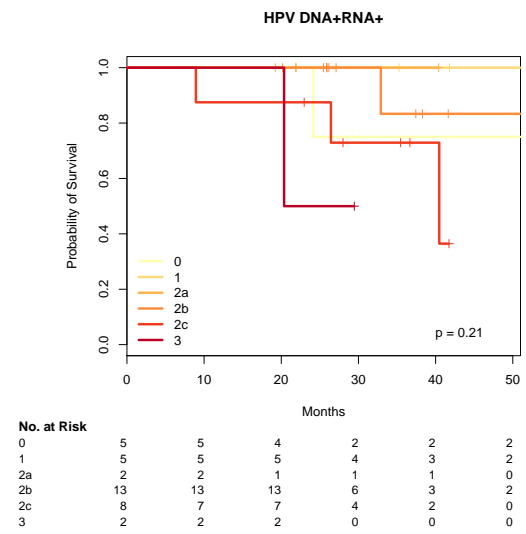
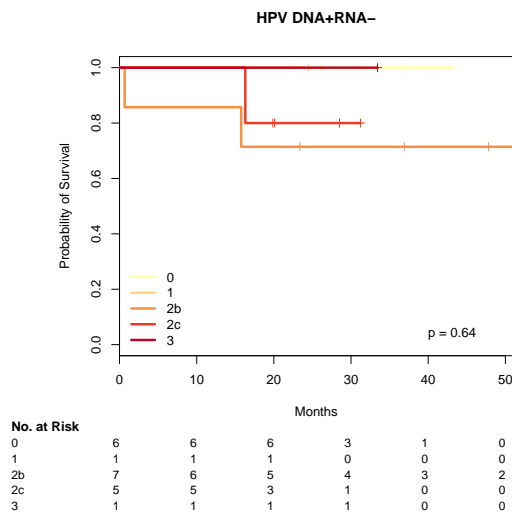
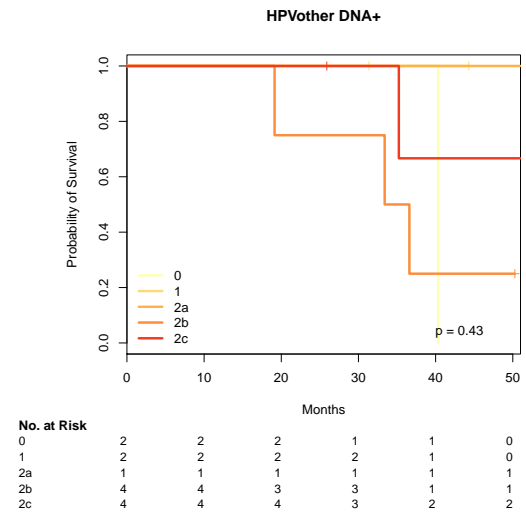
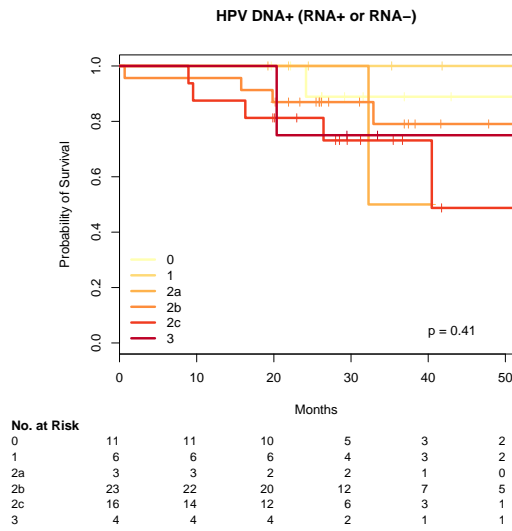
```

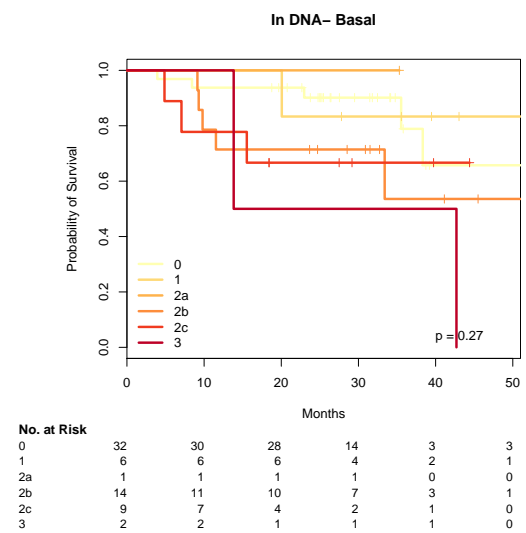
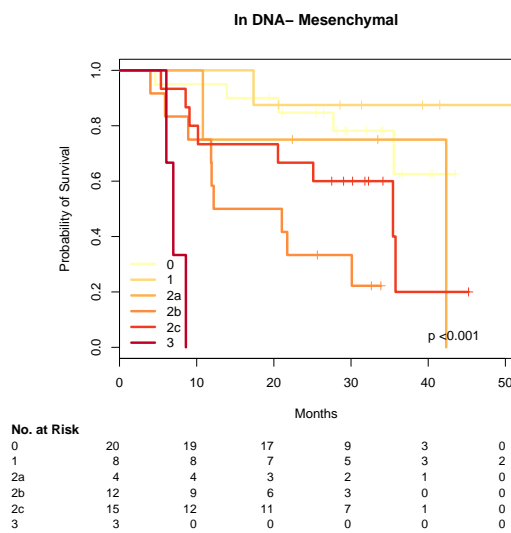
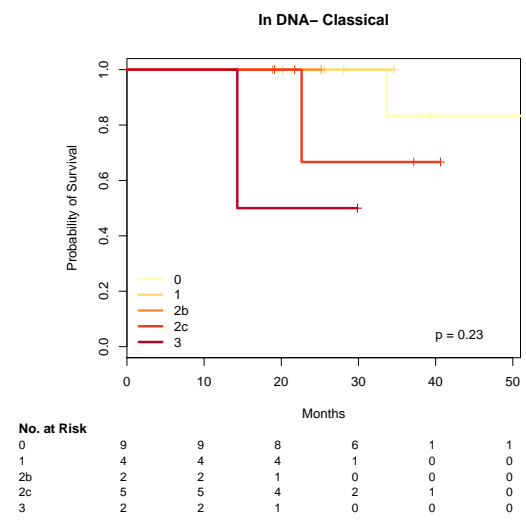
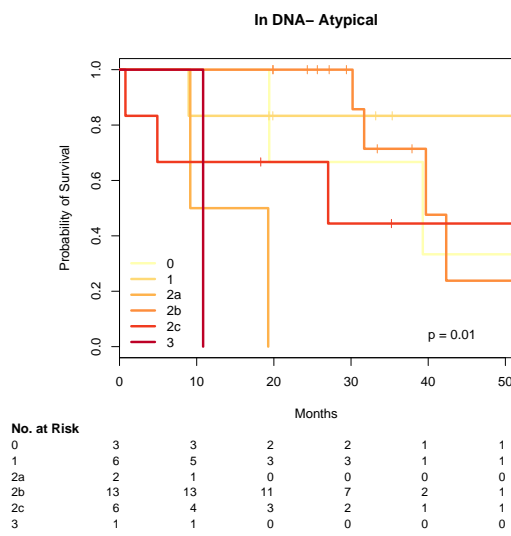
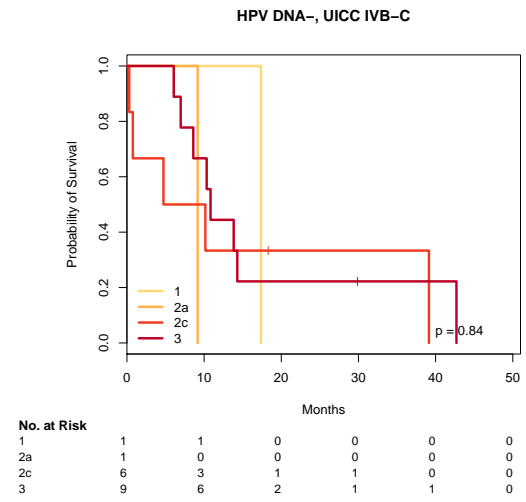
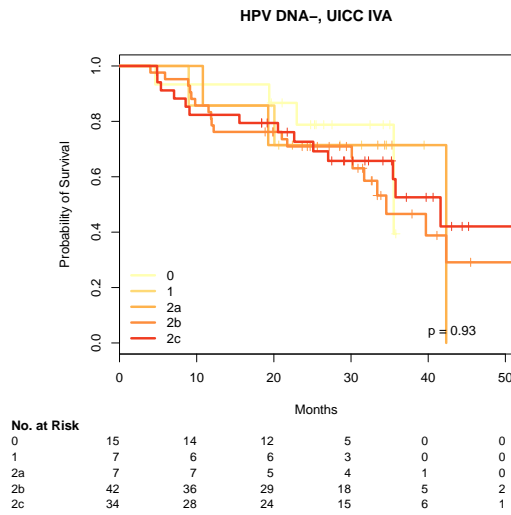
## Wald test          = 26.2  on 5 df,    p=8.14e-05
## Score (logrank) test = 31.3  on 5 df,    p=8.32e-06
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 209, number of events= 75
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.241    0.786   0.520 -0.46  0.6428
## split[cur.subset]2a  1.088    2.968   0.565  1.93  0.0540 .
## split[cur.subset]2b  0.871    2.389   0.334  2.61  0.0091 **
## split[cur.subset]2c  0.977    2.657   0.343  2.85  0.0044 **
## split[cur.subset]3  1.898    6.671   0.442  4.29  1.8e-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    0.786    1.273    0.284    2.18
## split[cur.subset]2a    2.968    0.337    0.981    8.98
## split[cur.subset]2b    2.389    0.419    1.241    4.60
## split[cur.subset]2c    2.657    0.376    1.356    5.20
## split[cur.subset]3    6.671    0.150    2.804   15.87
##
## Concordance= 0.657 (se = 0.036 )
## Rsquare= 0.113 (max possible= 0.965 )
## Likelihood ratio test= 25  on 5 df,    p=0.000142
## Wald test          = 25  on 5 df,    p=0.000138
## Score (logrank) test = 29.2  on 5 df,    p=2.07e-05
##
## 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      12.0000      0.7510      0.0708
## lower 95% CI upper 95% CI
##              0.6242      0.9034
##
##              split[cur.subset]=1
##              time      n.risk      n.event      survival      std.err
##              36.0000      8.0000      4.0000      0.8425      0.0725
## lower 95% CI upper 95% CI
##              0.7118      0.9972
##

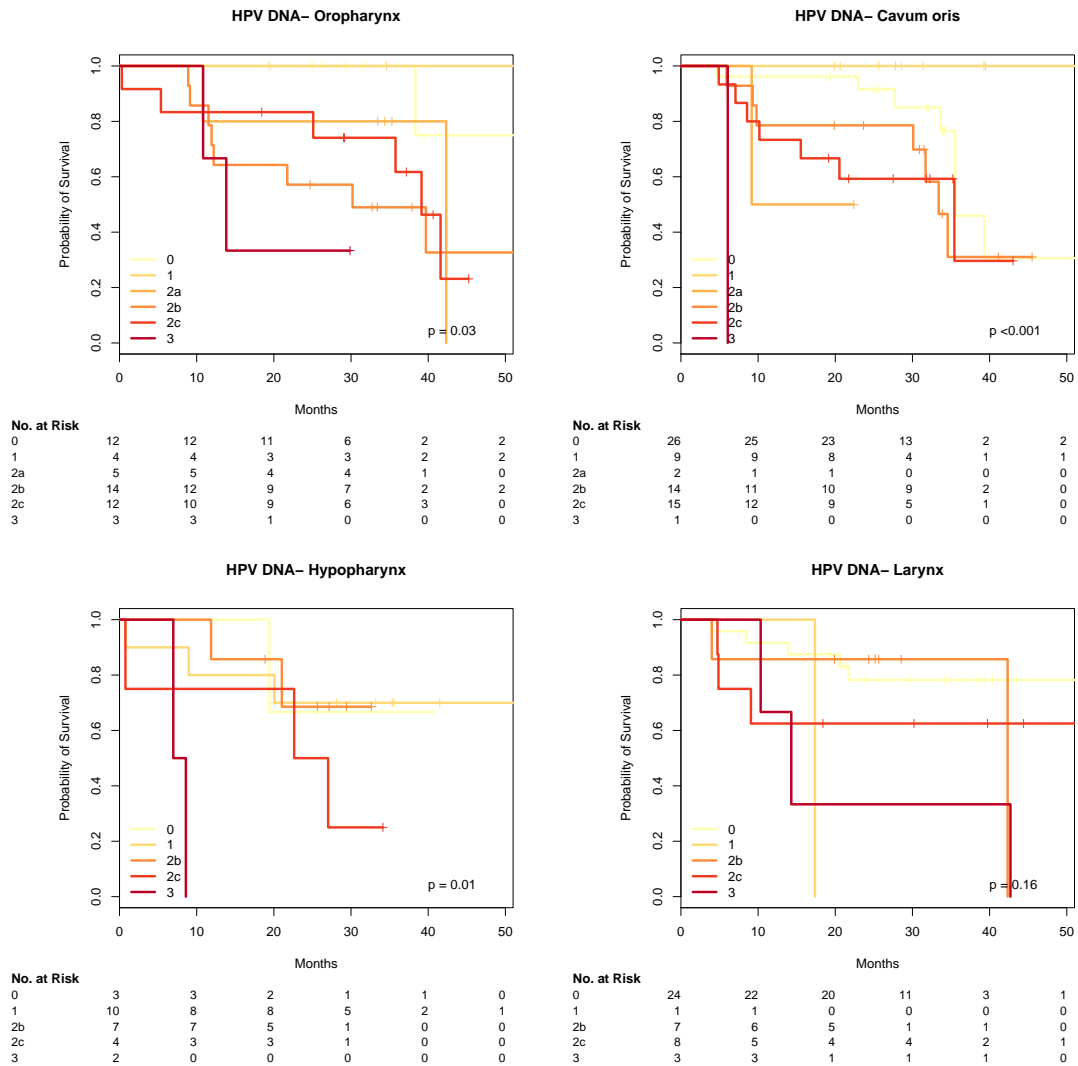
```

```
##                               split[cur.subset]=2a
##           time           n.risk           n.event       survival       std.err
##           36.000           1.000           3.000         0.625         0.171
## lower 95% CI upper 95% CI
##           0.365           1.000
##
##                               split[cur.subset]=2b
##           time           n.risk           n.event       survival       std.err
##           36.0000          11.0000          19.0000        0.5220         0.0883
## lower 95% CI upper 95% CI
##           0.3747           0.7272
##
##                               split[cur.subset]=2c
##           time           n.risk           n.event       survival       std.err
##           36.0000          9.0000          18.0000        0.5084         0.0953
## lower 95% CI upper 95% CI
##           0.3521           0.7343
##
##                               split[cur.subset]=3
##           time           n.risk           n.event       survival       std.err
##           36.000           1.000           7.000         0.300         0.145
## lower 95% CI upper 95% CI
##           0.116           0.773
```









3.13 N0 stage vs. N1-N3

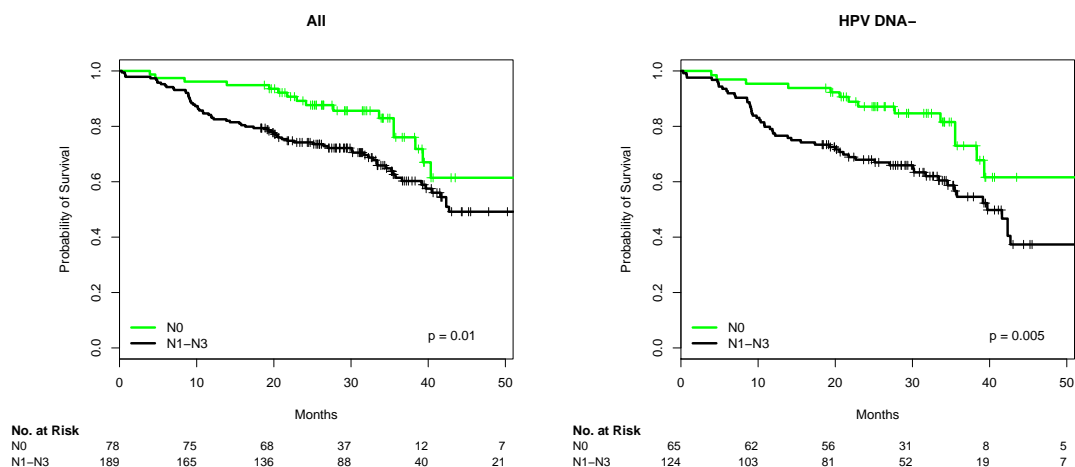
```
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset]N1-N3 0.646      1.907    0.269 2.4  0.017 *
## ---
## 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  1.91      0.524    1.12    3.23
##
```

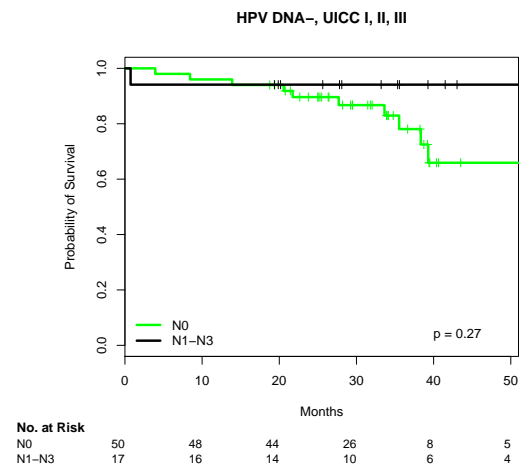
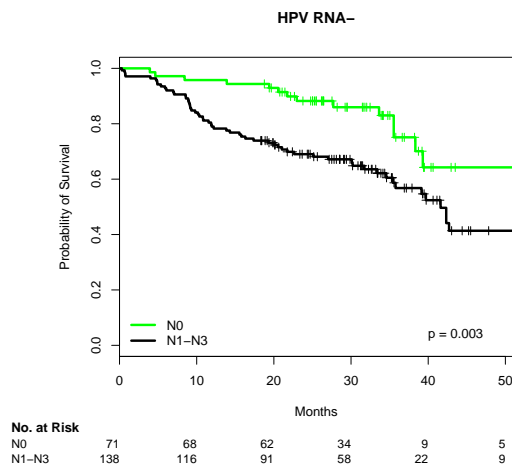
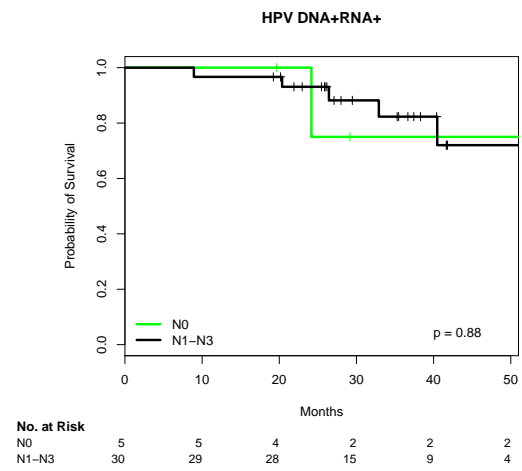
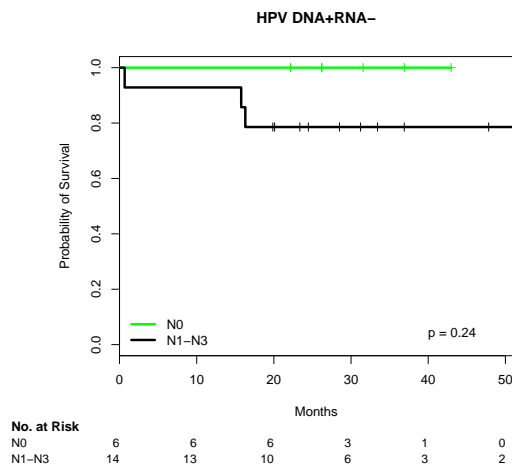
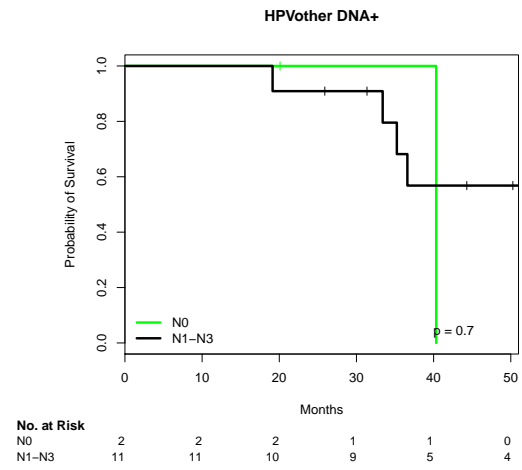
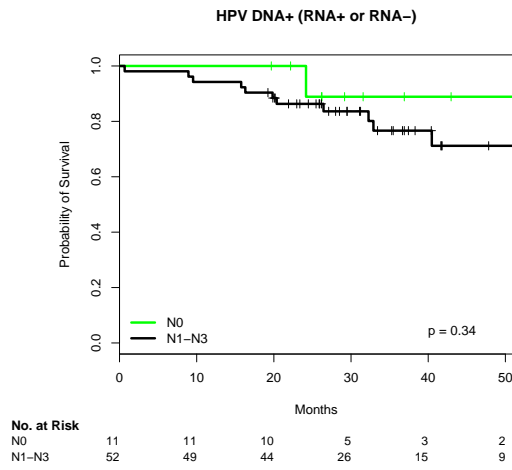
```

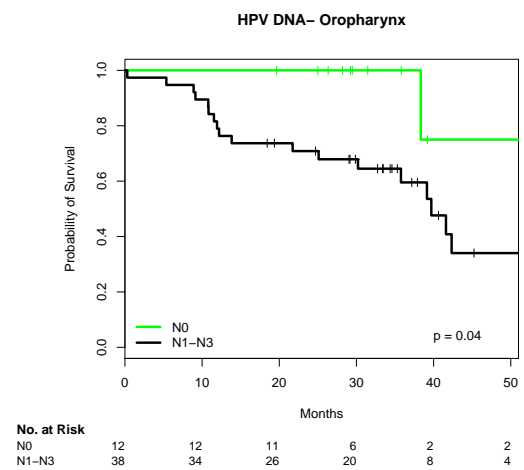
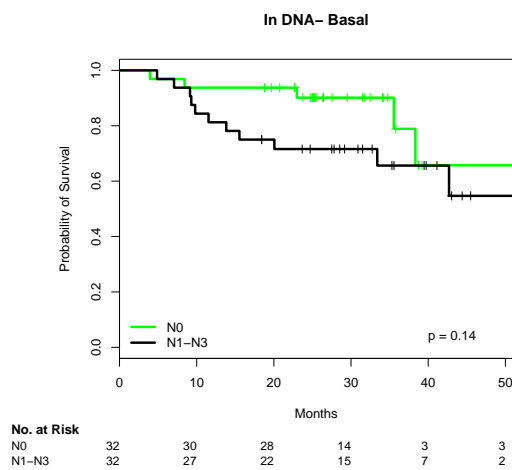
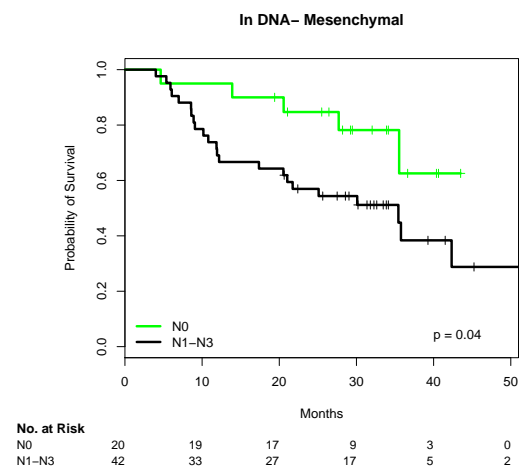
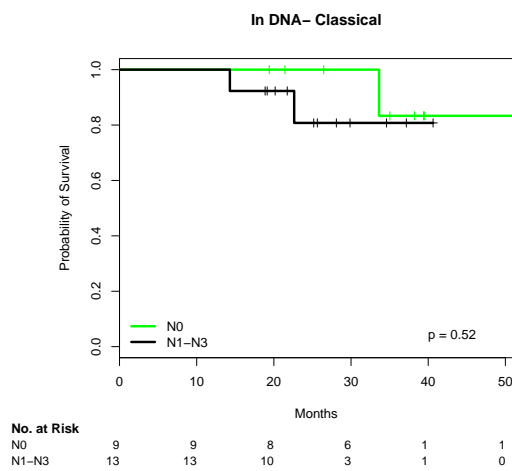
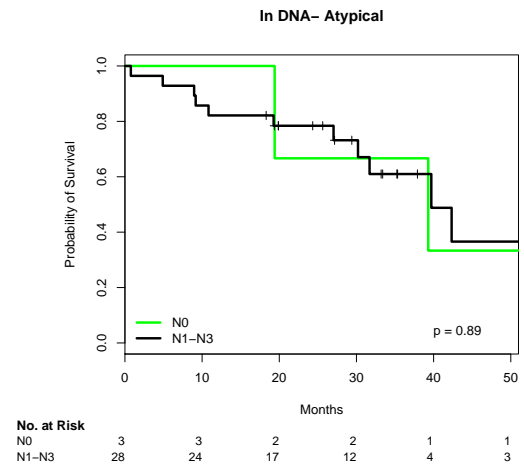
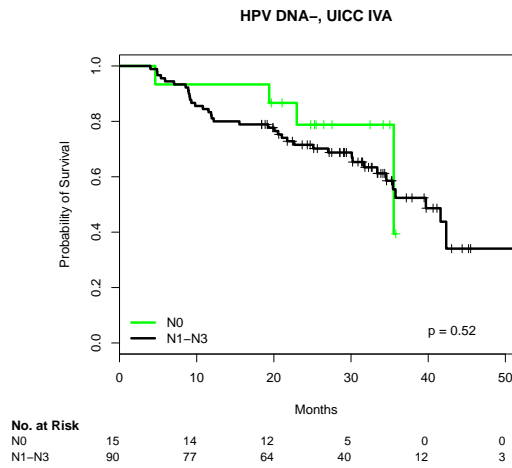
## Concordance= 0.575 (se = 0.027 )
## Rsquare= 0.024 (max possible= 0.967 )
## Likelihood ratio test= 6.52 on 1 df, p=0.0107
## Wald test = 5.75 on 1 df, p=0.0165
## Score (logrank) test = 5.95 on 1 df, p=0.0147
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=N0
##      time      n.risk      n.event      survival      std.err
##    36.000      21.000      13.000         0.760         0.065
## lower 95% CI upper 95% CI
##    0.643         0.899
##
##               split[cur.subset]=N1-N3
##      time      n.risk      n.event      survival      std.err
##   36.0000      52.0000      62.0000         0.6145         0.0415
## lower 95% CI upper 95% CI
##    0.5383         0.7013
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.793      2.210      0.292 2.72  0.0066 **
## ---
## 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      2.21      0.453      1.25      3.92
##
## Concordance= 0.599 (se = 0.032 )
## Rsquare= 0.044 (max possible= 0.968 )
## Likelihood ratio test= 8.43 on 1 df, p=0.00368
## Wald test = 7.38 on 1 df, p=0.00661
## Score (logrank) test = 7.76 on 1 df, p=0.00533
##
##
## #####
## Cox model1 in HPV RNA-
## Call:

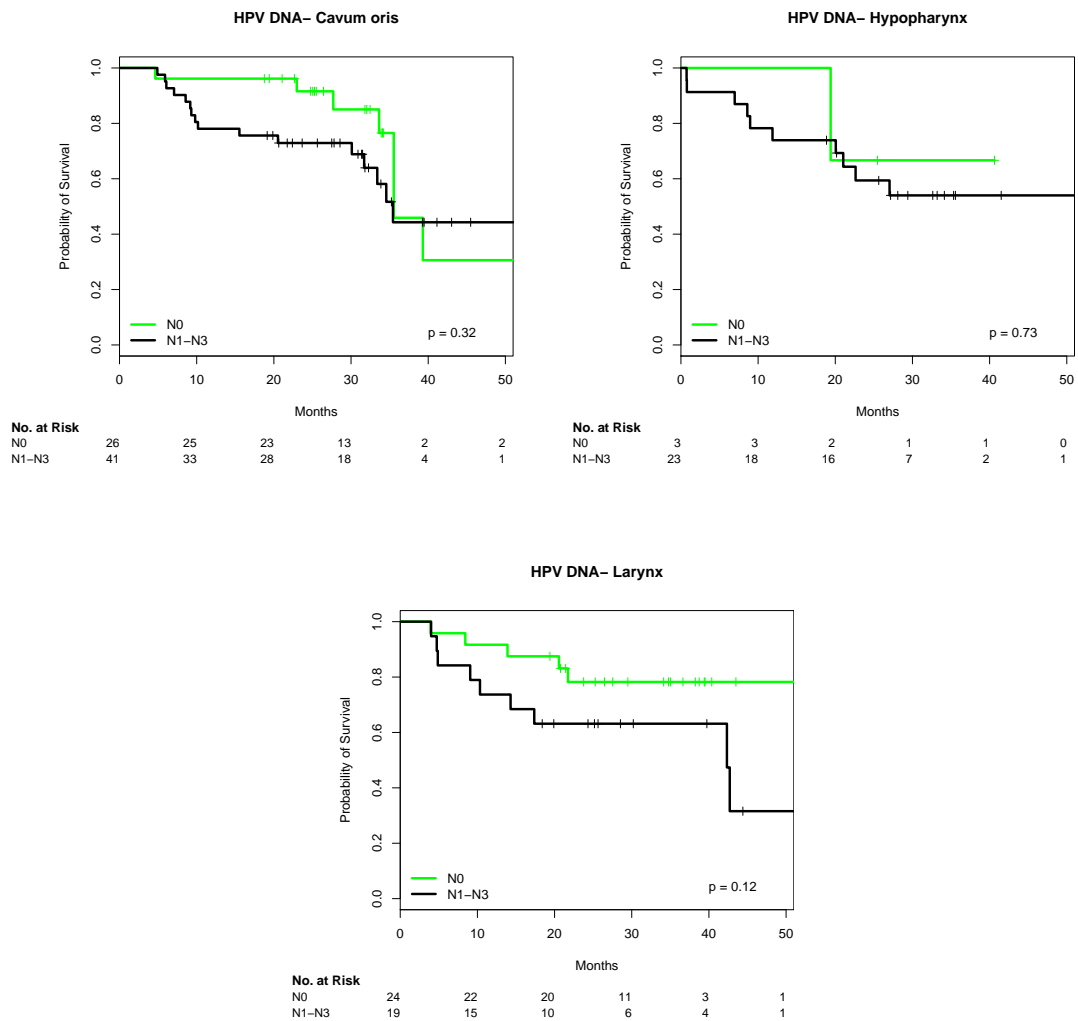
```

```
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 75
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.837      2.309      0.290 2.89   0.0039 **
## ---
## 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      2.31      0.433      1.31      4.07
##
## Concordance= 0.602 (se = 0.031 )
## Rsquare= 0.045 (max possible= 0.965 )
## Likelihood ratio test= 9.68 on 1 df,  p=0.00186
## Wald test = 8.34 on 1 df,  p=0.00387
## Score (logrank) test = 8.84 on 1 df,  p=0.00295
##
## 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      18.0000      12.0000      0.7510      0.0708
## lower 95% CI upper 95% CI
##              0.6242      0.9034
##
##              split[cur.subset]=N1-N3
##              time      n.risk      n.event      survival      std.err
##              36.0000      30.0000      51.0000      0.5678      0.0507
## lower 95% CI upper 95% CI
##              0.4767      0.6764
```









3.14 N0-N1 stages vs. N2-N3

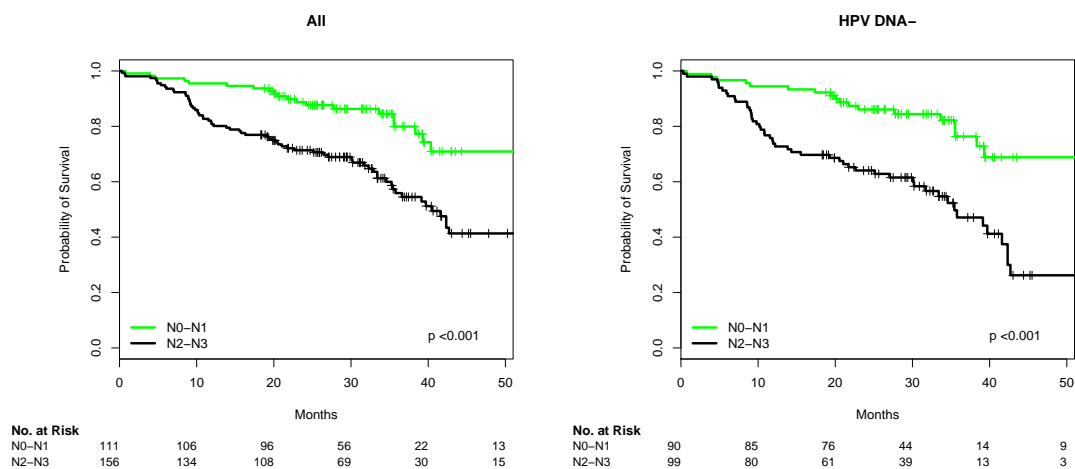
```
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N2-N3 0.961      2.613    0.244 3.93 8.5e-05 ***
## ---
## 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  2.61      0.383    1.62    4.22
##
```

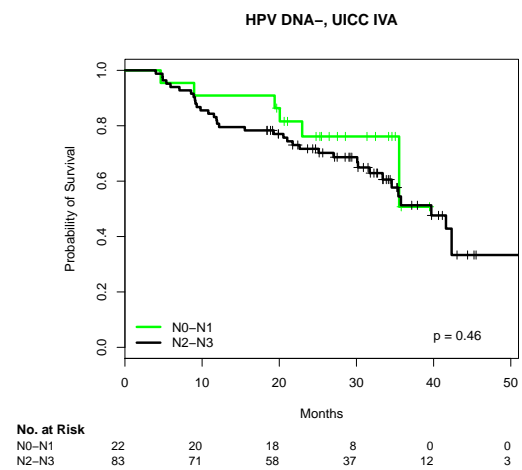
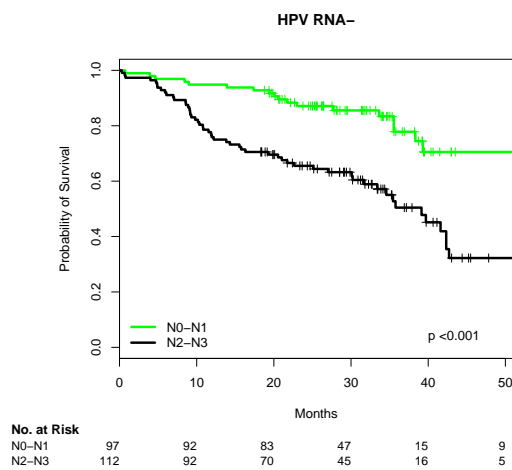
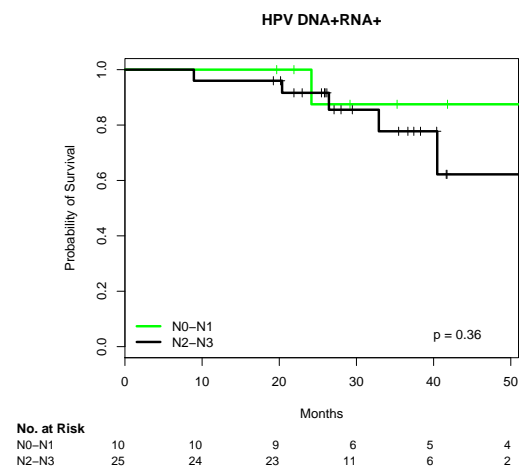
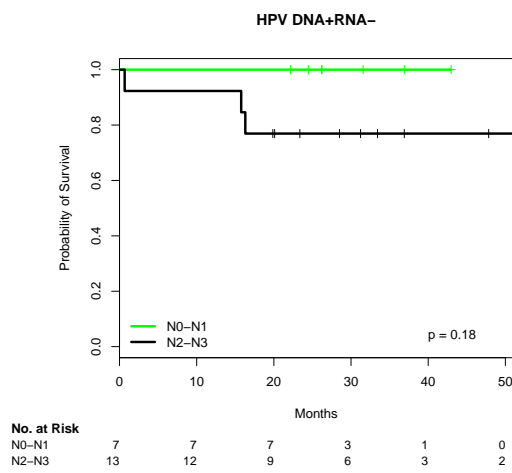
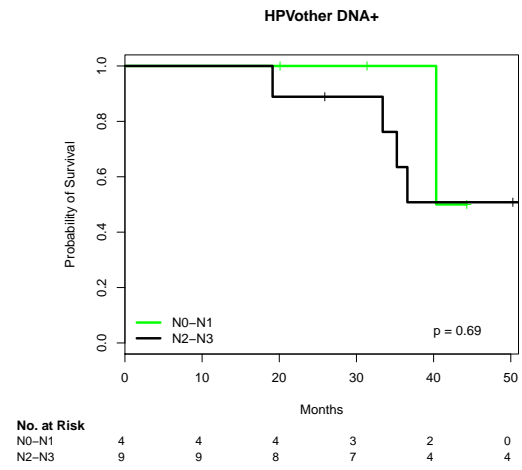
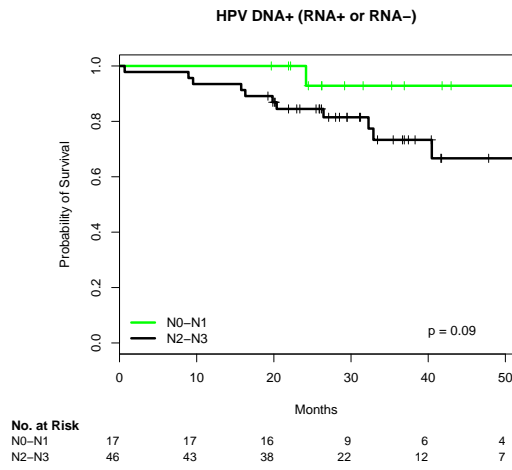
```

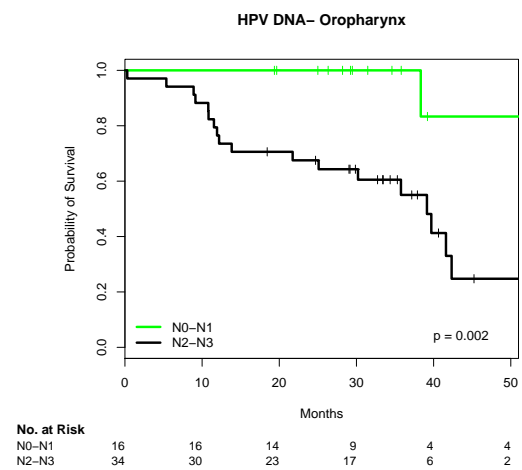
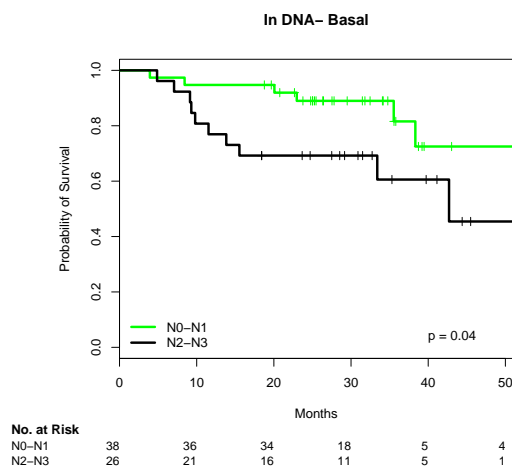
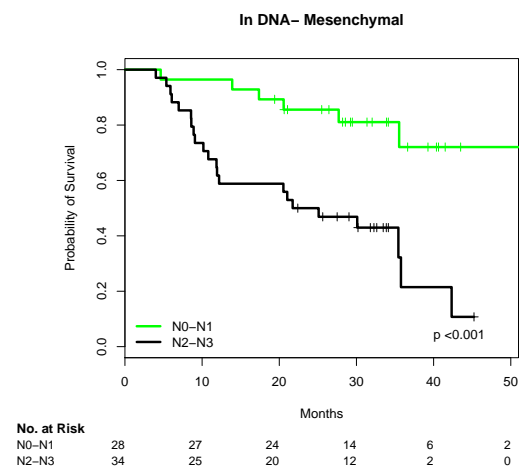
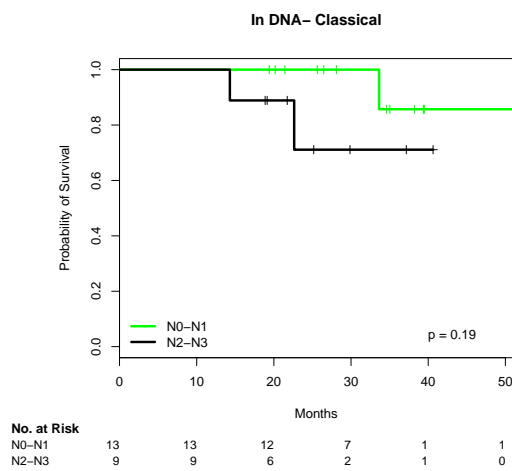
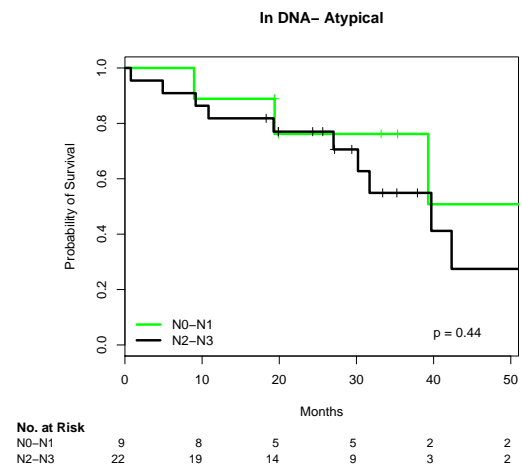
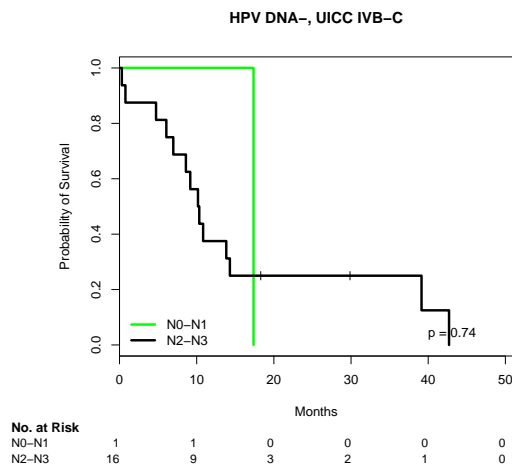
## Concordance= 0.613 (se = 0.029 )
## Rsquare= 0.064 (max possible= 0.967 )
## Likelihood ratio test= 17.8 on 1 df, p=2.48e-05
## Wald test = 15.4 on 1 df, p=8.49e-05
## Score (logrank) test = 16.7 on 1 df, p=4.48e-05
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=N0-N1
##      time      n.risk      n.event      survival      std.err
## 36.0000    33.0000    17.0000    0.7993    0.0478
## lower 95% CI upper 95% CI
## 0.7108    0.8987
##
##               split[cur.subset]=N2-N3
##      time      n.risk      n.event      survival      std.err
## 36.0000    40.0000    58.0000    0.5590    0.0472
## lower 95% CI upper 95% CI
## 0.4737    0.6596
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N2-N3 1.103    3.013    0.266 4.14 3.5e-05 ***
## ---
## 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    3.01    0.332    1.79    5.08
##
## Concordance= 0.634 (se = 0.033 )
## Rsquare= 0.097 (max possible= 0.968 )
## Likelihood ratio test= 19.3 on 1 df, p=1.13e-05
## Wald test = 17.1 on 1 df, p=3.47e-05
## Score (logrank) test = 18.9 on 1 df, p=1.4e-05
##
##
## #####
## Cox model1 in HPV RNA-
## Call:

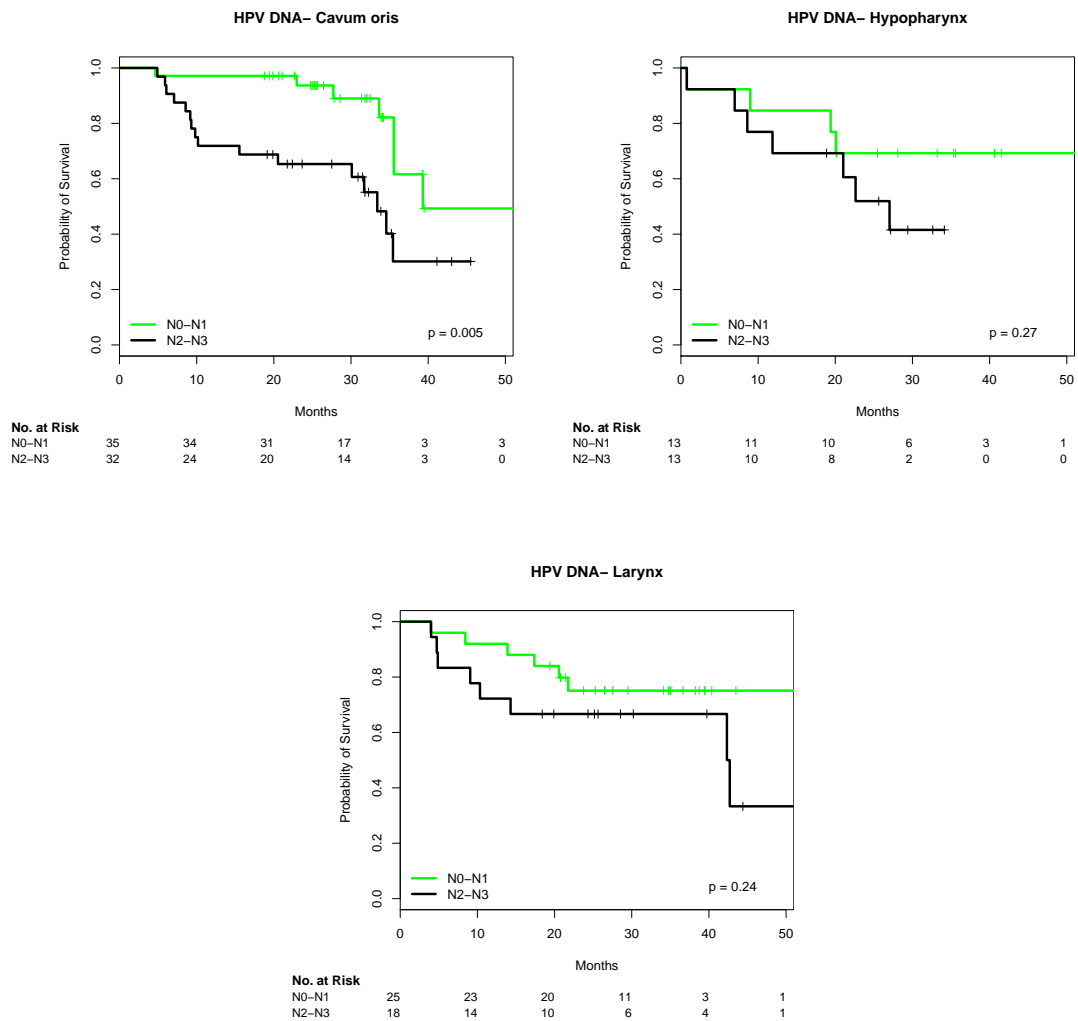
```

```
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 75
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N2-N3 1.087      2.966    0.262 4.14  3.4e-05 ***
## ---
## 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      2.97      0.337      1.77      4.96
##
## Concordance= 0.634 (se = 0.032 )
## Rsquare= 0.089 (max possible= 0.965 )
## Likelihood ratio test= 19.5 on 1 df,  p=9.9e-06
## Wald test               = 17.2 on 1 df,  p=3.41e-05
## Score (logrank) test = 18.9 on 1 df,  p=1.39e-05
##
## 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      16.0000      0.7784      0.0548
## lower 95% CI upper 95% CI
##              0.6780      0.8935
##
##              split[cur.subset]=N2-N3
##              time      n.risk      n.event      survival      std.err
##              36.0000      22.0000      47.0000      0.5044      0.0581
## lower 95% CI upper 95% CI
##              0.4025      0.6322
```







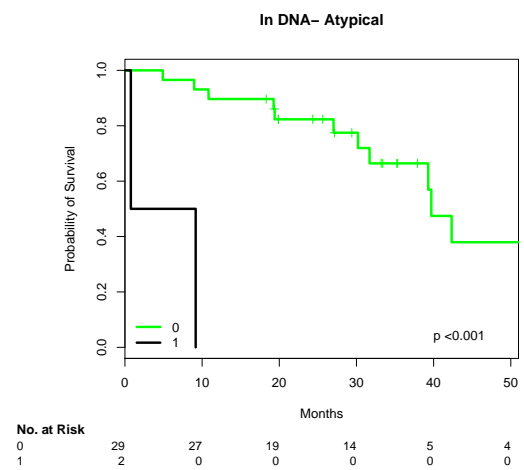
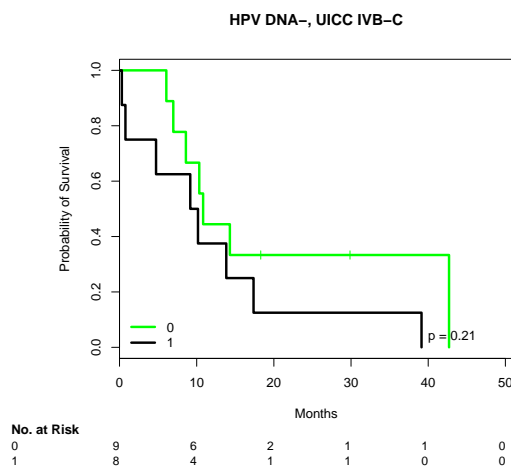
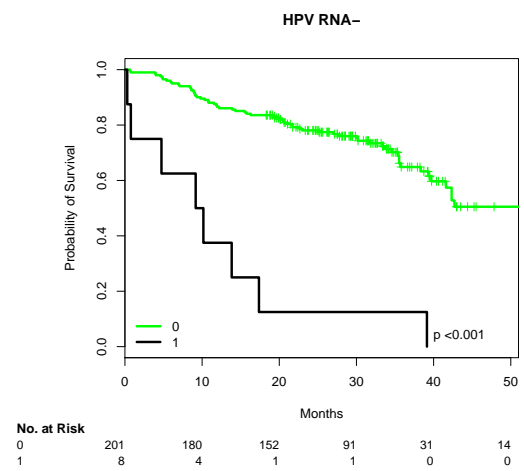
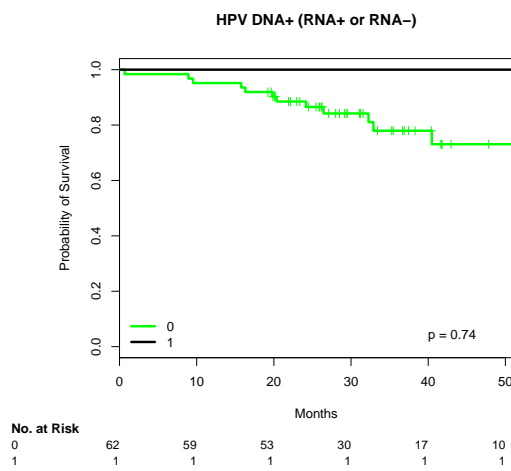
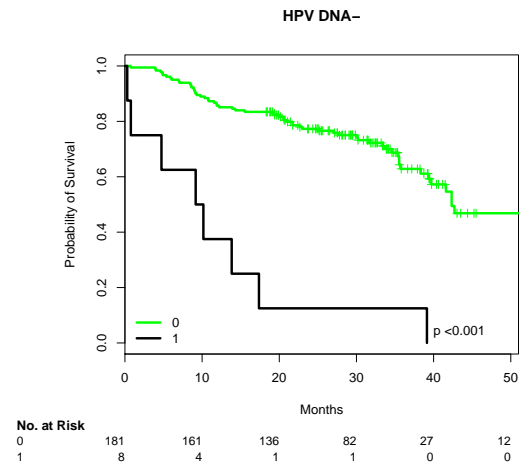
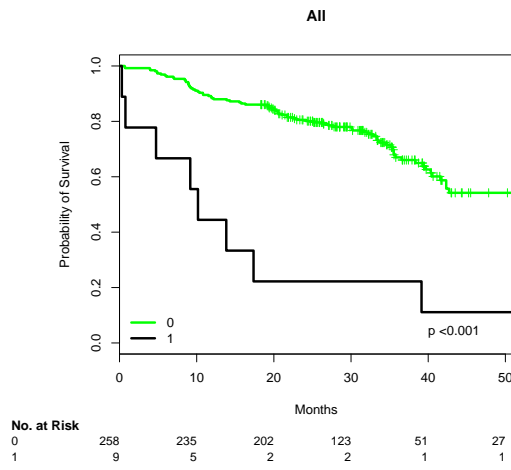


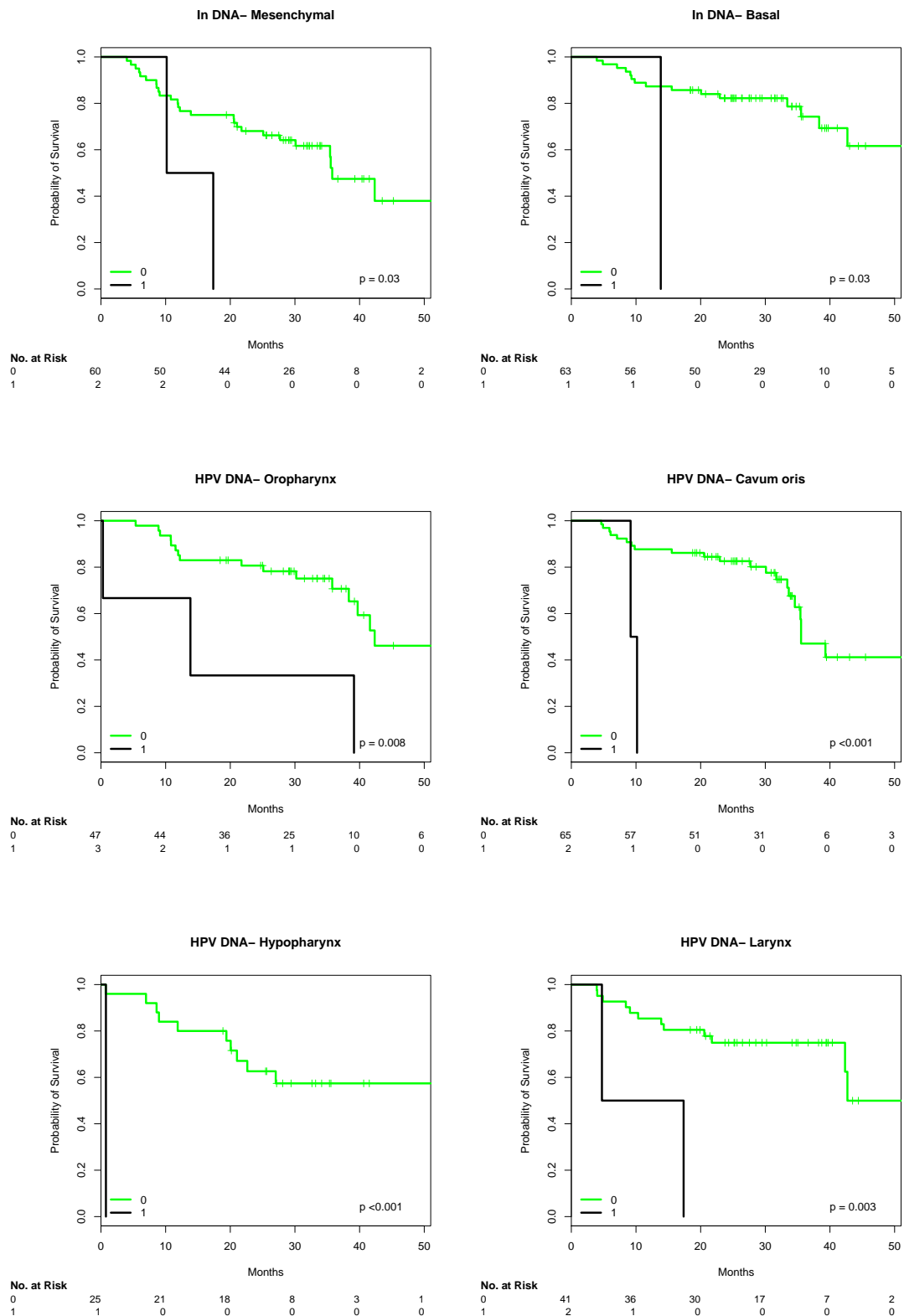
3.15 M (TNM staging)

```
## 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= 94
##
##               coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset] 1.455      4.286    0.364 4  6.3e-05 ***
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      4.29      0.233      2.1      8.74
##
## Concordance= 0.546 (se = 0.008 )
## Rsquare= 0.042 (max possible= 0.967 )
## Likelihood ratio test= 11.4 on 1 df,  p=0.000748
## Wald test = 16 on 1 df,  p=6.32e-05
## Score (logrank) test = 18.6 on 1 df,  p=1.57e-05
##
## 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      71.0000      68.0000      0.6699      0.0359
## lower 95% CI upper 95% CI
## 0.6031      0.7441
##
##               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= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 1.972      7.188      0.384 5.14 2.7e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      7.19      0.139      3.39      15.2
##
## Concordance= 0.56 (se = 0.01 )
## Rsquare= 0.085 (max possible= 0.968 )
## Likelihood ratio test= 16.8 on 1 df,  p=4.16e-05
## Wald test = 26.4 on 1 df,  p=2.71e-07
## Score (logrank) test = 36.1 on 1 df,  p=1.84e-09
```

```
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset] 2.024      7.570    0.382 5.3 1.2e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      7.57      0.132      3.58      16
##
## Concordance= 0.557 (se = 0.009 )
## Rsquare= 0.081 (max possible= 0.965 )
## Likelihood ratio test= 17.5 on 1 df,  p=2.81e-05
## Wald test              = 28.1 on 1 df,  p=1.18e-07
## Score (logrank) test = 39 on 1 df,  p=4.31e-10
##
## 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      47.0000      56.0000      0.6485      0.0427
## lower 95% CI upper 95% CI
##           0.5701      0.7377
##
##               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= 94
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.941    0.390   0.817 -1.15  0.2495
## split[cur.subset]III -0.286    0.751   0.692 -0.41  0.6797
## split[cur.subset]IVA  0.659    1.933   0.592  1.11  0.2658
## split[cur.subset]IVB  1.647    5.193   0.653  2.52  0.0117 *
## split[cur.subset]IVC  1.887    6.599   0.676  2.79  0.0052 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.390    2.562   0.0787    1.94
## split[cur.subset]III    0.751    1.331   0.1935    2.92
## split[cur.subset]IVA    1.933    0.517   0.6054    6.17
## split[cur.subset]IVB    5.193    0.193   1.4437   18.68
## split[cur.subset]IVC    6.599    0.152   1.7555   24.81
##
## Concordance= 0.674 (se = 0.03 )
## Rsquare= 0.138 (max possible= 0.967 )
## Likelihood ratio test= 39.7 on 5 df, p=1.71e-07
## Wald test = 37.8 on 5 df, p=4.07e-07
## Score (logrank) test = 47.2 on 5 df, p=5.2e-09
##
## 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
## 36.0000      3.0000      2.0000      0.8705      0.0856
## lower 95% CI upper 95% CI
## 0.7180      1.0000
##
##              split[cur.subset]=II
##      time      n.risk      n.event      survival      std.err
## 36.0000     11.0000      2.0000      0.8928      0.0733
## lower 95% CI upper 95% CI
## 0.7601      1.0000
##
##              split[cur.subset]=III
##      time      n.risk      n.event      survival      std.err
## 36.0000     16.0000      5.0000      0.8337      0.0706
```



```

## lower 95% CI upper 95% CI
##      0.7062      0.9843
##
##              split[cur.subset]=IVA
##      time      n.risk      n.event      survival      std.err
##      36.0000      40.0000      49.0000      0.6095      0.0481
## lower 95% CI upper 95% CI
##      0.5222      0.7114
##
##              split[cur.subset]=IVB
##      time      n.risk      n.event      survival      std.err
##      36.000      1.000      10.000      0.299      0.148
## lower 95% CI upper 95% CI
##      0.113      0.789
##
##              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= 71
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.811      0.444      0.817 -0.99 0.32063
## split[cur.subset]III -0.138      0.871      0.696 -0.20 0.84320
## split[cur.subset]IVA 0.771      2.163      0.600 1.29 0.19861
## split[cur.subset]IVB 1.857      6.402      0.696 2.67 0.00767 **
## split[cur.subset]IVC 2.505     12.247      0.684 3.66 0.00025 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II      0.444      2.2505      0.0896      2.20
## split[cur.subset]III      0.871      1.1475      0.2228      3.41
## split[cur.subset]IVA      2.163      0.4624      0.6672      7.01
## split[cur.subset]IVB      6.402      0.1562      1.6352     25.06
## split[cur.subset]IVC     12.247      0.0817      3.2042     46.81
##
## Concordance= 0.693 (se = 0.035 )
## Rsquare= 0.192 (max possible= 0.968 )

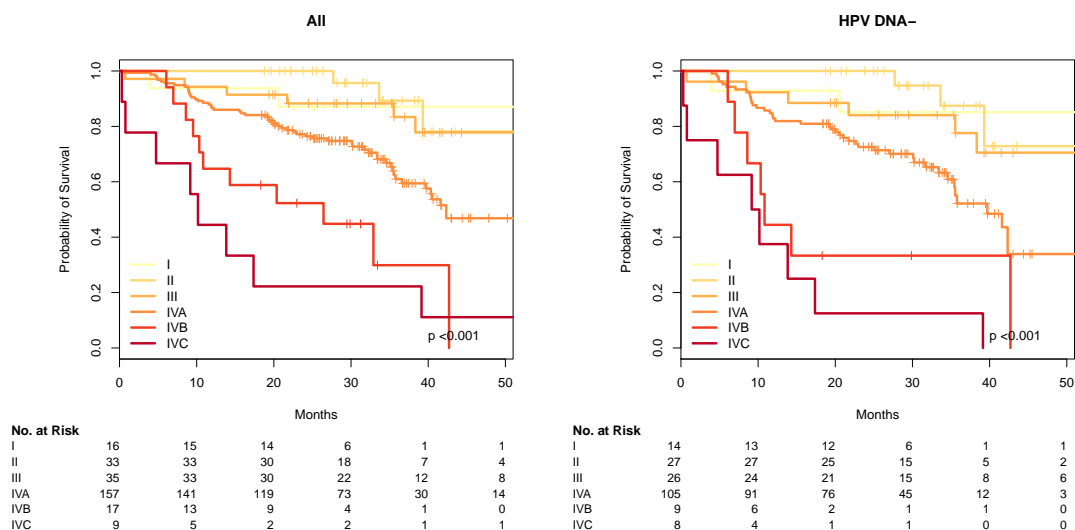
```

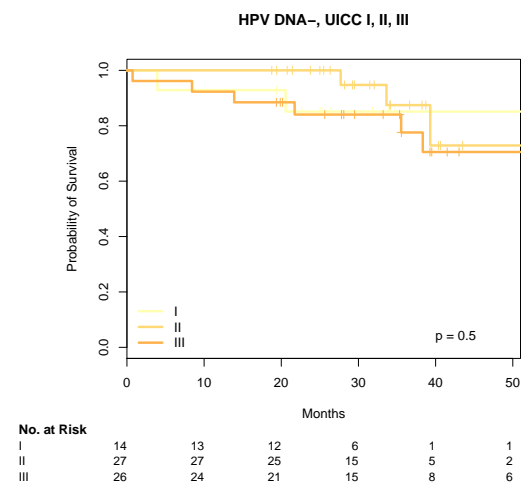
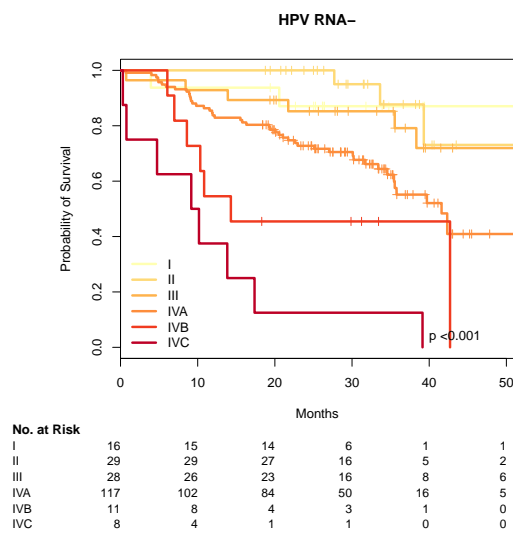
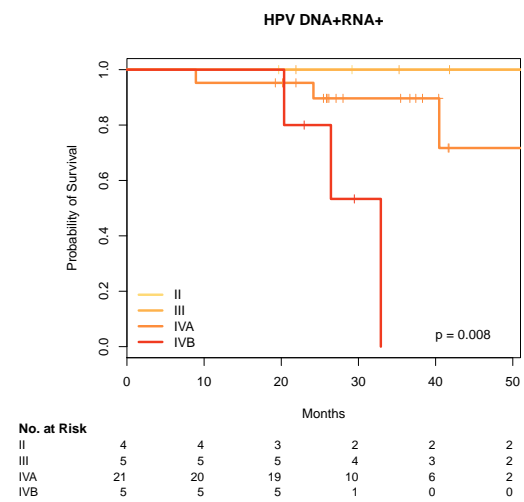
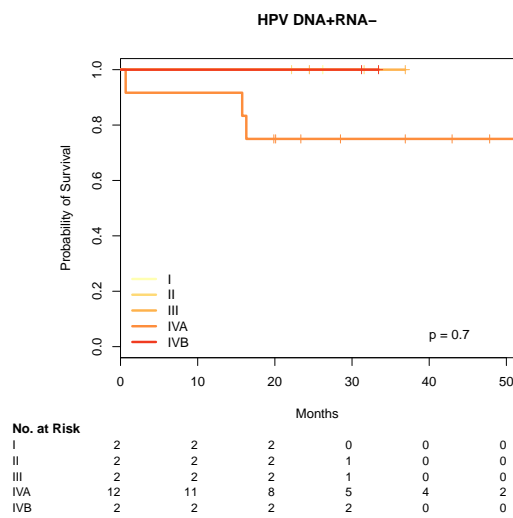
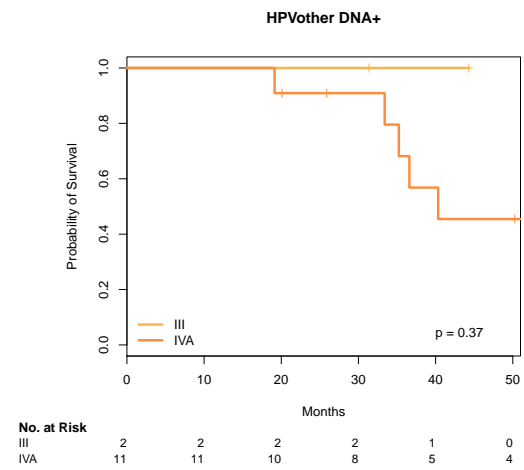
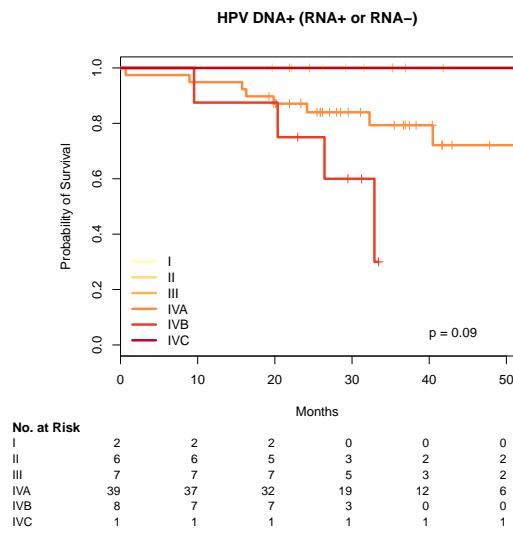
```

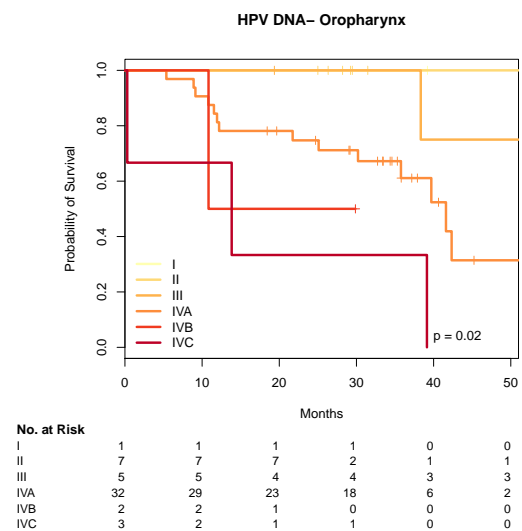
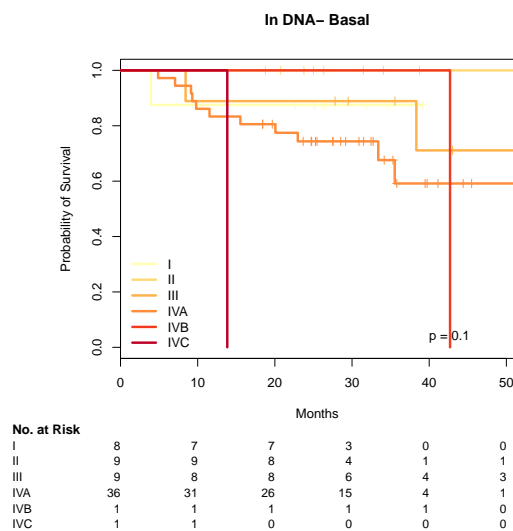
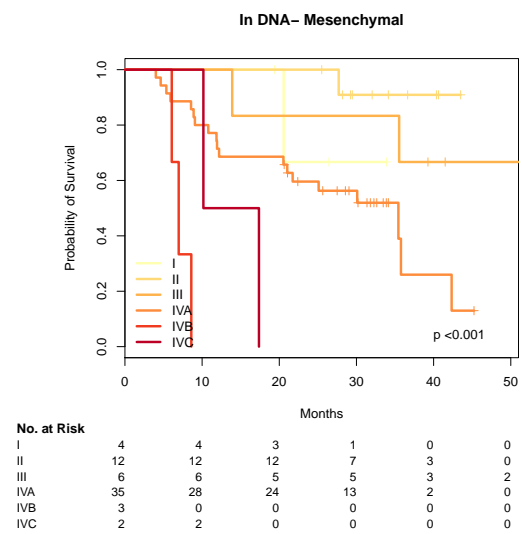
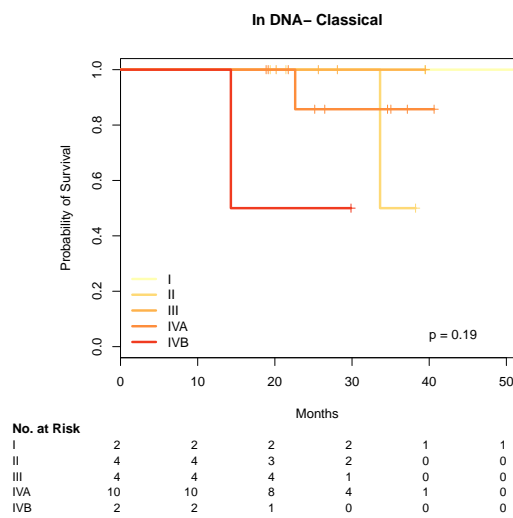
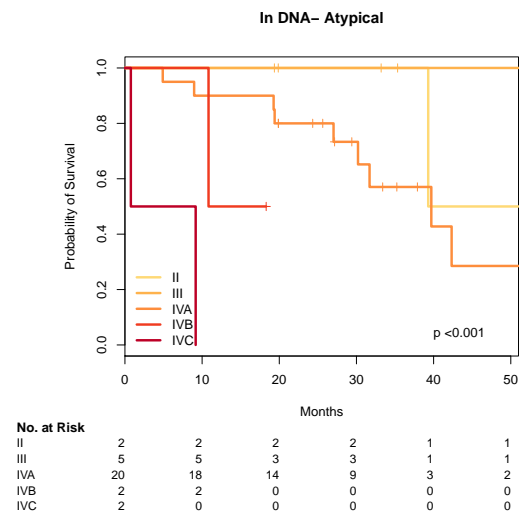
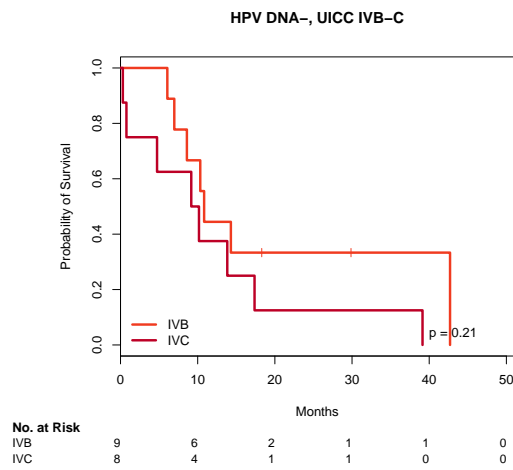
## Likelihood ratio test= 40.3 on 5 df, p=1.32e-07
## Wald test = 43.6 on 5 df, p=2.79e-08
## Score (logrank) test = 60.1 on 5 df, p=1.15e-11
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.7501  0.4723  0.8167 -0.92  0.35844
## split[cur.subset]III -0.0698  0.9326  0.6940 -0.10  0.91989
## split[cur.subset]IVA  0.8141  2.2570  0.5970  1.36  0.17268
## split[cur.subset]IVB  1.6667  5.2945  0.6935  2.40  0.01625 *
## split[cur.subset]IVC  2.6003 13.4676  0.6826  3.81  0.00014 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.472    2.1171    0.0953    2.34
## split[cur.subset]III    0.933    1.0723    0.2393    3.63
## split[cur.subset]IVA    2.257    0.4431    0.7005    7.27
## split[cur.subset]IVB    5.295    0.1889    1.3600   20.61
## split[cur.subset]IVC   13.468    0.0743    3.5338   51.33
##
## Concordance= 0.686 (se = 0.034 )
## Rsquare= 0.17 (max possible= 0.965 )
## Likelihood ratio test= 38.9 on 5 df, p=2.51e-07
## Wald test = 42.4 on 5 df, p=4.89e-08
## Score (logrank) test = 58.7 on 5 df, p=2.22e-11
##
## 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
##           36.0000      3.0000      2.0000      0.8705      0.0856
## lower 95% CI upper 95% CI
##           0.7180      1.0000
##
##               split[cur.subset]=II
##           time      n.risk      n.event      survival      std.err
##           36.0000      9.0000      2.0000      0.8769      0.0834
## lower 95% CI upper 95% CI
##           0.7278      1.0000

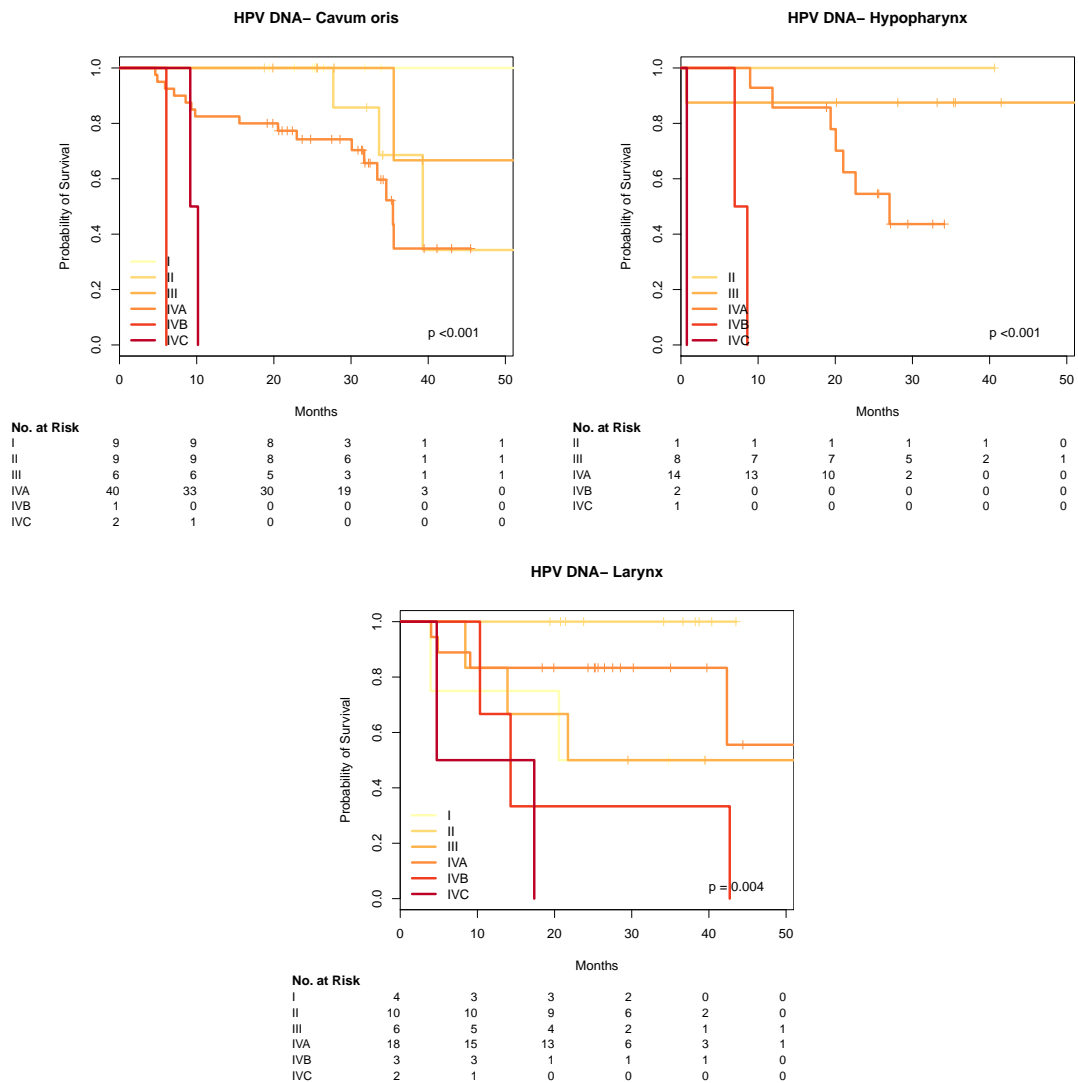
```

```
##
##          split[cur.subset]=III
##      time      n.risk      n.event      survival      std.err
##    36.0000      12.0000      5.0000      0.7914      0.0865
## lower 95% CI upper 95% CI
##    0.6388      0.9804
##
##          split[cur.subset]=IVA
##      time      n.risk      n.event      survival      std.err
##    36.0000      22.0000      41.0000      0.5514      0.0604
## lower 95% CI upper 95% CI
##    0.4449      0.6833
##
##          split[cur.subset]=IVB
##      time      n.risk      n.event      survival      std.err
##    36.000      1.000      6.000      0.455      0.150
## lower 95% CI upper 95% CI
##    0.238      0.868
##
##          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

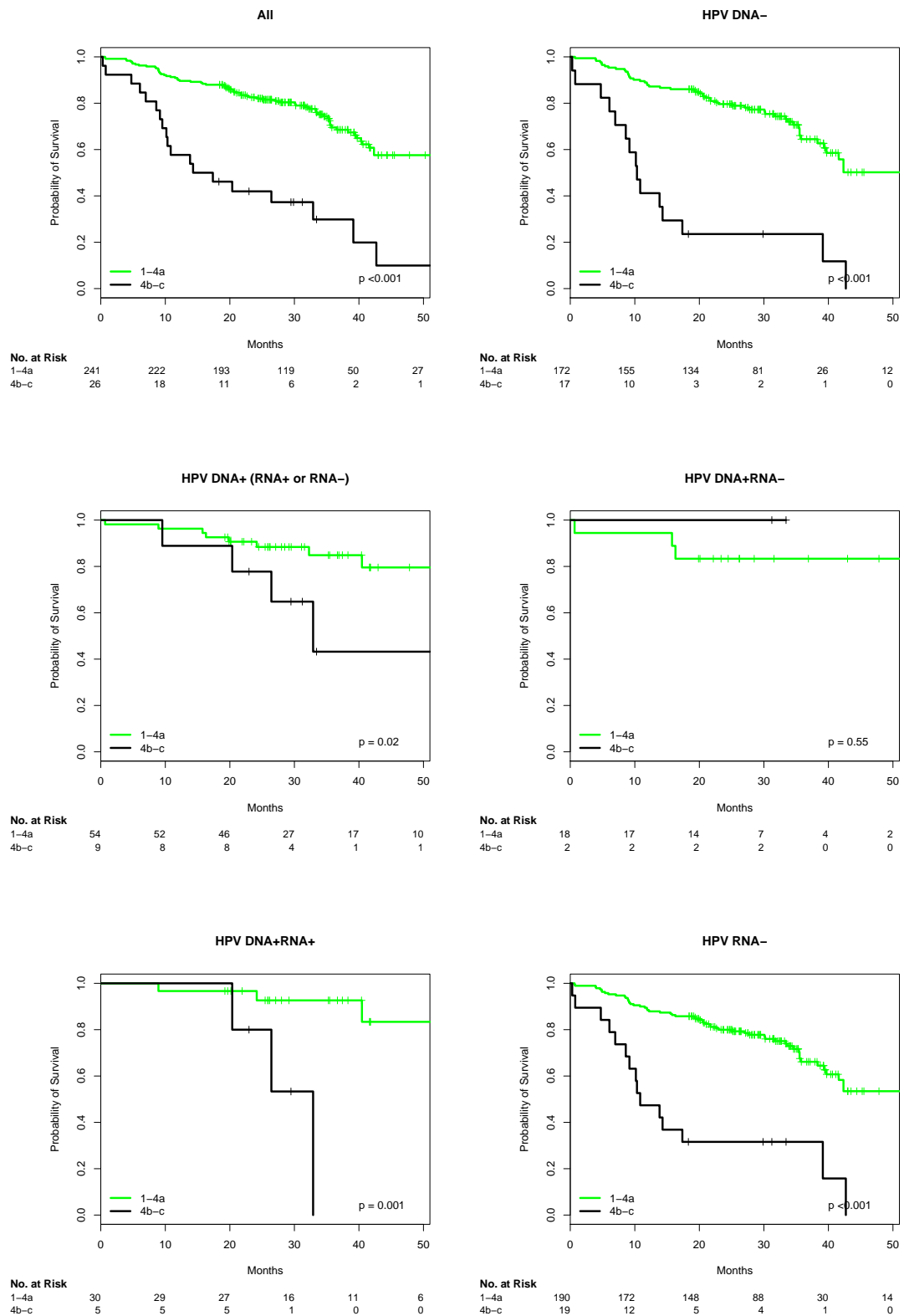
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.384      3.992    0.256 5.41 6.4e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```

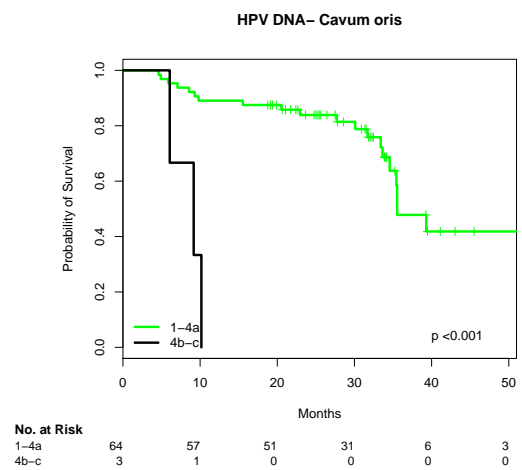
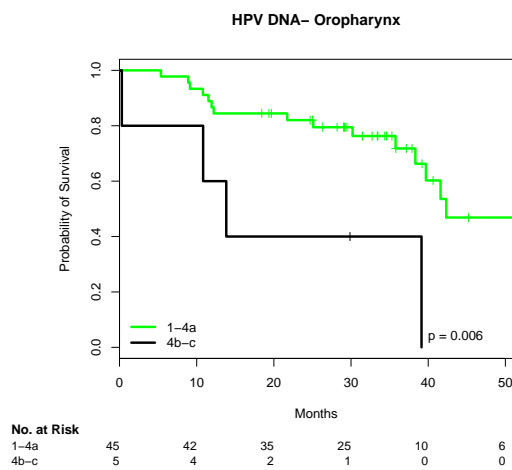
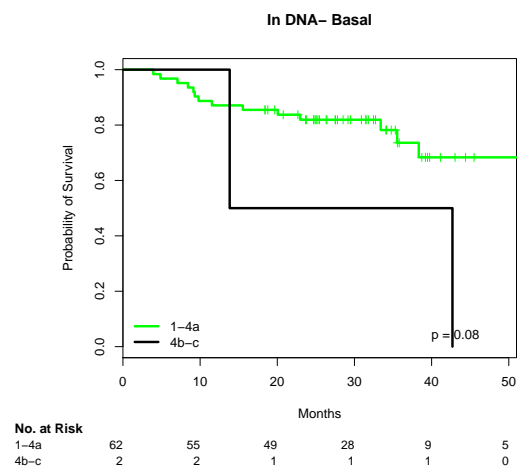
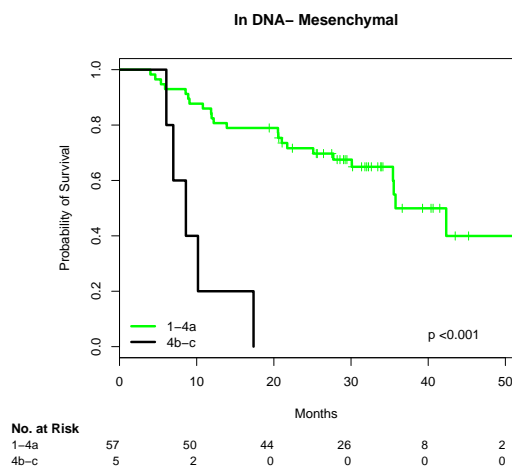
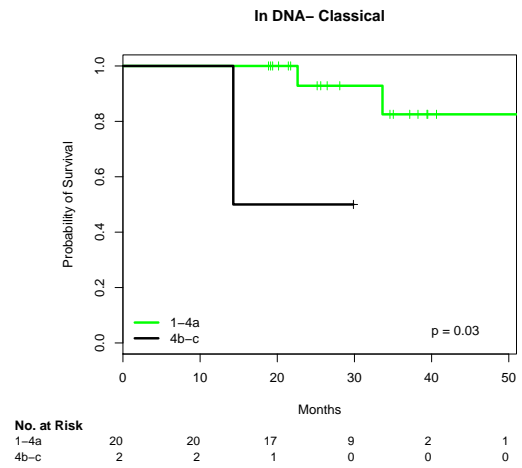
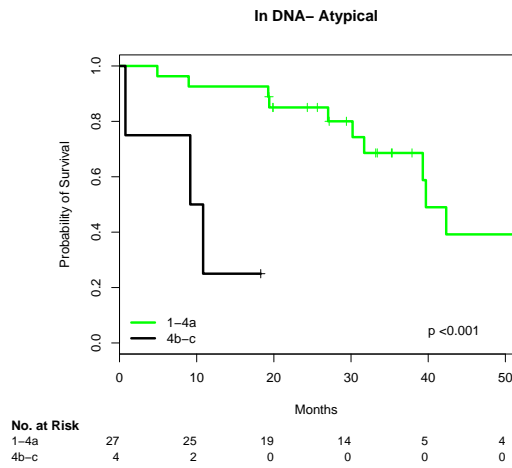
```

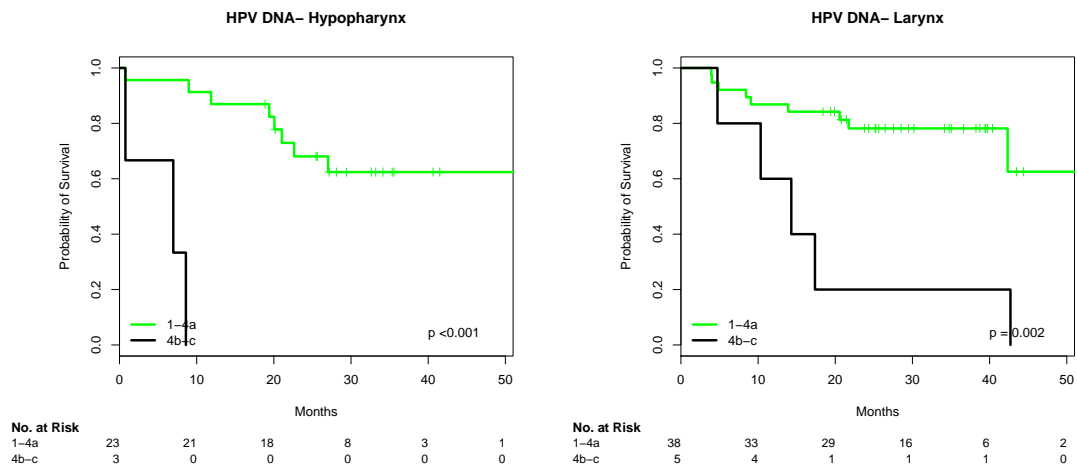
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4b-c      3.99      0.251      2.42      6.59
##
## Concordance= 0.591 (se = 0.015 )
## Rsquare= 0.08 (max possible= 0.967 )
## Likelihood ratio test= 22.3 on 1 df, p=2.34e-06
## Wald test = 29.2 on 1 df, p=6.38e-08
## Score (logrank) test = 34 on 1 df, p=5.48e-09
##
## 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      70.0000      58.0000      0.6952      0.0364
## lower 95% CI upper 95% CI
##      0.6274      0.7705
##
##               split[cur.subset]=4b-c
##           time      n.risk      n.event      survival      std.err
##      36.000      3.000      17.000      0.298      0.102
## lower 95% CI upper 95% CI
##      0.152      0.585
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]4b-c 1.725      5.612      0.298 5.8 6.7e-09 ***
## ---
## 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      5.61      0.178      3.13      10.1
##
## Concordance= 0.602 (se = 0.015 )
## Rsquare= 0.12 (max possible= 0.968 )
## Likelihood ratio test= 24.1 on 1 df, p=8.94e-07
## Wald test = 33.6 on 1 df, p=6.72e-09
## Score (logrank) test = 42.6 on 1 df, p=6.77e-11
##
##

```

```
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 209, number of events= 75
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.566      4.788    0.294 5.33    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]4b-c      4.79      0.209      2.69      8.52
##
## Concordance= 0.593 (se = 0.016 )
## Rsquare= 0.095 (max possible= 0.965 )
## Likelihood ratio test= 20.8 on 1 df,  p=5.17e-06
## Wald test               = 28.4 on 1 df,  p=9.99e-08
## Score (logrank) test = 34.5 on 1 df,  p=4.15e-09
##
## 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      46.0000      50.0000      0.6613      0.0438
## lower 95% CI upper 95% CI
##      0.5808      0.7529
##
##              split[cur.subset]=4b-c
##      time      n.risk      n.event      survival      std.err
##      36.000      2.000      13.000      0.316      0.107
## lower 95% CI upper 95% CI
##      0.163      0.612
```





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

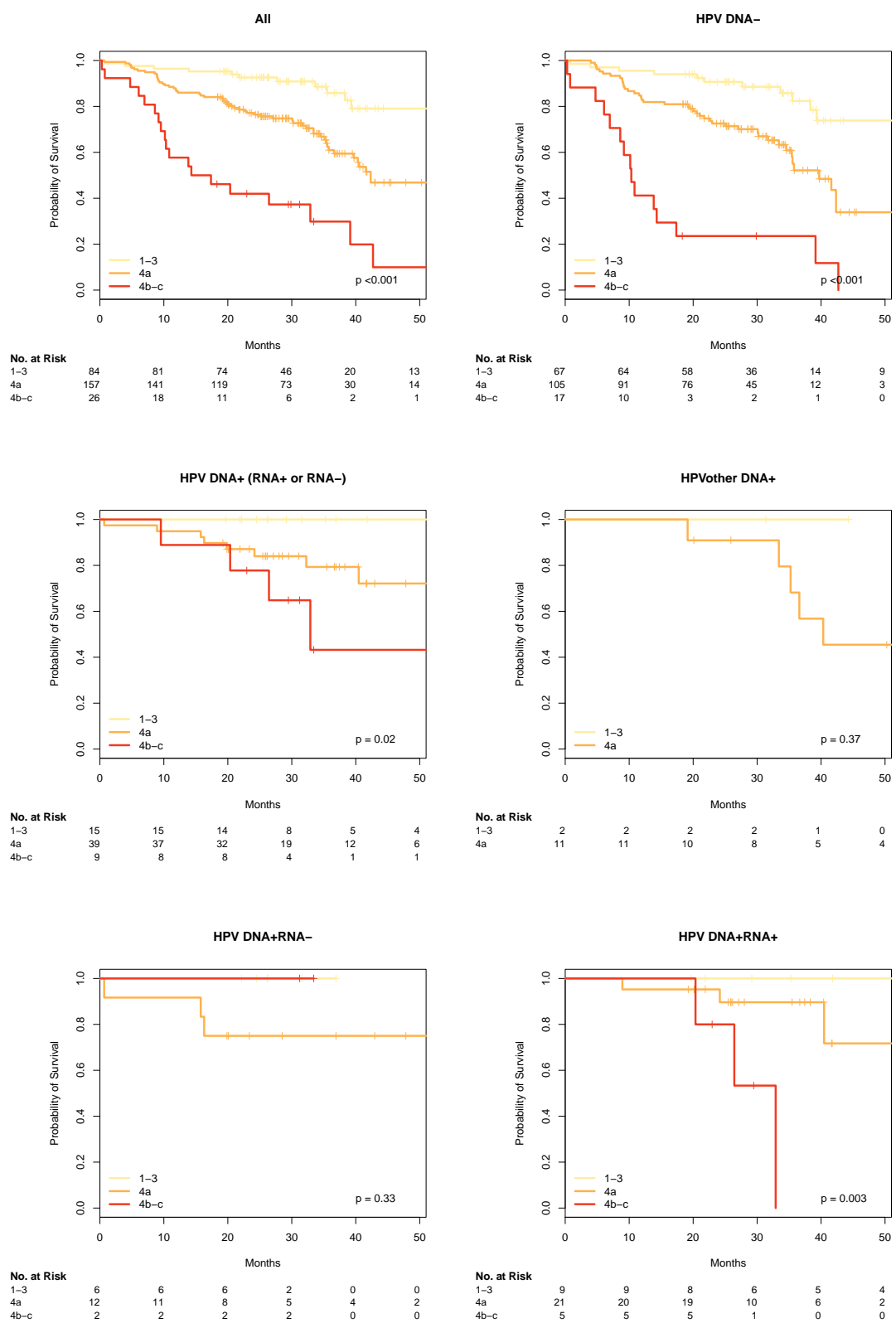
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  1.092    2.980   0.307  3.56  0.00037 ***
## split[cur.subset]4b-c 2.178    8.826   0.359  6.06  1.4e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      2.98    0.336    1.63    5.44
## split[cur.subset]4b-c     8.83    0.113    4.36   17.85
##
## Concordance= 0.668 (se = 0.029 )
## Rsquare= 0.132 (max possible= 0.967 )
## Likelihood ratio test= 37.9 on 2 df,  p=5.91e-09
## Wald test               = 37.7 on 2 df,  p=6.61e-09
## Score (logrank) test = 45.8 on 2 df,  p=1.13e-10
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=1-3
```

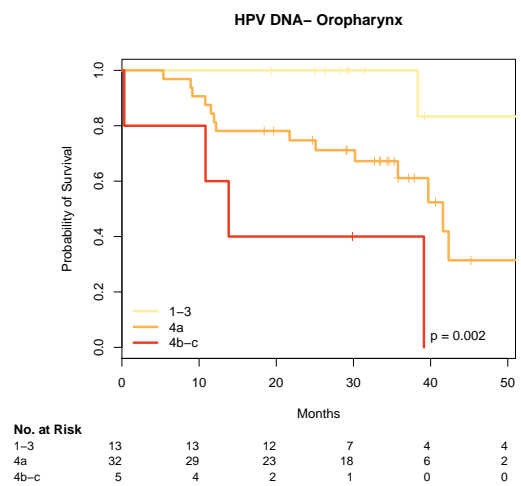
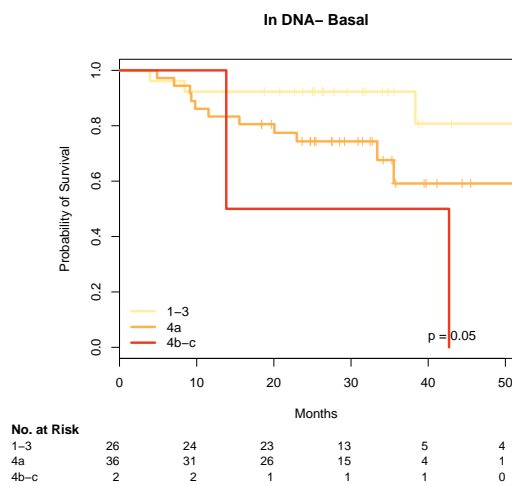
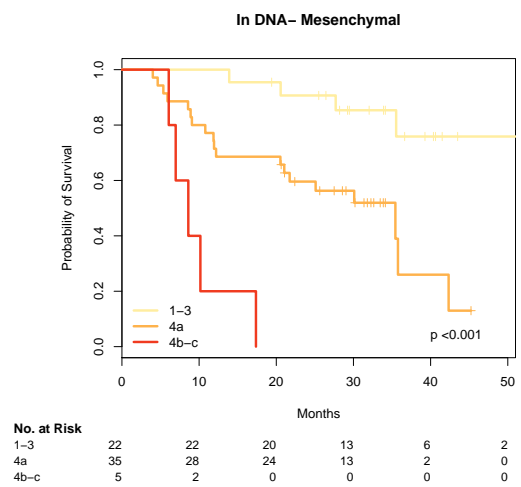
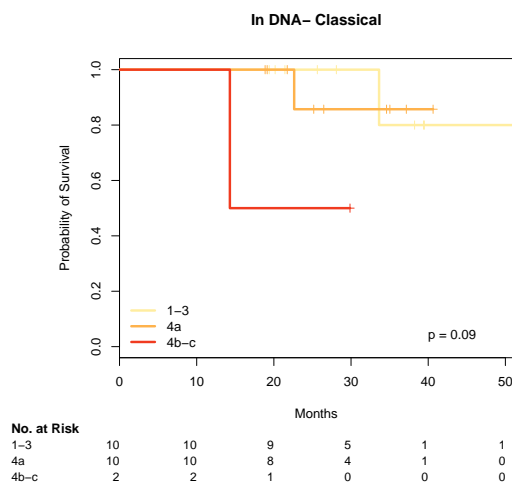
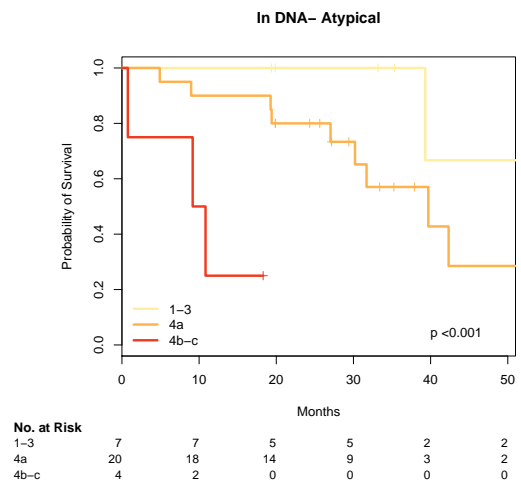
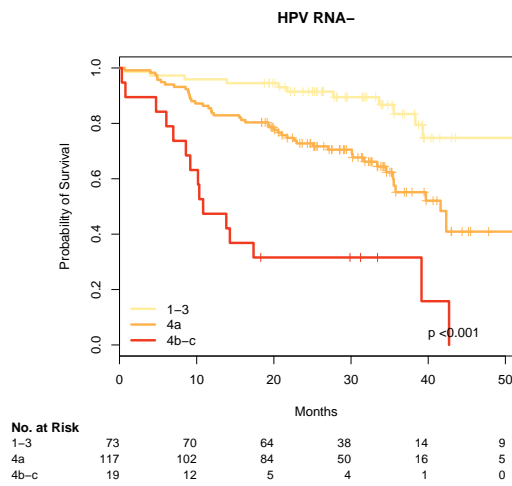
```

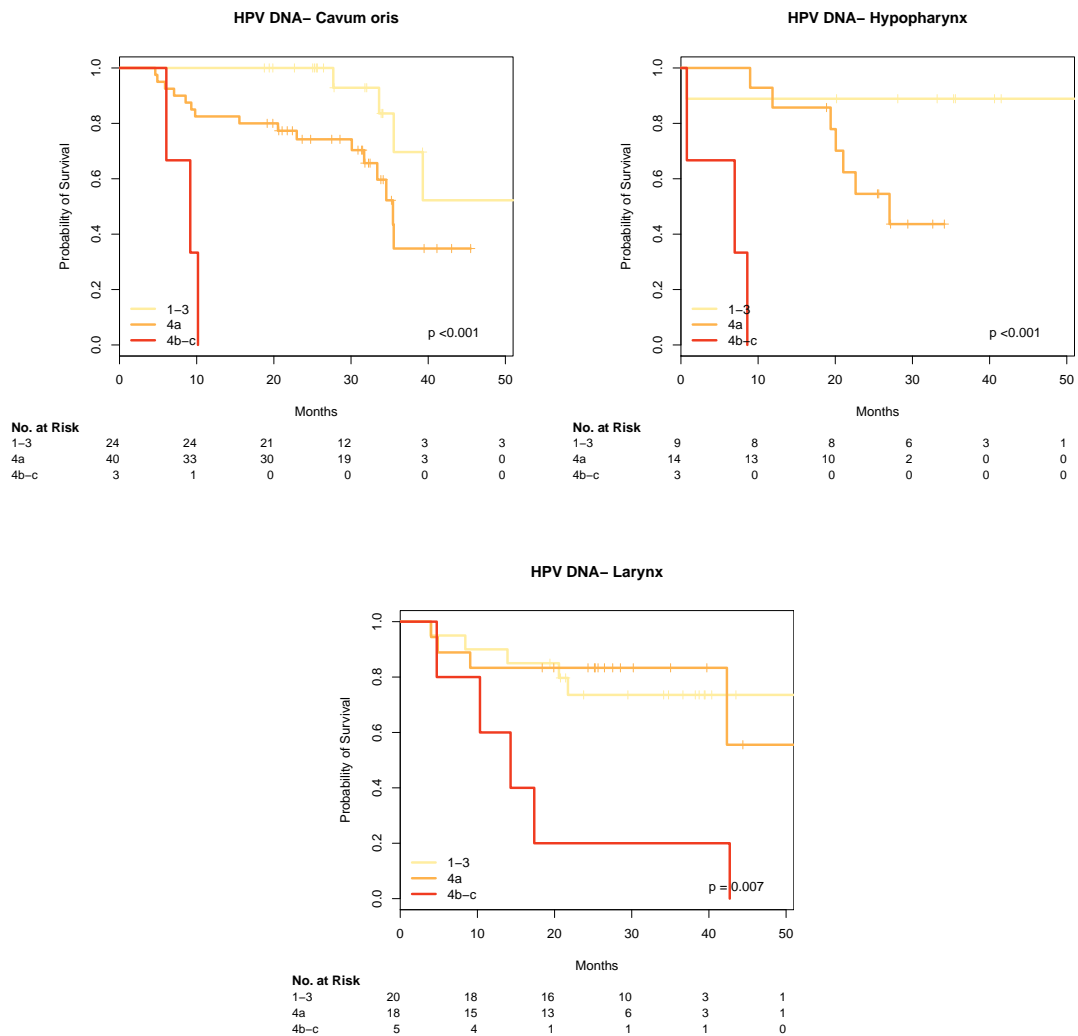
##           time           n.risk      n.event      survival      std.err
##      36.0000      30.0000      9.0000      0.8584      0.0469
## lower 95% CI upper 95% CI
##      0.7711      0.9555
##
##           split[cur.subset]=4a
##           time           n.risk      n.event      survival      std.err
##      36.0000      40.0000      49.0000      0.6095      0.0481
## lower 95% CI upper 95% CI
##      0.5222      0.7114
##
##           split[cur.subset]=4b-c
##           time           n.risk      n.event      survival      std.err
##      36.000      3.000      17.000      0.298      0.102
## lower 95% CI upper 95% CI
##      0.152      0.585
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 189, number of events= 71
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  1.086    2.963    0.323 3.36 0.00077 ***
## split[cur.subset]4b-c 2.465   11.768    0.391 6.30 2.9e-10 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a    2.96    0.338    1.57    5.58
## split[cur.subset]4b-c  11.77    0.085    5.47   25.32
##
## Concordance= 0.685 (se = 0.034 )
## Rsquare= 0.179 (max possible= 0.968 )
## Likelihood ratio test= 37.4 on 2 df,  p=7.66e-09
## Wald test = 40.7 on 2 df,  p=1.46e-09
## Score (logrank) test = 52.9 on 2 df,  p=3.31e-12
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##

```

```
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a    1.076     2.932    0.317 3.40  0.00068 ***
## split[cur.subset]4b-c  2.317    10.146    0.388 5.97  2.3e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      2.93     0.3411      1.58      5.45
## split[cur.subset]4b-c    10.15     0.0986      4.74     21.70
##
## Concordance= 0.678 (se = 0.033 )
## Rsquare= 0.152 (max possible= 0.965 )
## Likelihood ratio test= 34.4 on 2 df,  p=3.32e-08
## Wald test               = 36.1 on 2 df,  p=1.42e-08
## Score (logrank) test = 45.2 on 2 df,  p=1.5e-10
##
## 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      9.0000      0.8339      0.0548
## lower 95% CI upper 95% CI
##           0.7331      0.9486
##
##               split[cur.subset]=4a
##           time      n.risk      n.event      survival      std.err
##           36.0000     22.0000     41.0000      0.5514      0.0604
## lower 95% CI upper 95% CI
##           0.4449      0.6833
##
##               split[cur.subset]=4b-c
##           time      n.risk      n.event      survival      std.err
##           36.000      2.000     13.000      0.316      0.107
## lower 95% CI upper 95% CI
##           0.163      0.612
```







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= 94
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein -0.0915   0.9126  0.2756 -0.33   0.74
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein   0.913      1.1    0.532    1.57
##
## Concordance= 0.505 (se = 0.022 )
## Rsquare= 0 (max possible= 0.967 )
## Likelihood ratio test= 0.11 on 1 df,  p=0.737
```

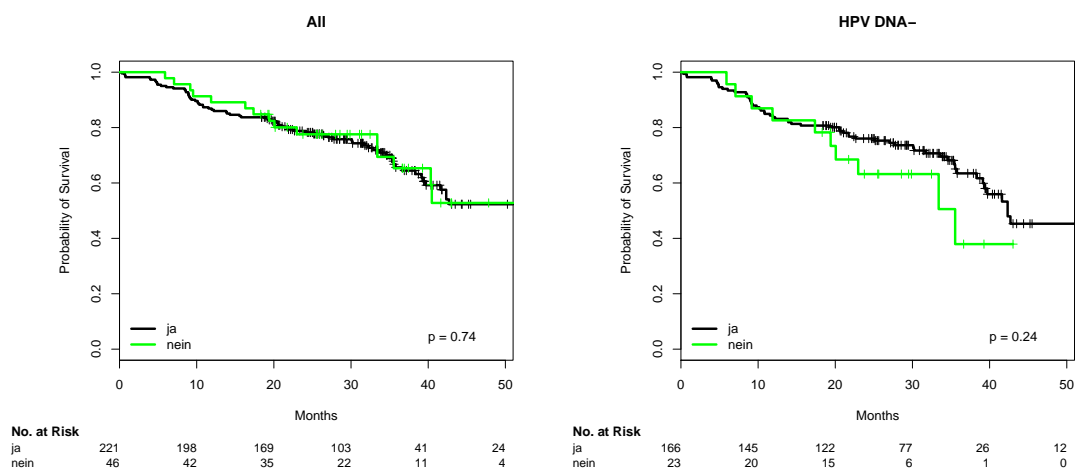


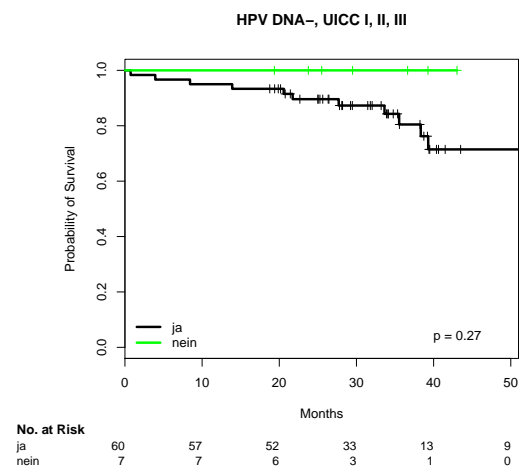
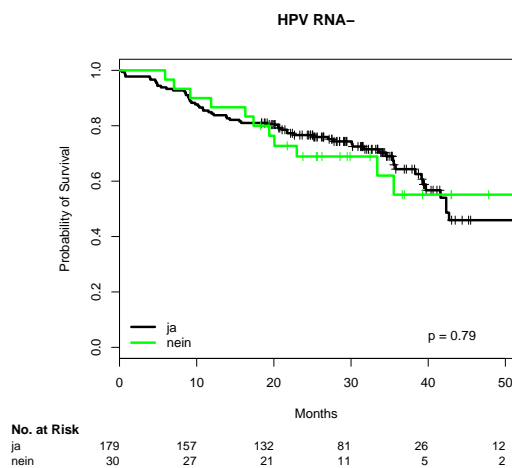
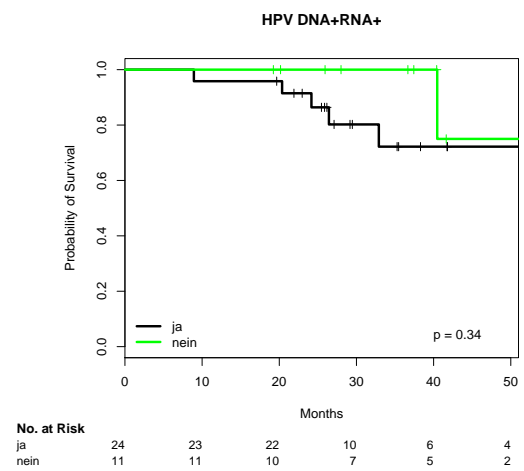
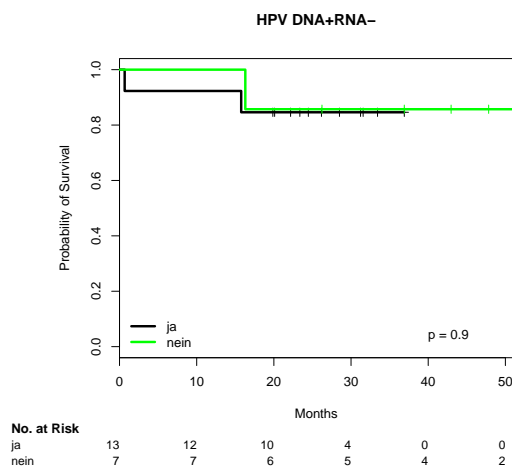
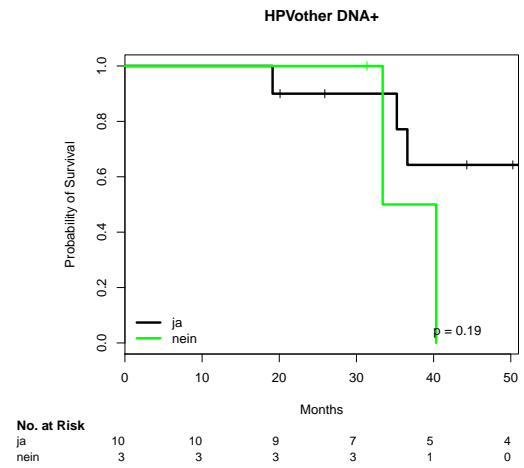
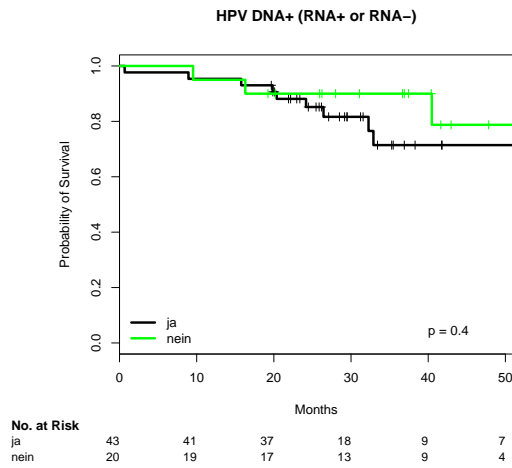
```

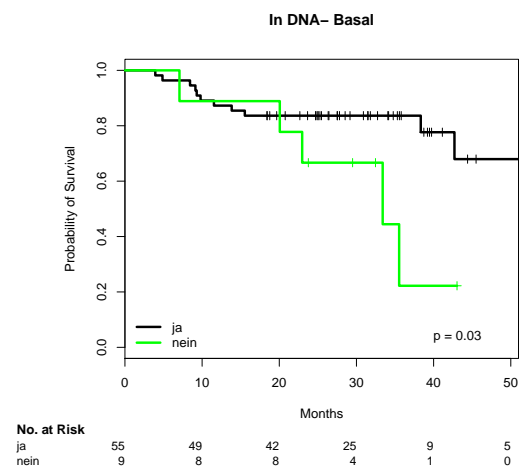
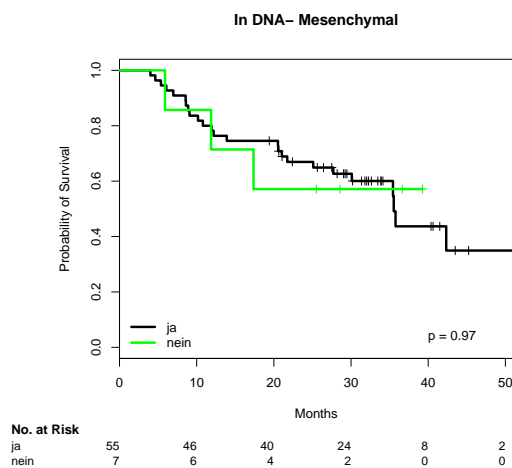
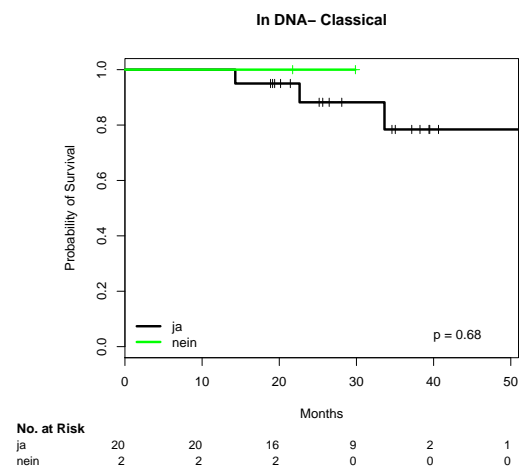
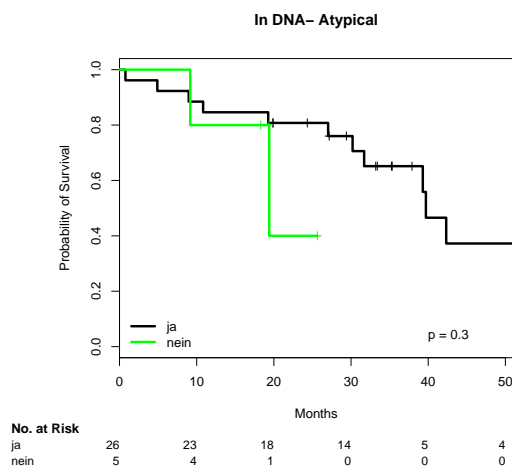
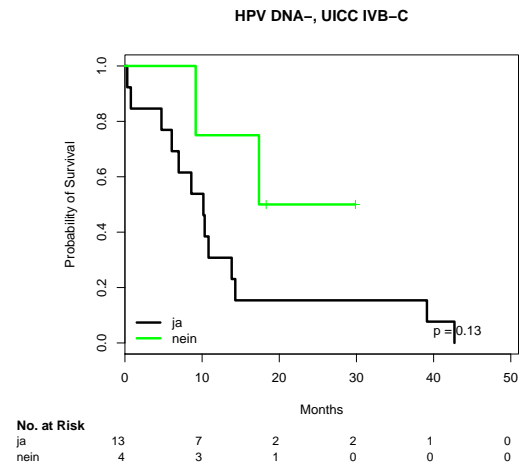
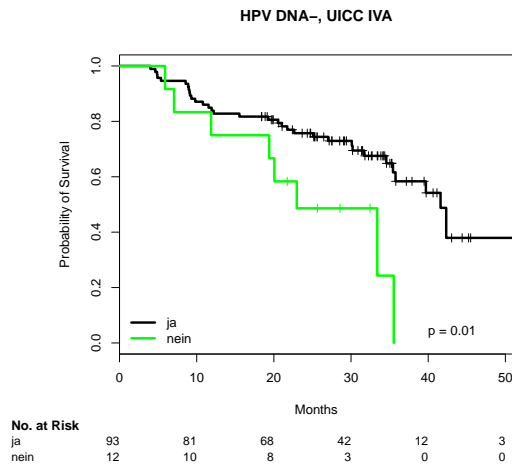
## Wald test          = 0.11  on 1 df,    p=0.74
## Score (logrank) test = 0.11  on 1 df,    p=0.74
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=ja
##      time      n.risk      n.event      survival      std.err
## 36.0000      57.0000      62.0000      0.6563      0.0389
## lower 95% CI upper 95% CI
## 0.5843      0.7371
##
##               split[cur.subset]=nein
##      time      n.risk      n.event      survival      std.err
## 36.0000      16.0000      13.0000      0.6532      0.0837
## lower 95% CI upper 95% CI
## 0.5082      0.8397
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein 0.405      1.499      0.344 1.18      0.24
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein      1.5      0.667      0.763      2.94
##
## Concordance= 0.52 (se = 0.021 )
## Rsquare= 0.007 (max possible= 0.968 )
## Likelihood ratio test= 1.26 on 1 df,    p=0.262
## Wald test          = 1.38 on 1 df,    p=0.24
## Score (logrank) test = 1.4 on 1 df,    p=0.236
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)

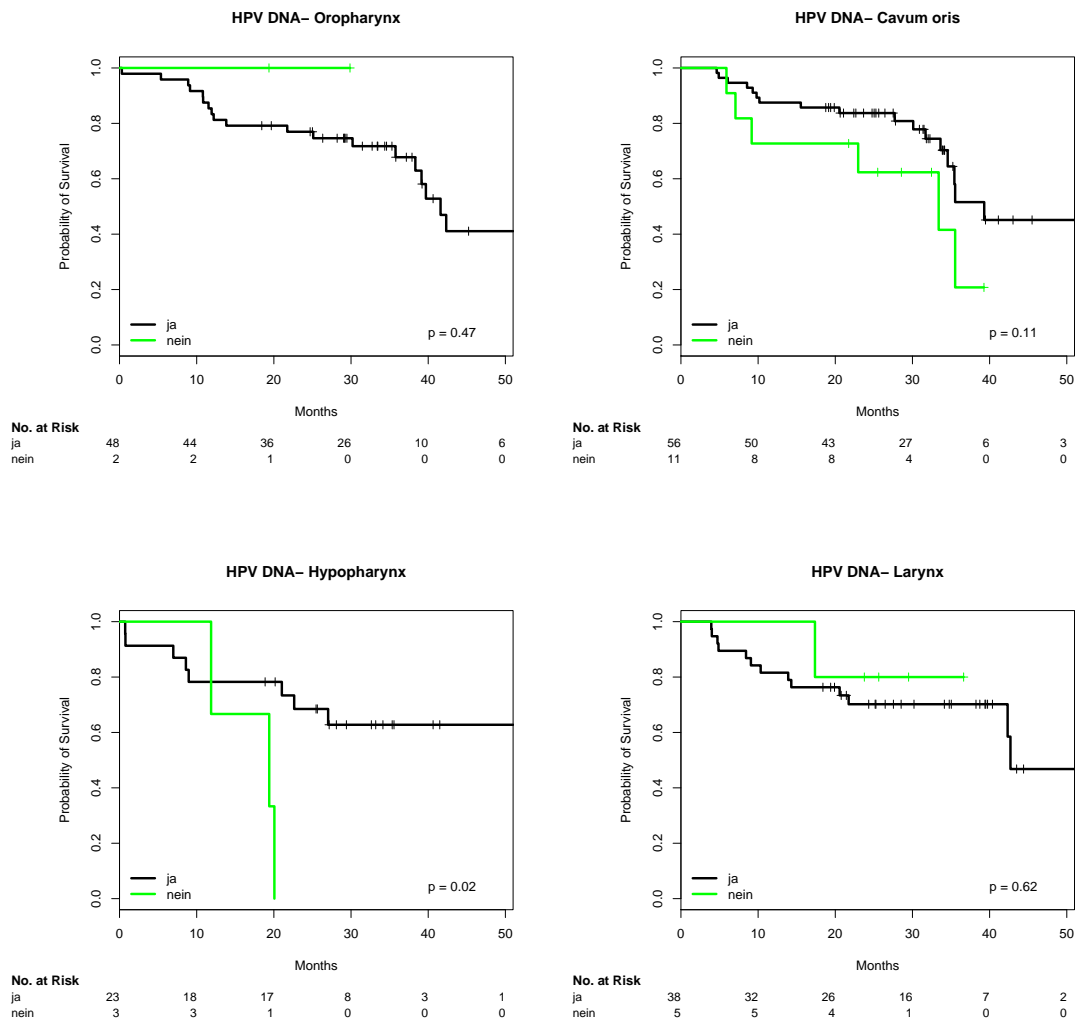
```

```
## split[cur.subset]nein 0.0845    1.0882    0.3155 0.27    0.79
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein      1.09      0.919    0.586    2.02
##
## Concordance= 0.509  (se = 0.023 )
## Rsquare= 0      (max possible= 0.965 )
## Likelihood ratio test= 0.07  on 1 df,   p=0.791
## Wald test          = 0.07  on 1 df,   p=0.789
## Score (logrank) test = 0.07  on 1 df,   p=0.789
##
## 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    40.0000    52.0000    0.6433    0.0447
## lower 95% CI upper 95% CI
## 0.5613    0.7372
##
##                      split[cur.subset]=nein
##      time      n.risk      n.event      survival      std.err
## 36.000    8.000    11.000    0.551    0.111
## lower 95% CI upper 95% CI
## 0.371    0.819
```









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= 93
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](10,30) -0.4472   0.6394  0.3136 -1.43   0.15
## split[cur.subset](30,44)  0.2665   1.3054  0.2825  0.94   0.35
## split[cur.subset](44,125) 0.0812   1.0846  0.2907  0.28   0.78
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](10,30)    0.639    1.564    0.346    1.18
## split[cur.subset](30,44)    1.305    0.766    0.750    2.27
```

```

## split[cur.subset](44,125]      1.085      0.922      0.613      1.92
##
## Concordance= 0.557 (se = 0.033 )
## Rsquare= 0.022 (max possible= 0.967 )
## Likelihood ratio test= 5.88 on 3 df, p=0.118
## Wald test = 5.48 on 3 df, p=0.14
## Score (logrank) test = 5.63 on 3 df, p=0.131
##
## 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      20.0000      20.0000      0.6297      0.0714
## lower 95% CI upper 95% CI
##           0.5041      0.7864
##
##           split[cur.subset]=(10,30]
##           time      n.risk      n.event      survival      std.err
##           36.0000      22.0000      14.0000      0.7507      0.0614
## lower 95% CI upper 95% CI
##           0.6395      0.8813
##
##           split[cur.subset]=(30,44]
##           time      n.risk      n.event      survival      std.err
##           36.0000      14.0000      21.0000      0.6021      0.0779
## lower 95% CI upper 95% CI
##           0.4673      0.7759
##
##           split[cur.subset]=(44,125]
##           time      n.risk      n.event      survival      std.err
##           36.0000      16.0000      20.0000      0.6162      0.0749
## lower 95% CI upper 95% CI
##           0.4856      0.7819
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 188, number of events= 70
## (3 observations deleted due to missingness)
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](10,30] -0.881      0.414      0.390 -2.26      0.024 *
## split[cur.subset](30,44] -0.102      0.903      0.346 -0.29      0.768

```

```

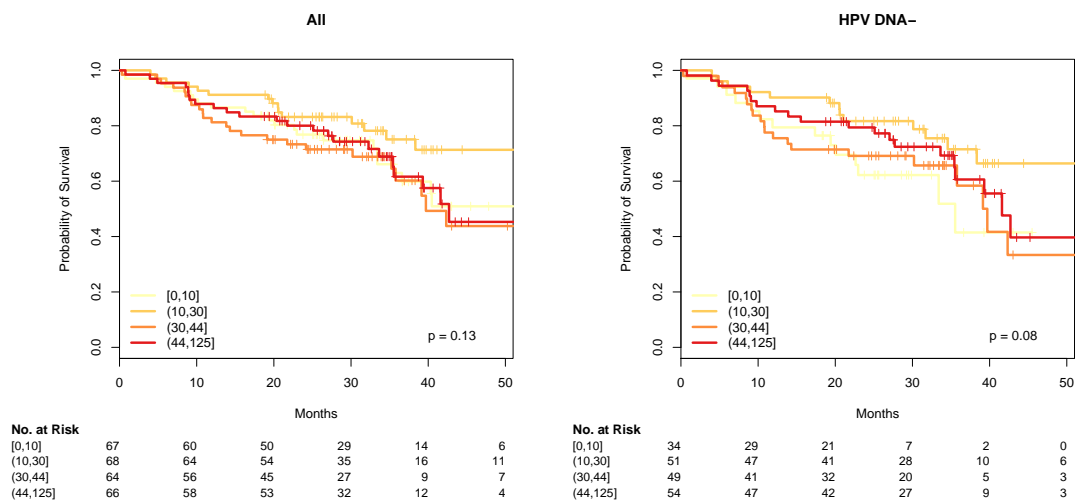
## split[cur.subset](44,125] -0.354      0.702      0.348 -1.02      0.309
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](10,30]      0.414      2.41      0.193      0.89
## split[cur.subset](30,44]      0.903      1.11      0.459      1.78
## split[cur.subset](44,125]      0.702      1.42      0.355      1.39
##
## Concordance= 0.579 (se = 0.037 )
## Rsquare= 0.037 (max possible= 0.967 )
## Likelihood ratio test= 7.07 on 3 df,  p=0.0698
## Wald test = 6.47 on 3 df,  p=0.091
## Score (logrank) test = 6.74 on 3 df,  p=0.0806
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 74
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](10,30] -0.6972    0.4980  0.3692 -1.89    0.059 .
## split[cur.subset](30,44]  0.0581    1.0599  0.3207  0.18    0.856
## split[cur.subset](44,125] -0.2076    0.8125  0.3275 -0.63    0.526
## ---
## 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]      0.498      2.008      0.242      1.03
## split[cur.subset](30,44]      1.060      0.944      0.565      1.99
## split[cur.subset](44,125]      0.812      1.231      0.428      1.54
##
## Concordance= 0.572 (se = 0.036 )
## Rsquare= 0.028 (max possible= 0.965 )
## Likelihood ratio test= 5.83 on 3 df,  p=0.12
## Wald test = 5.3 on 3 df,  p=0.151
## Score (logrank) test = 5.49 on 3 df,  p=0.139
##
## 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

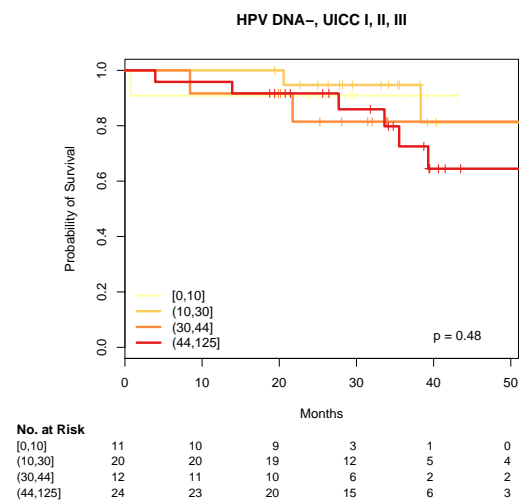
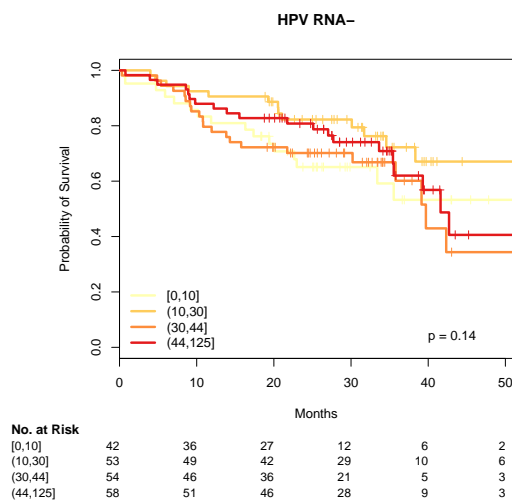
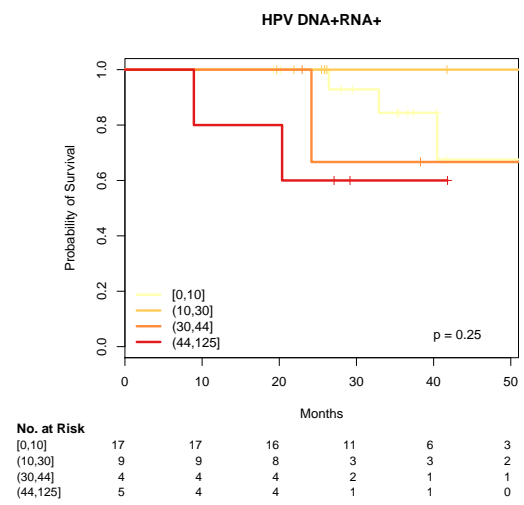
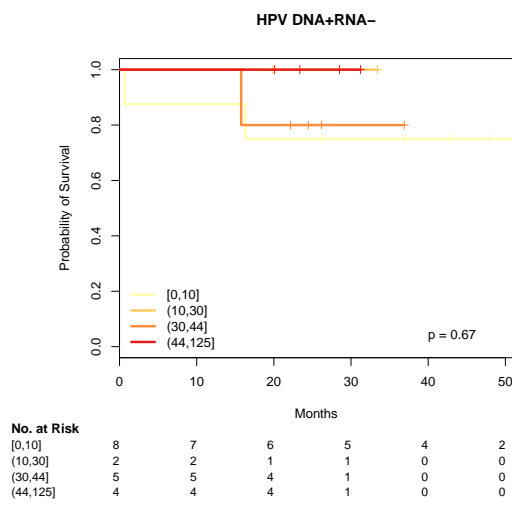
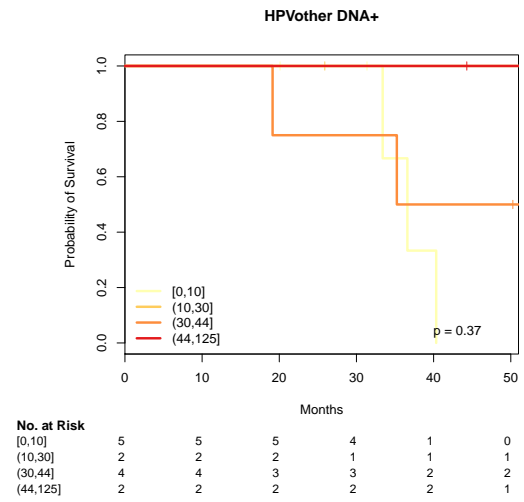
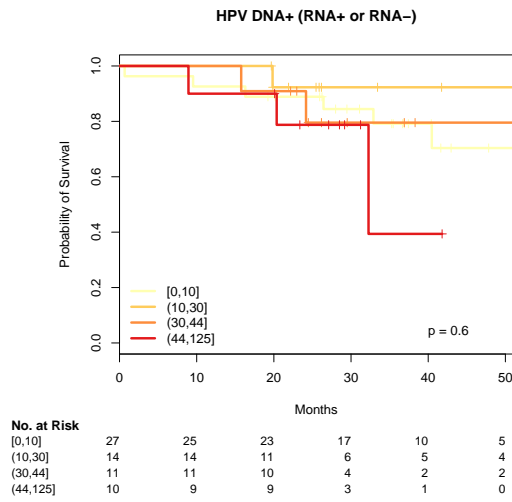
```

```

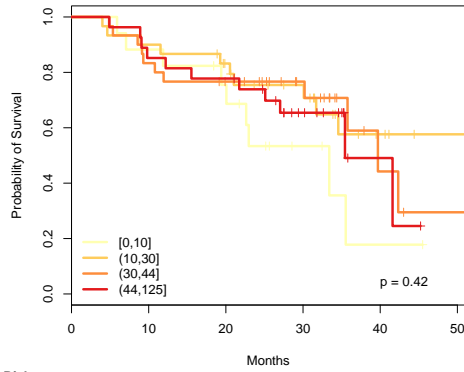
##      36.000      9.000      16.000      0.533      0.098
## lower 95% CI upper 95% CI
##      0.371      0.764
##
##      split[cur.subset]=(10,30)
##      time      n.risk      n.event      survival      std.err
##      36.0000      16.0000      12.0000      0.7223      0.0726
## lower 95% CI upper 95% CI
##      0.5931      0.8797
##
##      split[cur.subset]=(30,44)
##      time      n.risk      n.event      survival      std.err
##      36.0000      9.0000      18.0000      0.6014      0.0881
## lower 95% CI upper 95% CI
##      0.4513      0.8013
##
##      split[cur.subset]=(44,125]
##      time      n.risk      n.event      survival      std.err
##      36.0000      13.0000      17.0000      0.6200      0.0823
## lower 95% CI upper 95% CI
##      0.4780      0.8041

```





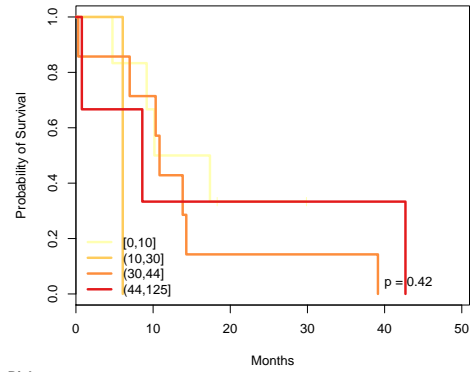
HPV DNA-, UICC IVA



No. at Risk

	0	10	20	30	40	50
[0,10]	17	15	11	4	1	0
(10,30]	30	27	22	16	5	2
(30,44]	30	25	21	13	3	1
(44,125]	27	23	21	11	2	0

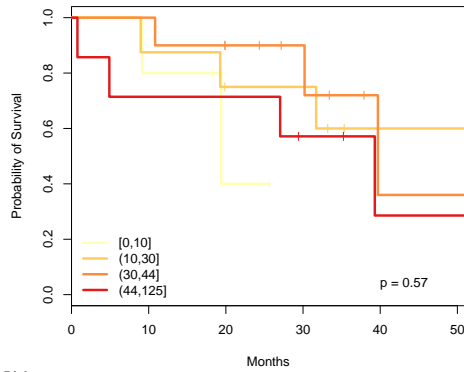
HPV DNA-, UICC IVB-C



No. at Risk

	0	10	20	30	40	50
[0,10]	6	4	1	0	0	0
(10,30]	1	0	0	0	0	0
(30,44]	7	5	1	1	0	0
(44,125]	3	1	1	1	1	0

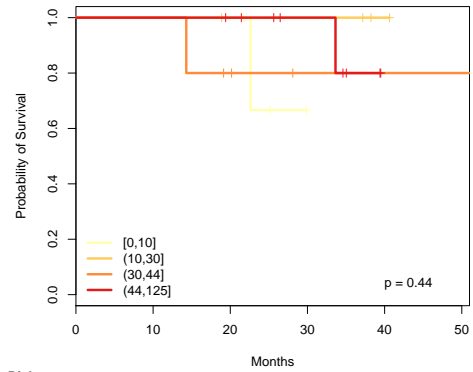
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
[0,10]	5	4	1	0	0	0
(10,30]	8	7	5	5	2	2
(30,44]	10	10	7	5	1	1
(44,125]	7	5	5	3	1	1

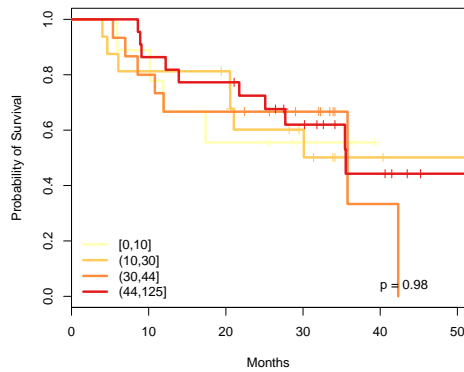
In DNA- Classical



No. at Risk

	0	10	20	30	40	50
[0,10]	4	4	4	0	0	0
(10,30]	4	4	3	3	1	0
(30,44]	5	5	3	1	1	1
(44,125]	9	9	8	5	0	0

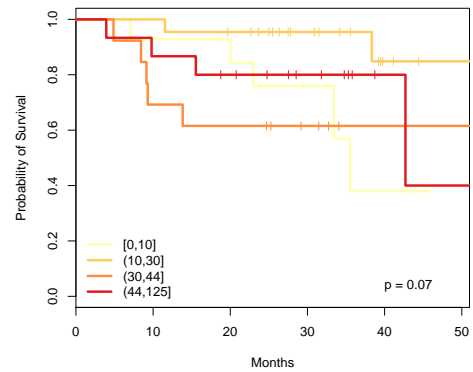
In DNA- Mesenchymal



No. at Risk

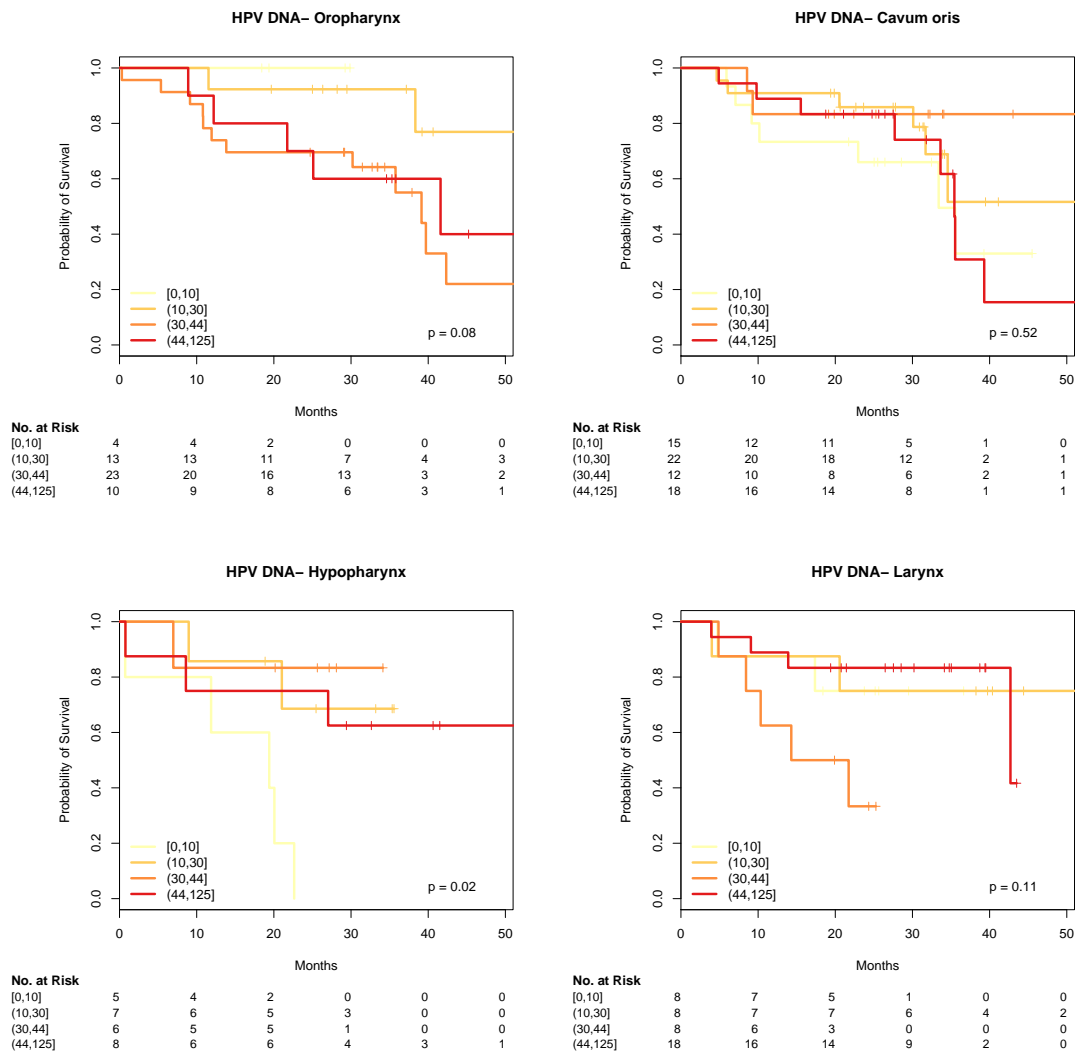
	0	10	20	30	40	50
[0,10]	9	8	5	2	0	0
(10,30]	16	13	12	6	2	1
(30,44]	15	12	10	7	1	0
(44,125]	22	19	17	11	5	1

In DNA- Basal



No. at Risk

	0	10	20	30	40	50
[0,10]	14	13	11	5	2	0
(10,30]	22	22	20	13	5	3
(30,44]	13	9	8	4	1	1
(44,125]	15	13	11	7	2	1



3.21 Smoking. Pack-years. Cut at 10

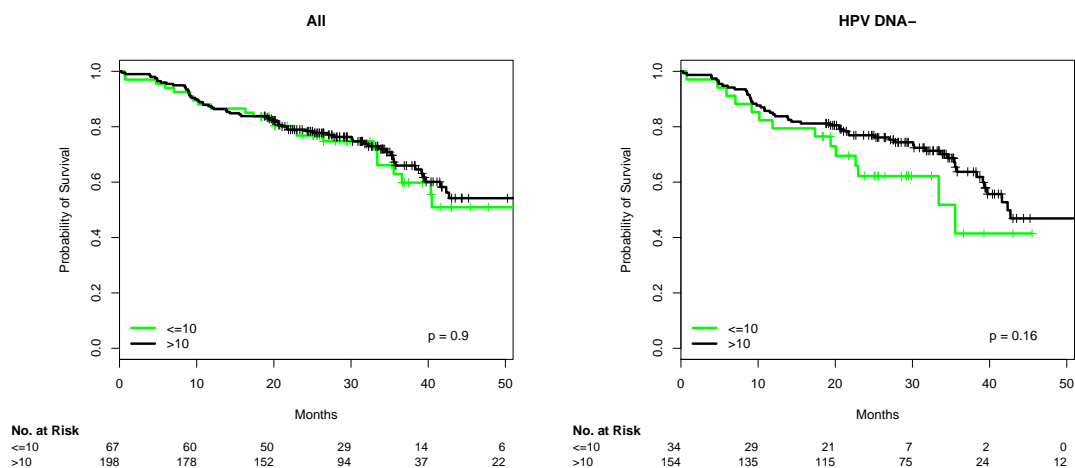
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 265, number of events= 93
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.0299   0.9705  0.2375 -0.13    0.9
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.97      1.03    0.609    1.55
##
## Concordance= 0.507 (se = 0.025 )
## Rsquare= 0 (max possible= 0.967 )
```

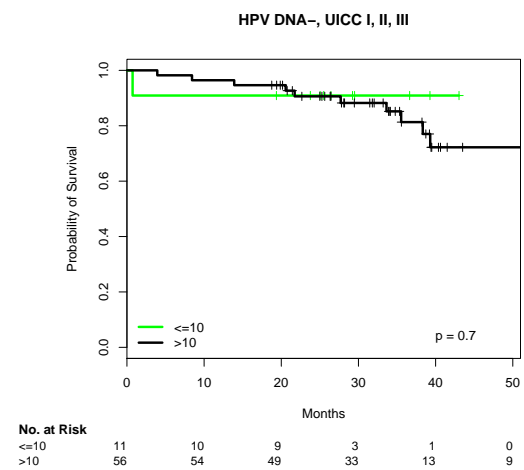
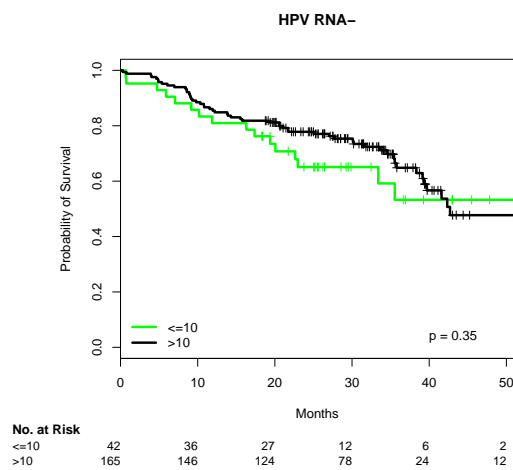
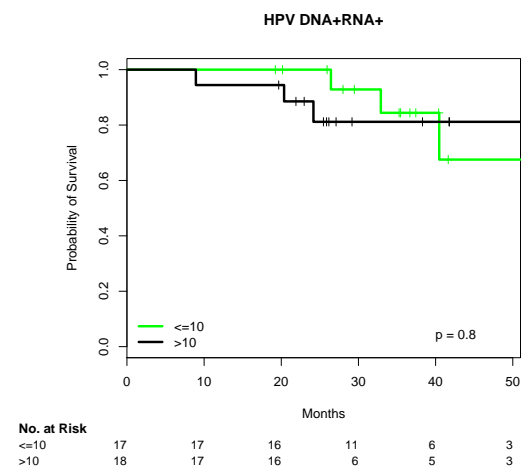
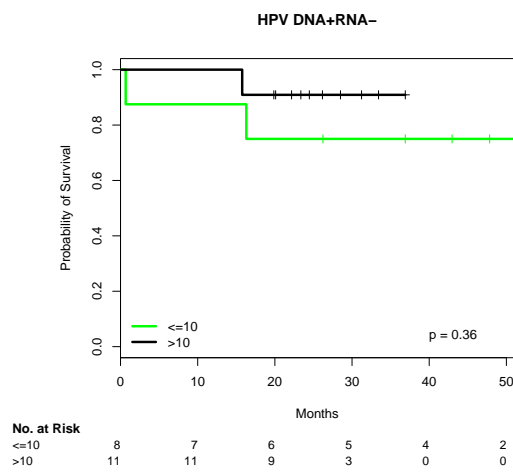
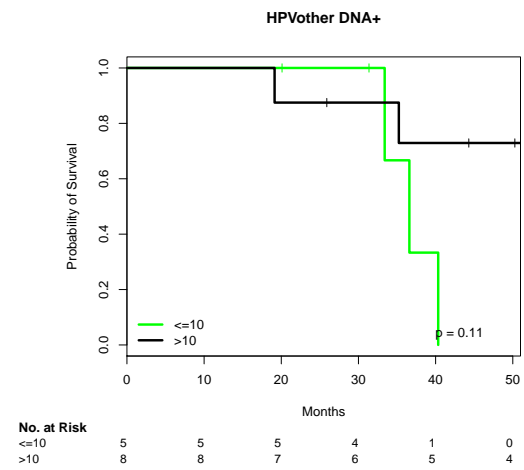
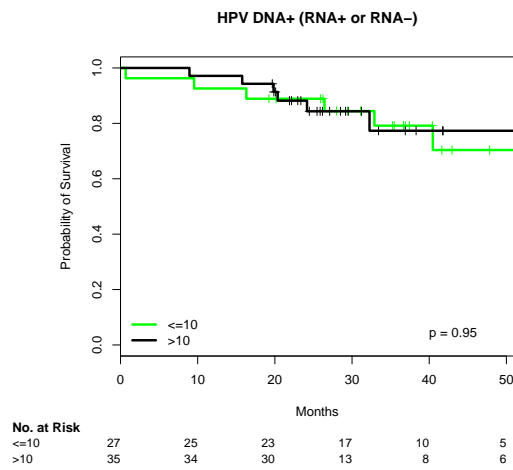
```

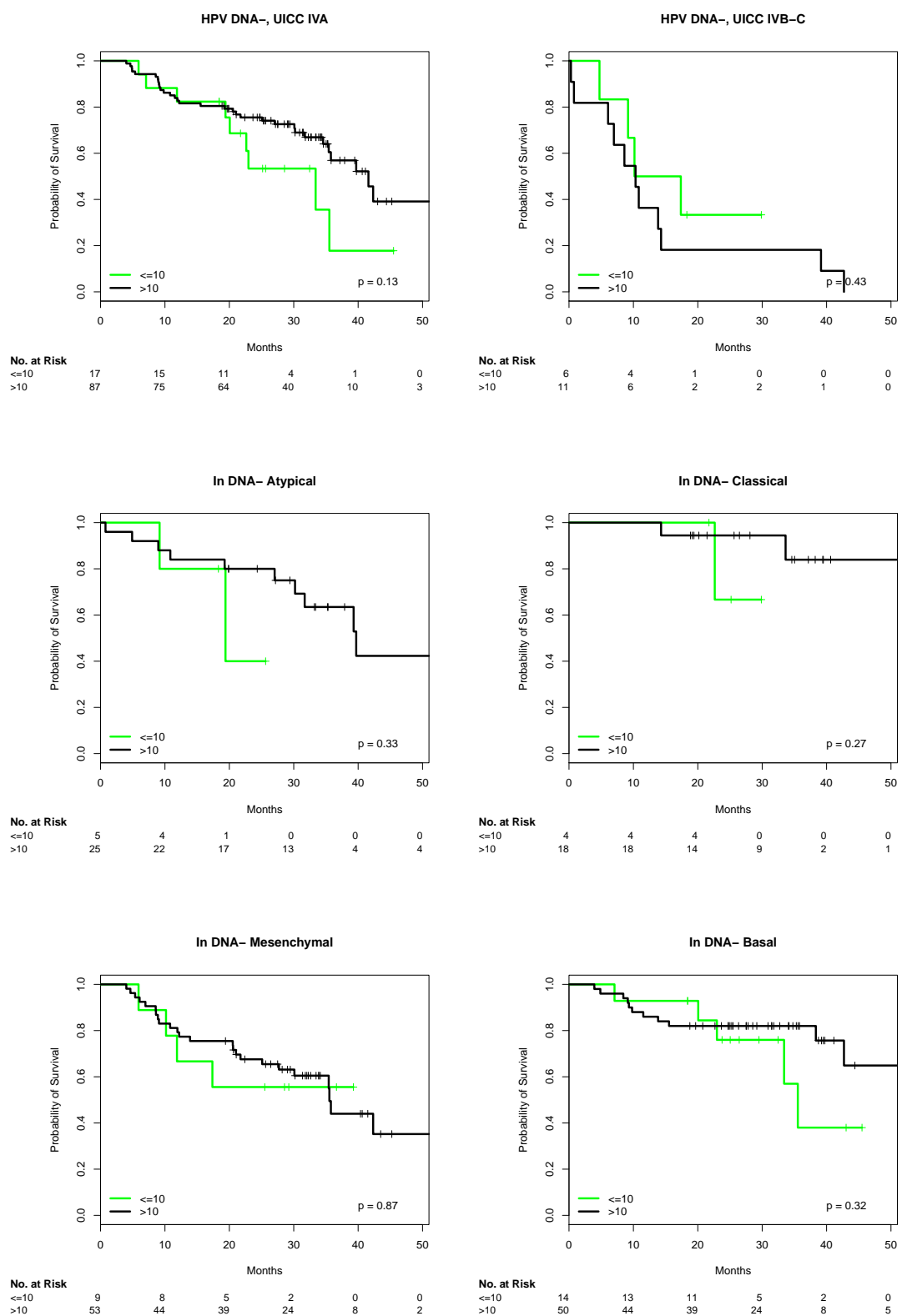
## Likelihood ratio test= 0.02  on 1 df,    p=0.9
## Wald test              = 0.02  on 1 df,    p=0.9
## Score (logrank) test = 0.02  on 1 df,    p=0.9
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##           split[cur.subset]<=10
##           time      n.risk      n.event      survival      std.err
##           36.0000      20.0000      20.0000      0.6297      0.0714
## lower 95% CI upper 95% CI
##           0.5041      0.7864
##
##           split[cur.subset]>=10
##           time      n.risk      n.event      survival      std.err
##           36.0000      52.0000      55.0000      0.6598      0.0411
## lower 95% CI upper 95% CI
##           0.5840      0.7454
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 188, number of events= 70
## (3 observations deleted due to missingness)
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.419    0.658    0.303 -1.38    0.17
##
##           exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.658      1.52    0.363    1.19
##
## Concordance= 0.533 (se = 0.025 )
## Rsquare= 0.009 (max possible= 0.967 )
## Likelihood ratio test= 1.77  on 1 df,    p=0.184
## Wald test              = 1.92  on 1 df,    p=0.166
## Score (logrank) test = 1.94  on 1 df,    p=0.163
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 74

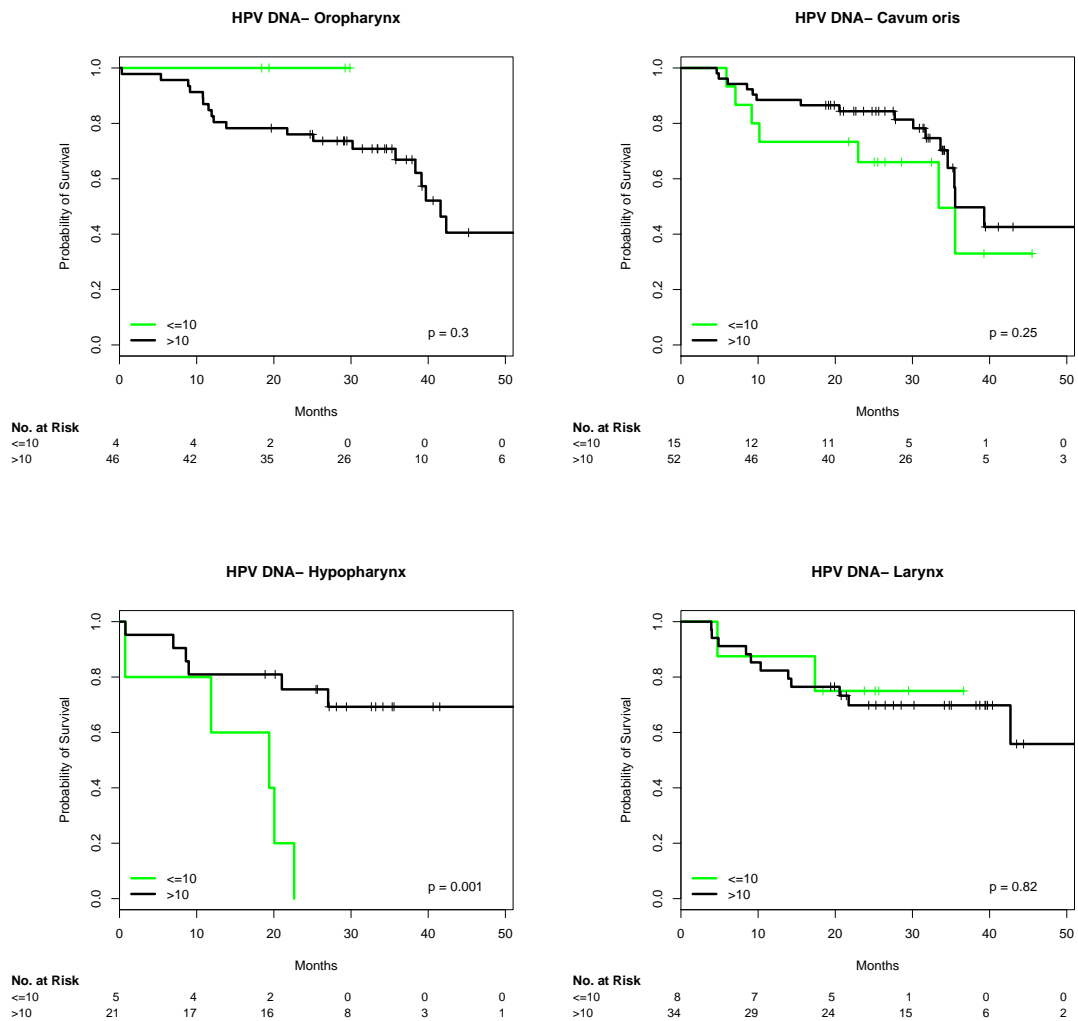
```

```
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.256      0.774    0.277 -0.92    0.35
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.774      1.29    0.45    1.33
##
## Concordance= 0.532  (se = 0.025 )
## Rsquare= 0.004  (max possible= 0.965 )
## Likelihood ratio test= 0.82  on 1 df,   p=0.366
## Wald test               = 0.86  on 1 df,   p=0.355
## Score (logrank) test = 0.86  on 1 df,   p=0.354
##
## 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
##              36.000      9.000     16.000      0.533      0.098
## lower 95% CI upper 95% CI
##              0.371      0.764
##
##              split[cur.subset]>=10
##              time      n.risk      n.event      survival      std.err
##              36.0000     38.0000     47.0000      0.6483      0.0464
## lower 95% CI upper 95% CI
##              0.5634      0.7460
```









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= 93
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.388      1.474    0.212 1.83    0.068 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30    1.47      0.679    0.972    2.23
##
```

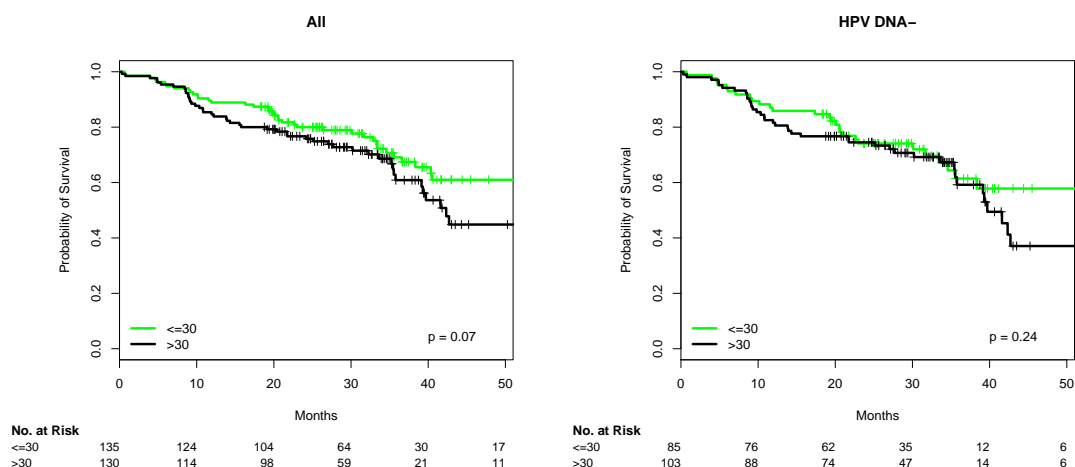


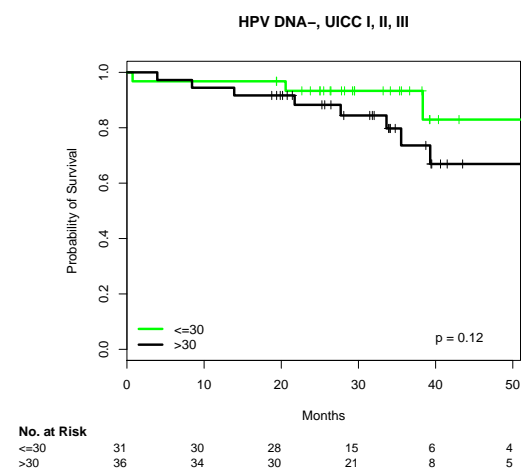
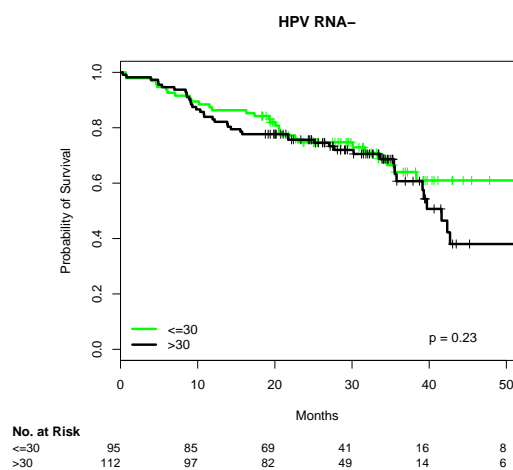
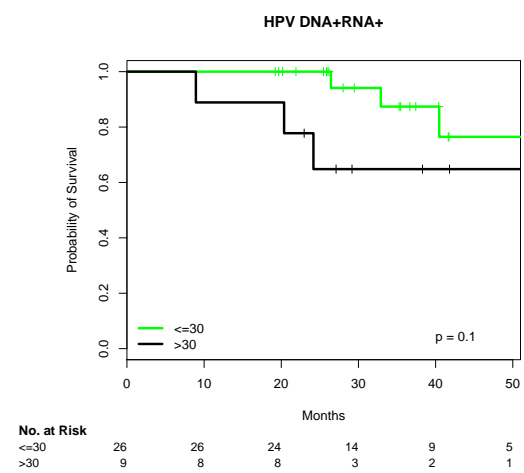
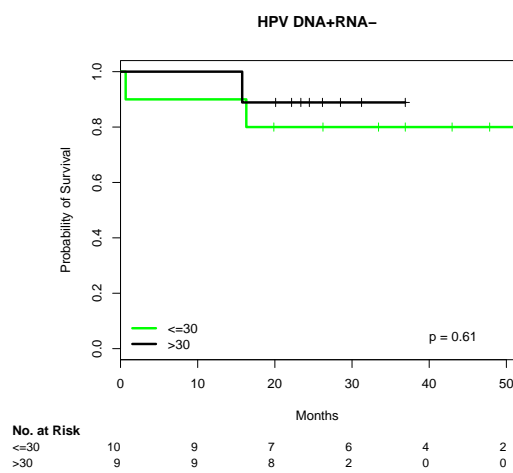
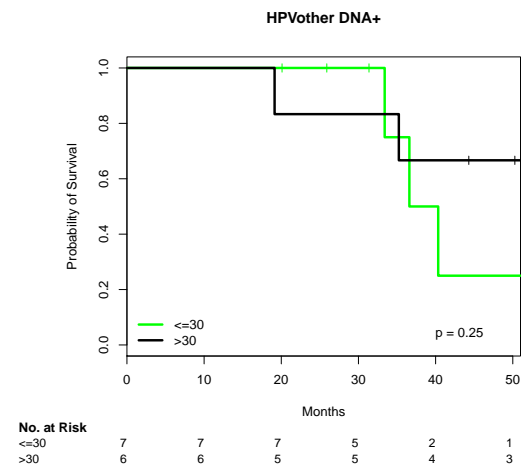
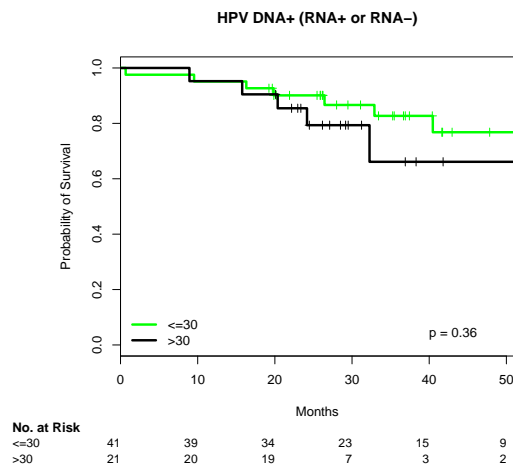
```

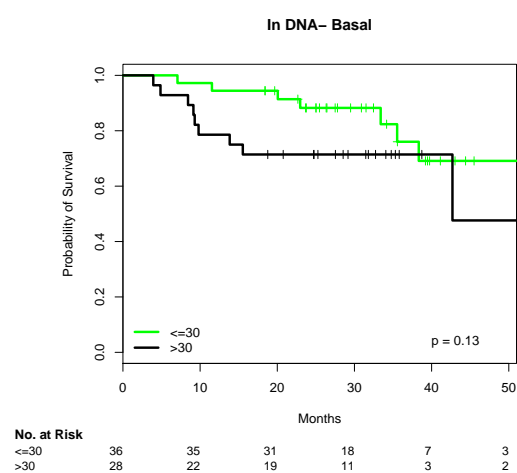
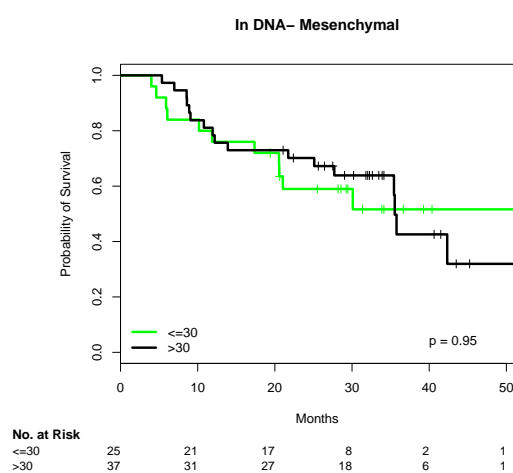
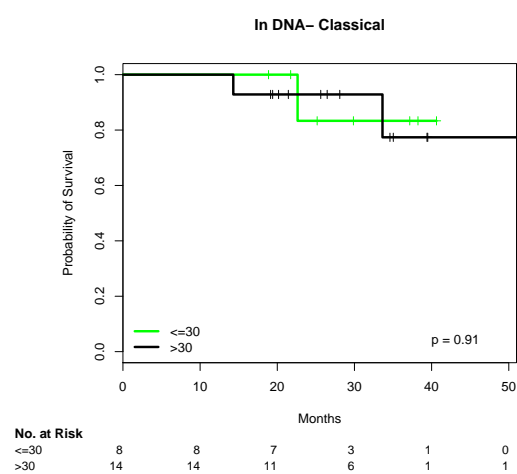
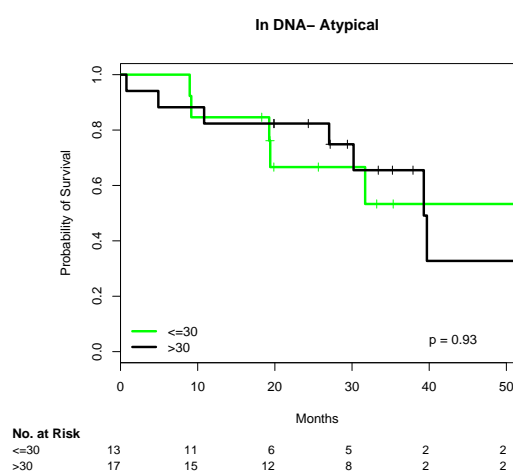
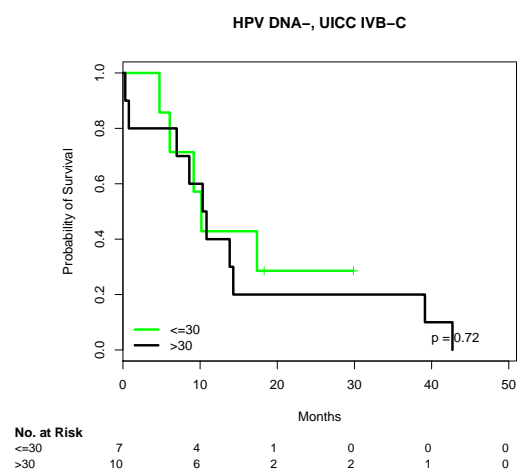
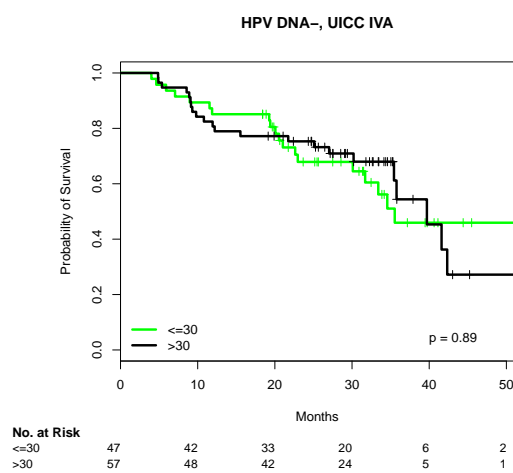
## Concordance= 0.536 (se = 0.029 )
## Rsquare= 0.013 (max possible= 0.967 )
## Likelihood ratio test= 3.37 on 1 df, p=0.0662
## Wald test = 3.34 on 1 df, p=0.0675
## Score (logrank) test = 3.38 on 1 df, p=0.0659
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## 2 observations deleted due to missingness
##
##           split[cur.subset]<=30
##           time      n.risk      n.event      survival      std.err
##           36.0000      42.0000      34.0000      0.6910      0.0473
## lower 95% CI upper 95% CI
##           0.6042      0.7902
##
##           split[cur.subset]>=30
##           time      n.risk      n.event      survival      std.err
##           36.0000      30.0000      41.0000      0.6088      0.0538
## lower 95% CI upper 95% CI
##           0.5119      0.7240
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 188, number of events= 70
## (3 observations deleted due to missingness)
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.286      1.330      0.246 1.16      0.25
##
##           exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30      1.33      0.752      0.821      2.16
##
## Concordance= 0.518 (se = 0.033 )
## Rsquare= 0.007 (max possible= 0.967 )
## Likelihood ratio test= 1.37 on 1 df, p=0.242
## Wald test = 1.35 on 1 df, p=0.246
## Score (logrank) test = 1.36 on 1 df, p=0.244
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])

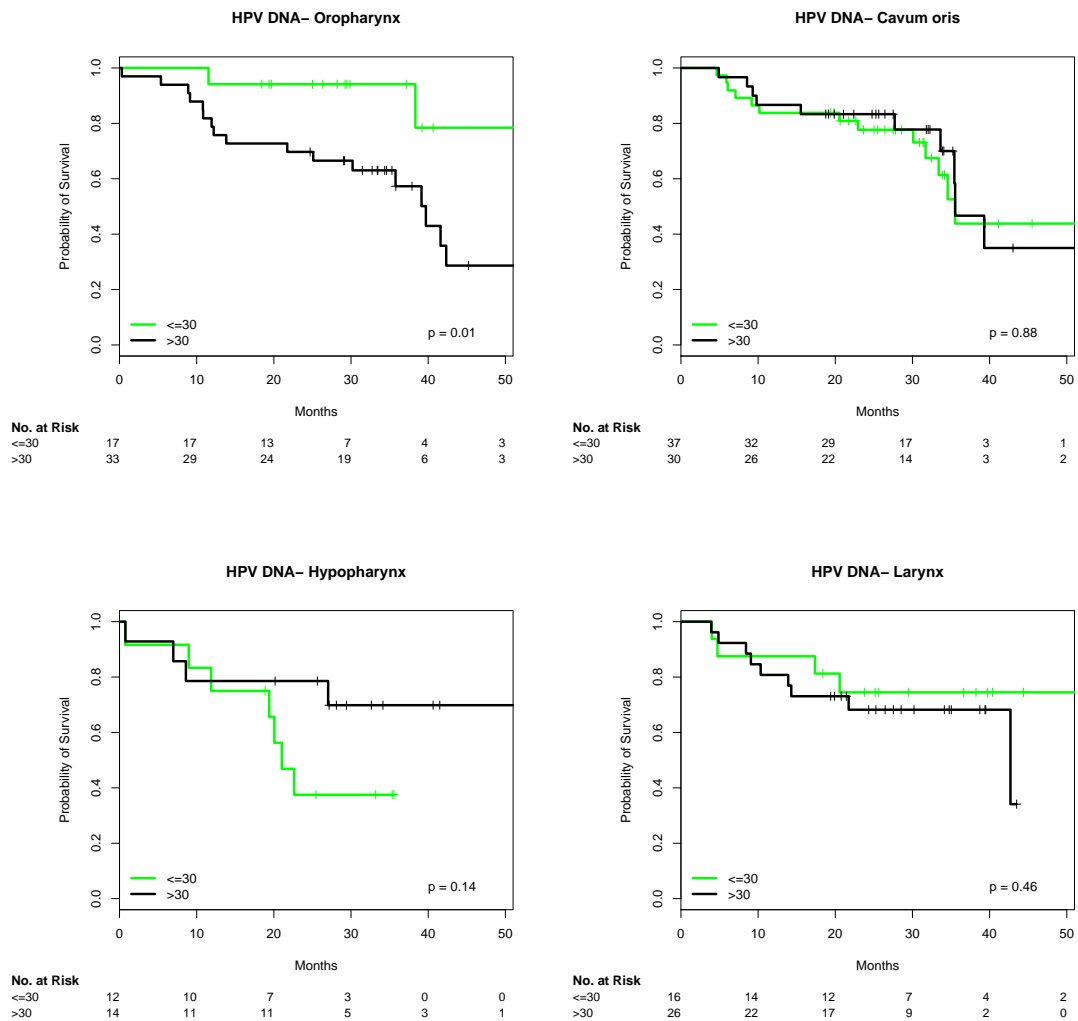
```

```
##
## n= 207, number of events= 74
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)  z Pr(>|z|)
## split[cur.subset]>30 0.285      1.329    0.238 1.2    0.23
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30      1.33      0.752    0.834    2.12
##
## Concordance= 0.516 (se = 0.032 )
## Rsquare= 0.007 (max possible= 0.965 )
## Likelihood ratio test= 1.46 on 1 df,  p=0.227
## Wald test = 1.44 on 1 df,  p=0.231
## Score (logrank) test = 1.45 on 1 df,  p=0.229
##
## 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      25.0000      28.0000      0.6402      0.0596
## lower 95% CI upper 95% CI
##               0.5334      0.7684
##
##               split[cur.subset]>=30
##               time      n.risk      n.event      survival      std.err
##               36.0000      22.0000      35.0000      0.6070      0.0605
## lower 95% CI upper 95% CI
##               0.4993      0.7380
```









3.23 Alcohol consumption

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30  0.0334    1.0339   0.3778  0.09    0.93
## split[cur.subset]31 bis 60  0.3126    1.3670   0.3835  0.82    0.41
## split[cur.subset]>60      0.3777    1.4589   0.3597  1.05    0.29
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30    1.03    0.967    0.493    2.17
## split[cur.subset]31 bis 60    1.37    0.732    0.645    2.90
## split[cur.subset]>60    1.46    0.685    0.721    2.95
```

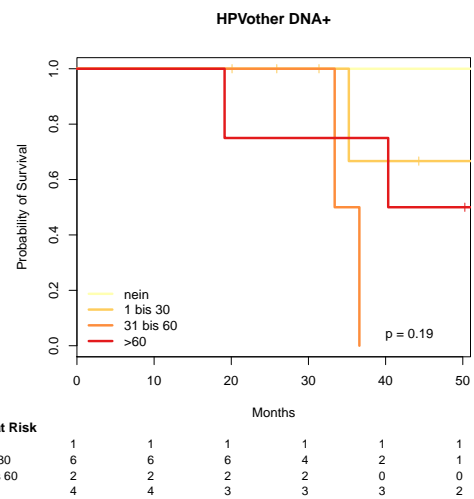
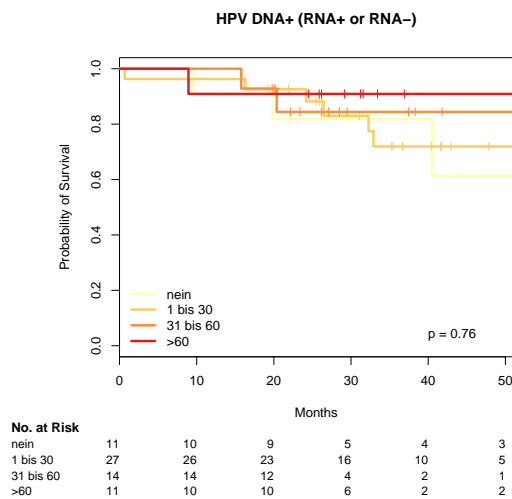
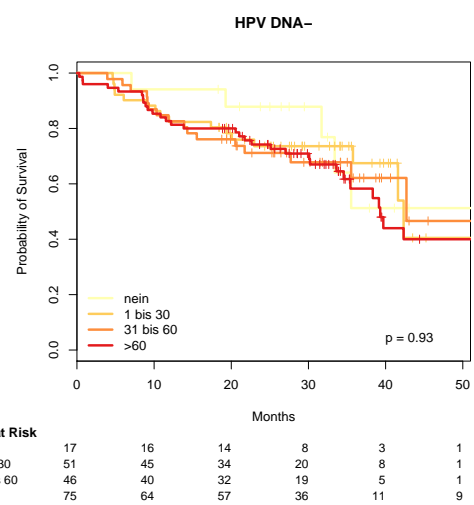
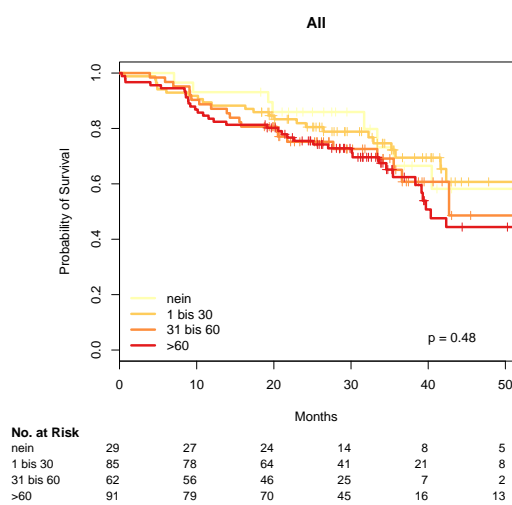
```
##
## Concordance= 0.55 (se = 0.032 )
## Rsquare= 0.009 (max possible= 0.967 )
## Likelihood ratio test= 2.49 on 3 df, p=0.477
## Wald test = 2.44 on 3 df, p=0.486
## Score (logrank) test = 2.46 on 3 df, p=0.482
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## split[cur.subset]=nein
## time n.risk n.event survival std.err
## 36.000 10.000 7.000 0.665 0.111
## lower 95% CI upper 95% CI
## 0.479 0.923
##
## split[cur.subset]=1 bis 30
## time n.risk n.event survival std.err
## 36.0000 25.0000 21.0000 0.6945 0.0603
## lower 95% CI upper 95% CI
## 0.5859 0.8233
##
## split[cur.subset]=31 bis 60
## time n.risk n.event survival std.err
## 36.0000 15.0000 18.0000 0.6507 0.0736
## lower 95% CI upper 95% CI
## 0.5212 0.8122
##
## split[cur.subset]>=60
## time n.risk n.event survival std.err
## 36.0000 23.0000 29.0000 0.6243 0.0602
## lower 95% CI upper 95% CI
## 0.5168 0.7543
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]1 bis 30 -0.0125 0.9876 0.4791 -0.03 0.98
## split[cur.subset]31 bis 60 0.1553 1.1680 0.4752 0.33 0.74
## split[cur.subset]>=60 0.1722 1.1880 0.4468 0.39 0.70
##
```

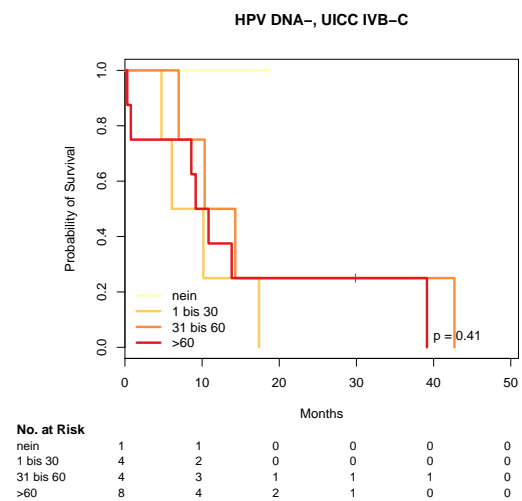
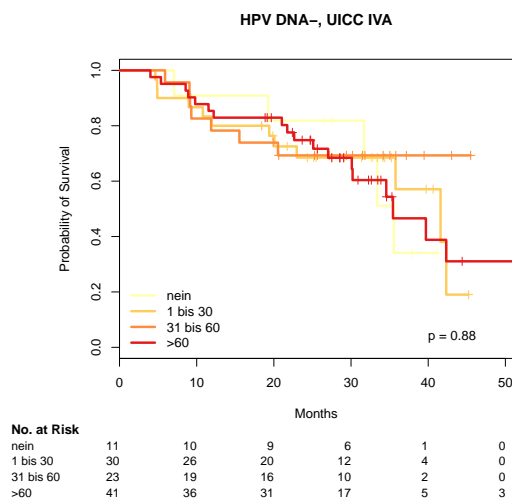
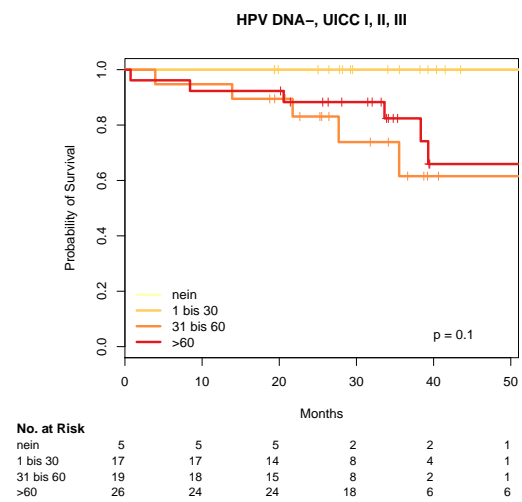
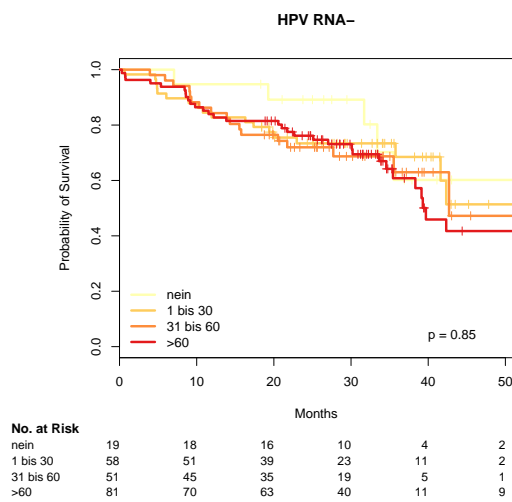
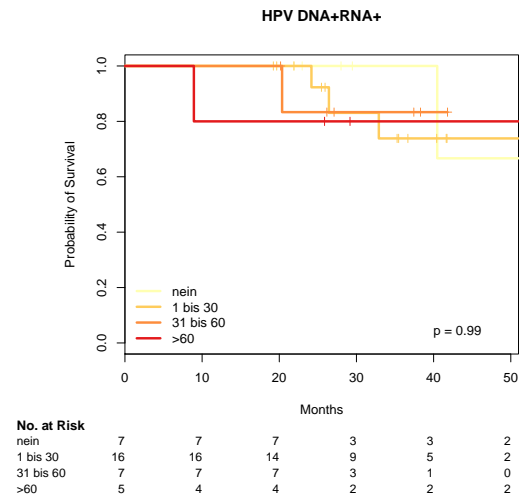
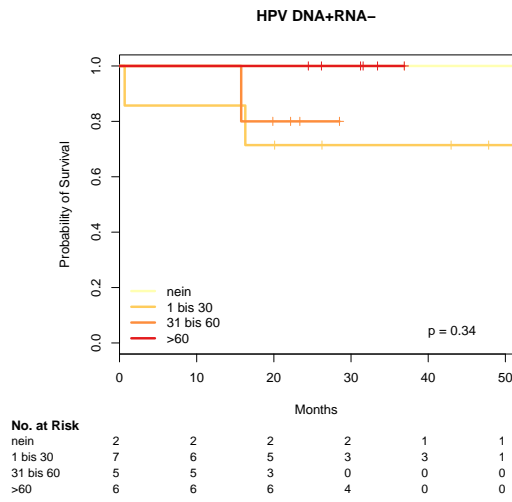
```

##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30      0.988      1.013      0.386      2.53
## split[cur.subset]31 bis 60      1.168      0.856      0.460      2.96
## split[cur.subset]>60           1.188      0.842      0.495      2.85
##
## Concordance= 0.522 (se = 0.036 )
## Rsquare= 0.003 (max possible= 0.968 )
## Likelihood ratio test= 0.47 on 3 df, p=0.925
## Wald test = 0.46 on 3 df, p=0.927
## Score (logrank) test = 0.47 on 3 df, p=0.926
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##                                coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30  0.250      1.284      0.470 0.53      0.60
## split[cur.subset]31 bis 60 0.388      1.474      0.474 0.82      0.41
## split[cur.subset]>60      0.350      1.419      0.445 0.79      0.43
##
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30      1.28      0.779      0.511      3.23
## split[cur.subset]31 bis 60      1.47      0.678      0.582      3.73
## split[cur.subset]>60           1.42      0.705      0.593      3.39
##
## Concordance= 0.529 (se = 0.035 )
## Rsquare= 0.004 (max possible= 0.965 )
## Likelihood ratio test= 0.86 on 3 df, p=0.836
## Wald test = 0.8 on 3 df, p=0.849
## Score (logrank) test = 0.81 on 3 df, p=0.847
##
## 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      6.000      5.000      0.602      0.147
## lower 95% CI upper 95% CI
##                                0.373      0.970
##
##                                split[cur.subset]=1 bis 30
##                                time      n.risk      n.event      survival      std.err
##                                36.0000     14.0000     16.0000     0.6849      0.0727
## lower 95% CI upper 95% CI

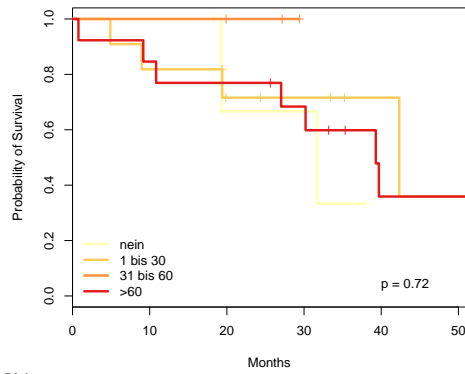
```

```
##      0.5562      0.8434
##
##      split[cur.subset]=31 bis 60
##      time      n.risk      n.event      survival      std.err
##      36.0000      10.0000      16.0000      0.6297      0.0836
## lower 95% CI upper 95% CI
##      0.4854      0.8168
##
##      split[cur.subset]>=60
##      time      n.risk      n.event      survival      std.err
##      36.0000      18.0000      26.0000      0.6080      0.0671
## lower 95% CI upper 95% CI
##      0.4898      0.7547
```





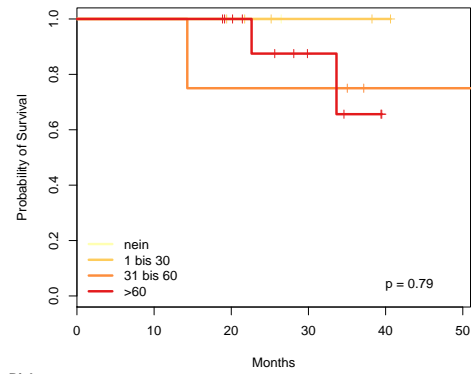
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
nein	4	4	2	2	0	0
1 bis 30	11	9	5	4	2	1
31 bis 60	3	3	2	0	0	0
>60	13	11	10	8	3	3

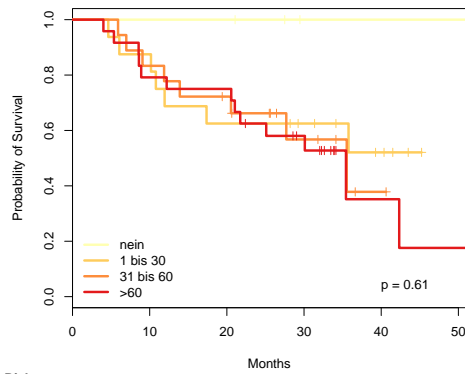
In DNA- Classical



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	3	1	1
>60	12	12	10	4	0	0

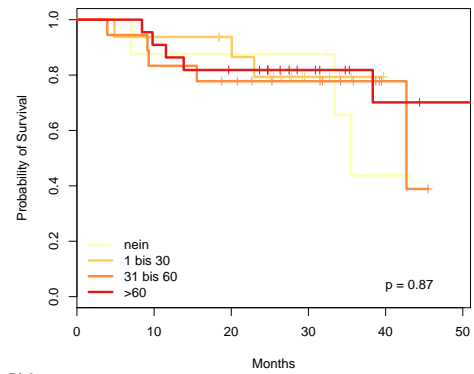
In DNA- Mesenchymal



No. at Risk

	0	10	20	30	40	50
nein	4	4	4	1	1	1
1 bis 30	16	14	10	8	4	0
31 bis 60	18	15	12	6	1	0
>60	24	19	18	11	2	1

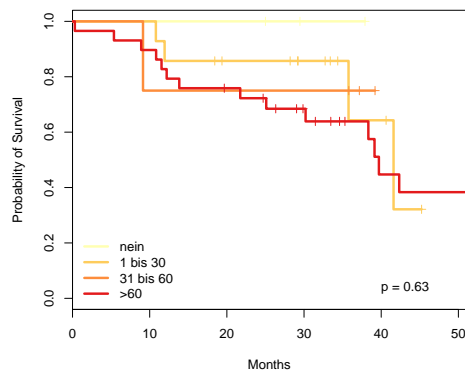
In DNA- Basal



No. at Risk

	0	10	20	30	40	50
nein	8	7	7	5	2	0
1 bis 30	16	15	13	4	0	0
31 bis 60	18	15	13	9	2	0
>60	22	20	17	11	6	5

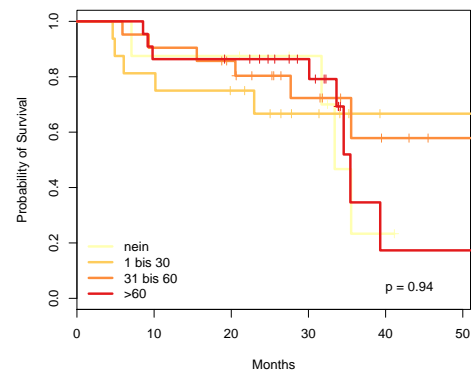
HPV DNA- Oropharynx



No. at Risk

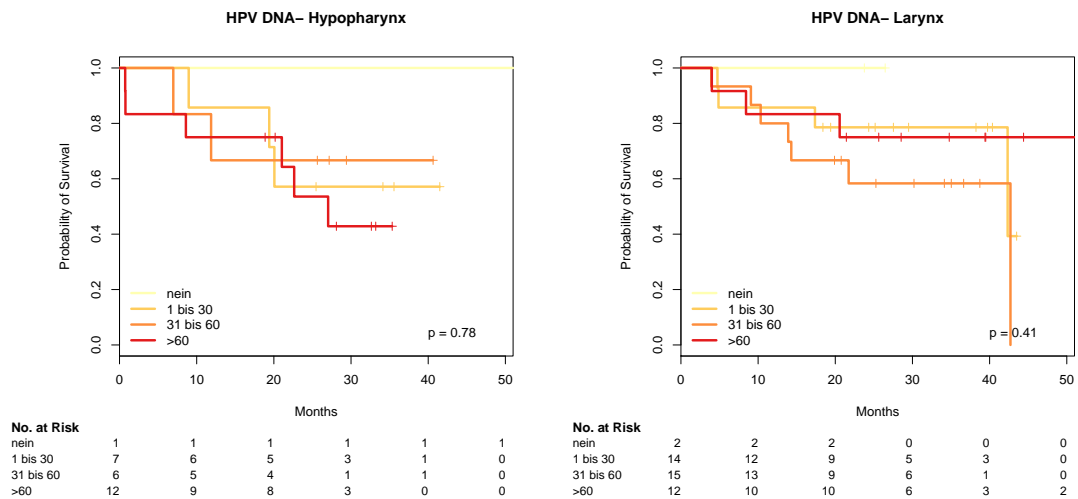
	0	10	20	30	40	50
nein	3	3	3	1	0	0
1 bis 30	14	14	10	7	3	0
31 bis 60	4	3	3	3	0	0
>60	29	26	21	15	7	6

HPV DNA- Cavum oris



No. at Risk

	0	10	20	30	40	50
nein	8	7	7	5	1	0
1 bis 30	16	13	10	5	1	1
31 bis 60	21	19	16	9	3	1
>60	22	19	18	12	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= 93
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.2019   0.8172  0.2590 -0.78   0.44
## split[cur.subset]hypopharynx  0.3822   1.4656  0.3404  1.12   0.26
## split[cur.subset]larynx      -0.0227   0.9776  0.3255 -0.07   0.94
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx  0.817    1.224    0.492    1.36
## split[cur.subset]hypopharynx  1.466    0.682    0.752    2.86
## split[cur.subset]larynx      0.978    1.023    0.516    1.85
##
## Concordance= 0.544 (se = 0.032 )
## Rsquare= 0.011 (max possible= 0.967 )
## Likelihood ratio test= 3.03 on 3 df,  p=0.387
## Wald test               = 3.26 on 3 df,  p=0.353
## Score (logrank) test = 3.32 on 3 df,  p=0.345
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
```

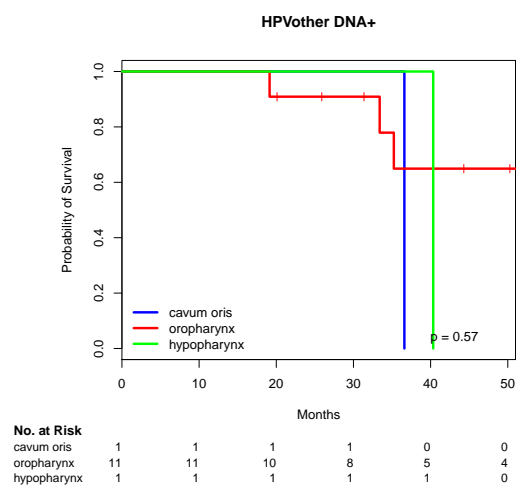
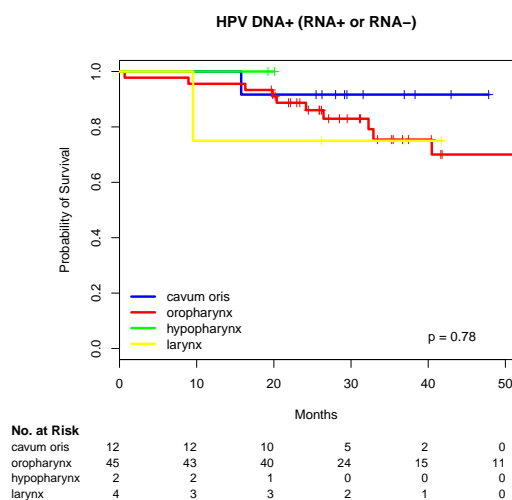
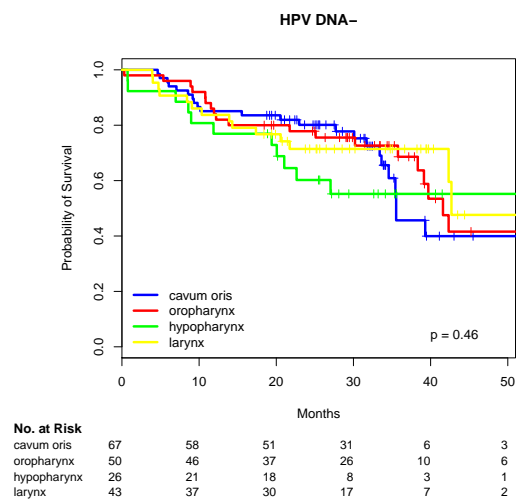
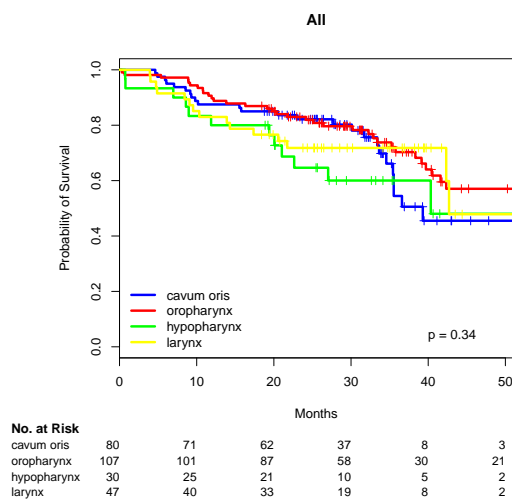
```
##
## 3 observations deleted due to missingness
##           split[cur.subset]=cavum oris
##           time      n.risk      n.event      survival      std.err
##           36.0000      14.0000      23.0000      0.5446      0.0841
## lower 95% CI upper 95% CI
##           0.4024      0.7370
##
##           split[cur.subset]=oropharynx
##           time      n.risk      n.event      survival      std.err
##           36.0000      38.0000      27.0000      0.7029      0.0504
## lower 95% CI upper 95% CI
##           0.6107      0.8091
##
##           split[cur.subset]=hypopharynx
##           time      n.risk      n.event      survival      std.err
##           36.0000      5.0000      11.0000      0.6003      0.0955
## lower 95% CI upper 95% CI
##           0.4395      0.8200
##
##           split[cur.subset]=larynx
##           time      n.risk      n.event      survival      std.err
##           36.0000      15.0000      13.0000      0.7180      0.0666
## lower 95% CI upper 95% CI
##           0.5987      0.8611
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 186, number of events= 70
##      (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.0979   0.9067  0.3053 -0.32   0.75
## split[cur.subset]hypopharynx  0.4184   1.5195  0.3549  1.18   0.24
## split[cur.subset]larynx      -0.1383   0.8708  0.3389 -0.41   0.68
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx   0.907    1.103    0.498    1.65
## split[cur.subset]hypopharynx   1.520    0.658    0.758    3.05
## split[cur.subset]larynx       0.871    1.148    0.448    1.69
##
## Concordance= 0.529 (se = 0.037 )
## Rsquare= 0.012 (max possible= 0.968 )
## Likelihood ratio test= 2.28 on 3 df,  p=0.516
```

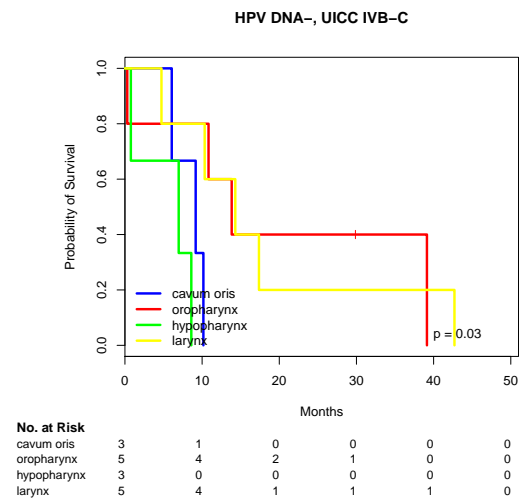
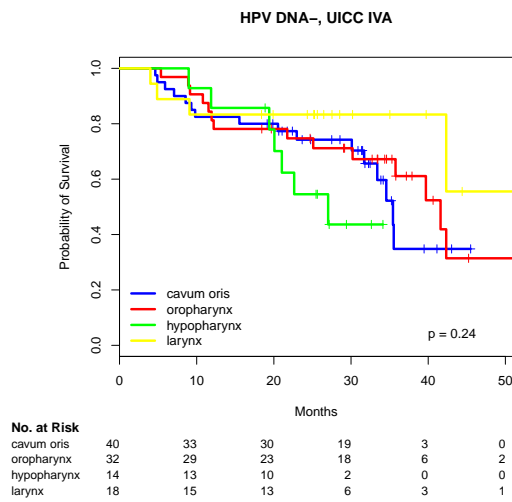
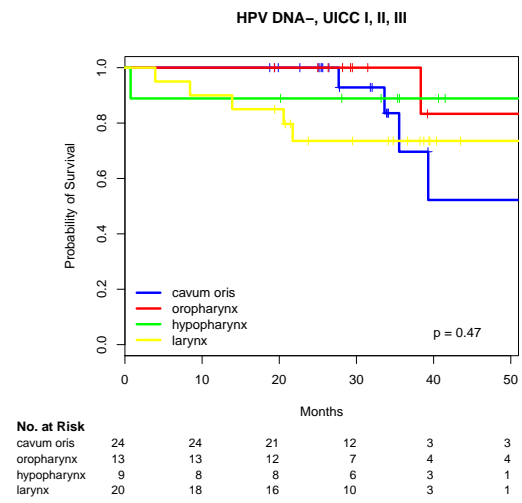
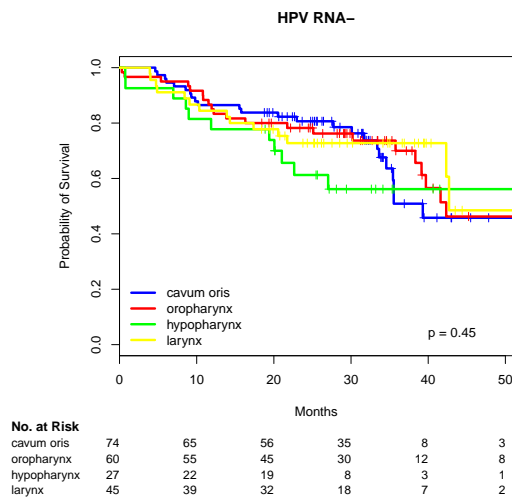
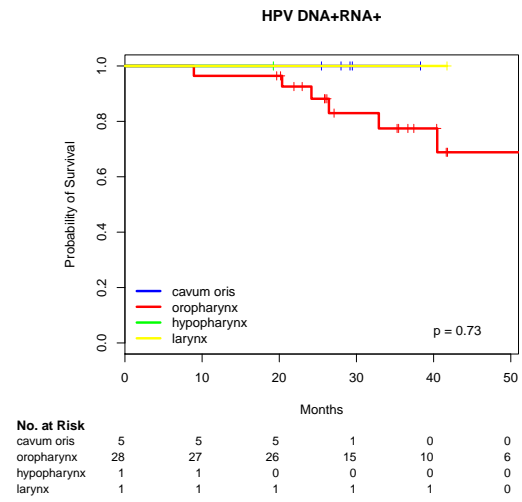
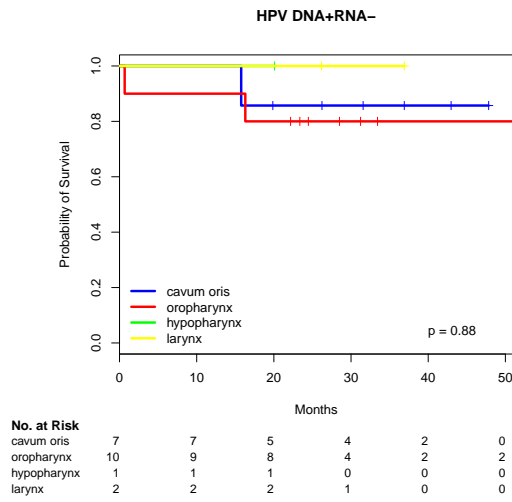
```

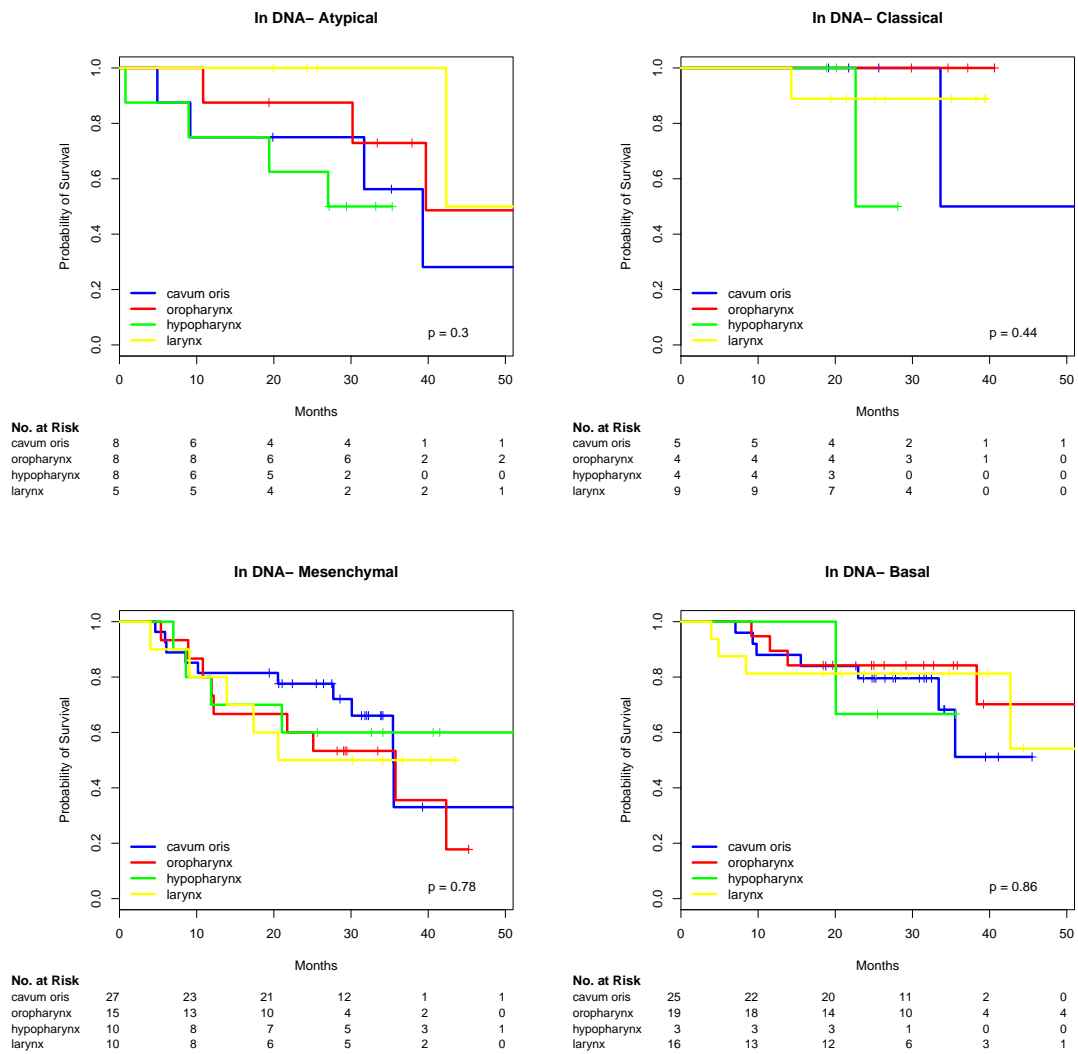
## Wald test          = 2.5  on 3 df,   p=0.475
## Score (logrank) test = 2.55  on 3 df,   p=0.467
##
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 206, number of events= 74
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.0489    0.9523  0.2913 -0.17    0.87
## split[cur.subset]hypopharynx  0.4625    1.5880  0.3523  1.31    0.19
## split[cur.subset]larynx      -0.0994    0.9054  0.3352 -0.30    0.77
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx    0.952      1.05    0.538    1.69
## split[cur.subset]hypopharynx    1.588      0.63    0.796    3.17
## split[cur.subset]larynx        0.905      1.10    0.469    1.75
##
## Concordance= 0.526 (se = 0.036 )
## Rsquare= 0.011 (max possible= 0.965 )
## Likelihood ratio test= 2.34 on 3 df,   p=0.505
## Wald test          = 2.6  on 3 df,   p=0.458
## Score (logrank) test = 2.65 on 3 df,   p=0.449
##
## 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      12.0000      23.0000      0.5089      0.0884
## lower 95% CI upper 95% CI
##               0.3620      0.7153
##
##               split[cur.subset]=oropharynx
##               time      n.risk      n.event      survival      std.err
##               36.0000      18.0000      16.0000      0.6999      0.0669
## lower 95% CI upper 95% CI
##               0.5804      0.8441
##
##               split[cur.subset]=hypopharynx
##               time      n.risk      n.event      survival      std.err
##               36.000      3.000      11.000      0.561      0.101
## lower 95% CI upper 95% CI

```

```
##          0.394          0.800
##
##          split[cur.subset]=larynx
##          time          n.risk          n.event          survival          std.err
##    36.0000          14.0000          12.0000          0.7275          0.0674
## lower 95% CI upper 95% CI
##    0.6067          0.8724
```







3.25 Sex

```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)  z Pr(>|z|)
## split[cur.subset]M 0.111    1.117    0.275 0.4    0.69
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M    1.12    0.895    0.651    1.92
##
## Concordance= 0.519 (se = 0.022 )
## Rsquare= 0.001 (max possible= 0.967 )
## Likelihood ratio test= 0.17 on 1 df,  p=0.683
```

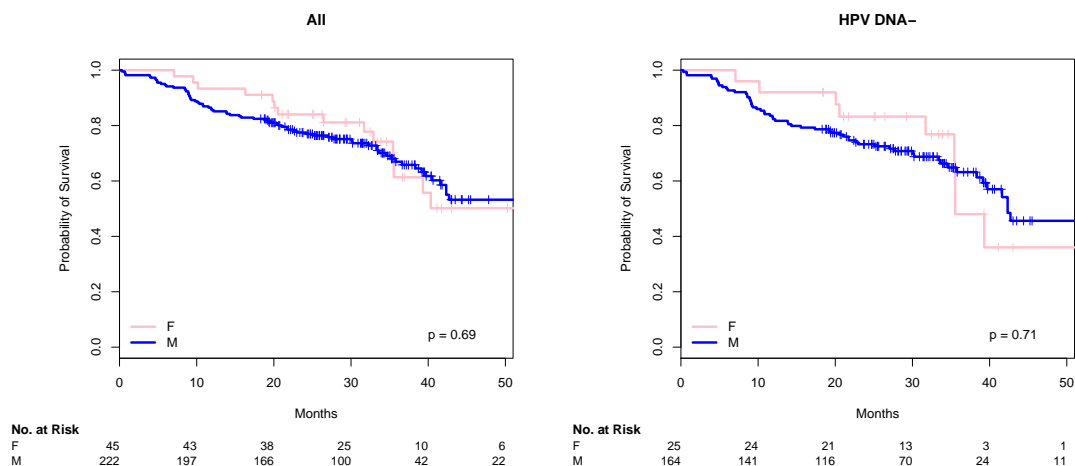


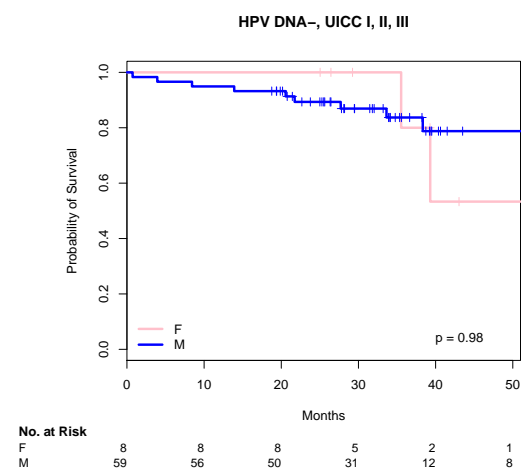
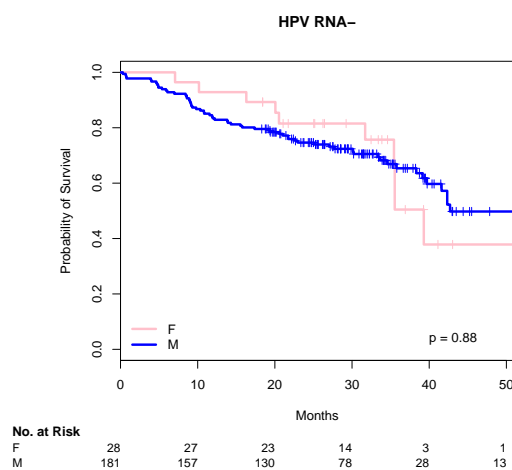
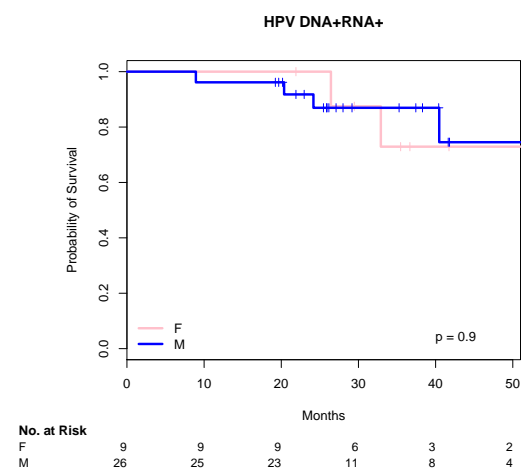
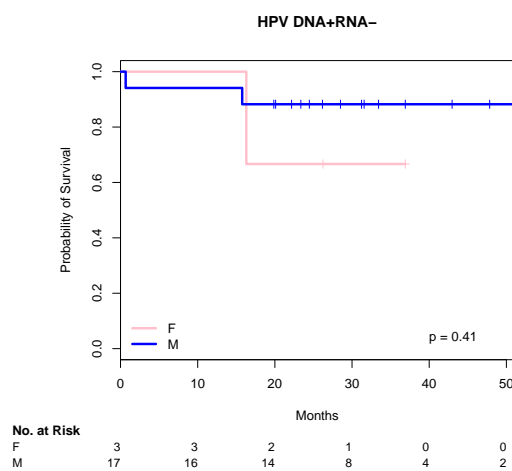
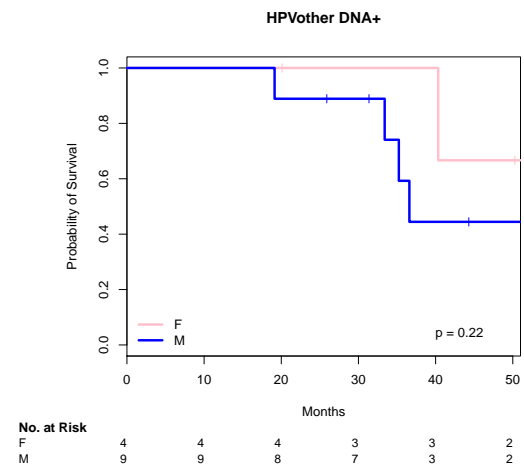
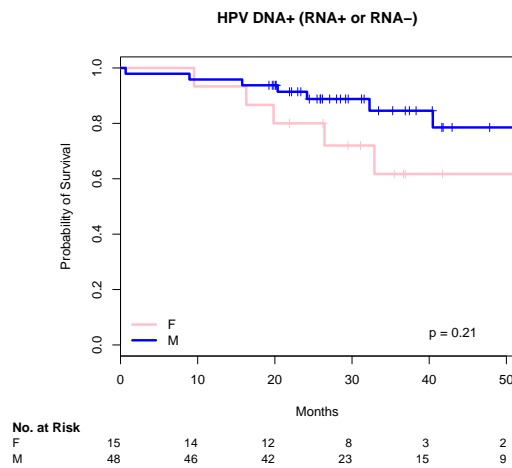
```

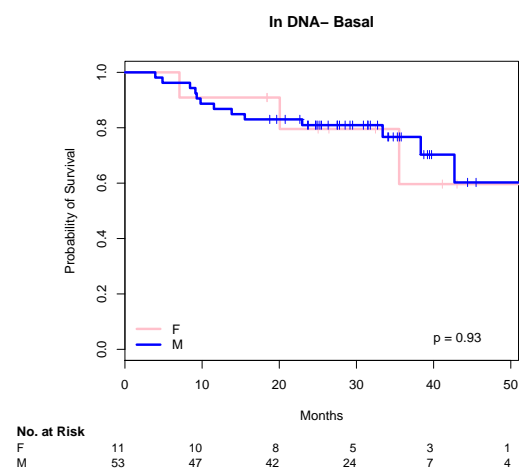
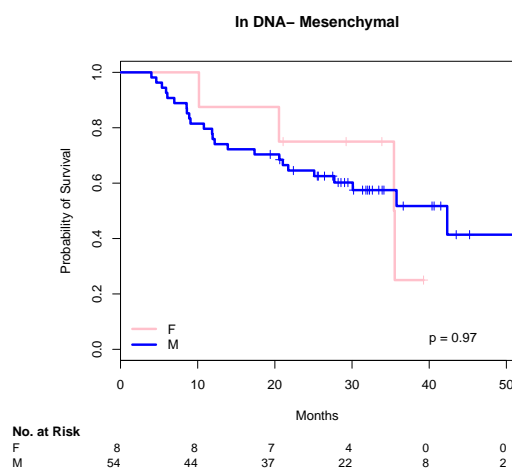
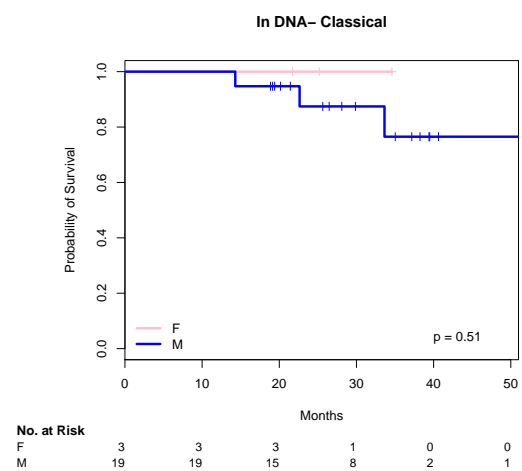
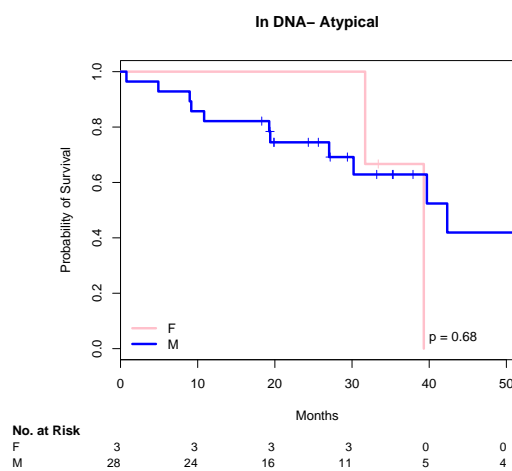
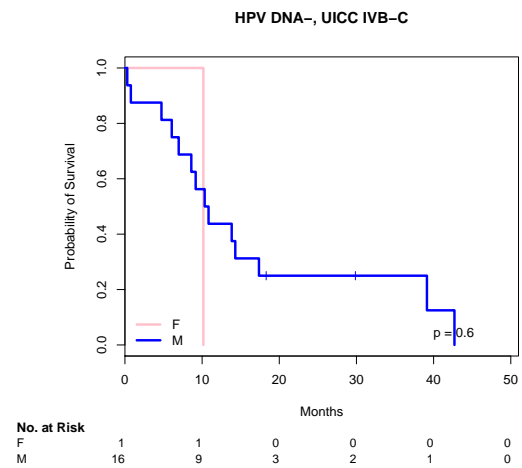
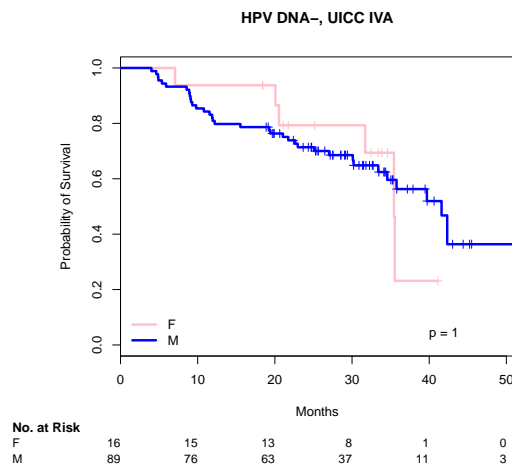
## Wald test          = 0.16  on 1 df,    p=0.687
## Score (logrank) test = 0.16  on 1 df,    p=0.687
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=F
##      time      n.risk      n.event      survival      std.err
## 36.0000      14.0000      13.0000      0.6134      0.0905
## lower 95% CI upper 95% CI
## 0.4594      0.8190
##
##               split[cur.subset]=M
##      time      n.risk      n.event      survival      std.err
## 36.0000      59.0000      62.0000      0.6695      0.0373
## lower 95% CI upper 95% CI
## 0.6003      0.7467
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M 0.133      1.142      0.358 0.37      0.71
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M      1.14      0.875      0.567      2.3
##
## Concordance= 0.522 (se = 0.023 )
## Rsquare= 0.001 (max possible= 0.968 )
## Likelihood ratio test= 0.14  on 1 df,    p=0.705
## Wald test          = 0.14  on 1 df,    p=0.71
## Score (logrank) test = 0.14  on 1 df,    p=0.71
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)

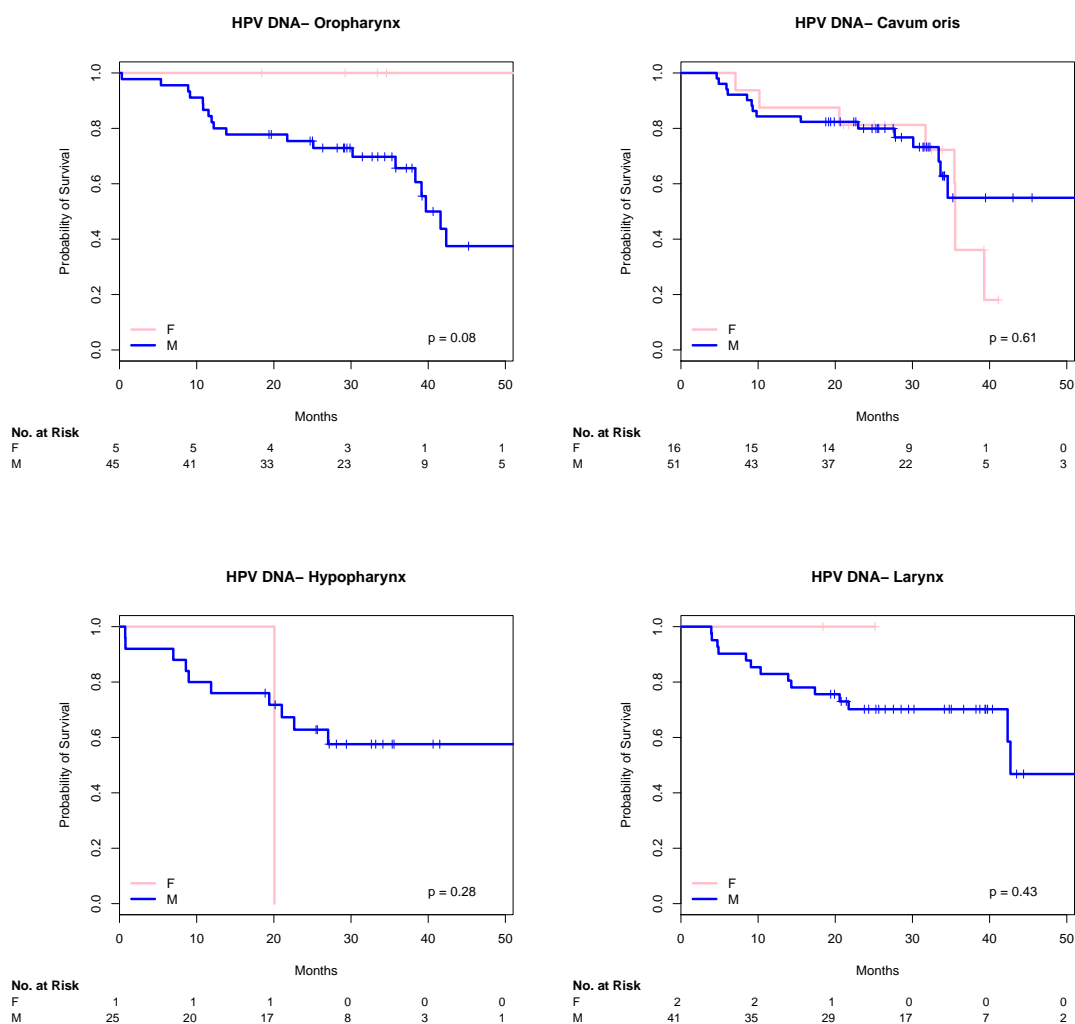
```

```
## split[cur.subset]M 0.0479    1.0490    0.3404 0.14    0.89
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M      1.05      0.953    0.538    2.04
##
## Concordance= 0.517  (se = 0.023 )
## Rsquare= 0      (max possible= 0.965 )
## Likelihood ratio test= 0.02  on 1 df,   p=0.887
## Wald test          = 0.02  on 1 df,   p=0.888
## Score (logrank) test = 0.02  on 1 df,   p=0.888
##
## 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      9.000      0.505      0.133
## lower 95% CI upper 95% CI
## 0.301      0.846
##
##                      split[cur.subset]=M
##      time      n.risk      n.event      survival      std.err
## 36.0000     42.0000     54.0000     0.6535      0.0417
## lower 95% CI upper 95% CI
## 0.5768      0.7405
```









3.26 Age, cut at 60

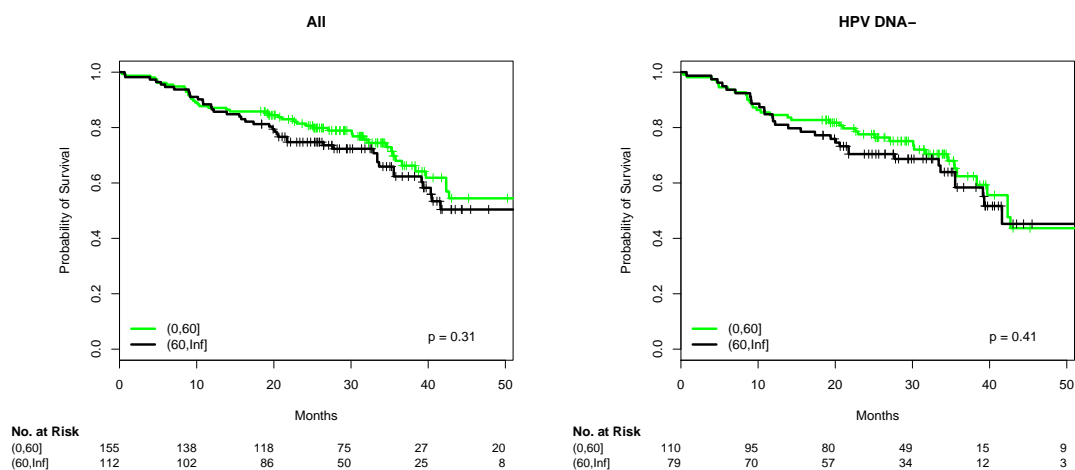
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset](60,Inf) 0.210    1.234    0.207 1.02    0.31
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf)    1.23    0.81    0.823    1.85
##
## Concordance= 0.529 (se = 0.029 )
## Rsquare= 0.004 (max possible= 0.967 )
## Likelihood ratio test= 1.03 on 1 df,  p=0.311
```

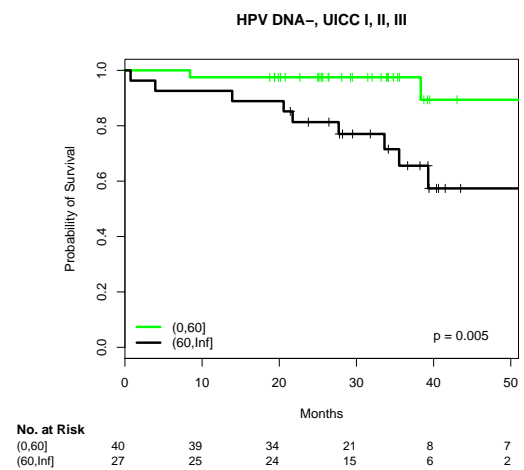
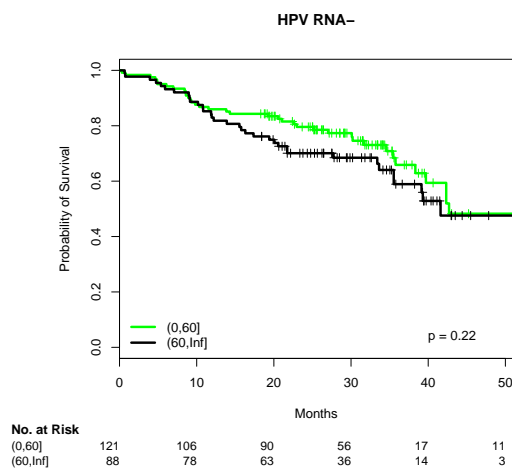
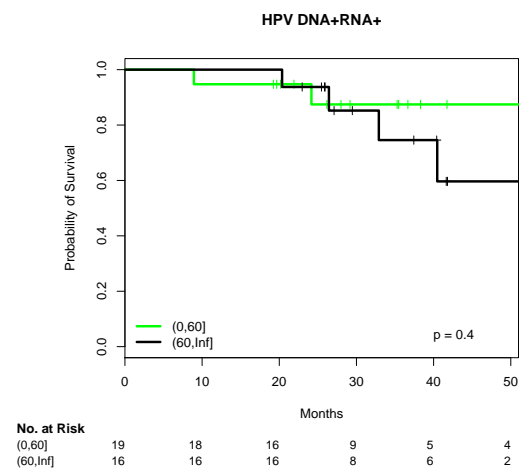
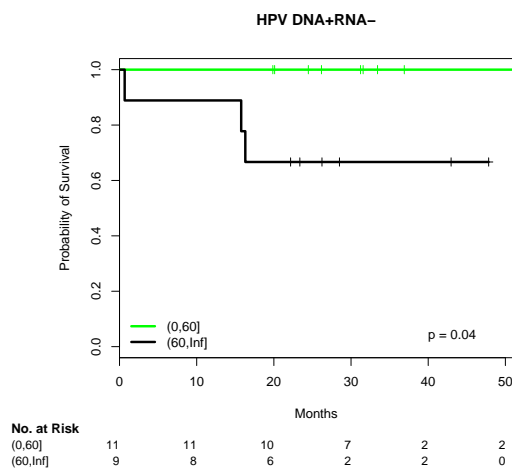
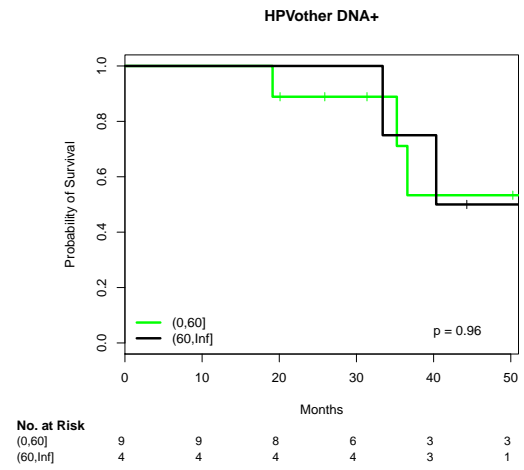
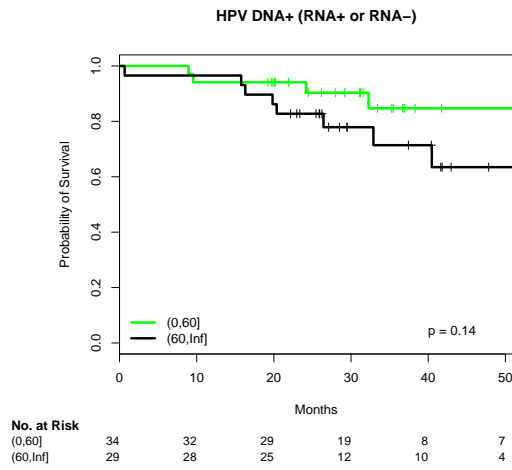
```

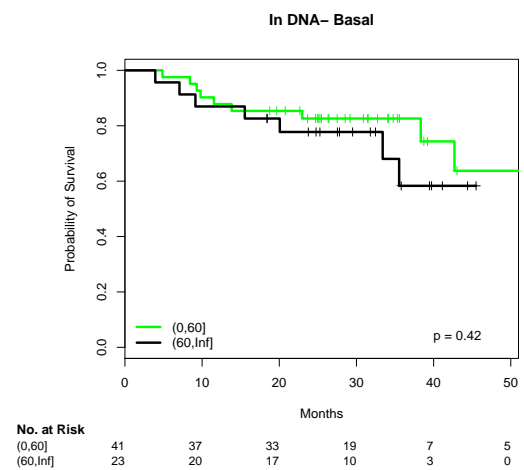
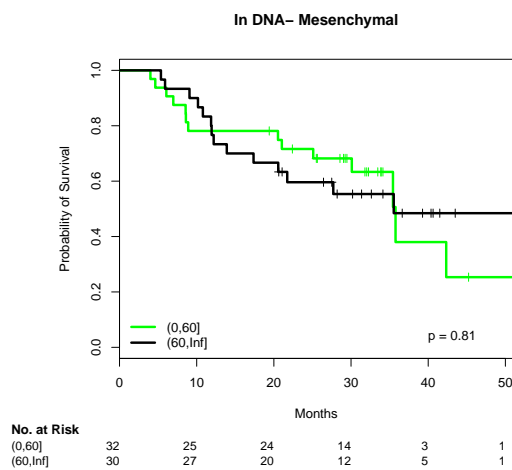
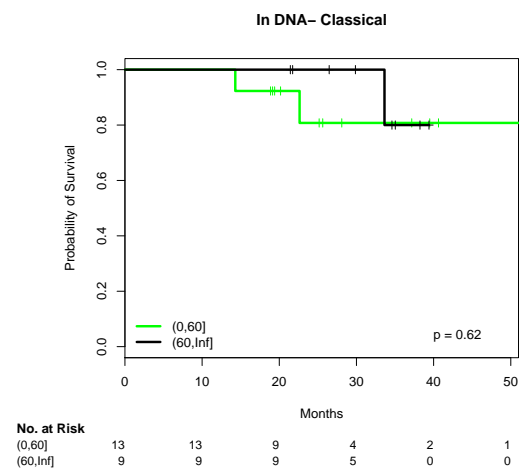
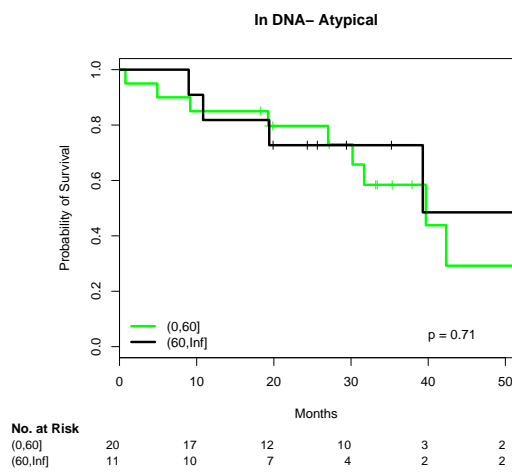
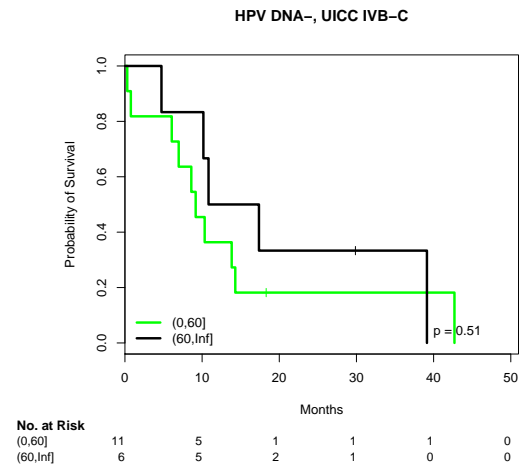
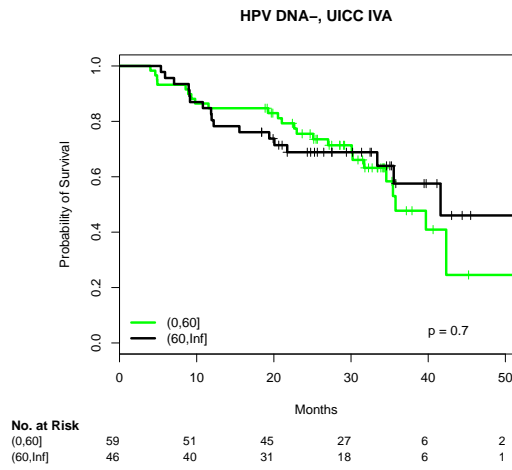
## Wald test          = 1.03  on 1 df,    p=0.31
## Score (logrank) test = 1.04  on 1 df,    p=0.309
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=(0,60]
##      time      n.risk      n.event      survival      std.err
## 36.0000      39.0000      39.0000      0.6798      0.0471
## lower 95% CI upper 95% CI
## 0.5936      0.7786
##
##               split[cur.subset]=(60,Inf]
##      time      n.risk      n.event      survival      std.err
## 36.0000      34.0000      36.0000      0.6235      0.0533
## lower 95% CI upper 95% CI
## 0.5273      0.7372
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](60,Inf] 0.197      1.217      0.239 0.82      0.41
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf]      1.22      0.822      0.763      1.94
##
## Concordance= 0.525 (se = 0.033 )
## Rsquare= 0.004 (max possible= 0.968 )
## Likelihood ratio test= 0.68  on 1 df,    p=0.411
## Wald test          = 0.68  on 1 df,    p=0.41
## Score (logrank) test = 0.68  on 1 df,    p=0.409
##
## #####
## Cox model in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)

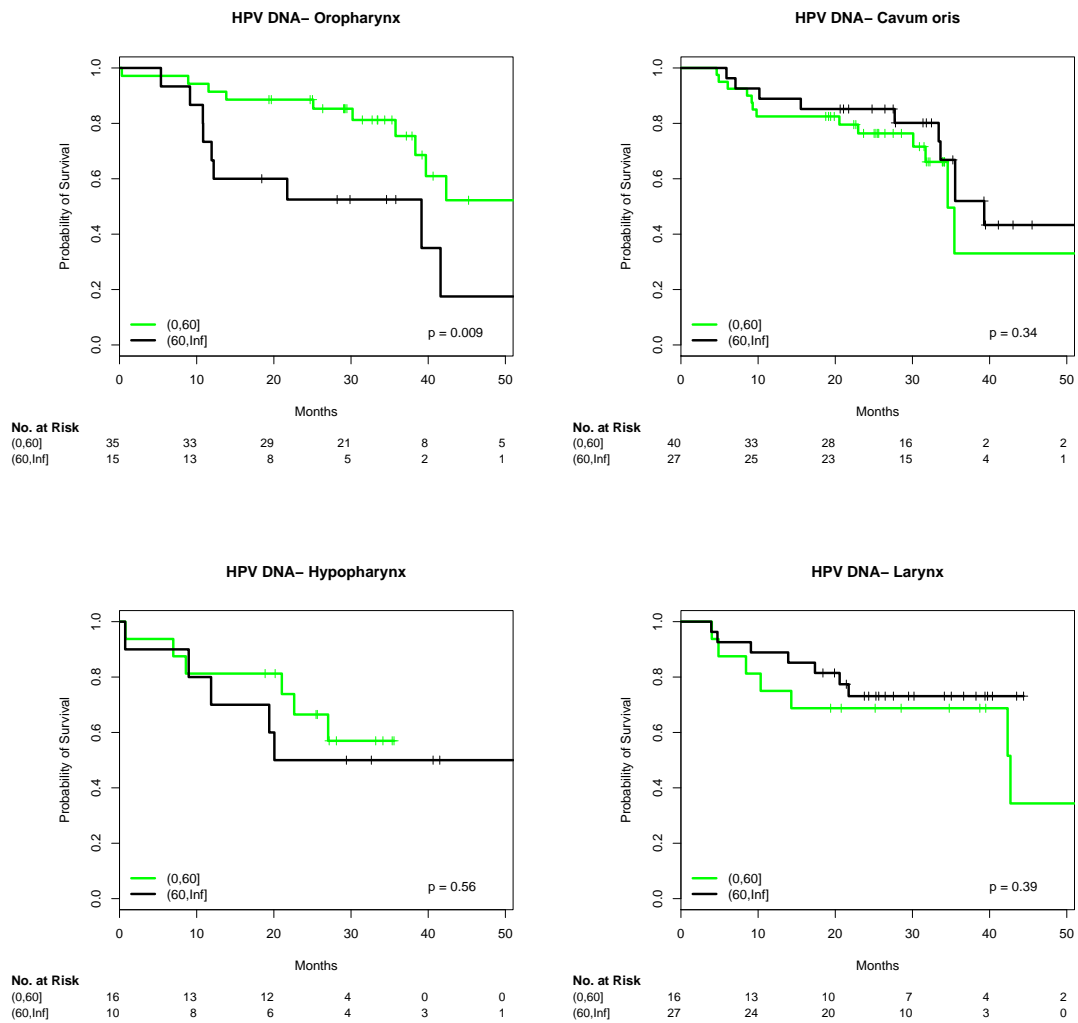
```

```
## split[cur.subset](60,Inf] 0.283      1.327      0.232 1.22      0.22
##
##                               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf]      1.33      0.754      0.842      2.09
##
## Concordance= 0.54 (se = 0.032 )
## Rsquare= 0.007 (max possible= 0.965 )
## Likelihood ratio test= 1.48 on 1 df,  p=0.224
## Wald test               = 1.49 on 1 df,  p=0.223
## Score (logrank) test = 1.5 on 1 df,  p=0.221
##
## 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    26.0000    32.0000      0.6587      0.0563
## lower 95% CI upper 95% CI
## 0.5571      0.7788
##
##               split[cur.subset]=(60,Inf]
##      time      n.risk      n.event      survival      std.err
## 36.0000    22.0000    31.0000      0.5891      0.0623
## lower 95% CI upper 95% CI
## 0.4788      0.7249
```









3.27 Age, cut at 50, 70

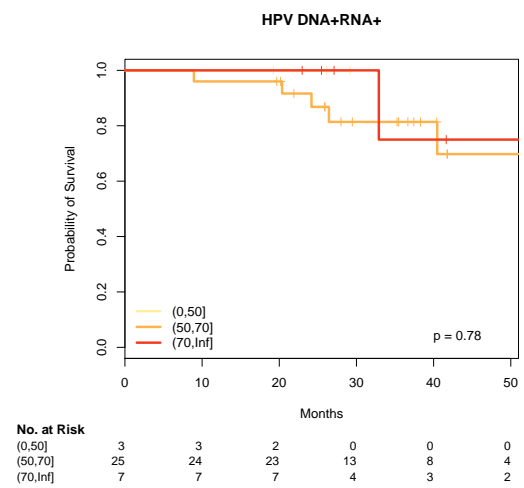
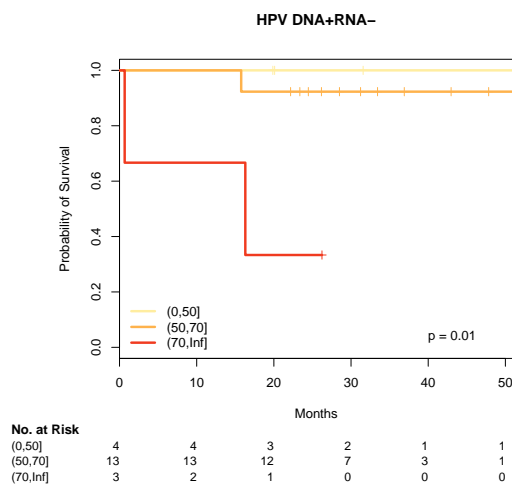
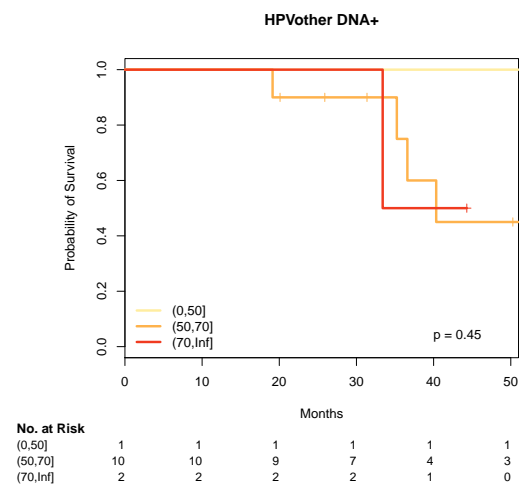
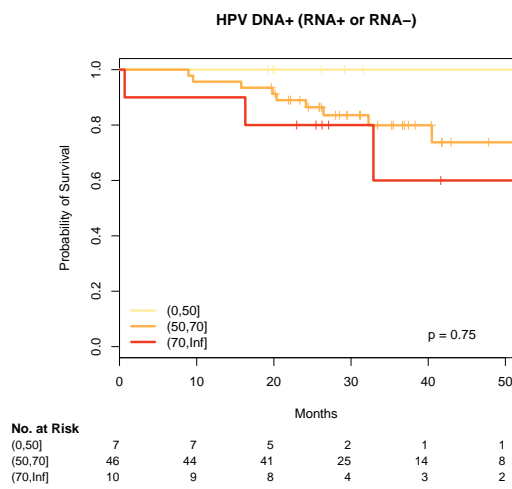
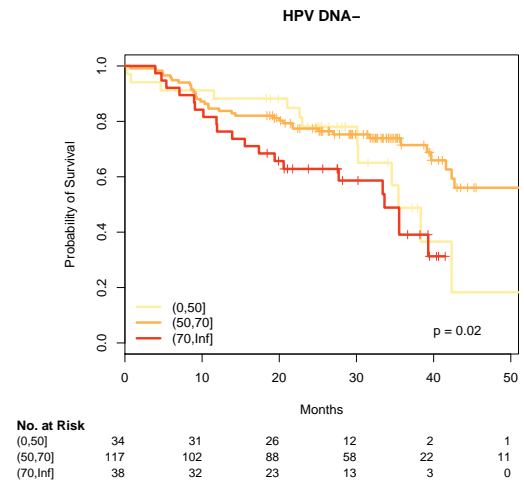
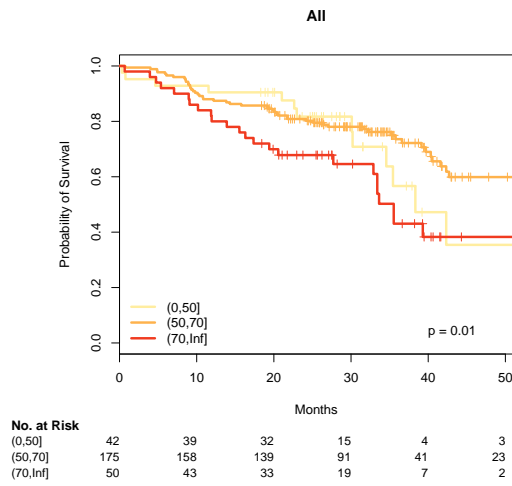
```
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 267, number of events= 94
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70) -0.356    0.700   0.294 -1.21   0.23
## split[cur.subset](70,Inf)  0.344    1.411   0.330  1.04   0.30
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70)    0.70    1.428    0.394    1.25
## split[cur.subset](70,Inf)    1.41    0.709    0.739    2.69
##
## Concordance= 0.56 (se = 0.028 )
```

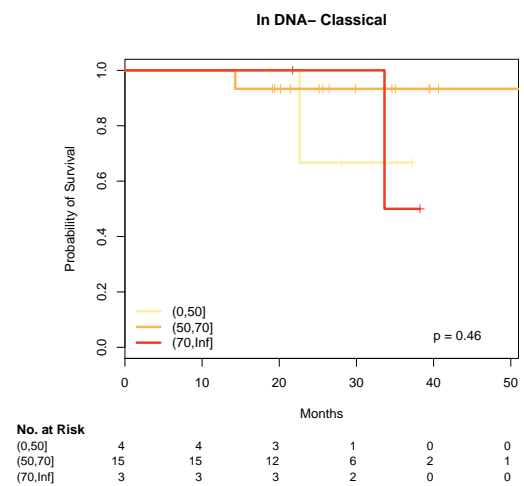
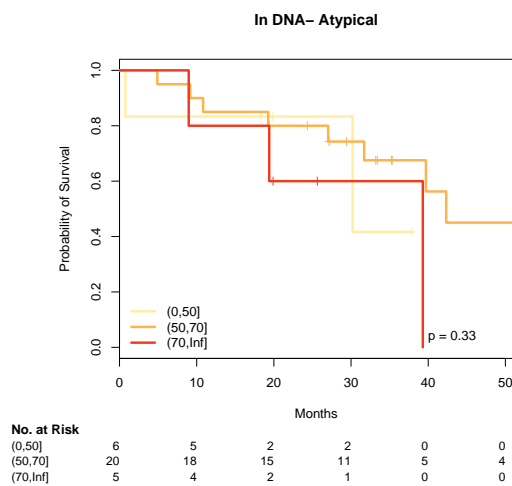
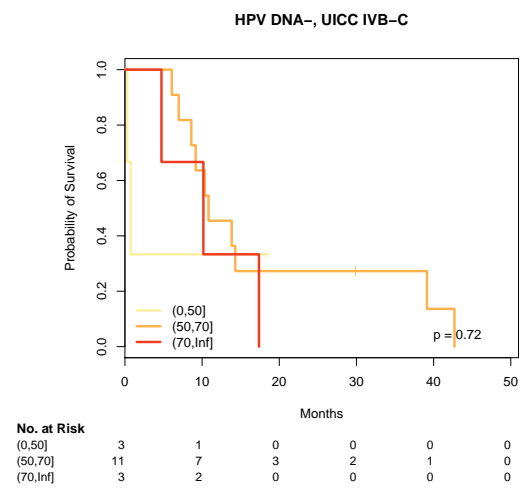
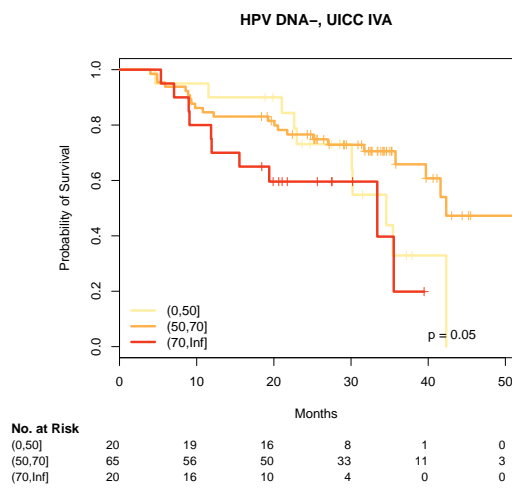
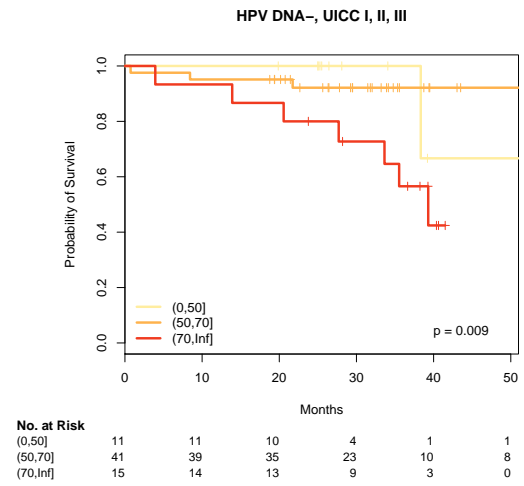
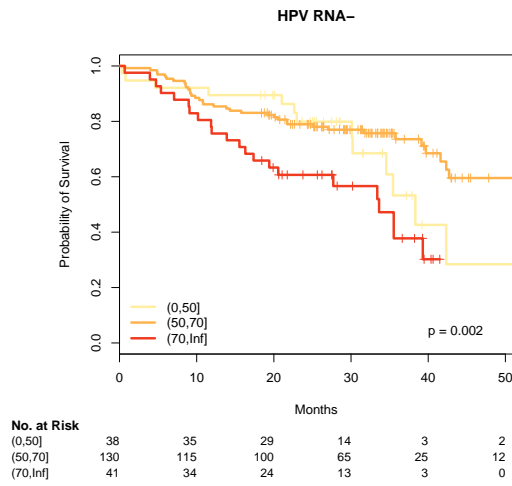
```

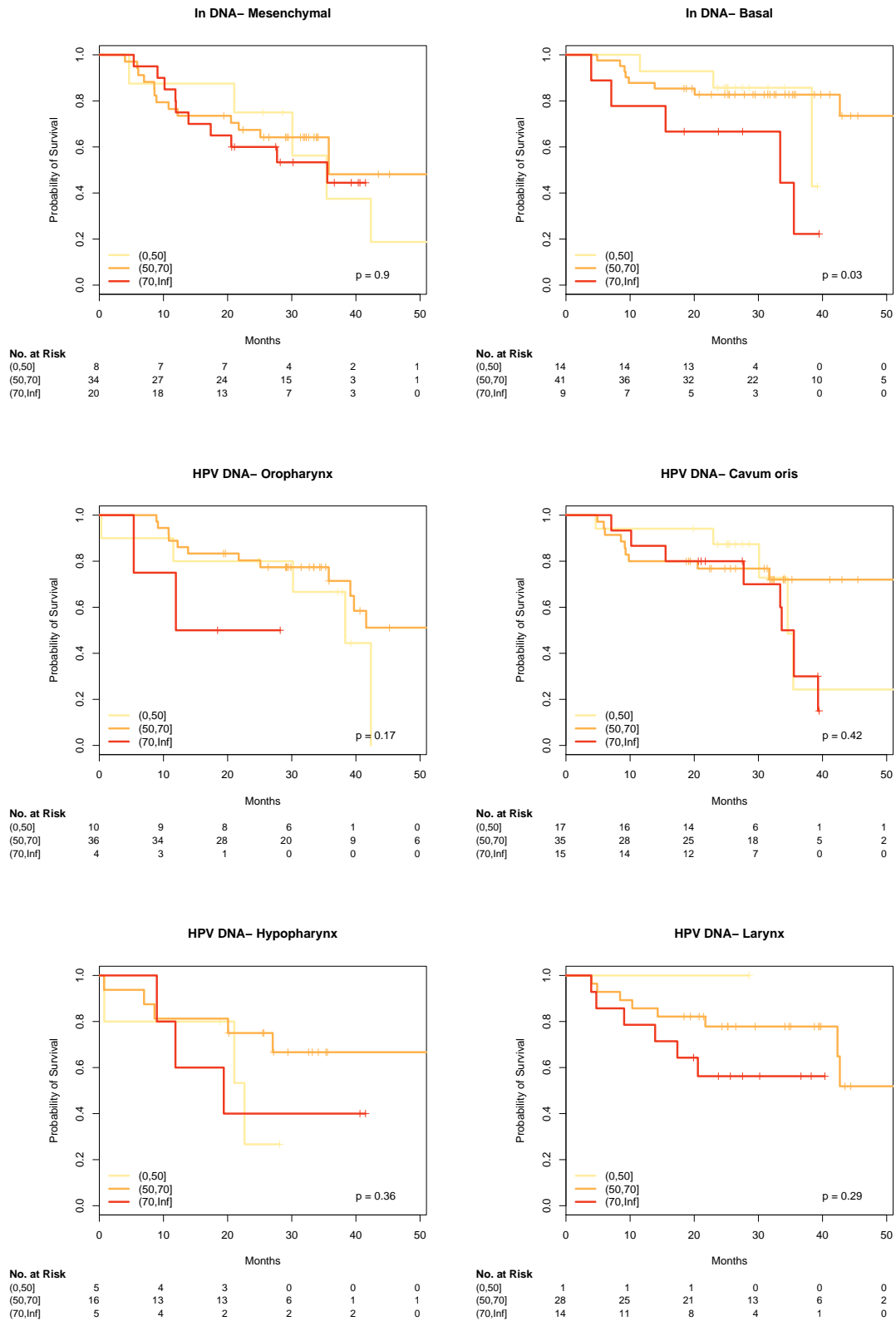
## Rsquare= 0.028 (max possible= 0.967 )
## Likelihood ratio test= 7.64 on 2 df, p=0.0219
## Wald test = 8.22 on 2 df, p=0.0164
## Score (logrank) test = 8.5 on 2 df, p=0.0143
##
## 3-Year survival rates:
## Call: survfit(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##               split[cur.subset]=(0,50]
##      time      n.risk      n.event      survival      std.err
##    36.000      8.000     11.000      0.567      0.115
## lower 95% CI upper 95% CI
##    0.381      0.844
##
##               split[cur.subset]=(50,70]
##      time      n.risk      n.event      survival      std.err
##   36.0000     53.0000     41.0000     0.7358      0.0374
## lower 95% CI upper 95% CI
##    0.6659      0.8129
##
##               split[cur.subset]=(70,Inf]
##      time      n.risk      n.event      survival      std.err
##   36.0000     12.0000     23.0000     0.4306      0.0858
## lower 95% CI upper 95% CI
##    0.2914      0.6364
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 189, number of events= 71
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70] -0.343   0.710   0.325 -1.05   0.29
## split[cur.subset](70,Inf]  0.453   1.572   0.359  1.26   0.21
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70]    0.71    1.409    0.375    1.34
## split[cur.subset](70,Inf]    1.57    0.636    0.777    3.18
##
## Concordance= 0.563 (se = 0.033 )
## Rsquare= 0.038 (max possible= 0.968 )
## Likelihood ratio test= 7.35 on 2 df, p=0.0254
## Wald test = 7.88 on 2 df, p=0.0194
## Score (logrank) test = 8.23 on 2 df, p=0.0163

```

```
##
##
## #####
## Cox modell in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 209, number of events= 75
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70) -0.383    0.682    0.314 -1.22    0.223
## split[cur.subset](70,Inf)  0.573    1.773    0.345  1.66    0.097 .
## ---
## 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)    0.682    1.466    0.369    1.26
## split[cur.subset](70,Inf)    1.773    0.564    0.902    3.49
##
## Concordance= 0.576 (se = 0.032 )
## Rsquare= 0.052 (max possible= 0.965 )
## Likelihood ratio test= 11.1 on 2 df,  p=0.00389
## Wald test = 12.1 on 2 df,  p=0.0024
## Score (logrank) test = 12.8 on 2 df,  p=0.00162
##
## 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      7.000      11.000      0.533      0.120
## lower 95% CI upper 95% CI
## 0.342      0.829
##
##               split[cur.subset]=(50,70]
##      time      n.risk      n.event      survival      std.err
## 36.0000     33.0000     31.0000     0.7356      0.0436
## lower 95% CI upper 95% CI
## 0.6549      0.8263
##
##               split[cur.subset]=(70,Inf]
##      time      n.risk      n.event      survival      std.err
## 36.0000      8.0000     21.0000     0.3776      0.0943
## lower 95% CI upper 95% CI
## 0.2314      0.6161
```







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= 93
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.8642    0.4214  0.4799 -1.80  0.072 .
## split[cur.subset]3  0.2136    1.2381  0.4643  0.46  0.645
## split[cur.subset]4 -0.3126    0.7315  0.5202 -0.60  0.548
## split[cur.subset]5 -0.4555    0.6341  0.4123 -1.10  0.269
## split[cur.subset]6  0.0483    1.0494  0.4937  0.10  0.922
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.421      2.373      0.165      1.08
## split[cur.subset]3      1.238      0.808      0.498      3.08
## split[cur.subset]4      0.732      1.367      0.264      2.03
## split[cur.subset]5      0.634      1.577      0.283      1.42
## split[cur.subset]6      1.049      0.953      0.399      2.76
##
## Concordance= 0.573 (se = 0.032 )
## Rsquare= 0.037 (max possible= 0.967 )
## Likelihood ratio test= 9.92 on 5 df, p=0.0775
## Wald test = 10.1 on 5 df, p=0.0729
## Score (logrank) test = 10.6 on 5 df, p=0.0609
##
## 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
##               36.000      3.000      5.000      0.479      0.186
## lower 95% CI upper 95% CI
##               0.224      1.000
##
##               split[cur.subset]=2
##               time      n.risk      n.event      survival      std.err
##               36.0000     18.0000      9.0000      0.8137      0.0566
## lower 95% CI upper 95% CI
##               0.7100      0.9325
##
##               split[cur.subset]=3
##               time      n.risk      n.event      survival      std.err
```



```

##      36.000      6.000      14.000      0.375      0.112
## lower 95% CI upper 95% CI
##      0.209      0.674
##
##              split[cur.subset]=4
##      time      n.risk      n.event      survival      std.err
##      36.000      5.000      6.000      0.606      0.145
## lower 95% CI upper 95% CI
##      0.379      0.970
##
##              split[cur.subset]=5
##      time      n.risk      n.event      survival      std.err
##      36.0000      34.0000      32.0000      0.7006      0.0477
## lower 95% CI upper 95% CI
##      0.6131      0.8006
##
##              split[cur.subset]=6
##      time      n.risk      n.event      survival      std.err
##      36.000      6.000      9.000      0.499      0.130
## lower 95% CI upper 95% CI
##      0.299      0.832
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 188, number of events= 70
##      (3 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.329      0.720      0.580 -0.57      0.57
## split[cur.subset]3  0.446      1.562      0.517  0.86      0.39
## split[cur.subset]4 -0.234      0.792      0.563 -0.42      0.68
## split[cur.subset]5 -0.501      0.606      0.454 -1.10      0.27
## split[cur.subset]6  0.198      1.219      0.519  0.38      0.70
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.720      1.39      0.231      2.24
## split[cur.subset]3      1.562      0.64      0.567      4.31
## split[cur.subset]4      0.792      1.26      0.263      2.39
## split[cur.subset]5      0.606      1.65      0.249      1.48
## split[cur.subset]6      1.219      0.82      0.441      3.37
##
## Concordance= 0.571 (se = 0.035 )
## Rsquare= 0.04 (max possible= 0.967 )
## Likelihood ratio test= 7.75 on 5 df, p=0.171

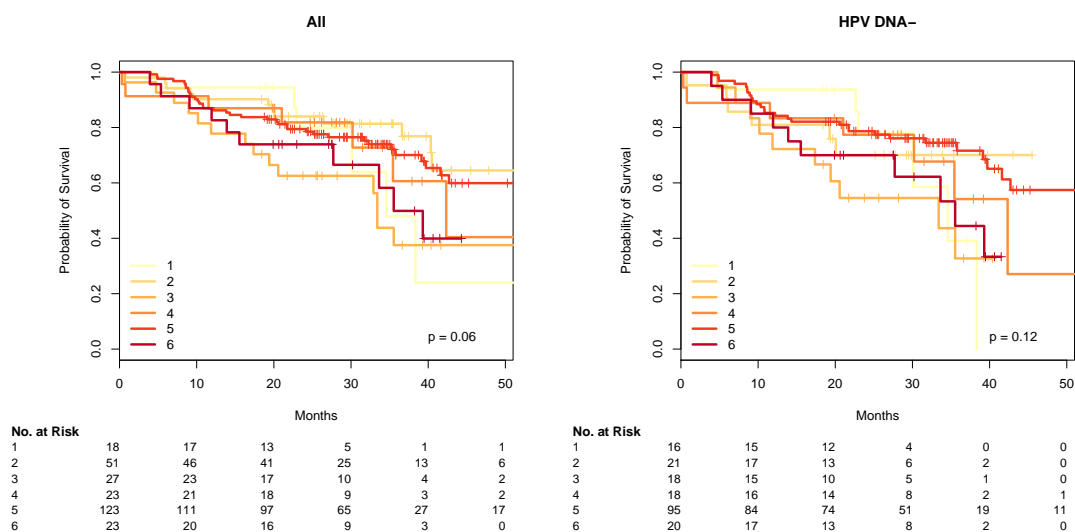
```

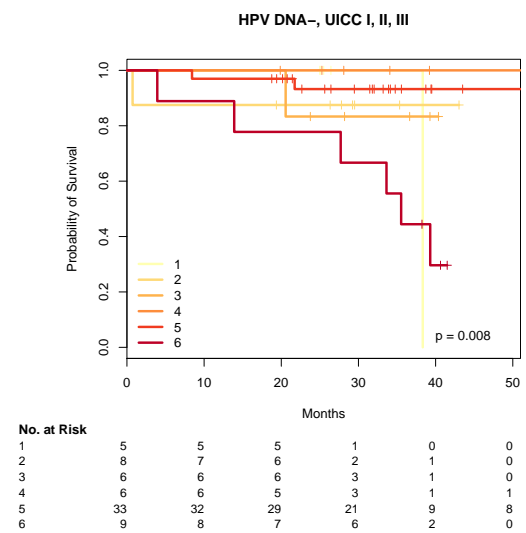
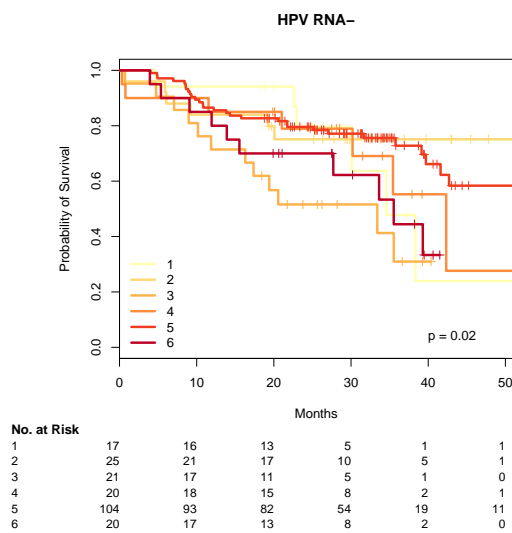
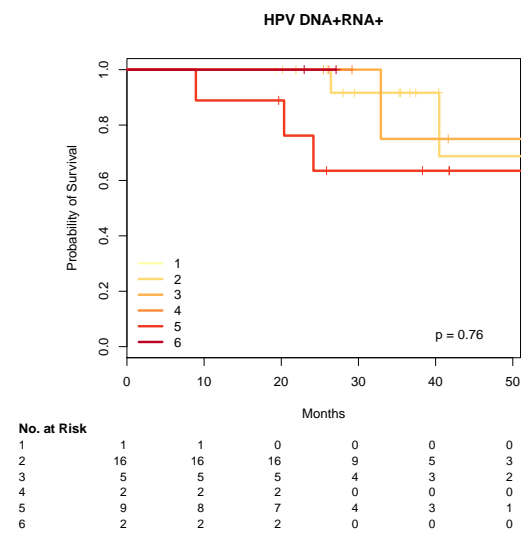
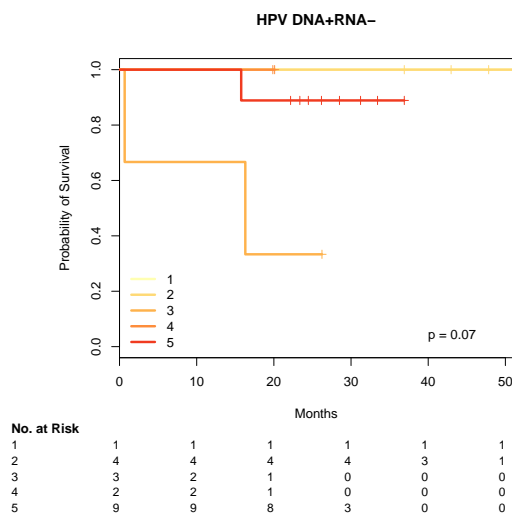
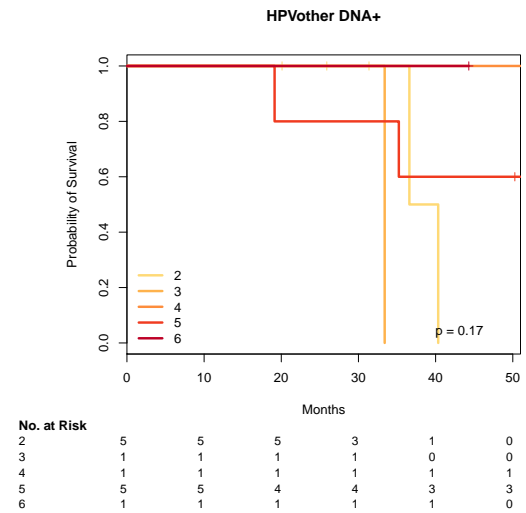
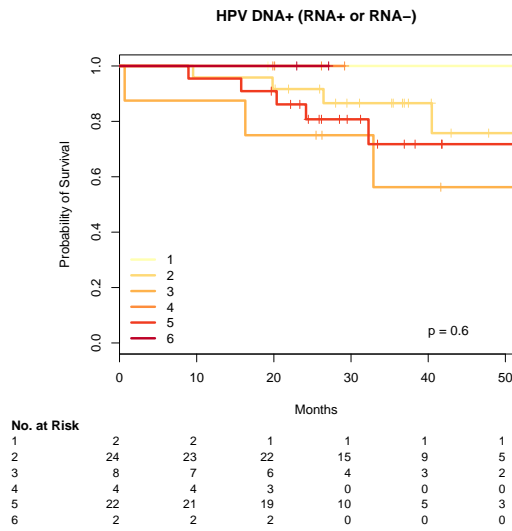
```

## Wald test          = 8.35  on 5 df,    p=0.138
## Score (logrank) test = 8.77  on 5 df,    p=0.118
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 207, number of events= 74
##    (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.737      0.478    0.560 -1.32    0.19
## split[cur.subset]3  0.553      1.739    0.477  1.16    0.25
## split[cur.subset]4 -0.273      0.761    0.538 -0.51    0.61
## split[cur.subset]5 -0.520      0.595    0.421 -1.23    0.22
## split[cur.subset]6  0.227      1.255    0.495  0.46    0.65
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.478      2.090      0.160      1.43
## split[cur.subset]3      1.739      0.575      0.683      4.43
## split[cur.subset]4      0.761      1.314      0.265      2.18
## split[cur.subset]5      0.595      1.681      0.261      1.36
## split[cur.subset]6      1.255      0.797      0.476      3.31
##
## Concordance= 0.576 (se = 0.034 )
## Rsquare= 0.057 (max possible= 0.965 )
## Likelihood ratio test= 12  on 5 df,    p=0.0342
## Wald test          = 13.1  on 5 df,    p=0.0223
## Score (logrank) test = 14.1  on 5 df,    p=0.0149
##
## 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
##              36.000      3.000      5.000      0.478      0.186
## lower 95% CI upper 95% CI
##              0.223      1.000
##
##              split[cur.subset]=2
##              time      n.risk      n.event      survival      std.err
##              36.0000      7.0000      6.0000      0.7511      0.0886
## lower 95% CI upper 95% CI
##              0.5960      0.9465
##

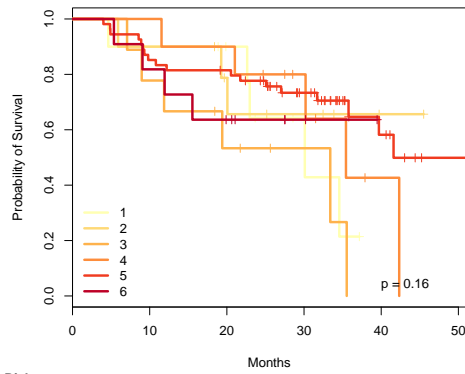
```

```
##                               split[cur.subset]=3
##           time           n.risk           n.event           survival           std.err
##           36.000           3.000           12.000           0.310           0.131
## lower 95% CI upper 95% CI
##           0.135           0.710
##
##                               split[cur.subset]=4
##           time           n.risk           n.event           survival           std.err
##           36.000           4.000           6.000           0.552           0.158
## lower 95% CI upper 95% CI
##           0.315           0.969
##
##                               split[cur.subset]=5
##           time           n.risk           n.event           survival           std.err
##           36.0000          25.0000          25.0000          0.7280           0.0506
## lower 95% CI upper 95% CI
##           0.6353           0.8341
##
##                               split[cur.subset]=6
##           time           n.risk           n.event           survival           std.err
##           36.000           5.000           9.000           0.444           0.135
## lower 95% CI upper 95% CI
##           0.245           0.807
```





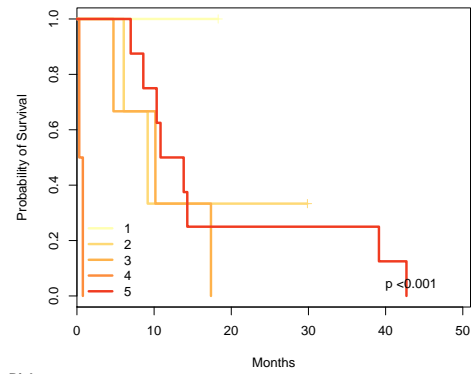
HPV DNA-, UICC IVA



No. at Risk

1	10	9	7	3	0	0
2	10	9	6	4	1	0
3	9	7	4	2	0	0
4	10	10	9	5	1	0
5	54	46	43	28	9	3
6	11	9	6	2	0	0

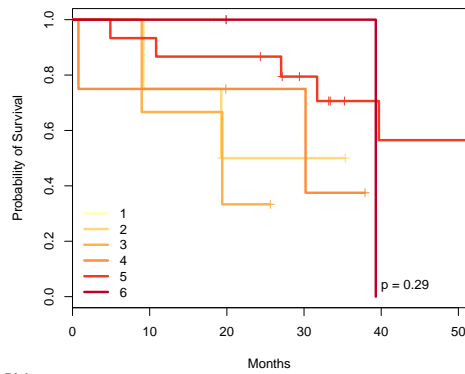
HPV DNA-, UICC IVB-C



No. at Risk

1	1	1	0	0	0	0
2	3	1	1	0	0	0
3	3	2	0	0	0	0
4	2	0	0	0	0	0
5	8	6	2	2	1	0

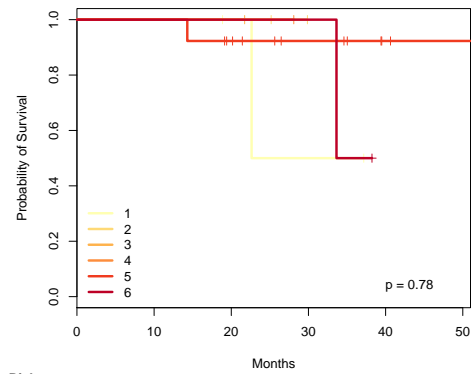
In DNA- Atypical



No. at Risk

1	2	2	0	0	0	0
2	4	3	1	1	0	0
3	3	2	1	0	0	0
4	4	3	2	2	0	0
5	15	14	13	9	4	4
6	2	2	1	1	0	0

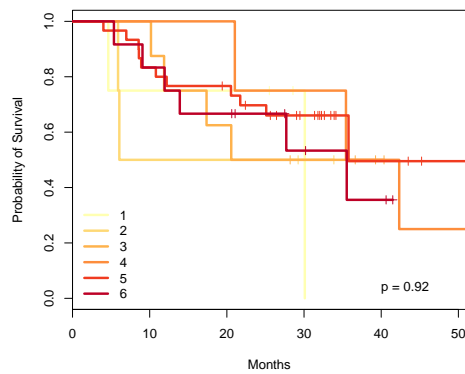
In DNA- Classical



No. at Risk

1	3	3	2	1	0	0
2	2	2	2	0	0	0
3	1	1	1	0	0	0
4	1	1	1	0	0	0
5	13	13	10	6	2	1
6	2	2	2	2	0	0

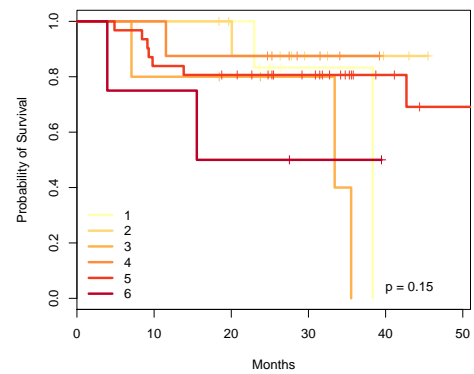
In DNA- Mesenchymal



No. at Risk

1	4	3	3	1	0	0
2	4	2	2	1	0	0
3	8	8	5	3	1	0
4	4	4	4	3	2	1
5	30	25	22	14	3	1
6	12	10	8	4	2	0

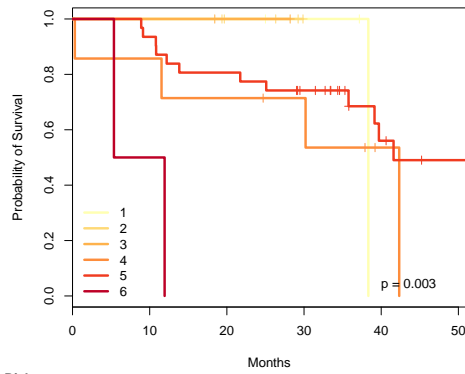
In DNA- Basal



No. at Risk

1	6	6	6	1	0	0
2	10	10	8	4	2	0
3	5	4	3	2	0	0
4	8	8	7	3	0	0
5	31	26	24	18	8	5
6	4	3	2	1	0	0

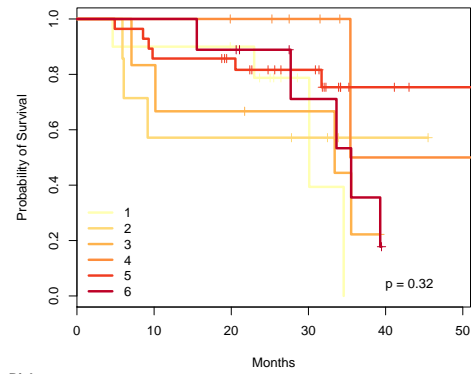
HPV DNA- Oropharynx



No. at Risk

1	3	3	3	2	0	0
2	5	5	3	0	0	0
3	2	2	1	0	0	0
4	7	6	5	4	1	0
5	31	29	25	20	9	6
6	2	1	0	0	0	0

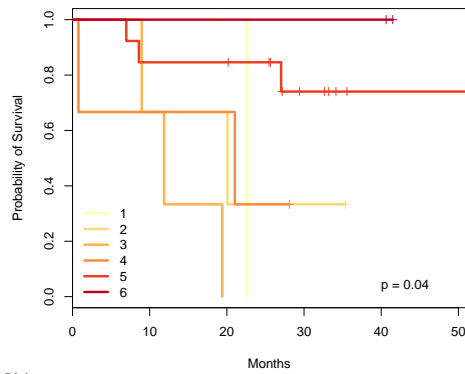
HPV DNA- Cavum oris



No. at Risk

1	10	9	8	2	0	0
2	7	4	4	3	1	0
3	6	5	4	3	0	0
4	7	7	6	4	1	1
5	28	24	21	15	4	2
6	9	9	8	4	0	0

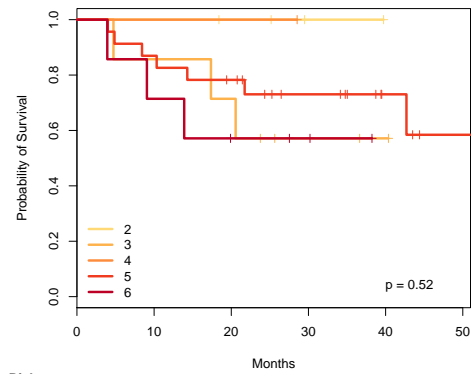
HPV DNA- Hypopharynx



No. at Risk

1	2	2	1	0	0	0
2	3	2	2	1	0	0
3	3	2	0	0	0	0
4	3	2	2	0	0	0
5	13	11	11	5	1	1
6	2	2	2	2	2	0

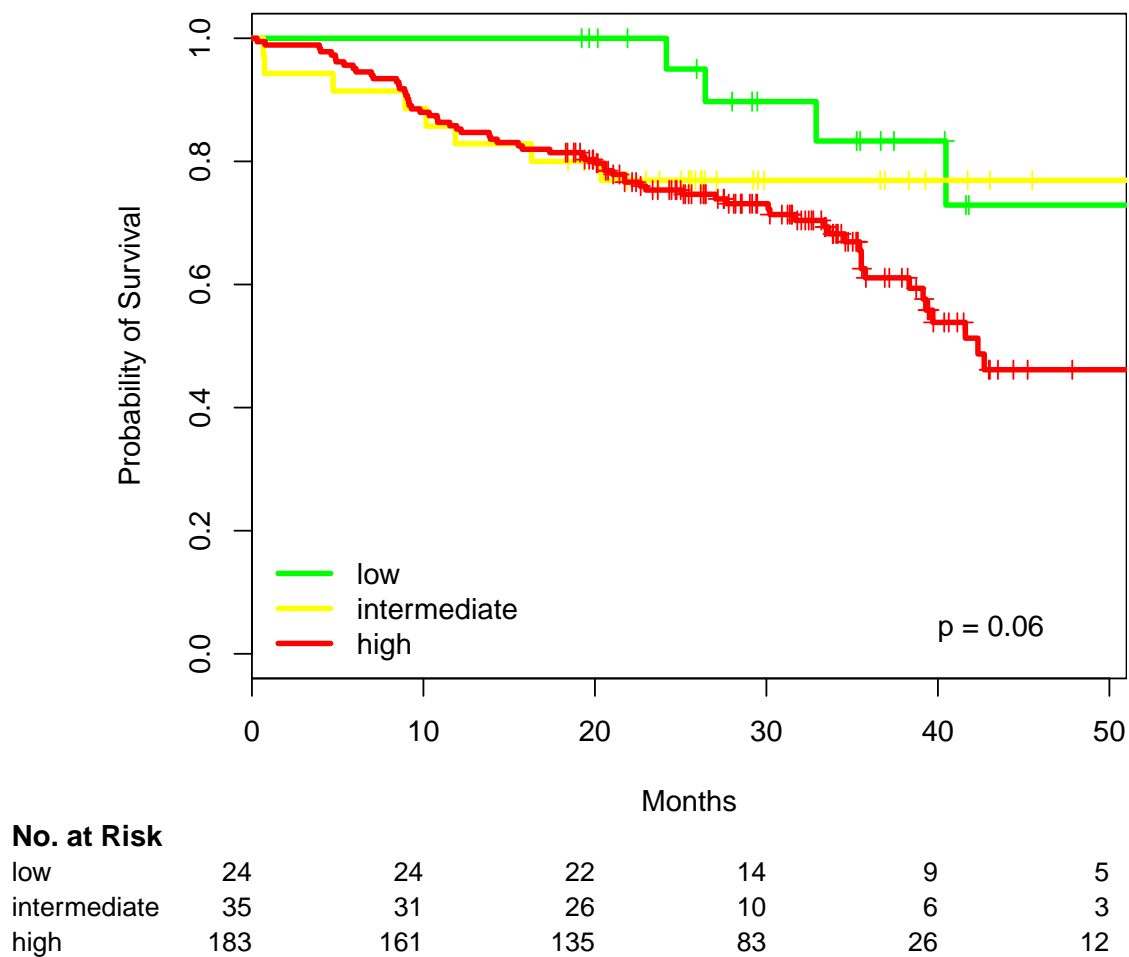
HPV DNA- Larynx

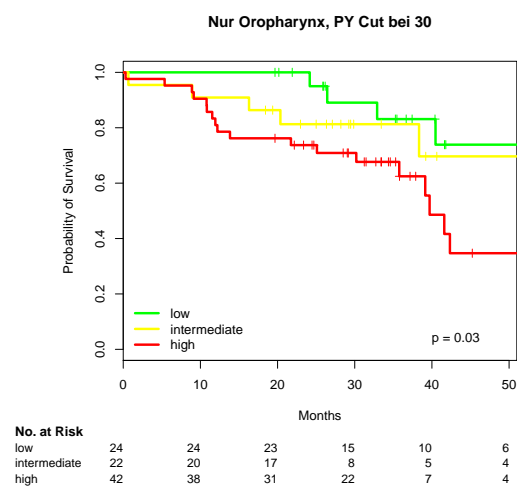
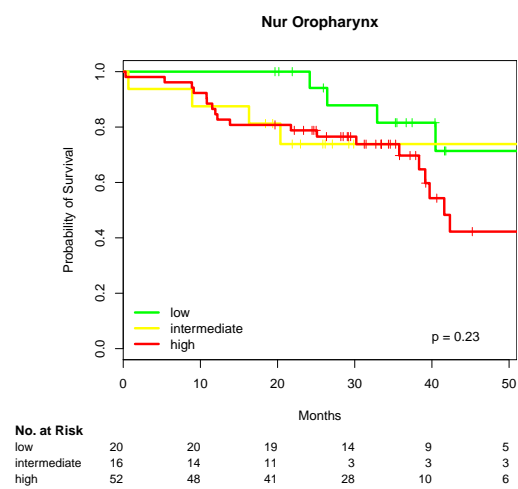
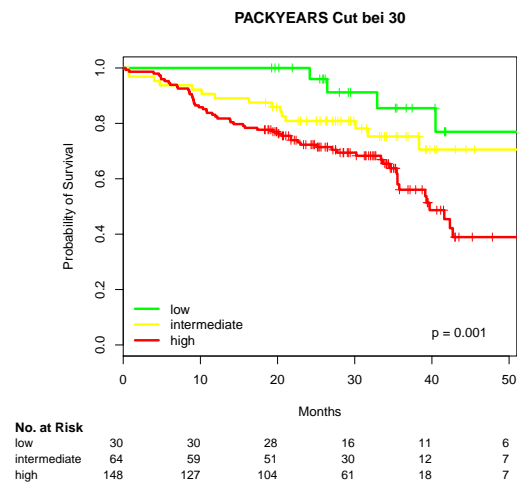


No. at Risk

2	4	4	3	1	0	0
3	7	6	5	2	1	0
4	1	1	1	0	0	0
5	23	20	17	11	5	2
6	7	5	3	2	0	0

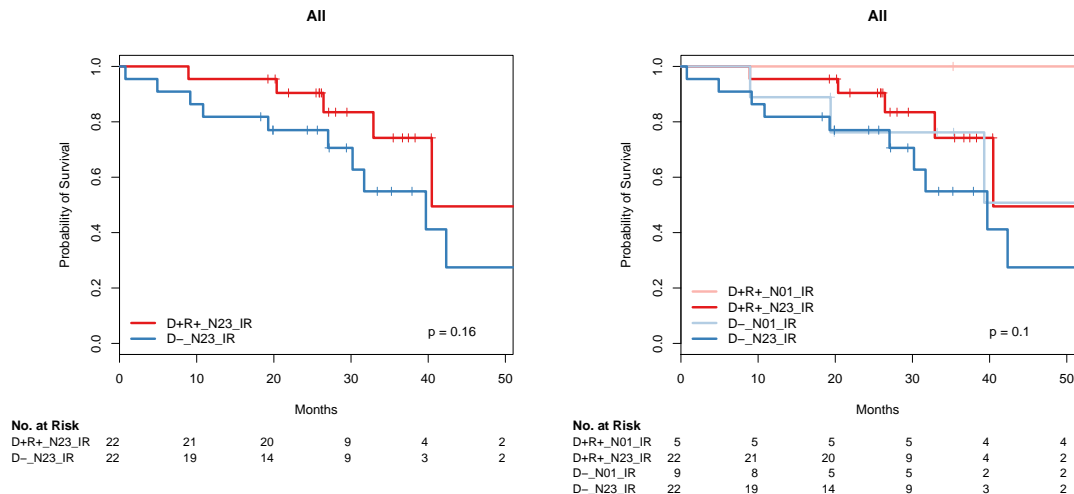
3.29 Risk groups according to Ang et al. Instead of p16+ (immunohisto) HPV16 DNA+RNA+ status is used.





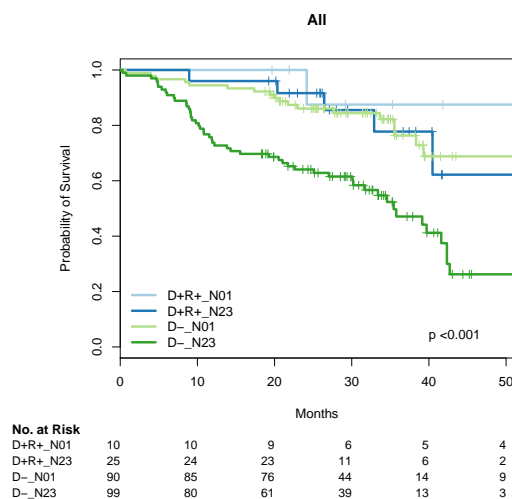
4 Question of whether the lymph node metastases in HPV- and in HPV+ are different.

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



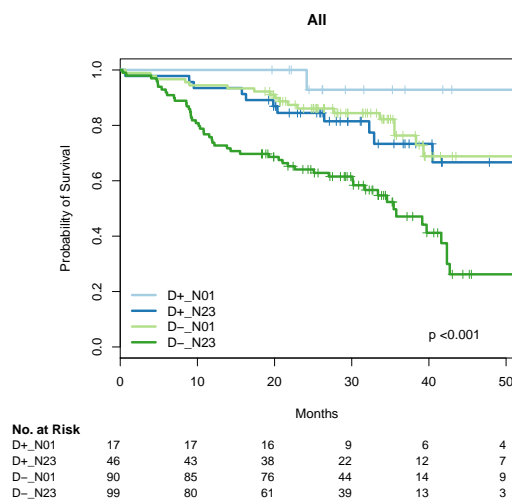
4.2 Interaction of HPV16 DNA RNA status with N0-N1

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 224, number of events= 77
## (43 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+R+_N23 1.04      2.82      1.10 0.94   0.345
## split[cur.subset]D-_N01   1.12      3.07      1.03 1.09   0.274
## split[cur.subset]D-_N23   2.22      9.22      1.01 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]D+R+_N23      2.82      0.354      0.328      24.2
## split[cur.subset]D-_N01        3.07      0.326      0.411      22.9
## split[cur.subset]D-_N23        9.22      0.108      1.268      67.1
##
## Concordance= 0.659 (se = 0.034 )
## Rsquare= 0.116 (max possible= 0.963 )
## Likelihood ratio test= 27.6 on 3 df,  p=4.49e-06
## Wald test               = 24 on 3 df,  p=2.53e-05
## Score (logrank) test = 27.6 on 3 df,  p=4.35e-06
```



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= 86
##   (15 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23  1.62      5.03      1.04 1.55   0.1204
## split[cur.subset]D-_N01  1.50      4.50      1.03 1.47   0.1425
## split[cur.subset]D-_N23  2.62     13.69      1.01 2.59   0.0097 **
## ---
## 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      5.03      0.1988      0.655      38.6
## split[cur.subset]D-_N01      4.50      0.2223      0.603      33.6
## split[cur.subset]D-_N23     13.69      0.0731      1.887     99.3
##
## Concordance= 0.661 (se = 0.033 )
## Rsquare= 0.119 (max possible= 0.963 )
## Likelihood ratio test= 31.9 on 3 df,  p=5.41e-07
## Wald test               = 26.8 on 3 df,  p=6.44e-06
## Score (logrank) test = 31.9 on 3 df,  p=5.41e-07
```



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= 77
##      (43 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_extremesDNA+RNA+ -1.174    0.309   0.427 -2.75   0.006 **
## N_2CATN2-N3           1.097    2.994   0.259  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
## HPV16_extremesDNA+RNA+  0.309      3.235    0.134    0.714
## N_2CATN2-N3           2.994      0.334    1.802    4.973
##
## Concordance= 0.659 (se = 0.034 )
## Rsquare= 0.116 (max possible= 0.963 )
## Likelihood ratio test= 27.6 on 2 df,  p=1.04e-06
## Wald test               = 23.9 on 2 df,  p=6.61e-06
## Score (logrank) test = 25.9 on 2 df,  p=2.39e-06
```

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= 77
##      (43 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z
## HPV16_extremesDNA+RNA+      -1.1217   0.3257   1.0264 -1.09
## N_2CATN2-N3                1.0999   3.0040   0.2660  4.14
## HPV16_extremesDNA+RNA+:N_2CATN2-N3 -0.0629   0.9391   1.1281 -0.06
##
##              Pr(>|z|)
## HPV16_extremesDNA+RNA+          0.27
## N_2CATN2-N3                    3.5e-05 ***
## HPV16_extremesDNA+RNA+:N_2CATN2-N3 0.96
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## HPV16_extremesDNA+RNA+      0.326      3.070      0.0436
## N_2CATN2-N3                3.004      0.333      1.7835
## HPV16_extremesDNA+RNA+:N_2CATN2-N3 0.939      1.065      0.1029
##
##              upper .95
## HPV16_extremesDNA+RNA+      2.43
## N_2CATN2-N3                5.06
## HPV16_extremesDNA+RNA+:N_2CATN2-N3 8.57
##
## Concordance= 0.659 (se = 0.034 )
## Rsquare= 0.116 (max possible= 0.963 )
## Likelihood ratio test= 27.6 on 3 df,  p=4.49e-06
## Wald test              = 24 on 3 df,  p=2.53e-05
## Score (logrank) test = 27.6 on 3 df,  p=4.35e-06

```

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

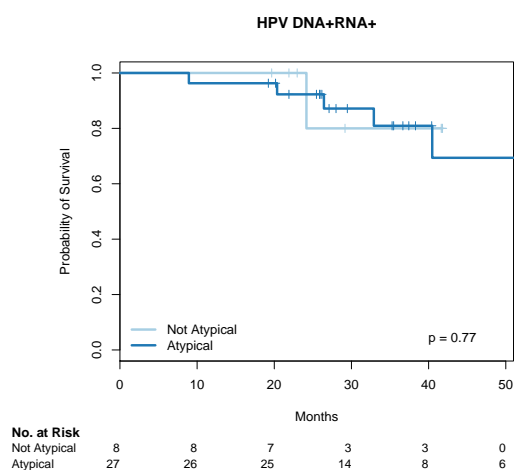
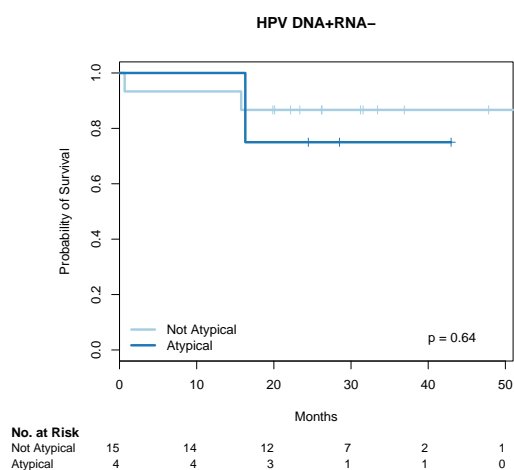
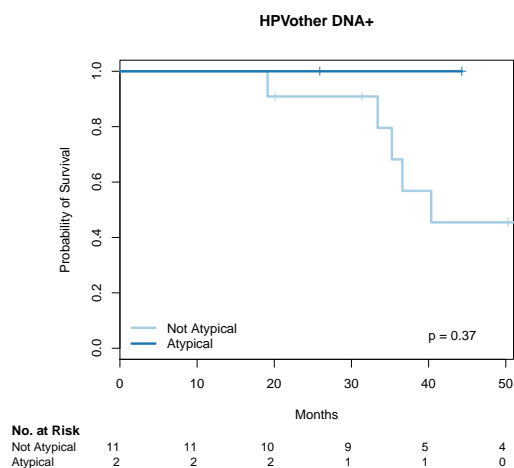
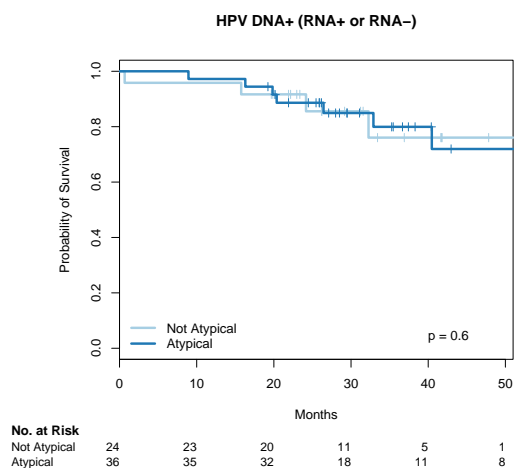
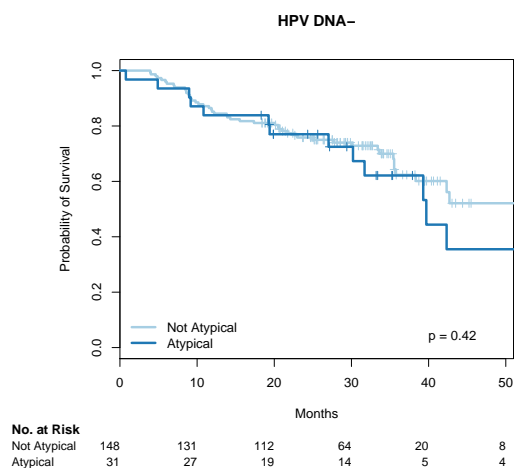
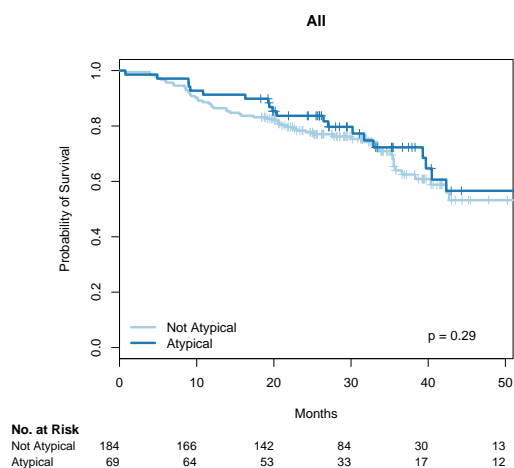
```

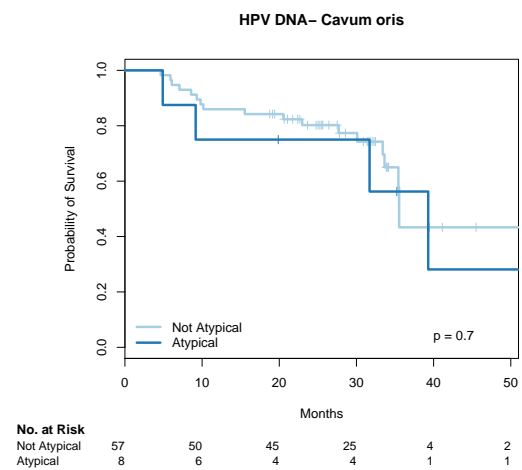
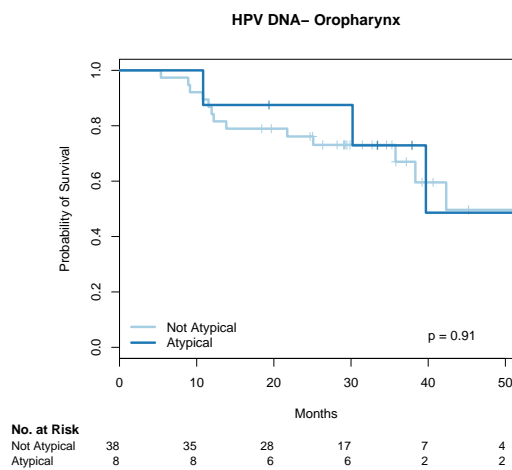
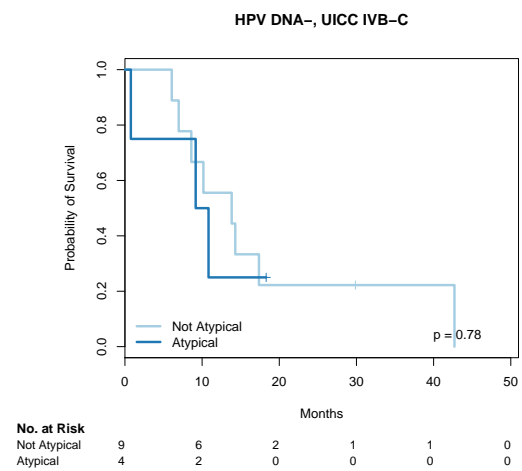
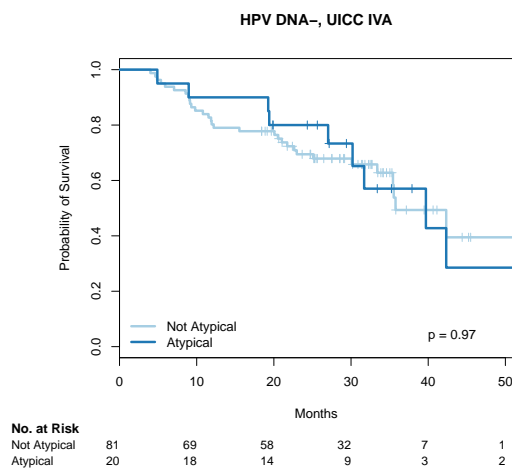
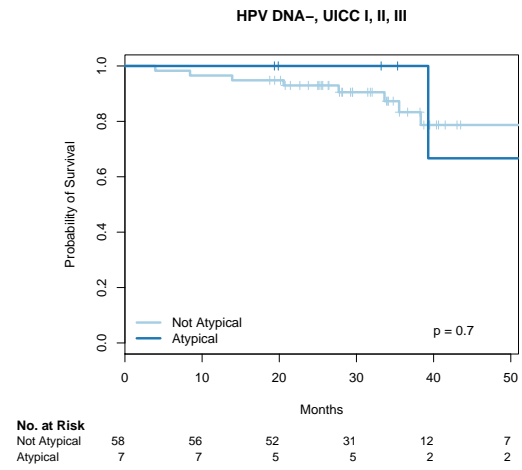
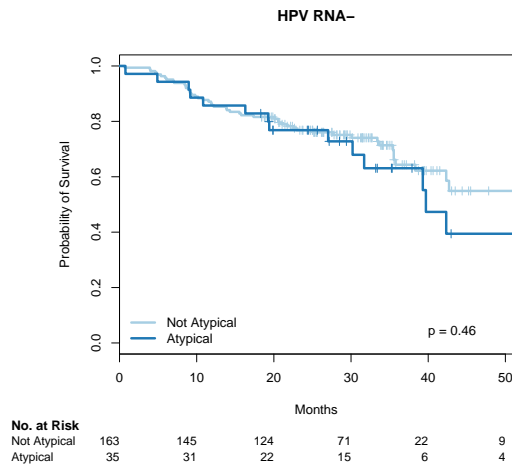
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 253, number of events= 85
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical -0.267    0.766    0.251 -1.06    0.29
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical    0.766    1.31    0.468    1.25
##
## Concordance= 0.524 (se = 0.028 )
## Rsquare= 0.005 (max possible= 0.959 )
## Likelihood ratio test= 1.17 on 1 df, p=0.278
## Wald test = 1.13 on 1 df, p=0.288
## Score (logrank) test = 1.14 on 1 df, p=0.287
##
## 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    44.0000    52.0000    0.6394    0.0452
## lower 95% CI upper 95% CI
##      0.5567    0.7344
##
##               split[cur.subset]=Atypical
##           time      n.risk      n.event      survival      std.err
##      36.0000    23.0000    16.0000    0.7229    0.0616
## lower 95% CI upper 95% CI
##      0.6116    0.8544
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 179, number of events= 63
## (12 observations deleted due to missingness)

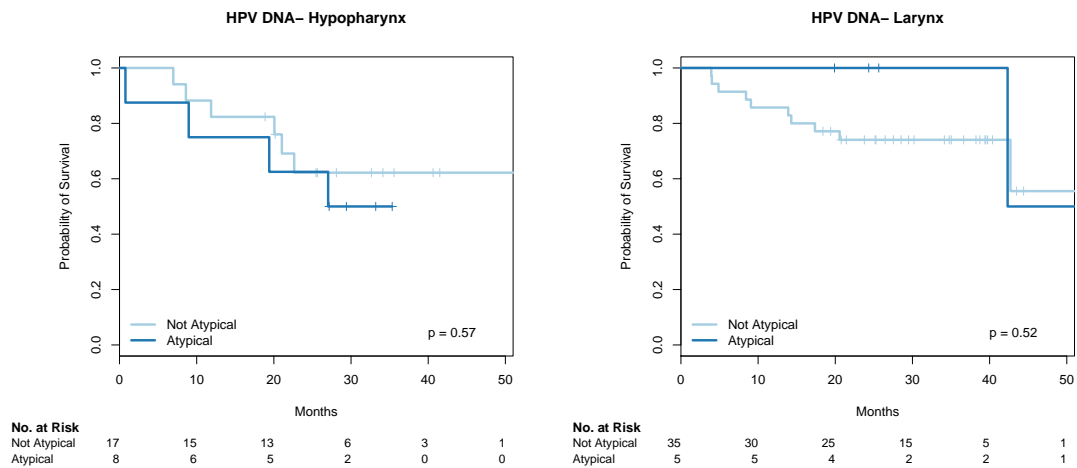
```

```
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset]Atypical 0.244      1.276    0.305 0.8    0.42
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical      1.28      0.784    0.702    2.32
##
## Concordance= 0.51 (se = 0.026 )
## Rsquare= 0.003 (max possible= 0.959 )
## Likelihood ratio test= 0.61 on 1 df,    p=0.434
## Wald test              = 0.64 on 1 df,    p=0.424
## Score (logrank) test = 0.64 on 1 df,    p=0.423
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 198, number of events= 67
##    (11 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset]Atypical 0.217      1.242    0.295 0.74    0.46
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical      1.24      0.805    0.697    2.21
##
## Concordance= 0.511 (se = 0.026 )
## Rsquare= 0.003 (max possible= 0.956 )
## Likelihood ratio test= 0.52 on 1 df,    p=0.471
## Wald test              = 0.54 on 1 df,    p=0.462
## Score (logrank) test = 0.54 on 1 df,    p=0.461
##
## 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      35.0000      46.0000      0.6435      0.0487
## lower 95% CI upper 95% CI
##               0.5548      0.7464
##
##               split[cur.subset]=Atypical
##               time      n.risk      n.event      survival      std.err
##               36.0000      9.0000      11.0000      0.6308      0.0935
## lower 95% CI upper 95% CI
```

0.4718 0.8433







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= 85
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N23_  1.204    3.334   0.287  4.19  2.8e-05 ***
## split[cur.subset]N01_IR -0.384    0.681   0.629 -0.61  0.542
## split[cur.subset]N23_IR  0.644    1.905   0.337  1.91  0.055 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N23_    3.334    0.300    1.899    5.85
## split[cur.subset]N01_IR    0.681    1.468    0.198    2.34
## split[cur.subset]N23_IR    1.905    0.525    0.985    3.68
##
## Concordance= 0.655 (se = 0.034 )
## Rsquare= 0.093 (max possible= 0.959 )
## Likelihood ratio test= 24.7 on 3 df, p=1.77e-05
## Wald test = 22.2 on 3 df, p=5.9e-05
## Score (logrank) test = 24.9 on 3 df, p=1.65e-05
##
## 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      24.0000      13.0000          0.7944          0.0574
## lower 95% CI upper 95% CI
##       0.6895          0.9151
##
##               split[cur.subset]=N23_
##           time      n.risk      n.event      survival      std.err
##       36.0000      20.0000      39.0000          0.4958          0.0637
## lower 95% CI upper 95% CI
##       0.3854          0.6376
##
##               split[cur.subset]=N01_IR
##           time      n.risk      n.event      survival      std.err
##       36.0000          9.0000          2.0000          0.8784          0.0807
## lower 95% CI upper 95% CI
##       0.7337          1.0000
##
##               split[cur.subset]=N23_IR
##           time      n.risk      n.event      survival      std.err
##       36.0000      14.0000      14.0000          0.6544          0.0807
## lower 95% CI upper 95% CI
##       0.5138          0.8333
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 179, number of events= 63
##      (12 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N23_  1.320      3.743   0.316  4.18  2.9e-05 ***
## split[cur.subset]N01_IR 0.524      1.688   0.635  0.82   0.4094
## split[cur.subset]N23_IR 1.080      2.944   0.398  2.71   0.0067 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N23_      3.74      0.267      2.016      6.95
## split[cur.subset]N01_IR      1.69      0.592      0.486      5.86
## split[cur.subset]N23_IR      2.94      0.340      1.349      6.42
##
## Concordance= 0.666 (se = 0.037 )
## Rsquare= 0.11 (max possible= 0.959 )
## Likelihood ratio test= 20.9 on 3 df, p=0.000111

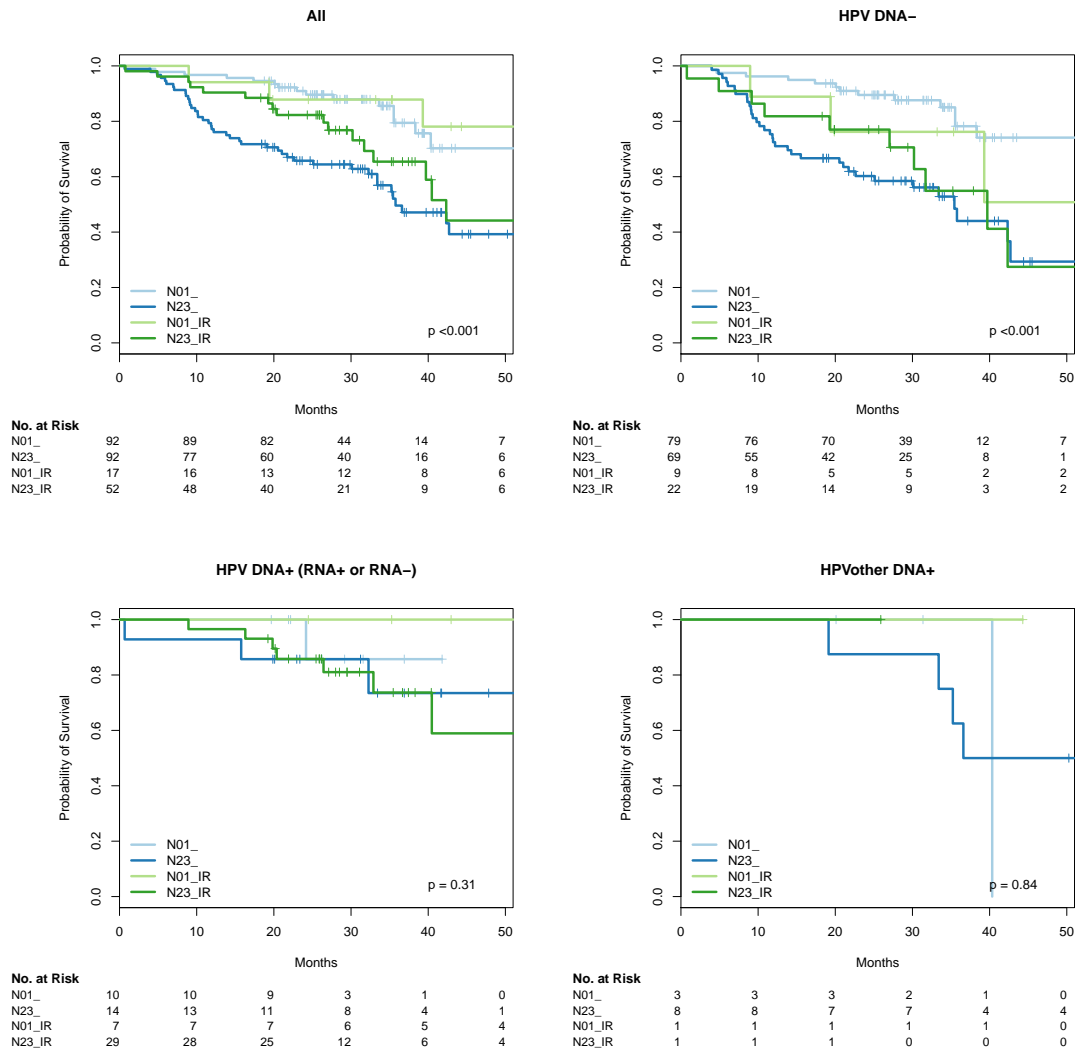
```

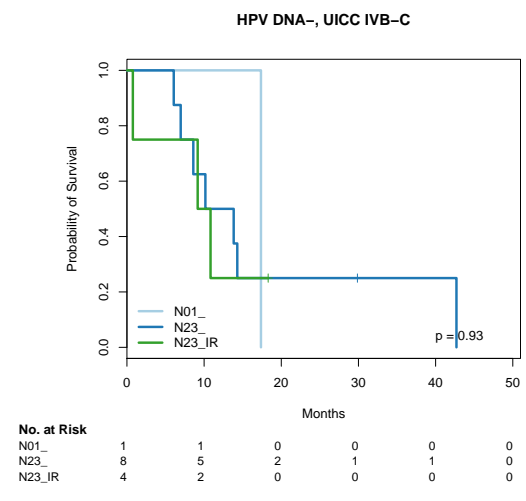
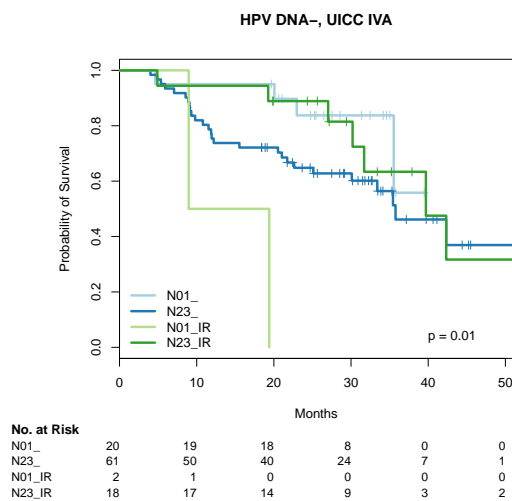
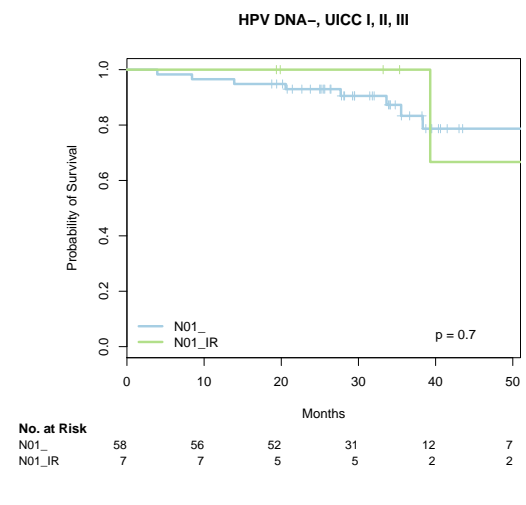
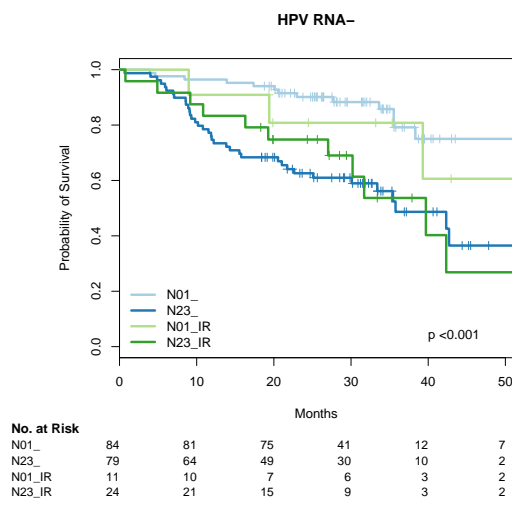
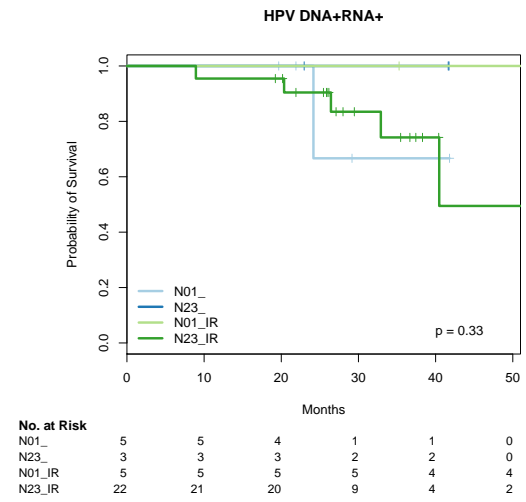
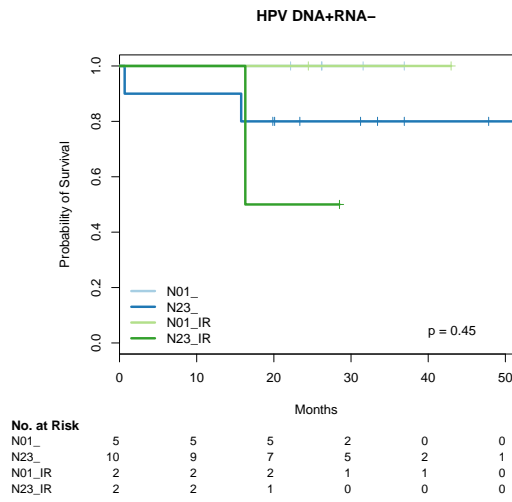
```

## Wald test          = 18.3  on 3 df,    p=0.000385
## Score (logrank) test = 20.6  on 3 df,    p=0.000127
##
##
## #####
## Cox model1 in HPV RNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 198, number of events= 67
##    (11 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N23_  1.313     3.717   0.312 4.20  2.6e-05 ***
## split[cur.subset]N01_IR 0.347     1.415   0.635 0.55  0.5843
## split[cur.subset]N23_IR 1.149     3.155   0.388 2.96  0.0031 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N23_      3.72      0.269      2.015      6.85
## split[cur.subset]N01_IR      1.42      0.707      0.408      4.91
## split[cur.subset]N23_IR      3.16      0.317      1.473      6.76
##
## Concordance= 0.663 (se = 0.036 )
## Rsquare= 0.107 (max possible= 0.956 )
## Likelihood ratio test= 22.4  on 3 df,    p=5.52e-05
## Wald test          = 19.3  on 3 df,    p=0.000232
## Score (logrank) test = 21.8  on 3 df,    p=7.11e-05
##
## 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      22.0000      12.0000      0.7918      0.0604
## lower 95% CI upper 95% CI
##              0.6817      0.9195
##
##              split[cur.subset]=N23_
##              time      n.risk      n.event      survival      std.err
##              36.0000      13.0000      34.0000      0.4866      0.0726
## lower 95% CI upper 95% CI
##              0.3632      0.6519
##
##              split[cur.subset]=N01_IR
##              time      n.risk      n.event      survival      std.err

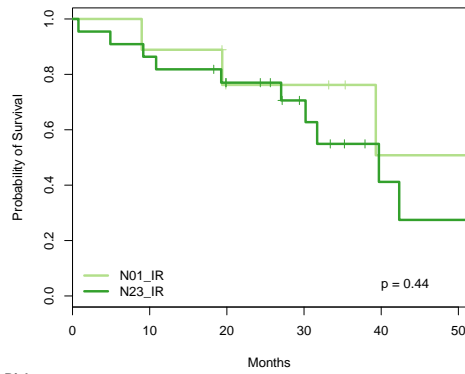
```

```
##      36.000      4.000      2.000      0.808      0.122
## lower 95% CI upper 95% CI
##      0.600      1.000
##
##      split[cur.subset]=N23_IR
##      time      n.risk      n.event      survival      std.err
##      36.000      5.000      9.000      0.537      0.123
## lower 95% CI upper 95% CI
##      0.343      0.841
```





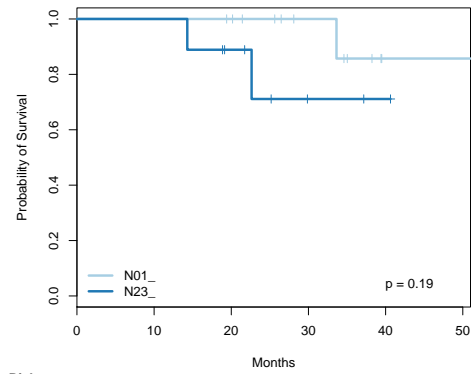
In DNA- Atypical



No. at Risk

N01_IR	9	8	5	5	2	2
N23_IR	22	19	14	9	3	2

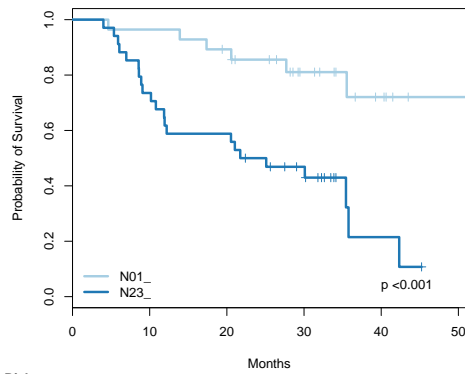
In DNA- Classical



No. at Risk

N01_	13	13	12	7	1	1
N23_	9	9	6	2	1	0

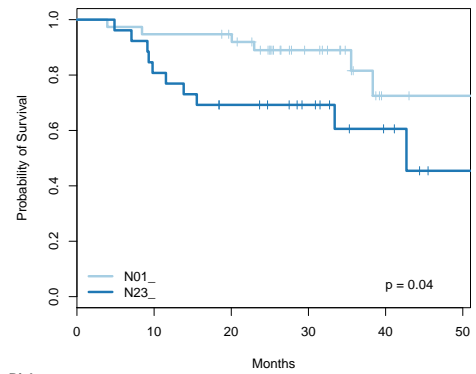
In DNA- Mesenchymal



No. at Risk

N01_	28	27	24	14	6	2
N23_	34	25	20	12	2	0

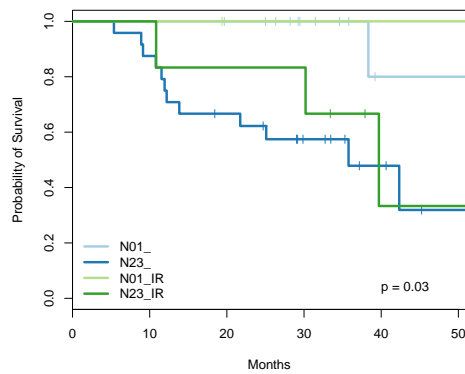
In DNA- Basal



No. at Risk

N01_	38	36	34	18	5	4
N23_	26	21	16	11	5	1

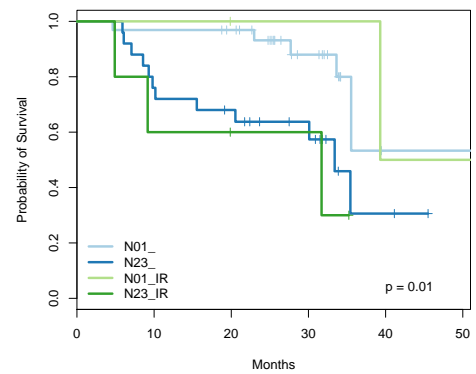
HPV DNA- Oropharynx



No. at Risk

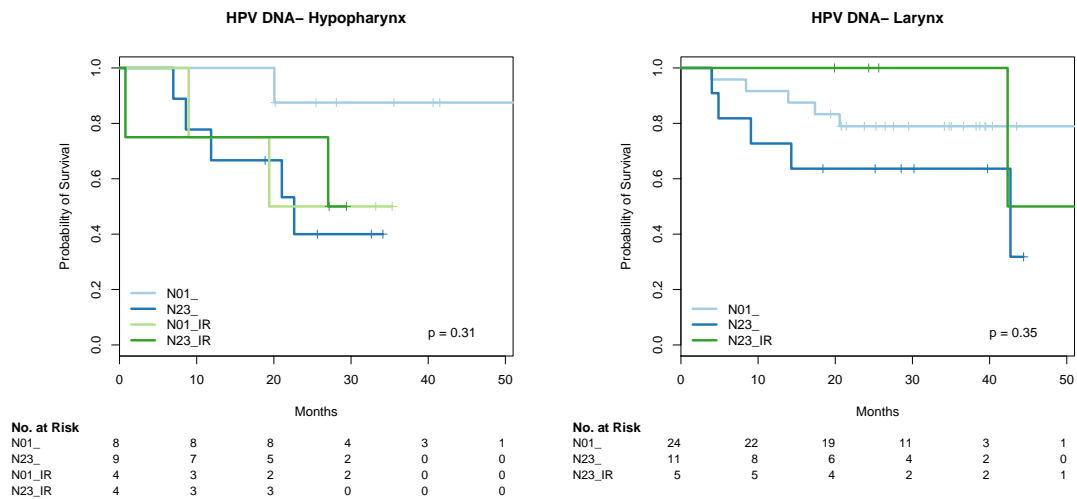
N01_	14	14	13	8	3	3
N23_	24	21	15	9	4	1
N01_IR	2	2	1	1	1	1
N23_IR	6	6	5	5	1	1

HPV DNA- Cavum oris



No. at Risk

N01_	32	31	29	15	2	2
N23_	25	19	16	10	2	0
N01_IR	3	3	2	2	1	1
N23_IR	5	3	2	2	0	0



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= 63
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      1.1994    3.3181  0.2887  4.15 3.3e-05 ***
## IS_ATYPICALatypical -0.0899    0.9140  0.3151 -0.29  0.78
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3          3.318    0.301    1.884    5.84
## IS_ATYPICALatypical    0.914    1.094    0.493    1.70
##
## Concordance= 0.655 (se = 0.037 )
## Rsquare= 0.105 (max possible= 0.959 )
## Likelihood ratio test= 19.9 on 2 df,  p=4.81e-05
## Wald test               = 17.6 on 2 df,  p=0.000147
## Score (logrank) test = 19.7 on 2 df,  p=5.3e-05
```

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= 63
##    (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      1.320      3.743   0.316  4.18  2.9e-05
## IS_ATYPICALtypical  0.524      1.688   0.635  0.82    0.41
## N_2CATN2-N3:IS_ATYPICALtypical -0.764      0.466   0.727 -1.05    0.29
##
## N_2CATN2-N3          ***
## IS_ATYPICALtypical
## N_2CATN2-N3:IS_ATYPICALtypical
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3          3.743      0.267      2.016      6.95
## IS_ATYPICALtypical    1.688      0.592      0.486      5.86
## N_2CATN2-N3:IS_ATYPICALtypical  0.466      2.147      0.112      1.94
##
## Concordance= 0.666 (se = 0.037 )
## Rsquare= 0.11 (max possible= 0.959 )
## Likelihood ratio test= 20.9 on 3 df,  p=0.000111
## Wald test              = 18.3 on 3 df,  p=0.000385
## Score (logrank) test = 20.6 on 3 df,  p=0.000127

```

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= 94
```

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
UICC_3CATIVA	1.092	2.980	0.307	3.56	0.00037 ***
UICC_3CATIVB-C	2.178	8.826	0.359	6.06	1.4e-09 ***

```
## ---
```

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

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
UICC_3CATIVA	2.98	0.336	1.63	5.44
UICC_3CATIVB-C	8.83	0.113	4.36	17.85

```
##
```

```
## Concordance= 0.668 (se = 0.029 )
```

```
## Rsquare= 0.132 (max possible= 0.967 )
```

```
## Likelihood ratio test= 37.9 on 2 df, p=5.91e-09
```

```
## Wald test = 37.7 on 2 df, p=6.61e-09
```

```
## Score (logrank) test = 45.8 on 2 df, p=1.13e-10
```

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

```
##
```

	rho	chisq	p
UICC_3CATIVA	-0.0329	0.0991	0.753
UICC_3CATIVB-C	-0.1080	1.0564	0.304
GLOBAL	NA	1.3834	0.501

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= 81
```

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

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
HPV16_DNADNA+	-0.917	0.400	0.339	-2.71	0.0067 **

```
## ---
```

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

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
HPV16_DNADNA+	0.4	2.5	0.206	0.776

```
##
```

```
## Concordance= 0.566 (se = 0.026 )
## Rsquare= 0.037 (max possible= 0.96 )
## Likelihood ratio test= 9.16 on 1 df, p=0.00248
## Wald test = 7.34 on 1 df, p=0.00674
## Score (logrank) test = 7.86 on 1 df, p=0.00504

cox.zph(surv.res)

## rho chisq p
## HPV16_DNADNA+ 0.0208 0.0347 0.852
```

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= 81
## (23 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA  1.197      3.310   0.317  3.78 0.00016 ***
## UICC_3CATIVB-C 2.563     12.969   0.378  6.79 1.2e-11 ***
## HPV16_DNADNA+ -1.180      0.307   0.341 -3.46 0.00054 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.310      0.3021      1.778      6.161
## UICC_3CATIVB-C    12.969      0.0771      6.187     27.185
## HPV16_DNADNA+      0.307      3.2557      0.157      0.599
##
## Concordance= 0.705 (se = 0.034 )
## Rsquare= 0.201 (max possible= 0.96 )
## Likelihood ratio test= 54.6 on 3 df, p=8.25e-12
## Wald test = 54.7 on 3 df, p=7.98e-12
## Score (logrank) test = 65.4 on 3 df, p=4.03e-14

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA -0.00926 0.00657 0.935
## UICC_3CATIVB-C -0.02234 0.03825 0.845
## HPV16_DNADNA+ 0.02941 0.06696 0.796
## GLOBAL NA 0.09945 0.992
```

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= 81
##      (23 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.761    0.467    0.515 -1.48    0.139
## HPV16_DNA_RNADNA+RNA+ -1.009    0.364    0.426 -2.37    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-    0.467      2.14    0.170    1.28
## HPV16_DNA_RNADNA+RNA+    0.364      2.74    0.158    0.84
##
## Concordance= 0.568 (se = 0.027 )
## Rsquare= 0.037 (max possible= 0.96 )
## Likelihood ratio test= 9.3 on 2 df,  p=0.00955
## Wald test               = 7.37 on 2 df,  p=0.025
## Score (logrank) test = 7.94 on 2 df,  p=0.0189

cox.zph(surv.res)

##              rho chisq      p
## HPV16_DNA_RNADNA+RNA- -0.0163 0.0215 0.884
## HPV16_DNA_RNADNA+RNA+  0.0397 0.1275 0.721
## GLOBAL                  NA 0.1563 0.925
```

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= 81
## (23 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.194      3.300      0.317  3.76  0.00017 ***
## UICC_3CATIVB-C      2.561     12.949      0.378  6.78  1.2e-11 ***
## HPV16_DNA_RNADNA+RNA- -1.078      0.340      0.518 -2.08  0.03748 *
## HPV16_DNA_RNADNA+RNA+ -1.243      0.289      0.428 -2.91  0.00367 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.300      0.3030      1.773      6.145
## UICC_3CATIVB-C     12.949      0.0772      6.178     27.141
## HPV16_DNA_RNADNA+RNA-  0.340      2.9390      0.123      0.939
## HPV16_DNA_RNADNA+RNA+  0.289      3.4658      0.125      0.667
##
## Concordance= 0.709 (se = 0.034 )
## Rsquare= 0.201 (max possible= 0.96 )
## Likelihood ratio test= 54.7 on 4 df, p=3.77e-11
## Wald test = 54.7 on 4 df, p=3.76e-11
## Score (logrank) test = 65.5 on 4 df, p=2.06e-13

cox.zph(surv.res)

##          rho  chisq    p
## UICC_3CATIVA -0.00817 0.00509 0.943
## UICC_3CATIVB-C -0.02223 0.03802 0.845
## HPV16_DNA_RNADNA+RNA- -0.04768 0.18288 0.669
## HPV16_DNA_RNADNA+RNA+  0.07287 0.41517 0.519
## GLOBAL      NA 0.67599 0.954
```

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= 80
## (25 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
```

```
## UICC_3CATIVA          1.183      3.266      0.318  3.72      0.0002 ***
## UICC_3CATIVB-C        2.519     12.414      0.379  6.65     2.9e-11 ***
## HPV16_DNA_RNADNA+RNA- -0.983      0.374      0.523 -1.88     0.0602 .
## HPV16_DNA_RNADNA+RNA+ -1.151      0.316      0.438 -2.63     0.0086 **
## I(PACKYEARS > 30)TRUE  0.242      1.274      0.235  1.03     0.3040
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.266      0.3062      1.752      6.088
## UICC_3CATIVB-C        12.414      0.0806      5.911     26.071
## HPV16_DNA_RNADNA+RNA-  0.374      2.6723      0.134      1.043
## HPV16_DNA_RNADNA+RNA+  0.316      3.1628      0.134      0.746
## I(PACKYEARS > 30)TRUE  1.274      0.7850      0.803      2.021
##
## Concordance= 0.714 (se = 0.035 )
## Rsquare= 0.203 (max possible= 0.96 )
## Likelihood ratio test= 54.8 on 5 df, p=1.45e-10
## Wald test = 55.4 on 5 df, p=1.06e-10
## Score (logrank) test = 66.3 on 5 df, p=5.99e-13

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA      -0.0218 0.0357 0.850
## UICC_3CATIVB-C     -0.0459 0.1636 0.686
## HPV16_DNA_RNADNA+RNA- -0.0191 0.0290 0.865
## HPV16_DNA_RNADNA+RNA+  0.1051 0.9098 0.340
## I(PACKYEARS > 30)TRUE  0.1025 0.9006 0.343
## GLOBAL              NA  1.7116 0.887
```

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= 80
## (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)
```

```

## UICC_3CATIVA                1.197      3.310      0.319
## UICC_3CATIVB-C              2.519     12.414      0.379
## HPV16_DNA_RNADNA+RNA-      -0.906      0.404      0.619
## HPV16_DNA_RNADNA+RNA+      -1.595      0.203      0.612
## I(PACKYEARS > 30)TRUE       0.174      1.190      0.248
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.344      0.709      1.193
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.149      3.155      0.858
##                               z Pr(>|z|)
## UICC_3CATIVA                3.75  0.00018 ***
## UICC_3CATIVB-C              6.64  3.2e-11 ***
## HPV16_DNA_RNADNA+RNA-      -1.46  0.14333
## HPV16_DNA_RNADNA+RNA+      -2.61  0.00912 **
## I(PACKYEARS > 30)TRUE       0.70  0.48242
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.29  0.77304
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.34  0.18077
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                               exp(coef) exp(-coef) lower .95
## UICC_3CATIVA                3.310      0.3022      1.7703
## UICC_3CATIVB-C             12.414      0.0806      5.9017
## HPV16_DNA_RNADNA+RNA-       0.404      2.4752      0.1200
## HPV16_DNA_RNADNA+RNA+       0.203      4.9274      0.0612
## I(PACKYEARS > 30)TRUE       1.190      0.8404      0.7325
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.709      1.4108      0.0684
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  3.155      0.3170      0.5865
##                               upper .95
## UICC_3CATIVA                6.187
## UICC_3CATIVB-C             26.113
## HPV16_DNA_RNADNA+RNA-       1.360
## HPV16_DNA_RNADNA+RNA+       0.673
## I(PACKYEARS > 30)TRUE       1.933
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  7.350
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 16.972
##
## Concordance= 0.718 (se = 0.035 )
## Rsquare= 0.209 (max possible= 0.96 )
## Likelihood ratio test= 56.6 on 7 df, p=7e-10
## Wald test = 55.2 on 7 df, p=1.37e-09
## Score (logrank) test = 66.9 on 7 df, p=6.17e-12

cox.zph(surv.res)

##                               rho chisq    p
## UICC_3CATIVA                -0.0181 0.0252 0.874
## UICC_3CATIVB-C              -0.0396 0.1225 0.726
## HPV16_DNA_RNADNA+RNA-      -0.0481 0.1843 0.668
## HPV16_DNA_RNADNA+RNA+       0.1602 1.9734 0.160
## I(PACKYEARS > 30)TRUE       0.1067 0.9234 0.337

```

```
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.0379 0.1153 0.734
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.1000 0.7997 0.371
## GLOBAL NA 3.1034 0.875
```

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= 81
## (23 observations deleted due to missingness)
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
UICC_3CATIVA	1.1850	3.2707	0.3168	3.74	0.00018 ***
UICC_3CATIVB-C	2.5391	12.6679	0.3778	6.72	1.8e-11 ***
HPV16_DNA_RNADNA+RNA-	-0.9490	0.3871	0.5213	-1.82	0.06871 .
HPV16_DNA_RNADNA+RNA+	-1.3978	0.2471	0.4349	-3.21	0.00131 **
ALTER	0.0264	1.0267	0.0119	2.22	0.02648 *

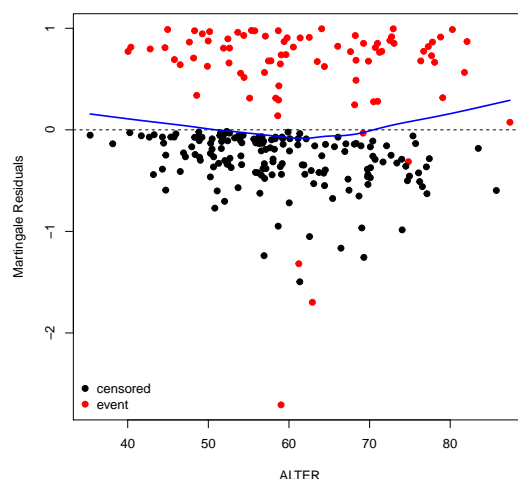
```
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

	exp(coef)	exp(-coef)	lower .95	upper .95
UICC_3CATIVA	3.271	0.3057	1.758	6.09
UICC_3CATIVB-C	12.668	0.0789	6.041	26.57
HPV16_DNA_RNADNA+RNA-	0.387	2.5830	0.139	1.08
HPV16_DNA_RNADNA+RNA+	0.247	4.0462	0.105	0.58
ALTER	1.027	0.9739	1.003	1.05

```
## Concordance= 0.734 (se = 0.036 )
## Rsquare= 0.217 (max possible= 0.96 )
## Likelihood ratio test= 59.5 on 5 df, p=1.51e-11
## Wald test = 58 on 5 df, p=3.2e-11
## Score (logrank) test = 68.9 on 5 df, p=1.72e-13
```

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

	rho	chisq	p
UICC_3CATIVA	-0.0149	0.0168	0.897
UICC_3CATIVB-C	-0.0277	0.0583	0.809
HPV16_DNA_RNADNA+RNA-	-0.0474	0.1899	0.663
HPV16_DNA_RNADNA+RNA+	0.0728	0.4217	0.516
ALTER	-0.0169	0.0324	0.857
GLOBAL	NA	0.6841	0.984



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= 81
##     (23 observations deleted due to missingness)
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)	
## UICC_3CATIVA	1.211	3.355	0.318	3.81	0.00014	***
## UICC_3CATIVB-C	2.666	14.385	0.385	6.92	4.5e-12	***
## HPV16_DNA_RNADNA+RNA-	-0.980	0.375	0.523	-1.87	0.06104	.
## HPV16_DNA_RNADNA+RNA+	-1.394	0.248	0.437	-3.19	0.00143	**
## poly(ALTER, 2)1	3.194	24.395	1.787	1.79	0.07379	.
## poly(ALTER, 2)2	3.628	37.649	1.524	2.38	0.01728	*

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

##

	exp(coef)	exp(-coef)	lower .95	upper .95
## UICC_3CATIVA	3.355	0.2980	1.799	6.258
## UICC_3CATIVB-C	14.385	0.0695	6.760	30.611
## HPV16_DNA_RNADNA+RNA-	0.375	2.6637	0.135	1.046
## HPV16_DNA_RNADNA+RNA+	0.248	4.0300	0.105	0.584
## poly(ALTER, 2)1	24.395	0.0410	0.735	809.275
## poly(ALTER, 2)2	37.649	0.0266	1.899	746.428

##

Concordance= 0.729 (se = 0.036)


```
## Rsquare= 0.232    (max possible= 0.96 )
## Likelihood ratio test= 64.5   on 6 df,    p=5.46e-12
## Wald test         = 63.6   on 6 df,    p=8.17e-12
## Score (logrank) test = 74.8   on 6 df,    p=4.29e-14

cox.zph(surv.res)

##                rho    chisq      p
## UICC_3CATIVA      0.0074 0.00426 0.948
## UICC_3CATIVB-C    0.0109 0.00942 0.923
## HPV16_DNA_RNADNA+RNA- -0.0592 0.29649 0.586
## HPV16_DNA_RNADNA+RNA+ 0.0670 0.35673 0.550
## poly(ALTER, 2)1    -0.0430 0.16982 0.680
## poly(ALTER, 2)2     0.1649 1.91348 0.167
## GLOBAL            NA 2.58658 0.859
```

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= 81
## (23 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.261     3.528   0.319   3.95 7.9e-05 ***
## UICC_3CATIVB-C     2.757    15.754   0.386   7.14 9.6e-13 ***
## HPV16_DNA_RNADNA+RNA- -1.023     0.360   0.519  -1.97 0.04891 *
## HPV16_DNA_RNADNA+RNA+ -1.328     0.265   0.431  -3.08 0.00206 **
## ALTER_3CAT(50,70]   -0.799     0.450   0.233  -3.43 0.00061 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.528     0.2834    1.887     6.597
## UICC_3CATIVB-C    15.754     0.0635    7.388    33.593
## HPV16_DNA_RNADNA+RNA- 0.360     2.7810    0.130     0.995
## HPV16_DNA_RNADNA+RNA+ 0.265     3.7753    0.114     0.617
## ALTER_3CAT(50,70]   0.450     2.2242    0.285     0.710
```

```
##
## Concordance= 0.727 (se = 0.035 )
## Rsquare= 0.237 (max possible= 0.96 )
## Likelihood ratio test= 66.1 on 5 df, p=6.74e-13
## Wald test = 63.6 on 5 df, p=2.2e-12
## Score (logrank) test = 75.2 on 5 df, p=8.44e-15

cox.zph(surv.res)

##
## rho chisq p
## UICC_3CATIVA 0.0267 0.0540 0.816
## UICC_3CATIVB-C 0.0323 0.0796 0.778
## HPV16_DNA_RNADNA+RNA- -0.0615 0.2996 0.584
## HPV16_DNA_RNADNA+RNA+ 0.0367 0.1079 0.743
## ALTER_3CAT(50,70] -0.1561 2.1724 0.141
## GLOBAL NA 2.7743 0.735
```

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= 80
## (25 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 1.252 3.496 0.319 3.92 8.9e-05 ***
## UICC_3CATIVB-C 2.735 15.414 0.387 7.06 1.6e-12 ***
## HPV16_DNA_RNADNA+RNA- -0.837 0.433 0.525 -1.59 0.11073
## HPV16_DNA_RNADNA+RNA+ -1.190 0.304 0.439 -2.71 0.00663 **
## ALTER_3CAT(50,70] -0.931 0.394 0.245 -3.80 0.00014 ***
## I(PACKYEARS > 30)TRUE 0.476 1.610 0.242 1.96 0.04948 *
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 3.496 0.2860 1.869 6.539
## UICC_3CATIVB-C 15.414 0.0649 7.216 32.922
## HPV16_DNA_RNADNA+RNA- 0.433 2.3090 0.155 1.211
```

```
## HPV16_DNA_RNADNA+RNA+      0.304      3.2886      0.129      0.718
## ALTER_3CAT(50,70]          0.394      2.5366      0.244      0.637
## I(PACKYEARS > 30)TRUE      1.610      0.6211      1.001      2.590
##
## Concordance= 0.736 (se = 0.036 )
## Rsquare= 0.248 (max possible= 0.96 )
## Likelihood ratio test= 68.9 on 6 df, p=6.95e-13
## Wald test = 64.8 on 6 df, p=4.63e-12
## Score (logrank) test = 77.9 on 6 df, p=9.77e-15

cox.zph(surv.res)

##              rho    chisq      p
## UICC_3CATIVA      0.00901 0.00596 0.9385
## UICC_3CATIVB-C     0.00751 0.00425 0.9480
## HPV16_DNA_RNADNA+RNA- -0.01533 0.01851 0.8918
## HPV16_DNA_RNADNA+RNA+ 0.07753 0.49526 0.4816
## ALTER_3CAT(50,70]   -0.18599 2.96819 0.0849
## I(PACKYEARS > 30)TRUE 0.12801 1.30543 0.2532
## GLOBAL              NA 4.13601 0.6583
```

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= 80
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)
## UICC_3CATIVA      1.258      3.517      0.321
## UICC_3CATIVB-C     2.719     15.171      0.388
## HPV16_DNA_RNADNA+RNA- -0.749      0.473      0.623
## HPV16_DNA_RNADNA+RNA+ -1.538      0.215      0.614
## ALTER_3CAT(50,70]   -0.907      0.404      0.246
## I(PACKYEARS > 30)TRUE 0.422      1.525      0.258
```

```

## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.370      0.690      1.196
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  0.846      2.330      0.868
##
##              z Pr(>|z|)
## UICC_3CATIVA          3.92 8.8e-05 ***
## UICC_3CATIVB-C        7.01 2.3e-12 ***
## HPV16_DNA_RNADNA+RNA- -1.20 0.22883
## HPV16_DNA_RNADNA+RNA+ -2.50 0.01225 *
## ALTER_3CAT(50,70]    -3.69 0.00022 ***
## I(PACKYEARS > 30)TRUE  1.64 0.10127
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.31 0.75679
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  0.97 0.33005
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## UICC_3CATIVA          3.517      0.2844      1.8757
## UICC_3CATIVB-C        15.171      0.0659      7.0958
## HPV16_DNA_RNADNA+RNA-  0.473      2.1153      0.1395
## HPV16_DNA_RNADNA+RNA+  0.215      4.6533      0.0645
## ALTER_3CAT(50,70]      0.404      2.4759      0.2495
## I(PACKYEARS > 30)TRUE   1.525      0.6556      0.9206
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.690      1.4483      0.0662
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.330      0.4292      0.4247
##
##              upper .95
## UICC_3CATIVA          6.593
## UICC_3CATIVB-C        32.438
## HPV16_DNA_RNADNA+RNA-  1.602
## HPV16_DNA_RNADNA+RNA+  0.716
## ALTER_3CAT(50,70]      0.654
## I(PACKYEARS > 30)TRUE   2.527
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  7.197
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  12.783
##
## Concordance= 0.74 (se = 0.036 )
## Rsquare= 0.251 (max possible= 0.96 )
## Likelihood ratio test= 70 on 8 df, p=5e-12
## Wald test              = 64.9 on 8 df, p=5.04e-11
## Score (logrank) test = 78.2 on 8 df, p=1.11e-13

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA          0.0124 0.0114 0.9149
## UICC_3CATIVB-C        0.0120 0.0110 0.9164
## HPV16_DNA_RNADNA+RNA- -0.0520 0.2149 0.6430
## HPV16_DNA_RNADNA+RNA+  0.1322 1.3269 0.2494
## ALTER_3CAT(50,70]    -0.1939 3.3600 0.0668
## I(PACKYEARS > 30)TRUE  0.1263 1.3029 0.2537
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.0504 0.2034 0.6520

```

```
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0855 0.6111 0.4344
## GLOBAL NA 5.6826 0.6827
```

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= 80
## (25 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## T_2CAT3-4         1.168     3.215   0.292
## N_2CATN2-N3        0.805     2.236   0.269
## M                 2.125     8.375   0.399
## HPV16_DNA_RNADNA+RNA- -0.348     0.706   0.623
## HPV16_DNA_RNADNA+RNA+ -1.069     0.343   0.623
## ALTER_3CAT(50,70] -0.894     0.409   0.242
## I(PACKYEARS > 30)TRUE  0.491     1.634   0.258
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.460     0.631   1.191
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.025     2.786   0.863
##
##               z Pr(>|z|)
## T_2CAT3-4         4.00 6.4e-05 ***
## N_2CATN2-N3        2.99 0.00281 **
## M                 5.33 9.7e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.56 0.57628
## HPV16_DNA_RNADNA+RNA+ -1.72 0.08599 .
## ALTER_3CAT(50,70] -3.70 0.00022 ***
## I(PACKYEARS > 30)TRUE  1.90 0.05684 .
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.39 0.69939
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.19 0.23496
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95
```

```
## T_2CAT3-4 3.215 0.311 1.8139
## N_2CATN2-N3 2.236 0.447 1.3189
## M 8.375 0.119 3.8348
## HPV16_DNA_RNADNA+RNA- 0.706 1.417 0.2081
## HPV16_DNA_RNADNA+RNA+ 0.343 2.914 0.1012
## ALTER_3CAT(50,70] 0.409 2.444 0.2548
## I(PACKYEARS > 30)TRUE 1.634 0.612 0.9858
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.631 1.584 0.0612
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.786 0.359 0.5137
## upper .95
## T_2CAT3-4 5.699
## N_2CATN2-N3 3.791
## M 18.290
## HPV16_DNA_RNADNA+RNA- 2.394
## HPV16_DNA_RNADNA+RNA+ 1.163
## ALTER_3CAT(50,70] 0.657
## I(PACKYEARS > 30)TRUE 2.707
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 6.516
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 15.109
##
## Concordance= 0.755 (se = 0.036 )
## Rsquare= 0.275 (max possible= 0.96 )
## Likelihood ratio test= 77.8 on 9 df, p=4.44e-13
## Wald test = 73.4 on 9 df, p=3.26e-12
## Score (logrank) test = 97.6 on 9 df, p=0

cox.zph(surv.res)

## rho chisq p
## T_2CAT3-4 -0.039363 1.33e-01 0.7152
## N_2CATN2-N3 -0.012463 1.26e-02 0.9106
## M 0.049287 1.96e-01 0.6577
## HPV16_DNA_RNADNA+RNA- 0.000762 4.61e-05 0.9946
## HPV16_DNA_RNADNA+RNA+ 0.130273 1.36e+00 0.2442
## ALTER_3CAT(50,70] -0.259783 5.87e+00 0.0154
## I(PACKYEARS > 30)TRUE 0.182811 2.69e+00 0.1012
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.019633 3.05e-02 0.8615
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.103304 8.23e-01 0.3643
## GLOBAL NA 8.70e+00 0.4651
```

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= 80
## (25 observations deleted due to missingness)
##
##
##               coef exp(coef) se(coef)
## T_2CAT3-4         1.2273      3.4119  0.4688
## N_2CATN2-N3        0.8066      2.2402  0.2695
## M                 2.1197      8.3284  0.3999
## HPV16_DNA_RNADNA+RNA- -0.3385      0.7129  0.6257
## HPV16_DNA_RNADNA+RNA+ -1.0572      0.3474  0.6271
## ALTER_3CAT(50,70]   -0.8971      0.4078  0.2425
## I(PACKYEARS > 30)TRUE  0.5696      1.7676  0.5476
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.0959      0.9086  0.5862
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.4689      0.6257  1.1919
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.0101      2.7459  0.8670
##
##               z Pr(>|z|)
## T_2CAT3-4        2.62  0.00885 **
## N_2CATN2-N3       2.99  0.00276 **
## M                5.30  1.2e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.54  0.58852
## HPV16_DNA_RNADNA+RNA+ -1.69  0.09183 .
## ALTER_3CAT(50,70]   -3.70  0.00022 ***
## I(PACKYEARS > 30)TRUE  1.04  0.29827
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.16  0.87006
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.39  0.69400
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.17  0.24398
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##               exp(coef) exp(-coef) lower .95
## T_2CAT3-4         3.412      0.293  1.3613
## N_2CATN2-N3        2.240      0.446  1.3210
## M                 8.328      0.120  3.8037
## HPV16_DNA_RNADNA+RNA- 0.713      1.403  0.2091
## HPV16_DNA_RNADNA+RNA+ 0.347      2.878  0.1016
## ALTER_3CAT(50,70]   0.408      2.452  0.2535
## I(PACKYEARS > 30)TRUE 1.768      0.566  0.6043

```



```
## T_2CAT3-4:I(PACKYEARS > 30)TRUE      0.909      1.101      0.2880
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE      0.626      1.598      0.0605
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE      2.746      0.364      0.5020
##                                     upper .95
## T_2CAT3-4                                     8.551
## N_2CATN2-N3                                    3.799
## M                                              18.236
## HPV16_DNA_RNADNA+RNA-                        2.430
## HPV16_DNA_RNADNA+RNA+                        1.188
## ALTER_3CAT(50,70]                            0.656
## I(PACKYEARS > 30)TRUE                        5.170
## T_2CAT3-4:I(PACKYEARS > 30)TRUE              2.866
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE      6.470
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE     15.020
##
## Concordance= 0.756 (se = 0.036 )
## Rsquare= 0.275 (max possible= 0.96 )
## Likelihood ratio test= 77.8 on 10 df, p=1.34e-12
## Wald test = 73.1 on 10 df, p=1.12e-11
## Score (logrank) test = 98.7 on 10 df, p=1.11e-16

cox.zph(surv.res)

##                                     rho   chisq    p
## T_2CAT3-4                        0.03792 0.13202 0.7163
## N_2CATN2-N3                     -0.00914 0.00668 0.9349
## M                                0.04052 0.13440 0.7139
## HPV16_DNA_RNADNA+RNA-            0.01164 0.01096 0.9166
## HPV16_DNA_RNADNA+RNA+            0.13704 1.58467 0.2081
## ALTER_3CAT(50,70]                -0.26150 6.20627 0.0127
## I(PACKYEARS > 30)TRUE              0.14414 2.02460 0.1548
## T_2CAT3-4:I(PACKYEARS > 30)TRUE    -0.08015 0.56073 0.4540
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.01447 0.01670 0.8972
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.10960 0.97820 0.3226
## GLOBAL                           NA 9.28025 0.5057

# 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=729
## Surv(OS/30, OS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##   poly(ALTER, 2)[, 2] + I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS >
##   30) + GESCHLECHT
##
##
##               Df AIC
## - HPV16_DNA_RNA:I(PACKYEARS > 30)  2 726
## - poly(ALTER, 2)[, 2]              1 727
## - GESCHLECHT                      1 727
## <none>                             729
## - ALTER_3CAT                      1 732
## - UICC_3CAT                       2 775
##
## Step:  AIC=726.2
## Surv(OS/30, OS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##   poly(ALTER, 2)[, 2] + I(PACKYEARS > 30) + GESCHLECHT
##
##               Df AIC
## - GESCHLECHT                      1 725
## - poly(ALTER, 2)[, 2]             1 725
## <none>                             726
## - I(PACKYEARS > 30)               1 729
## - ALTER_3CAT                     1 729
## - HPV16_DNA_RNA                  2 734
## - UICC_3CAT                       2 772
##
## Step:  AIC=724.5
## Surv(OS/30, OS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##   poly(ALTER, 2)[, 2] + I(PACKYEARS > 30)
##
##               Df AIC
## - poly(ALTER, 2)[, 2]             1 723
## <none>                             725
## - I(PACKYEARS > 30)               1 727
## - ALTER_3CAT                     1 728
## - HPV16_DNA_RNA                  2 732
## - UICC_3CAT                       2 770
##
## Step:  AIC=722.9
## Surv(OS/30, OS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##   I(PACKYEARS > 30)
##
##               Df AIC
## <none>                             723

```

```
## - I(PACKYEARS > 30) 1 725
## - HPV16_DNA_RNA 2 730
## - ALTER_3CAT 1 735
## - UICC_3CAT 2 768

best.model

## Call:
## coxph(formula = Surv(OS/30, OS_EVENT) ~ UICC_3CAT + HPV16_DNA_RNA +
## ALTER_3CAT + 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")]))
##
##
##              coef exp(coef) se(coef)      z      p
## UICC_3CATIVA      1.252      3.496   0.319   3.92 8.9e-05
## UICC_3CATIVB-C      2.735     15.414   0.387   7.06 1.6e-12
## HPV16_DNA_RNADNA+RNA- -0.837    0.433   0.525  -1.59 1.1e-01
## HPV16_DNA_RNADNA+RNA+ -1.190    0.304   0.439  -2.71 6.6e-03
## ALTER_3CAT(50,70]   -0.931    0.394   0.245  -3.80 1.4e-04
## I(PACKYEARS > 30)TRUE  0.476    1.610   0.242   1.96 4.9e-02
##
## Likelihood ratio test=68.9  on 6 df, p=6.95e-13  n= 242, number of events= 80
```

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= 93
## (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## PACKYEARS 0.00111   1.00111  0.00464  0.24    0.81
##
##              exp(coef) exp(-coef) lower .95 upper .95
## PACKYEARS           1         0.999   0.992   1.01
##
## Concordance= 0.515 (se = 0.034 )
## Rsquare= 0 (max possible= 0.967 )
## Likelihood ratio test= 0.06  on 1 df,  p=0.811
## Wald test              = 0.06  on 1 df,  p=0.81
```

```
## Score (logrank) test = 0.06  on 1 df,   p=0.81

cox.zph(surv.res)

##              rho chisq      p
## PACKYEARS 0.103 0.871 0.351
```

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= 80
## (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.1785    3.2496  0.3182  3.70 0.00021 ***
## UICC_3CATIVB-C     2.5541   12.8595  0.3780  6.76 1.4e-11 ***
## HPV16_DNA_RNADNA+RNA- -1.0768    0.3407  0.5210 -2.07 0.03877 *
## HPV16_DNA_RNADNA+RNA+ -1.2931    0.2744  0.4377 -2.95 0.00314 **
## PACKYEARS        -0.0027    0.9973  0.0051 -0.53 0.59585
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.250    0.3077    1.742    6.063
## UICC_3CATIVB-C    12.859    0.0778    6.130   26.975
## HPV16_DNA_RNADNA+RNA-  0.341    2.9352    0.123    0.946
## HPV16_DNA_RNADNA+RNA+  0.274    3.6439    0.116    0.647
## PACKYEARS         0.997    1.0027    0.987    1.007
##
## Concordance= 0.705 (se = 0.036 )
## Rsquare= 0.2 (max possible= 0.96 )
## Likelihood ratio test= 54 on 5 df,   p=2.1e-10
## Wald test            = 54.6 on 5 df,   p=1.58e-10
## Score (logrank) test = 65.1 on 5 df,   p=1.08e-12

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA    -0.01920 0.027459 0.868
## UICC_3CATIVB-C  -0.01880 0.026863 0.870
```

```
## HPV16_DNA_RNADNA+RNA- -0.06030 0.283439 0.594
## HPV16_DNA_RNADNA+RNA+ 0.07237 0.426461 0.514
## PACKYEARS                0.00353 0.000903 0.976
## GLOBAL                    NA 0.818386 0.976
```

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= 80
##    (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.25103   3.49395  0.32077   3.90  9.6e-05 ***
## UICC_3CATIVB-C     2.75974  15.79569  0.38844   7.10  1.2e-12 ***
## HPV16_DNA_RNADNA+RNA- -0.97100   0.37870  0.52090  -1.86  0.06231 .
## HPV16_DNA_RNADNA+RNA+ -1.29357   0.27429  0.43667  -2.96  0.00305 **
## ALTER_3CAT(50,70]  -0.83200   0.43518  0.24663  -3.37  0.00074 ***
## PACKYEARS          0.00239   1.00239  0.00508   0.47  0.63890
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.494      0.2862      1.863      6.552
## UICC_3CATIVB-C       15.796      0.0633      7.377     33.821
## HPV16_DNA_RNADNA+RNA-  0.379      2.6406      0.136      1.051
## HPV16_DNA_RNADNA+RNA+  0.274      3.6458      0.117      0.646
## ALTER_3CAT(50,70]     0.435      2.2979      0.268      0.706
## PACKYEARS             1.002      0.9976      0.992      1.012
##
## Concordance= 0.731 (se = 0.036 )
## Rsquare= 0.236 (max possible= 0.96 )
## Likelihood ratio test= 65.2 on 6 df, p=3.98e-12
## Wald test               = 62.3 on 6 df, p=1.51e-11
## Score (logrank) test = 74.1 on 6 df, p=5.82e-14

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0204 0.0305 0.861
## UICC_3CATIVB-C     0.0321 0.0765 0.782
```

```
## HPV16_DNA_RNADNA+RNA- -0.0445 0.1546 0.694
## HPV16_DNA_RNADNA+RNA+ 0.0561 0.2518 0.616
## ALTER_3CAT(50,70] -0.1702 2.5475 0.110
## PACKYEARS 0.0514 0.1699 0.680
## GLOBAL NA 3.1600 0.789
```

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= 80
## (25 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.22985   3.42073  0.32134   3.83  0.00013
## UICC_3CATIVB-C     2.78716  16.23478  0.38855   7.17  7.3e-13
## HPV16_DNA_RNADNA+RNA- -0.59664   0.55066  0.61713  -0.97  0.33365
## HPV16_DNA_RNADNA+RNA+ -1.51587   0.21962  0.57096  -2.65  0.00793
## ALTER_3CAT(50,70] -0.82133   0.43985  0.24816  -3.31  0.00093
## PACKYEARS         0.00289   1.00290  0.00590   0.49  0.62420
## HPV16_DNA_RNADNA+RNA-:PACKYEARS -0.02031   0.97990  0.02369  -0.86  0.39137
## HPV16_DNA_RNADNA+RNA+:PACKYEARS  0.00992   1.00997  0.01328   0.75  0.45521
##
## 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          3.421    0.2923    1.8222    6.422
## UICC_3CATIVB-C        16.235    0.0616    7.5808   34.768
## HPV16_DNA_RNADNA+RNA-    0.551    1.8160    0.1643    1.846
## HPV16_DNA_RNADNA+RNA+    0.220    4.5534    0.0717    0.672
```

```
## ALTER_3CAT(50,70]          0.440      2.2735      0.2704      0.715
## PACKYEARS                  1.003      0.9971      0.9914      1.015
## HPV16_DNA_RNADNA+RNA-:PACKYEARS 0.980      1.0205      0.9354      1.026
## HPV16_DNA_RNADNA+RNA+:PACKYEARS 1.010      0.9901      0.9840      1.037
##
## Concordance= 0.738 (se = 0.036 )
## Rsquare= 0.242 (max possible= 0.96 )
## Likelihood ratio test= 67 on 8 df, p=1.93e-11
## Wald test = 63.9 on 8 df, p=7.85e-11
## Score (logrank) test = 76.2 on 8 df, p=2.81e-13

cox.zph(surv.res)

##                rho  chisq    p
## UICC_3CATIVA      0.0237 0.0416 0.838
## UICC_3CATIVB-C     0.0240 0.0423 0.837
## HPV16_DNA_RNADNA+RNA- -0.1185 1.0922 0.296
## HPV16_DNA_RNADNA+RNA+  0.1061 0.7041 0.401
## ALTER_3CAT(50,70] -0.1697 2.6802 0.102
## PACKYEARS          0.0304 0.0700 0.791
## HPV16_DNA_RNADNA+RNA-:PACKYEARS 0.0857 0.3836 0.536
## HPV16_DNA_RNADNA+RNA+:PACKYEARS -0.0749 0.2802 0.597
## GLOBAL              NA 5.0916 0.748
```

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= 80
## (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.17352   3.23337  0.31789   3.69  0.00022 ***
## UICC_3CATIVB-C     2.66182  14.32235  0.38459   6.92  4.5e-12 ***
## HPV16_RNARNA+    -1.45210   0.23408  0.55944  -2.60  0.00944 **
## ALTER_3CAT(50,70] -0.85252   0.42634  0.24688  -3.45  0.00055 ***
## PACKYEARS         0.00170   1.00170  0.00502   0.34  0.73481
## HPV16_RNARNA+:PACKYEARS 0.01096   1.01102  0.01279   0.86  0.39174
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.233      0.3093      1.7341      6.029
## UICC_3CATIVB-C        14.322      0.0698      6.7398     30.435
## HPV16_RNARNA+         0.234      4.2721      0.0782      0.701
## ALTER_3CAT(50,70]      0.426      2.3456      0.2628      0.692
## PACKYEARS             1.002      0.9983      0.9919      1.012
## HPV16_RNARNA+:PACKYEARS 1.011      0.9891      0.9860      1.037
##
## Concordance= 0.731  (se = 0.036 )
## Rsquare= 0.223  (max possible= 0.96 )
## Likelihood ratio test= 61.2  on 6 df,   p=2.56e-11
## Wald test               = 58.2  on 6 df,   p=1.04e-10
## Score (logrank) test = 70.3  on 6 df,   p=3.52e-13

cox.zph(surv.res)

##               rho    chisq      p
## UICC_3CATIVA      -0.00766 0.00423 0.9481
## UICC_3CATIVB-C     0.01533 0.01719 0.8957
## HPV16_RNARNA+     0.14344 1.27640 0.2586
## ALTER_3CAT(50,70] -0.19025 3.26421 0.0708
## PACKYEARS         0.15815 1.46191 0.2266
## HPV16_RNARNA+:PACKYEARS -0.13402 0.81385 0.3670
## GLOBAL            NA 4.64969 0.5895

stepAIC(surv.res)

## Start:  AIC=730.5
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT + PACKYEARS +
##   HPV16_RNA:PACKYEARS
##
##               Df  AIC
## - HPV16_RNA:PACKYEARS  1 729
## <none>                  731
## - ALTER_3CAT           1 740
## - UICC_3CAT             2 773
##
## Step:  AIC=729.2
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT + PACKYEARS

## Error:  number of rows in use has changed:  remove missing values?
```

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= 80
##      (25 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z
## UICC_3CATIVA      1.187      3.276   0.319   3.72
## UICC_3CATIVB-C      2.704     14.933   0.391   6.91
## HPV16_RNARNA+     -1.322      0.267   0.630  -2.10
## ALTER_3CAT(50,70]  -0.872      0.418   0.243  -3.59
## I(PACKYEARS > 10)TRUE      0.177      1.194   0.290   0.61
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE  0.307      1.360   0.867   0.35
##
##              Pr(>|z|)
## UICC_3CATIVA      0.00020 ***
## UICC_3CATIVB-C      4.9e-12 ***
## HPV16_RNARNA+      0.03587 *
## ALTER_3CAT(50,70]  0.00033 ***
## I(PACKYEARS > 10)TRUE      0.54181
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE  0.72282
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## UICC_3CATIVA      3.276      0.305   1.7537
## UICC_3CATIVB-C     14.933      0.067   6.9357
## HPV16_RNARNA+      0.267      3.751   0.0775
## ALTER_3CAT(50,70]   0.418      2.392   0.2597
## I(PACKYEARS > 10)TRUE      1.194      0.838   0.6757
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE   1.360      0.735   0.2487
##
##              upper .95
## UICC_3CATIVA      6.121
## UICC_3CATIVB-C     32.151
## HPV16_RNARNA+      0.917
## ALTER_3CAT(50,70]   0.673
## I(PACKYEARS > 10)TRUE      2.109
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE   7.436
##
## Concordance= 0.727 (se = 0.035 )
## Rsquare= 0.222 (max possible= 0.96 )
## Likelihood ratio test= 60.9 on 6 df, p=2.98e-11

```



```
## Wald test          = 58 on 6 df,    p=1.13e-10
## Score (logrank) test = 70.3 on 6 df,    p=3.62e-13

cox.zph(surv.res)

##                rho    chisq    p
## UICC_3CATIVA      -0.00522 0.00199 0.964
## UICC_3CATIVB-C     0.02716 0.05470 0.815
## HPV16_RNARNA+     0.13865 1.45741 0.227
## ALTER_3CAT(50,70] -0.17599 2.61968 0.106
## I(PACKYEARS > 10)TRUE 0.10189 0.81164 0.368
## HPV16_RNARNA+:I(PACKYEARS > 10)TRUE -0.11519 1.03713 0.308
## GLOBAL              NA 4.12032 0.660

stepAIC(surv.res)

## Start:  AIC=730.9
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT + I(PACKYEARS >
##    10) + HPV16_RNA:I(PACKYEARS > 10)
##
##                Df AIC
## - HPV16_RNA:I(PACKYEARS > 10)  1 729
## <none>                        731
## - ALTER_3CAT                  1 741
## - UICC_3CAT                    2 774
##
## Step:  AIC=729
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_RNA + ALTER_3CAT + I(PACKYEARS >
##    10)

## Error:  number of rows in use has changed:  remove missing values?
```

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= 80
##    (25 observations deleted due to missingness)
##
##                coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.17025   3.22281  0.31793   3.68  0.00023 ***
```

```

## UICC_3CATIVB-C          2.53086  12.56428  0.37828  6.69  2.2e-11 ***
## HPV16_DNA_RNADNA+RNA- -0.95135   0.38622  0.52447 -1.81  0.06969 .
## HPV16_DNA_RNADNA+RNA+ -1.43205   0.23882  0.44243 -3.24  0.00121 **
## ALTER                   0.02568   1.02601  0.01183  2.17  0.03000 *
## PACKYEARS               -0.00210   0.99791  0.00496 -0.42  0.67288
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.223      0.3103      1.728      6.010
## UICC_3CATIVB-C       12.564      0.0796      5.986     26.371
## HPV16_DNA_RNADNA+RNA-  0.386      2.5892      0.138      1.080
## HPV16_DNA_RNADNA+RNA+  0.239      4.1873      0.100      0.568
## ALTER                 1.026      0.9746      1.002      1.050
## PACKYEARS             0.998      1.0021      0.988      1.008
##
## Concordance= 0.731 (se = 0.036 )
## Rsquare= 0.215 (max possible= 0.96 )
## Likelihood ratio test= 58.7 on 6 df,  p=8.37e-11
## Wald test              = 58 on 6 df,  p=1.17e-10
## Score (logrank) test = 68.7 on 6 df,  p=7.43e-13

cox.zph(surv.res)

##                rho    chisq    p
## UICC_3CATIVA      -0.02611 0.05041 0.822
## UICC_3CATIVB-C    -0.02599 0.05050 0.822
## HPV16_DNA_RNADNA+RNA- -0.05574 0.25457 0.614
## HPV16_DNA_RNADNA+RNA+  0.07115 0.41306 0.520
## ALTER             -0.01357 0.02018 0.887
## PACKYEARS         -0.00701 0.00334 0.954
## GLOBAL              NA 0.79296 0.992

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

##                hr 2.5 % 97.5 %    p
## UICC_3CATIVA      3.22  1.73   6.01 0.000
## UICC_3CATIVB-C    12.56  5.99  26.37 0.000
## HPV16_DNA_RNADNA+RNA- 0.39  0.14   1.08 0.070
## HPV16_DNA_RNADNA+RNA+ 0.24  0.10   0.57 0.001
## ALTER             1.03  1.00   1.05 0.030
## PACKYEARS         1.00  0.99   1.01 0.673

# 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 46.33    8.7e-11 ***
## HPV16_DNA_RNA  2 13.01     0.0015 **
## ALTER          1  4.71     0.0300 *
## PACKYEARS       1  0.18     0.6729
## 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.su
  ], 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= 79
##      (28 observations deleted due to missingness)
##
##                                     coef
## UICC_3CATIVA                        1.16914
## UICC_3CATIVB-C                      2.73213
## HPV16_DNA_RNADNA+RNA-              -0.94476
## HPV16_DNA_RNADNA+RNA+             -1.40362
## ALTER                             0.02523
## PACKYEARS                         -0.00205
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.18029
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.70693
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    -0.27307
##                                     exp(coef)
## UICC_3CATIVA                        3.21921
## UICC_3CATIVB-C                     15.36561
## HPV16_DNA_RNADNA+RNA-              0.38877
## HPV16_DNA_RNADNA+RNA+              0.24571
## ALTER                             1.02555
## PACKYEARS                         0.99795
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.19757
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 2.02776
```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.76104
##                                                                    se(coef)
## UICC_3CATIVA                                                    0.32463
## UICC_3CATIVB-C                                                  0.39940
## HPV16_DNA_RNADNA+RNA-                                          0.52947
## HPV16_DNA_RNADNA+RNA+                                          0.46657
## ALTER                                                            0.01218
## PACKYEARS                                                       0.00519
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.30037
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.37096
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.35442
##                                                                    z
## UICC_3CATIVA                                                    3.60
## UICC_3CATIVB-C                                                  6.84
## HPV16_DNA_RNADNA+RNA-                                          -1.78
## HPV16_DNA_RNADNA+RNA+                                          -3.01
## ALTER                                                            2.07
## PACKYEARS                                                       -0.39
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.60
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.91
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      -0.77
##                                                                    Pr(>|z|)
## UICC_3CATIVA                                                    0.00032
## UICC_3CATIVB-C                                                  7.9e-12
## HPV16_DNA_RNADNA+RNA-                                          0.07437
## HPV16_DNA_RNADNA+RNA+                                          0.00263
## ALTER                                                            0.03836
## PACKYEARS                                                       0.69287
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.54835
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.05669
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.44102
##
## 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                                                    3.219
## UICC_3CATIVB-C                                                  15.366
## HPV16_DNA_RNADNA+RNA-                                          0.389

```

```

## HPV16_DNA_RNADNA+RNA+ 0.246
## ALTER 1.026
## PACKYEARS 0.998
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.198
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 2.028
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.761
## exp(-coef)
## UICC_3CATIVA 0.3106
## UICC_3CATIVB-C 0.0651
## HPV16_DNA_RNADNA+RNA- 2.5722
## HPV16_DNA_RNADNA+RNA+ 4.0699
## ALTER 0.9751
## PACKYEARS 1.0021
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.8350
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.4932
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.3140
## lower .95
## UICC_3CATIVA 1.7038
## UICC_3CATIVB-C 7.0239
## HPV16_DNA_RNADNA+RNA- 0.1377
## HPV16_DNA_RNADNA+RNA+ 0.0985
## ALTER 1.0014
## PACKYEARS 0.9879
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.6647
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.9801
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.3799
## upper .95
## UICC_3CATIVA 6.082
## UICC_3CATIVB-C 33.614
## HPV16_DNA_RNADNA+RNA- 1.097
## HPV16_DNA_RNADNA+RNA+ 0.613
## ALTER 1.050
## PACKYEARS 1.008
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 2.158
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 4.195
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.524
##
## Concordance= 0.732 (se = 0.036 )
## Rsquare= 0.235 (max possible= 0.96 )
## Likelihood ratio test= 64 on 9 df, p=2.22e-10
## Wald test = 62.3 on 9 df, p=4.92e-10
## Score (logrank) test = 75.1 on 9 df, p=1.52e-12

cox.zph(surv.res)

## rho
## UICC_3CATIVA 7.93e-05
## UICC_3CATIVB-C 3.69e-02
## HPV16_DNA_RNADNA+RNA- -7.61e-02

```

```

## HPV16_DNA_RNADNA+RNA+ 4.73e-02
## ALTER -1.20e-02
## PACKYEARS 4.52e-03
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 3.66e-02
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 2.20e-02
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -1.86e-01
## GLOBAL NA
## chisq
## UICC_3CATIVA 4.45e-07
## UICC_3CATIVB-C 1.18e-01
## HPV16_DNA_RNADNA+RNA- 4.58e-01
## HPV16_DNA_RNADNA+RNA+ 1.72e-01
## ALTER 1.62e-02
## PACKYEARS 1.45e-03
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.13e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 3.94e-02
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 2.52e+00
## GLOBAL 4.68e+00
## p
## UICC_3CATIVA 0.999
## UICC_3CATIVB-C 0.731
## HPV16_DNA_RNADNA+RNA- 0.499
## HPV16_DNA_RNADNA+RNA+ 0.678
## ALTER 0.899
## PACKYEARS 0.970
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.736
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.843
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.112
## GLOBAL 0.861

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

## hr 2.5 %
## UICC_3CATIVA 3.22 1.70
## UICC_3CATIVB-C 15.37 7.02
## HPV16_DNA_RNADNA+RNA- 0.39 0.14
## HPV16_DNA_RNADNA+RNA+ 0.25 0.10
## ALTER 1.03 1.00
## PACKYEARS 1.00 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.20 0.66
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 2.03 0.98
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.76 0.38
## 97.5 %
## UICC_3CATIVA 6.08
## UICC_3CATIVB-C 33.61
## HPV16_DNA_RNADNA+RNA- 1.10
## HPV16_DNA_RNADNA+RNA+ 0.61
## ALTER 1.05

```

```
## PACKYEARS 1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 2.16
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 4.20
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.52
## p
## UICC_3CATIVA 0.000
## UICC_3CATIVB-C 0.000
## HPV16_DNA_RNADNA+RNA- 0.074
## HPV16_DNA_RNADNA+RNA+ 0.003
## ALTER 0.038
## PACKYEARS 0.693
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.548
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.057
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.441

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 48.87 2.4e-11
## HPV16_DNA_RNA 2 11.25 0.0036
## ALTER 1 4.29 0.0384
## PACKYEARS 1 0.16 0.6929
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") 3 5.95 0.1141
## 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= 79
## (28 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        1.49998
## UICC_3CATIVB-C                      3.07146
## HPV16_DNA_RNADNA+RNA-              -0.85528
## HPV16_DNA_RNADNA+RNA+              -1.30493
## ALTER                              0.02010
## PACKYEARS                          -0.00369
## ALKOHOL1 bis 30                     0.47118
## ALKOHOL31 bis 60                    0.45198
## ALKOHOL>60                         0.60718
## THERAPIE_GROBmulti                  -0.78192
## THERAPIE_GROBpalliative             -0.26772
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris  0.50075
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx  0.21418
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 1.10060
##                                     exp(coef)
## UICC_3CATIVA                        4.48162
## UICC_3CATIVB-C                      21.57336
## HPV16_DNA_RNADNA+RNA-              0.42516
## HPV16_DNA_RNADNA+RNA+              0.27119
## ALTER                              1.02030
## PACKYEARS                          0.99632
## ALKOHOL1 bis 30                     1.60189
## ALKOHOL31 bis 60                    1.57142
## ALKOHOL>60                         1.83524
## THERAPIE_GROBmulti                  0.45753
## THERAPIE_GROBpalliative             0.76512
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris  1.64995
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx  1.23885
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx  3.00597
##                                     se(coef)      z
## UICC_3CATIVA                        0.35506   4.22
## UICC_3CATIVB-C                      0.43510   7.06
## HPV16_DNA_RNADNA+RNA-              0.53767  -1.59
## HPV16_DNA_RNADNA+RNA+              0.49574  -2.63
## ALTER                              0.01381   1.46
## PACKYEARS                          0.00552  -0.67
## ALKOHOL1 bis 30                     0.47995   0.98
## ALKOHOL31 bis 60                    0.51132   0.88
## ALKOHOL>60                         0.49889   1.22
## THERAPIE_GROBmulti                  0.31013  -2.52
```



```

## THERAPIE_GROBpalliative 0.69725 -0.38
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.36413 1.38
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.37869 0.57
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.42004 2.62
## Pr(>|z|)
## UICC_3CATIVA 2.4e-05 ***
## UICC_3CATIVB-C 1.7e-12 ***
## HPV16_DNA_RNADNA+RNA- 0.1117
## HPV16_DNA_RNADNA+RNA+ 0.0085 **
## ALTER 0.1455
## PACKYEARS 0.5040
## ALKOHOL1 bis 30 0.3262
## ALKOHOL31 bis 60 0.3767
## ALKOHOL>60 0.2236
## THERAPIE_GROBmulti 0.0117 *
## THERAPIE_GROBpalliative 0.7010
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.1691
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.5717
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.0088 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef)
## UICC_3CATIVA 4.482
## UICC_3CATIVB-C 21.573
## HPV16_DNA_RNADNA+RNA- 0.425
## HPV16_DNA_RNADNA+RNA+ 0.271
## ALTER 1.020
## PACKYEARS 0.996
## ALKOHOL1 bis 30 1.602
## ALKOHOL31 bis 60 1.571
## ALKOHOL>60 1.835
## THERAPIE_GROBmulti 0.458
## THERAPIE_GROBpalliative 0.765
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 1.650
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.239
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 3.006
## exp(-coef)
## UICC_3CATIVA 0.2231
## UICC_3CATIVB-C 0.0464
## HPV16_DNA_RNADNA+RNA- 2.3520
## HPV16_DNA_RNADNA+RNA+ 3.6874
## ALTER 0.9801
## PACKYEARS 1.0037
## ALKOHOL1 bis 30 0.6243
## ALKOHOL31 bis 60 0.6364
## ALKOHOL>60 0.5449
## THERAPIE_GROBmulti 2.1857

```

```

## THERAPIE_GROBpalliative 1.3070
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.6061
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.8072
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.3327
## lower .95
## UICC_3CATIVA 2.235
## UICC_3CATIVB-C 9.195
## HPV16_DNA_RNADNA+RNA- 0.148
## HPV16_DNA_RNADNA+RNA+ 0.103
## ALTER 0.993
## PACKYEARS 0.986
## ALKOHOL1 bis 30 0.625
## ALKOHOL31 bis 60 0.577
## ALKOHOL>60 0.690
## THERAPIE_GROBmulti 0.249
## THERAPIE_GROBpalliative 0.195
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.808
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.590
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 1.320
## upper .95
## UICC_3CATIVA 8.988
## UICC_3CATIVB-C 50.614
## HPV16_DNA_RNADNA+RNA- 1.220
## HPV16_DNA_RNADNA+RNA+ 0.717
## ALTER 1.048
## PACKYEARS 1.007
## ALKOHOL1 bis 30 4.104
## ALKOHOL31 bis 60 4.281
## ALKOHOL>60 4.879
## THERAPIE_GROBmulti 0.840
## THERAPIE_GROBpalliative 3.001
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.368
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.602
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 6.847
##
## Concordance= 0.749 (se = 0.036 )
## Rsquare= 0.261 (max possible= 0.96 )
## Likelihood ratio test= 72.4 on 14 df, p=6.95e-10
## Wald test = 70.2 on 14 df, p=1.8e-09
## Score (logrank) test = 83.7 on 14 df, p=5.7e-12

cox.zph(surv.res)

## rho
## UICC_3CATIVA -0.05886
## UICC_3CATIVB-C 0.00745
## HPV16_DNA_RNADNA+RNA- -0.09184
## HPV16_DNA_RNADNA+RNA+ -0.00555
## ALTER -0.04238

```

```

## PACKYEARS                                0.02363
## ALKOHOL1 bis 30                          -0.16148
## ALKOHOL31 bis 60                         -0.15014
## ALKOHOL>60                              -0.18514
## THERAPIE_GROBmulti                       0.07236
## THERAPIE_GROBpalliative                  0.05708
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.19894
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.19205
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.16324
## GLOBAL                                    NA
##                                           chisq      p
## UICC_3CATIVA                            0.35336 0.552
## UICC_3CATIVB-C                          0.00651 0.936
## HPV16_DNA_RNADNA+RNA-                  0.65980 0.417
## HPV16_DNA_RNADNA+RNA+                  0.00265 0.959
## ALTER                                   0.23659 0.627
## PACKYEARS                               0.03873 0.844
## ALKOHOL1 bis 30                         1.98870 0.158
## ALKOHOL31 bis 60                       1.78472 0.182
## ALKOHOL>60                             2.52589 0.112
## THERAPIE_GROBmulti                     0.61095 0.434
## THERAPIE_GROBpalliative                 0.31936 0.572
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.23649 0.072
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.53529 0.111
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 2.33200 0.127
## GLOBAL                                  9.11847 0.823

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

##                                           hr 2.5 %
## UICC_3CATIVA                            4.48 2.23
## UICC_3CATIVB-C                          21.57 9.20
## HPV16_DNA_RNADNA+RNA-                  0.43 0.15
## HPV16_DNA_RNADNA+RNA+                  0.27 0.10
## ALTER                                   1.02 0.99
## PACKYEARS                               1.00 0.99
## ALKOHOL1 bis 30                         1.60 0.63
## ALKOHOL31 bis 60                       1.57 0.58
## ALKOHOL>60                             1.84 0.69
## THERAPIE_GROBmulti                     0.46 0.25
## THERAPIE_GROBpalliative                 0.77 0.20
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 1.65 0.81
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.24 0.59
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 3.01 1.32
##                                           97.5 %      p
## UICC_3CATIVA                            8.99 0.000
## UICC_3CATIVB-C                          50.61 0.000
## HPV16_DNA_RNADNA+RNA-                  1.22 0.112

```

```
## HPV16_DNA_RNADNA+RNA+ 0.72 0.008
## ALTER 1.05 0.146
## PACKYEARS 1.01 0.504
## ALKOHOL1 bis 30 4.10 0.326
## ALKOHOL31 bis 60 4.28 0.377
## ALKOHOL>60 4.88 0.224
## THERAPIE_GROBmulti 0.84 0.012
## THERAPIE_GROBpalliative 3.00 0.701
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.37 0.169
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.60 0.572
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 6.85 0.009

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 51.55 6.4e-12 ***
## HPV16_DNA_RNA 2 8.41 0.015 *
## ALTER 1 2.12 0.146
## PACKYEARS 1 0.45 0.504
## ALKOHOL 3 1.50 0.681
## THERAPIE_GROB 2 6.51 0.039 *
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx") 3 7.91 0.048 *
## 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 Threrapy 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 + ALKOHOL + 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 + ALKOHOL + 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= 76
##      (33 observations deleted due to missingness)
##
##                                     coef
## UICC_3CATIVA                        0.93817
## UICC_3CATIVB-C                      2.49970
## HPV16_DNA_RNADNA+RNA-             -0.77317
## HPV16_DNA_RNADNA+RNA+             -1.39495
## ALTER                             0.02455
## PACKYEARS                         -0.00461
## ALKOHOL1 bis 30                    0.58733
## ALKOHOL31 bis 60                   0.51995
## ALKOHOL>60                        0.63183
## THERAPIE_GROB_NOPALLIATIVEmono    -0.22794
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris  0.50261
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx  0.17259
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 1.10283
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 1.36017
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 1.12292
##                                     exp(coef)
## UICC_3CATIVA                        2.55530
## UICC_3CATIVB-C                      12.17885
## HPV16_DNA_RNADNA+RNA-              0.46155
## HPV16_DNA_RNADNA+RNA+              0.24785
## ALTER                             1.02485
## PACKYEARS                         0.99540
## ALKOHOL1 bis 30                    1.79918
## ALKOHOL31 bis 60                   1.68194
## ALKOHOL>60                        1.88106
## THERAPIE_GROB_NOPALLIATIVEmono     0.79617
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris  1.65303
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx  1.18838
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 3.01269
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 3.89685
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 3.07383
##                                     se(coef)      z
## UICC_3CATIVA                        0.41173   2.28
## UICC_3CATIVB-C                      0.50403   4.96
## HPV16_DNA_RNADNA+RNA-              0.54236  -1.43
## HPV16_DNA_RNADNA+RNA+              0.50195  -2.78
## ALTER                             0.01431   1.72
## PACKYEARS                         0.00564  -0.82
## ALKOHOL1 bis 30                    0.51433   1.14
## ALKOHOL31 bis 60                   0.54009   0.96
## ALKOHOL>60                        0.52391   1.21
## THERAPIE_GROB_NOPALLIATIVEmono     0.59191  -0.39
```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.36674 1.37
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.38473 0.45
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.42413 2.60
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.68836 1.98
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.85617 1.31
## Pr(>|z|)
## UICC_3CATIVA 0.0227 *
## UICC_3CATIVB-C 7.1e-07 ***
## HPV16_DNA_RNADNA+RNA- 0.1540
## HPV16_DNA_RNADNA+RNA+ 0.0055 **
## ALTER 0.0863 .
## PACKYEARS 0.4139
## ALKOHOL1 bis 30 0.2535
## ALKOHOL31 bis 60 0.3357
## ALKOHOL>60 0.2278
## THERAPIE_GROB_NOPALLIATIVEmono 0.7002
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.1705
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.6537
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.0093 **
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.0482 *
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.1897
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef)
## UICC_3CATIVA 2.555
## UICC_3CATIVB-C 12.179
## HPV16_DNA_RNADNA+RNA- 0.462
## HPV16_DNA_RNADNA+RNA+ 0.248
## ALTER 1.025
## PACKYEARS 0.995
## ALKOHOL1 bis 30 1.799
## ALKOHOL31 bis 60 1.682
## ALKOHOL>60 1.881
## THERAPIE_GROB_NOPALLIATIVEmono 0.796
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 1.653
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.188
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 3.013
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 3.897
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 3.074
## exp(-coef)
## UICC_3CATIVA 0.3913
## UICC_3CATIVB-C 0.0821
## HPV16_DNA_RNADNA+RNA- 2.1666
## HPV16_DNA_RNADNA+RNA+ 4.0348
## ALTER 0.9758
## PACKYEARS 1.0046
## ALKOHOL1 bis 30 0.5558

```

```

## ALKOHOL31 bis 60 0.5945
## ALKOHOL>60 0.5316
## THERAPIE_GROB_NOPALLIATIVEmono 1.2560
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.6050
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.8415
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.3319
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.2566
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.3253
## lower .95
## UICC_3CATIVA 1.1402
## UICC_3CATIVB-C 4.5350
## HPV16_DNA_RNADNA+RNA- 0.1594
## HPV16_DNA_RNADNA+RNA+ 0.0927
## ALTER 0.9965
## PACKYEARS 0.9845
## ALKOHOL1 bis 30 0.6566
## ALKOHOL31 bis 60 0.5836
## ALKOHOL>60 0.6737
## THERAPIE_GROB_NOPALLIATIVEmono 0.2496
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.8056
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.5591
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 1.3120
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 1.0111
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.5740
## upper .95
## UICC_3CATIVA 5.727
## UICC_3CATIVB-C 32.707
## HPV16_DNA_RNADNA+RNA- 1.336
## HPV16_DNA_RNADNA+RNA+ 0.663
## ALTER 1.054
## PACKYEARS 1.006
## ALKOHOL1 bis 30 4.930
## ALKOHOL31 bis 60 4.848
## ALKOHOL>60 5.252
## THERAPIE_GROB_NOPALLIATIVEmono 2.540
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.392
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.526
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 6.918
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 15.019
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 16.461
##
## Concordance= 0.751 (se = 0.037 )
## Rsquare= 0.266 (max possible= 0.957 )
## Likelihood ratio test= 72.5 on 15 df, p=1.61e-09
## Wald test = 71 on 15 df, p=3.03e-09
## Score (logrank) test = 89.7 on 15 df, p=1.12e-12

cox.zph(surv.res)

```

```

##                                rho
## UICC_3CATIVA                  0.06767
## UICC_3CATIVB-C               0.10534
## HPV16_DNA_RNADNA+RNA-      -0.10150
## HPV16_DNA_RNADNA+RNA+      -0.00348
## ALTER                       -0.07988
## PACKYEARS                   0.00275
## ALKOHOL1 bis 30             -0.16683
## ALKOHOL31 bis 60            -0.12925
## ALKOHOL>60                  -0.17702
## THERAPIE_GROB_NOPALLIATIVEmono 0.07675
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 0.18224
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 0.19075
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 0.15314
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono -0.09243
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono -0.07973
## GLOBAL                      NA
##                                chisq      p
## UICC_3CATIVA                 0.383893 0.536
## UICC_3CATIVB-C               1.175046 0.278
## HPV16_DNA_RNADNA+RNA-       0.791621 0.374
## HPV16_DNA_RNADNA+RNA+       0.001006 0.975
## ALTER                       0.779553 0.377
## PACKYEARS                   0.000507 0.982
## ALKOHOL1 bis 30             2.102565 0.147
## ALKOHOL31 bis 60            1.360150 0.244
## ALKOHOL>60                  2.430975 0.119
## THERAPIE_GROB_NOPALLIATIVEmono 0.518395 0.472
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 2.686814 0.101
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.467580 0.116
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 2.036673 0.154
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 0.714716 0.398
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 0.551317 0.458
## GLOBAL                      8.705427 0.892

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

##                                hr 2.5 %
## UICC_3CATIVA                 2.56  1.14
## UICC_3CATIVB-C              12.18  4.54
## HPV16_DNA_RNADNA+RNA-       0.46  0.16
## HPV16_DNA_RNADNA+RNA+       0.25  0.09
## ALTER                       1.02  1.00
## PACKYEARS                   1.00  0.98
## ALKOHOL1 bis 30             1.80  0.66
## ALKOHOL31 bis 60            1.68  0.58
## ALKOHOL>60                  1.88  0.67
## THERAPIE_GROB_NOPALLIATIVEmono 0.80  0.25

```



```
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 1.65 0.81
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 1.19 0.56
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 3.01 1.31
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 3.90 1.01
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 3.07 0.57
## 97.5 % p
## UICC_3CATIVA 5.73 0.023
## UICC_3CATIVB-C 32.71 0.000
## HPV16_DNA_RNADNA+RNA- 1.34 0.154
## HPV16_DNA_RNADNA+RNA+ 0.66 0.005
## ALTER 1.05 0.086
## PACKYEARS 1.01 0.414
## ALKOHOL1 bis 30 4.93 0.253
## ALKOHOL31 bis 60 4.85 0.336
## ALKOHOL>60 5.25 0.228
## THERAPIE_GROB_NOPALLIATIVEmono 2.54 0.700
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")cavum oris 3.39 0.171
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")oropharynx 2.53 0.654
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx")hypopharynx 6.92 0.009
## UICC_3CATIVA:THERAPIE_GROB_NOPALLIATIVEmono 15.02 0.048
## UICC_3CATIVB-C:THERAPIE_GROB_NOPALLIATIVEmono 16.46 0.190

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 46.74 7.1e-11 ***
## HPV16_DNA_RNA 2 8.73 0.013 *
## ALTER 1 2.94 0.086 .
## PACKYEARS 1 0.67 0.414
## ALKOHOL 3 1.55 0.670
## THERAPIE_GROB_NOPALLIATIVE 1 6.46 0.011 *
## relevel(LOKALISATION_GROB_TEXT, ref = "larynx") 3 8.02 0.046 *
## UICC_3CAT:THERAPIE_GROB_NOPALLIATIVE 2 3.94 0.140
## 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= 19
##      (22 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.88775   6.60447  1.06325   1.78  0.07582 .
## UICC_3CATIVB-C      4.26041  70.83904  1.19902   3.55  0.00038 ***
## HPV16_DNA_RNADNA+RNA- -0.59442   0.55188  1.06560  -0.56  0.57696
## HPV16_DNA_RNADNA+RNA+ -1.74655   0.17437  0.69238  -2.52  0.01165 *
## ALTER              0.03257   1.03310  0.03044   1.07  0.28474
## PACKYEARS          0.00989   1.00994  0.01086   0.91  0.36261
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          6.604      0.1514      0.8219    53.074
## UICC_3CATIVB-C        70.839      0.0141      6.7556   742.821
## HPV16_DNA_RNADNA+RNA-   0.552      1.8120      0.0684     4.455
## HPV16_DNA_RNADNA+RNA+   0.174      5.7348      0.0449     0.677
## ALTER                 1.033      0.9680      0.9733     1.097
## PACKYEARS              1.010      0.9902      0.9887     1.032
##
## Concordance= 0.812 (se = 0.075 )
## Rsquare= 0.345 (max possible= 0.881 )
## Likelihood ratio test= 25.8 on 6 df,  p=0.000242
## Wald test              = 19.9 on 6 df,  p=0.00295
## Score (logrank) test = 29 on 6 df,  p=5.97e-05

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      -0.1370 0.2701 0.603
## UICC_3CATIVB-C      -0.0878 0.1122 0.738
## HPV16_DNA_RNADNA+RNA- -0.1828 0.5728 0.449
## HPV16_DNA_RNADNA+RNA+  0.0313 0.0268 0.870
## ALTER              0.1399 0.5841 0.445

```

```
## PACKYEARS          -0.0672 0.0979 0.754
## GLOBAL              NA 2.5491 0.863

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

##              hr 2.5 % 97.5 %      p
## UICC_3CATIVA      6.60 0.82 53.07 0.076
## UICC_3CATIVB-C    70.84 6.76 742.82 0.000
## HPV16_DNA_RNADNA+RNA- 0.55 0.07 4.46 0.577
## HPV16_DNA_RNADNA+RNA+ 0.17 0.04 0.68 0.012
## ALTER            1.03 0.97 1.10 0.285
## PACKYEARS         1.01 0.99 1.03 0.363

# 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 17.15 0.00019 ***
## HPV16_DNA_RNA  2  6.40 0.04068 *
## ALTER          1  1.14 0.28474
## PACKYEARS      1  0.83 0.36261
## 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= 85
##    (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## IS_MESENCHYMALMesenchymal 0.692      1.998      0.225 3.08   0.0021 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## IS_MESENCHYMALMesenchymal      2      0.501      1.29      3.1
##
## Concordance= 0.59 (se = 0.028 )
## Rsquare= 0.035 (max possible= 0.959 )
## Likelihood ratio test= 9.03 on 1 df,  p=0.00266
## Wald test              = 9.49 on 1 df,  p=0.00206
## Score (logrank) test = 9.86 on 1 df,  p=0.00168

cox.zph(surv.res)

##              rho chisq      p
## IS_MESENCHYMALMesenchymal -0.0696 0.407 0.523
```

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= 85
##    (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.417      4.123      0.332 4.27   2e-05 ***
## UICC_3CATIVB-C      2.383     10.835      0.408 5.85   5e-09 ***
## IS_MESENCHYMALMesenchymal 0.896      2.449      0.231 3.88   1e-04 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.12      0.2426      2.15      7.90
```

```
## UICC_3CATIVB-C          10.83      0.0923      4.87      24.09
## IS_MESENCHYMALMesenchymal      2.45      0.4083      1.56      3.85
##
## Concordance= 0.718 (se = 0.034 )
## Rsquare= 0.176 (max possible= 0.959 )
## Likelihood ratio test= 48.9 on 3 df, p=1.36e-10
## Wald test = 43.4 on 3 df, p=1.98e-09
## Score (logrank) test = 50.4 on 3 df, p=6.64e-11

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA      -0.0561 0.2594 0.611
## UICC_3CATIVB-C      -0.1347 1.5008 0.221
## IS_MESENCHYMALMesenchymal -0.0317 0.0874 0.767
## GLOBAL              NA  1.7196 0.633
```

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= 73
## (34 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNADNA+      -0.695      0.499      0.343 -2.02   0.0430 *
## IS_MESENCHYMALMesenchymal  0.626      1.871      0.238  2.63   0.0086 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNADNA+          0.499      2.003      0.255      0.978
## IS_MESENCHYMALMesenchymal  1.871      0.535      1.172      2.985
##
## Concordance= 0.621 (se = 0.035 )
## Rsquare= 0.054 (max possible= 0.951 )
## Likelihood ratio test= 12.9 on 2 df, p=0.0016
## Wald test = 12.2 on 2 df, p=0.00221
## Score (logrank) test = 12.8 on 2 df, p=0.00163

cox.zph(surv.res)
```

```
##               rho chisq    p
## HPV16_DNADNA+      0.0478 0.165 0.685
## IS_MESENCHYMALMesenchymal -0.1116 0.901 0.343
## GLOBAL              NA 1.158 0.560
```

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= 73
##    (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.499      4.476   0.346  4.34 1.5e-05 ***
## UICC_3CATIVB-C     2.893     18.044   0.431  6.71 2.0e-11 ***
## HPV16_DNADNA+    -1.007      0.365   0.348 -2.89 0.00380 **
## IS_MESENCHYMALMesenchymal  0.828      2.290   0.243  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      4.476      0.2234    2.273    8.815
## UICC_3CATIVB-C    18.044      0.0554    7.746   42.030
## HPV16_DNADNA+     0.365      2.7381    0.185    0.722
## IS_MESENCHYMALMesenchymal  2.290      0.4368    1.422    3.688
##
## Concordance= 0.745 (se = 0.037 )
## Rsquare= 0.228 (max possible= 0.951 )
## Likelihood ratio test= 60.2 on 4 df,  p=2.57e-12
## Wald test              = 55.8 on 4 df,  p=2.2e-11
## Score (logrank) test = 66 on 4 df,  p=1.57e-13

cox.zph(surv.res)

##               rho chisq    p
## UICC_3CATIVA     -0.0473 0.1545 0.694
## UICC_3CATIVB-C   -0.0144 0.0145 0.904
## HPV16_DNADNA+     0.0543 0.2078 0.648
## IS_MESENCHYMALMesenchymal -0.0342 0.0853 0.770
## GLOBAL              NA 0.5360 0.970
```

5.2.5 HPV16 DNA RNA, Mesenchymal

```

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + IS_MESENCHYMAL,
##       data = ds[cur.subset, ])
##
##      n= 233, number of events= 73
##      (34 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA-    -0.516     0.597   0.517 -1.00   0.3177
## HPV16_DNA_RNADNA+RNA+    -0.800     0.449   0.432 -1.85   0.0640 .
## IS_MESENCHYMALMesenchymal  0.617     1.853   0.239  2.58   0.0099 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-     0.597      1.68   0.217   1.64
## HPV16_DNA_RNADNA+RNA+     0.449      2.23   0.193   1.05
## IS_MESENCHYMALMesenchymal  1.853      0.54   1.160   2.96
##
## Concordance= 0.627 (se = 0.035 )
## Rsquare= 0.055 (max possible= 0.951 )
## Likelihood ratio test= 13.1 on 3 df,  p=0.00451
## Wald test               = 12.2 on 3 df,  p=0.00678
## Score (logrank) test = 12.9 on 3 df,  p=0.00488

cox.zph(surv.res)

##              rho chisq      p
## HPV16_DNA_RNADNA+RNA-    0.0463 0.1567 0.692
## HPV16_DNA_RNADNA+RNA+    0.0347 0.0861 0.769
## IS_MESENCHYMALMesenchymal -0.1131 0.9163 0.338
## GLOBAL                   NA 1.2216 0.748

```

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= 73
##      (34 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.498      4.472    0.346  4.33 1.5e-05 ***
## UICC_3CATIVB-C      2.890     17.997    0.432  6.69 2.2e-11 ***
## HPV16_DNA_RNADNA+RNA- -0.966      0.381    0.524 -1.84 0.06516 .
## HPV16_DNA_RNADNA+RNA+ -1.034      0.355    0.437 -2.37 0.01794 *
## IS_MESENCHYMALMesenchymal 0.824      2.280    0.246  3.35 0.00081 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.472      0.2236      2.271      8.808
## UICC_3CATIVB-C     17.997      0.0556      7.716     41.976
## HPV16_DNA_RNADNA+RNA- 0.381      2.6271      0.136      1.063
## HPV16_DNA_RNADNA+RNA+ 0.355      2.8133      0.151      0.837
## IS_MESENCHYMALMesenchymal 2.280      0.4386      1.407      3.694
##
## Concordance= 0.745 (se = 0.037 )
## Rsquare= 0.228 (max possible= 0.951 )
## Likelihood ratio test= 60.3 on 5 df,  p=1.07e-11
## Wald test              = 55.8 on 5 df,  p=9.03e-11
## Score (logrank) test = 66 on 5 df,  p=6.89e-13

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      -0.0472 0.1535 0.695
## UICC_3CATIVB-C      -0.0136 0.0134 0.908
## HPV16_DNA_RNADNA+RNA- 0.0201 0.0313 0.860
## HPV16_DNA_RNADNA+RNA+ 0.0566 0.2235 0.636
## IS_MESENCHYMALMesenchymal -0.0305 0.0690 0.793
## GLOBAL              NA 0.5716 0.989
```

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= 73
## (34 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.560      4.757   0.349  4.46  8.0e-06 ***
## UICC_3CATIVB-C     2.989     19.870   0.436  6.85  7.2e-12 ***
## HPV16_DNA_RNADNA+RNA- -0.886    0.412   0.522 -1.70  0.0898 .
## HPV16_DNA_RNADNA+RNA+ -1.111    0.329   0.440 -2.53  0.0115 *
## ALTER_3CAT(50,70] -0.618    0.539   0.246 -2.51  0.0120 *
## IS_MESENCHYMALMesenchymal 0.707    2.027   0.249  2.84  0.0046 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.757    0.2102    2.399    9.435
## UICC_3CATIVB-C     19.870    0.0503    8.452   46.711
## HPV16_DNA_RNADNA+RNA- 0.412    2.4262    0.148    1.147
## HPV16_DNA_RNADNA+RNA+ 0.329    3.0364    0.139    0.780
## ALTER_3CAT(50,70]  0.539    1.8547    0.333    0.873
## IS_MESENCHYMALMesenchymal 2.027    0.4932    1.244    3.304
##
## Concordance= 0.758 (se = 0.037 )
## Rsquare= 0.248 (max possible= 0.951 )
## Likelihood ratio test= 66.4 on 6 df, p=2.19e-12
## Wald test = 61.6 on 6 df, p=2.11e-11
## Score (logrank) test = 71.2 on 6 df, p=2.35e-13

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA     -0.0225 0.0345 0.853
## UICC_3CATIVB-C    0.0203 0.0279 0.867
## HPV16_DNA_RNADNA+RNA- 0.0154 0.0178 0.894
## HPV16_DNA_RNADNA+RNA+ 0.0189 0.0256 0.873
## ALTER_3CAT(50,70] -0.1576 2.0544 0.152
## IS_MESENCHYMALMesenchymal -0.0883 0.6222 0.430
## GLOBAL              NA 2.6518 0.851
```

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= 72
## (36 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.52041   4.57411  0.34761  4.37  1.2e-05 ***
## UICC_3CATIVB-C     2.87906  17.79755  0.43254  6.66  2.8e-11 ***
## HPV16_DNA_RNADNA+RNA- -0.81854  0.44108  0.52439 -1.56  0.11854
## HPV16_DNA_RNADNA+RNA+ -1.24455  0.28807  0.45197 -2.75  0.00589 **
## ALTER              0.02619  1.02654  0.01220  2.15  0.03180 *
## PACKYEARS          -0.00269  0.99732  0.00506 -0.53  0.59569
## IS_MESENCHYMALMesenchymal 0.82839  2.28963  0.24933  3.32  0.00089 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.574      0.2186      2.314      9.040
## UICC_3CATIVB-C    17.798      0.0562      7.624     41.547
## HPV16_DNA_RNADNA+RNA- 0.441      2.2672      0.158      1.233
## HPV16_DNA_RNADNA+RNA+ 0.288      3.4714      0.119      0.699
## ALTER              1.027      0.9741      1.002      1.051
## PACKYEARS          0.997      1.0027      0.987      1.007
## IS_MESENCHYMALMesenchymal 2.290      0.4368      1.405      3.732
##
## Concordance= 0.763 (se = 0.038 )
## Rsquare= 0.243 (max possible= 0.951 )
## Likelihood ratio test= 64.4 on 7 df,  p=1.97e-11
## Wald test              = 60 on 7 df,  p=1.5e-10
## Score (logrank) test = 68.7 on 7 df,  p=2.72e-12

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA     -0.07525  0.368226  0.544
## UICC_3CATIVB-C   -0.00910  0.005662  0.940
## HPV16_DNA_RNADNA+RNA- -0.00132  0.000134  0.991
## HPV16_DNA_RNADNA+RNA+  0.04261  0.131783  0.717
## ALTER            -0.01942  0.035203  0.851
## PACKYEARS        -0.06193  0.241967  0.623
## IS_MESENCHYMALMesenchymal 0.00583  0.002518  0.960
## GLOBAL           NA 1.075154  0.994

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

```
##           hr 2.5 % 97.5 %      p
## UICC_3CATIVA      4.57  2.31   9.04 0.000
## UICC_3CATIVB-C    17.80  7.62  41.55 0.000
## HPV16_DNA_RNADNA+RNA-  0.44  0.16   1.23 0.119
## HPV16_DNA_RNADNA+RNA+  0.29  0.12   0.70 0.006
## ALTER            1.03  1.00   1.05 0.032
## PACKYEARS         1.00  0.99   1.01 0.596
## IS_MESENCHYMALMesenchymal 2.29  1.40   3.73 0.001
```

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

	hr	2.5 %	97.5 %	p
UICC_3CATIVA	4.57	2.31	9.04	0.000
UICC_3CATIVB-C	17.80	7.62	41.55	0.000
HPV16_DNA_RNADNA+RNA-	0.44	0.16	1.23	0.119
HPV16_DNA_RNADNA+RNA+	0.29	0.12	0.70	0.006
ALTER	1.03	1.00	1.05	0.032
PACKYEARS	1.00	0.99	1.01	0.596
IS_MESENCHYMALMesenchymal	2.29	1.40	3.73	0.001

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= 72
```

```

##      (22 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.46424    4.32424  0.34782   4.21 2.6e-05
## UICC_3CATIVB-C      2.87934   17.80255  0.43166   6.67 2.6e-11
## HPV16_DNA_RNADNA+RNA- -0.80771    0.44588  0.52499  -1.54  0.124
## HPV16_DNA_RNADNA+RNA+ -1.49387    0.22450  0.48257  -3.10  0.002
## ALTER              0.02560    1.02593  0.01230   2.08  0.037
## PACKYEARS         -0.00282    0.99718  0.00512  -0.55  0.582
## CONSENSUS_CLUSTERAtypical  0.79724    2.21940  0.57603   1.38  0.166
## CONSENSUS_CLUSTERBasal    0.39070    1.47802  0.56645   0.69  0.490
## CONSENSUS_CLUSTERMesenchymal 1.30484    3.68709  0.53948   2.42  0.016
##
## 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      4.324    0.2313    2.1870    8.550
## UICC_3CATIVB-C     17.803    0.0562    7.6393   41.487
## HPV16_DNA_RNADNA+RNA-  0.446    2.2428    0.1593    1.248
## HPV16_DNA_RNADNA+RNA+  0.225    4.4543    0.0872    0.578
## ALTER              1.026    0.9747    1.0015    1.051
## PACKYEARS          0.997    1.0028    0.9872    1.007
## CONSENSUS_CLUSTERAtypical  2.219    0.4506    0.7177    6.864
## CONSENSUS_CLUSTERBasal    1.478    0.6766    0.4870    4.486
## CONSENSUS_CLUSTERMesenchymal 3.687    0.2712    1.2808   10.614
##
## Concordance= 0.771 (se = 0.038 )
## Rsquare= 0.251 (max possible= 0.951 )
## Likelihood ratio test= 66.9 on 9 df, p=6.19e-11
## Wald test = 61.9 on 9 df, p=5.65e-10
## Score (logrank) test = 71.1 on 9 df, p=9.14e-12
##
## # cox.zph(surv.res) stepAIC(surv.res)
## coxtable(surv.res)
##
##              hr 2.5 % 97.5 %      p
## UICC_3CATIVA      4.32  2.19   8.55 0.000
## UICC_3CATIVB-C     17.80  7.64  41.49 0.000
## HPV16_DNA_RNADNA+RNA-  0.45  0.16   1.25 0.124

```

```
## HPV16_DNA_RNADNA+RNA+      0.22  0.09   0.58 0.002
## ALTER                      1.03  1.00   1.05 0.037
## PACKYEARS                  1.00  0.99   1.01 0.582
## CONSENSUS_CLUSTERAtypical  2.22  0.72   6.86 0.166
## CONSENSUS_CLUSTERBasal     1.48  0.49   4.49 0.490
## CONSENSUS_CLUSTERMesenchymal 3.69  1.28  10.61 0.016

# 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 44.73   1.9e-10 ***
## HPV16_DNA_RNA  2 11.36    0.0034 **
## ALTER          1  4.33    0.0374 *
## PACKYEARS      1  0.30    0.5816
## CONSENSUS_CLUSTER 3 12.49    0.0059 **
## 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= 71
##    (25 observations deleted due to missingness)
##
##                                     coef
## UICC_3CATIVA                        1.43392
## UICC_3CATIVB-C                      3.05920
## HPV16_DNA_RNADNA+RNA-              -0.86957
## HPV16_DNA_RNADNA+RNA+              -1.59827
## ALTER                             0.02760
## PACKYEARS                          -0.00365
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.00457
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.33147
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     -0.53215
## CONSENSUS_CLUSTERAtypical          0.74310
## CONSENSUS_CLUSTERBasal              0.44272
## CONSENSUS_CLUSTERMesenchymal        1.24040
##                                     exp(coef)
## UICC_3CATIVA                        4.19511
## UICC_3CATIVB-C                      21.31040
## HPV16_DNA_RNADNA+RNA-              0.41913
## HPV16_DNA_RNADNA+RNA+              0.20225
## ALTER                             1.02798
## PACKYEARS                          0.99636
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.00458
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.39301
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     0.58734
## CONSENSUS_CLUSTERAtypical          2.10244
## CONSENSUS_CLUSTERBasal              1.55694
## CONSENSUS_CLUSTERMesenchymal        3.45700
##                                     se(coef)
## UICC_3CATIVA                        0.35479
## UICC_3CATIVB-C                      0.45022
## HPV16_DNA_RNADNA+RNA-              0.53244
## HPV16_DNA_RNADNA+RNA+              0.52371

```

```

## ALTER 0.01296
## PACKYEARS 0.00547
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.32132
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.39438
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.41522
## CONSENSUS_CLUSTERAtypical 0.59074
## CONSENSUS_CLUSTERBasal 0.57866
## CONSENSUS_CLUSTERMesenchymal 0.55489
## z
## UICC_3CATIVA 4.04
## UICC_3CATIVB-C 6.79
## HPV16_DNA_RNADNA+RNA- -1.63
## HPV16_DNA_RNADNA+RNA+ -3.05
## ALTER 2.13
## PACKYEARS -0.67
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.01
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.84
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -1.28
## CONSENSUS_CLUSTERAtypical 1.26
## CONSENSUS_CLUSTERBasal 0.77
## CONSENSUS_CLUSTERMesenchymal 2.24
## Pr(>|z|)
## UICC_3CATIVA 5.3e-05
## UICC_3CATIVB-C 1.1e-11
## HPV16_DNA_RNADNA+RNA- 0.1024
## HPV16_DNA_RNADNA+RNA+ 0.0023
## ALTER 0.0332
## PACKYEARS 0.5045
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.9886
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.4006
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.2000
## CONSENSUS_CLUSTERAtypical 0.2084
## CONSENSUS_CLUSTERBasal 0.4442
## CONSENSUS_CLUSTERMesenchymal 0.0254
##
## UICC_3CATIVA ***
## UICC_3CATIVB-C ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+ **
## ALTER *
## PACKYEARS
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx
## releval(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                        4.195
## UICC_3CATIVB-C                     21.310
## HPV16_DNA_RNADNA+RNA-              0.419
## HPV16_DNA_RNADNA+RNA+              0.202
## ALTER                              1.028
## PACKYEARS                           0.996
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.005
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.393
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.587
## CONSENSUS_CLUSTERAtypical          2.102
## CONSENSUS_CLUSTERBasal              1.557
## CONSENSUS_CLUSTERMesenchymal       3.457
##                                     exp(-coef)
## UICC_3CATIVA                        0.2384
## UICC_3CATIVB-C                     0.0469
## HPV16_DNA_RNADNA+RNA-              2.3859
## HPV16_DNA_RNADNA+RNA+              4.9445
## ALTER                              0.9728
## PACKYEARS                           1.0037
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.9954
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.7179
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      1.7026
## CONSENSUS_CLUSTERAtypical          0.4756
## CONSENSUS_CLUSTERBasal              0.6423
## CONSENSUS_CLUSTERMesenchymal       0.2893
##                                     lower .95
## UICC_3CATIVA                        2.0929
## UICC_3CATIVB-C                     8.8178
## HPV16_DNA_RNADNA+RNA-              0.1476
## HPV16_DNA_RNADNA+RNA+              0.0725
## ALTER                              1.0022
## PACKYEARS                           0.9857
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.5352
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.6431
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.2603
## CONSENSUS_CLUSTERAtypical          0.6605
## CONSENSUS_CLUSTERBasal              0.5009
## CONSENSUS_CLUSTERMesenchymal       1.1651
##                                     upper .95
## UICC_3CATIVA                        8.409
## UICC_3CATIVB-C                     51.502
## HPV16_DNA_RNADNA+RNA-              1.190
## HPV16_DNA_RNADNA+RNA+              0.564
## ALTER                              1.054
## PACKYEARS                           1.007

```



```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris      1.886
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx    3.018
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx         1.325
## CONSENSUS_CLUSTERAtypical                                         6.692
## CONSENSUS_CLUSTERBasal                                           4.840
## CONSENSUS_CLUSTERMesenchymal                                    10.257
##
## Concordance= 0.767  (se = 0.038 )
## Rsquare= 0.265  (max possible= 0.95 )
## Likelihood ratio test= 70.1  on 12 df,  p=3.05e-10
## Wald test               = 63.4  on 12 df,  p=5.47e-09
## Score (logrank) test = 74.8  on 12 df,  p=3.95e-11

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

##                                     hr 2.5 %
## UICC_3CATIVA                      4.20  2.09
## UICC_3CATIVB-C                    21.31  8.82
## HPV16_DNA_RNADNA+RNA-            0.42  0.15
## HPV16_DNA_RNADNA+RNA+            0.20  0.07
## ALTER                            1.03  1.00
## PACKYEARS                         1.00  0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris    1.00  0.54
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx    1.39  0.64
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx         0.59  0.26
## CONSENSUS_CLUSTERAtypical       2.10  0.66
## CONSENSUS_CLUSTERBasal          1.56  0.50
## CONSENSUS_CLUSTERMesenchymal    3.46  1.17
##                                     97.5 %
## UICC_3CATIVA                      8.41
## UICC_3CATIVB-C                    51.50
## HPV16_DNA_RNADNA+RNA-            1.19
## HPV16_DNA_RNADNA+RNA+            0.56
## ALTER                            1.05
## PACKYEARS                         1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris    1.89
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx    3.02
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx         1.33
## CONSENSUS_CLUSTERAtypical       6.69
## CONSENSUS_CLUSTERBasal          4.84
## CONSENSUS_CLUSTERMesenchymal    10.26
##                                     p
## UICC_3CATIVA                      0.000
## UICC_3CATIVB-C                    0.000
## HPV16_DNA_RNADNA+RNA-            0.102
## HPV16_DNA_RNADNA+RNA+            0.002
## ALTER                            0.033
## PACKYEARS                         0.504

```

```
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.989
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.401
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.200
## CONSENSUS_CLUSTERAtypical 0.208
## CONSENSUS_CLUSTERBasal 0.444
## CONSENSUS_CLUSTERMesenchymal 0.025

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 46.65 7.4e-11
## HPV16_DNA_RNA 2 11.09 0.0039
## ALTER 1 4.54 0.0332
## PACKYEARS 1 0.45 0.5045
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") 3 3.48 0.3230
## CONSENSUS_CLUSTER 3 9.73 0.0210
## 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= 71
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 1.086 2.963 0.323 3.36 0.00077 ***
```

```
## UICC_3CATIVB-C 2.465 11.768 0.391 6.30 2.9e-10 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 2.96 0.338 1.57 5.58
## UICC_3CATIVB-C 11.77 0.085 5.47 25.32
##
## Concordance= 0.685 (se = 0.034 )
## Rsquare= 0.179 (max possible= 0.968 )
## Likelihood ratio test= 37.4 on 2 df, p=7.66e-09
## Wald test = 40.7 on 2 df, p=1.46e-09
## Score (logrank) test = 52.9 on 2 df, p=3.31e-12

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA -0.000468 1.47e-05 0.997
## UICC_3CATIVB-C -0.066681 2.95e-01 0.587
## GLOBAL NA 5.06e-01 0.776
```

5.3.2 UICC, AGE

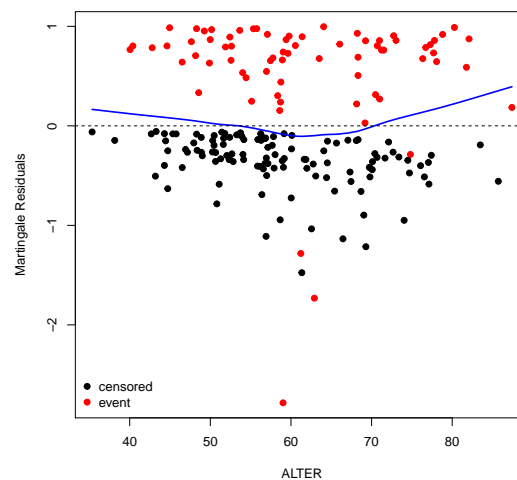
```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER, data = ds[cur.subset,
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER, data = ds[cur.subset,
## ], model = TRUE)
##
## n= 189, number of events= 71
##
## coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 1.0804 2.9457 0.3223 3.35 0.0008 ***
## UICC_3CATIVB-C 2.4600 11.7052 0.3906 6.30 3e-10 ***
## ALTER 0.0237 1.0240 0.0125 1.90 0.0579 .
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 2.95 0.3395 1.566 5.54
## UICC_3CATIVB-C 11.71 0.0854 5.444 25.17
## ALTER 1.02 0.9766 0.999 1.05
##
## Concordance= 0.714 (se = 0.038 )
## Rsquare= 0.195 (max possible= 0.968 )
```

```
## Likelihood ratio test= 40.9 on 3 df, p=6.8e-09
## Wald test = 43.6 on 3 df, p=1.79e-09
## Score (logrank) test = 56.1 on 3 df, p=4.07e-12
```

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

```
##           rho   chisq    p
## UICC_3CATIVA -0.00751 0.00374 0.951
## UICC_3CATIVB-C -0.07041 0.32274 0.570
## ALTER        0.01575 0.02427 0.876
## GLOBAL              NA 0.51751 0.915
```



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= 71
```

```
##
```

```
##           coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA  1.168    3.216   0.326   3.58  0.00034 ***
## UICC_3CATIVB-C  2.692   14.763   0.402   6.69  2.2e-11 ***
## ALTER_3CAT(50,70] -0.831    0.436   0.252  -3.30  0.00096 ***
```

```
## ---
```

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

```
##
```

```
##           exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.216    0.3109    1.697    6.097
```

```
## UICC_3CATIVB-C      14.763      0.0677      6.710      32.481
## ALTER_3CAT(50,70]    0.436      2.2951      0.266      0.713
##
## Concordance= 0.711 (se = 0.037 )
## Rsquare= 0.224 (max possible= 0.968 )
## Likelihood ratio test= 48 on 3 df, p=2.12e-10
## Wald test           = 49.8 on 3 df, p=8.79e-11
## Score (logrank) test = 62.9 on 3 df, p=1.39e-13

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.045439 1.38e-01 0.710
## UICC_3CATIVB-C     0.000216 3.06e-06 0.999
## ALTER_3CAT(50,70] -0.165980 2.11e+00 0.146
## GLOBAL              NA 2.52e+00 0.471
```

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= 70
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.148      3.150    0.326  3.52 0.00044 ***
## UICC_3CATIVB-C     2.690     14.725    0.403  6.67 2.6e-11 ***
## ALTER_3CAT(50,70] -0.965      0.381    0.267 -3.61 0.00030 ***
## I(PACKYEARS > 30)TRUE 0.443      1.557    0.260  1.70 0.08918 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.150    0.3174    1.662    5.971
## UICC_3CATIVB-C     14.725    0.0679    6.678   32.467
## ALTER_3CAT(50,70]    0.381    2.6261    0.226    0.643
## I(PACKYEARS > 30)TRUE  1.557    0.6423    0.934    2.594
##
## Concordance= 0.718 (se = 0.038 )
## Rsquare= 0.236 (max possible= 0.967 )
## Likelihood ratio test= 50.5 on 4 df, p=2.77e-10
```

```
## Wald test          = 51  on 4 df,    p=2.23e-10
## Score (logrank) test = 65  on 4 df,    p=2.62e-13

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA      0.0193 0.0242 0.876
## UICC_3CATIVB-C    -0.0213 0.0293 0.864
## ALTER_3CAT(50,70] -0.2005 3.0657 0.080
## I(PACKYEARS > 30)TRUE 0.1423 1.4526 0.228
## GLOBAL              NA 4.1006 0.393
```

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= 71
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.174      3.233   0.327   3.59 0.00033 ***
## UICC_3CATIVB-C      2.708     15.001   0.405   6.68 2.3e-11 ***
## ALTER_3CAT(50,70] -0.866      0.420   0.256  -3.39 0.00070 ***
## ALKOHOL1 bis 30      0.235      1.265   0.484   0.49 0.62668
## ALKOHOL31 bis 60      0.259      1.296   0.483   0.54 0.59145
## ALKOHOL>60          0.366      1.442   0.455   0.81 0.42041
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.23    0.3093    1.703    6.138
## UICC_3CATIVB-C        15.00    0.0667    6.780   33.188
## ALTER_3CAT(50,70]      0.42    2.3783    0.255    0.694
## ALKOHOL1 bis 30        1.27    0.7903    0.490    3.266
## ALKOHOL31 bis 60        1.30    0.7715    0.503    3.343
## ALKOHOL>60            1.44    0.6933    0.592    3.516
```

```
##
## Concordance= 0.717 (se = 0.038 )
## Rsquare= 0.227 (max possible= 0.968 )
## Likelihood ratio test= 48.8 on 6 df, p=8.34e-09
## Wald test = 49.7 on 6 df, p=5.31e-09
## Score (logrank) test = 63.4 on 6 df, p=9.26e-12

cox.zph(surv.res)

##               rho   chisq    p
## UICC_3CATIVA      0.0343 0.07922 0.778
## UICC_3CATIVB-C    -0.0102 0.00723 0.932
## ALTER_3CAT(50,70] -0.1183 1.11182 0.292
## ALKOHOL1 bis 30   -0.1675 2.01993 0.155
## ALKOHOL31 bis 60  -0.1912 2.62197 0.105
## ALKOHOL>60        -0.1983 3.00497 0.083
## GLOBAL            NA 5.44741 0.488
```

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= 70
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## PACKYEARS -0.00427  0.99574  0.00601 -0.71    0.48
##
##               exp(coef) exp(-coef) lower .95 upper .95
## PACKYEARS      0.996          1    0.984      1.01
##
## Concordance= 0.517 (se = 0.038 )
## Rsquare= 0.003 (max possible= 0.967 )
## Likelihood ratio test= 0.51 on 1 df, p=0.473
## Wald test = 0.5 on 1 df, p=0.477
## Score (logrank) test = 0.5 on 1 df, p=0.478

cox.zph(surv.res)

##               rho chisq    p
## PACKYEARS 0.077 0.417 0.518
```

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= 70
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.07965    2.94365  0.32391   3.33 0.00086 ***
## UICC_3CATIVB-C    2.45890   11.69196  0.39182   6.28 3.5e-10 ***
## PACKYEARS        -0.00316    0.99684  0.00582  -0.54 0.58662
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          2.944    0.3397    1.560    5.55
## UICC_3CATIVB-C       11.692    0.0855    5.425   25.20
## PACKYEARS             0.997    1.0032    0.986    1.01
##
## Concordance= 0.688 (se = 0.038 )
## Rsquare= 0.181 (max possible= 0.967 )
## Likelihood ratio test= 37.5 on 3 df, p=3.61e-08
## Wald test              = 40.9 on 3 df, p=6.83e-09
## Score (logrank) test = 53.2 on 3 df, p=1.64e-11

cox.zph(surv.res)

##              rho    chisq      p
## UICC_3CATIVA   -0.01197 0.00946 0.923
## UICC_3CATIVB-C -0.06108 0.24223 0.623
## PACKYEARS      -0.00773 0.00397 0.950
## GLOBAL         NA 0.32855 0.955
```

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= 70
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.07094    2.91811  0.32331  3.31 0.00092 ***
## UICC_3CATIVB-C    2.45094   11.59926  0.39158  6.26 3.9e-10 ***
## ALTER            0.02299    1.02326  0.01235  1.86 0.06266 .
## PACKYEARS        -0.00273    0.99727  0.00565 -0.48 0.62899
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          2.918      0.3427      1.548      5.50
## UICC_3CATIVB-C       11.599      0.0862      5.384     24.99
## ALTER                1.023      0.9773      0.999      1.05
## PACKYEARS            0.997      1.0027      0.986      1.01
##
## Concordance= 0.712 (se = 0.038 )
## Rsquare= 0.196 (max possible= 0.967 )
## Likelihood ratio test= 40.9 on 4 df,  p=2.76e-08
## Wald test              = 44 on 4 df,  p=6.36e-09
## Score (logrank) test = 56.6 on 4 df,  p=1.52e-11

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA   -0.0190 0.0237 0.878
## UICC_3CATIVB-C -0.0664 0.2804 0.596
## ALTER          0.0184 0.0319 0.858
## PACKYEARS      -0.0171 0.0185 0.892
## GLOBAL         NA 0.3948 0.983
```

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= 70
##      (1 observation deleted due to missingness)
```

```
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.15853   3.18523  0.32744  3.54  0.0004 ***
## UICC_3CATIVB-C     2.72025  15.18410  0.40659  6.69  2.2e-11 ***
## ALTER_3CAT(50,70] -0.87444   0.41710  0.26983 -3.24  0.0012 **
## PACKYEARS          0.00331   1.00332  0.00598  0.55  0.5796
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.185      0.3139      1.677      6.051
## UICC_3CATIVB-C       15.184      0.0659      6.844     33.688
## ALTER_3CAT(50,70]     0.417      2.3975      0.246      0.708
## PACKYEARS             1.003      0.9967      0.992      1.015
##
## Concordance= 0.715 (se = 0.038 )
## Rsquare= 0.225 (max possible= 0.967 )
## Likelihood ratio test= 47.9 on 4 df, p=9.91e-10
## Wald test               = 49.5 on 4 df, p=4.67e-10
## Score (logrank) test = 62.9 on 4 df, p=7.12e-13

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA      0.03459 0.077732 0.780
## UICC_3CATIVB-C    -0.00196 0.000243 0.988
## ALTER_3CAT(50,70] -0.16691 2.247783 0.134
## PACKYEARS         0.02730 0.049836 0.823
## GLOBAL            NA 2.742027 0.602
```

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= 20
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      2.0205   7.5423  1.0473  1.93  0.0537 .
```

```
## UICC_3CATIVB-C      3.6921   40.1297   1.1594   3.18   0.0015 **
## ALTER_3CAT(50,70] -1.2514    0.2861   0.5700 -2.20   0.0281 *
## PACKYEARS           0.0115    1.0116   0.0117   0.98   0.3260
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA         7.542    0.1326    0.9684   58.745
## UICC_3CATIVB-C       40.130    0.0249    4.1356  389.394
## ALTER_3CAT(50,70]    0.286    3.4953    0.0936    0.874
## PACKYEARS            1.012    0.9885    0.9886    1.035
##
## Concordance= 0.769 (se = 0.075 )
## Rsquare= 0.298 (max possible= 0.923 )
## Likelihood ratio test= 17.7 on 4 df, p=0.00143
## Wald test = 12.9 on 4 df, p=0.0116
## Score (logrank) test = 17.6 on 4 df, p=0.00146

# 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= 63
## (10 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## IS_MESENCHYMALMesenchymal 0.630    1.877    0.254  2.48   0.013 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## IS_MESENCHYMALMesenchymal    1.88    0.533    1.14    3.09
##
## Concordance= 0.585 (se = 0.033 )
## Rsquare= 0.033 (max possible= 0.959 )
## Likelihood ratio test= 5.97 on 1 df, p=0.0146
```

```
## Wald test          = 6.16  on 1 df,    p=0.0131
## Score (logrank) test = 6.36  on 1 df,    p=0.0117

cox.zph(surv.res)

##                               rho chisq    p
## IS_MESENCHYMALMesenchymal -0.0872 0.476 0.49
```

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= 63
## (12 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.364      3.913   0.351 3.89  0.0001 ***
## UICC_3CATIVB-C     2.803     16.487   0.452 6.20  5.8e-10 ***
## IS_MESENCHYMALMesenchymal 0.824      2.279   0.260 3.17  0.0015 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA           3.91    0.2555     1.97     7.79
## UICC_3CATIVB-C        16.49    0.0607     6.79    40.01
## IS_MESENCHYMALMesenchymal 2.28    0.4389     1.37     3.79
##
## Concordance= 0.732 (se = 0.039 )
## Rsquare= 0.219 (max possible= 0.959 )
## Likelihood ratio test= 44.1 on 3 df,    p=1.41e-09
## Wald test              = 43.4 on 3 df,    p=2.06e-09
## Score (logrank) test = 55.1 on 3 df,    p=6.62e-12

cox.zph(surv.res)

##               rho    chisq    p
## UICC_3CATIVA     -0.0551 0.17704 0.674
## UICC_3CATIVB-C    -0.0564 0.19191 0.661
## IS_MESENCHYMALMesenchymal -0.0049 0.00156 0.968
## GLOBAL              NA 0.22554 0.973
```

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= 63
##      (12 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.4097    4.0946  0.3527  4.00  6.4e-05 ***
## UICC_3CATIVB-C     2.8054   16.5333  0.4517  6.21  5.3e-10 ***
## ALTER             0.0245    1.0248  0.0129  1.91  0.0567 .
## IS_MESENCHYMALMesenchymal 0.8097    2.2472  0.2613  3.10  0.0019 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          4.09    0.2442    2.051    8.17
## UICC_3CATIVB-C       16.53    0.0605    6.821   40.07
## ALTER                1.02    0.9758    0.999    1.05
## IS_MESENCHYMALMesenchymal 2.25    0.4450    1.347    3.75
##
## Concordance= 0.747 (se = 0.041 )
## Rsquare= 0.234 (max possible= 0.959 )
## Likelihood ratio test= 47.7 on 4 df,  p=1.07e-09
## Wald test              = 46.6 on 4 df,  p=1.86e-09
## Score (logrank) test = 57.6 on 4 df,  p=9.23e-12

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA    -0.0617 0.2145 0.643
## UICC_3CATIVB-C  -0.0559 0.1833 0.669
## ALTER           0.0363 0.1064 0.744
## IS_MESENCHYMALMesenchymal 0.0201 0.0264 0.871
## GLOBAL          NA 0.4379 0.979

```

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= 63
##      (12 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.442     4.228   0.356   4.05  5.2e-05 ***
## UICC_3CATIVB-C     2.906    18.277   0.457   6.36  2.1e-10 ***
## ALTER_3CAT(50,70] -0.634     0.531   0.268  -2.37  0.0180 *
## IS_MESENCHYMALMesenchymal  0.693     1.999   0.264   2.62  0.0088 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.228     0.2365    2.104    8.498
## UICC_3CATIVB-C    18.277     0.0547    7.460   44.779
## ALTER_3CAT(50,70]  0.531     1.8843    0.314    0.897
## IS_MESENCHYMALMesenchymal  1.999     0.5002    1.191    3.356
##
## Concordance= 0.747 (se = 0.04 )
## Rsquare= 0.242 (max possible= 0.959 )
## Likelihood ratio test= 49.7 on 4 df,  p=4.24e-10
## Wald test = 49 on 4 df,  p=5.83e-10
## Score (logrank) test = 60.4 on 4 df,  p=2.44e-12

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA    -0.0195 0.0219 0.882
## UICC_3CATIVB-C  -0.0193 0.0212 0.884
## ALTER_3CAT(50,70] -0.1759 2.1419 0.143
## IS_MESENCHYMALMesenchymal -0.0735 0.3762 0.540
## GLOBAL          NA 2.3144 0.678

```

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= 62
## (13 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.391      4.019   0.355  3.92  9.0e-05 ***
## UICC_3CATIVB-C     2.930     18.734   0.457  6.41  1.5e-10 ***
## ALTER_3CAT(50,70] -0.760      0.468   0.283 -2.69  0.0072 **
## I(PACKYEARS > 30)TRUE  0.418      1.519   0.279  1.50  0.1340
## IS_MESENCHYMALMesenchymal 0.626      1.870   0.269  2.32  0.0201 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          4.019      0.2488      2.004      8.060
## UICC_3CATIVB-C       18.734      0.0534      7.643     45.921
## ALTER_3CAT(50,70]     0.468      2.1390      0.269      0.814
## I(PACKYEARS > 30)TRUE   1.519      0.6584      0.879      2.624
## IS_MESENCHYMALMesenchymal 1.870      0.5349      1.103      3.169
##
## Concordance= 0.747 (se = 0.04 )
## Rsquare= 0.252 (max possible= 0.958 )
## Likelihood ratio test= 51.6 on 5 df, p=6.42e-10
## Wald test = 50 on 5 df, p=1.36e-09
## Score (logrank) test = 62.4 on 5 df, p=3.82e-12

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA     -0.0545 0.170 0.6804
## UICC_3CATIVB-C    -0.0369 0.074 0.7856
## ALTER_3CAT(50,70] -0.2178 3.195 0.0739
## I(PACKYEARS > 30)TRUE  0.1228 1.027 0.3108
## IS_MESENCHYMALMesenchymal -0.0863 0.530 0.4665
## GLOBAL           NA 3.773 0.5825
```

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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## I(PACKYEARS > 30)TRUE 1.253      3.502    0.819 1.53      0.13
##
##              exp(coef) exp(-coef) lower .95 upper .95
## I(PACKYEARS > 30)TRUE      3.5      0.286    0.703    17.5
##
## Concordance= 0.721  (se = 0.096 )
## Rsquare= 0.061  (max possible= 0.653 )
## Likelihood ratio test= 2.2  on 1 df,   p=0.138
## Wald test               = 2.34  on 1 df,   p=0.126
## Score (logrank) test = 2.66  on 1 df,   p=0.103

cox.zph(surv.res)

##              rho chisq      p
## I(PACKYEARS > 30)TRUE -0.846    3.8 0.0513

```

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= 6
##
##              coef exp(coef) se(coef) z Pr(>|z|)
## T_CAT3-4 2.18e+01  2.85e+09 1.72e+04 0      1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4 2.85e+09    3.5e-10      0      Inf
##
## Concordance= 0.809  (se = 0.111 )

```



```
## Rsquare= 0.277    (max possible= 0.653 )
## Likelihood ratio test= 11.4  on 1 df,   p=0.000751
## Wald test          = 0   on 1 df,   p=0.999
## Score (logrank) test = 9.42  on 1 df,   p=0.00214

cox.zph(surv.res)

##              rho      chisq p
## T_CAT3-4 0.926 1.61e-10 1
```

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

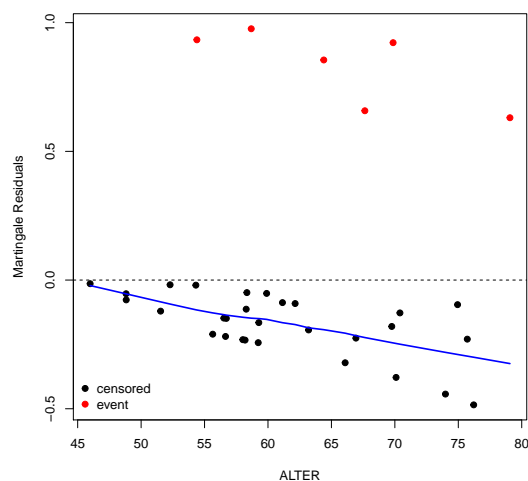
5.5.3 AGE continuous

```
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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER 0.0406      1.0415    0.0500 0.81      0.42
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER          1.04          0.96    0.944      1.15
##
## Concordance= 0.551  (se = 0.131 )
## Rsquare= 0.019    (max possible= 0.653 )
## Likelihood ratio test= 0.66  on 1 df,   p=0.418
## Wald test          = 0.66  on 1 df,   p=0.416
## Score (logrank) test = 0.67  on 1 df,   p=0.412

cox.zph(surv.res)

##              rho chisq      p
## ALTER 0.46    1.12 0.291
```



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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4          2.20e+01  3.55e+09 1.61e+04 0.00    0.999
## I(PACKYEARS > 30)TRUE 1.79e+00  5.99e+00 9.39e-01 1.91    0.057 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4          3.55e+09  2.82e-10    0.000      Inf
## I(PACKYEARS > 30)TRUE  5.99e+00  1.67e-01    0.951    37.8
##
## Concordance= 0.908 (se = 0.122 )
## Rsquare= 0.348 (max possible= 0.653 )
## Likelihood ratio test= 15 on 2 df,  p=0.000558
## Wald test               = 3.63 on 2 df,  p=0.163
## Score (logrank) test = 12.8 on 2 df,  p=0.00165

cox.zph(surv.res)

##              rho      chisq      p
## T_CAT3-4          0.246 1.70e-10 1.000
## I(PACKYEARS > 30)TRUE -0.576 1.43e+00 0.232
## GLOBAL              NA 1.43e+00 0.490
```

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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4          2.24e+01  5.07e+09 1.50e+04 0.00    0.999
## ALTER_60(60,Inf]    1.53e+00  4.62e+00 1.20e+00 1.28    0.201
## I(PACKYEARS > 30)TRUE 2.67e+00  1.44e+01 1.29e+00 2.07    0.038 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4          5.07e+09  1.97e-10    0.000      Inf
## ALTER_60(60,Inf]    4.62e+00  2.16e-01    0.442    48.4
## I(PACKYEARS > 30)TRUE 1.44e+01  6.93e-02    1.159   179.5
##
## Concordance= 0.93 (se = 0.128 )
## Rsquare= 0.385 (max possible= 0.653 )
## Likelihood ratio test= 17 on 3 df,  p=0.000701
## Wald test            = 4.3 on 3 df,  p=0.23
## Score (logrank) test = 13.3 on 3 df,  p=0.00411

cox.zph(surv.res)

##              rho      chisq      p
## T_CAT3-4          0.5341 3.31e-09 1.000
## ALTER_60(60,Inf]    0.5435 1.62e+00 0.203
## I(PACKYEARS > 30)TRUE 0.0139 4.95e-04 0.982
## GLOBAL              NA 2.61e+00 0.456
```

```
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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## PACKYEARS 0.0121      1.0121  0.0127 0.95      0.34
##
##              exp(coef) exp(-coef) lower .95 upper .95
## PACKYEARS      1.01      0.988  0.987      1.04
##
## Concordance= 0.75 (se = 0.128 )
## Rsquare= 0.021 (max possible= 0.653 )
## Likelihood ratio test= 0.75 on 1 df,  p=0.386
## Wald test              = 0.9 on 1 df,  p=0.342
## Score (logrank) test = 0.94 on 1 df,  p=0.333

cox.zph(surv.res)

##              rho chisq      p
## PACKYEARS -0.875  2.19 0.139

```

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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA  2.01e+01  5.23e+08 1.42e+04 0.00      1.0
## UICC_3CATIVB-C 2.25e+01  5.71e+09 1.42e+04 0.00      1.0
## PACKYEARS      2.19e-02  1.02e+00 1.34e-02 1.64      0.1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA  5.23e+08  1.91e-09  0.000      Inf
## UICC_3CATIVB-C 5.71e+09  1.75e-10  0.000      Inf

```

```
## PACKYEARS      1.02e+00  9.78e-01    0.996    1.05
##
## Concordance= 0.89 (se = 0.129 )
## Rsquare= 0.285 (max possible= 0.653 )
## Likelihood ratio test= 11.7 on 3 df, p=0.00834
## Wald test          = 5.33 on 3 df, p=0.149
## Score (logrank) test = 14 on 3 df, p=0.00296

cox.zph(surv.res)

##              rho    chisq    p
## UICC_3CATIVA    0.578 2.17e-09 1.000
## UICC_3CATIVB-C  0.676 1.49e-08 1.000
## PACKYEARS      -0.294 1.25e-01 0.724
## GLOBAL          NA 1.86e+00 0.603
```

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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    2.05e+01  8.17e+08 1.50e+04  0.00    0.999
## UICC_3CATIVB-C  2.38e+01  2.20e+10 1.50e+04  0.00    0.999
## ALTER          -8.30e-02  9.20e-01 7.16e-02 -1.16    0.247
## PACKYEARS       2.93e-02  1.03e+00 1.70e-02  1.72    0.085 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA    8.17e+08  1.22e-09    0.000      Inf
## UICC_3CATIVB-C  2.20e+10  4.55e-11    0.000      Inf
## ALTER          9.20e-01  1.09e+00    0.800    1.06
## PACKYEARS       1.03e+00  9.71e-01    0.996    1.06
##
## Concordance= 0.912 (se = 0.131 )
## Rsquare= 0.316 (max possible= 0.653 )
## Likelihood ratio test= 13.3 on 4 df, p=0.01
## Wald test          = 6.16 on 4 df, p=0.188
## Score (logrank) test = 14.8 on 4 df, p=0.0052
```

```
cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA    0.0953 2.91e-11 1.0000
## UICC_3CATIVB-C -0.1231 3.94e-10 1.0000
## ALTER          0.7713 3.56e+00 0.0591
## PACKYEARS      -0.8483 2.24e+00 0.1345
## GLOBAL         NA 6.67e+00 0.1545
```

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.subset, ], 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= 6
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    2.13e+01  1.85e+09  1.59e+04  0.00   0.999
## UICC_3CATIVB-C  2.49e+01  6.27e+10  1.59e+04  0.00   0.999
## ALTER          -1.20e-01  8.87e-01  7.44e-02 -1.61   0.108
## PACKYEARS       3.43e-02  1.03e+00  1.83e-02  1.87   0.061 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA    1.85e+09  5.41e-10   0.000      Inf
## UICC_3CATIVB-C  6.27e+10  1.59e-11   0.000      Inf
## ALTER          8.87e-01  1.13e+00   0.767    1.03
## PACKYEARS       1.03e+00  9.66e-01   0.998    1.07
##
## Concordance= 0.927 (se = 0.131 )
## Rsquare= 0.426 (max possible= 0.71 )
## Likelihood ratio test= 15.5 on 4 df, p=0.00373
## Wald test = 6.86 on 4 df, p=0.143
## Score (logrank) test = 16.6 on 4 df, p=0.00226

cox.zph(surv.res)

##              rho      chisq      p
```

```
## UICC_3CATIVA      0.3169 1.82e-10 1.0000
## UICC_3CATIVB-C    0.0669 9.29e-11 1.0000
## ALTER             0.8170 2.89e+00 0.0892
## PACKYEARS         -0.8141 1.50e+00 0.2214
## GLOBAL            NA 5.37e+00 0.2514
```

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= 15
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.94e+01  2.76e+08 9.04e+03 0.00      1.00
## UICC_3CATIVB-C  2.01e+01  5.62e+08 9.04e+03 0.00      1.00
## ALTER          3.62e-02  1.04e+00 3.20e-02 1.13      0.26
## PACKYEARS       3.29e-03  1.00e+00 9.56e-03 0.34      0.73
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA    2.76e+08  3.63e-09      0.000      Inf
## UICC_3CATIVB-C  5.62e+08  1.78e-09      0.000      Inf
## ALTER          1.04e+00  9.64e-01      0.974      1.10
## PACKYEARS       1.00e+00  9.97e-01      0.985      1.02
##
## Concordance= 0.753  (se = 0.088 )
## Rsquare= 0.165    (max possible= 0.796 )
## Likelihood ratio test= 11.2  on 4 df,   p=0.0248
## Wald test            = 3.64  on 4 df,   p=0.457
## Score (logrank) test = 9.27  on 4 df,   p=0.0546

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA    -0.29930 1.17e-09 1.000
## UICC_3CATIVB-C  0.00835 2.22e-12 1.000
## ALTER          0.00660 5.82e-04 0.981
## PACKYEARS       0.06791 4.96e-02 0.824
## GLOBAL          NA 4.25e-01 0.980
```

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= 13
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.94e+01  2.66e+08 9.30e+03 0.00    1.00
## UICC_3CATIVB-C  1.99e+01  4.27e+08 9.30e+03 0.00    1.00
## ALTER          4.16e-02  1.04e+00 3.31e-02 1.26    0.21
## PACKYEARS       2.83e-03  1.00e+00 9.95e-03 0.28    0.78
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA    2.66e+08  3.75e-09    0.000      Inf
## UICC_3CATIVB-C  4.27e+08  2.34e-09    0.000      Inf
## ALTER          1.04e+00  9.59e-01    0.977    1.11
## PACKYEARS       1.00e+00  9.97e-01    0.983    1.02
##
## Concordance= 0.74 (se = 0.096 )
## Rsquare= 0.184 (max possible= 0.818 )
## Likelihood ratio test= 9.18 on 4 df, p=0.0568
## Wald test              = 2.58 on 4 df, p=0.631
## Score (logrank) test = 7.07 on 4 df, p=0.132

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA   -0.2528 9.03e-10 1.000
## UICC_3CATIVB-C  0.1620 6.97e-10 1.000
## ALTER         -0.0840 7.36e-02 0.786
## PACKYEARS      0.0667 3.71e-02 0.847
## GLOBAL        NA 8.08e-01 0.937

```