

Additional survival analyses of the data set from Wichmann et al. (Int. J. Canc. 2015). Head and neck tumor patients. Only patients with mutation data available. Association of mutations with overall survival.

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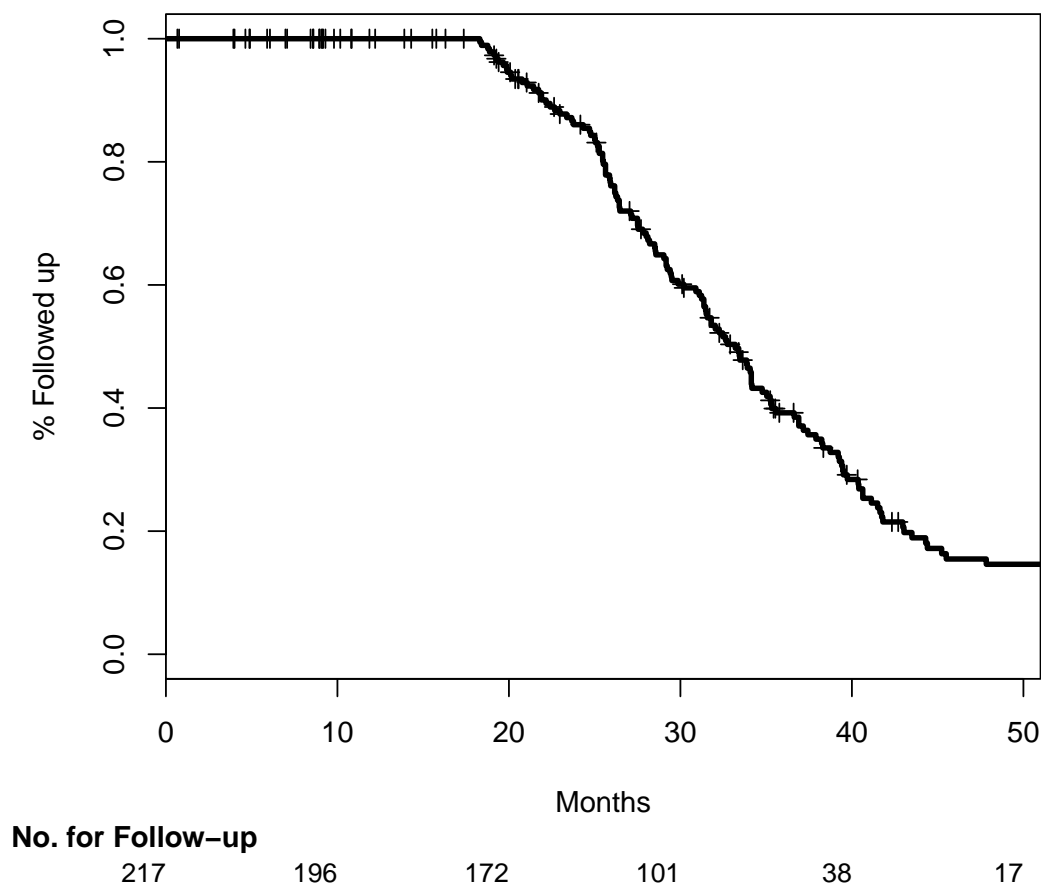
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PLEASE NOTE: For historical reasons, the Immune Response (IR) Cluster (one of the Consensus Clusters determined by gene expression) is sometimes called *Atypical* Cluster in this document.

1 Follow-up



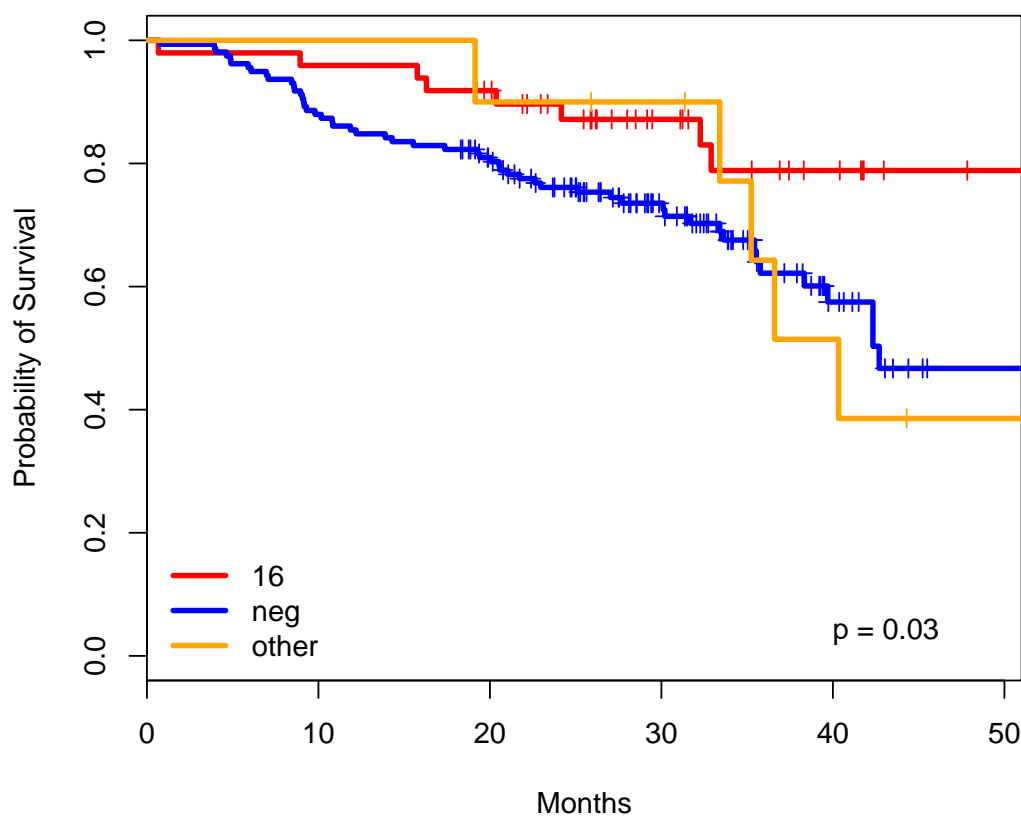
2 Exploration of single variables

2.1 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]neg  0.843    2.323   0.361  2.33   0.020 *
## split[cur.subset]other 1.127    3.086   0.507  2.22   0.026 *
```

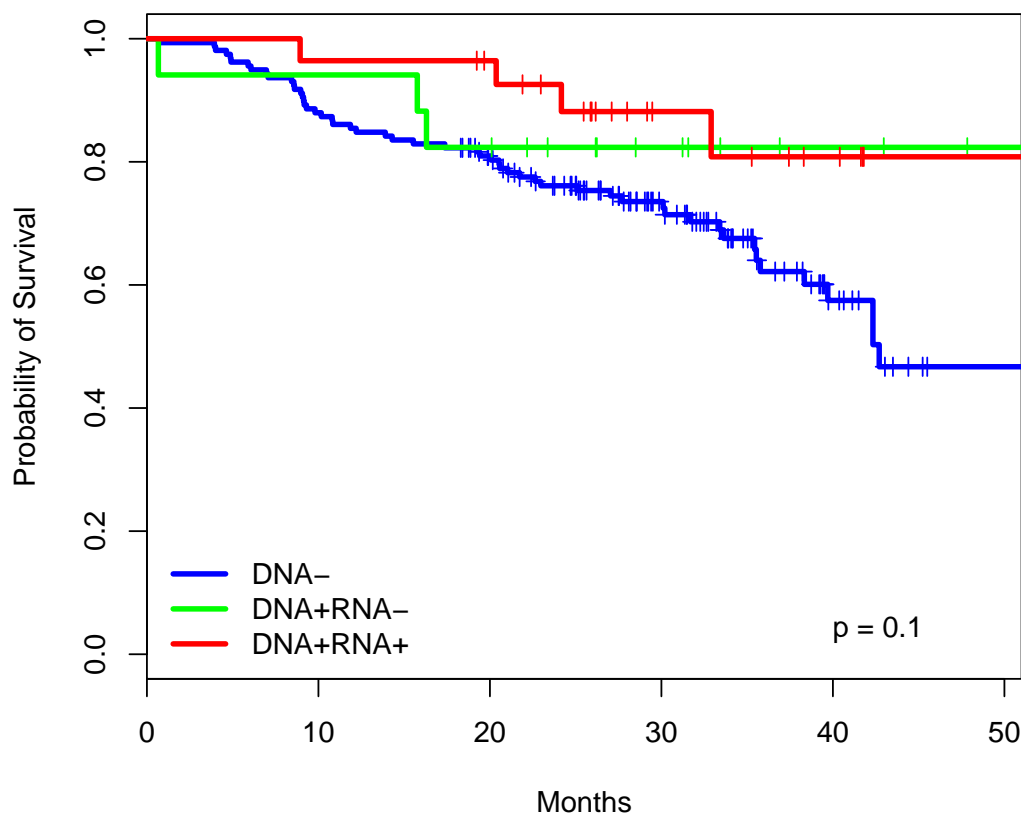
```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]neg      2.32      0.430      1.14      4.71
## split[cur.subset]other     3.09      0.324      1.14      8.34
##
## Concordance= 0.549  (se = 0.03 )
## Rsquare= 0.035   (max possible= 0.954 )
## Likelihood ratio test= 7.76  on 2 df,   p=0.0207
## Wald test            = 6.47  on 2 df,   p=0.0393
## Score (logrank) test = 6.89  on 2 df,   p=0.0319
```



No. at Risk							
16	49	47	43	24	13	7	
neg	158	139	120	69	21	8	
other	10	10	9	8	4	2	

2.2 HPV DNA RNA

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 203, number of events= 63
##    (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]DNA+RNA- -0.436    0.646    0.519 -0.84    0.400
## split[cur.subset]DNA+RNA+ -1.021    0.360    0.519 -1.97    0.049 *
## ---
## 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-    0.646      1.55    0.234    1.787
## split[cur.subset]DNA+RNA+    0.360      2.78    0.130    0.997
##
## Concordance= 0.557 (se = 0.03 )
## Rsquare= 0.027 (max possible= 0.946 )
## Likelihood ratio test= 5.61 on 2 df,  p=0.0604
## Wald test               = 4.36 on 2 df,  p=0.113
## Score (logrank) test = 4.7 on 2 df,  p=0.0955
```

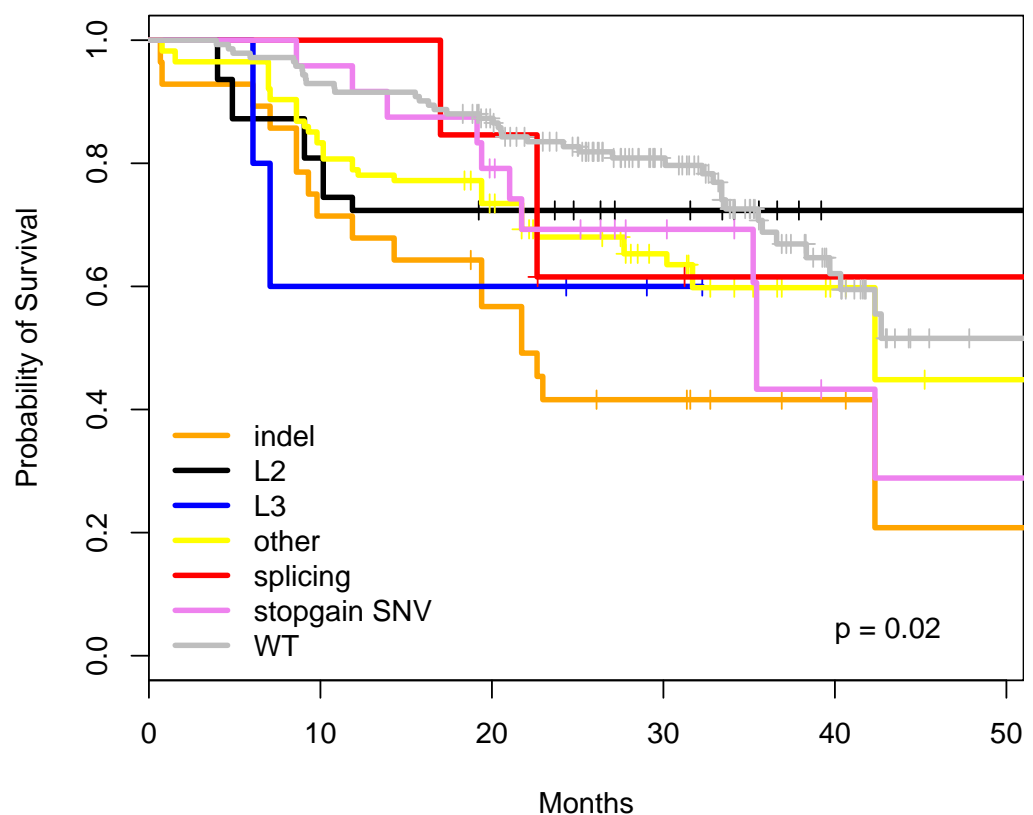



No. at Risk						
DNA-	158	139	120	69	21	8
DNA+RNA-	17	16	14	8	3	1
DNA+RNA+	28	27	25	12	8	4

2.3 Types of TP53 mutations by functional domain as in Gross et al. (Nat Genet 2014). Cases with multiple TP53 mutations are represented multiple times in this plot (as in Gross et al.).

```
## mut_combinations
##               indel               indel_L2
##               4                1
## indel_L2_other_stopgain SNV      indel_L3
##               1                1
##               indel_L3_other      indel_other
##               1                10
## indel_other_splicing indel_other_stopgain SNV
##               1                4
```

##	L2	L2_other
##	9	3
##	L2_stopgain SNV	L3
##	5	3
##	other	other_stopgain SNV
##	24	3
##	splicing	stopgain SNV
##	7	7
##	WT	<NA>
##	142	0



No. at Risk

indel	28	20	15	10	5	2
L2	47	38	31	23	4	4
L3	15	9	9	3	0	0
other	114	95	77	37	18	9
splicing	13	13	11	6	5	5
stopgain SNV	24	23	18	10	3	2

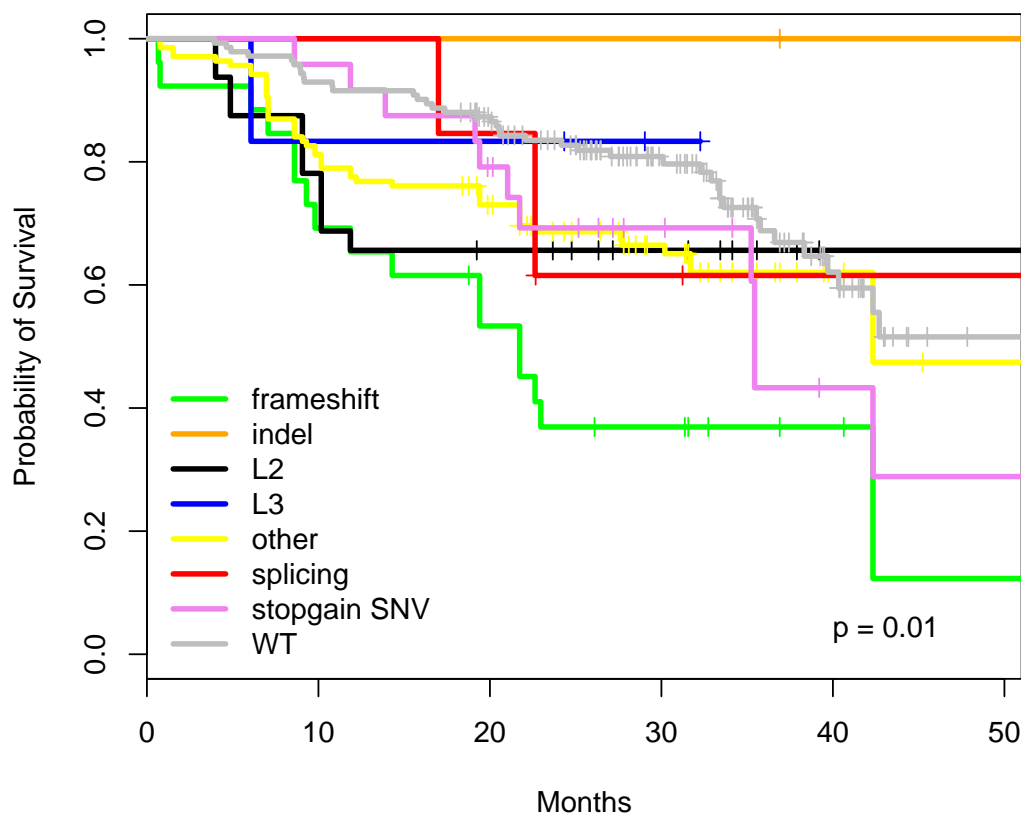
2.4 Types of TP53 mutations by functional domain. Similar but NOT identical to Gross et al. (Nat Genet 2014).

Changes compared to Gross et al.:

1. frameshift mutations are in their own category and are not classified as indel.
2. for a mutation to be classified as L2 or L3 it has to fullfill also the polarity criteria of Poeta et al.

Cases with multiple TP53 mutations are represented multiple times in this plot (as in Gross et al.).

```
## mut_combinations
##          frameshift          frameshift_indel_other
##          4          1
##          frameshift_L2_other frameshift_L2_other_stopgain SNV
##          1          1
##          frameshift_L3_other          frameshift_other
##          1          9
##          frameshift_other_splicing frameshift_other_stopgain SNV
##          1          4
##          indel_other          L2_other
##          1          11
##          L2_other_stopgain SNV          L2_stopgain SNV
##          1          4
##          L3_other          other
##          3          25
##          other_stopgain SNV          splicing
##          3          7
##          stopgain SNV          WT
##          7          142
##          <NA>
##          0
```

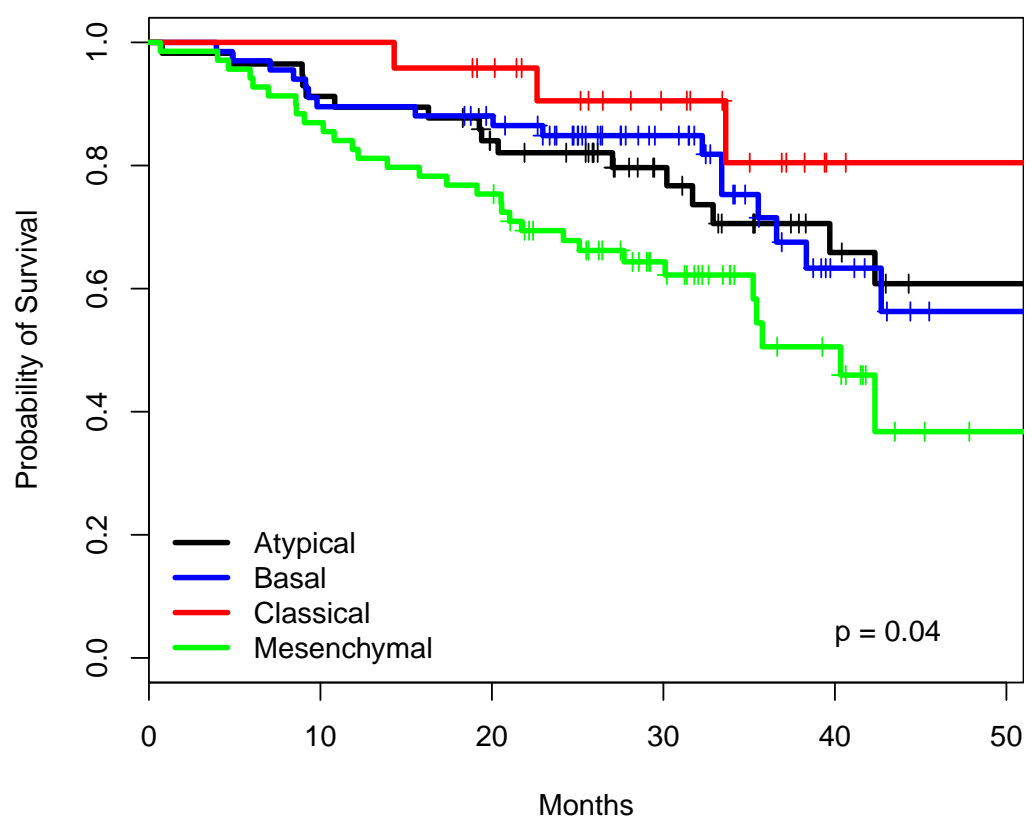


No. at Risk						
frameshift	26	18	13	8	4	1
indel	2	2	2	2	1	1
L2	32	25	19	13	3	3
L3	6	5	5	2	0	0
other	138	112	93	48	19	10
splicing	13	13	11	6	5	5

2.5 Consensus Clusters

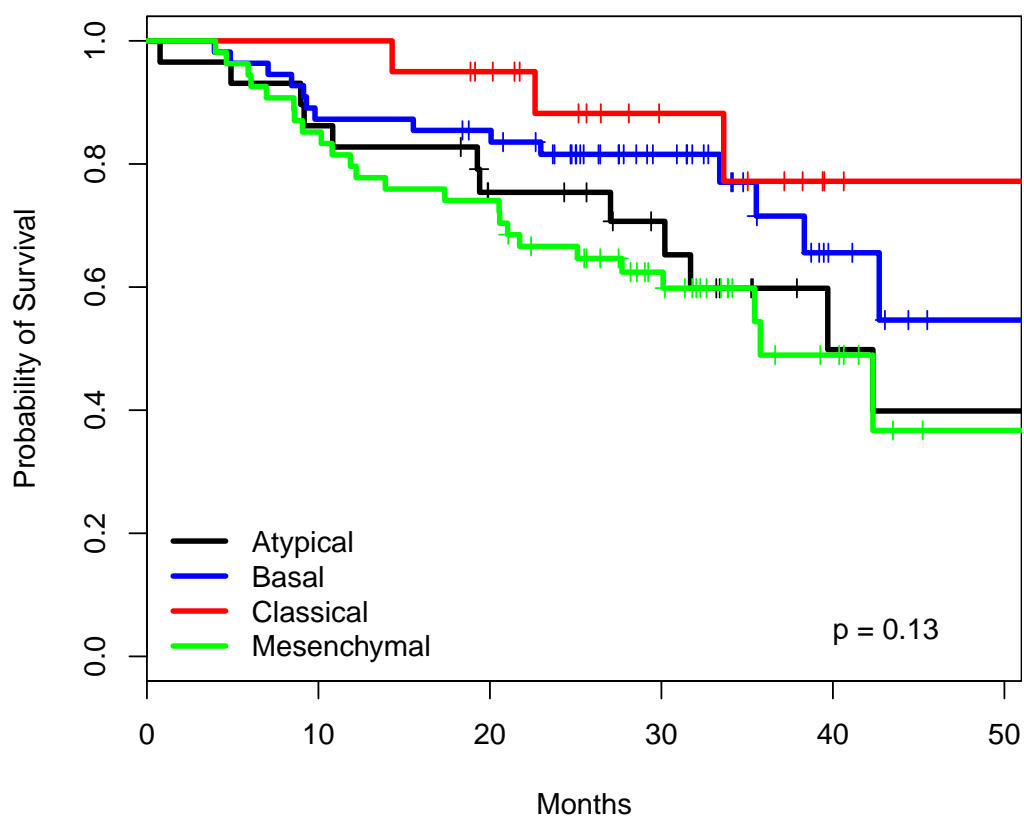
```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal    0.146    1.157   0.334  0.44   0.661
## split[cur.subset]Classical -0.430    0.650   0.559 -0.77   0.441
## split[cur.subset]Mesenchymal 0.674    1.962   0.309  2.18   0.029 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```
## split[cur.subset]Basal      1.16      0.864      0.602      2.23
## split[cur.subset]Classical  0.65      1.538      0.217      1.94
## split[cur.subset]Mesenchymal 1.96      0.510      1.070      3.60
##
## Concordance= 0.603 (se = 0.037 )
## Rsquare= 0.038 (max possible= 0.954 )
## Likelihood ratio test= 8.32 on 3 df, p=0.0399
## Wald test = 8.18 on 3 df, p=0.0424
## Score (logrank) test = 8.58 on 3 df, p=0.0354
```



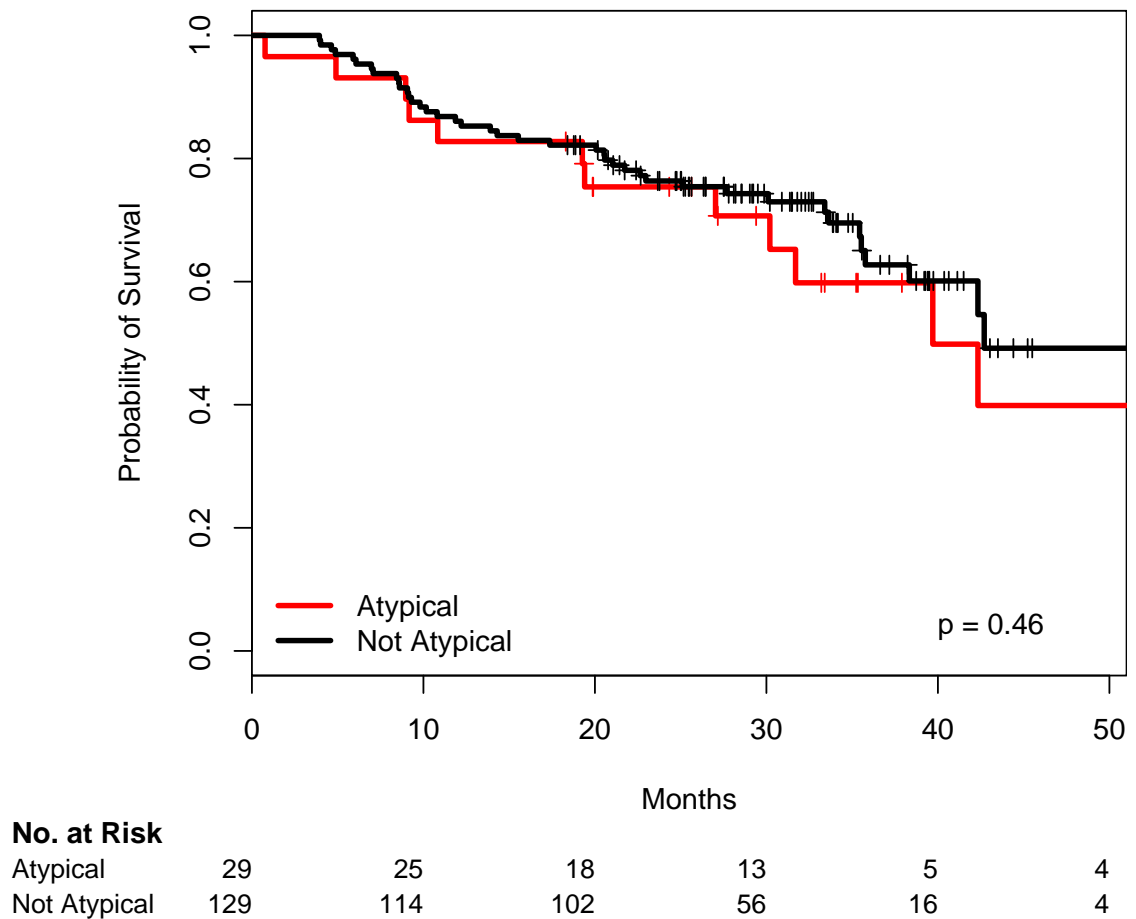
No. at Risk						
Atypical	57	52	43	27	14	10
Basal	67	60	56	32	11	5
Classical	24	24	21	12	2	1
Mesenchymal	69	60	52	30	11	1

2.5.1 Consensus Clusters in HPV DNA-



No. at Risk						
Atypical	29	25	18	13	5	4
Basal	55	48	45	24	7	2
Classical	20	20	17	8	2	1
Mesenchymal	54	46	40	24	7	1

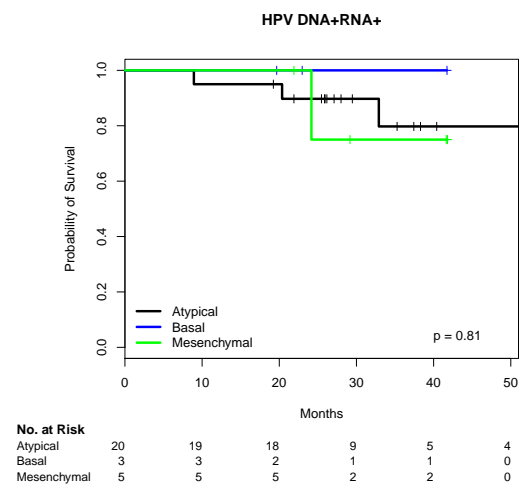
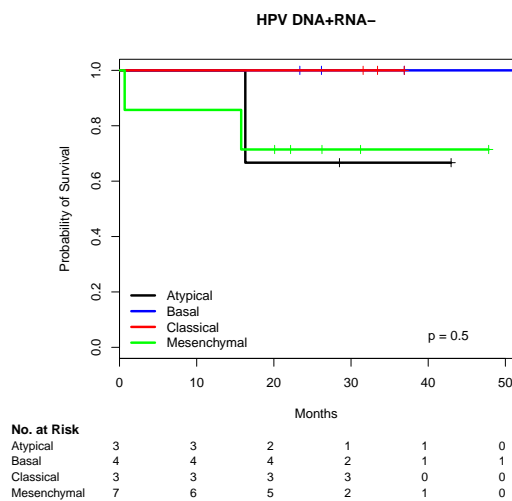
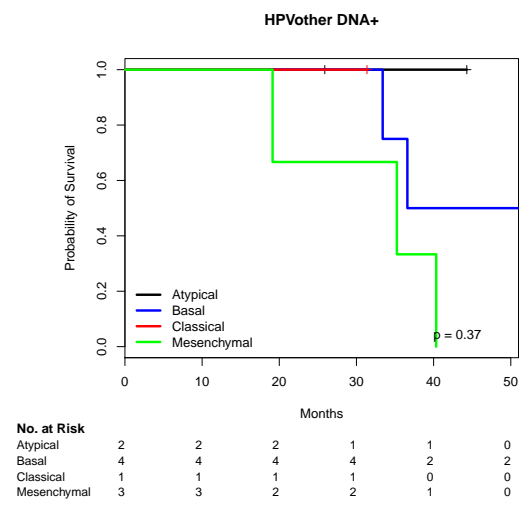
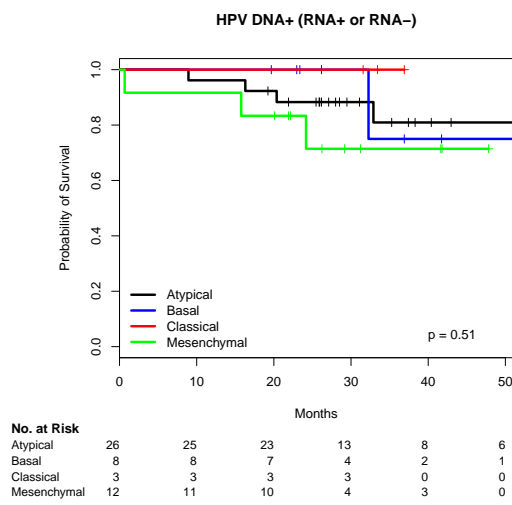
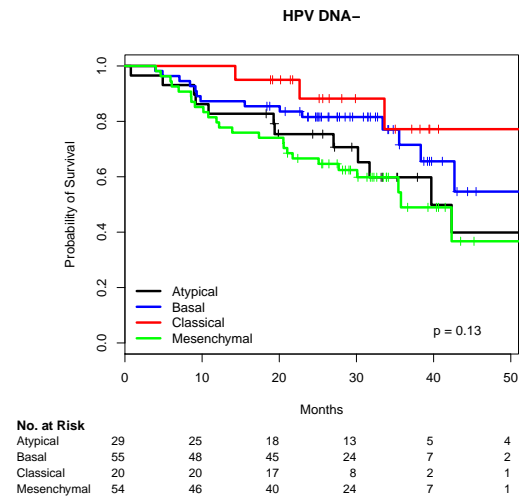
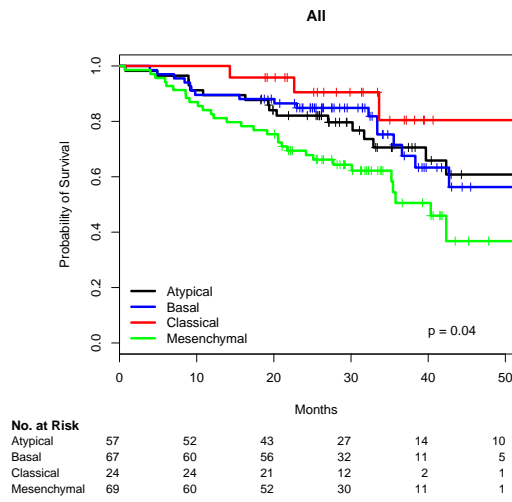
2.5.2 Consensus Clusters in HPV DNA-, Atypical vs. other Consensus Clusters

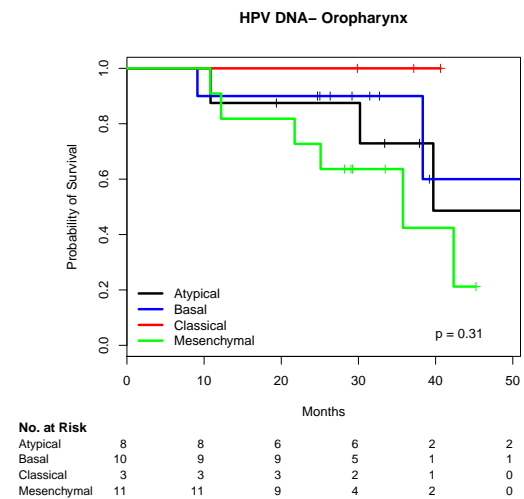
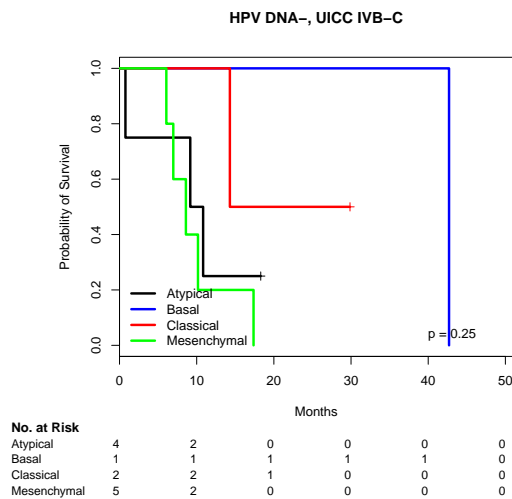
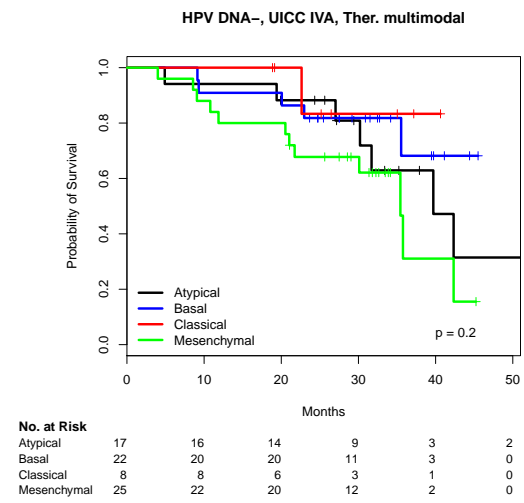
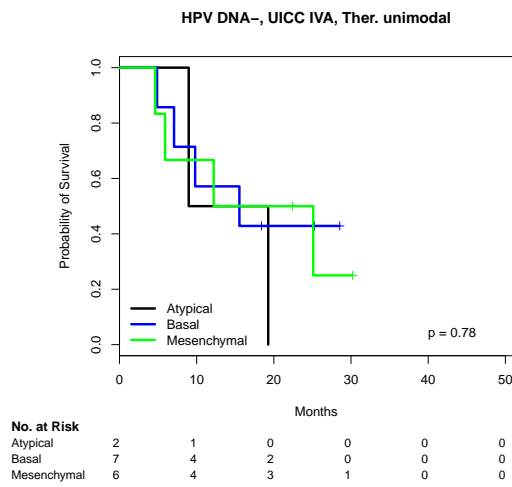
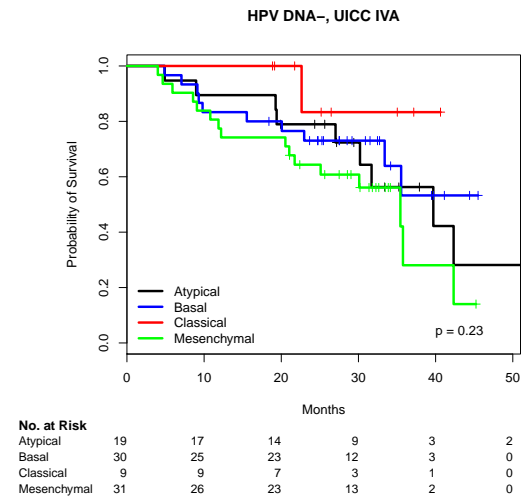
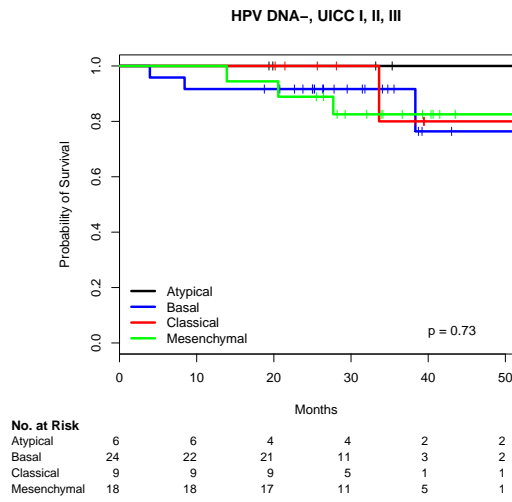


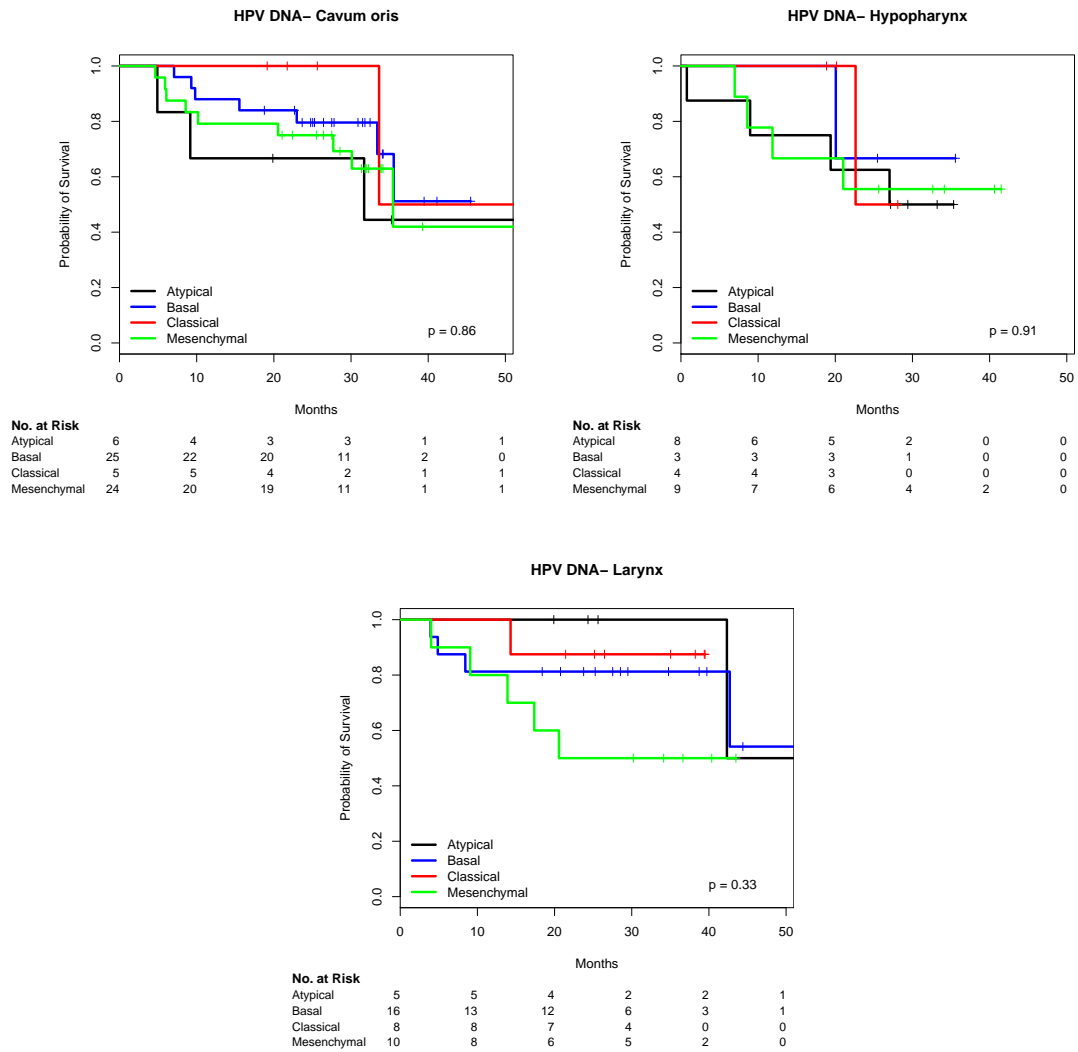
2.6 Consensus Clusters

```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      0.146    1.157    0.334  0.44    0.661
## split[cur.subset]Classical -0.430    0.650    0.559 -0.77    0.441
## split[cur.subset]Mesenchymal 0.674    1.962    0.309  2.18    0.029 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      1.16      0.864    0.602    2.23
## split[cur.subset]Classical  0.65      1.538    0.217    1.94
## split[cur.subset]Mesenchymal 1.96      0.510    1.070    3.60
##
## Concordance= 0.603 (se = 0.037 )
## Rsquare= 0.038 (max possible= 0.954 )
## Likelihood ratio test= 8.32 on 3 df,  p=0.0399
## Wald test = 8.18 on 3 df,  p=0.0424
## Score (logrank) test = 8.58 on 3 df,  p=0.0354
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal     -0.513    0.598    0.388 -1.32    0.19
## split[cur.subset]Classical -0.788    0.455    0.574 -1.37    0.17
## split[cur.subset]Mesenchymal 0.119    1.127    0.347  0.34    0.73
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      0.598      1.671    0.280    1.28
## split[cur.subset]Classical  0.455      2.200    0.147    1.40
## split[cur.subset]Mesenchymal 1.127      0.888    0.571    2.22
##
## Concordance= 0.608 (se = 0.041 )
## Rsquare= 0.036 (max possible= 0.954 )
## Likelihood ratio test= 5.85 on 3 df,  p=0.119
## Wald test = 5.45 on 3 df,  p=0.142
## Score (logrank) test = 5.68 on 3 df,  p=0.128
```

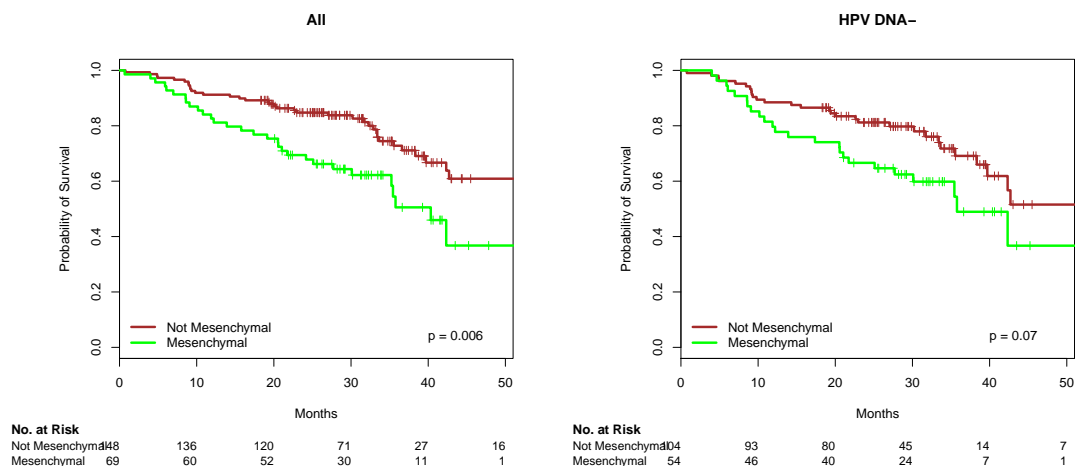


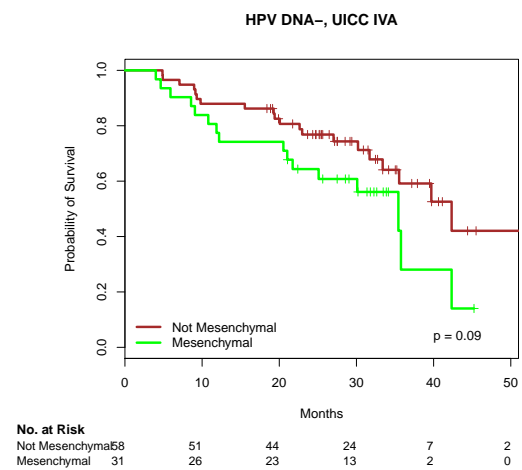
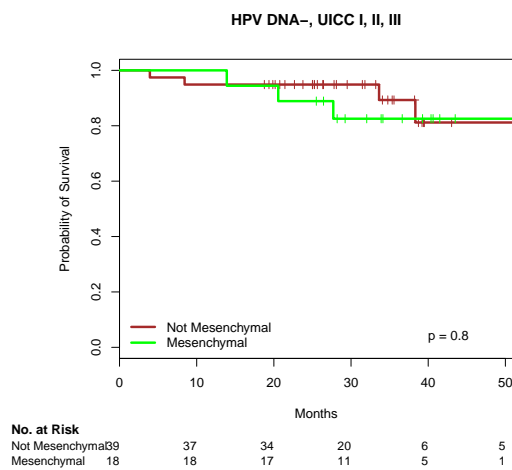
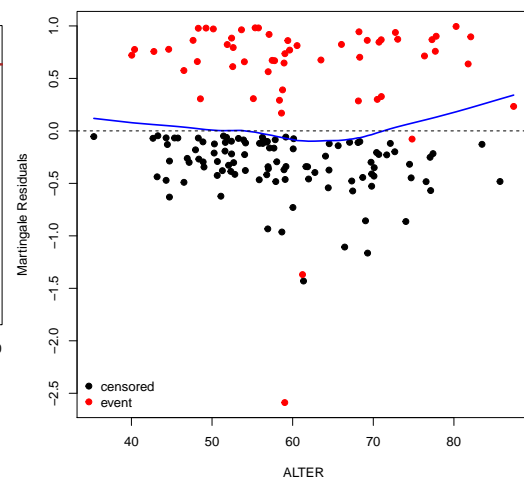
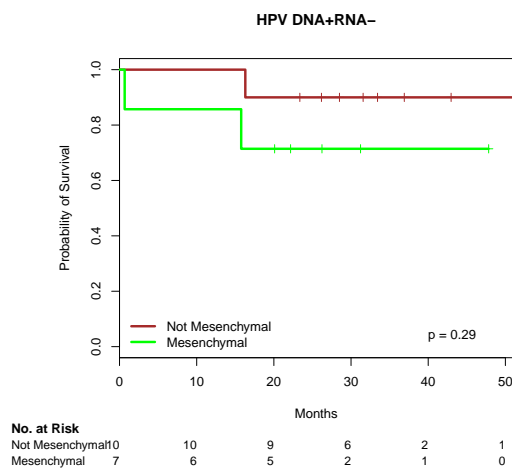
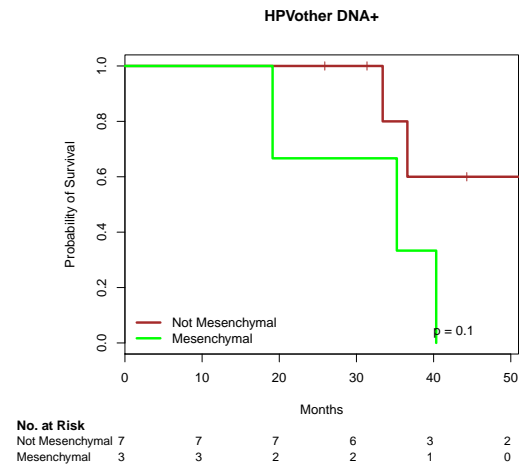
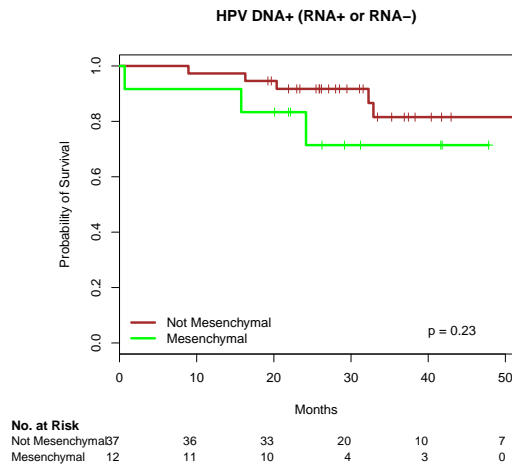


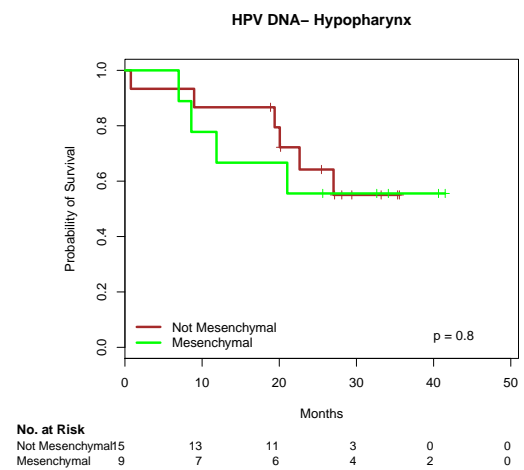
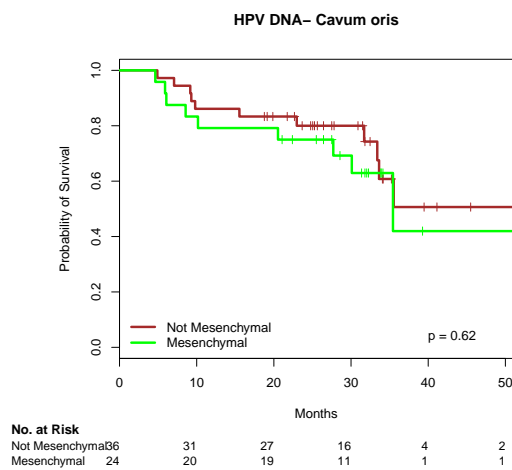
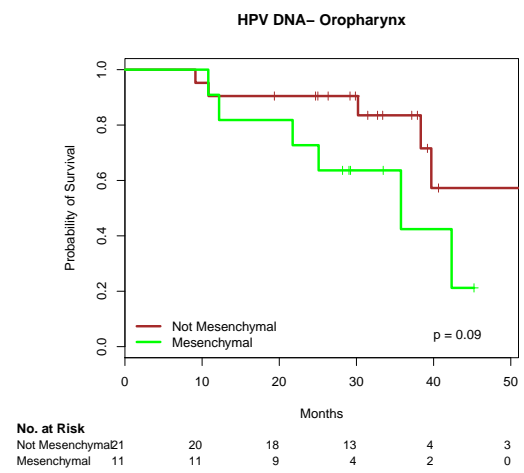
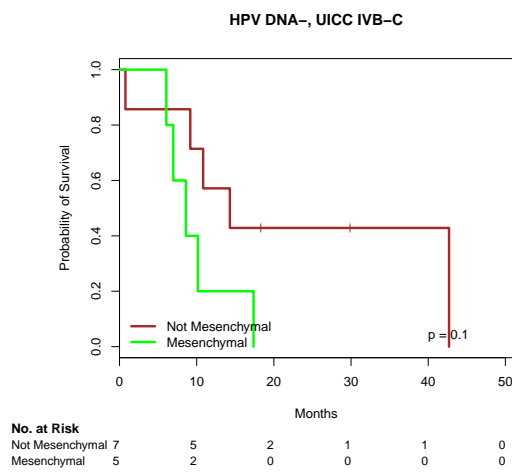
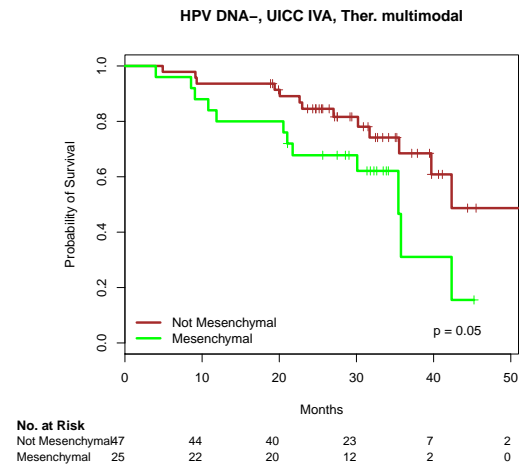
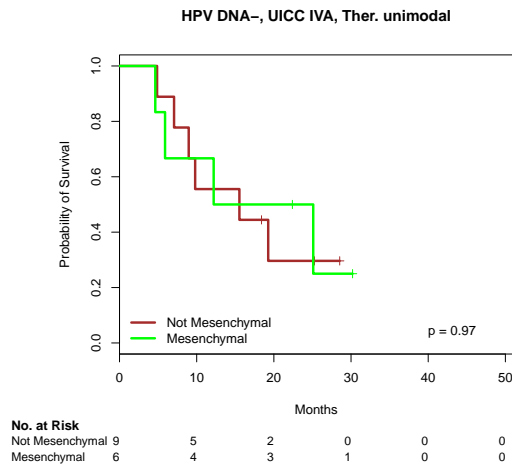
2.7 “Mesenchymal“ vs. other Consensus Clusters

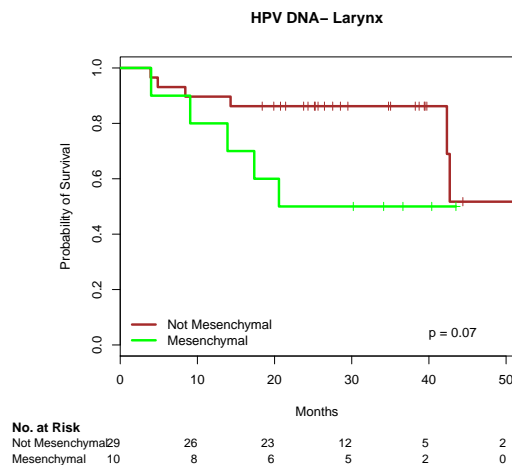
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.660      1.936      0.243 2.72  0.0065 **
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.94      0.517      1.2      3.12
##
## Concordance= 0.592  (se = 0.031 )
## Rsquare= 0.032   (max possible= 0.954 )
## Likelihood ratio test= 7.06  on 1 df,   p=0.00787
## Wald test          = 7.4   on 1 df,   p=0.00651
## Score (logrank) test = 7.67  on 1 df,   p=0.00562
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.496      1.643      0.273 1.82   0.069 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.64      0.609      0.962      2.8
##
## Concordance= 0.576  (se = 0.035 )
## Rsquare= 0.02   (max possible= 0.954 )
## Likelihood ratio test= 3.21  on 1 df,   p=0.0734
## Wald test          = 3.3   on 1 df,   p=0.0691
## Score (logrank) test = 3.37  on 1 df,   p=0.0663
```





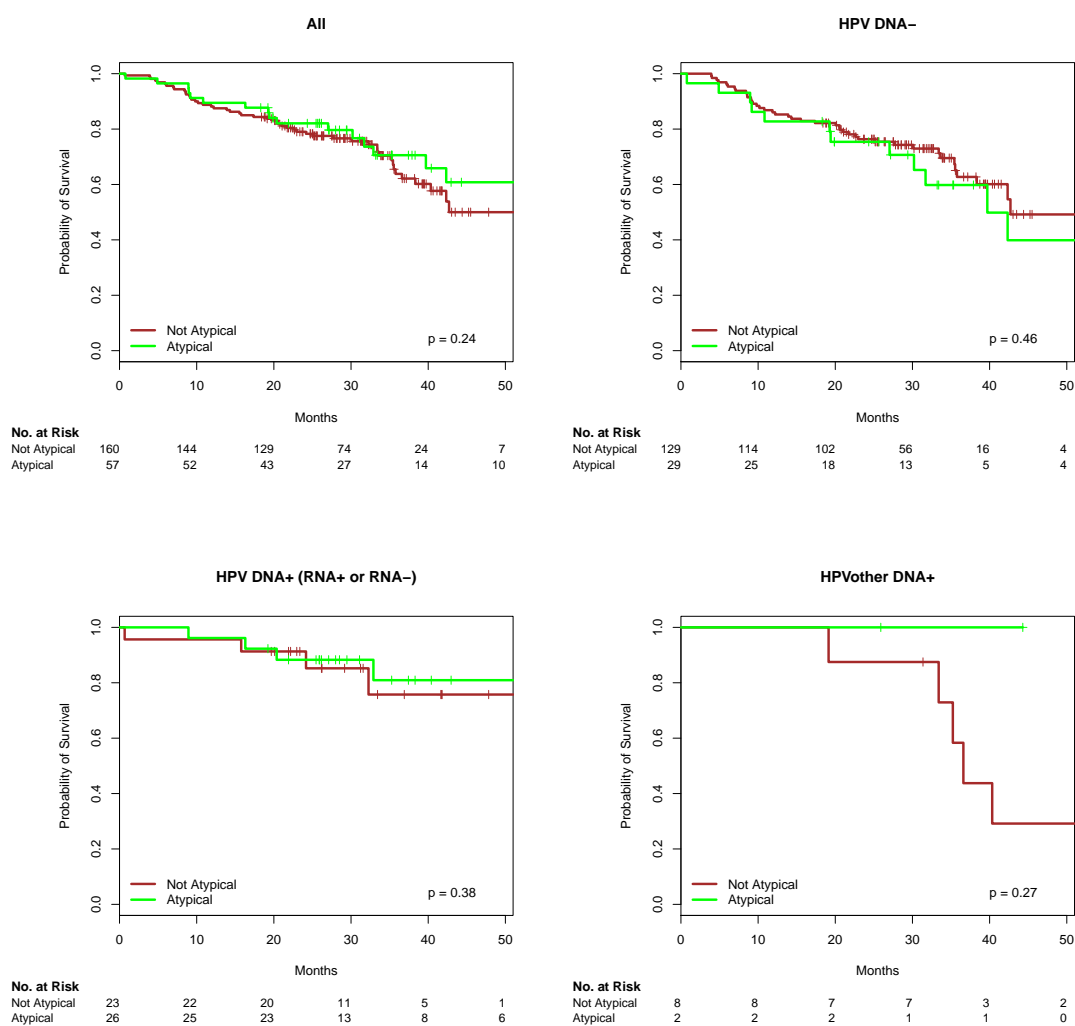


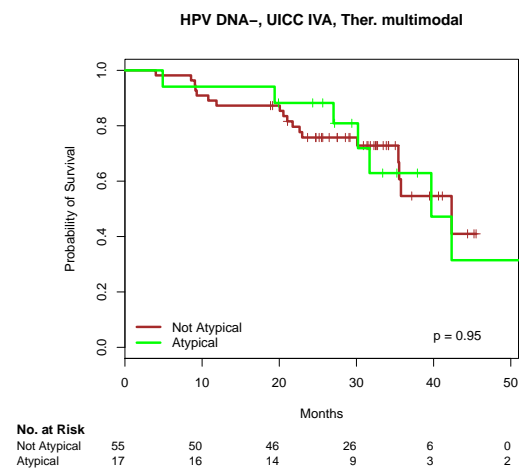
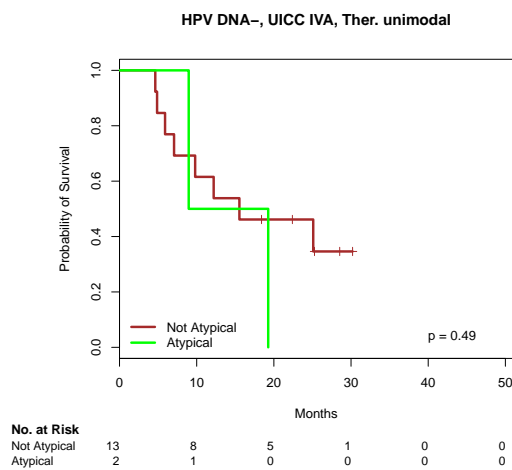
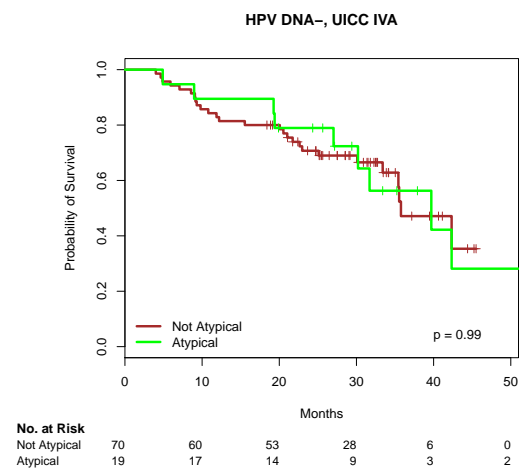
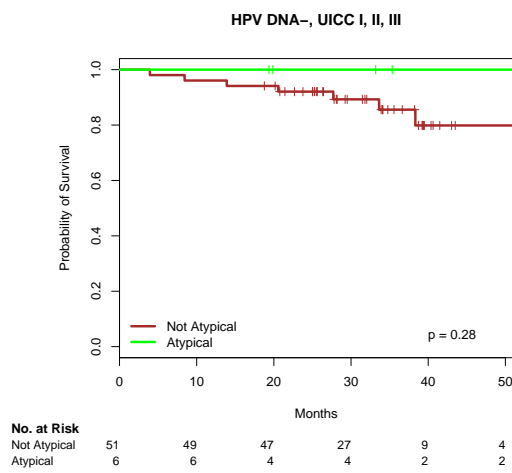
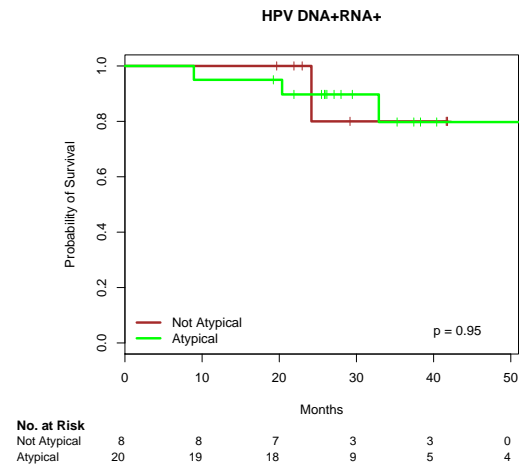
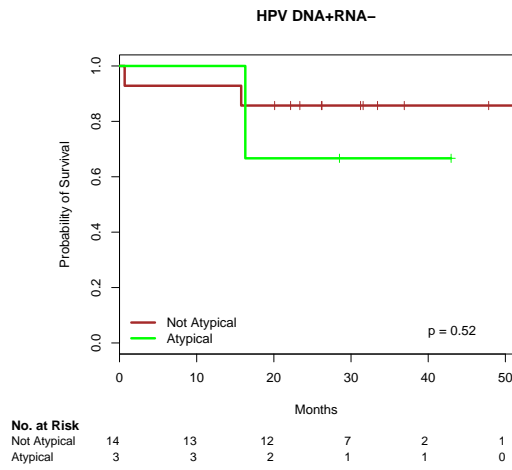


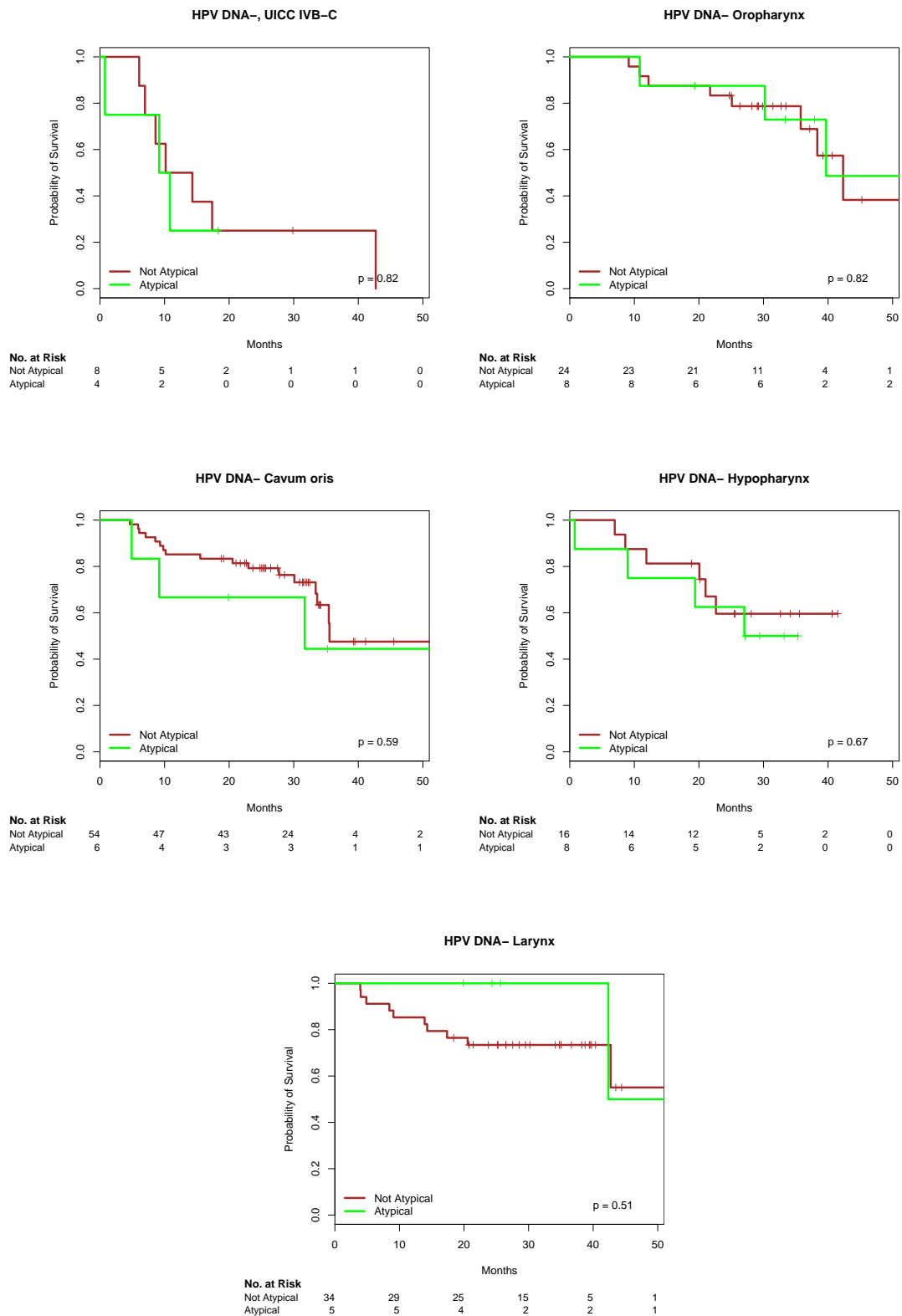
2.8 “Atypical” vs. other Consensus Clusters

```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical -0.332    0.718    0.283 -1.17    0.24
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical    0.718    1.39    0.412    1.25
##
## Concordance= 0.516 (se = 0.029 )
## Rsquare= 0.007 (max possible= 0.954 )
## Likelihood ratio test= 1.45 on 1 df,  p=0.229
## Wald test               = 1.37 on 1 df,  p=0.242
## Score (logrank) test = 1.38 on 1 df,  p=0.24
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
```

```
##
##   n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical 0.238      1.269    0.321 0.74    0.46
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical      1.27      0.788    0.676    2.38
##
## Concordance= 0.516 (se = 0.029 )
## Rsquare= 0.003 (max possible= 0.954 )
## Likelihood ratio test= 0.53 on 1 df,  p=0.468
## Wald test               = 0.55 on 1 df,  p=0.458
## Score (logrank) test = 0.55 on 1 df,  p=0.457
```







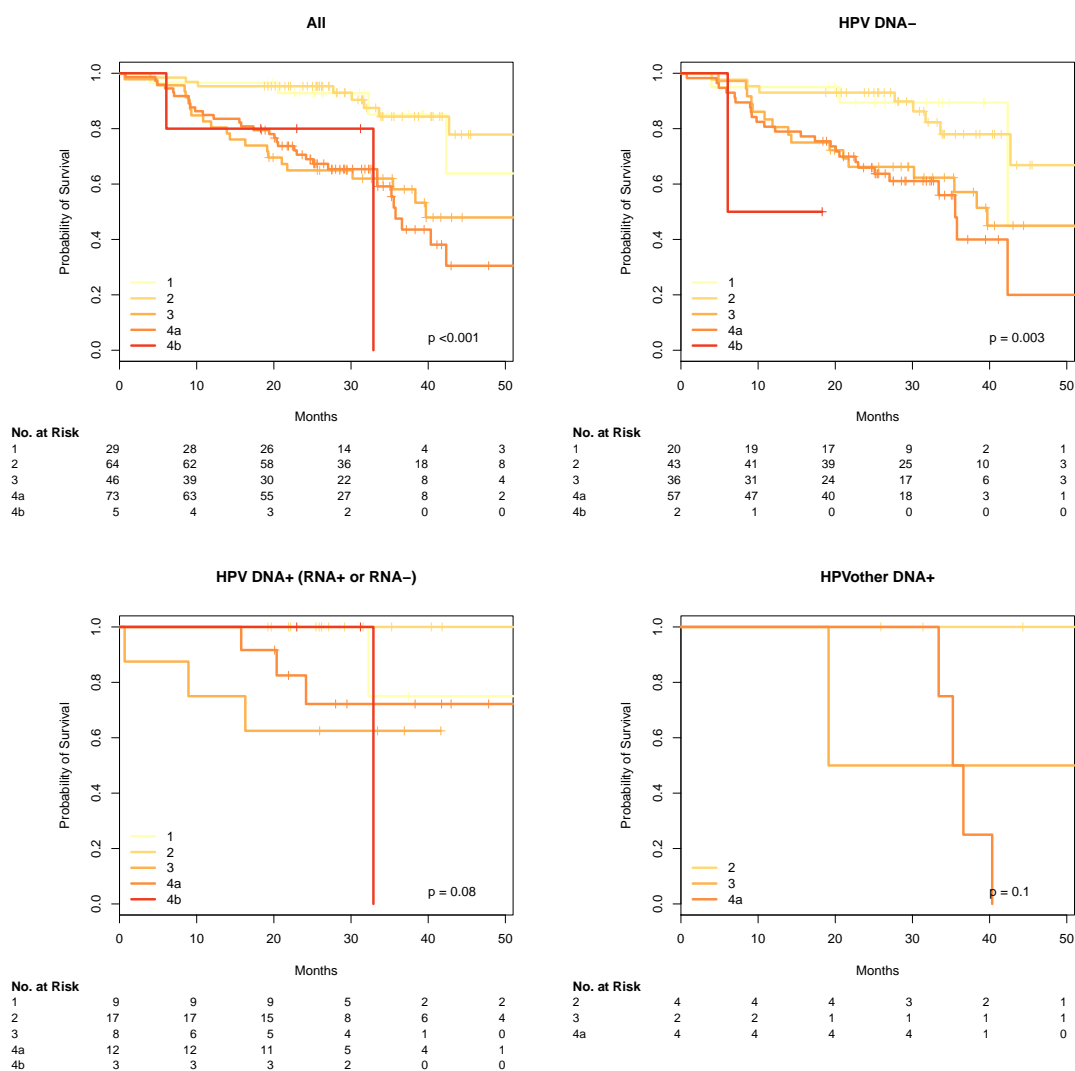
2.9 T (TNM staging)

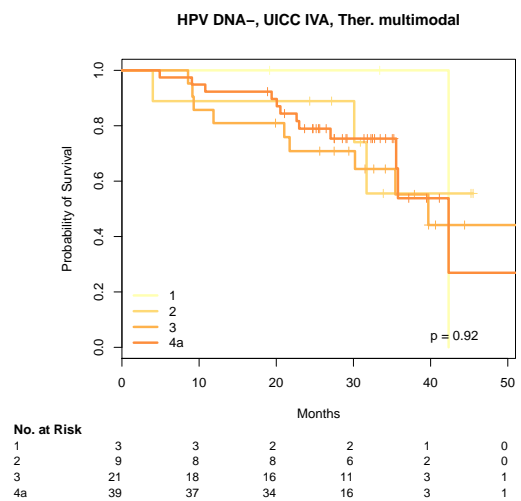
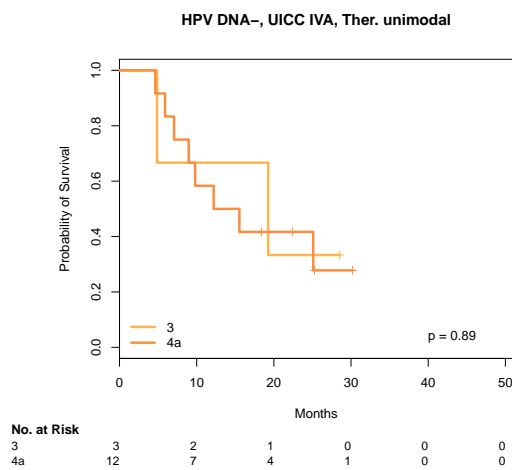
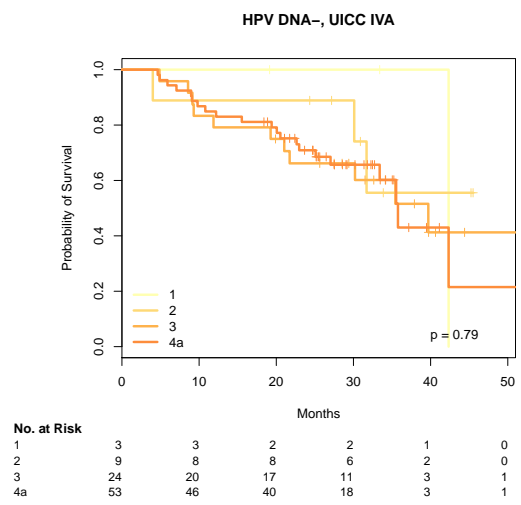
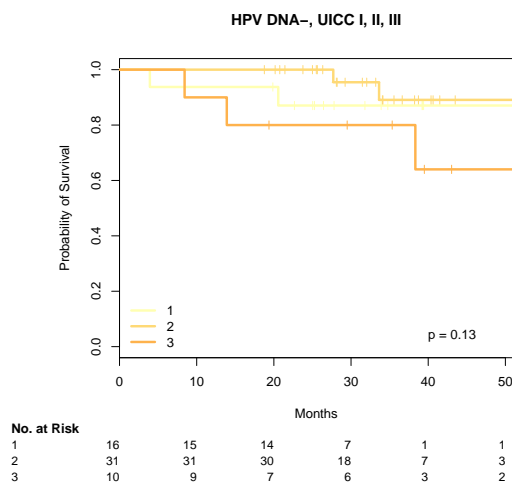
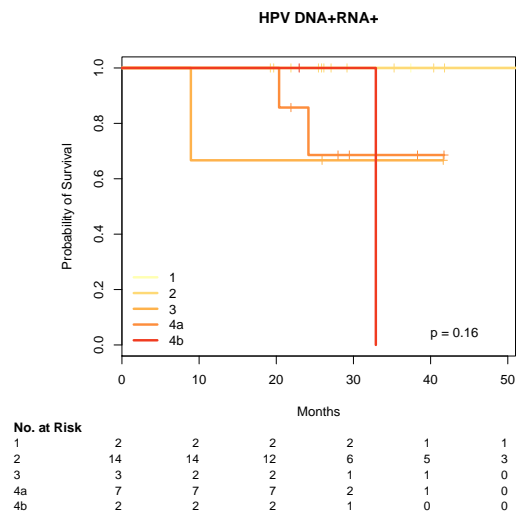
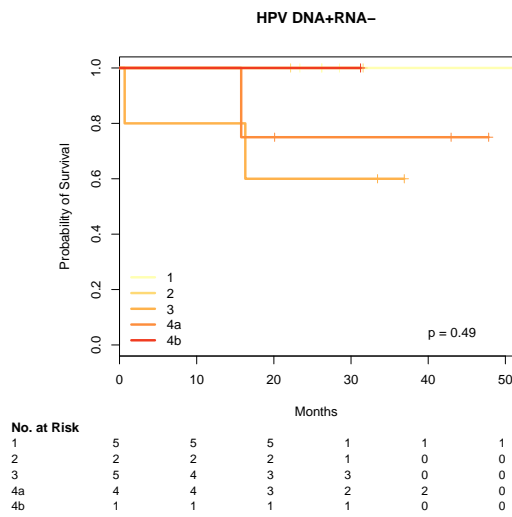
```

## 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= 217, number of events= 73
##
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.581    0.559    0.529 -1.10    0.272
## split[cur.subset]3  0.886    2.425    0.464  1.91    0.056 .
## split[cur.subset]4a 0.968    2.632    0.445  2.18    0.030 *
## split[cur.subset]4b 1.217    3.376    0.820  1.48    0.138
## 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    0.559    1.788    0.198    1.58
## split[cur.subset]3    2.425    0.412    0.976    6.02
## split[cur.subset]4a    2.632    0.380    1.101    6.29
## split[cur.subset]4b    3.376    0.296    0.676   16.85
## split[cur.subset]x         NA         NA         NA         NA
##
## Concordance= 0.656 (se = 0.037 )
## Rsquare= 0.116 (max possible= 0.954 )
## Likelihood ratio test= 26.7 on 4 df,  p=2.25e-05
## Wald test = 21 on 4 df,  p=0.000315
## Score (logrank) test = 24.6 on 4 df,  p=6.06e-05
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.242    0.785    0.614 -0.39    0.694
## split[cur.subset]3  0.821    2.273    0.562  1.46    0.144
## split[cur.subset]4a 1.074    2.928    0.540  1.99    0.046 *
## split[cur.subset]4b 2.078    7.986    1.129  1.84    0.066 .
## split[cur.subset]x    NA         NA    0.000    NA         NA
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##

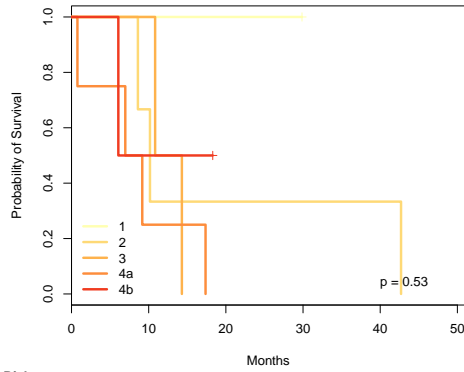
```

```
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2            0.785      1.273      0.236      2.62
## split[cur.subset]3            2.273      0.440      0.756      6.84
## split[cur.subset]4a           2.928      0.342      1.017      8.43
## split[cur.subset]4b           7.986      0.125      0.873     73.04
## split[cur.subset]x              NA          NA          NA          NA
##
## Concordance= 0.645  (se = 0.041 )
## Rsquare= 0.097   (max possible= 0.954 )
## Likelihood ratio test= 16.1  on 4 df,   p=0.00289
## Wald test           = 14.2  on 4 df,   p=0.00663
## Score (logrank) test = 16.1  on 4 df,   p=0.00285
```





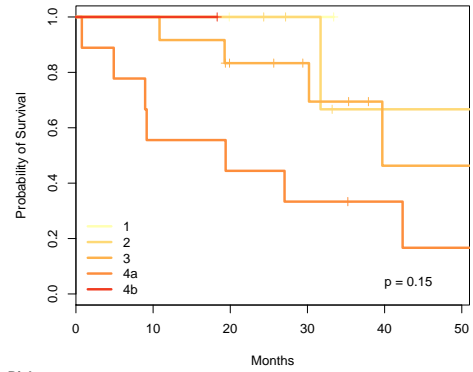
HPV DNA-, UICC IVB-C



No. at Risk

	0	10	20	30	40	50
1	1	1	1	0	0	0
2	3	2	1	1	1	0
3	2	2	0	0	0	0
4a	4	1	0	0	0	0
4b	2	1	0	0	0	0

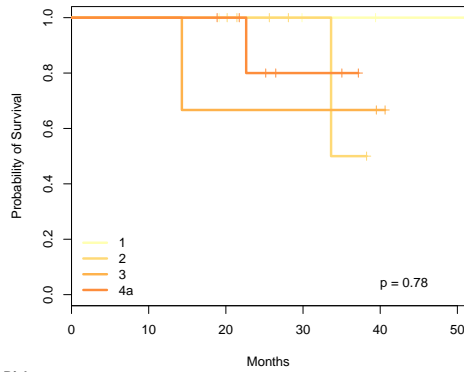
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
1	2	2	1	1	0	0
2	5	5	5	3	1	1
3	12	12	8	6	2	2
4a	9	5	4	3	2	1
4b	1	1	0	0	0	0

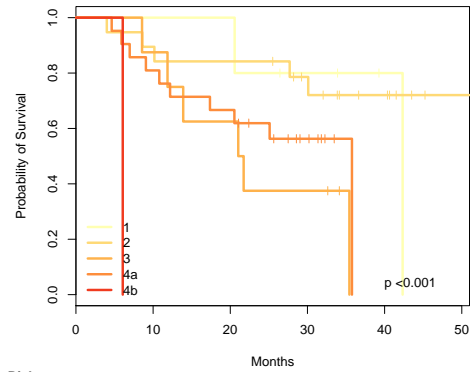
In DNA- Classical



No. at Risk

	0	10	20	30	40	50
1	4	4	3	2	1	1
2	6	6	6	2	0	0
3	3	3	2	2	1	0
4a	7	7	6	2	0	0

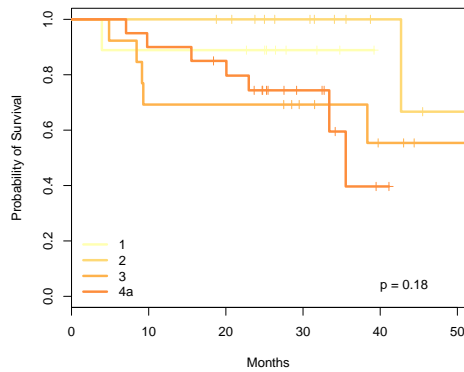
In DNA- Mesenchymal



No. at Risk

	0	10	20	30	40	50
1	5	5	5	3	1	0
2	19	17	16	12	6	1
3	8	7	5	3	0	0
4a	21	17	14	6	0	0
4b	1	0	0	0	0	0

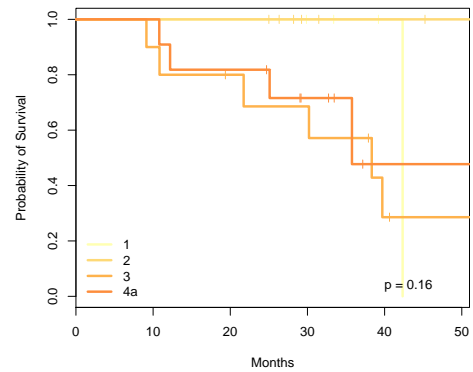
In DNA- Basal



No. at Risk

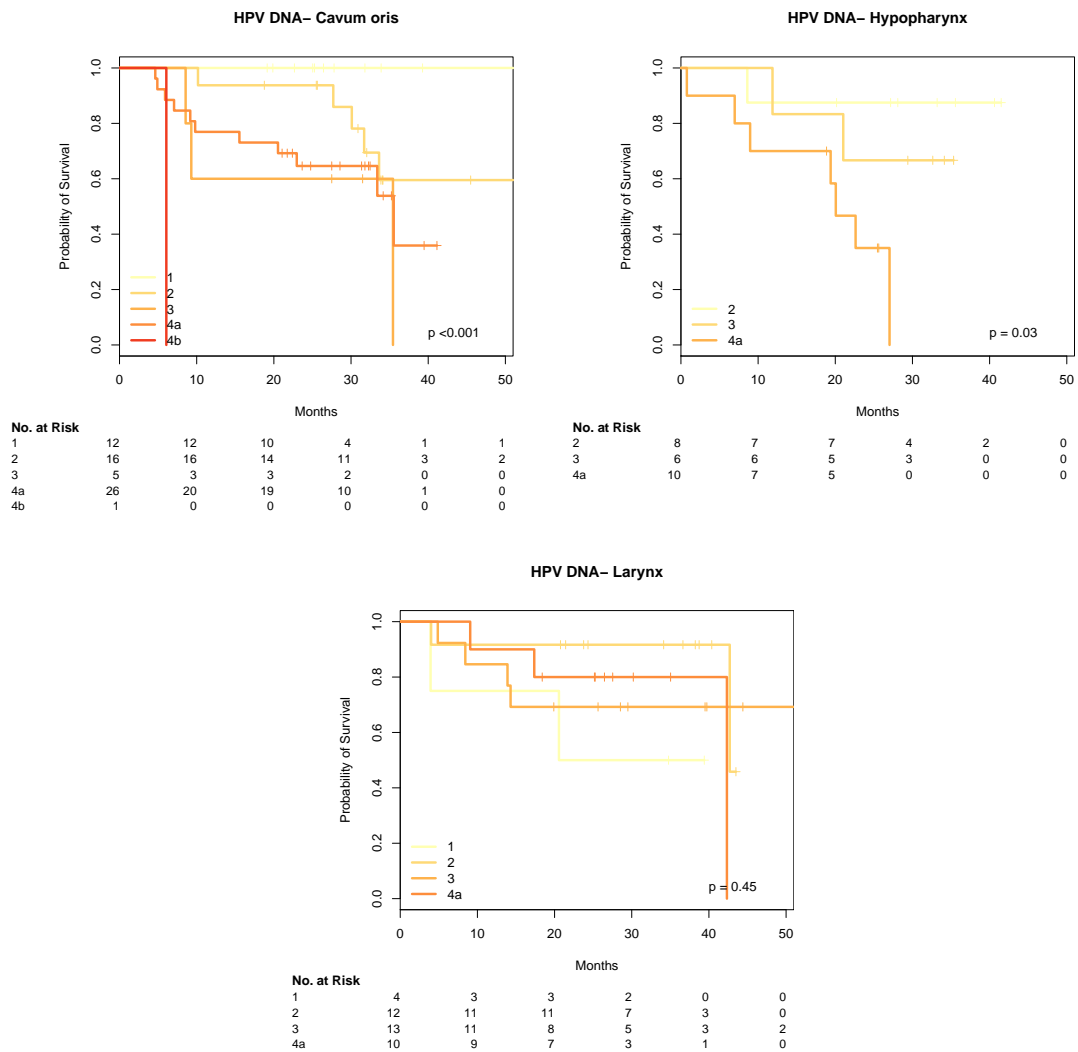
	0	10	20	30	40	50
1	9	8	8	3	0	0
2	13	13	12	8	3	1
3	13	9	9	6	3	1
4a	20	18	16	7	1	0

HPV DNA- Oropharynx



No. at Risk

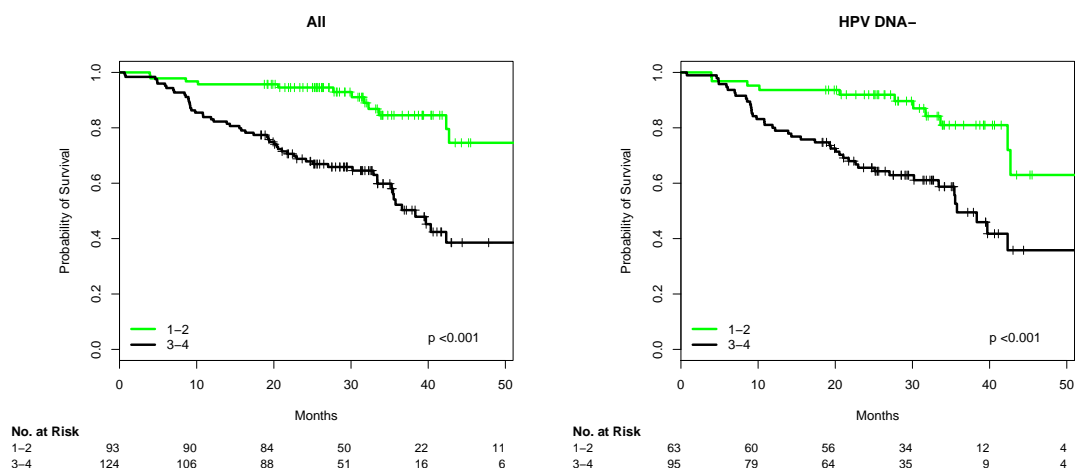
	0	10	20	30	40	50
1	4	4	4	3	1	0
2	7	7	7	3	2	1
3	10	9	7	6	2	1
4a	11	11	9	5	1	1

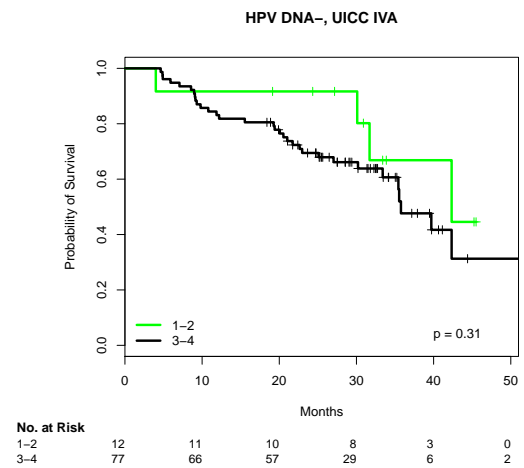
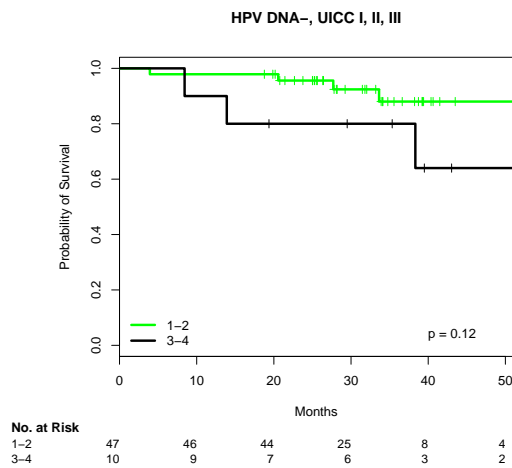
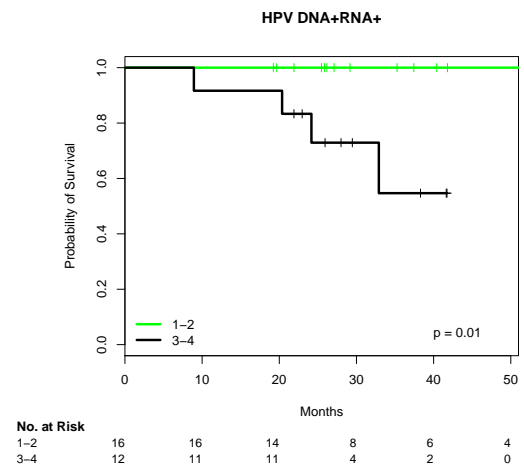
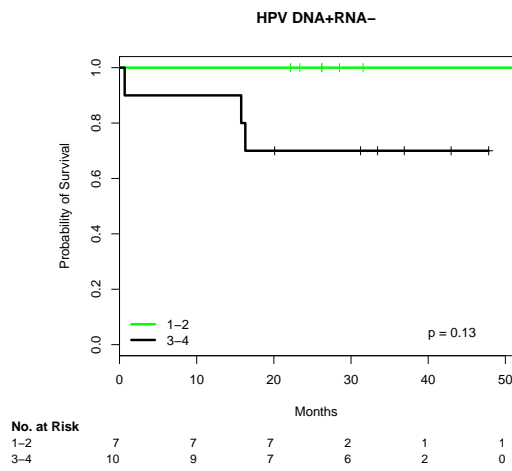
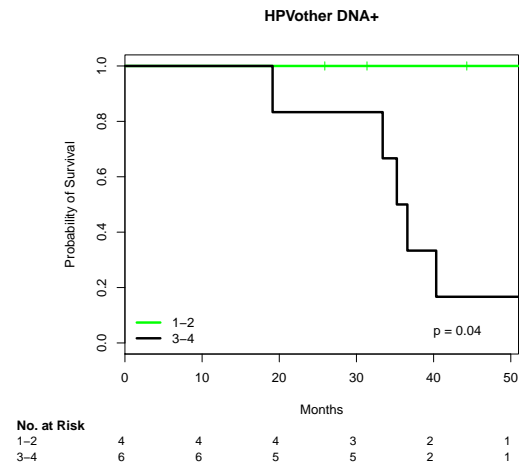
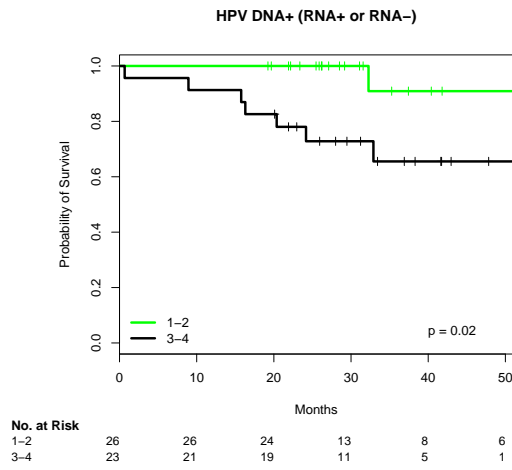


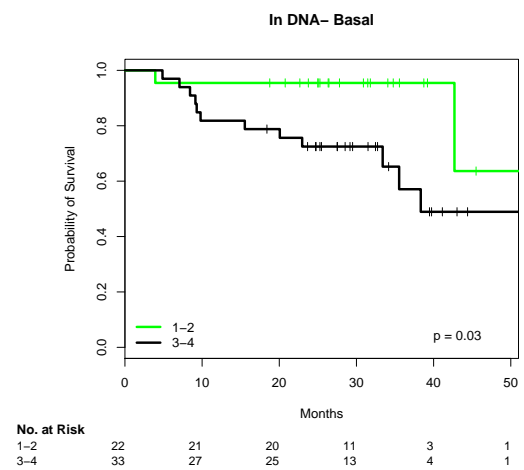
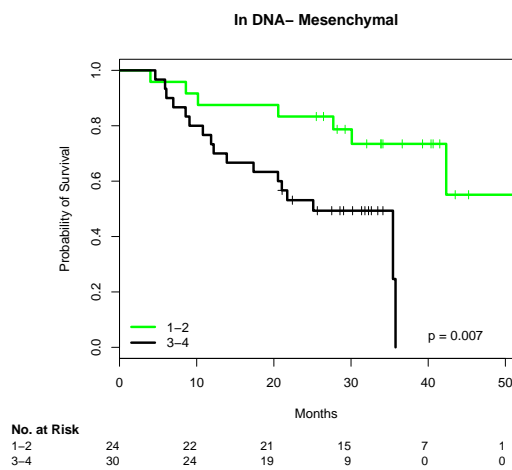
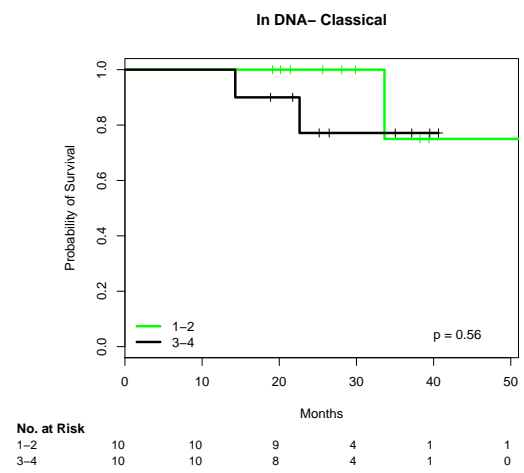
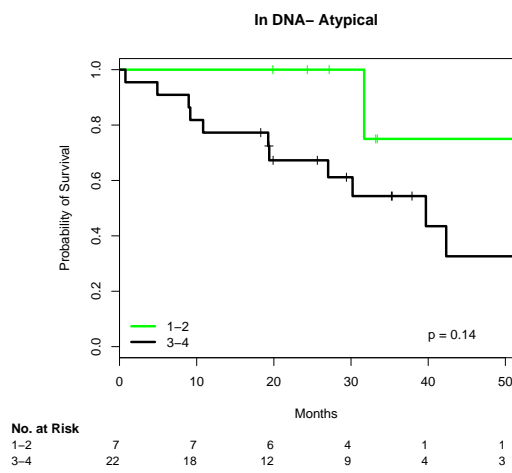
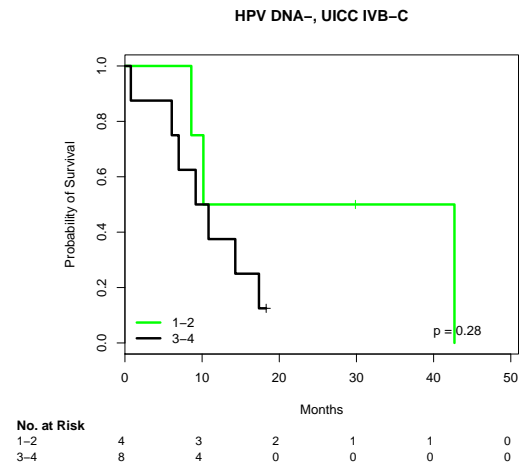
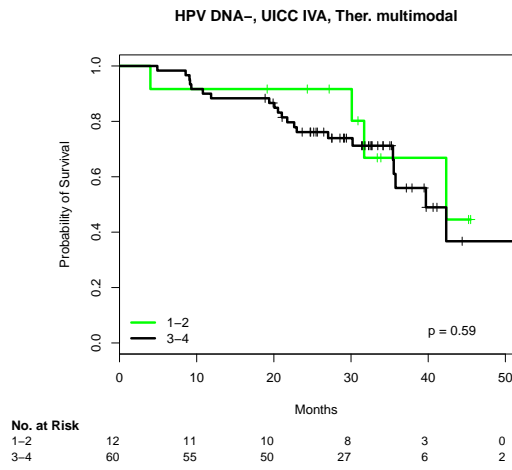
2.10 T stages 1,2 vs. 3,4

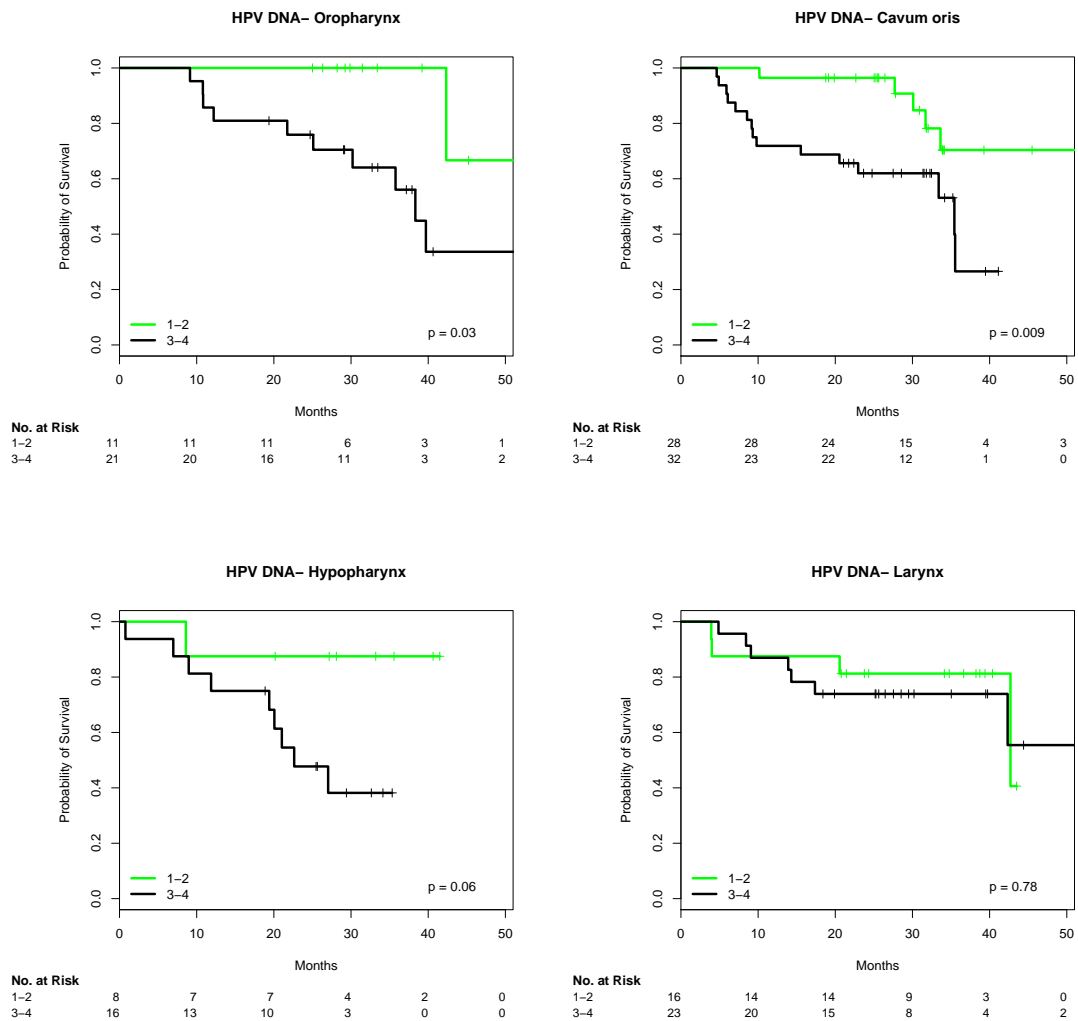
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 1.329      3.775    0.292 4.54 5.5e-06 ***
## ---
## 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      3.78      0.265      2.13      6.7
##
## Concordance= 0.658 (se = 0.033 )
## Rsquare= 0.11 (max possible= 0.954 )
## Likelihood ratio test= 25.4 on 1 df, p=4.73e-07
## Wald test = 20.6 on 1 df, p=5.53e-06
## Score (logrank) test = 23.7 on 1 df, p=1.12e-06
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 1.15      3.15      0.33 3.49 0.00049 ***
## ---
## 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      3.15      0.317      1.65      6.02
##
## Concordance= 0.634 (se = 0.037 )
## Rsquare= 0.088 (max possible= 0.954 )
## Likelihood ratio test= 14.5 on 1 df, p=0.00014
## Wald test = 12.2 on 1 df, p=0.00049
## Score (logrank) test = 13.5 on 1 df, p=0.000242
```





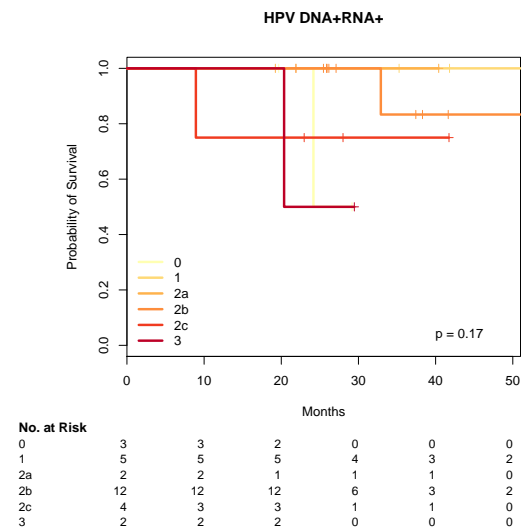
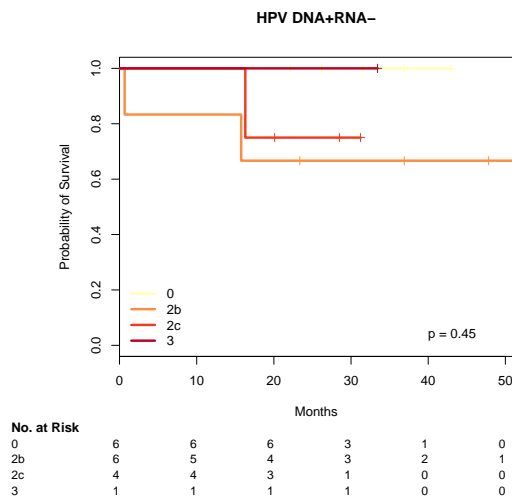
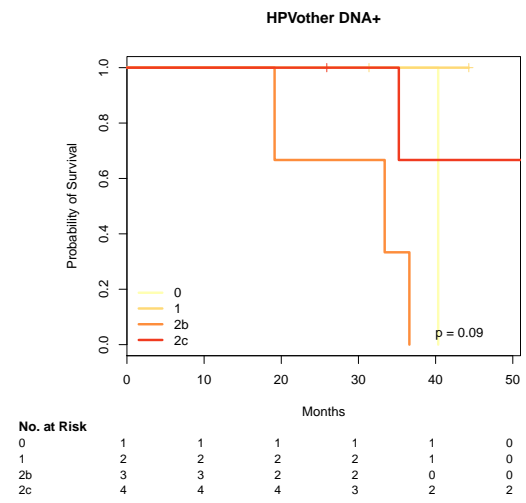
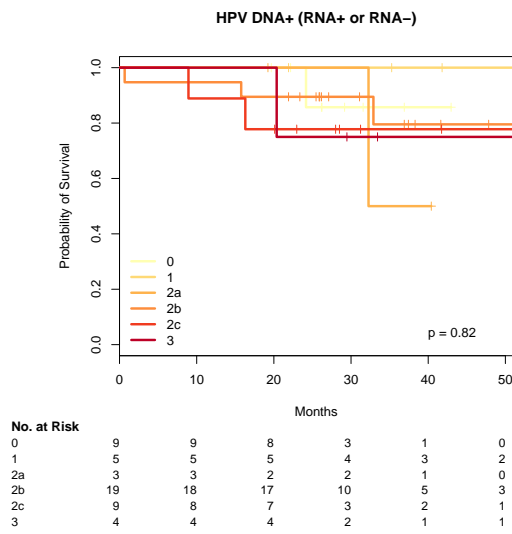
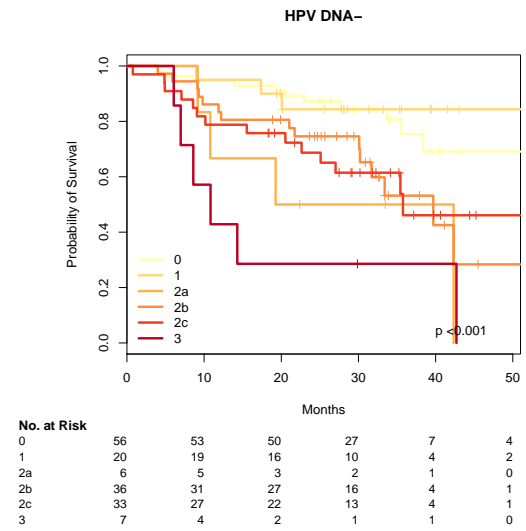
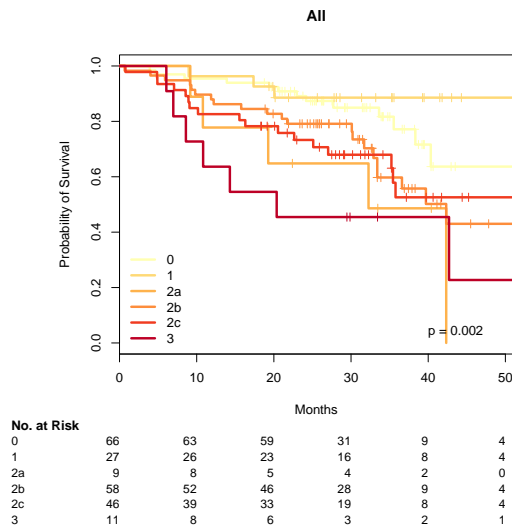




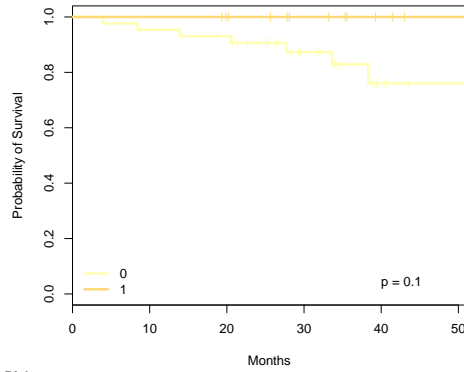
2.11 N (TNM staging)

```
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.794    0.452  0.637 -1.25  0.2131
## split[cur.subset]2a  1.174    3.235  0.523  2.24  0.0248 *
## split[cur.subset]2b  0.698    2.010  0.340  2.05  0.0400 *
## split[cur.subset]2c  0.726    2.066  0.354  2.05  0.0402 *
## split[cur.subset]3  1.264    3.540  0.457  2.76  0.0057 **
## ---
```

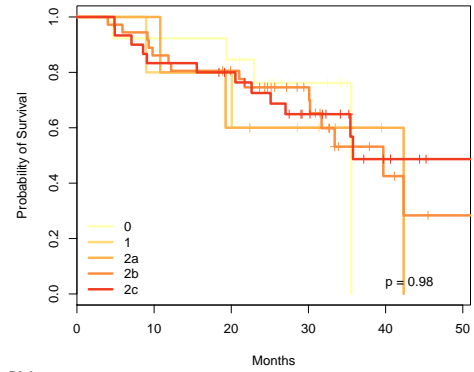
```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1      0.452      2.211      0.13      1.58
## split[cur.subset]2a      3.235      0.309      1.16      9.01
## split[cur.subset]2b      2.010      0.498      1.03      3.91
## split[cur.subset]2c      2.066      0.484      1.03      4.13
## split[cur.subset]3      3.540      0.282      1.44      8.67
##
## Concordance= 0.645 (se = 0.037 )
## Rsquare= 0.084 (max possible= 0.954 )
## Likelihood ratio test= 19.1 on 5 df, p=0.00185
## Wald test = 16.2 on 5 df, p=0.00625
## Score (logrank) test = 18.5 on 5 df, p=0.00236
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.477      0.621      0.650 -0.73 0.46307
## split[cur.subset]2a  1.424      4.156      0.581  2.45 0.01417 *
## split[cur.subset]2b  0.835      2.305      0.386  2.16 0.03058 *
## split[cur.subset]2c  0.885      2.423      0.396  2.23 0.02543 *
## split[cur.subset]3  1.929      6.884      0.507  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]1      0.621      1.611      0.174      2.22
## split[cur.subset]2a      4.156      0.241      1.332     12.97
## split[cur.subset]2b      2.305      0.434      1.081      4.91
## split[cur.subset]2c      2.423      0.413      1.115      5.27
## split[cur.subset]3      6.884      0.145      2.550     18.59
##
## Concordance= 0.662 (se = 0.041 )
## Rsquare= 0.125 (max possible= 0.954 )
## Likelihood ratio test= 21.1 on 5 df, p=0.000777
## Wald test = 21.2 on 5 df, p=0.000735
## Score (logrank) test = 25.5 on 5 df, p=0.000112
```



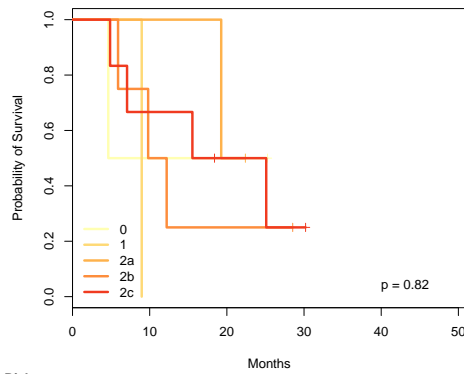
HPV DNA-, UICC I, II, III



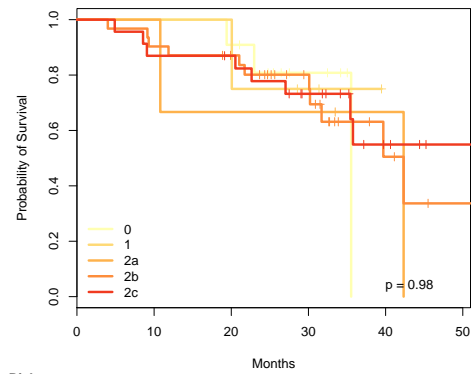
HPV DNA-, UICC IVA



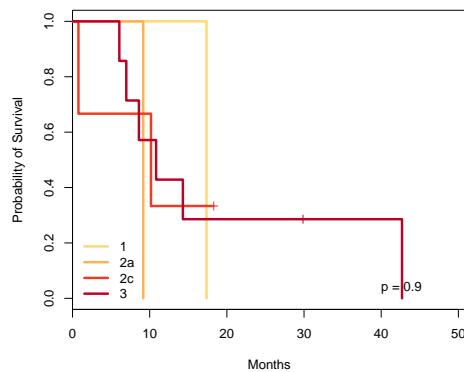
HPV DNA-, UICC IVA, Ther. unimodal



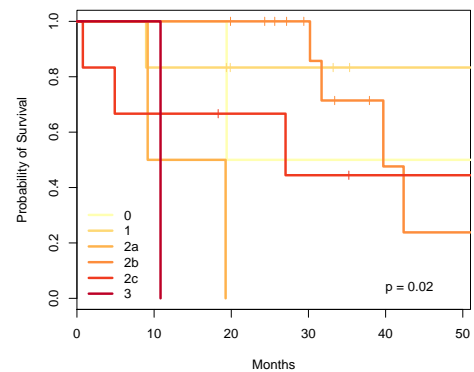
HPV DNA-, UICC IVA, Ther. multimodal



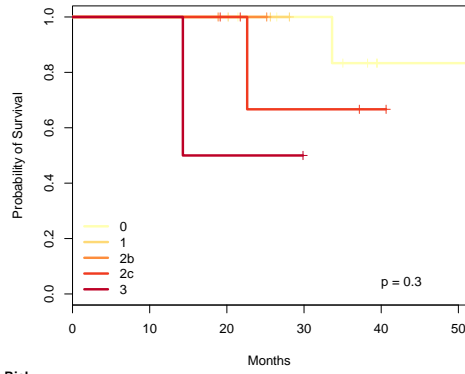
HPV DNA-, UICC IVB-C



In DNA- Atypical

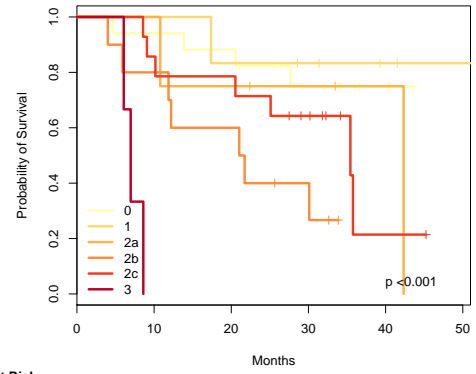


In DNA- Classical



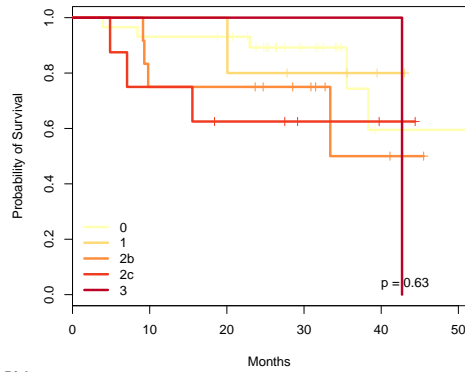
No. at Risk	0	10	20	30	40	50
0	8	8	8	6	1	1
1	3	3	3	0	0	0
2b	2	2	1	0	0	0
2c	5	5	4	2	1	0
3	2	2	1	0	0	0

In DNA- Mesenchymal



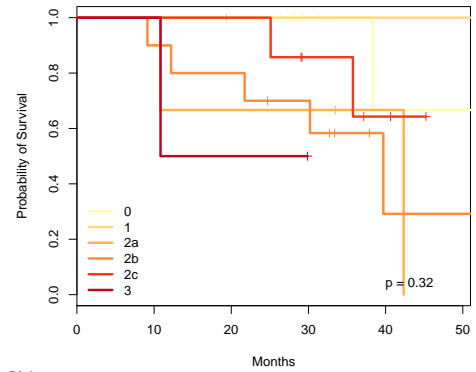
No. at Risk	0	10	20	30	40	50
0	17	16	15	8	3	0
1	6	6	5	4	2	1
2a	4	4	3	2	1	0
2b	10	8	6	3	0	0
2c	14	12	11	7	1	0
3	3	0	0	0	0	0

In DNA- Basal



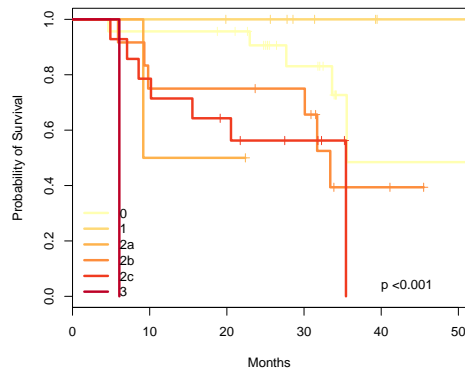
No. at Risk	0	10	20	30	40	50
0	29	27	26	12	2	2
1	5	5	5	3	1	0
2b	12	9	9	6	2	0
2c	8	6	4	2	1	0
3	1	1	1	1	1	0

HPV DNA- Oropharynx



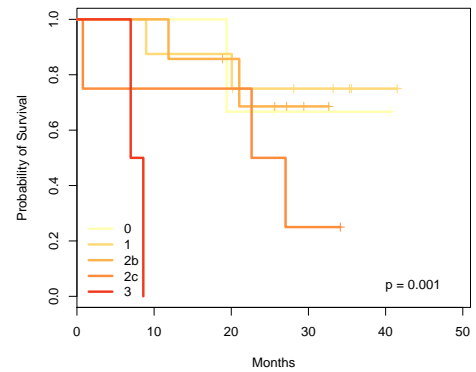
No. at Risk	0	10	20	30	40	50
0	8	8	8	4	1	1
1	2	2	1	1	1	1
2a	3	3	2	2	1	0
2b	10	9	8	6	1	1
2c	7	7	7	4	2	0
3	2	2	1	0	0	0

HPV DNA- Cavum oris

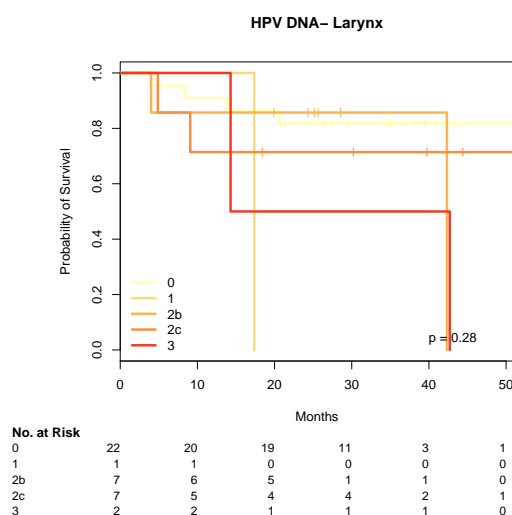


No. at Risk	0	10	20	30	40	50
0	23	22	21	11	2	2
1	8	8	7	4	1	1
2a	2	1	1	0	0	0
2b	12	9	9	8	2	0
2c	14	11	8	4	0	0
3	1	0	0	0	0	0

HPV DNA- Hypopharynx



No. at Risk	0	10	20	30	40	50
0	3	3	2	1	1	0
1	8	7	7	4	1	0
2a	7	7	5	1	0	0
2b	4	3	3	1	0	0
2c	2	0	0	0	0	0
3	2	0	0	0	0	0

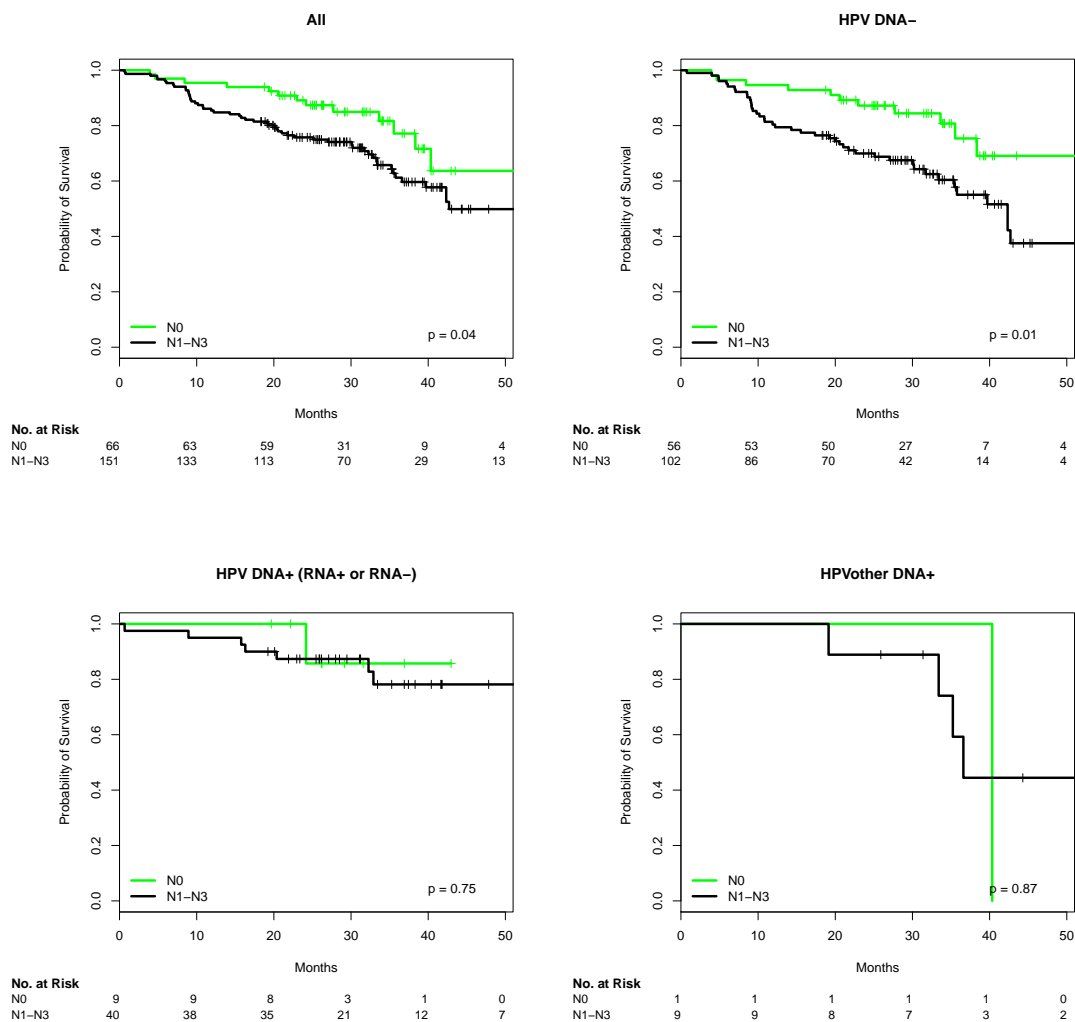


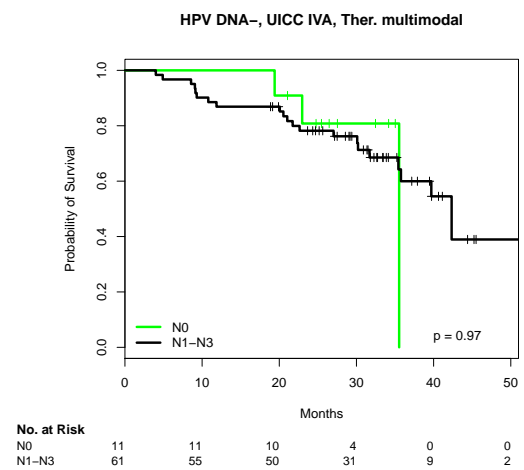
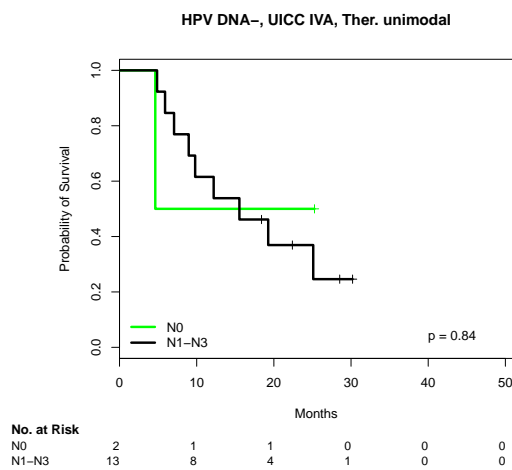
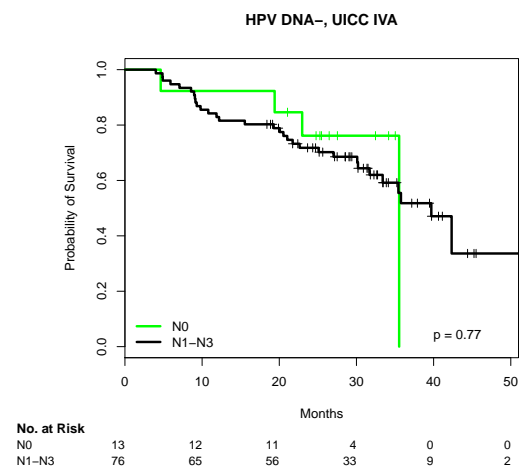
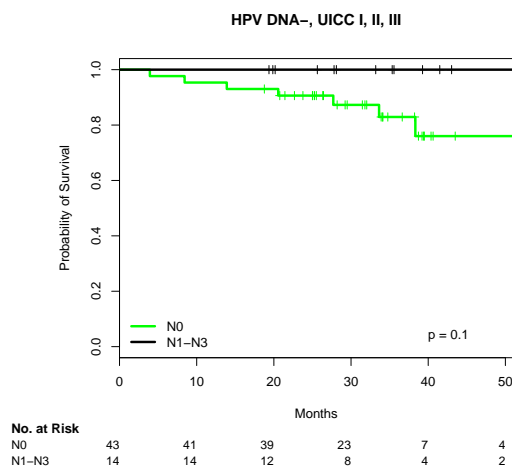
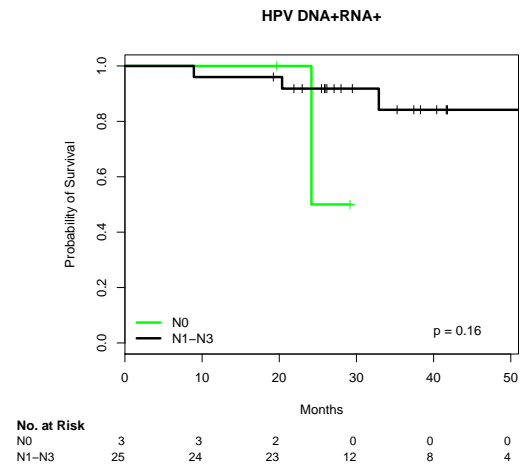
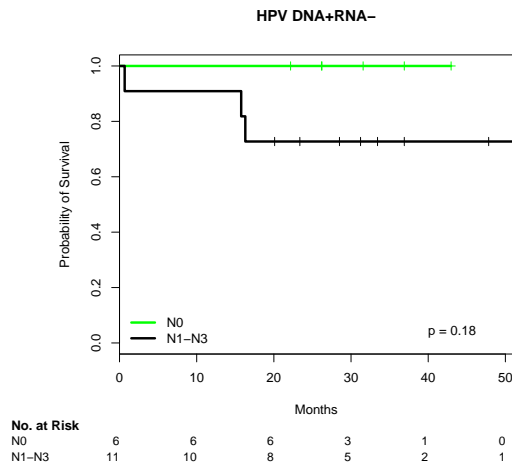
2.12 N0 stage vs. N1-N3

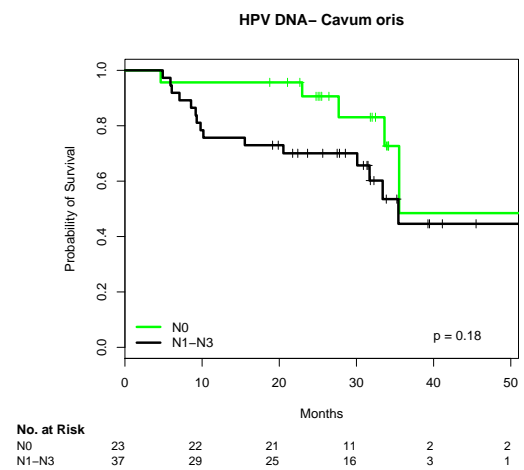
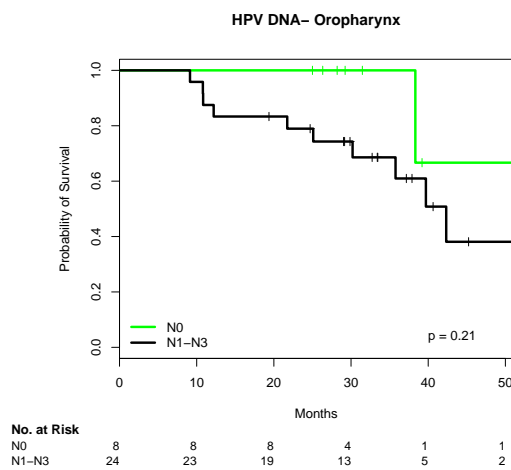
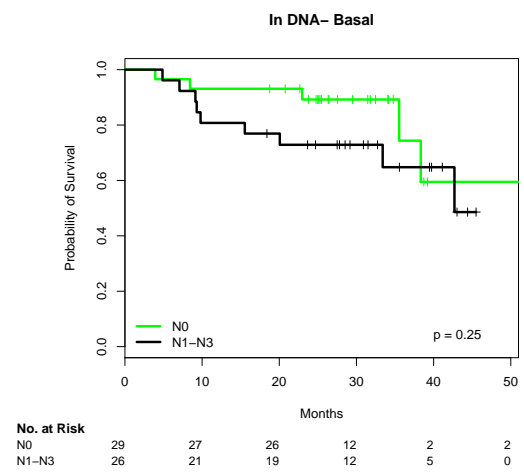
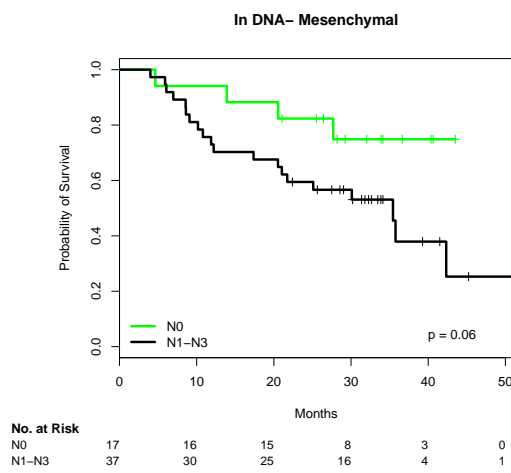
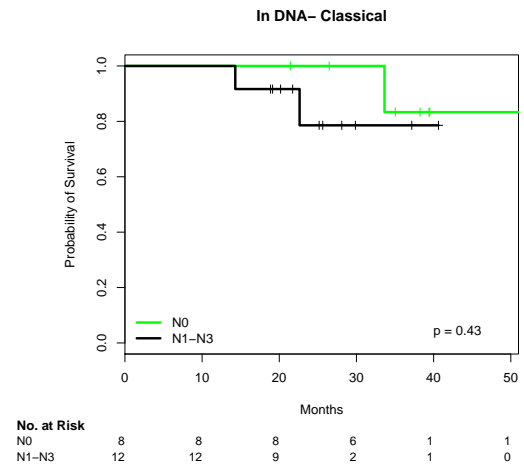
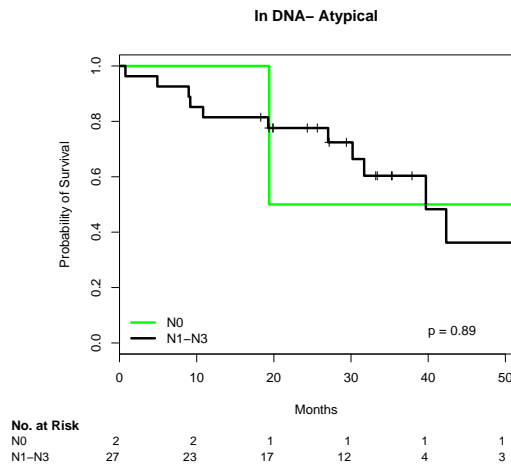
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.619      1.856    0.299 2.07    0.039 *
## ---
## 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      1.86      0.539      1.03      3.34
##
## Concordance= 0.57 (se = 0.031 )
## Rsquare= 0.022 (max possible= 0.954 )
## Likelihood ratio test= 4.79 on 1 df,  p=0.0287
## Wald test               = 4.27 on 1 df,  p=0.0388
## Score (logrank) test = 4.41 on 1 df,  p=0.0358
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
```

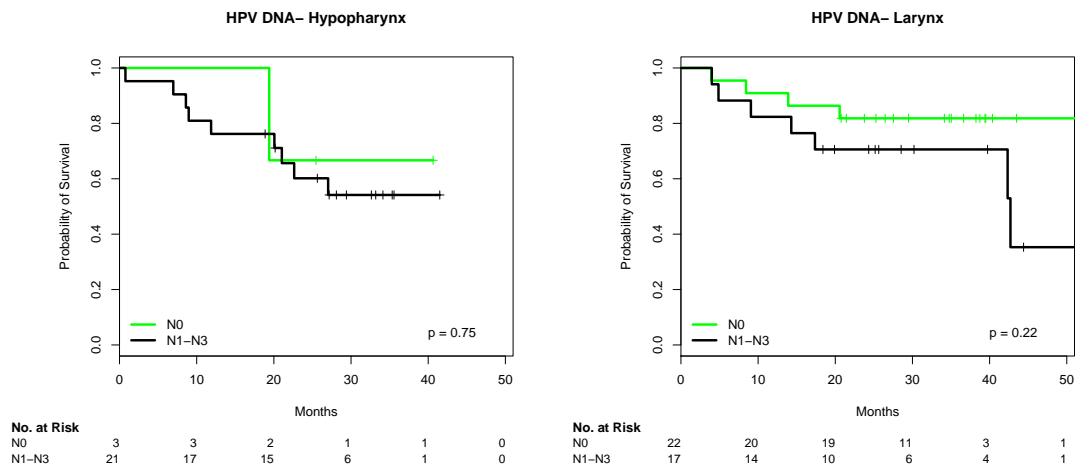


```
## n= 158, number of events= 55
##
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.800      2.225    0.328 2.44    0.015 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3      2.23      0.449      1.17      4.24
##
## Concordance= 0.595 (se = 0.036 )
## Rsquare= 0.042 (max possible= 0.954 )
## Likelihood ratio test= 6.76 on 1 df,  p=0.00932
## Wald test               = 5.94 on 1 df,  p=0.0148
## Score (logrank) test = 6.25 on 1 df,  p=0.0124
```





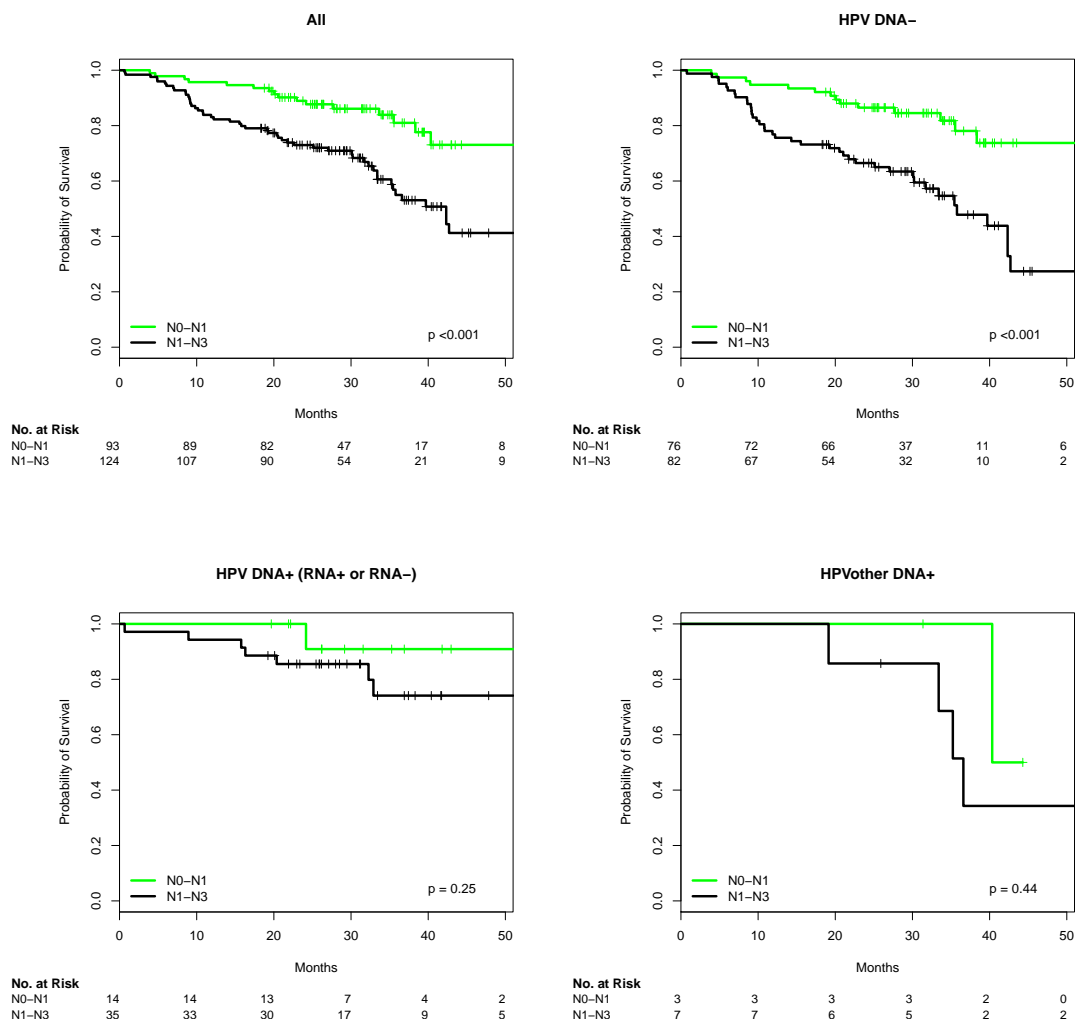


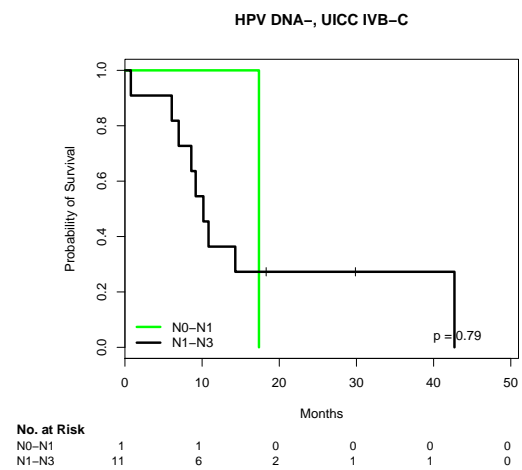
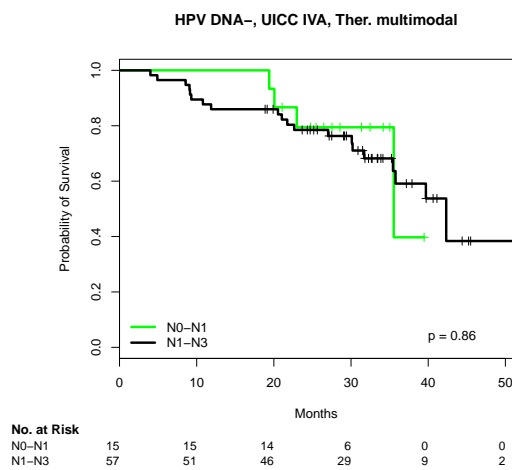
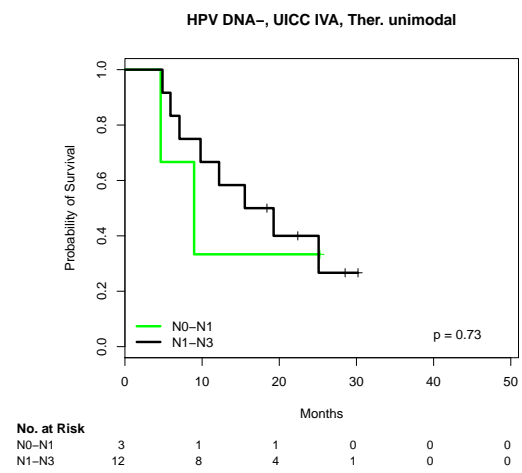
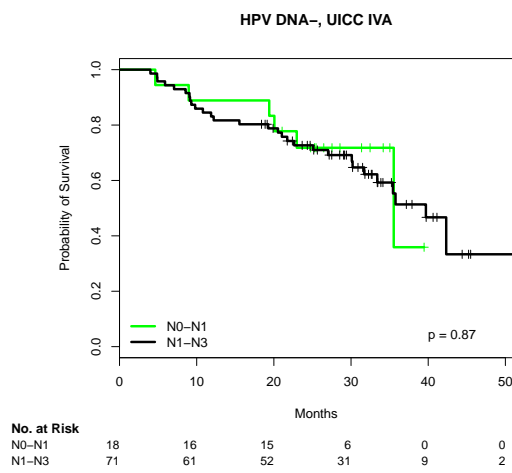
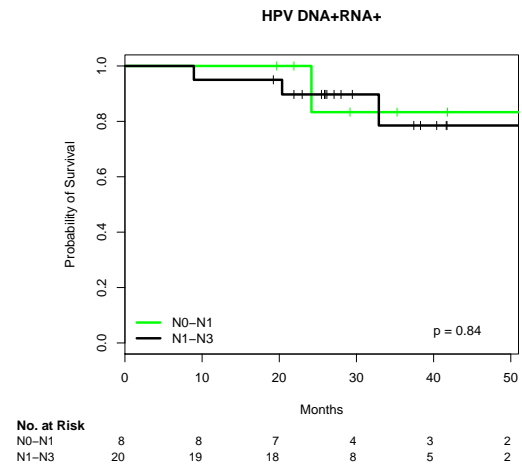
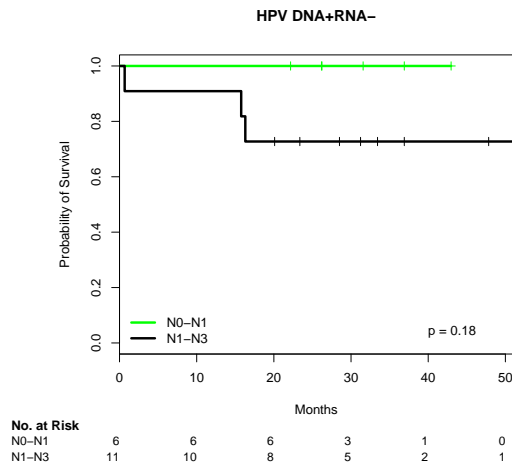


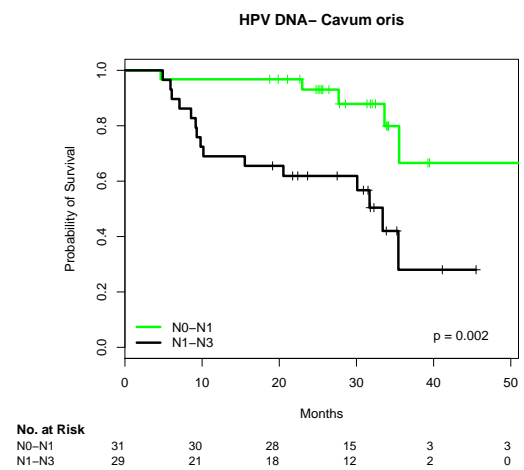
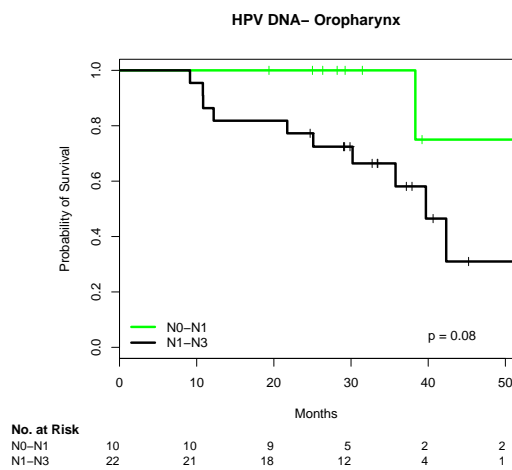
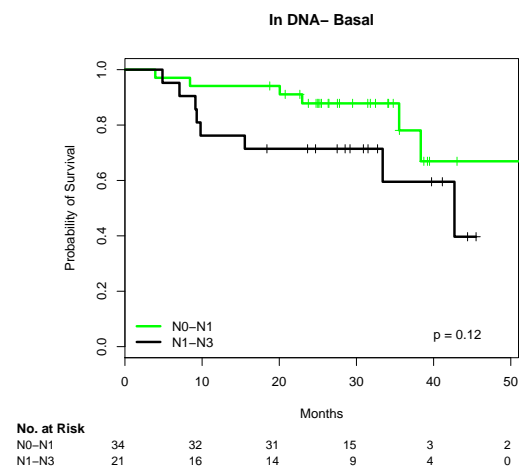
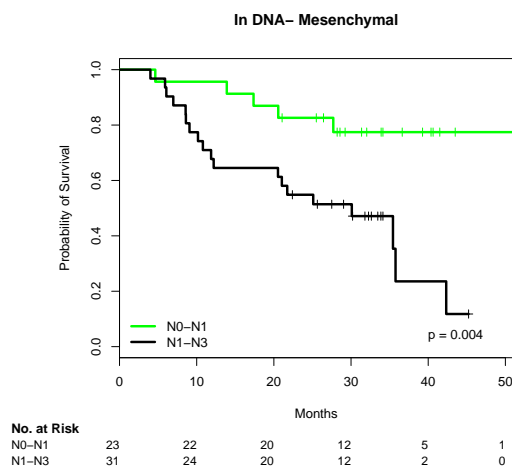
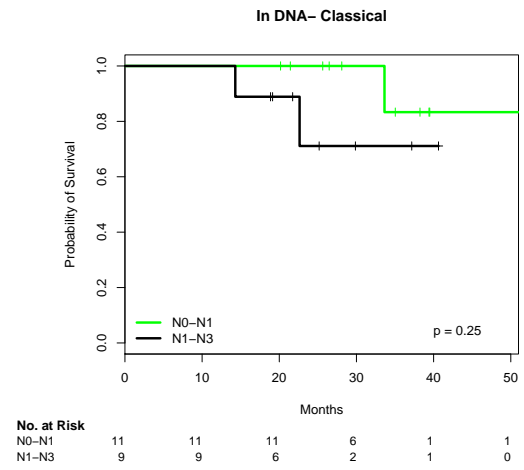
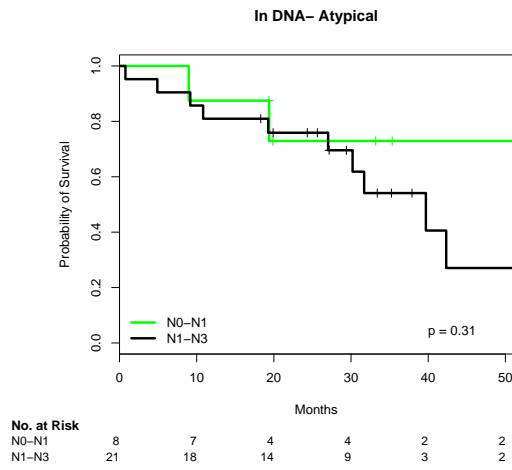
2.13 N0-N1 stages vs. N2-N3

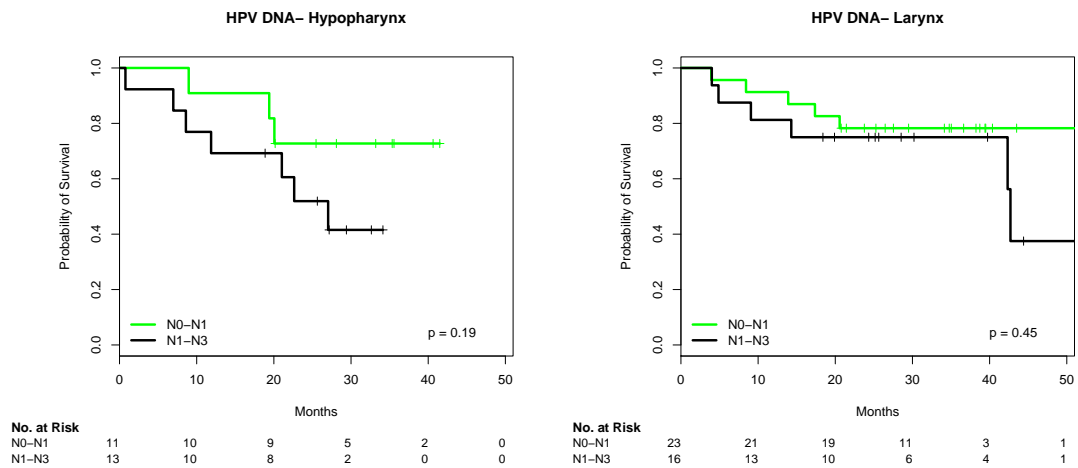
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 1.001      2.720    0.279 3.59  0.00033 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3      2.72      0.368      1.58      4.7
##
## Concordance= 0.611 (se = 0.033 )
## Rsquare= 0.066 (max possible= 0.954 )
## Likelihood ratio test= 14.9 on 1 df,  p=0.000114
## Wald test               = 12.9 on 1 df,  p=0.000328
## Score (logrank) test = 14 on 1 df,  p=0.000182
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
```

```
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 1.123      3.075    0.305 3.69  0.00023 ***
## ---
## 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      3.08      0.325      1.69      5.59
##
## Concordance= 0.63 (se = 0.037 )
## Rsquare= 0.093 (max possible= 0.954 )
## Likelihood ratio test= 15.4 on 1 df,  p=8.51e-05
## Wald test               = 13.6 on 1 df,  p=0.000225
## Score (logrank) test = 15.1 on 1 df,  p=0.000105
```







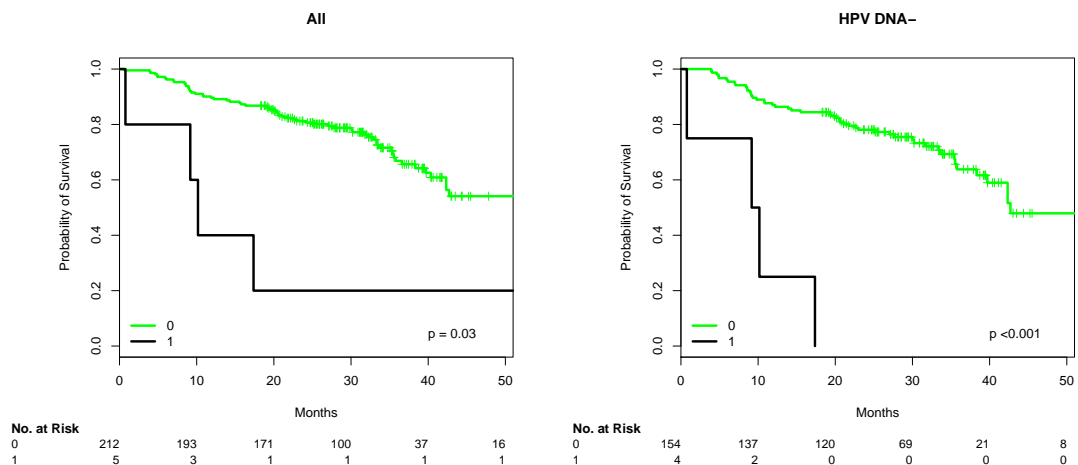


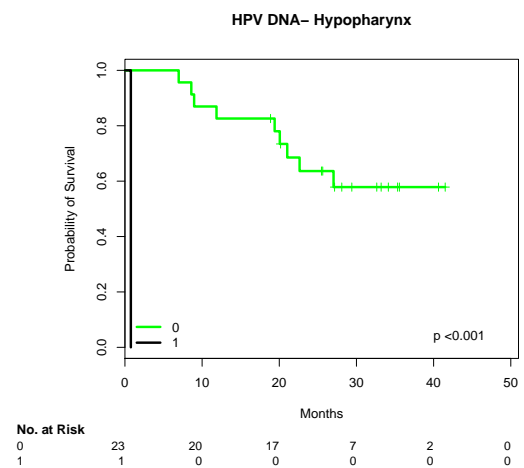
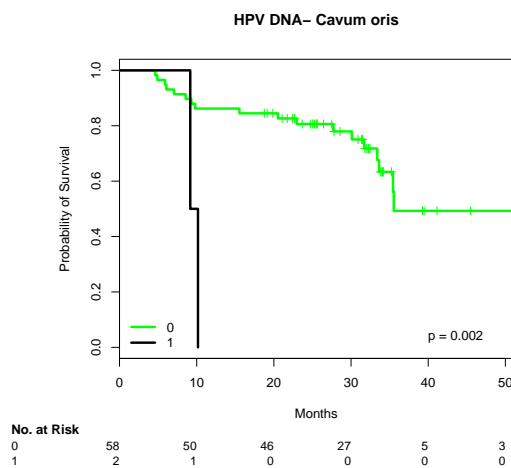
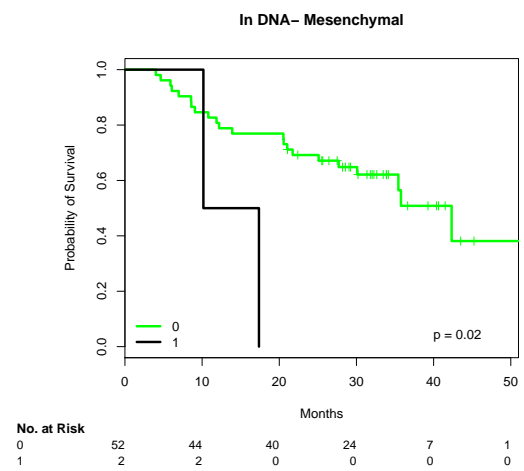
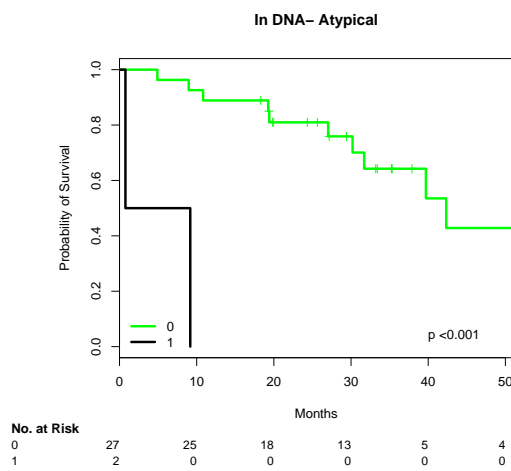
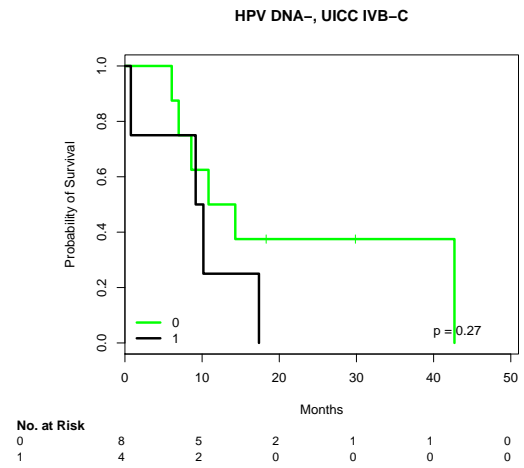
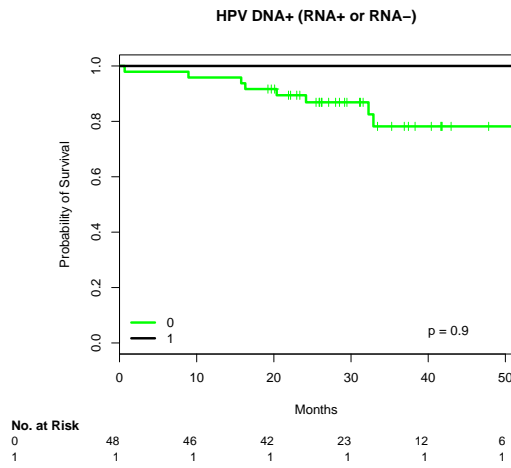
2.14 M (TNM staging)

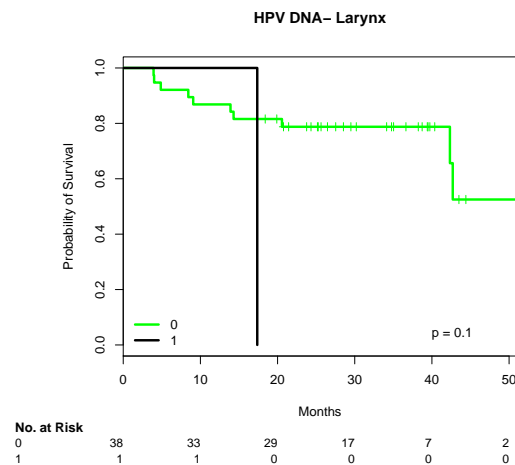
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 1.058      2.880   0.514  2.06   0.039 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      2.88      0.347      1.05      7.88
##
## Concordance= 0.533 (se = 0.008 )
## Rsquare= 0.015 (max possible= 0.954 )
## Likelihood ratio test= 3.37 on 1 df,  p=0.0665
```



```
## Wald test          = 4.24  on 1 df,    p=0.0394
## Score (logrank) test = 4.49  on 1 df,    p=0.0342
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset] 2.343    10.415    0.545 4.3 1.7e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      10.4      0.096      3.58      30.3
##
## Concordance= 0.543 (se = 0.008 )
## Rsquare= 0.067 (max possible= 0.954 )
## Likelihood ratio test= 10.9 on 1 df,    p=0.000943
## Wald test          = 18.5 on 1 df,    p=1.72e-05
## Score (logrank) test = 28.6 on 1 df,    p=8.9e-08
```



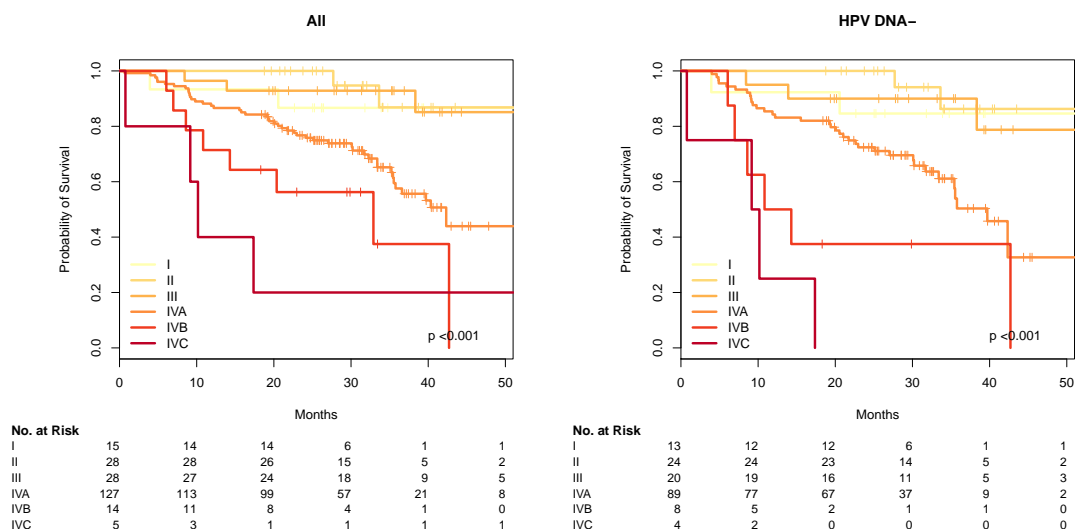


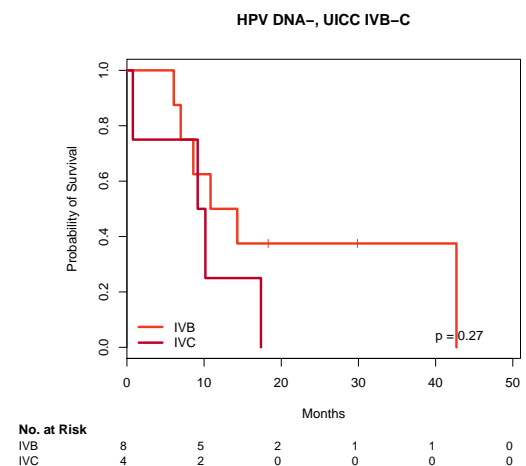
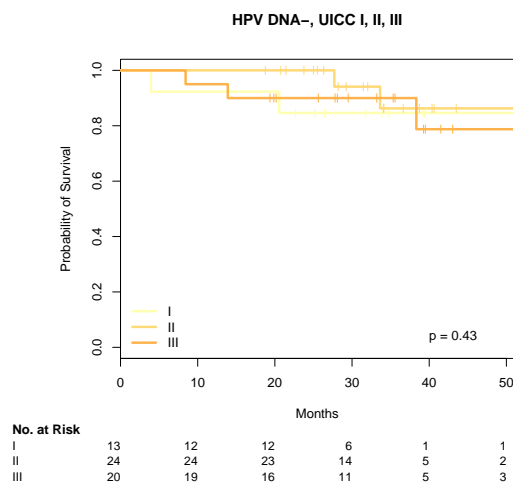
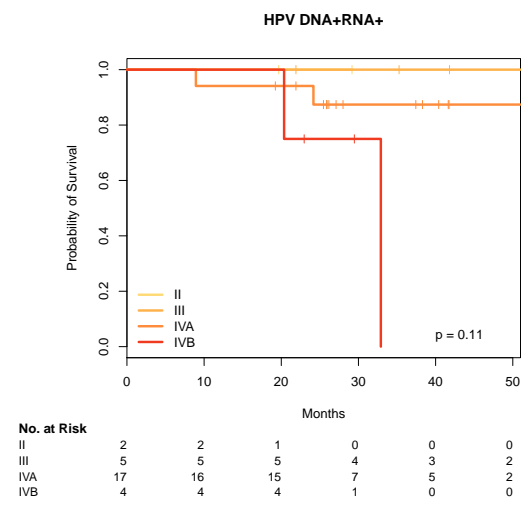
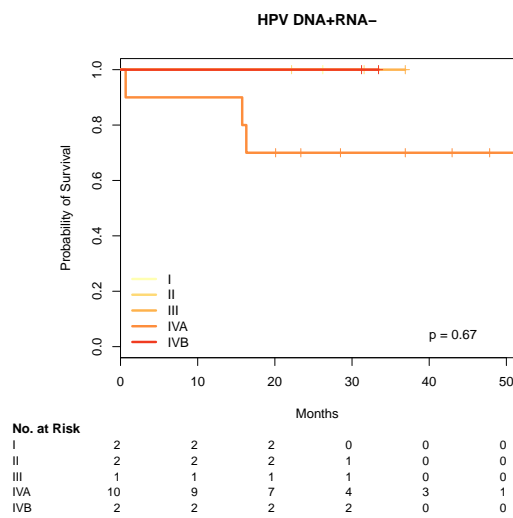
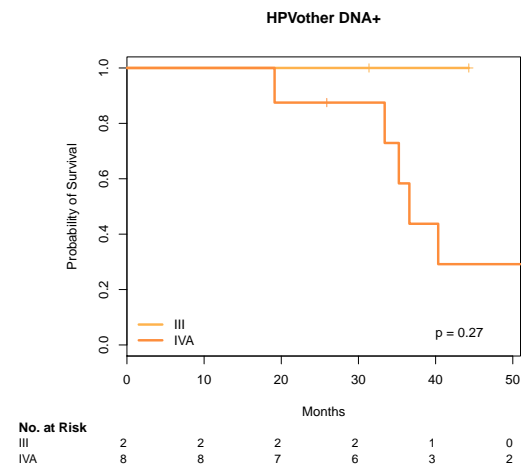
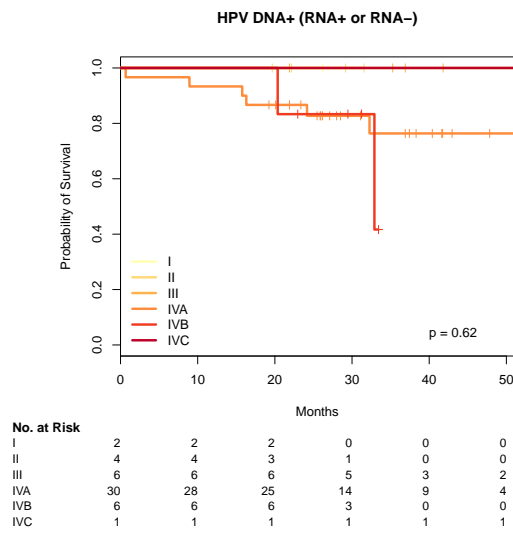


2.15 UICC staging

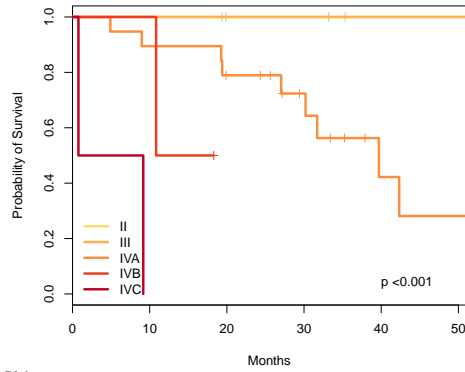
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -1.163    0.313   0.913 -1.27   0.203
## split[cur.subset]III -0.897    0.408   0.819 -1.10   0.273
## split[cur.subset]IVA  0.721    2.057   0.595  1.21   0.226
## split[cur.subset]IVB  1.459    4.304   0.680  2.15   0.032 *
## split[cur.subset]IVC  1.454    4.278   0.762  1.91   0.056 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.313    3.198   0.0522    1.87
## split[cur.subset]III    0.408    2.452   0.0820    2.03
## split[cur.subset]IVA    2.057    0.486   0.6403    6.61
## split[cur.subset]IVB    4.304    0.232   1.1350   16.32
## split[cur.subset]IVC    4.278    0.234   0.9609   19.05
##
## Concordance= 0.671 (se = 0.034 )
## Rsquare= 0.136 (max possible= 0.954 )
```

```
## Likelihood ratio test= 31.7 on 5 df, p=6.83e-06
## Wald test = 23 on 5 df, p=0.000334
## Score (logrank) test = 29.6 on 5 df, p=1.79e-05
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -1.178      0.308   0.913 -1.29  0.19695
## split[cur.subset]III -0.661      0.516   0.821 -0.81  0.42073
## split[cur.subset]IVA  0.743      2.102   0.605  1.23  0.21921
## split[cur.subset]IVB  1.750      5.754   0.716  2.44  0.01453 *
## split[cur.subset]IVC  2.843     17.162   0.788  3.61  0.00031 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II      0.308      3.2487   0.0514   1.84
## split[cur.subset]III      0.516      1.9373   0.1032   2.58
## split[cur.subset]IVA      2.102      0.4757   0.6426   6.88
## split[cur.subset]IVB      5.754      0.1738   1.4142  23.41
## split[cur.subset]IVC     17.162      0.0583   3.6656  80.35
##
## Concordance= 0.698 (se = 0.039 )
## Rsquare= 0.204 (max possible= 0.954 )
## Likelihood ratio test= 36 on 5 df, p=9.36e-07
## Wald test = 35.1 on 5 df, p=1.41e-06
## Score (logrank) test = 52.9 on 5 df, p=3.59e-10
```





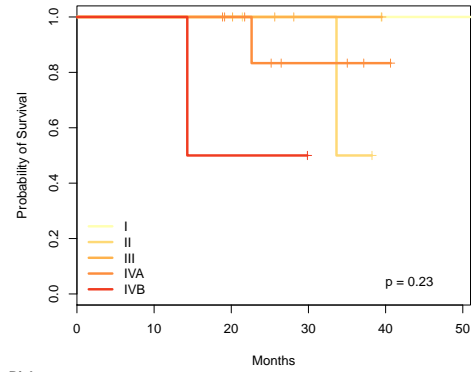
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
II	1	1	1	1	1	1
III	5	5	3	3	1	1
IVA	19	17	14	9	3	2
IVB	2	2	0	0	0	0
IVC	2	0	0	0	0	0

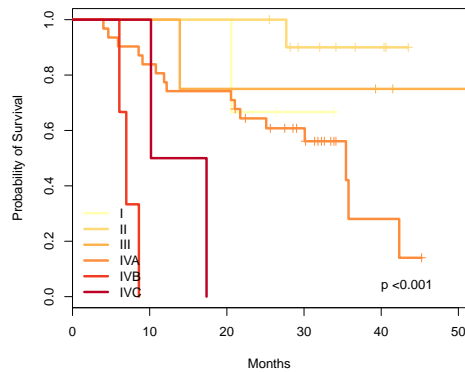
In DNA- Classical



No. at Risk

	0	10	20	30	40	50
I	2	2	2	2	1	1
II	3	3	3	2	0	0
III	4	4	4	1	0	0
IVA	9	9	7	3	1	0
IVB	2	2	1	0	0	0

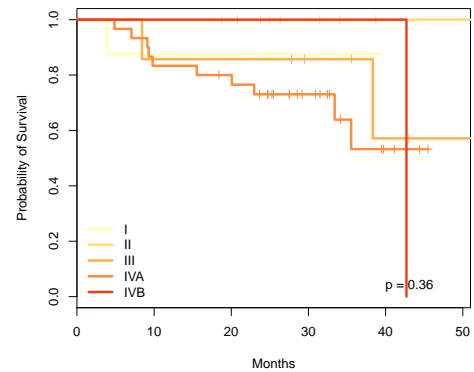
In DNA- Mesenchymal



No. at Risk

	0	10	20	30	40	50
I	3	3	3	1	0	0
II	11	11	11	7	3	0
III	4	4	3	3	2	1
IVA	31	26	23	13	2	0
IVB	3	0	0	0	0	0
IVC	2	2	0	0	0	0

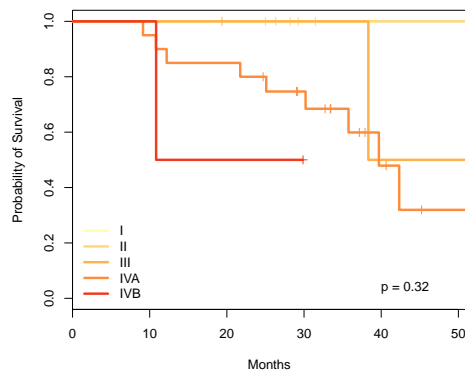
In DNA- Basal



No. at Risk

	0	10	20	30	40	50
I	8	7	7	3	0	0
II	9	9	8	4	1	1
III	7	6	6	4	2	1
IVA	30	25	23	12	3	0
IVB	1	1	1	1	1	0

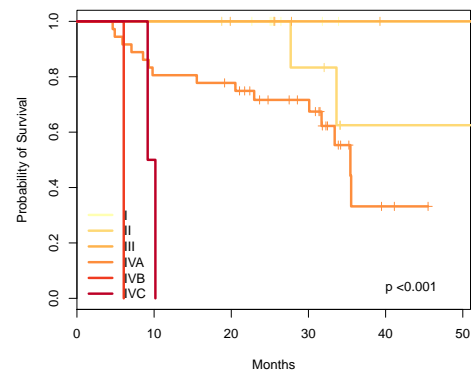
HPV DNA- Oropharynx



No. at Risk

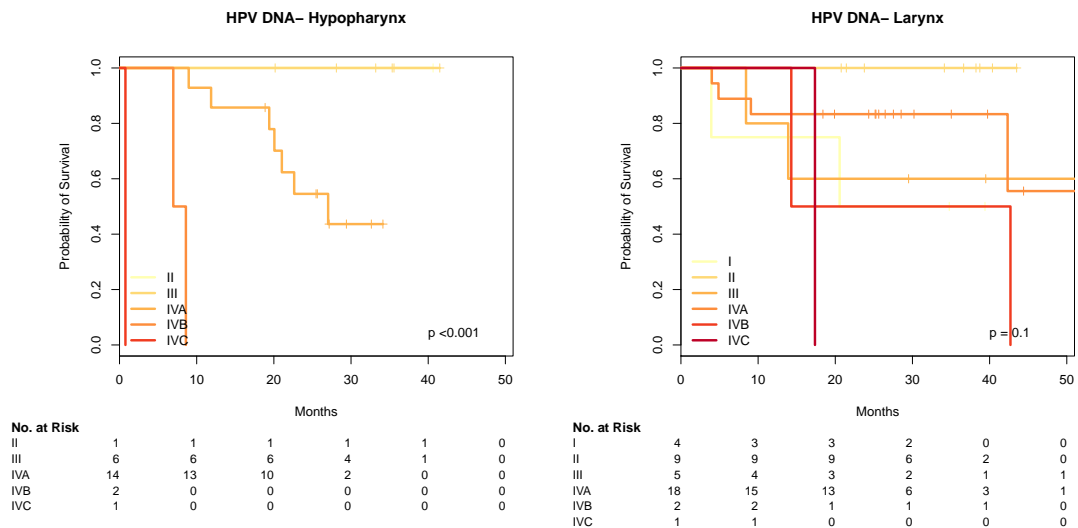
	0	10	20	30	40	50
I	1	1	1	1	0	0
II	6	6	6	2	1	1
III	3	3	2	2	1	1
IVA	20	19	17	12	4	1
IVB	2	2	1	0	0	0

HPV DNA- Cavum oris



No. at Risk

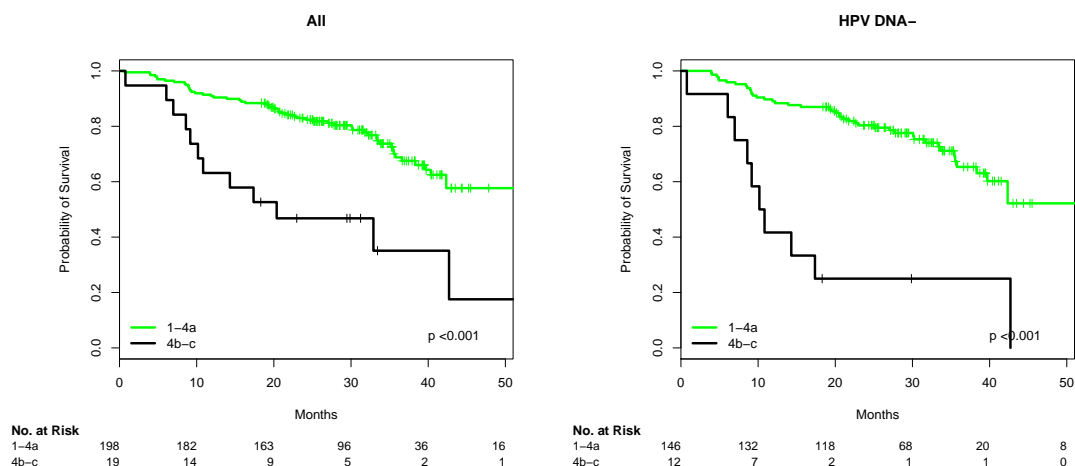
	0	10	20	30	40	50
I	8	8	8	3	1	1
II	8	8	7	5	1	1
III	5	5	4	2	1	1
IVA	36	29	27	17	2	0
IVB	1	0	0	0	0	0
IVC	2	1	0	0	0	0

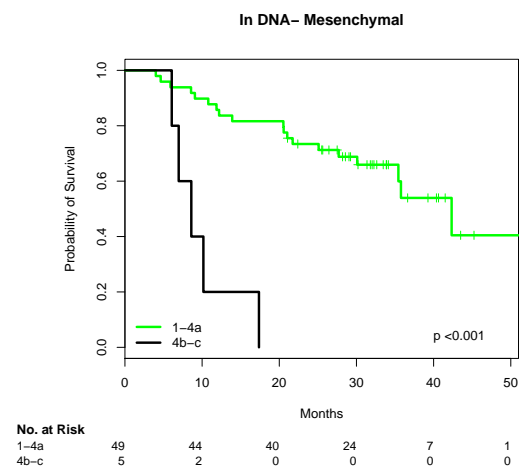
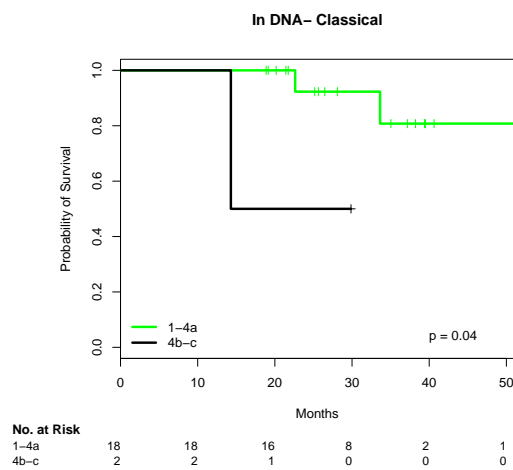
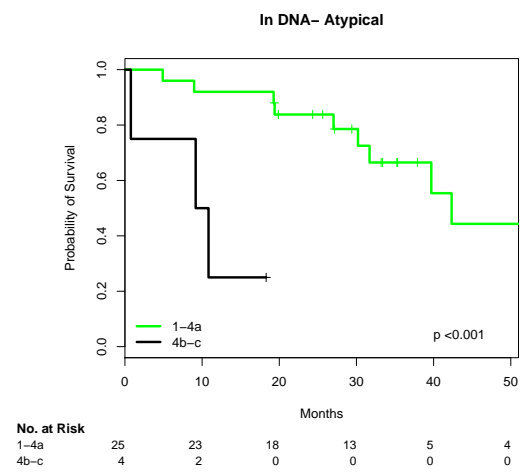
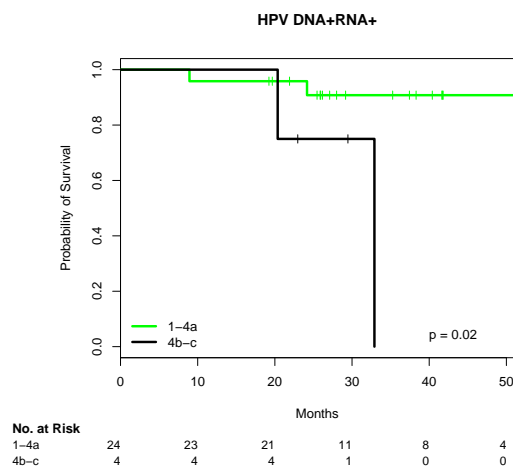
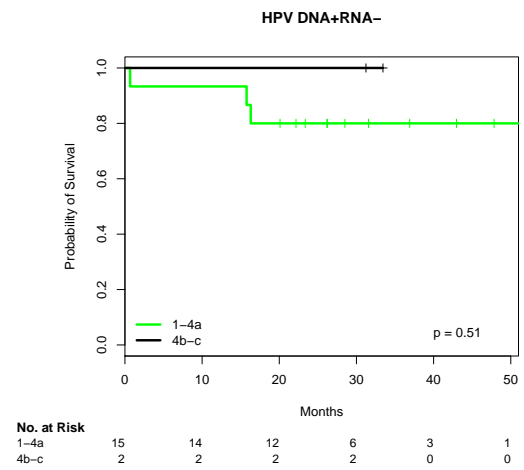
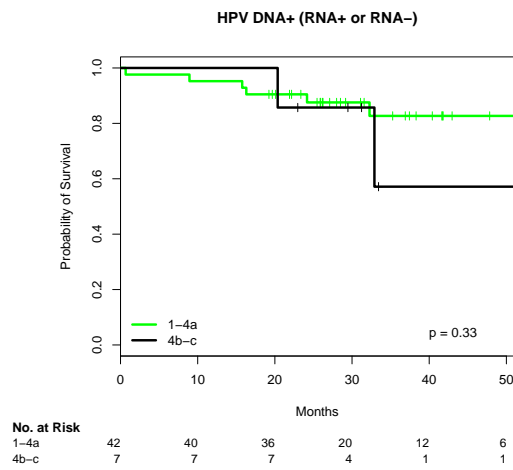


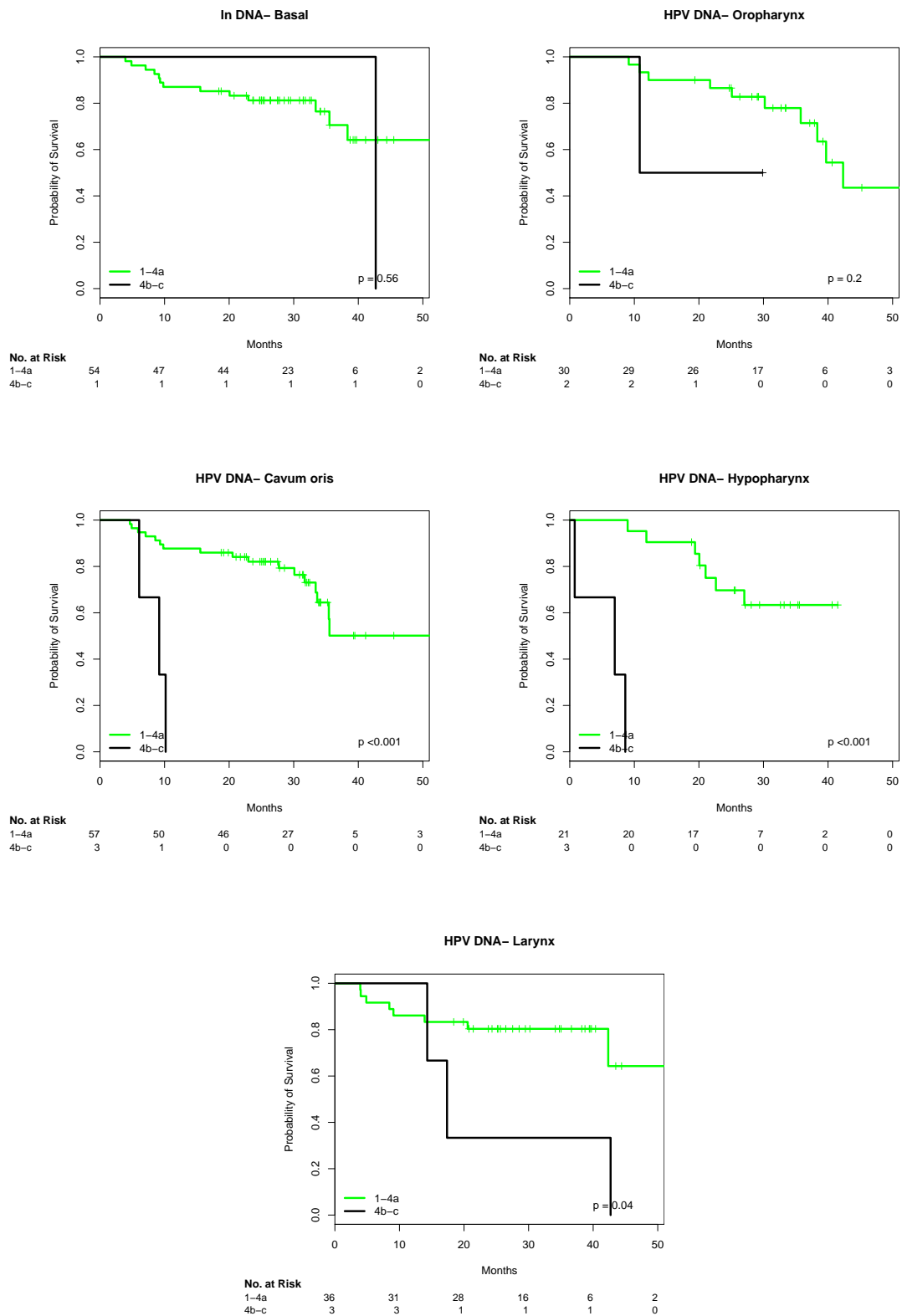
2.16 UICC, stages 1,2,3,4a vs. 4b,4c

```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.101      3.008    0.315 3.49  0.00048 ***
## ---
## 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      3.01      0.332      1.62      5.58
##
## Concordance= 0.571 (se = 0.017 )
## Rsquare= 0.044 (max possible= 0.954 )
## Likelihood ratio test= 9.7 on 1 df,  p=0.00184
## Wald test               = 12.2 on 1 df,  p=0.000478
## Score (logrank) test = 13.3 on 1 df,  p=0.000265
##
##
```

```
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.711      5.537    0.359 4.77  1.9e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4b-c      5.54      0.181      2.74      11.2
##
## Concordance= 0.589 (se = 0.016 )
## Rsquare= 0.097 (max possible= 0.954 )
## Likelihood ratio test= 16.1 on 1 df,  p=6.03e-05
## Wald test               = 22.7 on 1 df,  p=1.86e-06
## Score (logrank) test = 28.7 on 1 df,  p=8.46e-08
```







2.17 UICC, 1,2,3 vs. 4a vs. 4b,4c

```

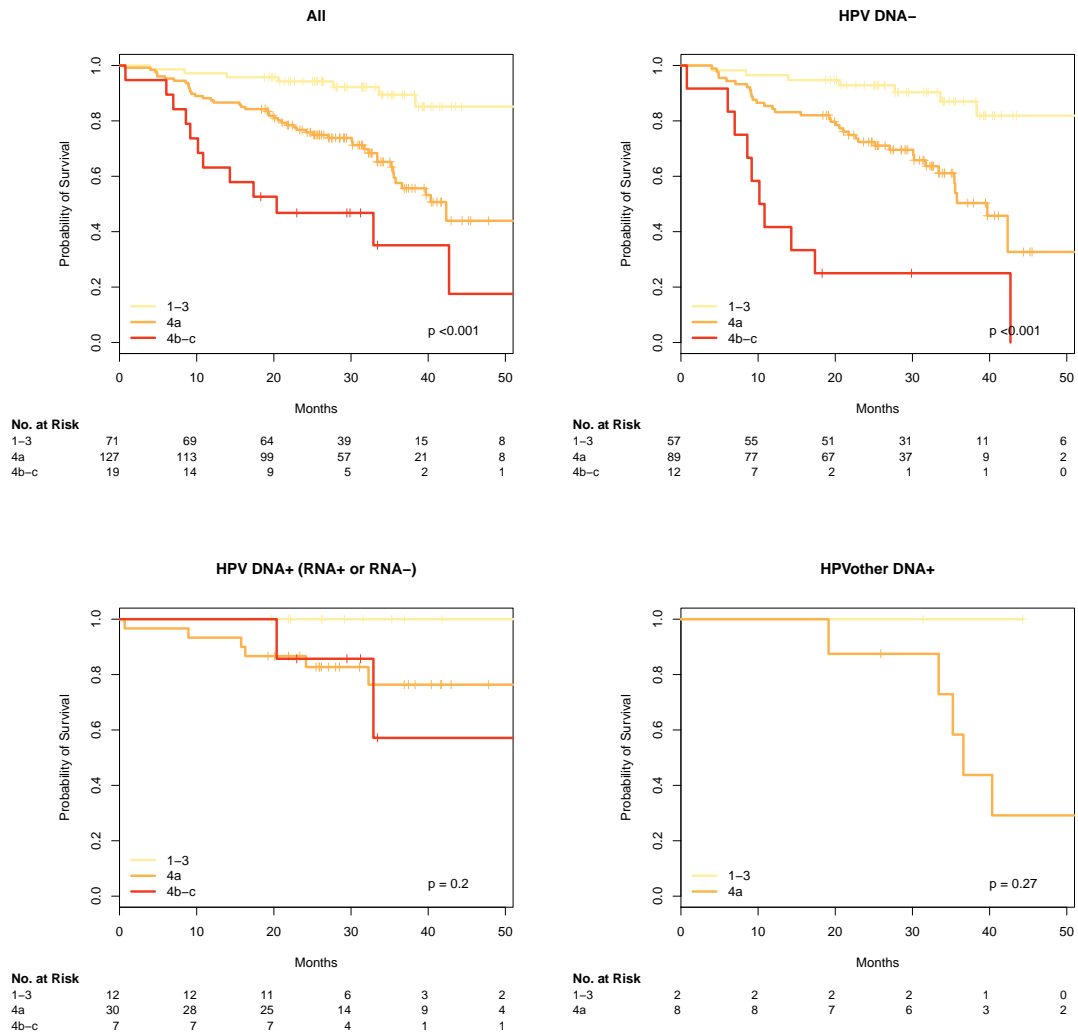
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  1.460     4.307   0.381 3.83  0.00013 ***
## split[cur.subset]4b-c 2.196     8.987   0.455 4.82  1.4e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      4.31      0.232      2.04      9.09
## split[cur.subset]4b-c      8.99      0.111      3.68     21.95
##
## Concordance= 0.668 (se = 0.034 )
## Rsquare= 0.129 (max possible= 0.954 )
## Likelihood ratio test= 29.9 on 2 df, p=3.21e-07
## Wald test = 23.5 on 2 df, p=7.93e-06
## Score (logrank) test = 28.9 on 2 df, p=5.27e-07
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  1.384     3.991   0.394 3.51  0.00045 ***
## split[cur.subset]4b-c 2.693    14.771   0.486 5.54   3e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      3.99      0.2505      1.84      8.65
## split[cur.subset]4b-c    14.77      0.0677      5.70     38.30
##

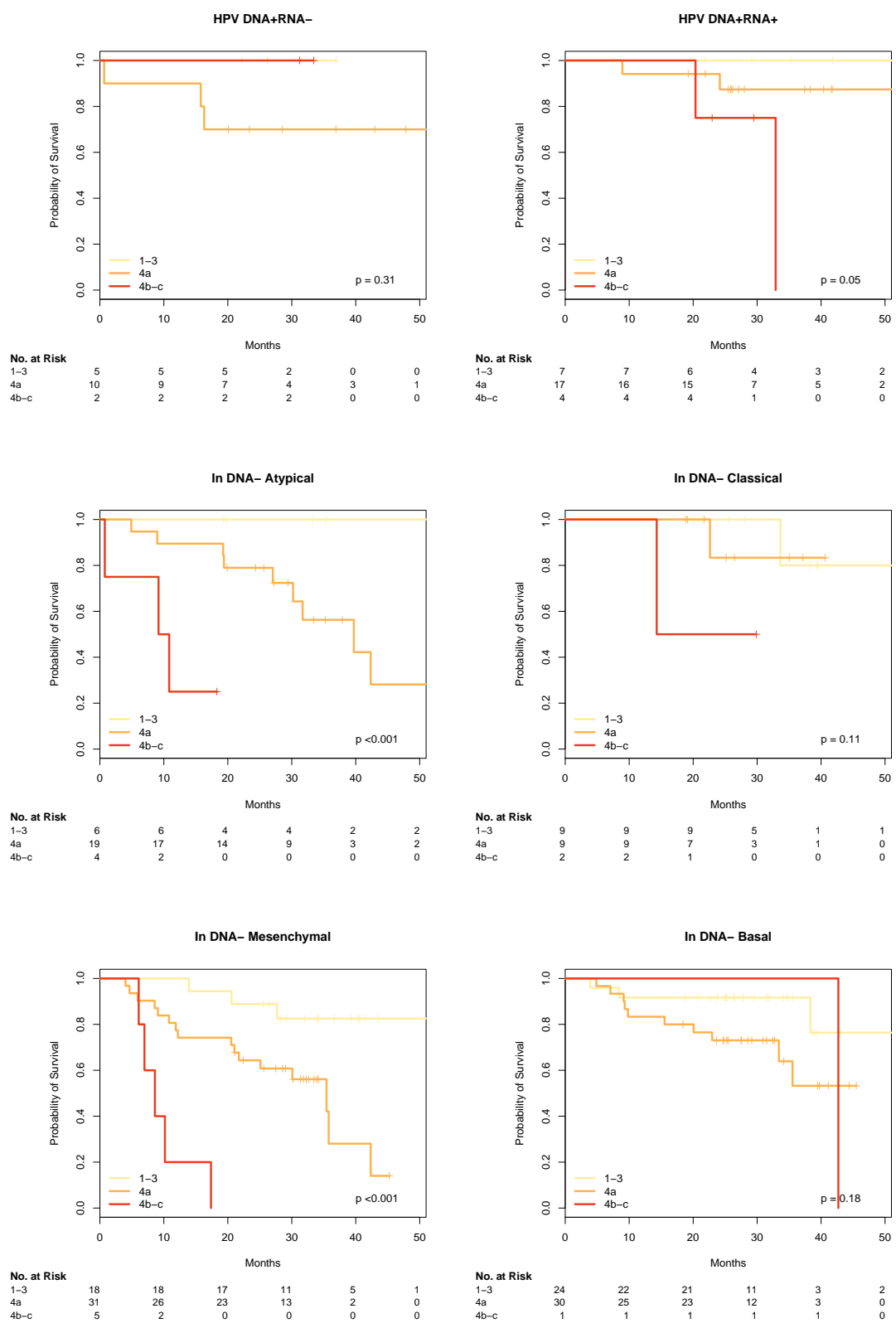
```

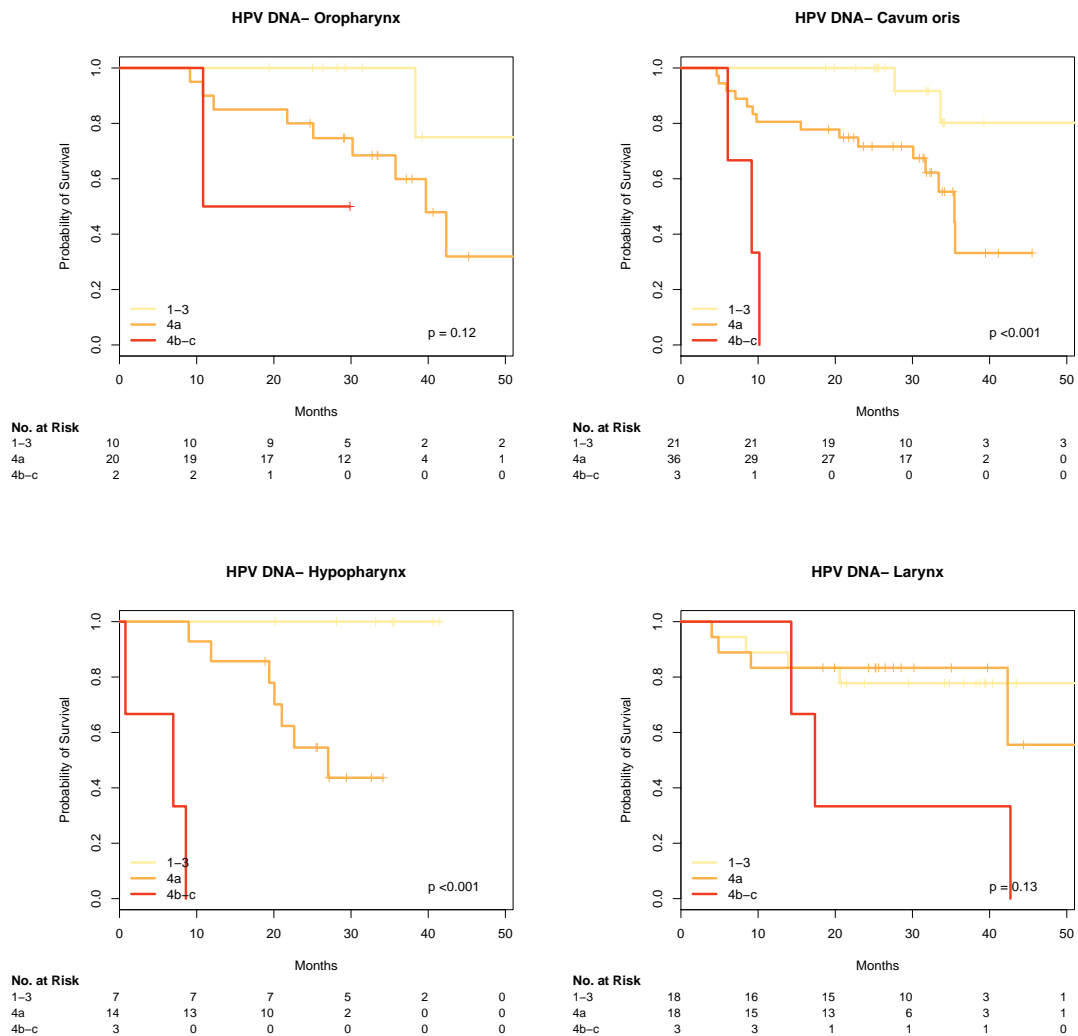
```

## Concordance= 0.69 (se = 0.038 )
## Rsquare= 0.183 (max possible= 0.954 )
## Likelihood ratio test= 31.9 on 2 df, p=1.2e-07
## Wald test = 30.8 on 2 df, p=2.07e-07
## Score (logrank) test = 40.9 on 2 df, p=1.31e-09

```



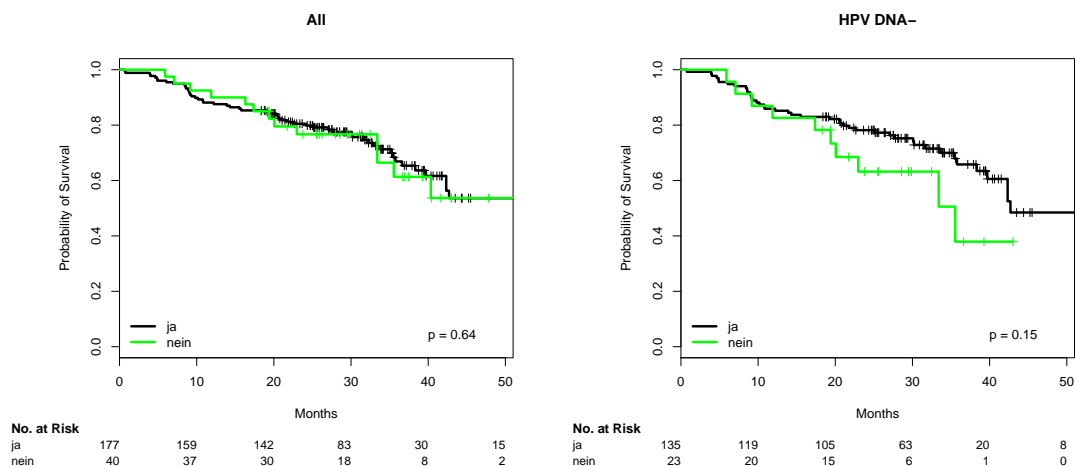


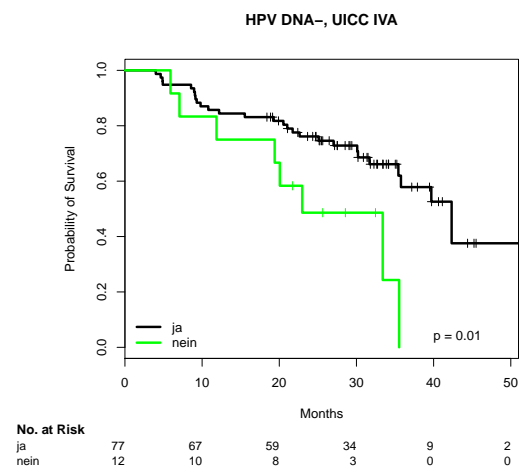
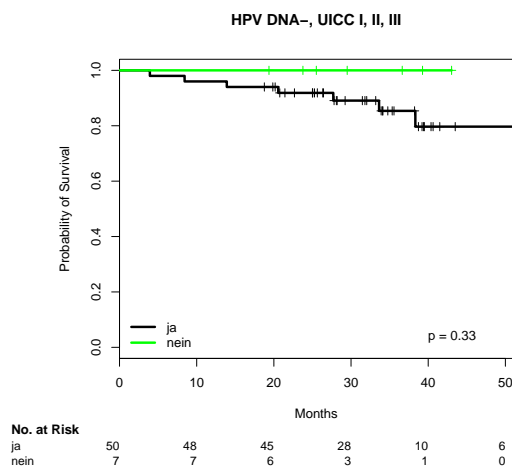
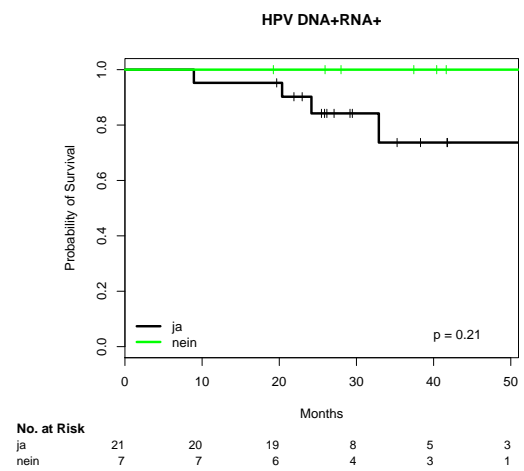
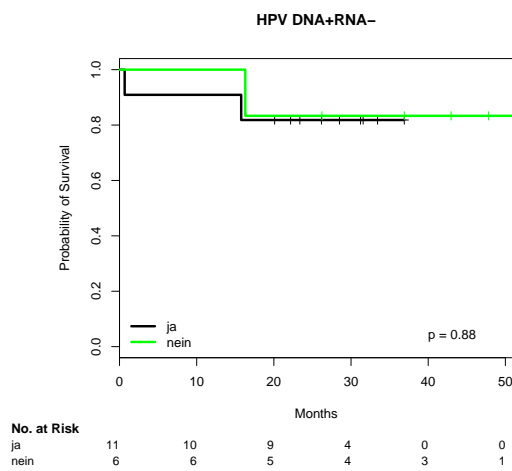
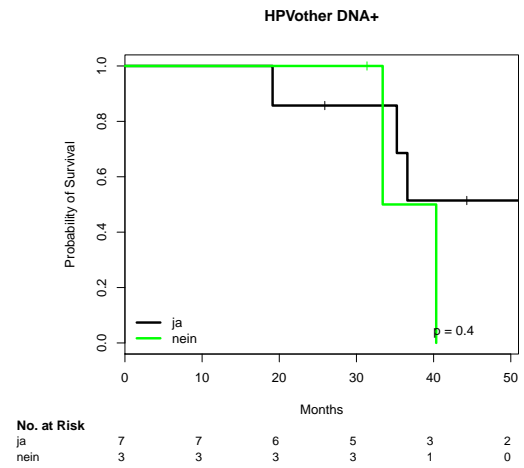
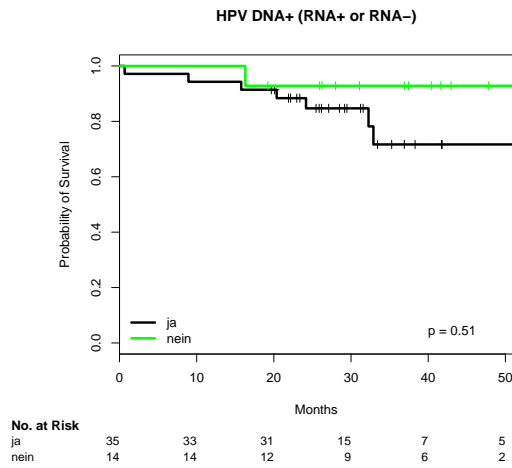


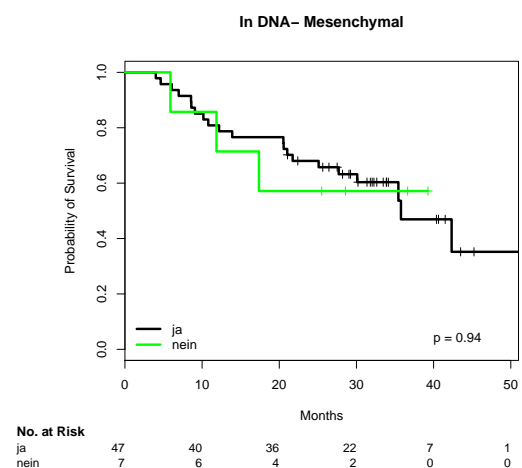
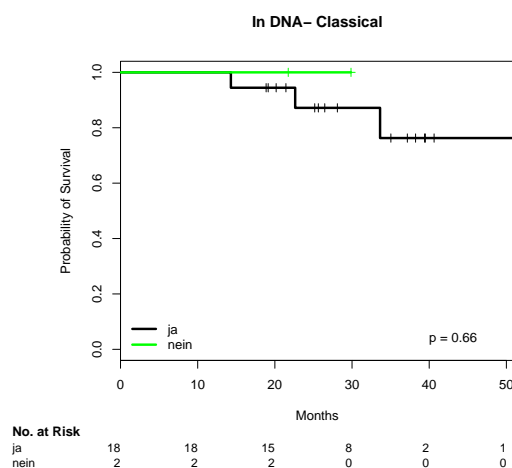
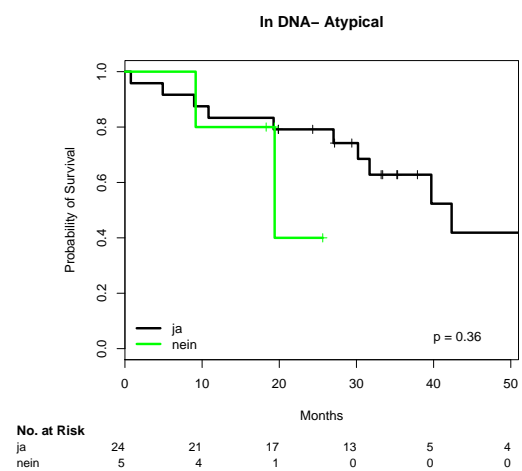
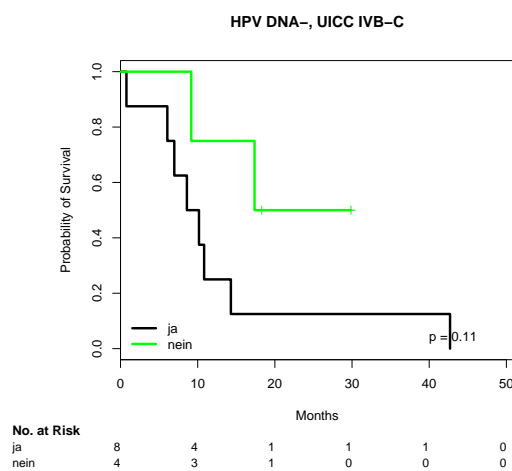
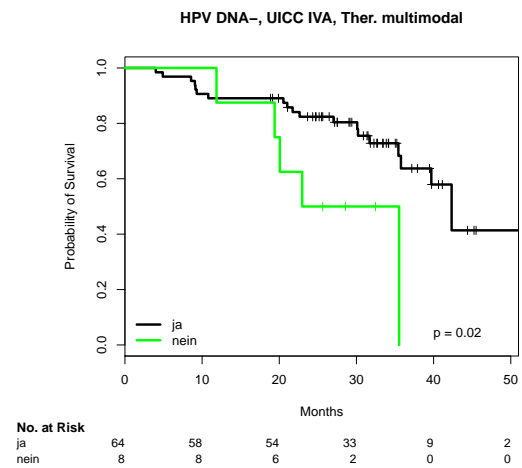
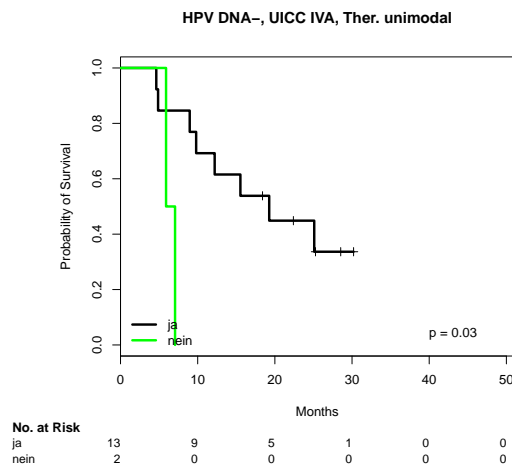
2.18 Smoking: yes vs. no

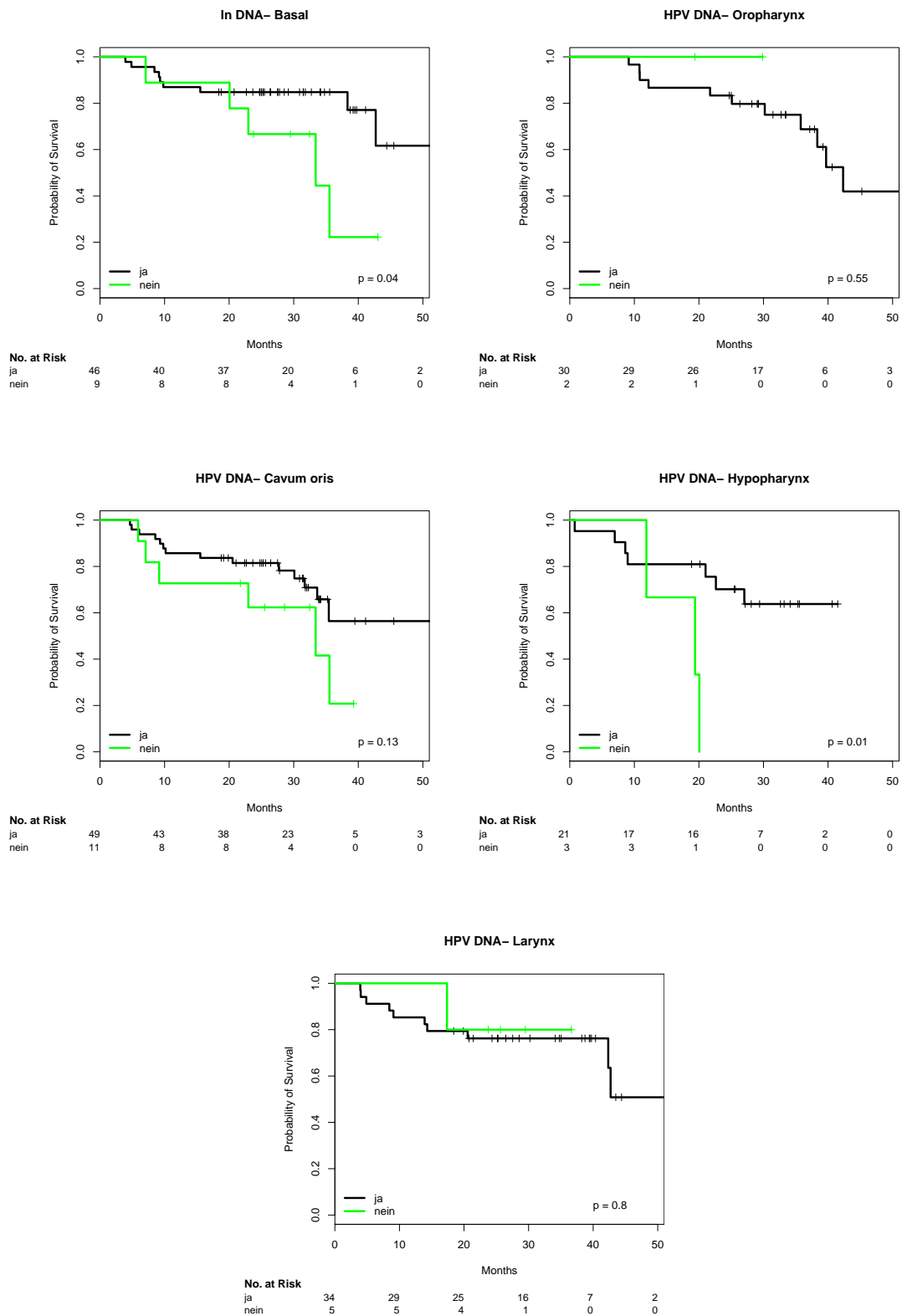
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein 0.141    1.151   0.301 0.47    0.64
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein    1.15    0.869   0.639   2.08
##
## Concordance= 0.504 (se = 0.026 )
```

```
## Rsquare= 0.001 (max possible= 0.954 )
## Likelihood ratio test= 0.21 on 1 df, p=0.644
## Wald test = 0.22 on 1 df, p=0.639
## Score (logrank) test = 0.22 on 1 df, p=0.639
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein 0.501      1.650    0.353 1.42    0.16
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein      1.65      0.606    0.826    3.3
##
## Concordance= 0.531 (se = 0.026 )
## Rsquare= 0.011 (max possible= 0.954 )
## Likelihood ratio test= 1.81 on 1 df, p=0.178
## Wald test = 2.01 on 1 df, p=0.156
## Score (logrank) test = 2.05 on 1 df, p=0.152
```







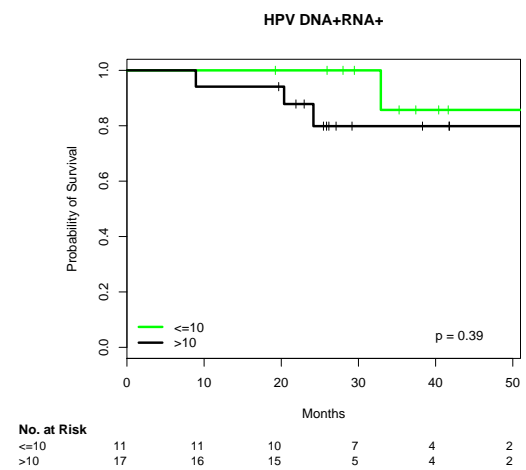
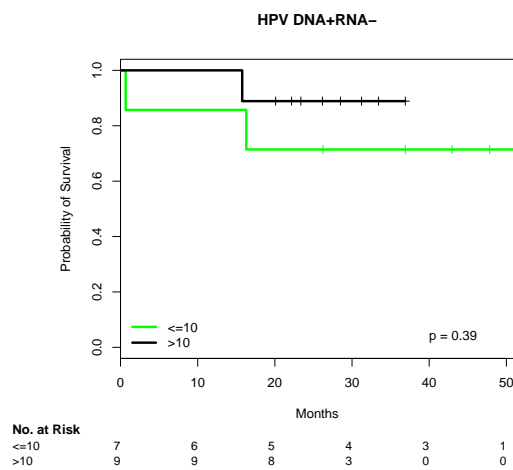
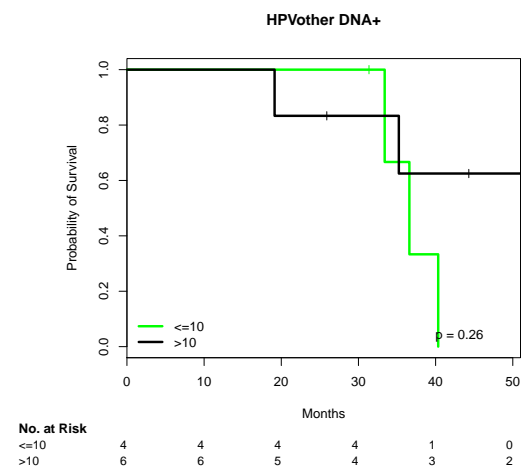
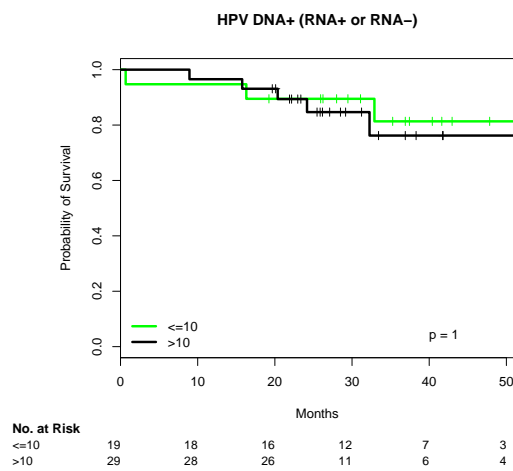
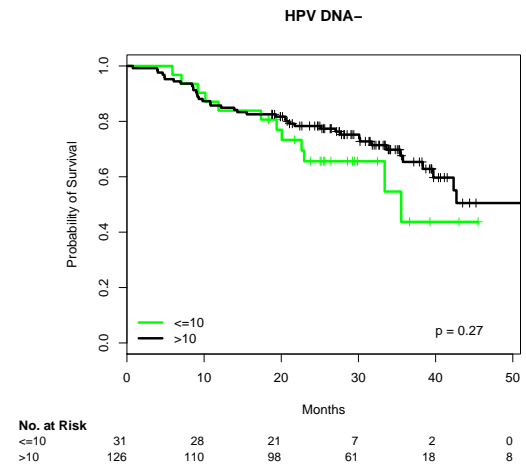
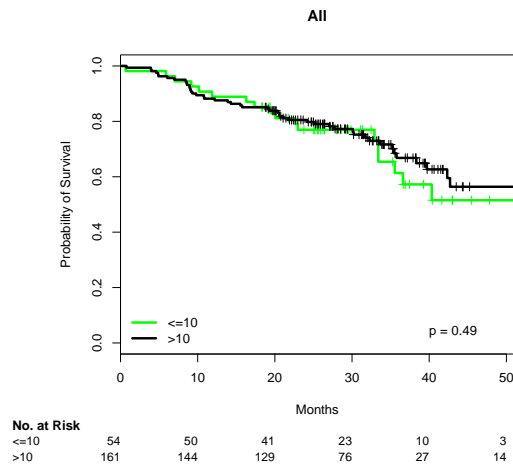


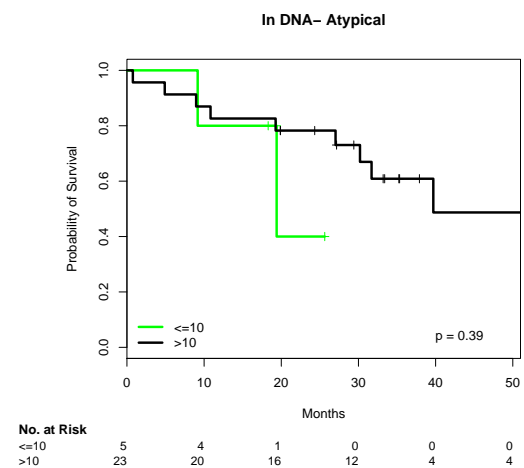
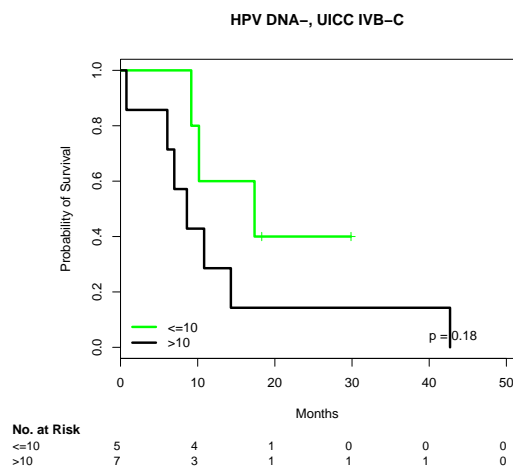
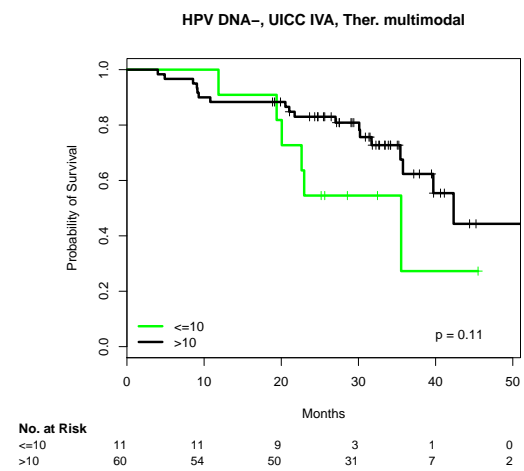
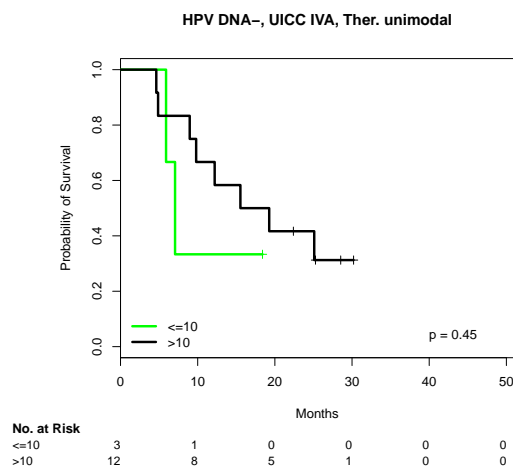
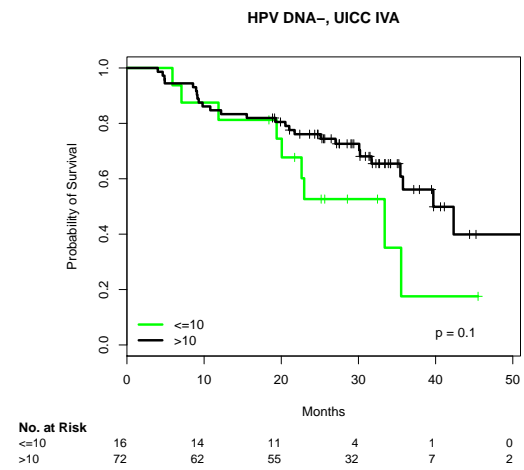
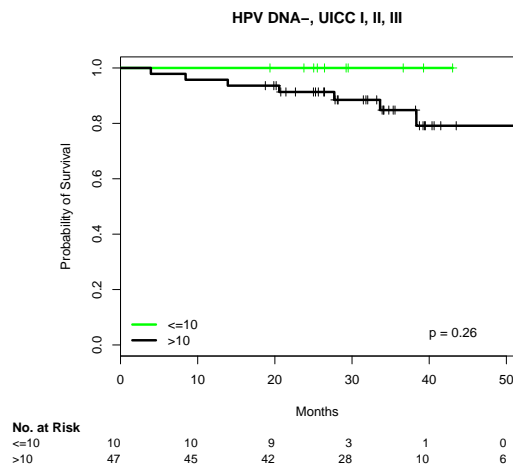
2.19 Smoking. Pack-years. Cut at 10

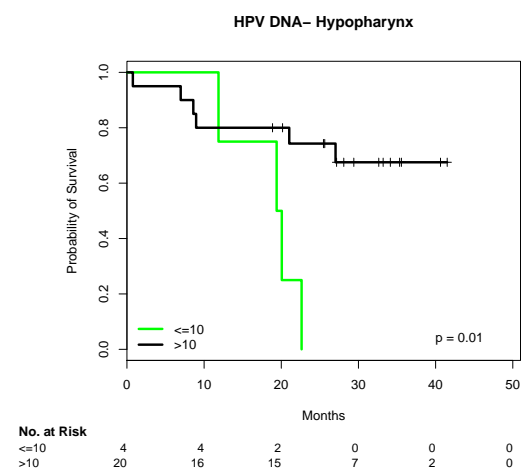
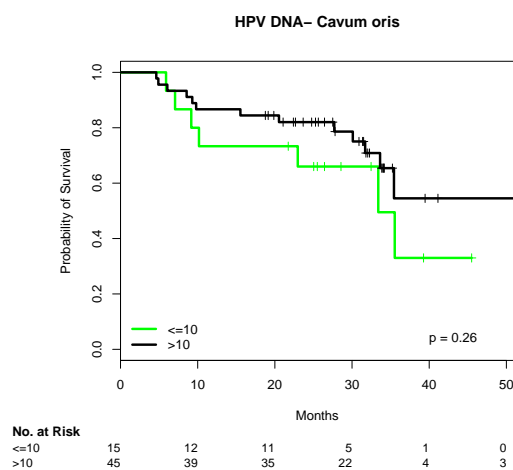
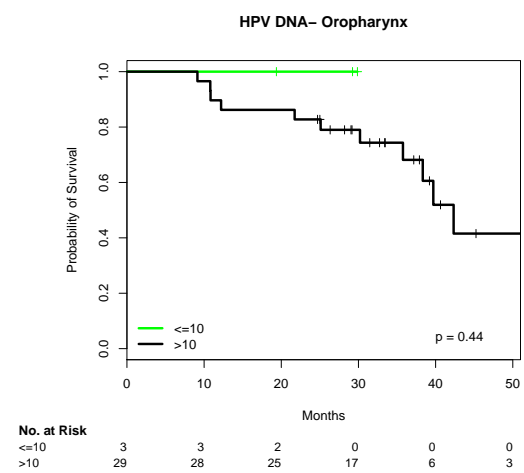
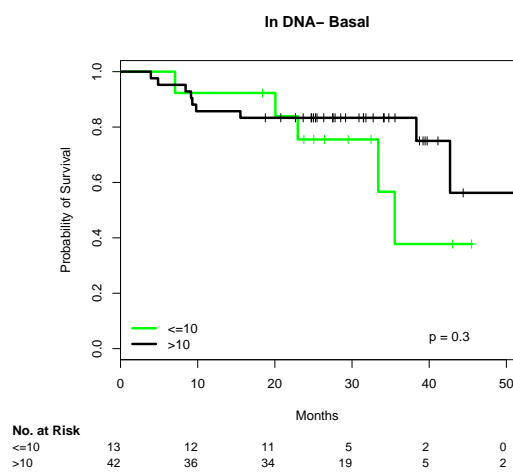
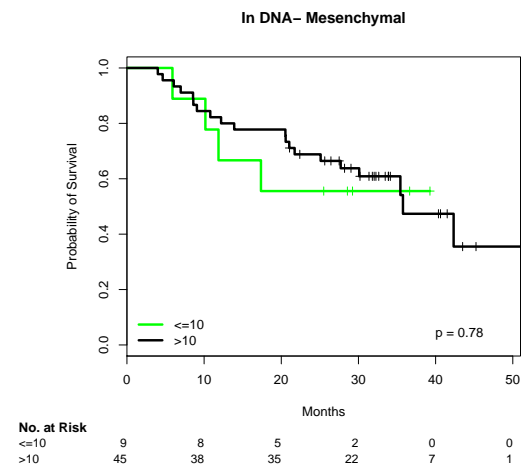
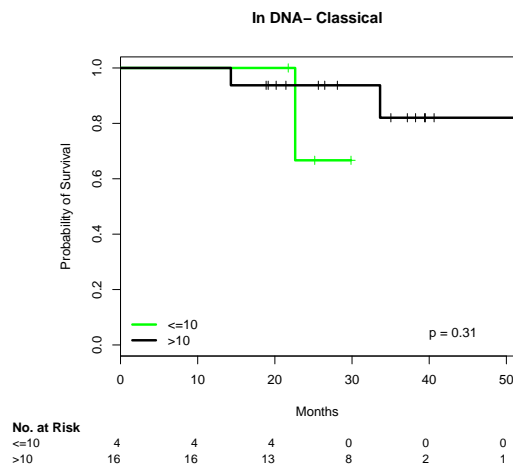
```

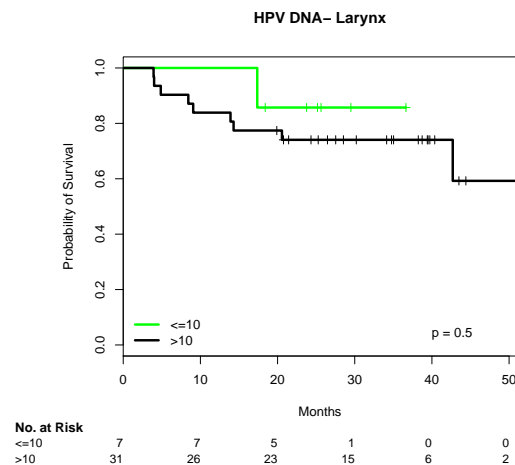
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 215, number of events= 72
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.187      0.829    0.272 -0.69    0.49
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.829      1.21    0.487    1.41
##
## Concordance= 0.507 (se = 0.029 )
## Rsquare= 0.002 (max possible= 0.953 )
## Likelihood ratio test= 0.46 on 1 df,  p=0.497
## Wald test               = 0.47 on 1 df,  p=0.491
## Score (logrank) test = 0.48 on 1 df,  p=0.49
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 157, number of events= 54
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.361      0.697    0.331 -1.09    0.27
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.697      1.44    0.364    1.33
##
## Concordance= 0.527 (se = 0.029 )
## Rsquare= 0.007 (max possible= 0.953 )
## Likelihood ratio test= 1.12 on 1 df,  p=0.291
## Wald test               = 1.19 on 1 df,  p=0.275
## Score (logrank) test = 1.2 on 1 df,  p=0.272

```





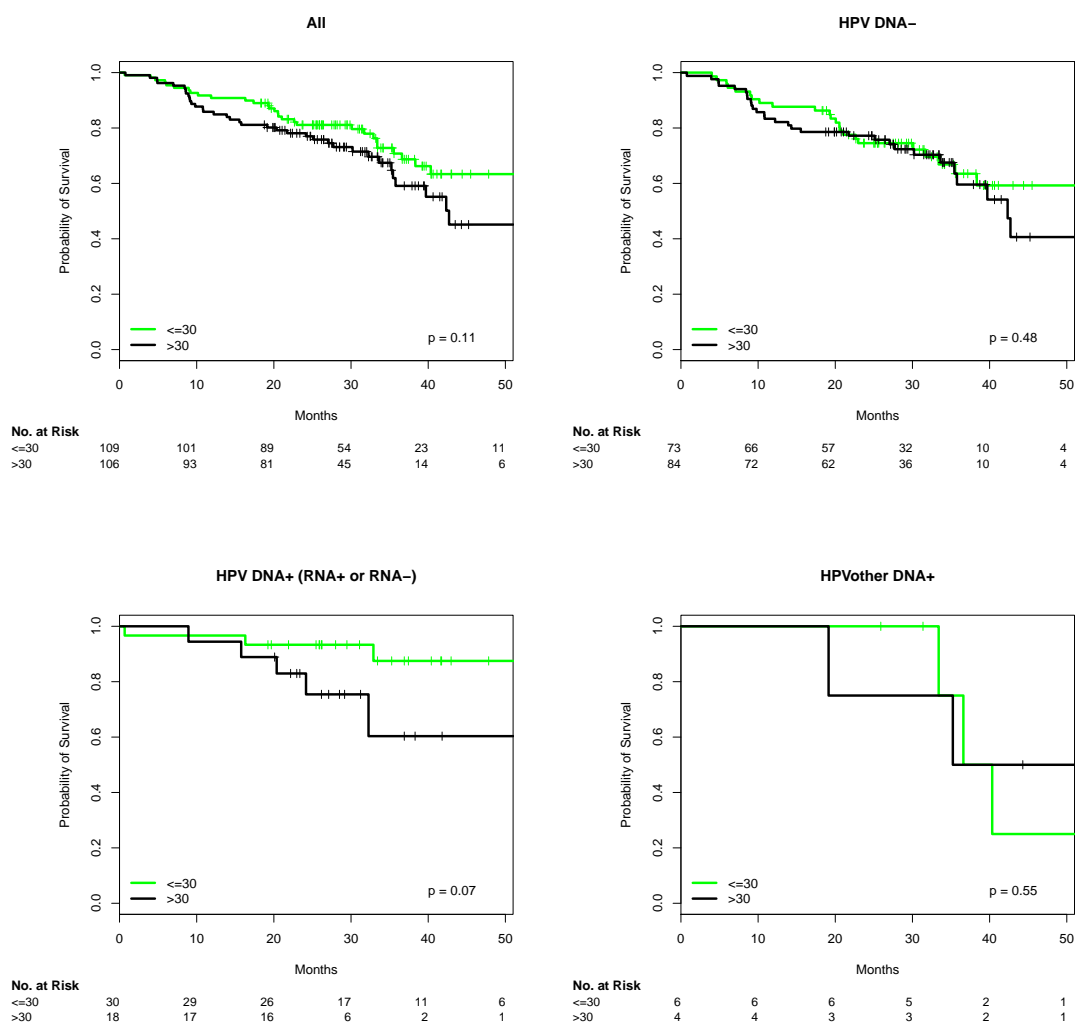


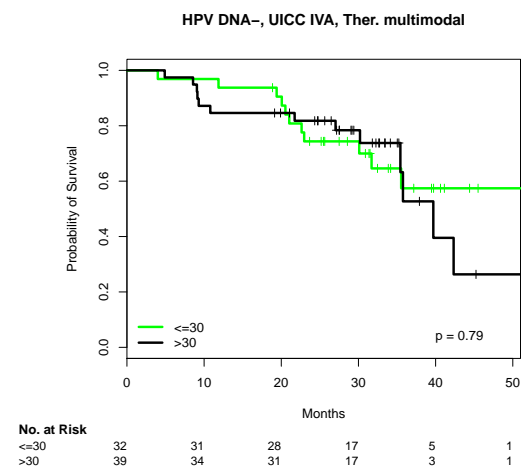
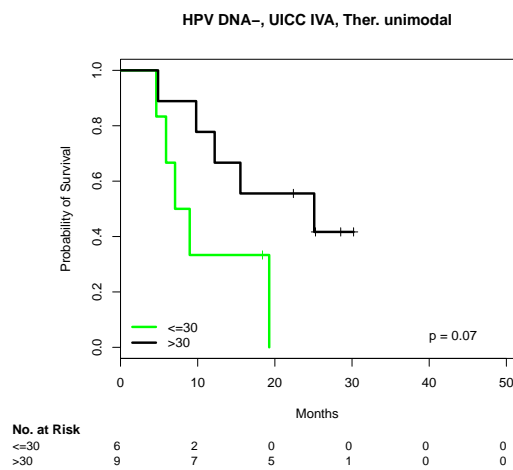
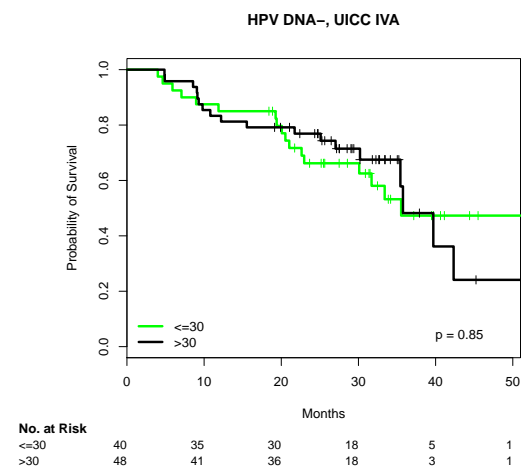
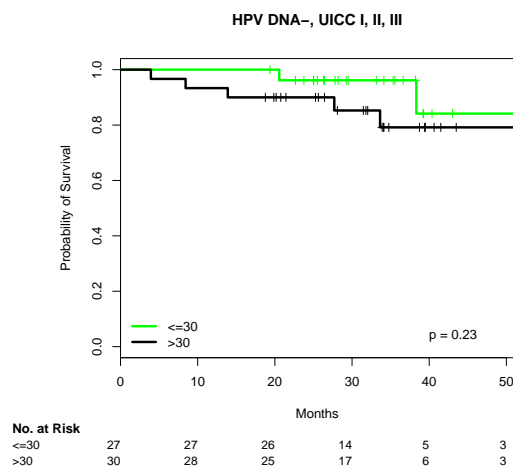
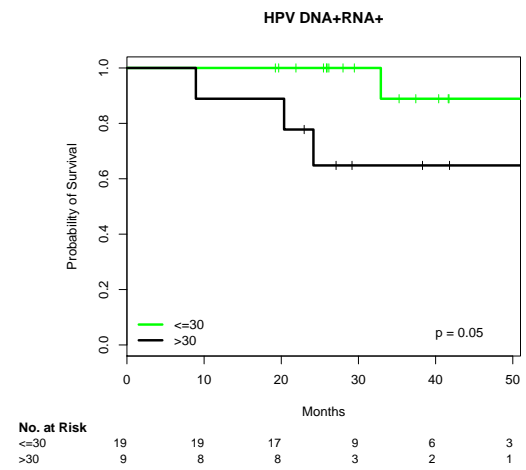
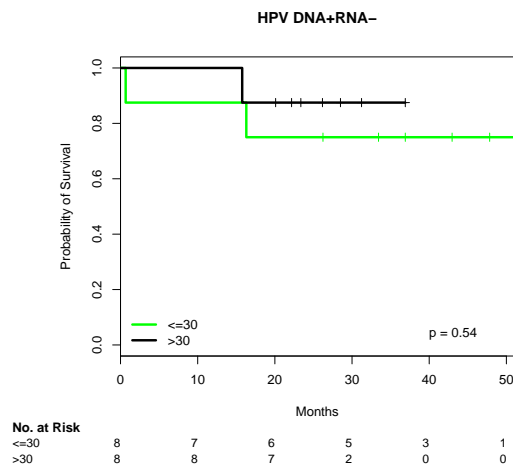


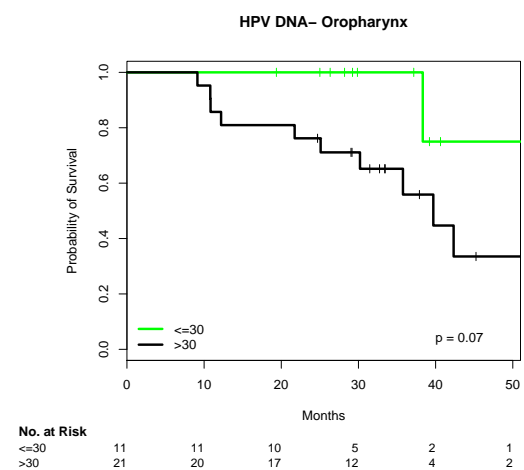
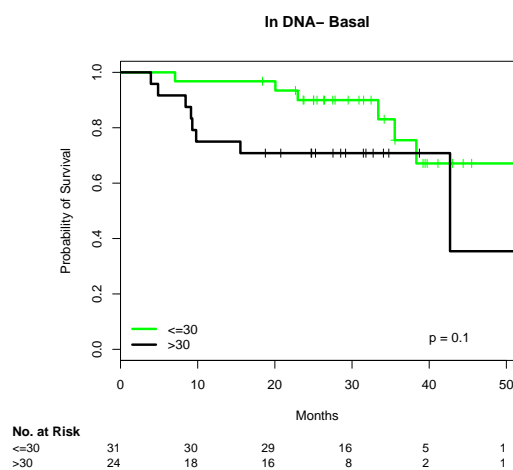
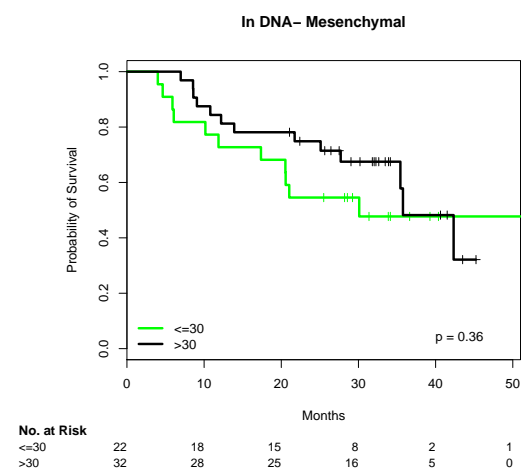
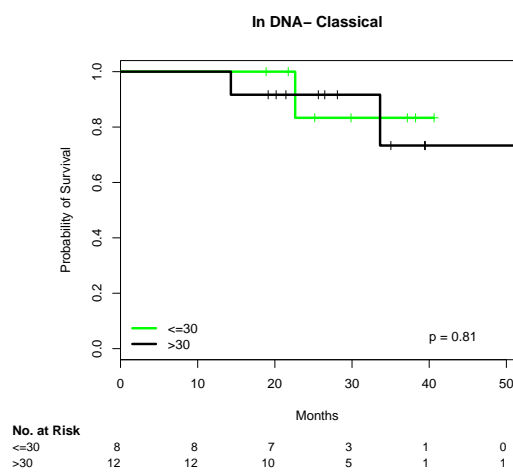
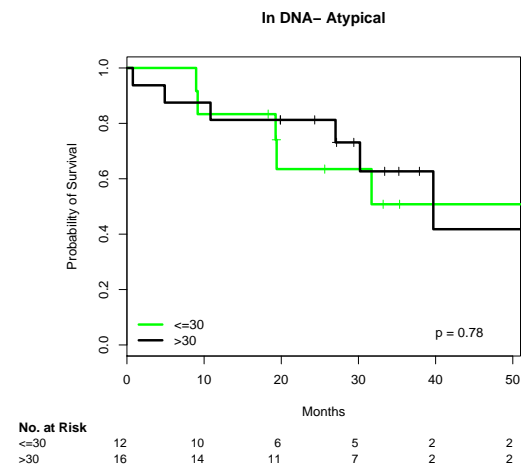
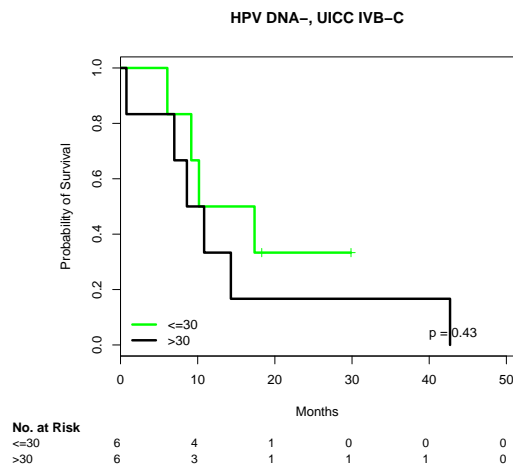
2.20 Smoking. Pack-years. Cut at 30

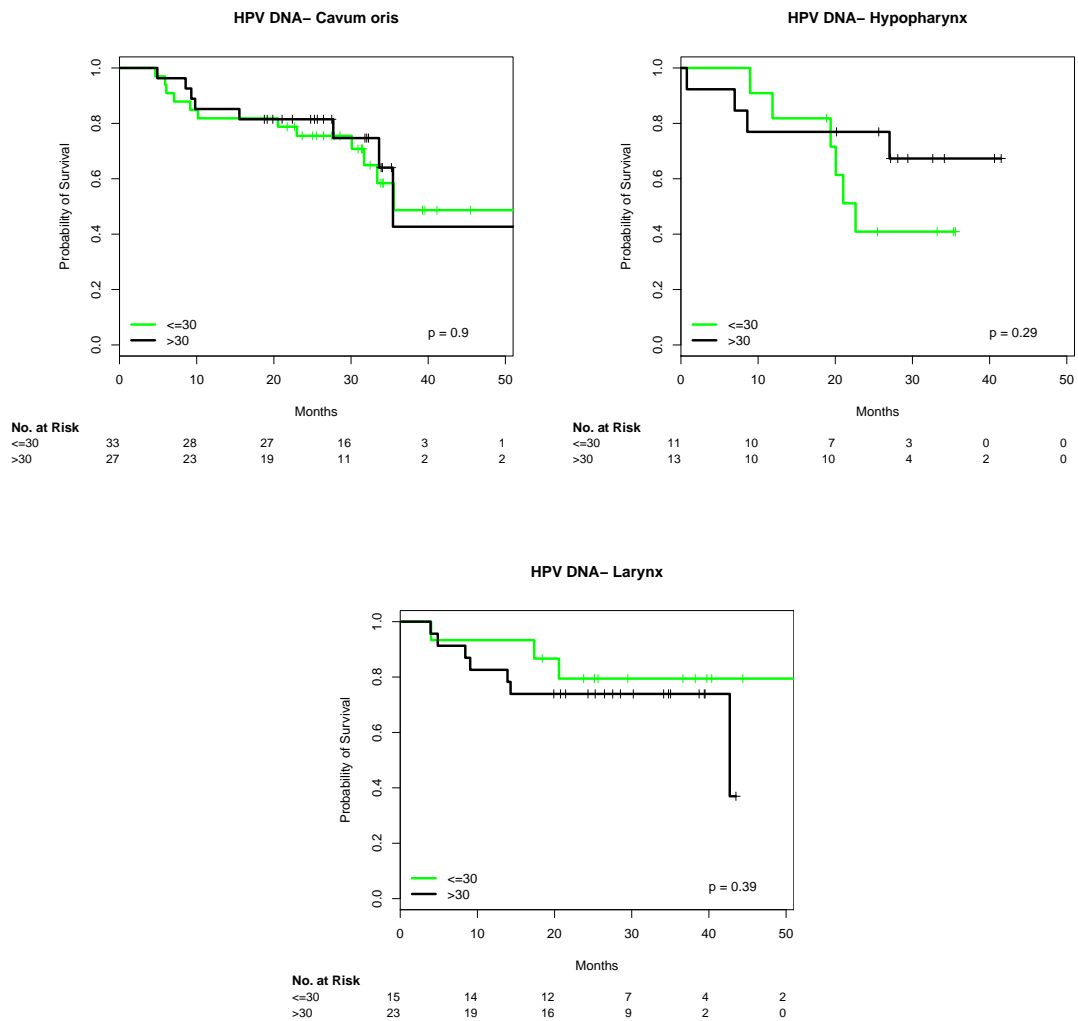
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 215, number of events= 72
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)  z Pr(>|z|)
## split[cur.subset]>30 0.387      1.473   0.242 1.6    0.11
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30    1.47      0.679   0.916    2.37
##
## Concordance= 0.543 (se = 0.033 )
## Rsquare= 0.012 (max possible= 0.953 )
## Likelihood ratio test= 2.58 on 1 df,  p=0.108
## Wald test               = 2.56 on 1 df,  p=0.11
## Score (logrank) test = 2.59 on 1 df,  p=0.108
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 157, number of events= 54
## (1 observation deleted due to missingness)
```

```
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.196      1.216    0.276 0.71    0.48
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30      1.22      0.822    0.708    2.09
##
## Concordance= 0.512 (se = 0.037 )
## Rsquare= 0.003 (max possible= 0.953 )
## Likelihood ratio test= 0.51 on 1 df,  p=0.476
## Wald test               = 0.5 on 1 df,  p=0.478
## Score (logrank) test = 0.5 on 1 df,  p=0.477
```





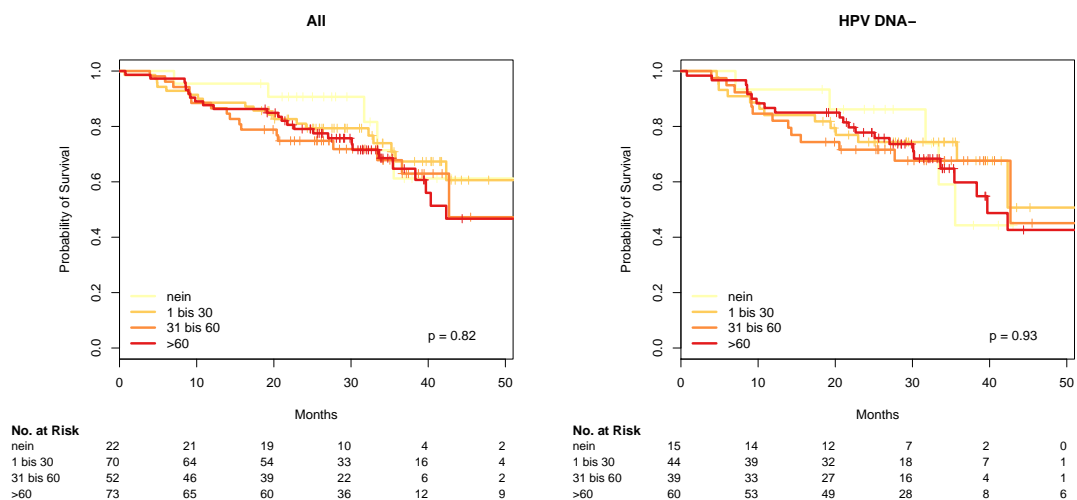


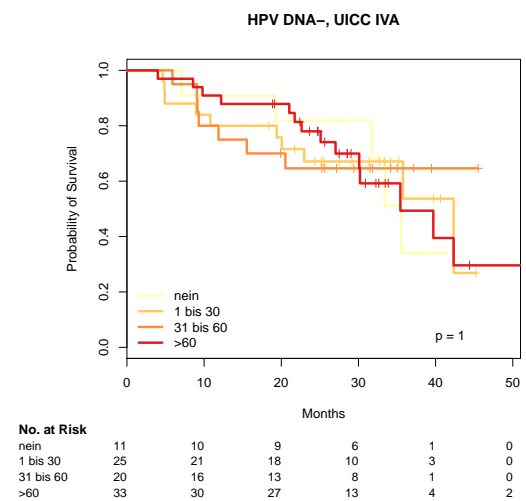
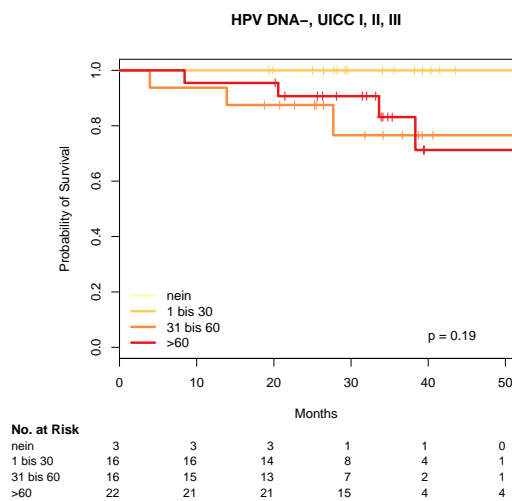
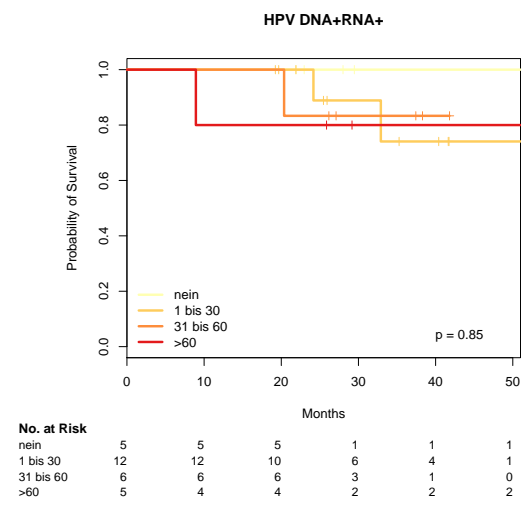
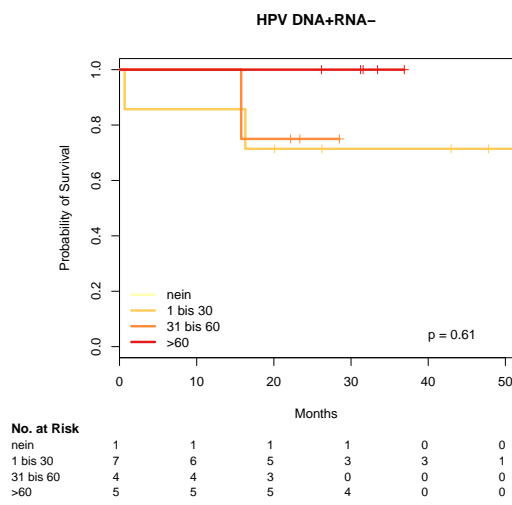
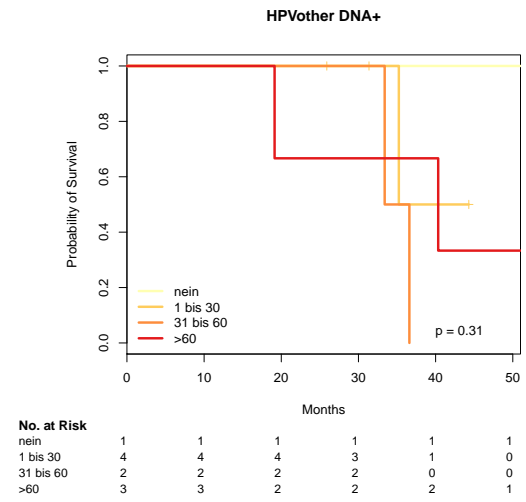
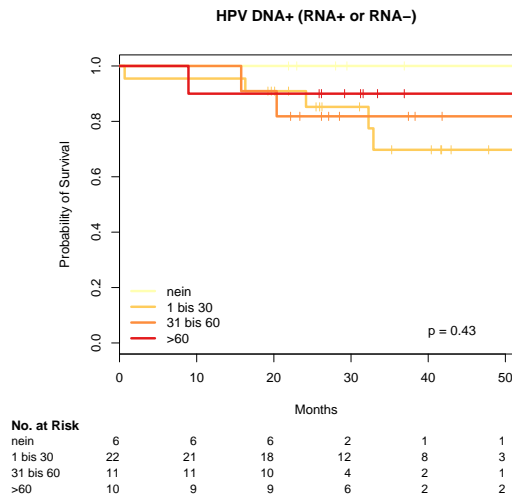


2.21 Alcohol consumption

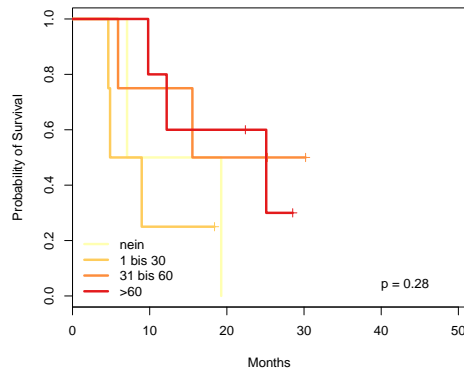
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset]1 bis 30  0.0891   1.0931  0.4639 0.19    0.85
## split[cur.subset]31 bis 60  0.2978   1.3469  0.4733 0.63    0.53
## split[cur.subset]>60      0.3019   1.3524  0.4522 0.67    0.50
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30    1.09    0.915    0.440    2.71
```

```
## split[cur.subset]31 bis 60      1.35      0.742      0.533      3.41
## split[cur.subset]>60            1.35      0.739      0.557      3.28
##
## Concordance= 0.535 (se = 0.037 )
## Rsquare= 0.004 (max possible= 0.954 )
## Likelihood ratio test= 0.95 on 3 df, p=0.812
## Wald test = 0.93 on 3 df, p=0.818
## Score (logrank) test = 0.94 on 3 df, p=0.817
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30 -0.1138  0.8924  0.5266 -0.22  0.83
## split[cur.subset]31 bis 60  0.1292  1.1380  0.5214  0.25  0.80
## split[cur.subset]>60      0.0508  1.0521  0.4967  0.10  0.92
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30  0.892    1.121    0.318    2.51
## split[cur.subset]31 bis 60  1.138    0.879    0.410    3.16
## split[cur.subset]>60      1.052    0.950    0.397    2.79
##
## Concordance= 0.524 (se = 0.041 )
## Rsquare= 0.003 (max possible= 0.954 )
## Likelihood ratio test= 0.43 on 3 df, p=0.935
## Wald test = 0.42 on 3 df, p=0.936
## Score (logrank) test = 0.42 on 3 df, p=0.936
```



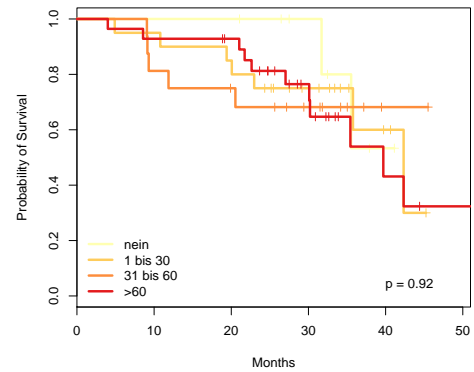


HPV DNA-, UICC IVA, Ther. unimodal



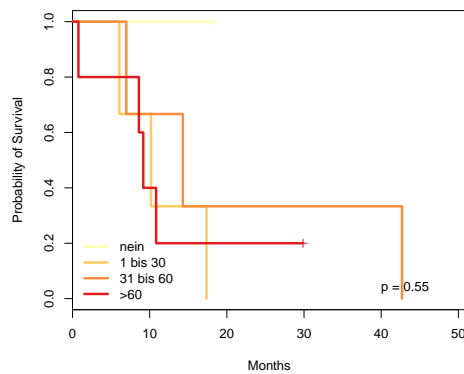
No. at Risk						
nein	2	1	0	0	0	0
1 bis 30	4	1	0	0	0	0
31 bis 60	4	3	2	1	0	0
>60	5	4	3	0	0	0

HPV DNA-, UICC IVA, Ther. multimodal



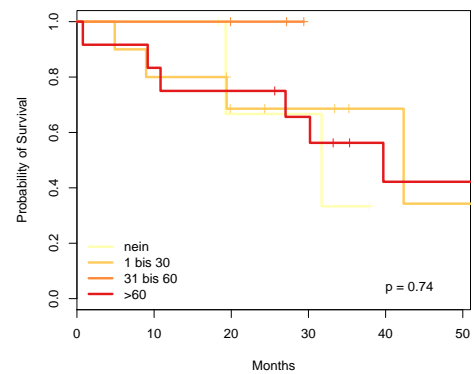
No. at Risk						
nein	8	8	8	5	1	0
1 bis 30	20	19	17	10	3	0
31 bis 60	16	13	11	7	1	0
>60	28	26	24	13	4	2

HPV DNA-, UICC IVB-C



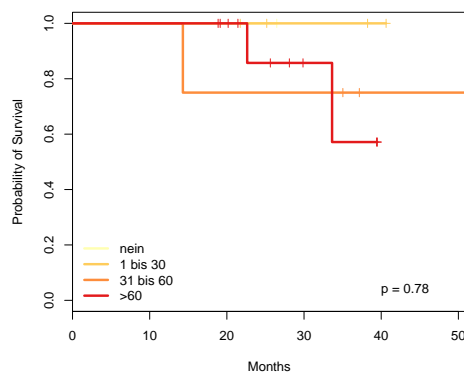
No. at Risk						
nein	1	1	0	0	0	0
1 bis 30	3	2	0	0	0	0
31 bis 60	3	2	1	1	1	0
>60	5	2	1	0	0	0

In DNA- Atypical



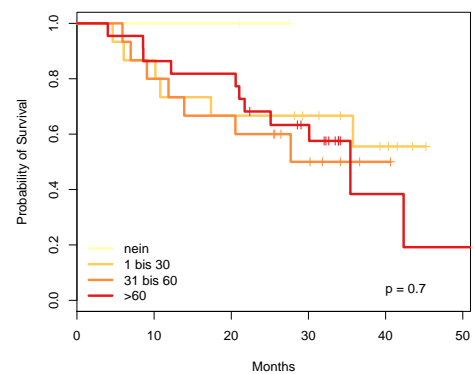
No. at Risk						
nein	4	4	2	2	0	0
1 bis 30	10	8	5	4	2	1
31 bis 60	3	3	2	0	0	0
>60	12	10	9	7	3	3

In DNA- Classical

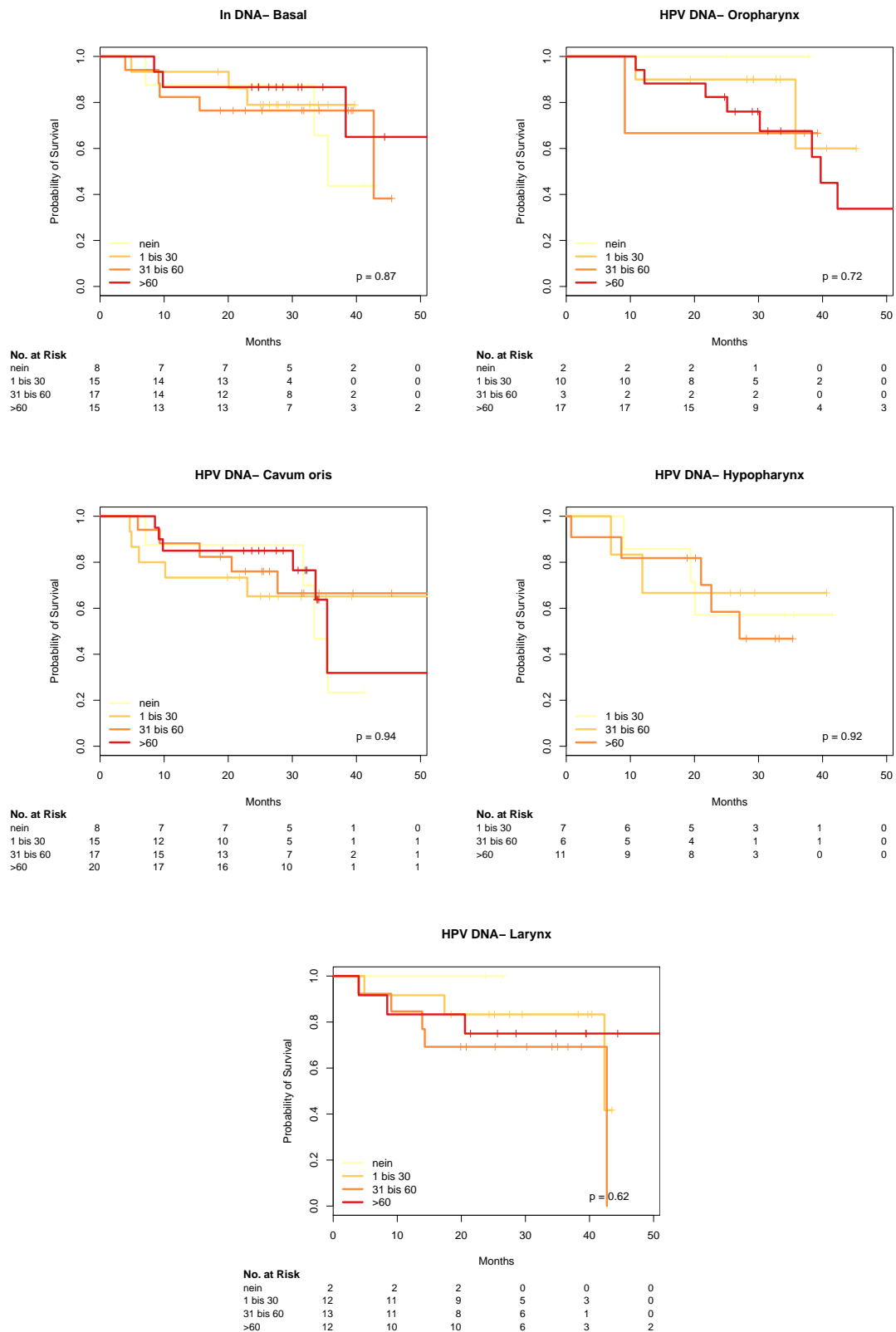


No. at Risk						
nein	1	1	1	0	0	0
1 bis 30	4	4	4	2	1	0
31 bis 60	4	4	3	3	1	1
>60	11	11	9	3	0	0

In DNA- Mesenchymal



No. at Risk						
nein	2	2	2	0	0	0
1 bis 30	15	13	10	8	4	0
31 bis 60	15	12	10	5	1	0
>60	22	19	18	11	2	1



2.22 Localisation

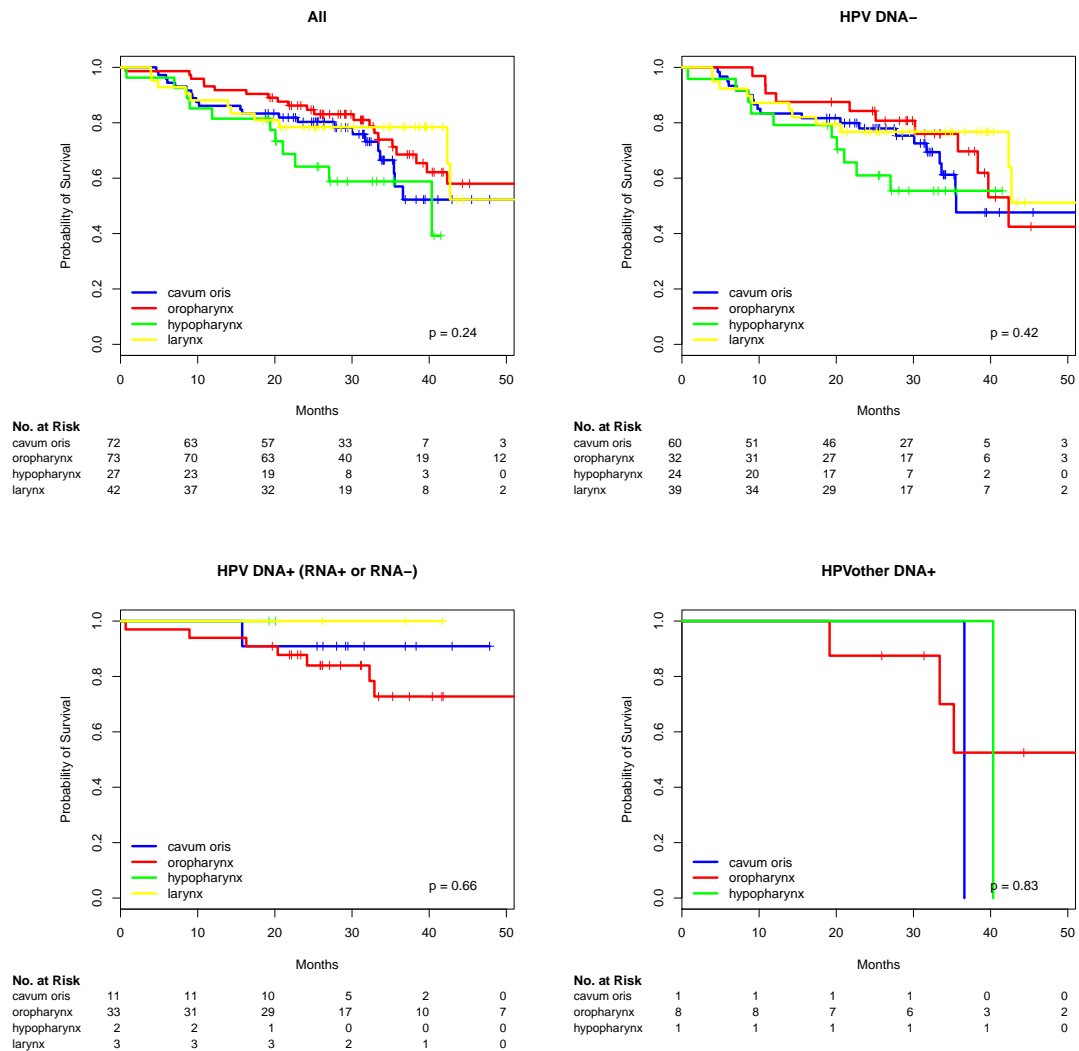
```

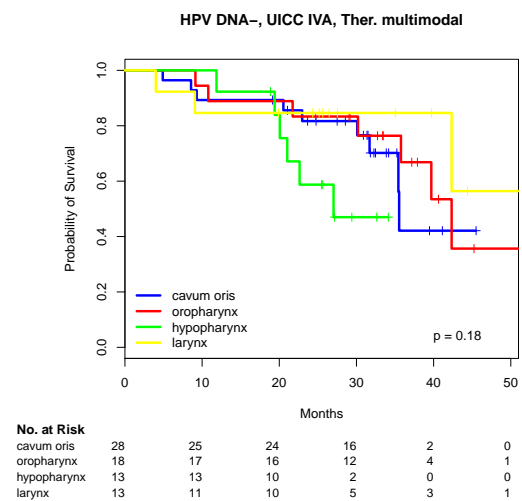
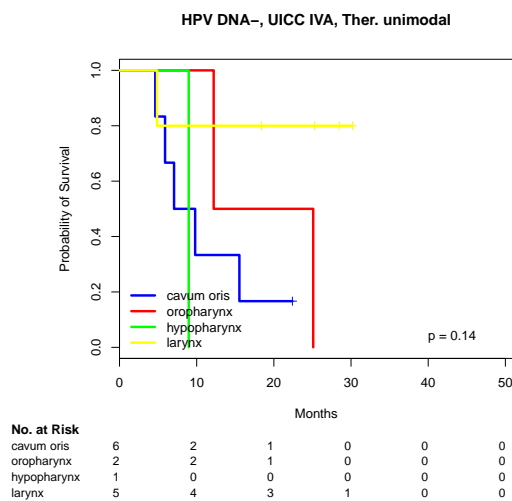
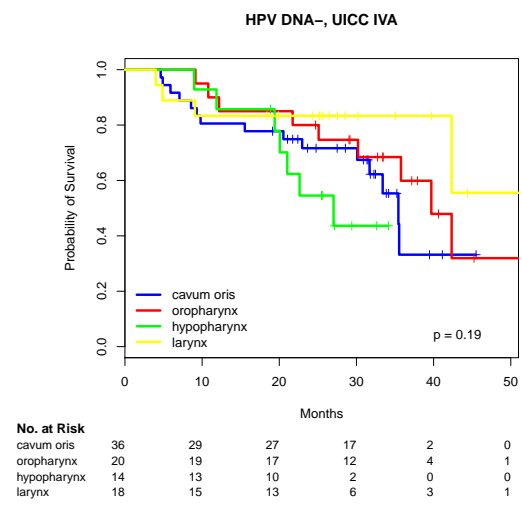
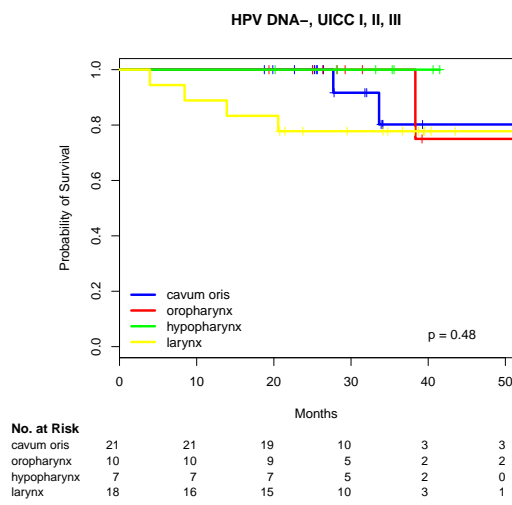
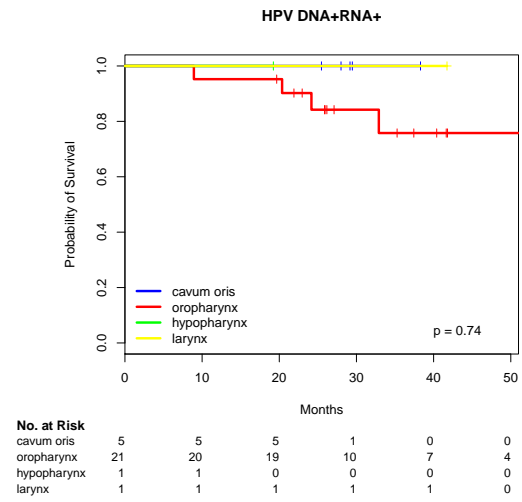
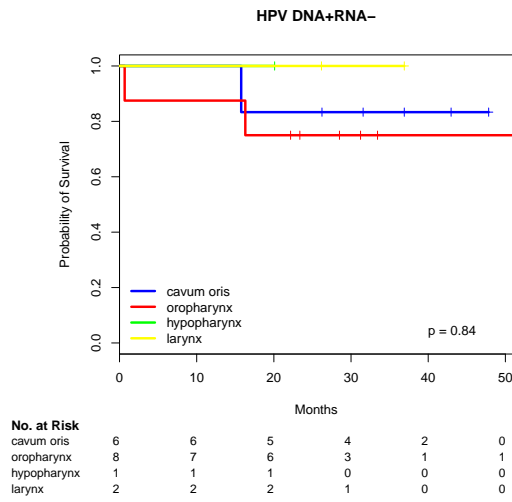
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 214, number of events= 72
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.201    0.818   0.292 -0.69    0.49
## split[cur.subset]hypopharynx  0.481    1.618   0.370  1.30    0.19
## split[cur.subset]larynx      -0.255    0.775   0.369 -0.69    0.49
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx    0.818    1.223    0.461    1.45
## split[cur.subset]hypopharynx    1.618    0.618    0.784    3.34
## split[cur.subset]larynx        0.775    1.290    0.376    1.60
##
## Concordance= 0.554 (se = 0.037 )
## Rsquare= 0.017 (max possible= 0.953 )
## Likelihood ratio test= 3.66 on 3 df, p=0.301
## Wald test = 4.03 on 3 df, p=0.258
## Score (logrank) test = 4.16 on 3 df, p=0.245
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 155, number of events= 54
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.186    0.830   0.364 -0.51    0.61
## split[cur.subset]hypopharynx  0.384    1.468   0.388  0.99    0.32
## split[cur.subset]larynx      -0.308    0.735   0.377 -0.82    0.41
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx    0.830    1.205    0.406    1.70
## split[cur.subset]hypopharynx    1.468    0.681    0.686    3.14
## split[cur.subset]larynx        0.735    1.360    0.351    1.54

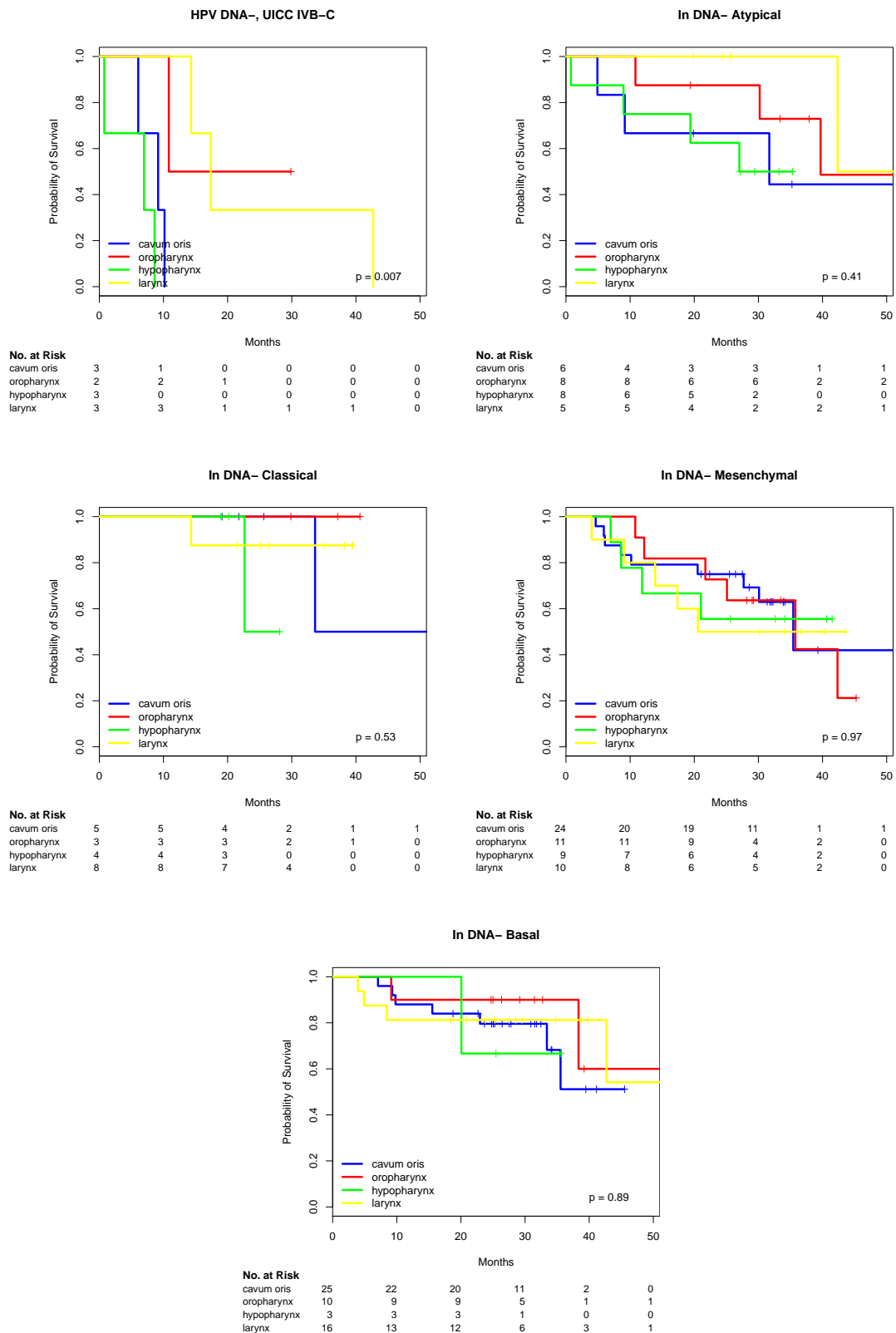
```



```
##
## Concordance= 0.56 (se = 0.042 )
## Rsquare= 0.017 (max possible= 0.953 )
## Likelihood ratio test= 2.63 on 3 df, p=0.452
## Wald test = 2.77 on 3 df, p=0.429
## Score (logrank) test = 2.83 on 3 df, p=0.418
```





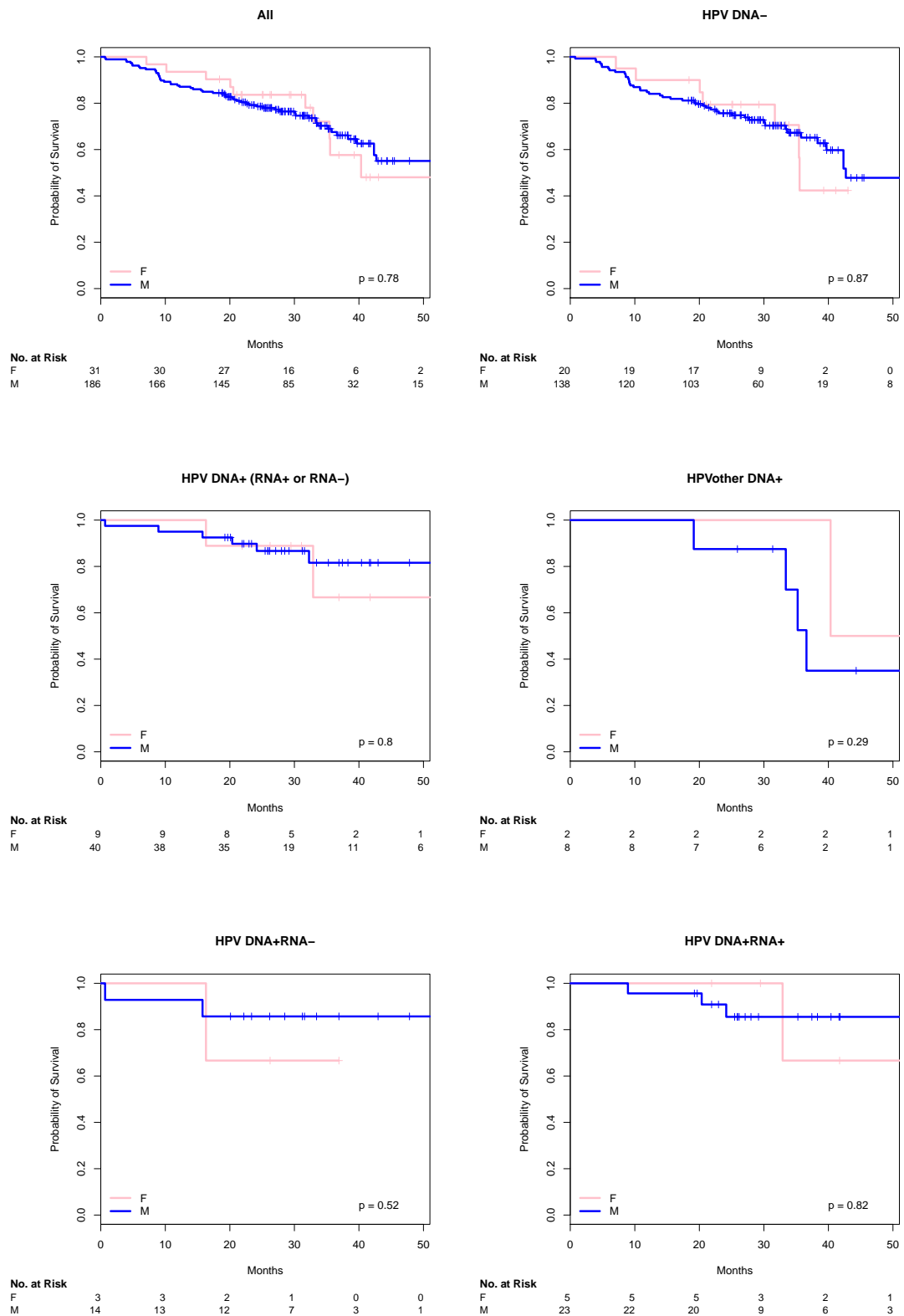


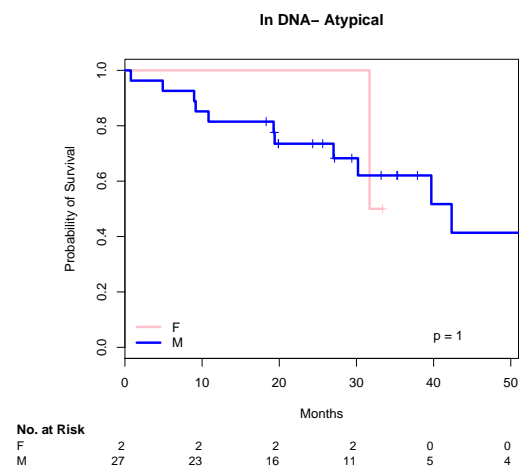
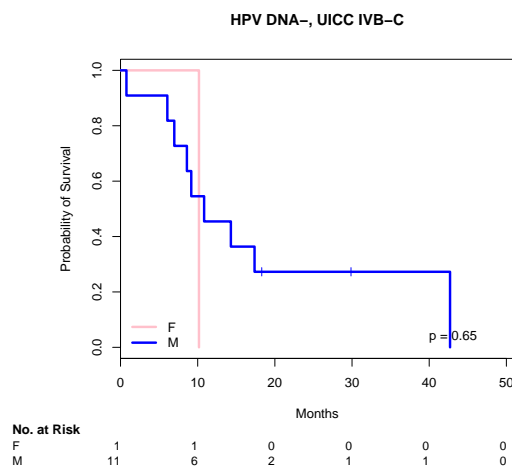
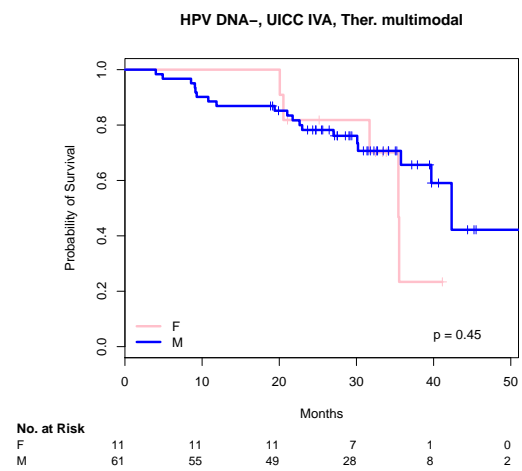
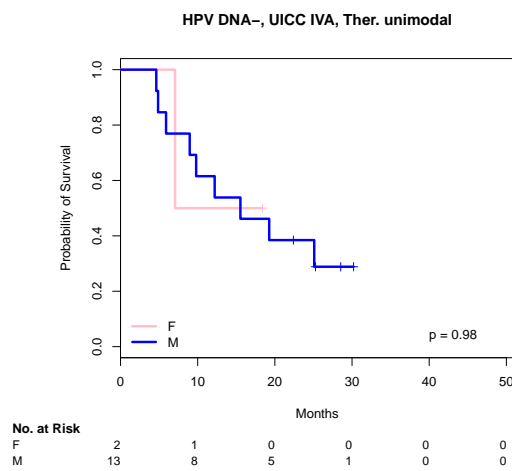
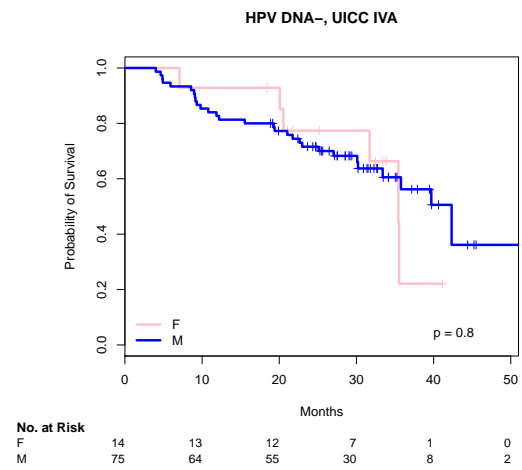
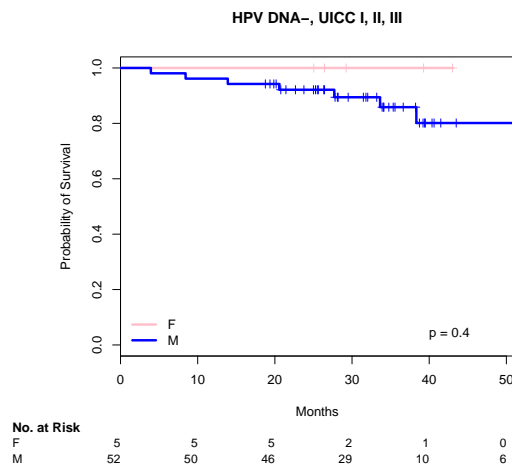
2.23 Sex

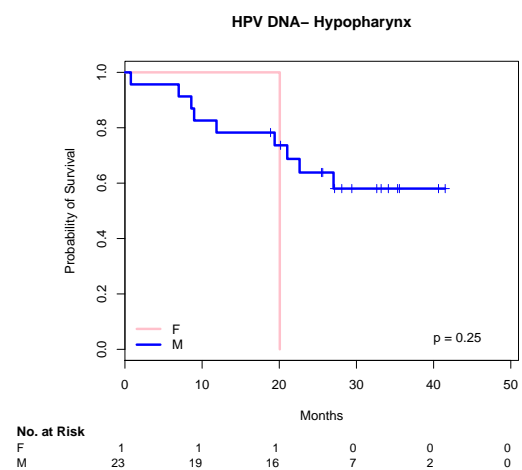
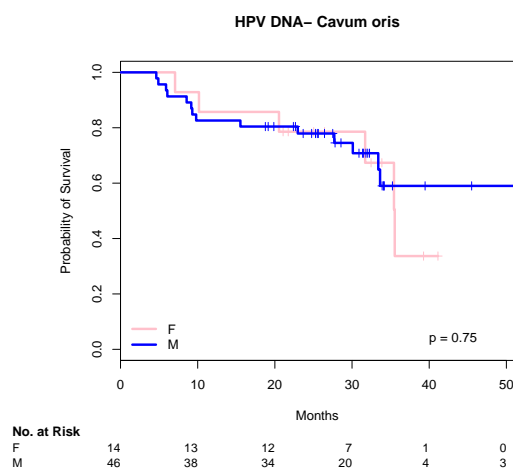
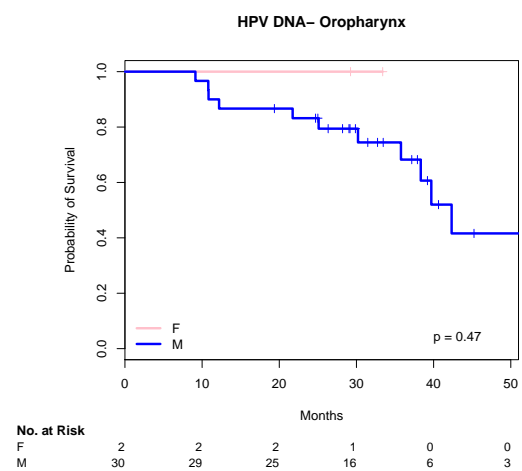
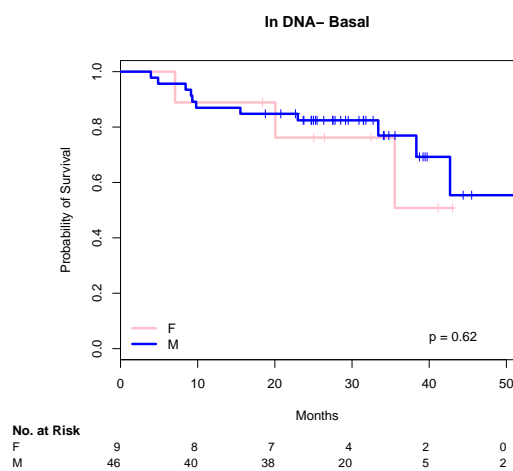
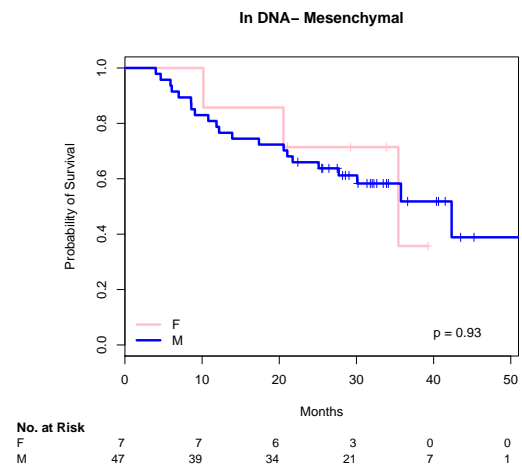
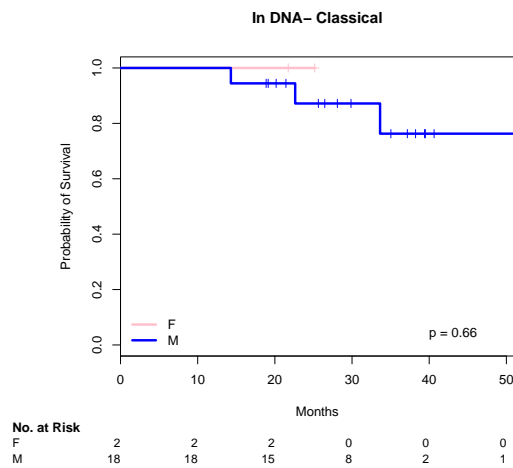
```

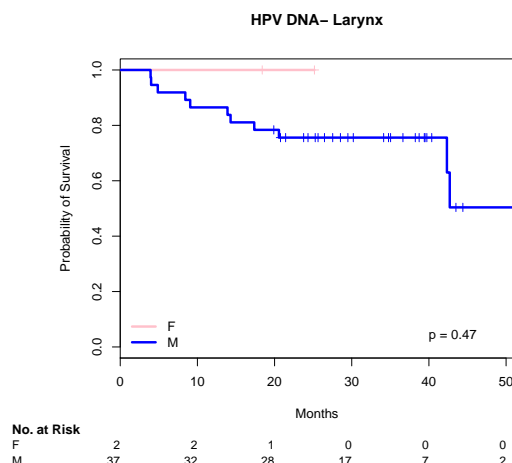
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M -0.0909    0.9131  0.3291 -0.28    0.78
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M    0.913      1.1    0.479    1.74
##
## Concordance= 0.488 (se = 0.024 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.07 on 1 df, p=0.785
## Wald test = 0.08 on 1 df, p=0.782
## Score (logrank) test = 0.08 on 1 df, p=0.782
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M -0.0662    0.9359  0.4063 -0.16    0.87
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M    0.936      1.07    0.422    2.08
##
## Concordance= 0.491 (se = 0.025 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.03 on 1 df, p=0.872
## Wald test = 0.03 on 1 df, p=0.871
## Score (logrank) test = 0.03 on 1 df, p=0.871

```







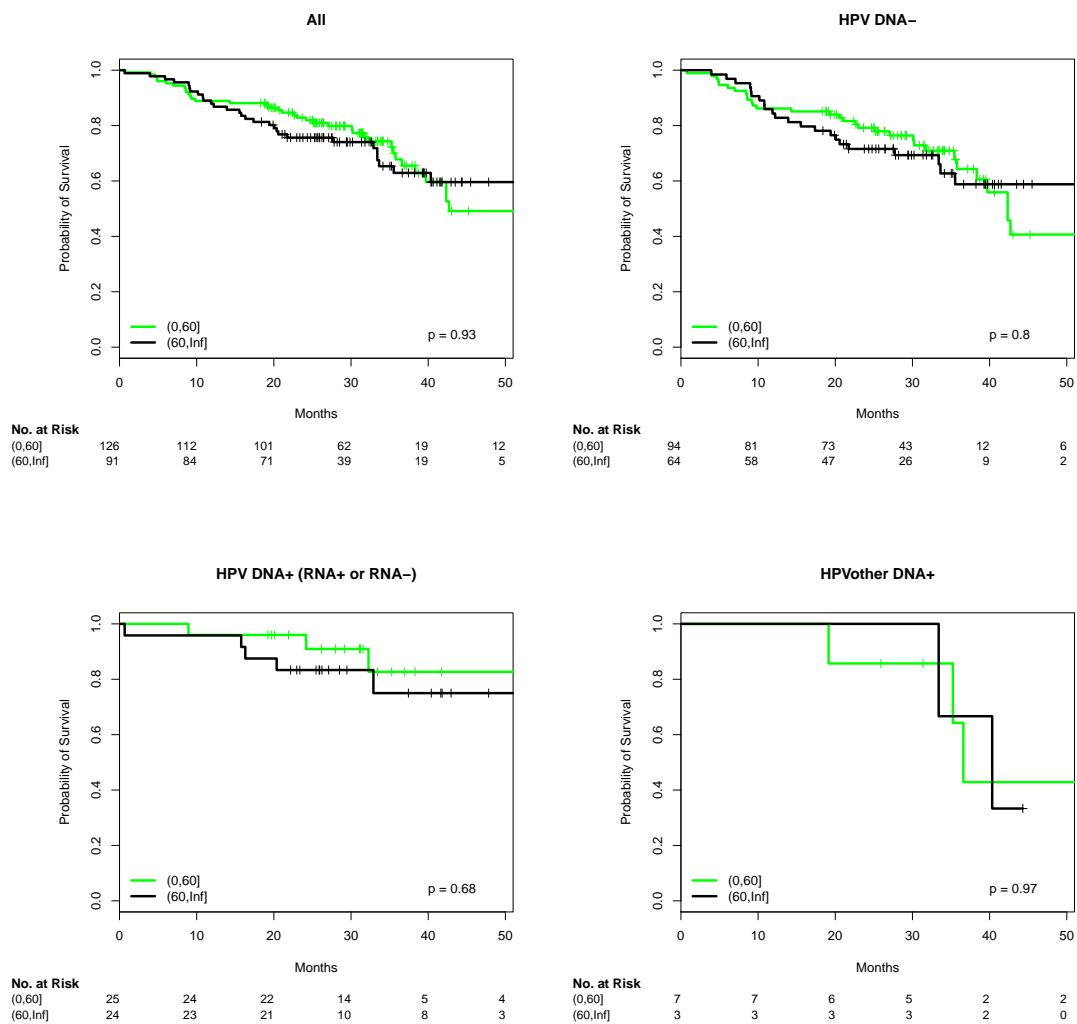


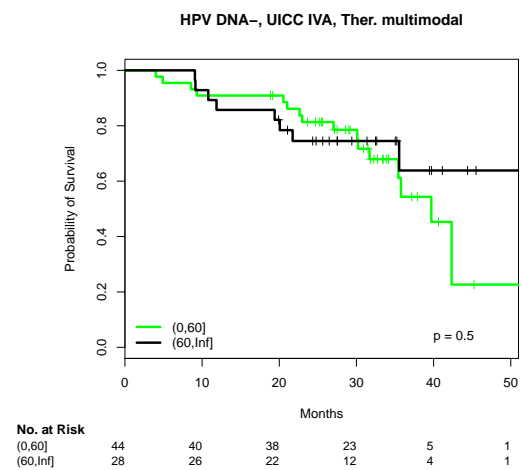
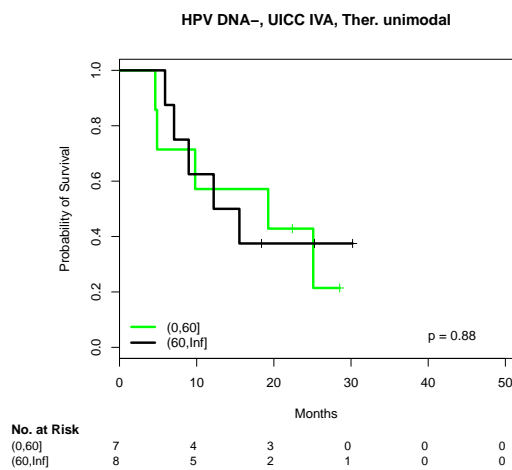
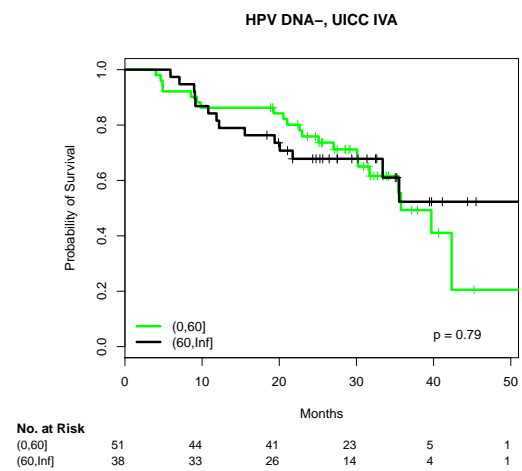
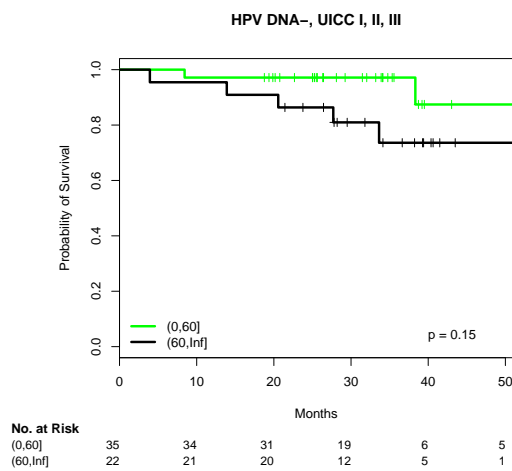
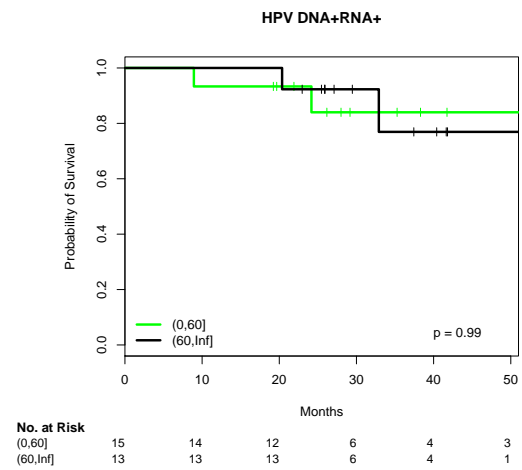
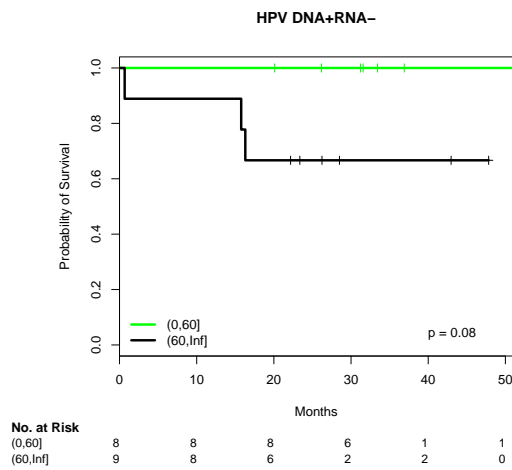
2.24 Age, cut at 60

```
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](60,Inf) -0.0223    0.9779  0.2415 -0.09    0.93
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf)    0.978      1.02    0.609    1.57
##
## Concordance= 0.474 (se = 0.033 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.01 on 1 df, p=0.926
## Wald test = 0.01 on 1 df, p=0.926
## Score (logrank) test = 0.01 on 1 df, p=0.926
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
```

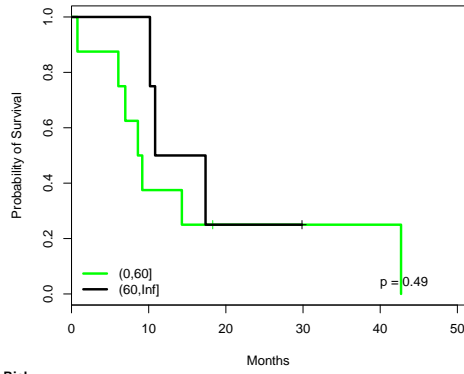


```
## split[cur.subset](60,Inf] 0.0671    1.0694    0.2737 0.25    0.81
##
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf]      1.07      0.935    0.625    1.83
##
## Concordance= 0.526  (se = 0.037 )
## Rsquare= 0    (max possible= 0.954 )
## Likelihood ratio test= 0.06  on 1 df,   p=0.807
## Wald test            = 0.06  on 1 df,   p=0.806
## Score (logrank) test = 0.06  on 1 df,   p=0.806
```





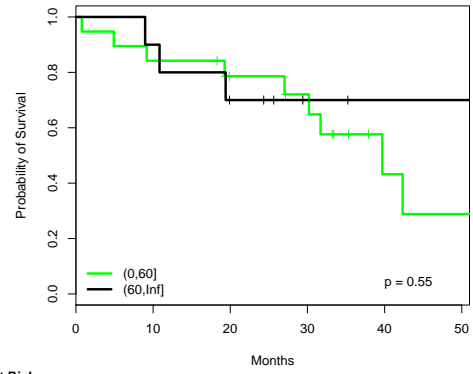
HPV DNA-, UICC IVB-C



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

8	3	1	1	1	0
4	4	1	0	0	0

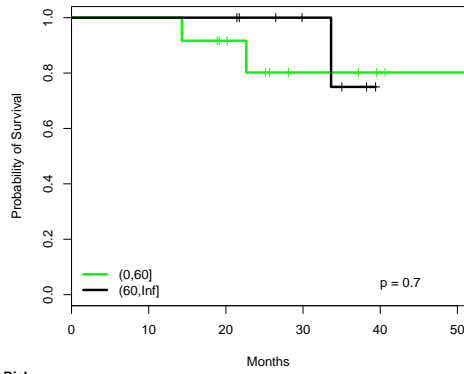
In DNA- Atypical



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

19	16	12	10	3	2
10	9	6	3	2	2

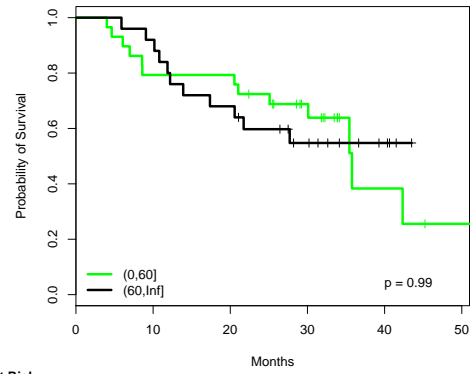
In DNA- Classical



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

12	12	9	4	2	1
8	8	8	4	0	0

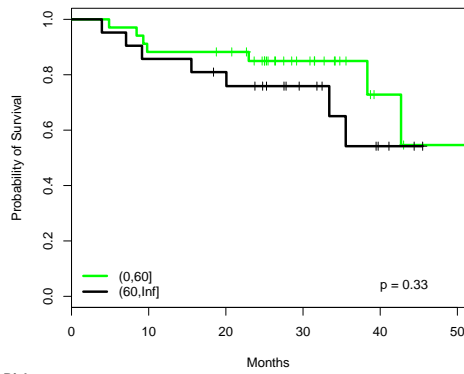
In DNA- Mesenchymal



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

29	23	23	14	3	1
25	23	17	10	4	0

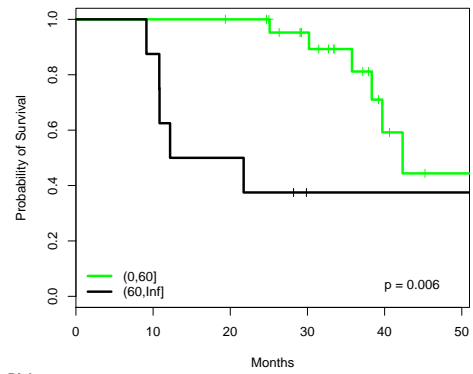
In DNA- Basal



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

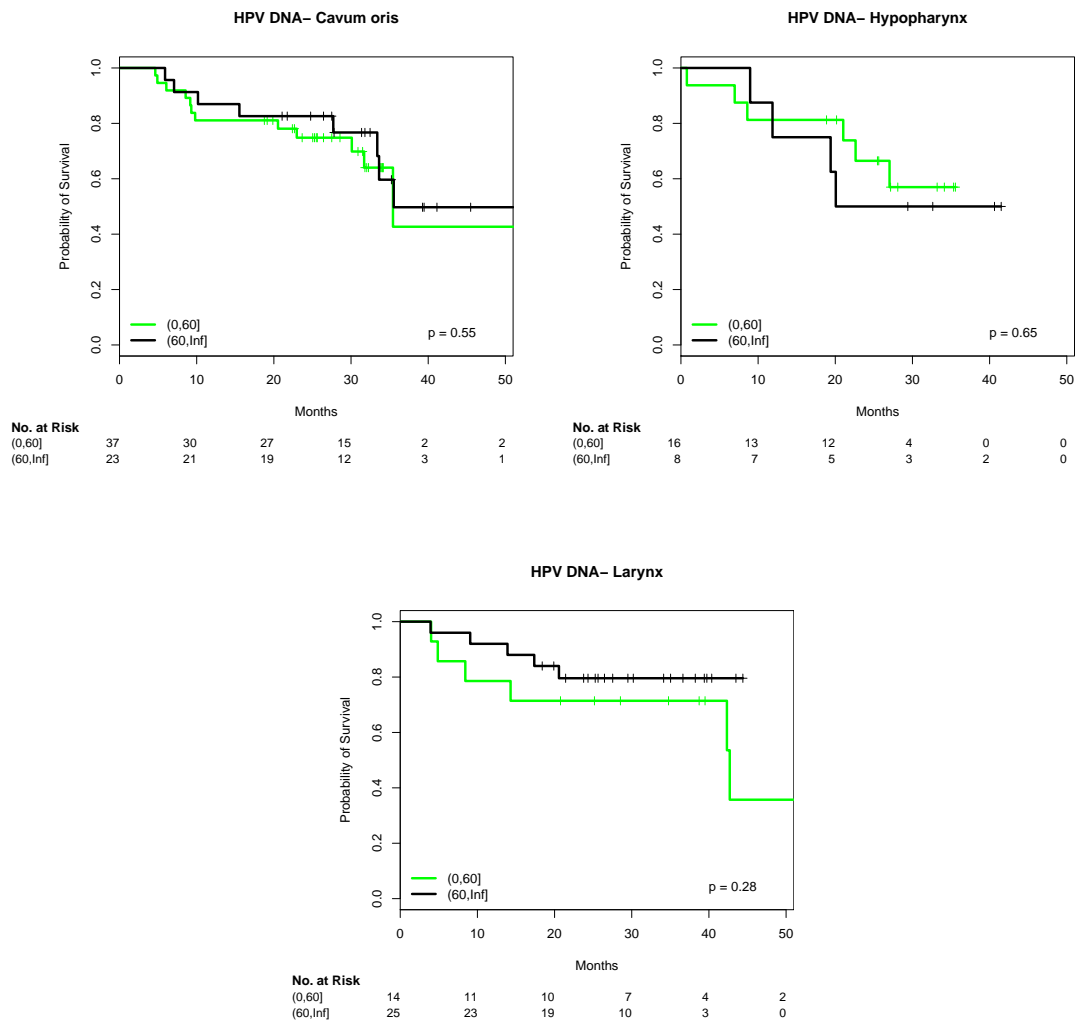
34	30	29	15	4	2
21	18	16	9	3	0

HPV DNA- Oropharynx



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

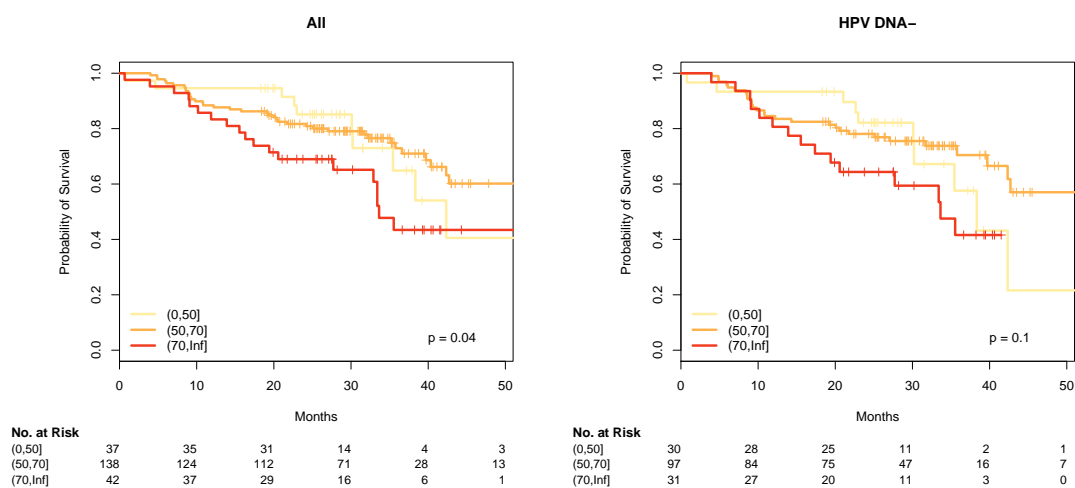
24	24	23	16	5	2
8	7	4	1	1	1

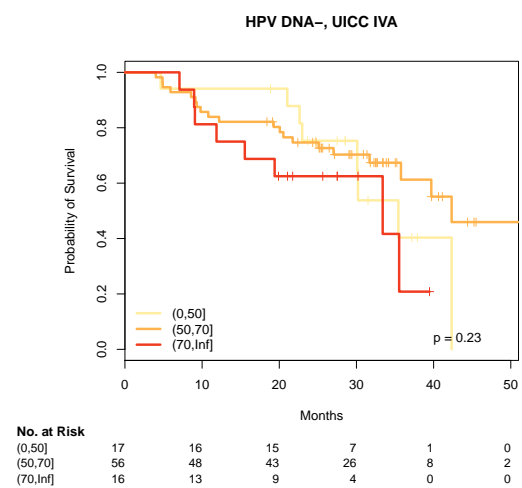
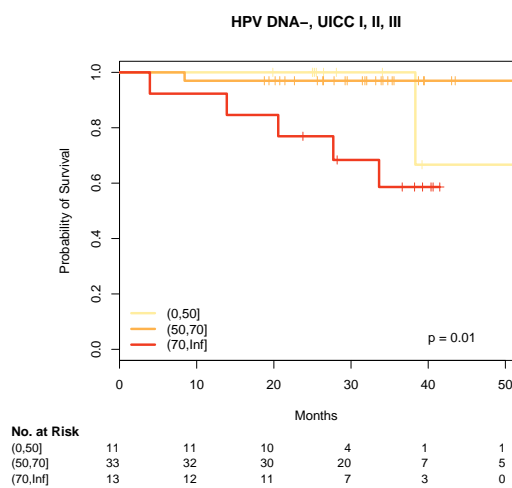
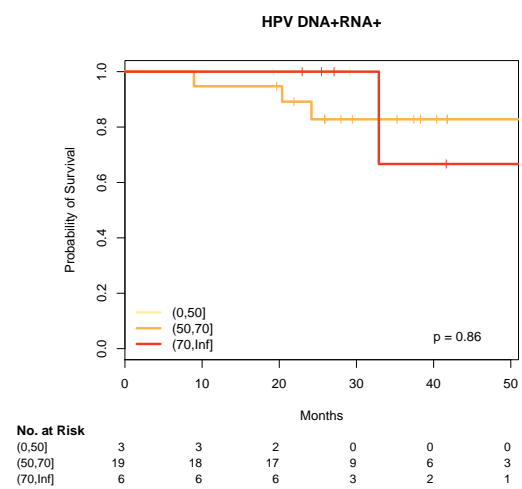
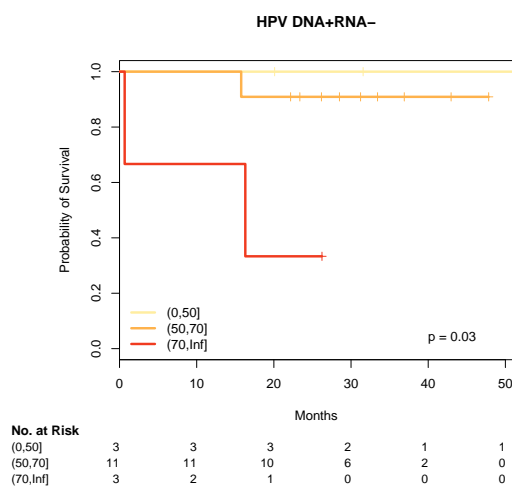
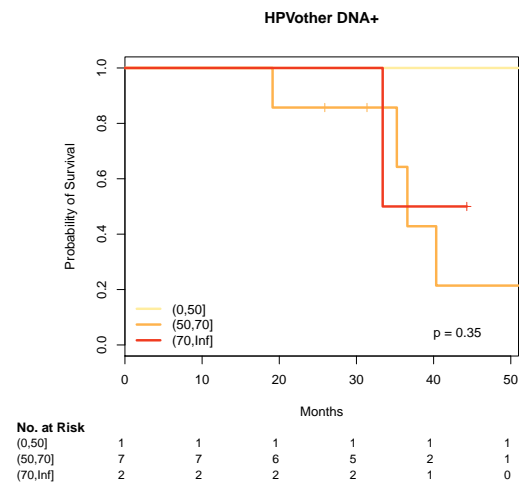
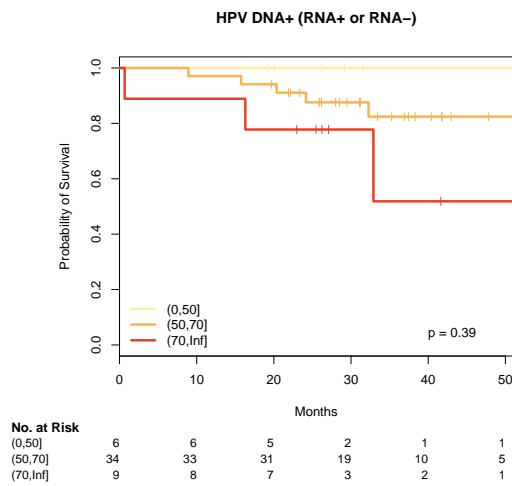


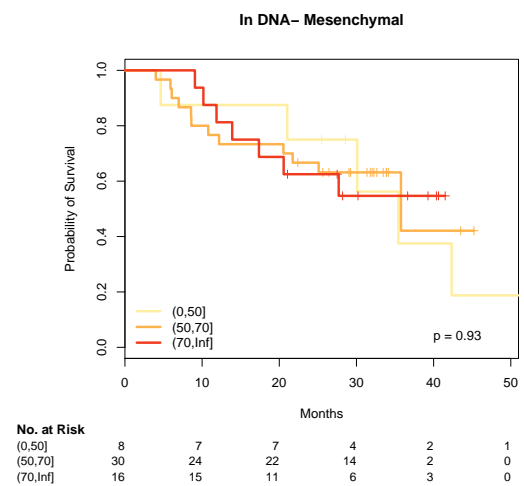
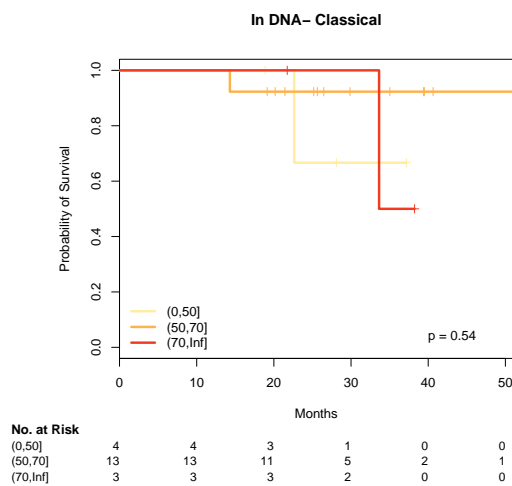
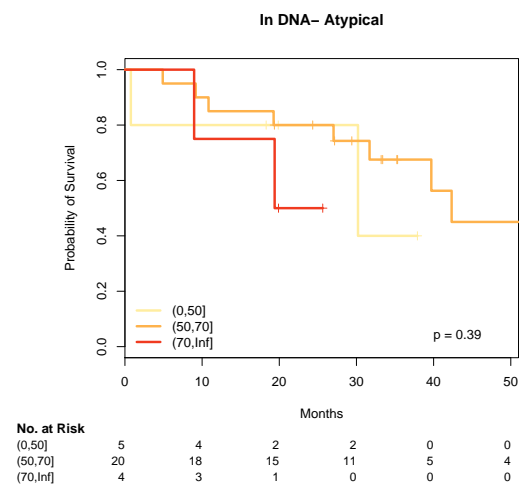
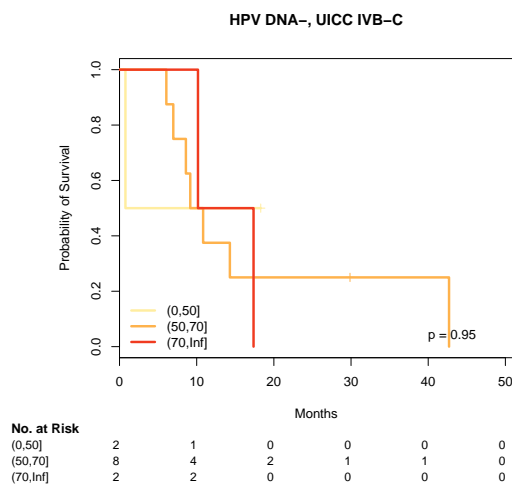
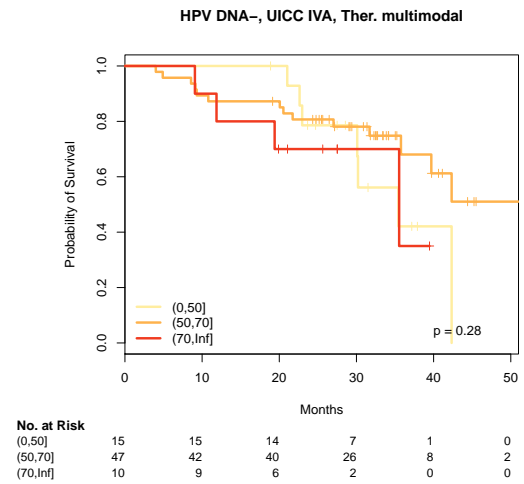
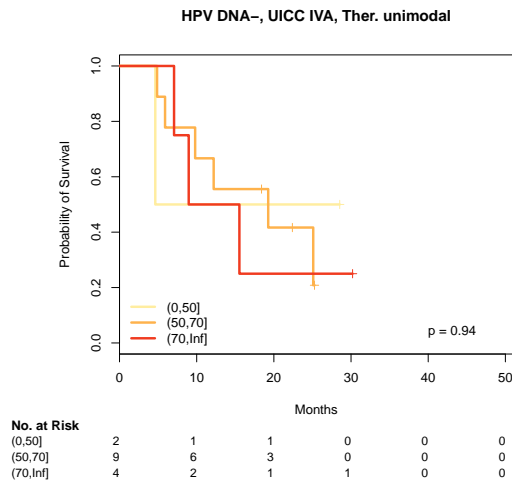
2.25 Age, cut at 50, 70

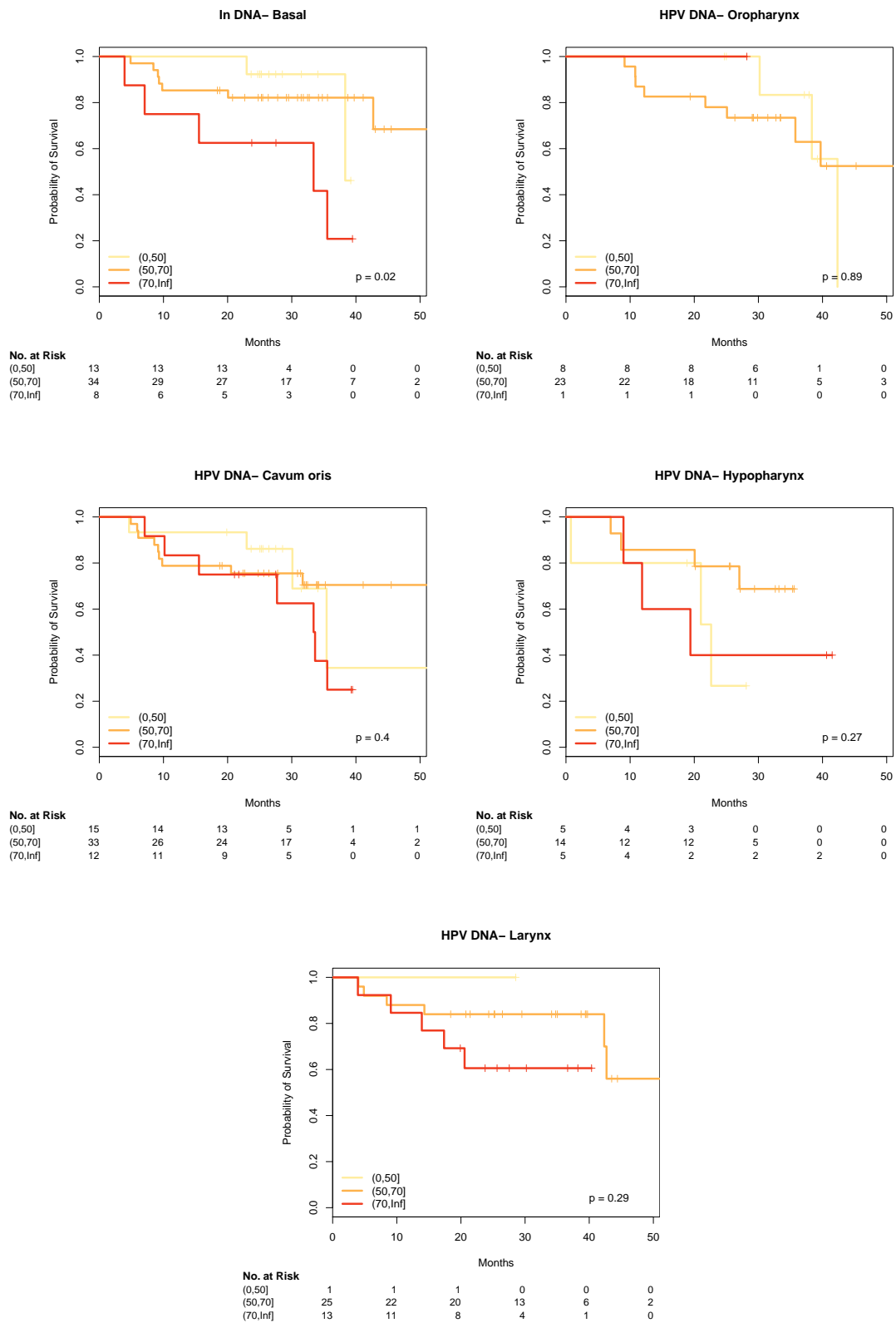
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70) -0.203    0.816   0.330 -0.62    0.54
## split[cur.subset](70,Inf)  0.489    1.631   0.372  1.32    0.19
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70)    0.816    1.225    0.427    1.56
## split[cur.subset](70,Inf)    1.631    0.613    0.787    3.38
```

```
##
## Concordance= 0.553 (se = 0.033 )
## Rsquare= 0.025 (max possible= 0.954 )
## Likelihood ratio test= 5.5 on 2 df, p=0.064
## Wald test = 6 on 2 df, p=0.0497
## Score (logrank) test = 6.22 on 2 df, p=0.0446
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70] -0.133   0.875   0.369 -0.36   0.72
## split[cur.subset](70,Inf]  0.547   1.729   0.414  1.32   0.19
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70]   0.875   1.143   0.424   1.81
## split[cur.subset](70,Inf]   1.729   0.578   0.768   3.89
##
## Concordance= 0.549 (se = 0.037 )
## Rsquare= 0.026 (max possible= 0.954 )
## Likelihood ratio test= 4.12 on 2 df, p=0.127
## Wald test = 4.51 on 2 df, p=0.105
## Score (logrank) test = 4.67 on 2 df, p=0.0968
```









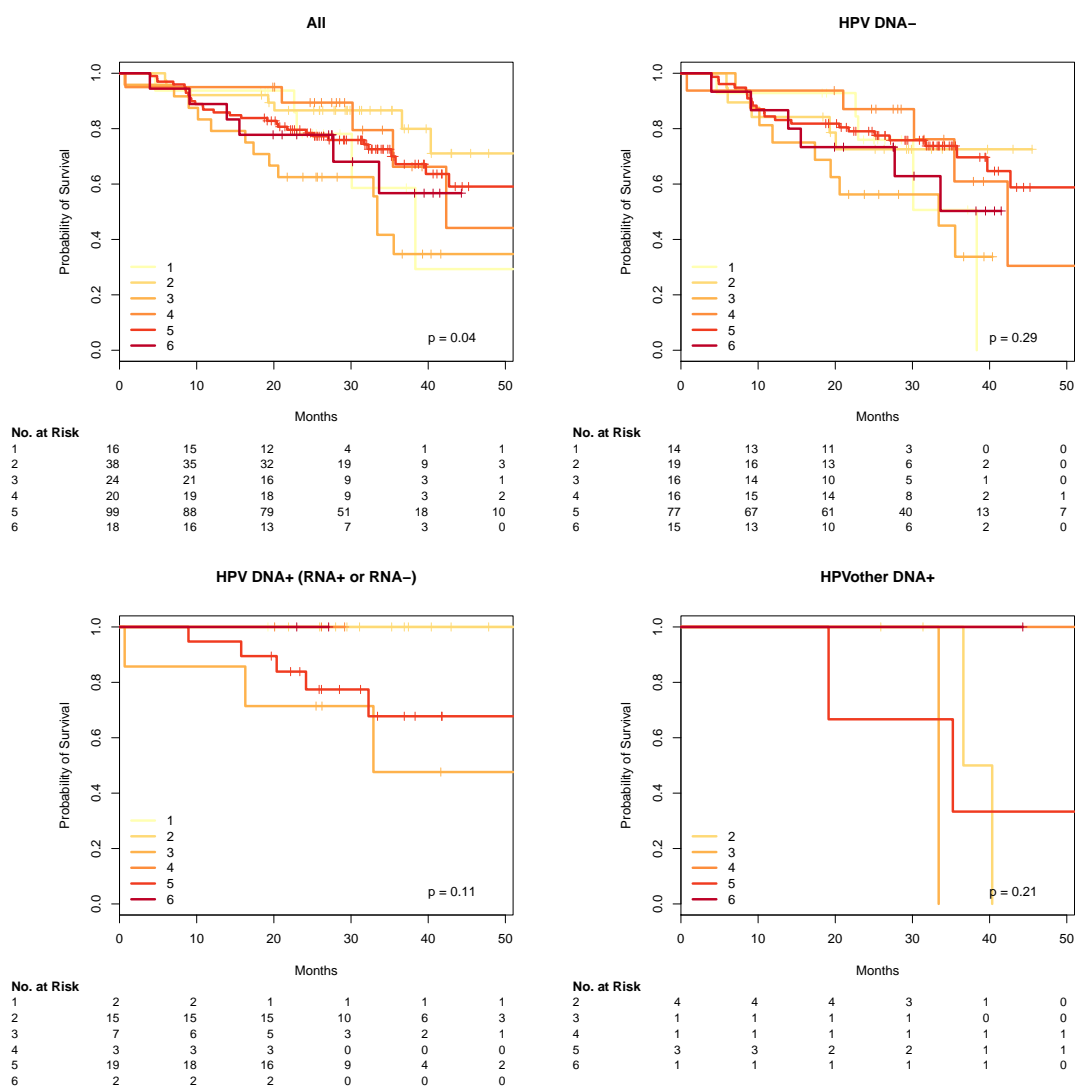
2.26 Age, Pack-years

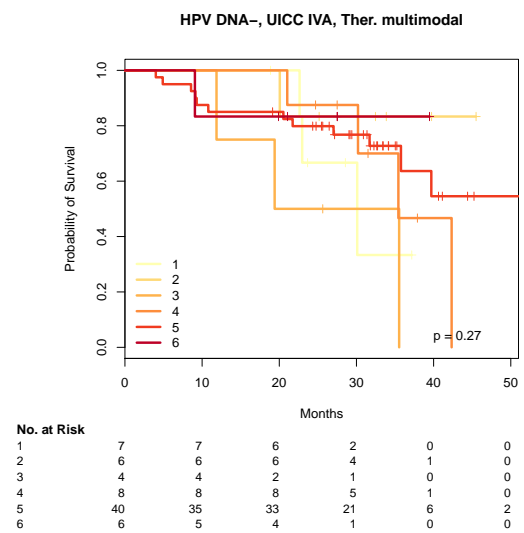
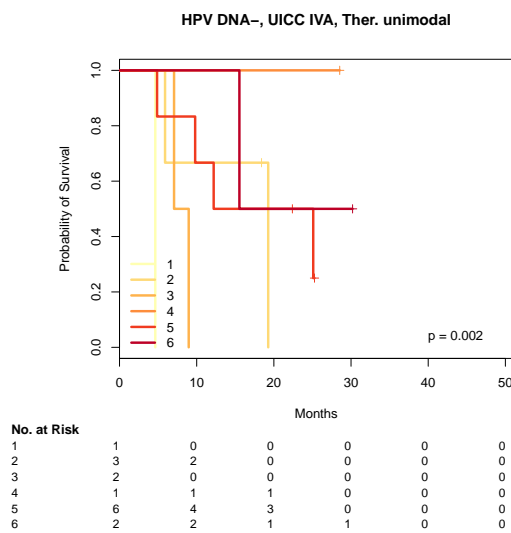
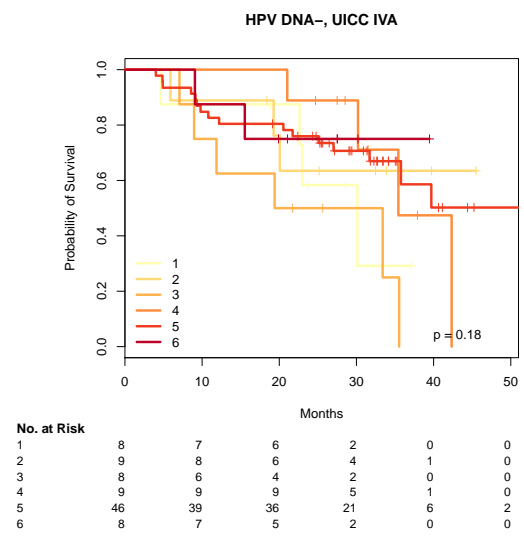
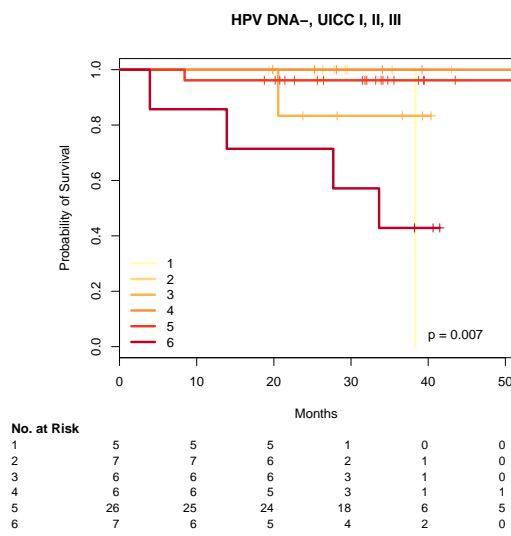
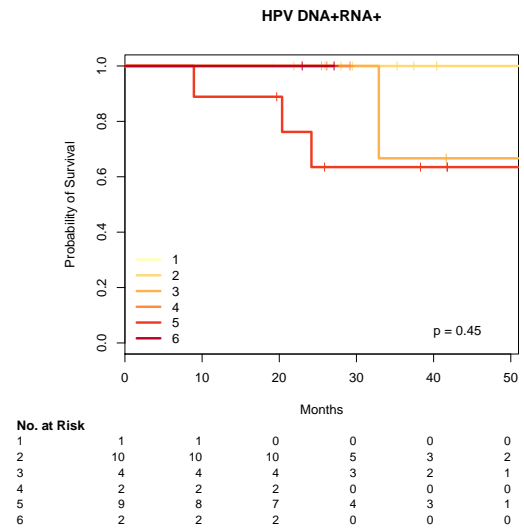
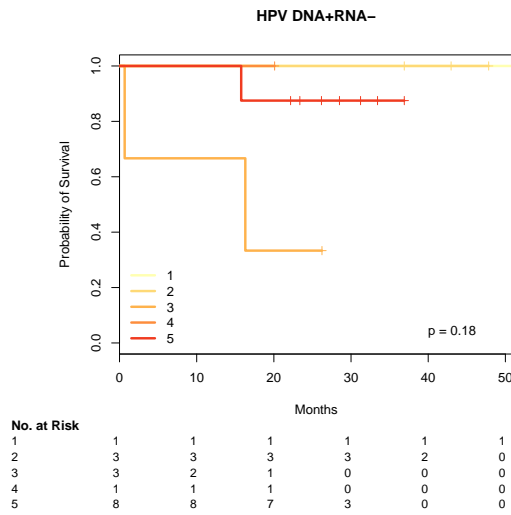

```

## 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= 215, number of events= 72
## (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -1.079      0.340    0.561 -1.92   0.055 .
## split[cur.subset]3  0.347      1.414    0.494  0.70   0.483
## split[cur.subset]4 -0.565      0.569    0.583 -0.97   0.333
## split[cur.subset]5 -0.406      0.666    0.448 -0.91   0.365
## split[cur.subset]6 -0.201      0.818    0.578 -0.35   0.728
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.340      2.941      0.113      1.02
## split[cur.subset]3      1.414      0.707      0.537      3.73
## split[cur.subset]4      0.569      1.759      0.181      1.78
## split[cur.subset]5      0.666      1.500      0.277      1.60
## split[cur.subset]6      0.818      1.223      0.263      2.54
##
## Concordance= 0.595 (se = 0.036 )
## Rsquare= 0.049 (max possible= 0.953 )
## Likelihood ratio test= 10.7 on 5 df, p=0.0569
## Wald test = 10.7 on 5 df, p=0.0579
## Score (logrank) test = 11.5 on 5 df, p=0.0421
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 157, number of events= 54
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.4172      0.6589    0.6352 -0.66   0.51
## split[cur.subset]3  0.4398      1.5524    0.5590  0.79   0.43
## split[cur.subset]4 -0.5248      0.5917    0.6440 -0.81   0.42
## split[cur.subset]5 -0.4287      0.6513    0.4987 -0.86   0.39
## split[cur.subset]6  0.0139      1.0140    0.6075  0.02   0.98
##

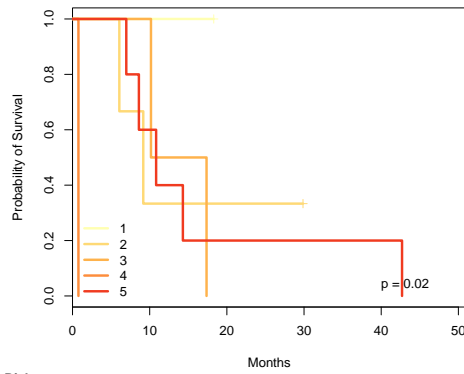
```

```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.659      1.518      0.190      2.29
## split[cur.subset]3      1.552      0.644      0.519      4.64
## split[cur.subset]4      0.592      1.690      0.167      2.09
## split[cur.subset]5      0.651      1.535      0.245      1.73
## split[cur.subset]6      1.014      0.986      0.308      3.34
##
## Concordance= 0.573  (se = 0.04 )
## Rsquare= 0.033  (max possible= 0.953 )
## Likelihood ratio test= 5.29  on 5 df,  p=0.382
## Wald test              = 5.88  on 5 df,  p=0.318
## Score (logrank) test = 6.18  on 5 df,  p=0.289
```





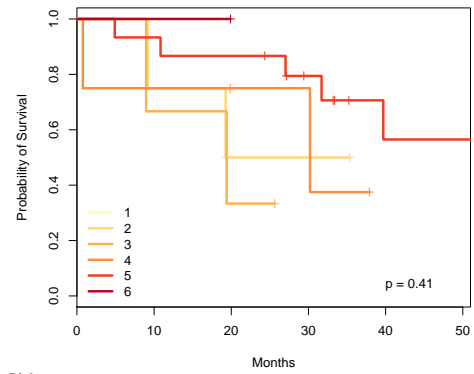
HPV DNA-, UICC IVB-C



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	1	0	0	0	0
2	3	1	1	0	0
3	2	2	0	0	0
4	1	0	0	0	0
5	5	3	1	1	0

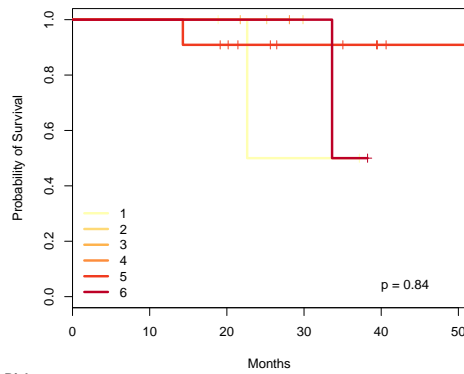
In DNA- Atypical



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	1	0	0	0	0
2	4	3	1	1	0
3	3	2	1	0	0
4	4	3	2	2	0
5	15	14	13	9	4
6	1	1	0	0	0

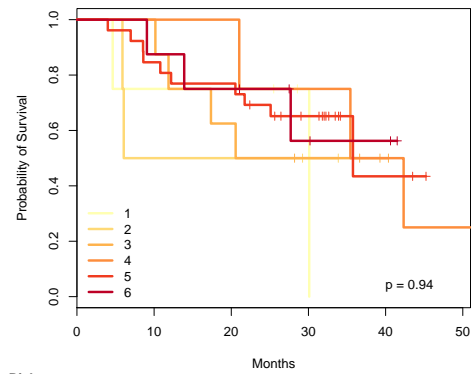
In DNA- Classical



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	3	2	1	0	0
2	3	2	0	0	0
3	1	1	0	0	0
4	1	1	0	0	0
5	11	11	9	5	2
6	2	2	2	0	0

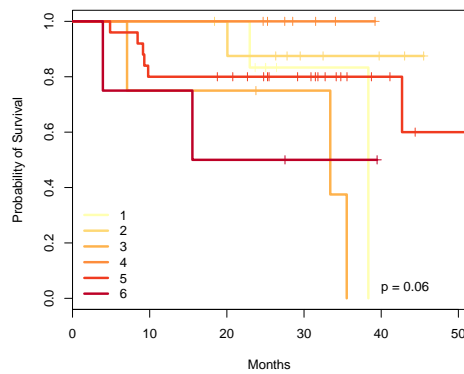
In DNA- Mesenchymal



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	4	3	1	0	0
2	4	2	1	0	0
3	8	8	5	3	1
4	4	4	3	2	0
5	26	22	20	13	2
6	8	7	6	3	2

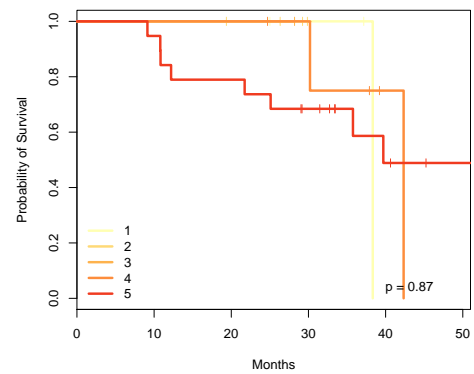
In DNA- Basal



No. at Risk

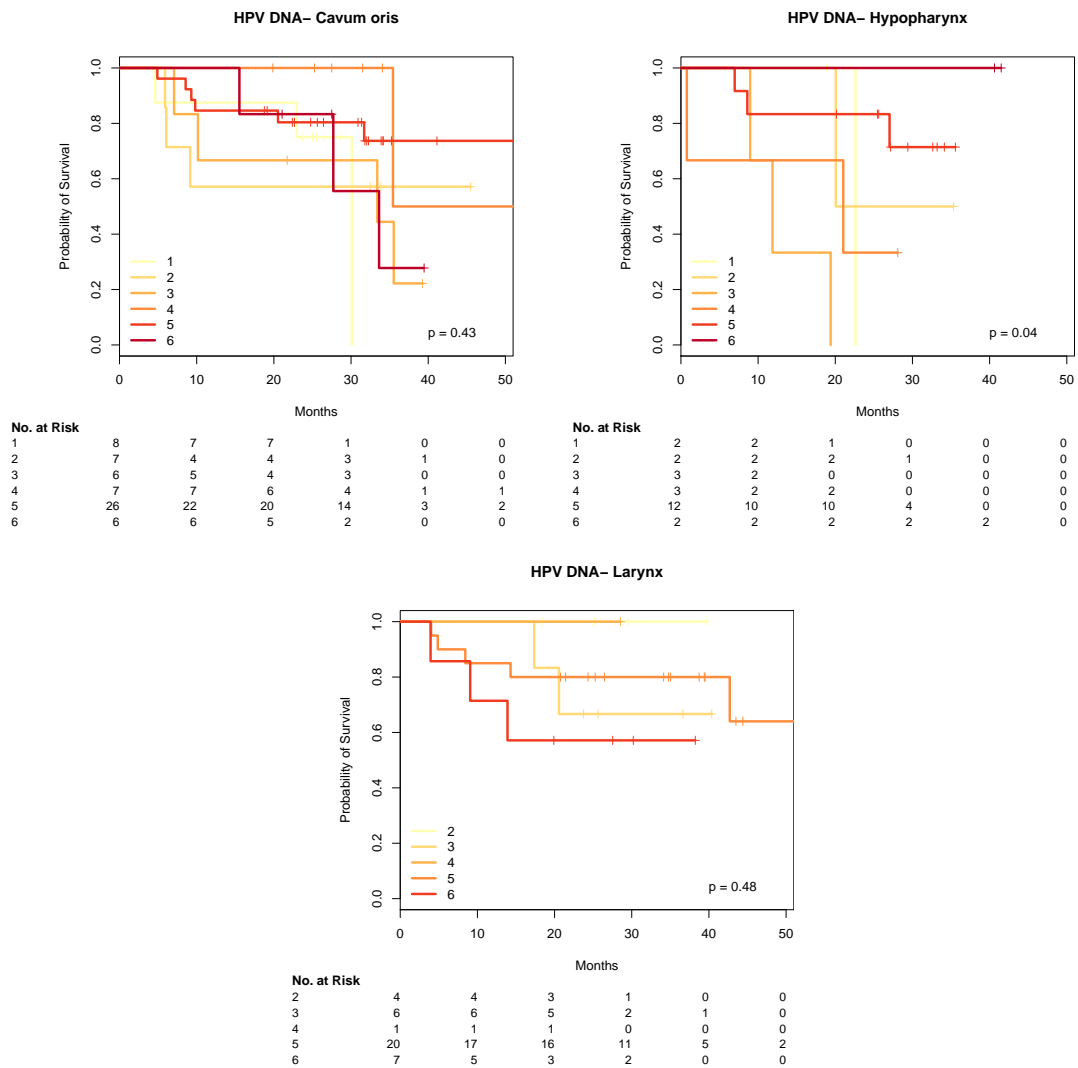
	0-10	10-20	20-30	30-40	40-50
1	6	6	1	0	0
2	9	9	8	4	2
3	4	3	3	0	0
4	7	7	7	3	0
5	25	20	19	13	5
6	4	3	2	1	0

HPV DNA- Oropharynx



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	3	3	2	0	0
2	4	4	3	0	0
3	1	1	0	0	0
4	5	5	4	1	0
5	19	18	15	11	5



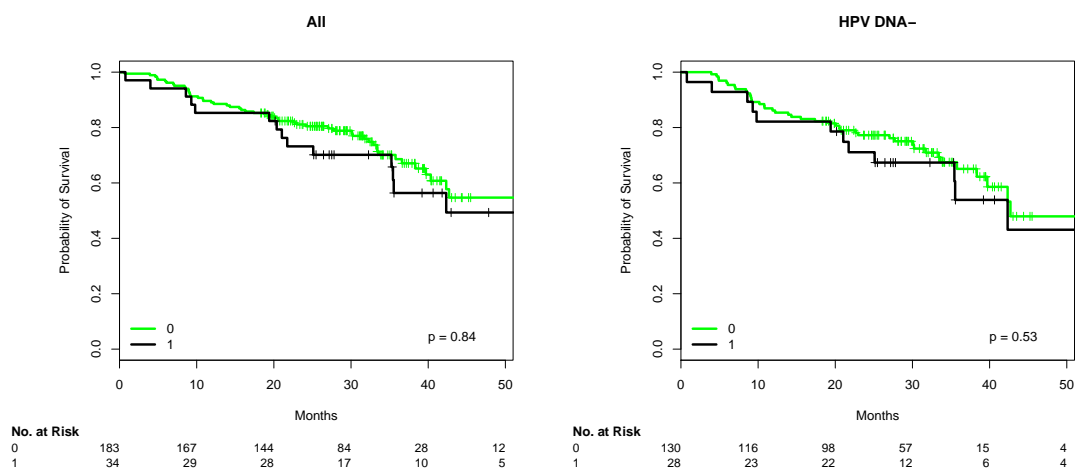
2.27 Mutational complexity

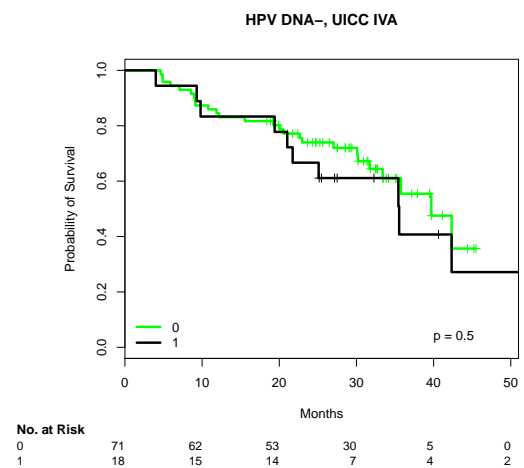
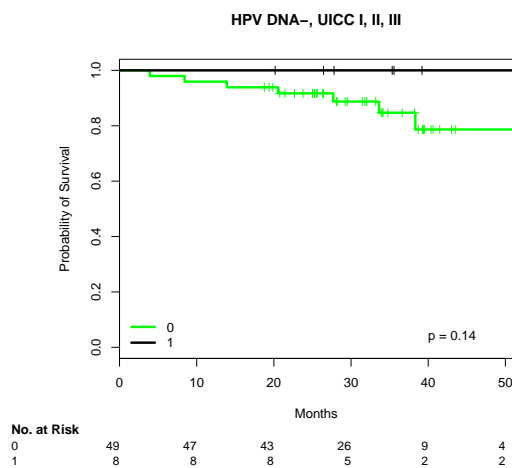
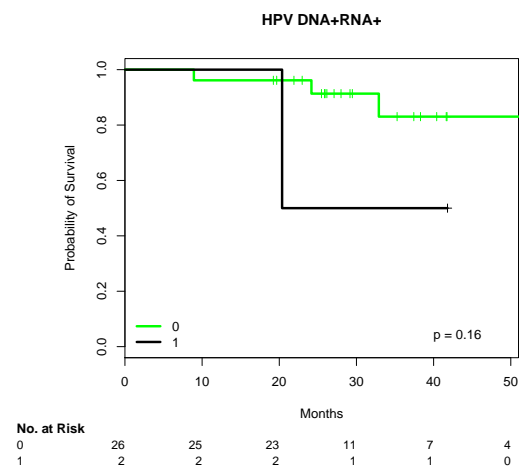
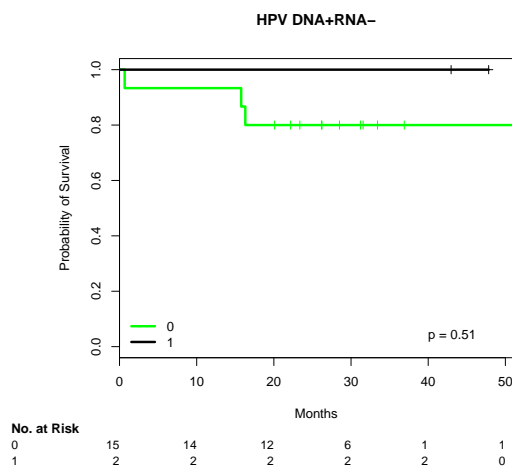
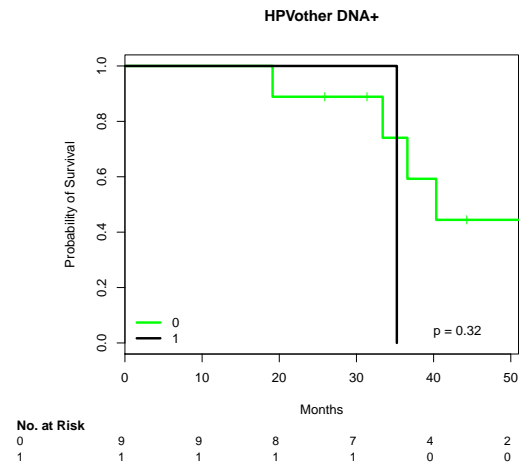
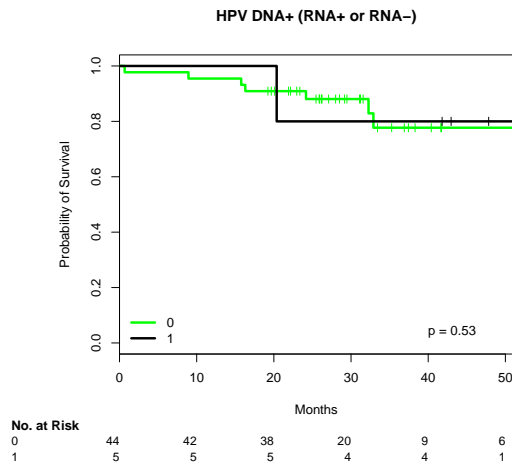
Equal to 1, if the number of mutated genes is greater than the median and 0 else.

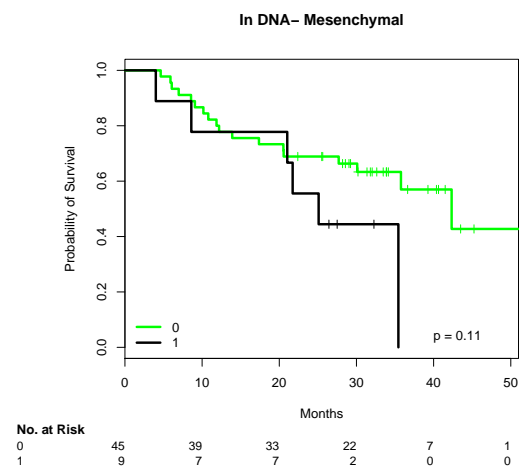
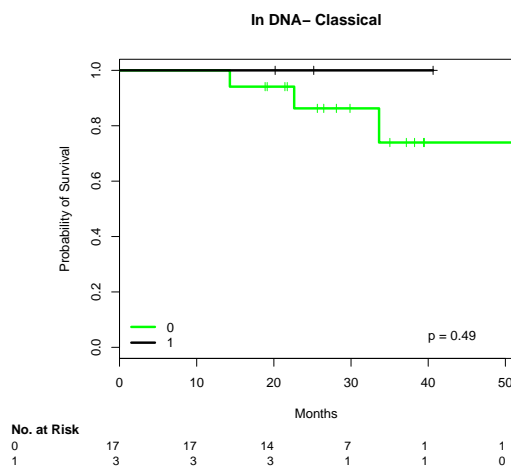
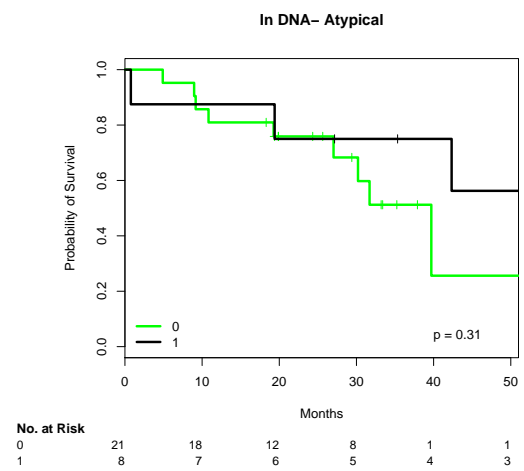
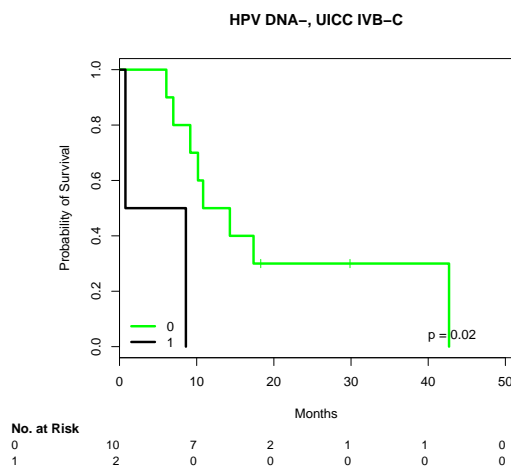
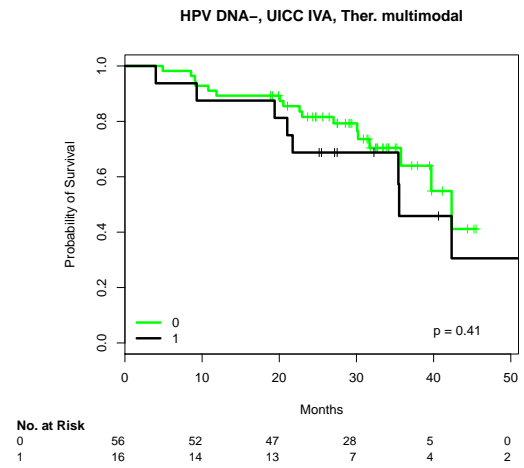
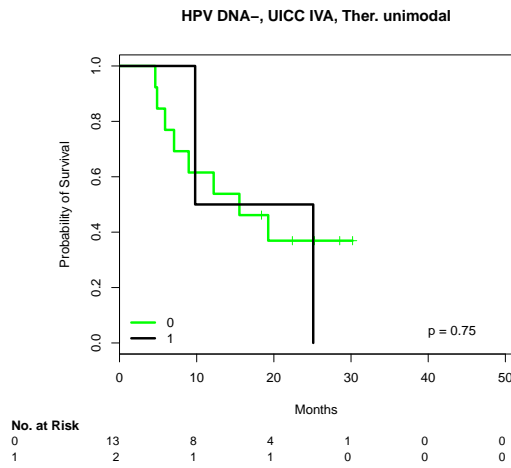
```
## Error: There is only 1 group
## Error: There is only 1 group

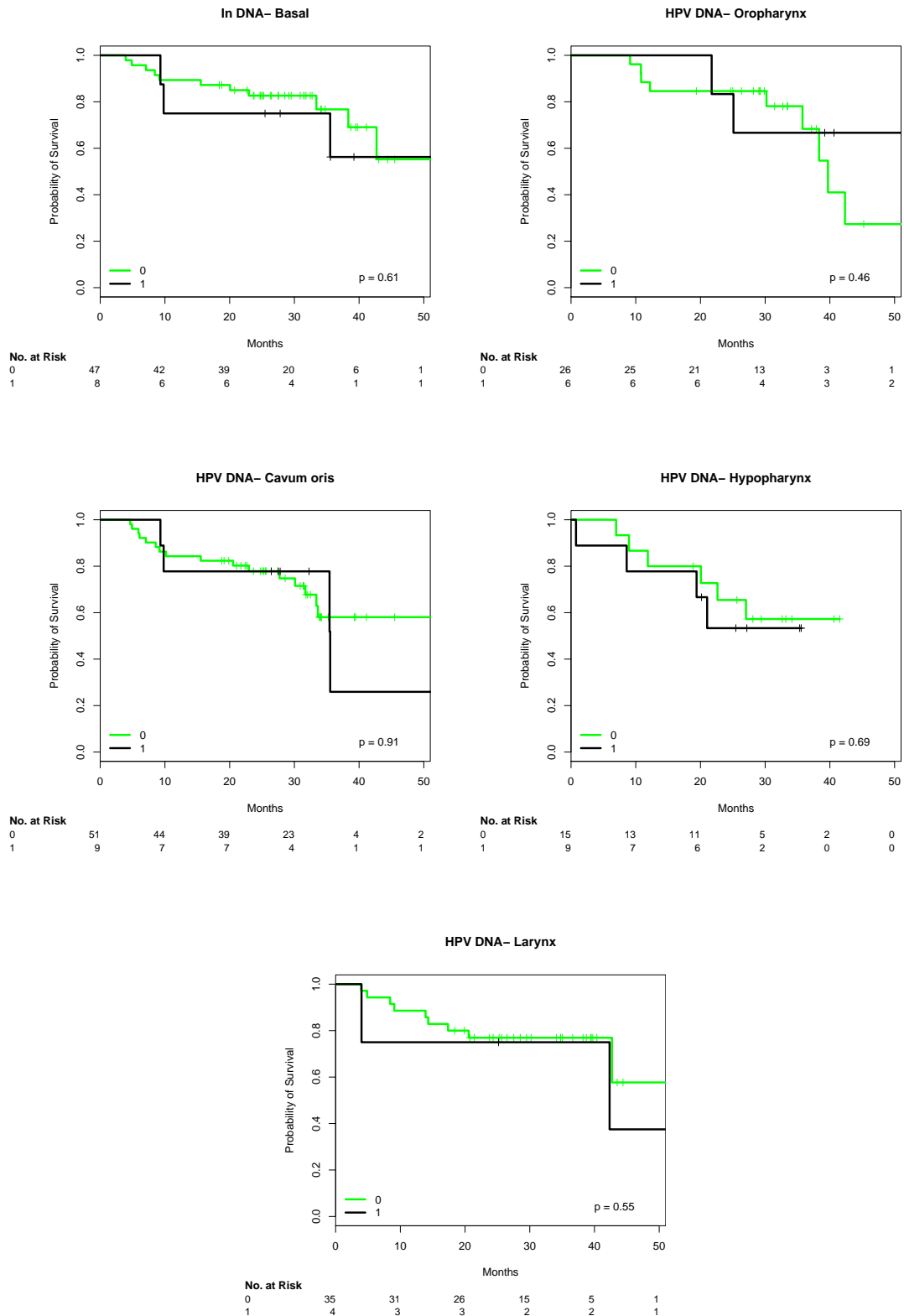
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset] 0.0615   1.0634  0.2981 0.21    0.84
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.06      0.94   0.593    1.91
```

```
##
## Concordance= 0.521 (se = 0.024 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.04 on 1 df, p=0.837
## Wald test = 0.04 on 1 df, p=0.837
## Score (logrank) test = 0.04 on 1 df, p=0.837
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.204      1.226   0.323 0.63    0.53
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.23      0.816   0.651      2.31
##
## Concordance= 0.52 (se = 0.028 )
## Rsquare= 0.002 (max possible= 0.954 )
## Likelihood ratio test= 0.38 on 1 df, p=0.536
## Wald test = 0.4 on 1 df, p=0.529
## Score (logrank) test = 0.4 on 1 df, p=0.528
```







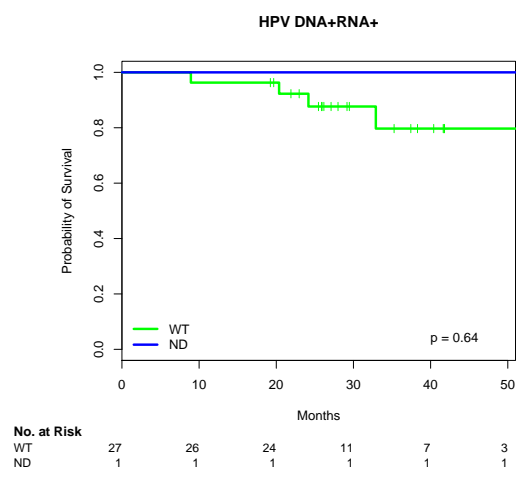
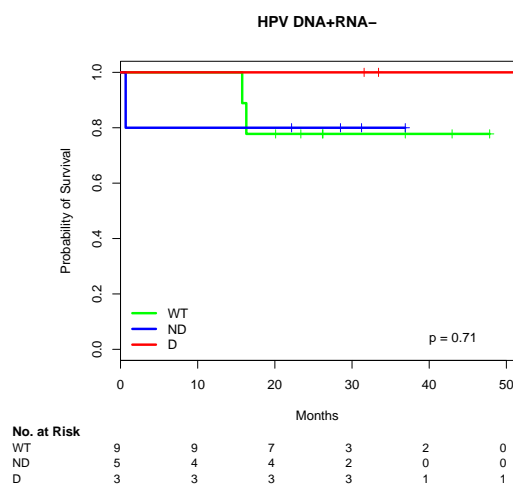
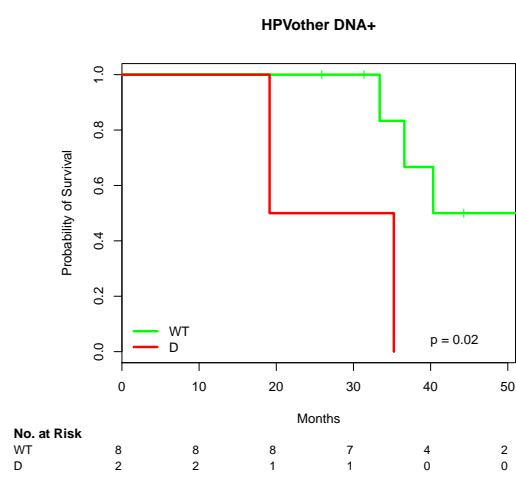
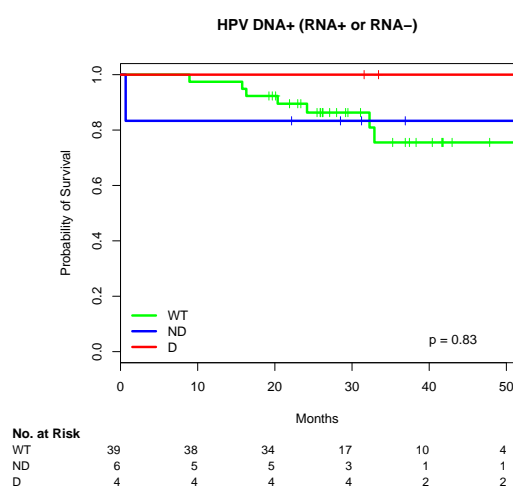
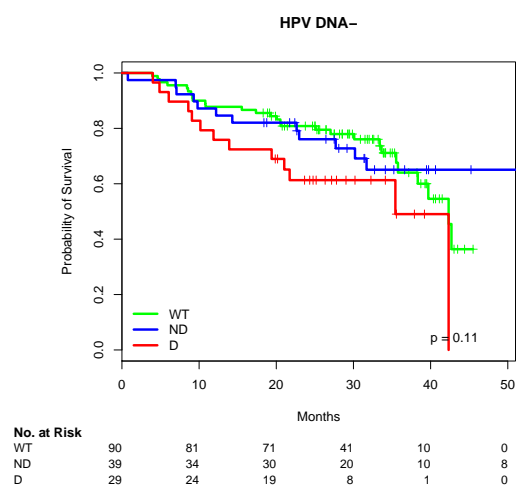
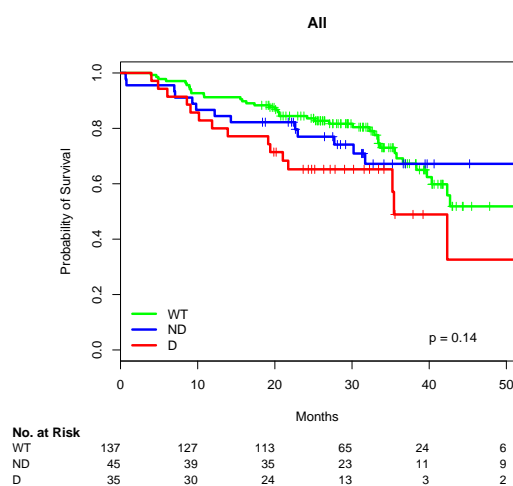


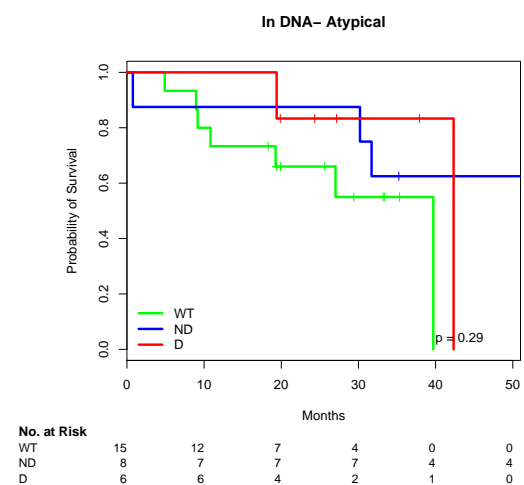
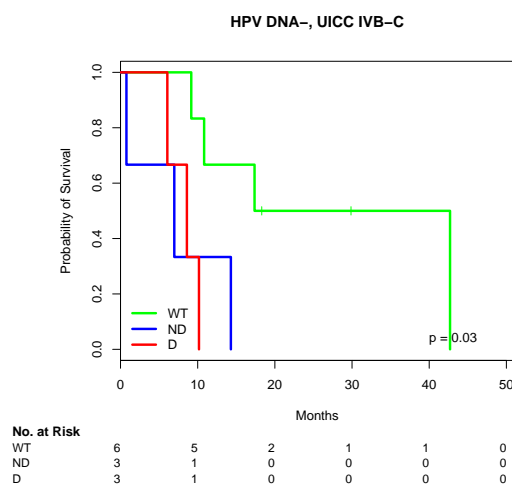
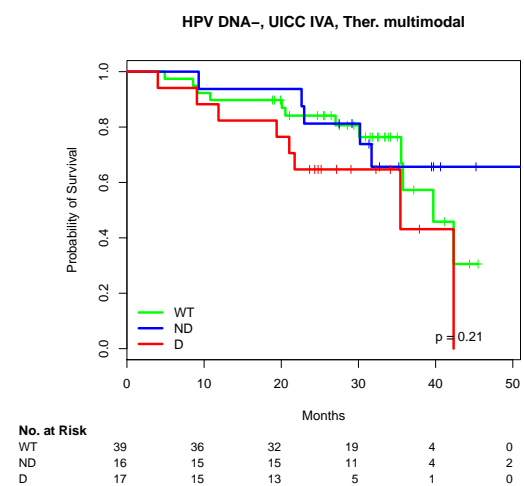
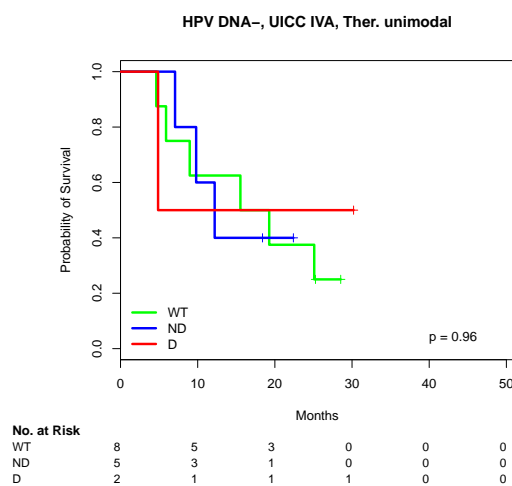
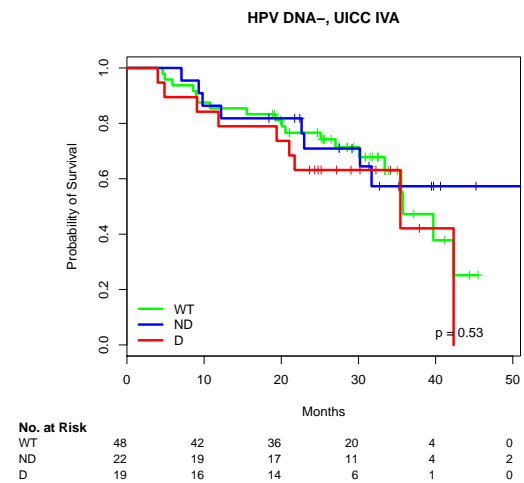
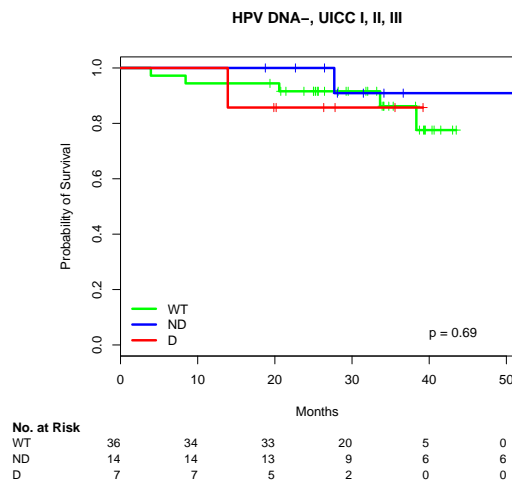
2.28 TP53: disruptive (D), non-disruptive (ND), wt as in Gross et al. (Nat Genet 2014) (frameshift treated as non-disruptive)

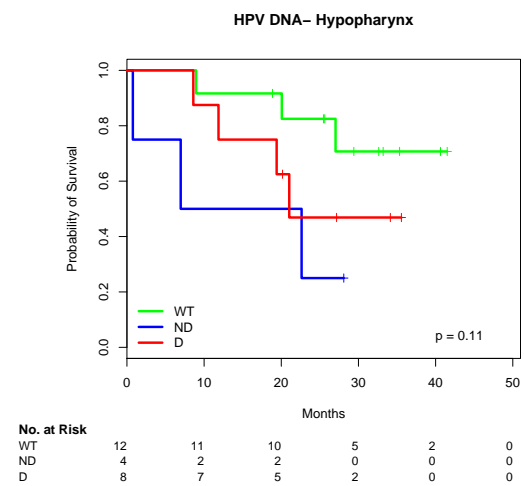
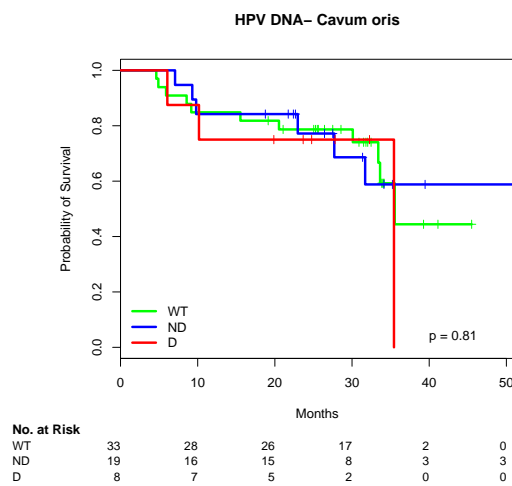
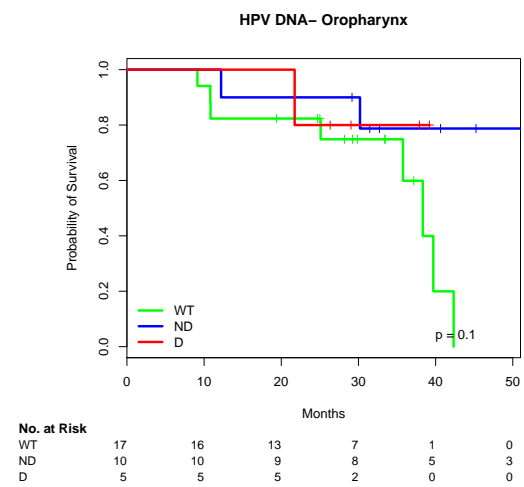
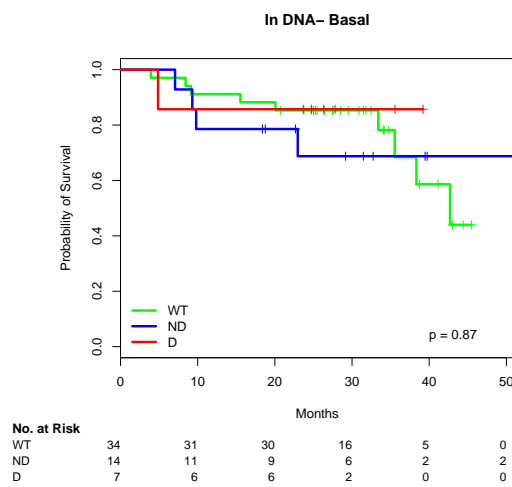
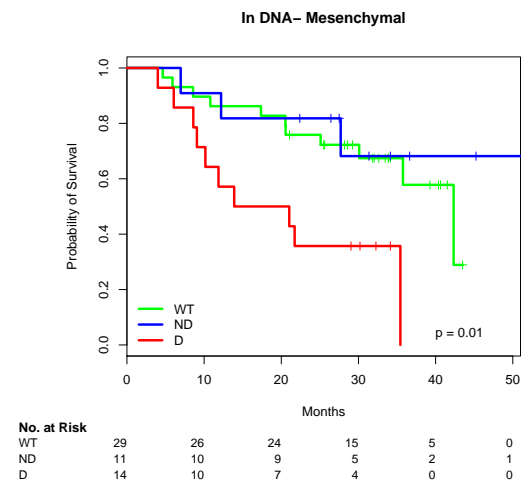
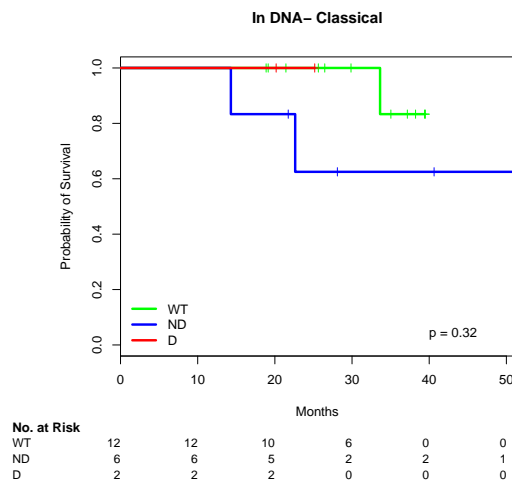
```

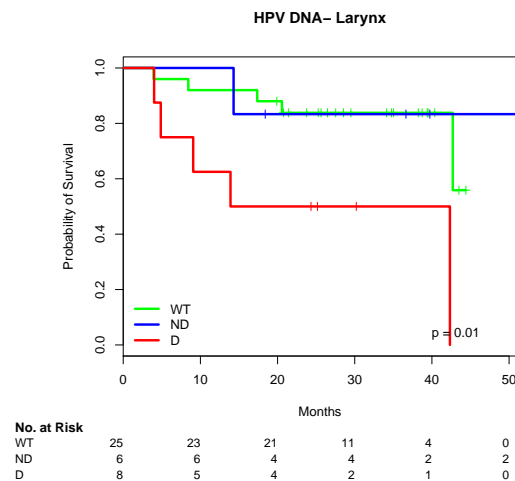
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.0907    0.9133  0.3107 -0.29   0.770
## split[cur.subset]D   0.5304    1.6997  0.2980  1.78   0.075 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND     0.913      1.095     0.497     1.68
## split[cur.subset]D     1.700      0.588     0.948     3.05
##
## Concordance= 0.534 (se = 0.033 )
## Rsquare= 0.016 (max possible= 0.954 )
## Likelihood ratio test= 3.46 on 2 df,  p=0.177
## Wald test               = 3.83 on 2 df,  p=0.148
## Score (logrank) test = 3.92 on 2 df,  p=0.141
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.186    0.830  0.351 -0.53   0.596
## split[cur.subset]D   0.600    1.822  0.337  1.78   0.075 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND     0.83      1.205     0.417     1.65
## split[cur.subset]D     1.82      0.549     0.941     3.53
##
## Concordance= 0.545 (se = 0.038 )
## Rsquare= 0.025 (max possible= 0.954 )
## Likelihood ratio test= 3.96 on 2 df,  p=0.138
## Wald test               = 4.35 on 2 df,  p=0.114
## Score (logrank) test = 4.51 on 2 df,  p=0.105

```





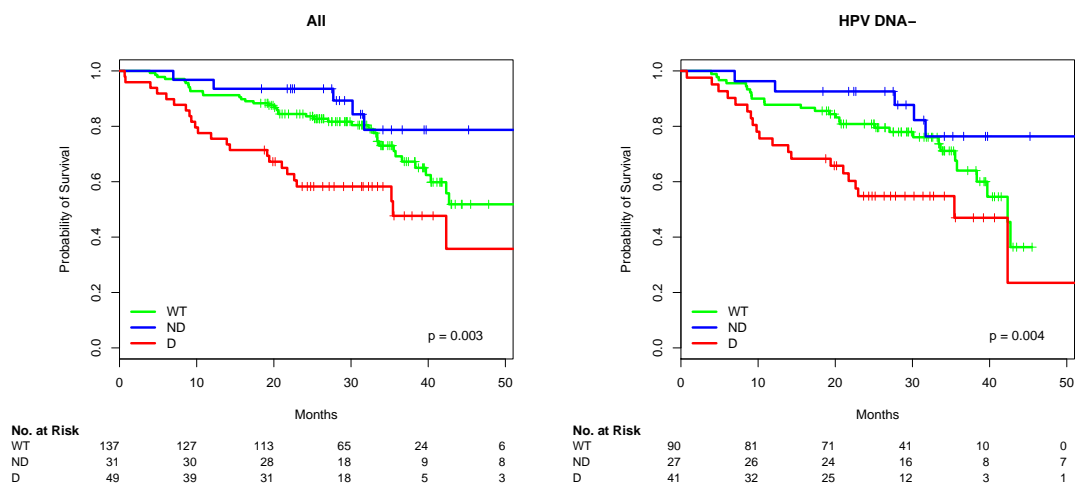


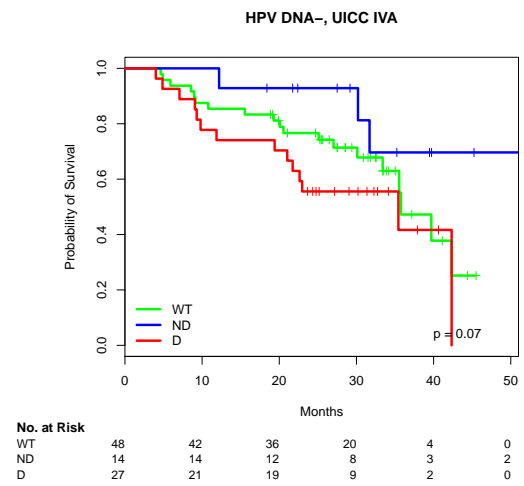
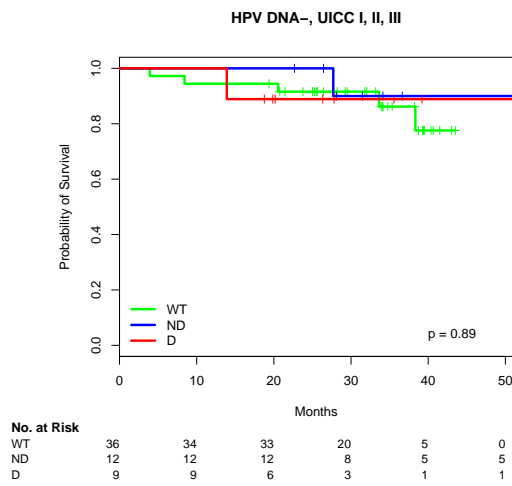
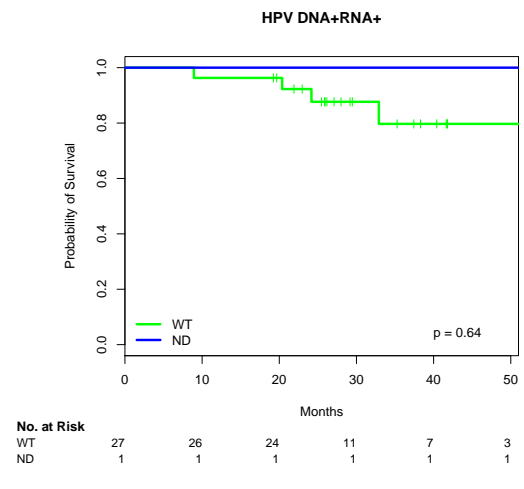
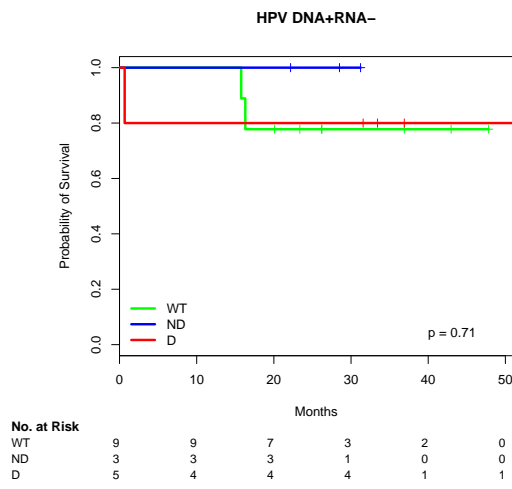
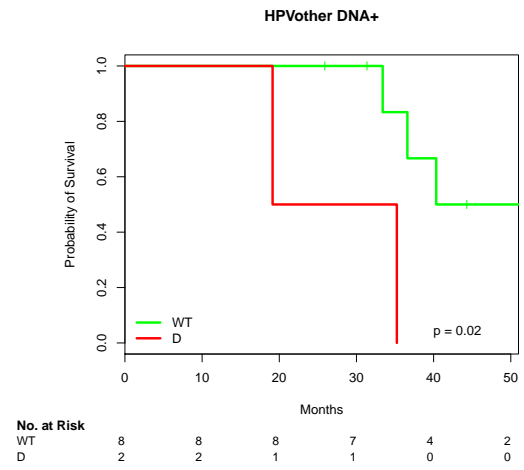
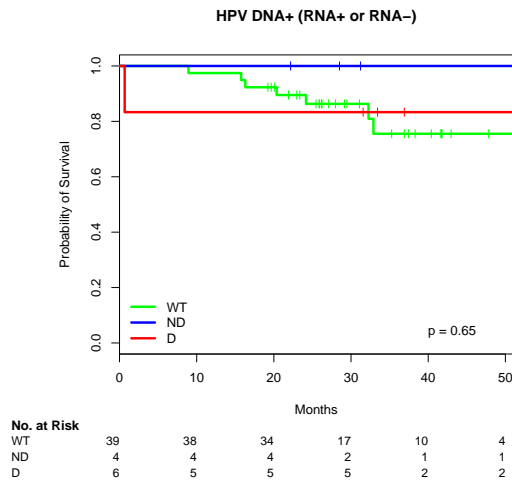


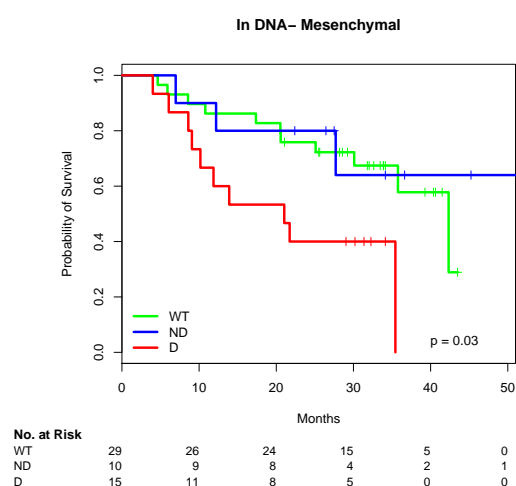
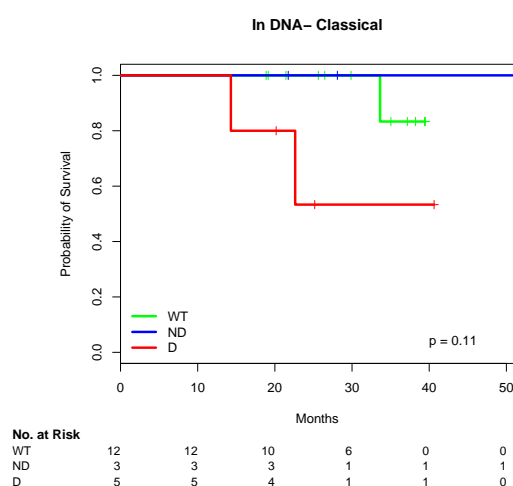
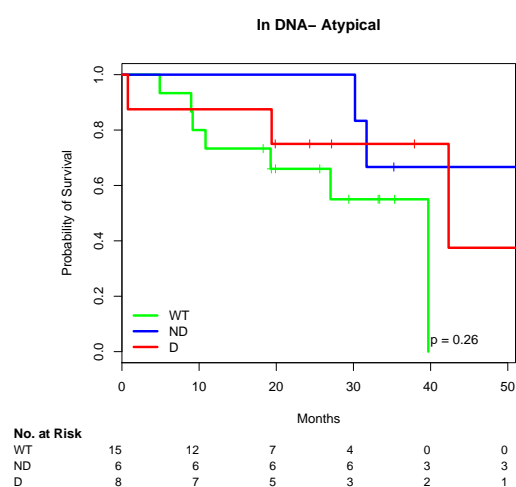
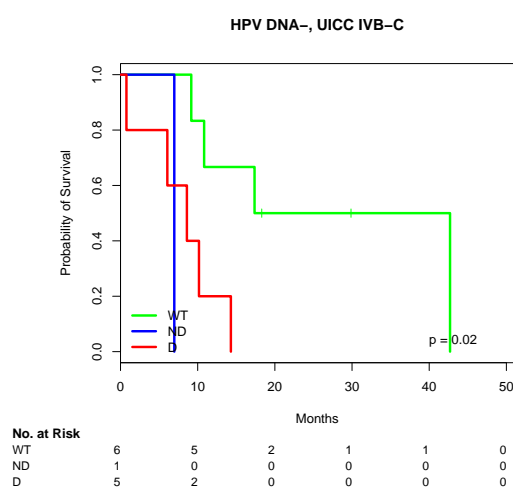
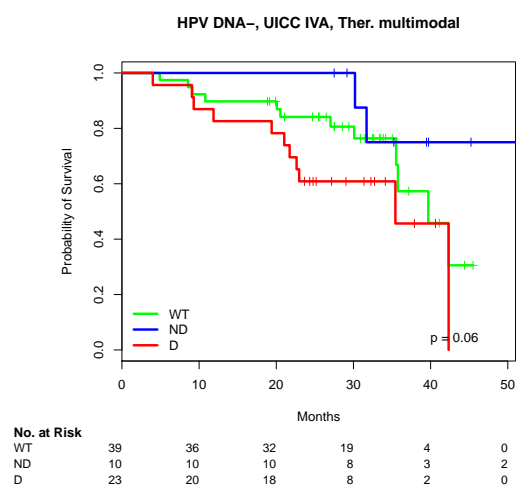
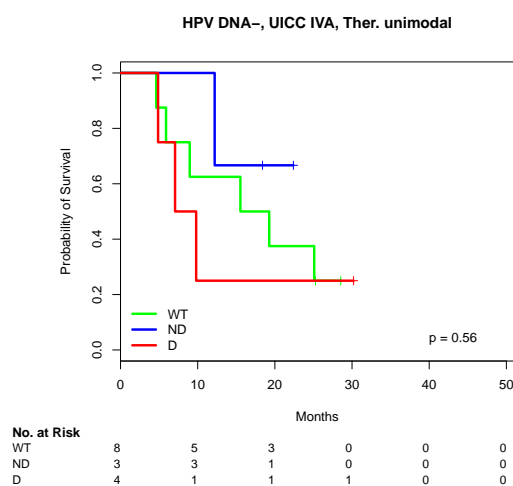
2.29 TP53: disruptive (D), non-disruptive (ND), wt with the convention that frameshift is treated as disruptive (following advice of David Masica)

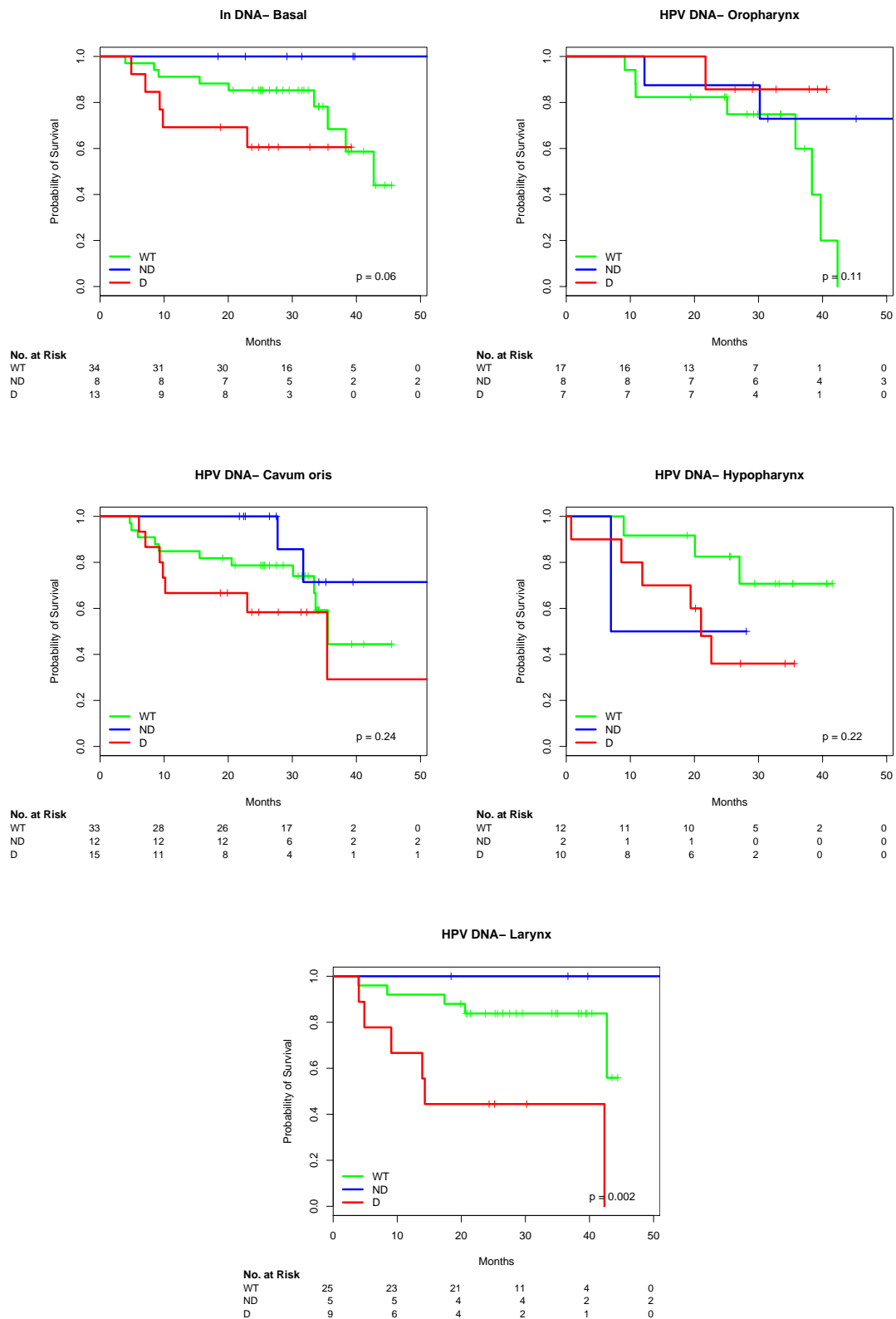
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.645    0.524   0.418 -1.55  0.122
## split[cur.subset]D   0.631    1.880   0.260  2.43  0.015 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND    0.524    1.907    0.231    1.19
## split[cur.subset]D    1.880    0.532    1.129    3.13
##
## Concordance= 0.623 (se = 0.033 )
## Rsquare= 0.049 (max possible= 0.954 )
## Likelihood ratio test= 10.9 on 2 df,  p=0.0043
## Wald test               = 10.7 on 2 df,  p=0.00466
## Score (logrank) test = 11.5 on 2 df,  p=0.00321
##
##
## #####
## Cox model in HPV DNA-
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.753      0.471      0.464 -1.62      0.105
## split[cur.subset]D   0.659      1.932      0.295  2.23      0.026 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND      0.471      2.122      0.19      1.17
## split[cur.subset]D       1.932      0.518      1.08      3.44
##
## Concordance= 0.626 (se = 0.038 )
## Rsquare= 0.066 (max possible= 0.954 )
## Likelihood ratio test= 10.8 on 2 df,  p=0.00456
## Wald test               = 10.3 on 2 df,  p=0.00573
## Score (logrank) test = 11.2 on 2 df,  p=0.00372
```









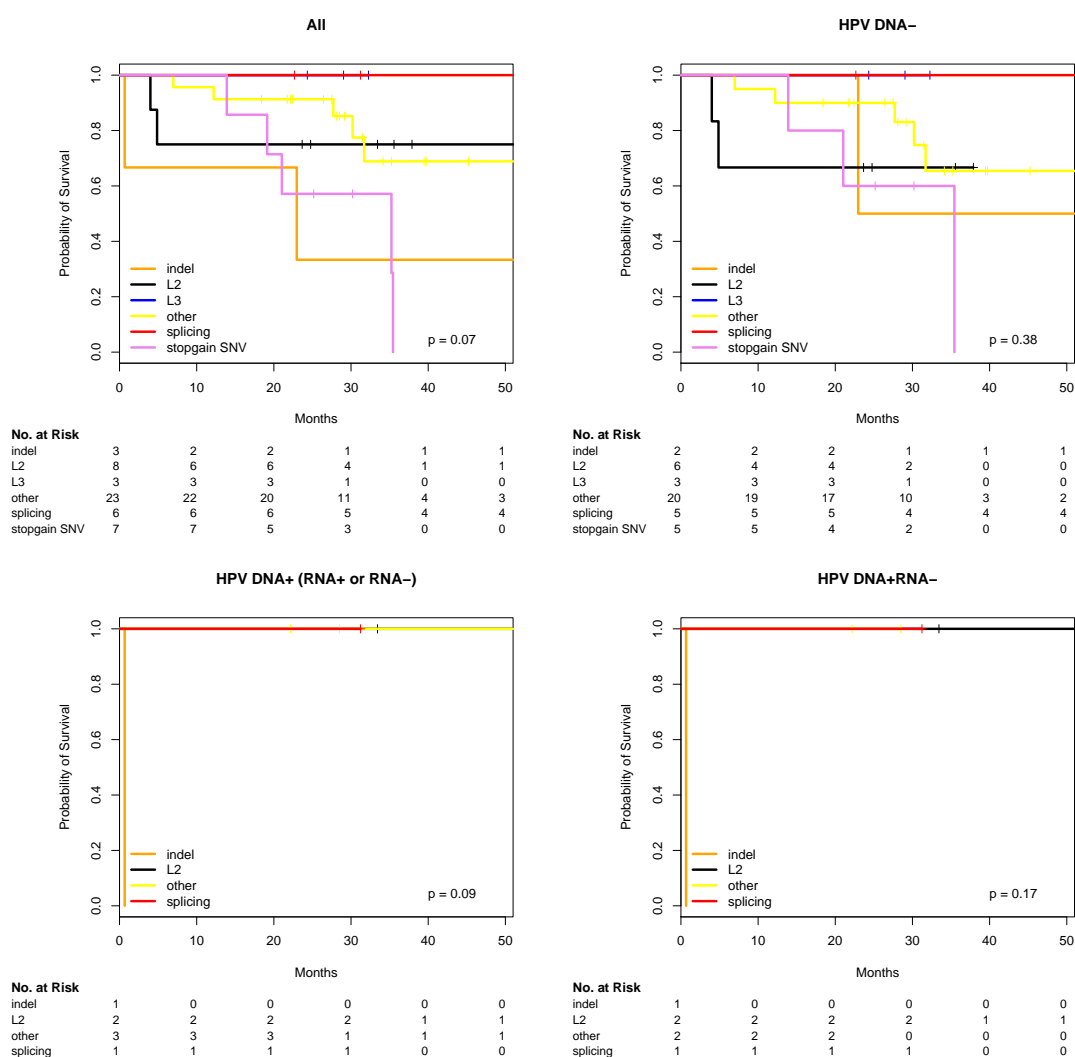
2.30 TP53: various types of mutations as in Gross et al. Patients which have only one type of TP53 mutation

```

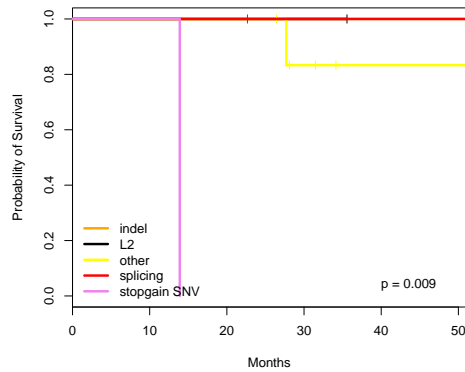
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 50, number of events= 16
## (167 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]L2      -1.81e-01  8.34e-01  1.02e+00 -0.18    0.86
## split[cur.subset]L3      -1.79e+01  1.63e-08  7.34e+03  0.00    1.00
## split[cur.subset]other    -7.26e-01  4.84e-01  9.57e-01 -0.76    0.45
## split[cur.subset]splicing -1.90e+00  1.50e-01  1.23e+00 -1.55    0.12
## split[cur.subset]stopgain SNV  6.41e-01  1.90e+00  9.74e-01  0.66    0.51
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]L2      8.34e-01  1.20e+00    0.1133    6.14
## split[cur.subset]L3      1.63e-08  6.12e+07    0.0000    Inf
## split[cur.subset]other    4.84e-01  2.07e+00    0.0741    3.16
## split[cur.subset]splicing  1.50e-01  6.68e+00    0.0135    1.66
## split[cur.subset]stopgain SNV  1.90e+00  5.27e-01    0.2818   12.80
##
## Concordance= 0.729 (se = 0.077 )
## Rsquare= 0.176 (max possible= 0.88 )
## Likelihood ratio test= 9.67 on 5 df, p=0.085
## Wald test = 7.44 on 5 df, p=0.19
## Score (logrank) test = 10.3 on 5 df, p=0.0659
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 41, number of events= 12
## (117 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]L2      6.42e-01  1.90e+00  1.42e+00  0.45    0.65
## split[cur.subset]L3      -1.81e+01  1.35e-08  1.10e+04  0.00    1.00
## split[cur.subset]other    1.32e-01  1.14e+00  1.31e+00  0.10    0.92
## split[cur.subset]splicing -1.11e+00  3.31e-01  1.41e+00 -0.78    0.43
## split[cur.subset]stopgain SNV  1.15e+00  3.16e+00  1.36e+00  0.85    0.40

```

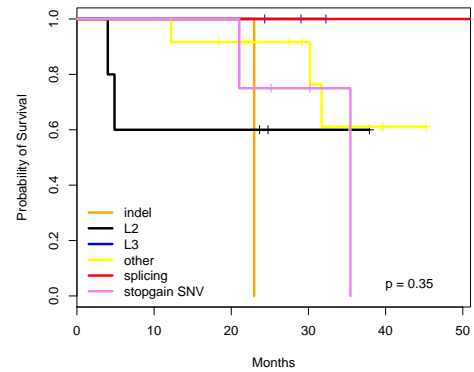
```
##
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]L2      1.90e+00  5.26e-01  0.1183  30.51
## split[cur.subset]L3      1.35e-08  7.42e+07  0.0000   Inf
## split[cur.subset]other    1.14e+00  8.77e-01  0.0879  14.81
## split[cur.subset]splicing  3.31e-01  3.02e+00  0.0207   5.29
## split[cur.subset]stopgain SNV 3.16e+00  3.16e-01  0.2199  45.54
##
## Concordance= 0.682 (se = 0.087 )
## Rsquare= 0.127 (max possible= 0.845 )
## Likelihood ratio test= 5.56 on 5 df, p=0.351
## Wald test               = 3.64 on 5 df, p=0.603
## Score (logrank) test = 5.3 on 5 df, p=0.38
```



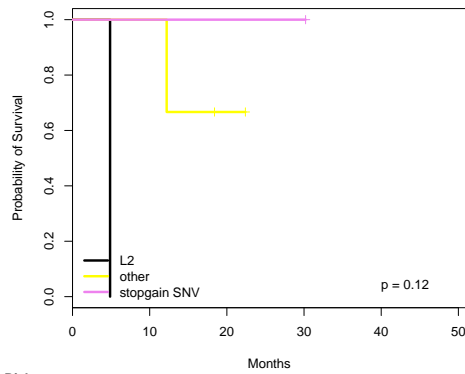
HPV DNA-, UICC I, II, III



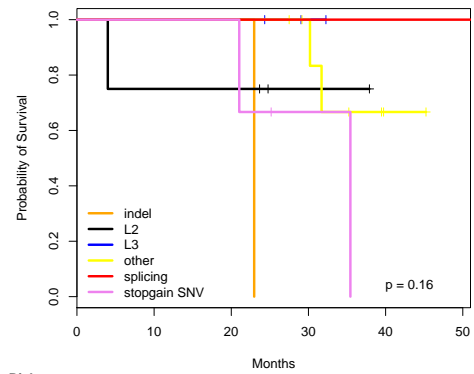
HPV DNA-, UICC IVA



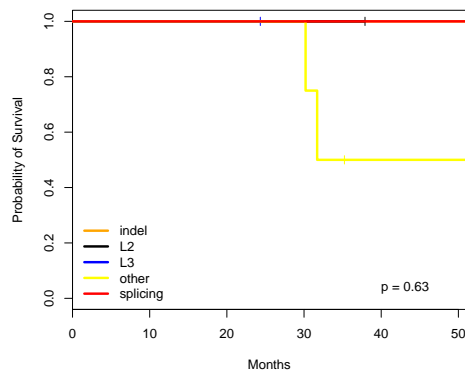
HPV DNA-, UICC IVA, Ther. unimodal



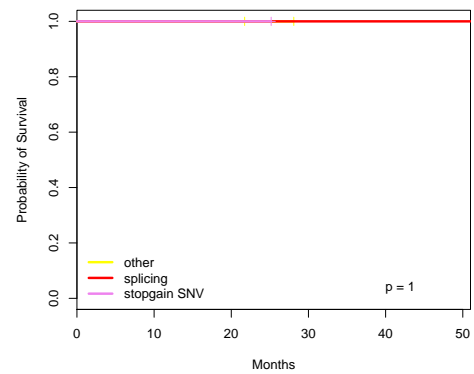
HPV DNA-, UICC IVA, Ther. multimodal



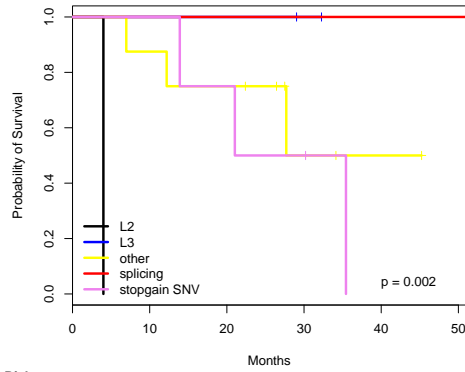
In DNA- Atypical



In DNA- Classical



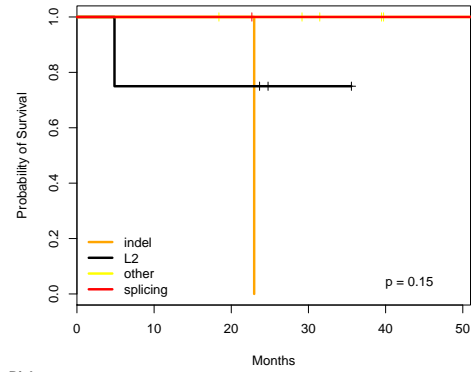
In DNA- Mesenchymal



No. at Risk

	0	10	20	30	40	50
L2	1	0	0	0	0	0
L3	2	2	2	1	0	0
other	8	7	6	2	1	0
splicing	1	1	1	1	1	1
stopgain SNV	4	4	3	2	0	0

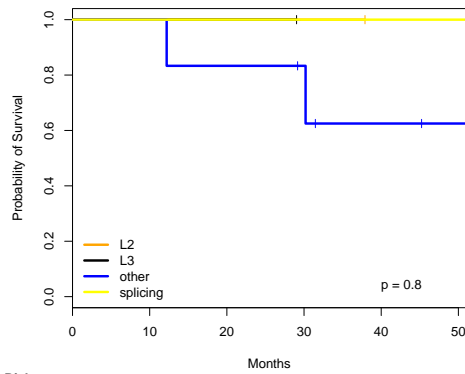
In DNA- Basal



No. at Risk

	0	10	20	30	40	50
indel	1	1	1	0	0	0
L2	4	3	3	1	0	0
other	6	6	5	4	1	1
splicing	2	2	2	1	1	1

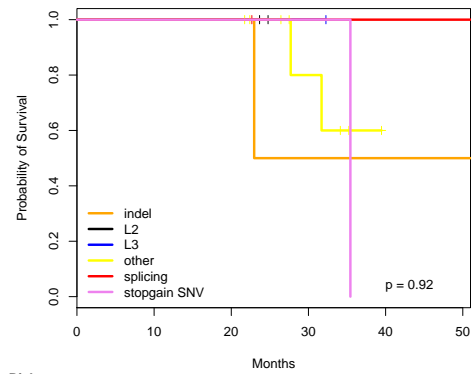
HPV DNA- Oropharynx



No. at Risk

	0	10	20	30	40	50
L2	1	1	1	1	0	0
L3	1	1	1	0	0	0
other	6	6	5	4	2	1
splicing	1	1	1	1	1	1

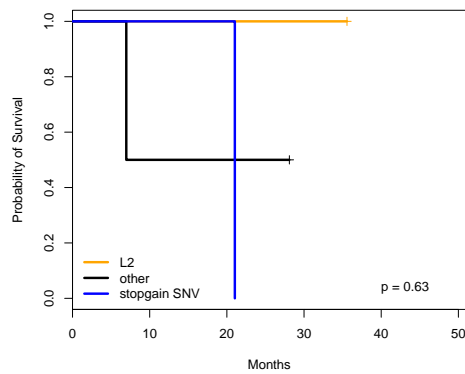
HPV DNA- Cavum oris



No. at Risk

	0	10	20	30	40	50
indel	2	2	2	1	1	1
L2	2	2	2	0	0	0
L3	1	1	1	1	0	0
other	9	9	9	4	0	0
splicing	3	3	3	2	2	2
stopgain SNV	1	1	1	1	0	0

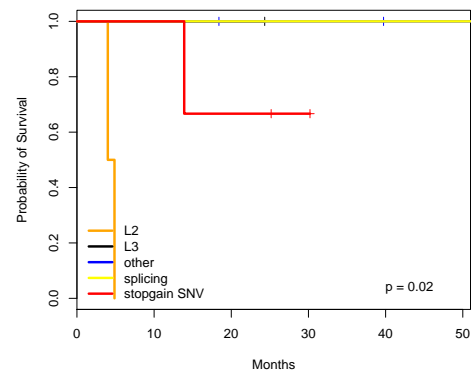
HPV DNA- Hypopharynx



No. at Risk

	0	10	20	30	40	50
L2	1	1	1	1	0	0
other	2	1	1	0	0	0
stopgain SNV	1	1	1	0	0	0

HPV DNA- Larynx



No. at Risk

	0	10	20	30	40	50
L2	2	0	0	0	0	0
L3	1	1	1	0	0	0
other	3	3	2	2	1	1
splicing	1	1	1	1	1	1
stopgain SNV	3	3	2	1	0	0

2.31 TP53: various types of mutations similar but NOT identical as in Gross et al.

Changes: category for frameshift, L2, L3 have to fullfill polarity conditions of Poeta et al.
Patients who have only one type of TP53 mutation.

```
## 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= 40, number of events= 13
## (177 observations deleted due to missingness)
##
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
split[cur.subset]other	-0.967	0.380	0.939	-1.03	0.30
split[cur.subset]splicing	-1.883	0.152	1.226	-1.54	0.12
split[cur.subset]stopgain SNV	0.440	1.553	0.942	0.47	0.64

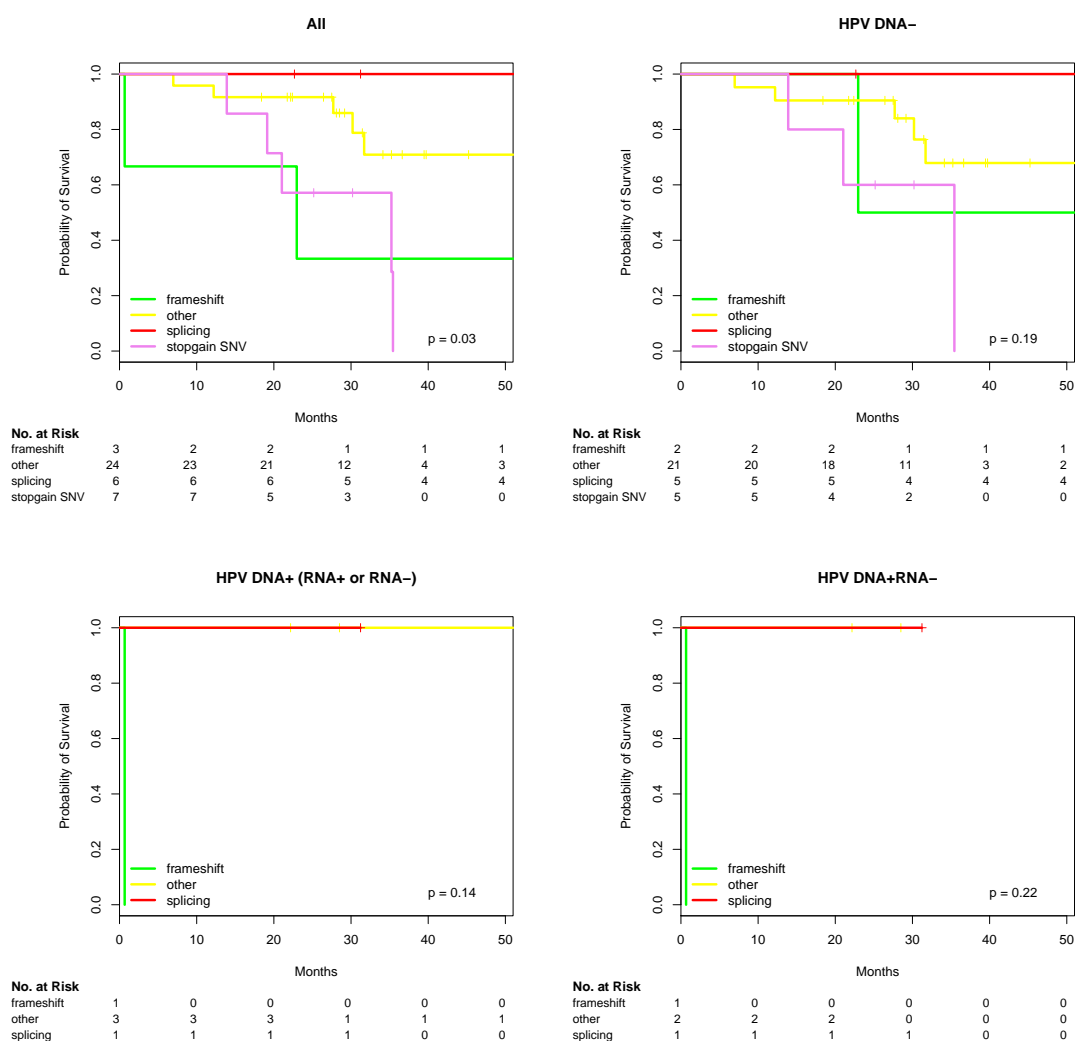
```
##
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
split[cur.subset]other	0.380	2.629	0.0604	2.39
split[cur.subset]splicing	0.152	6.571	0.0138	1.68
split[cur.subset]stopgain SNV	1.553	0.644	0.2450	9.84

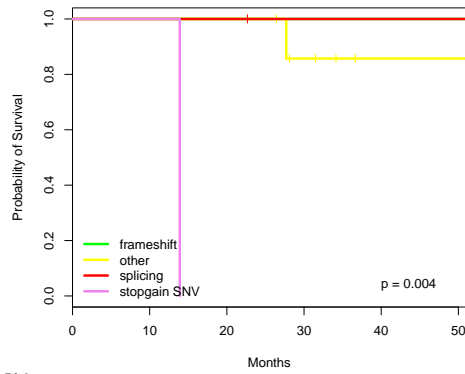
```
##
## Concordance= 0.726 (se = 0.079 )
## Rsquare= 0.174 (max possible= 0.87 )
## Likelihood ratio test= 7.65 on 3 df, p=0.0538
## Wald test = 7.46 on 3 df, p=0.0585
## Score (logrank) test = 9.25 on 3 df, p=0.0261
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 33, number of events= 10
## (125 observations deleted due to missingness)
##
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
split[cur.subset]other	0.0884	1.0924	1.3111	0.07	0.95
split[cur.subset]splicing	-1.1223	0.3255	1.4151	-0.79	0.43
split[cur.subset]stopgain SNV	1.2258	3.4068	1.3650	0.90	0.37

```
##
##                                     exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]other              1.092      0.915    0.0836    14.27
## split[cur.subset]splicing            0.326      3.072    0.0203     5.21
## split[cur.subset]stopgain SNV        3.407      0.294    0.2347    49.46
##
## Concordance= 0.643  (se = 0.09 )
## Rsquare= 0.115   (max possible= 0.833 )
## Likelihood ratio test= 4.05  on 3 df,   p=0.256
## Wald test               = 4.02  on 3 df,   p=0.26
## Score (logrank) test = 4.74  on 3 df,   p=0.192
```



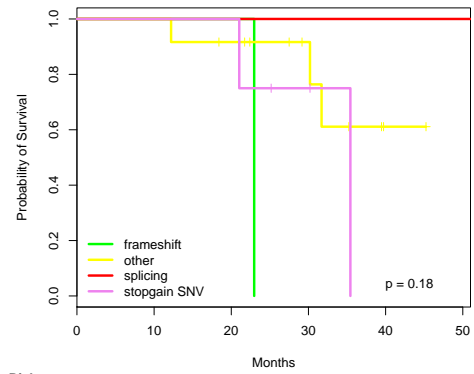
HPV DNA-, UICC I, II, III



No. at Risk

frameshift	1	1	1	1	1	1
other	8	8	8	5	2	2
splicing	4	4	4	3	3	3
stopgain SNV	1	1	0	0	0	0

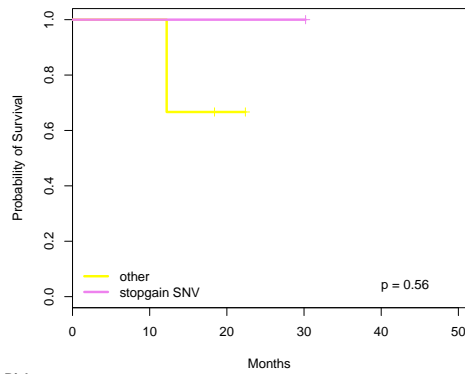
HPV DNA-, UICC IVA



No. at Risk

frameshift	1	1	1	0	0	0
other	12	12	10	6	1	0
splicing	1	1	1	1	1	1
stopgain SNV	4	4	4	2	0	0

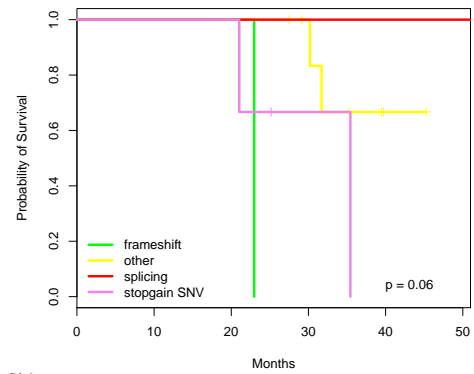
HPV DNA-, UICC IVA, Ther. unimodal



No. at Risk

other	3	3	1	0	0	0
stopgain SNV	1	1	1	1	0	0

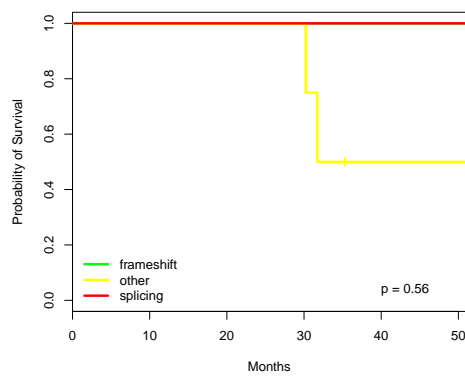
HPV DNA-, UICC IVA, Ther. multimodal



No. at Risk

frameshift	1	1	1	0	0	0
other	8	8	8	6	1	0
splicing	1	1	1	1	1	1
stopgain SNV	3	3	3	1	0	0

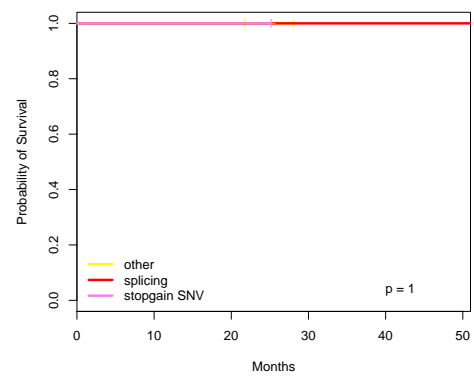
In DNA- Atypical



No. at Risk

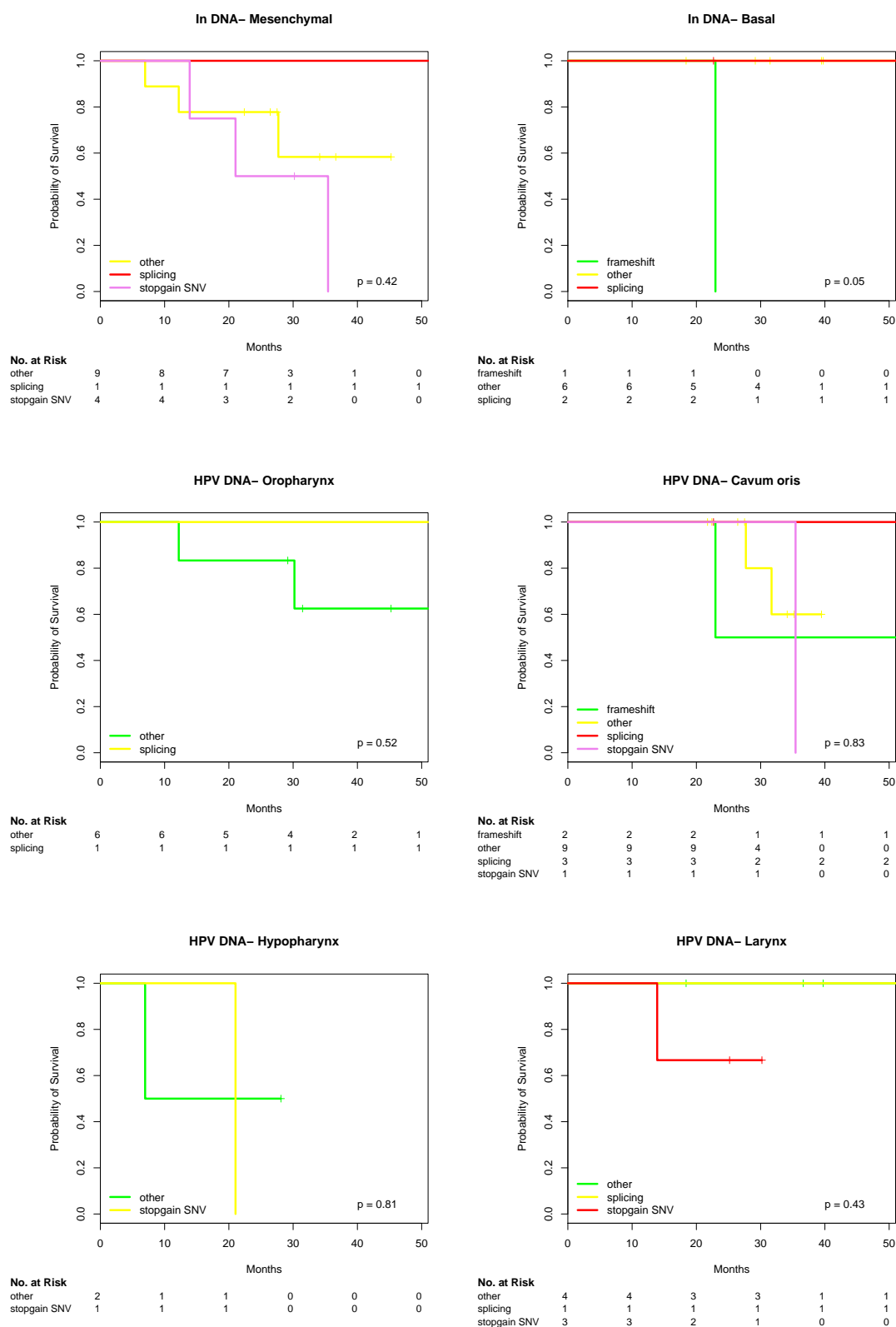
frameshift	1	1	1	1	1	1
other	4	4	4	4	1	1
splicing	1	1	1	1	1	1

In DNA- Classical



No. at Risk

other	2	2	2	0	0	0
splicing	1	1	1	1	1	1
stopgain SNV	1	1	1	0	0	0



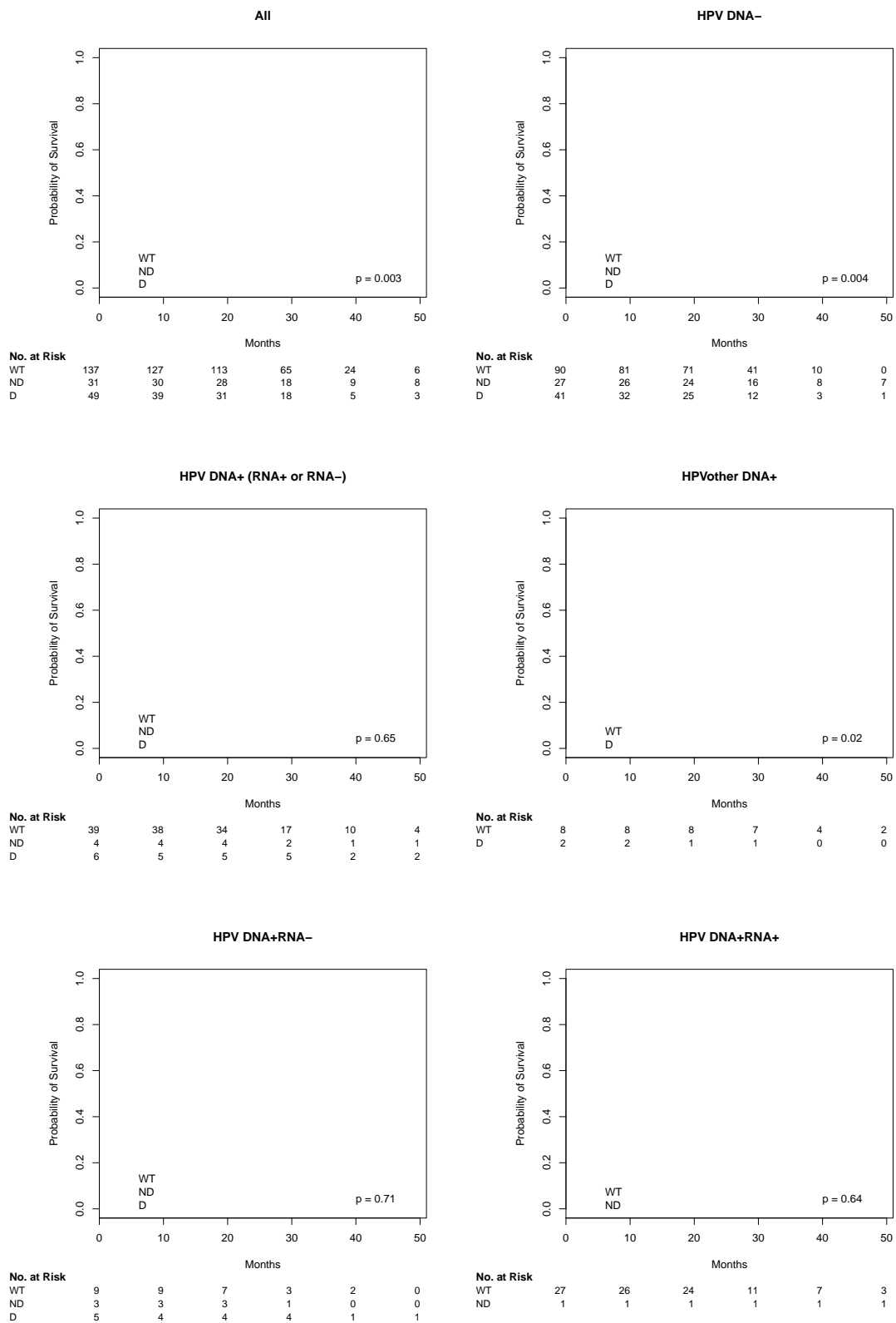
2.32 TP53 (association of mutations in TP53 with survival)

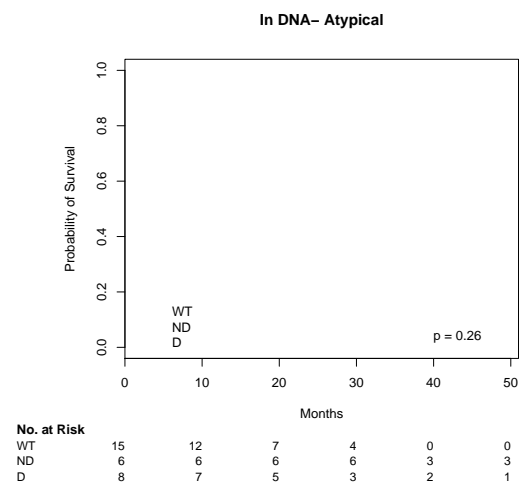
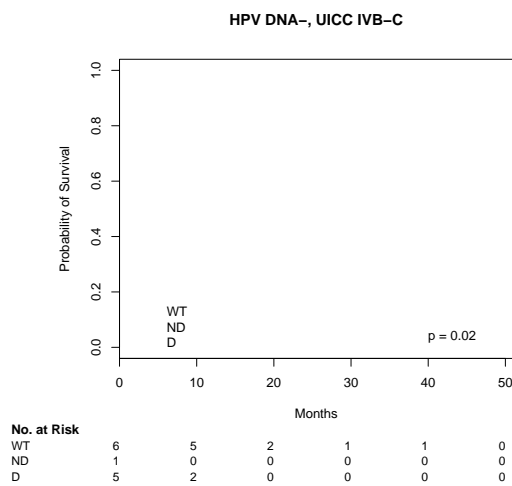
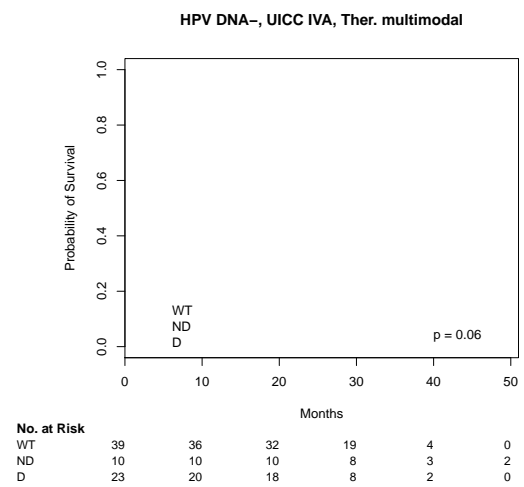
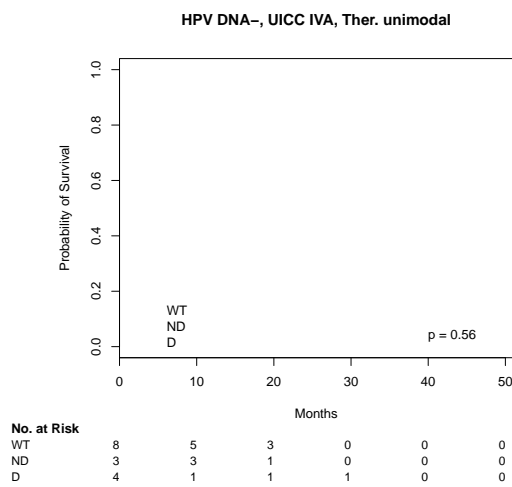
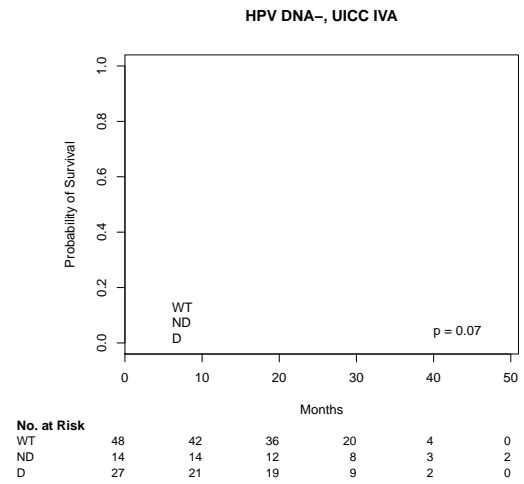
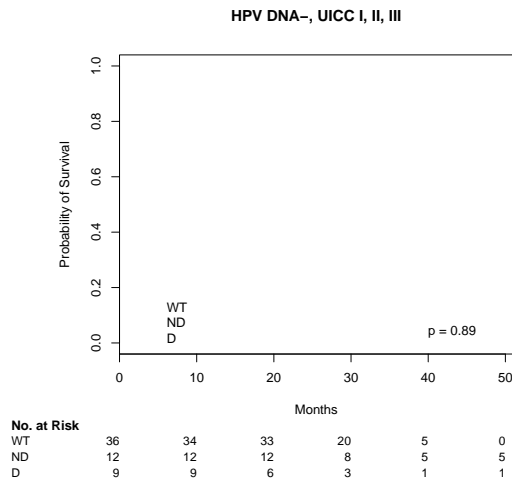
```

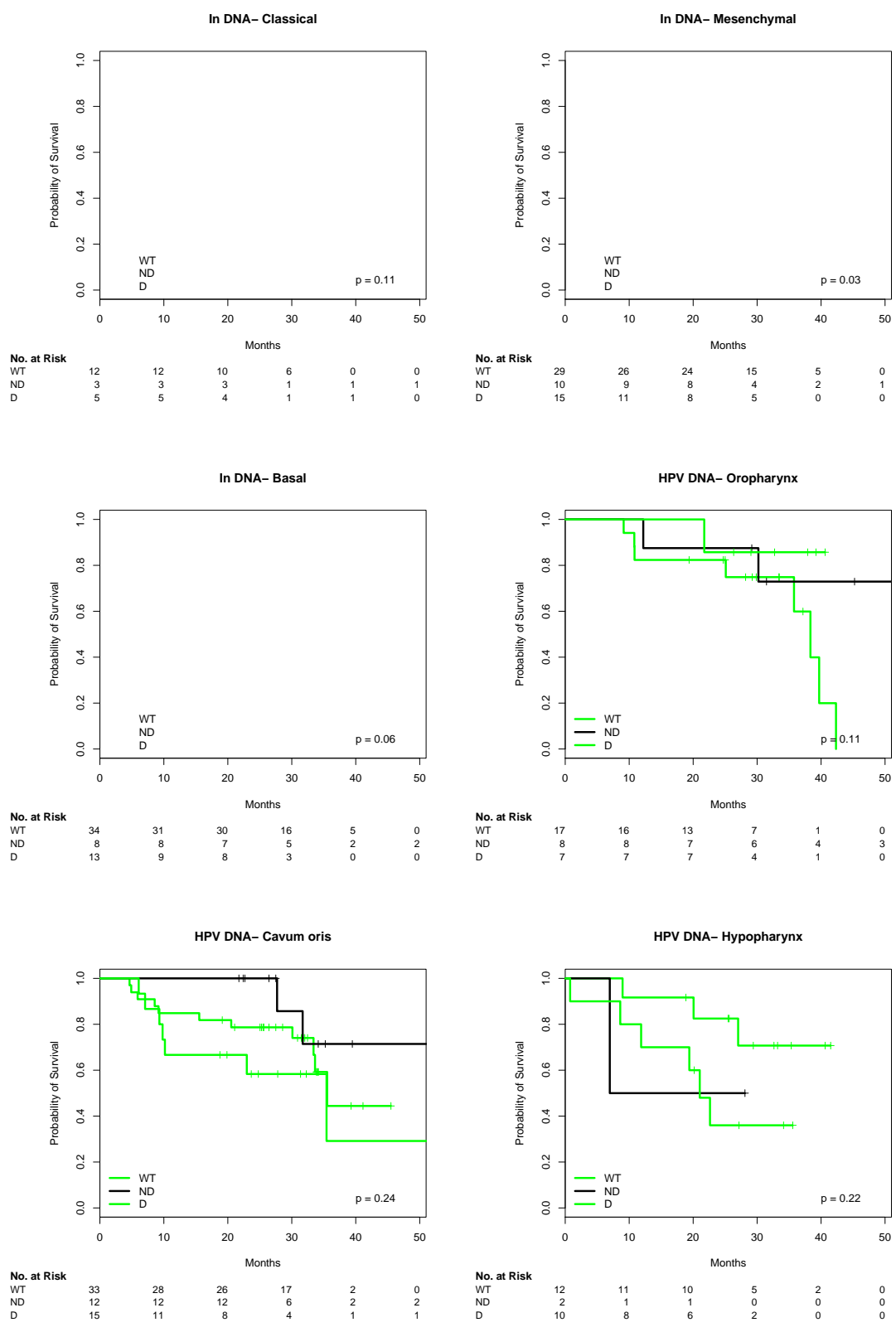
## Error: Attribut 'names' [3] muss dieselbe Länge haben wie der Vektor [2]
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.645      0.524    0.418 -1.55    0.122
## split[cur.subset]D   0.631      1.880    0.260  2.43    0.015 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND      0.524      1.907      0.231      1.19
## split[cur.subset]D      1.880      0.532      1.129      3.13
##
## Concordance= 0.623 (se = 0.033 )
## Rsquare= 0.049 (max possible= 0.954 )
## Likelihood ratio test= 10.9 on 2 df,  p=0.0043
## Wald test               = 10.7 on 2 df,  p=0.00466
## Score (logrank) test = 11.5 on 2 df,  p=0.00321
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.753      0.471    0.464 -1.62    0.105
## split[cur.subset]D   0.659      1.932    0.295  2.23    0.026 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND      0.471      2.122      0.19      1.17
## split[cur.subset]D      1.932      0.518      1.08      3.44
##
## Concordance= 0.626 (se = 0.038 )
## Rsquare= 0.066 (max possible= 0.954 )
## Likelihood ratio test= 10.8 on 2 df,  p=0.00456
## Wald test               = 10.3 on 2 df,  p=0.00573

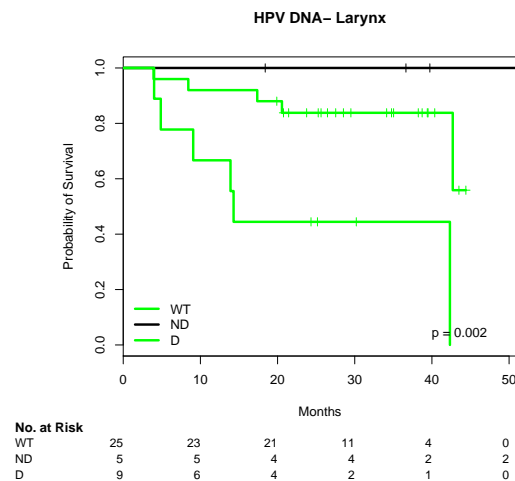
```

Score (logrank) test = 11.2 on 2 df, p=0.00372





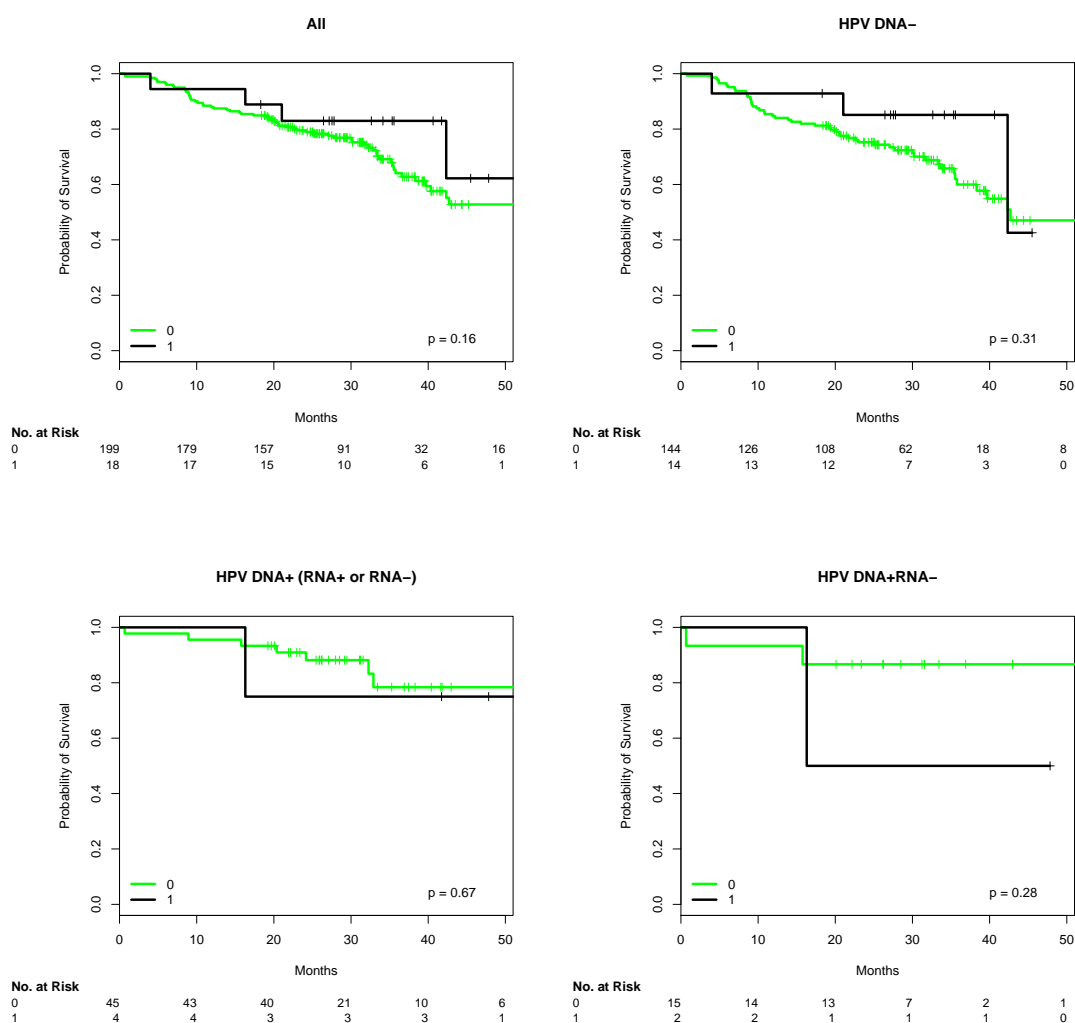


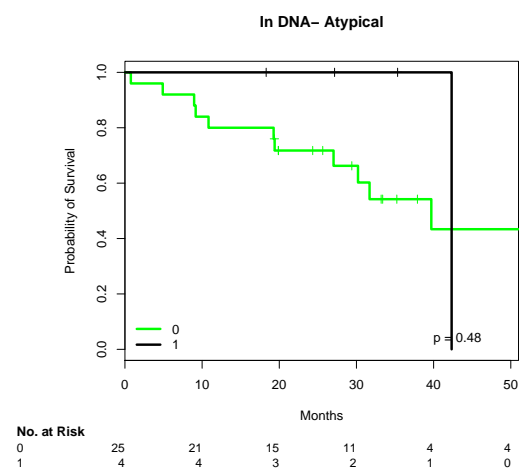
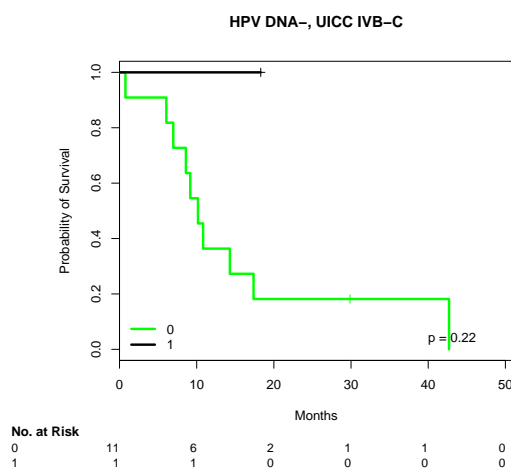
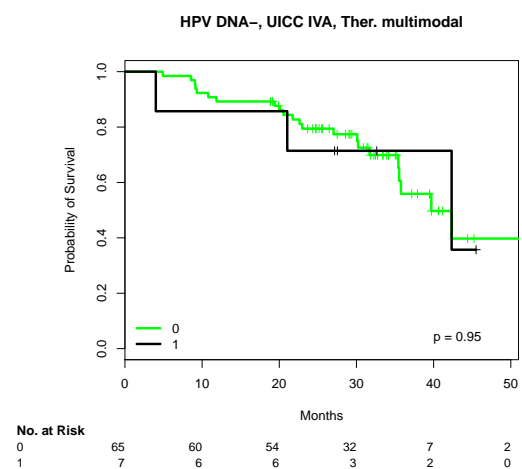
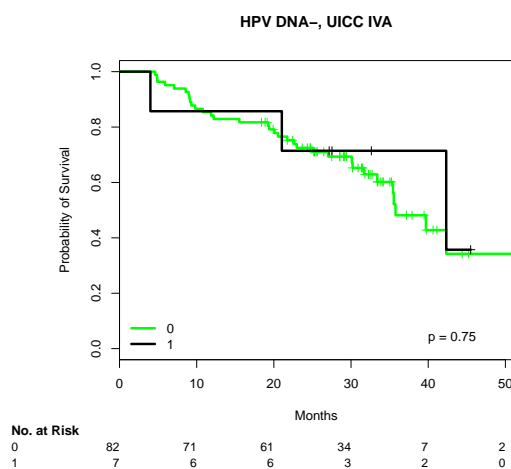
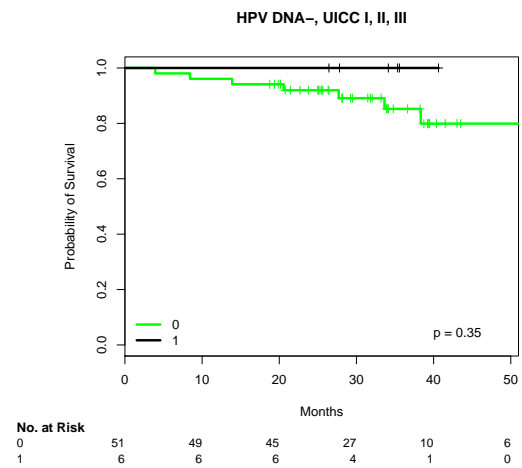
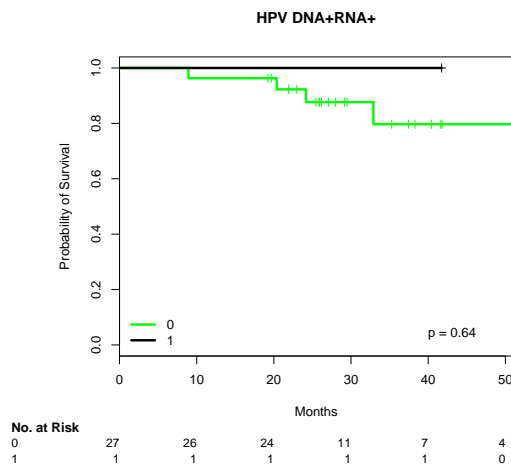


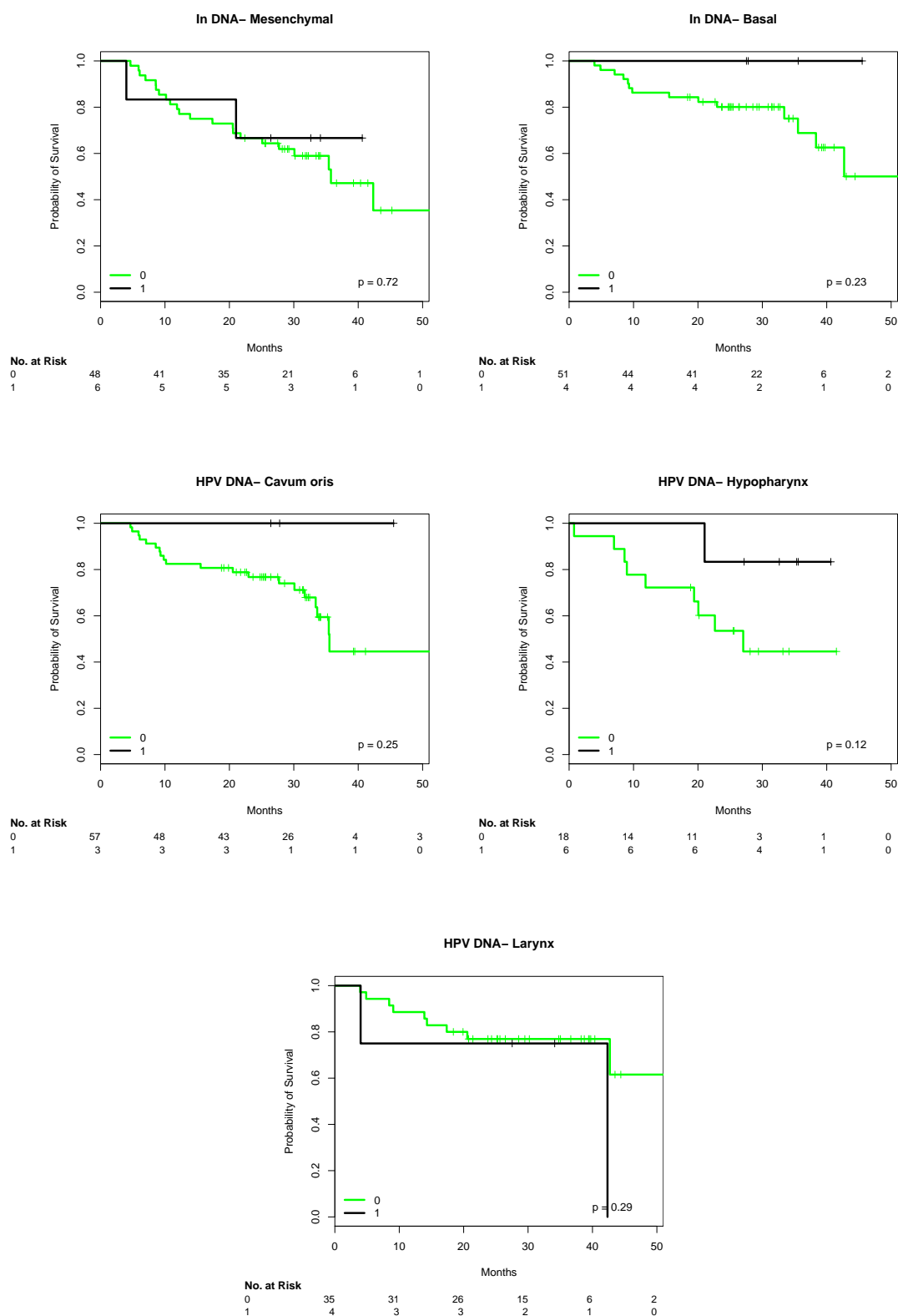
2.33 APC

```
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.708      0.493    0.521 -1.36    0.17
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.493      2.03    0.178    1.37
##
## Concordance= 0.516 (se = 0.019 )
## Rsquare= 0.01 (max possible= 0.954 )
## Likelihood ratio test= 2.27 on 1 df,  p=0.132
## Wald test               = 1.85 on 1 df,  p=0.174
## Score (logrank) test = 1.92 on 1 df,  p=0.166
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
```

```
##
##   n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.586      0.557    0.595 -0.98    0.32
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.557        1.8    0.174    1.79
##
## Concordance= 0.523 (se = 0.022 )
## Rsquare= 0.007 (max possible= 0.954 )
## Likelihood ratio test= 1.16 on 1 df,  p=0.282
## Wald test               = 0.97 on 1 df,  p=0.325
## Score (logrank) test = 1 on 1 df,  p=0.318
```





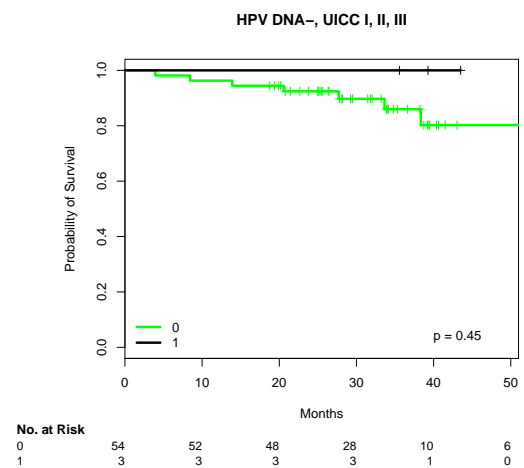
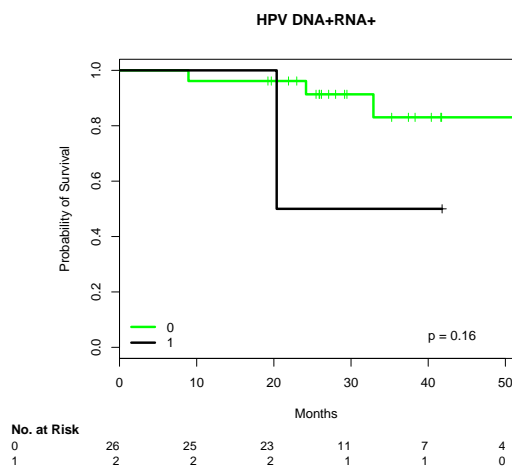
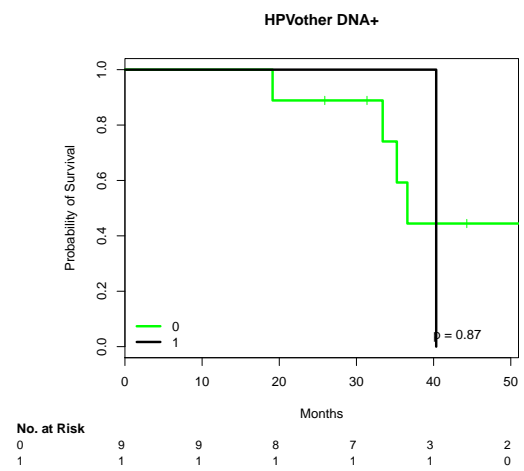
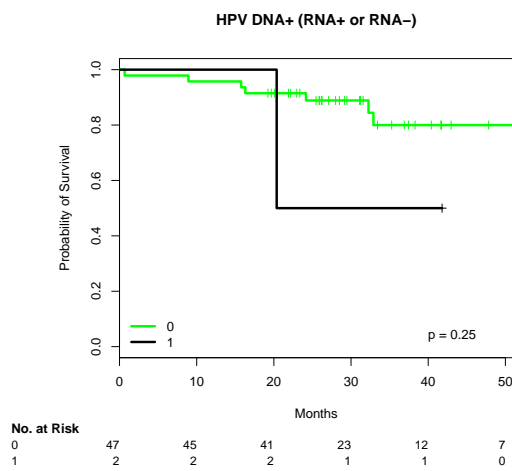
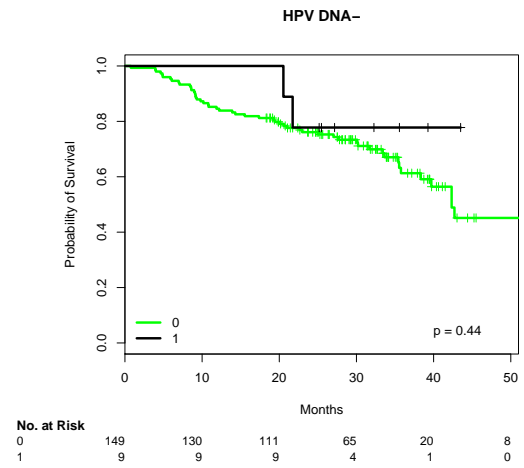
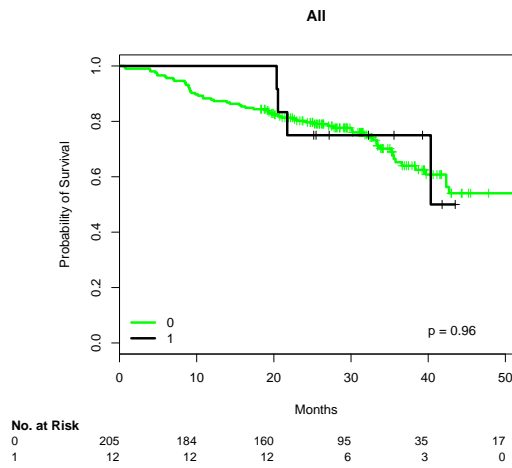


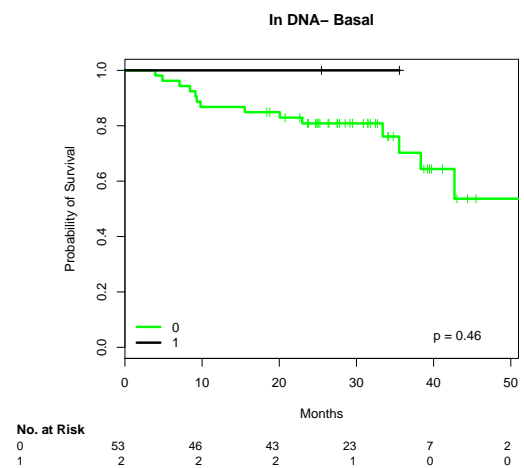
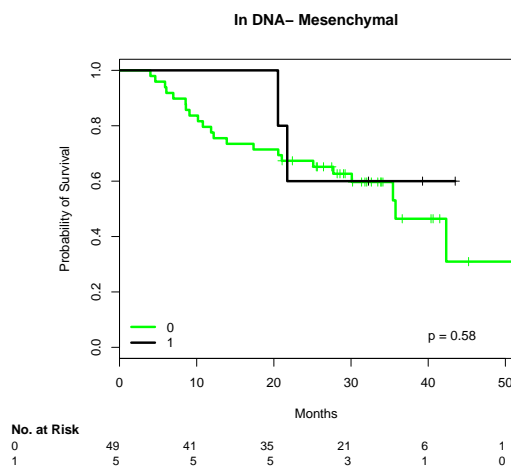
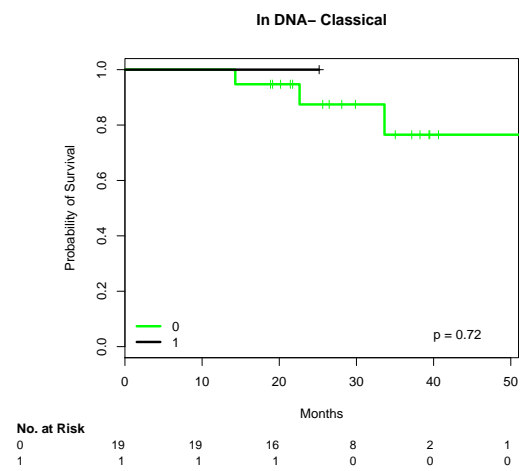
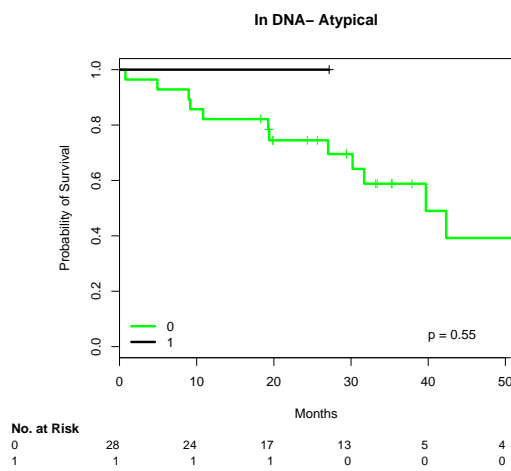
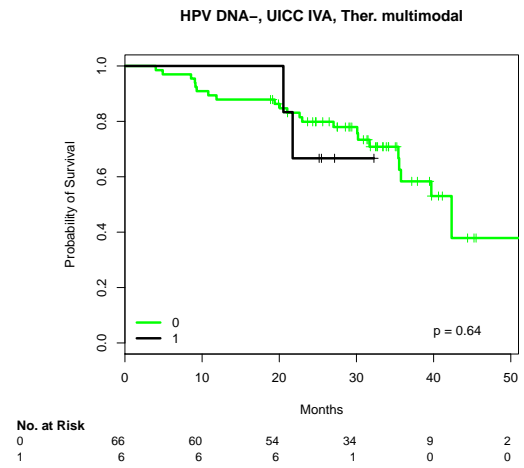
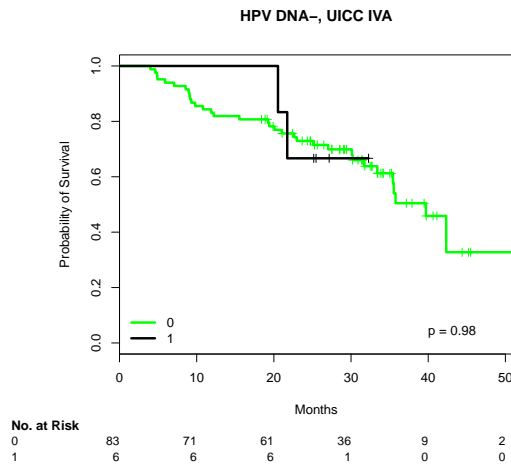
2.34 CDKN2A

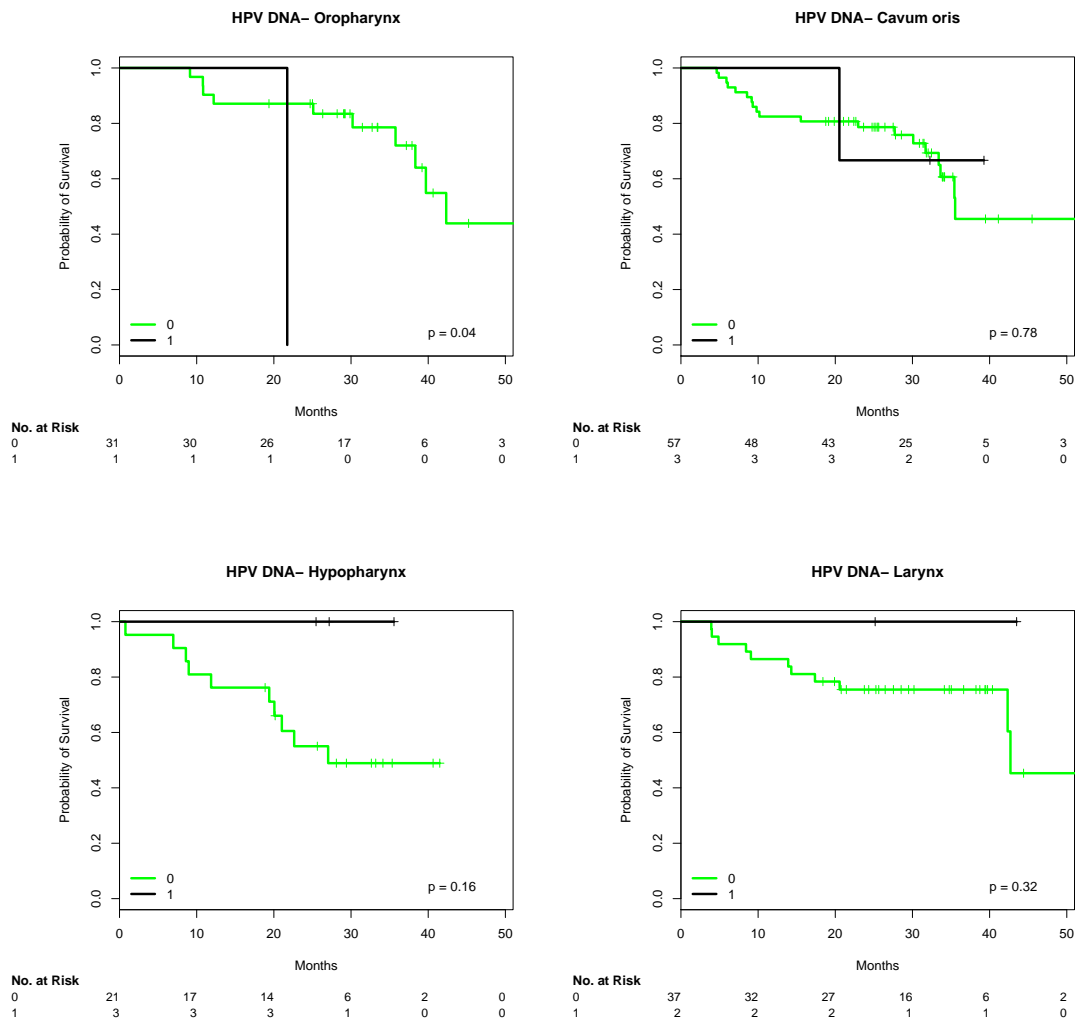
```

## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.0259    0.9744   0.5162 -0.05    0.96
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.974      1.03    0.354    2.68
##
## Concordance= 0.504 (se = 0.016 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0 on 1 df, p=0.96
## Wald test = 0 on 1 df, p=0.96
## Score (logrank) test = 0 on 1 df, p=0.96
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.555    0.574   0.721 -0.77    0.44
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.574      1.74    0.14    2.36
##
## Concordance= 0.512 (se = 0.018 )
## Rsquare= 0.004 (max possible= 0.954 )
## Likelihood ratio test= 0.71 on 1 df, p=0.4
## Wald test = 0.59 on 1 df, p=0.441
## Score (logrank) test = 0.61 on 1 df, p=0.435

```



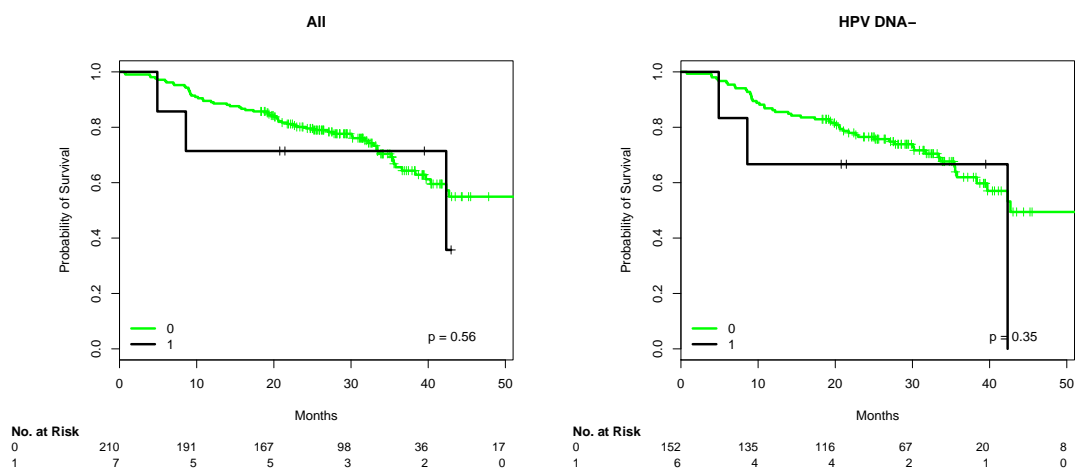


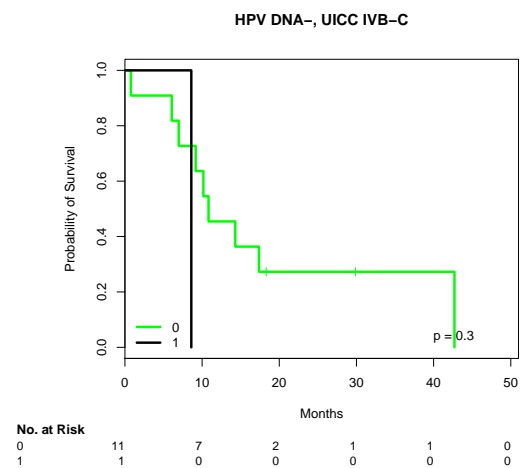
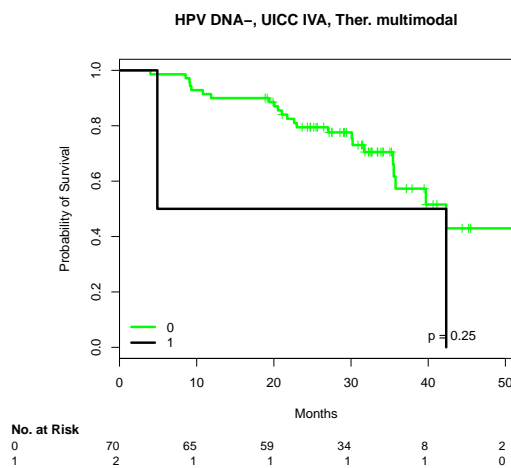
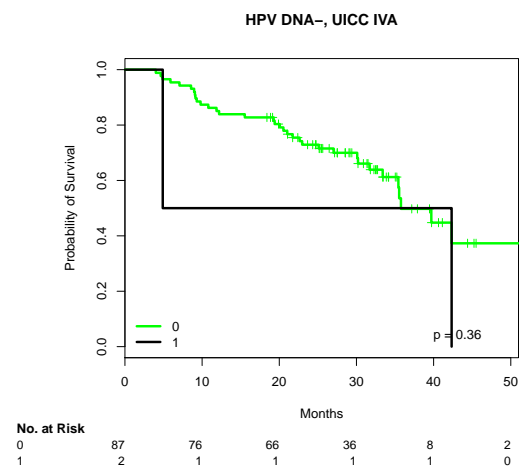
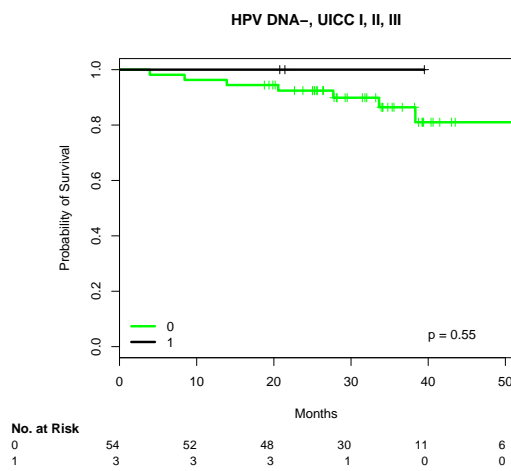
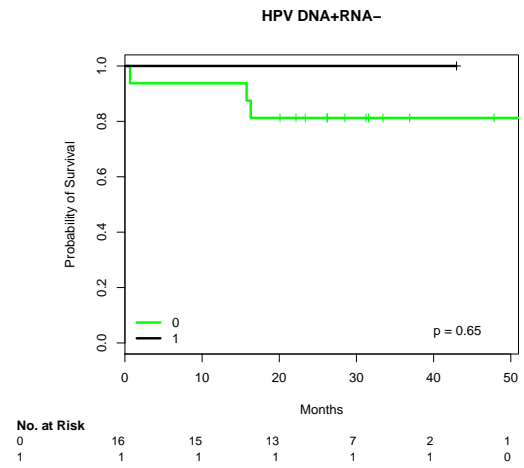
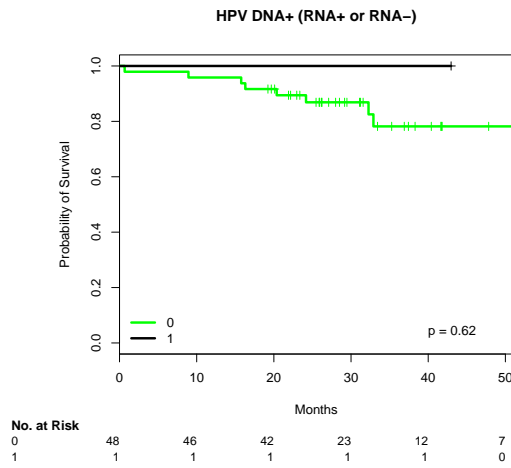


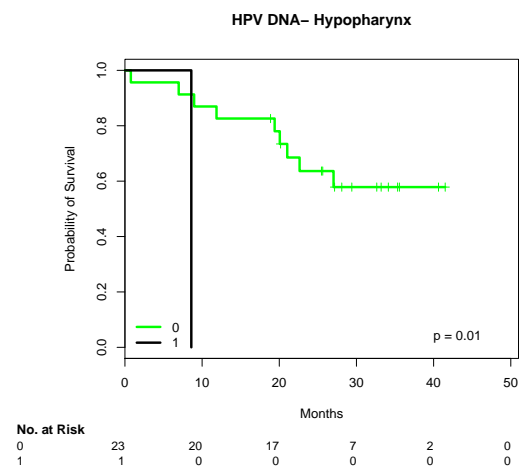
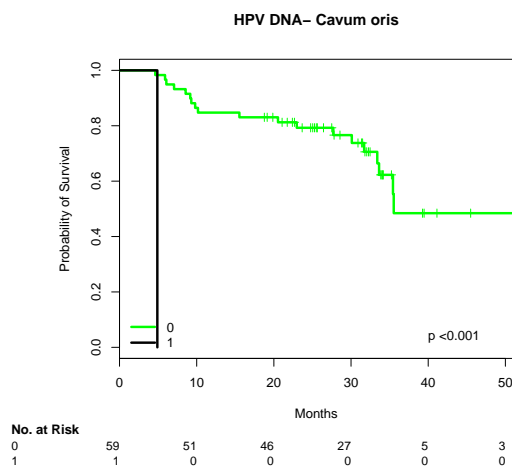
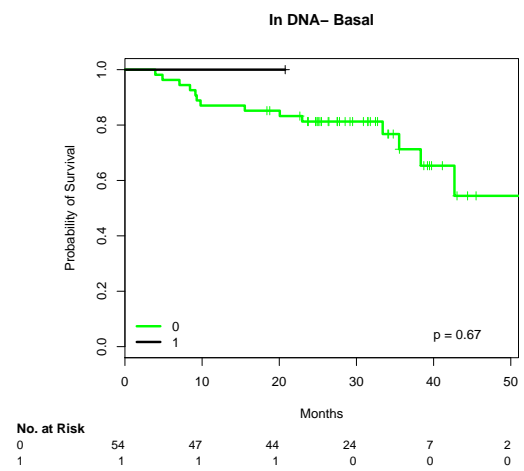
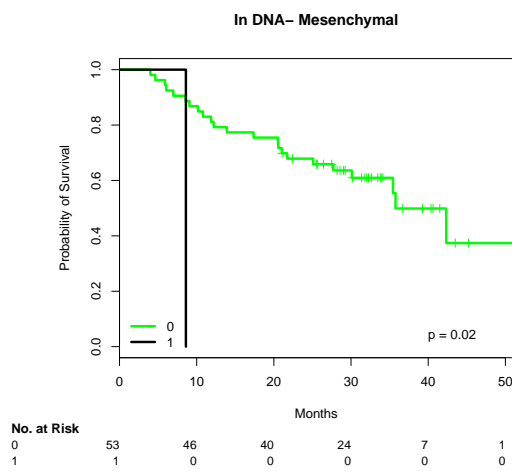
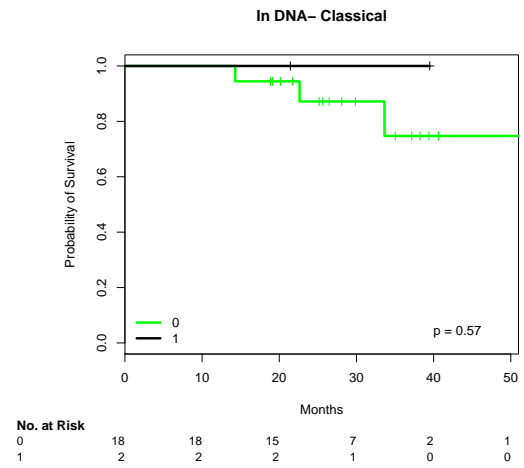
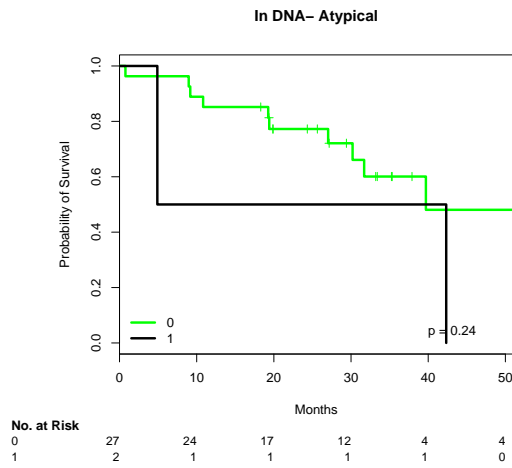
2.35 PIK3CA

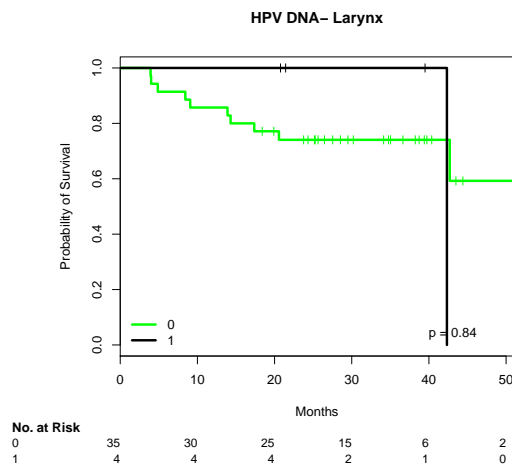
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)  z Pr(>|z|)
## split[cur.subset] 0.354      1.425    0.592 0.6    0.55
##
```

```
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.42      0.702      0.446      4.55
##
## Concordance= 0.508 (se = 0.011 )
## Rsquare= 0.001 (max possible= 0.954 )
## Likelihood ratio test= 0.32 on 1 df, p=0.571
## Wald test = 0.36 on 1 df, p=0.55
## Score (logrank) test = 0.36 on 1 df, p=0.548
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.563      1.757      0.596 0.95      0.34
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.76      0.569      0.546      5.65
##
## Concordance= 0.511 (se = 0.013 )
## Rsquare= 0.005 (max possible= 0.954 )
## Likelihood ratio test= 0.76 on 1 df, p=0.383
## Wald test = 0.89 on 1 df, p=0.345
## Score (logrank) test = 0.92 on 1 df, p=0.338
```





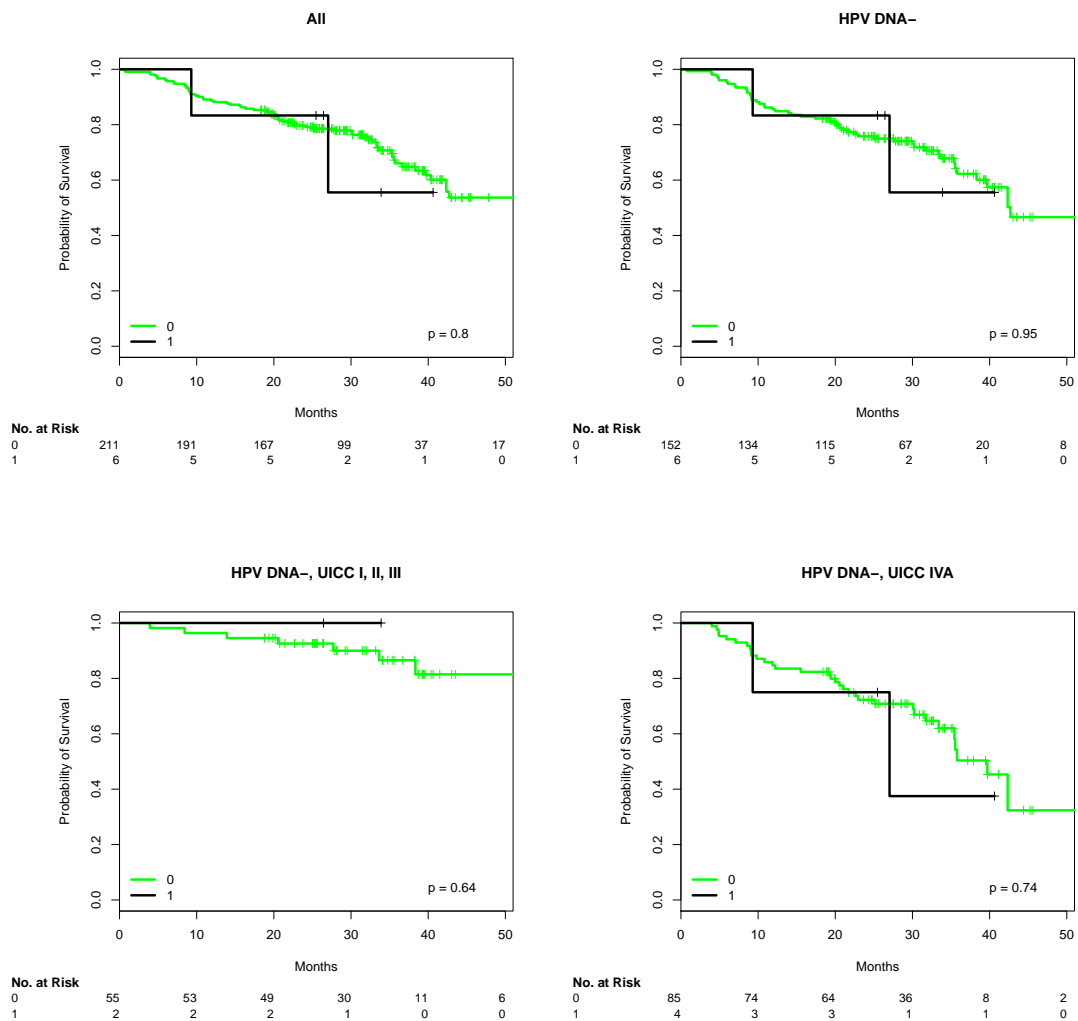


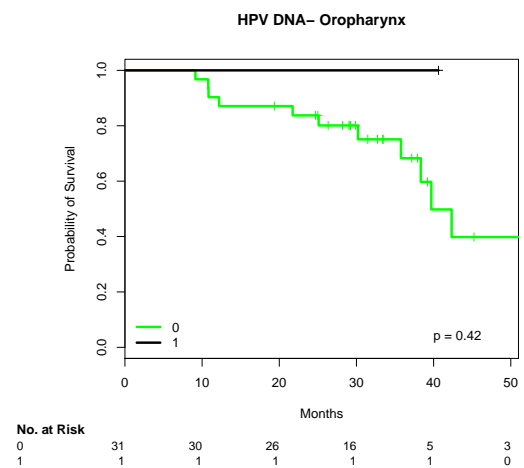
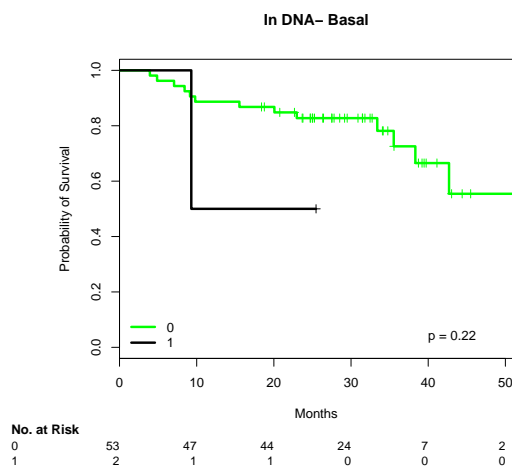
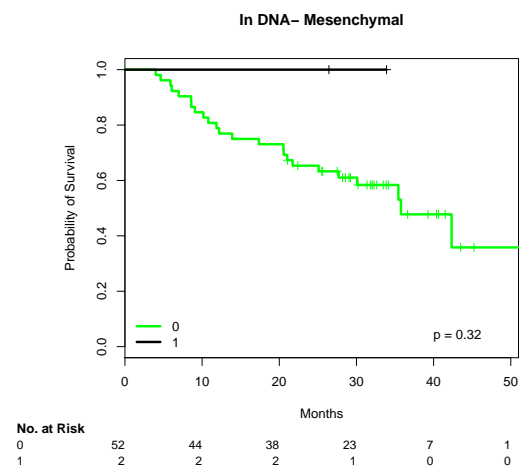
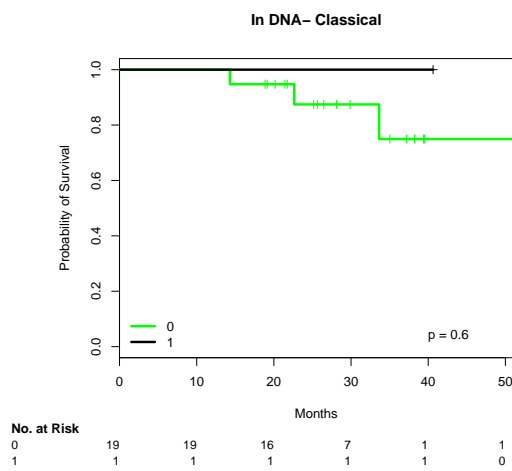
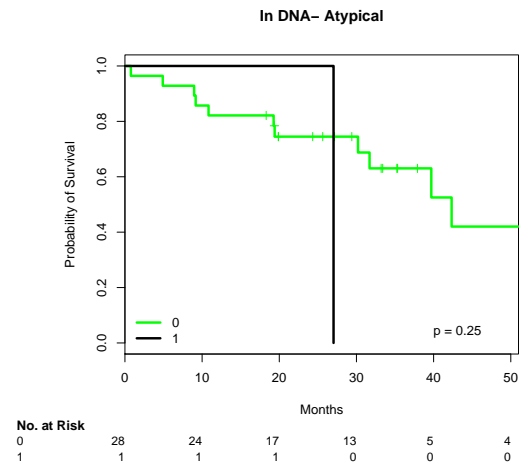
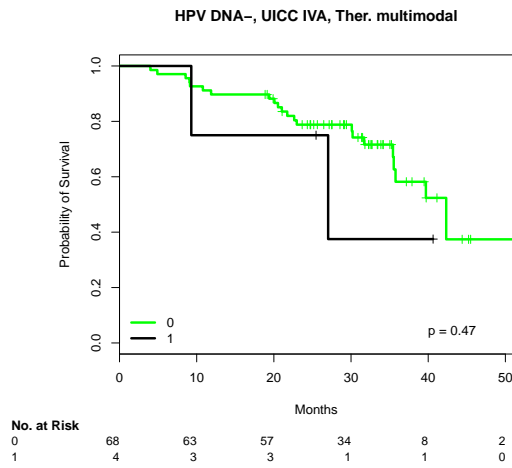


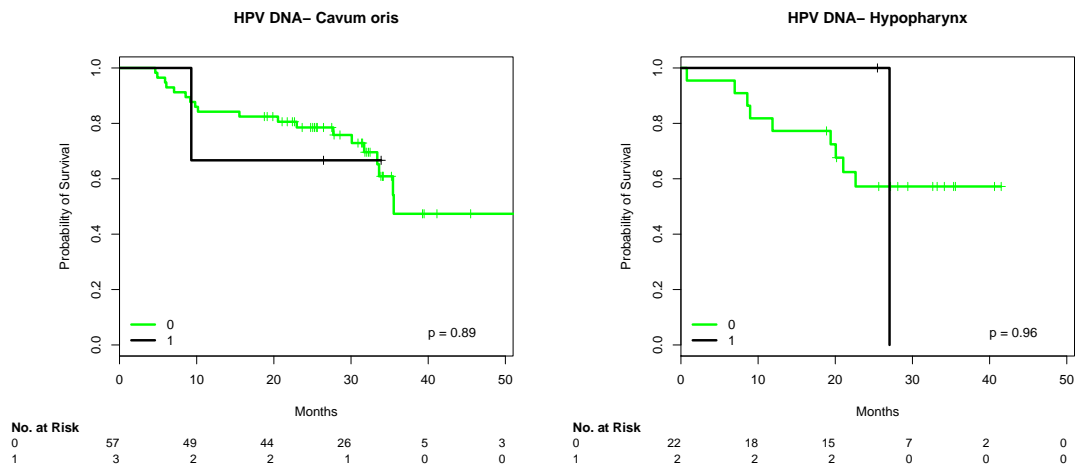
2.36 SMO

```
## 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
## 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= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.182    1.200    0.719 0.25      0.8
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.2      0.833    0.293    4.91
##
## Concordance= 0.502 (se = 0.011 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.06 on 1 df,  p=0.805
## Wald test               = 0.06 on 1 df,  p=0.8
## Score (logrank) test = 0.06 on 1 df,  p=0.799
##
##
## #####
```

```
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.0437    1.0447   0.7220 0.06    0.95
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.04      0.957   0.254    4.3
##
## Concordance= 0.5 (se = 0.015 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0 on 1 df, p=0.952
## Wald test = 0 on 1 df, p=0.952
## Score (logrank) test = 0 on 1 df, p=0.952
```



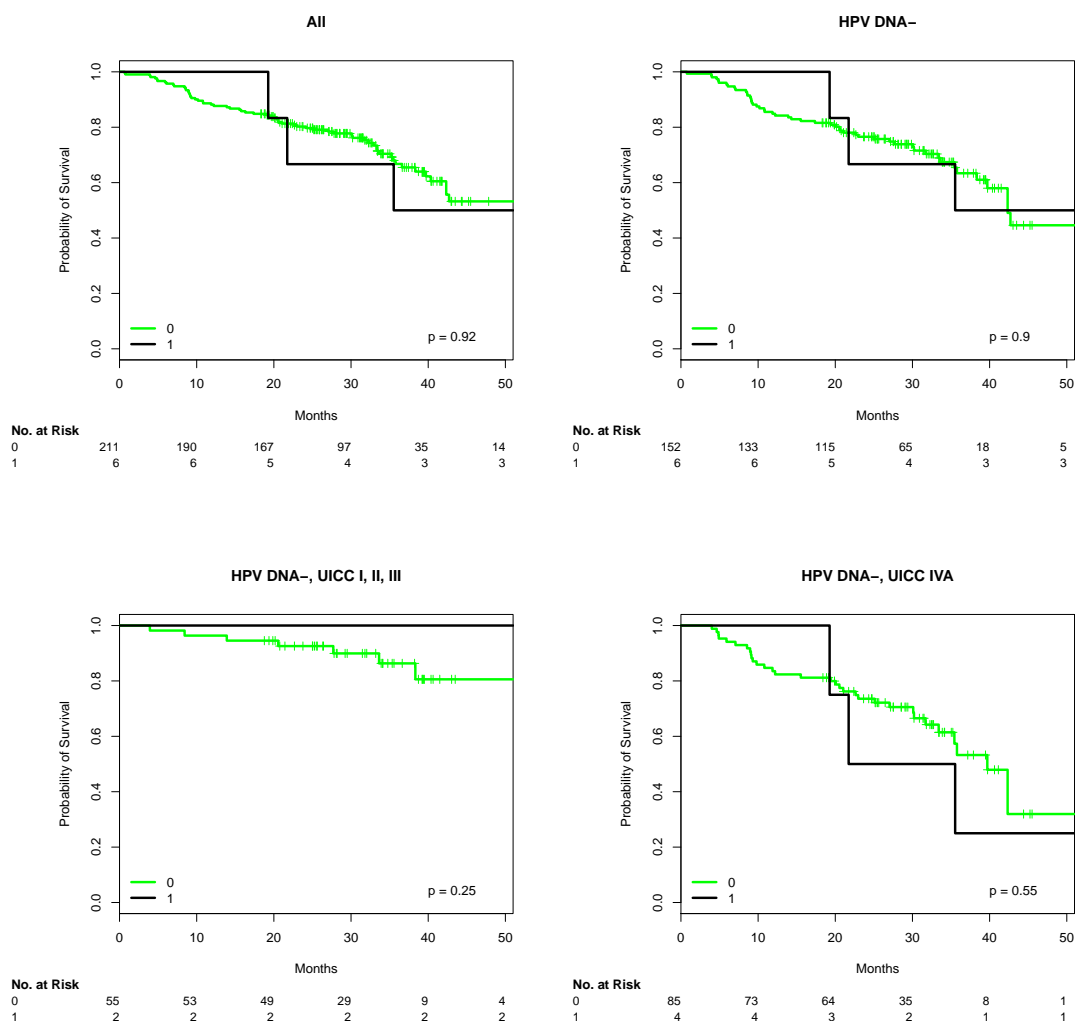


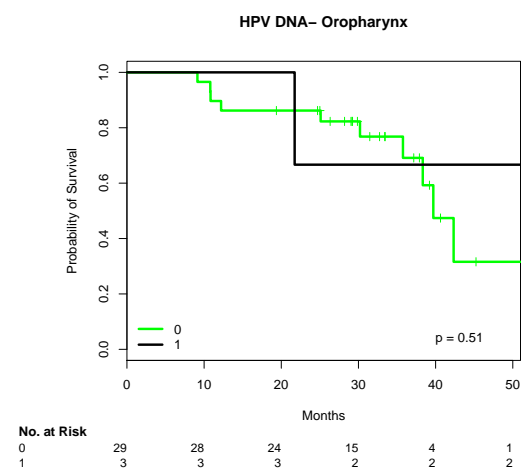
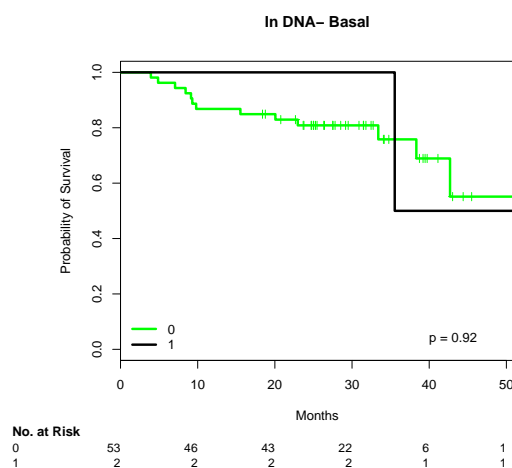
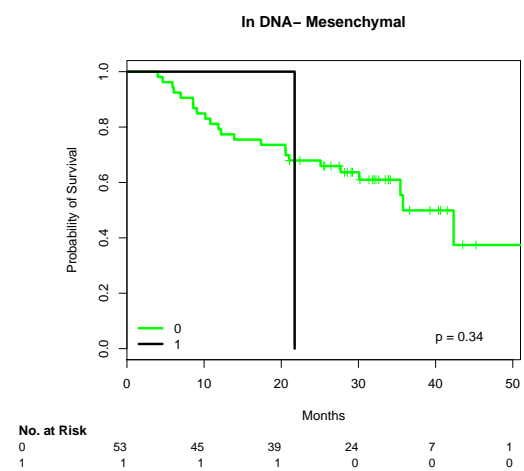
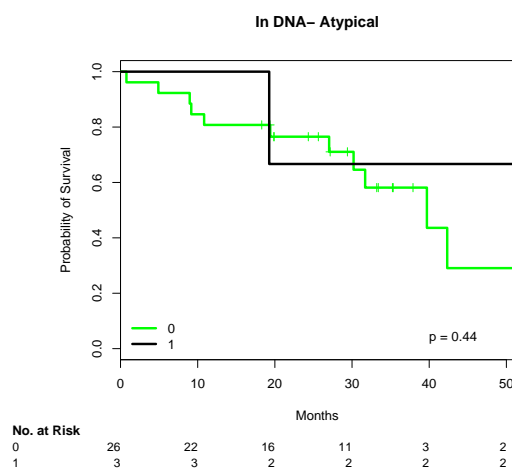
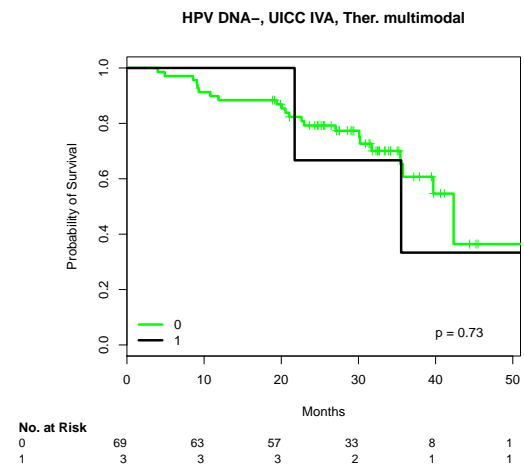
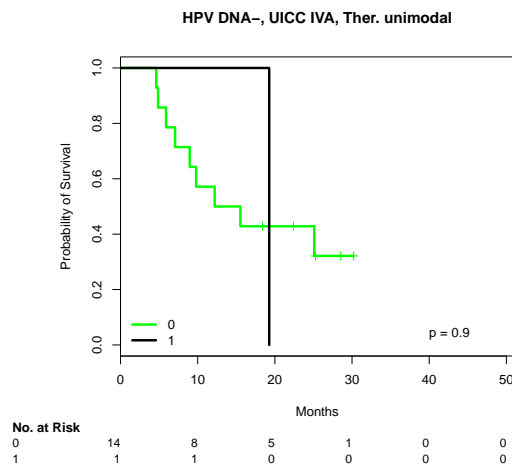


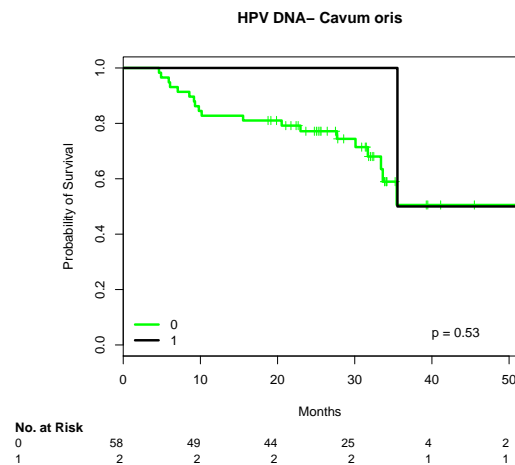
2.37 NOTCH1

```
## 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
## 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= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.0539   0.9476  0.5424 -0.1    0.92
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]    0.948      1.06  0.327    2.74
##
## Concordance= 0.497 (se = 0.012 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.01 on 1 df, p=0.92
## Wald test = 0.01 on 1 df, p=0.921
## Score (logrank) test = 0.01 on 1 df, p=0.921
##
##
```

```
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.0757    0.9271   0.5597 -0.14    0.89
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.927      1.08    0.309    2.78
##
## Concordance= 0.5  (se = 0.015 )
## Rsquare= 0  (max possible= 0.954 )
## Likelihood ratio test= 0.02  on 1 df,   p=0.891
## Wald test               = 0.02  on 1 df,   p=0.892
## Score (logrank) test = 0.02  on 1 df,   p=0.892
```





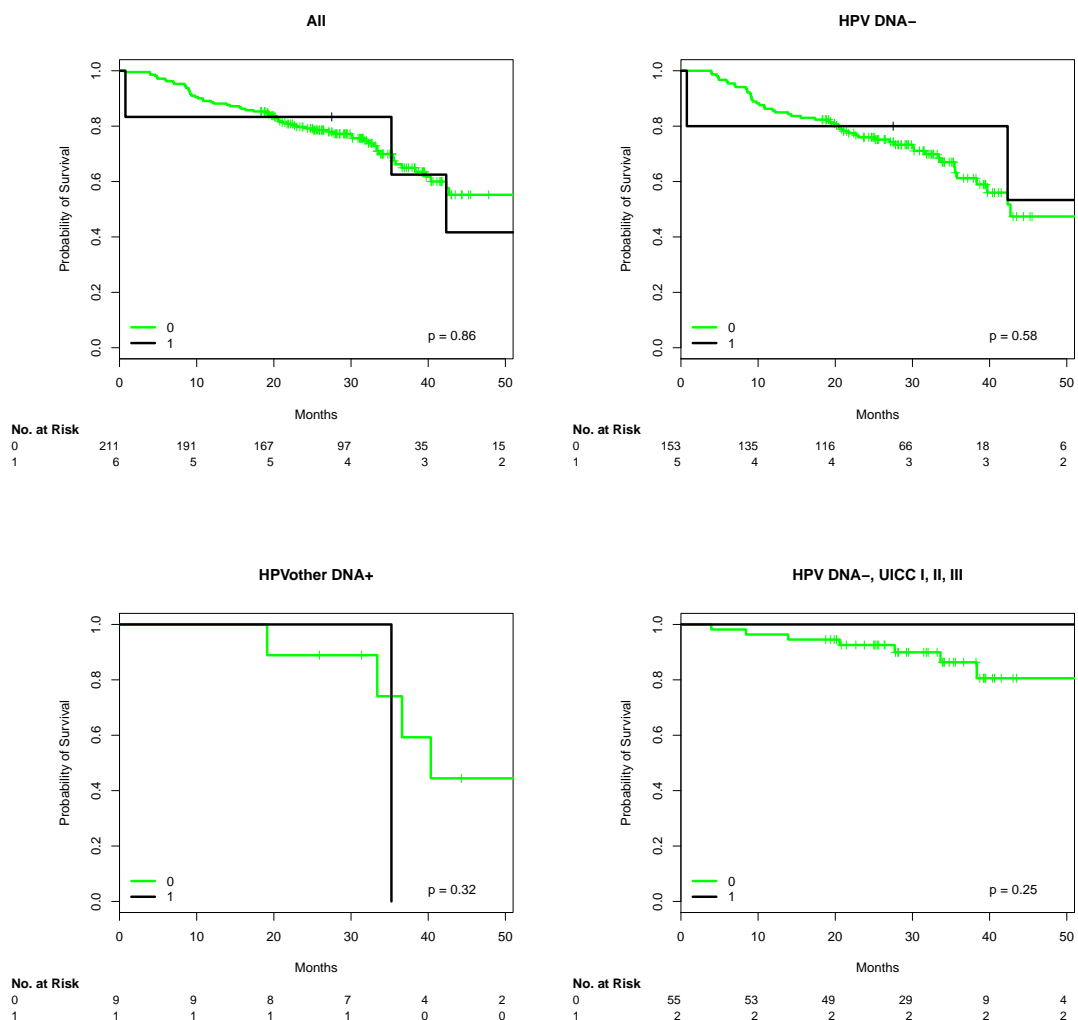


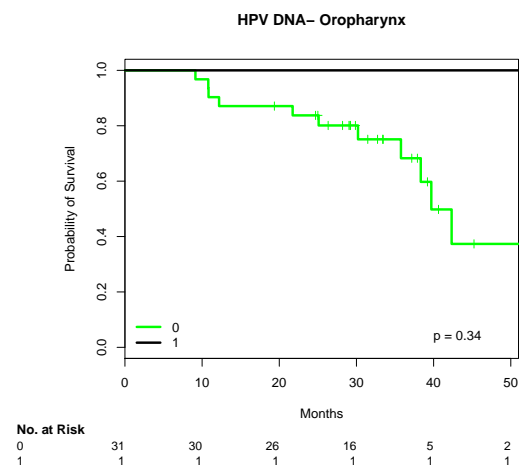
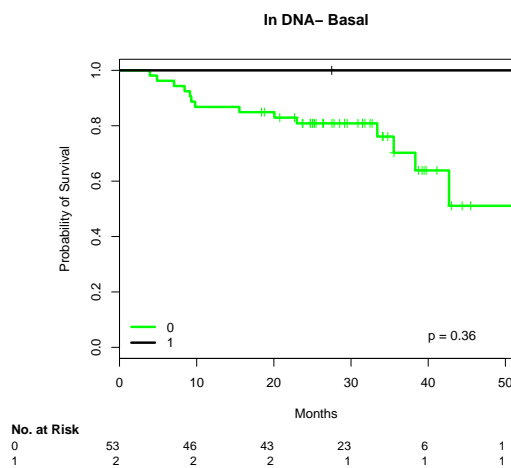
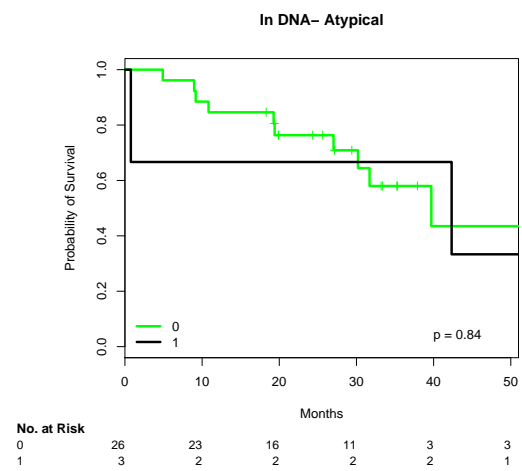
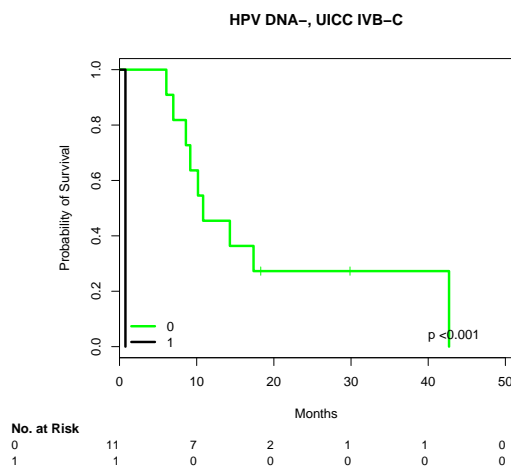
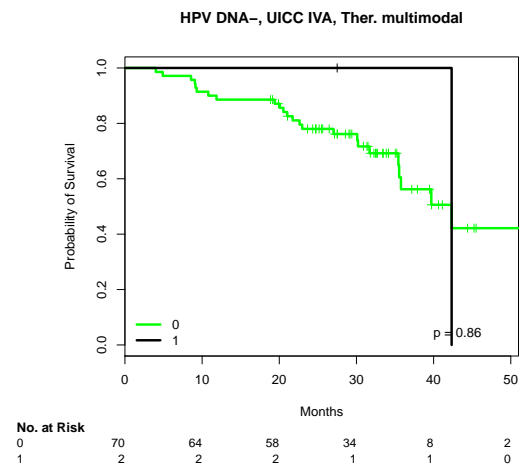
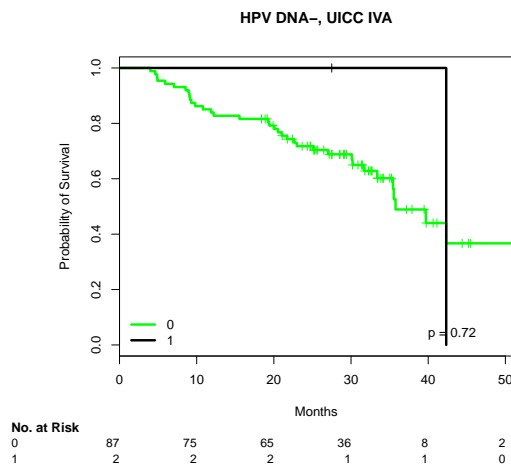
2.38 STK11

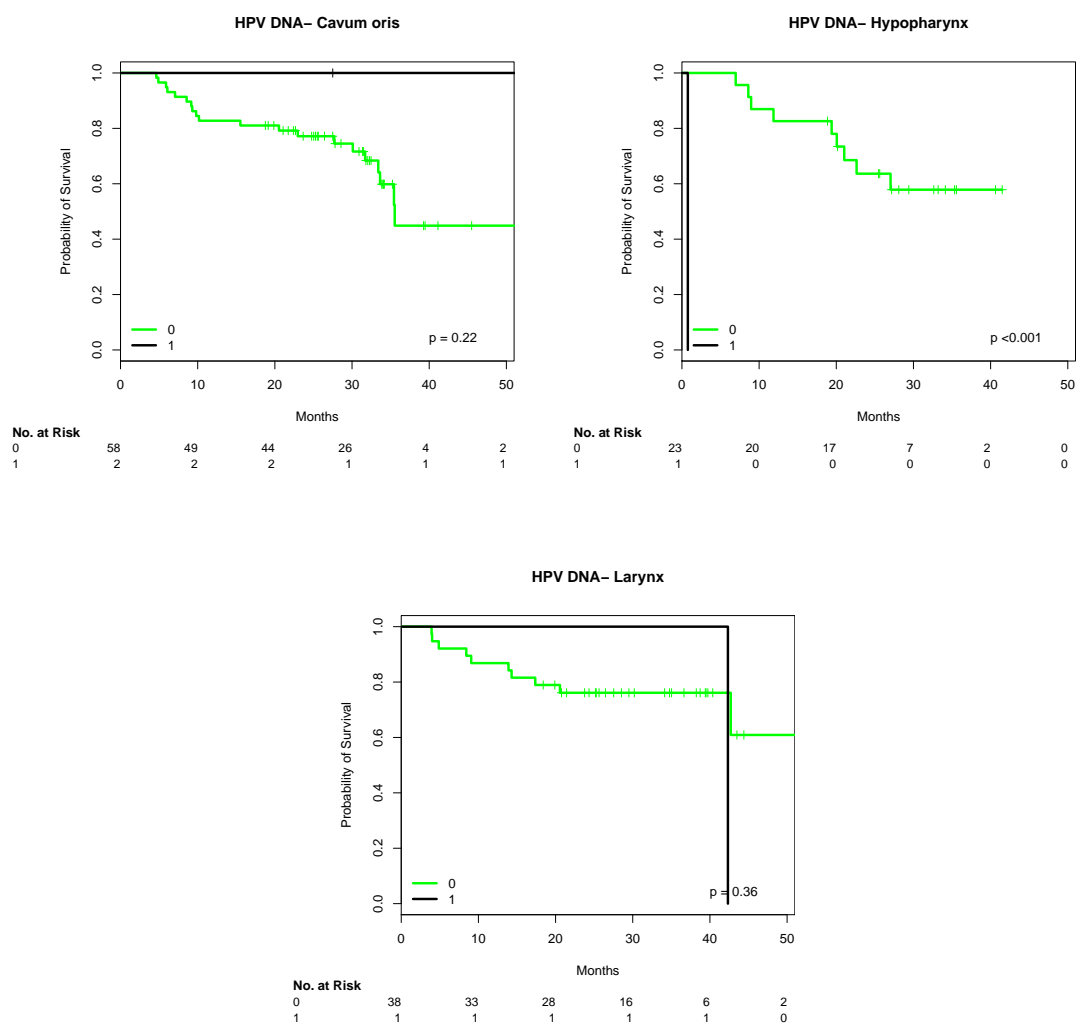
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.100      0.905   0.605 -0.17    0.87
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.905        1.11    0.277    2.96
##
## Concordance= 0.5 (se = 0.011 )
## Rsquare= 0 (max possible= 0.954 )
## Likelihood ratio test= 0.03 on 1 df,  p=0.867
## Wald test               = 0.03 on 1 df,  p=0.869
## Score (logrank) test = 0.03 on 1 df,  p=0.869
##
##
## #####
## Cox model in HPV DNA-
```



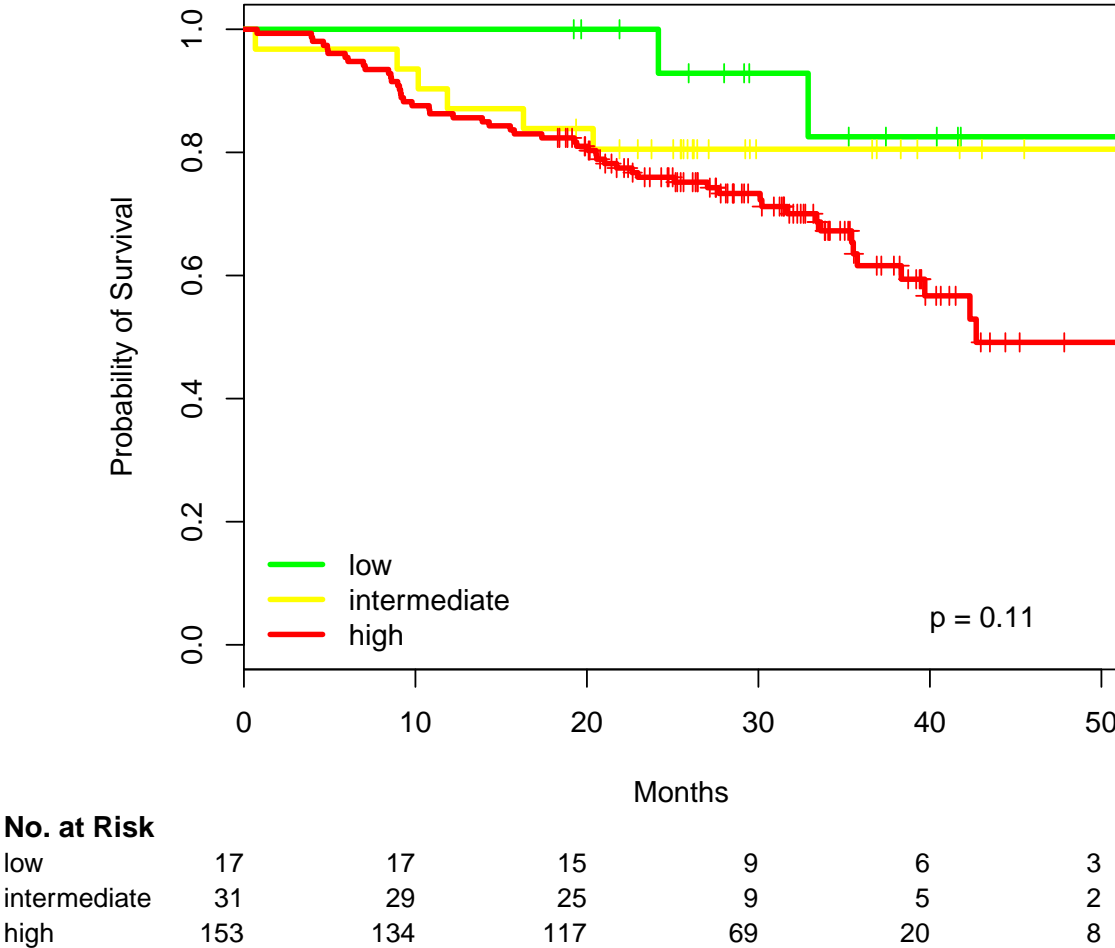
```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.394      0.674    0.742 -0.53      0.6
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.674      1.48    0.157      2.89
##
## Concordance= 0.502 (se = 0.013 )
## Rsquare= 0.002 (max possible= 0.954 )
## Likelihood ratio test= 0.31 on 1 df,  p=0.575
## Wald test               = 0.28 on 1 df,  p=0.596
## Score (logrank) test = 0.28 on 1 df,  p=0.594
```







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



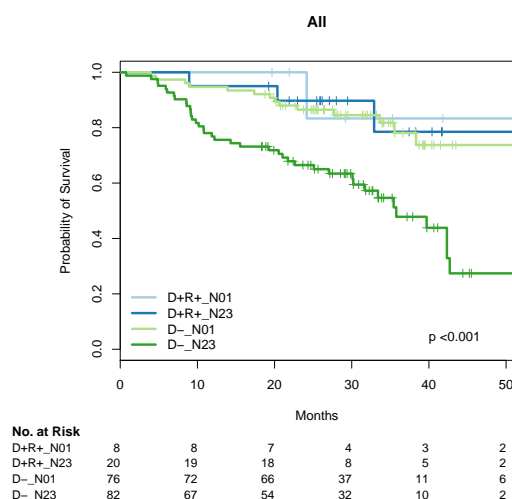
3 Question of whether the lymph node metastases in HPV- and in HPV+ are different.

3.1 3 groups, in which die lymph node metastases co-occur with HPV (DNA+ RNA+), IR (immune response phenotype) or TP53 mutations.

Error: There is only 1 group
Error: There is only 1 group

3.2 Interaction of HPV16 DNA RNA with N0-N1

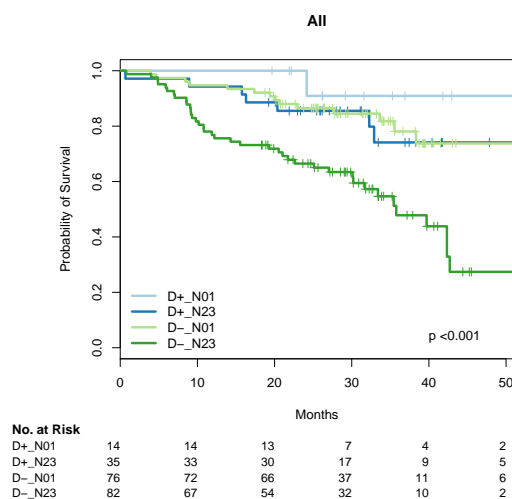
```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 186, number of events= 59
##      (31 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+R+_N23 0.325      1.384    1.155 0.28    0.779
## split[cur.subset]D-_N01   0.560      1.751    1.034 0.54    0.588
## split[cur.subset]D-_N23   1.688      5.407    1.014 1.66    0.096 .
## ---
## 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      1.38      0.723    0.144    13.3
## split[cur.subset]D-_N01       1.75      0.571    0.231    13.3
## split[cur.subset]D-_N23       5.41      0.185    0.742    39.4
##
## Concordance= 0.65 (se = 0.038 )
## Rsquare= 0.105 (max possible= 0.947 )
## Likelihood ratio test= 20.7 on 3 df,  p=0.000121
## Wald test               = 18.6 on 3 df,  p=0.000329
## Score (logrank) test = 21.1 on 3 df,  p=0.000101
```



3.3 Interaction of HPV16 DNA RNA status with N0-N1

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 207, number of events= 66
```

```
##      (10 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 1.14      3.13      1.06 1.08      0.282
## split[cur.subset]D-_N01 1.09      2.97      1.03 1.05      0.293
## split[cur.subset]D-_N23 2.22      9.21      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+_N23      3.13      0.319      0.391      25.1
## split[cur.subset]D-_N01      2.97      0.337      0.391      22.5
## split[cur.subset]D-_N23      9.21      0.109      1.265      67.1
##
## Concordance= 0.654  (se = 0.037 )
## Rsquare= 0.108   (max possible= 0.947 )
## Likelihood ratio test= 23.8  on 3 df,   p=2.79e-05
## Wald test            = 21.1  on 3 df,   p=0.000101
## Score (logrank) test = 24.4  on 3 df,   p=2.02e-05
```



3.4 Interaction of N0-N1 with TP53 Mut

```
## 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
## 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
## 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
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients

## Error: No (non-missing) observations

## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 66
## (10 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 1.14      3.13      1.06 1.08    0.282
## split[cur.subset]D-_N01 1.09      2.97      1.03 1.05    0.293
## split[cur.subset]D-_N23 2.22      9.21      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+_N23      3.13      0.319      0.391      25.1
## split[cur.subset]D-_N01      2.97      0.337      0.391      22.5
## split[cur.subset]D-_N23      9.21      0.109      1.265      67.1
##
## Concordance= 0.654 (se = 0.037 )
## Rsquare= 0.108 (max possible= 0.947 )
## Likelihood ratio test= 23.8 on 3 df, p=2.79e-05
## Wald test               = 21.1 on 3 df, p=0.000101
## Score (logrank) test = 24.4 on 3 df, p=2.02e-05
##
##
## #####
## Cox model in HPV DNA-

## Error: No (non-missing) observations

## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 207, number of events= 66

```

```
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 1.14      3.13      1.06 1.08      0.282
## split[cur.subset]D-_N01 1.09      2.97      1.03 1.05      0.293
## split[cur.subset]D-_N23 2.22      9.21      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+_N23      3.13      0.319      0.391      25.1
## split[cur.subset]D-_N01      2.97      0.337      0.391      22.5
## split[cur.subset]D-_N23      9.21      0.109      1.265      67.1
##
## Concordance= 0.654  (se = 0.037 )
## Rsquare= 0.108    (max possible= 0.947 )
## Likelihood ratio test= 23.8  on 3 df,    p=2.79e-05
## Wald test          = 21.1  on 3 df,    p=0.000101
## Score (logrank) test = 24.4  on 3 df,    p=2.02e-05
```

3.5 Interaction of N0-N1, TP53 Mut and the IR Consensus Cluster

```
## Error: Attribut 'names' [12] muss dieselbe Länge haben wie der Vektor [8]
## 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= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N01__ND -9.34e-01  3.93e-01  1.02e+00 -0.92      0.360
## split[cur.subset]N01__WT  5.68e-02  1.06e+00  7.69e-01  0.07      0.941
## split[cur.subset]N01_IR_D -7.65e-02  9.26e-01  1.25e+00 -0.06      0.951
## split[cur.subset]N01_IR_ND -1.51e+01  2.69e-07  2.98e+03 -0.01      0.996
## split[cur.subset]N01_IR_WT -9.20e-01  3.98e-01  1.23e+00 -0.75      0.454
## split[cur.subset]N23__D  1.66e+00  5.27e+00  7.44e-01  2.23      0.026 *
## split[cur.subset]N23__ND  1.96e-01  1.22e+00  1.00e+00  0.20      0.845
## split[cur.subset]N23__WT  6.77e-01  1.97e+00  7.48e-01  0.90      0.366
## split[cur.subset]N23_IR_D -2.02e-01  8.17e-01  1.03e+00 -0.20      0.845
## split[cur.subset]N23_IR_ND  7.74e-02  1.08e+00  9.30e-01  0.08      0.934
## split[cur.subset]N23_IR_WT  5.66e-01  1.76e+00  7.76e-01  0.73      0.466
## ---
```

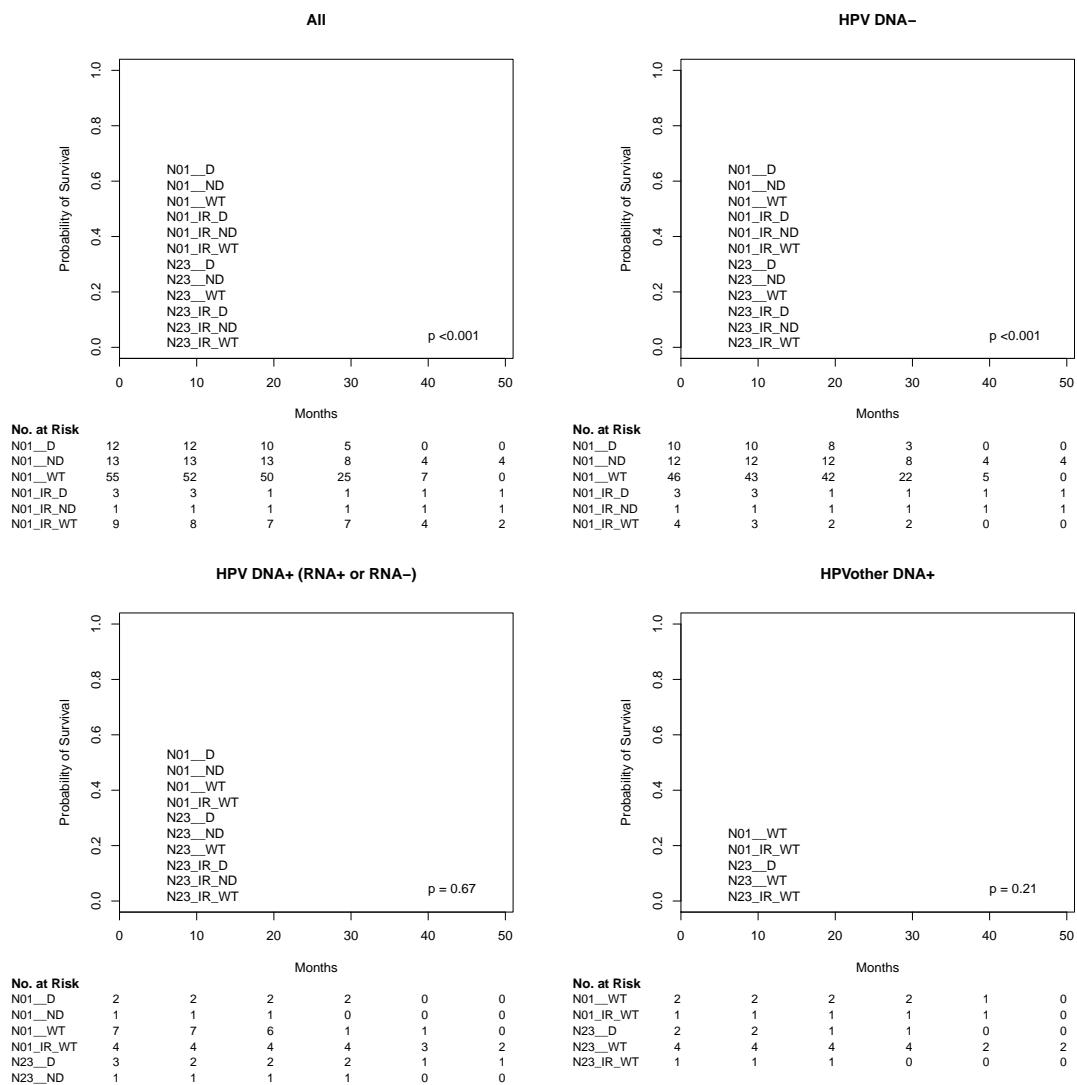


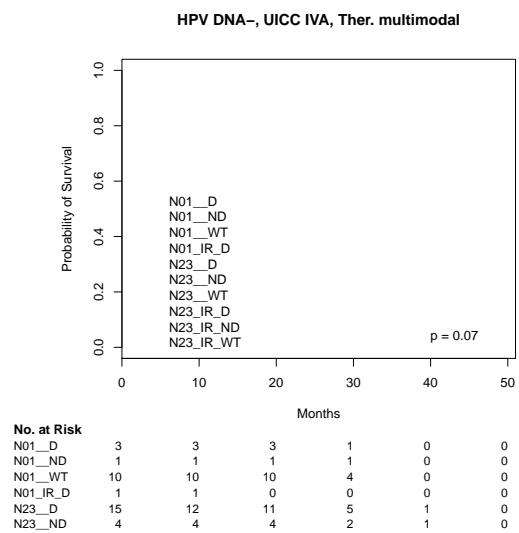
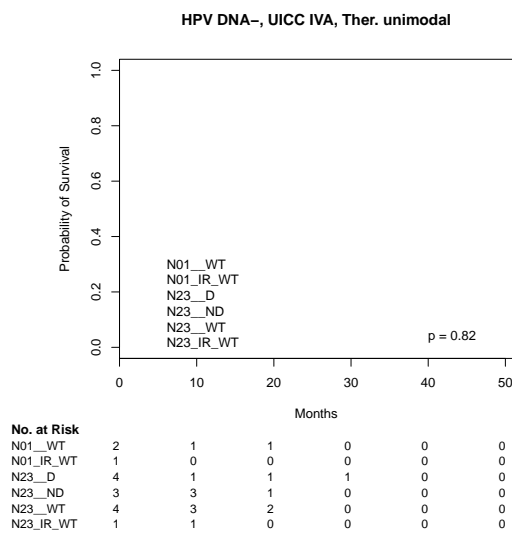
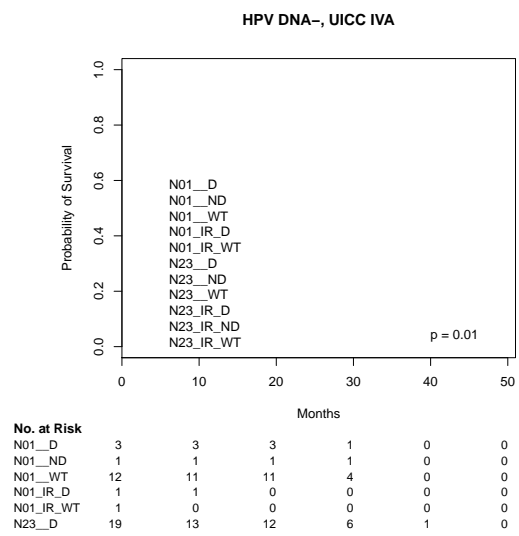
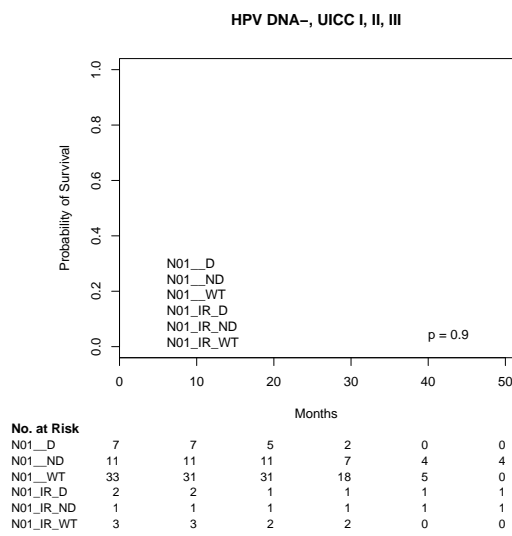
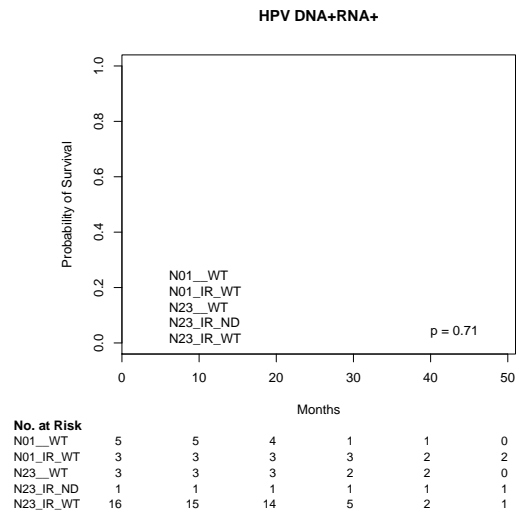
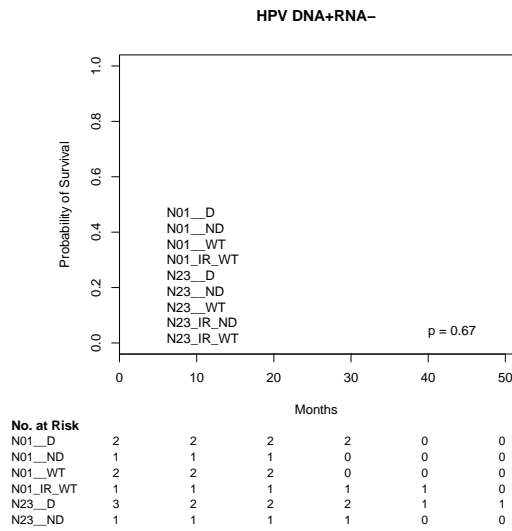
```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N01__ND    3.93e-01  2.54e+00   0.0533    2.90
## split[cur.subset]N01__WT    1.06e+00  9.45e-01   0.2343    4.78
## split[cur.subset]N01_IR_D    9.26e-01  1.08e+00   0.0795   10.79
## split[cur.subset]N01_IR_ND    2.69e-07  3.71e+06   0.0000    Inf
## split[cur.subset]N01_IR_WT    3.98e-01  2.51e+00   0.0358    4.44
## split[cur.subset]N23__D      5.27e+00  1.90e-01   1.2243   22.64
## split[cur.subset]N23__ND      1.22e+00  8.22e-01   0.1710    8.65
## split[cur.subset]N23__WT      1.97e+00  5.08e-01   0.4540    8.53
## split[cur.subset]N23_IR_D      8.17e-01  1.22e+00   0.1082    6.17
## split[cur.subset]N23_IR_ND      1.08e+00  9.26e-01   0.1746    6.68
## split[cur.subset]N23_IR_WT      1.76e+00  5.68e-01   0.3851    8.05
##
## Concordance= 0.671  (se = 0.038 )
## Rsquare= 0.144  (max possible= 0.954 )
## Likelihood ratio test= 33.7  on 11 df,  p=0.000401
## Wald test               = 33  on 11 df,  p=0.000528
## Score (logrank) test = 41.3  on 11 df,  p=2.12e-05
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N01__ND   -1.16e+00  3.13e-01  1.04e+00 -1.11   0.267
## split[cur.subset]N01__WT   -2.23e-01  8.00e-01  7.83e-01 -0.28   0.776
## split[cur.subset]N01_IR_D  -2.41e-01  7.86e-01  1.28e+00 -0.19   0.851
## split[cur.subset]N01_IR_ND -1.61e+01  9.81e-08  4.01e+03  0.00   0.997
## split[cur.subset]N01_IR_WT  3.85e-01  1.47e+00  1.23e+00  0.31   0.754
## split[cur.subset]N23__D     1.50e+00  4.49e+00  7.54e-01  1.99   0.046 *
## split[cur.subset]N23__ND   -5.08e-03  9.95e-01  1.00e+00 -0.01   0.996
## split[cur.subset]N23__WT     5.07e-01  1.66e+00  7.68e-01  0.66   0.509
## split[cur.subset]N23_IR_D    4.98e-01  1.65e+00  1.00e+00  0.50   0.620
## split[cur.subset]N23_IR_ND -4.81e-02  9.53e-01  9.86e-01 -0.05   0.961
## split[cur.subset]N23_IR_WT  1.21e+00  3.35e+00  8.17e-01  1.48   0.139
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N01__ND    3.13e-01  3.19e+00   0.0404    2.43
## split[cur.subset]N01__WT      8.00e-01  1.25e+00   0.1724    3.72
## split[cur.subset]N01_IR_D      7.86e-01  1.27e+00   0.0640    9.66
```

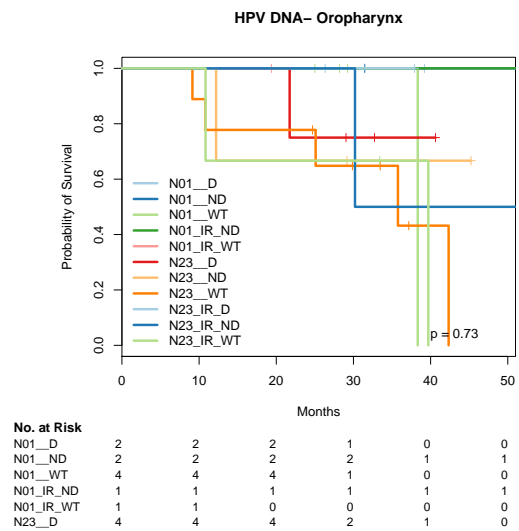
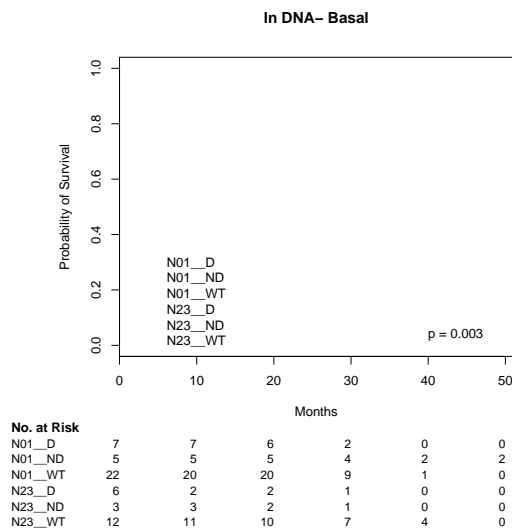
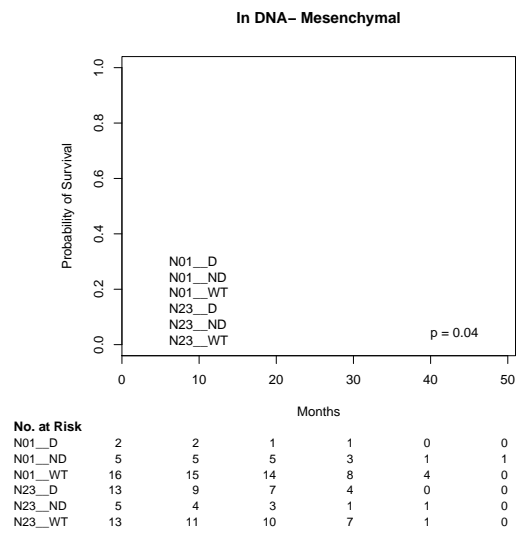
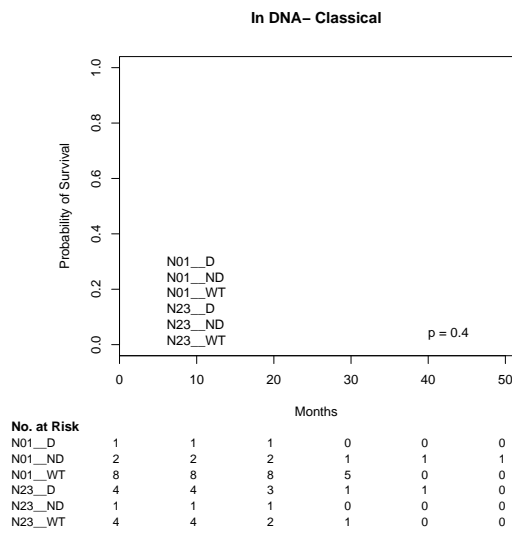
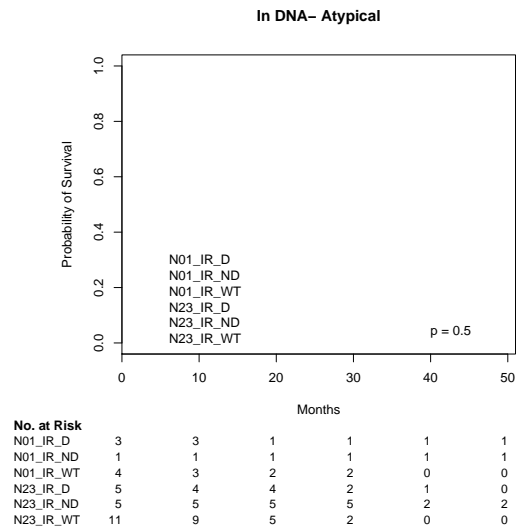
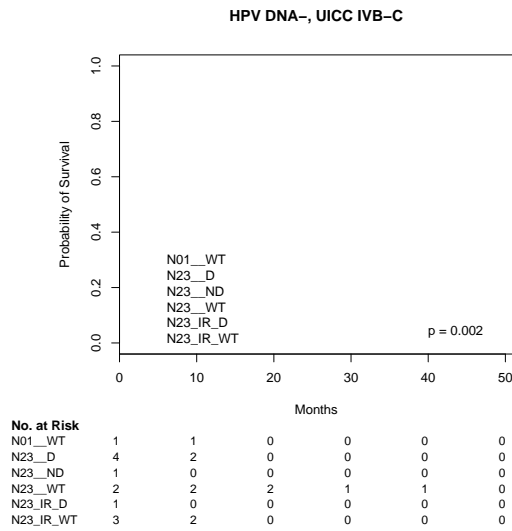
```

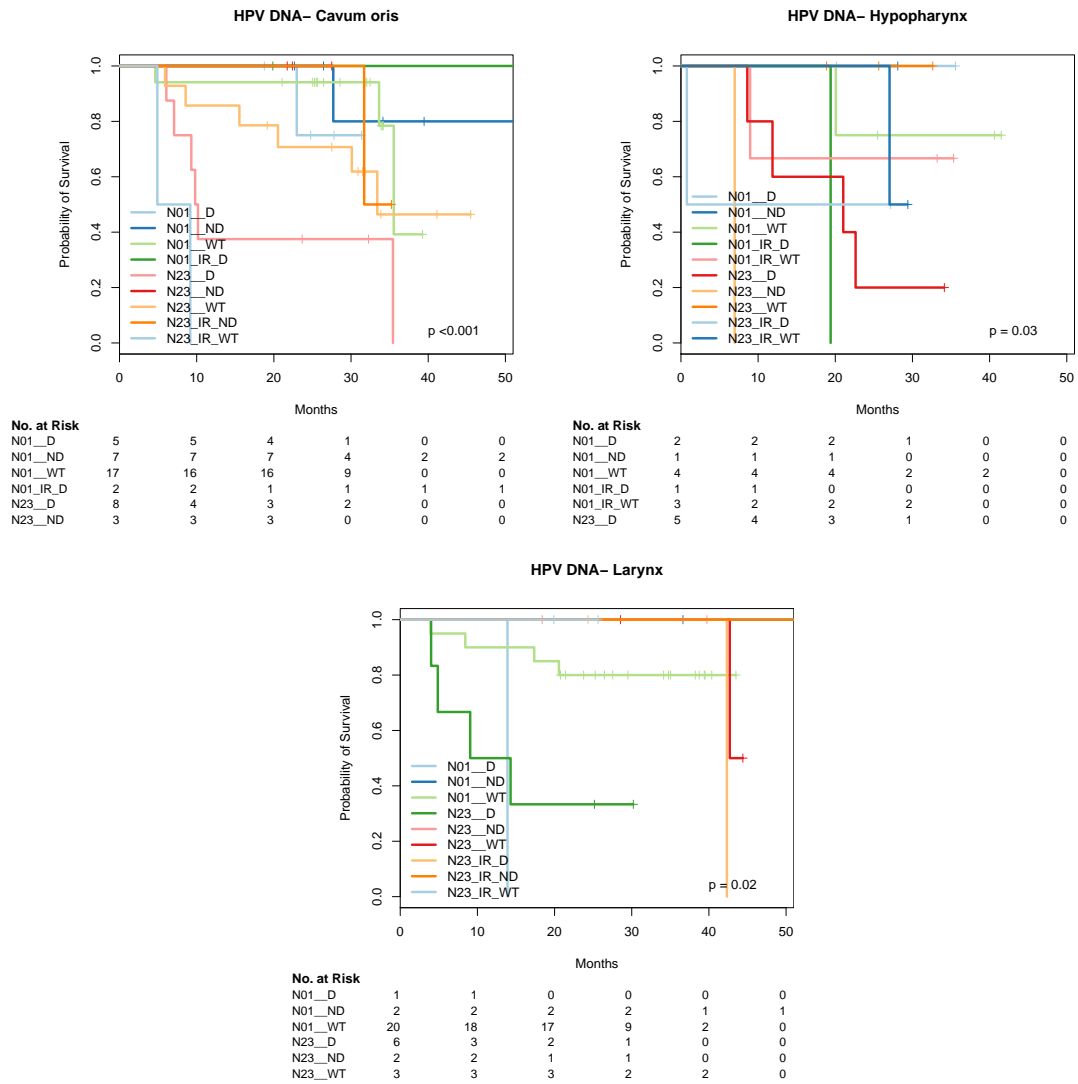
## split[cur.subset]N01_IR_ND 9.81e-08 1.02e+07 0.0000 Inf
## split[cur.subset]N01_IR_WT 1.47e+00 6.80e-01 0.1329 16.25
## split[cur.subset]N23__D 4.49e+00 2.23e-01 1.0259 19.68
## split[cur.subset]N23__ND 9.95e-01 1.01e+00 0.1391 7.12
## split[cur.subset]N23__WT 1.66e+00 6.02e-01 0.3686 7.49
## split[cur.subset]N23_IR_D 1.65e+00 6.08e-01 0.2298 11.78
## split[cur.subset]N23_IR_ND 9.53e-01 1.05e+00 0.1379 6.59
## split[cur.subset]N23_IR_WT 3.35e+00 2.98e-01 0.6757 16.63
##
## Concordance= 0.695 (se = 0.042 )
## Rsquare= 0.167 (max possible= 0.954 )
## Likelihood ratio test= 29 on 11 df, p=0.0023
## Wald test = 26.6 on 11 df, p=0.00533
## Score (logrank) test = 33.4 on 11 df, p=0.000451

```









3.5.1 In DNA- and TP53wt and N2-N3. Factor: IR (yes/no)

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg" & !is.na(ds$INNO_LIPA_GROB) &
  (ds$TP53 == 0) & ds$N_2CAT == "N2-N3"
surv.res <- coxph(surv.obj[cur.subset] ~ IS_ATYPICAL, data = ds[cur.subset,
])

## Error: No (non-missing) observations

summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N01__ND -1.16e+00  3.13e-01  1.04e+00 -1.11   0.267
## split[cur.subset]N01__WT -2.23e-01  8.00e-01  7.83e-01 -0.28   0.776
```

```
## split[cur.subset]N01_IR_D -2.41e-01 7.86e-01 1.28e+00 -0.19 0.851
## split[cur.subset]N01_IR_ND -1.61e+01 9.81e-08 4.01e+03 0.00 0.997
## split[cur.subset]N01_IR_WT 3.85e-01 1.47e+00 1.23e+00 0.31 0.754
## split[cur.subset]N23__D 1.50e+00 4.49e+00 7.54e-01 1.99 0.046 *
## split[cur.subset]N23__ND -5.08e-03 9.95e-01 1.00e+00 -0.01 0.996
## split[cur.subset]N23__WT 5.07e-01 1.66e+00 7.68e-01 0.66 0.509
## split[cur.subset]N23_IR_D 4.98e-01 1.65e+00 1.00e+00 0.50 0.620
## split[cur.subset]N23_IR_ND -4.81e-02 9.53e-01 9.86e-01 -0.05 0.961
## split[cur.subset]N23_IR_WT 1.21e+00 3.35e+00 8.17e-01 1.48 0.139
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N01__ND 3.13e-01 3.19e+00 0.0404 2.43
## split[cur.subset]N01__WT 8.00e-01 1.25e+00 0.1724 3.72
## split[cur.subset]N01_IR_D 7.86e-01 1.27e+00 0.0640 9.66
## split[cur.subset]N01_IR_ND 9.81e-08 1.02e+07 0.0000 Inf
## split[cur.subset]N01_IR_WT 1.47e+00 6.80e-01 0.1329 16.25
## split[cur.subset]N23__D 4.49e+00 2.23e-01 1.0259 19.68
## split[cur.subset]N23__ND 9.95e-01 1.01e+00 0.1391 7.12
## split[cur.subset]N23__WT 1.66e+00 6.02e-01 0.3686 7.49
## split[cur.subset]N23_IR_D 1.65e+00 6.08e-01 0.2298 11.78
## split[cur.subset]N23_IR_ND 9.53e-01 1.05e+00 0.1379 6.59
## split[cur.subset]N23_IR_WT 3.35e+00 2.98e-01 0.6757 16.63
##
## Concordance= 0.695 (se = 0.042 )
## Rsquare= 0.167 (max possible= 0.954 )
## Likelihood ratio test= 29 on 11 df, p=0.0023
## Wald test = 26.6 on 11 df, p=0.00533
## Score (logrank) test = 33.4 on 11 df, p=0.000451
```

3.6 Interaction of TP53 Mut (disruptive (D), non-disruptive (ND)), IR Cluster

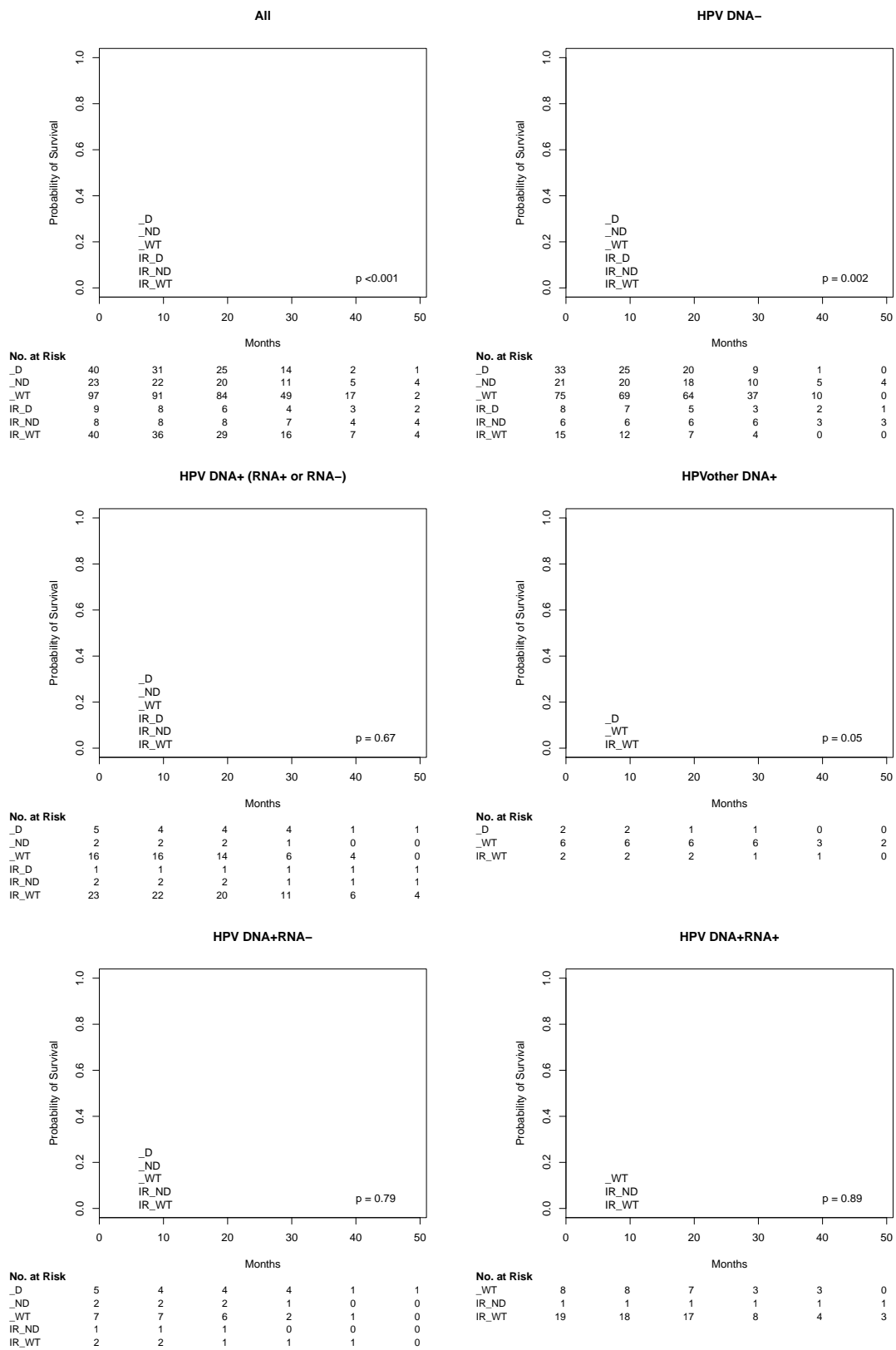
```
## Error: Attribut 'names' [6] muss dieselbe Länge haben wie der Vektor [4]
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 73
##
## coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]_ND -1.857 0.156 0.567 -3.28 0.0011 **
```

```

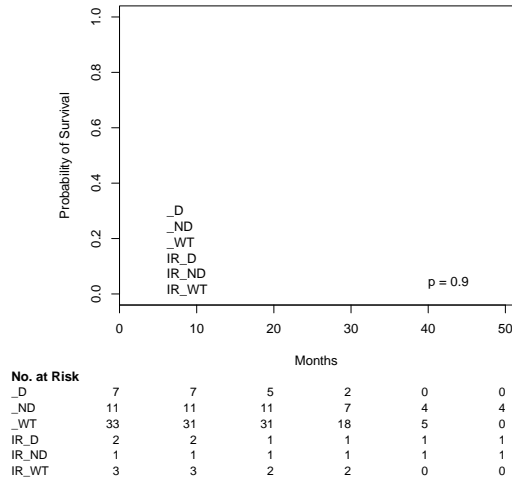
## split[cur.subset]_WT -0.923 0.397 0.289 -3.19 0.0014 **
## split[cur.subset]IR_D -1.523 0.218 0.662 -2.30 0.0215 *
## split[cur.subset]IR_ND -1.401 0.246 0.639 -2.19 0.0283 *
## split[cur.subset]IR_WT -1.019 0.361 0.373 -2.73 0.0063 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]_ND 0.156 6.40 0.0514 0.474
## split[cur.subset]_WT 0.397 2.52 0.2255 0.700
## split[cur.subset]IR_D 0.218 4.59 0.0595 0.799
## split[cur.subset]IR_ND 0.246 4.06 0.0705 0.862
## split[cur.subset]IR_WT 0.361 2.77 0.1739 0.749
##
## Concordance= 0.613 (se = 0.036 )
## Rsquare= 0.081 (max possible= 0.954 )
## Likelihood ratio test= 18.3 on 5 df, p=0.00257
## Wald test = 18.9 on 5 df, p=0.00197
## Score (logrank) test = 21.1 on 5 df, p=0.000759
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 55
##
## coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]_ND -1.858 0.156 0.594 -3.13 0.0018 **
## split[cur.subset]_WT -1.025 0.359 0.332 -3.08 0.0020 **
## split[cur.subset]IR_D -0.930 0.395 0.651 -1.43 0.1532
## split[cur.subset]IR_ND -1.352 0.259 0.698 -1.94 0.0526 .
## split[cur.subset]IR_WT -0.118 0.889 0.449 -0.26 0.7929
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]_ND 0.156 6.41 0.0487 0.499
## split[cur.subset]_WT 0.359 2.79 0.1870 0.688
## split[cur.subset]IR_D 0.395 2.53 0.1102 1.413
## split[cur.subset]IR_ND 0.259 3.87 0.0659 1.015
## split[cur.subset]IR_WT 0.889 1.13 0.3683 2.145
##
## Concordance= 0.655 (se = 0.04 )
## Rsquare= 0.103 (max possible= 0.954 )
## Likelihood ratio test= 17.2 on 5 df, p=0.00421
## Wald test = 16.6 on 5 df, p=0.0054

```

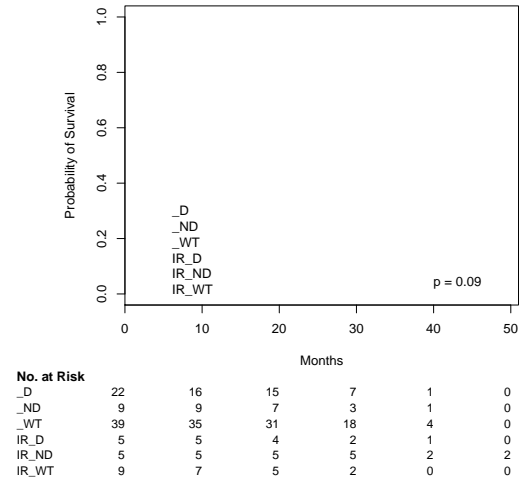
Score (logrank) test = 18.6 on 5 df, p=0.00223



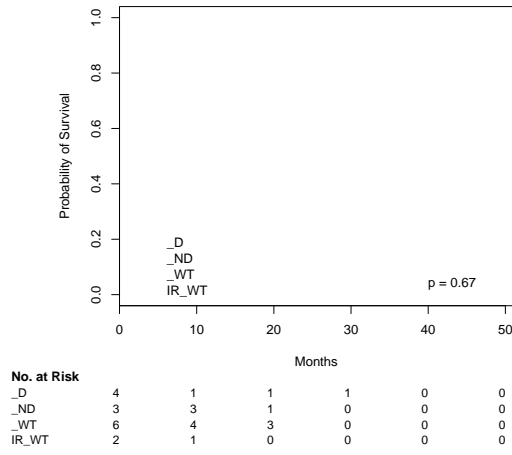
HPV DNA-, UICC I, II, III



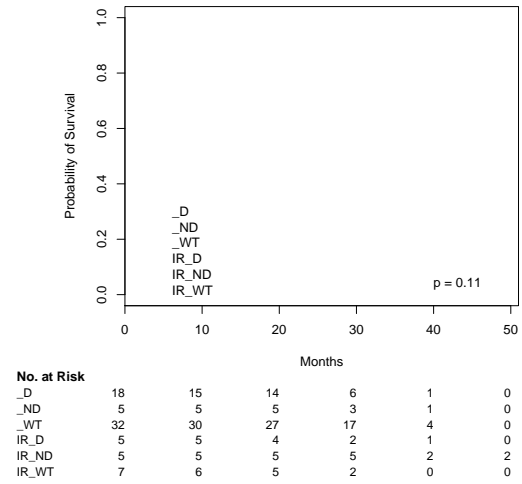
HPV DNA-, UICC IVA



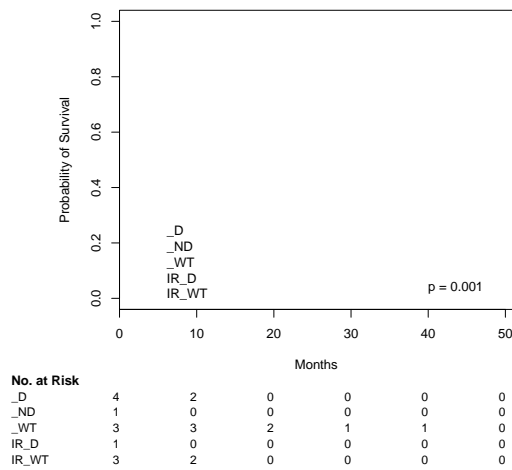
HPV DNA-, UICC IVA, Ther. unimodal



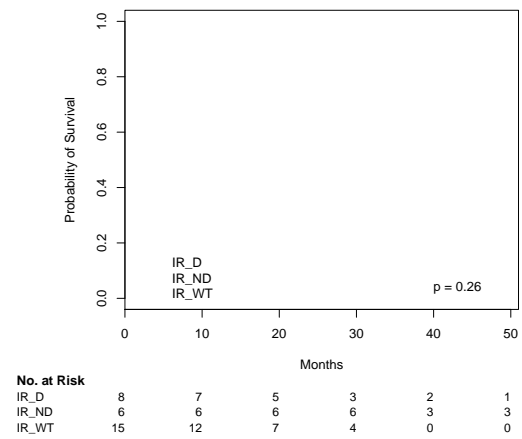
HPV DNA-, UICC IVA, Ther. multimodal



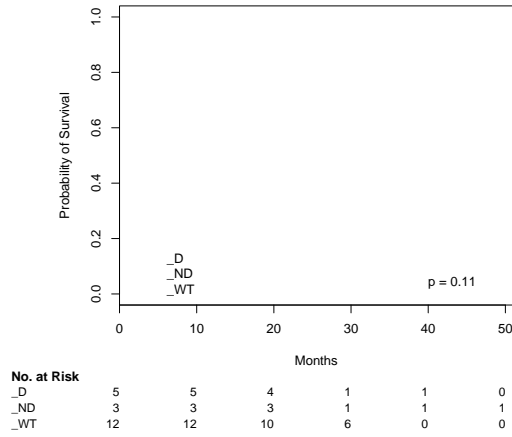
HPV DNA-, UICC IVB-C



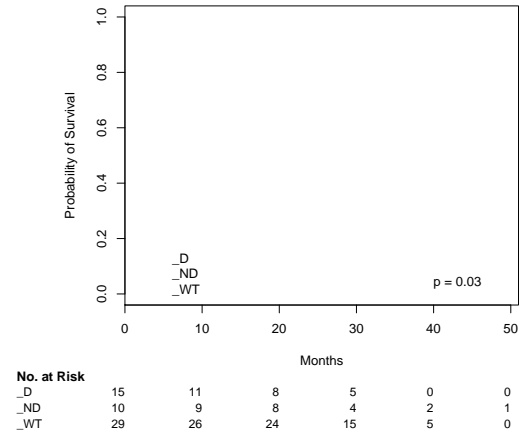
In DNA- Atypical



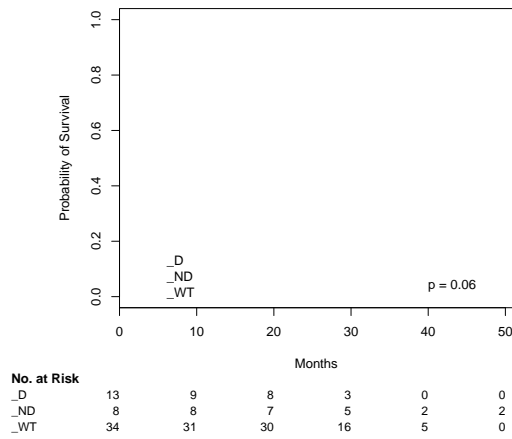
In DNA- Classical



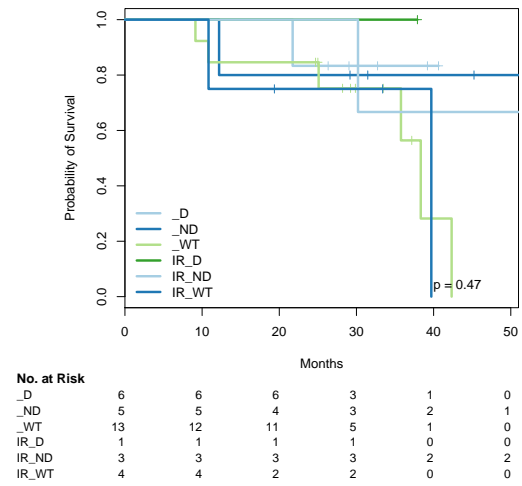
In DNA- Mesenchymal



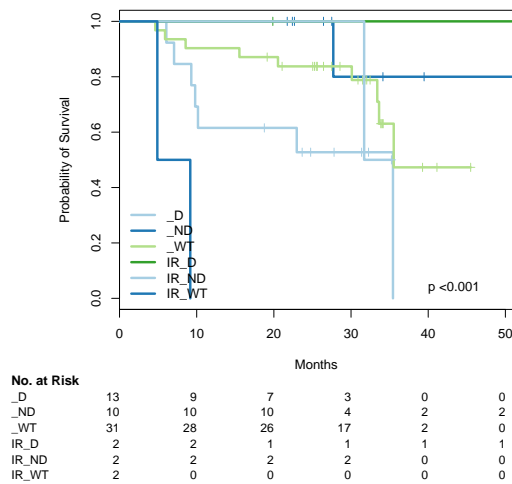
In DNA- Basal



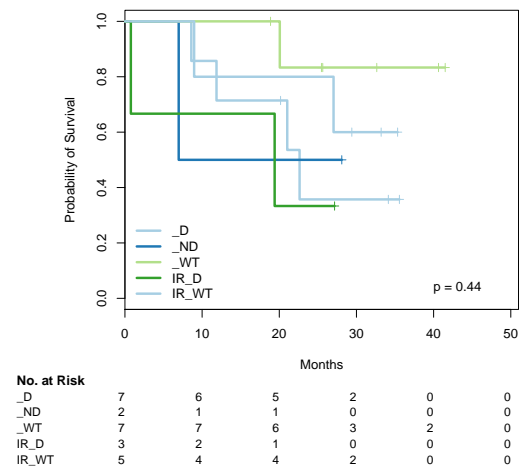
HPV DNA- Oropharynx

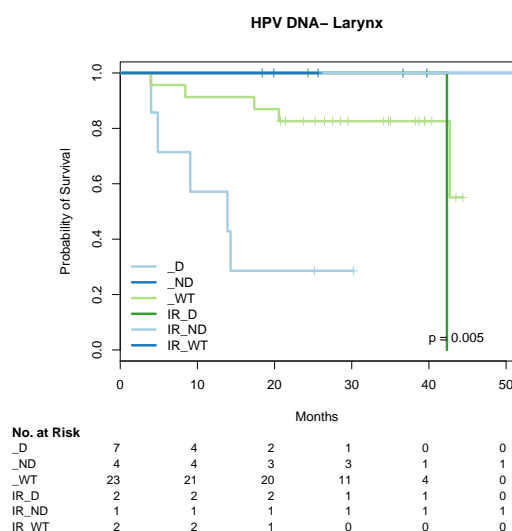


HPV DNA- Cavum oris



HPV DNA- Hypopharynx





4 Multivariate models

4.1 In all patients

4.1.1 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= 217, number of events= 73

##

	coef	exp(coef)	se(coef)	z	Pr(> z)
UICC_3CATIVA	1.460	4.307	0.381	3.83	0.00013 ***
UICC_3CATIVB-C	2.196	8.987	0.455	4.82	1.4e-06 ***

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

##

	exp(coef)	exp(-coef)	lower .95	upper .95
UICC_3CATIVA	4.31	0.232	2.04	9.09
UICC_3CATIVB-C	8.99	0.111	3.68	21.95

##

Concordance= 0.668 (se = 0.034)

Rsquare= 0.129 (max possible= 0.954)

Likelihood ratio test= 29.9 on 2 df, p=3.21e-07

Wald test = 23.5 on 2 df, p=7.93e-06

Score (logrank) test = 28.9 on 2 df, p=5.27e-07

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

```
##              rho   chisq    p
## UICC_3CATIVA  -0.00655 0.00306 0.956
## UICC_3CATIVB-C -0.11577 0.96808 0.325
## GLOBAL              NA 1.87134 0.392
```

4.1.2 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= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNADNA+ -0.771      0.463    0.380 -2.03   0.043 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNADNA+      0.463        2.16      0.22    0.974
##
## Concordance= 0.555 (se = 0.029 )
## Rsquare= 0.024 (max possible= 0.946 )
## Likelihood ratio test= 4.94 on 1 df,  p=0.0262
## Wald test               = 4.11 on 1 df,  p=0.0425
## Score (logrank) test = 4.32 on 1 df,  p=0.0377

cox.zph(surv.res)

##              rho   chisq    p
## HPV16_DNADNA+ 0.0202 0.0255 0.873
```

4.1.3 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= 203, number of events= 63
##   (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.499      4.477    0.390   3.85 0.00012 ***
## UICC_3CATIVB-C  2.726     15.265    0.472   5.78 7.7e-09 ***
## HPV16_DNADNA+ -1.100      0.333    0.385  -2.86 0.00427 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.477     0.2234     2.085     9.610
## UICC_3CATIVB-C    15.265     0.0655     6.054    38.495
## HPV16_DNADNA+     0.333     3.0053     0.156     0.708
##
## Concordance= 0.701 (se = 0.038 )
## Rsquare= 0.186 (max possible= 0.946 )
## Likelihood ratio test= 41.9 on 3 df, p=4.25e-09
## Wald test = 37.6 on 3 df, p=3.42e-08
## Score (logrank) test = 45.1 on 3 df, p=8.8e-10

cox.zph(surv.res)

##               rho   chisq    p
## UICC_3CATIVA    0.00685 0.00278 0.958
## UICC_3CATIVB-C -0.00525 0.00166 0.968
## HPV16_DNADNA+   0.02187 0.02949 0.864
## GLOBAL          NA 0.04064 0.998
```

4.1.4 HPV16 DNA RNA

```
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= 203, number of events= 63
##   (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.436      0.646    0.519  -0.84    0.400
## HPV16_DNA_RNADNA+RNA+ -1.021      0.360    0.519  -1.97    0.049 *
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.646      1.55    0.234    1.787
## HPV16_DNA_RNADNA+RNA+    0.360      2.78    0.130    0.997
##
## Concordance= 0.557  (se = 0.03 )
## Rsquare= 0.027   (max possible= 0.946 )
## Likelihood ratio test= 5.61  on 2 df,   p=0.0604
## Wald test          = 4.36  on 2 df,   p=0.113
## Score (logrank) test = 4.7   on 2 df,   p=0.0955

cox.zph(surv.res)

##               rho      chisq      p
## HPV16_DNA_RNADNA+RNA- 0.02660 0.04453 0.833
## HPV16_DNA_RNADNA+RNA+ 0.00524 0.00174 0.967
## GLOBAL                NA 0.04525 0.978
```

4.1.5 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= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.497     4.470   0.390   3.84 0.00012 ***
## UICC_3CATIVB-C     2.722    15.206   0.472   5.77 8.1e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.795     0.451   0.524  -1.52 0.12887
## HPV16_DNA_RNADNA+RNA+ -1.333     0.264   0.523  -2.55 0.01076 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.470     0.2237   2.0823    9.595
## UICC_3CATIVB-C    15.206     0.0658   6.0296   38.350
## HPV16_DNA_RNADNA+RNA- 0.451     2.2154   0.1617    1.260
## HPV16_DNA_RNADNA+RNA+ 0.264     3.7922   0.0947    0.734
##
## Concordance= 0.703  (se = 0.038 )
```

```
## Rsquare= 0.189    (max possible= 0.946 )
## Likelihood ratio test= 42.5  on 4 df,    p=1.34e-08
## Wald test          = 37.8  on 4 df,    p=1.26e-07
## Score (logrank) test = 45.4  on 4 df,    p=3.3e-09

cox.zph(surv.res)

##                rho    chisq    p
## UICC_3CATIVA      0.00512 0.00155 0.969
## UICC_3CATIVB-C    -0.00686 0.00284 0.958
## HPV16_DNA_RNADNA+RNA- 0.00747 0.00364 0.952
## HPV16_DNA_RNADNA+RNA+ 0.01857 0.02096 0.885
## GLOBAL            NA 0.03460 1.000
```

4.1.6 UICC, HPV16 DNA RNA, PACKYEARS

```
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= 201, number of events= 62
## (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.479      4.388   0.391   3.79  0.00015 ***
## UICC_3CATIVB-C     2.704     14.940   0.473   5.72  1.1e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.730      0.482   0.527  -1.38  0.16638
## HPV16_DNA_RNADNA+RNA+ -1.274      0.280   0.528  -2.41  0.01595 *
## I(PACKYEARS > 30)TRUE  0.221      1.247   0.262   0.84  0.39887
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.388      0.2279   2.0411   9.435
## UICC_3CATIVB-C    14.940      0.0669   5.9154  37.730
## HPV16_DNA_RNADNA+RNA-  0.482      2.0747   0.1715   1.355
## HPV16_DNA_RNADNA+RNA+  0.280      3.5735   0.0993   0.788
## I(PACKYEARS > 30)TRUE  1.247      0.8020   0.7467   2.082
##
## Concordance= 0.71 (se = 0.04 )
## Rsquare= 0.19    (max possible= 0.945 )
## Likelihood ratio test= 42.3  on 5 df,    p=5.21e-08
## Wald test          = 38.1  on 5 df,    p=3.58e-07
```

```
## Score (logrank) test = 45.8 on 5 df, p=1.01e-08
```

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

```
##              rho    chisq    p
## UICC_3CATIVA      -0.00888 0.00459 0.946
## UICC_3CATIVB-C    -0.02073 0.02578 0.872
## HPV16_DNA_RNADNA+RNA- 0.01786 0.02051 0.886
## HPV16_DNA_RNADNA+RNA+ 0.03357 0.07223 0.788
## I(PACKYEARS > 30)TRUE 0.02037 0.02667 0.870
## GLOBAL           NA 0.11549 1.000
```

4.1.7 UICC, HPV16 DNA RNA, PACKYEARS, 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= 201, number of events= 62
```

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

```
##
```

```
##              coef exp(coef) se(coef)
## UICC_3CATIVA      1.5036      4.4981  0.3918
## UICC_3CATIVB-C    2.6928     14.7732  0.4741
## HPV16_DNA_RNADNA+RNA- -0.5614      0.5704  0.6225
## HPV16_DNA_RNADNA+RNA+ -2.3371      0.0966  1.0240
## I(PACKYEARS > 30)TRUE  0.1311      1.1401  0.2776
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.5860      0.5566  1.1977
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.9895      7.3121  1.1943
```

```
##              z Pr(>|z|)
## UICC_3CATIVA      3.84 0.00012 ***
## UICC_3CATIVB-C    5.68 1.3e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.90 0.36712
## HPV16_DNA_RNADNA+RNA+ -2.28 0.02248 *
## I(PACKYEARS > 30)TRUE  0.47 0.63678
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.49 0.62465
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.67 0.09576 .
```

```
## ---
```

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

```
##
```

```
##              exp(coef) exp(-coef) lower .95
```



```
## UICC_3CATIVA 4.4981 0.2223 2.0869
## UICC_3CATIVB-C 14.7732 0.0677 5.8337
## HPV16_DNA_RNADNA+RNA- 0.5704 1.7531 0.1684
## HPV16_DNA_RNADNA+RNA+ 0.0966 10.3508 0.0130
## I(PACKYEARS > 30)TRUE 1.1401 0.8771 0.6616
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.5566 1.7968 0.0532
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 7.3121 0.1368 0.7037
## upper .95
## UICC_3CATIVA 9.695
## UICC_3CATIVB-C 37.411
## HPV16_DNA_RNADNA+RNA- 1.932
## HPV16_DNA_RNADNA+RNA+ 0.719
## I(PACKYEARS > 30)TRUE 1.964
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 5.821
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 75.975
##
## Concordance= 0.716 (se = 0.04 )
## Rsquare= 0.205 (max possible= 0.945 )
## Likelihood ratio test= 46 on 7 df, p=8.75e-08
## Wald test = 37.9 on 7 df, p=3.21e-06
## Score (logrank) test = 47.4 on 7 df, p=4.58e-08

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA -0.0027 0.000433 0.983
## UICC_3CATIVB-C -0.0103 0.006379 0.936
## HPV16_DNA_RNADNA+RNA- -0.0197 0.024391 0.876
## HPV16_DNA_RNADNA+RNA+ 0.0859 0.446025 0.504
## I(PACKYEARS > 30)TRUE 0.0156 0.014939 0.903
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.0270 0.045033 0.832
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0528 0.177356 0.674
## GLOBAL NA 0.615431 0.999
```

4.1.8 UICC, HPV16 DNA RNA, Age

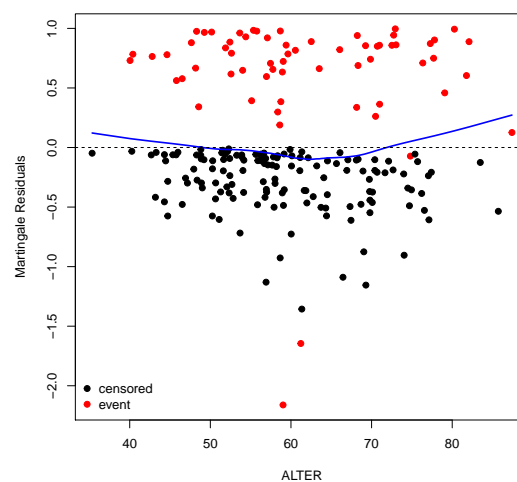
```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## ALTER, data = ds[cur.subset, ], model = TRUE)
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.4726    4.3605   0.3897  3.78  0.00016 ***
## UICC_3CATIVB-C     2.6921   14.7626   0.4723  5.70  1.2e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.7176    0.4879   0.5252 -1.37  0.17178
## HPV16_DNA_RNADNA+RNA+ -1.4746    0.2289   0.5321 -2.77  0.00559 **
## ALTER              0.0207    1.0209   0.0130  1.59  0.11096
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          4.361    0.2293    2.0316    9.359
## UICC_3CATIVB-C       14.763    0.0677    5.8493   37.258
## HPV16_DNA_RNADNA+RNA-  0.488    2.0496    0.1743    1.366
## HPV16_DNA_RNADNA+RNA+  0.229    4.3693    0.0807    0.649
## ALTER                1.021    0.9795    0.9953    1.047
##
## Concordance= 0.723 (se = 0.04 )
## Rsquare= 0.199 (max possible= 0.946 )
## Likelihood ratio test= 45 on 5 df,  p=1.48e-08
## Wald test              = 39.5 on 5 df,  p=1.92e-07
## Score (logrank) test = 46.9 on 5 df,  p=5.97e-09

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA     -0.00161  0.000156  0.990
## UICC_3CATIVB-C    -0.00986  0.005864  0.939
## HPV16_DNA_RNADNA+RNA- -0.00366  0.000901  0.976
## HPV16_DNA_RNADNA+RNA+  0.03736  0.087145  0.768
## ALTER            -0.10430  0.945642  0.331
## GLOBAL              NA  0.973356  0.965
```



4.1.9 UICC, HPV16 DNA RNA, Age (linear und 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= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.515      4.552    0.392  3.87  0.00011 ***
## UICC_3CATIVB-C      2.806     16.547    0.481  5.84  5.2e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.712      0.491    0.527 -1.35  0.17726
## HPV16_DNA_RNADNA+RNA+ -1.477      0.228    0.535 -2.76  0.00575 **
## poly(ALTER, 2)1      2.290      9.873    1.789  1.28  0.20062
## poly(ALTER, 2)2      3.098     22.143    1.527  2.03  0.04247 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.552      0.2197    2.1110    9.814
## UICC_3CATIVB-C     16.547      0.0604    6.4524   42.436
## HPV16_DNA_RNADNA+RNA-  0.491      2.0374    0.1746    1.380
## HPV16_DNA_RNADNA+RNA+  0.228      4.3776    0.0801    0.651
## poly(ALTER, 2)1      9.873      0.1013    0.2961  329.166
## poly(ALTER, 2)2     22.143      0.0452    1.1110  441.351
##
## Concordance= 0.725 (se = 0.04 )
## Rsquare= 0.213 (max possible= 0.946 )
## Likelihood ratio test= 48.6 on 6 df,  p=8.95e-09
## Wald test              = 43.6 on 6 df,  p=8.86e-08
## Score (logrank) test = 51 on 6 df,  p=3.02e-09

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA      0.0379 0.08890 0.7656
## UICC_3CATIVB-C      0.0417 0.10797 0.7425
## HPV16_DNA_RNADNA+RNA- -0.0120 0.00964 0.9218
## HPV16_DNA_RNADNA+RNA+  0.0290 0.05238 0.8190
## poly(ALTER, 2)1      -0.1345 1.28550 0.2569
## poly(ALTER, 2)2      0.2382 3.05759 0.0804
## GLOBAL              NA  3.56520 0.7353

```

4.1.10 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= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.561      4.764   0.392   3.98  6.9e-05 ***
## UICC_3CATIVB-C      2.861     17.476   0.480   5.97  2.4e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.746      0.474   0.524  -1.42   0.1548
## HPV16_DNA_RNADNA+RNA+ -1.415      0.243   0.526  -2.69   0.0072 **
## ALTER_3CAT(50,70]   -0.652      0.521   0.261  -2.50   0.0124 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.764      0.2099    2.2084    10.278
## UICC_3CATIVB-C     17.476      0.0572    6.8277    44.732
## HPV16_DNA_RNADNA+RNA-  0.474      2.1088    0.1697     1.325
## HPV16_DNA_RNADNA+RNA+  0.243      4.1182    0.0866     0.681
## ALTER_3CAT(50,70]    0.521      1.9196    0.3125     0.869
##
## Concordance= 0.718 (se = 0.039 )
## Rsquare= 0.213 (max possible= 0.946 )
## Likelihood ratio test= 48.5 on 5 df, p=2.74e-09
## Wald test              = 42.6 on 5 df, p=4.52e-08
## Score (logrank) test = 50.1 on 5 df, p=1.31e-09

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA      0.04648 0.12532 0.7233
## UICC_3CATIVB-C      0.05299 0.16452 0.6850
## HPV16_DNA_RNADNA+RNA- -0.01265 0.01014 0.9198
## HPV16_DNA_RNADNA+RNA+ -0.00876 0.00478 0.9449
## ALTER_3CAT(50,70]   -0.20743 2.89881 0.0886
## GLOBAL              NA 2.98255 0.7027
```

4.1.11 UICC, HPV16 DNA RNA, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), 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= 201, number of events= 62
## (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.529      4.616   0.392  3.90  9.6e-05 ***
## UICC_3CATIVB-C      2.856     17.395   0.480  5.95  2.7e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.622    0.537   0.529 -1.18  0.2398
## HPV16_DNA_RNADNA+RNA+ -1.333    0.264   0.531 -2.51  0.0121 *
## ALTER_3CAT(50,70]   -0.749    0.473   0.272 -2.76  0.0058 **
## I(PACKYEARS > 30)TRUE  0.394    1.483   0.269  1.46  0.1430
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.616    0.2166    2.140    9.956
## UICC_3CATIVB-C     17.395    0.0575    6.785   44.598
## HPV16_DNA_RNADNA+RNA-  0.537    1.8621    0.190    1.514
## HPV16_DNA_RNADNA+RNA+  0.264    3.7935    0.093    0.747
## ALTER_3CAT(50,70]    0.473    2.1159    0.278    0.805
## I(PACKYEARS > 30)TRUE  1.483    0.6745    0.875    2.511
##
## Concordance= 0.725 (se = 0.04 )
## Rsquare= 0.219 (max possible= 0.945 )
## Likelihood ratio test= 49.7 on 6 df, p=5.33e-09
## Wald test = 43.5 on 6 df, p=9.2e-08
## Score (logrank) test = 51.6 on 6 df, p=2.21e-09

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0233 0.0311 0.8601
## UICC_3CATIVB-C      0.0341 0.0669 0.7960
## HPV16_DNA_RNADNA+RNA- 0.0174 0.0191 0.8902
## HPV16_DNA_RNADNA+RNA+ 0.0167 0.0179 0.8935
```

```
## ALTER_3CAT(50,70]      -0.2428 3.6400 0.0564
## I(PACKYEARS > 30)TRUE  0.0763 0.3392 0.5603
## GLOBAL                 NA 3.7194 0.7146
```

4.1.12 UICC, HPV16 DNA RNA, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), PACKYEARS, 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= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##
##              coef exp(coef) se(coef)
## UICC_3CATIVA          1.5530    4.7254  0.3936
## UICC_3CATIVB-C         2.8332   17.0004  0.4817
## HPV16_DNA_RNADNA+RNA- -0.4649    0.6282  0.6274
## HPV16_DNA_RNADNA+RNA+ -2.3354    0.0968  1.0255
## ALTER_3CAT(50,70]    -0.7178    0.4878  0.2711
## I(PACKYEARS > 30)TRUE  0.3041    1.3554  0.2861
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.5703    0.5653  1.2030
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.8277    6.2195  1.1999
##
##              z Pr(>|z|)
## UICC_3CATIVA      3.95 8.0e-05 ***
## UICC_3CATIVB-C     5.88 4.1e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.74 0.4586
## HPV16_DNA_RNADNA+RNA+ -2.28 0.0228 *
## ALTER_3CAT(50,70]    -2.65 0.0081 **
## I(PACKYEARS > 30)TRUE  1.06 0.2879
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.47 0.6354
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.52 0.1277
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## UICC_3CATIVA          4.7254    0.2116    2.1847
```

```
## UICC_3CATIVB-C 17.0004 0.0588 6.6130
## HPV16_DNA_RNADNA+RNA- 0.6282 1.5919 0.1837
## HPV16_DNA_RNADNA+RNA+ 0.0968 10.3341 0.0130
## ALTER_3CAT(50,70] 0.4878 2.0500 0.2868
## I(PACKYEARS > 30)TRUE 1.3554 0.7378 0.7736
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.5653 1.7689 0.0535
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 6.2195 0.1608 0.5921
## upper .95
## UICC_3CATIVA 10.221
## UICC_3CATIVB-C 43.704
## HPV16_DNA_RNADNA+RNA- 2.148
## HPV16_DNA_RNADNA+RNA+ 0.722
## ALTER_3CAT(50,70] 0.830
## I(PACKYEARS > 30)TRUE 2.375
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 5.974
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 65.330
##
## Concordance= 0.734 (se = 0.04 )
## Rsquare= 0.231 (max possible= 0.945 )
## Likelihood ratio test= 52.9 on 8 df, p=1.14e-08
## Wald test = 43.5 on 8 df, p=7.03e-07
## Score (logrank) test = 52.9 on 8 df, p=1.15e-08

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA 0.0300 0.0529 0.8182
## UICC_3CATIVB-C 0.0396 0.0914 0.7624
## HPV16_DNA_RNADNA+RNA- -0.0348 0.0741 0.7855
## HPV16_DNA_RNADNA+RNA+ 0.0764 0.3491 0.5546
## ALTER_3CAT(50,70] -0.2428 3.7533 0.0527
## I(PACKYEARS > 30)TRUE 0.0621 0.2363 0.6269
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.0467 0.1348 0.7135
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0532 0.1864 0.6659
## GLOBAL NA 4.4746 0.8120
```

4.1.13 T, N, M, HPV16 DNA RNA, AGE(in categories: up to 50 or over 70 vs. between 50 and 70), PACKYEARS, 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= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##
```

	coef	exp(coef)	se(coef)
T_2CAT3-4	0.9901	2.6915	0.3408
N_2CATN2-N3	0.8302	2.2938	0.3195
M	2.4109	11.1438	0.5697
HPV16_DNA_RNADNA+RNA-	-0.0858	0.9178	0.6321
HPV16_DNA_RNADNA+RNA+	-1.8306	0.1603	1.0358
ALTER_3CAT(50,70]	-0.6671	0.5132	0.2692
I(PACKYEARS > 30)TRUE	0.4017	1.4944	0.2993
HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE	-0.6767	0.5083	1.2003
HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE	1.8387	6.2885	1.1995

```
##
##              z Pr(>|z|)
## T_2CAT3-4      2.91  0.0037 **
## N_2CATN2-N3    2.60  0.0094 **
## M              4.23  2.3e-05 ***
## HPV16_DNA_RNADNA+RNA- -0.14  0.8920
## HPV16_DNA_RNADNA+RNA+ -1.77  0.0772 .
## ALTER_3CAT(50,70] -2.48  0.0132 *
## I(PACKYEARS > 30)TRUE  1.34  0.1796
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.56  0.5729
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.53  0.1253
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
```

	exp(coef)	exp(-coef)	lower .95
T_2CAT3-4	2.692	0.3715	1.3801
N_2CATN2-N3	2.294	0.4359	1.2263
M	11.144	0.0897	3.6483
HPV16_DNA_RNADNA+RNA-	0.918	1.0896	0.2659
HPV16_DNA_RNADNA+RNA+	0.160	6.2373	0.0211
ALTER_3CAT(50,70]	0.513	1.9485	0.3028
I(PACKYEARS > 30)TRUE	1.494	0.6692	0.8311
HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE	0.508	1.9674	0.0483
HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE	6.289	0.1590	0.5992

```
##
##              upper .95
## T_2CAT3-4      5.25
## N_2CATN2-N3    4.29
## M              34.04
## HPV16_DNA_RNADNA+RNA- 3.17
```



```
## HPV16_DNA_RNADNA+RNA+ 1.22
## ALTER_3CAT(50,70] 0.87
## I(PACKYEARS > 30)TRUE 2.69
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 5.34
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 66.00
##
## Concordance= 0.75 (se = 0.04 )
## Rsquare= 0.233 (max possible= 0.945 )
## Likelihood ratio test= 53.4 on 9 df, p=2.42e-08
## Wald test = 49.1 on 9 df, p=1.56e-07
## Score (logrank) test = 69.7 on 9 df, p=1.78e-11

cox.zph(surv.res)

## rho chisq p
## T_2CAT3-4 -0.1023 0.7167 0.3972
## N_2CATN2-N3 0.0201 0.0279 0.8675
## M 0.0519 0.1734 0.6771
## HPV16_DNA_RNADNA+RNA- -0.0150 0.0139 0.9062
## HPV16_DNA_RNADNA+RNA+ 0.0719 0.3280 0.5668
## ALTER_3CAT(50,70] -0.2757 4.8036 0.0284
## I(PACKYEARS > 30)TRUE 0.0822 0.4299 0.5120
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.0332 0.0673 0.7953
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0626 0.2408 0.6236
## GLOBAL NA 6.8910 0.6485
```

4.1.14 T, N, M, HPV16 DNA RNA, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), PACKYEARS, 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= 201, number of events= 62
## (16 observations deleted due to missingness)
```

```
##
##
##          coef exp(coef) se(coef)
## T_2CAT3-4      0.9190    2.5069    0.4778
## N_2CATN2-N3     0.8185    2.2670    0.3244
## M              2.4067   11.0971    0.5701
## HPV16_DNA_RNADNA+RNA- -0.0904    0.9136    0.6327
## HPV16_DNA_RNADNA+RNA+ -1.8431    0.1583    1.0379
## ALTER_3CAT(50,70] -0.6613    0.5162    0.2706
## I(PACKYEARS > 30)TRUE  0.2945    1.3424    0.5944
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.1354    1.1450    0.6496
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.6731    0.5101    1.2008
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.8548    6.3906    1.2023
##
##          z Pr(>|z|)
## T_2CAT3-4      1.92    0.054 .
## N_2CATN2-N3     2.52    0.012 *
## M              4.22  2.4e-05 ***
## HPV16_DNA_RNADNA+RNA- -0.14    0.886
## HPV16_DNA_RNADNA+RNA+ -1.78    0.076 .
## ALTER_3CAT(50,70] -2.44    0.015 *
## I(PACKYEARS > 30)TRUE  0.50    0.620
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.21    0.835
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.56    0.575
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.54    0.123
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95
## T_2CAT3-4      2.507    0.3989    0.9826
## N_2CATN2-N3     2.267    0.4411    1.2004
## M             11.097    0.0901    3.6301
## HPV16_DNA_RNADNA+RNA-  0.914    1.0946    0.2644
## HPV16_DNA_RNADNA+RNA+  0.158    6.3163    0.0207
## ALTER_3CAT(50,70]    0.516    1.9374    0.3037
## I(PACKYEARS > 30)TRUE  1.342    0.7449    0.4187
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  1.145    0.8733    0.3205
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.510    1.9603    0.0485
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  6.391    0.1565    0.6056
##
##          upper .95
## T_2CAT3-4      6.395
## N_2CATN2-N3     4.281
## M             33.924
## HPV16_DNA_RNADNA+RNA-  3.157
## HPV16_DNA_RNADNA+RNA+  1.210
## ALTER_3CAT(50,70]    0.877
## I(PACKYEARS > 30)TRUE  4.304
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  4.091
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  5.368
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  67.438
```

```
##
## Concordance= 0.749 (se = 0.04 )
## Rsquare= 0.234 (max possible= 0.945 )
## Likelihood ratio test= 53.5 on 10 df, p=6.07e-08
## Wald test = 49.3 on 10 df, p=3.59e-07
## Score (logrank) test = 70.6 on 10 df, p=3.33e-11

cox.zph(surv.res)

##
## rho chisq p
## T_2CAT3-4 0.00408 0.00116 0.9729
## N_2CATN2-N3 0.03933 0.10076 0.7509
## M 0.05641 0.20371 0.6517
## HPV16_DNA_RNADNA+RNA- -0.01357 0.01142 0.9149
## HPV16_DNA_RNADNA+RNA+ 0.07711 0.38521 0.5348
## ALTER_3CAT(50,70] -0.27635 5.06725 0.0244
## I(PACKYEARS > 30)TRUE 0.14021 1.31100 0.2522
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.11626 0.83409 0.3611
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.03194 0.06240 0.8027
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.06842 0.29700 0.5858
## GLOBAL NA 7.68301 0.6598

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

4.1.15 UICC, HPV16 DNA RNA, AGE, PACKYEARS, Interaction HPV DNA RNA with 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 = ds[cur.subset, ])
best.model <- stepAIC(surv.res)

## Start: AIC=550.3
## 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
##
## Df AIC
## - GESCHLECHT 1 549
## - poly(ALTER, 2)[, 2] 1 549
## - HPV16_DNA_RNA:I(PACKYEARS > 30) 2 550
## - ALTER_3CAT 1 550
## <none> 550
## - UICC_3CAT 2 585
##
## Step: AIC=548.7
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
```

```
##      poly(ALTER, 2)[, 2] + I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS >
##      30)
##
##                                     Df AIC
## - poly(ALTER, 2)[, 2]                1 547
## - HPV16_DNA_RNA:I(PACKYEARS > 30)    2 548
## - ALTER_3CAT                        1 548
## <none>                               549
## - UICC_3CAT                          2 584
##
## Step:   AIC=547.4
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##      I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30)
##
##                                     Df AIC
## - HPV16_DNA_RNA:I(PACKYEARS > 30)    2 547
## <none>                               547
## - ALTER_3CAT                        1 552
## - UICC_3CAT                          2 582
##
## Step:   AIC=546.5
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##      I(PACKYEARS > 30)

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

best.model

## Error:  Objekt 'best.model' nicht gefunden
```

4.1.16 TP53, N1-N0 vs. N2-N3

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT + TP53, data = ds[cur.subset,
##      ])
##
##      n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3  0.918     2.504   0.280   3.27   0.0011 **
## TP53ND       -0.574     0.563   0.415  -1.39   0.1660
## TP53D         0.542     1.720   0.260   2.08   0.0371 *
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      2.504      0.399      1.45      4.34
## TP53ND           0.563      1.776      0.25      1.27
## TP53D            1.720      0.581      1.03      2.86
##
## Concordance= 0.673 (se = 0.037 )
## Rsquare= 0.101 (max possible= 0.954 )
## Likelihood ratio test= 23.1 on 3 df,  p=3.84e-05
## Wald test          = 21 on 3 df,  p=0.000106
## Score (logrank) test = 22.8 on 3 df,  p=4.39e-05

cox.zph(surv.res)

##               rho  chisq    p
## N_2CATN2-N3 -0.0130 0.0118 0.914
## TP53ND      0.0341 0.0818 0.775
## TP53D      -0.2430 4.3038 0.038
## GLOBAL      NA 5.0419 0.169
```

4.1.17 TP53, N1-N0 vs. N2-N3, Interaction

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT * TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT * TP53, data = ds[cur.subset,
##    ])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.7441    2.1046  0.3447  2.16  0.031 *
## TP53ND          -0.8207    0.4401  0.7741 -1.06  0.289
## TP53D           0.0844    1.0880  0.6485  0.13  0.896
## N_2CATN2-N3:TP53ND 0.3417    1.4073  0.9094  0.38  0.707
## N_2CATN2-N3:TP53D  0.5628    1.7556  0.7086  0.79  0.427
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      2.10      0.475      1.0710      4.14
## TP53ND           0.44      2.272      0.0965      2.01
## TP53D            1.09      0.919      0.3053      3.88
## N_2CATN2-N3:TP53ND 1.41      0.711      0.2368      8.36
```

```
## N_2CATN2-N3:TP53D      1.76      0.570      0.4378      7.04
##
## Concordance= 0.673 (se = 0.037 )
## Rsquare= 0.104 (max possible= 0.954 )
## Likelihood ratio test= 23.8 on 5 df, p=0.000235
## Wald test = 22.3 on 5 df, p=0.000456
## Score (logrank) test = 25.8 on 5 df, p=9.64e-05

cox.zph(surv.res)

##              rho chisq      p
## N_2CATN2-N3      0.0533 0.203 0.652
## TP53ND           0.0991 0.665 0.415
## TP53D           -0.0469 0.162 0.688
## N_2CATN2-N3:TP53ND -0.0938 0.610 0.435
## N_2CATN2-N3:TP53D -0.0600 0.263 0.608
## GLOBAL           NA 5.988 0.307
```

4.1.18 TP53, UICC

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + TP53, data = ds[cur.subset,
##      ])
##
## n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.367      3.922   0.383   3.57  0.00036 ***
## UICC_3CATIVB-C    2.151      8.591   0.458   4.69  2.7e-06 ***
## TP53ND           -0.384      0.681   0.416  -0.92  0.35497
## TP53D            0.632      1.881   0.261   2.42  0.01548 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.922      0.255      1.852      8.31
## UICC_3CATIVB-C    8.591      0.116      3.498     21.10
## TP53ND           0.681      1.469      0.302      1.54
## TP53D            1.881      0.532      1.128      3.14
##
## Concordance= 0.715 (se = 0.037 )
## Rsquare= 0.16 (max possible= 0.954 )
## Likelihood ratio test= 37.8 on 4 df, p=1.23e-07
```

```
## Wald test          = 31.5  on 4 df,    p=2.47e-06
## Score (logrank) test = 37.9  on 4 df,    p=1.18e-07

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA    0.00221 0.000341 0.9853
## UICC_3CATIVB-C -0.09740 0.686595 0.4073
## TP53ND          0.05335 0.203471 0.6519
## TP53D           -0.19862 2.931171 0.0869
## GLOBAL          NA 4.903684 0.2973
```

4.1.19 TP53, HPV16 DNA RNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + TP53,
##       data = ds[cur.subset, ])
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.601      0.548    0.523 -1.15    0.251
## HPV16_DNA_RNADNA+RNA+ -0.952      0.386    0.533 -1.79    0.074 .
## TP53ND                -0.864      0.421    0.463 -1.87    0.062 .
## TP53D                  0.626      1.870    0.283  2.21    0.027 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.548      1.823    0.197    1.53
## HPV16_DNA_RNADNA+RNA+    0.386      2.590    0.136    1.10
## TP53ND                   0.421      2.373    0.170    1.04
## TP53D                    1.870      0.535    1.074    3.26
##
## Concordance= 0.647 (se = 0.038 )
## Rsquare= 0.085 (max possible= 0.946 )
## Likelihood ratio test= 18 on 4 df, p=0.00123
## Wald test          = 16.5 on 4 df, p=0.00246
## Score (logrank) test = 18.2 on 4 df, p=0.00112

cox.zph(surv.res)
```

	rho	chisq	p
HPV16_DNA_RNADNA+RNA-	-0.0108	0.00722	0.932
HPV16_DNA_RNADNA+RNA+	-0.0409	0.10674	0.744
TP53ND	-0.0524	0.17593	0.675
TP53D	-0.1453	1.29155	0.256
GLOBAL	NA	1.33417	0.856

4.1.20 TP53, UICC, HPV16 DNA RNA

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + TP53, data = ds[
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       TP53, data = ds[cur.subset, ])
##
##    n= 203, number of events= 63
##    (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.434      4.195   0.394   3.64  0.00028 ***
## UICC_3CATIVB-C     2.622     13.763   0.476   5.51  3.7e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.890      0.411   0.529  -1.68  0.09284 .
## HPV16_DNA_RNADNA+RNA+ -1.231      0.292   0.535  -2.30  0.02129 *
## TP53ND            -0.751      0.472   0.473  -1.59  0.11221
## TP53D              0.543      1.722   0.286   1.90  0.05724 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.195      0.2384      1.937      9.084
## UICC_3CATIVB-C    13.763      0.0727      5.412     35.005
## HPV16_DNA_RNADNA+RNA- 0.411      2.4348      0.145      1.159
## HPV16_DNA_RNADNA+RNA+ 0.292      3.4245      0.102      0.833
## TP53ND            0.472      2.1194      0.187      1.192
## TP53D             1.722      0.5809      0.983      3.014
##
## Concordance= 0.737 (se = 0.04 )
## Rsquare= 0.224 (max possible= 0.946 )
## Likelihood ratio test= 51.4 on 6 df, p=2.5e-09
## Wald test              = 45.2 on 6 df, p=4.21e-08
## Score (logrank) test = 55.7 on 6 df, p=3.41e-10

cox.zph(surv.res)

##              rho  chisq      p

```



```
## UICC_3CATIVA          0.0383 0.0856 0.770
## UICC_3CATIVB-C        0.0134 0.0109 0.917
## HPV16_DNA_RNADNA+RNA- -0.0320 0.0653 0.798
## HPV16_DNA_RNADNA+RNA+ -0.0152 0.0140 0.906
## TP53ND                -0.0646 0.2769 0.599
## TP53D                 -0.0891 0.4894 0.484
## GLOBAL                NA 0.7891 0.992
```

4.1.21 TP53, N0-N1 vs. N2-N3, HPV16 DNA RNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT + HPV16_DNA_RNA + TP53, data = ds[cur
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT + HPV16_DNA_RNA +
##       TP53, data = ds[cur.subset, ])
##
##      n= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      1.100      3.004   0.296  3.72  0.0002 ***
## HPV16_DNA_RNADNA+RNA- -0.719      0.487   0.526 -1.37  0.1714
## HPV16_DNA_RNADNA+RNA+ -1.187      0.305   0.535 -2.22  0.0265 *
## TP53ND           -0.930      0.395   0.467 -1.99  0.0467 *
## TP53D             0.463      1.589   0.285  1.63  0.1039
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      3.004      0.333   1.682   5.364
## HPV16_DNA_RNADNA+RNA- 0.487      2.053   0.174   1.365
## HPV16_DNA_RNADNA+RNA+ 0.305      3.278   0.107   0.871
## TP53ND           0.395      2.533   0.158   0.987
## TP53D            1.589      0.629   0.909   2.775
##
## Concordance= 0.705 (se = 0.04 )
## Rsquare= 0.153 (max possible= 0.946 )
## Likelihood ratio test= 33.8 on 5 df,  p=2.6e-06
## Wald test              = 30 on 5 df,  p=1.49e-05
## Score (logrank) test = 33.7 on 5 df,  p=2.76e-06

cox.zph(surv.res)

##              rho chisq      p
## N_2CATN2-N3      0.0319 0.0602 0.806
```

```
## HPV16_DNA_RNADNA+RNA- -0.0371 0.0816 0.775
## HPV16_DNA_RNADNA+RNA+ -0.0379 0.0912 0.763
## TP53ND -0.0604 0.2322 0.630
## TP53D -0.1318 1.0279 0.311
## GLOBAL NA 1.1872 0.946
```

4.1.22 TP53, N0-N1 vs. N2-N3, HPV16 DNA RNA, IR Cluster

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT + HPV16_DNA_RNA + TP53 + IS_ATYPICAL,
  data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT + HPV16_DNA_RNA +
##       TP53 + IS_ATYPICAL, data = ds[cur.subset, ])
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      1.0973    2.9961  0.2986  3.67 0.00024 ***
## HPV16_DNA_RNADNA+RNA- -0.7163    0.4886  0.5280 -1.36 0.17494
## HPV16_DNA_RNADNA+RNA+ -1.1984    0.3017  0.5637 -2.13 0.03351 *
## TP53ND          -0.9329    0.3934  0.4704 -1.98 0.04733 *
## TP53D           0.4615    1.5864  0.2855  1.62 0.10598
## IS_ATYPICALAtypical  0.0197    1.0199  0.3130  0.06 0.94975
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      2.996    0.334    1.6686    5.379
## HPV16_DNA_RNADNA+RNA- 0.489    2.047    0.1736    1.375
## HPV16_DNA_RNADNA+RNA+ 0.302    3.315    0.0999    0.911
## TP53ND          0.393    2.542    0.1565    0.989
## TP53D           1.586    0.630    0.9066    2.776
## IS_ATYPICALAtypical 1.020    0.980    0.5523    1.884
##
## Concordance= 0.708 (se = 0.04 )
## Rsquare= 0.153 (max possible= 0.946 )
## Likelihood ratio test= 33.8 on 6 df,  p=7.31e-06
## Wald test = 30 on 6 df,  p=3.98e-05
## Score (logrank) test = 33.7 on 6 df,  p=7.71e-06

cox.zph(surv.res)

##              rho chisq      p
## N_2CATN2-N3      0.0394 0.0902 0.764
```

```
## HPV16_DNA_RNADNA+RNA- -0.0413 0.1027 0.749
## HPV16_DNA_RNADNA+RNA+ -0.0185 0.0225 0.881
## TP53ND -0.0536 0.1849 0.667
## TP53D -0.1255 0.9707 0.325
## IS_ATYPICALAtypical -0.0521 0.1898 0.663
## GLOBAL NA 1.3921 0.966
```

4.1.23 TP53, AGE (in categories: up to 50 or over 70 vs. between 50 and 70)

```
surv.res <- coxph(surv.obj[cur.subset] ~ ALTER_3CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ ALTER_3CAT + TP53, data = ds[cur.subset,
##      ])
##
##      n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.479      0.619   0.242 -1.98   0.048 *
## TP53ND -0.643      0.526   0.419 -1.53   0.125
## TP53D 0.640      1.896   0.260 2.46   0.014 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70] 0.619      1.615   0.385   0.995
## TP53ND 0.526      1.902   0.231   1.195
## TP53D 1.896      0.528   1.139   3.155
##
## Concordance= 0.631 (se = 0.037 )
## Rsquare= 0.066 (max possible= 0.954 )
## Likelihood ratio test= 14.7 on 3 df, p=0.00207
## Wald test = 14.6 on 3 df, p=0.00219
## Score (logrank) test = 15.4 on 3 df, p=0.00149

cox.zph(surv.res)

##              rho chisq      p
## ALTER_3CAT(50,70] -0.10586 0.8338 0.3612
## TP53ND -0.00967 0.0066 0.9352
## TP53D -0.24914 4.6319 0.0314
## GLOBAL NA 5.7489 0.1245
```

4.1.24 TP53, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), UICC

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + TP53, data = ds[cur
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       TP53, data = ds[cur.subset, ])
##
##    n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.400      4.054   0.384   3.65  0.00026 ***
## UICC_3CATIVB-C     2.260      9.584   0.462   4.89   1e-06 ***
## ALTER_3CAT(50,70] -0.602      0.548   0.245  -2.45  0.01413 *
## TP53ND            -0.363      0.696   0.417  -0.87  0.38417
## TP53D              0.631      1.879   0.262   2.41  0.01592 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.054      0.247   1.912      8.597
## UICC_3CATIVB-C     9.584      0.104   3.875     23.706
## ALTER_3CAT(50,70]  0.548      1.826   0.339      0.886
## TP53ND            0.696      1.437   0.308      1.575
## TP53D             1.879      0.532   1.125      3.139
##
## Concordance= 0.718 (se = 0.038 )
## Rsquare= 0.182 (max possible= 0.954 )
## Likelihood ratio test= 43.6 on 5 df,  p=2.74e-08
## Wald test            = 37.3 on 5 df,  p=5.23e-07
## Score (logrank) test = 44 on 5 df,  p=2.29e-08

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0124 0.0104 0.9186
## UICC_3CATIVB-C    -0.0747 0.3899 0.5323
## ALTER_3CAT(50,70] -0.1278 1.2064 0.2720
## TP53ND            0.0486 0.1689 0.6811
## TP53D            -0.1965 2.8683 0.0903
## GLOBAL              NA  5.7182 0.3346

```

4.1.25 TP53, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), HPV16 DNA RNA

```

surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + ALTER_3CAT + TP53,
  data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + ALTER_3CAT +
##       TP53, data = ds[cur.subset, ])
##
##      n= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.628    0.534    0.527 -1.19   0.233
## HPV16_DNA_RNADNA+RNA+ -0.907    0.404    0.533 -1.70   0.089 .
## ALTER_3CAT(50,70]      -0.449    0.638    0.257 -1.75   0.081 .
## TP53ND                  -0.837    0.433    0.464 -1.80   0.071 .
## TP53D                   0.635    1.887    0.284  2.24   0.025 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.534      1.87    0.190    1.50
## HPV16_DNA_RNADNA+RNA+    0.404      2.48    0.142    1.15
## ALTER_3CAT(50,70]        0.638      1.57    0.386    1.06
## TP53ND                   0.433      2.31    0.174    1.08
## TP53D                    1.887      0.53    1.082    3.29
##
## Concordance= 0.65 (se = 0.04 )
## Rsquare= 0.098 (max possible= 0.946 )
## Likelihood ratio test= 21 on 5 df, p=0.000807
## Wald test              = 19.3 on 5 df, p=0.00166
## Score (logrank) test = 21.2 on 5 df, p=0.000729

cox.zph(surv.res)

##              rho chisq      p
## HPV16_DNA_RNADNA+RNA- -0.0286 0.0500 0.823
## HPV16_DNA_RNADNA+RNA+ -0.0340 0.0733 0.787
## ALTER_3CAT(50,70]      -0.1413 1.2930 0.256
## TP53ND                  -0.0571 0.2091 0.647
## TP53D                   -0.1416 1.2386 0.266
## GLOBAL                  NA 2.7004 0.746

```

4.1.26 TP53, UICC, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), HPV16 DNA RNA

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
  TP53, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER_3CAT + TP53, data = ds[cur.subset, ])
##
##      n= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.478    4.384   0.396   3.73 0.00019 ***
## UICC_3CATIVB-C      2.743   15.531   0.483   5.68 1.3e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.896    0.408   0.535  -1.67 0.09394 .
## HPV16_DNA_RNADNA+RNA+ -1.283    0.277   0.536  -2.39 0.01671 *
## ALTER_3CAT(50,70]   -0.593    0.553   0.260  -2.28 0.02263 *
## TP53ND             -0.702    0.495   0.474  -1.48 0.13871
## TP53D              0.526    1.692   0.287   1.83 0.06677 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.384    0.2281    2.016    9.533
## UICC_3CATIVB-C     15.531    0.0644    6.028   40.012
## HPV16_DNA_RNADNA+RNA-  0.408    2.4487    0.143    1.165
## HPV16_DNA_RNADNA+RNA+  0.277    3.6061    0.097    0.793
## ALTER_3CAT(50,70]    0.553    1.8097    0.332    0.920
## TP53ND             0.495    2.0185    0.196    1.255
## TP53D              1.692    0.5910    0.964    2.969
##
## Concordance= 0.738 (se = 0.04 )
## Rsquare= 0.243 (max possible= 0.946 )
## Likelihood ratio test= 56.5 on 7 df,  p=7.69e-10
## Wald test              = 49.4 on 7 df,  p=1.86e-08
## Score (logrank) test = 59.8 on 7 df,  p=1.64e-10

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0703 0.2814 0.5958
## UICC_3CATIVB-C      0.0633 0.2347 0.6280
## HPV16_DNA_RNADNA+RNA- -0.0641 0.2577 0.6117
## HPV16_DNA_RNADNA+RNA+ -0.0298 0.0539 0.8165
## ALTER_3CAT(50,70]   -0.2057 2.7155 0.0994
## TP53ND             -0.0629 0.2612 0.6093
## TP53D             -0.1008 0.6297 0.4275
## GLOBAL              NA 3.9090 0.7902

```

4.1.27 TP53, UICC, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), HPV16 DNA RNA, PACKYEARS (cut at 30)

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + I(PACKYEARS >
  30) + ALTER_3CAT + TP53, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       I(PACKYEARS > 30) + ALTER_3CAT + TP53, data = ds[cur.subset,
##       ])
##
##      n= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.457    4.294   0.397   3.67  0.00024 ***
## UICC_3CATIVB-C     2.743   15.532   0.483   5.68  1.3e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.711    0.491   0.543  -1.31  0.19026
## HPV16_DNA_RNADNA+RNA+ -1.215    0.297   0.540  -2.25  0.02457 *
## I(PACKYEARS > 30)TRUE  0.383    1.466   0.272   1.41  0.15955
## ALTER_3CAT(50,70]    -0.674    0.510   0.271  -2.49  0.01278 *
## TP53ND             -0.705    0.494   0.473  -1.49  0.13617
## TP53D              0.496    1.643   0.292   1.70  0.08923 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.294    0.2329    1.974    9.343
## UICC_3CATIVB-C    15.532    0.0644    6.030   40.011
## HPV16_DNA_RNADNA+RNA-  0.491    2.0358    0.170    1.423
## HPV16_DNA_RNADNA+RNA+  0.297    3.3701    0.103    0.856
## I(PACKYEARS > 30)TRUE  1.466    0.6819    0.860    2.500
## ALTER_3CAT(50,70]    0.510    1.9624    0.300    0.866
## TP53ND            0.494    2.0237    0.196    1.249
## TP53D            1.643    0.6088    0.927    2.911
##
## Concordance= 0.75 (se = 0.04 )
## Rsquare= 0.247 (max possible= 0.945 )
## Likelihood ratio test= 57.1 on 8 df,  p=1.72e-09
## Wald test              = 50.4 on 8 df,  p=3.44e-08
## Score (logrank) test = 60.8 on 8 df,  p=3.28e-10

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0544 0.1672 0.6826
## UICC_3CATIVB-C      0.0513 0.1485 0.7000

```

```
## HPV16_DNA_RNADNA+RNA- -0.0283 0.0503 0.8225
## HPV16_DNA_RNADNA+RNA+ -0.0131 0.0107 0.9176
## I(PACKYEARS > 30)TRUE 0.0651 0.2528 0.6151
## ALTER_3CAT(50,70] -0.2376 3.2611 0.0709
## TP53ND -0.0456 0.1336 0.7147
## TP53D -0.1504 1.3318 0.2485
## GLOBAL NA 4.7032 0.7888
```

4.1.28 TP53, UICC, AGE, HPV16 DNA RNA, PACKYEARS, Interaction HPV16 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) + ALTER_3CAT + TP53, data = ds[cur.subset,
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##      I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30) + ALTER_3CAT +
##      TP53, data = ds[cur.subset, ])
##
##      n= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##
##              coef exp(coef) se(coef)
## UICC_3CATIVA      1.497      4.469   0.398
## UICC_3CATIVB-C     2.727     15.291   0.484
## HPV16_DNA_RNADNA+RNA- -0.824    0.439   0.651
## HPV16_DNA_RNADNA+RNA+ -2.236    0.107   1.030
## I(PACKYEARS > 30)TRUE  0.243    1.276   0.288
## ALTER_3CAT(50,70] -0.639    0.528   0.271
## TP53ND -0.695    0.499   0.482
## TP53D  0.514    1.673   0.295
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.204    1.226   1.241
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 1.860    6.425   1.201
##
##              z Pr(>|z|)
## UICC_3CATIVA      3.76 0.00017 ***
## UICC_3CATIVB-C     5.63 1.8e-08 ***
## HPV16_DNA_RNADNA+RNA- -1.27 0.20550
## HPV16_DNA_RNADNA+RNA+ -2.17 0.02993 *
## I(PACKYEARS > 30)TRUE  0.85 0.39794
## ALTER_3CAT(50,70] -2.36 0.01838 *
## TP53ND -1.44 0.14918
## TP53D  1.74 0.08099 .
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.16 0.86960
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 1.55 0.12133
## ---
```



```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
## exp(coef) exp(-coef) lower .95
## UICC_3CATIVA 4.469 0.2238 2.0481
## UICC_3CATIVB-C 15.291 0.0654 5.9212
## HPV16_DNA_RNADNA+RNA- 0.439 2.2791 0.1226
## HPV16_DNA_RNADNA+RNA+ 0.107 9.3540 0.0142
## I(PACKYEARS > 30)TRUE 1.276 0.7840 0.7255
## ALTER_3CAT(50,70] 0.528 1.8951 0.3102
## TP53ND 0.499 2.0028 0.1943
## TP53D 1.673 0.5979 0.9386
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 1.226 0.8157 0.1077
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 6.425 0.1556 0.6107
##
## upper .95
## UICC_3CATIVA 9.750
## UICC_3CATIVB-C 39.490
## HPV16_DNA_RNADNA+RNA- 1.571
## HPV16_DNA_RNADNA+RNA+ 0.805
## I(PACKYEARS > 30)TRUE 2.243
## ALTER_3CAT(50,70] 0.898
## TP53ND 1.283
## TP53D 2.980
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 13.949
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 67.593
##
## Concordance= 0.757 (se = 0.04 )
## Rsquare= 0.258 (max possible= 0.945 )
## Likelihood ratio test= 59.9 on 10 df, p=3.71e-09
## Wald test = 49.8 on 10 df, p=2.97e-07
## Score (logrank) test = 61.9 on 10 df, p=1.61e-09

cox.zph(surv.res)

##
## rho chisq p
## UICC_3CATIVA 0.0634 0.236 0.6274
## UICC_3CATIVB-C 0.0600 0.208 0.6483
## HPV16_DNA_RNADNA+RNA- -0.0576 0.206 0.6500
## HPV16_DNA_RNADNA+RNA+ 0.0604 0.218 0.6403
## I(PACKYEARS > 30)TRUE 0.0552 0.188 0.6646
## ALTER_3CAT(50,70] -0.2389 3.479 0.0621
## TP53ND -0.0534 0.196 0.6576
## TP53D -0.1417 1.178 0.2777
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.0532 0.187 0.6655
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0559 0.205 0.6510
## GLOBAL NA 5.561 0.8507
```

4.1.29 TP53, T, N, M, HPV16 DNA RNA, AGE, PACKYEARS, Interaction HPV DNA RNA with PACKYEARS, Interaction T with PACKYEARS

```

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 + TP53, 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 + TP53, data = ds[cur.subset,
## ])
##
## n= 201, number of events= 62
## (16 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## T_2CAT3-4        0.9931    2.6996  0.4837
## N_2CATN2-N3       0.7661    2.1513  0.3253
## M                2.2955    9.9297  0.5730
## HPV16_DNA_RNADNA+RNA- -0.3620    0.6963  0.6475
## HPV16_DNA_RNADNA+RNA+ -1.8178    0.1624  1.0434
## ALTER_3CAT(50,70] -0.5637    0.5691  0.2721
## I(PACKYEARS > 30)TRUE  0.2962    1.3447  0.6042
## TP53ND           -0.8643    0.4213  0.4901
## TP53D            0.3957    1.4855  0.2984
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.0633    1.0653  0.6599
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.2609    0.7703  1.2168
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.8458    6.3335  1.2014
##
##               z Pr(>|z|)
## T_2CAT3-4      2.05   0.040 *
## N_2CATN2-N3    2.35   0.019 *
## M              4.01  6.2e-05 ***
## HPV16_DNA_RNADNA+RNA- -0.56   0.576
## HPV16_DNA_RNADNA+RNA+ -1.74   0.081 .
## ALTER_3CAT(50,70] -2.07   0.038 *
## I(PACKYEARS > 30)TRUE  0.49   0.624
## TP53ND         -1.76   0.078 .
## TP53D           1.33   0.185
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.10   0.924
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.21   0.830
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.54   0.124
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95

```

```

## T_2CAT3-4                2.700      0.370      1.0461
## N_2CATN2-N3              2.151      0.465      1.1371
## M                        9.930      0.101      3.2299
## HPV16_DNA_RNADNA+RNA-    0.696      1.436      0.1957
## HPV16_DNA_RNADNA+RNA+    0.162      6.159      0.0210
## ALTER_3CAT(50,70]       0.569      1.757      0.3339
## I(PACKYEARS > 30)TRUE    1.345      0.744      0.4115
## TP53ND                   0.421      2.373      0.1612
## TP53D                    1.485      0.673      0.8277
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 1.065      0.939      0.2923
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.770      1.298      0.0709
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 6.333      0.158      0.6012
##
##                                upper .95
## T_2CAT3-4                    6.97
## N_2CATN2-N3                  4.07
## M                           30.53
## HPV16_DNA_RNADNA+RNA-       2.48
## HPV16_DNA_RNADNA+RNA+       1.26
## ALTER_3CAT(50,70]           0.97
## I(PACKYEARS > 30)TRUE       4.39
## TP53ND                      1.10
## TP53D                       2.67
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 3.88
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 8.36
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 66.72
##
## Concordance= 0.77 (se = 0.04 )
## Rsquare= 0.261 (max possible= 0.945 )
## Likelihood ratio test= 60.9 on 12 df, p=1.55e-08
## Wald test = 55 on 12 df, p=1.81e-07
## Score (logrank) test = 78.7 on 12 df, p=7.26e-12

cox.zph(surv.res)

##                                rho  chisq    p
## T_2CAT3-4                    -0.0156 0.0168 0.8968
## N_2CATN2-N3                   0.0635 0.2576 0.6118
## M                             0.0443 0.1244 0.7243
## HPV16_DNA_RNADNA+RNA-        -0.0548 0.1833 0.6686
## HPV16_DNA_RNADNA+RNA+         0.0538 0.1868 0.6656
## ALTER_3CAT(50,70]           -0.2836 5.1241 0.0236
## I(PACKYEARS > 30)TRUE         0.1048 0.7346 0.3914
## TP53ND                      -0.0871 0.5359 0.4641
## TP53D                       -0.1926 2.2047 0.1376
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.0717 0.3166 0.5737
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.0471 0.1384 0.7099
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0728 0.3369 0.5616
## GLOBAL                       NA 9.2132 0.6846

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

```

4.1.30 TP53, UICC, HPV16 RNA, AGE as a continuous covariate, PACK-YEARS continuous

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER + PACKYEARS + TP53, data = ds[cur.subset, ], model = TRUE)
##
##      n= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.428024  4.170451  0.396793   3.60  0.00032 ***
## UICC_3CATIVB-C      2.599620 13.458623  0.479549   5.42  5.9e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.775510  0.460469  0.536578  -1.45  0.14838
## HPV16_DNA_RNADNA+RNA+ -1.373083  0.253325  0.543195  -2.53  0.01148 *
## ALTER              0.025735  1.026069  0.012916   1.99  0.04631 *
## PACKYEARS          -0.000127  0.999873  0.005725  -0.02  0.98228
## TP53ND             -0.721241  0.486148  0.470711  -1.53  0.12546
## TP53D              0.658723  1.932323  0.295792   2.23  0.02595 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.170      0.2398    1.9162    9.077
## UICC_3CATIVB-C     13.459      0.0743    5.2578   34.450
## HPV16_DNA_RNADNA+RNA-  0.460      2.1717    0.1609    1.318
## HPV16_DNA_RNADNA+RNA+  0.253      3.9475    0.0874    0.735
## ALTER              1.026      0.9746    1.0004    1.052
## PACKYEARS          1.000      1.0001    0.9887    1.011
## TP53ND             0.486      2.0570    0.1932    1.223
## TP53D              1.932      0.5175    1.0822    3.450
##
## Concordance= 0.756 (se = 0.04 )
## Rsquare= 0.236 (max possible= 0.945 )
## Likelihood ratio test= 54.2 on 8 df,  p=6.24e-09
## Wald test              = 47.3 on 8 df,  p=1.32e-07
## Score (logrank) test = 57.5 on 8 df,  p=1.43e-09

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.03021 0.051663 0.820
## UICC_3CATIVB-C      0.02309 0.031529 0.859
## HPV16_DNA_RNADNA+RNA- -0.05357 0.187806 0.665

```

```
## HPV16_DNA_RNADNA+RNA+ -0.00274 0.000467 0.983
## ALTER -0.12621 1.299258 0.254
## PACKYEARS -0.05991 0.213341 0.644
## TP53ND -0.04046 0.104516 0.746
## TP53D -0.12609 0.950448 0.330
## GLOBAL NA 2.301912 0.970

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

##          hr 2.5 % 97.5 %      p
## UICC_3CATIVA      4.17  1.92   9.08 0.000
## UICC_3CATIVB-C    13.46  5.26  34.45 0.000
## HPV16_DNA_RNADNA+RNA- 0.46  0.16   1.32 0.148
## HPV16_DNA_RNADNA+RNA+ 0.25  0.09   0.73 0.011
## ALTER            1.03  1.00   1.05 0.046
## PACKYEARS         1.00  0.99   1.01 0.982
## TP53ND            0.49  0.19   1.22 0.125
## TP53D             1.93  1.08   3.45 0.026

# 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 29.54    3.8e-07 ***
## HPV16_DNA_RNA  2  7.98    0.0185 *
## ALTER          1  3.97    0.0463 *
## PACKYEARS       1  0.00    0.9823
## TP53           2  9.82    0.0074 **
## Residuals     193
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

4.1.31 TP53, 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") + TP53,
  data = ds[cur.subset, ], model = TRUE)
```

```
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER + PACKYEARS + relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") +
##       TP53, data = ds[cur.subset, ], model = TRUE)
##
##      n= 198, number of events= 61
##      (19 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        1.37382
## UICC_3CATIVB-C                      2.75973
## HPV16_DNA_RNADNA+RNA-              -0.82892
## HPV16_DNA_RNADNA+RNA+              -1.48832
## ALTER                             0.02812
## PACKYEARS                          0.00112
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.07614
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.32604
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     -0.51036
## TP53ND                             -0.72932
## TP53D                              0.57895
##                                     exp(coef)
## UICC_3CATIVA                        3.95042
## UICC_3CATIVB-C                      15.79559
## HPV16_DNA_RNADNA+RNA-              0.43652
## HPV16_DNA_RNADNA+RNA+              0.22575
## ALTER                             1.02852
## PACKYEARS                          1.00112
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.07911
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.38546
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     0.60028
## TP53ND                             0.48224
## TP53D                             1.78417
##                                     se(coef)
## UICC_3CATIVA                        0.40203
## UICC_3CATIVB-C                      0.50022
## HPV16_DNA_RNADNA+RNA-              0.54818
## HPV16_DNA_RNADNA+RNA+              0.57988
## ALTER                             0.01367
## PACKYEARS                          0.00584
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.34569
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.43415
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     0.43590
## TP53ND                             0.47609
## TP53D                             0.30172
##                                     z
## UICC_3CATIVA                        3.42
```

```

## UICC_3CATIVB-C 5.52
## HPV16_DNA_RNADNA+RNA- -1.51
## HPV16_DNA_RNADNA+RNA+ -2.57
## ALTER 2.06
## PACKYEARS 0.19
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.22
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.75
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -1.17
## TP53ND -1.53
## TP53D 1.92
## Pr(>|z|)
## UICC_3CATIVA 0.00063
## UICC_3CATIVB-C 3.4e-08
## HPV16_DNA_RNADNA+RNA- 0.13050
## HPV16_DNA_RNADNA+RNA+ 0.01027
## ALTER 0.03971
## PACKYEARS 0.84759
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.82568
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.45267
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.24168
## TP53ND 0.12555
## TP53D 0.05500
##
## 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
## TP53ND
## TP53D .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef)
## UICC_3CATIVA 3.950
## UICC_3CATIVB-C 15.796
## HPV16_DNA_RNADNA+RNA- 0.437
## HPV16_DNA_RNADNA+RNA+ 0.226
## ALTER 1.029
## PACKYEARS 1.001
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.079
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.385
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.600
## TP53ND 0.482

```

```

## TP53D 1.784
## exp(-coef)
## UICC_3CATIVA 0.2531
## UICC_3CATIVB-C 0.0633
## HPV16_DNA_RNADNA+RNA- 2.2908
## HPV16_DNA_RNADNA+RNA+ 4.4296
## ALTER 0.9723
## PACKYEARS 0.9989
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.9267
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.7218
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.6659
## TP53ND 2.0737
## TP53D 0.5605
## lower .95
## UICC_3CATIVA 1.7965
## UICC_3CATIVB-C 5.9258
## HPV16_DNA_RNADNA+RNA- 0.1491
## HPV16_DNA_RNADNA+RNA+ 0.0725
## ALTER 1.0013
## PACKYEARS 0.9897
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.5480
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.5916
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.2555
## TP53ND 0.1897
## TP53D 0.9877
## upper .95
## UICC_3CATIVA 8.687
## UICC_3CATIVB-C 42.104
## HPV16_DNA_RNADNA+RNA- 1.278
## HPV16_DNA_RNADNA+RNA+ 0.703
## ALTER 1.056
## PACKYEARS 1.013
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 2.125
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 3.244
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.411
## TP53ND 1.226
## TP53D 3.223
##
## Concordance= 0.756 (se = 0.041 )
## Rsquare= 0.251 (max possible= 0.944 )
## Likelihood ratio test= 57.2 on 11 df, p=3.08e-08
## Wald test = 49.8 on 11 df, p=6.77e-07
## Score (logrank) test = 61.1 on 11 df, p=5.75e-09

cox.zph(surv.res)

## rho
## UICC_3CATIVA 0.0220
## UICC_3CATIVB-C 0.0608

```



```

## HPV16_DNA_RNADNA+RNA- -0.0886
## HPV16_DNA_RNADNA+RNA+ -0.0665
## ALTER -0.0806
## PACKYEARS -0.0390
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.0812
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.0453
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -0.2307
## TP53ND -0.0535
## TP53D -0.1498
## GLOBAL NA
## chisq
## UICC_3CATIVA 0.0268
## UICC_3CATIVB-C 0.2671
## HPV16_DNA_RNADNA+RNA- 0.4856
## HPV16_DNA_RNADNA+RNA+ 0.2631
## ALTER 0.5739
## PACKYEARS 0.0884
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.4127
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.1307
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 3.2470
## TP53ND 0.1868
## TP53D 1.3317
## GLOBAL 5.8352
## p
## UICC_3CATIVA 0.8699
## UICC_3CATIVB-C 0.6053
## HPV16_DNA_RNADNA+RNA- 0.4859
## HPV16_DNA_RNADNA+RNA+ 0.6080
## ALTER 0.4487
## PACKYEARS 0.7662
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.5206
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.7177
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.0716
## TP53ND 0.6656
## TP53D 0.2485
## GLOBAL 0.8841

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

## hr 2.5 %
## UICC_3CATIVA 3.95 1.80
## UICC_3CATIVB-C 15.80 5.93
## HPV16_DNA_RNADNA+RNA- 0.44 0.15
## HPV16_DNA_RNADNA+RNA+ 0.23 0.07
## ALTER 1.03 1.00
## PACKYEARS 1.00 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.08 0.55
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.39 0.59

```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.60  0.26
## TP53ND                                                            0.48  0.19
## TP53D                                                             1.78  0.99
##                                                                    97.5 %
## UICC_3CATIVA                                                       8.69
## UICC_3CATIVB-C                                                    42.10
## HPV16_DNA_RNADNA+RNA-                                             1.28
## HPV16_DNA_RNADNA+RNA+                                             0.70
## ALTER                                                             1.06
## PACKYEARS                                                         1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris   2.12
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx  3.24
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      1.41
## TP53ND                                                            1.23
## TP53D                                                             3.22
##                                                                    p
## UICC_3CATIVA                                                       0.001
## UICC_3CATIVB-C                                                    0.000
## HPV16_DNA_RNADNA+RNA-                                             0.131
## HPV16_DNA_RNADNA+RNA+                                             0.010
## ALTER                                                             0.040
## PACKYEARS                                                         0.848
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.826
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.453
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.242
## TP53ND                                                            0.126
## TP53D                                                             0.055

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 30.89    2e-07
## HPV16_DNA_RNA                                                     2  7.98    0.019
## ALTER                                                             1  4.23    0.040
## PACKYEARS                                                         1  0.04    0.848
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")             3  3.26    0.354
## TP53                                                             2  8.13    0.017
## Residuals                                                         187
##
## UICC_3CAT                                                         ***
## HPV16_DNA_RNA                                                     *
## ALTER                                                             *
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")
## TP53                                                             *
## Residuals

```

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

4.1.32 TP53, Consensus Clusters

```
surv.res <- coxph(surv.obj[cur.subset] ~ CONSENSUS_CLUSTER + TP53, data = ds[cur.subs
], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ CONSENSUS_CLUSTER + TP53,
##       data = ds[cur.subset, ], model = TRUE)
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## CONSENSUS_CLUSTERBasal      0.180      1.197   0.339  0.53   0.596
## CONSENSUS_CLUSTERClassical -0.425      0.654   0.564 -0.75   0.451
## CONSENSUS_CLUSTERMesenchymal 0.750      2.117   0.318  2.36   0.018 *
## TP53ND                      -0.701      0.496   0.421 -1.66   0.096 .
## TP53D                        0.663      1.941   0.261  2.54   0.011 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## CONSENSUS_CLUSTERBasal      1.197      0.835      0.616      2.33
## CONSENSUS_CLUSTERClassical    0.654      1.529      0.217      1.97
## CONSENSUS_CLUSTERMesenchymal  2.117      0.472      1.135      3.95
## TP53ND                      0.496      2.015      0.218      1.13
## TP53D                        1.941      0.515      1.164      3.24
##
## Concordance= 0.662 (se = 0.038 )
## Rsquare= 0.09 (max possible= 0.954 )
## Likelihood ratio test= 20.5 on 5 df,  p=0.000996
## Wald test = 20 on 5 df,  p=0.00125
## Score (logrank) test = 21.2 on 5 df,  p=0.000736
# coxtable(surv.res)
Anova(surv.res, type = 2, test.statistic = "Wald")
## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##               Df Chisq Pr(>Chisq)
## CONSENSUS_CLUSTER    3  9.46   0.0238 *
## TP53                  2 11.96   0.0025 **
## Residuals            212
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

4.1.33 TP53, HPV16 DNA RNA, Consensus Clusters

```

surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + CONSENSUS_CLUSTER +
  TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + CONSENSUS_CLUSTER +
##       TP53, data = ds[cur.subset, ], model = TRUE)
##
##    n= 203, number of events= 63
##    (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA-   -0.474    0.623   0.524 -0.90   0.366
## HPV16_DNA_RNADNA+RNA+   -1.126    0.324   0.559 -2.01   0.044 *
## CONSENSUS_CLUSTERBasal  -0.506    0.603   0.373 -1.36   0.175
## CONSENSUS_CLUSTERClassical -0.905    0.405   0.571 -1.59   0.113
## CONSENSUS_CLUSTERMesenchymal 0.197    1.218   0.329  0.60   0.549
## TP53ND                  -0.909    0.403   0.461 -1.97   0.048 *
## TP53D                    0.618    1.856   0.286  2.16   0.031 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.623    1.606    0.223    1.738
## HPV16_DNA_RNADNA+RNA+    0.324    3.082    0.108    0.971
## CONSENSUS_CLUSTERBasal    0.603    1.658    0.290    1.253
## CONSENSUS_CLUSTERClassical 0.405    2.472    0.132    1.238
## CONSENSUS_CLUSTERMesenchymal 1.218    0.821    0.639    2.322
## TP53ND                   0.403    2.483    0.163    0.994
## TP53D                     1.856    0.539    1.059    3.254
##
## Concordance= 0.698 (se = 0.04 )
## Rsquare= 0.121 (max possible= 0.946 )
## Likelihood ratio test= 26.1 on 7 df, p=0.000478
## Wald test               = 24.7 on 7 df, p=0.000852
## Score (logrank) test = 27.4 on 7 df, p=0.000288

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

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##              Df Chisq Pr(>Chisq)
## HPV16_DNA_RNA    2  4.67   0.0969 .
## CONSENSUS_CLUSTER 3  7.45   0.0590 .

```

```
## TP53                2 11.86      0.0027 **
## Residuals          196
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

4.1.34 TP53, UICC, HPV16 RNA, Consensus Clusters

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + CONSENSUS_CLUSTER +
  TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##   CONSENSUS_CLUSTER + TP53, data = ds[cur.subset, ], model = TRUE)
##
##   n= 203, number of events= 63
##   (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.393     4.028   0.398   3.50  0.00047 ***
## UICC_3CATIVB-C     2.744    15.552   0.482   5.70  1.2e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.738     0.478   0.530  -1.39  0.16419
## HPV16_DNA_RNADNA+RNA+ -1.330     0.264   0.563  -2.36  0.01817 *
## CONSENSUS_CLUSTERBasal -0.334     0.716   0.379  -0.88  0.37932
## CONSENSUS_CLUSTERClassical -0.922     0.398   0.586  -1.57  0.11561
## CONSENSUS_CLUSTERMesenchymal 0.358     1.431   0.334   1.07  0.28307
## TP53ND            -0.849     0.428   0.474  -1.79  0.07315 .
## TP53D              0.517     1.678   0.290   1.79  0.07389 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          4.028     0.2482    1.8453    8.794
## UICC_3CATIVB-C       15.552     0.0643    6.0486   39.985
## HPV16_DNA_RNADNA+RNA-  0.478     2.0911    0.1691    1.352
## HPV16_DNA_RNADNA+RNA+  0.264     3.7826    0.0877    0.797
## CONSENSUS_CLUSTERBasal  0.716     1.3960    0.3405    1.507
## CONSENSUS_CLUSTERClassical 0.398     2.5142    0.1261    1.254
## CONSENSUS_CLUSTERMesenchymal 1.431     0.6988    0.7438    2.753
## TP53ND                0.428     2.3381    0.1689    1.083
## TP53D                 1.678     0.5960    0.9512    2.959
##
## Concordance= 0.764 (se = 0.04 )
## Rsquare= 0.257 (max possible= 0.946 )
## Likelihood ratio test= 60.3 on 9 df,  p=1.19e-09
## Wald test               = 54 on 9 df,  p=1.87e-08
## Score (logrank) test = 65.4 on 9 df,  p=1.23e-10
```

```
# coxtable(surv.res)
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 33.03   6.7e-08 ***
## HPV16_DNA_RNA  2  7.18    0.028 *
## CONSENSUS_CLUSTER 3  8.10    0.044 *
## TP53           2  8.85    0.012 *
## Residuals     194
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

4.1.35 TP53, UICC, HPV16 RNA, Consensus Clusters, Interaction Consensus Clusters with TP53

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + CONSENSUS_CLUSTER *
  TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       CONSENSUS_CLUSTER * TP53, data = ds[cur.subset, ], model = TRUE)
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z
## UICC_3CATIVA      1.46e+00  4.28e+00  4.18e-01  3.48
## UICC_3CATIVB-C      2.81e+00  1.66e+01  5.16e-01  5.45
## HPV16_DNA_RNADNA+RNA- -9.78e-01  3.76e-01  5.59e-01 -1.75
## HPV16_DNA_RNADNA+RNA+ -1.59e+00  2.03e-01  5.80e-01 -2.75
## CONSENSUS_CLUSTERBasal -8.40e-01  4.32e-01  4.87e-01 -1.72
## CONSENSUS_CLUSTERClassical -1.83e+00  1.61e-01  1.06e+00 -1.72
## CONSENSUS_CLUSTERMesenchymal  1.30e-02  1.01e+00  4.47e-01  0.03
## TP53ND            -1.30e+00  2.73e-01  7.70e-01 -1.69
## TP53D             -4.00e-01  6.70e-01  6.92e-01 -0.58
## CONSENSUS_CLUSTERBasal:TP53ND -1.58e+01  1.43e-07  3.65e+03  0.00
## CONSENSUS_CLUSTERClassical:TP53ND  2.83e+00  1.69e+01  1.61e+00  1.76
## CONSENSUS_CLUSTERMesenchymal:TP53ND  6.11e-01  1.84e+00  9.71e-01  0.63
## CONSENSUS_CLUSTERBasal:TP53D  1.63e+00  5.12e+00  8.87e-01  1.84
## CONSENSUS_CLUSTERClassical:TP53D  1.50e+00  4.47e+00  1.42e+00  1.05
## CONSENSUS_CLUSTERMesenchymal:TP53D  9.14e-01  2.49e+00  8.17e-01  1.12
##
##               Pr(>|z|)
## UICC_3CATIVA      0.0005 ***
```

```

## UICC_3CATIVB-C 5e-08 ***
## HPV16_DNA_RNADNA+RNA- 0.0801 .
## HPV16_DNA_RNADNA+RNA+ 0.0060 **
## CONSENSUS_CLUSTERBasal 0.0845 .
## CONSENSUS_CLUSTERClassical 0.0852 .
## CONSENSUS_CLUSTERMesenchymal 0.9767
## TP53ND 0.0912 .
## TP53D 0.5634
## CONSENSUS_CLUSTERBasal:TP53ND 0.9966
## CONSENSUS_CLUSTERClassical:TP53ND 0.0786 .
## CONSENSUS_CLUSTERMesenchymal:TP53ND 0.5292
## CONSENSUS_CLUSTERBasal:TP53D 0.0655 .
## CONSENSUS_CLUSTERClassical:TP53D 0.2920
## CONSENSUS_CLUSTERMesenchymal:TP53D 0.2632
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95
## UICC_3CATIVA 4.28e+00 2.33e-01 1.8881
## UICC_3CATIVB-C 1.66e+01 6.01e-02 6.0549
## HPV16_DNA_RNADNA+RNA- 3.76e-01 2.66e+00 0.1258
## HPV16_DNA_RNADNA+RNA+ 2.03e-01 4.93e+00 0.0652
## CONSENSUS_CLUSTERBasal 4.32e-01 2.32e+00 0.1662
## CONSENSUS_CLUSTERClassical 1.61e-01 6.21e+00 0.0201
## CONSENSUS_CLUSTERMesenchymal 1.01e+00 9.87e-01 0.4220
## TP53ND 2.73e-01 3.67e+00 0.0603
## TP53D 6.70e-01 1.49e+00 0.1727
## CONSENSUS_CLUSTERBasal:TP53ND 1.43e-07 7.00e+06 0.0000
## CONSENSUS_CLUSTERClassical:TP53ND 1.69e+01 5.91e-02 0.7239
## CONSENSUS_CLUSTERMesenchymal:TP53ND 1.84e+00 5.43e-01 0.2747
## CONSENSUS_CLUSTERBasal:TP53D 5.12e+00 1.95e-01 0.9007
## CONSENSUS_CLUSTERClassical:TP53D 4.47e+00 2.24e-01 0.2757
## CONSENSUS_CLUSTERMesenchymal:TP53D 2.49e+00 4.01e-01 0.5030
## upper .95
## UICC_3CATIVA 9.724
## UICC_3CATIVB-C 45.690
## HPV16_DNA_RNADNA+RNA- 1.124
## HPV16_DNA_RNADNA+RNA+ 0.632
## CONSENSUS_CLUSTERBasal 1.121
## CONSENSUS_CLUSTERClassical 1.288
## CONSENSUS_CLUSTERMesenchymal 2.432
## TP53ND 1.232
## TP53D 2.602
## CONSENSUS_CLUSTERBasal:TP53ND Inf
## CONSENSUS_CLUSTERClassical:TP53ND 394.835
## CONSENSUS_CLUSTERMesenchymal:TP53ND 12.356
## CONSENSUS_CLUSTERBasal:TP53D 29.126
## CONSENSUS_CLUSTERClassical:TP53D 72.603

```

```
## CONSENSUS_CLUSTERMesenchymal:TP53D      12.366
##
## Concordance= 0.778 (se = 0.04 )
## Rsquare= 0.286 (max possible= 0.946 )
## Likelihood ratio test= 68.3 on 15 df, p=9.05e-09
## Wald test = 53.4 on 15 df, p=3.3e-06
## Score (logrank) test = 74.5 on 15 df, p=6.94e-10
```

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

```
Anova(surv.res, type = 3, test.statistic = "Wald")
```

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

```
##
```

```
## Response: surv.obj[cur.subset]
```

```
##              Df Chisq Pr(>Chisq)
## UICC_3CAT      2 30.23  2.7e-07 ***
## HPV16_DNA_RNA  2  9.83  0.0073 **
## CONSENSUS_CLUSTER  3  6.69  0.0825 .
## TP53           2  2.86  0.2388
## CONSENSUS_CLUSTER:TP53  6  6.29  0.3916
## Residuals      188
```

```
## ---
```

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

4.1.36 TP53, UICC, HPV16 RNA, IR Cluster

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + IS_ATYPICAL +
  TP53, data = ds[cur.subset, ], model = TRUE)
```

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

```
## Call:
```

```
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
## IS_ATYPICAL + TP53, data = ds[cur.subset, ], model = TRUE)
```

```
##
```

```
## n= 203, number of events= 63
```

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

```
##
```

```
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.4268    4.1655  0.3964  3.60 0.00032 ***
## UICC_3CATIVB-C      2.6181   13.7097  0.4767  5.49 4e-08 ***
## HPV16_DNA_RNADNA+RNA- -0.8848    0.4128  0.5301 -1.67 0.09510 .
## HPV16_DNA_RNADNA+RNA+ -1.2608    0.2834  0.5643 -2.23 0.02547 *
## IS_ATYPICALAtypical  0.0516    1.0530  0.3125  0.17 0.86886
## TP53ND             -0.7598    0.4678  0.4757 -1.60 0.11020
## TP53D              0.5408    1.7175  0.2859  1.89 0.05856 .
```

```
## ---
```

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



```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.166      0.2401      1.9153      9.059
## UICC_3CATIVB-C    13.710      0.0729      5.3855     34.900
## HPV16_DNA_RNADNA+RNA-  0.413      2.4225      0.1461      1.167
## HPV16_DNA_RNADNA+RNA+  0.283      3.5282      0.0938      0.857
## IS_ATYPICALAtypical  1.053      0.9497      0.5707      1.943
## TP53ND            0.468      2.1379      0.1841      1.188
## TP53D             1.717      0.5823      0.9806      3.008
##
## Concordance= 0.738 (se = 0.04 )
## Rsquare= 0.224 (max possible= 0.946 )
## Likelihood ratio test= 51.4 on 7 df, p=7.7e-09
## Wald test = 45.2 on 7 df, p=1.25e-07
## Score (logrank) test = 55.7 on 7 df, p=1.1e-09

# coxtable(surv.res)
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 30.37 2.5e-07 ***
## HPV16_DNA_RNA  2  7.47  0.024 *
## IS_ATYPICAL    1  0.03  0.869
## TP53           2  8.35  0.015 *
## Residuals     196
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

4.1.37 TP53, UICC, HPV16 DNA RNA, IR, Interaction IR with TP53 mutation status

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + IS_ATYPICAL *
  TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       IS_ATYPICAL * TP53, data = ds[cur.subset, ], model = TRUE)
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.412      4.103   0.407   3.47 0.00053 ***
```

```

## UICC_3CATIVB-C          2.543      12.714      0.488  5.22  1.8e-07 ***
## HPV16_DNA_RNADNA+RNA-   -1.016      0.362      0.537 -1.89  0.05830 .
## HPV16_DNA_RNADNA+RNA+   -1.539      0.215      0.584 -2.64  0.00835 **
## IS_ATYPICALAtypical      0.549      1.732      0.406  1.35  0.17664
## TP53ND                  -0.575      0.563      0.566 -1.01  0.31032
## TP53D                   0.798      2.220      0.321  2.48  0.01311 *
## IS_ATYPICALAtypical:TP53ND -0.806      0.447      0.914 -0.88  0.37798
## IS_ATYPICALAtypical:TP53D -1.247      0.287      0.767 -1.63  0.10407
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          4.103      0.2438      1.8466      9.114
## UICC_3CATIVB-C        12.714      0.0787      4.8895     33.059
## HPV16_DNA_RNADNA+RNA-  0.362      2.7633      0.1264      1.036
## HPV16_DNA_RNADNA+RNA+  0.215      4.6603      0.0684      0.673
## IS_ATYPICALAtypical    1.732      0.5774      0.7808      3.841
## TP53ND                0.563      1.7766      0.1855      1.708
## TP53D                 2.220      0.4504      1.1823      4.169
## IS_ATYPICALAtypical:TP53ND 0.447      2.2380      0.0745      2.679
## IS_ATYPICALAtypical:TP53D 0.287      3.4797      0.0639      1.293
##
## Concordance= 0.744 (se = 0.04 )
## Rsquare= 0.235 (max possible= 0.946 )
## Likelihood ratio test= 54.5 on 9 df, p=1.54e-08
## Wald test = 48.3 on 9 df, p=2.28e-07
## Score (logrank) test = 59.4 on 9 df, p=1.78e-09

# coxtable(surv.res) Type 3 III Anova
# ?????????????????????????????????????????????????????????????????
# Anova(surv.res, type = 2, test.statistic = 'Wald')
Anova(surv.res, type = 3, test.statistic = "Wald")

## Analysis of Deviance Table (Type III tests)
##
## Response: surv.obj[cur.subset]
##              Df Chisq Pr(>Chisq)
## UICC_3CAT      2 27.41  1.1e-06 ***
## HPV16_DNA_RNA  2  9.73  0.0077 **
## IS_ATYPICAL    1  1.83  0.1766
## TP53           2  8.83  0.0121 *
## IS_ATYPICAL:TP53 2  2.89  0.2363
## Residuals     194
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

4.1.38 TP53, UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, Consensus Clusters

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + CONSENSUS_CLUSTER + TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER + PACKYEARS + CONSENSUS_CLUSTER + TP53, data = ds[cur.subset,
##       ], model = TRUE)
##
##      n= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.42518   4.15860  0.39994   3.56 0.00037
## UICC_3CATIVB-C     2.72923  15.32111  0.48449   5.63 1.8e-08
## HPV16_DNA_RNADNA+RNA- -0.67643   0.50843  0.53524  -1.26 0.20631
## HPV16_DNA_RNADNA+RNA+ -1.48889   0.22562  0.57269  -2.60 0.00933
## ALTER            0.02197   1.02221  0.01299   1.69 0.09086
## PACKYEARS        -0.00166   0.99834  0.00589  -0.28 0.77760
## CONSENSUS_CLUSTERBasal -0.34818   0.70597  0.38828  -0.90 0.36986
## CONSENSUS_CLUSTERClassical -0.87739   0.41587  0.59607  -1.47 0.14104
## CONSENSUS_CLUSTERMesenchymal 0.32879   1.38929  0.34709   0.95 0.34349
## TP53ND           -0.78951   0.45407  0.47800  -1.65 0.09860
## TP53D            0.59466   1.81241  0.29927   1.99 0.04692
##
## UICC_3CATIVA      ***
## UICC_3CATIVB-C     ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+  **
## ALTER            .
## PACKYEARS
## CONSENSUS_CLUSTERBasal
## CONSENSUS_CLUSTERClassical
## CONSENSUS_CLUSTERMesenchymal
## TP53ND           .
## TP53D            *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.159      0.2405   1.8990   9.107
## UICC_3CATIVB-C    15.321      0.0653   5.9278  39.599
## HPV16_DNA_RNADNA+RNA- 0.508      1.9668   0.1781   1.452
## HPV16_DNA_RNADNA+RNA+ 0.226      4.4322   0.0734   0.693
## ALTER            1.022      0.9783   0.9965   1.049

```

```
## PACKYEARS                0.998      1.0017    0.9869    1.010
## CONSENSUS_CLUSTERBasal    0.706      1.4165    0.3298    1.511
## CONSENSUS_CLUSTERClassical 0.416      2.4046    0.1293    1.338
## CONSENSUS_CLUSTERMesenchymal 1.389      0.7198    0.7036    2.743
## TP53ND                    0.454      2.2023    0.1779    1.159
## TP53D                     1.812      0.5518    1.0081    3.258
##
## Concordance= 0.778 (se = 0.04 )
## Rsquare= 0.266 (max possible= 0.945 )
## Likelihood ratio test= 62.2 on 11 df, p=3.54e-09
## Wald test = 56.3 on 11 df, p=4.42e-08
## Score (logrank) test = 66.5 on 11 df, p=5.56e-10
```

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

```
##                rho  chisq      p
## UICC_3CATIVA      0.0666 0.2412 0.6234
## UICC_3CATIVB-C     0.0518 0.1632 0.6863
## HPV16_DNA_RNADNA+RNA- -0.1045 0.7068 0.4005
## HPV16_DNA_RNADNA+RNA+ 0.0136 0.0120 0.9129
## ALTER             -0.0786 0.4876 0.4850
## PACKYEARS         -0.0581 0.2192 0.6396
## CONSENSUS_CLUSTERBasal 0.0368 0.0908 0.7631
## CONSENSUS_CLUSTERClassical 0.2490 4.3137 0.0378
## CONSENSUS_CLUSTERMesenchymal 0.0881 0.5255 0.4685
## TP53ND            -0.0318 0.0638 0.8006
## TP53D             -0.1281 1.0097 0.3150
## GLOBAL            NA 6.8172 0.8137
```

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

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

```
##                hr 2.5 % 97.5 %      p
## UICC_3CATIVA      4.16  1.90   9.11 0.000
## UICC_3CATIVB-C    15.32  5.93  39.60 0.000
## HPV16_DNA_RNADNA+RNA- 0.51  0.18   1.45 0.206
## HPV16_DNA_RNADNA+RNA+ 0.23  0.07   0.69 0.009
## ALTER            1.02  1.00   1.05 0.091
## PACKYEARS         1.00  0.99   1.01 0.778
## CONSENSUS_CLUSTERBasal 0.71  0.33   1.51 0.370
## CONSENSUS_CLUSTERClassical 0.42  0.13   1.34 0.141
## CONSENSUS_CLUSTERMesenchymal 1.39  0.70   2.74 0.343
## TP53ND            0.45  0.18   1.16 0.099
## TP53D             1.81  1.01   3.26 0.047
```

```
# 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 32.09   1.1e-07 ***
## HPV16_DNA_RNA  2  7.92   0.0190 *
## ALTER          1  2.86   0.0909 .
## PACKYEARS       1  0.08   0.7776
## CONSENSUS_CLUSTER 3  7.38   0.0607 .
## TP53           2  9.28   0.0096 **
## Residuals      190
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

4.1.39 TP53, UICC, HPV16 RNA, AGE continuous, PACKYEARS continuous, LOCALISATION, Consensus Clusters

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER +
  PACKYEARS + relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") + CONSENSUS_CLUSTER +
  TP53, data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##     ALTER + PACKYEARS + relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") +
##     CONSENSUS_CLUSTER + TP53, data = ds[cur.subset, ], model = TRUE)
##
## n= 198, number of events= 61
## (19 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        1.36313
## UICC_3CATIVB-C                      2.83173
## HPV16_DNA_RNADNA+RNA-              -0.74974
## HPV16_DNA_RNADNA+RNA+             -1.58010
## ALTER                             0.02464
## PACKYEARS                         -0.00141
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.02532
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx  0.15994
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      -0.43891
## CONSENSUS_CLUSTERBasal          -0.23008
## CONSENSUS_CLUSTERClassical      -0.77918
## CONSENSUS_CLUSTERMesenchymal     0.35745

```

```

## TP53ND -0.78056
## TP53D 0.54948
## exp(coef)
## UICC_3CATIVA 3.90841
## UICC_3CATIVB-C 16.97483
## HPV16_DNA_RNADNA+RNA- 0.47249
## HPV16_DNA_RNADNA+RNA+ 0.20595
## ALTER 1.02494
## PACKYEARS 0.99859
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.97499
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.17344
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.64474
## CONSENSUS_CLUSTERBasal 0.79447
## CONSENSUS_CLUSTERClassical 0.45878
## CONSENSUS_CLUSTERMesenchymal 1.42968
## TP53ND 0.45815
## TP53D 1.73236
## se(coef)
## UICC_3CATIVA 0.40441
## UICC_3CATIVB-C 0.49738
## HPV16_DNA_RNADNA+RNA- 0.54404
## HPV16_DNA_RNADNA+RNA+ 0.60937
## ALTER 0.01407
## PACKYEARS 0.00615
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.35534
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.43505
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.44879
## CONSENSUS_CLUSTERBasal 0.41156
## CONSENSUS_CLUSTERClassical 0.61849
## CONSENSUS_CLUSTERMesenchymal 0.36093
## TP53ND 0.48267
## TP53D 0.30433
## z
## UICC_3CATIVA 3.37
## UICC_3CATIVB-C 5.69
## HPV16_DNA_RNADNA+RNA- -1.38
## HPV16_DNA_RNADNA+RNA+ -2.59
## ALTER 1.75
## PACKYEARS -0.23
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.07
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.37
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -0.98
## CONSENSUS_CLUSTERBasal -0.56
## CONSENSUS_CLUSTERClassical -1.26
## CONSENSUS_CLUSTERMesenchymal 0.99
## TP53ND -1.62
## TP53D 1.81
## Pr(>|z|)

```

```

## UICC_3CATIVA 0.00075
## UICC_3CATIVB-C 1.2e-08
## HPV16_DNA_RNADNA+RNA- 0.16817
## HPV16_DNA_RNADNA+RNA+ 0.00951
## ALTER 0.07990
## PACKYEARS 0.81921
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.94318
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.71315
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.32808
## CONSENSUS_CLUSTERBasal 0.57613
## CONSENSUS_CLUSTERClassical 0.20774
## CONSENSUS_CLUSTERMesenchymal 0.32200
## TP53ND 0.10584
## TP53D 0.07099
##
## UICC_3CATIVA ***
## UICC_3CATIVB-C ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+ **
## ALTER .
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx
## CONSENSUS_CLUSTERBasal
## CONSENSUS_CLUSTERClassical
## CONSENSUS_CLUSTERMesenchymal
## TP53ND
## TP53D .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef)
## UICC_3CATIVA 3.908
## UICC_3CATIVB-C 16.975
## HPV16_DNA_RNADNA+RNA- 0.472
## HPV16_DNA_RNADNA+RNA+ 0.206
## ALTER 1.025
## PACKYEARS 0.999
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.975
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.173
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.645
## CONSENSUS_CLUSTERBasal 0.794
## CONSENSUS_CLUSTERClassical 0.459
## CONSENSUS_CLUSTERMesenchymal 1.430
## TP53ND 0.458
## TP53D 1.732
## exp(-coef)

```

```

## UICC_3CATIVA 0.2559
## UICC_3CATIVB-C 0.0589
## HPV16_DNA_RNADNA+RNA- 2.1165
## HPV16_DNA_RNADNA+RNA+ 4.8555
## ALTER 0.9757
## PACKYEARS 1.0014
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.0256
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.8522
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.5510
## CONSENSUS_CLUSTERBasal 1.2587
## CONSENSUS_CLUSTERClassical 2.1797
## CONSENSUS_CLUSTERMesenchymal 0.6995
## TP53ND 2.1827
## TP53D 0.5772
## lower .95
## UICC_3CATIVA 1.7692
## UICC_3CATIVB-C 6.4038
## HPV16_DNA_RNADNA+RNA- 0.1627
## HPV16_DNA_RNADNA+RNA+ 0.0624
## ALTER 0.9971
## PACKYEARS 0.9866
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.4859
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.5002
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.2675
## CONSENSUS_CLUSTERBasal 0.3546
## CONSENSUS_CLUSTERClassical 0.1365
## CONSENSUS_CLUSTERMesenchymal 0.7047
## TP53ND 0.1779
## TP53D 0.9541
## upper .95
## UICC_3CATIVA 8.63
## UICC_3CATIVB-C 45.00
## HPV16_DNA_RNADNA+RNA- 1.37
## HPV16_DNA_RNADNA+RNA+ 0.68
## ALTER 1.05
## PACKYEARS 1.01
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.96
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 2.75
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.55
## CONSENSUS_CLUSTERBasal 1.78
## CONSENSUS_CLUSTERClassical 1.54
## CONSENSUS_CLUSTERMesenchymal 2.90
## TP53ND 1.18
## TP53D 3.15
##
## Concordance= 0.777 (se = 0.041 )
## Rsquare= 0.274 (max possible= 0.944 )
## Likelihood ratio test= 63.4 on 14 df, p=2.91e-08

```



```
## Wald test          = 57.5  on 14 df,    p=3.27e-07
## Score (logrank) test = 68.6  on 14 df,    p=3.4e-09
```

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

```
##                                     rho
## UICC_3CATIVA                      0.0482
## UICC_3CATIVB-C                    0.0810
## HPV16_DNA_RNADNA+RNA-            -0.1346
## HPV16_DNA_RNADNA+RNA+            -0.0328
## ALTER                            -0.0138
## PACKYEARS                         -0.0298
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.0552
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.0241
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    -0.2414
## CONSENSUS_CLUSTERBasal          0.0902
## CONSENSUS_CLUSTERClassical      0.2512
## CONSENSUS_CLUSTERMesenchymal    0.1028
## TP53ND                           -0.0398
## TP53D                            -0.1402
## GLOBAL                           NA
##                                     chisq
## UICC_3CATIVA                      0.1213
## UICC_3CATIVB-C                    0.4577
## HPV16_DNA_RNADNA+RNA-            1.1210
## HPV16_DNA_RNADNA+RNA+            0.0698
## ALTER                            0.0168
## PACKYEARS                         0.0606
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.2080
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.0378
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    3.5746
## CONSENSUS_CLUSTERBasal          0.5162
## CONSENSUS_CLUSTERClassical      4.6621
## CONSENSUS_CLUSTERMesenchymal    0.7150
## TP53ND                           0.1015
## TP53D                            1.1841
## GLOBAL                           10.5353
##                                     p
## UICC_3CATIVA                      0.7276
## UICC_3CATIVB-C                    0.4987
## HPV16_DNA_RNADNA+RNA-            0.2897
## HPV16_DNA_RNADNA+RNA+            0.7916
## ALTER                            0.8970
## PACKYEARS                         0.8055
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.6483
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.8458
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    0.0587
## CONSENSUS_CLUSTERBasal          0.4725
## CONSENSUS_CLUSTERClassical      0.0308
```

```

## CONSENSUS_CLUSTERMesenchymal 0.3978
## TP53ND 0.7500
## TP53D 0.2765
## GLOBAL 0.7221

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

## hr 2.5 %
## UICC_3CATIVA 3.91 1.77
## UICC_3CATIVB-C 16.97 6.40
## HPV16_DNA_RNADNA+RNA- 0.47 0.16
## HPV16_DNA_RNADNA+RNA+ 0.21 0.06
## ALTER 1.02 1.00
## PACKYEARS 1.00 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.97 0.49
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.17 0.50
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.64 0.27
## CONSENSUS_CLUSTERBasal 0.79 0.35
## CONSENSUS_CLUSTERClassical 0.46 0.14
## CONSENSUS_CLUSTERMesenchymal 1.43 0.70
## TP53ND 0.46 0.18
## TP53D 1.73 0.95
## 97.5 %
## UICC_3CATIVA 8.63
## UICC_3CATIVB-C 45.00
## HPV16_DNA_RNADNA+RNA- 1.37
## HPV16_DNA_RNADNA+RNA+ 0.68
## ALTER 1.05
## PACKYEARS 1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.96
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 2.75
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 1.55
## CONSENSUS_CLUSTERBasal 1.78
## CONSENSUS_CLUSTERClassical 1.54
## CONSENSUS_CLUSTERMesenchymal 2.90
## TP53ND 1.18
## TP53D 3.15
## p
## UICC_3CATIVA 0.001
## UICC_3CATIVB-C 0.000
## HPV16_DNA_RNADNA+RNA- 0.168
## HPV16_DNA_RNADNA+RNA+ 0.010
## ALTER 0.080
## PACKYEARS 0.819
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.943
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.713
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.328
## CONSENSUS_CLUSTERBasal 0.576

```

```
## CONSENSUS_CLUSTERClassical 0.208
## CONSENSUS_CLUSTERMesenchymal 0.322
## TP53ND 0.106
## TP53D 0.071

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 33.06 6.6e-08
## HPV16_DNA_RNA 2 7.89 0.019
## ALTER 1 3.07 0.080
## PACKYEARS 1 0.05 0.819
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") 3 1.62 0.654
## CONSENSUS_CLUSTER 3 5.87 0.118
## TP53 2 8.05 0.018
## Residuals 184
##
## UICC_3CAT ***
## HPV16_DNA_RNA *
## ALTER .
## PACKYEARS
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")
## CONSENSUS_CLUSTER
## TP53 *
## Residuals
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
surv.res <- coxph(surv.obj[cur.subset] ~ CONSENSUS_CLUSTER + TP53, data = ds[cur.subset,
], model = TRUE)
surv.res <- coxph(surv.obj[cur.subset] ~ CONSENSUS_CLUSTER + TP53 + CONSENSUS_CLUSTER
data = ds[cur.subset, ], model = TRUE)
summary(surv.res)
cox.zph(surv.res)
# stepAIC(surv.res)
coxtable(surv.res)
Anova(surv.res, type = 2, test.statistic = "Wald")
```

4.1.40 CDKN2A mutation status, UICC

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + CDKN2A, data = ds[cur.subset,
])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + CDKN2A, data = ds[cur.subset,
##      ])
##
##      n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.464     4.325   0.382 3.84 0.00012 ***
## UICC_3CATIVB-C  2.201     9.030   0.456 4.83 1.4e-06 ***
## CDKN2A          0.130     1.139   0.518 0.25 0.80186
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          4.32      0.231      2.047      9.14
## UICC_3CATIVB-C        9.03      0.111      3.694     22.07
## CDKN2A                1.14      0.878      0.413      3.14
##
## Concordance= 0.666 (se = 0.034 )
## Rsquare= 0.129 (max possible= 0.954 )
## Likelihood ratio test= 30 on 3 df,  p=1.41e-06
## Wald test              = 23.5 on 3 df,  p=3.12e-05
## Score (logrank) test = 29 on 3 df,  p=2.29e-06

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA   -0.000882 0.000056 0.994
## UICC_3CATIVB-C -0.109495 0.876366 0.349
## CDKN2A         0.106742 0.834943 0.361
## GLOBAL        NA 2.698153 0.441
```

4.1.41 CDKN2A, HPV16 DNA RNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + CDKN2A, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + CDKN2A,
##      data = ds[cur.subset, ])
##
##      n= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.448     0.639   0.520 -0.86 0.389
```

```
## HPV16_DNA_RNADNA+RNA+ -1.020      0.361      0.519 -1.96      0.049 *
## CDKN2A                  -0.198      0.820      0.594 -0.33      0.738
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.639      1.56      0.231      1.770
## HPV16_DNA_RNADNA+RNA+    0.361      2.77      0.130      0.998
## CDKN2A                   0.820      1.22      0.256      2.625
##
## Concordance= 0.564  (se = 0.032 )
## Rsquare= 0.028    (max possible= 0.946 )
## Likelihood ratio test= 5.73  on 3 df,   p=0.125
## Wald test           = 4.48  on 3 df,   p=0.215
## Score (logrank) test = 4.81  on 3 df,   p=0.186

cox.zph(surv.res)

##               rho      chisq      p
## HPV16_DNA_RNADNA+RNA- 0.02903 0.05328 0.817
## HPV16_DNA_RNADNA+RNA+ 0.00486 0.00149 0.969
## CDKN2A                 0.04170 0.10796 0.742
## GLOBAL                 NA 0.15339 0.985
```

4.1.42 CDKN2A, UICC, HPV16 DNA RNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + CDKN2A,
  data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       CDKN2A, data = ds[cur.subset, ])
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.498      4.471    0.390   3.84  0.00012 ***
## UICC_3CATIVB-C     2.723     15.219    0.473   5.75  8.8e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.795      0.452    0.524  -1.52  0.12955
## HPV16_DNA_RNADNA+RNA+ -1.333      0.264    0.523  -2.55  0.01078 *
## CDKN2A             0.014      1.014    0.597   0.02  0.98126
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```
## UICC_3CATIVA          4.471      0.2236      2.0819      9.604
## UICC_3CATIVB-C        15.219      0.0657      6.0194     38.477
## HPV16_DNA_RNADNA+RNA-  0.452      2.2142      0.1616      1.262
## HPV16_DNA_RNADNA+RNA+  0.264      3.7938      0.0946      0.735
## CDKN2A                1.014      0.9861      0.3146      3.269
##
## Concordance= 0.701 (se = 0.038 )
## Rsquare= 0.189 (max possible= 0.946 )
## Likelihood ratio test= 42.5 on 5 df, p=4.77e-08
## Wald test              = 37.8 on 5 df, p=4.24e-07
## Score (logrank) test = 45.4 on 5 df, p=1.2e-08

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.008415 4.22e-03 0.948
## UICC_3CATIVB-C    -0.000634 2.48e-05 0.996
## HPV16_DNA_RNADNA+RNA- 0.011136 8.07e-03 0.928
## HPV16_DNA_RNADNA+RNA+ 0.015846 1.51e-02 0.902
## CDKN2A            0.082828 4.26e-01 0.514
## GLOBAL            NA 4.60e-01 0.993
```

4.1.43 CDKN2A, AGE in categories

```
surv.res <- coxph(surv.obj[cur.subset] ~ ALTER_3CAT + CDKN2A, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ ALTER_3CAT + CDKN2A, data = ds[cur.subset,
##      ])
##
##      n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.478      0.620      0.243 -1.96      0.05 *
## CDKN2A              0.103      1.108      0.521  0.20      0.84
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.62      1.612      0.385      0.999
## CDKN2A                  1.11      0.902      0.399      3.079
##
## Concordance= 0.538 (se = 0.033 )
## Rsquare= 0.017 (max possible= 0.954 )
## Likelihood ratio test= 3.76 on 2 df, p=0.153
```

```
## Wald test          = 3.86  on 2 df,    p=0.145
## Score (logrank) test = 3.93  on 2 df,    p=0.14

cox.zph(surv.res)

##                rho chisq      p
## ALTER_3CAT(50,70] -0.0965 0.672 0.412
## CDKN2A            0.0867 0.532 0.466
## GLOBAL            NA 1.059 0.589
```

4.1.44 CDKN2A, AGE in categories, UICC

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + CDKN2A, data = ds[c
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       CDKN2A, data = ds[cur.subset, ])
##
##    n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.520     4.572   0.383   3.97 7.2e-05 ***
## UICC_3CATIVB-C     2.329    10.267   0.460   5.06 4.2e-07 ***
## ALTER_3CAT(50,70] -0.643     0.526   0.250  -2.57  0.01 *
## CDKN2A            0.368     1.444   0.529   0.69  0.49
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.572     0.2187    2.158    9.682
## UICC_3CATIVB-C    10.267     0.0974    4.165   25.308
## ALTER_3CAT(50,70]  0.526     1.9024    0.322    0.858
## CDKN2A            1.444     0.6924    0.512    4.074
##
## Concordance= 0.689 (se = 0.037 )
## Rsquare= 0.154 (max possible= 0.954 )
## Likelihood ratio test= 36.4 on 4 df,    p=2.39e-07
## Wald test            = 29.7 on 4 df,    p=5.55e-06
## Score (logrank) test = 35.3 on 4 df,    p=4.05e-07

cox.zph(surv.res)

##                rho chisq      p
## UICC_3CATIVA      0.0165 0.0191 0.890
## UICC_3CATIVB-C    -0.0759 0.4094 0.522
```

```
## ALTER_3CAT(50,70] -0.1393 1.4230 0.233
## CDKN2A              0.1285 1.2195 0.269
## GLOBAL              NA 3.7040 0.448
```

4.1.45 APC, UICC

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + APC, data = ds[cur.subset,
##      ])
##
##      n= 217, number of events= 73
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.489     4.431   0.382  3.90 9.7e-05 ***
## UICC_3CATIVB-C  2.159     8.660   0.457  4.72 2.4e-06 ***
## APC            -0.703     0.495   0.522 -1.35  0.18
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.431      0.226    2.096     9.37
## UICC_3CATIVB-C    8.660      0.115    3.533    21.23
## APC              0.495      2.019    0.178     1.38
##
## Concordance= 0.674 (se = 0.035 )
## Rsquare= 0.138 (max possible= 0.954 )
## Likelihood ratio test= 32.1 on 3 df,  p=4.93e-07
## Wald test            = 25.1 on 3 df,  p=1.5e-05
## Score (logrank) test = 30.6 on 3 df,  p=1.02e-06

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA    0.0151 0.0162 0.899
## UICC_3CATIVB-C -0.1340 1.3135 0.252
## APC            -0.1366 1.3922 0.238
## GLOBAL         NA 4.1285 0.248
```

4.1.46 APC, HPV16 DNA RNA


```

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + APC, data = ds[cur.subset,
##      ])
##
##      n= 203, number of events= 63
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.420    0.657    0.519 -0.81    0.419
## HPV16_DNA_RNADNA+RNA+ -1.038    0.354    0.519 -2.00    0.046 *
## APC                    -0.415    0.660    0.518 -0.80    0.423
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.657      1.52    0.238    1.818
## HPV16_DNA_RNADNA+RNA+    0.354      2.82    0.128    0.981
## APC                      0.660      1.51    0.239    1.824
##
## Concordance= 0.572 (se = 0.033 )
## Rsquare= 0.031 (max possible= 0.946 )
## Likelihood ratio test= 6.34 on 3 df,  p=0.0963
## Wald test               = 5.02 on 3 df,  p=0.17
## Score (logrank) test = 5.37 on 3 df,  p=0.146

cox.zph(surv.res)

##              rho    chisq      p
## HPV16_DNA_RNADNA+RNA- 0.02915 0.05275 0.818
## HPV16_DNA_RNADNA+RNA+ 0.00659 0.00274 0.958
## APC                   0.02233 0.03079 0.861
## GLOBAL                NA 0.08724 0.993

```

4.1.47 APC, UICC, HPV16 DNA RNA

```

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

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

```

```
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.498    4.472    0.390  3.84 0.00012 ***
## UICC_3CATIVB-C      2.711   15.049    0.472  5.74 9.3e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.780    0.459    0.525 -1.49 0.13718
## HPV16_DNA_RNADNA+RNA+ -1.344    0.261    0.523 -2.57 0.01015 *
## APC              -0.366    0.693    0.519 -0.71 0.48055
## ---
## 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    2.0832    9.600
## UICC_3CATIVB-C     15.049    0.0665    5.9656   37.962
## HPV16_DNA_RNADNA+RNA-  0.459    2.1809    0.1640    1.282
## HPV16_DNA_RNADNA+RNA+  0.261    3.8345    0.0936    0.727
## APC              0.693    1.4424    0.2505    1.918
##
## Concordance= 0.708 (se = 0.038 )
## Rsquare= 0.191 (max possible= 0.946 )
## Likelihood ratio test= 43 on 5 df, p=3.68e-08
## Wald test = 38.2 on 5 df, p=3.46e-07
## Score (logrank) test = 46 on 5 df, p=9.22e-09

cox.zph(surv.res)

##          rho  chisq    p
## UICC_3CATIVA  0.00824 0.00402 0.949
## UICC_3CATIVB-C -0.00912 0.00502 0.944
## HPV16_DNA_RNADNA+RNA- 0.01017 0.00667 0.935
## HPV16_DNA_RNADNA+RNA+ 0.02060 0.02580 0.872
## APC          0.01601 0.01550 0.901
## GLOBAL      NA 0.07200 1.000
```

4.1.48 APC, AGE in categories

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ ALTER_3CAT + APC, data = ds[cur.subset,
##    ])
##
## n= 217, number of events= 73
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.439      0.645    0.242 -1.82    0.069 .
## APC                -0.636      0.529    0.523 -1.22    0.224
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.645      1.55    0.401    1.03
## APC                    0.529      1.89    0.190    1.48
##
## Concordance= 0.54 (se = 0.034 )
## Rsquare= 0.025 (max possible= 0.954 )
## Likelihood ratio test= 5.5 on 2 df,  p=0.064
## Wald test               = 5.18 on 2 df,  p=0.0749
## Score (logrank) test = 5.33 on 2 df,  p=0.0695

cox.zph(surv.res)

##               rho chisq      p
## ALTER_3CAT(50,70] -0.0668 0.334 0.563
## APC                -0.1048 0.866 0.352
## GLOBAL              NA 1.296 0.523
```

4.1.49 APC, AGE in categories, UICC

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       APC, data = ds[cur.subset, ])
##
## n= 217, number of events= 73
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.523      4.586    0.382  3.98 6.7e-05 ***
## UICC_3CATIVB-C     2.279      9.768    0.461  4.95 7.5e-07 ***
## ALTER_3CAT(50,70] -0.585      0.557    0.245 -2.38    0.017 *
## APC                -0.616      0.540    0.521 -1.18    0.237
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.586      0.218    2.168    9.698
## UICC_3CATIVB-C     9.768      0.102    3.961   24.089
## ALTER_3CAT(50,70]  0.557      1.795    0.344    0.901
```

```
## APC                0.540        1.852        0.194        1.500
##
## Concordance= 0.686 (se = 0.037 )
## Rsquare= 0.159 (max possible= 0.954 )
## Likelihood ratio test= 37.6 on 4 df, p=1.33e-07
## Wald test          = 30.4 on 4 df, p=3.98e-06
## Score (logrank) test = 36.2 on 4 df, p=2.69e-07

cox.zph(surv.res)

##                rho  chisq      p
## UICC_3CATIVA      0.0191 0.0254 0.873
## UICC_3CATIVB-C    -0.1089 0.8331 0.361
## ALTER_3CAT(50,70] -0.0899 0.6000 0.439
## APC              -0.1093 0.8963 0.344
## GLOBAL            NA 3.8831 0.422
```

4.1.50 APC, AGE in categories, HPV16 DNA RNA

```
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_DNA_RNA + ALTER_3CAT + APC, data = ds[
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_DNA_RNA + ALTER_3CAT +
##       APC, data = ds[cur.subset, ])
##
## n= 203, number of events= 63
## (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.399    0.671    0.520 -0.77  0.443
## HPV16_DNA_RNADNA+RNA+ -1.014    0.363    0.520 -1.95  0.051 .
## ALTER_3CAT(50,70]    -0.462    0.630    0.256 -1.80  0.072 .
## APC                  -0.355    0.701    0.520 -0.68  0.494
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.671      1.49    0.242    1.86
## HPV16_DNA_RNADNA+RNA+    0.363      2.76    0.131    1.00
## ALTER_3CAT(50,70]       0.630      1.59    0.381    1.04
## APC                     0.701      1.43    0.253    1.94
##
## Concordance= 0.589 (se = 0.038 )
## Rsquare= 0.046 (max possible= 0.946 )
## Likelihood ratio test= 9.53 on 4 df, p=0.0492
```

```
## Wald test          = 8.26  on 4 df,    p=0.0825
## Score (logrank) test = 8.69  on 4 df,    p=0.0693

cox.zph(surv.res)

##                rho    chisq      p
## HPV16_DNA_RNADNA+RNA-  0.02125 0.02786 0.867
## HPV16_DNA_RNADNA+RNA+  0.00663 0.00276 0.958
## ALTER_3CAT(50,70]      -0.13158 1.15537 0.282
## APC                    0.03504 0.07679 0.782
## GLOBAL                  NA 1.21999 0.875
```

4.1.51 APC, UICC, AGE in categories, HPV16 DNA RNA

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER_3CAT + APC, data = ds[cur.subset, ])
##
##    n= 203, number of events= 63
##    (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.562     4.770   0.392  3.98  6.8e-05 ***
## UICC_3CATIVB-C     2.866    17.566   0.480  5.97  2.4e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.734     0.480   0.525 -1.40  0.1621
## HPV16_DNA_RNADNA+RNA+ -1.434     0.238   0.527 -2.72  0.0065 **
## ALTER_3CAT(50,70]   -0.654     0.520   0.261 -2.50  0.0123 *
## APC               -0.371     0.690   0.519 -0.71  0.4752
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.770     0.2097   2.2110   10.289
## UICC_3CATIVB-C    17.566     0.0569   6.8511   45.040
## HPV16_DNA_RNADNA+RNA-  0.480     2.0831   0.1716   1.343
## HPV16_DNA_RNADNA+RNA+  0.238     4.1963   0.0848   0.670
## ALTER_3CAT(50,70]   0.520     1.9225   0.3118   0.868
## APC               0.690     1.4486   0.2496   1.909
##
## Concordance= 0.72 (se = 0.04 )
## Rsquare= 0.215 (max possible= 0.946 )
## Likelihood ratio test= 49.1 on 6 df,    p=7.05e-09
## Wald test          = 42.6 on 6 df,    p=1.42e-07
## Score (logrank) test = 50.5 on 6 df,    p=3.78e-09
```

```
cox.zph(surv.res)

##              rho    chisq    p
## UICC_3CATIVA      0.04741 0.13043 0.718
## UICC_3CATIVB-C    0.04977 0.14562 0.703
## HPV16_DNA_RNADNA+RNA- -0.01253 0.00986 0.921
## HPV16_DNA_RNADNA+RNA+ -0.00535 0.00179 0.966
## ALTER_3CAT(50,70] -0.19942 2.66929 0.102
## APC              0.03888 0.09287 0.761
## GLOBAL           NA 2.85908 0.826
```

4.1.52 APC, UICC, AGE in categories, HPV16 DNA RNA, PACKYEARS (cut at 30)

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       I(PACKYEARS > 30) + ALTER_3CAT + APC, data = ds[cur.subset,
##       ])
##
##      n= 201, number of events= 62
##      (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.522      4.583   0.392   3.88   0.0001 ***
## UICC_3CATIVB-C    2.857     17.411   0.482   5.93   3e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.610      0.543   0.529  -1.15   0.2486
## HPV16_DNA_RNADNA+RNA+ -1.358      0.257   0.533  -2.55   0.0108 *
## I(PACKYEARS > 30)TRUE  0.376      1.456   0.269   1.39   0.1631
## ALTER_3CAT(50,70]  -0.756      0.470   0.273  -2.77   0.0056 **
## APC              -0.476      0.621   0.596  -0.80   0.4245
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.583      0.2182    2.1242    9.887
## UICC_3CATIVB-C    17.411      0.0574    6.7746   44.746
## HPV16_DNA_RNADNA+RNA-  0.543      1.8413    0.1925    1.532
## HPV16_DNA_RNADNA+RNA+  0.257      3.8889    0.0905    0.730
## I(PACKYEARS > 30)TRUE  1.456      0.6867    0.8587    2.470
## ALTER_3CAT(50,70]    0.470      2.1291    0.2753    0.801
## APC              0.621      1.6097    0.1932    1.998
##
## Concordance= 0.724 (se = 0.04 )
```

```
## Rsquare= 0.222    (max possible= 0.945 )
## Likelihood ratio test= 50.5  on 7 df,    p=1.17e-08
## Wald test          = 43.6  on 7 df,    p=2.53e-07
## Score (logrank) test = 52   on 7 df,    p=5.85e-09
```

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

```
##              rho  chisq      p
## UICC_3CATIVA      0.0228 0.0300 0.8626
## UICC_3CATIVB-C    0.0320 0.0591 0.8079
## HPV16_DNA_RNADNA+RNA- 0.0191 0.0228 0.8801
## HPV16_DNA_RNADNA+RNA+ 0.0158 0.0162 0.8986
## I(PACKYEARS > 30)TRUE 0.0733 0.3040 0.5814
## ALTER_3CAT(50,70]   -0.2359 3.4343 0.0639
## APC               -0.0543 0.1762 0.6747
## GLOBAL              NA  3.6766 0.8162
```

4.1.53 APC, UICC, AGE in categories, HPV16 DNA RNA, PACKYEARS, Interaction HPV16 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) + ALTER_3CAT + APC, data = ds[cur.subset,
  ])
```

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

```
## Call:
```

```
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##      I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30) + ALTER_3CAT +
##      APC, data = ds[cur.subset, ])
```

```
##
```

```
##      n= 201, number of events= 62
```

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

```
##
```

```
##              coef exp(coef) se(coef)
## UICC_3CATIVA      1.544      4.684    0.394
## UICC_3CATIVB-C    2.835     17.023    0.483
## HPV16_DNA_RNADNA+RNA- -0.423      0.655    0.629
## HPV16_DNA_RNADNA+RNA+ -2.354      0.095    1.026
## I(PACKYEARS > 30)TRUE  0.291      1.338    0.287
## ALTER_3CAT(50,70]   -0.724      0.485    0.272
## APC               -0.490      0.612    0.598
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.640      0.527    1.204
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.814      6.136    1.199
```

```
##
```

```
##              z Pr(>|z|)
## UICC_3CATIVA      3.92  8.8e-05 ***
## UICC_3CATIVB-C    5.87  4.4e-09 ***
## HPV16_DNA_RNADNA+RNA- -0.67  0.5010
```

```

## HPV16_DNA_RNADNA+RNA+                -2.29    0.0217 *
## I(PACKYEARS > 30)TRUE                  1.02    0.3095
## ALTER_3CAT(50,70]                     -2.66    0.0077 **
## APC                                    -0.82    0.4120
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.53    0.5952
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.51    0.1304
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                     exp(coef) exp(-coef) lower .95
## UICC_3CATIVA                        4.684      0.2135    2.1650
## UICC_3CATIVB-C                     17.023      0.0587    6.6064
## HPV16_DNA_RNADNA+RNA-              0.655      1.5273    0.1907
## HPV16_DNA_RNADNA+RNA+              0.095     10.5300    0.0127
## I(PACKYEARS > 30)TRUE               1.338      0.7473    0.7631
## ALTER_3CAT(50,70]                  0.485      2.0627    0.2846
## APC                                0.612      1.6330    0.1898
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.527      1.8964    0.0498
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  6.136      0.1630    0.5847
##                                     upper .95
## UICC_3CATIVA                       10.134
## UICC_3CATIVB-C                     43.866
## HPV16_DNA_RNADNA+RNA-              2.248
## HPV16_DNA_RNADNA+RNA+              0.709
## I(PACKYEARS > 30)TRUE               2.346
## ALTER_3CAT(50,70]                  0.826
## APC                                1.976
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  5.589
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  64.397
##
## Concordance= 0.737 (se = 0.04 )
## Rsquare= 0.234 (max possible= 0.945 )
## Likelihood ratio test= 53.7 on 9 df, p=2.2e-08
## Wald test               = 43.7 on 9 df, p=1.6e-06
## Score (logrank) test = 53.2 on 9 df, p=2.62e-08

cox.zph(surv.res)

##                                     rho  chisq      p
## UICC_3CATIVA                        0.0291 0.0500 0.8230
## UICC_3CATIVB-C                     0.0378 0.0838 0.7722
## HPV16_DNA_RNADNA+RNA-              -0.0349 0.0723 0.7880
## HPV16_DNA_RNADNA+RNA+              0.0766 0.3493 0.5545
## I(PACKYEARS > 30)TRUE               0.0593 0.2116 0.6455
## ALTER_3CAT(50,70]                  -0.2346 3.5003 0.0614
## APC                                -0.0506 0.1509 0.6977
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.0453 0.1249 0.7238
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.0540 0.1919 0.6614
## GLOBAL                             NA 4.3836 0.8844

```


4.1.54 APC, T, N, M, HPV16 DNA RNA, AGE, PACKYEARS, Interaction HPV DNA RNA with PACKYEARS, Interaction T with PACKYEARS

```

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 + APC, 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 + APC, data = ds[cur.subset,
##       ])
##
## n= 201, number of events= 62
## (16 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## T_2CAT3-4         0.92745    2.52807  0.48017
## N_2CATN2-N3        0.81672    2.26306  0.32461
## M                 2.38115   10.81732  0.57133
## HPV16_DNA_RNADNA+RNA- 0.00118    1.00119  0.64804
## HPV16_DNA_RNADNA+RNA+ -1.83257    0.16000  1.03875
## ALTER_3CAT(50,70]   -0.65806    0.51786  0.27100
## I(PACKYEARS > 30)TRUE  0.30759    1.36014  0.59789
## APC               -0.36551    0.69384  0.61369
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.10952    1.11574  0.65250
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.78340    0.45685  1.21217
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.82580    6.20779  1.20377
##
##               z Pr(>|z|)
## T_2CAT3-4         1.93    0.053 .
## N_2CATN2-N3        2.52    0.012 *
## M                 4.17  3.1e-05 ***
## HPV16_DNA_RNADNA+RNA- 0.00    0.999
## HPV16_DNA_RNADNA+RNA+ -1.76    0.078 .
## ALTER_3CAT(50,70]   -2.43    0.015 *
## I(PACKYEARS > 30)TRUE  0.51    0.607
## APC               -0.60    0.551
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.17    0.867
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.65    0.518
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  1.52    0.129
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95
## T_2CAT3-4         2.528    0.3956    0.9864
## N_2CATN2-N3        2.263    0.4419    1.1978

```

```

## M 10.817 0.0924 3.5302
## HPV16_DNA_RNADNA+RNA- 1.001 0.9988 0.2811
## HPV16_DNA_RNADNA+RNA+ 0.160 6.2499 0.0209
## ALTER_3CAT(50,70] 0.518 1.9310 0.3045
## I(PACKYEARS > 30)TRUE 1.360 0.7352 0.4214
## APC 0.694 1.4413 0.2084
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 1.116 0.8963 0.3106
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.457 2.1889 0.0425
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 6.208 0.1611 0.5865
## upper .95
## T_2CAT3-4 6.479
## N_2CATN2-N3 4.276
## M 33.146
## HPV16_DNA_RNADNA+RNA- 3.566
## HPV16_DNA_RNADNA+RNA+ 1.226
## ALTER_3CAT(50,70] 0.881
## I(PACKYEARS > 30)TRUE 4.390
## APC 2.310
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 4.008
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 4.916
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 65.703
##
## Concordance= 0.75 (se = 0.04 )
## Rsquare= 0.235 (max possible= 0.945 )
## Likelihood ratio test= 53.9 on 11 df, p=1.25e-07
## Wald test = 49.5 on 11 df, p=7.55e-07
## Score (logrank) test = 71 on 11 df, p=7.95e-11

cox.zph(surv.res)

## rho chisq p
## T_2CAT3-4 0.00833 0.004937 0.9440
## N_2CATN2-N3 0.03684 0.089067 0.7654
## M 0.05190 0.171791 0.6785
## HPV16_DNA_RNADNA+RNA- 0.00151 0.000141 0.9905
## HPV16_DNA_RNADNA+RNA+ 0.07887 0.406194 0.5239
## ALTER_3CAT(50,70] -0.26924 4.832302 0.0279
## I(PACKYEARS > 30)TRUE 0.14097 1.361389 0.2433
## APC -0.07841 0.363054 0.5468
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.11961 0.904697 0.3415
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.02163 0.028623 0.8657
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.07176 0.330186 0.5655
## GLOBAL NA 7.862779 0.7255

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

```

4.1.55 APC, LOCALISATION

```

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ LOKALISATION_GROB_TEXT +
##       APC, data = ds[cur.subset, ])
##
##      n= 214, number of events= 72
##      (3 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## LOKALISATION_GROB_TEXToropharynx -0.226    0.798    0.292 -0.77    0.440
## LOKALISATION_GROB_TEXThypopharynx  0.644    1.905    0.376  1.71    0.087
## LOKALISATION_GROB_TEXTlarynx      -0.227    0.797    0.370 -0.61    0.539
## APC                               -0.900    0.407    0.531 -1.69    0.090
##
## LOKALISATION_GROB_TEXToropharynx
## LOKALISATION_GROB_TEXThypopharynx .
## LOKALISATION_GROB_TEXTlarynx
## APC
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## LOKALISATION_GROB_TEXToropharynx    0.798    1.253    0.450    1.41
## LOKALISATION_GROB_TEXThypopharynx    1.905    0.525    0.911    3.98
## LOKALISATION_GROB_TEXTlarynx         0.797    1.255    0.386    1.65
## APC                                0.407    2.460    0.144    1.15
##
## Concordance= 0.577 (se = 0.037 )
## Rsquare= 0.034 (max possible= 0.953 )
## Likelihood ratio test= 7.29 on 4 df,  p=0.121
## Wald test = 7.46 on 4 df,  p=0.113
## Score (logrank) test = 7.55 on 4 df,  p=0.11

cox.zph(surv.res)

##              rho chisq      p
## LOKALISATION_GROB_TEXToropharynx  0.0976 0.662 0.416
## LOKALISATION_GROB_TEXThypopharynx  0.0548 0.220 0.639
## LOKALISATION_GROB_TEXTlarynx      -0.0468 0.159 0.690
## APC                               -0.0938 0.689 0.406
## GLOBAL                             NA 2.132 0.711

```

4.2 In HPV DNA-

4.2.1 UICC

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "neg"
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= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.384      3.991    0.394 3.51 0.00045 ***
## UICC_3CATIVB-C    2.693     14.771    0.486 5.54 3e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.99    0.2505      1.84      8.65
## UICC_3CATIVB-C       14.77    0.0677      5.70     38.30
##
## Concordance= 0.69 (se = 0.038 )
## Rsquare= 0.183 (max possible= 0.954 )
## Likelihood ratio test= 31.9 on 2 df,  p=1.2e-07
## Wald test               = 30.8 on 2 df,  p=2.07e-07
## Score (logrank) test = 40.9 on 2 df,  p=1.31e-09

cox.zph(surv.res)

##              rho  chisq      p
## UICC_3CATIVA    0.0161 0.0135 0.908
## UICC_3CATIVB-C -0.0590 0.1777 0.673
## GLOBAL          NA  0.4725 0.790
```

4.2.2 UICC, AGE

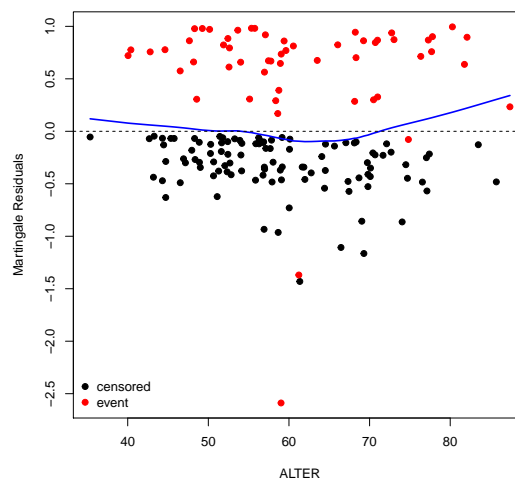
```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER, data = ds[cur.subset,
], model = TRUE)
summary(surv.res)

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

```
## n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA   1.3680    3.9273   0.3942  3.47  0.00052 ***
## UICC_3CATIVB-C  2.6767   14.5364   0.4859  5.51  3.6e-08 ***
## ALTER          0.0178    1.0180   0.0137  1.30  0.19396
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA         3.93    0.2546    1.814    8.50
## UICC_3CATIVB-C       14.54    0.0688    5.608   37.68
## ALTER                1.02    0.9823    0.991    1.05
##
## Concordance= 0.717 (se = 0.043 )
## Rsquare= 0.191 (max possible= 0.954 )
## Likelihood ratio test= 33.5 on 3 df, p=2.48e-07
## Wald test              = 32.2 on 3 df, p=4.7e-07
## Score (logrank) test = 42.4 on 3 df, p=3.25e-09

cox.zph(surv.res)

##              rho    chisq      p
## UICC_3CATIVA   0.00912 0.00436 0.947
## UICC_3CATIVB-C -0.06169 0.19395 0.660
## ALTER         -0.07449 0.41182 0.521
## GLOBAL                NA 0.83522 0.841
```



4.2.3 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= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.3680    3.9273   0.3942  3.47  0.00052 ***
## UICC_3CATIVB-C  2.6767   14.5364   0.4859  5.51  3.6e-08 ***
## ALTER          0.0178    1.0180   0.0137  1.30  0.19396
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA         3.93      0.2546      1.814      8.50
## UICC_3CATIVB-C       14.54      0.0688      5.608     37.68
## ALTER                1.02      0.9823      0.991      1.05
##
## Concordance= 0.717 (se = 0.043 )
## Rsquare= 0.191 (max possible= 0.954 )
## Likelihood ratio test= 33.5 on 3 df, p=2.48e-07
## Wald test              = 32.2 on 3 df, p=4.7e-07
## Score (logrank) test = 42.4 on 3 df, p=3.25e-09

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA    0.00912 0.00436 0.947
## UICC_3CATIVB-C -0.06169 0.19395 0.660
## ALTER          -0.07449 0.41182 0.521
## GLOBAL          NA 0.83522 0.841
```

4.2.4 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= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    1.459    4.302   0.398  3.67  0.00024 ***
## UICC_3CATIVB-C  2.840   17.111   0.495  5.74  9.7e-09 ***
```

```
## ALTER_3CAT(50,70] -0.631      0.532      0.282 -2.24  0.02494 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.302      0.2325      1.973      9.378
## UICC_3CATIVB-C     17.111      0.0584      6.485     45.149
## ALTER_3CAT(50,70]   0.532      1.8800      0.306      0.924
##
## Concordance= 0.71 (se = 0.042 )
## Rsquare= 0.208 (max possible= 0.954 )
## Likelihood ratio test= 36.8 on 3 df,  p=5.09e-08
## Wald test          = 35 on 3 df,  p=1.22e-07
## Score (logrank) test = 45.5 on 3 df,  p=7.3e-10

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.06464 0.211570 0.646
## UICC_3CATIVB-C     0.00389 0.000743 0.978
## ALTER_3CAT(50,70] -0.20462 2.377244 0.123
## GLOBAL              NA 2.801396 0.423
```

4.2.5 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= 157, number of events= 54
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.425      4.157   0.398  3.58  0.00035 ***
## UICC_3CATIVB-C     2.858     17.424   0.495  5.77  7.9e-09 ***
## ALTER_3CAT(50,70]  -0.703      0.495   0.294 -2.39  0.01673 *
## I(PACKYEARS > 30)TRUE  0.303      1.355   0.288  1.05  0.29267
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.157      0.2405      1.905      9.072
## UICC_3CATIVB-C     17.424      0.0574      6.601     45.992
```

```
## ALTER_3CAT(50,70]          0.495      2.0196      0.278      0.881
## I(PACKYEARS > 30)TRUE      1.355      0.7382      0.770      2.384
##
## Concordance= 0.713 (se = 0.043 )
## Rsquare= 0.213 (max possible= 0.953 )
## Likelihood ratio test= 37.6 on 4 df, p=1.33e-07
## Wald test = 35.9 on 4 df, p=2.99e-07
## Score (logrank) test = 46.9 on 4 df, p=1.59e-09

cox.zph(surv.res)

##              rho   chisq      p
## UICC_3CATIVA      0.04040 0.08259 0.7738
## UICC_3CATIVB-C    -0.00903 0.00387 0.9504
## ALTER_3CAT(50,70] -0.23045 2.85121 0.0913
## I(PACKYEARS > 30)TRUE 0.05763 0.17578 0.6750
## GLOBAL              NA 3.26747 0.5141
```

4.2.6 UICC, AGE, ALCOHOL consumption

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       ALKOHOL, data = ds[cur.subset, ], model = TRUE)
##
## n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.482      4.402      0.400  3.71 0.00021 ***
## UICC_3CATIVB-C      2.878     17.781      0.502  5.74 9.6e-09 ***
## ALTER_3CAT(50,70] -0.674      0.509      0.286 -2.35 0.01854 *
## ALKOHOL1 bis 30      0.319      1.375      0.536  0.59 0.55229
## ALKOHOL31 bis 60      0.360      1.434      0.533  0.68 0.49953
## ALKOHOL>60          0.427      1.533      0.506  0.84 0.39862
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      4.402      0.2272      2.010      9.638
## UICC_3CATIVB-C     17.781      0.0562      6.652     47.529
## ALTER_3CAT(50,70]  0.509      1.9627      0.291      0.893
## ALKOHOL1 bis 30      1.375      0.7271      0.481      3.935
## ALKOHOL31 bis 60      1.434      0.6976      0.504      4.078
## ALKOHOL>60          1.533      0.6522      0.568      4.136
```



```
##
## Concordance= 0.715 (se = 0.043 )
## Rsquare= 0.212 (max possible= 0.954 )
## Likelihood ratio test= 37.6 on 6 df, p=1.36e-06
## Wald test = 35.4 on 6 df, p=3.66e-06
## Score (logrank) test = 46.1 on 6 df, p=2.8e-08

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.04714 0.113407 0.736
## UICC_3CATIVB-C      0.00245 0.000319 0.986
## ALTER_3CAT(50,70] -0.16972 1.667859 0.197
## ALKOHOL1 bis 30    -0.12055 0.803382 0.370
## ALKOHOL31 bis 60   -0.14149 1.088385 0.297
## ALKOHOL>60         -0.08825 0.427402 0.513
## GLOBAL              NA 3.890692 0.691
```

4.2.7 TP53 mutation status, N0-N1 vs. N2-N3

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT + TP53, data = ds[cur.subset,
##      ])
##
## n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3  1.054      2.869   0.309   3.41  0.00064 ***
## TP53ND       -0.793      0.453   0.467  -1.70  0.08949 .
## TP53D         0.492      1.635   0.298   1.65  0.09857 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      2.869      0.349   1.567      5.25
## TP53ND           0.453      2.210   0.181      1.13
## TP53D            1.635      0.612   0.912      2.93
##
## Concordance= 0.686 (se = 0.042 )
## Rsquare= 0.14 (max possible= 0.954 )
## Likelihood ratio test= 23.9 on 3 df, p=2.65e-05
## Wald test = 21.2 on 3 df, p=9.37e-05
## Score (logrank) test = 23.7 on 3 df, p=2.92e-05
```

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

```
##               rho  chisq    p
## N_2CATN2-N3  0.0350 0.0624 0.803
## TP53ND      -0.0416 0.0946 0.758
## TP53D       -0.1289 0.8630 0.353
## GLOBAL              NA 0.8833 0.829
```

4.2.8 TP53 mutation status, N0-N1 vs. N2-N3 and interaction

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT * TP53, data = ds[cur.subset,
])
```

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

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT * TP53, data = ds[cur.subset,
##      ])
```

```
##
```

```
## n= 158, number of events= 55
```

```
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.874      2.397    0.396  2.21   0.027 *
## TP53ND          -1.037      0.355    0.811 -1.28   0.201
## TP53D           0.096      1.101    0.669  0.14   0.886
## N_2CATN2-N3:TP53ND 0.335      1.398    0.931  0.36   0.719
## N_2CATN2-N3:TP53D 0.512      1.669    0.752  0.68   0.496
```

```
## ---
```

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

```
##
```

```
##               exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      2.397      0.417    1.1037    5.21
## TP53ND           0.355      2.820    0.0723    1.74
## TP53D            1.101      0.908    0.2963    4.09
## N_2CATN2-N3:TP53ND 1.398      0.715    0.2253    8.68
## N_2CATN2-N3:TP53D 1.669      0.599    0.3822    7.29
```

```
##
```

```
## Concordance= 0.687 (se = 0.042 )
```

```
## Rsquare= 0.143 (max possible= 0.954 )
```

```
## Likelihood ratio test= 24.4 on 5 df, p=0.000182
```

```
## Wald test = 22.2 on 5 df, p=0.000489
```

```
## Score (logrank) test = 26.4 on 5 df, p=7.29e-05
```

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

```
##               rho  chisq    p
## N_2CATN2-N3  0.0813 0.3506 0.554
## TP53ND      0.0753 0.2715 0.602
```

```
## TP53D -0.0298 0.0517 0.820
## N_2CATN2-N3:TP53ND -0.1287 0.8051 0.370
## N_2CATN2-N3:TP53D -0.0305 0.0535 0.817
## GLOBAL NA 1.6158 0.899
```

4.2.9 TP53 mutation status, N0-N1 vs. N2-N3, IR Cluster

```
surv.res <- coxph(surv.obj[cur.subset] ~ N_2CAT + TP53 + IS_ATYPICAL, data = ds[cur.s
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ N_2CAT + TP53 + IS_ATYPICAL,
##       data = ds[cur.subset, ])
##
## n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      1.05508   2.87222  0.31219  3.38  0.00073 ***
## TP53ND          -0.79141   0.45321  0.47058 -1.68  0.09261 .
## TP53D           0.49239   1.63623  0.29952  1.64  0.10019
## IS_ATYPICALAtypical -0.00795   0.99208  0.33421 -0.02  0.98103
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3          2.872      0.348      1.558      5.30
## TP53ND              0.453      2.207      0.180      1.14
## TP53D              1.636      0.611      0.910      2.94
## IS_ATYPICALAtypical  0.992      1.008      0.515      1.91
##
## Concordance= 0.682 (se = 0.042 )
## Rsquare= 0.14 (max possible= 0.954 )
## Likelihood ratio test= 23.9 on 4 df, p=8.45e-05
## Wald test = 21.2 on 4 df, p=0.000283
## Score (logrank) test = 23.7 on 4 df, p=9.08e-05

cox.zph(surv.res)

##              rho chisq      p
## N_2CATN2-N3      0.0377 0.0727 0.787
## TP53ND          -0.0384 0.0819 0.775
## TP53D           -0.1219 0.8145 0.367
## IS_ATYPICALAtypical -0.0187 0.0209 0.885
## GLOBAL          NA 0.8965 0.925
```

4.2.10 TP53, UICC

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + TP53, data = ds[cur.subset,
##      ])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.301      3.674   0.400   3.26  0.0011 **
## UICC_3CATIVB-C      2.588     13.305   0.495   5.23  1.7e-07 ***
## TP53ND           -0.538      0.584   0.476  -1.13   0.2580
## TP53D              0.607      1.835   0.300   2.02   0.0432 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.674      0.2722      1.68      8.04
## UICC_3CATIVB-C       13.305      0.0752      5.05     35.07
## TP53ND                0.584      1.7124      0.23      1.48
## TP53D                 1.835      0.5451      1.02      3.30
##
## Concordance= 0.733 (se = 0.042 )
## Rsquare= 0.219 (max possible= 0.954 )
## Likelihood ratio test= 39.1 on 4 df,  p=6.77e-08
## Wald test               = 36.6 on 4 df,  p=2.21e-07
## Score (logrank) test = 48.3 on 4 df,  p=8.24e-10

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0496 0.125 0.724
## UICC_3CATIVB-C    -0.0451 0.109 0.741
## TP53ND            -0.0535 0.169 0.681
## TP53D             -0.0974 0.531 0.466
## GLOBAL              NA 1.085 0.897
```

4.2.11 TP53, AGE (in categories: up to 50 or over 70 vs. between 50 and 70)

```
surv.res <- coxph(surv.obj[cur.subset] ~ ALTER_3CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ ALTER_3CAT + TP53, data = ds[cur.subset,
##      ])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.420      0.657   0.277 -1.52   0.130
## TP53ND            -0.720      0.487   0.466 -1.54   0.123
## TP53D             0.683      1.980   0.295  2.31   0.021 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.657      1.522    0.382    1.13
## TP53ND                 0.487      2.055    0.195    1.21
## TP53D                 1.980      0.505    1.110    3.53
##
## Concordance= 0.631 (se = 0.042 )
## Rsquare= 0.079 (max possible= 0.954 )
## Likelihood ratio test= 13 on 3 df,  p=0.00454
## Wald test               = 12.5 on 3 df,  p=0.00574
## Score (logrank) test = 13.5 on 3 df,  p=0.00373

cox.zph(surv.res)

##              rho chisq      p
## ALTER_3CAT(50,70] -0.1234 0.888 0.346
## TP53ND            -0.0457 0.118 0.731
## TP53D             -0.1335 0.971 0.324
## GLOBAL              NA 1.984 0.576
```

4.2.12 TP53, AGE(in categories: up to 50 or over 70 vs. between 50 and 70), UICC

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + TP53, data = ds[cur
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##      TP53, data = ds[cur.subset, ])
##
##      n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.362      3.904   0.403  3.38 0.00072 ***
```

```
## UICC_3CATIVB-C      2.728      15.308      0.503      5.42      5.9e-08 ***
## ALTER_3CAT(50,70] -0.599       0.549      0.282     -2.13      0.03358 *
## TP53ND              -0.484       0.616      0.478     -1.01      0.31146
## TP53D                0.611       1.842      0.301      2.03      0.04212 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.904      0.2561      1.773      8.595
## UICC_3CATIVB-C        15.308      0.0653      5.709     41.048
## ALTER_3CAT(50,70]      0.549      1.8208      0.316      0.954
## TP53ND                0.616      1.6229      0.241      1.574
## TP53D                 1.842      0.5428      1.022      3.321
##
## Concordance= 0.734 (se = 0.043 )
## Rsquare= 0.241 (max possible= 0.954 )
## Likelihood ratio test= 43.5 on 5 df, p=2.94e-08
## Wald test              = 40.6 on 5 df, p=1.13e-07
## Score (logrank) test = 52.7 on 5 df, p=3.88e-10

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA      0.0932 0.4322 0.511
## UICC_3CATIVB-C    0.0140 0.0101 0.920
## ALTER_3CAT(50,70] -0.2060 2.3999 0.121
## TP53ND            -0.0472 0.1318 0.717
## TP53D             -0.0904 0.4577 0.499
## GLOBAL            NA 3.4646 0.629
```

4.2.13 TP53, UICC, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), PACKYEARS (cut at 30)

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + I(PACKYEARS > 30) + ALTER_3CAT +
  TP53, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + I(PACKYEARS >
## 30) + ALTER_3CAT + TP53, data = ds[cur.subset, ])
##
## n= 157, number of events= 54
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.346      3.843      0.403  3.34 0.00083 ***
## UICC_3CATIVB-C     2.744     15.556      0.503  5.46 4.8e-08 ***
```

```
## I(PACKYEARS > 30)TRUE    0.245      1.277      0.290  0.84  0.39875
## ALTER_3CAT(50,70]      -0.640      0.527      0.294 -2.18  0.02962 *
## TP53ND                  -0.462      0.630      0.478 -0.97  0.33327
## TP53D                    0.586      1.797      0.307  1.91  0.05620 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          3.843      0.2602      1.745      8.467
## UICC_3CATIVB-C        15.556      0.0643      5.809     41.660
## I(PACKYEARS > 30)TRUE    1.277      0.7830      0.724      2.254
## ALTER_3CAT(50,70]        0.527      1.8968      0.296      0.939
## TP53ND                 0.630      1.5873      0.247      1.606
## TP53D                  1.797      0.5564      0.985      3.281
##
## Concordance= 0.739 (se = 0.043 )
## Rsquare= 0.242 (max possible= 0.953 )
## Likelihood ratio test= 43.5 on 6 df, p=9.13e-08
## Wald test              = 41.1 on 6 df, p=2.72e-07
## Score (logrank) test = 53.5 on 6 df, p=9.33e-10

cox.zph(surv.res)

##                rho    chisq      p
## UICC_3CATIVA      0.07483 0.28003 0.5967
## UICC_3CATIVB-C    0.00712 0.00251 0.9600
## I(PACKYEARS > 30)TRUE 0.05858 0.18245 0.6693
## ALTER_3CAT(50,70] -0.23097 2.80061 0.0942
## TP53ND            -0.03327 0.06407 0.8002
## TP53D             -0.13646 0.98231 0.3216
## GLOBAL            NA 4.12433 0.6599
```

4.2.14 TP53, T, N, M, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), PACKYEARS (cut at 30), Interaktion T mit PACKYEARS

```
surv.res <- coxph(surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + ALTER_3CAT +
  I(PACKYEARS > 30) + T_2CAT:I(PACKYEARS > 30) + TP53, data = ds[cur.subset,
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M +
##       ALTER_3CAT + I(PACKYEARS > 30) + T_2CAT:I(PACKYEARS > 30) +
##       TP53, data = ds[cur.subset, ])
##
## n= 157, number of events= 54
## (1 observation deleted due to missingness)
```

```
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## T_2CAT3-4      0.9081   2.4795   0.5192  1.75   0.080
## N_2CATN2-N3    0.7465   2.1095   0.3417  2.18   0.029
## M              2.3494  10.4791   0.5805  4.05  5.2e-05
## ALTER_3CAT(50,70] -0.4939   0.6103   0.2916 -1.69   0.090
## I(PACKYEARS > 30)TRUE 0.3769   1.4578   0.6167  0.61   0.541
## TP53ND        -0.7387   0.4777   0.4795 -1.54   0.123
## TP53D          0.4149   1.5142   0.3113  1.33   0.183
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.0272   0.9731   0.6954 -0.04   0.969
##
## T_2CAT3-4      .
## N_2CATN2-N3    *
## M              ***
## ALTER_3CAT(50,70] .
## I(PACKYEARS > 30)TRUE
## TP53ND
## TP53D
## T_2CAT3-4:I(PACKYEARS > 30)TRUE
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## T_2CAT3-4      2.480      0.4033      0.896      6.86
## N_2CATN2-N3    2.110      0.4740      1.080      4.12
## M              10.479      0.0954      3.359     32.69
## ALTER_3CAT(50,70] 0.610      1.6387      0.345      1.08
## I(PACKYEARS > 30)TRUE 1.458      0.6860      0.435      4.88
## TP53ND         0.478      2.0933      0.187      1.22
## TP53D          1.514      0.6604      0.823      2.79
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 0.973      1.0276      0.249      3.80
##
## Concordance= 0.737 (se = 0.043 )
## Rsquare= 0.239 (max possible= 0.953 )
## Likelihood ratio test= 42.8 on 8 df,  p=9.43e-07
## Wald test = 42.7 on 8 df,  p=1.02e-06
## Score (logrank) test = 59 on 8 df,  p=7.45e-10
cox.zph(surv.res)
##               rho chisq      p
## T_2CAT3-4      0.0279 0.0464 0.8295
## N_2CATN2-N3    0.0743 0.2907 0.5898
## M              0.0527 0.1531 0.6956
## ALTER_3CAT(50,70] -0.2880 4.3428 0.0372
## I(PACKYEARS > 30)TRUE 0.1412 1.0708 0.3008
## TP53ND        -0.0558 0.1783 0.6728
## TP53D         -0.1916 1.9038 0.1677
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.1077 0.5877 0.4433
```



```
## GLOBAL NA 7.0667 0.5294

best.model <- stepAIC(surv.res)

## Start: AIC=453.8
## surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + ALTER_3CAT + I(PACKYEARS >
## 30) + T_2CAT:I(PACKYEARS > 30) + TP53
##
##
## Df AIC
## - T_2CAT:I(PACKYEARS > 30) 1 452
## <none> 454
## - ALTER_3CAT 1 455
## - TP53 2 456
## - N_2CAT 1 457
## - M 1 462
##
## Step: AIC=451.9
## surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + ALTER_3CAT + I(PACKYEARS >
## 30) + TP53

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

best.model

## Error: Objekt 'best.model' nicht gefunden
```

4.2.15 Consensus Clusters

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ CONSENSUS_CLUSTER, data = ds[cur.subset,
## ], model = TRUE)
##
## n= 158, number of events= 55
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## CONSENSUS_CLUSTERBasal -0.513    0.598  0.388 -1.32    0.19
## CONSENSUS_CLUSTERClassical -0.788    0.455  0.574 -1.37    0.17
## CONSENSUS_CLUSTERMesenchymal 0.119    1.127  0.347  0.34    0.73
##
##      exp(coef) exp(-coef) lower .95 upper .95
## CONSENSUS_CLUSTERBasal    0.598    1.671    0.280    1.28
## CONSENSUS_CLUSTERClassical 0.455    2.200    0.147    1.40
## CONSENSUS_CLUSTERMesenchymal 1.127    0.888    0.571    2.22
##
```

```
## Concordance= 0.608 (se = 0.041 )
## Rsquare= 0.036 (max possible= 0.954 )
## Likelihood ratio test= 5.85 on 3 df, p=0.119
## Wald test = 5.45 on 3 df, p=0.142
## Score (logrank) test = 5.68 on 3 df, p=0.128

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

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##              Df Chisq Pr(>Chisq)
## CONSENSUS_CLUSTER 3 5.45 0.14
## Residuals      155
```

4.2.16 TP53, Consensus Clusters

```
surv.res <- coxph(surv.obj[cur.subset] ~ CONSENSUS_CLUSTER + TP53, data = ds[cur.subset], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ CONSENSUS_CLUSTER + TP53,
##       data = ds[cur.subset, ], model = TRUE)
##
## n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## CONSENSUS_CLUSTERBasal -0.461    0.631  0.398 -1.16  0.247
## CONSENSUS_CLUSTERClassical -0.753    0.471  0.579 -1.30  0.194
## CONSENSUS_CLUSTERMesenchymal 0.175    1.192  0.356  0.49  0.622
## TP53ND -0.803    0.448  0.465 -1.73  0.084 .
## TP53D 0.610    1.841  0.301  2.03  0.043 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## CONSENSUS_CLUSTERBasal 0.631    1.585    0.289    1.38
## CONSENSUS_CLUSTERClassical 0.471    2.123    0.151    1.47
## CONSENSUS_CLUSTERMesenchymal 1.192    0.839    0.593    2.39
## TP53ND 0.448    2.233    0.180    1.11
## TP53D 1.841    0.543    1.020    3.32
##
## Concordance= 0.667 (se = 0.043 )
## Rsquare= 0.099 (max possible= 0.954 )
## Likelihood ratio test= 16.5 on 5 df, p=0.00546
```

```
## Wald test          = 15.7  on 5 df,    p=0.00788
## Score (logrank) test = 16.8  on 5 df,    p=0.00482

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

## Analysis of Deviance Table (Type II tests)
##
## Response: surv.obj[cur.subset]
##              Df Chisq Pr(>Chisq)
## CONSENSUS_CLUSTER  3  5.40    0.1447
## TP53                2  9.88    0.0072 **
## Residuals          153
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

4.2.17 TP53, UICC, IR, interaction IR with TP53

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + IS_ATYPICAL * TP53, data = ds[cu
  ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + IS_ATYPICAL *
##       TP53, data = ds[cur.subset, ], model = TRUE)
##
##    n= 158, number of events= 55
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.268    3.555   0.410   3.09   0.002 **
## UICC_3CATIVB-C     2.476   11.893   0.507   4.88   1e-06 ***
## IS_ATYPICALAtypical  0.610    1.840   0.449   1.36   0.174
## TP53ND            -0.439    0.645   0.570  -0.77   0.442
## TP53D              0.874    2.397   0.339   2.58   0.010 **
## IS_ATYPICALAtypical:TP53ND -0.711    0.491   0.933  -0.76   0.446
## IS_ATYPICALAtypical:TP53D -1.300    0.273   0.799  -1.63   0.104
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      3.555    0.2813    1.5907    7.94
## UICC_3CATIVB-C    11.893    0.0841    4.4017   32.14
## IS_ATYPICALAtypical  1.840    0.5434    0.7640    4.43
## TP53ND            0.645    1.5505    0.2108    1.97
## TP53D              2.397    0.4172    1.2326    4.66
## IS_ATYPICALAtypical:TP53ND  0.491    2.0370    0.0789    3.05
## IS_ATYPICALAtypical:TP53D  0.273    3.6691    0.0570    1.30
```

```
##
## Concordance= 0.74 (se = 0.042 )
## Rsquare= 0.233 (max possible= 0.954 )
## Likelihood ratio test= 42 on 7 df, p=5.29e-07
## Wald test = 39.4 on 7 df, p=1.65e-06
## Score (logrank) test = 52 on 7 df, p=5.79e-09

# coxtable(surv.res) Type 3 III Anova
# ?????????????????????????????????????????????????????????????????
# Anova(surv.res, type = 2, test.statistic = 'Wald') Anova(surv.res, type
# = 3, test.statistic = 'Wald')
```

4.3 In HPV16 DNA+

4.3.1 PACKYEARS (cut at 30)

```
cur.subset <- is.primary & ds$INNO_LIPA_GROB == "16"
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= 48, number of events= 11
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## I(PACKYEARS > 30)TRUE 1.27      3.56    0.74 1.72   0.086 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## I(PACKYEARS > 30)TRUE    3.56    0.281    0.836    15.2
##
## Concordance= 0.643 (se = 0.088 )
## Rsquare= 0.062 (max possible= 0.727 )
## Likelihood ratio test= 3.08 on 1 df, p=0.0794
## Wald test = 2.95 on 1 df, p=0.0858
## Score (logrank) test = 3.34 on 1 df, p=0.0675

cox.zph(surv.res)

##              rho chisq      p
## I(PACKYEARS > 30)TRUE 0.0324 0.0114 0.915
```

4.3.2 T (TNM staging) categorized, 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= 49, number of events= 11
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4 1.751      5.759   0.811 2.16   0.031 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4      5.76      0.174      1.17      28.2
##
## Concordance= 0.743 (se = 0.092 )
## Rsquare= 0.115 (max possible= 0.721 )
## Likelihood ratio test= 6.01 on 1 df,  p=0.0142
## Wald test            = 4.66 on 1 df,  p=0.0309
## Score (logrank) test = 5.79 on 1 df,  p=0.0161

cox.zph(surv.res)

##              rho chisq      p
## T_CAT3-4 -0.129 0.147 0.701
```

4.3.3 HPV16 RNA

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

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_RNA, data = ds[cur.subset,
##      ])
##
##      n= 45, number of events= 8
##      (4 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+ -0.657      0.518   0.710 -0.93   0.35
```

```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+    0.518      1.93    0.129      2.08
##
## Concordance= 0.576  (se = 0.095 )
## Rsquare= 0.019   (max possible= 0.692 )
## Likelihood ratio test= 0.84  on 1 df,   p=0.359
## Wald test          = 0.86  on 1 df,   p=0.355
## Score (logrank) test = 0.89  on 1 df,   p=0.346

cox.zph(surv.res)

##               rho chisq      p
## HPV16_RNARNA+ 0.0602  0.03 0.862
```

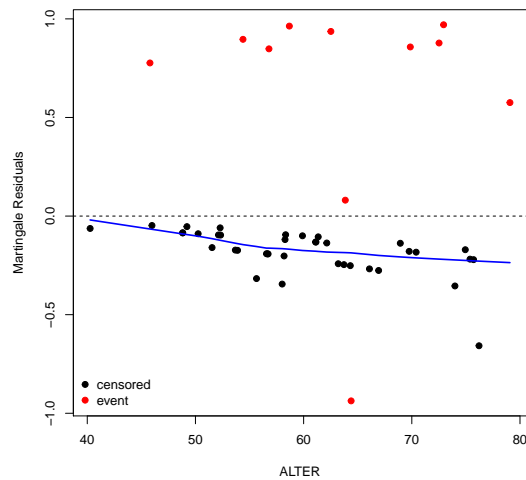
4.3.4 AGE

```
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= 49, number of events= 11
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER 0.0355    1.0361   0.0369 0.96    0.34
##
##           exp(coef) exp(-coef) lower .95 upper .95
## ALTER          1.04      0.965    0.964      1.11
##
## Concordance= 0.661  (se = 0.107 )
## Rsquare= 0.019   (max possible= 0.721 )
## Likelihood ratio test= 0.92  on 1 df,   p=0.337
## Wald test          = 0.93  on 1 df,   p=0.336
## Score (logrank) test = 0.94  on 1 df,   p=0.333

cox.zph(surv.res)

##           rho chisq      p
## ALTER -0.119 0.192 0.661
```



4.3.5 LOCALISATION

```
ds$OROPHARYNX_VS_OTHER <- ds$LOKALISATION_GROB_TEXT
levels(ds$OROPHARYNX_VS_OTHER) <- c("other", "oropharynx", "other", "other")
surv.res <- coxph(surv.obj[cur.subset] ~ OROPHARYNX_VS_OTHER, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ OROPHARYNX_VS_OTHER, data = ds[cur.subset,
##    ])
##
##    n= 49, number of events= 11
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## OROPHARYNX_VS_OTHERoropharynx 1.21      3.34      1.07 1.13      0.26
##
##              exp(coef) exp(-coef) lower .95 upper .95
## OROPHARYNX_VS_OTHERoropharynx      3.34      0.299      0.411      27.2
##
## Concordance= 0.588  (se = 0.087 )
## Rsquare= 0.034  (max possible= 0.721 )
## Likelihood ratio test= 1.69  on 1 df,   p=0.193
## Wald test               = 1.27  on 1 df,   p=0.259
## Score (logrank) test = 1.44  on 1 df,   p=0.231

cox.zph(surv.res)

##              rho  chisq    p
## OROPHARYNX_VS_OTHERoropharynx 0.0574 0.0357 0.85
```

4.3.6 LOCALISATION, HPV16 RNA

```

ds$OROPHARYNX_VS_OTHER <- ds$LOKALISATION_GROB_TEXT
levels(ds$OROPHARYNX_VS_OTHER) <- c("other", "oropharynx", "other", "other")
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_RNA + OROPHARYNX_VS_OTHER, data = ds[c
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_RNA + OROPHARYNX_VS_OTHER,
##       data = ds[cur.subset, ])
##
##      n= 45, number of events= 8
##      (4 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+    -1.003     0.367    0.726 -1.38    0.17
## OROPHARYNX_VS_OTHERoropharynx  1.564     4.776    1.106  1.41    0.16
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+         0.367      2.726    0.0885    1.52
## OROPHARYNX_VS_OTHERoropharynx  4.776     0.209    0.5463   41.75
##
## Concordance= 0.663  (se = 0.107 )
## Rsquare= 0.075   (max possible= 0.692 )
## Likelihood ratio test= 3.51  on 2 df,   p=0.173
## Wald test            = 3.22  on 2 df,   p=0.2
## Score (logrank) test = 3.37  on 2 df,   p=0.185

cox.zph(surv.res)

##              rho  chisq    p
## HPV16_RNARNA+    0.0496 0.0165 0.898
## OROPHARYNX_VS_OTHERoropharynx 0.1604 0.1850 0.667
## GLOBAL           NA 0.2357 0.889

```

4.3.7 LOCALISATION, T categorized, 1-2 vs. 3-4

```

surv.res <- coxph(surv.obj[cur.subset] ~ T_2CAT + OROPHARYNX_VS_OTHER, data = ds[cur.
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_2CAT + OROPHARYNX_VS_OTHER,
##       data = ds[cur.subset, ])
##
##      n= 49, number of events= 11
##
##              coef exp(coef) se(coef)      z Pr(>|z|)

```



```
## T_2CAT3-4                2.047      7.741      0.809 2.53      0.011 *
## OROPHARYNX_VS_OTHERoropharynx 1.783      5.947      1.079 1.65      0.099 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## T_2CAT3-4                7.74      0.129      1.586      37.8
## OROPHARYNX_VS_OTHERoropharynx  5.95      0.168      0.717      49.3
##
## Concordance= 0.808  (se = 0.101 )
## Rsquare= 0.184  (max possible= 0.721 )
## Likelihood ratio test= 9.99  on 2 df,   p=0.00677
## Wald test               = 8.25  on 2 df,   p=0.0162
## Score (logrank) test = 10.1  on 2 df,   p=0.00638

cox.zph(surv.res)

##                      rho  chisq      p
## T_2CAT3-4                -0.1333 0.1534 0.695
## OROPHARYNX_VS_OTHERoropharynx  0.0598 0.0402 0.841
## GLOBAL                    NA 0.2155 0.898
```

4.3.8 LOKALISATION, HPV16 RNA, PACKYEARS

```
ds$OROPHARYNX_VS_OTHER <- ds$LOKALISATION_GROB_TEXT
levels(ds$OROPHARYNX_VS_OTHER) <- c("other", "oropharynx", "other", "other")
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_RNA + OROPHARYNX_VS_OTHER + I(PACKYEARS
  30), data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_RNA + OROPHARYNX_VS_OTHER +
##       I(PACKYEARS > 30), data = ds[cur.subset, ])
##
##      n= 44, number of events= 8
##      (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+   -0.885     0.413   0.735 -1.20   0.23
## OROPHARYNX_VS_OTHERoropharynx  1.452     4.271   1.103  1.32   0.19
## I(PACKYEARS > 30)TRUE      0.810     2.247   0.795  1.02   0.31
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+         0.413     2.423   0.0977   1.74
## OROPHARYNX_VS_OTHERoropharynx  4.271     0.234   0.4920  37.09
## I(PACKYEARS > 30)TRUE      2.247     0.445   0.4729  10.68
##
```

```
## Concordance= 0.772 (se = 0.111 )
## Rsquare= 0.096 (max possible= 0.698 )
## Likelihood ratio test= 4.43 on 3 df, p=0.219
## Wald test = 4.13 on 3 df, p=0.248
## Score (logrank) test = 4.43 on 3 df, p=0.219

cox.zph(surv.res)

##
## rho chisq p
## HPV16_RNARNA+ 0.0314 0.00844 0.927
## OROPHARYNX_VS_OTHERoropharynx 0.1738 0.22275 0.637
## I(PACKYEARS > 30)TRUE 0.1100 0.10724 0.743
## GLOBAL NA 0.35362 0.950
```

4.3.9 LOCALISATION, HPV16 RNA, PACKYEARS, AGE

```
ds$OROPHARYNX_VS_OTHER <- ds$LOKALISATION_GROB_TEXT
levels(ds$OROPHARYNX_VS_OTHER) <- c("other", "oropharynx", "other", "other")
surv.res <- coxph(surv.obj[cur.subset] ~ HPV16_RNA + OROPHARYNX_VS_OTHER + I(PACKYEARS
  30) + ALTER, data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ HPV16_RNA + OROPHARYNX_VS_OTHER +
## I(PACKYEARS > 30) + ALTER, data = ds[cur.subset, ])
##
## n= 44, number of events= 8
## (5 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## HPV16_RNARNA+ -1.3554 0.2578 0.8380 -1.62 0.11
## OROPHARYNX_VS_OTHERoropharynx 1.3886 4.0093 1.1350 1.22 0.22
## I(PACKYEARS > 30)TRUE 0.8197 2.2697 0.8146 1.01 0.31
## ALTER 0.0609 1.0628 0.0418 1.46 0.15
##
## exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+ 0.258 3.878 0.0499 1.33
## OROPHARYNX_VS_OTHERoropharynx 4.009 0.249 0.4335 37.08
## I(PACKYEARS > 30)TRUE 2.270 0.441 0.4598 11.20
## ALTER 1.063 0.941 0.9791 1.15
##
## Concordance= 0.794 (se = 0.114 )
## Rsquare= 0.139 (max possible= 0.698 )
## Likelihood ratio test= 6.6 on 4 df, p=0.158
## Wald test = 5.83 on 4 df, p=0.212
## Score (logrank) test = 6.49 on 4 df, p=0.166

cox.zph(surv.res)
```

	rho	chisq	p
HPV16_RNARNA+	-0.00266	8.47e-05	0.993
OROPHARYNX_VS_OTHERoropharynx	0.21483	4.09e-01	0.522
I(PACKYEARS > 30)TRUE	0.05375	2.49e-02	0.874
ALTER	-0.26436	6.84e-01	0.408
GLOBAL	NA	1.24e+00	0.872

4.3.10 T categorized, 1-2 vs, 3-4, PACKYEARS (cut at 30)

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

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_CAT + I(PACKYEARS >
##      30), data = ds[cur.subset, ])
##
##      n= 48, number of events= 11
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4          1.748      5.743   0.812 2.15   0.031 *
## I(PACKYEARS > 30)TRUE 1.307      3.695   0.742 1.76   0.078 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4              5.74      0.174    1.170    28.2
## I(PACKYEARS > 30)TRUE    3.69      0.271    0.863    15.8
##
## Concordance= 0.802 (se = 0.102 )
## Rsquare= 0.172 (max possible= 0.727 )
## Likelihood ratio test= 9.06 on 2 df,  p=0.0108
## Wald test               = 7.61 on 2 df,  p=0.0222
## Score (logrank) test = 9.06 on 2 df,  p=0.0108

cox.zph(surv.res)
```

	rho	chisq	p
T_CAT3-4	-0.1279	0.1401	0.708
I(PACKYEARS > 30)TRUE	0.0359	0.0145	0.904
GLOBAL	NA	0.1561	0.925

4.3.11 T categorized, 1-2 vs, 3-4, PACKYEARS (cut at 30), AGE (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= 48, number of events= 11
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4          1.767      5.852   0.805 2.20   0.028 *
## ALTER_60(60,Inf]   0.577      1.780   0.734 0.79   0.432
## I(PACKYEARS > 30)TRUE 1.515      4.552   0.799 1.90   0.058 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4              5.85      0.171    1.209    28.33
## ALTER_60(60,Inf]      1.78      0.562    0.422     7.51
## I(PACKYEARS > 30)TRUE  4.55      0.220    0.950    21.81
##
## Concordance= 0.829 (se = 0.106 )
## Rsquare= 0.183 (max possible= 0.727 )
## Likelihood ratio test= 9.68 on 3 df,  p=0.0215
## Wald test              = 7.82 on 3 df,  p=0.0498
## Score (logrank) test = 9.32 on 3 df,  p=0.0254

cox.zph(surv.res)

##              rho      chisq      p
## T_CAT3-4        -0.13888 0.185130 0.667
## ALTER_60(60,Inf] -0.12759 0.183007 0.669
## I(PACKYEARS > 30)TRUE -0.00601 0.000352 0.985
## GLOBAL          NA 0.373516 0.946

```

4.3.12 T categorized, 1-2 vs, 3-4, PACKYEARS, AGE (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) +
  strata(HPV16_RNA), data = ds[cur.subset, ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_CAT + ALTER_60 + I(PACKYEARS >

```

```
##      30) + strata(HPV16_RNA), data = ds[cur.subset, ])
```

```
##
```

```
##      n= 44, number of events= 8
```

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

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
## T_CAT3-4	2.19e+01	3.26e+09	1.46e+04	0.00	0.999
## ALTER_60(60,Inf]	1.87e+00	6.51e+00	1.02e+00	1.83	0.067 .
## I(PACKYEARS > 30)TRUE	1.81e+00	6.11e+00	9.81e-01	1.84	0.065 .

```
## ---
```

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

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
## T_CAT3-4	3.26e+09	3.07e-10	0.000	Inf
## ALTER_60(60,Inf]	6.52e+00	1.53e-01	0.875	48.5
## I(PACKYEARS > 30)TRUE	6.10e+00	1.64e-01	0.893	41.7

```
##
```

```
## Concordance= 0.871 (se = 0.162 )
```

```
## Rsquare= 0.303 (max possible= 0.601 )
```

```
## Likelihood ratio test= 15.9 on 3 df, p=0.00119
```

```
## Wald test = 4.41 on 3 df, p=0.221
```

```
## Score (logrank) test = 11.7 on 3 df, p=0.00866
```

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

```
##
```

	rho	chisq	p
## T_CAT3-4	0.295	8.06e-10	1.000
## ALTER_60(60,Inf]	0.230	4.16e-01	0.519
## I(PACKYEARS > 30)TRUE	0.357	7.56e-01	0.385
## GLOBAL	NA	8.03e-01	0.849

4.3.13 TP53: WT, non-disruptive (ND), disruptive (D)

```
surv.res <- coxph(surv.obj[cur.subset] ~ TP53, data = ds[cur.subset, ])
```

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

```
## Call:
```

```
## coxph(formula = surv.obj[cur.subset] ~ TP53, data = ds[cur.subset,
```

```
##      ])
```

```
##
```

```
##      n= 49, number of events= 11
```

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
## TP53ND	-1.82e+01	1.28e-08	9.46e+03	0.00	1.00
## TP53D	-5.19e-02	9.49e-01	8.32e-01	-0.06	0.95

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
## TP53ND	1.28e-08	7.81e+07	0.000	Inf
## TP53D	9.49e-01	1.05e-01	0.475	2.08

```
## TP53ND 1.28e-08 7.84e+07 0.000 Inf
## TP53D 9.49e-01 1.05e+00 0.186 4.85
##
## Concordance= 0.529 (se = 0.075 )
## Rsquare= 0.033 (max possible= 0.721 )
## Likelihood ratio test= 1.65 on 2 df, p=0.439
## Wald test = 0 on 2 df, p=0.998
## Score (logrank) test = 0.87 on 2 df, p=0.648

cox.zph(surv.res)

## rho chisq p
## TP53ND 0.448 7.37e-10 1.000
## TP53D -0.179 3.71e-01 0.543
## GLOBAL NA 3.71e-01 0.831
```

4.3.14 TP53, UICC

```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + TP53, data = ds[cur.subset,
## ])
##
## n= 49, number of events= 11
##
##              coef exp(coef) se(coef) z Pr(>|z|)
## UICC_3CATIVA 1.95e+01 2.85e+08 1.02e+04 0.00 1.00
## UICC_3CATIVB-C 1.99e+01 4.22e+08 1.02e+04 0.00 1.00
## TP53ND -1.94e+01 3.89e-09 1.62e+04 0.00 1.00
## TP53D 3.18e-02 1.03e+00 8.39e-01 0.04 0.97
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA 2.85e+08 3.51e-09 0.000 Inf
## UICC_3CATIVB-C 4.22e+08 2.37e-09 0.000 Inf
## TP53ND 3.89e-09 2.57e+08 0.000 Inf
## TP53D 1.03e+00 9.69e-01 0.199 5.34
##
## Concordance= 0.689 (se = 0.1 )
## Rsquare= 0.136 (max possible= 0.721 )
## Likelihood ratio test= 7.15 on 4 df, p=0.128
## Wald test = 0.3 on 4 df, p=0.99
## Score (logrank) test = 4.38 on 4 df, p=0.357

cox.zph(surv.res)
```

```
##           rho      chisq      p
## UICC_3CATIVA -0.6720 2.80e-09 1.000
## UICC_3CATIVB-C -0.0984 2.16e-10 1.000
## TP53ND         0.4170 2.57e-10 1.000
## TP53D         -0.1606 2.55e-01 0.613
## GLOBAL         NA 6.33e-01 0.959
```

4.3.15 TP53, AGE (in categories: up to 50 or over 70 vs. between 50 and 70)

```
surv.res <- coxph(surv.obj[cur.subset] ~ ALTER_3CAT + TP53, data = ds[cur.subset,
])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ ALTER_3CAT + TP53, data = ds[cur.subset,
##      ])
##
##      n= 49, number of events= 11
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -9.30e-01  3.95e-01  6.95e-01 -1.34    0.18
## TP53ND             -1.85e+01  9.53e-09  9.25e+03  0.00    1.00
## TP53D             -2.44e-01  7.83e-01  8.54e-01 -0.29    0.78
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]  3.95e-01  2.53e+00    0.101    1.54
## TP53ND             9.53e-09  1.05e+08    0.000    Inf
## TP53D             7.83e-01  1.28e+00    0.147    4.18
##
## Concordance= 0.607 (se = 0.095 )
## Rsquare= 0.066 (max possible= 0.721 )
## Likelihood ratio test= 3.34 on 3 df,  p=0.342
## Wald test              = 1.79 on 3 df,  p=0.617
## Score (logrank) test = 2.66 on 3 df,  p=0.447

cox.zph(surv.res)

##           rho      chisq      p
## ALTER_3CAT(50,70] -0.1767 3.47e-01 0.556
## TP53ND            -0.0646 9.27e-11 1.000
## TP53D            -0.2338 5.06e-01 0.477
## GLOBAL            NA 7.19e-01 0.869
```

4.3.16 TP53, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), UICC

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT + TP53, data = ds[cur
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + ALTER_3CAT +
##       TP53, data = ds[cur.subset, ])
##
##    n= 49, number of events= 11
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## UICC_3CATIVA      1.94e+01  2.70e+08  1.02e+04  0.00    1.00
## UICC_3CATIVB-C     1.98e+01  3.87e+08  1.02e+04  0.00    1.00
## ALTER_3CAT(50,70] -7.87e-01  4.55e-01  6.82e-01 -1.15    0.25
## TP53ND            -1.96e+01  2.97e-09  1.62e+04  0.00    1.00
## TP53D             -8.77e-02  9.16e-01  8.78e-01 -0.10    0.92
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      2.70e+08  3.71e-09    0.000      Inf
## UICC_3CATIVB-C     3.87e+08  2.58e-09    0.000      Inf
## ALTER_3CAT(50,70]  4.55e-01  2.20e+00    0.120    1.73
## TP53ND            2.97e-09  3.37e+08    0.000      Inf
## TP53D             9.16e-01  1.09e+00    0.164    5.12
##
## Concordance= 0.702  (se = 0.104 )
## Rsquare= 0.158    (max possible= 0.721 )
## Likelihood ratio test= 8.41  on 5 df,   p=0.135
## Wald test            = 1.65  on 5 df,   p=0.896
## Score (logrank) test = 5.76  on 5 df,   p=0.33

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA     -0.6623 3.28e-09 1.000
## UICC_3CATIVB-C   -0.1633 5.87e-10 1.000
## ALTER_3CAT(50,70] -0.1456 2.13e-01 0.645
## TP53ND           0.0381 7.94e-12 1.000
## TP53D            -0.1968 3.18e-01 0.573
## GLOBAL           NA 8.40e-01 0.974

```

4.3.17 TP53, UICC, AGE (in categories: up to 50 or over 70 vs. between 50 and 70), PACKYEARS (cut at 30)

```

surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + I(PACKYEARS > 30) + ALTER_3CAT +
  TP53, data = ds[cur.subset, ])
summary(surv.res)

```



```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + I(PACKYEARS >
##      30) + ALTER_3CAT + TP53, data = ds[cur.subset, ])
##
##      n= 48, number of events= 11
##      (1 observation deleted due to missingness)
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## UICC_3CATIVA      2.00e+01  5.00e+08  1.02e+04  0.00   0.998
## UICC_3CATIVB-C      2.05e+01  8.07e+08  1.02e+04  0.00   0.998
## I(PACKYEARS > 30)TRUE  2.07e+00  7.96e+00  8.32e-01  2.49   0.013 *
## ALTER_3CAT(50,70]   -7.79e-01  4.59e-01  6.97e-01 -1.12   0.264
## TP53ND              -2.02e+01  1.70e-09  1.97e+04  0.00   0.999
## TP53D               4.67e-01  1.60e+00  1.01e+00  0.46   0.643
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      5.00e+08  2.00e-09   0.000      Inf
## UICC_3CATIVB-C      8.07e+08  1.24e-09   0.000      Inf
## I(PACKYEARS > 30)TRUE  7.96e+00  1.26e-01   1.558    40.7
## ALTER_3CAT(50,70]   4.59e-01  2.18e+00   0.117     1.8
## TP53ND              1.70e-09  5.87e+08   0.000      Inf
## TP53D               1.60e+00  6.27e-01   0.221    11.5
##
## Concordance= 0.859 (se = 0.106 )
## Rsquare= 0.268 (max possible= 0.727 )
## Likelihood ratio test= 15 on 6 df,  p=0.0205
## Wald test = 7.67 on 6 df,  p=0.263
## Score (logrank) test = 13.3 on 6 df,  p=0.0384

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA     -0.3735 3.84e-09 1.000
## UICC_3CATIVB-C     -0.0750 3.39e-10 1.000
## I(PACKYEARS > 30)TRUE  0.0278 8.50e-03 0.927
## ALTER_3CAT(50,70]   -0.1572 2.50e-01 0.617
## TP53ND            0.1959 9.22e-11 1.000
## TP53D             -0.2568 6.21e-01 0.431
## GLOBAL              NA 1.60e+00 0.952
```

4.3.18 TP53, PACKYEARS (cut at 30)

```
surv.res <- coxph(surv.obj[cur.subset] ~ I(PACKYEARS > 30) + TP53, data = ds[cur.subs
])
summary(surv.res)
```

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ I(PACKYEARS > 30) + TP53,
##       data = ds[cur.subset, ])
##
## n= 48, number of events= 11
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## I(PACKYEARS > 30)TRUE  1.37e+00  3.95e+00  7.35e-01  1.87   0.062 .
## TP53ND                -1.85e+01  9.16e-09  9.61e+03  0.00   0.998
## TP53D                  8.76e-02  1.09e+00  8.50e-01  0.10   0.918
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## I(PACKYEARS > 30)TRUE  3.95e+00  2.53e-01    0.934    16.68
## TP53ND                9.16e-09  1.09e+08    0.000      Inf
## TP53D                 1.09e+00  9.16e-01    0.206     5.78
##
## Concordance= 0.714 (se = 0.097 )
## Rsquare= 0.104 (max possible= 0.727 )
## Likelihood ratio test= 5.3 on 3 df,  p=0.151
## Wald test               = 3.49 on 3 df,  p=0.322
## Score (logrank) test = 4.9 on 3 df,  p=0.179

cox.zph(surv.res)

##               rho      chisq      p
## I(PACKYEARS > 30)TRUE  0.0168 2.98e-03 0.956
## TP53ND                0.4077 1.28e-09 1.000
## TP53D                 -0.2083 5.34e-01 0.465
## GLOBAL                 NA 5.40e-01 0.910
```