

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 progression-free survival.

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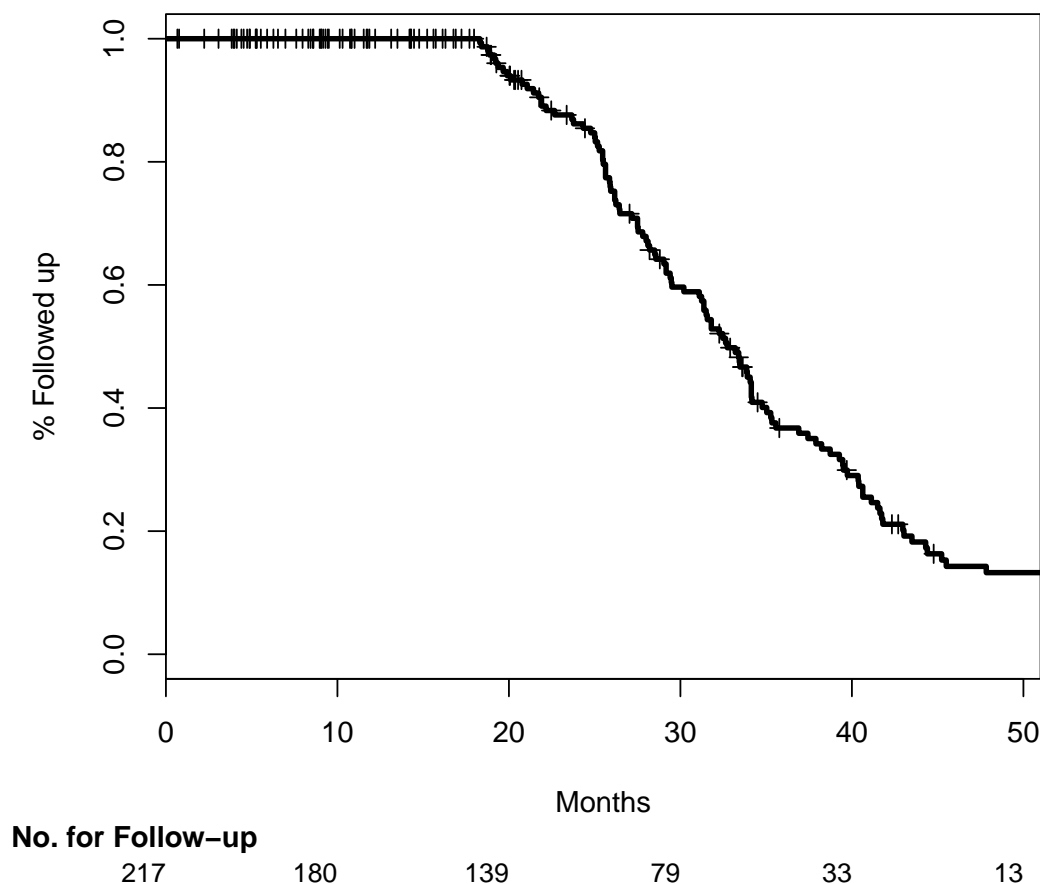
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**PLEASE NOTE:** For historical reasons, the Immune Response (IR) Cluster (one of the Consensus Clusters determined by gene expression) is sometimes called *Atypical* Cluster in this document.

## 1 Follow-up



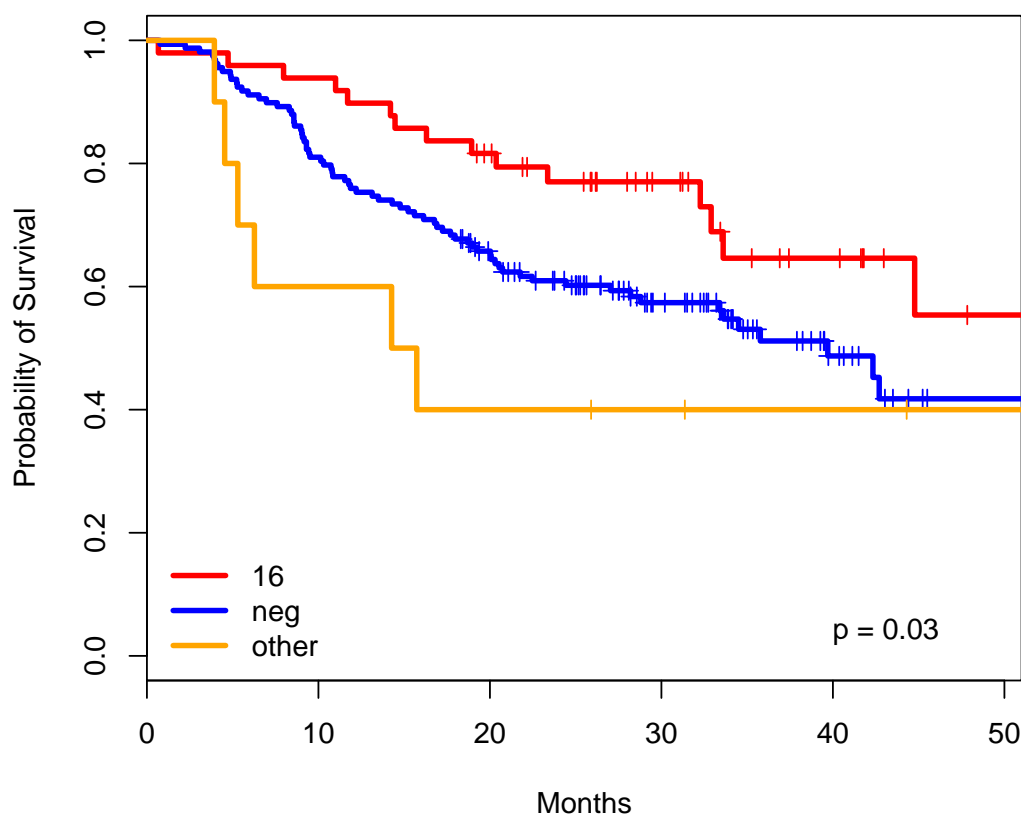
## 2 Exploration of single variables

### 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= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]neg  0.565    1.759   0.277  2.04   0.041 *
## split[cur.subset]other 1.131    3.099   0.455  2.48   0.013 *
```

```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]neg      1.76      0.568      1.02      3.03
## split[cur.subset]other     3.10      0.323      1.27      7.57
##
## Concordance= 0.57 (se = 0.025 )
## Rsquare= 0.033 (max possible= 0.987 )
## Likelihood ratio test= 7.25 on 2 df,  p=0.0266
## Wald test               = 7.05 on 2 df,  p=0.0295
## Score (logrank) test = 7.36 on 2 df,  p=0.0252
```

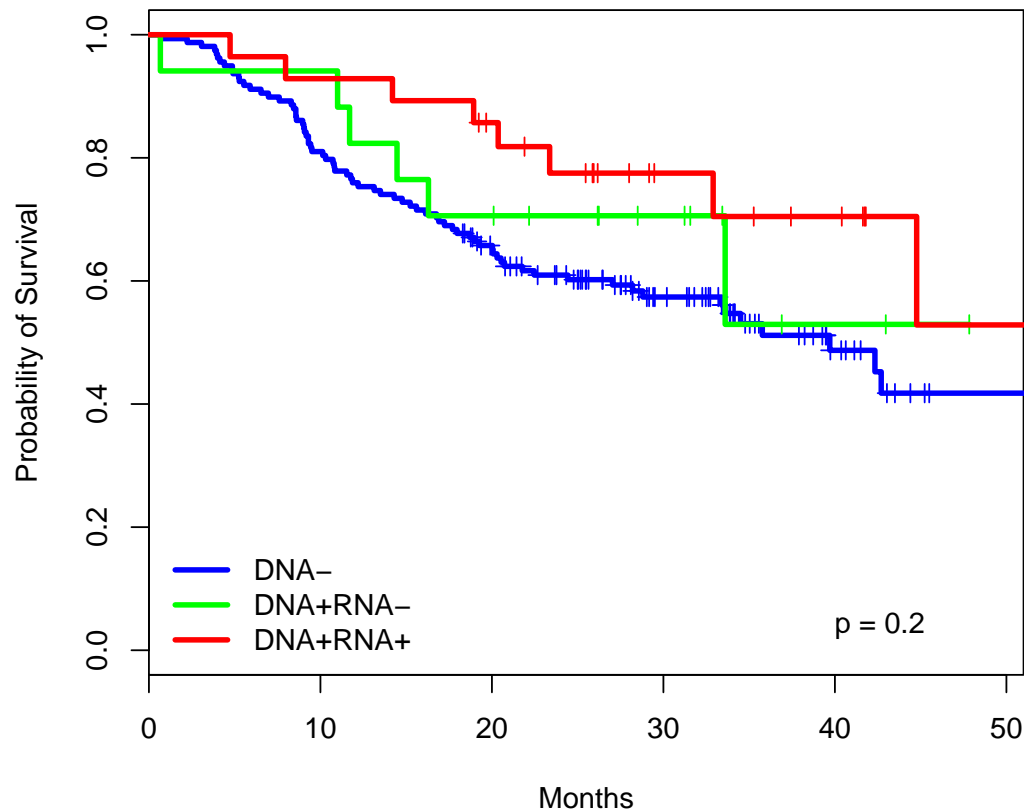


No. at Risk						
16	49	46	38	22	12	5
neg	158	128	97	54	19	7
other	10	6	4	3	2	1

## 2.2 HPV DNA RNA

```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 203, number of events= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]DNA+RNA- -0.313    0.731    0.425 -0.74    0.462
## split[cur.subset]DNA+RNA+ -0.591    0.554    0.354 -1.67    0.095 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]DNA+RNA-    0.731      1.37    0.318    1.68
## split[cur.subset]DNA+RNA+    0.554      1.81    0.277    1.11
##
## Concordance= 0.549 (se = 0.025 )
## Rsquare= 0.017 (max possible= 0.985 )
## Likelihood ratio test= 3.55 on 2 df,  p=0.17
## Wald test               = 3.13 on 2 df,  p=0.209
## Score (logrank) test = 3.21 on 2 df,  p=0.201
```



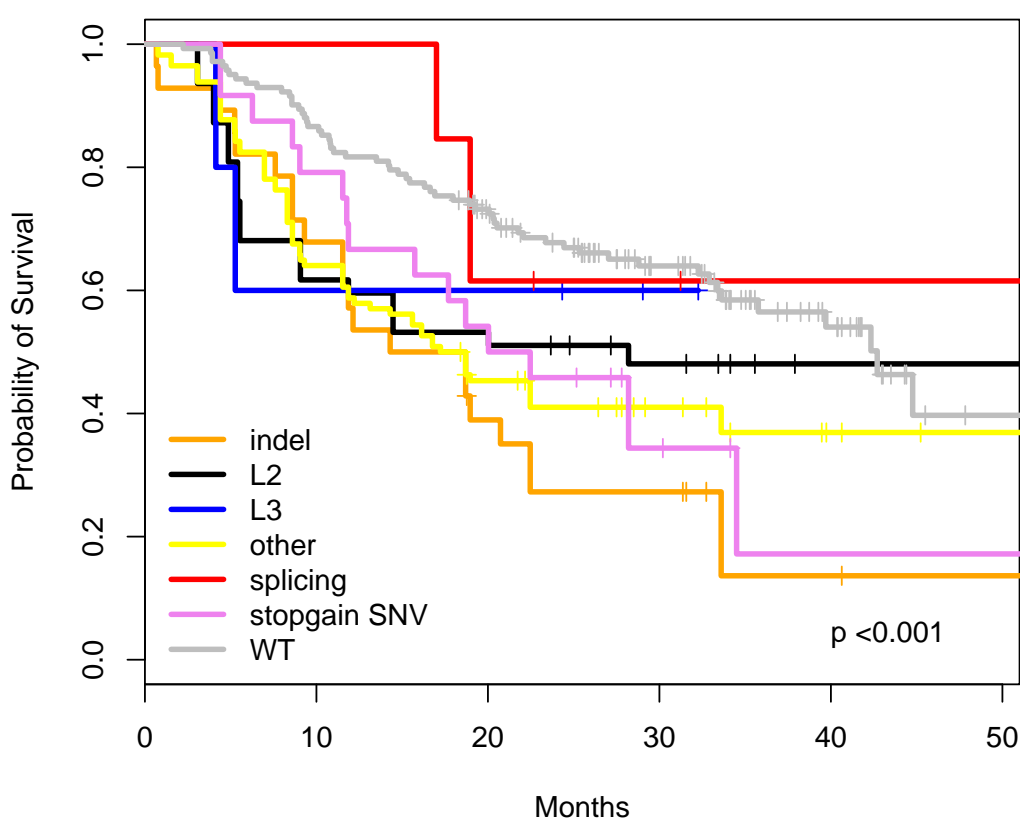


No. at Risk						
	0	10	20	30	40	50
DNA-	158	128	97	54	19	7
DNA+RNA-	17	16	12	7	2	0
DNA+RNA+	28	26	22	11	8	3

**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	19	10	7	2	1
L2	47	29	25	16	1	1
L3	15	9	9	3	0	0
other	114	73	47	23	12	7
splicing	13	13	8	6	5	5
stopgain SNV	24	19	13	6	2	2

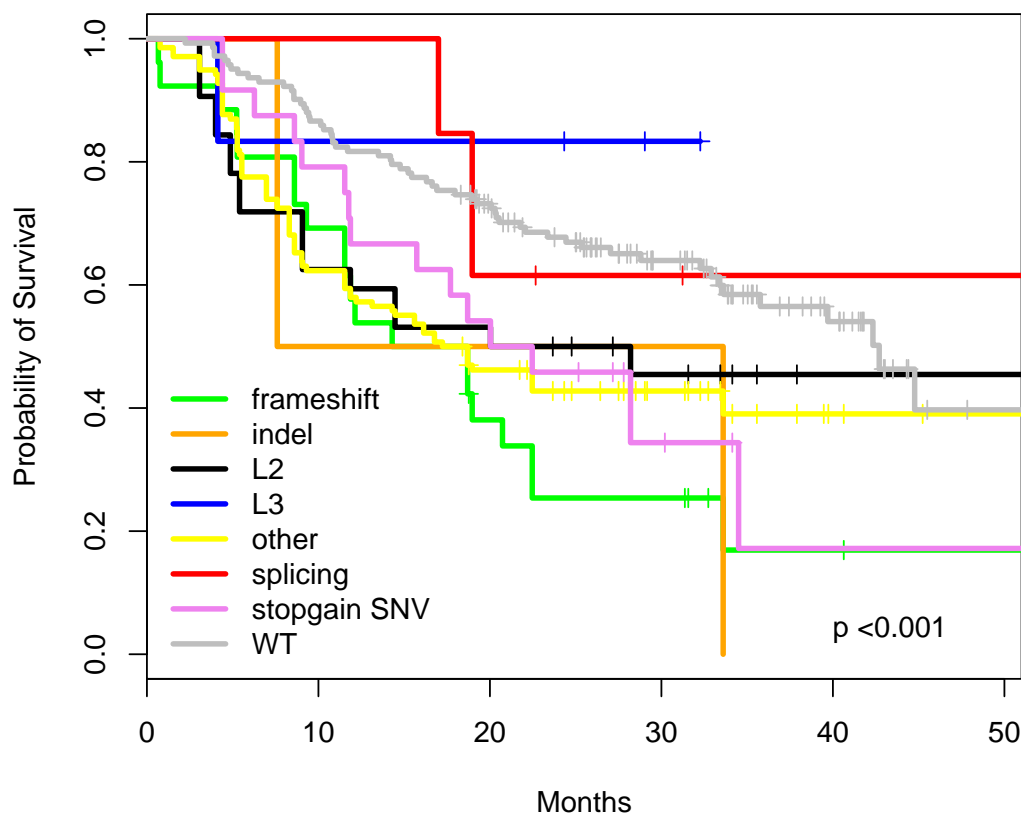
## 2.4 Types of TP53 mutations by functional domain. Similar but NOT identical to Gross et al. (Nat Genet 2014).

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
```

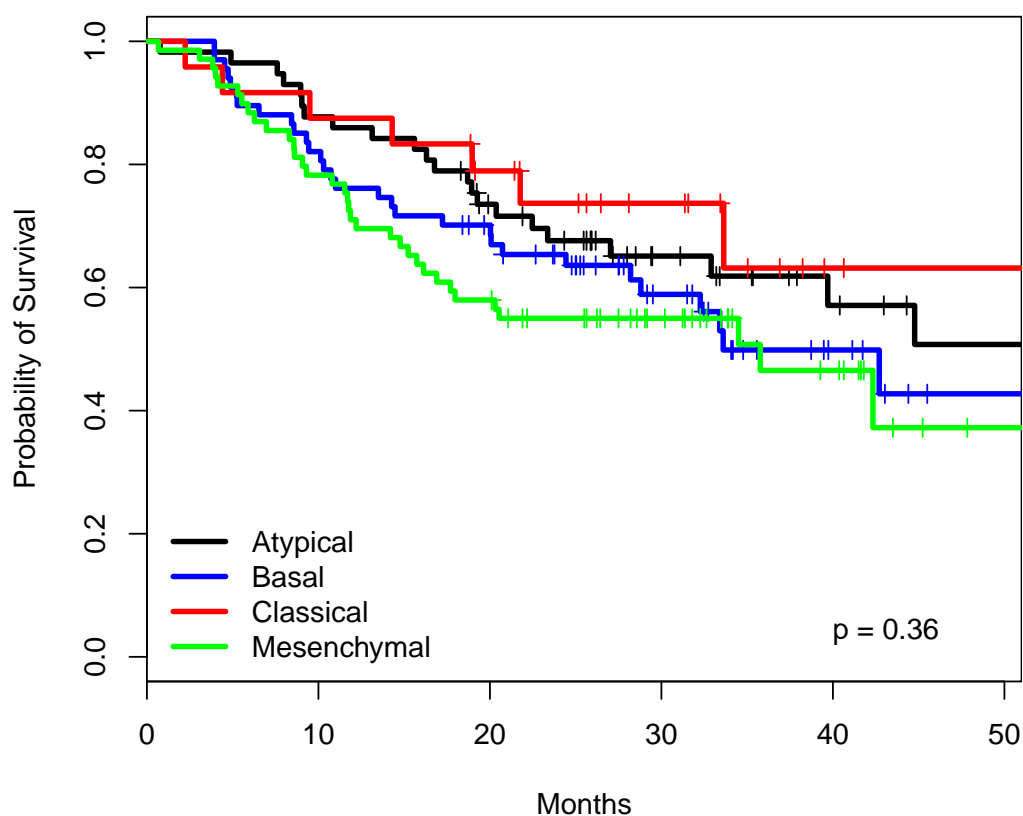


No. at Risk						
frameshift	26	18	9	6	2	1
indel	2	1	1	1	0	0
L2	32	20	17	10	1	1
L3	6	5	5	2	0	0
other	138	86	59	30	12	7
splicing	13	13	8	6	5	5

## 2.5 Consensus Clusters

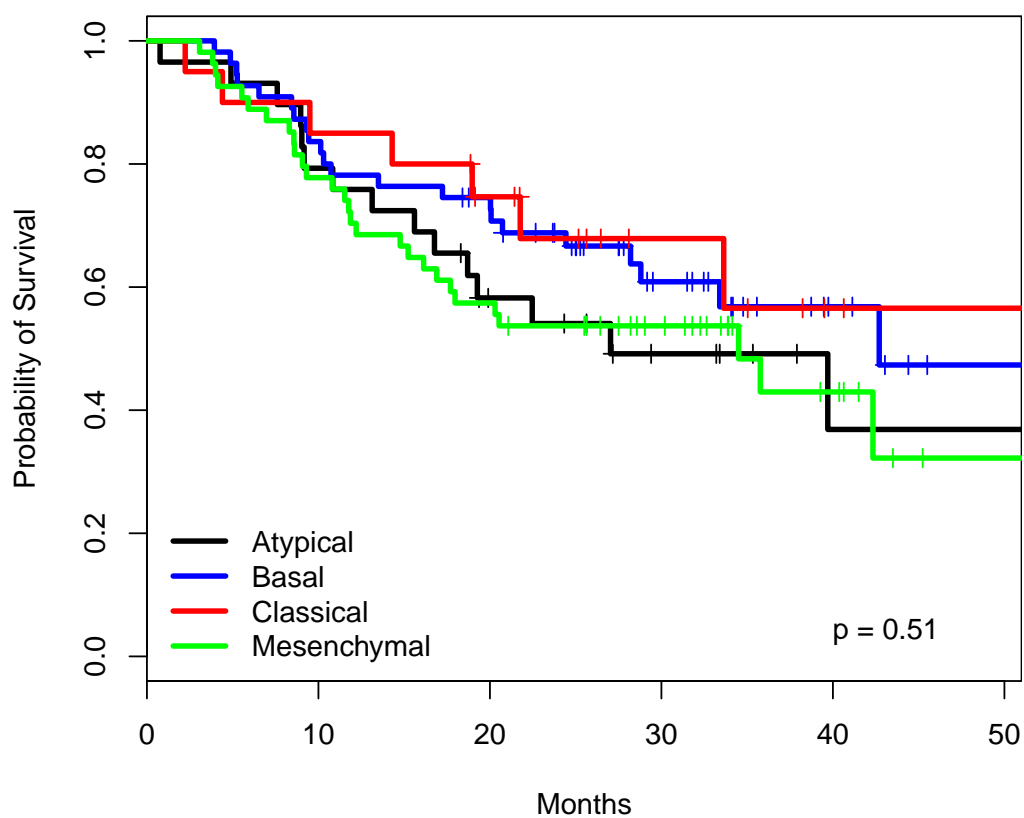
```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      0.2646    1.3029  0.2736  0.97   0.33
## split[cur.subset]Classical -0.0947    0.9096  0.4111 -0.23   0.82
## split[cur.subset]Mesenchymal 0.4100    1.5069  0.2698  1.52   0.13
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      1.30      0.768    0.762    2.23
## split[cur.subset]Classical  0.91      1.099    0.406    2.04
```

```
## split[cur.subset]Mesenchymal      1.51      0.664      0.888      2.56
##
## Concordance= 0.565 (se = 0.03 )
## Rsquare= 0.015 (max possible= 0.987 )
## Likelihood ratio test= 3.29 on 3 df, p=0.35
## Wald test = 3.21 on 3 df, p=0.361
## Score (logrank) test = 3.25 on 3 df, p=0.355
```



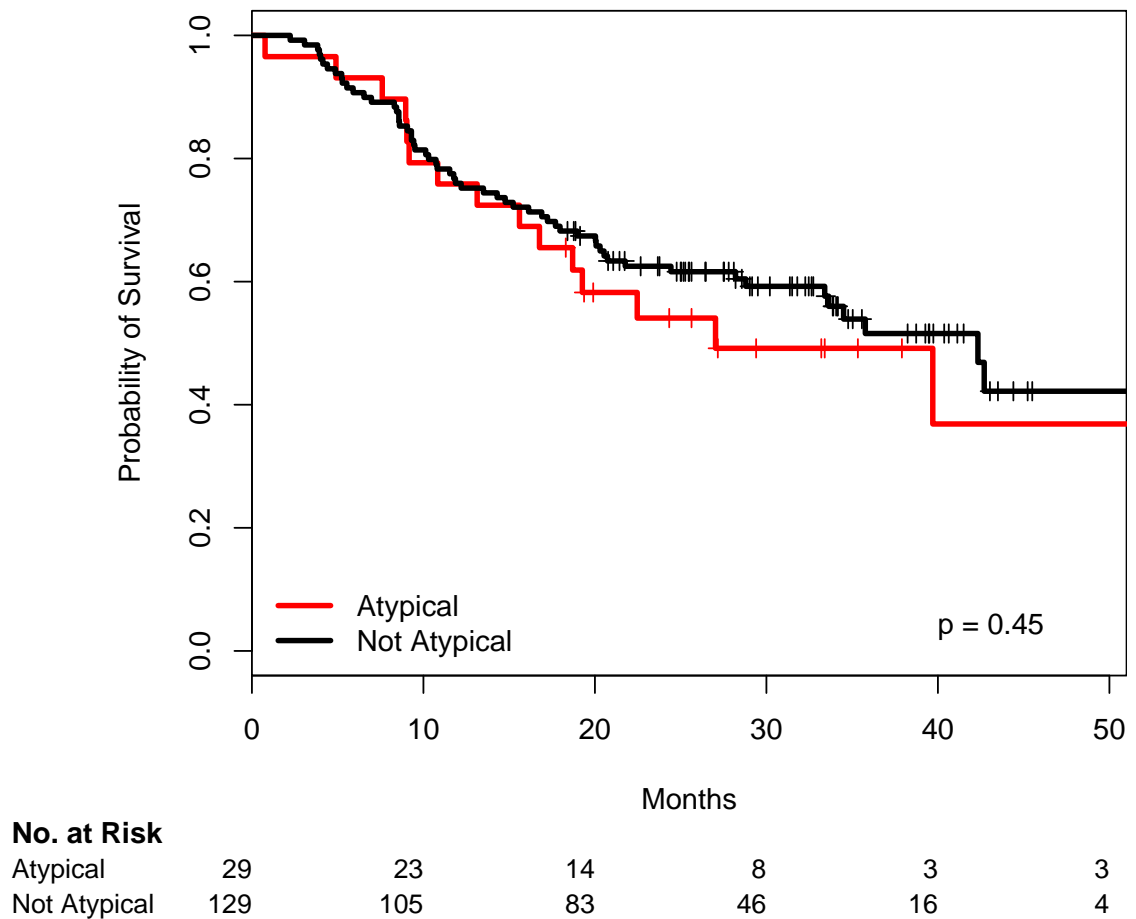
No. at Risk						
Atypical	57	50	38	21	12	8
Basal	67	55	44	23	9	3
Classical	24	21	17	10	2	1
Mesenchymal	69	54	40	25	10	1

### 2.5.1 Consensus Clusters in HPV DNA-



No. at Risk						
Atypical	29	23	14	8	3	3
Basal	55	46	39	19	7	2
Classical	20	17	13	6	2	1
Mesenchymal	54	42	31	21	7	1

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

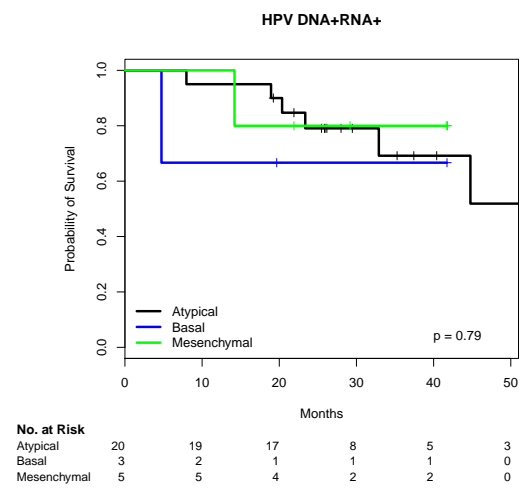
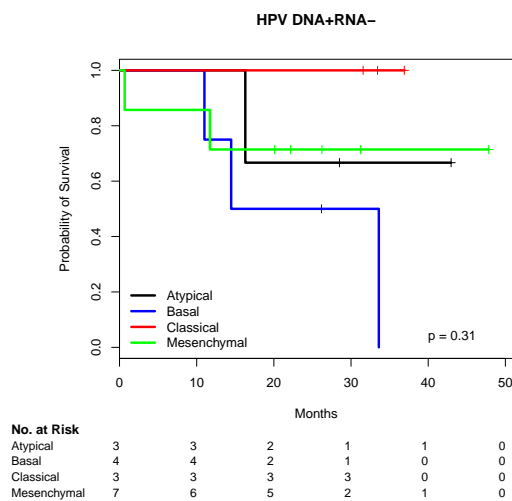
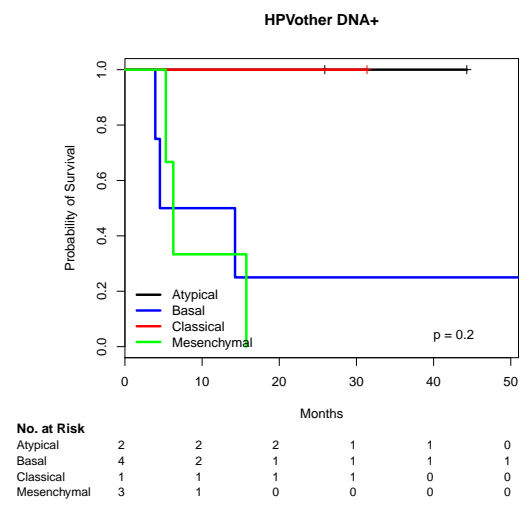
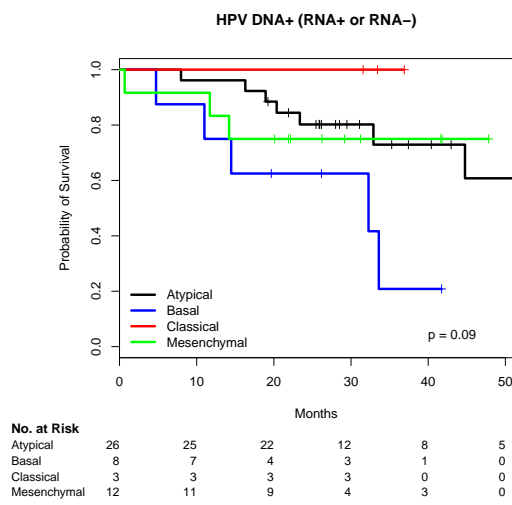
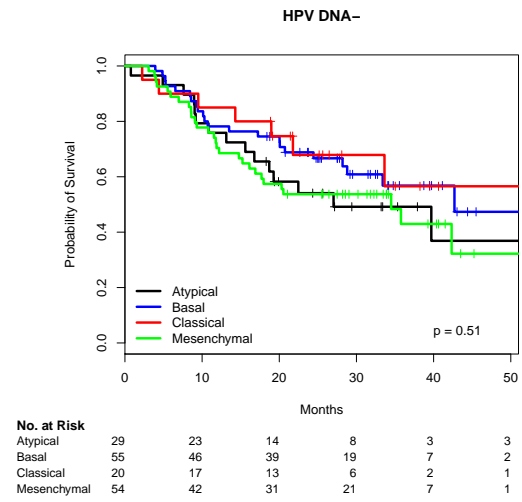
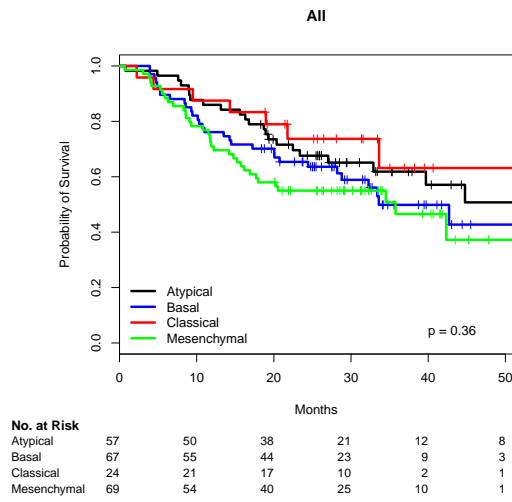


## 2.6 Consensus Clusters

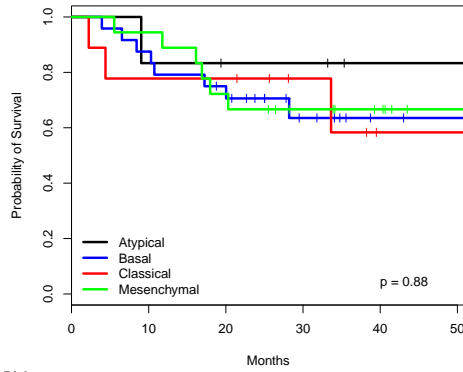
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
```

```
##
##   n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal      0.2646    1.3029   0.2736   0.97    0.33
## split[cur.subset]Classical -0.0947    0.9096   0.4111  -0.23    0.82
## split[cur.subset]Mesenchymal 0.4100    1.5069   0.2698   1.52    0.13
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      1.30      0.768    0.762    2.23
## split[cur.subset]Classical  0.91      1.099    0.406    2.04
## split[cur.subset]Mesenchymal 1.51      0.664    0.888    2.56
##
## Concordance= 0.565 (se = 0.03 )
## Rsquare= 0.015 (max possible= 0.987 )
## Likelihood ratio test= 3.29 on 3 df, p=0.35
## Wald test = 3.21 on 3 df, p=0.361
## Score (logrank) test = 3.25 on 3 df, p=0.355
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##   n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Basal     -0.3750    0.6873   0.3297  -1.14    0.26
## split[cur.subset]Classical -0.3460    0.7075   0.4344  -0.80    0.43
## split[cur.subset]Mesenchymal -0.0132    0.9869   0.3149  -0.04    0.97
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Basal      0.687      1.45    0.360    1.31
## split[cur.subset]Classical  0.708      1.41    0.302    1.66
## split[cur.subset]Mesenchymal 0.987      1.01    0.532    1.83
##
## Concordance= 0.547 (se = 0.034 )
## Rsquare= 0.015 (max possible= 0.986 )
## Likelihood ratio test= 2.34 on 3 df, p=0.505
## Wald test = 2.3 on 3 df, p=0.513
## Score (logrank) test = 2.32 on 3 df, p=0.508
```





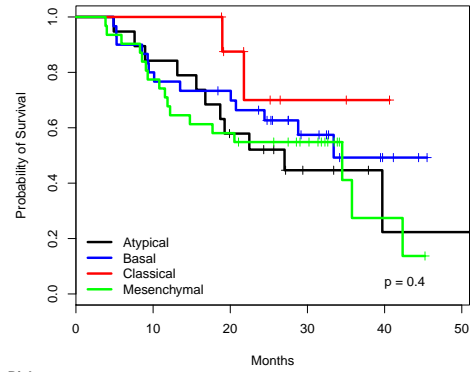
HPV DNA-, UICC I, II, III



No. at Risk

	6	5	4	4	2	2
Atypical	6	5	4	4	2	2
Basal	24	21	17	8	3	2
Classical	9	7	7	4	1	1
Mesenchymal	18	17	13	9	5	1

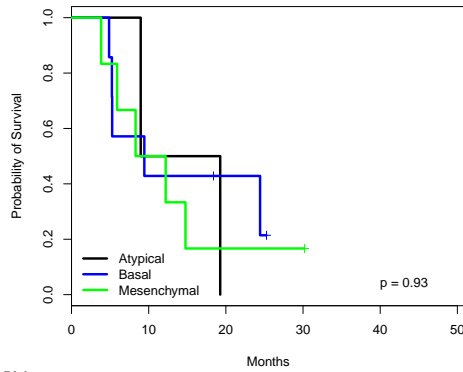
HPV DNA-, UICC IVA



No. at Risk

	19	16	10	4	1	1
Atypical	19	16	10	4	1	1
Basal	30	24	21	10	3	0
Classical	9	9	6	2	1	0
Mesenchymal	31	24	18	12	2	0

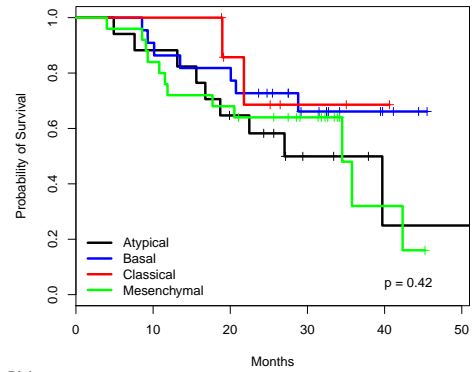
HPV DNA-, UICC IVA, Ther. unimodal



No. at Risk

	2	1	0	0	0	0
Atypical	2	1	0	0	0	0
Basal	7	3	2	0	0	0
Mesenchymal	6	3	1	1	0	0

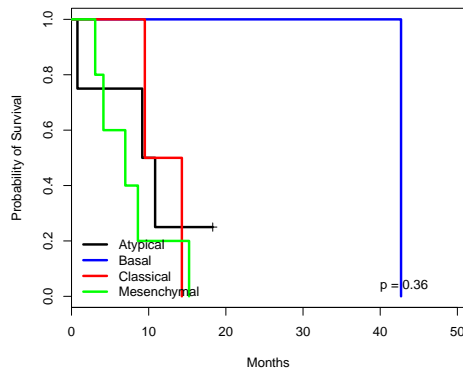
HPV DNA-, UICC IVA, Ther. multimodal



No. at Risk

	17	15	10	4	1	1
Atypical	17	15	10	4	1	1
Basal	22	20	18	9	3	0
Classical	8	8	5	2	1	0
Mesenchymal	25	21	17	11	2	0

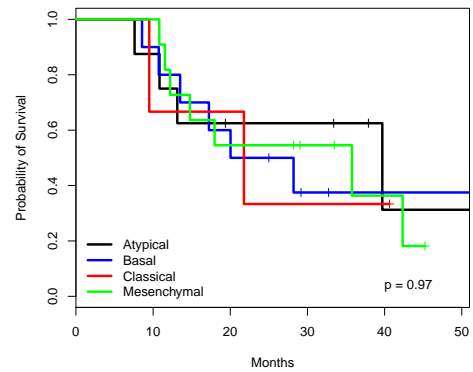
HPV DNA-, UICC IVB-C



No. at Risk

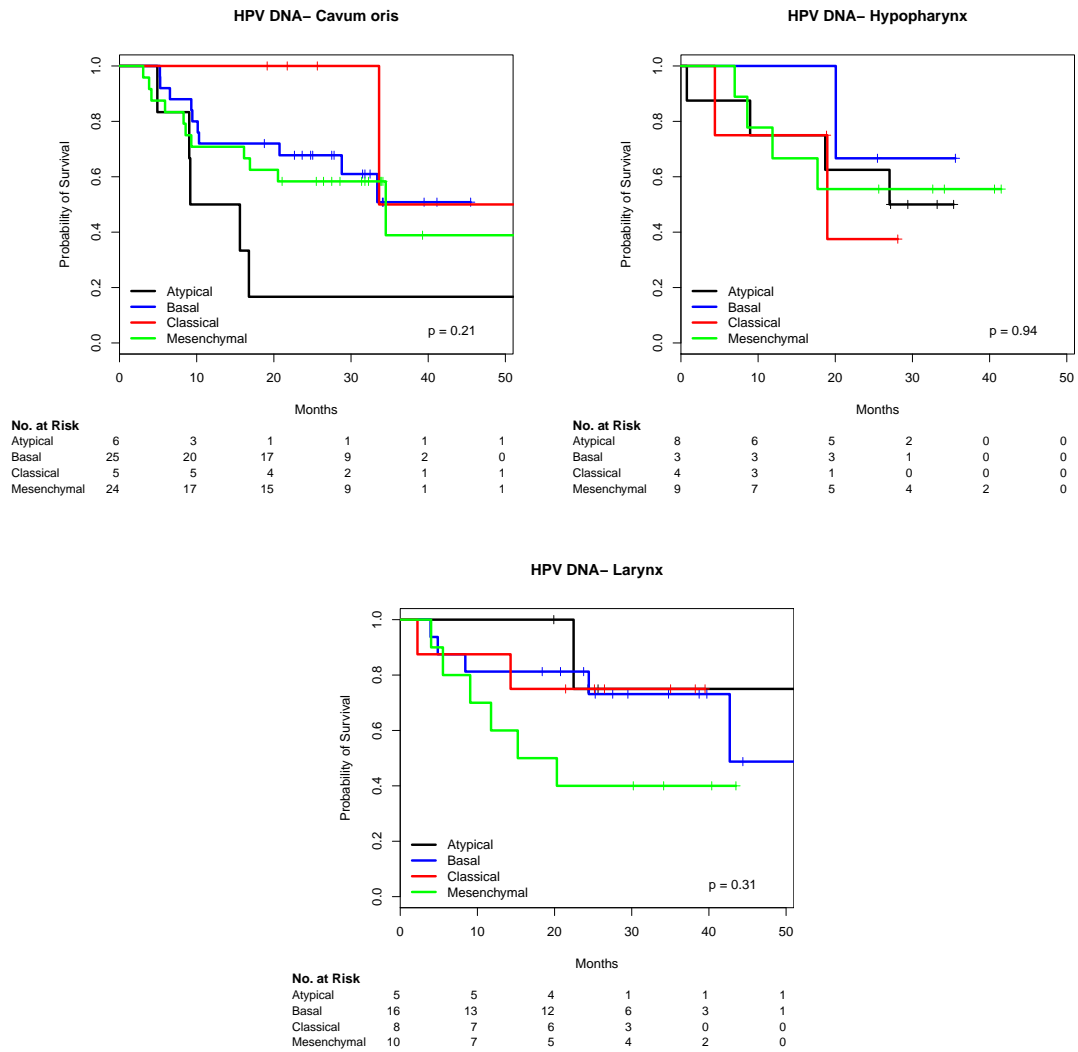
	4	2	0	0	0	0
Atypical	4	2	0	0	0	0
Basal	1	1	1	1	1	0
Classical	2	1	0	0	0	0
Mesenchymal	5	1	0	0	0	0

HPV DNA- Oropharynx



No. at Risk

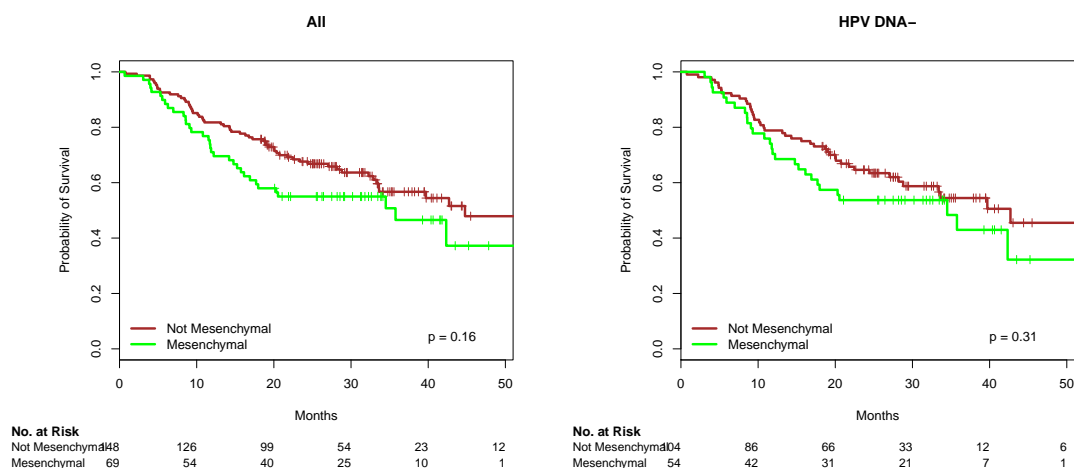
	8	7	4	4	1	1
Atypical	8	7	4	4	1	1
Basal	10	9	6	2	1	1
Classical	3	2	2	1	1	0
Mesenchymal	11	11	6	4	2	0

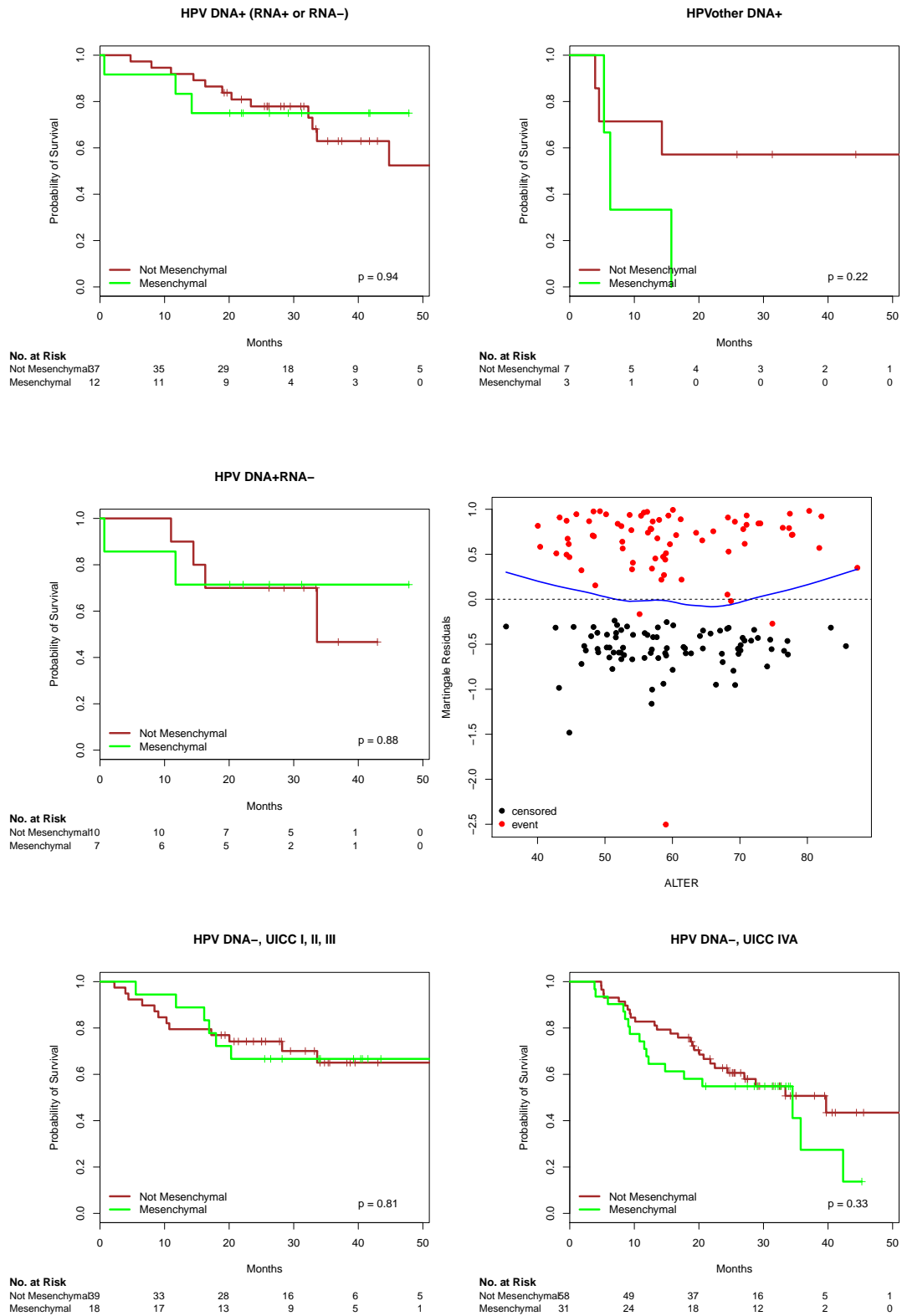


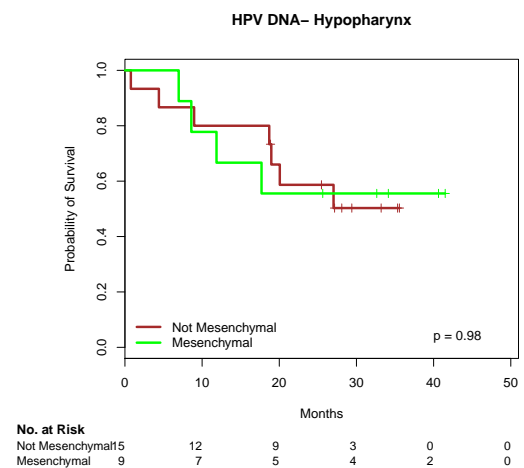
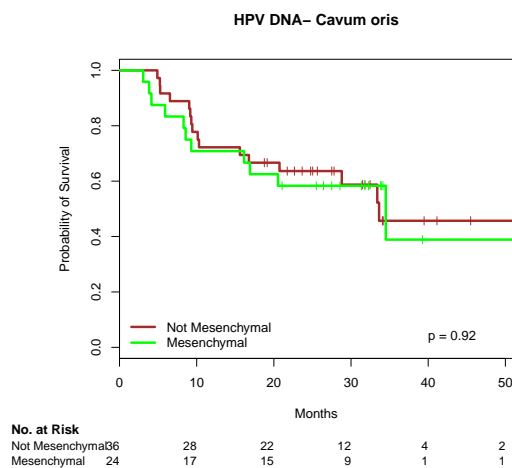
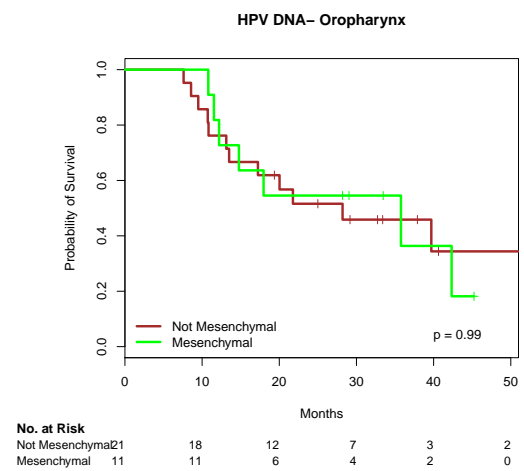
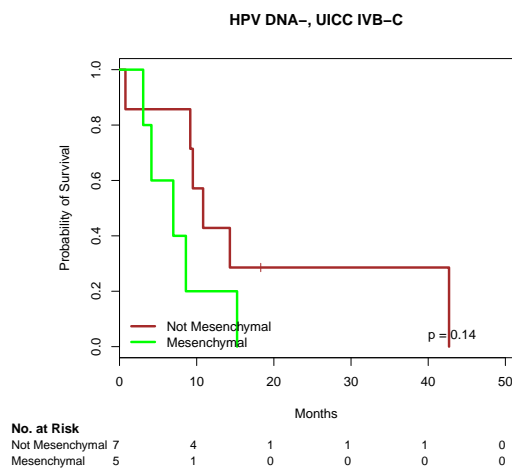
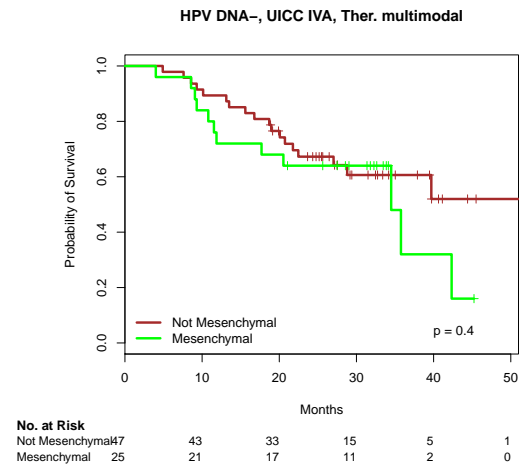
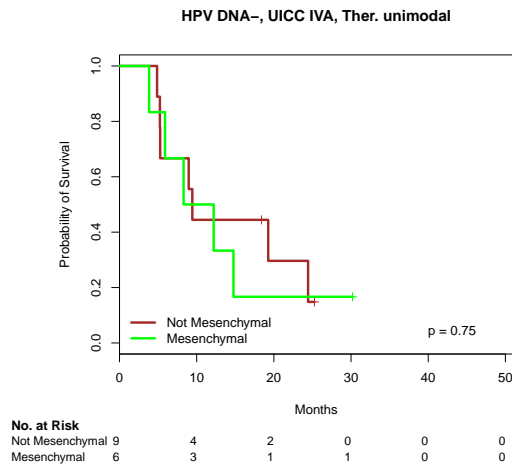
## 2.7 “Mesenchymal“ vs. other Consensus Clusters

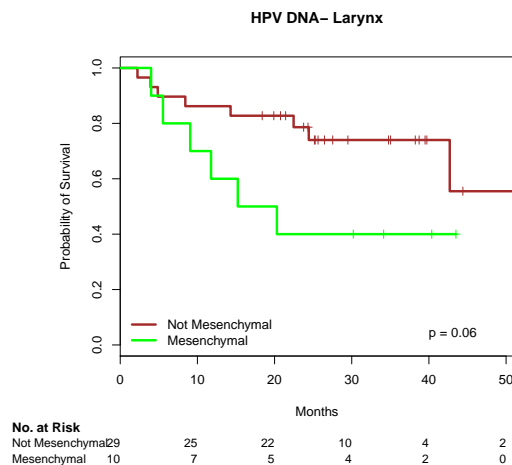
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.302      1.352      0.214 1.41      0.16
##
```

```
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.35      0.74      0.889      2.06
##
## Concordance= 0.545 (se = 0.025 )
## Rsquare= 0.009 (max possible= 0.987 )
## Likelihood ratio test= 1.93 on 1 df,  p=0.165
## Wald test               = 1.99 on 1 df,  p=0.158
## Score (logrank) test = 2 on 1 df,  p=0.157
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##                                coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Mesenchymal 0.242      1.274      0.240 1.01      0.31
##
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Mesenchymal      1.27      0.785      0.795      2.04
##
## Concordance= 0.536 (se = 0.029 )
## Rsquare= 0.006 (max possible= 0.986 )
## Likelihood ratio test= 0.99 on 1 df,  p=0.319
## Wald test               = 1.01 on 1 df,  p=0.314
## Score (logrank) test = 1.02 on 1 df,  p=0.313
```





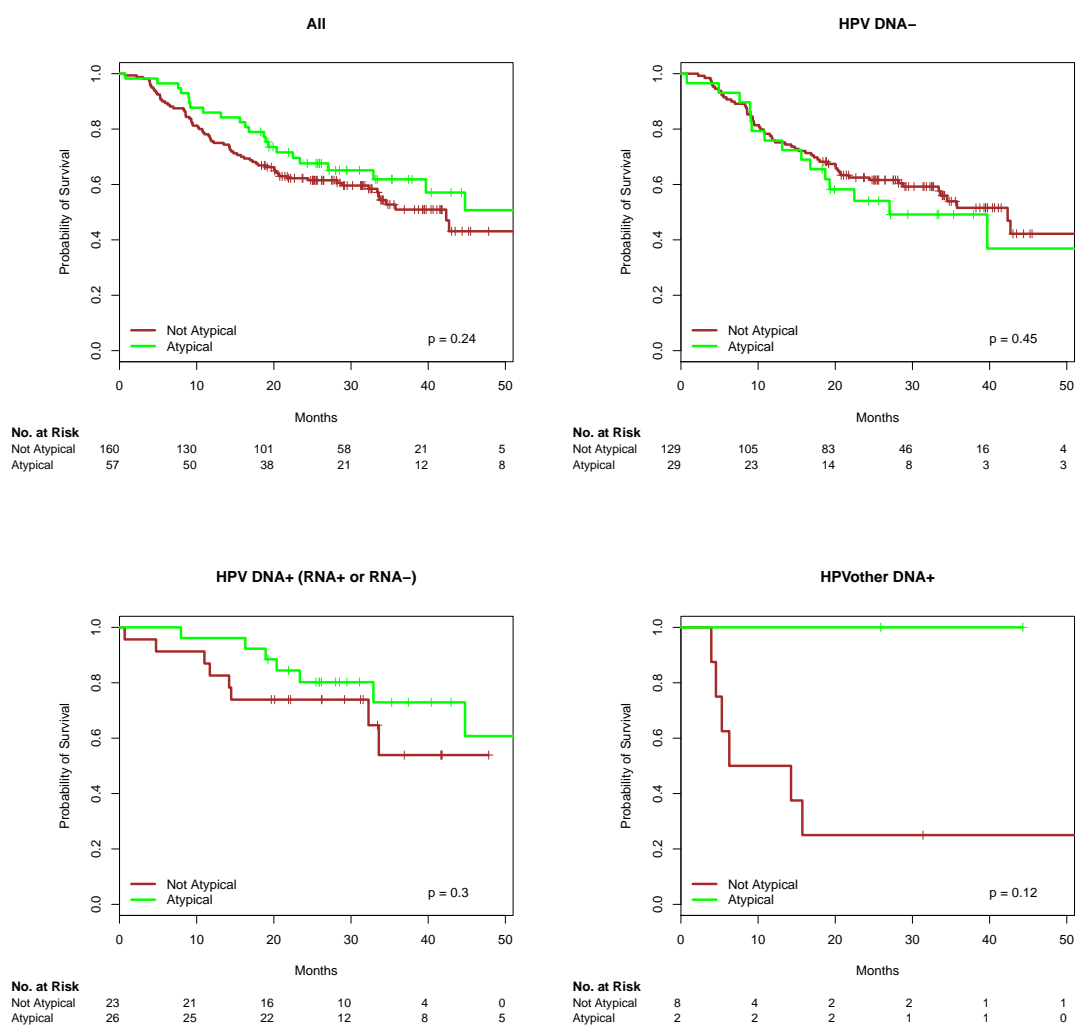




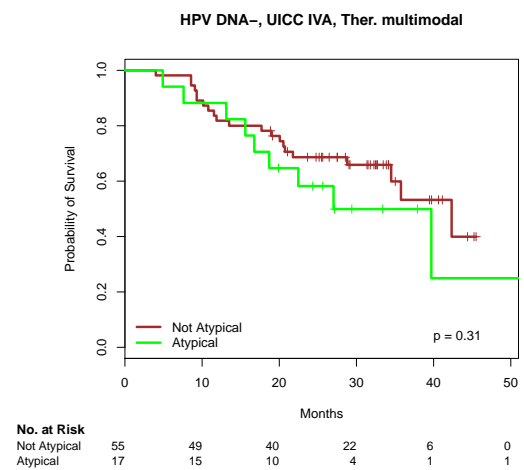
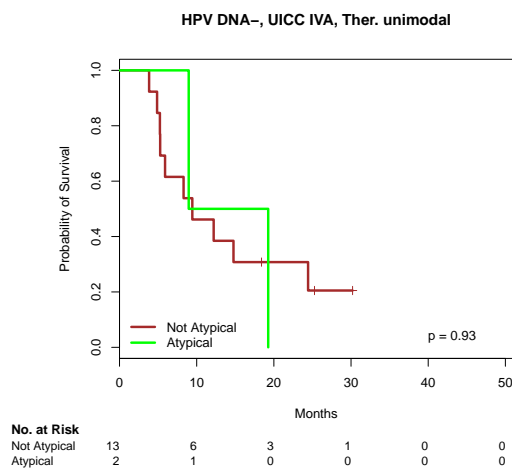
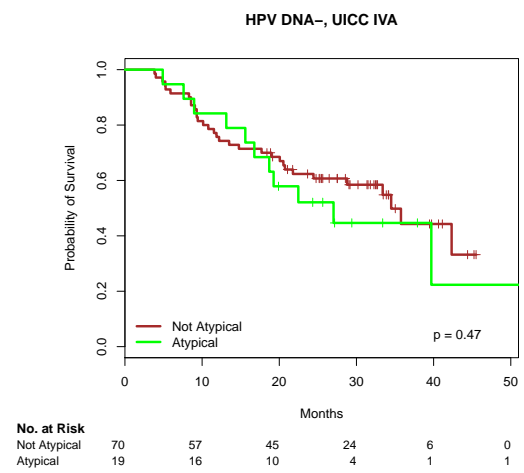
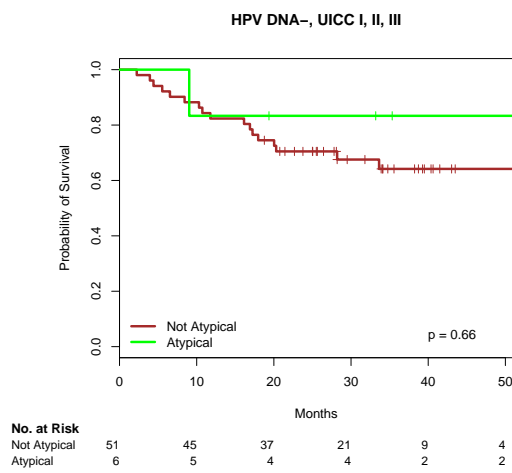
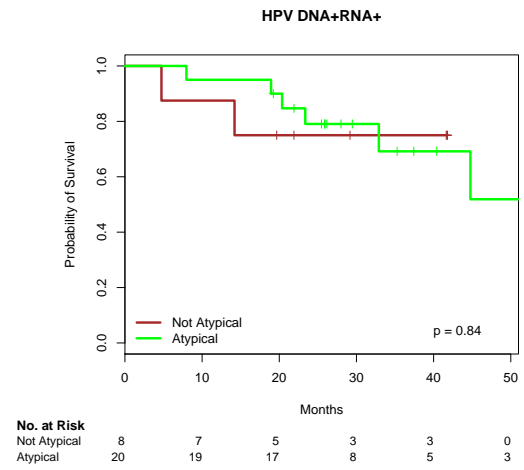
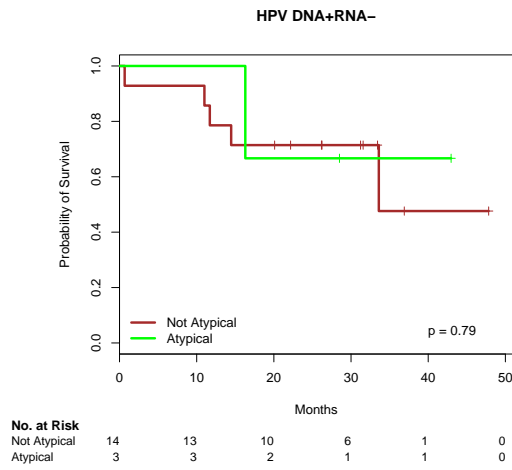
## 2.8 “Atypical” vs. other Consensus Clusters

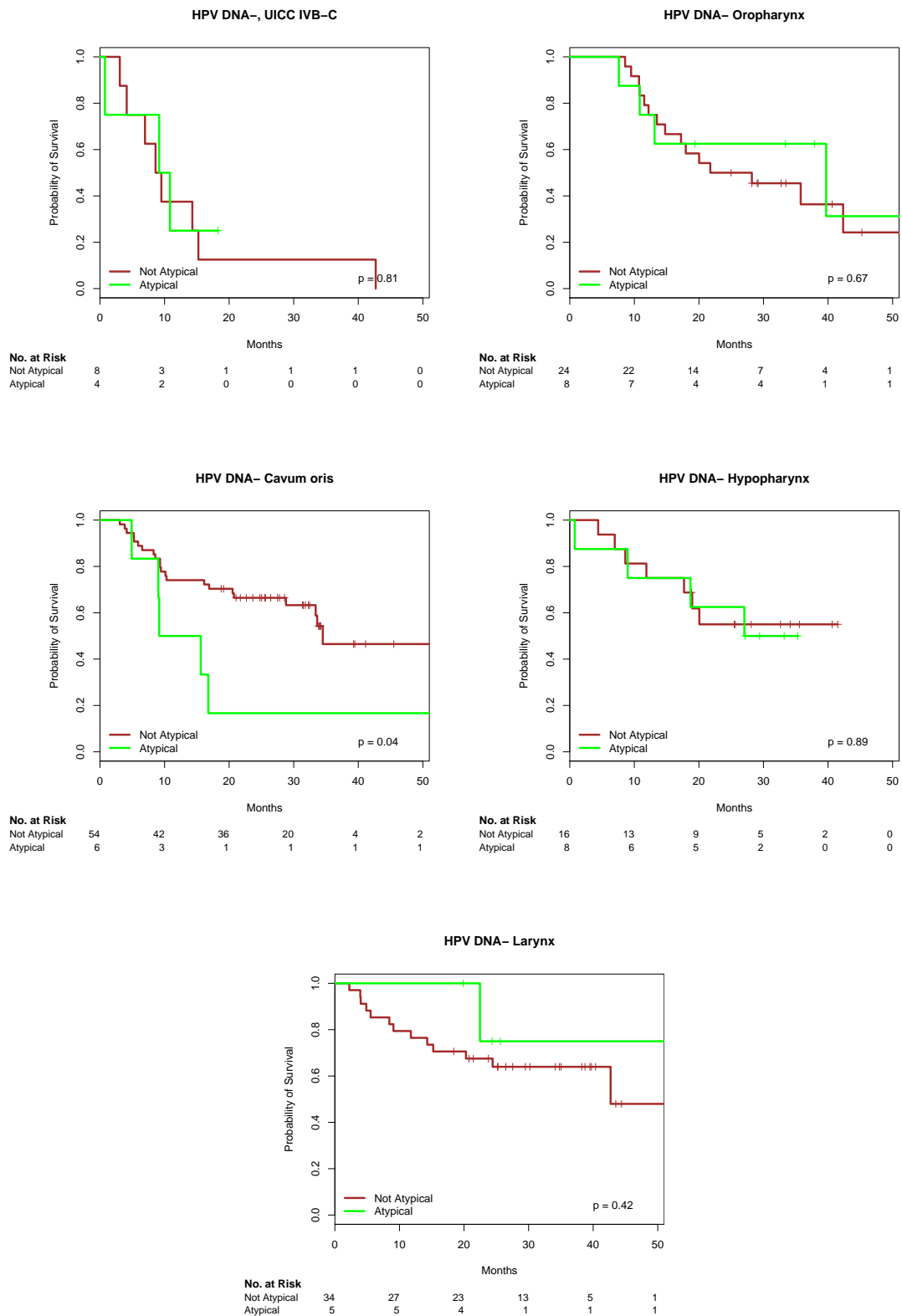
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical -0.281    0.755    0.238 -1.18    0.24
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical    0.755    1.32    0.473    1.2
##
## Concordance= 0.531 (se = 0.024 )
## Rsquare= 0.007 (max possible= 0.987 )
## Likelihood ratio test= 1.45 on 1 df,  p=0.228
## Wald test               = 1.39 on 1 df,  p=0.238
## Score (logrank) test = 1.4 on 1 df,  p=0.237
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
```

```
##
##   n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]Atypical 0.212      1.237    0.284 0.75    0.45
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]Atypical      1.24      0.809    0.709    2.16
##
## Concordance= 0.515 (se = 0.024 )
## Rsquare= 0.003 (max possible= 0.986 )
## Likelihood ratio test= 0.54 on 1 df,  p=0.463
## Wald test               = 0.56 on 1 df,  p=0.454
## Score (logrank) test = 0.56 on 1 df,  p=0.454
```





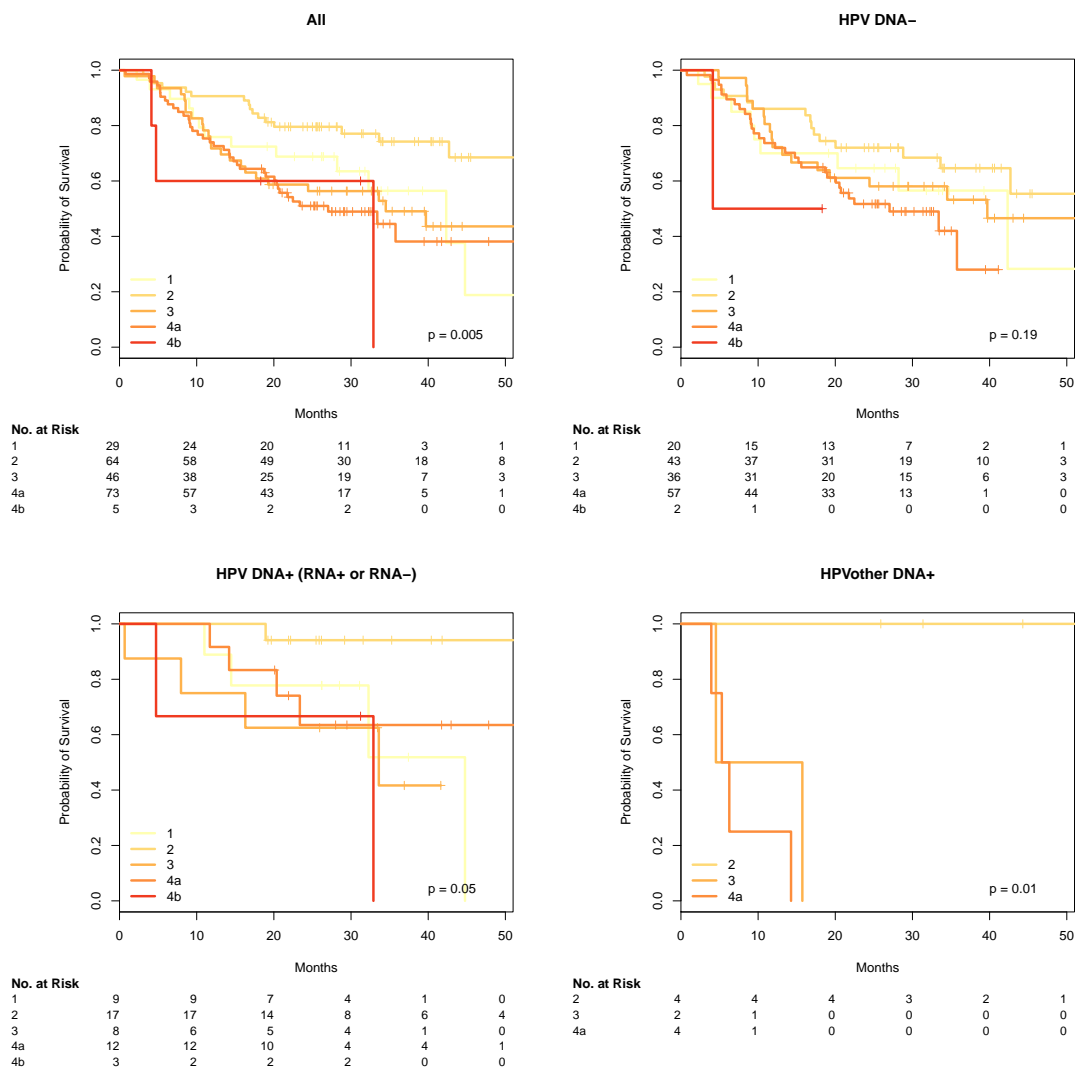


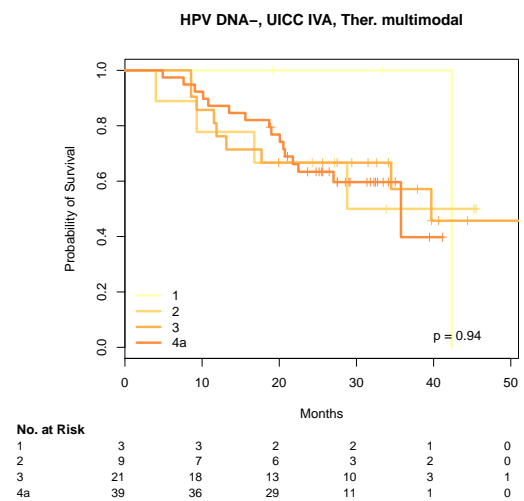
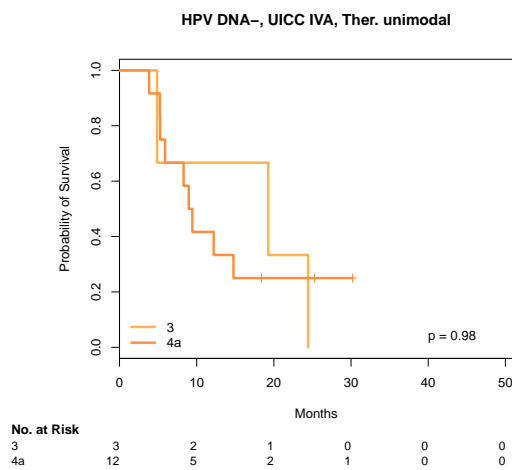
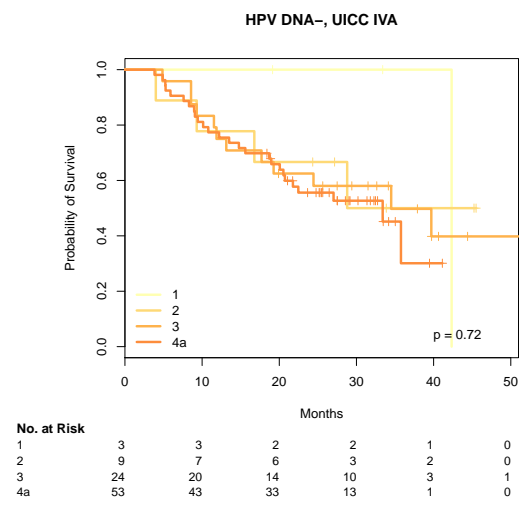
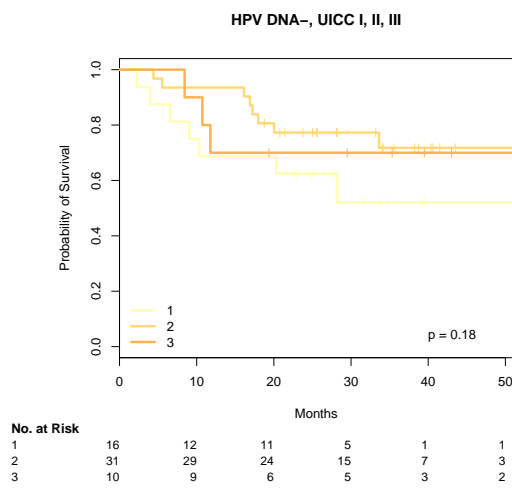
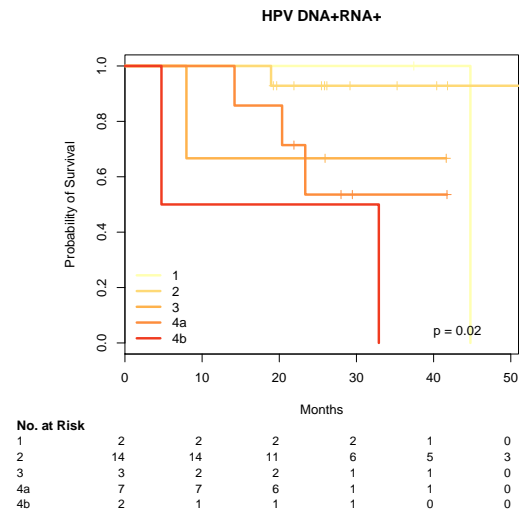
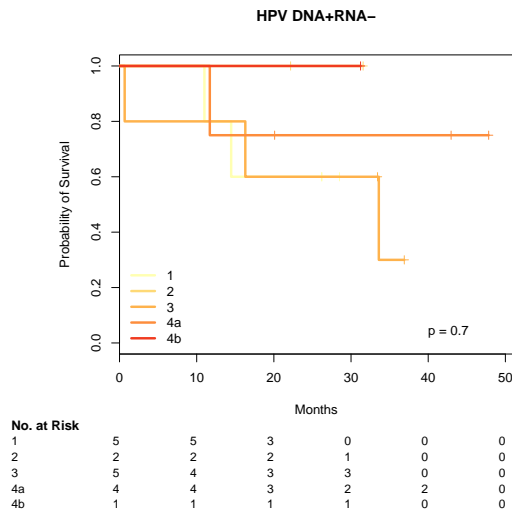


## 2.9 T (TNM staging)

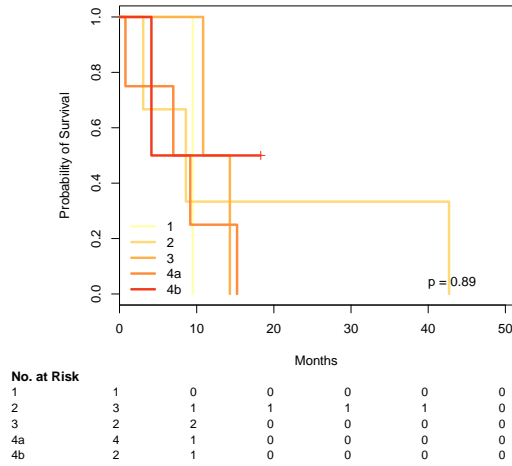
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.7991    0.4497  0.3581 -2.23   0.026 *
## split[cur.subset]3  0.0151    1.0152  0.3397  0.04   0.965
## split[cur.subset]4a 0.2001    1.2215  0.3130  0.64   0.523
## split[cur.subset]4b 0.6142    1.8481  0.6375  0.96   0.335
## split[cur.subset]x      NA         NA  0.0000   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    0.45      2.224    0.223    0.907
## split[cur.subset]3    1.02      0.985    0.522    1.976
## split[cur.subset]4a    1.22      0.819    0.661    2.256
## split[cur.subset]4b    1.85      0.541    0.530    6.447
## split[cur.subset]x      NA         NA      NA      NA
##
## Concordance= 0.605 (se = 0.03 )
## Rsquare= 0.07 (max possible= 0.987 )
## Likelihood ratio test= 15.7 on 4 df, p=0.00345
## Wald test = 13.8 on 4 df, p=0.0078
## Score (logrank) test = 14.8 on 4 df, p=0.00517
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.541    0.582  0.409 -1.32   0.19
## split[cur.subset]3 -0.176    0.839  0.400 -0.44   0.66
## split[cur.subset]4a 0.186    1.204  0.367  0.51   0.61
## split[cur.subset]4b 0.756    2.129  1.053  0.72   0.47
## split[cur.subset]x      NA         NA  0.000   NA      NA
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2    0.582      1.72    0.261    1.30
```

```
## split[cur.subset]3      0.839      1.19      0.383      1.84
## split[cur.subset]4a     1.204      0.83      0.586      2.47
## split[cur.subset]4b     2.129      0.47      0.270     16.76
## split[cur.subset]x      NA          NA          NA          NA
##
## Concordance= 0.57 (se = 0.035 )
## Rsquare= 0.038 (max possible= 0.986 )
## Likelihood ratio test= 6.12 on 4 df, p=0.19
## Wald test = 5.91 on 4 df, p=0.206
## Score (logrank) test = 6.14 on 4 df, p=0.189
```

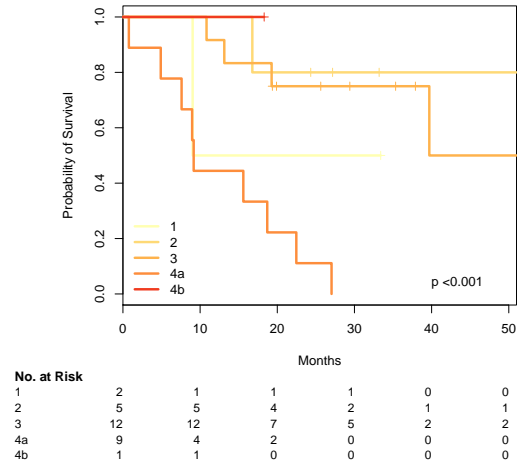




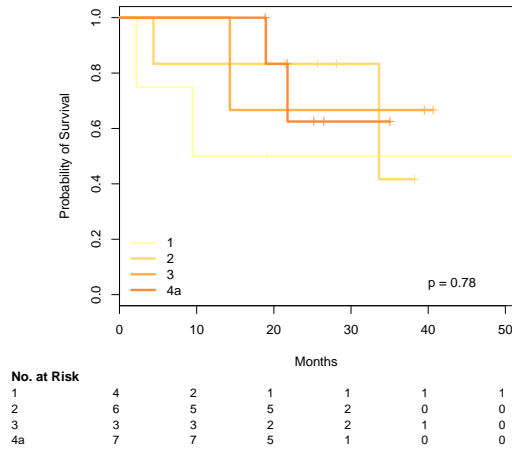
HPV DNA-, UICC IVB-C



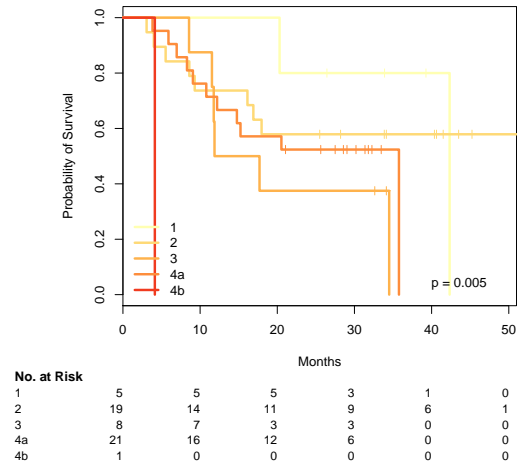
In DNA- Atypical



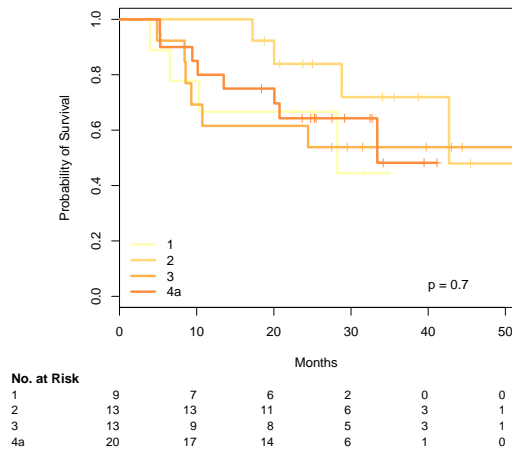
In DNA- Classical



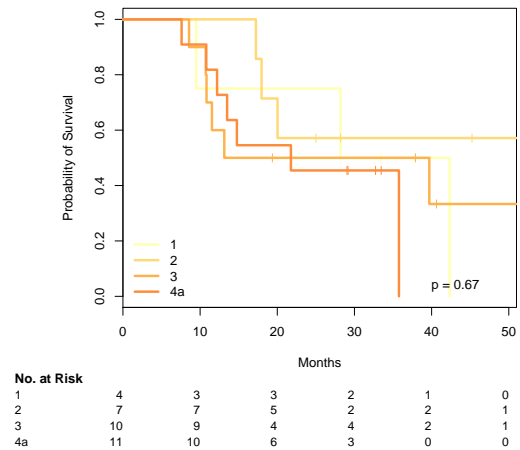
In DNA- Mesenchymal

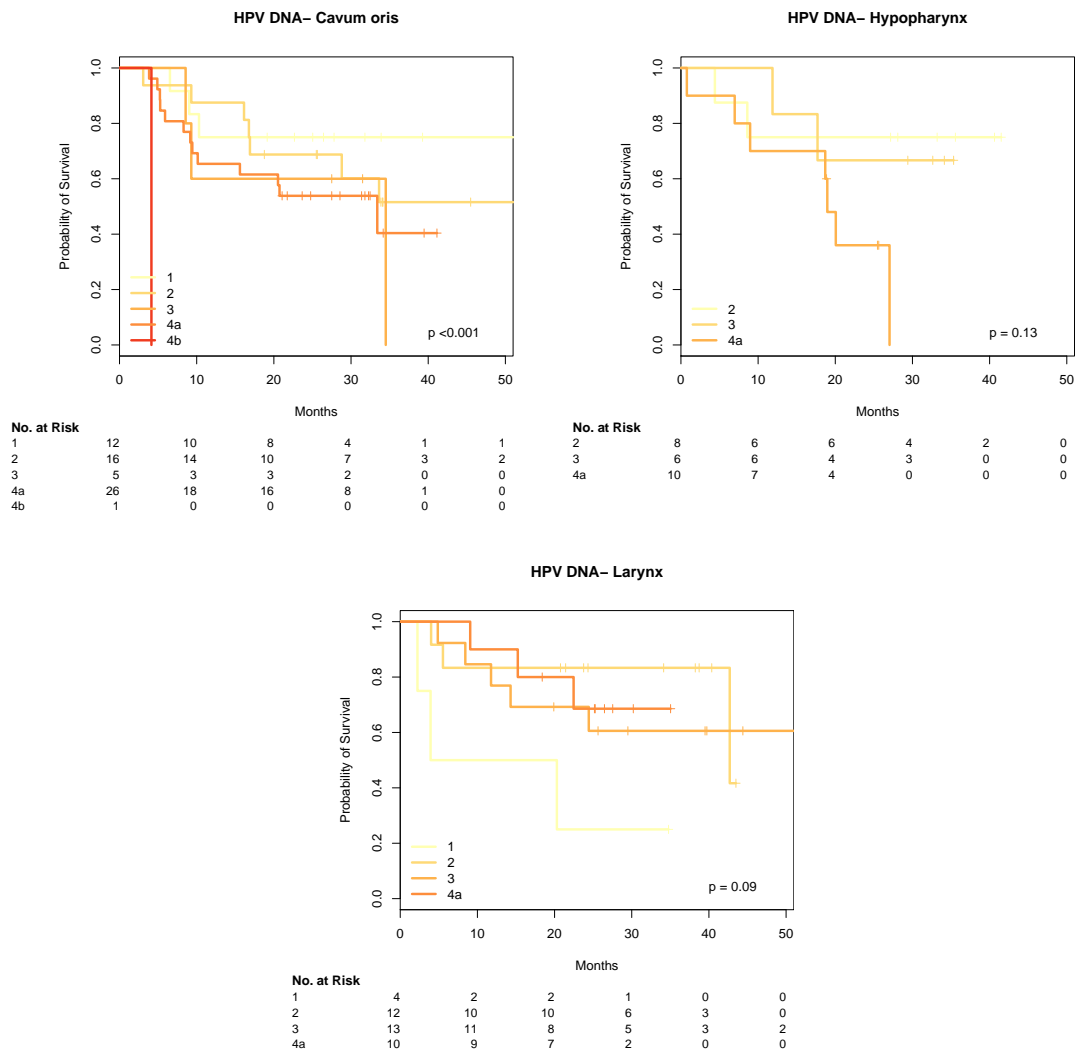


In DNA- Basal



HPV DNA- Oropharynx

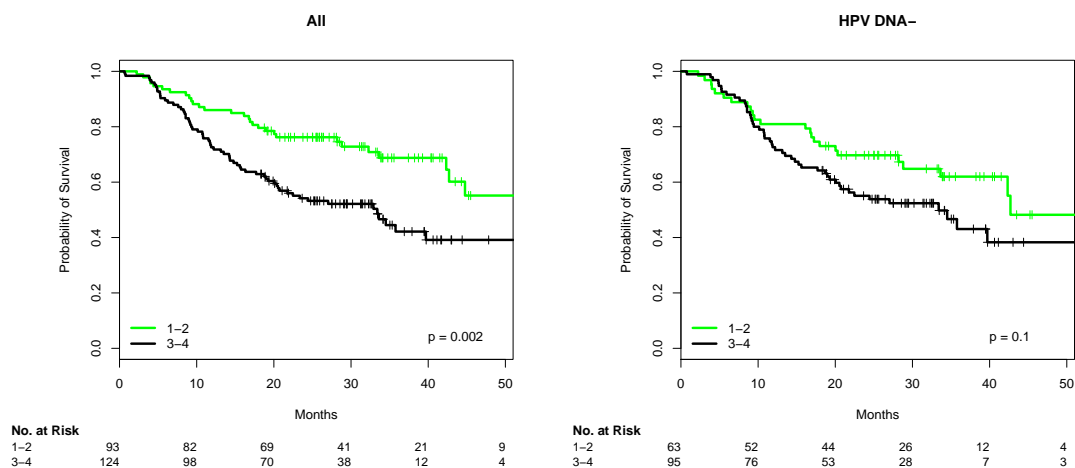




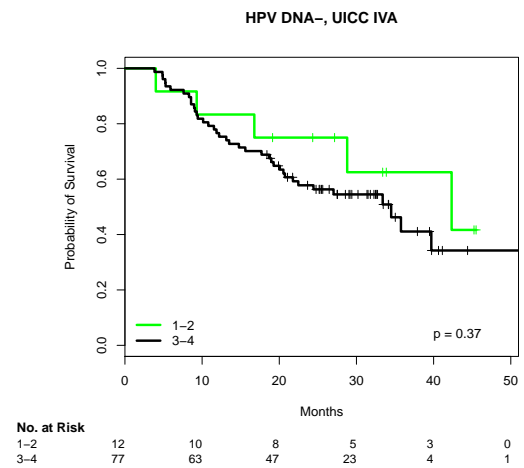
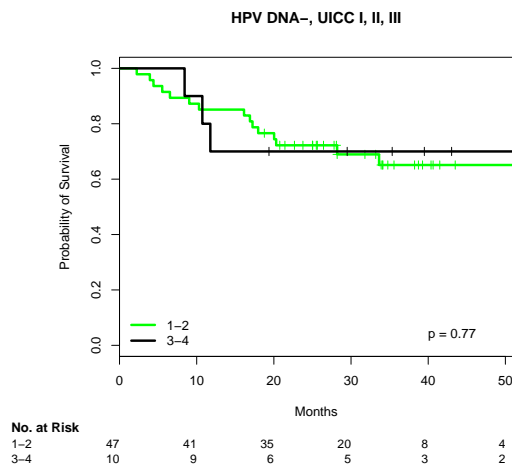
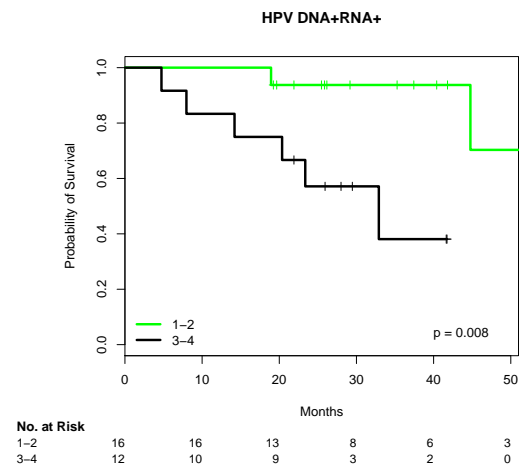
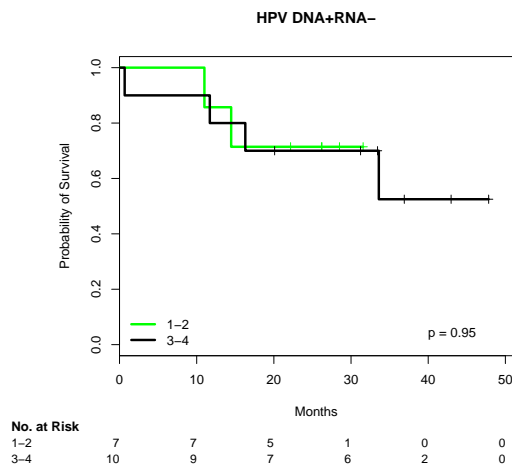
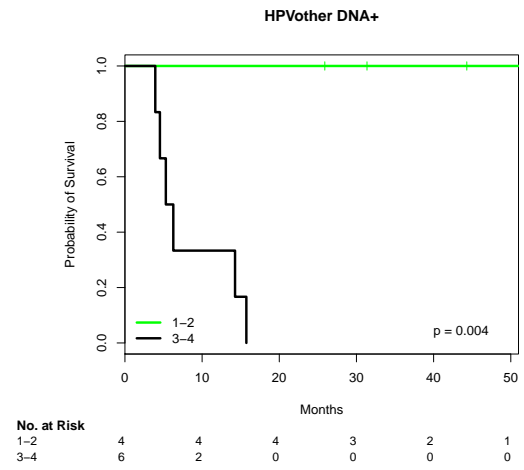
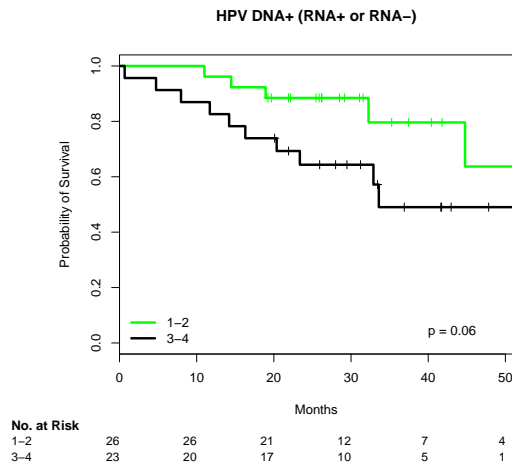
## 2.10 T stages 1,2 vs. 3,4

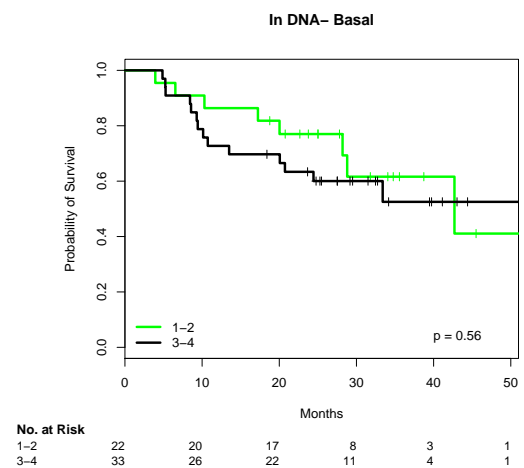
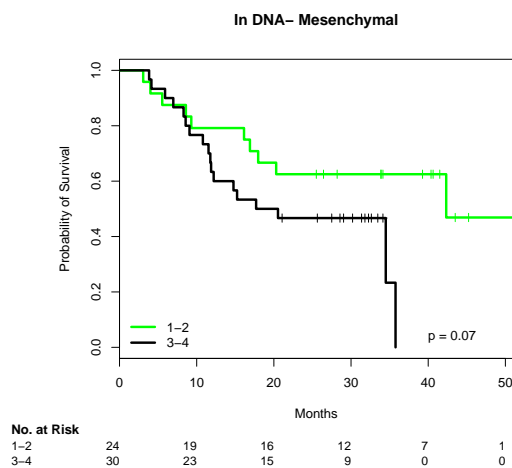
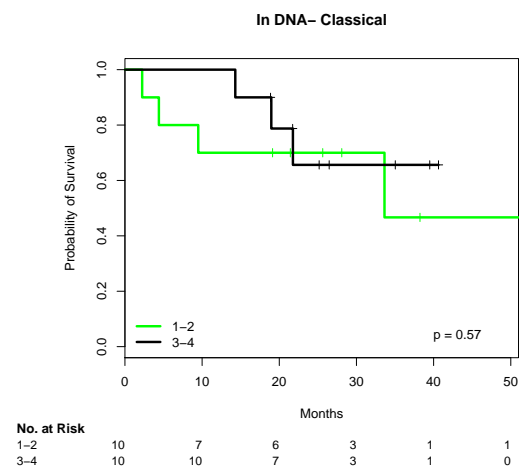
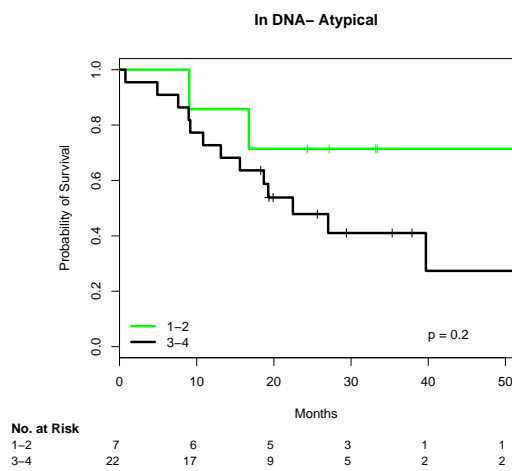
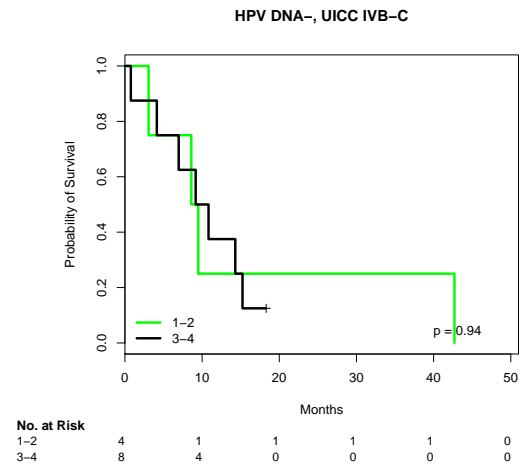
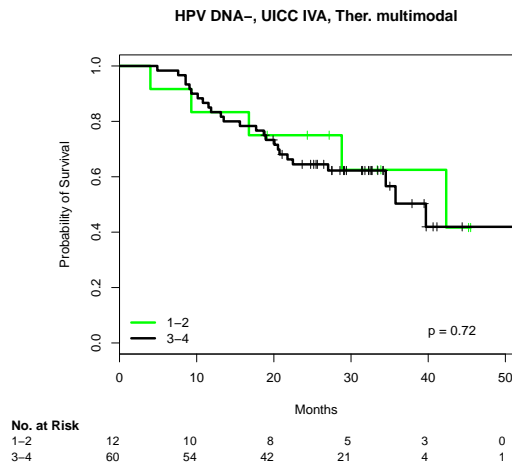
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset]3-4 0.665      1.944   0.217 3.07  0.0022 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

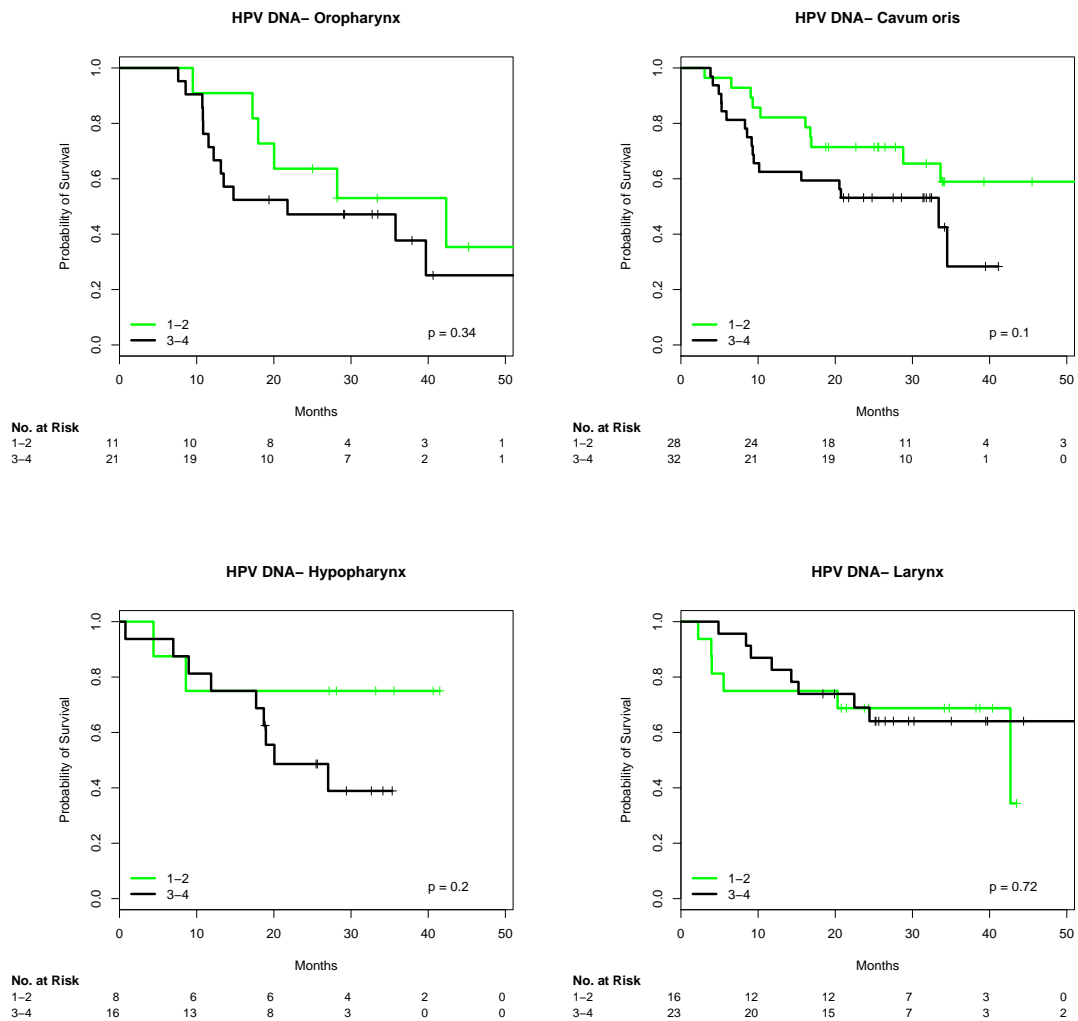
```
## split[cur.subset]3-4      1.94      0.514      1.27      2.97
##
## Concordance= 0.587 (se = 0.027 )
## Rsquare= 0.045 (max possible= 0.987 )
## Likelihood ratio test= 9.94 on 1 df, p=0.00161
## Wald test = 9.4 on 1 df, p=0.00217
## Score (logrank) test = 9.73 on 1 df, p=0.00181
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]3-4 0.400      1.492      0.248 1.61      0.11
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]3-4      1.49      0.67      0.917      2.43
##
## Concordance= 0.548 (se = 0.031 )
## Rsquare= 0.017 (max possible= 0.986 )
## Likelihood ratio test= 2.7 on 1 df, p=0.101
## Wald test = 2.6 on 1 df, p=0.107
## Score (logrank) test = 2.63 on 1 df, p=0.105
```







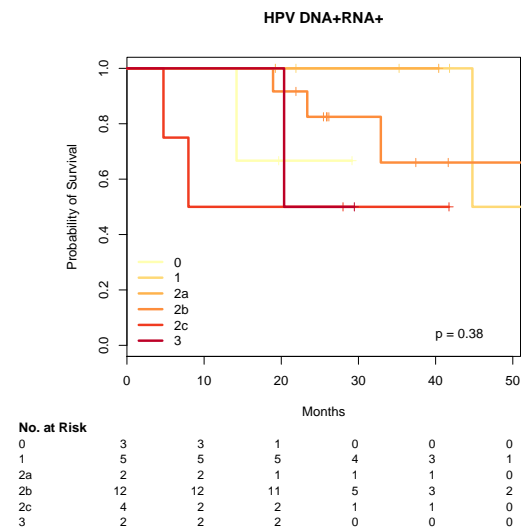
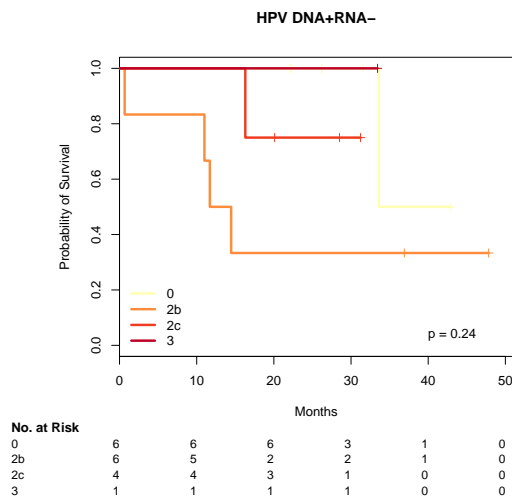
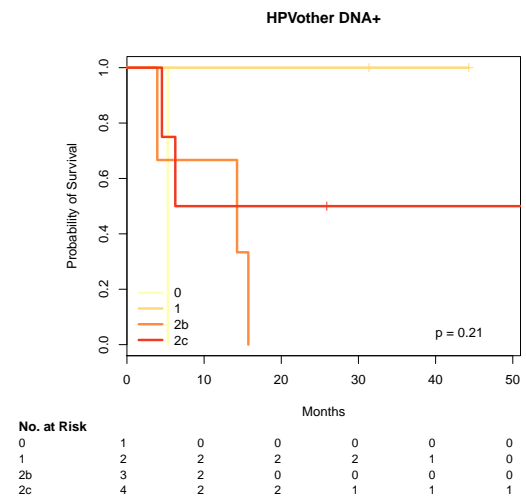
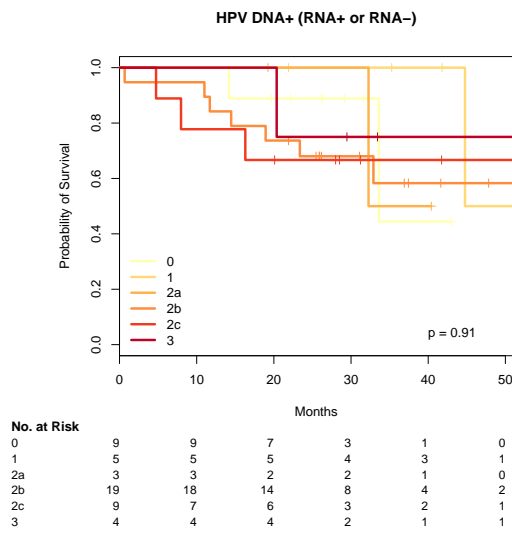
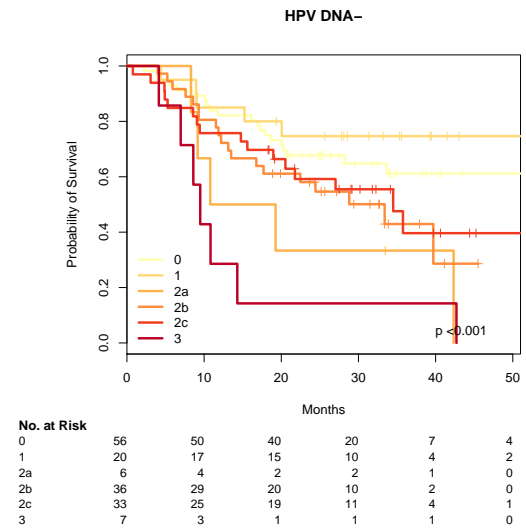
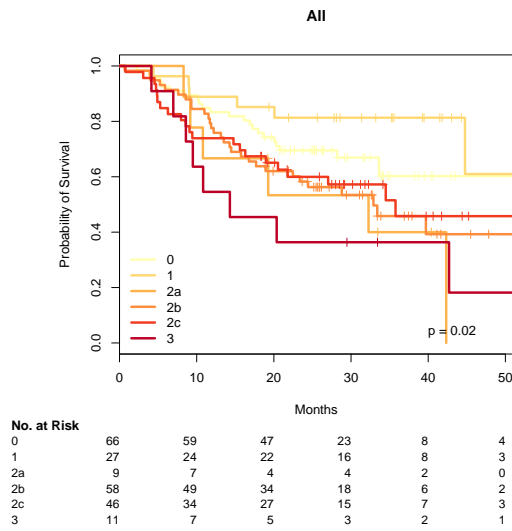




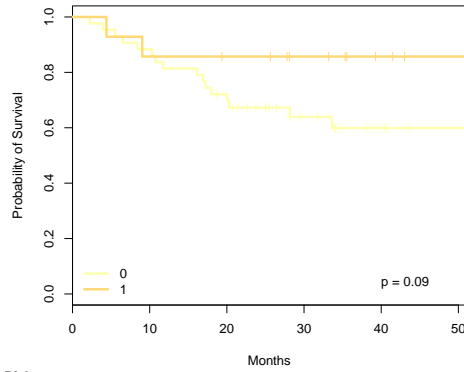
## 2.11 N (TNM staging)

```
## 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= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.715    0.489  0.455 -1.57  0.116
## split[cur.subset]2a  0.707    2.029  0.456  1.55  0.121
## split[cur.subset]2b  0.428    1.534  0.272  1.58  0.115
## split[cur.subset]2c  0.305    1.356  0.293  1.04  0.298
## split[cur.subset]3   0.831    2.296  0.399  2.08  0.037 *
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1      0.489      2.045      0.200      1.19
## split[cur.subset]2a      2.029      0.493      0.830      4.96
## split[cur.subset]2b      1.534      0.652      0.901      2.61
## split[cur.subset]2c      1.356      0.737      0.764      2.41
## split[cur.subset]3      2.296      0.436      1.051      5.01
##
## Concordance= 0.592 (se = 0.031 )
## Rsquare= 0.061 (max possible= 0.987 )
## Likelihood ratio test= 13.8 on 5 df, p=0.0171
## Wald test = 12.2 on 5 df, p=0.0319
## Score (logrank) test = 13.2 on 5 df, p=0.0216
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 -0.560      0.571      0.496 -1.13  0.25861
## split[cur.subset]2a  1.059      2.885      0.499  2.12  0.03375 *
## split[cur.subset]2b  0.500      1.649      0.317  1.58  0.11482
## split[cur.subset]2c  0.356      1.428      0.331  1.08  0.28199
## split[cur.subset]3  1.596      4.934      0.443  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]1      0.571      1.751      0.216      1.51
## split[cur.subset]2a      2.885      0.347      1.085      7.67
## split[cur.subset]2b      1.649      0.606      0.886      3.07
## split[cur.subset]2c      1.428      0.700      0.746      2.73
## split[cur.subset]3      4.934      0.203      2.072     11.75
##
## Concordance= 0.606 (se = 0.035 )
## Rsquare= 0.105 (max possible= 0.986 )
## Likelihood ratio test= 17.6 on 5 df, p=0.00348
## Wald test = 19.6 on 5 df, p=0.00147
## Score (logrank) test = 22.8 on 5 df, p=0.000374
```



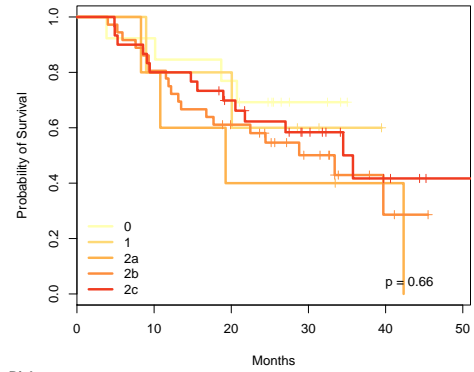
HPV DNA-, UICC I, II, III



No. at Risk

0	43	38	30	17	7	4
1	14	12	11	8	4	2

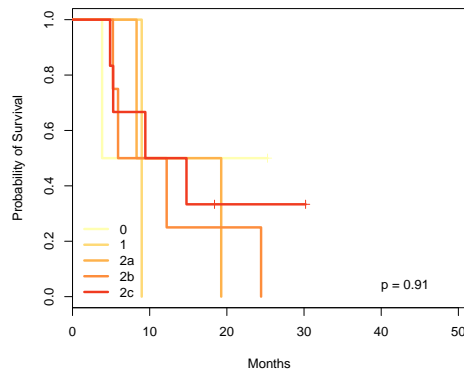
HPV DNA-, UICC IVA



No. at Risk

0	13	12	10	3	0	0
1	5	4	4	2	0	0
2a	5	4	2	2	1	0
2b	36	29	20	10	2	0
2c	30	24	19	11	4	1

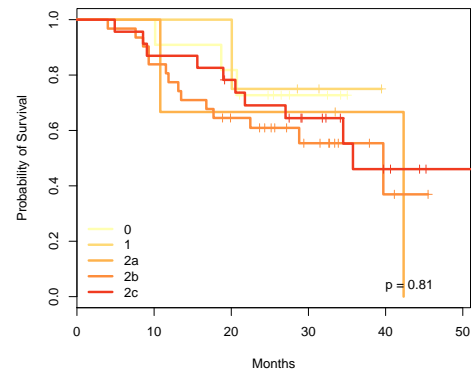
HPV DNA-, UICC IVA, Ther. unimodal



No. at Risk

0	2	1	1	0	0	0
1	1	0	0	0	0	0
2a	2	1	0	0	0	0
2b	4	2	1	0	0	0
2c	6	3	1	1	0	0

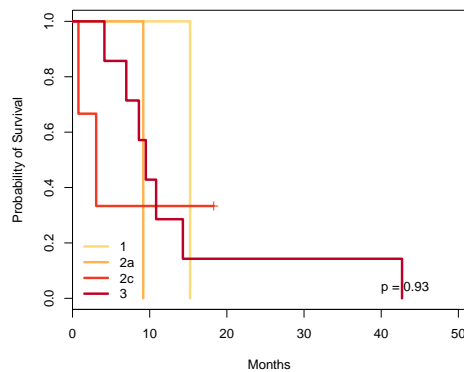
HPV DNA-, UICC IVA, Ther. multimodal



No. at Risk

0	11	11	9	3	0	0
1	4	4	4	2	0	0
2a	3	3	2	2	1	0
2b	31	26	18	9	2	0
2c	23	20	17	10	4	1

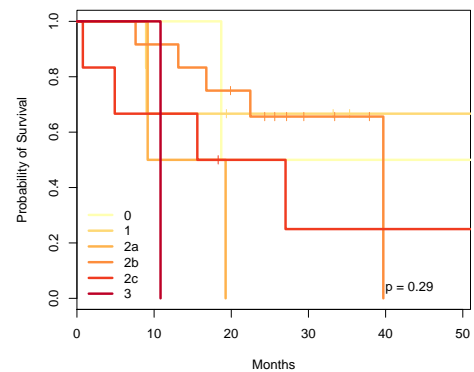
HPV DNA-, UICC IVB-C



No. at Risk

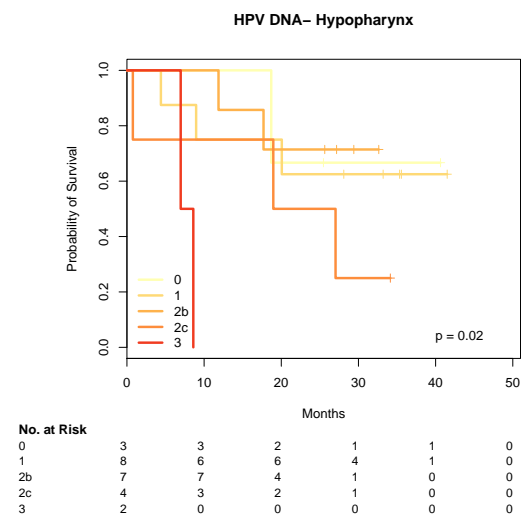
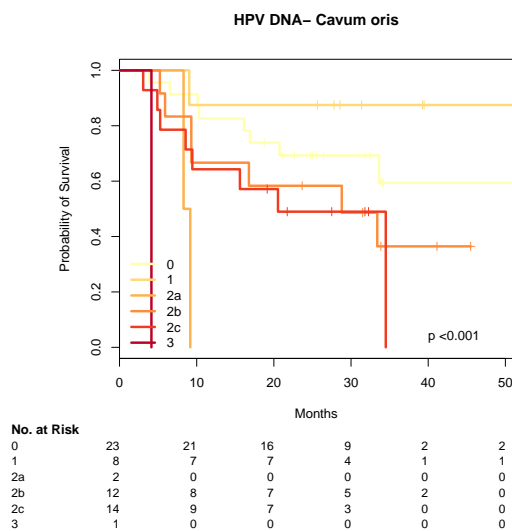
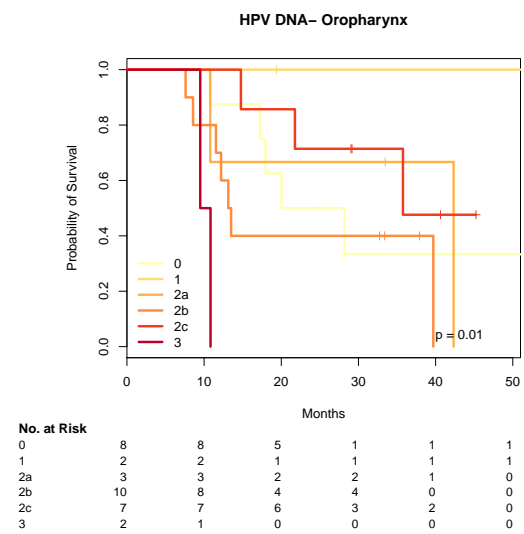
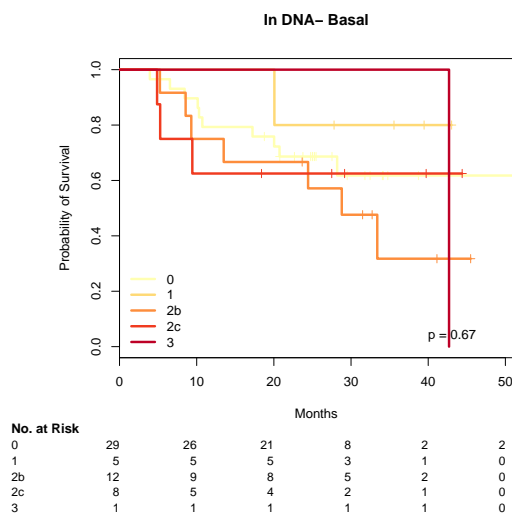
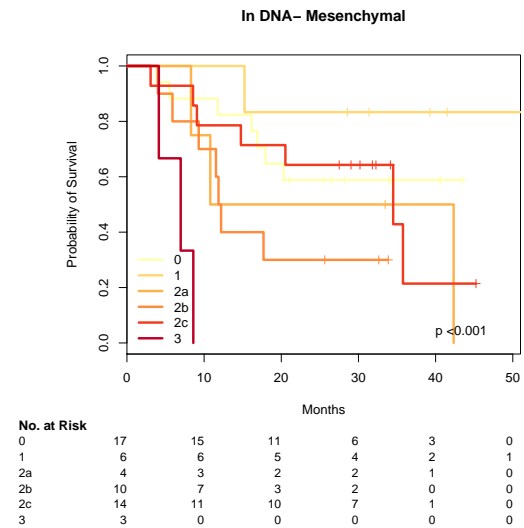
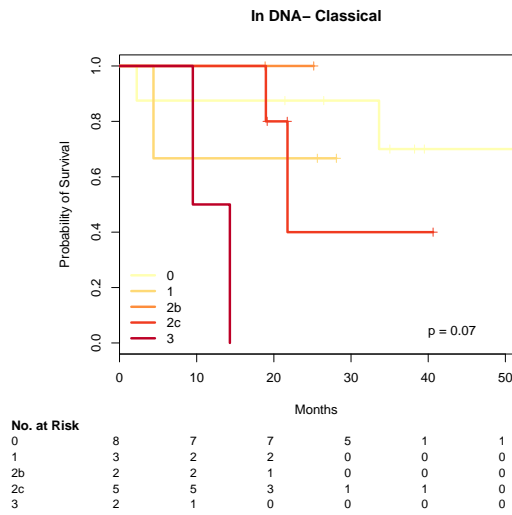
1	1	1	0	0	0	0
2a	1	0	0	0	0	0
2b	3	1	0	0	0	0
3	7	3	1	1	1	0

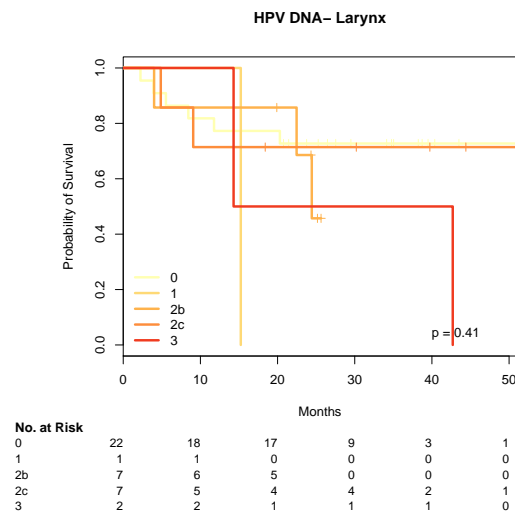
In DNA- Atypical



No. at Risk

0	2	2	1	1	1	1
1	6	4	3	3	1	1
2a	2	1	0	0	0	0
2b	12	11	8	3	0	0
2c	6	4	2	1	1	1
3	1	1	0	0	0	0



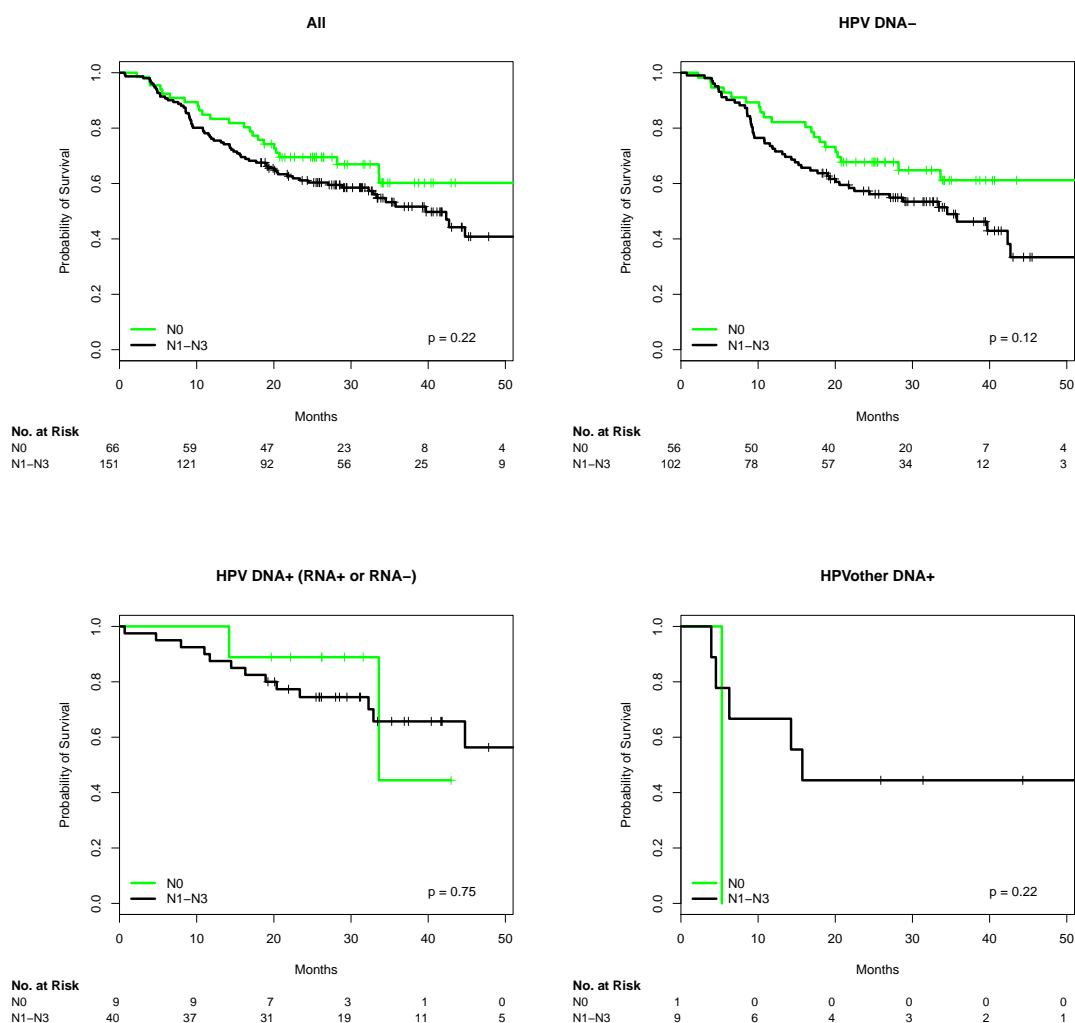


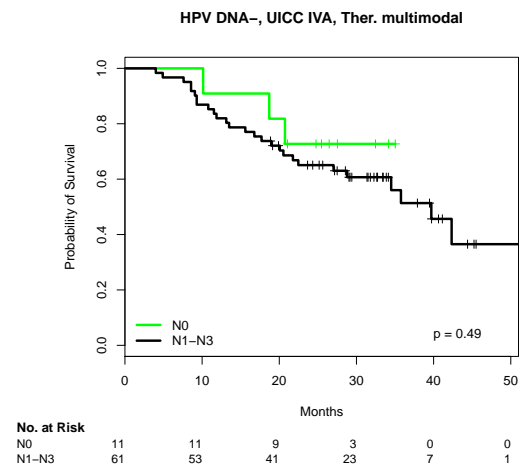
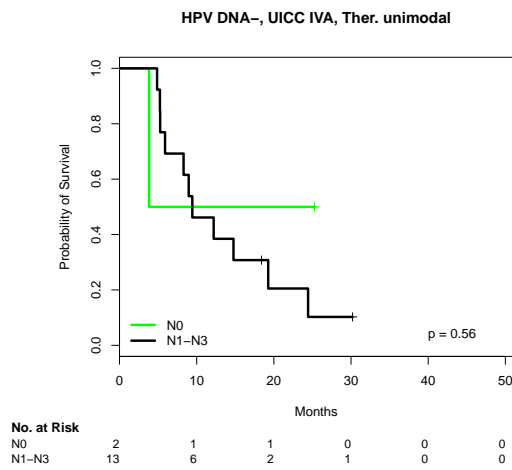
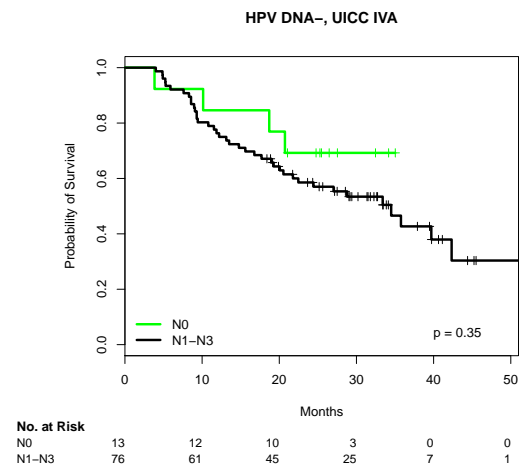
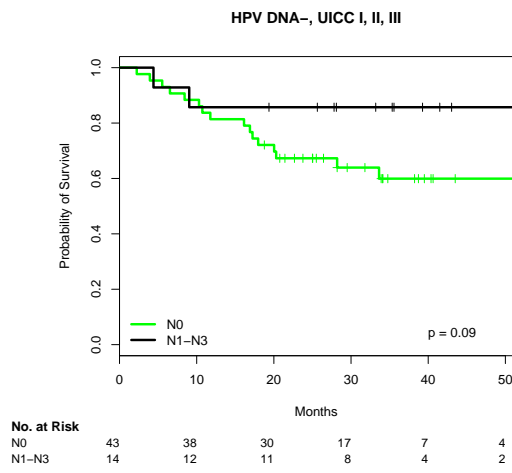
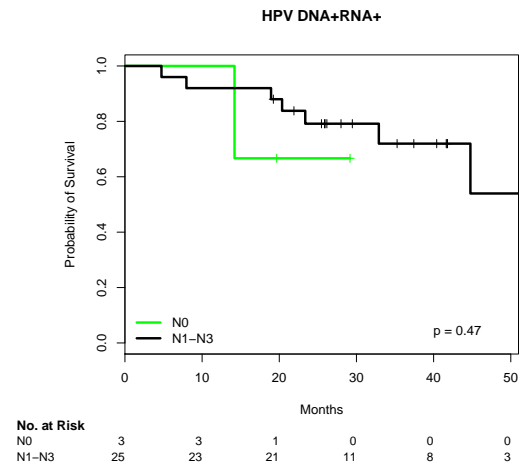
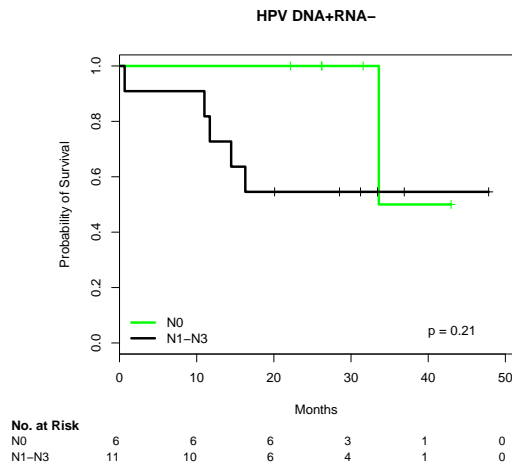
## 2.12 N0 stage vs. N1-N3

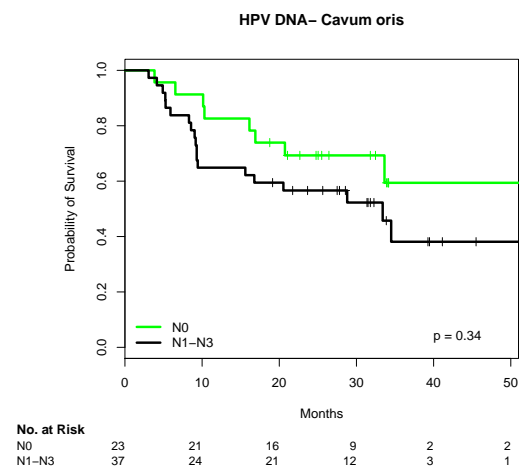
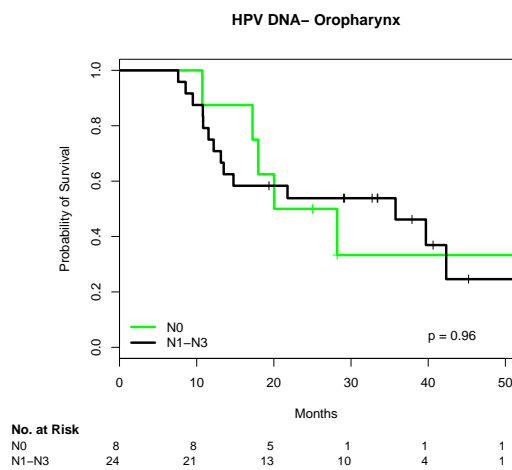
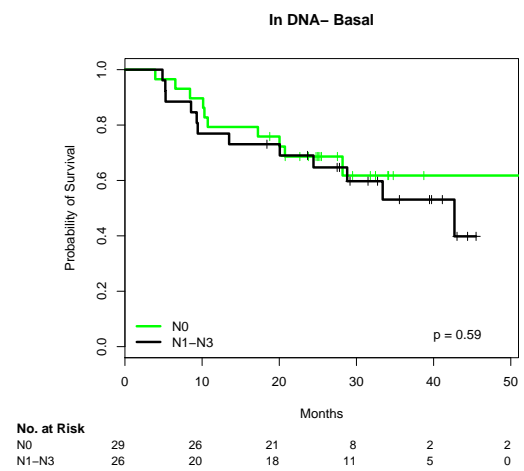
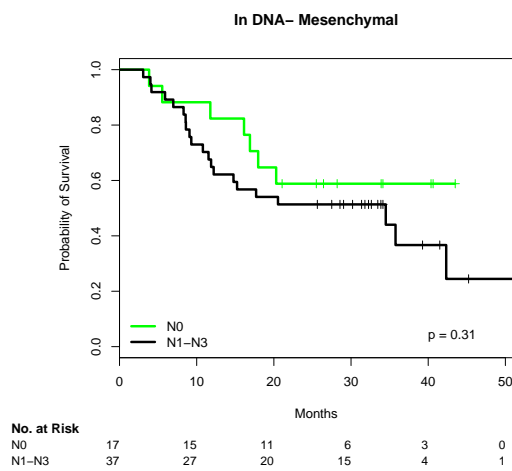
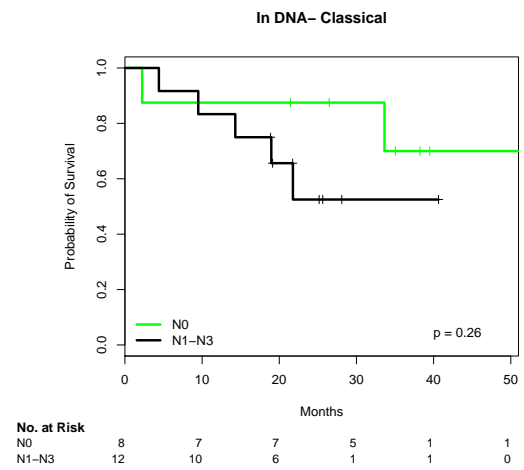
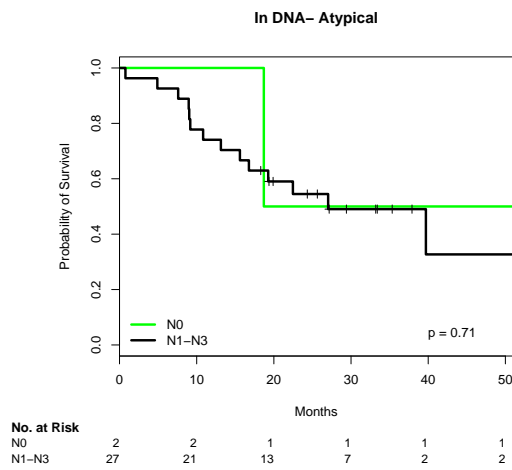
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.282      1.325    0.232 1.21    0.23
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3    1.33      0.755    0.84    2.09
##
## Concordance= 0.533 (se = 0.025 )
## Rsquare= 0.007 (max possible= 0.987 )
## Likelihood ratio test= 1.53 on 1 df,  p=0.216
## Wald test               = 1.47 on 1 df,  p=0.226
## Score (logrank) test = 1.48 on 1 df,  p=0.224
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
```

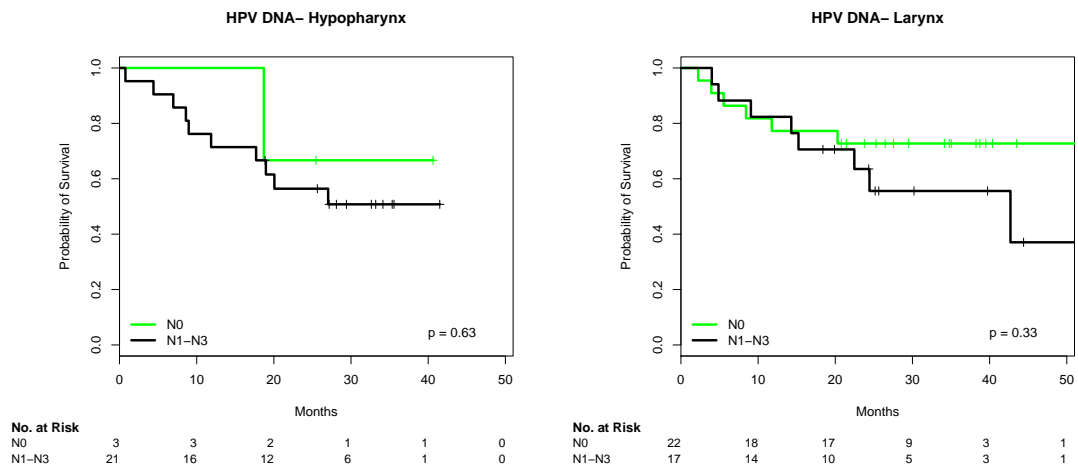


```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.393    1.482    0.255 1.54    0.12
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N1-N3    1.48    0.675    0.898    2.44
##
## Concordance= 0.546 (se = 0.03 )
## Rsquare= 0.016 (max possible= 0.986 )
## Likelihood ratio test= 2.48 on 1 df,  p=0.115
## Wald test               = 2.37 on 1 df,  p=0.124
## Score (logrank) test = 2.4 on 1 df,  p=0.122
```





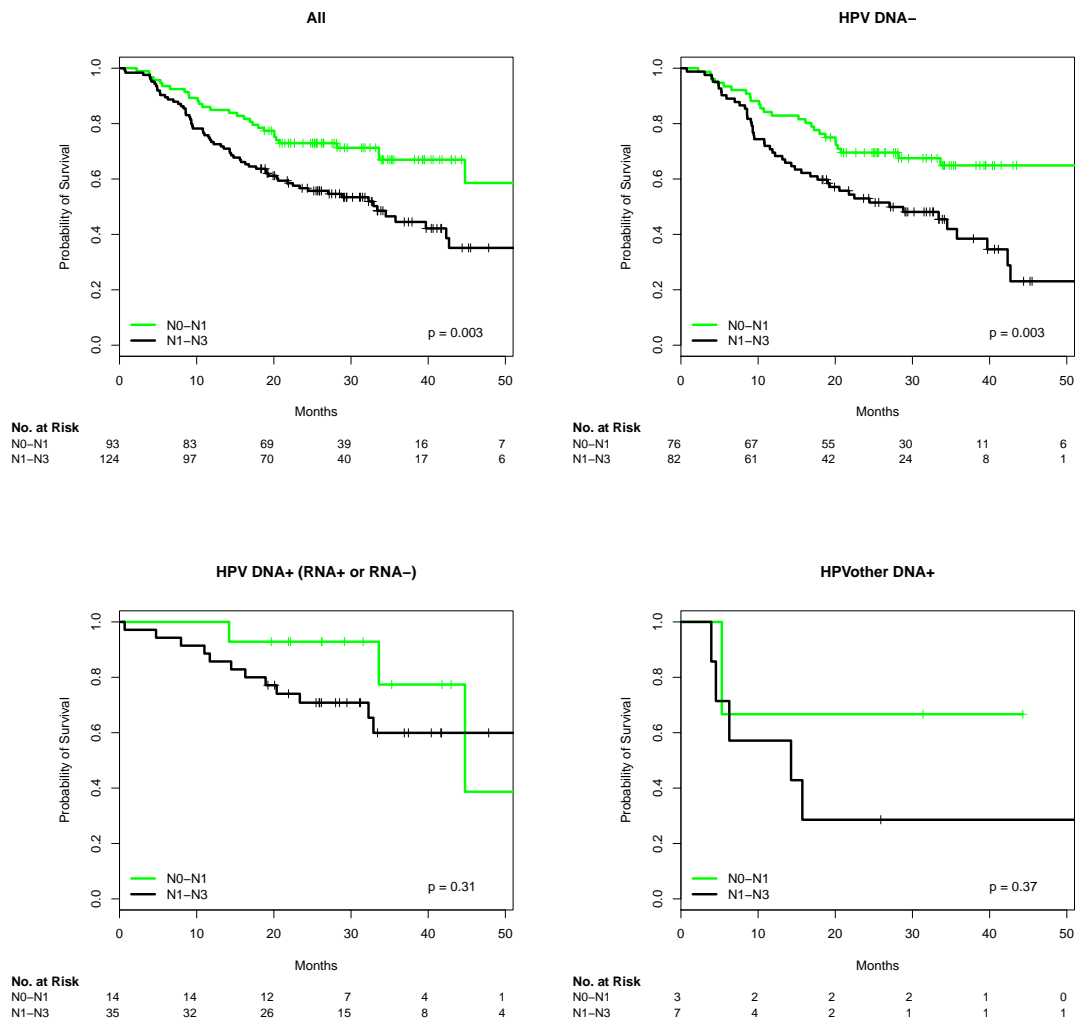


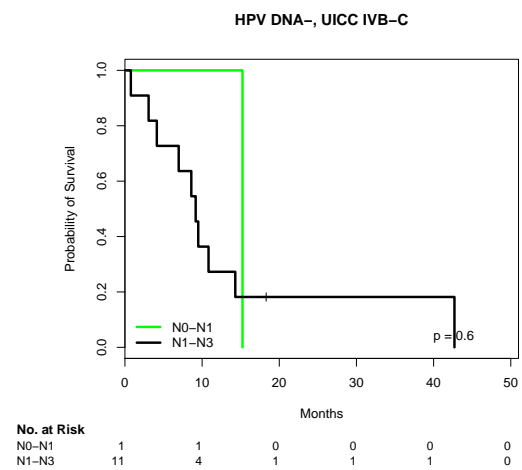
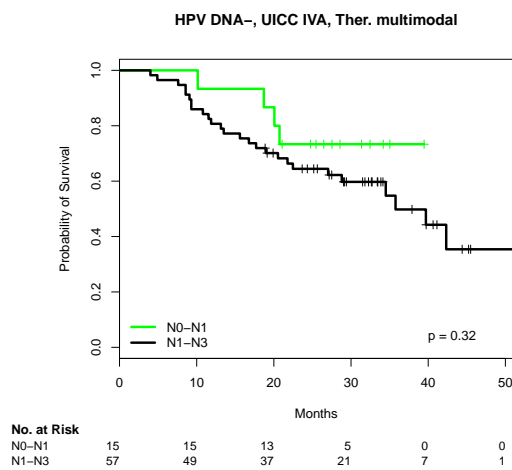
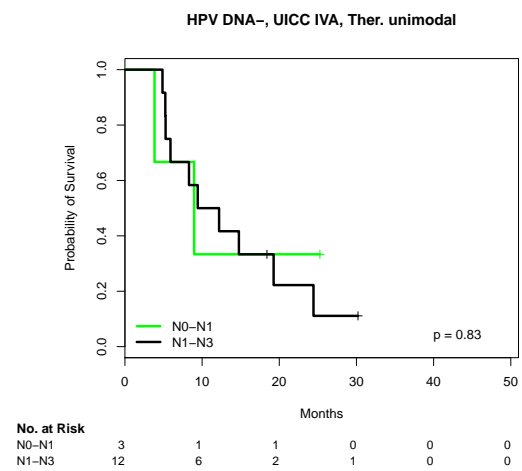
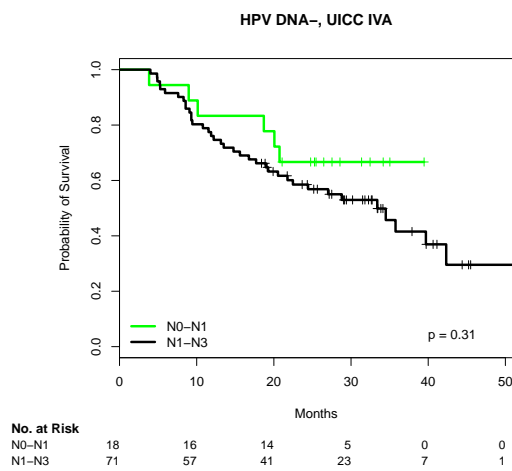
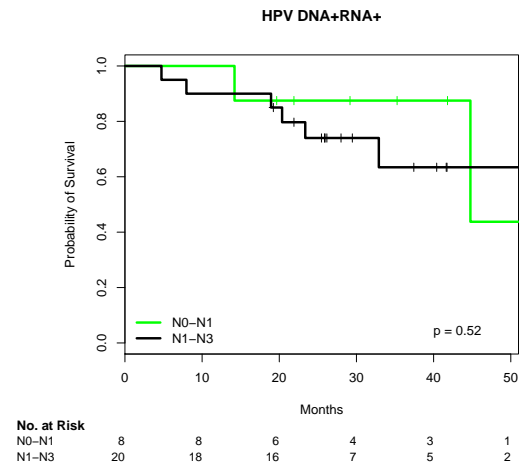
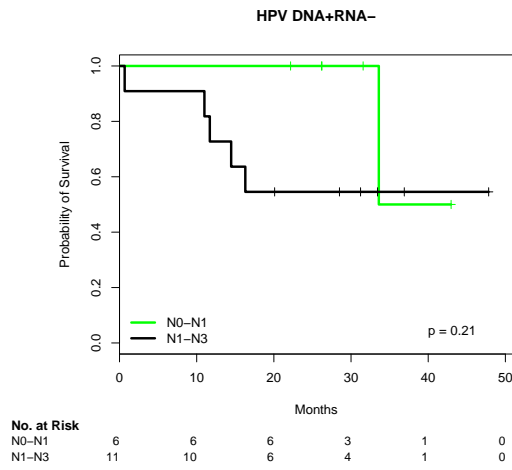


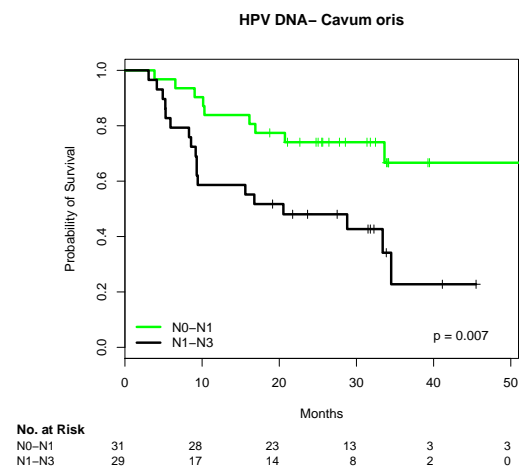
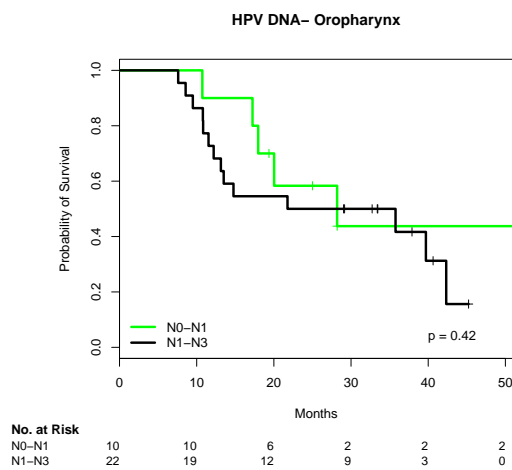
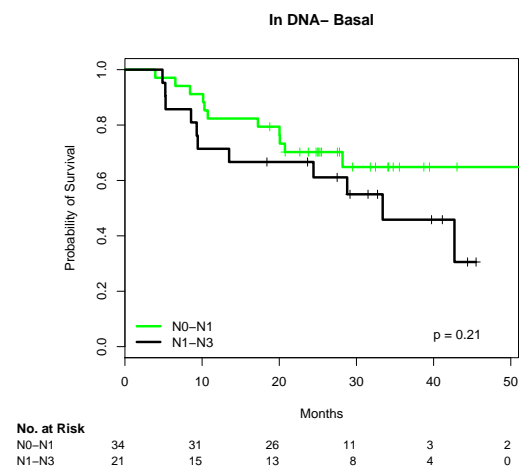
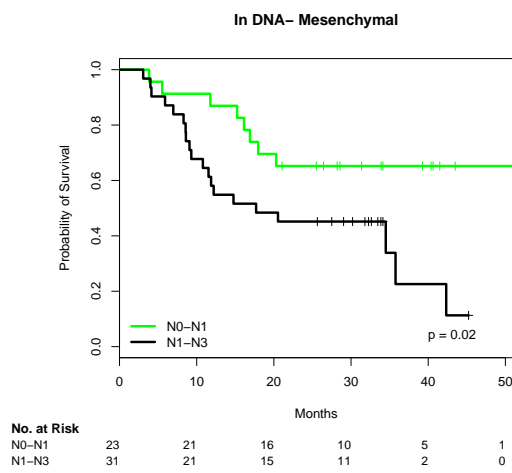
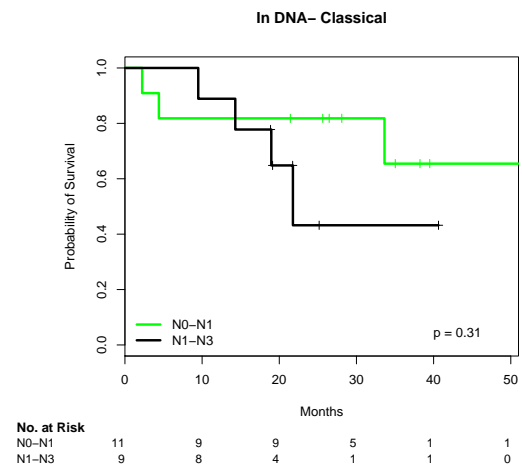
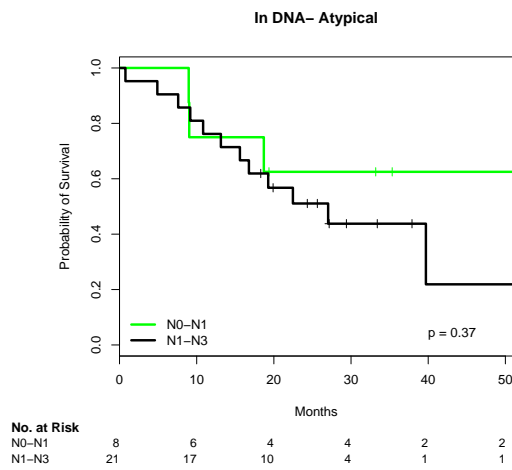
## 2.13 N0-N1 stages vs. N2-N3

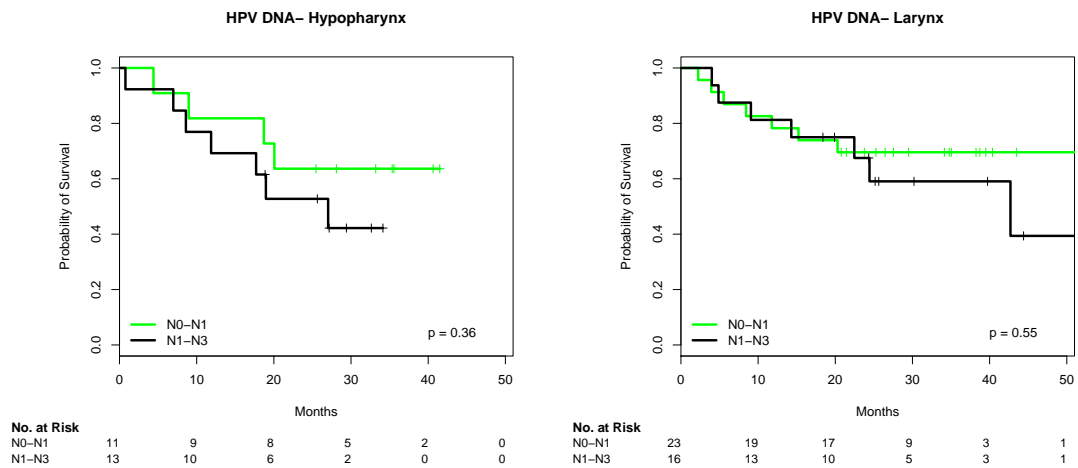
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset]N1-N3 0.633      1.883   0.218 2.9   0.0037 **
## ---
## 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    1.88    0.531    1.23    2.89
##
## Concordance= 0.574 (se = 0.027 )
## Rsquare= 0.04 (max possible= 0.987 )
## Likelihood ratio test= 8.96 on 1 df, p=0.00276
## Wald test = 8.42 on 1 df, p=0.0037
## Score (logrank) test = 8.71 on 1 df, p=0.00317
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
```

```
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N1-N3 0.722      2.058    0.246 2.93  0.0034 **
## ---
## 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      2.06      0.486      1.27      3.33
##
## Concordance= 0.578 (se = 0.031 )
## Rsquare= 0.056 (max possible= 0.986 )
## Likelihood ratio test= 9.04 on 1 df,  p=0.00264
## Wald test               = 8.6 on 1 df,  p=0.00336
## Score (logrank) test = 8.97 on 1 df,  p=0.00274
```









## 2.14 M (TNM staging)

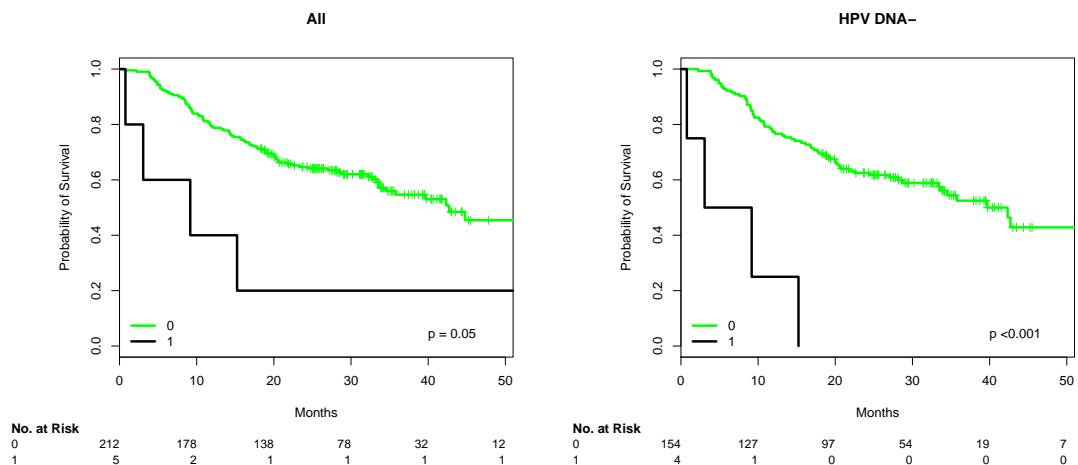
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: 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= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.938      2.555    0.500 1.88    0.06 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      2.55      0.391    0.959      6.8
##
## Concordance= 0.52 (se = 0.006 )
## Rsquare= 0.013 (max possible= 0.987 )
## Likelihood ratio test= 2.82 on 1 df,  p=0.0931
```

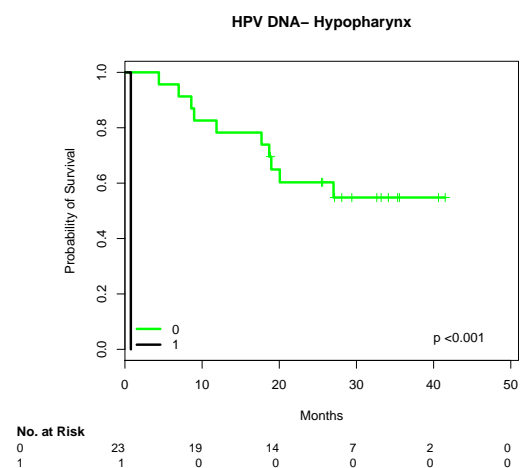
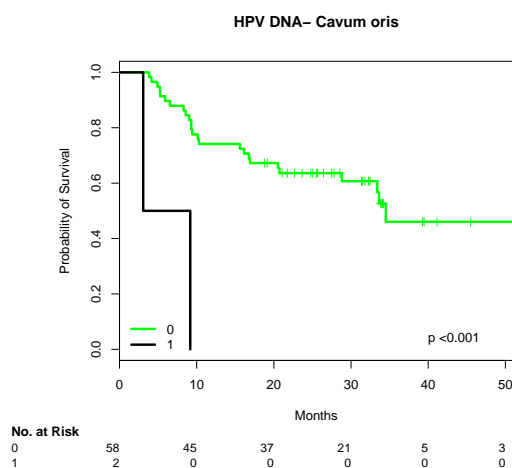
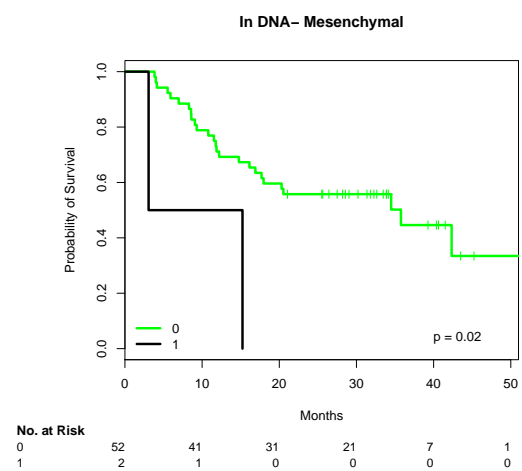
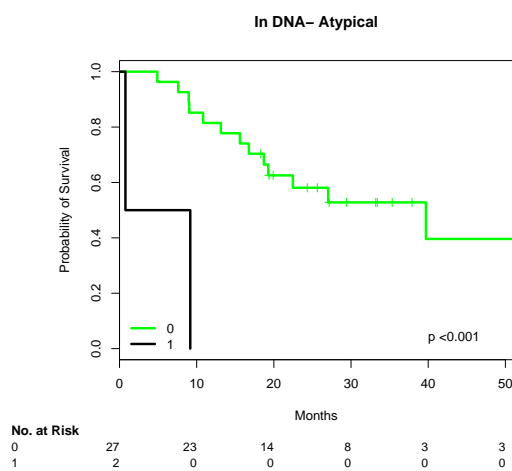
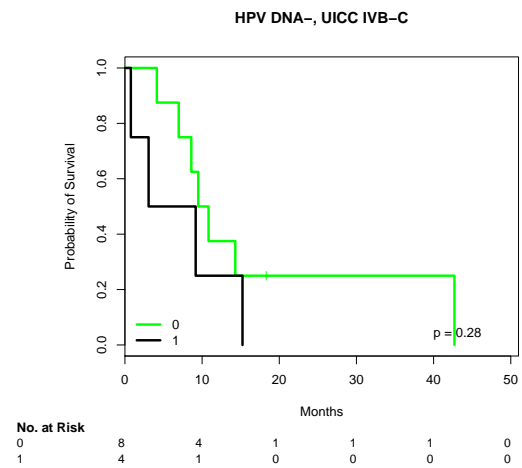
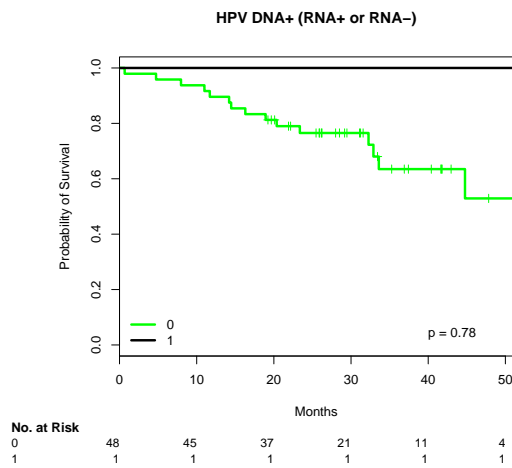


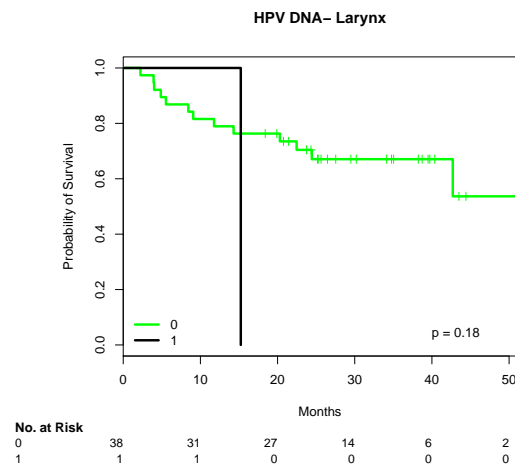
```

## Wald test          = 3.52  on 1 df,   p=0.0605
## Score (logrank) test = 3.69  on 1 df,   p=0.0546
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 2.113      8.272   0.527 4.01   6e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      8.27      0.121      2.95      23.2
##
## Concordance= 0.53 (se = 0.006 )
## Rsquare= 0.059 (max possible= 0.986 )
## Likelihood ratio test= 9.55  on 1 df,   p=0.002
## Wald test          = 16.1  on 1 df,   p=6.01e-05
## Score (logrank) test = 23  on 1 df,   p=1.59e-06

```



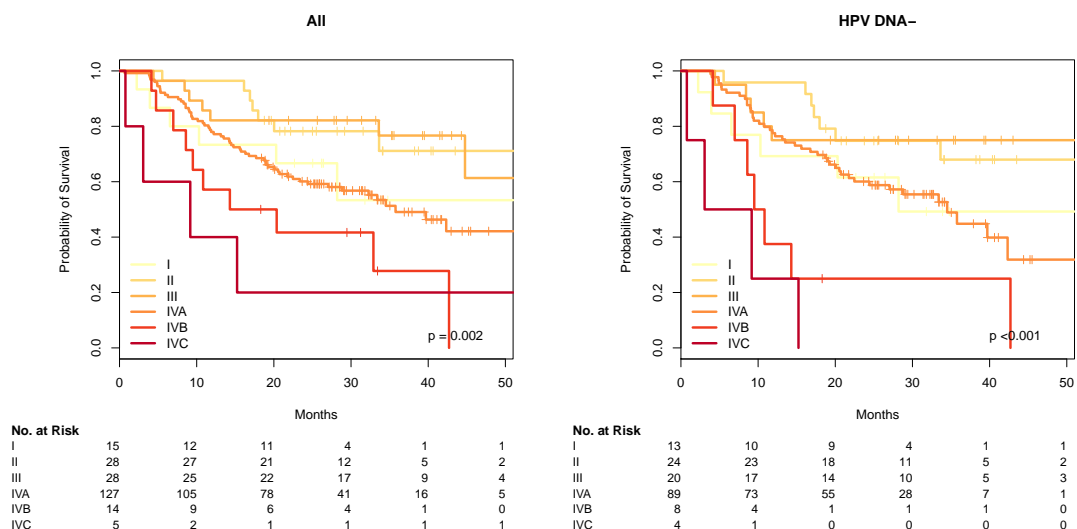


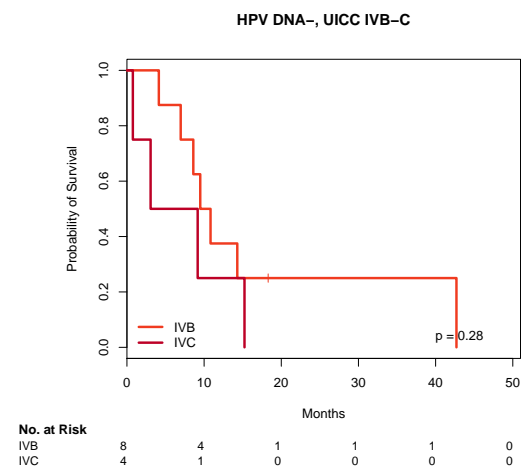
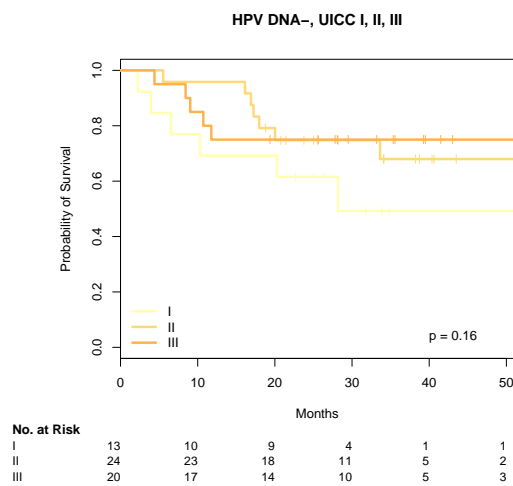
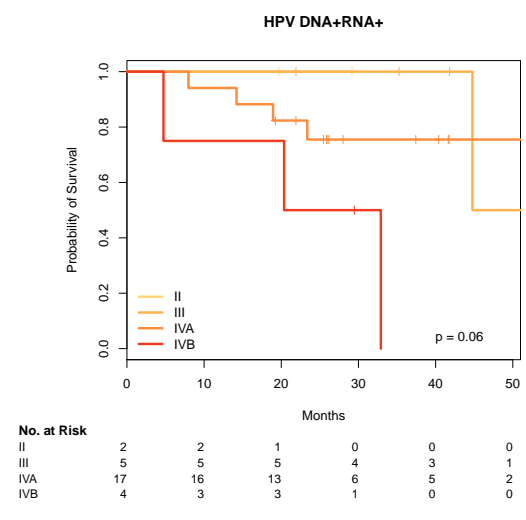
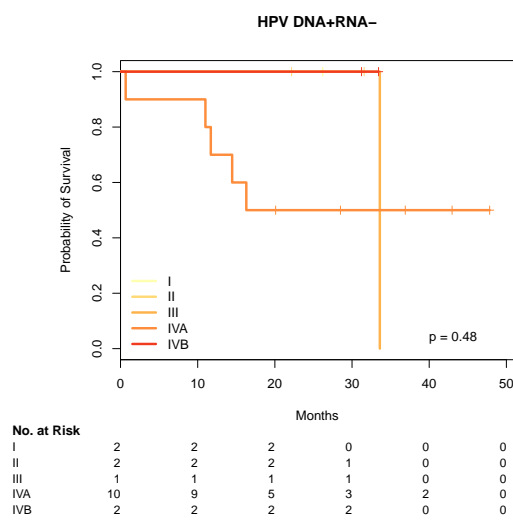
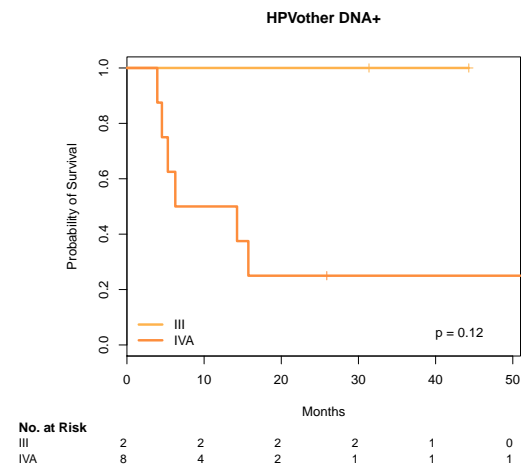
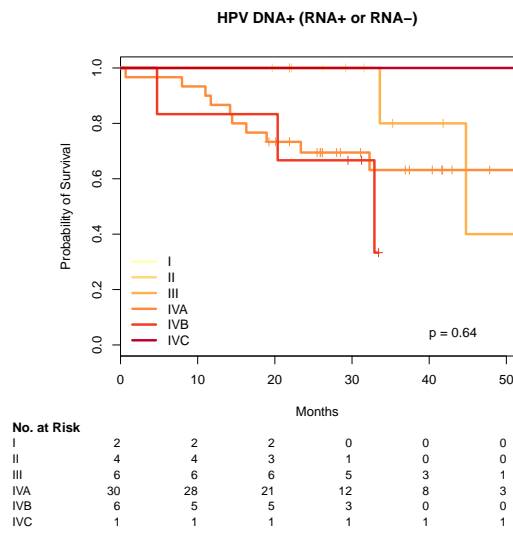


## 2.15 UICC staging

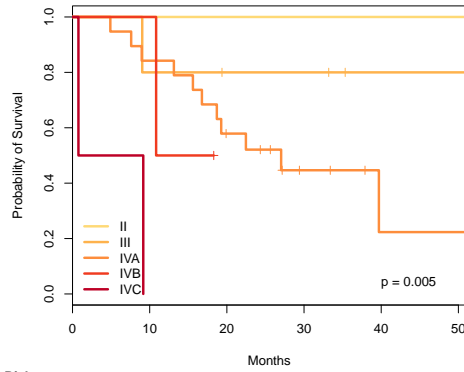
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.7739   0.4612  0.5194 -1.49   0.136
## split[cur.subset]III -0.9687   0.3796  0.5368 -1.80   0.071 .
## split[cur.subset]IVA -0.0351   0.9655  0.3996 -0.09   0.930
## split[cur.subset]IVB  0.6408   1.8980  0.4938  1.30   0.194
## split[cur.subset]IVC  0.7104   2.0348  0.6254  1.14   0.256
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.461    2.168    0.167    1.28
## split[cur.subset]III    0.380    2.634    0.133    1.09
## split[cur.subset]IVA    0.965    1.036    0.441    2.11
## split[cur.subset]IVB    1.898    0.527    0.721    5.00
## split[cur.subset]IVC    2.035    0.491    0.597    6.93
##
## Concordance= 0.607 (se = 0.028 )
## Rsquare= 0.081 (max possible= 0.987 )
```

```
## Likelihood ratio test= 18.4 on 5 df, p=0.0025
## Wald test = 17.4 on 5 df, p=0.00384
## Score (logrank) test = 19.1 on 5 df, p=0.00185
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]II -0.830    0.436   0.527 -1.58  0.1151
## split[cur.subset]III -1.089    0.336   0.590 -1.85  0.0648 .
## split[cur.subset]IVA -0.127    0.881   0.409 -0.31  0.7559
## split[cur.subset]IVB  0.933    2.543   0.541  1.73  0.0842 .
## split[cur.subset]IVC  1.903    6.703   0.639  2.98  0.0029 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]II    0.436    2.293    0.155    1.22
## split[cur.subset]III    0.336    2.973    0.106    1.07
## split[cur.subset]IVA    0.881    1.136    0.395    1.96
## split[cur.subset]IVB    2.543    0.393    0.881    7.33
## split[cur.subset]IVC    6.703    0.149    1.915   23.47
##
## Concordance= 0.616 (se = 0.032 )
## Rsquare= 0.144 (max possible= 0.986 )
## Likelihood ratio test= 24.6 on 5 df, p=0.000166
## Wald test = 30 on 5 df, p=1.48e-05
## Score (logrank) test = 39.8 on 5 df, p=1.61e-07
```





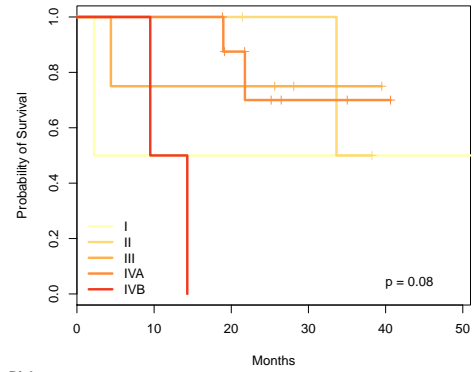
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
II	1	1	1	1	1	1
III	5	4	3	3	1	1
IVA	19	16	10	4	1	1
IVB	2	2	0	0	0	0
IVC	2	0	0	0	0	0

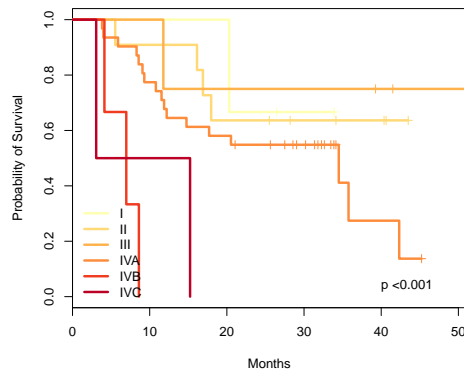
In DNA- Classical



No. at Risk

	0	10	20	30	40	50
I	2	1	1	1	1	1
II	3	3	3	2	0	0
III	4	3	3	1	0	0
IVA	9	9	6	2	1	0
IVB	2	1	0	0	0	0

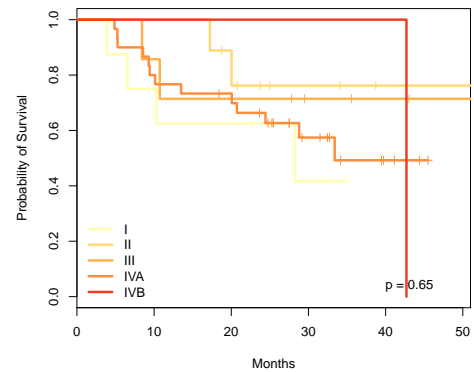
In DNA- Mesenchymal



No. at Risk

	0	10	20	30	40	50
I	3	3	3	1	0	0
II	11	10	7	5	3	0
III	4	4	3	3	2	1
IVA	31	24	18	12	2	0
IVB	3	0	0	0	0	0
IVC	2	1	0	0	0	0

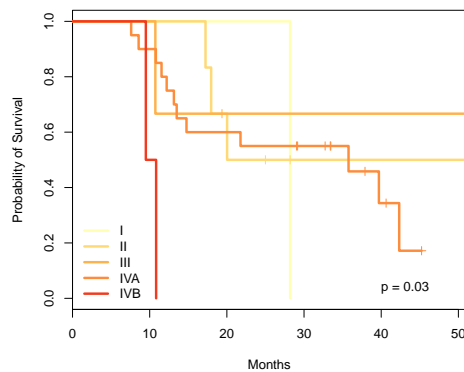
In DNA- Basal



No. at Risk

	0	10	20	30	40	50
I	8	6	5	2	0	0
II	9	9	7	3	1	1
III	7	6	5	3	2	1
IVA	30	24	21	10	3	0
IVB	1	1	1	1	1	0

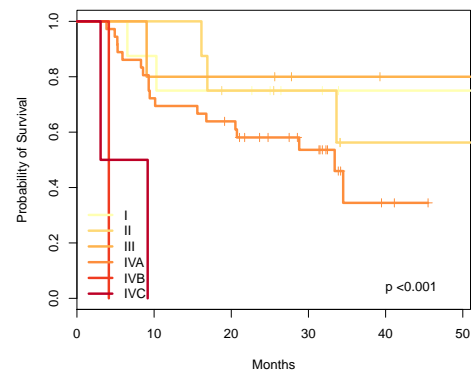
HPV DNA- Oropharynx



No. at Risk

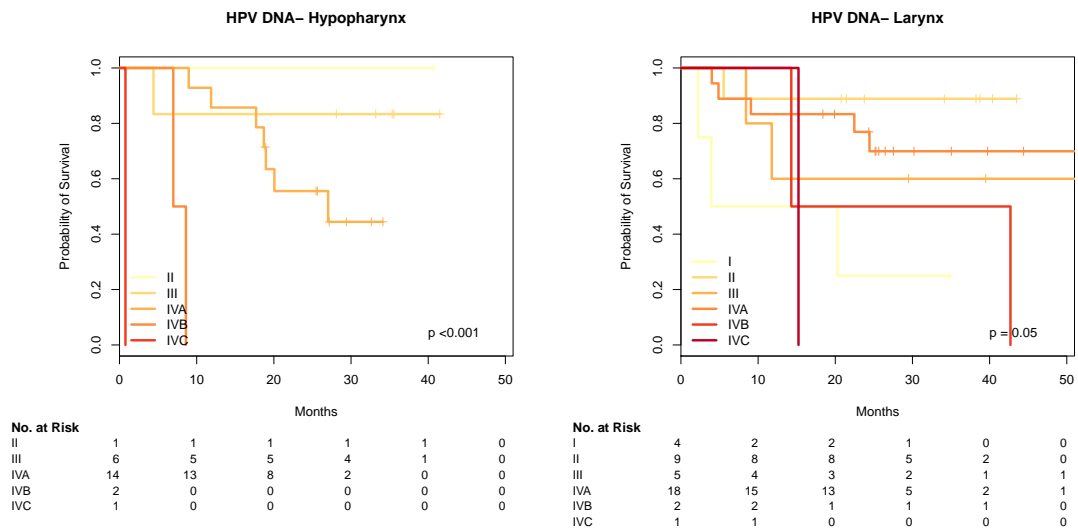
	0	10	20	30	40	50
I	1	1	1	0	0	0
II	6	6	4	1	1	1
III	3	3	1	1	1	1
IVA	20	18	12	9	3	0
IVB	2	1	0	0	0	0

HPV DNA- Cavum oris



No. at Risk

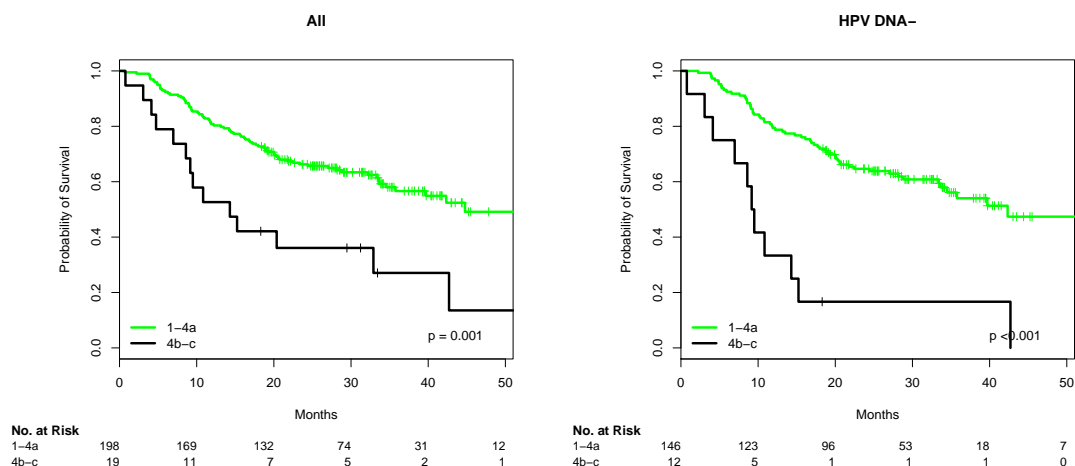
	0	10	20	30	40	50
I	8	7	6	3	1	1
II	8	8	5	4	1	1
III	5	4	4	2	1	1
IVA	36	26	22	12	2	0
IVB	1	0	0	0	0	0
IVC	2	0	0	0	0	0



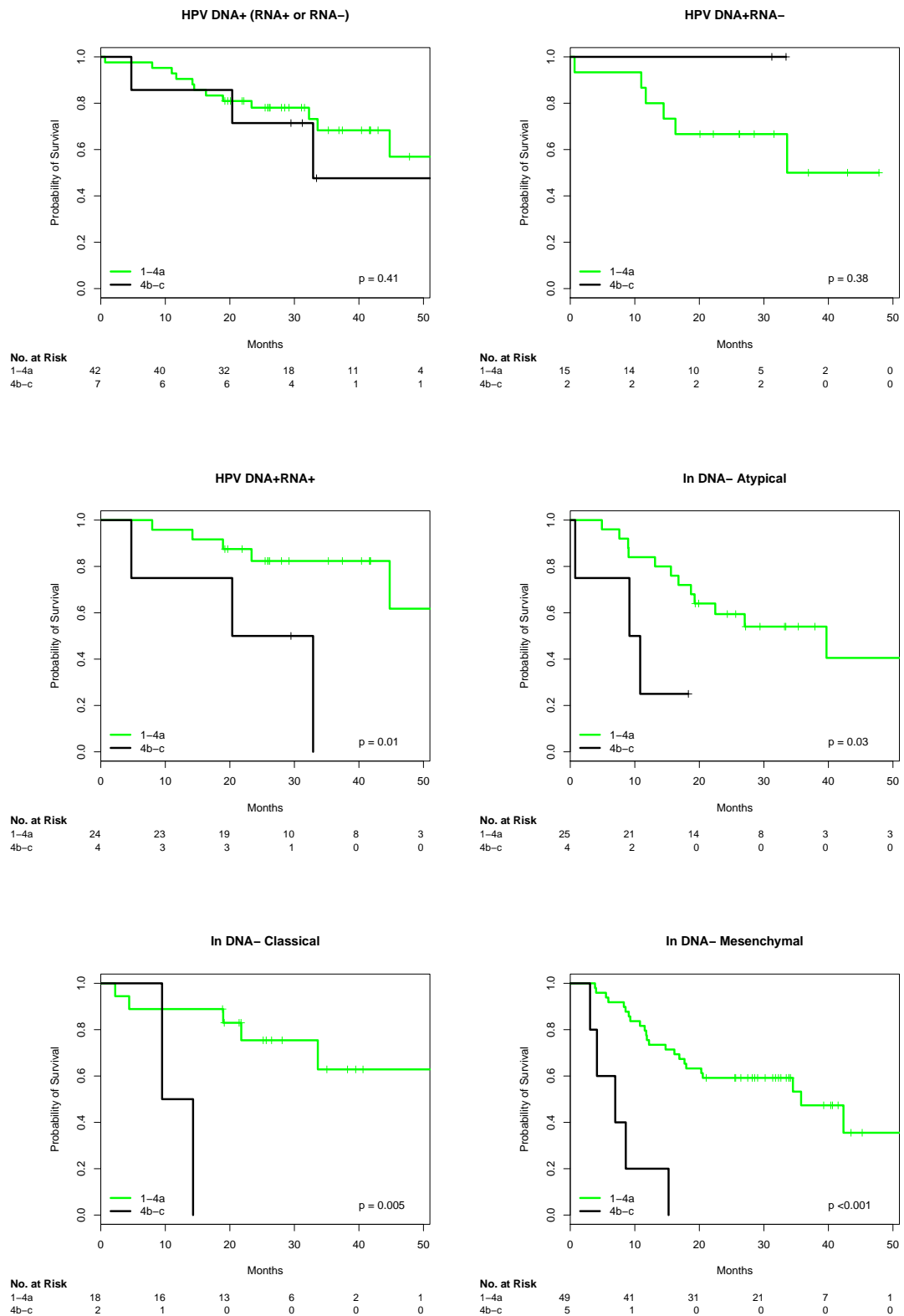
## 2.16 UICC, stages 1,2,3,4a vs. 4b,4c

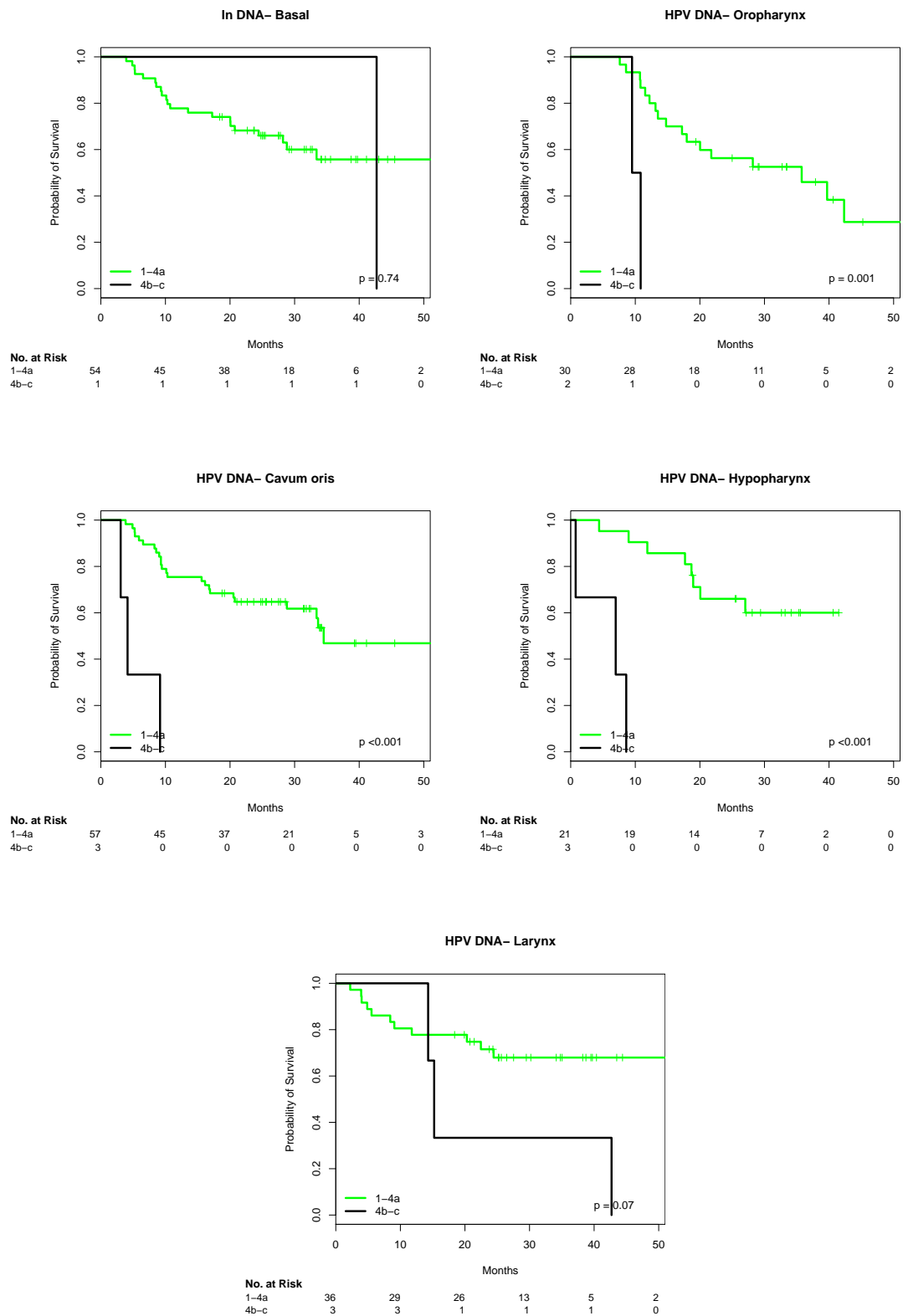
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 0.907      2.477    0.286 3.17   0.0015 **
## ---
## 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      2.48      0.404      1.41      4.34
##
## Concordance= 0.547 (se = 0.014 )
## Rsquare= 0.037 (max possible= 0.987 )
## Likelihood ratio test= 8.2 on 1 df,  p=0.00419
## Wald test               = 10.1 on 1 df,  p=0.00151
## Score (logrank) test = 10.7 on 1 df,  p=0.00107
##
##
```

```
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4b-c 1.512      4.536    0.334 4.52  6.2e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4b-c      4.54      0.22      2.35      8.74
##
## Concordance= 0.563 (se = 0.013 )
## Rsquare= 0.089 (max possible= 0.986 )
## Likelihood ratio test= 14.7 on 1 df,  p=0.000126
## Wald test               = 20.4 on 1 df,  p=6.16e-06
## Score (logrank) test = 24.6 on 1 df,  p=7.18e-07
```









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

```

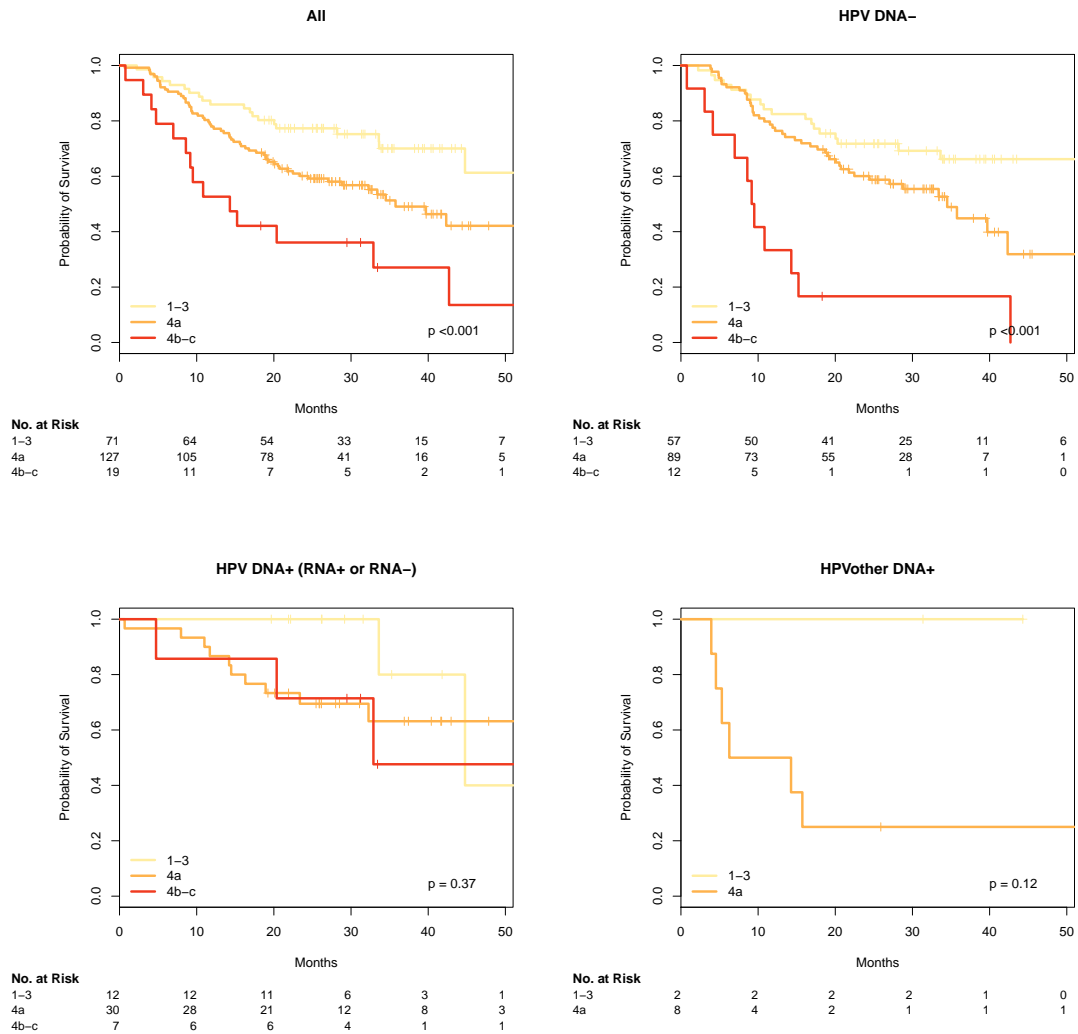
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  0.628    1.873    0.250 2.51    0.012 *
## split[cur.subset]4b-c 1.327    3.769    0.340 3.91   9.3e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      1.87      0.534      1.15      3.06
## split[cur.subset]4b-c     3.77      0.265      1.94      7.33
##
## Concordance= 0.601 (se = 0.027 )
## Rsquare= 0.067 (max possible= 0.987 )
## Likelihood ratio test= 15.1 on 2 df,  p=0.000536
## Wald test = 15.5 on 2 df,  p=0.000431
## Score (logrank) test = 16.7 on 2 df,  p=0.000238
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]4a  0.551    1.734    0.279 1.97    0.049 *
## split[cur.subset]4b-c 1.866    6.461    0.388 4.81   1.5e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]4a      1.73      0.577      1.00      3.0
## split[cur.subset]4b-c     6.46      0.155      3.02     13.8
##

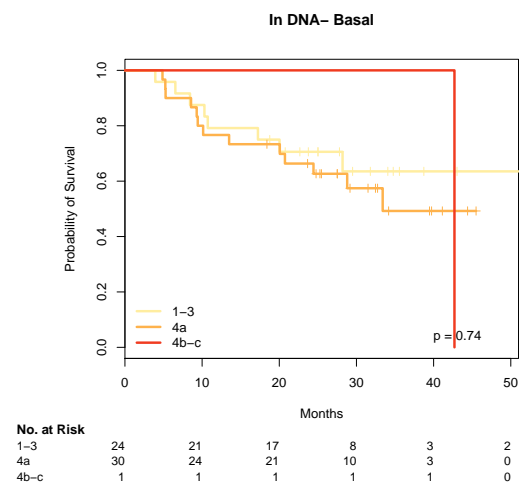
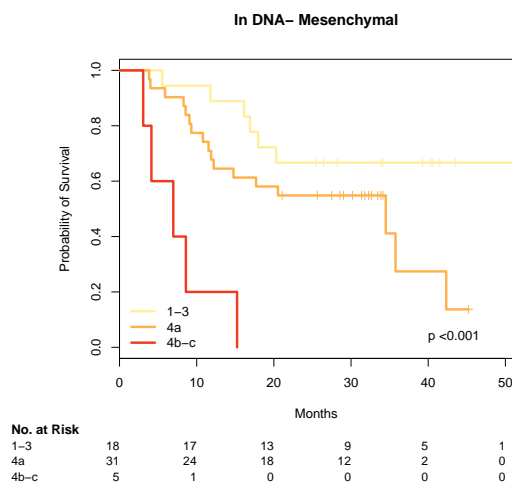
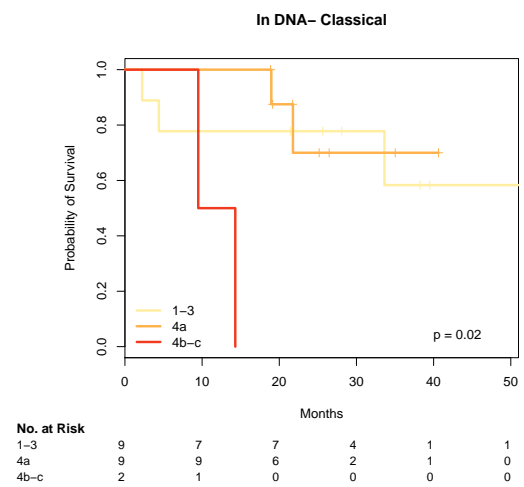
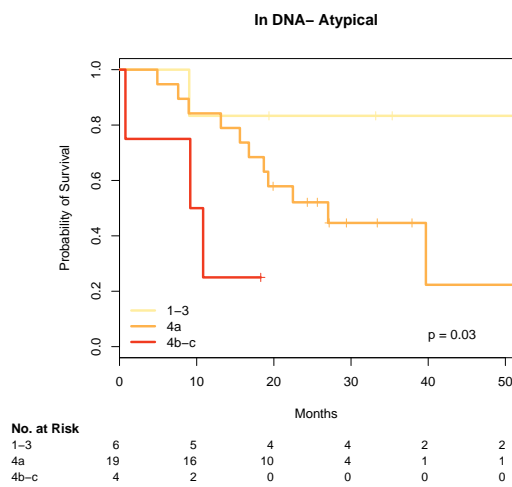
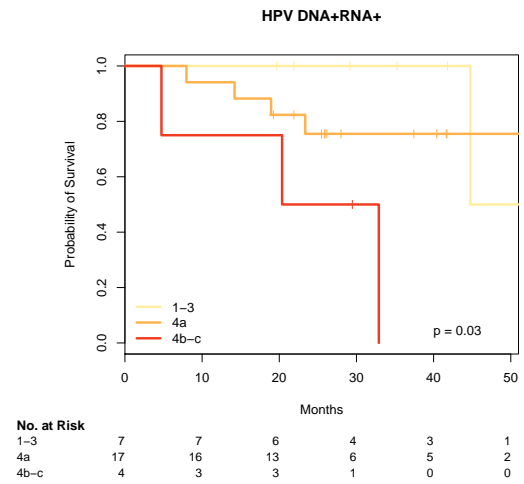
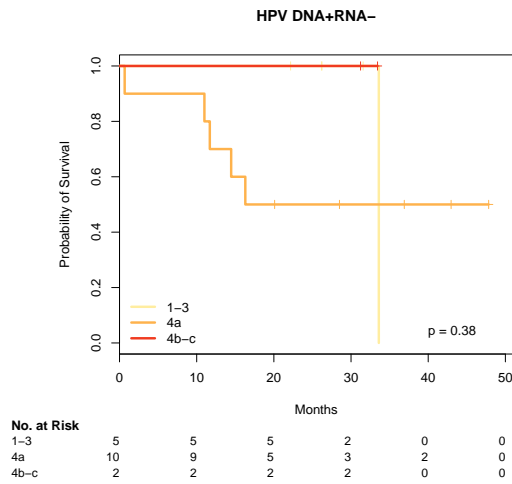
```

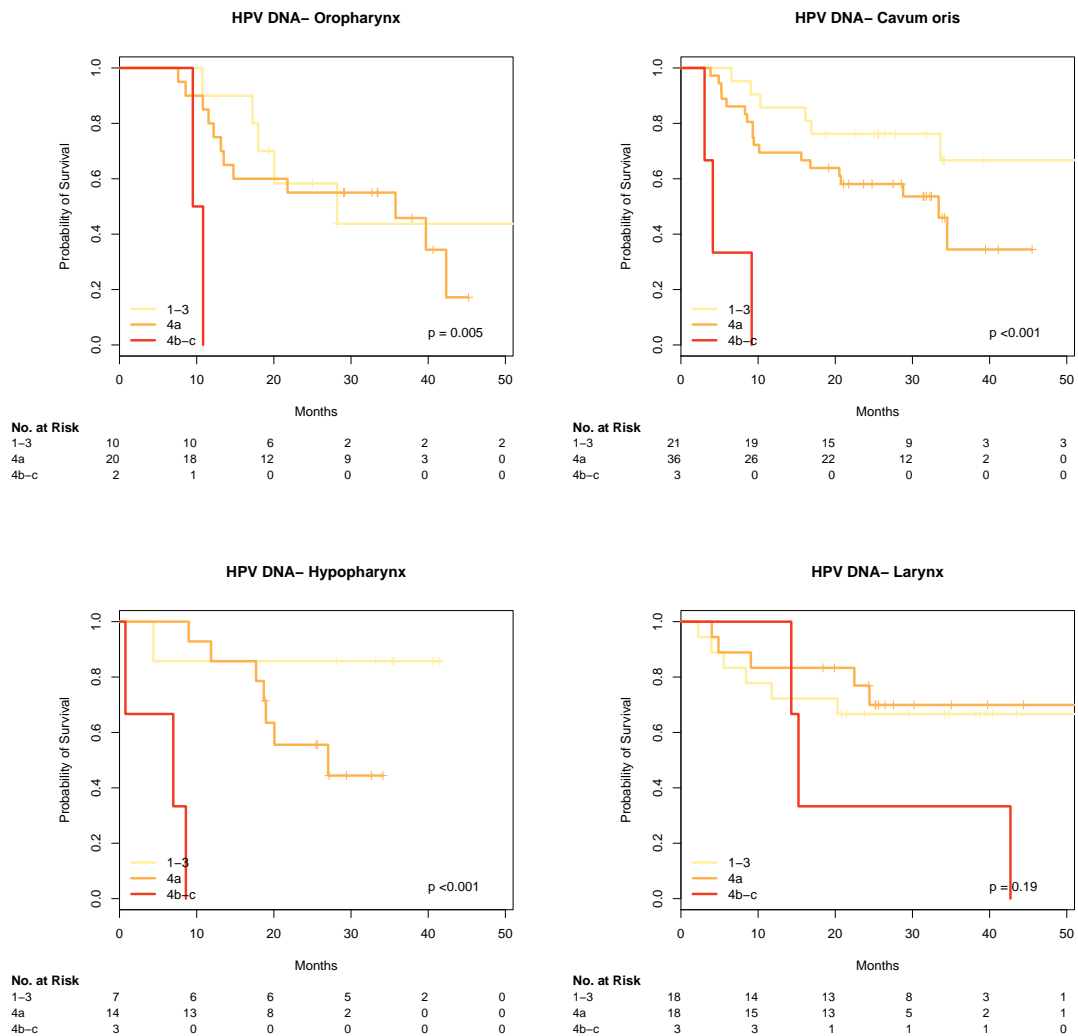
```

## Concordance= 0.602 (se = 0.031 )
## Rsquare= 0.112 (max possible= 0.986 )
## Likelihood ratio test= 18.8 on 2 df, p=8.1e-05
## Wald test = 23.4 on 2 df, p=8.08e-06
## Score (logrank) test = 28.1 on 2 df, p=7.93e-07

```



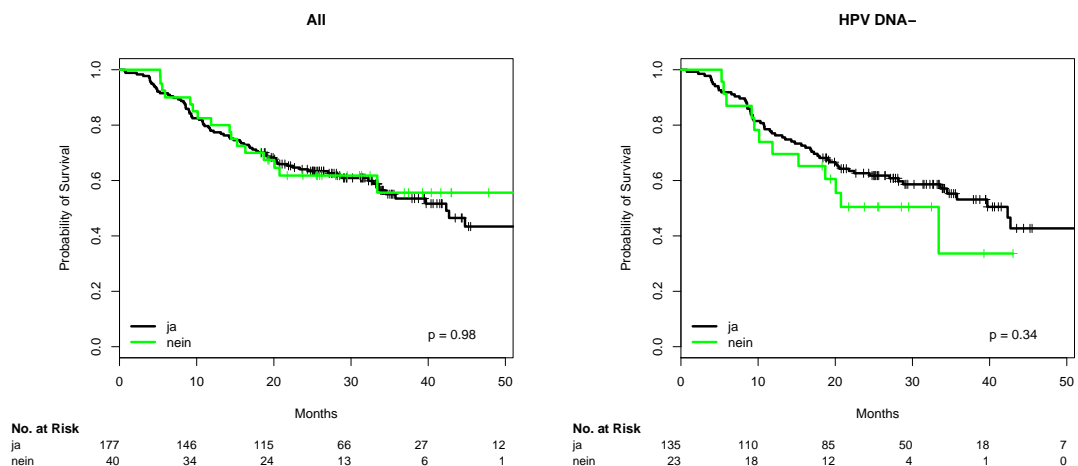


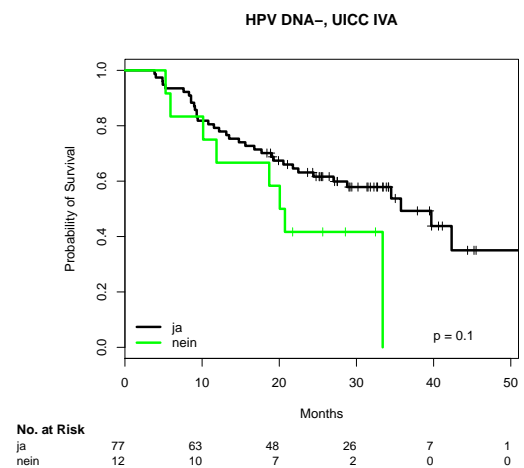
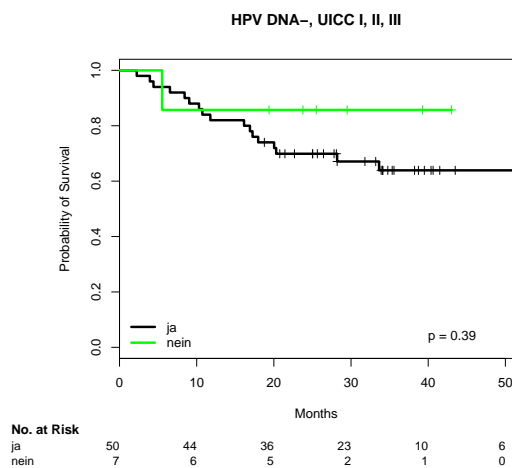
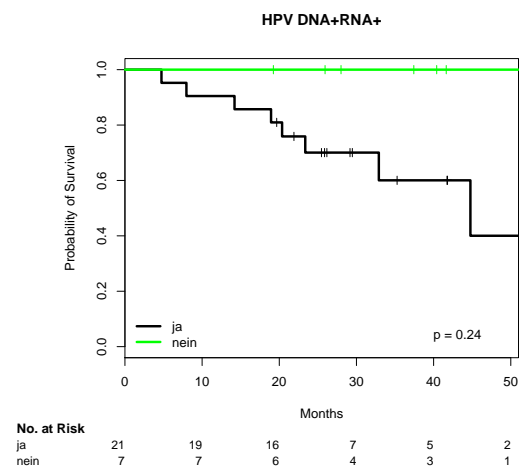
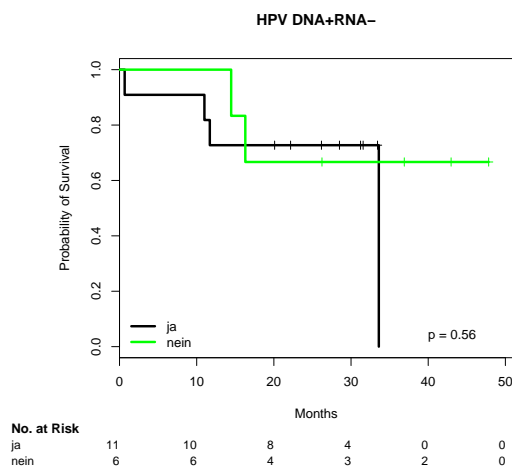
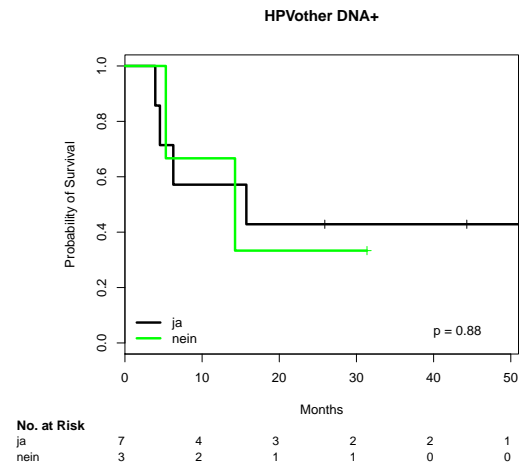
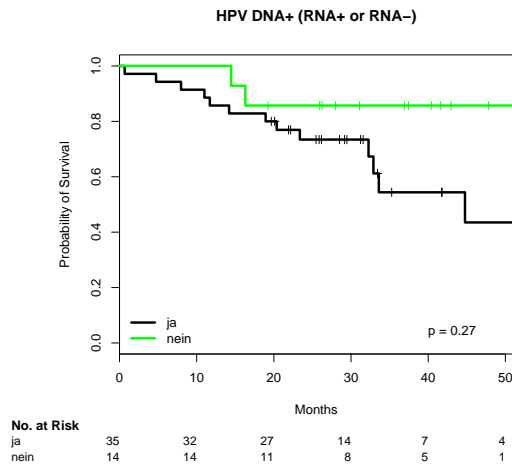


## 2.18 Smoking: yes vs. no

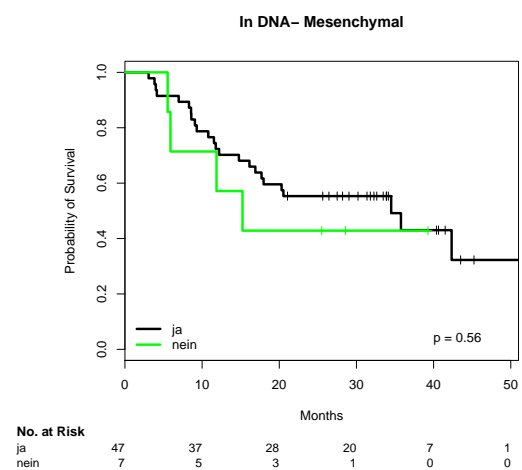
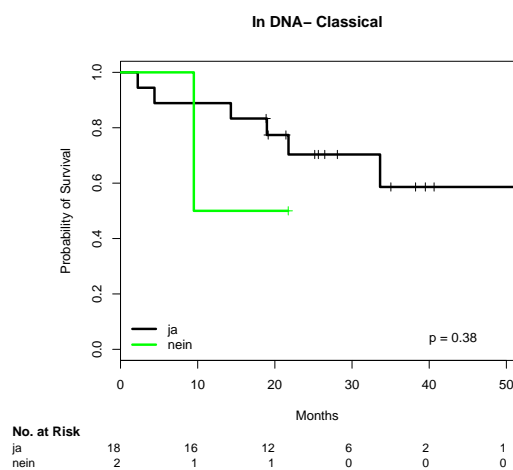
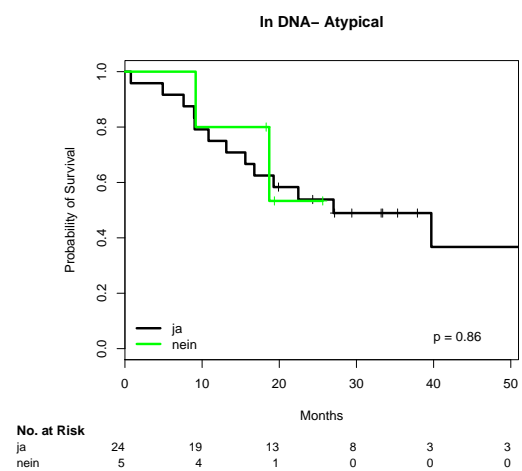
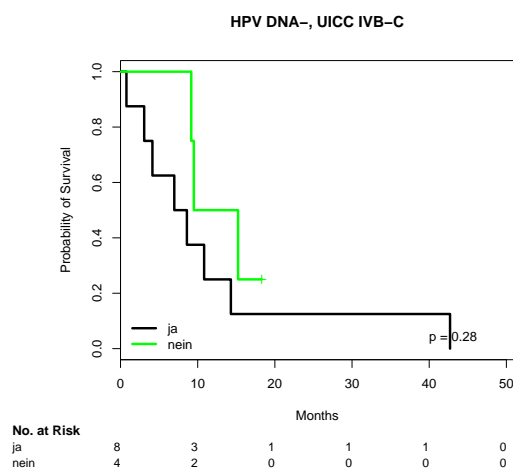
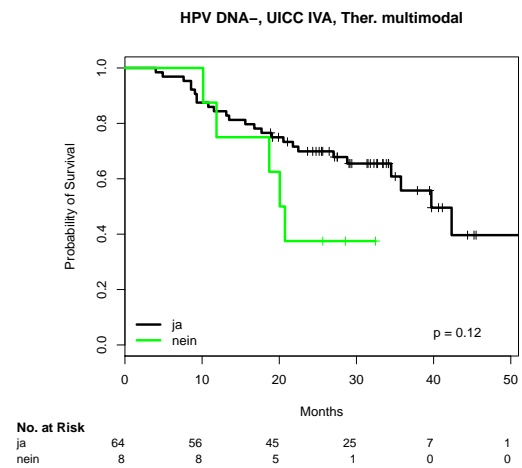
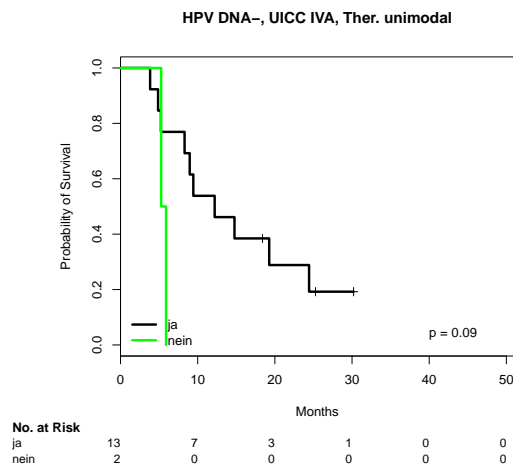
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein -0.00786  0.99217  0.26799 -0.03    0.98
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein   0.992      1.01   0.587   1.68
##
## Concordance= 0.502 (se = 0.021 )
```

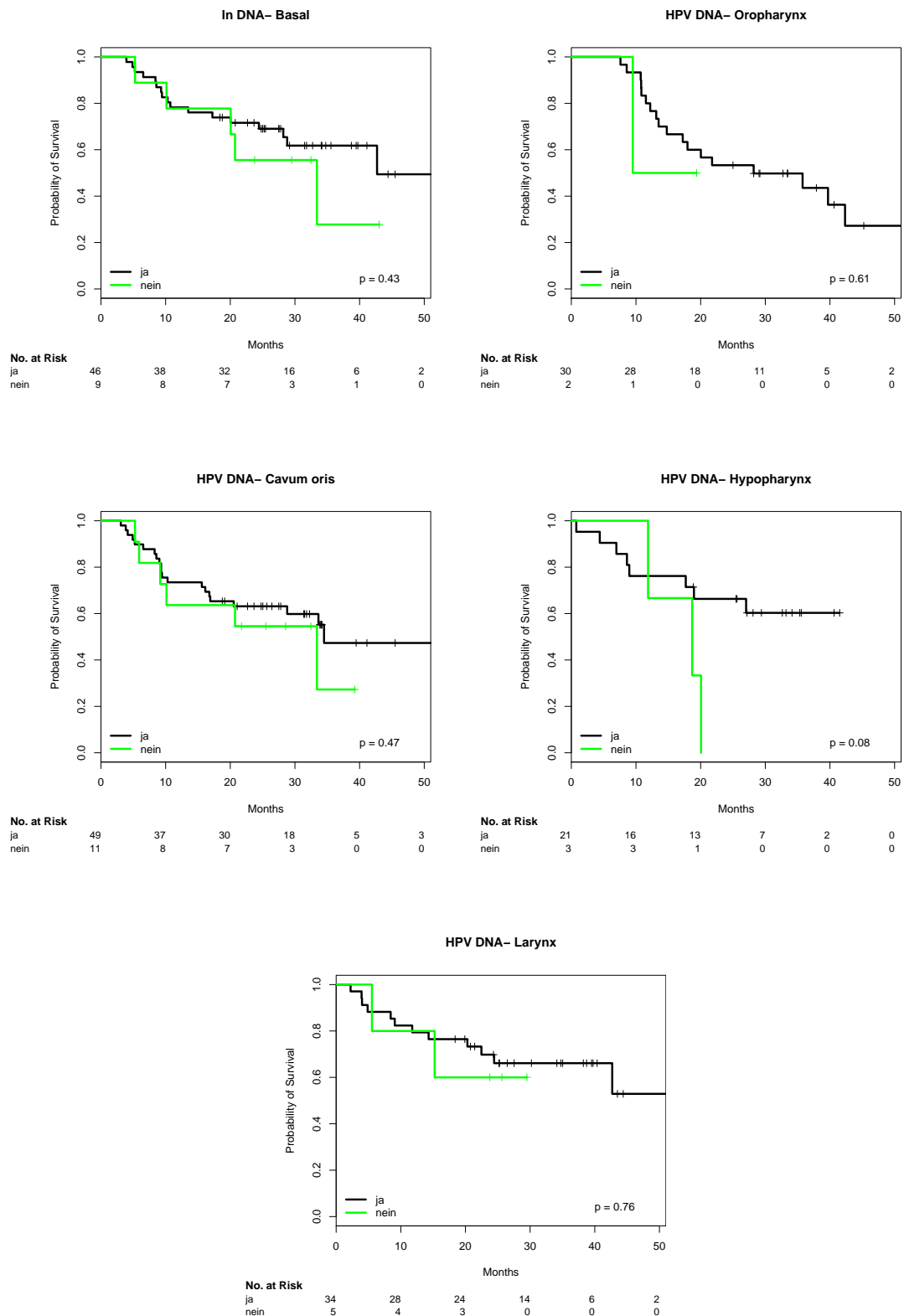
```
## Rsquare= 0    (max possible= 0.987 )
## Likelihood ratio test= 0    on 1 df,    p=0.977
## Wald test      = 0    on 1 df,    p=0.977
## Score (logrank) test = 0    on 1 df,    p=0.977
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]nein 0.302      1.352    0.317 0.95     0.34
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]nein      1.35      0.739    0.726    2.52
##
## Concordance= 0.517  (se = 0.022 )
## Rsquare= 0.005    (max possible= 0.986 )
## Likelihood ratio test= 0.85  on 1 df,    p=0.358
## Wald test            = 0.9   on 1 df,    p=0.342
## Score (logrank) test = 0.91  on 1 df,    p=0.34
```









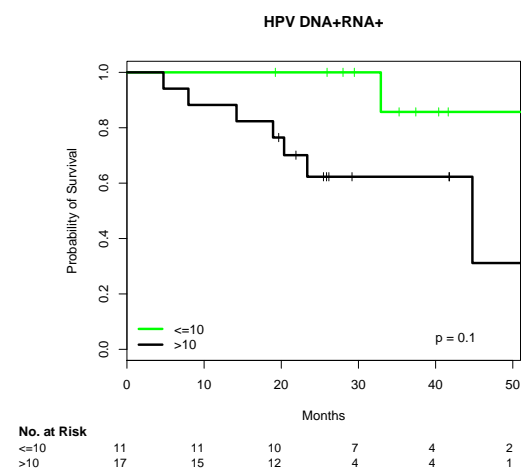
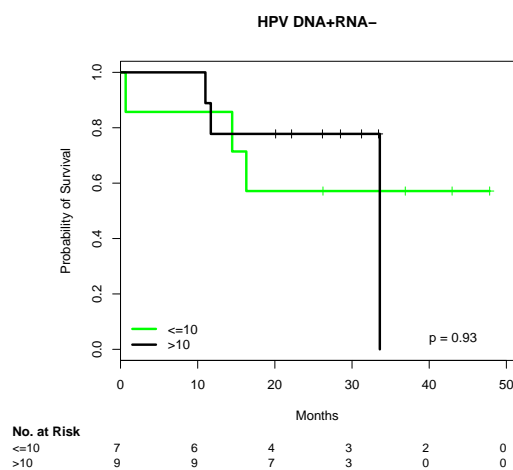
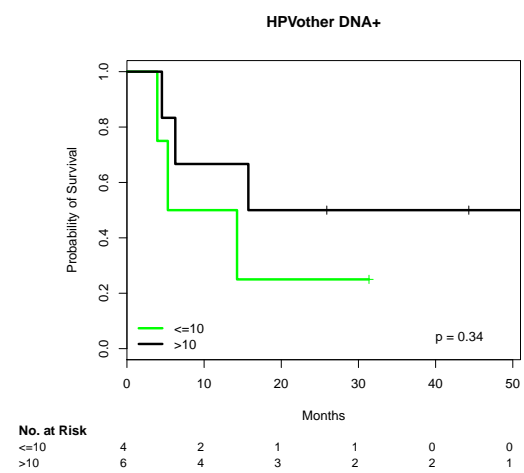
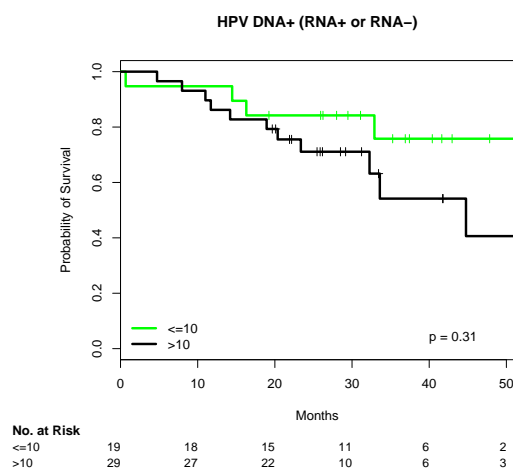
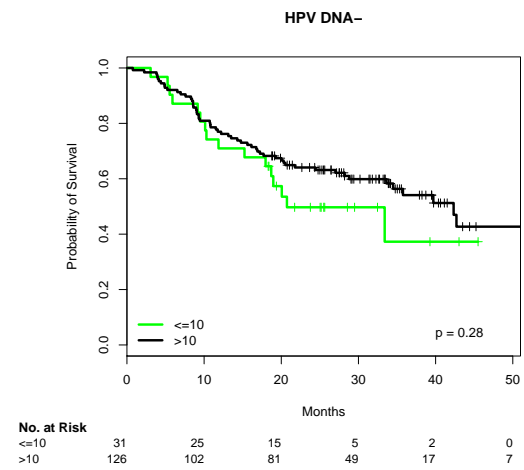
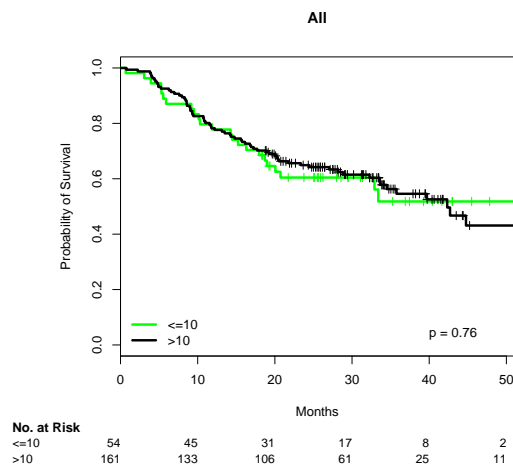


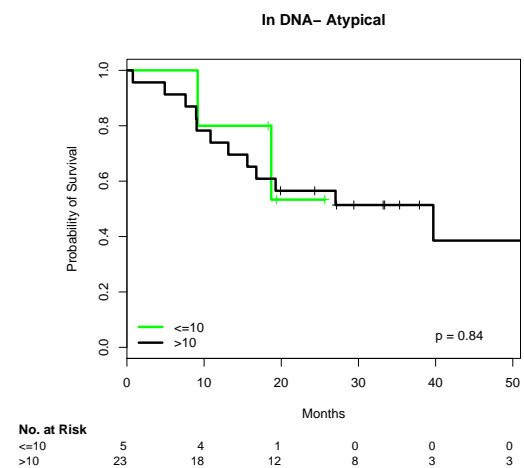
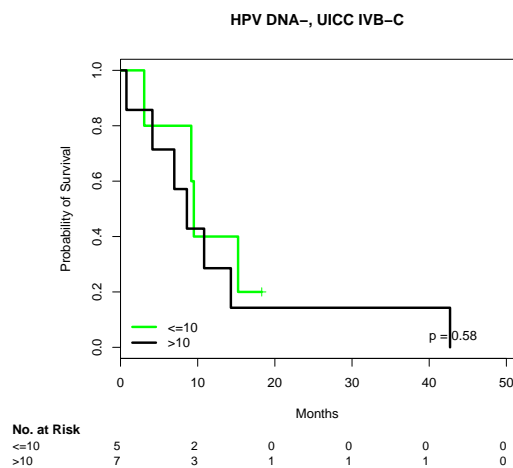
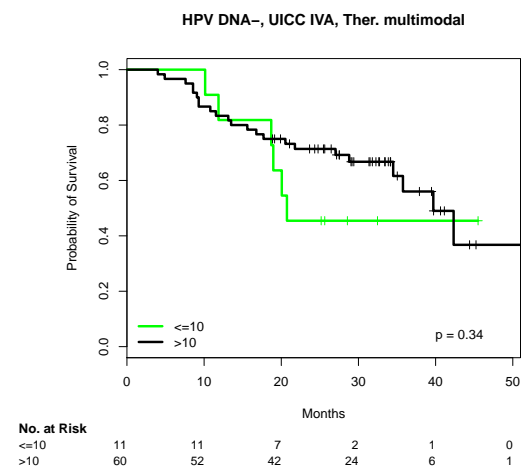
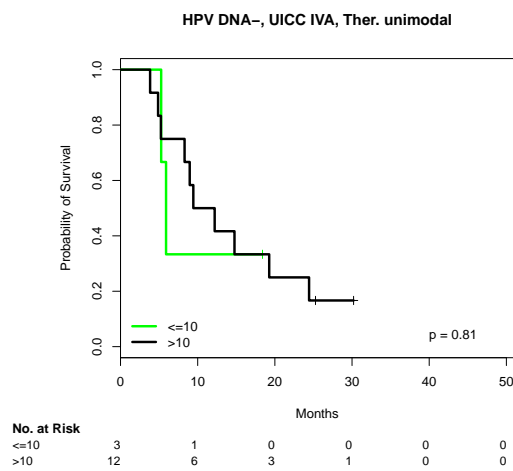
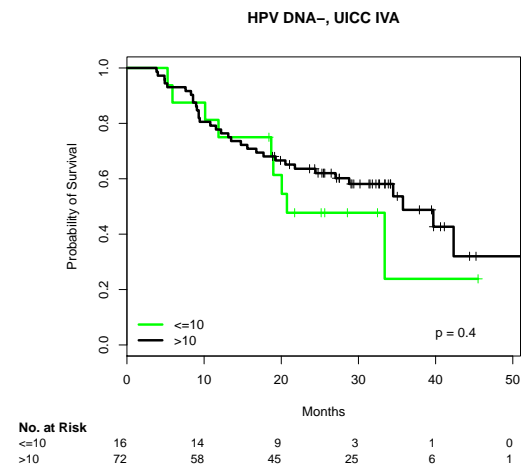
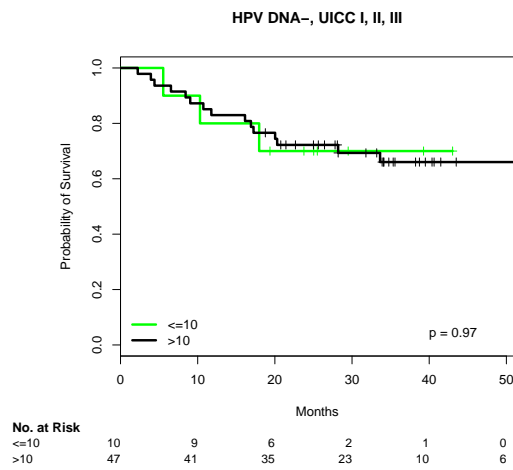
## 2.19 Smoking. Pack-years. Cut at 10

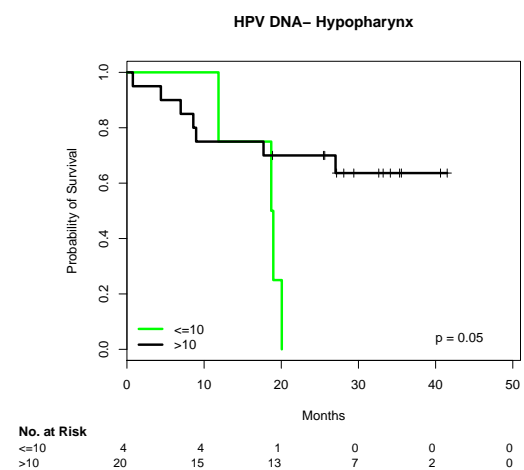
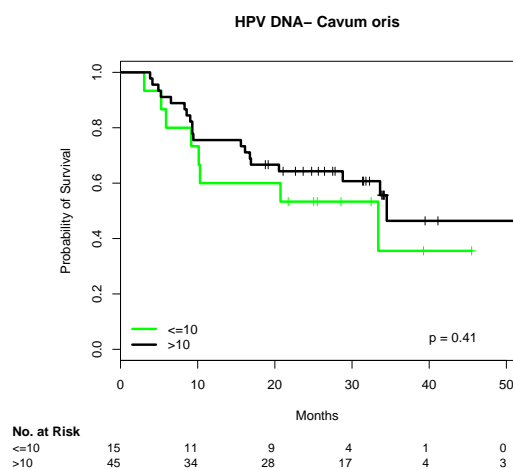
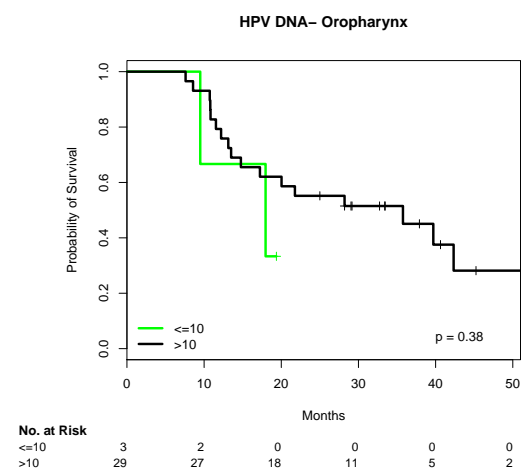
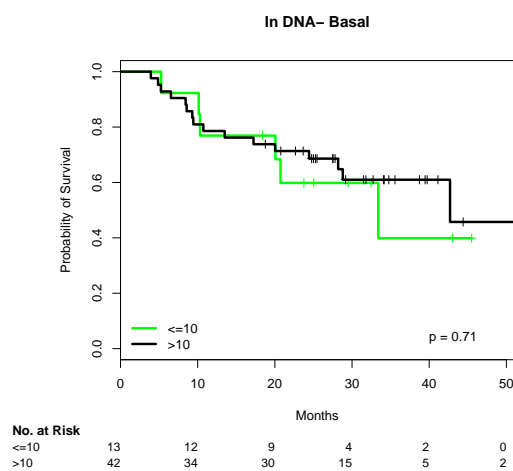
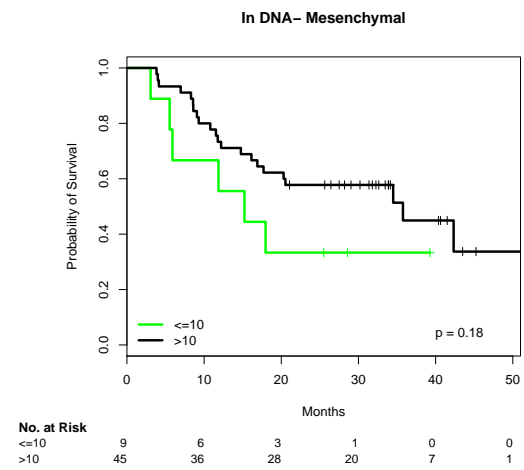
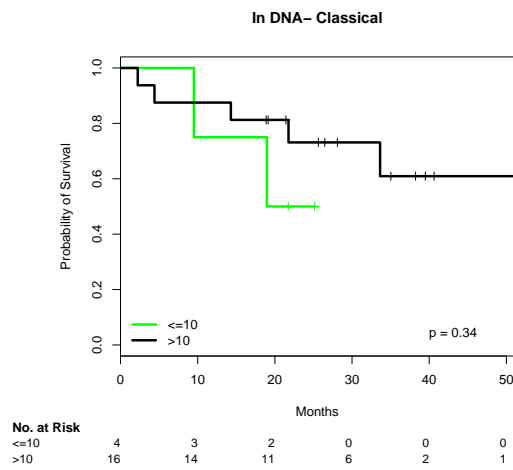
```

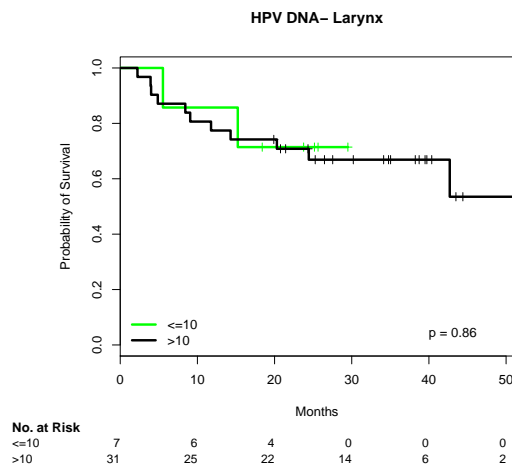
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 215, number of events= 98
##      (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.0736    0.9291    0.2367 -0.31    0.76
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.929      1.08    0.584    1.48
##
## Concordance= 0.509 (se = 0.024 )
## Rsquare= 0 (max possible= 0.987 )
## Likelihood ratio test= 0.1 on 1 df, p=0.757
## Wald test = 0.1 on 1 df, p=0.756
## Score (logrank) test = 0.1 on 1 df, p=0.756
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 157, number of events= 73
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>10 -0.307    0.736    0.285 -1.07    0.28
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>10    0.736      1.36    0.421    1.29
##
## Concordance= 0.524 (se = 0.025 )
## Rsquare= 0.007 (max possible= 0.985 )
## Likelihood ratio test= 1.09 on 1 df, p=0.296
## Wald test = 1.15 on 1 df, p=0.283
## Score (logrank) test = 1.16 on 1 df, p=0.281

```





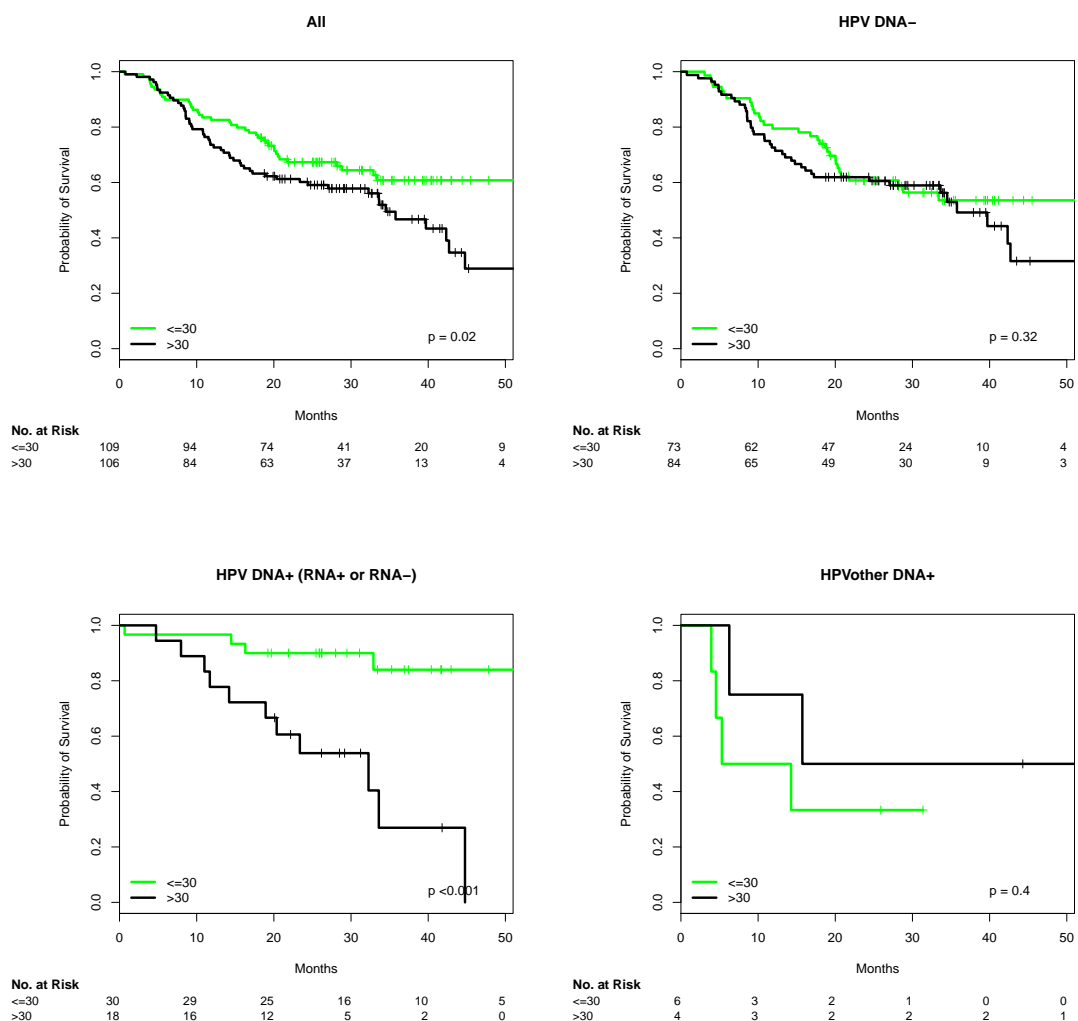




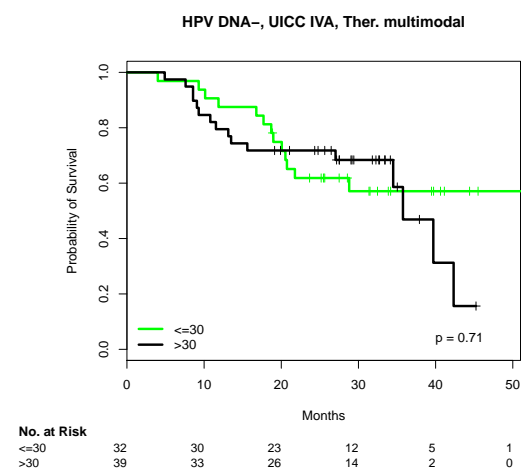
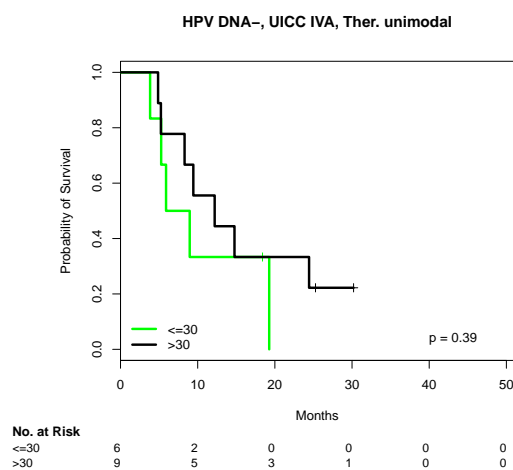
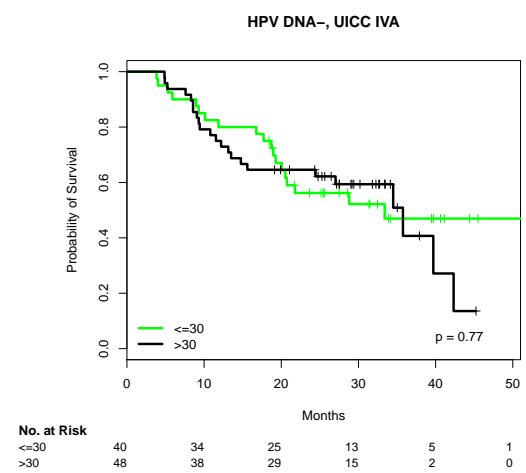
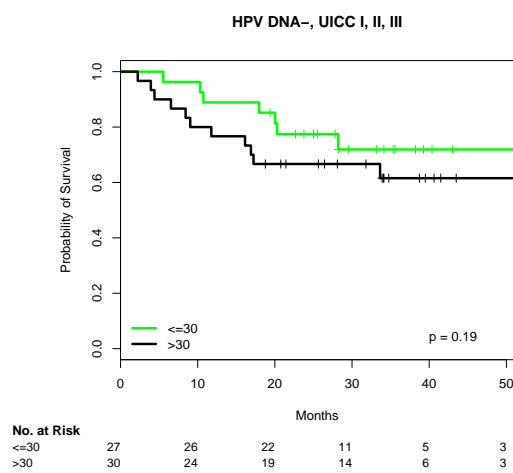
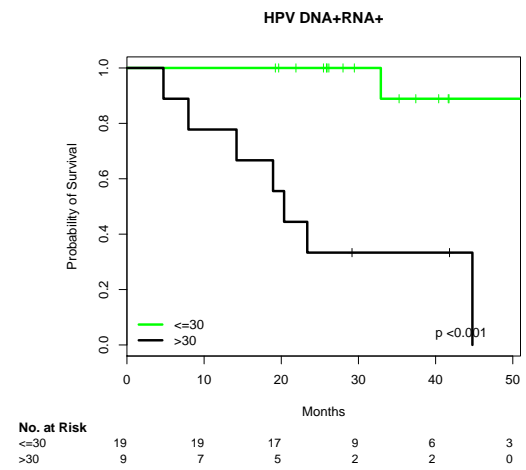
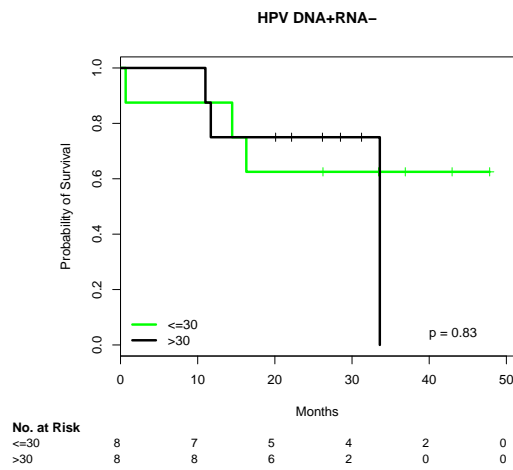
## 2.20 Smoking. Pack-years. Cut at 30

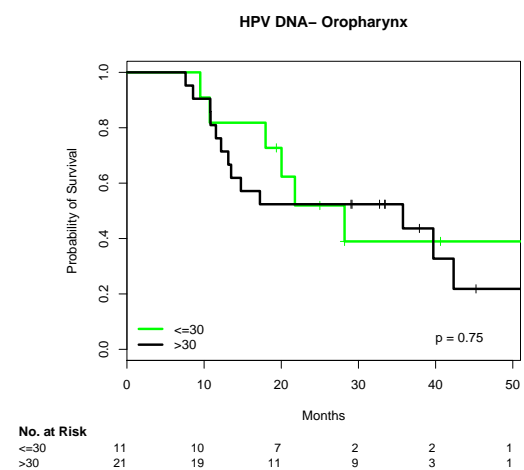
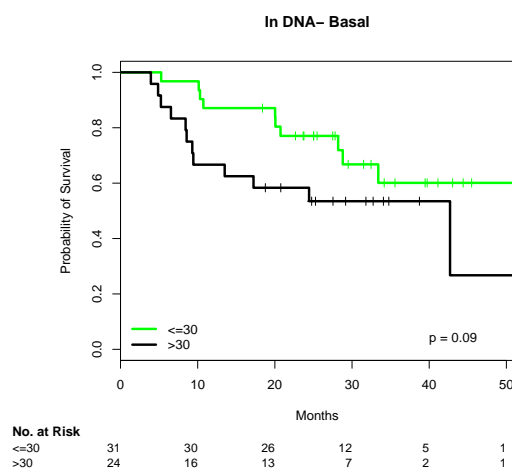
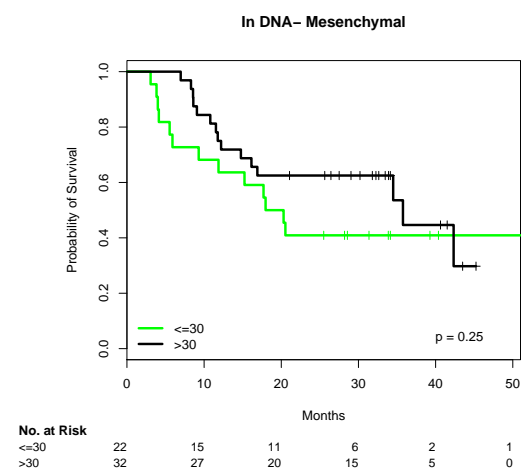
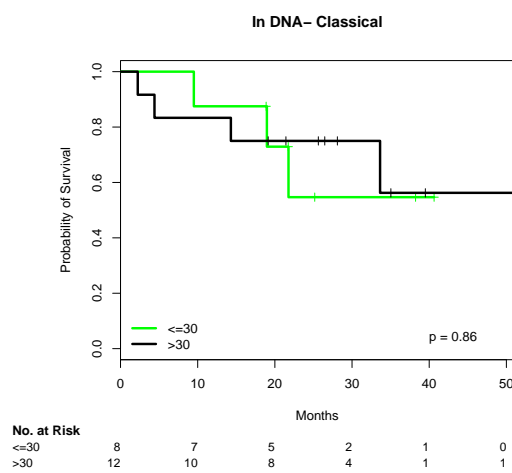
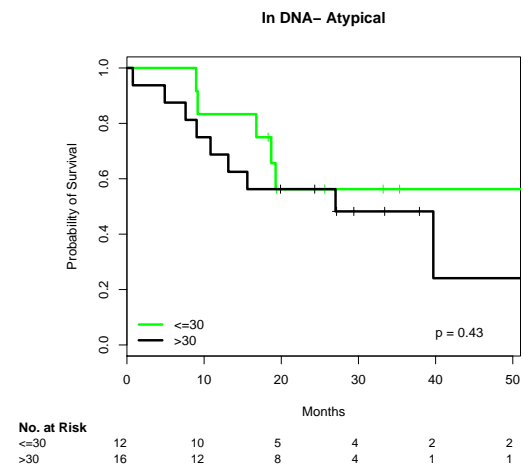
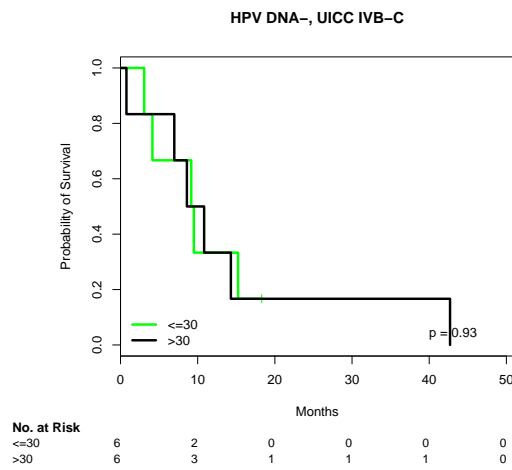
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 215, number of events= 98
## (2 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.486      1.626   0.208 2.34   0.019 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30    1.63      0.615    1.08    2.44
##
## Concordance= 0.545 (se = 0.027 )
## Rsquare= 0.026 (max possible= 0.987 )
## Likelihood ratio test= 5.58 on 1 df,  p=0.0182
## Wald test               = 5.48 on 1 df,  p=0.0192
## Score (logrank) test = 5.59 on 1 df,  p=0.0181
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
```

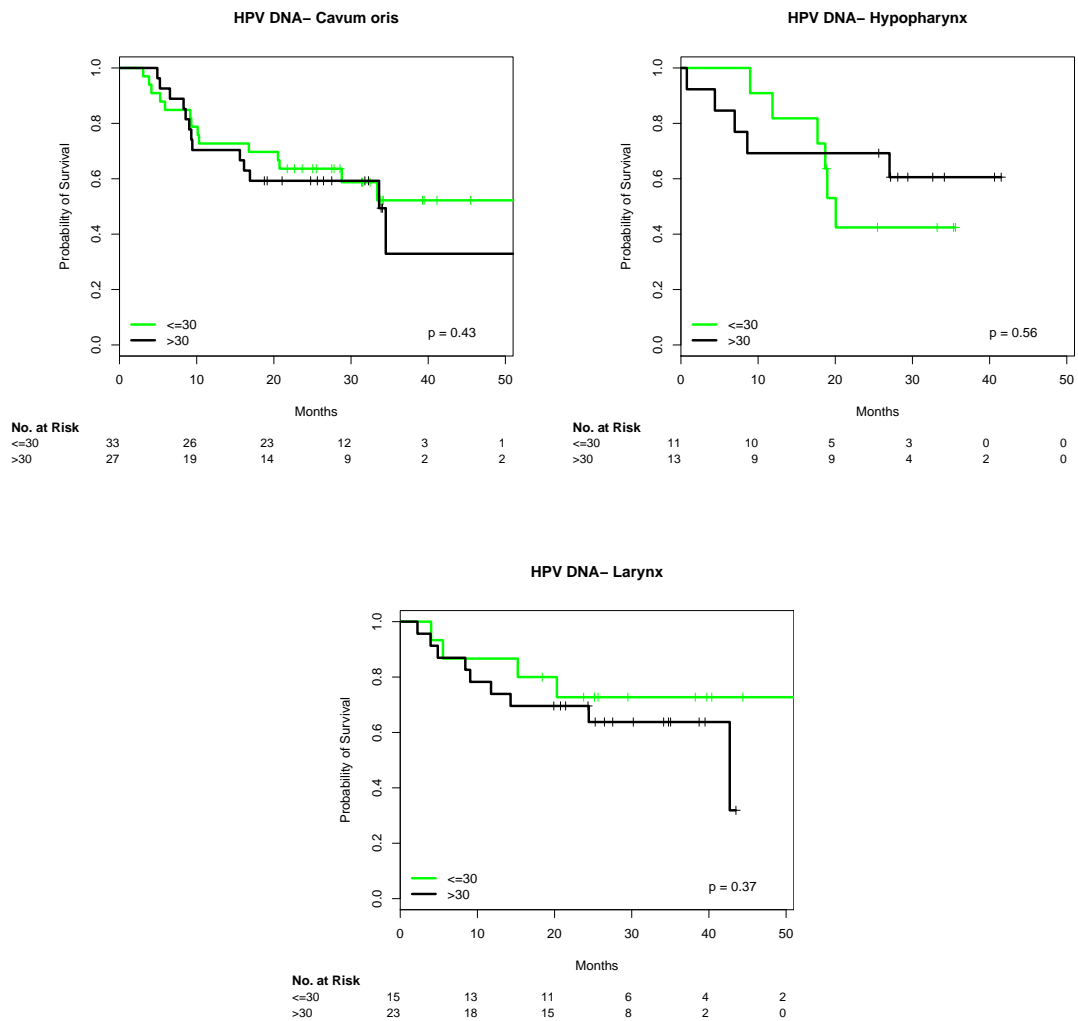
```
## n= 157, number of events= 73
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]>30 0.233      1.263    0.237 0.98    0.33
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]>30      1.26      0.792    0.793    2.01
##
## Concordance= 0.522 (se = 0.031 )
## Rsquare= 0.006 (max possible= 0.985 )
## Likelihood ratio test= 0.98 on 1 df, p=0.323
## Wald test = 0.97 on 1 df, p=0.325
## Score (logrank) test = 0.97 on 1 df, p=0.324
```







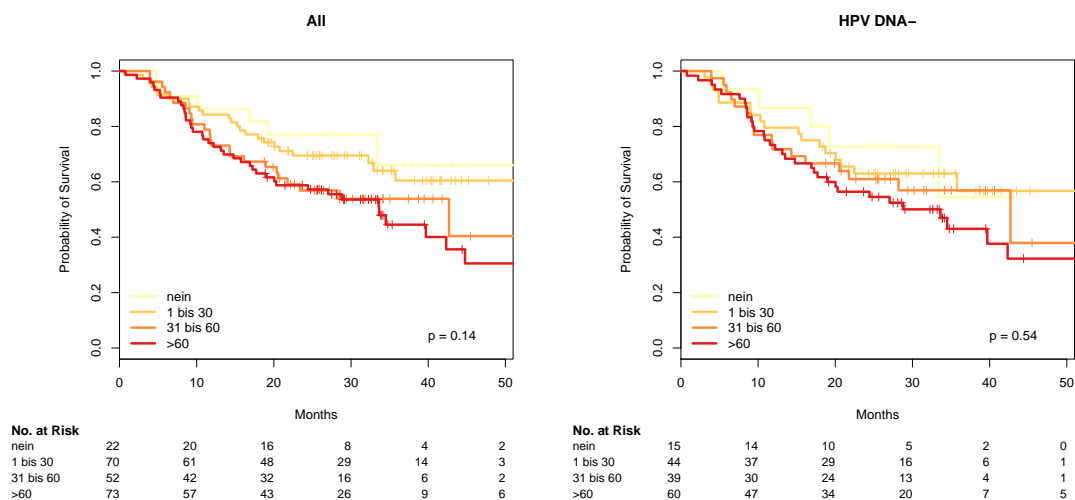


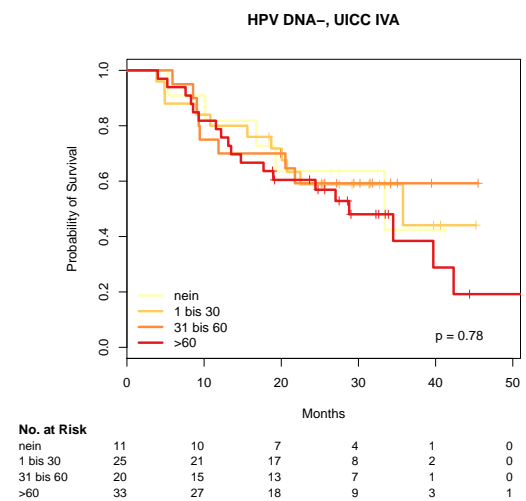
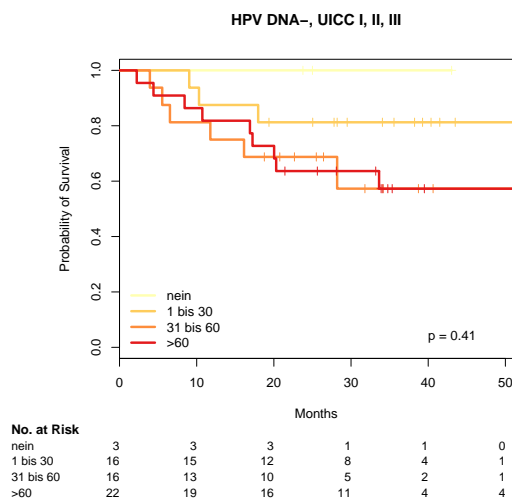
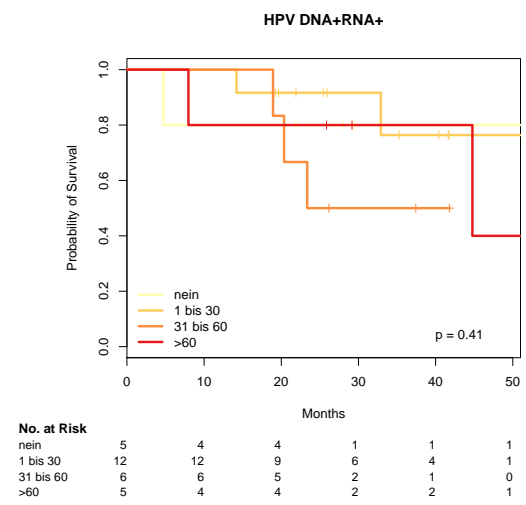
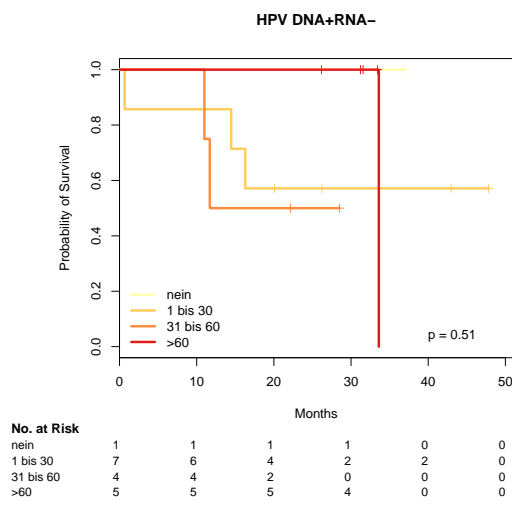
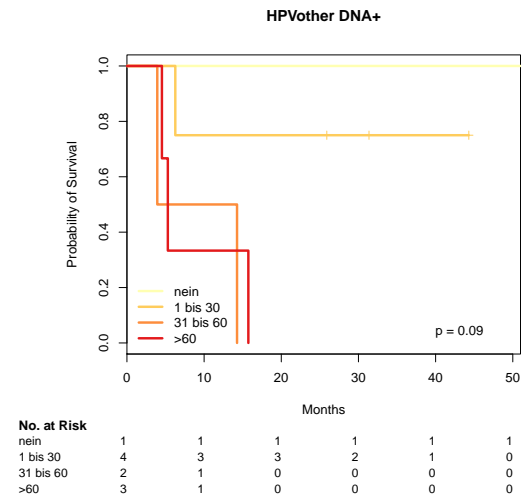
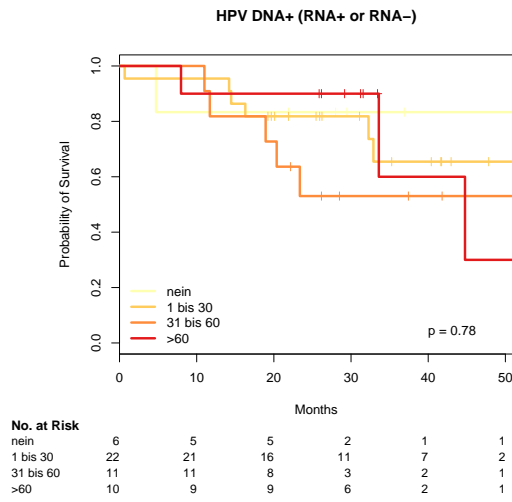


## 2.21 Alcohol consumption

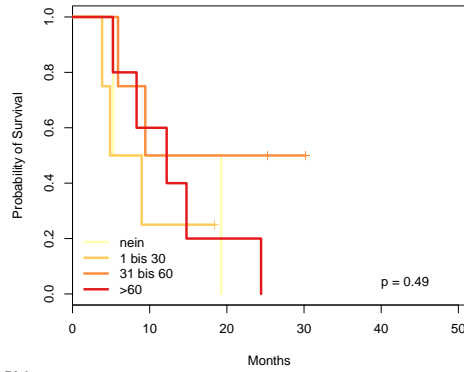
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30  0.181    1.198   0.426  0.42   0.67
## split[cur.subset]31 bis 60  0.546    1.727   0.429  1.27   0.20
## split[cur.subset]>60      0.669    1.953   0.410  1.63   0.10
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30    1.20    0.835    0.519    2.76
```

```
## split[cur.subset]31 bis 60      1.73      0.579      0.745      4.00
## split[cur.subset]>60            1.95      0.512      0.874      4.36
##
## Concordance= 0.566 (se = 0.03 )
## Rsquare= 0.026 (max possible= 0.987 )
## Likelihood ratio test= 5.69 on 3 df, p=0.128
## Wald test = 5.43 on 3 df, p=0.143
## Score (logrank) test = 5.55 on 3 df, p=0.136
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]1 bis 30  0.217      1.243    0.506  0.43    0.67
## split[cur.subset]31 bis 60  0.412      1.510    0.506  0.81    0.42
## split[cur.subset]>60        0.552      1.736    0.481  1.15    0.25
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]1 bis 30      1.24      0.805    0.461    3.35
## split[cur.subset]31 bis 60      1.51      0.662    0.560    4.07
## split[cur.subset]>60          1.74      0.576    0.676    4.46
##
## Concordance= 0.55 (se = 0.034 )
## Rsquare= 0.014 (max possible= 0.986 )
## Likelihood ratio test= 2.24 on 3 df, p=0.524
## Wald test = 2.14 on 3 df, p=0.543
## Score (logrank) test = 2.17 on 3 df, p=0.537
```



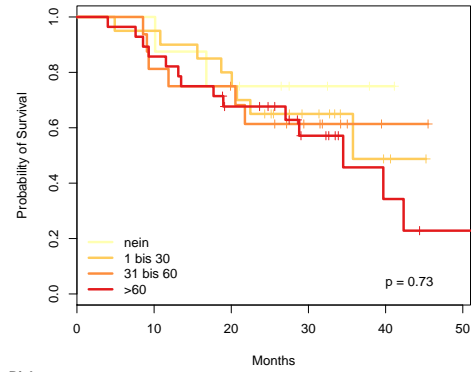


HPV DNA-, UICC IVA, Ther. unimodal



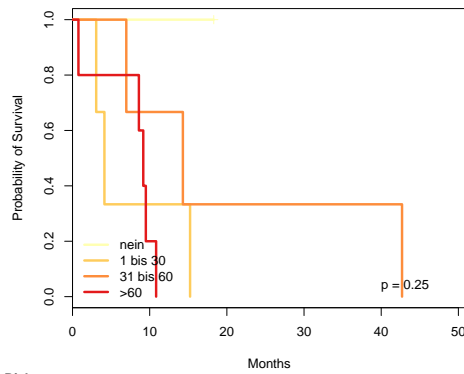
No. at Risk						
nein	2	1	0	0	0	0
1 bis 30	4	1	0	0	0	0
31 bis 60	4	2	2	1	0	0
>60	5	3	1	0	0	0

HPV DNA-, UICC IVA, Ther. multimodal



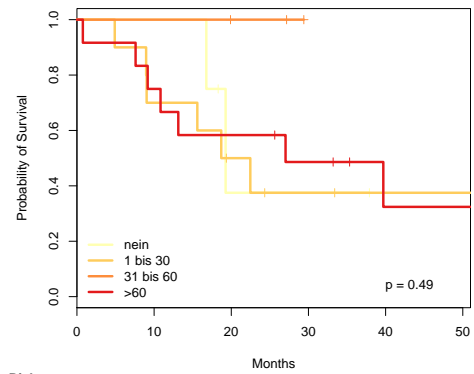
No. at Risk						
nein	8	8	6	3	1	0
1 bis 30	20	19	16	8	2	0
31 bis 60	16	13	11	6	1	0
>60	28	24	17	9	3	1

HPV DNA-, UICC IVB-C



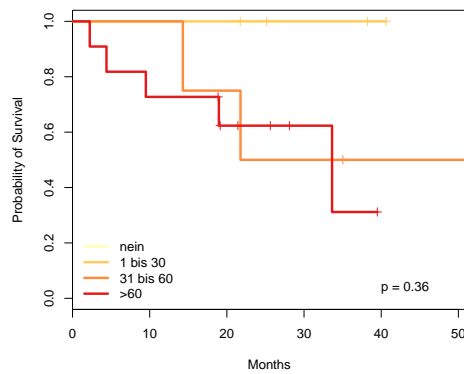
No. at Risk						
nein	1	1	0	0	0	0
1 bis 30	3	1	0	0	0	0
31 bis 60	3	2	1	1	1	0
>60	5	1	0	0	0	0

In DNA- Atypical



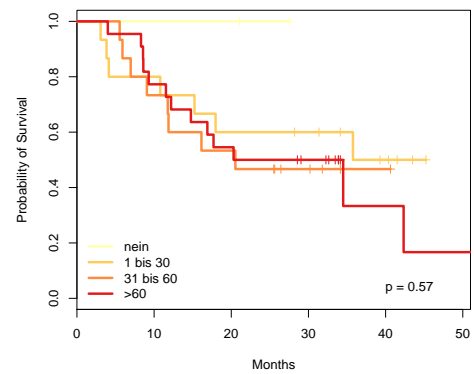
No. at Risk						
nein	4	4	1	1	0	0
1 bis 30	10	7	4	2	1	1
31 bis 60	3	3	2	0	0	0
>60	12	9	7	5	2	2

In DNA- Classical

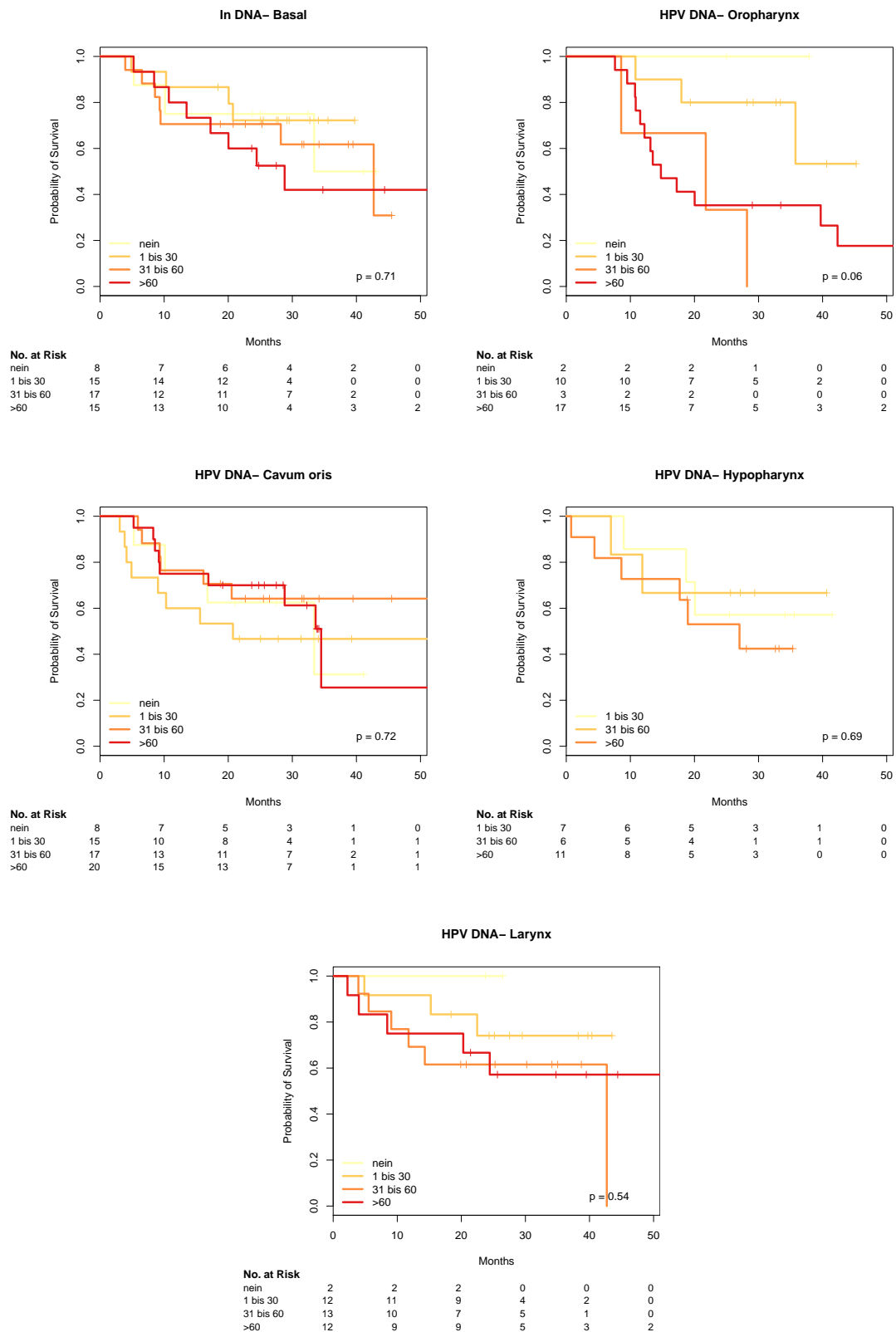


No. at Risk						
nein	1	1	1	0	0	0
1 bis 30	4	4	4	2	1	0
31 bis 60	4	4	3	2	1	1
>60	11	8	5	2	0	0

In DNA- Mesenchymal



No. at Risk						
nein	2	2	2	0	0	0
1 bis 30	15	12	9	8	4	0
31 bis 60	15	11	8	4	1	0
>60	22	17	12	9	2	1



## 2.22 Localisation

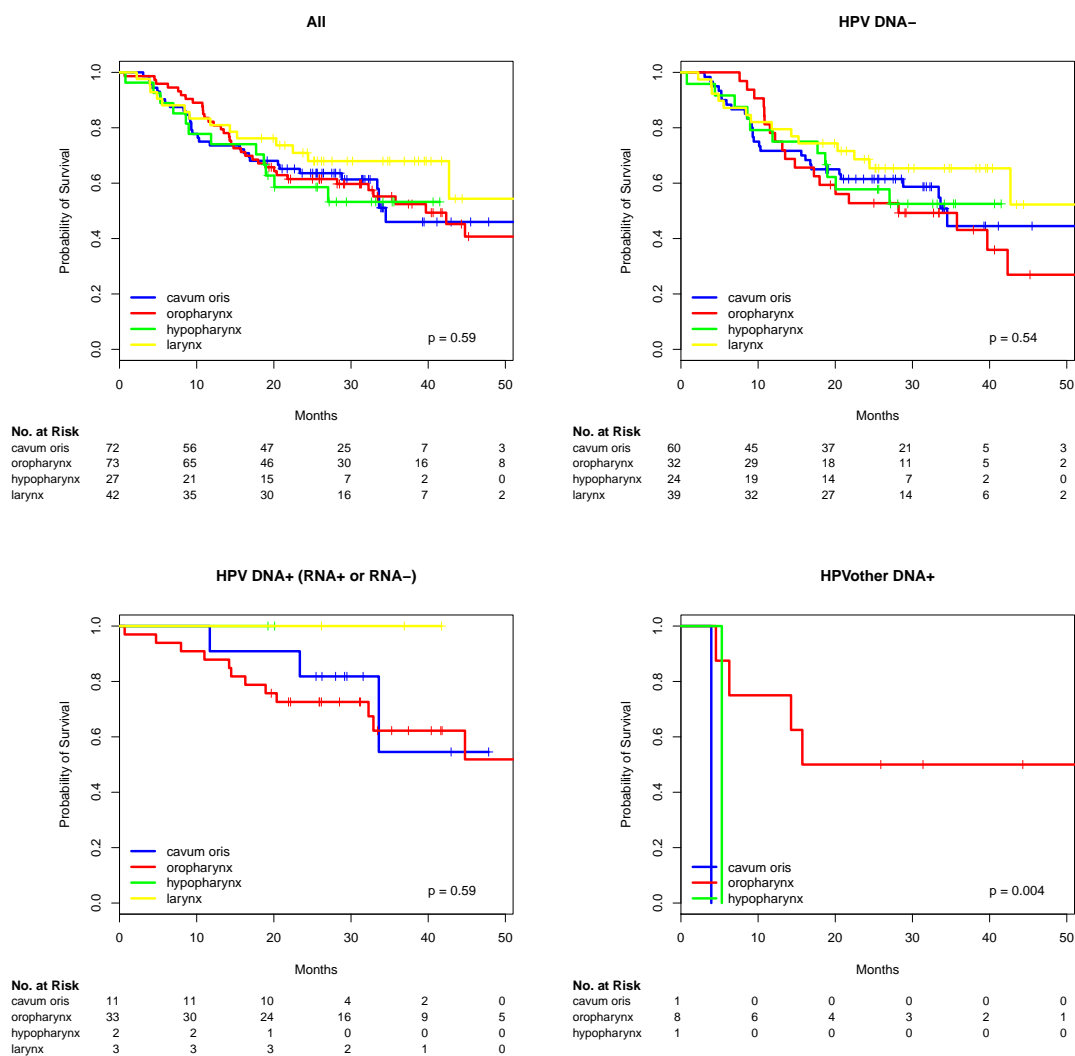
```

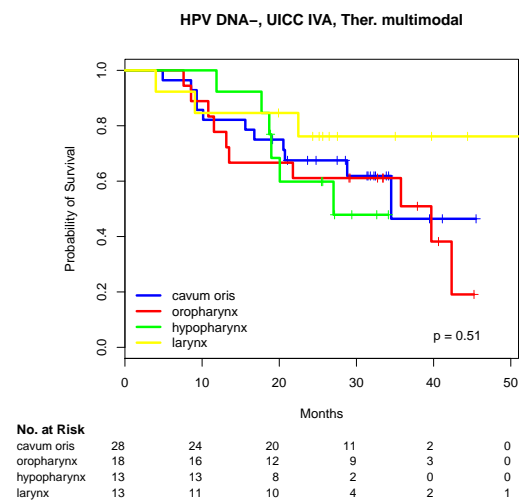
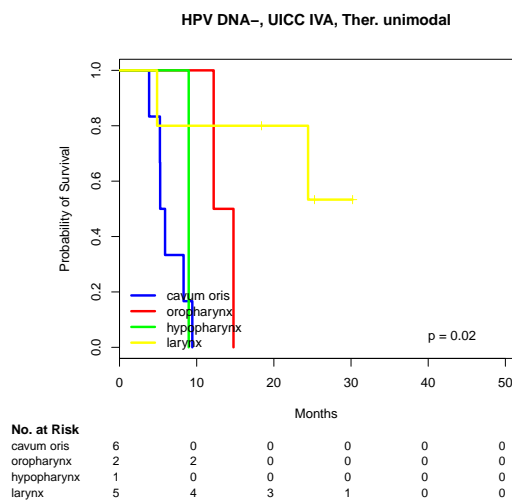
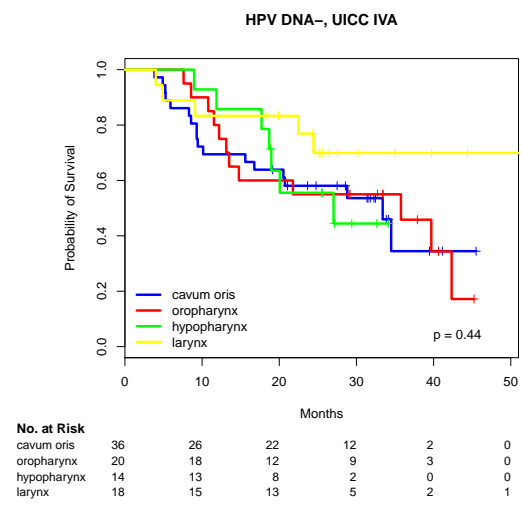
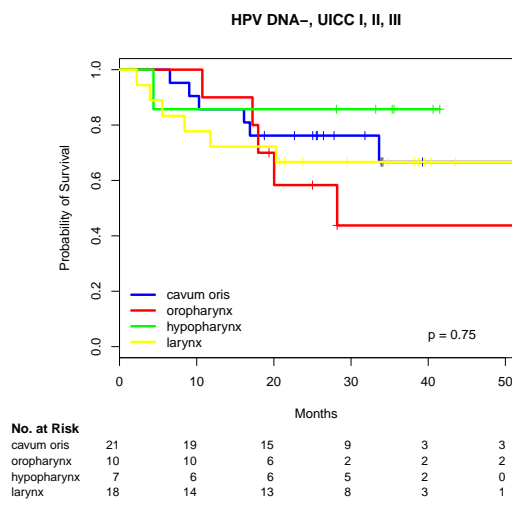
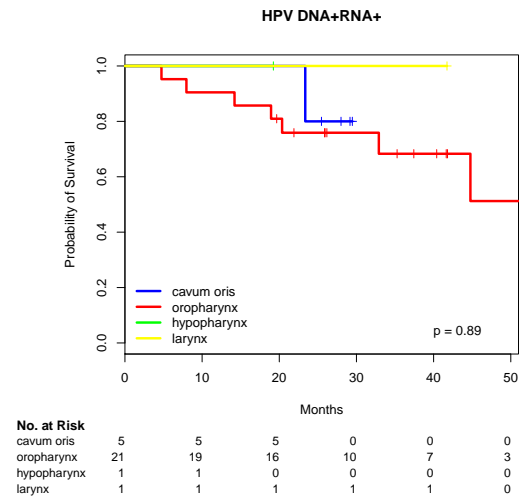
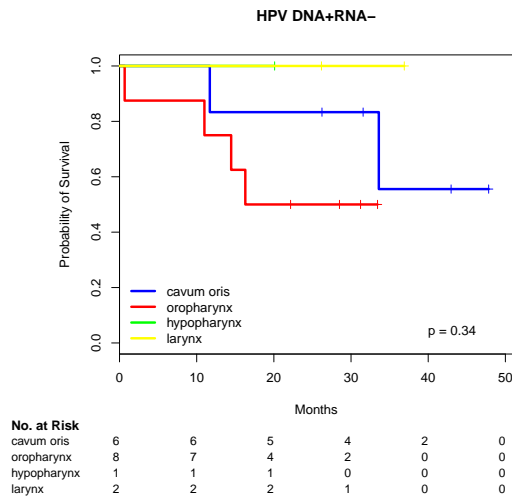
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 214, number of events= 98
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx -0.0355    0.9651  0.2409 -0.15    0.88
## split[cur.subset]hypopharynx  0.0784    1.0816  0.3382  0.23    0.82
## split[cur.subset]larynx      -0.3887    0.6780  0.3198 -1.22    0.22
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx    0.965    1.036    0.602    1.55
## split[cur.subset]hypopharynx    1.082    0.925    0.557    2.10
## split[cur.subset]larynx        0.678    1.475    0.362    1.27
##
## Concordance= 0.532 (se = 0.03 )
## Rsquare= 0.009 (max possible= 0.987 )
## Likelihood ratio test= 2.03 on 3 df, p=0.567
## Wald test = 1.87 on 3 df, p=0.599
## Score (logrank) test = 1.9 on 3 df, p=0.594
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 155, number of events= 73
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]oropharynx  0.10790    1.11393  0.29593  0.36    0.72
## split[cur.subset]hypopharynx -0.00272    0.99729  0.35578 -0.01    0.99
## split[cur.subset]larynx      -0.38684    0.67920  0.32704 -1.18    0.24
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]oropharynx    1.114    0.898    0.624    1.99
## split[cur.subset]hypopharynx    0.997    1.003    0.497    2.00
## split[cur.subset]larynx        0.679    1.472    0.358    1.29

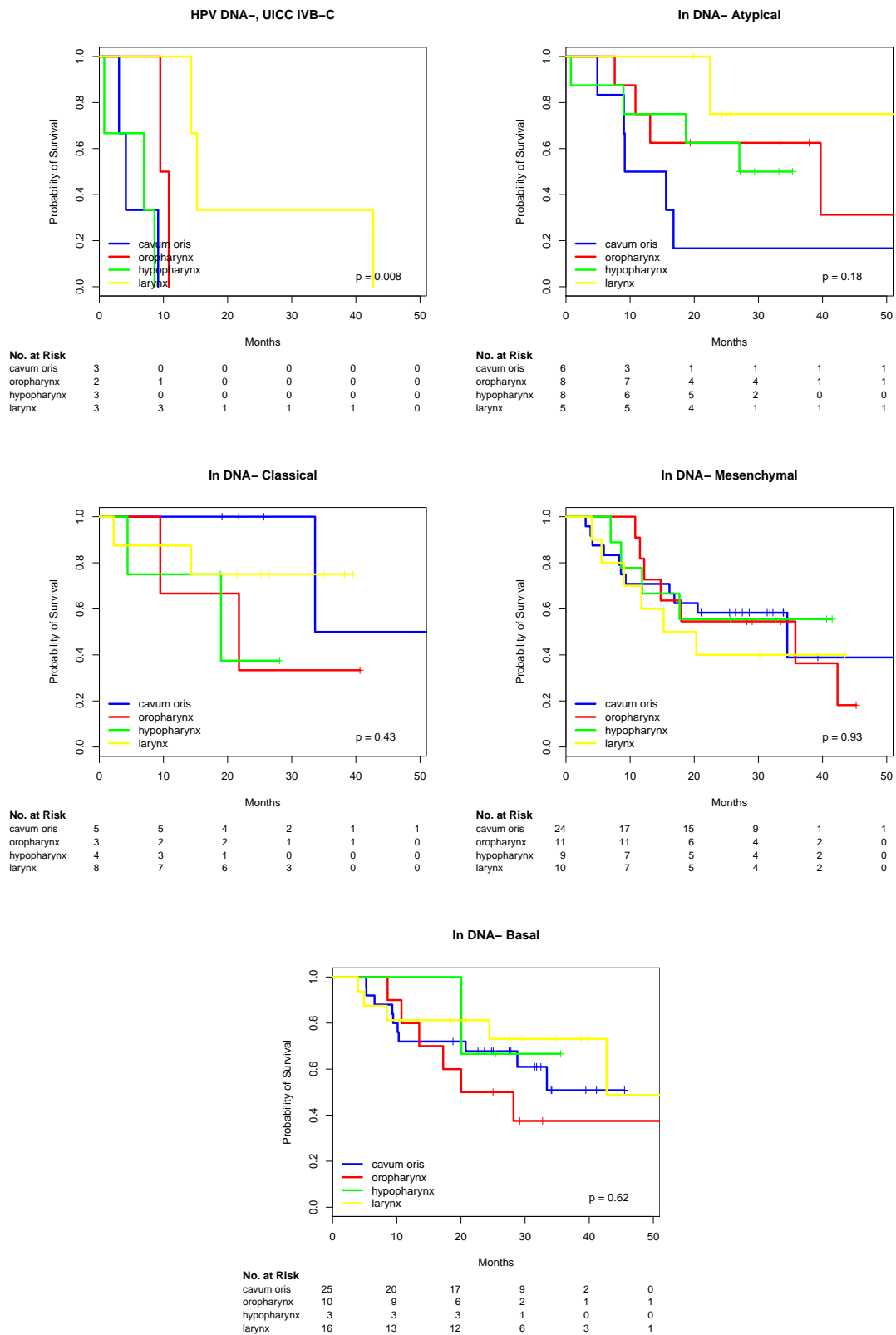
```



```
##
## Concordance= 0.526 (se = 0.035 )
## Rsquare= 0.015 (max possible= 0.986 )
## Likelihood ratio test= 2.3 on 3 df, p=0.513
## Wald test = 2.14 on 3 df, p=0.543
## Score (logrank) test = 2.18 on 3 df, p=0.537
```





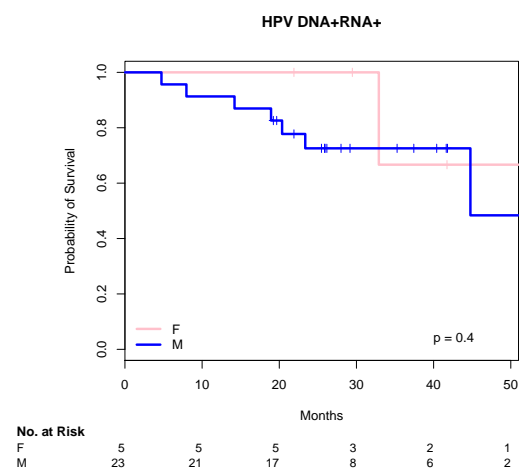
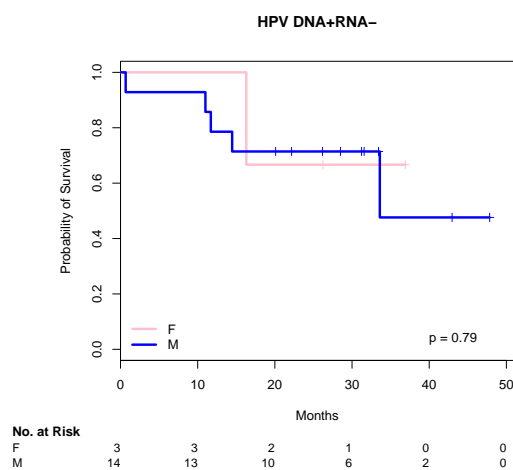
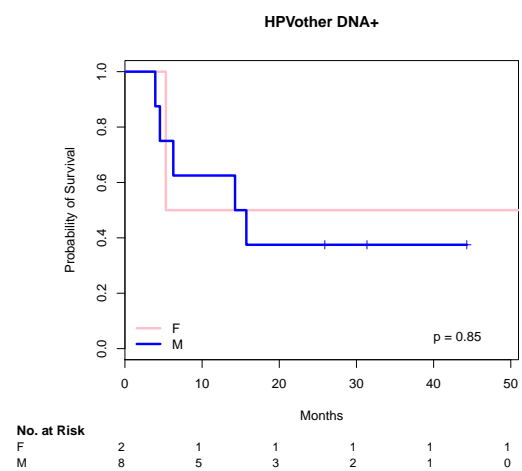
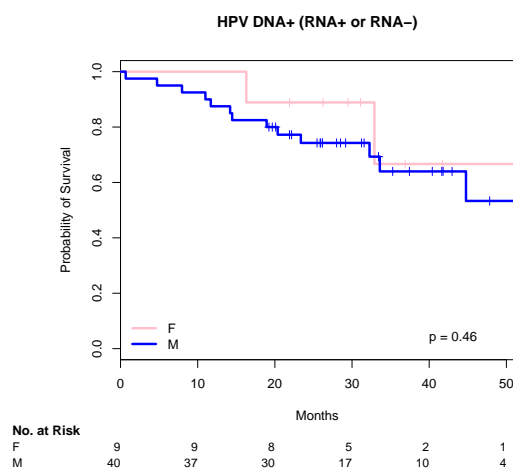
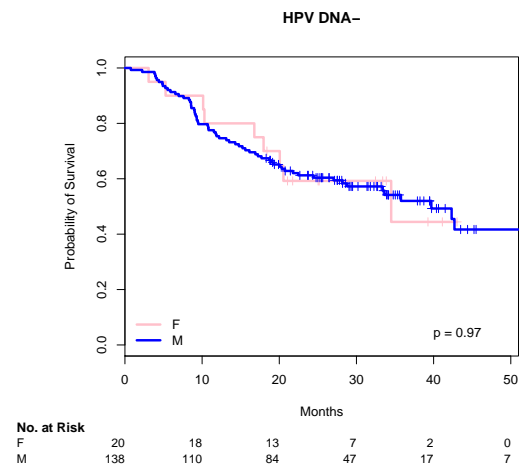
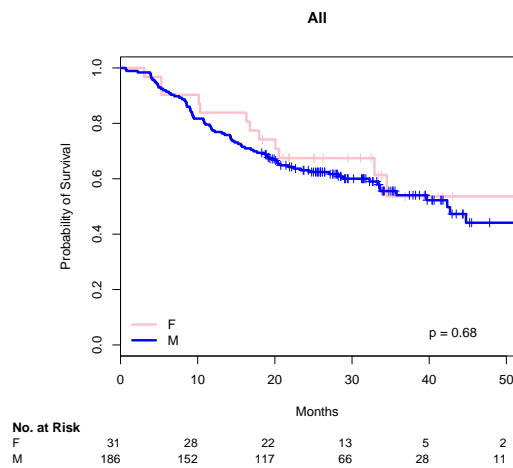


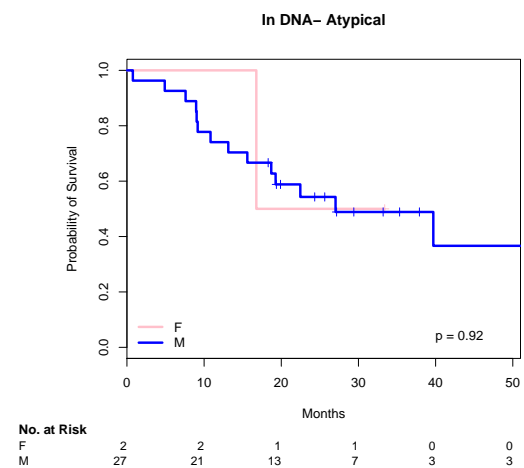
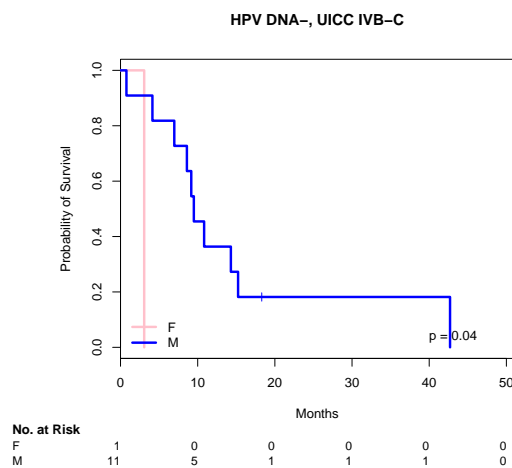
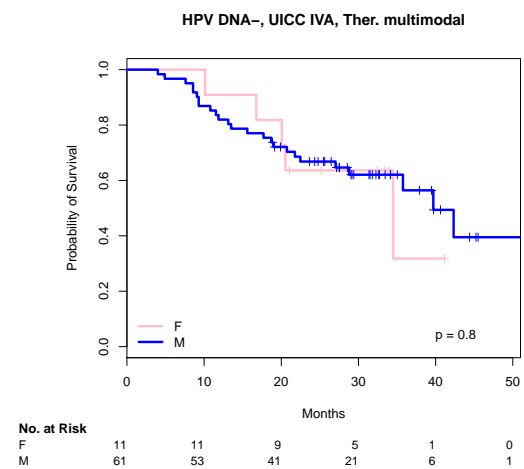
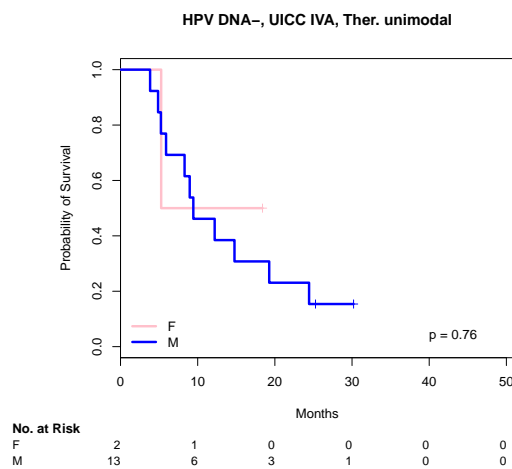
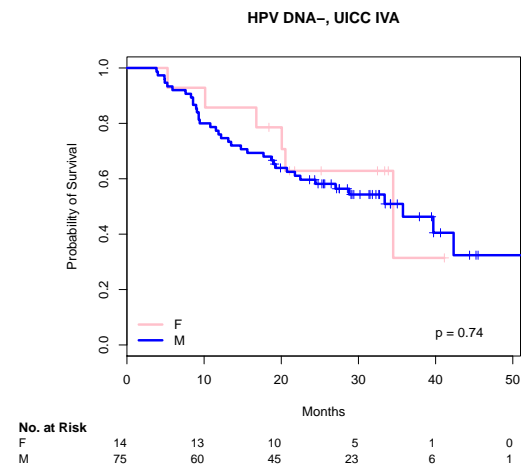
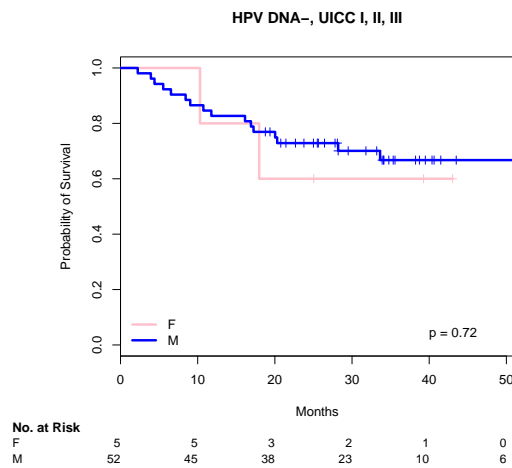
## 2.23 Sex

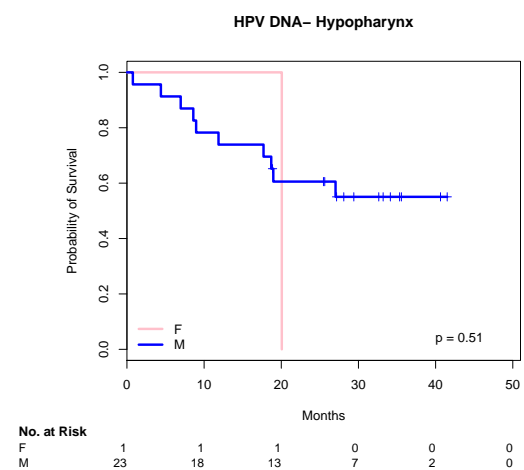
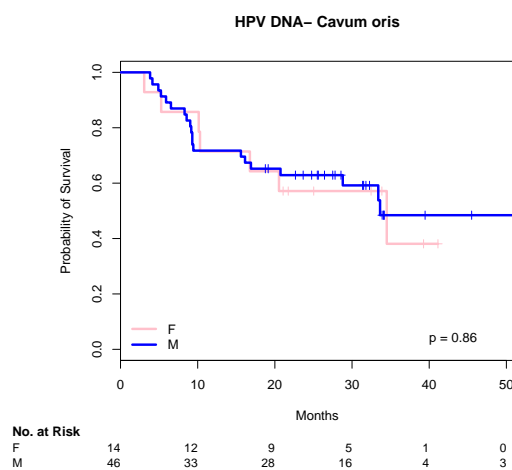
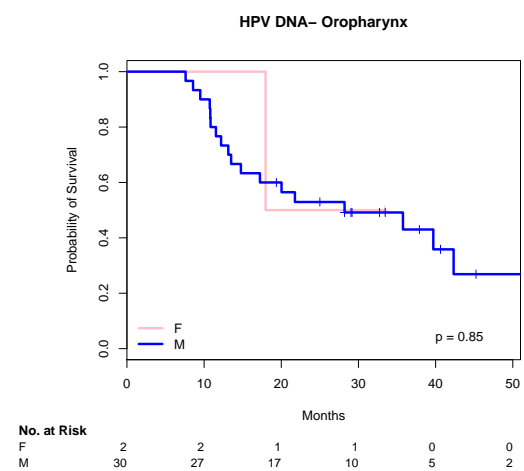
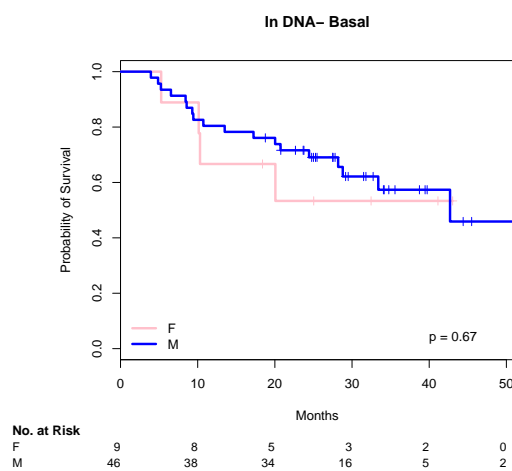
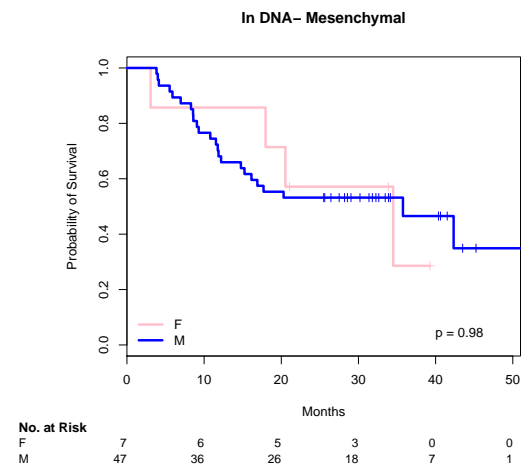
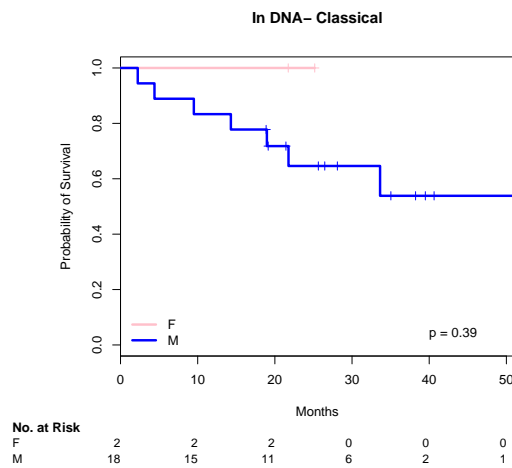
```

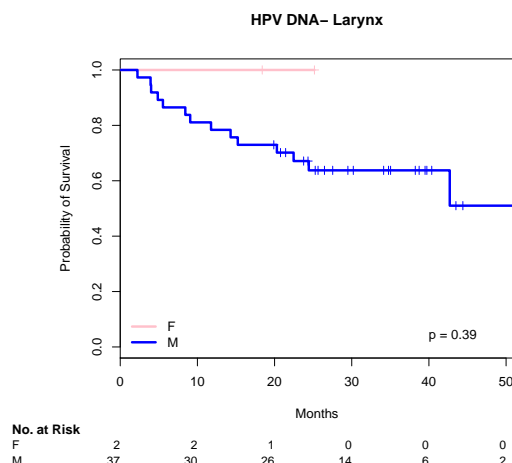
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M 0.123      1.131    0.298 0.41      0.68
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M      1.13      0.885      0.63      2.03
##
## Concordance= 0.513 (se = 0.019 )
## Rsquare= 0.001 (max possible= 0.987 )
## Likelihood ratio test= 0.17 on 1 df, p=0.676
## Wald test = 0.17 on 1 df, p=0.681
## Score (logrank) test = 0.17 on 1 df, p=0.681
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]M 0.015      1.015    0.357 0.04      0.97
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]M      1.02      0.985      0.505      2.04
##
## Concordance= 0.504 (se = 0.021 )
## Rsquare= 0 (max possible= 0.986 )
## Likelihood ratio test= 0 on 1 df, p=0.966
## Wald test = 0 on 1 df, p=0.967
## Score (logrank) test = 0 on 1 df, p=0.967

```







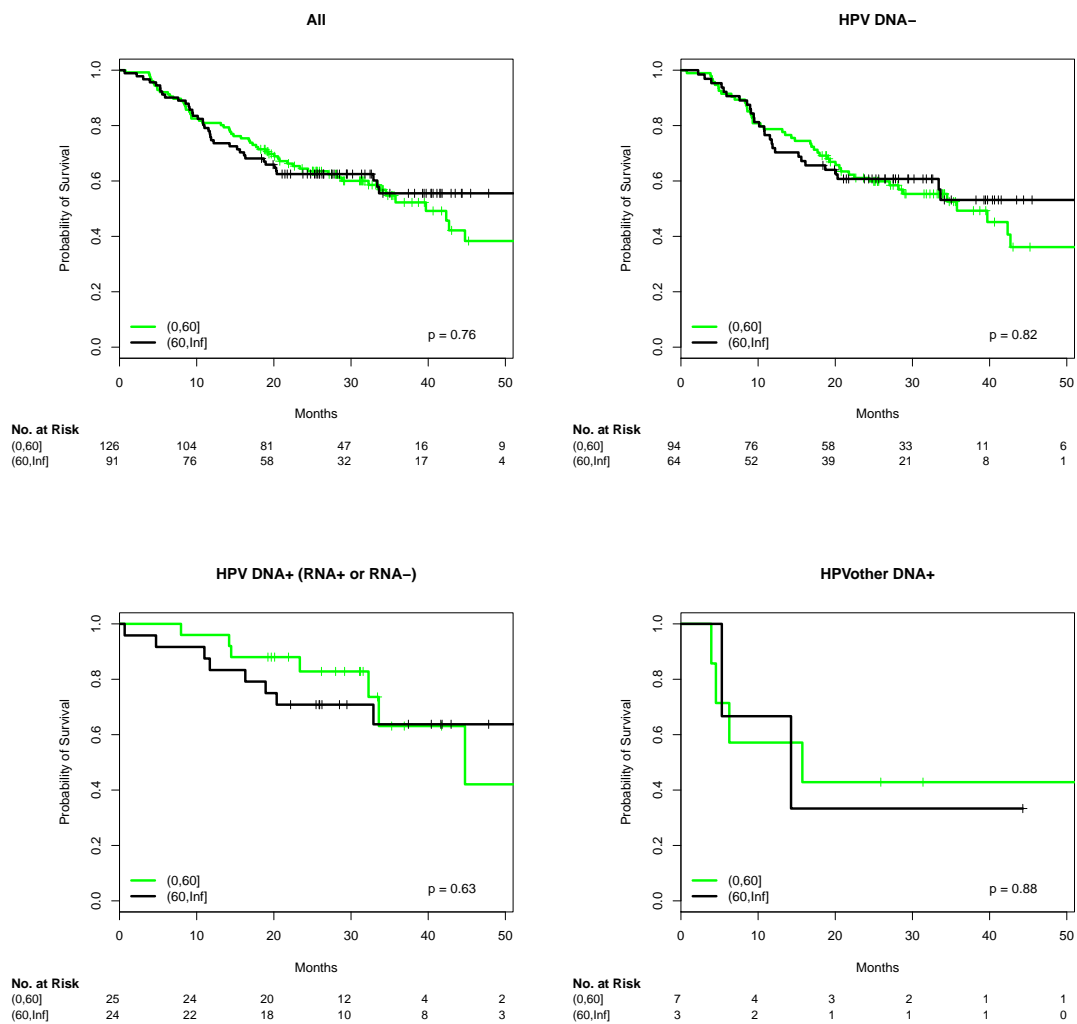


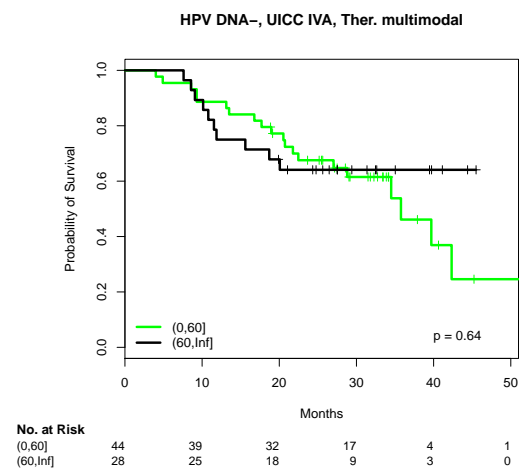
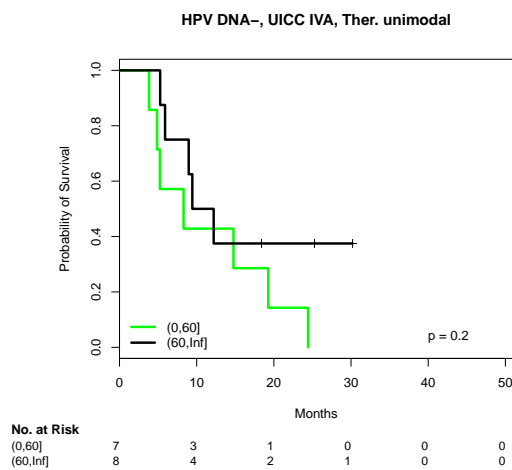
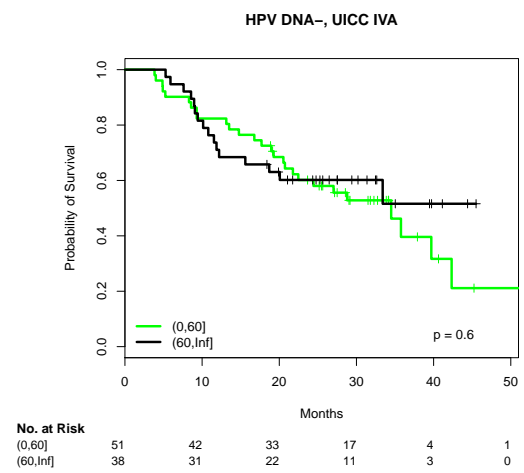
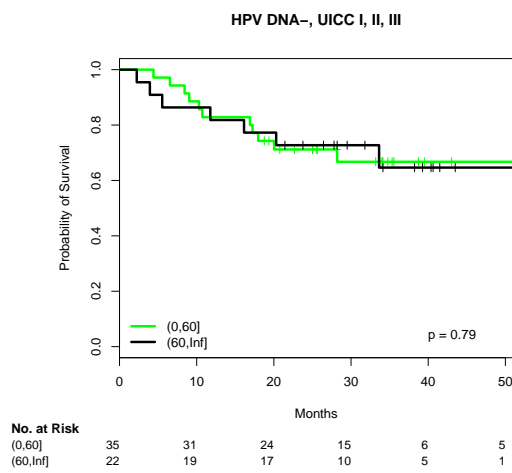
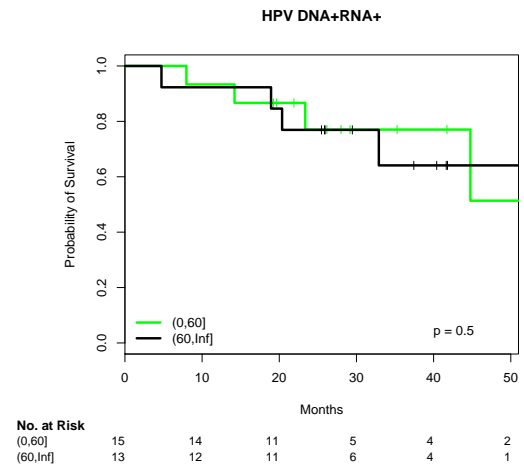
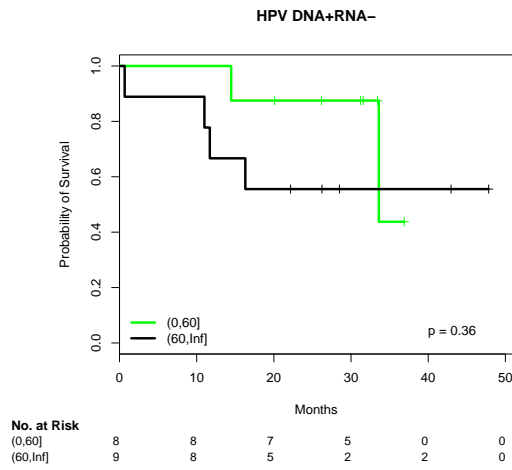
## 2.24 Age, cut at 60

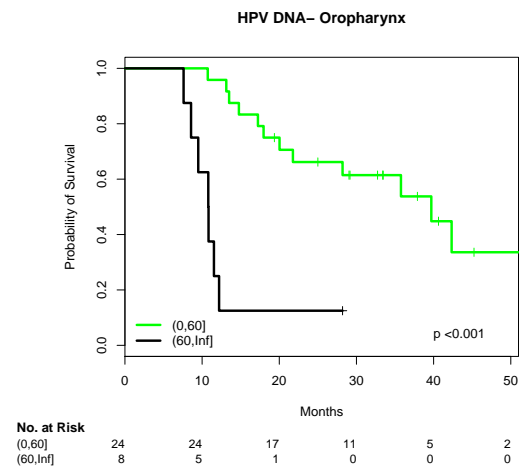
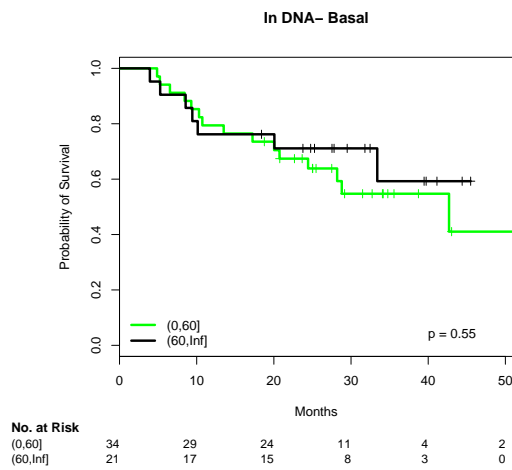
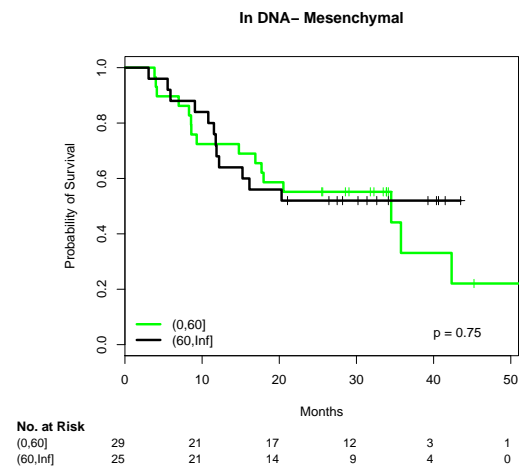
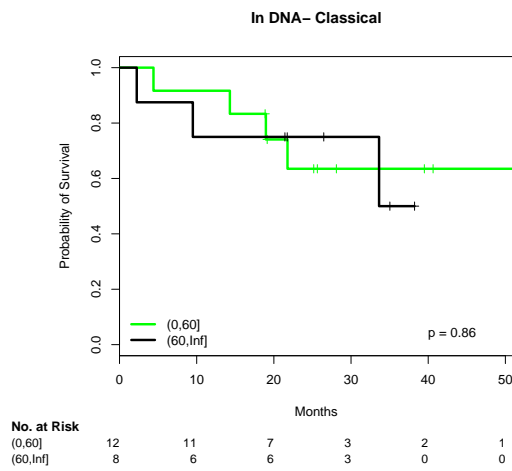
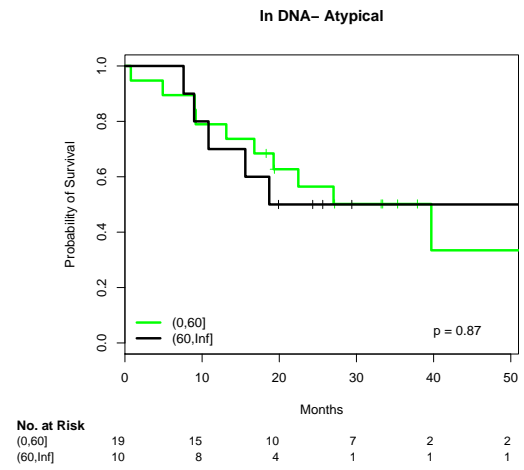
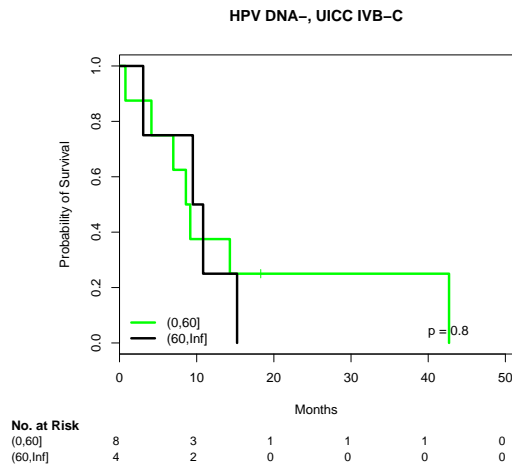
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](60,Inf) -0.0634    0.9385   0.2075 -0.31    0.76
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf)    0.939      1.07    0.625    1.41
##
## Concordance= 0.495 (se = 0.027 )
## Rsquare= 0 (max possible= 0.987 )
## Likelihood ratio test= 0.09 on 1 df, p=0.759
## Wald test = 0.09 on 1 df, p=0.76
## Score (logrank) test = 0.09 on 1 df, p=0.76
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
```

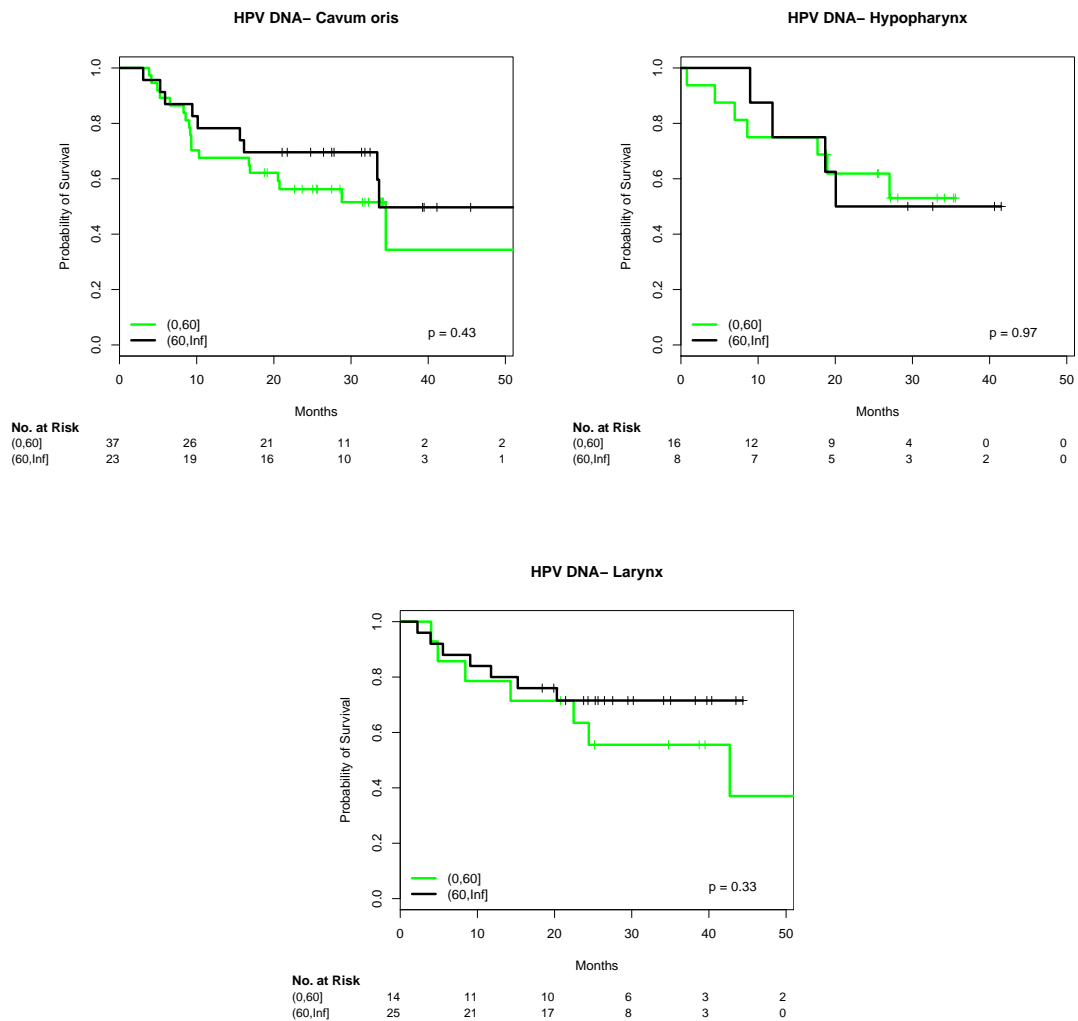


```
## split[cur.subset](60,Inf] -0.0562    0.9454    0.2403 -0.23    0.82
##
##                                exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](60,Inf]      0.945      1.06      0.59      1.51
##
## Concordance= 0.499  (se = 0.031 )
## Rsquare= 0      (max possible= 0.986 )
## Likelihood ratio test= 0.05  on 1 df,   p=0.815
## Wald test            = 0.05  on 1 df,   p=0.815
## Score (logrank) test = 0.05  on 1 df,   p=0.815
```





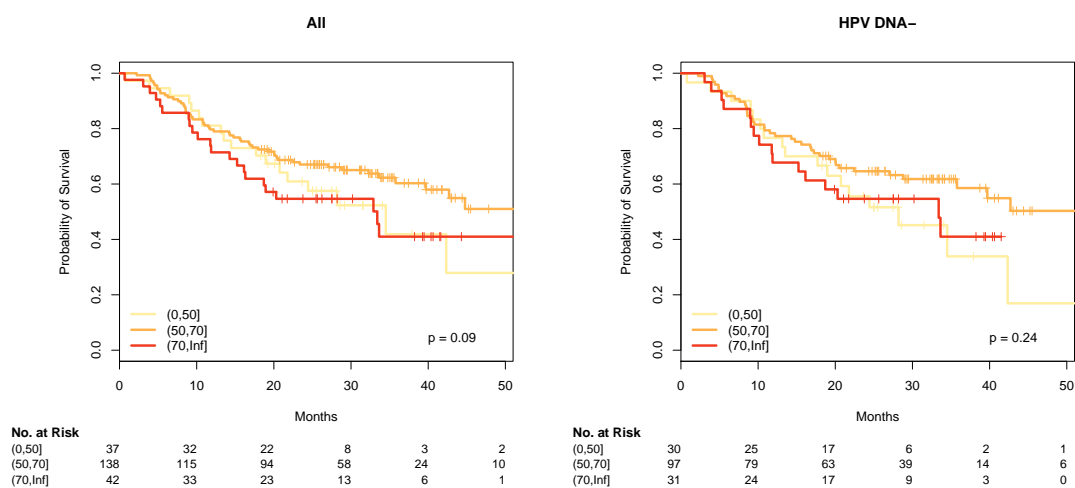


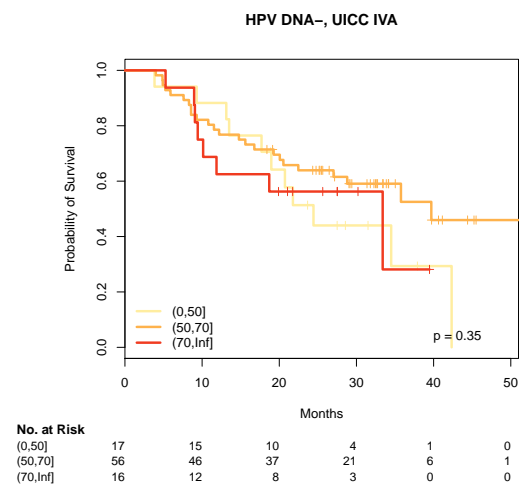
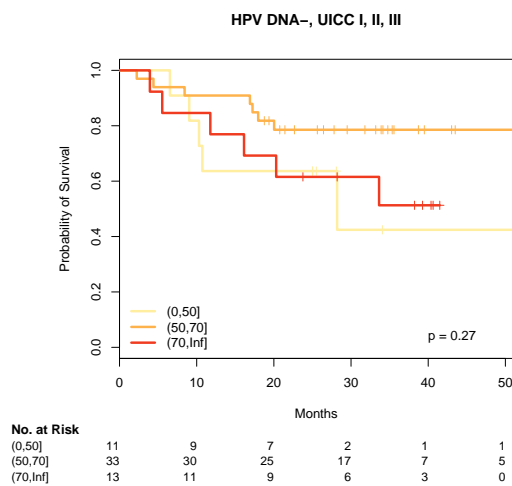
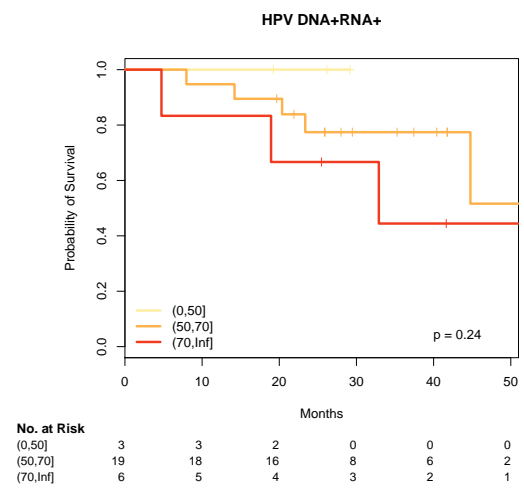
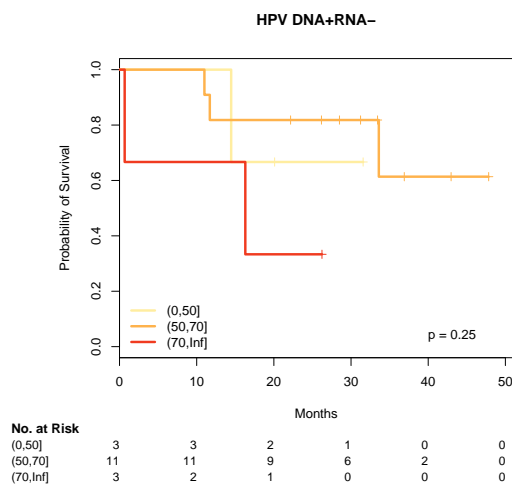
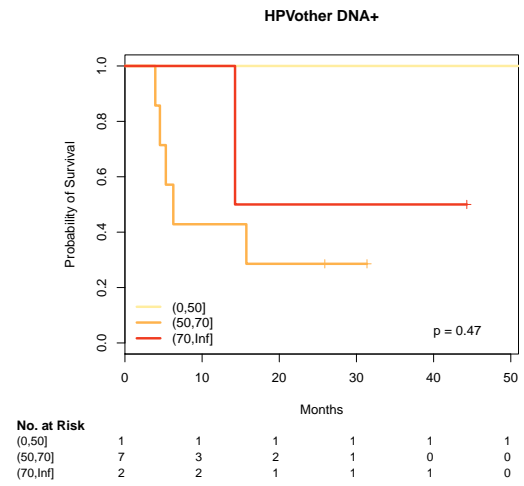
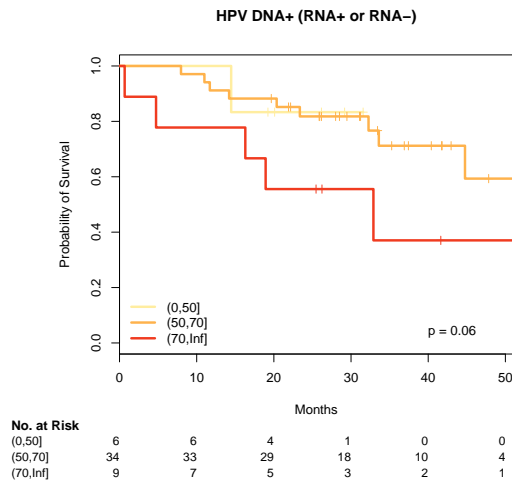


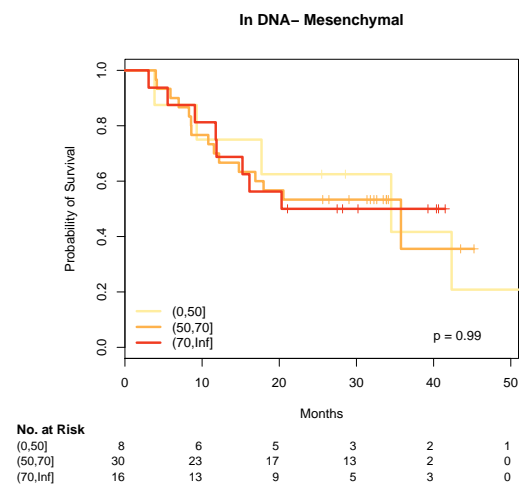
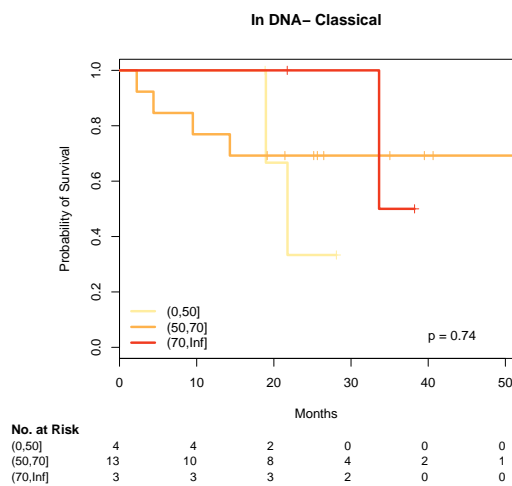
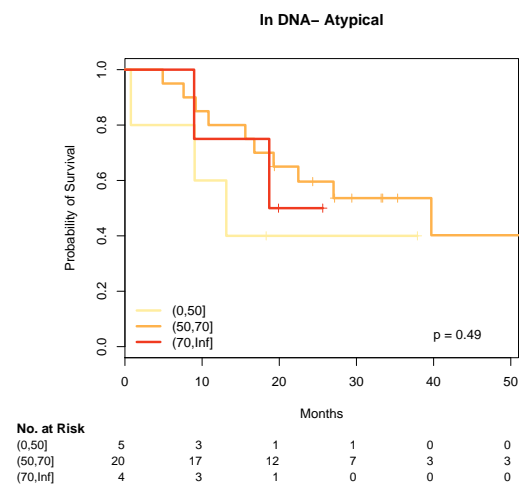
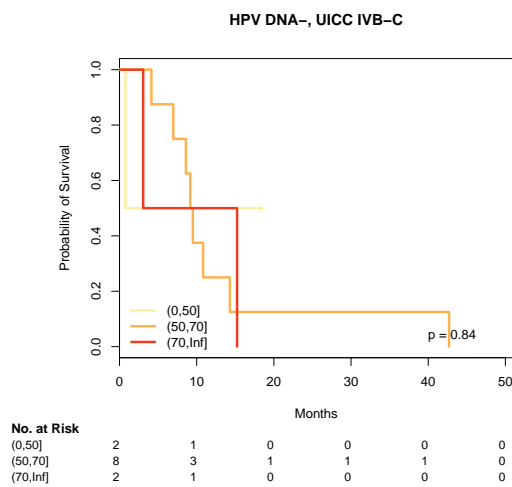
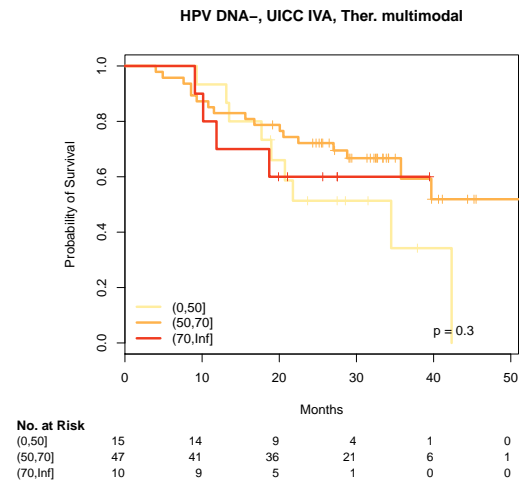
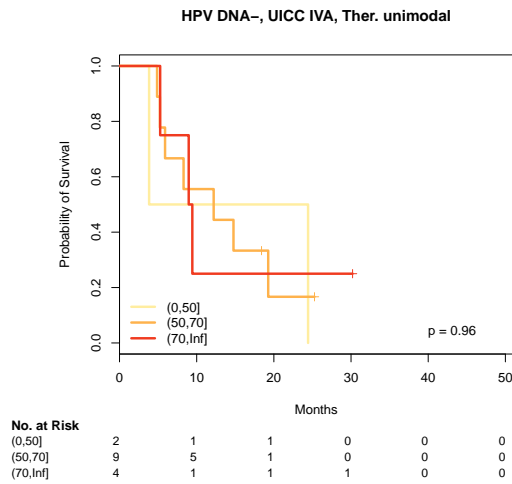
## 2.25 Age, cut at 50, 70

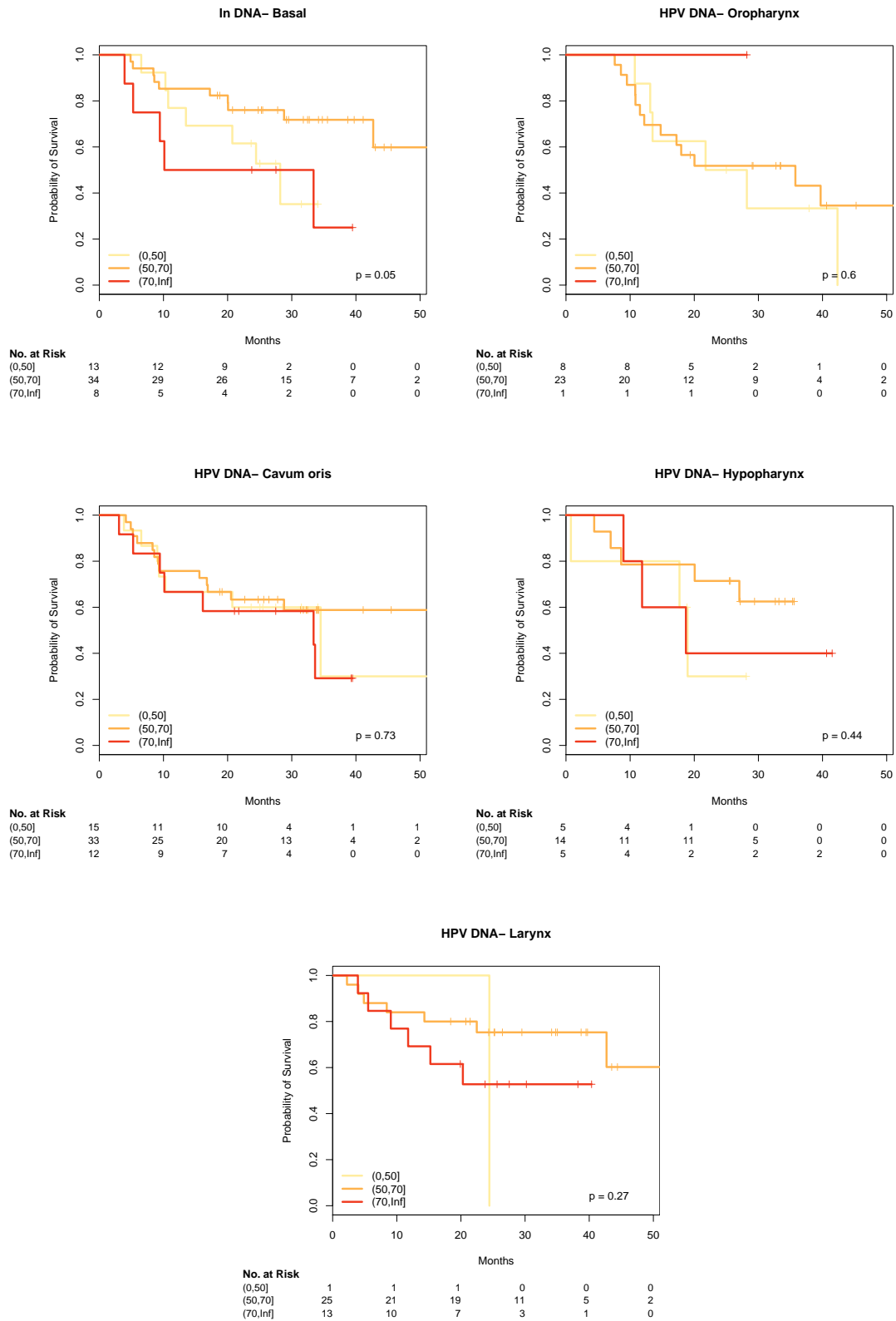
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70) -0.353    0.703   0.267 -1.32    0.19
## split[cur.subset](70,Inf)  0.149    1.160   0.312  0.48    0.63
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70)    0.703    1.423    0.416    1.19
## split[cur.subset](70,Inf)    1.160    0.862    0.630    2.14
```

```
##
## Concordance= 0.545 (se = 0.027 )
## Rsquare= 0.021 (max possible= 0.987 )
## Likelihood ratio test= 4.51 on 2 df, p=0.105
## Wald test = 4.67 on 2 df, p=0.0968
## Score (logrank) test = 4.75 on 2 df, p=0.093
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset](50,70) -0.4100  0.6636  0.2901 -1.41  0.16
## split[cur.subset](70,Inf) -0.0248  0.9755  0.3501 -0.07  0.94
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset](50,70)  0.664      1.51  0.376  1.17
## split[cur.subset](70,Inf)  0.976      1.03  0.491  1.94
##
## Concordance= 0.538 (se = 0.031 )
## Rsquare= 0.018 (max possible= 0.986 )
## Likelihood ratio test= 2.8 on 2 df, p=0.247
## Wald test = 2.85 on 2 df, p=0.24
## Score (logrank) test = 2.89 on 2 df, p=0.236
```









## 2.26 Age, Pack-years

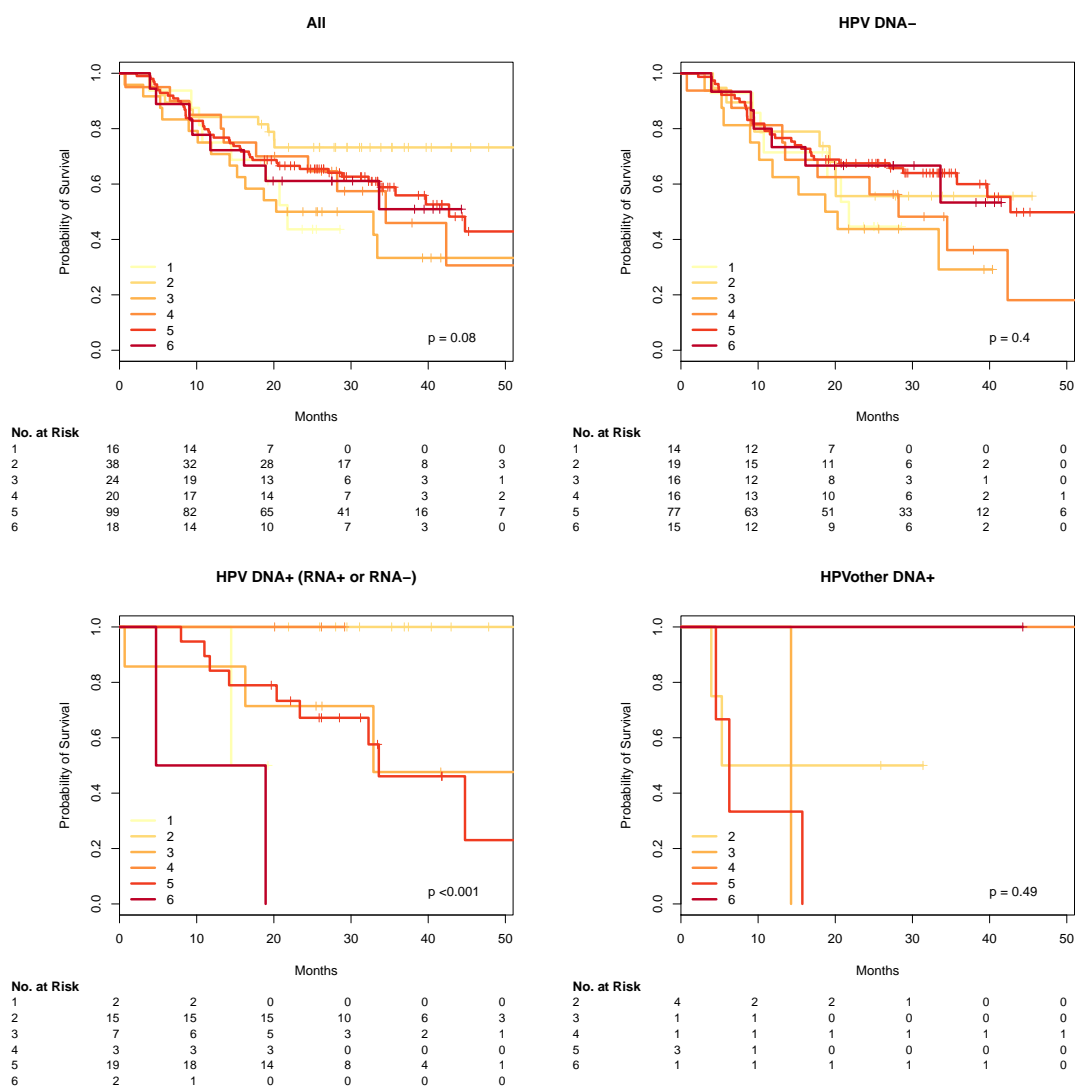


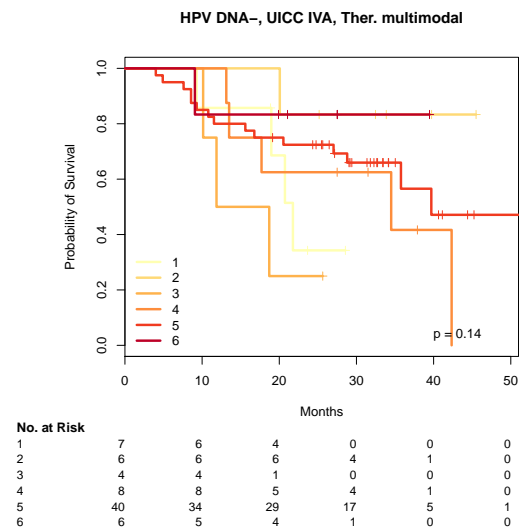
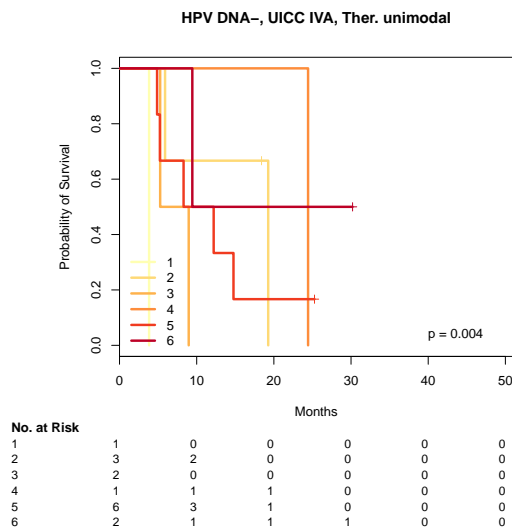
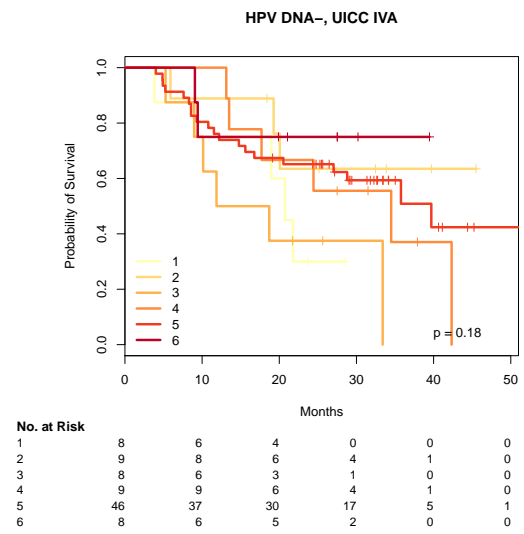
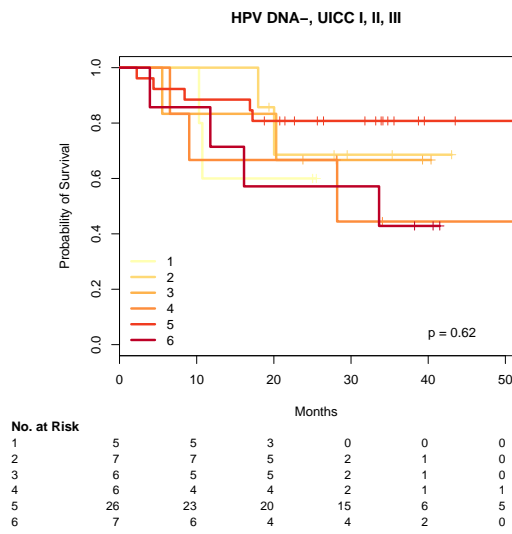
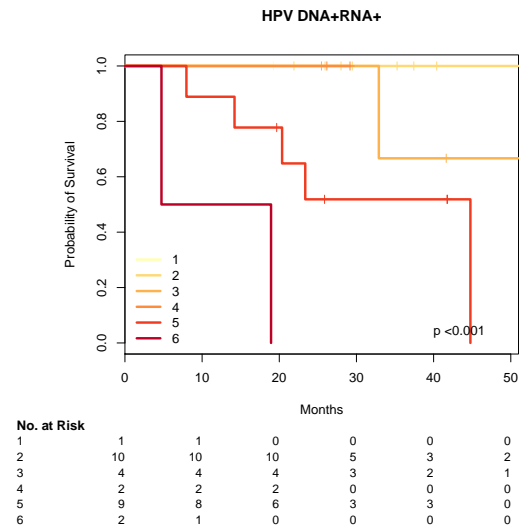
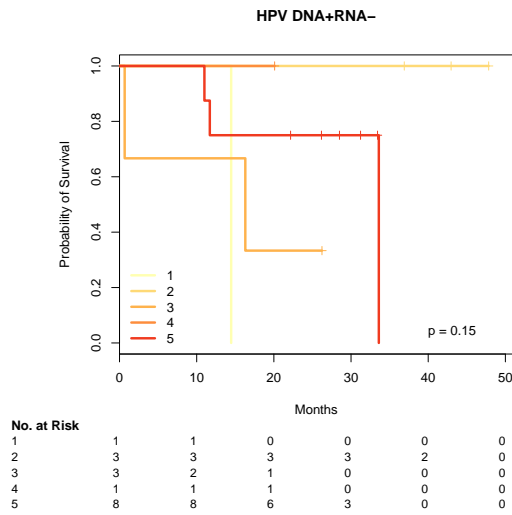
```

## 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= 98
## (2 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -1.067      0.344    0.480 -2.22    0.026 *
## split[cur.subset]3  0.123      1.131    0.440  0.28    0.779
## split[cur.subset]4 -0.267      0.766    0.470 -0.57    0.571
## split[cur.subset]5 -0.405      0.667    0.388 -1.04    0.297
## split[cur.subset]6 -0.303      0.739    0.503 -0.60    0.547
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.344      2.907      0.134      0.882
## split[cur.subset]3      1.131      0.884      0.478      2.678
## split[cur.subset]4      0.766      1.305      0.305      1.926
## split[cur.subset]5      0.667      1.500      0.311      1.428
## split[cur.subset]6      0.739      1.353      0.276      1.978
##
## Concordance= 0.565 (se = 0.03 )
## Rsquare= 0.047 (max possible= 0.987 )
## Likelihood ratio test= 10.3 on 5 df,  p=0.0682
## Wald test              = 9.47 on 5 df,  p=0.0917
## Score (logrank) test = 10 on 5 df,  p=0.0753
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 157, number of events= 73
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]2 -0.3715      0.6897    0.5202 -0.71    0.48
## split[cur.subset]3  0.2477      1.2811    0.4938  0.50    0.62
## split[cur.subset]4 -0.0393      0.9615    0.4986 -0.08    0.94
## split[cur.subset]5 -0.4666      0.6272    0.4232 -1.10    0.27
## split[cur.subset]6 -0.4043      0.6675    0.5589 -0.72    0.47
##

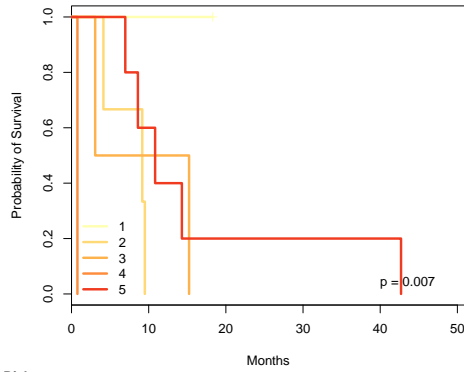
```

```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]2      0.690      1.450      0.249      1.91
## split[cur.subset]3      1.281      0.781      0.487      3.37
## split[cur.subset]4      0.962      1.040      0.362      2.55
## split[cur.subset]5      0.627      1.595      0.274      1.44
## split[cur.subset]6      0.667      1.498      0.223      2.00
##
## Concordance= 0.556 (se = 0.034 )
## Rsquare= 0.029 (max possible= 0.985 )
## Likelihood ratio test= 4.66 on 5 df, p=0.458
## Wald test = 5.02 on 5 df, p=0.414
## Score (logrank) test = 5.16 on 5 df, p=0.396
```





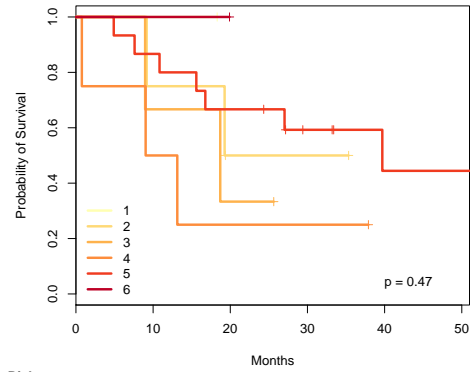
HPV DNA-, UICC IVB-C



No. at Risk

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

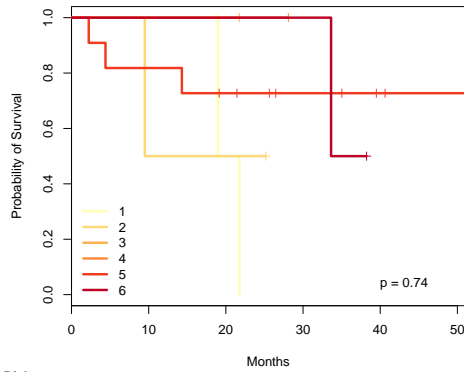
In DNA- Atypical



No. at Risk

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

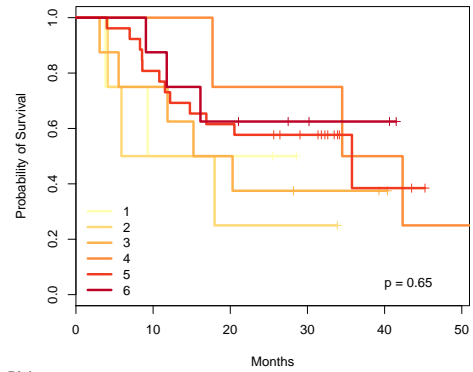
In DNA- Classical



No. at Risk

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

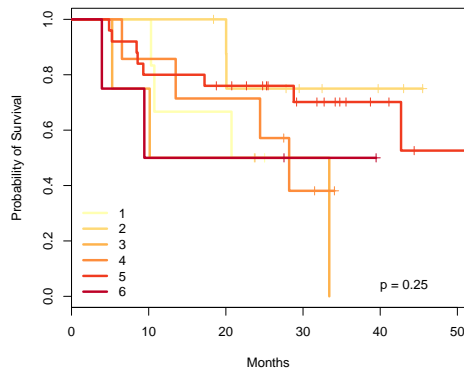
In DNA- Mesenchymal



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	4	2	2	0	0
2	4	2	1	1	0
3	8	6	4	2	1
4	4	4	3	3	2
5	26	21	16	12	2
6	8	7	5	3	2

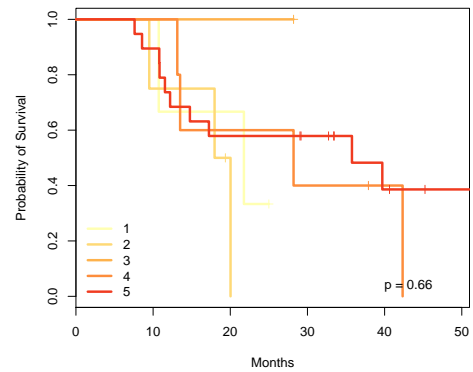
In DNA- Basal



No. at Risk

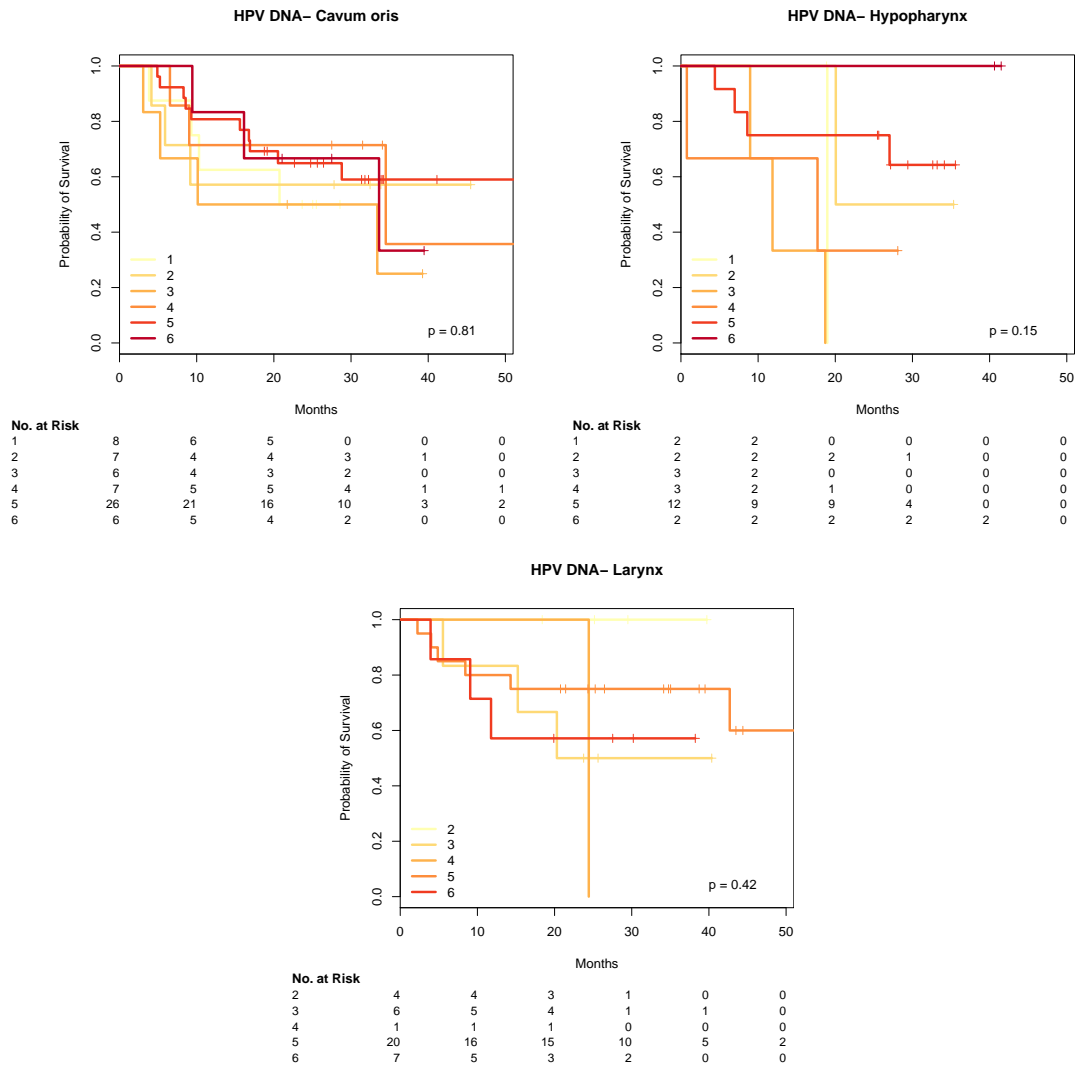
	0-10	10-20	20-30	30-40	40-50
1	6	6	4	0	0
2	9	9	8	4	2
3	4	3	2	1	0
4	7	6	5	2	0
5	25	20	18	11	5
6	4	2	2	1	0

HPV DNA- Oropharynx



No. at Risk

	0-10	10-20	20-30	30-40	40-50
1	3	3	2	0	0
2	4	3	1	0	0
3	1	1	1	0	0
4	5	5	3	2	1
5	19	17	11	9	4



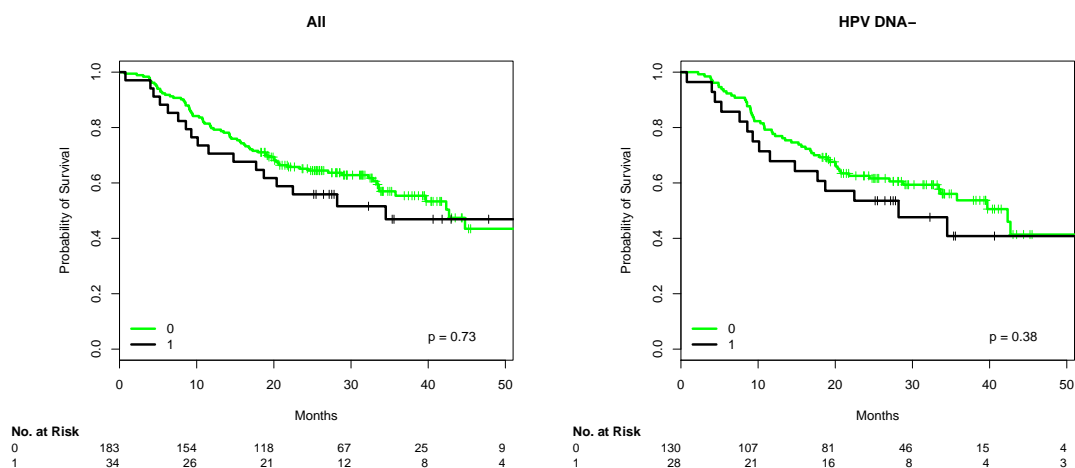
## 2.27 Mutational complexity

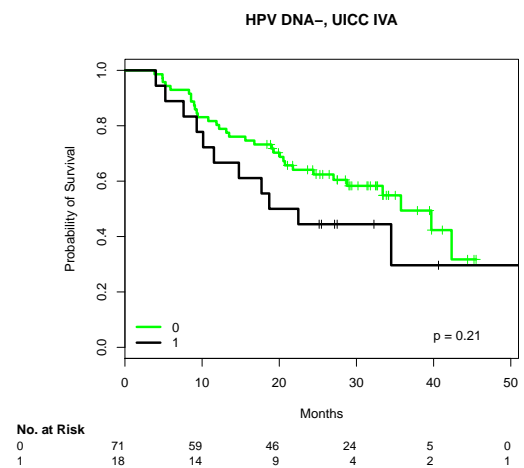
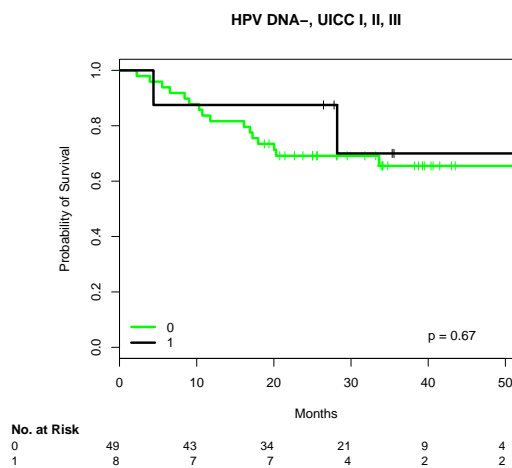
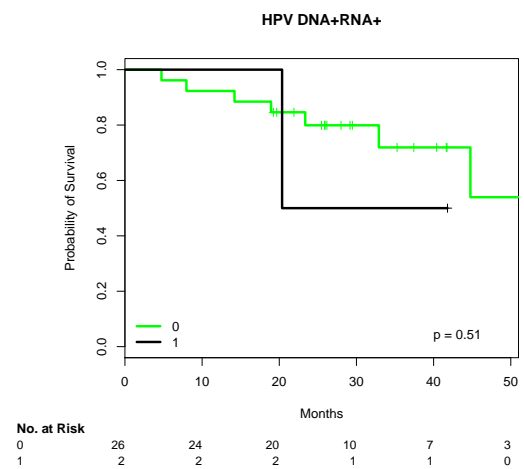
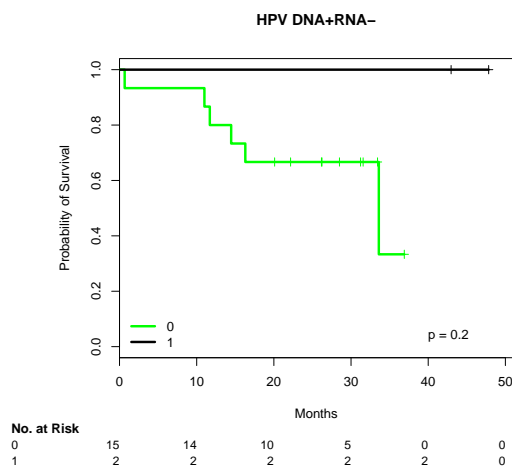
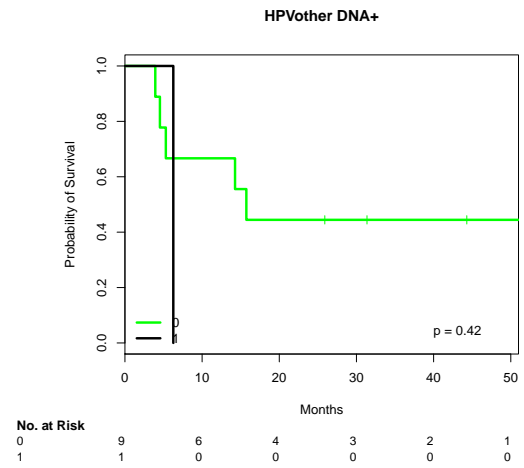
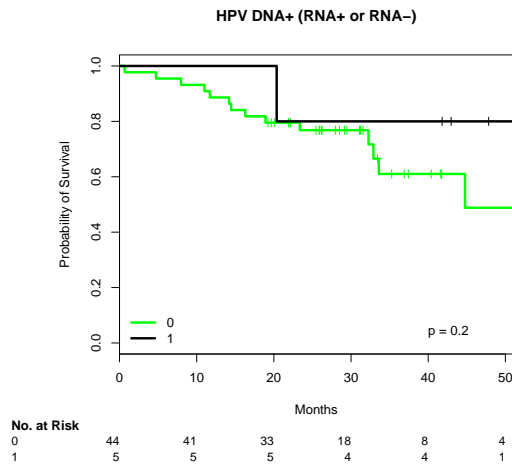
Equal to 1, if the number of mutated genes is greater than the median and 0 else.

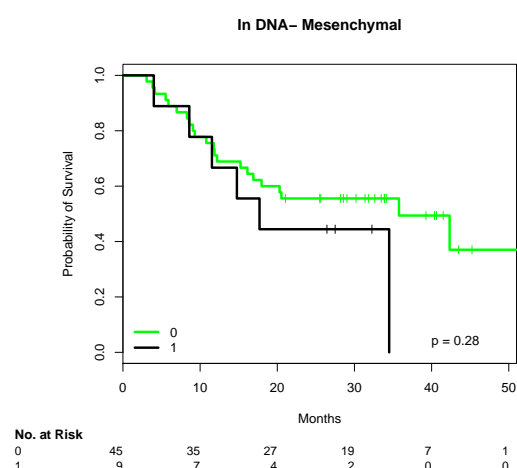
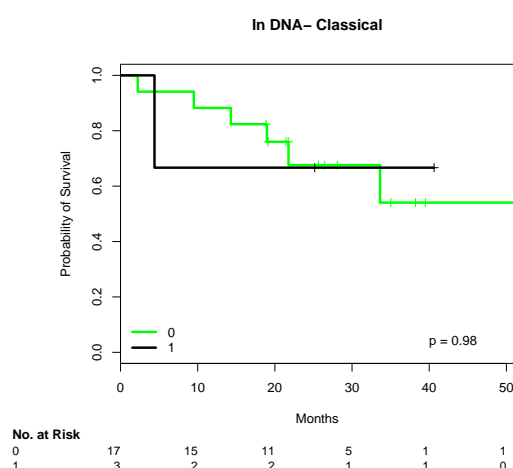
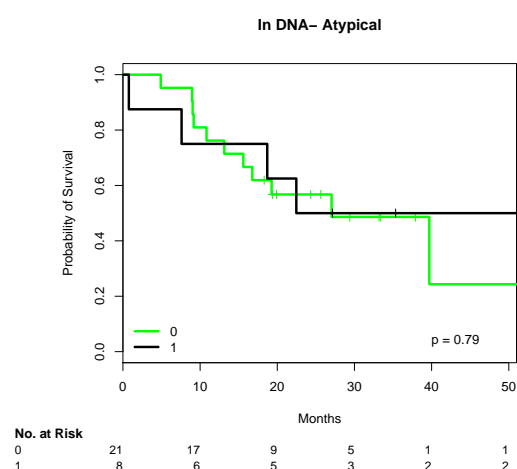
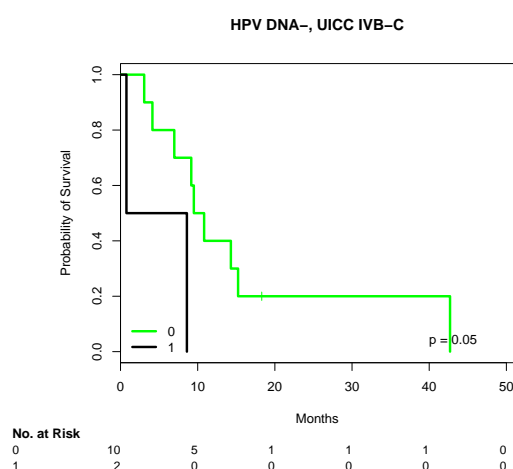
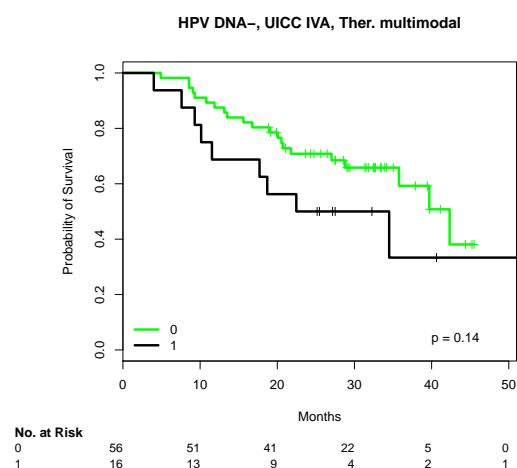
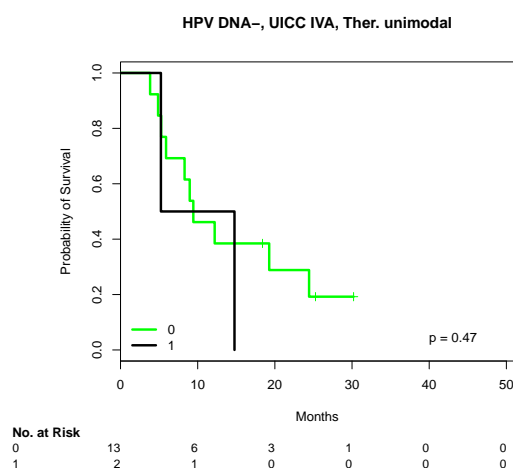
```
## Error: There is only 1 group
## Error: There is only 1 group

##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)    z Pr(>|z|)
## split[cur.subset] 0.0925    1.0969  0.2661 0.35    0.73
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.1      0.912    0.651    1.85
```

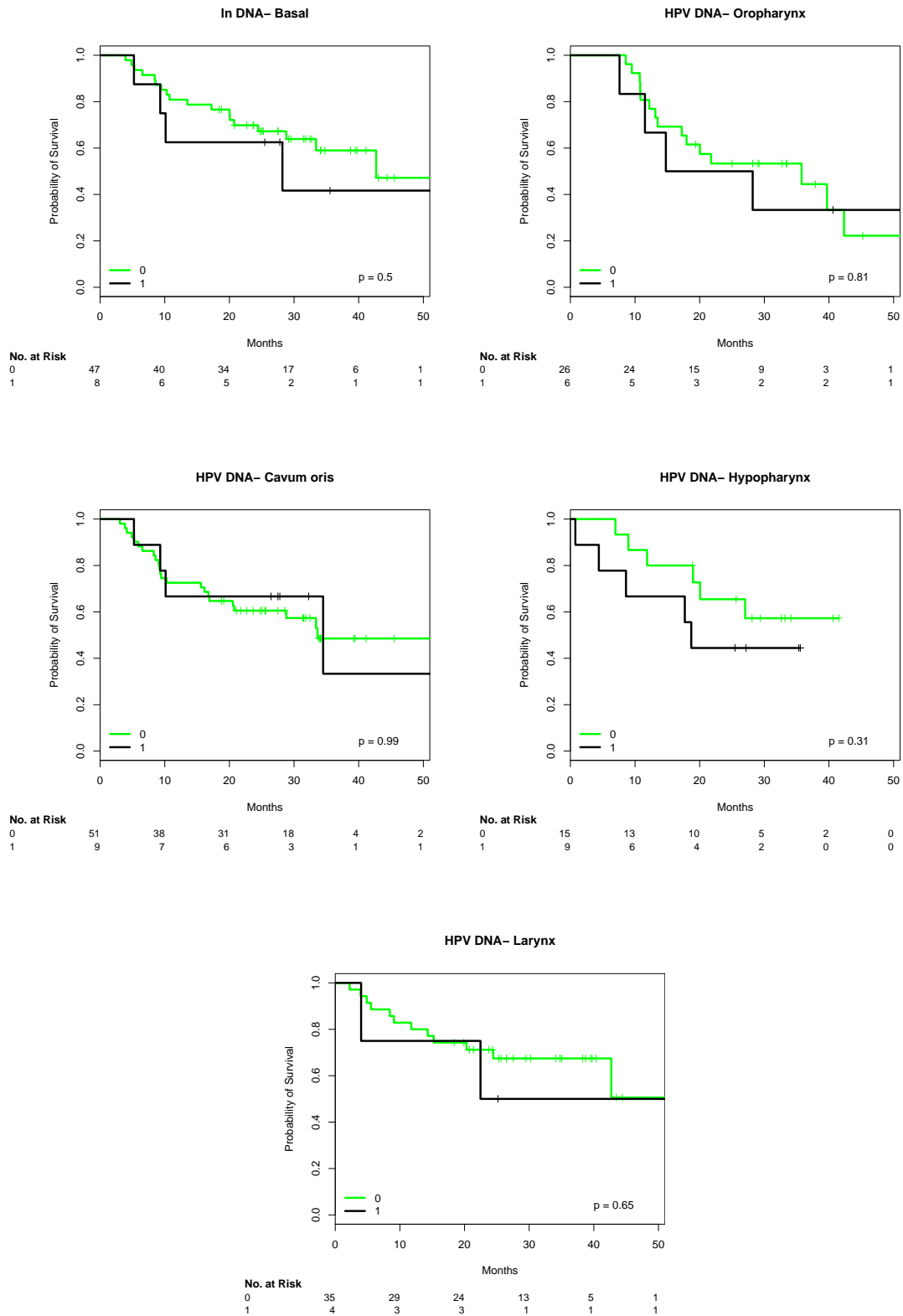
```
##
## Concordance= 0.521 (se = 0.019 )
## Rsquare= 0.001 (max possible= 0.987 )
## Likelihood ratio test= 0.12 on 1 df, p=0.731
## Wald test = 0.12 on 1 df, p=0.728
## Score (logrank) test = 0.12 on 1 df, p=0.728
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.253      1.288   0.286 0.88    0.38
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.29      0.776   0.735    2.26
##
## Concordance= 0.526 (se = 0.023 )
## Rsquare= 0.005 (max possible= 0.986 )
## Likelihood ratio test= 0.74 on 1 df, p=0.388
## Wald test = 0.78 on 1 df, p=0.377
## Score (logrank) test = 0.78 on 1 df, p=0.376
```









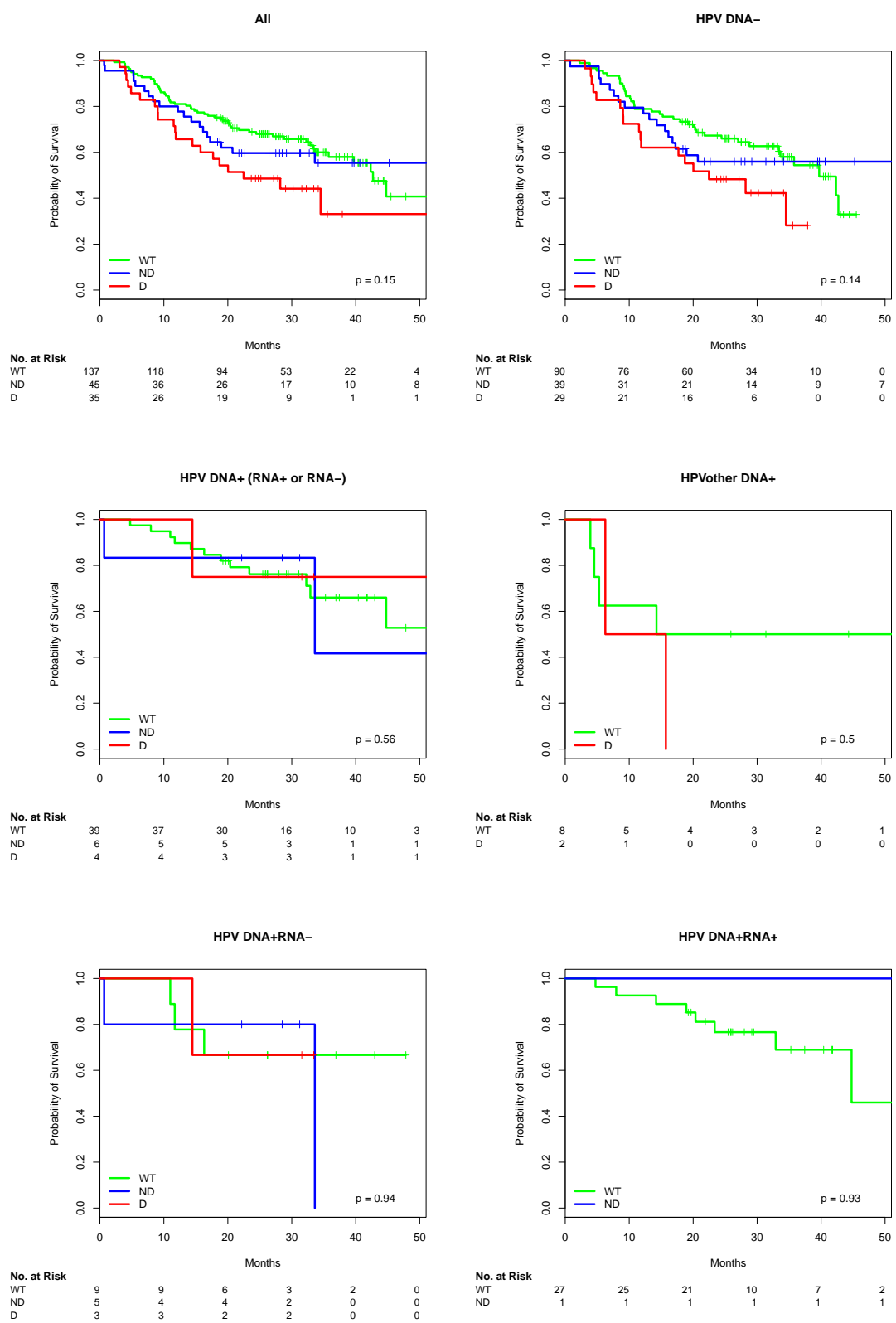


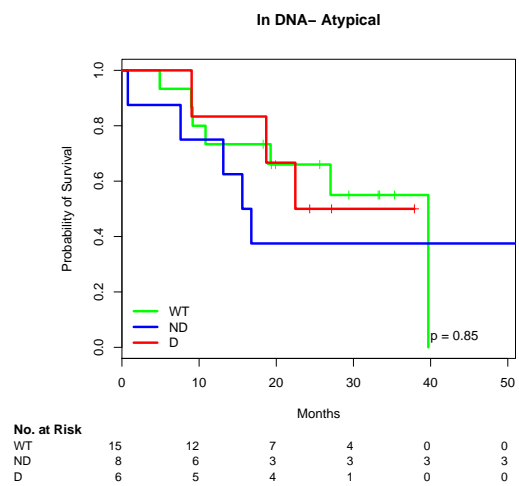
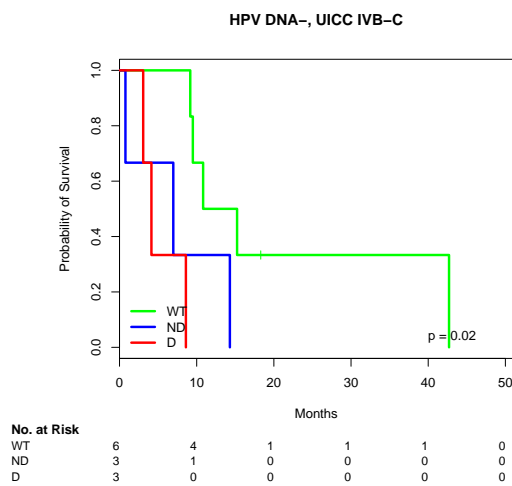
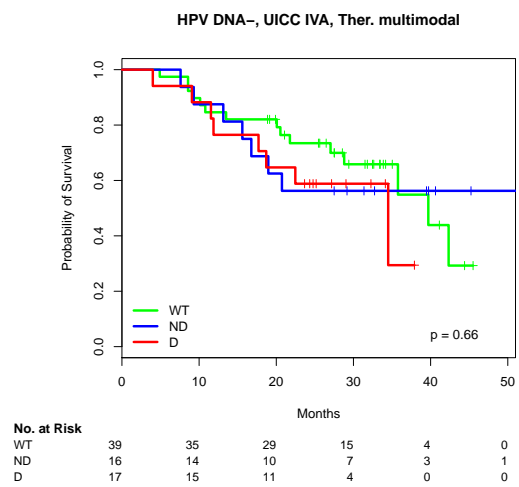
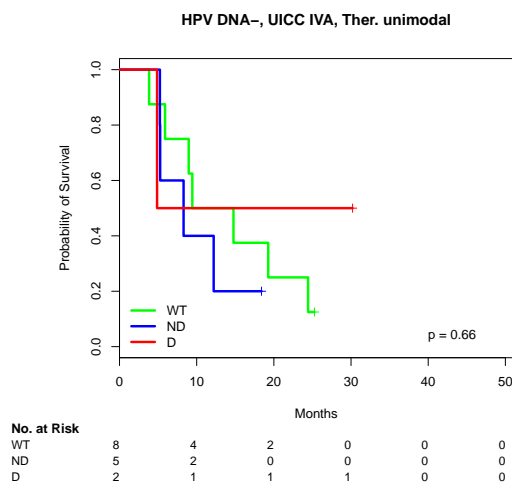
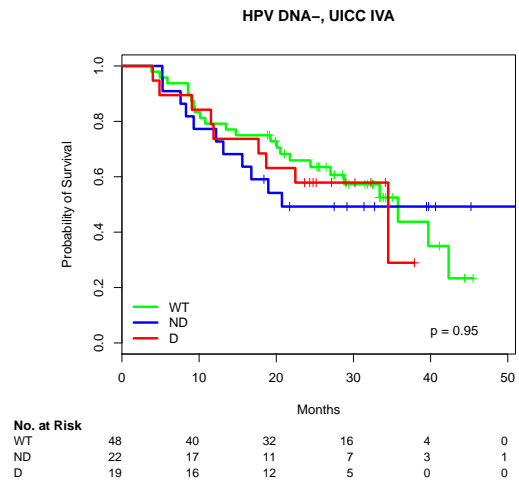
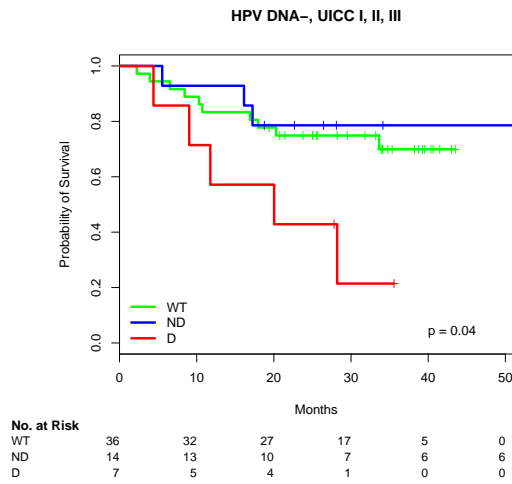
2.28 TP53: disruptive (D), non-disruptive (ND), wt as in Gross et al. (Nat Genet 2014) (frameshift treated as non-disruptive)

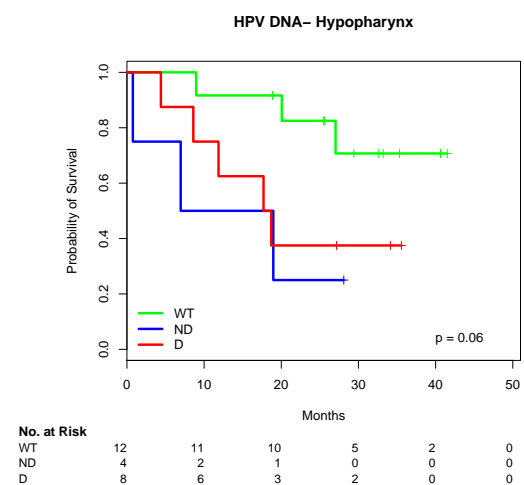
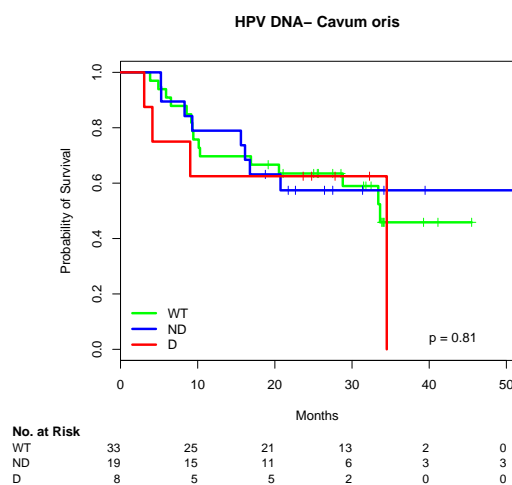
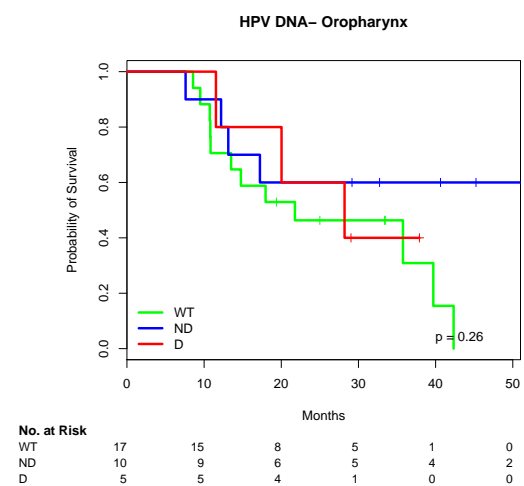
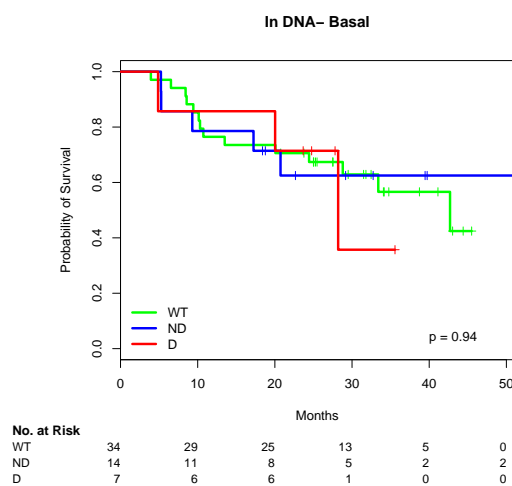
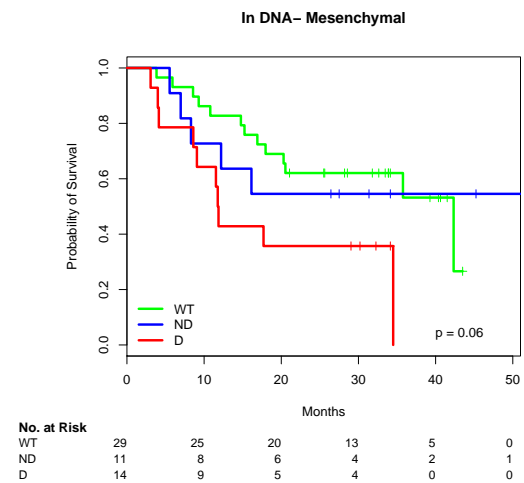
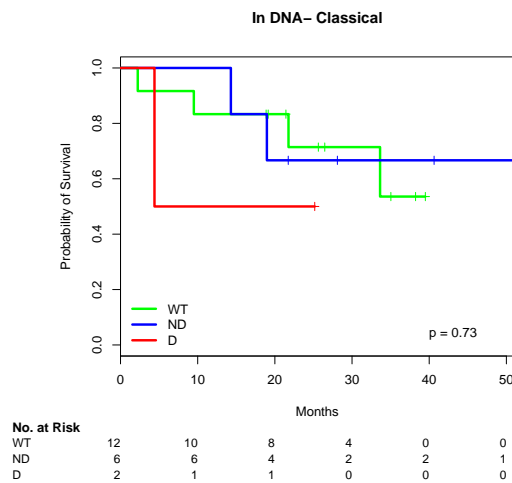
```

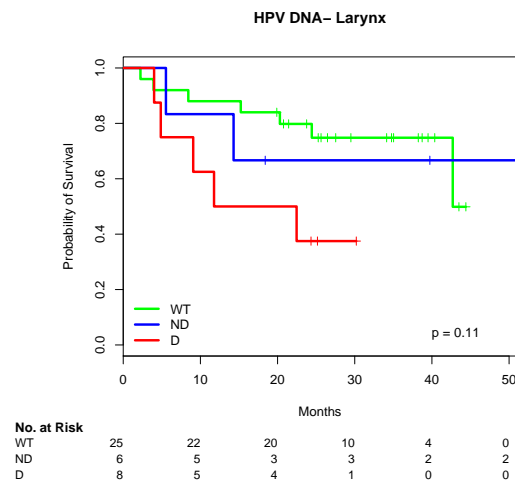
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND 0.116      1.123   0.257 0.45   0.650
## split[cur.subset]D  0.508      1.662   0.263 1.93   0.053 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND      1.12      0.890   0.679   1.86
## split[cur.subset]D      1.66      0.602   0.993   2.78
##
## Concordance= 0.56 (se = 0.027 )
## Rsquare= 0.016 (max possible= 0.987 )
## Likelihood ratio test= 3.44 on 2 df,  p=0.179
## Wald test               = 3.74 on 2 df,  p=0.154
## Score (logrank) test = 3.81 on 2 df,  p=0.149
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND 0.0232      1.0235   0.2948 0.08   0.937
## split[cur.subset]D  0.5594      1.7497   0.2932 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]ND      1.02      0.977   0.574   1.82
## split[cur.subset]D      1.75      0.572   0.985   3.11
##
## Concordance= 0.561 (se = 0.032 )
## Rsquare= 0.022 (max possible= 0.986 )
## Likelihood ratio test= 3.53 on 2 df,  p=0.171
## Wald test               = 3.89 on 2 df,  p=0.143
## Score (logrank) test = 3.99 on 2 df,  p=0.136

```





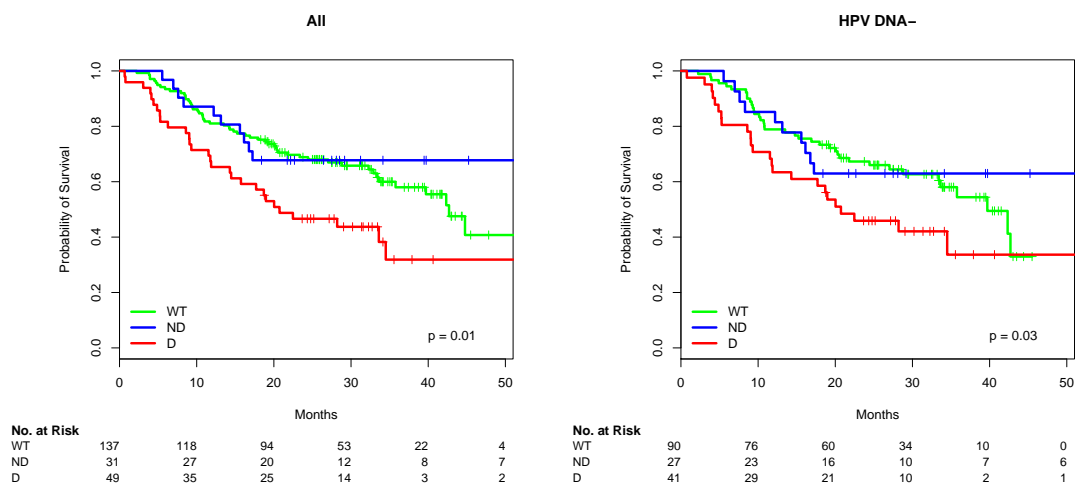


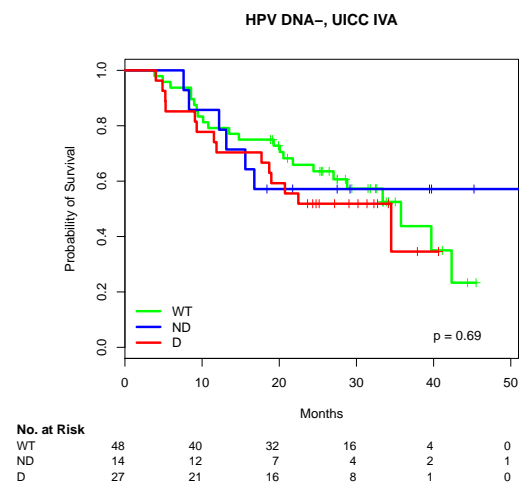
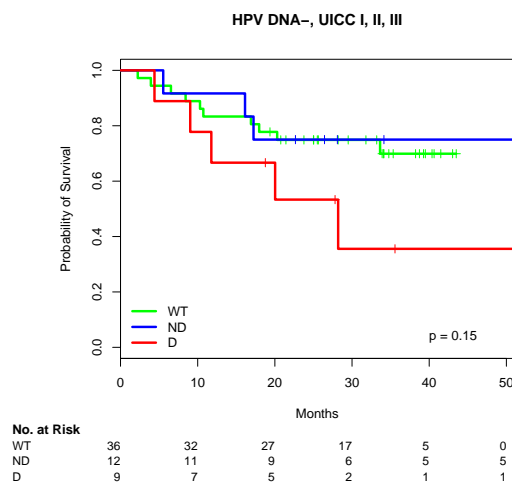
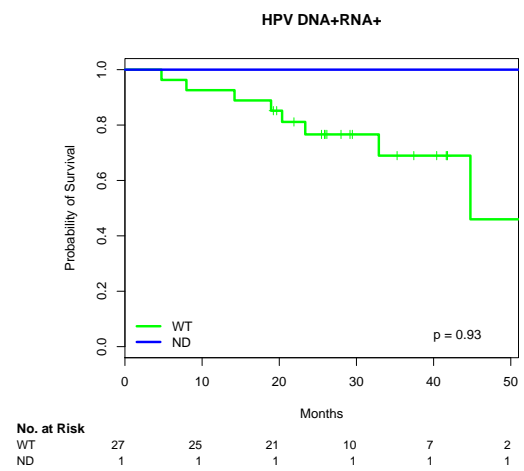
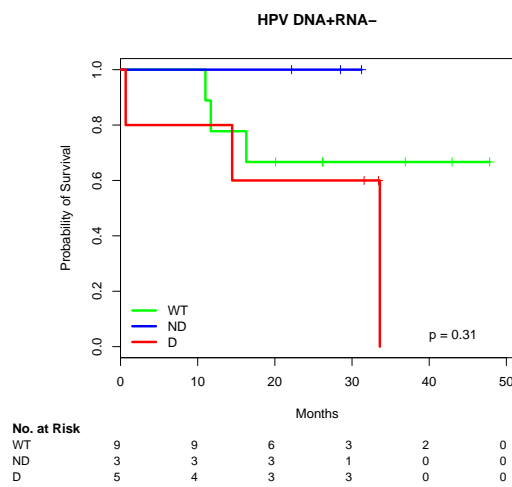
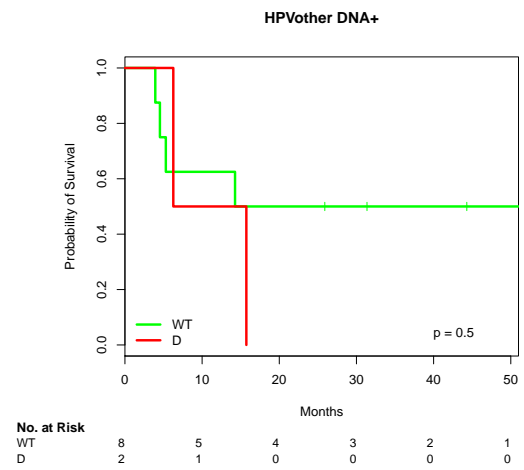
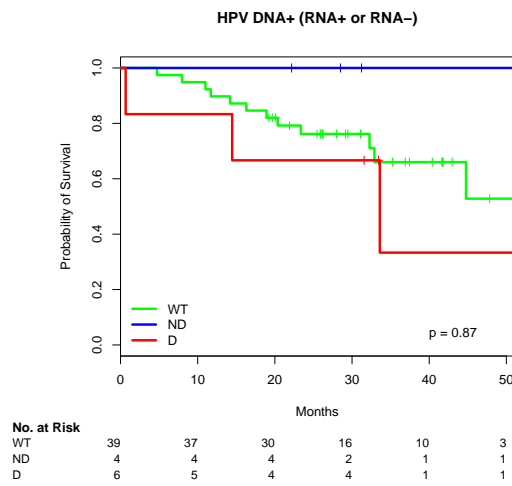


## 2.29 TP53: disruptive (D), non-disruptive (ND), wt with the convention that frameshift is treated as disruptive (following advice of David Masica)

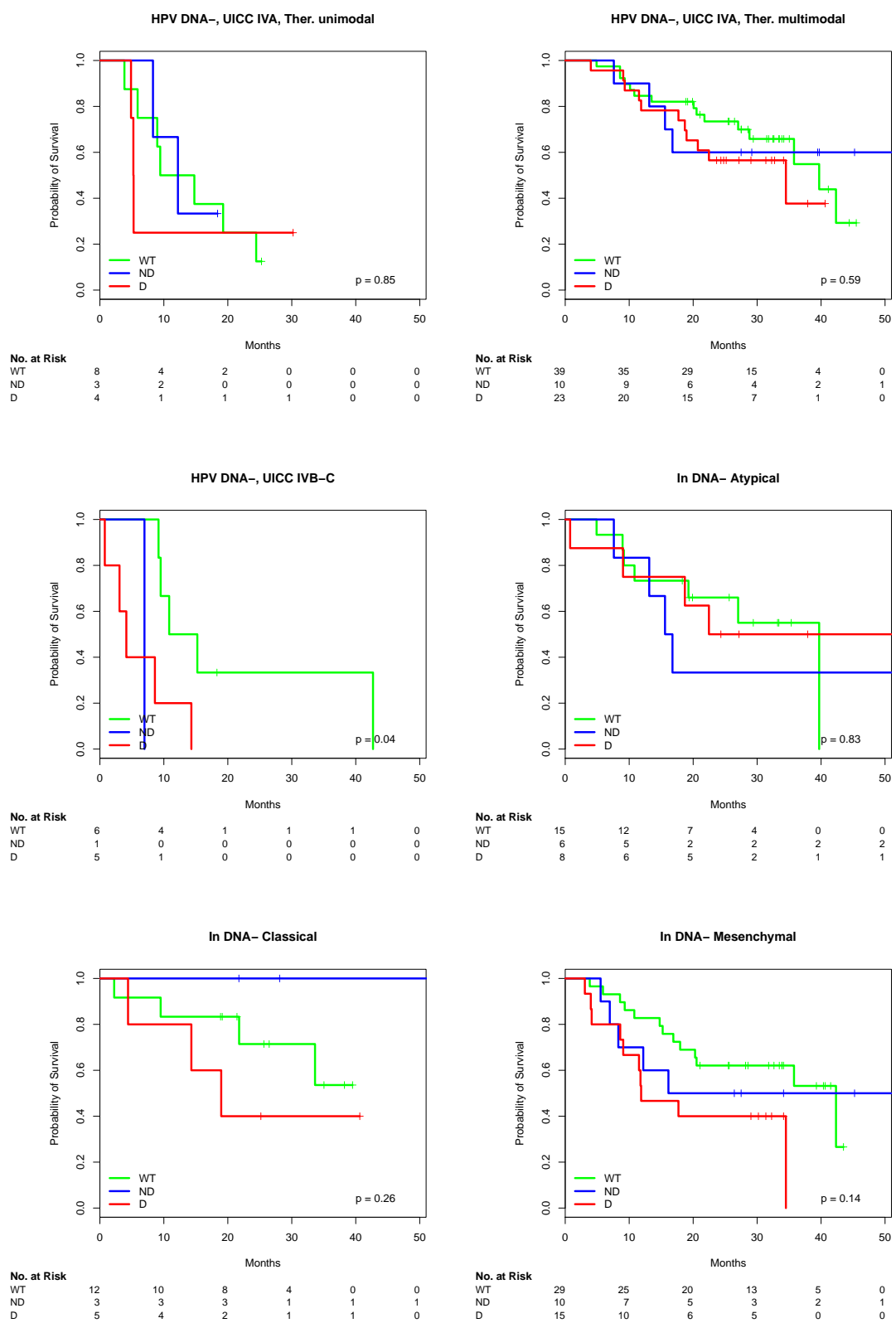
```
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.223    0.800   0.323 -0.69   0.49
## split[cur.subset]D   0.585    1.795   0.228  2.56   0.01 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND      0.8      1.250    0.425    1.51
## split[cur.subset]D      1.8      0.557    1.147    2.81
##
## Concordance= 0.571 (se = 0.027 )
## Rsquare= 0.036 (max possible= 0.987 )
## Likelihood ratio test= 7.86 on 2 df,  p=0.0197
## Wald test               = 8.43 on 2 df,  p=0.0148
## Score (logrank) test = 8.71 on 2 df,  p=0.0128
##
##
## #####
## Cox model in HPV DNA-
```

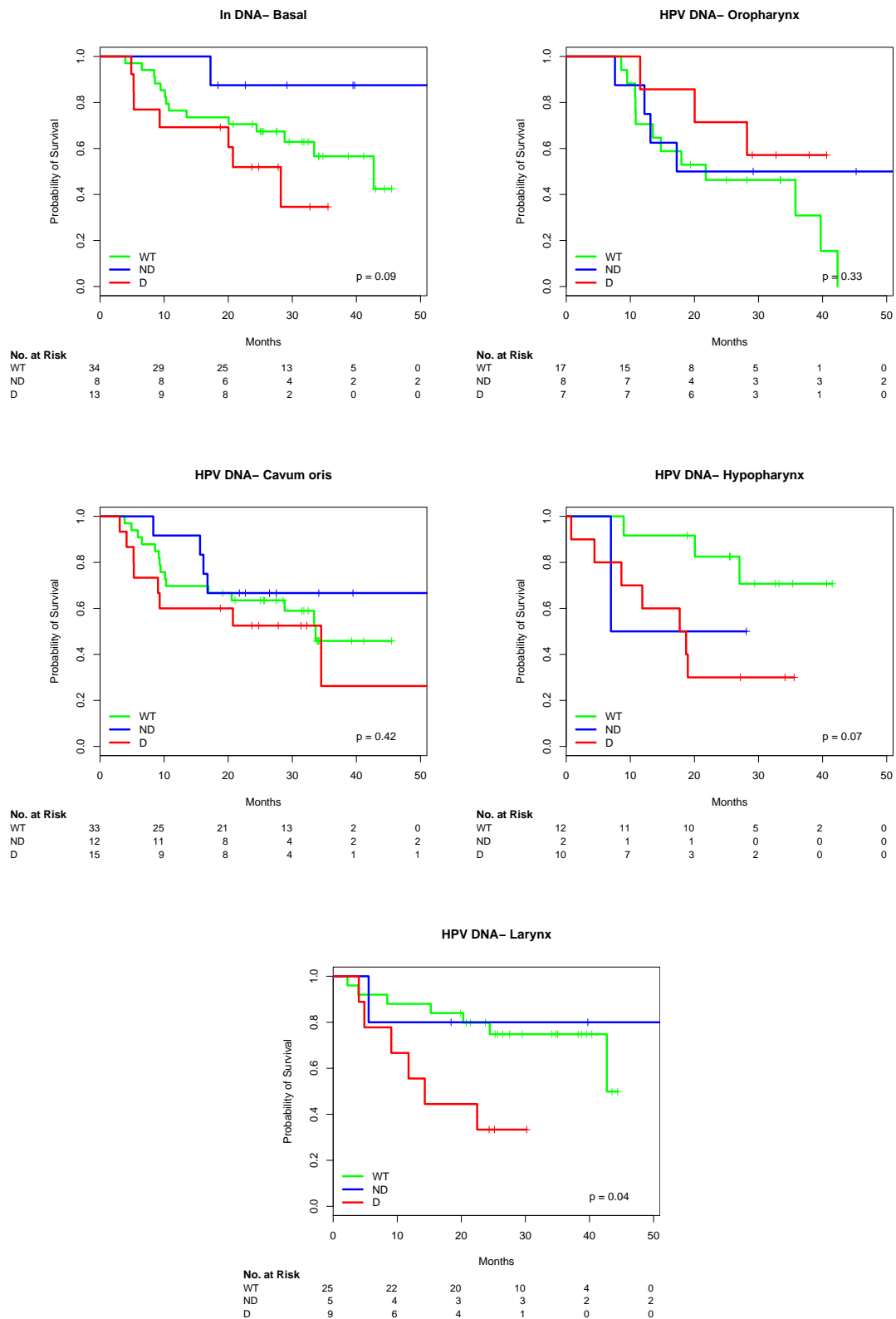
```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##    n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.248    0.780   0.356 -0.70   0.486
## split[cur.subset]D  0.561    1.752   0.259  2.16   0.031 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND    0.78    1.281    0.389    1.57
## split[cur.subset]D    1.75    0.571    1.054    2.91
##
## Concordance= 0.563 (se = 0.032 )
## Rsquare= 0.039 (max possible= 0.986 )
## Likelihood ratio test= 6.31 on 2 df,  p=0.0427
## Wald test               = 6.65 on 2 df,  p=0.036
## Score (logrank) test = 6.87 on 2 df,  p=0.0322
```











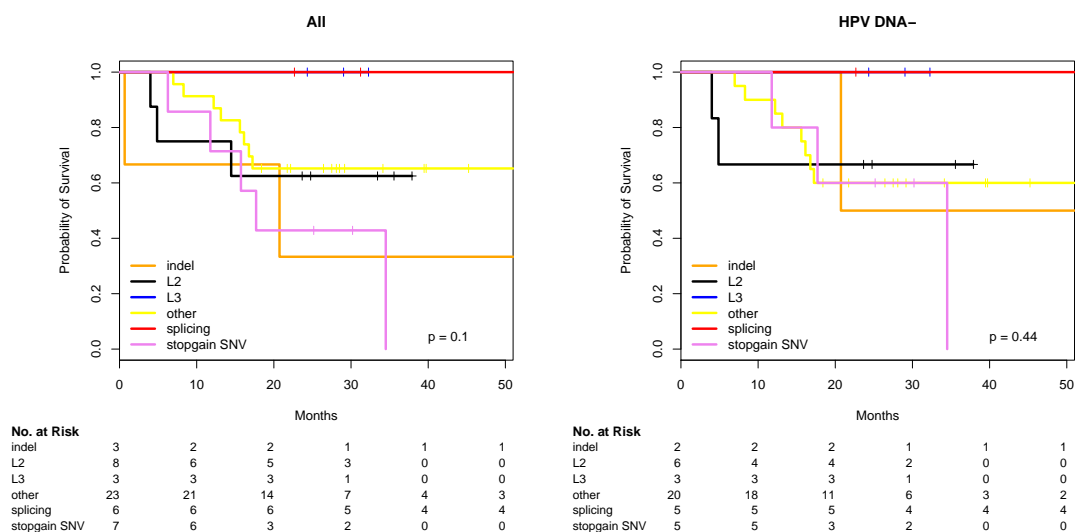
## 2.30 TP53: various types of mutations as in Gross et al. Patients which have only one type of TP53 mutation

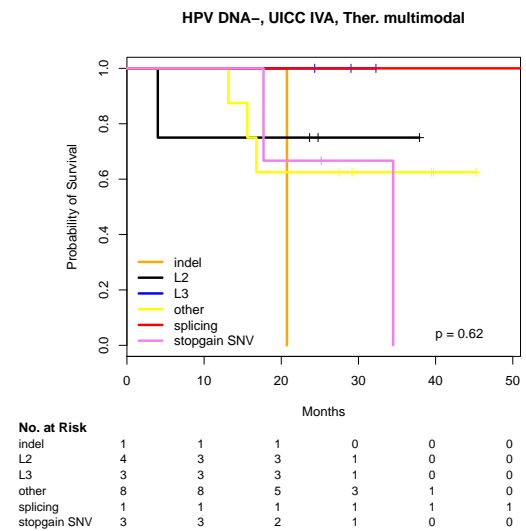
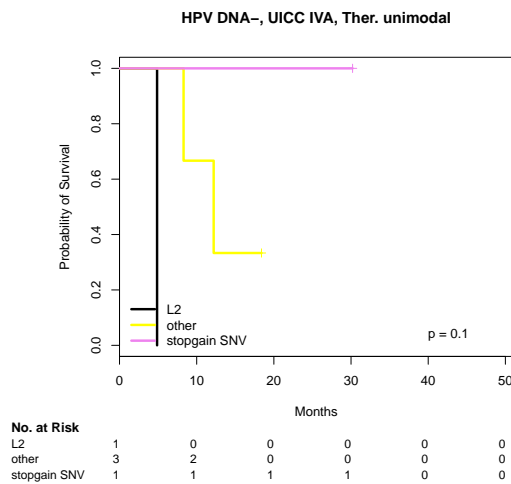
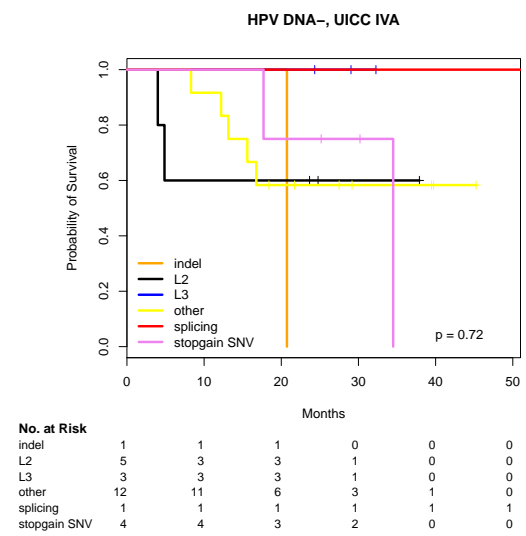
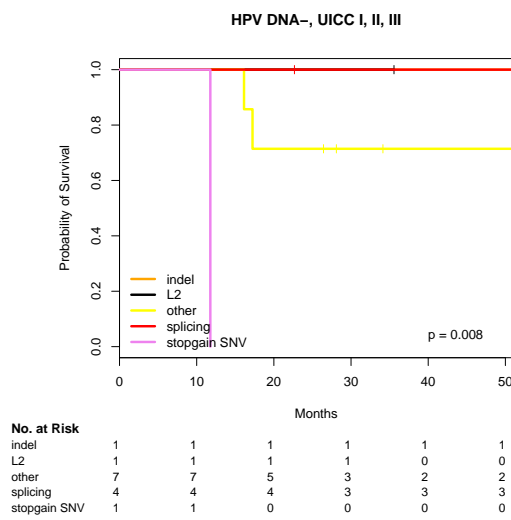
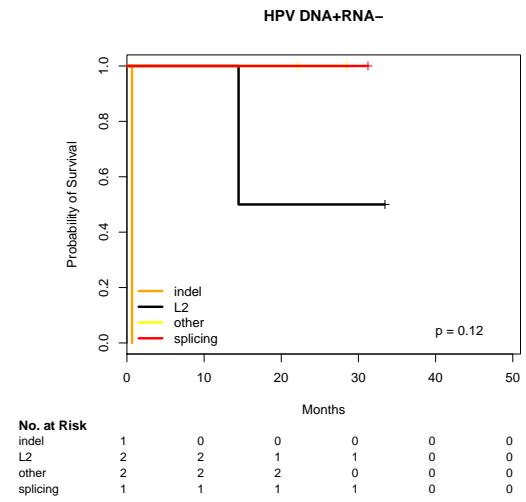
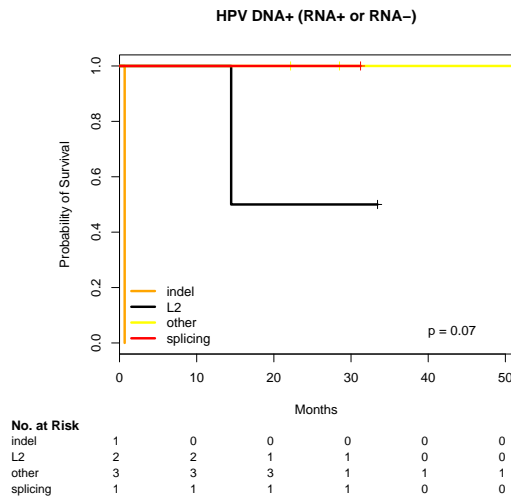
```

## 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= 21
## (167 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]L2      -3.07e-01  7.36e-01  9.13e-01 -0.34   0.737
## split[cur.subset]L3      -1.88e+01  7.19e-09  8.35e+03  0.00   0.998
## split[cur.subset]other     -5.28e-01  5.90e-01  7.57e-01 -0.70   0.485
## split[cur.subset]splicing  -2.14e+00  1.17e-01  1.16e+00 -1.85   0.064
## split[cur.subset]stopgain SNV  3.52e-01  1.42e+00  8.39e-01  0.42   0.675
##
## split[cur.subset]L2
## split[cur.subset]L3
## split[cur.subset]other
## split[cur.subset]splicing      .
## split[cur.subset]stopgain SNV
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]L2      7.36e-01  1.36e+00   0.1230   4.40
## split[cur.subset]L3      7.19e-09  1.39e+08   0.0000   Inf
## split[cur.subset]other     5.90e-01  1.70e+00   0.1337   2.60
## split[cur.subset]splicing  1.17e-01  8.53e+00   0.0121   1.14
## split[cur.subset]stopgain SNV 1.42e+00  7.03e-01   0.2748   7.36
##
## Concordance= 0.676 (se = 0.066 )
## Rsquare= 0.189 (max possible= 0.942 )
## Likelihood ratio test= 10.5 on 5 df, p=0.063
## Wald test = 6.04 on 5 df, p=0.302
## Score (logrank) test = 9.25 on 5 df, p=0.0997
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 41, number of events= 16

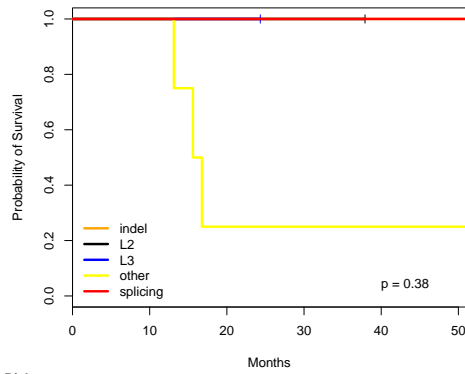
```

```
##      (117 observations deleted due to missingness)
##
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## split[cur.subset]L2      -4.94e-02  9.52e-01  1.12e+00 -0.04      0.96
## split[cur.subset]L3      -1.83e+01  1.08e-08  8.23e+03  0.00      1.00
## split[cur.subset]other    -3.47e-02  9.66e-01  9.24e-01 -0.04      0.97
## split[cur.subset]splicing  -1.65e+00  1.93e-01  1.23e+00 -1.34      0.18
## split[cur.subset]stopgain SNV  3.96e-01  1.49e+00  1.04e+00  0.38      0.70
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]L2      9.52e-01  1.05e+00    0.1060    8.55
## split[cur.subset]L3      1.08e-08  9.22e+07    0.0000    Inf
## split[cur.subset]other    9.66e-01  1.04e+00    0.1580    5.90
## split[cur.subset]splicing  1.93e-01  5.19e+00    0.0173    2.15
## split[cur.subset]stopgain SNV  1.49e+00  6.73e-01    0.1918   11.51
##
## Concordance= 0.605  (se = 0.075 )
## Rsquare= 0.145  (max possible= 0.92 )
## Likelihood ratio test= 6.4  on 5 df,  p=0.269
## Wald test            = 2.85  on 5 df,  p=0.723
## Score (logrank) test = 4.81  on 5 df,  p=0.44
```





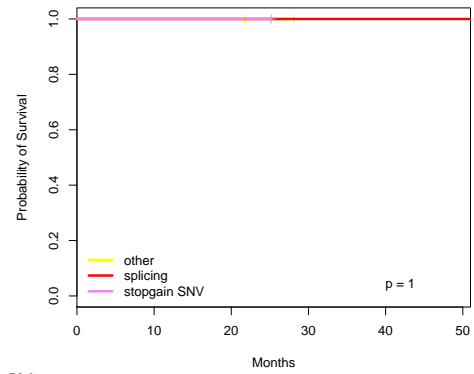
In DNA- Atypical



No. at Risk

	0	10	20	30	40	50
indel	1	1	1	1	1	1
L2	1	1	1	1	0	0
L3	1	1	1	0	0	0
other	4	4	1	1	1	1
splicing	1	1	1	1	1	1

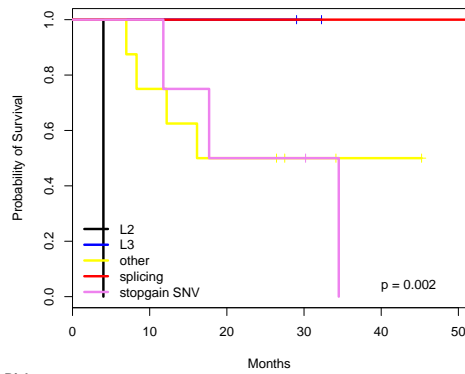
In DNA- Classical



No. at Risk

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

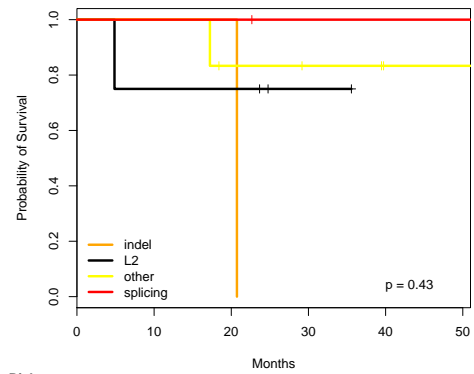
In DNA- Mesenchymal



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	6	4	2	1	0
splicing	1	1	1	1	1	1
stopgain SNV	4	4	2	2	0	0

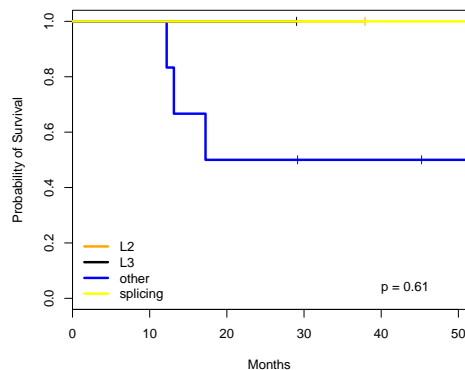
In DNA- Basal



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	4	3	1	1
splicing	2	2	2	1	1	1

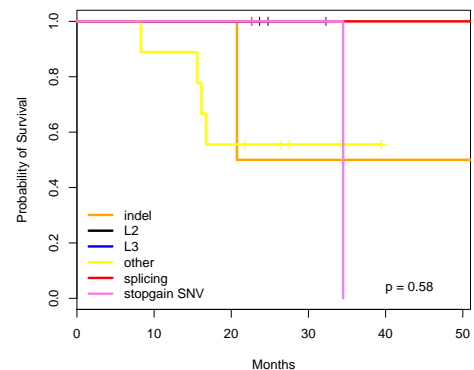
HPV DNA- Oropharynx



No. at Risk

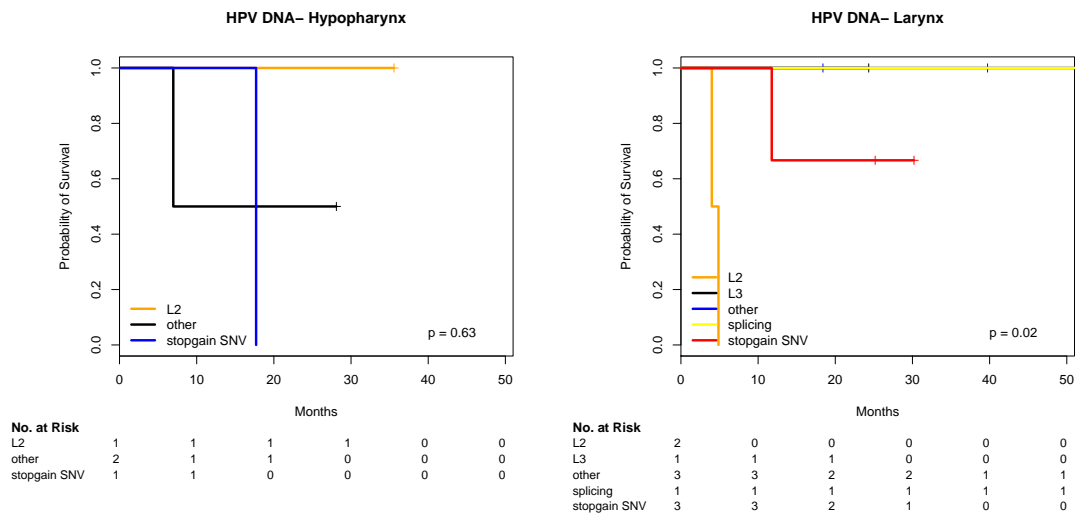
	0	10	20	30	40	50
L2	1	1	1	1	0	0
L3	1	1	1	0	0	0
other	6	6	3	2	2	1
splicing	1	1	1	1	1	1

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	8	5	2	0	0
splicing	3	3	3	2	2	2
stopgain SNV	1	1	1	1	0	0



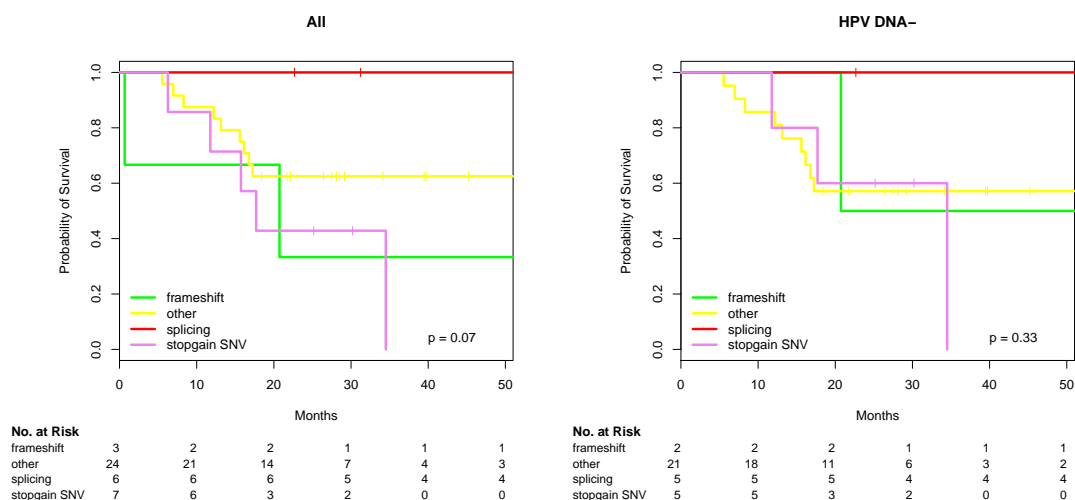
## 2.31 TP53: various types of mutations similar but NOT identical as in Gross et al.

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

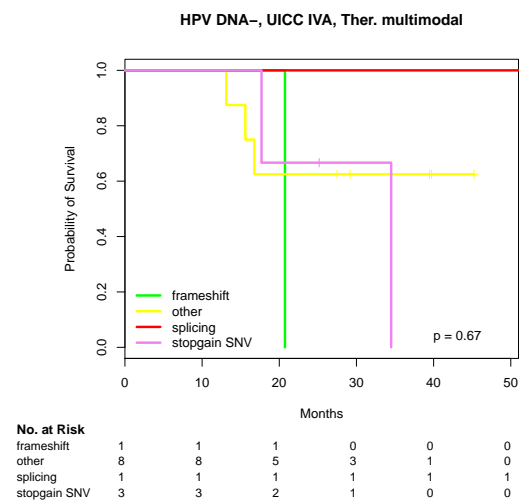
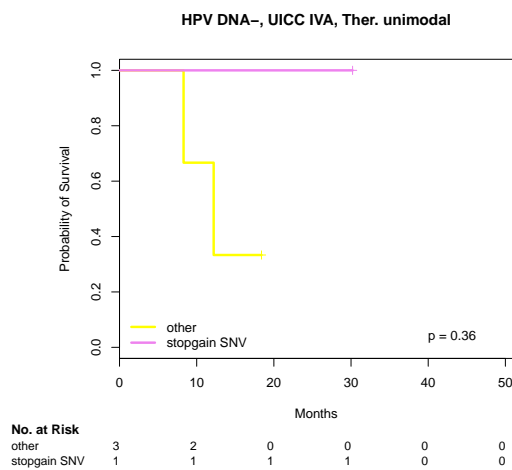
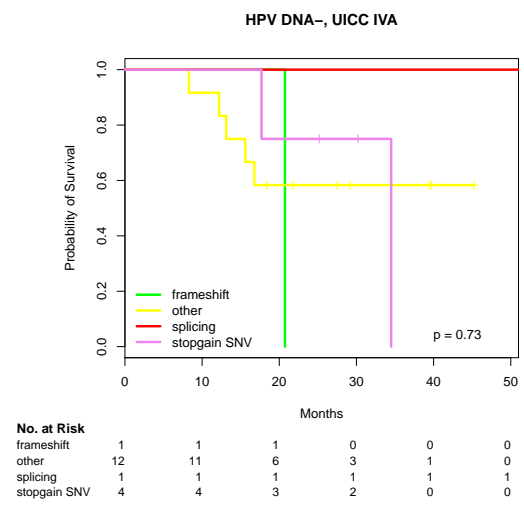
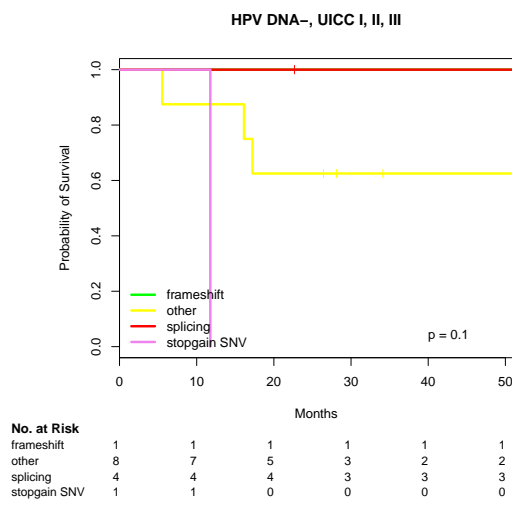
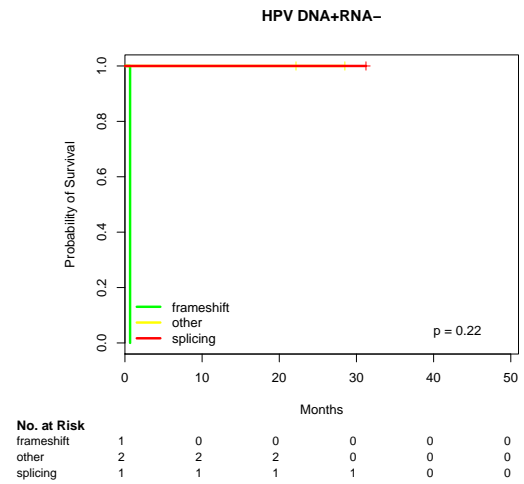
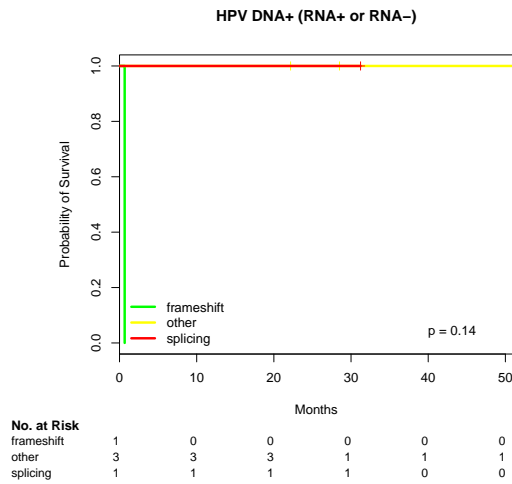
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group

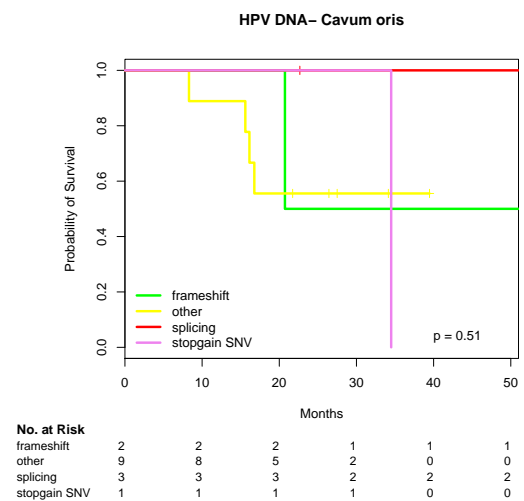
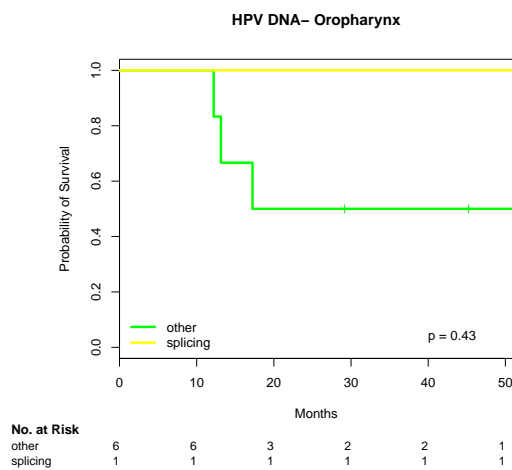
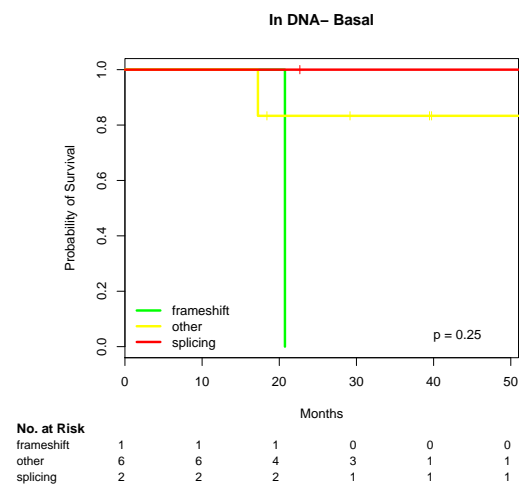
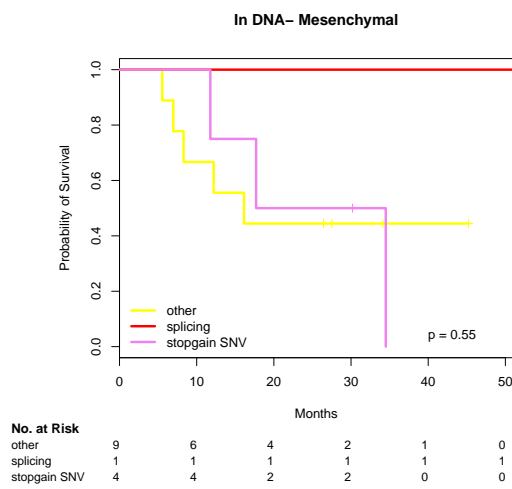
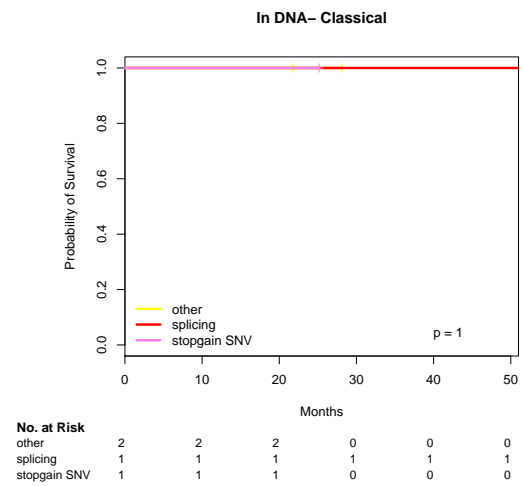
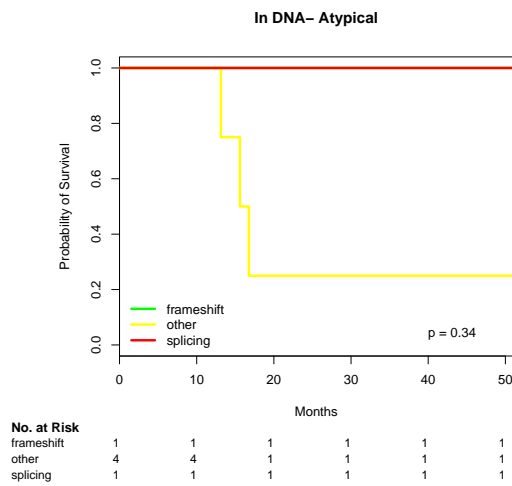
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 40, number of events= 19
## (177 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]other    -0.427    0.652   0.748 -0.57   0.568
## split[cur.subset]splicing  -2.143    0.117   1.159 -1.85   0.064
## split[cur.subset]stopgain SNV  0.358    1.431   0.834  0.43   0.668
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]other    0.652    1.533   0.1507    2.82
## split[cur.subset]splicing  0.117    8.526   0.0121    1.14
## split[cur.subset]stopgain SNV  1.431    0.699   0.2789    7.34
##
## Concordance= 0.649 (se = 0.065 )
```

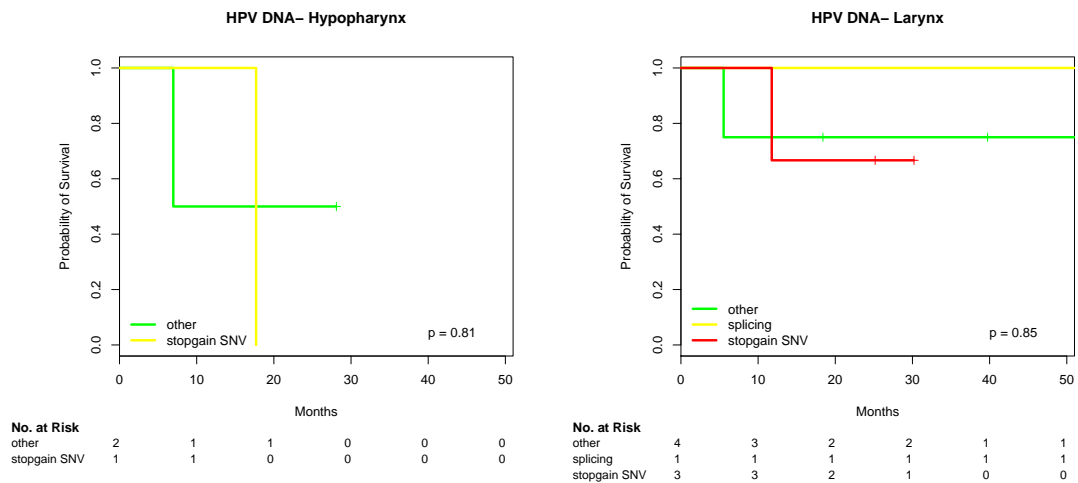
```
## Rsquare= 0.178 (max possible= 0.95 )
## Likelihood ratio test= 7.86 on 3 df, p=0.049
## Wald test = 5.7 on 3 df, p=0.127
## Score (logrank) test = 7.2 on 3 df, p=0.0658
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 33, number of events= 15
## (125 observations deleted due to missingness)
##
## coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]other 0.0907 1.0949 0.9140 0.10 0.92
## split[cur.subset]splicing -1.6466 0.1927 1.2305 -1.34 0.18
## split[cur.subset]stopgain SNV 0.3996 1.4913 1.0409 0.38 0.70
##
## exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]other 1.095 0.913 0.1826 6.57
## split[cur.subset]splicing 0.193 5.190 0.0173 2.15
## split[cur.subset]stopgain SNV 1.491 0.671 0.1939 11.47
##
## Concordance= 0.601 (se = 0.074 )
## Rsquare= 0.123 (max possible= 0.935 )
## Likelihood ratio test= 4.33 on 3 df, p=0.228
## Wald test = 2.88 on 3 df, p=0.411
## Score (logrank) test = 3.44 on 3 df, p=0.329
```







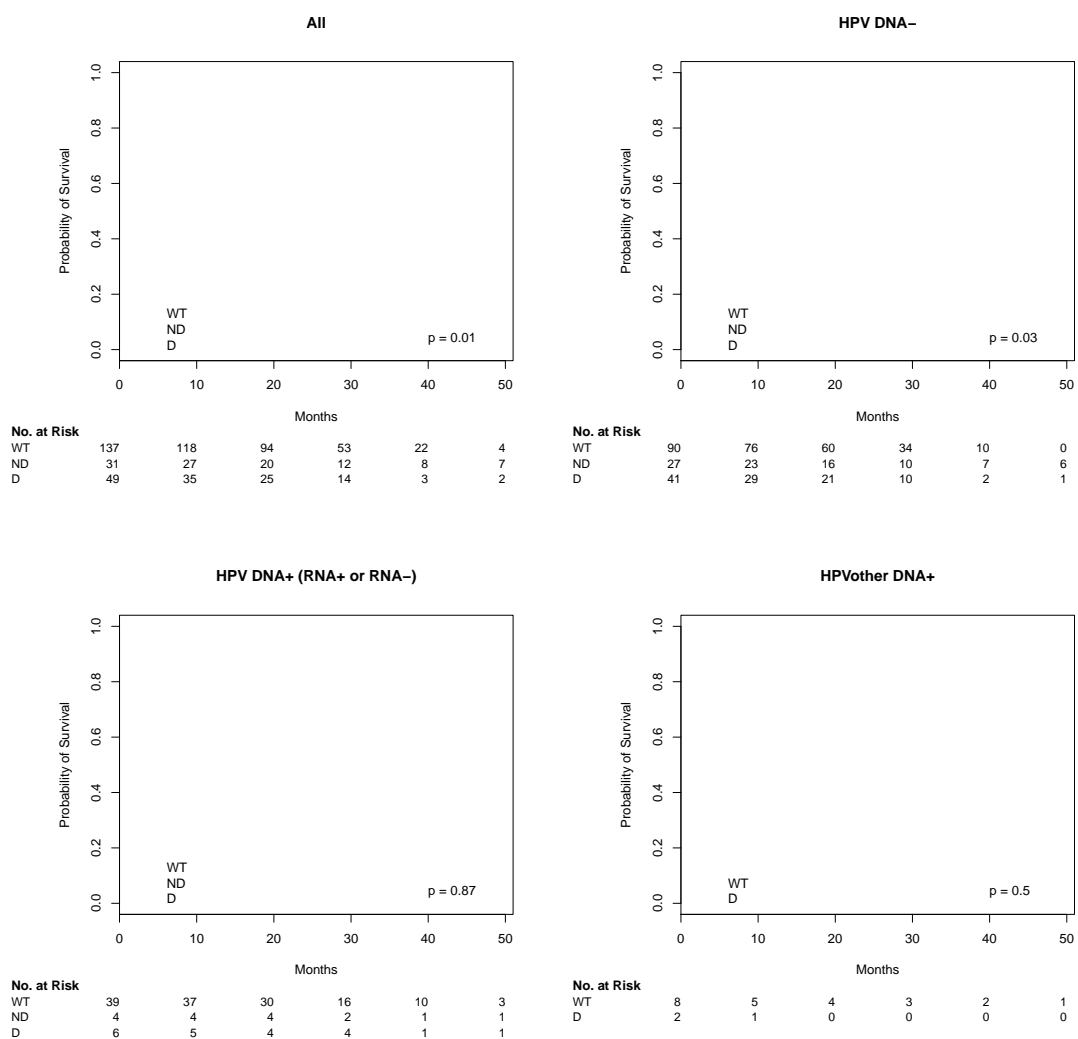


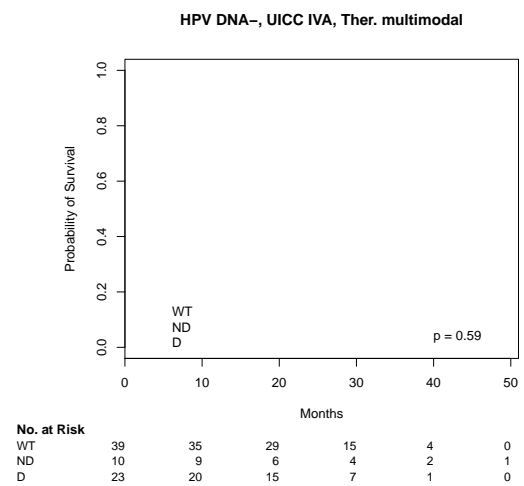
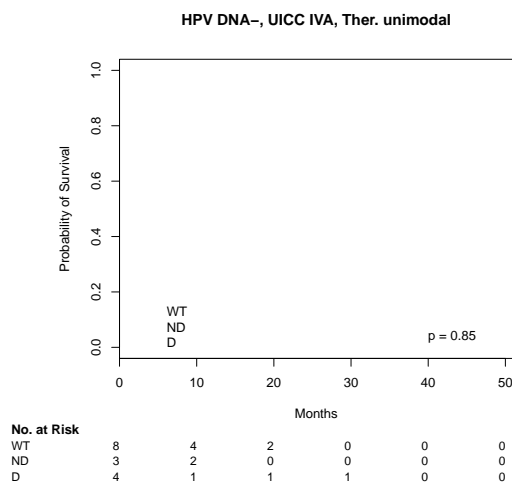
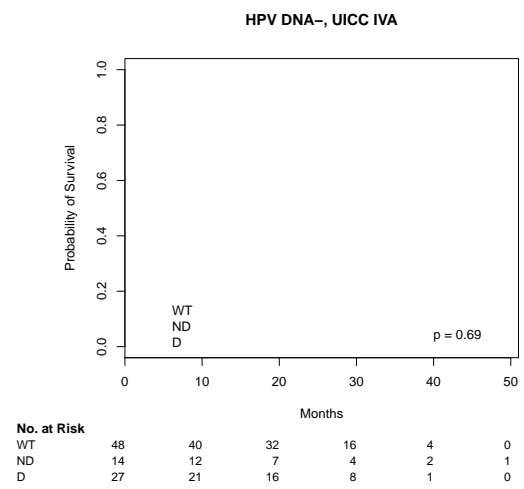
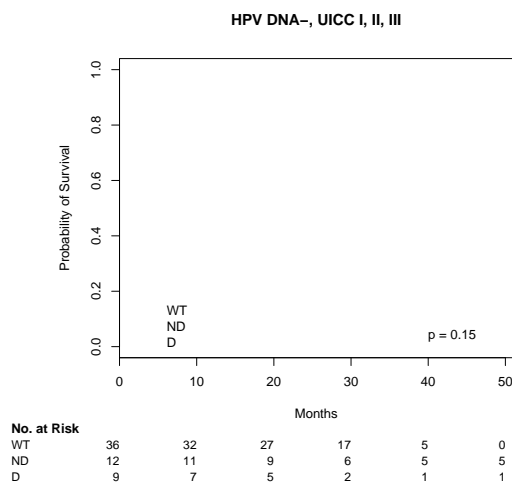
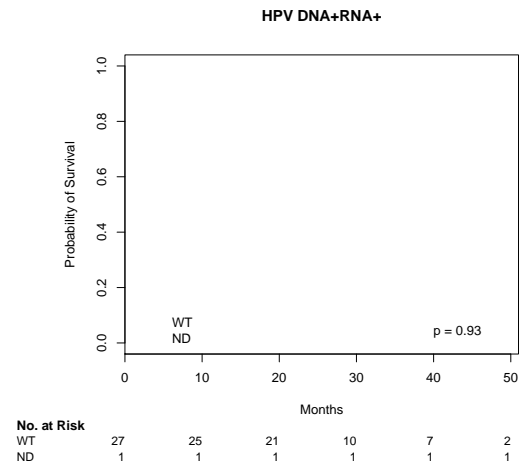
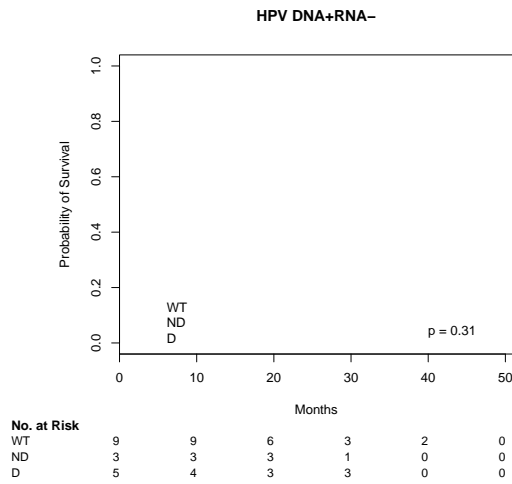


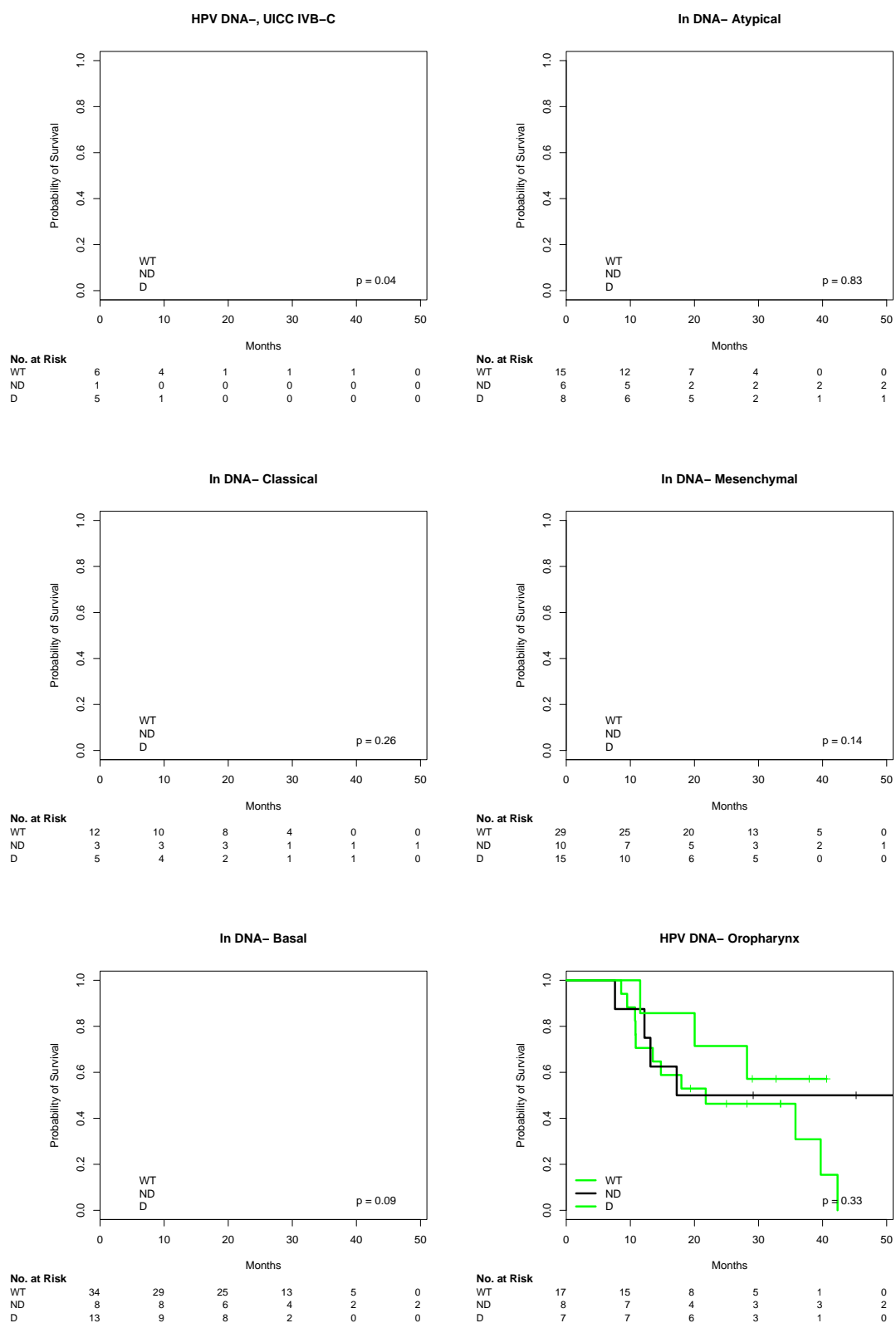
## 2.32 TP53 (association of mutations in TP53 with survival)

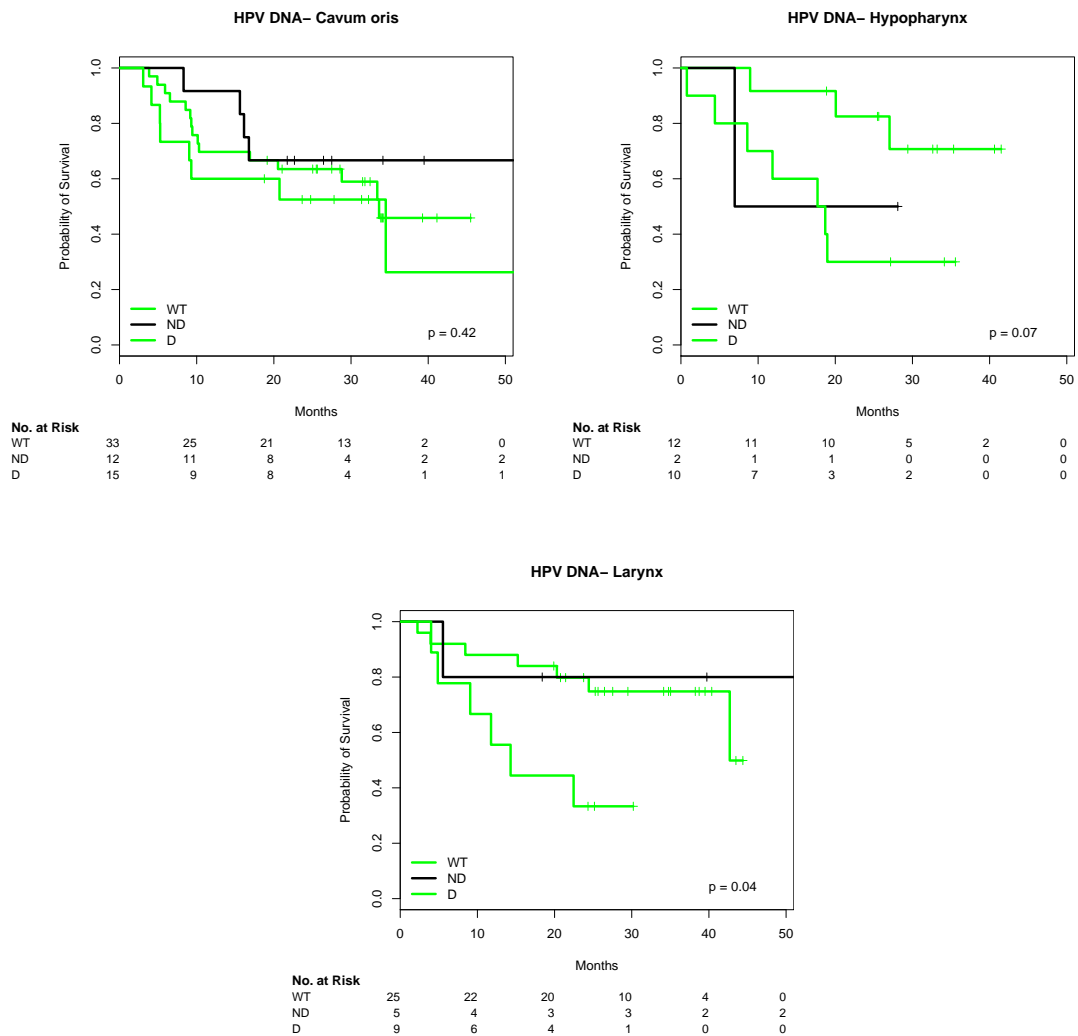
```
## Error: Attribut 'names' [3] muss dieselbe Länge haben wie der Vektor [2]
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.223     0.800   0.323 -0.69   0.49
## split[cur.subset]D   0.585     1.795   0.228  2.56   0.01 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND     0.8      1.250    0.425    1.51
## split[cur.subset]D     1.8      0.557    1.147    2.81
##
## Concordance= 0.571 (se = 0.027 )
## Rsquare= 0.036 (max possible= 0.987 )
## Likelihood ratio test= 7.86 on 2 df,  p=0.0197
## Wald test               = 8.43 on 2 df,  p=0.0148
## Score (logrank) test = 8.71 on 2 df,  p=0.0128
##
##
## #####
## Cox model in HPV DNA-
## Call:
```

```
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]ND -0.248      0.780    0.356 -0.70    0.486
## split[cur.subset]D   0.561      1.752    0.259  2.16    0.031 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]ND      0.78      1.281      0.389      1.57
## split[cur.subset]D      1.75      0.571      1.054      2.91
##
## Concordance= 0.563 (se = 0.032 )
## Rsquare= 0.039 (max possible= 0.986 )
## Likelihood ratio test= 6.31 on 2 df,  p=0.0427
## Wald test               = 6.65 on 2 df,  p=0.036
## Score (logrank) test = 6.87 on 2 df,  p=0.0322
```





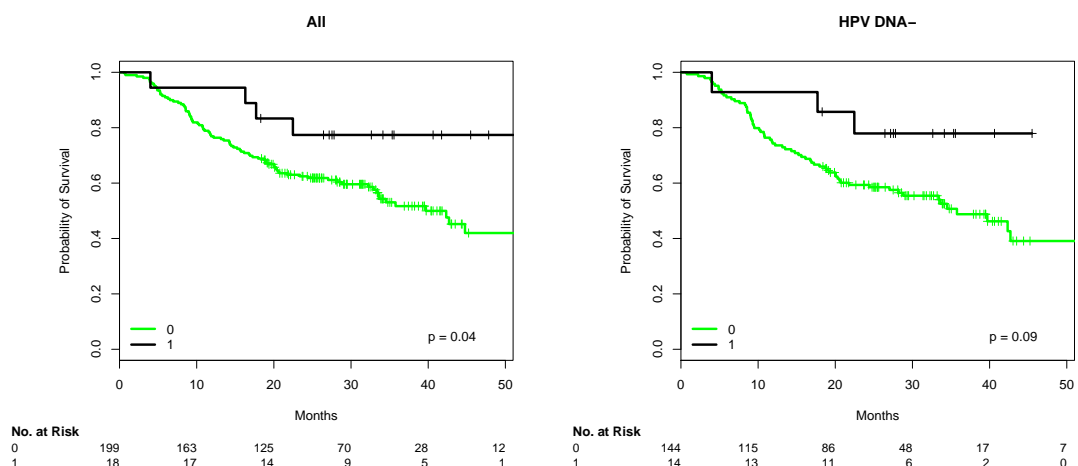




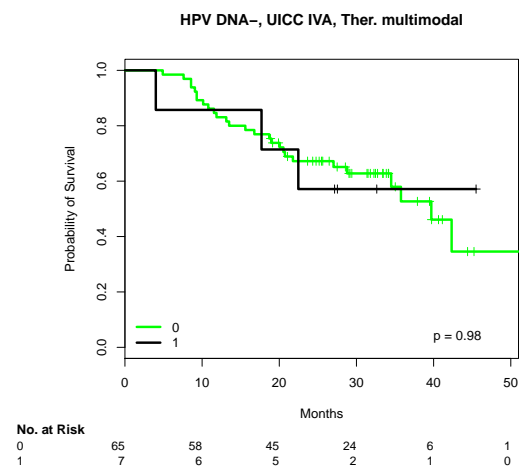
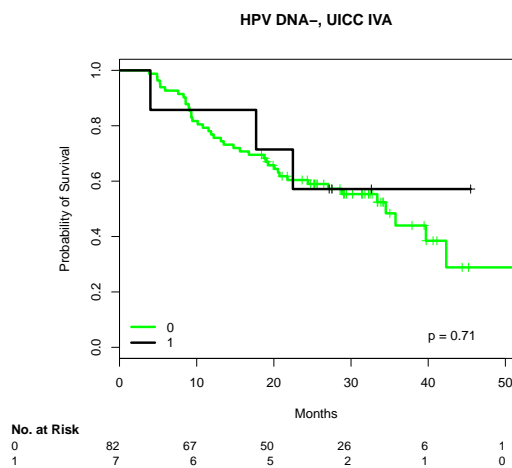
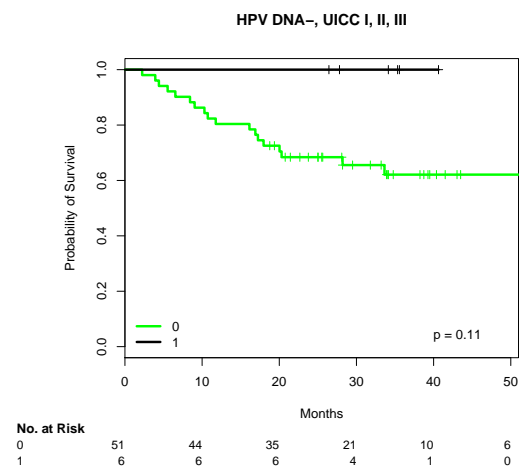
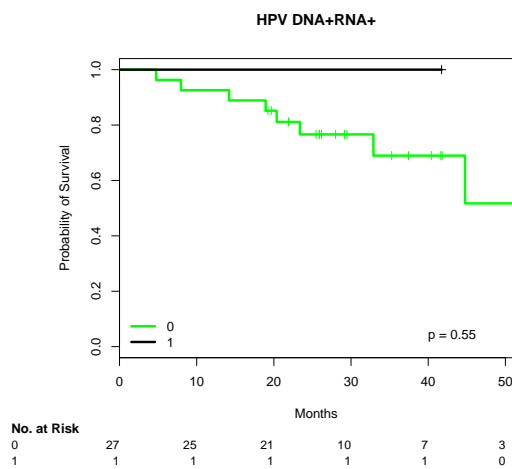
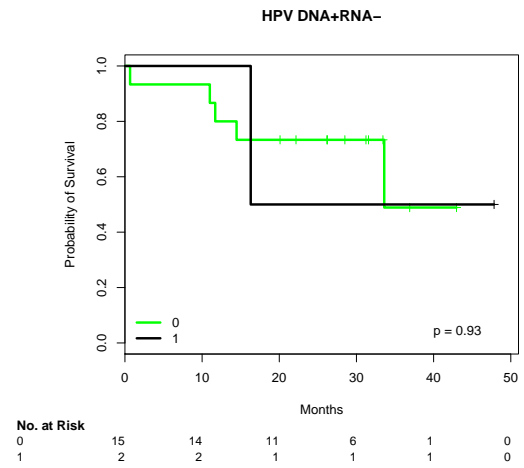
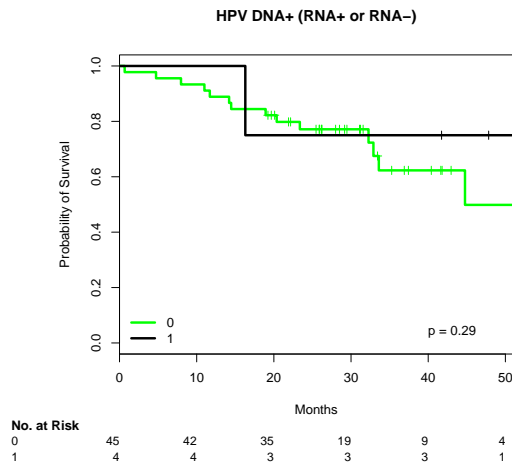
## 2.33 APC

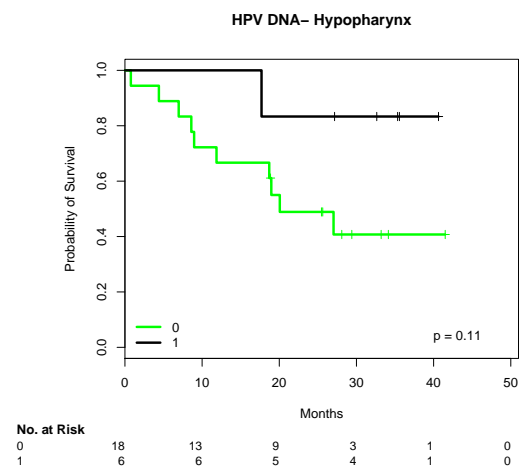
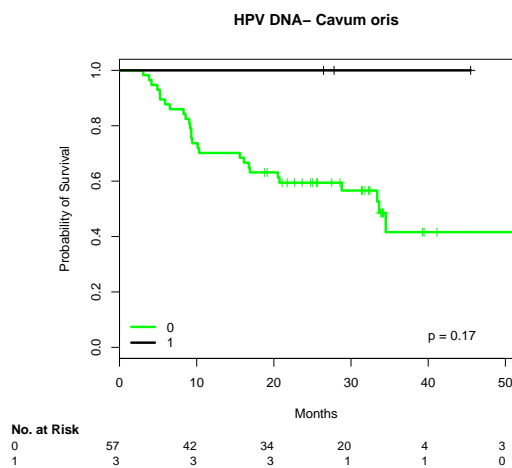
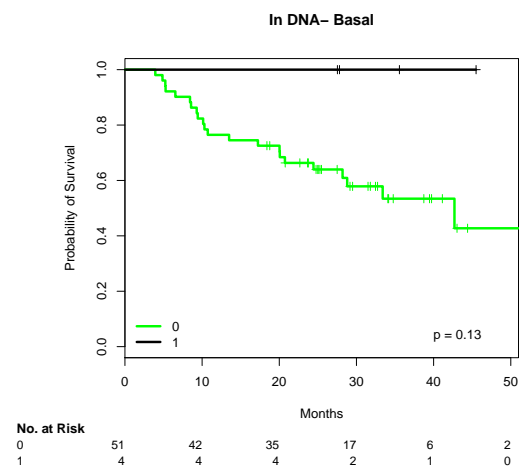
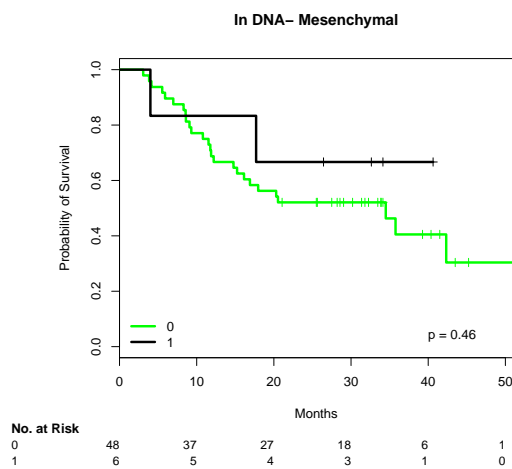
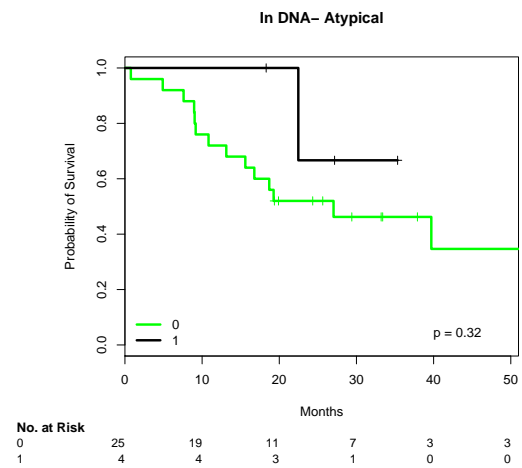
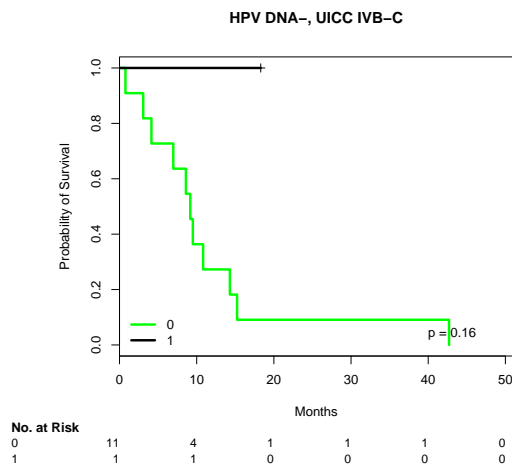
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -1.036      0.355   0.514 -2.01   0.044 *
## ---
```

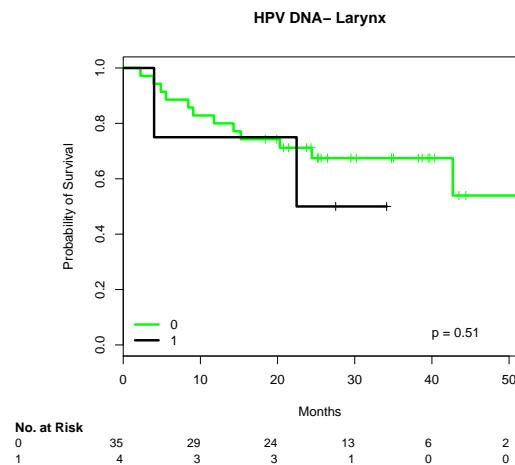
```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.355      2.82      0.129      0.972
##
## Concordance= 0.526  (se = 0.016 )
## Rsquare= 0.026   (max possible= 0.987 )
## Likelihood ratio test= 5.61  on 1 df,   p=0.0179
## Wald test           = 4.06  on 1 df,   p=0.044
## Score (logrank) test = 4.42  on 1 df,   p=0.0356
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.963      0.382    0.590 -1.63      0.1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.382      2.62      0.12      1.21
##
## Concordance= 0.529  (se = 0.019 )
## Rsquare= 0.023   (max possible= 0.986 )
## Likelihood ratio test= 3.62  on 1 df,   p=0.0571
## Wald test           = 2.66  on 1 df,   p=0.103
## Score (logrank) test = 2.87  on 1 df,   p=0.09
```







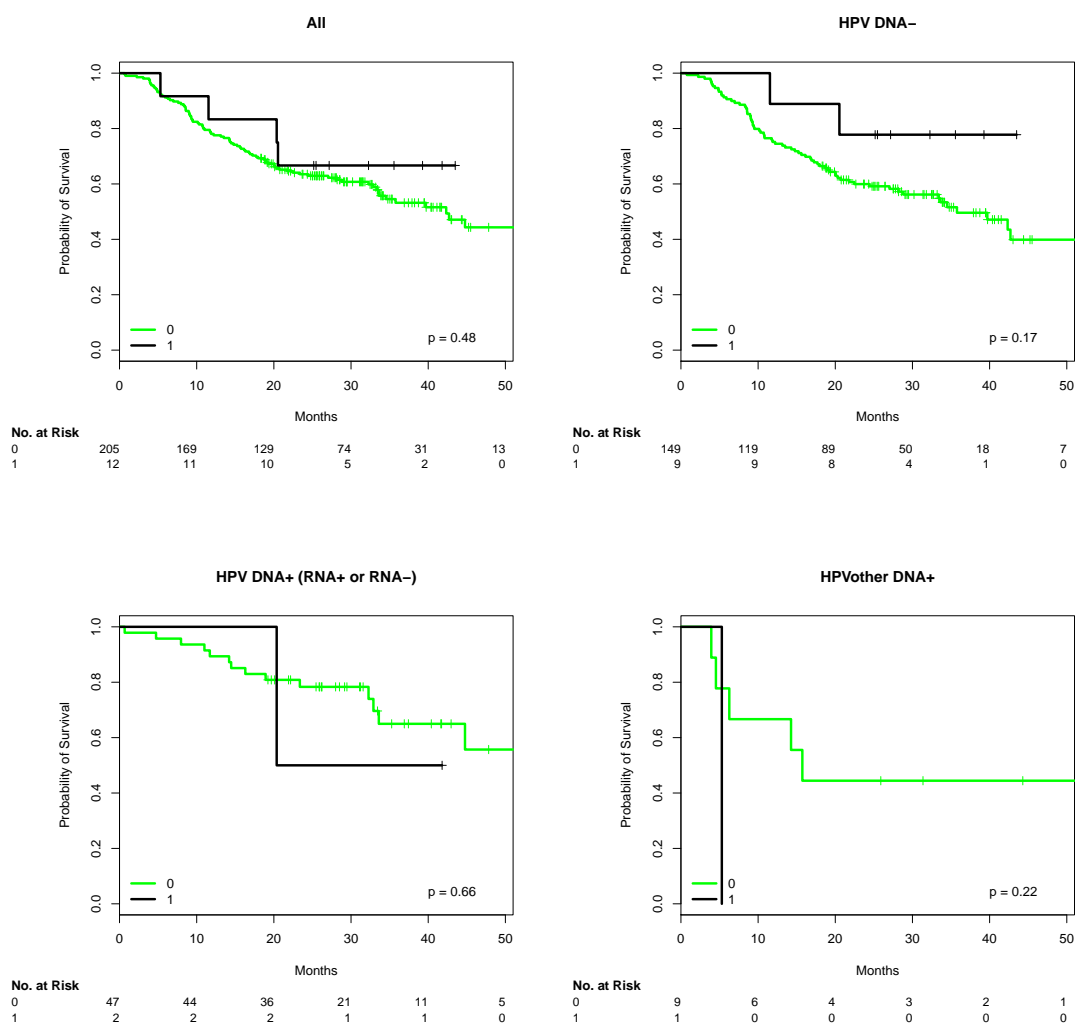


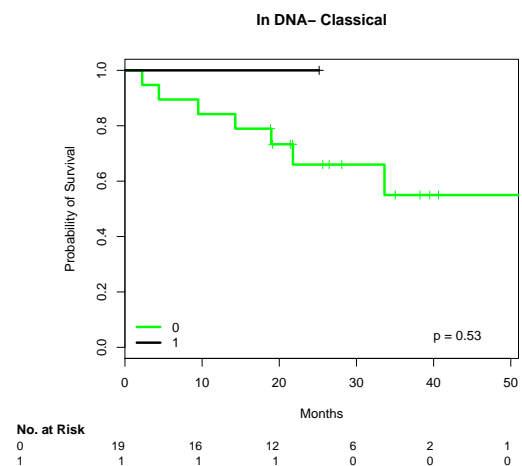
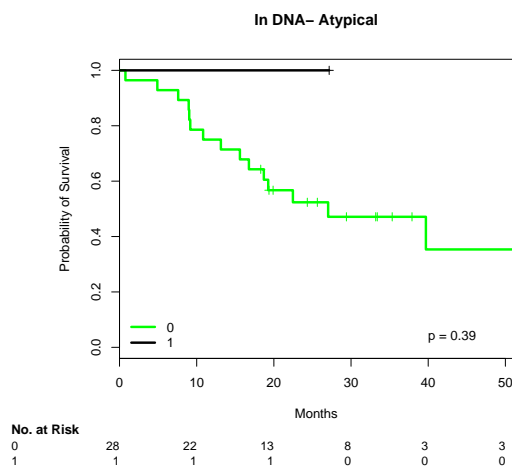
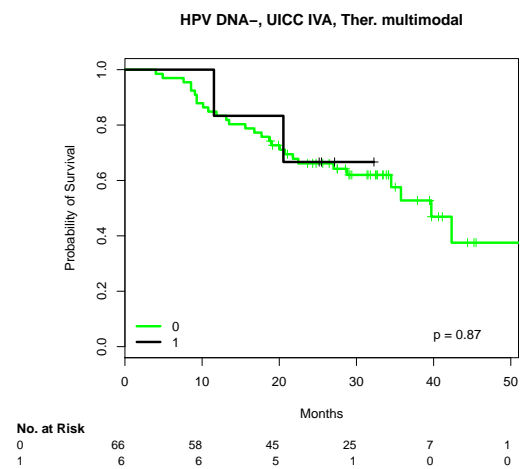
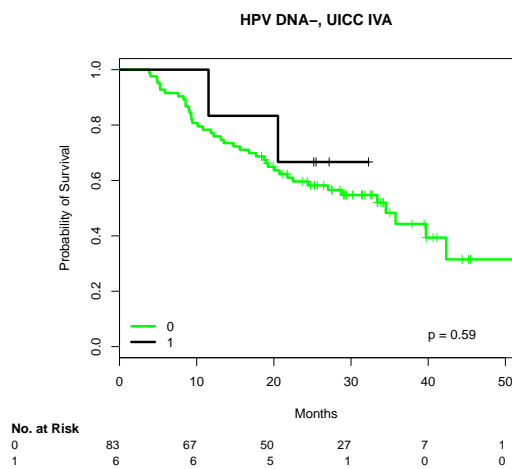
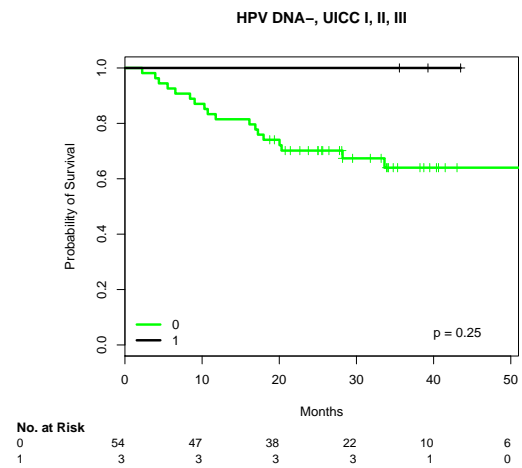
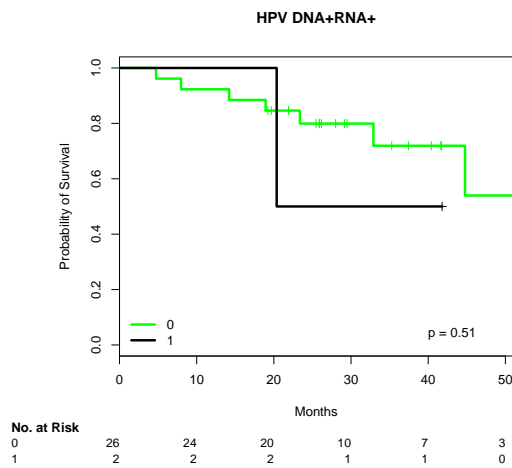


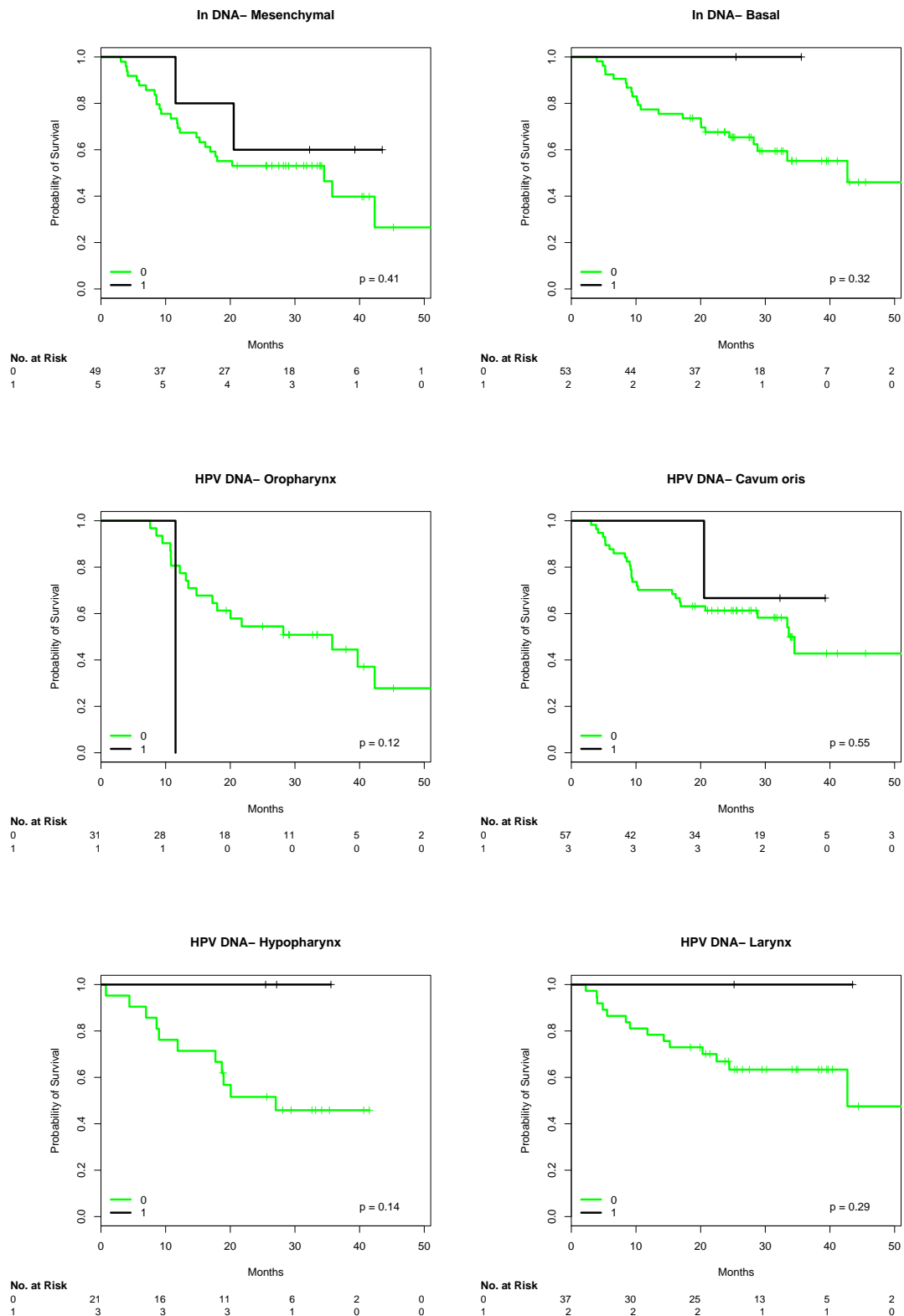
## 2.34 CDKN2A

```
## 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.357      0.700    0.511 -0.7    0.49
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.7      1.43    0.257    1.91
##
## Concordance= 0.508 (se = 0.013 )
## Rsquare= 0.003 (max possible= 0.987 )
## Likelihood ratio test= 0.54 on 1 df,  p=0.461
## Wald test               = 0.49 on 1 df,  p=0.485
## Score (logrank) test = 0.49 on 1 df,  p=0.483
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
```

```
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.952    0.386    0.717 -1.33    0.18
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.386      2.59    0.0946    1.57
##
## Concordance= 0.521 (se = 0.016 )
## Rsquare= 0.015 (max possible= 0.986 )
## Likelihood ratio test= 2.42 on 1 df,  p=0.12
## Wald test               = 1.76 on 1 df,  p=0.185
## Score (logrank) test = 1.9 on 1 df,  p=0.168
```





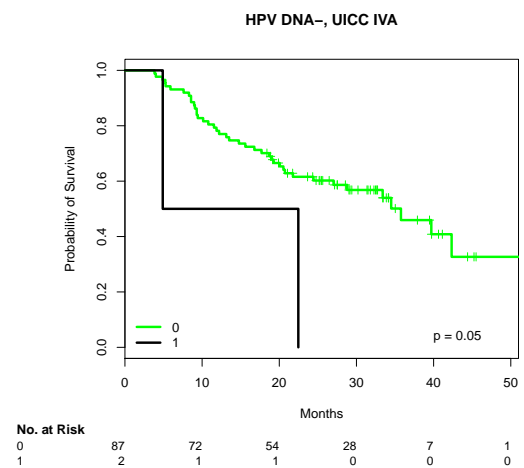
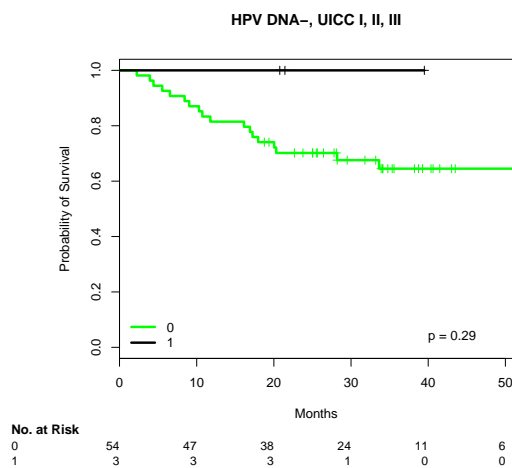
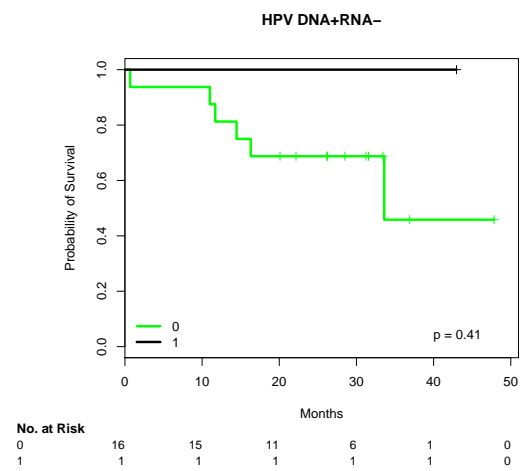
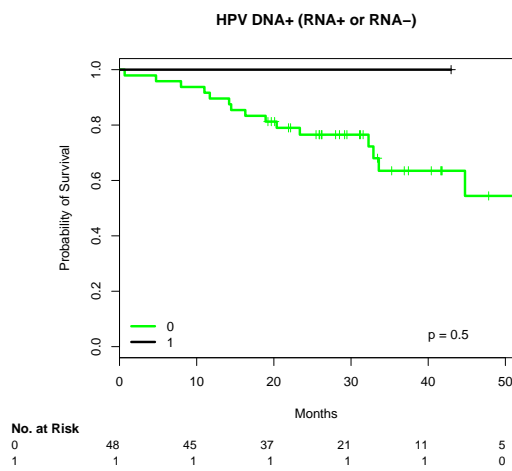
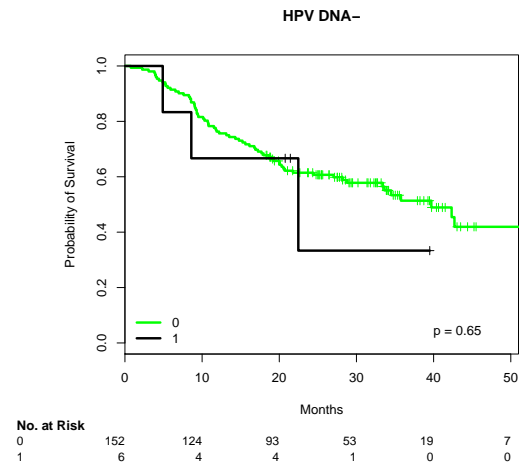
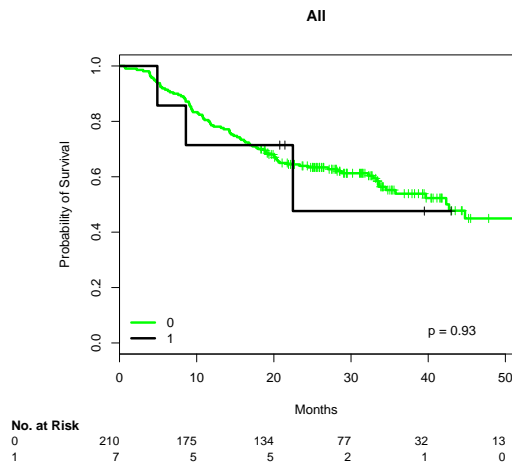


## 2.35 PIK3CA

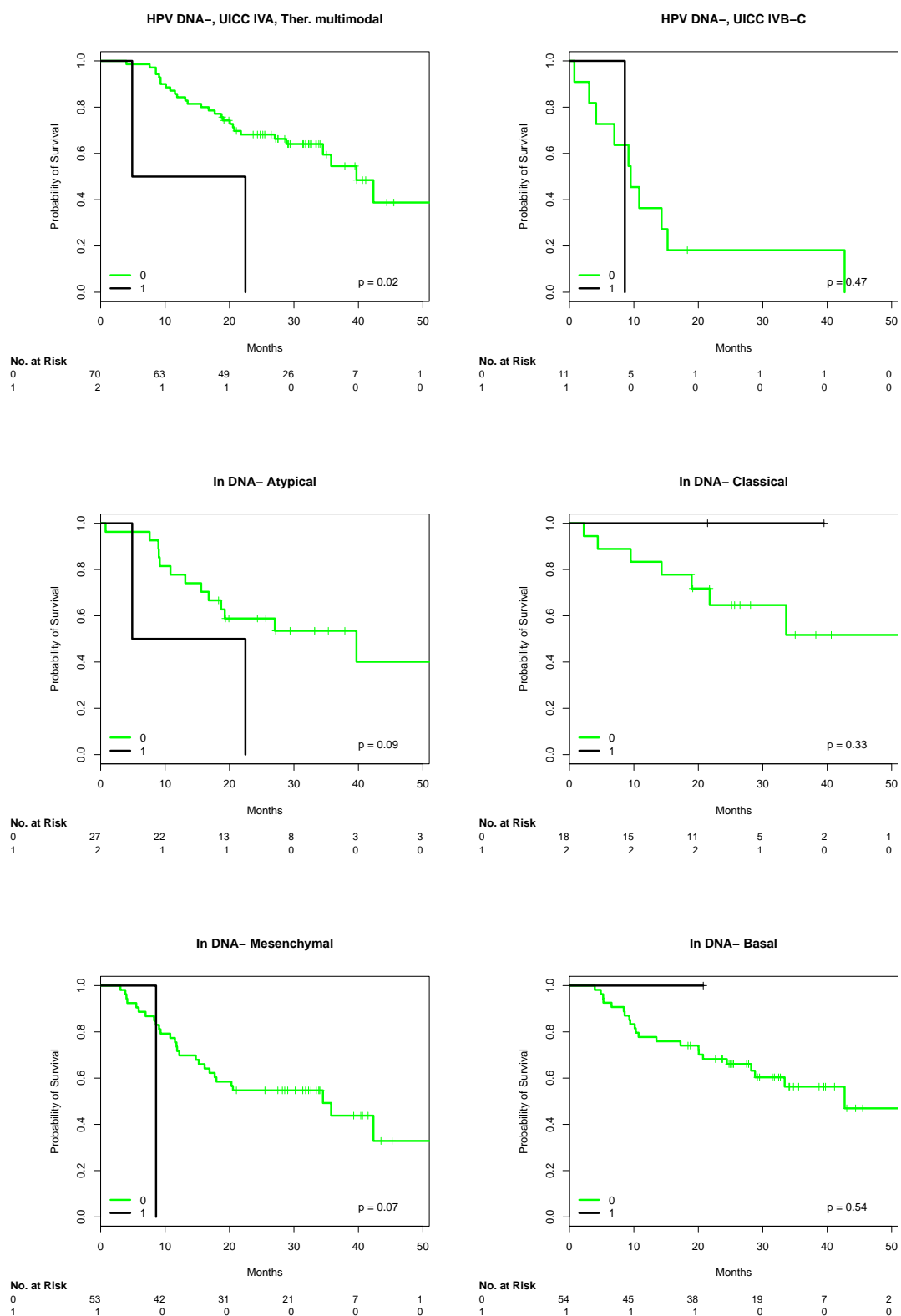
```

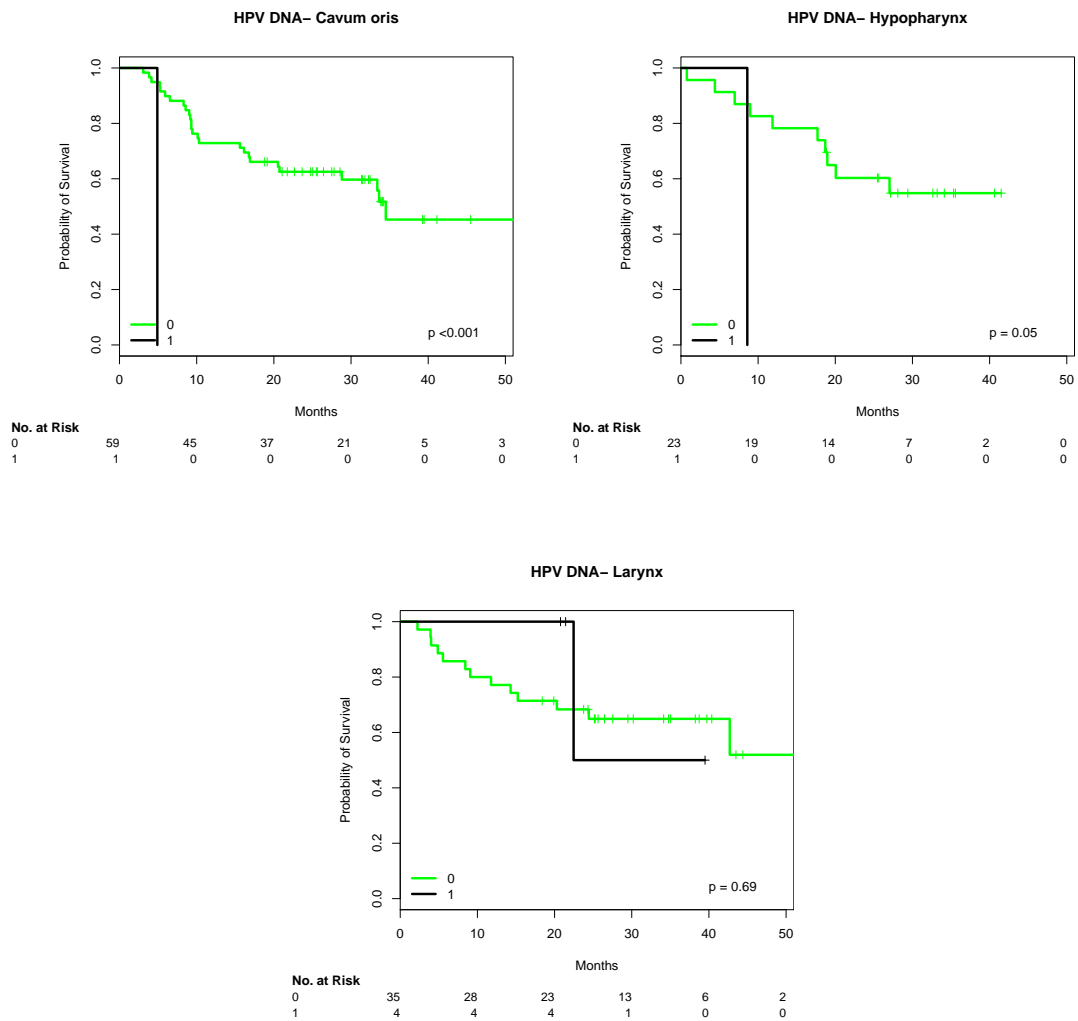
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.0538    1.0553  0.5872 0.09    0.93
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.06      0.948    0.334    3.34
##
## Concordance= 0.502 (se = 0.009 )
## Rsquare= 0 (max possible= 0.987 )
## Likelihood ratio test= 0.01 on 1 df, p=0.928
## Wald test = 0.01 on 1 df, p=0.927
## Score (logrank) test = 0.01 on 1 df, p=0.927
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.270    1.310  0.591 0.46    0.65
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.31      0.763    0.412    4.17
##
## Concordance= 0.506 (se = 0.011 )
## Rsquare= 0.001 (max possible= 0.986 )
## Likelihood ratio test= 0.19 on 1 df, p=0.66
## Wald test = 0.21 on 1 df, p=0.647
## Score (logrank) test = 0.21 on 1 df, p=0.646

```





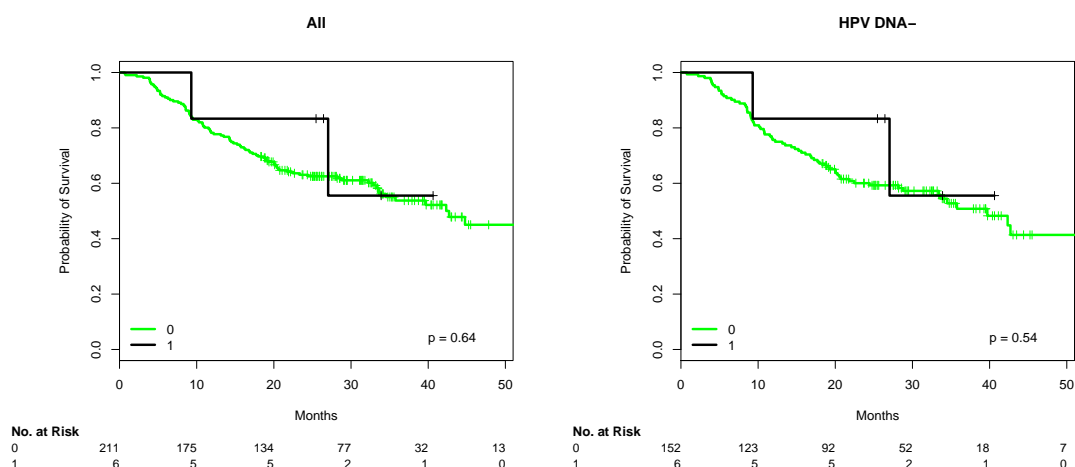


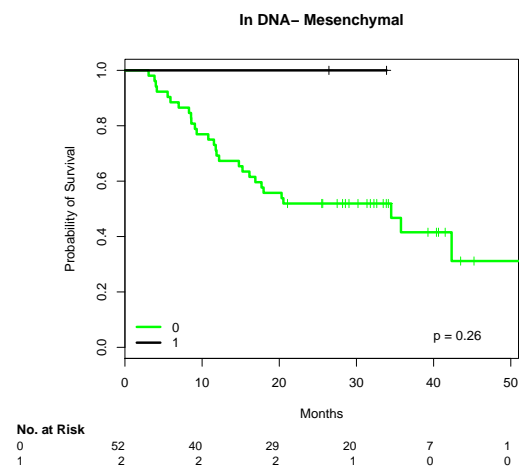
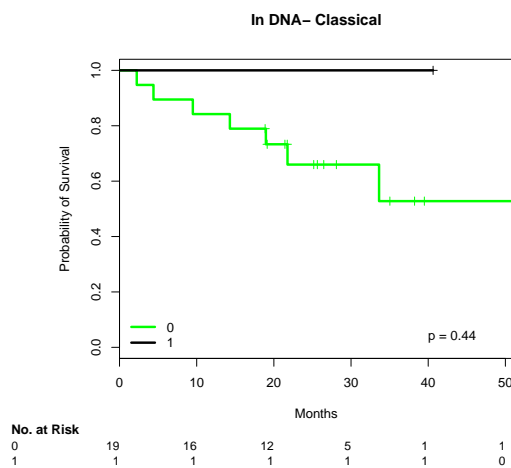
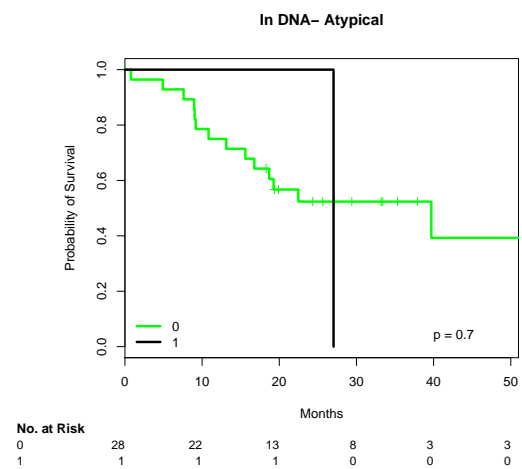
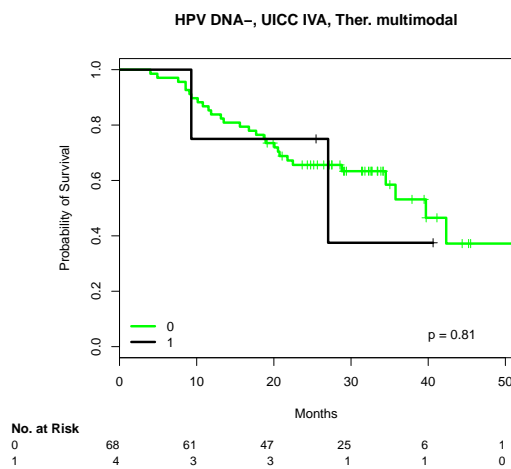
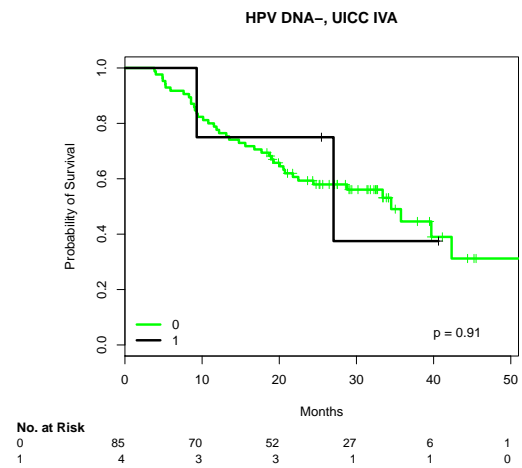
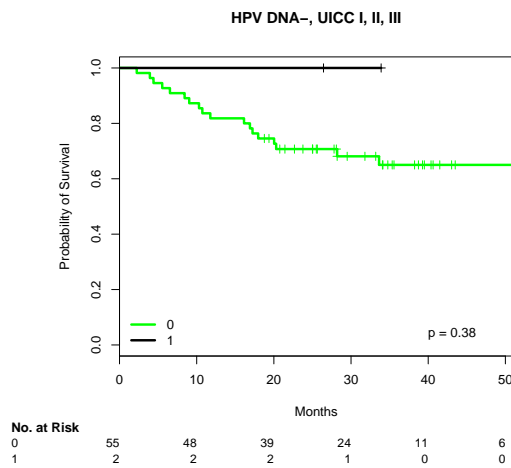


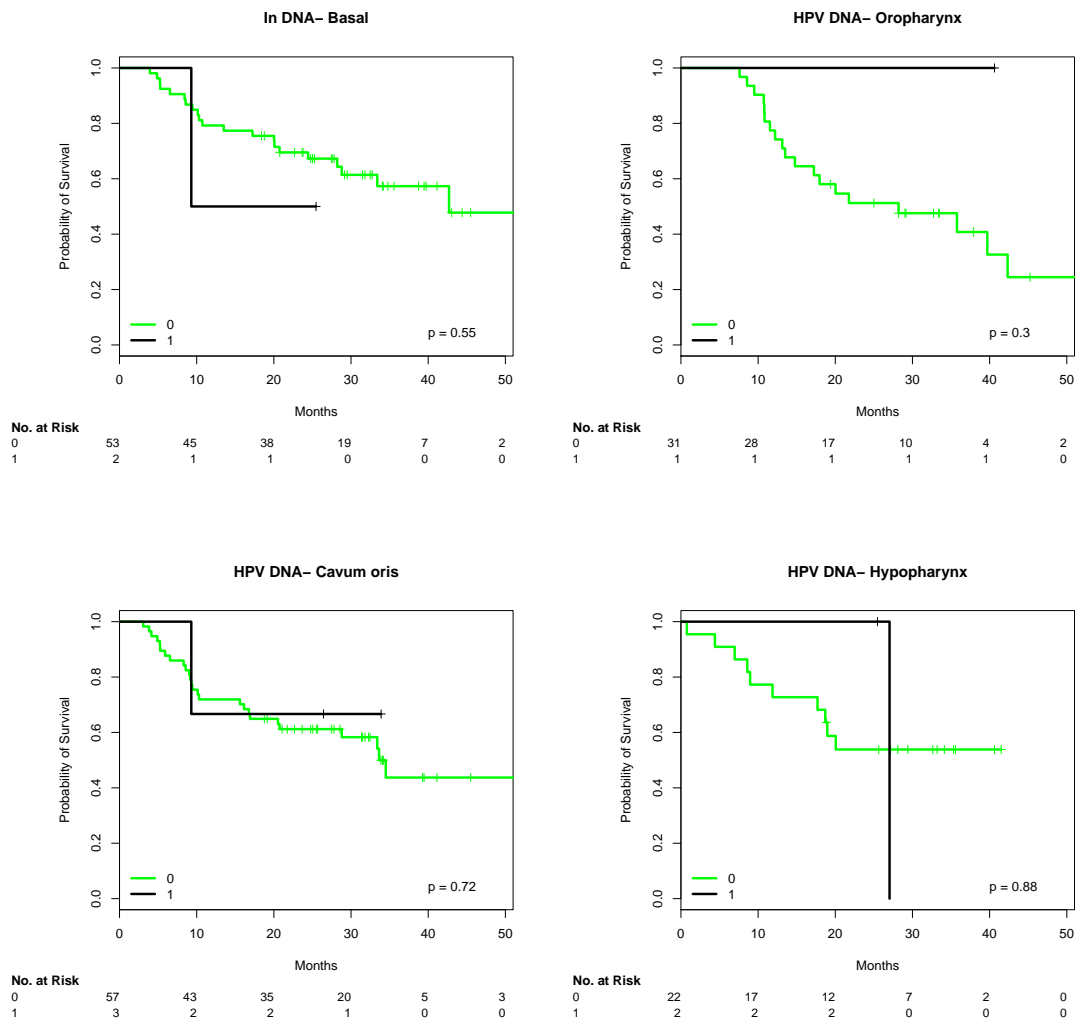
## 2.36 SMO

```
## 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
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.336      0.714      0.715 -0.47      0.64
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.714      1.4      0.176      2.9
##
## Concordance= 0.506 (se = 0.009 )
## Rsquare= 0.001 (max possible= 0.987 )
## Likelihood ratio test= 0.25 on 1 df,  p=0.619
## Wald test = 0.22 on 1 df,  p=0.638
## Score (logrank) test = 0.22 on 1 df,  p=0.636
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.432      0.649      0.718 -0.6      0.55
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.649      1.54      0.159      2.65
##
## Concordance= 0.509 (se = 0.013 )
## Rsquare= 0.003 (max possible= 0.986 )
## Likelihood ratio test= 0.42 on 1 df,  p=0.518
## Wald test = 0.36 on 1 df,  p=0.547
## Score (logrank) test = 0.37 on 1 df,  p=0.544
```



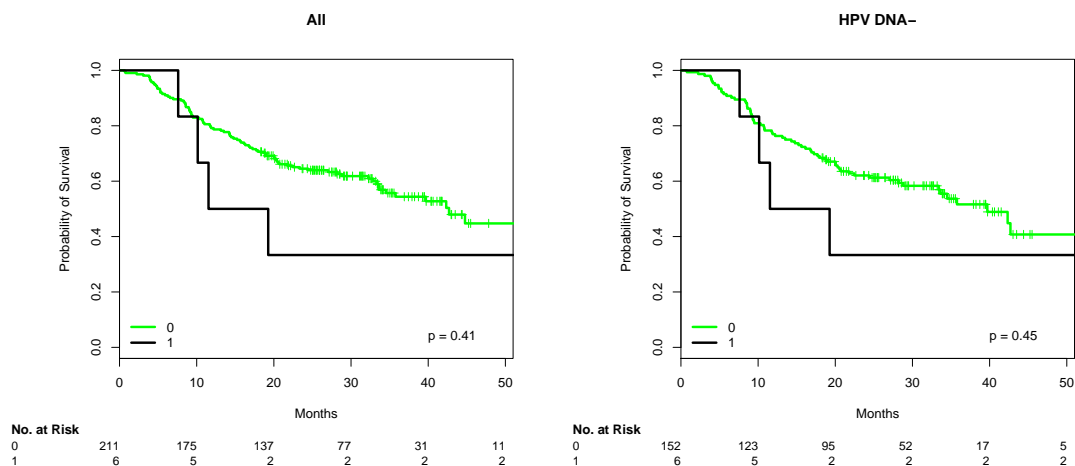


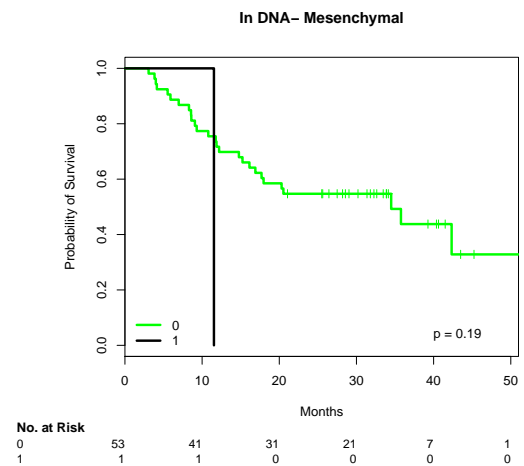
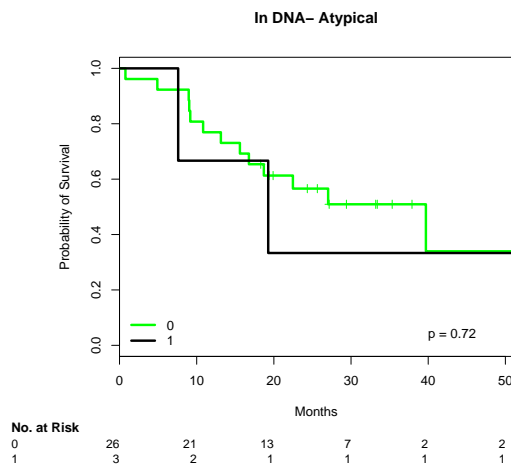
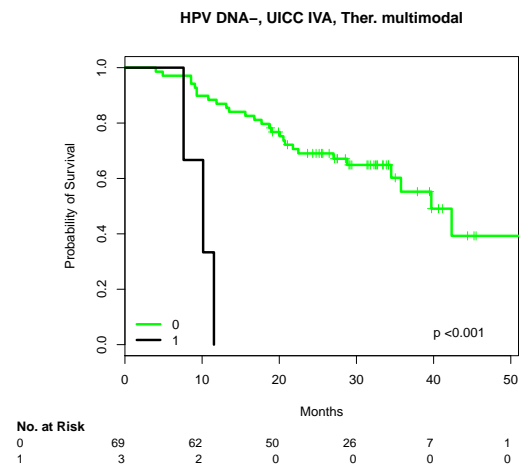
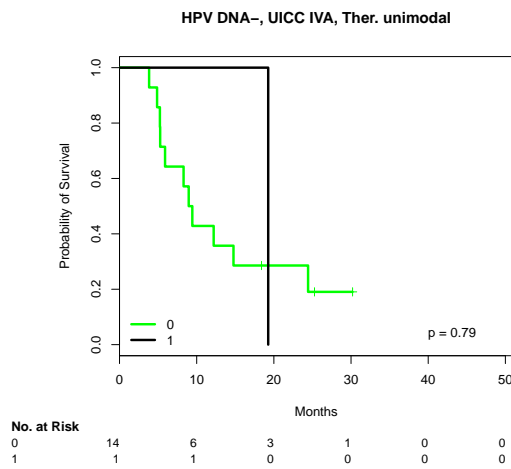
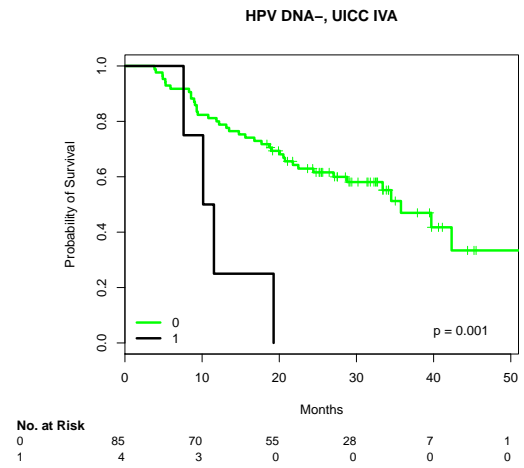
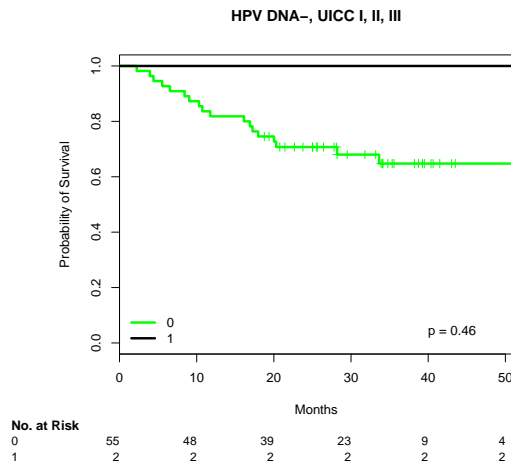


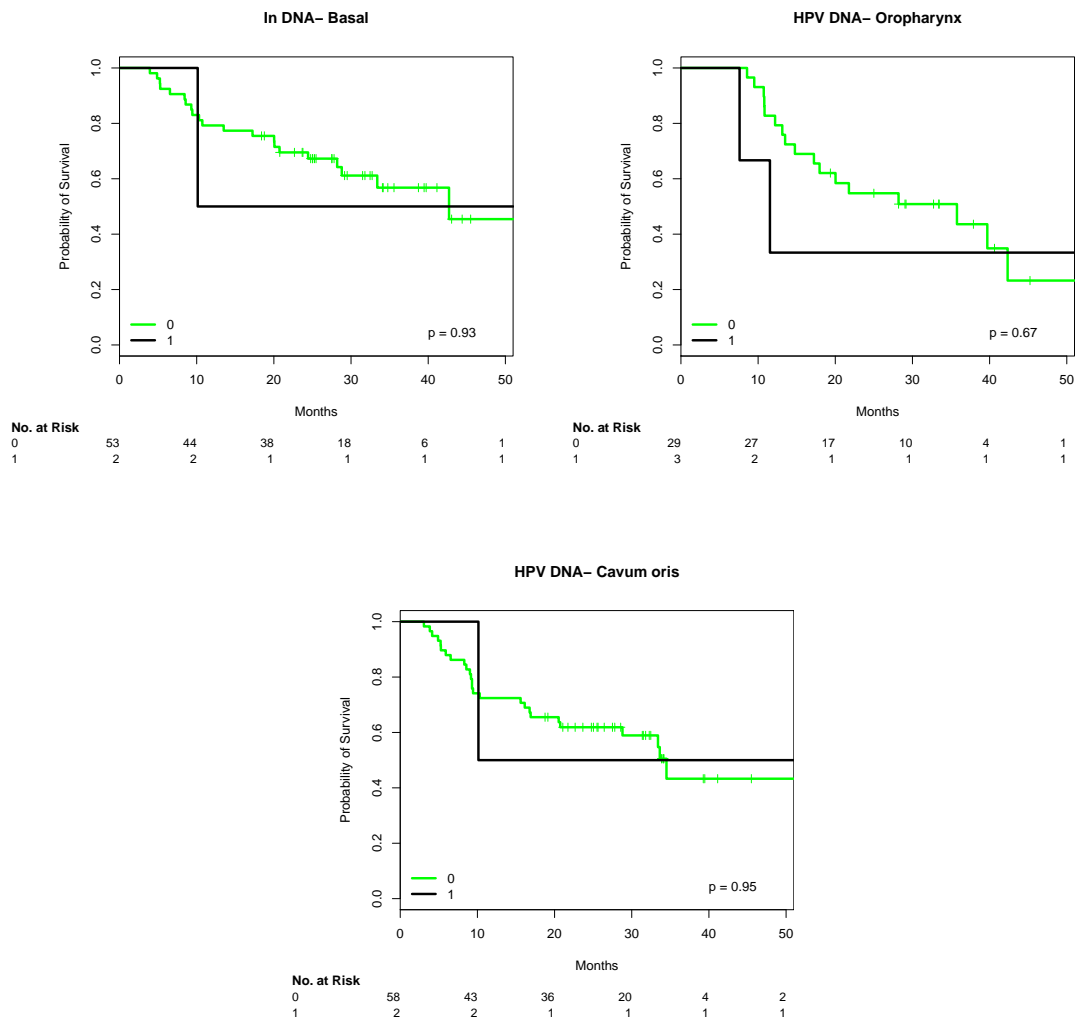
## 2.37 NOTCH1

```
## 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= 99
```

```
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.392      1.480    0.483 0.81    0.42
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.48      0.676    0.574    3.81
##
## Concordance= 0.511 (se = 0.008 )
## Rsquare= 0.003 (max possible= 0.987 )
## Likelihood ratio test= 0.6 on 1 df,  p=0.44
## Wald test = 0.66 on 1 df,  p=0.417
## Score (logrank) test = 0.66 on 1 df,  p=0.415
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] 0.376      1.456    0.498 0.76    0.45
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.46      0.687    0.549    3.86
##
## Concordance= 0.513 (se = 0.011 )
## Rsquare= 0.003 (max possible= 0.986 )
## Likelihood ratio test= 0.52 on 1 df,  p=0.471
## Wald test = 0.57 on 1 df,  p=0.45
## Score (logrank) test = 0.57 on 1 df,  p=0.448
```





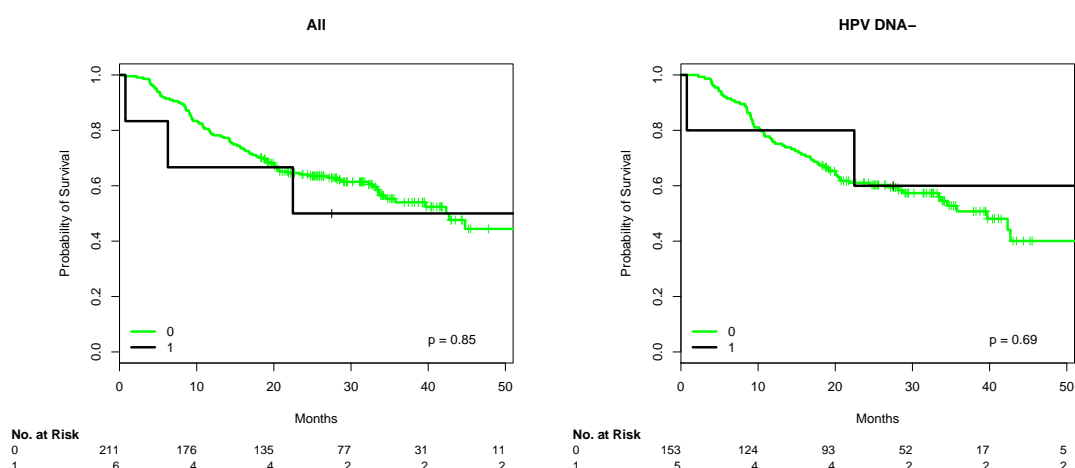


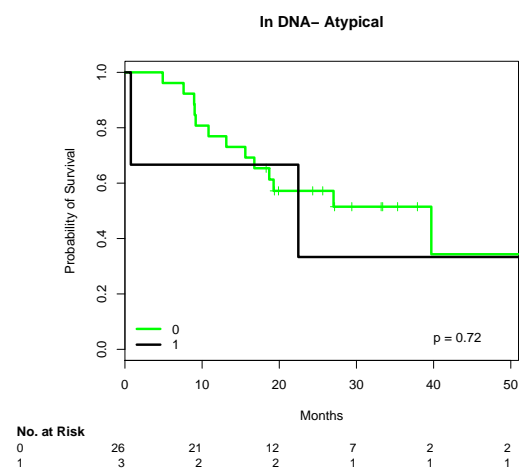
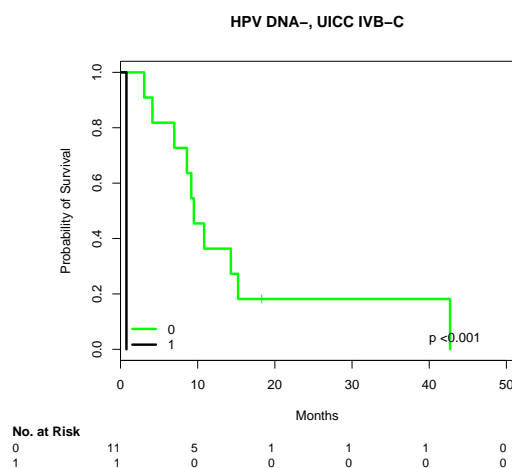
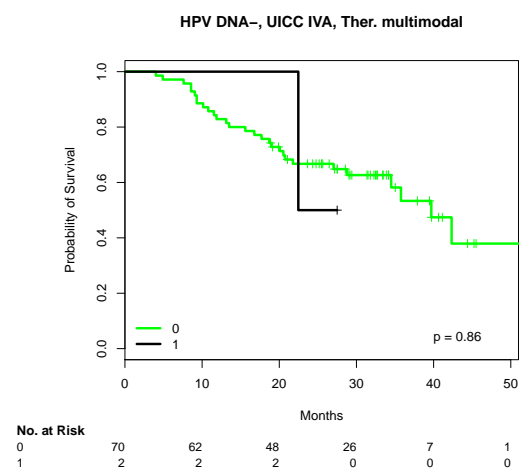
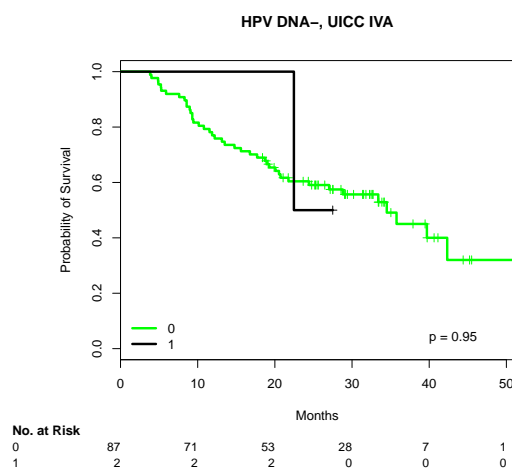
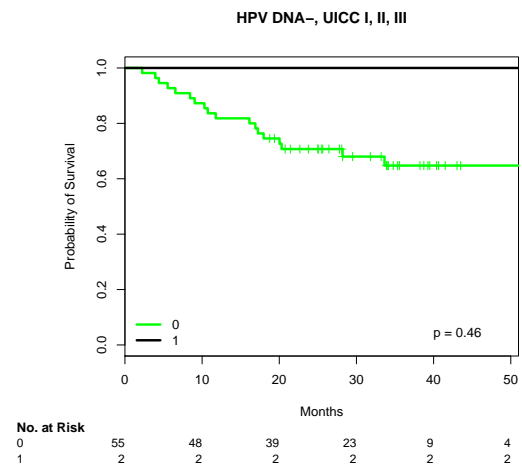
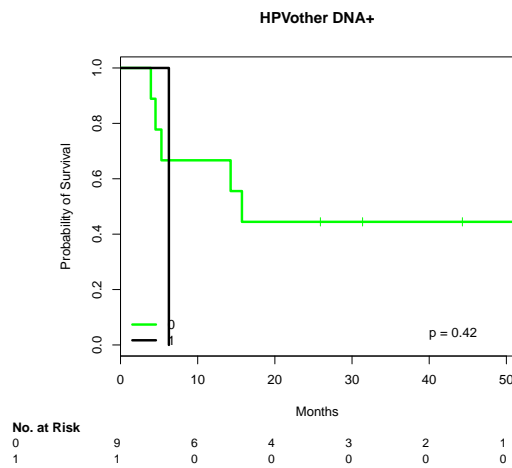
## 2.38 STK11

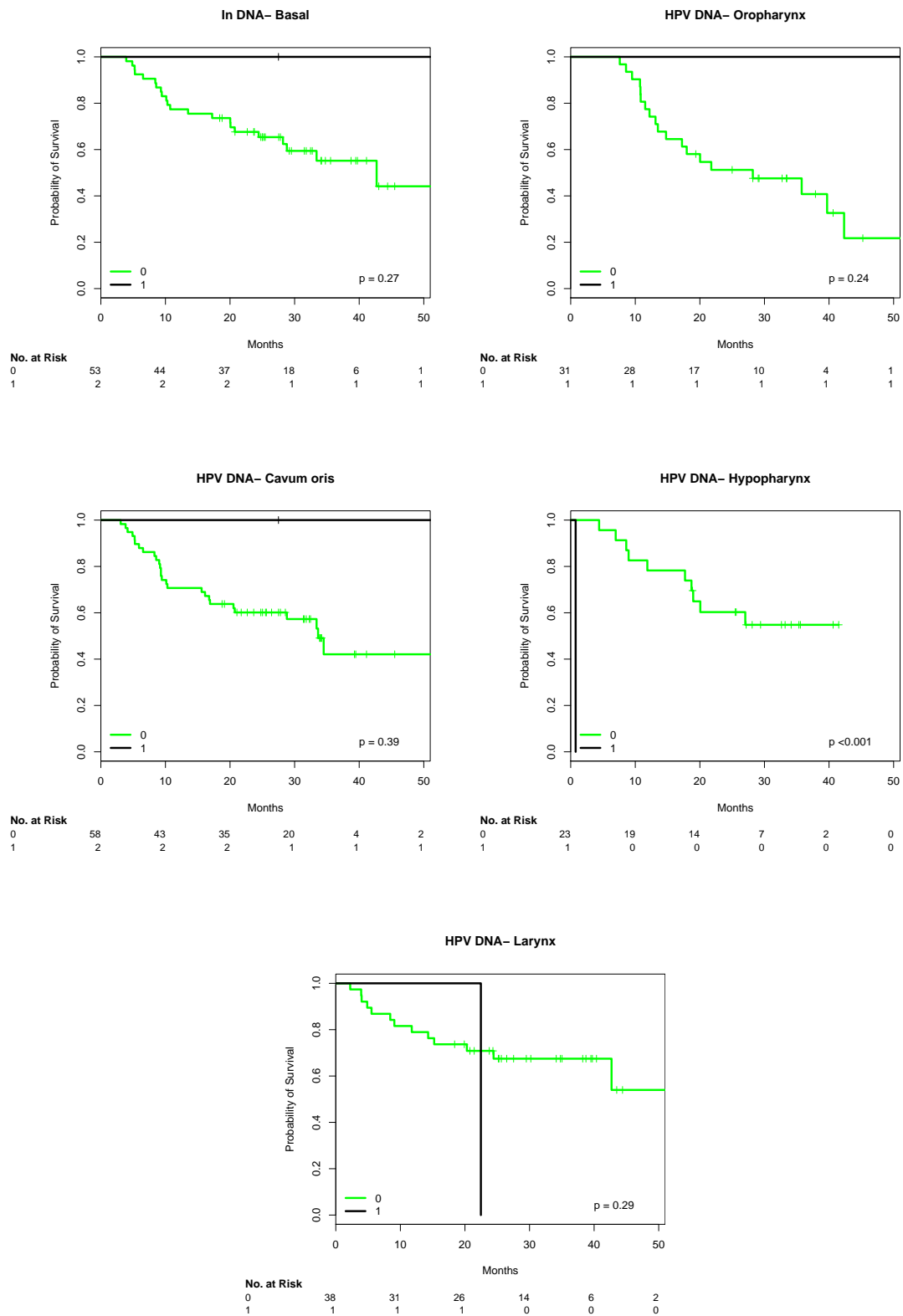
```
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
## Error: There is only 1 group
##
## Cox model for all patients
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 217, number of events= 99
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
```



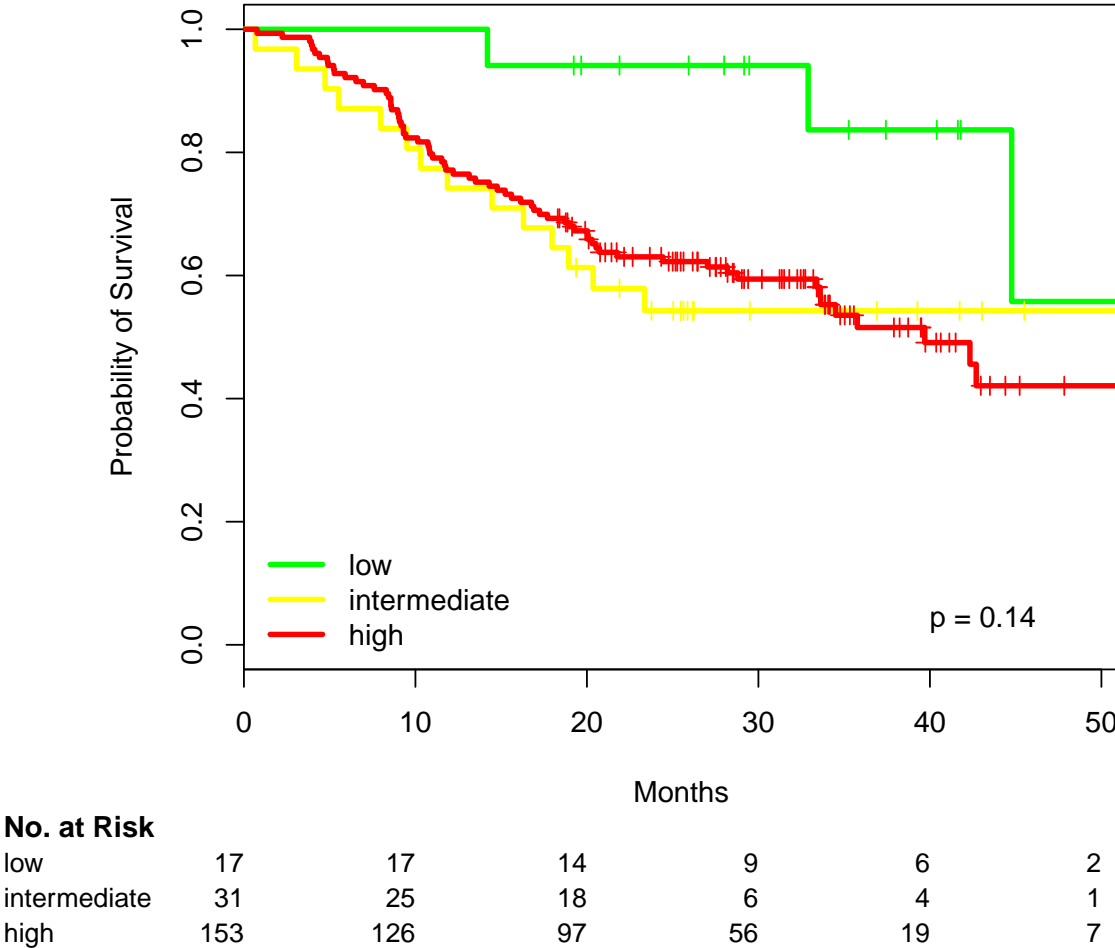
```
## split[cur.subset] 0.101      1.106      0.533 0.19      0.85
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      1.11      0.904      0.389      3.14
##
## Concordance= 0.506 (se = 0.008 )
## Rsquare= 0 (max possible= 0.987 )
## Likelihood ratio test= 0.03 on 1 df, p=0.852
## Wald test = 0.04 on 1 df, p=0.85
## Score (logrank) test = 0.04 on 1 df, p=0.85
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset] -0.253      0.777      0.634 -0.4      0.69
##
##              exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]      0.777      1.29      0.224      2.69
##
## Concordance= 0.502 (se = 0.011 )
## Rsquare= 0.001 (max possible= 0.986 )
## Likelihood ratio test= 0.17 on 1 df, p=0.68
## Wald test = 0.16 on 1 df, p=0.69
## Score (logrank) test = 0.16 on 1 df, p=0.69
```







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



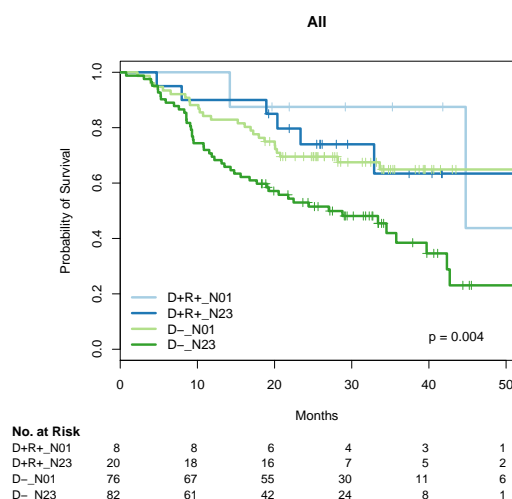
3 Question of whether the lymph node metastases in HPV- and in HPV+ are different.

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

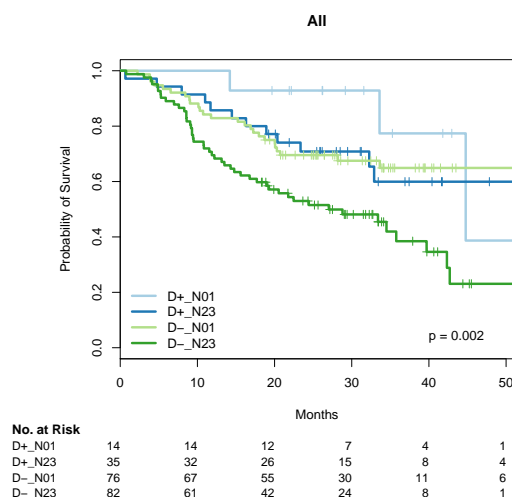
```
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 186, number of events= 83
##      (31 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+R+_N23 0.488      1.628    0.802 0.61    0.543
## split[cur.subset]D-_N01   0.548      1.729    0.735 0.75    0.456
## split[cur.subset]D-_N23   1.287      3.621    0.725 1.78    0.076 .
## ---
## 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      1.63      0.614    0.338    7.85
## split[cur.subset]D-_N01       1.73      0.578    0.410    7.30
## split[cur.subset]D-_N23       3.62      0.276    0.875   14.98
##
## Concordance= 0.603 (se = 0.032 )
## Rsquare= 0.068 (max possible= 0.985 )
## Likelihood ratio test= 13.1 on 3 df,  p=0.00439
## Wald test               = 12.6 on 3 df,  p=0.00566
## Score (logrank) test = 13.3 on 3 df,  p=0.004
```



## 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= 92
```

```
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 0.625      1.867    0.642 0.97    0.330
## split[cur.subset]D-_N01 0.657      1.929    0.609 1.08    0.281
## split[cur.subset]D-_N23 1.380      3.973    0.596 2.31    0.021 *
## ---
## 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      1.87      0.535    0.531    6.57
## split[cur.subset]D-_N01      1.93      0.518    0.584    6.37
## split[cur.subset]D-_N23      3.97      0.252    1.234   12.79
##
## Concordance= 0.607 (se = 0.031 )
## Rsquare= 0.07 (max possible= 0.985 )
## Likelihood ratio test= 15.1 on 3 df,  p=0.00175
## Wald test               = 14.4 on 3 df,  p=0.00243
## Score (logrank) test = 15.4 on 3 df,  p=0.00153
```



### 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= 92
## (10 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 0.625      1.867    0.642 0.97    0.330
## split[cur.subset]D-_N01 0.657      1.929    0.609 1.08    0.281
## split[cur.subset]D-_N23 1.380      3.973    0.596 2.31    0.021 *
## ---
## 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      1.87      0.535    0.531    6.57
## split[cur.subset]D-_N01      1.93      0.518    0.584    6.37
## split[cur.subset]D-_N23      3.97      0.252    1.234   12.79
##
## Concordance= 0.607 (se = 0.031 )
## Rsquare= 0.07 (max possible= 0.985 )
## Likelihood ratio test= 15.1 on 3 df,  p=0.00175
## Wald test               = 14.4 on 3 df,  p=0.00243
## Score (logrank) test = 15.4 on 3 df,  p=0.00153
##
##
## #####
## 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= 92

```

```
##      (10 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]D+_N23 0.625      1.867    0.642 0.97    0.330
## split[cur.subset]D-_N01 0.657      1.929    0.609 1.08    0.281
## split[cur.subset]D-_N23 1.380      3.973    0.596 2.31    0.021 *
## ---
## 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      1.87      0.535    0.531    6.57
## split[cur.subset]D-_N01      1.93      0.518    0.584    6.37
## split[cur.subset]D-_N23      3.97      0.252    1.234   12.79
##
## Concordance= 0.607 (se = 0.031 )
## Rsquare= 0.07 (max possible= 0.985 )
## Likelihood ratio test= 15.1 on 3 df, p=0.00175
## Wald test = 14.4 on 3 df, p=0.00243
## Score (logrank) test = 15.4 on 3 df, p=0.00153
```

### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N01__ND -9.63e-01  3.82e-01  6.58e-01 -1.46    0.14
## split[cur.subset]N01__WT -6.01e-01  5.48e-01  4.79e-01 -1.25    0.21
## split[cur.subset]N01_IR_D  2.18e-01  1.24e+00  7.39e-01  0.29    0.77
## split[cur.subset]N01_IR_ND -1.54e+01  1.99e-07  2.12e+03 -0.01    0.99
## split[cur.subset]N01_IR_WT -1.22e+00  2.95e-01  8.21e-01 -1.49    0.14
## split[cur.subset]N23__D    6.64e-01  1.94e+00  4.69e-01  1.42    0.16
## split[cur.subset]N23__ND -5.16e-01  5.97e-01  7.08e-01 -0.73    0.47
## split[cur.subset]N23__WT  1.28e-01  1.14e+00  4.57e-01  0.28    0.78
## split[cur.subset]N23_IR_D -9.41e-01  3.90e-01  8.46e-01 -1.11    0.27
## split[cur.subset]N23_IR_ND  1.64e-01  1.18e+00  6.16e-01  0.27    0.79
## split[cur.subset]N23_IR_WT -3.58e-01  6.99e-01  4.98e-01 -0.72    0.47
##
```



```

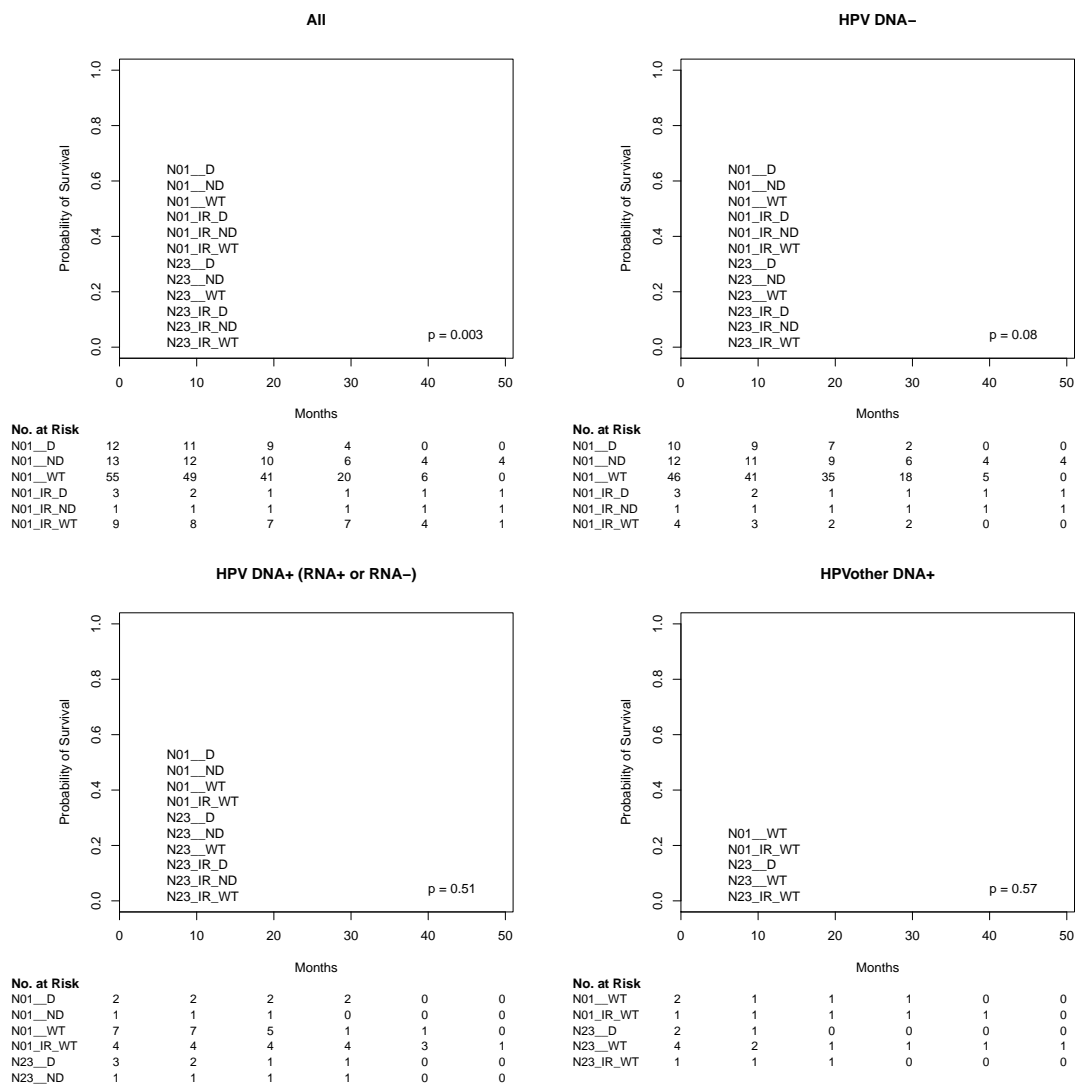
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N01__ND    3.82e-01  2.62e+00    0.1052    1.39
## split[cur.subset]N01__WT    5.48e-01  1.82e+00    0.2143    1.40
## split[cur.subset]N01_IR_D    1.24e+00  8.04e-01    0.2921    5.29
## split[cur.subset]N01_IR_ND    1.99e-07  5.03e+06    0.0000    Inf
## split[cur.subset]N01_IR_WT    2.95e-01  3.39e+00    0.0589    1.47
## split[cur.subset]N23__D    1.94e+00  5.15e-01    0.7746    4.87
## split[cur.subset]N23__ND    5.97e-01  1.67e+00    0.1491    2.39
## split[cur.subset]N23__WT    1.14e+00  8.80e-01    0.4640    2.78
## split[cur.subset]N23_IR_D    3.90e-01  2.56e+00    0.0744    2.05
## split[cur.subset]N23_IR_ND    1.18e+00  8.49e-01    0.3519    3.94
## split[cur.subset]N23_IR_WT    6.99e-01  1.43e+00    0.2635    1.86
##
## Concordance= 0.635   (se = 0.031 )
## Rsquare= 0.116   (max possible= 0.987 )
## Likelihood ratio test= 26.8   on 11 df,   p=0.00495
## Wald test               = 24.6   on 11 df,   p=0.0103
## Score (logrank) test = 28.5   on 11 df,   p=0.00274
##
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
##      n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N01__ND   -9.38e-01  3.92e-01  6.93e-01 -1.35    0.18
## split[cur.subset]N01__WT   -6.21e-01  5.38e-01  5.22e-01 -1.19    0.23
## split[cur.subset]N01_IR_D    2.23e-01  1.25e+00  7.81e-01  0.29    0.78
## split[cur.subset]N01_IR_ND  -1.64e+01  7.57e-08  3.22e+03 -0.01    1.00
## split[cur.subset]N01_IR_WT  -7.04e-01  4.94e-01  1.10e+00 -0.64    0.52
## split[cur.subset]N23__D     5.44e-01  1.72e+00  5.17e-01  1.05    0.29
## split[cur.subset]N23__ND   -4.43e-01  6.42e-01  7.32e-01 -0.61    0.54
## split[cur.subset]N23__WT     5.53e-02  1.06e+00  5.11e-01  0.11    0.91
## split[cur.subset]N23_IR_D   -2.32e-01  7.93e-01  8.37e-01 -0.28    0.78
## split[cur.subset]N23_IR_ND    4.71e-01  1.60e+00  6.83e-01  0.69    0.49
## split[cur.subset]N23_IR_WT    1.31e-01  1.14e+00  6.06e-01  0.22    0.83
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N01__ND    3.92e-01  2.55e+00    0.1006    1.52
## split[cur.subset]N01__WT    5.38e-01  1.86e+00    0.1932    1.50
## split[cur.subset]N01_IR_D    1.25e+00  8.00e-01    0.2705    5.78
## split[cur.subset]N01_IR_ND    7.57e-08  1.32e+07    0.0000    Inf
## split[cur.subset]N01_IR_WT    4.94e-01  2.02e+00    0.0577    4.24
## split[cur.subset]N23__D     1.72e+00  5.81e-01    0.6252    4.74
## split[cur.subset]N23__ND     6.42e-01  1.56e+00    0.1528    2.70

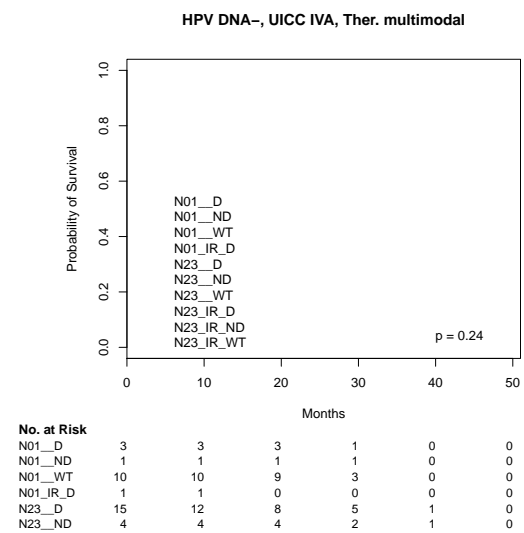
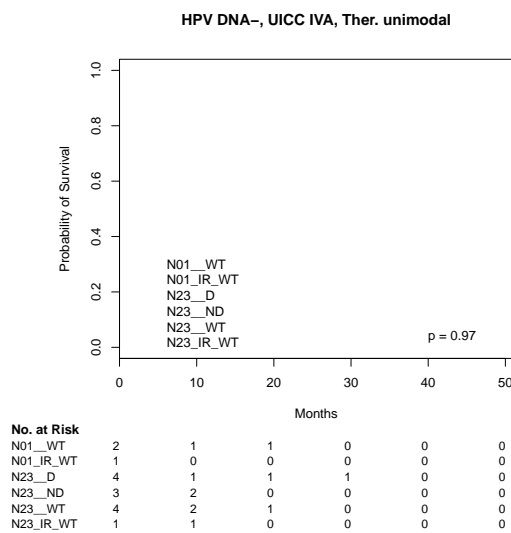
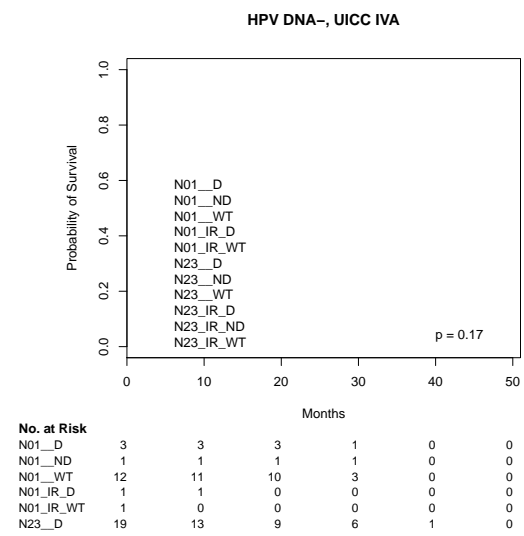
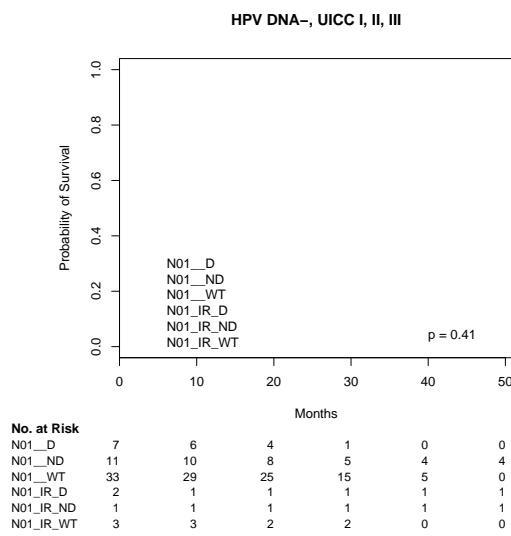
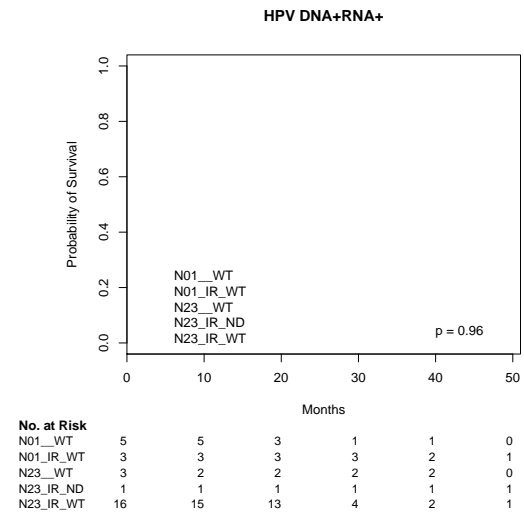
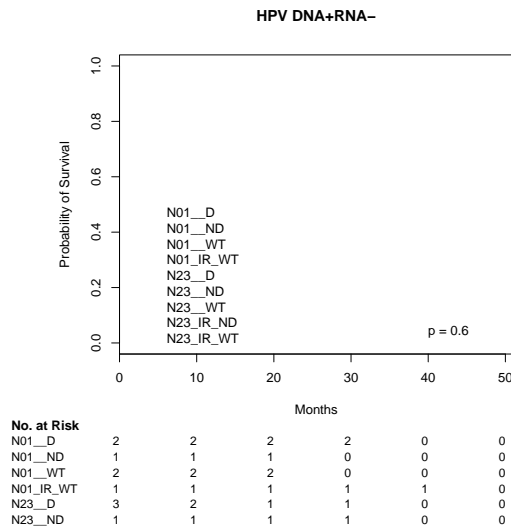
```

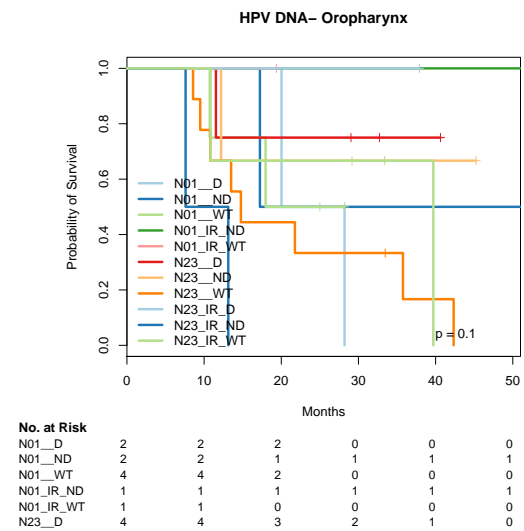
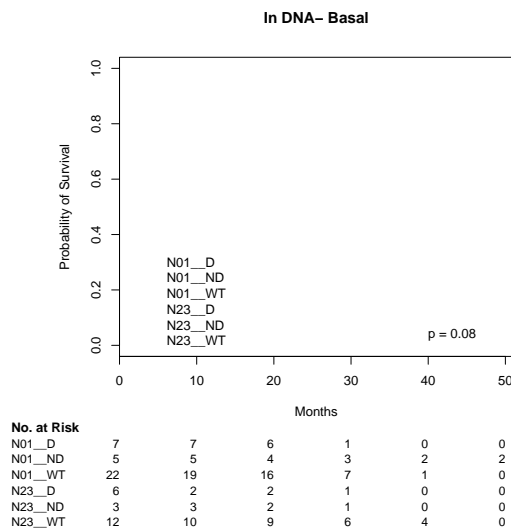
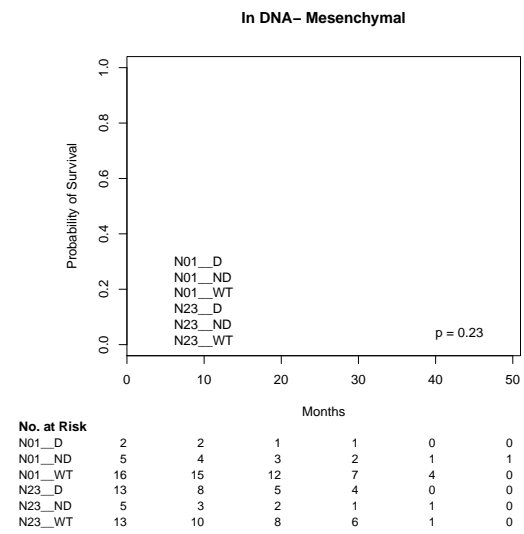
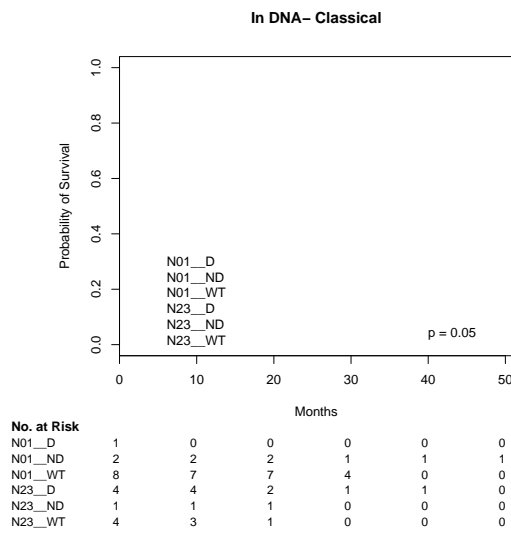
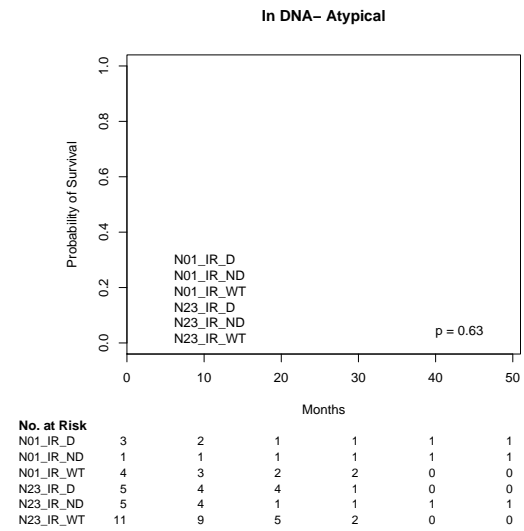
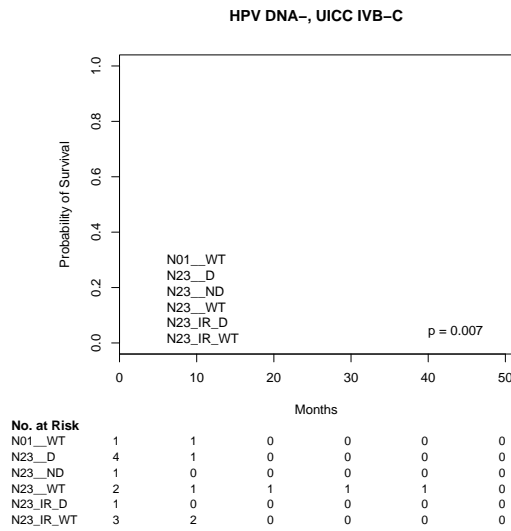
```

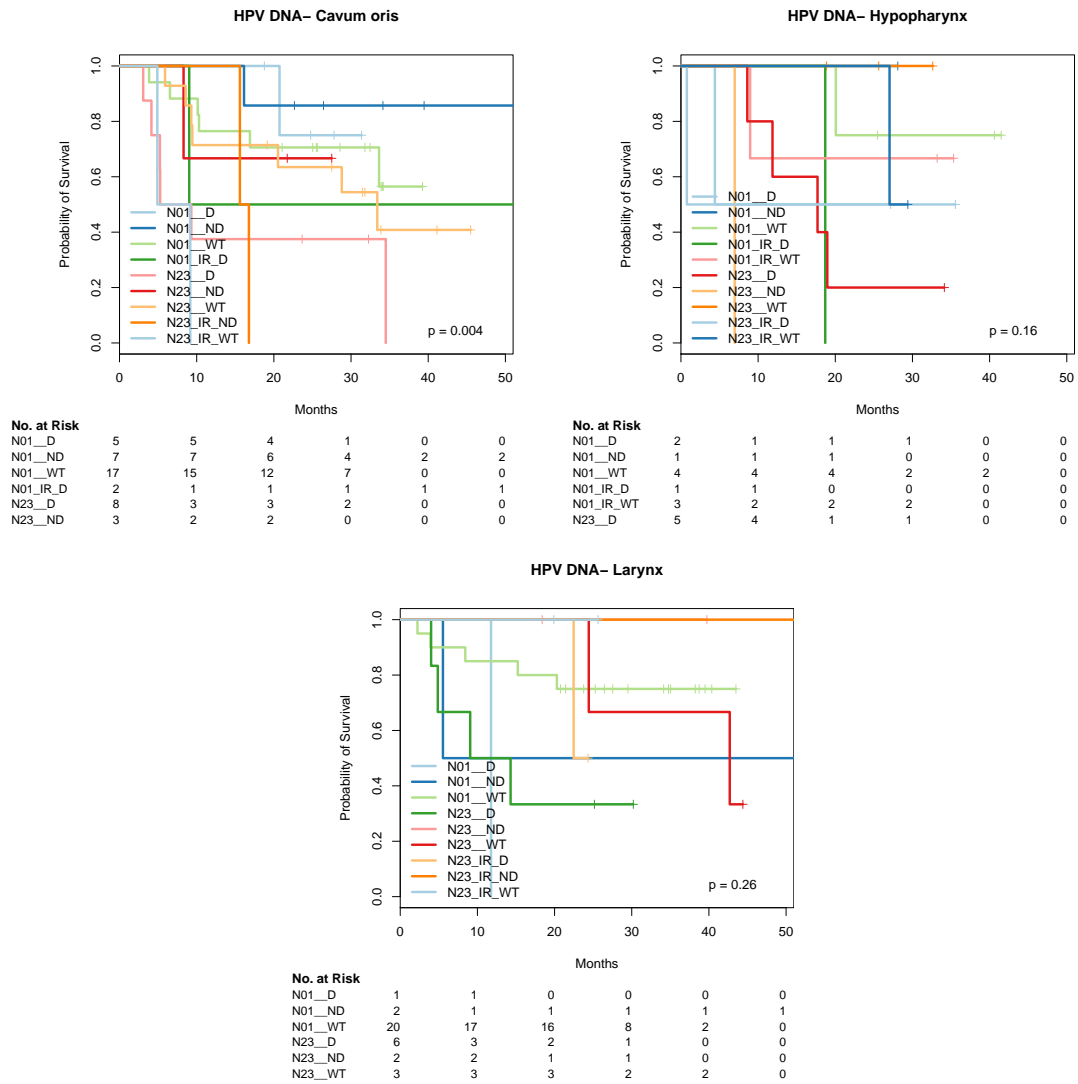
## split[cur.subset]N23__WT      1.06e+00    9.46e-01    0.3881    2.88
## split[cur.subset]N23_IR_D      7.93e-01    1.26e+00    0.1536    4.09
## split[cur.subset]N23_IR_ND      1.60e+00    6.24e-01    0.4196    6.11
## split[cur.subset]N23_IR_WT      1.14e+00    8.77e-01    0.3477    3.74
##
## Concordance= 0.625   (se = 0.035 )
## Rsquare= 0.108     (max possible= 0.986 )
## Likelihood ratio test= 18.1   on 11 df,   p=0.0803
## Wald test          = 15.4   on 11 df,   p=0.163
## Score (logrank) test = 18.1   on 11 df,   p=0.0795

```









### 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= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]N01__ND -9.38e-01  3.92e-01  6.93e-01 -1.35    0.18
## split[cur.subset]N01__WT -6.21e-01  5.38e-01  5.22e-01 -1.19    0.23
```

```
## split[cur.subset]N01_IR_D 2.23e-01 1.25e+00 7.81e-01 0.29 0.78
## split[cur.subset]N01_IR_ND -1.64e+01 7.57e-08 3.22e+03 -0.01 1.00
## split[cur.subset]N01_IR_WT -7.04e-01 4.94e-01 1.10e+00 -0.64 0.52
## split[cur.subset]N23__D 5.44e-01 1.72e+00 5.17e-01 1.05 0.29
## split[cur.subset]N23__ND -4.43e-01 6.42e-01 7.32e-01 -0.61 0.54
## split[cur.subset]N23__WT 5.53e-02 1.06e+00 5.11e-01 0.11 0.91
## split[cur.subset]N23_IR_D -2.32e-01 7.93e-01 8.37e-01 -0.28 0.78
## split[cur.subset]N23_IR_ND 4.71e-01 1.60e+00 6.83e-01 0.69 0.49
## split[cur.subset]N23_IR_WT 1.31e-01 1.14e+00 6.06e-01 0.22 0.83
##
##
## exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]N01__ND 3.92e-01 2.55e+00 0.1006 1.52
## split[cur.subset]N01__WT 5.38e-01 1.86e+00 0.1932 1.50
## split[cur.subset]N01_IR_D 1.25e+00 8.00e-01 0.2705 5.78
## split[cur.subset]N01_IR_ND 7.57e-08 1.32e+07 0.0000 Inf
## split[cur.subset]N01_IR_WT 4.94e-01 2.02e+00 0.0577 4.24
## split[cur.subset]N23__D 1.72e+00 5.81e-01 0.6252 4.74
## split[cur.subset]N23__ND 6.42e-01 1.56e+00 0.1528 2.70
## split[cur.subset]N23__WT 1.06e+00 9.46e-01 0.3881 2.88
## split[cur.subset]N23_IR_D 7.93e-01 1.26e+00 0.1536 4.09
## split[cur.subset]N23_IR_ND 1.60e+00 6.24e-01 0.4196 6.11
## split[cur.subset]N23_IR_WT 1.14e+00 8.77e-01 0.3477 3.74
##
## Concordance= 0.625 (se = 0.035 )
## Rsquare= 0.108 (max possible= 0.986 )
## Likelihood ratio test= 18.1 on 11 df, p=0.0803
## Wald test = 15.4 on 11 df, p=0.163
## Score (logrank) test = 18.1 on 11 df, p=0.0795
```

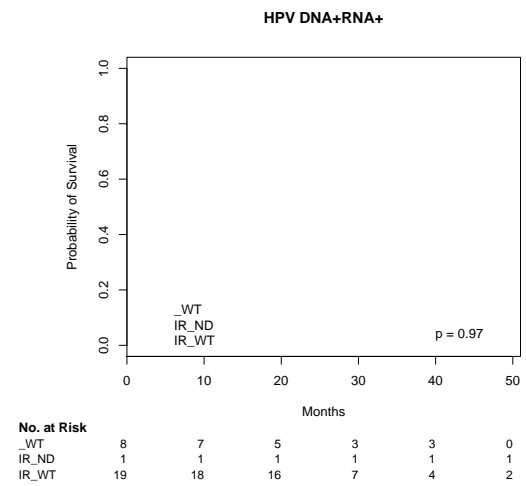
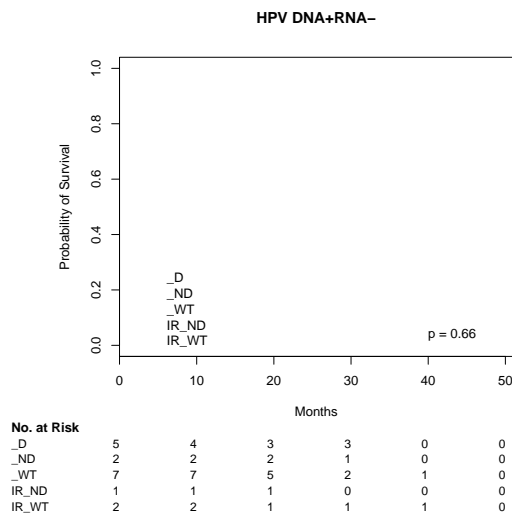
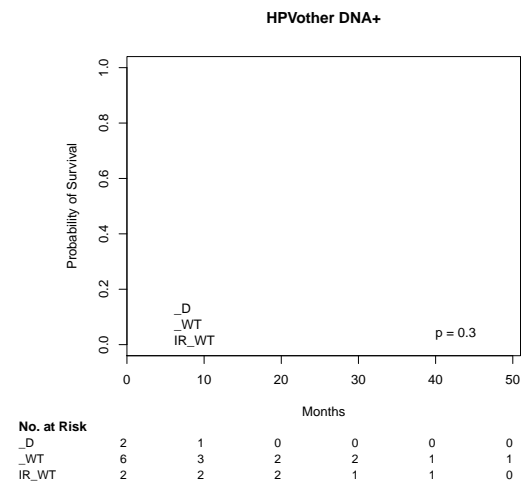
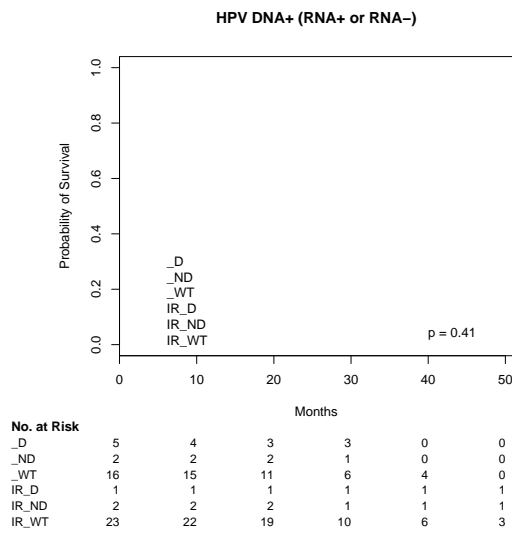
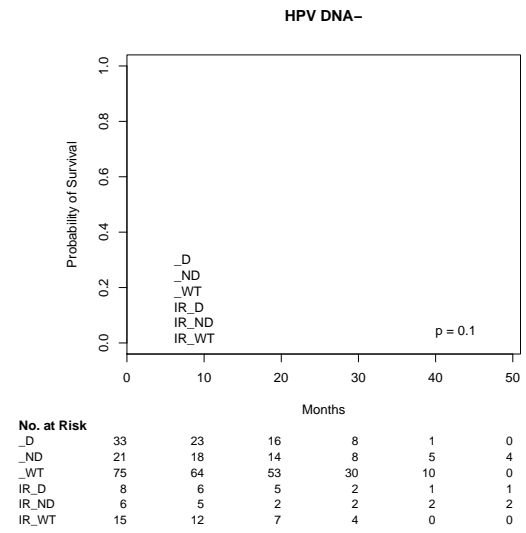
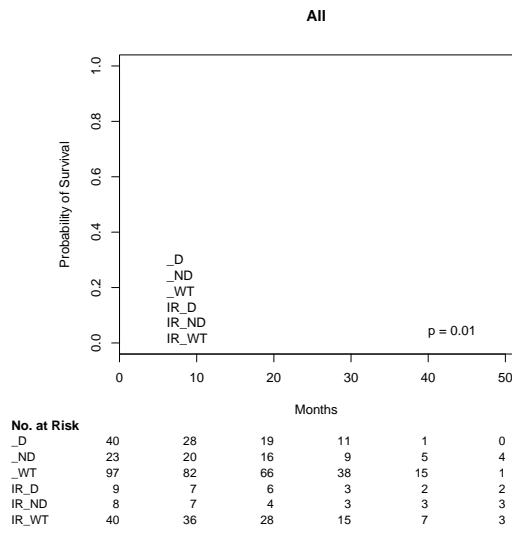
### 3.6 Interaction of TP53 Mut (disruptive (D), non-disruptive (ND)), IR Cluster

```
## 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= 99
##
## coef exp(coef) se(coef) z Pr(>|z|)
## split[cur.subset]_ND -1.267 0.282 0.438 -2.89 0.0038 **
## split[cur.subset]_WT -0.681 0.506 0.255 -2.67 0.0077 **
## split[cur.subset]IR_D -0.878 0.416 0.527 -1.67 0.0955 .
```

```

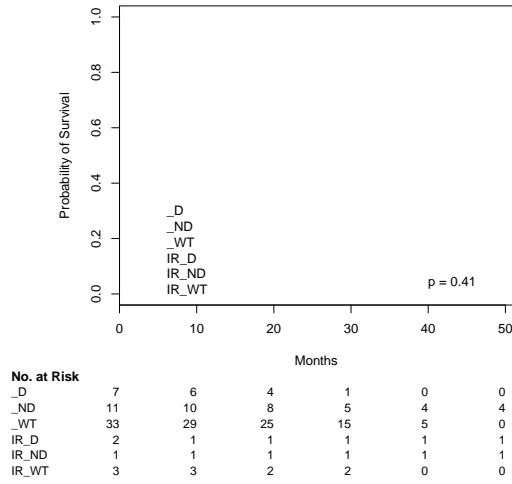
## split[cur.subset]IR_ND -0.538      0.584      0.505 -1.07      0.2869
## split[cur.subset]IR_WT -0.984      0.374      0.332 -2.96      0.0031 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]_ND      0.282      3.55      0.119      0.665
## split[cur.subset]_WT      0.506      1.98      0.307      0.835
## split[cur.subset]IR_D      0.416      2.41      0.148      1.167
## split[cur.subset]IR_ND      0.584      1.71      0.217      1.572
## split[cur.subset]IR_WT      0.374      2.68      0.195      0.717
##
## Concordance= 0.595 (se = 0.03 )
## Rsquare= 0.06 (max possible= 0.987 )
## Likelihood ratio test= 13.4 on 5 df,  p=0.0198
## Wald test = 14.1 on 5 df,  p=0.0151
## Score (logrank) test = 15 on 5 df,  p=0.0105
##
## #####
## Cox model in HPV DNA-
## Call:
## coxph(formula = surv.obj[cur.subset] ~ split[cur.subset])
##
## n= 158, number of events= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## split[cur.subset]_ND -1.127      0.324      0.455 -2.48      0.013 *
## split[cur.subset]_WT -0.683      0.505      0.289 -2.36      0.018 *
## split[cur.subset]IR_D -0.359      0.698      0.516 -0.69      0.487
## split[cur.subset]IR_ND -0.309      0.734      0.568 -0.54      0.587
## split[cur.subset]IR_WT -0.417      0.659      0.439 -0.95      0.342
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## split[cur.subset]_ND      0.324      3.09      0.133      0.79
## split[cur.subset]_WT      0.505      1.98      0.287      0.89
## split[cur.subset]IR_D      0.698      1.43      0.254      1.92
## split[cur.subset]IR_ND      0.734      1.36      0.241      2.24
## split[cur.subset]IR_WT      0.659      1.52      0.279      1.56
##
## Concordance= 0.591 (se = 0.034 )
## Rsquare= 0.054 (max possible= 0.986 )
## Likelihood ratio test= 8.7 on 5 df,  p=0.121
## Wald test = 8.75 on 5 df,  p=0.119
## Score (logrank) test = 9.18 on 5 df,  p=0.102

```

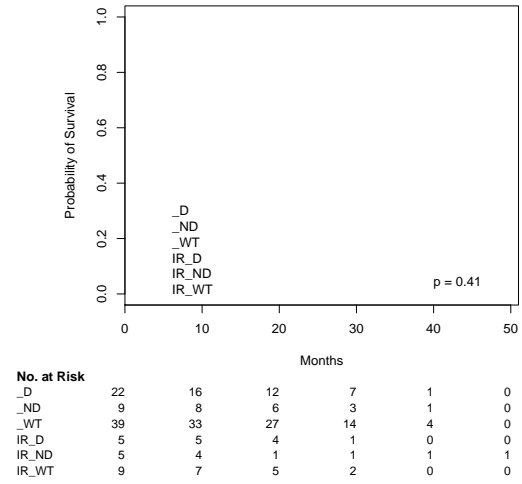




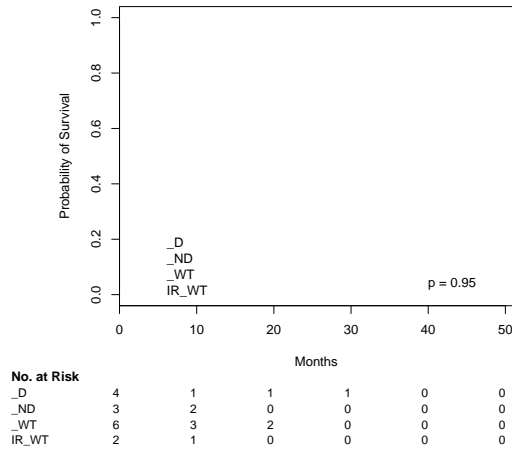
HPV DNA-, UICC I, II, III



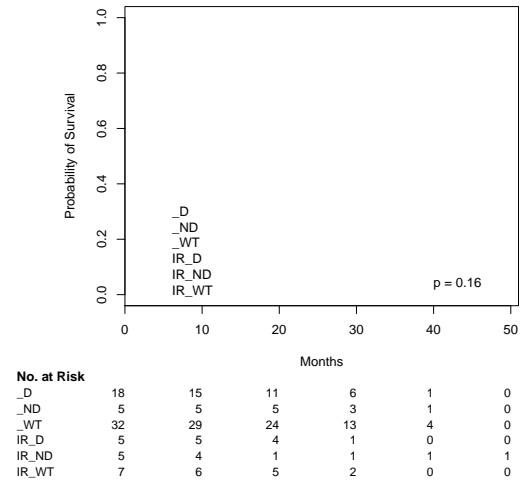
HPV DNA-, UICC IVA



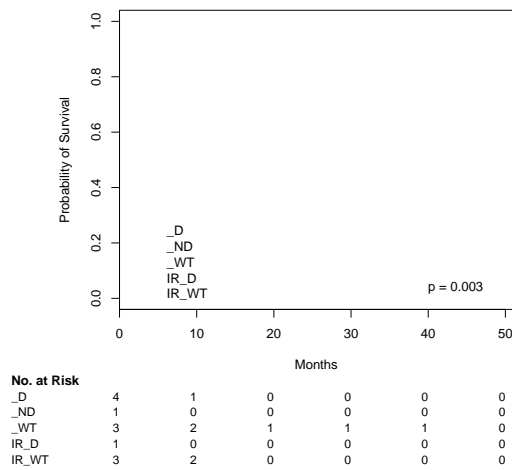
HPV DNA-, UICC IVA, Ther. unimodal



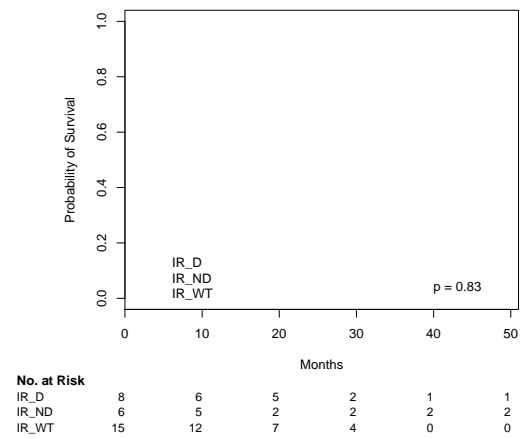
HPV DNA-, UICC IVA, Ther. multimodal

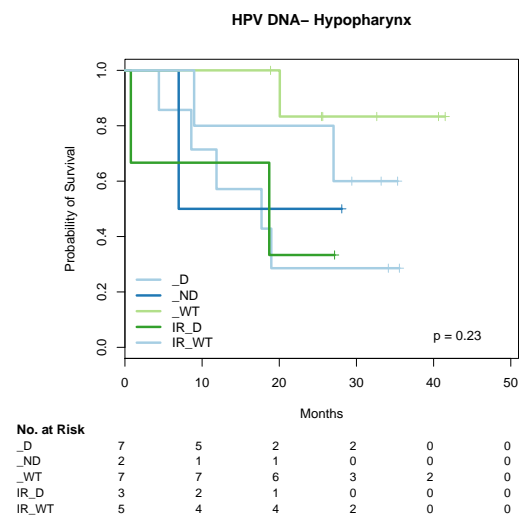
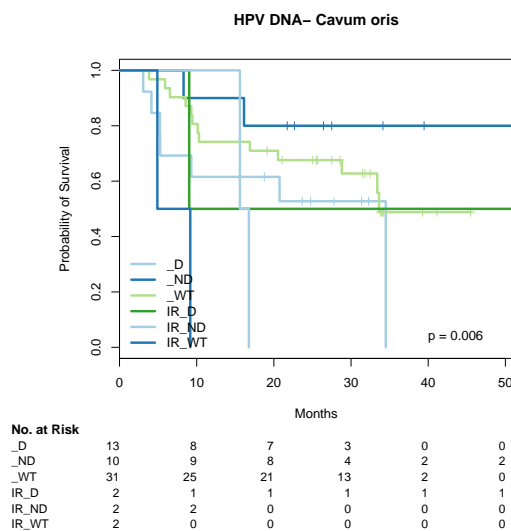
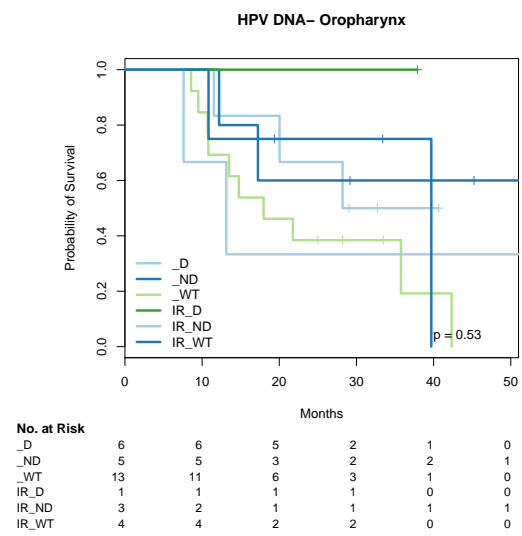
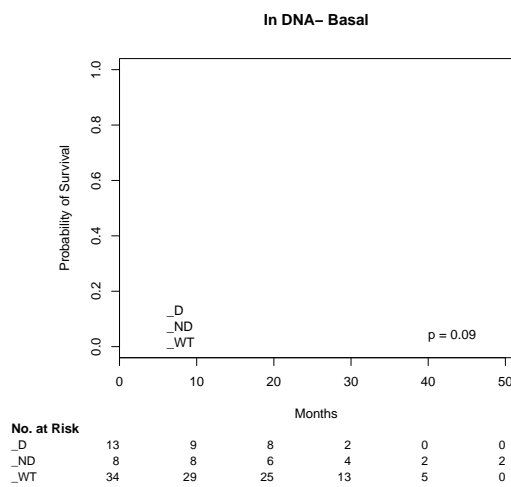
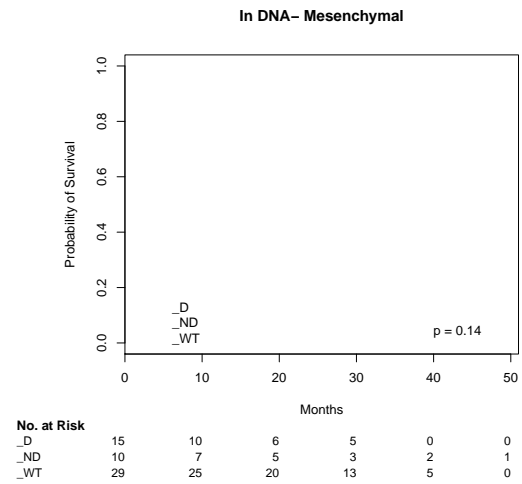
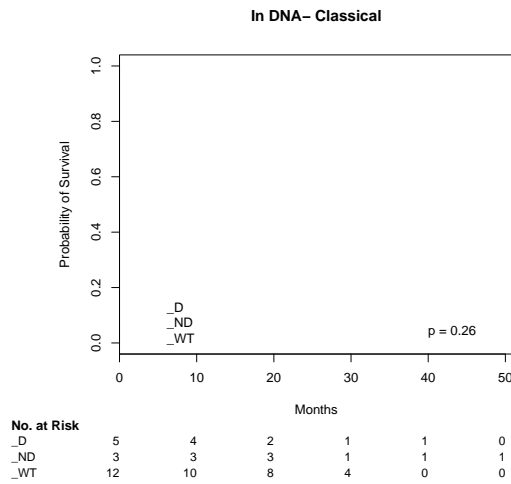


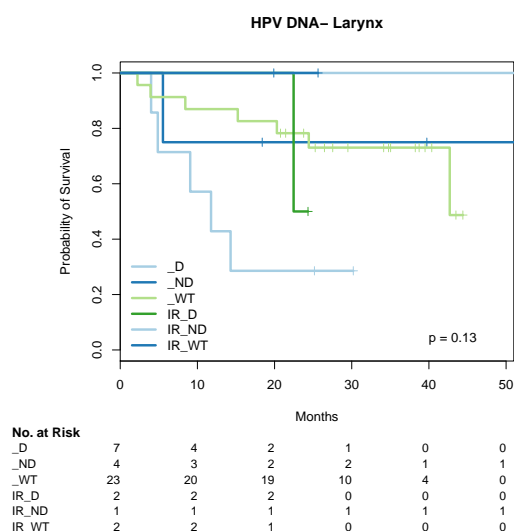
HPV DNA-, UICC IVB-C



In DNA- Atypical







## 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= 99

##

	coef	exp(coef)	se(coef)	z	Pr(> z )
UICC_3CATIVA	0.628	1.873	0.250	2.51	0.012 *
UICC_3CATIVB-C	1.327	3.769	0.340	3.91	9.3e-05 ***

## ---

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

##

	exp(coef)	exp(-coef)	lower .95	upper .95
UICC_3CATIVA	1.87	0.534	1.15	3.06
UICC_3CATIVB-C	3.77	0.265	1.94	7.33

##

## Concordance= 0.601 (se = 0.027 )

## Rsquare= 0.067 (max possible= 0.987 )

## Likelihood ratio test= 15.1 on 2 df, p=0.000536

## Wald test = 15.5 on 2 df, p=0.000431

## Score (logrank) test = 16.7 on 2 df, p=0.000238

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

```
##              rho    chisq    p
## UICC_3CATIVA  -0.00252 0.000615 0.980
## UICC_3CATIVB-C -0.08597 0.714041 0.398
## GLOBAL              NA 0.976455 0.614
```

### 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNADNA+ -0.488      0.614      0.284 -1.72   0.086 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNADNA+      0.614          1.63      0.352      1.07
##
## Concordance= 0.547 (se = 0.024 )
## Rsquare= 0.016 (max possible= 0.985 )
## Likelihood ratio test= 3.28 on 1 df,  p=0.0702
## Wald test               = 2.96 on 1 df,  p=0.0855
## Score (logrank) test = 3.02 on 1 df,  p=0.0825

cox.zph(surv.res)

##              rho chisq    p
## HPV16_DNADNA+ 0.118  1.22 0.27
```

### 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= 89
##   (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.639      1.894    0.261  2.45   0.014 *
## UICC_3CATIVB-C  1.774      5.896    0.359  4.95  7.5e-07 ***
## HPV16_DNADNA+ -0.713      0.490    0.290 -2.45   0.014 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.89      0.528      1.136      3.161
## UICC_3CATIVB-C        5.90      0.170      2.920     11.904
## HPV16_DNADNA+        0.49      2.040      0.277      0.866
##
## Concordance= 0.618 (se = 0.031 )
## Rsquare= 0.115 (max possible= 0.985 )
## Likelihood ratio test= 24.7 on 3 df,  p=1.79e-05
## Wald test               = 26.8 on 3 df,  p=6.58e-06
## Score (logrank) test = 29.1 on 3 df,  p=2.14e-06

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA    0.0764 0.5120 0.474
## UICC_3CATIVB-C  0.0109 0.0105 0.918
## HPV16_DNADNA+  0.1098 1.0806 0.299
## GLOBAL          NA 1.7070 0.635
```

#### 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= 89
##   (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.313      0.731    0.425 -0.74   0.462
## HPV16_DNA_RNADNA+RNA+ -0.591      0.554    0.354 -1.67   0.095 .
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.731      1.37    0.318    1.68
## HPV16_DNA_RNADNA+RNA+    0.554      1.81    0.277    1.11
##
## Concordance= 0.549  (se = 0.025 )
## Rsquare= 0.017   (max possible= 0.985 )
## Likelihood ratio test= 3.55  on 2 df,   p=0.17
## Wald test          = 3.13  on 2 df,   p=0.209
## Score (logrank) test = 3.21  on 2 df,   p=0.201

cox.zph(surv.res)

##               rho  chisq    p
## HPV16_DNA_RNADNA+RNA- 0.0128 0.0147 0.903
## HPV16_DNA_RNADNA+RNA+ 0.1567 2.0933 0.148
## GLOBAL                NA 2.0933 0.351
```

#### 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= 89
##      (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.641     1.899   0.261   2.45   0.014 *
## UICC_3CATIVB-C     1.770     5.870   0.359   4.93  8.1e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.565     0.568   0.432  -1.31   0.190
## HPV16_DNA_RNADNA+RNA+ -0.800     0.449   0.359  -2.23   0.026 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.899     0.527   1.138   3.168
## UICC_3CATIVB-C     5.870     0.170   2.906  11.859
## HPV16_DNA_RNADNA+RNA- 0.568     1.760   0.244   1.324
## HPV16_DNA_RNADNA+RNA+ 0.449     2.225   0.223   0.908
##
## Concordance= 0.63  (se = 0.031 )
```

```
## Rsquare= 0.115    (max possible= 0.985 )
## Likelihood ratio test= 24.9  on 4 df,    p=5.3e-05
## Wald test          = 26.9  on 4 df,    p=2.13e-05
## Score (logrank) test = 29.2  on 4 df,    p=7.05e-06

cox.zph(surv.res)

##                rho    chisq    p
## UICC_3CATIVA      0.074627 4.89e-01 0.485
## UICC_3CATIVB-C    0.011577 1.21e-02 0.912
## HPV16_DNA_RNADNA+RNA- 0.000994 9.64e-05 0.992
## HPV16_DNA_RNADNA+RNA+ 0.157935 2.06e+00 0.151
## GLOBAL           NA 2.72e+00 0.606
```

#### 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= 88
## (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.637      1.890   0.263   2.42   0.015 *
## UICC_3CATIVB-C    1.726      5.617   0.359   4.81  1.5e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.473      0.623   0.433  -1.09   0.275
## HPV16_DNA_RNADNA+RNA+ -0.653      0.521   0.366  -1.79   0.074 .
## I(PACKYEARS > 30)TRUE  0.435      1.545   0.223   1.95   0.051 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.890      0.529   1.130      3.16
## UICC_3CATIVB-C    5.617      0.178   2.780     11.35
## HPV16_DNA_RNADNA+RNA-  0.623      1.605   0.267      1.46
## HPV16_DNA_RNADNA+RNA+  0.521      1.921   0.254      1.07
## I(PACKYEARS > 30)TRUE  1.545      0.647   0.998      2.39
##
## Concordance= 0.64 (se = 0.033 )
## Rsquare= 0.129    (max possible= 0.985 )
## Likelihood ratio test= 27.8  on 5 df,    p=3.92e-05
## Wald test          = 30.1  on 5 df,    p=1.43e-05
```

```
## Score (logrank) test = 32.6 on 5 df, p=4.47e-06
```

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

```
##              rho      chisq      p
## UICC_3CATIVA      0.085429 6.35e-01 0.4256
## UICC_3CATIVB-C      0.000297 7.91e-06 0.9978
## HPV16_DNA_RNADNA+RNA- 0.021065 4.32e-02 0.8354
## HPV16_DNA_RNADNA+RNA+ 0.173838 2.86e+00 0.0906
## I(PACKYEARS > 30)TRUE 0.078947 6.35e-01 0.4256
## GLOBAL              NA 3.86e+00 0.5696
```

#### 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= 88
```

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

```
##
```

```
##              coef exp(coef) se(coef)
## UICC_3CATIVA      0.718      2.050    0.265
## UICC_3CATIVB-C      1.752      5.765    0.360
## HPV16_DNA_RNADNA+RNA- -0.542      0.582    0.612
## HPV16_DNA_RNADNA+RNA+ -1.950      0.142    0.733
## I(PACKYEARS > 30)TRUE  0.205      1.228    0.238
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.110      1.116    0.856
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.350     10.485    0.843
```

```
##              z Pr(>|z|)
## UICC_3CATIVA      2.70  0.0068 **
## UICC_3CATIVB-C      4.87  1.1e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.89  0.3758
## HPV16_DNA_RNADNA+RNA+ -2.66  0.0078 **
## I(PACKYEARS > 30)TRUE  0.86  0.3883
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.13  0.8981
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.79  0.0053 **
```

```
## ---
```

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

```
##
```

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



```
## UICC_3CATIVA                2.050      0.4878      1.2184
## UICC_3CATIVB-C              5.765      0.1735      2.8479
## HPV16_DNA_RNADNA+RNA-      0.582      1.7190      0.1754
## HPV16_DNA_RNADNA+RNA+      0.142      7.0292      0.0338
## I(PACKYEARS > 30)TRUE      1.228      0.8146      0.7704
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  1.116      0.8962      0.2086
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  10.485      0.0954      2.0098
##                               upper .95
## UICC_3CATIVA                3.450
## UICC_3CATIVB-C             11.669
## HPV16_DNA_RNADNA+RNA-      1.929
## HPV16_DNA_RNADNA+RNA+      0.599
## I(PACKYEARS > 30)TRUE      1.956
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  5.968
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  54.703
##
## Concordance= 0.66 (se = 0.033 )
## Rsquare= 0.17 (max possible= 0.985 )
## Likelihood ratio test= 37.5 on 7 df, p=3.74e-06
## Wald test = 34.9 on 7 df, p=1.17e-05
## Score (logrank) test = 39.5 on 7 df, p=1.58e-06

cox.zph(surv.res)

##                               rho  chisq      p
## UICC_3CATIVA                0.1194 1.2925 0.2556
## UICC_3CATIVB-C              0.0195 0.0344 0.8528
## HPV16_DNA_RNADNA+RNA-      -0.0812 0.6150 0.4329
## HPV16_DNA_RNADNA+RNA+      0.2377 4.5538 0.0328
## I(PACKYEARS > 30)TRUE      0.0152 0.0209 0.8850
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.1348 1.6316 0.2015
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.1225 1.2525 0.2631
## GLOBAL                      NA 9.7198 0.2050
```

#### 4.1.8 UICC, HPV16 DNA RNA, Age

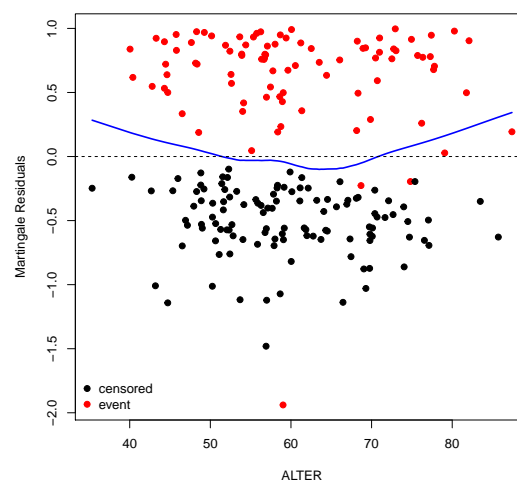
```
surv.res <- coxph(surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER,
  data = ds[cur.subset, ], model = TRUE)
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA +
##       ALTER, data = ds[cur.subset, ], model = TRUE)
##
## n= 203, number of events= 89
## (14 observations deleted due to missingness)
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.63185   1.88108  0.26147   2.42   0.016 *
## UICC_3CATIVB-C     1.75965   5.81038  0.35940   4.90  9.8e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.54356   0.58068  0.43215  -1.26   0.208
## HPV16_DNA_RNADNA+RNA+ -0.84127   0.43116  0.36401  -2.31   0.021 *
## ALTER              0.00766   1.00769  0.01063   0.72   0.471
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.881      0.532      1.127      3.14
## UICC_3CATIVB-C         5.810      0.172      2.873     11.75
## HPV16_DNA_RNADNA+RNA-   0.581      1.722      0.249      1.35
## HPV16_DNA_RNADNA+RNA+   0.431      2.319      0.211      0.88
## ALTER                 1.008      0.992      0.987      1.03
##
## Concordance= 0.63 (se = 0.033 )
## Rsquare= 0.118 (max possible= 0.985 )
## Likelihood ratio test= 25.4 on 5 df, p=0.000116
## Wald test              = 27.1 on 5 df, p=5.46e-05
## Score (logrank) test = 29.5 on 5 df, p=1.85e-05

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA      0.07400  0.481648  0.488
## UICC_3CATIVB-C     0.01042  0.009740  0.921
## HPV16_DNA_RNADNA+RNA- -0.00245  0.000591  0.981
## HPV16_DNA_RNADNA+RNA+  0.16110  2.123618  0.145
## ALTER             -0.02861  0.091287  0.763
## GLOBAL              NA  2.767668  0.736
```



#### 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.651    1.917    0.262  2.48   0.013 *
## UICC_3CATIVB-C     1.799    6.043    0.362  4.97  6.7e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.508    0.602    0.434 -1.17   0.241
## HPV16_DNA_RNADNA+RNA+ -0.821    0.440    0.366 -2.24   0.025 *
## poly(ALTER, 2)1      0.817    2.264    1.478  0.55   0.580
## poly(ALTER, 2)2      2.433   11.398    1.330  1.83   0.067 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.917    0.5217    1.146    3.205
## UICC_3CATIVB-C     6.043    0.1655    2.973   12.282
## HPV16_DNA_RNADNA+RNA- 0.602    1.6623    0.257    1.408
## HPV16_DNA_RNADNA+RNA+ 0.440    2.2725    0.215    0.902
## poly(ALTER, 2)1      2.264    0.4417    0.125   40.982
## poly(ALTER, 2)2     11.398    0.0877    0.840  154.584
##
## Concordance= 0.642 (se = 0.033 )
## Rsquare= 0.131 (max possible= 0.985 )
## Likelihood ratio test= 28.4 on 6 df, p=7.82e-05
## Wald test            = 30.1 on 6 df, p=3.77e-05
## Score (logrank) test = 32.7 on 6 df, p=1.2e-05

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA      0.08267 0.60801 0.436
## UICC_3CATIVB-C     0.01679 0.02533 0.874
## HPV16_DNA_RNADNA+RNA- 0.00759 0.00574 0.940
## HPV16_DNA_RNADNA+RNA+ 0.16300 2.19290 0.139
## poly(ALTER, 2)1    -0.04807 0.21547 0.643
## poly(ALTER, 2)2     0.14454 1.58682 0.208
## GLOBAL              NA  4.30509 0.635

```

#### 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.659      1.933   0.262  2.52   0.012 *
## UICC_3CATIVB-C      1.843      6.318   0.360  5.11  3.2e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.475      0.622   0.432 -1.10   0.271
## HPV16_DNA_RNADNA+RNA+ -0.821      0.440   0.360 -2.28   0.023 *
## ALTER_3CAT(50,70]   -0.552      0.576   0.218 -2.54   0.011 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.933      0.517   1.157   3.227
## UICC_3CATIVB-C      6.318      0.158   3.117  12.806
## HPV16_DNA_RNADNA+RNA-  0.622      1.609   0.267   1.450
## HPV16_DNA_RNADNA+RNA+  0.440      2.273   0.217   0.891
## ALTER_3CAT(50,70]    0.576      1.737   0.376   0.882
##
## Concordance= 0.651 (se = 0.032 )
## Rsquare= 0.142 (max possible= 0.985 )
## Likelihood ratio test= 31.2 on 5 df,  p=8.7e-06
## Wald test              = 32.8 on 5 df,  p=4.1e-06
## Score (logrank) test = 35.3 on 5 df,  p=1.32e-06

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.0769 0.5192 0.471
## UICC_3CATIVB-C      0.0181 0.0290 0.865
## HPV16_DNA_RNADNA+RNA- 0.0104 0.0106 0.918
## HPV16_DNA_RNADNA+RNA+ 0.1443 1.7112 0.191
## ALTER_3CAT(50,70]   -0.0724 0.4880 0.485
## GLOBAL              NA  2.9332 0.710
```

#### 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= 88
## (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.644    1.903   0.263  2.45  0.0144 *
## UICC_3CATIVB-C     1.836    6.273   0.362  5.07  4e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.335    0.715   0.434 -0.77  0.4404
## HPV16_DNA_RNADNA+RNA+ -0.639    0.528   0.367 -1.74  0.0817 .
## ALTER_3CAT(50,70]   -0.709    0.492   0.226 -3.13  0.0017 **
## I(PACKYEARS > 30)TRUE  0.589    1.802   0.228  2.58  0.0099 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.903    0.525    1.137    3.187
## UICC_3CATIVB-C     6.273    0.159    3.085   12.755
## HPV16_DNA_RNADNA+RNA-  0.715    1.398    0.305    1.676
## HPV16_DNA_RNADNA+RNA+  0.528    1.894    0.257    1.084
## ALTER_3CAT(50,70]   0.492    2.031    0.316    0.767
## I(PACKYEARS > 30)TRUE  1.802    0.555    1.152    2.818
##
## Concordance= 0.665 (se = 0.033 )
## Rsquare= 0.17 (max possible= 0.985 )
## Likelihood ratio test= 37.4 on 6 df, p=1.47e-06
## Wald test = 37.9 on 6 df, p=1.16e-06
## Score (logrank) test = 41.3 on 6 df, p=2.49e-07

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA      0.08446 0.61909 0.431
## UICC_3CATIVB-C     0.00863 0.00653 0.936
## HPV16_DNA_RNADNA+RNA- 0.03610 0.12719 0.721
## HPV16_DNA_RNADNA+RNA+ 0.16665 2.59424 0.107
```

```
## ALTER_3CAT(50,70]      -0.09185 0.73992 0.390
## I(PACKYEARS > 30)TRUE  0.08685 0.72412 0.395
## GLOBAL                  NA 4.29722 0.637
```

#### 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= 88
##      (16 observations deleted due to missingness)
##
##
##              coef exp(coef) se(coef)
## UICC_3CATIVA      0.7379      2.0916  0.2663
## UICC_3CATIVB-C     1.8828      6.5717  0.3632
## HPV16_DNA_RNADNA+RNA- -0.3556      0.7007  0.6133
## HPV16_DNA_RNADNA+RNA+ -1.9429      0.1433  0.7355
## ALTER_3CAT(50,70] -0.7129      0.4902  0.2277
## I(PACKYEARS > 30)TRUE  0.3648      1.4402  0.2438
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.0179      1.0180  0.8561
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.3521     10.5074  0.8456
##
##              z Pr(>|z|)
## UICC_3CATIVA      2.77  0.0056 **
## UICC_3CATIVB-C     5.18  2.2e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.58  0.5620
## HPV16_DNA_RNADNA+RNA+ -2.64  0.0083 **
## ALTER_3CAT(50,70] -3.13  0.0017 **
## I(PACKYEARS > 30)TRUE  1.50  0.1346
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.02  0.9833
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.78  0.0054 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95
## UICC_3CATIVA      2.092      0.4781  1.2412
```

```
## UICC_3CATIVB-C 6.572 0.1522 3.2246
## HPV16_DNA_RNADNA+RNA- 0.701 1.4271 0.2106
## HPV16_DNA_RNADNA+RNA+ 0.143 6.9786 0.0339
## ALTER_3CAT(50,70] 0.490 2.0400 0.3137
## I(PACKYEARS > 30)TRUE 1.440 0.6944 0.8930
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 1.018 0.9823 0.1901
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 10.507 0.0952 2.0033
## upper .95
## UICC_3CATIVA 3.525
## UICC_3CATIVB-C 13.393
## HPV16_DNA_RNADNA+RNA- 2.331
## HPV16_DNA_RNADNA+RNA+ 0.606
## ALTER_3CAT(50,70] 0.766
## I(PACKYEARS > 30)TRUE 2.323
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 5.451
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 55.111
##
## Concordance= 0.684 (se = 0.033 )
## Rsquare= 0.209 (max possible= 0.985 )
## Likelihood ratio test= 47.1 on 8 df, p=1.48e-07
## Wald test = 42.9 on 8 df, p=9.22e-07
## Score (logrank) test = 47.6 on 8 df, p=1.2e-07

cox.zph(surv.res)

## rho chisq p
## UICC_3CATIVA 0.1255 1.4347 0.2310
## UICC_3CATIVB-C 0.0353 0.1103 0.7398
## HPV16_DNA_RNADNA+RNA- -0.0629 0.3777 0.5388
## HPV16_DNA_RNADNA+RNA+ 0.2255 4.0121 0.0452
## ALTER_3CAT(50,70] -0.1084 1.0646 0.3022
## I(PACKYEARS > 30)TRUE 0.0218 0.0423 0.8371
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.1259 1.4444 0.2294
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.1033 0.8810 0.3479
## GLOBAL NA 10.5896 0.2261
```

#### 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= 88
##      (16 observations deleted due to missingness)
##
##
```

	coef	exp(coef)	se(coef)
## T_2CAT3-4	0.1836	1.2016	0.2624
## N_2CATN2-N3	0.8083	2.2441	0.2604
## M	2.3378	10.3584	0.5550
## HPV16_DNA_RNADNA+RNA-	-0.1675	0.8458	0.6139
## HPV16_DNA_RNADNA+RNA+	-1.7892	0.1671	0.7487
## ALTER_3CAT(50,70]	-0.6308	0.5322	0.2225
## I(PACKYEARS > 30)TRUE	0.4168	1.5172	0.2522
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE	-0.0168	0.9833	0.8570
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE	2.4242	11.2937	0.8526

```
##
##              z Pr(>|z|)
## T_2CAT3-4      0.70  0.4839
## N_2CATN2-N3    3.10  0.0019 **
## M              4.21  2.5e-05 ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+
## ALTER_3CAT(50,70]
## I(PACKYEARS > 30)TRUE
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
```

	exp(coef)	exp(-coef)	lower .95
## T_2CAT3-4	1.202	0.8322	0.7185
## N_2CATN2-N3	2.244	0.4456	1.3470
## M	10.358	0.0965	3.4904
## HPV16_DNA_RNADNA+RNA-	0.846	1.1824	0.2539
## HPV16_DNA_RNADNA+RNA+	0.167	5.9849	0.0385
## ALTER_3CAT(50,70]	0.532	1.8791	0.3440
## I(PACKYEARS > 30)TRUE	1.517	0.6591	0.9254
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE	0.983	1.0170	0.1833
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE	11.294	0.0885	2.1237

```
##
##              upper .95
## T_2CAT3-4      2.009
## N_2CATN2-N3    3.739
## M              30.740
## HPV16_DNA_RNADNA+RNA-
##              2.817
```



```
## HPV16_DNA_RNADNA+RNA+ 0.725
## ALTER_3CAT(50,70] 0.823
## I(PACKYEARS > 30)TRUE 2.487
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 5.274
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 60.059
##
## Concordance= 0.682 (se = 0.033 )
## Rsquare= 0.216 (max possible= 0.985 )
## Likelihood ratio test= 48.8 on 9 df, p=1.82e-07
## Wald test = 47.3 on 9 df, p=3.43e-07
## Score (logrank) test = 60.7 on 9 df, p=9.68e-10

cox.zph(surv.res)

## rho chisq p
## T_2CAT3-4 0.0501 0.2657 0.6062
## N_2CATN2-N3 0.0344 0.1137 0.7360
## M 0.0173 0.0268 0.8699
## HPV16_DNA_RNADNA+RNA- -0.0728 0.4783 0.4892
## HPV16_DNA_RNADNA+RNA+ 0.2161 3.8893 0.0486
## ALTER_3CAT(50,70] -0.1287 1.4254 0.2325
## I(PACKYEARS > 30)TRUE 0.0253 0.0616 0.8040
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.1302 1.5220 0.2173
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.1206 1.1803 0.2773
## GLOBAL NA 9.0757 0.4303
```

#### 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= 88
## (16 observations deleted due to missingness)
```

```
##
##
##          coef exp(coef) se(coef)
## T_2CAT3-4 -0.3219    0.7247  0.3729
## N_2CATN2-N3 0.7845    2.1912  0.2635
## M 2.4847    11.9976  0.5658
## HPV16_DNA_RNADNA+RNA- -0.1086    0.8971  0.6143
## HPV16_DNA_RNADNA+RNA+ -1.9594    0.1409  0.7570
## ALTER_3CAT(50,70] -0.6033    0.5470  0.2230
## I(PACKYEARS > 30)TRUE -0.1388    0.8704  0.3894
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 0.8540    2.3490  0.4708
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.0803    0.9228  0.8574
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.6590    14.2816  0.8649
##
##          z Pr(>|z|)
## T_2CAT3-4 -0.86    0.3880
## N_2CATN2-N3 2.98    0.0029 **
## M 4.39    1.1e-05 ***
## HPV16_DNA_RNADNA+RNA- -0.18    0.8597
## HPV16_DNA_RNADNA+RNA+ -2.59    0.0096 **
## ALTER_3CAT(50,70] -2.70    0.0068 **
## I(PACKYEARS > 30)TRUE -0.36    0.7215
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 1.81    0.0697 .
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.09    0.9254
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 3.07    0.0021 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
##          exp(coef) exp(-coef) lower .95
## T_2CAT3-4 0.725    1.3798    0.349
## N_2CATN2-N3 2.191    0.4564    1.307
## M 11.998    0.0834    3.958
## HPV16_DNA_RNADNA+RNA- 0.897    1.1147    0.269
## HPV16_DNA_RNADNA+RNA+ 0.141    7.0952    0.032
## ALTER_3CAT(50,70] 0.547    1.8281    0.353
## I(PACKYEARS > 30)TRUE 0.870    1.1489    0.406
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 2.349    0.4257    0.934
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.923    1.0836    0.172
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 14.282    0.0700    2.621
##
##          upper .95
## T_2CAT3-4 1.505
## N_2CATN2-N3 3.672
## M 36.364
## HPV16_DNA_RNADNA+RNA- 2.991
## HPV16_DNA_RNADNA+RNA+ 0.621
## ALTER_3CAT(50,70] 0.847
## I(PACKYEARS > 30)TRUE 1.867
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 5.910
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 4.954
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 77.807
```

```
##
## Concordance= 0.689 (se = 0.033 )
## Rsquare= 0.228 (max possible= 0.985 )
## Likelihood ratio test= 52 on 10 df, p=1.11e-07
## Wald test = 50.6 on 10 df, p=2.05e-07
## Score (logrank) test = 65.3 on 10 df, p=3.55e-10

cox.zph(surv.res)

##
## rho chisq p
## T_2CAT3-4 0.0662 0.5052 0.4772
## N_2CATN2-N3 0.0393 0.1457 0.7027
## M 0.0182 0.0312 0.8598
## HPV16_DNA_RNADNA+RNA- -0.0668 0.3951 0.5296
## HPV16_DNA_RNADNA+RNA+ 0.2109 3.7911 0.0515
## ALTER_3CAT(50,70] -0.1151 1.1611 0.2812
## I(PACKYEARS > 30)TRUE 0.0694 0.4703 0.4928
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.0553 0.2946 0.5873
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.1200 1.2789 0.2581
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.1185 1.1917 0.2750
## GLOBAL NA 8.6603 0.5646

# 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=814
## 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
## - poly(ALTER, 2)[, 2] 1 812
## - GESCHLECHT 1 812
## <none> 814
## - ALTER_3CAT 1 816
## - HPV16_DNA_RNA:I(PACKYEARS > 30) 2 820
## - UICC_3CAT 2 834
##
## Step: AIC=812.1
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
```

```

##      I(PACKYEARS > 30) + GESCHLECHT + HPV16_DNA_RNA:I(PACKYEARS >
##      30)
##
##                                Df AIC
## - GESCHLECHT                    1 810
## <none>                          812
## - HPV16_DNA_RNA:I(PACKYEARS > 30)  2 818
## - ALTER_3CAT                    1 820
## - UICC_3CAT                      2 832
##
## Step:  AIC=810.4
## surv.obj[cur.subset] ~ UICC_3CAT + HPV16_DNA_RNA + ALTER_3CAT +
##      I(PACKYEARS > 30) + HPV16_DNA_RNA:I(PACKYEARS > 30)
##
##                                Df AIC
## <none>                          810
## - HPV16_DNA_RNA:I(PACKYEARS > 30)  2 816
## - ALTER_3CAT                    1 818
## - UICC_3CAT                      2 831
##
best.model

## 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, ])
##
##
##                                coef exp(coef) se(coef)
## UICC_3CATIVA                    0.7379      2.092   0.266
## UICC_3CATIVB-C                  1.8828      6.572   0.363
## HPV16_DNA_RNADNA+RNA-          -0.3556      0.701   0.613
## HPV16_DNA_RNADNA+RNA+          -1.9429      0.143   0.735
## ALTER_3CAT(50,70]              -0.7129      0.490   0.228
## I(PACKYEARS > 30)TRUE           0.3648      1.440   0.244
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.0179      1.018   0.856
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.3521     10.507   0.846
##
##                                z      p
## UICC_3CATIVA                    2.7716 5.6e-03
## UICC_3CATIVB-C                  5.1832 2.2e-07
## HPV16_DNA_RNADNA+RNA-          -0.5799 5.6e-01
## HPV16_DNA_RNADNA+RNA+          -2.6417 8.3e-03
## ALTER_3CAT(50,70]              -3.1304 1.7e-03
## I(PACKYEARS > 30)TRUE           1.4960 1.3e-01
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE  0.0209 9.8e-01
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.7817 5.4e-03
##
## Likelihood ratio test=47.1 on 8 df, p=1.48e-07 n= 201, number of events= 88
##      (16 observations deleted due to missingness)

```

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3  0.580      1.785   0.219  2.64   0.0082 **
## TP53ND      -0.184      0.832   0.322 -0.57   0.5674
## TP53D        0.530      1.698   0.229  2.31   0.0207 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      1.785      0.560      1.161      2.74
## TP53ND           0.832      1.202      0.442      1.56
## TP53D            1.698      0.589      1.084      2.66
##
## Concordance= 0.608 (se = 0.03 )
## Rsquare= 0.068 (max possible= 0.987 )
## Likelihood ratio test= 15.2 on 3 df,  p=0.00162
## Wald test               = 15.3 on 3 df,  p=0.0016
## Score (logrank) test = 15.8 on 3 df,  p=0.00122

cox.zph(surv.res)

##              rho      chisq      p
## N_2CATN2-N3 -0.00272 0.000731 0.978
## TP53ND      -0.06740 0.444005 0.505
## TP53D       -0.13001 1.682962 0.195
## GLOBAL              NA 1.829074 0.609
```

#### 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= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.644      1.904    0.287  2.24   0.025 *
## TP53ND           -0.335      0.715    0.560 -0.60   0.550
## TP53D            0.776      2.174    0.411  1.89   0.059 .
## N_2CATN2-N3:TP53ND 0.242      1.274    0.681  0.36   0.722
## N_2CATN2-N3:TP53D -0.345      0.708    0.492 -0.70   0.484
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      1.904      0.525    1.085    3.34
## TP53ND           0.715      1.398    0.239    2.14
## TP53D            2.174      0.460    0.972    4.86
## N_2CATN2-N3:TP53ND 1.274      0.785    0.336    4.84
## N_2CATN2-N3:TP53D 0.708      1.412    0.270    1.86
##
## Concordance= 0.61 (se = 0.03 )
## Rsquare= 0.071 (max possible= 0.987 )
## Likelihood ratio test= 16 on 5 df,  p=0.00677
## Wald test = 14.8 on 5 df,  p=0.0111
## Score (logrank) test = 15.9 on 5 df,  p=0.00711

cox.zph(surv.res)

##               rho   chisq      p
## N_2CATN2-N3      0.13284 1.74956 0.1859
## TP53ND           0.00838 0.00685 0.9340
## TP53D            0.13926 1.90801 0.1672
## N_2CATN2-N3:TP53ND -0.04853 0.23061 0.6311
## N_2CATN2-N3:TP53D -0.25574 6.45530 0.0111
## GLOBAL           NA 8.30877 0.1400
```

#### 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= 99
##
```

```
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.559    1.750    0.252  2.22  0.02639 *
## UICC_3CATIVB-C  1.314    3.721    0.340  3.86  0.00011 ***
## TP53ND         -0.100    0.905    0.323 -0.31  0.75630
## TP53D          0.581    1.788    0.229  2.54  0.01114 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.750      0.572      1.07      2.87
## UICC_3CATIVB-C    3.721      0.269      1.91      7.25
## TP53ND            0.905      1.105      0.48      1.70
## TP53D             1.788      0.559      1.14      2.80
##
## Concordance= 0.63 (se = 0.03 )
## Rsquare= 0.096 (max possible= 0.987 )
## Likelihood ratio test= 21.9 on 4 df,  p=0.000215
## Wald test = 23 on 4 df,  p=0.000129
## Score (logrank) test = 24.6 on 4 df,  p=6.14e-05

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA   -0.000193 3.72e-06 0.998
## UICC_3CATIVB-C -0.070717 4.79e-01 0.489
## TP53ND         -0.059684 3.46e-01 0.556
## TP53D          -0.104158 1.09e+00 0.296
## GLOBAL         NA 1.73e+00 0.785
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.339    0.713    0.425 -0.80    0.426
## HPV16_DNA_RNADNA+RNA+ -0.476    0.621    0.369 -1.29    0.197
## TP53ND                -0.317    0.728    0.340 -0.93    0.350
## TP53D                  0.589    1.802    0.247  2.38    0.017 *
```

```
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.713      1.403      0.310      1.64
## HPV16_DNA_RNADNA+RNA+    0.621      1.609      0.302      1.28
## TP53ND                    0.728      1.374      0.374      1.42
## TP53D                     1.802      0.555      1.110      2.93
##
## Concordance= 0.6  (se = 0.031 )
## Rsquare= 0.057  (max possible= 0.985 )
## Likelihood ratio test= 11.8  on 4 df,   p=0.0188
## Wald test               = 12.2  on 4 df,   p=0.016
## Score (logrank) test = 12.8  on 4 df,   p=0.0124

cox.zph(surv.res)

##               rho    chisq    p
## HPV16_DNA_RNADNA+RNA-  0.00716 0.00455 0.946
## HPV16_DNA_RNADNA+RNA+  0.11003 1.03945 0.308
## TP53ND                 -0.12744 1.50544 0.220
## TP53D                  -0.06575 0.37453 0.541
## GLOBAL                 NA 3.35075 0.501
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.569      1.766   0.264   2.16   0.031 *
## UICC_3CATIVB-C    1.702      5.484   0.361   4.71  2.4e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.582      0.559   0.435  -1.34   0.181
## HPV16_DNA_RNADNA+RNA+ -0.674      0.510   0.372  -1.81   0.070 .
## TP53ND           -0.245      0.783   0.342  -0.71   0.475
## TP53D            0.532      1.702   0.249   2.14   0.033 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```



```
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.766      0.566      1.054      2.96
## UICC_3CATIVB-C      5.484      0.182      2.702     11.13
## HPV16_DNA_RNADNA+RNA- 0.559      1.790      0.238      1.31
## HPV16_DNA_RNADNA+RNA+ 0.510      1.962      0.246      1.06
## TP53ND            0.783      1.277      0.400      1.53
## TP53D             1.702      0.588      1.045      2.77
##
## Concordance= 0.642 (se = 0.033 )
## Rsquare= 0.142 (max possible= 0.985 )
## Likelihood ratio test= 31.1 on 6 df, p=2.4e-05
## Wald test = 33.5 on 6 df, p=8.36e-06
## Score (logrank) test = 36.8 on 6 df, p=1.95e-06

cox.zph(surv.res)

##               rho  chisq    p
## UICC_3CATIVA      0.08198 0.6073 0.436
## UICC_3CATIVB-C      0.01318 0.0159 0.900
## HPV16_DNA_RNADNA+RNA- 0.00763 0.0059 0.939
## HPV16_DNA_RNADNA+RNA+ 0.11886 1.1604 0.281
## TP53ND            -0.13178 1.6316 0.201
## TP53D             -0.05600 0.2758 0.599
## GLOBAL              NA 4.2727 0.640
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.692      1.998      0.232  2.99  0.0028 **
## HPV16_DNA_RNADNA+RNA- -0.380      0.684      0.425 -0.89  0.3716
## HPV16_DNA_RNADNA+RNA+ -0.644      0.525      0.372 -1.73  0.0835 .
## TP53ND           -0.340      0.712      0.340 -1.00  0.3175
## TP53D             0.485      1.624      0.249  1.95  0.0512 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```

```
##               exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3          1.998      0.500      1.269      3.15
## HPV16_DNA_RNADNA+RNA- 0.684      1.462      0.297      1.57
## HPV16_DNA_RNADNA+RNA+ 0.525      1.905      0.253      1.09
## TP53ND              0.712      1.404      0.366      1.39
## TP53D               1.624      0.616      0.998      2.65
##
## Concordance= 0.636 (se = 0.032 )
## Rsquare= 0.1 (max possible= 0.985 )
## Likelihood ratio test= 21.3 on 5 df, p=0.000718
## Wald test = 21.1 on 5 df, p=0.000759
## Score (logrank) test = 22.2 on 5 df, p=0.000471

cox.zph(surv.res)

##               rho      chisq      p
## N_2CATN2-N3      0.03673 0.120522 0.728
## HPV16_DNA_RNADNA+RNA- 0.00302 0.000809 0.977
## HPV16_DNA_RNADNA+RNA+ 0.10167 0.882939 0.347
## TP53ND          -0.12814 1.497390 0.221
## TP53D          -0.05890 0.302991 0.582
## GLOBAL          NA 3.245612 0.662
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.6947    2.0030   0.2340   2.97   0.003 **
## HPV16_DNA_RNADNA+RNA- -0.3811    0.6831   0.4257  -0.90   0.371
## HPV16_DNA_RNADNA+RNA+ -0.6338    0.5306   0.4024  -1.58   0.115
## TP53ND          -0.3390    0.7125   0.3400  -1.00   0.319
## TP53D           0.4859    1.6257   0.2490   1.95   0.051 .
## IS_ATYPICALatypical -0.0186    0.9816   0.2675  -0.07   0.945
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
```

```
## N_2CATN2-N3          2.003      0.499      1.266      3.17
## HPV16_DNA_RNADNA+RNA- 0.683      1.464      0.297      1.57
## HPV16_DNA_RNADNA+RNA+ 0.531      1.885      0.241      1.17
## TP53ND                0.712      1.404      0.366      1.39
## TP53D                 1.626      0.615      0.998      2.65
## IS_ATYPICALAtypical   0.982      1.019      0.581      1.66
##
## Concordance= 0.637 (se = 0.033 )
## Rsquare= 0.1 (max possible= 0.985 )
## Likelihood ratio test= 21.3 on 6 df, p=0.00163
## Wald test = 21.2 on 6 df, p=0.00171
## Score (logrank) test = 22.3 on 6 df, p=0.00108

cox.zph(surv.res)

##              rho    chisq      p
## N_2CATN2-N3      0.0260 0.05946 0.807
## HPV16_DNA_RNADNA+RNA- 0.0054 0.00258 0.959
## HPV16_DNA_RNADNA+RNA+ 0.0650 0.37757 0.539
## TP53ND          -0.1307 1.55254 0.213
## TP53D           -0.0606 0.32336 0.570
## IS_ATYPICALAtypical 0.0709 0.45451 0.500
## GLOBAL          NA 3.70234 0.717
```

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.442      0.643   0.207 -2.14  0.0322 *
## TP53ND            -0.210      0.810   0.324 -0.65  0.5167
## TP53D             0.599      1.821   0.228  2.62  0.0087 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.643      1.556      0.429      0.963
## TP53ND                  0.810      1.234      0.429      1.530
## TP53D                   1.821      0.549      1.164      2.849
```

```
##
## Concordance= 0.587 (se = 0.03 )
## Rsquare= 0.055 (max possible= 0.987 )
## Likelihood ratio test= 12.3 on 3 df, p=0.00635
## Wald test = 13 on 3 df, p=0.00471
## Score (logrank) test = 13.3 on 3 df, p=0.00396

cox.zph(surv.res)

##               rho chisq      p
## ALTER_3CAT(50,70] -0.1160 1.359 0.244
## TP53ND            -0.0969 0.932 0.334
## TP53D             -0.1259 1.578 0.209
## GLOBAL            NA 3.506 0.320
```

#### 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= 99
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.5658    1.7609  0.2521  2.24  0.0248 *
## UICC_3CATIVB-C    1.4143    4.1136  0.3436  4.12 3.8e-05 ***
## ALTER_3CAT(50,70] -0.5232    0.5926  0.2091 -2.50  0.0123 *
## TP53ND           -0.0793    0.9238  0.3240 -0.24  0.8067
## TP53D            0.6045    1.8303  0.2300  2.63  0.0086 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.761    0.568    1.074    2.886
## UICC_3CATIVB-C    4.114    0.243    2.098    8.066
## ALTER_3CAT(50,70] 0.593    1.687    0.393    0.893
## TP53ND            0.924    1.082    0.490    1.743
## TP53D            1.830    0.546    1.166    2.873
##
## Concordance= 0.636 (se = 0.031 )
## Rsquare= 0.121 (max possible= 0.987 )
## Likelihood ratio test= 27.9 on 5 df, p=3.75e-05
```

```
## Wald test          = 28.7  on 5 df,    p=2.63e-05
## Score (logrank) test = 30.7  on 5 df,    p=1.09e-05

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.000988 9.75e-05 0.992
## UICC_3CATIVB-C    -0.054825 2.89e-01 0.591
## ALTER_3CAT(50,70] -0.109503 1.24e+00 0.266
## TP53ND            -0.071400 4.99e-01 0.480
## TP53D             -0.090165 8.35e-01 0.361
## GLOBAL            NA 2.91e+00 0.714
```

#### 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.308      0.735      0.426 -0.72      0.469
## HPV16_DNA_RNADNA+RNA+ -0.445      0.641      0.368 -1.21      0.227
## ALTER_3CAT(50,70]      -0.478      0.620      0.216 -2.22      0.027 *
## TP53ND                 -0.302      0.739      0.341 -0.88      0.377
## TP53D                  0.599      1.819      0.247  2.43      0.015 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-      0.735      1.36      0.319      1.693
## HPV16_DNA_RNADNA+RNA+      0.641      1.56      0.312      1.319
## ALTER_3CAT(50,70]          0.620      1.61      0.406      0.946
## TP53ND                    0.739      1.35      0.379      1.444
## TP53D                     1.819      0.55      1.122      2.950
##
## Concordance= 0.613 (se = 0.032 )
## Rsquare= 0.079 (max possible= 0.985 )
## Likelihood ratio test= 16.6 on 5 df, p=0.00529
## Wald test          = 17 on 5 df, p=0.00447
## Score (logrank) test = 17.8 on 5 df, p=0.00328
```

```
cox.zph(surv.res)

##               rho  chisq    p
## HPV16_DNA_RNADNA+RNA-  0.0154 0.0211 0.885
## HPV16_DNA_RNADNA+RNA+  0.1102 1.0356 0.309
## ALTER_3CAT(50,70]     -0.0989 0.9017 0.342
## TP53ND                 -0.1483 2.0682 0.150
## TP53D                  -0.0594 0.3054 0.581
## GLOBAL                 NA 4.6583 0.459
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.576      1.780   0.264   2.18   0.029 *
## UICC_3CATIVB-C     1.786      5.963   0.363   4.92  8.7e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.510      0.601   0.435  -1.17   0.241
## HPV16_DNA_RNADNA+RNA+ -0.685      0.504   0.372  -1.84   0.066 .
## ALTER_3CAT(50,70]  -0.555      0.574   0.218  -2.54   0.011 *
## TP53ND            -0.227      0.797   0.345  -0.66   0.510
## TP53D              0.546      1.726   0.249   2.19   0.029 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.780      0.562   1.060      2.99
## UICC_3CATIVB-C     5.963      0.168   2.928     12.15
## HPV16_DNA_RNADNA+RNA-  0.601      1.665   0.256      1.41
## HPV16_DNA_RNADNA+RNA+  0.504      1.983   0.243      1.05
## ALTER_3CAT(50,70]    0.574      1.742   0.374      0.88
## TP53ND              0.797      1.255   0.406      1.57
## TP53D               1.726      0.579   1.059      2.81
##
## Concordance= 0.659 (se = 0.033 )
## Rsquare= 0.168 (max possible= 0.985 )
## Likelihood ratio test= 37.4 on 7 df, p=3.87e-06
```

```
## Wald test          = 39 on 7 df,    p=1.92e-06
## Score (logrank) test = 42.7 on 7 df,    p=3.78e-07
```

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

```
##              rho  chisq    p
## UICC_3CATIVA      0.0834 0.6339 0.426
## UICC_3CATIVB-C     0.0158 0.0224 0.881
## HPV16_DNA_RNADNA+RNA- 0.0191 0.0367 0.848
## HPV16_DNA_RNADNA+RNA+ 0.1100 0.9815 0.322
## ALTER_3CAT(50,70] -0.0803 0.6001 0.439
## TP53ND            -0.1618 2.5087 0.113
## TP53D             -0.0588 0.3105 0.577
## GLOBAL            NA 5.5660 0.591
```

#### 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= 88
## (16 observations deleted due to missingness)
```

```
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.558      1.746    0.266  2.09  0.0364 *
## UICC_3CATIVB-C     1.769      5.866    0.364  4.86  1.2e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.296    0.744    0.438 -0.68  0.4991
## HPV16_DNA_RNADNA+RNA+ -0.520    0.595    0.378 -1.38  0.1688
## I(PACKYEARS > 30)TRUE  0.559      1.749    0.229  2.44  0.0146 *
## ALTER_3CAT(50,70] -0.704      0.495    0.227 -3.10  0.0019 **
## TP53ND            -0.239      0.787    0.343 -0.70  0.4860
## TP53D             0.504      1.655    0.253  1.99  0.0465 *
```

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

```
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.746      0.573    1.036    2.944
## UICC_3CATIVB-C     5.866      0.170    2.873   11.974
## HPV16_DNA_RNADNA+RNA- 0.744      1.345    0.315    1.756
## HPV16_DNA_RNADNA+RNA+ 0.595      1.682    0.283    1.247
```

```
## I(PACKYEARS > 30)TRUE      1.749      0.572      1.117      2.741
## ALTER_3CAT(50,70]         0.495      2.022      0.317      0.771
## TP53ND                     0.787      1.270      0.402      1.542
## TP53D                      1.655      0.604      1.008      2.716
##
## Concordance= 0.68 (se = 0.033 )
## Rsquare= 0.192 (max possible= 0.985 )
## Likelihood ratio test= 42.9 on 8 df, p=9.2e-07
## Wald test = 43.9 on 8 df, p=5.96e-07
## Score (logrank) test = 48.1 on 8 df, p=9.44e-08

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA      0.0946 0.8186 0.366
## UICC_3CATIVB-C     0.0161 0.0227 0.880
## HPV16_DNA_RNADNA+RNA- 0.0464 0.2201 0.639
## HPV16_DNA_RNADNA+RNA+ 0.1292 1.5132 0.219
## I(PACKYEARS > 30)TRUE 0.0719 0.5017 0.479
## ALTER_3CAT(50,70]   -0.0943 0.7845 0.376
## TP53ND              -0.1384 1.7976 0.180
## TP53D                -0.0907 0.7368 0.391
## GLOBAL              NA 6.1222 0.634
```

#### 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= 88
## (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)
## UICC_3CATIVA      0.661      1.937      0.270
## UICC_3CATIVB-C     1.831      6.237      0.365
## HPV16_DNA_RNADNA+RNA- -0.516      0.597      0.621
## HPV16_DNA_RNADNA+RNA+ -1.836      0.160      0.741
## I(PACKYEARS > 30)TRUE  0.299      1.349      0.246
## ALTER_3CAT(50,70]   -0.700      0.496      0.229
```



```

## TP53ND -0.218 0.804 0.355
## TP53D 0.533 1.704 0.255
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.393 1.481 0.880
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.384 10.843 0.847
## z Pr(>|z|)
## UICC_3CATIVA 2.45 0.0143 *
## UICC_3CATIVB-C 5.01 5.4e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.83 0.4060
## HPV16_DNA_RNADNA+RNA+ -2.48 0.0132 *
## I(PACKYEARS > 30)TRUE 1.22 0.2238
## ALTER_3CAT(50,70] -3.06 0.0022 **
## TP53ND -0.61 0.5394
## TP53D 2.09 0.0365 *
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.45 0.6551
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.81 0.0049 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95
## UICC_3CATIVA 1.937 0.5163 1.1413
## UICC_3CATIVB-C 6.237 0.1603 3.0490
## HPV16_DNA_RNADNA+RNA- 0.597 1.6749 0.1769
## HPV16_DNA_RNADNA+RNA+ 0.160 6.2683 0.0374
## I(PACKYEARS > 30)TRUE 1.349 0.7416 0.8330
## ALTER_3CAT(50,70] 0.496 2.0142 0.3170
## TP53ND 0.804 1.2433 0.4012
## TP53D 1.704 0.5870 1.0341
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 1.481 0.6750 0.2641
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 10.843 0.0922 2.0611
## upper .95
## UICC_3CATIVA 3.287
## UICC_3CATIVB-C 12.760
## HPV16_DNA_RNADNA+RNA- 2.015
## HPV16_DNA_RNADNA+RNA+ 0.681
## I(PACKYEARS > 30)TRUE 2.183
## ALTER_3CAT(50,70] 0.778
## TP53ND 1.612
## TP53D 2.807
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 8.309
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 57.042
##
## Concordance= 0.698 (se = 0.033 )
## Rsquare= 0.231 (max possible= 0.985 )
## Likelihood ratio test= 52.7 on 10 df, p=8.38e-08
## Wald test = 48.3 on 10 df, p=5.52e-07
## Score (logrank) test = 54.4 on 10 df, p=4.07e-08

cox.zph(surv.res)

```

	rho	chisq	p
## UICC_3CATIVA	0.13459	1.74059	0.1871
## UICC_3CATIVB-C	0.04838	0.20850	0.6479
## HPV16_DNA_RNADNA+RNA-	-0.06766	0.45515	0.4999
## HPV16_DNA_RNADNA+RNA+	0.20210	3.24918	0.0715
## I(PACKYEARS > 30)TRUE	-0.00526	0.00256	0.9596
## ALTER_3CAT(50,70]	-0.10263	0.96044	0.3271
## TP53ND	-0.15947	2.67710	0.1018
## TP53D	-0.07459	0.50023	0.4794
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE	0.14232	2.08866	0.1484
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE	-0.10350	0.87305	0.3501
## GLOBAL	NA	13.17677	0.2140

#### 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= 88
## (16 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## T_2CAT3-4      -0.331      0.718   0.370
## N_2CATN2-N3      0.744      2.104   0.264
## M               2.491     12.070   0.569
## HPV16_DNA_RNADNA+RNA- -0.205      0.815   0.617
## HPV16_DNA_RNADNA+RNA+ -1.871      0.154   0.762
## ALTER_3CAT(50,70] -0.567      0.567   0.223
## I(PACKYEARS > 30)TRUE -0.174      0.840   0.392
## TP53ND          -0.213      0.808   0.354
## TP53D            0.483      1.621   0.259
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 0.792      2.208   0.471
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.169      1.185   0.871
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 2.692     14.762   0.868
##
##               z Pr(>|z|)
## T_2CAT3-4      -0.89   0.3713
## N_2CATN2-N3      2.82   0.0049 **

```

```

## M 4.37 1.2e-05 ***
## HPV16_DNA_RNADNA+RNA- -0.33 0.7399
## HPV16_DNA_RNADNA+RNA+ -2.46 0.0141 *
## ALTER_3CAT(50,70] -2.54 0.0111 *
## I(PACKYEARS > 30)TRUE -0.44 0.6568
## TP53ND -0.60 0.5472
## TP53D 1.87 0.0619 .
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 1.68 0.0925 .
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.19 0.8458
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 3.10 0.0019 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95
## T_2CAT3-4 0.718 1.3918 0.3480
## N_2CATN2-N3 2.104 0.4753 1.2539
## M 12.070 0.0829 3.9535
## HPV16_DNA_RNADNA+RNA- 0.815 1.2274 0.2430
## HPV16_DNA_RNADNA+RNA+ 0.154 6.4948 0.0346
## ALTER_3CAT(50,70] 0.567 1.7638 0.3659
## I(PACKYEARS > 30)TRUE 0.840 1.1903 0.3896
## TP53ND 0.808 1.2374 0.4040
## TP53D 1.621 0.6169 0.9762
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 2.208 0.4529 0.8775
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 1.185 0.8442 0.2150
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 14.762 0.0677 2.6935
## upper .95
## T_2CAT3-4 1.483
## N_2CATN2-N3 3.530
## M 36.847
## HPV16_DNA_RNADNA+RNA- 2.731
## HPV16_DNA_RNADNA+RNA+ 0.686
## ALTER_3CAT(50,70] 0.878
## I(PACKYEARS > 30)TRUE 1.812
## TP53ND 1.617
## TP53D 2.692
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 5.557
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 6.527
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 80.899
##
## Concordance= 0.699 (se = 0.033 )
## Rsquare= 0.246 (max possible= 0.985 )
## Likelihood ratio test= 56.8 on 12 df, p=8.72e-08
## Wald test = 56.4 on 12 df, p=1.01e-07
## Score (logrank) test = 71.8 on 12 df, p=1.5e-10
cox.zph(surv.res)
## rho chisq p

```

```
## T_2CAT3-4 0.05443 3.31e-01 0.5651
## N_2CATN2-N3 0.06388 3.84e-01 0.5352
## M -0.00069 4.36e-05 0.9947
## HPV16_DNA_RNADNA+RNA- -0.08083 5.86e-01 0.4441
## HPV16_DNA_RNADNA+RNA+ 0.18305 2.85e+00 0.0914
## ALTER_3CAT(50,70] -0.12381 1.33e+00 0.2493
## I(PACKYEARS > 30)TRUE 0.04442 1.93e-01 0.6603
## TP53ND -0.17445 3.05e+00 0.0806
## TP53D -0.09458 8.26e-01 0.3633
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.04546 1.99e-01 0.6555
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.13692 1.77e+00 0.1830
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.11574 1.13e+00 0.2869
## GLOBAL NA 1.15e+01 0.4850

# 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= 88
## (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.542156  1.719711  0.264587  2.05   0.040 *
## UICC_3CATIVB-C     1.661515  5.267285  0.363493  4.57  4.9e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.498777  0.607273  0.436223 -1.14   0.253
## HPV16_DNA_RNADNA+RNA+ -0.703651  0.494776  0.378687 -1.86   0.063 .
## ALTER              0.010814  1.010873  0.010714  1.01   0.313
## PACKYEARS          0.000455  1.000456  0.004699  0.10   0.923
## TP53ND             -0.233863  0.791470  0.343670 -0.68   0.496
## TP53D              0.572702  1.773051  0.256077  2.24   0.025 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.720      0.581      1.024      2.89
## UICC_3CATIVB-C     5.267      0.190      2.583     10.74
## HPV16_DNA_RNADNA+RNA- 0.607      1.647      0.258      1.43
## HPV16_DNA_RNADNA+RNA+ 0.495      2.021      0.236      1.04
```

```

## ALTER                1.011      0.989      0.990      1.03
## PACKYEARS            1.000      1.000      0.991      1.01
## TP53ND               0.791      1.263      0.404      1.55
## TP53D                1.773      0.564      1.073      2.93
##
## Concordance= 0.648 (se = 0.033 )
## Rsquare= 0.143 (max possible= 0.985 )
## Likelihood ratio test= 31.1 on 8 df, p=0.000133
## Wald test = 33.2 on 8 df, p=5.7e-05
## Score (logrank) test = 36.5 on 8 df, p=1.41e-05

cox.zph(surv.res)

##                rho    chisq    p
## UICC_3CATIVA      0.0852 0.64668 0.421
## UICC_3CATIVB-C    0.0124 0.01417 0.905
## HPV16_DNA_RNADNA+RNA- 0.0048 0.00234 0.961
## HPV16_DNA_RNADNA+RNA+ 0.1276 1.44157 0.230
## ALTER            -0.0551 0.33304 0.564
## PACKYEARS         0.0499 0.23603 0.627
## TP53ND            -0.1305 1.59056 0.207
## TP53D            -0.0889 0.71374 0.398
## GLOBAL            NA 4.74646 0.784

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

##                hr 2.5 % 97.5 %    p
## UICC_3CATIVA      1.72  1.02   2.89 0.040
## UICC_3CATIVB-C    5.27  2.58  10.74 0.000
## HPV16_DNA_RNADNA+RNA- 0.61  0.26   1.43 0.253
## HPV16_DNA_RNADNA+RNA+ 0.49  0.24   1.04 0.063
## ALTER            1.01  0.99   1.03 0.313
## PACKYEARS         1.00  0.99   1.01 0.923
## TP53ND            0.79  0.40   1.55 0.496
## TP53D            1.77  1.07   2.93 0.025

# 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 21.15      2.6e-05 ***
## HPV16_DNA_RNA  2  4.39        0.11
## ALTER         1  1.02        0.31
## PACKYEARS      1  0.01        0.92
## TP53          2  7.04        0.03 *
## 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= 87
## (19 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        4.75e-01
## UICC_3CATIVB-C                      1.82e+00
## HPV16_DNA_RNADNA+RNA-              -7.50e-01
## HPV16_DNA_RNADNA+RNA+              -1.08e+00
## ALTER                             1.49e-02
## PACKYEARS                          5.29e-05
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -1.67e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -3.38e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     -8.64e-01
## TP53ND                           -3.47e-01
## TP53D                             4.92e-01
##
## exp(coef)
## UICC_3CATIVA                      1.61e+00
## UICC_3CATIVB-C                    6.20e+00
## HPV16_DNA_RNADNA+RNA-             4.72e-01
## HPV16_DNA_RNADNA+RNA+             3.41e-01
## ALTER                             1.01e+00
## PACKYEARS                         1.00e+00
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  8.46e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 7.13e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     4.22e-01
```

```

## TP53ND 7.07e-01
## TP53D 1.64e+00
## se(coef)
## UICC_3CATIVA 2.67e-01
## UICC_3CATIVB-C 3.82e-01
## HPV16_DNA_RNADNA+RNA- 4.53e-01
## HPV16_DNA_RNADNA+RNA+ 4.14e-01
## ALTER 1.13e-02
## PACKYEARS 4.80e-03
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 2.74e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 3.75e-01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 3.64e-01
## TP53ND 3.49e-01
## TP53D 2.60e-01
## z
## UICC_3CATIVA 1.78
## UICC_3CATIVB-C 4.78
## HPV16_DNA_RNADNA+RNA- -1.65
## HPV16_DNA_RNADNA+RNA+ -2.60
## ALTER 1.32
## PACKYEARS 0.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.61
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.90
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -2.37
## TP53ND -0.99
## TP53D 1.89
## Pr(>|z|)
## UICC_3CATIVA 0.0747
## UICC_3CATIVB-C 1.8e-06
## HPV16_DNA_RNADNA+RNA- 0.0982
## HPV16_DNA_RNADNA+RNA+ 0.0093
## ALTER 0.1875
## PACKYEARS 0.9912
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.5422
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.3683
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.0177
## TP53ND 0.3199
## TP53D 0.0589
## .
## 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                        1.608
## UICC_3CATIVB-C                      6.200
## HPV16_DNA_RNADNA+RNA-              0.472
## HPV16_DNA_RNADNA+RNA+              0.341
## ALTER                              1.015
## PACKYEARS                           1.000
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.846
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.713
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.422
## TP53ND                             0.707
## TP53D                              1.635
##
##                                     exp(-coef)
## UICC_3CATIVA                        0.622
## UICC_3CATIVB-C                      0.161
## HPV16_DNA_RNADNA+RNA-              2.117
## HPV16_DNA_RNADNA+RNA+              2.935
## ALTER                              0.985
## PACKYEARS                           1.000
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.182
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.402
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      2.372
## TP53ND                             1.415
## TP53D                              0.612
##
##                                     lower .95
## UICC_3CATIVA                        0.954
## UICC_3CATIVB-C                      2.934
## HPV16_DNA_RNADNA+RNA-              0.194
## HPV16_DNA_RNADNA+RNA+              0.151
## ALTER                              0.993
## PACKYEARS                           0.991
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.494
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.342
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.207
## TP53ND                             0.357
## TP53D                              0.982
##
##                                     upper .95
## UICC_3CATIVA                        2.711
## UICC_3CATIVB-C                      13.102
## HPV16_DNA_RNADNA+RNA-              1.149
## HPV16_DNA_RNADNA+RNA+              0.767
## ALTER                              1.038
## PACKYEARS                           1.010

```



```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris      1.448
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx    1.489
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx          0.860
## TP53ND                                                                1.400
## TP53D                                                                  2.723
##
## Concordance= 0.658 (se = 0.033 )
## Rsquare= 0.176 (max possible= 0.985 )
## Likelihood ratio test= 38.3 on 11 df, p=7.01e-05
## Wald test                    = 39 on 11 df, p=5.29e-05
## Score (logrank) test = 43.5 on 11 df, p=9.04e-06

cox.zph(surv.res)

##                                                                rho
## UICC_3CATIVA                                                    0.0722
## UICC_3CATIVB-C                                                  0.0342
## HPV16_DNA_RNADNA+RNA-                                          -0.0198
## HPV16_DNA_RNADNA+RNA+                                           0.0544
## ALTER                                                            -0.0135
## PACKYEARS                                                        0.0516
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.0976
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.0350
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     -0.1800
## TP53ND                                                           -0.1345
## TP53D                                                            -0.1254
## GLOBAL                                                            NA
##                                                                chisq
## UICC_3CATIVA                                                    0.4546
## UICC_3CATIVB-C                                                  0.1269
## HPV16_DNA_RNADNA+RNA-                                          0.0408
## HPV16_DNA_RNADNA+RNA+                                           0.2691
## ALTER                                                            0.0207
## PACKYEARS                                                        0.2600
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.8855
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.1032
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx     2.8948
## TP53ND                                                           1.7424
## TP53D                                                            1.4077
## GLOBAL                                                            7.7676
##                                                                p
## UICC_3CATIVA                                                    0.5002
## UICC_3CATIVB-C                                                  0.7217
## HPV16_DNA_RNADNA+RNA-                                          0.8398
## HPV16_DNA_RNADNA+RNA+                                           0.6039
## ALTER                                                            0.8856
## PACKYEARS                                                        0.6101
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.3467
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.7481

```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.0889
## TP53ND                                                            0.1868
## TP53D                                                             0.2354
## GLOBAL                                                            0.7340

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

##                                                                    hr 2.5 %
## UICC_3CATIVA                                                       1.61  0.95
## UICC_3CATIVB-C                                                     6.20  2.93
## HPV16_DNA_RNADNA+RNA-                                             0.47  0.19
## HPV16_DNA_RNADNA+RNA+                                             0.34  0.15
## ALTER                                                             1.01  0.99
## PACKYEARS                                                         1.00  0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.85  0.49
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.71  0.34
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.42  0.21
## TP53ND                                                            0.71  0.36
## TP53D                                                             1.64  0.98
##                                                                    97.5 %
## UICC_3CATIVA                                                       2.71
## UICC_3CATIVB-C                                                     13.10
## HPV16_DNA_RNADNA+RNA-                                             1.15
## HPV16_DNA_RNADNA+RNA+                                             0.77
## ALTER                                                             1.04
## PACKYEARS                                                         1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  1.45
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.49
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.86
## TP53ND                                                            1.40
## TP53D                                                             2.72
##                                                                    p
## UICC_3CATIVA                                                       0.075
## UICC_3CATIVB-C                                                     0.000
## HPV16_DNA_RNADNA+RNA-                                             0.098
## HPV16_DNA_RNADNA+RNA+                                             0.009
## ALTER                                                             0.188
## PACKYEARS                                                         0.991
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris  0.542
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.368
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.018
## TP53ND                                                            0.320
## TP53D                                                             0.059

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 23.60 7.5e-06
## HPV16_DNA_RNA 2 8.27 0.016
## ALTER 1 1.74 0.188
## PACKYEARS 1 0.00 0.991
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx") 3 5.95 0.114
## TP53 2 6.35 0.042
## 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= 99
##
## coef exp(coef) se(coef) z Pr(>|z|)
## CONSENSUS_CLUSTERBasal 0.276 1.318 0.276 1.00 0.3180
## CONSENSUS_CLUSTERClassical -0.140 0.869 0.414 -0.34 0.7344
## CONSENSUS_CLUSTERMesenchymal 0.429 1.536 0.273 1.57 0.1163
## TP53ND -0.259 0.772 0.325 -0.80 0.4258
## TP53D 0.595 1.813 0.229 2.60 0.0094 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## CONSENSUS_CLUSTERBasal 1.318 0.759 0.767 2.26
## CONSENSUS_CLUSTERClassical 0.869 1.151 0.386 1.96
## CONSENSUS_CLUSTERMesenchymal 1.536 0.651 0.899 2.62
## TP53ND 0.772 1.296 0.408 1.46
## TP53D 1.813 0.552 1.157 2.84
```

```
##
## Concordance= 0.598 (se = 0.031 )
## Rsquare= 0.052 (max possible= 0.987 )
## Likelihood ratio test= 11.7 on 5 df, p=0.0397
## Wald test = 12.1 on 5 df, p=0.0332
## Score (logrank) test = 12.5 on 5 df, p=0.029

# 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 3.69 0.297
## TP53 2 8.96 0.011 *
## 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= 89
## (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.2980 0.7423 0.4278 -0.70 0.486
## HPV16_DNA_RNADNA+RNA+ -0.5595 0.5715 0.3983 -1.40 0.160
## CONSENSUS_CLUSTERBasal -0.1770 0.8378 0.3044 -0.58 0.561
## CONSENSUS_CLUSTERClassical -0.4233 0.6549 0.4275 -0.99 0.322
## CONSENSUS_CLUSTERMesenchymal 0.0512 1.0525 0.2911 0.18 0.860
## TP53ND -0.3209 0.7255 0.3390 -0.95 0.344
## TP53D 0.5940 1.8112 0.2487 2.39 0.017 *
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA- 0.742 1.347 0.321 1.72
## HPV16_DNA_RNADNA+RNA+ 0.572 1.750 0.262 1.25
```

```
## CONSENSUS_CLUSTERBasal      0.838      1.194      0.461      1.52
## CONSENSUS_CLUSTERClassical   0.655      1.527      0.283      1.51
## CONSENSUS_CLUSTERMesenchymal 1.053      0.950      0.595      1.86
## TP53ND                       0.726      1.378      0.373      1.41
## TP53D                        1.811      0.552      1.112      2.95
##
## Concordance= 0.619 (se = 0.033 )
## Rsquare= 0.065 (max possible= 0.985 )
## Likelihood ratio test= 13.7 on 7 df, p=0.0566
## Wald test = 14.3 on 7 df, p=0.0466
## Score (logrank) test = 14.9 on 7 df, p=0.0369

# 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  2.32    0.313
## CONSENSUS_CLUSTER  3  1.80    0.614
## TP53                2  8.72    0.013 *
## 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= 89
## (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.5509    1.7348  0.2655  2.08  0.038 *
## UICC_3CATIVB-C    1.7621    5.8248  0.3642  4.84 1.3e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.5030    0.6047  0.4394 -1.14  0.252
## HPV16_DNA_RNADNA+RNA+ -0.6934    0.4999  0.4041 -1.72  0.086 .
## CONSENSUS_CLUSTERBasal -0.0226    0.9777  0.3103 -0.07  0.942
## CONSENSUS_CLUSTERClassical -0.4637    0.6289  0.4378 -1.06  0.289
## CONSENSUS_CLUSTERMesenchymal 0.1648    1.1791  0.2961  0.56  0.578
```

```

## TP53ND                -0.2618    0.7697    0.3426 -0.76    0.445
## TP53D                  0.5711    1.7701    0.2522  2.26    0.024 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                      exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.735      0.576      1.031      2.92
## UICC_3CATIVB-C        5.825      0.172      2.853     11.89
## HPV16_DNA_RNADNA+RNA- 0.605      1.654      0.256      1.43
## HPV16_DNA_RNADNA+RNA+ 0.500      2.001      0.226      1.10
## CONSENSUS_CLUSTERBasal 0.978      1.023      0.532      1.80
## CONSENSUS_CLUSTERClassical 0.629      1.590      0.267      1.48
## CONSENSUS_CLUSTERMesenchymal 1.179      0.848      0.660      2.11
## TP53ND                0.770      1.299      0.393      1.51
## TP53D                  1.770      0.565      1.080      2.90
##
## Concordance= 0.663 (se = 0.033 )
## Rsquare= 0.153 (max possible= 0.985 )
## Likelihood ratio test= 33.8 on 9 df,  p=9.78e-05
## Wald test               = 35.8 on 9 df,  p=4.26e-05
## Score (logrank) test = 39.3 on 9 df,  p=1.01e-05

# 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 23.81  6.7e-06 ***
## HPV16_DNA_RNA  2  3.99   0.136
## CONSENSUS_CLUSTER  3  2.44   0.486
## TP53           2  7.33   0.026 *
## 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= 89
##   (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z
## UICC_3CATIVA      0.5358      1.7088   0.2720   1.97
## UICC_3CATIVB-C     1.8168      6.1521   0.3821   4.75
## HPV16_DNA_RNADNA+RNA- -0.5004      0.6063   0.4490  -1.11
## HPV16_DNA_RNADNA+RNA+ -0.7099      0.4917   0.4235  -1.68
## CONSENSUS_CLUSTERBasal  0.0301      1.0306   0.4151   0.07
## CONSENSUS_CLUSTERClassical -0.1724      0.8417   0.6058  -0.28
## CONSENSUS_CLUSTERMesenchymal  0.1517      1.1638   0.4186   0.36
## TP53ND            0.2641      1.3022   0.5699   0.46
## TP53D             0.3294      1.3901   0.5808   0.57
## CONSENSUS_CLUSTERBasal:TP53ND -1.8066      0.1642   1.1701  -1.54
## CONSENSUS_CLUSTERClassical:TP53ND -0.3801      0.6838   1.2505  -0.30
## CONSENSUS_CLUSTERMesenchymal:TP53ND -0.4583      0.6324   0.7725  -0.59
## CONSENSUS_CLUSTERBasal:TP53D  0.5037      1.6548   0.7124   0.71
## CONSENSUS_CLUSTERClassical:TP53D -0.3845      0.6808   0.9935  -0.39
## CONSENSUS_CLUSTERMesenchymal:TP53D  0.3486      1.4170   0.7064   0.49
##               Pr(>|z|)
## UICC_3CATIVA      0.049 *
## UICC_3CATIVB-C     2e-06 ***
## HPV16_DNA_RNADNA+RNA- 0.265
## HPV16_DNA_RNADNA+RNA+ 0.094 .
## CONSENSUS_CLUSTERBasal  0.942
## CONSENSUS_CLUSTERClassical 0.776
## CONSENSUS_CLUSTERMesenchymal 0.717
## TP53ND            0.643
## TP53D             0.571
## CONSENSUS_CLUSTERBasal:TP53ND 0.123
## CONSENSUS_CLUSTERClassical:TP53ND 0.761
## CONSENSUS_CLUSTERMesenchymal:TP53ND 0.553
## CONSENSUS_CLUSTERBasal:TP53D 0.480
## CONSENSUS_CLUSTERClassical:TP53D 0.699
## CONSENSUS_CLUSTERMesenchymal:TP53D 0.622
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95
## UICC_3CATIVA      1.709      0.585      1.0027
## UICC_3CATIVB-C     6.152      0.163      2.9092
## HPV16_DNA_RNADNA+RNA- 0.606      1.649      0.2515
## HPV16_DNA_RNADNA+RNA+ 0.492      2.034      0.2144
## CONSENSUS_CLUSTERBasal  1.031      0.970      0.4568
## CONSENSUS_CLUSTERClassical 0.842      1.188      0.2567
## CONSENSUS_CLUSTERMesenchymal 1.164      0.859      0.5124
## TP53ND            1.302      0.768      0.4262
```

```

## TP53D 1.390 0.719 0.4453
## CONSENSUS_CLUSTERBasal:TP53ND 0.164 6.090 0.0166
## CONSENSUS_CLUSTERClassical:TP53ND 0.684 1.462 0.0589
## CONSENSUS_CLUSTERMesenchymal:TP53ND 0.632 1.581 0.1391
## CONSENSUS_CLUSTERBasal:TP53D 1.655 0.604 0.4096
## CONSENSUS_CLUSTERClassical:TP53D 0.681 1.469 0.0971
## CONSENSUS_CLUSTERMesenchymal:TP53D 1.417 0.706 0.3549
## upper .95
## UICC_3CATIVA 2.91
## UICC_3CATIVB-C 13.01
## HPV16_DNA_RNADNA+RNA- 1.46
## HPV16_DNA_RNADNA+RNA+ 1.13
## CONSENSUS_CLUSTERBasal 2.32
## CONSENSUS_CLUSTERClassical 2.76
## CONSENSUS_CLUSTERMesenchymal 2.64
## TP53ND 3.98
## TP53D 4.34
## CONSENSUS_CLUSTERBasal:TP53ND 1.63
## CONSENSUS_CLUSTERClassical:TP53ND 7.93
## CONSENSUS_CLUSTERMesenchymal:TP53ND 2.87
## CONSENSUS_CLUSTERBasal:TP53D 6.69
## CONSENSUS_CLUSTERClassical:TP53D 4.77
## CONSENSUS_CLUSTERMesenchymal:TP53D 5.66
##
## Concordance= 0.669 (se = 0.033 )
## Rsquare= 0.175 (max possible= 0.985 )
## Likelihood ratio test= 39.2 on 15 df, p=0.000604
## Wald test = 39.4 on 15 df, p=0.000553
## Score (logrank) test = 44.9 on 15 df, p=7.83e-05

# 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 23.17 9.3e-06 ***
## HPV16_DNA_RNA 2 3.75 0.15
## CONSENSUS_CLUSTER 3 0.38 0.94
## TP53 2 0.40 0.82
## CONSENSUS_CLUSTER:TP53 6 4.28 0.64
## 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef)  se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.568797  1.766142  0.264986  2.15   0.032 *
## UICC_3CATIVB-C      1.701864  5.484161  0.362642  4.69  2.7e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.582187  0.558675  0.435370 -1.34   0.181
## HPV16_DNA_RNADNA+RNA+ -0.674116  0.509607  0.405194 -1.66   0.096 .
## IS_ATYPICALAtypical  0.000346  1.000346  0.268610  0.00   0.999
## TP53ND             -0.244516  0.783083  0.342331 -0.71   0.475
## TP53D              0.531714  1.701847  0.249061  2.13   0.033 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.766      0.566      1.051      2.97
## UICC_3CATIVB-C      5.484      0.182      2.694     11.16
## HPV16_DNA_RNADNA+RNA-  0.559      1.790      0.238      1.31
## HPV16_DNA_RNADNA+RNA+  0.510      1.962      0.230      1.13
## IS_ATYPICALAtypical  1.000      1.000      0.591      1.69
## TP53ND             0.783      1.277      0.400      1.53
## TP53D              1.702      0.588      1.045      2.77
##
## Concordance= 0.641 (se = 0.033 )
## Rsquare= 0.142 (max possible= 0.985 )
## Likelihood ratio test= 31.1 on 7 df,  p=5.91e-05
## Wald test               = 33.5 on 7 df,  p=2.13e-05
## Score (logrank) test = 36.8 on 7 df,  p=5.14e-06

# 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 22.27   1.5e-05 ***
## HPV16_DNA_RNA  2  4.28    0.117
## IS_ATYPICAL    1  0.00    0.999
## TP53           2  6.50    0.039 *
## 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.5239    1.6886  0.2659  1.97   0.049 *
## UICC_3CATIVB-C     1.6774    5.3518  0.3664  4.58  4.7e-06 ***
## HPV16_DNA_RNADNA+RNA- -0.6066    0.5452  0.4357 -1.39   0.164
## HPV16_DNA_RNADNA+RNA+ -0.6942    0.4995  0.4235 -1.64   0.101
## IS_ATYPICALAtypical -0.0328    0.9677  0.3704 -0.09   0.929
## TP53ND            -0.5017    0.6055  0.4285 -1.17   0.242
## TP53D              0.5831    1.7915  0.2755  2.12   0.034 *
## IS_ATYPICALAtypical:TP53ND 0.7458    2.1081  0.6920  1.08   0.281
## IS_ATYPICALAtypical:TP53D -0.2836    0.7531  0.6401 -0.44   0.658
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.689      0.592    1.003    2.84
## UICC_3CATIVB-C         5.352      0.187    2.610   10.97
## HPV16_DNA_RNADNA+RNA-  0.545      1.834    0.232    1.28
## HPV16_DNA_RNADNA+RNA+  0.499      2.002    0.218    1.15
## IS_ATYPICALAtypical    0.968      1.033    0.468    2.00
## TP53ND                0.605      1.652    0.261    1.40
## TP53D                 1.792      0.558    1.044    3.07
## IS_ATYPICALAtypical:TP53ND 2.108      0.474    0.543    8.18
## IS_ATYPICALAtypical:TP53D 0.753      1.328    0.215    2.64
##
## Concordance= 0.653 (se = 0.033 )
## Rsquare= 0.149 (max possible= 0.985 )
## Likelihood ratio test= 32.9 on 9 df, p=0.000141
## Wald test              = 35.4 on 9 df, p=5.11e-05
## Score (logrank) test = 38.8 on 9 df, p=1.27e-05
```

```
# 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 21.32   2.4e-05 ***
## HPV16_DNA_RNA  2  4.29    0.117
## IS_ATYPICAL    1  0.01    0.929
## TP53           2  7.44    0.024 *
## IS_ATYPICAL:TP53 2  1.77    0.413
## 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= 88
##      (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.53470   1.70694  0.26563  2.01   0.044
## UICC_3CATIVB-C     1.73426   5.66472  0.36712  4.72  2.3e-06
## HPV16_DNA_RNADNA+RNA- -0.44707   0.63950  0.43833 -1.02   0.308
## HPV16_DNA_RNADNA+RNA+ -0.71259   0.49037  0.41013 -1.74   0.082
## ALTER            0.00921   1.00925  0.01073  0.86   0.391
## PACKYEARS        -0.00050   0.99950  0.00477 -0.10   0.917
## CONSENSUS_CLUSTERBasal  0.00805   1.00808  0.31678  0.03   0.980
## CONSENSUS_CLUSTERClassical -0.39785   0.67176  0.44281 -0.90   0.369
## CONSENSUS_CLUSTERMesenchymal 0.18270   1.20046  0.30437  0.60   0.548
## TP53ND           -0.23758   0.78853  0.34640 -0.69   0.493
## TP53D            0.60365   1.82879  0.25916  2.33   0.020
##
## 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          1.707      0.586      1.014      2.87
## UICC_3CATIVB-C         5.665      0.177      2.759     11.63
## HPV16_DNA_RNADNA+RNA-  0.639      1.564      0.271      1.51
## HPV16_DNA_RNADNA+RNA+  0.490      2.039      0.219      1.10
## ALTER                 1.009      0.991      0.988      1.03
## PACKYEARS             1.000      1.000      0.990      1.01
## CONSENSUS_CLUSTERBasal 1.008      0.992      0.542      1.88
## CONSENSUS_CLUSTERClassical 0.672      1.489      0.282      1.60
## CONSENSUS_CLUSTERMesenchymal 1.200      0.833      0.661      2.18
## TP53ND                 0.789      1.268      0.400      1.55
## TP53D                  1.829      0.547      1.100      3.04
##
## Concordance= 0.656 (se = 0.033 )
## Rsquare= 0.153 (max possible= 0.985 )
## Likelihood ratio test= 33.4 on 11 df, p=0.000462
## Wald test = 35.3 on 11 df, p=0.000222
## Score (logrank) test = 38.7 on 11 df, p=6e-05

cox.zph(surv.res)

##               rho  chisq    p
## UICC_3CATIVA      0.0805 0.5626 0.453
## UICC_3CATIVB-C    -0.0120 0.0131 0.909
## HPV16_DNA_RNADNA+RNA- -0.0137 0.0201 0.887
## HPV16_DNA_RNADNA+RNA+  0.0981 0.8781 0.349
## ALTER            -0.0369 0.1468 0.702
## PACKYEARS         0.0694 0.4923 0.483
## CONSENSUS_CLUSTERBasal -0.0681 0.4274 0.513
## CONSENSUS_CLUSTERClassical  0.0824 0.6349 0.426
## CONSENSUS_CLUSTERMesenchymal -0.0718 0.4840 0.487
## TP53ND            -0.1306 1.6040 0.205
## TP53D             -0.0977 0.9180 0.338
## GLOBAL            NA 6.8278 0.813

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

```

```
##
```

	hr	2.5 %	97.5 %	p
## UICC_3CATIVA	1.71	1.01	2.87	0.044
## UICC_3CATIVB-C	5.66	2.76	11.63	0.000
## HPV16_DNA_RNADNA+RNA-	0.64	0.27	1.51	0.308
## HPV16_DNA_RNADNA+RNA+	0.49	0.22	1.10	0.082
## ALTER	1.01	0.99	1.03	0.391
## PACKYEARS	1.00	0.99	1.01	0.917
## CONSENSUS_CLUSTERBasal	1.01	0.54	1.88	0.980
## CONSENSUS_CLUSTERClassical	0.67	0.28	1.60	0.369
## CONSENSUS_CLUSTERMesenchymal	1.20	0.66	2.18	0.548
## TP53ND	0.79	0.40	1.55	0.493
## TP53D	1.83	1.10	3.04	0.020

```
##
```

*# 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	22.70	1.2e-05 ***
## HPV16_DNA_RNA	2	3.80	0.150
## ALTER	1	0.74	0.391
## PACKYEARS	1	0.01	0.917
## CONSENSUS_CLUSTER	3	2.07	0.558
## TP53	2	7.63	0.022 *
## 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= 87
##    (19 observations deleted due to missingness)
##
##
##                                     coef
## UICC_3CATIVA                        0.46903
## UICC_3CATIVB-C                      1.89719
## HPV16_DNA_RNADNA+RNA-              -0.68993
## HPV16_DNA_RNADNA+RNA+              -1.06250
## ALTER                             0.01372
## PACKYEARS                          -0.00112
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.21150
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.37750
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    -0.84412
## CONSENSUS_CLUSTERBasal              0.09441
## CONSENSUS_CLUSTERClassical          -0.32543
## CONSENSUS_CLUSTERMesenchymal        0.19002
## TP53ND                              -0.34389
## TP53D                               0.53491
##                                     exp(coef)
## UICC_3CATIVA                        1.59844
## UICC_3CATIVB-C                      6.66716
## HPV16_DNA_RNADNA+RNA-              0.50161
## HPV16_DNA_RNADNA+RNA+              0.34559
## ALTER                             1.01382
## PACKYEARS                          0.99888
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.80937
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.68557
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    0.42994
## CONSENSUS_CLUSTERBasal              1.09901
## CONSENSUS_CLUSTERClassical          0.72222
## CONSENSUS_CLUSTERMesenchymal        1.20927
## TP53ND                              0.70901
## TP53D                               1.70730
##                                     se(coef)
## UICC_3CATIVA                        0.26634
## UICC_3CATIVB-C                      0.38392
## HPV16_DNA_RNADNA+RNA-              0.45450
## HPV16_DNA_RNADNA+RNA+              0.44451
## ALTER                             0.01147
## PACKYEARS                          0.00492
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.27766
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.37847
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx    0.37241
## CONSENSUS_CLUSTERBasal              0.33436
## CONSENSUS_CLUSTERClassical          0.46026
## CONSENSUS_CLUSTERMesenchymal        0.31351
## TP53ND                              0.35200

```

```

## TP53D 0.26284
## z
## UICC_3CATIVA 1.76
## UICC_3CATIVB-C 4.94
## HPV16_DNA_RNADNA+RNA- -1.52
## HPV16_DNA_RNADNA+RNA+ -2.39
## ALTER 1.20
## PACKYEARS -0.23
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.76
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -1.00
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -2.27
## CONSENSUS_CLUSTERBasal 0.28
## CONSENSUS_CLUSTERClassical -0.71
## CONSENSUS_CLUSTERMesenchymal 0.61
## TP53ND -0.98
## TP53D 2.04
## Pr(>|z|)
## UICC_3CATIVA 0.078
## UICC_3CATIVB-C 7.7e-07
## HPV16_DNA_RNADNA+RNA- 0.129
## HPV16_DNA_RNADNA+RNA+ 0.017
## ALTER 0.231
## PACKYEARS 0.820
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.446
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.319
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.023
## CONSENSUS_CLUSTERBasal 0.778
## CONSENSUS_CLUSTERClassical 0.480
## CONSENSUS_CLUSTERMesenchymal 0.544
## TP53ND 0.329
## TP53D 0.042
##
## UICC_3CATIVA .
## UICC_3CATIVB-C ***
## HPV16_DNA_RNADNA+RNA-
## HPV16_DNA_RNADNA+RNA+ *
## ALTER
## PACKYEARS
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx
## releval(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx *
## CONSENSUS_CLUSTERBasal
## CONSENSUS_CLUSTERClassical
## CONSENSUS_CLUSTERMesenchymal
## TP53ND
## TP53D *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

##
##
## UICC_3CATIVA 1.598
## UICC_3CATIVB-C 6.667
## HPV16_DNA_RNADNA+RNA- 0.502
## HPV16_DNA_RNADNA+RNA+ 0.346
## ALTER 1.014
## PACKYEARS 0.999
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.809
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.686
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.430
## CONSENSUS_CLUSTERBasal 1.099
## CONSENSUS_CLUSTERClassical 0.722
## CONSENSUS_CLUSTERMesenchymal 1.209
## TP53ND 0.709
## TP53D 1.707
##
## exp(-coef)
## UICC_3CATIVA 0.626
## UICC_3CATIVB-C 0.150
## HPV16_DNA_RNADNA+RNA- 1.994
## HPV16_DNA_RNADNA+RNA+ 2.894
## ALTER 0.986
## PACKYEARS 1.001
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.236
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.459
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 2.326
## CONSENSUS_CLUSTERBasal 0.910
## CONSENSUS_CLUSTERClassical 1.385
## CONSENSUS_CLUSTERMesenchymal 0.827
## TP53ND 1.410
## TP53D 0.586
##
## lower .95
## UICC_3CATIVA 0.948
## UICC_3CATIVB-C 3.142
## HPV16_DNA_RNADNA+RNA- 0.206
## HPV16_DNA_RNADNA+RNA+ 0.145
## ALTER 0.991
## PACKYEARS 0.989
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.470
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.327
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.207
## CONSENSUS_CLUSTERBasal 0.571
## CONSENSUS_CLUSTERClassical 0.293
## CONSENSUS_CLUSTERMesenchymal 0.654
## TP53ND 0.356
## TP53D 1.020
##
## upper .95
## UICC_3CATIVA 2.694

```



```

## UICC_3CATIVB-C 14.149
## HPV16_DNA_RNADNA+RNA- 1.222
## HPV16_DNA_RNADNA+RNA+ 0.826
## ALTER 1.037
## PACKYEARS 1.009
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.395
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.439
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.892
## CONSENSUS_CLUSTERBasal 2.116
## CONSENSUS_CLUSTERClassical 1.780
## CONSENSUS_CLUSTERMesenchymal 2.236
## TP53ND 1.413
## TP53D 2.858
##
## Concordance= 0.668 (se = 0.033 )
## Rsquare= 0.183 (max possible= 0.985 )
## Likelihood ratio test= 40 on 14 df, p=0.000258
## Wald test = 40.1 on 14 df, p=0.000246
## Score (logrank) test = 44.8 on 14 df, p=4.47e-05

cox.zph(surv.res)

## rho
## UICC_3CATIVA 0.06999
## UICC_3CATIVB-C 0.01179
## HPV16_DNA_RNADNA+RNA- -0.03604
## HPV16_DNA_RNADNA+RNA+ 0.05776
## ALTER 0.01049
## PACKYEARS 0.07525
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris -0.07582
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx -0.01720
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx -0.18532
## CONSENSUS_CLUSTERBasal -0.00297
## CONSENSUS_CLUSTERClassical 0.11564
## CONSENSUS_CLUSTERMesenchymal -0.04440
## TP53ND -0.13641
## TP53D -0.12669
## GLOBAL NA
## chisq
## UICC_3CATIVA 0.417575
## UICC_3CATIVB-C 0.014708
## HPV16_DNA_RNADNA+RNA- 0.140403
## HPV16_DNA_RNADNA+RNA+ 0.312619
## ALTER 0.012652
## PACKYEARS 0.614612
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.560706
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.024980
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 3.208478
## CONSENSUS_CLUSTERBasal 0.000834

```

```

## CONSENSUS_CLUSTERClassical 1.317979
## CONSENSUS_CLUSTERMesenchymal 0.187368
## TP53ND 1.825453
## TP53D 1.522382
## GLOBAL 9.972781
##
## p
## UICC_3CATIVA 0.5181
## UICC_3CATIVB-C 0.9035
## HPV16_DNA_RNADNA+RNA- 0.7079
## HPV16_DNA_RNADNA+RNA+ 0.5761
## ALTER 0.9104
## PACKYEARS 0.4331
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.4540
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.8744
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.0733
## CONSENSUS_CLUSTERBasal 0.9770
## CONSENSUS_CLUSTERClassical 0.2510
## CONSENSUS_CLUSTERMesenchymal 0.6651
## TP53ND 0.1767
## TP53D 0.2173
## GLOBAL 0.7642

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

##
## hr 2.5 %
## UICC_3CATIVA 1.60 0.95
## UICC_3CATIVB-C 6.67 3.14
## HPV16_DNA_RNADNA+RNA- 0.50 0.21
## HPV16_DNA_RNADNA+RNA+ 0.35 0.14
## ALTER 1.01 0.99
## PACKYEARS 1.00 0.99
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.81 0.47
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.69 0.33
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx 0.43 0.21
## CONSENSUS_CLUSTERBasal 1.10 0.57
## CONSENSUS_CLUSTERClassical 0.72 0.29
## CONSENSUS_CLUSTERMesenchymal 1.21 0.65
## TP53ND 0.71 0.36
## TP53D 1.71 1.02
##
## 97.5 %
## UICC_3CATIVA 2.69
## UICC_3CATIVB-C 14.15
## HPV16_DNA_RNADNA+RNA- 1.22
## HPV16_DNA_RNADNA+RNA+ 0.83
## ALTER 1.04
## PACKYEARS 1.01
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 1.39
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 1.44

```

```

## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.89
## CONSENSUS_CLUSTERBasal      2.12
## CONSENSUS_CLUSTERClassical      1.78
## CONSENSUS_CLUSTERMesenchymal      2.24
## TP53ND      1.41
## TP53D      2.86
##
## p
## UICC_3CATIVA      0.078
## UICC_3CATIVB-C      0.000
## HPV16_DNA_RNADNA+RNA-      0.129
## HPV16_DNA_RNADNA+RNA+      0.017
## ALTER      0.231
## PACKYEARS      0.820
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")cavum oris 0.446
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")hypopharynx 0.319
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")larynx      0.023
## CONSENSUS_CLUSTERBasal      0.778
## CONSENSUS_CLUSTERClassical      0.480
## CONSENSUS_CLUSTERMesenchymal      0.544
## TP53ND      0.329
## TP53D      0.042

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 25.26      3.3e-06
## HPV16_DNA_RNA      2  7.14      0.028
## ALTER      1  1.43      0.231
## PACKYEARS      1  0.05      0.820
## relevel(LOKALISATION_GROB_TEXT, ref = "oropharynx")      3  5.38      0.146
## CONSENSUS_CLUSTER      3  1.57      0.665
## TP53      2  7.03      0.030
## 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.subs
], 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.620      1.860   0.250   2.48   0.013 *
## UICC_3CATIVB-C    1.325      3.763   0.340   3.90  9.5e-05 ***
## CDKN2A           -0.319      0.727   0.512  -0.62   0.533
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.860      0.538    1.139    3.04
## UICC_3CATIVB-C        3.763      0.266    1.935    7.32
## CDKN2A                0.727      1.376    0.266    1.98
##
## Concordance= 0.604 (se = 0.028 )
## Rsquare= 0.069 (max possible= 0.987 )
## Likelihood ratio test= 15.5 on 3 df,  p=0.00144
## Wald test               = 15.9 on 3 df,  p=0.0012
## Score (logrank) test = 17.1 on 3 df,  p=0.000684

cox.zph(surv.res)

##              rho   chisq    p
## UICC_3CATIVA   -0.00333 0.00108 0.974
## UICC_3CATIVB-C -0.08762 0.74211 0.389
## CDKN2A         0.03410 0.11502 0.734
## GLOBAL         NA 1.10861 0.775

```

#### 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.346      0.708      0.426 -0.81      0.417
## HPV16_DNA_RNADNA+RNA+ -0.588      0.556      0.354 -1.66      0.097 .
## CDKN2A                  -0.643      0.526      0.589 -1.09      0.275
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.708      1.41      0.307      1.63
## HPV16_DNA_RNADNA+RNA+    0.556      1.80      0.277      1.11
## CDKN2A                    0.526      1.90      0.166      1.67
##
## Concordance= 0.564 (se = 0.026 )
## Rsquare= 0.024 (max possible= 0.985 )
## Likelihood ratio test= 5.01 on 3 df,  p=0.171
## Wald test               = 4.34 on 3 df,  p=0.227
## Score (logrank) test = 4.46 on 3 df,  p=0.216

cox.zph(surv.res)

##              rho  chisq    p
## HPV16_DNA_RNADNA+RNA- 0.0165 0.0243 0.876
## HPV16_DNA_RNADNA+RNA+ 0.1556 2.0614 0.151
## CDKN2A                 0.0787 0.5451 0.460
## GLOBAL                 NA 2.6189 0.454
```

#### 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= 89
```

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

```
##
```

	coef	exp(coef)	se(coef)	z	Pr(> z )
## UICC_3CATIVA	0.632	1.882	0.261	2.42	0.016 *
## UICC_3CATIVB-C	1.758	5.803	0.358	4.91	9.1e-07 ***
## HPV16_DNA_RNADNA+RNA-	-0.592	0.553	0.432	-1.37	0.171
## HPV16_DNA_RNADNA+RNA+	-0.779	0.459	0.358	-2.18	0.030 *
## CDKN2A	-0.594	0.552	0.590	-1.01	0.314

```
## ---
```

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

```
##
```

	exp(coef)	exp(-coef)	lower .95	upper .95
## UICC_3CATIVA	1.882	0.531	1.128	3.140
## UICC_3CATIVB-C	5.803	0.172	2.877	11.707
## HPV16_DNA_RNADNA+RNA-	0.553	1.807	0.237	1.290
## HPV16_DNA_RNADNA+RNA+	0.459	2.180	0.227	0.925
## CDKN2A	0.552	1.811	0.174	1.754

```
##
```

```
## Concordance= 0.636 (se = 0.031 )
```

```
## Rsquare= 0.121 (max possible= 0.985 )
```

```
## Likelihood ratio test= 26.1 on 5 df, p=8.49e-05
```

```
## Wald test = 28.1 on 5 df, p=3.46e-05
```

```
## Score (logrank) test = 30.5 on 5 df, p=1.19e-05
```

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

	rho	chisq	p
## UICC_3CATIVA	0.07073	0.44028	0.507
## UICC_3CATIVB-C	0.01366	0.01686	0.897
## HPV16_DNA_RNADNA+RNA-	0.00417	0.00168	0.967
## HPV16_DNA_RNADNA+RNA+	0.15050	1.85079	0.174
## CDKN2A	0.08499	0.63260	0.426
## GLOBAL	NA	3.16345	0.675

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.418      0.658    0.207 -2.02    0.044 *
## CDKN2A            -0.245      0.783    0.515 -0.48    0.635
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.658      1.52    0.438    0.988
## CDKN2A                 0.783      1.28    0.285    2.148
##
## Concordance= 0.543 (se = 0.027 )
## Rsquare= 0.021 (max possible= 0.987 )
## Likelihood ratio test= 4.52 on 2 df,  p=0.104
## Wald test               = 4.58 on 2 df,  p=0.101
## Score (logrank) test = 4.66 on 2 df,  p=0.0974

cox.zph(surv.res)

##              rho chisq      p
## ALTER_3CAT(50,70] -0.1054 1.0895 0.297
## CDKN2A            0.0282 0.0771 0.781
## GLOBAL            NA 1.1138 0.573
```

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.635      1.887    0.250  2.54    0.011 *
## UICC_3CATIVB-C     1.410      4.097    0.342  4.12  3.7e-05 ***
## ALTER_3CAT(50,70] -0.495      0.609    0.210 -2.36    0.018 *
## CDKN2A            -0.164      0.849    0.518 -0.32    0.751
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.887      0.530    1.155    3.08
```

```
## UICC_3CATIVB-C      4.097      0.244      2.096      8.01
## ALTER_3CAT(50,70]   0.609      1.641      0.404      0.92
## CDKN2A              0.849      1.178      0.308      2.34
##
## Concordance= 0.618 (se = 0.031 )
## Rsquare= 0.092 (max possible= 0.987 )
## Likelihood ratio test= 20.9 on 4 df, p=0.00033
## Wald test = 21.3 on 4 df, p=0.000272
## Score (logrank) test = 22.6 on 4 df, p=0.00015

cox.zph(surv.res)

##              rho      chisq      p
## UICC_3CATIVA      0.00127 0.000159 0.990
## UICC_3CATIVB-C    -0.06723 0.439156 0.508
## ALTER_3CAT(50,70] -0.10869 1.182467 0.277
## CDKN2A            0.04547 0.203682 0.652
## GLOBAL            NA 2.129968 0.712
```

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.651      1.917      0.251  2.60  0.00945 **
## UICC_3CATIVB-C    1.290      3.634      0.342  3.78  0.00016 ***
## APC              -1.004      0.367      0.514 -1.95  0.05065 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.917      0.522      1.173      3.13
## UICC_3CATIVB-C      3.634      0.275      1.861      7.10
## APC              0.367      2.728      0.134      1.00
##
## Concordance= 0.61 (se = 0.029 )
## Rsquare= 0.089 (max possible= 0.987 )
## Likelihood ratio test= 20.3 on 3 df, p=0.000148
## Wald test = 19 on 3 df, p=0.000276
## Score (logrank) test = 20.6 on 3 df, p=0.000126
```



```
cox.zph(surv.res)

##               rho  chisq    p
## UICC_3CATIVA    0.0205 0.0405 0.841
## UICC_3CATIVB-C -0.1043 1.0640 0.302
## APC             -0.0661 0.4361 0.509
## GLOBAL          NA  2.1696 0.538
```

#### 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= 89
##      (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.282    0.754    0.425 -0.66   0.507
## HPV16_DNA_RNADNA+RNA+ -0.624    0.536    0.355 -1.76   0.078 .
## APC                   -0.835    0.434    0.513 -1.63   0.104
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.754      1.33    0.328    1.74
## HPV16_DNA_RNADNA+RNA+    0.536      1.87    0.267    1.07
## APC                      0.434      2.30    0.159    1.19
##
## Concordance= 0.57 (se = 0.027 )
## Rsquare= 0.034 (max possible= 0.985 )
## Likelihood ratio test= 6.98 on 3 df,  p=0.0724
## Wald test               = 5.86 on 3 df,  p=0.119
## Score (logrank) test = 6.1 on 3 df,  p=0.107

cox.zph(surv.res)

##               rho  chisq    p
## HPV16_DNA_RNADNA+RNA- 0.01986 0.03490 0.852
## HPV16_DNA_RNADNA+RNA+ 0.15809 2.12606 0.145
## APC                   0.00653 0.00374 0.951
## GLOBAL                 NA  2.12973 0.546
```

#### 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= 89
##      (14 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.636    1.888    0.261  2.43   0.015 *
## UICC_3CATIVB-C     1.764    5.836    0.360  4.91  9.3e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.543    0.581    0.434 -1.25   0.211
## HPV16_DNA_RNADNA+RNA+ -0.833    0.435    0.359 -2.32   0.020 *
## APC              -0.814    0.443    0.513 -1.59   0.113
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.888    0.530    1.131    3.152
## UICC_3CATIVB-C     5.836    0.171    2.884   11.808
## HPV16_DNA_RNADNA+RNA- 0.581    1.721    0.248    1.359
## HPV16_DNA_RNADNA+RNA+ 0.435    2.299    0.215    0.879
## APC              0.443    2.256    0.162    1.212
##
## Concordance= 0.635 (se = 0.032 )
## Rsquare= 0.129 (max possible= 0.985 )
## Likelihood ratio test= 28.1 on 5 df, p=3.44e-05
## Wald test              = 29.2 on 5 df, p=2.14e-05
## Score (logrank) test = 31.9 on 5 df, p=6.27e-06

cox.zph(surv.res)

##              rho    chisq    p
## UICC_3CATIVA      0.08051 0.57167 0.450
## UICC_3CATIVB-C     0.00712 0.00460 0.946
## HPV16_DNA_RNADNA+RNA- 0.01108 0.01215 0.912
## HPV16_DNA_RNADNA+RNA+ 0.16195 2.16653 0.141
## APC              0.01009 0.00895 0.925
## GLOBAL            NA 2.90764 0.714

```

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -0.397      0.672    0.206 -1.93    0.054 .
## APC                -0.986      0.373    0.515 -1.91    0.056 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.672      1.49    0.449    1.01
## APC                    0.373      2.68    0.136    1.02
##
## Concordance= 0.556 (se = 0.028 )
## Rsquare= 0.042 (max possible= 0.987 )
## Likelihood ratio test= 9.24 on 2 df,  p=0.00985
## Wald test               = 7.8 on 2 df,  p=0.0202
## Score (logrank) test = 8.24 on 2 df,  p=0.0162

cox.zph(surv.res)

##              rho chisq      p
## ALTER_3CAT(50,70] -0.0868 0.753 0.386
## APC                -0.0571 0.337 0.562
## GLOBAL              NA 1.148 0.563

```

#### 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= 99
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.660      1.935    0.251  2.63    0.0084 **

```

```
## UICC_3CATIVB-C      1.395      4.035      0.345  4.05  5.2e-05 ***
## ALTER_3CAT(50,70] -0.485      0.616      0.209 -2.32   0.0202 *
## APC                 -0.960      0.383      0.513 -1.87   0.0612 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.935      0.517      1.184      3.161
## UICC_3CATIVB-C        4.035      0.248      2.053      7.931
## ALTER_3CAT(50,70]     0.616      1.624      0.409      0.927
## APC                   0.383      2.612      0.140      1.046
##
## Concordance= 0.624 (se = 0.031 )
## Rsquare= 0.111 (max possible= 0.987 )
## Likelihood ratio test= 25.5 on 4 df,  p=3.91e-05
## Wald test              = 24 on 4 df,  p=8.15e-05
## Score (logrank) test = 25.7 on 4 df,  p=3.57e-05

cox.zph(surv.res)

##                rho  chisq      p
## UICC_3CATIVA      0.0168 0.0272 0.869
## UICC_3CATIVB-C    -0.0859 0.7258 0.394
## ALTER_3CAT(50,70] -0.0780 0.6197 0.431
## APC               -0.0482 0.2318 0.630
## GLOBAL            NA  2.4029 0.662
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##                coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_DNA_RNADNA+RNA- -0.232      0.793      0.426 -0.54   0.587
## HPV16_DNA_RNADNA+RNA+ -0.605      0.546      0.355 -1.70   0.089 .
## ALTER_3CAT(50,70]     -0.459      0.632      0.216 -2.13   0.033 *
## APC                   -0.791      0.453      0.514 -1.54   0.123
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## HPV16_DNA_RNADNA+RNA-    0.793      1.26    0.344    1.829
## HPV16_DNA_RNADNA+RNA+    0.546      1.83    0.272    1.096
## ALTER_3CAT(50,70]        0.632      1.58    0.414    0.964
## APC                      0.453      2.21    0.166    1.240
##
## Concordance= 0.597 (se = 0.031 )
## Rsquare= 0.055 (max possible= 0.985 )
## Likelihood ratio test= 11.4 on 4 df, p=0.0222
## Wald test = 10.4 on 4 df, p=0.0341
## Score (logrank) test = 10.8 on 4 df, p=0.0295

cox.zph(surv.res)

##               rho chisq p
## HPV16_DNA_RNADNA+RNA- 0.0275 0.0678 0.795
## HPV16_DNA_RNADNA+RNA+ 0.1532 1.9953 0.158
## ALTER_3CAT(50,70]    -0.0770 0.5470 0.460
## APC                  0.0120 0.0127 0.910
## GLOBAL               NA 2.5000 0.645
```

#### 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= 89
## (14 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.659      1.932   0.262  2.52   0.012 *
## UICC_3CATIVB-C     1.874      6.511   0.364  5.15  2.5e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.454      0.635   0.434 -1.05   0.295
## HPV16_DNA_RNADNA+RNA+ -0.868      0.420   0.362 -2.40   0.016 *
## ALTER_3CAT(50,70]   -0.563      0.569   0.219 -2.57   0.010 *
## APC               -0.836      0.433   0.514 -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      1.932      0.518   1.157   3.228
```

```
## UICC_3CATIVB-C          6.511      0.154      3.193      13.277
## HPV16_DNA_RNADNA+RNA-   0.635      1.575      0.271      1.486
## HPV16_DNA_RNADNA+RNA+   0.420      2.381      0.207      0.853
## ALTER_3CAT(50,70]       0.569      1.756      0.371      0.874
## APC                     0.433      2.308      0.158      1.186
##
## Concordance= 0.65 (se = 0.033 )
## Rsquare= 0.157 (max possible= 0.985 )
## Likelihood ratio test= 34.6 on 6 df, p=5.17e-06
## Wald test = 34.3 on 6 df, p=5.83e-06
## Score (logrank) test = 37.5 on 6 df, p=1.4e-06

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA      0.0812 0.5792 0.447
## UICC_3CATIVB-C     0.0114 0.0116 0.914
## HPV16_DNA_RNADNA+RNA- 0.0189 0.0356 0.850
## HPV16_DNA_RNADNA+RNA+ 0.1492 1.8332 0.176
## ALTER_3CAT(50,70] -0.0605 0.3426 0.558
## APC               0.0204 0.0369 0.848
## GLOBAL            NA 3.0231 0.806
```

#### 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= 88
##      (16 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.632      1.882      0.263  2.40   0.0162 *
## UICC_3CATIVB-C     1.851      6.366      0.365  5.07  3.9e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.321      0.725      0.436 -0.74   0.4609
## HPV16_DNA_RNADNA+RNA+ -0.697      0.498      0.368 -1.89   0.0584 .
## I(PACKYEARS > 30)TRUE  0.556      1.744      0.229  2.43   0.0150 *
## ALTER_3CAT(50,70]   -0.724      0.485      0.228 -3.18   0.0015 **
## APC               -1.009      0.365      0.590 -1.71   0.0874 .
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.882      0.531      1.124      3.151
## UICC_3CATIVB-C     6.366      0.157      3.114     13.015
## HPV16_DNA_RNADNA+RNA-  0.725      1.379      0.308      1.704
## HPV16_DNA_RNADNA+RNA+  0.498      2.008      0.242      1.025
## I(PACKYEARS > 30)TRUE  1.744      0.573      1.114      2.730
## ALTER_3CAT(50,70]    0.485      2.063      0.310      0.758
## APC               0.365      2.743      0.115      1.159
##
## Concordance= 0.669  (se = 0.033 )
## Rsquare= 0.186   (max possible= 0.985 )
## Likelihood ratio test= 41.4  on 7 df,   p=6.66e-07
## Wald test          = 40  on 7 df,   p=1.24e-06
## Score (logrank) test = 43.7  on 7 df,   p=2.44e-07

cox.zph(surv.res)

##               rho      chisq      p
## UICC_3CATIVA      0.086149 6.48e-01 0.421
## UICC_3CATIVB-C     0.000288 7.44e-06 0.998
## HPV16_DNA_RNADNA+RNA-  0.043305 1.86e-01 0.666
## HPV16_DNA_RNADNA+RNA+  0.167814 2.64e+00 0.104
## I(PACKYEARS > 30)TRUE  0.085614 6.88e-01 0.407
## ALTER_3CAT(50,70]   -0.081316 5.85e-01 0.444
## APC               -0.025652 5.65e-02 0.812
## GLOBAL              NA 4.42e+00 0.730
```

#### 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= 88
## (16 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## UICC_3CATIVA      0.726      2.066      0.266
```

```

## UICC_3CATIVB-C 1.911 6.758 0.367
## HPV16_DNA_RNADNA+RNA- -0.238 0.788 0.617
## HPV16_DNA_RNADNA+RNA+ -1.995 0.136 0.736
## I(PACKYEARS > 30)TRUE 0.346 1.414 0.244
## ALTER_3CAT(50,70] -0.734 0.480 0.230
## APC -1.024 0.359 0.593
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE -0.160 0.852 0.857
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 2.340 10.381 0.845
## z Pr(>|z|)
## UICC_3CATIVA 2.72 0.0065 **
## UICC_3CATIVB-C 5.21 1.9e-07 ***
## HPV16_DNA_RNADNA+RNA- -0.39 0.6998
## HPV16_DNA_RNADNA+RNA+ -2.71 0.0067 **
## I(PACKYEARS > 30)TRUE 1.42 0.1562
## ALTER_3CAT(50,70] -3.19 0.0014 **
## APC -1.73 0.0843 .
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE -0.19 0.8519
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 2.77 0.0056 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95
## UICC_3CATIVA 2.066 0.4839 1.2257
## UICC_3CATIVB-C 6.758 0.1480 3.2916
## HPV16_DNA_RNADNA+RNA- 0.788 1.2687 0.2351
## HPV16_DNA_RNADNA+RNA+ 0.136 7.3498 0.0321
## I(PACKYEARS > 30)TRUE 1.414 0.7072 0.8760
## ALTER_3CAT(50,70] 0.480 2.0834 0.3060
## APC 0.359 2.7842 0.1123
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 0.852 1.1736 0.1588
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 10.381 0.0963 1.9810
## upper .95
## UICC_3CATIVA 3.484
## UICC_3CATIVB-C 13.874
## HPV16_DNA_RNADNA+RNA- 2.643
## HPV16_DNA_RNADNA+RNA+ 0.576
## I(PACKYEARS > 30)TRUE 2.283
## ALTER_3CAT(50,70] 0.753
## APC 1.148
## HPV16_DNA_RNADNA+RNA-: I(PACKYEARS > 30)TRUE 4.572
## HPV16_DNA_RNADNA+RNA+: I(PACKYEARS > 30)TRUE 54.397
##
## Concordance= 0.694 (se = 0.033 )
## Rsquare= 0.225 (max possible= 0.985 )
## Likelihood ratio test= 51.2 on 9 df, p=6.45e-08
## Wald test = 44.8 on 9 df, p=1.03e-06
## Score (logrank) test = 49.8 on 9 df, p=1.17e-07
cox.zph(surv.res)

```



	rho	chisq	p
## UICC_3CATIVA	0.1261	1.4588	0.2271
## UICC_3CATIVB-C	0.0298	0.0807	0.7763
## HPV16_DNA_RNADNA+RNA-	-0.0504	0.2431	0.6220
## HPV16_DNA_RNADNA+RNA+	0.2280	4.0978	0.0429
## I(PACKYEARS > 30)TRUE	0.0222	0.0436	0.8346
## ALTER_3CAT(50,70]	-0.0964	0.8526	0.3558
## APC	-0.0163	0.0223	0.8813
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE	0.1169	1.2280	0.2678
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE	-0.1058	0.9240	0.3364
## GLOBAL	NA	10.4569	0.3148

#### 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= 88
## (16 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)
## T_2CAT3-4      -0.3398    0.7119  0.3758
## N_2CATN2-N3     0.7940    2.2122  0.2652
## M              2.4326   11.3879  0.5658
## HPV16_DNA_RNADNA+RNA-  0.0606    1.0625  0.6176
## HPV16_DNA_RNADNA+RNA+ -2.0080    0.1343  0.7605
## ALTER_3CAT(50,70] -0.5824    0.5586  0.2243
## I(PACKYEARS > 30)TRUE -0.1535    0.8577  0.3950
## APC            -0.9051    0.4045  0.5995
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.8368    2.3090  0.4733
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.2927    0.7463  0.8613
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE  2.6567   14.2494  0.8683
##
##               z Pr(>|z|)
## T_2CAT3-4      -0.90  0.3659
## N_2CATN2-N3     2.99  0.0028 **
## M              4.30  1.7e-05 ***
## HPV16_DNA_RNADNA+RNA-  0.10  0.9218

```

```

## HPV16_DNA_RNADNA+RNA+ -2.64 0.0083 **
## ALTER_3CAT(50,70] -2.60 0.0094 **
## I(PACKYEARS > 30)TRUE -0.39 0.6975
## APC -1.51 0.1311
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 1.77 0.0771 .
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE -0.34 0.7340
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 3.06 0.0022 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95
## T_2CAT3-4 0.712 1.4047 0.3408
## N_2CATN2-N3 2.212 0.4520 1.3154
## M 11.388 0.0878 3.7569
## HPV16_DNA_RNADNA+RNA- 1.063 0.9412 0.3167
## HPV16_DNA_RNADNA+RNA+ 0.134 7.4483 0.0302
## ALTER_3CAT(50,70] 0.559 1.7903 0.3599
## I(PACKYEARS > 30)TRUE 0.858 1.1660 0.3955
## APC 0.405 2.4721 0.1249
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 2.309 0.4331 0.9131
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.746 1.3400 0.1380
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 14.249 0.0702 2.5985
## upper .95
## T_2CAT3-4 1.487
## N_2CATN2-N3 3.720
## M 34.519
## HPV16_DNA_RNADNA+RNA- 3.564
## HPV16_DNA_RNADNA+RNA+ 0.596
## ALTER_3CAT(50,70] 0.867
## I(PACKYEARS > 30)TRUE 1.860
## APC 1.310
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 5.839
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 4.037
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE 78.139
##
## Concordance= 0.692 (se = 0.033 )
## Rsquare= 0.24 (max possible= 0.985 )
## Likelihood ratio test= 55 on 11 df, p=7.63e-08
## Wald test = 52.2 on 11 df, p=2.53e-07
## Score (logrank) test = 67.4 on 11 df, p=3.85e-10

cox.zph(surv.res)

## rho chisq p
## T_2CAT3-4 0.0506 0.3056 0.5804
## N_2CATN2-N3 0.0442 0.1890 0.6637
## M 0.0201 0.0379 0.8456
## HPV16_DNA_RNADNA+RNA- -0.0478 0.1962 0.6578
## HPV16_DNA_RNADNA+RNA+ 0.2037 3.6263 0.0569

```

```
## ALTER_3CAT(50,70] -0.1066 1.0278 0.3107
## I(PACKYEARS > 30)TRUE 0.0543 0.2991 0.5845
## APC -0.0415 0.1433 0.7050
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.0413 0.1689 0.6811
## HPV16_DNA_RNADNA+RNA-:I(PACKYEARS > 30)TRUE 0.1061 0.9793 0.3224
## HPV16_DNA_RNADNA+RNA+:I(PACKYEARS > 30)TRUE -0.1148 1.1464 0.2843
## GLOBAL NA 8.3231 0.6841

# 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= 98
## (3 observations deleted due to missingness)
##
##               coef exp(coef) se(coef)      z
## LOKALISATION_GROB_TEXToropharynx -0.0645    0.9376   0.2410 -0.27
## LOKALISATION_GROB_TEXThypopharynx  0.2549    1.2904   0.3429  0.74
## LOKALISATION_GROB_TEXTlarynx      -0.3675    0.6925   0.3202 -1.15
## APC                               -1.0801    0.3396   0.5236 -2.06
##
##               Pr(>|z|)
## LOKALISATION_GROB_TEXToropharynx    0.789
## LOKALISATION_GROB_TEXThypopharynx    0.457
## LOKALISATION_GROB_TEXTlarynx         0.251
## APC                                0.039 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## LOKALISATION_GROB_TEXToropharynx    0.938    1.067    0.585    1.504
## LOKALISATION_GROB_TEXThypopharynx    1.290    0.775    0.659    2.527
## LOKALISATION_GROB_TEXTlarynx         0.692    1.444    0.370    1.297
## APC                                0.340    2.945    0.122    0.948
##
## Concordance= 0.568 (se = 0.031 )
## Rsquare= 0.036 (max possible= 0.987 )
## Likelihood ratio test= 7.81 on 4 df, p=0.0989
## Wald test = 6.28 on 4 df, p=0.179
## Score (logrank) test = 6.56 on 4 df, p=0.161
```

```
cox.zph(surv.res)

##                                rho  chisq    p
## LOKALISATION_GROB_TEXToropharynx  0.0491 0.2347 0.628
## LOKALISATION_GROB_TEXThypopharynx  0.0137 0.0184 0.892
## LOKALISATION_GROB_TEXTlarynx      -0.0697 0.4778 0.489
## APC                                -0.0618 0.4000 0.527
## GLOBAL                             NA  1.6266 0.804
```

## 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.551     1.734   0.279 1.97   0.049 *
## UICC_3CATIVB-C  1.866     6.461   0.388 4.81  1.5e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.73     0.577     1.00     3.0
## UICC_3CATIVB-C        6.46     0.155     3.02    13.8
##
## Concordance= 0.602 (se = 0.031 )
## Rsquare= 0.112 (max possible= 0.986 )
## Likelihood ratio test= 18.8 on 2 df,  p=8.1e-05
## Wald test               = 23.4 on 2 df,  p=8.08e-06
## Score (logrank) test = 28.1 on 2 df,  p=7.93e-07

cox.zph(surv.res)

##              rho  chisq    p
## UICC_3CATIVA    0.1427 1.521 0.217
## UICC_3CATIVB-C  0.0411 0.121 0.728
## GLOBAL          NA  1.623 0.444
```

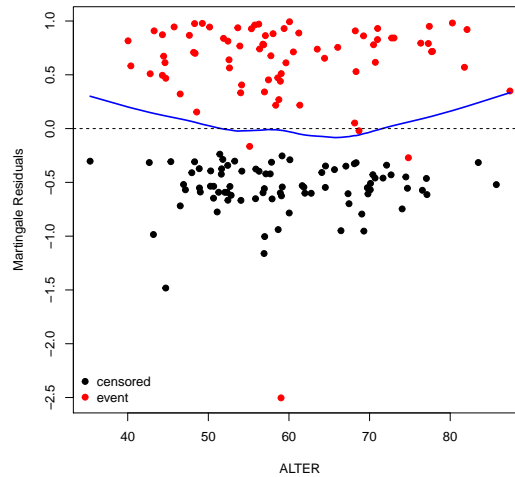
### 4.2.2 UICC, AGE

```
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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.54981   1.73293  0.27918 1.97   0.049 *
## UICC_3CATIVB-C  1.86592   6.46188  0.38769 4.81  1.5e-06 ***
## ALTER          0.00139   1.00140  0.01150 0.12   0.903
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.73      0.577      1.003      3.00
## UICC_3CATIVB-C          6.46      0.155      3.022     13.82
## ALTER                 1.00      0.999      0.979      1.02
##
## Concordance= 0.601 (se = 0.036 )
## Rsquare= 0.113 (max possible= 0.986 )
## Likelihood ratio test= 18.9 on 3 df,  p=0.000293
## Wald test               = 23.5 on 3 df,  p=3.24e-05
## Score (logrank) test = 28.1 on 3 df,  p=3.45e-06

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA    0.1436 1.545 0.214
## UICC_3CATIVB-C  0.0412 0.121 0.728
## ALTER          -0.0431 0.171 0.679
## GLOBAL          NA 1.795 0.616
```



### 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA    0.54981   1.73293  0.27918  1.97   0.049 *
## UICC_3CATIVB-C  1.86592   6.46188  0.38769  4.81  1.5e-06 ***
## ALTER          0.00139   1.00140  0.01150  0.12   0.903
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.73      0.577      1.003      3.00
## UICC_3CATIVB-C          6.46      0.155      3.022     13.82
## ALTER                 1.00      0.999      0.979      1.02
##
## Concordance= 0.601 (se = 0.036 )
## Rsquare= 0.113 (max possible= 0.986 )
## Likelihood ratio test= 18.9 on 3 df,  p=0.000293
## Wald test               = 23.5 on 3 df,  p=3.24e-05
## Score (logrank) test = 28.1 on 3 df,  p=3.45e-06

cox.zph(surv.res)

##              rho chisq      p

```

```
## UICC_3CATIVA      0.1436 1.545 0.214
## UICC_3CATIVB-C    0.0412 0.121 0.728
## ALTER             -0.0431 0.171 0.679
## GLOBAL            NA 1.795 0.616
```

#### 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.574      1.775   0.280  2.05   0.040 *
## UICC_3CATIVB-C    1.932      6.905   0.389  4.96   7e-07 ***
## ALTER_3CAT(50,70] -0.475      0.622   0.238 -2.00   0.046 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.775      0.563      1.03      3.071
## UICC_3CATIVB-C          6.905      0.145      3.22     14.814
## ALTER_3CAT(50,70]      0.622      1.608      0.39      0.991
##
## Concordance= 0.623 (se = 0.035 )
## Rsquare= 0.134 (max possible= 0.986 )
## Likelihood ratio test= 22.8 on 3 df,  p=4.56e-05
## Wald test               = 27.3 on 3 df,  p=5.08e-06
## Score (logrank) test = 32 on 3 df,  p=5.13e-07

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.1518 1.720 0.190
## UICC_3CATIVB-C      0.0539 0.203 0.652
## ALTER_3CAT(50,70] -0.0925 0.640 0.424
## GLOBAL            NA 2.368 0.500
```

#### 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= 73
## (1 observation deleted due to missingness)
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.550    1.733   0.281  1.96   0.050 .
## UICC_3CATIVB-C    1.921    6.829   0.390  4.93  8.3e-07 ***
## ALTER_3CAT(50,70] -0.571    0.565   0.248 -2.30   0.021 *
## I(PACKYEARS > 30)TRUE 0.325    1.384   0.246  1.32   0.186
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.733    0.577    0.999    3.007
## UICC_3CATIVB-C    6.829    0.146    3.180   14.665
## ALTER_3CAT(50,70] 0.565    1.769    0.348    0.919
## I(PACKYEARS > 30)TRUE 1.384    0.723    0.855    2.240
##
## Concordance= 0.643 (se = 0.036 )
## Rsquare= 0.144 (max possible= 0.985 )
## Likelihood ratio test= 24.4 on 4 df, p=6.61e-05
## Wald test = 28.4 on 4 df, p=1.04e-05
## Score (logrank) test = 33.4 on 4 df, p=9.84e-07

cox.zph(surv.res)

##               rho   chisq    p
## UICC_3CATIVA      0.1445 1.55031 0.213
## UICC_3CATIVB-C    0.0403 0.11121 0.739
## ALTER_3CAT(50,70] -0.0914 0.60584 0.436
## I(PACKYEARS > 30)TRUE -0.0113 0.00938 0.923
## GLOBAL            NA 2.36578 0.669

```

#### 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= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.595    1.814    0.280  2.12   0.034 *
## UICC_3CATIVB-C    2.040    7.690    0.399  5.11  3.3e-07 ***
## ALTER_3CAT(50,70] -0.548    0.578    0.242 -2.26   0.024 *
## ALKOHOL1 bis 30    0.562    1.754    0.515  1.09   0.275
## ALKOHOL31 bis 60    0.604    1.829    0.514  1.17   0.240
## ALKOHOL>60        0.868    2.383    0.491  1.77   0.077 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.814    0.551    1.047    3.143
## UICC_3CATIVB-C    7.690    0.130    3.515   16.825
## ALTER_3CAT(50,70] 0.578    1.729    0.360    0.929
## ALKOHOL1 bis 30    1.754    0.570    0.640    4.809
## ALKOHOL31 bis 60    1.829    0.547    0.668    5.009
## ALKOHOL>60        2.383    0.420    0.911    6.235
##
## Concordance= 0.64 (se = 0.036 )
## Rsquare= 0.156 (max possible= 0.986 )
## Likelihood ratio test= 26.8 on 6 df, p=0.000157
## Wald test              = 30.4 on 6 df, p=3.34e-05
## Score (logrank) test = 35.7 on 6 df, p=3.16e-06

cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA      0.1458 1.583 0.208
## UICC_3CATIVB-C    0.0564 0.243 0.622
## ALTER_3CAT(50,70] -0.0582 0.262 0.609
## ALKOHOL1 bis 30   -0.0450 0.155 0.694
## ALKOHOL31 bis 60  -0.0539 0.219 0.640
## ALKOHOL>60        -0.0579 0.259 0.611
## GLOBAL            NA 2.284 0.892
```

#### 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3  0.650      1.916   0.249  2.61   0.0092 **
## TP53ND      -0.254      0.776   0.356 -0.71   0.4760
## TP53D       0.446      1.562   0.263  1.70   0.0895 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3      1.916      0.522      1.175      3.12
## TP53ND           0.776      1.289      0.386      1.56
## TP53D           1.562      0.640      0.933      2.61
##
## Concordance= 0.604 (se = 0.035 )
## Rsquare= 0.081 (max possible= 0.986 )
## Likelihood ratio test= 13.4 on 3 df, p=0.00385
## Wald test = 13.2 on 3 df, p=0.00416
## Score (logrank) test = 13.8 on 3 df, p=0.00315

cox.zph(surv.res)

##              rho chisq      p
## N_2CATN2-N3  0.0862 0.554 0.457
## TP53ND      -0.1820 2.630 0.105
## TP53D       -0.1061 0.807 0.369
## GLOBAL              NA 3.279 0.351
```

#### 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## N_2CATN2-N3      0.699      2.012   0.333  2.10   0.035 *
## TP53ND          -0.465      0.628   0.589 -0.79   0.431
## TP53D           0.686      1.985   0.448  1.53   0.126
```

```
## N_2CATN2-N3:TP53ND 0.358 1.430 0.723 0.49 0.621
## N_2CATN2-N3:TP53D -0.345 0.708 0.552 -0.63 0.532
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3 2.012 0.497 1.049 3.86
## TP53ND 0.628 1.591 0.198 2.00
## TP53D 1.985 0.504 0.825 4.77
## N_2CATN2-N3:TP53ND 1.430 0.699 0.347 5.90
## N_2CATN2-N3:TP53D 0.708 1.412 0.240 2.09
##
## Concordance= 0.604 (se = 0.035 )
## Rsquare= 0.087 (max possible= 0.986 )
## Likelihood ratio test= 14.3 on 5 df, p=0.0137
## Wald test = 13 on 5 df, p=0.0238
## Score (logrank) test = 14 on 5 df, p=0.0157

cox.zph(surv.res)

## rho chisq p
## N_2CATN2-N3 0.22338 3.60389 0.0576
## TP53ND -0.00775 0.00437 0.9473
## TP53D 0.13850 1.38993 0.2384
## N_2CATN2-N3:TP53ND -0.11661 0.97101 0.3244
## N_2CATN2-N3:TP53D -0.25169 4.55020 0.0329
## GLOBAL NA 7.35979 0.1952
```

#### 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= 74
##
## coef exp(coef) se(coef) z Pr(>|z|)
## N_2CATN2-N3 0.6466 1.9090 0.2522 2.56 0.010 *
## TP53ND -0.2546 0.7752 0.3561 -0.71 0.475
## TP53D 0.4443 1.5594 0.2629 1.69 0.091 .
## IS_ATYPICALatypical 0.0292 1.0297 0.2889 0.10 0.919
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
##               exp(coef) exp(-coef) lower .95 upper .95
## N_2CATN2-N3          1.909      0.524      1.165      3.13
## TP53ND                0.775      1.290      0.386      1.56
## TP53D                 1.559      0.641      0.932      2.61
## IS_ATYPICALAtypical   1.030      0.971      0.584      1.81
##
## Concordance= 0.604 (se = 0.035 )
## Rsquare= 0.081 (max possible= 0.986 )
## Likelihood ratio test= 13.4 on 4 df, p=0.00943
## Wald test              = 13.2 on 4 df, p=0.0102
## Score (logrank) test = 13.8 on 4 df, p=0.00785

cox.zph(surv.res)

##               rho  chisq    p
## N_2CATN2-N3      0.0819 0.4976 0.481
## TP53ND           -0.1825 2.6284 0.105
## TP53D            -0.1084 0.8498 0.357
## IS_ATYPICALAtypical 0.0265 0.0525 0.819
## GLOBAL           NA 3.3290 0.504
```

#### 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= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.4566    1.5787  0.2837  1.61   0.107
## UICC_3CATIVB-C    1.8294    6.2302  0.3943  4.64 3.5e-06 ***
## TP53ND           -0.0697    0.9327  0.3609 -0.19   0.847
## TP53D             0.5617    1.7536  0.2639  2.13   0.033 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.579      0.633      0.905      2.75
## UICC_3CATIVB-C    6.230      0.161      2.877     13.49
## TP53ND            0.933      1.072      0.460      1.89
## TP53D             1.754      0.570      1.045      2.94
```

```
##
## Concordance= 0.627 (se = 0.035 )
## Rsquare= 0.14 (max possible= 0.986 )
## Likelihood ratio test= 23.8 on 4 df, p=8.75e-05
## Wald test = 28.6 on 4 df, p=9.63e-06
## Score (logrank) test = 33.6 on 4 df, p=8.89e-07

cox.zph(surv.res)

##
## rho chisq p
## UICC_3CATIVA 0.1427 1.5813 0.209
## UICC_3CATIVB-C 0.0247 0.0451 0.832
## TP53ND -0.1792 2.6318 0.105
## TP53D -0.0997 0.7496 0.387
## GLOBAL NA 4.4775 0.345
```

#### 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= 74
##
##
## coef exp(coef) se(coef) z Pr(>|z|)
## ALTER_3CAT(50,70] -0.403 0.669 0.237 -1.70 0.089 .
## TP53ND -0.216 0.806 0.358 -0.60 0.546
## TP53D 0.579 1.784 0.259 2.23 0.026 *
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70] 0.669 1.496 0.42 1.06
## TP53ND 0.806 1.241 0.40 1.62
## TP53D 1.784 0.561 1.07 2.97
##
## Concordance= 0.581 (se = 0.035 )
## Rsquare= 0.056 (max possible= 0.986 )
## Likelihood ratio test= 9.14 on 3 df, p=0.0275
## Wald test = 9.51 on 3 df, p=0.0232
## Score (logrank) test = 9.79 on 3 df, p=0.0205

cox.zph(surv.res)
```

```
##              rho chisq      p
## ALTER_3CAT(50,70] -0.0888 0.593 0.4413
## TP53ND            -0.1924 2.992 0.0837
## TP53D             -0.0921 0.607 0.4359
## GLOBAL            NA 3.829 0.2805
```

#### 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.4672    1.5954  0.2850  1.64   0.101
## UICC_3CATIVB-C    1.9158    6.7926  0.3971  4.82 1.4e-06 ***
## ALTER_3CAT(50,70] -0.4917    0.6116  0.2390 -2.06   0.040 *
## TP53ND           -0.0243    0.9760  0.3637 -0.07   0.947
## TP53D            0.5910    1.8058  0.2660  2.22   0.026 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.595      0.627    0.913    2.789
## UICC_3CATIVB-C    6.793      0.147    3.119   14.792
## ALTER_3CAT(50,70] 0.612      1.635    0.383    0.977
## TP53ND            0.976      1.025    0.478    1.991
## TP53D             1.806      0.554    1.072    3.042
##
## Concordance= 0.639 (se = 0.036 )
## Rsquare= 0.162 (max possible= 0.986 )
## Likelihood ratio test= 27.9 on 5 df, p=3.74e-05
## Wald test = 32.2 on 5 df, p=5.39e-06
## Score (logrank) test = 37.7 on 5 df, p=4.37e-07

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.1500 1.7682 0.1836
## UICC_3CATIVB-C    0.0335 0.0815 0.7753
## ALTER_3CAT(50,70] -0.0773 0.4470 0.5038
```

```
## TP53ND          -0.1890  2.9630  0.0852
## TP53D           -0.0979  0.7545  0.3850
## GLOBAL          NA  5.5128  0.3565
```

#### 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= 73
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.4537    1.5741  0.2863  1.58    0.113
## UICC_3CATIVB-C     1.8966    6.6635  0.3972  4.77 1.8e-06 ***
## I(PACKYEARS > 30)TRUE 0.2726    1.3134  0.2477  1.10    0.271
## ALTER_3CAT(50,70] -0.5676    0.5669  0.2491 -2.28    0.023 *
## TP53ND           -0.0144    0.9857  0.3625 -0.04    0.968
## TP53D            0.5459    1.7262  0.2700  2.02    0.043 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      1.574      0.635    0.898    2.759
## UICC_3CATIVB-C     6.664      0.150    3.059   14.515
## I(PACKYEARS > 30)TRUE 1.313      0.761    0.808    2.134
## ALTER_3CAT(50,70]  0.567      1.764    0.348    0.924
## TP53ND            0.986      1.015    0.484    2.006
## TP53D             1.726      0.579    1.017    2.930
##
## Concordance= 0.653 (se = 0.036 )
## Rsquare= 0.167 (max possible= 0.985 )
## Likelihood ratio test= 28.7 on 6 df, p=7e-05
## Wald test = 32.8 on 6 df, p=1.14e-05
## Score (logrank) test = 38.3 on 6 df, p=9.72e-07

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      0.1457 1.6623 0.197
## UICC_3CATIVB-C     0.0266 0.0503 0.822
```

```
## I(PACKYEARS > 30)TRUE -0.0171 0.0222 0.882
## ALTER_3CAT(50,70] -0.0764 0.4229 0.515
## TP53ND -0.1761 2.5214 0.112
## TP53D -0.1143 1.0159 0.314
## GLOBAL NA 5.1705 0.522
```

#### 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= 73
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_2CAT3-4      -0.406    0.666   0.397 -1.02   0.307
## N_2CATN2-N3     0.668    1.950   0.287  2.33   0.020
## M              2.511   12.315   0.577  4.35  1.3e-05
## ALTER_3CAT(50,70] -0.456    0.634   0.245 -1.86   0.063
## I(PACKYEARS > 30)TRUE -0.120    0.887   0.403 -0.30   0.766
## TP53ND        -0.113    0.893   0.362 -0.31   0.754
## TP53D          0.465    1.591   0.273  1.70   0.089
## T_2CAT3-4:I(PACKYEARS > 30)TRUE  0.715    2.044   0.510  1.40   0.161
##
## 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          0.666    1.5008    0.306    1.45
## N_2CATN2-N3         1.950    0.5127    1.112    3.42
## M                 12.315    0.0812    3.978   38.12
```



```

## ALTER_3CAT(50,70]                0.634      1.5778      0.392      1.03
## I(PACKYEARS > 30)TRUE              0.887      1.1276      0.402      1.95
## TP53ND                            0.893      1.1199      0.439      1.82
## TP53D                             1.591      0.6284      0.932      2.72
## T_2CAT3-4:I(PACKYEARS > 30)TRUE   2.044      0.4892      0.753      5.55
##
## Concordance= 0.648 (se = 0.036 )
## Rsquare= 0.175 (max possible= 0.985 )
## Likelihood ratio test= 30.3 on 8 df, p=0.000188
## Wald test = 35.7 on 8 df, p=2.02e-05
## Score (logrank) test = 44.1 on 8 df, p=5.5e-07

cox.zph(surv.res)

##                rho chisq      p
## T_2CAT3-4        0.0746 0.495 0.4818
## N_2CATN2-N3      0.0763 0.412 0.5211
## M                -0.0466 0.163 0.6860
## ALTER_3CAT(50,70] -0.1028 0.730 0.3929
## I(PACKYEARS > 30)TRUE 0.0403 0.122 0.7265
## TP53ND           -0.1999 3.290 0.0697
## TP53D            -0.1420 1.557 0.2121
## T_2CAT3-4:I(PACKYEARS > 30)TRUE -0.0659 0.330 0.5654
## GLOBAL              NA 5.502 0.7028

best.model <- stepAIC(surv.res)

## Start:  AIC=650.1
## surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + ALTER_3CAT + I(PACKYEARS >
##    30) + T_2CAT:I(PACKYEARS > 30) + TP53
##
##                Df AIC
## - TP53          2 650
## - T_2CAT:I(PACKYEARS > 30) 1 650
## <none>          650
## - ALTER_3CAT    1 652
## - N_2CAT        1 654
## - M             1 660
##
## Step:  AIC=649.6
## surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M + ALTER_3CAT + I(PACKYEARS >
##    30) + T_2CAT:I(PACKYEARS > 30)
##
##                Df AIC
## <none>          650
## - T_2CAT:I(PACKYEARS > 30) 1 650
## - ALTER_3CAT    1 651
## - N_2CAT        1 654
## - M             1 659

```

```
best.model

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_2CAT + N_2CAT + M +
##       ALTER_3CAT + I(PACKYEARS > 30) + T_2CAT:I(PACKYEARS > 30),
##       data = ds[cur.subset, ])
##
##
##               coef exp(coef) se(coef)      z      p
## T_2CAT3-4        -0.3871    0.679   0.398 -0.972 3.3e-01
## N_2CATN2-N3        0.7209    2.056   0.284  2.535 1.1e-02
## M                2.4691   11.812   0.571  4.324 1.5e-05
## ALTER_3CAT(50,70] -0.4865    0.615   0.245 -1.988 4.7e-02
## I(PACKYEARS > 30)TRUE -0.0973    0.907   0.401 -0.243 8.1e-01
## T_2CAT3-4:I(PACKYEARS > 30)TRUE 0.7631    2.145   0.510  1.497 1.3e-01
##
## Likelihood ratio test=26.8 on 6 df, p=0.000156 n= 157, number of events= 73
## (1 observation deleted due to missingness)
```

#### 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= 74
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## CONSENSUS_CLUSTERBasal -0.3750    0.6873   0.3297 -1.14    0.26
## CONSENSUS_CLUSTERClassical -0.3460    0.7075   0.4344 -0.80    0.43
## CONSENSUS_CLUSTERMesenchymal -0.0132    0.9869   0.3149 -0.04    0.97
##
##               exp(coef) exp(-coef) lower .95 upper .95
## CONSENSUS_CLUSTERBasal    0.687    1.45    0.360    1.31
## CONSENSUS_CLUSTERClassical 0.708    1.41    0.302    1.66
## CONSENSUS_CLUSTERMesenchymal 0.987    1.01    0.532    1.83
##
## Concordance= 0.547 (se = 0.034 )
## Rsquare= 0.015 (max possible= 0.986 )
## Likelihood ratio test= 2.34 on 3 df, p=0.505
## Wald test = 2.3 on 3 df, p=0.513
## Score (logrank) test = 2.32 on 3 df, p=0.508
```

```
# 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    2.3      0.51
## Residuals        155
```

#### 4.2.16 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= 158, number of events= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## CONSENSUS_CLUSTERBasal -0.2988    0.7417  0.3333 -0.90    0.37
## CONSENSUS_CLUSTERClassical -0.2834    0.7532  0.4366 -0.65    0.52
## CONSENSUS_CLUSTERMesenchymal 0.0464    1.0475  0.3180  0.15    0.88
## TP53ND -0.2515    0.7776  0.3554 -0.71    0.48
## TP53D 0.5372    1.7112  0.2614  2.06    0.04 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## CONSENSUS_CLUSTERBasal 0.742    1.348    0.386    1.43
## CONSENSUS_CLUSTERClassical 0.753    1.328    0.320    1.77
## CONSENSUS_CLUSTERMesenchymal 1.047    0.955    0.562    1.95
## TP53ND 0.778    1.286    0.388    1.56
## TP53D 1.711    0.584    1.025    2.86
##
## Concordance= 0.597 (se = 0.036 )
## Rsquare= 0.051 (max possible= 0.986 )
## Likelihood ratio test= 8.22 on 5 df, p=0.145
## Wald test = 8.52 on 5 df, p=0.13
## Score (logrank) test = 8.77 on 5 df, p=0.119

# 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  1.88      0.597
## TP53                2  6.15      0.046 *
## 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= 74
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.420      1.522   0.285  1.47   0.141
## UICC_3CATIVB-C     1.804      6.071   0.402  4.48 7.3e-06 ***
## IS_ATYPICALAtypical -0.019     0.981   0.429 -0.04   0.965
## TP53ND            -0.292     0.747   0.433 -0.67   0.500
## TP53D              0.606     1.832   0.294  2.06   0.039 *
## IS_ATYPICALAtypical:TP53ND 0.767     2.154   0.770  1.00   0.319
## IS_ATYPICALAtypical:TP53D -0.193     0.825   0.680 -0.28   0.777
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA          1.522      0.657   0.871   2.66
## UICC_3CATIVB-C         6.071      0.165   2.760  13.35
## IS_ATYPICALAtypical    0.981      1.019   0.423   2.27
## TP53ND                 0.747      1.339   0.320   1.75
## TP53D                  1.832      0.546   1.030   3.26
## IS_ATYPICALAtypical:TP53ND 2.154      0.464   0.476   9.75
## IS_ATYPICALAtypical:TP53D 0.825      1.212   0.217   3.13
##
## Concordance= 0.639 (se = 0.035 )
## Rsquare= 0.148 (max possible= 0.986 )
## Likelihood ratio test= 25.2 on 7 df,  p=0.00069
## Wald test               = 29.8 on 7 df,  p=0.000104
## Score (logrank) test = 35 on 7 df,  p=1.09e-05
```

```
# 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= 18
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## I(PACKYEARS > 30)TRUE 1.965      7.133    0.595 3.3 0.00096 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## I(PACKYEARS > 30)TRUE      7.13      0.14      2.22      22.9
##
## Concordance= 0.701 (se = 0.066 )
## Rsquare= 0.235 (max possible= 0.894 )
## Likelihood ratio test= 12.8 on 1 df,  p=0.000341
## Wald test              = 10.9 on 1 df,  p=0.000956
## Score (logrank) test = 14.4 on 1 df,  p=0.000145

cox.zph(surv.res)

##              rho chisq      p
## I(PACKYEARS > 30)TRUE 0.136 0.356 0.551
```

### 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= 18
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4 0.937      2.553    0.515 1.82    0.068 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4      2.55      0.392    0.931      7
##
## Concordance= 0.637 (se = 0.07 )
## Rsquare= 0.069 (max possible= 0.891 )
## Likelihood ratio test= 3.52 on 1 df,  p=0.0607
## Wald test = 3.32 on 1 df,  p=0.0685
## Score (logrank) test = 3.55 on 1 df,  p=0.0595

cox.zph(surv.res)

##              rho chisq      p
## T_CAT3-4 -0.0896 0.127 0.722

```

### 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= 15
##      (4 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+ -0.395      0.674    0.543 -0.73    0.47
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+      0.674      1.48    0.232      1.95
##
## Concordance= 0.561 (se = 0.07 )

```

```
## Rsquare= 0.011 (max possible= 0.884 )
## Likelihood ratio test= 0.52 on 1 df, p=0.472
## Wald test = 0.53 on 1 df, p=0.467
## Score (logrank) test = 0.54 on 1 df, p=0.464

cox.zph(surv.res)

## rho chisq p
## HPV16_RNARNA+ 0.116 0.194 0.66
```

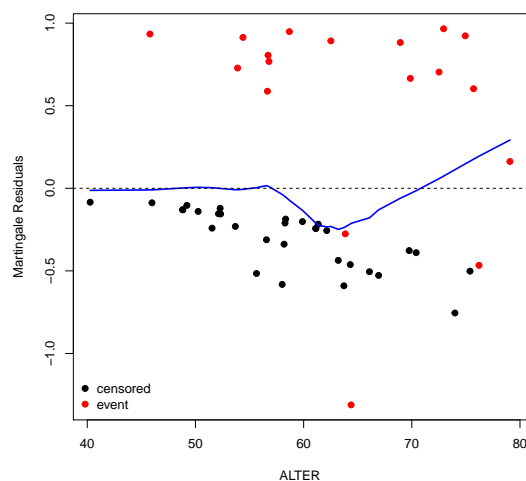
#### 4.3.4 AGE

```
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= 18
##
## coef exp(coef) se(coef) z Pr(>|z|)
## ALTER 0.0508 1.0521 0.0290 1.75 0.08 .
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## exp(coef) exp(-coef) lower .95 upper .95
## ALTER 1.05 0.95 0.994 1.11
##
## Concordance= 0.632 (se = 0.081 )
## Rsquare= 0.06 (max possible= 0.891 )
## Likelihood ratio test= 3.06 on 1 df, p=0.0804
## Wald test = 3.07 on 1 df, p=0.0797
## Score (logrank) test = 3.15 on 1 df, p=0.076

cox.zph(surv.res)

## rho chisq p
## ALTER -0.0361 0.0292 0.864
```



### 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= 18
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## OROPHARYNX_VS_OTHERoropharynx 0.658      1.932    0.649 1.02     0.31
##
##              exp(coef) exp(-coef) lower .95 upper .95
## OROPHARYNX_VS_OTHERoropharynx      1.93      0.518    0.542     6.89
##
## Concordance= 0.584  (se = 0.067 )
## Rsquare= 0.023  (max possible= 0.891 )
## Likelihood ratio test= 1.16  on 1 df,   p=0.281
## Wald test               = 1.03  on 1 df,   p=0.31
## Score (logrank) test = 1.07  on 1 df,   p=0.302
```

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

```
##              rho chisq      p
## OROPHARYNX_VS_OTHERoropharynx -0.139 0.335 0.563
```

### 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= 15
##      (4 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+    -0.820     0.440   0.596 -1.38   0.17
## OROPHARYNX_VS_OTHERoropharynx  1.112     3.040   0.704  1.58   0.11
##
##              exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+         0.44      2.272    0.137    1.41
## OROPHARYNX_VS_OTHERoropharynx  3.04     0.329    0.765   12.08
##
## Concordance= 0.655  (se = 0.079 )
## Rsquare= 0.072   (max possible= 0.884 )
## Likelihood ratio test= 3.36  on 2 df,   p=0.187
## Wald test            = 3.22  on 2 df,   p=0.2
## Score (logrank) test = 3.25  on 2 df,   p=0.197

cox.zph(surv.res)

##              rho chisq      p
## HPV16_RNARNA+    0.117 0.218 0.640
## OROPHARYNX_VS_OTHERoropharynx -0.227 0.757 0.384
## GLOBAL           NA 0.780 0.677

```

#### 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= 18
##
##              coef exp(coef) se(coef)      z Pr(>|z|)

```

```
## T_2CAT3-4          1.198      3.312      0.528 2.27      0.023 *
## OROPHARYNX_VS_OTHERoropharynx 1.070      2.917      0.665 1.61      0.107
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                  exp(coef) exp(-coef) lower .95 upper .95
## T_2CAT3-4          3.31      0.302      1.177      9.32
## OROPHARYNX_VS_OTHERoropharynx 2.92      0.343      0.792     10.73
##
## Concordance= 0.695 (se = 0.077 )
## Rsquare= 0.125 (max possible= 0.891 )
## Likelihood ratio test= 6.55 on 2 df,  p=0.0377
## Wald test          = 6.4 on 2 df,  p=0.0407
## Score (logrank) test = 6.75 on 2 df,  p=0.0343

cox.zph(surv.res)

##                  rho chisq      p
## T_2CAT3-4          -0.124 0.225 0.635
## OROPHARYNX_VS_OTHERoropharynx -0.138 0.296 0.587
## GLOBAL              NA 0.425 0.808
```

#### 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= 15
## (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+ -0.434      0.648   0.599 -0.72   0.469
## OROPHARYNX_VS_OTHERoropharynx 0.899      2.457   0.688  1.31   0.191
## I(PACKYEARS > 30)TRUE      1.678      5.353   0.611  2.75   0.006 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                  exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+      0.648      1.543      0.200      2.10
## OROPHARYNX_VS_OTHERoropharynx 2.457      0.407      0.638      9.47
```

```
## I(PACKYEARS > 30)TRUE          5.353      0.187      1.617      17.73
##
## Concordance= 0.777 (se = 0.082 )
## Rsquare= 0.234 (max possible= 0.888 )
## Likelihood ratio test= 11.7 on 3 df, p=0.00848
## Wald test = 10.4 on 3 df, p=0.0155
## Score (logrank) test = 12.7 on 3 df, p=0.00538

cox.zph(surv.res)

##
## rho chisq p
## HPV16_RNARNA+ 0.118 0.283 0.594
## OROPHARYNX_VS_OTHERoropharynx -0.262 1.025 0.311
## I(PACKYEARS > 30)TRUE 0.187 0.679 0.410
## GLOBAL NA 1.633 0.652
```

#### 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= 15
## (5 observations deleted due to missingness)
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## HPV16_RNARNA+ -0.8364    0.4333  0.6467 -1.29  0.1959
## OROPHARYNX_VS_OTHERoropharynx 0.4663    1.5941  0.7570  0.62  0.5379
## I(PACKYEARS > 30)TRUE 2.0955    8.1293  0.6810  3.08  0.0021 **
## ALTER 0.0905    1.0948  0.0379  2.39  0.0169 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

##
##          exp(coef) exp(-coef) lower .95 upper .95
## HPV16_RNARNA+ 0.433    2.308    0.122    1.54
## OROPHARYNX_VS_OTHERoropharynx 1.594    0.627    0.362    7.03
## I(PACKYEARS > 30)TRUE 8.129    0.123    2.140   30.88
## ALTER 1.095    0.913    1.016    1.18
##
## Concordance= 0.804 (se = 0.084 )
## Rsquare= 0.337 (max possible= 0.888 )
```

```
## Likelihood ratio test= 18.1 on 4 df, p=0.00119
## Wald test = 14.2 on 4 df, p=0.00661
## Score (logrank) test = 18.4 on 4 df, p=0.00105

cox.zph(surv.res)

##                rho chisq    p
## HPV16_RNARNA+    0.102 0.207 0.649
## OROPHARYNX_VS_OTHERoropharynx -0.257 1.399 0.237
## I(PACKYEARS > 30)TRUE    0.272 1.867 0.172
## ALTER            0.108 0.280 0.597
## GLOBAL            NA 2.625 0.622
```

#### 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.sub
  ])
summary(surv.res)

## Call:
## coxph(formula = surv.obj[cur.subset] ~ T_CAT + I(PACKYEARS >
##      30), data = ds[cur.subset, ])
##
## n= 48, number of events= 18
## (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4        1.083      2.953   0.524 2.07  0.03889 *
## I(PACKYEARS > 30)TRUE 2.095      8.122   0.607 3.45  0.00056 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4            2.95      0.339      1.06      8.25
## I(PACKYEARS > 30)TRUE  8.12      0.123      2.47     26.71
##
## Concordance= 0.761 (se = 0.077 )
## Rsquare= 0.304 (max possible= 0.894 )
## Likelihood ratio test= 17.4 on 2 df, p=0.000168
## Wald test = 14.8 on 2 df, p=0.000622
## Score (logrank) test = 18.7 on 2 df, p=8.84e-05

cox.zph(surv.res)

##                rho chisq    p
## T_CAT3-4        -0.0321 0.0155 0.901
## I(PACKYEARS > 30)TRUE  0.1554 0.5016 0.479
## GLOBAL            NA 0.5432 0.762
```

#### 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= 18
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4          1.191      3.289   0.530 2.24  0.0248 *
## ALTER_60(60,Inf]    0.799      2.222   0.548 1.46  0.1450
## I(PACKYEARS > 30)TRUE 2.411     11.148   0.666 3.62  0.0003 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4              3.29      0.3041      1.163      9.3
## ALTER_60(60,Inf]      2.22      0.4500      0.759      6.5
## I(PACKYEARS > 30)TRUE  11.15      0.0897      3.020     41.2
##
## Concordance= 0.786 (se = 0.08 )
## Rsquare= 0.334 (max possible= 0.894 )
## Likelihood ratio test= 19.5 on 3 df,  p=0.000211
## Wald test              = 15.3 on 3 df,  p=0.00159
## Score (logrank) test = 19.6 on 3 df,  p=0.000208
```

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

```
##              rho chisq      p
## T_CAT3-4       -0.0626 0.0681 0.794
## ALTER_60(60,Inf] -0.0924 0.1431 0.705
## I(PACKYEARS > 30)TRUE 0.1332 0.4126 0.521
## GLOBAL              NA 0.9375 0.816
```

#### 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= 15
##    (5 observations deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## T_CAT3-4        1.716     5.562   0.718 2.39   0.0168 *
## ALTER_60(60,Inf] 1.223     3.396   0.603 2.03   0.0428 *
## I(PACKYEARS > 30)TRUE 2.252     9.503   0.672 3.35   0.0008 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## T_CAT3-4            5.56      0.180      1.36      22.7
## ALTER_60(60,Inf]    3.40      0.294      1.04      11.1
## I(PACKYEARS > 30)TRUE 9.50      0.105      2.55      35.4
##
## Concordance= 0.824 (se = 0.118 )
## Rsquare= 0.339 (max possible= 0.827 )
## Likelihood ratio test= 18.2 on 3 df,  p=0.000396
## Wald test              = 14.3 on 3 df,  p=0.00251
## Score (logrank) test = 17.4 on 3 df,  p=0.000596

cox.zph(surv.res)

##              rho chisq      p
## T_CAT3-4        0.1330 0.349 0.555
## ALTER_60(60,Inf] 0.0984 0.126 0.723
## I(PACKYEARS > 30)TRUE 0.2758 1.387 0.239
## GLOBAL          NA 1.497 0.683
```

#### 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= 18
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## TP53ND -0.424     0.654   1.044 -0.41   0.68
## TP53D   0.199     1.221   0.663 0.30   0.76
```

```
##
##          exp(coef) exp(-coef) lower .95 upper .95
## TP53ND      0.654      1.528    0.0846    5.06
## TP53D       1.221      0.819    0.3330    4.47
##
## Concordance= 0.576 (se = 0.057 )
## Rsquare= 0.006 (max possible= 0.891 )
## Likelihood ratio test= 0.31 on 2 df, p=0.858
## Wald test = 0.29 on 2 df, p=0.867
## Score (logrank) test = 0.29 on 2 df, p=0.865

cox.zph(surv.res)

##          rho chisq      p
## TP53ND  0.308  1.46 0.228
## TP53D  -0.216  1.01 0.315
## GLOBAL      NA  2.76 0.251
```

#### 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= 18
##
##          coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA  0.924      2.518    0.772  1.20    0.23
## UICC_3CATIVB-C 1.221      3.391    0.880  1.39    0.17
## TP53ND      -0.507      0.602    1.045 -0.49    0.63
## TP53D        0.263      1.301    0.660  0.40    0.69
##
##          exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      2.518      0.397    0.5545    11.44
## UICC_3CATIVB-C    3.391      0.295    0.6039    19.05
## TP53ND            0.602      1.661    0.0777     4.67
## TP53D            1.301      0.768    0.3571     4.74
##
## Concordance= 0.688 (se = 0.075 )
## Rsquare= 0.054 (max possible= 0.891 )
## Likelihood ratio test= 2.7 on 4 df, p=0.61
## Wald test = 2.31 on 4 df, p=0.679
## Score (logrank) test = 2.47 on 4 df, p=0.65
```

```
cox.zph(surv.res)

##               rho chisq      p
## UICC_3CATIVA   -0.343   2.03 0.154
## UICC_3CATIVB-C -0.216   0.72 0.396
## TP53ND         0.319   1.57 0.210
## TP53D         -0.221   1.02 0.312
## GLOBAL         NA     4.81 0.307
```

#### 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= 18
##
##               coef exp(coef) se(coef)      z Pr(>|z|)
## ALTER_3CAT(50,70] -1.050      0.350   0.540 -1.94   0.052 .
## TP53ND            -0.842      0.431   1.096 -0.77   0.443
## TP53D             0.184      1.201   0.661  0.28   0.781
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## ALTER_3CAT(50,70]      0.350      2.857   0.1214   1.01
## TP53ND                 0.431      2.320   0.0503   3.70
## TP53D                 1.201      0.832   0.3286   4.39
##
## Concordance= 0.626 (se = 0.072 )
## Rsquare= 0.077 (max possible= 0.891 )
## Likelihood ratio test= 3.92 on 3 df,  p=0.271
## Wald test               = 3.98 on 3 df,  p=0.263
## Score (logrank) test = 4.27 on 3 df,  p=0.234

cox.zph(surv.res)

##               rho chisq      p
## ALTER_3CAT(50,70] -0.0804 0.115 0.735
## TP53ND            0.2386 0.652 0.419
## TP53D            -0.1965 0.815 0.367
## GLOBAL            NA     1.976 0.577
```



#### 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= 18
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      0.871      2.389   0.777   1.12   0.263
## UICC_3CATIVB-C     1.248      3.483   0.889   1.40   0.160
## ALTER_3CAT(50,70] -1.036      0.355   0.539  -1.92   0.055 .
## TP53ND            -0.899      0.407   1.096  -0.82   0.412
## TP53D              0.326      1.385   0.665   0.49   0.624
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      2.389      0.419   0.5206    10.97
## UICC_3CATIVB-C     3.483      0.287   0.6104    19.87
## ALTER_3CAT(50,70]  0.355      2.817   0.1235     1.02
## TP53ND            0.407      2.457   0.0475     3.49
## TP53D             1.385      0.722   0.3763     5.10
##
## Concordance= 0.681 (se = 0.079 )
## Rsquare= 0.119 (max possible= 0.891 )
## Likelihood ratio test= 6.22 on 5 df, p=0.285
## Wald test = 5.85 on 5 df, p=0.321
## Score (logrank) test = 6.28 on 5 df, p=0.28

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA    -0.3682  2.374  0.123
## UICC_3CATIVB-C  -0.2370  0.848  0.357
## ALTER_3CAT(50,70] -0.0757  0.105  0.746
## TP53ND          0.2869  0.929  0.335
## TP53D           -0.2061  0.869  0.351
## GLOBAL          NA  4.399  0.494

```

#### 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= 18
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## UICC_3CATIVA      2.395   10.963    0.958  2.50   0.0124 *
## UICC_3CATIVB-C      3.061   21.351    1.104  2.77   0.0055 **
## I(PACKYEARS > 30)TRUE 3.424   30.693    0.813  4.21  2.5e-05 ***
## ALTER_3CAT(50,70]  -1.579    0.206    0.603 -2.62   0.0089 **
## TP53ND             -1.316    0.268    1.068 -1.23   0.2180
## TP53D              1.200    3.321    0.791  1.52   0.1293
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## UICC_3CATIVA      10.963    0.0912    1.6775    71.642
## UICC_3CATIVB-C     21.351    0.0468    2.4547   185.716
## I(PACKYEARS > 30)TRUE 30.693    0.0326    6.2415   150.937
## ALTER_3CAT(50,70]    0.206    4.8516    0.0632    0.672
## TP53ND             0.268    3.7289    0.0330    2.177
## TP53D              3.321    0.3011    0.7041   15.662
##
## Concordance= 0.898 (se = 0.08 )
## Rsquare= 0.485 (max possible= 0.894 )
## Likelihood ratio test= 31.9 on 6 df,  p=1.74e-05
## Wald test              = 22.1 on 6 df,  p=0.00116
## Score (logrank) test = 32.2 on 6 df,  p=1.47e-05

cox.zph(surv.res)

##              rho chisq      p
## UICC_3CATIVA      -0.2653 0.829 0.363
## UICC_3CATIVB-C     -0.0913 0.109 0.741
## I(PACKYEARS > 30)TRUE 0.1645 0.649 0.421
## ALTER_3CAT(50,70]  -0.2169 0.865 0.352
## TP53ND             0.2296 0.811 0.368
## TP53D             -0.3246 2.398 0.121
## GLOBAL              NA 8.271 0.219

```

#### 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= 18
##      (1 observation deleted due to missingness)
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## I(PACKYEARS > 30)TRUE  2.015     7.498   0.593  3.40  0.00068 ***
## TP53ND                -0.882     0.414   1.048 -0.84  0.39973
## TP53D                 0.259     1.295   0.675  0.38  0.70177
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## I(PACKYEARS > 30)TRUE    7.498      0.133   2.3455    23.97
## TP53ND                   0.414      2.417   0.0531     3.23
## TP53D                    1.295      0.772   0.3447     4.87
##
## Concordance= 0.761 (se = 0.072 )
## Rsquare= 0.253 (max possible= 0.894 )
## Likelihood ratio test= 14 on 3 df,  p=0.00294
## Wald test               = 12.2 on 3 df,  p=0.00682
## Score (logrank) test = 16 on 3 df,  p=0.00115

cox.zph(surv.res)

##              rho chisq      p
## I(PACKYEARS > 30)TRUE  0.102 0.201 0.654
## TP53ND                0.332 1.931 0.165
## TP53D                 -0.265 1.597 0.206
## GLOBAL                NA 4.166 0.244

```