

Sex-based differences in survival after liver transplantation for colorectal cancer liver metastases: A multivariable analysis

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Summary

Supplementary File 1

This supplementary file, referred to as 'Supplementary File 1,' provides a detailed examination of the primary assumptions underlying the models used, including those related to the comparison between 'male' and 'female' groups (discussed on pages 3-8). Following revisions made after peer review (e.g., replacing the variable "pN+" with "pN2" in the Cox-related models and Fine & Gray models), this document now serves merely as a sensitivity analysis. In particular, the reader can assess how the inclusion and exclusion of variables have impacted the results (e.g., by comparing the previous models - shown here - with the new ones). A brief introduction to S-values as tools to enhance the understanding of statistical compatibility is provided on page 4.

Supplementary File 2

Supplementary File 2 (".xlsx" format) fully reports all tables related to the sensitivity analysis summarized in Supplementary File 2. These provide point estimates, 95% confidence/compatibility intervals, P-values, and S-values. Information regarding the number of events, events per parameter, concordance, likelihood ratio test, Wald test, score (log-rank) test, and variance inflation factor (VIF; maximum observed VIF <3) is available in the various dedicated sheets. In this regard, given the main etiological purpose of the research, we emphasize that this sensitivity analysis provides more useful and interpretable information on the validity of the background assumptions than methods such as Schoenfeld residuals.

Supplementary File 3

Supplementary File 3 fully reports all datasets and all R codes used to analyze the data. Moreover, it briefly summarizes the results of the sensitivity analysis concerning models with penalizations and restrictions on the included variables according to selective and hierarchical criteria. The models identified as the most informative are presented in Tables 2-4 of the main manuscript. The comparison between models composed of categorical variables only and models with mixed variables is also presented here. Finally, Kaplan-Meier curves are reported for all variables.

Table S1. Main inclusion and exclusion criteria for liver transplantation for non-resectable colorectal liver metastasis applied in the collaborating Centres of the study

Table S1. Main inclusion and exclusion criteria for LT for non-resectable colorectal liver metastasis applied in the collaborating Centres of the study		
Transplant protocol	Inclusion criteria	Exclusion criteria
SECA-I (NCT00294827) ¹ Oslo, NO	<ul style="list-style-type: none"> Radical excision of the primary tumor. ECOG PS ≤ 1. Minimum 6 weeks of chemotherapy. No extrahepatic disease. 	<ul style="list-style-type: none"> Weight loss > 10%. Standard contraindications for LT. Other malignancies.
RAPID (NCT02215889) ¹ Oslo, NO	<ul style="list-style-type: none"> Histologically verified CRC. No signs of local recurrence. ECOG PS ≤ 1. Minimum 8 weeks of chemotherapy. No extrahepatic disease (except patients may have 1-3 resectable lung lesions all <15mm). 	<ul style="list-style-type: none"> Weight loss > 10% the last 6 months. BMI > 30. Previous diagnosed bone or CNS metastatic disease. Previous diagnosed cancer mammae or malignant melanoma. Palliative resection of primary CRC tumor.
SECA-II (NCT01479608) ¹ Oslo, NO	<ul style="list-style-type: none"> Histologically verified CRC. Adequate resection margins including circumferential resection margins (CRM) of at least ≥2mm for rectal cancer. No signs of local recurrence. ECOG PS ≤ 1. At least 3 cycles of chemotherapy (6 weeks of treatment), with no increase in size of the lesions according to RECIST-criteria. Before start of chemotherapy, no lesion should be larger than 10 cm, if more than 30 lesions all should be less than 5cm and the patients should have at least 30% response by RECIST-criteria. At least 10% response (RECIST-criteria) on chemotherapy; patients must be accepted for transplantation before progressive disease on ongoing chemotherapy. Patients with less than 10% response on chemotherapy may be included if they obtain at least 20% response after TACE (DEB-IRI) or by 90Y-spheres. At least 1-year time span from CRC diagnosis and date of being listed. No extrahepatic disease. 	<ul style="list-style-type: none"> Weight loss >10% the last 6 months. BMI > 30. Other malignancies. Prior extra hepatic metastatic disease or local relapse. Patients who have not received standard pre-operative, per-operative or post-operative treatment for the primary CRC. Palliative resection of primary CRC tumor. Know hypersensitivity to rapamycin. Women who are pregnant or breast feeding Previous randomization in this trial.
SECA-II arm D: use of extended criteria donors. (NCT01479608) ¹ Oslo, NO	<ul style="list-style-type: none"> Histologically verified CRC. Adequate resection margins including CRM of at least ≥2mm for patients with rectal cancer. No signs of local recurrence. ECOG PS ≤ 1. The patient may be included without further chemotherapy treatment. If treated by chemotherapy, the patient should have response or stable disease according to RECIST 1.1. If previous local relapse or extrahepatic lymph node metastases, these lesions should have been treated curatively more than 1 year before inclusion in the study. No extrahepatic disease at time of liver transplantation, except patients may have resectable pulmonary lesions (<15mm) at time of inclusion in the study. 	<ul style="list-style-type: none"> Weight loss >10% the last 6 months. BMI > 30. Other malignancy not treated curatively. Known hypersensitivity to rapamycin. Largest liver metastasis >10cm. Palliative resection of primary colorectal cancer. Pregnant or breastfeeding women.
RAPID-Padova (NCT04865471) ¹ Padua, IT	<ul style="list-style-type: none"> Age < 70 years. Histologically verified CRC. BRAF wild-type CRC or liver metastases. High standard oncological surgical resection of the primary tumor. ECOG PS ≤ 1. At least one line (3 months) of chemotherapy. At least 8 weeks of tumor control: SD or PR according to RECIST 1.1 criteria. CEA stable or in decrease. At least 6 months' time span from CRC resection and date of being listed on the transplantation list. No signs of extra hepatic disease, except patients may have <3 lung lesions all <15mm resected or treated by radiotherapy or metastatic hilar nodes treated by resection and without recurrence at 3 months from resection or radiotherapy. 	<ul style="list-style-type: none"> Weight loss >10% the last 6 months. BMI > 30. General contraindication to LT. Other malignancies in the previous 5 years. Pregnancy or breast feeding.
LITORALE2020 (NCT05185245) ¹ Bologna, IT	<ul style="list-style-type: none"> Age < 73 years. Primary tumor resected according to standard oncological practice, pT4a, R0 resection. No signs of local recurrence. ECOG PS score ≤ 1. 	<ul style="list-style-type: none"> Presence of other malignancies. Local recurrence of primary tumor. Extra-hepatic metastatic disease. Patients who did not receive any neoadjuvant or adjuvant therapy.

	<ul style="list-style-type: none"> At least 1 line of chemotherapy for at least 3 months with PR or SD according to modified RECIST CEA < 80 µg/L or reduction of ≥ 50% of highest CEA level observed. No extrahepatic disease. No other contraindications to liver transplantation. 	<ul style="list-style-type: none"> Palliative resection of primary tumor.
COLT (NCT03803436)¹ Milan, IT	<ul style="list-style-type: none"> Histologically confirmed non-mucinous colon adenocarcinoma Primary tumor as pT1-3, pN0 or pN1 (metastases in < 4 regional lymph nodes), confirmed R0 resection. RAS and BRAF wild-type & MSS molecular status as per local testing. ECOG PS score = 0. Objective response according to RECIST 1.1 to first-line treatment, with sustained response for at least 4 months, OR disease control (CR+PR+SD) during second-line treatment for at least 4 months. A maximum of two prior chemotherapy treatment lines. CEA<50 ng/ml. No Extrahepatic Disease. 	<ul style="list-style-type: none"> Hereditary CRC syndromes including FAP and Lynch syndrome. Prior extra hepatic metastatic disease or primary tumor local relapse. Extra-peritoneal cancers (rectum). Other malignancies in the previous 5 years. Active intra-venous or alcohol abusers. HIV infection.
Université Catholique de Louvain (UCL) Louvain, BE	<ul style="list-style-type: none"> Age ≤70 years. Histologically confirmed BRAF wild-type colorectal cancer. Primary tumor resected according to standard oncological practice, p≤T4a, R0 resection. ECOG PS score ≤ 1. ≥ 3 months of hepatic tumour control under the last line of chemotherapy according to RECIST criteria. No Extrahepatic Disease. 	<ul style="list-style-type: none"> General contraindication to LT Other malignancies either concomitant or within 5 years before LT No standard treatment for the primary CRC according to recommended guidelines Prior extra hepatic metastatic disease or local relapse Pregnancy at the time of inclusion
University of Rochester^{2,3} (NCT05248581)¹ Rochester (NY), US	<ul style="list-style-type: none"> Age ≤65 years. Histologically verified CRC. Adequate resection margins including CRM of at least ≥1mm for patients with rectal cancer. Absence of synergistic tumor mutations (KRAS & TP53). ECOG PS score ≤ 1. Patients should have had least one line of fluorouracil-based, oxaliplatin-based, or irinotecan-based chemotherapy. Radiological response to chemotherapy using the RECIST criteria (with or without Chun criteria) a complete response, a partial response of at least 30%, or stable disease with a response using Chun criteria. Response to Chemotherapy ≥12 months. CEA <80ng/dL. Oslo Score ≤ 2. No Extrahepatic Disease. 	<ul style="list-style-type: none"> Primary tumour histology of undifferentiated adenocarcinoma or signet ring cell carcinoma. Standard contraindications for LT. Other malignancies.
Cleveland Clinic^{2,3} Cleveland (OH), US	<ul style="list-style-type: none"> Age ≤65 years. Histologically verified CRC. Adequate resection margins including CRM of at least ≥1mm for patients with rectal cancer Absence of tumor mutation (BRAF). ECOG PS score ≤ 1. Patients should have had least one line of fluorouracil-based, oxaliplatin-based, or irinotecan-based chemotherapy. Radiological response to chemotherapy using the RECIST criteria (with or without Chun criteria) a complete response, a partial response of at least 30%, or stable disease with a response using Chun criteria. Response to Chemotherapy 6-12months. CEA <100ng/dL. At least 1-year time span from CRC resection and date of being listed. No Extrahepatic Disease. 	<ul style="list-style-type: none"> Primary tumour histology of undifferentiated adenocarcinoma or signet ring cell carcinoma. Standard contraindications for LT. Other malignancies.
LT, liver transplantation; ECOG PS, Eastern Cooperative Group Performance Status; BMI, body mass index; CRC, colorectal cancer; CNS, central nervous system; CRM, circumferential resection margins; SD, stable disease; PR, partial response; CEA, carcinoembryonic antigen.		
¹ https://clinicaltrials.gov/		
² Bonney GK, Chew CA, Lodge P, et al. Liver transplantation for non-resectable colorectal liver metastases: the International Hepato-Pancreato-Biliary Association consensus guidelines. Lancet Gastroenterol Hepatol. 2021 Nov;6(11):933-946. Erratum in: Lancet Gastroenterol Hepatol. 2021 Nov;6(11):e7.		
³ Hernandez-Alejandro R, Ruffolo LI, Sasaki K, et al. Recipient and Donor Outcomes After Living-Donor Liver Transplant for Unresectable Colorectal Liver Metastases. JAMA Surg. 2022 Jun 1;157(6):524-530. Erratum in: JAMA Surg. 2022 Nov 1;157(11):1067		

SUPPLEMENTARY FILE 1

INCOMPATIBILITY (P-VALUES) RANGE BASED ON S-VALUES

As widely described in the literature, p-values exhibit counterintuitive behaviors: for instance, the information gap between $p=0.05$ and $p=0.10$ is much different from that between $p=0.90$ and $p=0.95$, despite $\Delta p=0.05$ in both cases.¹⁻⁴ This can be easily observed when considering that $0.10/0.05=2$ while $0.95/0.90=1.1$. To address this issue, it is possible to transform the p-value into the s-value, or surprisal: specifically, by adopting a statistical test whose underlying assumptions are true, the s-value represents the number of consecutive heads – when tossing a fair coin – we would need to achieve to match the statistical surprise (incompatibility) of our experimental result compared to the prediction of the target hypothesis. For example, in such a scenario, $s=4$ indicates that the experimental result is as surprising as obtaining 4 consecutive heads compared to the prediction of the target hypothesis (in accordance with the chosen statistical test whose underlying assumptions must be true). In this regard, it is worth emphasizing that situations like $s=3.3$ cannot be read as "3.3 consecutive heads" but as "little more than surprising than 3 consecutive heads".⁴ Based on this, we have established the following incompatibility ranges as a general, non-absolute guideline:

$0.20 < p \leq 1$ is minimally incompatible since $s < 2$ (approximately)

$0.10 < p \leq 0.20$ is weakly incompatible since $2 < s < 3$ (approximately)

$0.05 < p \leq 0.10$ is marginally incompatible since $3 < s < 4$ (approximately)

$0.01 < p \leq 0.05$ is moderately incompatible since $4 < s < 7$ (approximately)

$0.001 < p \leq 0.01$ is highly incompatible since $7 < s < 10$ (approximately)

$p \leq .001$ is markedly incompatible since $s > 10$ (approximately)

This scale was also designed to maintain a certain cognitive consonance with the standard thresholds. However, the first objective is to stress that the p-value is a continuous measure that cannot be used in a dichotomous manner (e.g., significant vs. non-significant), while the second objective is to make its reading and interpretation easier.

BACKGROUND ASSUMPTIONS: TABLE 1 DATA

1. Age

1.1. STATISTICAL TEST: Welch t-test.

1.1.1. BACKGROUND TESTABLE STATISTICAL ASSUMPTIONS: i) data normality, ii) absence of outliers.

- VERIFICATION METHODS: i) Shapiro-Wilk test plus Kolmogorov-Smirnov D for the effect size, frequency histograms, Q-Q plot, ii) Tukey's fences ($k=1.5$), frequency histograms, Q-Q plot.
- VERIFICATION RESULTS: i) Considering that the Welch t-test is robust under violation of the normality assumption,^{5,6} compatibility of the data with the latter was deemed sufficient (male p-value = 0.45, male KS-D = 0.07, female p-value = 0.13, female KS-D = 0.11), ii) no outliers identified (see Figures S1-S4).

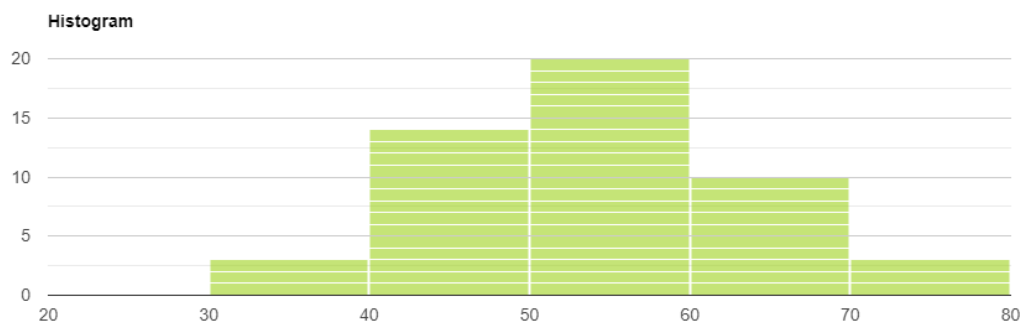


Figure S1. Male histogram of frequencies: age data.

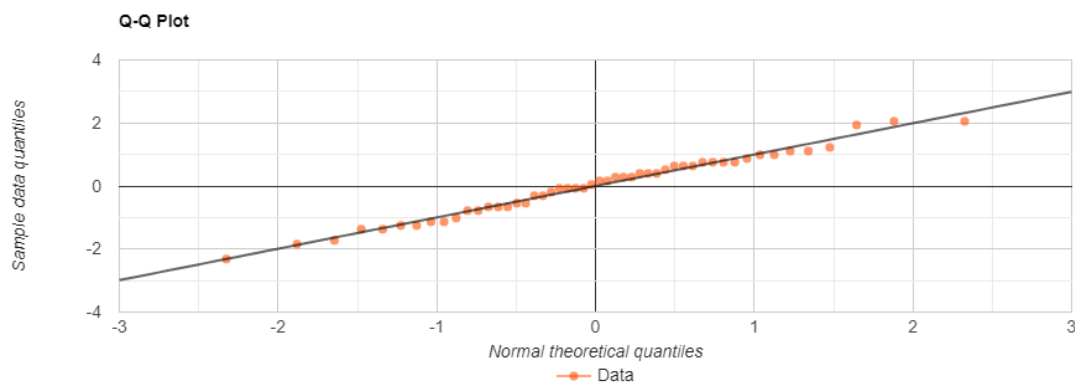


Figure S2. Male Q-Q plot: age data.

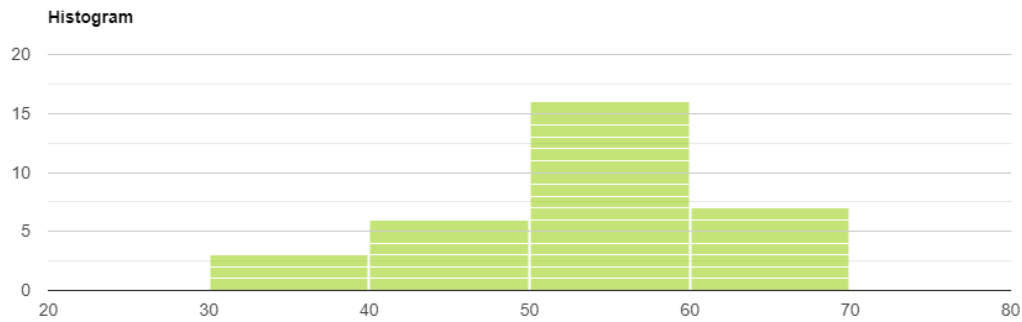


Figure S3. Female histogram of frequencies: age data.

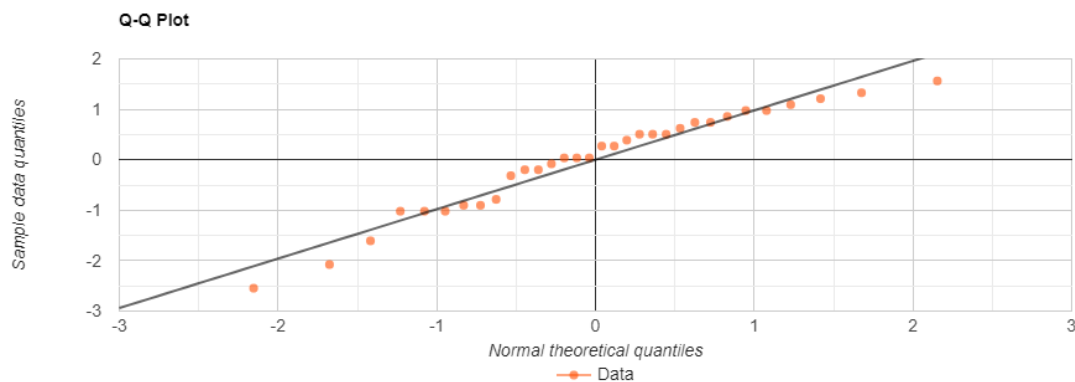


Figure S4. Female Q-Q plot: age data.

1.1.2. BACKGROUND UNTESTABLE STATISTICAL ASSUMPTIONS: i) continuous data: yes, ii) independence of samples: yes, iii) random sampling: the sample is subject to a collection bias as it concerns patients from specific geographical regions. Furthermore, the small size may not ensure full representativeness of all clinical characteristics of the population of interest.

1.2. STATISTICAL EFFECT SIZE MEASURE: Cohen's d.

1.2.1. BACKGROUND STATISTICAL CONDITIONS AND VALIDATION METHODS⁷: i) data normality (sufficiently met, see the point 1.1.1), ii) homogeneity of variances: Levene's test null $p=0.91$, i.e., very high compatibility of the data with the hypothesis of equal variances. Indeed, $SD_m=8.52$ and $SD_f=8.47$, iii) continuous data: yes, iv) independence of samples: yes.

2. Age > 55

2.1. STATISTICAL TEST: Pearson Chi-square test (with Yates correction).

2.1.1. BACKGROUND STATISTICAL ASSUMPTIONS: we list the underlying assumptions of the Chi-square test, easily verifiable by the reader⁸: i) the data in the cells should be frequencies or counts of cases, ii) the levels or categories of the variables are mutually exclusive, iii) each subject may contribute data to one and only one cell in the χ^2 , iv) the study groups must be independent, v) there are 2 variables, and both are measured as categories, usually at the

nominal level, vi) the expected frequencies of the cells should be 5 or more in at least 80% of the cells, and no cell should have an expected of less than one.

- 2.1.2. RESULTS: In the table we have reported the P-value least compatible with the null hypothesis, i.e. the one obtained with the Yates correction (null $p=0.899$). This was done to present the reader with the most unfavorable scenario possible; nevertheless, even with this precaution, the p-value turned out to be very compatible with the null hypothesis.

2.2. STATISTICAL EFFECT SIZE MEASURE: Cohen's w .

- 2.2.1. BACKGROUND STATISTICAL ASSUMPTIONS: we list the underlying assumptions of the Cohen's w ,⁹ easily verifiable by the reader: i) categorical data, ii) random sample, iii) independence of observations, iv) adequate sample size, v) contingency table, vi) no low expected frequencies in cells (i.e., the cell values should be 5 or more).

3. Oslo

3.1. STATISTICAL TEST: Pearson Chi-square test.

- 3.1.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.1.1. We chose the result least compatible with the null hypothesis between the Pearson Chi-square test (null $p=0.16$) and the Pearson Chi-square with Yates correction (null $p=0.25$). This was done to present the reader with the most unfavorable scenario possible. Considering this precaution, the p-value turned out to be quite compatible with the null hypothesis.

3.2. STATISTICAL EFFECT SIZE MEASURE: Cohen's w .

- 3.2.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.2.1.

4. Living donor, Previous liver therapy, BMI > 25 Kg/m², pN+, pN1, pN2, Synchronous CRLM, Right location CRC, Time ≤ 24 months, Progressive disease, CEA > 80 µg/L

4.1. STATISTICAL TEST: Pearson Chi-square test.

- 4.1.1. BACKGROUND STATISTICAL ASSUMPTIONS AND VERIFICATION METHODS: see the point 2.1.1. In all scenarios the worst P-value was shown. Despite this precaution, all results were strongly compatible with the null hypothesis.

4.2. STATISTICAL EFFECT SIZE MEASURE: Cohen's w .

- 4.2.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.2.1. Where there were cell values less than 5 (Synchronous CRLM), it was concluded that, as the consistency between Fisher's and Chi-square tests was high (Fisher p -value = 0.705 vs. Chi-square p -value = 0.503), the 'w' metric was reliable for the purpose of the paper. In particular, in the current

scenario, at most, it was plausible to expect an overestimate; nevertheless, the statistical effect size was very limited.

5. Number of nodules

5.1. STATISTICAL TEST: Mann-Whitney U test

5.1.1. BACKGROUND STATISTICAL ASSUMPTIONS ¹⁰: in order to compare the medians, the data distributions must have the same shape. For untestable background assumptions, the considerations made in 1.1.2 apply.

5.1.2. VERIFICATION METHODS AND RESULTS: i) test for asymmetry (right/positive asymmetry male p-value < 0.001, female p-value = 0.007) plus frequency histograms (Figures S5 and S6).

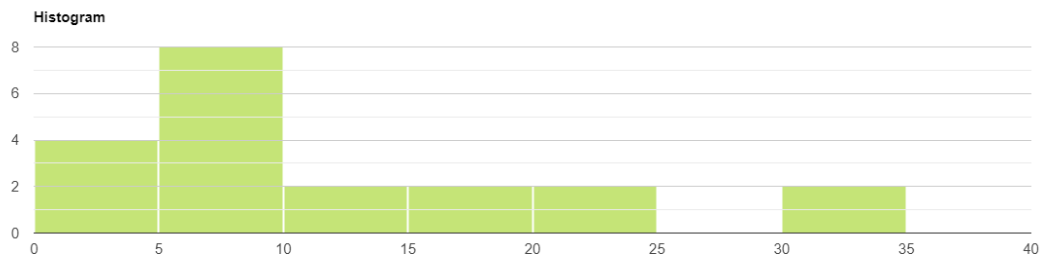


Figure S5. Male histogram of frequencies: number of nodules data.

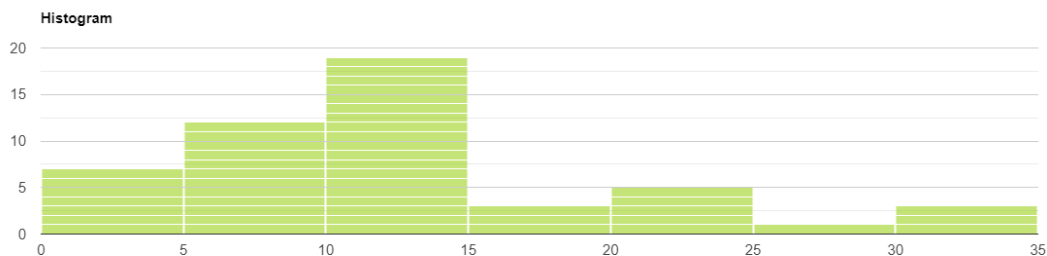


Figure S6. Female histogram of frequencies: number of nodules data.

5.2. STATISTICAL EFFECT SIZE MEASURE: Mann-Whitney standardized effect size $'z/(n_1+n_2)^{1/2}.'$

6. N° > 10

6.1. STATISTICAL TEST: Pearson Chi-square test.

6.1.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.1.1.

6.2. STATISTICAL EFFECT SIZE MEASURE: Cohen's w.

6.2.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.2.1.

7. Diameter largest nodule (cm)

7.1. STATISTICAL TEST: Mann-Whitney U test

7.1.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 5.1.1.

7.1.2. VERIFICATION METHODS AND RESULTS: test for asymmetry: right/positive asymmetry for male (p-value = 0.008) and higher symmetry for female (p-value = 0.10) as shown in the frequencies histograms (Figures S7 and S8). Nonetheless, the test remains informative even in this instance (since the differences in shape between the distributions might have clinical relevance).

7.2. STATISTICAL EFFECT SIZE MEASURE: : Mann-Whitney standardized effect size $'z/(n_1+n_2)^{1/2}.'$

8. Diameter > 5.5 cm, KRAS mutated

8.1. STATISTICAL TEST: Pearson Chi-square test.

8.1.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.1.1.

8.2. STATISTICAL EFFECT SIZE MEASURE: Cohen's w.

8.2.1. BACKGROUND STATISTICAL ASSUMPTIONS: see the point 2.2.1.

CALCULATORS

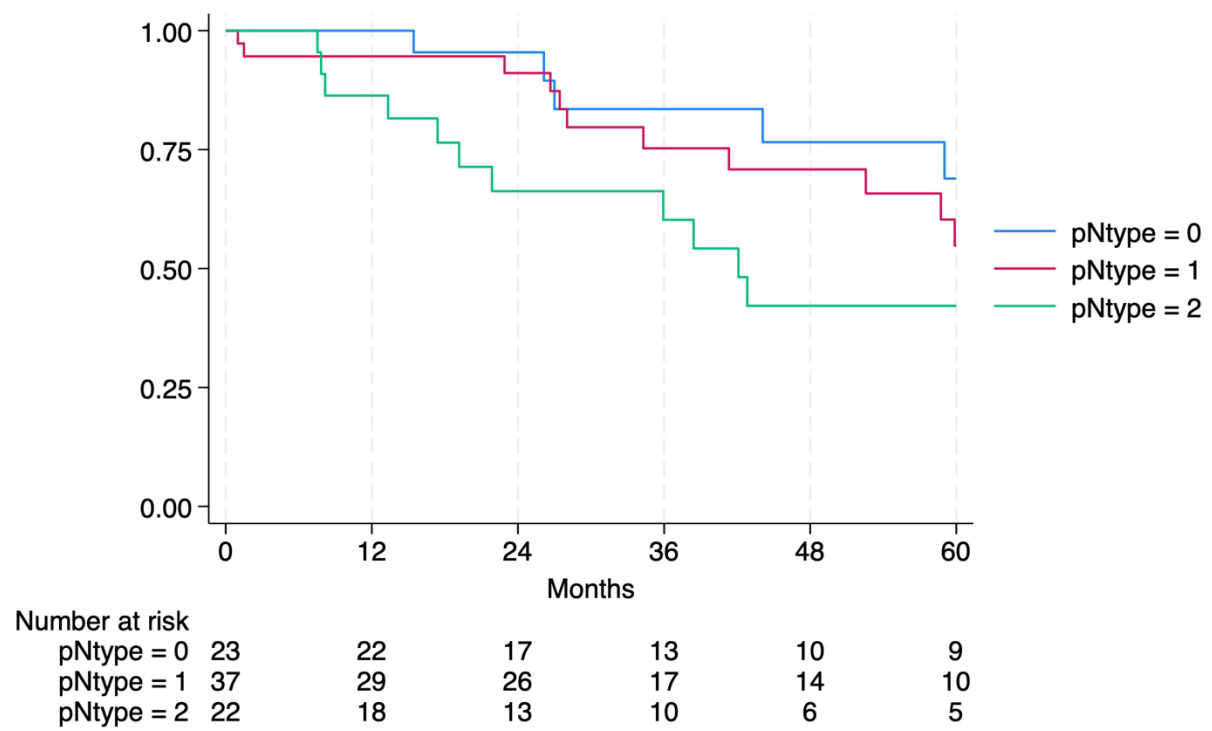
The following online calculators have been used (latest access Jan 24, 2024):

Statistics Kingdom - <https://www.statskingdom.com/>

Social Science Statistics - <https://www.socscistatistics.com/tests/>

SELECTION OF pN VARIABLES

KAPLAN MEIER SURVIVAL CURVE.



UNIVARIABLE COX MODEL EVALUATION.

```

1. stcox i.pN

      Failure _d:  censor==0
      Analysis time _t:  os

Iteration 0:  Log likelihood = -121.58155
Iteration 1:  Log likelihood = -120.21334
Iteration 2:  Log likelihood = -120.19468
Iteration 3:  Log likelihood = -120.19467
Refining estimates:
Iteration 0:  Log likelihood = -120.19467

Cox regression with no ties

No. of subjects =      82                Number of obs =      82
No. of failures =     33
Time at risk   =  3,828.2

LR chi2(1)      =    2.77
Prob > chi2     =  0.0958

Log likelihood = -120.19467

```

_t	Haz. ratio	Std. err.	z	P> z	[95% conf. interval]
1.pN	1.963504	.842846	1.57	0.116	.8465418 4.554233

```
2. stcox i.pNtype

      Failure _d: censor==0
      Analysis time _t: os

Iteration 0: Log likelihood = -121.58155
Iteration 1: Log likelihood = -119.21256
Iteration 2: Log likelihood = -119.1352
Iteration 3: Log likelihood = -119.13517
Refining estimates:
Iteration 0: Log likelihood = -119.13517

Cox regression with no ties

No. of subjects =      82                Number of obs =      82
No. of failures =      33
Time at risk   = 3,828.2

LR chi2(2)      =      4.89
Prob > chi2     = 0.0866

Log likelihood = -119.13517
```

_t	Haz. ratio	Std. err.	z	P> z	[95% conf. interval]	
pNtype						
1	1.523845	.7197564	0.89	0.372	.6038004	3.845812
2	2.722572	1.284141	2.12	0.034	1.080184	6.862162

```
3. stcox i.pN2

      Failure _d: censor==0
      Analysis time _t:  os

Iteration 0:  Log likelihood = -121.58155
Iteration 1:  Log likelihood = -119.61512
Iteration 2:  Log likelihood = -119.54698
Iteration 3:  Log likelihood = -119.54697
Refining estimates:
Iteration 0:  Log likelihood = -119.54697

Cox regression with no ties

No. of subjects =      82                Number of obs =      82
No. of failures =      33
Time at risk    =  3,828.2

LR chi2(1)      =    4.07
Prob > chi2     =    0.0437

Log likelihood = -119.54697
```

_t	Haz. ratio	Std. err.	z	P> z	[95% conf. interval]
1.pN2	2.111228	.7547266	2.09	0.037	1.047721 4.254266

We decided to use the pN2 variable in the main survival analysis based on the Kaplan-Meier figure and univariable Cox analysis to limit degrees of freedom and multivariable model overfitting.

BACKGROUND ASSUMPTIONS: TYPE 2 MODEL (OLD VERSION FOR SENSITIVITY ANALYSIS)

BACKGROUND STATISTICAL ASSUMPTIONS: i) linearity in the covariates, ii) Independence of errors, iii) non-informative censoring, iv) proportional hazards, v) absence of multicollinearity, and vi) correct specification of the model.

VERIFICATION METHODS: The assumptions i), ii), and iii) have been considered automatically verified given the nature of the data (categorical variables with possible values "0" and "1") and the scientific scenario. iv) The dataset showed very high compatibility with the target hypothesis: "The hazard ratios remain constant over time for all independent variables in the model," according to the Schoenfeld test (global p-value = 0.40, Table S2). Also, graphical inspection of the Schoenfeld residuals, dfbeta values, and deviance residuals¹¹⁻¹³ did not reveal – in our judgment – evident violations of the hazard proportionality assumption nor other anomalous behaviors (Figures S7-S10). v) We found no evident multicollinearity (all VIF < 2.4 in the associated linear regression model). Furthermore, the model remained highly consistent when leaving all 13 variables, changing variable 2, and removing variables 4 and 2 (the latter due to its possible violation of the hazard proportionality, p-value = 0.10). This indicates a certain stability. Finally, we observed that a weighted Cox regression provided results totally compatible with those in Table 2 (Table S4,¹⁴).

Table S2. Schoenfeld test results.

Variable	Chi-Square	df	p-value
0	0.49082	1	0.48
1	0.10550	1	0.75
2	2.67017	1	0.10
3	1.25440	1	0.26
4	-	-	-
5	0.00459	1	0.95
6	0.37498	1	0.54
7	0.01247	1	0.91
8	0.05199	1	0.82
9	0.01415	1	0.91
10	0.90192	1	0.34
11	1.56491	1	0.21
12	0.37973	1	0.54
GLOBAL	10.0563	12	0.40

vi) In Table S3, we present the results of fitting various models in terms of the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Specifically, this scenario is compatible with the hypothesis that the Cox model was the best choice according to both criteria.

Table S3. Correct specification of the type 2 model.		
MODEL	AIC	BIC
Cox	225	251
Weibull	360	389
Log-normal	372	400
Exponential	369	396
Frechet	380	408
Log-logistic	365	394

Global Schoenfeld Test p: 0.399

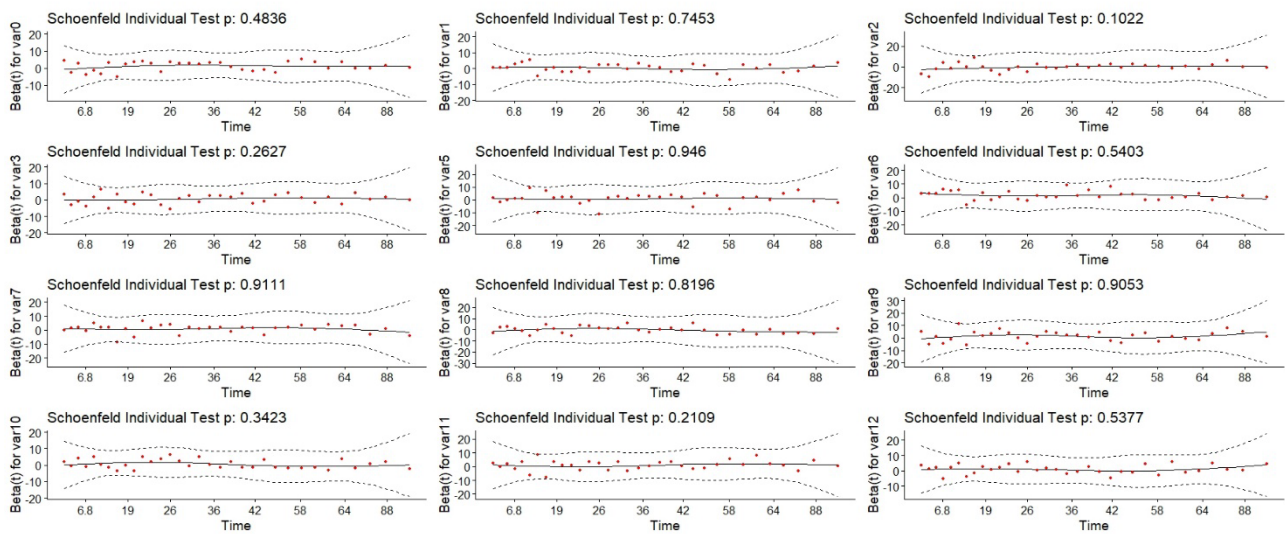


Figure S7. Type 2 model, Schoenfeld residuals.

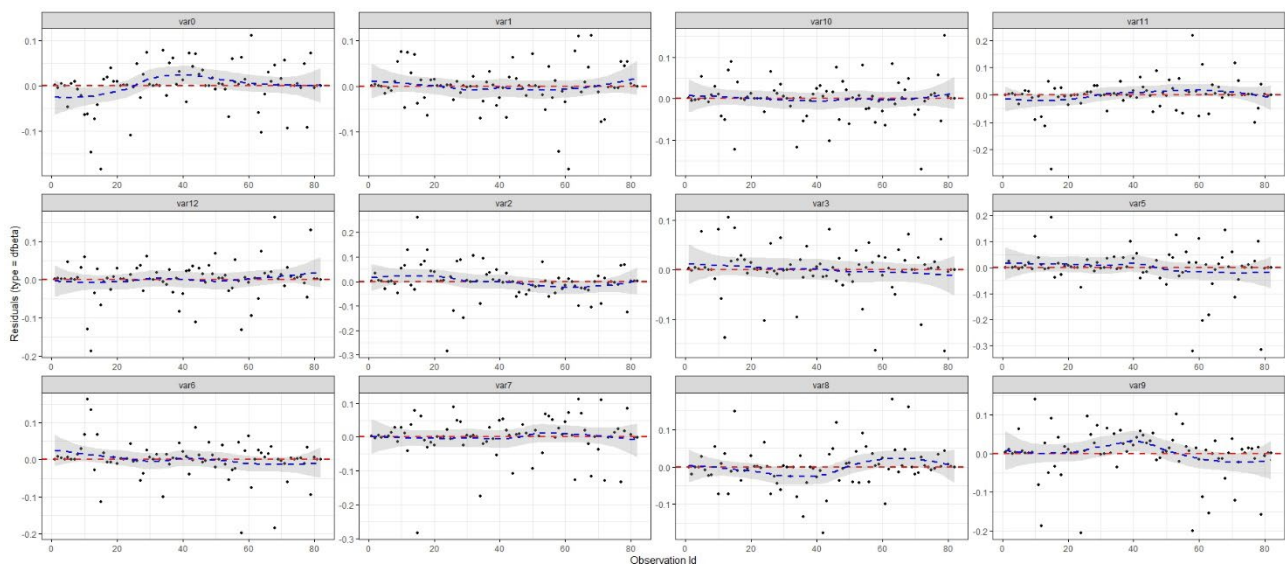


Figure S8. Type 2 model, dfbeta values.

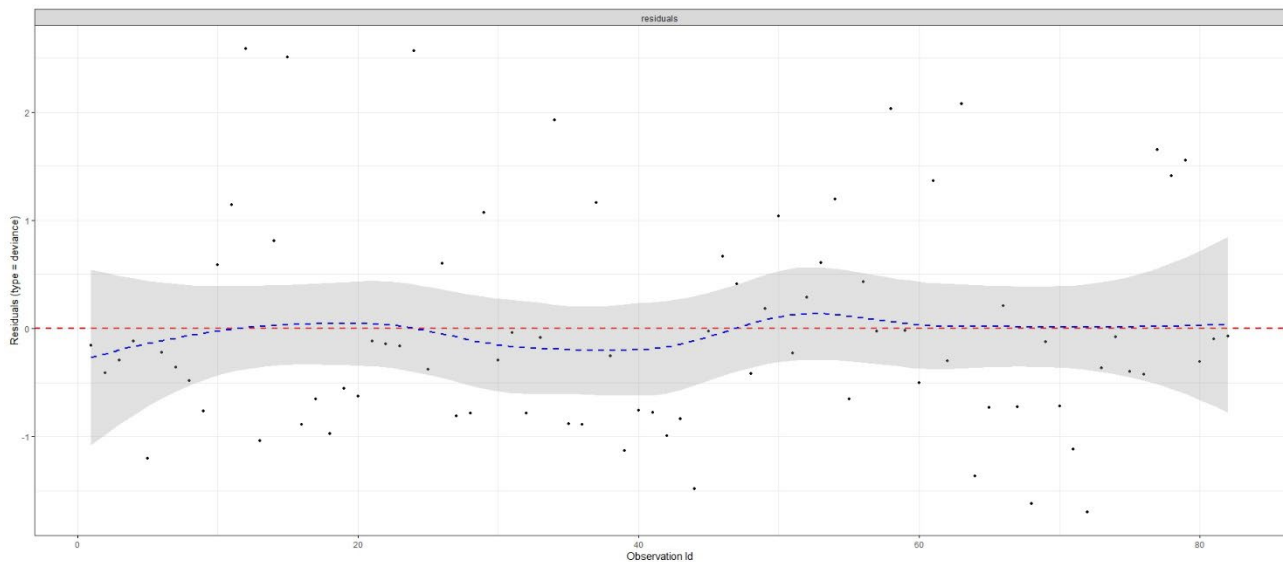


Figure S9. Type 2 model, deviance residuals.

Other notes: We point out that the categorical variable "synchronous colorectal liver metastases" was excluded as it was unsuitable for the model (although its inclusion/exclusion did not cause major differences in the outcomes). We also report the modification of variable 2 (var 2) from "low-volume centers" (patients whose transplant occurred in low-volume centers, i.e., with a number of cases ≤ 5) to "Oslo" (patients whose transplant occurred at the Oslo center vs. all other centers). However, this modification also did not produce substantial differences in the model.

Table S4. Type 2 model, weighted Cox regression (R-studio 4.3.2, package "coxphw", see Dunkler et al., 2018).

Variables	HR	95% CI		Null P-value
Female gender	3.0	1.3	7.1	0.01
Age>55 years	1.5	0.6	3.3	0.36
Oslo center	0.8	0.2	2.5	0.64
BMI > 25 Kg/m ²	1.9	0.8	4.4	0.16
pN+	2.3	0.6	8.3	0.21
Right location CRC	4.8	2.0	11.8	<0.001
Time \leq 24 months	2.1	0.7	6.0	0.18
Progressive disease	0.9	0.3	2.2	0.74
Diameter largest > 5.5 cm	4.8	1.6	14.2	0.004
Number of nodules > 10	1.7	0.7	4.0	0.23
CEA > 80 μ g/L	2.6	1.0	6.8	0.06
KRAS mutated	2.9	1.2	7.0	0.02

BACKGROUND ASSUMPTIONS: TABLE 4 DATA (OLD VERSION FOR SENSITIVITY ANALYSIS)

BACKGROUND STATISTICAL ASSUMPTIONS: i) linearity in the covariates, ii) Independence of errors, iii) non-informative censoring, iv) absence of multicollinearity, v) competing events, vi) correct specification of the model, and vii) proportional hazards.

VERIFICATION METHODS: The assumptions i), ii), and iii) have been considered automatically verified given the nature of the data (categorical variables with possible values "0" and "1") and the scientific scenario. The assumption iv) was previously verified (see the assumption v) in section C). iv) The assumption of competing events was theoretically assumed to be true based on the bio-genetic mechanisms governing the variables under examination. vi) In light of the above scenario, we deemed it sufficient to show the low compatibility of the null hypothesis with the data through the pseudo-likelihood ratio test: null $p=0.12$ and null $p<0.001$, respectively. vii) We applied the Zhou, Fine, & Laird test¹⁵, obtaining very good compatibility with the assumption of proportional risks (null $p=0.98$ and null $p=0.67$, respectively).

Other notes: We openly inform the reader about possible interpretative challenges associated with this model (see ¹⁶).

TYPE 1 MODEL (OLD VERSION FOR SENSITIVITY ANALYSIS)

BACKGROUND STATISTICAL ASSUMPTIONS: i) linearity in the covariates, ii) Independence of errors, iii) non-informative censoring, iv) proportional hazards, v) absence of multicollinearity, and vi) correct specification of the model.

VERIFICATION METHODS: The assumptions i), ii), and iii) have been considered automatically verified given the nature of the data (categorical variables with possible values "0" and "1") and the scientific scenario. iv) The dataset showed very high compatibility with the target hypothesis: "The hazard ratios remain constant over time for all independent variables in the model," according to the Schoenfeld test (global p-value = 0.48). Also, graphical inspection of the Schoenfeld residuals, log-log curves, dfbeta values, and deviance residuals did not reveal – in our judgment – evident violations of the hazard proportionality assumption nor other anomalous behaviors (Figures S10-S12, next pages).

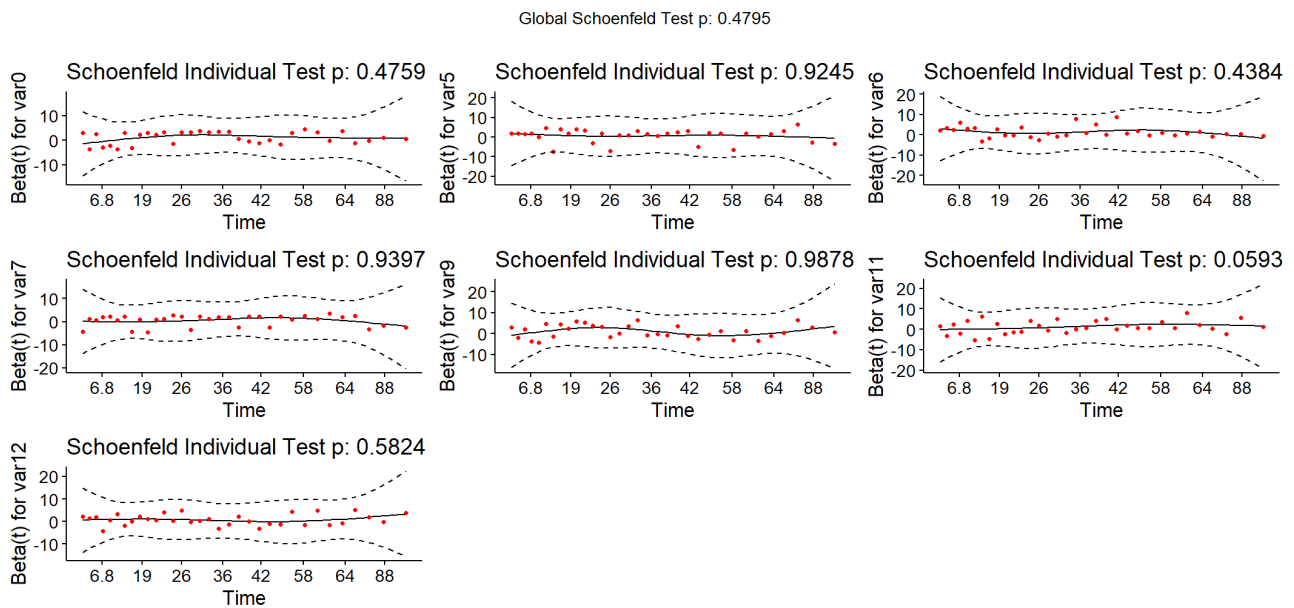


Figure S10. Model type 1 Schoenfeld residuals.

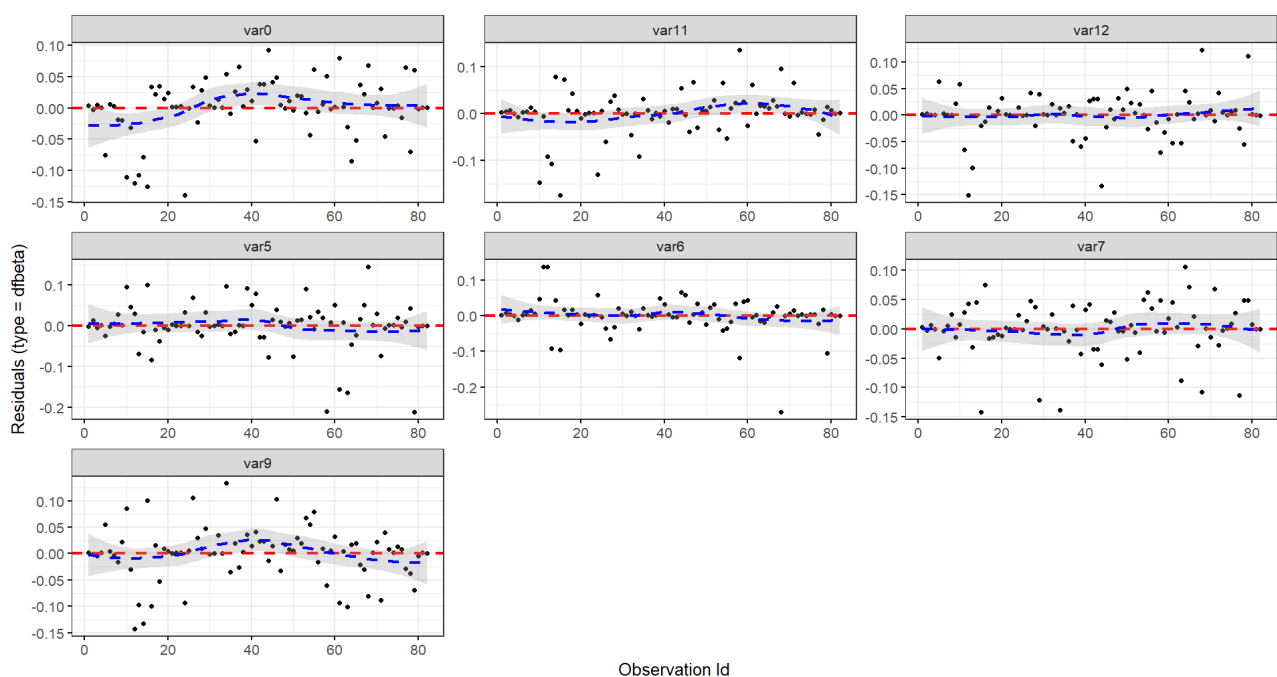


Figure S11. Model type 1 dfbeta values.

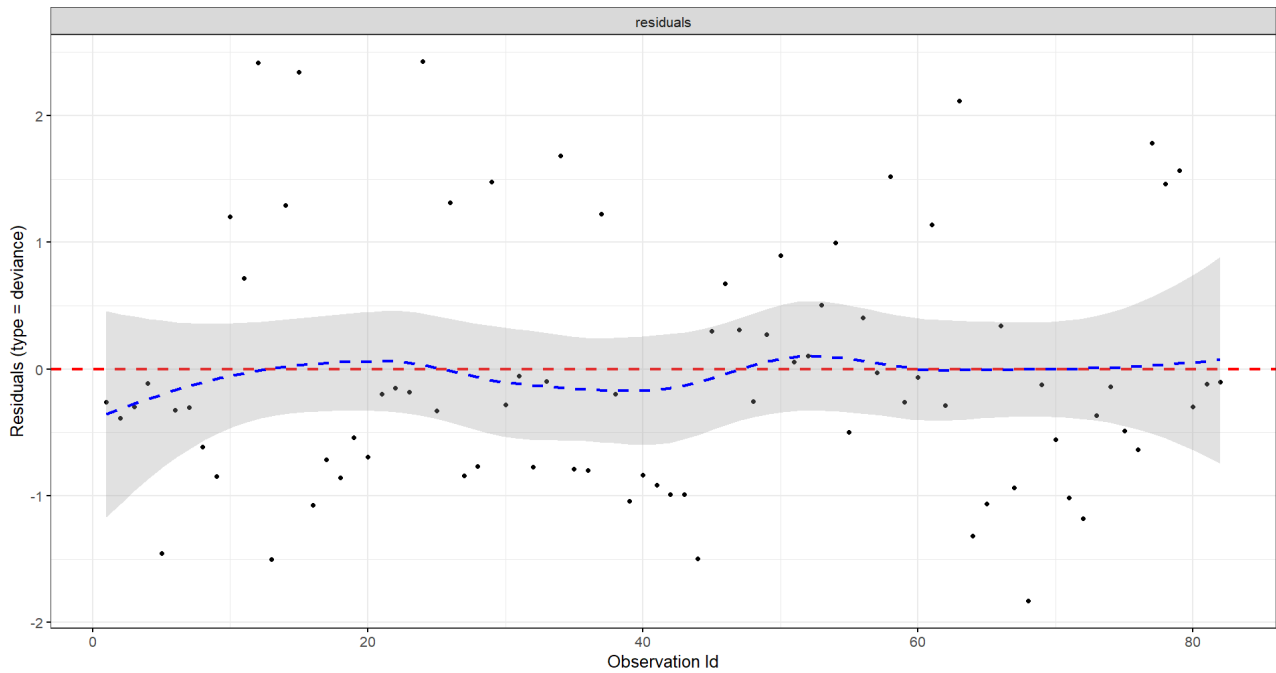


Figure S12. Model type 1 deviance analysis.

v) See section C, “verification methods” subsection, point v). vi) In light of the scientific objective (comparing the two type 1 and 2 models) and the high concordance (0.83, Likelihood ratio, Wald, and Score (logrank) tests null $P < 0.001$), we considered this assumption satisfied.

TYPE 1 MODEL RESULTS

The results of the Cox type 1 model (only variables with – approximately – null P-value ≤ 10 in the univariate analysis) are shown in Table S5.

Table S5. Type 1 model results (only covariates with – approximately – null P-value ≤ 0.10 in the univariate Cox regression were included).

Variables	HR	95%CI		Null P-value
Female gender	2.7	1.3	5.9	0.01
pN+	2.1	0.8	5.4	0.14
Right location CRC	3.8	1.5	9.7	0.004
Time ≤ 24 months	1.6	0.7	3.5	0.29
Largest diameter > 5.5 cm	2.8	1.1	6.9	0.02
CEA > 80 $\mu\text{g/L}$	3.2	1.3	7.9	0.01
KRAS mutated	2.3	1.0	5.2	0.05

UNIVARIATE: BACKGROUND ASSUMPTIONS OF TABLE 3 DATA (OLD VERSION FOR SENSITIVITY ANALYSIS)

BACKGROUND STATISTICAL ASSUMPTIONS: i) linearity in the covariates, ii) Independence of errors, iii) non-informative censoring, iv) proportional hazards.

VERIFICATION METHODS: For i), ii), and iii) see section C. iv) Schoenfeld tests were performed (see Table S6).

Table S6. Schoenfeld test results.		
Variable	Male null P-value	Female null P-value
Var 1	0.73	0.17
Var 2	0.25	0.69
Var 3	0.44	0.53
Var 4	-	-
Var 5	0.07	0.89
Var 6	0.08	0.61
Var 7	0.05	0.08
Var 8	0.21	0.98
Var 9	0.46	0.21
Var 10	0.45	0.27
Var 11	0.33	0.29
Var 12	0.15	0.67

Alongside this, we also calculated the univariate weighted Cox regressions, obtaining good compatibility with the data in Table 3 (Table S7, next page).

Table S7. Weighted Cox regression for Table 3 data.

Table S7. Weighted Cox regression for Tabel 3 data (see Table S4 for other details).				
Variables	Univariable			
	Average HR	95% CI		N p-value
Males				
Age > 55 years	0.8	0.3	2.3	0.79
Oslo center	4.6	0.6	34.5	0.14
BMI > 25 Kg/m ²	1.2	0.4	3.6	0.71
pN+	2.3	0.8	6.7	0.14
Right location CRC	6.6	1.9	23.9	0.004
Time ≤ 24 months	0.9	0.4	2.4	0.90
Progressive Disease	0.9	0.2	3.8	0.84
Largest diameter > 5.5 cm	1.8	0.6	4.9	0.28
Number of nodules > 10	1.3	0.5	3.5	0.631
CEA > 80 µg/L	4.8	2.1	11.1	<0.001
KRAS mutated	1.4	0.5	4.5	0.52
Females				
Age > 55 years	0.4	0.1	0.9	0.03
Oslo center	0.4	0.1	1.5	0.16
BMI > 25	0.8	0.3	2.1	0.69
pN+	0.9	0.3	2.6	0.80
Right location CRC	5.1	1.7	14.9	0.003
Time ≤ 24 months	2.3	0.6	8.9	0.22
Progressive Disease	4.2	1.4	12.2	0.009
Largest diameter > 5.5 cm	9.3	2.9	29.6	<0.001
Number of nodules > 10	1.6	0.6	4.4	0.36
CEA > 80 (µg/L)	13.8	3.7	50.8	<0.001
KRAS mutated	4.2	1.6	10.9	0.004

Table S8. Treatment of recurrence after liver transplantation according to recurrence pattern and sex.

Table S8. Treatment of recurrence after liver transplantation according to recurrence pattern and biological sex.				
Variables	N° of patients N° (%)	Males (n=38) N° (%)	Females (n=24) N° (%)	Null p-value
Liver only recurrence	6 patients	3 patients	3 patients	0.37
Surgery or ablation	3 (50.0)	2 (31.5)	1 (16.7)	
Chemotherapy ± Radiotherapy	2 (33.3)	-	2 (33.3)	
No treatment	1 (16.7)	1	-	
Lung only recurrence	23 patients	19 patients	4 patients	0.46
Surgery or ablation	12 (52.2)	11 (57.9)	1 (25.0)	
Chemotherapy ± Radiotherapy	3 (13.0)	2 (10.5)	1 (25.0)	
No treatment	8 (34.8)	6 (31.6)	2 (50.0)	
Multisite	32 patients	16 patients	16 patients	0.08
Surgery or ablation	15 (46.9)	10 (62.5)	5 (31.3)	
Chemotherapy ± Radiotherapy	13 (40.6)	6 (37.5)	7 (43.7)	
No treatment	4 (12.5)	-	4 (25)	
Single organ no liver, no lung	3 patients	2 patients	1 patient	NA
Surgery or ablation	2 (66.7)	1 (50)	1 (100)	
Chemotherapy ± Radiotherapy	-	-	-	
No treatment	1 (33.3)	1 (50)	-	
Null p-value, p-value for the null hypothesis of no risk difference;				
Notes: Two-tailed Welch t-test and Mann-Whitney U test were used to compare continuous variables; two-tailed Pearson's Chi-squared test and Fisher's exact test were used to compare categorical variables.				

References for Supplementary File 1

1. Greenland S. Valid P -Values Behave Exactly as They Should: Some Misleading Criticisms of P -Values and Their Resolution With S -Values. *Am Stat*. 2019 Mar 29;73(sup1):106–14.
2. Greenland S, Mansournia MA, Joffe M. To curb research misreporting, replace significance and confidence by compatibility. *Prev Med (Baltim)*. 2022 Nov;164:107127.
3. Rafi Z, Greenland S. Semantic and cognitive tools to aid statistical science: replace confidence and significance by compatibility and surprise. *BMC Med Res Methodol*. 2020 Sep 30;20(1):244.
4. Rovetta A. Compatibility ranges as a practical alternative to the “significant/non-significant” statistical dichotomy. *Public Health and Toxicology*. 2024 Jun 27;4(2):1–7.
5. Fagerland MW. t -tests, non-parametric tests, and large studies—a paradox of statistical practice? *BMC Med Res Methodol*. 2012 Dec 14;12(1):78.
6. Fagerland MW, Sandvik L. Performance of five two-sample location tests for skewed distributions with unequal variances. *Contemp Clin Trials*. 2009 Sep;30(5):490–6.
7. Li JCH. Effect size measures in a two-independent-samples case with nonnormal and nonhomogeneous data. *Behav Res Methods*. 2016 Dec 20;48(4):1560–74.
8. McHugh ML. The Chi-square test of independence. *Biochem Med (Zagreb)*. 2013;143–9.
9. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Routledge; 2013.
10. Sundjaja JH, Shrestha R, Krishan K. McNemar And Mann-Whitney U Tests. 2024.
11. STHDA. Cox model assumptions. Statistical tools for high-throughput data analysis. [Internet]. 2024 [cited 2024 Nov 23]. Available from: <https://www.sthda.com/english/wiki/cox-model-assumptions?title=cox-model-assumptions>
12. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in cox regression. *Stat Med*. 1995 Aug 15;14(15):1707–23.
13. Kuitunen I, Ponkilainen VT, Uimonen MM, Eskelinen A, Reito A. Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review. *BMC Musculoskelet Disord*. 2021 Dec 28;22(1):489.
14. Dunkler D, Ploner M, Schemper M, Heinze G. Weighted Cox Regression Using the *R* Package **coxphw**. *J Stat Softw*. 2018;84(2).
15. Zhou B, Fine J, Laird G. Goodness-of-fit test for proportional subdistribution hazards model. *Stat Med*. 2013 Sep 30;32(22):3804–11.
16. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012 Jun;41(3):861–70.
17. Shmueli G. To Explain or to Predict? *Statistical Science*. 2010 Aug 1;25(3).
18. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ*. 2016 Apr 27;i1981.
19. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*. 2006 May 6;332(7549):1080.

SUPPLEMENTARY FILE 2

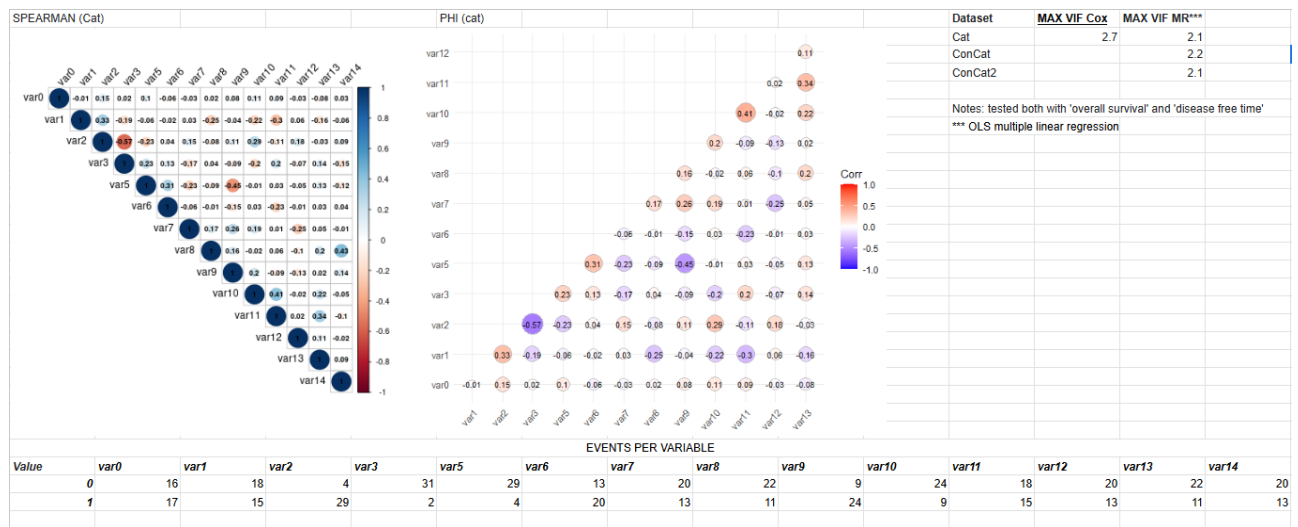
Cox regression models were performed to test the adjusted associations between covariates and outcomes. This aim is usually defined as explanatory modelling.¹⁷ It needs to be more inclusive than ultra-selective to avoid the risk of excluding clinically relevant variables that could have an essential causal role.¹⁸ However, explanatory modelling risks overfitting and sparse data bias. We conducted an extensive sensitivity analysis to detect these biases, assessing the consistency of various sensible models and evaluating the role of possible violated assumptions (Supplementary Files 1-3). For the dichotomous categorisation ('D-Cat') dataset, made of categorical variables, the following multivariable Cox regression models (CR) were compared: standard CR, weighted CR, Firth's penalised CR, and LASSO CR. The 'Null p-value' expression indicated the p-value calculated for the null hypothesis of no effect, association, or difference. Three variable selection criteria were applied to assess overfitting: all variables, variables with a Null p-value<0.10 in the univariable analysis, and variables with a Null p-value<0.20 in the univariable analysis.¹⁸

A hierarchical CR model was also realised based on four groups of variables: tumour biology and therapeutic response, characteristics of metastases and biomarkers, technical-logistic clinical factors, and patient-related clinical factors; the corrected Akaike information criterion was then employed (Supplementary File 2). Proportional hazard, weighted, and Firth's penalised CR models were also computed for the D-ConCat dataset, which consisted of continuous and categorical variables. Finally, the Cat and ConCat models were compared to evaluate the overall level of agreement, as dichotomous categorisation of continuous variables could lead to unnoticed methodological issues and information loss (Supplementary Files 2,3).¹⁹

Informativeness of censorship

Characteristic	Early censored (N=241) ≤36 months	Uncensored early (N=581)	p-value***
Female gender			
0	17 (71%)	33 (57%)	0.2
1	7 (29%)	25 (43%)	
Age > 55 years			
0	14 (58%)	29 (50%)	0.5
1	10 (42%)	29 (50%)	
Oslo centre			
0	19 (79%)	9 (16%)	<0.001
1	5 (21%)	49 (84%)	
Living donor			
0	15 (63%)	55 (95%)	<0.001
1	9 (38%)	3 (5.2%)	
Previous liver therapy			
0	16 (67%)	45 (78%)	0.3
1	8 (33%)	13 (22%)	
BMI > 25 kg/m ²			
0	10 (42%)	23 (40%)	0.9
1	14 (58%)	35 (60%)	
pN2			
0	20 (83%)	40 (69%)	0.2
1	4 (17%)	18 (31%)	
Right location CRC			
0	19 (79%)	46 (79%)	>0.9
1	5 (21%)	12 (21%)	
Time ≤ 24 months			
0	12 (50%)	20 (34%)	0.2
1	12 (50%)	38 (66%)	
Progressive Disease			
0	21 (88%)	45 (78%)	0.4
1	3 (13%)	13 (22%)	
Largest diameter > 5.5 cm			
0	16 (67%)	37 (64%)	0.8
1	8 (33%)	21 (36%)	
Number of nodules > 10			
0	18 (75%)	37 (64%)	0.3
1	6 (25%)	21 (36%)	
CEA > 80 µg/L			
0	20 (83%)	46 (79%)	0.8
1	4 (17%)	12 (21%)	
KRAS mutated			
0	21 (88%)	42 (72%)	0.14
1	3 (13%)	16 (28%)	
*** Pearson's Chi-squared test; Fisher's exact test			

Collinearity and events per variable



Hierarchy

ALL MODELS ARE CATEGORICAL				
VAR10	Progressive Disease	Tumor biology and therapeutic response		
VAR14	KRAS			
VAR7	pN2			
VAR11	Size	Characteristics of metastases and biomarkers		
VAR12	Number			
VAR13	CEA			
VAR8	Location			
VAR9	Time	Technical-logistic clinical factors		
VAR3	Living donor			
VAR5	Previous liver therapy			
VAR1	Age	Patient related clinical factors		
VAR2	Oslo			
VAR6	BMI			
VAR0	Gender			

Model	AICc	
model_coxB	235	
model_coxMB	222	
model_coxTL	226	
model_coxG	218	
model_coxA	228	
model_coxO	228	
model_coxBMI	227	
model_coxG+Age	221	
model_coxG+Oslo	220	
model_coxG+BMI	218	
model_all	222	
modello_coxMBTime	222	
modello_coxMBLD	223	
modello_coxMBPLT	223	
modello_coxMBTimeG	216	
modello_coxMBLDG	217	
modello_coxMBPLTG	214	
modello_coxMBPLTGBMI	214	
modello_cox_Best	212	***
model_p≤0.10	213	
model_p≤0.20	216	

Hierarchical 1 (AICc=214)									Concordance= 0.836 (se = 0.034)
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			Likelihood ratio test= 49.82 on 9 df, p=1e-07
VAR0	Female gender	4,29	1,84	9,99	0,001		10,4		Wald test = 47.94 on 9 df, p=3e-07
VAR1	Age > 55 years								Score (logrank) test = 71.51 on 9 df, p=8e-12
VAR2	Oslo center								
VAR3	Living donor								
VAR5	Previous liver therapy	0,32	0,09	1,07	0,06		4,0		
VAR6	BMI > 25 Kg/m2								
VAR7	pN2	2,03	0,85	4,85	0,11		3,1		
VAR8	Right location CRC	2,94	1,09	7,94	0,03		4,9		
VAR9	Time ≤ 24 months								
VAR10	Progressive Disease	0,78	0,25	2,44	0,67		0,6		
VAR11	Largest diameter > 5.5 cm	2,68	1,09	6,64	0,03		4,9		
VAR12	Number of nodules > 10	1,70	0,78	3,71	0,19		2,4		
VAR13	CEA > 80 µg/L	3,82	1,32	11,06	0,01		6,2		
VAR14	KRAS mutated	2,17	0,84	5,59	0,11		3,2		
Hierarchical 2 (AICc=214)									Concordance= 0.83 (se = 0.037)
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			Likelihood ratio test= 52.68 on 10 df, p=9e-08
VAR0	Female gender	5,20	2,14	12,65	0,000		11,8		Wald test = 47.31 on 10 df, p=8e-07
VAR1	Age > 55 years								Score (logrank) test = 71.95 on 10 df, p=2e-11
VAR2	Oslo center								
VAR3	Living donor								
VAR5	Previous liver therapy	0,22	0,06	0,86	0,03		5,1		
VAR6	BMI > 25 Kg/m2	2,18	0,87	5,50	0,10				
VAR7	pN2	2,20	0,89	5,42	0,09		3,5		
VAR8	Right location CRC	2,84	1,04	7,77	0,04		4,6		
VAR9	Time ≤ 24 months								
VAR10	Progressive Disease	0,64	0,21	2,00	0,45		1,2		
VAR11	Largest diameter > 5.5 cm	4,34	1,47	12,79	0,01		7,0		
VAR12	Number of nodules > 10	1,88	0,83	4,24	0,13		3,0		
VAR13	CEA > 80 µg/L	3,51	1,23	10,00	0,02		5,7		
VAR14	KRAS mutated	2,34	0,88	6,21	0,09		3,5		
Hierarchical 3 (AICc=212)									Concordance= 0.839 (se = 0.036)
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			Likelihood ratio test= 52.07 on 9 df, p=4e-08
VAR0	Female gender	4,70	2,03	10,89	0,000		11,7		Wald test = 48.17 on 9 df, p=2e-07
VAR1	Age > 55 years								Score (logrank) test = 71.29 on 9 df, p=8e-12
VAR2	Oslo center								
VAR3	Living donor								
VAR5	Previous liver therapy	0,25	0,07	0,91	0,04		4,8		
VAR6	BMI > 25 Kg/m2	2,01	0,82	4,91	0,12				
VAR7	pN2	2,09	0,85	5,18	0,11		3,2		
VAR8	Right location CRC	2,94	1,06	8,17	0,04		4,7		
VAR9	Time ≤ 24 months								
VAR10	Progressive Disease								
VAR11	Largest diameter > 5.5 cm	3,52	1,38	8,99	0,008		6,9		
VAR12	Number of nodules > 10	1,96	0,87	4,41	0,10		3,3		
VAR13	CEA > 80 µg/L	3,16	1,15	8,70	0,03		5,3		
VAR14	KRAS mutated	2,24	0,84	5,96	0,11		3,2		

PH Cox

ALL MODELS ARE CATEGORICAL							
Proportional hazards Cox model							
Univariable							
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s	n = 82, number of events = 33
VAR0	Female gender	2,10	1,10	4,20	0,04	4,8 **	
VAR1	Age > 55 years	0,70	0,30	1,30	0,23	2,1	
VAR2	Oslo center	1,40	0,50	4,20	0,50	1,0	
VAR3	Living donor	1,36	0,31	5,92	0,68	0,6	
VAR5	Previous liver therapy	0,37	0,13	1,05	0,06	4,0 **	
VAR6	BMI > 25 Kg/m2	0,90	0,50	1,90	0,82	0,3	
VAR7	pN2	2,10	1,00	4,30	0,04	4,8 **	
VAR8	Right location CRC	5,50	2,60	11,80	0,000	16,3 **	
VAR9	Time ≤ 24 months	1,90	0,90	4,00	0,11	3,2 *	
VAR10	Progressive Disease	1,90	0,90	4,20	0,10	3,3 **	
VAR11	Largest diameter > 5.5 cm	2,40	1,20	4,90	0,01	6,3 **	
VAR12	Number of nodules > 10	1,30	0,60	2,50	0,51	1,0	
VAR13	CEA > 80 µg/L	4,10	2,00	8,60	0,000	12,3 **	
VAR14	KRAS mutated	2,30	1,20	4,70	0,02	5,7 **	
Multivariable all							
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s	Concordance= 0.84 (se = 0.036)
VAR0	Female gender	5,13	2,04	12,90	0,0005	10,9	Likelihood ratio test= 55.29 on 14 df, p=8e-07
VAR1	Age > 55 years	1,33	0,55	3,24	0,53	0,9	Wald test = 48.05 on 14 df, p=1e-05
VAR2	Oslo center	0,30	0,05	1,77	0,18	2,5	Score (logrank) test = 76.12 on 14 df, p=1e-10
VAR3	Living donor	0,79	0,09	7,27	0,84	0,3	
VAR5	Previous liver therapy	0,22	0,05	0,98	0,05	4,4	
VAR6	BMI > 25 Kg/m2	2,43	0,94	6,30	0,07	3,9	
VAR7	pN2	2,37	0,92	6,14	0,07	3,7	
VAR8	Right location CRC	3,36	1,15	9,79	0,03	5,3	
VAR9	Time ≤ 24 months	1,37	0,44	4,26	0,59	0,8	
VAR10	Progressive Disease	0,82	0,23	2,98	0,76	0,4	
VAR11	Largest diameter > 5.5 cm	4,38	1,39	13,77	0,01	6,5	
VAR12	Number of nodules > 10	2,48	0,99	6,22	0,05	4,2	
VAR13	CEA > 80 µg/L	3,55	1,22	10,30	0,02	5,6	
VAR14	KRAS mutated	2,86	1,01	8,08	0,05	4,4	
Multivariable p≤0.10							
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s	Concordance= 0.839 (se = 0.033)
VAR0	Female gender	4,07	1,76	9,43	0,001	9,9	Likelihood ratio test= 48.11 on 8 df, p=9e-08
VAR1	Age > 55 years						Wald test = 46.8 on 8 df, p=2e-07
VAR2	Oslo center						Score (logrank) test = 68.97 on 8 df, p=8e-12
VAR3	Living donor						
VAR5	Previous liver therapy	0,31	0,10	1,04	0,06	4,1	
VAR6	BMI > 25 Kg/m2						
VAR7	pN2	1,76	0,75	4,16	0,20	2,3	
VAR8	Right location CRC	2,79	1,08	7,21	0,03	4,9	
VAR9	Time ≤ 24 months						
VAR10	Progressive Disease	0,71	0,22	2,22	0,55	0,9	
VAR11	Largest diameter > 5.5 cm	2,69	1,07	6,78	0,04	4,8	
VAR12	Number of nodules > 10						
VAR13	CEA > 80 µg/L	4,47	1,62	12,35	0,004	8,0	
VAR14	KRAS mutated	2,12	0,85	5,31	0,11	3,2	
Multivariable p≤0.20							
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s	Concordance= 0.841 (se = 0.032)
VAR0	Female gender	4,12	1,72	9,88	0,002	9,4	Likelihood ratio test= 48.12 on 9 df, p=2e-07
VAR1	Age > 55 years						Wald test = 46.87 on 9 df, p=4e-07
VAR2	Oslo center						Score (logrank) test = 69.32 on 9 df, p=2e-11
VAR3	Living donor						
VAR5	Previous liver therapy	0,30	0,08	1,22	0,09	3,4	
VAR6	BMI > 25 Kg/m2						
VAR7	pN2	1,76	0,75	4,15	0,20	2,3	
VAR8	Right location CRC	2,80	1,08	7,25	0,03	4,9	
VAR9	Time ≤ 24 months	0,95	0,34	2,65	0,92	0,1	
VAR10	Progressive Disease	0,72	0,21	2,43	0,60	0,7	
VAR11	Largest diameter > 5.5 cm	2,67	1,04	6,80	0,04	4,6	
VAR12	Number of nodules > 10						
VAR13	CEA > 80 µg/L	4,46	1,61	12,34	0,004	8,0	
VAR14	KRAS mutated	2,11	0,83	5,35	0,12	3,1	

Weight Cox

ALL MODELS ARE CATEGORICAL										
Univariable							n= 82, number of events = 33			
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s				
VAR0	Female gender	2,00	1,00	4,10	0,04	4,6 **				
VAR1	Age > 55 years	0,70	0,30	1,30	0,27	1,9				
VAR2	Oslo center	1,50	0,50	4,40	0,48	1,1				
VAR3	Living donor	1,35	0,30	6,06	0,69	0,5				
VAR5	Previous liver therapy	0,38	0,14	1,07	0,07	3,9 **				
VAR6	BMI > 25 Kg/m2	1,00	0,50	1,90	0,91	0,1				
VAR7	pN2	2,00	1,00	4,10	0,07	3,8 **				
VAR8	Right location CRC	5,40	2,20	13,10	0,000	>10 **				
VAR9	Time ≤ 24 months	1,70	0,80	3,50	0,14	2,8 *				
VAR10	Progressive Disease	1,90	0,80	4,50	0,17	2,6 *				
VAR11	Largest diameter > 5.5 cm	2,60	1,30	5,10	0,01	6,6 **				
VAR12	Number of nodules > 10	1,30	0,60	2,50	0,50	1,0				
VAR13	CEA > 80 µg/L	4,20	2,20	8,10	0,000	>10 **				
VAR14	KRAS mutated	2,30	1,10	4,80	0,03	5,1 **				
Multivariable all							Wald Chi-square = 76.36594 on 14 df p = 1.327799e-10 n = 82			
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s				
VAR0	Female gender	5,64	1,75	18,16	0,004	8,1				
VAR1	Age > 55 years	1,41	0,64	3,11	0,39	1,3				
VAR2	Oslo center	0,31	0,05	1,78	0,19	2,4				
VAR3	Living donor	0,77	0,09	6,39	0,81	0,3				
VAR5	Previous liver therapy	0,19	0,04	0,89	0,03	4,8				
VAR6	BMI > 25 Kg/m2	2,66	0,94	7,55	0,07	3,9				
VAR7	pN2	2,25	0,87	5,85	0,09	3,4				
VAR8	Right location CRC	3,19	1,16	8,78	0,02	5,4				
VAR9	Time ≤ 24 months	1,21	0,36	4,05	0,75	0,4				
VAR10	Progressive Disease	0,79	0,27	2,36	0,67	0,6				
VAR11	Largest diameter > 5.5 cm	5,12	1,72	15,27	0,003	8,2				
VAR12	Number of nodules > 10	2,38	0,95	5,95	0,06	4,0				
VAR13	CEA > 80 µg/L	3,79	1,33	10,84	0,01	6,3				
VAR14	KRAS mutated	2,95	1,01	8,63	0,05	4,4				

Multivariable p≤0,10							Wald Chi-square = 46.24756 on 7 df p = 7.823904e-08 n = 82			
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s				
VAR0	Female gender	3,93	1,55	10,02	0,004	7,9				
VAR1	Age > 55 years									
VAR2	Oslo center									
VAR3	Living donor									
VAR5	Previous liver therapy	0,32	0,11	0,93	0,04	4,8				
VAR6	BMI > 25 Kg/m2									
VAR7	pN2	1,57	0,71	3,43	0,26	1,9				
VAR8	Right location CRC	2,76	1,09	6,99	0,03	5,0				
VAR9	Time ≤ 24 months									
VAR10	Progressive Disease									
VAR11	Largest diameter > 5.5 cm	2,59	1,17	5,74	0,02	5,7				
VAR12	Number of nodules > 10									
VAR13	CEA > 80 µg/L	4,38	1,68	11,38	0,002	8,7				
VAR14	KRAS mutated	2,10	0,95	4,61	0,07	3,9				
Multivariable p≤0,20							Wald Chi-square = 45.86574 on 9 df p = 6.3777e-07 n = 82			
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s				
VAR0	Female gender	4,41	1,53	12,75	0,006	7,4				
VAR1	Age > 55 years									
VAR2	Oslo center									
VAR3	Living donor									
VAR5	Previous liver therapy	0,28	0,06	1,25	0,10	3,4				
VAR6	BMI > 25 Kg/m2									
VAR7	pN2	1,69	0,75	3,83	0,21	2,3				
VAR8	Right location CRC	2,69	1,08	6,70	0,03	4,9				
VAR9	Time ≤ 24 months	0,86	0,27	2,77	0,80	0,3				
VAR10	Progressive Disease	0,71	0,20	2,50	0,59	0,8				
VAR11	Largest diameter > 5.5 cm	2,92	1,12	7,61	0,03	5,2				
VAR12	Number of nodules > 10									
VAR13	CEA > 80 µg/L	4,80	1,81	12,72	0,002	9,3				
VAR14	KRAS mutated	2,15	0,90	5,16	0,09	3,5				

Firths P Cox

ALL MODELS ARE CATEGORICAL									
Univariable									
n= 82, number of events = 33									
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			
VAR0	Female gender	2,10	1,10	4,20	0,03	5,1 **	2,1	1,1	4,2 0,03
VAR1	Age > 55 years	0,70	0,30	1,30	0,23	2,1	0,7	0,3	1,3 0,23
VAR2	Oslo center	1,30	0,50	4,20	0,59	0,8	1,3	0,5	4,2 0,59
VAR3	Living donor	1,65	0,33	5,28	0,49	1,0	1,7	0,3	5,3 0,49
VAR5	Previous liver therapy	0,41	0,13	1,00	0,05	4,3 **	0,4	0,1	1,0 0,05
VAR6	BMI > 25 Kg/m2	0,90	0,50	1,90	0,79	0,3	0,9	0,5	1,9 0,79
VAR7	pN2	2,10	1,00	4,20	0,04	4,6 **	2,1	1,0	4,2 0,04
VAR8	Right location CRC	5,60	2,60	11,70	0,000	>10 **	5,6	2,6	11,7 0,000
VAR9	Time ≤ 24 months	1,80	0,90	4,00	0,11	3,2 *	1,8	0,9	4,0 0,11
VAR10	Progressive Disease	2,00	0,90	4,10	0,09	3,5 **	2,0	0,9	4,1 0,09
VAR11	Largest diameter > 5.5 cm	2,50	1,20	4,90	0,01	6,6 **	2,5	1,2	4,9 0,01
VAR12	Number of nodules > 10	1,30	0,60	2,50	0,49	1,0	1,3	0,6	2,5 0,49
VAR13	CEA > 80 µg/L	4,20	2,00	8,50	0,000	>10 **	4,2	2,0	8,5 0,000
VAR14	KRAS mutated	2,40	1,20	4,70	0,02	5,6 **	2,4	1,2	4,7 0,02
Multivariable all									
Likelihood ratio test=54.5495 on 14 df, p=1.034452e-06, n=82									
Wald test = 44.67514 on 14 df, p = 4.605252e-05									
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			
VAR0	Female gender	4,53	1,91	11,24	0,001	10,7			
VAR1	Age > 55 years	1,27	0,55	3,07	0,58	0,8			
VAR2	Oslo center	0,28	0,06	1,73	0,15	2,7			
VAR3	Living donor	0,84	0,10	6,62	0,87	0,2			
VAR5	Previous liver therapy	0,26	0,06	1,00	0,05	4,3			
VAR6	BMI > 25 Kg/m2	2,32	0,94	6,00	0,07	3,9			
VAR7	pN2	2,32	0,91	5,78	0,08	3,7			
VAR8	Right location CRC	3,38	1,17	9,13	0,03	5,3			
VAR9	Time ≤ 24 months	1,35	0,46	4,14	0,58	0,8			
VAR10	Progressive Disease	0,84	0,23	2,72	0,77	0,4			
VAR11	Largest diameter > 5.5 cm	4,03	1,38	12,33	0,01	6,5			
VAR12	Number of nodules > 10	2,35	0,97	5,75	0,06	4,1			
VAR13	CEA > 80 µg/L	3,20	1,15	9,04	0,03	5,2			
VAR14	KRAS mutated	2,68	0,98	7,33	0,05	4,2			

Multivariable p≤0.10									
Likelihood ratio test=48.53945 on 8 df, p=7.789893e-08, n=82									
Wald test = 45.3525 on 8 df, p = 3.155011e-07									
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			
VAR0	Female gender	3,76	1,69	8,71	0,001	9,7			
VAR1	Age > 55 years								
VAR2	Oslo center								
VAR3	Living donor								
VAR5	Previous liver therapy	0,35	0,10	1,01	0,05	4,2			
VAR6	BMI > 25 Kg/m2								
VAR7	pN2	1,76	0,75	4,06	0,19	2,4			
VAR8	Right location CRC	2,83	1,07	6,87	0,04	4,7			
VAR9	Time ≤ 24 months								
VAR10	Progressive Disease	0,74	0,22	2,10	0,59	0,8			
VAR11	Largest diameter > 5.5 cm	2,56	1,04	6,33	0,04	4,6			
VAR12	Number of nodules > 10								
VAR13	CEA > 80 µg/L	4,24	1,55	11,51	0,005	7,6			
VAR14	KRAS mutated	2,03	0,82	4,94	0,13	3,0			
Multivariable p≤0.20									
Likelihood ratio test=48.36055 on 9 df, p=2.186827e-07, n=82									
Wald test = 45.17005 on 9 df, p = 8.581862e-07									
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p	Null s			
VAR0	Female gender	3,77	1,65	9,06	0,002	9,2			
VAR1	Age > 55 years								
VAR2	Oslo center								
VAR3	Living donor								
VAR5	Previous liver therapy	0,34	0,08	1,21	0,10	3,4			
VAR6	BMI > 25 Kg/m2								
VAR7	pN2	1,76	0,75	4,04	0,19	2,4			
VAR8	Right location CRC	2,82	1,07	6,84	0,04	4,8			
VAR9	Time ≤ 24 months	0,93	0,35	2,63	0,89	0,2			
VAR10	Progressive Disease	0,75	0,21	2,28	0,63	0,7			
VAR11	Largest diameter > 5.5 cm	2,56	1,04	6,40	0,04	4,6			
VAR12	Number of nodules > 10								
VAR13	CEA > 80 µg/L	4,21	1,55	11,36	0,01	7,6			
VAR14	KRAS mutated	2,02	0,80	4,95	0,14	2,9			

LASSO Cox

COX PH (original)		HR	95-	95+	null p	null s	COX WEIGHTED	Variable	HR	95% CI - Lower	95% CI - Upper	P-value
VAR0	Female gender	4.09	1.82	9.19	0.001	10.6	VAR0	Female gender	4.21	1.62	10.98	0.003
VAR1	Age > 55 years						VAR1	Age > 55 years				
VAR2	Oslo center						VAR2	Oslo center				
VAR3	Living donor						VAR3	Living donor				
VAR5	Previous liver therapy	0.33	0.10	1.09	0.07	3.9	VAR5	Previous liver therapy	0.32	0.10	0.96	0.04
VAR6	BMI > 25 Kg/m2						VAR6	BMI > 25 Kg/m2				
VAR7	pN2	1.97	0.83	4.69	0.13	3.0	VAR7	pN2	1.85	0.82	4.21	0.14
VAR8	Right location CRC	3.01	1.11	8.14	0.03	5.0	VAR8	Right location CRC	2.87	1.13	7.27	0.03
VAR9	Time ≤ 24 months						VAR9	Time ≤ 24 months				
VAR10	Progressive Disease						VAR10	Progressive Disease				
VAR11	Largest diameter > 5.5 cm	2.47	1.09	5.62	0.03	5.0	VAR11	Largest diameter > 5.5 cm	2.70	1.25	5.83	0.01
VAR12	Number of nodules > 10	1.74	0.80	3.78	0.16	2.6	VAR12	Number of nodules > 10	1.69	0.87	3.29	0.12
VAR13	CEA > 80 µg/L	3.57	1.29	9.85	0.01	6.1	VAR13	CEA > 80 µg/L	3.83	1.37	10.71	0.01
VAR14	KRAS mutated	2.13	0.83	5.46	0.12	3.1	VAR14	KRAS mutated	2.20	0.96	5.05	0.06
Concordance= 0.836 (se = 0.034)												
Likelihood ratio test= 49.64 on 8 df, p=5e-08												
Wald test = 48.21 on 8 df, p=9e-08												
Score (logrank) test = 70.42 on 8 df, p=4e-12												
COX FIRTH'S PEN	Variable	HR	95% CI - Lower	95% CI - Upper	P-value							
VAR0	Female gender	3.84	1.75	8.59	0.0008							
VAR1	Age > 55 years											
VAR2	Oslo center											
VAR3	Living donor											
VAR5	Previous liver therapy	0.36	0.10	1.05	0.06							
VAR6	BMI > 25 Kg/m2											
VAR7	pN2	1.94	0.81	4.49	0.13							
VAR8	Right location CRC	3.05	1.09	7.72	0.03							
VAR9	Time ≤ 24 months											
VAR10	Progressive Disease											
VAR11	Largest diameter > 5.5 cm	2.41	1.08	5.40	0.03							
VAR12	Number of nodules > 10	1.71	0.79	3.63	0.17							
VAR13	CEA > 80 µg/L	3.46	1.26	9.29	0.02							
VAR14	KRAS mutated	2.05	0.80	5.12	0.13							

pN1

Proportional hazards Cox model with pN1 (Cat)												
Multivariable												
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p							
var0	Female gender		5,62	2,17	14,58	0,000	Concordance= 0.827 (se = 0.042)					
var1	Age > 55 years		1,30	0,52	3,28	0,57	Likelihood ratio test= 52.74 on 14 df, p=2e-06					
var2	Oslo center		0,30	0,05	1,85	0,19	Wald test = 46.92 on 14 df, p=2e-05					
var3	Living donor		1,01	0,12	8,70	1,00	Score (logrank) test = 72.7 on 14 df, p=6e-10					
var5	Previous liver therapy		0,16	0,04	0,70	0,01						
var6	BMI > 25 Kg/m2		2,09	0,81	5,38	0,13						
var7	pN1		0,70	0,27	1,81	0,46	null p univariable = 0.77					
var8	Right location CRC		3,41	1,17	9,93	0,02						
var9	Time ≤ 24 months		1,31	0,43	4,02	0,64						
var10	Progressive Disease		0,97	0,26	3,60	0,96						
var11	Largest diameter > 5.5 cm		3,41	1,01	11,45	0,05						
var12	Number of nodules > 10		2,20	0,86	5,59	0,10						
var13	CEA > 80 µg/L		5,00	1,82	13,76	0,002						
var14	KRAS mutated		2,18	0,84	5,67	0,11						
Firth's penalized Cox model with pN1 (Cat)												
Multivariable												
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p							
var0	Female gender		4,99	2,04	12,78	0,000	Likelihood ratio test=51.87138 on 14 df, p=2.956541e-06, n=82					
var1	Age > 55 years		1,27	0,53	3,18	0,60	Wald test = 43.24707 on 14 df, p = 7.821396e-05					
var2	Oslo center		0,28	0,06	1,80	0,16						
var3	Living donor		1,06	0,14	7,97	0,95						
var5	Previous liver therapy		0,19	0,04	0,73	0,02						
var6	BMI > 25 Kg/m2		2,01	0,81	5,10	0,13						
var7	pN1		0,73	0,28	1,82	0,50	null p univariable = 0.77					
var8	Right location CRC		3,36	1,17	9,17	0,03						
var9	Time ≤ 24 months		1,29	0,45	3,96	0,64						
var10	Progressive Disease		1,00	0,27	3,30	1,00						
var11	Largest diameter > 5.5 cm		3,15	1,01	10,43	0,05						
var12	Number of nodules > 10		2,08	0,83	5,14	0,12						
var13	CEA > 80 µg/L		4,52	1,71	12,01	0,003						
var14	KRAS mutated		2,07	0,81	5,14	0,13						

CoxConCat

COX MODELS FOR CONTINUOUS AND CATEGORICAL VARIABLES												
Proportional hazards Cox model												
Variable	Multivariable VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	5.77	2.18	15.23	0.000							
var1	Age	1.02	0.97	1.08	0.38			1.38	0.68	2.83	46.9	60.3
var2 (cat.)	Oslo center	0.52	0.09	2.98	0.47							
var3 (cat.)	Living donor	1.37	0.16	12.02	0.78							
var5 (cat.)	Previous liver therapy	0.15	0.02	0.97	0.05							
var6 (cat.)	BMI	1.58	0.79	3.17	0.20			1.58	0.78	3.20	4.76	5.77
var7 (cat.)	pN2	2.94	1.17	7.38	0.02							
var8 (cat.)	Right location CRC	4.96	1.56	15.83	0.007							
var9 (cat.)	Time Idt.	1.22	0.89	1.68	0.21			1.82	0.71	4.67	3.73	6.71
var10 (cat.)	Progressive Disease	1.28	0.38	4.28	0.69							
var11	Diameter	1.20	1.02	1.42	0.03			2.94	1.11	7.82	3.00	8.81
var12 (cat.)	Number of nodules	1.39	1.10	1.74	0.005			2.04	1.24	3.35	2.50	4.69
var13 (cat.)	CEA	1.01	0.98	1.04	0.64			1.01	0.96	1.07	0.70	2.44
var14 (cat.)	KRAS mutated	2.62	1.02	6.75	0.05							
						Concordance= 0.847 (se = 0.031)						
						Likelihood ratio test= 52.05 on 14 df. p=3e-06						
						Wald test = 45.32 on 14 df. p=4e-05						
						Score (logrank) test = 69.76 on 14 df. p=2e-09						
Variable	Multivariable 2 VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	7.70	2.74	21.62	0.000							
var1	Age	1.03	0.97	1.09	0.33			1.45	0.69	3.05	46.9	60.3
var2 (cat.)	Oslo center	0.37	0.07	2.07	0.26							
var3 (cat.)	Living donor	1.34	0.16	11.38	0.79							
var5 (cat.)	Previous liver therapy	0.10	0.02	0.60	0.01							
var6 (cat.)	BMI	1.63	0.83	3.19	0.16			1.63	0.83	3.22	4.76	5.77
var7 (cat.)	pN2	2.35	0.91	6.05	0.08							
var8 (cat.)	Right location CRC	4.59	1.45	14.56	0.01							
var9 (cat.)	Time Idt.	1.23	0.90	1.70	0.20			1.87	0.73	4.83	3.73	6.71
var10 (cat.)	Progressive Disease	1.25	0.36	4.42	0.72							
var11	Diameter	1.16	0.98	1.37	0.09			2.36	0.88	6.33	3.00	8.81
var12 (cat.)	Number of nodules	1.38	1.09	1.74	0.008			2.02	1.21	3.38	2.50	4.69
var13 (cat.)	CEA	4.19	1.43	12.27	0.01			12.12	1.87	78.46	0.70	2.44
var14 (cat.)	KRAS mutated	2.12	0.81	5.57	0.13							
						Concordance= 0.858 (se = 0.032)						
						Likelihood ratio test= 58.46 on 14 df. p=2e-07						
						Wald test = 47.69 on 14 df. p=1e-05						
						Score (logrank) test = 78.79 on 14 df. p=5e-11						
Variable	Univariable 2 VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	2.09	1.05	4.18	0.04	**						
var1	Age	0.99	0.95	1.03	0.46			0.82	0.48	1.39	46.9	60.3
var2 (cat.)	Oslo center	1.45	0.50	4.21	0.50							
var3 (cat.)	Living donor	1.36	0.31	5.92	0.68							
var5 (cat.)	Previous liver therapy	0.37	0.13	1.05	0.06	**						
var6 (cat.)	BMI	0.94	0.53	1.67	0.84	**		0.94	0.53	1.68	4.76	5.77
var7 (cat.)	pN2	2.11	1.05	4.25	0.04	**						
var8 (cat.)	Right location CRC	5.49	2.56	11.79	0.000	**						
var9 (cat.)	Time Idt.	0.79	0.62	1.01	0.06	**		0.50	0.24	1.04	3.73	6.71
var10 (cat.)	Progressive Disease	1.92	0.89	4.17	0.10	**						
var11	Diameter	1.14	1.03	1.26	0.01	**		2.11	1.17	3.78	3.00	8.81
var12 (cat.)	Number of nodules	1.19	0.99	1.43	0.06	**		1.47	0.98	2.20	2.50	4.69
var13 (cat.)	CEA	4.09	1.95	8.59	0.000	**		11.81	3.20	42.20	0.70	2.44
var14 (cat.)	KRAS mutated	2.33	1.15	4.72	0.02	**						
Variable	Multivariable p=0.20 VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	5.55	2.18	14.08	0.000							
var1	Age							0.00	0.00	0.00	46.9	60.3
var2 (cat.)	Oslo center											
var3 (cat.)	Living donor											
var5 (cat.)	Previous liver therapy											
var6 (cat.)	BMI							0.00	0.00	0.00	4.76	5.77
var7 (cat.)	pN2	0.19	0.04	0.92	0.04							
var8 (cat.)	Right location CRC	3.81	1.32	11.00	0.01							
var9 (cat.)	Time Idt.	1.19	0.87	1.63	0.27			1.69	0.66	4.29	3.73	6.71
var10 (cat.)	Progressive Disease	0.89	0.27	2.92	0.85							
var11	Diameter	1.15	0.98	1.35	0.08			2.26	0.91	5.64	3.00	8.81
var12 (cat.)	Number of nodules	1.29	1.02	1.62	0.03			1.74	1.05	2.90	2.50	4.69
var13 (cat.)	CEA	3.45	1.22	9.76	0.02			8.64	1.42	52.71	0.70	2.44
var14 (cat.)	KRAS mutated	1.92	0.74	4.98	0.18							

Weighted Cox model												
Variable	Multivariable VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	6.31	1.95	20.42	0.002							
var1	Age	1.03	0.98	1.08	0.27			1.43	0.76	2.68	46.9	60.3
var2 (cat.)	Oslo center	0.56	0.10	3.03	0.50							
var3 (cat.)	Living donor	1.29	0.15	11.44	0.82							
var5 (cat.)	Previous liver therapy	0.13	0.02	0.82	0.03							
var6 (scat.)	BMI	1.69	0.82	3.49	0.15			1.70	0.82	3.53	4.76	5.77
var7 (cat.)	pN2	2.80	1.04	7.57	0.04							
var8 (cat.)	Right location CRC	4.61	1.48	14.33	0.008							
var9 (scat.)	Time Idi	1.24	0.92	1.68	0.16			1.90	0.77	4.66	3.73	6.71
var10 (cat.)	Progressive Disease	1.13	0.39	3.30	0.82							
var11	Diameter	1.24	1.03	1.49	0.03			3.44	1.16	10.15	3.00	8.81
var12 (scat.)	Number of nodules	1.36	1.17	1.58	0.000			1.97	1.42	2.74	2.50	4.69
var13 (cat.)	CEA	1.01	0.98	1.04	0.42			1.02	0.97	1.07	0.70	2.44
var14 (cat.)	KRAS mutated	2.62	1.11	6.18	0.03							
Weighted Cox model												
Variable	Multivariable 2 VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	8.47	2.13	33.70	0.002							
var1	Age	1.03	0.98	1.08	0.23			1.49	0.78	2.85	46.9	60.3
var2 (cat.)	Oslo center	0.38	0.08	1.84	0.23							
var3 (cat.)	Living donor	1.27	0.18	8.87	0.81							
var5 (cat.)	Previous liver therapy	0.09	0.02	0.53	0.008							
var6 (scat.)	BMI	1.71	0.90	3.23	0.10			1.71	0.90	3.26	4.76	5.77
var7 (cat.)	pN2	2.26	0.86	5.96	0.10							
var8 (cat.)	Right location CRC	4.39	1.58	12.22	0.005							
var9 (scat.)	Time Idi	1.25	0.93	1.67	0.14			1.92	0.81	4.58	3.73	6.71
var10 (cat.)	Progressive Disease	1.15	0.42	3.21	0.78							
var11	Diameter	1.19	1.01	1.40	0.04			2.73	1.04	7.18	3.00	8.81
var12 (scat.)	Number of nodules	1.37	1.17	1.60	0.000			1.98	1.41	2.79	2.50	4.69
var13 (cat.)	CEA	4.44	1.44	13.67	0.009							
var14 (cat.)	KRAS mutated	2.20	0.94	5.13	0.07							
Wald Chi-square = 65.68237 on 14 df p = 1.155411e-08 n = 82												
Univariable 2												
Variable	VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	2.04	1.02	4.07	0.04	**						
var1	Age	0.99	0.95	1.03	0.50			0.87	0.50	1.49	46.9	60.3
var2 (cat.)	Oslo center	1.48	0.50	4.43	0.48							
var3 (cat.)	Living donor	1.35	0.30	6.06	0.70							
var5 (cat.)	Previous liver therapy	0.38	0.14	1.07	0.07	**						
var6 (scat.)	BMI	0.95	0.55	1.65	0.86			0.95	0.55	1.66	4.76	5.77
var7 (cat.)	pN2	1.97	0.95	4.09	0.07	**						
var8 (cat.)	Right location CRC	5.39	2.21	13.15	0.000	**						
var9 (scat.)	Time Idi	0.81	0.64	1.02	0.07	**		0.53	0.26	1.06	3.73	6.71
var10 (cat.)	Progressive Disease	1.86	0.76	4.53	0.18	*						
var11	Diameter	1.14	1.05	1.25	0.003	**		2.14	1.33	3.66	3.00	8.81
var12 (scat.)	Number of nodules	1.19	1.03	1.38	0.02	**		1.46	1.07	2.02	2.50	4.69
var13 (cat.)	CEA	4.19	2.16	8.12	0.000	**						
var14 (cat.)	KRAS mutated	2.29	1.10	4.78	0.03	**						
Multivariable p=0.20												
Variable	VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	5.97	1.96	18.17	0.002							
var1	Age											
var2 (cat.)	Oslo center											
var3 (cat.)	Living donor											
var5 (cat.)	Previous liver therapy	0.17	0.03	0.97	0.05							
var6 (scat.)	BMI											
var7 (cat.)	pN2	2.12	0.86	5.22	0.10							
var8 (cat.)	Right location CRC	3.57	1.40	9.09	0.008							
var9 (scat.)	Time Idi	1.21	0.88	1.66	0.25			1.76	0.68	4.53	3.73	6.71
var10 (cat.)	Progressive Disease	0.84	0.30	2.36	0.74							
var11	Diameter	1.17	1.01	1.36	0.04			2.49	1.06	5.97	3.00	8.81
var12 (scat.)	Number of nodules	1.27	1.08	1.50	0.003			1.69	1.18	2.43	2.50	4.69
var13 (cat.)	CEA	3.68	1.34	10.05	0.01			9.65	1.66	55.43	0.70	2.44
var14 (cat.)	KRAS mutated	2.00	0.89	4.48	0.09							

By Sex

ALL MODELS ARE CATEGORICAL AND UNVARIABLE						
Firth's penalized Cox						
Male	VARIABLE	HR	95-	95+	Null p	Null s
VAR1	Age > 55 years	0,80	0,30	2,20	0,72	0,5
VAR2	Oslo center	2,80	0,60	25,60	0,19	2,4
VAR3	Living donor	-	-	-	-	-
VAR5	Previous liver therapy	0,35	0,04	1,43	0,16	2,6
VAR6	BMI > 25 Kg/m2	1,10	0,40	3,20	0,91	0,1
VAR7	pN2	3,00	1,10	7,90	0,03	5
VAR8	Right location CRC	7,40	2,50	21,20	0,000	12
VAR9	Time ≤ 24 months	1,20	0,40	3,30	0,75	0,4
VAR10	Progressive Disease	1,10	0,30	3,40	0,84	0,2
VAR11	Largest diameter > 5.5 cm	1,50	0,50	4,20	0,41	1,3
VAR12	Number of nodules > 10	1,20	0,40	3,10	0,77	0,4
VAR13	CEA > 80 µg/L	4,00	1,40	11,00	0,01	6,3
VAR14	KRAS mutated	1,70	0,60	4,60	0,32	1,7
Female	VARIABLE	HR	95-	95+	Null p	Null s
VAR1	Age > 55 years	0,40	0,10	1,10	0,07	3,9
VAR2	Oslo center	0,40	0,10	1,50	0,15	2,8
VAR3	Living donor	2,47	0,46	9,09	0,25	2,0
VAR5	Previous liver therapy	0,42	0,11	1,22	0,11	3,1
VAR6	BMI > 25 Kg/m2	0,80	0,30	2,10	0,68	0,6
VAR7	pN2	1,60	0,50	4,10	0,41	1,3
VAR8	Right location CRC	5,20	1,60	15,70	0,008	7,0
VAR9	Time ≤ 24 months	2,30	0,80	9,00	0,13	3,0
VAR10	Progressive Disease	4,20	1,40	12,40	0,01	6,2
VAR11	Largest diameter > 5.5 cm	8,10	2,60	29,70	0,000	12
VAR12	Number of nodules > 10	1,60	0,60	4,10	0,35	1,5
VAR13	CEA > 80 µg/L	13,50	3,80	47,40	0,000	13
VAR14	KRAS mutated	4,10	1,50	10,70	0,007	7,1
Weighted Cox						
Males	VARIABLE	HR	95-	95+	Null p	Null s
VAR1	Age > 55 years	0,80	0,30	2,30	0,79	0,3
VAR2	Oslo center	4,60	0,60	34,50	0,14	2,8
VAR3	Living donor	-	-	-	-	-
VAR5	Previous liver therapy	0,38	0,07	1,99	0,25	2,0
VAR6	BMI > 25 Kg/m2	1,20	0,40	3,60	0,71	0,5
VAR7	pN2	2,30	0,80	6,70	0,14	2,8
VAR8	Right location CRC	6,60	1,90	23,90	0,004	8,1
VAR9	Time ≤ 24 months	0,90	0,40	2,40	0,90	0,2
VAR10	Progressive Disease	0,90	0,20	3,80	0,84	0,3
VAR11	Largest diameter > 5.5 cm	1,80	0,60	4,90	0,28	1,8
VAR12	Number of nodules > 10	1,30	0,50	3,50	0,63	0,7
VAR13	CEA > 80 µg/L	4,80	2,10	11,10	0,000	12
VAR14	KRAS mutated	1,40	0,50	4,50	0,52	0,9
Females	VARIABLE	HR	95-	95+	Null p	Null s
VAR1	Age > 55 years	0,40	0,10	0,90	0,03	5,1
VAR2	Oslo center	0,40	0,10	1,50	0,16	2,6
VAR3	Living donor	2,14	0,44	10,30	0,34	2
VAR5	Previous liver therapy	0,41	0,11	1,54	0,19	2
VAR6	BMI > 25 Kg/m2	0,80	0,30	2,10	0,69	0,5
VAR7	pN2	0,90	0,30	2,80	0,80	0,3
VAR8	Right location CRC	5,10	1,70	14,90	0,000	8,4
VAR9	Time ≤ 24 months	2,30	0,60	8,90	0,22	2,2
VAR10	Progressive Disease	4,20	1,40	12,20	0,01	6,8
VAR11	Largest diameter > 5.5 cm	9,30	2,90	29,60	0,000	13
VAR12	Number of nodules > 10	1,60	0,60	4,40	0,36	1,5
VAR13	CEA > 80 µg/L	13,80	3,70	50,80	0,000	14
VAR14	KRAS mutated	4,20	1,60	10,90	0,004	8

SexConCat

ALL MODELS ARE UNVARIABLE FOR CONTINUOUS AND CATEGORICAL VARIABLES

Firth's penalized Cox

Male	VARIABLE	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+		AVG -	AVG +
var1	Age > 55 years	0.99	0.94	1.05	0.81			0.91	0.42	2.02		46.9	60.3
var2 (cat)	Oslo center	2.76	0.65	25.61	0.19								
var3 (cat)	Living donor	-	-	-	-								
var5 (cat)	Previous liver therapy	0.35	0.04	1.43	0.16								
var6 (sqrt)	BMI > 25 Kg/m2	1.00	0.15	1.69	1.00			1.00	0.14	1.70		4.76	5.77
var7 (cat)	pN2	2.97	1.12	7.86	0.03								
var8 (cat)	Right location CRC	7.40	2.46	21.24	0.001								
var9 (sqrt)	Time ≤ 24 months	0.90	0.60	1.25	0.56			0.73	0.22	1.95		3.73	6.71
var10 (cat)	Progressive Disease	1.13	0.29	3.35	0.84								
var11	Largest diameter > 5.5 cm	1.09	0.92	1.26	0.31			1.63	0.61	3.87		3.00	8.81
var12 (sqrt)	Number of nodules > 10	1.21	0.91	1.51	0.17			1.52	0.81	2.45		2.50	4.69
var13 (cat)	CEA > 80 µg/L	4.02	1.38	11.03	0.01								
var14 (cat)	KRAS mutated	1.71	0.58	4.62	0.32								

Female	VARIABLE	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+		AVG -	AVG +
var1	Age > 55 years	0.97	0.92	1.02	0.24			0.64	0.33	1.37		46.9	60.3
var2 (cat)	Oslo center	0.35	0.10	1.51	0.15								
var3 (cat)	Living donor	2.47	0.46	9.09	0.25								
var5 (cat)	Previous liver therapy	0.42	0.11	1.22	0.11								
var6 (sqrt)	BMI > 25 Kg/m2	1.38	0.66	2.40	0.35			1.39	0.66	2.42		4.76	5.77
var7 (cat)	pN2	1.55	0.52	4.10	0.41								
var8 (cat)	Right location CRC	5.16	1.59	15.74	0.01								
var9 (sqrt)	Time ≤ 24 months	0.80	0.57	1.03	0.09			0.52	0.19	1.08		3.73	6.71
var10 (cat)	Progressive Disease	4.16	1.37	12.39	0.01								
var11	Largest diameter > 5.5 cm	1.30	1.12	1.52	0.001			4.56	1.93	11.26		3.00	8.81
var12 (sqrt)	Number of nodules > 10	1.35	1.00	1.73	0.05			1.93	0.99	3.34		2.50	4.69
var13 (cat)	CEA > 80 µg/L	13.55	3.85	47.44	0.000								
var14 (cat)	KRAS mutated	4.07	1.49	10.89	0.007								

Weighted Cox

Male	VARIABLE	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+		AVG -	AVG +
var1	Age > 55 years	0.99	0.94	1.05	0.83			0.92	0.42	1.99		46.9	60.3
var2 (cat)	Oslo center	4.60	0.61	34.49	0.14								
var3 (cat)	Living donor	-	-	-	-								
var5 (cat)	Previous liver therapy	0.38	0.07	1.99	0.25								
var6 (sqrt)	BMI > 25 Kg/m2	0.64	0.18	2.23	0.48			0.64	0.18	2.25		4.76	5.77
var7 (cat)	pN2	2.43	0.85	6.93	0.10								
var8 (cat)	Right location CRC	6.66	1.86	23.89	0.004								
var9 (sqrt)	Time ≤ 24 months	0.95	0.70	1.30	0.77			0.87	0.34	2.20		3.73	6.71
var10 (cat)	Progressive Disease	0.86	0.20	3.77	0.84								
var11	Largest diameter > 5.5 cm	1.11	0.99	1.24	0.07			1.82	0.95	3.48		3.00	8.81
var12 (sqrt)	Number of nodules > 10	1.19	0.98	1.45	0.08			1.47	0.96	2.26		2.50	4.69
var13 (cat)	CEA > 80 µg/L	4.79	2.06	11.13	0.000								
var14 (cat)	KRAS mutated	1.45	0.46	4.53	0.52								

Female	VARIABLE	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+		AVG -	AVG +
var1	Age > 55 years	0.97	0.91	1.02	0.25			0.63	0.29	1.37		46.9	60.3
var2 (cat)	Oslo center	0.38	0.10	1.49	0.16								
var3 (cat)	Living donor	2.14	0.44	10.30	0.34								
var5 (cat)	Previous liver therapy	0.41	0.11	1.54	0.19								
var6 (sqrt)	BMI > 25 Kg/m2	1.31	0.62	2.78	0.48			1.32	0.62	2.81		4.76	5.77
var7 (cat)	pN2	1.49	0.50	4.40	0.47								
var8 (cat)	Right location CRC	5.07	1.73	14.86	0.003								
var9 (sqrt)	Time ≤ 24 months	0.79	0.58	1.08	0.13			0.49	0.19	1.24		3.73	6.71
var10 (cat)	Progressive Disease	4.19	1.44	12.19	0.009								
var11	Largest diameter > 5.5 cm	1.31	1.17	1.47	0.000			4.74	2.43	9.27		3.00	8.81
var12 (sqrt)	Number of nodules > 10	1.32	1.09	1.61	0.005			1.84	1.20	2.83		2.50	4.69
var13 (cat)	CEA > 80 µg/L	13.75	3.72	50.81	0.000								
var14 (cat)	KRAS mutated	4.15	1.59	10.85	0.004								

C.Risk Liver

ALL MODELS ARE CATEGORICAL										
Univariable										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p					
var0	Female gender	1,81	0,93	3,54	0,08	*				
var1	Age > 55 years	1,15	0,58	2,24	0,69					
var2	Oslo center	1,51	0,69	3,31	0,30					
var3	Living donor	0,79	0,26	2,41	0,67					
var5	Previous liver therapy	0,98	0,46	2,10	0,96					
var6	BMI > 25 Kg/m2	1,04	0,52	2,10	0,91					
var7	pN2	2,99	1,45	6,16	0,003	*				
var8	Right location CRC	1,77	0,83	3,80	0,14	*				
var9	Time ≤ 24 months	1,59	0,76	3,31	0,22					
var10	Progressive Disease	1,71	0,80	3,67	0,17	*				
var11	Largest diameter > 5.5 cm	0,78	0,37	1,65	0,51					
var12	Number of nodules > 10	1,06	0,53	2,12	0,86					
var13	CEA > 80 µg/L	1,00	0,30	3,26	0,99					
var14	KRAS mutated	1,09	0,40	2,95	0,86					
Multivariable										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		Num. cases = 82			
var0	Female gender	2,07	0,86	5,01	0,11		Pseudo Log-likelihood = -124			
var1	Age > 55 years	1,31	0,59	2,93	0,51		Pseudo likelihood ratio test = 21.6 on 14 df,			
var2	Oslo center	0,84	0,26	2,73	0,77		Competing Risks Regression			
var3	Living donor	0,73	0,12	4,65	0,74					
var5	Previous liver therapy	2,10	0,31	14,40	0,45					
var6	BMI > 25 Kg/m2	0,69	0,33	1,45	0,33					
var7	pN2	4,60	1,49	14,18	0,008					
var8	Right location CRC	2,41	0,93	6,24	0,07					
var9	Time ≤ 24 months	1,29	0,22	7,68	0,78					
var10	Progressive Disease	2,23	0,79	6,30	0,13					
var11	Largest diameter > 5.5 cm	0,54	0,21	1,38	0,20					
var12	Number of nodules > 10	2,56	0,91	7,18	0,08					
var13	CEA > 80 µg/L	1,00	0,30	3,26	0,99					
var14	KRAS mutated	1,09	0,40	2,95	0,86					
Multivariable null p≤0.20										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		Num. cases = 82			
var0	Female gender	1,81	0,90	3,66	0,10		Pseudo Log-likelihood = -127			
var1	Age > 55 years						Pseudo likelihood ratio test = 14.4 on 4 df,			
var2	Oslo center						Competing Risks Regression			
var3	Living donor									
var5	Previous liver therapy									
var6	BMI > 25 Kg/m2									
var7	pN2	2,93	1,44	5,99	0,003					
var8	Right location CRC	1,78	0,87	3,65	0,11					
var9	Time ≤ 24 months									
var10	Progressive Disease	1,50	0,67	3,37	0,33					
var11	Largest diameter > 5.5 cm									
var12	Number of nodules > 10									
var13	CEA > 80 µg/L									
var14	KRAS mutated									
Hierarchical 1										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		Num. cases = 82			
var0	Female gender						Pseudo Log-likelihood = -127			
var1	Age > 55 years						Pseudo likelihood ratio test = 14.8 on 7 df,			
var2	Oslo center						Competing Risks Regression			
var3	Living donor									
var5	Previous liver therapy									
var6	BMI > 25 Kg/m2									
var7	pN2	3,42	1,44	8,12	0,005					
var8	Right location CRC	2,24	0,95	5,31	0,07					
var9	Time ≤ 24 months									
var10	Progressive Disease	1,76	0,75	4,10	0,19					
var11	Largest diameter > 5.5 cm	0,66	0,30	1,45	0,30					
var12	Number of nodules > 10	1,90	0,80	4,52	0,15					
var13	CEA > 80 µg/L	0,86	0,32	2,30	0,76					
var14	KRAS mutated	1,05	0,41	2,69	0,92					

C.Risk Lung

ALL MODELS ARE CATEGORICAL

Univariable							
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		
var0	Female gender	0,27	0,09	0,78	0,02	**	
var1	Age > 55 years	0,78	0,35	1,75	0,54		
var2	Oslo center	1,68	0,63	4,48	0,30		
var3	Living donor	0,37	0,05	2,83	0,34		
var5	Previous liver therapy	0,88	0,33	2,33	0,79		
var6	BMI > 25 Kg/m2	1,13	0,50	2,58	0,77		
var7	pN2	0,67	0,26	1,73	0,40		
var8	Right location CRC	0,55	0,16	1,83	0,33		
var9	Time ≤ 24 months	0,74	0,33	1,68	0,47		
var10	Progressive Disease	1,45	0,58	3,61	0,42		
var11	Largest diameter > 5.5 cm	1,49	0,67	3,35	0,33		
var12	Number of nodules > 10	1,29	0,56	2,97	0,55		
var13	CEA > 80 µg/L	1,99	0,76	5,20	0,16	*	
var14	KRAS mutated	1,52	0,64	3,65	0,35		
Multivariable							
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		
var0	Female gender	0,16	0,03	0,75	0,02		Num. cases = 82
var1	Age > 55 years	0,53	0,18	1,51	0,23		Pseudo Log-likelihood = -83.9
var2	Oslo center	2,59	0,48	14,10	0,27		Pseudo likelihood ratio test = 22.8 on 14 df,
var3	Living donor	0,51	0,05	5,06	0,56		
var5	Previous liver therapy	1,60	0,33	7,77	0,56		
var6	BMI > 25 Kg/m2	0,83	0,28	2,45	0,74		
var7	pN2	0,55	0,18	1,71	0,30		
var8	Right location CRC	0,23	0,05	1,12	0,07		
var9	Time ≤ 24 months	0,93	0,31	2,82	0,90		
var10	Progressive Disease	0,83	0,16	4,28	0,82		
var11	Largest diameter > 5.5 cm	2,08	0,60	7,16	0,25		
var12	Number of nodules > 10	1,14	0,49	2,66	0,76		
var13	CEA > 80 µg/L	3,34	0,98	11,38	0,05		
var14	KRAS mutated	2,97	1,15	7,70	0,03		

Hierarchical 1							
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		
var0	Female gender						Num. cases = 82
var1	Age > 55 years						Pseudo Log-likelihood = -91
var2	Oslo center						Pseudo likelihood ratio test = 8.49 on 7 df,
var3	Living donor						
var5	Previous liver therapy						
var6	BMI > 25 Kg/m2						
var7	pN2	0,75	0,24	2,38	0,63		
var8	Right location CRC	0,20	0,02	1,70	0,14		
var9	Time ≤ 24 months						
var10	Progressive Disease	1,02	0,25	4,12	0,98		
var11	Largest diameter > 5.5 cm	1,58	0,51	4,87	0,42		
var12	Number of nodules > 10	1,25	0,50	3,12	0,63		
var13	CEA > 80 µg/L	2,53	0,62	10,38	0,20		
var14	KRAS mutated	2,87	0,97	8,53	0,06		
Hierarchical 2							
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		
var0	Female gender						Num. cases = 82
var1	Age > 55 years						Pseudo Log-likelihood = -89.5
var2	Oslo center						Pseudo likelihood ratio test = 11.7 on 10 df,
var3	Living donor	0,25	0,02	2,96	0,27		
var5	Previous liver therapy	0,78	0,21	2,91	0,71		
var6	BMI > 25 Kg/m2						
var7	pN2	0,67	0,19	2,34	0,53		
var8	Right location CRC	0,22	0,03	1,72	0,15		
var9	Time ≤ 24 months	0,64	0,20	2,04	0,45		
var10	Progressive Disease	0,83	0,12	5,82	0,85		
var11	Largest diameter > 5.5 cm	1,93	0,41	9,10	0,40		
var12	Number of nodules > 10	1,17	0,46	2,97	0,74		
var13	CEA > 80 µg/L	3,30	0,72	15,25	0,13		
var14	KRAS mutated	2,96	0,89	9,88	0,08		

CRConCatLiver

COMPETING RISK REGRESSION FOR CONTINUOUS AND CATEGORICAL VARIABLES											
Univariable											
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	1.81	0.93	3.54	0.08	**					
var1	Age	1.02	0.98	1.05	0.41		1.30	0.75	1.92	46.9	60.3
var2 (cat.)	Oslo center	1.51	0.69	3.31	0.30						
var3 (cat.)	Living donor	0.79	0.26	2.41	0.67						
var5 (cat.)	Previous liver therapy	0.98	0.46	2.10	0.96						
var6 (sqr)	BMI	1.09	0.83	1.42	0.54		1.09	0.83	1.42	4.76	5.77
var7 (cat.)	pN2	2.99	1.45	6.16	0.003	**					
var8 (cat.)	Right location CRC	1.77	0.83	3.80	0.14	*					
var9 (sqr)	Time ldt	0.83	0.67	1.02	0.07	**	0.57	0.31	1.06	3.73	6.71
var10 (cat.)	Progressive Disease	1.71	0.80	3.67	0.17	*					
var11	Diameter	1.00	0.90	1.12	0.96		1.00	0.53	1.93	3.00	8.81
var12 (sqr)	Number of nodules	1.12	0.95	1.32	0.17	*	1.28	0.90	1.84	2.50	4.69
var13 (cat.)	CEA > 80 µg/L	1.10	0.44	2.81	0.83						
var14 (cat.)	KRAS mutated	1.12	0.49	2.57	0.79						
Multivariable											
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	2.74	0.95	7.91	0.06						
var1	Age	1.04	0.99	1.10	0.10		1.74	0.90	3.59	46.9	60.3
var2 (cat.)	Oslo center	0.81	0.24	2.70	0.73						
var3 (cat.)	Living donor	0.48	0.07	3.36	0.46						
var5 (cat.)	Previous liver therapy	3.40	0.66	17.39	0.14						
var6 (sqr)	BMI	1.27	0.73	2.20	0.40		1.27	0.73	2.22	4.76	5.77
var7 (cat.)	pN2	3.92	1.37	11.21	0.01						
var8 (cat.)	Right location CRC	2.03	0.74	5.57	0.17						
var9 (sqr)	Time ldt	0.79	0.57	1.08	0.14		0.49	0.19	1.26	3.73	6.71
var10 (cat.)	Progressive Disease	1.95	0.67	5.67	0.22						
var11	Diameter	0.96	0.83	1.11	0.59		0.79	0.34	1.83	3.00	8.81
var12 (sqr)	Number of nodules	1.45	1.16	1.82	0.001		2.26	1.38	3.71	2.50	4.69
var13 (cat.)	CEA > 80 µg/L	1.01	0.38	2.69	0.99						
var14 (cat.)	KRAS mutated	1.09	0.41	2.93	0.86						
						Num. cases = 82 Pseudo Log-likelihood = -120 Pseudo likelihood ratio test = 28.1 on 14 df, Competing Risks Regression					
Multivariable 2 with ps0.20											
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	2.32	1.04	5.18	0.04						
var1	Age										
var2 (cat.)	Oslo center										
var3 (cat.)	Living donor										
var5 (cat.)	Previous liver therapy										
var6 (sqr)	BMI										
var7 (cat.)	pN2	3.20	1.40	7.33	0.01						
var8 (cat.)	Right location CRC	1.93	0.89	4.21	0.10						
var9 (sqr)	Time ldt	0.94	0.78	1.14	0.55		0.84	0.48	1.48	3.73	6.71
var10 (cat.)	Progressive Disease	1.68	0.75	3.74	0.21						
var11	Diameter										
var12 (sqr)	Number of nodules	1.34	1.10	1.62	0.003		1.88	1.24	2.88	2.50	4.69
var13 (cat.)	CEA > 80 µg/L										
var14 (cat.)	KRAS mutated										
						Num. cases = 82 Pseudo Log-likelihood = -124 Pseudo likelihood ratio test = 20.2 on 6 df,					
Hierarchical											
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	AVG -	AVG +
var0 (cat.)	Female gender	2.18	0.91	5.24	0.08						
var1	Age										
var2 (cat.)	Oslo center										
var3 (cat.)	Living donor	0.56	0.13	2.41	0.43						
var5 (cat.)	Previous liver therapy	4.01	0.99	16.27	0.05						
var6 (sqr)	BMI										
var7 (cat.)	pN2	3.65	1.48	8.98	0.005						
var8 (cat.)	Right location CRC	2.19	0.88	5.43	0.09						
var9 (sqr)	Time ldt	0.79	0.58	1.06	0.11		0.49	0.20	1.19	3.73	6.71
var10 (cat.)	Progressive Disease	1.74	0.69	4.42	0.24						
var11	Diameter	0.96	0.84	1.10	0.58						
var12 (sqr)	Number of nodules	1.43	1.17	1.75	0.001		2.18	1.40	3.41	2.50	4.69
var13 (cat.)	CEA > 80 µg/L	0.87	0.31	2.43	0.79						
var14 (cat.)	KRAS mutated	1.00	0.36	2.77	1.00						
						Num. cases = 82 Pseudo Log-likelihood = -122 Pseudo likelihood ratio test = 24.9 on 11 df,					
Notes: Hierarchical = category 1 + 2 + 3 + all variables of category 4 with null ps0.20 in the univariable analysis											

CRConCat Lung

COMPETING RISK REGRESSION FOR CONTINUOUS AND CATEGORICAL VARIABLES										
Univariable										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	
var0 (cat.)	Female gender	0,27	0,09	0,78	0,02 **					
var1	Age	0,99	0,94	1,04	0,69		0,87	0,46	1,69	46,9 60,3
var2 (cat.)	Oslo center	1,68	0,63	4,48	0,30					
var3 (cat.)	Living donor	0,37	0,05	2,83	0,34					
var5 (cat.)	Previous liver therapy	0,88	0,33	2,33	0,79					
var6 (sqr)	BMI	0,82	0,58	1,17	0,28		0,82	0,57	1,17	4,76 5,77
var7 (cat.)	pN2	0,67	0,26	1,73	0,40					
var8 (cat.)	Right location CRC	0,55	0,16	1,83	0,33					
var9 (sqr)	Time Idt	0,99	0,84	1,17	0,92		0,98	0,60	1,60	3,73 6,71
var10 (cat.)	Progressive Disease	1,45	0,58	3,61	0,42					
var11	Diameter	1,07	0,94	1,21	0,29		1,48	0,69	3,03	3,00 8,81
var12 (sqr)	Number of nodules	1,06	0,95	1,33	0,63		1,14	0,88	1,87	2,50 4,69
var13 (cat.)	CEA > 80 µg/L	1,99	0,50	5,20	0,16 *					
var14 (cat.)	KRAS mutated	1,52	0,66	3,65	0,35					
Multivariable										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat.)	Female gender	0,12	0,02	0,65	0,01					
var1	Age	0,95	0,90	1,01	0,11		0,52	0,24	1,14	46,9 60,3
var2 (cat.)	Oslo center	2,93	0,64	13,44	0,17					
var3 (cat.)	Living donor	0,70	0,11	4,58	0,71					
var5 (cat.)	Previous liver therapy	2,28	0,41	12,52	0,34					
var6 (sqr)	BMI	0,56	0,26	1,21	0,14		0,56	0,25	1,22	4,76 5,77
var7 (cat.)	pN2	0,58	0,20	1,68	0,31					
var8 (cat.)	Right location CRC	0,24	0,06	0,97	0,05					
var9 (sqr)	Time Idt	0,99	0,71	1,38	0,94		0,96	0,36	2,59	3,73 6,71
var10 (cat.)	Progressive Disease	0,80	0,18	3,51	0,76					
var11	Diameter	1,14	0,94	1,39	0,19		2,16	0,68	6,89	3,00 8,81
var12 (sqr)	Number of nodules	1,01	0,80	1,27	0,94		1,02	0,62	1,68	2,50 4,69
var13 (cat.)	CEA > 80 µg/L	2,98	0,85	10,55	0,09					
var14 (cat.)	KRAS mutated	3,28	1,28	8,37	0,01					
						Num. cases = 82				
						Pseudo Log-likelihood = -82.9				
						Pseudo likelihood ratio test = 24.8 on 14 df,				
Hierarchical										
CODED VARIABLE NAME (R)	VARIABLE NAME	SHR	95-	95+	Null p		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat.)	Female gender	0,17	0,03	0,89	0,04					
var1	Age									
var2 (cat.)	Oslo center									
var3 (cat.)	Living donor	0,31	0,04	2,64	0,28					
var5 (cat.)	Previous liver therapy	1,28	0,29	5,59	0,74					
var6 (sqr)	BMI									
var7 (cat.)	pN2	0,50	0,15	1,68	0,26					
var8 (cat.)	Right location CRC	0,26	0,05	1,20	0,08					
var9 (sqr)	Time Idt	0,96	0,68	1,35	0,80		0,88	0,32	2,42	3,73 6,71
var10 (cat.)	Progressive Disease	1,26	0,29	5,38	0,76					
var11	Diameter	1,12	0,92	1,37	0,25		1,29	0,84	2,00	2,50 4,69
var12 (sqr)	Number of nodules	1,03	0,80	1,32	0,83		1,06	0,62	1,83	2,50 4,69
var13 (cat.)	CEA > 80 µg/L	2,75	0,79	9,59	0,11					
var14 (cat.)	KRAS mutated	2,93	1,08	7,95	0,04					
						Num. cases = 82				
Notes: Hierarchical = category 1 + 2 + 3 + all variables of category 4 with null p≤0.20 in the univariable analysis						Pseudo Log-likelihood = -85.5				
						Pseudo likelihood ratio test = 19.6 on 11 df,				

CS Liver

CAUSE-SPECIFIC LIVER, CATEGORICAL					
Proportional hazards Cox					
Multivariable all					
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p
VAR0	Female gender	1.94	0.83	4.55	0.13
VAR1	Age > 55 years	1.46	0.60	3.53	0.40
VAR2	Oslo center	0.59	0.17	2.08	0.41
VAR3	Living donor	1.10	0.21	5.70	0.91
VAR5	Previous liver therapy	1.59	0.39	6.49	0.52
VAR6	BMI > 25 Kg/m2	0.75	0.33	1.70	0.49
VAR7	pN2	4.16	1.46	11.83	0.01
VAR8	Right location CRC	2.42	0.82	7.14	0.11
VAR9	Time ≤ 24 months	1.03	0.31	3.41	0.96
VAR10	Progressive Disease	2.38	0.72	7.86	0.15
VAR11	Largest diameter > 5.5 cm	0.62	0.23	1.70	0.36
VAR12	Number of nodules > 10	2.52	0.98	6.47	0.05
VAR13	CEA > 80 µg/L	1.74	0.54	5.66	0.36
VAR14	KRAS mutated	2.20	0.72	6.72	0.17
Univariable					
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p
VAR0	Female gender	1.65	0.83	3.27	0.15 *
VAR1	Age > 55 years	0.97	0.49	1.92	0.93
VAR2	Oslo center	1.20	0.54	2.67	0.66
VAR3	Living donor	1.09	0.33	3.63	0.89
VAR5	Previous liver therapy	0.91	0.41	2.03	0.82
VAR6	BMI > 25 Kg/m2	0.97	0.48	1.94	0.92
VAR7	pN2	2.83	1.40	5.73	0.004 **
VAR8	Right location CRC	2.98	1.36	6.54	0.006 **
VAR9	Time ≤ 24 months	1.68	0.80	3.54	0.17 *
VAR10	Progressive Disease	1.74	0.81	3.74	0.16 *
VAR11	Largest diameter > 5.5 cm	0.98	0.46	2.06	0.95
VAR12	Number of nodules > 10	1.05	0.52	2.14	0.89
VAR13	CEA > 80 µg/L	2.81	1.10	7.22	0.03 **
VAR14	KRAS mutated	2.34	1.03	5.35	0.04 **
Model	AICc				
modello_coxB	238.7885				
modello_coxMB	241.7043				
modello_coxTL	247.2182				
modello_coxG	247.3396				
modello_coxA	249.3995				
modello_coxO	249.8582				
modello_coxBMI	248.4999				
modello_coxGAos	249.6615				
modello_coxGoslo	249.6165				
modello_coxGBMI	249.2744				
modello_cox	253.9939				
modello_coxMBTime	244.1617				
modello_coxMBLD	243.2594				
modello_coxMBPLT	243.0922				
modello_coxMBTimeG	243.0559				
modello_coxMBLDG	242.7583				
modello_coxMBPLTG	242.3633				
modello_coxMBPLTGMBMI	244.2773				
modello_coxBG	238.1591	#modello_coxB + Gender			
modello_coxMBG	240.6651	#modello_coxMB + Gender	#Good compromise		
modello_coxMBGTime	243.0559	#modello_coxMB + Gender + Time			
Best hierarchical					
CODED VARIABLE NAME (R)	VARIABLE NAME	HR	95-	95+	Null p
VAR0	Female gender	1.97		1.02	3.75
VAR1	Age > 55 years				0.06
VAR2	Oslo center				
VAR3	Living donor				
VAR5	Previous liver therapy				
VAR6	BMI > 25 Kg/m2				
VAR7	pN2	2.98	1.35	6.65	0.01
VAR8	Right location CRC	2.35	0.79	6.89	0.10
VAR9	Time ≤ 24 months				
VAR10	Progressive Disease	1.65	0.64	4.30	0.29
VAR11	Largest diameter > 5.5 cm	0.73	0.29	1.83	0.49
VAR12	Number of nodules > 10	2.05	0.88	4.80	0.09
VAR13	CEA > 80 µg/L	1.86	0.66	5.39	0.29
VAR14	KRAS mutated	1.94	0.65	5.85	0.21

CS Lung

CAUSE-SPECIFIC LUNG, CATEGORICAL						
Proportional hazards Cox						
Multivariable all						
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nullp	
VAR0	Female gender	0,37	0,10	1,34	0,13	Concordance= 0.769 (se = 0.059)
VAR1	Age > 55 years	0,74	0,26	2,11	0,57	Likelihood ratio test= 24.45 on 14 df, p=0.04
VAR2	Oslo center	1,56	0,36	6,70	0,55	Wald test = 21.53 on 14 df, p=0.09
VAR3	Living donor	0,95	0,08	11,74	0,97	Score (logrank) test= 28.86 on 14 df, p=0.01
VAR5	Previous liver therapy	1,25	0,26	5,99	0,78	
VAR6	BMI > 25 Kg/m2	0,67	0,20	2,27	0,52	
VAR7	pN2	0,91	0,22	3,73	0,90	
VAR8	Rightlocation CRC	0,47	0,10	2,23	0,34	
VAR9	Time ≤ 24 months	0,78	0,20	2,95	0,71	
VAR10	Progressive Disease	1,37	0,26	7,20	0,71	
VAR11	Largestdiameter > 5.5 cm	1,88	0,49	7,29	0,36	
VAR12	Number of nodules > 10	1,22	0,42	3,53	0,71	
VAR13	CEA > 80 µg/L	6,73	1,68	26,93	0,01	
VAR14	KRASmutated	6,93	1,91	25,13	0,003	
Univariable						
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nullp	
VAR0	Female gender	0,35	0,12	1,02	0,05	**
VAR1	Age > 55 years	0,67	0,29	1,55	0,35	
VAR2	Oslo center	1,36	0,50	3,69	0,55	
VAR3	Living donor	0,58	0,08	4,37	0,60	
VAR5	Previous liver therapy	0,80	0,30	2,17	0,67	
VAR6	BMI > 25 Kg/m2	0,94	0,41	2,18	0,89	
VAR7	pN2	1,18	0,43	3,24	0,75	
VAR8	Rightlocation CRC	1,29	0,38	4,44	0,68	
VAR9	Time ≤ 24 months	0,98	0,43	2,25	0,97	
VAR10	Progressive Disease	1,66	0,65	4,21	0,29	
VAR11	Largestdiameter > 5.5 cm	1,90	0,83	4,35	0,13	*
VAR12	Number of nodules > 10	1,17	0,50	2,70	0,72	
VAR13	CEA > 80 µg/L	6,28	2,10	18,81	0,001	**
VAR14	KRASmutated	3,70	1,45	9,46	0,006	**

Firth's penalized Cox						
Multivariable all						
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nullp	
VAR0	Female gender	0,42	0,11	1,28	0,13	Likelihood ratio test=23.19992 on 14 df, p=0.05709341, n=82
VAR1	Age > 55 years	0,74	0,27	2,04	0,56	Wald test= 18.81135 on 14 df, p= 0.1722835
VAR2	Oslo center	1,41	0,38	6,00	0,61	
VAR3	Living donor	1,36	0,11	10,56	0,79	
VAR5	Previous liver therapy	1,42	0,32	6,50	0,64	
VAR6	BMI > 25 Kg/m2	0,68	0,22	2,24	0,52	
VAR7	pN2	1,05	0,25	3,62	0,95	
VAR8	Rightlocation CRC	0,57	0,11	2,08	0,41	
VAR9	Time ≤ 24 months	0,88	0,25	3,12	0,84	
VAR10	Progressive Disease	1,26	0,26	6,07	0,77	
VAR11	Largestdiameter > 5.5 cm	1,88	0,53	6,98	0,33	
VAR12	Number of nodules > 10	1,25	0,44	3,38	0,67	
VAR13	CEA > 80 µg/L	5,17	1,42	19,71	0,01	
VAR14	KRAS mutated	6,00	1,83	21,17	0,003	
Univariable						
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nullp	
VAR0	Female gender	0,38	0,12	0,97	0,04	**
VAR1	Age > 55 years	0,68	0,29	1,54	0,36	
VAR2	Oslo center	1,26	0,52	3,64	0,63	
VAR3	Living donor	0,85	0,09	3,38	0,85	
VAR5	Previous liver therapy	0,86	0,30	2,11	0,76	
VAR6	BMI > 25 Kg/m2	0,92	0,41	2,17	0,85	
VAR7	pN2	1,25	0,43	3,11	0,65	
VAR8	Rightlocation CRC	1,46	0,38	4,14	0,53	
VAR9	Time ≤ 24 months	0,97	0,43	2,24	0,94	
VAR10	Progressive Disease	1,73	0,65	4,06	0,26	
VAR11	Largestdiameter > 5.5 cm	1,91	0,83	4,30	0,13	*
VAR12	Number of nodules > 10	1,18	0,50	2,66	0,69	
VAR13	CEA > 80 µg/L	6,20	2,06	17,91	0,002	**
VAR14	KRAS mutated	3,80	1,44	9,24	0,008	**

CSConCat Liver

CAUSE-SPECIFIC LIVER ConCat										
Proportional hazards Cox										
Multivariable all										
CODED VARIABLENAME(R)	VARIABLENAME	HR	95-	95+	Nullp		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	2.47	1.00	6.14	0.05					
var1	Age > 55 years	1.04	0.99	1.10	0.11		1.80	0.88	3.67	46.9 60.3
var2 (cat)	Oslo center	0.57	0.16	2.03	0.39					
var3 (cat)	Living donor	0.87	0.15	5.16	0.87					
var5 (cat)	Previous liver therapy	2.77	0.60	12.79	0.19					
var6 (sqr)	BMI> 25 Kg/m2	1.04	0.61	1.80	0.88		1.04	0.60	1.81	4.76 5.77
var7 (cat)	pN2	3.61	1.36	9.61	0.01					
var8 (cat)	Rightlocation CRC	2.13	0.68	6.72	0.20					
var9 (sqr)	Time ≤ 24 months	0.85	0.63	1.15	0.29		0.62	0.26	1.50	3.73 6.71
var10 (cat)	Progressive Disease	2.16	0.59	7.84	0.24					
var11	Largestdiameter > 5.5 cm	0.95	0.80	1.13	0.57		0.75	0.28	2.02	3.00 8.81
var12 (sqr)	Number ofnodules > 10	1.40	1.12	1.75	0.003		2.09	1.29	3.40	2.50 4.69
var13 (cat)	CEA> 80 µg/L	1.62	0.51	5.17	0.42					
var14 (cat)	KRASmutated	2.20	0.73	6.60	0.16					
						Concordance= 0.751 (se = 0.043)				
						Likelihood ratio test= 31.16 on 14 df, p=0.005				
						Wald test = 32.86 on 14 df, p=0.003				
						Score (logrank) test= 39.31 on 14 df, p=3e-04				
Univariable										
CODED VARIABLENAME(R)	VARIABLENAME	HR	95-	95+	Nullp		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	1.65	0.83	3.27	0.15	*				
var1	Age > 55 years	1.01	0.97	1.05	0.80		1.07	0.64	1.80	46.9 60.3
var2 (cat)	Oslo center	1.20	0.54	2.67	0.66					
var3 (cat)	Living donor	1.09	0.33	3.63	0.89					
var5 (cat)	Previous liver therapy	0.91	0.41	2.03	0.82					
var6 (sqr)	BMI> 25 Kg/m2	1.07	0.76	1.50	0.71		1.07	0.76	1.51	4.76 5.77
var7 (cat)	pN2	2.83	1.40	5.73	0.004	**				
var8 (cat)	Rightlocation CRC	2.98	1.36	6.54	0.006	**				
var9 (sqr)	Time ≤ 24 months	0.82	0.66	1.02	0.08	*	0.56	0.29	1.07	3.73 6.71
var10 (cat)	Progressive Disease	1.74	0.81	3.74	0.16	*				
var11	Largestdiameter > 5.5 cm	1.05	0.94	1.17	0.42		1.30	0.69	2.44	3.00 8.81
var12 (sqr)	Number ofnodules > 10	1.12	0.94	1.34	0.21	*	1.28	0.87	1.88	2.50 4.69
var13 (cat)	CEA> 80 µg/L	2.81	1.10	7.22	0.03	**				
var14 (cat)	KRASmutated	2.34	1.03	5.35	0.04	**				
Multivariable 2 with p≤0.20										
CODED VARIABLENAME(R)	VARIABLENAME	HR	95-	95+	Nullp		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	2.09	1.00	4.34	0.05					
var1	Age > 55 years									
var2 (cat)	Oslo center									
var3 (cat)	Living donor									
var5 (cat)	Previous liver therapy									
var6 (sqr)	BMI> 25 Kg/m2									
var7 (cat)	pN2	2.49	1.08	5.74	0.03					
var8 (cat)	Rightlocation CRC	2.35	0.85	6.47	0.10					
var9 (sqr)	Time ≤ 24 months	0.97	0.79	1.18	0.75		0.91	0.50	1.64	3.73 6.71
var10 (cat)	Progressive Disease	1.46	0.61	3.49	0.40					
var11	Largestdiameter > 5.5 cm									
var12 (sqr)	Number ofnodules > 10	1.28	1.05	1.57	0.01		1.73	1.11	2.67	2.50 4.69
var13 (cat)	CEA> 80 µg/L	1.84	0.58	5.80	0.30					
var14 (cat)	KRASmutated	1.79	0.63	5.06	0.27					
						Concordance= 0.751 (se = 0.042)				
						Likelihood ratio test= 25.12 on 8 df, p=0.001				
						Wald test = 29.59 on 8 df, p=3e-04				
						Score (logrank) test= 32.82 on 8 df, p=7e-05				

Weighted Cox										
Multivariable all										
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nul <p></p>		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	2.39	0.83	6.85	0.11					
var1	Age > 55 years	1.04	0.99	1.10	0.12		1.71	0.86	3.39	46.9 60.3
var2 (cat)	Oslo center	0.52	0.14	1.93	0.33					
var3 (cat)	Living donor	1.00	0.17	5.92	1.00					
var5 (cat)	Previous liver therapy	2.58	0.46	14.46	0.28					
var6 (sqrt)	BMi > 25 Kg/m2	1.04	0.85	1.68	0.87		1.04	0.64	1.69	4.76 5.77
var7 (cat)	pN2	3.22	1.11	9.35	0.03					
var8 (cat)	Rightlocation CRC	1.75	0.54	5.71	0.35					
var9 (sqrt)	Time ≤ 24 months	0.87	0.64	1.16	0.34		0.65	0.27	1.57	3.73 6.71
var10 (cat)	Progressive Disease	2.38	0.64	8.89	0.20					
var11	Largestdiameter > 5.5 cm	0.94	0.80	1.11	0.47		0.71	0.28	1.82	3.00 8.81
var12 (sqrt)	Number ofnodules > 10	1.42	1.14	1.77	0.002		2.16	1.33	3.51	2.50 4.69
var13 (cat)	CEA> 80 µg/L	1.75	0.58	5.30	0.32					
var14 (cat)	KRASmutated	2.50	0.85	7.35	0.10					
						Wald Chi-square = 46.62634 on 14 df p=2.213973e-05 n= 82				
Univariable										
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nul <p></p>		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	1.65	0.83	3.27	0.15	*				
var1	Age > 55 years	1.01	0.97	1.05	0.80		1.07	0.64	1.80	46.9 60.3
var2 (cat)	Oslo center	1.20	0.54	2.67	0.66					
var3 (cat)	Living donor	1.09	0.33	3.63	0.89					
var5 (cat)	Previous liver therapy	0.91	0.41	2.03	0.82					
var6 (sqrt)	BMi > 25 Kg/m2	1.07	0.76	1.50	0.71		1.07	0.76	1.51	4.76 5.77
var7 (cat)	pN2	2.83	1.40	5.73	0.004	**				
var8 (cat)	Rightlocation CRC	2.98	1.36	6.54	0.006	**				
var9 (sqrt)	Time ≤ 24 months	0.82	0.66	1.02	0.08	*	0.56	0.29	1.07	3.73 6.71
var10 (cat)	Progressive Disease	1.74	0.81	3.74	0.16	*				
var11	Largestdiameter > 5.5 cm	1.05	0.94	1.17	0.42		1.30	0.69	2.44	3.00 8.81
var12 (sqrt)	Number ofnodules > 10	1.12	0.94	1.34	0.21	*	1.28	0.87	1.88	2.50 4.69
var13 (cat)	CEA> 80 µg/L	2.81	1.10	7.22	0.03	**				
var14 (cat)	KRAS mutated	2.34	1.03	5.35	0.04	**				
Multivariable 2 with p≤0.20										
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nul <p></p>		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	1.97	0.89	4.38	0.09					
var1	Age > 55 years									
var2 (cat)	Oslo center									
var3 (cat)	Living donor									
var5 (cat)	Previous liver therapy									
var6 (sqrt)	BMi > 25 Kg/m2									
var7 (cat)	pN2	2.19	0.84	5.88	0.11					
var8 (cat)	Rightlocation CRC	1.98	0.74	5.28	0.17					
var9 (sqrt)	Time ≤ 24 months	0.97	0.81	1.15	0.72		0.91	0.54	1.52	3.73 6.71
var10 (cat)	Progressive Disease	1.53	0.67	3.52	0.31					
var11	Largestdiameter > 5.5 cm									
var12 (sqrt)	Number ofnodules > 10	1.29	1.09	1.54	0.004		1.76	1.20	2.59	2.50 4.69
var13 (cat)	CEA> 80 µg/L	1.94	0.64	5.94	0.24					
var14 (cat)	KRAS mutated	1.96	0.75	5.14	0.17					
						Wald Chi-square = 40.41158 on 8 df p=2.684894e-06 n= 82				
Firth's penalized Cox										
Multivariable all										
CODED VARIABLENAME (R)	VARIABLENAME	HR	95-	95+	Nul <p></p>		AVG HR	AVG 95-	AVG 95+	AVG - AVG +
var0 (cat)	Female gender	2.35	0.99	5.84	0.05					
var1	Age > 55 years	1.04	0.99	1.10	0.12		1.69	0.89	3.59	46.9 60.3
var2 (cat)	Oslo center	0.56	0.17	1.96	0.35					
var3 (cat)	Living donor	0.88	0.15	4.55	0.88					
var5 (cat)	Previous liver therapy	2.62	0.59	11.33	0.20					
var6 (sqrt)	BMi > 25 Kg/m2	1.07	0.81	1.71	0.79		1.07	0.61	1.72	4.76 5.77
var7 (cat)	pN2	3.58	1.39	9.40	0.01					
var8 (cat)	Rightlocation CRC	2.05	0.66	6.21	0.21					
var9 (sqrt)	Time ≤ 24 months	0.88	0.64	1.12	0.33		0.68	0.26	1.41	3.73 6.71
var10 (cat)	Progressive Disease	1.98	0.56	6.83	0.28					
var11	Largestdiameter > 5.5 cm	0.97	0.81	1.13	0.67		0.82	0.30	2.06	3.00 8.81
var12 (sqrt)	Number ofnodules > 10	1.38	1.10	1.70	0.007		2.01	1.23	3.18	2.50 4.69
var13 (cat)	CEA> 80 µg/L	1.67	0.51	4.78	0.38					
var14 (cat)	KRAS mutated	2.18	0.72	6.15	0.16					
						Likelihood ratio test=31.4429 on 14 df,p=0.004803657, n=82				
						Wald test= 30.15312 on 14 df,p = 0.007269787				

[illegible]

[illegible]

#conversion from 'cat' to 'factors'

```
dati$var0 <- as.factor(dati$var0)
```

```
dati$var2 <- as.factor(dati$var2)
```

```
dati$var3 <- as.factor(dati$var3)
```

```
dati$var5 <- as.factor(dati$var5)
```

```
dati$var7 <- as.factor(dati$var7)
```

```
dati$var8 <- as.factor(dati$var8)
```

```
dati$var10 <- as.factor(dati$var10)
```

```
dati$var13 <- as.factor(dati$var13)
```

```
dati$var14 <- as.factor(dati$var14)
```



```

c(1.4142,1.4142,4.4721,3.8730,2.2361,3.1623,4.6904,1.4142,3.1623,3.1623,1.7321,3.1623,3.1623,3.
3166,3.1623,2.6458,3.1623,3.1623,3.1623,3.1623,3.1623,3.1623,3.1623,3.1623,3.1623,4.4721,2.000
0,2.0000,4.4721,2.0000,1.7321,3.4641,2.2361,2.2361,2.0000,3.6056,2.2361,4.5826,2.2361,2.2361,2.
6458,2.6458,2.6458,6.3246,2.2361,3.6056,3.0000,2.0000,5.9161,3.1623,2.0000,2.8284,5.3852,5.477
2,3.8730,2.6458,2.8284,2.4495,2.8284,4.6904,2.8284,4.6904,10.0000,3.3166,2.6458,4.4721,3.1623,
2.2361,3.8730,3.6056,3.4641,4.1231,3.8730,2.0000,1.7321,1.4142,8.3666,2.8284,4.6904,3.0000,1.7
321,2.4495), var13 =
c(0,0,0,0,0,0,0,0,0,0,0,0,1,1,0,0,0,0,0,1,1,0,0,0,0,0,0,1,1,0,1,0,0,0,0,0,0,0,0,0,0,0,0,1,1,1,0,0,1,
0,1,1,0,0,1,0,1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0), var14 =
c(0,0,0,0,0,0,0,0,0,1,0,0,1,1,0,0,0,0,0,0,0,1,1,1,0,0,1,1,0,0,0,0,0,0,0,0,0,1,1,0,0,0,1,0,0,0,0,1,1,1,0,
0,0,1,1,1,0,1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0,0,1))

```

```
#conversion from 'cat' to 'factors'
```

```
dati$var0 <- as.factor(dati$var0)
```

```
dati$var2 <- as.factor(dati$var2)
```

```
dati$var3 <- as.factor(dati$var3)
```

```
dati$var5 <- as.factor(dati$var5)
```

```
dati$var7 <- as.factor(dati$var7)
```

```
dati$var8 <- as.factor(dati$var8)
```

```
dati$var10 <- as.factor(dati$var10)
```

```
dati$var13 <- as.factor(dati$var13)
```

```
dati$var14 <- as.factor(dati$var14)
```

Cox models

Proportional hazards

```
library(survival)
```

```
#define Cox model
```

```
modello_cox <- coxph(Surv(time, status) ~ var0 + var1 + var2 + var3 + var5 + var6 + var7 + var8 + var9 +  
var10 + var11 + var12 + var13 + var14, data = dati)
```

```
#print Cox model results
```

```
summary(modello_cox)
```

Weighted

```
library(coxphw)
```

```
#define wCox model
```

```
weighted_model <- coxphw(Surv(time, status) ~ var0 + var1 + var2 + var3 + var5 + var6 + var7 + var8 +  
var9 + var10 + var11 + var12 + var13 + var14,  
data = dati)
```

```
#print wCox model results
```

```
summary(weighted_model)
```

Firth's penalized

```
library(survival)
```

```
library(coxphf)
```

```
#define Firth's pCox model
```

```
firth_model <- coxphf(Surv(time, status) ~ var0 + var1 + var2 + var3 + var5 + var6 + var7 + var8 + var9 +  
var10 + var11 + var12 + var13 + var14, data = dati, maxstep = 0.5, maxit = 500)
```

```
#print Firth's pCox model results
```

```
summary(firth_model)
```

LASSO

```
# Carica i pacchetti necessari
```

```
library(survival)
```

```
library(glmnet)
```

```
# Step 1: Matrice delle covariate (X) e oggetto Surv (y)
```

```
X <- model.matrix(~ var0 + var1 + var2 + var3 + var5 + var6 + var7 + var8 + var9 + var10 + var11 + var12 +  
var13 + var14, data = dati)[-1]
```

```
y <- Surv(dati$time, dati$status)
```

```
# Step 2: Cross-validation LASSO Cox
```

```
set.seed(123)
```

```
cvfit <- cv.glmnet(X, y, family = "cox", alpha = 1)
```

```
# Step 3: Estrai il lambda ottimale
```

```
lambda_min <- cvfit$lambda.min
```

```
# Step 4: Modello LASSO finale con lambda ottimale
```

```
lasso_model <- glmnet(X, y, family = "cox", alpha = 1, lambda = lambda_min)
```

```
# Step 5: Estrai i nomi delle variabili selezionate (con coefficiente ≠ 0)
```

```
coeff <- coef(lasso_model)
```

```
selected_vars <- rownames(coeff)[as.vector(coeff != 0)]
```

```
# Step 6: Crea formula dinamica per Cox classico
```

```
formula_finale <- as.formula(  
  paste("Surv(time, status) ~", paste(selected_vars, collapse = " + "))  
)
```

```
# Step 7: Modello di Cox finale con variabili selezionate
```

```
modello_cox_finale <- coxph(formula_finale, data = dati)
```

```
# Step 8: Risultati del modello finale
```

```
summary(modello_cox_finale)
```

Hierarchical

```
library(AICcmodavg)
```

```
#define Cox model biological
```

```
modello_coxB <- coxph(Surv(time, status) ~ var7 + var10 + var14, data = dati)
```

```
#define Cox model metastases and biomarkers
```

```
modello_coxMB <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13, data = dati)
```

```
#define Cox model technical-logistic
```

```
modello_coxTL <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 + var3 + var5 + var9, data = dati)
```

```
#define Cox model gender
```

```
modello_coxG <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 + var3 + var5 + var9 + var0, data = dati)
```

```
#define Cox model age
```

```
modello_coxA <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 + var3 + var5 + var9 + var1, data = dati)
```

```
#define Cox model oslo
```

```
modello_coxO <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 + var3 + var5 + var9 + var2, data = dati)
```

```
#define Cox model bmi
```

```
modello_coxBMI <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 + var3 + var5 + var9 + var6, data = dati)
```

```
#define Cox model gender + age
```

```
modello_coxGAge <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var3 + var5 + var9 + var0 + var1, data = dati)
```

```
#define Cox model gender + oslo
```

```
modello_coxGOslo <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var3 + var5 + var9 + var0 + var2, data = dati)
```

```
#define Cox model gender + bmi
```

```
modello_coxGBMI <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var3 + var5 + var9 + var0 + var6, data = dati)
```

```
#define Cox model all
```

```
modello_cox <- coxph(Surv(time, status) ~ var0 + var1 + var2 + var3 + var5 + var6 + var7 + var8 + var9 +
var10 + var11 + var12 + var13 + var14, data = dati)
```

```
#define Cox model metastases and biomarkers + time
```

```
modello_coxMBTime <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var9, data = dati)
```

```
#define Cox model metastases and biomarkers + LD
```

```
modello_coxMBLD <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var3, data = dati)
```

```
#define Cox model metastases and biomarkers + PLT
```

```
modello_coxMBPLT <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var5, data = dati)
```

```
#define Cox model metastases and biomarkers + time + gender
```

```
modello_coxMBTimeG <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13
+ var9 + var0, data = dati)
```

```
#define Cox model metastases and biomarkers + LD + gender
```

```
modello_coxMBLDG <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13 +
var3 + var0, data = dati)
```

```
#define Cox model metastases and biomarkers + PLT + gender
```

```
modello_coxMBPLTG <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 + var13  
+ var5 + var0, data = dati)
```

```
#define Cox model metastases and biomarkers + PLT + gender + BMI
```

```
modello_coxMBPLTGBMI <- coxph(Surv(time, status) ~ var7 + var10 + var14 + var8 + var11 + var12 +  
var13 + var5 + var0 + var6, data = dati)
```

```
#define Cox model best
```

```
modello_cox_Best <- coxph(Surv(time, status) ~ var0 + var5 + var6 + var7 + var8 + var11 + var12 + var13  
+ var14, data = dati)
```

```
#AICc for each model
```

```
aicc_model_B <- AICc(modello_coxB)
```

```
aicc_model_MB <- AICc(modello_coxMB)
```

```
aicc_model_TL <- AICc(modello_coxTL)
```

```
aicc_model_G <- AICc(modello_coxG)
```

```
aicc_model_A <- AICc(modello_coxA)
```

```
aicc_model_O <- AICc(modello_coxO)
```

```
aicc_model_BMI <- AICc(modello_coxBMI)
```

```
aicc_model_GAge <- AICc(modello_coxGAge)
```

```
aicc_model_GOslo <- AICc(modello_coxGOslo)
```

```
aicc_model_GBMI <- AICc(modello_coxGBMI)
```

```
aicc_model_all <- AICc(modello_cox)
```

```
aicc_model_MBTime <- AICc(modello_coxMBTime)
```

```
aicc_model_MBLD <- AICc(modello_coxMBLD)
```

```
aicc_model_MBPLT <- AICc(modello_coxMBPLT)
```

```
aicc_model_MBTimeG <- AICc(modello_coxMBTimeG)
```

```
aicc_model_MBLDG <- AICc(modello_coxMBLDG)
```

```
aicc_model_MBPLTG <- AICc(modello_coxMBPLTG)
```

```
aicc_model_MBPLTGBMI <- AICc(modello_coxMBPLTGBMI)
```

```
aicc_model_Best <- AICc(modello_cox_Best)
```

#Comparison

```
aicc_results <- data.frame(

  Model = c("modello_coxB", "modello_coxMB", "modello_coxTL", "modello_coxG", "modello_coxA",
"modello_coxO", "modello_coxBMI", "modello_coxGAge", "modello_coxGOslo", "modello_coxGBMI",
"modello_cox", "modello_coxMBTime", "modello_coxMBLD", "modello_coxMBPLT",
"modello_coxMBTimeG", "modello_coxMBLDG", "modello_coxMBPLTG", "modello_coxMBPLTGBMI",
"modello_cox_Best"),

  AICc = c(aicc_model_B, aicc_model_MB, aicc_model_TL, aicc_model_G, aicc_model_A,
aicc_model_O, aicc_model_BMI, aicc_model_GAge, aicc_model_GOslo, aicc_model_GBMI,
aicc_model_all, aicc_model_MBTime, aicc_model_MBLD, aicc_model_MBPLT, aicc_model_MBTimeG,
aicc_model_MBLDG, aicc_model_MBPLTG, aicc_model_MBPLTGBMI, aicc_model_Best)

)
```

#Show results

```
print(aicc_results)
```

Multicollinearity

Spearman correlation matrix

```
library(dplyr)
```

```
library(corrplot)
```

```
#Select variables var0 to var14 and calculate the Spearman correlation matrix
```

```
correlation_matrix <- dati %>%
```

```
  select(starts_with("var")) %>% #Select all columns starting with "var"
```

```
  cor(method = "spearman", use = "pairwise.complete.obs") #Calculate the Spearman correlation
```

```
#Show matrix correlation
```

```
print(correlation_matrix)
```

```
#Create a correlation matrix graph with numeric values
```

```
corrplot(correlation_matrix, method = "circle",
```

```
  type = "upper",
```

```
  tl.col = "black",
```

```
  tl.srt = 45,
```

```
  addCoef.col = "black", # Aggiungi i coefficienti in nero
```



```
number.cex = 0.7)    # Dimensione del testo dei coefficienti
```

VIF Cat

```
library(car)
```

```
#Pearson or Spearman matrix
```

```
correlazione <- cor(dati[, c("var0", "var1", "var2", "var3", "var5", "var6", "var7", "var8", "var9", "var10",  
"var11", "var12", "var13", "var14")], use = "complete.obs", method = "pearson")
```

```
print(correlazione)
```

```
# For each covariate, we calculate the VIF with a linear regression
```

```
# All variables
```

```
covariate <- c("var0", "var1", "var2", "var3", "var5", "var6", "var7", "var8", "var9", "var10", "var11", "var12",  
"var13", "var14")
```

```
# Calculate the VIF for each covariate
```

```
vif_results <- data.frame(variable = covariate, VIF = NA)
```

```
for (cov in covariate) {
```

```
  # Create a formula for linear regression, where 'cov' is the dependent variable
```

```
  formula <- as.formula(paste(cov, "~", paste(setdiff(covariate, cov), collapse = "+")))
```

```
  # Run linear regression
```

```
  lm_model <- lm(formula, data = dati)
```

```
  # Calculate the VIF for the regression model
```

```
  vif_value <- vif(lm_model)
```

```
  # Assign the calculated VIF
```

```
  vif_results[vif_results$variable == cov, "VIF"] <- max(vif_value)
```

```
}
```

```
# Show VIF results
```

```
print(vif_results)
```

```
#VIF cox
```

```
vif(modello_cox)
```

<https://www.stata.com/statalist/archive/2009-09/msg00334.html>

<<You can use the vif command after running a regression. "Because the concern is with the relationship among the independent variables, the functional form of the model for the dependent variable is irrelevant to the estimation of collinearity." (Menard 2002, p. 76). Menard, 2002. Applied logistic regression analysis, 2nd Ed.>>

VIF ConCat

```
# Trasformiamo le variabili categoriali in dummies con model.matrix()
```

```
dati_dummies <- model.matrix(~ var0 + var1 + var2 + var3 + var5 + var6 + var7 + var8 + var9 + var10 +  
var11 + var12 + var13 + var14, data = dati)[, -1]
```

```
# Creiamo una lista di tutte le variabili indipendenti dummy
```

```
covariate <- colnames(dati_dummies)
```

```
# Calcoliamo il VIF per ogni covariata nel modello
```

```
vif_results <- data.frame(variable = covariate, VIF = NA)
```

```
for (cov in covariate) {
```

```
  # Creiamo la formula per la regressione lineare
```

```
  formula <- as.formula(paste(cov, "~", paste(setdiff(covariate, cov), collapse = "+")))
```

```
  # Eseguiamo la regressione lineare sulle variabili dummy
```

```
  lm_model <- lm(formula, data = as.data.frame(dati_dummies))
```

```
# Calcoliamo il VIF per il modello

vif_value <- vif(lm_model)

# Assegniamo il massimo valore di VIF calcolato
vif_results[vif_results$variable == cov, "VIF"] <- max(vif_value)
}

# Stampa dei risultati VIF
print(vif_results)
```

Kaplan-Meier curves

All variables

```
# Caricamento pacchetti

library(survival)
library(survminer)
library(dplyr)

# Etichette leggibili per i grafici
etichette <- c(
  var0 = "Female gender",
  var1 = "Age > 55 years",
  var2 = "Oslo centre",
  var3 = "Living donor",
  var5 = "Previous liver therapy",
  var6 = "BMI > 25 kg/m2",
  var7 = "pN2",
  var8 = "Right location CRC",
  var9 = "Time ≤ 24 months",
  var10 = "Progressive Disease",
  var11 = "Largest diameter > 5.5 cm",
  var12 = "Number of nodules > 10",
```

```

var13 = "CEA > 80 µg/L",
var14 = "KRAS mutated"
)

# Lista delle variabili (escludendo var4)
variabili <- names(etichette)

# Assicurati che siano tutte fattori
dati[variabili] <- lapply(dati[variabili], factor)

# Ciclo su ogni variabile
for (var in variabili) {

  # Crea variabile temporanea per la formula
  dati$temp_var <- dati[[var]]

  # Fit Kaplan-Meier
  fit <- survfit(Surv(time, status) ~ temp_var, data = dati)

  # Log-rank test
  test <- survdiff(Surv(time, status) ~ temp_var, data = dati)
  pval <- 1 - pchisq(test$chisq, length(test$n) - 1)
  pval_label <- paste0("p = ", format.pval(pval, digits = 3, eps = 0.001))

  # Plot
  g <- gg survplot(
    fit,
    data = dati,
    risk.table = TRUE,
    conf.int = TRUE,
    pval = pval_label,
    pval.coord = c(2, 0.03),

```

```

  censor = TRUE,
  ggtheme = theme_minimal(),
  palette = "Set2",
  title = paste("Kaplan-Meier by", etichette[[var]]),
  legend.title = etichette[[var]],
  xlim = c(0, 60),
  break.time.by = 12 # Mostra i tempi a intervalli di 12 mesi
)
print(g)
}

```

Male

```

library(survival)
library(survminer)

```

```
maschi <- subset(dati, var0 == 0)
```

```
# var1
```

```

ggsurvplot(survfit(Surv(time, status) ~ var1, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Male - Age > 55 years", legend.labs = c("No", "Yes"),
  legend.title = "Age > 55", palette = "Set1")

```

```
# var2
```

```

ggsurvplot(survfit(Surv(time, status) ~ var2, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Male - Oslo centre", legend.labs = c("No", "Yes"),
  legend.title = "Oslo centre", palette = "Set1")

```

```
# var3
```

```
ggsurvplot(survfit(Surv(time, status) ~ var3, data = maschi), data = maschi,
```

```
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - Living donor", legend.labs = c("No", "Yes"),
legend.title = "Living donor", palette = "Set1")
```

```
# var5
```

```
ggsurvplot(survfit(Surv(time, status) ~ var5, data = maschi), data = maschi,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - Previous liver therapy", legend.labs = c("No", "Yes"),
legend.title = "Prev. liver therapy", palette = "Set1")
```

```
# var6
```

```
ggsurvplot(survfit(Surv(time, status) ~ var6, data = maschi), data = maschi,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - BMI > 25", legend.labs = c("No", "Yes"),
legend.title = "BMI > 25", palette = "Set1")
```

```
# var7
```

```
ggsurvplot(survfit(Surv(time, status) ~ var7, data = maschi), data = maschi,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - pN2", legend.labs = c("No", "Yes"),
legend.title = "pN2", palette = "Set1")
```

```
# var8
```

```
ggsurvplot(survfit(Surv(time, status) ~ var8, data = maschi), data = maschi,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - Right location CRC", legend.labs = c("No", "Yes"),
legend.title = "Right CRC", palette = "Set1")
```

```
# var9
```

```
ggsurvplot(survfit(Surv(time, status) ~ var9, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Male - Time ≤ 24 months", legend.labs = c("No", "Yes"),
  legend.title = "≤ 24 months", palette = "Set1")
```

```
# var10
```

```
ggsurvplot(survfit(Surv(time, status) ~ var10, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Male - Progressive Disease", legend.labs = c("No", "Yes"),
  legend.title = "Progressive Disease", palette = "Set1")
```

```
# var11
```

```
ggsurvplot(survfit(Surv(time, status) ~ var11, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Male - Diameter > 5.5 cm", legend.labs = c("No", "Yes"),
  legend.title = "Diameter > 5.5", palette = "Set1")
```

```
# var12
```

```
ggsurvplot(survfit(Surv(time, status) ~ var12, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Male - Nodules > 10", legend.labs = c("No", "Yes"),
  legend.title = "Nodules > 10", palette = "Set1")
```

```
# var13
```

```
ggsurvplot(survfit(Surv(time, status) ~ var13, data = maschi), data = maschi,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
```

```
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - CEA > 80", legend.labs = c("No", "Yes"),
legend.title = "CEA > 80", palette = "Set1")
```

```
# var14
```

```
ggsurvplot(survfit(Surv(time, status) ~ var14, data = maschi), data = maschi,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Male - KRAS mutated", legend.labs = c("No", "Yes"),
legend.title = "KRAS mutated", palette = "Set1")
```

Female

```
femmene <- subset(dati, var0 == 1)
```

```
# var1
```

```
ggsurvplot(survfit(Surv(time, status) ~ var1, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Female - Age > 55 years", legend.labs = c("No", "Yes"),
legend.title = "Age > 55", palette = "Set1")
```

```
# var2
```

```
ggsurvplot(survfit(Surv(time, status) ~ var2, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Female - Oslo centre", legend.labs = c("No", "Yes"),
legend.title = "Oslo centre", palette = "Set1")
```

```
# var3
```

```
ggsurvplot(survfit(Surv(time, status) ~ var3, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
```



```
title = "Female - Living donor", legend.labs = c("No", "Yes"),
legend.title = "Living donor", palette = "Set1")
```

```
# var5
```

```
ggsurvplot(survfit(Surv(time, status) ~ var5, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Female - Previous liver therapy", legend.labs = c("No", "Yes"),
legend.title = "Prev. liver therapy", palette = "Set1")
```

```
# var6
```

```
ggsurvplot(survfit(Surv(time, status) ~ var6, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Female - BMI > 25", legend.labs = c("No", "Yes"),
legend.title = "BMI > 25", palette = "Set1")
```

```
# var7
```

```
ggsurvplot(survfit(Surv(time, status) ~ var7, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Female - pN2", legend.labs = c("No", "Yes"),
legend.title = "pN2", palette = "Set1")
```

```
# var8
```

```
ggsurvplot(survfit(Surv(time, status) ~ var8, data = femmine), data = femmine,
pval = TRUE, conf.int = TRUE, risk.table = TRUE,
xlim = c(0, 60), break.time.by = 12, xlab = "Months",
title = "Female - Right location CRC", legend.labs = c("No", "Yes"),
legend.title = "Right CRC", palette = "Set1")
```

```
# var9
```

```

ggsurvplot(survfit(Surv(time, status) ~ var9, data = femmine), data = femmine,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Female - Time ≤ 24 months", legend.labs = c("No", "Yes"),
  legend.title = "≤ 24 months", palette = "Set1")

```

```
# var10
```

```

ggsurvplot(survfit(Surv(time, status) ~ var10, data = femmine), data = femmine,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Female - Progressive Disease", legend.labs = c("No", "Yes"),
  legend.title = "Progressive Disease", palette = "Set1")

```

```
# var11
```

```

ggsurvplot(survfit(Surv(time, status) ~ var11, data = femmine), data = femmine,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Female - Diameter > 5.5 cm", legend.labs = c("No", "Yes"),
  legend.title = "Diameter > 5.5", palette = "Set1")

```

```
# var12
```

```

ggsurvplot(survfit(Surv(time, status) ~ var12, data = femmine), data = femmine,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Female - Nodules > 10", legend.labs = c("No", "Yes"),
  legend.title = "Nodules > 10", palette = "Set1")

```

```
# var13
```

```

ggsurvplot(survfit(Surv(time, status) ~ var13, data = femmine), data = femmine,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Female - CEA > 80", legend.labs = c("No", "Yes"),

```

```
legend.title = "CEA > 80", palette = "Set1")
```

```
# var14
```

```
ggsurvplot(survfit(Surv(time, status) ~ var14, data = femmine), data = femmine,
  pval = TRUE, conf.int = TRUE, risk.table = TRUE,
  xlim = c(0, 60), break.time.by = 12, xlab = "Months",
  title = "Female - KRAS mutated", legend.labs = c("No", "Yes"),
  legend.title = "KRAS mutated", palette = "Set1")
```

Informativeness of censoring

```
library(dplyr)
```

```
library(gtsummary)
```

```
# Etichette in formato accettato da tbl_summary
```

```
etichette <- list(
  var0 ~ "Female gender",
  var1 ~ "Age > 55 years",
  var2 ~ "Oslo centre",
  var3 ~ "Living donor",
  var5 ~ "Previous liver therapy",
  var6 ~ "BMI > 25 kg/m2",
  var7 ~ "pN2",
  var8 ~ "Right location CRC",
  var9 ~ "Time ≤ 24 months",
  var10 ~ "Progressive Disease",
  var11 ~ "Largest diameter > 5.5 cm",
  var12 ~ "Number of nodules > 10",
  var13 ~ "CEA > 80 µg/L",
  var14 ~ "KRAS mutated"
)
```

```

# Definisci le variabili da includere

variabili <- c("var0", "var1", "var2", "var3", "var5", "var6", "var7",
             "var8", "var9", "var10", "var11", "var12", "var13", "var14")

# Crea la variabile di censura precoce

dati$censura_precoce <- ifelse(dati$status == 0 & dati$time <= 36, "Censurato precoce", "Non
censurato precoce")

# Tabella riepilogativa con nomi clinici leggibili

dati %>%

select(censura_precoce, all_of(variabili)) %>%

mutate(across(everything(), as.factor)) %>%

tbl_summary(

  by = censura_precoce,

  label = etichette,

  statistic = list(all_categorical() ~ "{n} ({p}%)",

  missing = "no"

) %>%

add_p() %>%

bold_labels()

```

Stratified analysis (by sex)

Male

```

#Male filter(var0 = 0)

data_male<- subset(dati, var0 == 0)

```

Female

```

#Feale filter(var0 = 1)

data_female <- subset(dati, var0 == 1)

```

Fine and Gray competing risk

Multivariable

```
library(survival)
```

```
library(cmprsk)
```

```
#Fine & Gray for liver recurrency
```

```
fg_liver <- crr(ftime = dati$time,
               fstatus = dati$status,
               cov1 = as.matrix(dati[, c('var0', 'var1', 'var2', 'var3', 'var5',
                                         'var6', 'var7', 'var8', 'var9', 'var10', 'var11', 'var12','var13','var14'))],
               failcode = 1)
```

```
#Fine & Gray for lung recurrency
```

```
fg_lung <- crr(ftime = dati$time,
               fstatus = dati$status,
               cov1 = as.matrix(dati[, c('var0', 'var1', 'var2', 'var3', 'var5',
                                         'var6', 'var7', 'var8', 'var9', 'var10', 'var11', 'var12','var13','var14'))],
               failcode = 2)
```

```
#Liver recurrency results
```

```
summary(fg_liver)
```

```
#Lung recurrency results
```

```
summary(fg_lung)
```

Univariable

```
#Liver recurrency
```

```
for (i in 0:14) {
  if (i == 4) next
  var_name <- paste0("var", i)
  model <- crr(ftime = dati$time,
               fstatus = dati$status,
               cov1 = as.matrix(dati[, var_name, drop=FALSE]),
               failcode = 1)
  print(paste("Results for", var_name))
}
```

```

print(summary(model))
}

#Lung recurrency
for (i in 0:14) {
  if (i == 4) next
  var_name <- paste0("var", i)
  model <- crr(ftime = dati$time,
               fstatus = dati$status,
               cov1 = as.matrix(dati[, var_name, drop=FALSE]),
               failcode = 2)
  print(paste("Results for", var_name))
  print(summary(model))
}

```

Competing risk of recurrences in males vs. females

Database

```

dati <- data.frame(dfs =
c(27.96667,20.8,15.4,13.03333,11.93333,8.7,13.5,38.26667,43.46667,6.966667,9.733333,3.333333,
5.433333,5,2.7,45.93333,68,8.5,4.333333,5,3.433333,15.2,4.4,0.5,3.5,6.633333,22.63333,12.93333,
0,8.4,1.933333,11.76667,3.833333,5.233333,12.33333,23.6,13.16667,5.666667,23,10,22,3,46,11,11,
15,12,6,2,3,7,12,12,3,3,16,3,3,3,2,31,18.6,43.1,11.5975,5.8809,5.9466,11.7618,24.3121,24.36667,7
1.6,66.7,64,24.26667,15.1,82.3,42.8,2.7269,13.7331,11.9918,12.86667,4.666667,1.7), rec =
c(0,1,2,2,1,1,2,0,0,1,1,1,1,1,3,0,3,1,3,2,0,1,4,3,1,1,1,4,0,0,2,2,1,3,1,2,1,2,2,2,2,2,1,1,1,1,1,1,2,2,
2,2,2,2,3,1,2,2,1,1,1,1,1,1,2,2,0,0,0,0,0,0,0,1,1,1,0,0,0), sex =
c(0,1,0,0,1,0,0,1,1,0,0,0,1,0,0,0,0,0,0,0,0,0,0,0,0,0,1,1,1,0,1,0,0,0,0,1,1,0,1,0,0,0,1,1,0,1,1,0,1,0,
0,0,0,0,1,1,1,0,1,0,0,1,1,1,0,0,0,0,0,1,1,1,0,1,1,0,1,1,0,0))

```

Analysis code

```

=== PACCHETTI NECESSARI ===

if (!require("cmprsk")) install.packages("cmprsk")

if (!require("dplyr")) install.packages("dplyr")

library(cmprsk)

library(dplyr)

```

```
# === CODIFICA EVENTI ===
```

```
# Recidiva epatica
```

```
dati$event_liver <- ifelse(dati$rec == 1, 1,
  ifelse(dati$rec %in% c(2, 3), 2,
    ifelse(dati$rec %in% c(0, 4), 0, NA)))
```

```
# Recidiva polmonare
```

```
dati$event_lung <- ifelse(dati$rec == 2, 1,
  ifelse(dati$rec %in% c(1, 3), 2,
    ifelse(dati$rec %in% c(0, 4), 0, NA)))
```

```
# === FUNZIONE DI PLOT CIF CON CI ===
```

```
plot_cif_ci <- function(evento, title, ylim_max = 1) {
```

```
  # Subset
```

```
  dati_m <- subset(dati, sex == 0)
```

```
  dati_f <- subset(dati, sex == 1)
```

```
  # Cuminc per ciascun gruppo
```

```
  cif_m <- cuminc(ftime = dati_m$dfs, fstatus = dati_m[[evento]], cencode = 0)
```

```
  cif_f <- cuminc(ftime = dati_f$dfs, fstatus = dati_f[[evento]], cencode = 0)
```

```
  # Estrai la curva principale
```

```
  male <- cif_m[[1]]
```

```
  female <- cif_f[[1]]
```

```
  # Calcola i CI manualmente
```

```
  male$lower <- pmax(0, male$est - 1.96 * sqrt(male$var))
```

```
  male$upper <- pmin(1, male$est + 1.96 * sqrt(male$var))
```

```
  female$lower <- pmax(0, female$est - 1.96 * sqrt(female$var))
```

```
  female$upper <- pmin(1, female$est + 1.96 * sqrt(female$var))
```

```

# Plot
plot(female$time, female$est, type = "s", col = "red", lwd = 2,
     xlab = "Months", ylab = "Cumulative incidence",
     main = title,
     xlim = c(0, 60), ylim = c(0, ylim_max))

# Aggiungi bande CI per femmine (rosso chiaro)
polygon(c(female$time, rev(female$time)),
       c(female$lower, rev(female$upper)),
       col = rgb(1, 0, 0, 0.2), border = NA)

# Linea femmine
lines(female$time, female$est, type = "s", col = "red", lwd = 2)

# Aggiungi bande CI per maschi (blu chiaro)
polygon(c(male$time, rev(male$time)),
       c(male$lower, rev(male$upper)),
       col = rgb(0, 0, 1, 0.2), border = NA)

# Linea maschi
lines(male$time, male$est, type = "s", col = "blue", lwd = 2)

# Legenda
legend("topleft", legend = c("Female", "Male"),
     col = c("red", "blue"), lwd = 2, bg = "white")
}

# === GRAFICO POLMONARE ===
plot_cif_ci(evento = "event_lung", title = "Lung recurrence: Female vs. Male", ylim_max = 0.5)

# === GRAFICO EPATICO ===
plot_cif_ci(evento = "event_liver", title = "Liver recurrence: Female vs. Male", ylim_max = 0.6)

```


Gray's test liver

```
# Ricodifica evento epatico

dati$event_liver <- ifelse(dati$rec == 1, 1,
                          ifelse(dati$rec %in% c(2, 3), 2,
                                ifelse(dati$rec %in% c(0, 4), 0, NA)))

# Test di Gray: CIF per liver, group = sesso

cif_liver_test <- cuminc(ftime = dati$dfs,
                        fstatus = dati$event_liver,
                        group = dati$sex,
                        cencode = 0)
```

Gray's test lung

```
print(cif_liver_test)

Gray's test lung

# Ricodifica evento polmonare

dati$event_lung <- ifelse(dati$rec == 2, 1,
                        ifelse(dati$rec %in% c(1, 3), 2,
                              ifelse(dati$rec %in% c(0, 4), 0, NA)))

# Test di Gray: CIF per lung, group = sesso

cif_lung_test <- cuminc(ftime = dati$dfs,
                       fstatus = dati$event_lung,
                       group = dati$sex,
                       cencode = 0)

# Risultati del test di Gray

print(cif_lung_test)
```

Cause-specific hazard ratio

```
#change 'coxph' to 'coxphw' to have the weighted model (library(coxphw)) or to 'coxphf' to have Firth's
penalized model (library(coxphf)).
```

Liver multivariable

#Cause-specific liver

```
cs_liver <- coxph(Surv(time, status == 1) ~ var0 + var1 + var2 + var3 + var5 +
  var6 + var7 + var8 + var9 + var10 + var11 + var12 + var13 + var14,
  data = dati)
```

#Results liver

```
summary(cs_liver)
```

Lung multivariable

#Cause-specific lung

```
cs_lung <- coxph(Surv(time, status == 2) ~ var0 + var1 + var2 + var3 + var5 +
  var6 + var7 + var8 + var9 + var10 + var11 + var12 + var13 + var14,
  data = dati)
```

#Results lung

```
summary(cs_lung)
```

Liver univariable

Liver recurrency

```
for (i in 0:14) {
  if (i == 4) next # Skip var4
```

Name of the current variable

```
var_name <- paste0("var", i)
```

Defines the model using only the current variable and other fixed covariates

```
formula <- as.formula(paste("Surv(time, status == 1) ~", var_name))
```

Runs the Cox model with the selected covariate

```
model <- coxph(formula, data = dati)
```

```
# Prints the results for the current variable

cat("Results for", var_name, "\n")

print(summary(model))

cat("\n-----\n")}
```

Lung univariable

```
# Lung recurrency

for (i in 0:14) {

  if (i == 4) next # Skip var4

  # Name of the current variable

  var_name <- paste0("var", i)

  # Defines the model using only the current variable and other fixed covariates

  formula <- as.formula(paste("Surv(time, status == 2) ~", var_name))

  # Runs the Cox model with the selected covariate

  model <- coxph(formula, data = dati)

  # Prints the results for the current variable

  cat("Results for", var_name, "\n")

  print(summary(model))

  cat("\n-----\n")}
```

Sensitivity analysis results (short summary)

Cox multivariable models for Table 2

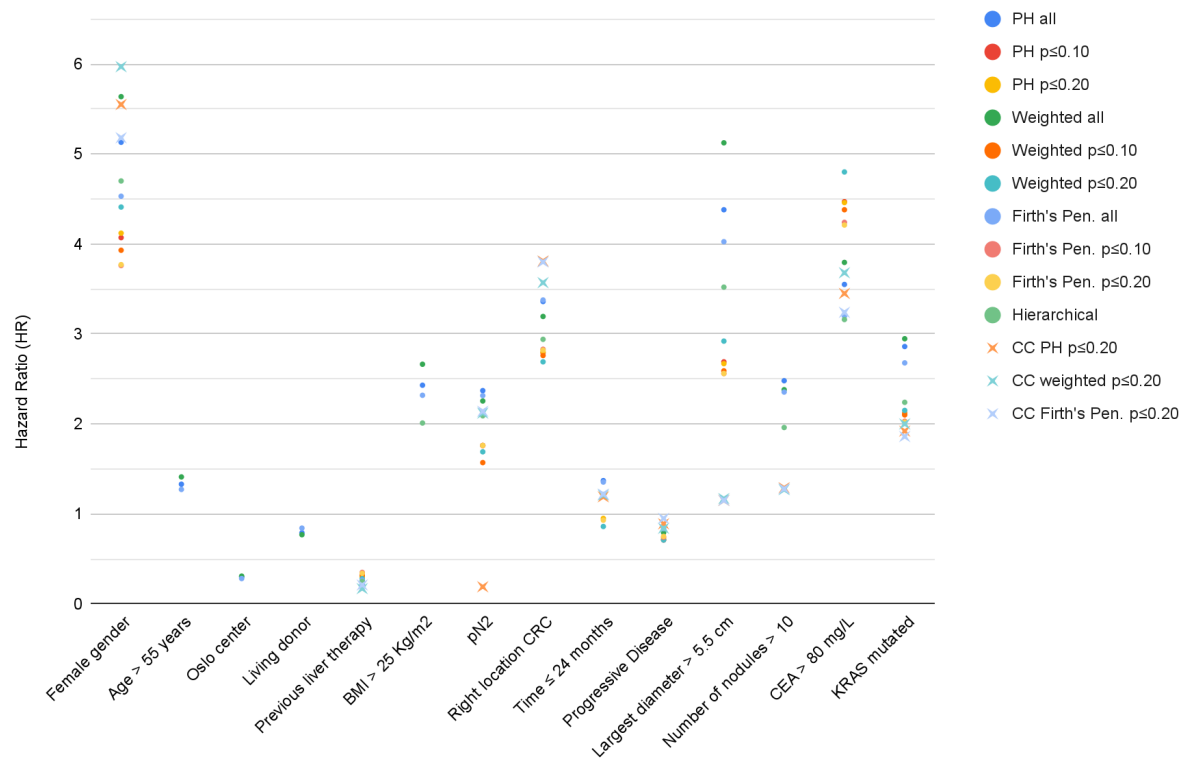


Figure S2.1. Hazard ratio (HR) point estimates for Table 2 according to various models. P-values (p) concern the null hypothesis 'HR = 1.' Legend: PH = proportional hazards; Pen. = Firth's penalized; CC = ConCat.

Cox univariable models for Table 3

Male

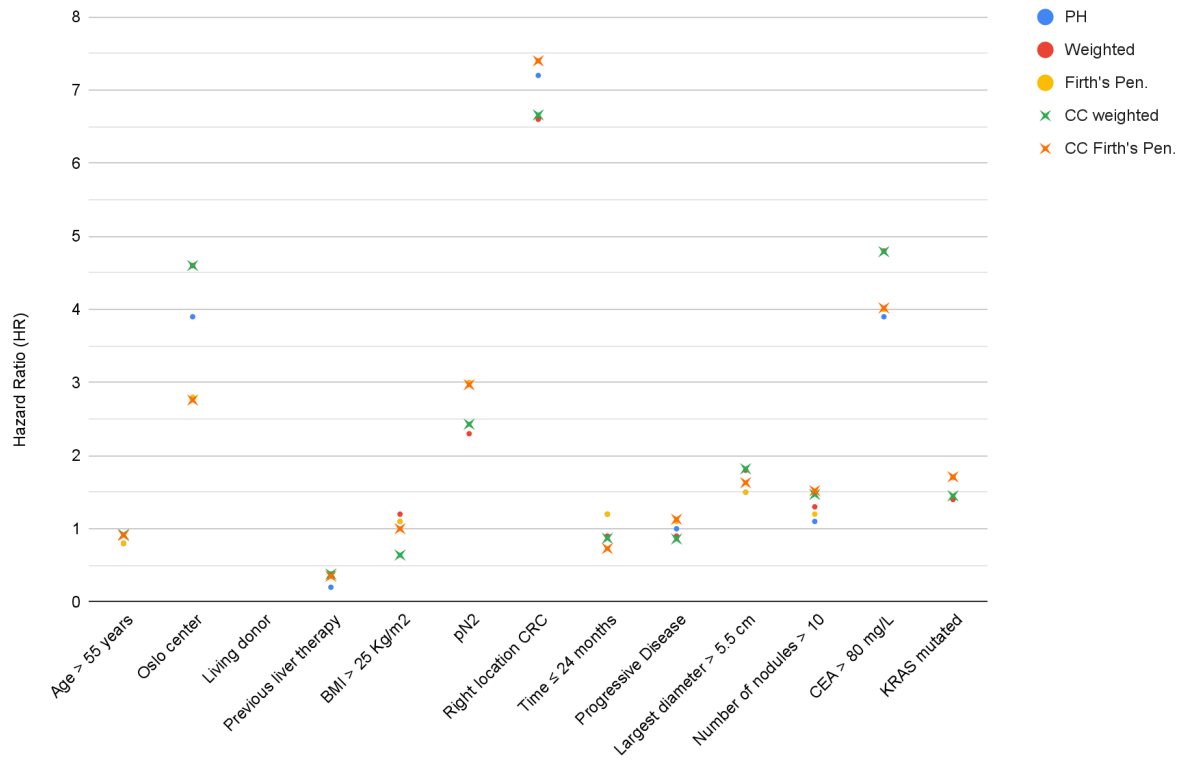


Figure S2.2. Hazard ratio (HR) point estimates for Table 3 (males) according to various models. P-values (p) concern the null hypothesis 'HR = 1.' Legend: PH = proportional hazards; Pen. = Firth's penalized; CC = ConCat.

Female

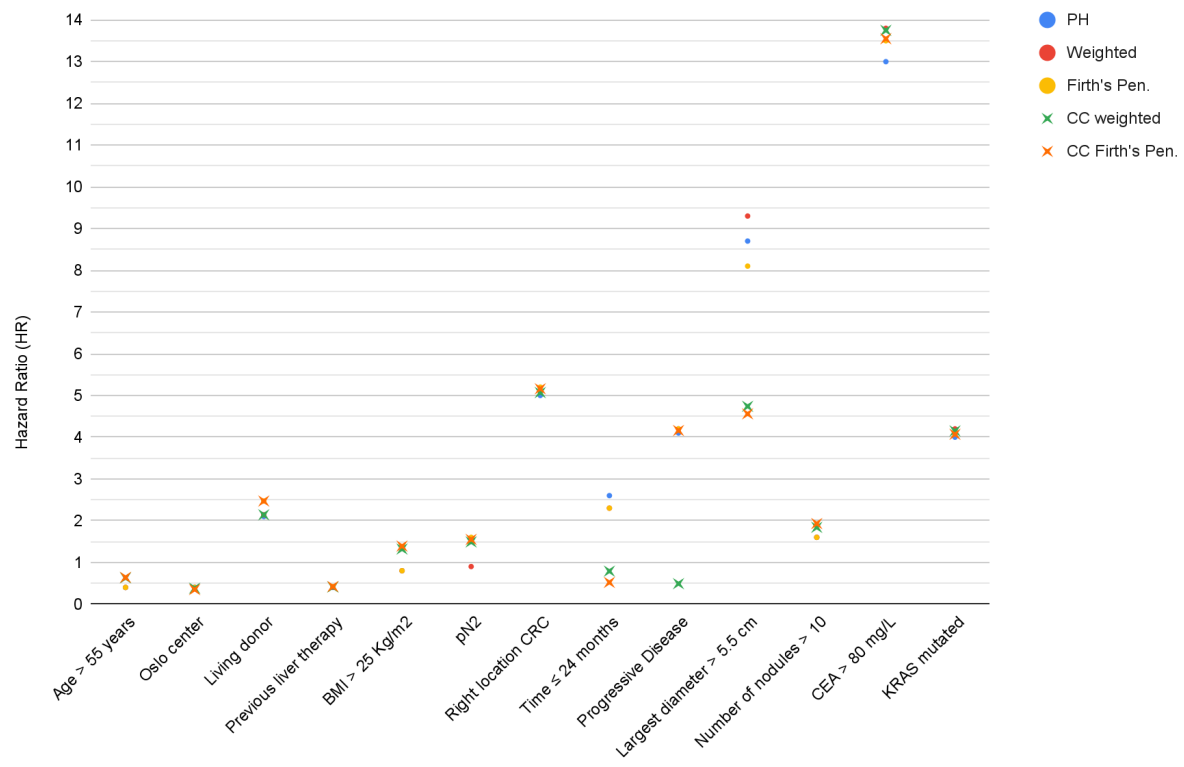


Figure S2.3. Hazard ratio (HR) point estimates for Table 3 (females) according to various models. P-values (p) concern the null hypothesis 'HR = 1.' Legend: PH = proportional hazards; Pen. = Firth's penalized; CC = ConCat.

Cause-specific multivariable models for Table 4

Liver recurrence

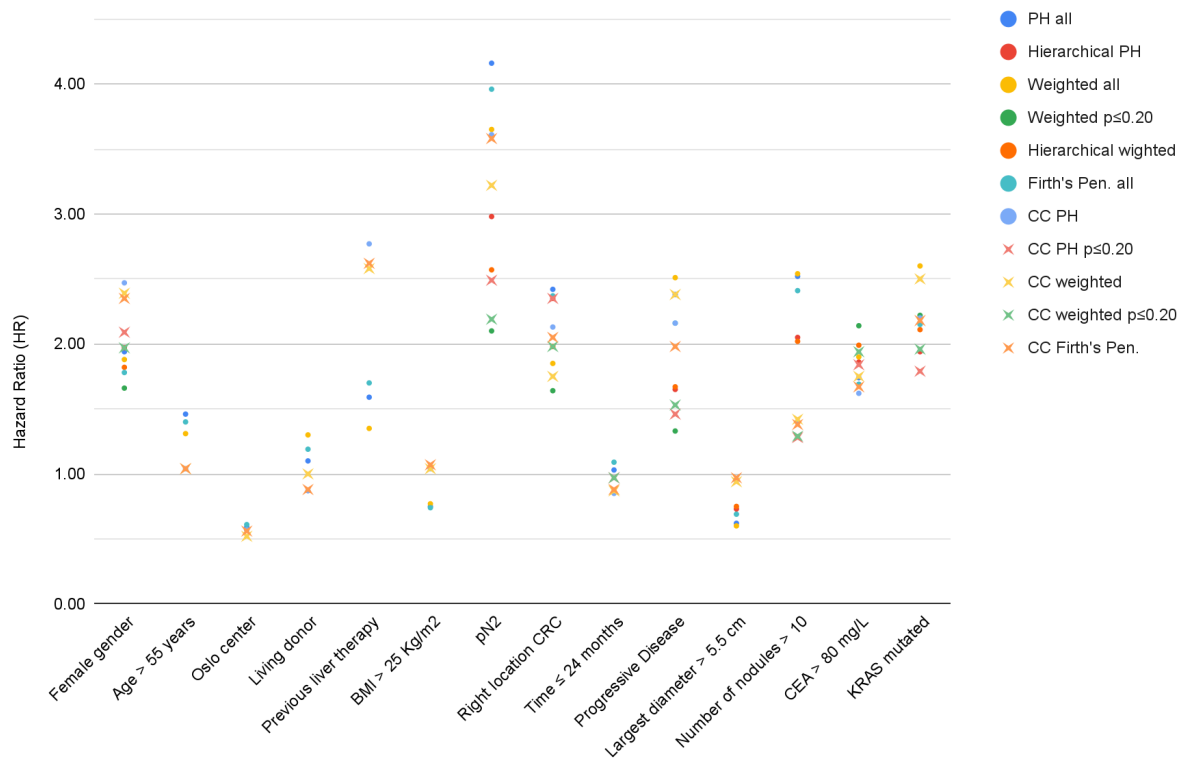


Figure S2.4. Hazard ratio (HR) point estimates for Table 4 (liver) according to various models. P-values (p) concern the null hypothesis 'HR = 1.' Legend: PH = proportional hazards; Pen. = Firth's penalized; CC = ConCat.

Non-liver (lung) recurrence

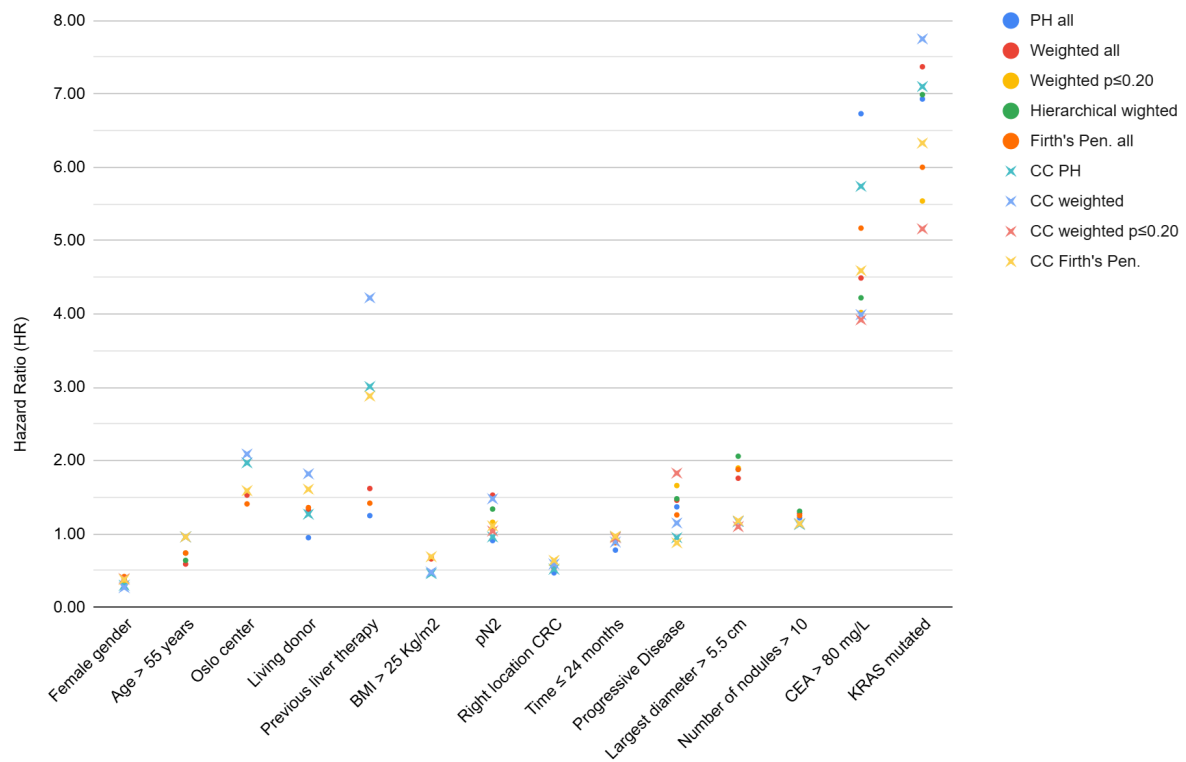
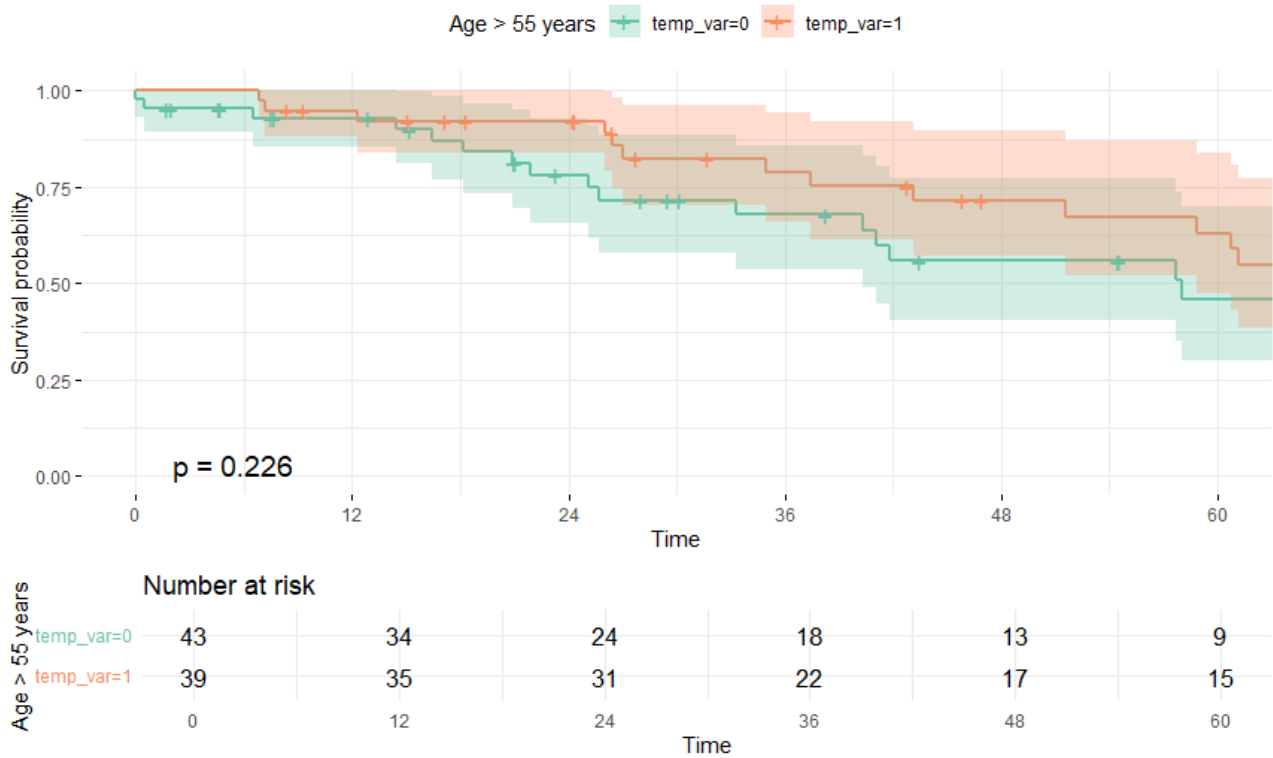


Figure S2.4. Hazard ratio (HR) point estimates for Table 4 (non-liver, lung) according to various models. P-values (p) concern the null hypothesis 'HR = 1.' Legend: PH = proportional hazards; Pen. = Firth's penalized; CC = ConCat.

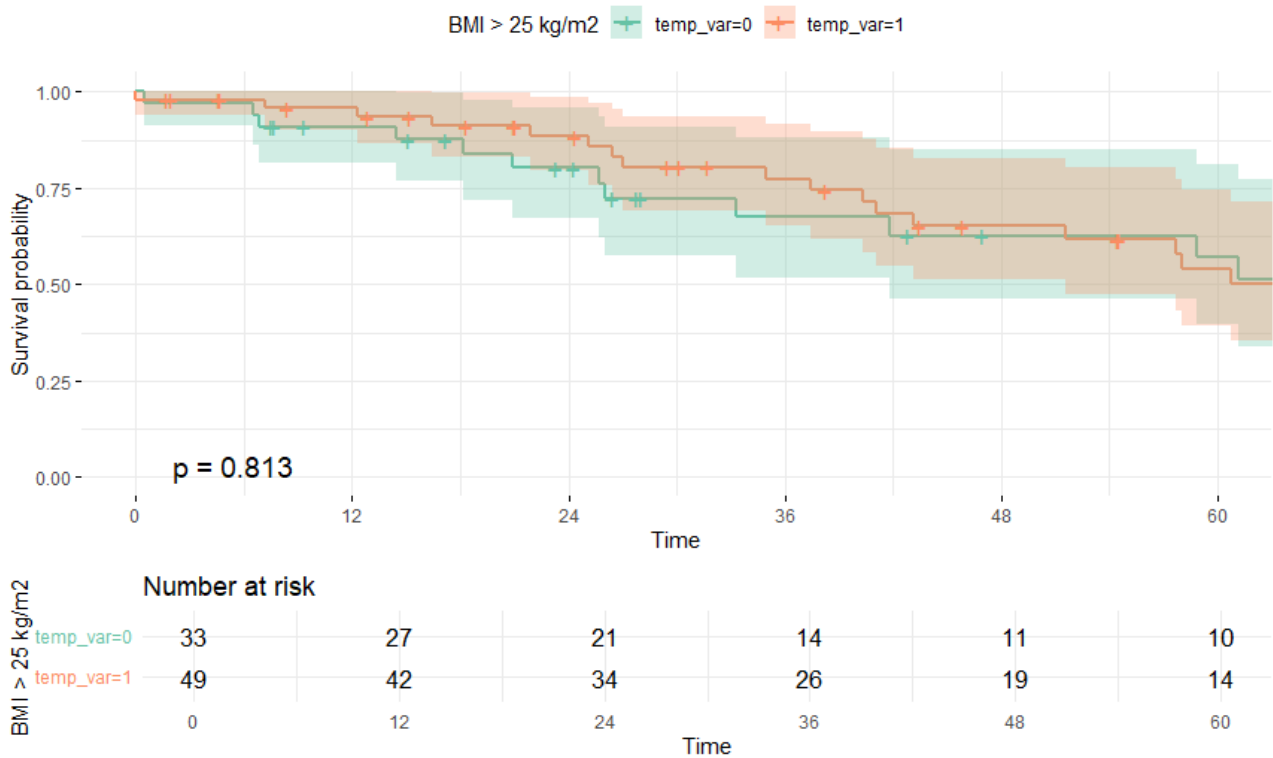
Kaplan-Meier curves

Table 2 variables

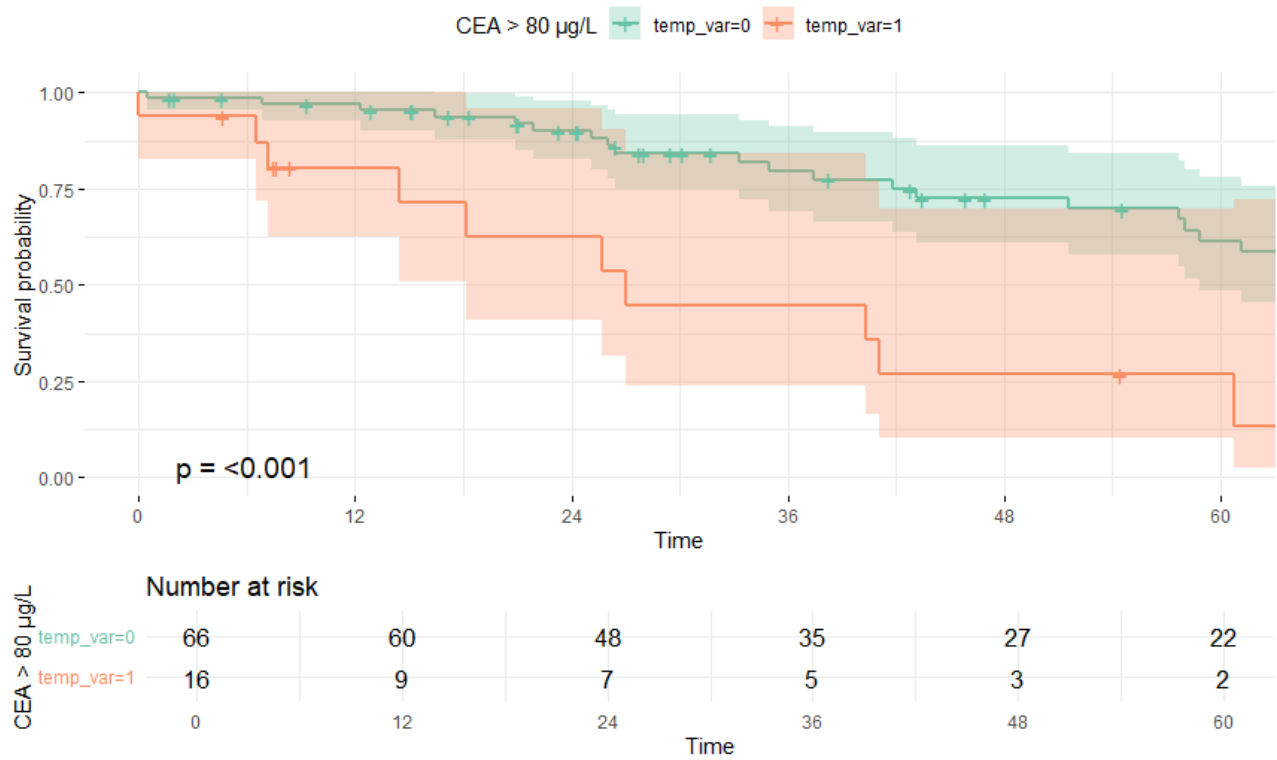
Kaplan-Meier by Age > 55 years



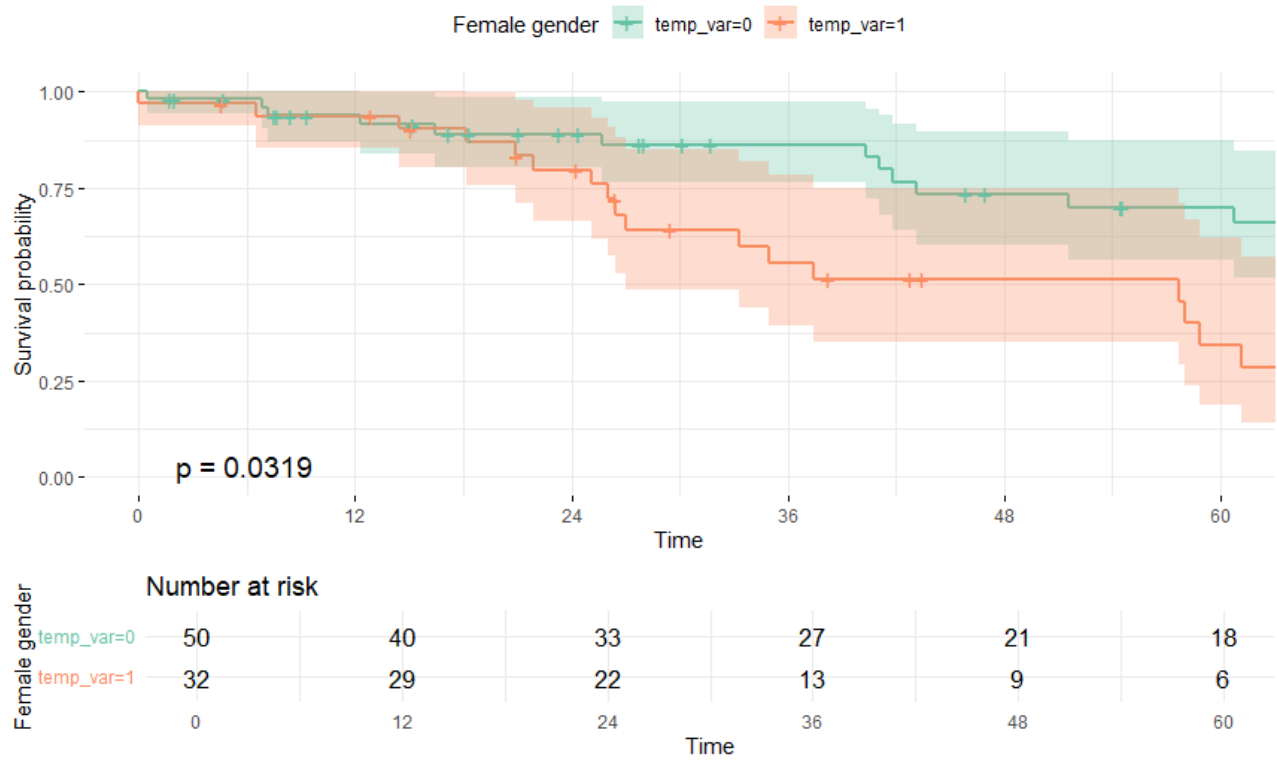
Kaplan-Meier by BMI > 25 kg/m²



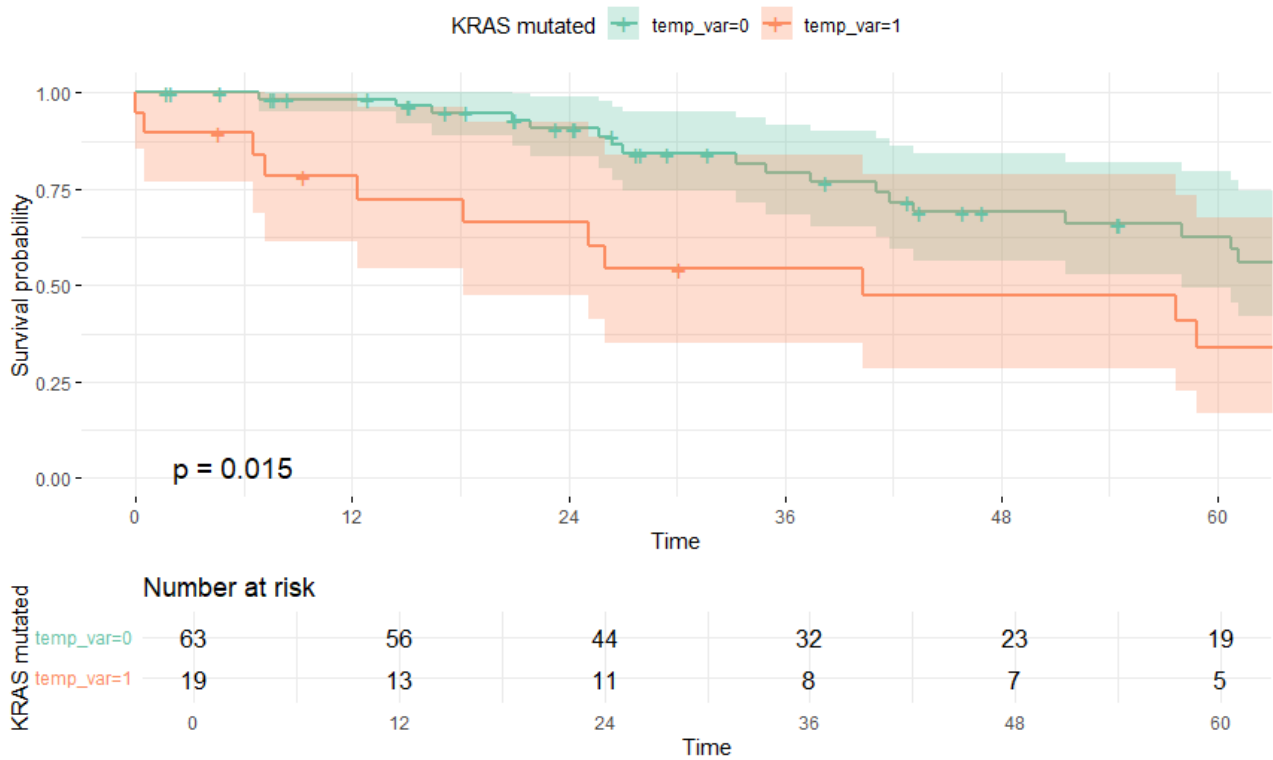
Kaplan-Meier by CEA > 80 µg/L



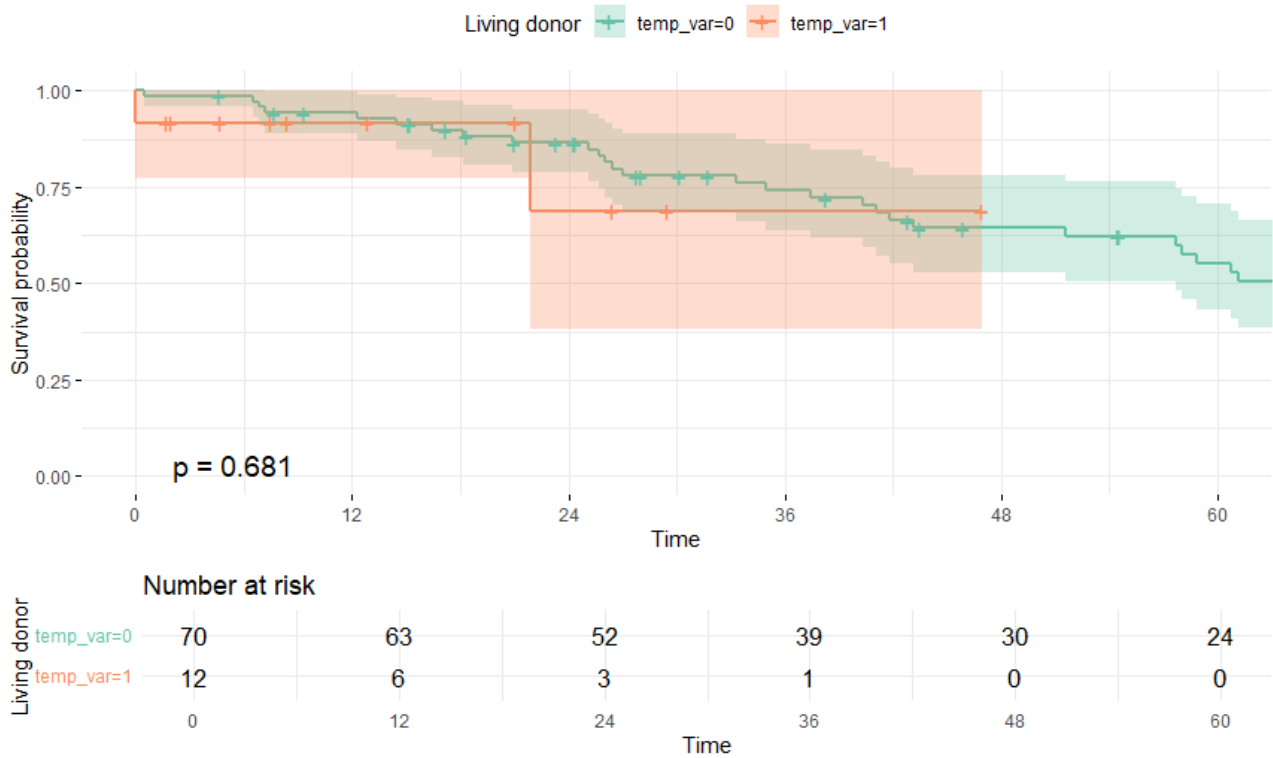
Kaplan-Meier by Female gender



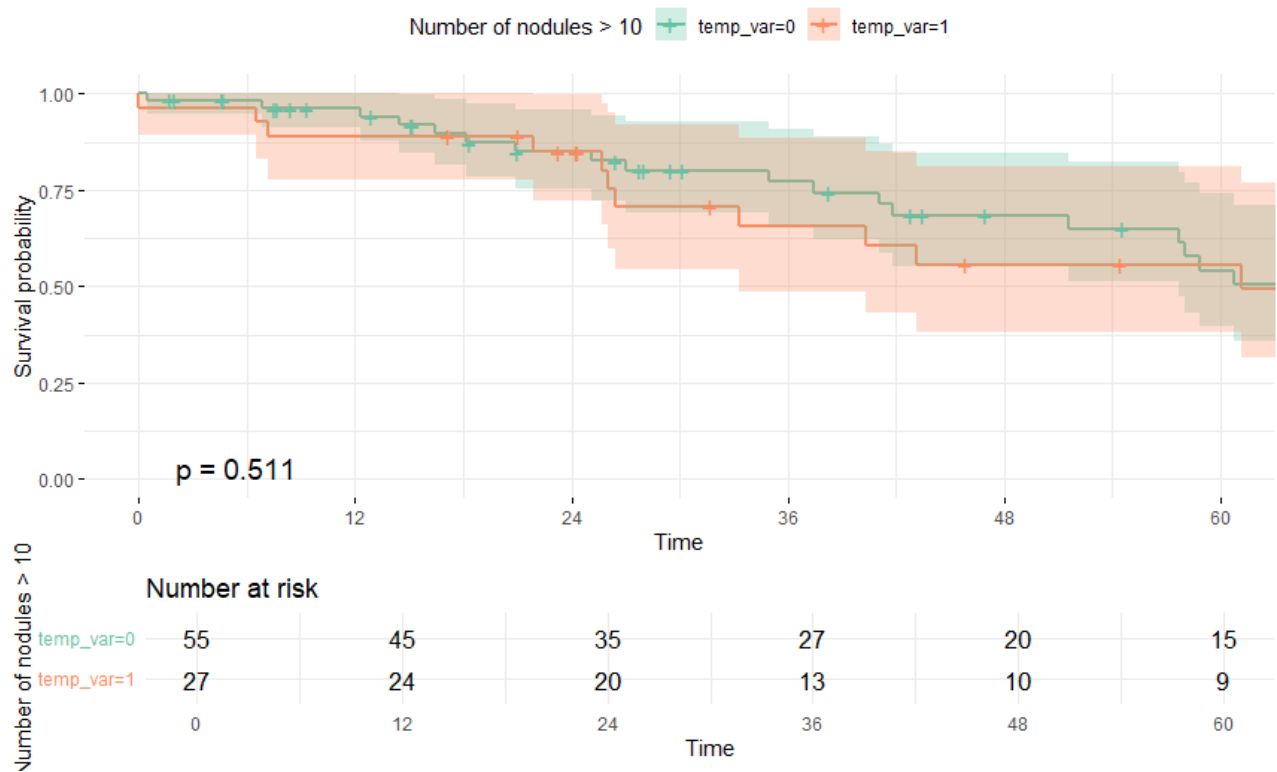
Kaplan-Meier by KRAS mutated



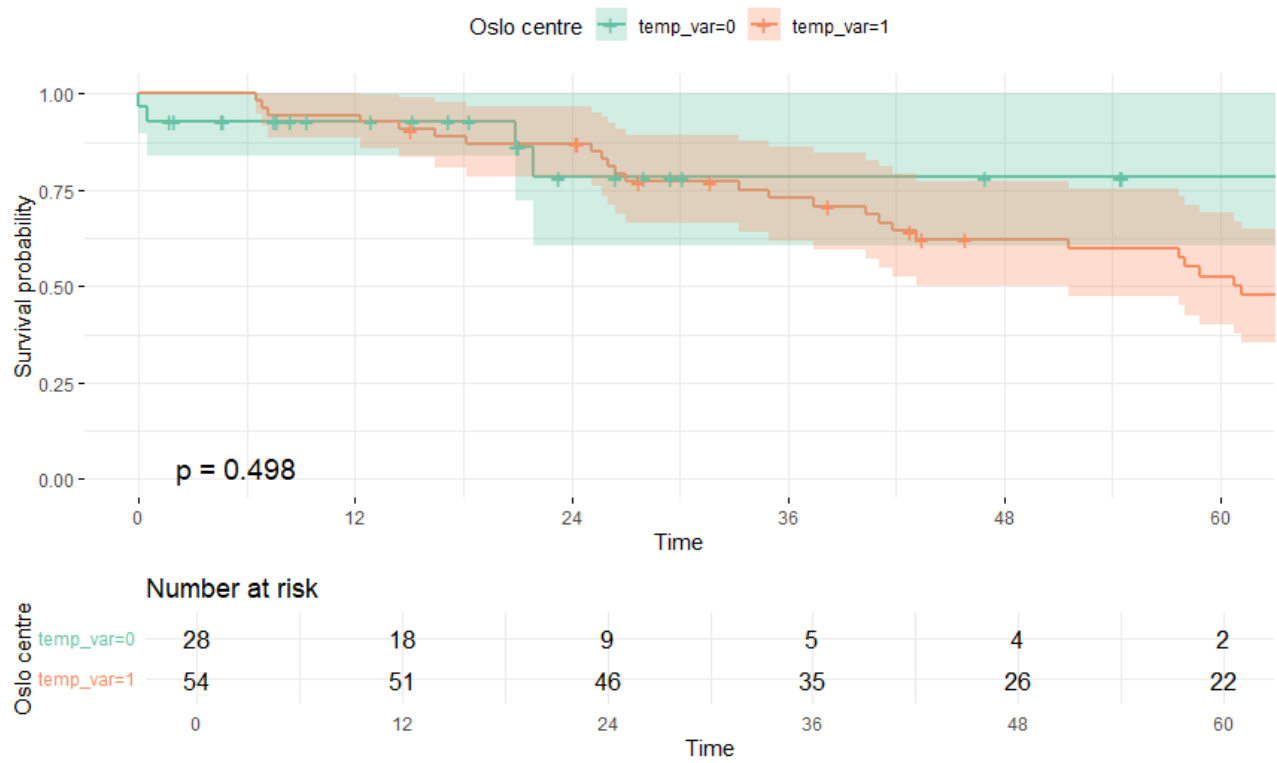
Kaplan-Meier by Living donor



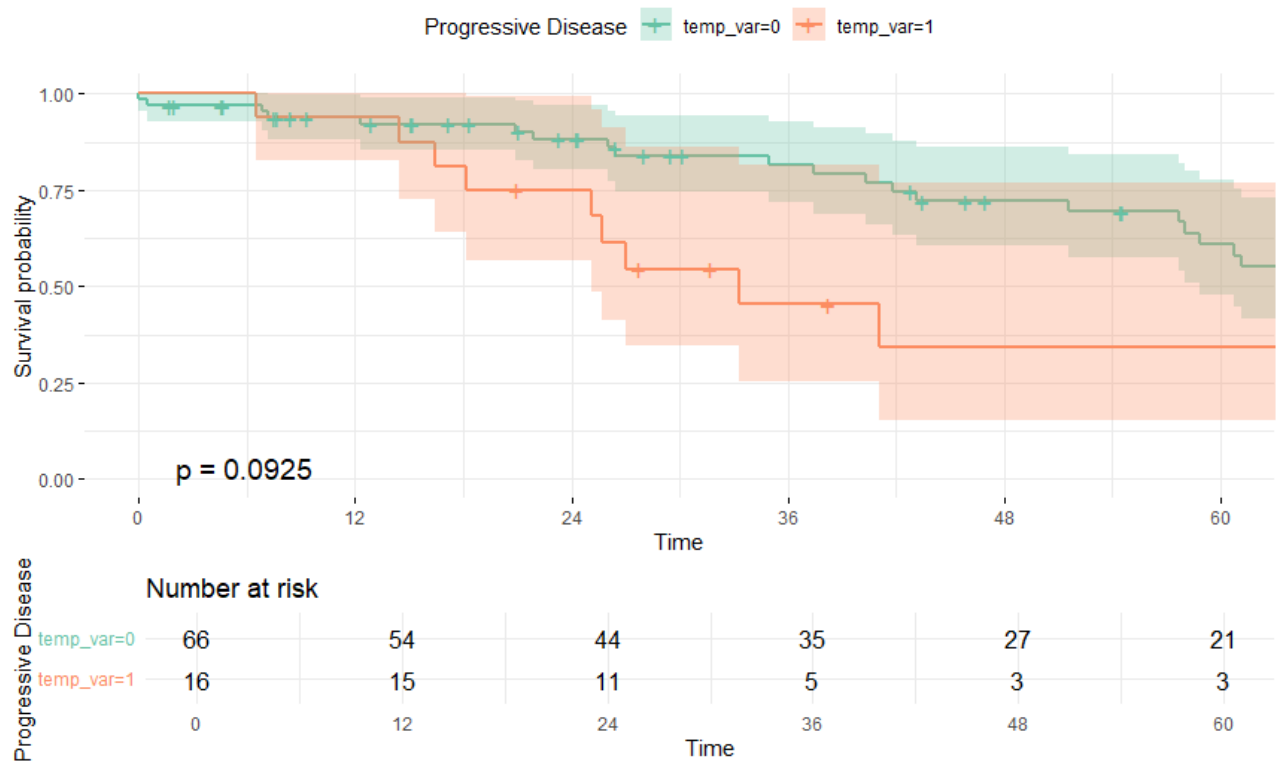
Kaplan-Meier by Number of nodules > 10



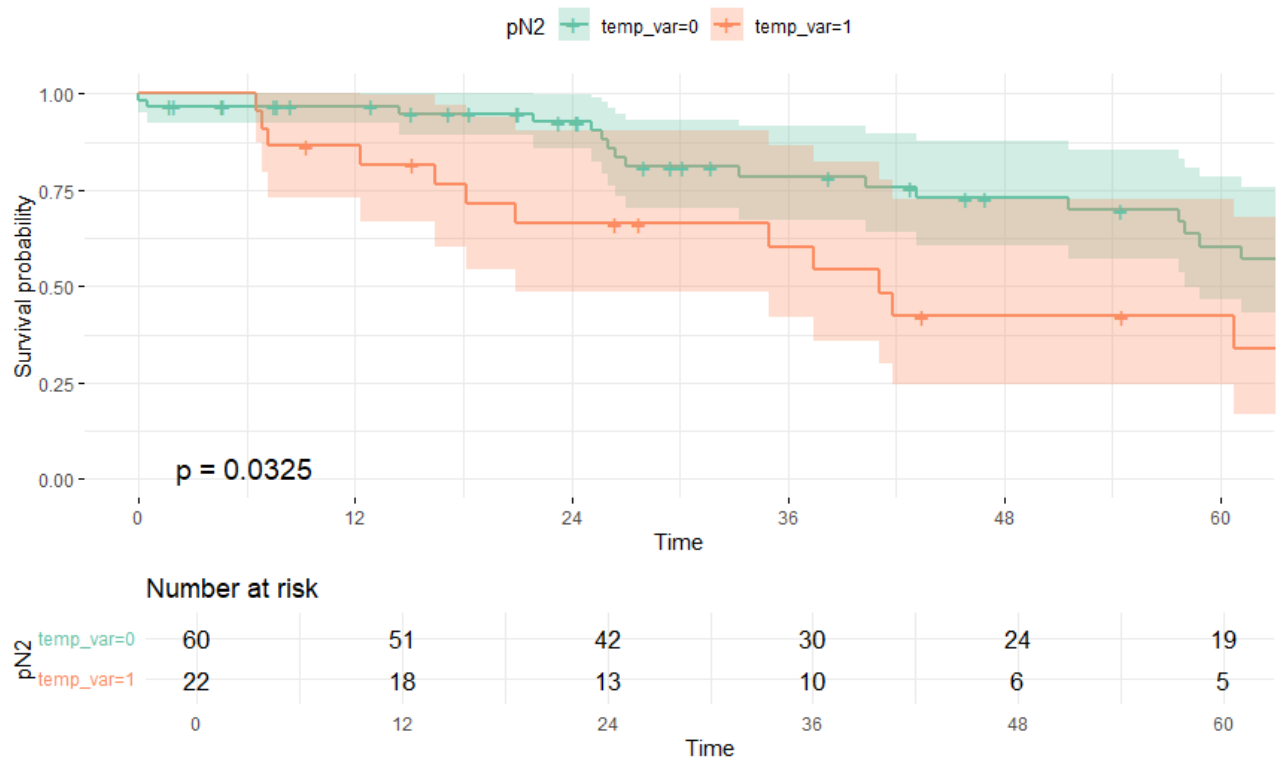
Kaplan-Meier by Oslo centre



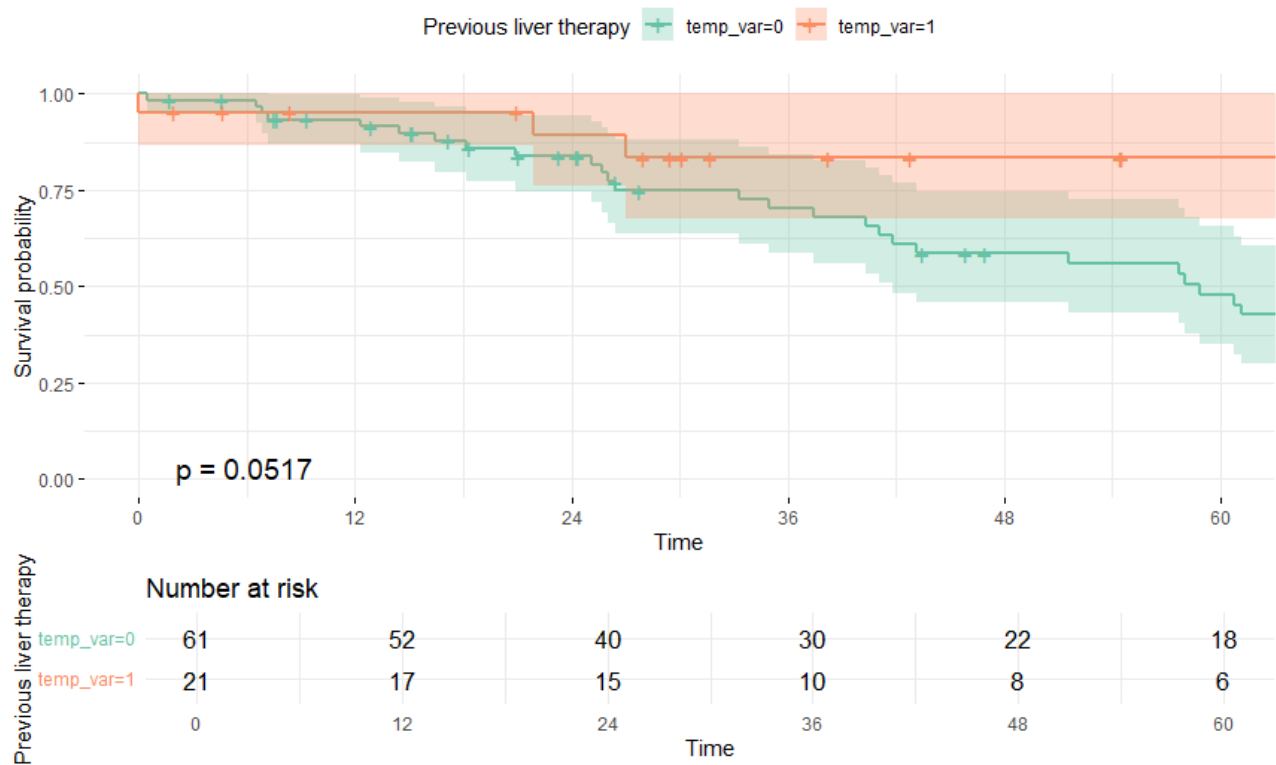
Kaplan-Meier by Progressive Disease



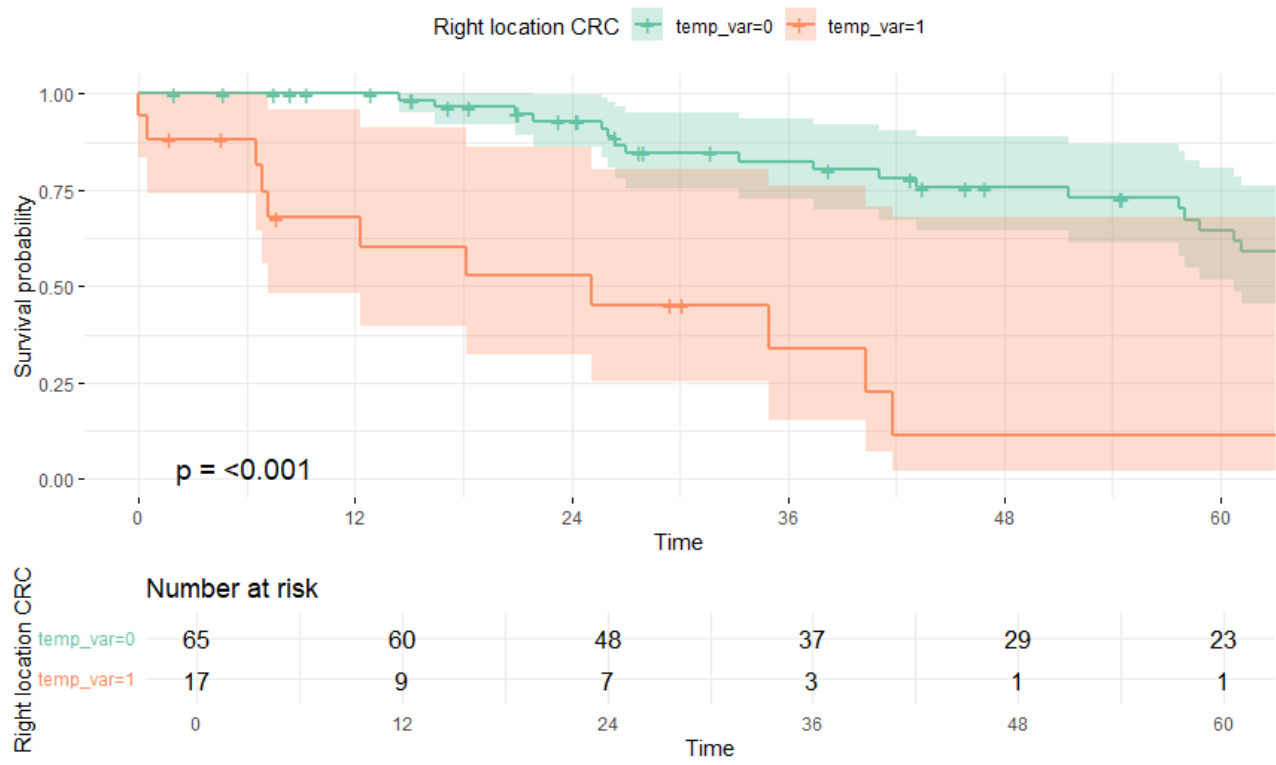
Kaplan-Meier by pN2



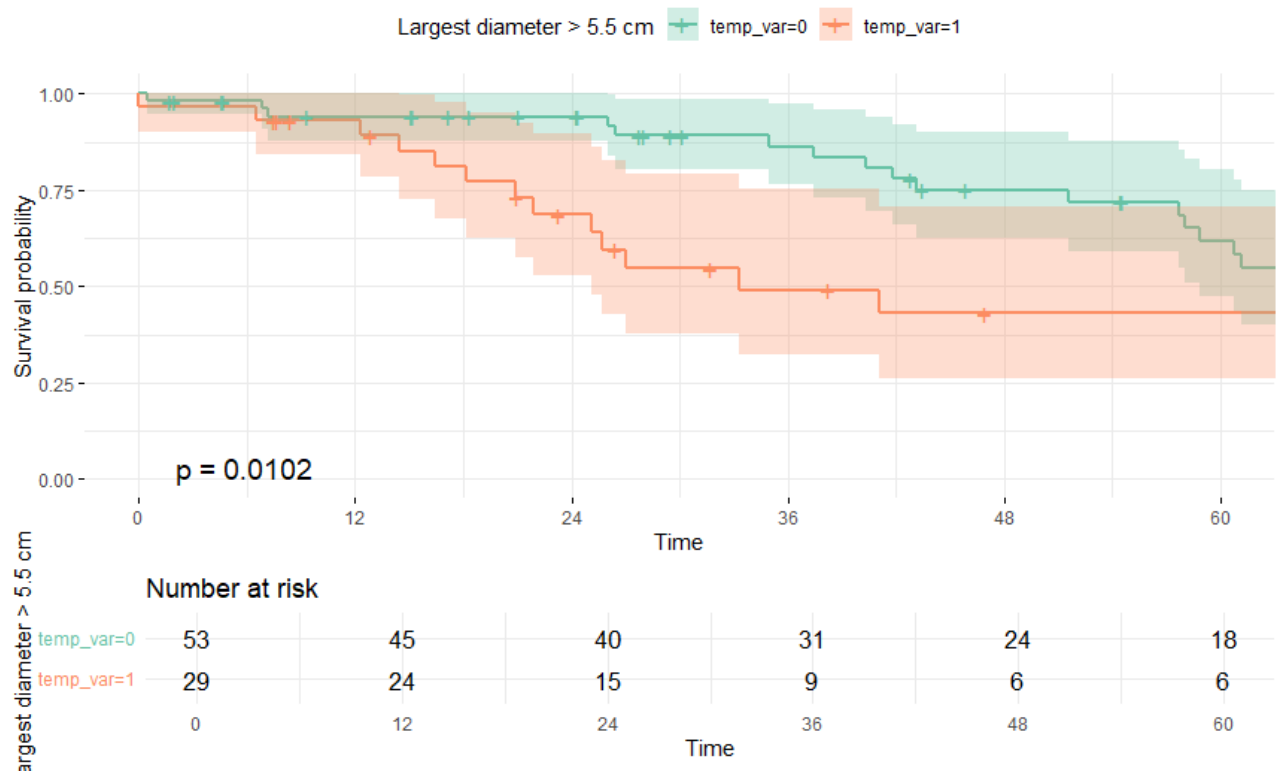
Kaplan-Meier by Previous liver therapy



Kaplan-Meier by Right location CRC



Kaplan-Meier by Largest diameter > 5.5 cm



Kaplan-Meier by Time ≤ 24 months

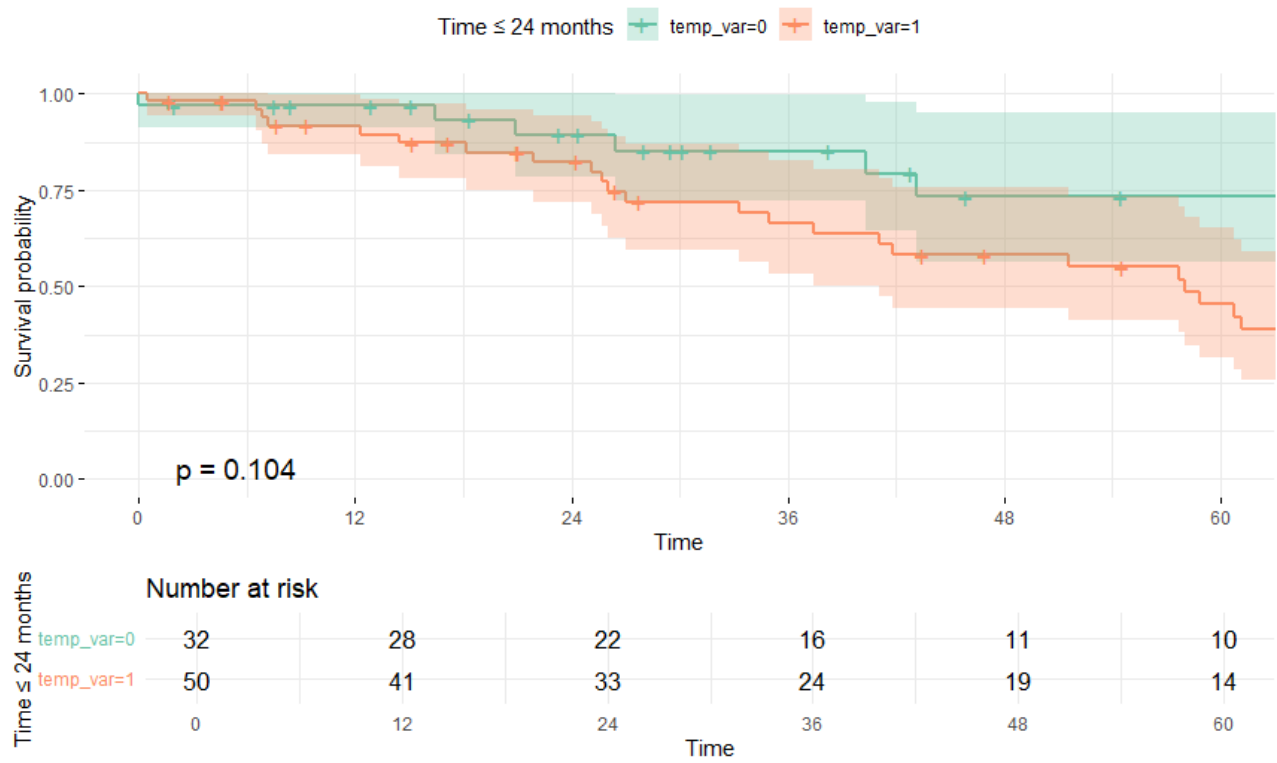
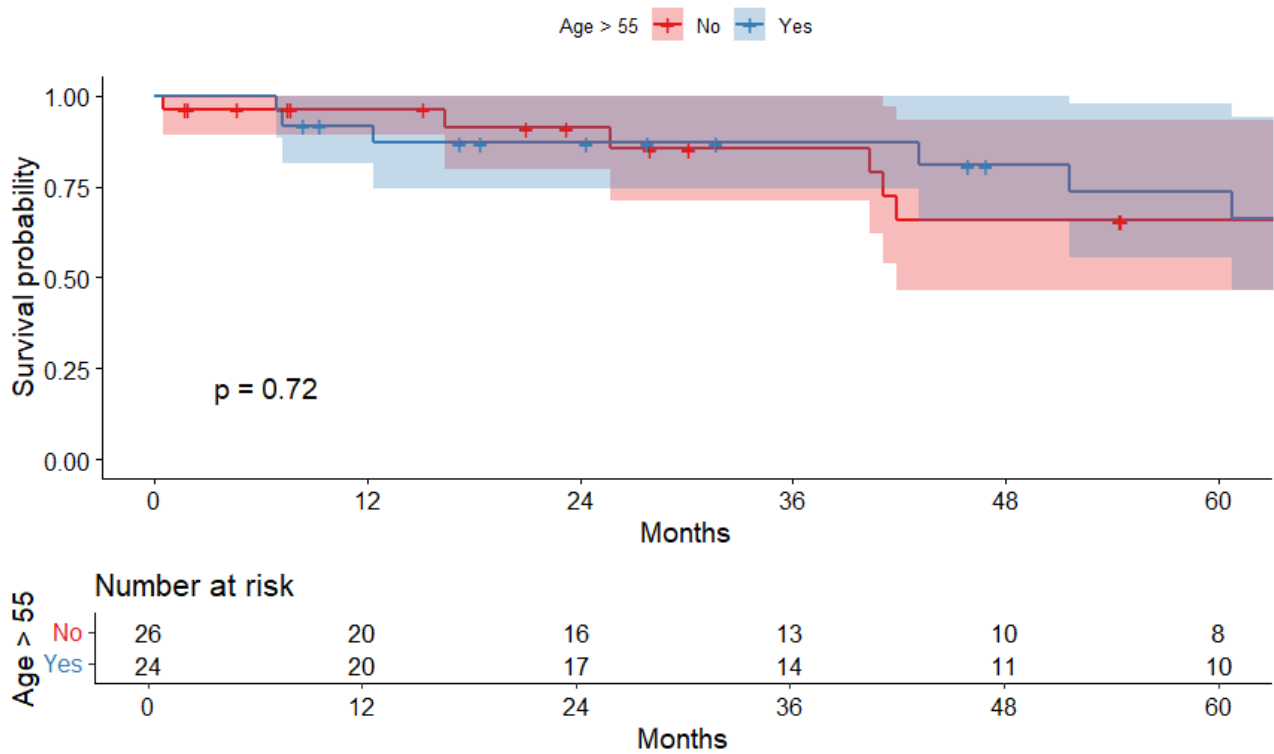
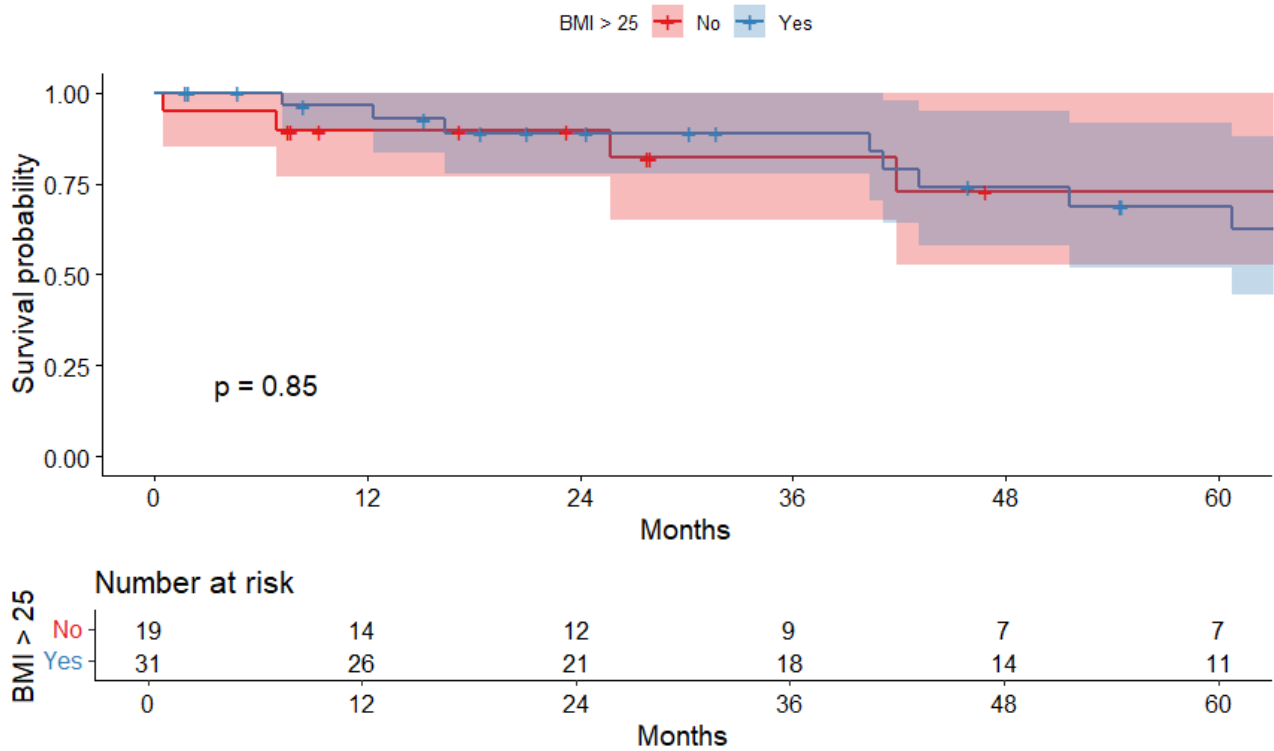


Table 3 variables

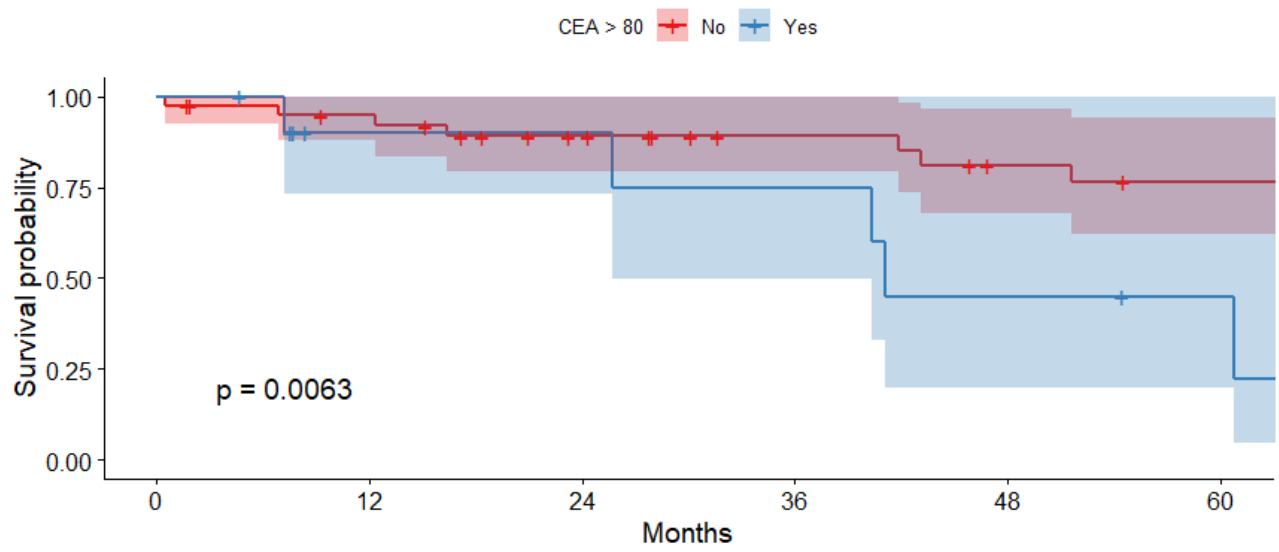
Male - Age > 55 years



Male - BMI > 25



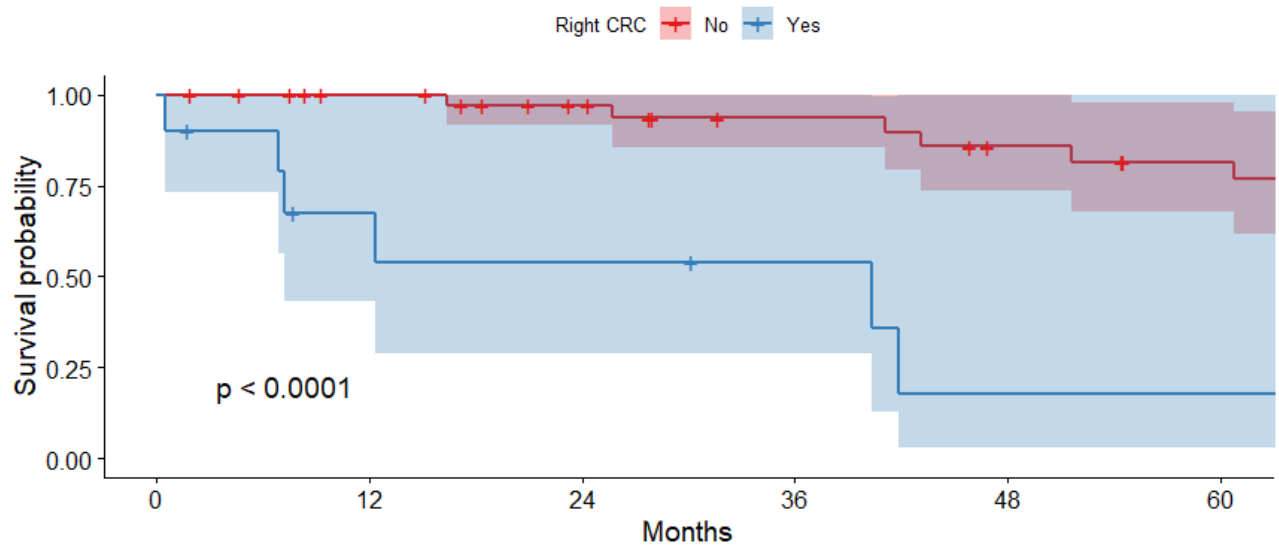
Male - CEA > 80



CEA > 80

Number at risk		Months					
No	Yes	0	12	24	36	48	60
39	11	34	6	27	5	18	16
				6		3	2

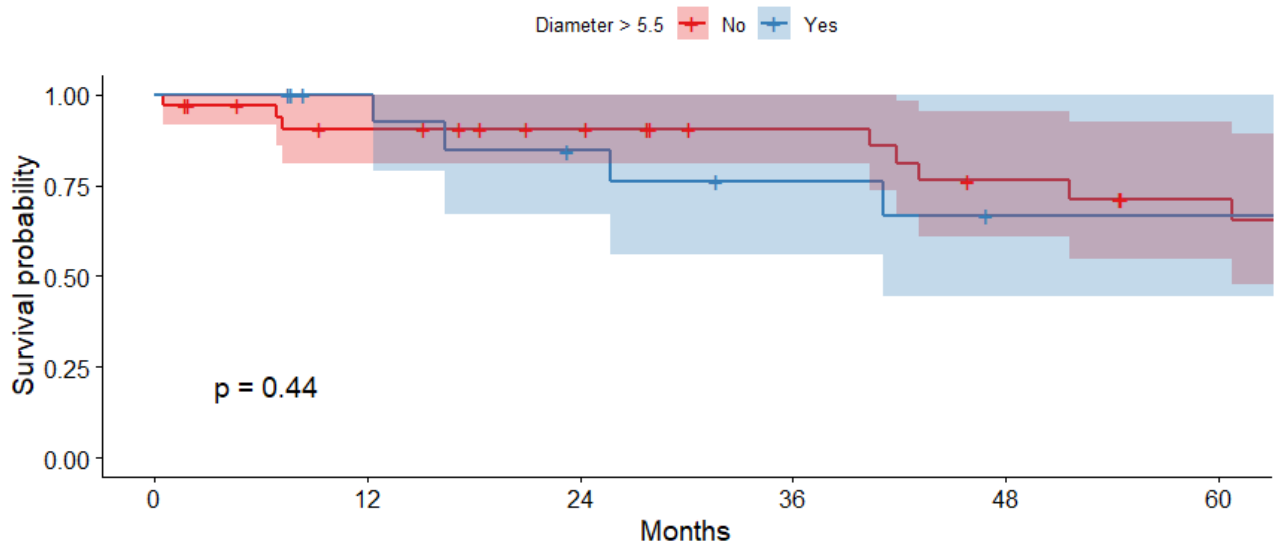
Male - Right location CRC



Right CRC

Number at risk		Months					
No	Yes	0	12	24	36	48	60
40	10	35	5	29	3	20	17
				4		1	1

Male - Diameter > 5.5 cm



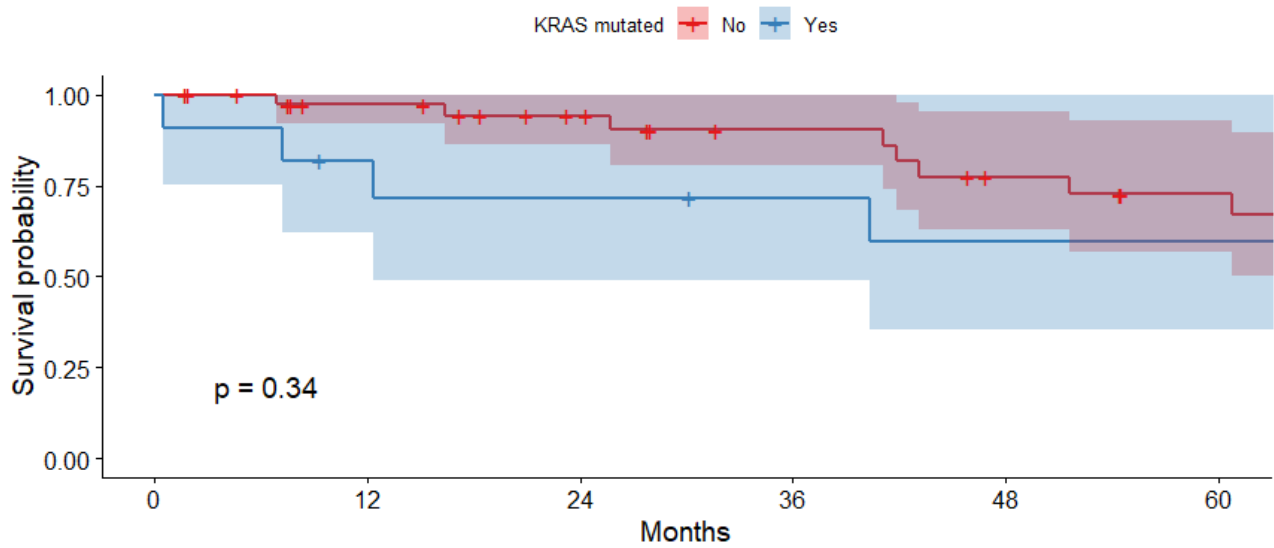
Diameter > 5.5

Number at risk

No	34	27	23	19	15	12
Yes	16	13	10	8	6	6
	0	12	24	36	48	60

Months

Male - KRAS mutated



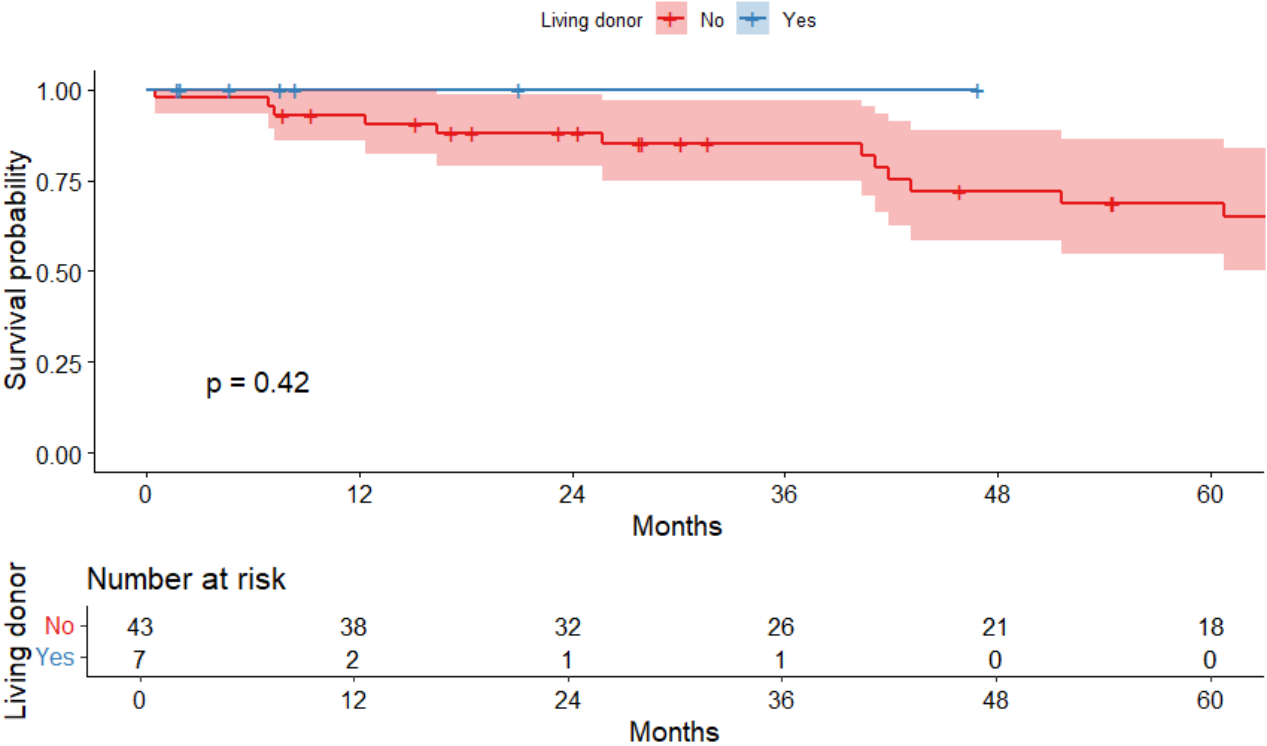
KRAS mutated

Number at risk

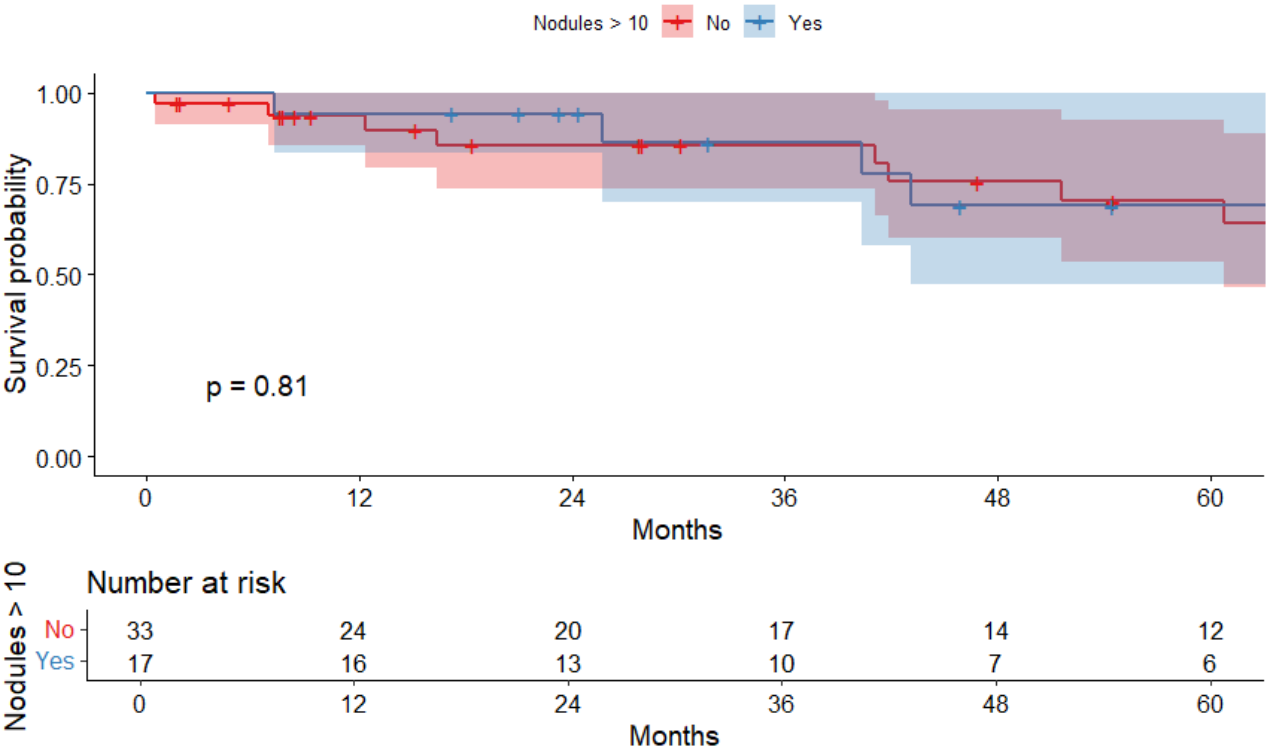
No	39	32	26	21	16	13
Yes	11	8	7	6	5	5
	0	12	24	36	48	60

Months

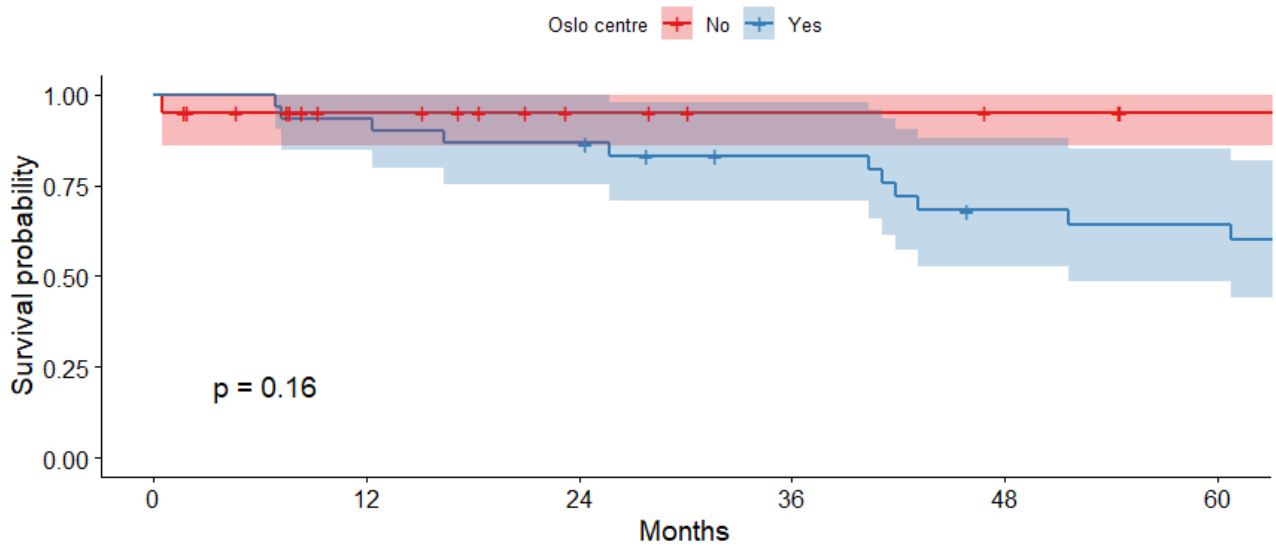
Male - Living donor



Male - Nodules > 10

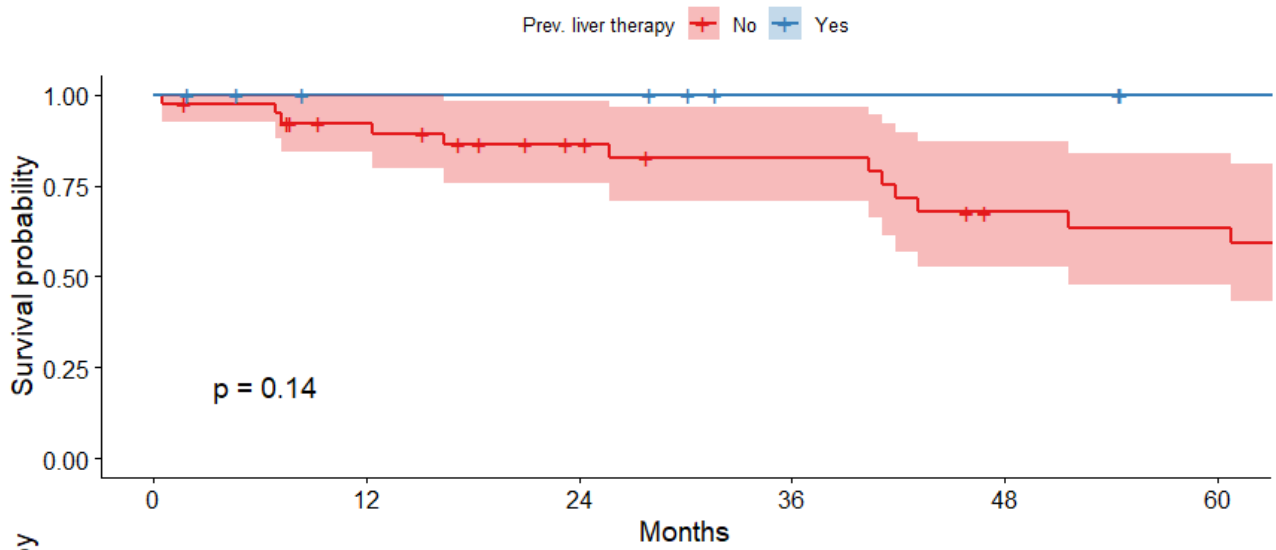


Male - Oslo centre



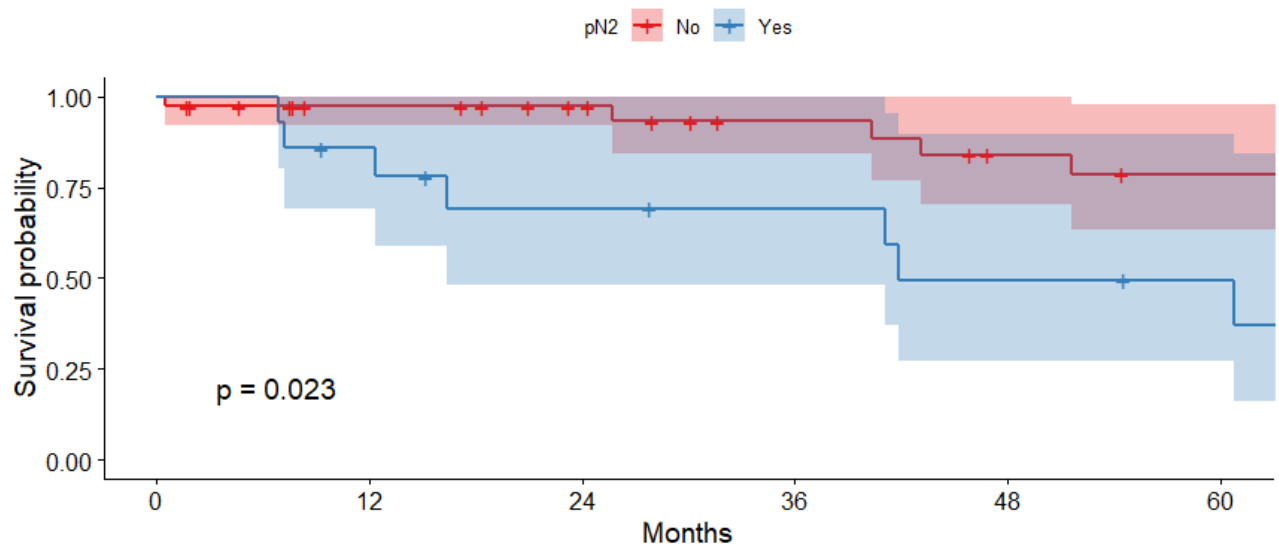
		Number at risk					
Oslo centre	No	20	12	7	5	4	2
	Yes	30	28	26	22	17	16
		0	12	24	36	48	60
		Months					

Male - Previous liver therapy



		Number at risk					
Prev. liver therapy	No	39	32	25	22	16	15
	Yes	11	8	8	5	5	3
		0	12	24	36	48	60
		Months					

Male - pN2

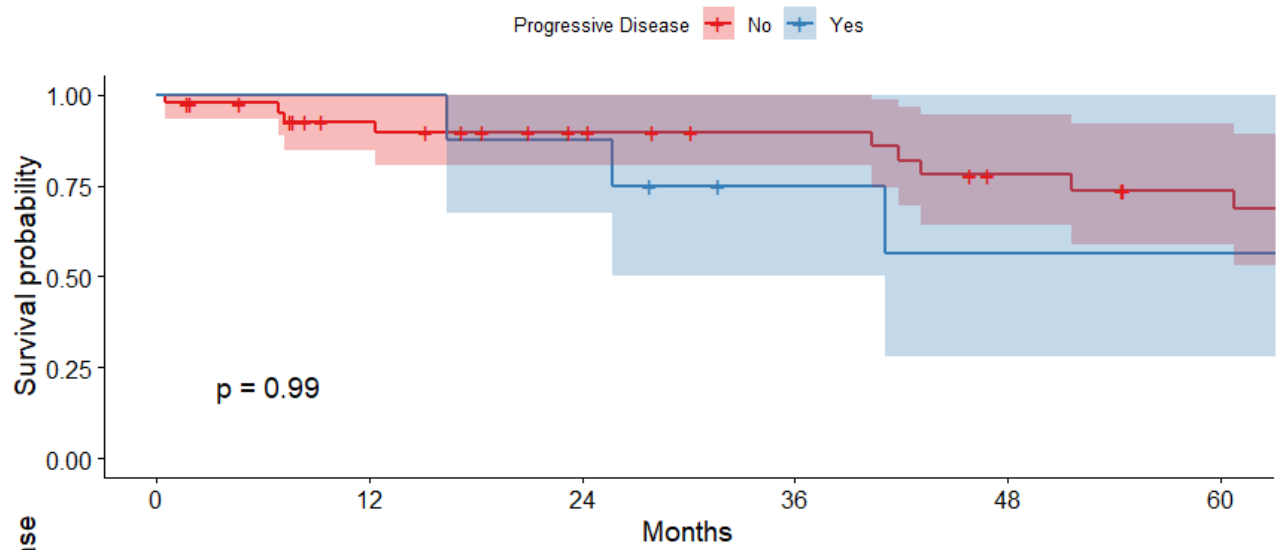


Number at risk

pN2 No	36	29	25	20	16	14
Yes	14	11	8	7	5	4
	0	12	24	36	48	60

Months

Male - Progressive Disease

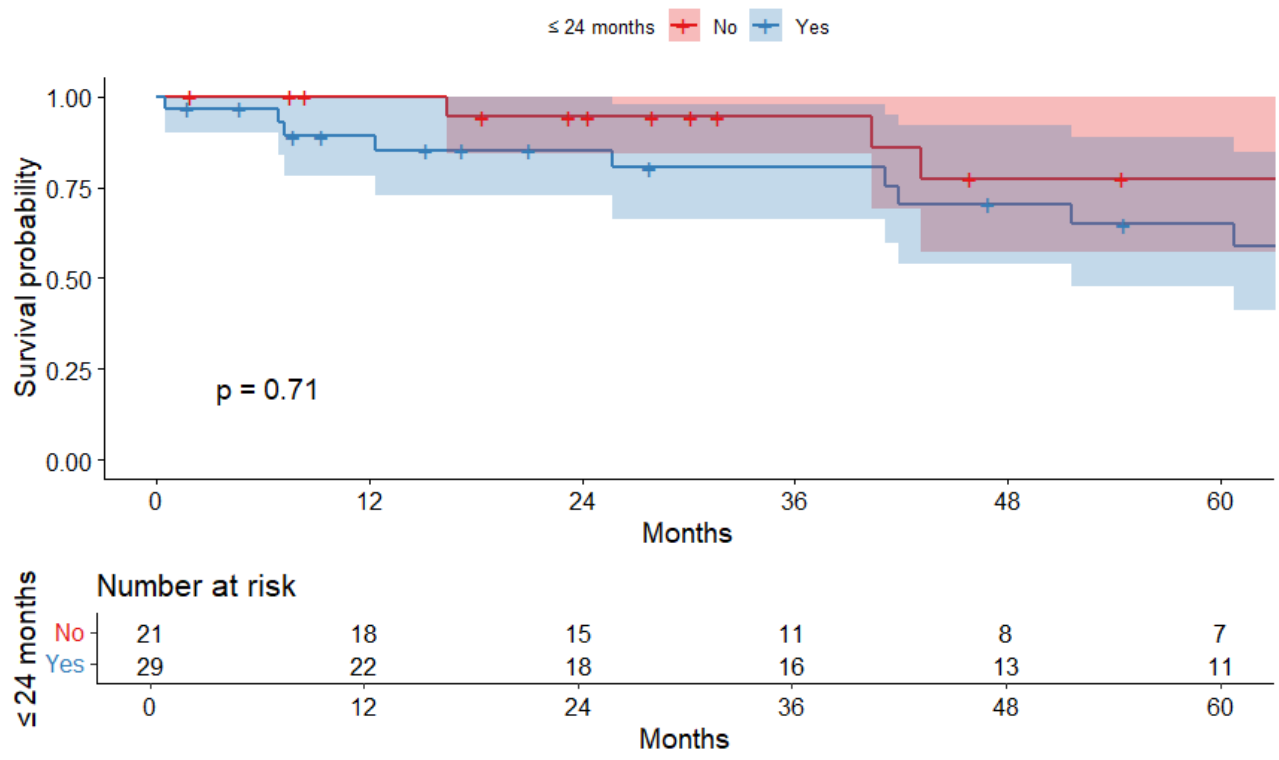


Number at risk

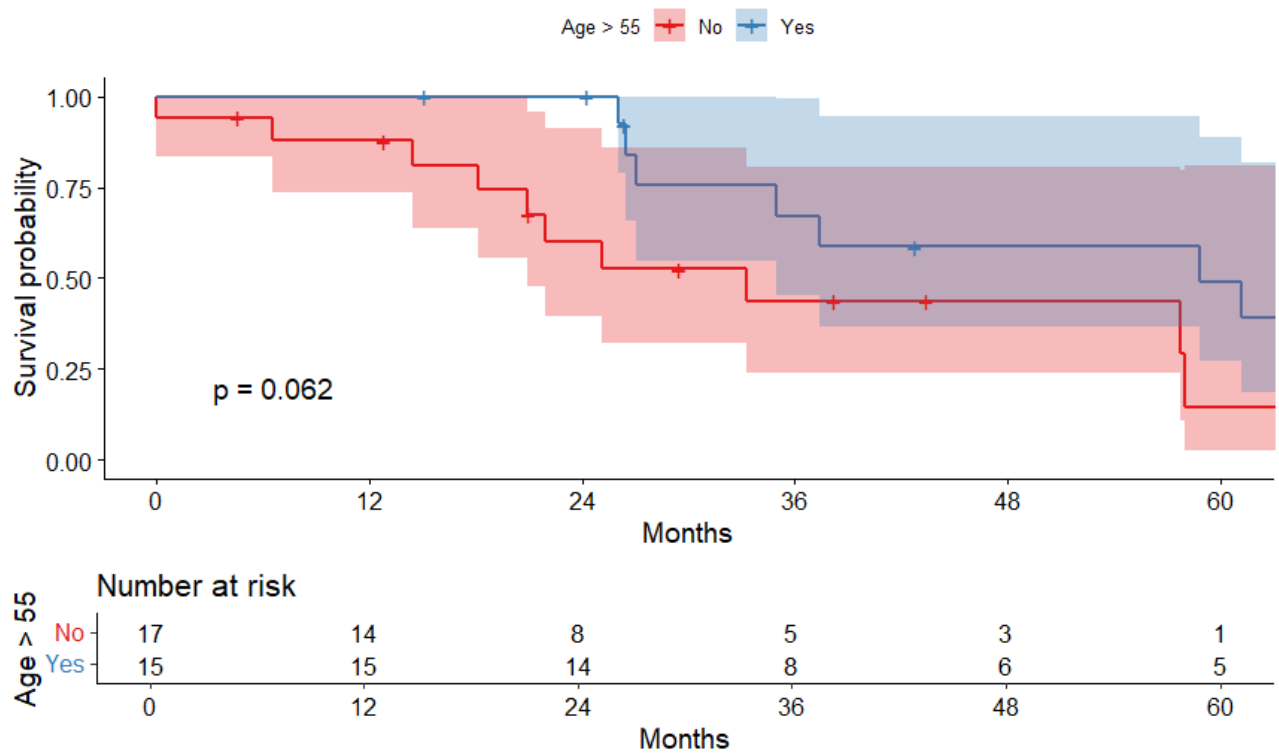
Progressive Disease No	42	32	26	23	18	15
Yes	8	8	7	4	3	3
	0	12	24	36	48	60

Months

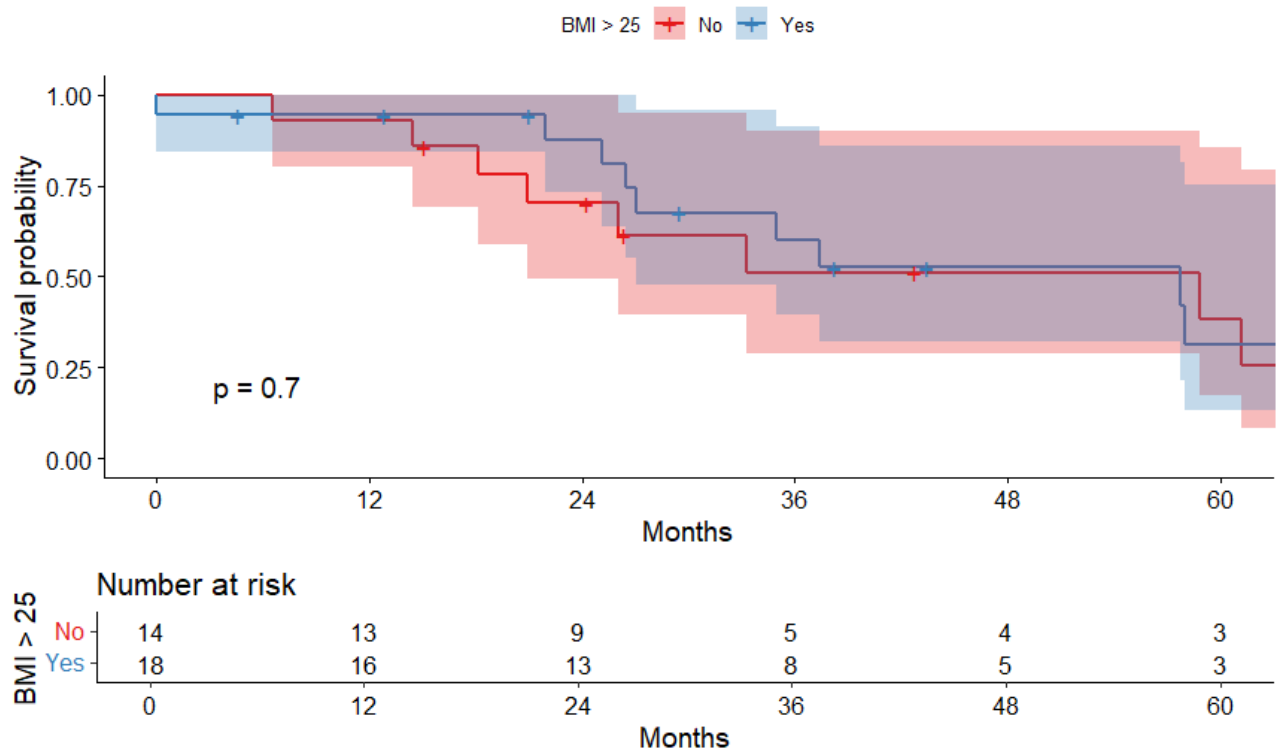
Male - Time \leq 24 months



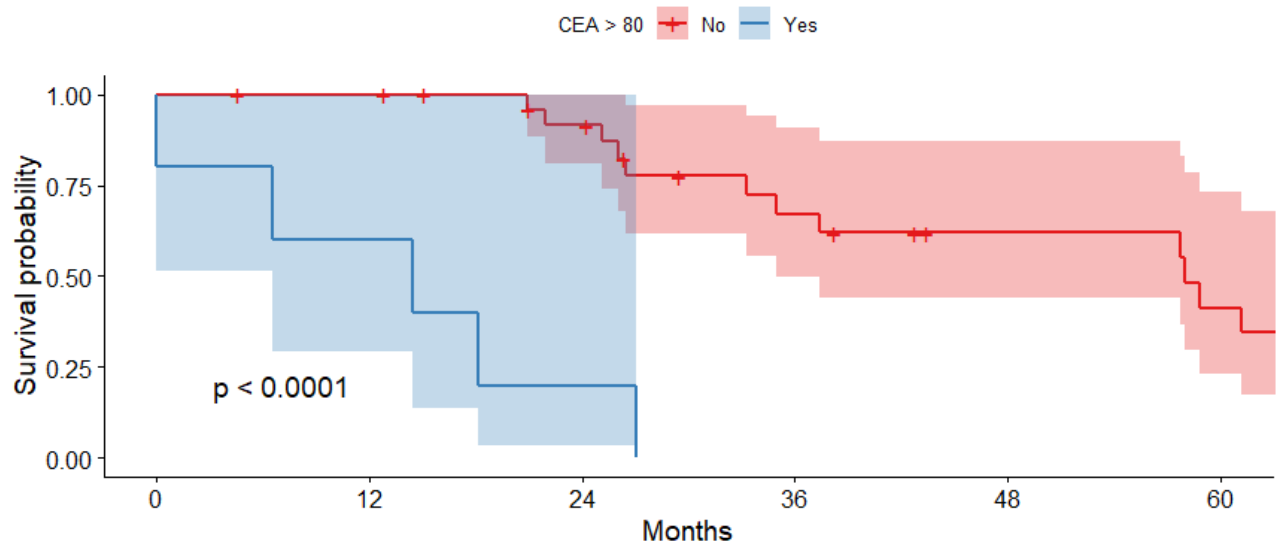
Female - Age > 55 years



Female - BMI > 25



Female - CEA > 80



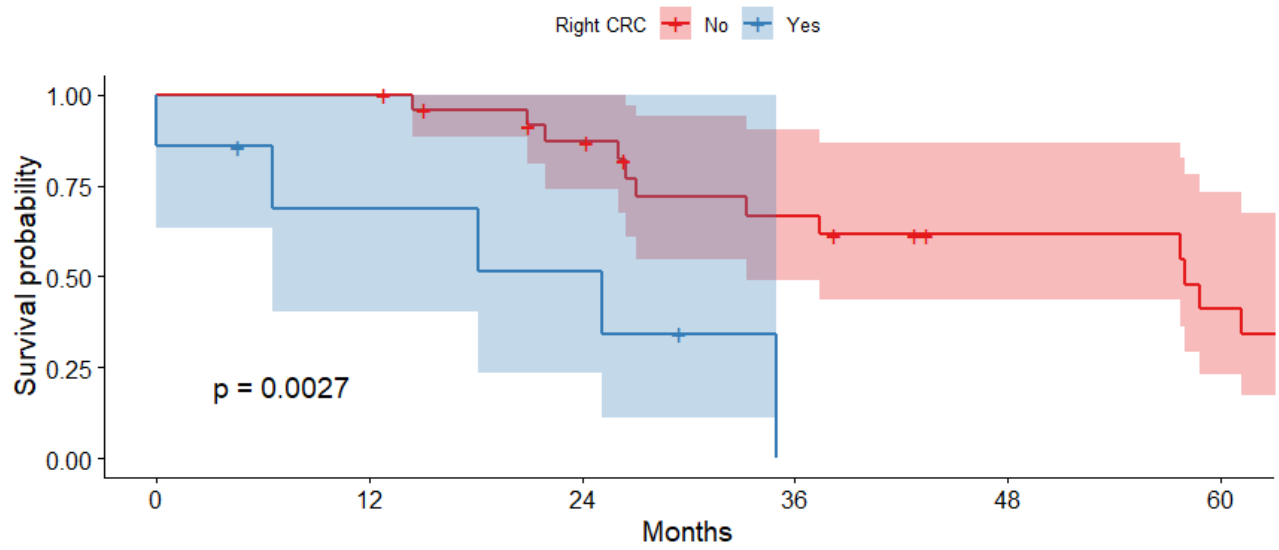
CEA > 80

Number at risk

No	27	26	21	13	9	6
Yes	5	3	1	0	0	0

Months

Female - Right location CRC



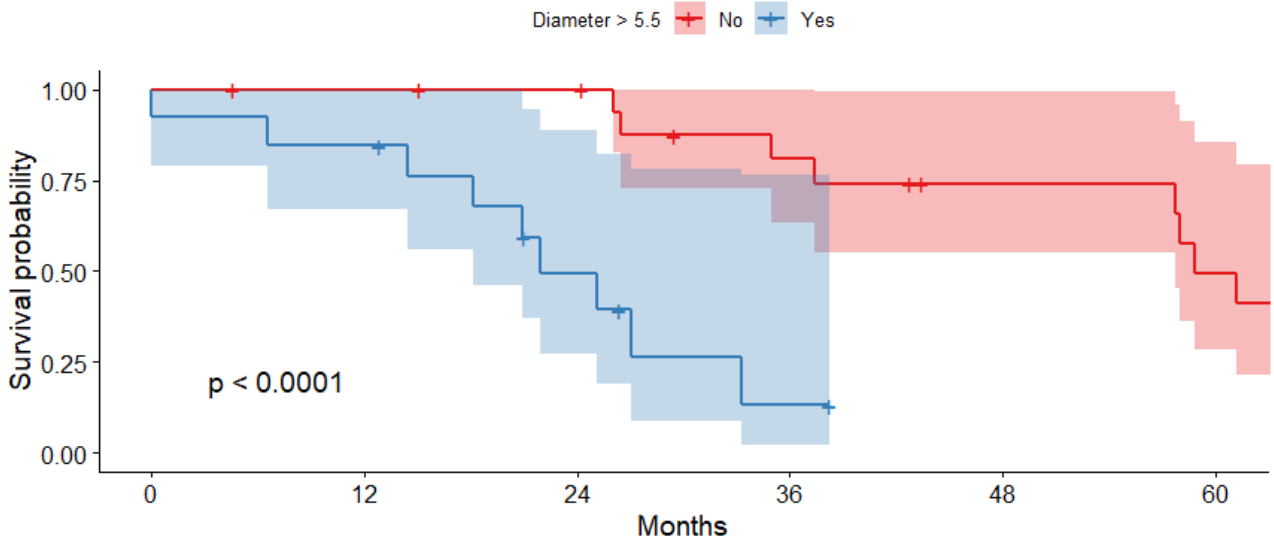
Right CRC

Number at risk

No	25	25	19	13	9	6
Yes	7	4	3	0	0	0

Months

Female - Diameter > 5.5 cm

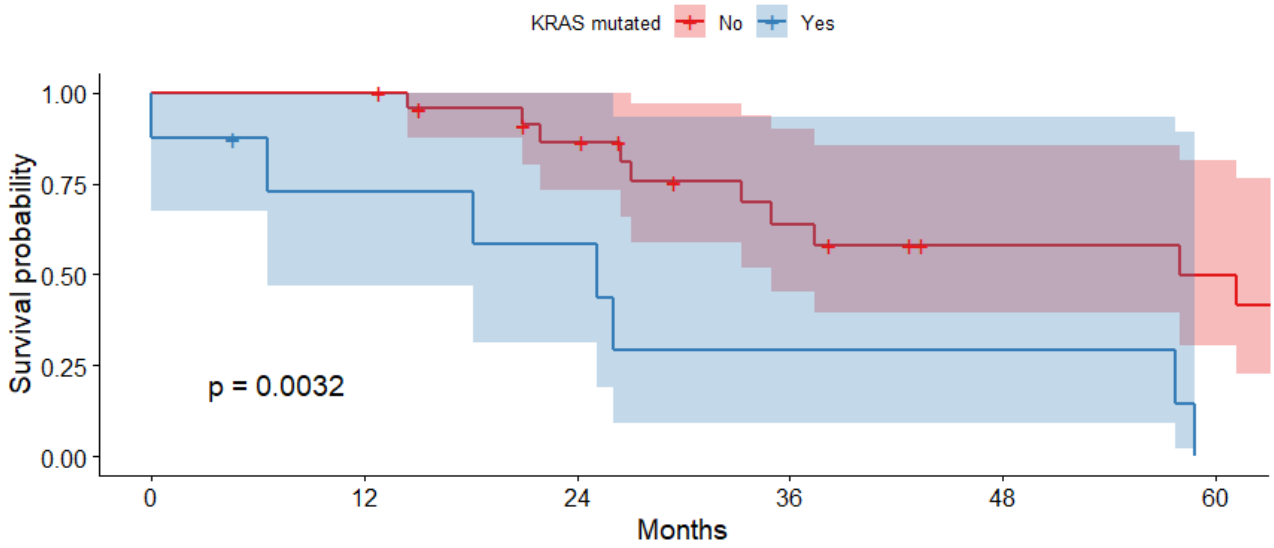


Diameter > 5.5

Number at risk						
No	19	18	17	12	9	6
Yes	13	11	5	1	0	0
	0	12	24	36	48	60

Months

Female - KRAS mutated

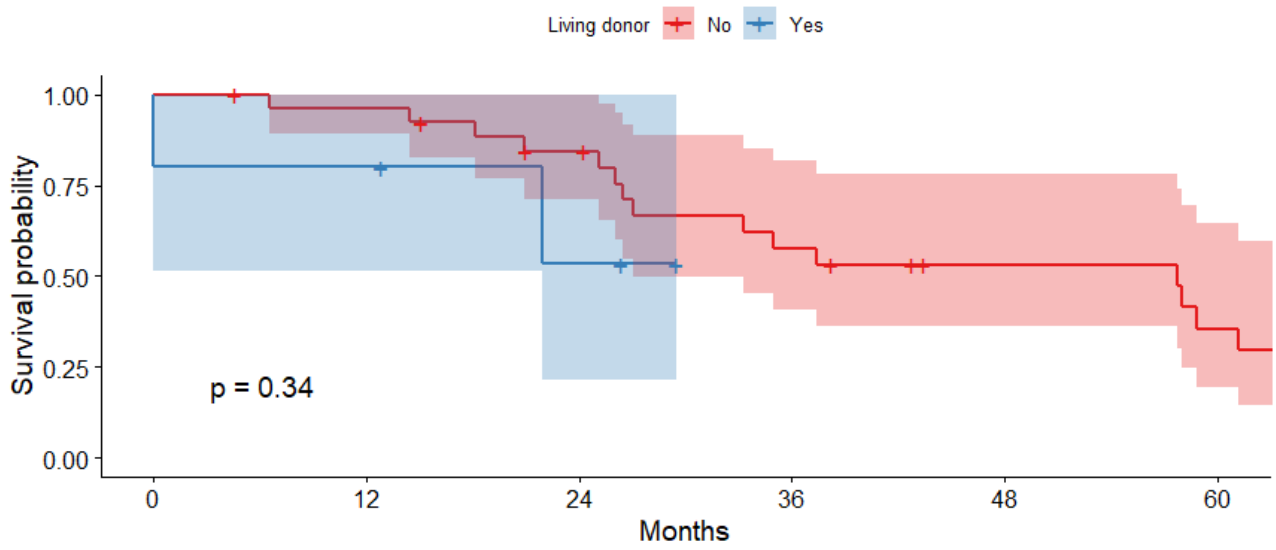


KRAS mutated

Number at risk						
No	24	24	18	11	7	6
Yes	8	5	4	2	2	0
	0	12	24	36	48	60

Months

Female - Living donor

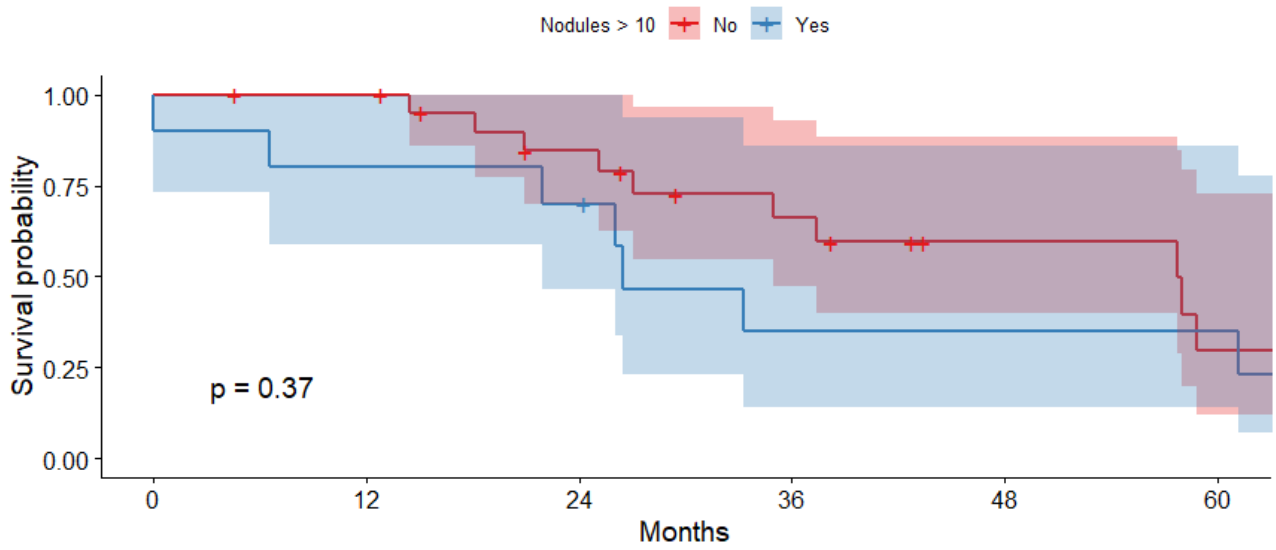


Number at risk

Living donor	0	12	24	36	48	60
No	27	25	20	13	9	6
Yes	5	4	2	0	0	0

Months

Female - Nodules > 10

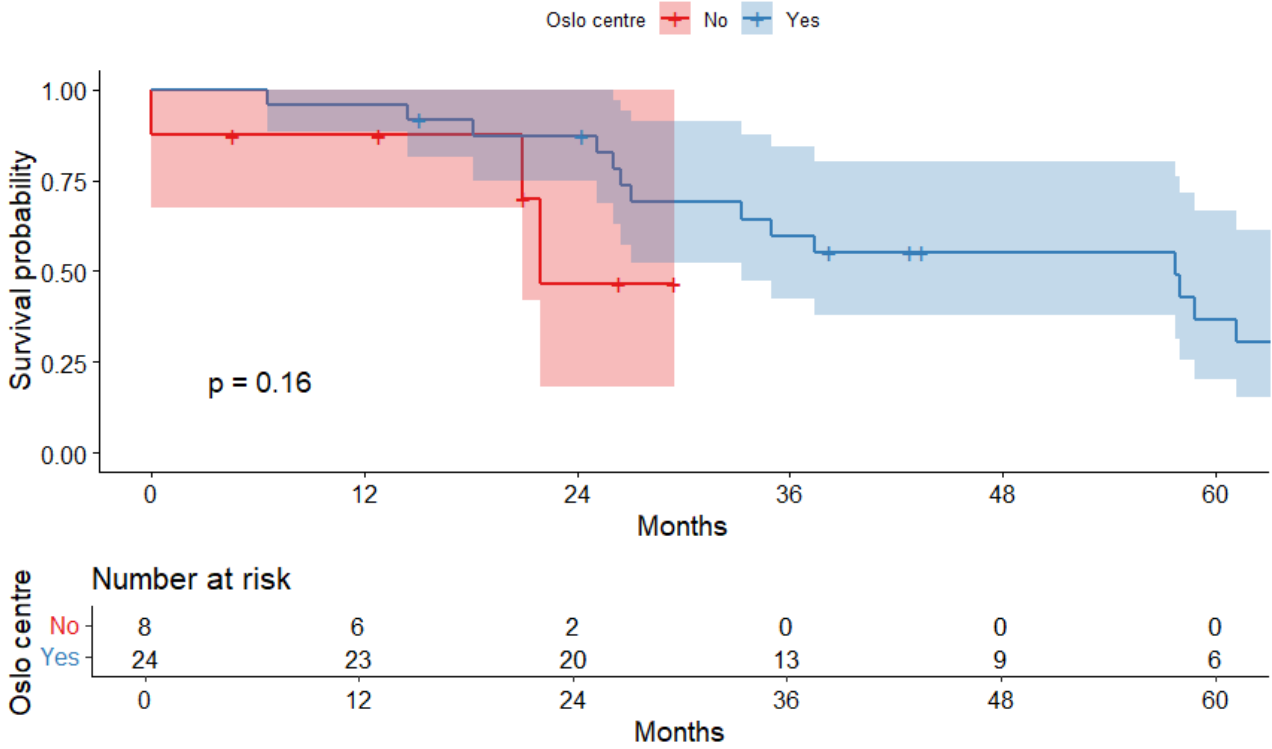


Number at risk

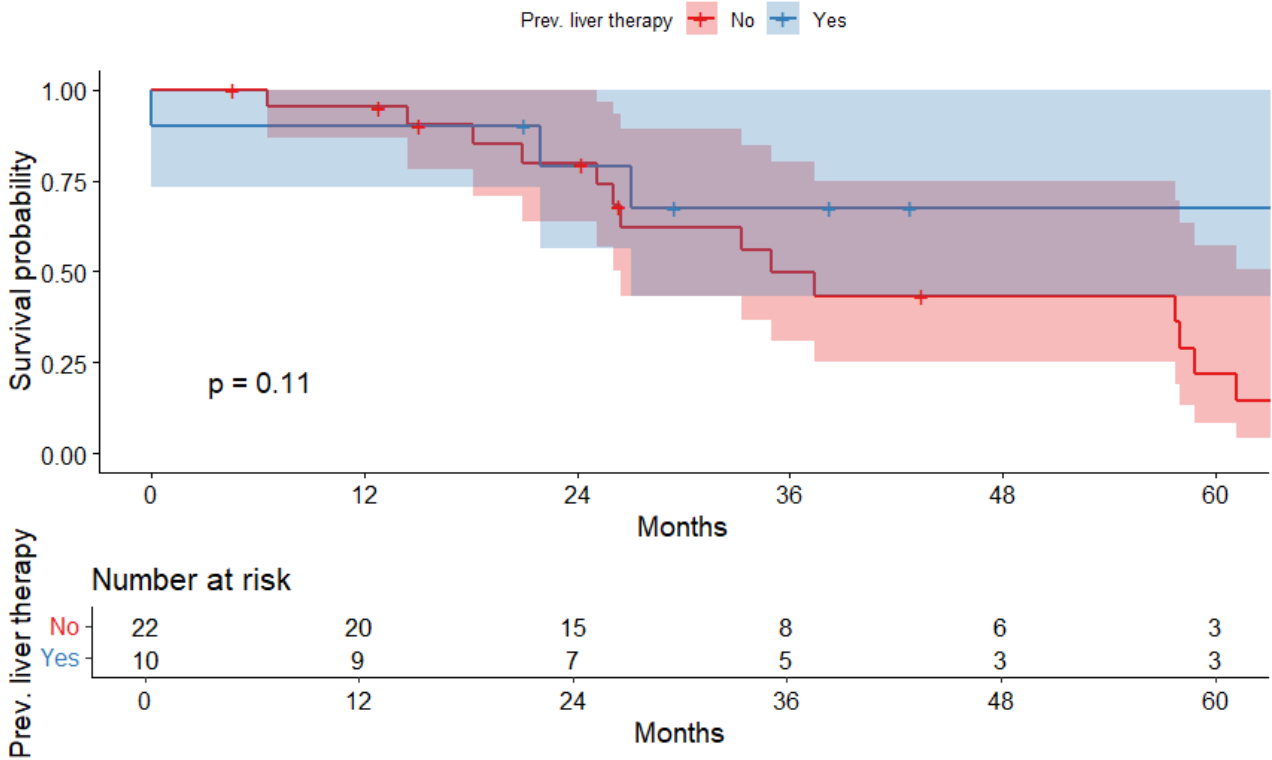
Nodules > 10	0	12	24	36	48	60
No	22	21	15	10	6	3
Yes	10	8	7	3	3	3

Months

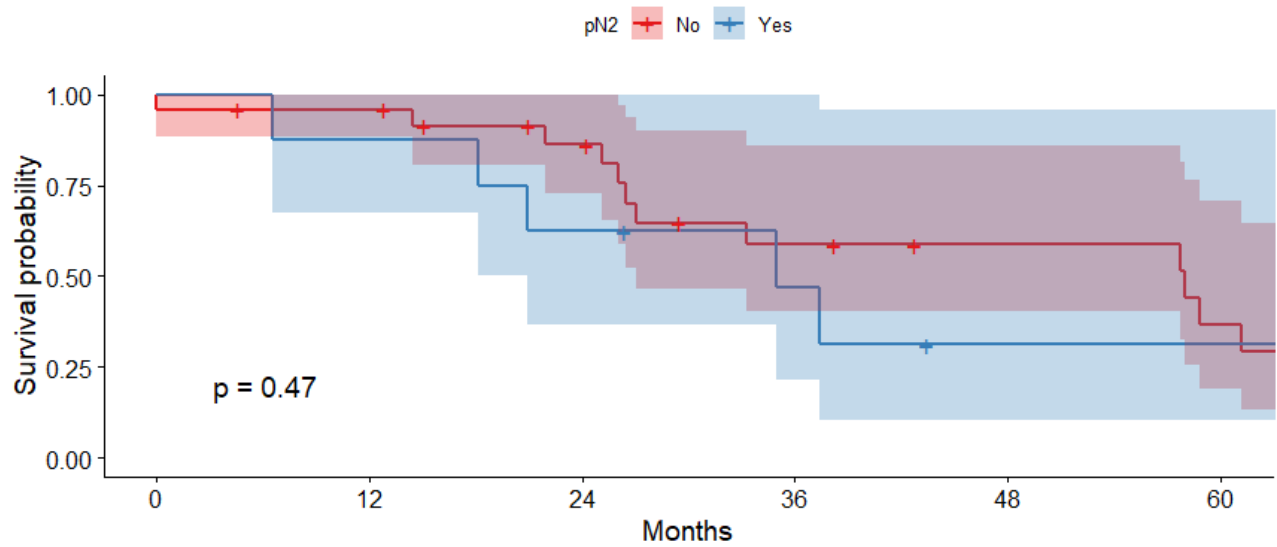
Female - Oslo centre



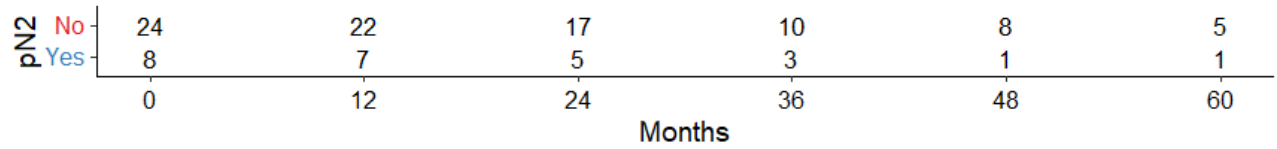
Female - Previous liver therapy



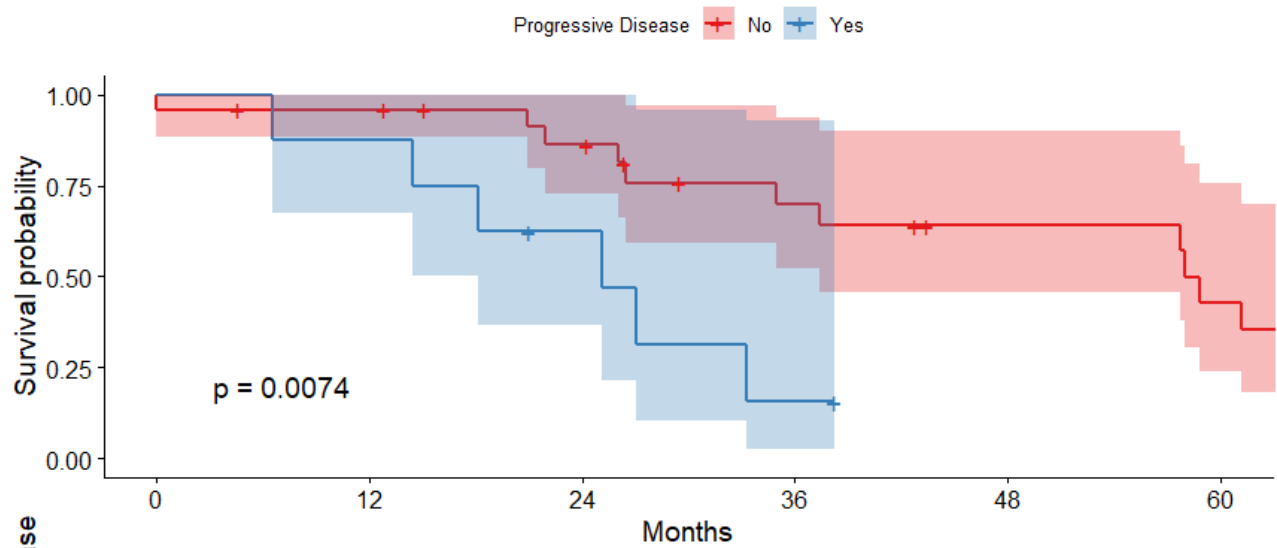
Female - pN2



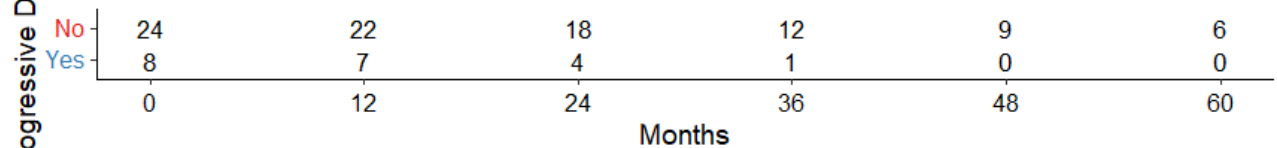
Number at risk



Female - Progressive Disease



Number at risk



Female - Time ≤ 24 months

