

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

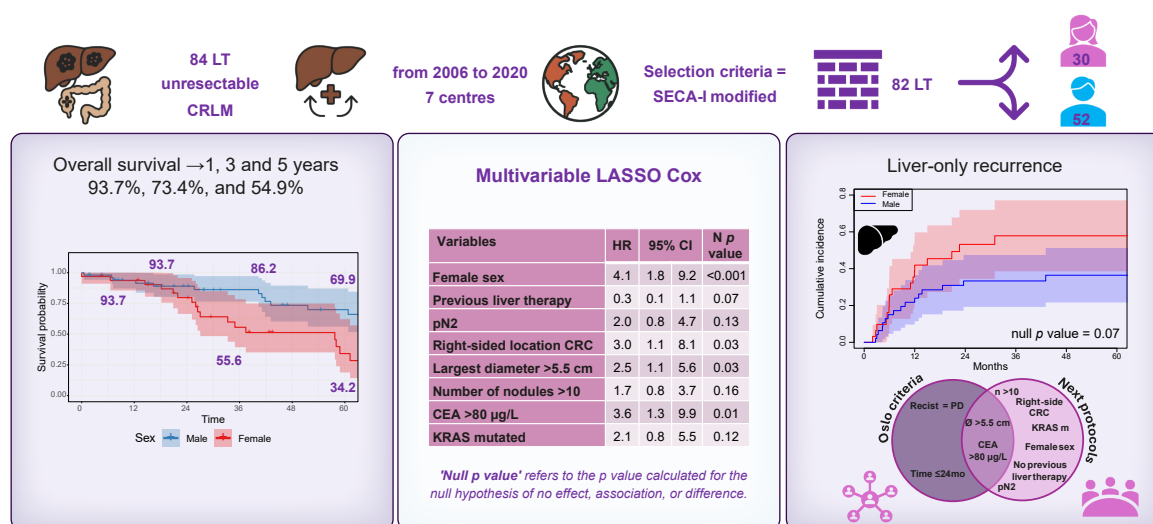
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## Graphical abstract



## Highlights:

- First multivariable survival analysis of LT for CRLMs.
- Higher mortality in female patients aligns with a potential relationship between sex and outcomes, which requires further exploration.
- Post LT recurrence is more likely in the liver for women, but only in the lungs for men.
- The prognostic strength of some variables used in clinical practice is not confirmed.
- Future prognostic models should prioritise improved discrimination and calibration in relation to the defined endpoint.

## Impact and implications:

This multicentre retrospective study analysed survival outcomes in 82 patients undergoing liver transplantation for colorectal liver metastases across seven US and European centres. Several factors, including female sex, high carcinoembryonic antigen levels, right-sided colorectal cancer, larger tumours, KRAS mutation, pN2-positive CRC, number of nodules, and no prior liver therapy, were linked to poorer outcomes. The study questions current prognostic models and selection criteria, emphasizing the need for more accurate tools to guide decision-making in patients with colorectal liver metastases.

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

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**Background & aims:** Liver transplantation (LT) for colorectal liver metastases (CRLMs) is attracting increasing interest, especially after publication of the TransMet trial. However, multivariable survival analyses are lacking. Here, we performed such an analysis in a multicentre cohort.

**Methods:** We conducted a retrospective multicentre study of 82 patients with CRLMs undergoing LT (from 2006 to 2020) across seven US and European centres, using multivariable Cox, competing-risk models, and extensive sensitivity analyses.

**Results:** Overall survival rates after 1, 3, and 5 years were 93.7%, 73.4%, and 54.9%, respectively. The findings align with an association between higher risk and the female sex (estimated hazard ratio (HR) 4.1, 95% CI: 1.8–9.2), and the following variables: carcinoembryonic antigen >80 µg/L, right-located colorectal cancer (CRC), largest diameter >5.5 cm, KRAS mutation, and absence of previous liver therapy. Other possible associations with higher uncertainty were pN2-positive CRC and the number of nodules (>10). Variables such as progressive disease after pretransplant chemotherapy and time from primary CRC surgery to LT of ≤24 months, exhibited weaker, less consistent associations.

**Conclusions:** This first multivariable survival analysis of LT for CRLM suggests that female sex is associated with worse outcomes, whereas the prognostic strength of the model currently used in clinical practice is not confirmed. Our findings challenge current selection criteria, highlighting the need for improved prognostic models with better discrimination and calibration.

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## Introduction

Liver transplantation (LT) offers a potentially curative treatment for highly selected patients with unresectable colorectal liver metastases (CRLMs).<sup>1</sup> Despite growing interest, evidenced by >1,700 publications on CRLMs and LT (PubMed search, June 2024),<sup>2</sup> fewer than 200 actual transplant cases have been documented worldwide. This limited clinical experience likely explains the absence of robust multivariable survival analyses in this field.

Currently, the Oslo criteria<sup>3,4</sup> are the most widely used selection guidelines for LT in CRLMs, although they are based only on univariable survival analyses. These criteria include a disease-free interval of >2 years after primary tumour resection, no progressive disease (PD) after pretransplant chemotherapy, a maximum tumour diameter of <5.5 cm, and a carcinoembryonic antigen (CEA) level <80 µg/L at the time of

LT.<sup>3</sup> Despite their limitations, these criteria have been effective in guiding patient selection.<sup>4</sup>

More recently, additional tumour biology-related predictors of post-transplant outcomes have been identified, including low metabolic tumour volume (MTV) on positron emission tomography (PET)/computed tomography (CT) (<70 cm<sup>3</sup>),<sup>5,6</sup> left-sided primary colorectal cancer (CRC), and its histological differentiation.<sup>7,8</sup>

Conversely, several prognostic factors, such as the number of positive lymph nodes, previous surgical liver treatments (resection or ablation), and biological sex, remain underexplored. For example, preclinical studies suggest that female sex hormones increase the hepatic tropism of CRC cells.<sup>9</sup> Given the complexity and interplay of known and unknown variables influencing post-transplant outcomes, there is a pressing need for multicentre studies with robust multivariable

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analyses.<sup>1,10</sup> This urgency was heightened by the TransMet trial<sup>11</sup> results, which, despite excellent per-protocol outcomes, showed reduced benefit in intention-to-treat analyses. This discrepancy could reflect ‘biological selection’, where patients with aggressive tumours are excluded because of disease progression during wait times. The trial underscores the need for validated, rigorous selection criteria to optimise graft allocation and patient outcomes. To address this gap, we conducted the first exploratory multivariable survival analysis of patients undergoing LT for CRLM using a multicentre dataset. Our goal was to identify patterns of risk association to support the refinement of prognostic criteria, enabling better candidate selection, avoiding exclusion of patients with potentially curable disease, and ensuring judicious use of scarce liver grafts.

## Patients and methods

### Study population

This multicentre retrospective study enrolled all consecutive patients with unresectable CRLM undergoing LT from January 2006 to December 2020 across two US and five European centres.

In all centres, LT was indicated for unresectable liver-only metastases. The non-resectability of CRLM was always determined by a multidisciplinary team comprising at least one of the following: a hepatobiliary surgeon, a transplant surgeon, a hepatologist, a radiologist, and an oncologist.

Only patients meeting the SECA-I study<sup>3</sup> criteria were included in this study to minimise selection bias and the centre effect. Thus, the following criteria were considered absolute exclusion criteria: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score >1; lack of radical excision of the primary CRC; <6 weeks of pretransplant chemotherapy; and presence of extrahepatic disease. Further exclusion criteria included age ≥72 years (increased from 60 years in the original trial for consistency with subsequent trials), weight loss exceeding 10%, standard contraindications for LT,<sup>12</sup> and concurrent other malignancies. Both deceased and living donor liver transplants (LDLTs) were eligible for the study. Each patient received at least 6 weeks of chemotherapy, which was the standard of care based on each patient’s stage and previous lines of therapy, if any. The specific criteria used by each participating centre (within the broad range of SECA-I criteria) are described in Table S1.

Before LT, all patients underwent radiological staging with either CT or magnetic resonance imaging (MRI), depending on centre protocols. A PET/CT scan was performed for each patient to exclude extrahepatic disease. However, PET values were not included in the analysis because of potential variability in calculation methods and the lack of standardised metabolic tumour volume (MTV) measurements before 2018.<sup>5</sup>

Each patient underwent a perioperative staging laparotomy, including frozen-section analysis of hepatic ligament lymph nodes. LT proceeded per institutional protocol only if no extrahepatic malignancy was detected.

The study adhered to the ethical guidelines of the 2013 revised Declaration of Helsinki. Each patient underwent LT for unresectable CRLM solely as part of a non-randomised controlled trial approved by the ethics committee of each sponsoring centre participating in this observational cohort.

Before inclusion, each patient provided written informed consent for every procedure performed in the hospital and for the use of data for research and publication purposes. All procedures were carried out following the Declaration of Istanbul. No individual received compensation or was offered any incentive for participating in this study.

The parameters included in the current analysis were as follows: demographics (age, sex); BMI; Oslo centre; primary tumour-related factors (location of the primary tumour, positive lymph nodes at pathology [pN+, pN1, pN2]); KRAS status; time from primary CRC resection and LT; previous liver therapy (resection or ablation) before LT; liver metastases variables (PD after pretransplant systemic therapy according to response evaluation criteria in solid tumours [RECIST 1.1]:<sup>13</sup> number of lesions; size of the largest lesion from the last available radiology; last CEA level); LDLT; and follow-up parameters (recurrence site and patient status). Positive lymph nodes (*i.e.* at least one positive lymph node) in the pathological report of primary tumour resection (pN+) were categorised into pN1 (one to three positive lymph nodes) and pN2 (four to nine positive lymph nodes). According to the chosen analysis, these three categories (pN+, pN1, and pN2) were tested separately to observe the most influential one (File S1, Supplementary data). Synchronous CRLMs were not considered given that each group had only four cases of metachronous CRLMs.

It was decided to include only radiological measures of liver lesions to identify potential predictors of post-LT outcomes, focusing exclusively on the variables available in the preoperative outpatient setting. Finally, patients with a BMI >25 kg/m<sup>2</sup> were considered overweight.

### Statistical analysis

The fundamental assumptions of all statistical models are discussed in the main text and Files S1 and S2, following established evaluation standards.<sup>14,15</sup> Categorical variables are presented as frequencies (%), whereas continuous variables are shown as medians with IQRs. Differences between groups were assessed using a two-tailed Welch *t* test or Mann-Whitney *U* test for continuous variables, and Pearson’s Chi-square or Fisher’s exact test for categorical variables, as appropriate. Effect sizes were calculated using Cohen’s *d* and Mann-Whitney  $z/(n_1+n_2)^{1/2}$  for continuous variables, and Cohen’s *w* for categorical variables, to estimate statistical (non-clinical) relevance. The entry ‘standardised size difference’ (last column of Table 1) refers to Cohen’s *d* and Mann-Whitney  $z/(n_1+n_2)^{1/2}$  for continuous variables and Cohen’s *w* for categorical variables: low values (<0.3) corroborate high group similarity at the statistical (but not necessarily clinical) level.

The primary endpoint was overall survival (OS), defined from the date of LT to death or the last follow-up (July 2022), with follow-up durations expressed as medians (IQR). OS was analysed using Kaplan–Meier curves and compared via the log-rank test under the null hypothesis of no difference. The term ‘null *p*’ refers to the *p* value calculated for the null hypothesis of no effect, association, or difference.

To assess covariate effects, Cox regression models were constructed hierarchically across four domains: (1) tumour biology and response to therapy; (2) metastatic and biomarker characteristics; (3) technical-logistical factors; and (4) patient-related clinical features. Model selection was guided by the

**Table 1. Demographical and clinical characteristics of enrolled patients.**

Variables	Study group (n = 82); median (IQR) no. (%)	Males (n = 50); median (IQR) no. (%)	Females (n = 32); median (IQR) no. (%)	Null p value (male vs. female)	Standardised size difference (male vs. female)
Age	54 (47–59)	54 (48–60)	54 (45–59)	0.63	0.11
Age >55 years	39 (48)	24 (48)	15 (47)	0.90	<0.01
Oslo centre	54 (66)	30 (60)	24 (75)	0.16	0.22
Living donor	12 (15)	7 (14)	5 (16)	0.84	0.05
Previous liver therapy	21 (26)	11 (22)	10 (32)	0.44	0.21
BMI >25 kg/m <sup>2</sup>	48 (59)	30 (60)	18 (56)	0.74	0.01
pN1	37 (45)	21 (42)	16 (50)	0.43	0.06
pN2	22 (27)	14 (28)	8 (25)	0.97	<0.01
Synchronous CRLM	74 (90)	46 (92)	28 (88)	0.71	0.03
Right-sided CRC	16 (20)	9 (18)	7 (22)	0.67	0.02
Time from CRC surgery to LT ≤24 months	50 (61)	29 (58)	21 (66)	0.49	0.05
Progressive disease	16 (20)	8 (16)	8 (25)	0.32	0.11
CEA >80 µg/L	16 (20)	11 (22)	5 (16)	0.48	0.06
No. of nodules	10 (5–14)	10 (7–14)	8 (4–15)	0.47	0.04
>10 nodules	27 (33)	17 (34)	10 (31)	0.80	<0.01
Diameter (cm)	4 (3–7)	4 (3–7)	4 (2–8)	0.67	<0.01
Diameter >5.5 cm	29 (35)	16 (32)	13 (41)	0.43	0.07
KRAS mutated	20 (25)	12 (24)	8 (25)	0.87	<0.01

Two-tailed Welch *t* test and Mann-Whitney *U* test were used to compare continuous variables; two-tailed Pearson's Chi-square test and Fisher's exact test were used to compare categorical variables. The 'Standardised size difference' column refers to Cohen's *d* and Mann-Whitney  $z/(n_1+n_2)^{1/2}$  for continuous variables and Cohen's *w* for categorical variables: low values (<0.3) corroborate high group similarity at the statistical (but not necessarily clinical) level. Given a markedly asymmetric distribution, synchronous CRLM was not included in the main analysis. CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal liver metastases; pN1, metastasis in one to three regional lymph nodes after colorectal surgery; pN2, metastasis in four to nine regional lymph nodes after colorectal surgery.

corrected Akaike information criterion (AICc) and least absolute shrinkage and selection operator (LASSO), using 10-fold cross-validation. The final multivariable model was selected following sensitivity analyses (detailed in File S2).

Dichotomisation of continuous variables was based on thresholds reported in the literature, except for age. Given that age as a continuous covariate was not associated with risk of death or recurrence (Files S1 and S2), we dichotomised it at 55 years, close to the cohort median.

Stratified Kaplan–Meier survival curves were used to illustrate interaction effects. By stratifying curves based on levels of interacting variables, we examined whether the influence of one variable on survival was modified by another. In addition, a sex-based stratified analysis was conducted.

Considering literature suggesting that post-transplant prognosis is influenced by the site of recurrence, we incorporated recurrence patterns as exploratory endpoints. We used a time-varying Cox model to evaluate the impact of recurrence type (liver, lung, or no recurrence) on OS. Follow-up was divided into two periods for patients with recurrence: from LT to diagnosis of recurrence; and from recurrence to death or last follow-up. The recurrence type was included as a time-dependent covariate, altering its value upon diagnosis.

Conventional disease-free survival (DFS) and cause-specific Cox analyses were used to investigate predictors of tumour recurrence.<sup>16</sup> DFS was defined as the period from LT to recurrence or death, whichever occurred first, with censoring at the last follow-up (July 2022). Variables with a null *p* < 0.20 in univariable analyses were included in the multivariable DFS model.

In cause-specific analyses, competing events were defined as lung-only recurrence, liver-involved recurrence, extrahepatic non-lung-only recurrence, and death without recurrence. In cases of extrahepatic non-lung-only recurrence, lung involvement was possible as part of multisite progression. Fine & Gray competing-risk models were also explored as a supplementary analysis (Files S2 and S3).

Missing covariate data were present in <10% of patients and were handled via multiple imputation (details in File S1).<sup>17</sup> The strength of observed associations was assessed using *p* values and 95% CIs.<sup>18,19</sup> *p* values close to 1 indicate strong compatibility with the null hypothesis, while those close to 0 indicate lower compatibility. Following recent methodological recommendations, we used an unconditional interpretation of *p* values, allowing for nuanced assessment across plausible hypotheses, including limitations.<sup>20,21</sup> Additional quantification of *p* value information was carried out using the *s*-value metric (File S1). All analyses were conducted using R (RStudio 4.2.3, RStudio, Inc., Boston, MA, USA) and STATA (Stata/SE 18.0, StataCorp LLC, College Station, TX, USA).

## Results

### Patients' characteristics

This study population comprised 84 patients who underwent LT for unresectable CRLMs between January 2006 and December 2020. One patient was excluded because of a weight loss exceeding 10%, and another had an ECOG PS >1. Ultimately, 82 patients were included in the analysis.

Most of the patients were men (61%), with a median age of 54 (IQR 47–59). Table 1 presents the characteristics of the enrolled patients.

Twelve patients (14.6%) received an LDLT, with most (66%) undergoing transplants in Oslo. Most patients were overweight (59%), had positive lymph nodes (72%) in the primary tumour specimen, and underwent LT within 24 months (61%) of primary tumour resection. A minority of enrolled patients (20%) had a right-sided primary tumour, experienced PD after systemic therapy (20%), and had a pretransplant CEA level >80 µg/L (20%). In addition, a considerable proportion of patients had >10 liver nodules (33%), a diameter of the largest nodule >5.5 cm (35%), and presented with a KRAS mutation (25%). The distributions of these variables in male and female

patients were similar, which aligns with the low value of standardised mean differences (Table 1).

### Overall survival analysis of the study population

In the whole population, the median follow-up for survivors was 70.0 months (IQR 26.4–91.0), median OS was 72.7 months (IQR 34.9–not reached), and OS after 1, 3, and 5 years was 93.7% (95% CI: 87.8–99.6%), 73.4% (95% CI: 62.7–84.1%), and 54.9% (95% CI: 41.7–68.1%), respectively. Thirty-three deaths were recorded during the follow-up period, and only two deaths (6.1%) occurred in patients without tumour recurrence. Thus, OS analysis in this setting almost coincided with a cancer-related death analysis.

The multivariable analysis agreed with an association between higher risk and the following variables (Table 2): female sex; CEA >80 µg/L; right-sided CRC; largest diameter >5.5 cm; absence of previous liver therapy; KRAS mutation; pN2; and number of nodules >10. We observed a high degree of concordance between the hierarchical and LASSO models. The most evident divergences in Kaplan–Meier survival curves were observed for right-sided CRC, CEA >80 µg/L, and KRAS mutation, all displaying an early separation (File S3). Additional variables associated with later divergence included pN2 status (separation at 6 months), largest diameter >5.5 cm, PD, female sex, and absence of prior liver therapy (separation at 12–18 months). A more modest divergence was noted for time from CRC surgery to LT ≤24 months (separation at 6 months). We also noted a more uncertain separation at 30 months for the variable Oslo, which is compatible with the hypothesis that the centre handles more severe cases; at 24 months up to 60 patients with >10 nodules, and around 12 months for the older group, which, surprisingly, showed a lower frequency of events. Such findings should be interpreted cautiously, because these curves do not account for confounding factors.

The median follow-up for survivors was 70.0 months (IQR 29.5–91.0) for women and 68 (IQR 23.3–88.3) for men. OS after 1, 3, and 5 years was 93.7%, 55.6%, and 34.2%, respectively

**Table 2. Multivariable survival analysis of enrolled patients.**

Variable	LASSO Cox			
	HR	95% CI		Null p value
Female sex	4.1	1.8	9.2	<0.001
Age >55 years	–	–	–	–
Oslo centre	–	–	–	–
Living donor	–	–	–	–
Previous liver therapy	0.3	0.1	1.1	0.07
BMI >25 kg/m <sup>2</sup>	–	–	–	–
pN2	2.0	0.8	4.7	0.13
Right-sided CRC	3.0	1.1	8.1	0.03
Time ≤24 months	–	–	–	–
Progressive disease	–	–	–	–
Largest diameter >5.5 cm	2.5	1.1	5.6	0.03
No. of nodules >10	1.7	0.8	3.7	0.16
CEA >80 µg/L	3.6	1.3	9.9	0.01
KRAS mutated	2.1	0.8	5.5	0.12

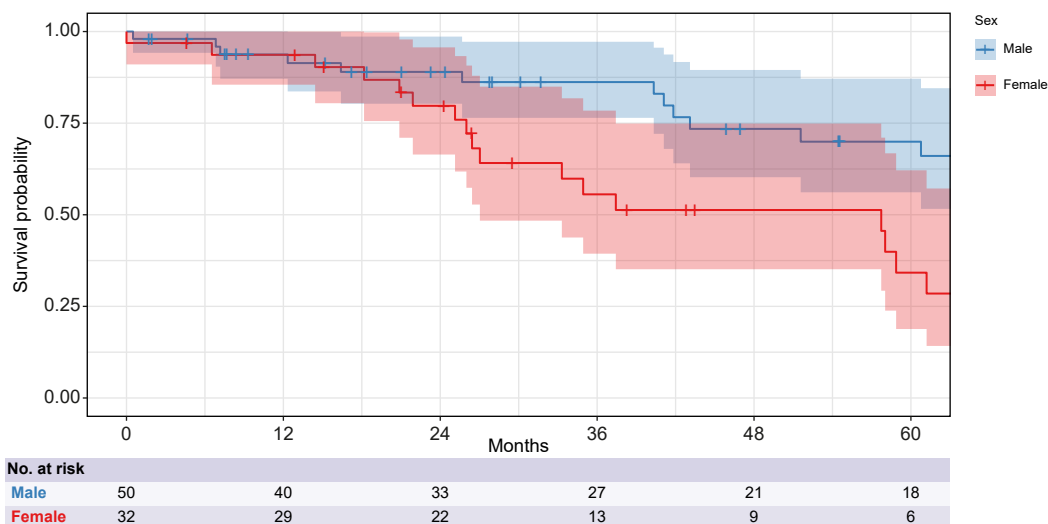
Interval estimates and p-values are from the LASSO Cox model (Wald Z-test). Concordance = 0.836 (SE = 0.034), Likelihood ratio test  $p < 0.001$ , Wald test  $p < 0.001$ , Score (log-rank) test  $p < 0.001$ . The coherence with the hierarchical model was strong (File S2). CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal metastasis; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; pN2, metastasis in four or more regional lymph nodes after colorectal surgery.

in the female population, compared with 93.7%, 86.2%, and 69.9%, respectively in the male population (Fig. 1), although there were similar baseline characteristics (Table 1).

Given the potential association between sex and two factors, such as the diameter of the largest nodule (Fig. 2A,B) and the KRAS mutation (Fig. 2C,D), we performed a stratified survival analysis according to sex. Table 3 shows the results of univariable Cox survival analyses in men and women.

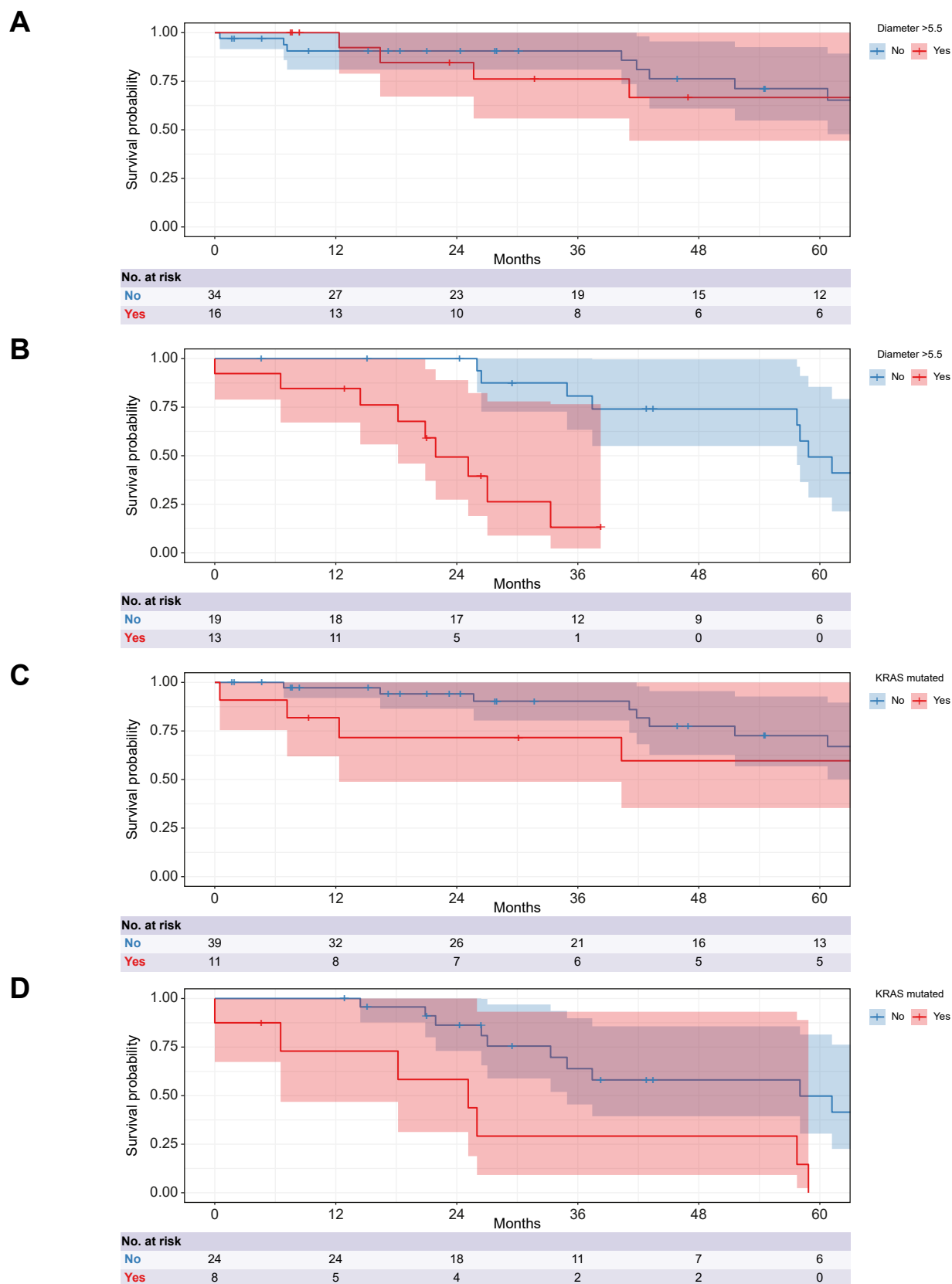
The original research intent was to perform a Cox multivariable survival analysis by sex. However, we encountered substantial violations of the basic assumptions (severe sparse-data bias), which might signal the need for larger sample sizes.

Univariable analysis agreed with an inverse association between risk and previous liver therapy, and a direct association between risk and right-sided CRC and CEA >80 µg/L in both sexes (Table 3). In women, the results were also



**Fig. 1. Overall survival curves of men vs. women.** Compatibility with the null hypothesis:  $p = 0.03$  (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). Shaded areas represent 95% CIs.





**Fig. 2.** Overall survival curves according to the diameter of the largest nodule and KRAS mutation. (A) Diameter of the largest nodule in men. Compatibility with the null hypothesis:  $p = 0.44$  (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). (B) Diameter of the largest nodule in women. Compatibility with the null hypothesis:  $p < 0.001$  (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference); (C) KRAS mutation in men. Compatibility with the null hypothesis:  $p = 0.35$  (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference); (D) KRAS mutation in women. Compatibility with the null hypothesis:  $p = 0.03$  (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). Shaded areas represent 95% CIs.

**Table 3. Univariable survival analysis stratified by sex.**

Variables	Proportional hazards Cox			Null p value
	HR	95% CI		
Males				
Age >55 years	0.8	0.3	2.2	0.72
Oslo centre	3.9	0.5	31	0.19
Living donor*	–	–	–	–
Previous liver therapy	0.2	0.0	1.8	0.17
BMI >25 kg/m <sup>2</sup>	1.1	0.4	3.2	0.84
pN2	3.0	1.1	8.0	0.03
Right-sided CRC	7.2	2.4	21	0.004
Time ≤24 months	1.2	0.4	3.4	0.71
Progressive disease	1.0	0.3	3.6	0.99
Largest diameter >5.5 cm	1.5	0.5	4.3	0.44
No. of nodules >10	1.1	0.4	3.1	0.81
CEA >80 µg/L	3.9	1.4	11	0.01
KRAS mutated	1.7	0.6	4.7	0.34
Females				
Age >55 years	0.4	0.2	1.1	0.07
Oslo centre	0.4	0.1	1.5	0.18
Living donor	2.1	0.4	10	0.35
Previous liver therapy	0.4	0.1	1.3	0.12
BMI >25 kg/m <sup>2</sup>	0.8	0.3	2.2	0.70
pN2	1.5	0.5	4.2	0.47
Right-sided CRC	5.0	1.6	16	0.007
Time ≤24 months	2.6	0.8	9.1	0.13
Progressive disease	4.1	1.4	13	0.01
Largest diameter >5.5 cm	8.7	2.5	30	0.001
No. of nodules >10	1.6	0.6	4.1	0.38
CEA >80 µg/L	13	3.8	48	<0.001
KRAS mutated	4.0	1.5	11	0.006

Interval estimates and p-values are from the proportional hazards Cox model (Wald Z-test). CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal metastasis; HR, hazard ratio; pN2, colorectal cancer with metastasis in four or more regional lymph nodes after colorectal surgery.

\*Not evaluable because of the absence of events in this group (i.e. seven patients, zero deaths).

consistent with a stronger direct association between risk and PD, largest diameter >5.5 cm, and KRAS mutations, and an inverse association between risk and age >55. Inspection of the Kaplan–Meier curves revealed a pattern consistent with the univariable analysis, although the latter remained susceptible to confounding (File S3). This corroborates the sex-related differences highlighted in the previous multivariable analysis.

### Role of recurrence site on survival and its interaction with female sex

Sixty-two patients (75.6%) developed post-LT tumour recurrence after a median time of 12 months (IQR 5.2–23.6). The lungs were the only organ involved in 23 patients with recurrence (37.1%). The liver was the only organ involved in six patients (9.7%), whereas in 27 (43.5%), multiple organs, including the liver, were involved. Two patients had single bone and lymph node metastases (3.2%), and four patients had numerous metastases not involving the liver (lung and bone, lung and brain, multisite involving lung, multisite not involving lung; 6.5%). In summary, 20 patients had no recurrence, 33 had recurrences involving the liver, and 29 showed non-liver recurrences (23 lung-only recurrences and six extrahepatic-non-lung-only recurrences).

OS after 1, 3, and 5 years was 90.0%, 90.0%, and 90.0%, respectively, for patients without recurrence, 100.0%, 86.3%, and 60.1%, respectively, for patients with lung-only

recurrences, and 90.9%, 58.8%, and 37.2%, respectively, for patients with liver recurrences (Fig. 3).

We conducted a conventional DFS survival analysis, which showed no clear association with female sex. However, KRAS mutation and CEA >80 µg/L consistently correlated with poorer DFS (Table S9).

Next, we analysed liver and lung-only recurrence risks (Table 4). In the liver recurrence model, higher risk was linked to pN2-positive lymph nodes, >10 nodules, KRAS mutation, and female sex. Right-sided primary tumour, CEA >80 µg/L, and PD also indicated increased risk, although with statistical uncertainty. In the lung recurrence model, KRAS mutation, CEA >80 µg/L, and largest diameter >5.5 cm were significant risk factors. Notably, some variables, including female sex, appeared inversely related to lung-only recurrence risk, suggesting sex-specific patterns, namely higher liver recurrence in women, but lower lung-only recurrence (Fig. 4 and Table 4).

Table S8 details post-LT treatments by sex and recurrence type. Treatment strategy was driven by recurrence location, not biological sex, and no substantial sex-based differences in treatment were observed despite differences in recurrence patterns.

## Discussion

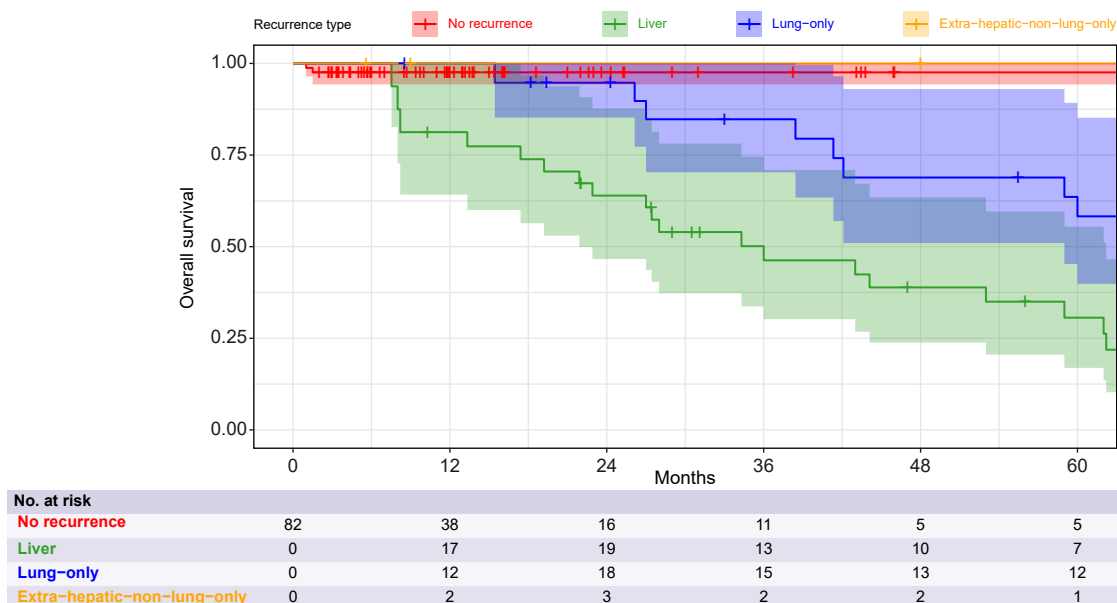
To our knowledge, this study includes the largest cohort of patients with CRLM undergoing LT published to date. It is also the first to conduct a multivariable survival analysis aimed at identifying independent aetiological predictors of post-transplant outcomes. Given the increasing interest in LT for CRLMs, especially following the publication of the TransMet trial,<sup>11</sup> our findings are of considerable clinical and scientific relevance.

Here, we reported the number and size of nodules based on the last available radiological assessment before LT. Although our cohort appears to differ from that of the TransMet trial, particularly in terms of the initial tumour burden, these differences can be largely explained by methodological distinctions. The TransMet trial presented imaging characteristics at the time of diagnosis or randomisation, whereas we focused on imaging immediately before LT. Moreover, the trial used a central radiological review, likely resulting in more accurate nodule characterisation.

Our results confirm the excellent OS associated with LT for CRLMs. The 5-year OS rate in our cohort was 55%, closely matching the 54% reported in the UNOS database.<sup>22</sup> Although this is somewhat lower than survival for traditional LT indications,<sup>23</sup> it compares favourably with other accepted indications, such as LT in patients >70 years of age, those with obesity, combined organ transplantation, or re-LT.<sup>22</sup>

Consistent with previous literature, our findings also highlight the weak correlation between OS and DFS, supporting the notion that DFS might not be a reliable marker of treatment efficacy in this context. The median time to recurrence was ~12 months. Thus, LT could serve to transform CRLM into a chronic disease for many patients, while offering the potential for long-term cure in a select group, particularly those who undergo successful treatment of lung metastases.<sup>24–26</sup>

A significant finding of this study is that two variables previously suggested as negative prognostic factors for LT in CRLM (PD and an interval of <24 months between surgery of



**Fig. 3. Time-varying overall survival curves according to the recurrence site.** Recurrence type was considered a time-varying covariate. Compatibility with the null hypothesis:  $p < 0.001$ . Lung only vs. no-recurrence, compatibility with the null hypothesis:  $p = 0.27$ . Liver vs. no recurrence, compatibility with the null hypothesis: null  $p = 0.03$ . Liver vs. lung only, compatibility with the null hypothesis:  $p = 0.05$  (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). Shaded areas represent 95% CIs.

**Table 4. Multivariable cause-specific analyses (liver vs. lung recurrence).**

	Hierarchical weighted Cox*			
Variables	HR	95% CI		Null <i>p</i> value
Risk of liver recurrence				
Female sex	1.8	0.9	3.8	0.11
Age >55 years	–	–	–	–
Oslo centre	–	–	–	–
Living donor	–	–	–	–
Previous liver therapy	–	–	–	–
BMI >25 kg/m <sup>2</sup>	–	–	–	–
pN2	2.6	1.0	6.3	0.04
Right-sided CRC	2.0	0.7	5.3	0.18
Time ≤24 months	–	–	–	–
Progressive disease	1.7	0.7	3.9	0.24
Largest diameter >5.5 cm	0.7	0.3	1.6	0.46
No. of nodules >10	2.0	1.0	4.2	0.06
CEA >80 µg/L	2.0	0.7	6.0	0.22
KRAS mutated	2.1	0.9	5.2	0.11
Risk of lung recurrence				
Female sex	0.4	0.1	1.4	0.16
Age >55 years	0.6	0.3	1.6	0.36
Oslo	–	–	–	–
Living donor	–	–	–	–
Previous liver therapy	–	–	–	–
BMI >25 kg/m <sup>2</sup>	–	–	–	–
pN2	1.3	0.4	4.2	0.6
Right location CRC	0.6	0.2	2.0	0.38
Time ≤24 months	–	–	–	–
Progressive disease	1.5	0.5	4.7	0.51
Largest diameter >5.5 cm	2.1	0.8	5.3	0.13
No. of nodules >10	1.3	0.5	3.2	0.54
CEA >80 µg/L	4.2	1.4	13	0.01
KRAS mutated	7.0	2.7	18	<0.001

Interval estimates and  $p$ -values are from the weighted Cox model (Wald Z-test). CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal metastasis; HR, hazard ratio; pN2, colorectal cancer with metastasis in four or more regional lymph nodes after colorectal surgery.

\*The hierarchical model was realised by dividing the variables into four categories of importance, as shown in Files S2 and S3.

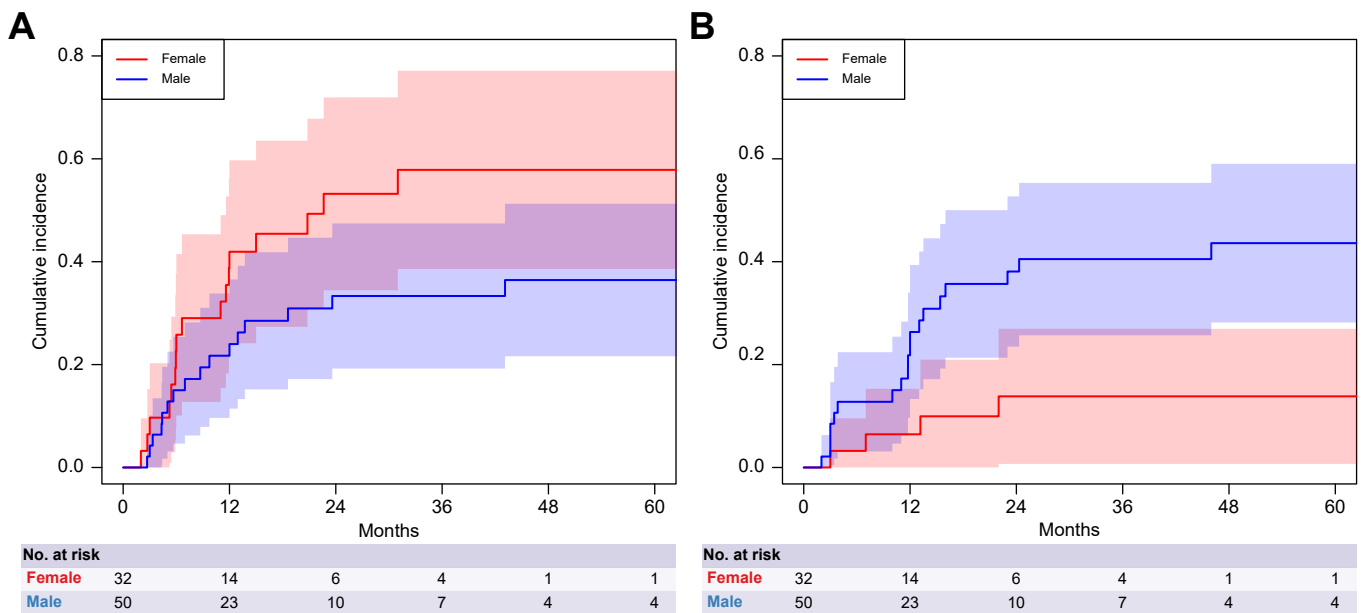
the primary tumour and LT [Oslo criteria<sup>3</sup>]) did not show strong independent associations in our multivariable analysis. High statistical uncertainty and relatively weak risk estimates compared with other variables limited their significance. By contrast, several other factors emerged as more consistent predictors of poorer post-LT outcomes: CEA levels >80 µg/L, right-sided primary tumour, largest nodule diameter >5.5 cm, KRAS mutation, presence of four to nine positive lymph nodes, and >10 liver metastases (Table 2). These findings align with established knowledge of tumour biology and support the continued evaluation of these variables in refining prognostic models.

Despite their clinical utility, such categorical thresholds should not be applied rigidly. For example, a nodule diameter of 5.49 cm vs. 5.51 cm should not lead to categorically different clinical decisions. Similarly, BMI >25 kg/m<sup>2</sup> might have prognostic relevance according to our hierarchical model (File S2), warranting further exploration.

Given that many patients do not fully meet existing LT criteria, a better understanding of the individual predictive value of each factor is essential. Notably, previous liver-directed therapies appeared to have a potential protective effect, whereas treating the interval from primary surgery to LT as a continuous variable could enhance prognostic accuracy, an area requiring further research. By contrast, CEA was more reliably analysed as a categorical variable because of its skewed distribution and outliers.

Another unexpected observation was the potential prognostic impact of female sex, especially when combined with KRAS mutation and the largest nodule diameter >5.5 cm (Fig. 2 and Table 3). This suggests that women experience worse outcomes under certain biological conditions, possibly requiring sex-specific selection strategies for LT. However, this finding might reflect statistical fluctuation resulting from limited external





**Fig. 4. Cumulative incidence of liver and lung-only recurrences according to sex, accounting for competing risks.** (A) Cumulative incidence of liver-only recurrence in men vs. women. (B) Cumulative incidence of lung-only recurrence in men vs. women. At 60 months, the cumulative incidence of liver recurrence was 58% in women and 36% in men (Gray's test null  $p = 0.07$ ), and the cumulative incidence of lung-only recurrence was 14% in women and 44% in men (Gray's test null  $p = 0.01$ ). Shaded areas represent 95% CIs.

validity. It underscores the need for future research to investigate potential oncogenetic and epidemiological mechanisms before implementing changes in clinical practice. Here, we outline several such hypotheses to be explored in subsequent studies.

Sex-related differences in CRC and its CRLM might result from both biological (sexual dimorphism) and non-biological (sociobehavioural) factors. Globally, women show a lower age-standardised incidence and mortality from CRC compared with males, who also have a higher cumulative risk.<sup>27</sup> CRC incidence increases with age, particularly after 50, although recent years have seen a relative rise in younger adults (20–40 years), despite their smaller absolute numbers.<sup>28</sup> Sex hormones significantly influence CRC initiation and progression, with effects that vary by age. Premenopausal women generally have better survival rates compared with age-matched men,<sup>29</sup> whereas women over 65 often have poorer outcomes, potentially because of later-stage diagnosis or more aggressive tumour biology.<sup>30–32</sup>

Women also present more frequently with right-sided tumours and BRAF mutations, both associated with a worse prognosis.<sup>33</sup> Sexual dimorphism affects tumour pathways, including Wnt/ $\beta$ -catenin signalling, hypoxia response, ion channel expression, and X-linked genes.<sup>34</sup> Sex-based differences have also been observed in treatment response, such as with circadian chemotherapy and anti-tumour immunity.<sup>35,36</sup> However, consistent sex-specific survival differences following liver resection for CRLM have not been consistently reported and are not evident in registries such as the LiverMet Survey.<sup>37</sup>

This study was not designed to uncover the mechanisms behind sex differences in post-LT outcomes, but does offer potential insights (Fig. 4). Women experienced liver recurrence more often than men, a pattern associated with worse prognosis compared with no-liver recurrence (Fig. 3). This might also explain why large metastasis size had a more negative impact in women.

One hypothesis involves sex-specific immunology: the female immune system tends towards greater immune tolerance, likely as an evolutionary adaptation for pregnancy.<sup>38</sup> Oestrogens enhance this tolerance, particularly by promoting regulatory T cell activity, which dampens anti-tumour immunity.<sup>39</sup> This is especially relevant in the liver, an oestrogen-sensitive organ. Preclinical studies suggest that oestrogens facilitate the development of an immunosuppressive micro-environment that favours liver metastasis growth, an effect reversible by ovariectomy or oestrogen antagonists.<sup>9</sup> Clinically, oestrogen receptor expression in CRC has been linked to increased tumour angiogenesis, proliferation, and migration. These mechanisms could explain why women with active oestrogen signalling are more prone to liver metastases compared with men, especially in younger age groups.<sup>34,36,40–42</sup> The worse prognosis of younger women aligns with this hypothesis (Table 3). Consequently, women might experience fewer lung-only recurrences, given that recurrence categories are mutually exclusive.

These findings support the hypothesis of oestrogen-mediated liver tropism in women and suggest a need for further investigation. Future research should explore the inclusion of circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) in LT candidate assessments. These biomarkers could help refine patient selection, monitor treatment response, and better understand disease behaviour.<sup>43</sup> In addition, expanded genetic profiling, covering mutations in RAS, RAF, P53, and hormonal receptor status, could enhance prognostic accuracy and prediction of disease progression after LT.<sup>44</sup>

Non-biological factors might also contribute to sex-related differences in outcomes. Studies show that female patients are less likely to undergo liver resection for CRLM.<sup>45,46</sup> This trend is evident in large registries, including the LiverMet Survey.<sup>37</sup> For example, Ljunggren *et al.*<sup>46</sup> reported that women

received 23% less metastatic surgery and had slightly higher post-diagnosis mortality. The cause of this disparity remains unclear. Importantly, given that survival outcomes after resection showed no significant sex-based differences, these findings might indicate preselection bias that disadvantages women. In our cohort, comprising exclusively patients with unresectable disease, such bias could have influenced who was referred for LT consideration.

It is essential to clarify that this study does not suggest excluding women from LT for CRLMs. Our findings are exploratory and require validation in larger, dedicated cohorts. Moreover, it is not appropriate to assume that data derived from predominantly male cohorts can be directly applied to women. Many clinical trials, both historical and recent, disproportionately enrol male participants,<sup>47</sup> introducing potential sex bias in research and treatment approaches across various specialities, including gastroenterology and hepatology.<sup>48</sup>

Publication bias and statistical limitations might further obscure true sex-related differences in outcomes.<sup>49,50</sup> Given these concerns, our study highlights the need for more inclusive research and calls attention to potential sex-specific prognostic factors in LT for CRLMs. Ultimately, our aim is to support the development of more equitable and precise patient selection strategies that consider both biological and non-biological differences, ensuring that all eligible patients, regardless of sex, have access to potentially curative therapies.

## Limitations and implications

Our analysis could not differentiate between synchronous and metachronous metastases because of the strong asymmetry in the synchronous CRLM distribution variable. In addition, the lack of PET/CT data limited the depth of our analysis and might have introduced bias. The small sample size, limited understanding of biological sex- or gender-related mechanisms, and potential residual confounding prevented us from establishing any causal link between sex and LT outcomes in CRLMs. Further studies with better control of uncertainties and a focus on biological mechanisms are needed. Integrating previous knowledge into future models will improve their robustness. Sparse-data bias is a concern with small cohorts, but the alignment between penalised and non-penalised models, along with credible HR estimates, suggests this risk is limited.<sup>15,51</sup> Although the long study period broadens the scope, it introduces variability resulting from evolving patient selection and treatment practices. Future research should focus on more recent cohorts to enhance comparability and relevance. Despite these limitations, our cohort is larger than those informing current guidelines, highlighting the importance of sharing our findings. Future studies should refine prognostic models by improving discrimination, calibration, and variable categorisation, ideally using continuous variables where appropriate.

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## Abbreviations

AIcC, corrected Akaike information criterion; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal cancer liver metastases; CT, computed tomography; CTCs, circulating tumour cells; ctDNA, circulating tumour DNA; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; LDLT, living donor liver transplants; LT, Liver transplantation; MRI, magnetic resonance imaging; MTV, metabolic tumour volume; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PS, performance status.

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## Conflicts of interest

All authors have completed the Unified Competing Interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have had an interest in the submitted work over

the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

Conceptualisation and methodology: AV, JL, UC, PDL. Provision of study resources: JL, UC, MC, MS, FA, BE, LC, SI, VM, CS, RHA, KT, MH, SD, PDL. Data curation: AV, JL, IB. Formal analysis: AV, IB, AR, MAM.

Investigation: AV, JL, UC, SD, PDL. Project administration: JL, PDL. Supervision: UC, PDL. Validation: AV, AR, MAM. Visualisation: AV, JL. Writing – original draft: AV, JL. Writing – review and editing: AV, JL, UC, AR, SD, PDL. Final approval of manuscript: All authors. AV, JL, and PDL had full access to all the data in the study and verified the data. All authors had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that all others meeting the criteria have been included.

## Data availability

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, are available from the corresponding author on reasonable request, as are deidentified participant data and a data

dictionary. No additional documents will be available. Data will be available from the publication date until December 2034. Data will be shared with consultants, clinicians, and researchers with PhDs for retrospective cohort studies after approval of a proposal and a signed data access agreement. We may balance the potential benefits and risks for each request and then provide the data that can be shared.

## Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2025.101505>.

## References

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- [1] Hibi T, Rela M, Eason JD, et al. Liver transplantation for colorectal and neuroendocrine liver metastases and hepatoblastoma. Working group report from the ILTS transplant oncology consensus conference. *Transplantation* 2020;104:1131–1135.
- [2] National Center for Biotechnology Information (NCBI). <https://pubmed.ncbi.nlm.nih.gov/> Accessed 9 July 2025.
- [3] Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 2013;257:800–806.
- [4] Dueland S, Syversveen T, Solheim JM, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. *Ann Surg* 2020;271:212–218.
- [5] Grut H, Dueland S, Line PD, et al. The prognostic value of 18F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. *Eur J Nucl Med Mol Imaging* 2018;45:218–225.
- [6] Grut H, Line PD, Syversveen T, et al. Metabolic tumor volume predicts long-term survival after transplantation for unresectable colorectal liver metastases: 15 years of experience from the SECA study. *Ann Nucl Med* 2022;36:1073–1081.
- [7] Smedman TM, Line P-D, Hagness M, et al. Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (SECA-II arm D study). *BJS Open* 2020;4:467–477.
- [8] Missiaglia E, Jacobs B, D'Ario G, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann Oncol* 2014;25:1995–2001.
- [9] Milette S, Hashimoto M, Perrino S, et al. Sexual dimorphism and the role of estrogen in the immune microenvironment of liver metastases. *Nat Commun* 2019;10:5745.
- [10] Moekli B, Ivanics T, Claassen M, et al. Recent developments and ongoing trials in transplant oncology. *Liver Int* 2020;40:2326–2344.
- [11] Adam R, Piedvache C, Chiche L, et al. Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. *Lancet* 2024;404:1107–1118.
- [12] European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation. *J Hepatol* 2016;64:433–485.
- [13] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
- [14] Mansournia MA, Nazemipour M. Recommendations for accurate reporting in medical research statistics. *Lancet* 2024;403:611–612.
- [15] Mansournia MA, Collins GS, Nielsen RO, et al. CChecklist for statistical assessment of medical papers: the CHAMP statement. *Br J Sports Med* 2021;55:1002–1003.
- [16] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- [17] Lee KJ, Simpson JA. Introduction to multiple imputation for dealing with missing data. *Respirology* 2014;19:162–167.
- [18] Wasserstein RL, Lazar NA. The ASA's statement on p-values: context, process, and purpose. *Am Statistician* 2016;70:129–133.
- [19] Rovetta A, Mansournia MA, Vitale A. For a proper use of frequentist inferential statistics in public health. *Glob Epidemiol* 2024;8:100151.
- [20] Greenland S, Rafi Z, Matthews R, et al. To aid scientific inference, emphasize unconditional compatibility descriptions of statistics. *arXiv* 2019; arXiv.1909.08583:1–44.
- [21] Greenland S, Mansournia MA, Joffe M. To curb research misreporting, replace significance and confidence by compatibility. *Prev Med* 2022;164:107127.
- [22] Ciria R, Ivanics T, Aliseda D, et al. Liver transplantation for primary and secondary liver tumors: patient-level meta-analyses compared to UNOS conventional indications. *Hepatology* 2025;81:1700–1713.
- [23] Adam R, Karam V, Cailliez V, et al. 2018 annual report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. *Transpl Int* 2018;31:1293–1317.
- [24] Solheim JM, Dueland S, Line PD, et al. Transplantation for nonresectable colorectal liver metastases: long-term follow-up of the first prospective pilot study. *Ann Surg* 2023;278:239–245.
- [25] Dueland S, Smedman TM, Rosok B, et al. Treatment of relapse and survival outcomes after liver transplantation in patients with colorectal liver metastases. *Transpl Int* 2021;34:2205–2213.
- [26] Dueland S, Smedman TM, Grut H, et al. PET-uptake in liver metastases as method to predict tumor biological behavior in patients transplanted for colorectal liver metastases developing lung recurrence. *Cancers* 2022;14:5042.
- [27] Favoriti P, Carbone G, Greco M, et al. Worldwide burden of colorectal cancer: a review. *Updates Surg* 2016;68:7–11.
- [28] Vukic FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 2019;68:1820–1826.
- [29] Koo JH, Jalaludin B, Wong SKC, et al. Improved survival in young women with colorectal cancer. *Am J Gastroenterol* 2008;103:1488–1495.
- [30] Majek O, Gondos A, Jansen L, et al. Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. *PLoS ONE* 2013;8:e68077.
- [31] Hendifar A, Yang D, Lenz F, et al. Gender disparities in metastatic colorectal cancer survival. *Clin Cancer Res* 2009;15:6391–6397.
- [32] Schmuck R, Gerken M, Teegen EM, et al. Gender comparison of clinical, histopathological, therapeutic and outcome factors in 185,967 colon cancer patients. *Langenbecks Arch Surg* 2020;405:71–80.
- [33] Lee MS, Menter DG, Kopetz S. Right versus left colon cancer biology: integrating the consensus molecular subtypes. *J Natl Compr Canc Netw* 2017;15:411–419.
- [34] Abancens M, Bustos V, Harvey H, et al. Sexual dimorphism in colon cancer. *Front Oncol* 2020;10:607909.
- [35] Giacchetti S, Dugué PA, Innominato PF, et al. Sex moderates circadian chemotherapy effects on survival of patients with metastatic colorectal cancer: a meta-analysis. *Ann Oncol* 2012;23:3110–3116.
- [36] Baraibar I, Ros J, Saoudi N, et al. Sex and gender perspectives in colorectal cancer. *ESMO Open* 2023;8:101204.
- [37] Aide et Recherche en Cancérologie Digestive (ARCAD) Foundation. The LiverMetSurvey. [www.fondationarcad.org/](http://www.fondationarcad.org/) Accessed 9 July 2025.
- [38] Rackaityte E, Halkias J. Mechanisms of fetal T cell tolerance and immune regulation. *Front Immunol* 2020;11:588.
- [39] Muralidhara P, Sood V, Vinayak Ashok V, et al. Pregnancy and tumour: the parallels and differences in regulatory T cells. *Front Immunol* 2022;13:866937.
- [40] Topi G, Ghatak S, Satapathy SR, et al. Combined estrogen alpha and beta receptor expression has a prognostic significance for colorectal cancer patients. *Front Med* 2022;9:739620.
- [41] Horak J, Kubecek O, Siskova A, et al. Differences in genome, transcriptome, miRNAome, and methylome in synchronous and metachronous liver metastasis of colorectal cancer. *Front Oncol* 2023;13:1133598.
- [42] Fang YJ, Lu ZH, Wang GQ, et al. Elevated expressions of MMP7, TROP2, and survivin are associated with survival, disease recurrence, and liver metastasis of colon cancer. *Int J Colorectal Dis* 2009;24:875–884.
- [43] Vidal J, Muinelo L, Dalmases A, et al. Plasma ctDNA RAS mutation analysis for the diagnosis and treatment monitoring of metastatic colorectal cancer patients. *Ann Oncol* 2017;28:1325–1332.
- [44] Løes IM, Immervoll H, Sorbye H, et al. Impact of KRAS, BRAF, PIK3CA, TP53 status and intraindividual mutation heterogeneity on outcome after liver resection for colorectal cancer metastases. *Int J Cancer* 2016;139:647–656.
- [45] Fenton HM, Taylor JC, Lodge JPA, et al. Variation in the use of resection for colorectal cancer liver metastases. *Ann Surg* 2019;270:892–898.
- [46] Ljunggren M, Weibull CE, Palmer G, et al. Sex differences in metastatic surgery following diagnosis of synchronous metastatic colorectal cancer. *Int J Cancer* 2023;152:363–373.
- [47] Barlek MH, Rouan JR, Wyatt TG, et al. The persistence of sex bias in high-impact clinical research. *J Surg Res* 2022;278:364–374.

- [48] Burra P, Zanetto A, Germani G. Sex bias in clinical trials in gastroenterology and hepatology. *Nat Rev Gastroenterol Hepatol* 2022;19:413–414.
- [49] Herrmann D, Sinnott P, Holmes J, et al. Statistical controversies in clinical research: publication bias evaluations are not routinely conducted in clinical oncology systematic reviews. *Ann Oncol* 2017;28:931–937.
- [50] Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019;567:305–307.
- [51] Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016;352:i1981.

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## **Supplemental information**

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

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

	<ul style="list-style-type: none"> <li>At least 1 line of chemotherapy for at least 3 months with PR or SD according to modified RECIST</li> <li>CEA &lt; 80 µg/L or reduction of ≥ 50% of highest CEA level observed.</li> <li>No extrahepatic disease.</li> <li>No other contraindications to liver transplantation.</li> </ul>	<ul style="list-style-type: none"> <li>Palliative resection of primary tumor.</li> </ul>
<b>COLT</b> <b>(NCT03803436)<sup>1</sup></b> <b>Milan, IT</b>	<ul style="list-style-type: none"> <li>Histologically confirmed non-mucinous colon adenocarcinoma</li> <li>Primary tumor as pT1-3, pN0 or pN1 (metastases in &lt; 4 regional lymph nodes), confirmed R0 resection.</li> <li>RAS and BRAF wild-type &amp; MSS molecular status as per local testing.</li> <li>ECOG PS score = 0.</li> <li>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.</li> <li>A maximum of two prior chemotherapy treatment lines.</li> <li>CEA&lt;50 ng/ml.</li> <li>No Extrahepatic Disease.</li> </ul>	<ul style="list-style-type: none"> <li>Hereditary CRC syndromes including FAP and Lynch syndrome.</li> <li>Prior extra hepatic metastatic disease or primary tumor local relapse.</li> <li>Extra-peritoneal cancers (rectum).</li> <li>Other malignancies in the previous 5 years.</li> <li>Active intra-venous or alcohol abusers.</li> <li>HIV infection.</li> </ul>
<b>Université Catholique de Louvain (UCL)</b> <b>Louvain, BE</b>	<ul style="list-style-type: none"> <li>Age ≤70 years.</li> <li>Histologically confirmed BRAF wild-type colorectal cancer.</li> <li>Primary tumor resected according to standard oncological practice, p≤T4a, R0 resection.</li> <li>ECOG PS score ≤ 1.</li> <li>≥ 3 months of hepatic tumour control under the last line of chemotherapy according to RECIST criteria.</li> <li>No Extrahepatic Disease.</li> </ul>	<ul style="list-style-type: none"> <li>General contraindication to LT</li> <li>Other malignancies either concomitant or within 5 years before LT</li> <li>No standard treatment for the primary CRC according to recommended guidelines</li> <li>Prior extra hepatic metastatic disease or local relapse</li> <li>Pregnancy at the time of inclusion</li> </ul>
<b>University of Rochester<sup>2,3</sup></b> <b>(NCT05248581)<sup>1</sup></b> <b>Rochester (NY), US</b>	<ul style="list-style-type: none"> <li>Age ≤65 years.</li> <li>Histologically verified CRC.</li> <li>Adequate resection margins including CRM of at least ≥1mm for patients with rectal cancer.</li> <li>Absence of synergistic tumor mutations (KRAS &amp; TP53).</li> <li>ECOG PS score ≤ 1.</li> <li>Patients should have had least one line of fluorouracil-based, oxaliplatin-based, or irinotecan-based chemotherapy.</li> <li>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.</li> <li>Response to Chemotherapy ≥12 months.</li> <li>CEA &lt;80ng/dL.</li> <li>Oslo Score ≤ 2.</li> <li>No Extrahepatic Disease.</li> </ul>	<ul style="list-style-type: none"> <li>Primary tumour histology of undifferentiated adenocarcinoma or signet ring cell carcinoma.</li> <li>Standard contraindications for LT.</li> <li>Other malignancies.</li> </ul>
<b>Cleveland Clinic<sup>2,3</sup></b> <b>Cleveland (OH), US</b>	<ul style="list-style-type: none"> <li>Age ≤65 years.</li> <li>Histologically verified CRC.</li> <li>Adequate resection margins including CRM of at least ≥1mm for patients with rectal cancer</li> <li>Absence of tumor mutation (BRAF).</li> <li>ECOG PS score ≤ 1.</li> <li>Patients should have had least one line of fluorouracil-based, oxaliplatin-based, or irinotecan-based chemotherapy.</li> <li>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.</li> <li>Response to Chemotherapy 6-12months.</li> <li>CEA &lt;100ng/dL.</li> <li>At least 1-year time span from CRC resection and date of being listed.</li> <li>No Extrahepatic Disease.</li> </ul>	<ul style="list-style-type: none"> <li>Primary tumour histology of undifferentiated adenocarcinoma or signet ring cell carcinoma.</li> <li>Standard contraindications for LT.</li> <li>Other malignancies.</li> </ul>
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.		
<sup>1</sup> <a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>		
<sup>2</sup> 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.		
<sup>3</sup> 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.<sup>1-4</sup> 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".<sup>4</sup> 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,<sup>5,6</sup> 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).

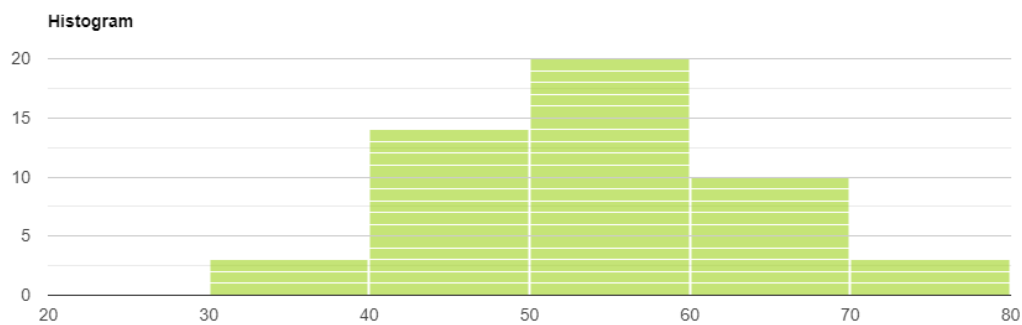


Figure S1. Male histogram of frequencies: age data.

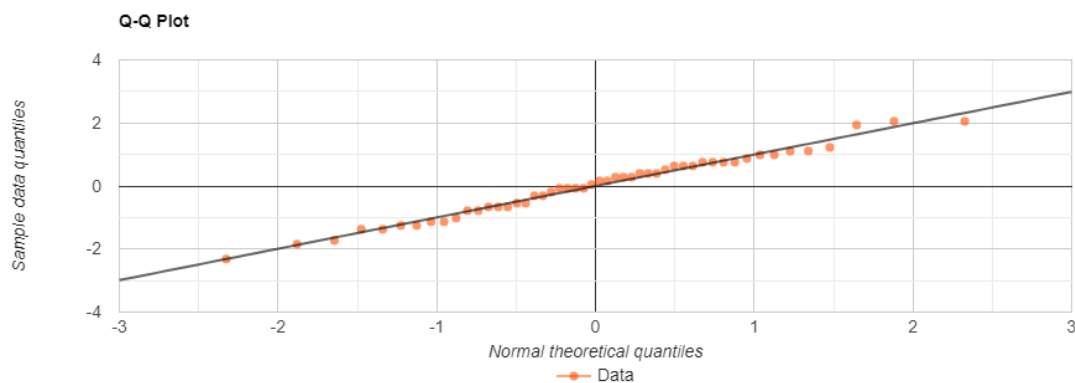


Figure S2. Male Q-Q plot: age data.

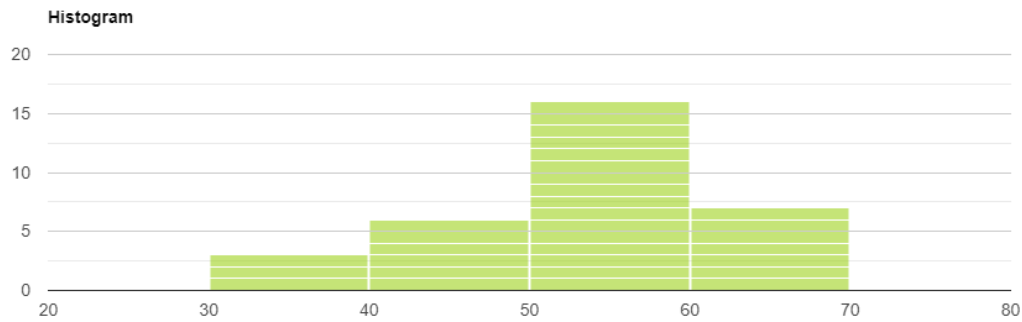


Figure S3. Female histogram of frequencies: age data.

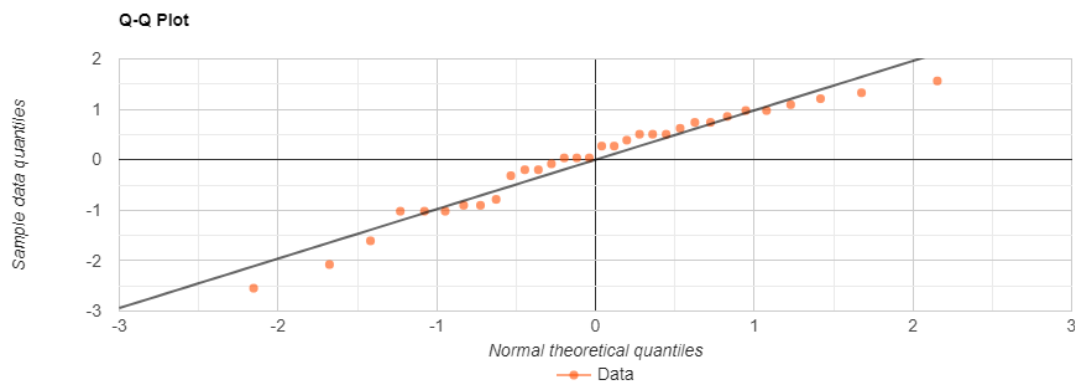


Figure S4. Female Q-Q plot: age data.

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 METHODS<sup>7</sup>: 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 reader<sup>8</sup>: 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  $\chi^2$ , 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  $w$ ,<sup>9</sup> 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/m<sup>2</sup>, 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 <sup>10</sup>: 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).

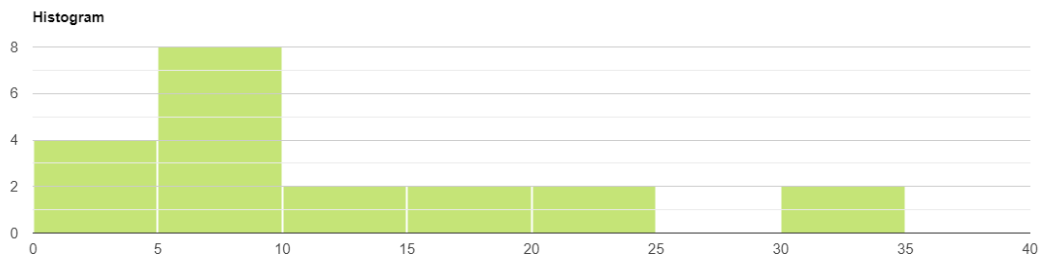


Figure S5. Male histogram of frequencies: number of nodules data.

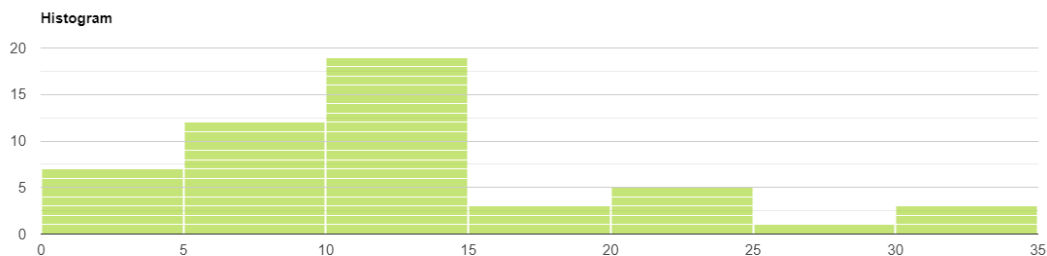


Figure S6. Female histogram of frequencies: number of nodules data.

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):

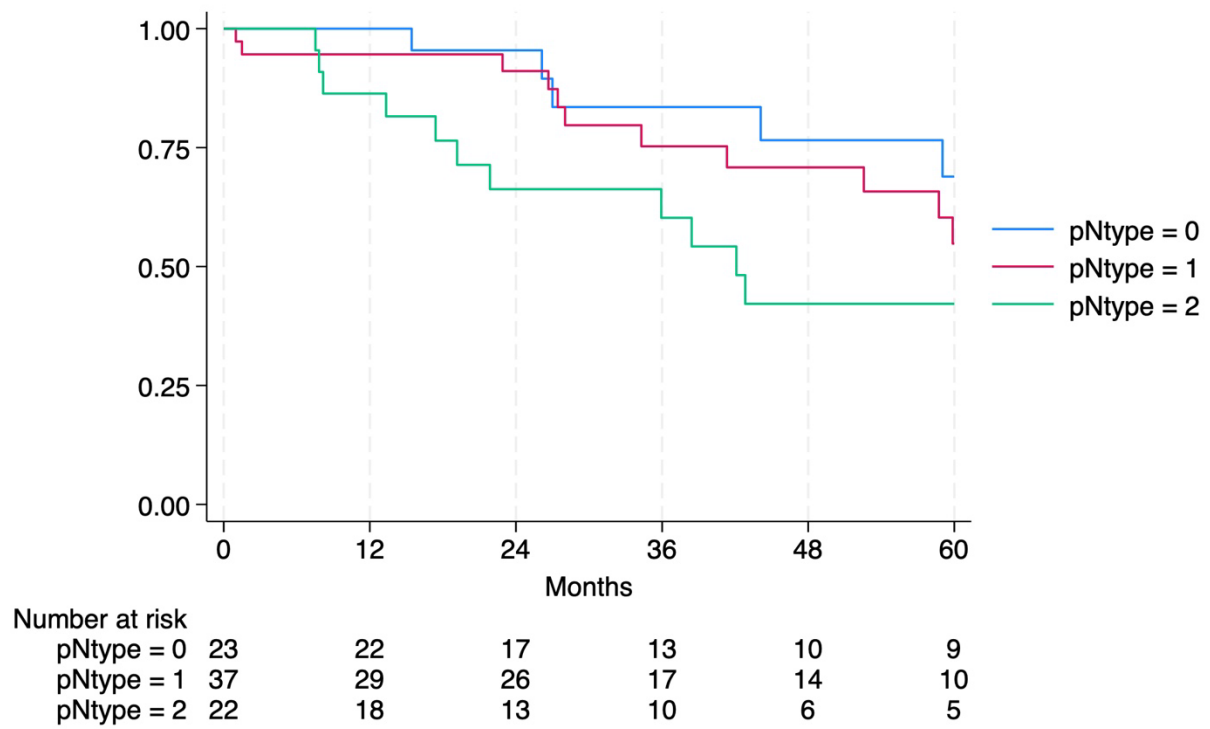
Statistics Kingdom - <https://www.statskingdom.com/>

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



## SELECTION OF pN VARIABLES

KAPLAN MEIER SURVIVAL CURVE.





## 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 residuals <sup>11-13</sup> 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,<sup>14</sup>).

**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

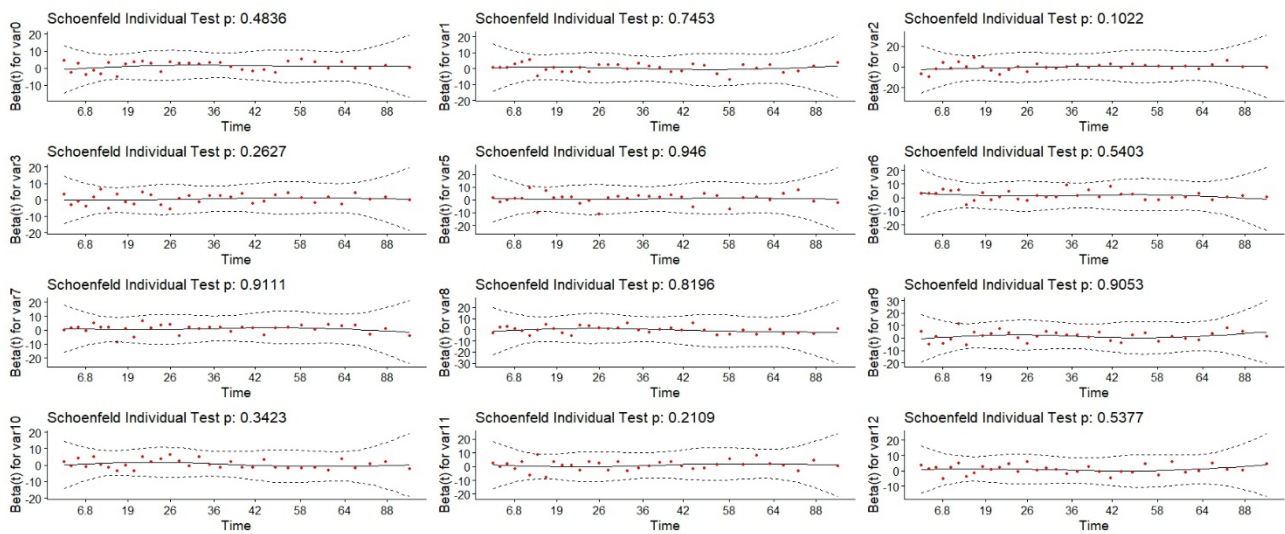


Figure S7. Type 2 model, Schoenfeld residuals.

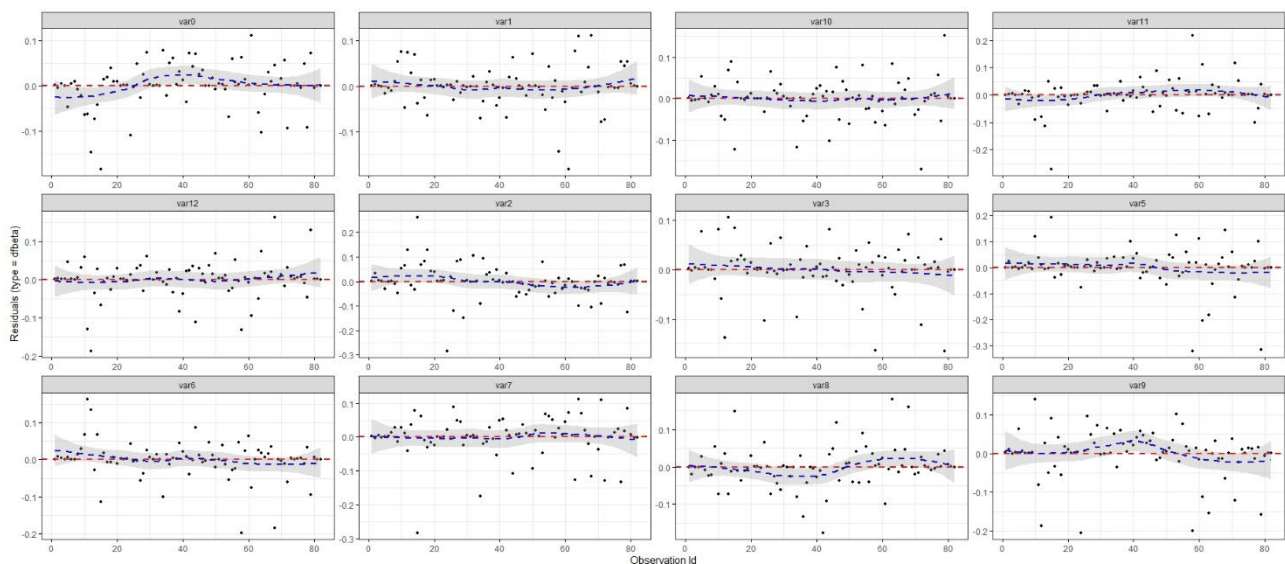


Figure S8. Type 2 model, dfbeta values.

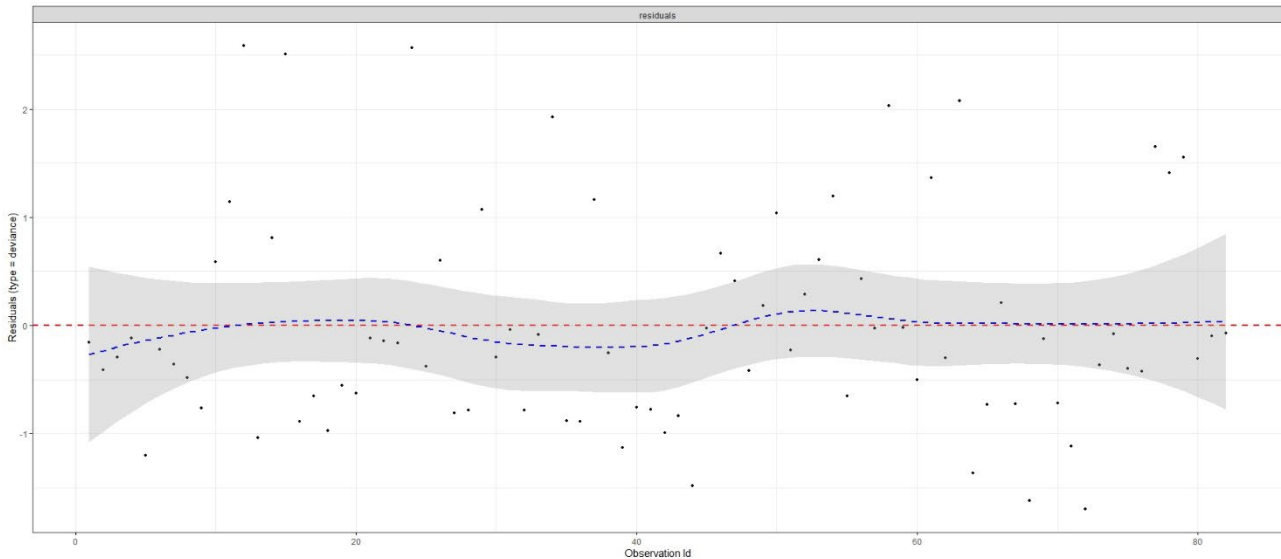


Figure S9. Type 2 model, deviance residuals.

**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  $\leq 5$ ) 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 <sup>2</sup>	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 $\mu$ 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 test<sup>15</sup>, 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 <sup>16</sup>).

## 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).

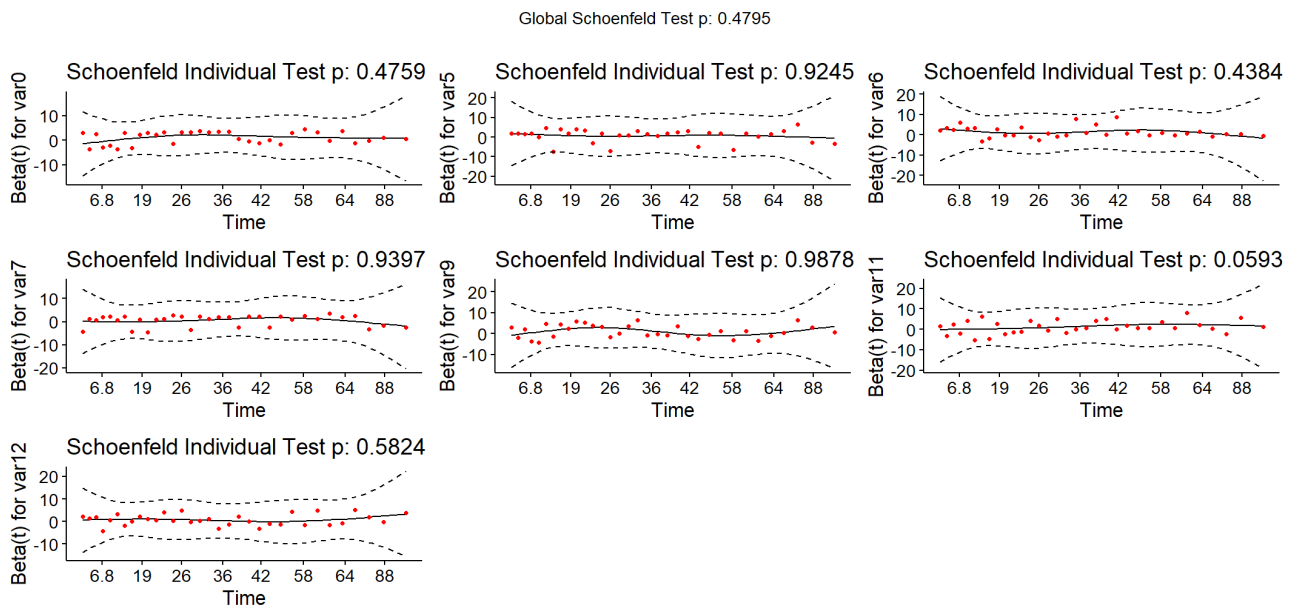


Figure S10. Model type 1 Schoenfeld residuals.

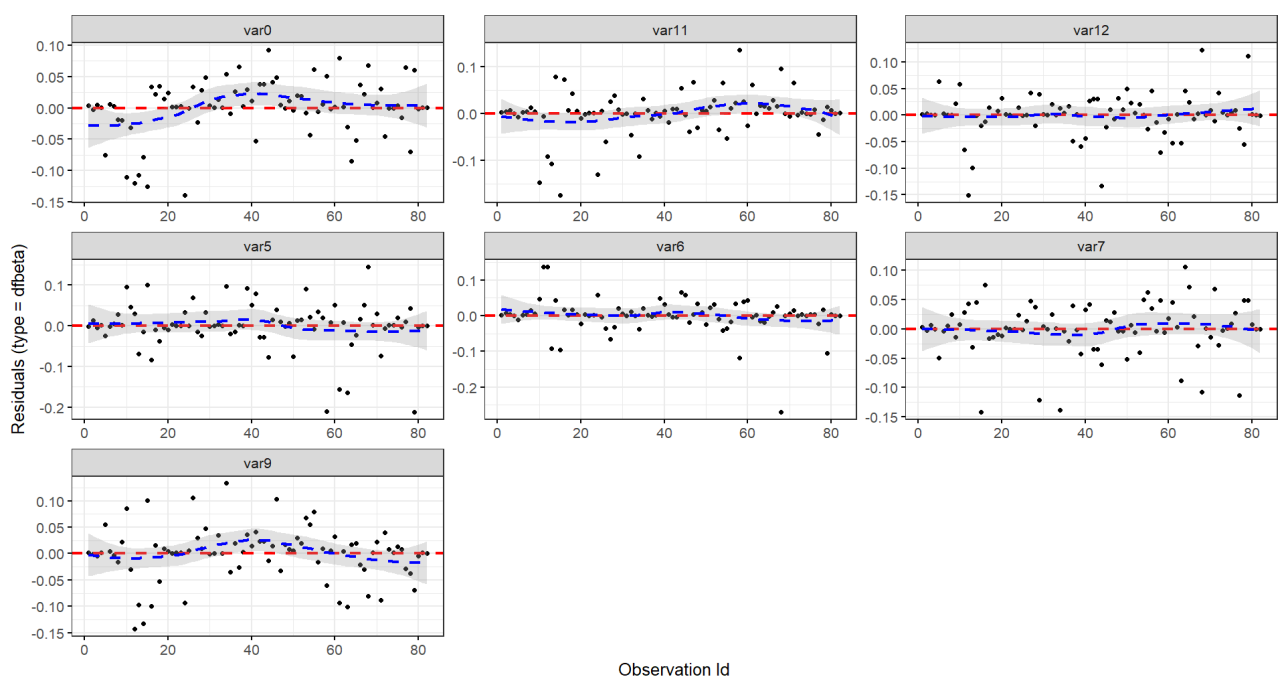


Figure S11. Model type 1 dfbeta values.

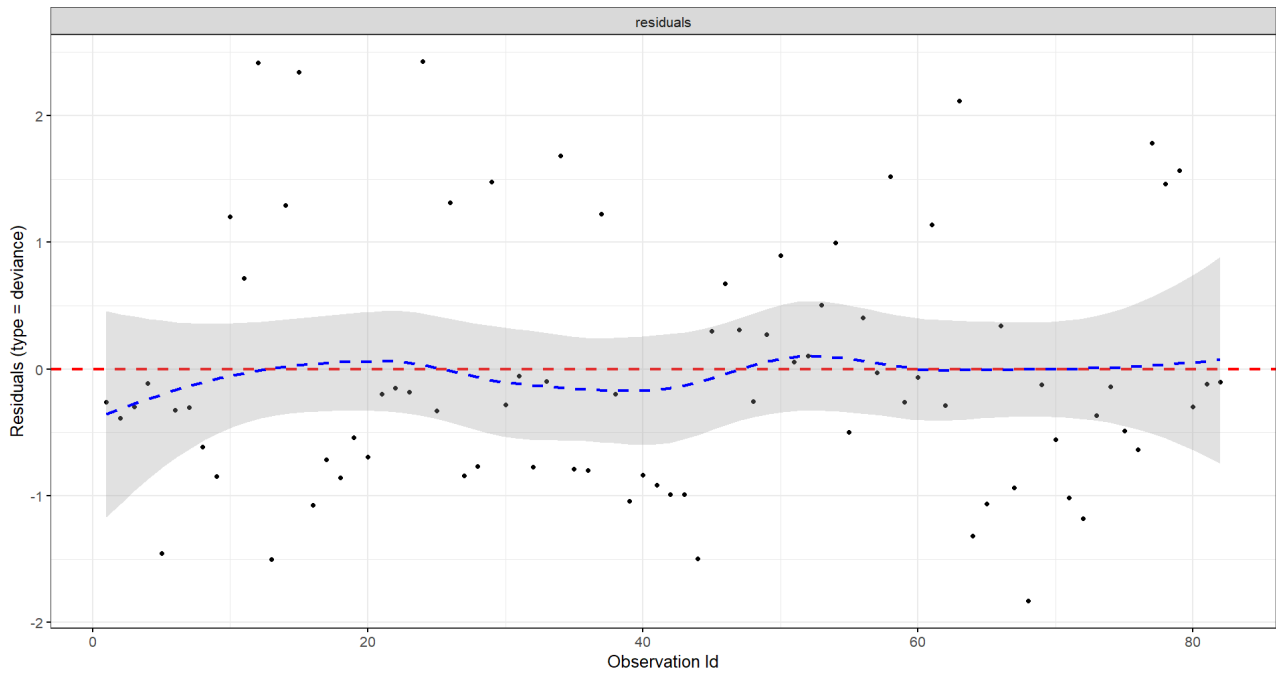


Figure S12. Model type 1 deviance analysis.

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  $\leq 10$  in the univariate analysis) are shown in Table S5.

**Table S5. Type 1 model results (only covariates with – approximately – null P-value  $\leq 0.10$  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 $\leq 24$ 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).

<b>Table S6. Schoenfeld test results.</b>		
<b>Variable</b>	<b>Male null P-value</b>	<b>Female null P-value</b>
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
<b>Males</b>				
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 <sup>2</sup>	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
<b>Females</b>				
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.

<b>Table S8. Treatment of recurrence after liver transplantation according to recurrence pattern and biological sex.</b>				
<b>Variables</b>	<b>N° of patients N° (%)</b>	<b>Males (n=38) N° (%)</b>	<b>Females (n=24) N° (%)</b>	<b>Null p-value</b>
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

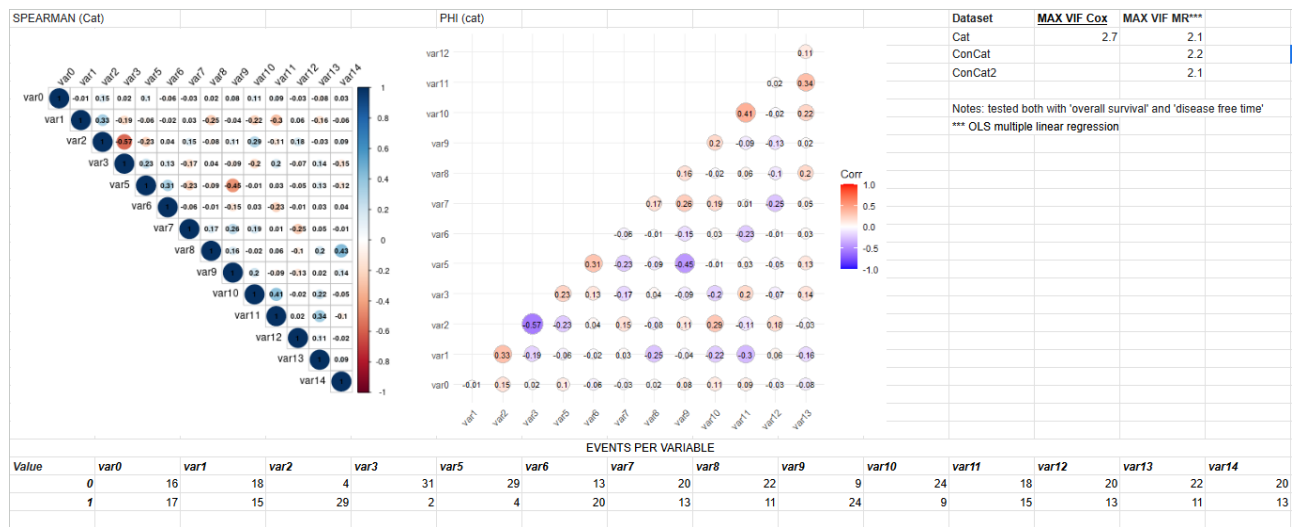
Cox regression models were performed to test the adjusted associations between covariates and outcomes. This aim is usually defined as explanatory modelling.<sup>17</sup> It needs to be more inclusive than ultra-selective to avoid the risk of excluding clinically relevant variables that could have an essential causal role.<sup>18</sup> 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.<sup>18</sup>

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).<sup>19</sup>

## 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 <sup>2</sup>			
	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	
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	
VAR0	Female gender	5,13	2,04	12,90	0,0005	10,9	Concordance= 0.84 (se = 0.036 )
VAR1	Age > 55 years	1,33	0,55	3,24	0,53	0,9	Likelihood ratio test= 55.29 on 14 df, p=8e-07
VAR2	Oslo center	0,30	0,05	1,77	0,18	2,5	Wald test = 48.05 on 14 df, p=1e-05
VAR3	Living donor	0,79	0,09	7,27	0,84	0,3	Score (logrank) test = 76.12 on 14 df, p=1e-10
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	
VAR0	Female gender	4,07	1,76	9,43	0,001	9,9	Concordance= 0.839 (se = 0.033 )
VAR1	Age > 55 years						Likelihood ratio test= 48.11 on 8 df, p=9e-08
VAR2	Oslo center						Wald test = 46.8 on 8 df, p=2e-07
VAR3	Living donor						Score (logrank) test = 68.97 on 8 df, p=8e-12
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	
VAR0	Female gender	4,12	1,72	9,88	0,002	9,4	Concordance= 0.841 (se = 0.032 )
VAR1	Age > 55 years						Likelihood ratio test= 48.12 on 9 df, p=2e-07
VAR2	Oslo center						Wald test = 46.87 on 9 df, p=4e-07
VAR3	Living donor						Score (logrank) test = 69.32 on 9 df, p=2e-11
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
VAR1	Age > 55 years	0,70	0,30	1,30	0,23	2,1	0,7	0,3	1,3
VAR2	Oslo center	1,30	0,50	4,20	0,59	0,8	1,3	0,5	4,2
VAR3	Living donor	1,65	0,33	5,28	0,49	1,0	1,7	0,3	5,3
VAR5	Previous liver therapy	0,41	0,13	1,00	0,05	4,3 **	0,4	0,1	1,0
VAR6	BMI > 25 Kg/m2	0,90	0,50	1,90	0,79	0,3	0,9	0,5	1,9
VAR7	pN2	2,10	1,00	4,20	0,04	4,6 **	2,1	1,0	4,2
VAR8	Right location CRC	5,60	2,60	11,70	0,000	>10 **	5,6	2,6	11,7
VAR9	Time ≤ 24 months	1,80	0,90	4,00	0,11	3,2 *	1,8	0,9	4,0
VAR10	Progressive Disease	2,00	0,90	4,10	0,09	3,5 **	2,0	0,9	4,1
VAR11	Largest diameter > 5.5 cm	2,50	1,20	4,90	0,01	6,6 **	2,5	1,2	4,9
VAR12	Number of nodules > 10	1,30	0,60	2,50	0,49	1,0	1,3	0,6	2,5
VAR13	CEA > 80 µg/L	4,20	2,00	8,50	0,000	>10 **	4,2	2,0	8,5
VAR14	KRAS mutated	2,40	1,20	4,70	0,02	5,6 **	2,4	1,2	4,7
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						
var1	Age > 55 years		1,30	0,52	3,28	0,57						
var2	Oslo center		0,30	0,05	1,85	0,19						
var3	Living donor		1,01	0,12	8,70	1,00						
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						
var1	Age > 55 years		1,27	0,53	3,18	0,60						
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	5.52	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+	
var0 (cat.)	Female gender	6.31	1.95	20.42	0.002						AVG -
var1	Aoe	1.03	0.98	1.08	0.27			1.43	0.76	2.68	46.9
var2 (cat.)	Oslo center	0.56	0.10	3.03	0.50						60.3
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	1.89	0.82	3.49	0.15			1.70	0.82	3.53	4.76
var7 (cat.)	pN2	2.80	1.04	7.57	0.04						5.77
var8 (cat.)	Right location CRC	4.61	1.48	14.33	0.008						
var9 (scat.)	Time Idt	1.24	0.92	1.68	0.16			1.90	0.77	4.66	3.73
var10 (cat.)	Proressive Disease	1.13	0.39	3.30	0.82						6.71
var11	Diameter	1.24	1.03	1.49	0.03			3.44	1.16	10.15	3.00
var12 (scat.)	Number of nodules	1.36	1.17	1.56	0.000			1.97	1.42	2.74	8.81
var13 (scat.)	CEA	1.01	0.98	1.04	0.42			1.02	0.97	1.07	2.50
var14 (cat.)	KRAS mutated	2.62	1.11	6.18	0.03						4.69
Wald Chi-square = 65.68237 on 14 df p = 1.155411e-08 n = 82											
Weighted Cox model											
Variable	Multivariable 2 VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	
var0 (cat.)	Female gender	8.47	2.13	33.70	0.002						AVG -
var1	Aoe	1.03	0.98	1.08	0.23			1.49	0.78	2.85	46.9
var2 (cat.)	Oslo center	0.38	0.08	1.84	0.23						60.3
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
var7 (cat.)	pN2	2.26	0.86	5.96	0.10						5.77
var8 (cat.)	Right location CRC	4.39	1.58	12.22	0.005						
var9 (scat.)	Time Idt	1.25	0.93	1.67	0.14			1.92	0.81	4.58	3.73
var10 (cat.)	Proressive Disease	1.15	0.42	3.21	0.78						6.71
var11	Diameter	1.19	1.01	1.40	0.04			2.73	1.04	7.18	3.00
var12 (scat.)	Number of nodules	1.37	1.17	1.60	0.000			1.98	1.41	2.79	8.81
var13 (cat.)	CEA	4.44	1.44	13.67	0.009						2.50
var14 (cat.)	KRAS mutated	2.20	0.94	5.13	0.07						4.69
Univariable 2											
Variable	VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	
var0 (cat.)	Female gender	2.04	1.02	4.07	0.04	**					AVG -
var1	Aoe	0.99	0.95	1.03	0.50			0.87	0.50	1.49	46.9
var2 (cat.)	Oslo center	1.48	0.50	4.43	0.48						60.3
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
var7 (cat.)	pN2	1.97	0.95	4.09	0.07	**					5.77
var8 (cat.)	Right location CRC	5.39	2.21	13.15	0.000	**					
var9 (scat.)	Time Idt	0.81	0.64	1.02	0.07	**		0.53	0.26	1.06	3.73
var10 (cat.)	Proressive Disease	1.86	0.76	4.53	0.18	*					6.71
var11	Diameter	1.14	1.05	1.25	0.003	**		2.14	1.33	3.66	3.00
var12 (scat.)	Number of nodules	1.19	1.03	1.38	0.02	**		1.46	1.07	2.02	8.81
var13 (cat.)	CEA	4.19	2.16	8.12	0.000	**					2.50
var14 (cat.)	KRAS mutated	2.29	1.10	4.78	0.03	**					4.69
Multivariable pS0.20											
Variable	VARIABLE NAME	HR	95-	95+	Null p			AVG HR	AVG 95-	AVG 95+	
var0 (cat.)	Female gender	5.97	1.96	18.17	0.002						AVG -
var1	Aoe										AVG +
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			1.76	0.68	4.53	3.73
var9 (scat.)	Time Idt	1.21	0.88	1.66	0.25						6.71
var10 (cat.)	Proressive 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
var12 (scat.)	Number of nodules	1.27	1.08	1.50	0.003			1.69	1.18	2.43	8.81
var13 (cat.)	CEA	3.68	1.34	10.05	0.01			9.65	1.66	55.43	2.50
var14 (cat.)	KRAS mutated	2.00	0.89	4.48	0.09						4.69





## 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	2,60	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	Num. cases = 82	
var0	Female gender	0,16	0,03	0,75	0,02	Pseudo Log-likelihood = -83.9	
var1	Age > 55 years	0,53	0,18	1,51	0,23	Pseudo likelihood ratio test = 22.8 on 14 df,	
var2	Oslo center	2,59	0,48	14,10	0,27		
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	Num. cases = 82	
var0	Female gender					Pseudo Log-likelihood = -91	
var1	Age > 55 years					Pseudo likelihood ratio test = 8.49 on 7 df,	
var2	Oslo center						
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	Num. cases = 82	
var0	Female gender					Pseudo Log-likelihood = -89.5	
var1	Age > 55 years					Pseudo likelihood ratio test = 11.7 on 10 df,	
var2	Oslo center						
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 p≤0.20												
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 p≤0.20 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 ldt	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 ldt	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 ldt	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
Concordance= 0.727 (se = 0.048 )					
Likelihood ratio test= 26.18 on 14 df. p=0.02					
Wald test = 28.68 on 14 df. p=0.01					
Score (logrank) test = 33.65 on 14 df. p=0.002					
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 (sqrt)	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 (sqrt)	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 (sqrt)	Number of nodules > 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 (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 of nodules > 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	**					
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											
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 (sqrt)	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 (sqrt)	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 (sqrt)	Number of nodules > 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+	Nullp		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	0.65	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 of nodules > 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+	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 (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	2.88	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 of nodules > 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+	Nullp		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	5.68	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 of nodules > 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+	Nullp		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	0.61	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 of nodules > 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					



## SUPPLEMENTARY FILE 3

## Dataset

## Cat Cox (overall survival)

```
#database
```

[illegible]













```

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 <- ggsurvplot(
    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(0,1,2,2,1,1,2,0,0,1,1,1,1,1,3,0,3,1,3,2,0,1,4,3,1,1,1,4,0,0,2,2,1,3,1,2,1,2,2,2,2,2,1,1,1,1,1,2,2,
2,2,2,2,3,1,2,2,1,1,1,1,1,2,2,0,0,0,0,0,0,0,1,1,1,0,0,0), 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

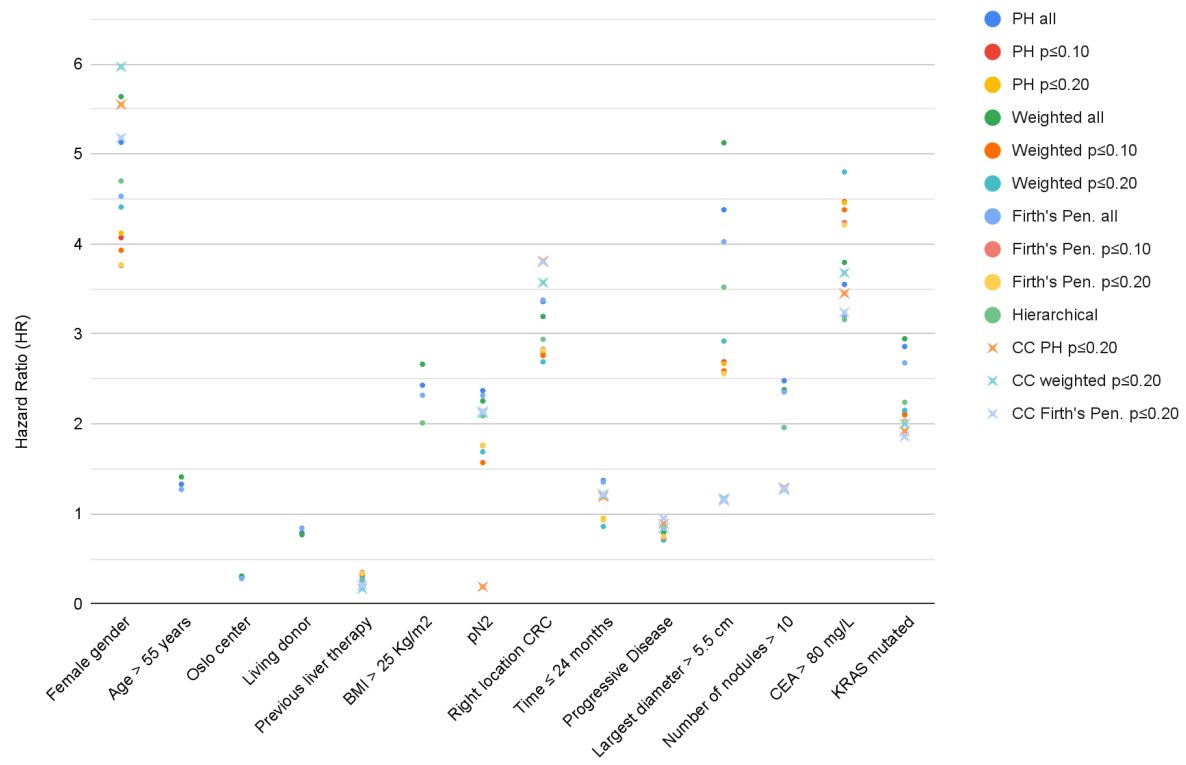
  cat("Results for", var_name, "\n")

  print(summary(model))

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

## Sensitivity analysis results (short summary)

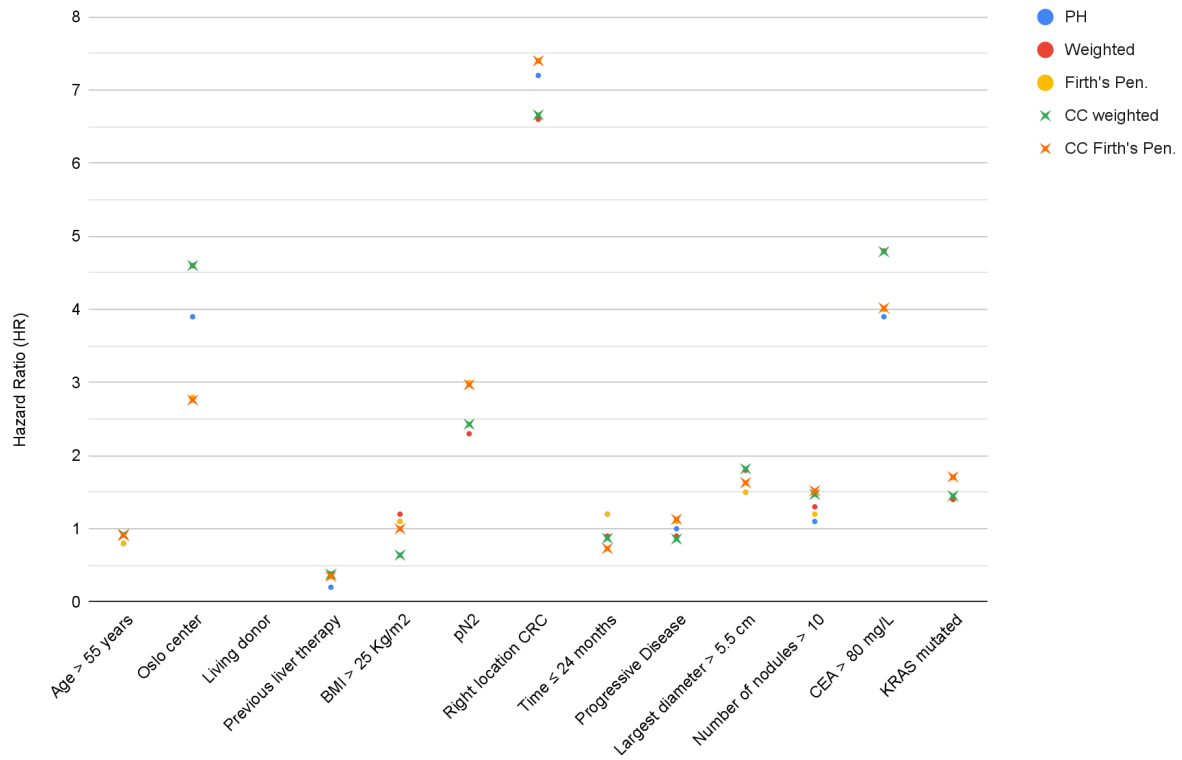
### Cox multivariable models for Table 2



**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.

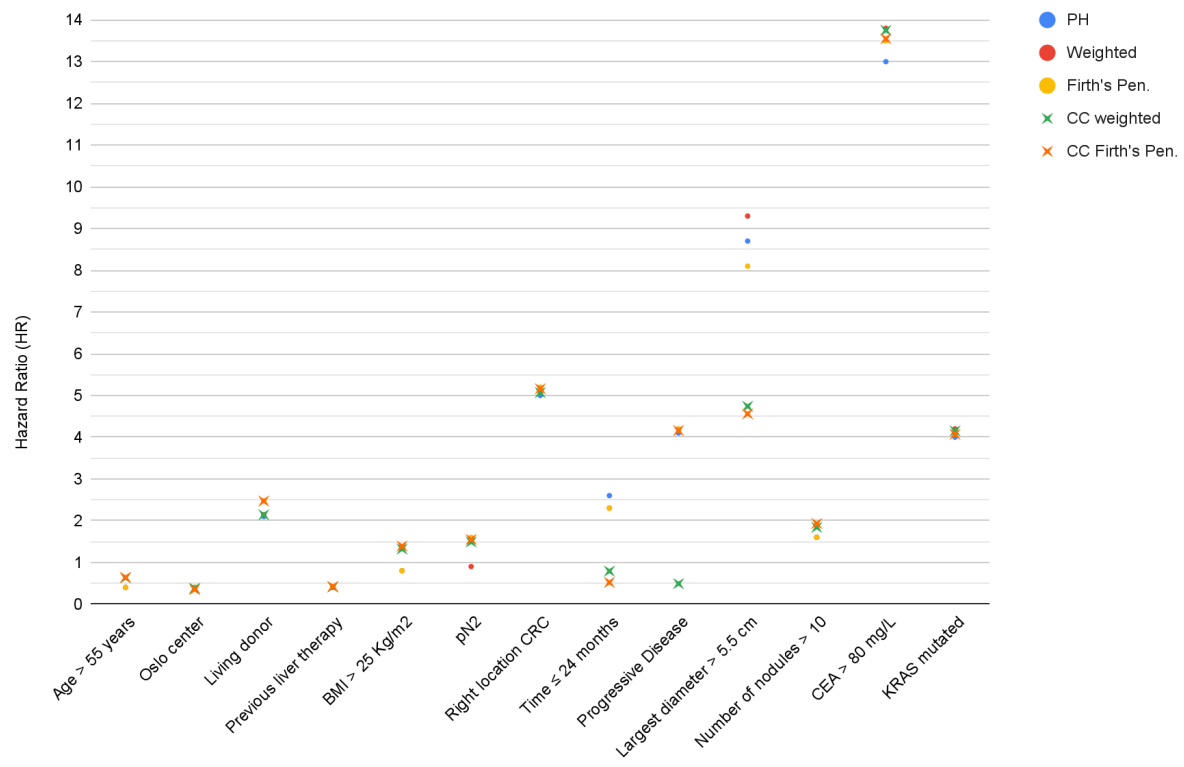
## Cox univariable models for Table 3

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.

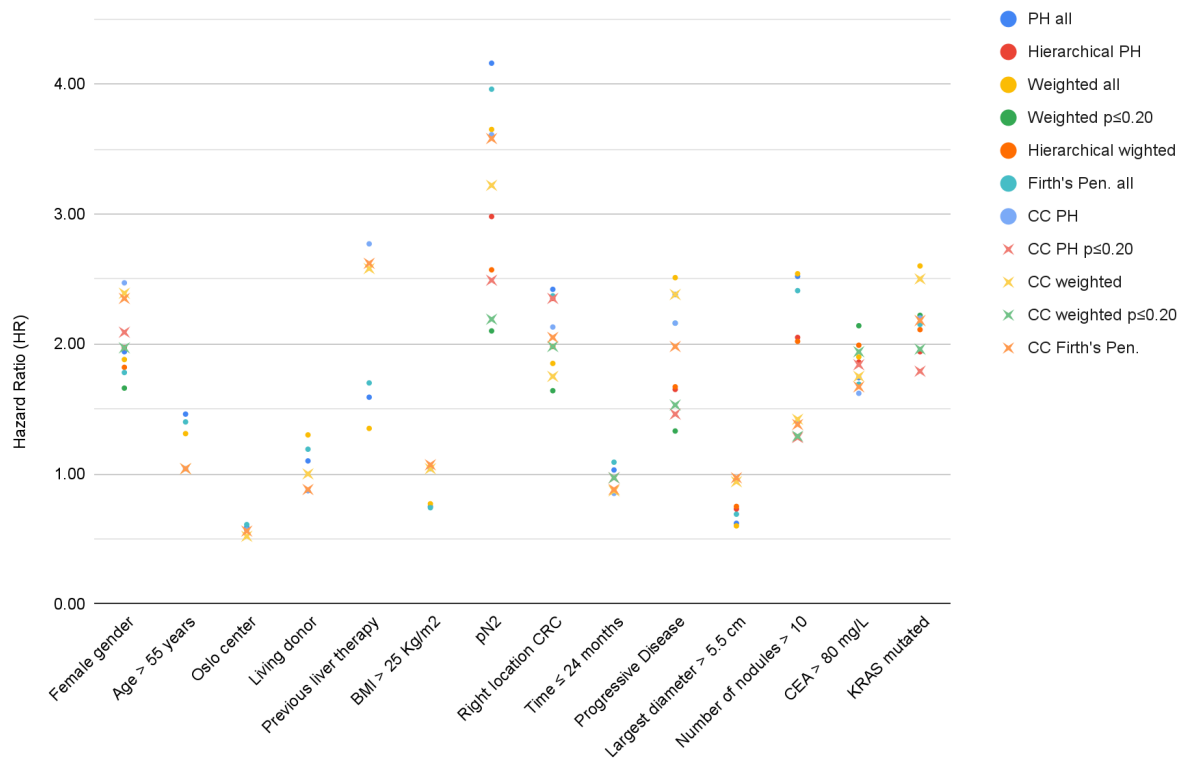
## Female



**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.

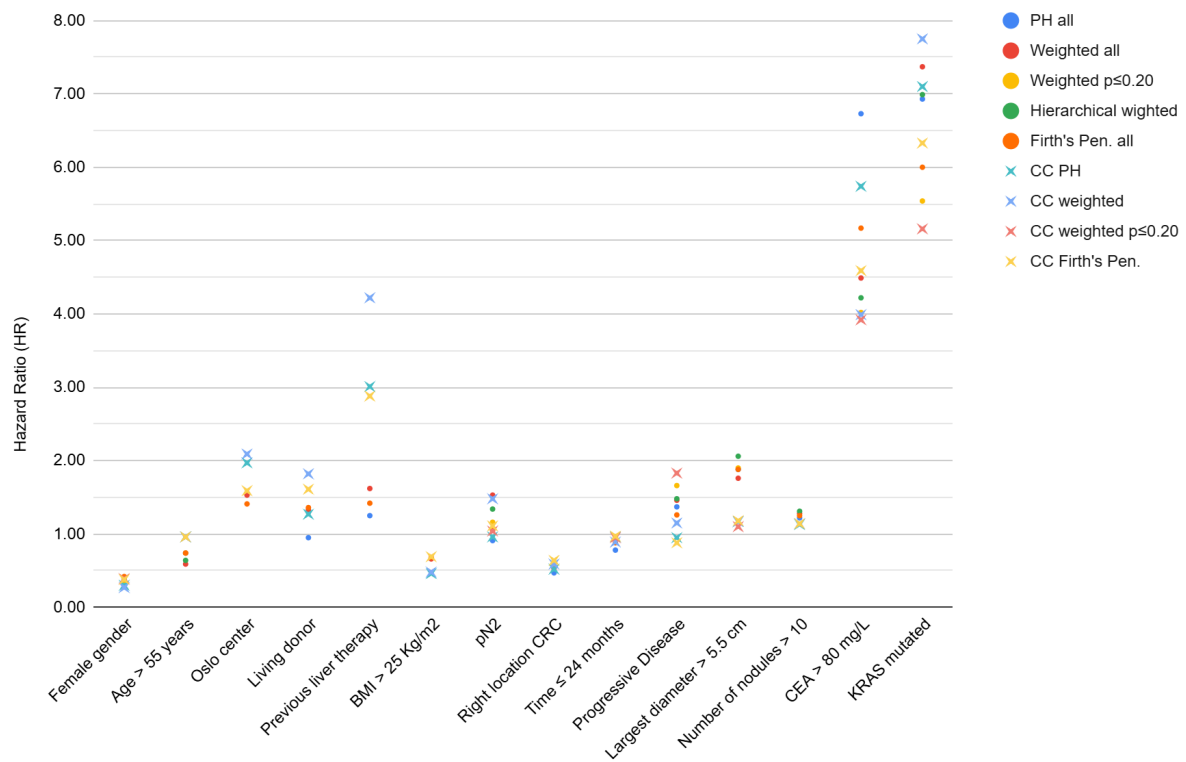
## Cause-specific multivariable models for Table 4

### 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



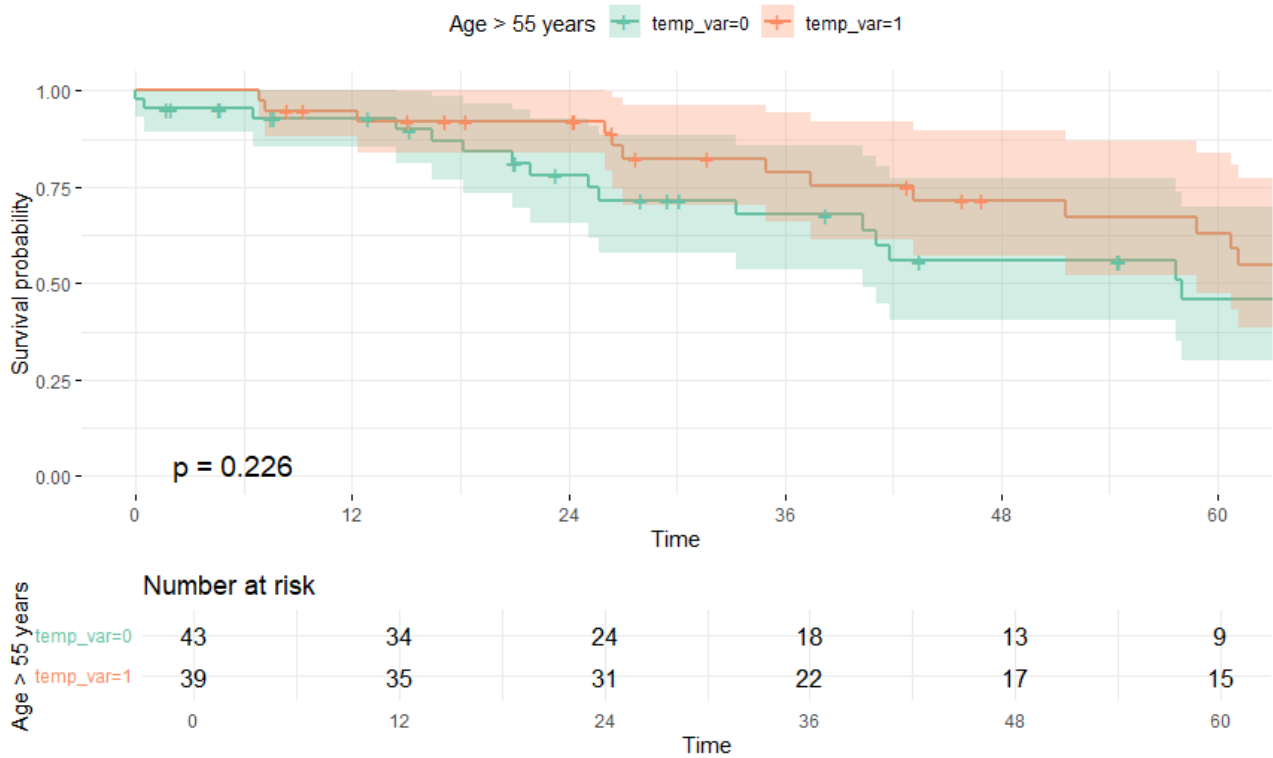
**Figure S2.4.** Hazard ratio (HR) point estimates for Table 4 (non-liver, lung) according to various models. P-values (p) concern the null hypothesis 'HR = 1.' Legend: PH = proportional hazards; Pen. = Firth's penalized; CC = ConCat.



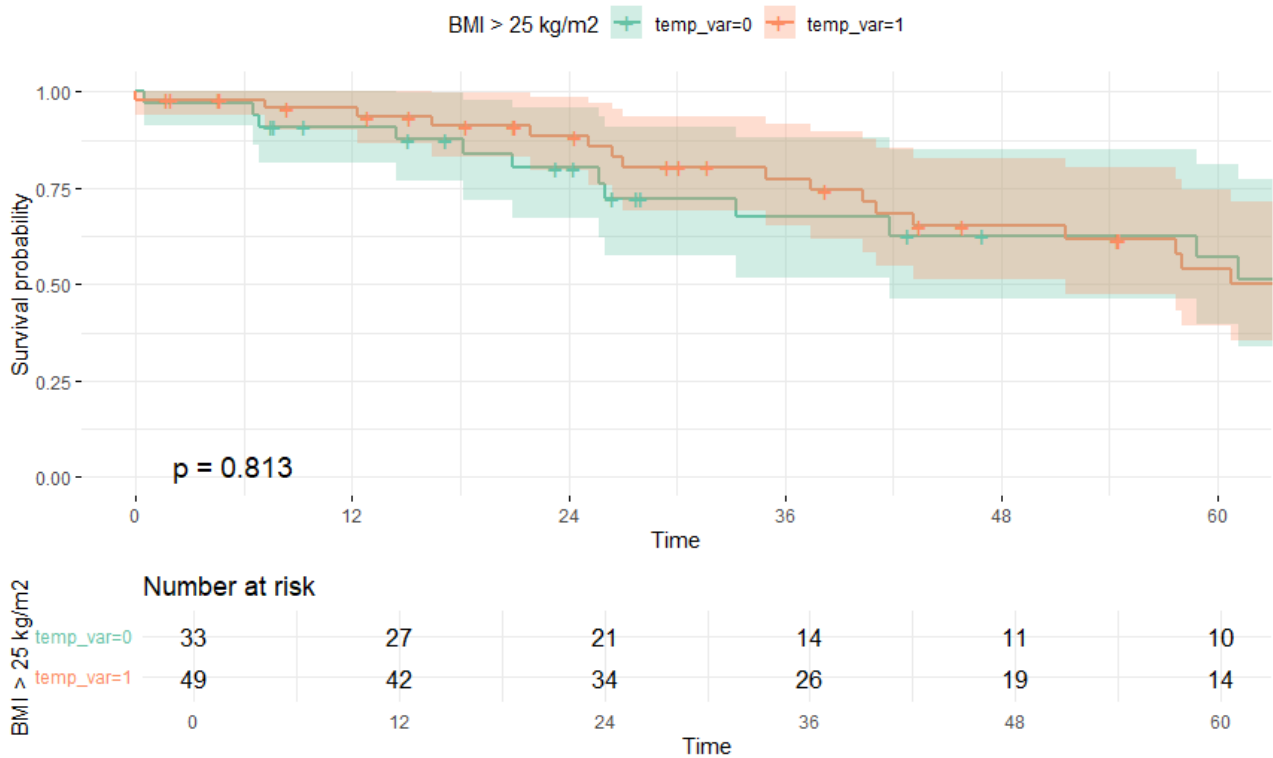
# Kaplan-Meier curves

## Table 2 variables

### Kaplan-Meier by Age > 55 years

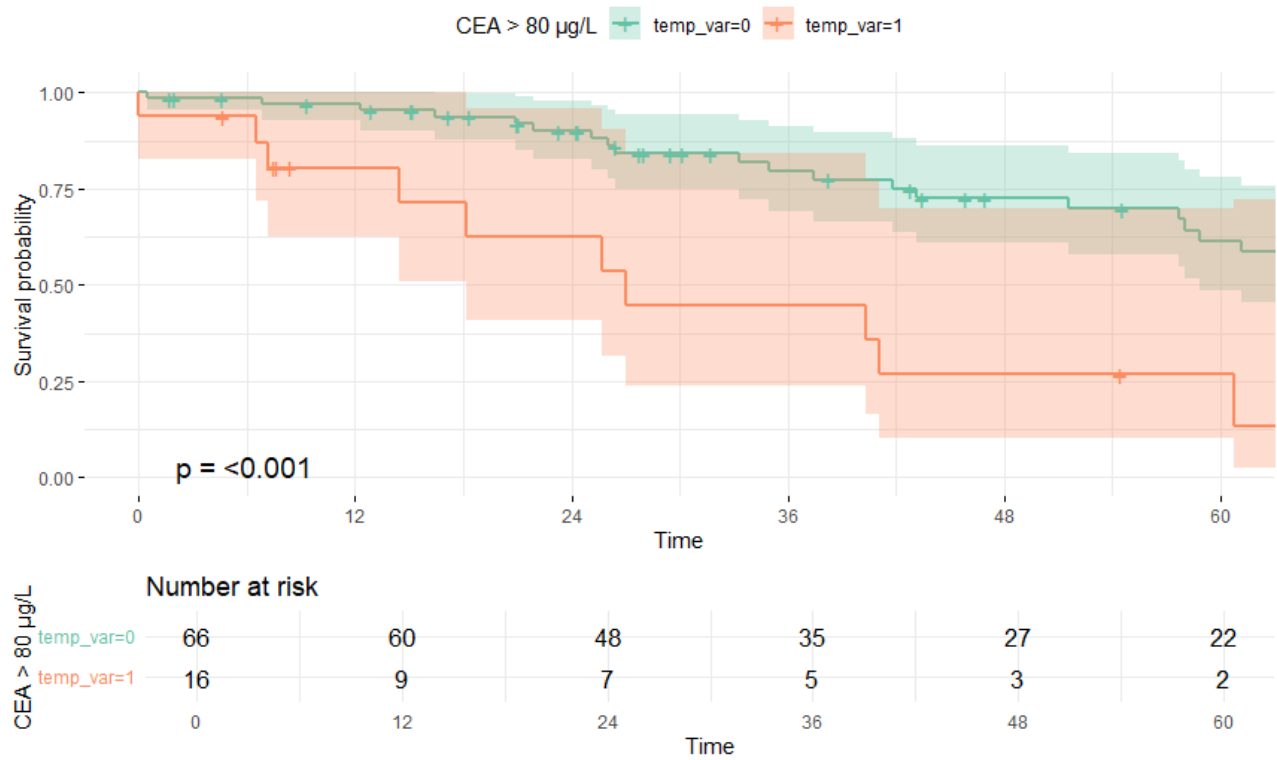


### Kaplan-Meier by BMI > 25 kg/m<sup>2</sup>

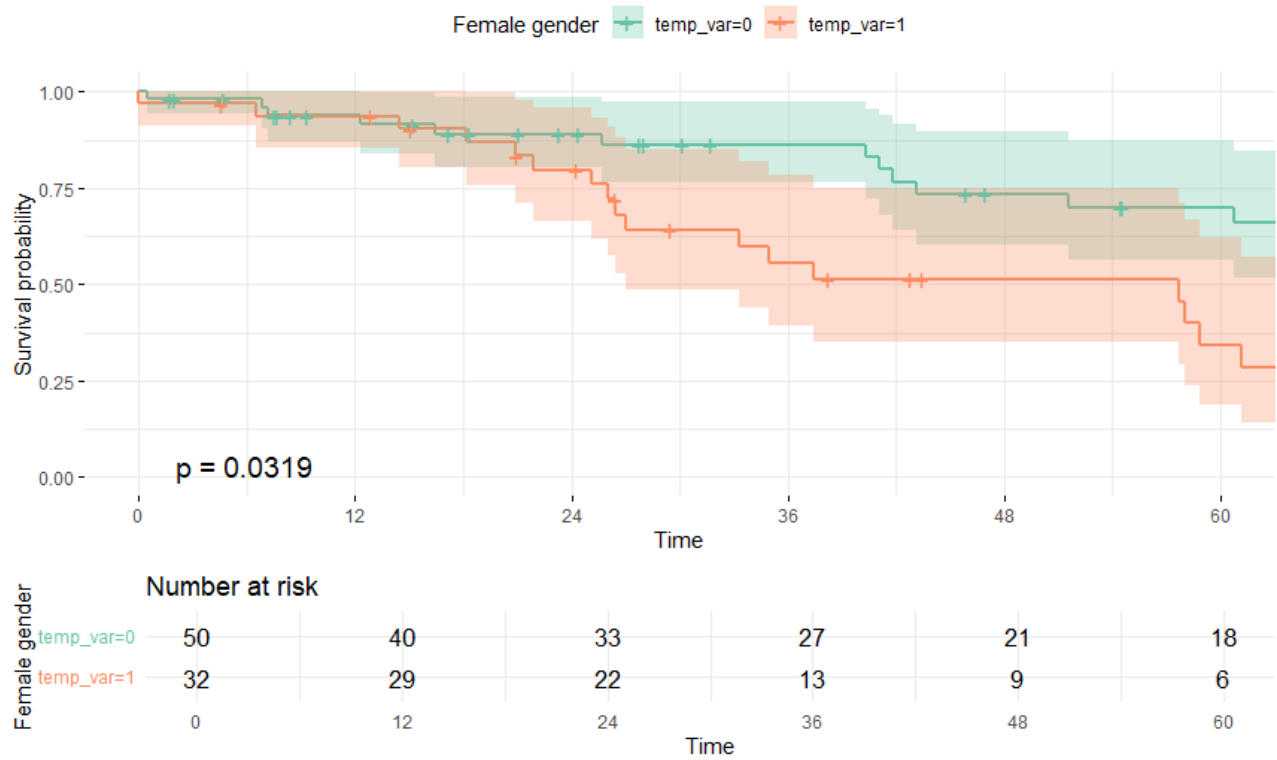




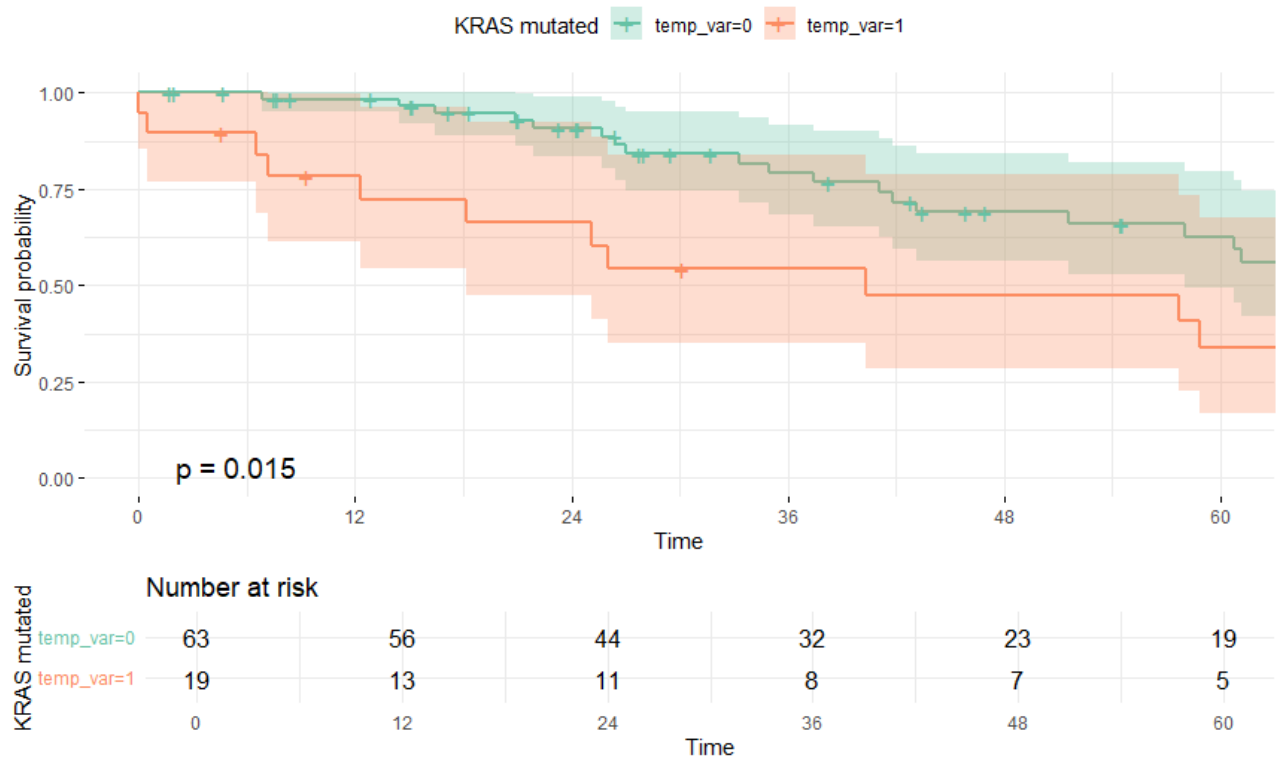
Kaplan-Meier by CEA > 80 µg/L



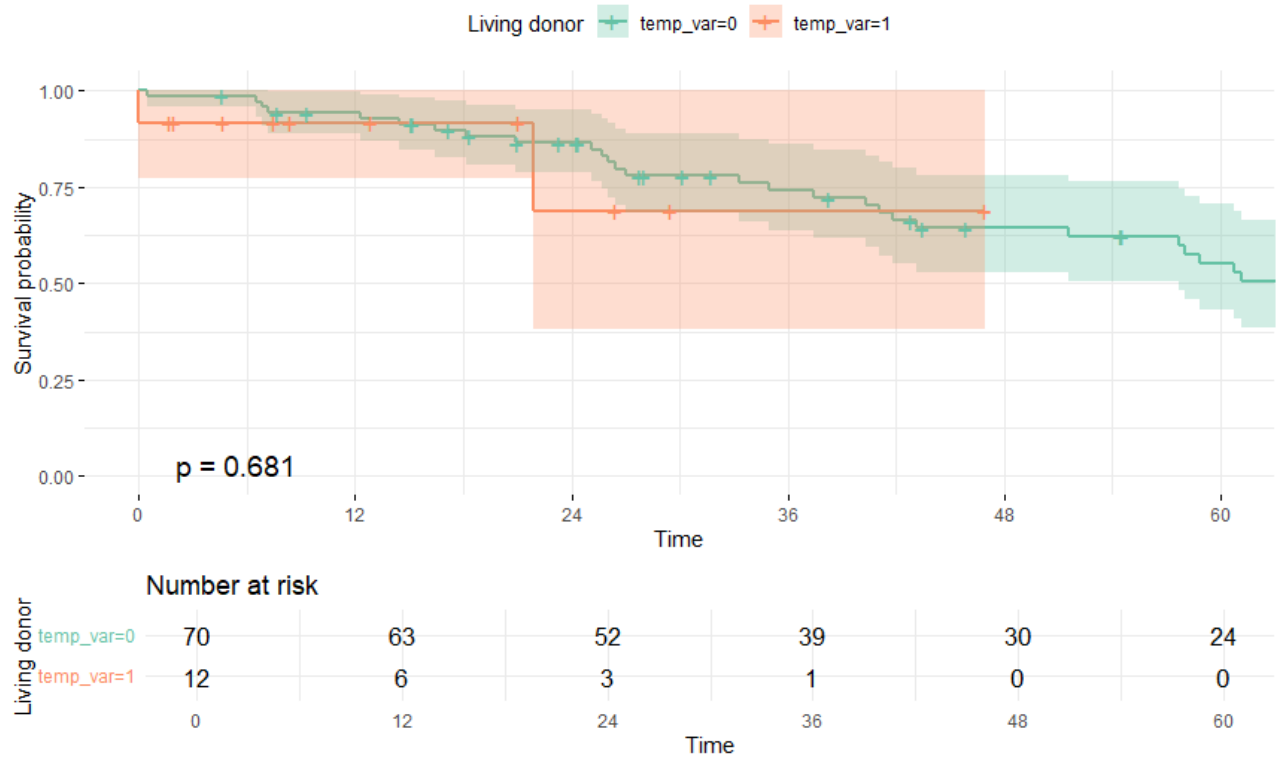
Kaplan-Meier by Female gender



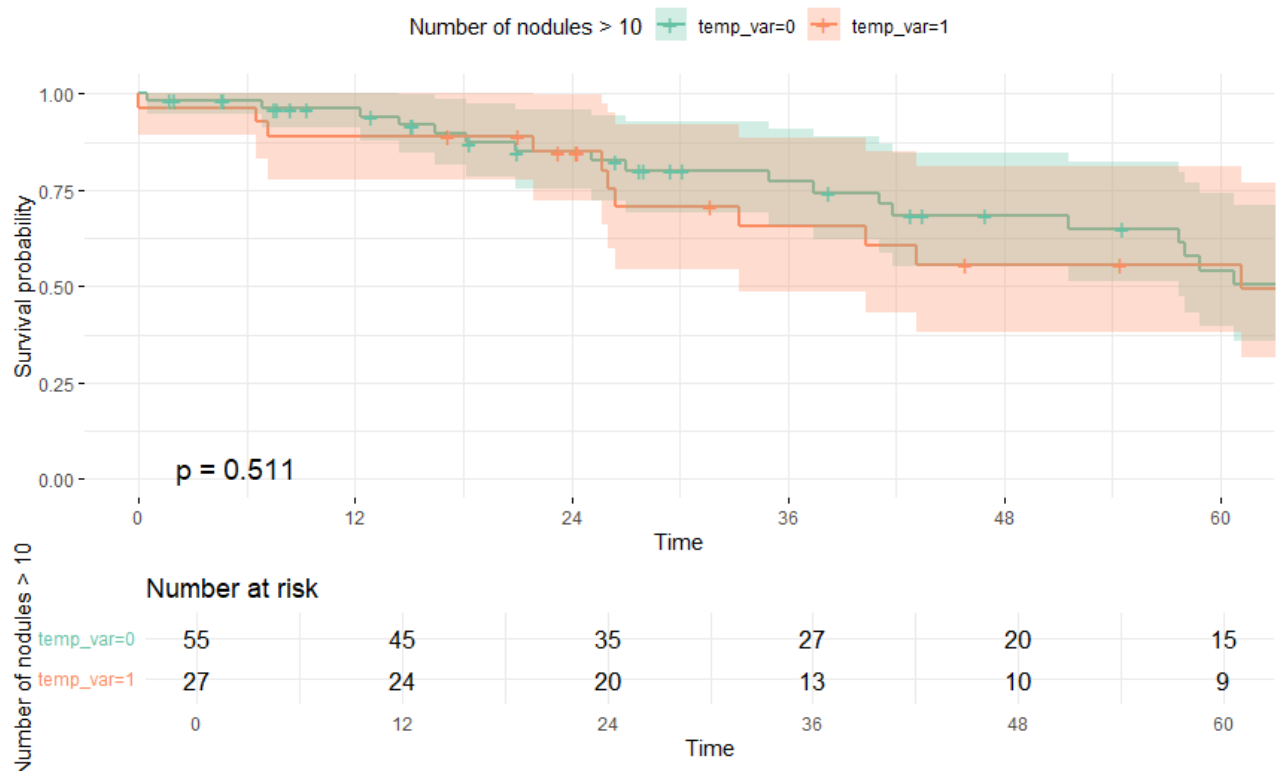
Kaplan-Meier by KRAS mutated



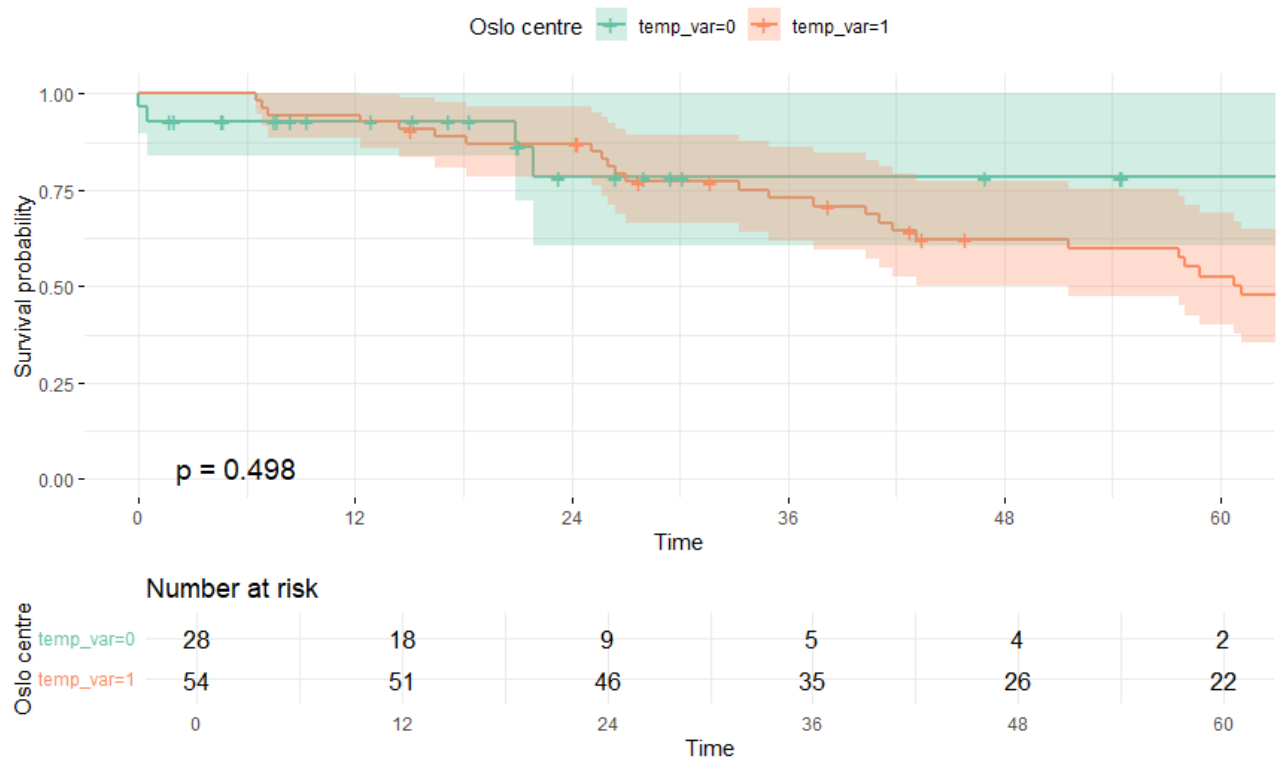
Kaplan-Meier by Living donor



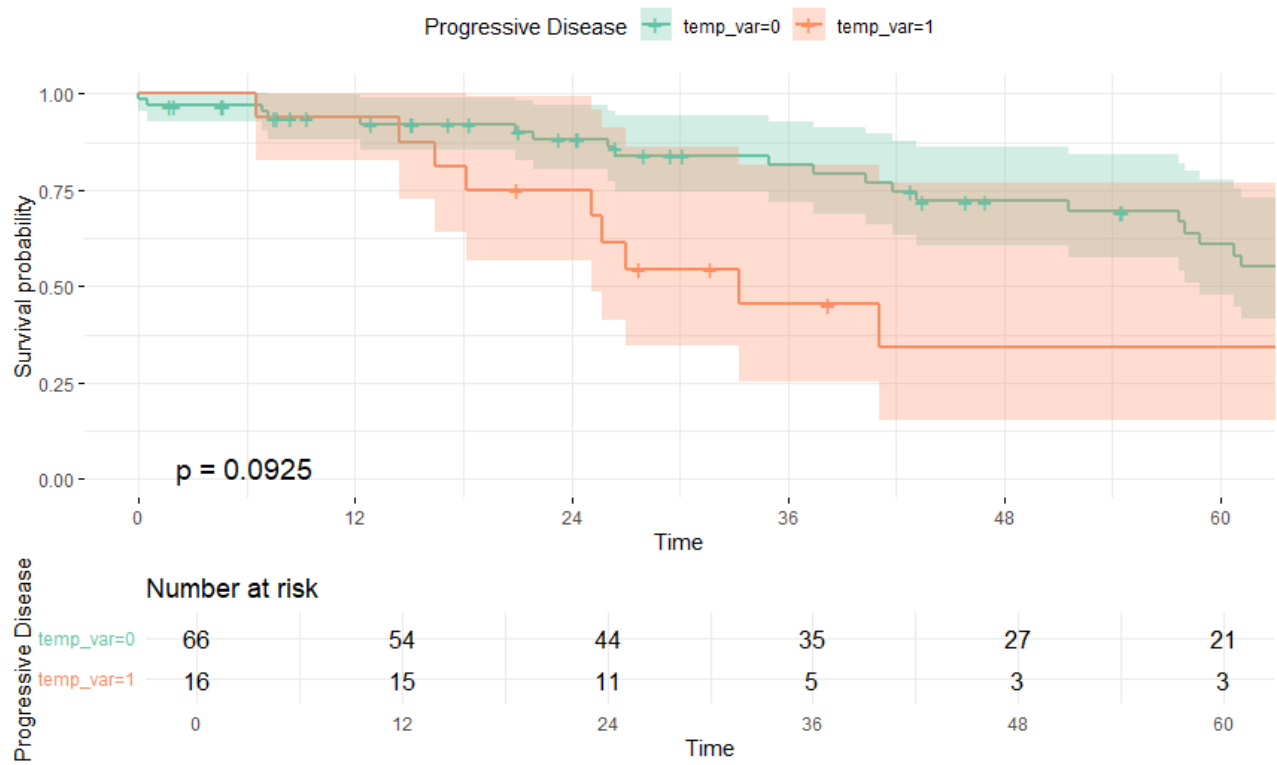
Kaplan-Meier by Number of nodules > 10



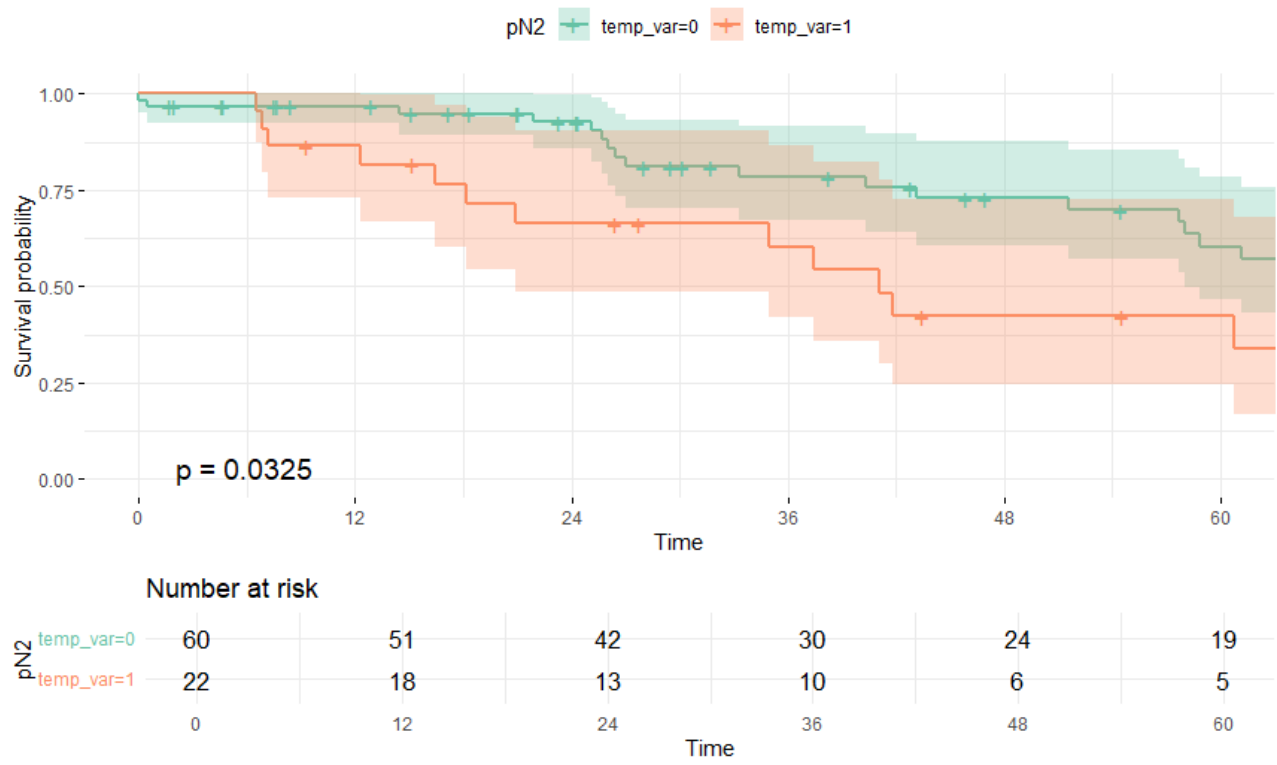
Kaplan-Meier by Oslo centre



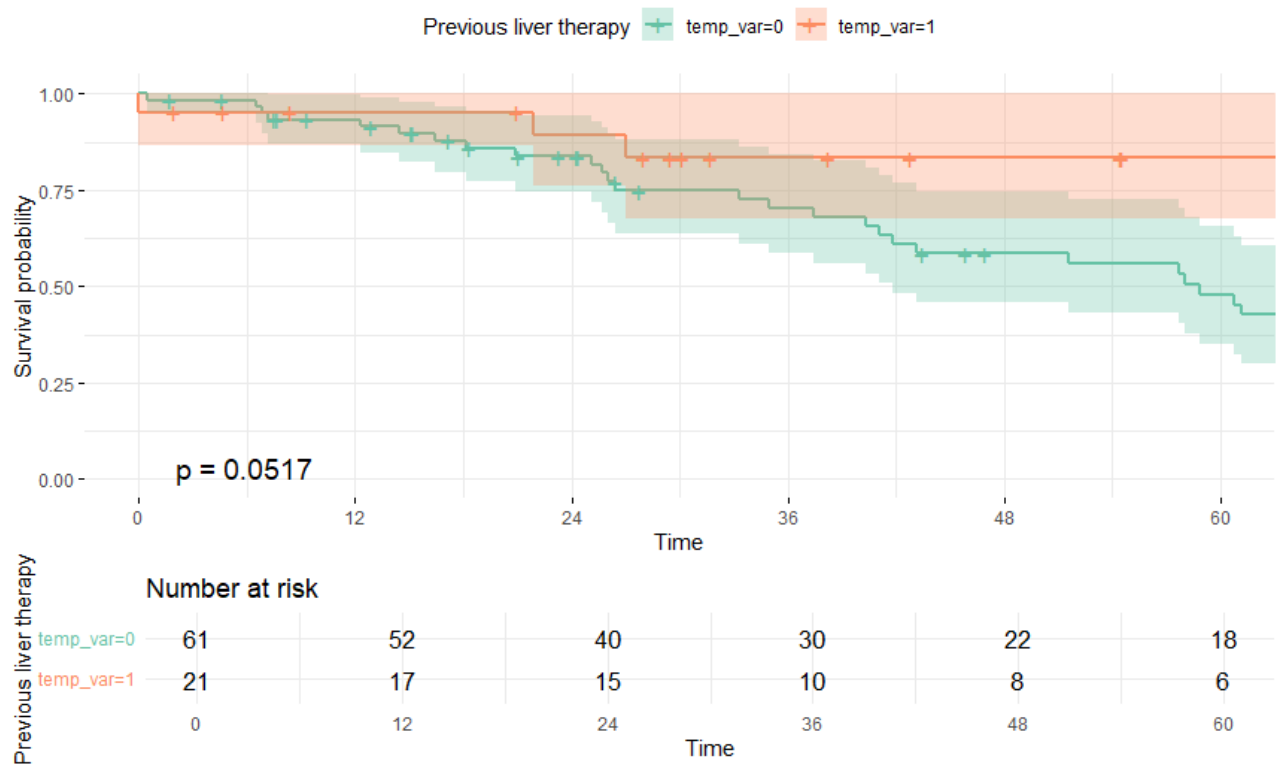
Kaplan-Meier by Progressive Disease



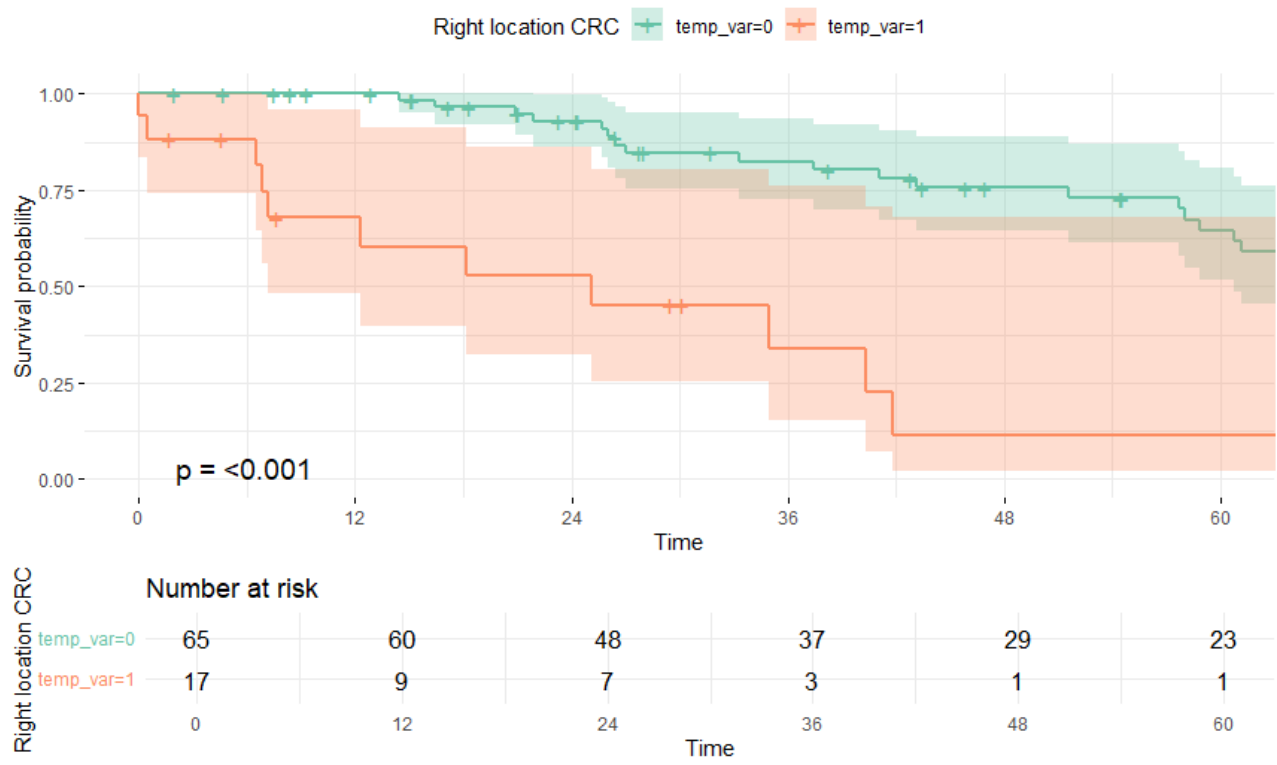
Kaplan-Meier by pN2



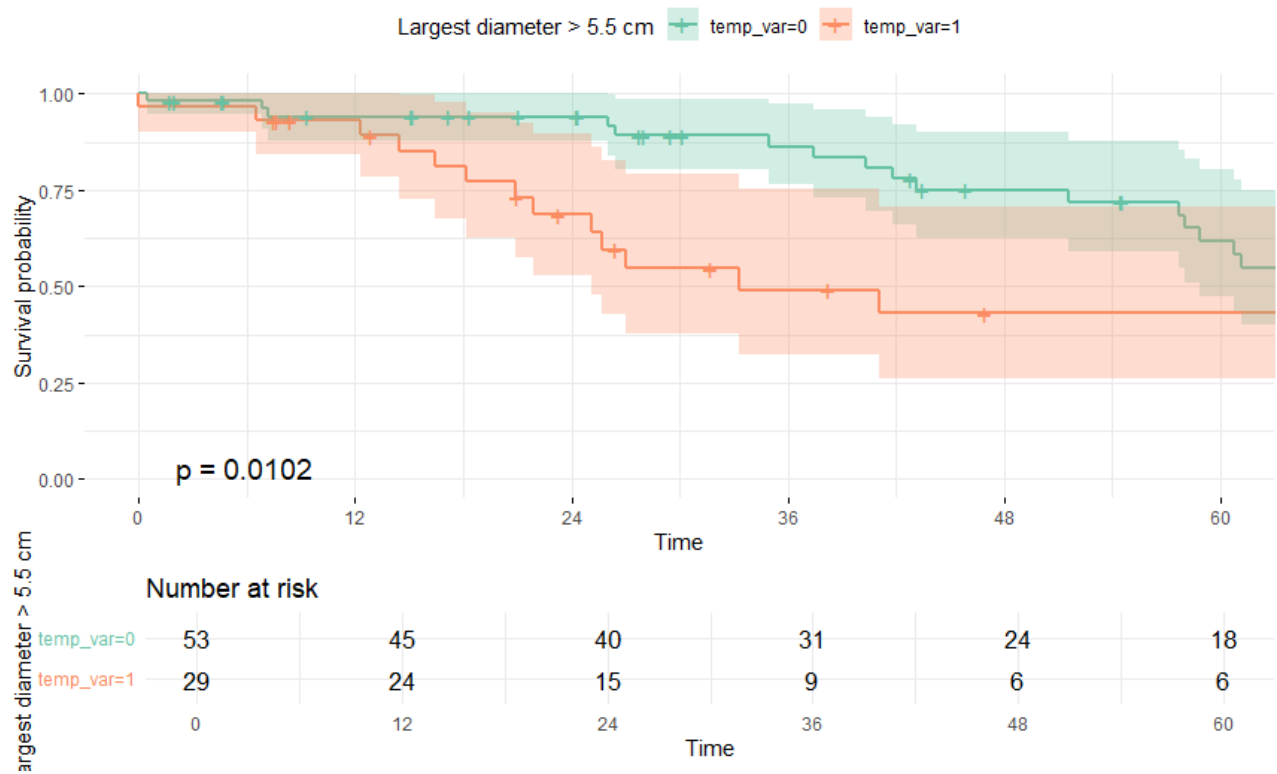
Kaplan-Meier by Previous liver therapy



Kaplan-Meier by Right location CRC



Kaplan-Meier by Largest diameter > 5.5 cm



Kaplan-Meier by Time ≤ 24 months

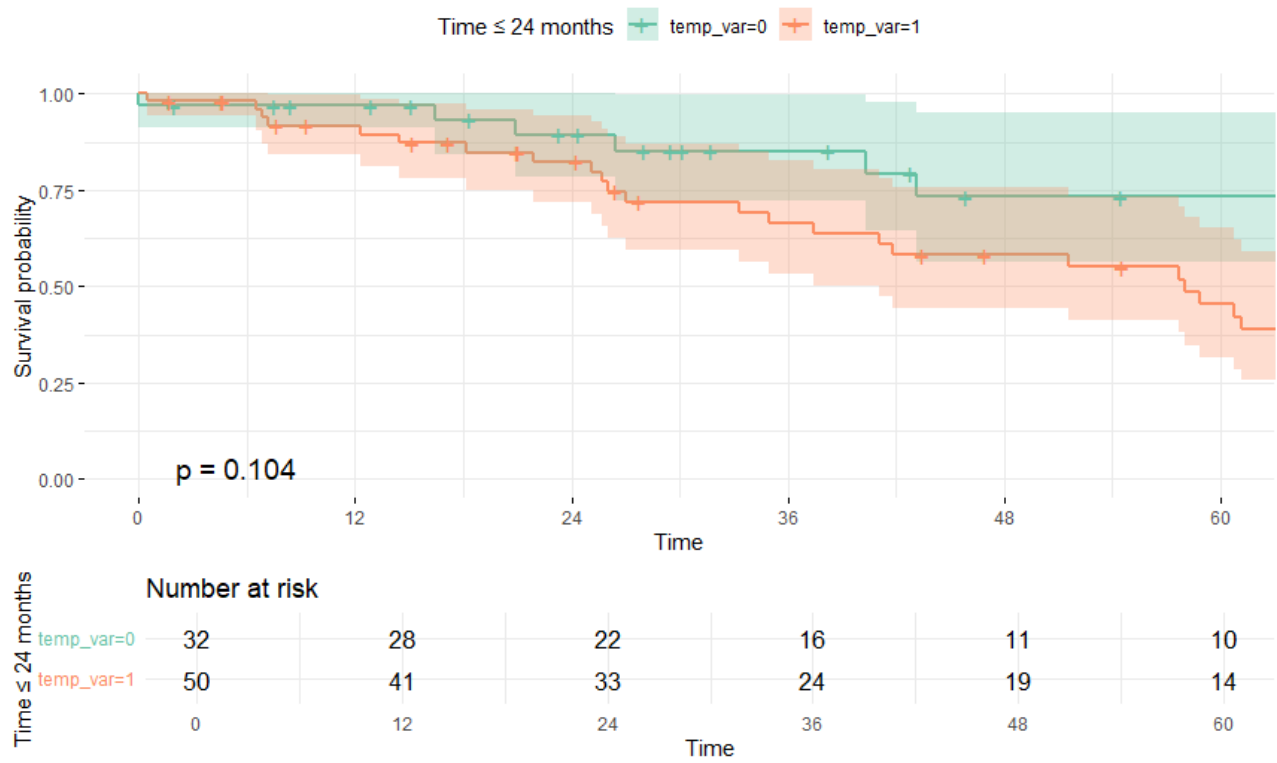
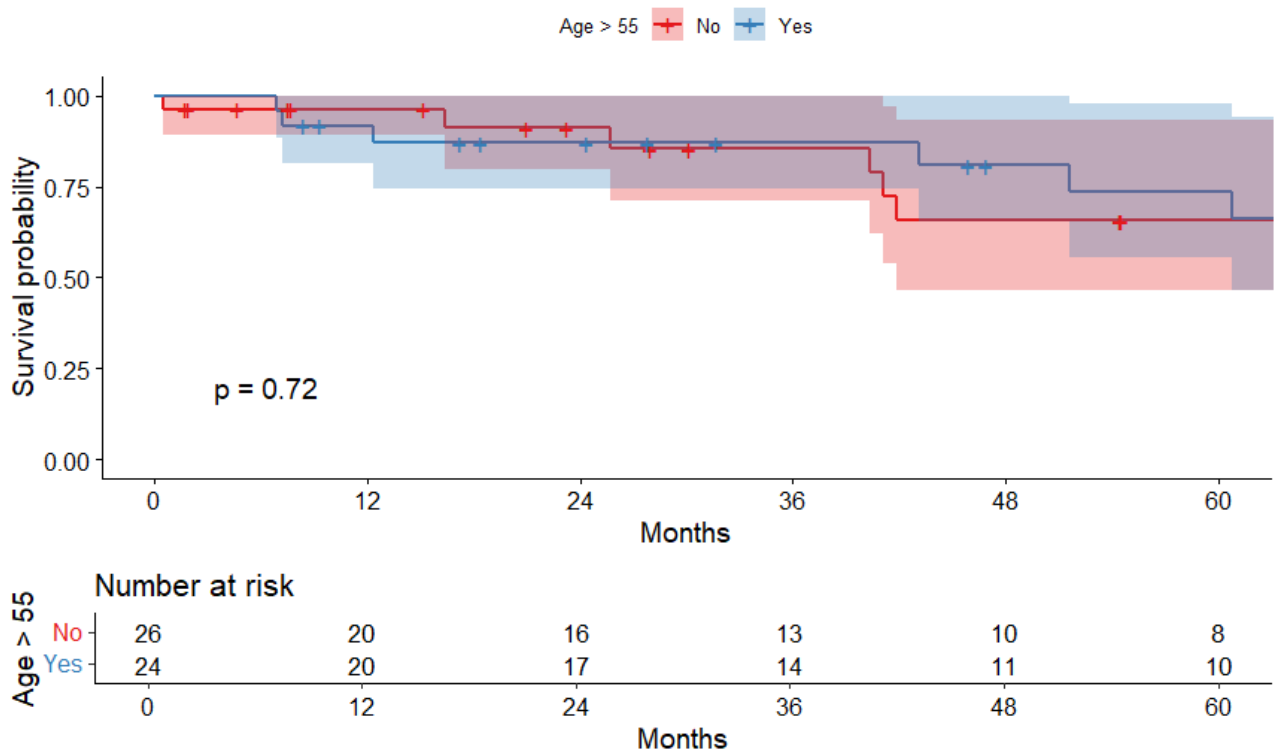
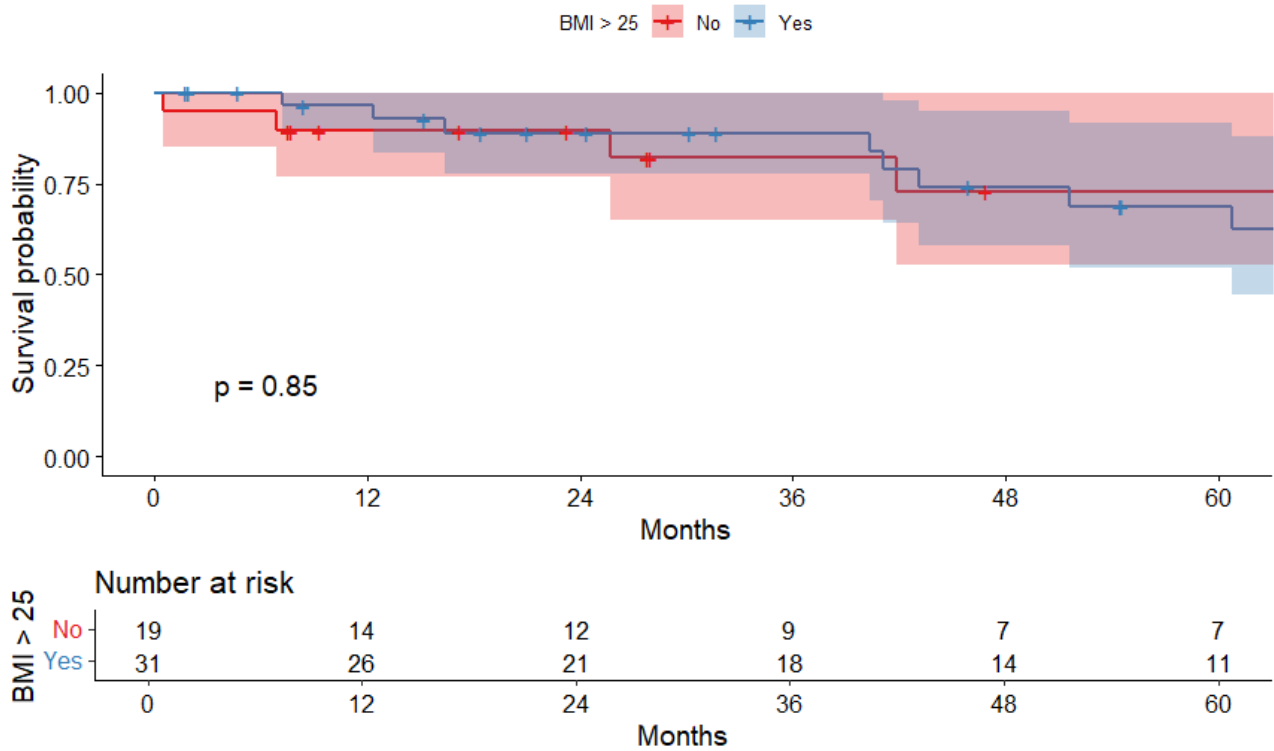


Table 3 variables

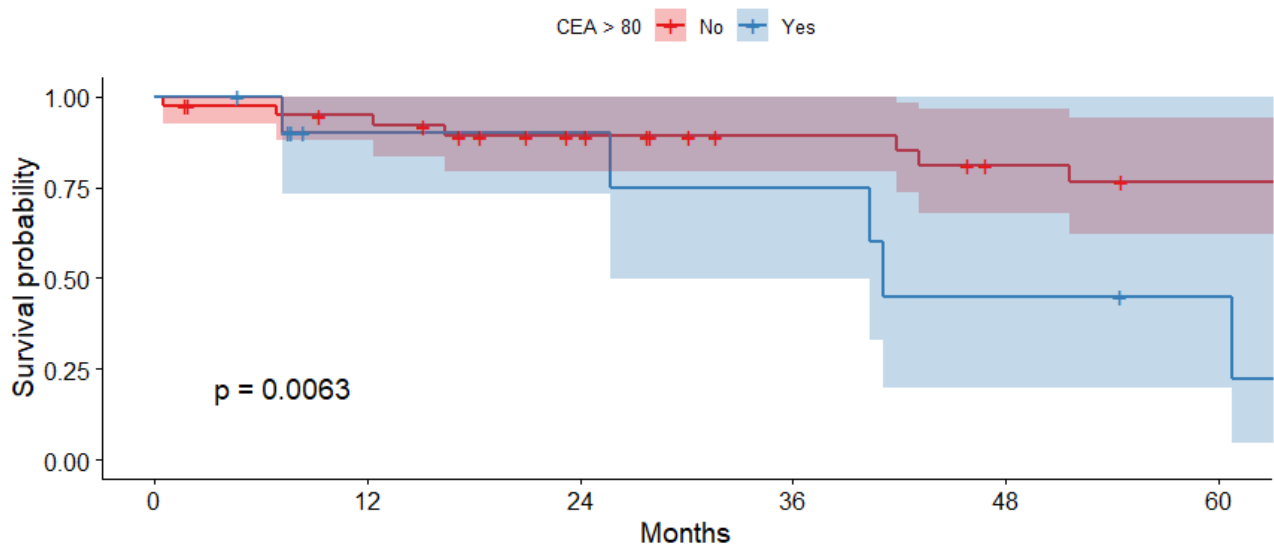
## Male - Age &gt; 55 years



## Male - BMI &gt; 25



## Male - CEA &gt; 80



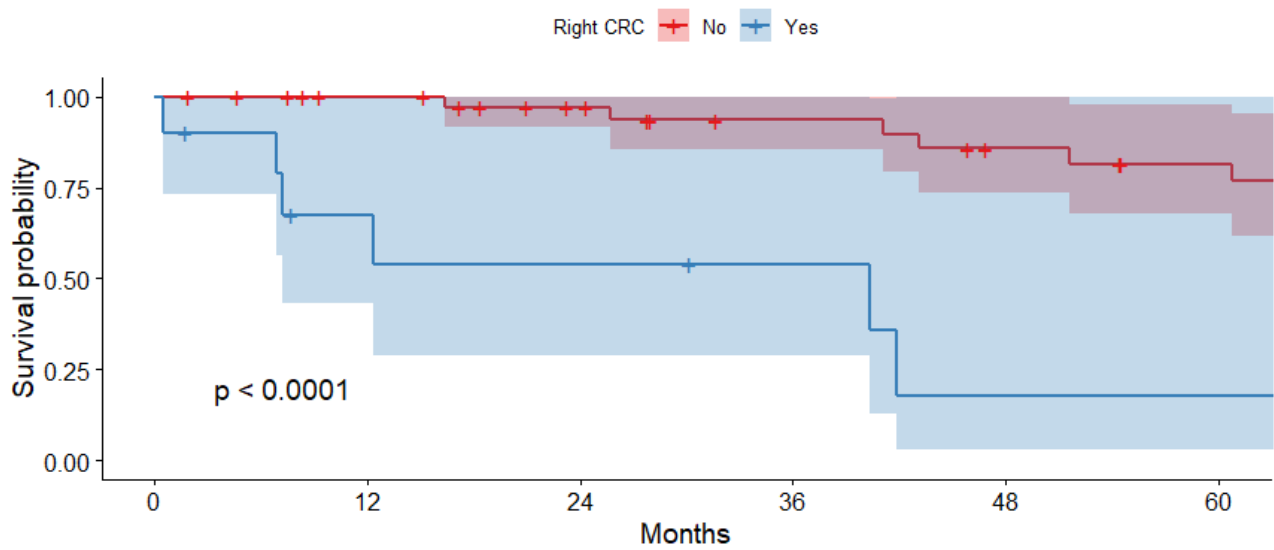
CEA > 80

Number at risk

No	39	34	27	22	18	16
Yes	11	6	6	5	3	2
	0	12	24	36	48	60

Months

## Male - Right location CRC



Right CRC

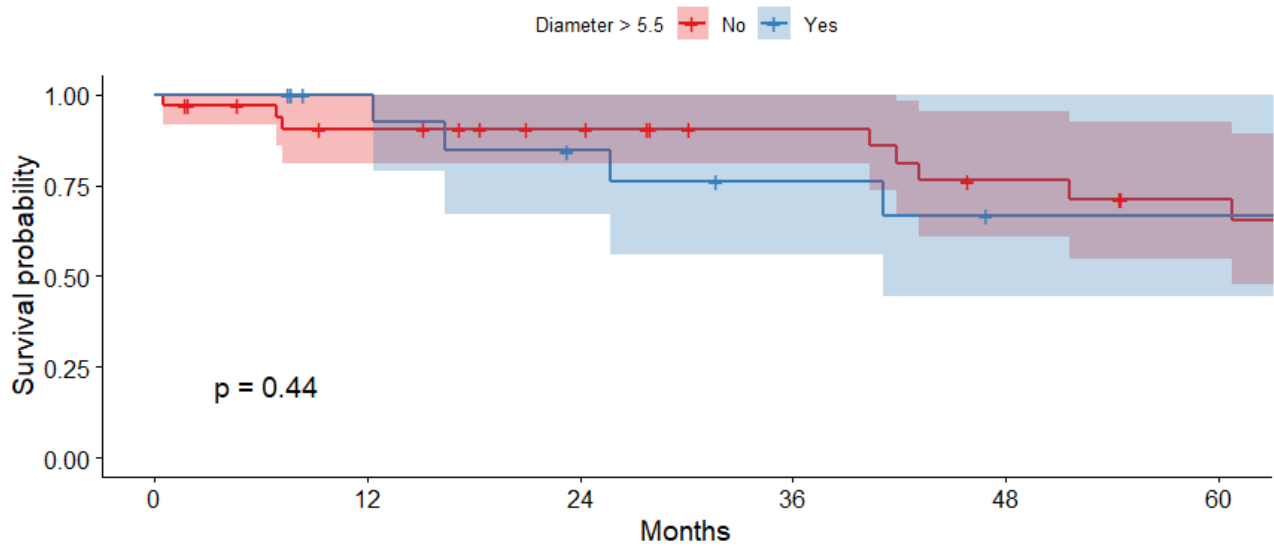
Number at risk

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

Months



## Male - Diameter &gt; 5.5 cm



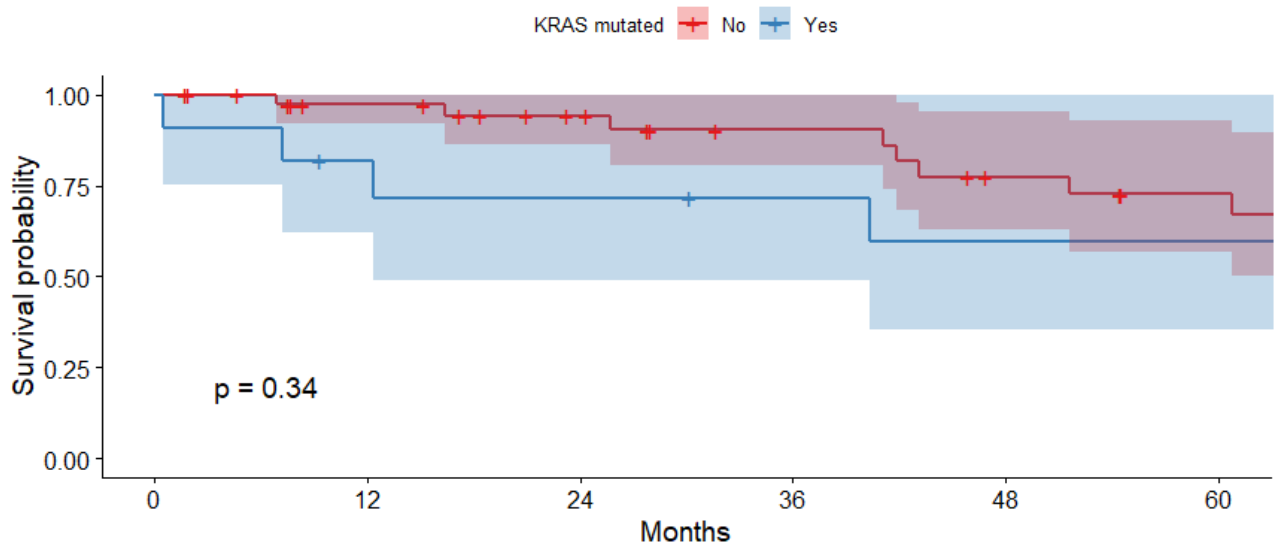
Diameter > 5.5

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



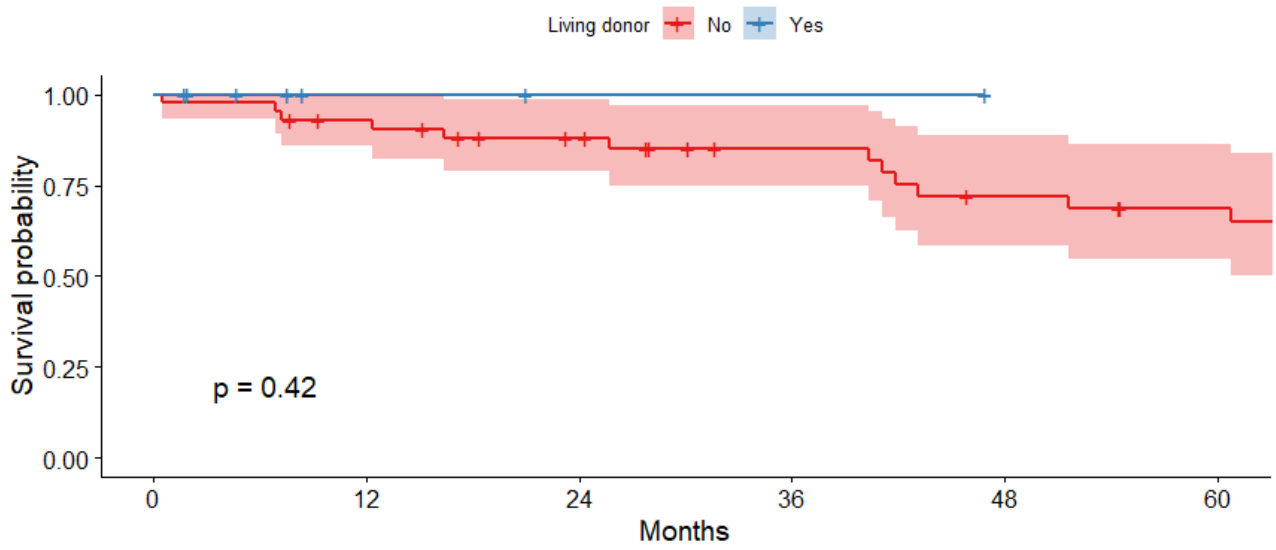
KRAS mutated

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

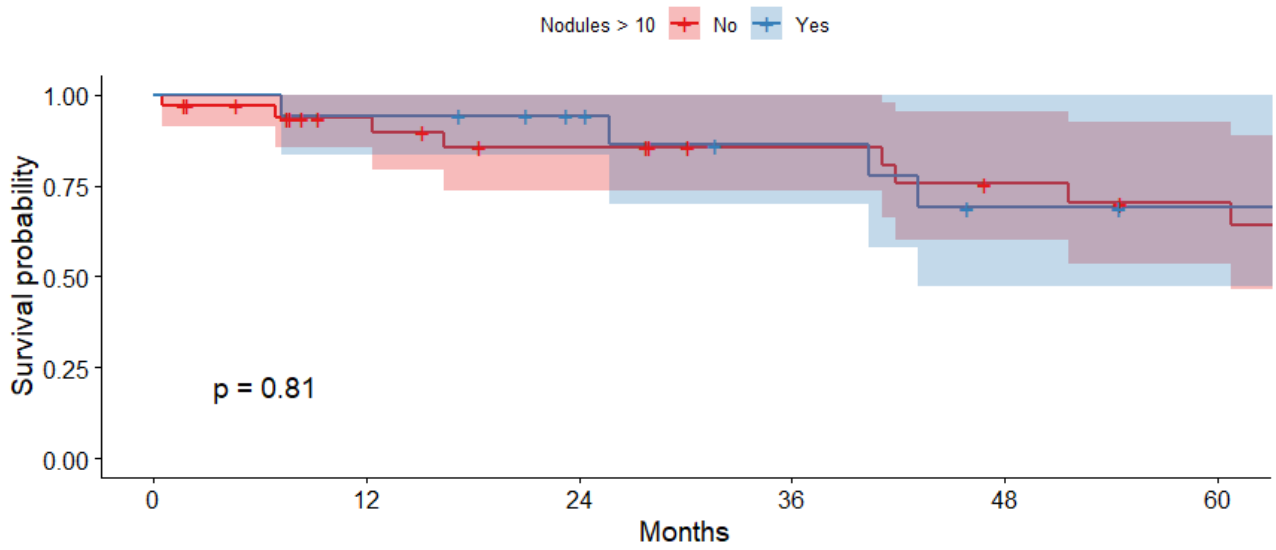


Number at risk

Living donor	0	12	24	36	48	60
No	43	38	32	26	21	18
Yes	7	2	1	1	0	0

Months

### Male - Nodules > 10

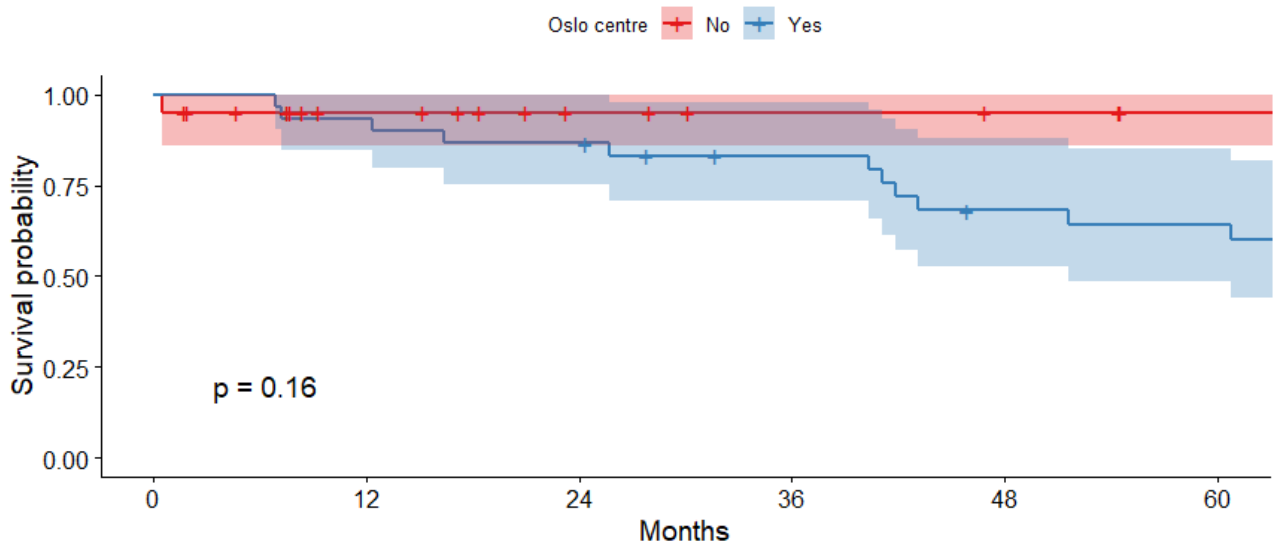


Number at risk

Nodules > 10	0	12	24	36	48	60
No	33	24	20	17	14	12
Yes	17	16	13	10	7	6

Months

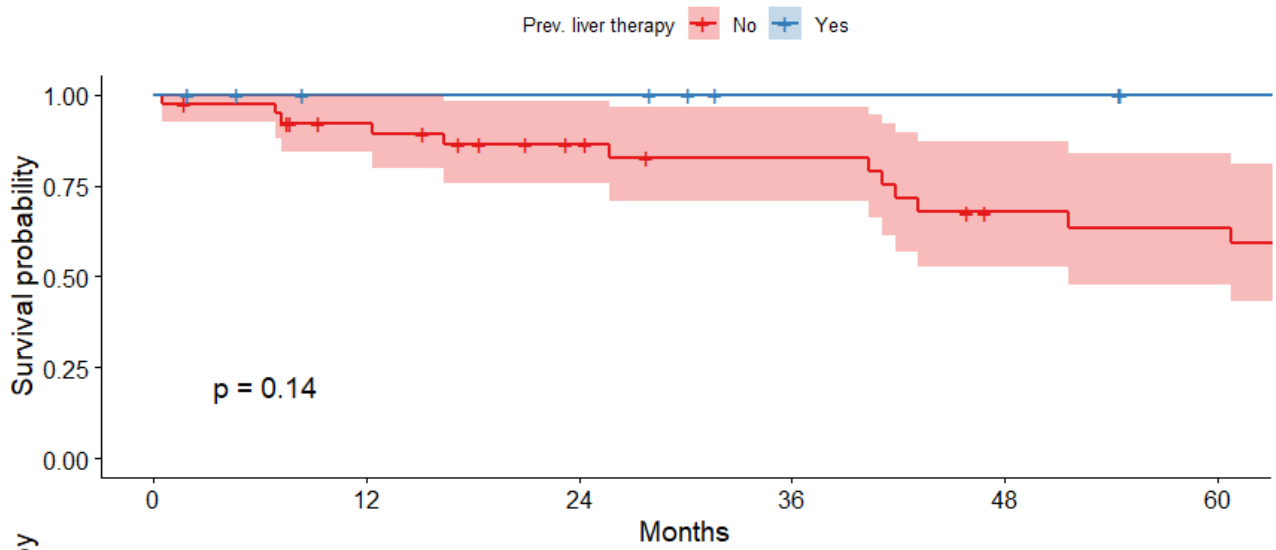
### Male - Oslo centre



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					

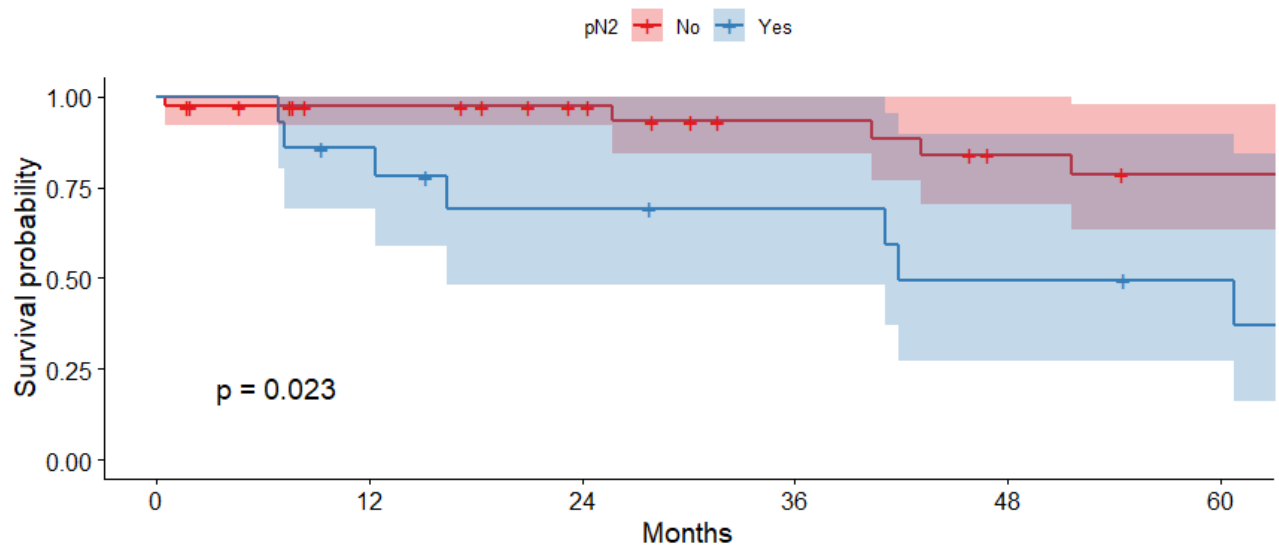
### Male - Previous liver therapy



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

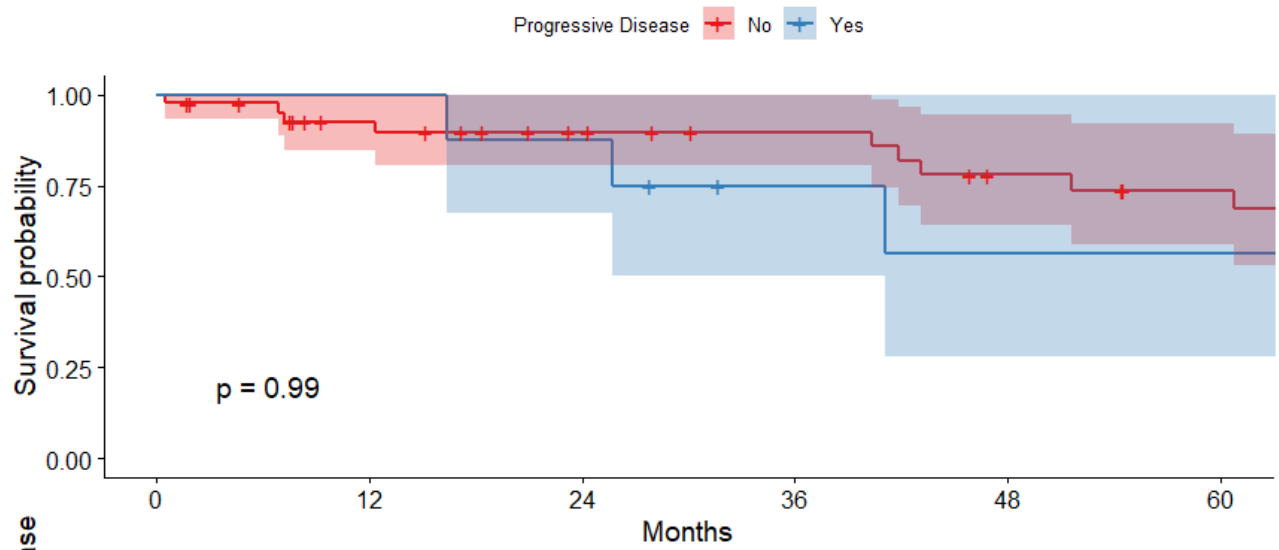


Number at risk

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

Months

Male - Progressive Disease

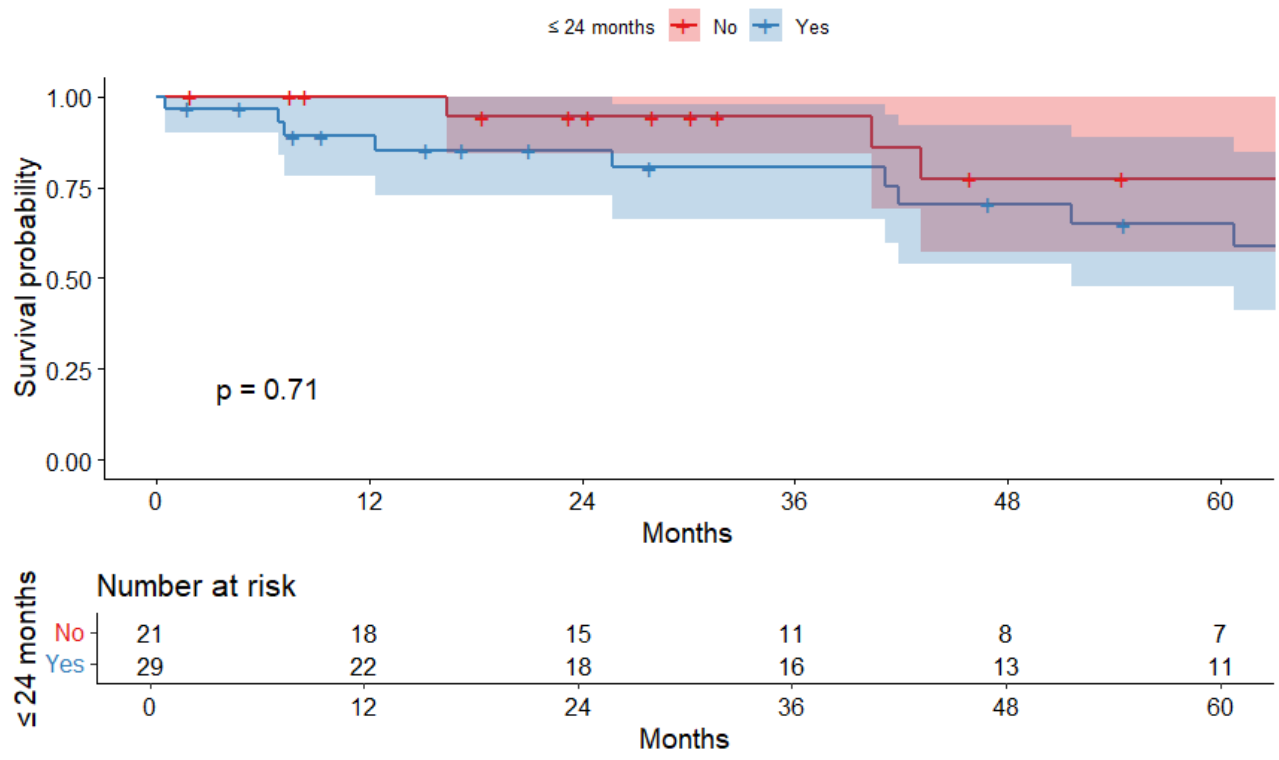


Number at risk

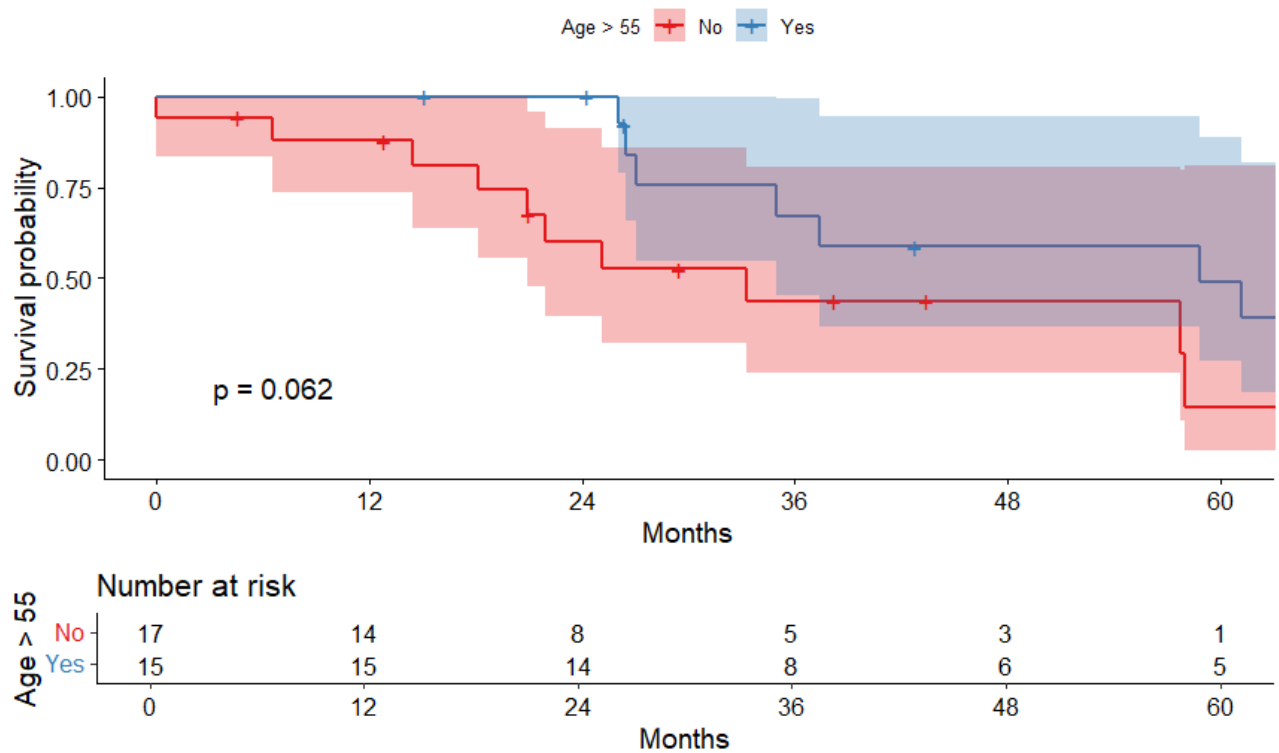
Progressive Disease No	42	32	26	23	18	15
Progressive Disease Yes	8	8	7	4	3	3
	0	12	24	36	48	60

Months

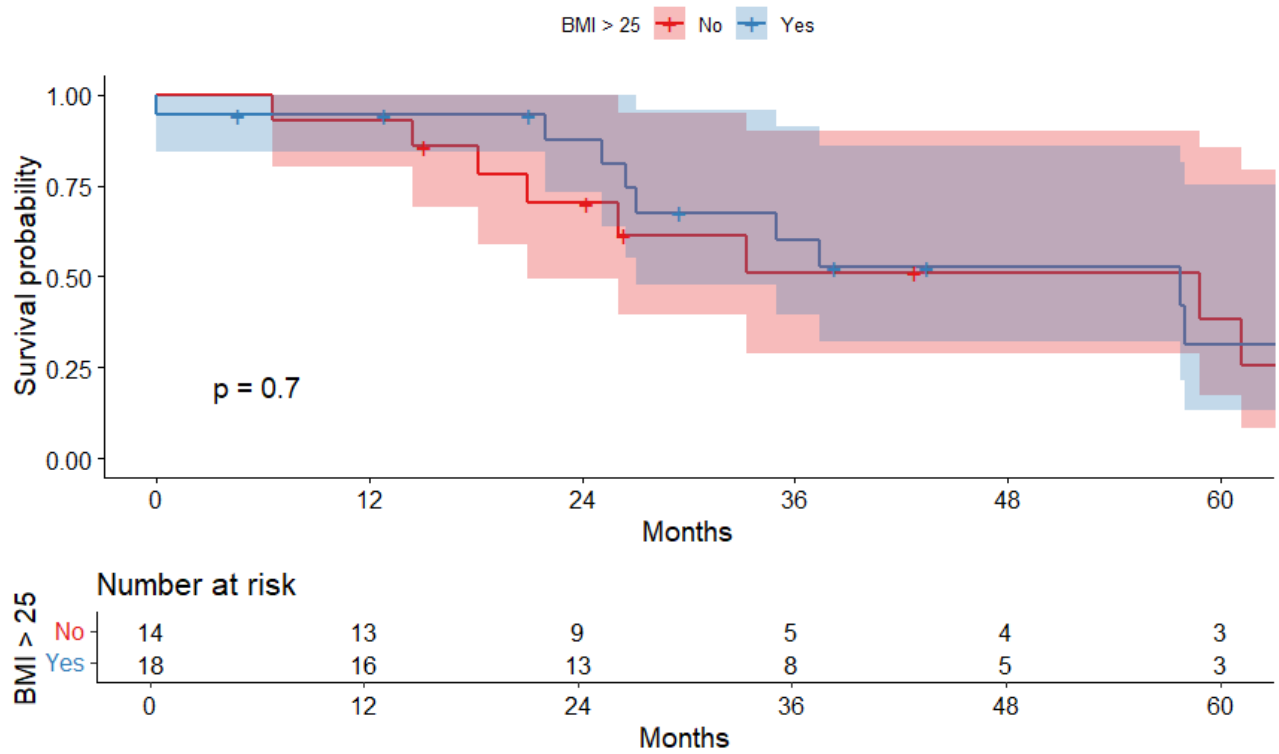
Male - Time  $\leq$  24 months



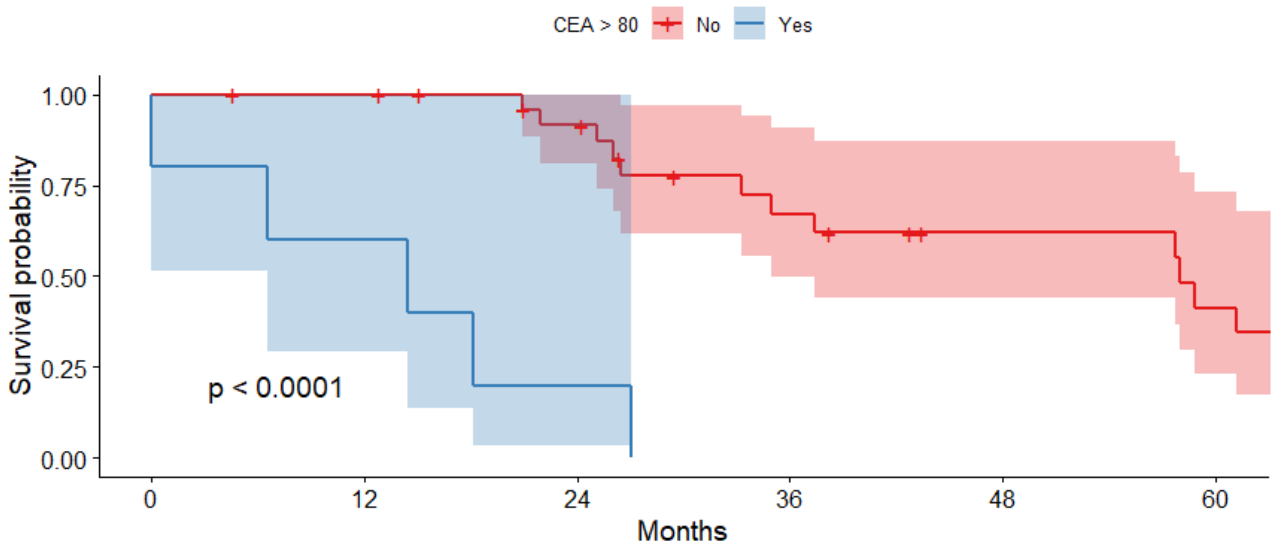
Female - Age > 55 years



Female - BMI > 25



Female - CEA > 80



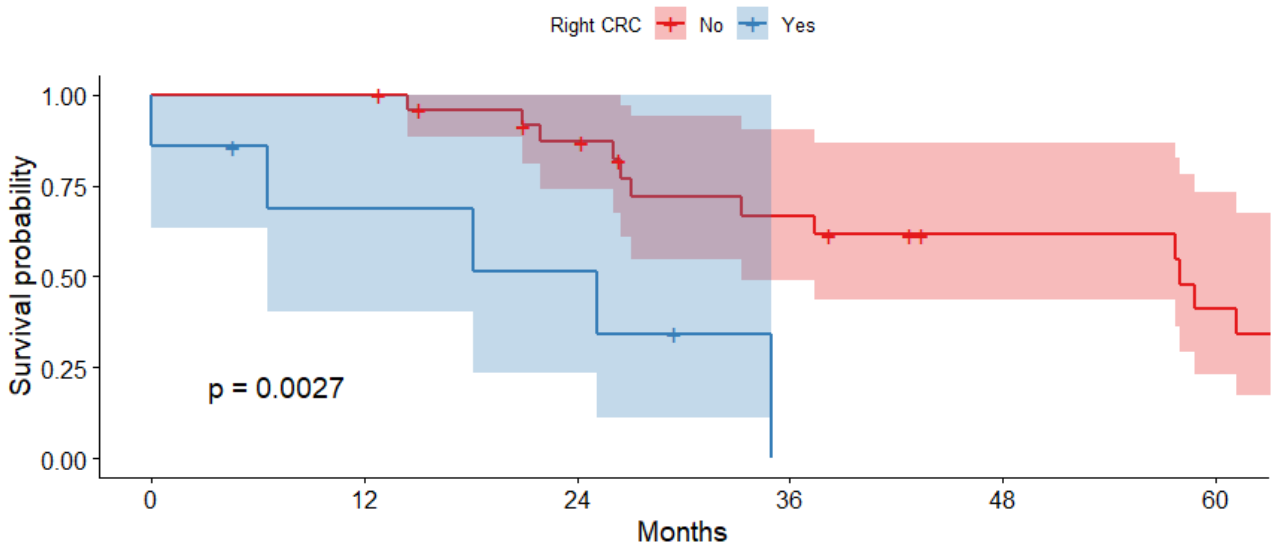
CEA > 80

Number at risk

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

Months

Female - Right location CRC



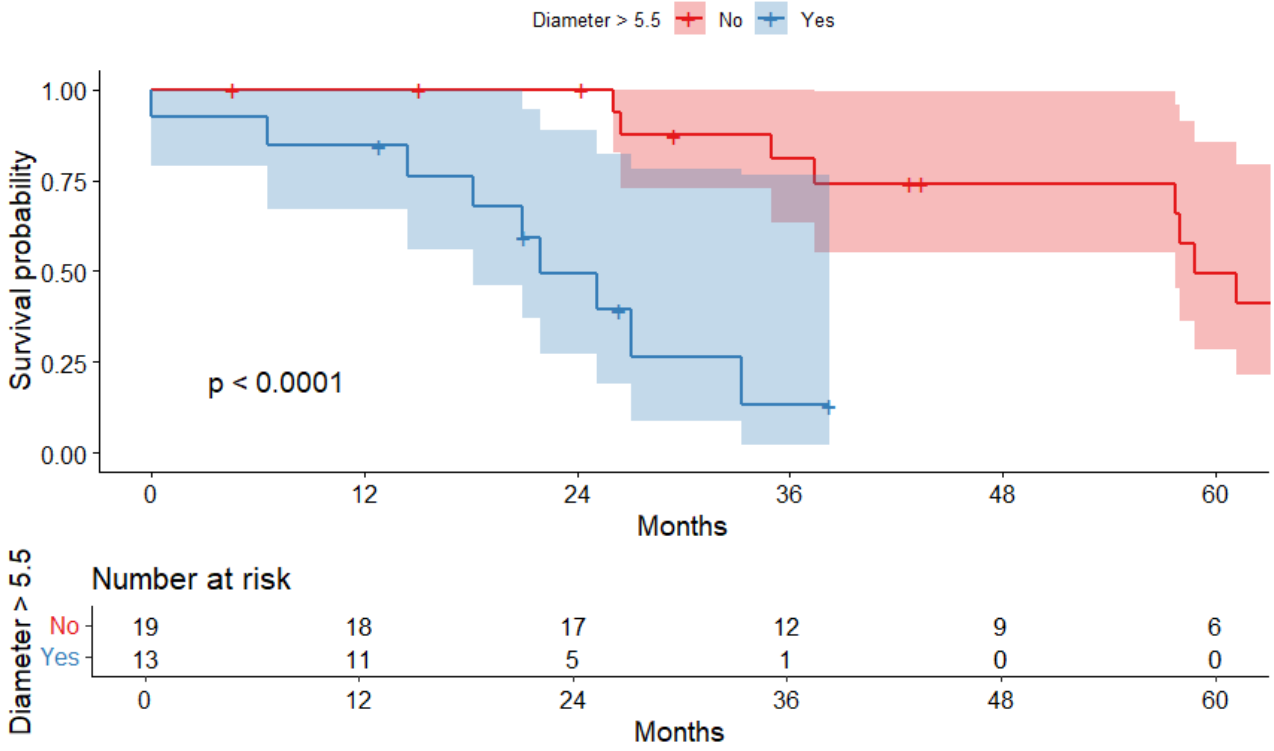
Right CRC

Number at risk

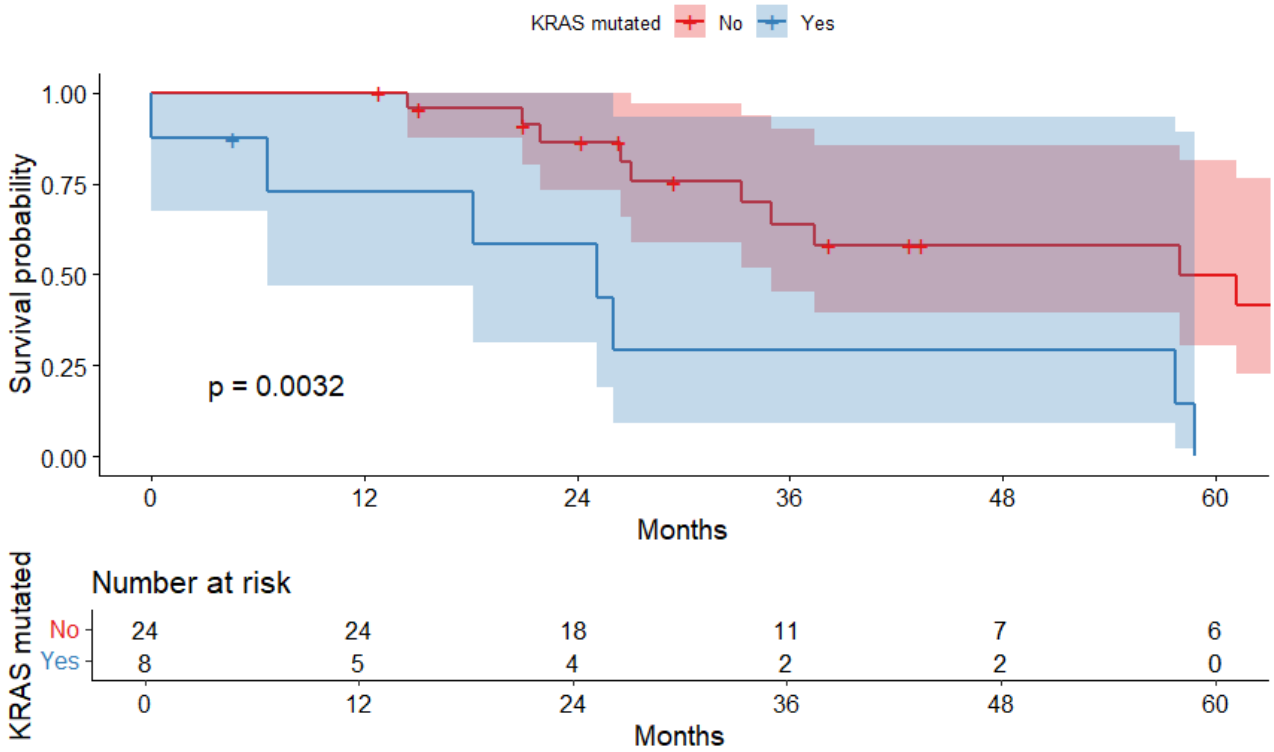
No	25	25	19	13	9	6
Yes	7	4	3	0	0	0

Months

Female - Diameter > 5.5 cm

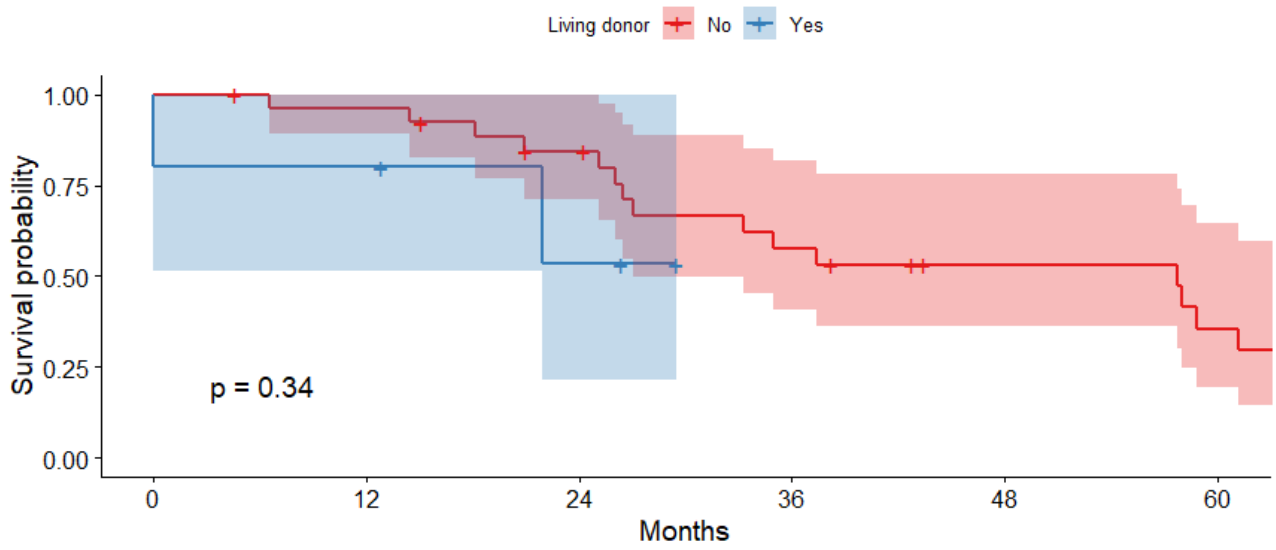


Female - KRAS mutated





### Female - Living donor

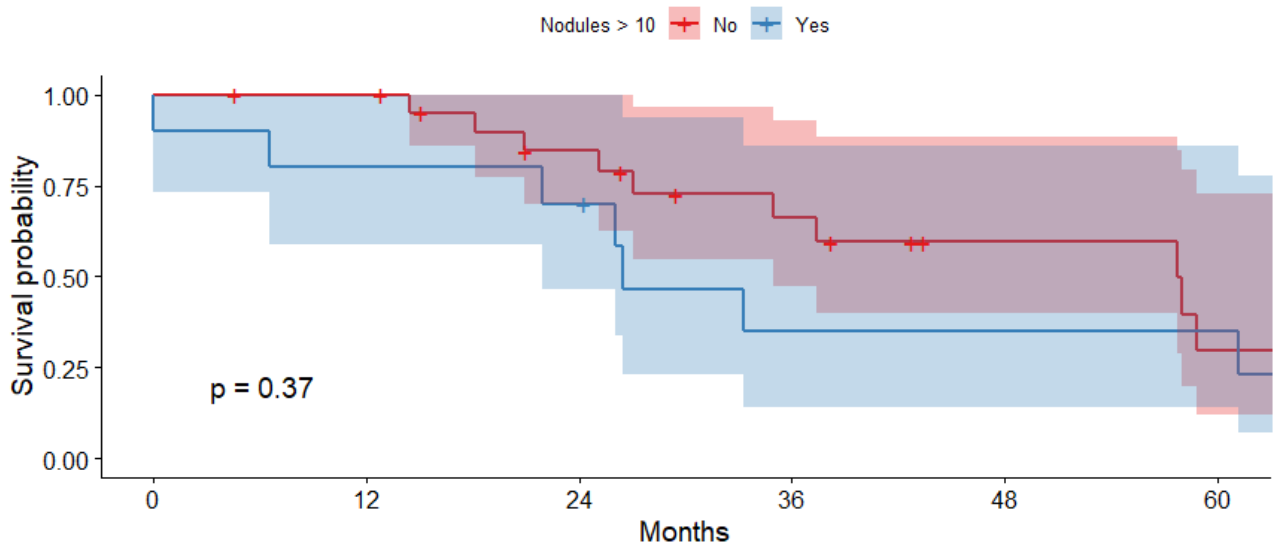


Number at risk

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

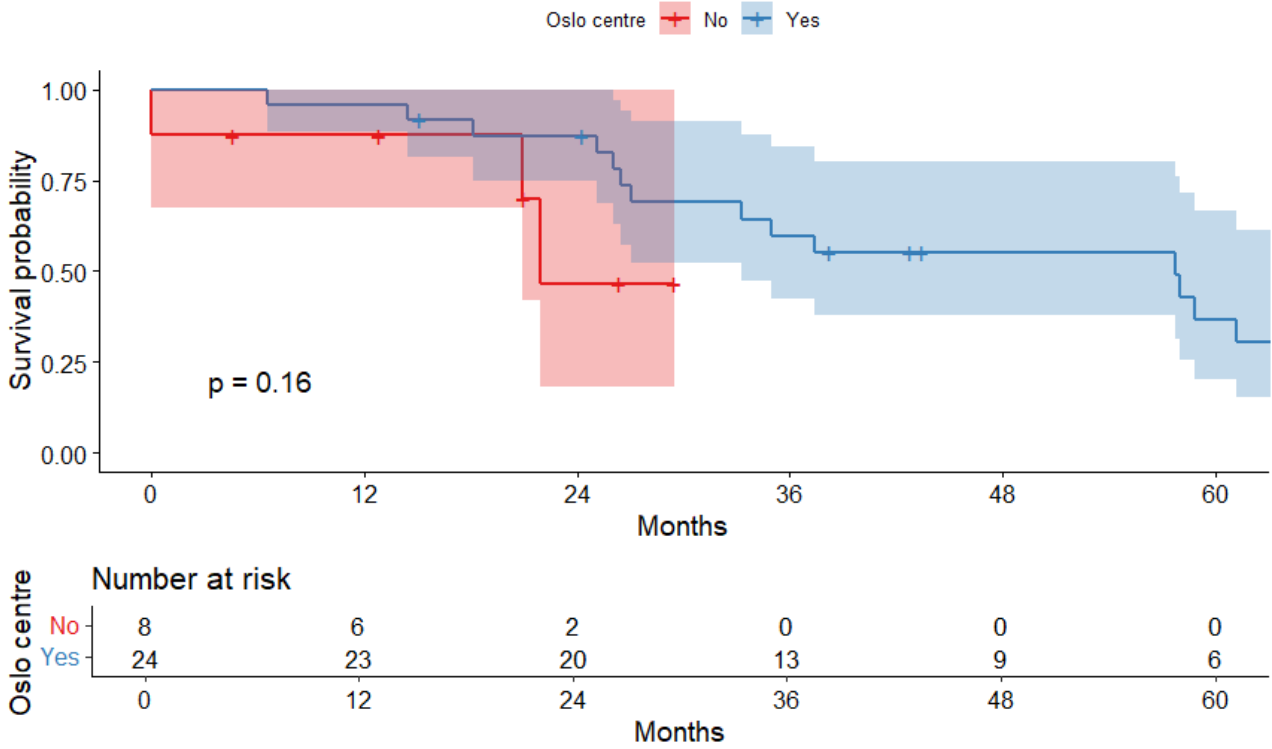


Number at risk

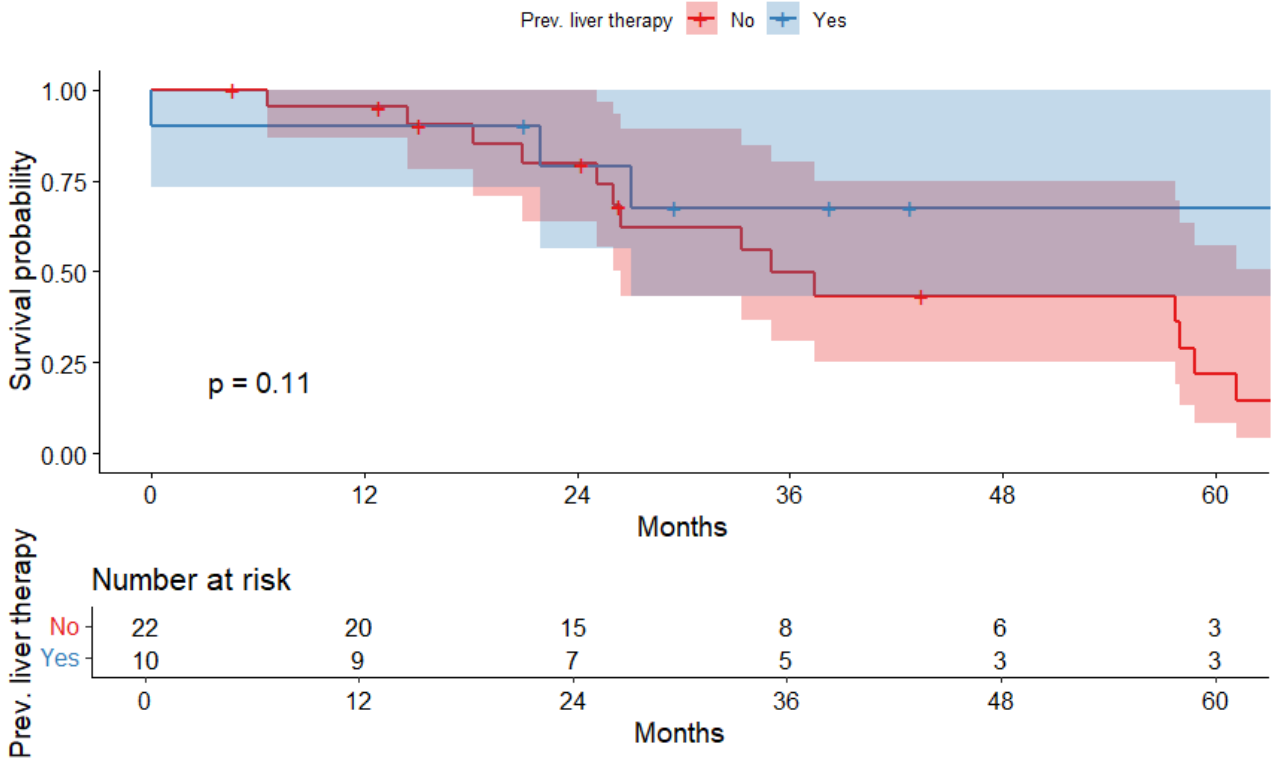
Nodules > 10	0	12	24	36	48	60
No	22	21	15	10	6	3
Yes	10	8	7	3	3	3

Months

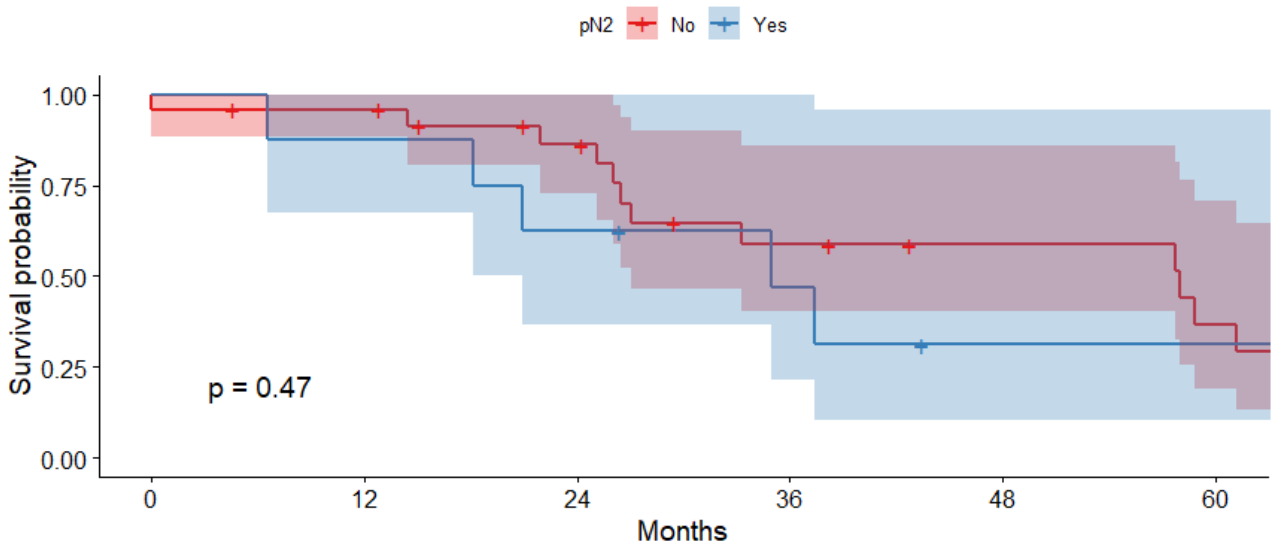
Female - Oslo centre



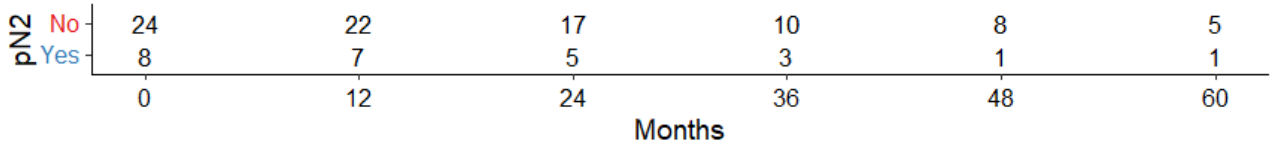
Female - Previous liver therapy



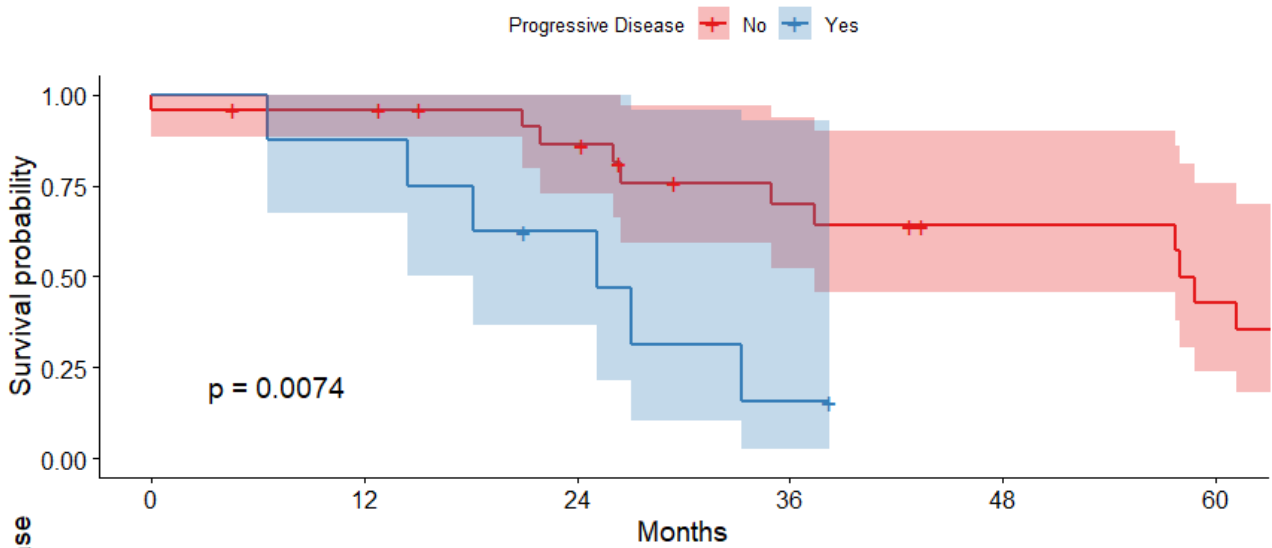
Female - pN2



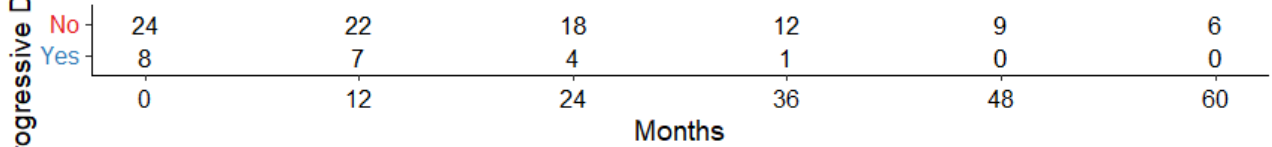
Number at risk



Female - Progressive Disease



Number at risk



Female - Time  $\leq$  24 months

