Behrenbruch Corina (Orcid ID: 0000-0002-2942-2480)
Prabhakaran Sowmya (Orcid ID: 0000-0003-2977-2226)
Udayasiri Dilshan (Orcid ID: 0000-0002-3943-7862)
Heriot Alexander (Orcid ID: 0000-0001-9846-8776)

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Names of Authors and Academic Degrees:
Dr Corina Behrenbruch: MBBS(hons), FRACS
Dr Sowmya Prabhakaran: MBBS BMedSc
Mr Dilshan Udayasiri: MBBS FRACS
Professor Frederic Hollande: MSci, PhD
Professor Michael Michael: MBBS(Hons), FRACP
Associate Professor Ian Hayes: MBBS, FRACS
Professor Alexander Heriot: MA FRACS
Mr Brett Knowles: MBBS FRACS
Associate Professor Thomson: MBBS, FRACS

Name and initials of each author and affiliations:
Behrenbruch C[1,2,3], Prabhakaran S[2], Udayasiri D[2,7,8], Hollande F[3,4], Michael M[1,6], Hayes I[2,7,8], Heriot AG[1,5,9], Knowles B[2,5,], Thomson BN[2,5,7]
[1] The University of Melbourne, Sir Peter MacCallum Department of Oncology, Victorian Comprehensive Cancer Centre, Melbourne 3000, Australia.
[2] Department of General Surgical Specialties, The Royal Melbourne Hospital, 300 Grattan St Parkville 3050, Australia.
[3]The University of Melbourne, Department of Clinical Pathology, Victorian Comprehensive Cancer Centre, Melbourne 3000, Australia
[4] The University of Melbourne, Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Melbourne 3000, Australia
[5]Department of Cancer Surgery, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, Melbourne 3000, Australia.
[6]Department of Medical Oncology, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, Melbourne 3000, Australia
[7]The University of Melbourne, Royal Melbourne Hospital Department of Surgery, 300 Grattan St Parkville 3050, Australia.
[8]Colorectal Surgery Unit, The Royal Melbourne Hospital, 300 Grattan St Parkville 3050, Australia.
[9]The University of Melbourne, Department of Surgery, St Vincent's Hospital, Fitzroy 3065, Australia

Author Contributions

Dr Corina Behrenbruch: Conceptualisation, Data Curation, Writing -original draft, Writing-review and editing
Dr Sowmya Prabhakaran: Data Curation, Writing-review and editing
Mr Dilshan Udayasiri: Methodology, Formal Analysis, Writing-review and editing
Professor Michael Michael: Writing-review and editing
Professor Frederic Hollande: Writing-review and editing
Associate Professor Ian Hayes: Conceptualisation, Methodology, Formal Analysis, Writing-review and editing
Professor Alexander Heriot: Conceptualisation, Writing-review and editing
Mr Brett Knowles: Writing-review and editing
Associate Professor Thomson: Conceptualisation, Writing-review and editing

Corresponding Author e :
Dr Corina Behrenbruch
Address : c/o Department of Surgery, Royal Melbourne Hospital, 300 Grattan St Parkville 3050, Australia.
Ph: +61493428212 Fax: +61493428057
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The Survival Benefit of Neoadjuvant Chemotherapy and Surgery versus Surgery First for Resectable Colorectal Liver Metastases : A Cohort Study

Behrenbruch C, Prabhakaran S, Udayasiri D, Michael M, Hollande F, Hayes I, Heriot S, Knowles B, Thomson BN

ABSTRACT

Background and Objectives

There is continued debate about the survival benefit of neoadjuvant chemotherapy (neoCT) in patients with resectable colorectal liver metastases (CRLM).

Methods

In this retrospective cohort study, we included 201 patients with metastatic colorectal cancer who underwent their first colorectal liver metastases (CRLM) resection and achieved resection of all sites of disease. We compared the overall survival (OS) and progression free survival (PFS) between patients who received neoCT prior to CRLM resection, with those who underwent CRLM upfront. A multivariable, Cox proportional hazard (PH) regression analysis was performed to adjust for potential confounders.

Results

A total of 101/201 (51.2%) patients received chemotherapy prior to CRLM resection and 100/201 had surgery upfront. Multivariable Cox PH regression showed no statistically significant difference in the hazard of death for those given neoCT prior to resection of CRLM compared with surgery first for both OS and PFS (OS: HR 1.74, 95% CI 0.85-3.55, p=0.127, PFS: HR 1.42, 95% CI 0.93-2.19, p=0.107).

Conclusion

In our series of patients with metastatic colorectal cancer who achieved surgical resection of all sites of disease, neoCT prior to CRLM resection was not associated with any survival benefit.

Keywords: Colorectal Metastases, Neoadjuvant chemotherapy, Regression Analysis

Introduction

The overall survival (OS) for metastatic colorectal cancer (mCRC) has significantly improved over the last three decades(1, 2). Despite this, patients managed only with chemotherapy, even in the setting of a complete clinical response, have a poor 5-year OS of approximately 10%(3). Surgery with resection of all sites of disease offers the only chance of cure for these patients, with a 5-year overall survival of up to 50%(4). The liver is the most common site of colorectal metastases, with approximately 70% of patients developing liver metastases at some time during the course of their disease(5). While there is clear benefit of chemotherapy in patients with inoperable and therefore incurable mCRC, the evidence to support the use of neoadjuvant chemotherapy (neoCT) in patients with operable metastases is less clear and has been a subject of debate for many years.

There has been only one randomised controlled trial (RCT) addressing the question of the benefit of neoCT in patients with resectable colorectal liver metastases (CRLM) versus surgery alone(6). This trial of 364 patients, across 78 centres, compared peri-operative FOLFOX (5-Fluorouracil/Oxaliplatin) treatment prior to and following liver resection versus surgery alone. No difference was found in OS with the addition of FOLFOX, however there was some improvement in progression free survival (PFS). More recently a meta-analysis included 17 cohort studies (n=6254 patients) and the above-mentioned randomised trial (7). Again, the

conclusion was no improvement in OS. The authors commented that there was significant heterogeneity in the protocols of neoCT given, as well as heterogeneity in the number, size and location of liver metastases may affect the interpretation of the results. The aim of this study was to determine if neoCT prior to CRLM resection was associated with improved survival compared with upfront liver resection in patients with resectable liver metastases, who specifically achieved resection of all sites of disease.

Patients and Methods

This was a retrospective cohort study. Patients were identified from a prospective database of all CRLM resections performed by two surgeons (within a unit of multiple surgeons), across two tertiary referral hospitals, from 2003-2018. Two of the authors independently reviewed and collected data from available electronic and hard copy medical records. Patients were included in the study if 1) colorectal adenocarcinoma was confirmed on histologically 2) it was their first CRLM resection 3) there was resection of all sites of disease . Patients selected for this study had either been exposed to neoCT prior to resection of liver metastases (neoCT group) or had proceeded to liver resection upfront (surgery first group). All of the patients' imaging results were reviewed to ensure that they had been considered resectable prior to chemotherapy. The definition of resectability was a future liver remnant of at least 20-30%, maintenance of portal inflow, venous outflow and biliary drainage of the segments of the remnant liver and the possibility of removing all sites of disease with microscopically clear margin. Patients with both synchronous and metachronous CRLM were included.

Patients were excluded from the study if they did not achieve resection of all sites of disease during the primary operation or metastasectomy or had an R2 (macroscopic residual disease)

resection. Additionally, patients were excluded if they had radiofrequency or microwave ablation prior to liver resection. Patients were not excluded if there were additional sites of extrahepatic disease as long as all sites of disease were resected. The study was performed according to ethical standards of World Medical Association Declaration of Helsinki of 2013 and ethics was approved by both hospital sites (QA2018007 and 18/84R).

Statistics

Baseline data were presented as absolute numbers and percentages. Continuous variables were presented as median and interquartile range (IQR). For survival analysis, starting date was defined as date of diagnosis of the CRLM. Date of last follow up was defined as date of last clinic visit, imaging or pathology test. For OS, patients were censored by date of last follow up or death date. For PFS, patients were censored by date of recurrence or date of last follow up or death. Date of recurrence was defined as the date on which there was imaging confirmation of recurrence or the date of recurrence found at colonoscopy or laparoscopy/laparotomy.

To adjust for the intrinsic heterogeneity within the patient groups, a multivariable Cox proportional hazard (PH) regression analysis was performed. The principal exposure of interest was neoCT and the principle outcome of interest was overall survival (OS) and the secondary outcome of interest progression free survival (PFS). For both the OS and PFS analysis, univariable Cox proportional hazard (PH) regression analysis assessing hazard of death and recurrence, was performed for each baseline variable. Multivariable Cox PH regression analysis was then performed to adjust for potentially confounding variables, retaining neoCT as the principal exposure of interest. Co-variables from the univariable

analysis which were associated with a greater than 10% change in hazard ratio and had less than 20% missing data were included in the multivariable Cox PH regression analysis. A similar analysis of OS and PFS was repeated for the subgroup restricted to FOLFOX neoCT as FOLFOX chemotherapy is the most commonly administered regimen in the neoadjuvant setting (8). The PH assumption was tested using Schoenfeld residuals complemented by visual assessment of cumulative hazard graphs.

A power and sample size calculation were not performed as the database was a fixed available sample. Data was analysed using Stata version 15.0 (College Station, Texas, USA) statistical software.

Results

Patients

A total of 201 patients (62% male) were included in the study with a median age of 60 (IQR 51-68). Sixty-seven patients had metachronous CRLM and 134 had synchronous disease. Prior to resection, 101/201 (51.2%) patients underwent neoCT. All patients were discussed at a multidisciplinary meeting prior to liver resection and staged with the minimum of a computed tomography (CT) chest/abdomen/pelvis. Additionally,198/200 (99%) patients were staged with a fluorodeoxyglucose positron emission tomography (FDG PET) CT scan. The decision to administer neoCT was on a case by cases basis with no standard criteria. All patients who underwent neoCT had restaging scans prior to liver resection to determine their response. Specifically, all patients had pre and post treatment structural imaging (CT or MRI) and 60/101 (59%) were restaged with an FDG-PET scan. On FDG-PET 10/60 (16%) had progressive disease,

27/60 (45%) had stable disease/partial response and 23/60 (38%) had a complete metabolic response.

In terms of specific neoCT regimens, the majority of patients received oxaliplatin/5-fluorouracil combination (41/101 (41%)) or oxaliplatin/5-fluorouracil/Bevacizumab (40/101 (40%)) and the remainder of patients receiving a heterogenous mix of chemotherapy regimens. Only three patients received cetuximab, two in combination with FOLFIRI and one with FOLFOX. Follow-up assessment was performed every 3 months and included carcinoembryonic antigen (CEA) levels and CT or MRI. A summary of patient demographics and clinical characteristics that were potential confounders are shown in **Table 1.**

Patient Recurrence and Survival Outcomes

Overall Survival

For OS, the median follow- up time for the study population was 3.85 years (IQR 2.65 – 6.44) and follow-up time was similar across cohorts: surgery first, 4.13 years (IQR 2.47 – 6.53); neoCT, 3.78 years (IQR 2.74 – 6.25). At the time of last follow up 35% of the neoCT group and 31% of the surgery first group had died. Kaplan Meier curves in **Figure 1** display the raw survival data *prior* to adjustment.

Although univariable Cox proportion PH regression showed a 25% increased hazard of death from all causes in those that had neoCT compared to those that had surgery first, there was no evidence of effect (HR 1.25, 95%CI 0.76 – 2.06, P=0.376). Multivariable Cox PH regression, adjusted for the effects of age, American Society of Anesthesiologists (ASA) score, primary tumour grade, adjuvant therapy after primary resection (metachronous patients), synchronous versus metachronous tumours, bilobar spread, complex operation, number of CRLM, size of CRLM, positive liver resection margin (R1), adjuvant therapy post liver resection and site of primary cancer, showed no statistically significant difference in the hazard of death in those that had neoCT compared to surgery first (HR 1.74, 95% CI 0.85-3.55, p=0.127) (**Table 2**). Additionally the subgroup analysis of FOLFOX only patients showed no difference in OS in those having neoCT compared to surgery first on both the univariable and multivariable analysis having adjusted for potential confounders (HR 1.11. 95% CI 0.71-1.73, p=0.652, HR 1.86, 95% CI 0.74-4.68, p=0.190 respectively) **(Table 3)**.

Progression Free Survival

For PFS, the median follow- up time for the study population was 2.09 years (IQR 1.26 – 3.84) and follow-up time was similar across cohorts: surgery first, 2.12 years (IQR 1.34 – 3.56); neoCT, 2.06 years (IQR 1.00 – 3.56). Following resection of all sites of disease, 80/101 (79%) patients had further disease recurrence in the neoCT group compared with 62/100 (62%) in the surgery first group. Kaplan Meier curves in **Figure 1** displays the raw survival data *prior* to adjustment.

Of the patients who had further recurrence in the neoCT group, recurrence was in potentially resectable sites (liver, lung, peritoneum, ovary, adrenal) in 48/80 (60%) patients and 31/80

(39%) went on to re-resection of all sites of recurrence. In the surgery first group, 53/62 (85%) patients had potentially resectable sites of disease recurrence (liver, lung, peritoneum, ovary, adrenal) and 20/62 (32%) underwent re-resection of all sites of disease recurrence. In the neoCT group 22/80 (28%) of patients had nodal recurrence (distant abdominal, retroperitoneal, mediastinal) compared with 5/62 (8%) in the surgery only group.

Although univariable Cox PH regression showed a 32% increase in PFS in the neoCT cohort compared to the surgery first cohort, there was no evidence of effect (HR 1.32, 95%CI 0.94 – 1.85, P=0.108). Multivariable Cox PH regression adjusted for the effects of nodal metastases, primary T stage, adjuvant therapy post resection of primary, bilobar spread, number of liver metastases, size of liver metastases, positive liver resection margin (R1), adjuvant therapy post liver resection and site of primary cancer also showed no difference between the cohorts (HR 1.42, 95% CI 0.93 – 2.19, P=0.107) **(Table 4)**.

The subgroup analysis of FOLFOX only patients showed no difference in PFS survival on univariable or multivariable analysis ((HR 1.11, 95%CI 0.71 – 1.73, P=0.652) and (HR 1.07, 95%CI 0.61 – 1.89, P=0.807) respectively).

Discussion

Our results showed that there was no improvement in overall survival or progression free survival when patients with resectable liver metastases received neoadjuvant chemotherapy prior to liver resection.

The limitations of the study include small sample size and the retrospective nature of the study. Additionally, there was some heterogeneity not adjusted for in the regression analysis that may contribute to confounding. This includes chemotherapy regimens (neoadjuvant and adjuvant)– particularly in the case of patients with rectal cancer, sequence of treatment, development of complications from either the primary operation or liver resection and perioperative treatment including the type of anaesthetic. There was residual bias in the study despite the multivariate analysis, due to selection bias. Patients with resectable metastatic disease who became unresectable during chemotherapy or while awaiting resection of all sites of disease were not included in the analysis. Finally, in terms of the generalisability of the study, the results are only relevant to a specific subset of patients who have potentially resectable disease and who go on to achieve resection of all sites of disease.

No randomised trial or meta-analysis assessing the benefit of neoCT for patients with resectable CRLM has shown an improvement in OS. Recent cohort studies have tried to use clinic-pathological criteria to stratify patients into low and high-risk groups to try and better select patients who may benefit from “peri-operative” chemotherapy. High risk groups include pathological node positive primary, >1 CRLM, size of CRLM > 5cm(9-11). A randomised trial (CHARISMA) is underway which utilises Fong’s clinical risk score to examine

OS benefit of neoCT versus surgery alone in high risk patients with resectable colorectal liver metastases.

In addition to Fong's clinical risk score, a number of other risk stratification criteria have been developed to try to predict which patients will benefit from CRLM resection. However, it is important to note there is no accepted clinical risk score to predict which patients will benefit specifically from chemotherapy(12-15). It may be that selecting patients who might benefit from neoCT using clinico-pathological characteristics is an over simplification and the old dogma of giving chemotherapy to "test the biology" may not be appropriate. The negative results of neoCT in patients with resectable disease suggest that we do not understand the interactions between neoadjuvant chemotherapy and the individual's tumour biology, nor the biological differences between effects of adjuvant chemotherapy on micro-metastatic disease versus neoCT on macro-metastatic disease.

To look beyond a patient's clinico-pathological features, pre-treatment genomic analysis has been used with some success to guide the types of neoCT. Left sided tumours with wild-type KRAS status are more likely to benefit from epidermal growth factor (EGFR) inhibitors than right sided and BRAF mutants may benefit from checkpoint inhibitors(16, 17). Additionally tumour polymorphisms have shown some promise in predicting the response the chemotherapy such as XRCC1 polymorphisms for oxaliplatin(18). One major limitation of stratifying patients based on a single tumour sample is the significant intra-tumoural and inter-tumoural heterogeneity in colorectal cancer, meaning a single biopsy is unlikely to represent the composition of the entire tumour or other metastases(19, 20). More recently some study groups have shown that patient derived 3D mini tumoroids or organoids may be able to predict patient response to chemotherapy rather than exposing patients blindly to the

toxicity of treatment based on a single conventional biopsy(21, 22). Additionally, circulating tumour cells and DNA may help guide which patients would benefit from treatment as has been shown stage II and III colorectal cancer(23, 24).

Conclusion : Within the limitations of our study, in patients with mCRC who achieved surgical resection of all sites of disease , neoadjuvant chemotherapy prior to liver resection did not offer any survival benefit. The results of this study in addition to current available studies indicate that surgery first is a viable option. Further clinical trials with strict inclusion criteria, incorporation of genomic analysis, collection of circulating tumour DNA and concurrent patient derived organoid response may allow a better understanding of the role of neoadjuvant chemotherapy in resectable colorectal liver metastases.

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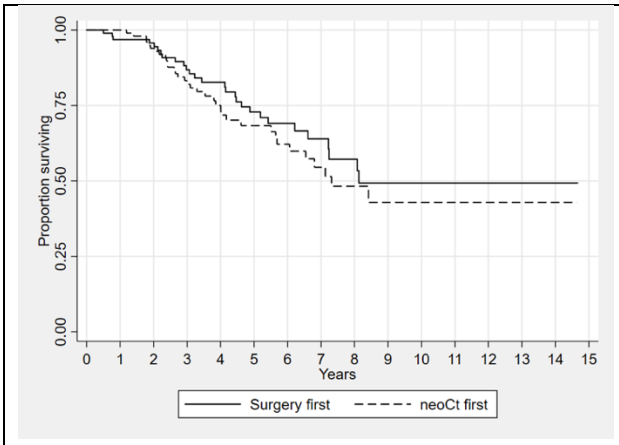
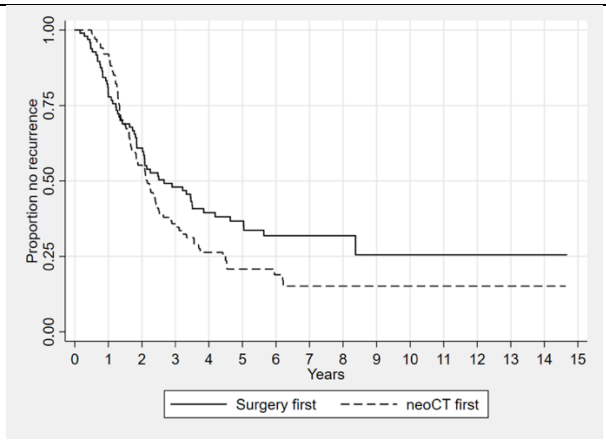
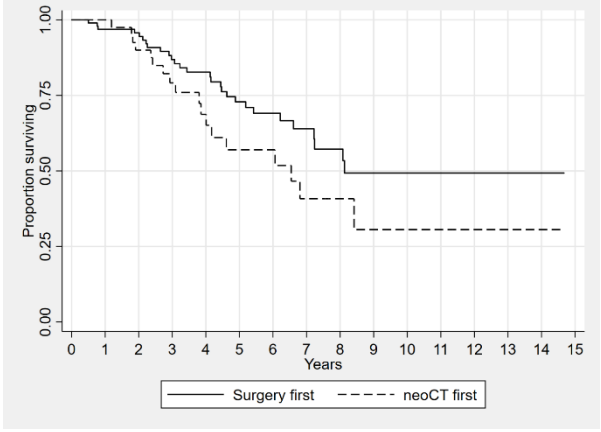


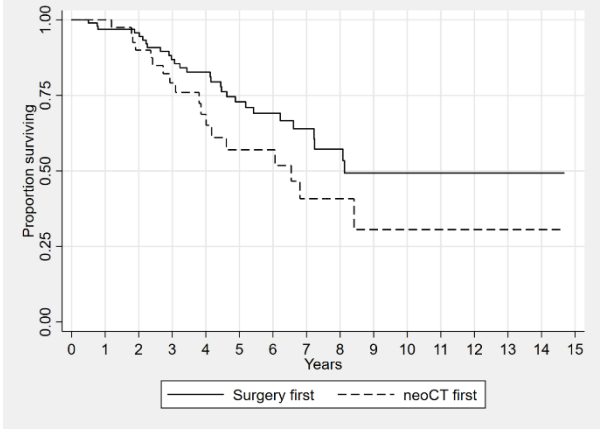
a) Overall Survival – Whole Cohort



b) Progression Free Survival – Whole Cohort



c) Overall Survival – FOLFOX only



d) Progression Free Survival- FOLFOX only

Figure 1. Kaplan Meier curves of whole cohort and subgroup analysis. a) OS comparing surgery first vs neoCT b) PFS comparing surgery first vs neoCT c) OS comparing surgery first vs neoCT (FOLFOX) d) PFS comparing surgery first vs neoCT (FOLFOX)

Variables	Categories	Surgery (total =100) n(%)	NeoCT(total =101) n(%)
Age (years)	≤55	33 (33.0)	35 (34.7)
	>55	67 (67.0)	66 (65.4)
Sex	M	66 (66.0)	58 (57.4)
	F	34 (34.0)	43 (42.6)
ASA Score	2	71 (71.0)	82 (81.2)
	3	20 (20.0)	14 (13.9)
	Missing	9 (9.0)	5 (5.0)
Nodal Status of Primary (Pathological)	Negative	37 (37.0)	32 (31.7)
	Positive	62 (62.0)	63 (62.4)
Grade of Primary (Pathological)	Other	68 (68.0)	61 (60.4)
	Poor	11 (11.0)	11 (10.9)
	Missing	21 (21.0)	29 (28.7)
Primary resection margin	R0	73 (73.0)	62 (61.4)
	R1	1 (1.0)	5 (5.0)
	Missing	26 (26.0)	34 (33.7)
T stage of Primary (Pathological)	0-3	78 (78.0)	54 (53.5)
	4	18 (18.0)	34 (33.7)
	Missing	4 (4.0)	13 (12.9)
Adjuvant Chemotherapy (Post primary resection	No	69 (69.0)	88 (87.1)
	Yes	31 (31.0)	12 (11.9)
	Missing	0 (0.0)	1 (1.0)
Metachronous/synchronous	Metachronous	49 (49.0)	18 (17.8)
	Synchronous	51 (51.0)	83 (82.2)
Distribution of liver metastases	Unilobar	84 (84.0)	47 (46.5)
	Bilobar	16 (16.0)	53 (52.5)
	Missing	0 (0.0)	1 (1.0)
Complexity of liver resection (Minor = ≤3 , major=≥3 segments)	Minor	67 (67.0)	35 (34.7)
	Major	33 (33.0)	66 (65.4)
	Missing	0 (0.0)	1 (1.0)
Number of liver metastases	1-3	92 (92.0)	75 (74.3)
	≥4	6 (6.0)	25 (24.8)
	Missing	2 (2.0)	1 (1.0)
Size of liver metastases (cm)	0-5	87 (87.0)	86 (85.2)
	≥5	11 (11.0)	15 (14.9)
	Missing	2 (2.0)	0 (0.0)
Liver resection margin	R0	88 (88.0)	82 (81.2)
	R1	11 (11.0)	19 (18.8)
	Missing	1 (1.0)	0 (0.0)
Adjuvant chemotherapy (Post liver resection)	No	21 (21.0)	28 (27.7)
	Yes	76 (76.0)	66 (65.4)
	Missing	3 (3.0)	7 (6.9)

Table 1. Baseline Clinical Characteristics of Patients. ASA=American Society of Anaesthesiologists , R0=Microscopically clear margin, R1=Macroscopically clear margin.

		Univariable						Multivariable				
		n	Death	HR	95% CI		P	n	HR	95% CI		P
Primary Exposure	1st chemo vs 1st surgery	101/100	35/30	1.25	0.76	2.06	0.376	160	1.74	0.85	3.55	0.127
Age (years)	>55 vs ≤55	133/68	46/19	1.20	0.69	2.10	0.515	160	0.87	0.45	1.69	0.689
Sex	Female vs Male	77/124	25/40	0.94	0.57	1.56	0.814					
ASA score	3 vs 2	34/154	12/47	1.16	0.61	2.20	0.646	160	1.06	0.49	2.30	0.883
Primary nodal metastasis (pathological)	Yes vs No	124/70	47/17	2.01	1.15	3.52	0.014	160	1.63	0.84	3.15	0.149
Primary tumour grade (pathological)	Yes vs No	22/129	11/35	2.44	1.16	5.13	0.018					
Primary resection margin	R1 vs R0	6/135	1/44	0.80	0.11	5.89	0.827					
Primary T stage (pathological)	T4 vs T0-3	52/132	21/39	1.27	0.73	2.20	0.395	160	0.85	0.43	1.68	0.631
Adj CT (post primary resection)	Yes vs No	43/157	19/46	1.96	1.14	3.36	0.015	160	3.84	1.00	14.71	0.050
Synchronous/Metachronous CRLM	Synchronous vs metachronous	134/67	41/24	0.84	0.51	1.40	0.505	160	2.50	0.72	8.66	0.150
Distribution of liver metastases	Bilobar vs Unilobar	69/131	19/45	0.80	0.47	1.38	0.424	160	0.52	0.26	1.03	0.061
Complexity of operation	Major vs minor	99/102	34/31	1.21	0.74	1.99	0.445	160	1.37	0.71	2.64	0.349
Number of liver metastases	≥4 vs 1-3	31/167	6/58	0.62	0.27	1.45	0.271	160	0.55	0.22	1.42	0.219
Size of liver metastases	≥5 vs 0-5	26/173	7/58	1.11	0.51	2.46	0.790	160	1.64	0.66	4.10	0.287
Liver resection margin	R1 vs R0	30/170	17/48	2.25	1.29	3.92	0.004	160	3.73	1.80	7.75	0.000
Adj CT (post liver resection)	Yes vs No	142/49	43/19	0.69	0.40	1.19	0.186	160	1.05	0.51	2.17	0.898
Site of primary resection	Rectum vs colon	69/132	23/42	1.09	0.65	1.82	0.743					

Table 2. Univariable and multivariable Cox PH regression analysis – Overall Survival, Whole Cohort. ASA=American Society of Anaesthesiologists , CRLM= colorectal liver metastases, Adj CT=Adjuvant Chemotherapy, R0=Microscopically clear margin, R1=Macroscopically clear margin, HR=hazard ratio, CI=confidence interval.

		Univariable						Multivariable				
		n	Death	HR	95% CI		P	n	HR	95% CI		P
Primary Exposure	1st chemo vs 1st surg	40/100	18/30	1.11	0.71	1.73	0.652	114	1.86	0.74	4.68	0.190
Age (years)	>55 vs ≤55	96/44	35/13	0.92	0.58	1.45	0.708	114	1.16	0.51	2.60	0.728
Sex	Female vs Male	54/86	19/29	1.15	0.76	1.76	0.508					
ASA score	3 v 2	27/103	8/36	1.09	0.64	1.83	0.757	114	0.60	0.24	1.55	0.295
Primary nodal metastasis (pathological)	Yes vs No	88/50	37/11	1.58	1.00	2.47	0.048	114	2.07	0.84	5.07	0.112
Primary tumour grade (pathological)	Yes vs No	15/94	9/26	1.02	0.47	2.24	0.952					
Primary resection margin	R1 vs R0	2/99	1/34	0.69	0.10	4.99	0.714					
Primary T stage (pathological)	T4 vs T0-3	30/100	12/32	1.50	0.91	2.46	0.112	114	0.71	0.29	1.72	0.447
Adj CT (post primary resection)	Yes vs No	34/106	15/33	1.13	0.69	1.86	0.637	114	3.40	0.79	14.62	0.099
Synchronous/Metachronous CRLM	Synchronous v metachronous	84/56	28/20	1.08	0.70	1.66	0.723	114	2.17	0.60	7.83	0.239
Distribution of liver metastases	Bilobar v Unilobar	36/104	12/36	1.08	0.69	1.71	0.728					
Complexity of operation	Major v minor	55/85	23/25	0.98	0.64	1.50	0.939	114	1.24	0.57	2.71	0.594
Number of liver metastases	≥4 vs 1-3	13/124	5/42	1.4	0.72	2.70	0.322	114	0.97	0.34	2.72	0.950
Size of liver metastases	≥5 vs 0-5	16/122	4/44	0.96	0.48	1.91	0.907					
Liver resection margin	R1 vs R0	23/116	15/33	1.54	0.92	2.59	0.102	114	3.86	1.72	8.64	0.001
Adj CT (post liver resection)	Yes vs No	102/34	35/12	0.73	0.46	1.18	0.198	114	1.56	0.59	4.10	0.368
Site of primary resection	Rectum vs colon	50/90	19/29	1.33	0.73	2.39	0.349	114	1.21	0.57	2.58	0.625

Table 3. Univariable and multivariable Cox PH regression analysis – Overall Survival, FOLFOX group only. ASA=American Society of Anaesthesiologists , CRLM= colorectal liver metastases, Adj CT=Adjuvant Chemotherapy, R0=Microscopically clear margin, R1=Macroscopically clear margin, HR=hazard ratio, CI=confidence interval.

		Univariable						Multivariable				
		n	Recurrence	HR	95% CI		P	n	HR	95% CI		P
Primary Exposure	1st chemo vs 1st surg	101/100	79/62	1.32	0.94	1.85	0.108	169	1.42	0.93	2.19	0.107
Age (years)	>55 vs ≤55	133/68	95/46	0.96	0.67	1.38	0.832					
Sex	Female vs Male	77/124	55/86	1.06	0.76	1.49	0.726					
ASA score	3 vs 2	34/154	23/110	0.99	0.63	1.55	0.959					
Primary nodal metastasis (pathological)	Yes vs No	124/70	91/43	1.54	1.07	2.21	0.020	169	1.70	1.16	2.50	0.007
Primary tumour grade (pathological)	Yes vs No	22/129	14/91	1.00	0.55	1.83	0.999					
Primary resection margin	R1 vs R0	6/135	4/98	1.03	0.38	2.79	0.961					
Primary T stage (pathological)	T4 vs T0-3	52/132	42/90	1.36	0.94	1.98	0.103	169	1.01	0.65	1.56	0.967
Adj CT (post primary resection)	Yes vs No	43/157	27/113	1.12	0.73	1.70	0.608	169	1.18	0.73	1.91	0.506
Synchronous/Metachronous CRLM	Synchronous vs metachronous	134/67	99/42	1.09	0.76	1.56	0.653					
Distribution of liver metastases	Bilobar vs Unilobar	69/131	53/87	1.16	0.83	1.64	0.386	169	0.97	0.62	1.51	0.878
Complexity of operation	Major vs minor	99/102	71/70	1.00	0.72	1.40	0.999					
Number of liver metastases	≥4 vs 1-3	31/167	24/115	1.29	0.83	2.01	0.256	169	1.12	0.67	1.89	0.667
Size of liver metastases	≥5 vs 0-5	26/173	18/122	1.10	0.67	1.81	0.697	169	1.38	0.80	2.39	0.244
Liver resection margin	R1 vs R0	30/170	22/119	1.19	0.76	1.88	0.446	169	1.15	0.64	2.08	0.634
Adj CT (post liver resection)	Yes vs No	142/49	99/37	0.83	0.57	1.22	0.346	169	0.97	0.62	1.52	0.893
Site of primary resection	Rectum vs colon	69/132	44/97	0.75	0.53	1.08	0.119	169	0.79	0.53	1.17	0.237

Table 4. Univariable and multivariable Cox PH regression analysis – Progression Free Survival, Whole Cohort. ASA=American Society of Anaesthesiologists , CRLM= colorectal liver metastases, Adj CT=Adjuvant Chemotherapy, R0=Microscopically clear margin, R1=Macroscopically clear margin, HR=hazard ratio, CI=confidence interval.