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Article

The Role of Chemotherapy in Patients with Synchronous Colorectal Liver Metastases: A Nationwide Study

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Simple Summary: The role of peri-operative chemotherapy in patients with colorectal cancer and synchronous (upfront) resectable liver metastases is still under debate. One advantage of giving neoadjuvant chemotherapy is the idea of 'test of tumor biology'. That is, to allow a period of time after chemotherapy to assess whether the metastases progress despite treatment. Arguably, this may preclude futile surgery. Neoadjuvant treatment may also downsize tumors, which can lead to a smaller liver resection (parenchymal-sparing surgery) and hopefully improve survival. On the other hand, a substantial number of patients experience adverse events during the course of treatment, and chemotherapy may lead to an increase in post-operative complications. The aim of this nationwide study was to assess long-term oncological outcomes of patients receiving neoadjuvant and adjuvant chemotherapy compared to those who underwent upfront hepatectomy.

Abstract: There is still no consensus as to whether patients with upfront resectable synchronous colorectal liver metastases (sCRLM) should receive neoadjuvant treatment prior to liver surgery. Two randomized controlled trials have assessed the role of peri-operative chemotherapy in sCRLM; neither have shown a survival benefit in the neoadjuvant group. The aim of this population-based study was to examine overall survival in patients treated with neoadjuvant chemotherapy and hepatectomy compared to patients who had upfront surgery. This is a retrospective observational study between 2009 and 2017 containing data extracted from two Swedish national registries. Descriptive statistics and Cox regression analyses were employed. Results: 2072 patients with sCRLM were treated with liver surgery between 2009-2017. A majority (n=1238, 60%) were treated with neoadjuvant chemotherapy, and 834 patients (40%) had upfront surgery. Patients in the upfront surgery group were older (median age 70 compared to 65 years, $p < 0.001$). Median overall survival in the upfront surgery group was 26 months (95% CI 23-29 months) compared to 57 months (95% CI 42-48 months) in the neoadjuvant group, log rank $p < 0.001$. In the multivariable Cox regression analysis, age ≥ 70 years (HR 1.46, 95% CI 1.25-1.70), T category of primary cancer (HR 1.41, 95% CI 1.09-1.84), lymphatic spread of primary cancer (HR 1.68, 95% CI 1.41-1.99) and number of liver metastases (six or more metastases resulted in HR 2.05, 95% CI 1.38-3.01), negatively influenced overall survival. By contrast, adjuvant therapy was protective (HR 0.80, 95% CI 0.69-0.94), whereas neoadjuvant treatment compared to upfront surgery did not influence overall survival (HR 1.04, 95% CI 0.86-1.26). In conclusion, neoadjuvant treatment in sCRLM did not confer a survival benefit compared to upfront surgery.

Keywords: colorectal cancer; liver metastases; metastasectomy; liver surgery; peri-operative chemotherapy; neoadjuvant chemotherapy; adjuvant chemotherapy.

1. Introduction

The role of peri-operative chemotherapy in patients with upfront resectable synchronous colorectal cancer with liver metastases (sCRLM) is not clear. The most common location for metastasis is the liver [1]. Chemotherapy, in combination with surgery may both reduce the risk of relapse and improve overall survival [2–4]. Today, three randomized controlled trials exist [5–8] that have examined the role of chemotherapy in patients with resectable CRLM. In the EORTC Intergroup Trial 40983 [5] an improved progression free survival was seen in the perioperative chemotherapy group with 8.1% at 3 years compared to surgery alone. However, at a median follow-up of 8.5 years no difference could be discerned between the perioperative chemotherapy group versus the surgery alone group in terms of overall survival [6].

As a rational extension of the EORTC trial – also known as the EPOC-trial – another trial, the so-called, new EPOC-trial, randomized patients with *KRAS* exon 2 wild-type resectable CRLM in a 1:1 ratio to receive chemotherapy with or without cetuximab before and after liver resection [9]. This trial was closed at the interim analysis since it met the protocol-defined futility criteria; since the addition of cetuximab shortened the progression free survival. In a more recent randomized trial (JCOGO603) a modified infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX6) was added to liver surgery for liver-only metastatic colorectal cancer. This study demonstrated an improved disease-free survival at 5 years (50% versus 39%, $p=0.006$), in the chemotherapy group, but there was no difference in overall survival [7]. Notably, in the EPOC-trial 63% ($n=236$) of the patients had metachronous liver metastases, whereas in the JCOGO603 trial 44% ($n=133$) had metachronous disease. In Sweden, the standard of care has been the treatment plan described in the EORTC Intergroup Trial 40983 (EPOC trial), which includes six cycles of fluorouracil, leucovorin and oxaliplatin before and after surgery.

In our previous study, neoadjuvant chemotherapy did not confer an improved overall survival in patients with a solitary colorectal liver metastasis [10]. The aim of the present study is to examine the role of neoadjuvant and adjuvant chemotherapy in patients with synchronous colorectal liver metastasis (sCRLM) on overall survival.

2. Materials and Methods

2.1. Patients

This nationwide population-based cohort study comprised consecutive patients who underwent a resection for sCRLM and were registered in the National Quality of Registry for Liver, Bile Duct, and Gallbladder cancer (SweLiv) between 1st January 2009 and 31st of December 2017. To obtain information about the primary cancer, data were also retrieved and cross-linked with the Swedish Colorectal Cancer Registry (SCRCR).

2.2. National Quality Registries

Both SweLiv and SCRCR are prospectively maintained quality registries that contain data about the primary colorectal cancer, surgical, oncological and interventional results. SweLiv was established in 2008, and is continuously updated against the Total Population Register at Statistics Sweden, which provides information regarding whether a patient is dead or alive. Both SweLiv and SCRCR have excellent coverage rates when compared with the Swedish Cancer Registry [11,12]. Data that were extracted included demographics, and *inter alia* information about the primary cancer diagnosis (primary cancer T stage, lymphatic spread of primary cancer), type of liver resection (major or minor), complications according to Clavien-Dindo classification, and information about neoadjuvant and adjuvant treatment.

2.3. Work-Up of Patients

All patients were discussed in colorectal- and liver-specific inter-disciplinary team conferences prior to treatment. Synchronous liver metastases were defined as the presence of metastases at the

time of diagnosis or detected during staging of the primary cancer diagnosis. Patients were divided into two groups, those who had upfront surgery without neoadjuvant treatment, and those who had neoadjuvant treatment prior to liver surgery.

2.4. Permissions

The study was approved by the regional ethical board (DnR 2019-00016).

2.5. Statistics

Continuous data are presented with median and interquartile ranges (IQR). Categorical data are presented with proportions and percentages. Categorical variables were compared using Chi Square Test or Fisher's Exact Test, and continuous variables with the Mann-Whitney-U test. Overall survival was calculated from the date of surgery until death of any cause, or lost to follow-up. Overall survival between the groups were visually compared with Kaplan-Meier curves, and any difference assessed with the log-rank test. In the multivariable Cox regression analyses, backward elimination was used. In the univariable and multivariable analyses hazard ratios (HR) are presented with 95% Confidence Intervals (CI). Statistical significance was set as a two-sided $p < 0.05$. Data analyses were performed using SPSS IBM statistics Version 28, 2021.

3. Results

4943 patients were assessed for eligibility. After excluding metachronous CRLM, and patients who had been treated with ablation, 2072 patients with sCRLM were included in the analysis (Figure 1). 1238 patients (60%) were first treated with neoadjuvant chemotherapy before liver surgery. Forty percent ($n=834$) had upfront surgery. In the neoadjuvant group 755 patients (61%) had adjuvant treatment compared to 245 patients (29%) in the upfront surgery group.

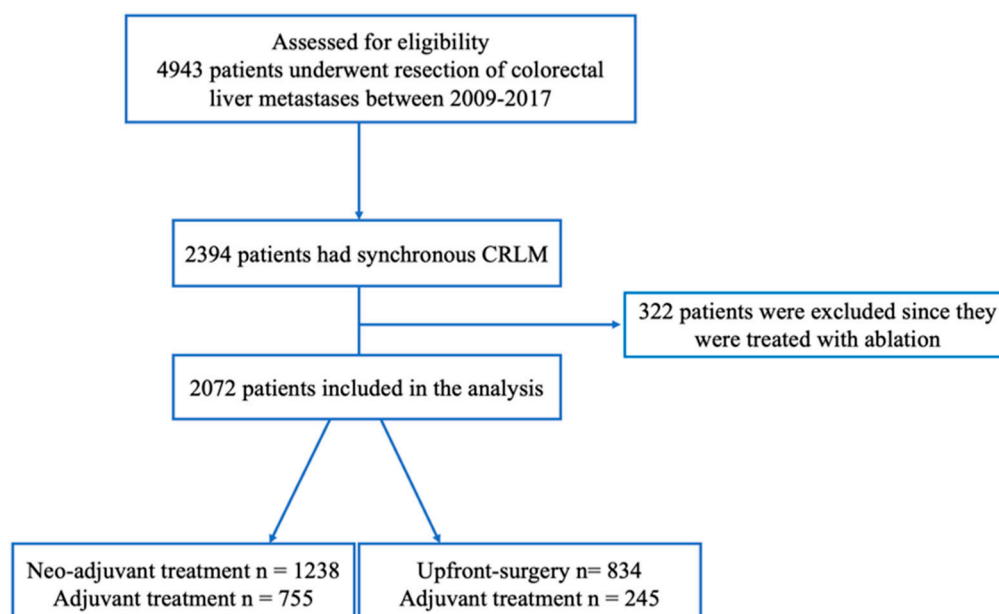


Figure 1. A flowchart of the study population.

Median age at surgery was 65 years (IQR 57-70 years) in the neoadjuvant group compared to 70 years (IQR 60-71 years) in the upfront surgery group ($p < 0.001$) (Table 1). Nearly fifty percent ($n=404$, 48%) were older than 70 years in the upfront surgery group, compared to 28% ($n=343$) the

neoadjuvant group ($p<0.001$). In both groups the majority of patients were men. Most patients in both groups belonged to ASA classification 2 or 3 (80% in the neoadjuvant group compared to 84% in upfront surgery); a higher proportion of patients in the upfront surgery group belonged to ASA classification 4 ($p=0.006$). Differences were discerned in the two groups in terms of T category of primary cancer ($p<0.027$), lymphatic spread of primary cancer ($p=<0.006$), tumor diameter ($p=0.019$), and number of liver metastases ($p=<0.001$). In the neoadjuvant group 26% ($n=284$) compared to 32% ($n=192$) in the upfront surgery group had a T4 primary cancer; and 72% ($n=805$) compared to 67% ($n=394$) had a N1-N2 lymphatic spread of primary cancer. In the neoadjuvant group 610 patients (51%) had three or more liver metastases, compared to 263 patients (36%) in the upfront surgery group (Table 1).

Table 1. Baseline characteristics of study population.

	No. Patients N= 2072	Neoadjuvant N=1238	Upfront surgery N=834	<i>p</i> Value
Age (years)				
Median (IQR)	66 (58-72)	65 (57-70)	70 (60-71)	<0.001
Age >70	747 (36)	343 (28)	404 (48)	<0.001
Sex				
Men	1269 (61)	765 (62)	504 (60)	0.282
Women	803 (39)	473 (38)	330 (40)	
ASA				
1	289 (17)	206 (19)	83 (14)	0.006
2	947 (57)	631 (57)	316 (55)	
3	419 (25)	249 (23)	170 (29)	
4	21 (1)	12 (1)	9 (2)	
Missing	396	140	256	
T category of primary cancer				
T1	21 (1)	13 (1)	8 (1)	0.027
T2	137 (8)	98 (9)	39 (7)	
T3	1045 (62)	692 (64)	353 (60)	
T4	476 (29)	284 (26)	192 (32)	
Tx/missing 592	393	151	242	
Lymphatic spread of primary cancer				
N0	503 (30)	308 (28)	195 (33)	0.006
N1	642 (38)	449 (40)	193 (33)	
N2	557 (32)	356 (32)	201 (34)	
Nx/missing	370	125	245	
Tumor diameter (mm)				
Median (IQR)	20 (13-33)	20 (14-35)	20 (13-30)	0.019
Number of liver metastases				
1	666 (35)	328 (28)	338 (47)	<0.001
2	372 (19)	249 (21)	123 (17)	
3-5	502 (26)	373 (31)	129 (18)	
6	253 (13)	181 (15)	72 (10)	
>6	118 (6)	56 (5)	62 (9)	
Missing	161	51	110	

3.1. Surgical Results and Morbidity

In both groups 12% were treated with an emergency operation because of the primary cancer (Table 2). In the neoadjuvant group 392 patients (32%) compared to 141 patients (17%) had a rectal cancer. In the upfront surgery group 23% (n=194) of the patients had a right colectomy, compared to 19% (n=232) in the neoadjuvant group ($p<0.001$). Forty-three percent (n=527) in the neoadjuvant group had a major hepatectomy (3 or more liver segments), compared to 6% (n= 50) in the upfront surgery group ($p<0.001$). In the neoadjuvant group 39% (n= 481) had a complete or partial response on the neoadjuvant chemotherapy treatment prior to surgery. In the neoadjuvant group a radical resection (R0) was obtained in 81% (n=898), compared to 80% (n=298) in the upfront surgery group ($p=0.390$). Rectal resection, and left colectomies were more common in the neoadjuvant group (Table 2). Radical resection was defined as a resection margin of at least 1 millimeter. More patients in the neoadjuvant group experienced a complication graded as Clavien Dindo 3a or greater compared to the upfront surgery group ($p<0.001$). Eighty-one patients (7%) in the neoadjuvant group were admitted within 30 days compared to 36 patients (4%) in the upfront surgery group ($p<0.001$).

Table 2. Details of primary cancer resection, hepatectomy and surgical results.

	Neoadjuvant N=1238	Upfront surgery N=834	p Value
Emergency primary cancer operation		99 (12)	
	144 (12)		
Type of colorectal resection			
Rectal resection	392 (32)	141 (17)	0.059
Left colectomy	423 (34)	195 (23)	
Right colectomy	232 (19)	194 (23)	
Colectomy, other	62 (5)	37 (4)	<0.001
Unspecified	117 (10)	225 (27)	
Laparotomy only	42 (1)	42 (5)	
Major hepatectomy			
3 or more liver segments	527 (43)	50 (6)	<0.001
Intraoperative blood loss			
Median (IQR)	600 (300-1100)	300 (125-475)	0.083
Response on neoadjuvant treatment			
Complete/partial	481 (39)		
Stable disease	98 (8)	N/A	
Progress	34 (3)		
Unclear	625 (50)		
Liver resection			
R0	898 (81)	298 (80)	0.390
R1	125 (11)	36 (10)	
Unclear	89 (8)	37 (10)	
Missing	126	463	
Post-operative complications			
Re-admission within 30 days	81 (7)	36 (4)	<0.001
Clavien Dindo 3a	87 (7)	25 (3)	<0.001
Clavien Dindo 3b	41 (3)	16 (2)	

Clavien Dindo 4a	15 (1)	5 (1)
Clavien Dindo 4b	4 (0)	2 (0)
Clavien Dindo 5	5 (0)	2 (0)

3.2. Overall Survival and Cox Regression Analysis

In the univariable analysis several factors negatively influenced overall survival, such as advanced age (above 70 years), ASA classification 3 or 4, T3-T4 category, lymphatic spread of primary cancer, number of liver metastases and upfront surgery (Table 3a). In the Kaplan-Meier analysis there was a clear difference in overall survival between the neoadjuvant group compared to the upfront surgery group (Figure 2). The median overall survival in the neoadjuvant group was 57 months (95% CI 53-61 months), compared to 26 months (95% CI 23-29 months) in the upfront surgery group (log rank $p < 0.001$).

In the multivariable analyses, however, neoadjuvant treatment (HR 1.04, 95% CI 0.86-1.26) did not confer an overall survival advantage. Adjuvant treatment was protective, and prolonged overall survival (HR 0.80, 95% CI 0.69-0.94). Number of liver metastases strongly influenced overall survival, with more than six liver metastases doubled the risk of dying compared to one metastasis (HR 2.05, 95% CI 1.38-3.01). Moreover, several factors negatively influenced overall survival, including, lymphatic spread (HR 1.68, 95% CI 1.41-1.99) and T3-T4 category of the primary cancer (HR 1.41, 95% CI 1.09-1.84), and age above 70 years (HR 1.46, 95% CI 1.25-1.70) (Table 3a).

Table 3. a. Cox regression analyses and overall survival; b. Cox regression model for overall survival for patients with six or more than six liver metastases.

a. Cox regression analyses and overall survival.

	Univariable HR, 95% CI	P value	Multivariable HR, 95% CI	P value
Age (years)				
<70	Reference		Reference	
≥70	1.38 (1.26-1.56)	<0.001	1.46 (1.25-1.70)	0.007
Gender				
Women	Reference		Reference	
Men	1.05 (0.90-1.11)	0.931	1.03 (0.89-1.19)	0.719
ASA				
1-2	Reference		Reference	
3-4	1.26 (1.09-1.46)	0.002	1.16 (0.98-1.38)	0.087
T category of primary cancer				
T1-T2	Reference		Reference	
T3-T4	1.91 (1.53-2.39)	<0.001	1.41 (1.09-1.84)	0.010
Lymphatic spread of primary cancer				
N0	Reference		Reference	
N1-N2	1.89 (1.64-2.16)	<0.001	1.68 (1.41-1.99)	<0.001
Number of liver metastases				
1	Reference			
2	1.33 (1.13-1.56)	<0.001	1.52 (1.26-1.84)	<0.001
3-5	1.40 (1.21-1.63)	<0.001	1.38 (1.14-1.66)	<0.001
6	1.80 (1.51-2.15)	<0.001	1.54 (1.22-1.96)	<0.001
>6	3.04 (2.44-3.79)	<0.001	2.05 (1.38-3.01)	<0.001

Chemotherapy				
Upfront surgery	Reference			
Neoadjuvant	0.56 (0.51-0.63)	<0.001	1.04 (0.86-1.26)	0.681
No adjuvant				
Adjuvant	0.62 (0.55-0.69)	<0.001	0.80 (0.69-0.94)	0.007

b. Cox regression model for overall survival for patients with six or more than six liver metastases.

	Univariable HR, 95% CI	P value	Multivariable HR, 95% CI	P value
Age (years)				
<70	Reference		Reference	
≥70	1.61 (1.25-2.07)	<0.001	1.93 (1.30-2.87)	0.002
Gender				
Women	Reference		Reference	
Men	0.99 (0.78-1.25)	0.928	1.21 (0.82-1.76)	0.335
ASA				
1-2	Reference		Reference	
3-4	1.33 (0.95-1.86)	0.094	1.58 (1.06-2.36)	0.026
T category of primary cancer				
T1-T2	Reference		Reference	
T3-T4	3.81 (1.87-7.73)	<0.001	3.30(1.53-7.11)	0.002
Lymphatic spread of primary cancer				
N0	Reference		Reference	
N1-N2	1.94 (1.33-2.83)	<0.001	1.34 (0.82-2.17)	0.241
Chemotherapy				
Upfront surgery	Reference		Reference	
Neoadjuvant	0.301 (0.24-0.38)	<0.001	1.53 (0.67-3.53)	0.314
No adjuvant				
Adjuvant	0.70 (0.54-0.90)	0.005	1.06 (0.72-1.54)	0.778

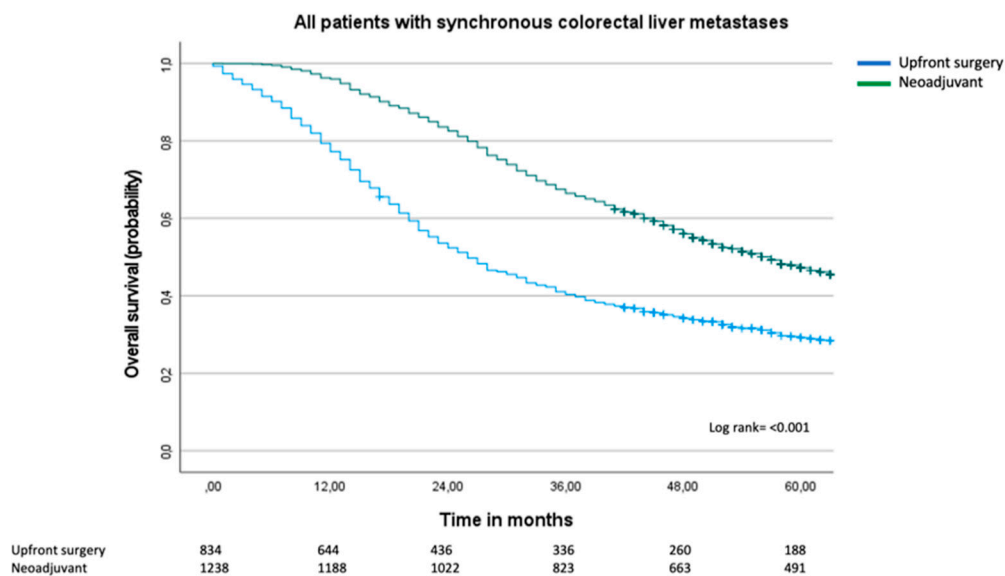


Figure 2. Overall survival including all patients with synchronous colorectal liver metastases. Median overall for the upfront surgery group was 26 months (95% CI 23-29 months), and for the neoadjuvant group 57 months (95% CI 53-61 months), log rank= $p < 0.001$.

3.3. Sub-Group Analyses

Since the multivariable Cox regression analyses clearly indicated that adjuvant treatment, as opposed to neoadjuvant treatment, conferred improved overall survival, a Kaplan Meier curve was performed comparing all patients that had received adjuvant treatment (Figure 3). In this graph, we can see that the median overall survival improved in both the upfront surgery group and neoadjuvant group, and that there still was a difference in survival (44 months compared to 65 months, log rank test $p < 0.002$). Visually, a greater improvement was made in the upfront surgery group, with an improvement of 18 months, compared to 8 months in the neoadjuvant group.

To test the hypothesis that neoadjuvant treatment is especially important for patients with extensive liver metastases, we examined its role in patients with six or more liver metastases. In the multivariable analysis of this sub-group of patients (Table 3b) neither neoadjuvant treatment (HR 1.53, 95% CI 0.67-3.53), nor adjuvant treatment (HR 1.06, 95% CI 0.72-1.54) improved overall survival. In this analysis advanced age (HR 1.93, 95% CI 1.30-2.87), ASA classification 3 or 4 (HR 1.58, 95% CI 1.06-2.36), and T3-T4 category of primary cancer of T3-T4 (HR 3.30, 95% CI 1.53-7.11), played an important role on overall survival.

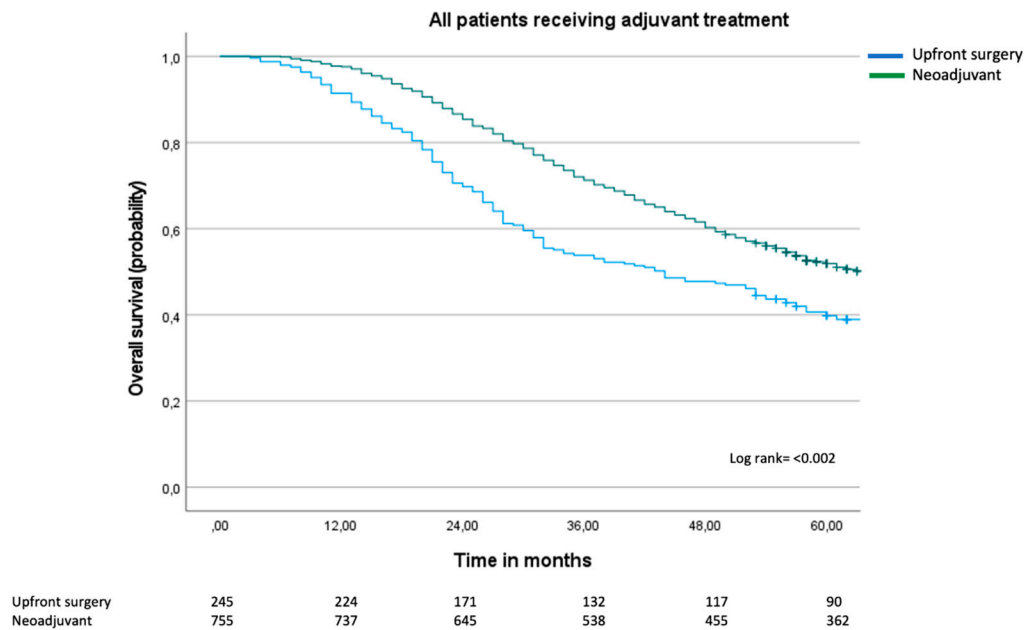


Figure 3. Overall survival including all patients with synchronous colorectal liver metastases who received adjuvant treatment. Median overall for the upfront surgery group was 44 months (95% CI 32-56- months), and for the neoadjuvant group 65 months (95% CI 58-72 months), log rank= $p < 0.002$.

3.4. Supplemental Analysis

To further examine the role of neoadjuvant and adjuvant chemotherapy on overall survival in sCRLM. We performed a multivariable analysis with all patients who had received adjuvant treatment (Table S1). In this subgroup of patients advanced age (≥ 70 years), lymphatic spread of primary cancer (N1-N2) and number of liver metastases (two or more metastases) negatively influenced overall survival. Neoadjuvant treatment (HR 1.04, 95% CI 0.81-1.34) and T category of primary cancer influenced overall survival in the univariable analysis, but not in multivariable analysis. We also examined the role of chemotherapy on all patients who had received neoadjuvant treatment (Table S2). In this group, advanced age (≥ 70 years), lymphatic spread of primary cancer, T category of primary cancer, and more than two liver metastases conferred worse overall survival. Notably, adjuvant treatment also positively prolonged overall survival (HR 0.82, 95% CI 0.68-0.97).

4. Discussion

The role of neoadjuvant chemotherapy in patients with resectable sCRLM is not clear. The present nationwide population-based study between 2009 and 2017 aimed to assess the influence of neoadjuvant and adjuvant chemotherapy on overall survival in sCRLM. In the univariable analysis there was a survival advantage in the neoadjuvant group, compared to upfront surgery. In the multivariable analyses, however, no survival benefit was seen in the neoadjuvant group. By contrast, adjuvant treatment appears to confer a survival benefit in the multivariable analyses.

Patients in the neoadjuvant group were younger (median age 65 compared to 70 years), and healthier, since fewer patients belonged to ASA classification 3 and 4. A greater proportion in the upfront surgery group (32%, $n=192$) had a T4 primary cancer, compared to 26% ($n=284$) in the neoadjuvant group ($p=0.027$). By contrast, 72% ($n=805$) in the neoadjuvant group compared to 67% ($n=394$) in the upfront surgery group belonged to N1 or N2 category of the primary cancer ($p=0.006$). Unfortunately, we only have data from patients who underwent liver surgery. An intention-to-treat analysis is therefore not possible, since we cannot report on the number of patients who were treated with neoadjuvant treatment with the intention of receiving liver surgery, but due to unforeseen reasons, such as progression of the disease, or adverse events of the chemotherapy treatment.

Despite a vast amount of discussion in the literature, there is no consensus on the administration of chemotherapy and its ideal timepoint in resectable CRLM [13–15]. To date, there are three randomized controlled trials [5,7,9] that assess the importance of chemotherapy in resectable CRLM. In the EORTC trial 364 patients were randomized to either peri-operative chemotherapy (six cycles before and six cycles after surgery of FOLFOX4) [5]. In this study 35% (n=128) had synchronous CRLM, and they were allowed to have between one to four liver metastases. In fact, more than 50% percent had only one liver metastasis, and only 7% (n=26) had four liver metastases. This, in comparison to the current study where 72% (n=1483) of patients had three or more metastases. In the EORTC trial an improved progression free survival at 3 years of 8.1% was seen in the chemotherapy arm; however, no difference was discerned in overall survival after 8.5 years follow-up [6]. In a more recent RCT, 300 patients were randomly assigned to either hepatectomy, or a combination of hepatectomy and modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) [7]. Severe adverse events were reported in approximately half of the patients, and there was no difference in overall survival.

Mitry *et al* performed a pooled analysis of two phase 3 trials to assess the importance of chemotherapy after hepatectomy. A comparison was made between patients that received surgery alone (n= 140) and patients that were first treated with hepatectomy and thereafter six months of adjuvant chemotherapy [16]. Adjuvant chemotherapy was associated with progression-free survival and overall survival in the multivariable analysis. Araujo *et al* performed a systematic review and meta-analysis, which included 3 RCTs, and 2 observational comparative studies [2]. This study performed Forest plots both for recurrence-free survival, and overall survival (surgery + chemotherapy versus surgery alone), and concluded that chemotherapy improved overall survival (HR 0.77, 95% CI 0.67-0.88) and recurrence-free survival (HR 0.71, 95% CI 0.61-0.83). In a recent multicenter retrospective observational study by Di Martino and colleagues, which included 252 patients between 2010 and 2015, concluded that peri-operative chemotherapy for resectable CRLM, was beneficial compared to neoadjuvant only, in terms of overall survival and recurrence-free survival [17].

To assess the role of neoadjuvant therapy on patients with multiple liver metastases, we performed a sub-group analysis. In this analysis we examined the role of neoadjuvant treatment on all patients with six or more liver metastases. To our surprise, not even in this group did neoadjuvant treatment prolong overall survival in the multivariable analysis. The assessment of whether a patient would benefit from peri-operative chemotherapy is complex, and requires risk stratification and be determined individually in a multidisciplinary team conference [18]. Patients with resectable CRLM with a low risk of recurrence are likely to benefit from upfront surgery, and the role of adjuvant treatment post-operatively is not always easy to determine. By contrast, patients with resectable disease with a high risk of recurrence may benefit from peri-operative chemotherapy, since a course of neoadjuvant treatment may function as a *test of biology*, where patients who clearly progress during the course of treatment are likely not to benefit from surgery. Treatment decisions in metastatic colorectal cancer need to be influenced by a rigorous understanding of the unique tumor characteristics of the primary cancer and the metastasis, such as molecular profiling, presence or absence of microsatellite instability, extent of tumor involvement and previous treatment, as well as each patient's underlying co-morbidity [19]. Patients with metastatic colorectal cancer are highly heterogeneous. With advancements in surgical technique, the definition of resectability is also becoming more elusive. Today, technically, resectability is not determined by number and extent of liver metastases or bilobar disease, as long as sufficient future liver remnant is preserved ($\geq 30\%$ of remnant liver) [15]. We today perform more complex liver surgery on elderly patients and have acquired an improved understanding of the molecular biology of colorectal cancer [19,20]. We should therefore become better at stratifying patients into low-medium-high risk groups, and weigh this information against *oncological criteria*, concerning prognostic factors, and the biology of the disease, for each patient.

One limitation of the study is the fact that the registers do not allow us to differentiate between patients with primarily unresectable disease, who became resectable as a result of neoadjuvant treatment, from those who were resectable from the outstart. Although, the definition of resectability is *prima facie* easy to define, what exactly constitutes resectable disease is highly influenced by local practices [21] and constantly evolving. Unfortunately, the registers do not allow us to provide detailed information on type of chemotherapy, or number of cycles [22,23]. On the other hand, the aim of the study was, not to assess specific treatment responses or tolerability to oncological agents, but to examine real-world data. Lastly, although the registers show high accuracy and validity, there was a degree of missing data for some variables.

One strength of the present study is its population-based design. Moreover, data obtained for the study come from national quality registers with high accuracy and validity. The long follow-up period entails that few patients have been censored, which adds stability to the overall survival analyses. Another advantage of the present study, is that it focus solely on synchronous CRLM, which makes the study population somewhat more homogenous. Although, our study is a population-based study, and there might be a risk of unmeasured confounding variables; we believe the results suggest a more cautionary approach in administrating peri-operative treatment to all patients with resectable sCRLM. This position is convincingly presented by Booth and Berry [24], when reflecting on the findings presented in the RCT by Kanemitsu et al (JCOG0603) [7]. According to them, the JCOG0603 trial 'signals' the 'end of an era' in which perioperative and postoperative chemotherapy can be viewed as the 'default standard for patients with resectable CRLM' [24]. Since, chemotherapy may only delay recurrence, without any clear evidence that it prolongs survival; a six months chemotherapy treatment period with frequent clinic visits, and the risk of severe adverse events may be questioned.

5. Conclusions

To our knowledge this is the largest population-based study to examine the role of chemotherapy on resectable synchronous CRLM and overall survival. In the present study an association between adjuvant chemotherapy and overall survival was found; this was not the case for neoadjuvant treatment.

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Data Availability Statement: The data may be available from the corresponding author based on reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

The appendix is an optional section that can contain details and data supplemental to the main text—for example, explanations of experimental details that would disrupt the flow of the main text but nonetheless remain crucial to understanding and reproducing the research shown; figures of replicates for experiments of which representative data is shown in the main text can be added here if brief, or as Supplementary data. Mathematical proofs of results not central to the paper can be added as an appendix.

Appendix B

All appendix sections must be cited in the main text. In the appendices, Figures, Tables, etc. should be labeled starting with "A" –e.g., Figure A1, Figure A2, etc.

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