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Chemotherapy in patients with a solitary colorectal liver metastasis – A nationwide propensity score matched study

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ABSTRACT

Introduction: Chemotherapy is widely used as an adjunct to surgery in the treatment of patients with resectable colorectal liver metastases. The aim of this study was to examine whether chemotherapy confers a survival benefit in patients with a solitary colorectal liver metastasis.

Methods: All consecutive patients between 2009 and 2017 in Sweden who were resected for a solitary colorectal liver metastasis were included. Patients treated with chemotherapy were compared with patients who had surgery alone. Unmatched and propensity score matched analyses were performed to compare overall survival, morbidity and mortality.

Results: Of 1224 eligible patients, 641 (52.4%) patients had chemotherapy, and 583 (47.6%) had surgery alone. After propensity score matching, two balanced groups with 102 patients in each, were analyzed. There was no difference in readmission within 30-days ($p = 0.250$), or morbidity, defined as Clavien-Dindo 3a or greater, between the groups ($p = 0.761$). There were no mortalities within ninety days. Radical resection margins were achieved in 92 ($n = 94$) per cent in the chemotherapy group, and 77 ($n = 78$) per cent in the surgery alone group ($p = 0.016$). Median overall survival was 91 (95% CI 73–109) months in the chemotherapy group, and 78 (95% CI 37–119) months in the surgery-alone group ($p = 0.652$).

Conclusion: This nationwide register-based study showed no difference in overall survival between patients treated with chemotherapy compared to surgery alone. Upfront surgery may be advisable in resectable solitary colorectal liver metastasis.

1. Introduction

The most common site of distant spread in colorectal cancer is the liver, and it occurs in 25–30% of patients [1]. Surgical resection is considered standard of care, and the only treatment modality that can offer long-term survival. Recurrence is common, and often occurs within two years of diagnosis. At five years, nearly 70% of patients will have a recurrence [2,3], and it is often located in the liver, followed by the lungs [3].

Unfortunately, only around 15% of patients with colorectal liver metastases are resectable at the time of diagnosis [4,5]. The standard of care in Sweden with regards to peri-operative chemotherapy, follows the treatment regimen reported in the EORTC Intergroup trial 40983 [6], which entails six cycles of fluorouracil, leucovorin, and oxaliplatin before and after surgery. The role of neoadjuvant chemotherapy in the setting of resectable colorectal liver metastases is questionable [7]. The primary objective of this study was to examine the effect of chemotherapy (neoadjuvant and/or adjuvant) on overall survival in patients with a solitary colorectal liver metastasis. Secondary outcomes were mortality and morbidity.

2. Material and methods

2.1. Study population

All consecutive patients who underwent a resection for a colorectal liver metastasis that were registered in the National Quality of Registry for Liver, Bile Duct, and Gallbladder Cancer (SweLiv) were included. Data regarding the primary colorectal cancer were retrieved from the Swedish Colorectal Cancer Registry (SCRCR). The study period was January 1, 2009 to December

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31, 2017. The study was approved by the regional ethical board (Dnr 2019-00016).

SweLiv registry is a prospectively maintained nationwide quality registry with information on surgical and interventional treatment of liver tumors in patients older than 16 years of age. The registry was established in 2008, and is continuously updated regarding vital status by linkage to the Total Population Register at Statistics Sweden. Both SweLiv and the SCRCR have excellent coverage rates compared with the Swedish Cancer Registry [8,9]. Data that were extracted included information about date of diagnosis, type of liver resection (number of segments resected), procedure-related complications according to Clavien-Dindo Classification [10], American Society of Anesthesiologists (ASA) classification, neo-adjuvant chemotherapy (yes/no) and treatment response, and histopathological report on microscopic completeness after resection. To obtain information about the histopathological report of the primary colorectal cancer, type of surgery of the primary cancer, and adjuvant treatment, the dataset from SweLiv was cross-linked with data from the SCRCR.

In the present study, a solitary colorectal liver metastasis was defined as a radiologically/or biopsy verified tumor that was considered resectable. Synchronous colorectal liver metastasis was defined as a tumor detected during staging of the primary cancer. All patients were discussed in liver- and colorectal-specific tumor board meetings. Patients were divided up into two groups; those who had received oncological treatment (either neoadjuvant and/or adjuvant treatment), and those who had surgery alone. All patients with extrahepatic spread were excluded (Fig. 1).

2.2. Statistical methods

Categorial variables are presented with proportions and percentages, and continuous data with median and interquartile ranges (IQR). Categorial variables were compared using the Chi-square test, and Kruskal-Wallis (if more than two groups) or Mann-Whitney *U* test (if two groups) were compared. In the matched cohort a paired *t*-test was used for continuous variables, and McNemar or McNemar-Bowker for categorical variables [11]. Overall survival was defined as the time period between date of liver surgery and death from any cause. Time was censored at the last follow-up for patients that were still alive. Median follow-up time was calculated using reversed Kaplan-Meier method [12]. Survival was analyzed with the Kaplan-Meier method, and survival curves were compared with stratified log-rank or log-rank test [13]. Univariable and multivariable Cox regression models were used to identify an association between patient characteristics and overall survival. In the multivariable regression model, a backward stepwise elimination method was used. Univariable and multivariable hazard ratios are presented with 95% confidence intervals (CI).

Before matching, baseline characteristics between the chemotherapy group and the surgery alone group were compared. Propensity score matching was used to minimize imbalances, to reduce selection bias, and to create two comparable groups. Patients were matched in a 1:1 ratio, based on their estimated propensity score. The caliper was set equal to 0.020, and matching was performed without replacement. The propensity scores were generated using a multivariable logistic regression model. The model included age, sex, size of liver metastasis, ASA group classification, primary cancer tumor and nodal stages and whether it was a synchronous or metachronous metastasis. A visual comparison of the total propensity scores before and after matching is provided with Kernel density distribution plots.

To assess the degree of imbalance before and after matching for each covariate a standardized mean difference (SMD) was calculated. SMD is the difference in the mean of a variable between two groups divided by an estimate of the standard deviation of that variable [11]. After matching a subgroup analysis using a Cox proportional hazards model was performed to identify any differences between the chemotherapy and surgery alone groups. The level of statistical significance for all analyses was defined as a two-sided $p < 0.05$. Data analyses were performed using IBM SPSS Statistics Version 28, 2021, and STATA/SE version 15.1 (StataCorp, College Station, Texas, USA).

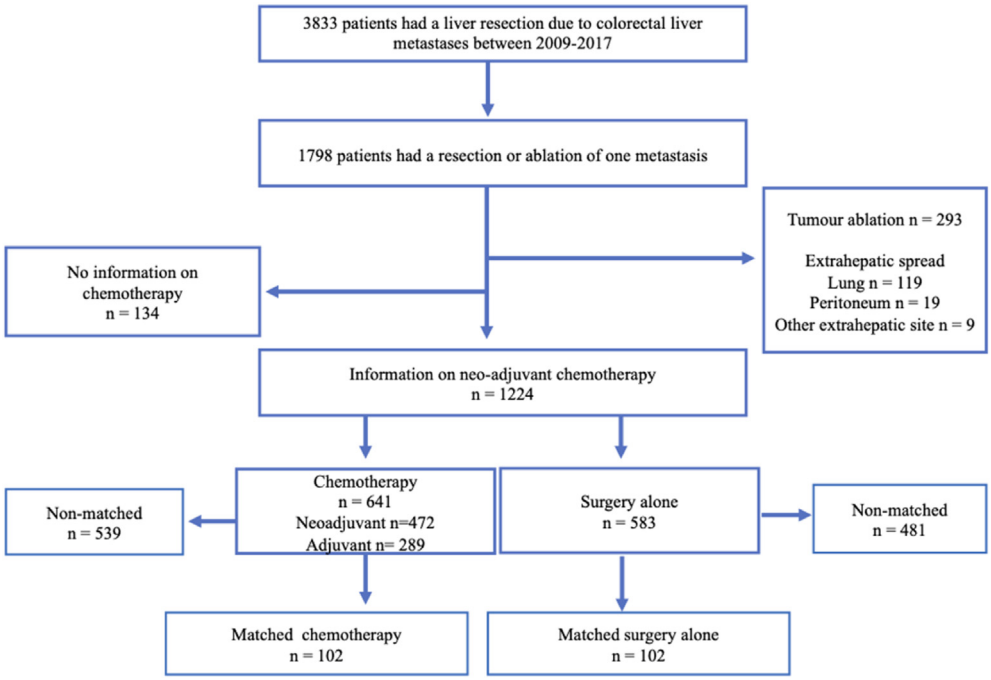

Fig. 1. Flow-chart of study population.

3. Results

3.1. Analysis of all patients before propensity score matching

The total number of patients who underwent a liver resection or ablation because of a solitary colorectal liver metastasis was 1798 (Fig. 1). Patients with extrahepatic metastases, treated with ablation or with missing data regarding oncological treatment were excluded. In total, 1224 patients were included in the analysis. Six-hundred and forty-one (52.4%) patients received chemotherapy, and 583 patients (47.6%) were treated with surgery alone.

3.2. Patient characteristics and tumor characteristics before matching

At baseline, differences were found between the groups in terms of age, ASA classification, and primary cancer tumor nodal (N) stages (Table 1). Before matching, median age, in the surgery alone group, was 71 (IQR 63–76) years, compared to 66 (IQR 60–72) years, in the chemotherapy group. Fifty-five per cent of patients in the surgery alone group were older than 70 years, compared to 35% in the chemotherapy group. The distribution of men and women was similar between the groups, with a majority of patients being men. Hundred and sixty-eight patients in the surgery alone group belonged to ASA group 3, compared to 120 patients in the chemotherapy group. Two-hundred and forty-nine patients (38.8%) in the chemotherapy group had synchronous disease, compared to 137 patients (23.5%) in the surgery alone group. A majority of the liver tumors in both the chemotherapy and the surgery alone groups, were smaller than 30 mm. Tumors larger than ≥50 mm were found in approximately 15% of patients.

3.3. Analysis of patients after propensity score matching

After matching two balanced groups were created with 102 patients in the chemotherapy group, and 102 patients in the surgery alone group (**Supplementary**, *Figs. S1a–1b*). In the matched cohort the median age was 69 years (IQR 64–74 years) in the chemotherapy group, and 71 years (IQR 64–76 years) in surgery alone group (Table 1). The distribution of men and women, was similar between the groups, and a majority were men. There was no difference in ASA classification or tumor size between the chemotherapy and surgery alone groups. Roughly, 80% of patients belonged to ASA classification two or three (chemotherapy n = 85, surgery alone n = 83). Seventy per cent of patients in respective group had liver tumors less than 30 mm in diameter. Eleven patients (10.8%) in the surgery alone group, and seven patients (6.9%) in the chemotherapy group, had liver tumors larger than 50 mm in diameter. Details of the whole cohort before matching is provided in the **Supplementary material** (Tables S1–S3).

3.4. Details of primary cancer operation and the liver resection

Less than ten patients, in each group, had an emergency colorectal resection (Table 2). Left sided colectomies or rectal resections were performed in 80 patients (78.4%) and 65 patients (63.7%) in the chemotherapy and surgery alone groups, respectively. Microscopically negative resections (R0) were obtained in the primary cancer operation in approximately 90% of patients in both groups (p = 0.983). With regards to the liver resection, R0 resection was achieved in 94 patients (92.2%) in the chemotherapy group, and in 78 patients (76.5%) in the surgery-alone group (p = 0.016). Differences between the treatment arms were seen in the type of liver

Table 1
Baseline patient and tumor characteristics (a) before and (b) after propensity score matching.

	(a) Cohort before matching (n = 1224)[b]			(b) Cohort after matching (n = 204)		
	Chemotherapy N = 641	Surgery N = 583	SMD[a]	Chemotherapy N = 102	Surgery alone N = 102	SMD[a]
Age (years)[c]	66 (60–72)	71 (63–76)	0.445	69 (64–74)	71 (64–76)	0.043
Age >70	226 (35.3)	321 (55.1)	0.406	50 (49.0)	56 (54.9)	0.117
Men	390 (60.8)	367 (63.0)	0.050	70 (69.1)	69 (67.2)	0.041
ASA						
1	144 (22.5)	88 (15.1)	0.285	17 (16.7)	19 (18.6)	0.110
2	373 (58.2)	314 (53.9)		61 (59.8)	64 (62.8)	
3	120 (18.7)	168 (28.8)		24 (23.5)	19 (18.6)	
4	1 (0.2)	4 (0.7)				
Missing	3 (0.5)	9 (1.5)				
Primary cancer T stage						
pT0-2	73 (11.4)	62(10.6)	0.063	3 (2.9)	2 (2.0)	0.157
pT3	335 (52.3)	228 (39.1)		15 (14.7)	10 (9.8)	
pT4	116 (18.1)	78 (13.4)		84 (82.4)	90 (88.2)	
Missing	117 (18.3)	215 (36.9)				
Primary cancer N stage						
pN0	151 (23.6)	194 (33.3)	0.476	37 (36.2)	39 (38.2)	0.050
pN1	217 (33.9)	111 (19.0)		43 (42.2)	35 (34.3)	
pN2	156 (24.3)	63 (10.8)		22 (21.6)	28 (27.5)	
Missing	117 (18.2)	215 (36.9)				
Synchronous	249 (38.8)	137 (23.5)	0.140	102 (100.0)	101 (99.0)	0.022
Metachronous	392 (61.2)	446 (76.5)		0	1 (1.0)	
Size liver metastasis (mm)[c]	24 (15–38)	20 (15–35)	0.178	20 (15–30)	20 (14–30)	0.119
<30	369 (57.6)	375 (64.3)			71 (69.6)	
30 - <50	150 (23.4)	117 (20.1)	0.153	71 (69.6)	20 (19.6)	0.111
50 - < 80	72 (11.2)	56 (9.6)		24 (23.5)	7 (6.9)	
≥80	37 (5.8)	21 (3.6)		7 (6.9)	4 (3.9)	
Missing	13 (2.0)	14 (2.4)				

ASA, American Society of Anesthesiologists.
[a] SMD, standardized mean difference. A SMD of less than 0.1 indicates a very small difference, and values between 0.1 and 0.3 a small difference.
[b] With percentages in parentheses unless indicated otherwise.
[c] Values are median (iqr).

Table 2
Details of primary cancer resection and liver surgery in the matched cohort (n = 204)[c].

	Chemotherapy (n = 102)	Surgery-alone (n = 102)	P value[a]
Emergency primary cancer operation	8 (7.8)	9 (8.8)	0.990
Type of colorectal resection			
Rectal resection	40 (39.2)	27 (26.5)	0.182
L colectomy	40 (39.2)	38 (37.3)	
R colectomy	17 (16.7)	33 (32.3)	
Colectomy, unspecified	4 (3.9)	3 (2.9)	
Unspecified	1 (1.0)	1 (1.0)	
Intraoperative blood loss (ml)[d]	300 (100–700)	250 (100–600)	0.806[b]
Primary colorectal cancer			
R0	93 (91.2)	94 (92.2)	0.983
R1	6 (5.9)	5 (4.9)	
*Unclear	3 (2.9)	3 (2.9)	
Neoadjuvant	80 (78.4)	NA	
Adjuvant	44 (43.1)	NA	
Response on neoadjuvant treatment			
1. Complete/partial	21 (26.3)		
2. Stable disease	6 (7.5)	NA	
3. Progress	2 (2.5)		
4. Unclear	51 (63.7)		
Type of liver resection			
Atypical	25 (24.5)	43 (42.2)	0.010
One segment	20 (19.6)	22 (21.6)	
Two segments	17 (16.7)	8 (7.8)	
Three segments	1 (1.0)	0	
Right hemihepatectomy	3 (2.9)	10 (9.8)	
Left hemihepatectomy	1 (1.0)	2 (2.0)	
Unclear/unspecified	35 (34.3)	17 (16.7)	
Intraoperative blood loss (ml)[c]	300 (150–813)	300 (113–688)	0.935[b]
Liver resection			
R0	94 (92.2)	78 (76.5)	0.016
R1	5 (4.9)	16 (15.6)	
*Unclear	3 (2.9)	8 (7.8)	

NA, not applicable.
[a] McNemar or McNemar-Bowker test, unless specified otherwise.
[b] Paired T test.
[c] With percentages in parentheses unless indicated otherwise.
[d] Values are median (iqr).

resection (p = 0.010). Forty-three patients (42.2%) in the surgery-alone group, compared to 25 patients (24.5%) in the chemotherapy arm had an atypical liver resection. Most patients had a minor liver resection (less than three liver segments). Four patients in the chemotherapy group, compared to 12 patients in the surgery alone group had a left or right hemihepatectomy.

3.5. Perioperative mortality and morbidity

There were five re-admissions (4.9%) in the chemotherapy group and eleven in the surgery alone group (10.8%) (p = 0.777) (Table 3). There were no mortalities within ninety days. There was no difference in morbidity, classified as Clavien-Dindo 3a or greater, between the groups. Nine patients (8.8%) in the chemotherapy group, and 14 patients (13.7%) in the surgery alone group suffered from a Clavien-Dindo 3a or greater.

3.6. Overall survival and follow-up

Median overall survival was 91 (95% CI 73–109) months in the chemotherapy group, and 78 (95% CI 37–119) months in surgery alone group (Fig. 2, stratified log-rank p = 0.652). Five-year survival was 48.0% in chemotherapy group, and 43.1% in the surgery alone group. For visual comparison of survival between the groups Kaplan Meier curves were constructed both before (Fig. 3) and after matching (Fig. 2). No differences were found in overall survival neither before nor after matching between the groups. Median follow-up time was 88 (IQR 76–100) months for the whole cohort.

Table 3
Postoperative complications and overall survival in the matched cohort after liver surgery (n = 204).

	Chemotherapy N = 102	Surgery alone N = 102	P value[a]
Re-admission within 30 days	5 (4.9)	11 (10.8)	0.250
90-day mortality	0	0	
Clavien Dindo			
3a	3 (2.9)	8 (7.8)	0.761
≥3b	6 (5.9)	6 (5.9)	
Median overall survival (months)	91 (73–109)	78 (37–119)	0.652[b]
Survival (%)			
1 year	93.1	90.2	
3 year	77.5	70.6	
5 year	48.0	43.1	

[a] McNemar test.
[b] Stratified log-rank test.

3.7. Univariable and multivariable analyses before and after matching

Before matching, ASA classification three, size of liver tumor, and primary cancer nodal stage were associated with worse overall

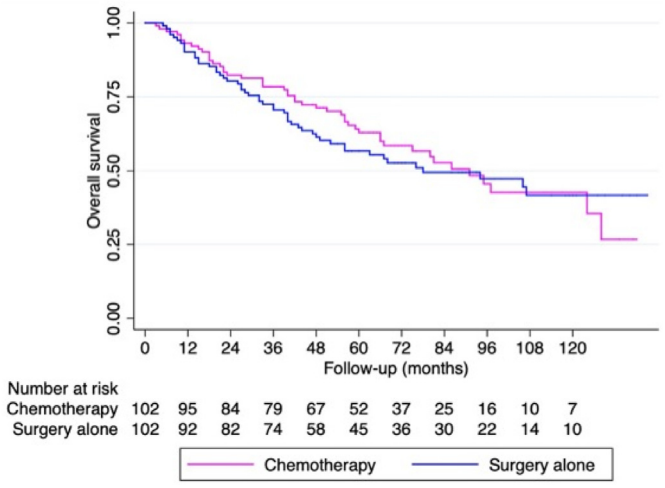

Fig. 2. Overall survival in the matched cohort. Median overall survival in the chemotherapy groups was 91 (95% CI 73–109) months, and in surgery alone 78 (95% CI 37–119) months. Stratified log rank p = 0.652.

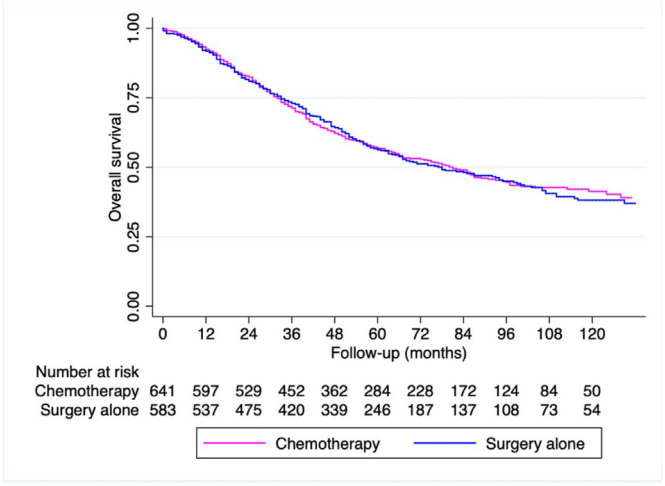

Fig. 3. Overall survival before matching. Median overall survival in the chemotherapy groups was 81 (95% CI 68–94) months, and in surgery alone 79 (95% CI 64–92) months. Log rank p = 0.922.

survival in the univariable analyses. In the multivariable analyses, ASA classification three, size of liver tumor (≥50 mm) and primary cancer nodal stage N1 and N2, negatively influenced overall survival (**Supplementary**, Table S3). In the univariable analysis in matched cohort, size of liver tumor and primary cancer nodal stage N2, were associated with worse overall survival. In the multivariable analyses, nodal stage N2 (HR 3.27, 95% CI 1.95–5.48) and tumor size 30-<50 mm (HR 1.88, 95% CI 1.19–2.99), and ≥50-<80 mm (HR 2.30, 95% CI 1.20–4.44), and ≥80 mm (HR 3.86, 95% CI 1.18–12.55) were associated with worse overall survival (**Supplementary**, Table S4).

4. Discussion

The present study examined the role of neoadjuvant and adjuvant treatment in patients with solitary colorectal liver metastasis without extrahepatic spread. In this nationwide population-based study there were no differences in overall survival between patients treated with surgery alone compared to patients who had received either neoadjuvant or adjuvant treatment.

Peri-operative chemotherapy in patients with colorectal liver metastases has become standard of care in many countries since the publication of the randomized controlled trial EORTC Intergroup 40983, EPOC trial [6]. This study randomized patients into either six cycles of FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin) before and after surgery, or to surgery alone. Although the study showed an improved progression-free survival in the chemotherapy-arm after three years, this did not translate into an improved overall survival after a median follow-up time of 8.5 years, [14]. In a recent, much awaited, randomized controlled trial (JCOG0603) Kanemitsu et al., examined whether adjuvant infusional fluorouracil, leucovorin, and oxaliplatin (m-FOLFOX) were superior to liver-surgery alone for colorectal liver metastases without extrahepatic spread [15]. The primary endpoint was disease-free survival, and secondary endpoints were overall survival, adverse events and pattern of recurrence. While the five-year follow-up showed an expected 13% absolute improvement in disease-free survival in m-FOLFOX group (p = 0.002), the study interestingly suggested a 14% decrease in overall survival for the same group (p = not significant). Moreover, approximately fifty per cent of the patients treated with m-FOLFOX suffered from severe adverse events, such as neutropenia, sensory neuropathy, and allergic reactions [15].

The potential benefits of giving neoadjuvant chemotherapy is questionable. In the literature, there is a discrepancy whether it confers prolonged overall survival, an increase in disease-free survival, and whether it is associated with an increase in morbidity and mortality after liver surgery. For example, Ayes et al., reports in a retrospective study from 2015, which included 363 patients, an improved overall survival (46 vs 33 months, p = 0.004) among high-risk patients, stratified according to Fong score [16,17]. Similarly, Zhu et al. published a retrospective study in 2014 with 466 patients, which suggests that patients classified as high-risk (for example with four or more liver metastases, and primary tumor stage 4) received a 5-year survival benefit (39% vs 33%, p = 0.028) if they received neoadjuvant treatment [16]. In a recent review and meta-analysis, which included only randomized controlled trials, which examined the efficacy of perioperative chemotherapy in patients with resected CRLM, found that perioperative chemotherapy improved disease-free survival, but not overall survival [18].

Furthermore, Adam et al., reports from a large retrospective study, that patients treated with neoadjuvant treatment were found to have an increased risk of postoperative complications, without an improved overall survival [19]. Likewise, Faron et al., reports no difference in disease-free survival or overall survival in patients with resectable CRLM receiving neoadjuvant treatment [20].

Marques et al., could not find an overall increase in perioperative morbidity due to neoadjuvant treatment. However, in patients who underwent major hepatectomy, defined as a resection of three or more liver segments, there was a trend towards higher morbidity and more severe complications (23.1% compared to 14.2%, p = 0.06). After adjusting for baseline characteristics between the two groups, the authors, conclude that neoadjuvant treatment was not found to improve disease-free survival or overall survival [2]. In another recent case-matched study from 2019, which included patients with synchronous resectable CRLM, 73 patients who had received upfront surgery, were compared with 73 patients who were treated with neoadjuvant chemotherapy before surgery. The authors conclude that neoadjuvant treatment did not reduce the risk of recurrence, but was associated with an increase in risk of intraoperative blood loss, and morbidity (24.7% versus 32.9%, p = 0.043) [21].

In a recent systematic review and meta-analysis by Liu et al. [22], which included seventeen retrospective studies, and the

randomized controlled trial by Nordlinger et al. [14], the study concluded that preoperative chemotherapy may confer an improved overall survival in patients at a high risk of recurrence. However, the authors also reflect on the difficulty to define high risk of recurrence, and the great heterogeneity of the studies included. By contrast, Di Martino et al., published a retrospective multicenter study in 2021, which rather counter-intuitively suggests that perioperative chemotherapy may prolong overall survival in patients with resectable CRLM in whom there is a low risk of recurrence [23].

In the present study no differences were found between the chemotherapy and surgery alone groups in postoperative morbidity and mortality. These results are similar to the findings in a recent population-based study by Elfrink et al., which also found that there were significant differences in the use of neoadjuvant systemic chemotherapy in patients with CRLM [24]. Another study which highlights this treatment disparity is a French population-based study from 2021, which showed that more than one third of all patients with synchronous CRLM did not receive chemotherapy; and that a majority of patients of advanced age (75 years of older) did not receive any antitumor treatment [25]. These findings, are similar to the present study.

Before matching nearly forty per cent of patients received neoadjuvant treatment in the setting of a resectable colorectal liver metastasis. Moreover, there was a clear difference in median age (66 years vs 71 years), and in percentage of patients that were 70 years or older (35.3 and 55.1%). Patients in the chemotherapy group were also more likely to be classified as ASA group one or two, and nearly 30% of patients in the surgery alone group belonged to ASA group three or four, compared to around 19% in the chemotherapy group. Hence, patients treated with chemotherapy were on the whole both younger and healthier.

The strength of the present paper is its population-based design with high accuracy and coverage, and long follow-up period. A primary limitation of the present study is that it was not possible to differentiate those patients with resectable disease from those with primarily unresectable disease. What exactly constitutes resectable disease, however, is disputed and is influenced by local practices, and the choice of treatment strategy varies across hepatobiliary centers [26]. Information regarding choice of neoadjuvant and adjuvant treatment, and number of cycles were also missing. On the other hand, the aim of the study, was not to assess the efficacy or tolerability of specific chemotherapy agents, by contrast the data provide an insight into daily practice (real-world data), which is not rigorously controlled by set inclusion/exclusion criteria that are part of a randomized controlled trial [27,28]. Given the observational nature of the study and the risk of unmeasured confounding variables, as well as the potential shortcomings of propensity score matching as a method the results should be interpreted with caution.

Notwithstanding, as pointed out by Booth et al. [29], the EPOC and JCOG0603 trials clearly call into the question the use of perioperative and postoperative chemotherapy in patients with resectable CRLM as the default standard. Hence, a more nuanced discussion with patients is necessary that focuses on the risk-benefit ratio of the treatment. Later image-based progression of the disease (improved disease-free survival) therefore has to be weighed against frequent clinic visits during the chemotherapy treatment, and the risk of side-effects, which may negatively impact on quality of life.

4.1. Conclusion

In the present population-based study patients who received neoadjuvant and or adjuvant treatment were compared with patients who had surgery alone for resectable solitary CRLM. To minimize imbalances between the two groups, a propensity score matching was performed. Chemotherapy treatment was not associated with a higher risk of morbidity or mortality, and did not confer a prolonged overall survival compared to surgery alone.

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CRediT authorship contribution statement

P. Frühling: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **J. Urdzik:** Formal analysis, Investigation, Methodology, Resources, Validation, Writing – review & editing. **B. Isaksson:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that this work was carried out without any source of financial support. The authors have nothing to declare, and no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.05.020.

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