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ABSTRACT

Introduction: Routine treatment with preoperative systemic chemotherapy (CTx) in patients with colorectal liver metastases (CRLM) remains controversial due to lack of consistent evidence demonstrating associated survival benefits. This study aimed to determine the effect of preoperative CTx on overall survival (OS) compared to surgery alone and to assess hospital and oncological network variation in 5-year OS.

Methods: This was a population-based study of all patients who underwent liver resection for CRLM between 2014 and 2017 in the Netherlands. After 1:1 propensity score matching (PSM), OS was compared between patients treated with and without preoperative CTx. Hospital and oncological network variation in 5-year OS corrected for case-mix factors was calculated using an observed/expected ratio.

Results: Of 2820 patients included, 852 (30.2%) and 1968 (69.8%) patients were treated with preoperative CTx and surgery alone, respectively. After PSM, 537 patients remained in each group, median number of CRLM; 3 [IQR 2–4], median size of CRLM; 28 mm [IQR 18–44], synchronous CLRM (71.1%). Median follow-up was 80.8 months. Five-year OS rates after PSM for patients treated with and without preoperative chemotherapy were 40.2% versus 38.3% (log-rank P = 0.734). After stratification for low, medium, and high tumour burden based on the tumour burden score (TBS) OS was similar for preoperative

Abbreviations: CRLM, colorectal liver metastases; PSM, propensity score matching; TBS, tumour burden score; OS, overall survival; CTx, chemotherapy; DHBA, Dutch Hepato Biliary Audit.

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chemotherapy vs. surgery alone (log-rank P = 0.486, P = 0.914, and P = 0.744, respectively). After correction for non-modifiable patient and tumour characteristics, no relevant hospital or oncological network variation in five-year OS was observed.

Conclusion: In patients eligible for surgical resection, preoperative chemotherapy does not provide an overall survival benefit compared to surgery alone.

1. Introduction

Surgical resection is considered the only potential cure for colorectal liver metastases (CRLM) and provides 5-year overall survival (OS) rates of approximately 50% in selected patients [1,2]. Recent improvements in operative techniques combined with more effective chemotherapy (CTx) increased the proportion of patients eligible for surgical resection, thereby improving survival rates [3,4].

The main advantage of preoperative CTx can be seen in patients with unresectable CRLM, where it is used as induction therapy to downstage CRLM [5,6]. The EORTC 40983 trial reported an improved disease-free survival (DFS) but without an OS benefit in patients with resectable CRLM treated with perioperative CTx [7]. More recently, these results were confirmed for adjuvant chemotherapy by the findings of the JCOG0603 trial reporting an improved DFS but no OS benefit in patients treated with adjuvant CTx compared to upfront surgery [8]. These studies were interpreted differently by various countries and even within countries.

Generalising these results to all patients with resectable metastases is difficult as both studies mainly included patients with a single liver metastasis, typically representing patients with more favourable prognoses [7,8]. With reference to the results of preceding RCTs, advocates of preoperative CTx will emphasize the improved DFS, whereas opponents of preoperative CTx will emphasize the lack of OS benefit. As a result, there is considerable practice variation in the administration of preoperative chemotherapy [9]. The use of real-world data can be informative in capturing additional outcomes that are not identified by these RCTs [10].

The aim of this nationwide population-based study was to assess if preoperative CTx was associated with improved 5-year overall survival compared to surgery alone stratified to tumour burden score. Additionally, the variation between hospitals and oncology networks in 5-year OS was assessed.

2. Methods

This nationwide, population-based study was conducted with data from the Dutch Hepato Biliary Audit (DHBA) registry, Vektis, and the Dutch Municipal Personal Records Database (BPR). Since 2013, the DHBA is a compulsory clinical audit that registers all patients undergoing surgery with the intent of liver resection or thermal ablation [11]. In 2017 data was verified, and data completeness was estimated at 97% [12]. In the Netherlands, hospitals are required to perform a minimum of 20 liver resections per year. Seven oncological networks exist, these include at least one tertiary referral centre and several regional hospitals. Oncological networks have been established to optimize collaboration and decrease variation [13]. The DHBA scientific committee approved this study. No ethical approval or informed consent was needed under the Dutch law, as data was handled anonymously.

The DHBA does not contain long-term follow-up data. Therefore, the DHBA was combined with the Vektis and BPR databases to assess overall survival. Vektis is the Dutch national claim database for health insurance companies and receives the date of death of all the deceased with healthcare insurance from the BPR, covering over 99% of Dutch inhabitants. However, in three hospitals (10.2%) linkage with the Vektis database was not possible; therefore, for assessment of overall survival in patients treated in these hospitals, DHBA data was directly linked with the BPR database. Data of colorectal resections are registered in a separate audit (Dutch Colorectal Audit). Merging of data is prohibited due to general data protection regulation (GDPR). This means that data on the site of the colon tumour (left vs. right), and pathological T stage are missing. N stage was requested in the DHBA if available.

Datasets were combined based on unique personal citizen service numbers. To guarantee privacy, linkage of datasets was performed by a third-trusted party Medical Research Data Management (MRDM). After linkage of the datasets, follow-up data of 99.3% of the patients in the DHBA was covered. Patients not registered as deceased at the time of merging the datasets (2022, July) were assumed to be alive.

Overall survival was calculated from the date of surgery to the date of death of any cause. Date of start of preoperative CTx is not registered in the DHBA.

2.1. Patients

All patients of ≥18 years old, who underwent liver resection for CRLM between 1st of January 2014 and the 31st of December 2017 were included in this study. Patients with a history of liver resection or treated with ablation alone were excluded. Furthermore, patients with missing essential data on preoperative chemotherapy or the type of tumour treatment were excluded. For analyses of overall survival, patients with in-hospital or 30-day mortality were excluded.

At the time included patients were operated on, the Dutch guidelines for (metastatic) colorectal cancer disclosed no clear preference for perioperative chemotherapy. For patients with primarily resectable metastases chemotherapy was not considered standard treatment, yet definitions of resectability were lacking. This contributed to practice variation between centres and networks [14]. Adjuvant chemotherapy was and is not supported and therefore rare as opposed to many countries where it is common practice.

2.2. Treatment groups

For analyses, patients were divided into two treatment groups: patients who received preoperative CTx and liver resection and those who underwent surgery without receiving preoperative CTx. Preoperative chemotherapy was defined as any form (e.g., neo-adjuvant or induction therapy) of CTx administrated as a treatment for CRLM prior to surgery. It is difficult to distinguish between true neo-adjuvant or induction therapy, and possibly these definitions overlap. This results from nuances in the presentation of the individual patient, which can blur the boundaries of what is meant by upfront resectable [15].

In a subsequent part of the patients registered in the DHBA,

indication for preoperative chemotherapy was reported (as neo-adjuvant or induction), planned additional analyses for this share of patients on OS were performed to account for possible bias by indication for preoperative chemotherapy.

2.3. Variables for analyses

Patient characteristics used for analysis included sex, age, body mass index (BMI), American Society of Anaesthesiologists (ASA) grade, and Charlson Comorbidity Index (CCI). Tumour characteristics used for analysis included number of CRLM, diameter of the largest CRLM before tumour-specific treatment, synchronous or metachronous metastases, CEA, pathological N-stage of primary tumour, location of primary tumour (rectal/colon), bilobar disease, and extrahepatic disease. In the registry location within the colon was not specified (i.e., left-sided or right-sided). Treatment characteristics used for analysis included surgical procedure (open/laparoscopic), major liver resection (resection of $\geq$3 adjacent Couinaud segments), and type of hospital where treatment took place (tertiary referral centre or regional hospital).

2.4. Statistical analyses

Categorical variables were presented as frequencies and proportions. In the unmatched and matched cohort, the significance of variables was tested using the Chi-square test or Fisher's exact test for categoric variables and the student's t-test for continuous data.

To compare outcomes of patients treated with or without preoperative chemotherapy and reduce baseline differences in these groups propensity score matching (PSM) was performed. Propensity scores were obtained from a logistic regression model. Variables used to calculate propensity scores included age, ASA score, extrahepatic disease, location of primary tumour, timing of CRLM (synchronous *vs.* metachronous), number of CRLM, diameter of largest CRLM before start of tumour specific treatment, and major liver resection. N-stage of primary tumour and CEA-level were not used as variables in PSM analysis since over 25% data was missing. This is because no information was available when colorectal resections were performed after the liver resection. PSM was performed with a 1:1 ratio using the nearest neighbour method with a calliper of 0.07. All patients without a matching counterpart were excluded from the analyses. Balance after PSM was assessed using standardised mean difference (SMD). SMD <0.10 indicates an optimal balance of confounding factors.

Kaplan-Meier survival analyses with the log-rank test were used to compare overall survival between patients treated with preoperative CTx and surgery alone. A planned subgroup analysis was performed in the original unmatched and matched cohort for three zones of the Tumour Burden Score (TBS). The TBS is calculated as $(TBS)^2 = (\text{diameter of largest CRLM in cm})^2 + (\text{number of CRLM})^2$. The TBS is stratified into a low (TBS of 0–2), medium (TBS of 3–8) and high (TBS $\geq$9) tumour burden [16].

Between hospital and oncology network variation in five-year OS corrected for case-mix factors was calculated using an observed/expected ratio. In this O/E ratio, the authors accounted for the possibility of censoring since this is one of the most distinguished features of survival data. The observed (O) was calculated by the number of events for each patient at the specified follow-up period. The expected (E) was the number of events expected in a centre or network, based on the number of patients, their follow-up, and their patient and tumour characteristics, when the centre performed according to the benchmark. The benchmark was determined by fitting a single Cox model to the complete data of all centres, representing the average performance of all centres. More details are described previously [17]. An O/E ratio above 1 indicated that a hospital's or network's five-year OS was worse than expected. The 95% confidence intervals were calculated to indicate whether a hospital's or network's performance was statistically different from the other hospitals.

All analyses were performed using R version 4.2.0 (R Core Team (2021). (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 2820 patients were included in this study (Fig. 1). Of these patients, 852 (30.2%) received preoperative CTx, and 1968 (69.8%) were treated with surgery alone.

Patients treated with preoperative CTx were younger, had more CRLM, higher TBS, greater diameter of CRLM, and more often had synchronous metastases, bilobar metastases, and extrahepatic disease compared to patients who underwent surgery alone (Table 1). In the surgery-alone group none of the patients received treatment with adjuvant CTx.

3.1. Propensity score matching

After propensity score matching, 537 patients remained in each group. SMD was below 0.10 for most patients and tumour characteristics, except histopathology of the liver ($P < 0.001$, SMD = 0.288), N-stage of the primary tumour ($P = 0.080$, SMD = 0.173) and CEA-level ($P = 0.019$, SMD = 0.173) (Table 1).

3.2. Treatment effects of preoperative chemotherapy on overall survival

The median follow-up time in the preoperative CTx group was 84.3 months (95% CI 73.3–95.4) versus 83.6 months (95% CI 73.9–96.7) in the surgery alone group. Five-year OS rates before matching for preoperative CTx versus surgery alone were 49.1% versus 36.9% (*P < 0.001)*. Within the original unmatched cohort, median survival in the preoperative CTx cohort was 39.9 months (95% CI 35.9–45.1 versus 58.1 months (95% CI 54.0–63.9) in the surgery alone cohort.

After PSM, median follow-up time in the preoperative CTx cohort was 83.3 months (95% CI 72.9–92.7) versus 82.6 months (95% CI 73.2–93.9) in the surgery alone group. Five-year OS for preoperative CTx versus surgery alone was 43.3% versus 42.6% ($P = 0.734$), respectively (Fig. 2). In the matched cohort, the median survival time in the preoperative CTx cohort was 43.3 months (95% CI 37.7–47.9) versus 42.6 months (95% CI 37.3–48.2) in the surgery alone cohort. Additional OS analyses to account for possible bias by indication of preoperative chemotherapy showed no differences in OS between treatment groups (Supplementary Figs. 1 and 2). The purpose of chemotherapy (i.e., neoadjuvant or induction) was clearly stated in the patients included in these analyses.

3.3. Treatment effects of preoperative chemotherapy on overall survival in sub-groups based on tumour burden score (TBS)

After stratification for TBS score, preoperative chemotherapy did not improve overall survival. In the unmatched cohort five-year OS in the TBS low group was 52.9% in the preoperative CTx group and 59.0% in the surgery alone group, ($P = 0.0160$). For TBS medium, and TBS high burden five-year OS rates were, respectively, 37.2% vs. 42.6% (*P = 0.039*), 31.9% vs. 31.9% ($P = 0.914$) (Fig. 3).

Five-year OS for TBS low, medium and high group after PSM were 54.8%, 37.3% and 35.6% in the preoperative CTx group, 49.4%, 36.9% and 31.6% in the surgery alone group ($P = 0.486$, $P = 0.914$, and $P = 0.744$), respectively. Median survival time after PSM for TBS

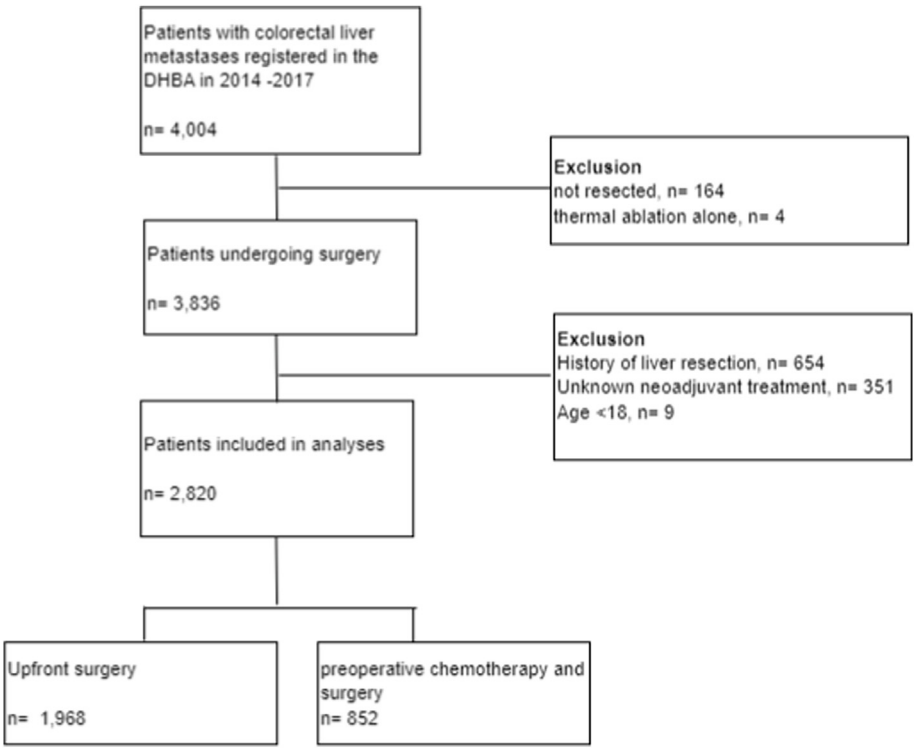

Fig. 1. Flowchart of this study.

low, medium and high were 75.2 months (95% CI 49.8 - NA), 39.3 months (95% CI 33.0–45.1) and 40.8 months (95% CI 35.0–62.9) in the preoperative CTx group and 59.7 months (95% CI 47.1 - NA), 39.7 months (95% CI 34.5–46.8), and 36.1 months (95% CI 21.1 – NA) in the surgery alone group, respectively.

3.4. Synchronous versus metachronous CRLM

After PSM, no difference in overall survival was observed in patients treated with and without preoperative CTx in subgroups of synchronous CRLM ($p = 0.55$) and metachronous ($p = 0.13$) CRLM, respectively (Supplementary Figs. 4 and 5).

3.5. Hospital and oncology network variation in OS

Unadjusted hospital variance in OS ranged between 0.67 and 1.20 (Supplementary Fig. 3). Unadjusted oncological network variance ranged between 0.95 and 1.04 (Supplementary Fig. 6A). After correction for case-mix factors, adjusted hospital variance ranged between 0.68 and 1.26 (Fig. 4), and adjusted network variance ranged between 0.97 and 1.06 (Supplementary Fig. 6B). No hospital or oncological network fell out of the 95% confidence interval of variance for five-year OS.

4. Discussion

In this analysis of real-world data preoperative chemotherapy did not improve survival as compared to surgery alone. In subanalyses in which patients were divided according to tumour burden scores or recorded intention of treatment (induction or neoadjuvant) preoperative chemotherapy did not prolong overall survival in patients either. Variation between hospitals and networks in use of preoperative chemotherapy did not lead to variation in overall survival after correction for case-mix.

Randomised Controlled Trials (RCTs) represent the gold standard in the assessment of the efficacy of a therapy, but a major criticism is that results cannot always be extrapolated to the real-world setting due to strict selection criteria [10]. Results of this real-world data study were concordant with important RCTs (EORTC 40983 trial and JCOG0603 trial), describing no OS benefit in patients treated with perioperative chemotherapy or surgery alone [7,8,18]. The same results were also described in a Swedish real-world data study regarding patients with solitary CRLM [18]. Unfortunately, results on DFS could not be confirmed since the DHBA does not contain any information on disease-free survival of all registered patients. Moreover, Ecker et al. described a poor correlation between disease-free survival and overall survival in patients with CRLM since development of recurrent CRLM after liver resection did not reflect non-curability [19].

In theory, administration of neoadjuvant chemotherapy in patients with resectable CRLM could reduce risk of recurrence by treatment of micro-metastatic disease, also it could downsize the CRLM and improve obtaining negative resection margins [6]. However, in practice, up to 75% of all patients who undergo a liver resection with curative intent endure recurrent intrahepatic disease [2,19–21]. Previous studies found no differences in intrahepatic recurrent disease in patients treated with or without perioperative chemotherapy, but they observed an overall survival benefit in high-risk patients [22]. Prognosis of patients with recurrent disease is favourable if local treatment of recurrent metastases is possible. This could explain why earlier mentioned improved DFS in patients treated with preoperative chemotherapy did not translate into improved OS [6,23].

Several small observational studies suggested a potential survival benefit of administering preoperative chemotherapy to patients with high-risk of recurrence [24–30]. The current study accounted for 'low-, medium- and high-risk patients' by stratification based on TBS and did not observe a beneficial effect of

Table 1
Baseline characteristics of patients with CRLM treated with surgery alone, or preoperative systemic chemotherapy and surgery between 2014 and 2017. Before and after propensity score matching.

Table 1	Before PSM		p-value	SMD	After PSM		p-value	SMD
Factor	**Surgery alone** N = 1968	**Preoperative chemotherapy** N = 852			**Surgery alone** N = 537	**Preoperative chemotherapy** N = 537		
Patient characteristics								
Sex			0.317	0.068			0.574	0.038
Male	1218 (61.9)	519 (60.9)			331 (61.6)	321 (59.8)		
Missing	9 (0.5)	1 (0.1)						
Age (years)			**<0.001**	0.379			0.968	0.031
<50	106 (5.4)	78 (9.2)			45 (8.4)	46 8.6)		
50-64	597 (30.3)	342 (40.1)			204 (38.0)	197 (36.7)		
65-80	1063 (54.0)	408 (47.9)			268 (49.9)	272 (50.7)		
>80	202 (10.3)	24 (2.8)			20 (3.7)	22 (4.1)		
Charlson Comorbidity Index			**<0.001**	0.157			0.092	0.108
CCI 0/1	1484 (75.4)	697 (81.8)			419 (78.0)	442 (82.3)		
CCI 2+	484 (24.6)	155 (18.2)			118 (22.0)	95 (17.7)		
BMI *			**<0.001**	0.179			0.057	0.117
Mean (SD)	26.29 (4.33)	25.54 (4.02)			25.93 (4.35)	25.45 (3.83)		
ASA score *			**0.012**	0.125			0.730	0.026
ASA 1/2	1584 (80.5)	722 (84.7)			456 (84.9)	461 (85.8)		
ASA 3+	364 (18.5)	119 (14.0)			81 (15.1)	76 (14.2)		
Missing	20 (1.0)	11 (1.3)						
Tumour characteristics								
Extrahepatic disease			**<0.001**	0.216			0.596	0.038
Yes	196 (10.0)	143 (16.8)			466 (86.8)	459 (85.5)		
No	1738 (88.3)	686 (80.5)			71 (13.2)	78 (14.5)		
Missing	34 (1.7)	23 (2.7)						
CEA			**<0.001**	0.202			**0.019**	0.173
<200	1465 (74.4)	607 (71.2)			378 (70.4)	411 (76.5)		
>200	43 (2.2)	53 (6.2)			20 (3.7)	25 (4.7)		
Missing	460 (23.4)	192 (22.5)			139 (25.9)	101 (18.8)		
Location primary tumour			0.061	0.093			0.290	0.068
Colon	1272 (64.6)	518 (60.8)			330 (61.5)	312 (58.1)		
Rectal	694 (35.3)	331 (38.8)			207 (38.5)	225 (41.9)		
Missing	2 (0.1)	3 (0.4)						
N-stage primary tumour			**<0.001**	0.449			0.080	0.177
pN0	622 (31.6)	161 (18.9)			127 (23.6)	109 (20.3)		
pN1	537 (27.3)	192 (22.5)			147 (27.4)	131 (24.4)		
pN2	385 (19.6)	154 (18.1)			100 (18.6)	93 (17.3)		
pNx	10 (0.5)	4 (0.5)			1 (0.2)	4 (0.7)		
Missing	414 (21.0)	341 (40.0)			162 (30.2)	200 (37.2)		
Timing of metastases			**<0.001**	0.709			0.840	0.016
Metachronous	1131 (57.5)	212 (24.9)			155 (28.9)	159 (29.6)		
Synchronous	821 (41.7)	636 (74.6)			382 (71.1)	378 (70.4)		
Missing	16 (0.8)	4 (0.5)						
Bilobar disease			**<0.001**	0.542			0.363	0.087
Yes	816 (41.5)	574 (67.4)			120 (22.3)	102 (19.0)		
No	536 (27.2)	141 (16.5)			346 (64.4)	356 (66.3)		
Missing	616 (31.3)	137 (16.1)			71 (13.2)	79 (14.7)		
Number of tumours			**<0.001**	0.998			0.913	0.060
1	1031 (52.4)	149 (17.5)			123 (22.9)	124 (23.1)		
2	459 (23.3)	152 (17.8)			125 (23.3)	128 (23.8)		
3	194 (9.9)	122 (14.3)			101 (18.8)	89 (16.6)		
4	103 (5.2)	94 (11.0)			69 (12.8)	73 (13.6)		
≥5	149 (7.6)	294 (34.5)			119 (22.2)	123 (22.9)		
Missing	32 (1.6)	41 (4.8)						
Diameter of the largest tumour in mm			**<0.001**	0.333			0.456	0.077
<20	581 (29.5)	192 (22.5)			145 (27.0)	153 (28.5)		
20-50	984 (50.0)	370 (43.4)			282 (52.5)	262 (48.8)		
>50	216 (11.0)	188 (22.1)			110 (20.5)	122 (22.7)		
Missing	187 (9.5)	102 (12.0)						
TBS			**<0.001**	0.709			0.846	0.055
1 - 2	735 (37.3)	105 (12.3)			89 (16.6)	94 (17.5)		
3–8	972 (49.4)	492 (57.7)			402 (74.9)	390 (72.6)		
≥9	48 (2.4)	119 (14.0)			39 (7.3)	45 (8.4)		
Missing	213 (10.8)	136 (16.0)			7 (1.3)	8 (1.5)		
Histopathology of the liver parenchyma			**<0.001**	0.267			**<0.001**	0.288
Normal liver	1364 (69.3)	492 (57.7)			374 (69.6)	311 (57.9)		
Steatosis	292 (14.8)	174 (20.4)			79 (14.7)	112 (20.9)		
Other	50 (2.5)	50 (5.9)			15 (2.8)	38 (7.1)		
Missing	262 (13.3)	136 (16.0)			69 (12.8)	76 (14.2)		
Treatment characteristics								
Surgical approach			**<0.001**	0.444			**0.002**	0.219
Open	1363 (69.3)	742 (87.1)			420 (78.2)	463 (86.2)		

(*continued on next page*)

Table 1 (*continued*)

Table 1	Before PSM		p-value	SMD	After PSM		p-value	SMD
Factor	**Surgery alone** N = 1968	**Preoperative chemotherapy** N = 852			**Surgery alone** N = 537	**Preoperative chemotherapy** N = 537		
Laparoscopic	600 (30.5)	108 (12.7)			116 (21.6)	72 (13.4)		
Missing	5 (0.3)	2 (0.2)			1 (0.2)	2 (0.4)		
Major liver resection			**<0.001**	0.299			0.688	0.029
Yes	361 (18.3)	265 (31.1)			161 (30.0)	154 (28.7)		
Timing of resection			**<0.001**	0.633			**<0.001**	0.287
Primary first	1452 (73.8)	422 (49.5)			324 (60.3)	286 (53.3)		
Liver First	207 (10.5)	300 (35.2)			113 (21.0)	178 (33.1)		
Combined	269 (13.7)	108 (12.7)			90 (16.8)	63 (11.7)		
Missing	40 (2.0)	22 (2.6)			10 (1.9)	10 (1.9)		
Type of hospital*			**<0.001**	0.395			**<0.001**	0.275
Other hospitals	1222 (62.1)	364 (42.7)			322 (60.0)	249 (46.4)		
Tertiary Centres	746 (37.9)	488 (57.3)			215 (40.0)	288 (53.6)		
Annual hospital volume			**<0.001**	0.351			**<0.001**	0.305
20-39	1260 (64.0)	419 (49.2)			341 (63.5)	272 (50.7)		
40–59	510 (25.9)	270 (31.7)			145 (27.0)	168 (31.3)		
60 - 79	156 (7.9)	104 (12.2)			40 (7.4)	70 (13.0)		
>80	42 (2.1)	59 (6.9)			11 (2.0)	27 (5.0)		
Adjuvant chemotherapy			**<0.001**	0.770			**<0.001**	0.742
Yes	0 (0.0)	111 (13.0)			0 (0.0)	72 (13.4)		

Bold p-values indicates a statistical significant values ($p < 0.05$). Abbreviations: Standardised mean differences (SMD), BMI indicates body mass index; ASA score indicates American Association of Anaesthesiologist; type of hospital tertiary centre indicates hospitals with the highest expertise on oncological surgery.

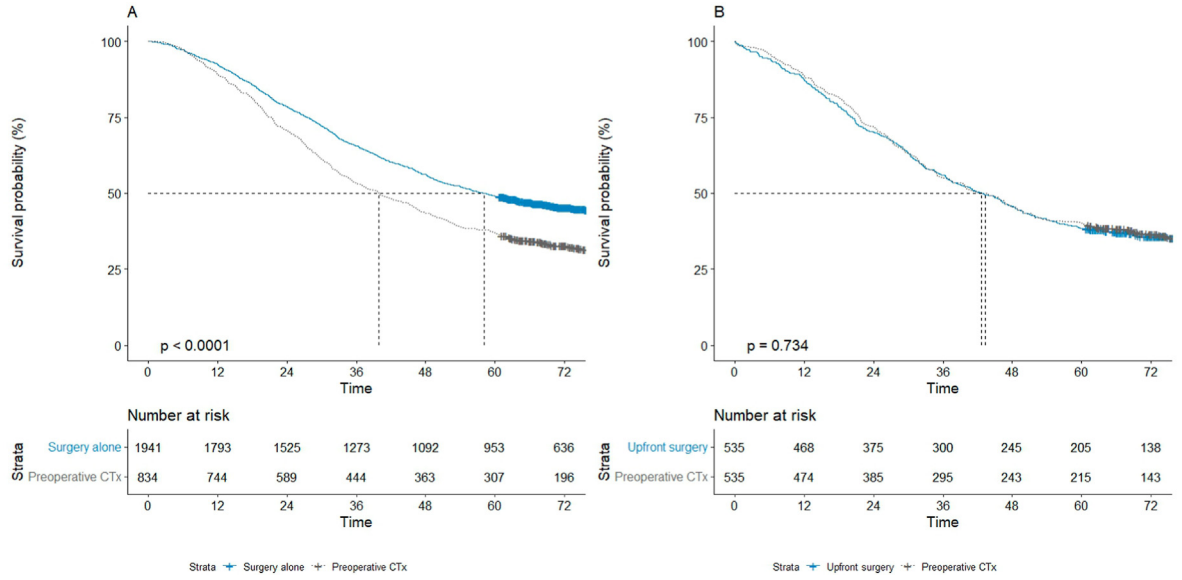

Fig. 2. Kaplan – Meier survival curves presenting OS of patients with CRLM receiving preoperative systemic chemotherapy and surgery or surgery alone between 2014 and 2017. A. OS for surgery alone (blue) and surgery and preoperative CTx (grey) before matching B. OS after PSM for surgery alone (blue) and surgery and preoperative CTx (grey). Time in months.

preoperative CTx within these groups [16]. The discrepancy in described survival benefits of preoperative CTx in high-risk patients could be attributed to the absence of uniform criteria to define high risk; different risk scores were used in literature based on various clinicopathological and biological factors. Clinical risk scores have been validated to predict overall survival in patients, but have not been validated to guide decisions in the management of CRLM, such as treatment with preoperative chemotherapy [31]. Moreover, decision on which patients need to be treated with preoperative CTx probably depends more on the clinical experience and personal preference of multidisciplinary teams rather than outcomes of scoring systems only [24–29,32].

Determined by previous studies, various results and interpretations on the use of preoperative chemotherapy in resectable CRLM could influence the different personal preferences of multidisciplinary teams. Consequently, practice variation occurs. Elfrink et al. reported significant practice variation (2%–55%) regarding the use of preoperative CTx between Dutch hospitals [14]. However, this did not result in varying survival between hospitals or oncological networks before and after adjustment for case-mix factors. These results, can be interpreted as reassuring as patients seem to have a rather similar chance of survival wherever they are treated in the Netherlands. Caution is needed, however, as residual confounding cannot be ruled out. Only the patients who finally underwent resection were included.

The authors advocate that *routine* use of chemotherapy in patients with upfront, clearly resectable, CRLM should stop [7,8]. They would like to emphasize that this does not mean that preoperative

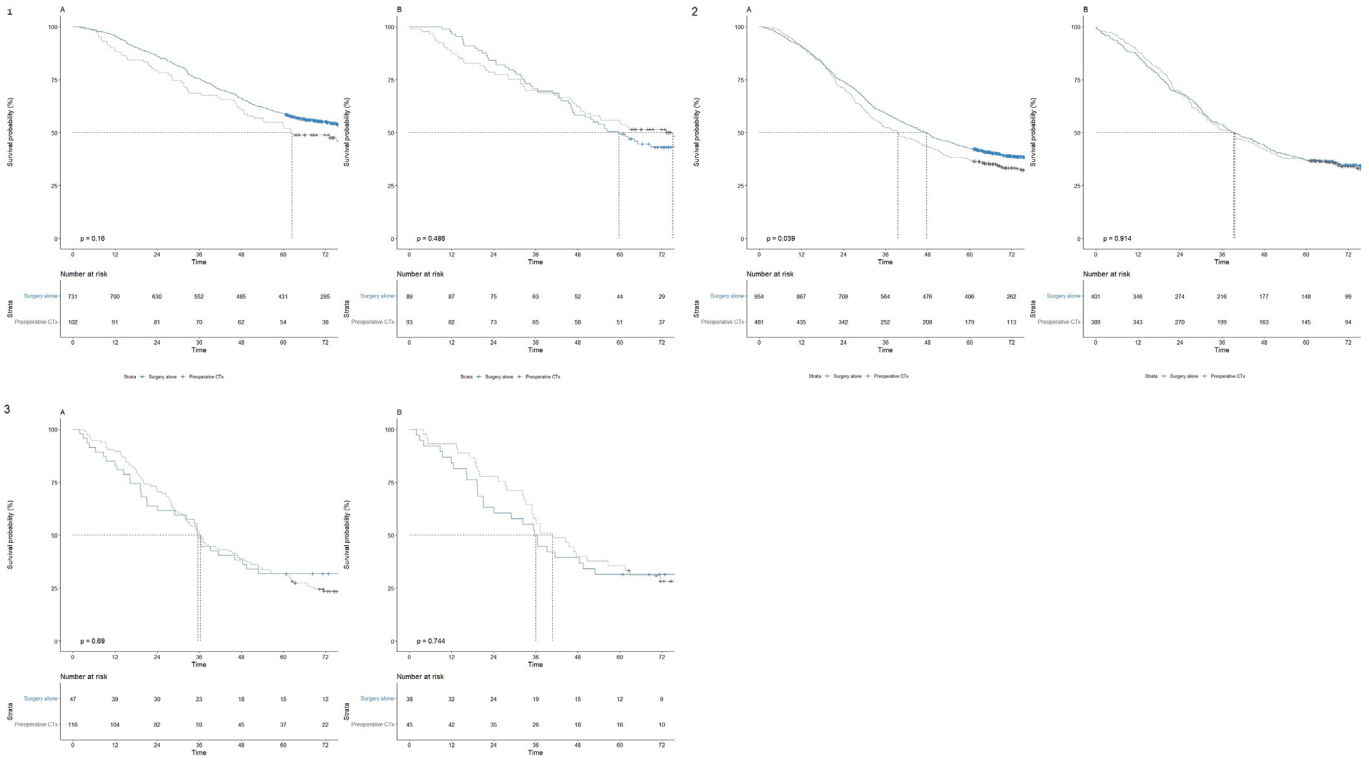

Fig. 3. Kaplan − Meier survival curves presenting OS of patients with CRLM receiving preoperative CTx and surgery alone between 2014 and 2017 stratified for Tumour Burden Score (TBS) in the unmatched cohort. A: the unmatched cohort, B: PS matched cohort. 1. OS for preoperative CTx (grey) and surgery alone (blue) after stratification for TBS 0−2. 2. OS for preoperative CTx (grey) and surgery alone (blue) after stratification for TBS 3−8. 3. OS for preoperative CTx (grey) and surgery alone (blue) after stratification for TBS ≥9. Time in months.

chemotherapy should never been given. When downstaging of the primary tumour or metastases is needed, there is a clear indication to start with chemotherapy [6]. When oncologically unfavourable characteristics such as extrahepatic disease or multiple metastases are present, chemotherapy is likely needed. The main aim of chemotherapy here is to rule out patients with rapidly progressive and unfavourable metastatic disease and, therefore, would not benefit from a potential morbid surgical resection. The international HPB community should put effort into determining these high-risk patients.

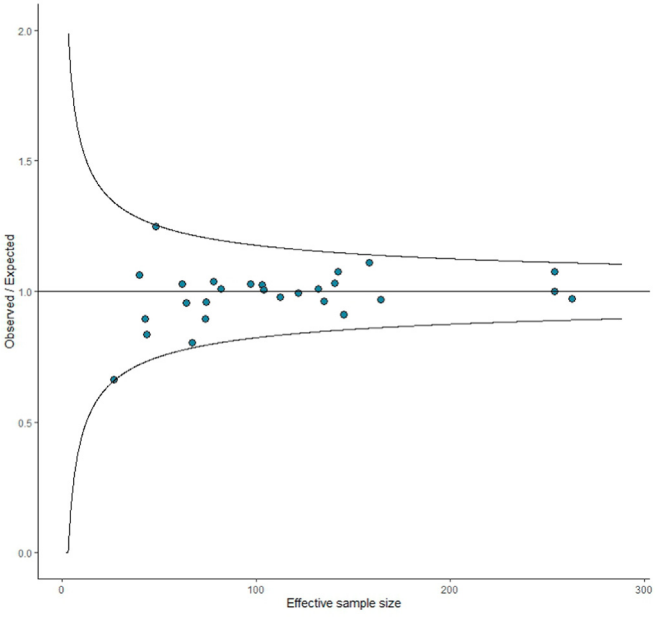

Fig. 4. Benchmarked five-year OS between hospital in the Netherlands for patients with CRLM between 2014−201. Hospital variation in five-year OS between 2014 and 2017 corrected for case-mix factors*
*Case-mix correction for the following variables: Age, sex, BMI, ASA score, Charlson Comorbidity score, Number of CRLM, Diameter of largest CRLM, major liver resection, Timing of disease, Extrahepatic disease, location of primary tumour.

This study was unique by the fact that it used real-world (audit) data of all patients who underwent liver resection, reflecting daily practice in the Netherlands. These results complement the evidence from RCTs with information about use or preoperative chemotherapy on a broader population. Limitations of the present study include the use of clinical audit data. Important details, including the decision to administer chemotherapy of the multidisciplinary team (MDT), exact reason for chemotherapy, start date, type, and number of cycles of chemotherapy, were lacking. PSM was used to balance groups but could not rule out residual confounding. Patients who were not eligible for liver resection after chemotherapy were missing. The DHBA did not register any data on recurrence, meaning disease-free survival could not be analysed. As expected, few patients were available for analysis of the effect of preoperative chemotherapy on survival in the high tumour burden score group. Most of these patients did get systemic treatment first, which aligns with the common perception that patients with the highest risk of recurrence need perioperative chemotherapy. Unfortunately, several attempts to study this high-risk group in a randomised settings failed [33]. The current study could not provide enough evidence to answer whether patients with high TBS scores and resectable CRLM should get preoperative chemotherapy. These data have been included in a national meeting of liver surgeons in the Netherlands. The authors are keen to observe a decline

in the use of preoperative chemotherapy in these patients in the Netherlands over the following years.

5. Conclusion

In conclusion, this study did not observe an overall survival benefit for patients who received preoperative chemotherapy compared to surgery alone in real-world data. Therefore, routine use of preoperative CTx should not be recommended in patients with low and medium TBS who are eligible for surgical resection.

CRediT authorship contribution statement

Michelle.R. de Graaff: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Joost M. Klaase:** Conceptualization, Data curation, Writing – review & editing, Formal analysis, Supervision. **Ronald M. van Dam:** Conceptualization, Data curation, Writing – review & editing. **Koert F.D. Kuhlmann:** Conceptualization, Data curation, Writing – review & editing. **Geert Kazemier:** Conceptualization, Data curation, Writing – review & editing. **Rutger-Jan Swijnenburg:** Conceptualization, Data curation, Writing – review & editing. **Arthur K.E. Elfrink:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Cees Verhoef:** Conceptualization, Data curation, Writing – review & editing. **J.Sven Mieog:** Conceptualization, Data curation, Writing – review & editing. **Peter B. van den Boezem:** Conceptualization, Data curation, Writing – review & editing. **Paul Gobardhan:** Conceptualization, Data curation, Writing – review & editing. **Arjen M. Rijken:** Conceptualization, Data curation, Writing – review & editing. **Daan J. Lips:** Conceptualization, Data curation, Writing – review & editing. **Wouter G.K. leclercq:** Conceptualization, Data curation, Writing – review & editing. **Hendrik A. Marsman:** Conceptualization, Data curation, Writing – review & editing. **Peter van Duijvendijk:** Conceptualization, Data curation, Writing – review & editing. **Joost A.B. van der Hoeven:** Conceptualization, Data curation, Writing – review & editing. **Maarten Vermaas:** Conceptualization, Data curation, Writing – review & editing. **Marcel den Dulk:** Conceptualization, Data curation, Writing – review & editing, Formal analysis, Supervision. **Dirk J. Grünhagen:** Conceptualization, Data curation, Writing – review & editing, Formal analysis, Supervision. **Niels F.M. Kok:** Conceptualization, Data curation, Writing – review & editing, Formal analysis, Supervision. **Carlijn I. Buis:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Jeroen Hagendoorn:** Conceptualization, Data curation, Writing – review & editing. **Wouter J.M. Derksen:** Conceptualization, Data curation, Writing – review & editing. **Hans Torrenga:** Conceptualization, Data curation. **Eric Manusama:** Conceptualization, Data curation, Writing – review & editing. **N. Tjarda van Heek:** Conceptualization, Data curation, Writing – review & editing. **Steven J. Oosterling:** Conceptualization, Data curation, Writing – review & editing. **Koop Bosscha:** Conceptualization, Data curation, Writing – review & editing. **Andries E. Braat:** Conceptualization, Data curation, Writing – review & editing. **Frederik J.H. Hoogwater:** Conceptualization, Data curation, Writing – review & editing. **Esther C.J. Consten:** Conceptualization, Data curation, Writing – review & editing. **Christiaan van der Leij:** Conceptualization, Data curation, Writing – review & editing. **Mark C. Burgmans:** Conceptualization, Data curation, Writing – review & editing. **Mike S.L. Liem:** Conceptualization, Data curation, Writing – review & editing. **Eric J.Th Belt:** Conceptualization, Data curation, Writing – review & editing. **Gijs A. Patijn:** Conceptualization, Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.05.007.

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