https://doi.org/10.1016/j.hpb.2022.09.001 HPB

ORIGINAL ARTICLE

A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden

Petter Frühling[1], Cecilia Strömberg[2], Bengt Isaksson[1] & Jozef Urdzik[1]

[1]Department of Surgical Sciences, Uppsala University, Uppsala, and [2]Division of Surgery, Department for Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Abstract

Background: The optimal treatment strategy for patients with synchronous colorectal liver metastases (CRLM) is unclear. The aim of this study was to compare the outcome of the *simultaneous*, *liver-first*, and *colorectal-first* surgical approaches.

Methods: All consecutive patients who had been resected with curative intent for CRLM were included. A Cox regression model was constructed, and an intention-to-treat analysis was performed between the liver-first and the simultaneous approaches, after propensity score matching.

Results: 658 patients were included in the analysis. 92 patients had a *simultaneous* resection, 163 patients had *liver-first*, and 403 patients had a *colorectal-first approach.* Overall survival was 54.9 months (95% CI 39.2–70.4) in the liver-first group, 54.5 months (95% CI 46.8–62.3) in *colorectal-first group,* and 59.6 months (95% CI 42.2–77.0) in the simultaneous group (log-rank p =0.850). In the matched cohort there were no differences in Clavien-Dindo 3a (p = 0.992) or 3b and greater (p = 0.999). Median overall survival was for *liver-first* group 42.2 months (95% CI 26.3–58.2), and for the *simultaneous* group 56.2 months (95% CI 47.1–65.4) (stratified log-rank p = 0.455).

Conclusion: A *simultaneous* approach was not associated with worse overall survival or morbidity compared to a liver-first approach.

Received 8 November 2021; accepted 4 September 2022

Correspondence

Petter Frühling, Department of Surgical Sciences, Akademiska sjukhuset Ingång 70 1 trappa, 751 85 Uppsala, Uppsala University, Uppsala, Sweden. E-mail: petter.fruhling@surgsci.uu.se

Introduction

Colorectal cancer is the second most common cause of cancer-related deaths in the Western world. The most common site of metastasis is the liver. Approximately 15–25% of patients have colorectal liver metastases (CRLM) at the time of diagnosis.[1–3] The optimal treatment strategy for patients with synchronous CRLM is unclear. Many of these patients often present with initially unresectable disease,[4] and have worse cancer biology,[4] with shorter disease-free survival and overall survival.[5,6] In brief, there are three established treatment strategies for patients with CRLM where curative intent is deemed feasible. These include, the *simultaneous* approach or a staged approach (either *liver-first,* or *colorectal-first* approach).

In the *simultaneous* approach the liver and bowel resections are performed at the same time. Whereas in a staged approach, either the primary cancer is resected first (*colorectal-first* approach) or the liver metastases (*liver-first*), with a period of recovery between the two resections. In the only published randomized controlled trial on the topic, *colorectal-first* approach was compared to the *simultaneous* approach.[7] Inclusion criteria were resectable synchronous CRLM, and primary endpoint was major postoperative complications. The study could not find any differences in complication rates between the groups. Given the complexity of patients with synchronous colorectal liver metastases, some patients never receive all the intended treatment plan. In a study by Sturesson et al., roughly two-thirds of all patients completed both the liver and colorectal resections.[8]

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Arguments for the *colorectal-first* approach, include early resection of the source of metastases (primary cancer), as well as a reduction of the risk of bowel obstruction, perforation or bleeding. Since these patients often commence chemotherapy treatment, this may help to identify those patients who progress during treatment, and who may not benefit from a liver resection.[4,6,9] Arguments for the *liver-first* approach include early resection of liver metastases, which are known to be the drivers of prognosis. In addition, many patients with synchronous CRLM have an advanced hepatic involvement where resectability is borderline, or where surgery has been made possible thanks to chemotherapy. In these instances, the *liver-first* approach seems favorable, since it makes use of the window of opportunity for curability.[10] Benefits of the *simultaneous* approach include definitive treatment of both the primary cancer and the metastases at the same time; an important incentive given that about one-third of patients fail to receive the intended treatment.[8] Additionally, it may entail only one anesthetic induction and overall likely shorter hospital length of stay.[11] *Prima facie*, the *simultaneous* approach appears attractive; with a potential to offer prolonged survival, shorter hospital stay, and reduced healthcare costs. The aim of the present study was to examine overall survival and morbidity and mortality across the *simultaneous*, *liver-first*, and *colorectal-first* approaches.

Methods

Between 2005 and 2015, 703 consecutive patients with synchronous CRLM treated with liver resection with curative intent were identified at Karolinska University Hospital (Stockholm) and Uppsala University Hospital. Since data were retrieved from local liver-surgery data bases all patients had received liver surgery, but not necessarily the colorectal resection. Consequently, a few of the liver-first patients in the data bases never had all the intended treatment (both the colorectal and liver resections). Therefore, to create three comparable groups, the initial analysis included only patients that had received both the liver resection and the primary cancer operation. Forty-five patients in the liver-first group were thus excluded since they never received a colorectal resection. A flow-diagram of all patients is provided in Fig. S1 (Supplementary Material). In order to make an intention-to-treat analysis a subgroup analysis was performed that compared the *simultaneous* and *liver-first* approaches. This analysis included all liver-first patients regardless of whether they had received both the liver-resection and the colorectal resection. Demographic and clinicopathological data were collected, including data on age, sex, center of surgery, body mass index (BMI), and date of eventual death. Data were also collected on tumor characteristics, such as location of tumor, R0/R1 resection margin after liver surgery, maximum size and number of metastases, type of colorectal and liver surgery (minor, major or extended) were collected. The study was approved by the regional Ethical Review Boards (Dnr 2010/1872-31, 2018/086).

Pre-operative assessment and treatment

All patients were discussed in both colorectal and hepatobiliary multidisciplinary treatment (MDT) conferences, with oncologists, radiologists, hepatobiliary and colorectal surgeons present. Treatment strategy decisions were made during MDT conferences and individually tailored for each patient – which involve both assessing the patient's operability and the tumors' resectability. If a patient required an extensive liver resection with an increased risk of post-operative liver failure; a volumetric assessment of future liver remnant (FLR) was calculated based on radiological imaging. If FLR was deemed insufficient based on the patient's body weight, either portal vein embolization (PVE), or associating liver partition and portal ligation for staged hepatectomy (ALPPS), was considered. At our centers PVE was the standard technique used for augmenting FLR up until 2012, thereafter ALPPS has been used in selected patients.

The treatment for synchronous CRLM is highly complex, with often several competing potential treatment strategies. To determine, which treatment strategy to use several factors were assessed. Are the liver metastases resectable or potentially resectable with chemotherapy? What type of liver surgery is required (extensive or minor)? Is the primary cancer advanced, and is there a high risk of anastomotic leakage, or is the tumor easily resectable? Does the patient suffer from symptoms from the primary cancer, and will the patient benefit from chemotherapy?

Evidently, quite few patients will be candidates for the *simultaneous* approach, since this strategy is often only warranted in medically fit patients, with less extensive liver metastases, and a potentially easily resectable primary cancer. Liver-first approach was often considered in patients with extensive liver metastases in need of downstaging chemotherapy with an asymptomatic primary cancer; and in patients with a rectal cancer whom received chemoradiation. Colorectal-first was mainly considered in patients with an advanced and/or symptomatic primary cancer, with either limited or extensive liver metastases. In general, most patients received peri-operative chemotherapy, that comprised chemotherapy three months before and three months after surgery.[12] During neo-adjuvant chemotherapy, contrast-enhanced computed tomography (CE-CT) scans of the liver and thorax were performed every 3–4 cycles to assess response.[13] If no progression of the disease was radiologically evident, and the liver metastases were still deemed resectable a laparotomy was performed four or five weeks after the last course of systemic chemotherapy.

Follow-up

Patients were followed-up at the hepatobiliary and colorectal outpatient clinics four to six weeks after surgery. Thereafter, patients were followed-up according to the national guidelines for colorectal cancer with liver metastases, which as a minimum entail a yearly contrast-enhanced computed tomography of the abdomen and thorax.

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Statistical analysis

Descriptive statistics are expressed as median (range) and interquartile ranges (IQR), while the categorical variables are presented with proportions and percentages. Categorical variables were compared using the Chi-square test, for continuous variables either the Kruskal–Wallis test (if more than two groups) or Mann–Whitney U test (if two groups) were used. When more than two cells were compared for categorical variables, a *z* test for column proportions for each row in the Chi Square contingency table, was calculated. Thereafter the *z* tests were adjusted using Bonferroni correction. Survival analysis was performed using the Kaplan–Meier method, and the proportional-hazards assumption was assessed. If the proportional-hazards assumption was not violated, the log-rank test was used to assess difference between groups. When the proportional hazards assumption was violated, the Peto–Peto test was used to assess differences.[14] The proportional hazards assumption was tested based on Schoenfeld residuals. 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. To compare survival differences between groups after propensity score matching, the stratified log-rank test was used.[15] In the matched cohort a paired *t* test was used for continuous variables, and McNemar or McNemar-Bowker for categorical variables.[16] Median follow-up period was calculated using reversed Kaplan–Meier method.[17] In the Cox model, backward elimination was used to assess the relationship between relevant clinico-pathological variables, and overall survival. Entry level in the multivariable analysis was set at a $p = 0.05$, and removal at 0.10. A subgroup intention-to-treat analysis was performed that compared *simultaneous* and *liver-first* resections. To minimize imbalances between the groups propensity score matching was used in a 1:1 ratio, using a multivariable logistic regression model. The variables included in the model were age, ASA group classification, primary tumor stage, primary nodal status, type of liver resection (minor versus major/extended) and number of colorectal liver metastases. The caliper was set equal to 0.020, and matching was performed without replacement. The total propensity scores of each group were graphically compared with Kernel density distribution plots. The degree of imbalance between each covariate was assessed with standardized mean difference (SMD), which is the difference in the mean of a variable between two groups divided by the estimated standard deviation of that variable.[16] Values of $p < 0.05$ were considered statistically significant. Data analyses were performed using IBM SPSS Statistics Version 28, 2021, and STATA/SE version 15.1 (StataCorp, College Station, Texas, USA).

Results

A total of 658 consecutive patients were included in the analysis. Ninety-two patients were treated with the *simultaneous* approach, 163 patients with *liver-first*, and 403 patients with the *colorectal-first* approach. Baseline characteristics of all patients included in the study are provided in Table 1. Median age at liver surgery for the whole cohort was 65.3 years; 61.1% of the patients were men, and median Body Mass Index (BMI) was 25.1 kg/m^2. In the aforementioned variables there were no differences between the groups.

Differences between the three treatment groups were discerned in the location of the primary cancer (p=<0.001). In the *liver-first* group, 66.3% (n = 108) had a primary rectal cancer, compared to 26.1% (n = 24), and 27.6% (n = 107) in the *simultaneous* and *colorectal-first* groups, respectively. Right-sided colon cancer in the *simultaneous* group occurred in 35.9% (n = 33), compared to 23.3% (n = 94) in the *colorectal-first* group, and 5.5% (n = 9) in the *liver-first* group. In addition, there was a difference in the number of liver metastases between the groups (p = 0.018). In the *simultaneous* group, 70.7% (n = 65) of patients had one or two liver metastases, compared to 47.9% (n = 78) of patients in the *liver-first* group. In the latter group, 21.4% (n = 86) had five or more metastases. Overall, most patients had a primary cancer staged T2-3 (62.3%), or T4 (24.2%). Lymphatic spread (N1/N2) occurred in more than fifty percent of cases in the *simultaneous* and *colorectal-first* groups, compared to 38.6% in the *liver-first* group. Overall, roughly 90% of patients belonged to either ASA classification 2 or 3. Only four patients were classified as ASA 4.

Details of surgery, post-operative complications, and prognostic scores

In the *simultaneous* group, 70.7% (n = 65) had a minor resection (<3 liver segment), compared to 49.6% (n = 200) in the *colorectal-first* and 47.2% (n = 77) in the *liver-first* groups (Table 2) (p = 0.001). In the *liver-first* group 29 patients (17.8%) had an extended resection (>4 liver segments); 15 patients (9.2%) had portal vein embolization, and 6 patients (3.7%) ALPPS. By contrast, in the *simultaneous* group, one patient (1.1%) underwent portal vein embolization, and 4 patients (4.3%) had an extended resection. Peri-operative ablation was performed in 25 patients (3.8%) in all three treatment groups together. Median blood loss across the treatment groups was 700 ml (iqr 350–1300). Differences between the groups were found in operation time, and hospital length of stay (Table 2). Median operative time for a simultaneous resection was 320 min (iqr 203–408), compared to 195 min (iqr 135–251) and 217 min (iqr 160–275), for the colorectal-first and liver-first approaches, respectively (p=<0.001). Patients who underwent a simultaneous resection had a median length of hospital stay of 12 days (iqr 10–16), compared to 10 days (iqr 8–14), and 10 days (iqr 8–13), for the liver-first and colorectal-first groups, respectively (p = 0.001). There were no differences in R0/R1 resection margins (p = 0.111) between the treatment groups. R0 resection margin was obtained in 74.5% (n = 490) of the patients (Table 2).

A post-operative complication, classified as Clavien-Dindo 3a occurred in 15.2%, 12.3%, and 16.6% in the *simultaneous*, *liver-*

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Table 1 Baseline characteristics of study population

	Total N = 658*	Simultaneous N = 92	Liver-first N = 163	Colorectal-first N = 403	P value[a]
Age (years)[c]	65.3 (57.6–71.6)	64.6 (57.0–73.0)	65.1 (54.7–71.1)	65.4 (58.6–71.9)	0.145[b]
Age >70 years	198 (30.1)	28 (30.4)	44 (27.9)	126 (31.3)	0.613
Sex (Women/Men)	39: 61	42: 58	39: 61	38: 62	0.771
BMI (kg/m^2)[c]	25.1 (23.0–28.0)	24.8 (22.9–27.1)	25.1 (22.8–28.4)	25.2 (23.1–28.0)	0.588[b]
ASA classification					
ASA 1	64 (9.7)	10 (10.9)		38 (9.4)	0.550
ASA 2	410 (62.3)	56 (60.9)	16 (9.8)	254 (63.0)	
ASA 3	179 (27.2)	24 (26.1)	100 (61.3)	109 (27.0)	
ASA 4	4 (0.6)	2 (2.2)	46 (28.2)	1 (0.2)	
[a]missing	1 (0.2)		1 (0.6)	1 (0.2)	
Location of primary cancer					
Right	136 (20.7)	33 (35.9)	9 (5.5)	94 (23.3)	<0.001
Left	253 (38.4)	27 (29.3)	44 (27.0)	182 (45.2)	
Transverse	22 (3.3)	7 (7.6)	2 (1.2)	13 (3.2)	
Rectum	238 (36.2)	23 (25.0)	108 (66.3)	107 (27.6)	
Rectal and right	5 (0.8)	1 (1.1)	0	4 (1.0)	
Unclear colon/missing	4 (0.7)	1 (1.1)	0	3 (0.7)	
Midgut embryonic origin	163 (24.8)	41 (43.5)	11 (6.7)	111 (27.5)	<0.001
Number of liver metastases					
1–2	362 (55.0)	65 (70.7)	78 (47.9)	219 (54.3)	0.018
3–4	148 (22.5)	14 (15.2)	36 (22.1)	98 (24.3)	
5–6	78 (11.9)	6 (6.5)	25 (15.3)	47 (11.7)	
>6	69 (10.5)	7 (7.6)	23 (14.1)	39 (9.7)	
Missing	1 (0.2)		1 (0.6)	0	
Size of metastasis (mm) median IQR	25 (16–40)	20 (12–30)	30 (17–42)	25 (17–40)	0.012[b]
T category of primary cancer					
T0-1	12 (1.8)	0 (0)	5 (3.1)	7 (1.7)	0.385
T2-3	410 (62.3)	61 (66.3)	95 (58.3)	254 (63.0)	
T4	160 (24.3)	24 (26.1)	33 (20.2)	103 (25.6)	
Missing/not possible to specify	76 (11.6)	7 (7.6)	30 (18.4)	39 (9.7)	
N category of primary cancer					
N0	164 (24.9)	20 (21.7)	39 (23.9)	105 (26.1)	0.683
N1	171 (26.0)	27 (29.3)	33 (20.2)	111 (27.5)	
N2	164 (24.9)	24 (26.1)	30 (18.4)	110 (27.3)	
Missing or not possible to specify	159 (24.2)	21 (22.8)	61 (37.4)	77 (19.1)	

BMI, Body Mass Index; ASA, American Society of Anesthesiologists Classification; ALPPS, Associating Liver Partition and Portal Vein Embolization for Staged Hepatectomy; PVE, Portal Vein Embolization; Primary cancer stage defined according to World Health Organization's classification of tumors.
*With percentages in parentheses unless indicated otherwise.
[a] Chi–Square test unless indicated otherwise.
[b] Kruskall-Wallis.
[c] Values are median (iqr).

first, and *colorectal-first* groups, respectively (Table 2). In the *simultaneous* group 15.2% suffered from a Clavien-Dindo 3b or greater compared to 9.8% in the *liver-first* group. There were no differences in Clavien Dindo 3a (p = 0.429), Clavien-Dindo >3a (p = 0.334), nor mortality (p = 0.686). The overall 90-day mortality rate for all treatment groups, after liver-surgery (or colorectal and liver surgery combined, as is the case in the simultaneous group) was 1.2%.

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Table 2 Baseline characteristics about liver surgery, post-operative complications and prognostic scores

	Total N = 658	Simultaneous N = 92	Liver-first N = 163	Colorectal-first N = 403	P value[a]
Type of liver resection					
Minor (<3 liver seg)	342 (52.0)	65 (70.7)	77 (47.2)	200 (49.6)	0.001
Major (3–4 liver seg)	224 (34.0)	23 (25.0)	57 (35.0)	144 (35.7)	
Extended (>4 liver seg)	92 (14.0)	4 (4.3)	29 (17.8)	59 (14.6	
Operation time (min)[c]	208 (148–280)	320 (203–408)	217 (160–275)	195 (135–251)	<0.001
Blood loss (ml)[c]	700 (350–1300)	600 (320–1100)	700 (357–1300)	700 (350–1500)	0.289
Hospital length of stay (days)[d]	10 (8–13)	12 (10–16)	10 (8–14)	10 (8–13)	0.001
ALLPS	18 (2.7)	0	6 (3.7)	12 (3.0)	0.070
PVE	39 (5.9)	1 (1.1)	15 (9.2)	23 (5.7)	0.014
Perioperative ablation	25 (38.0)	4 (4.3)	6 (3.7)	15 (3.7)	0.957
R0	490 (74.5)	69 (75.0)	132 (81.0)	289 (71.7)	0.111
R1	104 (15.8)	13 (14.1)	23 (14.0)	68 (16.8)	
Unclear[e]	64 (9.7)	9 (0.9)	8 (5.0)	47 (11.6)	
Clavien-Dindo classification					
Grade 1	199 (30.2)	28 (30.8)	54 (33.1)	117 (29.0)	0.025
Grade 2	186 (28.3)	31 (34.1)	42 (25.8)	113 (28.0)	
Grade 3a	101 (15.3)	14 (15.4)	20 (12.3)	67 (16.6)	
Grade 3b	38 (5.8)	10 (11.0)	12 (7.4)	16 (4.0)	
Grade 4a	17 (2.6)	2 (2.2)	2 (1.2)	13 (3.2)	
Grade 4b	13 (2.0)	1 (1.1)	2 (1.2)	10 (2.5)	
Grade 5	3 (0.5)	1 (1.1)	0	2 (0.5)	
Major complications					
Grade 3a	101 (15.3)	14 (15.4)	20 (12.3)	67 (16.6)	0.429
Grade 3b or greater	71 (15.2)	14 (15.4)	16 (9.8)	41 (10.2)	0.334
Mortality 90-day (after liver surgery)	8 (1.2)	1 (1.1)	1 (0.6)	6 (1.5)	0.686
Tumor Burden Score					
TBS 1	189 (28.7)	28 (30.4)	49 (30.1)	113 (28.0)	0.395
TBS 2	396 (60.1)	58 (63.0)	95 (58.3)	242 (60.0)	
TBS 3	67 (10.2)	4 (4.3)	18 (11.0)	45 (11.2)	
Missing	6 (0.9)	2 (2.2)	1	3 (0.7)	
Midgut	162 (24.6)	40 (43.5)	11 (6.7)	111 (27.3)	
Composite Score					
Composite Score Low	197 (30.0)	27 (29.3)	45 (27.6)	126 (31.3)	0.548
Composite Score Medium	428 (64.9)	62 (67.4)	112 (68.7)	253 (62.8)	
Composite Score High	33 (5.0)	3 (3.3)	6 (3.7)	24 (6.0)	
Overall survival (%)					
1 year	90.9	90.2	90.8	90.8	0.850[b]
3 years	64.3	70.7	61.9	63.5	
5 years	44.7	48.9	43.6	44.2	

ALPPS, Associating Liver Partition and Portal Vein Embolization for Staged Hepatectomy; PVE, Portal Vein Embolization; TBS, Tumor Burden Score.
[a] Chi-Square test. With percentages in parentheses unless indicated otherwise.
[b] Log-rank test.
[c] Values are median (iqr).
[d] Hospital stay after liver surgery only.
[e] Not possible to determine from either the medical notes or histopathological report.

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

For each patient a tumor burden score was calculated, which takes into account the number of tumors and the largest size of tumor.[18] Furthermore, patients were stratified as *low* risk, *medium* risk, and *high* risk, according to a *Composite Score*, a validated predictive tool to calculate overall survival, recently published by the authors of the present study.[19] The *Composite Score* takes into account age at surgery, c-reactive protein, serum albumin levels, embryonic origin of primary cancer, and whether it was an extended liver resection (>4 liver segments). There were no differences in distribution of either tumor burden score (TBS)[18] or *Composite Score* between the treatment groups. A majority of patients belonged to TBS 2, or medium-risk according to the Composite Score. In the *liver-first* and *simultaneous* groups approximately, three per cent belonged to high-risk, whereas six percent of patients in colorectal-first belonged to this risk category (Table 2). Overall survival according to the Composite Score is provided in Fig. S2, Supplementary Material.

Follow-up and overall survival

After a median follow-up time of 104 months (IQR 97–112 months), there were no differences in overall survival between the groups (Fig. 1, log rank p = 0.850). The median overall survival for *liver-first* was 54.9 (95% CI 39.2–70.4) months, and for the *colorectal-first* and *simultaneous* groups, 54.5 (95% CI 46.8–62.3), and 59.6 (95% CI 42.2–77.0) months, respectively. Overall survival after 1 year was above 90% for all three groups, and five-year survival was 48.9% (*simultaneous*), 44.2% (*colorectal-first*) and 43.6% (*liver-first*) (Table 2).

Prognostic clinicopathological factors

In the univariable Cox regression analysis age over 70 years (HR = 1.43, 95% CI 1.16–1.76), primary lymph node status N2 (HR = 1.73, 95% CI 1.32–2.26), primary tumor stage T4 (HR = 3.75, 95% CI 1.19–11.81), major liver resection (HR = 1.35, 95% CI 1.02–1.77), and five to six (HR 1.73, 95% CI 1.29–2.32), or more than six colorectal liver metastases (HR 1.78, 95% CI 1.31–2.41) were found to negatively influence overall survival (Table 3). In the multivariable Cox regression analysis, age over 70 years (HR 1.30, 95% CI 1.01–1.65), primary lymph node status N2 (HR 1.62, 95% CI 1.23–2.14), and five to six (HR 1.74, 95% CI 1.23–2.46), and more than six liver metastases (HR 1.69, 95 CI 1.18–2.43) remained significant.

A subgroup intention-to-treat analysis of the simultaneous and liver-first approaches.

To compare the *simultaneous* approach to the liver-first approach in an intention-to-treat analysis, a propensity score matching was performed. In this analysis all liver-first patients were included, that is, also those who for various reasons never had the intended colorectal resection (Table 4). Before matching, a comparison of overall survival between *liver-first simultaneous* approach is provided in Fig. S3 (Supplementary Material). After matching in a 1:1 ratio, two groups with 58 patients in each

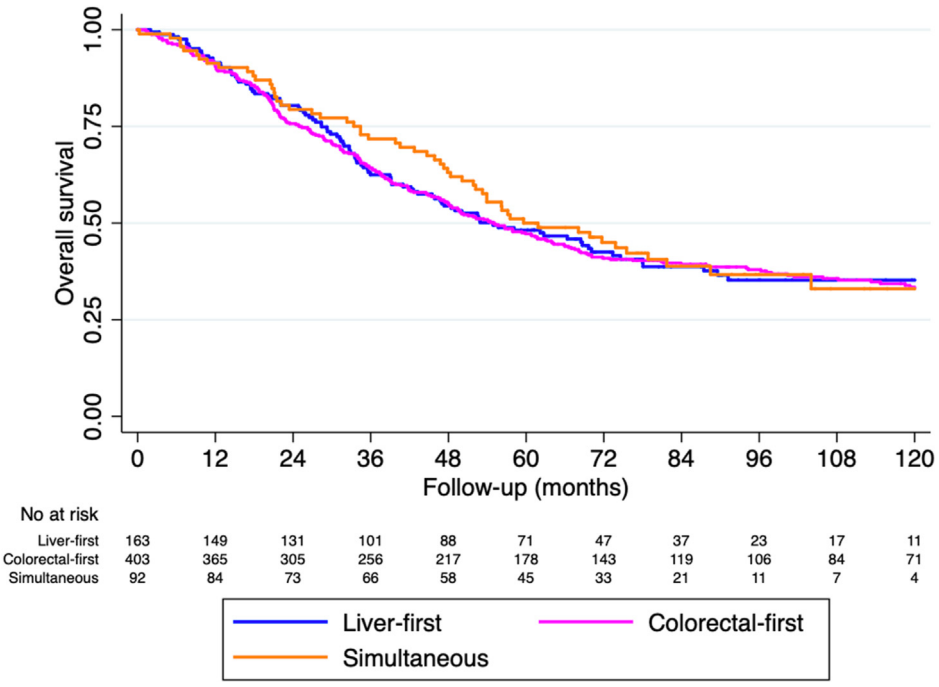

Figure 1 Overall survival of the three different treatment strategies: *liver-first*, *colorectal*, and *simultaneous*. The median overall survival for *liver-first* was 54.9 (95% CI 39.2–70.4) months, and for the *colorectal* and *simultaneous* groups, 54.5 (95% CI 46.8–62.3), and 59.6 (95% CI 42.2–77.0) months, respectively. Log rank p = 0.850

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Table 3 Univariable and multivariable Cox regression of prognostic factors for overall survival

Variable	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age <70 years	Reference			
Age ≥70 years	1.43 (1.16–1.76)	<0.001	1.30 (1.01–1.65)	0.036
Women	Reference			
Men	0.98 (0.80–1.19)	0.838	NA	
N category of primary cancer				
N0	Reference			
N1	1.11 (0.84–1.47)	0.460	1.06 (0.80–1.41)	0.664
N2	1.73 (1.32–2.26)	<0.001	1.62 (1.23–2.14)	<0.001
T category of primary cancer				
0–1	Reference			
3	2.93 (0.94–9.13)	0.065	2.34 (0.74–7.40)	0.149
4	3.75 (1.19–11.81)	0.024	2.88 (0.89–9.25)	0.076
Number of liver metastases				
1–2	Reference			
3–4	1.18 (0.93–1.51)	0.178	1.08 (0.82–1.42)	0.587
5–6	1.73 (1.29–2.32)	<0.001	1.74 (1.23–2.46)	0.002
>6	1.78 (1.31–2.41)	<0.001	1.69 (1.18–2.43)	0.004
Size liver tumor				
<5 cm	Reference			
≥5 cm	1.25 (0.98–1.25)	0.088	NA	
Resection type				
Minor (<3 liver seg)	Reference			
Major (3–4 liver seg)	1.35 (1.02–1.77)	0.035	1.12 (0.78–1.60)	0.543
Extended (>4 liver seg)	1.04 (0.84–1.29)	0.718	0.95 (0.74–1.22)	0.689
Hindgut	Reference			
Midgut	1.19 (0.96–1.48)	0.121	NA	

group, were created with similar distribution of propensity scores. A comparison of propensity scores before and after matching is provided in Figs. S4a–S4b (Supplementary Material). Baseline patient and tumor characteristics can be found in Table 4. After matching no differences could be discerned in the matched variables, that is, age, number of liver metastases, ASA classification, type of liver resection, primary cancer T and N stages.

A complication classified as Clavien Dindo 3a, occurred in 12.1% (n = 7) in the simultaneous group, and 8.6% (n = 5) in the liver-first group (p = 0.992). A complication classified as 3b or greater, occurred in 9 patients (15.5%) in the simultaneous group, and 7 patients (12.1%) in the liver-first group (p = 0.999) (Table 5). Five-year survival was 44.8% in the *simultaneous* group, and 34.5% in the *liver-first* group. Median overall survival was 56.2 months (47.1–65.4 months), and 42.2 months (26.3–58.2 months) for the *simultaneous* and *liver-first* groups, respectively (stratified log rank p = 0.455) (Fig. 2).

Discussion

The present study describes a more than a decade experience in two large hepatobiliary centers of three different treatment strategies for synchronous CRLM. The study compares the outcome for patients treated with the *simultaneous*, *liver-first*, and *colorectal-first* approaches, and who had all the intended surgical treatment. Overall survival for patients who underwent a *simultaneous* approach were not found to live shorter than patients who underwent either the *liver-first* or *colorectal-first* approaches (Fig. 1). Moreover, in a subgroup intention-to-treat analysis between the *liver-first* and the *simultaneous* groups, overall survival for patients in the *simultaneous* group, was found to be similar to patients in the *liver-first* group (Fig. 2). Morbidity and mortality were not found to be any higher in the *simultaneous* group compared to a staged approach (Table 2).

Determining the best surgical strategy for each individual patient with CRLM is complex. A number of important factors

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Table 4 Baseline patient and tumor characteristics with intention-to-treat analysis of liver-first* and simultaneous groups (a) before and (b) after propensity score matching

(a) Cohort before matching (n = 300)				(b) Cohort after matching (n = 114)		
	Liver-first	Simultaneous	SMD[#]	Liver-first	Simultaneous	SMD[#]
	N = 208	N = 92		N = 58	N = 58	
Age (years)[a]	66 (56–71)	65 (57–73)	0.265	68 (58–72)	64 (57–70)	0.148
Number of liver metastases						
1–2	91 (43.4)	65 (70.7)		32 (55.2)	35 (60.3)	0.001
3–4	51 (24.3)	14 (15.2)		16 (27.6)	13 (22.4)	
5–6	33 (15.7)	6 (6.5)		7 (12.1)	4 (6.9)	
>6	34 (16.2)	7 (7.6)	0.518	3 (5.2)	6 (10.3)	
Liver resection						
Minor (<3 seg)	101 (48.1)	65 (70.7)		37 (63.8)	36 (62.1)	0.035
Major/extended (≥3 seg)	107 (51.9)	27 (29.3)	0.472	21 (36.2)	22 (37.9)	
ASA						
1	20 (9.6)	10 (10.9)			8 (13.8)	0.079
2	125 (60.1)	56 (60.9)		6 (10.3)	33 (56.9)	
3	61 (29.3)	24 (26.1)		33 (56.9)	16 (27.6)	
4	2 (1.0)	2 (2.2)	0.270	19 (32.8)	1 (1.7)	
T category of primary cancer						
T0-1	5 (2.4)	0 (0)				0.320
T2-3	102 (49.0)	61 (65.6)		4 (6.9)	0	
T4	41 (19.7)	24 (25.8)		46 (79.3)	46 (79.3)	
Missing/not possible to specify	60 (28.8)	8 (8.6)	0.198	8 (13.8)	12 (20.7)	
N category of primary cancer						
N0	40 (19.2)	20 (21.5)				0.021
N1	33 (15.9)	27 (29.0)		23 (39.7)	19 (32.8)	
N2	41 (19.7)	24 (25.8)		15 (25.9)	22 (37.9)	
Missing/not possible to specify	94 (54.8)	22 (23.7)	0.076	20 (34.5)	17 (29.3)	

ASA, American Society of Anesthesiologists; *This group includes all patients who underwent liver-first surgery, regardless of whether they also had the primary cancer resected.
[#]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. With percentages in parentheses unless indicated otherwise.
[a] Values are median (iqr).

need to be considered such as location and extent of primary tumor and liver metastases, patient performance status and presence of symptoms, and underlying co-morbidities. All patients are not suitable for all treatment options. To exemplify, at our institutions a *simultaneous* resection is primarily a potential strategy in the setting of a fit patient, with limited liver metastases (with the aim of parenchymal-sparing approach), with a low-risk primary cancer. By contrast, a patient with borderline resectable liver metastases that require conversion chemotherapy, and a high-risk primary rectal cancer, is more likely to benefit from a *liver-surgery* approach. Whereas, a patient with a symptomatic primary in the form of bleeding or signs of obstruction, may benefit from a *colorectal-first* approach. Hence, since patient selection between the treatment strategies differs from the outstart, any comparison of morbidity, mortality and overall survival, between these treatment strategies is subject to a risk of bias.

A testament to the complexity involved in determining treatment strategy and the heterogeneity of patients, is the recent multicenter randomized controlled study (RCT) published by Boudjema et al.[7] This is the first RCT on the topic, which randomized patients with synchronous initially resectable CRLM at ten French tertiary centers to either the *simultaneous* or *colorectal-first* approaches. The primary endpoint was major complications within 60 days following surgery, and secondary outcome overall survival and disease-free survival. After ten years of accrual only 220 patients were assessed for eligibility, and 105 patients were deemed suitable to be randomized. The final analysis included 39 patients in the *simultaneous* group, and 46 patients in the

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

Table 5 Morbidity and mortality after propensity score matching

	Simultaneous N = 58	Liver-first N = 58	P value[a]
Complications			
Clavien Dindo 3a	7 (12.1)	5 (8.6)	0.992
Clavien Dindo >3a	9 (15.5)	7 (12.1)	0.999
Mortality 90-day	1 (1.7)	0	
Median overall survival (months)	56 (47–65)	42 (26–58)	0.455[b]
Overall survival (%)			
1 year	87.9	84.5	
3 years	65.5	55.2	
5 years	44.8	34.5	

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

colorectal-first group. The study found no differences in major complications between the two treatment groups, but patients in the *simultaneous* group had a shorter hospital stay compared to the colorectal-first group (12 versus 17 days, p = 0.002). Median overall survival in the *simultaneous* group was 5.9 years, compared to 3.9 years in the *colorectal-first* approach (p = 0.07).

A number of retrospective studies have been published, that compare simultaneous versus staged resection.[20–22] In a study by Slesser et al., no differences in post-operative complications or mortality, nor three-year overall survival were found between the *simultaneous* and *staged* approaches. Median length of hospital stay was shorter in the *simultaneous* group compared to *staged* resection (14 days compared to 18.5 days, p = 0.03).[20] In a more recent study by Abelson et al., similar results were found. There was no difference in major complication rates between *simultaneous* and *staged* approach, and there was a shorter length of hospital stay and reduced healthcare costs.[21] In the present study, which included hospital stay after liver surgery only, patients in the simultaneous group had a median hospital stay of 12 days compared to 10 days in the staged approach. One limitation of this comparison, however, is that it does not include the length of hospital stay after the primary cancer operation. There were no differences in R0/R1 resection margins (p = 0.111) between the treatment groups. In the present study R0 resection margin was obtained in 74.5% of patients (n = 490), and R1 resection in 15.8% (n = 104) of the patients, which is similar to the results reported by Silberhumer and co-workers[23].

Similar to the results of the present study Mayo et al.,[22] reports no differences in morbidity, mortality or overall survival between *simultaneous* and *staged* approaches. Furthermore, several reviews and meta-analyses have been published.[11,24–27] Three of these meta-analyses report a lower rate of morbidity in the simultaneous group compared to patients undergoing staged resection,[25–27] whereas two could not discern any difference.[11,24] Overall survival was similar across all studies and treatment strategies, whereas total length of hospital stay was found to be shorter among patients in the *simultaneous*

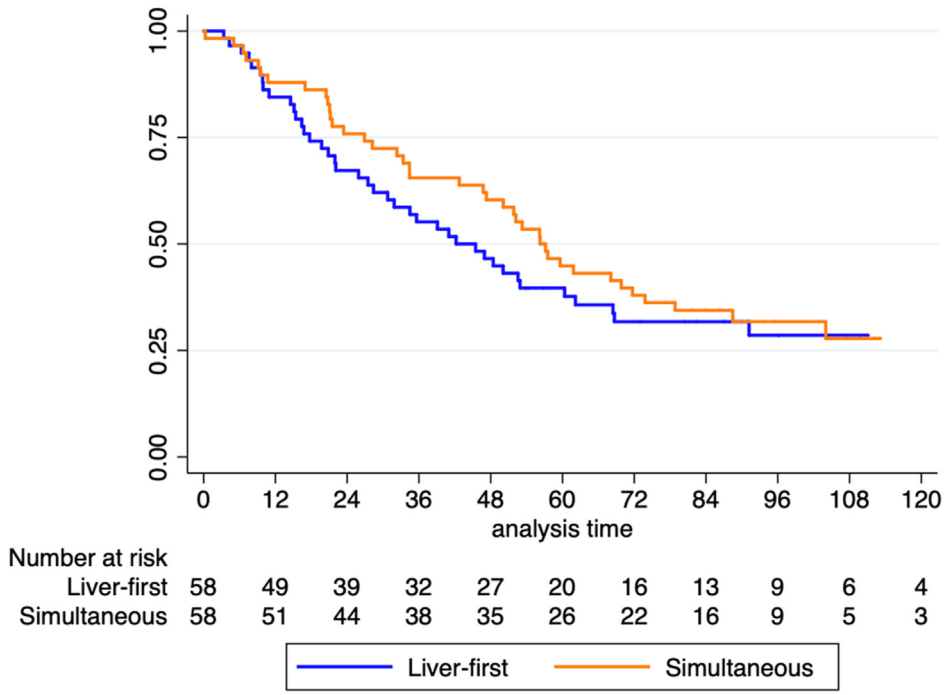

Figure 2 Median overall survival was 56.2 months (95% CI 47.1–65.4 months), and 42.2 months (95% CI 26.3–58.2 months) for the *simultaneous* and *liver-first* groups, respectively. Stratified log-rank p = 0.455

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

group.[11,24,27] As expected patients with more extensive metastatic liver disease, that required a major hepatectomy were less commonly offered a simultaneous approach,[11,25,26] and staged resection appeared to be reserved to patients with advanced age and locally advanced rectal disease.[24]

The present study also found that patients in the *simultaneous* group had fewer liver metastases, and underwent less extensive liver surgery. Strengths of the present study include its large study population. Moreover, it is, to our knowledge, one of the largest studies, to examine all three treatment strategies, without grouping *colorectal* and *liver-first* into a staged approach. Furthermore, this study provides the longest reported median follow-up period of 104 months (IQR 97–112 months). In addition, to address baseline imbalances between the *simultaneous* and *liver-first* approaches, a subgroup intention-to-treat analysis was performed after propensity score matching. After matching overall survival, morbidity and mortality, were similar in the *simultaneous* group compared to the *liver-first* approach.

Limitations of the present study include its retrospective design. Furthermore, since the analysis relies on surgery-based databases at two hepatobiliary tertiary centers, we were not able to perform an intention-to-treat analysis of all patients (including *colorectal-first*). We have only been able to analyze patients that have been referred to our MDT conference, and have had liver surgery. Patients who underwent a *colorectal-first* approach, but whom, for various reasons, such as disease progression, side-effects of the chemotherapy, post-operative complications after treatment of the primary cancer) never became subject to a liver resection, could therefore not be included in the analysis.

Patients with synchronous CRLM are a heterogenous group that can be treated with a staged approach (*liver-first*, or *colorectal-first*) or a *simultaneous* approach. The choice of treatment strategy is highly complex, and patients benefit from an individualized approach. The present paper could not find that the *simultaneous* approach was any worse than a staged approach in terms of morbidity, mortality or overall survival.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors of the present study declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Van Cutsem E, Nordlinger B, Adam R, Kohne CH, Pozzo C, Poston G *et al*. (2006) Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 42:2212–2221.
2. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M *et al*. (2018) Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 103:356–387.
3. Haddad AJ, Bani Hani M, Pawlik TM, Cunningham SC. (2011) Colorectal liver metastases. *Int J Surg Oncol* 2011285840.
4. Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E *et al*. (2015) Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev* 41:729–741.
5. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. (1995) Resection of colorectal liver metastases. *World J Surg* 19:59–71.
6. Allen PJ, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. (2003) Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg* 7:109–117.
7. Boudjema K, Locher C, Sabbagh C, Ortega-Deballon P, Heyd B, Bachellier P *et al*. (2021) Simultaneous versus delayed resection for initially resectable synchronous colorectal cancer liver metastases: a prospective, open-label, randomized, controlled trial. *Ann Surg* 273: 49–56.
8. Sturesson C, Valdimarsson VT, Blomstrand E, Eriksson S, Nilsson JH, Syk I *et al*. (2017) Liver-first strategy for synchronous colorectal liver metastases - an intention-to-treat analysis. *HPB* 19:52–58.
9. Lambert LA, Colacchio TA, Barth RJ, Jr.. (2000) Interval hepatic resection of colorectal metastases improves patient selection. *Arch Surg* 135:473–479. discussion 9-80.
10. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. (2006) Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg* 93:872–878.
11. Gavriilidis P, Sutcliffe RP, Hodson J, Marudanayagam R, Isaac J, Azoulay D *et al*. (2018) Simultaneous versus delayed hepatectomy for synchronous colorectal liver metastases: a systematic review and meta-analysis. *HPB* 20:11–19.
12. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D *et al*. (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27:1386–1422.
13. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B *et al*. (2006) Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 243:1–7.
14. Pinar Gunel Karadeniz IE. (2017) Examining tests for comparing survival curves with right censored data. *Stat Transit New Ser* 18:311–328.
15. Austin PC. (2014) The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 33:1242–1258.
16. Austin PC. (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 46:399–424.
17. Schemper M, Smith TL. (1996) A note on quantifying follow-up in studies of failure time. *Contr Clin Trials* 17:343–346.
18. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A *et al*. (2018) The tumor burden score: a new "Metro-ticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. *Ann Surg* 267:132–141.
19. Fruhling P, Urdzik J, Stromberg C, Isaksson B. (2021) Composite Score: prognostic tool to predict survival in patients undergoing surgery for colorectal liver metastases. *BJS Open* 5.

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001

20. Slesser AA, Chand M, Goldin R, Brown G, Tekkis PP, Mudan S. (2013) Outcomes of simultaneous resections for patients with synchronous colorectal liver metastases. *Eur J Surg Oncol* 39:1384–1393.

21. Abelson JS, Michelassi F, Sun T, Mao J, Milsom J, Samstein B *et al*. (2017) Simultaneous resection for synchronous colorectal liver metastasis: the new standard of care? *J Gastrointest Surg* 21: 975–982.

22. Mayo SC, Pulitano C, Marques H, Lamelas J, Wolfgang CL, de Saussure W *et al*. (2013) Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. *J Am Coll Surg* 216:707–716. discussion 16-8.

23. Silberhumer GR, Paty PB, Temple LK, Araujo RL, Denton B, Gonen M *et al*. (2015) Simultaneous resection for rectal cancer with synchronous liver metastasis is a safe procedure. *Am J Surg* 209:935–942.

24. Slesser AA, Simillis C, Goldin R, Brown G, Mudan S, Tekkis PP. (2013) A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases. *Surg Oncol* 22: 36–47.

25. Yin Z, Liu C, Chen Y, Bai Y, Shang C, Yin R *et al*. (2013) Timing of hepatectomy in resectable synchronous colorectal liver metastases (SCRLM): simultaneous or delayed? *Hepatology* 57:2346–2357.

26. Feng Q, Wei Y, Zhu D, Ye L, Lin Q, Li W *et al*. (2014) Timing of hepatectomy for resectable synchronous colorectal liver metastases: for whom simultaneous resection is more suitable–a meta-analysis. *PLoS One* 9e104348.

27. Chen J, Li Q, Wang C, Zhu H, Shi Y, Zhao G. (2011) Simultaneous vs. staged resection for synchronous colorectal liver metastases: a meta-analysis. *Int J Colorectal Dis* 26:191–199.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.09.001.

Please cite this article as: Frühling P et al., A comparison of the *simultaneous*, *liver-first*, and *colorectal-first* strategies for surgical treatment of synchronous colorectal liver metastases at two major liver-surgery institutions in Sweden, HPB, https://doi.org/10.1016/j.hpb.2022.09.001