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Short-Term Outcomes of Secondary Liver Surgery for Initially Unresectable Colorectal Liver Metastases Following Modern Induction Systemic Therapy in the Dutch CAIRO5 Trial

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Objective: To present short-term outcomes of liver surgery in patients with initially unresectable colorectal liver metastases (CRLM) downsized by chemotherapy plus targeted agents.

Background: The increase of complex hepatic resections of CRLM, technical innovations pushing boundaries of respectability, and use of intensified induction systemic regimens warrant for safety data in a homogeneous multicenter prospective cohort.

Methods: Patients with initially unresectable CRLM, who underwent complete resection after induction systemic regimens with doublet or triplet chemotherapy, both plus targeted therapy, were selected from the ongoing phase III CAIRO5 study (NCT02162563). Short-term outcomes and risk factors for severe postoperative morbidity (Clavien Dindo grade ≥ 3) were analyzed using logistic regression analysis.

Results: A total of 173 patients underwent resection of CRLM after induction systemic therapy. The median number of metastases was 9 and 161 (93%) patients had bilobar disease. Thirty-six (20.8%) 2-stage resections and 88 (51%) major resections (>3 liver segments) were performed. Severe postoperative morbidity and 90-day mortality was 15.6% and 2.9%, respectively. After multivariable analysis, blood transfusion (odds ratio [OR] 2.9 [95% confidence interval (CI) 1.1–6.4], $P = 0.03$), major resection (OR 2.9 [95% CI 1.1–7.5], $P = 0.03$), and triplet chemotherapy (OR 2.6 [95% CI 1.1–7.5], $P = 0.03$) were independently correlated with severe postoperative complications. No association was found between number of cycles of systemic therapy and severe complications ($r = -0.038$, $P = 0.31$).

Conclusion: In patients with initially unresectable CRLM undergoing modern induction systemic therapy and extensive liver surgery, severe postoperative morbidity and 90-day mortality were 15.6% and 2.7%, respectively. Triplet chemotherapy, blood transfusion, and major resections were associated with severe postoperative morbidity.

Keywords: ablation, colorectal cancer, colorectal liver metastases, mortality, postoperative morbidity, resection, surgery

INTRODUCTION

Over the last decennium, the number of complex hepatic resections in patients with colorectal liver metastases (CRLM) has increased gradually, with improved long-term survival outcomes.[1–4] Short-term postoperative morbidity and mortality rates of major liver resections are reported up to 45% and 7%, respectively.[4–8] Perioperative blood transfusion and major liver

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resections are independent prognostic factors for severe short-term complications[9] and occurrence of postoperative complications after liver resection has been associated with deprived long-term oncological outcomes.[10] Innovations in treatment strategies in patients with advanced CRLM have led to an increased number of patients deemed technically eligible for resection. This is mainly attributable to technical improvements with advances in liver augmentation and parenchymal-sparing techniques like treatment combinations with local ablative therapy, portal vein embolization, 2-stage resections, and Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS).[11,12] Second, novel systemic regimens consisting of chemotherapy including targeted agents with high efficacy have become available with response rates of up to 80% and allowing secondary resections in 40% of patients with CRLM initially deemed unresectable.[13–15] After induction therapy, patients often require complex resections to clear the liver from tumor. Still, 5-year survival rates of up to 40% have been described with this regimen.[4,16]

Systemic treatment may compromise the liver, with histologic changes such as portal and parenchymal inflammation, sinusoidal obstruction syndrome associated with oxaliplatin-based chemotherapy, and steatohepatitis associated with irinotecan-based chemotherapy with a risk of progressing to fibrosis, cirrhosis, and liver failure.[17,18] Parenchymal necrosis and sinusoidal dilatation were found to be increased in patients with triplet chemotherapy as compared with controls without systemic therapy.[19] The presence of hepatic parenchymal toxicity is correlated with an increased risk of postoperative morbidity and mortality after secondary resection as a result of impaired liver function, bleeding, or infection.[17,18,20–23] In contrast, bevacizumab has been reported to reduce the risk of oxaliplatin-based sinusoidal injury[20].

Reported postoperative morbidity and mortality rates after induction systemic therapy and extensive hepatic resections of CRLM range widely,[9,21,24–26] and data are derived mostly from single-center retrospective studies.[5] These studies concern heterogeneous patient populations with varying numbers of metastases, types of resections, and number of cycles, type, and intention of systemic therapy (neo-adjuvant or induction).[21,22] With increasing use of modern intensified induction systemic therapy in combination with ongoing innovations leading to increased surgical possibilities, safety data in this specific patient group in a multicenter prospective cohort on a national level are warranted.

The aim of this study was to describe short-term postoperative morbidity and mortality after modern induction systemic therapy followed by hepatic resection and to determine risk factors for severe postoperative morbidity in patients participating in the ongoing phase 3 CAIRO5 study.

METHODS

Patient Selection

Patients were selected from the ongoing CAIRO5 study, a phase 3 clinical trial of the Dutch Colorectal Cancer Group (DCCG), investigating the currently most effective first-line systemic regimens of chemotherapy (5-fluorouracil, oxaliplatin, and/or irinotecan) plus targeted therapy in patients with initially unresectable, liver-only CRLM.[27] Patients are randomized between FOLFOX/FOLFIRI-Bevacizumab and FOLFOX/FOLFIRI-Panitumumab, or FOLFOX/FOLFIRI-Bevacizumab and FOLFOXIRI-Bevacizumab according to *RAS/BRAF* tumor mutation status and sidedness (right-sided or left-sided hemicolon) of primary tumor. A central expert panel of liver surgeons and abdominal radiologists evaluates patients at baseline for eligibility based on predefined baseline resectability criteria. Given the lack of (inter)national consensus on criteria for (un)resectability, these criteria were selected to allow a homogeneous study population. Following these baseline criteria, CRLM is deemed unresectable if an R0 resection cannot be achieved in one procedure with one surgical intervention based on computed tomography (CT) and/or magnetic resonance imaging (MRI) scan. Thereafter, patients are evaluated by the panel every 2 months during systemic treatment to assess resectability of CRLM according to current and more liberal guidelines,[28,29] and thus abandoning baseline resectability criteria. If CRLM is deemed resectable, a surgical plan is provided and forwarded with the resectability assessment to the local multidisciplinary team (MDT).[30] According to the CAIRO5 study protocol, adjuvant therapy after surgery of CRLM is initiated until a total length of induction and adjuvant systemic therapy of 12 cycles. Accrual of patients started in July 2014. All patients from the start of the study until April 2019 who underwent complete resection with or without local ablative treatment of CRLM were included for this study. Patients with planned 2-stage resections and who underwent only the first (minor) stage of surgery, for reasons other than postoperative complications, were excluded. All patients signed a written consent form and the study was conducted according to the ethical standards of the Helsinki Declaration of 1975.

Data Selection

All data in the CAIRO5 study were prospectively collected by certified local data managers and checked by central data managers of The Netherlands Comprehensive Cancer Institute. Baseline characteristics were collected such as: age, sex, site of primary tumor, time to metastases, *RAS/BRAF* mutational status, and Fong clinical risk score categorized in low risk (0 or 1 point), moderate risk (2 or 3 points), and high risk (4 or 5 pionts).[31] Synchronous disease was defined as a disease-free interval (DFI) of <6 months after initial diagnosis of CRC.[32] Furthermore, oncological characteristics were scored such as: the number and largest diameter of metastases, hepatic location (unilobar/bilobar and segments as described by Couinaud[33]) and involvement of diaphragm, hepatic arteries, and veins and inferior vena cava. Information about induction systemic therapy, such as type of systemic therapy (triplet vs doublet and anti-EGFR vs anti-VEGF therapy), response to therapy according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1),[34] the number of cycles and days between the last chemotherapy and surgery, were collected. Surgical-technical details were collected such as: type of surgery (1-stage vs 2-stage), combination with local ablative treatment, portal vein embolization (PVE) yes/no, and R0/R1-resection status (R1 was defined as microscopic tumor involvement in the resection margin[35]), blood loss, and number of days of hospitalization. Major resections were defined as resections of ≥4 segments.[36] Postoperative morbidity was scored according to Clavien Dindo grading system.[37] Severe complications were defined as Clavien Dindo 3a and higher. Mortality was scored at 30 and 90 days.

Histopathological Analysis

The assessment of hepatic resection specimens available at time of analysis was centrally performed by reviewing the original hematoxylin and eosin- stained slides of liver metastases by a dedicated pathologist (C.M.). Pathologic response was scored based on the Tumor Regression Grading,[38] and correlation analysis was performed for number of cycles of induction systemic therapy and pathologic response. Furthermore, liver parenchymal inflammation surrounding the liver metastases based on lymphocyte infiltration (peritumoral, portal, and combined inflammation) was assessed and the association of parenchymal inflammation and occurrence of severe postoperative complications was assessed.[23]

Statistical Analysis

Patient and tumor characteristics were displayed with counts and percentages or medians with interquartile range (IQR). Differences between groups were analyzed using chi-square tests and Fisher exact tests, as appropriate. Values of $P < 0.05$ were considered statistically significant. Potential predictive factors were analyzed following logistic regression analyses. After univariable analyses were performed, multicollinearity was tested. Variables with significant interaction were not tested in the multivariable model. Because of the limited number of events a maximum of 3 factors were selected for multivariable analysis. Based on the literature and variable of interest, blood transfusion and chemotherapy (triplet versus doublet) were selected in advance for multivariable testing. The third factor was selected with backward selection. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated. Correlation was tested by the Spearman's correlation coefficient. Analyses were performed using SPSS software version 26 (IBM, NY).

RESULTS

Patient Cohort

A total of 395 patients were registered for the CAIRO5 trial between the start of the study and April 2019. Thirty-six patients were excluded due to ineligibility for the study. The remaining 359 patients were enrolled and randomized to systemic treatment. After systemic treatment, 131 patients with permanently unresectable CRLM as assessed by central expert panel evaluation were excluded for this analysis. Of the remaining 228 patients deemed to have resectable disease after induction systemic therapy, 55 (24.1%) were excluded because resection was not successfully completed. In 27 of these 55 patients, surgery was abandoned due to new intrahepatic (n = 6) or extrahepatic (n = 5) metastases as shown by additional imaging, decision of the local MDT (n = 8), condition (n = 4) or request (n=2) of the patients, complete radiological response (n = 1) and in 1 patient the reason was missing. Twenty-one patients were considered unresectable perioperatively. Last, 7 of 43 patients (16.3%) scheduled for a 2-stage resection, did not undergo the second resection due to progression of disease (n = 5), comorbidity (n = 1), or insufficient future liver remnant (FLR) (n = 1). After applying inclusion and exclusion criteria, 173 of 359 (48.2%) randomized patients, who underwent liver surgery with curative intent in 19 centers, were analyzed. Resections were performed in a total of 8 university and 14 non-university hospitals. The flow-diagram with reasons of inclusion and exclusion of patients is shown in Figure 1.

Baseline Characteristics

Patient characteristics are provided in Table 1 and showed predominantly synchronous disease in 146 (84.4%) patients, bilobar distribution of liver metastases in 161 (93%) patients, with a median of 5 (IQR 4–6) liver segments involved and a median of 9 (IQR 5–14) CRLM per patient. No patients had a low Fong clinical risk score, whereas 97 patients (56.1%) had a medium and 73 patients (42.2%) had a high Fong clinical risk score.[31] The tumor carried a *RAS* or *BRAF* mutation in 83 patients (48.0%). All patients (100%) were treated with chemotherapy with targeted therapy before resection. FOLFOX/

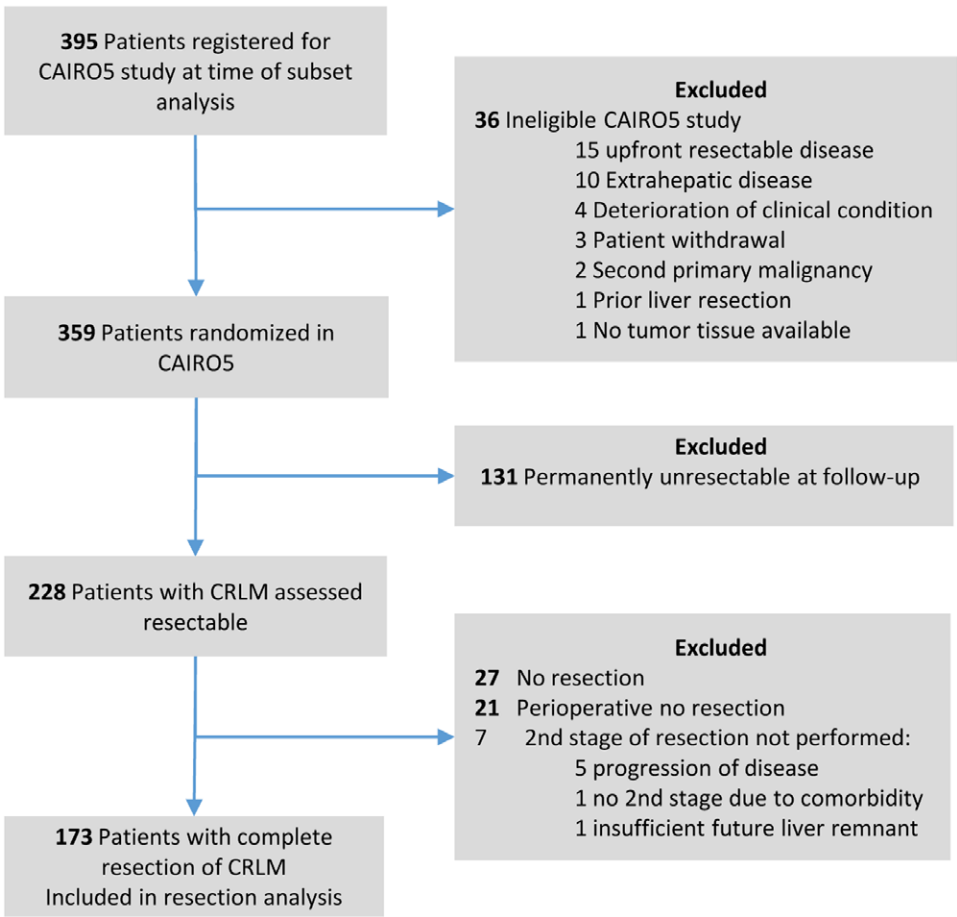

FIGURE 1. Flowchart of patients.

FOLFIRI-Bevacizumab, FOLFOX/FOLFIRI-Panitumumab and FOLFOXIRI-Bevacizumab was administered in 92 (53.2%), 37 (21.4%), and 44 (25.4%) of patients, respectively. Patients received a median of 6 cycles of induction systemic therapy before resection and had a median interval between last administration of systemic therapy and liver resection of 41 days in patients without PVE and 47 days in patients with PVE before resection. At baseline, diaphragm, portal vein, and inferior vena cava were clinically involved in 52 (30.1%), 60 (34.7%), and 35 (20.2%) patients, respectively, as assessed by a central radiologic assessment by the panel radiologist.

Surgical Techniques

Thirty-six patients (20.8%) underwent a 2-stage resection including 10 (5.7%) ALPPS procedures. PVE was performed in 40 patients (23.1%) and 88 (50.8%) resections were classified as major resections. In 67 patients (38.5%), liver resection was combined with local tumor ablation. Surgeries had a median duration of 241 minutes, and in 136 patients (78.6%), an R0 resection was achieved. In patients with synchronous CRLM (n = 97), 88 patients (82.1%) underwent a liver-first procedure, 6 patients (6.2%) underwent combined liver and primary tumor resection and three (3.1%) patients had their primary tumor resected first. Approximately, half of the surgeries (54.3%) were performed in a university referral hospital. Blood transfusions were transmitted to 29 (16.8%) patients. Table 2 summarizes all the surgical-technical specifications.

Overall, 119 postoperative complications were documented in 66 (38.2%) patients. A total of 41 severe complications were reported in 27 (15.6%) patients. The number and type of severe complications are shown in Table 3. Thirty-day and 90-day mortality rates were 1.7% and 2.9%, respectively.

Predictive Factors Associated With Severe Complications

After univariable analyses, 4 factors were significantly correlated with severe postoperative complications: perioperative blood transfusion, 2-stage resection including ALPSS, major surgery, and triplet chemotherapy. No multicollinearity was found. After backward selection based on the highest *P* value of 2 factors, intraoperative blood transfusion, major surgery, and triplet chemotherapy were analyzed in a multivariable model. All 3 factors remained independently correlated with severe postoperative complications. This resulted for blood transfusion in an OR of 2.9 (95% CI 1.1–6.4, *P* = 0.03), for triplet chemotherapy in an OR of 2.6 (95% CI 1.1–7.5, *P* = 0.03), and for major resections in an OR of 2.9 (95% CI 1.1–7.5, *P* = 0.03). See Table 4.

Importantly, no correlation was found in the number of cycles of induction systemic therapy and occurrence of both overall postoperative morbidity and severe postoperative morbidity (OR 0.92, 95% CI 0.82–1.04, *P* = 0.18 and OR 0.92, 95% CI 0.78–1.09, *P* = 0.32, respectively), neither in the subgroup of patients who underwent major resections (OR 0.96, 95% CI 0.80–1.15, *P* = 0.69 and OR 0.96, 95% CI 0.78–1.19, *P* = 0.72, respectively). Furthermore, after categorizing the number of cycles of preoperative systemic therapy in 1 to 4 cycles, 5 to 8 cycles, and > 8 cycles, corresponding to 0 to 2, 2 to 4, and >4 months, no difference was found between the groups and severe complications (Fig. 2). In patients with an indication for further adjuvant systemic therapy after resection (until total length of 12 cycles), less patients with severe complications received adjuvant systemic therapy, as compared to patients without severe complications, 5 (18.5%) versus 52 (41.9%) patients, *P* = 0.023.

Major Resections and Severe Postoperative Complications

Severe complications were more common after major resections compared to minor resections, 23.9% versus 8.2%, *P* = 0.005. The 90-day mortality after major versus minor resections was 4.5% versus 1.2%, *P* = 0.186. Ten (6%) patients underwent an ALPPS procedure. Among patients who underwent the ALPPS procedure compared to patients with other liver procedures, the severe complication rate was 30% versus 15.3% and the 90-day mortality rate was 10% compared to 2.5%, respectively. However, this difference was not statistically significant. Nine of 10 ALPPS procedures were performed in a university hospital.

TABLE 1.

Baseline Patient Characteristics Total Cohort

Clinical Characteristics	All Patients (N = 173)
Age, years	
Median (IQR)	62 (55–70)
Sex, no (%)	
Male	112 (64.7)
Female	61 (35.3)
Site of primary tumor, no (%)	
Right colon	35 (20.2)
Left colon or rectum	138 (79.8)
Time to metastases, no (%)	
Synchronous	146 (84.4)
Metachronous	27 (15.6)
Mutational status, no (%)	
RAS/BRAF wildtype	90 (52.0)
RAS/BRAF mutation	83 (48.0)
Fong risk score, no (%)	
Low	0
Medium	97 (56.1)
High	73 (42.2)
Unknown	3 (1.7)
No. liver metastases, no	
Median (IQR)	9 (5–14)
Diameter of largest metastases, mm	
Median (IQR)	34 (24–58)
Diaphragm involved, no (%)	
Yes	52 (30.1)
No	113 (65.3)
Unknown	8 (4.6)
Hepatic vein involved, no (%)	
Yes	109 (63.0)
No	59 (34.1)
Unknown	5 (2.9)
Portal vein involved, no (%)	
Yes	60 (34.7)
No	109 (63.0)
Unknown	4 (2.3)
Vena cava involved, no (%)	
Yes	35 (20.2)
No	137 (79.2)
Unknown	1 (0.6)
No. liver segments involved, no	
Median (IQR)	5 (4–6)
Distribution of liver metastases, no (%)	
Unilobar	13 (7.5)
Bilobar	161 (92.5)
Induction systemic therapy, no (%)	
Doublet + bevacizumab	92 (53.2)
Doublet + panitumumab	37 (21.4)
Triplet + bevacizumab	44 (25.4)
No. cycles induction systemic therapy	
Median (IQR)	6 (5–9)
Days between last systemic therapy and surgery	
Median (IQR)	42 (32–42)
Best radiological response, no (%)	
Partial response	110 (63.6)
Stable disease	61 (35.3)
Progressive disease	2 (1.2)

IQR indicates interquartile range.

TABLE 2.

Surgical Specifications Total Cohort

Surgical Specifications	Total Cohort (N = 173)
Surgical and/or ablative treatment, no (%)	
Surgery only	98 (56.3)
Surgery + local ablative treatment	67 (38.5)
Local ablative treatment only	9 (5.2)
Two-stage procedure, no (%)	
Yes	36 (20.8)
Conventional two stage	26
ALPPS	10
No	137 (79.2)
Portal vein embolization, no (%)	
Yes	40 (23.1)
Right	39
Left	1
No	133 (76.9)
Type of procedure, no (%)	
Right HHT only	13 (7.5)
Right HHT with local resection and/or local ablative treatment	46 (26.6)
Left HHT only	2 (1.2)
Left HHT with local resection and/or local ablative treatment	6 (3.5)
Extended HHT only	6 (3.6)
Extended HHT with local resection and/or local ablative treatment	8 (4.6)
Local resection with/without local ablative treatment	83 (48.0)
Local ablative treatment only	9 (5.2)
Major resection	
Yes	88 (51)
No	85 (49)
Margin status, no (%)	
R0	136 (78.6)
R1	27 (15.6)
Local ablative treatment only	9 (5.2)
Unknown	1 (0.6)
Primary tumor resection, no (%)	
Resection at baseline	76 (43.9)
Combined primary and liver resection	6 (3.5)
Liver-first procedure	69 (39.9)
Primary-first procedure	3 (1.7)
Primary tumor not resected	17 (9.8)
Primary tumor resection unknown	2 (1.2)
Duration of surgery, min	
Median (IQR)	237 (176–335)
Hospital setting of resections	
University hospital	95 (54.3)
Non-university hospital	79 (45.7)
LOH	
One-stage procedure	
Median (IQR)	8 (6–10)
Two-stage procedure, total LOH of both procedures	
Median (IQR)	18 (15–23)
Blood transfusion	
Yes	29 (16.8)
Median amounts of units RBC, (IQR)	2 (2 – 4)
No	140 (80.9)
Unknown	4 (2.3)

HHT indicates hemihepatectomy; IQR, interquartile range; LOH, length of hospital stay; RBC, red blood cells.

Pathologic Response, Parenchymal Inflammation, and Number of Cycles

Central histopathological analysis was performed on resection specimens of 84 patients. A minor or no pathological response was found in 28 (33%) patients, and partial and major pathological responses were found in 28 (33%) and 28 (33%) patients, respectively. The number of cycles of induction systemic therapy was comparable across the pathological response groups, with a median of 6 cycles and no correlation was found between the number of cycles of systemic therapy and pathologic response (r = –0.108, P = 0.336). Peritumoral lymphocyte infiltration was present in 69 (81%) patients and portal lymphocyte infiltration in 23 (27%) patients. Combined peritumoral and portal lymphocyte infiltration was present in 23 (22%) patients. The number of severe complications was the same among patients with and without peritumoral, portal, or combined lymphocyte infiltration (data not shown).

TABLE 3.

Type of Postoperative Morbidity According to Clavien Dindo and Type of Severe Complications in Total Cohort

	Total Complications (n = 119)
Clavien Dindo Grade	
1	29 (24.0)
2	48 (39.7)
3a	23 (19.0)
3b	6 (5.0)
4a	5 (4.1)
4b	4 (3.3)
5	3 (2.5)
Type of severe complications (Clavien Dindo grade ≥ 3a only, n = 41)	
Aspiration	1
Sepsis	4
Biliary leakage	3
Wound infection	3
Shock	1
Ascites	2
Thromboembolic event	3
(Anastomotic) leakage	1
Urine retention	1
Gastroparesis	4
Inadequate nerve block	1
Fluid collection at resection site	1
Pneumothorax	1
Saturation decrease	1
Renal insufficiency and hypotension	1
Intraabdominal infection/abcess	4
Fever	1
Ileus	1
Supraventricular tachycardia	1
Pleural effusion	2
Liver failure	1
Diabetic ketoacidosis	1
Fever, biloma abdomen, and pneumonia	1
Breath depression and delirium	1

Patients may have had more than one complication.

DISCUSSION

In this prospective multicenter study, a well-defined group of patients with initially unresectable CRLM underwent extensive liver resections after modern induction systemic therapy. We report acceptable short-term postoperative morbidity and 90-day mortality. Risk factors independently correlated with severe postoperative complications were intraoperative blood transfusions, triplet chemotherapy, and major liver resection. The number of cycles of preoperative systemic therapy was not related to severe postoperative complications.

We observed an overall postoperative severe complication rate of 15.6% in the total cohort and 23.9% after major resections. The overall 90-day mortality rate was 2.9%. The cohort comprised mostly patients with very advanced disease based on number of liver metastases, the bilobar distribution of metastases and radiological involvement of diaphragm, portal vein, or inferior vena cava. This subsequently resulted in extensive and complex hepatic resections with a high PVE rate and high major resection rate of 51%.

Previously published data in the last decade on postoperative morbidity and mortality of resections of CRLM after preoperative systemic therapy comprise predominantly retrospective, single-center studies and are depicted in Table 5.[4,6–8,21,23–25,39–51]

TABLE 4.

Univariable and Multivariable Analysis Factors Predicting Severe Postoperative Complications

	Univariable Analysis			Multivariable Analysis		
Parameter	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age > 67	1.6	0.70–3.8	0.26	—		
RAS/BRAF mutation vs wildtype	1.0	0.44–2.3	0.99	—		
Bilobar disease	0.6	0.17–2.5	0.52	—		
Blood transfusion yes vs no	**3.1**	**1.2–7.7**	**0.019**	**2.9**	**1.1–6.4**	**0.03**
Triplet vs doublet chemotherapy	**2.4**	**1.0–5.4**	**0.041**	**2.6**	**1.1–7.5**	**0.03**
Targeted therapy; Anti-EGFR vs anti-VEGF therapy	0.9	0.34–2.4	0.81	—		
2-stage vs 1-stage	**2.7**	**1.1–6.6**	**0.028**	—		
PVE yes vs no	1.0	0.37–2.6	0.98	—		
ALPPS	2.3	0.57–9.8	0.23	—		
Major vs Minor resection	**3.0**	**1.1–7.9**	**0.028**	**2.9**	**1.1–7.5**	**0.03**
Primary tumor first vs liver first resection	3.5	0.76–16.1	0.11	—		
University vs non-university hospitals	1.5	0.65–3.6	0.33	—		
Number of cycles chemotherapy before resection	0.92	0.78–1.1	0.32	—		
Number of days between last chemotherapy and resection	0.99	0.97–1.0	0.41	—		

Severe postoperative morbidity and 90-day mortality in these studies ranged from 0% to 39.0% and 0% to 10.3%, respectively. The studies vary widely in the median number of metastases (2–8 metastases), the number of cycles of preoperative systemic therapy (6–12 cycles), and major resection rates (25% to 100%). This probably contributes to the variation in reported short-term postoperative outcomes. Furthermore, in 8 studies, the preoperative systemic therapy was specified as induction therapy for initially unresectable CRLM,[4,7,24,39–42] 1 study comprised neo-adjuvant therapy,[48] whereas the other studies did not specify the intention of preoperative therapy (neo-adjuvant/induction). Percentage of patients receiving targeted therapy ranged from 23% to 100% and was missing in 5 studies. Three studies[23,45,51] described patients who had received FOLFOXIRI induction systemic therapy, and only 1 study reported on postoperative morbidity or mortality outcomes in these patients.[51]

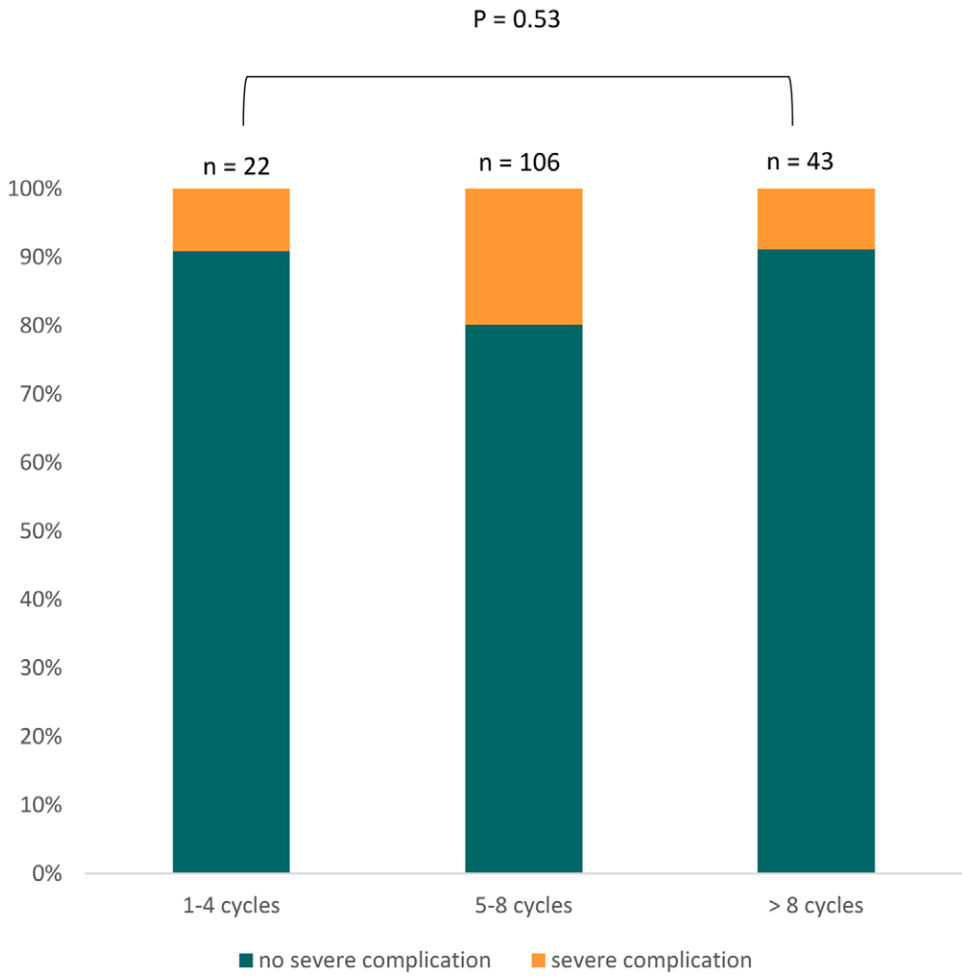

FIGURE 2. Number of cycles induction systemic therapy and severe complication rate following resection of colorectal liver metastases.

TABLE 5.

Overview of Characteristics and Short-Term Postoperative Outcomes of Studies or Subgroups of Studies Published After 2010 Regarding Patients With Resection of Colorectal Liver Metastases After Preoperative Systemic Therapy and Compared to This Study

Study	Type Study	Total Patients	Study Period	Preoperative Systemic Rx %	Intention syst Rx %	Targeted Rx %	Triplet Rx %	Median Number Cycles	Median Number CRLM	Major Resection %	Morbidity %	Severe Morbidity %	90-day Mortality %	Remark
CAIRO5 trial 2021	RCT	173	2014–2019	100	Induction	100	25	6	9	51	38	16	2.9	Present study
BECOME trial 2020—JCO	RCT	34	2013–2017	100	Induction	79	0	—	—	—	—	15	—	No data reported on surgical specifications
PLANET-TTD 2017—EJC	RCT	28	2009–2012	100	Induction	100	0	—	—	—	32	—	—	No data reported on surgical specifications
OLIVIA 2015—*Ann Oncol*	RCT	44	2008–2011	100	Induction	100	51	6	—	—	68	36	4.5	No data reported on surgical specifications
EPOC-2 2014—*Lancet*	RCT	198	2007–2012	100	Neo-adjuvant	50	0	—	<3	—	—	23	—	Resectable CRLM only
Ye et al. 2013—*JCO*	RCT	22	2008–2011	100	Induction	51	0	—	—	—	0	0	0	No data published on surgical specifications. No explanation morbidity and mortality rates
Tsim et al. 2011 *Ann Surg Oncol*	Prosp.	38	2003–2006	100	Induction	—	—	8–10	4	100	33	12	0	All patients underwent 2-stage resections
Brouquet et al 2011–*JCO*	Prosp	47	2002–2010	100	Induction	74	0	6	7	85	49	26	6.4	All patients underwent 2-stage resections Reported rates of completed 2-stage resection
Elfrink et al 2020—*EJSO*	Retrosp	1314	2014–2018	100	n.r.	—	—	—	—	33	15	10	1.9	Major resection defined as segmentectomy of 3 or more.
Wiseman et al 2019—*JACS*	Retrosp.	1416	2014–2016	100	n.r.	—	—	—	< 3	25	34	—	0.8	Type of systemic therapy unknown
Fukuoka et al 2017—*WJS*	Retrosp	439	2005–2014	19	n.r.	38	0	187*	2	25	29	2	0	Systemic therapy comprised: systemic therapy for CRLM including adjuvant systemic therapy primary tumor
Ubink et al 2016—*Clin Colorect* Canc	Retrosp.	270	2000–2015	29	n.r.	—	—	—	2	43	—	27	4	Type of systemic therapy unknown
Lock et al 2017—*JACS*	Retrosp.	204	2006–2012	62	n.r.	59	14	11	—	53	—	14	3	Any Chemotherapy < 12 months prior to liver resection
Passot et al. 2016—*JACS*	Retrosp.	89	2003–2014	100	n.r.	—	—	6	6	82	—	26	7	All patients underwent 2-stage resections Reported rates of patients with completed 2-stage resection
Giakoustidis et al. 2014—*Hepat Oncol*	Retrosp	236	2005–2012	100	n.r.	44	0	6	2	57	37	17	3	Only 2-stage >80% VPE 12 % extrahepatic disease
Reissfelder et al 2014—*Surgery*	Retrosp.	119	2002–2010	100	n.r.	47	20	—	—	50	30	—	1.6	No effect of FOLFOXIRI described
Wolf et al 2013—*JACS*	Retrosp	506	2003–2007	65	n.r.	29	0	168^	—	61	32	10	0	Any Chemotherapy < 6 months prior to liver resection
Shindoh et al 2013—*Ann Surg Oncol*	Retrosp.	194	1993–2011	66	n.r.	63	0	—	—	100	48	24	4	All extended right hemihepatectomy
Turrini et al 2012—*EJSO*	Retrosp.	48	2000–2010	100	Induction	42	0	8	8	71	20	12	6	All patients underwent 2-stage resections
Cauchy et al 2012—*Ann Surg*	Retrosp.	257	2000–2011	100	Induction	55	—	12	6	94	84	39	10.3	All patients underwent VPO as this was the definition of initially unresectable disease
Spelt et al 2012—*WJS*	Retrosp.	97	2000–2009	100	n.r.	23	—	7	2	63	63	4	0	—

*Value presents the number of days of systemic therapy.

n.r. indicates not reported; Prosp, prospective; RCT, randomized clinical trial; Retrosp, retrospective; Rx, therapy.

Five prospective RCTs published data on short-term postoperative outcomes after 2010, although this data were minimal for resections details, postoperative complications, and 90-day mortality rate.[40,41,48,51–54] Although these factors hamper inter-study comparison, the severe morbidity and mortality rate reported in the present study compare favorably with the majority of previously reported data after preoperative systemic therapy and support the increase of complex liver surgeries, whereas the long-term survival benefits need to be taken into account as well. These acceptable short-term outcomes might reflect the overall improvement of surgical (parenchymal-sparing) techniques[55] and careful selection of patients based on FLR volume and function.[1,8]

Varying results have been published concerning the association between the number of cycles of systemic therapy and severe postoperative outcomes. In patients with >12 cycles induction systemic therapy, Cauchy et al[24] reported remarkably high postoperative mortality (19%) and major morbidity (55%) rates strongly correlated with parenchymal liver injury, and Aloia et al[56] reported a higher reoperation rate in these patients. Other studies deny a correlation of postoperative severe morbidity and the number of cycles of preoperative systemic therapy.[1,23,24] However, the cohort of Cauchy et al concerned a heavily pretreated population with a median number of cycles of 12, 30% of patients had received >1 line systemic therapy before liver surgery and all patients underwent portal vein occlusion as this was their definition of initially unresectable CRLM. In the present study, no correlation was found between both the number of cycles of induction systemic therapy and liver parenchymal inflammation and severe postoperative complications, neither in the subgroup with major resections, but it should be noted that the median number of cycles in our cohort was 6 and comprised the first-line systemic therapy in all patients. Furthermore, bevacizumab has shown to prevent liver parenchymal injury caused by cytotoxic agents and this might have played a role in our results since 75% of patients in our cohort received bevacizumab.[43,57,58]

To our knowledge, this study is the first to analyze the prognostic impact of triplet and doublet chemotherapy in combination with targeted agents in regard to postoperative morbidity and mortality after liver resection. A surprising outcome was the strong association between severe postoperative complications and triplet chemotherapy as compared to doublet chemotherapy. This is in line with the results of the OLIVIA trial, which reported a severe postoperative morbidity rate of 40% in patients receiving triplet induction chemotherapy with bevacizumab.[51] Since oxaliplatin is known to contribute to occurrence of a "blue liver" based on sinusoidal injury[59] and irinotecan may cause a "yellow liver" by steatohepatitis,[16,60] the combination of both oxaliplatin and irinotecan in triplet chemotherapy may have an extra detrimental effect on the liver. Further histopathological analysis of livers of patients receiving triplet chemotherapy might help to further analyze the association between postoperative complications and triplet chemotherapy. For clinicians treating patients with CRLM, this study shows that intensification of systemic therapy in an attempt to increase resection rates and long-term outcomes comes at a cost of increased short-term postoperative outcomes. The postoperative mortality did not differ between doublet and triplet chemotherapy backbone.

This study has some limitations. Histopathologic assessment was performed on liver metastases only and to better assess the liver injury caused by cytotoxic agents and association with postoperative morbidity rate, assessment of liver parenchyma for the presence of sinusoidal obstruction syndrome, steatohepatitis, and parenchymal necrosis would be informative. Furthermore, underlying liver disease is an important risk factor for postoperative complications, but remains difficult to predict without the availability of a preoperative tissue biopsy or liver function tests.

CONCLUSION

In this large prospective multicenter randomized controlled trial in patients with advanced initially unresectable CRLM undergoing liver resections after modern induction systemic therapy, we report acceptable postoperative morbidity and mortality rates. The number of cycles of preoperative systemic therapy was not related to severe postoperative complications. These results support the increase of complex liver surgery and number of cycles of first-line induction systemic therapy should not be a contraindication to liver resection. Risk factors that independently correlated with severe postoperative complications were major resection, intraoperative blood transfusions, and triplet induction chemotherapy. Careful patient selection considering the type of preoperative systemic treatment as well as efforts to perform parenchymal-sparing resections might help to further reduce the severe complication and mortality rate.

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