Journal of Gastrointestinal Surgery
https://doi.org/10.1007/s11605-023-05633-9

ORIGINAL ARTICLE

Predicting Limited Survival After Resection of Synchronous Colorectal Liver Metastases: a Propensity Score Matched Comparison Between The Primary First And The Simultaneous Strategy

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Received: 29 November 2022 / Accepted: 11 February 2023

Abstract

Background The best surgical approach to treat synchronous colorectal liver metastases (CRLM) remains unclear. Here, we aimed to identify prognostic factors associated with limited survival comparing patients undergoing primary-first resection (PF) and simultaneous resection (SR) approaches.

Methods We retrospectively reviewed clinical data of 217 patients who underwent resection for synchronous CRLMs between January 1, 2011, and December 31, 2021. There were 133 (61.2%) PF resection and 84 (38.8%) SRS. The two groups of patients were compared using propensity score matching (PSM) analysis and cox analysis was performed to identify prognostic factors for overall survival (OS).

Results After PSM, two groups of 71 patients were compared. Patients undergoing SR had longer operative time (324 ± 104 min vs 250 ± 101 min; $p < 0.0001$), similar transfusion (33.3% vs 28.1%; $p = 0.57$), and similar complication rates (35.9% vs 27.2%; $p = 0.34$) than patients undergoing PF. The median overall survival and 5-year survival rates were comparable ($p = 0.94$) between patients undergoing PF (48.2 months and 44%) and patients undergoing SR (45.9 months and 30%). Multivariate Cox analysis identified pre-resection elevated CEA levels (HR: 2.38; 95% CI: 1.20–4.70; $P = .01$), left colonic tumors (HR: 0.34; 95% CI: 0.17–0.68; $P = .002$), and adjuvant treatment (HR: 0.43; 95% CI: 0.22–0.83; $P = .01$) as independent prognostic factors for OS.

Conclusions In the presence of synchronous CRLM, right colonic tumors, persistent high CEA levels before surgery, and the absence of adjuvant treatment identified patients characterized by a limited survival rate after resection. The approach used (PF vs SR) does not influence short and long-term outcomes.

Keywords Colorectal liver metastases · Liver resection · Simultaneous resection · Colorectal resection · Survival

Introduction

Synchronous liver metastases are present at the time of diagnosis of colorectal cancer (CRC) in up to 25% of patients, and nearly 50% of patients with a CRC will later develop liver metastases.[1,2] Progresses in chemotherapy include multidrug chemotherapeutics combined with targeted therapies (bevacizumab and cetuximab). These strategies have led to a dramatic improvement in the overall survival of patients diagnosed with synchronous colorectal liver metastases (CLRM).[1]

Surgical strategies for synchronous CRLM include the primary-first approach, simultaneous resection of the primary and the LM, and the reverse approach.[3–5] In the primary-first approach, the colonic tumor is removed first and then a staged liver resection is performed later.[6] In the simultaneous strategy, the primary and the LM are resected simultaneously. The reverse approach is mainly used for patients with a high tumor liver burden: Here, resection of the LM is performed first before the primary colorectal tumor is removed.[7]

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Published online: 01 March 2023

The best strategy for resection for synchronous CRLM remains unclear, and none of the three approaches has shown superiority over the others.[5] Analysis of the recent literature indicates that (1) the three approaches carried similar morbidity and mortality[5]; (2) a primary-first strategy has been associated with impaired overall survival in a recent randomized trial[3]; and (3) the reverse approach is associated with shorter disease–free survival and a higher rate of extrahepatic recurrence.[8,9] Patients with synchronous CRLM require prognostic factors associated with higher recurrence rates and limited OS to avoid futile resection, adapt clinical surveillance, and give adjuvant therapy. This study aims to identify prognostic survival factors after resection of synchronous CRLM and identify factors associated with limited long-term survival.

Methods

Data Selection

This retrospective cohort study was conducted at the Hepato-Pancreato-Biliary Surgery and Liver Transplantation Center of the University of Strasbourg, France. Data were prospectively collected in our institutional database and retrospectively analyzed under IRB approval for all patients who underwent resection of synchronous colorectal liver metastases between January 1, 2011 and December 31, 2021. The exclusion criteria were patients undergoing resection of metachronous CRLM ($n=90$) and/or simultaneous resection of CLRM associated with peritoneal nodules resection and hyperthermic intraperitoneal chemotherapy ($n=15$).

Indications for Surgery, Data Collection, and Study Definitions

Indications for surgery were discussed during multidisciplinary meetings among surgeons as well as an oncologist, radiologist, and radiotherapist. The preferred approach among patients first referred at our institution with a primary colorectal and synchronous CLRM was simultaneous resection.[6] These patients generally underwent neoadjuvant chemotherapy followed by restaging and synchronous resection of both the primary colorectal tumors and liver metastases.

In the case of staged resection, the medical oncologist usually referred patients after neoadjuvant chemotherapy with the primary colorectal tumors already removed by colorectal surgeons (primary-first approach). For all patients, surgical strategy was tailored according to the number, distribution (unilobar versus bilobar), and vascular contact of LMs. A parenchymal-sparing strategy entailing either multiple liver resections and/or resection combined with radiofrequency ablation was preferred over major hepatectomies.[10,11] However, major hepatectomy were performed as needed in the case of extensive bilobar disease and/or vascular or biliary invasion (portal, caval). Finally, some patients had extensive bilobar disease treated via a two-stage strategy—the first stage consisted of primary tumor resection and clearance of the future liver remnant (usually the left liver) followed by a percutaneous right portal vein embolization. Right and extended right hepatectomies were then performed 8 weeks later, and adjuvant chemotherapy was still administered in the interval between portal vein embolization and right hepatectomy.

Per our policy, colorectal resections were performed first followed by liver resection when the simultaneous resection strategy was selected.[12] A temporary diverting ileostomy was systematically performed in the case of low rectal resection and/or after pre-operative radiotherapy to reduce the risk of colorectal fistula. The ilesoostmy was usually taken down 8 weeks after surgery or at the end of the adjuvant chemotherapy. Adjuvant chemotherapy was considered in all patients except for patients presenting poor post-operative performance status and/or in the presence of extensive pre-operative chemotherapy (> 12 cycles).

The data collected included demographics as well as operative and survival variables (including operative time, transfusion requirement, and 90-day morbidity and mortality rates). The presence, type, and duration of pre-operative and post-operative chemotherapy was recorded. The type and extent of liver surgery was classified according to the Coinaud's classification (i.e., major hepatectomy ≥ 3 contiguous liver segments).[13] The use and duration of pedicular clamping and radiofrequency ablation were recorded as well. Morbidity was graded according to the Clavien-Dindo classification with major morbidity including complications classified as IIIA or above[14] Liver failure and post-operative bile leaks were defined according to the international guidelines.[15–18] Resection was defined as R1 based on the presence of tumor cells within 1.0 mm of any margins of resection. Overall survival (OS) was calculated as the length of time from surgery to the patient's death; recurrence-free survival was defined as the length of time from surgery to the detection of any form of recurrent disease. The date of last follow-up was September 1, 2022.

Statistical analysis

The results for continuous data were expressed as the mean ± standard deviation or the median and range, where appropriate. Categorical variables are presented as numbers

and percentages. Differences between groups were assessed by the chi-squared or Fisher's exact test for categorical variables, where appropriate. In the case of continuous variables, the Wilcoxon rank-sum test or the student's *t*-test was used, where appropriate. The estimated survivals were calculated according to Kaplan–Meier methods; differences were assessed by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model with a stepwise approach in the whole cohort. Variables with $P < 0.20$ were included in the multivariate model. In a second step, a propensity score matching (PSM) was performed to minimize the risk of selection bias related to patients and tumor characteristics due to the retrospective nature of this study. The PSM scores were built using a logistic regression model that included the following six covariables: primary tumor location (right versus left), gender (male versus female), patient's age ($\leq$ or $>$ 70 years), tumor numbers ($\leq$ or $>$ 3), distribution of tumors (unilobar versus bilobar), use of adjuvant chemotherapy (yes versus not). A 1/1 "nearest neighbor" match paradigm was used, each patients in the group primary first was matched with one patient of the simultaneous group who had the closest estimated propensity score. The two groups were controlled for covariate balance and similarity in the baseline covariates. The two matched groups were compared with respect to the main outcomes of this study. Multivariable analysis for OS was performed for the PSM matched population. The level of significance was set at 0.05, and two-sided *P*-values were computed. Statistical analyses used SAS software (release 9.4, SAS institute, Cary, NC).

Results

Operative Procedures and Post-operative Outcomes

According to our selection criteria during the study period, 217 consecutive patients underwent resection for synchronous CRLM. Of these, 133 (61.2%) underwent resection of the primary colorectal tumor resection followed by resection of LM (primary-first approach); 84 (38.8%) underwent a simultaneous resection of the primary colorectal tumor and LM (simultaneous resection approach). Among patients undergoing the primary-first approach, the mean interval of time between the resection of the primary and the resection of CRLMs was 4.4 ± 6.3 months (median 4.06 months). The median age was 64 years (range: 18–87 years; 126 men and 91 women) (Table 1). The primary colorectal tumor was located in the rectum, left colon, and right /transverse colon in 27%, 49%, and 24% of the patients, respectively. Before liver resection, pre-operative chemotherapy was administered to most of the patients (90.3%) with a median number of six pre-operative cycles (range: 2–24 cycles); 41 patients (18%) underwent ≥ 12 cycles.

Table 1 Clinical characteristics of patient population ($n = 217$)

Age	64 (18–87)
Age > 70	44 (20.8%)
F/M	91/126
BMI	25 (16–54)
Charlson comorbidity index	8 (6–17)
CEA (μ/l) (mean, median, range)	62.7/5.15 (0.8–3438)
CA19-9 (kU/l) (mean, median, range)	114.7/19.6 (0.7–3693)
Primary tumor	
Rectum	59 (27%)
Left colon	107 (49%)
Right/transverse colon	51 (24%)
Lymphnode-positive primary tumor	140 (64%)
Preoperative chemotherapy	196 (90.3%)
Median number of preoperative chemotherapy cycles	6.0 (0–24)
> 12 cycles	41 (18.8%)
Type of approach	
Primary first	133 (61.2%)
Simultaneous resection	84 (38.8%)
Operative time	265 (75–545)
Hepatic pedicle clamping	111 (51%)
Median total duration of clamping	15 min (0–105)
Two-stage hepatectomy	40 (18.4%)
Colo-rectal resection	84 (39%)
Ileostomy closure	24(11%)
Trasfusions	62 (28.5%)
Morbidity	59 (27.1%)
Mortality	2 (0.9%)
Reoperation	6 (2.7%)
R1 resection	37 (17%)
Adjuvant chemotherapy	156 (72%)
Recurrence	167 (77%)
Rehepatectomy for recurrence	57 (26%)

Data were expressed as median(range).

Elevated CEA was present in 72 patients (33.1%) with a mean serum value of 62.7 ng/ml (median 5.15, range 0.5–3438 ng/mL). Elevated CA19-9 was present in 58 patients (26.7%) with a mean serum value of 114 U/mL (median 19 range: 0.7–3693U/mL). The median operative time was 265 min; 28.5% of the patients were transfused and 51% had intermittent hepatic pedicle clamping during CRLM resection. The overall mortality and morbidity were 0.9% ($n = 2$) and 27%, respectively.

Specific complications of colorectal surgery, such as leaks, occurred in three patients—two (2.3%) after simultaneous resection of a rectal cancer and LM, and one into the primary-first group due to a leak after colostomy reversal.

In 14.7% ($n=32$) of the patients, an R1 resection was performed, and adjuvant chemotherapy was used in 72% of patients. Patients not undergoing adjuvant chemotherapy were more likely to have 12 or more pre-operative cycles (63.4% vs 36.5%; $p<0.0001$) and had had higher post-operative morbidity (45% vs 22%; $p<0.0001$).

Among the 40 patients for whom a two-stage hepatectomy approach was planned, five (12.5%) did not achieve the second stage because of disease progression. The median OS was 49.8 months (95% CI: 38.1–56.2), and OS rates at 1, 3, 5, and 10 years were 91%, 61%, 39%, and 12%, respectively. The median recurrence-free survival was 9.24 months (95% CI: 8.1–11.6).

Median OS was longer in the presence of pre-resection normal CEA values (53.2 vs 26.0 months; $P=0.001$), wild type KRAS tumors (56.2 vs 33.1 months; $P=0.05$), less than 8 LMs (53.3vs 23.4 months; $P=0.01$), and when adjuvant chemotherapy was given (54.7 vs 23.4 months; $P=0.0001$). Multivariate Cox analysis found pre-resection elevated CEA levels (HR: 1.70; 95% CI: 1.06–2.73; $P=0.02$), and adjuvant treatment (HR: 0.53; 95% CI: 0.32–0.86; $P=0.01$) as independent prognostic factors for OS (Table 2). During a median follow-up of 28 months (range, 0.6–140.1 months), recurrence was detected in 77% of the patients. Type of recurrence was intrahepatic ($n=84$; 51, 8%), extrahepatic ($n=35$; 21; 6%), and intrahepatic and extrahepatic ($n=43$; 26.5%). Fifty seven patients with liver recurrence ($n=57$; 26.5%) underwent repeat liver resection.

The Impact of Surgical Approach on Post-operative and Oncological Outcomes After Propensity Score Matching

Tables 3 and 4 depicted comparison between patients with the primary-first approach and simultaneous resection before and after PSM matching. The PSM procedure generated two groups of 71 patients each. After PSM patients undergoing PF strategy showed longer time elapsed from diagnosis to complete clearance of all disease compared with SF strategy (9.7 ± 6.01 months vs 6.1 ± 4.23 months; $p=0.003$).

Patients undergoing the primary-first resection had comparable pre-operative characteristics but lower mean CEA pre-resection levels (27.13 ± 116 vs 136 ± 489.3; $p=0.08$), and higher rate of colorectal resection performed laparoscopically (43% vs 5.63%; $p<0.0001$).

After PSM matching, patients undergoing simultaneous resection had lower rate of pre-operative chemotherapy (78.8% vs 97.1 = %; $p=0.001$), but comparable tumor burden mean maximum tumor size and rate of a two-stage hepatectomies ($p>0.05$) (Table 3). Synchronous resections took longer operative time (324 ± 104 min vs 250 ± 101 min; $p<0.0001$) but a comparable transfusion (33.3% vs 28.1%; $p=0.57$) and complication rates (27.2% vs 35.9%; $p=0.34$). Interestingly, in the group of synchronous resections, there was no differences in morbidity between patients undergoing minor and major hepatectomies (16/64 (25%) vs 7/20 (35%); $p=0.40$).

Median overall survival and 5-year survival rates were slightly longer in patients undergoing a primary-first strategy (48.2 months and 44%) versus simultaneous resection (45.9 months and 30%), but this did not reach statistical significance ($p=0.94$). Patients undergoing primary-first and simultaneous resections had comparable rates of intrahepatic and extrahepatic recurrence and a similar rate of repeat hepatectomy for hepatic recurrence (26% vs 25.7%; $p=1.00$) and similar recurrence-free survival (8.13 months vs 11.5; $p=1.00$) (Table 4). In the PSM population, multivariate Cox analysis identified pre-resection elevated CEA levels (HR: 2.38; 95% CI: 1.20–4.70; $P=0.01$), left colonic tumors (HR: 0.34; 95% CI: 0.17–0.68; $P=0.002$), and adjuvant treatment (HR: 0.43; 95% CI: 0.22–0.83; $P=0.01$) as independent prognostic factors for OS.

Discussion

This study confirmed that the simultaneous resection and the primary-first approach achieve similar morbidity and mortality in presence of synchronous liver metastases. The type of surgical strategy was not identified as a statically significant prognostic factor for overall survival. Indeed, right colonic tumors, elevated CEA levels before resection of liver metastases as well as administration of adjuvant treatment were identified as independent prognostic factors. The concurrent presence of these factors identified a group of patients characterized by limited survival rate after resection of synchronous CRLM.

The combination of simultaneous liver resection and colorectal surgery can theoretically carry a higher rate of specific complications. In particular, the performance of hepatic pedicular clamping during simultaneous resection of the primary and CRLM could lead to bowel edema and leaks in the colorectal sutures[19] . A recent study by Snyder et al.[20] found that patients undergoing a simultaneous colorectal and liver resection for synchronous CRLM present higher morbidity and mortality rates than isolated colorectal or liver resection. Interestingly, these authors reported that the rate of anastomotic leakage was also higher when a simultaneous resection was performed (7.9 vs 3.8%). However, this study lacked details about the type of liver resection, the use of pedicular clamping, and the use of diverting stoma probably leading to a biased comparison. In the current study, the rate of colorectal leaks was within the range of the literature among patients undergoing the simultaneous strategy; both groups had similar rates of hepatic pedicle clamping and major liver resection. Guerra

Table 2 Univariate and multivariate Cox regression analysis of overall survival

Characteristics		Univariate analysis			Multivariate analysis			Multivariate analysis after PSM		
	Median survival Log-rank (months)	HR	95% CI	*p*	HR	95% CI	*p*	HR	95%CI	*p*
Gender										
Female	51.31	0.88	(0.61–1.29)	0.53						
Male	45.90									
Age(years)										
< 70 vs	50.69									
> 70 years	38.16	1.30	(0.83–2.05)	0.24						
Elevated CEA										
Yes	26.42	1.94	(1.31–2.89)	0.001	1.78	(1.13–2.81)	0.01	1.90	(1.00–3.59)	0.04
Not	53.21									
Tumor localization										
Right colon	46.88	1.36	(0.90–2.05)	0.13				0.37	(0.19–0.71)	0.002
Left colon and rectum	56.31									
Elevated CA19.9										
Yes	26.62	1.81	(1.20–	0.004						
Not	50.68		2.72)							
Lymphnode positivity of the primary										
Yes	47.4									
Not	49.2	1.12	(0.73–1.69)	0.59						
Preoperative chemotherapy										
Yes	51.02									
No	49.08	0.96	(0.55–1.68)	0.91						
Surgical approach										
Primary first	61.14	0.64	(0.42–0.95)	0.03						
Simultaneousresection	41.83									
LM distribution										
Unilobar	57.93									
Bilobar	41.83	1.53	(1.03–2.30)	0.03						
K-RAS										
Wild	56.2									
Mutated	33.1	1.52	(0.98–2.37)	0.05						
Number of LM										
≥ 3	38.14									
1–2	55.73	1.38	(0.93–2.02)	0.10						
Number of LM										
≥ 8	23.41	1.64	(1.08–2.50)	0.01						
1–7	51.31									
Major hepatectomy										
Yes	32.49	1.40	(0.91–2.16)	0.12						
Not	51.21									
Radiofrequency ablation										
Yes	49.08	1.01	(0.69–1.47)	0.95						
Not	50.6									
Two-stage										
Yes	39.01									
Not	51.31		(0.95–2.23)	0.08						
Transfusion										

Table 2 (continued)

Characteristics		Univariate analysis			Multivariate analysis			Multivariate analysis after PSM		
	Median survival Log-rank (months)	HR	95% CI	*p*	HR	95% CI	*p*	HR	95%CI	*p*
Yes	28.78									
No	52.62	1.64	(1.10–1.44)	0.01						
Morbidity										
Yes	25.80									
No	51.21	2.65	(1.07–2.56)	0.02						
Margin status										
R0	51.21									
R1	33.67	1.56	(0.91–2.68)	0.10						
Adjuvantchemotheraphy										
Yes	54.72				0.49	(0.31–0.77)	0.0009	0.37	(0.20–0.70)	0.002
Not	23.47	2.11	(1.43–3.10)	0.0001						

et al. recently demonstrated similar leaks rate (9.4% vs 6.3%) in patients undergoing simultaneous strategy and isolated resection of colorectal cancer after propensity score matching of patients based on several clinical characteristics including the type and technique of colorectal resection.[21] These authors identified longer operative times as the sole risk factors for anastomotic leakage underlying the need for accurate selection of the patients for simultaneous procedures and/or to choose a staged approach when higher technical complexity is reasonably expected.

Perioperative chemotherapy is currently the main pillar for the treatment of synchronous CRLM. Pre-operative treatment provides a valuable time to observe the disease evolution and its response to treatment. We found that the rate of pre-operative chemotherapy administration was as high as 90% with 20% of patients receiving more than 12 pre-operative cycles. This reflects a longer interval of time needed to achieve radiological and biological response in patients with elevated tumoral burden and aggressive disease. This could also be related to a selection bias with some of our patients

Table 3 Comparison between patients undergoing simultaneous and primary-first resection for synchronous colorectal liver metastases

Before propensity score matching				After propensity score matching		
	Primary first ($n=133$)	Simultaneous resection ($n=84$)	*P*	Primary first ($n=71$)	Simultaneous resection ($n=71$)	*P*
AGE[1]	62 ± 11	61 ± 10	0.39	59.73 ± 11.70	60.88 ± 10.33	0.53
AGE > 70	28(21%)	16(19%)	0.86	11(15.4%)	13(18.3%)	0.82
Male	77(58%)	49(58%)	1.00	41(57.5%)	42(59.1%)	1.00
CCI score	8.07 ± 1.50	8.51 ± 1.79	0.06	8.16 ± 1.61	8.04 ± 1.55	0.75
BMI	25.4 ± 4.6	25.9 ± 5.7	0.44	25.39 ± 4.13	25.65 ± 4.72	0.29
Localization Primary tumor						
Rectal primary	35	24	0.92	20	21	
Left colon	66	41		36	34	0.94
right-Trasverse colon	32	19		15	16	
Chemotherapy before colonic resection	31.06%	78.5%	< 0.0001	38.03%	78.87%	< 0.0001
Lymphnode-positive primary tumor	67.2%	69.8%	0.76	67%	71%	0.71
Mean LN-positive	2.53 ± 3.72	2.49 ± 4.47	0.94			
KRAS-mutated tumors	45	27	0.41	24	23	0.33
Surgical approach for the primary tumor						
Laparotomy	81	80	< 0.0001	40	67	< 0.0001
Laparoscopy	51(38%)	4(4.7%)		31(43%)	4(5.63%)	

Table 4 Comparison between patients undergoing primary-first resection and simultaneous resection for synchronous colorectal liver metastases

Before propensity score matching				After propsensity score matching		
	Primary first ($n=133$)	Synchronous resection ($n=84$)	*P*	Primary first ($n=71$)	Synchronous resection ($n=71$)	*P*
Mean time to achieve the complete surgical planning (months)	10.5 ± 7.08	6.4 ± 4.4	< 0.0001	9.71 ± 6.01	6.17 ± 4.23	0.003
ACE	25 ± 90	123 ± 451	0.02	27.13 ± 116.7	136.1 ± 489.3	0.08
Preoperative chemotherapy	130(97.7%)	66(78.5%)	< 0.0001	69(97.1%)	56(78.8%)	0.001
Mean preoperative cycles	6.4 ± 3.7	6.3 ± 5.2	0.89	5.9 ± 3.5	5.9 ± 4.7	0.90
> 12 cycles	16%	24%	0.15	14%	20%	0.50
FOLFOXIRI	5(3.8%)	8(9.5%)	0.13	2(2.8%)	4(5.6%)	1.00
FOLFOX	85(65.3%)	32(48.4%)	0.02	45(63.3%)	35(49.2%)	0.12
FOLFIRI	33(27%)	23(35%)	0.31	15(21.1%)	17(23%)	0.84
CETUXIMAB	13(10%)	12(14.2%)	0.51	6(8.4%)	9(12.6%)	0.58
BEVACIZUMAB	55(42.3%)	25(29.7%)	0.44	30(42.2%)	21(29.5%)	0.16
Number of liver lesion at imaging	6.3 ± 7.6	5.9 ± 6.9	0.68	7.24 ± 7.41	5.94 ± 7.30	0.30
Bilobar distribution	78(59.9%)	59(70.2%)	0.11	47(66.2%)	46(64.7%)	1.00
≥ 3 lesions	59(47.5%)	49(59.7%)	0.09	43(60%)	42(59.1%)	1.00
≥ 8 lesions	32(25.8%)	16(19.5%)	0.31	20(30.7%)	13(18.8%)	0.15
≥ 15 lesions	14(11.2%)	8(9.76%)	0.82	10(15.3%)	7(10.1%)	0.44
Missing metastases	24(19%)	10(12%)	0.18	14(21.5%)	7(10.11%)	0.09
Number of liver lesion found intra-operatively	7.6 ± 9.8	7.2 ± 7.5	0.76	8.58 ± 10.01	6.81 ± 7.46	0.24
Maximum tumor size (mean)	32.2 ± 25.0	39.6 ± 29.6	0.05	34.96 ± 26.46	40.82 ± 30.85	0.21
Major hepatectomy	26(19.5%)	20(23.1%)	0.49	12(15.9%)	18(25.3%)	0.30
Two-stage	18(13.5%)	22 (26.1%)	0.03	14(19%)	20(28%)	0.32
Radiofrequency ablation	47(35%)	32(38%)	0.77	28(39.4%)	25(35.2%)	0.72
Hepatic pedicle clampage	71(58%)	40(50.6%)	0.31	35(54.6%)	34(51.5%)	0.72
Operative time	243 ± 92	327 ± 103	< 0.0001	250 ± 101	324 ± 104	< 0.0001
transfusions	35(28.6%)	27(34.1%)	0.43	18(28.1%)	22(33.3%)	0.57
Mortality	1(0.07%)	1(0.01%)	0.99	1	1	1.00

Table 4 (continued)

Before propensity score matching				After propsensity score matching		
	Primary first ($n=133$)	Synchronous resection ($n=84$)	*P*	Primary first ($n=71$)	Synchronous resection ($n=71$)	*P*
morbidity	37(30.3%)	22(27.8%)	0.75	23(35.9%)	18(27.2%)	0.34
Reoperation	1(0.7%)	4(4.7%)	0.21	2(2%)	3(4.2%)	0.41
R1 resection	17(14.5%)	15(20.5%)	0.28	7(11.6%)	11(18.3%)	0.44
Adjuvant chemotherapy	99(74.4%)	57(67.8%)	0.35	54(76%)	50(70.4%)	0.56
Recurrence	80%	75%	0.50	57(80%)	57(80%)	1.00
Median recurrence-free survival (months)	11.6	8.1	0.03	11.5	8.13	0.18
Type of recurrene						
Intrahepatic	48(50%)	36(54%)	0.65	25(43.8%)	31(54.3%)	0.52
Extrahepatic	20(20%)	15(23%)		18(34%)	14(26.4%)	
Intrahepatic and extrahepatic	28(30%)	15(23%)		14(26.4%)	12(22.6%)	
Rehepatectomy	36(27%)	20(23.8%)	0.63	19(26%)	18(25.7%)	1.00
Median OS (months)	54.7	42.3	0.25	48.2	45.9	0.94
5-year survival	45%	30%		44%	30%	

initially deemed unresectable by the medical oncologist who was secondarily consulted after a longer interval of pre-operative chemotherapy. This could also explain the longer interval of time needed to achieve complete clearance of all disease in patients undergoing the primary resection first observed in our study even after PSM (9.71 ± 6.01 months vs 6.1 ± 4.2 months; $p = 0.003$).

The administration of post-operative chemotherapy was also identified as a significant prognostic factor associated with decreased overall survival. Not having adjuvant chemotherapy was associated either with having higher number of chemotherapy cycles given pre-operatively (> 12 cycles) or the occurrence of post-operative morbidity. In a previous study on synchronous strategy for CRLM resection, Driedger et al. demonstrated that the occurrence of post-operative morbidity was associated with failure to receive adjuvant chemotherapy and worsened survival.[22] They found that 37.5% of patients undergoing major colorectal resection with major liver surgery had post-operative morbidity that precluded adjuvant chemotherapy. We did not find any increase in the morbidity of patients with major hepatectomy in the synchronous group perhaps because of the use of portal vein embolization in patients undergoing a two-stage strategy and the institutional long-lasting experience in synchronous resection.[6]

The importance of having adjuvant chemotherapy, even in patients having low recurrence risk, was recently underlined by several large studies.[23–26] Peri-operative chemotherapy could reduce the risk of cancer related recurrence due to micrometasatic untreated disease and/or early recurrence due to immunosuppressive effect of post-operative complications. Based on the results of our and other studies[26] we recommend adjuvant chemotherapy in patients with synchronous CRLM who can tolerate it post-operatively even if the limit of 12 cycles has been reached. This could be especially valuable when extensive prolonged chemotherapy is needed to achieve downstaging and resectability of synchronous CRLM especially in presence of poor prognostic factors identified in the current study.

Pre-hepatectomy elevated values of CEA were identified in our study as a prognostic factor for overall survival. Variation in pre-hepatectomy CEA levels has been associated with tumor burden, response, and receipt of pre-operative chemotherapy and were included into the Fong risk clinical score to predict survival after resection of CRLM.[27,28] We found that elevated pre-operative CEA values independently correlated with decreased survival even in presence of pre-operative chemotherapy. This was evident in patients undergoing a simultaneous strategy in whom CEA levels were statistically significant higher despite a comparable rate of pre-operative chemotherapy. This group of patients, however, presented with higher tumor burden in term of number and size of CRLM. This more frequently required a two-stage strategy to achieve complete liver clearance. Elevated CEA levels pre-hepatectomy thus represent a good marker of aggressive disease, which indicates partial and/or suboptimal response to pre-operative chemotherapy and a tendency toward earlier recurrence such as those observed in our study. The persistence of elevated CEA levels before hepatectomy could guide post-operative surveillance and administration of adjuvant treatment.

Because of its retrospective nature, our study was underpowered to detect differences in survival between the two groups of patients compared. Importantly, however, patients undergoing simultaneous resection had a decreased but not significantly reduced overall 5-year survival rates versus patients undergoing the primary-first strategy (30% vs44%). This was probably the result of a selection bias toward patients with less aggressive disease into the group of patients who received the primary-first strategy. It is more likely that many patients with more aggressive liver disease treated by the primary-first approach were not referred to us for evaluation. However, this difference in survival should be considered when discussing surgical indications for synchronous CRLM. Even though morbidity and mortality of patients treated by a synchronous resection remained acceptable, and resection was feasible in presence of higher tumoral burden, the trend toward earlier recurrence was remarkable perhaps indicating the need for more extensive selection and/or pre-operative treatment before surgery. Proponents of the reverse approach seldom highlight the need for early treatment of LM before progression.[7] We showed that even though synchronous resection is feasible in patients with high tumor burden, this was characterized by decreasing survival rates probably related to biological aggressive disease.

The prognostic role of the primary tumor location on the prognosis of patients presenting with simultaneous CRLM has been largely debated. Our multivariate analysis found that right colonic tumors were independently associated with worse overall survival. A recent metanalysis found that compared with left colonic tumor right colonic tumors were associated with worse overall and disease-free survival. Possible explanation of this finding include the different embryological origin of the right colon, the different bacterial content of the right colon, the higher rate of poorly differentiate tumors, mucinous tumors, tumors harboring KRAS and BRAF mutations, microsatellites instability. In addition, right colonic tumors seem to have a lower response rate to preoperative chemotherapy. The finding of our matched population seem to confirm the worse trend

found in patients with synchronous CRLM originating from right colonic tumor.[29]

This study presents several limitations that deserve commentary. First, this was a retrospective analysis characterized by a limited statistical power. Second, as discussed before, there was a noteworthy section bias toward patients with less aggressive disease into the group referred after primary tumor resection that could explain the difference in survival observed. Third, the favorable morbidity rates observed might be related to the long-lasting institutional experience and could be difficult to repeat in a different setting.

Conclusions

The surgical strategy used did not affect the overall survival in the presence of synchronous liver metastases from colorectal cancer. Persistently elevated pre-operative CEA levels, left colonic tumors, and the absence of adjuvant treatment had a major impact on long-term outcomes and helped identify a population of patients with limited overall survival.

Author Contribution Substantial contributions to the conception or design of the work: All.

Acquisition, analysis, or interpretation of data for the work: All.

Drafting the work or revising it critically for important intellectual content: PA, MF, PDM PB.

Final approval of the version to be published: All.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work is appropriately investigated and resolved: All.

Data Availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no competing interests.

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