Ann Surg Oncol (2009) 16:1809–1819
DOI 10.1245/s10434-008-0181-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC TUMORS

Timing of Multimodality Therapy for Resectable Synchronous Colorectal Liver Metastases: A Retrospective Multi-Institutional Analysis

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ABSTRACT The optimal timing of chemotherapy relative to resection of synchronous colorectal liver metastases (SCRLM) is not known. The objective of this retrospective multi-institutional study was to assess the influence of chemotherapy administered before and after hepatic resection on long-term outcomes among patients with initially resectable SCRLM treated from 1995 to 2005. Clinicopathologic data, treatments, and long-term outcomes from patients with initially resectable SCRLM who underwent partial hepatectomy at three hepatobiliary centers were reviewed. Four hundred ninety-nine consecutive patients underwent resection; 297 (59.5%) and 264 (52.9%) were treated with chemotherapy before and after resection. Chemotherapy strategies included pre-hepatectomy alone ($n = 148$, 24.7%), post-hepatectomy alone ($n = 115$, 23.0%), perioperative ($n = 149$, 29.0%), and no chemotherapy ($n = 87$, 17.4%). Male gender ($p = 0.0029$, HR = 1.41 [1.12–1.77]), node-positive primary tumor ($p = 0.0046$, HR = 1.40 [1.11–1.77]), four or more SCRLM ($p = 0.0005$, HR = 1.65 [1.24–2.18]), and post-hepatectomy chemotherapy treatment for 6 months or longer ($p = 0.039$, HR = 0.75 [0.57–0.99]) were associated with recurrence-free survival after discovery of SCRLM. Carcinoembryonic antigen >200 ng/ml ($p = 0.0003$, HR = 2.33 [1.48–3.69]), extrahepatic metastatic disease ($p = 0.0025$, HR = 2.34 [1.35–4.05]), four or more SCRLM ($p = 0.033$, HR = 1.43 [1.03–2.00]), and post-hepatectomy chemotherapy treatment for 2 months or longer ($p < 0.0001$, HR = 0.59 [0.45–0.76]) were associated with overall survival. Pre-hepatectomy chemotherapy was not associated with recurrence-free or overall survival. Patients treated with perioperative chemotherapy had similar outcomes as patients treated with post-hepatectomy chemotherapy only. We conclude that chemotherapy administered after but not before resection of SCRLM was associated with improved recurrence-free and overall survival. However, prospective randomized trials are needed to determine the optimal timing of chemotherapy.

First Received: 4 July 2008;
Published Online: 1 November 2008

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Despite advances in systemic chemotherapy, surgical resection of colorectal liver metastases remains critical to long-term survival. Recent series of resected patients indicate improvements in 5-year actuarial survival from 30–40% to 45–60%.[1–6] Extrapolating from gains made for unresectable metastatic disease, it is assumed that these survival improvements are in part secondary to modern systemic adjuvant and/or salvage chemotherapy.[7–9] Contemporary chemotherapeutics increase the number of patients able to undergo resection and improve recurrence-free survival when administered as a supplement to resection.[10,11] Given these considerations, patients with resectable hepatic metastases are typically approached with a combination of resection and systemic therapy. However, the appropriate timing of systemic therapy in resectable patients remains controversial—especially in patients with synchronous colorectal liver metastases (SCRLM), who comprise 23–51% of all resected patients.[12] To date, no prospective randomized study has evaluated the importance of timing of chemotherapy relative to resection for SCRLM.

To better understand the optimal timing of systemic therapy for resectable SCRLM, we conducted a multi-institutional retrospective review of patients with SCRLM who underwent hepatic extirpation over a 20-year inclusion interval. The objectives of this study were: (1) to identify factors associated with long-term survival after partial hepatectomy and (2) to determine whether the timing of chemotherapy relative to hepatic resection influenced long-term survival among this patient population.

PATIENTS AND METHODS

After obtaining Institutional Review Board approval, patients who underwent resection of SCRLM from 1985 to 2005 were identified from hepatectomy databases at three high-volume hepatobiliary centers. To focus on patients with truly synchronous disease, SCRLM were defined as being discovered before or during primary tumor resection. Demographics, clinicopathologic tumor characteristics, medical and surgical treatments, perioperative course, and long-term outcomes were reviewed. As the aim of this study was to assess long-term outcomes of patients initially presenting with resectable disease, we excluded patients who: (1) underwent previous hepatic resection and/or ablation, (2) initially presented with unresectable liver disease and underwent extirpation after downsizing with chemotherapy, (3) had gross disease at any location after hepatic resection, and (4) suffered postoperative mortality during hospitalization or within 90 days after resection. The decision of whether SCRLM were initially resectable was made by a multidisciplinary team at each center. Lesions were detected via computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and/or at exploration during colorectal resection. Hepatic resections were described according to standard nomenclature.[13] Major hepatectomy was defined as resection of three or more anatomic segments. Chemotherapy included any systemic or regional chemotherapy. Pre-hepatectomy, post-hepatectomy, and perioperative chemotherapy included treatment after discovery and before resection of SCRLM; after resection of SCRLM and before disease recurrence; and both prior to and after partial hepatectomy, respectively. Chemotherapy regimens were separated as multi-agent (any combination of oxaliplatin, irinotecan, bevacizumab, and/or cetuximab with or without fluoropyrimidines) and fluoropyrimidine (intravenous, oral, or hepatic arterial infusion) monotherapy. Durations of chemotherapy treatment were grouped as greater than 6 months, 2–6 months, and less than 2 months. Patients with primary rectal cancer who only received fluoropyrimidine-based therapy for 2 months or less with the intended purpose of acting as a "sensitizing" agent for neoadjuvant radiotherapy were not considered to have received pre-hepatectomy chemotherapy.

Statistical analyses were performed with Stats Direct® version 2.4.5 (StatsDirect Limited© Software, Cheshire, England) and GraphPad Prism® version 3.0 (GraphPad Software, San Diego, CA, USA) software packages. Categorical variables were summarized with percentages and compared with the Yates-corrected χ^2 or Fisher's exact test (in cases of low frequencies). Continuous variables were summarized with medians and interquartile (25–75%) ranges and compared with the Mann–Whitney U test. Two-sided p values are reported. Overall and recurrence-free survival for patients were estimated using the Kaplan–Meier method. Time zero for survival analyses was the date of discovery of SCRLM. Cox univariable and multivariable analyses for overall and recurrence-free survival were performed. Multivariable models were created using variables that showed possible association ($p \leq 0.1$) with overall or recurrence-free survival on univariable analysis. To determine the influence of chemotherapy on long-term outcomes, three separate multivariable analyses were performed. The first included pre-hepatectomy and post-hepatectomy chemotherapy treatment as separate categorical variables. Because some patients in this study may have been treated with an upfront decision upon discovery of SCRLM to deliver both pre-hepatectomy and post-hepatectomy chemotherapy, we performed a second multivariable analysis which categorized systemic treatment according to the ultimate treatment paradigm administered (pre-hepatectomy, perioperative, and post-hepatectomy chemotherapy) as one variable with no chemotherapy as the reference. To examine the influence of chemotherapy in a "low-risk" population where wider acceptance of hepatic resection prior to systemic chemotherapy is likely, we repeated the multivariable analysis which categorized systemic treatment according to the ultimate treatment paradigm administered on a restricted population of patients with fewer than four SCRLM, no extrahepatic metastatic disease, and no concurrent ablation. This restricted population was similar to that studied in the EORTC 40983 trial. Statistical significance for all analyses was defined as $p < 0.05$; hazard ratios with 95% confidence intervals (CI) are reported.

RESULTS

Patient and Treatment Characteristics

From 1985 to 2005, 584 patients underwent resection of SCRLM. Two hundred eighty-five (48.8%), 199 (34.1%), and 100 (17.1%) patients underwent resection at the

University of Texas MD Anderson Cancer Center, Johns Hopkins Medical Institutions, and Duke University Medical Center, respectively. After excluding patients with initially unresectable disease ($n = 42$), residual gross disease after hepatectomy ($n = 19$), and postoperative mortality ($n = 24$), 499 subjects were included in this study. Median follow-up after diagnosis of SCRLM for living patients was 48 months. Two hundred ninety-seven (59.5%) and 264 (52.9%) patients received pre-hepatectomy and post-hepatectomy chemotherapy. Chemotherapy strategies included pre-hepatectomy alone ($n = 148$, 24.7%), post-hepatectomy alone ($n = 115$, 23.0%), and perioperative ($n = 149$, 29.0%). Eighty-seven patients (17.4%) were not treated with chemotherapy. Multi-agent pre-hepatectomy chemotherapy included oxaliplatin-based therapy with bevacizumab ($n = 21$), cetuximab ($n = 2$), and without antibiologic agents ($n = 39$); irinotecan-based therapy with ($n = 6$) and without ($n = 117$) bevacizumab; and fluoropyrimidine therapy with bevacizumab ($n = 3$). Seven patients received sequential irinotecan and oxaliplatin therapy before hepatic resection. Multi-agent post-hepatectomy chemotherapy included oxaliplatin-based therapy with bevacizumab ($n = 15$), cetuximab ($n = 1$), and without antibiologic agents ($n = 47$); irinotecan-based therapy with bevacizumab ($n = 4$), with cetuximab ($n = 1$), and without antibiologic agents ($n = 87$); and fluoropyrimidine therapy with bevacizumab ($n = 6$). Three patients received sequential irinotecan and oxaliplatin therapy after hepatic resection. Full details on chemotherapy regimens and/or treatment durations were unknown for 4 and 13 patients, respectively.

Patients selected to receive chemotherapy either before or after hepatic resection possessed a number of factors often predictive of diminished long-term survival (Table 1). In comparison with patients not treated with pre-hepatectomy chemotherapy, treated patients had a greater number of SCRLM, were more likely to have a node-positive primary tumor, and more often required adjunctive ablation to clear the liver of clinically evident disease. Pre-hepatectomy patients were younger at date of discovery of SCRLM, more commonly diagnosed in years 2000–2005, more often required major hepatectomy, and had a longer interval from discovery of SCRLM to extirpation. Despite the increased application of major hepatectomy in those patients receiving pre-hepatectomy chemotherapy, the morbidity rate was not increased.[13] Similarly, patients treated with post-hepatectomy chemotherapy had more metastases and more advanced primary rectal cancers compared with untreated patients (Table 1). Post-hepatectomy patients were younger and more commonly diagnosed in years 2000–2005. Differences in extrahepatic metastatic disease (EHD) and concurrent ablation were not statistically significant.

Survival Analyses

When considering the decision to administer pre- or post-hepatectomy chemotherapy as independent variables (Table 2), univariable analyses identified male gender, concurrent ablation, node-positive primary disease, era of diagnosis, EHD, and four or more SCRLM as factors associated with recurrence-free survival. Of the systemic treatment variables, only post-hepatectomy chemotherapy of at least 6 months duration was associated with recurrence-free survival. On multivariable analyses, male gender, node-positive primary cancer, four or more SCRLM, and post-hepatectomy chemotherapy of at least 6 months duration were independently associated with recurrence-free survival after discovery of SCRLM. Concurrent ablation, era of diagnosis, multi-agent pre-hepatectomy chemotherapy, carcinoembryonic antigen (CEA) > 200 ng/ml, EHD, and four or more SCRLM were associated with overall survival on univariable analysis. Systemic treatment variables associated with overall survival included multi-agent pre-hepatectomy chemotherapy and any post-hepatectomy chemotherapy treatment for at least 2 months. Factors independently associated with overall survival on multivariable analysis included concurrent ablation, CEA > 200 ng/mL, EHD, four or more SCRLM, and any post-hepatectomy chemotherapy treatment for 2 months or longer. Patients treated with post-hepatectomy chemotherapy for 2 months or longer had median overall survival of 74 months (95% CI 62–99 months) compared with 47 months (95% CI 40–54 months) for all other patients.

As highlighted by EORTC 40983, many patients are approached with an upfront decision to deliver both pre- and post-hepatectomy chemotherapy (perioperative). With the retrospective nature of this study, we could not establish which patients receiving pre-hepatectomy chemotherapy were treated with this intent. To determine the relative influence of a perioperative approach, patients were analyzed according to the ultimate treatment strategy employed (pre- only, post- only, perioperative, none). Because post-hepatectomy chemotherapy was demonstrated in the initial analysis to be associated with overall survival when administered for at least 2 months duration, we defined a post-hepatectomy or perioperative chemotherapy strategy to include chemotherapy treatment after hepatic resection of at least 2 months. As with the first analysis, patients selected to receive preoperative only, postoperative only, or perioperative chemotherapy were associated with more adverse demographic factors in comparison with patients treated with surgery alone (data not shown). Independent predictors on multivariable analysis of recurrence-free survival when incorporating ultimate treatment strategies as systemic treatment

TABLE 1 Demographics, clinicopathologic tumor characteristics, and treatments of patients who underwent resection of synchronous colorectal liver metastases

	All		Pre-hepatectomy chemotherapy					Post-hepatectomy chemotherapy				
	(n = 499)		Yes (n = 297)		No (n = 202)			Yes (n = 264)		No (n = 235)		
	n	%	n	%	n	%	p	n	%	n	%	p
Age (years)	57 (49–66)		56 (48–65)		60 (51–68)		0.0122	54 (48–63)		61 (53–69)		<0.0001
Male gender	294	58.9	171	57.6	123	60.9	0.52	158	59.8	136	57.9	0.72
Primary rectal cancer	139	27.9	67	22.6	72	35.6	0.015	86	32.6	53	22.6	0.017
T_3/T_4 primary cancer	420	84.2	250	84.2	170	84.2	>0.99	232	87.9	188	80.0	0.022
Node-positive primary cancer	307	61.5	199	67.0	108	53.5	0.0031	167	63.3	140	59.6	0.45
Date of discovery 2000–2005	304	60.9	203	68.4	101	50.0	<0.0001	185	70.0	119	50.6	<0.0001
Interval to resection (months)*	5 (2–9)		8 (5–11)		2 (1–4)		<0.0001	5 (2–8)		7 (4–12)		<0.0001
Size of largest SCRLM (cm)	3.0 (2.0–5.0)		3.0 (2.0–4.8)		3.5 (2.0–5.5)		0.15	3.0 (2.0–5.0)		3.2 (2.0–5.0)		0.54
Number of SCRLM	2 (1–3)		2 (1–3)		1 (1–2)		0.0004	2 (1–3)		1 (1–3)		0.0055
≥4 SCRLM	89	17.8	65	21.9	24	11.9	0.0060	52	19.7	37	15.7	0.30
Extrahepatic metastatic disease	18	5.3	14	4.7	4	2.0	0.17	5	1.9	13	5.5	0.053
Pre-hepatectomy CEA (ng/ml)	6.8 (2.5–27.3)		6.0 (2.6–28.2)		7.3 (2.4–27.0)		0.65	7.0 (2.4–24.0)		6.2 (2.6–36.6)		0.43
Simultaneous CR	109	21.8	36	12.1	73	36.1	<0.0001	64	24.2	45	19.1	0.21
Major hepatic resection	259	51.9	176	59.3	83	41.9	<0.0001	134	50.8	125	53.2	0.65
Concurrent ablation	114	22.8	86	29.0	28	13.9	0.0001	69	26.1	45	19.1	0.080
Intraoperative RBC transfusion	87	17.4	40	13.5	47	23.3	0.0067	46	17.4	41	17.4	>0.99
Positive hepatic resection margin	15	3.0	8	2.7	7	3.5	0.81	10	3.8	5	2.1	0.52
Post-hepatectomy morbidity	121	24.2	78	26.3	43	21.3	0.2606	55	20.8	66	28.1	0.075
Pre-hepatectomy chemotherapy	297	59.5	–	–	–	–	–	149	56.4	148	63.0	0.17
Multi-agent therapy	195	39.1	195	65.7	–	–	–	108	40.9	87	37.0	0.0074
Monotherapy	102	20.4	102	34.3	–	–	–	38	14.4	60	25.5	
Duration ≥ 6 months	103	20.6	103	34.7	–	–	–	38	14.4	65	27.7	0.0037
Duration ≥ 2 and <6 months	165	33.1	170	57.2	–	–	–	98	37.1	72	30.6	
Duration <2 months	35	7.0	24	8.1	–	–	–	13	4.9	11	4.7	
Post-hepatectomy chemotherapy	264	52.9	149	50.2	115	56.9	0.16	–	–	–	–	–
Multi-agent therapy	164	32.9	100	33.7	64	31.7	0.053	164	62.1	–	–	–
Monotherapy	100	20.0	42	14.1	45	22.3	–	100	37.8	–	–	–
Duration ≥ 6 months	95	19.0	41	13.8	54	26.7	0.0013	95	36.0	–	–	–
Duration ≥ 2 and <6 months	113	22.6	102	34.3	53	26.2	–	155	58.7	–	–	–
Duration <2 months	14	2.8	6	2.0	8	4.0	–	14	5.3	–	–	–

Categorical variables reported with percentages, continuous variables reported as median (IQR)

Simultaneous CR, simultaneous colorectal and hepatic resections; major hepatic resection, resection of three or more segments; SCRLM, synchronous colorectal liver metastases; date of discovery, date of discovery of SCRLM; multi-agent, combinations of irinotecan, oxaliplatin, bevacizumab, and/or cetuximab with or without fluoropyrimidines; monotherapy, fluoropyrimidine-based therapy; RBC, red blood cell; CEA, carcinoembryonic antigen

* Interval from discovery of synchronous colorectal liver metastases and hepatic resection

variables included gender, concurrent ablation, node-positive primary tumor, and more than three metastases (Table 3). Recurrence-free survival did not differ according to the timing of chemotherapy treatment relative to hepatic resection (Fig. 1). In contrast, treatment with post-hepatectomy chemotherapy alone was independently associated with overall survival (Table 3). Concurrent ablation, era of diagnosis, preoperative CEA, EHD, and four or more SCRLM were also associated with overall survival. Median overall survival after discovery of SCRLM for patients treated with no chemotherapy, pre-hepatectomy chemotherapy, post-hepatectomy chemotherapy, and perioperative chemotherapy were 36 months (95% CI 24–48 months), 53 months (95% CI 46–60 months), 76 months (95% CI 47–104 months), and 67 months (95% CI 54–80 months), respectively (Fig. 1).

TABLE 2 Univariate and multivariate analysis for recurrence-free and overall survival from discovery of liver metastases

Variable	Recurrence-free survival			Overall survival		
	Univariate *p*	Multivariate *p*	95% CI	Univariate *p*	Multivariate *p*	CI
Age ≥ 65 years	0.35	–	–	0.40	–	–
Male	0.0024	0.0029	1.41 [1.12–1.77]	0.11	–	–
Major hepatectomy	0.34	–	–	0.46	–	–
Simultaneous CR resection	0.20	–	–	0.28	–	–
Concurrent ablation	<0.0001	0.063	1.28 [0.99–1.67]	0.013	0.017	1.46 [1.07–1.99]
Rectal primary cancer	0.96	–	–	0.57	–	–
T_3/T_4 primary cancer	0.22	–	–	0.40	–	–
Node-positive primary	0.0007	0.0046	1.40 [1.11–1.77]	0.11	–	–
Date of discovery 2000–2006	0.073	0.46	1.09 [0.87–1.37]	0.0016	0.079	0.75 [0.54–1.03]
CEA > 200 ng/ml	0.27	–	–	0.0013	0.0003	2.33 [1.48–3.69]
Extrahepatic disease	0.064	0.28	1.35 [0.78–2.34]	0.0022	0.0025	2.34 [1.35–4.05]
Intraoperative RBC transfusion	0.47	–	–	0.45	–	–
SCRLM size > 5 cm	0.29	–	–	0.51	–	–
≥4 SCRLM	<0.0001	0.0005	1.65 [1.24–2.18]	0.0095	0.033	1.43 [1.03–2.00]
Positive hepatic margin	0.32	–	–	0.54	–	–
Pre-hepatectomy chemotherapy						
Multi-agent*	0.55	–	–	0.036	0.46	0.86 [0.57–1.29]
Monotherapy**	0.61	–	–	0.092	0.065	1.39 [0.98–1.98]
≥6 months duration†	0.46	–	–	0.80	–	–
<6 and ≥2 months duration‡	0.31	–	–	0.35	–	–
Post-hepatectomy chemotherapy		–	–		<0.0001£	0.59 [0.45–0.76]£
Multi-agent*	0.58	–	–	0.0004	–	–
Monotherapy**	0.30	–	–	0.44	–	–
≥6 months duration†	0.011	0.039	0.75 [0.57–0.99]	0.0003	–	–
<6 and ≥2 months duration‡	0.21	–	–	0.66	–	–

Major hepatectomy, resection of three or more segments; date of discovery, date of discovery of SCRLM; CEA, carcinoembryonic antigen; RBC, red blood cell; CR, colorectal

* Compared with no pre-hepatectomy chemotherapy

** Compared with multi-agent therapy

† Compared with <2 months duration

‡ Compared with ≥6 months duration

£ Any chemotherapy for ≥2 months duration

Restricted Survival Analyses

To examine the impact of chemotherapy timing in a lower-risk patient population in which wider acceptance of hepatic resection prior to systemic therapy is likely, we performed a restricted analysis excluding patients with EHD, greater than three SCRLM, and in whom concurrent ablation was not required for tumor clearance. Patients receiving pre- or post-hepatectomy chemotherapy were more apt to have solitary lesions than patients receiving perioperative therapy (Table 4). Gender, hepatic tumor size, and node-positive primary tumor were independently associated with recurrence-free survival on multivariable analysis (Table 5). Although not associated with recurrence-free survival, timing of chemotherapy did impact overall survival (Fig. 2). Median overall survival after discovery of SCRLM for these restricted patients treated with no chemotherapy, pre-hepatectomy chemotherapy, post-hepatectomy chemotherapy, and perioperative chemotherapy were 39 months (95% CI 26–68 months), 56 months (95% CI 50–118 months), 99 months (95% CI 65–144 months), and 97 months (95% CI 65–129 months), respectively. Post-hepatectomy chemotherapy alone, node-positive primary tumor, and era of diagnosis were independently associated with overall survival (Table 5).

TABLE 3 Univariate and multivariate analysis for recurrence-free and overall survival from discovery of liver metastases (by ultimate adjuvant treatment strategy)

Variable	Recurrence-free survival			Overall survival		
	Univariate *p*	Multivariate *p*	95% CI	Univariate *p*	Multivariate *p*	CI
Age ≥ 65 years	0.35	–	–	0.40	–	–
Male	0.0024	0.0041	1.39 [1.11–1.73]	0.11	–	–
Major hepatectomy	0.34	–	–	0.46	–	–
Simultaneous CR resection	0.20	–	–	0.28	–	–
Concurrent ablation	<0.0001	0.023	1.35 [1.04–1.76]	0.013	0.021	1.45 [1.06–1.98]
Rectal primary cancer	0.96	–	–	0.57	–	–
T_3/T_4 primary cancer	0.22	–	–	0.40	–	–
Node-positive primary	0.0007	0.0011	1.47 [1.17–1.85]	0.11	–	–
Date of discovery 2000–2005	0.073	0.40	1.10 [0.87–1.38]	0.0016	0.020	0.72 [0.55–0.95]
CEA > 200 ng/ml	0.27	–	–	0.0013	0.0004	2.30 [1.46–3.64]
Extrahepatic disease	0.064	0.23	1.39 [0.81–2.41]	0.0022	0.0016	2.44 [1.41–4.23]
Intraoperative RBC transfusion	0.47	–	–	0.45	–	–
SCRLM size > 5 cm	0.29	–	–	0.51	–	–
≥4 SCRLM	<0.0001	0.0008	1.61 [1.22–2.12]	0.0095	0.021	1.50 [1.07–2.07]
Positive hepatic margin	0.32	–	–	0.54	–	–
Chemotherapy		–	–			
Pre-hepatectomy*	0.74	–	–	0.60	0.939	0.98 [0.66–1.47]
Pre-/Post-hepatectomy*†	0.53	–	–	0.020	0.082	0.72 [0.50–1.04]
Post-hepatectomy*†	0.55	–	–	0.001	0.0003	0.48 [0.32–0.71]

* Relative to no chemotherapy

† Post-hepatectomy chemotherapy of 2 months or longer

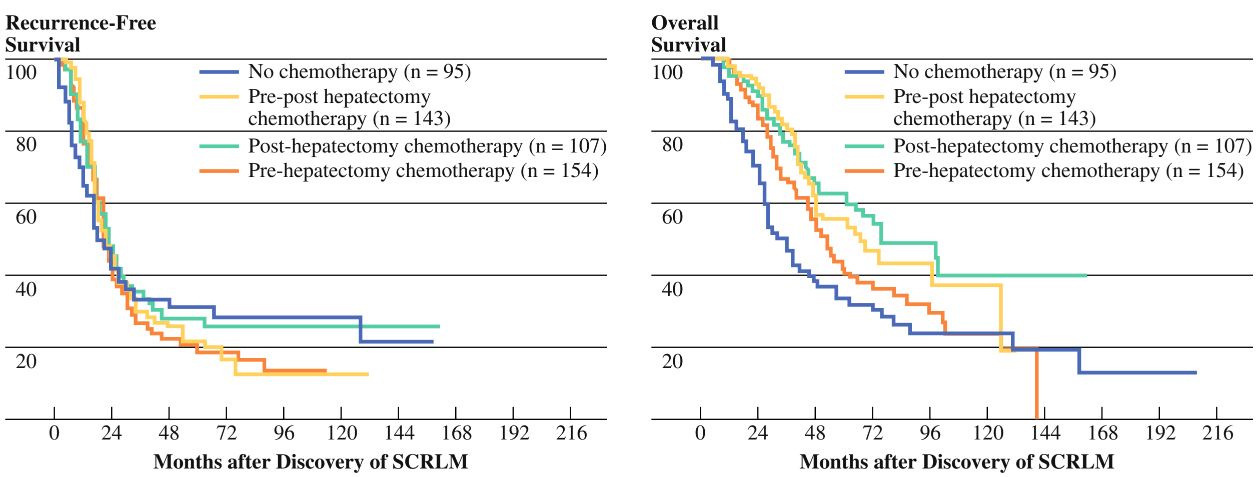

FIG. 1 Recurrence-free ($p = 0.85$) and overall ($p < 0.001$) survival after diagnosis of synchronous colorectal liver metastases (SCRLM) for all patients ($n = 499$)

DISCUSSION

The traditional treatment approach for SCRLM focuses upon initial resection of the primary tumor followed by systemic therapy for an arbitrary and often prolonged duration prior to hepatic resection. Partial hepatectomy is reserved for patients without significant interval disease progression. Additional chemotherapy is often considered after hepatic resection. Profound improvements in systemic therapy coupled with results of the European Organization for Research and Treatment of Cancer (EORTC) 40983 phase III study will likely further encourage the utilization of pre-hepatectomy chemotherapy.[11] The underlying assumptions supporting this classical approach include: (1)

TABLE 4 Demographics, clinicopathologic tumor characteristics, and treatment of patients who underwent resection of synchronous colorectal liver metastases by chemotherapy treatment (excluding EHD, concurrent ablation, and more than three lesions)

Timing of chemotherapy	Pre-hepatectomy	Post-hepatectomy	Perioperative	None	*p*
n	91	83	54	65	–
Age (years)	61 (52–69)	57 (48–65)	54 (46–59)	65 (54–70)	<0.0001
Male gender	56 (61.5)	48 (57.8)	43 (51.8)	44 (60.3)	0.148
Primary rectal cancer	17 (18.7)	32 (38.6)	21 (25.3)	24 (32.9)	0.0233
T_3/T_4 primary cancer	68 (74.7)	72 (86.7)	75 (90.4)	62 (84.9)	0.032
Node-positive primary cancer	61 (67.0)	52 (62.7)	55 (66.3)	36 (49.3)	0.0864
Date of discovery 2000–2005	55 (60.4)	51 (61.4)	64 (77.2)	24 (32.9)	<0.0001
Interval to resection (months)*	9 (6–15)	2 (0–3)	6 (4–9)	3 (1–5)	<0.0001
Size of largest SCRLM (cm)	3.0 (2.0–5.0)	3.7 (1.5–6.5)	3.0 (2.0–4.3)	2.9 (2.0–5.0)	0.849
Multiple SCRLM	34 (37.4)	30 (36.1)	44 (53.0)	22 (30.1)	0.023
Pre-hepatectomy CEA (ng/ml)	4.1 (2.1–12.4)	6.0 (2.0–16.8)	4.3 (2.1–18.9)	6.1 (2.5–27.0)	0.581
Simultaneous CR	10 (11.0)	35 (42.2)	15 (18.1)	29 (39.7)	<0.0001
Major hepatic resection	53 (58.2)	33 (39.8)	50 (60.2)	30 (41.1)	0.0009
Intraoperative RBC transfusion	13 (14.3)	20 (24.1)	9 (10.8)	20 (27.4)	0.0214
Positive hepatic resection margin	3 (3.3)	4 (4.8)	3 (3.6)	1 (1.4)	0.692
Post-hepatectomy morbidity	28 (30.7)	16 (19.3)	20 (24.1)	18 (24.7)	0.376

Categorical variables reported with percentages, continuous variables reported as median (IQR)

Simultaneous CR, simultaneous colorectal and hepatic resections; major hepatic resection, resection of three or more segments; SCRLM, synchronous colorectal liver metastases; date of discovery, date of discovery of SCRLM; multi-agent, combinations of irinotecan, oxaliplatin, bevacizumab, and/or cetuximab with or without fluoropyrimidines; monotherapy, fluoropyrimidine-based therapy; RBC, red blood cell; CEA, carcinoembryonic antigen

* Interval from discovery of synchronous colorectal liver metastases and hepatic resection

the delivery of chemotherapy prior to hepatic resection ensures that all resected patients are treated, (2) patients with SCRLM have an unfavorable tumor biology precluding long-term survival, (3) asymptomatic primary tumors should be resected early to prevent urgent complications, (4) pre-hepatectomy chemotherapy excludes a substantial number of patients with aggressive disease from an unnecessary and morbid hepatic resection, (5) the morbidity of simultaneous hepatic and primary resections is prohibitive, (6) the timing of systemic therapy does not impact long-term oncologic outcomes in resected patients, and (7) post-hepatectomy chemotherapy choices are best dictated by responses to pre-hepatectomy regimens.

Recent studies suggest that a more selective application of this traditional approach may be warranted for resectable SCRLM. It is clear from our and other experiences that a synchronous presentation, although often an adverse prognostic factor, does not preclude the possibility of long-term survival. Improvements in the safety profile of hepatic resection have not only liberalized the definition of "resectable" disease, but also prompted ourselves and others to selectively perform simultaneous resections of primary colorectal cancer and SCRLM.[14–27] Few patients with metastatic colorectal cancer experience early disease progression on contemporary chemotherapeutics, thereby questioning the ability of a short course of pre-hepatectomy chemotherapy to prevent unnecessary hepatic resections.[8,9,28] Utilizing a short course of pre-hepatectomy FOLFOX4, EORTC 40983 demonstrated a decrease in nontherapeutic laparotomies from 11% in the control arm to 5% in the treatment arm. Only 12 patients (7%) progressed on chemotherapy and of these only four (2.3%) had new hepatic lesions that precluded resection.[11] Moreover, a number of recent studies have revealed substantial hepatotoxicity (steatosis, steatohepatitis, and sinusoidal dilatation and congestion) from contemporary chemotherapy regimens related to the duration of treatment, which has been shown to increase the rate of blood transfusion, morbidity, and mortality after partial hepatectomy.[29–34] EORTC 40983 demonstrated that, even when limited in duration, pre-hepatectomy FOLFOX4 was associated with increased morbidity after hepatic resection.[11] In addition, it is well known that radiographically occult disease is commonly identified at the time of exploration.[35] By altering the architecture of the non-tumor-bearing liver, effective pre-hepatectomy chemotherapy may render this clinically relevant disease undetectable, thereby precluding appropriate resection.

In this retrospective study, chemotherapy administered after and not before hepatic resection was associated with survival among patients with SCRLM. Multivariable analysis which included factors that reflected decisions to deliver

TABLE 5 Univariate and multivariate analysis for recurrence-free and overall survival from discovery of liver metastases (excluding EHD, concurrent ablation, and more than three lesions)

Variable	Recurrence-free survival			Overall survival		
	Univariate *p*	Multivariate *p*	95% CI	Univariate *p*	Multivariate *p*	CI
Age ≥ 65 years	0.506			0.0522		
Male	0.0155	0.0077	1.50 [1.11–2.01]	0.1058		
Major hepatectomy	0.799			0.0547	0.43	1.86 [0.59–3.29]
Simultaneous CR resection	0.108			0.0646	0.24	2.37 [0.79–4.0]
Rectal primary cancer	0.839			0.882		
T_3/T_4 primary cancer	0.131			0.867		
Node-positive primary	<0.0001	<0.0001	2.00 [1.46–2.69]	0.018	0.0008	1.87 [1.29–2.70]
Date of discovery 2000–2005	0.388			0.0091	0.0027	0.47 [0.29–0.77]
CEA > 200 ng/mL	0.879			0.066		
Intraoperative RBC transfusion	0.469			0.386		
SCRLM size > 5 cm	0.0448	0.0242	1.45 [1.05–1.99]	0.834		
Multiple SCRLM	0.919			0.408		
Positive hepatic margin	0.964			0.974		
Chemotherapy						
Pre-hepatectomy*	0.190			0.638*		
Pre-/Post-hepatectomy*†	0.491			0.202*†		
Post-hepatectomy*†	0.712			0.0017*†	0.0007	0.45 [0.28–0.71]

SCRLM, synchronous colorectal liver metastases; CEA, carcinoembryonic antigen

* Relative to no chemotherapy treatment

† Post-hepatectomy chemotherapy of 2 months or longer

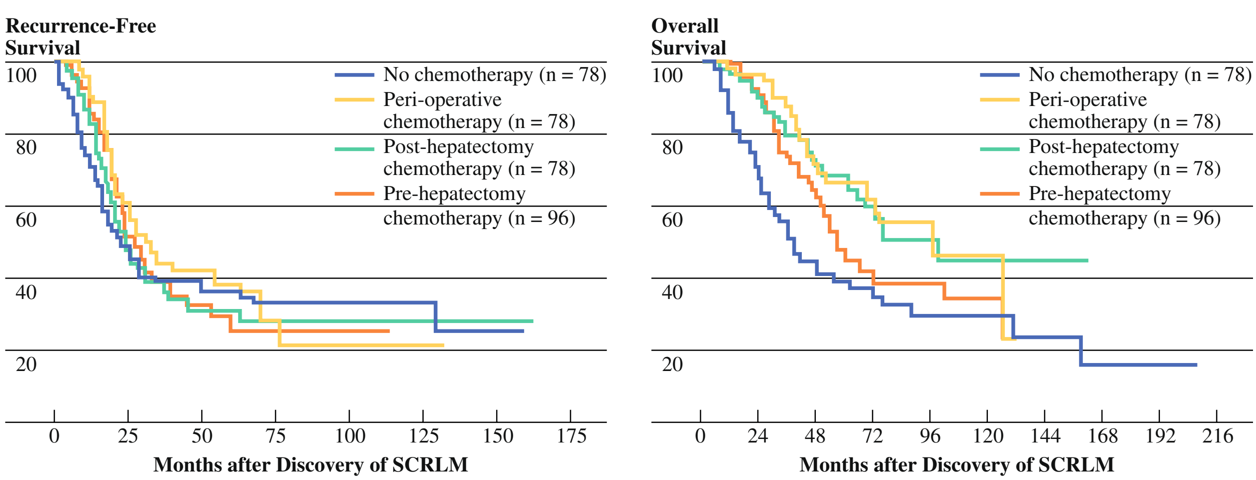

FIG. 2 Recurrence-free ($p = 0.62$) and overall ($p = 0.004$) survival among patients ($n = 330$) with SCRLM and without extrahepatic metastatic disease, more than four hepatic tumors, and who did not require concurrent ablative therapy to clear the liver remnant of disease

pre-hepatectomy and post-hepatectomy chemotherapy as distinct showed that post-hepatectomy chemotherapy (for a duration of at least 6 and 2 months, respectively) was associated with improved recurrence-free and overall survival (Table 2). In contrast, pre-hepatectomy chemotherapy was not associated with long-term outcomes. A number of patients received both pre- and post-hepatectomy chemotherapy and, as a result, it is possible that some of the benefits in the post-hepatectomy group may be attributable to a subset of patients receiving pre-hepatectomy chemotherapy. Given this consideration and because many patients are a priori approached with plans for both pre- and post-hepatectomy (perioperative), we conducted univariable and multivariable analyses utilizing pre-hepatectomy chemotherapy only, post-hepatectomy chemotherapy only, perioperative chemotherapy, and no chemotherapy as treatment variables.

Among these treatment variables, only post-hepatectomy chemotherapy was associated with overall survival on multivariable analysis (Table 3). None of these treatment factors were predictive of recurrence-free survival.

Reflecting an aggressive treatment approach, the study population includes a substantial proportion of patients with a higher burden of disease than in the EORTC 40983 phase III study.[11] Despite our results, it is unlikely that these high-risk patients would be considered for early hepatectomy in advance of systemic therapy at most institutions. We therefore examined a restricted, lower-risk population without EHD, who did not require concurrent ablation, and had fewer than four SCRLM. Post-hepatectomy chemotherapy, node-positive primary tumor, and diagnosis from 2000 to 2005 were the only factors associated with overall survival. Overall survival among patients receiving pre-hepatectomy chemotherapy alone and post-hepatectomy chemotherapy alone remained divergent despite having similar demographics and despite pre-hepatectomy patients having a median interval from diagnosis to hepatectomy of 9 months, potentially allowing for better selection. Patients receiving both perioperative chemotherapy and post-hepatectomy chemotherapy had overlapping survival curves, suggesting that the post-hepatectomy component of systemic therapy is most relevant (Fig. 2).

Other studies have also shown the value of post-hepatectomy chemotherapy. In the AURC 0992 trial, 6 months of post-hepatectomy 5-flourouracil (5-FU) provided longer recurrence-free survival (5-year 33.5% vs. 26.7%) after hepatic resection compared with observation.[10] The improvement in 3-year recurrence-free survival in this trial (43% vs. 33% by extrapolation) was almost identical to resected patients in EORTC 40983 (42.4% vs. 33.2%) where FOLFOX4 was utilized.[11] This may explain the absence of differences in recurrence-free or overall survival between multi-agent and fluoropyrimidine monotherapy whether administered before or after hepatic resection in our study. Large retrospective series have shown that post-hepatectomy chemotherapy treatment improves overall survival for patients with colorectal liver metastases.[36,37] In contrast, Minagawa et al. and Capussotti et al. did not observe a survival benefit from pre-hepatectomy chemotherapy for SCRLM.[12,38] Hewes et al. reported that patients with poor prognostic indicators who received pre-hepatectomy chemotherapy had worse overall survival compared with untreated patients, suggesting that pre-hepatectomy chemotherapy does not alter long-term outcome.[39] Kemeny et al. report that pre-hepatectomy chemotherapy did not improve long-term outcomes after resection among patients treated with post-hepatectomy hepatic arterial infusion and systemic chemotherapy.[40]

This study has several limitations. While the aim of this study was to determine whether the timing of chemotherapy for resectable SCRLM is important, the retrospective and multidisciplinary nature of this study makes it difficult to comprehend the intent and underlying factors governing treatment decisions. Substantial heterogeneity across institutions and time periods in criteria for resectability, resection techniques, quality of preoperative imaging, and chemotherapy treatment regimens and protocols prevent us from making definitive conclusions about optimal timing of chemotherapy relative to hepatic resection. It is clear that selection biases existed in patients receiving pre-hepatectomy and post-hepatectomy chemotherapy as patients selected to receive chemotherapy possessed clinicopathologic characteristics traditionally demonstrated to be adverse prognostic factors (Table 1). We performed multivariable analyses of those factors which differed between these patient groups that were shown to be associated with overall and recurrence-free survival on univariable analyses. While not as robust as a prospective randomized controlled trial, we believe these multivariable analyses adequately accounted for these differences given the large number of patients in this series. Moreover, the introduction of better systemic agents may have increased the level of enthusiasm for routine pre- and post-hepatectomy chemotherapy as these were more commonly administered in the 2000–2005 era. Importantly, subjects were identified from hepatectomy databases at each institution. Thus the number of patients who initially presented with resectable SCRLM and who did not undergo subsequent hepatic extirpation secondary to interval disease progression while treated with pre-hepatectomy chemotherapy was not known. These latter limitations may have masked the benefits of pre-hepatectomy chemotherapy in this selected patient population. Neither salvage chemotherapy nor hepatic resection after disease recurrence was accounted for in this study. While reflective of the current treatment environment, the variety of chemotherapy regimens may explain the absence of differences in survival outcomes between multi-agent and fluoropyrimidine-based chemotherapy. This study does not refute the benefits of pre-hepatectomy chemotherapy in patients with unresectable disease or where the likelihood of margin negative resection is low.[41] For higher-risk patients, such as those with suspected EHD and more than four SCRLM, it is likely that the ability of pre-hepatectomy chemotherapy to diminish unnecessary explorations (as demonstrated in EORTC 40983) will be further amplified.

Due to the above limitations, definitive conclusions regarding the relative merits of chemotherapy administered before and after resection of SCRLM cannot be discerned by this study. Thus, conclusions from this study should not be adopted as standard of care for patients with SCRLM. Instead, results of this large, multi-institutional retrospective study underscore the need for prospective randomized controlled trials designed to reevaluate the traditional approach to patients with resectable SCRLM and to determine the optimal timing of chemotherapy.

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