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Applicability of postoperative carcinoembryonic antigen levels in determining post-liver-resection adjuvant chemotherapy regimens for colorectal cancer hepatic metastasis

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Abstract

Liver resection (LR) is the standard procedure for treating colorectal cancer (CRC) hepatic metastasis; however, LR associated with a high recurrence incidence. This study aimed to determine an optimal post-LR adjuvant chemotherapeutic strategy to improve overall long-term patient outcomes. A retrospective study of 490 patients who had undergone curative LR for CRC hepatic metastasis was performed. Patients who underwent post-LR adjuvant chemotherapy demonstrated high overall survival (OS) rates (hazard ratio [HR] = 0.58, $P = .002$) but not high recurrence-free survival (RFS) rates (HR = 1.02, $P = .885$). Moreover, OS was significantly longer in patients who underwent 5-fluorouracil + leucovorin (5-FU/LV; HR = 0.63, $P = .039$), oxaliplatin-based chemotherapy (HR = 0.45, $P < .001$), or irinotecan-based chemotherapy with bevacizumab (HR = 0.64, $P = .040$) than in those who did not. Among patients with carcinoembryonic antigen (CEA) levels of <5 ng/mL at 1 month after LR, significant differences were noted only in those who underwent 5-FU/LV (HR = 0.58, $P = .035$) and oxaliplatin-based chemotherapy (HR = 0.38, $P < .001$). In conclusion, perioperative CEA levels are crucial in prognosis and treatment of patients with CRC hepatic metastasis after LR. Additionally, certain regimens of adjuvant chemotherapy alongside post-LR CEA levels may provide beneficial results.

Abbreviations: CEA = carcinoembryonic antigen, CI = confidence interval, CRC = colorectal cancer, CT = computed tomography, 5-FU/LV = 5-fluorouracil + leucovorin, HR = hazard ratio, LR = liver resection, OS = overall survival, PET = positron emission tomography, RFS = recurrence-free survival.

Keywords: adjuvant chemotherapy, CEA, colorectal cancer, liver resection, metastasis

1. Introduction

Liver is the most common organ of distant metastasis in primary colorectal cancer (CRC). Liver resection (LR) is the optimal treatment used for treating CRC with hepatic metastasis.[1,2] Peri-LR carcinoembryonic antigen (CEA) levels are potentially associated with post-LR CRC recurrence and patient survival.[3–6] High pre-LR CEA levels are considered poor prognostic factors and predictors of post-LR CRC recurrence. Moreover, high post-LR CEA levels (≥5 ng/mL) are independent prognostic factors for post-LR CRC recurrence.[7,8] In the era of modern chemotherapy, the incorporation of perioperative CEA monitoring with post-LR adjuvant chemotherapy has been proposed as an effective treatment modality.[9,10] Specifically, perioperative chemotherapy may lead to survival benefit in patients with higher pre-LR CEA levels (>30 ng/mL) but not in those with normal pre-LR CEA levels (<5 ng/mL).

Peri- or postmetastasectomy adjuvant chemotherapy may prevent CRC recurrence after metastasis resection.[11–14] However, the optimal adjuvant chemotherapy after resection of liver metastasis in terms of protocol and regimens remains uncertain.[15–17] Thus, relatively few studies have compared the effects of adjuvant chemotherapy on outcomes of patients after LR on the basis of different chemotherapy regimens. In addition, whether post-LR CEA levels can be/serve as surrogate markers for selecting post-LR adjuvant chemotherapy regimens warrants further research.

Therefore, this retrospective study investigated not only the effects of peri-LR CEA levels on patient outcomes but also the role of post-LR adjuvant chemotherapy and its relation with postoperative CEA levels.

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2. Materials and methods

2.1. Patient population

A retrospective analysis of patients who had undergone LR with curative intent for CRC hepatic metastasis between January 2008 and March 2016 at Chang Gung Memorial Hospital, Linkou Medical Centre, Taoyuan, Taiwan was performed. The study was fully reviewed and approved by the Internal Review Board of Chang Gung Memorial Hospital at Linkou (201700231B0), and owing to the retrospective design, the requirement for patients' written informed consent was waived.

2.2. Evaluation of hepatic metastases

In general, all patients with CRC were thoroughly assessed through computed tomography (CT) scans from the neck to pelvic areas before surgery. Positron emission tomography (PET) or PET/CT was occasionally performed in selected patients as appropriate to confirm occult metastasis. The therapeutic strategy for each patient was selected based on consensus of a multidisciplinary committee of CRC, as previously described.[1] The eligibility of LR for CRC hepatic metastases was mainly considered in relation to the ability for complete removal of all metastatic nodules and preservation of adequate remnant liver volume from LR. No patient received simultaneous radiofrequency tumor ablation and LR in this study.

2.3. Perioperative chemotherapy and follow-up

Administration of perioperative chemotherapy was mainly determined according to the consensus of the multidisciplinary committee for CRC, in which the selection of regimens was based on patient's physical condition, the availability and affordability of the chemotherapy drugs, and the criteria of chemotherapeutic drugs covered and reimbursed by National Health Insurance program. In general, neoadjuvant chemotherapy was recommended to patients with hepatic metastases initially considered unresectable or borderline resectable. Subsequently, patients may have been referred for re-evaluation of surgical resection for metastatic lesion after downstaging by neoadjuvant chemotherapy. Post-LR adjuvant chemotherapy was generally recommended for all patients unless it was contraindicated. The options of chemotherapeutic regimens included fluoropyrimidine-based chemotherapy (5-fluorouracil + leucovorin [5-FU/LV] or capecitabine alone), irinotecan-based chemotherapy (leucovorin, 5-fluorouracil, irinotecan [FOLFIRI] or capecitabine plus irinotecan [XELIRI]), oxaliplatin-based chemotherapy (leucovorin, 5-fluorouracil, oxaliplatin [FOLFOX] and capecitabine plus oxaliplatin [XELOX]), and chemotherapy in combination with bioagents such as bevacizumab or cetuximab as appropriate. Usually, the selection of post-LR adjuvant chemotherapeutic regimens was similar to the pre-LR chemotherapeutic regimens or an advanced chemotherapeutic regimens.

All patients who had curative resection of hepatic metastases were regularly followed at our department until death or the end of this study. During follow-up, serum CEA levels and liver ultrasonography were mandatorily assessed at regular intervals. CT or PET/CT scans were performed annually or whenever CRC recurrence was suspected based on the aforementioned clinical assessments.

2.4. Statistical analysis

Recurrence-free survival (RFS) or overall survival (OS) was recorded as the time from the date of LR until the date of disease recurrence or death from any cause. Survival analysis was based on the Kaplan–Meier method and compared using the log-rank test. Categorical and continuous variables were compared using the chi-square and Student *t* tests, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed using Cox proportional hazards models. All statistical analyses were performed on SPSS for Windows (version 20.0; IBM Inc., Armonk, NY). A P value of $<.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

The study recruited 490 patients (332 men [67.8%] and 158 women [32.2%]); median age at the time of LR, 60.3 (range, 28.8–88.0 years). After LR, the median follow-up period was 42.5 (range, 24–266) months. In total, 324 (66.1%) patients had post-LR CRC recurrence, with a median recurrence duration of 13.38 (range, 0.9–81.0) months. First recurrence site could be single or multiple including 62.7% (203 of 324 patients) single site, and 37.3% (121 of 324 patients) multiple sites. Of single site recurrence, liver was the most recurrence site (64.0%; 130 of 203 patients), followed by lung (19.2%; 39 of 203 patients) and intraabdominal (13.3%; 27 of 203 patients), and 4 patients were brain metastases and 2 patients were bone metastases, and 1 patient was noted recurrence at abdominal wall.

Table 1 summarizes the basic clinical characteristics of the study patients, and clinical features of patients were compared according to pre-LR CEA level ($\geq$5 ng/mL vs $<$5 ng/mL) as well. The majority of clinical features were similar between the 2 groups. However, patients with pre-LR CEA $\geq$5 ng/mL had significantly larger tumor size ($P<.001$) and higher ratio of patients undergone major LR with removal of $\geq$3 hepatic segments ($P=.011$) as compared with the other group of pre-LR CEA $<$5 ng/mL. Additionally, patients in pre-LR CEA $<$5 ng/mL had a higher percentage of CEA $<$5 ng/mL at 1 month ($P<.001$) and 3 months ($P=.010$) after LR than that of patients in pre-LR CEA $\geq$5 ng/mL.

During the follow-up period, 273 (55.7%) patients died; the remaining 217 (44.3%) remained alive until the end of this study. The cumulative OS and RFS after LR are illustrated in Figure 1, and no significant differences were observed between patients with pre-LR CEA level $\geq$5 ng/mL and $<$5 ng/mL. The 1-, 3-, and 5-year RFS rates in patients with pre-LR CEA $<$5 ng/mL were 57.1%, 29.1%, and 25.6%, respectively, and the 1-, 3-, and 5-year RFS rates in patients with pre-LR $\geq$5 ng/mL were 56.5%, 28.4%, and 24.7%, respectively (Fig. 1A, $P=.803$). The 1-, 3-, and 5-year OS rates for patients with pre-LR CEA $\geq$5 ng/mL were 91.5%, 56.5%, and 41.4%, respectively, and the 1-, 3-, and 5-year OS rates for patients with pre-LR $<$5 ng/mL were 90.9%, 65.9%, and 49.7%, respectively (Fig. 1B, $P=.189$).

3.2. Relationship between CEA levels and outcomes

At 1 month post-LR, patients with CEA $<$5 ng/mL demonstrated significantly favorable RFS (median, 15.6 vs 8.5 months; HR, 1.78; 95% CI, 1.38–2.28; $P<.001$) and OS (median, 34.4 vs 24.2 months; HR, 2.03; 95% CI, 1.57–2.64; $P<.001$) as compared with patients with $>$5 ng/mL CEA (Fig. 2). Table 2 presents the Cox proportional hazard analysis results. At 1, 3, and 5 years, HR comparison for survival demonstrated

Table 1

Clinical features of patients based on pre-liver resection CEA levels.

Clinical features	CEA < 5 (n = 150)	CEA ≥ 5 (n = 340)	*P* value
Age, y			.006
Median, range	59 (29–82)	60 (29–88)	
Gender			.225
Male	106 (70.7)	226 (66.5)	
Female	44 (29.3)	114 (33.5)	
Primary tumor			.720
Colon	105 (70.0)	224 (65.9)	
Rectum	45 (30.0)	116 (33.1)	
Metastatic type			.306
Synchronous	95 (63.3)	188 (55.3)	
Metachronous	55 (36.7)	152 (44.7)	
Tumor number			.839
Median, range	1 (1–11)	2 (1–20)	
Maximum tumor size, cm			<.001
Median, range	2.5 (0.3–12.6)	3.1 (0.4–14.5)	
Distribution of metastasis			.178
Unilobar	107 (71.3)	235 (69.1)	
Bilobar	43 (28.7)	105 (30.9)	
Extent of liver resection			.011
<3 segments	120 (80.0)	243 (71.5)	
≥3 segments	30 (20.0)	97 (28.5)	
Chemotherapy before LR			1.000
Yes	59 (39.3)	133 (49.3)	
No	91 (60.7)	207 (50.7)	
Chemotherapy after LR			.740
Yes	135 (90.0)	303 (89.1)	
No	15 (10.0)	37 (10.9)	
Post-LR CEA, 1 mo			<.001
<5 ng/mL	139 (92.7)	244 (71.8)	
≥5 ng/mL	11 (7.3)	96 (28.2)	
Post-LR CEA, 3 mo			.010
<5 ng/mL	136 (90.7)	277 (81.5)	
≥5 ng/mL	14 (9.3)	63 (18.5)	

CEA = carcinoembryonic antigen, LR = liver resection.

significant differences; at 3 months post-LR, patients with <5 ng/mL CEA demonstrated similar significant improvements in RFS (median, 15.7 vs 6.12 months; HR, 2.83; 95% CI, 2.16–3.72; $P < .001$) and OS (median 34.0 vs 23.8 months; HR, 2.50; 95% CI, 1.89–3.31; $P < .001$) (Fig. 3). Similarly, HR comparisons demonstrated significant differences based on CEA levels 3 months post-LR (Table 2). Additionally, patient outcomes in terms of pre-LR chemotherapy and post-LR CEA levels were analyzed and illustrated in Table 3. There was no significant correlation between pre-LR chemotherapy and post-LR CEA level at 1 month, but oxaliplatin-based chemotherapy and additional cetuximab regimen were significantly associated with post-LR CEA level at 3 months.

3.3. Effect of adjuvant chemotherapy on survival outcomes

Of all 490 patients, 438 (89.4%) received post-LR adjuvant chemotherapy. The initial chemotherapeutic regimens comprised fluoropyrimidine (n = 81, 16.5%), irinotecan (n = 37, 7.6%), oxaliplatin (n = 177, 36.0%), bevacizumab (n = 117, 24%), and cetuximab (n = 26, 5.3%). To investigate the impact of post-LR adjuvant chemotherapy on the survival outcomes, RFS and OS were compared between patients with and without post-LR adjuvant chemotherapy. After post-LR adjuvant chemotherapy, median RFS did not differ significantly (9.8 and 9.0 months in patients with and without post-LR adjuvant chemotherapy, respectively; HR, 1.02; 95% CI, 0.69–1.52; $P = .885$); however, median OS demonstrated a significant difference (25.7 and 22.1 months in patients with and without post-LR adjuvant chemotherapy, respectively; HR = 0.58; 95% CI = 0.40–0.83; $P = .002$) (Fig. 4).

The clinical features of patients based on post-LR adjuvant chemotherapy are summarized and compared in Table 4. Several significant differences were noted among the 6 treatment subgroups. This cohort composed of heterogeneous clinicopathological features among different chemotherapy subgroups. However, several significant differences related to chemotherapy subgroups were observed. Subsequently, multivariate regression model was performed to investigate the impact of different regimens on survival outcomes between 5 types of adjuvant chemotherapy (Table 5). The results demonstrated that patients receiving 5-FU/LV (HR, 0.63; 95% CI, 0.41–0.97; $P = .039$), oxaliplatin-based chemotherapy (HR, 0.45; 95% CI, 0.30–0.67; $P < .001$), or bevacizumab (HR, 0.64; 95% CI, 0.42–0.98;

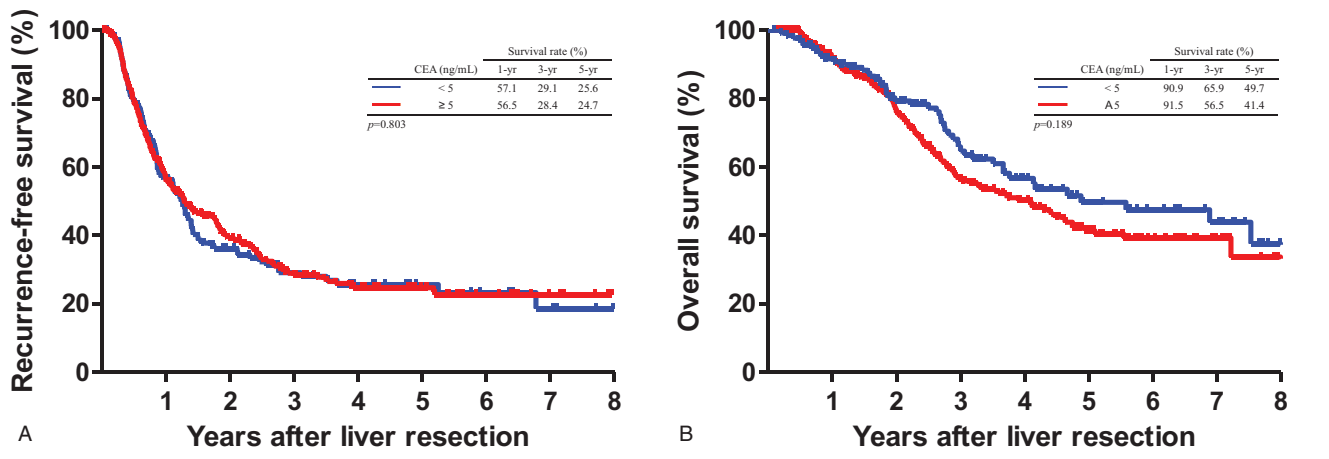

Figure 1. Comparison of cumulative Kaplan–Meier survival curves based on pre-liver resection carcinoembryonic antigen (CEA) levels (≥5 and <5 ng/mL). (A) Recurrence-free survival ($P = .803$). (B) Overall survival ($P = .189$). CEA < 5 ng/mL (n = 150) versus CEA ≥ 5 ng/mL (n = 340).

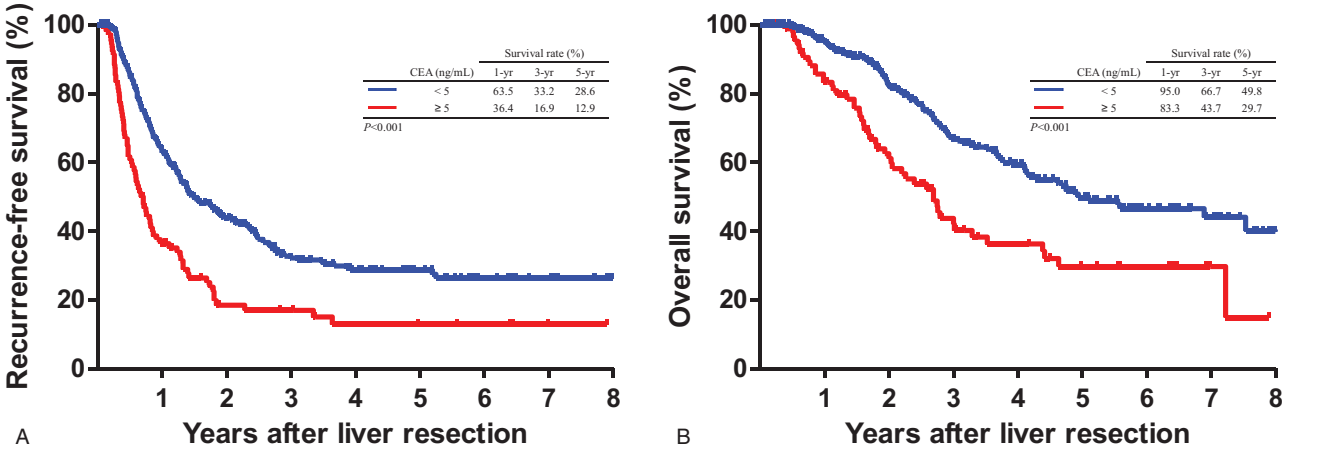

Figure 2. Comparison of Kaplan–Meier recurrence-free survival and overall survival curves based on carcinoembryonic antigen (CEA) levels at 1 month after liver resection. (A) Recurrence-free survival ($P < .001$). (B) Overall survival ($P < .001$). CEA < 5 ng/mL (n = 383) versus CEA ≥ 5 ng/mL (n = 107).

Table 2

Cox proportional hazard analysis of patient outcomes related to post-liver resection carcinoembryonic antigen levels.

	CEA ≥ 5 ng/mL versus CEA < 5 ng/mL							
	1 mo after LR				3 mo after LR			
	RFS		OS		RFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall	1.78 (1.38–2.28)	<.001	2.03 (1.57–2.64)	<.001	2.83 (2.16–3.72)	<.001	2.50 (1.89–3.31)	<.001
1-y	1.96 (1.45–2.64)	<.001	2.10 (1.22–3.61)	.007	3.85 (2.84–5.22)	<.001	2.33 (1.89–3.31)	<.001
3-y	1.64 (1.27–2.11)	.001	2.15 (1.60–2.87)	<.001	2.84 (2.16–3.72)	<.001	2.36 (1.72–3.23)	<.001
5-y	1.63 (1.27–2.10)	<.001	2.05 (1.57–2.68)	<.001	2.75 (2.10–3.61)	<.001	2.43 (1.83–3.24)	<.001

CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, LR = liver resection, OS = overall survival, RFS = recurrence free survival.

$P = .040$) had significantly longer OS than those did not receiving chemotherapy. However, no significant results related to RFS improvement were observed for any of the 5 regimens compared with LR alone.

To further clarify outcomes related to posthepatectomy CEA, the subgroup analysis was performed according to CEA levels (<5 and ≥5 ng/mL) 1 month after LR. Patients with <5 ng/mL CEA demonstrated significant differences that persisted for 5-FU/LV (HR, 0.58; 95% CI, 0.35–0.96; $P = .035$) and oxaliplatin-based chemotherapy (HR, 0.38; 95% CI, 0.24–0.62; $P < .001$) but not for other chemotherapy types, including irinotecan (HR, 0.93; 95% CI, 0.55–1.7; $P = .981$), bevacizumab (HR, 0.63; 95%

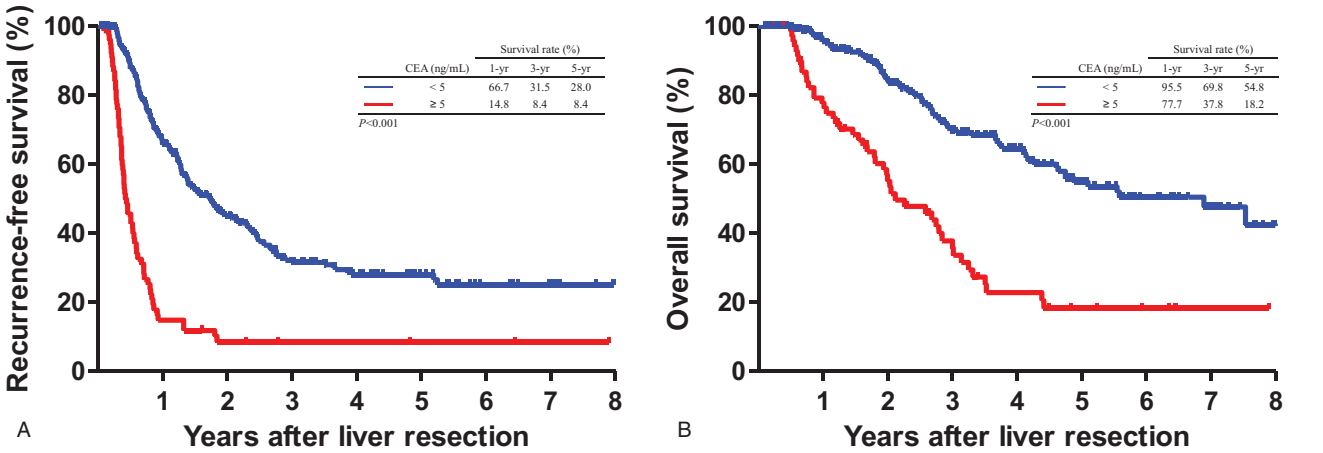

Figure 3. Comparison of Kaplan–Meier recurrence-free survival and overall survival curves according to carcinoembryonic antigen (CEA) levels at 3 months after liver resection. (A) Recurrence-free survival ($P < .001$). (B) Overall survival ($P < .001$). CEA < 5 ng/mL (n = 413) versus CEA ≥ 5 ng/mL (n = 77).

Table 3

Cox proportional hazard analysis of patient outcomes related to pre-liver resection chemotherapy and carcinoembryonic antigen levels.

	CEA ≥ 5 ng/mL versus CEA < 5 ng/mL			
	1 mo after LR		3 mo after LR	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
None	1	–	1	–
5 FU/LV	2.01 (0.82–4.93)	.125	1.45 (0.46–4.48)	.519
Oxaliplatin-based	1.31 (0.68–2.51)	.408	2.16 (1.08–4.31)	.029
Irinotecan-based	1.10 (0.29–4.06)	.886	2.90 (0.86–9.73)	.085
Additional bevacizumab	0.93 (0.46–1.85)	.839	1.34 (0.62–2.86)	.447
Additional cetuximab	1.61 (0.679–3.84)	.280	3.43 (1.44–8.16)	.005

CEA = carcinoembryonic antigen, CI = confidence interval, 5FU/LV = fluorouracil/leucovorin, HR = hazard ratio, LR = liver resection.

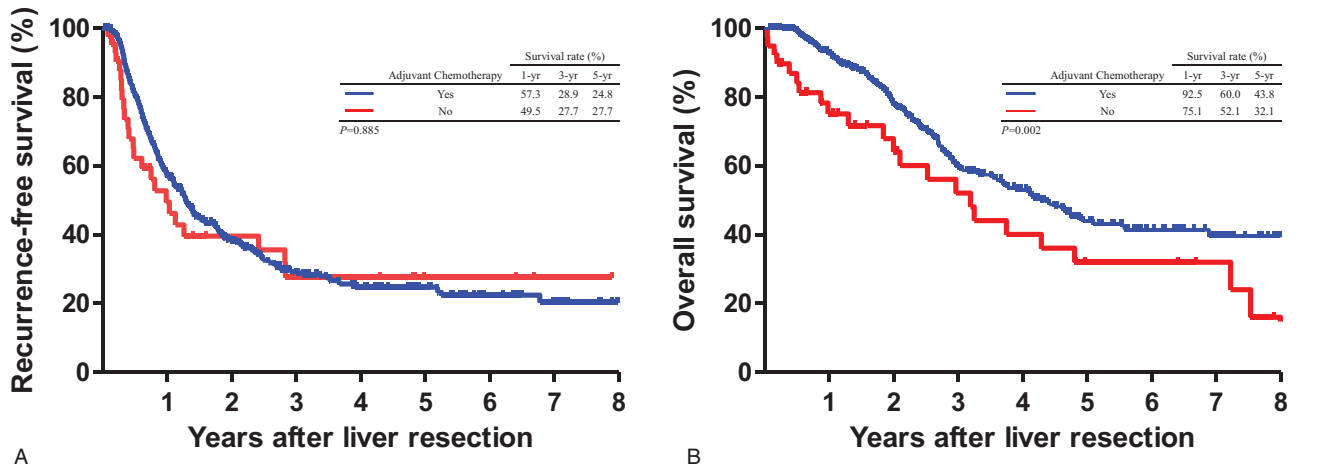

Figure 4. Comparison of Kaplan–Meier survival curves based on post-liver resection adjuvant chemotherapy. Significant differences were not observed for recurrence-free survival (A, *P* = .885) but were noted for overall survival (B, *P* = .002). Yes (n = 438) versus No (n = 52).

Table 4

Clinical features of patients based on post-liver resection adjuvant chemotherapy.

	None n = 52, %	5 FU/LV n = 81, %	Oxaliplatin-based n = 177, %	Irinotecan-based n = 37, %	Bevacizumab n = 117, %	Cetuximab n = 26, %	*P* value
Sex							.330
Male	40 (76.9)	52 (64.2)	125 (70.6)	24 (64.9)	72 (61.5)	18 (69.2)	
Female	12 (23.1)	29 (35.8)	52 (29.4)	13 (35.1)	45 (38.5)	8 (30.8)	
Age, y							.007*
>65	23 (44.2)	41 (50.6)	65 (36.7)	9 (24.3)	32 (27.4)	8 (30.8)	
≤65	29 (55.8))	40 (49.4)	112 (63.3)	28 (75.7)	85 (72.6)	18 (69.2)	
Primary tumor							.896
Right colon	11 (21.0)	14 (17.3)	23 (13.0)	5 (13.5)	25 (21.4)	5 (19.2)	
Left colon	41 (79.0)	67 (82.7)	154 (87.0)	32 (86.5)	92 (78.6)	21 (80.8)	
Metastatic types							.004*
Synchronous	24 (46.2)	43 (53.1)	112 (63.3)	17 (46.0)	71 (60.7)	21 (80.8)	
Metachronous	28 (53.8)	38 (46.9)	65 (36.7)	20 (54.0)	46 (39.3)	5 (19.2)	
Chemotherapy before LR							<.001*
No	36 (69.2)	52 (64.2)	120 (67.8)	9 (24.3)	76 (65.0)	10 (38.5)	
Yes	16 (30.8)	29 (35.8)	57 (32.2)	28 (75.7)	41 (35.0)	16 (61.5)	
Distribution of hepatic metastasis							.011*
Unilobar liver	36 (69.2)	55 (67.9)	122 (68.9)	32 (86.5)	88 (75.2)	11 (42.3)	
Bilobar liver	16 (30.8)	26 (32.1)	55 (31.1)	5 (13.5)	29 (24.8)	15 (57.7)	
CEA before LR							.816
≥40 ng/mL	12 (23.1)	22 (27.2)	37 (20.9)	11 (29.7)	26 (22.2)	6 (23.1)	
<40 ng/mL	40 (77.9)	59 (72.8)	140 (79.1)	26 (70.3)	91 (77.8)	20 (76.9)	
CEA after LR (1 mo)							.492
≥5 ng/mL	11 (21.2)	18 (22.2)	39 (22.0)	10 (27.0)	25 (21.4)	10 (38.5)	
<5 ng/mL	41 (78.8)	63 (77.8)	138 (78.0)	27 (73.0)	92 (78.6)	16 (61.5)	

CEA = carcinoembryonic antigen, 5FU/LV = fluorouracil/leucovorin, LR = liver resection.

Table 5

Multiple regression analysis of outcomes related to adjuvant chemotherapy after liver resection.

RFS	Overall		1-y		3-y		5-y	
Chemotherapy	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
None	1	–	1	–	1	–	1	–
All chemotherapy	1.02 (0.69–1.52)	.886	1.13 (0.70–1.84)	.606	1.35 (0.90–2.02)	.135	1.35 (0.91–2.01)	.131
5 FU/LV	1.05 (0.66–1.67)	.815	1.13 (0.64–2.01)	.659	1.41 (0.88–2.26)	.142	1.40 (0.88–2.22)	.148
Oxaliplatin-based	0.92 (0.60–1.39)	.697	1.05 (0.62–1.76)	.849	1.21 (0.79–1.86)	.370	1.23 (0.81–1.87)	.328
Irinotecan-based	1.47 (0.87–2.48)	.150	1.60 (0.84–3.06)	.148	1.97 (1.16–3.36)	.011	1.93 (1.14–3.26)	.013
Additional bevacizumab	1.00 (0.64–1.55)	.986	1.04 (0.60–1.80)	.881	1.29 (0.83–2.03)	.252	1.29 (0.83–2.00)	.253
Additional cetuximab	1.42 (0.8–2.54)	.229	1.58 (0.78–3.19)	.195	1.80 (1.00–3.24)	.046	1.76 (0.99–3.15)	.054
OS	**Overall**		**1-y**		**3-y**		**5-y**	
Chemotherapy	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**
None	1	–	1	–	1	–	1	–
All chemotherapy	0.58 (0.40–0.83)	.003	0.23 (0.12–0.41)	<.001	0.69 (0.45–1.06)	.095	0.66 (0.45–0.97)	.358
5 FU/LV	0.63 (0.41–0.97)	.039	0.16 (0.05–0.43)	.003	0.72 (0.42–1.21)	.219	0.78 (0.50–1.23)	.306
Oxaliplatin-based	0.45 (0.30–0.67)	<.001	0.31 (0.16–0.59)	.004	0.56 (0.35–0.90)	.017	0.54 (0.35–0.82)	.003
Irinotecan-based	0.98 (0.59–1.61)	.948	0.35 (0.12–0.96)	.041	1.24 (0.70–2.20)	.454	1.13 (0.67–1.91)	.631
Additional bevacizumab	0.64 (0.42–0.98)	.040	0.13 (0.05–0.33)	<.001	0.74 (0.45–1.21)	.233	0.69 (0.44–1.06)	.095
Additional cetuximab	0.67 (0.33–1.32)	.248	0.20 (0.04–0.86)	.031	0.67 (0.32–1.41)	.299	0.56 (0.28–1.12)	.104

CI = confidence interval, 5FU/LV = fluorouracil/leucovorin, HR = hazard ratio, OS = overall survival, RFS = recurrence free survival.

CI, 0.39–1.03; $P = .066$), and cetuximab (HR, 0.76; 95% CI, 0.32–1.75; $P = .521$) (Table 6). Significantly, the impact of oxaliplatin-based chemotherapy lasted until post-LR year 5, whereas the effects of 5-FU/LV remained significant only until post-LR year 1. In patients with ≥5 ng/mL CEA, no significant differences related to RFS or OS were noted for any chemotherapy types (Table 7).

4. Discussion

LR has been the standard treatment for CRC hepatic metastasis and can achieve prolonged survival. However, approximately 75% of patients who had undergone curative-intent LR develop CRC recurrence in post-LR year 1 or 2. Therefore, adjuvant chemotherapy with systemic or intrahepatic artery infusion after LR has been adopted to eradicate micrometastases and prevent CRC recurrence. However, the extent of the benefits of these adjuvant chemotherapies in patients who have undergone curative-intent LR remains unclear. Similarly, the benefit of adding bioagents in this setting for post-LR patients warrants investigation.

Studies have reported the potential benefit of systemic chemotherapy compared with surgery and follow-up alone.[18–20] Moreover, some studies have reported the nonsignificant effects of adjuvant chemotherapy on OS after LR.[21–23] Few recent studies have shown that doublet combination chemotherapy has no significant benefit or even has disadvantages compared with monochemotherapy.[17,24] Moreover, the beneficial effects of additional bioagents with cytotoxic chemotherapy in an adjuvant setting remain inconsistent.[25–27] Thus, recommending effective adjuvant chemotherapy for these patients after LR is difficult.

This retrospective study clarified the role of post-LR adjuvant chemotherapy for CRC hepatic metastasis and its effect on

Table 6

Multiple regression analysis of outcomes related to adjuvant chemotherapy in patients with <5 ng/mL CEA 1 mo post-liver resection.

RFS	Overall		1-y		3-y		5-y	
Chemotherapy	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
None	1	–	1	–	1	–	1	–
5 FU/LV	1.13 (0.67–1.90)	.638	1.34 (0.67–2.68)	.394	1.52 (0.89–2.60)	.119	1.50 (0.89–2.53)	.127
Oxaliplatin-based	0.91 (0.57–1.48)	.728	1.05 (0.56–2.00)	.861	1.20 (0.73–1.96)	.459	1.19 (0.74–1.92)	.466
Irinotecan-based	1.36 (0.73–2.51)	.320	1.80 (0.82–3.95)	.139	1.92 (1.03–3.57)	.039	1.84 (1.00–3.41)	.049
Additional bevacizumab	1.03 (0.63–1.71)	.882	1.18 (0.60–2.29)	.621	1.31 (0.78–2.19)	.292	1.30 (0.79–2.15)	.298
Additional cetuximab	1.48 (0.73–3.01)	.275	2.18 (0.9–5.19)	.076	1.99 (0.97–4.08)	.058	1.92 (0.94–3.91)	.071
OS	**Overall**		**1-y**		**3-y**		**5-y**	
Chemotherapy	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**
None	1	–	1	–	1	–	1	–
5 FU/LV	0.58 (0.35–0.96)	.035	0.09 (0.02–0.44)	.002	0.79 (0.42–1.49)	.478	0.77 (0.45–1.32)	.358
Oxaliplatin-based	0.38 (0.24–0.62)	<.001	0.29 (0.13–0.66)	.003	0.53 (0.29–0.97)	.039	0.49 (0.30–0.81)	.005
Irinotecan-based	0.99 (0.55–1.78)	.981	0.11 (0.01–0.87)	.036	1.45 (0.72–2.91)	.289	1.20 (0.64–2.22)	.561
Additional bevacizumab	0.63 (0.39–1.031)	.066	0.20 (0.07–0.54)	.001	0.86 (0.47–1.55)	.624	0.71 (0.43–1.19)	.198
Additional cetuximab	0.76 (0.329–1.75)	.521	0.19 (0.02–1.50)	.117	0.88 (0.34–2.25)	.795	0.70 (0.30–1.65)	.425

CEA = carcinoembryonic antigen, CI = confidence interval, 5FU/LV = fluorouracil/leucovorin, HR = hazard ratio, OS = overall survival, RFS = recurrence-free survival.

Table 7

Multiple regression analysis of outcomes related to adjuvant chemotherapy in patients with ≥5ng/mL CEA 1 mo post-liver resection.

RFS	Overall		1-y		3-y		5-y	
Chemotherapy	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
None	1	–	1	–	1	–	1	–
5 FU/LV	0.69 (0.26−1.82)	.458	0.65 (0.23−1.83)	.416	1.00 (0.38−2.65)	.988	1.02 (0.38−2.69)	.962
Oxaliplatin-based	0.79 (0.32−1.91)	.606	0.95 (0.38−2.33)	.916	1.18 (0.48−2.85)	.713	1.28 (0.53−3.08)	.579
Irinotecan-based	1.53 (0.54−4.31)	.422	1.04 (0.33−3.22)	.945	1.81 (0.64−5.12)	.257	1.87 (0.66−5.27)	.236
Additional bevacizumab	0.75 (0.29−1.88)	.542	0.68 (0.26−1.80)	.443	1.11 (0.44−2.80)	.810	1.14 (0.45−2.86)	.779
Additional cetuximab	0.87 (0.30−2.52)	.798	0.64 (0.19−2.11)	.466	1.13 (0.39−3.27)	.814	1.16 (0.40−3.35)	.781
OS	**Overall**		**1-y**		**3-y**		**5-y**	
Chemotherapy	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**
None	1	–	1	–	1	–	1	–
5 FU/LV	0.73 (0.32−1.68)	.467	0.25 (0.06−1.05)	.058	0.47 (0.18−1.16)	.104	0.65 (0.27−1.54)	.333
Oxaliplatin-based	0.60 (0.28−1.29)	.198	0.30 (0.10−0.94)	.039	0.47 (0.21−1.05)	.066	0.52 (0.23−1.16)	.111
Irinotecan-based	0.86 (0.33−2.25)	.764	0.64 (0.17−2.39)	.509	0.70 (0.25−1.95)	.506	0.79 (0.29−2.11)	.641
Additional bevacizumab	0.61 (0.27−1.38)	.244	–	–	0.42 (0.17−1.01)	.053	0.50 (0.21−1.17)	.113
Additional cetuximab	0.40 (0.12−1.33)	.137	0.14 (0.01−1.24)	.078	0.26 (0.07−0.87)	.028	0.24 (0.07−0.81)	.021

CEA = carcinoembryonic antigen, CI = confidence interval, 5FU/LV = fluorouracil/leucovorin, HR = hazard ratio, OS = overall survival, RFS = recurrence-free survival.

patient outcomes. The results demonstrated that post-LR adjuvant chemotherapy significantly prolonged OS. The adjuvant chemotherapy group was estimated to have a 41.7% increase in OS (HR, 0.58) compared with patients not receiving adjuvant chemotherapy. Moreover, certain chemotherapeutic regimens with 5FU as the backbone with or without oxaliplatin and in combination with bioagents (eg, bevacizumab) had a significant post-LR survival benefit in patients with CRC hepatic metastasis, thereby indicating the importance of chemotherapy in adjuvant settings.

However, adjuvant chemotherapy did not show a significant effect on RFS. In contrast, patients who received certain chemotherapeutic regimens such as irinotecan-based and/or additional cetuximab even had a higher risk of recurrence after LR. These findings are consistent with reports demonstrating a detrimental effect of cetuximab in the adjuvant or neoadjuvant setting of stage III colon cancer.[10] Nonetheless, the current study was not able to well elucidate these results. A possible explanation could be that patients who were subjected to these chemotherapeutic regimens had naturally more severe hepatic metastasis than other patients. As a result, patients who had received irinotecan-based and/or additional cetuximab chemotherapy had a poor outcome in terms of RFS. Additionally, the selection of chemotherapeutic regimens for adjuvant setting might also be affected by the policy of the national health insurance program that only covers and reimburses certain regimens. Hence, it is possible that the policy of national insurance health program would limit oncologist in selection of chemotherapeutic regimens perhaps leading to an existed bias in the current study. Theoretically, adjuvant chemotherapy can eradicate micrometastases. However, identifying subgroup patients that could be considered potential curative resection patients undergoing "true" adjuvant chemotherapy or which subgroup patients as potential noncurative resection cases to be treated as "truly" palliative goal was difficult. Therefore, few studies have used termed "pseudoadjuvant chemotherapy" for aforementioned circumstances. To identify the "true" adjuvant chemotherapy subgroup, this study stratified patients with CRC hepatic metastasis based on serum CEA levels 1 month post-LR (<5 and ≥5 ng/mL). The results indicated the importance of post-LR CEA levels related to adjuvant chemotherapy and chemotherapeutic regimens. In addition, compared with other patients, post-LR adjuvant chemotherapy may benefit more patients with postoperative CEA levels of <5 ng/mL. Consistent with previous studies, the current study supported that CRC recurrence and patient survival are strongly affected by post-LR CEA levels.

In this study, the post-LR CEA level was a significant factor affecting patient RFS and OS. Patients with <5 ng/mL CEA 3 months post-LR had favorable RFS outcomes. Therefore, regular monitoring of CEA levels after LR for metastasis at least within 3 months is strongly recommended. Nevertheless, perioperative FOLFOX may benefit patients with resectable hepatic metastasis, even when preoperative CEA levels are high, although a 5-year OS benefit may not be achieved. Furthermore, the current study observed that postoperative CEA trends were correlated with patient survival and possibly with recurrent patterns after LR for CRC hepatic metastasis. Patients with low post-LR CEA levels were more likely to have a single recurrence site. Therefore, this study concurred with most reports that post-LR CEA levels are important oncological surveillance components, possibly predicting recurrent patterns.

5. Conclusion

In summary, perioperative CEA levels are crucial for defining the prognosis and management of CRC hepatic metastasis after LR. The current study might be limited by its retrospective design; several significant observations may aid in decision-making for therapeutic options to treat CRC hepatic metastasis. The inherent biases might also be associated with retrospective data necessitate caution when interpreting the related results. Nevertheless, in the present study, CEA levels dropping to <5 ng/mL at 1 month post-LR was a favorable factor for both RFS and OS. Regarding post-LR adjuvant chemotherapy use, a beneficial effect may be obtained in terms of use of therapeutic regimens, including monochemotherapy (fluorouracil or leucovorin), oxaliplatin-based chemotherapy, or addition of bioagents (eg, bevacizumab), particularly in patients with <5 ng/mL CEA levels 1 month post-

LR. Moreover, in future, post-LR CEA levels might be considered as surrogate markers for therapeutic strategies in terms of selecting post-LR adjuvant chemotherapy. However, to achieve favorable long-term patient outcomes, efforts should be made toward the development of a therapeutic strategy involving surgery and chemotherapeutic regimens.

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