Post-chemotherapeutic CEA and CA19-9 Are Prognostic Factors in Patients with Colorectal Liver Metastases Treated with Hepatic Resection After Oxaliplatin-based Chemotherapy

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Abstract. *Background/Aim: The prognostic value of tumor markers remains unclear in patients with colorectal liver metastases (CRLM) who undergo hepatectomy following chemotherapy. The aim of the present study was to identify prognostic factors associated with recurrence and survival in such patients. Patients and Methods: Between 2005 and 2012, 62 patients with initially unresectable or marginally unresectable CRLM who underwent hepatectomy following chemotherapy were enrolled. A Cox proportional hazards model was used to identify the prognostic factors. Results: Multivariate analysis indicated that a high level of carbohydrate antigen 19-9 (CA19-9) in serum post-chemotherapy was significant factor, predictive of poor overall survival [Hazard Ratio (HR)=4.46, 95% Confidence Interval (CI)=1.68-11.8; p=0.003] and marginally significant regarding poorer relapse-free survival (HR=2.11, 95% CI=0.99-4.47; p=0.050). Non-response to preoperative chemotherapy was a significant prognostic factor regarding shorter relapse-free (HR=2.18, 95% CI=1.10-4.33; p=0.026) and overall survival (HR=3.14, 95% CI=1.22-8.08; p=0.018). High levels of carcinoembryonic antigen CEA in serum post-chemotherapy (HR=3.08, 95% CI=1.13-8.39; p=0.028) and the absence of adjuvant chemotherapy (HR=2.27, 95% CI=1.17-4.41; p=0.016) were independent risk factors for recurrence. Conclusion: Measurement of both CEA and CA19-9 level is strongly recommended for patients with CRLM treated with preoperative chemotherapy followed by hepatectomy because normalization of serum CEA and CA19-9 levels after chemotherapy will demonstrate a good prognosis after curative hepatectomy.*

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Key Words: Colorectal cancer, colorectal liver metastasis, hepatectomy, chemotherapy.

Colorectal cancer is one of the most common causes of cancer-related death worldwide. The median survival duration of patients with metastatic colorectal cancer treated with best supportive care alone is approximately 6 months (1). The liver is the most frequent site of colorectal cancer metastasis, and hepatic resection is the only available treatment that can achieve potential cure in patients with colorectal liver metastases (CRLM). The 5-year survival rate of patients who undergo curative liver resection now ranges from 37-58% (5, 28).

The development of new chemotherapeutic and molecular targeted drugs, such as oxaliplatin, irinotecan, bevacizumab, cetuximab and panitumumab, has improved the resectability of initially unresectable CRLM (1, 6). Nordlinger *et al*. recently reported on the EORTC 40983 trial involving the assessment of perioperative chemotherapy with the oxaliplatin plus fluorouracil and leucovorin (FOLFOX) 4 regimens for patients with initially resectable CRLM (22). It was reported that perioperative FOLFOX seems to be beneficial regarding progression-free survival for particular patients with high levels of serum carcinoembryonic antigen (CEA) on admission (27).

A number of prognostic factors have been reported in patients with CRLM undergoing hepatic resection including: a positive resection margin, node-positive primary disease, a short disease-free interval from the detection of the primary tumor to the development of metastases, a large number of CRLM, a large-sized hepatic tumor, histology of the primary tumor, and a high CEA level amongst others (8, 16, 21, 26, 30).

Recently, we developed a novel nomogram to predict disease-free survival (DFS) in 727 patients with CRLM

Table I. *Patients' clinical characteristics.*

Characteristic	n=62	%
Age (years)		
Median (range)	65 (35-82)	
Gender		
Male	38	61.3
Female	24	38.7
Tumor location		
Colon	39	62.9
Rectum	23	37.1
LN metastasis from primary tumor		
Positive	38	61.3
Negative	24	38.7
Timing of liver metastasis		
Synchronous	41	66.1
Metachronous	21	33.9
Extrahepatic metastasis		
Presence	7	11.3
Lung	6	
Lymph node	1	
Absence	55	88.7

LN: Lymph node.

Table II. *Type of perioperative chemotherapy.*

Therapy	n=62	%
Chemotherapy		
FOLFOX	52	83.9
XELOX	7	11.3
Other	3	4.8
Molecular-targeted drug		
Used	27	43.5
Bevacizumab	22	
Cetuximab	3	
Panitumumab	2	
Not used	35	56.5
Number of therarpy cycles		
Median (range)	6.5 (2-42)	
Postoperative adjuvant chemotherapy		
Used	36	58.1
Oxaliplatin based	26	
5-FU based	10	
Not used	26	41.9

FOLFOX: Chemotherapy with oxaliplatin plus 5-fluorouracil and leucovorin; XELOX: chemotherapy with oxaliplatin plus capecitabine; Other: other chemotherapy regimens with oxaliplatin.

Table III. *Characteristics of liver-metastatic tumor before and after chemotherapy.*

Characteristic	Prechemotherapy (n=62)	Postchemotherapy (n=62)	*p*-Value
Tumor size			
Median, mm	33	26	0.023
≤50/>50	40/20	49/13	
Unknown	2	-	
Number of tumors			
Median	2	2	0.865
<5/≥5	39/21	41/21	
N.A.	2	-	
CEA (ng/ml)			
Median (range)	20.4 (1-4112)	6.1 (1-348.8)	<0.001
Normal/elevated	9/51	15/47	
Unknown	2	-	
CA19-9 (U/ml)			
Median (range)	44.9 (0.1-3404)	19.5 (0.1-1245)	0.017
Normal/elevated	25/32	45/17	
Unknown	5	-	

N.A.: Not available; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; Normal: serum level is within normal limits; elevated: serum level exceeds normal limits.

Table IV. *Response to preoperative chemotherapy and surgical data.*

Variable	n=62	%
Radiological response		
Complete	0	0.0
Partial	39	62.9
Stable disease	16	25.8
Progressive disease	7	11.3
Surgical data		
Hepatectomy		
Partial resection	24	38.7
Anatomic resection	38	61.3
Synchronous resection of primary tumor		
Yes	10	16.1
No	52	83.9
Combined with RFA		
Yes	13	21.0
No	49	79.0
Duration of surgery, min		
Median (range)	385 (179-746)	
Blood loss, ml		
Median (range)	300 (10-1111)	
Postoperative complications		
All	14	22.6
Bile leakage	8	
SSI	3	
Other	3	
Pathological response		
Grade 1a/1b	36	58.1
Grade 2	23	37.1
Grade 3	3	4.8

RFA: Radiofrequency ablation; SSI: surgical site infection

treated with hepatic resection using the Japanese multi-center database (5). The factors affecting DFS were as follows: timing of the development of CRLM, primary tumor lymph node status, number of tumors present, largest tumor diameter, detection of extra-hepatic disease, and

Table V. *Univariate analyses of risk factors for recurrence after hepatectomy.*

			Univariate		
Variables		n=62	HR	95% CI	*p*-Value
Characteristic					
Age, years	<65	29	1.45	0.80-2.88	0.199
	≥65	33			
Gender	Male	38	0.91	0.48-1.73	0.764
	Female	24			
Location of primary tumor	Rectum	23	1.11	0.59-2.11	0.738
	Colon	39			
LN metastasis from primary tumor	Presence	38	1.05	0.56-1.97	0.884
	Absence	24			
Timing of liver metastasis	Synchronous	41	0.91	0.45-1.75	0.769
	Metachronous	21			
Prechemotherapy					
Tumor size, mm	>50	20	1.05	0.54-2.07	0.870
	≤50	40			
No. of tumors	≥5	21	1.86	1.04-4.50	0.040
	<5	39			
CEA	Elevated	51	1.32	0.55-3.12	0.549
	Normal	9			
CA19-9	Elevated	32	1.16	0.61-2.26	0.637
	Normal	25			
Postchemotherapy					
Tumor size, mm	>50	13	1.84	0.93-5.60	0.073
	≤50	49			
No. of tumors	≥5	21	1.56	0.84-3.36	0.142
	<5	41			
CEA	Elevated	47	3.33	1.46-5.51	0.002
	Normal	15			
CA19-9	Elevated	17	1.93	1.08-5.53	0.033
	Normal	45			
Response to chemotherapy					
Radiological non-responder	Yes	23	1.75	0.96-4.05	0.066
	No	39			
Pathological response	Grade 1a/1b	36	1.50	0.82-2.83	0.187
	Grade 2/3	26			
Oxaliplatin- based PAC	None	36	1.74	0.97-3.40	0.062
	Done	26			
Surgical data					
Partial hepatectomy	Yes	24	0.73	0.38-1.33	0.292
	No	38			
Synchronous resection	Yes	10	0.96	0.42-2.18	0.916
	No	52			
Combined with RFA	Yes	13	0.99	0.42-2.18	0.916
	No	49			
Duration of surgery, min	>400	35	0.87	0.46-2.10	0.967
	≤400	27			
Blood loss, ml	>300	32	1.01	0.55-1.88	0.967
	≤300	30			
Postoperative complications	Presence	14	1.25	0.59-2.81	0.521
	Absence	48			

LN: Lymph node; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PAC: postoperative adjuvant chemotherapy.

serum carbohydrate antigen 19-9 (CA19-9) level. In the present study, the preoperative CA19-9 level was found to be a significant predictive marker for both DFS and overall survival (OS); in contrast, serum CEA level was not found to be significantly predictive. However, this nomogram was developed for patients who underwent hepatic resection

Table VI. *Multivariate analyses of risk factors for recurrence after hepatectomy and prognostic factors for overall survival after hepatectomy.*

			Multivariate		
Variable		n=62	HR	95% CI	*p*-Value
Relapse-free survival					
Prechemotherapy					
No. of tumors	≥5	21	1.65	0.81-3.35	0.167
	<5	39			
Postchemotherapy					
Tumor size, mm	>50	13	1.26	0.58-2.74	0.557
	≤50	49			
CEA	Elevated	47	3.08	1.13-8.39	0.028
	Normal	15			
CA19-9	Elevated	17	2.11	0.99-4.47	0.050
	Normal	45			
Radiological non-responder	Yes	23	2.18	1.10-4.33	0.026
	No	39			
Oxaliplatin-based PAC	None	36	2.27	1.17-4.41	0.016
	Given	26			
Overall survival					
Postchemotherapy					
CEA	Elevated	47	2.10	0.53-8.38	0.292
	Normal	15			
CA19-9	Elevated	17	4.46	1.68-11.8	0.003
	Normal	45			
Radiological non-responder	Yes	23	3.14	1.22-8.08	0.018
	No	39			
Blood loss, ml	>300	32	1.827	0.68-4.88	0.230
	≤300	30			

HR: Hazard ratio; CI: confidence interval; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PAC: postoperative adjuvant chemotherapy.

mainly in the absence of perioperative chemotherapy using modern chemotherapeutic regimens. The optimal prognostic factor for patients with CRLM after hepatic resection following preoperative chemotherapy remains unclear. Furthermore, there have been few studies that evaluated preoperative prognostic factors in patients who underwent hepatic resection after chemotherapy. Adam *et al*. reported that tumor progression after chemotherapy, elevated pre-operative serum CA 19-9 level, the number of resected metastases and the number of lines of chemotherapy were independently associated with decreased OS in the limited number of their patients who underwent hepatic resection after preoperative chemotherapy.

The aim of the present study was to identify prognostic factors, focusing on tumor markers measured pre- and post-chemotherapy associated with recurrence and survival in patients with CRLM who underwent hepatic resection following oxaliplatin-based chemotherapy.

Patients and Methods

Patients. Between May 2005 and December 2012, 126 patients with CRLM underwent hepatic resection at the Department of Gastroenterological Surgery at the Graduate School of Medical Sciences, Kumamoto University, Japan. Of 126 patients, 62 undergoing hepatic resection with initially unresectable or marginally unresectable CRLM who underwent preoperative chemotherapy followed by hepatic resection were enrolled in this study. The definitions of unresectable CRLM included: i) extensive liver involvement (more than six liver subsegments involved, 65% liver invasion, or all three hepatic veins or Glissonean pedicles involved); ii) unresectable extrahepatic metastases; iii) major liver insufficiency; iv) patients unfit for or declining surgery. Marginally resectable CRLM included: i) oncologically non-resectable CRLM (*i.e*. five or more CRLM), ii) concomitant resectable extrahepatic metastases, iii) with a risk of non-curative resection. Patients who underwent non-curative hepatic resection or no initial hepatic resection were excluded. Additionally, patients who had residual primary colorectal cancer throughout the observation period were omitted. Patients who underwent hepatic resection combined with radiofrequency ablation (15), or with curatively resected extra-hepatic metastases were included.

Clinical data. Patients' characteristics were obtained retrospectively from the patient database and were: age; gender; tumor location; lymph node metastasis from the primary tumor; timing of the development of liver metastases; and extrahepatic metastasis. The surgical and chemotherapy data were obtained from the patient records. The number and diameter of liver metastases were evaluated using computed tomography pre- and postchemotherapy. Tumor markers were divided into two groups based on the serum level being within normal limits or higher than normal limits. The number of tumors present (≤4 or 4) and the diameter of liver metastases (≤50 mm or >50 mm) were also similarly divided (4). Pre- and postchemotherapy clinical data were assessed within two weeks before and after chemotherapy, respectively. Intraoperative parameters, namely duration of surgery and blood loss, were divided into two groups depending on the median value.

Radiological response rates were calculated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 (7, 29). Pathological responses were evaluated by pathologists based on the Japanese Classification of colorectal carcinoma (11). The pathological response grade was classified as follows: grade 0: with no necrosis or cellular or structural change; grade 1a, 1b, and 2: with necrosis or disappearance of tumor in <1/3, <2/3, and >2/3 of the entire lesion, respectively; and grade 3: with the entire lesion showing necrosis or fibrosis, and no viable tumor cells identified. The physician decided whether or not to perform postoperative adjuvant chemotherapy based on the risk of recurrence and the patient's condition. Data regarding both disease recurrence and survival were obtained from outpatient clinical visits. When a recurrence was diagnosed, the patients were treated in consultation with multidisciplinary teams. All patients agreed to our use of their data for this study, and provided their written informed consent.

Statistical analysis. The Mann-Whitney test was used to compare tumor status and tumor markers in patients pre- and post-chemotherapy. Kaplan-Meier survival curves and the log-rank test were used to analyze the survival rates. A Cox proportional hazards

Table VII. *Univariate analyses of prognostic factors for overall survival after hepatectomy.*

Variables		n=62	Univariate		
			HR	95% CI	*p*-Value
Characteristic					
Age, years	< 65	29	1.95	0.84-4.88	0.118
	≥65	33			
Gender	Male	38	0.62	0.23-1.51	0.273
	Female	24			
Location of primary tumor	Rectum	23	0.95	0.38-2.34	0.903
Colon	39				
LN metastasis from primary tumor	Presence	38	1.17	0.49-2.85	0.715
	Absence	24			
Timing of liver metastasis	Synchronous	41	0.98	0.39-2.45	0.960
	Metachronous	21			
Prechemotherapy					
Tumor size, mm	>50	20	0.92	0.36-2.34	0.858
	≤50	40			
No. of tumors	≥5	21	1.12	0.43-2.91	0.818
	<5	39			
CEA	Elevated	51	0.72	0.20-2.37	0.556
	Normal	9			
CA19-9	Elevated	32	1.12	0.43-2.89	0.819
	Normal	25			
Postchemotherapy					
Tumor size, mm	>50	13	1.99	0.79-6.80	0.127
	≤50	49			
No. of tumors	≥5	21	1.10	0.43-2.82	0.834
	<5	41			
CEA	Elevated	47	2.75	0.89-5.79	0.086
	Normal	15			
CA19-9	Elevated	17	4.42	2.97-30.2	<0.001
	Normal	45			
Response to chemotherapy					
Radiological non-responder	Yes	23	2.81	1.25-9.51	0.017
No	39				
Pathological response	Grade 1a/1b	36	1.38	0.58-3.30	0.463
	Grade 2/3	26			
Oxaliplatin- based AC	None	36	1.95	0.75-4.41	0.185
	Done	26			
Surgical data					
Partial hepatectomy	Yes	24	0.58	0.25-1.45	0.254
	No	38			
Synchronous resection	Yes	10	1.10	0.36-3.44	0.863
	No	52			
Combined with RFA	Yes	13	0.55	0.22-1.67	0.330
	No	49			
Duration of surgery, min	>400	35	0.90	0.37-2.16	0.809
	≤400	27			
Blood loss, ml	>300	32	2.22	0.90-5.16	0.084
	≤300	30			
Complications	Presence	14	1.89	0.74-6.23	0.158
	Absence	48			

LN: Lymph node; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PAC: postoperative adjuvant chemotherapy

model was used to analyze the risk factors and the prognostic factors in univariate and multivariate analysis. The factors with a p-value of less than 0.1 in univariate analysis were used for multivariate analysis. For the statistical analyses, we used JMP 11 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $p<0.05$.

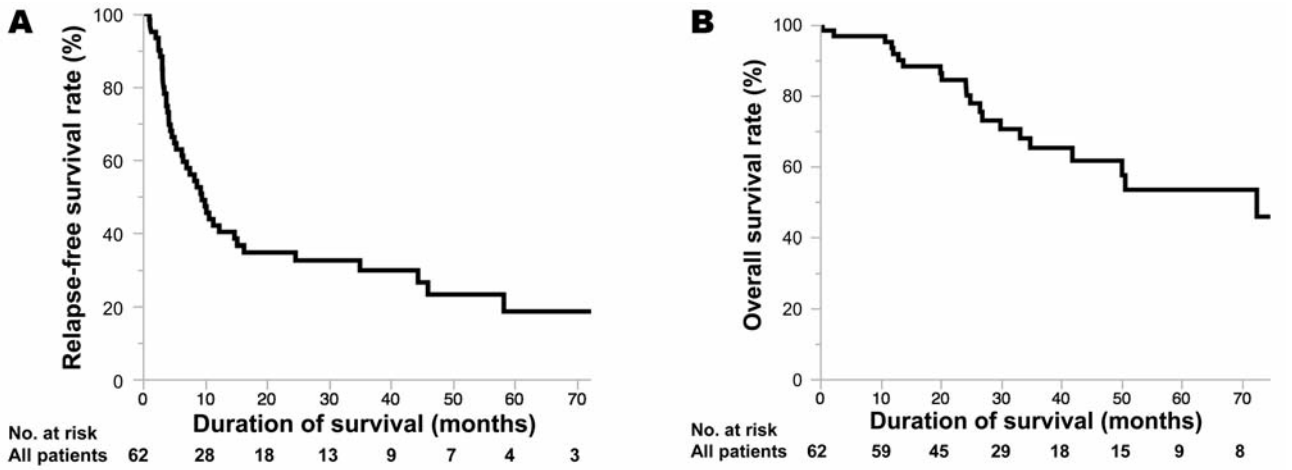

Figure 1. *Relapse-free (a) and overall (b) survival curves for all patients with colorectal liver metastases treated using oxaliplatin-based preoperative chemotherapy followed by hepatic resection.*

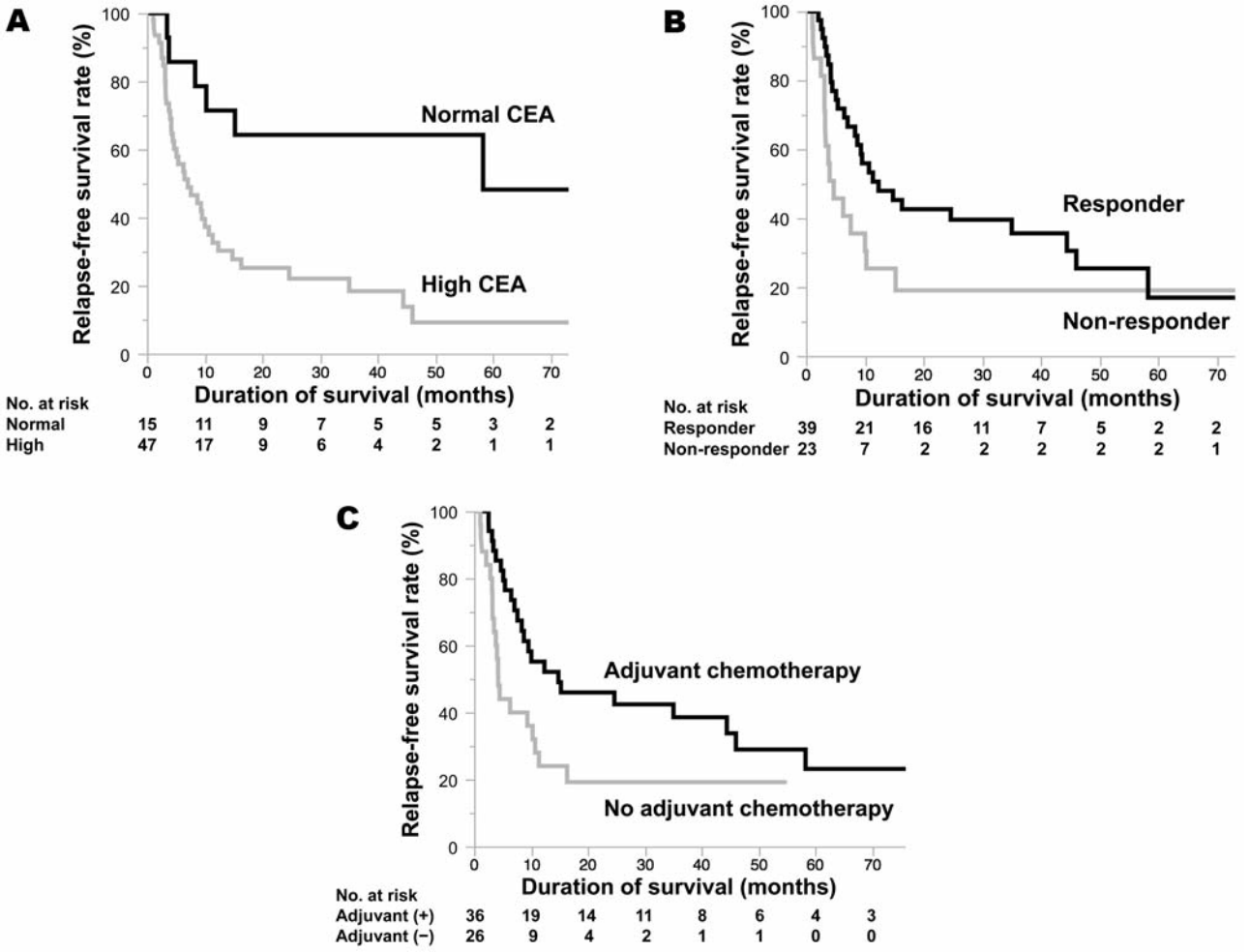

Figure 2. *Relapse-free survival curves for patients with colorectal liver metastases treated with oxaliplatin-based preoperative chemotherapy followed by hepatic resection according to serum carcinoembryonic antigen (CEA) level (a), radiological response (b) and postoperative oxaliplatin-based adjuvant chemotherapy (c).*

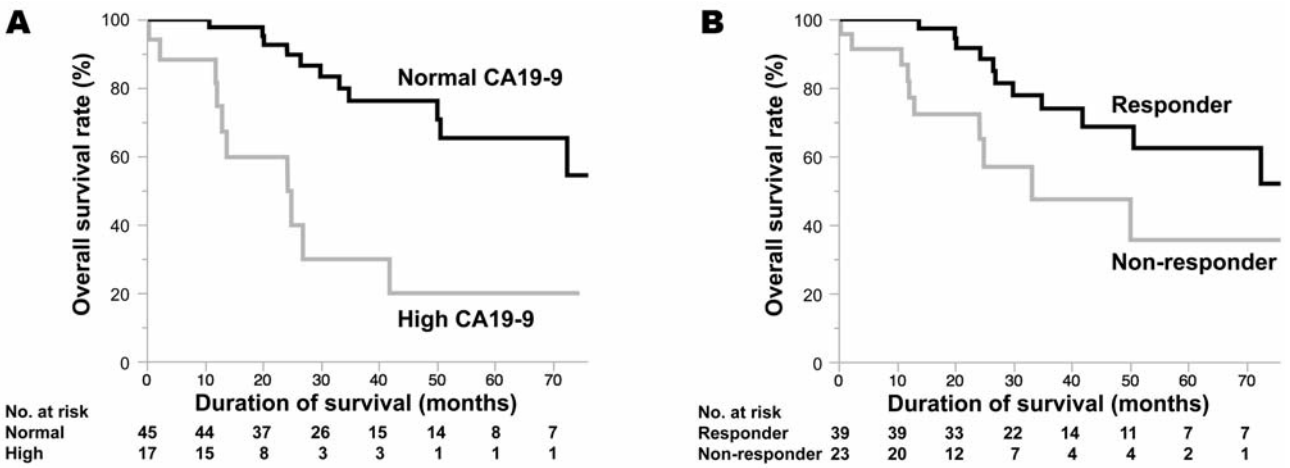

Figure 3. *Overall survival curves according to serum carbohydrate antigen 19-9 (CA19-9) (a) and radiological response (b) for patients with colorectal liver metastases treated preoperatively using oxaliplatin-based chemotherapy then by hepatic resection.*

Results

Clinical characteristics and type of chemotherapy. Sixty-two patients were included in this study. The clinical characteristics of patients pre-chemotherapy are detailed in Table I. Thirty-eight male and 24 female patients, with a median age of 65 (range=35-82) years received preoperative chemotherapy then underwent hepatic resection. The primary tumor location was the colon in 39 patients and the rectum in 23. Thirty-eight patients had lymph node metastasis from the primary tumor, and 41 patients had synchronous liver metastases.

The types of chemotherapy used are detailed in Table II. All patients were treated with preoperative chemotherapy including oxaliplatin. Out of 62 patients, 16 were treated using metachronous chemotherapy with irinotecan in addition to oxaliplatin. Fifty-two patients (83.9%) received FOLFOX, and 27 (43.5%) received FOLFOX in combination with a molecular targeted drug. Antibody against epidermal growth factor receptor was administered to the patients with wild-type Kirsten rat sarcoma viral oncogene homolog (*KRAS*). As a postoperative adjuvant therapy, 46 patients (74.1%) were treated using 5-fluorouracil-based chemotherapy, and oxaliplatin was additionally used in combination in 36 patients (58.1%).

Radiological response to chemotherapy and surgical data. The status of tumors and tumor markers before and after preoperative chemotherapy are detailed in Table III. While the number of tumors did not change significantly after chemotherapy, tumor size and the levels of tumor markers decreased significantly.

The response to preoperative chemotherapy and the surgical data are detailed in Table IV. No patient was able to obtain complete response; however, the response rate was relatively high at 62.9%. Thirty-eight patients (61.7%) underwent anatomic hepatic resection. Ten patients (16.1%) underwent synchronous resection of the primary tumor and CRLM, and 13 patients (21.0%) underwent radiofrequency ablation therapy combined with hepatic resection. Five patients (8.1%) underwent laparoscopy-assisted hepatectomy. The median operating time was 385 min and median blood loss was 300 ml.

Surgery-related complications occurred in 14 patients (22.6%); bile leakage in eight, surgical site infection in three, an intra-abdominal abscess in one, pulmonary embolism in one and pleural effusion in one.

Survival data. Relapse-free survival (RFS) and OS curves for the whole patient group are shown in Figure 1. The median follow-up period was 27 months after hepatic resection. The 1-, 3- and 5-year RFS rates were 40.2%, 29.9% and 18.6%, respectively and the OS rates were 91.7%, 65.2% and 53.4%, respectively. Recurrences developed in 43 patients and 21 died during the follow-up period. The most common site of first recurrence was the liver (30 patients). Other initial recurrence sites were the lung in 12 patients, the lymph nodes in seven patients, peritoneal dissemination in one patient, the adrenal gland in one patient and bone in one patient.

Risk factors for recurrence and prognostic factors for overall survival. The results of univariate analysis for risk factors regarding recurrence are detailed in Table V. Multivariate analysis (Table VI) indicated three independent risk factors for recurrence: a high serum level of CEA after chemotherapy [Hazard Ratio (HR)=3.08, range=1.13-8.39; p=0.028), radiological non-responders (HR=2.18, range=1.10-4.33;

p=0.026) and the absence of adjuvant chemotherapy (HR=2.27, range=1.17-4.41; p=0.016). A high level of serum CA19-9 after chemotherapy was found to be a marginally significant risk factor (HR=2.11, range=0.99-4.47; p=0.050). The RFS curves by risk factor are shown in Figure 2. The median RFS of the patients with normal or high serum levels of CEA after preoperative chemotherapy were 58.2 and 7.1 months, respectively; for responders and non-responders these were 12.3 and 4.7 months, respectively; and for patients receiving adjuvant chemotherapy or not, 14.8 and 6.2 months, respectively.

The results of the univariate analysis of prognostic factors for OS after hepatic resection are detailed in Table VII. Multivariate analysis (Table VI) indicated that a high level of serum CA19-9 after preoperative chemotherapy (HR=4.46, range=1.68-11.8; p=0.003) and no response to preoperative chemotherapy (HR=3.14, range=1.22-8.08; p=0.018) were independent prognostic factors after hepatic resection. The OS curves by prognostic factor are shown in Figure 3. It was not possible to calculate the median survival time of patients with normal serum levels of CA19-9 after preoperative chemotherapy; that for patients with a high serum level of CA19-9 was 24.3 months. Similarly, it was not possible to calculate the median survival time for responders; for non-responders it was 33.2 months.

Discussion

In the present study, a number of independent prognostic factors for patient with CRLM who had undergone hepatic resection following oxaliplatin-based chemotherapy were identified. Although several prognostic factors regarding patients after hepatic resection of CRLM have been proposed, most studies involved patients who did not undergo preoperative chemotherapy (8). The novelty of the current study is that only patients who received preoperative chemotherapy were included. Recent developments regarding anticancer drugs and molecular targeted agents can render unresectable CRLM resectable. The results of this study might therefore be useful for making a decision as to whether or not to perform hepatic resection during chemotherapy for patients with initially unresectable CRLM.

Focusing on tumor markers, there have been many studies to have reported that the serum CEA level is a prognostic factor for patients with CRLM who underwent hepatic resection (8, 16, 21, 26). Sorbye *et al*. reported that perioperative FOLFOX seems to benefit patients with resectable CRLM when the CEA level is elevated (27). In this study, the post-chemotherapeutic CEA level, and not the pre-chemotherapeutic CEA level, was one of the predictors of recurrence, even in patients who had undergone hepatic resection following preoperative chemotherapy. These results could mean that patients whose CEA level had decreased from high to normal limits after chemotherapy could benefit from a strategy involving preoperative chemotherapy followed by hepatic resection.

In the present study, CA19-9 was found to be a marginally significant factor regarding RFS and a significant factor regarding OS. CA19-9 has been reported to be a biomarker for high recurrence rate in cancer types such as gastric, pancreatic and intrahepatic cholangiocarcinoma [(9, 19, 23)]. Similarly, there have been several studies that have reported that CA19-9 is a biomarker for high recurrence rate in colorectal cancer after radical resection (20, 24)]. Furthermore, CA19-9 has been reported as a prognostic marker in unresectable colorectal cancer (15, 18). However, as compared with CEA, there have been few reports concerning CA19-9 in patients who underwent hepatic resection. One of the reasons for this may be that CA19-9 is not routinely measured, especially in Western countries. Most of the studies concerning the prognostic value of CA19-9 in patients who have undergone hepatic resection have been carried out in Japan (4, 10, 12, 14). We have also reported that a preoperative CA19-9 level >100 U/ml was an independent factor associated with poor DFS and OS in patients who underwent hepatectomy without chemotherapy (5). Moreover, there have been few studies involving patients who underwent hepatic resection after chemotherapy, Adam *et al*. reported that an elevated preoperative CA19-9 level was one of the significant factors for a worse prognosis, regarding RFS and OS in patients who had undergone hepatic resection following preoperative chemotherapy (2)]; our results were similar to theirs. Although CA19-9 assay is negative in 5-10% of the general population due to an absence of synthesis of the CA19-9 antigen, differences in its frequency between different ethnicities are not known [28]. These observations indicate the worldwide importance of CA19-9 measurement, in a similar manner to CEA, as part of the treatment strategy for CRLM, especially in patients who undergo hepatic resection after chemotherapy.

Patient non-response was also found to be an independent prognostic factor of both poor RFS and OS in the present study. Adam *et al*. reported that the 5-year OS in patients who exhibited a partial response to preoperative chemotherapy following hepatic resection was 37%. On the other hand, in patients with stable disease and progressive disease, the rates were 30% and 8%, respectively. Similarly, in the present study the 5-year OS ratein non-responders (35.6%) was worse than that in responders (62.4%). Even in non-responders, hepatic resection is recommended as being possible because patients who undergo hepatic resection have a better prognosis than patients who continue chemotherapy without hepatic resection (3). Nevertheless, in the present study, the RFS duration in non-responders was only 4.7 months, and the median survival time of non-responders was

12.3 months (Figure 2b and 3b). The reason for this might be the addition of molecular targeted drugs to modern chemotherapy regimens involving the treatment of recurrent disease. It will be necessary to develop a strategy for improving short-term RFS.

Oxaliplatin-based adjuvant chemotherapy was also shown to be a predictive factor regarding recurrence in the current study. However, the utility of oxaliplatin-based adjuvant chemotherapy for patients who undergo hepatic resection has not been fully established (17, 22). We reported that six cycles of adjuvant FOLFOX is feasible and might deliver a good prognosis for patients with CRLM who had undergone hepatic resection (25). A randomized controlled trial (JCOG0603) involving a comparison of hepatectomy alone with hepatectomy followed by 12 cycles of adjuvant FOLFOX as treatment for patients with curatively resected CRLM is ongoing (13).

In conclusion, even though image-based evaluation using RECIST is important in judging the effects of chemotherapy, we strongly propose the measurement of both CEA and CA19-9 levels in patients with CRLM after hepatic resection following preoperative chemotherapy; this is because the patients who respond to chemotherapy or have a decreased serum level of CEA and CA19-9 will be expected to have a good prognosis after curative hepatectomy. Furthermore, we recommend that radiological non-responders should not undergo hepatic resection and go on to additional lines of chemotherapy because the RFS for these patients was only 4 months. A novel therapeutic strategy and the development of new drugs will be necessary to extend RFS and OS times in patients with poor risk factors.

References

1 Adam R, Aloia T, Levi F, Wicherts DA, de Haas RJ, Paule B, Bralet MP, Bouchahda M, Machover D, Ducreux M, Castagne V, Azoulay D, and Castaing D: Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. J Clin Oncol *25*: 4593-4602, 2007.

2 Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghemard O, Levi F, and Bismuth H: Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg *240*: 644-657; discussion 657-648, 2004.

3 Beppu T, Hayashi N, Masuda T, Komori H, Horino K, Hayashi H, Okabe H, Baba Y, Kinoshita K, Akira C, Watanebe M, Takamori H, and Baba H: FOLFOX enables high resectability and excellent prognosis for initially unresectable colorectal liver metastases. Anticancer Res *30*: 1015-1020, 2010.

4 Beppu T, Miyamoto Y, Sakamoto Y, Imai K, Nitta H, Hayashi H, Chikamoto A, Watanabe M, Ishiko T, and Baba H: Chemotherapy and targeted therapy for patients with initially unresectable colorectal liver metastases, focusing on conversion hepatectomy and long-term survival. Ann Surg Oncol 21 *Suppl 3*: S405-413, 2014.

5 Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, Nitta H, Yoshidome H, Hatano E, Ueno M, Takamura H, Baba H, Kosuge T, Kokudo N, Takahashi K, Endo I, Wakabayashi G, Miyazaki M, Uemoto S, Ohta T, Kikuchi K, Yamaue H, Yamamoto M, and Takada T: A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci *19*: 72-84, 2012.

6 Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, Majno P, and Engerran L: Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg *224*: 509-520; discussion 520-502, 1996.

7 Bogaerts J, Ford R, Sargent D, Schwartz LH, Rubinstein L, Lacombe D, Eisenhauer E, Verweij J, Therasse P, and Party RW: Individual patient data analysis to assess modifications to the RECIST criteria. European journal of cancer *45*: 248-260, 2009.

8 Fong Y, Fortner J, Sun RL, Brennan MF, and Blumgart LH: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg *230*: 309-318; discussion 318-321, 1999.

9 Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, Colvin EK, Nagrial A, Chin VT, Chantrill LA, Samra JS, Gill AJ, Kench JG, Merrett ND, Das A, Musgrove EA, Sutherland RL, and Biankin AV: The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol *23*: 1713-1722, 2012.

10 Inoue Y, Hayashi M, Komeda K, Masubuchi S, Yamamoto M, Yamana H, Kayano H, Shimizu T, Asakuma M, Hirokawa F, Miyamoto Y, Takeshita A, Shibayama Y, and Uchiyama K: Resection margin with anatomic or nonanatomic hepatectomy for liver metastasis from colorectal cancer. J Gastrointest Surg *16*: 1171-1180, 2012.

11 Ishiguro S: [Pathological diagnosis of colorectal cancer according to Japanese classification of colorectal carcinoma]. Nihon rinsho Japanese journal of clinical medicine 69 *Suppl 3*: 325-329, 2011.

12 Ishizuka D, Shirai Y, Sakai Y, and Hatakeyama K: Colorectal carcinoma liver metastases: clinical significance of preoperative measurement of serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels. Int J Colorectal Dis *16*: 32-37, 2001.

13 Kanemitsu Y, Kato T, Shimizu Y, Inaba Y, Shimada Y, Nakamura K, Sato A, and Moriya Y: A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone as treatment for liver metastasis from colorectal cancer: Japan Clinical Oncology Group Study JCOG0603. Jpn J Clin Oncol *39*: 406-409, 2009.

14 Katoh H, Yamashita K, Kokuba Y, Satoh T, Ozawa H, Hatate K, Ihara A, Nakamura T, Onosato W, and Watanabe M: Surgical resection of stage IV colorectal cancer and prognosis. World J Surg *32*: 1130-1137, 2008.

15 Mima K, Beppu T, Chikamoto A, Miyamoto Y, Nakagawa S, Kuroki H, Okabe H, Hayashi H, Sakamoto Y, Watanabe M, Kikuchi K, and Baba H: Hepatic resection combined with radiofrequency ablation for initially unresectable colorectal liver metastases after effective chemotherapy is a safe procedure with a low incidence of local recurrence. Int J Clin Oncol *18*: 847-855, 2013.

16 Minagawa M, Yamamoto J, Kosuge T, Matsuyama Y, Miyagawa S, and Makuuchi M: Simplified staging system for predicting the prognosis of patients with resectable liver metastasis: development and validation. Arch Surg *142*: 269-276; discussion 277, 2007.

17 Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, Nitti D, Torri V, Elias D, O'Callaghan C, Langer B, Martignoni G, Bouche O, Lazorthes F, Van Cutsem E, Bedenne L, Moore MJ, and Rougier P: Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol *26*: 4906-4911, 2008.

18 Mitsuyama Y, Shiba H, Haruki K, Fujiwara Y, Furukawa K, Iida T, Hayashi T, Ogawa M, Ishida Y, Misawa T, Kashiwagi H, and Yanaga K: Carcinoembryonic antigen and carbohydrate antigen 19-9 are prognostic predictors of colorectal cancer with unresectable liver metastasis. Oncol Lett *3*: 767-771, 2012.

19 Nakagoe T, Sawai T, Tsuji T, Jibiki MA, Nanashima A, Yamaguchi H, Yasutake T, Ayabe H, Arisawa K, and Ishikawa H: Difference in prognostic value between sialyl Lewis(a) and sialyl Lewis(x) antigen levels in the preoperative serum of gastric cancer patients. J Clin Gastroenterol *34*: 408-415, 2002.

20 Nakayama T, Watanabe M, Teramoto T, and Kitajima M: CA19-9 as a predictor of recurrence in patients with colorectal cancer. J Surg Oncol *66*: 238-243, 1997.

21 Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, and Jaeck D: Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer *77*: 1254-1262, 1996.

22 Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, and Gruenberger T: Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol *14*: 1208-1215, 2013.

23 Ohtsuka M, Ito H, Kimura F, Shimizu H, Togawa A, Yoshidome H, and Miyazaki M: Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. Br J Surg *89*: 1525-1531, 2002.

24 Park IJ, Choi GS, and Jun SH: Prognostic value of serum tumor antigen CA19-9 after curative resection of colorectal cancer. Anticancer Res *29*: 4303-4308, 2009.

25 Sakamoto Y, Beppu T, Miyamoto Y, Okabe H, Ida S, Imai K, Chikamoto A, Watanabe M, Takamori H, and Baba H: Feasibility and short-term outcome of adjuvant FOLFOX after resection of colorectal liver metastases. J Hepatobiliary Pancreat Sci *20*: 307-312, 2013.

26 Schindl M, Wigmore SJ, Currie EJ, Laengle F, and Garden OJ: Prognostic scoring in colorectal cancer liver metastases: development and validation. Arch Surg *140*: 183-189, 2005.

27 Sorbye H, Mauer M, Gruenberger T, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Van Cutsem E, Scheithauer W, Lutz MP, and Nordlinger B: Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). Ann Surg *255*: 534-539, 2012.

28 Stangl R, Altendorf-Hofmann A, Charnley RM, and Scheele J: Factors influencing the natural history of colorectal liver metastases. Lancet *343*: 1405-1410, 1994.

29 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. Journal of the National Cancer Institute *92*: 205-216, 2000.

30 Zhang S, Gao F, Luo J, and Yang J: Prognostic factors in survival of colorectal cancer patients with synchronous liver metastasis. Colorectal Dis *12*: 754-761, 2010.

Received December 10, 2014
Revised December 30, 2014
Accepted January 8, 2015