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ORIGINAL ARTICLE

Survival Benefit of and Indications for Adjuvant Chemotherapy for Resected Colorectal Liver Metastases—a Japanese Nationwide Survey

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Abstract

Background The survival benefit of and indications for adjuvant chemotherapy (AC) for colorectal liver metastases (CRLM) remain unclear.

Methods Patients who were diagnosed with liver-limited CRLM between 2005 and 2007 and subsequently underwent R0 resection without preoperative chemotherapy were identified in a Japanese nationwide survey. This overall cohort was divided into synchronous and metachronous CRLM cohorts. In each of the three cohorts, the patients that were given AC were matched with those treated with surgery alone via 1:1 propensity score (PS) matching. Recurrence-free survival (RFS) and overall survival (OS) after the initial hepatectomy were compared.

Results The median follow-up period was 79.4 months and the overall, synchronous, and metachronous cohorts included 1145, 498, and 647 patients, respectively. After the PS matching, the patients' demographics were well balanced. AC was effective in terms of both RFS and OS in the overall cohort (RFS hazard ratio [HR] 0.784, $p = 0.045$; OS HR 0.716, $p = 0.028$) and synchronous cohort (RFS HR 0.677, $p = 0.027$; OS HR 0.642, $p = 0.036$), whereas AC was not effective in the metachronous cohort (RFS HR 0.875, $p = 0.378$; OS HR 0.881, $p = 0.496$). However, in the metachronous cohort, AC was effective in terms of

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OS in the subgroup that exhibited disease-free intervals of ≤ 1 year after primary tumor resection (RFS HR 0.667, $p = 0.068$; OS HR 0.572, $p = 0.042$).

Conclusion Adjuvant chemotherapy has a survival benefit for patients with resected CRLM. Synchronous CRLM is a favorable indication for AC, whereas in metachronous CRLM, the use of AC should be individualized according to each patient's risk factors.

Keywords Adjuvant chemotherapy · Colorectal liver metastasis · Real-world data

Introduction

The efficacy of adjuvant chemotherapy (AC) against resected colorectal liver metastases (CRLM) has been investigated in several randomized controlled trials (RCT), and recent RCT have focused on systemic chemotherapy rather than hepatic arterial infusion therapy.[1–10] The systemic administration of fluorouracil and folinic acid (5FU/LV) for 6 months was investigated in 173 patients with resected CRLM in the FFCD ACHBTH AURC 9002 trial. The recurrence-free survival (RFS) of the AC group was significantly better than that of the surgery alone (SA) group ($p = 0.028$). However, the overall survival (OS) of the AC group was not significantly better than that of the SA group ($p = 0.13$).[1] Hasegawa K et al. also investigated the efficacy of AC (6 months of systemic oral uracil-tegafur combined with leucovorin [UFT/LV]) in 177 patients. A survival benefit was detected in terms of RFS ($p = 0.003$), but not OS ($p = 0.409$).[2] Neither of these trials found that AC exhibited significantly greater efficacy than SA against resectable CRLM in terms of OS.

Although the efficacy of and indications for AC for CRLM remain unclear, the administration of AC after CRLM have been resected is already widespread in daily practice, not only in Japan, but also worldwide, as AC has been demonstrated to be effective against stage III colorectal cancer.[11,12] Therefore, both of the abovementioned RCT suffered from low patient accrual rates.[1,2,13,14] On the other hand, real-world data is increasingly being used to assess clinical effectiveness in daily practice because it is considered to represent the clinical setting better than data obtained in clinical trials.[15] Previous studies have suggested that propensity score (PS) matching analysis can be used to perform similar analyses to RCT.[16,17] Since it would be difficult to conduct a new RCT in which an SA group was used as the control arm,[1,2,13,14] we tried to investigate the effectiveness of and indications for AC for resected CRLM via PS-matching analysis of a large nationwide database.

The purpose of this study was to clarify the effectiveness of and indications for AC for resected CRLM using data collected during a Japanese nationwide survey. In order to obtain results that would be readily applicable to daily practice, we analyzed the data after dividing the patients into synchronous CRLM and metachronous CRLM groups.

Methods

Study Design and Data Sources

The Joint Committee for Nationwide Survey on Colorectal Liver Metastasis is composed of colorectal and hepatic surgeons, medical oncologists, and bio-statisticians, all of whom work at specialized centers in Japan. A nationwide database that contained data regarding CRLM was created by the committee and was made available to the participating institutions of the Japanese Society of Hepato-Biliary-Pancreatic Surgery and the Japanese Society for Cancer of the Colon and Rectum. A nationwide survey of CRLM was conducted in 2014, and data regarding patients that were newly diagnosed with CRLM between 2005 and 2007 were retrospectively registered.[18] Modern chemotherapy regimens against colorectal cancer, such as fluorouracil plus leucovorin with oxaliplatin (FOLFOX) and fluorouracil plus leucovorin with irinotecan (FOLFIRI), were approved for clinical use in Japan in 2005. Therefore, we decided to collect the data of patients that were newly diagnosed with CRLM between 2005 and 2007. Patients with resected CRLM that met the following criteria were identified: (1) No history of extrahepatic metastasis, (2) no history of preoperative chemotherapy for CRLM, and (3) underwent R0 resection. There were no limitations with regard to the number of CRLM nodules, and all technically resectable CRLM were included. Patients for whom complete datasets, i.e., data regarding age, sex, the number of CRLM nodules, the largest diameter of the CRLM nodules, the date of diagnosis of CRLM, the date of hepatectomy for CRLM, the timing of the CRLM (synchronous or metachronous), the disease-free interval (DFI) between the resection of the primary tumor and the diagnosis of CRLM, the administration of AC after CRLM resection, survival status, recurrence status, and the date of the last follow-up, were available were included. Cases involving in-hospital mortality were excluded. AC was defined as post-hepatectomy chemotherapy (any regimen, duration, or dose). Then, the overall cohort, i.e., the patients with liver-limited CRLM who underwent R0 resection without preoperative chemotherapy, was divided into synchronous and metachronous CRLM cohorts. Synchronous CRLM was defined as CRLM that was

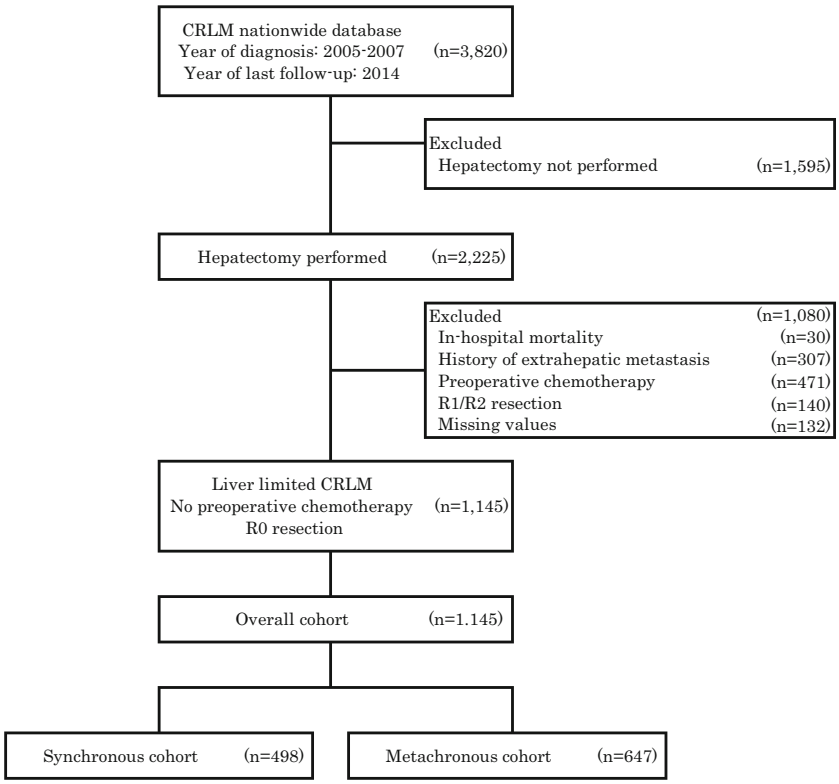


Fig. 1 Flow diagram of the present study

already present at the time of the diagnosis of primary colorectal cancer. PS-matching analysis was performed in each cohort. As for the surveillance schedule, the Japanese Society for Cancer of the Colon and Rectum guidelines recommend performing serial measurements of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9) levels every 3 months and thoracoabdominal computed tomography scans every 6 months after the resection of stage I to III colorectal cancer.[11] The same schedule or an even more intensive schedule is recommended after the resection of stage IV colorectal cancer or recurrent metastases.

All patient data were collected using an anonymous form. This study was approved by the review boards of the participating institutions.

Propensity Score Matching Analysis

In each cohort, Fisher's exact test was used to examine the correlations between AC and factors related to the patients' clinical backgrounds, the original tumor, CRLM, or hepatectomy. Logistic regression analysis was conducted to calculate the PS for receiving AC using factors that exhibited p values of < 0.20 in Fisher's exact test and for which data were missing in $< 25\%$ of all cases. Patients who were treated with AC were matched 1:1 with those that were treated with SA based on their PS, using the optimal matching method.

Statistical Analysis

In each PS-matched cohort, RFS and OS after the initial hepatectomy were compared between the two groups. The patients were also divided into several subgroups based on various preoperative factors, whose prognostic impact had previously been investigated,[19–24] and the effectiveness of AC was examined in each subgroup. In the metachronous cohort, we divided the patients into early and late metachronous groups according to the DFI from the date of the resection of the primary tumor. The effectiveness of AC was analyzed in each group using DFI cut-off values of 3 months, 6 months, 9 months, 1 year, 1.5 years, and 2 years. Then, the most appropriate DFI cut-off value, i.e., that at which the effectiveness of AC was greatest in the early metachronous group, was determined.

A survival analysis was carried out using the log-rank test and Cox proportional hazards regression analysis. p values of < 0.05 were considered to be statistically significant. All statistical analyses were conducted using the software EZR.[25]

Results

Propensity Score Matching Analysis

Out of 3820 patients that were registered during the nationwide survey, hepatectomy was performed in 2225 patients. There were 1145, 498, and 647 patients in the

Table 1 Patient backgrounds in overall cohort

				Primary cohort ($n = 1,145$)					Matching cohort ($n = 422$)				
				Adjuvant chemotherapy		Surgery alone			Adjuvant chemotherapy ($n = 211$)		Surgery alone (n = 211)		
		Missing value		($n = 771$)		($n = 374$)							
		n	(%)	*n*	(%)	*n*	(%)	*p*	*n*	(%)	*n*	(%)	*p*
Patient factors													
Age *	≥ 65	0	0.0	360	46.7	229	61.2	< 0.001	134	63.5	138	65.4	0.760
Sex	Male	0	0.0	496	64.3	235	62.8	0.646	127	60.2	141	66.8	0.189
BMI *	≥ 25.0 kg/m^2	158	13.8	136	20.2	47	15.0	0.053	34	16.1	30	14.2	0.684
HBsAg *	Positive	125	10.9	8	1.2	11	3.3	0.024	3	1.4	7	3.3	0.338
HCVAb *	Positive	124	10.8	11	1.6	19	5.7	< 0.001	6	2.8	14	6.6	0.107
Albumin *	< 3.5 g/dl	142	12.4	9	5.0	11	9.4	0.012	14	6.6	16	7.6	0.850
T.Bil	> 2.0 g/dl	118	10.3	2	0.3	2	0.6	0.593	1	0.5	2	1.0	0.619
Primary colorectal tumor factors													
Location of the primary colorectal tumor	Rectum	57	5.0	178	24.6	90	24.7	1.000	45	21.6	61	29.6	0.072
Depth of the primary colorectal tumor*	T4	62	5.4	229	31.8	95	26.1	0.058	54	25.6	47	22.3	0.494
Vessel invasion by the primary colorectal tumor	Yes	94	8.2	569	79.8	266	78.7	0.683	145	73.6	152	78.4	0.289
Lymphatic invasion by the primary colorectal tumor	Yes	87	7.6	537	74.8	254	74.7	1.000	141	70.5	145	73.6	0.504
Pathology of the primary colorectal tumor	Well diff.	69	6.0	252	34.6	133	38.3	0.248	74	36.1	77	38.5	0.681
Lymph node metastasis of the primary colorectal tumor *	Positive	65	5.7	461	64.1	211	58.4	0.073	138	65.4	130	61.6	0.479
Adjuvant chemotherapy after primary colorectal tumor resection	Yes	23	2.0	247	32.7	95	26.0	0.023	60	28.4	57	27.0	0.828
Liver metastasis factors													
Timing of liver metastasis *	Synchronous	0	0.0	370	48.0	128	34.2	<0.001	77	36.5	67	31.8	0.355
Number of liver metastases *	1	0	0.0	442,260 69	57.3	231	61.8	0.137	134	63.5	129	61.1	0.763
	2–4	0	0.0	96	8.9	56	32.4		63	29.9	70	33.2	
	≥ 5	5	0.4	194	12.5	88	5.9		14	6.6	12	5.7	
Diameter of liver metastasis	≥ 50 mm	207	18.1	325	25.3	176	15.0	0.265	22	10.4	27	12.8	0.544
Distribution of liver metastasis	Bilober	255	22.3	106	51.8	59	23.6	0.559	39	18.5	50	23.7	0.233
CEA level at hepatectomy *	≥ 10 ng/ml	207	18.1	325	51.8	176	56.8	0.164	117	55.5	117	55.5	1.000
CA19-9 level at hepatectomy	≥ 100 U/ml	255	22.3	106	17.8	59	20.1	0.411	31	15.0	35	17.2	0.593
Hepatectomy factors													
Portal embolization *	Yes	0	0.0	74	9.6	23	20.1	0.411	31	15.0	35	17.2	0.593
Type of hepatectomy *	Laparoscopic	44	3.8	14	1.9	15	6.1	0.054	19	9.0	15	7.1	0.592
Extent of hepatectomy	Major §	388	33.9	17	2.9	2	4.2	0.042	7	3.3	9	4.3	0.800
Intraoperative blood loss *	≥ 500 ml	115	10.0	373	54.0	160	1.2	0.272	3	2.1	1	0.7	0.622
Operation time *	≥ 5 h	0	0.0	325	42.2	128	47.2	0.047	99	46.9	98	46.4	1.000
Intraoperative transfusion	Yes	168	14.7	129	19.7	61	34.2	0.010	70	33.2	68	32.2	0.917
Postoperative complications (Clavian-Dindo grade ≥ III)	Yes	41	3.6	84	11.3	51	18.9	0.797	30	14.7	42	20.5	0.153

*Factors that were used to calculate propensity scores

§Major hepatectomy refers to ≥ 3 Couinaud's segments

overall cohort, synchronous cohort, and metachronous cohort, respectively (Fig. 1). The overall cohort comprised 771 (67.3%) patients that were treated with AC and 374 (32.7%) that were treated with SA. The factors that were

used to create the PS are indicated by asterisks in Tables 1, 2, and 3 (see Table 1 for the overall cohort, Table 2 for the synchronous cohort, and Table 3 for the metachronous cohort). The concordance index of the PS for receiving AC was 0.715 (95% confidence interval [95%CI] 0.672–0.763) in the overall cohort, 0.655 (95%CI 0.590–0.721) in the synchronous cohort, and 0.722 (95%CI 0.670–0.774) in the metachronous cohort. After the PS matching, the demographics of the AC and SA groups were well balanced in each cohort. There were 422, 170, and 294 PS-matched patients in the overall, synchronous, and metachronous cohorts, respectively. Thereafter, the subjects of the present investigation were limited to the PS-matched patients.

Table 2 Patient backgrounds in synchronous cohort

				Primary cohort ($n = 498$)					Matching cohort ($n = 170$)				
		Missing value		Adjuvant chemotherapy ($n = 370$)		Surgery alone ($n = 128$)		p	Adjuvant chemotherapy ($n = 85$)		Surgery alone (n = 85)		p
		n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	
Patient factors													
Age	≥ 65	0	0.0	166	44.9	73	57.0	0.019	52	61.2	52	61.2	1.000
Sex	Male	0	0.0	241	62.1	71	55.5	0.057	47	55.3	47	55.3	1.000
BMI	≥ 25.0 kg/m	62	12.4	58	17.6	11	10.4	0.092	5	5.9	7	8.2	0.766
HBsAg	Positive	52	10.4	4	1.2	3	2.7	0.377	0	0.0	2	2.4	0.246
HCVAb	Positive	56	11.2	6	1.8	6	5.3	0.086	4	4.7	5	5.9	1.000
Albumin	< 3.5 g/dl	69	13.9	28	8.8	16	14.5	0.101	10	11.8	11	12.9	1.000
T.Bil	> 2.0 g/dl	54	10.8	1	0.3	0	0.0	1.000	0	0.0	0	0.0	NA
Primary colorectal tumor factors													
Location of the primary colorectal tumor	Rectum	18	3.6	86	24.4	31	24.4	1.000	21	25.6	26	31.0	0.493
Depth of the primary colorectal tumor	T4	14	2.8	131	36.7	39	30.7	0.236	34	41.5	26	30.6	0.151
Vessel invasion by the primary colorectal tumor	Yes	27	5.4	300	85.5	107	89.2	0.356	74	89.2	73	89.0	1.000
Lymphatic invasion by the primary colorectal tumor	Yes	27	5.4	257	73.2	92	76.7	0.546	60	72.3	60	72.3	1.000
Pathology of the primary colorectal tumor *	Well diff.	14	2.8	115	32.0	51	40.8	0.081	32	37.6	34	40.0	0.875
Lymph node metastasis of the primary colorectal tumor	Positive	23	4.6	247	70.2	89	72.4	0.730	56	67.5	63	76.8	0.225
Liver metastasis factors													
Number of liver metastases	1	0	0.0	184	49.7	72	56.2	0.407	47	55.3	47	55.3	1.000
	2–4			133	35.9	42	32.8		29	34.1	30	35.3	
	≥ 5			53	14.3	14	10.9		9	10.6	8	9.49.4	
Diameter of liver metastasis	≥ 50 mm	0	0.0	64	17.3	25	19.5	0.593	12	14.1	14	16.5	0.832
Distribution of liver metastasis	Bilober	3	0.6	123	33.5	35	27.3	0.226	20	23.8	25	29.4	0.487
CEA level at hepatectomy	≥ 10 ng/ml	121	24.3	160	56.7	56	58.9	0.721	46	61.3	40	58.0	0.735
CA19-9 level at hepatectomy	≥ 100 U/ml	138	27.7	66	24.5	25	27.5	0.579	17	22.7	15	22.1	1.000
Hepatectomy factors													
Portal embolization	Yes	0	0.0	45	12.2	12	9.4	0.426	11	12.9	8	9.4	0.627
Type of hepatectomy *	Laparoscopic	13	2.6	3	0.8	5	4.1	0.028	1	1.2	4	4.7	0.368
Extent of hepatectomy	Major §	181	36.3	5	2.1	2	2.6	0.683	0	0.0	1	1.7	1.000
Intraoperative blood loss *	≥ 500 ml	52	10.4	200	60.8	59	50.4	0.063	43	50.6	43	50.6	1.000
Operation time	≥ 5 h.	0	0.0	199	53.8	61	47.7	0.259	45	52.9	44	51.8	1.000
Intraoperative transfusion	Yes	74	14.9	83	26.7	30	26.5	1.000	23	28.0	24	28.9	1.000
Postoperative complications (Clavian-Dindo grade ≥ III)	Yes	20	4.0	52	14.8	19	15.1	1.000	16	19.0	12	14.1	0.415

*Factors that were used to calculate propensity scores

§Major hepatectomy refers to ≥ 3 Couinaud's segments

Table 3 Patient backgrounds in metachronous cohort

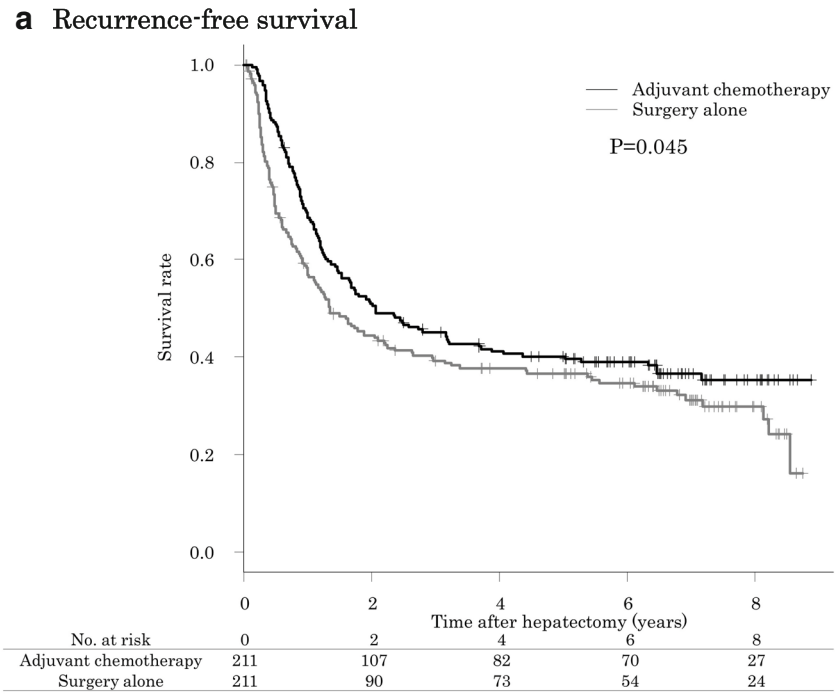
				Primary cohort ($n = 647$)					Matching cohort ($n = 294$)				
		Missing value		Adjuvant chemotherapy ($n = 401$)		Surgery alone ($n = 246$)		p	Adjuvant chemotherapy ($n = 147$)		Surgery alone ($n = 147$)		p
		n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	
Patient factors													
Age	≥ 65	0	0.0	194	48.4	156	63.4	< 0.001	97	66.0	98	67.7	1.000
Sex	Male	0	0.0	225	63.3	164	66.7	0.446	93	63.3	105	71.4	0.071
BMI	≥ 25.0 kg/m^2	96	14.8	78	22.7	36	17.4	0.158	24	16.3	21	14.3	0.746
HBsAg	Positive	73	11.3	4	1.1	8	3.7	0.066	3	2.0	5	3.4	0.723
HCVAb	Positive	68	10.5	5	1.4	13	5.9	0.005	3	2.0	9	6.1	0.138
Albumin	< 3.5 g/dl	73	11.3	6	1.6	14	6.7	0.003	2	1.4	6	4.1	0.282
T.Bil	> 2.0 g/dl	64	9.9	1	0.3	2	1.0	0.291	1	0.7	2	1.4	0.616
Primary colorectal tumor factors													
Location of the primary colorectal tumor	Rectum	39	6.0	92	24.9	59	24.8	1.000	28	19.6	42	29.4	0.073
Depth of the primary colorectal tumor	T4	48	7.4	98	27.1	56	23.6	0.390	38	26.4	28	19.2	0.162
Vessel invasion by the primary colorectal tumor	Yes	67	10.4	269	74.3	159	72.9	0.770	102	73.9	97	72.9	0.891
Lymphatic invasion by the primary colorectal tumor	Yes	60	9.3	280	76.3	162	73.6	0.490	96	68.1	96	71.1	0.603
Pathology of the primary colorectal tumor	Well diff.	55	8.5	137	37.0	82	36.9	1.000	49	34.8	50	36.2	0.804
Lymph node metastasis of the primary colorectal tumor	Positive	42	6.5	214	58.3	122	51.3	0.094	82	55.8	78	53.8	0.725
Adjuvant chemotherapy after primary colorectal tumor resection	Yes	23	3.6	247	64.0	95	39.9	<0.001	70	47.6	58	39.5	0.196
Liver metastasis factors													
Number of liver metastases	1	0	0.0	258	64.3	159	64.6	0.923	103	701	96	65.3	0.721
	2–4			127	31.7	79	32.1		40	27.2	46	31.3	
	≥ 5			16	4.0	8	3.3		4	2.7	5	3.4	
Diameter of liver metastasis *	≥ 50 mm	0	0.0	32	8.0	31	12.6	0.057	12	8.2	17	11.6	0.434
Distribution of liver metastasis	Bilober	2	0.3	71	17.8	53	21.6	0.057	25	17.0	28	19.0	0.762
CEA level at hepatectomy *	≥ 10 ng/ml	86	13.3	165	47.7	120	55.8	0.068	76	51.7	81	55.1	0.640
CA19-9 level at hepatectomy *	≥ 100 U/ml	117	18.1	40	12.2	34	16.7	0.157	20	13.6	26	17.7	0.422
Hepatectomy factors													
Portal embolization *	Yes	0	0.0	29	7.2	11	4.5	0.180	8	5.4	7	4.8	1.000
Type of hepatectomy	Laparoscopic	31	4.8	11	2.9	10	4.3	0.370	4	2.9	6	4.3	0.749
Extent of hepatectomy	Major §	207	32.0	9	3.1	3	2.0	0.556	6	5.5	1	1.1	0.129
Intraoperative blood loss	≥ 500 ml	63	9.7	173	47.8	101	45.5	0.609	62	45.3	62	43.7	0.810
Operation time	≥ 5 h	0	0.0	126	31.4	67	27.2	0.228	44	29.9	35	23.8	0.293
Intraoperative transfusion	Yes	94	14.5	46	13.4	31	14.8	0.705	16	12.2	23	16.5	0.87
Postoperative complications (Clavian-Dindo grade ≧III) *	Yes	21	3.2	32	8.2	32	13.5	0.041	14	9.5	21	14.3	0.280

*Factors that were used to calculate propensity scores

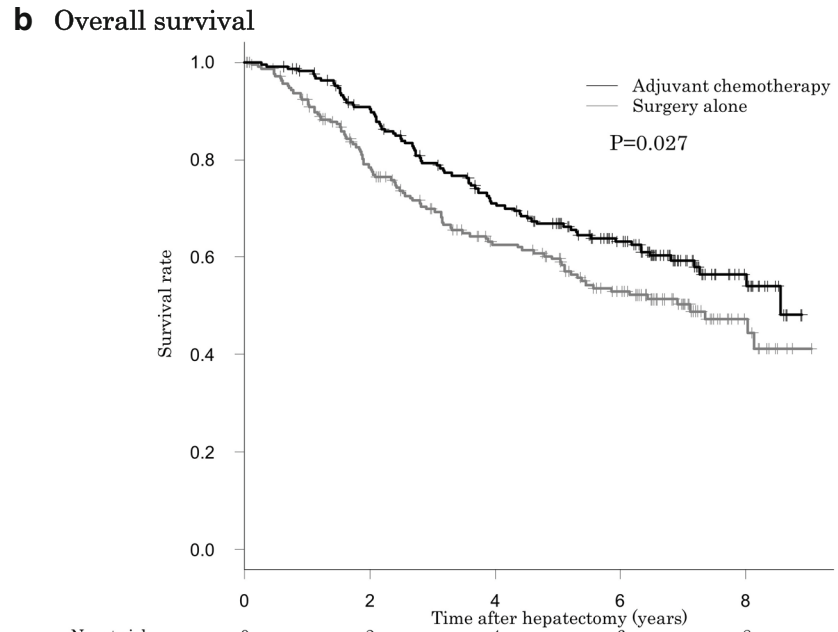
§ Major hepatectomy refers to ≥ 3 Couinaud's segments

Adjuvant Chemotherapy Regimens

The following AC regimens were used to treat the patients in the PS-matched overall cohort: FOLFOX, 54 cases; FOLFIRI, 3 cases; capecitabine with oxaliplatin (CapeOx), 1 case; 5FU/LV, 21 cases; UFT/LV, 86 cases; S-1, 26 cases; hepatic arterial infusion, 14 cases; doxifluridine, 2 cases; unknown, 4 cases. The duration of the AC was ≥ 3 months in 189 patients (89.6%), while it was < 3 months in 22 patients (10.4%).



No. at risk	0	2	4	6	8
Adjuvant chemotherapy	211	107	82	70	27
Surgery alone	211	90	73	54	24

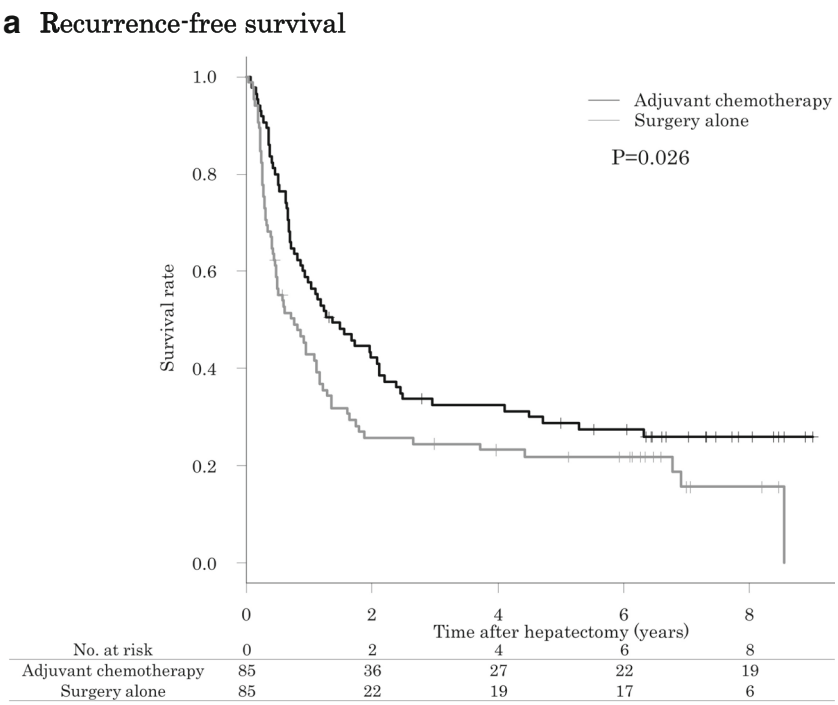


No. at risk	0	2	4	6	8
Adjuvant chemotherapy	211	183	137	97	37
Surgery alone	211	152	107	75	31

Fig. 2 Survival curves of the propensity score-matched overall cohort. **a** The adjuvant chemotherapy (AC) group exhibited significantly better recurrence-free survival (RFS) than the surgery alone (SA) group ($p = 0.045$). **b** The AC group also displayed significantly better overall survival (OS) than the SA group ($p = 0.027$). The 5-year OS rate of the AC group was 66.8%, and that of the SA group was 59.6%

Survival Analysis

The median duration of the follow-up period was 79.4 months in the overall cohort. Among the 422 PS-matched patients in the overall cohort, recurrence was identified in 255 cases (60.4%). The AC group exhibited significantly better RFS than the SA group ($p = 0.045$) (Fig. 2). The associated hazard ratio (HR) was 0.784 (95%CI 0.618–0.995). The median duration of the RFS period was 25.2 months [95%CI 18.6–38.9] in the AC group and 16.4 months [12.2–26.9] in the SA group. The 3- and 5-year RFS rates of the AC group were 45.1% [95%CI 38.3–51.7%] and 40.1% [33.4–46.7%], respectively, and those of the SA group were 39.3% [95%CI 32.6–46.0%] and 36.6% [30.0–43.3%], respectively. The sites of recurrence (intrahepatic alone vs. extrahepatic alone vs. both intra- and extrahepatic) did not differ between the two



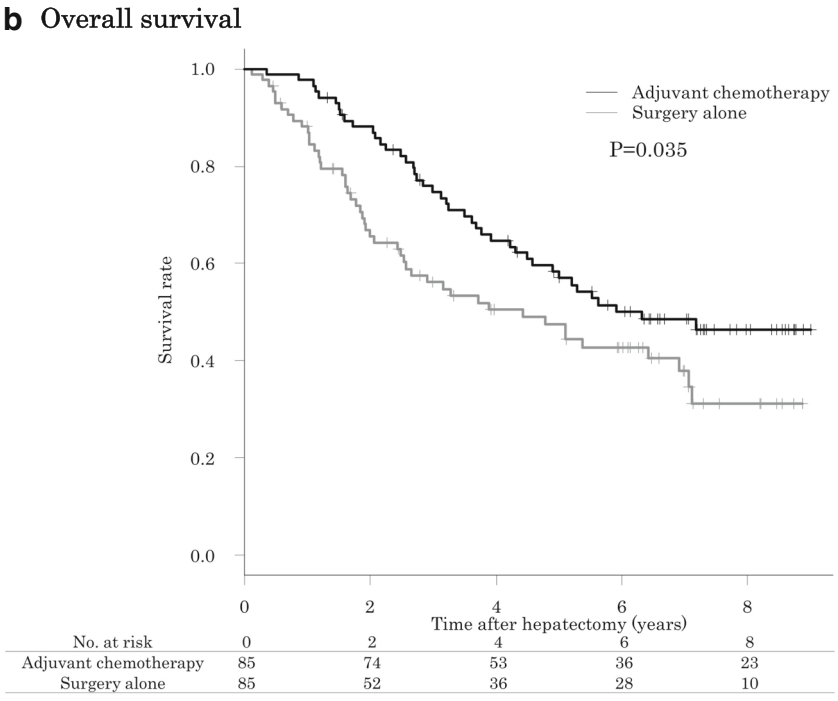
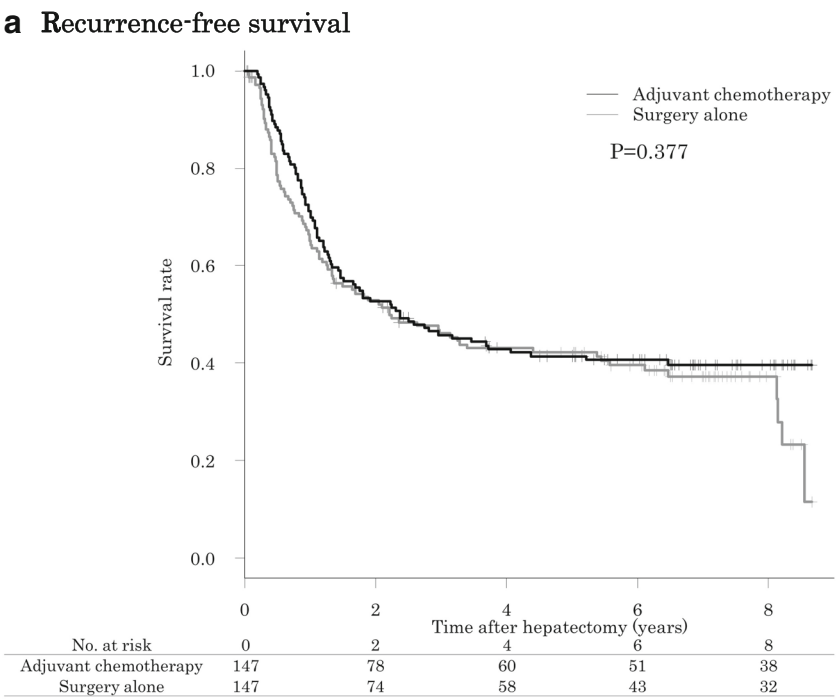


Fig. 3 Survival curves of the propensity score-matched synchronous cohort. **a** The AC group demonstrated significantly better RFS than the SA group ($p = 0.026$). **b** The AC group exhibited significantly better OS than the SA group ($p = 0.035$)

groups (AC group 51.2 vs. 35.0 vs. 13.0%, SA group 41.8 vs. 37.2 vs. 17.1%, $p = 0.393$). The frequency of re-resection for recurrence did not differ significantly between the AC and SA groups (43.9 vs. 32.6%, $p = 0.070$).

The AC group also displayed significantly better OS than the SA group ($p = 0.027$) (Fig. 2). The associated HR was 0.716 (95%CI 0.532–0.964). The median duration of the OS period was 104.1 months [95%CI 88.4–not available] in the AC group and 86.7 months [62.2–not available] in the SA group. The 5-year OS rate of the AC group was 66.8% [95%CI 59.7–72.9%], and that of the SA group was 59.6% [52.1–66.2%]. Among the patients that underwent re-resection for recurrence, OS after the initial hepatectomy was better in the AC group than in the SA group, but the difference was not statistically significant (median duration 102.6 vs. 66.8 months, $p = 0.091$).



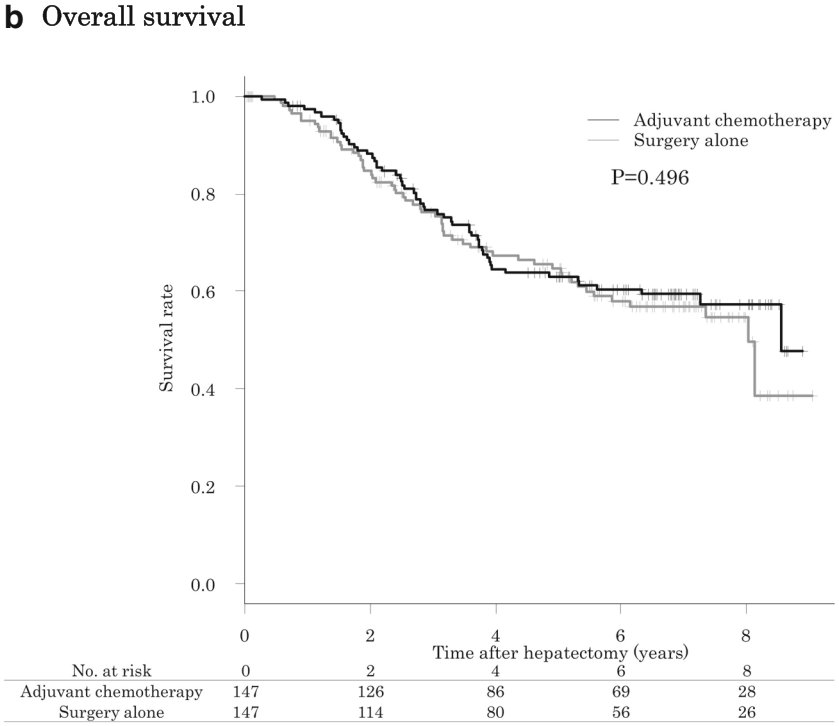


Fig. 4 Survival curves of the propensity score-matched metachronous cohort. **a** The AC group did not display significantly better RFS than the SA group ($p = 0.377$). **b** The AC group did not demonstrate significantly better OS than the SA group ($p = 0.496$)

In the PS-matched synchronous cohort, the AC group also demonstrated significantly better RFS (HR 0.677, 95%CI 0.479–0.956, $p = 0.027$) and OS (HR 0.642, 95%CI 0.424–0.972, $p = 0.036$) than the SA group (Fig. 3). However, in the metachronous cohort, the AC group did not exhibit significantly better survival than the SA group in terms of either RFS (HR 0.875, 95%CI 0.651–1.176, $p = 0.378$) or OS (HR 0.881, 95%CI 0.611–1.270, $p = 0.496$) (Fig. 4).

Subgroup Analyses

In the PS-matched overall cohort, the AC group displayed significantly better RFS and OS than the SA group in the subgroups involving lymph node metastasis from the primary colorectal tumor, synchronous CRLM, a serum CEA level of ≥ 10 ng/ml, a serum CA19-9 level of ≥ 37 IU/ml, a clinical risk score (CRS)[19] of ≥ 3, or a CRLM size of < 50 mm

Table 4 Subgroups analysis of overall cohort

a) Recurrence-free survival					
		n	HR	(95% CI)	*p*
Overall cohort		422	0.784	(0.618–0.995)	0.045
Lymph node metastasis from primary tumor	Yes	268	0.704	(0.529–0.937)	0.016
	No	152	0.917	(0.595–1.414)	0.695
Timing of liver metastasis	Synchronous	144	0.512	(0.349–0.753)	< 0.001
	Metachronous	276	0.927	(0.684–1.258)	0.627
Number of liver metastasis	1	263	0.817	(0.595–1.121)	0.211
	2–4	133	0.790	(0.527–1.182)	0.251
	5 ≤	26	0.262	(0.106–0.644)	0.004
Diameter of liver metastasis	< 50 mm	373	0.750	(0.581–0.967)	0.026
	≥ 50 mm	49	1.057	(0.532–2.097)	0.875
CEA at hepatectomy	< 10 ng/ml	186	0.922	(0.636–1.337)	0.669
	≥ 10 ng/ml	234	0.693	(0.507–0.948)	0.022
CA19-9 at hepatectomy	< 37 IU/ml	268	0.859	(0.634–1.165)	0.329
	≥ 37 IU/ml	142	0.637	(0.430–0.945)	0.025
Clinical risk score*[19]	0–1	156	1.054	(0.675–1.646)	0.817
	2	165	0.682	(0.468–0.992)	0.045
	3 ≤	101	0.599	(0.387–0.928)	0.022
b) Overall survival					
		n	HR	(95% CI)	*p*
Overall cohort		422	0.716	(0.532–0.964)	0.028
Lymph node metastasis from primary tumor	Yes	268	0.668	(0.471–0.947)	0.024
	No	152	0.769	(0.434–1.361)	0.367
Timing of liver metastasis	Synchronous	144	0.512	(0.322–0.812)	0.004
	Metachronous	276	0.832	(0.564–1.229)	0.356
Number of liver metastasis	1	263	0.709	(0.471–1.066)	0.098
	2–4	133	0.766	(0.474–1.240)	0.279
	5 ≤	26	0.375	(0.128–1.097)	0.073
Diameter of liver metastasis	< 50 mm	373	0.717	(0.519–0.992)	0.045
	≥ 50 mm	49	0.688	(0.325–1.457)	0.329
CEA at hepatectomy	< 10 ng/ml	186	0.889	(0.561–1.408	0.616
	≥ 10 ng/ml	234	0.613	(0.414–0.907)	0.014
CA19-9 at hepatectomy	< 37 IU/ml	268	0.808	(0.545–1.198)	0.288
	≥ 37 IU/ml	142	0.547	(0.343–0.874)	0.012
Clinical risk score*[19]	0–1	156	0.933	(0.520–1.675)	0.817
	2	165	0.730	(0.458–1.163)	0.186
	3 ≤	101	0.479	(0.284–0.806)	0.006

*Clinical risk score is calculated as one point for each criterion met: positive lymph node metastasis from primary tumor, > 1 liver metastasis, largest diameter of liver metastasis > 50 mm, preoperative CEA > 200 ng/ml, and disease-free interval between primary tumor resection and diagnosis of liver metastasis < 12 months

(Table 4). The AC group also demonstrated significantly better RFS than the SA group in the subgroup with ≥ 5 CRLM and a CRS of 2 (Supplemental Figs. 1, 2, and 3). Regarding the AC regimens, the patients given oral AC regimens achieved significantly better RFS than those that underwent SA (HR 0.701, 95%CI 0.523–0.939, $p = 0.017$). As for OS, the patients treated with oral AC regimens also had better prognoses than those treated with SA, but the difference was not significant (HR 0.701, 95%CI 0.490–1.004, $p = 0.053$). The prognosis of the patients given FOLFOX/CapeOx and that of the patients treated with SA was comparable (RFS HR 1.005, 95%CI 0.704–1.436, $p = 0.976$; OS HR 0.806, 95%CI 0.502–1.295, $p = 0.373$).

In the PS-matched synchronous cohort, AC had beneficial effects on one or both of RFS and OS in the following subgroups: the patients with lymph node metastasis, ≥ 5 CRLM, or a CRLM size of < 50 mm. Also, AC was marginally effective ($p < 0.100$) in terms of RFS and/or OS in the subgroups

Table 5 Subgroup analysis of synchronous cohort

a) Recurrence-free survival					
		n	HR	(95% CI)	*p*
Synchronous cohort		170	0.677	(0.479–0.956)	0.027
Lymph node metastasis from primary tumor	Yes	119	0.644	(0.431–0.961)	0.031
	No	46	0.846	(0.407–1.758)	0.653
Number of liver metastasis	1	94	0.857	(0.532–1.379)	0.524
	2–4	59	0.617	(0.352–1.081)	0.019
	5≤	17	0.266	(0.078–0.900)	0.033
Diameter of liver metastasis	< 50 mm	144	0.591	(0.406–0.860)	0.006
	≥ 50 mm	26	1.371	(0.539–3.488)	0.508
CEA at hepatectomy	< 10 ng/ml	58	0.704	(0.375–1.321)	0.274
	≥ 10 ng/ml	86	0.660	(0.409–1.064)	0.088
CA19-9 at hepatectomy	< 37 IU/ml	79	0.745	(0.436–1.273)	0.281
	≥ 37 IU/ml	64	0.608	(0.354–1.047)	0.073
b) Overall survival					
		n	HR	(95% CI)	*p*
Synchronous cohort		170	0.642	(0.424–0.972)	0.036
Lymph node metastasis from primary tumor	Yes	119	0.669	(0.416–1.077)	0.098
	No	46	0.669	(0.277–1.618)	0.373
Number of liver metastasis	1	94	0.787	(0.436–1.424)	0.429
	2–4	59	0.564	(0.293–1.083)	0.085
	5≤	17	0.305	(0.077–1.202)	0.090
Diameter of liver metastasis	< 50 mm	144	0.565	(0.357–0.895)	0.015
	≥ 50 mm	26	1.316	(0.485–3.575)	0.590
CEA at hepatectomy	< 10 ng/ml	58	0.535	(0.259–1.105)	0.091
	≥ 10 ng/ml	86	0.664	(0.374–1.179)	0.162
CA19-9 at hepatectomy	< 37 IU/ml	78	0.738	(0.378–1.438)	0.372
	≥ 37 IU/ml	64	0.539	(0.290–1.002)	0.051

involving 2–4 metastases, a serum CEA level of ≥ 10 ng/ml, or a serum CA19-9 level of ≥ 37 IU/ml, all of which displayed HR of < 0.700 (Table 5).

In the PS-matched metachronous cohort, the most appropriate DFI was found to be 1 year. In the early metachronous group (DFI of ≤ 1 year), OS was significantly better in the AC group than in the SA group (OS HR 0.572, 95%CI 0.335–0.979, $p = 0.042$) (Table 6, Fig. 5). RFS was also better in the AC group, but the difference was not statistically significant (RFS HR 0.667, 95%CI 0.432–1.031, $p = 0.068$). AC was even more effective than SA in terms of both RFS and OS among the patients with early metachronous CRLM and serum CEA levels of ≥ 10 ng/ml (RFS HR 0.532, 95%CI 0.305–0.929, $p = 0.026$; OS HR 0.393, 95%CI 0.191–0.807, $p = 0.011$).

Discussion

Although several RCT have demonstrated that administering AC for resected CRLM was effective at increasing RFS, no survival benefit of AC in terms of OS has been demonstrated.[1–10] On the contrary, in the present study, AC was clearly demonstrated to improve both RFS and OS. Regarding the patients' backgrounds, the present study included more cases of highly malignant CRLM than previous RCT, i.e., more cases involving ≥ 5 CRLM, lymph node metastasis from the primary colorectal tumor, synchronous CRLM, early metachronous CRLM with a DFI of ≤ 1 year, or an elevated CEA level at hepatectomy (Table 7). It was presumed that the current study included more cases with higher CRS. As the effectiveness of AC gradually rose as the CRS increased, the abovementioned differences were considered to be one of the reasons why AC was demonstrated to be effective at promoting OS in this study. Recently, the indications for hepatectomy for CRLM have expanded to include highly malignant disease due to advances in chemotherapy and surgery.[12,26–28] The patients' backgrounds of the present study reflected those of the patients that currently undergo surgery for CRLM, and the present study indicated that AC was effective in this clinical settings. Also, the sample size was 422 in the PS-matched overall cohort, and the median duration of the follow-up period was 79.4 months, which were sufficient for investigating the effects of AC on OS. These

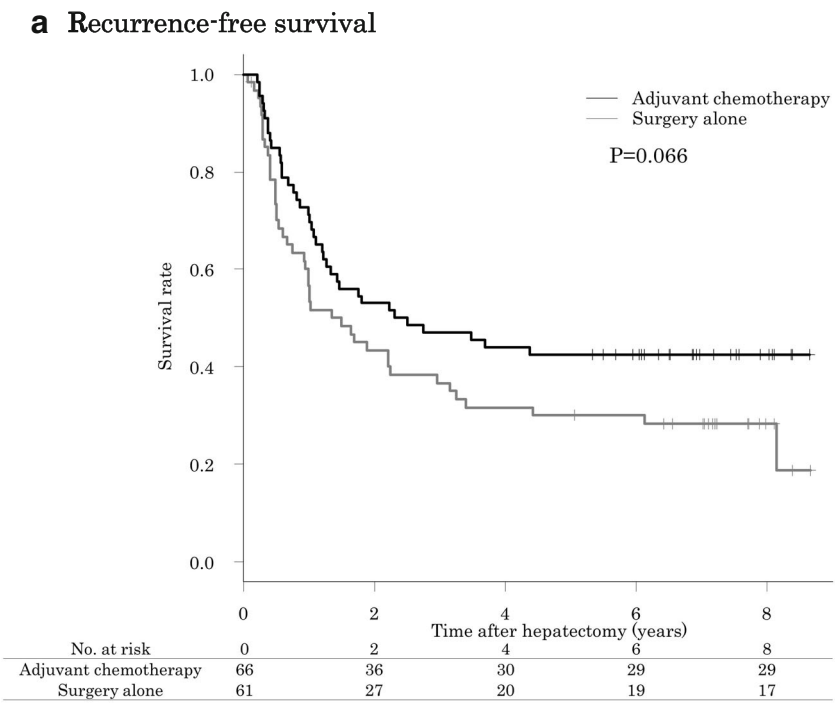
Table 6 Subgroup analysis of metachronous cohort

a) Recurrence-free survival					
		n	HR	(95% CI)	*p*
Metachronous cohort		294	0.875	(0.651–1.176)	0.378
Lymph node metastasis from	Yes	160	0.935	(0.637–1.372)	0.731
primary tumor	No	134	0.823	(0.516–1.311)	0.412
Disease-free interval after	≤ 1 year	127	0.667	(0.432–1.031)	0.068
original tumor resection	> 1 year	167	1.088	(0.725–1.631).	0.685
Adjuvant chemotherapy after	Yes	128	1.009	(0.642–1.584)	0.970
original tumor resection	No	166	0.740	(0.495–1.106)	0.142
Number of liver metastasis	1	199	0.851	(0.580–1.247)	0.407
	2–4	86	1.033	(0.627–1.702)	0.899
	5 ≤	9	0.129	(0.014–1.136)	0.065
Diameter of liver metastasis	< 50 mm	265	0.871	(0.638–1.189)	0.384
	≥ 50 mm	29	0.933	(0.352–2.473)	0.889
CEA at hepatectomy	< 10 ng/ml	137	1.044	(0.664–1.640)	0.853
	≥ 10 ng/ml	157	0.776	(0.523–1.150)	0.206
CA19-9 at hepatectomy	< 37 IU/ml	198	0.955	(0.666–1.371)	0.805
	≥ 37 IU/ml	96	0.730	(0.436–1.223)	0.232
b) Overall survival					
		n	HR	(95% CI)	*p*
Metachronous cohort		294	0.881	(0.611–1.270)	0.496
Lymph node metastasis from	Yes	160	0.926	(0.589–1.456)	0.738
primary tumor	No	134	0.807	(0.432–1.506)	0.500
Disease-free interval after	≤ 1 year	127	0.572	(0.335–0.979)	0.042
original tumor resection	> 1 year	167	1.326	(0.795–2.212)	0.279
Adjuvant chemotherapy after	Yes	128	0.972	(0.567–1.668)	0.919
original tumor resection	No	166	0.755	(0.453–1.258)	0.281
Number of liver metastasis	1	199	0.851	(0.527–1.375)	0.510
	2–4	86	0.924	(0500–1.709)	0.802
	5 ≤	9	1.474	(0.318–6.831)	0.620
Diameter of liver metastasis	< 50 mm	265	0.877	(0.592–1.298)	0.512
	≥ 50 mm	29	1.032	(0.371–2.866	0.952
CEA at hepatectomy	< 10 ng/ml	137	1.143	(0.646–2.024)	0.646
	≥ 10 ng/ml	157	0.738	(0.456–1.196)	0.217
CA19-9 at hepatectomy	< 37 IU/ml	198	1.025	(0.649–1.617)	0.917
	≥ 37 IU/ml	96	0.638	(0.344–1.180)	0.152

characteristics of the present study help to explain the significant difference in OS detected between the AC and SA groups.

Several studies have investigated the factors associated with prognosis after hepatectomy for CRLM, such as lymph node metastasis, a DFI of ≤ 1 year after the resection of the primary colorectal tumor, multiple CRLM, a CRLM size of > 50 mm, synchronous extrahepatic metastases, a serum CEA level of > 200 ng/ml, and a serum CA19-9 level of > 100 U/ml.[19–24] In the PS-matched overall cohort, AC had beneficial effects on one or both of RFS and OS in various subgroups, such as those involving lymph node metastasis, synchronous CRLM, ≥ 5 CRLM, a serum CEA level of ≥ 10 ng/ml, a serum CA19-9 level of ≥ 37 IU/ml, or a CRS of ≥ 2. These highly malignant cases of CRLM clearly benefited from AC and met the indications for AC. Regarding the size of CRLM, AC did not demonstrate a beneficial effect in the subgroup of patients with larger tumors (≥ 50 mm) in this study. In our previous study,[20] a tumor size of > 50 mm was found to have a minimal impact on RFS and did not have a significant impact on OS. Therefore, large CRLM do not appear to be highly malignant. This fact, as well as the small number of patients with large tumors, might explain why AC was not shown to be effective in the ≥ 50 mm CRLM subgroup.

We also investigated the survival benefit of and indications for AC in synchronous and metachronous CRLM



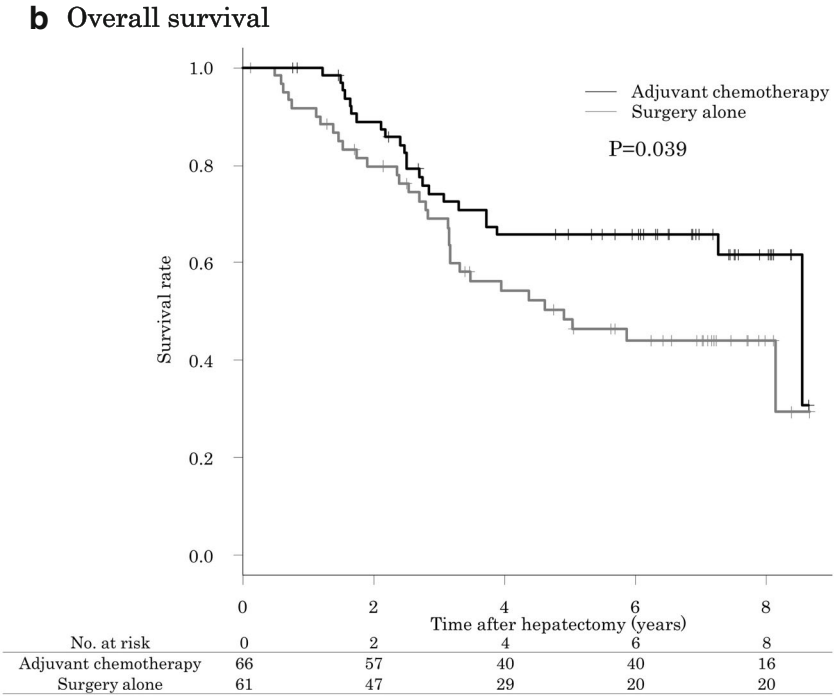


Fig. 5 Survival curves of patients with DFI ≤ 1 year in the propensity score-matched metachronous cohort. **a** The AC group demonstrated marginally better RFS than the SA group ($p = 0.066$). **b** The AC group exhibited significantly better OS than the SA group ($p = 0.039$)

cohorts. In the PS-matched synchronous CRLM cohort, AC was effective in terms of both RFS and OS. AC had beneficial effects on RFS and/or OS in various subgroups, such as those involving lymph node metastasis, ≥ 5 CRLM, or a CRLM size of < 50 mm. Also, AC was effective in terms of RFS and/or OS in the subgroups involving 2–4 metastases, a serum CEA level of ≥ 10 ng/ml, or a serum CA19-9 level of ≥ 37 IU/ml, although these differences were not significant ($p < 0.100$). As AC has demonstrated clear survival benefits when used against stage III colorectal cancer, synchronous CRLM should be considered to be a favorable indication for AC, especially in cases involving lymph node metastasis, ≥ 2 CRLM, a serum CEA level of ≥ 10 ng/ml, or a serum CA19-9 level of ≥ 37 IU/ml.

On the other hand, in the PS-matched metachronous CRLM cohort, AC was not markedly effective in terms

Table 7 Comparison of the current study with the previous clinical trials

	Sample size	Patient acrual period (years)	Number of CRLM lesions	Follow-up (months)	Chemotherapy regimen	Synchronous CRLM	DFI ≤ 1 year [§]	LNM	Elevated CEA[*]	RFS [†]	OS [†]
Present study (2019)	422	3.0	1–4: 93.8% ≥ 5: 6.2%	79.	4 Adjuvant any regimen	34.1%	64.2%	63.5%	69.9%	3 years 45.1 vs 39.3% [‡]	5 years 66.8 vs 59.6% [‡]
Hasegawa K (2016)[2]	177	6.9	1: 45.8% ≥ 2: 54.2%	57.1	Adjuvant UFT/LV p.o	–	44.6%	58.2%	–	3 years 38.6 vs 32.3% [‡]	5 years 66.1 vs 66.8%
Nordlinger B (2013)[3,4]	364	3.8	1–4: 100%	102	Perioperative FOLFOX4 iv.	35.2%	–	56.0%	63.2%	3 years 38.2 vs 30.3% [‡]	5 years 51.2 vs 47.8%
Portier G (2006)[1]	173	10.0	1–3: 94.2% ≥ 4: 4.6%	87.4	Adjuvant 5FU/LV iv.	–	28.3%	–	53.8%	5 years 33.5 vs 26.7% [‡]	5 years 51.1 vs 41.1%
Kemeny MM (2002)[5]	109	6.4	1–3: 100%	51	Adjuvant HAI + 5FU iv.	23.9%	–	–	–	4 years 45.7 vs 25.2% [‡]	4 years 61.5 vs 52.7%
Langer BHB (2002)[6]	129[#]	–	1-4: 100%	–	Adjuvant 5FU/LV iv.	–	–	–	–	Median 39 vs 20 months	Median 53 vs 43 months
Lorenz M (1998)[7]	226	5.7	1–6: 100%	–	Adjuvant HAI	37.2%	–	50.4%	–	Median 14.2 vs 13.7 months	Median 34.5 vs 40.8 months
Rudroff C (1999)[8]	30	1.4	1–3: 93.3% ≥ 4: 6.7%	–	Adjuvant HA	I43.3%	–	100%	–	Unknown period 23 vs 15%	5 years 31 vs 25%
Lygidakis NJ (1995)[9]	40	3.0	–	–	Adjuvant HAI	–	–	–	–	Unknown period 100 vs 55% [‡]	Mean 20 vs 11 months [‡]
Wagman LD (1990)[10]	11	4.4	1: 100%	–	Adjuvant HAI	27.3%	–	–	–	–	5 years 40.0 vs 50.0%

CRLM colorectal liver metastases, *DFI* disease-free interval, *LNM* lymph node metastases, *CEA* carcinoembryonic antigen, *RFS* recurrence-free survival, *OS* overall survival, *HAI* hepatic arterial infusion
p.o. per os, *iv.* intravenous

[*] CEA ≥ 5 ng/ml

[#] Includes13 patients with lung metastasis

[§] DFI ≤ 1 year includes synchronous and early metachronous CRLM in this section

[†] Intravenous indicated as AC vs SA

[‡] Statistically significant difference CRLM

of RFS or OS. However, in the subgroup involving DFI of ≤ 1 year, AC was significantly effective in terms of OS. Also, its significance was even more evident among the patients that exhibited both serum CEA levels of ≥ 10 ng/ml and DFI of ≤ 1 year. Previous studies have indicated that a DFI of ≤ 1 year is a risk factor for recurrence and should be used as an indication for AC.[19,29,30] Our findings are compatible with these previous results. On the contrary, in the subgroups involving DFI of > 1 year, AC was not effective in terms of both RFS and OS. Neoadjuvant chemotherapy for CRLM in patients that were with low risk of recurrence was reported to provide no survival benefit compared with upfront surgery,[31] which was similar to the present study. Therefore, we consider that early metachronous CRLM with a DFI of ≤ 1 year is a good indication for AC, whereas AC should be cautiously indicated for late metachronous CRLM with a DFI of > 1 year, after taking account of other clinical risk factors.

Regarding AC regimens, the present study included various regimens, such as FOLFOX/CapeOx (26.1%), 5FU/LV (10.0%), UFT/LV (40.8%), and S-1 (12.3%). As FOLFOX was only approved for clinical use in Japan in 2005, the proportion of patients treated with FOLFOX/CapeOx was relatively small. These characteristics represent the situation encountered in current daily practice in Japan, and so the findings of the present study indicate the effectiveness of AC in this clinical setting. The patients given oral regimens demonstrated significantly better RFS than those treated with SA. As FOLFOX/CapeOx tended to be offered for more advanced disease, it was not possible to assess whether these regimens were better than others, but oral regimens might be effective against CRLM, as demonstrated by a previous RCT of UFT/LV.[2] Taking account of the high recurrence rate and peripheral sensory neuropathy seen after oxaliplatin treatment, it might be worth considering a strategy involving the administration of oral AC regimens followed by treatment with FOLFOX/CapeOx plus targeted drugs for recurrence.

The limitations of the present study include the fact that it was not an RCT. However, it would be difficult to conduct a new RCT in which an SA group was used as the control arm.[1,2,13,14] As PS-matching studies based on large databases are considered to be an alternative to RCT,[16,17] we consider that the current study indicates the effectiveness of AC in the clinical setting. Second, the current study was based on a nationwide survey of 134 institutions in Japan, and the treatment strategies of the non-academic centers might have influenced the results. However, the nationwide survey reflected the current status of treatment for CRLM, and so the present study indicates the effectiveness of AC in clinical practice. Third, it was not possible to investigate in detail the effects of treatments that were administered for post-hepatectomy recurrence. OS after the initial resection of CRLM is reported to be influenced by the treatment employed for recurrence.[1–3,32] However, because the median duration of the OS period was longer in the AC group than in the SA group, even among patients who underwent re-resection, we consider that AC is effective against CRLM.

Conclusion

Adjuvant chemotherapy for resected CRLM had a survival benefit in terms of both RFS and OS in the clinical setting. Synchronous CRLM is a favorable indication for AC, whereas in metachronous CRLM the use of AC should be individualized according to each patient's risk factors.

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Author Contribution Each authors have contributed to designing the concept of the study, acquisition of data, analysis and interpretation of the results, and drafting and revision of the manuscript. Each authors have also thoroughly read the final version of the manuscript, agreed to its content, and shared the responsibility of all aspects of the study.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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