







Comprehensive data of 5085 patients newly diagnosed with colorectal liver metastasis between 2013 and 2017: Fourth report of a nationwide survey in Japan

Katsunori Sakamoto^{1,2}  | Toru Beppu^{1,3}  | Goro Honda^{1,4}  | Kenjiro Kotake^{1,5} | Masakazu Yamamoto^{1,6} | Keiichi Takahashi^{1,7} | Itaru Endo^{1,8}  | Kiyoshi Hasegawa^{1,9} | Michio Itabashi^{1,10} | Yojiro Hashiguchi^{1,11} | Yoshihito Kotera^{1,12} | Shin Kobayashi^{1,13}  | Tatsuro Yamaguchi^{1,14} | Kazushige Kawai^{1,15} | Soichiro Natsume^{1,15}  | Ken Tabuchi^{1,16}  | Hirotoshi Kobayashi^{1,17} | Kensei Yamaguchi^{1,18} | Kimitaka Tani^{1,4} | Satoshi Morita^{1,19} | Yoichi Ajioka²⁰ | Masaru Miyazaki²¹ | Kenichi Sugihara²²

Correspondence

Keiichi Takahashi, Grace Home Care Clinic Ito, 1-3-26 Hirono MC Building, 2nd floor, Hirono, Ito, Shizuoka 414-0038, Japan.
Email: kei0474da@gmail.com

Funding information

Nakayama Cancer Research Institute

Abstract

The Joint Committee for Nationwide Survey on colorectal liver metastasis (CRLM) was established to improve treatment outcomes in patients with CRLM. The aim of this study was to evaluate the transition in the characteristics and treatment strategies of patients with CRLM and to analyze the prognostic factors. The data of 5085 patients newly diagnosed between 2013 and 2017 were compared with those of 3820 patients from 2005 and 2007. In patients who underwent hepatectomy ($n = 2759$ and 2163), the number of CRLMs was significantly higher and in the 2013–2017 data than in the 2005–2007 data (median 2 vs. 1; $p = .005$). Overall survival (OS) rates after diagnosis of CRLM after hepatectomy were better in the 2013–2017 data than that in the 2005–2007 data (5-year OS, 62.4% vs. 56.7%, $p < .001$). Recurrence-free survival (RFS) after hepatectomy was comparable between the groups (5-year RFS, 30.5% vs. 30.7%; $p = .068$). Multivariate analyses identified age at diagnosis of CRLM ≥ 70 years, lymph node metastasis of primary lesion, preoperative carbohydrate antigen (CA) 19-9 value > 100 U/mL, number of CRLM 2–4, and R2 resection as independent predictors of OS. Synchronous CRLM, concomitant extrahepatic metastasis, lymphatic invasion, lymph node metastasis of primary lesion, preoperative CA19-9 value > 100 U/mL, number of CRLM 5–, and nonlaparoscopic approach were selected as that of RFS. Despite having a higher prevalence of advanced stage CRLM in the 2013–2017 patient

For affiliations refer to page 41.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *Journal of Hepato-Biliary-Pancreatic Sciences* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Society of Hepato-Biliary-Pancreatic Surgery.

population compared to the 2005–2007 cohort, prognostic outcomes demonstrably improved in the later period.

KEYWORDS

colorectal neoplasm, liver neoplasm, neoplasm metastasis

1 | INTRODUCTION

The liver is the most frequent location of metastatic tumors derived from colorectal cancer.^{1–4} To date, resection is the only curative treatment for patients with colorectal liver metastasis (CRLM).¹ The prognosis of patients with CRLM has shown improvement, with reported 5-year overall survival (OS) approaching 60% in post-hepatectomy patients.^{1,3,5} However, 70%–80% of tumors are considered unresectable at initial presentation, and prognosis is poor in patients who do not undergo hepatectomy.¹ Multidisciplinary treatment is required for marginally resectable or unresectable CRLM, and advances in surgical procedures, perioperative management, and chemotherapy have contributed to improved prognosis in these patients.¹ To further improve treatment outcomes in patients with CRLM, large-scale data are required. The Joint Committee for Nationwide Survey on CRLM was established by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS). The Joint Committee will provide raw anonymized data to researchers to perform studies that meet their aims as previously described.^{6–9}

The Joint Committee retrospectively collected the data of patients who were diagnosed with CRLM between 2005 and 2007 in 2014,⁵ and the data of patients newly diagnosed with CRLM after 2013 were continuously and prospectively registered.^{5,10,11} A follow-up period of up to 5 years was achieved for patients diagnosed with CRLM from 2013 to 2017. Therefore, this study aimed to show representative data of patients newly diagnosed with CRLM between 2013 and 2017 and compare the transition in characteristics, treatment strategies, and prognostic outcomes with those of patients newly diagnosed with CRLM between 2005 and 2007.

2 | METHODS

Among the institutions participating in the JSCCR and specially qualified board-certified training institutions or departments certified by the JSHBPS,¹² 209 departments from 201 institutions agreed to participate in this nationwide database system. All the data were registered using

the original comprehensive database system created by the Joint Committee.

To protect personal information, all data were registered using a linkable anonymous code that could be connected to and used only at each institution before registration. The registered data were rigorously managed by reducing and excluding data with deficiencies in six fundamental items (age, sex, verified latest date of survival, prognosis, number of liver metastases, and maximum size of liver tumor) and by checking and integrating duplicate registrations at the registration secretariat of the committee to maintain data quality.

A total of 5949 patients were newly diagnosed with CRLM between 2013 and 2017. After conducting a quality management process, the present report summarizes the data of 5085 patients in terms of patient characteristics, clinical findings associated with CRLM at the time of diagnosis, treatment strategies, postoperative outcomes of hepatectomy, time-series data on tumor markers, clinicopathological findings of the primary lesion, implementation status of chemotherapy, and prognostic data. Data of 5085 patients were compared with those of 3820 patients newly diagnosed with CRLM between 2005 and 2007. The prognosis of the data from 2013 to 2017 was compared with that of 2005–2007 according to the classification of CRLM using the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus (seventh edition, revised version, January 2009)¹³: H1 (1 to 4 metastatic tumors, all of which are 5 cm or less in maximum diameter), H2 (other than H1 or H3), and H3 (5 or more metastatic tumors, at least one of which is more than 5 cm in maximum diameter). Prognostic data were collected in 2014 for 2005–2007, and those for 2013, 2014, 2015, 2016, and 2017 were collected in 2019, 2020, 2021, 2022, and 2023, respectively. The median follow-up period was 29 months (interquartile range, 13–65 months) for the 2005–2007 data, and 26 months (interquartile range, 11–62 months) for the 2013–2017 data.

The prognostic factors associated with OS and RFS were analyzed by univariate and multivariate analyses in 2759 patients who underwent hepatectomy alone as local treatment for CRLM and were newly diagnosed with CRLM between 2013 and 2017. Patients who underwent R2 resection were included in the OS analyses but were excluded from the RFS analyses.

2.1 | Statistical analysis

Continuous variables are presented as medians and quartiles, and nominal and ordinal variables are presented as ratios. Local treatment for CRLM includes hepatectomy and ablation therapy (radiofrequency ablation and microwave coagulation therapy) but excludes hepatic arterial infusion chemotherapy. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses were performed using a Cox proportional hazards model. For the multivariate analyses, the data were screened for multicollinearity. Values of $p < .05$ were considered to indicate statistical significance. All statistical analyses were performed using the SPSS software (version 24.0; IBM Corp., Armonk, NY, USA).

2.2 | Ethical considerations

This study was approved by the Institutional Review Board of each institution (approval no. 1168: Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital; data analyzed at this institute) and was performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki in 1995 (as revised in Brazil in 2013). Informed consent was obtained on the basis of the opt-out principle.

The details of the study and right to refuse to participate were disclosed online to the public.

3 | RESULTS

3.1 | Clinical characteristics of patients who underwent hepatectomy

The patients who underwent concomitant ablation therapy as local treatment for CRLM ($n = 29$) were excluded from the analyses. The age of registered patients was significantly higher in the 2013–2017 data than in the 2005–2007 data (median 66-year-old vs. 64-year-old, $p < .001$, Table 1), but sex showed no significant difference (male sex 62.5% vs. 63.2%, $p = .626$). The proportion of the patients with synchronous CRLM and primary lesions was significantly higher in the 2013–2017 data than in the 2005–2007 data (55.1% vs. 49.8%, $p < .001$; Table 1). The number of CRLMs was significantly higher in the 2013–2017 data compared with the 2005–2007 data (median 2 vs. 1; $p = .005$; Table 2). In contrast, the maximum diameter of the CRLM was significantly smaller in the 2013–2017 data than in the 2005–2007 data (median: 24 mm vs. 26 mm, $p < .001$; Table 2). The incidence of marginally resectable/initially unresectable CRLM was significantly higher in the 2013–2017 data than in the 2005–2007 data (6.5%/6.5%,

TABLE 1 Patient characteristics who underwent hepatectomy for CRLM^a.

		2013–2017 <i>n</i> = 2759	2005–2007 <i>n</i> = 2163	<i>p</i> -value
Age, years	Median (25, 75%)	66 (59, 73)	64 (57, 71)	<.001
Sex	Male	1725 (62.5%)	1367 (63.2%)	.626
Height, cm	Median (25, 75%)	161.6 (155.0, 168.0)	161.0 (154.0, 167.5)	.009
	Missing	55	434	
Weight, kg	Median (25, 75%)	57.8 (50.0, 66.0)	57.0 (50.0, 65.0)	.045
	Missing	57	432	
BMI	Median (25, 75%)	22.10 (19.82, 24.45)	22.21 (20.06, 24.28)	.924
	Missing	57	436	
HBs-Ag	Positive	55 (2.1%)	35 (2.0%)	.799
	Missing	156	411	
HCV-Ab	Positive	80 (3.1%)	59 (3.4%)	.593
	Missing	159	419	
Emergence time of CRLM ^b	Synchronous	1521 (55.1%)	1074 (49.7%)	<.001
	Metachronous	1238 (44.9%)	1089 (50.3%)	
Resection of primary lesion	Yes	2729 (98.9%)	2150 (99.4%)	.069

Abbreviations: BMI, body mass index; CRLM, colorectal liver metastasis; HBs-Ag, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody.

^aPatients who underwent concomitant ablation therapy were excluded.

^bSynchronous liver metastasis was defined as a metastatic liver tumor diagnosed in the period of preoperative examination or surgery for primary lesion.

TABLE 2 Clinical findings of CRLM at diagnosis of patients who underwent hepatectomy for CRLM^a.

		2013–2017	2005–2007	p-value
		n = 2759	n = 2163	
Number of CRLMs	Median (25, 75%)	2 (1, 3)	1 (1, 3)	.005
Maximum diameter of CRLM, mm	Median (25, 75%)	24 (15, 38)	26 (17, 40)	<.001
Distribution of CRLMs	Bilobar	933 (34.0%)	678 (31.8%)	.114
	Unilobar	1813 (66.0)	1452 (68.2%)	
	Missing	13	33	
Local treatability on clinical findings ^b	Treatable	2397 (87.0%)	1874 (90.9%)	<.001
	Marginally treatable	179 (6.5%)	104 (5.0%)	
	Initially untreatable	179 (6.5%)	84 (4.1%)	
	Missing	4	101	
Concomitant extrahepatic metastasis	Yes	340 (12.4%)	282 (13.5%)	.260
	Missing	14	71	
Preoperative albumin, g/dL	Median (25, 75)	4.0 (3.8, 4.3)	4.1 (3.8, 4.4)	<.001
	Missing	140	321	
Preoperative T-Bil, mg/dL	Median (25, 75)	0.6 (0.5, 0.8)	0.7 (0.5, 0.9)	<.001
	Missing	131	364	
Preoperative prothrombin time, %	Median (25, 75)	99.2 (89.3, 107.0)	97.0 (86.7, 103.0)	<.001
	Missing	195	437	
Preoperative ICG-R15, %	Median (25, 75)	9.0 (5.7, 13.0)	8.0 (5.2, 11.8)	<.001
	Missing	655	833	
Preoperative hepatic coma	Yes	1 (0.0%)	1 (0.1%)	.644
	Missing	265	475	
Preoperative ascites	Yes	42 (1.7%)	15 (0.9%)	.030
	Missing	262	475	
JSHBPS nomogram score ^c	Median (25, 75)	7 (3, 10)	6 (3, 10)	<.001
JSHBPS nomogram risk score ^c	Low risk (–6)	1284 (46.5%)	1113 (51.5%)	<.001
	Moderate risk (7–10)	817 (29.6%)	623 (28.8%)	
	High risk (11–)	658 (23.8%)	427 (19.7%)	

Abbreviations: ASA, American Society of Anesthesiologists; CRLM, colorectal liver metastasis; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; ICG-R15, Indocyanine green retention rate at 15 minutes; T-Bil, total bilirubin.

^aPatients who underwent concomitant ablation therapy were excluded.

^bTreatable: All tumors could be removed with preservation of a negative surgical margin and sufficient remnant liver volume without performing two-stage hepatectomy with portal vein embolization or major vessel reconstruction. Marginally treatable: All tumors could be removed with preservation of remnant liver volume, regardless of surgical margin, in two-stage hepatectomy with portal vein embolization or major vessel reconstruction. Untreatable: All tumors could not be removed with preservation of sufficient remnant liver volume even if two-stage hepatectomy with portal vein embolization or major vessel reconstruction was performed. Lesions that could be completely ablated were included in the “treatable” category.

^cCalculated using the report from Beppu et al.¹²

5.0%/4.1%; $p < .001$; Table 2). The JSHBPS nomogram score was significantly higher in the 2013–2017 data than in the 2005–2007 data (median, 7 vs. 6, $p < .001$; Table 2). Regarding the operative findings (Table 3), the operative time was significantly longer in the 2013–2017 data compared with the 2005–2007 data (median 320 min vs. 289 min, $p < .001$), whereas the amount of blood loss was significantly lower in the 2013–2017 data compared with the 2005–2007 data (median 320 mL vs. 550 mL, $p < .001$). The incidence of red blood cell

transfusion was not significantly different between the groups (19.9% vs. 21.7%, $p = .145$). The proportion of patients who underwent neoadjuvant chemotherapy and laparoscopic surgery was significantly higher in the 2013–2017 data than those in the 2005–2007 data (20.8% vs. 5.2% and 26.1% vs. 2.3%, both $p < .001$, Table 3). Surgical curability showed no significant difference between both groups ($p = .163$). The other data associated with patients newly diagnosed with CRLM between 2013 and 2017 are presented in Data S9.

TABLE 3 Operative outcomes of patients who underwent hepatectomy for CRLM^a.

		2013–2017	2005–2007	p-value
		n = 2759	n = 2163	
Operation time ^b , min	Median (25, 75%)	320 (229, 433)	289 (210, 384)	<.001
	Missing	79	245	
Amount of blood loss, mL	Median (25, 75%)	320 (120, 700)	550 (270, 1031)	<.001
	Missing	258	268	
Red blood cell transfusion	Yes	517 (19.9%)	385 (21.7%)	.145
	Missing	159	389	
Final pathological number of CRLMs	Median (25, 75%)	2 (1, 3)	1 (1, 3)	.002
	Missing	40	85	
Procedure of hepatectomy	Hr2 or Hr3	14 (0.6%)	78 (3.8%)	<.001
	Hr1	614 (25.3%)	389 (19.2%)	
	HrS	268 (11.0%)	139 (6.8%)	
	Hr0	1535 (63.1%)	1425 (70.2%)	
	Missing	328	132	
Pathological surgical margin, mm	Median (25, 75%)	3 (1, 9)	5 (1, 10)	.043
	Missing	1140	1187	
Surgical curability ^c	R0	2462 (91.4%)	1876 (93.0%)	.163
	R1	183 (6.8%)	105 (5.2%)	
	R2	43 (1.6%)	33 (1.6%)	
	RX	6 (0.2%)	4 (0.2%)	
	Missing	65	145	
Neoadjuvant chemotherapy	Yes	574 (20.8%)	112 (5.2%)	<.001
Simultaneous resection of primary lesion and CRLM in synchronous metastasis patients	Yes	560 (20.0%)	603 (27.9%)	<.001
	Missing	5	6	
Laparoscopic surgery	Total	685 (26.1%)	47 (2.3%)	<.001
	HALS	28 (1.1%)	5 (0.2%)	
	Hybrid	44 (1.7%)	15 (0.7%)	
	Pure	613 (23.3%)	27 (1.3%)	
	Missing	125	100	
Preoperative portal vein embolization	Yes	463 (16.8%)	203 (9.4%)	<.001
Two-stage hepatectomy	Yes	40 (1.4%)	7 (0.3%)	<.001
Residual extrahepatic lesion	Yes	211 (7.8%)	132 (6.1%)	.023
	Missing	62	12	
Hilar lymph node dissection	Yes	68 (2.6%)	66 (3.4%)	.116
	Missing	138	215	
Pathological hilar lymph node metastasis	Yes	28 (1.4%)	24 (1.9%)	.266
	Missing	766	905	
Pathological effect of chemotherapy ^d	Grade 0	69/666 (10.4%) ^e	33/181 (18.2%) ^f	.027
	Grade 1	355/666 (53.3%) ^e	93/181 (51.4%) ^f	
	Grade 2	189/666 (28.4%) ^e	41/181 (22.7%) ^f	
	Grade 3	53/666 (8.0%) ^e	14/181 (7.7%) ^f	

TABLE 3 (Continued)

		2013–2017	2005–2007	p-value
		n = 2759	n = 2163	
Postoperative complication (Clavien-Dindo classification \geq III)	Yes	293 (10.8%)	272 (13.3%)	.007
	Missing	36	116	
Postoperative hospital stays, day	Median (25, 75%)	12 (9, 16)	14 (10, 21)	<.001
	Missing	216	953	
Postoperative in-hospital mortality	Yes	16 (0.6%)	29 (1.4%)	.005
	Mortality within 30 postoperative days	1 (0.0%)	2 (0.1%)	.410
	Mortality within 90 postoperative days	7 (0.3%)	9 (0.4%)	.321

Note: Neoadjuvant chemotherapy was performed in 623 of all CRLM patients, and of 623, 574 patients underwent hepatectomy. Neoadjuvant chemotherapy was performed in 130 of all CRLM patients, and of 130, 112 patients underwent hepatectomy.

Abbreviations: CRLM, colorectal liver metastasis; Hr0, partial hepatectomy; HrS, resection of one segment; Hr1, resection of one section; Hr2, resection of two sections; Hr3, resection of three sections; HALS, hand-assisted laparoscopic surgery; Hybrid, hybrid laparoscopic surgery; Pure, pure laparoscopic surgery.

^aPatients who underwent concomitant ablation therapy were excluded.

^bIf simultaneous resection of the primary lesion and CRLM was undertaken in patients with synchronous metastasis, the operation time was the sum of the duration of each procedure.

^cR0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; RX, presence of residual tumor cannot be assessed.

^dGrade 0, no change, no necrosis or cellular or structural change can be seen throughout the lesion; Grade 1, mild change, necrosis, or disappearance of the tumor is present in less than two-thirds of the whole lesion; Grade 2, moderate change, necrosis, or disappearance of the tumor is present in more than two-thirds of the whole lesion, but viable tumor cells still remain; Grade 3, severe change, the whole lesion shows necrosis, and no viable tumor cells are observed.

^eOf the 1012 patients who underwent chemotherapy before local treatment, the data of 346 patients were missing (final total, $n = 666$).

^fOf the 468 patients who underwent chemotherapy before local treatment, the data of 287 patients were missing (final total, $n = 181$).

3.2 | Survival analyses

The overall 1-, 3-, and 5-year survival (OS) rates after the diagnosis of CRLM in patients who underwent hepatectomy alone as local treatment for CRLM in the 2013–2017 data were 96.6%, 78.9%, and 62.4%, respectively (Figure 1a). The 1-, 3-, and 5-year recurrence-free survival (RFS) rates after hepatectomy in the patients who underwent hepatectomy alone as local treatment for CRLM between in the 2013–2017 data were 55.7%, 35.9%, and 30.5%, respectively (Figure 1b). In the patients who underwent hepatectomy, compared with the 2005–2007 data, OS rates was better in the 2013–2017 data (Figure 2a, 5-year OS 63.1% vs. 56.9%, $p < .001$), whereas RFS rates showed no significant differences between the groups (Figure 2b, 5-year RFS 30.5% vs. 30.7%, $p = .068$).

According to the classification of CRLM using the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus (seventh edition, revised version, January 2009), although OS in 2013–2017 data in H1 and H2 showed significantly better prognosis compared with 2005–2007 data (H1, 5-year OS 65.2% vs. 60.4%, $p = .014$; H2, 56.0% vs. 46.8%, $p < .001$; Data S1 and S2), OS in 2013–2017 data in H3 showed no significant difference compared with 2005–2007 data (5-year OS 44.4%

vs. 38.9%, $p = .182$; Data S3). RFS in all H1–H3 classifications showed no significant differences between the two groups (H1, 5-year RFS 34.8% vs. 34.0%, $p = .233$; H2, 5-year RFS 18.6% vs. 21.9%, $p = .190$; H3, 5-year RFS 8.2% vs. 8.2%, $p = .673$, Data S4–S6).

According to the classification of JSHBPS nomogram risk score,¹⁴ both the OS and RFS were clearly stratified (5-year OS 71.8% in low-risk vs. 57.0% in moderate-risk vs. 51.1% in high-risk; 5-year RFS were 45.2% in low-risk vs. 22.2% in moderate-risk vs. 13.9% in high-risk; Data S7 and S8).

3.3 | Prognostic factors of the 2013–2017 data in the patients underwent hepatectomy

Survival analyses of OS and RFS in patients who underwent hepatectomy alone as local treatment for CRLM using 2013 the 2017 data are presented in Tables 4 and 5. Preoperative chemotherapy included patients who underwent either neoadjuvant or induction therapy. Although survival rates were significantly lower in patients who underwent concomitant ablation therapy with hepatectomy and in those who had pathological hepatic hilar lymph node

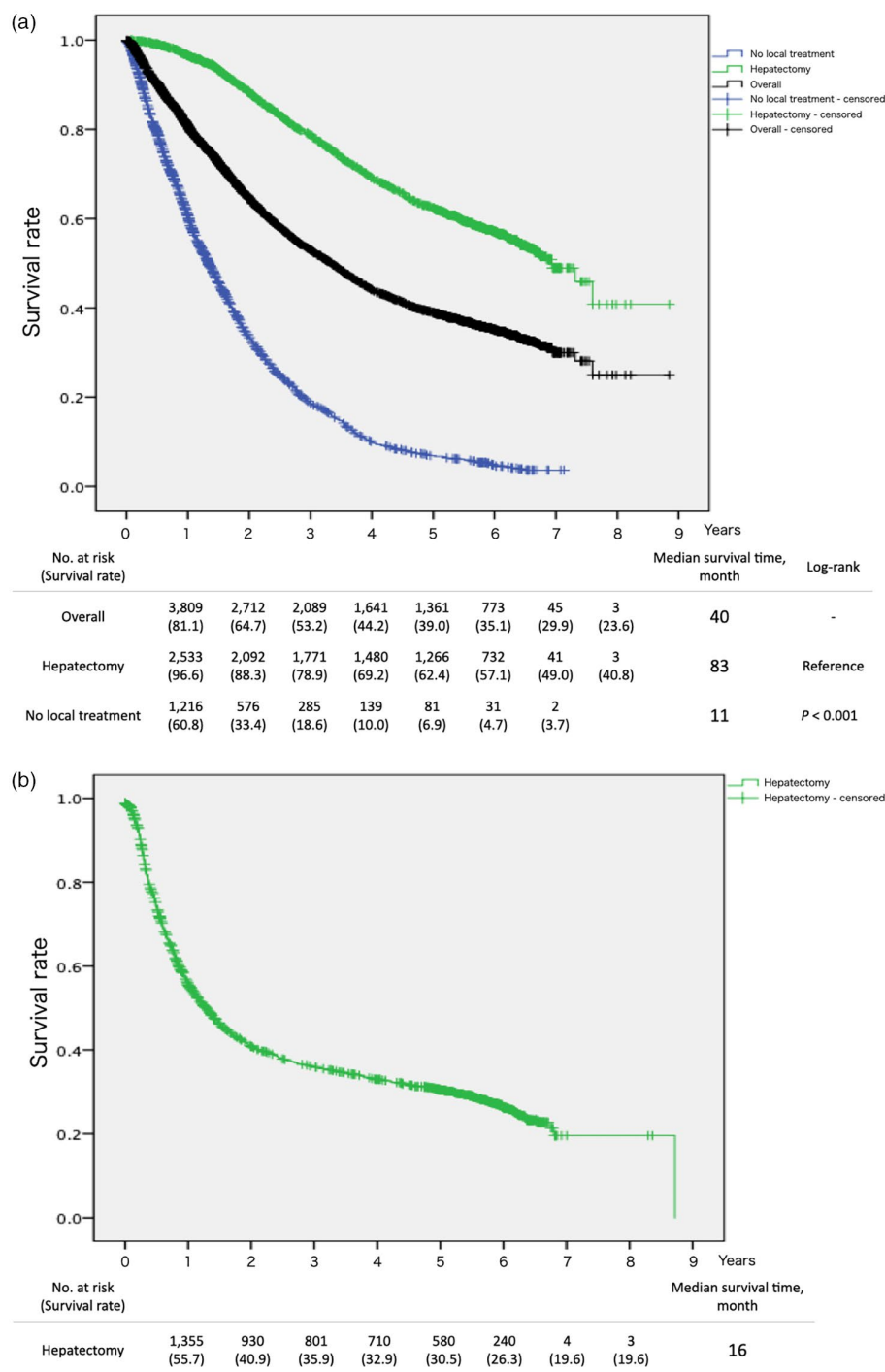


FIGURE 1 Overall survival and recurrence-free survival of patients newly diagnosed with colorectal liver metastasis between 2013 and 2017. The patients who underwent concomitant local ablation therapy were excluded from the group of hepatectomy. (a) Overall survival after diagnosis. Overall group includes the patients who underwent local ablation therapy (with/without hepatectomy). (b) Recurrence-free survival after hepatectomy.

metastasis than in those who did not, these patients were excluded from multivariate analyses because of the small sample size. Multivariate analyses identified age at diagnosis of CRLM ≥ 70 years, lymph node metastasis of primary lesion, preoperative carbohydrate antigen (CA) 19-9 value >100 U/mL, number of CRLM 2-4, and R2

resection as independent predictors of OS (Table 4); and identified synchronous CRLM, concomitant extrahepatic metastasis, lymphatic invasion, lymph node metastasis of primary lesion, preoperative CA19-9 value >100 U/mL, number of CRLM 5-, and nonlaparoscopic approach were selected as independent predictors of RFS (Table 5).

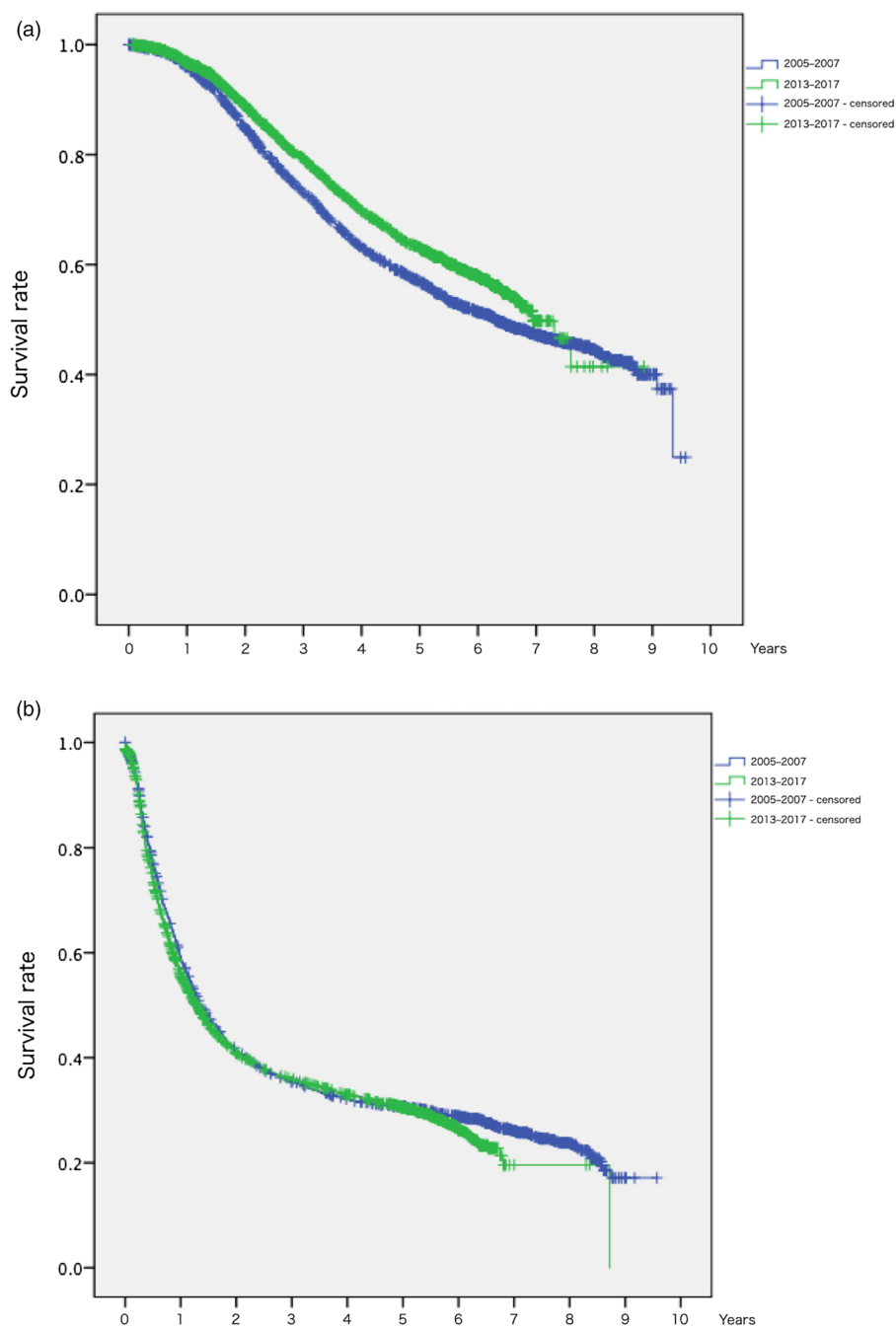


FIGURE 2 Comparison of survival among patients who underwent hepatectomy between 2013 and 2017 data and 2005 and 2007 data. (a) Overall survival after diagnosis. One-, 3-, and 5-year overall survival rates were 96.6%, 78.9% and 62.4% in 2013–2017 data ($n=2759$, median survival time 83 months) versus 95.6%, 72.7% and 56.6% in 2005–2007 data ($n=2163$, median survival time 75 months) ($p<.001$). (b) Recurrence-free survival after hepatectomy. One-, 3-, and 5-year recurrence-free survival rates were 55.7%, 35.9%, and 30.5% in 2013–2017 data ($n=2589$, median survival time 16 months) versus 59.2%, 35.4%, and 30.7% in 2005–2007 data ($n=1985$, median survival time 16 months) ($p=.068$).

4 | DISCUSSION

The present study included data registered in a comprehensive nationwide database by institutions certified by the JSCCR and JSHBPS. Accordingly, all patients were treated by colorectal cancer specialists

and board-certified hepatic surgeons, which ensured the quality and strategies of treatment. In summary, compared to the 2005–2007 data, the age at diagnosis of CRLM was higher in the 2013–2017 data, which might be due to societal aging. Regarding the CRLM characteristics, although the number of CRLM was higher

TABLE 4 Uni- and multivariate analyses for overall survival after the diagnosis of CRLM in patients who underwent hepatectomy using the data of 2013–2017.

	Univariate analysis ^a				Multivariate analysis		
	n	3-y	5-y	p-value	p-value	Hazard ratio	95% CI
Patient characteristics							
Age, years							
<70	1358	83.2	66.8	Reference	-	Reference	
≥70	1401	74.6	58.1	<.001	-	1.468	1.114 1.934
Sex							
Female	1034	78.9	63.7	Reference	-	NA	
Male	1725	78.9	61.7	.168	-		
Body mass index							
≥25	2141	77.8	61.4	Reference	-	NA	
<25	558	82.8	65.6	.323	-		
Preoperative MRI							
Yes	1058	76.9	63.2	Reference	-	NA	
No	1656	80.1	61.8	.858	-		
Preoperative chemotherapy ^b							
No	956	81.5	66.6	Reference	-	Reference	
Yes	1012	78.5	59.0	.003	-	1.435	0.897 2.295
Emergence time of CRLM							
Metachronous	1238	81.1	66.1	Reference	-	Reference	
Synchronous	1521	77.1	59.5	<.001	-	1.164	0.823 1.645
Concomitant extrahepatic metastasis							
No	2405	80.3	64.5	Reference	-	Reference	
Yes	340	69.5	48.6	<.001	-	1.382	0.971 1.967
Characteristics of primary lesion							
Location of primary lesion							
Left side	1982	80.7	64.9	Reference	-	Reference	
Right side	724	74.2	56.9	<.001	-	1.192	0.872 1.628
Pathological tumor depth of primary lesion ^c							
T1/T2	237	84.8	71.7	Reference	-	Reference	
T3/T4	2423	78.5	61.8	.004	-	1.338	0.787 2.274
Lymphatic invasion ^c							
ly0/1	2036	80.9	64.9	Reference	-	Reference	
ly2/3	626	71.6	54.1	<.001	-	1.230	0.878 1.723
Venous invasion ^c							
v0/1	1439	80.9	65.4	Reference	-	Reference	
v2/3	1206	76.0	59.1	.002	-	1.088	0.810 1.461
Lymph node metastasis ^c							
N0	887	85.5	73.0	Reference	-	Reference	
N1	1080	80.0	60.6	<.001	Reference	1.467	1.036 2.078
N2/3	678	69.2	52.6	<.001	<0.001	1.636	1.103 2.426
Histological type ^c							
tub1	703	82.1	66.2	Reference	-	Reference	
tub2	1842	78.4	62.0	.015	Reference	0.897	0.444 1.813
Others	147	66.8	51.7	<.001	0.022	1.113	0.580 2.133

TABLE 4 (Continued)

		Univariate analysis ^a				Multivariate analysis		
		n	3-y	5-y	p-value	p-value	Hazard ratio	95% CI
KRAS status	Wild	563	78.4	58.7	Reference	-	Reference	
	Mutant	893	69.7	49.9	.004	-	1.185	0.887 1.584
Tumor marker value								
CA19-9, U/mL, before hepatectomy	≤100	2207	81.2	65.0	Reference	-	Reference	
	>100	334	62.3	42.9	<.001	-	1.879	1.280 2.758
CEA, ng/mL, before hepatectomy	≤100	1530	83.0	66.5	Reference	-	Reference	
	>100	1025	72.4	55.5	<.001	-	1.376	0.815 2.322
Characteristics of CRLM								
Number of CRLMs	1	1321	81.5	67.7	Reference	-	Reference	
	2-4	977	77.5	60.0	<.001	Reference	1.484	1.014 2.174
	5-	461	74.4	52.7	<.001	.014	1.142	0.690 1.891
Maximum diameter of CRLM, cm	≤3	1845	80.6	64.6	Reference	-	Reference	
	>3, ≤5	514	78.8	61.1	.236	Reference	1.001	0.668 1.499
	>5	400	71.2	53.8	<.001	0.012	.898	0.570 1.413
Distribution of CRLM	Unilobar	1813	81.0	66.4	Reference	-	Reference	
	Bilobar	933	74.8	55.4	<.001	-	1.022	0.709 1.474
Initial resectability ^d	Resectable	2397	79.4	63.8	Reference	-	Reference	
	Marginally resectable	179	73.4	56.4	.012	Reference	1.044	0.623 1.748
	Initially unresectable	179	78.7	51.4	.004	0.743	0.969	0.567 1.658

Operative findings

Intraoperative red cell transfusion	No	2083	81.1	64.8	Reference	-	Reference	
	Yes	517	71.3	53.5	<.001	-	1.529	0.987 2.369
Amount of intraoperative blood loss, g	≤500	1625	81.5	66.4	Reference	-	Reference	
	>500, ≤1000	527	76.0	57.4	<.001	Reference	1.100	0.678 1.783
	>1000	368	72.9	52.6	<0.001	0.270	0.940	0.573 1.543
Operation time, min	≤240	737	82.5	68.1	Reference	-	Reference	
	>240, ≤480	1442	79.7	62.9	.043	Reference	0.920	0.639 1.325
	>480	468	71.7	51.8	<.001	<0.001	1.358	0.864 2.132

(Continues)

TABLE 4 (Continued)

	n	Univariate analysis ^a			Multivariate analysis		
		3-y	5-y	p-value	p-value	Hazard ratio	95% CI
Anatomical hepatectomy							
No	1508	80.3	64.5	Reference	-	NA	
Yes	1216	77.1	60.2	.055	-		
Laparoscopic surgery							
Yes	685	82.6	66.9	Reference	-	Reference	
No	1938	77.8	61.1	.002	-	1.192	0.838 1.697
Surgical curability ^c							
R0	2462	79.9	63.9	Reference	-	Reference	
R1	183	71.7	53.6	.003	Reference	1.238	0.666 2.303
R2	43	48.1	24.2	<.001	<0.001	2.593	1.246 5.396
≥10	403	84.8	67.6	Reference	Reference	Reference	
>0, <10	861	78.0	61.5	.042	Reference	1.033	0.705 1.512
0	355	72.5	56.1	<.001	0.041	1.018	0.632 1.639
Pathological hilar lymph node metastasis							
Negative	1965	78.7	61.4	Reference	-	NA ^e	
Positive	28	38.6	24.1	<.001	-		
Postoperative findings							
Postoperative complication (Clavien-Dindo classification ≥ III)							
No	2430	80.4	63.8	Reference	-	Reference	
Yes	293	66.9	50.2	<.001	-	1.384	0.855 2.242
Postoperative chemotherapy ^b							
Yes	468	84.0	68.4	Reference	-	Reference	
No	1464	78.7	60.9	.010	-	1.286	0.795 2.082

Abbreviations: CI, confidence interval; CRLM, colorectal liver metastasis; ly0, no lymphatic invasion; ly1, minimal lymphatic invasion; ly2, moderate lymphatic invasion; ly3, severe lymphatic invasion; NA, not applicable; N0, no evidence of lymph node metastasis; N1, metastasis in 1–3 pericolic/perirectal or intermediate lymph nodes; N2, metastasis in four or more pericolic/perirectal or intermediate lymph nodes; N3, metastasis in the main lymph node(s). In lower rectal cancer, metastasis in the main and/or lateral lymph node(s); R0, no residual tumor or no residual tumor with concomitant complete ablation therapy; R1, microscopic residual tumor; R2, macroscopic residual tumor; T1, tumor invades submucosa; T2, tumor invades muscularis propria; T3, tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues; T4, tumor directly invades other organs or structures, and/or perforates visceral peritoneum; tub1, well differentiated type tubular adenocarcinoma; tub2, moderately differentiated type tubular adenocarcinoma; v0, no venous invasion; v1, minimal venous invasion; v2, moderate venous invasion; v3, severe venous invasion; 3-y, 3-year survival rate; 5-y, 5-year survival rate.

^aPatients who underwent concomitant ablation therapy were excluded from the analyses.

^bThe patients who underwent postoperative chemotherapy alone were included in the group of postoperative chemotherapy and those who underwent preoperative chemotherapy alone or both pre- and postoperative chemotherapy were included in the group of preoperative chemotherapy.

^cDescribed in accordance with General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (seventh edition, revised version, January 2009).

^dResectable: All tumors could be removed with preservation of a negative surgical margin and sufficient remnant liver volume without performing two-stage hepatectomy with portal vein embolization or major vessel reconstruction. Marginally resectable: All tumors could be removed with preservation of remnant liver volume, regardless of surgical margin, in two-stage hepatectomy with portal vein embolization or major vessel reconstruction. Initially unresectable: All tumors could not be removed with preservation of sufficient remnant liver volume even if two-stage hepatectomy with portal vein embolization or major vessel reconstruction was performed.

^eExcluded from multivariate analyses because of small numbers.

TABLE 5 Uni- and multivariate analyses for recurrence-free survival after the hepatectomy alone for CRLM using the data of 2013–2017.

	Univariate analysis ^a				Multivariate analysis		
	n	3-y	5-y	p-value	p-value	Hazard ratio	95% CI
Patient characteristics							
Age, years							
<70	1273	35.9	31.4	Reference	-	NA	
≥70	1316	36.0	29.6	.689	-		
Sex							
Female	979	36.9	33.5	Reference	-	NA	
Male	1610	35.3	28.7	.103	-		
Body mass index							
≥25	522	37.9	32.4	Reference	-	NA	
<25	2010	35.4	29.9	.140	-		
Preoperative MRI							
Yes	1004	38.4	33.2	Reference	-	NA	
No	1543	34.5	28.8	.096	-		
Preoperative chemotherapy ^b							
No	912	41.7	35.8	Reference	-	Reference	
Yes	925	26.5	22.2	<.001	-	1.171	.923 1.484 .193
Emergence time of CRLM							
Metachronous	1185	44.6	38.6	Reference	-	Reference	
Synchronous	1404	28.7	23.8	<.001	-	1.268	1.047 1.536 .015
Concomitant extrahepatic metastasis							
No	2286	38.4	32.6	Reference	-	Reference	
Yes	294	17.2	14.9	<.001	-	1.431	1.123 1.823 .004
Characteristics of primary lesion							
Location of primary lesion							
Left side	1853	36.1	30.4	Reference	-	NA	
Right side	688	35.6	30.8	.873	-		
Pathological tumor depth of primary lesion ^c							
T1/T2	226	50.0	42.5	Reference	-	Reference	
T3/T4	2275	34.5	29.1	<.001	-	1.268	0.936 1.717 .126
Lymphatic invasion ^c							
ly0/1	1932	37.8	32.0	Reference	-	Reference	
ly2/3	574	29.4	25.1	<.001	-	1.308	1.057 1.619 .014
Venous invasion ^c							
v0/1	1363	38.4	33.0	Reference	-	Reference	
v2/3	1126	32.4	27.4	<.001	-	1.021	0.858 1.215 .815
Lymph node metastasis ^c							
N0	851	48.3	40.2	Reference	-	Reference	
N1	1027	32.6	28.3	<.001	Reference	1.421	1.171 1.724 <.001
N2/3	612	24.2	20.8	<.001	<0.001	1.435	1.137 1.810 .002
Histological type ^c							
tub1	670	42.7	36.7	Reference	-	Reference	
tub2	1721	33.5	28.4	<.001	Reference	1.053	0.694 1.596 .809
others	139	33.6	27.8	.005	0.588	1.355	0.915 2.005 .129

(Continues)

TABLE 5 (Continued)

	Univariate analysis ^a				Multivariate analysis		
	n	3-y	5-y	p-value	p-value	Hazard ratio	95% CI
KRAS status							
Wild	823	27.4	22.8	Reference	-	NA	
Mutant	534	25.5	22.3	.073	-		
Tumor marker value							
CA19-9, U/mL, before hepatectomy							
≤100	2088	38.5	32.6	Reference	-	Reference	
>100	309	19.0	16.1	<.001	-	1.752	1.374 2.233
CEA, ng/mL, before hepatectomy							
≤100	1444	40.7	35.1	Reference	-	Reference	
>100	967	29.1	23.7	<.001	-	1.060	.882 1.274
Characteristics of CRLM							
Number of CRLMs							
1	1266	45.8	39.9	Reference	-	Reference	
2-4	910	29.5	24.3	<.001	Reference	1.224	.982 1.526
5-	413	20.1	15.1	<.001	<0.001	1.376	1.017 1.862
≤3	1748	38.9	33.4	Reference	-	Reference	
>3, ≤5	483	34.5	29.7	.053	Reference	0.949	.761 1.183
>5	358	22.9	17.0	<.001	<0.001	1.019	.788 1.318
Distribution of CRLM							
Unilobar	1718	41.3	35.6	Reference	-	Reference	
Bilobar	862	25.3	20.2	<.001	-	1.090	.870 1.364
Initial resectability							
Resectable	2286	37.9	32.3	Reference	-	Reference	
Marginally resectable	157	22.4	16.9	<.001	Reference	1.071	.781 1.470
Initially unresectable	142	19.5	17.6	<.001	0.776	.868	0.598 1.259
Operative findings							
Intraoperative red cell transfusion							
No	1963	37.2	31.4	Reference	-	Reference	
Yes	483	29.6	25.1	<.001	-	1.062	0.792 1.422
Amount of intraoperative blood loss, g							
≤500	1533	40.1	34.5	Reference	-	Reference	
>500, ≤1000	494	28.2	23.3	<.001	Reference	1.225	.995 1.507
>1000	340	27.2	22.8	<.001	0.812	0.840	.616 1.145
Operation time, min							
≤240	699	44.5	38.7	Reference	-	Reference	
>240, ≤480	1364	34.9	29.3	<.001	Reference	1.223	.992 1.509
>480	422	25.0	21.0	<.001	<0.001	1.314	.995 1.737

TABLE 5 (Continued)

	Univariate analysis ^a				Multivariate analysis		
	n	3-y	5-y	p-value	p-value	Hazard ratio	95% CI
Anatomical hepatectomy							
No	1422	38.2	32.1	Reference	-	Reference	
Yes	1134	33.4	28.9	.019	-	1.035	.873 1.226
Laparoscopic surgery							
Yes	653	41.8	35.9	Reference	-	Reference	
No	1814	34.0	28.6	<.001	-	1.243	1.010 1.529
R0	2354	36.8	31.2	Reference	-	Reference	
Surgical curability ^{c,d}							
R1	175	25.4	21.7	<.001	Reference	1.357	.937 1.965
≥10	384	42.2	36.6	Reference	-	Reference	
>0, <10	815	35.1	30.6	.042	Reference	1.096	.888 1.353
0	333	26.2	20.8	<.001	<0.001	1.153	.873 1.522
Pathological hilar lymph node metastasis							
Negative	1841	35.2	29.4	Reference	-	NA ^e	
Positive	26	19.0	9.5	.008	-		
Postoperative findings							
Postoperative complication (Clavien-Dindo classification ≥ III)							
No	2291	36.9	31.4	Reference	-	Reference	
Yes	266	28.3	23.6	<.001	-	1.219	.942 1.576
Postoperative chemotherapy†							
Yes	448	40.6	34.7	Reference	-		
No	1358	32.0	27.0	<.001	-	1.240	.973 1.579

Note: Resectable: All tumors could be removed with preservation of a negative surgical margin and sufficient remnant liver volume without performing two-stage hepatectomy with portal vein embolization or major vessel reconstruction. Marginally resectable: All tumors could be removed with preservation of remnant liver volume, regardless of surgical margin, in two-stage hepatectomy with portal vein embolization or major vessel reconstruction. Initially unresectable: All tumors could not be removed with preservation of sufficient remnant liver volume even if two-stage hepatectomy with portal vein embolization or major vessel reconstruction was performed.

Abbreviations: CI, confidence interval; CRLM, colorectal liver metastasis; ly0, no lymphatic invasion; ly1, minimal lymphatic invasion; ly2, moderate lymphatic invasion; ly3, severe lymphatic invasion; MRI, magnetic resonance imaging; NA, not applicable; N0, no evidence of lymph node metastasis; N1, metastasis in 1–3 pericolic/perirectal or intermediate lymph nodes; N2, metastasis in four or more pericolic/perirectal or intermediate lymph nodes; N3, metastasis in the main lymph node(s). In lower rectal cancer, metastasis in the main and/or lateral lymph node(s); R0, no residual tumor or no residual tumor with concomitant complete ablation therapy; R1, microscopic residual tumor; R2, tumor invades submucosa; T2, tumor invades muscularis propria; T3, tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues; T4, tumor directly invades other organs or structures, and/or perforates visceral peritoneum; tub1, well differentiated type tubular adenocarcinoma; tub2, moderately differentiated type tubular adenocarcinoma; v0, no venous invasion; v1, minimal venous invasion; v2, moderate venous invasion; v3, severe venous invasion; 3-y, 3-year survival rate; 5-y, 5-year survival rate.

^aPatients who underwent concomitant ablation therapy were excluded from the analyses.

^bThe patients who underwent postoperative chemotherapy alone were included in the group of postoperative chemotherapy and those who underwent preoperative chemotherapy alone or both pre- and postoperative chemotherapy were included in the group of preoperative chemotherapy.

^cDescribed in accordance with General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (seventh edition, revised version, January 2009).

^dThe patients with R2 resection were excluded from the analyses.

^eExcluded from multivariate analyses because of small numbers.

in the 2013–2017 data, maximum CRLM tumor diameter at diagnosis was smaller in the 2013–2017 data. Several factors, such as advances in imaging modalities or more aggressive surgical approaches due to improvements in surgical outcomes, might have affected these results.² The higher rate of laparoscopic surgery in recent studies may have led to longer operative times and lesser blood losses. Furthermore, advances in surgical procedures and perioperative treatment might have led to lower 90-day mortality in these years. Analyzing the data from 2013 to 2017 compared to the prognostic data from 2005 to 2007, it is noteworthy that even though patients who underwent hepatectomy in the later period exhibited a higher burden of prognostic risk factors, including elevated CRLM numbers, synchronous metastasis and higher JSHBPS nomogram score, their OS was demonstrably improved ($p < .001$). In contrast, their RFS did not show a statistically significant difference ($p = .068$). Although RFS was affected by higher JSHBPS nomogram score in the data from 2013–2017, advance of treatment after recurrence might contribute to improve OS in the 2013–2017 data than the 2005–2007 data. The lower proportion of the patients who underwent adjuvant chemotherapy after hepatectomy in 2013–2017 group (50.7% vs. 67.2%, $p < .001$; Table S6) might have impact for the results of RFS in both groups as well. Furthermore, multidisciplinary treatment including infusional fluorouracil, leucovorin, and oxaliplatin/irinotecan (FOLFOX/FOLFIRI) therapy or molecular targeting agents might contribute to improve OS in the 2013–2017 data than the 2005–2007 data. However, no evidence was shown in the present study and further precise study should be warranted. In addition, the definitive reason for the disparities of OS and RFS is unclear, but differences in the follow-up periods might have affected the results. Although RFS had reportedly strong correlation with OS in CRLM,⁹ several reports showed the discrepancy between RFS and OS.^{14–17}

This study identified various independent prognostic predictors in patients who underwent hepatectomy for CRLM. However, regarding perioperative chemotherapy, both pre-/postoperative chemotherapy had significant impact for prognoses in the univariate analyses but none was selected as an independent prognosticator in multivariate analyses. The patients underwent preoperative chemotherapy showed poorer survival than those with no preoperative chemotherapy in both OS and RFS. However, since the definition of neoadjuvant, induction chemotherapy, or conversion chemotherapy was not unified in the present study, it was difficult to show clear evidence in the present study. Regarding postoperative chemotherapy, although the RFS was reportedly shown to be improved by adjuvant chemotherapy after hepatectomy

for CRLM.^{16,18–20} However, its impact for OS is inconsistent.^{16,18–20} The patients who underwent postoperative chemotherapy showed better survival in both OS and RFS in the present study only in univariate analysis. Nevertheless, since the data regarding perioperative chemotherapy showed some lacks in the present data, enough evidence was difficult to show.

Concomitant extrahepatic metastasis was selected as an independent predictor of RFS. Our previous study using data from 2005 to 2007 reported that the prognosis is more favorable for controllable lung metastasis than for distant lymph node metastasis or peritoneal dissemination.⁷ More detailed stratification of extrahepatic metastasis is required to select good candidates for resection of CRLM in patients with concomitant extrahepatic metastasis.

The present multivariate analysis selected lymph node metastases as an independent prognostic factor associated with the primary lesion. Many previous studies reported similar results.^{14,17,21–29} Although the present study highlights the importance of pathological findings of the primary lesion, its curability was not considered. Studies addressing the curability of primary lesions for the prognosis of CRLM should be considered.

Regarding preoperative tumor marker values, the present study identified CA19-9 levels >100 U/mL as an independent predictor of prognosis, whereas CEA >100 ng/mL were not considered. Hazard ratios (HRs) of CA19-9 >100 U/mL in the present study were higher for both OS and RFS than for other factors (1.698 and 1.476, respectively). Several studies have also shown a greater hazard ratio for CA19-9 than for CEA as a prognostic predictor in resectable CRLM.^{21,29–31} Although previous studies have reported that high CEA values are strong independent predictors of patient survival,^{22–28} these studies did not evaluate CA19-9 values. However, because the cutoff values varied among studies, further studies are needed to evaluate the usefulness of tumor markers in clinical practice.

Regarding the characteristics of CRLM, the number of CRLM was identified as an independent predictor of poor prognosis, whereas the CRLM diameter was not selected. Previous reports have shown that the hazard ratio for long-term prognosis is greater in tumors than in tumors.^{8,11,32} We previously published a novel H classification that focused more on tumor number than tumor size using data from 2005 to 2007.⁸ Number of CRLM ≥ 5 , which is high risk factor of recurrences, should be considered carefully for the indication of hepatectomy,^{32–35} and was selected as independent predictor of RFS in the present study. Not only for tumor recurrences, CRLM number ≥ 5 showed higher hazard ratio for OS than CRLM number 2–4 in the previous study (hazard ratio 2.69 and

1.51 with reference to solitary CRLM) which enrolled the patients in 2000–2004.¹⁴ However, the number of CRLM ≥ 5 was not selected as independent predictor of OS in the present study and its reason was unclear.

R2 resection was found to be the strongest independent predictor of OS. However, the surgical curability of R1 was not selected as an independent prognostic factor for either OS or RFS in patients who underwent hepatectomy for CRLM. Recently, for patients who underwent preoperative chemotherapy, several studies have shown a positive prognostic impact of hepatectomy, even in those who underwent R1 resection.^{36,37} Recent studies evaluated the prognostic impact of various types of R1, such as tumor exposure in adjacent major vessels.³⁸ Further studies are necessary to more precisely evaluate the relevance of R1.

Nonlaparoscopic approach was selected as independent predictor of poor RFS in the present study. Laparoscopic approach was significantly increased in the 2013–2017 data than that from the 2005–2007 data (Table 3). Although the patient selection criteria for laparoscopic surgery might have impact for RFS in the present study, no evidence was shown. Further precise study such as evaluating the difficulty of the laparoscopic procedure is needed.

A major limitation of this study was the single ethnicity of the patients. Furthermore, this study did not cover all the data of patients with CRLM in Japan. In addition, data were lacking because of the retrospective study design. As the database used in the present study was created in 2014, the latest important information, such as *BRAF* status, was not collected.^{2,39–41} Therefore, we are attempting to create a new database system. However, we believe that this study will be of use to physicians wishing to use our nationwide database to conduct meaningful studies for further development of treatments for CRLM and will also be of value to physicians involved in CRLM treatment. In conclusion, analyses conducted using a nationwide database system of patients diagnosed with CRLM revealed a transition in the characteristics of CRLM and various prognosticators in patients who underwent hepatectomy. The OS in the 2013–2017 data was better than that in the 2005–2007 data, although patients with more advanced CRLM were included.

AFFILIATIONS

¹Joint Committee for Nationwide Survey on Colorectal Liver Metastasis

²Department of Surgery, Graduate School of Medicine, Kyoto University 54 Kawahara-Cho, Shogoin, Sakyo-Ku, Kyoto, Japan

³Department of Surgery, Yamaga City Medical Center 511 Yamaga, Kumamoto, Japan

⁴Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University 8-1 Kawada-Cho, Shinjuku-ku Tokyo, Japan

⁵Department of Surgery, Sano City Hospital, Sano Tochigi, Japan

⁶Department of Surgery, Utsunomiya Memorial Hospital, Utsunomiya Tochigi, Japan

⁷Grace Home Care Clinic Ito, Shizuoka, Japan

⁸Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Kanazawa-ku Yokohama, Kanagawa, Japan

⁹Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo, Bunkyo-ku Tokyo, Japan

¹⁰Saiseikai Kazo Hospital, Kazo Saitama, Japan

¹¹Japanese Red Cross Omori Hospital, Ota-ku Tokyo, Japan

¹²Department of Hepatobiliary-Pancreatic Surgery, Juntendo University Graduate School of Medicine, Bunkyo-ku Tokyo, Japan

¹³Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital East, Kashiwa-shi Chiba, Japan

¹⁴Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku Tokyo, Japan

¹⁵Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku Tokyo, Japan

¹⁶Department of Pediatrics, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku Tokyo, Japan

¹⁷Department of Surgery, Teikyo University Hospital, Takatsu-ku Kawasaki, Japan

¹⁸Department of Gastrointestinal Chemotherapy, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku Tokyo, Japan

¹⁹Department of Biomedical Statistics and Bioinformatics, Graduate School of Medicine, Kyoto University, Sakyo-ku Kyoto, Japan

²⁰Division of Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences, Chuo-ku Niigata, Japan

²¹International University of Health and Welfare, Narita Hospital, Minato-ku Tokyo, Japan

²²Tokyo Medical and Dental University, Bunkyo-ku Tokyo, Japan

ACKNOWLEDGMENTS

Funding for this study was provided by Nakayama Cancer Research Institute. The funding source played no role in the study design, execution, or analysis. The authors appreciate the considerable contributions of the physicians who registered the data of patients with CRLM in this registry. The participating departments and their respective institutions are listed in Table S8.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflicts of interest to disclose regarding this study.

ORCID

Katsunori Sakamoto  <https://orcid.org/0000-0002-6431-0011>

<https://orcid.org/0000-0002-6431-0011>

Toru Beppu  <https://orcid.org/0000-0001-9046-0454>

Goro Honda  <https://orcid.org/0000-0002-1162-4535>

Itaru Endo  <https://orcid.org/0000-0001-5520-8114>

Shin Kobayashi  <https://orcid.org/0000-0001-9321-8452>

Ken Tabuchi  <https://orcid.org/0000-0001-7739-8780>

REFERENCES

- Imai K, Adam R, Baba H. How to increase the resectability of initially unresectable colorectal liver metastases: a surgical perspective. *Ann Gastroenterol Surg*. 2019;3(5):476–86. <https://doi.org/10.1002/ags3.12276>
- Yamamoto M, Yoshida M, Furuse J, Sano K, Ohtsuka M, Yamashita S, et al. Clinical practice guidelines for the management of liver metastases from extrahepatic primary cancers 2021. *J Hepatobiliary Pancreat Sci*. 2021;28(1):1–25. <https://doi.org/10.1002/jhbp.868>
- Takematsu T, Mima K, Hayashi H, Kitano Y, Nakagawa S, Hiyoshi Y, et al. RAS mutation status in combination with the JSHBPS nomogram may be useful for preoperative identification of colorectal liver metastases with high risk of recurrence and mortality after hepatectomy. *J Hepatobiliary Pancreat Sci*. 2024;31(2):69–79. <https://doi.org/10.1002/jhbp.1389>
- Sakano Y, Matoba D, Noda T, Kobayashi S, Yamada D, Tomimaru Y, et al. Clinical significance of ribosomal protein S15 expression in patients with colorectal cancer liver metastases. *J Hepatobiliary Pancreat Sci*. 2024;31(9):611–24. <https://doi.org/10.1002/jhbp.12012>
- Sakamoto K, Honda G, Beppu T, Kotake K, Yamamoto M, Takahashi K, et al. Comprehensive data of 3,820 patients newly diagnosed with colorectal liver metastasis between 2005 and 2007: report of a nationwide survey in Japan. *J Hepatobiliary Pancreat Sci*. 2018;25:115–23.
- Kobayashi S, Beppu T, Honda G, Yamamoto M, Takahashi K, Endo I, et al. Survival benefit of and indications for adjuvant chemotherapy for resected colorectal liver metastases—a Japanese nationwide survey. *J Gastrointest Surg*. 2019;24:1244–60. <https://doi.org/10.1007/s11605-019-04250-9>
- Sawada Y, Sahara K, Endo I, Sakamoto K, Honda G, Beppu T, et al. Long-term outcome of liver resection for colorectal metastases in the presence of extrahepatic disease: a multi-institutional Japanese study. *J Hepatobiliary Pancreat Sci*. 2020;27(11):810–8. <https://doi.org/10.1002/jhbp.810>
- Beppu T, Imai K, Honda G, Sakamoto K, Kobayashi S, Endo I. Et al; joint Committee for Nationwide Survey on colorectal liver metastasis. Proposal of a novel H category-based classification of colorectal liver metastases based on a Japanese nationwide survey. *J Hepatobiliary Pancreat Sci*. 2021 Apr;28(4):317–26. <https://doi.org/10.1002/jhbp.920>
- Kataoka K, Takahashi K, Takeuchi J, Ito K, Beppu N, Ceelen W, et al. Correlation between recurrence-free survival and overall survival after upfront surgery for resected colorectal liver metastases. *Br J Surg*. 2023;110(7):864–9. <https://doi.org/10.1093/bjs/znad127>
- Sakamoto K, Honda G, Beppu T, Kotake K, Yamamoto M, Takahashi K, et al. Comprehensive data of 3525 patients newly diagnosed with colorectal liver metastasis between 2013 and 2014: 2nd report of a nationwide survey in Japan. *J Hepatobiliary Pancreat Sci*. 2020;27(8):555–62. <https://doi.org/10.1002/jhbp.738>
- Sakamoto K, Beppu T, Honda G, Kotake K, Yamamoto M, Takahashi K, et al. Comprehensive data of 4502 patients newly diagnosed with colorectal liver metastasis between 2015 and 2017, and prognostic data of 2427 patients newly diagnosed with colorectal liver metastasis in 2013 and 2014: third report of a nationwide survey in Japan. *J Hepatobiliary Pancreat Sci*. 2023;30(5):570–90. <https://doi.org/10.1002/jhbp.1252>
- Miura F, Yamamoto M, Gotoh M, Konno H, Fujimoto J, Yanaga K, et al. Validation of the board certification system for expert surgeons (hepato-biliary-pancreatic field) using the data of the national clinical database for Japan. Part 1: hepatectomy of more than 1 segment. *J Hepatobiliary Pancreat Sci*. 2016;23:313–23.
- Japanese Society for Cancer of the colon and Rectum. General rules for clinical and pathological studies on cancer of the colon, Rectum and anus. 7th ed. Revised Version Tokyo: Kanehara & Co.Ltd; 2009.
- Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, et al. 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*. 2012;19(1):72–84.
- Oba M, Hasegawa K, Matsuyama Y, Shindoh J, Mise Y, Aoki T, et al. Discrepancy between recurrence-free survival and overall survival in patients with resectable colorectal liver metastases: a potential surrogate endpoint for time to surgical failure. *Ann Surg Oncol*. 2014;21(6):1817–24. <https://doi.org/10.1245/s10434-014-3504-1>
- Kanemitsu Y, Shimizu Y, Mizusawa J, Inaba Y, Hamaguchi T, Shida D. Et al; JCOG colorectal cancer study group. Hepatectomy followed by mFOLFOX6 versus hepatectomy alone for liver-only metastatic colorectal cancer (JCOG0603): a phase II or III randomized controlled trial. *J Clin Oncol*. 2021;39(34):3789–99. <https://doi.org/10.1200/JCO.21.01032> Epub 2021 Sep 14.
- Saiura A, Yamamoto J, Hasegawa K, Koga R, Sakamoto Y, Hata S, et al. Liver resection for multiple colorectal liver metastases with surgery up-front approach: bi-institutional analysis of 736 consecutive cases. *World J Surg*. 2012;36(9):2171–8. <https://doi.org/10.1007/s00268-012-1616-y> PMID: 22547015.
- Hasegawa K, Saiura A, Takayama T, Miyagawa S, Yamamoto J, Ijichi M, et al. Adjuvant Oral uracil-tegafur with leucovorin for colorectal cancer liver metastases: a randomized controlled trial. *PLoS One*. 2016;11(9):e0162400. <https://doi.org/10.1371/journal.pone.0162400>
- Kobayashi S, Bando H, Taketomi A, Takamoto T, Shinozaki E, Shiozawa M, et al. NEXUS trial: a multicenter phase II clinical study evaluating the efficacy and safety of the perioperative use of encorafenib, binimetinib, and cetuximab in patients with previously untreated surgically resectable BRAF V600E mutant colorectal oligometastases. *BMC Cancer*. 2023;23(1):779. <https://doi.org/10.1186/s12885-023-11311-5>
- Yoshizaki Y, Kawaguchi Y, Seki Y, Sasaki S, Ichida A, Akamatsu N, et al. Posthepatectomy but not prehepatectomy chemotherapy was associated with a longer time to recurrence in patients with resectable colorectal liver metastases: inverse probability of treatment weighting analysis. *J Hepatobiliary Pancreat Sci*. 2023;30(8):1006–14. <https://doi.org/10.1002/jhbp.1314>
- Passot G, Denbo JW, Yamashita S, Kopetz SE, Chun YS, Maru D, et al. Is hepatectomy justified for patients with RAS mutant colorectal liver metastases? An analysis of 524 patients undergoing curative liver resection. *Surgery*. 2017;161(2):332–40.
- Vauthey JN, Zimmitti G, Kopetz SE, Shindoh J, Chen SS, Andreou A, et al. RAS mutation status predicts survival and

- patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg*. 2013;258(4):619–27.
23. Smith MD, McCall JL. Systematic review of tumour number and outcome after radical treatment of colorectal liver metastases. *Br J Surg*. 2009;96(10):1101–13.
 24. Hamady ZZ, Lodge JP, Welsh FK, Toogood GJ, White A, John T, et al. One-millimeter cancer-free margin is curative for colorectal liver metastases: a propensity score case-match approach. *Ann Surg*. 2014;259(3):543–8.
 25. Sadot E, Groot Koerkamp B, Leal JN, Shia J, Gonen M, Allen PJ, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? *Ann Surg*. 2015;262(3):476–85.
 26. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230(3):309.
 27. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A, et al. The Tumor Burden Score: A New "Metro-ticket" Prognostic Tool For Colorectal Liver Metastases Based on Tumor Size and Number of Tumors. *Ann Surg*. 2018;267(1):132–41.
 28. Minagawa M, Yamamoto J, Kosuge T, Matsuyama Y, Miyagawa S, Makuuchi M. Simplified staging system for predicting the prognosis of patients with resectable liver metastasis: development and validation. *Arch Surg*. 2007;142(3):269–77.
 29. Imai K, Allard MA, Castro Benitez C, Vibert E, Sa Cunha A, Cherqui D, et al. Nomogram for prediction of prognosis in patients with initially unresectable colorectal liver metastases. *Br J Surg*. 2016;103(5):590–9. <https://doi.org/10.1002/bjs.10073>
 30. Hallet J, Sa Cunha A, Adam R, Goéré D, Bachellier P, Azoulay D, et al. French colorectal liver metastases working group, association Française de Chirurgie (AFC). Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg*. 2016;103(10):1366–76.
 31. Kobayashi K, Ono Y, Kitano Y, Oba A, Sato T, Ito H, et al. Prognostic impact of tumor markers (CEA and CA19-9) on patients with Resectable colorectal liver metastases stratified by tumor number and size: potentially valuable biologic markers for preoperative treatment. *Ann Surg Oncol*. 2023;30(12):7338–47. <https://doi.org/10.1245/s10434-023-13781-0>
 32. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386–422. <https://doi.org/10.1093/annonc/mdw235>
 33. Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, et al. Optimal cut-off value for the number of colorectal liver metastases: a project study for hepatic surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci*. 2014;21(3):169–75.
 34. Beppu T, Yamamura K, Imai K, Hayashi H, Miyamoto Y. Recurrence-risk stratification using the Beppu score and selection of perioperative chemotherapy for colorectal liver metastases. *J Surg Oncol*. 2024;129(5):893–900. <https://doi.org/10.1002/jso.27590>
 35. Beppu T, Yamamura K, Sakamoto K, Honda G, Kobayashi S, Endo I, et al. Joint Committee for Nationwide Survey on colorectal liver metastasis. Validation study of the JSHBPS nomogram for patients with colorectal liver metastases who underwent hepatic resection in the recent era - a nationwide survey in Japan. *J Hepatobiliary Pancreat Sci*. 2023;30(5):591–601. <https://doi.org/10.1002/jhbp.1256>
 36. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg*. 2008;248(4):626–37. [18936576](https://doi.org/10.1093/ajpgut/119.3.626)
 37. Ayez N, Lalmahomed ZS, Eggermont AM, Ijzermans JN, de Jonge J, van Montfort K, et al. Outcome of microscopic incomplete resection (R1) of colorectal liver metastases in the era of neoadjuvant chemotherapy. *Ann Surg Oncol*. 2012;19(5):1618–27.
 38. Viganò L, Procopio F, Cimino MM, Donadon M, Gatti A, Costa G, et al. Is tumor detachment from vascular structures equivalent to R0 resection in surgery for colorectal liver metastases? An Observational Cohort *Ann Surg Oncol*. 2016;23(4):1352–60.
 39. Gagnière J, Dupré A, Gholami SS, Pezet D, Boerner T, Gönen M, et al. Is hepatectomy justified for BRAF mutant colorectal liver metastases?: a multi-institutional analysis of 1497 patients. *Ann Surg*. 2018;271:147–54. <https://doi.org/10.1097/SLA.0000000000002968>
 40. Modest DP, Ricard I, Heinemann V, Hegewisch-Becker S, Schmiegel W, Porschen R, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. *Ann Oncol*. 2016;27(9):1746–53. <https://doi.org/10.1093/annonc/mdw261>
 41. Margonis GA, Buettner S, Andreatos N, Kim Y, Wagner D, Sasaki K, et al. Association of BRAF Mutations with Survival and Recurrence in Surgically Treated Patients With Metastatic Colorectal Liver Cancer. *JAMA Surg*. 2018;153(7):e180996. <https://doi.org/10.1001/jamasurg.2018.0996>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sakamoto K, Beppu T, Honda G, Kotake K, Yamamoto M, Takahashi K, et al. Comprehensive data of 5085 patients newly diagnosed with colorectal liver metastasis between 2013 and 2017: Fourth report of a nationwide survey in Japan. *J Hepatobiliary Pancreat Sci*. 2025;32:26–43. <https://doi.org/10.1002/jhbp.12078>