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Characteristics of Five-year Survivors After Liver Resection for Colorectal Liver Metastases in Modern Chemotherapy

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Abstract. *Background/Aim: The aim of this study was to evaluate whether modern chemotherapy has changed characteristics of actual five-year survivors after liver resection for colorectal liver metastasis (CRLM). Patients and Methods: The records of 210 patients, who underwent curative liver resection for CRLM at our institution between January 1990 and May 2014, were reviewed. The patients treated before 2004 when modern chemotherapy was not introduced were compared with the patients treated after 2005. Results: Actual five-year survivor rates were significantly higher after 2005 (33.3% vs. 49.0%, p=0.022). Preoperative characteristics of actual five-year survivors were not different. The median survival time after non-resectable recurrence was significantly longer after 2005 (20.3 vs. 8.7 months, p=0.002). The proportion of 5-year survivors with recurrent site was significantly higher after 2005 (34.0% vs. 10.5%, p=0.019). Conclusion: Actual five-year survivors have increased by modern chemotherapy. However, approximately one-third of them were not cured.*

The development of modern chemotherapies, including oxaliplatin, irinotecan and molecular-targeted drugs, including bevacizumab, cetuximab, and panitumumab, has improved the prognosis of metastatic colorectal cancer (CRC) (1-3). As a result, the median survival time (MST) for patients with non-resectable metastatic CRC has increased to more than 30 months (4). Surgical resection of metastatic regions, such as colorectal liver metastases (CRLM), pulmonary metastasis, and peritoneal metastasis, may also substantially extend the long-term survival of patients with metastatic CRC (5-7). For patients with CRLM, liver resection represents the only chance for a cure. Also, perioperative chemotherapy using modern chemotherapies has become an option for patients with CRLM (8, 9). Combining modern chemotherapy with liver resection may have a synergistic effect. Indeed, the five-year survival rate after liver resection for CRLM has reached approximately 50% (10, 11). However, many reports have included censored cases because of the relatively short observation periods (12-14). The five-year survival rates in these reports were estimated and were, therefore, not the actual five-year survival rates. Moreover, it has been reported that nearly one-third of the actual five-year survivors suffer cancer-related deaths (15-17). Therefore, cure remains elusive for patients with CRLM. It has been reported that 97% of actual 10-year survivors remain disease-free (18). However, because 10 years is too long a period to evaluate the therapeutic effect, the five-year survival rate is generally used as an indicator for the efficacy of liver resection for CRLM. However, few reports have been focused on the actual five-year survival after liver resection for CRLM (15-17). Furthermore, the patients evaluated in these reports underwent liver resection before 2004, when modern chemotherapies were not available. After 2005, modern chemotherapies became available and have since been used for non-resectable metastatic CRC and perioperative adjuvant chemotherapies (4, 8). The development of modern chemotherapies may have affected the five-year survival rate and five-year survivors' characteristics. However, to date, no reports have focused on the impact of modern chemotherapies based on actual, rather than estimated, five-year survivors who underwent liver resection for CRLM.

In this study, we compared the outcomes for patients who underwent liver resection before 2004 with the outcomes for those treated after 2005. Modern chemotherapies, including FOLOX and FOLFIRI were introduced to Japan in 2005, and molecular-targeted drugs, including bevacizumab, cetuximab, and panitumumab, became available afterwards. This study aimed to clarify whether modern chemotherapies affected the proportion and characteristics of actual five-year survivors after liver resection for CRLM.

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Key Words: Colorectal liver metastasis, CRLM, actual 5-year survivor, modern chemotherapy.

Patients and Methods

Study population. Between January 1990 and May 2014, the records of 210 patients who underwent curative liver resection for CRLM at Nara Medical University Hospital, Nara, Japan, were reviewed retrospectively. All patients were followed until death or for more than five years. The patients were divided into two groups, those who underwent liver resection before 2004, when modern chemotherapy was not available, and those who underwent liver resection after 2005, when modern chemotherapy could have been used. This study was approved by the ethics committee of Nara Medical University (No. 2376). Written informed consent for clinical research was obtained before liver resection, and an opt-out notification for this study was presented on our department's website.

Preoperative evaluation. Preoperative evaluation of patients with CRLM included a physical examination, routine blood biochemistry tests, and indocyanine green (ICG) tests, abdominal imaging by enhanced computed tomography (CT), enhanced magnetic resonance imaging, and chest imaging by CT. Assays for carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were also performed. Results of CEA and CA19-9 on a month before surgery were used for analysis. The indications for liver resection at our institution are as follows: First, all tumors are resectable, and the remnant liver is expected to be >35% of the standard liver volume (SLR). Second, the biochemistry and ICG test results satisfy Makuuchi's criteria (19, 20). Third, the primary CRC was previously resected or resectable. Fourth, there are no extrahepatic metastases or, if there are, all are resectable.

Treatment strategy. During the study period, up-front surgery was essentially applied for initially resectable CRLM in our institution. Therefore, preoperative chemotherapy was not routinely administered for initially resectable CRLM. Patients who had undergone chemotherapy for resectable CRLM at other hospitals were included in this study. Patients whose CRLM were converted from non-resectable to resectable were also included. Postoperative adjuvant chemotherapy was administered routinely, except for patients with poor performance status and those with a low risk of recurrence (*e.g.*, metachronous solitary CRLM). In the period before 2004, the main adjuvant chemotherapy regimen consisted of arterial infusion chemotherapy or 5-fluorouracil (5-FU)/leucovorin (LV), whereas, in the period after 2005, oxaliplatin-based regimens such as FOLFOX, XELOX, and SOX were mainly used. The main regimen of chemotherapy for non-resectable recurrence was 5-FU/LV and irinotecan before 2004, and FOLFOX, FOLFIRI and molecular-targeted drugs after 2005.

Patient management. The operative procedure and perioperative management have been reported previously (21-24). Hepatic parenchymal resection was performed with a clamp crushing technique, and an intermittent Pringle maneuver was used for almost all cases. Intraoperative ultrasound (IOUS) was used to assess the transection plane and detect occult tumors. The patients underwent CT of the thorax and abdomen every four months for up to three years after liver resection and then every six months thereafter. Repeat hepatectomy, or the resection of distant metastases, was performed if the recurrent metastases were resectable. If the recurrent metastases were non-resectable, the patients underwent chemotherapy where possible.

Statistical analysis. Continuous data were expressed as median (range) and compared using the independent-sample *t*-test or Mann–Whitney *U*-test. Categorical variables were compared with the chi-square test or Fisher's exact test, as appropriate. Survival analysis was performed with the Kaplan–Meier method. The survival curves were compared with log rank tests. A p-value<0.05 was considered to indicate statistically significant differences, and all statistical analyses were performed using SPSS for Windows version 26.0 (SPSS Inc. Armonk, NY, USA).

Results

Characteristics of patients treated before 2004 and after 2005. A total of 210 patients underwent liver resection for CRLM during the study period. All patients were followed until death or for more than five years. The median follow-up was 46.3 months (range=5.5-290 months). One hundred fourteen patients were treated before 2004, and 96 patients were treated after 2005. The patients' baseline characteristics and clinicopathological factors are summarized in Table I. The patients' median age was significantly higher after 2005 (61 *vs.* 63, p=0.011). Both preoperative and adjuvant chemotherapies were significantly more frequent after 2005 since these therapies were not administered using modern regimens before 2004. The number of tumors and the maximum tumor size of CRLMs were not significantly different between the two groups, nor were the CEA and CA19-9 levels. The Union for International Cancer Control (UICC) 7th T and N factors were not significantly different, and the proportion of patients with extrahepatic metastasis was significantly higher after 2005 (4.4% *vs.* 24.0%, p<0.001). The proportion of five-year survivors was significantly higher after 2005 (33.3% *vs.* 49.0%, p=0.022).

Perioperative chemotherapy regimens of patients treated before 2004 and after 2005. Preoperative chemotherapy regimen of patients treated before 2004 was hepatic arterial infusion (HAI). As for the patients treated after 2005, 26 patients underwent preoperative chemotherapy with modern regimens. Sixteen patients underwent FOLFOX. Among these, 4 patients were simultaneously administered bevacizumab, while 2 patients were administered cetuximab and 3 patients were administered panitumumab. Three patients underwent SOX, 2 patients underwent XELOX + bevacizumab, 3 patients underwent FOLFILI, and 2 patients underwent IRIS.

Among the patients treated before 2004 with adjuvant chemotherapy regimens, 29 cases received 5-FU/LV, 23 cases HAI, and 23 cases 5-FU. No patient underwent adjuvant chemotherapy with modern regimens. After 2005, 59 patients underwent adjuvant chemotherapy with modern regimens. Twenty-six patients underwent FOLFOX. Among these, 2 patients were simultaneously administered panitumumab, one patient was administered cetuximab, and one patient was administered bevacizumab. Another 22 patients underwent

Table I. *Characteristics of the patients with CRLM treated by liver resection before 2004 and after 2005.*

	Before 2004 n=114	After 2005 n=96	*p*-Value
Age, median (range)	61 (40-85)	63 (35-84)	0.011
Gender			
Male	70 (61.4%)	57 (59.4%)	0.765
Female	44 (38.6%)	39 (40.6%)	
Timing of liver metastasis			
Synchronous	62 (54.4%)	45 (46.9%)	0.278
Metachronous	52 (45.6%)	51 (53.1%)	
Preoperative chemotherapy			
Absent	113 (99.1%)	62 (64.6%)	<0.001
Present	1 (0.9%)	34 (35.4%)	
Preoperative chemotherapy with modern chemotherapy			
Absent	114 (100%)	70 (72.9%)	<0.001
Present	0	26 (27.1%)	
Adjuvant chemotherapy			
Absent	39 (34.2%)	19 (19.8%)	0.020
Present	75 (65.8%)	77 (80.2%)	
Adjuvant chemotherapy with modern chemotherapy			
Absent	114 (100%)	37 (38.5%)	<0.001
Present	0	59 (61.5%)	
Maximum tumor size, cm, median (range)	3.0 (0.5-15)	2.5 (0.8-20)	0.055
Tumor number, median (range)	2 (1-12)	2 (1-30)	0.624
Four or more CRLM, number	25 (21.9%)	27 (28.2%)	0.300
CEA, ng/ml, median (range)	19.4 (1.3-2,454)	11.6 (0.9-3,391)	0.137
CA19-9, U/ml, median (range)	24 (1.0-1,520)	26 (1-1,981)	0.954
Extrahepatic metastasis			
Absent	109 (95.6%)	73 (76.0%)	<0.001
Present	5 (4.4%)	23 (24.0%)	
Location of primary colorectal cancer			
Colon	69 (60.5%)	59 (61.5%)	0.890
Rectum	45 (39.5%)	37 (38.5%)	
T factor of primary colorectal canccer (UICC 7th)			
T1-3	79 (69.3%)	65 (67.7%)	0.805
T4	35 (30.7%)	31 (32.3%)	
N factor of primary colorectal cancer (UICC 7th)			
N0-1	70 (61.4%)	67 (69.8%)	0.204
N2-3	44 (38.6%)	29 (30.2%)	
Histological differentiation of primary colorectal cancer			
Well	51 (44.7%)	31 (32.3%)	0.066
Other	63 (55.3%)	65 (67.7%)	
Actual 5-year survivors	38 (33.3%)	47 (49.0%)	0.022
Actual 5-year recurrence free survivors	20 (17.5%)	22 (22.9%)	0.332

CRLM: Colorectal liver metastasis; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; UICC: Union for International Cancer Control.

XELOX and 3 of them were simultaneously administered bevacizumab. Another 8 patients underwent SOX, and 3 patients underwent IRIS. HAI or 5-FU/LV was performed in 18 patients after 2005.

Prognosis of patients treated before 2004 and after 2005. Figure 1 shows the Kaplan–Meier curves for the recurrence-free survival (RFS) and overall survival (OS) of the patients treated before 2004 and after 2005. The RFS and OS of patients treated after 2005 were not significantly different from the values for patients treated before 2004. The five-year survival rate was 48.9% after 2005 and 33.3% before 2004 (p=0.152). Figure 2 shows the RFS and OS for patients with no extrahepatic metastasis. The OS of patients treated after 2005 was significantly better than that of patients treated before 2004 (p=0.032), but no significant difference was observed in the RFS (p=0.675). The five-year survival rate was 59.6% after 2005 and 33.9% before 2004.

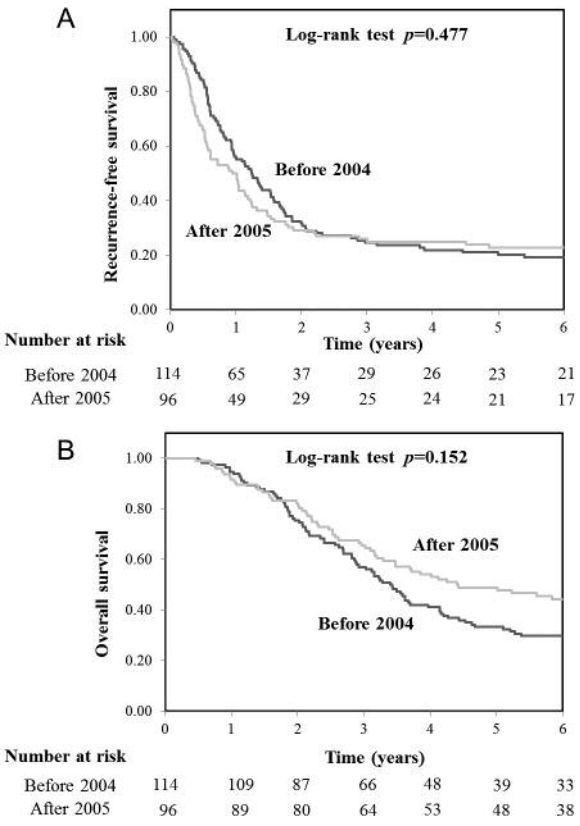

Figure 1. *Kaplan–Meier curve of recurrence-free survival (RFS) and overall survival (OS) for patients treated before 2004 and after 2005. (A) RFS did not differ significantly between the groups (p=0.477). (B) OS did not differ significantly between the groups (p=0.152).*

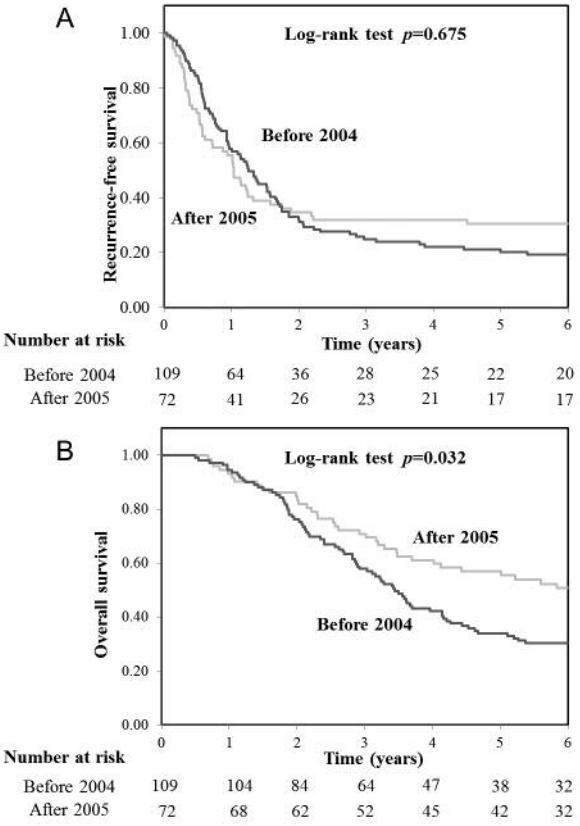

Figure 2. *Kaplan–Meier curve of recurrence-free survival (RFS) and overall survival (OS) for patients with no extrahepatic metastasis treated before 2004 and after 2005. (A) RFS did not differ significantly between the groups (p=0.675).(B) The OS for patients treated after 2005 was significantly better than that for patients treated before 2004 (p=0.032).*

Survival time after initial recurrence following resection for CRLM. Figure 3 shows the Kaplan–Meier curve for the survival time after initial recurrence following resection for CRLM. The prognosis of patients treated after 2005 was significantly better than that of patients treated before 2004 (p=0.005). The MST after recurrence was 32.4 months after 2005 and 19.9 months before 2004. Figure 4A shows the survival time after initial recurrence at a non-resectable site. The prognoses of such patients treated after 2005 were significantly better (p=0.002). The MST for these patients was 20.3 months after 2005 and 8.7 months before 2004. Figure 4B shows survival time after initial recurrence at a site that was surgically resected. There was no significant difference between such patients treated after 2005 and those treated before 2004 (p=0.309). The five-year survival rate for these patients was 45.5% after 2005 and 36.4% before 2004. *Characteristics of 5-year survivors and non-survivors who underwent liver resection for CRLM before 2004 and after 2005*. Table II summarizes the baseline characteristics and clinicopathological factors of the five-year survivors and non-survivors treated before 2004 and after 2005. Before 2004, the number of tumors found in five-year survivors was significantly lower than that in non-survivors (p=0.033). The proportion of four or more CRLMs was significantly higher in non-survivors (p=0.038), as was the proportion of stage N2-3 tumors (p=0.044). After 2005, the number of tumors and the proportion of four or more CRLMs were not significantly different between the five-year survivors and the non-survivors. The proportion of stage N2-3 tumors remained significantly higher in non-survivors (p<0.001). Further, the proportion of extrahepatic metastasis was significantly higher in non-survivors (p=0.007), and the proportion of patients who underwent preoperative chemotherapy was significantly higher in the non-survivors (25.5% *vs*. 44.9%, p=0.047). The maximum tumor size was significantly smaller in the five-year survivors (p=0.031). Additionally, the preoperative CEA and CA19-9 levels were significantly lower in the five-year

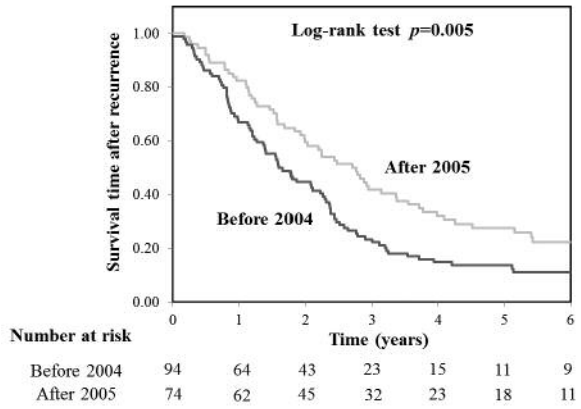

Figure 3. *Kaplan–Meier curve of survival time after recurrence for patients treated before 2004 and after 2005. The prognosis of patients treated after 2005 was significantly better than that of patients treated before 2004 (p=0.005). The median survival time was 32.4 months for patients treated after 2005 and 19.9 months for those treated before 2004.*

survivors (CEA; 9.0 *vs*. 19.0 ng/ml, p=0.004, CA19-9; 22.0 *vs*. 39.0 U/ml, p=0.035).

Characteristics of 5-year survivors who underwent liver resection for CRLM before 2004 and after 2005. Table III presents a comparison of the baseline characteristics and clinicopathological factors of the five-year survivors treated before 2004 and after 2005. The proportion of preoperative chemotherapy was significantly higher after 2005 (2.6% *vs*. 25.5%, p=0.004), while that of adjuvant chemotherapy was not significantly different (57.9% *vs*. 61.7%, p=0.722). None of the patients received preoperative or adjuvant chemotherapy using modern regimens before 2004. The maximum tumor size was also significantly smaller after 2005 (3.0 cm *vs*. 2.3 cm, p=0.017). The proportion of T3-4, N2-3, and extrahepatic metastasis was not significantly different before 2004 and after 2005. The preoperative CEA and CA19-9 levels were also not significantly different.

Prognostic status of 5-year survivors who underwent liver resection for CRLM before 2004 and after 2005. Table IV summarizes the status of the five-year survivors treated before 2004 and after 2005. Twenty out of 38 five-year survivors (52.5%) were recurrence-free before 2004, whereas 22 out of 47 (46.8%) were recurrence-free after 2005 (p=0.593). Before 2004, 14 of 18 (77.8%) patients with recurrence underwent repeat surgery and 21 of 25 (84.0%) did so after 2005 (p=0.701). The proportion of patients who had recurrent site at five years after the initial liver resection was significantly higher after 2005 (34.0% *vs*. 10.5%, p=0.019). The time to recurrence among these patients after initial liver resection was significantly shorter after 2005 (1.03 years *vs*. 2.90 years, p=0.014).

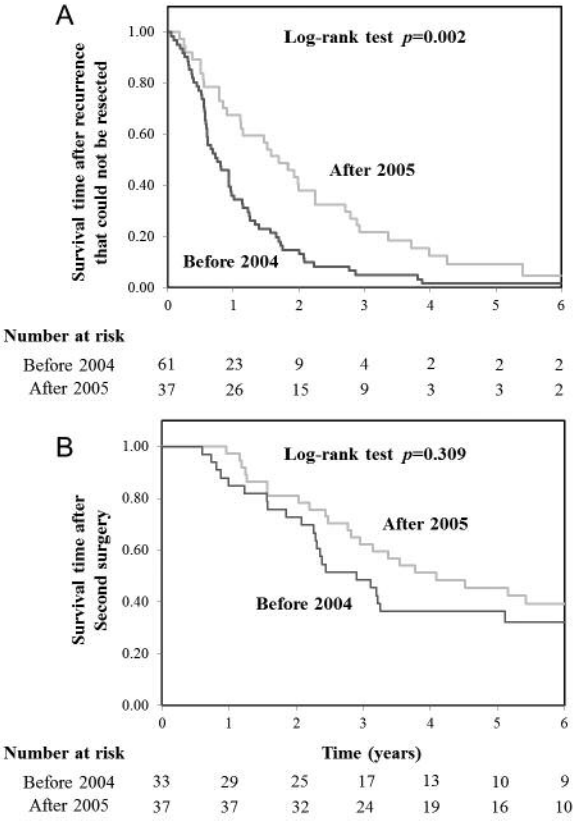

Figure 4. *Kaplan–Meier curves of survival times after recurrence for patients with non-resectable sites and those that could be surgically resected. (A) Kaplan–Meier curve of survival time after recurrence for patients with recurrent, non-resectable sites. The prognoses of patients treated after 2005 was significantly better than that of patients treated before 2004 (p=0.002). The median survival time was 20.3 months for patients treated after 2005 and 8.7 months for those treated before 2004. (B) Kaplan–Meier curve of survival time after recurrence for patients with recurrent sites that could be surgically resected. The prognoses of patients treated after 2005 was not significantly different than those of patients treated before 2004 (p=0.309).*

Discussion

The present study compared patients with CRLM who were treated before 2004 and after 2005. All patients were followed until death or for more than five years, which enabled the investigation of actual five-year survival rates and the characteristics of actual five-year survivors. Patients treated with modern chemotherapy (after 2005) were also compared with those treated without modern chemotherapy (before 2004). Therefore, the impact of modern chemotherapy on actual five-year survivors could be evaluated in this study.

Patients treated after 2005 were significantly older, and had a higher rate of extrahepatic metastasis, than those treated before 2004. Evolution of chemotherapy might

Table II. *Characterictics of five-year survivors and non-survivors who underwent liver resection for CRLM before 2004 and after 2005.*

	Before 2004			After 2005		
	5-year survivor n=38	Non-survivor n=76	*p*-Value	5-year survivor n=47	Non-survivor n=49	*p*-Value
Age, median (range)	59.5 (40-75)	62.5 (43-85)	0.328	63 (35-75)	66 (38-84)	0.253
Gender						
Male	23 (60.5%)	47 (61.8%)	0.892	27 (57.4%)	30 (61.2%)	0.706
Female	15 (39.5%)	29 (38.2%)		20 (42.6%)	19 (38.8%)	
Timing of liver metastasis						
Synchronous	18 (47.4%)	44 (57.9%)	0.288	20 (42.6%)	25 (51.0%)	0.406
Metachronous	20 (52.6%)	32 (42.1%)		27 (57.4%)	24 (49.0%)	
Preoperative chemotherapy						
Absent	37 (97.4%)	76 (100%)	0.333	35 (74.5%)	27 (55.1%)	0.047
Present	1 (2.6%)	0		12 (25.5%)	22 (44.9%)	
Preoperative chemotherapy with modern chemotherapy						
Absent	38 (100%)	76 (100%)	1,000	37 (78.7%)	35 (71.4%)	0.409
Present	0	0		10 (21.3%)	14 (28.6%)	
Adjuvant chemotherapy						
Absent	12 (31.6%)	27 (35.5%)	0.675	18 (38.3%)	21 (42.9%)	0.649
Present	26 (68.4%)	49 (64.5%)		29 (61.7%)	28 (57.1%)	
Adjuvant chemotherapy with modern chemotherapy						
Absent	38 (100%)	76 (100%)	1,000	27 (57.4%)	32 (65.3%)	0.429
Present	0	0		20 (42.6%)	17 (34.7%)	
Maximum tumor size, cm, median (range)	3.0 (0.5-13.5)	3.1 (0.8-15)	0.652	2.3 (0.8-10.0)	3.0 (1.0-20.0)	0.031
Tumor number, median (range)	1 (1-12)	2 (1-10)	0.033	2 (1-17)	2 (1-30)	0.210
Four or more CRLM, number	4 (10.5%)	21 (27.6%)	0.038	9 (19.1%)	18 (36.7%)	0.055
CEA, ng/ml, median (range)	10.1 (1.1-592)	25.0 (1.5-2,454)	0.074	9.0 (0.9-337)	19.0 (1.0-3,391)	0.004
CA19-9, U/ml, median (range)	16.3 (2-612)	31.0 (1.0-1,520)	0.057	22.0 (1.0-166)	39.0 (5.0-1,981)	0.035
Extrahepatic metastasis						
Absent	37 (97.4%)	72 (94.7%)	0.663	41 (87.2%)	31 (63.3%)	0.007
Present	1 (2.6%)	4 (5.3%)		6 (12.8%)	18 (36.7%)	
Location of primary colorectal cancer						
Colon	24 (63.2%)	45 (59.2%)	0.684	30 (63.8%)	29 (59.2%)	0.640
Rectum	14 (36.8%)	31 (40.8%)		17 (36.2%)	20 (40.8%)	
T factor of primary colorectal canccer (UICC 7th)						
T1-3	27 (71.1%)	52 (68.4%)	0.774	32 (68.1%)	33 (67.3%)	0.938
T4	11 (28.9%)	24 (31.6%)		15 (31.9%)	16 (32.7%)	
N factor of primary colorectal cancer (UICC 7th)						
N0-1	31 (81.6%)	48 (63.2%)	0.044	41 (87.2%)	27 (55.1%)	<0.001
N2-3	7 (18.4%)	28 (36.8%)		6 (12.8%)	22 (44.9%)	
Histological differentiation of primary colorectal cancer						
Well	17 (44.7%)	33 (43.4%)	0.894	21 (44.7%)	24 (49.0%)	0.673
Other	21 (55.3%)	43 (56.6%)		26 (55.3%)	25 (51.0%)	

CRLM: Colorectal liver metastasis; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; UICC: Union for International Cancer Control.

expand the surgical indications for CRLM with extrahepatic metastasis. However, the maximum tumor size, the tumor number, and the proportion of four or more CRLMs were not significantly different before 2004 and after 2005. These results demonstrated that the surgical indication for CRLM, determined based on the amount of remnant liver and liver function was not different before 2004 and after 2005. The proportions of preoperative and adjuvant chemotherapy were significantly higher after 2005. Before 2004, modern chemotherapy was not available. Therefore, the proportions of preoperative and adjuvant chemotherapy with modern regimens were naturally higher after 2005.

The proportion of five-year survivors was significantly higher after 2005 than before 2004 (49.0% *vs.* 33.3%, $p=0.022$). However, according to the log rank test results, the RFS and OS of the patients were not significantly different (Figure 1). As the proportion of patients with extrahepatic metastasis was significantly higher after 2005 (24.0% *vs.* 4.4%, $p<0.001$), the log rank test was repeated excluding patients with extrahepatic metastasis. The results

Table III. *Characteristics of five-year survivors who underwent liver resection for CRLM before 2004 and after 2005.*

	Before 2004 n=38	After 2005 n=47	*p*-Value
Age, median (range)	59.5 (40-75)	63 (35-75)	0.058
Gender			
Male	23 (60.5%)	27 (57.4%)	0.774
Female	15 (39.5%)	20 (42.6%)	
Timing of liver metastasis			
Synchronous	18 (47.4%)	20 (42.6%)	0.657
Metachronous	20 (52.6%)	27 (57.4%)	
Preoperative chemotherapy			
Absent	37 (97.4%)	35 (74.5%)	0.004
Present	1 (2.6%)	12 (25.5%)	
Preoperative chemotherapy with modern chemotherapy			
Absent	38 (100%)	37 (78.7%)	0.002
Present	0	10 (21.3%)	
Adjuvant chemotherapy			
Absent	12 (31.6%)	18 (38.3%)	0.675
Present	26 (68.4%)	29 (61.7%)	
Adjuvant chemotherapy with modern chemotherapy			
Absent	38 (100%)	27 (57.4%)	<0.001
Present	0	20 (42.6%)	
Maximum tumor size, cm, median (range)	3.0 (0.5-13.5)	2.3 (0.8-10.0)	0.017
Tumor number, median (range)	1 (1-12)	2 (1-17)	0.290
Four or more CRLM, number	4 (10.5%)	9 (19.1%)	0.368
CEA, ng/ml, median (range)	10.1 (1.1-592)	9.0 (0.9-337)	0.267
CA19-9, U/ml, median (range)	16.3 (2-612)	22.0 (1.0-166)	0.819
Extrahepatic metastasis			
Absent	37 (97.4%)	41 (87.2%)	0.093
Present	1 (2.6%)	6 (12.8%)	
Location of primary colorectal cancer			
Colon	24 (63.2%)	30 (63.8%)	0.949
Rectum	14 (36.8%)	17 (36.2%)	
T factor of primary colorectal canccer (UICC 7th)			
T1-2	27 (71.1%)	32 (68.1%)	0.768
T3-4	11 (28.9%)	15 (31.9%)	
N factor of primary colorectal cancer (UICC 7th)			
N0-1	31 (81.6%)	41 (87.2%)	0.471
N2-3	7 (18.4%)	6 (12.8%)	
Histological differentiation of primary colorectal cancer			
Well	17 (44.7%)	21 (44.7%)	0.996
Other	21 (55.3%)	26 (55.3%)	

CRLM: Colorectal liver metastasis; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; UICC: Union for International Cancer Control.

showed that the OS of patients treated after 2005 was significantly better than that of patients treated before 2004 (p=0.032), whereas a significant difference was not observed in RFS (Figure 2). Based on these results, the OS and the proportion of actual five-year survivors after liver resection for CRLM appear to have improved after 2005.

For patients who experienced recurrence after liver resection for CRLM, the survival time after recurrence was significantly longer after 2005 (Figure 3). These patients were divided into resectable and non-resectable groups. The prognoses for patients with recurrent sites that could not be resected was significantly better after 2005 (Figure 4A, p=0.002). These patients were treated with chemotherapy only after recurrence, and modern chemotherapy was used for their treatment after 2005. Therefore, the prognosis after 2005 could be considered better than that before 2004. However, survival after recurrence for patients with resectable recurrent sites was not significantly different before 2004 and after 2005. The efficacy of repeat hepatectomy had been reported before modern chemotherapy was introduced (25, 26). Therefore, the prognoses of patients with resectable recurrent sites were not seriously affected by

Table IV. *Prognostic status of five-year survivors after liver resection for CRLM before 2004 and after 2005.*

	Before 2004 n=38	After 2005 n=47	*p*-Value
Five-year recurrence-free survivors	20 (52.6%)	22 (46.8%)	0.593
Five-year survivor after recurrence	18 (47.4%)	25 (53.2%)	
With repeat surgery	14 (77.8%)	21 (84.0%)	0.701
Without repeat surgery	4 (22.2%)	4 (16.0%)	
Five-year survivor with recurrent site five years after liver resection	4 (10.5%)	16 (34.0%)	0.019
Years to recurrence of five-year survivor with recurrent site, median (range)	2.90 (1.86-3.88)	1.03 (0.16-4.86)	0.014

CRLM: Colorectal liver metastasis; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; UICC: Union for International Cancer Control.

the difference in chemotherapy. Based on these results, improved survival time after recurrence can be attributed to differences in chemotherapy after recurrence. The RFS was not significantly different before 2004 and after 2005. Therefore, the difference in OS was due to the difference in survival time after recurrence. Altogether, the difference in OS before 2004 and after 2005 was mainly due to the differences in chemotherapy after non-resectable recurrence.

The characteristics of the five-year survivors and non-survivors were compared next. The number of tumors and the proportion of four or more CRLMs were significantly lower in five-year survivors before 2004, but a significant difference was not observed after 2005. Modern chemotherapy may have reduced the influence of the number of tumors on prognoses after liver resection. In contrast, the levels of CEA and CA19-9 were significantly lower in five-year survivors after 2005, but significant differences were not observed before 2004. After 2005, 35.4% of patients underwent preoperative chemotherapy. The preoperative CEA and CA19-9 levels for the patients who underwent preoperative chemotherapy may indicate a response to preoperative chemotherapy. Hence, the levels of CEA and CA19-9 after preoperative chemotherapy may have a closer correlation with prognosis. The proportion of stage N2-3 primary CRC was significantly lower in five-year survivors both before 2004 and after 2005.

Next, the characteristics of the five-year survivors before 2004 and after 2005 were compared. The number of CRLMs, the levels of CEA and CA19-9, and the proportion of stage N2-3 were not significantly different. The maximum tumor size was significantly smaller after 2005, and the proportion of preoperative and adjuvant chemotherapy using modern regimens were significantly higher after 2005. Considering these results, although perioperative modern chemotherapy was significantly more frequent after 2005, five-year survivors' characteristics were not very different. Specifically, modern perioperative chemotherapy could not expand the possibility of five-year survival for more advanced CRLM.

Finally, the status of the five-year survivors was analyzed. The proportion of five-year recurrence-free survivors was not significantly different before 2004 and after 2005. Further, the proportion of patients who underwent repeat surgery was not significantly different. The proportion of patients who had recurrent site at five years after initial surgery was significantly higher after 2005 (34.0% *vs.* 10.5%, $p=0.019$). These patients' median time to recurrence was 1.03 years after 2005 and 2.90 years before 2004 ($p=0.014$). Due to prolonged survival time after non-resectable recurrence, recurrence site in five-year survivors was significantly more frequent in patients treated after 2005.

The study results indicate that five-year survival became more frequent after 2005. However, this development is mainly due to advances in chemotherapy administered after non-resectable recurrence. Moreover, 34.9% of five-year survivors had recurrent site at five years after the initial surgery. The results of this study demonstrate that improved five-year survival in the era of modern chemotherapy does not necessarily indicate a cure for CRLM. Recurrence after liver resection for CRLM is inevitable for some patients. Therefore, an attempt to maintain tolerance for chemotherapy is important when considering liver resection for CRLM.

This study has certain limitations. First, the study was retrospective in nature, with a relatively low number of patients. Second, the individual chemotherapy regimens were not standardized, and some patients treated before 2004 received modern chemotherapy after recurrence that was occurred after 2005. Third, the study had a historical controlled design, and the surgical techniques and perioperative management were not identical. Despite these limitations, this study provides useful information about treatment strategies for CRLM.

In conclusion, the proportion of five-year survivors after liver resection for CRLM has increased in the era of modern chemotherapy. However, about one-third of five-year survivors experienced recurrence and were not cured.

Modern chemotherapy contributed to prolonged survival time after non-resectable recurrence.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Study conception and design: TN, DH; Acquisition of data: TY, NK, YM, SO; Analysis and interpretation of data: TN, DH; Drafting of manuscript: DH; Critical revision of manuscript: TN, HK, FK, MS.

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