

## The Evaluation of Liver Resection for Colorectal Cancer Liver Metastasis

Masaichi OGAWA, Mamoru ISHIYAMA, Tomonori IMAKITA, Ryosuke HASHIZUME,  
Momoko KOGOU, Manabu KOJA, and Ken ETO

*Department of Surgery, The Jikei University School of Medicine*

### ABSTRACT

**Aim :** To retrospectively examine the treatment outcome of liver resection for colorectal cancer liver metastases.

**Patients and Methods :** The participants reviewed were 123 patients who had undergone liver resection from January 2004 through December 2015. The 5-year survival rate was compared on the basis of whether patients had (conversion resection) or had not (first resection) received chemotherapy before undergoing liver resection, whether they had been treated before or after molecular targeted drugs had been introduced, and whether the metastasis had been unilateral or bilateral. Poor prognostic factors after liver resection were analyzed.

**Results :** The 5-year overall survival rate for the 123 patients was 52.7%. The 5-year survival rate (both overall survival and disease-free survival) did not differ significantly between first resection patients (91 patients) or conversion resection patients (32 patients). Also, the 5-year overall survival rate did not differ significantly between patients treated before (48 patients) or after (75 patients) molecular targeted drugs had been introduced or between patients with unilateral (88 patients) or bilateral (35 patients) metastases. Multivariate analysis showed that postoperative chemotherapy was an independent prognostic factor.

**Conclusion :** Liver resection yielded a 5-year survival rate of 52.7% with a favorable outcome, and outcomes were similar regardless if patients had or had not received chemotherapy before liver resection. Postoperative chemotherapy was a positive prognostic factor for colorectal cancer liver metastases.

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**Key words :** liver resection, colorectal cancer liver metastasis, 5-year survival rate, prognostic factors, postoperative chemotherapy

### INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related deaths worldwide<sup>1</sup>, and the liver is the most common site of distant metastasis. When initially diagnosed, colorectal cancer has metastasized to the liver in 15% to 25% of patients<sup>2-6</sup>. For CRC that has metastasized to the liver and formed CRC liver metastasis (CRLM), the most

effective treatment is resection of the liver, and local control via surgery is required for long-term survival<sup>7-9</sup>. Complete resection of both the primary tumor and CRLM improves survival compared with systemic chemotherapy<sup>10-12</sup>. For colorectal cancer chemotherapy in Japan, national insurance coverage of the FOLFOX (folinic acid, fluorouracil, and oxaliplatin) regimen began in April 2004, and molecular targeted drugs were first covered in September 2009. Since

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小川匡市, 石山 守, 今北智則, 橋爪良輔, 小郷桃子, 古謝 学, 衛藤 謙

Mailing address : Masaichi OGAWA, Department of Surgery, The Jikei University Katsushika Medical Center, 6-41-2 Aoto, Katsushika-ku, Tokyo 125-8506, Japan

E-mail : masatchmo1962@yahoo.co.jp

2004, our department has expanded the indication for liver resection. Therefore, to examine the effects of liver resection for the treatment of CRLM, we reviewed the outcomes of liver resection performed with our strategy and analyzed factors of a poor prognosis.

## MATERIALS AND METHODS

We reviewed the clinical outcomes of 123 patients who had undergone liver resection via our strategy from January 2004 through December 2015.

Our operative strategy is as follows. Liver resection can be performed for patients who have an indocyanine green retention rate after 15 minutes  $\leq 20\%$ . Percutaneous transhepatic portal embolization is performed preoperatively in patients with a rate of liver remnant via volumetry  $\leq 30\%$ . The noncancerous part of the liver is conserved to the maximum extent. The lesion with clinical CR is not resected if it is undetectable with intraoperative ultrasonography.

Surgery is indicated if the patient's general condition is good, and liver resection is preferred if postoperative liver failure is unlikely. All cases excluded organ metastasis of lung, local recurrence or para-aortic lymph node metastasis.

The treatment criteria were as follows. Tumors were considered unresectable or unsuitable for radical resection if they had metastasized to multiple organs; if the residual liver volume was inadequate, if R0 resection could not be expected, and if the Japanese Classification of Colorectal Category of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) was H2 or H3. Patients were received chemotherapy following the JSCCR guidelines, and the regimen was primarily determined in regard to the patient's status and Ras protein mutations of the primary tumor.

Patients were divided into various groups and compared: (1) those who had first undergone liver resection (first liver resection) and those who had first received chemotherapy and later underwent liver resection (conversion resection); (2) those who been treated before or after molecular targeted drugs had been introduced; and (3) those with unilateral or bilateral metastases. Poor prognostic factors after liver resection were analyzed by univariate and multivariate analyses.

### Statistical Analysis

Overall survival (OS) and disease-free survival (DFS)

were calculated from the date on of liver resection and examined with the Kaplan-Meier method and log-rank analysis. Multivariate analysis was performed with the Cox proportional regression model, and all variables for which  $P < 0.05$  were included in univariate analysis. These analyses were performed with the software program IBM® SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). A P-value of less than 0.05 was considered to indicate significance.

This study was approved by the Ethics Committee of The Jikei University School of Medicine (#27-177).

## RESULTS

### The univariate analysis

Of the factors associated with the primary tumor, those that differed significantly among all patients with CRLM were lymph node metastasis and the number of metastases, and the only factor that was a significant predictor of DFS was whether the metastasis was unilateral or bilateral (Table 1). The only significant predictor of OS was postoperative chemotherapy.

### The multivariate analysis

Analysis of the DFS rate showed that the site of metastasis (unilateral or bilateral) was a significant independent predictor. Multivariate analysis revealed that postoperative chemotherapy and the number of lymph nodes were independent predictors of OS (Table 2).

### Survival rates of all patients

After liver resection the OS rates were 93.4% at 1 year, 70.4% at 3 years, and 52.7% at 5 years, and the DFS rates were 54.8% at 1 year, 33.7% at 3 years, and 28.7% at 5 years (Fig. 1).

### Survival rates of patients according to treatment strategy

Neither the 5-year DFS rate (31.4%,  $p = 0.477$ ; Fig. 2 a) nor the 5-year OS rate (57.3%,  $p = 0.063$ ; Fig. 2b) differed significantly between conversion liver resection patients (32 patients) and first resection patients (91 patients).

The 5-year OS rate did not differ significantly between patients who had been treated before (48 patients) or after (75 patients) the introduction of molecular targeted drugs ( $p = 0.279$ ; Fig. 3).

Table 1. Univariable Cox proportional hazards analysis of clinicopathological factors associated with overall survival after liver resection in patients with colorectal cancer liver metastasis.

Variable			Disease-free survival	Overall survival
			<i>p</i> -value	<i>p</i> -value
Age	< 65 years : ≥ 65 years	59 : 64	0.254	0.355
Sex	male : female	86 : 37	0.434	0.733
Primary lesion	colon : rectum	82 : 41	1.000	0.218
Lymph node metastasis	positive : negative	78 : 45	0.022	0.018
Number of metastases	> 4 : ≤ 4	96 : 27	0.038	0.002
Status of liver metastasis	simultaneous : metachronous	71 : 52	0.104	0.898
Preoperative chemotherapy	yes : no	32 : 91	0.477	0.063
Carcinoembryonic antigen	≥ 20 ng/ml : < 20 ng/ml	75 : 48	0.268	0.097
Metastatic site	unilateral : bilateral	88 : 35	0.003	0.135
Number of metastatic tumors	single : multiple	58 : 65	0.067	0.374
Maximum tumor diameter	≤ 5 cm : > 5 cm	93 : 30	0.661	0.276
Operative method	systematic : partial	62 : 61	0.313	0.363
Simultaneous primary resection	yes : no	31 : 92	0.367	0.797
Operative time	≤ 300 min : > 300 min	34 : 89	0.475	0.340
Blood loss	≤ 1,000 ml : > 1,000 ml	79 : 44	0.397	0.443
Blood transfusion	yes : no	62 : 61	0.431	0.088
Complication	yes : no	33 : 90	0.473	0.321
Adjuvant chemotherapy	yes : no	83 : 40	0.156	0.030
Molecular targeted agents	before : after	48 : 75	0.890	0.279

Table 2. Multivariable Cox proportional hazards analysis of clinicopathological factors associated with disease-free survival and overall survival after liver resection in patients with colorectal cancer liver metastasis.

Disease-free survival			
Variable	<i>P</i> value	Hazard ratio	95% confidence interval
Metastatic site (unilateral vs. bilateral)	0.03	2.038	1.275-3.258
Overall survival			
Variable	<i>P</i> value	Hazard ratio	95% confidence interval
Postoperative chemotherapy	0.021	0.478	0.255-0.895
Number of lymph nodes	0.010	2.429	1.238-4.767

The 5-year OS rate also did not differ significantly between patients who had unilateral metastases (88 patients) and those who had bilateral metastases (35 patients) (*p* = 0.135 ; Fig. 4).

Among patients who had unilateral metastases, the 5-year OS rate did not differ significantly (*p* = 0.057 ; Fig. 5) between conversion resection patients (18 patients) and first resection patients (70 patients). Similarly, among patients with bilateral metastases, the 5-year OS rate did not differ significantly (*p* = 0.640 ; Fig. 6) between conversion resection patients (14 patients) and first resection patients

(21 patients).

The 5-year OS rate was greater for patients who had received postoperative chemotherapy (83 patients) than for patients who had not (40 patients) (*p* = 0.0300 ; Fig. 7).

### DISCUSSION

A leading cause of cancer-related deaths worldwide is CRC, which will eventually spread to the liver to produce CRLM in 35% to 55% of patients. When CRLM occurs, the only option for long-term survival is now surgical resec-

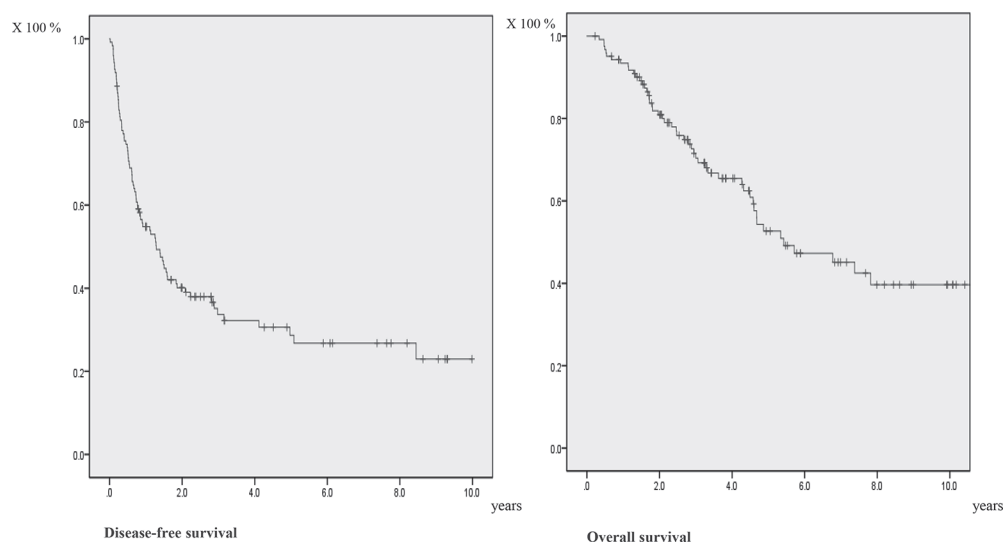


Fig. 1. Kaplan-Meier analysis of disease-free survival and overall survival after liver resection of all patients with colorectal cancer liver metastasis liver metastasis.

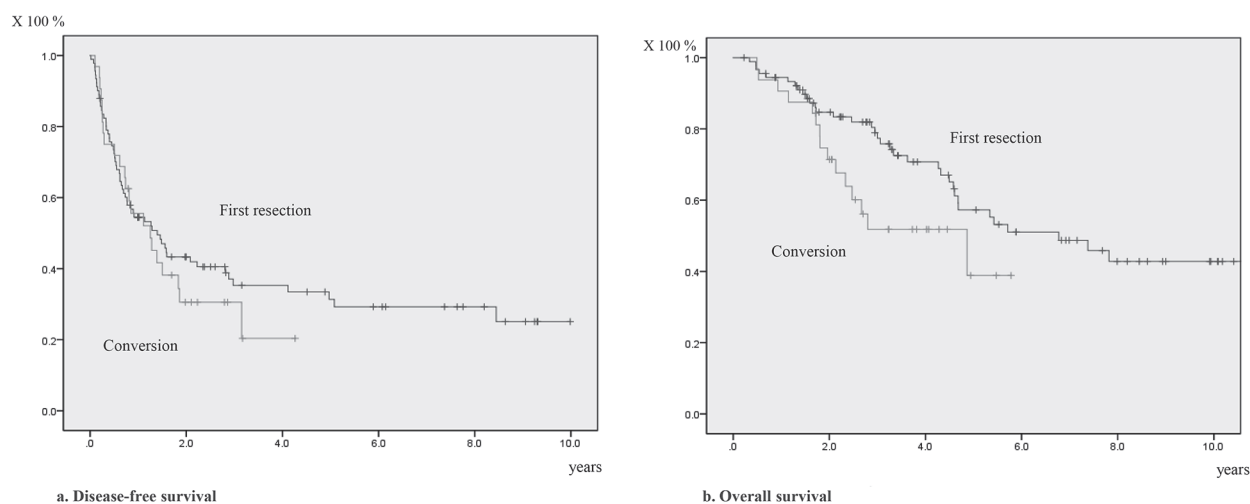


Fig. 2. Kaplan-Meier analysis of (a) disease-free survival and (b) overall survival after liver resection in patients with colorectal cancer liver metastasis liver metastasis. Comparative analysis of patients who had received chemotherapy before resection (conversion resection) and those who had not (first resection).

tion<sup>11,13</sup>. The reported 5-year OS rates after liver resection for CRLM are 47% to 60%<sup>14-16</sup>. However, recent advances in surgical techniques and perioperative chemotherapy options have improved significantly, with liver resection rates of 20% to 45% and 5-year OS rates after liver resection as high as 64%. The principle of surgery is based on resecting all metastases with negative histologic margins (R0-resection) while maintaining adequate residual liver function.

The present study at our hospital found that the 5-year OS rate after liver resection for patients with CRLM was 52.7% with favorable outcome. Our treatment strategies

have generally yielded acceptable results. On the basis of these results, we consider the following 2 points. The first point is about conversion liver resection, meaning resection performed after chemotherapy. Our criteria for clearly unresectable and unsuitable for radical resection are: (1) metastasis to multiple organs, (2) inadequate residual liver volume, (3) R0 resection cannot be expected, and (4) Japanese Classification of Colorectal Category of H2 or H3<sup>17</sup>. The patients of the present study were treated with chemotherapy, and the regimen was determined primarily on the basis of the patient's status and the primary tumor Ras mutation.

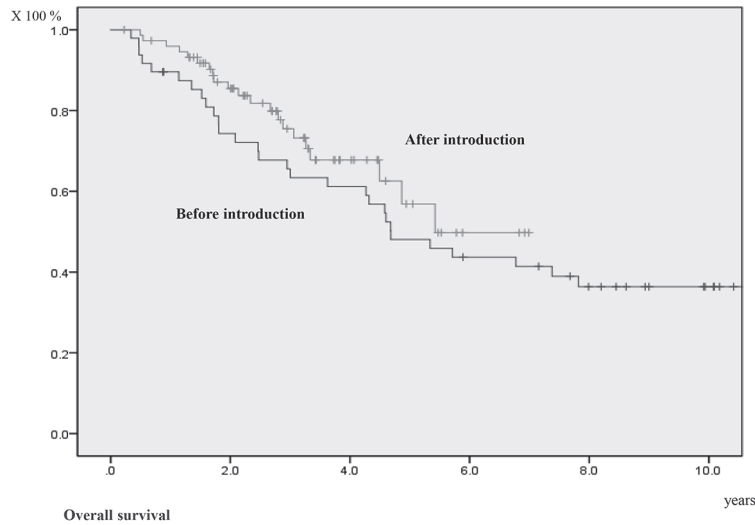


Fig. 3. Kaplan-Meier analysis of overall survival after liver resection in patients with colorectal cancer liver metastasis treated before and after the introduction of molecular targeted drugs.

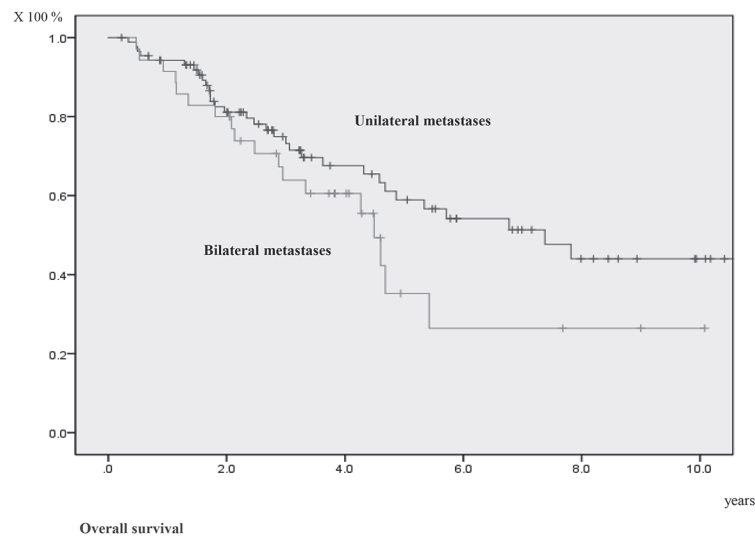


Fig. 4. Kaplan-Meier analysis of overall survival after liver resection in patients with colorectal cancer and unilateral or bilateral liver metastases.

Within these criteria, 32 patients underwent liver resection after chemotherapy (conversion resection) and had a prognosis comparable to that of patients who underwent resection before receiving chemotherapy (first resection). It was suggested that resection should be aggressively performed, even for patients with initially unresectable cases of CRLM, when resection becomes possible after chemotherapy.

The second point we considered concerns the prognostic factors for resection of CRLM. Of the factors that have been reported in the literature, the most common include hepatic hilar lymph node metastasis, surgical margins posi-

tive or less than 10 mm, the presence of extrahepatic metastases, and synchrony/metachronous. Differences between synchronous and metachronous metastases have also been investigated, and most studies have shown no prognostic value<sup>17</sup>. The primary tumor factors that have been reported to be important are the number of the positive lymph node metastases, poor differentiation, and maximum tumor size. Background factors for metastasis which have been reported to be associated with a poor prognosis are high carcinoembryonic antigen and a duration of DFS of less than 1 year before liver resection<sup>17,18</sup>. Regarding the

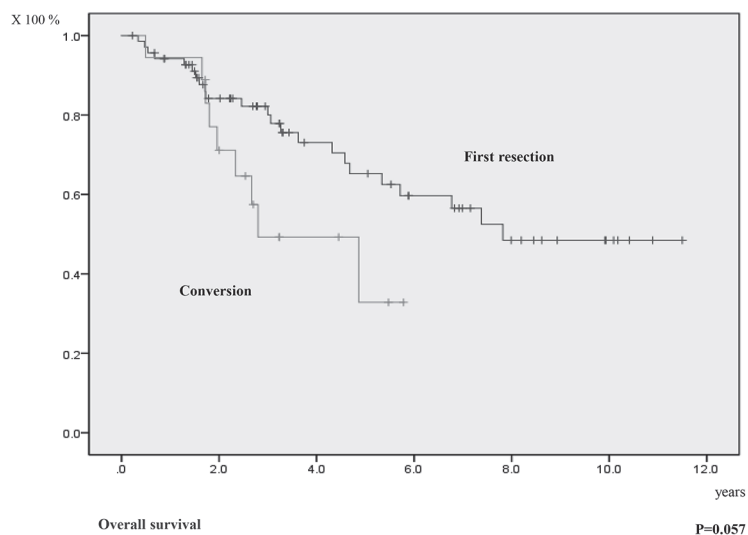


Fig. 5. Kaplan-Meier analysis of overall survival after liver resection in patients with unilateral colorectal cancer liver metastases who had received chemotherapy before resection (conversion resection) and those who had not (first resection).

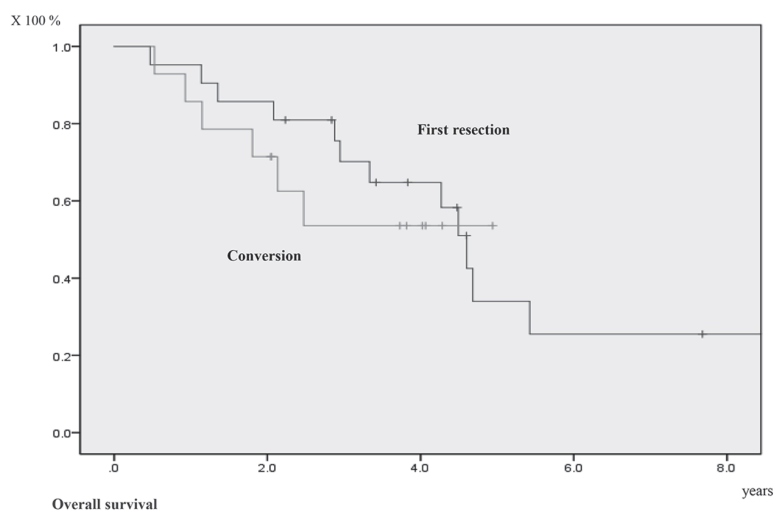


Fig. 6. Kaplan-Meier analysis of overall survival after liver resection in patients with bilateral colorectal cancer liver metastases who had received chemotherapy before resection (conversion resection) and those who had not (first resection).

duration of DFS, some studies support it as a predictor<sup>18-21</sup>, while others do not<sup>22,23</sup>. According to our analysis in the present study, the only prognostic factor for CRLM was postoperative chemotherapy. Because postoperative chemotherapy is suggested to be a prognostic factor for CRLM, individualized and effective chemotherapy is an issue for improving the prognosis.

Our study had several limitations. First, it was a single-center, retrospective study with a total number of 123 patients, which may have low statistical power. A second limitation is that the long duration of this study introduced

some biases. Recent technological advances in liver resection procedures have enabled the resection of liver metastases that were previously considered unresectable. A third and final limitation is that this study did not consider recently developed chemotherapy regimens. Therefore, to overcome these limitations, large multicenter studies with sufficient statistical power are needed.

In conclusion, for patients with CRLM, liver resection yielded a 5-year OS rate of 52.7% with a favorable outcome, and patients treated with conversion resection had a prognosis similar to that of patients treated with initial resection.

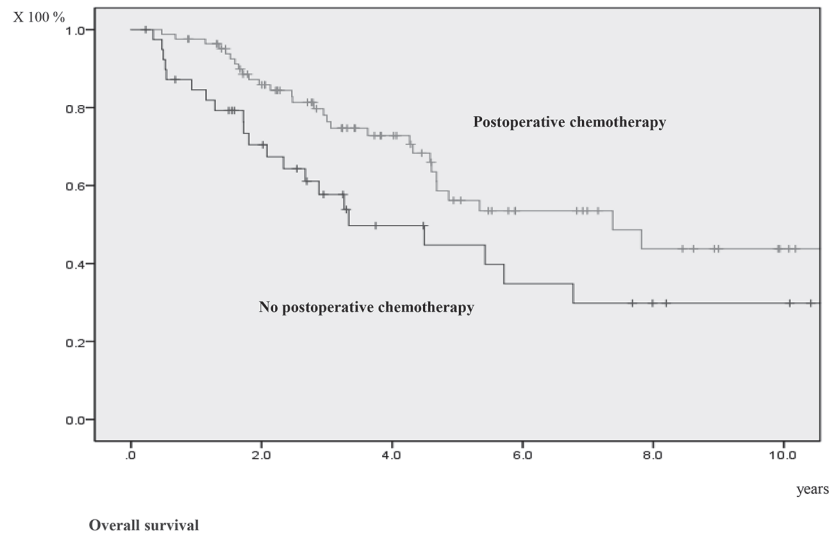


Fig. 7. Kaplan-Meier analysis of overall survival after liver resection of bilateral colorectal cancer liver metastasis of patients who had or had not received postoperative chemotherapy.

Postoperative chemotherapy was a positive prognostic factor for CRLM.

Authors have no conflict of interest.

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