Prognostic impact of conversion hepatectomy for initially unresectable colorectal liver metastasis

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Abstract
Purpose This study aimed to evaluate the prognostic impact of conversion hepatectomy in patients with initially unresectable colorectal liver metastasis (CRLM) and to identify prognostic factors after conversion hepatectomy.

Methods Correlations of conversion hepatectomy with relapse-free survival (RFS) and overall survival (OS) were retrospectively investigated in 554 consecutive patients who underwent hepatectomy for CRLM in 2000–2017. Prognostic factors after conversion hepatectomy were examined in multivariable analysis.

Results Five hundred and nine patients (92%) had initially resectable CRLM at diagnosis and underwent hepatectomy (primary resection group) and 45 (8%) underwent conversion hepatectomy following chemotherapy (conversion group). The 5-year RFS was 30.0% in the primary resection group and 19.8% in the conversion group (p = 0.042); the respective 5-year OS rates were 62.0% and 52.4% (p = 0.253). Multivariable analysis did not identify conversion hepatectomy as a significant prognostic factor for RFS (hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.64–1.37, p = 0.796) or OS (HR 1.12, 95% CI 0.67–1.79, p = 0.667). In the conversion group, multivariable analysis identified the following independent prognostic factors: timing of liver metastases for RFS (synchronous: HR 3.14, 95% CI 1.20–8.24, p = 0.020) and preoperative CEA level for RFS (> 5 ng/ml: HR 3.10, 95% CI 1.45–6.61, p = 0.003) and OS (> 5 ng/ml: HR 3.29, 95% CI 1.18–9.17, p = 0.023).

Conclusions RFS and OS rates after conversion hepatectomy were not inferior to those after primary resection in patients with CRLM. Patients with a normal CEA level before hepatectomy can be expected to have good long-term prognosis after conversion hepatectomy.

Keywords Colorectal cancer · Colorectal liver metastasis · Conversion hepatectomy · Chemotherapy

Introduction

The only curative treatment for colorectal liver metastasis (CRLM) is hepatectomy, even in the modern era of advanced chemotherapy. However, CRLM is found to be unresectable in approximately 80% of patients at the time of initial diagnosis, which limits the number of patients who can benefit from surgery[1, 2]. While most patients with unresectable CRLM undergo systemic chemotherapy after initial diagnosis, recent advances in chemotherapy, including the advent of molecularly targeted agents, have led to an increase in the number of patients with initially unresectable CRLM undergoing conversion hepatectomy[3, 4]. Patients with initially unresectable CRLM who were treated with conversion hepatectomy are reported to have better overall survival (OS) than those treated with chemotherapy alone[5–7]. Accordingly, the guidelines recommend conversion hepatectomy for patients with initially unresectable CRLM that becomes operable after chemotherapy[8–10].

Conversion hepatectomy has been reported to be associated with long-term survival or cure in selected patients with initially unresectable CRLM[11]; however, a large number of patients relapse in the early period after hepatectomy. Even among patients with CRLM that is initially resectable, 75% relapse following hepatectomy, and the 5-year OS rate after hepatectomy is reported to be 35–58%[9, 12, 13]. The
long-term prognosis of patients with initially unresectable CRLM who undergo conversion hepatectomy is reported to be inferior or equivalent to that of patients with initially resectable CRLM[14, 15]. The number of patients with CRLM who undergo conversion hepatectomy is expected to increase in the future, and further improvement in the long-term prognosis is required. Nevertheless, few studies have evaluated the long-term prognosis of conversion hepatectomy, and there is no consensus regarding factors affecting recurrence and survival after this procedure[1, 4, 6, 11, 14–17].

This study compared the prognostic impact of conversion hepatectomy on relapse-free survival (RFS) and OS in patients who had initially unresectable CRLM with that in patients who had initially resectable CRLM. We also reviewed the treatment course and background characteristics of patients with initially unresectable CRLM who underwent conversion hepatectomy and sought to identify prognostic factors affecting RFS and OS after conversion hepatectomy.

**Methods**

**Study population**

Participants were consecutive patients who underwent hepatectomy for CRLM and were referred to the Department of Colorectal Surgery or Department of Hepatobiliary and Pancreatic Surgery at Japan’s National Cancer Center Hospital between January 2000 and December 2017. Patients with missing clinicopathological data were excluded.

Resectability was determined based on the possibility of achieving R0 resection with ≥30% of future liver remnant (FLR) volume, regardless of the number or size of liver metastases. Percutaneous transhepatic portal embolization was used in patients with a small FLR or impaired liver function to prompt hypertrophy of the FLR[18]. In this study, patients with CRLM that was considered “unresectable” at the time of initial diagnosis of liver metastasis and treated with chemotherapy were as follows: (1) those with no more than 30% of FLR volume after hepatectomy even when combined with percutaneous transhepatic portal embolization; (2) those without adequate vascular inflow or outflow after hepatectomy; and (3) those with an unresectable primary tumor or unresectable extrahepatic metastases. Patients with tumor shrinkage after chemotherapy who were considered resectable underwent conversion hepatectomy. In accordance with the Japanese Society for Cancer of the Colon and Rectum guidelines, patients with CRLM that was considered “resectable” at the time of initial diagnosis typically did not receive chemotherapy for metachronous or synchronous liver metastases before or after hepatectomy.

In addition, preoperative chemotherapy, radiotherapy, or chemoradiotherapy was not routinely performed in patients with rectal cancer[8]. Treatment was determined at multidisciplinary team meetings attended by colorectal surgeons, hepatobiliary and pancreatic surgeons, respiratory surgeons, medical oncologists, pathologists, radiologists, and nurses. The study was approved by the National Cancer Center Hospital Institutional Review Board (code: 2017–437). The requirement for written informed consent was waived in view of the retrospective nature of the research and the anonymity of the study data.

**Data collection**

The following information was obtained from the medical records: treatment year, age, sex, location of primary tumor (right- or left-sided: right-sided defined as the cecum, ascending colon, hepatic flexure, and transverse colon and left-sided defined as the splenic flexure, descending colon, sigmoid colon, and rectum), T category of the primary tumor, N category of the primary tumor, timing of liver metastasis (metachronous or synchronous, with synchronous defined as metastasis diagnosed before or during resection of the primary tumor), extrahepatic metastasis at hepatectomy, preoperative serum carcinoembryonic antigen (CEA) level, perioperative chemotherapy before and after hepatectomy, surgical procedure (major hepatectomy or minor hepatectomy, with major hepatectomy defined as resection of 4 or more liver segments), concomitant radiofrequency ablation (RFA), number of liver metastases, and size of the largest liver metastatic lesion. For patients with CRLM who underwent conversion hepatectomy, the following information related to the treatment course was also obtained from the medical records: duration of chemotherapy (time from start of chemotherapy to hepatectomy), number of lines, the first-line regimen, use of anti-vascular endothelial growth factor (VEGF) antibody, use of anti-epithelial growth factor receptor antibody, tumor response rate (calculated using the Response Evaluation Criteria in Solid Tumors [RECIST] criteria 1.1 [19]), and the resection margin.

**Follow-up**

Follow-up consisted of serum tumor marker measurements and computed tomography scans at 3–6-month intervals. All patients underwent complete follow-up assessment, with a median follow-up duration of 64.8 months (range, 1–228) for survivors.

**Statistical analysis**

Categorical variables were compared using Pearson’s chi-squared test and continuous variables using the Wilcoxon...
rank-sum test. OS was defined as the interval between the date of hepatectomy and the date of death from any cause. RFS was defined as the interval between the date of hepatectomy and the date of recurrence or death from any cause. Survival rates were calculated by the Kaplan–Meier method, and survival curves were compared using the log-rank test. Survivors were censored as of the date of data cut-off (February 2020). Multivariate Cox proportional hazards regression models were used to evaluate the prognostic impact of conversion hepatectomy on RFS and OS with adjustment for key clinicopathological factors (age, sex, location of primary tumor, T category of primary tumor, N category of primary tumor, timing of liver metastasis, extrahepatic metastasis, postoperative chemotherapy, preoperative CEA level, surgical procedure, concomitant RFA, number of liver metastases, and size of largest liver metastasis). To evaluate prognostic factors in patients who underwent conversion hepatectomy, we also performed multivariable analysis for RFS and OS by adding factors related to the treatment course (duration of chemotherapy, number of lines, first-line regimen, use of anti-VEGF antibody, use of anti-epithelial growth factor receptor antibody, tumor response rate, and resection margin) to the above-mentioned factors. Considering the relatively small number of events, multivariable analysis was performed in patients who underwent conversion hepatectomy using variables that had a \( p \) value of \(<0.2\) in univariable analysis. Data are expressed as the number of patients, ratio (%), or hazard ratio (HR) and 95% confidence interval (CI) as appropriate. All analyses were performed using JMP14 software (SAS Institute Japan Ltd., Tokyo, Japan). A \( p \) value \(<0.05\) was considered statistically significant.

**Results**

**Study population**

A total of 573 patients who underwent hepatectomy for CRLM at the National Cancer Center Hospital between January 2000 and December 2017 were enrolled. Nineteen patients were excluded because of missing clinicopathological data. Five hundred and nine patients had initially resectable CRLM at the time of diagnosis and underwent hepatectomy (primary resection group). Fourteen of these patients did not have features suggesting unresectable disease at the time of initial diagnosis but had tumors that were considered to be progressing rapidly and chemotherapy was administered preoperatively. Forty-five patients had initially unresectable CRLM at the time of diagnosis and underwent hepatectomy followed by chemotherapy (conversion group) (Fig. 1).

**Patient characteristics**

The clinical characteristics of the primary resection group \((n = 509)\) and the conversion group \((n = 45)\) are shown in Table 1. The median age of the total study population was 62 years (range, 21–88), the median number of liver metastases was 2 (range, 1–19), and the median size of the largest liver metastasis was 30 mm (range, 5–125).

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**Fig. 1** Flow diagram showing the patient selection process. The final study cohort consisted of 509 patients in the primary resection group and 45 in the conversion group. The primary resection group included 14 patients who received preoperative chemotherapy but were considered to have initially resectable CRLM. CRLM, colorectal liver metastasis.
liver metastatic lesion was 3.0 cm (range, 0.1–23). Postoperative chemotherapy was administered in 62 patients (11%), many of whom were also participants in the JCOG0603 study[20]. Compared with the primary resection group, the conversion group had a significantly higher proportion of patients aged under 65 years (60% vs 76%, \( p = 0.042 \)) and significantly greater proportions of patients with a T4 tumor (16% vs 33%, \( p = 0.003 \)), synchronous liver metastasis (47% vs 27%, \( p < 0.001 \)), and extrahepatic metastases (5% vs 13%, \( p < 0.001 \)).

Table 1

| Description                              | All cases | Hepatectomy group | Conversion group | \( p \) value |
|------------------------------------------|-----------|-------------------|-----------------|-------------|
| Cases                                    | 554       | 509 (92%)         | 45 (8%)         |             |
| Age (years)                              |           |                   |                 |             |
| Median (range)                           |           |                   |                 |             |
| < 65                                     | 340 (61%) | 306 (60%)         | 34 (76%)        | 0.042       |
| ≥ 65                                     | 214 (39%) | 203 (40%)         | 11 (24%)        |             |
| Sex                                      |           |                   |                 |             |
| Male                                     | 358 (65%) | 333 (65%)         | 25 (56%)        | 0.185       |
| Female                                   | 196 (35%) | 176 (35%)         | 20 (44%)        |             |
| Location of primary tumor                |           |                   |                 |             |
| Right-sided                              | 129 (23%) | 119 (23%)         | 10 (22%)        | 0.860       |
| Left-sided                               | 425 (77%) | 390 (77%)         | 35 (78%)        |             |
| T category of primary tumor              |           |                   |                 |             |
| T1/T2/T3                                 | 458 (83%) | 428 (84%)         | 30 (67%)        | 0.003       |
| T4                                       | 96 (17%)  | 81 (16%)          | 15 (33%)        |             |
| N category of primary tumor              |           |                   |                 |             |
| N0                                       | 194 (35%) | 178 (35%)         | 16 (36%)        | 0.937       |
| N1/2                                     | 360 (65%) | 331 (65%)         | 29 (64%)        |             |
| Timing of liver metastases               |           |                   |                 |             |
| Metachronous                             | 281 (51%) | 272 (53%)         | 9 (20%)         | < 0.001     |
| Synchronous                              | 273 (49%) | 237 (47%)         | 36 (80%)        |             |
| Extrahepatic metastases                  |           |                   |                 |             |
| Yes                                      | 26 (5%)   | 18 (4%)           | 8 (18%)         | < 0.001     |
| No                                       | 528 (95%) | 491 (96%)         | 37 (82%)        |             |
| Preoperative CEA level                   |           |                   |                 |             |
| \( \leq 5 \text{ ng/ml} \)               | 172 (31%) | 155 (30%)         | 17 (38%)        | 0.309       |
| > 5 \text{ ng/ml}                       | 382 (69%) | 354 (70%)         | 26 (62%)        |             |
| Postoperative chemotherapy               |           |                   |                 |             |
| Yes                                      | 62 (11%)  | 60 (12%)          | 2 (4%)          | 0.134       |
| No                                       | 492 (89%) | 449 (88%)         | 43 (96%)        |             |
| Surgical procedure                       |           |                   |                 |             |
| Major                                    | 111 (20%) | 96 (19%)          | 15 (33%)        | 0.020       |
| Minor                                    | 443 (80%) | 413 (81%)         | 30 (67%)        |             |
| Concomitant RFA                          |           |                   |                 |             |
| Yes                                      | 4 (1%)    | 3 (1%)            | 1 (2%)          | 0.215       |
| No                                       | 550 (99%) | 506 (99%)         | 44 (98%)        |             |
| Number of liver metastases               |           |                   |                 |             |
| Median (range)                           | 2 (1–19)  | 1 (1–12)          | 3 (1–19)        | < 0.001     |
| 1                                        | 274 (49%) | 264 (52%)         | 10 (22%)        |             |
| ≥ 2                                      | 280 (51%) | 245 (48%)         | 35 (78%)        |             |
| Size of largest liver metastasis         |           |                   |                 |             |
| Median (range)                           | 3.0 (0.1–23) | 3.0 (0.1–23) | 3.7 (0.5–12) | < 0.001 |
| \( \leq 5 \text{ cm} \)                 | 453 (82%) | 425 (84%)         | 28 (62%)        |             |
| \( \geq 5.1 \text{ cm} \)               | 101 (18%) | 84 (16%)          | 17 (38%)        |             |

CEA, carcinoembryonic antigen; RFA, radiofrequency ablation
vs 80%, \( p < 0.001 \)), extrahepatic metastasis (4% vs 18%, \( p < 0.001 \)), and major heptectomy (19% vs 33%, \( p = 0.020 \)). Furthermore, the conversion group also had a higher proportion of patients with \( \geq 2 \) liver metastases (48% vs 78%, \( p < 0.001 \)) and a higher proportion with the largest liver metastatic lesion measuring \( > 5.1 \) cm (16% vs 38%, \( p < 0.001 \)) compared with the primary resection group.

**Treatment course in the conversion group**

The treatment course of patients with CRLM who underwent conversion hepatectomy is shown in Table 2. The median interval between the start of chemotherapy and hepatectomy was 9.6 months (range, 3–45). The most common first-line regimen was oxaliplatin-based (\( n = 29, 65\% \)). Chemotherapy regimens differed depending on the treatment year. Until 2006, the most common regimen was 5-fluorouracil (5-FU)-based systemic chemotherapy or hepatic arterial infusion; thereafter, the most common regimen was oxaliplatin-based or irinotecan-based systemic chemotherapy combined with molecular targeted agents. The median response rate was 32% (range, −23, 79). Ten patients (22%) had microscopic tumor invasion of the resection margin (R1 resection).

### Table 2  Treatment course in the conversion group

| Cases, \( n \) | Conversion group |
|----------------|-----------------|
| Duration of chemotherapy |              |
| Median (range)  | 9.6 months (3–45) |
| < 6 months  | 11 (24%) |
| \( \geq 6 \) months  | 34 (76%) |
| Lines, \( n \) |              |
| 1 | 33 (73%) |
| \( \geq 2 \) | 12 (27%) |
| First-line regimen |              |
| Oxaliplatin-based | 29 (65%) |
| Irinotecan-based | 2 (4%) |
| 5-FU-based | 4 (9%) |
| HAI | 10 (22%) |
| Anti-VEGF antibody |              |
| Combined | 19 (42%) |
| Not combined | 26 (58%) |
| Anti-EGFR antibody |              |
| Combined | 7 (16%) |
| Not combined | 38 (84%) |
| Response rate |              |
| Median (range) | 32% (−23, 79) |
| < 30% | 26 (58%) |
| \( \geq 30 \) | 19 (42%) |
| Resection margin |              |
| Negative (R0) | 35 (78%) |
| Positive (R1) | 10 (22%) |

5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; HAI, hepatic arterial infusion; VEGF, vascular endothelial growth factor

**Relapse-free survival**

The Kaplan–Meier curves for RFS are compared between the primary resection group and the conversion group in Fig. 2a. Median survival time was 14.8 months in the primary resection group and 9.3 months in the conversion group. The 3-year and 5-year RFS rates were 33.5% and 30.0%, respectively, in the primary resection group and 22.2% and 19.8% in the conversion group. In both groups, the RFS curve decreased sharply in the first 2 years after hepatectomy. The gap in the RFS curve between the primary resection group and the conversion group increased in the first year after hepatectomy and reached a plateau at 3 years while maintaining the gap (\( p = 0.042 \)).

**Overall survival**

The Kaplan–Meier curves for OS are compared between the primary resection group and the conversion group in Fig. 2b. Median survival time was 99.0 months in the primary resection group and 64.7 months in the conversion group. The 3-year and 5-year OS rates were 79.1% and 62.0%, respectively, in the primary resection group and 74.8% and 52.4% in the conversion group. The gap in the OS curves between the primary resection group and the conversion group was close during the first 4 years after hepatectomy, and gradually increased thereafter, although the difference was not significant (\( p = 0.253 \)).

**Clinical factors affecting the prognosis of all patients with CRLM**

The results of univariable and multivariable analyses for RFS and OS in all patients with CRLM who underwent hepatectomy are shown in Table 3. Multivariable analysis for RFS with adjustment for key clinical factors revealed the following as independent predictors of RFS: location of the primary tumor (right-sided: HR 1.29, 95% CI 1.01–1.63, \( p = 0.044 \)); N category of the primary tumor (N1/N2: HR 1.45, 95% CI 1.17–1.82, \( p < 0.001 \)); timing of liver metastasis (synchronous: HR 1.66, 95% CI 1.34–2.07, \( p < 0.001 \)); preoperative CEA level (\( > 5 \) ng/ml: HR 1.47, 95% CI 1.16–1.87, \( p = 0.001 \)); postoperative chemotherapy (No: HR 1.66, 95% CI 1.20–2.36, \( p = 0.002 \)); and number of liver metastases (\( \geq 2 \): HR 1.69, 95% CI 1.37–2.08, \( p < 0.001 \)). In univariable analysis, RFS was significantly worse in the conversion group than in the primary resection group (HR 1.43, 95% CI 1.01–2.01, \( p = 0.042 \); data not shown), whereas
no significant difference in RFS was found in multivariable analysis (HR 0.95, 95% CI 0.64–1.37, \( p = 0.796 \)).

Multivariable analysis for OS with adjustment for key clinical factors revealed the independent predictors of OS to be location of the primary tumor (right-sided: HR 1.45, 95% CI 1.05–1.96, \( p = 0.023 \)), N category of the primary tumor (N1/N2: HR 1.47, 95% CI 1.11–1.99, \( p = 0.008 \)), and preoperative CEA level (> 5 ng/ml: HR 1.43, 95% CI 1.05–1.96, \( p = 0.022 \)). There was no significant difference in OS between the conversion group and the primary resection group (HR 1.12, 95% CI 0.67–1.79, \( p = 0.667 \)).

**Clinical factors affecting prognosis of the conversion group**

Univariable and multivariable analyses for RFS and OS in patients with CRLM who underwent conversion hepatectomy are shown in Table 4. On multivariable analyses for RFS using variables with a \( p \) value of < 0.2 on univariate analyses, independent predictors were timing of liver metastasis (synchronous: HR 3.14, 95% CI 1.20–8.24, \( p = 0.020 \)) and preoperative CEA level (> 5 ng/ml: HR 3.10, 95% CI 1.45–6.61, \( p = 0.003 \)). On multivariable analyses for OS, the preoperative CEA level
Table 3  Results of multivariable analyses for relapse-free survival and overall survival in all patients with CRLM who underwent hepatectomy

| Variable                                | Category          | Control          | Multivariable |
|-----------------------------------------|-------------------|------------------|---------------|
| Relapse-free survival                   |                   |                  |               |
| Age (years)                             | ≥65               | <65              | 0.81 (0.65–1.00) 0.052 |
| Sex                                     | Female            | Male             | 1.05 (0.85–1.30) 0.643 |
| Location of primary tumor               | Right-sided       | Left-sided       | 1.29 (1.01–1.63) 0.044 |
| T category of primary tumor             | T4                | T1/T2/T3         | 1.16 (0.88–1.50) 0.294 |
| N category of primary tumor             | N1/N2             | N0               | 1.45 (1.17–1.82) <0.001 |
| Timing of liver metastases             | Synchronous       | Metachronous     | 1.66 (1.34–2.07) <0.001 |
| Extrahepatic metastases                | Yes               | No               | 1.08 (0.67–1.65) 0.741 |
| Preoperative CEA level                 | >5 ng/ml          | ≤5 ng/ml         | 1.47 (1.16–1.87) 0.001 |
| Postoperative chemotherapy             | No                | Yes              | 1.66 (1.20–2.36) 0.002 |
| Surgical procedure                     | Major             | Minor            | 1.03 (0.77–1.37) 0.820 |
| Concomitant RFA                        | Yes               | No               | 1.03 (0.25–2.77) 0.954 |
| Number of liver metastases             | ≥2                | 1                | 1.69 (1.37–2.08) <0.001 |
| Size of largest liver metastasis       | >5.1 cm           | ≤5 cm            | 1.17 (0.86–1.57) 0.311 |
| Hepatectomy                             | Conversion        | Primary resection | 0.95 (0.64–1.37) 0.796 |
| Overall survival                        |                   |                  |               |
| Age (years)                             | ≥65               | <65              | 0.89 (0.67–1.18) 0.434 |
| Sex                                     | Female            | Male             | 1.03 (0.78–1.34) 0.856 |
| Location of primary tumor               | Right-sided       | Left-sided       | 1.45 (1.05–1.96) 0.023 |
| T category of primary tumor             | T4                | T1/T2/T3         | 1.18 (0.82–1.66) 0.351 |
| N category of primary tumor             | N1/N2             | N0               | 1.47 (1.11–1.99) 0.008 |
| Timing of liver metastases             | Synchronous       | Metachronous     | 1.27 (0.96–1.69) 0.093 |
| Extrahepatic metastases                | Yes               | No               | 0.95 (0.46–1.69) 0.874 |
| Preoperative CEA level                 | >5 ng/ml          | ≤5 ng/ml         | 1.43 (1.05–1.96) 0.022 |
| Postoperative chemotherapy             | No                | Yes              | 1.10 (0.73–1.74) 0.652 |
| Surgical procedure                     | Major             | Minor            | 1.27 (0.87–1.84) 0.210 |
| Concomitant RFA                        | Yes               | No               | 0.61 (0.03–2.74) 0.590 |
| Number of liver metastases             | ≥2                | 1                | 1.14 (0.87–1.49) 0.350 |
| Size of largest liver metastasis       | >5.1 cm           | ≤5 cm            | 1.11 (0.75–1.62) 0.603 |
| Hepatectomy                             | Conversion        | Primary resection | 1.12 (0.67–1.79) 0.667 |

Multivariate analysis in all patients with CRLM who underwent hepatectomy was performed using all key clinical variables.

CEA, carcinoembryonic antigen; CI, confidence interval; CRLM, colorectal liver metastases; HR, hazard ratio; RFA, radiofrequency ablation

(>5 ng/ml: HR 3.29, 95% CI 1.18–9.17, p=0.023) was an independent predictor.

**Recurrence pattern**

In total, 342 patients in the primary resection group and 36 in the conversion group developed recurrence during the study period. There was no significant difference in the pattern of first recurrence between the groups. Recurrence localized to the liver was observed in 139 patients (41%) in the primary resection group and 17 (47%) in the conversion group (p = 0.548).

After first recurrence, surgical treatment was performed in 140 patients (41%) in the primary resection group and in 16 (44%) in the conversion group. Although there was no significant between-group difference, the proportion of patients who underwent hepatectomy tended to be higher in the conversion group than in the primary resection group (31% vs 23%, p = 0.893; Table 5).

**Discussion**

With the availability of advanced chemotherapy, the number of patients with CRLM undergoing conversion hepatectomy is expected to increase. Therefore, the impact of conversion hepatectomy on long-term prognosis and the factors that predict prognosis after conversion hepatectomy need to be
clarified. In the present study, we compared the prognosis of patients with initially unresectable CRLM who underwent conversion hepatectomy with that of those with initially resectable CRLM who underwent primary resection. Multivariable analysis revealed that conversion hepatectomy was not a significant prognostic factor for RFS (HR 0.95, 95% CI 0.64–1.37, \( p = 0.796 \)) or OS (HR 1.12, 95% CI 0.67–1.79, \( p = 0.667 \)). Moreover, in patients with initially unresectable CRLM who underwent conversion hepatectomy, we found that the timing of liver metastasis was an independent prognostic factor for RFS (synchronous: HR 3.14, 95% CI 1.20–8.24, \( p = 0.020 \)) and that the preoperative CEA level was an independent prognostic factor for both RFS (> 5 ng/ml: HR 3.10, 95% CI 1.45–6.61, \( p = 0.003 \)) and OS (> 5 ng/ml: HR 3.29, 95% CI 1.18–9.17, \( p = 0.023 \)). Considering that conversion hepatectomy is expected to have the same prognosis as primary resection for initially unresectable CRLM, conversion hepatectomy should be performed following chemotherapy whenever possible. Conversion hepatectomy may be expected to improve long-term survival in patients with CRLM and a normal CEA level after chemotherapy.

Although multivariable analysis did not identify any significant between-group difference in RFS or OS, the gap between the Kaplan–Meier curves for RFS in the conversion group and the primary resection group increased soon after hepatectomy and did not close thereafter. However, the Kaplan–Meier curves for OS were similar for both groups for up to 4 years after hepatectomy, which indicates that recurrence after hepatectomy does not lead immediately to death. In this study, there was no significant difference in the pattern of recurrence after hepatectomy between the two groups, and the rate of liver-only recurrence was similar between them. At the first hepatectomy, the preoperative number of hepatic metastases and size of the largest liver metastatic lesion were significantly greater in the conversion group than in the primary resection group, which might have reduced the liver remnant volume in the conversion group. However, there was no difference in the proportion of patients who were able to undergo a second hepatic resection for first recurrence between the two groups or in the resection rate for other organs. Surgical treatment after recurrence was performed in the conversion group as well as in the primary resection group, which may explain why the difference in recurrence in the early stage after hepatectomy did not lead immediately to death.

The preoperative CEA level was an independent prognostic factor for RFS and OS in our conversion group. CEA is a tumor marker that predicts survival and recurrence of colorectal cancer[21, 22], and some reports indicate that it

### Table 4

| Variable                  | Category         | Control            | Univariable HR (95% CI) p-value | Multivariable HR (95% CI) p-value |
|---------------------------|------------------|--------------------|---------------------------------|-----------------------------------|
| Relapse-free survival     |                  |                    |                                 |                                   |
| Timing of liver metastasis| Synchronous      | Metachronous       | 2.60 (1.01–6.74) 0.048           | 3.14 (1.20–8.24) 0.020            |
| Preoperative CEA level    | > 5 ng/ml        | ≤ 5 ng/ml          | 2.95 (1.41–6.18) 0.004           | 3.10 (1.45–6.61) 0.003            |
| Anti-VEGF antibody        | Not combined     | Combined           | 2.07 (1.06–4.06) 0.034           | 1.68 (0.86–3.30) 0.131            |
| Resection margin          | Positive (R1)    | Negative (R0)      | 2.72 (1.27–5.86) 0.010           | 2.11 (0.96–4.60) 0.062            |
| Overall survival          |                  |                    |                                 |                                   |
| Preoperative CEA level    | > 5 ng/ml        | ≤ 5 ng/ml          | 3.58 (1.30–9.86) 0.014           | 3.29 (1.18–9.17) 0.023            |
| Duration of chemotherapy  | ≥ 6 months       | < 6 months         | 2.28 (0.67–7.79) 0.189           | 1.78 (0.51–6.17) 0.366            |

Multivariable analysis in patients with CRLM who underwent conversion hepatectomy was performed using variables with a \( p \) value < 0.2 in univariable analysis. *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *CRLM*, colorectal liver metastases; *HR*, hazard ratio; *VEGF*, vascular endothelial growth factor

### Table 5

| Pattern of first recurrence and treatment thereafter | Hepatectomy | \( p \) value |
|-----------------------------------------------------|-------------|---------------|
|                                                     | Primary resection group | Conversion group |
| Total number of recurrences                         | 342         | 36            |
| Pattern of first recurrence                         | 0.548       |               |
| Liver only                                          | 139 (41%)   | 17 (47%)      |
| Lung only                                           | 69 (20%)    | 6 (17%)       |
| Others                                              | 52 (15%)    | 4 (8%)        |
| Multiple sites                                      | 82 (24%)    | 12 (28%)      |
| Treatment after first recurrence                    | 0.893       |               |
| Surgery                                             | 140 (41%)   | 16 (44%)      |
| Hepatectomy                                         | 78 (23%)    | 11 (31%)      |
| Pneumonectomy                                       | 45 (13%)    | 3 (8%)        |
| Others                                              | 17 (5%)     | 2 (5%)        |
| Chemotherapy/BSC                                    | 202 (59%)   | 20 (56%)      |

*BSC*, best supportive care
is specifically elevated in patients with liver metastasis[23]. A number of studies have found that the CEA level is a prognostic factor after hepatectomy in patients with CRLM, although the cut-off CEA level varies from 5 to 200 ng/ml depending on the study[14, 24–26]. In our study, a CEA level of 5 ng/ml most sensitively reflected the prognosis in the conversion group. Although no studies have evaluated the CEA level after chemotherapy as a prognostic factor after conversion hepatectomy, several have shown that the CEA level after preoperative chemoradiotherapy is associated with the histologic response and prognosis in patients with rectal cancer[27, 28]. It is possible that the preoperative CEA level reflected the reduction in tumor volume following chemotherapy and predicted survival and recurrence after conversion hepatectomy.

Few studies have evaluated the prognostic factors in patients with CRLM who undergo conversion hepatectomy. Previous studies have identified prognostic factors after conversion hepatectomy to include the response rate[15, 29], size of the largest liver metastatic lesion, number of liver metastases, and complete pathologic response status[11]. Our results are not consistent with these previous findings. However, all the studies performed to date have been retrospective with a small number of patients, and further evidence is required.

This study has some limitations. First, the retrospective and single-center design means there may have been a degree of selection bias. Second, although patients were enrolled consecutively, the study period (2000–2017) was long and saw significant changes in treatment strategies, such as chemotherapy. Therefore, our study may not fully reflect current medical practice. Third, many cases were missing data on RAS mutation status, which is one of the important prognostic factors in CRLM[30, 31]. Therefore, we were unable to evaluate the role of RAS mutation status in the prognosis of this cohort. Fourth, the study included only patients who underwent hepatectomy, which meant that we could not show the rate of conversion hepatectomy in all patients with initially unresectable CRLM.

Conclusion

In conclusion, RFS and OS after conversion hepatectomy were not inferior to those after primary resection in patients with CRLM. In patients who underwent conversion hepatectomy, the presence of synchronous liver metastasis was a poor prognostic factor for RFS, and preoperative elevation of CEA was a poor prognostic factor for both RFS and OS. Conversion hepatectomy for initially unresectable CRLM following chemotherapy should be performed whenever possible, and patients with a normal CEA level before hepatectomy can be expected to have a good long-term prognosis after conversion hepatectomy.

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Author’s contributions Study conception design: Takamizawa, Kanemitsu. Data acquisition: Takamizawa, Inoue, Moritani, Tsukamoto, Esaki, and Shimada, Kanemitsu. Data analysis and interpretation: Takamizawa, Inoue, Moritani, Tsukamoto, Esaki, Shimada, and Kanemitsu. Drafting the article: Takamizawa. Critical revision for intellectual content: Inoue, Moritani, Tsukamoto, Esaki, Shimada, and Kanemitsu. Final approval of the manuscript: Takamizawa, Inoue, Moritani, Tsukamoto, Esaki, Shimada, and Kanemitsu. Agree to be accountable for all aspects of work to ensure that questions regarding accuracy and integrity investigated and resolved: Takamizawa, Inoue, Moritani, Tsukamoto, Esaki, Shimada, and Kanemitsu.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This study was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (IRB code: 2017–437).

Consent to participate The requirement for written informed consent was waived in view of the retrospective nature of the research and the anonymity of the data.

Conflict of interest The authors declare no competing interests.

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