Child-Turcotte-Pugh Score as a Predictive Factor for Long-Term Survival After Repeat Hepatectomy for Recurrent Liver Metastases of Colorectal Cancer

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Objective: We aimed to evaluate the changes in liver function after repeat hepatectomy and their relationship with survival of patient with colorectal cancer.

Summary of Background Data: Repeat hepatectomy has been accepted as an effective treatment for recurrent liver metastases; however, how repeat hepatectomy changes the liver function during the follow-up period is not well understood.

Methods: Data regarding patients underwent R0 resections at initial hepatectomy for colorectal cancer with liver metastasis from 2012 to 2017 were retrospectively reviewed. Patients were divided into groups according to the total number of hepatectomies. Overall survival and Child-Turcotte-Pugh score after hepatectomy were analyzed.

Results: Fifty-three patients underwent single hepatectomy and 37 patients underwent repeat hepatectomy. There was no significant difference in the overall survival rates between the 2 groups. At 27 months after the initial hepatectomy, mean Child-Turcotte-Pugh scores of patients with repeat hepatectomy started to become statistically higher than those of patients with single hepatectomy. Overall survival of patients who survived after 27 months from the initial hepatectomy showed a statistical difference between the 2 groups. The total number of liver metastases ≥ 4 and Child-Turcotte-Pugh score ≥ 6 at 27 months after the initial hepatectomy were significant risk factors for overall survival of patient who survived after 27 months from the initial hepatectomy.

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Conclusions: Liver function after repeat hepatectomy can be deteriorated after a long-term period. Careful approach and continuous assessment of the liver function after hepatectomy are necessary to maintain long-term survival after repeat hepatectomy.

Key words: Repeat hepatectomy – Colorectal cancer – Liver metastasis – Liver function

Approximately 50% of colorectal cancer (CRC) patients experience liver metastasis during follow-up.1 Surgical resection of isolated hepatic metastasis from CRC may be curative if resectable and improves the long-term survival of patients.2,3 However, only 20% to 30% of liver metastases are resectable at diagnosis.4 Many trials have attempted to expand the resectability of liver metastases by more aggressive approaches, such as 2-stage hepatectomy after portal vein embolization or neoadjuvant chemotherapy.5,6 Advances in surgical approaches and systemic chemotherapy have enabled repeat hepatectomies for remnant liver recurrence. Previous studies have also demonstrated that repeat hepatectomy prolongs survival and leads to acceptable mortality and morbidity rates.7,8

Previous studies have reported that the median recurrence-free survival of patients with colorectal cancer liver metastasis (CRLM) is around 1 year after initial hepatectomy, and 80% experience recurrence within 2 years of initial hepatectomy.9,10 After repeat hepatectomy, the majority of patients receive second-line or more systemic chemotherapy with a reduced liver volume during the remainder of the follow-up. However, the chemotherapy-induced liver injury in metastatic colorectal cancer may be worse in patients with reduced liver function.11,12 We assumed that a deterioration of liver function may occur after repeat hepatectomy, and this can affect survival rates of patients. In the current study, we aimed to evaluate the characteristics of patients with repeat hepatectomy, their changes in liver function, and the relationship with survival.

Materials and Methods

We retrospectively reviewed the medical records of patients who underwent hepatectomy for CRLM in our institution from January 2012 to December 2017. Patients who were initially diagnosed with liver-only metastasis and underwent R0 resection at the first hepatectomy were included. Patients with extrahepatic metastasis at the first hepatectomy, or other liver diseases, including liver cirrhosis and hepatocellular cell carcinoma, were excluded. The clinical characteristics of patients, such as age at diagnosis of the primary cancer, sex, and American Society of Anesthesiologists (ASA) score at the first liver metastasis, were investigated.13 The primary cancer characteristics, such as a location, primary tumor and regional lymph node (TN) categories, and lymphovascular and perineural invasion, were also investigated, as were the level of carcinoembryonic antigen (CEA) at diagnosis of the initial liver metastasis, neoadjuvant chemotherapy, and the longest diameter, total number, and lobar involvement of liver metastases. The institutional review board of Korea University Guro Hospital approved this study with a waiver of informed consent (approval 2020GR0055).

All patients were divided into 2 groups according to the total number of hepatectomies: LR1 (liver resection 1) included patients with single hepatectomy and no more hepatic recurrence after the initial hepatectomy, and LR2 included patients with 2 or more hepatectomies for recurrence of liver metastases after the initial hepatectomy. The clinicopathologic parameters and survival rates were analyzed.

Neoadjuvant chemotherapy was administered to patients with initially unresectable or borderline resectable metastasis. An oxaliplatin-based regimen with or without target agents, such as cetuximab or bevacizumab, was selected. Surgery after neoadjuvant chemotherapy was performed after evaluating responses to chemotherapy following the approval of a multidisciplinary team conference. Second- or later-line adjuvant chemotherapy of oxaliplatin or irinotecan-based regimen in combination with target agent was recommended to all patients after hepatectomy.

The parameters of the Child-Turcotte-Pugh (CTP) score (albumin, bilirubin, international normalized ratio, ascites, and encephalopathy) were acquired from laboratory and clinical records on an electrical medical records system in our institution. To evaluate the changes in liver function over time, the CTP scores of all patients were measured at 3-month intervals from the initial hepatectomy to the
last follow-up. The mean CTP scores at every 3 months were calculated, and their changes were analyzed for each group.

Data were analyzed using SPSS software version 21.0 (SPSS, Armonk, New York). Discrete values, such as sex, ASA score, TN categories, and primary tumor locations, were compared using Pearson’s χ² test. Student t test was used to compare continuous values such as age, CEA level, total number and longest diameter of liver metastases, and mean CTP scores. The pattern of change in the CTP scores of both groups were compared by linear mixed model analysis for repeated measures. The overall survival (OS) was analyzed by the Kaplan-Meier method and log-rank test. Cox proportional hazards regression analysis was used to evaluate risk factors for OS, and logistic regression analysis was used to evaluate risk factors for high CTP score after hepatectomy. Two-sided P < 0.05 was considered statistically significant.

Results

A total of 103 patients were included in this study (Fig. 1). After the first hepatectomy, hepatic recurrence occurred in 50 patients; among them, 37 patients underwent repeat hepatectomy for recurrent hepatic metastasis and they were classified into the LR2 group. In total, 53 patients who underwent single hepatectomy and no hepatic recurrence during follow-up were classified into the LR1 group. The clinicopathologic characteristics of patients were analyzed (Table 1). The mean CEA level of the LR2 group was higher than that of the LR1 group, and there were no statistical differences in the other characteristics between the 2 groups.

The median follow-up period of all patients was 39.1 months (minimum, 10.1 months; maximum, 98.2 months). The OS of the 2 groups was not statistically different (P = 0.159; Fig. 2a). Both groups showed similar OS until 30 months from the initial hepatectomy. Thirty months after the first hepatectomy, however, the OS of LR2 group had a steep decrease. Figure 2b shows that the OS of patients who survived after 27 months from the initial hepatectomy and the OS of both groups was statistically different (P = 0.049).

Figure 3 shows the changes in the mean CTP scores of both groups. The CTP scores in the LR2 group started to be statistically higher than those in the LR1 group 27 months after the first hepatectomy, and the pattern of changes in the mean CTP scores of both groups were significantly different by the linear mixed model method (P < 0.001). All patients were divided according to CTP scores at 27 months after the first hepatectomy. Patients with a CTP score of 5 were grouped into CTP1, and patients with a CTP score ≥6 were grouped into CTP2; the OS of both groups was significantly different (5-year OS: 48.6% in CTP1 versus 19.5% in CTP2; P = 0.046; Fig. 4).

The risk factors for OS of patients who survived after 27 months from the initial hepatectomy were analyzed (Table 2). The total number of liver metastases ≥ 4 and CTP score at 27 months after initial hepatectomy ≥ 6 were analyzed as significant risk factors. Repeat resection was a single risk factor for CTP score at 27 months after initial hepatectomy ≥ 6 after a univariate analysis of the logistic regression model (Table 3).

Discussion

This study shows that liver function may deteriorate after repeat hepatectomy for recurrent liver metastasis of colorectal cancer and suggests the necessity for regular examination of the liver function during follow-up and a careful approach to aggressive treatments for liver metastasis. It is widely accepted that repeat hepatectomy for recurrent liver metasta-
Table 1  Clinicopathologic characteristics of patients, n (%)

|                  | LR1 (N = 53) | LR2 (N = 37) | P     |
|------------------|--------------|--------------|-------|
| Age, yr          | 62.6 ± 10.6  | 59.2 ± 9.4   | 0.294 |
| Sex, male        | 34 (63.6)    | 25 (67.6)    | 0.688 |
| ASA score        |              |              | 0.969 |
| 1                | 2 (3.8)      | 1 (2.8)      |       |
| 2                | 46 (86.8)    | 31 (86.1)    |       |
| 3                | 5 (9.4)      | 4 (11.1)     |       |
| Primary tumor characteristics |          |              |       |
| Location         |              |              | 0.237 |
| Right colon      | 9 (17.0)     | 8 (21.6)     |       |
| Left colon       | 21 (39.6)    | 19 (51.4)    |       |
| Rectum           | 23 (43.4)    | 10 (27.0)    |       |
| T category       |              |              | 0.266 |
| 1–2              | 7 (13.2)     | 1 (2.9)      |       |
| 3                | 35 (66.0)    | 27 (71.1)    |       |
| 4                | 11 (20.8)    | 7 (20.0)     |       |
| N categories     |              |              | 0.106 |
| 0                | 18 (34.0)    | 9 (25.7)     |       |
| 1                | 14 (26.4)    | 17 (48.6)    |       |
| 2                | 21 (39.6)    | 9 (25.7)     |       |
| Lymphovascular invasion | 23 (43.4) | 17 (48.6) | 0.672 |
| Perineural invasion | 21 (39.6) | 13 (37.1) | 0.859 |
| Liver metastasis characteristics |          |              |       |
| Synchronous metastasis | 36 (67.9) | 28 (75.7) | 0.422 |
| CEAa             | 43.7 ± 102.9 | 165.0 ± 476.0 | <0.001 |
| Neoadjuvant chemotherapy | 16 (30.2) | 17 (45.9) | 0.112 |
| Length of the longest diameter, cma | 3.5 ± 3.4 | 4.2 ± 4.1 | 0.137 |
| Total numbera    | 3.6 ± 4.9    | 4.5 ± 4.8    | 0.403 |
| Bilobar involvement | 24 (45.3) | 22 (59.5) | 0.173 |

CEA, carcinoembryonic agent at diagnosis of initial liver metastasis.

*aMean ± SD.

Fig. 2  (a) Kaplan-Meier curves comparing the OS of all patients. (b) Kaplan-Meier curves comparing the OS of patients who survived 27 months after initial hepatectomy. LR1, patients with single hepatectomy; LR2, patients with repeat hepatectomy.
Cirrhosis improves the survival rates of recurrent disease to a greater extent than chemotherapy-only treatment. In this study, there was no statistical difference in OS between the 2 groups. However, 30 months after initial hepatectomy, the survival of the LR2 group showed a steep decrease compared with that of LR1. In addition, the differences in liver function between the 2 groups began 27 months after the initial hepatectomy, and we consider that there is a certain relationship between the change in liver function and survival after repeat hepatectomies.

The liver function of the LR2 group was affected by a combination of repeat hepatectomy and chemotherapy toxicity. To maintain the liver function after hepatectomy, there should be a limit to hepatocyte death and metabolic stress with sufficient synthetic function. The lack of sufficient regeneration of the liver parenchyma can cause remnant liver function to fail after excessive resection. Intraoperative blood loss more than 1 L and blood transfusion have also been shown to be associated with decreased liver function. Moreover, chemotherapy-associated steatohepatitis is a preexisting parenchymal disease of the liver that can be a significant risk factor of posthepatectomy liver failure. Sinusoidal injury can occur as a result of oxaliplatin-based chemotherapy, and 5-fluorouracil and irinotecan treatment can reduce the regenerative capacity of remnant liver volume. As more patients with colorectal liver metastases are treated with neoadjuvant chemotherapy, chemotherapy-induced toxicity is a significant matter to consider before hepatectomy. Thus, repeat surgery itself and chemotherapy-induced toxicity, as well as the reduced liver volume, are significant risk factors of worsening the liver function of the LR2 group.

It has been demonstrated that patients with liver cirrhosis have a worse prognosis than patients without liver cirrhosis. The authors reported that the compliance to chemotherapy was lower in the liver cirrhosis group than in the non–liver cirrhosis group. It is difficult to identify an exact compliance to chemotherapy for colorectal cancer patients with liver cirrhosis because those patients are initially excluded in most studies. In this study, the reason for the worse OS of the LR2 group 30 months after the first hepatectomy can be carefully assumed to be a worse compliance with chemotherapy caused by a deterioration of liver function 27 months after the initial hepatectomy. Stage IV colorectal cancer patients generally receive second-line treatment or more chemotherapy during the follow-up period.
The oncologic outcomes of combination therapy of 3 major chemotherapy agents (fluorouracil, irinotecan, and oxaliplatin) with anti-EFGR (epidermal growth factor receptor) agents or tyrosine kinase inhibitor therapy have been shown in previous studies. The benefits as a second-line or third-line therapy were not only limited to disease-free survival, but they also improved OS for stage IV colorectal cancer patients in some studies. In cases of disease progression after second-line treatment, only 4 to 6 months of survival are possible with the best supportive care alone. Although some patients

Table 2  Hazard ratio for OS: analysis of patients who survived 27 months after initial hepatectomy

| Variable                                      | Univariate analyses | Multivariate analyses |
|-----------------------------------------------|---------------------|-----------------------|
|                                               | HR                  | 95% CI                | P        | HR                  | 95% CI                | P        |
| Age, yr                                       |                     |                       |         |                     |                       |          |
| <65                                           | 1                   |                       |         |                     |                       |          |
| ≥65                                           | 1.353               | 0.585                 | 3.129   |                     |                       |          |
| Sex                                           |                     |                       |         |                     |                       |          |
| Female                                        | 1                   |                       |         |                     |                       |          |
| Male                                          | 1.955               | 0.663, 5.765          | 0.224   |                     |                       |          |
| Primary tumor-related variables               |                     |                       |         |                     |                       |          |
| Location                                      |                     |                       |         |                     |                       |          |
| Right colon                                   | 1                   |                       | 0.339   |                     |                       |          |
| Left colon                                    | 0.689               | 0.223, 2.128          |         |                     |                       |          |
| Rectum                                        | 0.156               | 0.102, 1.442          |         |                     |                       |          |
| T category                                    |                     |                       |         |                     |                       |          |
| 1–2                                           | 1                   |                       |         |                     |                       |          |
| 3–4                                           | 1.236               | 0.543, 2.816          | 0.613   |                     |                       |          |
| N category                                    |                     |                       |         |                     |                       |          |
| 0                                             | 1                   |                       |         |                     |                       |          |
| 1–2                                           | 1.458               | 0.561, 3.790          | 0.439   |                     |                       |          |
| Lymphovascular invasion                       |                     |                       |         |                     |                       |          |
| No                                            | 1                   |                       |         |                     |                       |          |
| Yes                                           | 1.341               | 0.567, 3.167          | 0.504   |                     |                       |          |
| Perineural invasion                           |                     |                       |         |                     |                       |          |
| No                                            | 1                   |                       |         |                     |                       |          |
| Yes                                           | 0.942               | 0.399, 2.343          | 0.942   |                     |                       |          |
| Liver metastasis related variables            |                     |                       |         |                     |                       |          |
| CEA                                           |                     |                       |         |                     |                       |          |
| <5                                            | 1                   |                       |         |                     |                       |          |
| ≥5                                            | 2.49                | 0.917, 6.761          | 0.073   |                     |                       |          |
| Synchronous metastasis                        |                     |                       |         |                     |                       |          |
| No                                            | 1                   |                       |         |                     |                       |          |
| Yes                                           | 1.284               | 0.505, 3.264          | 0.599   |                     |                       |          |
| Tumor size                                    |                     |                       |         |                     |                       |          |
| <5                                            | 1                   |                       |         |                     |                       |          |
| ≥5                                            | 1.173               | 0.462, 2.979          | 0.738   |                     |                       |          |
| Neoadjuvant chemotherapy                      |                     |                       |         |                     |                       |          |
| No                                            | 1                   |                       |         |                     |                       |          |
| Yes                                           | 1.295               | 0.544, 3.083          | 0.559   |                     |                       |          |
| Total number of metastasis                    |                     |                       |         |                     |                       |          |
| <4                                            | 1                   |                       |         |                     |                       |          |
| ≥4                                            | 3.832               | 1.641, 8.952          | 0.002   | 3.650               | 1.256, 10.586         | 0.017   |
| CTP score at 27 months after initial hepatectomy |                 |                       |         |                     |                       |          |
| 5                                             | 1                   |                       |         |                     |                       |          |
| 6                                             | 11.197              | 3.842, 32.634         | <0.001  | 1                   | 2.216, 1.369          | 0.001   |
| Lobar involvement                             |                     |                       |         |                     |                       |          |
| Unilobar                                      | 1                   |                       |         |                     |                       |          |
| Bilobar                                       | 2.040               | 0.956, 4.356          | 0.065   |                     |                       |          |
| Repeat hepatectomy                            |                     |                       |         |                     |                       |          |
| No                                            | 1                   |                       |         |                     |                       |          |
| Yes                                           | 2.181               | 0.983, 4.842          | 0.055   |                     |                       |          |

CI, confidence interval; HR, hazard ratio.
are still able and willing to receive further therapy, not all patients can continue with more chemotherapy, especially those with aggravated liver function. Thus, monitoring liver function is important to maintain chemotherapy in stage IV colorectal cancer patients.

The recent trend of aggressive resection for liver metastasis has been supported by acceptable morbidity and mortality and improved survival.26,27 Furthermore, neoadjuvant chemotherapy enabled the conversion of borderline or unresectable liver metastasis to resectable metastasis in approximately 10% to 30% of cases and provides more chances for curative resection.28 However, we need to carefully consider when these kinds of therapies are applied before repeat hepatectomy. As the survival of stage IV patients is improved, the management and monitoring of changes in clinical findings during the long-term of follow-up are becoming more significant. Thus, further studies should be performed to determine methods to maintain compliance to chemotherapy after repeat hepatectomy, such as identification of a proper dose reduction for remnant liver function or regular measurement of portal hypertension during follow-up.

There are several limitations to this study. Among all variables in the CTP score, grading ascites and encephalopathy required subjective assessment, and all variables in the CTP score carried the same weight. In addition, because the CTP has only 10 different scores (5–15), statistical analysis using mean values may not be appropriate. Further study can be performed to assess the liver function after repeat hepatectomy more exactly by using another scoring system such as MELD score (model for end-stage liver disease) or by incorporating additional prognostic information on the portal blood velocity or hepatic venous pressure gradient.29

Conclusion

Colorectal cancer patients who underwent repeat hepatectomy for recurrent liver metastasis may experience a reduction in liver function after a long-term follow-up. A careful approach to repeat hepatectomy and monitoring of liver function after repeat hepatectomy should be required to maintain the survival of patient with recurred liver metastasis.

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