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Therapeutic Strategy of Colorectal Liver Metastasis Using Modified-JHBPS Nomogram

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Abstract. *Background/Aim: We attempted to stratify prognosis using the modified Journal of Hepato-Biliary-Pancreatic Sciences (mJHBPS) nomogram upon identification of colorectal liver metastasis (CRLM) and to investigate which strategy is better, surgery first (SF) or chemotherapy first (CF), in each risk group. Patients and Methods: A total of 137 patients with CRLM who underwent resection of the primary tumor were included. Patients with brain, bone, or perihilar lymph node metastases were excluded. Patients were scored using the mJHBPS nomogram upon identification of CRLM. Prognosis was investigated using event-free survival (EFS) and overall survival (OS). Results: The nomogram allowed stratification of patients using EFS and OS: low-risk (0-6 score, n=38), medium-risk (7-11 score, n=42), and high-risk (12≥ score, n=57). In the low-risk group, the EFS and OS of the CF group were significantly poorer than those of the SF group (p=0.019 and p=0.014, respectively). CF was an independent prognostic factor for both EFS and OS. Conclusion: The mJHBPS nomogram can stratify CRLM patients with sufficient differences in EFS and OS. SF was recommended for patients in the low-risk group.*

In technically resectable colorectal liver metastasis (CRLM), surgical resection is widely recommended to prolong survival; however, alternative effective systemic therapy regimens, such as FOLFOX, CapeOX, FOLFIRI, FOLFOXIRI, or targeted agents (1-7), have been introduced to prolong the survival of patients with resectable or unresectable CRLM. The treatment strategy for technically resectable CRLM has been introduced in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) clinical practice guidelines (8, 9). Although upfront surgery was introduced as an option for oligometastasis or obviously resectable disease, these guidelines do not introduce the decision criteria for surgery first (SF) and chemotherapy first (CF) for patients with resectable CRLM. Preoperative chemotherapy has been reported to have the potential to reduce the risk of tumor recurrence (10); however, it is unclear which strategy, SF or CF, is better to prolong survival in each case of CRLM.

To determine SF or CF for the treatment of CRLM, various prognostic scores which identified patients with survival benefits after resection, have been introduced (11-15). However, most of these previous reports developing the prognostic scores of CRLM analyzed only surgically resected patients. To determine the treatment strategy for CRLM, it is necessary to analyze not only the cases in which hepatectomy was performed but also those who were initially eligible candidates for hepatectomy but finally could not undergo hepatectomy after chemotherapy because of tumor progression. Moreover, to correctly evaluate the prognostic impact of SF and CF for CRLM, we should assess the patient's prognosis based on the recognition of CRLM. However, few retrospective analyses have evaluated prognosis upon the discovery of CRLM (11-15).

In this study, we focused on the JHBPS nomogram, which can predict disease-free survival after hepatectomy. This nomogram was calculated using the following parameters: timing of appearance of liver metastasis, lymph node status of the primary tumor, number of liver tumors, largest liver tumor diameter, extrahepatic metastatic disease, and CA19-9 levels. For the number of liver tumors, largest liver tumor diameter, extrahepatic metastasis, and CA19-9 levels parameters, the "preoperative score" using the timing "before hepatectomy" and not the CRLM discovery was adopted; especially in patients who underwent preoperative chemotherapy (15). Although the JHBPS nomogram is often used in patients who are candidates for hepatectomy for CRLM upon recognition, it was constructed using not only the preoperative parameters of patients with SF but also the preoperative parameters of CF

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Key Words: Colorectal liver metastasis, surgery, chemotherapy, nomograms, prognosis.

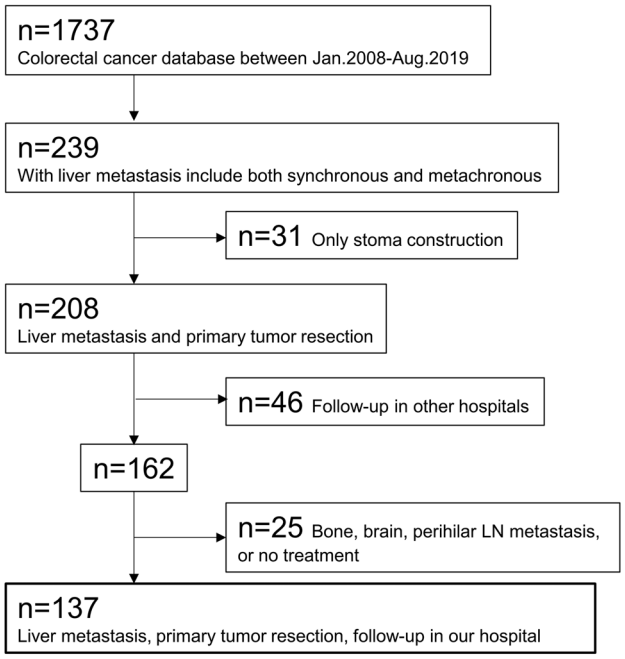

Figure 1. *Consort diagram of patient selection. LN: Lymph node.*

Table I. *mJHBPS nomogram.*

Risk factor	Score at CRLM discovery
Timing of liver metastases	
Metachronous	0
Synchronous	3
Primary tumor LN status	
Negative	0
Positive	3
Number of tumors (at CRLM discovery)	
1	0
2-4	4
≥5	9
Largest tumor diameter (at CRLM discovery)	
≤5 cm	0
>5 cm	2
Extrahepatic metastatic disease (at CRLM discovery)	
No	0
Yes	4
CA19-9 level (at CRLM discovery)	
≤100 U/ml	0
>100 U/ml	4

CRLM: Colorectal liver metastasis; LN: lymph node; CA19-9: carbohydrate antigen 19-9.

patients after preoperative chemotherapy. Hence, it remains unclear whether the JHBPS nomogram would truly be able to appropriately determine the treatment strategy for CRLM at the time of CRLM discovery. In this study, we developed a modified JHBPS (mJHBPS) nomogram, which was constructed using the same parameters as the JHBPS nomogram. However, the number of liver tumors, the largest liver tumor diameter, extrahepatic metastasis, and CA19-9 levels were analyzed using the timing of CRLM discovery. The mJHBPS nomogram reflected the condition at the time when CRLM was detected before chemotherapy. We included patients who were initially eligible candidates for hepatectomy but could not undergo surgery after chemotherapy. Moreover, we tried to stratify the prognosis using the mJHBPS nomogram, dividing patients into low-, medium-, and high-risk groups, and investigated the best treatment strategy for CRLM, whether SF or CF in each risk group.

Patients and Methods

A prospectively maintained database of patients with colorectal cancer in our hospital between January 2008 and August 2019 was reviewed to identify candidates. Of the 208 patients who underwent resection of the primary tumor with liver metastasis, including both synchronous and metachronous metastases, patients who were followed up in other hospitals (n=46) were excluded. Furthermore, patients who had bone, brain, or perihilar lymph node metastasis or no treatment for metastasis (n=25) were also excluded. Finally, 137 patients were examined in this study (Figure 1). The study protocol was approved by the Institutional Review Board of the Kyoto Prefectural University of Medicine (approval number: ERB-C-1359-2).

Preoperative CRLM was assessed using ultrasonography, dynamic multidetector-low computed tomography (CT), and enhanced magnetic resonance imaging (MRI). A volumetric study was performed using CT images. Liver function was evaluated using the indocyanine green (ICG) retention rate at 15 min. At our institution, CRLM is considered resectable if it is technically possible to remove all tumors and preserve a sufficient amount of liver parenchyma to meet the future liver remnant plasma clearance rate of ICG of ≥0.05 (16).

The treatment strategy for CRLM at our institution is as follows: Synchronous CRLM – after resection of the primary lesion, a specified amount of chemotherapy was administered for approximately 3-4 months. Subsequently, surgical resection was performed if the number of liver metastatic lesions was less than 5, all the liver metastatic lesions were expected to be resected completely, and the patient's future liver remnant plasma clearance rate of ICG was ≥0.05 (16). The chemotherapy regimen administered from 2013 to 2017 was CapeOX + Bmab before and after hepatectomy. In 2017 or later, FOLFOX + Pmab or Cmab for left-sided colorectum and RAS wild type and CapeOX + Bmab or FOLFOXIRI + Bmab for the others were administered pre-hepatectomy. The right-sided colon included the cecum, ascending colon, and transverse colon. The left-sided colorectum included the descending colon, sigmoid colon, and rectum. In exceptional circumstances, such as cases anticipated to have no complications, CRLM was resected along with the primary lesions. Metachronous CRLM – to detect metastatic lesions in the liver, surgical resection was performed with the same prerequisites as above. Patients who did not meet the criteria for resection underwent surgical

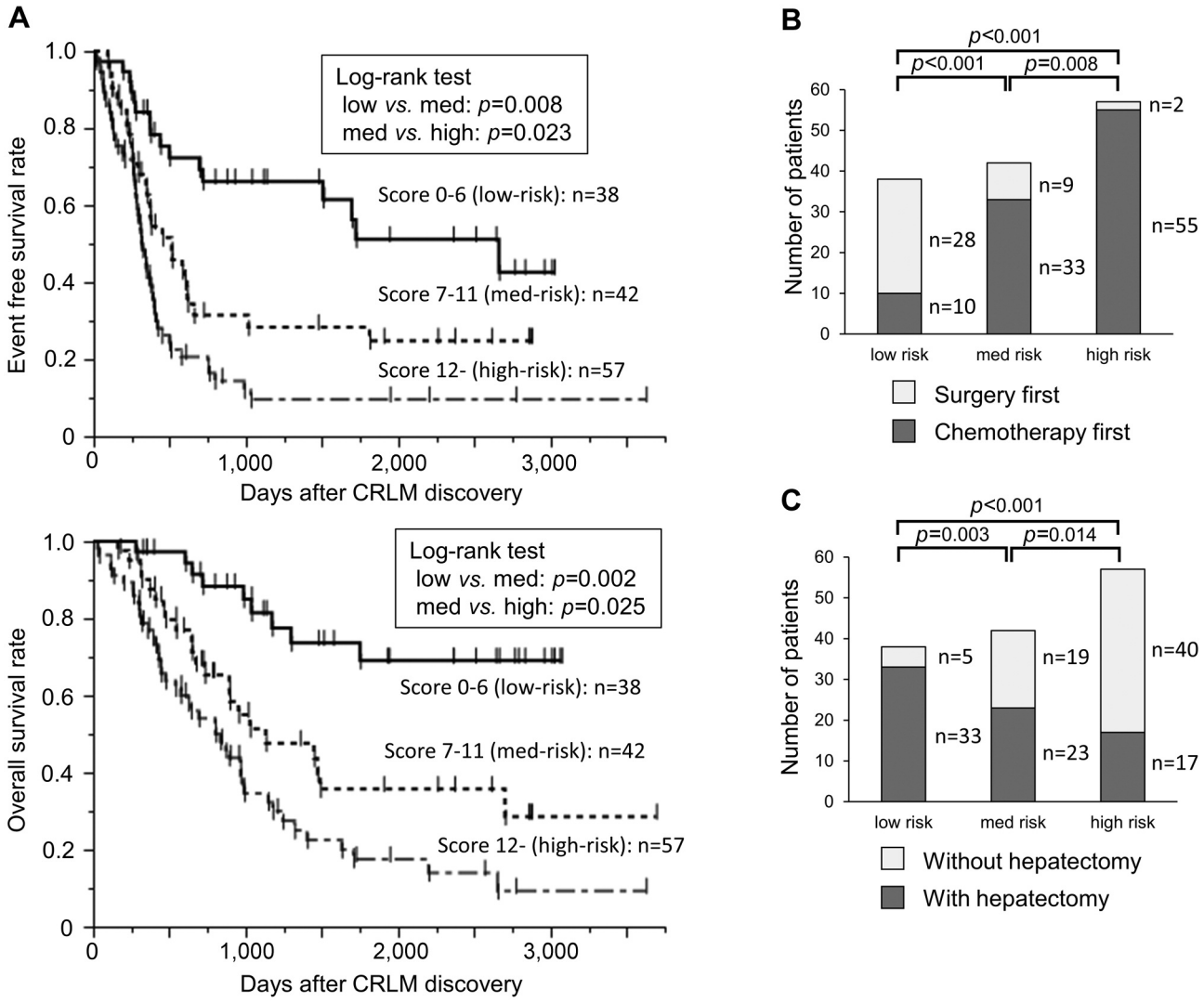

Figure 2. *Prognosis and treatment of patients in each risk group. A) The mJHBPS nomogram can stratify EFS and OS. A score of 0-6 is defined as the low-risk group, a score of 7-11 is defined as the medium-risk group, and a score of 12 or more is defined as the high-risk group. B) The number of patients of surgery first or chemotherapy first in each risk group. C) The number of patients with or without hepatectomy in each risk group. EFS: Event-free survival; OS: overall survival; med: medium.*

resection if both the attending physician and the liver surgeon reached the same decision.

Patients were followed up with tumor markers and CT every three-six months. Recurrence or disease progression was defined based on radiological examination. Hepatectomies were considered in patients with initially unresectable CRLM when all CRLMs were technically resectable after systemic therapy with a good response. Liver dissection was mainly performed using an ultrasonic device with Pringle maneuver clamping for 15 min, followed by a 5-min de-clamping time.

The mJHBPS nomogram was calculated using the following scores: timing of liver metastasis (metachronous, 0; synchronous, 3), primary tumor lymph node status (negative, 0; positive, 3), number of tumors (at identification of CRLM) (1, 0; 2-4, 4; 5≤, 9), largest tumor diameter (at identification of CRLM) (≤5 cm, 0; >5 cm, 2), extrahepatic metastatic disease (at identification of CRLM) (no, 0; yes, 4), CA19-9 (at identification of CRLM) (≤100, 0; >100, 4) (Table I). The number of tumors and tumor diameters was measured using CT or MRI.

Prognosis was evaluated as event-free survival (EFS) and overall survival (OS). EFS was determined from the time of CRLM discovery to recurrence in patients who underwent hepatectomy or progressive disease in patients without hepatectomy. Progressive disease was determined according to RECIST guidelines (17). OS was determined from the time of CRLM discovery until death.

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Survival curves were generated using the Kaplan–Meier method and compared using a log-rank test. Statistical significance was set at $p<0.05$. Independent prognostic

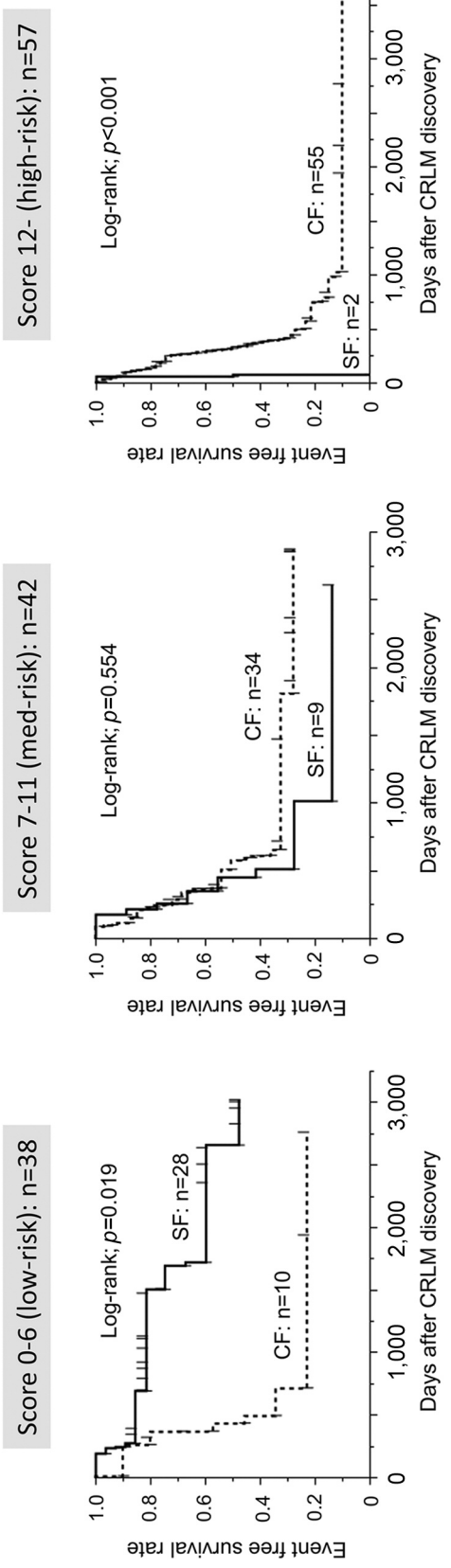

Figure 3. *EFS and OS by treatment order in each risk group. In the low-risk group, CF has a significantly poorer survival in EFS and OS. In the high-risk group, SF has a significantly poorer survival in EFS. Other analyses do not show statistical differences. EFS: Event-free survival; OS: overall survival; CF: chemotherapy first; SF: surgery first.*

Table II. *Patient characteristics*.

Variables(n=137)	n (%)
Gender	
Male	80 (58)
Female	57 (42)
Age (years old)	
<70	81 (59)
≥70	56 (41)
Location of primary tumor	
Right	44 (32)
Left	93 (68)
Timing of liver metastasis	
Metachronous	50 (36)
Synchronous	87 (64)
Lymph node metastasis of primary tumor	
Negative	39 (28)
Positive	98 (72)
Number of tumors (at CRLM discovery)	
1	46 (33)
2-4	49 (36)
≥5	42 (31)
Largest tumor diameter (cm) (at CRLM discovery)	
≤5	116 (85)
>5	21 (15)
Extrahepatic metastatic disease (at CRLM discovery)	
No	95 (69)
Yes	42 (31)
CA19-9 (U/ml) (at CRLM discovery)	
≤100	97 (71)
>100	40 (29)
CEA (ng/ml) (at CRLM discovery)	
<10	62 (45)
≥10	75 (55)
Treatment order	
Surgery first	39 (28)
Chemotherapy first	98 (72)
UFT/LV	4
Cape	3
S-1	5
SOX	1
CapeOX (±Bmab)	39
FOLFOX (±Bmab, Pmab, Cmab)	38
FOLFIRI (±Bmab)	4
FOLFOXIRI (±Bmab)	4
Chemotherapy after hepatectomy	
Absent	31 (23)
Present	42 (30)
UFT/LV	8
Cape	3
S-1	4
CapeOX (±Bmab)	20
FOLFOX	4
IRIS	1
FOLFIRI+Bmab	1
FOLFOXIRI	1
No hepatectomy	64 (47)
KRAS	
Wild type	50 (36)
Mutation	34 (25)
Not examined	53 (39)

CRLM: Colorectal liver metastasis; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; UFT: tegafur-uracil; LV: leucovorin; Cape: capecitabine; S-1: tegafur-gemeracil-oteracil potassium; SOX: S-1 plus oxaliplatin; CapeOX: Cape plus oxaliplatin; FOLFOX: oxaliplatin and infused fluorouracil plus leucovorin; FOLFORI: irinotecan and infused fluorouracil plus leucovorin; FOLFOXIRI: infusional fluorouracil, leucovorin, oxaliplatin and irinotecan; IRIS: S-1 plus irinotecan; Bmab: bevacizumab; Cmab: cetuximab; Pmab: panitumumab.

factors for survival were determined using the Cox proportional hazards model. Items of the mJHBPS nomogram were included in the multivariate analysis because these factors were reported to be associated with prognosis and were selected as items of the nomogram (15). However, factors that divided one group into n=0-3 were excluded from the multivariate analysis. Statistical analysis was performed using JMP13.0 software (SAS Institute, Cary, NC, USA).

Results

The characteristics of the 137 patients are shown in Table II. The five-year EFS and OS of the 137 patients with synchronous and metachronous CRLMs were 26% and 37%, respectively. Mortality was not observed in this study. Using the mJHBPS nomogram, we divided these 137 patients into 3 groups (0-6, 7-11, and ≥12 scores) and compared the EFS and OS. These three groups were stratified using the EFS and OS (Figure 2A). Using the mJHBPS nomogram, we defined scores of 0-6 as the low-risk group, 7-11 as the medium-risk group, and ≥12 as the high-risk group. SF tended to be selected in the low-risk group (*vs*. med-risk, $p<0.001$, *vs*. high-risk, $p<0.001$). In contrast, CF tended to be selected in the high-risk group (Figure 2B). Finally, five patients in the low-risk group, 19 patients in the medium-risk group, and 45 patients in the high-risk group did not undergo hepatectomy (Figure 2C).

In each risk group, we compared the EFS and OS between the SF and CF groups (Figure 3). In the low-risk group, the EFS and OS of the CF group were significantly worse than those of the SF group ($p=0.019$ and $p=0.014$, respectively). In contrast, the EFS of the SF group was significantly worse than that of the CF group in the high-risk group ($p<0.001$), whereas there was no significant difference in OS between the two groups in the high-risk group ($p=0.557$). In the medium-risk group, there was no significant difference in either EFS or OS between the two groups.

Table III. *Patient characteristics in the low-risk group according to treatment order.*

Variables	CF	SF	*p*-Value
Gender			
Male	6	18	0.809
Female	4	10	
Age (years old)			
<70	5	19	0.315
≥70	5	9	
Location of primary tumor			
Right	2	8	0.590
Left	8	20	
KRAS			
Wild type	4	6	0.464
Mutation	3	2	
Timing of liver metastasis (at CRLM discovery)			
Metachronous	5	20	0.220
Synchronous	5	8	
Primary tumor LN (at CRLM discovery)			
Negative	7	11	0.095
Positive	3	17	
Number of liver metastasis (at CRLM discovery)			
1	7	25	0.151
2-4	3	3	
Largest tumor diameter (cm) (at CRLM discovery)			
≤5	9	28	0.090
>5	1	0	
Extrahepatic metastatic disease (at CRLM discovery)			
No	8	27	0.054
Yes	2	1	
CA19-9 (U/ml) (at CRLM discovery)			
≤100	10	28	-
>100	0	0	
CEA (ng/ml) (at CRLM discovery)			
≤10	7	22	0.584
10<	3	6	
Chemotherapy after hepatectomy			
Present	3	11	0.388
Absent	2	17	

CRLM: Colorectal liver metastasis; LN: lymph node; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CF: chemotherapy first; SF: surgery first.

The patient characteristics of the low-risk group according to treatment order are shown in Table III. There was no significant difference between the SF and CF for each variable. Table IV shows the results of the multivariate prognostic analysis for EFS and OS in the low-risk group. Timing of liver metastasis, primary tumor LN status, number of liver metastasis, and treatment order were included in multivariate analysis. CF was an independent prognostic factor for both EFS (p=0.029) and OS (p=0.028). Primary tumor lymph node metastasis and the number of liver metastases were also independent prognostic factors for EFS. The number of liver metastases was also an independent prognostic factor for OS.

Discussion

In this study, after applying the factors for the identification of CRLM in the nomogram, the EFS and OS of our patients were well stratified. It was suggested that the mJHBPS nomogram may be useful not only for predicting the prognosis of patients but also for deciding which of the two treatments, hepatectomy or chemotherapy, should be prioritized. The JHBPS nomogram that could predict the recurrence risk of CRLM after hepatic resection was reported in 2012 (15). This nomogram has been validated and introduced as useful for predicting recurrence after hepatectomy (18, 19). However, in clinical practice, the initial treatment for CRLM must be decided when CRLM is detected. The JHBPS nomogram was constructed using not only the preoperative parameters of patients with SF but also preoperative parameters after preoperative chemotherapy in CF patients. Moreover, patients who were initially eligible candidates for hepatectomy but could not undergo hepatectomy after chemotherapy because of tumor progression were excluded. Hence, it is still unclear whether the JHBPS nomogram would truly be able to appropriately determine the treatment strategy for CRLM at the time of CRLM discovery. In this study, we included patients who received CF after the discovery of CRLM but could not undergo hepatectomy because of progression. We could predict a substantial prognosis by stratifying patients into low-, medium-, and high-risk patients using the mJHBPS nomogram at the time of CRLM discovery. The mJHBPS nomogram was useful for predicting EFS and OS and was useful for the selection of treatment strategies for SF or CF.

In the low-risk group, SF was selected in most cases, and the patients in this group had better EFS and OS than the other groups. Similar to our results, Okuno *et al*. reported that pre-hepatectomy chemotherapy for initially resectable CRLM had no survival benefit (18). Our results are consistent with those of a previous report (18). CF has disadvantages, such as the disappearance of tumor lesions (20) and liver damage due to chemotherapy (21, 22). However, in this study, the lesions did not disappear in the CF patients. Tamandl *et al*. reported that sinusoidal obstruction syndrome (SOS) after oxaliplatin-based chemotherapy was associated with early recurrence (23). Hepatic endothelial damage or downregulation of heme oxygenase 1 associated with SOS may be the cause of early recurrence (23). Oxaliplatin was included in the regimen of all patients who received CF in the low-risk group in this study. Although we did not pathologically assess the liver

Table IV. *Multivariate cox proportional hazard analysis of EFS and OS in the low-risk group.*

		EFS			OS		
			Multivariate			Multivariate	
	n	5-year EFS (%)	RR (95%CI)	*p*-Value	5-year OS (%)	RR (95%CI)	*p*-Value
Timing of liver metastasis							
Metachronous	25	49.4	1	0.622	75.9	1	0.629
Synchronous	13	53.9	1.44 (0.319-5.95)		62.3	1.84 (0.156-42.4)	
Primary tumor LN							
Negative	18	69.4	1	0.002	63.1	1	0.339
Positive	20	37.2	14.1 (2.32-278)		73.7	2.73 (0.384-54.7)	
Number of liver metastasis (at CRLM discovery)							
1	32	55.4	1	0.002	77.6	1	0.015
2-4	6	22.2	26.8 (3.07-612)		20.8	27.2 (1.81-1180)	
Largest tumor diameter (cm) (at CRLM discovery)							
≤5	37	52.6		-	71.0		-
>5	1	0			0		
Extrahepatic metastatic disease (at CRLM discovery)							
No	35	50.4		-	70.0		-
Yes	3	66.7			50		
CA19-9 (U/ml) (at CRLM discovery)							
≤100	38	51.2		-	69.1		-
>100	0	-			-		
Treatment order							
SF	28	59.9	1	0.029	83.4	1	0.028
CF	10	22.9	4.23 (1.16-18.4)		33.8	5.72 (1.20-41.6)	

EFS: Event free survival; OS: overall survival; LN: lymph node; CRLM: colorectal liver metastasis; CA19-9: carbohydrate antigen 19-9; SF: surgery first; CF: chemotherapy first; RR: risk ratio; CI: confidence interval.

damage in patients who underwent CF using oxaliplatin, oxaliplatin might have affected the shorter long-term survival of the CF group in our study.

In the high-risk group, SF was selected in only two cases, and immediate hepatic recurrence developed after hepatectomy in both cases. Hence, in the high-risk group, we should consider the possibility of a latent tumor other than multiple visible tumors. Ayez *et al*. (24) reported that in patients with a high-risk score using the clinical risk score (12), the prognosis of patients who underwent neoadjuvant chemotherapy prior to hepatectomy was better than that of SF. Although the high-risk group had only two cases, our results support this previous report. To control not only the visible lesions but also the latent lesions or other occult distant metastases, and to avoid the necessity of massive hepatectomy, CF tends to be selected in many high-risk groups. Jones *et al*. reported that the management of CRLM should be performed by a specialist in liver surgery (25) because there was a difference in the assessment of resectability between specialist and non-liver surgeons. In the high-risk group, CF may provide more survival benefits than SF, and it is important to discuss with a liver surgery specialist and to carefully decide the timing of hepatectomy.

The location of the primary tumor (26-28) and *KRAS* status (29, 30) were reported as prognostic factors and were not included in the mJHBPS nomogram. We compared EFS and OS according to the location of the primary tumor or *KRAS* in each risk group. In any case, there was no significant difference in EFS and OS (data not shown). The impact of mono-factors may be minimal for prognosis; hence, a better treatment strategy should be considered in the future using a new nomogram including these factors that were available at the time of liver metastasis detection.

The limitations of this study must be addressed. One major limitation is the retrospective nature of the study, as well as the limited number of patients enrolled from a single institution. There is a potential bias by including both resectable and unresectable cases at the time of CRLM discovery. Moreover, the treatment regimen and strategy were not uniform; therefore, to provide definitive conclusions from

the results of the present study, further accumulation of cases and follow-up are required. Finally, we should consider the effect of recent advancements in chemotherapy, such as triplet chemotherapy (4) or immunotherapy (7).

In conclusion, the mJHBPS nomogram can stratify CRLM patients with sufficient differences in EFS and OS. SF was recommended for patients in the low-risk group.

Conflicts of Interest

The Authors declare no potential competing interests in relation to this study.

Authors' Contributions

H.K., H.I., Y.Y., R.M., J.K., H.S., T.A., Y.K., K.O., and E.O were involved in study design and data interpretation. H.K., H.I., Y.Y., R.M. and Y.K. were involved in the data analysis. All Authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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