Efficacy of Adjuvant Chemotherapy According to the Classification of Recurrence Risk Based on Systemic Inflammatory Markers in Patients With Liver Metastases of Colorectal Cancer

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Abstract. *Background/Aim:* Although complete resection of liver metastases colorectal cancer (CLM) is the only potentially curative treatment, surgery alone is not enough, as the recurrence rate after resection is high. Therefore, in clinical practice, adjuvant chemotherapy is performed after resection of CLM. However, the evidence supporting the efficacy of such adjuvant chemotherapy is not sufficient. Previous reports have noted that adjuvant chemotherapy after resection of CLM is effective only in patients with a high risk of recurrence. The purpose of this study was to classify the risk of recurrence using systemic inflammatory markers reportedly associated with clinical outcomes in patients with various types of malignancies, and evaluate the efficacy of adjuvant chemotherapy according to the risk of recurrence. *Patients and Methods:* The medical records of 119 patients with CLM who underwent potentially curative surgery between 1996 and 2017 were retrospectively reviewed. Preoperative blood samples were obtained within 2 weeks before resection of CLM. was calculated from the blood samples Dividing the serum C-reactive protein level by the serum albumin level derived the C-reactive protein-to-albumin ratio (CAR), reflecting the risk of recurrence. The optimal cut-off value of the CAR was determined according to receiver operating characteristic curve analysis, and then the patients were classified into the high-CAR (high

recurrence risk) or low-CAR (low recurrence risk) group. The relationship between the CAR and relapse-free survival after resection of CLM was examined and the efficacy of adjuvant chemotherapy according to the risk of recurrence was evaluated. *Results:* The cut-off value of the CAR was set at 0.0471. The relapse-free survival rate was significantly better in the low-CAR group than in the high-CAR group. Efficacy of adjuvant chemotherapy after resection of CLM was not recognized in the low-CAR group, whereas the relapse-free survival rates were significantly better for patients who were treated with adjuvant chemotherapy after resection of CLM in the high-CAR group. *Conclusion:* The preoperative CAR, as a systemic inflammatory marker, was found to be useful as a prognostic marker in patients with CLM who were treated with potentially curative resection. Furthermore, it was suggested that adjuvant chemotherapy after resection of CLM may be effective for preventing recurrence in patients with high levels of inflammatory markers who have a high risk of recurrence.

Treatment of colorectal cancer liver metastasis (CLM) is crucial for improving the prognosis of colorectal cancer (CRC), as the liver is the most common site of metastasis of CRC (1). Although complete resection is the only potentially curative treatment and the most effective treatment in patients with CLM (2-5), surgery alone is not enough, as the rate of recurrence after resection of CLM is very high (70-80%) (6-8). Therefore, in clinical practice, adjuvant chemotherapy is performed after resection of CLM. However, evidence supporting the efficacy of adjuvant chemotherapy after resection of CLM is not sufficient at present.

Although there have been a few reports showing the efficacy of adjuvant chemotherapy after resection of CLM, its effects were limited, as it was shown effective in prolonging relapse-free survival but not in improving overall survival (9-12). In previous reports on the significance of

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adjuvant chemotherapy after resection of CLM, adjuvant chemotherapy after resection has been found to be more effective for patients with a higher risk of recurrence than for those with a lower risk (9, 13). In clinical practice, adjuvant chemotherapy is often provided for patients who are considered to have a high risk of recurrence (14).

The purpose of this study was to classify the risk of recurrence using systemic inflammatory markers which have been reported to be associated with clinical outcomes in patients with various types of malignancies, and evaluate the efficacy of adjuvant chemotherapy according to the risk of recurrence.

Patients and Methods

Patients. We retrospectively reviewed the medical records of 119 patients who underwent complete macroscopic and microscopic (R0) resection of CLM at Osaka City University Hospital between January 1996 and December 2017. All patients enrolled in this study had undergone resection of CLM for the first time. Patients who had extrahepatic metastasis were excluded from this study.

This retrospective study was approved by the Ethics Committee of the Osaka City University (approval number: 4182) and conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Methods. Pretreatment blood samples were obtained within 2 weeks before resection of CLM. The C-reactive protein (CRP)-to-albumin ratio (CAR) was calculated from the blood samples by dividing the serum CRP level by the serum albumin level. The optimal cut-off value of the CAR was determined based on receiver operating characteristic (ROC) curve analysis, and patients were classified based on this value into the high-CAR group or the low-CAR group. The modified Glasgow prognostic score (mGPS) was defined according to the methods of a previous report (15) using the combination of the serum CRP and albumin levels: Patients with a CRP level of <1.0 mg/dl were allocated a score of 0; those in whom the CRP and albumin levels were ≥ 1.0 mg/dl and ≥ 3.5 g/dl, respectively, were allocated a score of 1; and those in whom the CRP and albumin levels were ≥ 1.0 mg/dl and albumin <3.5 g/dl, respectively, were allocated a score of 2.

Adverse events were graded using Common Terminology Criteria for Adverse Events (Version 4.03) (16). The worst grade for each adverse event was recorded.

Statistical analyses. The chi-square test, Fisher's exact test and Mann-Whitney *U*-test were used to analyze the significance of correlations between the CAR and the clinicopathological factors, and the significance of correlations between the chemotherapeutic regimens and the tolerance of chemotherapy. Relapse-free survival was defined as the interval between the date of resection of CLM and the date of the diagnosis of the first recurrence, death from any cause or last follow-up. Survival curves were made using the Kaplan-Meier method. Differences in the survival curves were assessed using the log-rank test. A multivariate Cox proportional hazards model was used to evaluate the prognostic factors associated with the survival. Factors with a *p*-value of less than 0.1 on the univariate analysis were included in the multivariate analysis.

Table I. Patient characteristics.

Characteristic	Value
Age, years	
Median (range)	65 (22-87)
Gender, n	
Male	65
Female	54
Detection of CLM, n	
Synchronous	53
Metachronous	66
Number of CLM, n	
1	68
2-4	38
≥ 5	13
Maximum size of CLM, cm	
Median (range)	3.0 (0.4-13.0)
Histological type of primary tumor, n	
Well/moderately differentiated	114
Poorly differentiated/mucinous	4
Unknown	1
Depth of primary tumor, n	
T1-3	78
T4	41
Lymph node metastasis of primary tumor, n	
Negative	49
Positive	70
CEA level before resection of CLM, ng/ml	
≤ 5	28
> 5	91
Adjuvant chemotherapy after resection of CLM, n	
Single-agent	59
Combination	24
None	36

CLM: Colorectal cancer liver metastasis; CEA: carcinoembryonic antigen.

All of the statistical analyses were performed using SPSS statistical software program, version 19.0 (IBM Corp., Armonk, NY, USA). A value of *p*<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The patient characteristics are summarized in Table I. The study cohort included 65 males and 54 females, with a median age of 65 years (range=22-87 years). Fifty-three patients had synchronous CLM. Sixty-eight patients had a single CLM. Eighty-three patients (69.7%) received adjuvant chemotherapy. The distribution of the regimen of adjuvant chemotherapy was as follows: Single-agent therapy with fluoropyrimidines, such as 5-fluorouracil plus leucovorin, capecitabine, tegafur-uracil/ leucovorin, or S-1: 59 patients; combination therapy with fluoropyrimidines and oxaliplatin, such as 5-fluorouracil with leucovorin and oxaliplatin, or and capecitabine with oxaliplatin: 24 patients.

Figure 1. Receiver operating characteristic curve analysis of the C-reactive protein to albumin ratio. Area under the curve=0.601; 95% confidence interval=0.500-0.703; $p=0.058$.

Classifications according to preoperative inflammatory markers. the CAR, which was a continuous variable, was used as the test variable, and the median relapse-free survival time (14.1 months) as the state variable. The ROC curve analysis of the preoperative CAR suggested an appropriate cut-off of 0.0471, with an area under the curve of 0.601 (95% confidence interval: 0.500-0.703, and sensitivity of 62.0% and specificity of 58.5% (Figure 1). Thus, 0.0471 was adopted as the cut-off value of preoperative CAR, and the patients were classified into the high-CAR group ($n=53$) or low-CAR group ($n=66$) accordingly. Based on the definition of the mGPS, 109 patients were classified as having a score of 0, nine as having a score of 1, and one as having a score of 2.

Survival analysis based on the CAR. The relapse-free survival rate was significantly worse in the high-CAR group than in the low-CAR group ($p=0.0157$) (Figure 2). Similarly, the relapse-free survival rate was significantly worse in patients with a high mGPS than in those with an mGPS of 0 ($p<0.0001$) (Figure 2).

Correlation between the CAR and clinicopathological factors. The correlation between the CAR and the clinicopathological factors is shown in Table II. When compared to the low-CAR group, the high-CAR group had a significantly larger number of CLM. However, there were no significant differences in other factors.

Figure 2. Kaplan-Meier curves for relapse-free survival after resection of colorectal cancer liver metastasis according to C-reactive protein-to-albumin ratio (CAR) (A) and modified Glasgow prognostic score (mGPS) (B). The relapse-free survival rate was significantly worse in the group with a high CAR than in that with a low CAR and in patients with a higher mGPS than in those with a low mGPS.

Correlation between the CAR and the location of recurrence after resection of CLM. No significant differences were observed in the location of the first recurrence after resection of CLM between the high-CAR group and the low-CAR group (Table III).

Efficacy of adjuvant chemotherapy after resection of CLM according to the CAR. Efficacy of adjuvant chemotherapy after resection of CLM was not recognized in the low-CAR group, with a low risk of recurrence, whereas adjuvant chemotherapy provided a significant relapse-free survival

Table II. The correlation between the C-reactive protein-to-albumin ratio (CAR) and clinicopathological factors of patients with liver metastasis of colorectal cancer (CLM).

Factor	CAR		p-Value
	Low	High	
Number of CLMs			
<5	63 (52.9%)	43 (36.1%)	0.017
≥5	3 (2.5%)	10 (8.4%)	
Maximum size of CLM			
<5 cm	52 (43.7%)	44 (37.0%)	0.644
≥5 cm	14 (11.8%)	9 (7.6%)	
Depth of primary tumor			
T1-3	43 (36.1%)	35 (29.4%)	<0.999
T4	23 (19.3%)	18 (15.1%)	
Lymph node metastasis of primary tumor			
Negative	31 (26.1%)	18 (15.1%)	0.190
Positive	35 (29.4%)	35 (29.4%)	
CEA level before resection of CLM			
≤5 ng/ml	16 (13.4%)	12 (10.1%)	<0.999
>5 ng/ml	50 (42.0%)	41 (34.5%)	

CEA: Carcinoembryonic antigen.

Table III. The correlation between the C-reactive protein-to-albumin ratio (CAR) and the location of recurrence after resection of liver metastasis of colorectal cancer.

Location of recurrence	CAR, n (%)		p-Value
	Low	High	
Remnant liver			
Negative	20 (25.6%)	17 (21.8%)	0.356
Positive	27 (34.6%)	14 (17.9%)	
Extrahepatic organs			
Negative	21 (26.9%)	8 (10.3%)	0.102
Positive	26 (33.3%)	23 (29.5%)	

benefit in the high-CAR group, with a high risk of recurrence (Figure 3).

Survival analysis according to chemotherapeutic regimen, limited to the group with a high-CAR. We then performed a sub-group analysis limited to the high-CAR group, with a high risk of recurrence (Figure 4). Among these patients, the relapse-free survival rates were significantly better in both the single-agent therapy group and the combination therapy group than in the no-adjuvant therapy group. However, no significant differences were observed in the relapse-free

Table IV. A comparison of the feasibility of adjuvant monotherapy and doublet therapy.

Factor	Single-agent therapy	Combination therapy	p-Value
Completion rate, %			
Overall	77.8	66.7	0.616
Relative dose intensity, %			
Median (range)	100 (8-100)	63 (35-100)	0.119
Adverse events, %			
Grade ≥3	14.8	66.7	0.020

survival rates between the single-agent therapy group and the combination therapy group.

Feasibility assessment of adjuvant chemotherapy. No significant differences were observed in the completion rate or relative dose intensity between the single-agent therapy group and the combination therapy group. However, the incidence of grade 3 or more adverse events was significantly higher in the combination therapy group than in the single-agent therapy group (66.7% vs. 14.8%, $p=0.020$) (Table IV).

Discussion

In this study, we investigated the prognostic significance of systemic inflammatory markers, such as the CAR and mGPS, for predicting the prognosis in patients with CLM who underwent a potentially curative operation.

Systemic inflammatory markers have been reported to be associated with clinical outcomes, such as the survival time after an operation and the chemotherapeutic efficacy, in patients with various types of malignancies, including CRC (17, 18). However, to our knowledge, this is the first report regarding the correlation between the CAR and prognosis after resection of CLM. As systemic inflammation has been reported to promote proliferation, invasion and metastasis (19-21), preoperative systemic inflammation is considered to provide a favorable environment for the development of micrometastases, resulting in an increasing risk of recurrence.

Both the CAR and mGPS are systemic inflammatory markers that can be calculated from the serum CRP and albumin concentrations. However, most patients are classified into the group with a low risk of recurrence when using the mGPS, as mentioned in previous reports (22-24). In the present study, 91.6% of patients were classified as having an mGPS of 0, which is associated with a better prognosis. Therefore, the CAR is more useful for clinical application than the mGPS in terms of well-balanced risk classification.

Figure 3. Kaplan-Meier survival curves for relapse-free survival after resection of colorectal cancer liver metastasis according to treatment with adjuvant chemotherapy or surgery alone for the group with a low C-reactive protein-to-albumin ratio (CAR) (A) and with a high CAR (B). No significant differences were observed in the relapse-free survival between the group treated with surgery-alone and the adjuvant chemotherapy group ($p=0.4100$) for those with a low CAR. However, in the analysis of the high-CAR group, the relapse-free survival rate was significantly better in the group treated with adjuvant chemotherapy than in that which underwent surgery alone.

Furthermore, the results of this study suggested that adjuvant chemotherapy after resection of CLM was effective only in patients with a high risk of recurrence and that the CAR was useful for risk classification. Although no significant relationships were observed between the relapse-free survival rate and adjuvant chemotherapy in the group with a low risk of recurrence (low CAR), adjuvant chemotherapy helped prolong the relapse-free survival in the

Figure 4. The Kaplan-Meier survival curves for the relapse-free survival in an analysis limited to the group with a high C-reactive protein-to-albumin ratio (CAR) according to treatment. The relapse-free survival rates were significantly better in both the single-agent therapy group and the combination therapy group than in the group treated with surgery alone ($p=0.0017$, $p=0.0094$, respectively). However, no significant differences were observed in the relapse-free survival rates between the single-agent therapy group and the combination therapy group ($p=0.5238$).

group, with a high risk of recurrence (high CAR). Therefore, not all patients who undergo resection of CLM need adjuvant chemotherapy, and it may be better to administer adjuvant chemotherapy only to those with a high risk of recurrence.

In addition, we compared the chemotherapeutic efficacy of each regimen of adjuvant chemotherapy. In the analysis limited to the high-CAR group, with a high risk of recurrence, both single-agent therapy and combination therapy were effective in preventing the recurrence, and there was no significant difference in the efficacy between these two regimens. We hypothesized that the efficacy of combination therapy would not exceed that of single-agent therapy because the patients treated with combination therapy might receive an insufficient dose of their drug due to their poor condition after resection of CLM. However, no significant differences were observed regarding the relative dose intensity or completion rate between the single-agent therapy group and the combination therapy group, although the incidence of grade 3 or more adverse events was higher in the combination therapy group than in the single-agent therapy group. It is hard to conclude that the additional effect of oxaliplatin in adjuvant chemotherapy after resection of CLM is poor based on the results of this study alone. However, the efficacy of single-agent therapy and that of combination therapy may be equivalent, and single-agent therapy may therefore be sufficient as adjuvant chemotherapy after resection of CLM.

Several limitations associated with the present study warrant mentioning. Firstly, the current study was a retrospective study with a small cohort conducted at a single center. Therefore, the cut-off value of the CAR used in this study was a provisional value. A large, prospective study should be performed to confirm our findings and determine the appropriate cut-off value of the CAR, although it may be difficult to conduct such a study because there are not many cases of curative resection of CLM. Secondly, the endpoint assessed in this study was relapse-free survival. The present study enrolled patients who underwent resection of CLM as long as 20 years ago. With the development of new cytotoxic and molecular-targeted therapies, the survival time after recurrence has been significantly prolonged compared to 20 years ago. Therefore, we assessed only relapse-free survival, not overall survival. However, not only relapse-free survival time, but also overall survival time may have to be assessed when evaluating the efficacy of adjuvant chemotherapy.

Conclusion

The preoperative systemic inflammatory markers were found to be useful as prognostic markers in patients with CLM who were treated with potentially curative resection. Furthermore, it was suggested that adjuvant chemotherapy after resection of CLM may be effective for preventing recurrence in patients with high levels of inflammatory markers who have a high risk of recurrence.

Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

Authors' Contributions

MS designed the study, performed the statistical analysis and draft the article. HN, TF and YI collected the clinical data and revised the article critically. KH and MO designed the study and critically reviewed the article. All Authors read and approved the final article.

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