Significance of Markers of Systemic Inflammation for Predicting Survival and Chemotherapeutic Outcomes and Monitoring Tumor Progression in Patients with Unresectable Metastatic Colorectal Cancer

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Abstract. *Background: Markers of systemic inflammation, such as the neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP) level and Glasgow prognostic score (GPS), have been reported to be useful prognostic indicators for various types of cancers. However, most of the existing reports investigated the preoperative status, and the significance of markers of systemic inflammation remains unclear in patients with unresectable metastatic colorectal cancer. The aim of the present retrospective study was to evaluate the significance of markers of systemic inflammation for predicting the prognosis and chemotherapeutic outcomes and monitoring the progression of the tumor in patients with unresectable metastatic colorectal cancer receiving palliative chemotherapy. Patients and Methods: A total of 110 patients with unresectable metastatic colorectal cancer who underwent palliative chemotherapy for metastatic tumors were enrolled in the study. We evaluated the relationships between the survival/chemotherapeutic response and pre-/post-treatment markers of systemic inflammation. The pre-treatment markers of systemic inflammation were measured within one week before the initiation of chemotherapy and the post-treatment markers of systemic inflammation were measured eight weeks after initiation of chemotherapy. Results: The overall survival rates were significantly worse in the group with high pre-treatment NLR/CRP/GPS, and that with high post-treatment CRP/GPS; the progression-free survival rate was significantly worse in the high post-treatment CRP group. As for chemotherapeutic response, patients with a low post-treatment CRP level had a significantly higher disease control rate than those with a high post-treatment CRP level. Moreover, the patients with a high pre-treatment CRP level and normalization after treatment exhibited better overall and progression-free survival rates and had a significantly higher disease control rate than those with high pre- and post-treatment CRP levels. Conclusion: Pre-treatment markers of systemic inflammation are useful for predicting prognosis in patients with unresectable metastatic colorectal cancer who receive palliative chemotherapy. Moreover, the CRP level can be used as a marker for predicting chemotherapeutic outcome and monitoring the progression of the tumor.*

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Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide (1). In particular, patients with unresectable metastatic disease have the worst prognosis among those with CRC.

Despite major advances in chemotherapy for unresectable CRC within the last 10 years (2, 3), it remains difficult to achieve a complete response with chemotherapy alone. Moreover, some patients are expected to have worse survival due to ineffectiveness of chemotherapy. The guidelines of the European Society for Medical Oncology recommend that physicians individualize treatment of patients with metastatic CRC according to tumor- and disease-related characteristics, such as the clinical presentation and pattern of tumor biology (4). Therefore, it is necessary to identify patients with a high possibility of poor survival, and various biomarkers for predicting survival and the chemotherapeutic outcome have been examined.

Recently, markers of systemic inflammation have been reported to correlate with survival in various types of cancers, including CRC (5-16). However, most previous reports investigated the prognostic significance of preoperative markers of systemic inflammation in patients treated with surgery (5, 6, 9, 11, 12), and there exist only few reports focusing on patients with unresectable metastatic cancer (7, 8, 10, 13-16). Moreover, only a few reports have investigated the significance of post-treatment markers of systemic inflammation and their usefulness as predictors of the chemotherapeutic response, and of factors for monitoring tumor progression (7, 8, 16).

The aim of this retrospective study was to evaluate the significance of markers of systemic inflammation for predicting survival and chemotherapeutic outcomes and monitoring the progression of the tumor in patients with unresectable metastatic colorectal cancer receiving palliative chemotherapy.

Patients and Methods

Patients' characteristics. We retrospectively reviewed a database of 110 patients who underwent palliative combination chemotherapy for unresectable colorectal cancer at the Department of Surgical Oncology of Osaka City University between 2006 and 2011.

The patients' characteristics are listed in Table I. The patient population consisted of 63 males and 47 females, with a median age of 64 years (range=27 to 86). Sixty-four patients had primary tumors located in the colon and 46 patients had primary tumors located in the rectum. A total of 46 patients had metachronous unresectable cancer and 64 patients had synchronous unresectable cancer. Sixty-two patients had only one organ affected by metastasis and 48 patients had more than one organ affected by metastasis. All patients underwent combination chemotherapy with oxaliplatin or irinotecan plus 5-fluorouracil/leucovorin or a pro-drug of 5-fluorouracil as first-line chemotherapy.

Measurement and definition of markers of systemic inflammation. The pre-treatment blood samples were obtained within one week before the initiation of chemotherapy and the post-treatment blood samples were obtained 8 weeks after the initiation of chemotherapy. The differential white blood cell count was analyzed using an XE-5000 hematology analyzer (Sysmex, Kobe, Japan), and the serum C-reactive protein (CRP) and albumin concentrations were measured using a chemiluminescent immunoassay (Wako, Osaka, Japan) based on the manufacturer's protocol. The neutrophil to lymphocyte ratio (NLR) was calculated from the blood samples by dividing the absolute neutrophil count by the absolute lymphocyte count. We defined the Glasgow prognostic score (GPS) according to previous reports (17) using the combination of an elevated CRP level (≥1 mg/dl) and hypo-albuminemia (<3.5 g/dl). Patients with both abnormalities were allocated a GPS of 2, while patients with only one of these abnormalities were allocated a GPS of 1 and patients with normal values for both parameters were allocated a GPS of 0.

Distribution of patients based on the markers of pre-treatment systemic inflammation. The median pre-treatment NLR was 2.8. Therefore, we set 3 as the cut-off value. Based on a cut-off value of 3, 44 patients were classified into the high pre-treatment NLR group and 61 patients were classified into the low pre-treatment NLR group.

The cut-off value for the serum CRP concentration used in this study was determined according to the definition of the GPS. Based on a cut-off value of 1.0 mg/dl, 30 patients were classified into the high pre-treatment CRP group and 72 patients were classified into the low pre-treatment CRP group.

According to the definition of the GPS, 64 patients were classified as having a GPS of 0, 26 patients as having a GPS of 1 and nine patients as having a GPS of 2. The patients with a GPS of 0 exhibited a better prognosis than did the patients with a GPS of 1 ($p=0.0274$), while there were no significant differences between the patients with a GPS of 1 and the patients with a GPS of 2 as to the overall survival rate ($p=0.6990$). Therefore, the patients with a GPS of 1 or 2 were classified into the high pre-treatment GPS group and those with a GPS of 0 were classified into the low pre-treatment GPS group.

We then examined the correlations between the markers of systemic inflammation and survival and chemotherapeutic response.

Evaluation. Response evaluations were performed every 8 weeks. A variation of approximately 1 week was regarded as allowable error. All patients were followed up with a physical examination, computed tomography, ultrasonography and blood tests, including measurements of the levels of tumor markers, such as carcinoembryonic antigen (CEA). Some patients underwent ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET) or colonoscopy as needed.

We adopted the Response Evaluation Criteria in Solid Tumors (RECIST) (18) to classify the treatment response, as follows: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response was defined as CR or PR, while disease control was defined as CR, PR or SD. Progression-free survival was defined as the time from the date of initiation of the first-line chemotherapy to disease progression. Overall survival was defined as the time from the date of initiation of the first-line chemotherapy to death from any cause or the last contact.

Statistical analysis. The significance of correlations between the pre-treatment markers of systemic inflammation and the clinicopathological characteristics was analyzed using the χ^2 test. The duration of survival was calculated according to the Kaplan–Meier method. Differences in the survival curves were assessed with the log-rank test. A multivariate analysis was performed according to the Cox proportional hazard model. All statistical analyses were conducted using the SPSS software package for Windows (SPSS Japan, Tokyo, Japan). Statistical significance was set at a p-value of <0.05.

Ethics statement. This research conformed to the provisions of the Declaration of Helsinki in 1995. All patients were informed of the investigational nature of this study and provided their written informed consent.

Results

Correlations between the pre-treatment markers of systemic inflammation and the survival/chemotherapeutic response. Regarding the pre-treatment inflammatory status, an assessment of the prognosis showed that the overall survival rates were significantly worse in the high pre-treatment NLR/CRP/GPS groups (NLR: $p<0.0001$; CRP: $p=0.0002$;

GPS: *p*=0.0047) (Figure 1). However, no relationships were observed between progression-free survival and any of the pre-treatment inflammatory markers, including the NLR/CRP/GPS (Figure 2). The distribution of the chemotherapeutic response with reference to the pre-treatment markers of systemic inflammation is shown in Table II. Although the objective response rates did not differ according to the pre-treatment NLR/GPS (NLR: 37.3% *vs*. 25.0%, *p*=0.207; GPS: 36.5% *vs*. 25.7%, *p*=0.369), the low pre-treatment CRP group had a significantly higher objective response rate than the high pre-treatment CRP group (40.0% *vs*. 16.7%, *p*=0.036).

Correlations between the pre-treatment markers of systemic inflammation and clinicopathological factors. The correlations between the pre-treatment markers of systemic inflammation and the clinicopathological factors are shown in Table III. The pre-treatment NLR had significant relationships with timing of detection of unresectable tumors (*p*=0.005), the number of organs affected by metastasis (*p*=0.029) and the pre-treatment CEA level (*p*=0.007). In contrast, the pre-treatment CRP level had no significant relationships with any of the clinicopathological factors. The pre-treatment GPS had a significant relationship only with peritoneal dissemination (*p*=0.015).

Correlations between the post-treatment markers of systemic inflammation and the survival/chemotherapeutic response. For the post-treatment inflammatory status, an assessment of prognosis showed that the overall survival rates were significantly worse in the high post-treatment CRP/GPS groups (CRP: *p*<0.0001; GPS: *p*=0.0195), while no relationships were observed between the overall survival and post-treatment NLR (Figure 3). The progression-free survival rate was significantly worse in the high post-treatment CRP group (*p*=0.0402), whereas no relationships were observed between the overall survival and post-treatment NLR/GPS (Figure 4).

The distribution of the chemotherapeutic response with reference to the post-treatment markers of systemic inflammation is shown in Table IV. Although the objective response rates did not differ according to the post-treatment NLR/GPS (NLR: 34.1% *vs*. 18.8%, *p*=0.261; GPS: 33.9% *vs*. 25.0%, *p*=0.602), the low post-treatment CRP group tended to have a higher objective response rate than did the high post-treatment CRP group (36.0% *vs*. 11.8%, *p*=0.085) and demonstrated a significantly higher disease control rate than the high post-treatment CRP group (81.4% *vs*. 47.1%, *p*=0.005).

Prognostic factors influencing long-term survival. The correlations between overall survival and various clinicopathological factors are shown in Table V. According to univariate analysis, overall survival exhibited significant relationships with the number of organs affected by metastasis (*p*=0.012), pre-treatment CEA level (*p*=0.024),
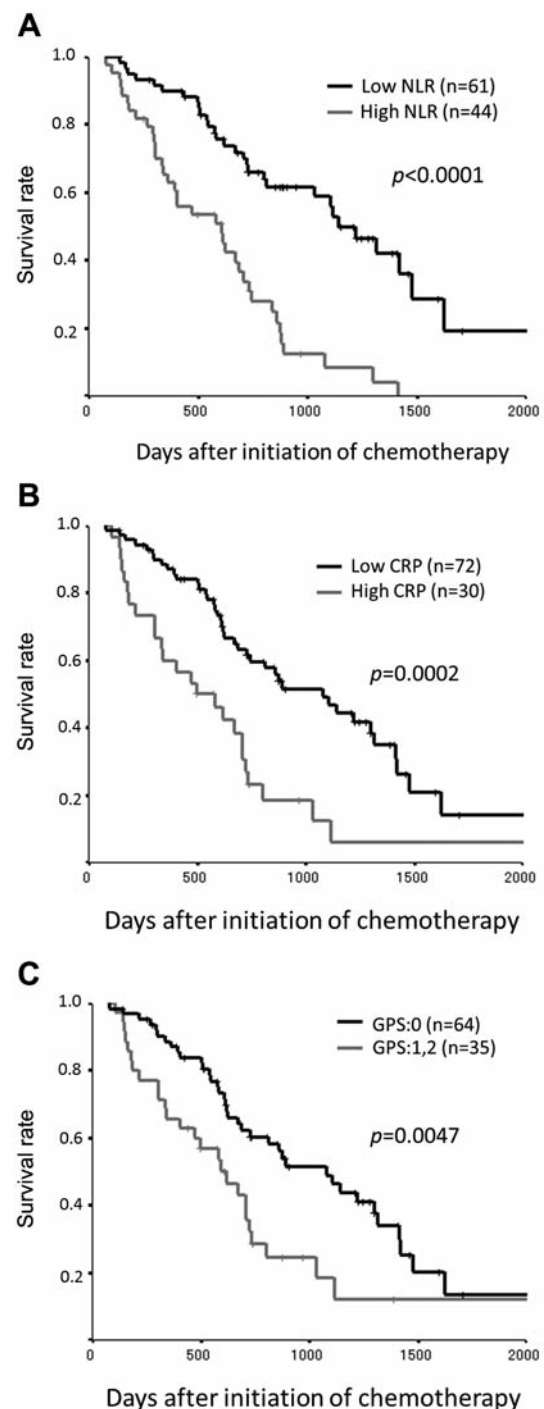

Figure 1. *A: Overall survival according to the pre-treatment neutrophil to lymphocyte ratio (NLR). The overall survival rate was significantly worse in the high pre-treatment NLR group (p<0.0001). B: Overall survival according to the pre-treatment C-reactive protein (CRP). The overall survival rate was significantly worse in the high pre-treatment CRP group (p=0.0002). C: Overall survival according to the pre-treatment Glasgow prognostic score (GPS). The overall survival rate was significantly worse in the high pre-treatment GPS group (p=0.0047).*
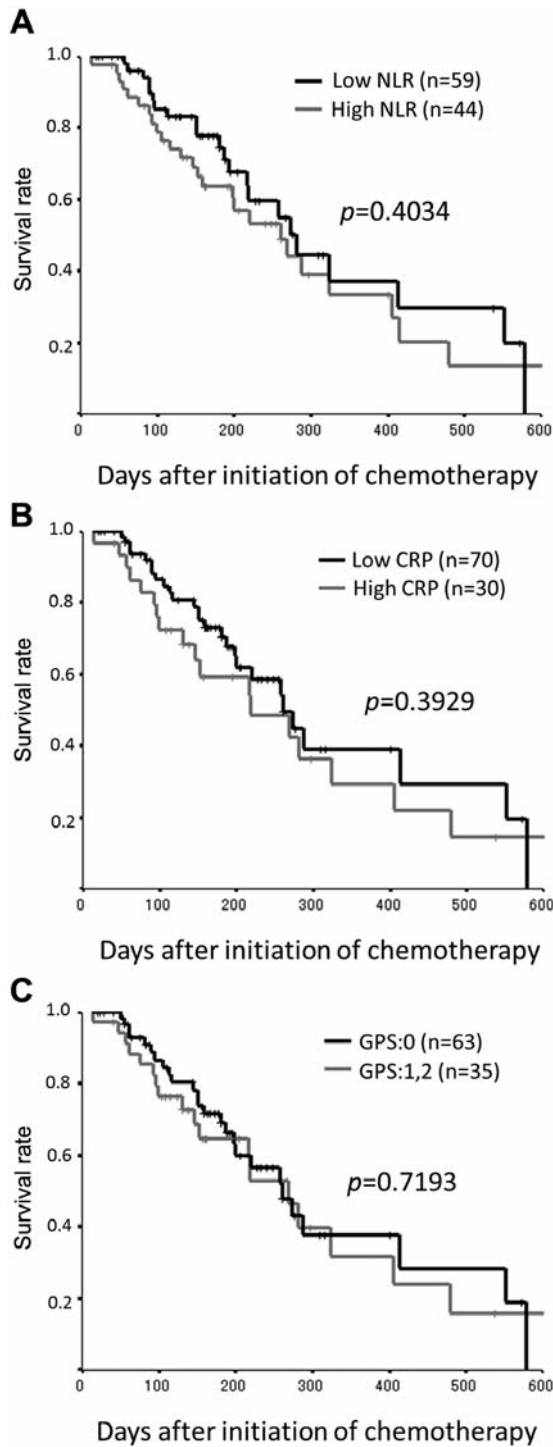
Figure 2. *A: Progression-free survival according to the pre-treatment neutrophil to lymphocyte ratio (NLR). There were no relationships between the pre-treatment NLR and tumor progression. B: Progression-free survival according to the pre-treatment C-reactive protein (CRP). There were no relationships between the pre-treatment CRP and tumor progression. C: Progression-free survival according to the pre-treatment Glasgow prognostic score (GPS). There were no relationships between the pre-treatment GPS and tumor progression.*
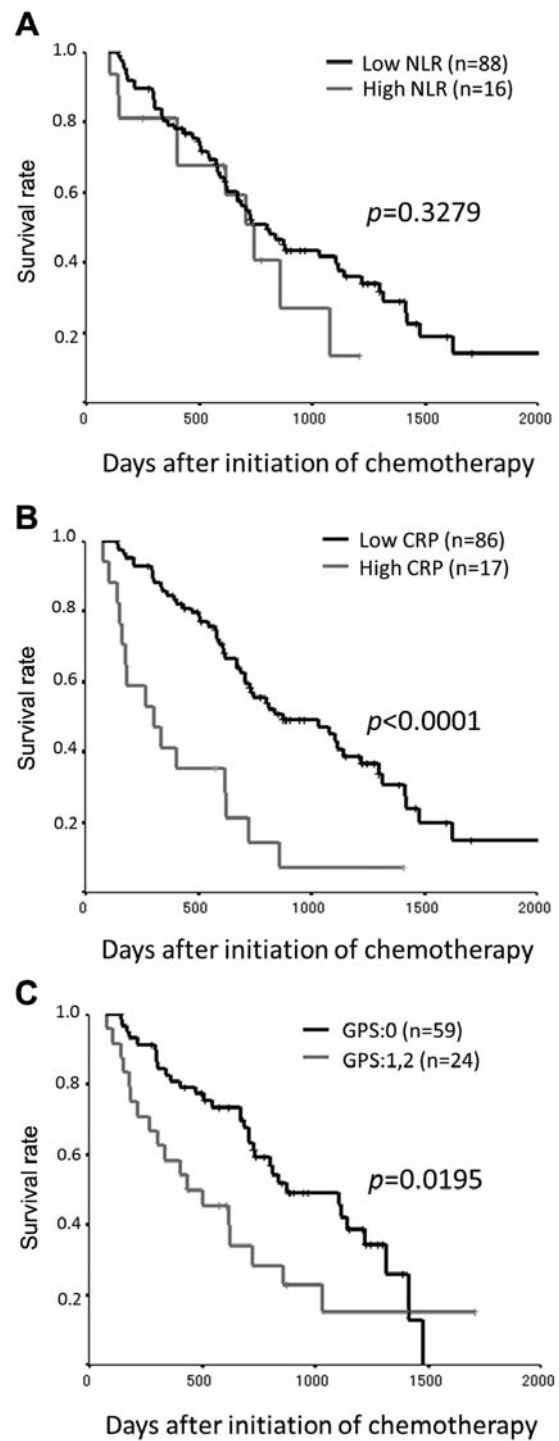
Figure 3. *A: Overall survival according to the post-treatment neutrophil to lymphocyte ratio (NLR). There were no relationships between the post-treatment NLR and mortality. B: Overall survival according to the post-treatment C-reactive protein (CRP). The overall survival rate was significantly worse in the high post-treatment CRP group (p<0.0001). C: Overall survival according to the post-treatment Glasgow prognostic score (GPS). The overall survival rate was significantly worse in the high post-treatment GPS group (p=0.0195).*
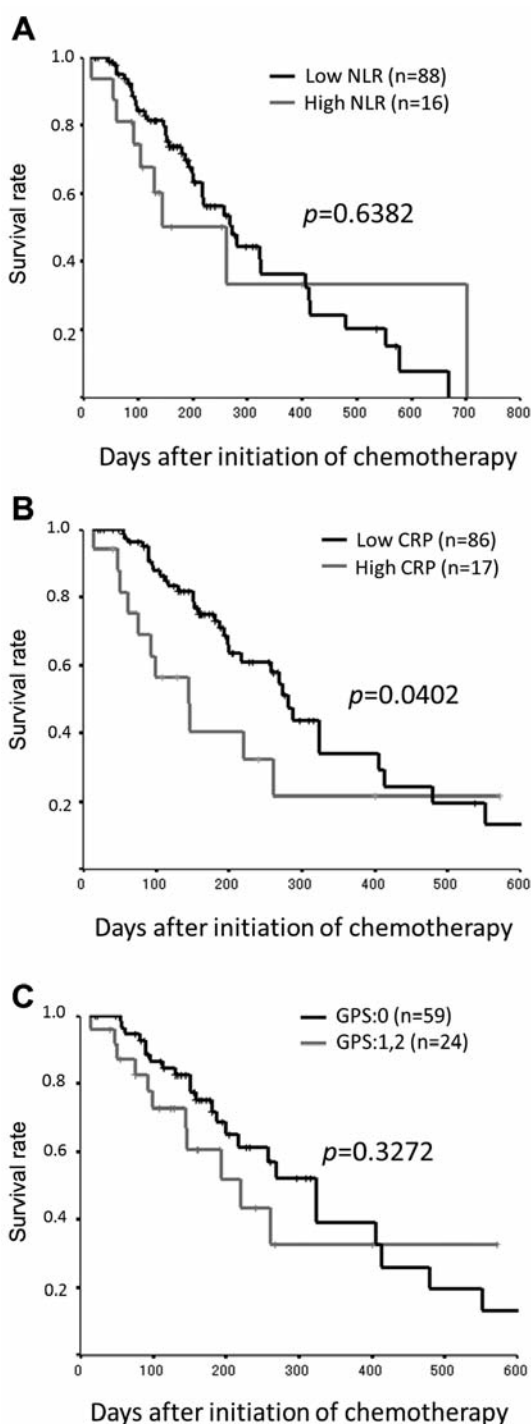
Figure 4. *A: Progression-free survival according to the post-treatment neutrophil to lymphocyte ratio (NLR). There were no relationships between the post-treatment NLR and tumor progression. B: Progression-free survival according to the post-treatment C-reactive protein (CRP). The progression-free survival rate was significantly worse in the high post-treatment CRP group (p=0.0402). C: Progression-free survival according to the post-treatment Glasgow prognostic score (GPS). There were no relationships between the post-treatment GPS and tumor progression.*

Table I. *Patients' characteristics*.

Characteristic	Value
Median age (range), years	64.0 (20-86)
Gender	
Male	63
Female	47
Location of primary tumor	
Colon	64
Rectum	46
Histological type	
Well, moderately diff.	87
Poorly diff., mucinous	14
Detection of unresectable tumor	
Synchronous	64
Metachronous	46
No. of organs affected by metastasis	
One	62
More than one	48
First-line chemotherapy	
FOLFOX	69
CapeOX	27
FOLFIRI	9
SOX	5
Pre-treatment inflammatory markers (mean±SD)	
NLR	3.196±2.268
Serum CRP, mg/dl	1.136±2.032
Serum albumin, g/dl	3.893±0.413

diff.: Differentiated; FOLFOX: 5-fluorouracil+leucovorin+oxaliplatin; CapeOX: capecitabine+oxaliplatin; FOLFIRI: 5-fluorouracil+ leucovorin+irinotecan; SOX: S-1+oxaliplatin; SD: standard deviation; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein.

pre-treatment NLR ($p<0.001$), pre-treatment serum CRP concentration ($p<0.001$), pre-treatment GPS ($p<0.001$), post-treatment CRP concentration ($p<0.001$) and post-treatment GPS ($p=0.022$). The GPS consists of the serum albumin and CRP concentrations, and no relationships were observed between serum albumin concentration and survival rate in this study. Therefore, a multivariate analysis was performed including the clinicopathological factors, except for GPS. The multivariate analysis indicated that the pre-treatment NLR ($p=0.001$), pre-treatment serum CRP concentration ($p=0.022$) and post-treatment serum CRP concentration ($p=0.006$) were independent risk factors for mortality.

The correlations between progression-free survival and various clinicopathological factors are shown in Table VI. Progression-free survival exhibited a significant relationship only with the post-treatment serum CRP concentration ($p=0.045$).

Correlation between normalization of CRP 8 weeks after initiation of chemotherapy and the survival/chemotherapeutic response. We evaluated the prognostic significance of the combination of the pre-treatment and post-treatment CRP

Table II. *Distribution of chemotherapeutic response with reference to the pre-treatment markers of systemic inflammation.*

Response	Pre-treatment NLR			Pre-treatment CRP			Pre-treatment GPS		
	Low (n=59)	High (n=44)	*p*-Value	Low (n=70)	High (n=30)	*p*-Value	0 (n=63)	1, 2 (n=35)	*p*-Value
CR	3	1		4	0		4	0	
PR	19	10		24	5		19	9	
SD	25	20		26	15		25	16	
PD	12	13		16	10		15	10	
Objective response rate	22 (37.3%)	11 (25.0%)	0.207	28 (40.0%)	5 (16.7%)	0.036	23 (36.5%)	9 (25.7%)	0.369

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; GPS: Glasgow prognostic score.

Table III. *Correlations between the pre-treatment inflammatory response and the clinicopathological factors.*

Factor	Pre-treatment NLR			Pre-treatment CRP			Pre-treatment GPS		
	Low	High	*p*-Value	Low	High	*p*-Value	Low	High	*p*-Value
Location of primary tumor									
Colon	36	25		41	18		37	20	
Rectum	25	19	0.844	31	12	0.829	27	15	1.000
Detection of unresectable tumor									
Synchronous	29	33		41	19		38	21	
Metachronous	32	11	0.005	31	11	0.660	26	14	1.000
Histological type									
Well, moderately diff.	46	36		58	22		51	27	
Poorly diff., mucinous	9	5	0.771	10	3	1.000	9	3	0.744
Peritoneal dissemination									
Negative	53	33		55	28		47	33	
Positive	8	11	0.132	17	2	0.053	17	2	0.015
No. of organs affected by metastasis									
One	40	19		42	15		35	19	
More than one	21	15	0.029	30	15	0.514	29	16	1.000
Pre-treatment CEA (ng/ml)									
>5	13	1		11	3		10	3	
≤5	47	42	0.007	59	27	0.544	53	31	0.533

NLR: Neutrophil to lymphocyte ratio; diff: differentiated; CRP: C-reactive protein; GPS: Glasgow prognostic score; CEA: carcinoembryonic antigen.

Table IV. *Distribution of the chemotherapeutic response with reference to the post-treatment markers of systemic inflammation.*

Response	Post-treatment NLR			Post-treatment CRP			Post-treatment GPS		
	Low (n=88)	High (n=16)	*p*-Value	Low (n=86)	High (n=17)	*p*-Value	0 (n=59)	1, 2 (n=24)	*p*-Value
CR	4	0		4	0		4	0	
PR	26	3		27	2		16	6	
SD	38	7		39	6		26	10	
PD	20	6		16	9		13	8	
Objective response rate	30 (34.1%)	3 (18.8%)	0.261	31 (36.0%)	2 (11.8%)	0.085	20 (33.9%)	6 (25.0%)	0.602
Disease control rate	68 (77.3%)	10 (62.5%)	0.221	70 (81.4%)	8 (47.1%)	0.005	46 (78.0%)	16 (66.7%)	0.107

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; GPS: Glasgow prognostic score.

Table V. *Correlations between overall survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
Factor	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Location of primary tumor (colon *vs.* rectum)	1.304	0.806-2.108	0.279			
Detection of unresectable tumor (synchronous *vs.* metachronous)	1.597	0.976-2.613	0.062			
Histological type (poorly diff., mucinous *vs.* well, moderately diff.)	1.318	0.665-2.614	0.429			
Peritoneal dissemination (yes *vs.* no)	1.122	0.623-2.018	0.702			
No. of organs affected by metastasis (≥2 *vs.* 1)	1.832	1.143-2.936	0.012	1.27	0.732-2.206	0.395
Pre-treatment CEA (>5 ng/ml *vs.* ≤5 ng/ml)	2.641	1.139-6.126	0.024	1.521	0.560-4.127	0.411
Pre-treatment NLR (>3 *vs.* ≤3)	3.565	2.134-5.957	<0.001	2.841	1.562-5.169	0.001
Pre-treatment CRP (>1.0 mg/dl *vs.* ≤1.0 mg/dl)	2.554	1.532-4.259	<0.001	1.937	1.102-3.406	0.022
Pre-treatment serum albumin (<3.5 g/dl *vs.* ≥3.5 g/dl)	1.269	0.626-2.574	0.509			
Post-treatment NLR (>3 *vs.* ≤3)	1.404	0.709-2.781	0.331			
Post-treatment CRP (>1.0 mg/dl *vs.* ≤1.0 mg/dl)	3.410	1.890-6.151	<0.001	2.566	1.318-4.994	0.006
Post-treatment serum albumin (<3.5 g/dl *vs.* ≥3.5 g/dl)	1.865	0.985-3.532	0.056			

CI: Confidence interval; CEA: carcinoembryonic antigen; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein.

Table VI. *Correlations between progression-free survival and various clinicopathological factors.*

	Univariate analysis		
Factor	Hazard ratio	95% CI	*p*-Value
Location of primary tumor (colon *vs.* rectum)	0.928	0.516-1.669	0.803
Detection of unresectable tumor (synchronous *vs.* metachronous)	1.109	0.621-1.981	0.728
Histological type (poorly diff., mucinous *vs.* well, moderately diff.)	1.525	0.700-3.322	0.288
Peritoneal dissemination (yes *vs.* no)	1.096	0.528-2.276	0.806
No. of organs affected by metastasis (≥2 *vs.* 1)	0.898	0.506-1.595	0.714
Pre-treatment CEA (>5 ng/ml *vs.* ≤5 ng/ml)	0.952	0.396-2.285	0.912
Pre-treatment NLR (>3 *vs.* ≤3)	1.277	0.718-2.268	0.405
Pre-treatment CRP (>1.0 mg/dl *vs.* ≤1.0 mg/dl)	1.300	0.711-2.377	0.395
Pre-treatment serum albumin (<3.5 g/dl *vs.* ≥3.5 g/dl)	0.616	0.217-1.744	0.362
Post-treatment NLR (>3 *vs.* ≤3)	1.203	0.556-2.606	0.639
Post-treatment CRP (>1.0 mg/dl *vs.* ≤1.0 mg/dl)	2.015	1.017-3.989	0.045
Post-treatment serum albumin (<3.5 g/dl *vs.* ≥3.5 g/dl)	1.764	0.747-4.162	0.195

CI: Confidence interval; CEA: carcinoembryonic antigen; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein.

levels, both of which correlated with survival and chemotherapeutic response. We categorized the patients into three groups according to the combination of the pre-treatment and post-treatment CRP levels. Patients with a low pre-treatment CRP level were categorized into group A, while patients with a high pre-treatment CRP level and normalization of CRP 8 weeks after the initiation of chemotherapy were categorized into group B; and patients with high pre-treatment and post-treatment CRP levels were categorized into group C. The patients in group B exhibited better overall and progression-free survival rates than did the patients in group C (overall survival: *p*=0.0002; progression-free survival: *p*=0.0001) (Figures 5 and 6). As for the chemotherapeutic response, although the objective response rates did not differ

according to the presence/absence of normalization after treatment (25.0% *vs.* 0%, *p*=0.153), there were no patients with an objective response in group C and the patients in group B had a significantly higher disease control rate than the patients in group C (85.0% *vs.* 33.3%, *p*=0.010) (Table VII).

Discussion

In the present study, we investigated the significance of CRP as a marker for predicting survival and chemotherapeutic response and monitoring tumor progression in patients with unresectable CRC receiving palliative chemotherapy. Recently, markers of systemic inflammation have been reported to correlate with survival in patients with various
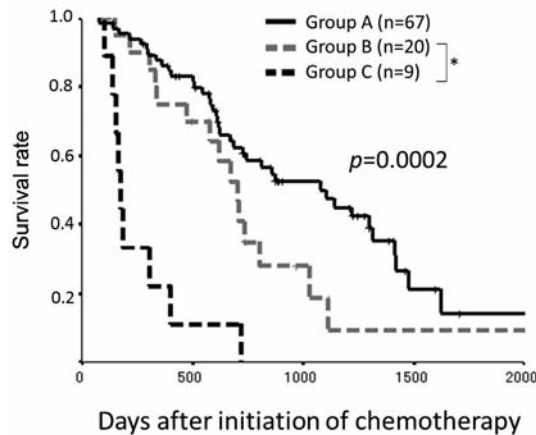
Figure 5. *Overall survival according to the combination of the pre-treatment and post-treatment C-reactive protein (CRP) levels. Group B: patients with a high pre-treatment CRP level and normalization of CRP 8 weeks after the initiation of chemotherapy. Group C: patients with high pre-treatment and post-treatment CRP levels. The patients in group B exhibited a better overall survival rate than the patients in group C (p=0.0002).*
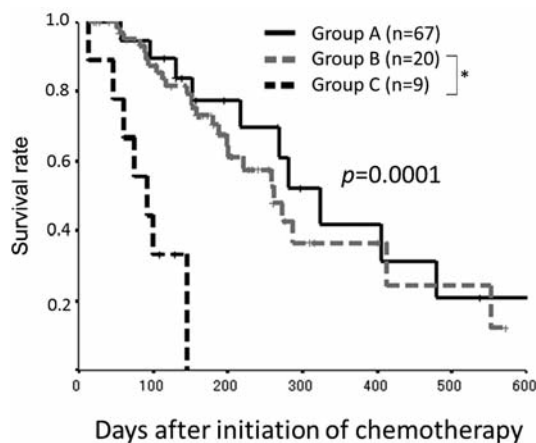

Figure 6. *Progression-free survival according to the combination of the pre-treatment and post-treatment C-reactive protein (CRP) levels. Group B: patients with a high pre-treatment CRP level and normalization of CRP 8 weeks after the initiation of chemotherapy. Group C: patients with high pre-treatment and post-treatment CRP levels. The patients in group B exhibited a better progression-free survival rate than the patients in group C (p=0.0001).*

cancer types. However, most targets in previous reports were patients treated with surgery, and there are few reports focusing on patients with unresectable metastatic CRC receiving palliative chemotherapy (7, 8, 10, 13-16). Moreover, only a few reports have evaluated the correlation between the status after treatment and the chemotherapeutic

Table VII. *Distribution of the chemotherapeutic response with reference to the combination of the pre-treatment and post-treatment markers of systemic inflammation. Group B: patients with a high pre-treatment CRP level and normalization of CRP 8 weeks after the initiation of chemotherapy. Group C: patients with high pre-treatment and post-treatment CRP levels.*

Response	Group B (n=20)	Group C (n=9)	p-Value
CR	0	0	
PR	5	0	
SD	12	3	
PD	3	6	
Objective response rate	5 (25.0%)	0 (0%)	0.153
Disease control rate	17 (85.0%)	3 (33.3%)	0.010

CRP: C-reactive protein; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

outcome (7, 8, 16). To the best of our knowledge, this is the first study to investigate the significance of CRP as a marker for predicting survival, as well as the chemotherapeutic outcome, and for monitoring the progression of the tumor in patients with unresectable metastatic CRC.

Neutrophils play a key role in tumor progression, producing a number of ligands that induce tumor cell proliferation and invasion and promoting tumor vascularization by releasing pro-angiogenic chemokines and other factors (19, 20). Lymphocytes play an important role in anti-tumor immunity, and the absolute lymphocyte count is assumed to reflect the degree of responsiveness of immune system of the host (21, 22). Therefore, an increased NLR correlates with tumor progression. In the current study, the pre-treatment NLR correlated with the overall survival, while the postoperative NLR did not. The reason for this finding is considered to be due to the fact that the onset of myelosuppression as a side-effect of chemotherapy causes neutropenia, meaning that the NLR value easily changes as a result of chemotherapy. Therefore, the post-treatment NLR is considered to be an unsuitable marker for predicting prognosis and chemotherapeutic response. Previous reports have investigated the prognostic value of the post-treatment NLR (8). However, the analyses targeted values measured after the first cycle, namely approximately 2 or 3 weeks after the initiation of chemotherapy, and NLR values have not been monitored over long periods.

CRP is an acute-phase protein produced in a state of inflammation (23). Cancer growth itself and secondary processes resulting from tumor necrosis cause tissue inflammation, leading to increases in the production of CRP (23). Moreover, the proinflammatory cytokines produced by cancer cells themselves induce the production of CRP (24). Elevation of the serum CRP concentration reflects hypercytokinemia, and such cytokines promote both tumor progression and metastasis (25).

In the present study, the pre-treatment serum CRP concentration correlated with the overall survival and objective response rate. Based on these results, the pre-treatment serum CRP concentration is considered to reflect the malignant potential and degree of progression of the tumor and be helpful for identifying patients expected to benefit from chemotherapy.

In the present study, the post-treatment serum CRP concentration correlated with the overall and progression-free survival and disease control rates. Based on these results, the post-treatment serum CRP concentration is considered to reflect the extent of tumor progression and resistance to chemotherapy. Because a continuously high CRP level despite the administration of chemotherapy is thought to indicate resistance to chemotherapy, the post-treatment CRP level is a useful marker for judging the chemotherapeutic outcome. Moreover, normalization of the CRP level after chemotherapy correlated with overall and progression-free survival and disease control rates. Based on these results, the CRP level was demonstrated to be a useful marker for monitoring tumor progression.

The GPS is a scoring system based on the degree of systemic inflammation, consisting of the serum CRP and albumin concentrations, and is a useful marker for the prognostication of patients with advanced cancer (13-16). In this study, both the pre-treatment and post-treatment GPS were found to correlate with overall survival. However, the serum CRP concentration alone had superior prognostic value to the GPS, as the serum albumin concentration demonstrated no relationships with survival. Moreover, no relationships were observed with the chemotherapeutic outcome. Although the pre-treatment serum albumin concentration has been reported to correlate with the survival rate in patients with various types of cancers, there is no evidence regarding the correlation between the pre-treatment serum albumin concentration and the chemotherapeutic outcome. Moreover, the post-treatment serum albumin concentration easily changes as a result of many factors, including malnutrition and dehydration, resulting from the appetite loss that accompanies chemotherapy. Therefore, the GPS may have inferior prognostic value compared to that of the serum CRP concentration alone.

There exist certain limitations associated with this study. Firstly, we evaluated a relatively small number of patients. Second is, the appropriate timing for measurement after treatment and the proper cut-off values for markers of systemic inflammation remain unclear. A large prospective study should therefore be performed to confirm our findings.

Conclusion

Pre-treatment markers of systemic inflammation, such as the NLR, CRP and GPS, are useful for predicting the prognosis in patients with unresectable metastatic colorectal cancer

who receive palliative chemotherapy. Moreover, the CRP level can be used as a marker for chemotherapeutic monitoring of the degree of tumor progression.

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