Prognostic Value of Preoperative Inflammation-based Prognostic Scores in Patients with Stage IV Colorectal Cancer who Undergo Palliative Resection of Asymptomatic Primary Tumors

KIYOSHI MAEDA, MASATSUNE SHIBUTANI, HIROSHI OTANI, HISASHI NAGAHARA, KENJI SUGANO, TETSURO IKEYA, RYOSUKE AMANO, KENJIRO KIMURA, KATSUNOBU SAKURAI, NAOSHI KUBO, KAZUYA MUGURUMA, HIROAKI TANAKA, TORU INOUE and KOSEI HIRAKAWA

Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Abeno-ku, Osaka, Japan

Abstract. *Background: The need for palliative resection of asymptomatic primary tumor in patients with unresectable metastatic colorectal cancer (CRC) is still controversial. In order to identify predictors of survival after palliative resection, we investigated the correlations between clinicopathological factors, preoperative Glasgow prognostic score (GPS) and neutrophil-to-lymphocyte ratio (NLR), and survival. Patients and Methods: A total of 94 patients were enrolled in the present study. The prognostic value of the clinicopathological factors, GPS and NLR were analyzed retrospectively. Results: A multivariate analysis revealed that both the GPS and NLR were independent predictors of survival along with the preoperative Eastern Cooperative Oncology Group performance status (PS) and extent of distant metastasis. We classified the patients using a combination of these factors, and categorized them into three risk groups. The median survival time was five months in the high-risk group, compared to 21.5 months in the intermediate-risk group and 37 months in the low-risk group. Conclusion: Sub-classification based on the GPS, NLR, PS and extent of distant metastasis can classify patients into three independent groups. There may be no survival benefits associated with palliative resection in the high–risk group.*

Approximately 20% of patients with colorectal cancer (CRC) present with stage IV disease at the time of diagnosis (1). The median survival time (MST) for patients with unresectable stage IV disease is approximately six to eight months for those who receive the best supportive care without chemotherapy (2). The recent development of chemotherapeutic and molecular targeting agents has markedly improved the MST to almost 24 months (3-5). In patients with symptoms related to the primary tumor, such as obstruction or bleeding, resection of the primary tumor may relieve symptoms. In contrast, the need for prophylactic resection of asymptomatic primary tumors in patients with unresectable metastatic disease remains unclear. Resection of the primary tumor is considered necessary to prevent local complications during subsequent chemotherapy (6-9). However, several recent studies have raised questions regarding the efficacy of this upfront surgical strategy (10-12). Currently, there is no consensus on the indications for resection of asymptomatic primary tumors in patients with unresectable metastatic CRC.

Several parameters for predicting survival in patients with stage IV CRC have been identified, including patient characteristics, such as performance status (PS), age and gender, and tumor characteristics, such as the extent of distant metastasis, pathological tumor differentiation and serum levels of carcinoembryonic antigen (CEA) (13). Recently, it was reported that tumor progression is not determined solely by the local characteristics of the tumor, but also by the host systemic immune/inflammatory responses (14). Therefore, identifying parameters that reflect both tumor characteristics and the systemic inflammatory status will help predict patient survival more precisely and select for optimal treatment, especially in patients with stage IV disease.

There is increasing evidence that inflammation-based prognostic parameters, such as the Glasgow prognostic score (GPS) and the neutrophil-to-lymphocyte ratio (NLR), are associated with survival in several types of malignant tumors (15-21). Both the GPS and NLR are based on laboratory data that are routinely recorded in the clinical setting and can easily be estimated before surgery.

Correspondence to: Kiyoshi Maeda, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka, Japan. Tel: +81 666453838, Fax: +81 666466450, e-mail: m1378386@med.osaka-cu.ac.jp

Key Words: Colorectal cancer, stage IV, asymptomatic primary tumor, palliative surgery, Glasgow prognostic score, neutrophil to lymphocyte ratio.

In the present study, in order to identify parameters to select for patients who will have a poor prognosis after palliative surgery, we retrospectively investigated the correlations between various clinicopathological factors, the preoperative GPS, NLR and prognosis in patients with stage IV CRC who underwent palliative resection of asymptomatic primary tumor.

Patients and Methods

We conducted a retrospective review of a database comprising of 1,701 patients with CRC who underwent surgical resection at the Department of Surgical Oncology, Osaka City University Hospital between January 2001 and December 2009. Among these individuals, we identified 141 patients with stage IV CRC disease. Out of these patients, 24 who underwent R0-1 resection and four who underwent emergency surgery due to colonic perforation were excluded from the study. Nineteen patients who exhibited symptoms associated with the primary tumor (16 patients with symptoms associated with obstruction, including constipation, ileus and abdominal fullness; and three patients with symptoms related to tumor bleeding, including melena and anemia) were also excluded from the study. The other 94 patients who underwent palliative resection were enrolled in the study. Palliative resection was defined as resection of a primary lesion of the colon and/or rectum, with regional lymphadenectomy, and no resection of incurable metastases such as peritoneal dissemination or hepatic or distant metastasis.

The following parameters were evaluated: age, gender, preoperative Eastern Cooperative Oncology Group performance status (PS), tumor location, histological type, depth of tumor invasion, lymph node metastasis, extent of distant metastasis (M1a; one organ affected by metastasis, and M1b; involvement with metastasis of more than one organ), the serum CEA level (cut-off level=5.0 mg/ml), postoperative complicaions, postoperative chemotherapy and molecular-targeting therapy. The pathological diagnosis and classification status were determined according to the seventh edition of the Union of International Cancer Control TNM Classification of Malignant Tumors (22). Routine laboratory measurements, including the serum level of C-reactive protein (CRP), albumin, and CEA, were obtained immediately before surgery in order to exclude any effects attributable to inflammation. None of the patients had clinical evidence of infection or other inflammatory conditions, and none had received preoperative chemotherapy or irradiation.

The GPS was estimated as previously described. Briefly, patients with both an elevated CRP level (>1.0 mg/dl) and hypoalbuminemia (<3.5 g/dl) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities were present were allocated a score of 1, and those in whom neither of these abnormalities was present were allocated a score of 0 (15-17).

The cut-off value of the NLR was determined to be three, based on previous reports by Ishizuka *et al*. (18) and Chiang *et al*. (19).

Statistical analysis. The statistical analyses were performed using the JMP 10 software program (SAS Institute Japan, Tokyo, Japan). The Chi-square test was used to compare the data. Survival curves were created according to the Kaplan–Meier method and analyzed using the log-rank test. A Cox proportional hazards model was used for the multivariate analysis to identify for independent prognostic factors. Values of $p<0.05$ were considered to be statistically significant.

Table I. *Characteristics of 94 patients with stage IV colorectal cancer who underwent palliative resection for asymptomatic primary tumor.*

Age (years)	Mean (range)	60.4 (39-87)
Gender	Male/female	51/43
PS	0/1/2	78/12/4
Location	Rectum /colon	18/76
Histological type	Well or mod /other	79/15
Depth of tumor invasion	T1-3/T4	23/71
Lymph node metastasis	N0-1/ N2-3/unknown	45/41/8
The extent of distant metastasis	M1a/M1b	57/37
Postoperative complications	Yes/no	20/80
Postoperative chemotherapy	Yes/no	80/14
Molecular targeting therapy	Yes/no	31/63

PS: Eastern Cooperative Oncology Group performance status, Well: well-differentiated adenocarcinoma, mod: moderately-differentiated adenocarcinoma.

Results

The clinicopathological features of the 94 patients are summarized in Table I. Fifty-seven patients had M1a disease, and 37 had M1b disease. Postoperative complications were observed in 20 patients including, superficial surgical site infections in seven patients, ileus in six patients, anastomotic leakage in four patients, anastomotic bleeding in two patients and pneumonia in one patient. However, all patients recovered with conservative treatment, without the need for surgical intervention. There were no postoperative deaths.

With regard to the administration of postoperative chemotherapy, eight patients refused to receive chemotherapy and six patients were judged to be contraindicated for chemotherapy due to a poor PS and/or severe co-morbidities. The other 80 patients underwent chemotherapy. Recently developed chemotherapeutic regimens, such as FOLFIRI (folic acid/fluorouracil plus irinotecan) and FOLFOX (folic acid/fluorouracil plus oxaliplatin), were introduced into our Department in 2005, therefore patients who underwent surgery before 2005 had been administered infusional 5-fluorouracil (5FU) or an oral pro-drug based on 5FU. Molecular-targeting therapy with bevacizumab became available in 2007, and cetuximab bacame available in 2008 in Japan. Therefore, in this study, only 31 patients received molecular targeting therapy. At the time of analysis, 90 (96%) patients had died, with a median follow-up of 30 months after surgery. The MST was 21 months.

The correlations between various clinicopathological factors and the GPS or NLR are shown in Tables II and III. There were no significant correlations between the GPS, NLR or any of the various clinicopathological factors examined. The frequency of postoperative complications, and the incidence of chemotherapy and molecular-targeting therapy did not differ according to the GPS status or NLR.

Table II. *The relationship between the Glasgow prognostic score and clinicopathological factors.*

	GPS			*p*-Value
	0 (n=53)	1 (n=24)	2 (n=17)	
Age (years)				
≥70	21	7	4	0.60
<70	32	17	13	
Gender				
Male	28	13	10	0.91
Female	25	11	7	
PS				
0	47	19	13	0.37
1, 2	6	5	4	
Location				
Rectum	11	5	2	0.69
Colon	42	19	15	
Histological type				
Well or mod	42	21	16	0.30
Other	11	3	1	
Depth of tumor invasion				
T1-3	13	8	2	0.29
T4	40	16	15	
Lymph node metastasis				
N0-1	24	13	8	0.70
N2-3	24	11	6	
Unknown	5	-	3	
The extent of distant metastasis				
M1a	35	14	8	0.54
M1b	18	10	9	
CEA (ng/ml)				
≥5	49	19	6	0.37
<5	4	5	1	
Postoperative complication				
No	39	21	14	0.55
Yes	14	3	3	
Postoperative chemotherapy				
None	5	6	3	0.74
5FU monotherapy	15	5	5	
5FU + irinotecan or oxaliplatin	33	13	9	
Postoperative molecular targeting therapy				
No	34	16	13	0.80
Yes	19	8	4	

CEA: Carcinoembryonic antigen, GPS: Glasgow prognostic score, PS: Eastern Cooperative Oncology Group performance status, Well or mod well- or moderately-differentiated adenocarcinoma, 5FU: 5-fluorouracil.

Table III. *The relationship between the neutrophil-to-lymphocyte ratio and clinicopathological factors.*

	NLR		*p*-Value
	>3 (n=51)	≤3 (n=43)	
Age (years)			
≥70	16	16	0.55
<70	35	27	
Gender			
Male	26	25	0.63
Female	25	18	
PS			
0	44	35	0.72
1, 2	7	8	
Location			
Rectum	7	11	0.23
Colon	44	32	
Histological type			
Well or mod	44	34	0.52
Other	7	9	
Depth of tumor invasion			
T1-3	11	12	0.48
T4	40	31	
Lymph node metastasis			
N0-1	24	21	0.99
N2-3	23	18	
Unknown	4	4	
The extent of distant metastasis			
M1a	31	26	0.97
M1b	20	17	
CEA (ng/ml)			
≥5	45	39	0.96
<5	6	4	
Postoperative complication			
No	41	33	0.80
Yes	10	10	
Postoperative chemotherapy			
None	10	4	0.56
5FU monotherapy	13	12	
5FU + irinotecan or oxaliplatin	28	27	
Postoperative molecular-targeting therapy			
No	36	27	0.42
Yes	15	16	

CEA: Carcinoembryonic antigen, GPS: Glasgow prognostic score, NLR: neutrophil-to-lymphocyte ratio, PS: Eastern Cooperative Oncology Group performance status, Well or mod: well- or moderately differentiated adenocarcinoma, 5FU: 5-fluorouracil.

Table IV shows the results of univariate and multivariate analyses of various clinicopathological characteristics as potential prognostic factors for survival, including the GPS and NLR. A univariate analysis revealed that a PS of 1 or more, the presence of T4 tumors, an M1b status, a GPS of 2 and an NLR of more than 3 were significantly associated with a worse survival. Moreover, according to the multivariate analysis using Cox's model, both a GPS of 2 and an NLR of more than 3 are independent significant prognostic factors in addition to a PS of 1 or more and an M1b status.

We classified the patients using a combination of these four prognostic factors into three risk groups: patients without any prognostic factor (low-risk group, n=20), patients with one or two prognostic factors (intermediate-risk group, n=62) and patients with three or four prognostic

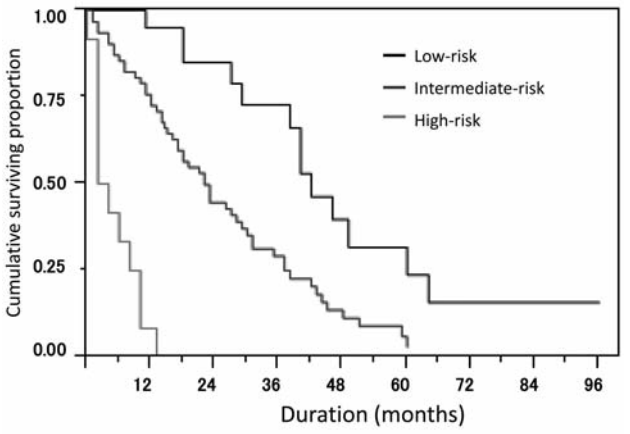

Figure 1. *The postoperative cancer-specific survival of the patients subdivided into low–, median–, and high–risk groups according to the Glasgow prognostic score, neutrophil-to-lymphocyte ratio, performance status and extent of distant metastasis. The median survival of the high-risk group was significantly (p=0.0001) worse than those of the other groups.*

factors (high-risk group, n=12). Consequently, there were significant (p<0.0001) differences in the postoperative cancer-specific survival rates between the three groups (Figure 1). The MST was only five months in the high-risk group, compared to 21.5 months in the intermediate-risk group and 37 months in the low-risk group.

The postoperative treatments were compared between the three risk groups (Table V). No significant correlations were found between the frequency of postoperative complications and the administration of chemotherapy and molecular targeting therapy in these groups. The incidence of the administration of 5-FU with irinotecan or oxaliplatin tended to be lower in the high-risk group than in the other groups; however, statistical significance was not reached.

Discussion

Palliative resection of asymptomatic primary tumors has traditionally been considered necessary to prevent the need for subsequent chemotherapy, resulting in prolonged survival (6-9). However, because the survival of such patients has been remarkably prolonged by the development of new chemotherapeutic and molecular-targeting agents, the prognostic benefits of palliative surgery are controversial (10-12). Using a multivariate analysis, the present study revealed that the PS, extent of distant metastasis, GPS and NLR are independent predictors of postoperative survival in patients who undergo palliative resection of asymptomatic primary tumors with unresectable metastasis.

The PS is an established strong prognostic factor in patients with advanced CRC, with the MST of patients with a PS of 2 being less than half that of patients with a PS of 0

Table IV. *The results of the univariate and multivariate analyses of the prognostic factors in patients with stage IV colorectal cancer who underwent palliative resection of the asymptomatic primary tumor.*

Variables	MST (months)	Univariate analysis	Multivariate analysis		
		p-value	OR	95%CI	*p*-value
Age (years)					
≥70 *vs.* <70	22 *vs.* 185	0.72			
Gender					
Male *vs.* female	23 *vs.* 19	0.80			
PS					
1, 2 *vs.* 0	10 *vs.* 23	0.03	2.70	1.14-4.06	0.02
Location					
Rectum *vs.* colon	23 *vs.* 19	0.39			
Histological type					
Well or mod *vs.* other	22.5 *vs.* 17	0.19			
Depth of tumor invasion					
T4 *vs.* T1-3	19 *vs.* 23	0.04	1.61	0.93-2.97	0.09
Lymph node metastasis					
N2-3 *vs.* N0-1	19 *vs.* 27	0.42			
The extent of distant metastasis					
M1b *vs.* M1a	14 *vs.* 23	0.04	1.66	1.00-2.72	0.04
CEA (ng/ml)					
≥5 *vs.* <5	15.5 *vs.* 21.5	0.94			
GPS					
2 *vs.* 0, 1	10 *vs.* 20	0.0005	1.95	1.05-2.72	0.03
NLR					
>3 *vs.* ≤3	18 *vs.* 27	0.004	1.97	1.74-3.39	0.01

CI: Confidence interval, CEA: carcinoembryonic antigen, GPS: Glasgow prognostic score, MST: median survival time, NLR: neutrophil-to-lymphocyte ratio, PS: Eastern Cooperative Oncology Group performance status, Well or mod: well- or moderately differentiated adenocarcinoma.

Table V. *The postoperative outcomes subdivided according to risk group.*

	Low-risk (n=20)	Intermediate-risk (n=62)	High-risk (n=12)	*p*-value
Median survival time (months)	37	21.5	5	<0.0001
Postoperative complications				
No	14	50	10	0.77
Yes	6	12	2	
Postoperative chemotherapy				
None	4	6	4	0.26
5FU monotherapy	4	16	5	
5FU + irinotecan or oxaliplatin	12	40	3	
Postoperative molecular tagetting therapy				
No	13	41	10	0.70
Yes	7	21	2	

5FU: 5-Fluorouracil.

at presentation (23, 24). In patients with a poor PS, the administration of aggressive combined chemotherapy, such as FOLFOX or FOLFIRI, is often avoided due to fear of severe adverse events. Sargent *et al*. analyzed several clinical trials and reported that the administration of aggressive chemotherapy increased the risk of toxicity and 60-day mortality (25). The seventh edition of the TNM staging (22) divides stage IV CRC into two sub-classes based on the extent of distant metastasis: stage IVa with M1a disease and stage IVb with M1b disease. Although this sub-classification facilitates making clear distinctions between the two groups, some discrepancies exist. For example, it is recognized that patients with M1a disease may exhibit different survival outcomes according to whether they have single or multiple metastases. Therefore, the prognosis is significantly different even in the same sub-class of stage IV disease, and other parameters should be identified to predict the survival of patients.

The GPS is simply calculated based on the serum levels of CRP and albumin and is thought to reflect the host systemic immune/inflammatory responses (14, 15). The mechanism of up–regulation of CRP is controlled by cytokines, and high levels of CRP may reflect increased levels of interleukins in patients with advanced cancer (26). However, in most cases, levels of interleukins are not routinely evaluated at the time of admission. Instead, the CRP can be used as an indirect parameter of the up-regulation of cytokines.

Albumin is a main component of plasma proteins that preserves the colloidal osmotic pressure and reflects the nutritional status. The presence of an inflammatory response has been proposed to be pathogenic in the development of cancer-associated malnutrition (27). Several studies have reported that patients with advanced gastrointestinal malignancies are often malnourished, and that the preoperative nutritional status is associated with tumor progression and a poor clinical outcome (28-30). There are several reports regarding the usefulness of the GPS as a predictor of survival in patients with various solid malignancies (14-16). Furthermore, a recent study revealed that the GPS was correlated with tolerance to chemotherapy (17). It is reasonable to speculate that the presence of an inflammatory response and associated nutritional decline affects tolerance and compliance with treatment.

Neutrophils play a key role in tumor proliferation, producing a number of ligands that induce tumor cell proliferation and invasion, and promoting tumor vascularization by releasing pro-angiogenic chemokines and other factors (18). Therefore, an increase in neutrophils can promote tumor growth and metastasis. On the other hand, lymphocytes also play a key role in tumor suppression (18). The function of lymphocytes is to induce cytotoxic cell death and the production of cytokines in cancer cells. Therefore, a decrease in the number of lymphocytes impairs the host's antitumor immune response and confers a poor prognosis. Chua *et al*. (20) and Shibutani *et al*. (21) reported that a high NLR leads to a reduced response rate to chemotherapy and poor survival.

Both the GPS and NLR are simple and easy to measure using standardized widely-available assays. Recently, it has been reported that many molecular parameters (such as proteins involved in cell-cycle regulation, apoptosis and angiogenesis) are associated with survival (31-33). However, measuring these molecular parameters requires sophisticated and expensive laboratory investigations and thus are less easily determined than the GPS or NLR.

In the present study, we presented sub-classification based on the PS, extent of distant metastasis, GPS and NLR. This classification can be used to stratify patients into three groups of different survival periods. In the present study, the MST of the high-risk group was five months, which was very short and similar to that reported for patients with stage IV CRC who received best supportive care without surgery or chemotherapy. Therefore, there may be no survival benefits associated with palliative resection in the high-risk group. On the other hand, relatively better survival is expected in the low-risk group. This risk classification is simple and easy to use and may be helpful for determining the optimal treatment for patients with stage IV CRC.

Conclusion

In this retrospective study, the GPS, NLR, PS and extent of distant metastasis were found to be independent predictors of survival in patients with stage IV CRC who underwent palliative resection of asymptomatic primary tumor. The sub-classification of patients based on these four factors appears not only to be capable of classifying patients into three independent risk groups before surgery, but also has the potential to be used as a novel method of predicting postoperative survival in such patients. This was a single-arm retrospective study; therefore, a prospective study is needed to confirm the present findings with respect to defining patients who will have a poor survival outcome after palliative resection for stage IV CRC.

Acknowledgements

There is no financial support or relationship that may pose a conflict of interest in association with this study.

References

1 Ries LA, Wingo PA and Millers DS: The Annual Report to the Nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer *88*: 2398-2424, 2000.

2 Simmonds PC: Palliative chemotherapy for advanced colorectal cancer: Systemic review and meta-analysis. Colorectal Cancer Collaborative Group. Br Med J *321*: 531-535, 2000.

3 Grothey A, Sargent D and Goldberg RM: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol *22*: 1209-1214, 2004.

4 Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichininster M, Yang TS, Rivera F, Couture F, Sirzen F and Cassidy J: Bevacizumab incombination with oxaliplatin-based chemotherapy as first–line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol *26*: 2013-2019, 2008.

5 Van Custem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haenes G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Teipar S, Schlichting M, Nippgen J and Rougier P: Cetuximab and chemotherapy as a initial treatment for metastatic colorectal cancer. N Engl J Med *360*: 1408-17, 2009.

6 Kemeny MM: Surgery should be the primary treatment of synchronous colorectal metastasis in the asymptomatic patient. Ann Surg Oncol *13*: 140-141, 2000.

7 Verberene CJ, de Bock GH, Pijl MEJ, Bass PC, Siesling S and Wiggers T: Palliative resection of the primary tumor in stage IV rectal cancer. Colorectal Dis *14*: 314-319, 2011.

8 Katoh H, Yamashita K, Kokuba Y, Satoh T, Ozawa H, Hatate K, Ihara A, Nakamura T, Onosato W and Watanabe M: Surgical resection of stage IV colorectal cancer. World J Surg *32*: 1130-7, 2008.

9 Cook AD, Single R and McCahill LE: Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: An analysis of Surveillance, Epidemiology, and End Results data, 1998 to 2000. Ann Surg Oncol *12*: 637-645, 2005.

10 Damjanov N, Weiss J and Haller DG: Resection of primary colorectal cancer is not necessary in nonobstructed patients with metastatic disease. Oncologist *14*: 963-969, 2009.

11 Rahban NN, Lordick F, Fink C, Bork U, Stange A, Jager D, Luntz SP, Englert S, Rossion I, Koch M, Buchler MW, Kieser M and Weitz: Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS–a randomized controlled multicenter trial (ISRCTN30964555). BMC Cancer *12*: 142-151, 2012.

12 Poultsides GA and Paty PB: Reassessing the need for primary tumor surgery in unresectable metastatic colorectal cancer: Overview and perspective. Ther Adv Med Oncol *3*: 35-42, 2011.

13 Chibaudel B, Tournigand C, Andre T and de Gramont A: Therapeutic strategy in unresectable metastatic colorectal cancer. Ther Adv Med Oncol *4*: 75-89, 2012.

14 McMillan DC: The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. Cancer Treat Rev *39*: 534-540, 2013.

15 Proctor MJ, Morrison DS, Talwar D, eBalmer SM, Fletcher CD, O'Reilly DSJ, Foulis AK, Horgan PG and Mcmillan DC: A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer *47*: 2633-2641, 2011.

16 Furukawa K, Shiba H, Haruki K, Fujiwara Y, Iida T, Mitsuyama Y, Ogawa M, Ishida Y, Misawa T and Yanaga K: The Glasgow prognostic score is valuable for colorectal cancer with both synchronous and metachronous unresectable liver metastases. Oncol Lett *4*: 324-328, 2012.

17 Kishii T, Masaki T, Matsuoka H, Kobayashi T, Suzuki Y, Abe N, Mori T and Sugiyama M: Modified Glasgow prognostic score in patients with incurable stage IV colorectal cancer. Am J Surg *206*: 234-240, 2013.

18 Ishizuka M, Nagata H, Takagi K, Iwase Y and Kubota K: Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. Br J Cancer *109*: 401-407, 2013.

19 Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, Chiang JM and Lin JR: Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis *27*: 1347-57, 2012.

20 Chua W, Charles KA, Baracos VE and Clarke SJ: Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer *104*: 1288-1295, 2011.

21 Shibutani M, Maeda K, Nagahara Noda E, Otani H, Nishiguchi Y and Hirakawa K: A high preoperative neutrophil-to-lymphocyte ratio is associated with colorectal cancer. AntiCancer Res *33*: 3291-3294, 2013.

22 Sobin L, Gospodarowicz M and Wittekind C: International against Cancer. TNM Classification of Malignant Tumors, Seventh edition, New York: Wiley-Blackwell, pp. 73-77, 2009.

23 Kemeney N and Braun DW Jr.: Prognostic factors in advanced colorectal carcinoma. Importance of lactic dehydrogenase level, performance status, and white blood cell count. Am J Med *74*: 786-794, 1983.

24 Kohne CH, Cunningham D, di Costanzo F, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, Pignatti F, Schffski P, Michel S and Hecker H: Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: Results of a multivariate analysis of 3825 patients. Ann Oncol *13*: 308-317, 2002.

25 Sargent DJ, Kohne CH, Sanoff K, Bot BM, Seymour T, de Gramont A, Porschen R, Saltz LB, Rougier P, Tournigand C, Douillard JY, Stephans RJ, Grothey A and Goldberg RM: Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. J Clin Oncol *27*: 1948-1955, 2009.

26 McMillan DC, Canna K and McArdle CS: Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Cancer *90*: 215-219, 2003.

27 Delmore G: Assessment of nutritional status in cancer patients: Widely neglected? Support Care Cancer *5*: 376-380, 1997.

28 Pinato DJ, North BV and Sharma R: A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: The prognostic nutritional index (PNI). Brti J Cancer *106*: 1439-1445, 2012.

29 Onodera T, Goseki N and Kosaki G: Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nippon Geka Gakkai Zasshi *85*: 1001-1005, 1984 (in Japanese).

30 Nozoe T, Kohno M, Iguchi T, Mori E, Maeda T, Matsukuma A and Ezaki T: The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. Surgery Today *42*: 532-535, 2012.

31 Kang SM, Maeda K, Onoda N, Chung YS, Nakata B, Nishiguchi Y and Sowa M: Combined analysis of p53 and vasucular endothelial growth factor expression in colorectal carcinoma for determination of tumor vascularuty and liver metastasis. Int J Cancer *74*: 502-507, 1997.

32 Maeda K, Chung YS, Takatsuka S, Ogawa Y, Sawada T, Yamashita Y, Onoda N, Kato Y, Nitta A, Arimoto Y, Kondo Y and Sowa M: Tumor angiogenesis as a predictor of recurrence in gastric carcinoma. J Clin Oncol *13*: 477-481, 1995.

33 Giatromanolaki A, Sivridis E and Koukourakis MI: Angiogenesis in colorectal cancer: prognostic and therapeutic implications. Am J Clin Oncol *29*: 408-417, 2006.

Received September 24, 2013
Revised October 24, 2013
Accepted October 25, 2013