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Inflammation-based prognostic system predicts survival after surgery for stage IV colorectal cancer

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Abstract

BACKGROUND: The aim of this study was to estimate whether the Glasgow prognostic score (GPS) is useful for predicting the survival of patients after surgery for stage IV colorectal cancer (CRC).

METHODS: The GPS was calculated on the basis of admission data as follows: patients with both an increased C-reactive protein (CRP) level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a score of 2, and patients showing one or none of these abnormalities were allocated a score of 1 or 0, respectively.

RESULTS: A total of 108 patients with stage IV CRC were enrolled. Although multivariate analyses showed that tumor pathology, subclass of stage IV CRC, and the GPS were associated with overall survival, the GPS could divide the patients into 3 independent groups showing significant differences in postoperative survival ($P = .018$).

CONCLUSIONS: The GPS is not only one of the most significant clinical characteristics associated with the overall survival of patients with stage IV CRC, but also a useful indicator that is capable of dividing such patients into 3 independent groups before surgery.

The 7th edition of the TNM classification of malignant tumors differs from the 6th edition in that stage IV colorectal cancer (CRC) is divided into 2 subclasses based on the extent of distant metastases (M1a, 1 organ; M1b, >1 organ). Although stage IV is the final stage of CRC, subclass analysis has been required for effective treatment of such patients. Because recent improvements in preoperative or postoperative chemotherapy regimens[1,2] and the introduction of novel antibody agents[3,4] have improved the postoperative survival of CRC patients with distant metastases, the significance of delegating specific treatments to selected patients has been increasing. As a result, it has been recognized that there is a need to develop other classifications for stage IV CRC to facilitate more effective treatment.

In contrast, there is increasing evidence that the presence of an ongoing systemic inflammatory response,[5] as assessed using the Glasgow prognostic score (GPS),[6] is associated with postoperative survival in patients with several kinds of advanced cancer.[7–9] Such responses are thought to reflect tumor versus host interaction[10] associated with hypercytokinemia-based immunoreaction[11,12] because the GPS is based on only 2 laboratory factors, C-reactive protein (CRP)[13,14] and albumin,[15] which can be estimated easily before surgery. Therefore, in stage IV CRC, it might be a useful tool for deciding which patients would benefit more from preoperative chemotherapy[16,17] or palliative surgery.

The authors have no conflicts of interest to declare.

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Although a few studies have investigated the use of the GPS for predicting the postoperative survival of patients with far advanced CRC,[18,19] few studies have focused on the prognostication of stage IV patients undergoing CRC resection with or without resection of distant metastasis.

Therefore, the aim of the present study was to evaluate the usefulness of the GPS for classification of stage IV CRC patients undergoing surgery, and for prediction of their postoperative survival.

Methods

A retrospective review was performed using a database of patients who had undergone elective surgery for CRC. All surgeries were performed by the same surgical team at the Department of Gastroenterological Surgery at Dokkyo Medical University Hospital, between March 2000 and June 2009. Among these patients, 108 were enrolled for this study on the basis of specific criteria. All the patients were diagnosed as having stage IV CRC, and all underwent CRC resection with or without resection of distant metastases.

Routine laboratory measurements including the serum levels of CRP, albumin, and tumor markers such as carcinoembryonic antigen (CEA) (upper physiological value, 5 ng/mL),[20] and carbohydrate antigen 19-9 (CA19-9) (upper physiological value, 37 U/mL),[21] were performed on the day of admission to exclude any effects attributable to inflammation associated with sequential preoperative examinations. None of the patients had clinical evidence of infection or other inflammatory conditions such as obstructive colitis, and none had received preoperative chemotherapy or irradiation.

For analysis, patients were classified into 3 groups on the basis of GPS (0/1/2). The chi-squared test was used to analyze the distribution of clinical background characteristics, including age ($\leq$70 vs $>$70 y), sex (male vs female), tumor site (colon vs rectum), number of tumors (1 vs $\geq$2), maximum tumor size ($\leq$40 vs $>$40 mm), pathology (tub1, tub2 vs others), lymphatic invasion (presence vs absence), venous invasion (presence vs absence), lymph node metastasis (presence vs absence), surgical curability (B vs C), and subclass of stage IV CRC (M1a vs M1b).

Relationships between the 3 groups and clinicolaboratory characteristics such as age (year); number of tumors; maximum tumor size (mm); serum levels of CRP (mg/dL), albumin (g/dL), CEA (ng/mL), and CA19-9 (U/mL); body mass index (BMI) (kg/m^2); and postoperative survival period (days) were analyzed by the Kruskal–Wallis test.

Univariate analysis was performed to evaluate the relationship between overall survival and clinical characteristics, including age ($\leq$70 vs $>$70 y); sex (female vs male); tumor site (colon vs rectum); number of tumors (1/vs $\geq$2); maximum tumor size ($\leq$40 vs $>$40 mm); pathology (tub1, tub2 vs others); lymphatic invasion (absence vs presence); venous invasion (absence vs presence); lymph node metastasis (absence vs presence); serum levels of CRP (mg/dL), albumin (g/dL), CEA (ng/mL) and CA19-9 (U/mL); BMI (kg/m^2); subclass of stage IV CRC (M1a vs M1b); and GPS (0, 1 vs 2).

Similarly, multivariate analysis was performed to assess the most valuable clinical characteristic associated with overall survival from among those selected by univariate analysis.

Estimation of GPS

The GPS was estimated as described previously. Briefly, patients with both an increased 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 was present were allocated a score of 1, and those in whom neither was present were allocated a score of 0.[6,22]

Definition of curability

Based on the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum, 2nd English ed), residual tumor is diagnosed as follows: R0, no residual tumor; R1, no residual tumor, but tumor suspected at the resection margin; and R2, macroscopically evident residual tumor. Based on this definition, surgical curability is defined as follows: curability A, R0 in TNM stage I, II, or III; curability B, R0 in TNM stage IV or R1 in any TNM stage; curability C, R2 in any TNM stage.

Administration of chemotherapy

Most stage IV patients undergoing surgery were considered for postoperative chemotherapy. Recently formulated chemotherapy regimens such as FOLFIRI and FOLFOX were introduced in our department in January 2005, and patients who had undergone surgery before that time were orally administered anticancer drug regimens based on 5-fluorouracil as postoperative chemotherapy.

Statistical analysis

Data are presented as mean $\pm$ standard deviation and 95% confidence interval (95% CI). Differences in values among the 3 groups were analyzed using the chi-squared test and the Kruskal–Wallis test. Differences in values between 2 groups were analyzed using the Mann–Whitney *U* test. Odds ratios with 95% CI were calculated using univariate and multivariate Cox proportional hazards model analyses. Kaplan–Meier analysis and log-rank test were used to compare postoperative survival among the GPS groups and subclasses of stage IV CRC. Deaths before March 31, 2010, were included in this analysis. Statistical analyses were performed using the SPSS statistical software

package, version 16.0 (SPSS, Inc, Chicago, IL) at a significance level of P less than .05.

Results

The relationships between the GPS and clinical background characteristics of the 108 patients who underwent surgery for stage IV CRC are shown in Table 1. There were 72 males and 36 females, and 74 colon cancers and 34 rectal cancers. Forty-five patients had a high level of CRP (>1.0 mg/dL) and 55 patients had a low level of albumin (<3.5 g/dL). Because 29 of the former 45 patients (64.4%) had a low level of albumin, they were the patients with GPS 2. There were no significant differences between GPS and clinical background characteristics including stage IV CRC subclass.

Table 1 Relationships between clinical characteristics and GPS of patients with stage IV CRC

Variable	GPS 0 (n = 37)	GPS 1 (n = 42)	GPS 2 (n = 29)	*P* value
Age, y				
≤70	26	29	14	
>70	11	13	15	.122
Sex				
Male	23	31	18	
Female	14	11	11	.454
Tumor site				
Colon	24	31	19	
Rectum	13	11	10	.639
Number of tumors				
1	34	37	25	
≥2	3	5	4	.745
Tumor size, mm				
≤40	14	7	5	
>40	23	35	24	.054
Pathology				
Tub1, tub2	31	38	25	
Others	6	4	4	.669
Lymphatic invasion				
Presence	35	40	29	
Absence	2	2	0	.461
Venous invasion				
Presence	34	41	28	
Absence	3	1	1	.452
Lymph node metastasis				
Presence	23	31	19	
Absence	12	7	8	
Undetermined	2	4	2	.567
Curability				
B	14	20	8	
C	23	22	21	.272
Subclass of stage IV CRC				
M1a	25	25	18	
M1b	12	17	11	.756

Chi-squared test: tub1; well differentiated adenocarcinoma, tub2; moderately differentiated adenocarcinoma.

Table 2 shows the relationship between clinicolaboratory characteristics and GPS in patients with stage IV CRC. There were no significant differences among the GPS groups with regard to clinical background characteristics such as age, number of tumors, serum levels of CEA and CA19-9, and body mass index (BMI). In contrast, there were significant differences among the GPS groups for maximum tumor size ($P = .026$), CRP level ($P < .001$), and albumin level ($P < .001$) (Kruskal–Wallis test).

Table 3 shows the results of univariate analyses. During the observation period, 79 patients died, of whom 72 died of cancer-related disease. Univariate analysis was performed to evaluate the influence of clinical characteristics on overall survival. The results revealed that tumor pathology (others vs tub1, 2) (odds ratio, .256; 95% CI, .136–.481; $P < .001$), CEA level (ng/mL) (odds ratio, 1.000; 95% CI, 1.000–1.001; $P = .009$), subclass of stage IV CRC (M1b vs M1a) (odds ratio, .611; 95% CI, .390–.957; $P = .031$), and GPS (2 vs 0, 1) (odds ratio, .510; 95% CI, .314–.827; $P = .006$) were associated with overall survival.

Multivariate analysis using these 4 characteristics revealed that tumor pathology (others vs tub1, 2) (odds ratio, .216; 95% CI, .113–.413; $P < .001$), subclass of stage IV CRC (M1b/M1a) (odds ratio, .026; 95% CI, .362–.939; $P = .026$), and GPS (2 vs 0, 1) (odds ratio, .451; 95% CI, .271–.753; $P = .002$) were associated with overall survival (Table 4).

The median and maximum follow-up periods for survivors were 494 and 3,529 days, respectively. The mean postoperative survival period was 674 ± 658 days (± standard deviation). The Mann–Whitney U test revealed a significant difference in the postoperative survival period between patients with M1a (median, 620 d; range, 27–3,300 d) and those with M1b (median, 303 d; range, 11–3,529 d) ($P = .035$). Similarly, Kaplan–Meier analysis and log-rank test revealed that patients with M1b had poorer postoperative survival than those with M1a ($P = .030$) (Fig. 1), and that patients with a higher GPS had poorer postoperative survival than those with a lower GPS ($P = .018$) (Fig. 2). There were significant differences in postoperative survival among the GPS groups (GPS 0: median, 662 d; range, 174–3,529 d; GPS 1: median, 577 d; range, 11–1,539 d; GPS 2: median, 246 d; range, 27–2,757 days).

Subclass analyses were performed using the GPS for patients with M1a and M1b. Although there were no significant differences among the 3 GPS groups in patients with M1a ($P = .204$) (Fig. 3A), there were significant intergroup differences among the patients with M1b ($P = .036$) (Fig. 3B).

Comments

It is well known that subclass analysis of patients with stage IV CRC presents certain difficulties. Because stage IV is regarded as the final stage of CRC, most clinicopathologic

Table 2 Relationships between clinicolaboratory characteristics and GPS of patients with stage IV CRC

Variable	GPS 0 (n = 37)	GPS 1 (n = 42)	GPS 2 (n = 29)	*P* value
Age, y	63 ± 12	66 ± 9	69 ± 12	.087
Number of tumors	1.1 ± .3	1.2 ± .6	1.2 ± .6	.912
Maximum tumor size, mm	49 ± 16	59 ± 20	64 ± 21	**.026**
CRP level, mg/dL	.3 ± .2	1.4 ± 1.8	5.2 ± 4.7	**<.001**
Albumin level, g/dL	3.9 ± .3	3.3 ± .6	2.8 ± .4	**<.001**
CEA level, ng/mL	143 ± 472	223 ± 539	361 ± 685	.103
CA19-9 level, U/mL	272 ± 676	690 ± 1,652	1,153 ± 2,531	.262
Body mass index, kg/m^2	22 ± 4	22 ± 3	22 ± 3	.938
Survival period, d	908 ± 799	592 ± 431	494 ± 669	**.004**

Mean ± SD shown, Kruskal–Wallis test.
Bolded P values means a significance level of $P < .05$.
CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CRP = C-reactive protein.

characteristics are not effective for evaluation of patients with such far advanced disease. Among tumor markers considered to reflect tumor growth or progression directly, even CEA[20] and CA19-9,[23] which are regarded as specific for CRC, are not effective for accurate prognostication of patients with stage IV CRC. In fact, the results of multivariate analysis revealed no relationships between overall survival and levels of tumor markers such as CEA and CA19-9.

Recent changes in the TNM staging of colorectal cancer (7th ed) have meant that patients with stage IV CRC are now divided into 2 groups based on the extent of metastasis: stage IVa (M1a; 1 organ affected by metastasis) and IVb (M1b; involvement of >1 organ). Although this classification facilitates clear division between the 2 groups, some discrepancies are considered to exist. Even if patients have the same subclass of stage IV CRC, they sometimes can show an obvious difference in overall survival. For example, with regard to liver metastasis, it is well known that patients with stage IVa (M1a) CRC may show a difference in overall survival according to whether they have single or multiple liver metastases, and that such a difference also may be evident in patients with stage IVa (M1a) CRC according to whether they have single or multiple lung metastases. In contrast, although our present survival curve analysis showed that patients with stage IVb CRC had poorer postoperative survival than patients with stage IVa CRC, it is well accepted that stage IVa CRC patients with multiple liver or lung metastases might show poorer postoperative survival than stage IVb CRC patients with single liver and lung metastasis. In addition, because it is difficult to estimate peritoneal dissemination before surgery, accurate and efficient preoperative classification of stage IV CRC patients with peritoneal dissemination might be problematic. Therefore, another method of subclass analysis would be desirable to compensate for these weak points of stage IV CRC subclassification.

Table 3 Univariate analysis of factors related to overall survival of patients undergoing surgery for stage IV CRC

Variable	*P* value	Odds ratio	95% CI
Age, >70 vs ≤70 y	.769	.931	.579–1.497
Sex, male vs female	.898	1.031	.649–1.636
Tumor site, rectum vs colon	.958	.987	.615–1.586
Number of tumors, ≥2 vs 1	.493	.783	.389–1.576
Tumor size, >40 vs ≤40 mm	.359	.788	.474–1.311
Pathology, others vs tub1, 2	**<.001**	.256	.136–.481
Lymphatic invasion, presence vs absence	.319	.367	.051–2.641
Venous invasion, presence vs absence	.845	.904	.329–2.484
Lymph node metastasis, presence vs absence	.123	.648	.374–1.125
CEA level, ng/mL	**.009**	1.000	1.000–1.001
CA19-9 level, U/mL	.201	1.000	1.000–1.000
BMI, kg/m^2	.584	.981	.916–1.051
Subclass of stage IV CRC, M1b vs M1a	**.031**	.611	.390–.957
GPS, 2 vs 0, 1	**.006**	.510	.314–.827

Bolded P values means a significance level of $P < .05$.
BMI = body mass index; CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; GPS = Glasgow Prognostic Score.

Because the GPS, which reflects the hypercytokinemia resulting from tumor versus host interaction, is based on only 2 clinical characteristics—serum CRP and albumin—the groups classified by GPS were not affected by clinicopathologic characteristics. In fact, the results of the present study revealed no unbalanced distributions of clinical background characteristics among the 3 GPS groups. In addition, because patients with a higher GPS had larger primary tumors than patients with a lower GPS, differences in the mechanisms of tumor growth and progression may exist between GPS and tumor markers, which would be reflected in tumor-related characteristics.[21]

In fact, the results of multivariate analysis revealed that several significant characteristics—the GPS, tumor pathology, and stage IV CRC subclass—were associated with overall survival. Moreover, Kaplan–Meier analysis and log-

Table 4 Multivariate analysis of factors related to overall survival of patients undergoing surgery for stage IV CRC

Variable	*P* value	Odds ratio	95% CI
Pathology, others vs tub1, 2	**<.001**	.216	.113–.413
CEA level, ng/mL	.172	1.000	1.000–1.001
Subclass of stage IV CRC, M1b vs M1a	**.026**	.583	.362–.939
GPS, 2 vs 0, 1	**.002**	.451	.271–.753

Bolded P values means a significance level of $P < .05$.
CEA = carcinoembryonic antigen; GPS = Glasgow Prognostic Score.

rank tests clearly showed significant differences in postoperative survival among the 3 GPS groups (Fig. 2) ($P = .018$).

Recently, several studies have shown that the GPS is not only a valuable predictor of overall survival but also a useful tool for subclass analysis of postoperative survival.[24] In fact, our previous study revealed that the GPS was able not only to divide hepatocellular carcinoma patients with a lower Cancer of the Liver Italian Program score into 3 independent groups, but also was able to predict the postoperative survival of patients undergoing surgery for hepatocellular carcinoma.[24]

Although there were no significant differences among the 3 GPS groups in patients with M1a ($P = .204$) (Fig. 3A), there were significant intergroup differences in patients with M1b ($P = .036$) (Fig. 3B). Striking a balance between these 2 results, stage IV CRC patients with a higher GPS tended to show poorer postoperative survival than those with a lower GPS. In addition, the GPS was a useful tool for dividing stage IVb CRC patients into 3 independent groups before surgery ($P = .036$) (Fig. 3B).

Several types of inflammation score are available for predicting the postoperative survival of patients undergoing surgery for CRC, such as differential counts of white blood cells[25] (neutrophils, lymphocytes, monocytes, and platelets), neutrophil-to-lymphocyte ratio,[26] platelet-to-lymphocyte ratio,[26] prognostic index,[26] prognostic nutritional index,[26] and the GPS. Recently, the GPS was modified

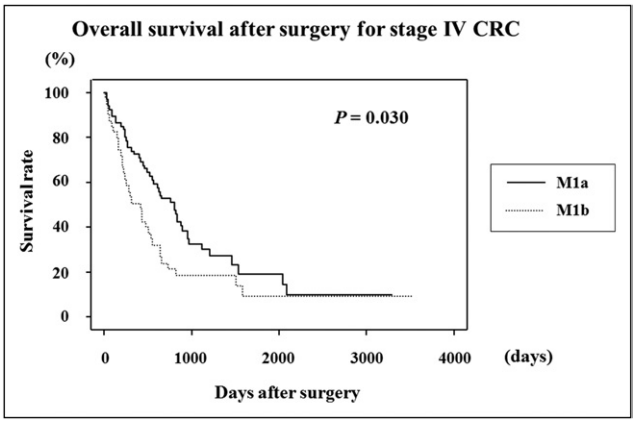

Figure 1 Relationship between subclass of stage IV CRC (M1a, M1b from top to bottom) and overall survival after surgery.

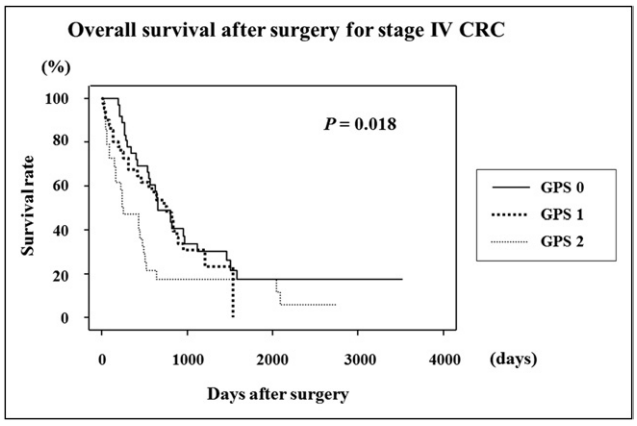

Figure 2 Relationship between GPS (GPS 0, 1, 2 from top to bottom) and overall survival after surgery in patients with stage IV CRC.

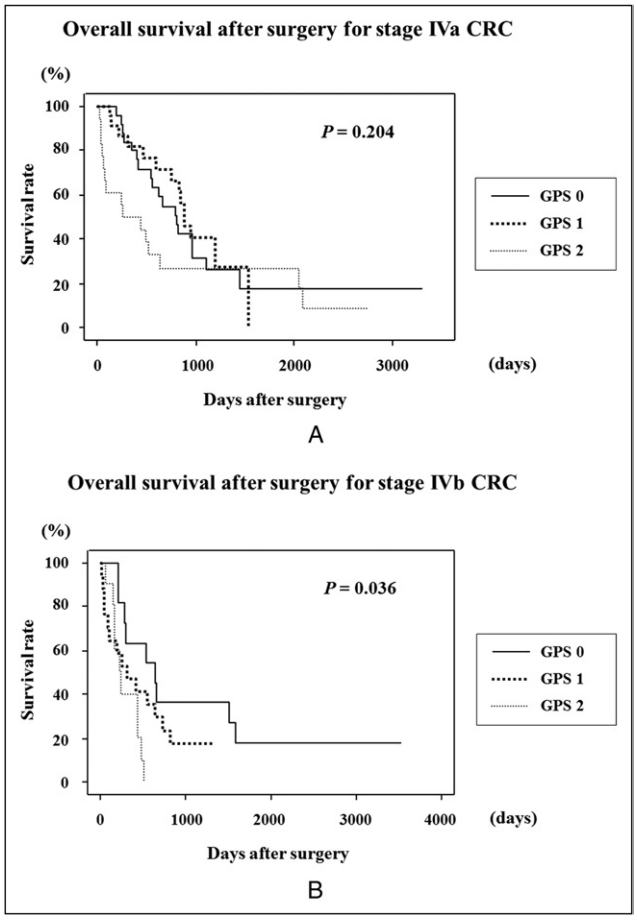

Figure 3 (A) Relationship between GPS (GPS 0, 1, 2 from top to bottom) and overall survival after surgery in patients with stage IV(a) CRC. (B) Relationship between GPS (GPS 0, 1, 2 from top to bottom) and overall survival after surgery in patients with stage IV(b) CRC.

(modified GPS [mGPS]) based on evidence that hypoalbuminemia in patients without an increased CRP concentration has no significant association with cancer-specific survival.[27] Therefore, patients with an increased CRP level were assigned an mGPS of 1 or 2 depending on the absence or presence of hypoalbuminemia. The mGPS was defined as follows: mGPS 0, CRP $<$ 1.0 mg/dL; mGPS 1, CRP $>$ 1.0 mg/dL; and mGPS 2, CRP $>$ 1.0 mg/dL and albumin $<$ 3.5 g/dL. Recent reports have revealed that the mGPS not only has a higher prognostic value than other inflammation-based prognostic systems such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio,[26] but also appears to be a superior predictor of survival in comparison with the differential counts of white blood cells.[25] Moreover, because the GPS, especially in early studies, was evaluated for its ability to predict the postoperative survival of patients with inoperable or far advanced cancer,[28,29] it is acceptable that the GPS would be more suitable than other inflammation-scoring systems for predicting the postoperative survival of patients undergoing surgery for stage IV CRC. In fact, the results of the Kaplan–Meier analysis revealed that although there was a significant difference among the groups of patients with stage IVb, there was no significant difference among the groups of patients with stage IVa.

In addition, a recent study showed that the positive-to-total-lymph-node ratio was associated with cancer-specific survival as well as mGPS in patients selected for potentially curative resection of gastroesophageal cancer.[30] However, there were only 3 (3%) patients with pTNM stage IV (pathological TNM [pTNM] stage I/II/III/IV = 28/31/38/3, respectively) and all the patients had an mGPS of 0 (87/100, 87%) or 1 (13/100, 13%). Comparison of such patients undergoing potentially curative surgery for gastroesophageal cancer with the present patients who underwent surgery for stage IV CRC is difficult because of several differences between the backgrounds of the 2 studies. In particular, lymph node dissection was insufficient in most of the patients in our series who underwent curability C surgery because the distant metastases were unresectable.

Because the GPS is an index that can be determined easily before surgery, it would be a useful guide for deciding the indications for palliative surgery or preoperative chemotherapy in stage IV CRC patients whose general condition is poor as a result of advanced cancer. On the other hand, because the subclass of stage IV CRC is finally decided by pathologic diagnosis after surgery, it cannot be used for preoperative allocation of patients to palliative surgery or preoperative chemotherapy.

In fact, the utility of surgery for multiple liver metastases from CRC (stage IVa) still is controversial because the indications for surgery differ not only among institutions but also among surgeons. Because the issue of whether it is better to perform surgery or to start preoperative chemotherapy still is unresolved,[31,32] preoperative estimation of the GPS might have potential utility for surgical decision making in stage IVa CRC patients with multiple liver metastases. In fact, the chief purpose of recently devised preoperative chemotherapy regimens including molecular-targeting antibody agents[33,34] is to reduce the size and number of metastatic liver tumors to allow liver resection,[35,36] and our previous study disclosed that among patients with far advanced or recurrent unresectable CRC receiving chemotherapy, those with a GPS of 2 had a poorer outcome than those with a GPS of 0 or 1.[18]

With regard to stage IVb CRC, because the outcome of patients with a GPS of 2 was much worse than that of patients with a GPS of 0 or 1, the former group already might be beyond any beneficial effect of palliative surgery or preoperative chemotherapy.

Preoperative estimation of GPS in patients with stage IV CRC might be clinically beneficial for subclass analysis, providing a supportive role that can complement existing prognostic indexes, and having utility for treatment decision making.

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