C-Reactive Protein is Associated with Distant Metastasis of T3 Colorectal Cancer

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Abstract. *Few studies have examined the relationship between systemic inflammatory response (SIR) and distant metastasis in patients with T3 colorectal cancer (T3 CRC). Uni- and multivariate analyses were performed in order to evaluate the influence of SIR on distant metastasis in patients with T3 CRC using collected clinical data. Between January 2000 and August 2009, 335 patients with pathologically diagnosed T3CRC were enrolled. Univariate analysis revealed that tumor differentiation, lymphatic invasion, venous invasion, lymph node metastasis, serum carcinoembryonic antigen (CEA) level, carbohydrate antigen 19-9 (CA 19-9) level, C-reactive protein (CRP) level and the Glasgow Prognostic Score (GPS) were associated with distant metastasis. Multivariate analysis using these selected characteristics disclosed that the CRP level was associated with distant metastasis of T3 CRC, as well as with lymph node metastasis, and CEA and CA19-9 levels. The level of CRP is one of the important clinical characteristics associated with distant metastasis of T3 CRC.*

A preliminary study conducted by our group (1) has demonstrated that the systemic inflammatory response (SIR) (2) including the Glasgow Prognostic Score (GPS) (3, 4), which reflects the levels of C-reactive protein (CRP) and albumin in serum, is associated with distant metastasis in patients with T1 or T2 colorectal cancer (CRC) (1). However, since only four patients with distant metastasis were included, the significance of the relationship between SIR and distant metastasis remained statistically unproven in that setting. Therefore, we considered that it would be valuable to examine the relationship between SIR and distant metastasis in the setting of T3 CRC, as T3 CRC is considered to be an ideal study model for this purpose in three respects.

Firstly, because T3 CRC is diagnosed on the basis not only of infiltration to the serosa or subserosa, but also the lack of direct infiltration to other organs, it is theoretically resectable, as well as T1 or T2 CRC. Secondly, because T3 CRC infiltrates more deeply than T1 or T2 CRC, the former is well known to have a much higher rate of distant metastasis than the latter two. Thirdly, since T3 CRC has three independent stages, it is acceptable to hypothesize that patients with T3 CRC with distant metastasis (stage IV) would have a greater degree of hypercytokinemia (5), which is thought to induce SIR, than patients without distant metastasis (stage III) or lymph node metastasis (stage II). In fact, recent studies have shown that evaluation of SIR, and especially the GPS (3), is more useful for predicting postoperative survival in patients with advanced cancer than in those with early-phase cancer (6-8). Moreover, several studies have demonstrated that there is a close relationship between SIR (9-11) and surgical outcome in patients with CRC.

In order to strengthen the evidence obtained in our previous study (1), the present investigation was conducted in a similar manner in order to evaluate the relationship between SIR and distant metastasis of T3 CRC using the clinical characteristics of the patients.

Patients and Methods

We retrospectively reviewed a database of 335 patients (male:female=222:113) who had undergone elective surgery for T3 CRC, performed by the same trained surgical team at the Department of Gastroenterological Surgery, Dokkyo Medical University, between January 2000 and August 2009.

Routine laboratory measurements including serum levels of CRP, albumin and tumor markers, such as carcinoembryonic antigen (CEA) (12) (upper physiological value 5 ng/ml) and carbohydrate antigen 19-9 (CA19-9) (13) (upper physiological value 37 U/ml), were carried out on the same day in order 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.

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The GPS was estimated as described previously (3, 4). 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 was present were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0.

All patients were finally diagnosed pathologically as having T3 CRC, and 90 patients had distant metastasis (stage IV) to sites such as the liver (n=61), peritoneum (n=13), lung (n=9) and others (n=7); 23 of those patients had metastatic lesions in more than two organs.

On the basis of the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum, Second English Edition) (14), the macroscopic types of tumors are defined as: Type 0, superficial; type 1, polypoid; type 2, ulcerative with a clear margin; type 3, ulcerative with infiltration; type 4, diffusely infiltrative; type 5, unclassified. The histological types of tumors are defined as: tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma.

Invasion of vessels, *i.e.* lymphatic invasion (ly) and venous invasion (v), is diagnosed as: ly0 (v0), no invasion; ly1 (v1), minimal invasion; ly2 (v2), moderate invasion; ly3 (v3), severe invasion. According to these definitions, we classified patients into two groups: those with absence (ly0, v0) and those with presence of invasion (ly1-3, v1-3).

Residual tumor is diagnosed as: R0, no residual tumor; R1, no residual tumor, but tumor at the resection margin suspected; R2, macroscopically evident residual tumor.

On the basis of this definition, operative curability is defined as: curability A (Cur A), R0 in TNM stage I, II or III; curability B (Cur B), R0 in TNM stage IV or R1 in any TNM stage; curability C (Cur C), R2 in any TNM stage.

Statistical analysis. Data are presented as mean±S.D. (standard deviation). Differences between groups were analyzed using the Mann-Whitney *U*-test, chi-squared test and Kruskal-Wallis test. Odds ratios with 95% confidence interval were calculated using logistic regression analysis. Deaths prior to 31st of May 2010 were included in this analysis. Statistical analyses were performed using the SPSS statistical software package, version 16.0 (SPSS Inc., Chicago, IL, USA), at a significance level of $p<0.05$.

Results

The relationship between the classified clinical characteristics of the 335 patients who underwent elective surgery for T3 CRC and overall survival period is shown in Table I. There were 222 males and 113 females, 222 colon and 113 rectal carcinomas. Differences in the following characteristics had no significant influence on the overall survival period: age (≤70/>70 years), gender (male/female), tumor site (colon/rectum), tumor type (1,2/3,4,5), number of tumors (1/≥2), maximum tumor diameter (≤40/>40 mm), and lymphatic invasion (absence/presence). However, overall survival was influenced by differences in the following: tumor differentiation (tub1, tub2/other) ($p=0.003$), venous invasion (absence/presence) ($p=0.008$), lymph node metastasis

Table I. *Relationships between classified clinical characteristics and overall survival period of patients with T3 colorectal cancer.*

Variable	Number	Overall survival period (days)	*p*-Value
Age (years)			
≤70	192	1216±891	
>70	143	1075±843	0.177
Gender			
Male	222	1126±873	
Female	113	1215±873	0.260
Tumor site			
Colon	222	1175±880	
Rectum	113	1120±861	0.544
Tumor type			
1, 2	285	1157±860	
3, 4, 5	50	1153±948	0.746
Number of tumors			
1	300	1154±870	
≥2	35	1176±910	0.956
Tumor diameter (mm)			
≤40	103	1115±750	
>40	232	1174±923	0.817
Tumor differentiation			
tub1, tub2	303	1198±874	
Other	32	762±760	0.003
Lymphatic invasion			
Absence	35	1375±987	
Presence	300	1131±856	0.171
Venous invasion			
Absence	46	1492±948	
Presence	289	1103±849	0.008
Lymph node metastasis			
Absence	154	1326±891	
Presence	171	1040±841	0.001
Not available	10	515±458	
Operative curability			
A	241	1366±879	
B, C	94	618±579	<0.001
CEA level (ng/ml)			
≤5	158	1353±849	
>5	173	949±843	<0.001
Not available	4	2324±108	
CA19-9 level (U/ml)			
≤37	230	1233±863	
>37	97	892±823	<0.001
Not available	8	2157±636	
Albumin level (g/dl)			
<3.5	137	931±785	
≥3.5	197	1307±898	<0.001
Not available	1	2197	
CRP level (mg/dl)			
≤1.0	255	1251±853	
>1.0	80	852±871	<0.001
GPS			
0, 1	282	1217±855	
2	52	804±889	<0.001
Not available	1	2197	
TNM stage			
II	133	1419±866	
III	112	1286±883	
IV	90	606±584	<0.001*

CEA: Carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma. Mann-Whitney *U*-test, mean±SD; *Kruskal-Wallis test.

Table II. *Relationships between clinical characteristics and TNM stage of patients with T3 colorectal cancer.*

Variable	Stage II, III (n=245)	Stage IV (n=90)	*p*-Value
Age (years)			
≤70	134	58	
>70	111	32	0.110
Gender			
Male	159	63	
Female	86	27	0.381
Tumor site			
Colon	162	60	
Rectum	83	30	0.926
Tumor type			
1, 2	208	77	
3, 4, 5	37	13	0.881
Number of tumors			
1	219	81	
≥2	26	9	0.871
Tumor diameter (mm)			
≤40	80	23	
>40	165	67	0.212
Tumor differentiation			
tub1, tub2	227	76	
Other	18	14	0.024
Lymphatic invasion			
Absence	31	4	
Presence	214	86	0.030
Venous invasion			
Absence	42	4	
Presence	203	86	0.003
Lymph node metastasis			
Absence	133	21	
Presence	112	59	<0.001
Not available	0	10	
Operative curability			
A	241	0	
B, C	4	90	<0.001
CEA level (ng/ml)			
≤5	140	18	
>5	101	72	<0.001
Not available	4	0	
CA19-9 level (U/ml)			
≤37	187	43	
>37	51	46	<0.001
Not available	7	1	
CRP level (mg/dl)			
≤1.0	205	50	
>1.0	40	40	<0.001
Albumin level (g/dl)			
<3.5	94	43	
≥3.5	150	47	0.259
Not available	1	0	
GPS			
0, 1	218	64	
2	26	26	<0.001
Not available	1	0	

CEA: Carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma. Chi-squared test.

Table III. *Relationships between clinicolaboratory characteristics and TNM stage of patients with T3 colorectal cancer.*

Variable	Stage II, III (n=245)	Stage IV (n=90)	*p*-Value
Age (years)	68.4±10.6	66.3±11.4	0.117
Number of tumors	1.1±0.4	1.1±0.4	0.932
Tumor diameter (mm)	53.9±21.3	55.9±18.8	0.372
CEA level (ng/ml)	11.1±20.5	240±587	<0.001
CA19-9 level (U/ml)	34.6±65.9	755±1850	<0.001
CRP level (mg/dl)	0.93±1.9	2.1±3.3	<0.001
Albumin level (g/dl)	3.6±0.6	3.4±0.6	0.045

CEA: Carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CRP: C-reactive protein. Mann-Whitney *U*-test, mean±SD.

(absence/presence) (p=0.001), operative curability (A/B, C) (p<0.001), serum CEA level (≤5/>5 ng/ml) (p<0.001), CA19-9 level (≤37/>37 U/ml) (p<0.001), albumin level (<3.5/≥3.5 g/dl) (p<0.001), CRP level (≤1.0/>1.0 mg/dl) (p<0.001), GPS (0, 1/2) (p<0.001) and TNM stage* (II, III/IV) (p<0.001) (Mann-Whitney *U*-test, *Kruskal-Wallis test).

Table II shows the relationship between the classified clinical characteristics and the TNM stage (stage II, III/IV) in the 335 patients using the same variables as those in Table I. Patients were divided into stages II/III (n=245) and stage IV (n=90). There were no significant differences in these variables according to stage, except for tumor differentiation (tub1, tub2/other) (p=0.024), lymphatic invasion (absence/presence) (p=0.030), venous invasion (absence/presence) (p=0.003), lymph node metastasis (absence/presence) (p<0.001), operative curability (A/B, C) (p<0.001), CEA level (≤5/>5 ng/ml) (p<0.001), CA 19-9 level (≤37/>37 U/ml) (p<0.001), CRP level (≤1.0/>1.0 mg/dl) (p<0.001) and GPS (0, 1/2) (p<0.001) (chi-squared test).

Table III shows the relationships between clinicolaboratory characteristics such as age, number of tumors, maximum tumor diameter, serum levels of CEA, CA19-9, CRP and albumin, and TNM stage (II, III/IV). Although there were no significant differences between the stage II/III and IV groups in clinicolaboratory characteristics such as age, number of tumors and maximum tumor diameter, there were significant differences in the levels of CEA (p<0.001), CA19-9 (p<0.001), CRP (p<0.001) and albumin (p=0.045) (Mann-Whitney *U*-test).

During the period of observation, 118 patients died, 98 due to CRC and the remaining 20 of other diseases.

Results of univariate analysis in stage IV CRC, using the same characteristics listed in Table I except for TNM stage, are presented in Table IV. No characteristics were associated with stage IV except for tumor differentiation (tub1, tub2/other) (p=0.027), lymphatic invasion (absence/presence)

Table IV. *Univariate analysis in relation to stage IV colorectal cancer.*

Variable	*p*-Value	Odds ratio	95% CI
Age (≤70/>70 years)	0.111	0.666	0.404-1.098
Sex (female/male)	0.382	1.262	0.749-2.126
Tumor site (colon/rectum)	0.926	0.976	0.585-1.628
Tumor type (1,2/3,4,5)	0.881	0.949	0.479-1.881
Number of tumors (1/>1)	0.871	0.936	0.421-2.082
Tumor diameter (≤40/>40 mm)	0.213	1.412	0.820-2.433
Tumor differentiation (tub1, tub2/other)	0.027	2.323	1.103-4.895
Lymphatic invasion (absence/presence)	0.038	3.114	1.067-9.089
Venous invasion (absence/presence)	0.006	4.448	1.547-12.79
Lymph node metastasis (absence/presence)	<0.001	3.336	1.910-5.829
CEA level (≤5/>5 ng/ml)	<0.001	5.545	3.115-9.868
CA19-9 level (≤37/>37 U/ml)	<0.001	3.922	2.336-6.587
CRP level (≤1.0/>1.0 mg/dl)	<0.001	4.100	2.398-7.010
Albumin level (≥3.5/<3.5 g/dl)	0.128	1.460	0.897-2.377
GPS (0,1/2)	<0.001	3.406	1.849-6.275

95% CI: 95% Confidence interval; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma.

Table V. *Multivariate analysis in relation to stage IV colorectal cancer.*

Variable	*p*-Value	Odds ratio	95% CI
Tumor differentiation (tub1, tub2/other)	0.267	1.700	0.667-4.336
Lymphatic invasion (absence/presence)	0.807	0.850	0.231-3.127
Venous invasion (absence/presence)	0.142	2.437	0.742-8.005
Lymph node metastasis (absence/presence)	0.005	2.697	1.357-5.363
CEA level (≤5.0/>5.0 ng/dl)	0.002	3.519	1.825-6.786
CA19-9 level (≤37/>37 U/ml)	0.028	1.988	1.076-3.675
CRP level (≤1.0/>1.0 mg/dl)	0.008	3.833	1.416-10.38
GPS (0,1/2)	0.572	0.722	0.233-2.237

95% CI: 95% Confidence interval; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma.

(p=0.038), venous invasion (absence/presence) (p=0.006), lymph node metastasis (absence/presence) (p<0.001), the serum levels of CEA (≤5/>5 ng/ml) (p<0.001), CA 19-9 (≤37/>37 U/ml) (p<0.001) and CRP (≤1.0/>1.0 mg/dl) (p<0.001), and GPS (0, 1/2) (p<0.001) (Table IV).

Table V shows the results of multivariate analysis using the eight clinical characteristics selected by univariate analysis. Four of these characteristics were associated with distant metastasis of T3 CRC (stage IV): lymph node metastasis (absence/presence) (odds ratio 2.697; 95% CI 1.357-5.363; p=0.005), CEA (≤5/>5 ng/ml) (odds ratio 3.519; 95% CI 1.825-6.786; p=0.002), CA19-9 (≤37/>37 U/ml) (odds ratio 1.988; 95% CI 1.076-3.675; p=0.028) and CRP (≤1.0/>1.0 mg/dl) (odds ratio 3.833; 95% CI 1.416-10.38; p=0.008).

Discussion

Analysis of the relationships between clinical background characteristics of patients with T3 CRC and overall survival period and TNM stage revealed that tumor differentiation, venous invasion, lymph node metastasis, operative curability, the levels of CEA, CA19-9 and CRP, and GPS were associated with overall survival period and were related to TNM stage IV. In addition, the serum level of albumin and TNM stage were associated with the overall survival period, and the lymphatic invasion was related to TNM stage IV. Similarly, patients with stage IV CRC had significantly higher levels of CEA, CA19-9 and CRP than patients with stage II or III CRC, but not of serum albumin.

Among these characteristics, it is not surprising that TNM stage and operative curability were associated with the surgical outcome of patients with T3 CRC. Because not all T3 CRCs are invasive to other organs, a primary T3 CRC can theoretically be resectable. However, patients with T3 CRC, with lymph node or distant metastasis are often diagnosed surgically as Cur B or C due to the presence of residual tumor. These patients have a poorer prognosis than those found to be Cur A at surgery. In fact, our results demonstrated such a relationship between the stage of T3 CRC and operative curability ($p<0.001$).

A particularly important finding was that the remaining nine clinical factors – tumor differentiation, lymphatic invasion, venous invasion, lymph node metastasis, the levels of CEA, CA19-9, albumin and CRP, and GPS – were able to divide the patients into two groups based on tumor- and SIR-related factors.

In general, conventional tumor markers, such as CEA and CA19-9, are significant indicators of tumor growth or progression (12, 15), and are thought to be secreted from the tumor itself. These are regarded as tumor-related factors, as well as being clinicopathological characteristics along with tumor differentiation, lymphatic invasion, venous invasion and lymph node metastasis.

On the other hand, because SIR-related characteristics are thought to reflect the tumor microenvironment, including tumor-*versus*-host interaction, and are regarded as host-related characteristics induced by the tumor, the latter three are regarded as SIR-related characteristics.

Several studies have revealed that cancer promotes the release of pro-inflammatory cytokines from tumor cells (16) or the immunovascular system (17), and that a close relationship exists between inflammation and cancer. For example, the mechanism of CRP up-regulation is controlled by cytokines such as interleukin-8 (IL-8) (18), IL-6 (19) and tumor necrosis factor α (20). Thus, a high CRP level might reflect an increased level of IL-6 in patients with advanced cancer (21, 22).

In most cases, as evaluation of interleukins is not performed routinely in hospitals at the time of admission, CRP can be used as an indirect indicator of interleukin up-regulation, particularly IL-6. Increased CRP levels in patients with cancer could also be caused by an inflammatory response to tumor infiltration or the microenvironment of a tumor infiltrated by lymphocytes (23), reflecting immunoreactive processes. There is increasing evidence that a high serum level of CRP is also correlated with shorter survival in patients with gastrointestinal malignancies, including cancer of the esophagus (24, 25), stomach (26), biliary system (27) and colorectum (28-30). Our present results revealed that a higher level of CRP was closely associated with stage IV disease ($p<0.001$) as well as with shorter overall survival ($p<0.001$).

Similarly, recent reports have also indicated that albumin concentration is a stage-independent prognostic factor in patients with advanced CRC (31, 32). This concept is consistent with the fact that all patients with hypoalbuminemia have an elevated CRP concentration (2, 33, 34). Indeed, our study reconfirmed that patients who had a low albumin level showed poorer overall survival than patients who had an adequate albumin level ($p<0.001$).

Furthermore, univariate analysis clearly indicated that CRP and GPS were characteristics closely associated with distant metastasis of T3 CRC, as well as with characteristics commonly believed to be tumor related, including tumor differentiation, lymphatic and venous invasion, lymph node metastasis, and serum CEA and CA19-9 levels.

Interestingly, however, a low albumin level was not associated with stage IV. It was considered that CRP was superior to albumin in terms of SIR sensitivity (35), reflecting the status of distant metastasis of T3 CRC. In accordance with this, the results of univariate analysis demonstrated that CRP and GPS were related to distant metastasis of T3 CRC.

Finally, among these eight clinical factors, multivariate analysis selected lymph node metastasis, and the serum levels of CEA, CA19-9 and CRP as stage IV-related characteristics.

In this ideal model of CRC, assuming that all the original tumors have the same depth, it seems acceptable that lymph node metastasis was related to distant metastasis because lymph node metastasis reflects the migrational ability of tumor cells, as well as the potential for distant metastasis of the original tumor. Similarly, it is well known that tumor markers such as CEA and CA19-9 are associated with distant metastasis. On the other hand, the relationship between CRP and distant metastasis is different from that with the tumor.

Although this study was a retrospective one, the relationship between SIR-related characteristics and distant metastasis was considered to be significant. Moreover, our present results appear to support our previous study that established an association between SIR and distant metastasis (1).

In conclusion, we have demonstrated a close relationship between SIR-related factors and tumor migration to distant organs in patients with T3 CRC. Evaluation of SIR, particularly elevation of the serum CRP level, would appear to be useful for the monitoring and management of distant metastasis of T3 CRC.

Conflicts of Interest

We have no conflicts of interest to declare.

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