ORIGINAL

Definition of Prognosis Based on Lymph Node Metastasis and Elevation of Serum C-Reactive Protein for Patients with Gastric Carcinoma Treated with Curative Resection

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Abstract : Purpose. The aim of this study was to develop prognostic criteria based on the combination of nodal metastasis and preoperative elevation of serum C-reactive protein (CRP) for patients with gastric carcinoma that have been treated with curative resection. Methods. Three hundred and twenty patients with gastric carcinoma who had been treated with curative resection were enrolled. One point was provided for each incidence of nodal metastasis and preoperative elevation of serum CRP and we examined whether this cumulative score system could provide a strict stratification of survival. Results. Significant differences regarding survival were observed both between patients with scores of 0 and 1 ($P < 0.0001$) and between patients with scores of 1 and 2 ($P < 0.0001$). Multivariate analysis showed that the cumulative score ($P = 0.0003$) and the depth of the tumor ($P = 0.016$) were independent prognostic indicators. Conclusions. Criteria for the prediction of prognosis in gastric carcinoma treated with curative resection based on tumor-related and host-related factors could provide a strict stratification. J. Med. Invest. 65 : 191-194, August, 2018

Keywords **:** *Gastric carcinoma, C-reactive protein, Lymph node metastasis*

INTRODUCTION

Establishment of a convenient and useful criteria based on clinicopathologic information that can easily determine the outcome of patients with gastric carcinoma could provide beneficial information for both the patients and the physicians.

Lymph node metastasis can be a representative parameter among the pathologic factors that predict tumor recurrence and the prognosis of patients with malignant tumors, including gastric carcinoma (1-3).

On the other hand, elevation of serum C-reactive protein, as part of the inflammatory response against the tumor, has been reported to be a useful predictor of the malignant potential of gastrointestinal tumors, including gastric carcinoma (4, 5).

However, progression and invasion of human malignant tumors can be influenced by the balance between the environmental conditions around the tumors and the physical state of the tumor-bearing patients.

In the current study, we developed a cumulative score, based on both the incidence of pathologic lymph node metastasis and preoperative elevation of serum CRP, and investigated whether it could provide a strict stratification of the prognosis of patients with gastric carcinoma who had been treated with curative resection.

PATIENTS AND METHODS

Patients, collection of blood samples, and measurement of C-reactive protein (CRP). Three hundred and twenty patients with gastric carcinoma, comprised of 222 men and 98 women who had been treated by curative resection, defined as a standard distal or total gastrectomy with a D1+ or D2 lymph node dissection, in our institute between 1998 and 2012, were enrolled in this study.

Patients who had a history of malignant tumors in other organs or had other chronic inflammatory diseases that could lead to elevation of serum CRP were excluded.

No neoadjuvant therapy was administered to the patients enrolled in this study.

All blood samples for serum CRP measurements were collected just before the surgical procedure. Normal value of CRP was 1.0 mg/dL and then, patients who had serum CRP concentrations > 1.0 mg/dL were regarded as CRP positive.

This study was approved by the institutional ethic committee of Fukuoka Higashi Medical Center.

Pathologic investigations. Pathologic factors were determined according to the TNM classification of malignant tumours prescribed by the International Union Against Cancer (6).

Definition of the cumulative score. Patients who had both elevated serum CRP and pathologic lymph node metastasis were allocated a Score of 2 and patients who had only one or neither were allocated Scores of 1 or 0, respectively.

Follow-up of the patients. The patients were followed-up until their death and only patients who died of gastric carcinoma were included in the tumor-related deaths. The period from the operation to the date of death was defined as the survival time. The follow-up interval after the operation ranged from 2 months to 9 years and 2 months.

Statistical analysis. All statistical analyses were performed using StatView (SAS Institute Inc, Cary, NC). Chi-square test and *t* test were used to compare the differences between values in each score group. Survival curves were constructed using the Kaplan-Meier method, and the Mantel-Cox test was used to analyze the equality of

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the survival curves. Cox proportional hazards model in a forward stepwise manner was used in the multivariate analysis to determine the independent prognostic indicators. P values < 0.05 were considered significant.

RESULTS

The correlations between the cumulative score and the clinicopathologic characteristics are shown in Table I. Significant differences were observed regarding the location of the tumor ($P = 0.021$), depth of the tumor ($P < 0.0001$), histological type ($P = 0.0007$), lymphatic invasion ($P < 0.0001$), venous invasion ($P < 0.0001$), stage of the tumors ($P < 0.0001$), and the surgical resection procedure ($P < 0.0001$). Additionally, a significant correlation of the cumulative score with carcinoembryonic antigen (CEA ; Table Ⅱ, $P = 0.004$) and with carbohydrate antigen 19-9 (CA19-9 ; Table Ⅲ, $P < 0.0001$) was observed. The 1-, 3- and 5-year survival rates of patients with a score of 0 were 100%, 100%, and 94.0%, respectively. These survival rates were 90.1%, 75.8%, and 69.1%, respectively, among patients with a score of 1, and 78.3%, 40.0% and 26.6%, respectively, among patients with a score of 2. Significant differences were observed between the survival of patients with scores of 0 and 1 ($P < 0.0001$) and also between those with scores of 1 and 2 ($P < 0.0001$, Figure. 1).

Table Ⅰ. Relationship between the cumulative score and clinicopathologic factors of the patients

Variable	Score 0 (n = 168)	Score 1 (n = 116)	Score 2 (n = 36)	P
Sex				
Male	116 (69.0)	76 (65.5)	30 (83.3)	0.127
Female	52 (31.0)	40 (34.5)	6 (16.7)	
Age	67.3 ± 11.1	69.2 ± 10.7	70.1 ± 9.8	0.136
Location of tumor				
Upper	20 (11.9)	21 (18.1)	11 (30.6)	0.021
Middle	112 (66.7)	55 (47.4)	16 (44.4)	
Lower	36 (21.4)	40 (34.5)	9 (25.0)	
Depth of tumor				
T1	127 (75.6)	15 (12.9)	0	< 0.0001
T2	16 (9.5)	19 (16.4)	4 (11.1)	
T3	22 (13.1)	59 (50.9)	20 (55.6)	
T4	3 (1.8)	23 (19.8)	12 (33.3)	
Histology				
Well or Moderately	101(60.1)	51 (44.0)	14 (38.9)	0.007
Poorly	67(39.9)	65 (56.0)	22 (61.1)	
Lymphatic invasion				
No	130 (77.4)	15 (12.9)	7 (19.4)	< 0.0001
Yes	38 (22.6)	101 (87.1)	29 (80.6)	
Venous invasion				
No	157 (93.5)	67 (57.8)	18 (50.0)	< 0.0001
Yes	11 (6.5)	49 (42.2)	18 (50.0)	
Tumor stage				
Ⅰ	143 (85.1)	13 (11.2)	0	< 0.0001
Ⅱ	25 (14.9)	44 (37.9)	9 (25.0)	
Ⅲ	0	59 (50.9)	27 (75.0)	
Surgical Procedure				
Distal	133 (79.2)	74 (63.8)	12 (33.3)	< 0.0001
Total	35 (20.8)	42 (36.2)	24 (66.7)	

Well well differentiated adenocarcinoma, *Moderately* moderately differentiated adenocarcinoma, *Poorly* poorly differentiated adenocarcinoma, *Distal* distal gasterectomy, *Total* total gastrectomy.
Values in the parenthesis are the percentages

Table Ⅱ. Relationship between the cumulative score and carcinoembryonic antigen (CEA)

	Score 0 (n = 150)	Score 1 (n = 102)	Score 2 (n = 34)	P
CEA				
Negative	131 (87.3)	86 (84.3)	21 (61.8)	0.004
Positive	19 (12.7)	16 (15.7)	13 (38.2)	

Values in the parenthesis are the percentages

Table Ⅲ. Relationship between the cumulative score and carbohydrate antigen 19-9 (CA19-9)

	Score 0 (n = 145)	Score 1 (n = 103)	Score 2 (n = 32)	P
CA19-9				
Negative	138 (95.2)	81 (78.6)	23 (71.9)	0.0001
Positive	7 (4.8)	22 (21.4)	9 (28.1)	

Values in the parenthesis are the percentages

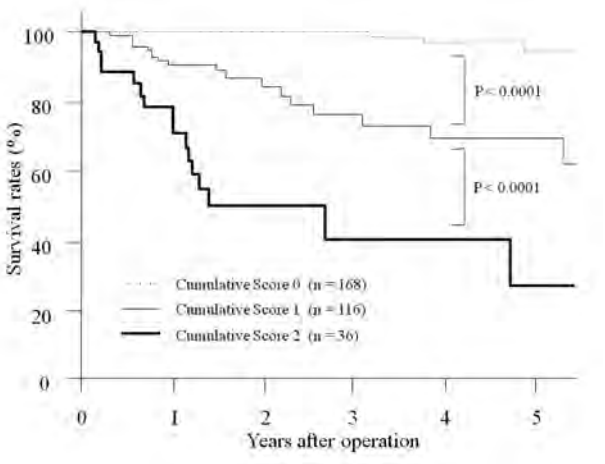

Fig. 1. Survival curves among whole patients.
Significant differences were observed between the survival of patients with cumulative scores of 0 and 1 ($P < 0.0001$) and those patients with cumulative scores of 1 and 2 ($P < 0.0001$).

Analysis restricted to patients with stage Ⅱ or Ⅲ are shown in Table Ⅳ. Significant differences were observed regarding the depth of the tumor ($P = 0.038$), lymphatic invasion ($P < 0.0001$), stage of the tumors ($P < 0.0001$), and the surgical resection procedure ($P = 0.013$). Similarly, significant differences were observed between the survival of patients with scores of 0 (with 5-year survival rate of 88.9%) and 1 (with 5-year survival rate of 61.4% ; $P = 0.010$) and also between those with scores of 1 and 2 (with 5-year survival rate of 61.4% ; $P = 0.0004$, Figure. 2).

Table Ⅳ. Relationship between the cumulative score and clinicopathologic factors of the patients with tumors of stage Ⅱ or Ⅲ

Variable	Score 0 (n = 25)	Score 1 (n = 103)	Score 2 (n = 36)	*P*
Sex				
Male	14 (56.0)	66 (64.1)	30 (83.3)	0.470
Female	11 (44.0)	37 (35.9)	6 (16.7)	
Age	66.2 ± 11.2	69.3 ± 10.9	70.1 ± 9.8	0.251
Location of tumor				
Upper	4 (16.0)	21 (20.4)	11 (30.6)	0.552
Middle	14 (56.0)	47 (45.6)	16 (44.4)	
Lower	7 (28.0)	35 (34.0)	9 (25.0)	
Depth of tumor				
T1	0	5 (4.8)	0	0.038
T2	0	16 (15.5)	4 (11.1)	
T3	22 (88.0)	59 (57.3)	20 (55.6)	
T4	3 (12.0)	23 (22.3)	12 (33.3)	
Histology				
Well or Moderately	8 (32.0)	45 (43.7)	14 (38.9)	0.546
Poorly	17 (68.0)	58 (56.3)	22 (61.1)	
Lymphatic invasion				
No	14 (56.0)	8 (7.8)	7 (19.4)	< 0.0001
Yes	11 (44.0)	95 (92.2)	29 (80.6)	
Venous invasion				
No	19 (76.0)	56 (54.4)	18 (50.0)	0.085
Yes	6 (24.0)	47 (45.6)	18 (50.0)	
Tumor stage				
Ⅱ	25 (100)	44 (42.7)	9 (25.0)	< 0.0001
Ⅲ	0	59 (57.3)	27 (75.0)	
Surgical Procedure				
Distal	16 (64.0)	62 (60.2)	12 (33.3)	0.013
Total	9 (36.0)	41 (39.8)	24 (66.7)	

Well well differentiated adenocarcinoma, *Moderately* moderately differentiated adenocarcinoma, *Poorly* poorly differentiated adenocarcinoma, *Distal* distal gasterectomy, *Total* total gastrectomy.
Values in the parenthesis are the percentages

Multivariate analysis demonstrated that the cumulative score ($P = 0.0003$) and the depth of the tumor ($P = 0.016$) were independent prognostic indicators (Table Ⅴ).

DISCUSSION

The most difficult and serious problem in the clinical treatment of gastric carcinoma is that the subsequent outcome of the patients could be desperate in cases of distant metastasis with detection of the tumor and the tumor recurrence. While recurrent liver or lung tumors derived from colorectal carcinoma are occasionally indicated for surgical treatment followed by the systemic chemotherapy under some restricted conditions, recurrent tumors metastasized from gastric carcinoma are rarely subjected to surgical treatment due to its small contribution to the prolongation of the survival (7, 8).

Therefore, in order to improve the prognosis of patients with gastric carcinoma, more useful and convenient information to predict tumor recurrence and the prognosis of patients with gastric carcinoma who have been treated with curative resection are necessary.

In establishing more useful prognostic criteria to predict the outcome of tumor-bearing disease that are both convenient and cost-effective, laboratory and histological examinations might be used for patients with malignant tumors. While all of the pathological factors, including lymphatic permeation, venous invasion and lymph node metastasis, are indicators that can predict the aggressiveness of

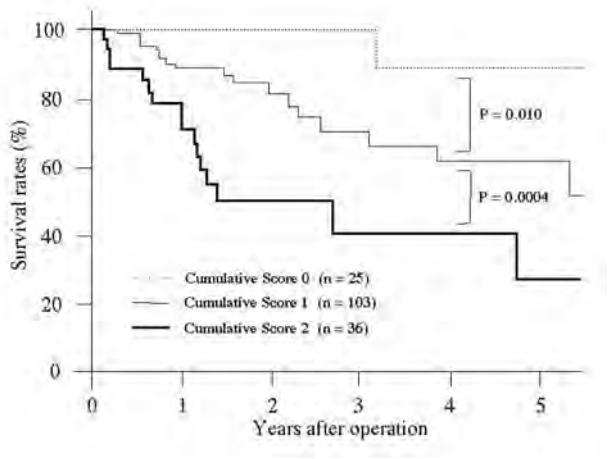

Fig. 2. Survival curves among patients with tumors of stage Ⅱ or Ⅲ. Significant differences were observed between the survival of patients with cumulative scores of 0 and 1 ($P = 0.0010$) and those patients with cumulative scores of 1 and 2 ($P = 0.0004$).

Table Ⅴ. Multivariate analysis to determine factors independently correlated with patients' prognosis

Variable	Odds Ratio (95% confidence interval)	*P*
Depth of tumor	5.00 (1.35-18.5)	0.016
Cumulative score	3.70 (1.83-7.52)	0.0003
Lymphatic invasion	2.37 (1.08-6.06)	0.072
Venous invasion	1.39 (0.71-2.72)	0.335

the gastric carcinomas that have been treated with curative surgical resection, lymph node metastasis, in both senses of their existence (1) and the number (3, 9) and/or proportion (2) of the nodes involved by the carcinoma cells, could be a representative indicator for the biological potential of the tumors among these pathologic elements.

As a prognostic indicator based on laboratory data, elevation of serum C-reactive protein (CRP) has come to be used as an indicator of patient outcome in some human malignant tumors of the digestive tracts, including gastric carcinoma, both independently[5] and by such combined forms as the Glasgow Prognostic Score (GPS) (4, 10).

While the scope of these investigations might suggest that criteria to determine patients' prognosis in gastric carcinoma based upon the combination of pathologic lymph node metastasis, as a representative of tumor-related factors, and elevation of serum CRP. as a representative of the host-related factors, appears to be much more useful, there has been no previous attempt to produce such criteria for patients with gastric cancer who had been treated with curative resection. Indeed, such attempts to readily reconstruct the criteria to determine and predict the prognosis of patients, based on both tumor-related and host related factors, have been introduced regarding colorectal carcinoma (11, 12).

Indeed, in the current study, the cumulative score system formed by the combination of the presence of pathologic lymph node metastasis and elevation of serum CRP could provide a strict stratification of survival of patients with gastric carcinoma who have been treated with curative resection. And a similar results could be demonstrated in analysis restricted to patients with TNM stage Ⅱ or Ⅲ tumors. Moreover, this cumulative score proved to be significant as an independent prognostic indicator of gastric carcinoma.

It holds true that the most popular criteria to determine prognosis in gastric cancer remains to be TNM staging system. However, our score system can be composed of two factors and simply classified to only three groups and the prognosis of the group could be clearly divided with a strict stratification, being the most outstanding advantage of our score system. And the most outstanding significance in this study is to create staging system based on both tumor-related and host-relates factors.

While determination of an existence of nodal metastasis might be found by diagnostic images including computed tomography (CT) and positron emission tomography (PET), our cumulative score system would exert an ability also to preoperatively predict the subsequent prognosis of the patients.

In conclusion, the cumulative score system generated by the basic data of pathologic nodal metastasis and elevation of serum CRP can be applied to the majority of the medical institutes and it could be an easy and useful information to predict outcome of the patients with gastric carcinoma that had been treated with curative surgical treatment.

DISCLOSURE

The authors have no financial interests or conflict of interest.

REFERENCES

1. Nozoe T, Iguchi T, Egashira A, Adachi E, Matsukuma A, and Ezaki T : Pathological prognostic score as a simple criterion to predict outcome in gastric carcinoma. J Surg Oncol *102* : 73-6, 2010
2. Xu DZ, Geng QR, Long ZJ, Zhan YQ, Li W, Zhou ZW, Chen YB, Sun XW, Chen G, Liu Q : Positive lymph node ratio is an independent prognostic factor in gastric cancer after d2 resection regardless of the examined number of lymph nodes. Ann Surg Oncol *16* : 319-326, 2009
3. Saito H, Fukumoto Y, Osaki T, Fukuda K, Tatebe S, Tsujitani S, Ikeguchi M : Prognostic significance of level and number of lymph node metastases in patients with gastric cancer. Ann Surg Oncol *14* : 1688-1693, 2007
4. Aurello P, Tierno SM, Berardi G, Tomassini F, Magistri P, D'Angelo F, Ramacciato G : Value of preoperative inflammation-based prognostic scores in predicting overall survival and disease-free survival in patients with gastric cancer. Ann Surg Oncol *21* : 1998-2004, 2014
5. Nozoe T, Iguchi T, Adachi E, Matsukuma A, Ezaki T : Preoperative elevation of serum C-reactive protein as an independent prognostic indicator for gastric cancer. Surg Today *41* : 510-513, 2011
6. Sobin L, Gospodarowicz M, Wittekind C :International Union Against Cancer. TNM classification of malignant tumours, 7th edition. New York : Wiley-Blackwell ; 2009 ; pp. 73-77
7. Shiono S, Sato T, Horio H, Chida M, Matsuguma H, Ozeki Y, Nakajima J, Okumura S ; Metastatic Lung Tumor Study Group of Japan : Outcomes and prognostic factors of survival after pulmonary resection for metastatic gastric cancer. Eur J Cardiothorac Surg *43* : 13-16, 2013
8. Koga R, Yamamoto J, Ohyama S, Saiura A, Seki M, Seto Y, Yamaguchi T : Liver resection for metastatic gastric cancer : experience with 42 patients including eight long-term survivors. Jpn J Clin Oncol *37* : 836-842, 2007
9. Espín F, Bianchi A, Llorca S, Feliu J, Palomera E, García O, Remon J, Suñol X : Metastatic lymph node ratio versus number of metastatic lymph nodes as a prognostic factor in gastric cancer.. Eur J Surg Oncol *38* : 497-502, 2012
10. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K : Inflammation-based prognostic system predicts postoperative survival of colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen. Ann Surg Oncol *19* : 3422-3431, 2012
11. Nozoe T, Matono R, Ijichi H, Ohga T, Ezaki T : Prognostic criteria in colorectal carcinoma constructed by the combination of tumor-related and host-related factors. Am J Surg *208* : 119-123, 2014
12. Canna K, McMillan DC, McKee RF, McNicol AM, Horgan PG, McArdle CS : Evaluation of a cumulative prognostic score based on the systemic inflammatory response in patients undergoing potentially curative surgery for colorectal cancer. Br J Cancer *90* : 1707-1709, 2004