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ORIGINAL ARTICLE

Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy

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Abstract
Purpose The present study evaluated baseline patient- or tumor-related prognostic factors in patients with advanced gastric adenocarcinoma.
Patients and methods A total of 304 consecutive patients with newly diagnosed metastatic or recurrent gastric cancer treated with one or more cycles of cisplatin-based chemotherapy at the Korea Cancer Center Hospital were enrolled in the current study.
Results Among the original 304 patients, only 4 patients were alive at the time of this analysis. The median survival for all patients was 7.3 (95% CI, 6.3–8.2) months. Five independent prognostic factors were identified by a multivariate analysis: poor performance status (hazard ratio [HR], 1.46; 95% CI, 1.32–2.92), elevated total bilirubin (HR, 2.04; 95% CI, 1.73–2.35), presence of peritoneal metastasis (HR, 1.73; 95% CI, 1.57–1.90), presence of bone metastasis (HR, 3.11; 95% CI, 2.69–3.53), and more than 1 metastatic site (HR, 1.22; 95% CI, 1.06–1.38). A prognostic index was constructed that divided the patients into a good ($n = 162$), moderate ($n = 82$), or poor ($n = 60$) risk group. The 1-year survival rates for the good, moderate, and poor risk groups were 34.6, 20.7, and 1.7%, respectively, and the survival differences among the groups were highly significant ($P < 0.0001$).
Conclusion Five prognostic factors were identified from patients receiving first-line cisplatin-based chemotherapy for advanced gastric cancer. A simple prognostic index was then developed that produced distinct survival rates among the different risk groups. Therefore, this prognostic model could help clinicians and patients in clinical decision-making and treatment tailoring based on the estimated prognosis.

Keywords Gastric cancer · Prognostic factor · Cisplatin · Chemotherapy

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Introduction

Despite a declining incidence in many developed countries, gastric cancer remains the second most common cancer-related death in the world [1]. Many patients with gastric cancer present with distant metastasis, plus the 5-year survival rate for these patients is only 3.1% [2]. Although, the

prognosis for advanced gastric cancer is poor, several randomized studies have found that combination chemotherapy improves the quality of life (QoL) and overall survival when compared with the best supportive care [3–5]. Among the various active chemotherapeutic agents (5-fluorouracil, anthracyclines, cisplatin, taxanes, and irinotecan), cisplatin-based combination chemotherapy is most commonly used, with a high response rate of 37–56% [6–9].

Determining the prognostic factors of survival for patients with advanced gastric cancer can help identify patients with worse prognosis to the current chemotherapeutic regimens. This would also allow risk stratification for patients in future phase III trials and ensure adequate assessment of new drugs. To date, several studies have investigated the prognostic factors for survival in patients with gastric cancer treated with surgery or chemotherapy [10–15]. For example, Bedikian et al. [12] reported that the status of the primary disease, liver metastasis, serum bilirubin level, ascites, extent of the tumor burden, and weight loss, in addition to the tumor stage, all showed a significant relationship to survival in 783 patients with histologically confirmed gastric carcinoma. Furthermore, Chau et al. [15] recently reported that a poor performance status, liver metastases, peritoneal metastases, and elevated alkaline phosphatase were independent prognostic factors in 1,080 patients with locally advanced or metastatic esophagogastric cancer. However, few studies have focused on patients with metastatic gastric cancer treated with systemic chemotherapy.

Accordingly, the present study evaluated baseline patient- or tumor-related prognostic factors in patients with metastatic or recurrent gastric adenocarcinoma treated with cisplatin-based chemotherapy.

Materials and methods

Patient population

The present retrospective study analyzed the outcomes of 304 consecutive patients with newly diagnosed metastatic or recurrent gastric cancer who were treated with one or more cycles of cisplatin-based chemotherapy at the Korea Cancer Center Hospital between January 1992 and December 1996. All patients had histologically confirmed adenocarcinoma and a metastatic lesion(s) at the time of diagnosis. Any patient with a prior history of radiation, or palliative chemotherapy was excluded from the study. Further exclusion criteria were: active infection or other serious underlying medical conditions that would impair the ability of the patient to receive the planned treatment, plus mental disorders not permitting adequate informed consent.

The pretreatment evaluation consisted of a complete medical history, physical examination, complete blood cell count and serum biochemistry, and computed tomography (CT) scan of the abdomen and chest when appropriate. The response to chemotherapy was evaluated by a CT scan. In patients with a measurable or evaluable disease, the response was evaluated using the WHO response criteria [16].

Prognostic factors analyzed

The pretreatment characteristics analyzed for prognostic significance were sex, age, eastern cooperative oncology group (ECOG) performance status (PS) (0 or I vs. II or III), history of weight loss (10% or more of usual weight), site of primary lesion, histologic differentiation, Borrmann type, chemotherapy regimen, sites of metastasis (peritoneum, ovaries, distant lymph nodes, liver, lung, bone, and others), number of metastatic site, WBC count, hemoglobin (Hb) level, platelet (PLT) count, and biochemical parameters, including serum albumin, serum total bilirubin, hepatic enzyme, and serum lactic dehydrogenase (LDH). All these factors were determined at the time of chemotherapy, while metastasis was diagnosed by histological or radiological findings. For example, the presence of peritoneal metastasis represented by peritoneal deposits or omental cakes seen on a computed tomography scan or cytologically confirmed malignant ascites.

Statistical analysis

Overall survival (OS) was used as the primary end point, and was calculated from the date of chemotherapy until death from any cause, or censored at the last follow-up using the Kaplan–Meier method. A survival curve comparison was performed using a log-rank test, and the survival analyses performed on an intention-to-treat basis. The construction of the prognostic model started with a univariate assessment of the prognostic effect of each factor, followed by a multivariate analysis using stepwise Cox proportional hazard regression modeling. Forward and backward stepwise regressions were both used to test the robustness of the model. As multiple statistical testing was performed, a two-sided P value of less than 0.05 was considered significant, and 95% confidential intervals were quoted. The laboratory variables were dichotomized with the cutoff points chosen as the upper normal value for each variable. Multivariate logistic regression was used to determine the factors predictive of the chemotherapy response. The statistical data were obtained using an SPSS software package (SPSS Inc. Chicago, IL, USA) or SAS Genetic software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The median age was 54 years (range 19–75 years) with 197 males and 107 females, and 218 patients (72%) had a metastatic disease, while the other 86 patients (28%) had a recurrent disease. The common metastatic site was distant lymph node, liver, and peritoneum, while 57 patients had more than 1 metastatic site (distant lymph node + liver, $n = 22$; distant lymph node + peritoneum, $n = 18$, distant lymph node + bone, $n = 3$; distant lymph node + lung, $n = 2$; 3 or 4 metastatic sites, $n = 12$). The chemotherapy regimens administered to the patients were as follows: FP (5-flourouracil 1,000 mg/m^2 + cisplatin 20 mg/m^2 on day 1 to day 5 in a 3-week cycle, $n = 158$), FEP (5-flourouracil 800 mg/m^2 on day 1 to day 5 + etoposide 100 mg/m^2 on days 1, 3, and 5 + cisplatin 20 mg/m^2 on day 1 to day 5 in a 3-week cycle, $n = 98$), FLEP (5-flourouracil 800 mg/m^2 on day 1 to day 5 + leucovorin 20 mg/m^2 on day 1 to day 5 + etoposide 100 mg/m^2 on days 1, 3, and 5 + cisplatin 20 mg/m^2 on day 1 to day 5 in a 3-week cycle, $n = 27$), and others ($n = 21$). Among the 304 patients enrolled in the current study, only 4 patients were alive at the time of this analysis. The median survival for all the patients was 7.3 months (95% confidential interval [CI], 6.3–8.2 months). The estimated 1- and 2-year survival rates were 24.3 ± 2.5 % and 7.2 ± 1.5 %, respectively. Figure 1 shows the overall survival for the whole group.

Uni- and multivariate analysis

Tables 1, 2, 3 summarize the results of the uni- and multivariate survival analyses. In the univariate analysis, the significant variables related to survival were as follows: performance status, total bilirubin, serum LDH, peritoneal metastasis, bone metastasis, and number of metastatic site (1 vs. ≥2). Meanwhile, the multivariate analysis showed that a poor performance status, elevated total bilirubin, presence of peritoneal metastasis or bone metastasis, and more than 1 metastatic site were independent prognostic factors. Bone metastasis was identified as the strongest predictor for survival (Table 4). The elevated total bilirubin was caused by a biliary tract obstruction due to lymph node metastasis in most patients (82%), plus the chemotherapy was delayed until median 13 (range 9–24) days after diagnosis. Among the original 304 patients, only 194 patients were evaluable for their response to chemotherapy and showed an overall response rate of 22.7% (95% CI: 16.7–28.7%). In the multivariate analysis, the patients with a performance status ≥2 had a significantly reduced probability of a tumor response to chemotherapy ($P = 0.005$, data not shown).

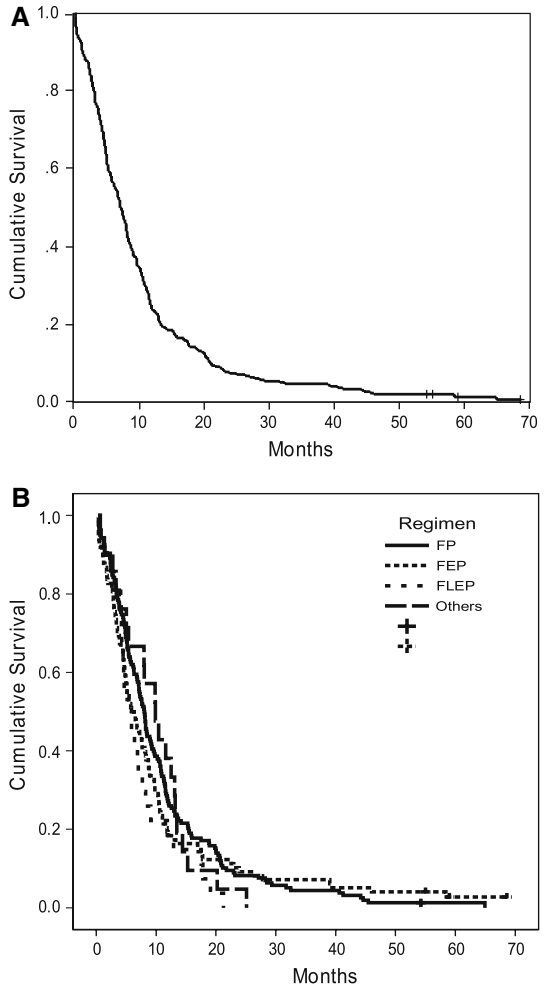

Fig. 1 Overall survival curves for all patients (**a**) and according to chemotherapy regimens (**b**)

Prognostic index and risk group

Since bone metastasis had the highest order of magnitude (Hazard ratio: 3.1109, β coefficient: 1.1349) among the five prognostic factors, the following prognostic index was developed: Prognostic index = performance status (0 or 1) + total bilirubin (0 or 1) + peritoneal metastasis (0 or 1) + bone metastasis (0 or 2) + number of metastatic site (0 or 1). Patients with a zero prognostic index were categorized as the good risk group ($n = 162$), those with a prognostic index of 1 were categorized as the moderate risk group ($n = 82$), and those with a prognostic index of more than 1 were categorized as the poor risk group ($n = 60$). Highly significant survival differences were observed among the three risk groups (log rank $P < 0.0001$, Table 5, Fig. 2), where the median survival for the good, moderate, and poor risk groups was 9.6, 7.6, and 3.6 months, respectively, while the 1-year survival rates were 34.6 ± 3.7%, 20.7 ± 4.5%, and 1.7 ± 1.6%, respectively. When com-

Table 1 Survival analysis (patient characteristics)

Variable	Number	Overall survival (median, months)	[a]*u–P*	[b]*m–P*
Sex				
Male	197	7.07		
Female	107	8.03	0.6156	
Age (years)				
≤60	228	7.67		
>60	76	5.40	0.5793	
Performance status (ECOG)				
0–1	223	8.23		
2–3	81	4.67	0.0000	0.0298
Weight loss				
Present	111	6.87		
Absent	163	7.63	0.2675	
Site of primary lesion				
Middle, lower	183	7.97		
Upper, whole	83	6.50	0.3422	
Differentiation				
Well to moderate	70	6.90		
Poorly	216	7.17	0.8811	
Borrmann type				
I–III	172	8.17		
IV	50	5.67	0.0967	
Chemotherapy regimen				
[c]FP	158	8.00		
[d]FEP	98	5.90		
[e]FLEP	27	5.87		
Others	21	9.87	0.3651	

[a] *u–P* univariate analysis: log-rank test was used, [b] *m–P* multivariate analysis: Cox proportional hazard model was used, [c] *FP* 5-fluorouracil + cisplatin, [d] *FEP* 5-fluorouracil + etoposide + cisplatin, [e] *FLEP* 5-fluorouracil + leucovorin + etoposide + cisplatin

Table 2 Survival analysis (sites of metastasis)

Variable	Number	Overall survival (median, months)	[a]*u–P*	[b]*m–P*
Peritoneum				
Present	63	4.63		
Absent	241	8.23	0.0000	0.0034
Ovary (female only)				
Present	10	10.8		
Absent	97	7.67	0.7302	
Distant lymph node				
Present	134	6.40		
Absent	170	7.97	0.8039	
Liver				
Present	74	6.87		
Absent	230	7.57	0.1157	
Lung				
Present	5	2.40		
Absent	299	7.43	0.2202	
Bone				
Present	6	2.80		
Absent	298	7.57	0.0092	0.0097
Others				
Present	5	3.37		
Absent	299	7.30	0.7808	
No. of metastatic sites				
1	247	8.17		
≥2	57	4.63	0.0000	0.0059

[a] *u–P* univariate analysis: log-rank test was used, [b] *m–P* multivariate analysis: Cox proportional hazard model was used

pared to the good risk group, the moderate risk group had a 2.7-fold (hazard ratio [HR], 2.65; 95% CI, 1.92–3.66) increased risk of death, while the poor risk group had a 3.8-fold (HR, 3.78; 95% CI, 2.67–5.36) increased risk of death.

Discussion

The present study analyzed individual patient data pooled from 304 consecutive patients with metastatic or recurrent gastric adenocarcinoma who were treated with cisplatin-based chemotherapy at a single institution. The performance status, serum bilirubin level, presence of peritoneum and/or bone metastasis, and number of metastatic sites were all identified as significant prognostic factors. A simple prognostic index was then developed, resulting in different risk groups with varying survival. Since information on all five prognostic factors is readily available to clinicians before commencing treatment, this would aid with clinical decision-making and risk stratification.

Recently, Chau et al. [15] reported that a poor performance status, the presence of liver and/or peritoneal metastasis, and elevated serum alkaline phosphatase were associated with poor survival in a multivariate analysis of 1,080 patients with locally advanced or metastatic esophago-gastric cancer treated with fluorouracil-based chemotherapy within three randomized studies. Plus, similar to the present study, patients with zero, one/two, or three/four risk factors had a significantly different survival, however, Chau's study included 295 patients (27.3%) with esophageal cancer and 240 (22.2%) patients with a locally advanced disease. Thus, since the biologic behavior and clinical outcomes are known to differ between esophageal and gastric cancer [17, 18], a subgroup analysis is needed to

Table 3 Survival analysis (laboratory parameters)

Variable	Number	Overall survival (median, months)	[a]*u–P*	[b]*m–P*
WBC ($\times 10^9$/l)				
4.0	285	7.60		
<4.0	19	4.47	0.0604	
Hemoglobin (g/dl)				
12	193	7.03		
<12	105	7.63	0.3314	
Platelet ($\times 10^9$/l)				
100	215	7.63		
<100	89	6.23	0.0942	
Albumin				
1 × normal	268	7.73		
<1 × normal	34	3.57	0.0000	0.0676
Total bilirubin				
1 × normal	291	7.43		
>1 × normal	11	6.33	0.0458	0.0190
Aspartate aminotransferase (AST)				
1 × normal	250	7.67		
>1 × normal	54	5.70	0.1846	
Aalanine aminotransferase (ALT)				
1 × normal	266	7.57		
>1 × normal	38	6.23	0.8831	
Alkaline phosphatase (ALP)				
1 × normal	252	7.59		
>1 × normal	52	5.87	0.2341	
Lactate dehydrogenase (LDH)				
1 × normal	156	8.07		
>1 × normal	113	5.83	0.0307	0.4370

[a] *u–P* univariate analysis: log-rank test was used, [b] *m–P* multivariate analysis: Cox proportional hazard model was used

Table 4 Multivariate survival analysis using Cox's model

Variable	Coefficient (β)	Standard error	Relative risk	*P* value
Performance status				
0–1 (0)	0.3814	0.1458	1.0000	
2–3 (1)			1.4643	0.0089
Peritoneal metastasis				
Present (1)	0.5505	0.1649	1.7341	
Absent (0)			1.0000	0.0008
Bone metastasis				
Present (2)	1.1349	0.4204	3.1109	
Absent (0)			1.0000	0.0069
No. of metastatic sites				
1 (0)	0.5088	0.1594	1.0000	
≥2 (1)			1.2170	0.0014
Total bilirubin				
1 × normal (0)	0.7126	0.3145	1.0000	
>1 × normal (1)			2.0392	0.0234

define the prognostic factors for patients with metastatic or recurrent gastric cancer.

A poor performance status is already widely accepted as one of the most important negative prognostic factors for all cancer patients [15, 19–21]. The importance of this marker was also confirmed in the present study. However, unlike the performance status, the prognostic role of weight loss at presentation remains somewhat controversial. While some studies have previously found significant weight loss to be a poor prognostic factor for patients with gastrointestinal cancer [19, 22], it was not identified as a prognostic factor in the present analysis.

The current study found peritoneum and bone metastases to be significant prognostic factors. It has already been shown that disseminated tumor cells in the peritoneum adversely affect survival, especially if the tumor cells are detected by immunocytologic methods rather than cytologic alone [23], yet their prognostic significance is less definitive than gross peritoneal metastases. More recently, a randomized study showed that aggressive surgical cytoreduction followed by hyperthermic intraperitoneal chemotherapy improved survival in patients with peritoneal carcinomatosis of colorectal origin [24], and such multimodality therapy has also been evaluated in gastric cancer [25]. Therefore, in future, aggressive therapy directed against peritoneal deposits may influence the survival of selected patients with gastric cancer. Although bone is an uncommon site of metastasis with gastric cancer, the survival of patients with bone metastasis was extremely poor in the current study. Etoh et al. [26] previously reported that the prognosis of gastric cancer with bone metastasis, sometimes invading the bone marrow diffusely, was very poor due to hematologic disorders, such as disseminated intravascular coagulation (DIC) and/or microangiopathic hemolytic anemia (MAHA).

An elevated serum total bilirubin level was also identified as an independent prognostic factor, although the presence of liver metastasis was not. In the present study, the elevated total bilirubin was caused by a biliary tract obstruction due to lymph node metastasis in most patients (82%), rather than liver metastasis. Thus, since obstructive jaundice needed percutaneous or endoscopic biliary drainage and the anticancer treatment was delayed until the bilirubin returned to normal, these issues may have adversely affected the prognosis. Chu et al. [27] also reported that the median survival of 41 patients with an extrahepatic biliary

Table 5 Comparison of survival stratified into three risk groups according to prognostic index

Risk group	Prognostic index	Number (%)	Overall survival (median, months)	95% Confidential interval	*P* value*
Good	0	162 (53%)	9.6	7.9–11.3	
Moderate	1	82 (27%)	7.6	5.4–9.7	0.0032
Poor	≥2	60 (20%)	3.6	2.8–4.3	<0001

* Log-rank test

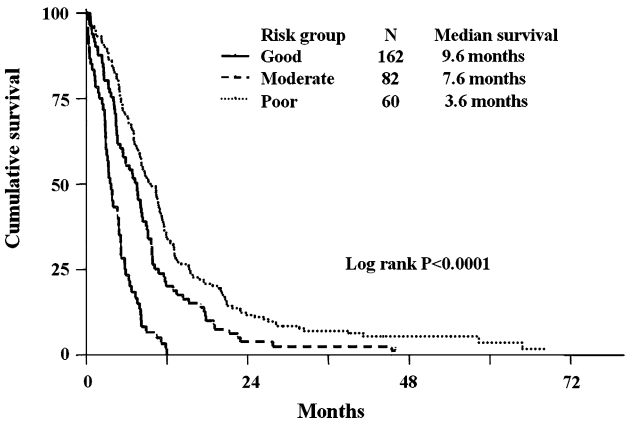

Fig. 2 Overall survival curves according to prognostic index

obstruction due to metastatic gastric carcinoma was only 70 days, plus the total bilirubin level at presentation ($P < 0.002$) was found to be independent factor predicting survival. Although serum alkaline phosphatase level, which can be elevated by biliary obstruction, liver metastasis or bone metastasis, was not a significant prognostic factor in the current study, it was found to be an independent prognostic factor to liver metastasis in Chau's study [15]. They suggested that alkaline phosphatase level might reflect the underlying tumor burden rather than the presence or absence of liver metastasis.

In the present study, the median survival of 7.3 months is relatively short compared to those of recent phase II or III studies [28, 29]. The selection of patients with good prognostic factors and introduction of new agents (irinotecan and taxanes) as second-line chemotherapy might improve the survival of patients enrolled in the recent clinical trials. However, four patients had survived more than 50 months after diagnosis in the present study. Three patients had only metastasis of intraabdominal distant lymph nodes (prognostic index 0), while 1 patient peritoneal metastasis (prognostic index 1). All patients were responded to palliative chemotherapy. The simple prognostic index presented allowed the identification of three distinct risk groups. When compared with the good risk group, the moderate risk group had a 2.7-fold increased risk of death, whereas the poor risk group had a 3.8-fold increased risk of death. Furthermore, there was a difference of 6.0 months in the median survival and 32.9% in the 1-year survival between the good and poor risk groups. Thus, the proposed index can be used in a similar fashion to the International Prognostic Index for aggressive non-Hodgkin's lymphoma, allowing risk stratification [21]. In future, molecular markers predictive of survival could also be incorporated into the proposed model to evaluate whether additional prognostic information has been obtained by these molecular markers. Nonetheless, the proposed prognostic index still requires further validation, which will be pursued using data from a randomized phase III study evaluating capecitabine instead of 5-flourouracil in an FP (5-flourouracil/cisplatin) regimen [30].

In conclusion, five prognostic factors were identified from patients receiving first-line cisplatin-based chemotherapy for metastatic or recurrent gastric cancer. A simple prognostic index was then developed with distinct survival rates among the different risk groups. Thus, the proposed prognostic model could be used to help clinicians and patients make clinical decisions and tailor treatment based on the estimated prognosis. In addition, the survival marker could also be applied in clinical research to stratify patients, avoid biases, and plan appropriate studies targeting different patient subgroups.

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