revealed that the ECOG PS score is an independent factor for OS, although this score was also an independent factor for OS in the placebo group.[20] The recent study in France has shown that in patients with advanced HCC administered sorafenib, the Child–Pugh class, BCLC stage, and ECOG PS score are prognostic factors for survival.[21] Therefore, the ECOG PS score at the start of sorafenib therapy may contribute a survival advantage in the treatment of advanced HCC.

Our study has some limitations, such as small sample size, retrospective design, which allowed for potential biases including selection, and recall bias. The retrospective nature of our analysis raises the potential limitation of accurate and complete documentation of ADRs. Despite these limitations, our data have some impact, especially in view of this first report of efficacy and safety profiles of sorafenib in Japanese older patients with HCC.

In conclusion, sorafenib has modest efficacy and acceptable toxicity profiles in younger (<75 years) Japanese patients with HCC; however, elderly patients experience some side effects with the standard dosage. A larger prospective study is necessary to determine the efficacy of sorafenib in this group of patients.

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Construction and Validation of a Prognostic Index for Patients With Metastatic Pancreatic Adenocarcinoma

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Objectives: To identify prognostic factors in patients with metastatic pancreatic adenocarcinoma.

Methods: The relationship between patient characteristics and outcome was examined by multivariate regression analyses of data from 409 consecutive patients with metastatic pancreatic adenocarcinoma who had been treated with a gemcitabine-containing regimen, and we stratified the patients into 3 risk groups according to the number of prognostic factors they had for a poor outcome. A validation data set obtained from 145 patients who had been treated with agents other than gemcitabine was analyzed. The prognostic index was applied the each of the patients.

Results: The multivariate regression analyses revealed that the presence of pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value significantly contributed to a shorter survival time. The patients were stratified into 3 groups according to their number of risk factors, and their outcomes of the 3 groups were significantly different. When the prognostic index was applied to the validation data set, the respective outcomes of the 3 groups were found to be significantly differed from each other.

Conclusions: Pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value are important prognostic factors for patients with metastatic pancreatic adenocarcinoma.

Key Words: pancreatic cancer, prognostic factor, validation, chemotherapy, multivariate analyses, prognostic index

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Despite the major advances in cancer management that have been achieved in recent years, pancreatic adenocarcinoma (PC) remains a challenge to clinicians because of the difficulty of early diagnosis. Most PC patients have locally advanced or metastatic disease by the time the diagnosis is made. Even when resection is performed, the recurrence rate is extremely high, and nonsurgical treatments after recurrence have largely been ineffective.[1,2] Although gemcitabine (GEM) has been demonstrated to provide a modest clinical benefit and therefore become the standard chemotherapy for advanced PC,[3,4] the median survival time of patients with advanced disease remains only around 6 months. Many clinical trials of treatments with combinations GEM and other agents have been conducted to improve treatment efficacy in patients with advanced PC, and one of them, a combination of GEM and erlotinib, has resulted in longer survival than treatment with single-agent GEM.[5] However, because the difference in median overall survival between the 2 regimens was only 0.3 months and the incidence of adverse events with GEM plus erlotinib tended to be higher, this combination has been considered a treatment option for patients in good general condition, not an alternative to GEM monotherapy. Because various treatment options according to the patient's general condition and prognosis are expected to be developed in the future, if the survival time of patients with metastatic PC could be predicted before the start of the treatment, those with an extremely poor prognosis could be offered supportive care alone or more conservative treatment, such as GEM monotherapy and spared the adverse effects of combination chemotherapy. A validated prognostic index would identify subgroups of patients for specific treatments and predict survival, and identification of prognostic factors would be helpful in designing clinical trials of systemic chemotherapy and analyzing their results. Furthermore, clinical trials of various new treatments will be conducted in the future, and because some of the candidate drug combinations for new treatment regimens may contain GEM and others may not, establishment of an accurate prognostic index that can be applied to various treatment regimens is needed. Although many possible prognostic factors, such as performance status,[6 8] the serum carbohydrate antigen (CA 19-9) level,[9 14] and the serum C-reactive protein (CRP) level[11,13,15,16] have been identified in advanced PC, most were identified in small numbers of patients, and the results were not validated, possibly making the analyses underpowered and unreliable.

The purposes of this study were (1) to identify the most helpful, readily available prognostic factors for predicting the survival time of metastatic PC patients and (2) to construct and validate a practical and universal prognostic index for metastatic PC patients.

MATERIALS AND METHODS

Cases Used as the Basis for Construction of the Prognostic Index (Construction Set)

Data from 409 consecutive patients with metastatic PC who had received GEM-containing systemic chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between March 2001 and January 2007 were reviewed to construct the prognostic index. None of the patients had been treated for their cancer before chemotherapy, except that some of them had undergone by pancreatectomy. All patients had distant metastasis based on diagnostic imaging findings obtained by various modalities, including chest radiography, ultrasonography, and computed tomography. The diagnosis of adenocarcinoma was confirmed pathologically in every case by examination of the surgical specimen or a fine-needle aspiration biopsy specimen. Whenever possible, peritoneal or pleural fluid cytodiagnosis was performed in patients with an intraperitoneal or intrapleural fluid collection. Percutaneous transhepatic or endoscopic retrograde biliary drainage was performed in all patients who had

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TABLE 1. Patient Characteristics

			Construction Set		Validation Set	*P*
Age		Median (range)	64 (21–81)		59.5 (39–75)	0.0005*
Sex	Male	n (%)	241 (59)		98 (68)	0.10†
	Female	n (%)	168 (41)		47 (32)	
Performance status	0–1	n (%)	395 (97)		138 (95)	0.40†
	2–3	n (%)	14 (3)		7 (5)	
Prior pancreatectomy	(+)	n (%)	66 (16)		16 (11)	0.24†
Abdominal and/or back pain‡	(+)	n (%)	138 (34)		62 (43)	0.074†
Diabetes mellitus	(+)	n (%)	171 (42)		46 (31)	0.037†
Location of primary tumor	Uncus and head	n (%)	191 (47)		48 (33)	0.01†
	Body or tail	n (%)	217 (53)		94 (65)	
Liver metastasis	(+)	n (%)	297 (73)		111 (77)	0.39†
Lymph node metastasis	(+)	n (%)	124 (30)		49 (34)	0.44†
Lung metastasis	(+)	n (%)	68 (17)		22 (15)	0.76†
Peritoneal dissemination	(+)	n (%)	88 (22)		37 (26)	0.40†
Pleural metastasis	(+)	n (%)	28 (7)		4 (3)	0.10†
Bone metastasis	(+)	n (%)	8 (2)		2 (1)	0.92†
Leukocytes count, /mL	(3900–6300)§	Median (range)	6100 (2100–35,500)		6800 (3400–18,000)	0.015*
Hemoglobin level, g/dL	(11.3–14.9)§	Median (range)	12.3 (6.7–16.1)		12.2 (8.6–15.9)	0.50*
Platelets count, /mL	(12.5–37.5)§	Median (range)	22.3 (9.2–57.4)		22.5 (9.5–47.1)	0.55*
Albumin level, g/dL	(3.7–5.2)§	Median (range)	3.7 (2.2–4.9)		3.7 (2.2–4.7)	0.50*
Total bilirubin level, mg/dL	(0.3–1.2)§	Median (range)	0.7 (0.2–3.1)		0.7 (0.3–3.2)	0.92*
AST level, IU/L	(13–33)§	Median (range)	27 (10–196)		26 (10–204)	0.46*
ALT level, IU/L	(6–27)§	Median (range)	29 (5–465)		28 (7–366)	0.90*
LDH level, IU/L	(119–229)§	Median (range)	188 (19–2311)		162 (15–2192)	0.001*
CRP level, mg/dL	(−0.1)§	Median (range)	0.6 (0.0–20.6)		0.8 (0–17.8)	0.15*
CEA level, ng/mL	(−5.0)§	Median (range)	6 (0.6–2090)		6.9 (0.4–9990)	0.55*
CA19-9 level, U/mL	(−37)§	Median (range)	1857 (1–1620,000)		3022 (1–1,857,600)	0.088*
Treatment		n (%)	GEM alone 302 (74)	Irinotecan	16 (11)	
		n (%)	GEM + S-1 41 (10)	Docetaxel	6 (4)	
		n (%)	GEM + 5-FU 27 (7)	S-1	29 (20)	
		n (%)	GEM + CDDP 39 (10)	UFT	22 (15)	
		n (%)		5-FU + CDDP	31 (21)	
		n (%)		MTX + 5-FU	41 (28)	

*Mann-Whitney *U* test.

†χ^2 test.

‡Abdominal and/or back pain: treated with opioid.

§Reference range.

CDDP indicates cisplatin; FU, fluorouracil; MTX, methotrexate.

obstructive jaundice before chemotherapy. All patients provided written informed consent before the start of treatment.

Factors Analyzed

The following 24 variables were selected for analysis in this study based on the results of previous investigations[12,13,15,17 23] and/or our own clinical experience: (1) age, sex, prior pancreatectomy, Eastern Cooperative Oncology Group performance status, abdominal and/or back pain treated with an opioid, diabetes mellitus, leukocyte count, hemoglobin level, platelet count, and serum level of albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin, CRP, as host-related variables, and (2) location of the primary tumor, liver metastasis, lymph node metastasis, lung metastasis, peritoneal dissemination, pleural metastasis, bone metastasis, serum level of carbohydrate antigen 19-9 (CA19-9), and CEA, as tumor-related variables. All data were obtained immediately before the start of systemic chemotherapy. Nodules more than 1 cm in diameter and/or a conspicuous volume of effusion in the abdominal or thoracic cavity observed by ultrasonography or computed tomography and cytologically proven malignant effusions were considered evidence of peritoneal dissemination or pleural metastasis in this study.

Cases Used as a Basis for Validation of the Prognostic Index (Validation Set)

A data set from 145 patients who participated in clinical trials of anticancer agents other than GEM at the National Cancer Center Hospital between August 1991 and January 2004 was used to validate the prognostic index. The treatment regimens were docetaxel,[24] irinotecan,[25] S-1,[26] UFT,[27] 5-fluorouracil + cisplatin,[28] and methotrexate + 5-fluorouracil.[29]

TABLE 2. Univariate Analysis

Categorical Variables			Continuous Variables		
	Median Survival Time, d	*P*		Coefficient (β)	*P*
Sex					
Male	209		Age, yr	−0.005	0.3542
Female	188	0.3543	Leukocytes count, /mL	7.59	<0.0001
Performance status					
0–1	207		Hemoglobin level, g/dL	−1.59	<0.0001
2–3	102	0.138	Platelets count, /mL	0.021	0.001
Prior pancreatectomy					
+	298		Albumin, g/dL	−0.867	<0.0001
−	191	<0.0001	Total bilirubin level, mg/dL	−0.088	0.3902
Abdominal and/or back pain*					
+	144		AST level, IU/l	0.008	<0.0001
−	238	<0.0001	ALT level, IU/L	0.003	0.0095
Diabetes mellitus					
+	201		LDH level, U/L	0.003	<0.0001
−	198	0.9802	CRP level, mg/dL	0.129	<0.0001
Location of primary tumor					
Uncus or head	200		CEA level, ng/mL	0.001	<0.0001
Body or tail	204	0.9885	CA19-9 level, U/mL	1.296	0.0004
Liver metastasis					
+	186				
−	243	<0.0001			
Lymph node metastasis					
+	167				
−	219	0.0584			
Lung metastasis					
+	224				
−	196	0.5835			
Peritoneal dissemination					
+	156				
−	219	0.0063			
Pleural metastasis					
+	198				
−	200	0.5435			
Bone metastasis					
+	113				
−	204	0.0336			

*Abdominal and/or back pain: treated with an opioid.

Statistical Analysis

Survival rates were calculated by the method of Kaplan and Meier.[30] All deaths regardless of cause were considered events. The stratified log-rank test was used to compare survival curves, and censored data were taken into account.[31]

Univariate Analysis

A univariate analysis was conducted to select candidate factors to adopt in the multivariable analysis. For categorical data, factors were divided into 2 categories, and the log-rank test was applied. Because dichotomizing continuous variable data, such as the serum biochemical and hematological data, by using arbitrary cutoff points might have resulted in major biases, we used the Cox proportional hazards model, which enables selection of candidate factors without dichotomization.[32,33] Differences with a $P < 0.01$ were considered significant.

Multivariate Analysis

The variables identified as having prognostic significance in the univariate analyses were included in the subsequent multivariate analysis. To construct a simple and practical prognostic index for routine clinical use, all factors were divided into 2 categories. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cutoff value to maximize both the sensitivity and the specificity of continuous variables. Each ROC curve was constructed as a predictor of death at 6.6 months, which was the median survival time of the cases in the construction set. The Cox proportional hazards model was used to identify the variables that made the most significant contribution to survival. Differences with a $P < 0.01$ were considered significant. All P values were 2 sided. All analyses were performed by using Dr SPSS statistical software (SPSS Inc, Chicago, Ill).

The numbers of risk factors present were used to construct the prognostic index. Patients were stratified into 3 risk groups on the basis of the number of risk factors present.

RESULTS

Patient Characteristics

There were 241 men and 168 women in the construction set. Their median age was 64 years (range, 21–81 years), and the performance status of 395 patients was 0 to 1. Liver metastasis had been diagnosed in 297 patients, and peritoneal dissemination had been diagnosed in 88 patients (Table 1). The treatment regimens were GEM alone in 302 patients, GEM + cisplatin, 39, GEM + 5-flurorouracil, 27, and GEM + S-1, 41.

Survival

As of the date of the survival analysis, 404 patients had died, and the median survival time and 1-year survival rate were 6.6 months and 22%, respectively.

Univariate Analysis

The following 14 of the 24 pretreatment variables evaluated were identified as significantly associated with shorter survival time (Table 2): absence of prior pancreatectomy ($P < 0.0001$), presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver metastasis ($P < 0.0001$), presence of peritoneal dissemination ($P = 0.0063$), elevated leukocyte count ($P < 0.0001$), elevated platelet count ($P = 0.001$), elevated serum AST level ($P < 0.0001$), elevated serum ALT level ($P < 0.0095$), elevated serum LDH level ($P < 0.0001$), elevated serum CRP level ($P < 0.0001$), elevated serum CA19-9 level ($P = 0.0004$), elevated serum CEA level ($P < 0.0001$), low hemoglobin level ($P < 0.0001$), and low serum albumin level ($P < 0.0001$).

Multivariate Analysis

The 14 variables found to be of prognostic significance in the univariate analysis were included in the subsequent multivariate Cox regression model. Receiver operating characteristic curve analysis was used to determine the cutoff point for continuous variables. Finally, to simplify the prognostic index, some cutoff values were approximated, thus: leukocyte count, from 7200/mL to 7000/mL; hemoglobin level, from 11.9 to 12 g/dL; platelet count, from $27.8 \times 10^4/\mu L$ to $28 \times 10^4/\mu L$; serum CRP level, from 0.9 to 1.0 mg/dL; serum CA19-9 level, from 3414 to 3000 U/mL; and serum CEA level, from 6.7 to 7 ng/mL. Originally simple values, such as serum albumin level (3.7 g/dL), serum AST level (22 IU/L), serum ALT level (28 IU/L), and serum LDH level (190U/L) were not approximated. Only 4 of the previously mentioned factors, presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver

TABLE 3. Multivariate Analysis

		Coefficient (β)	Hazards Ratio	99%CI	P
Prior pancreatectomy	−	0.297	1.346	0.906–2.000	0.530
Abdominal and/or back pain*	+	0.526	1.692	1.262–2.271	<0.0001
Liver metastasis	+	0.353	1.423	1.015–1.995	0.0071
Peritoneal dissemination	+	0.563	1.756	1.238–2.492	<0.0001
Leukocyte count	>7000 (/μL)	0.058	1.060	0.775–1.449	0.6313
Hemoglobin level	<12 (g/dL)	0.244	1.277	0.949–1.717	0.0337
Platelet count	>28 ($\times 10^4/\mu L$)	0.269	1.309	0.954–1.796	0.0285
Albumin level	<3.7 (g/dL)	0.124	1.132	0.841–1.523	0.2826
AST level	>22 (IU/L)	0.078	1.081	0.731–1.599	0.6089
ALT level	>28 (IU/L)	0.212	1.236	0.858–1.781	0.1352
LDH level	>190 (U/L)	0.259	1.295	0.951–1.764	0.0309
CRP level	>1 (mg/dL)	0.432	1.540	1.117–2.124	0.0005
CEA level	>7 (U/mL)	0.205	1.227	0.924–1.631	0.0634
CA19-9 level	>3000 (ng/mL)	0.101	1.106	0.825–1.482	0.3762

CI indicates confidence interval.

*Abdominal and/or back pain: treated with an opioid.

TABLE 4. Prognostic Index of Patients With Metastatic PC Receiving Systemic Chemotherapy

Risk Factors	
• Abdominal and/or back pain treated with an opioid	Present
• Liver metastasis	Present
• Peritoneal dissemination	Present
• Serum CRP level	>1 (mg/dL)
Risk groups	
No. risk factors	
0	Low risk
1–2	Intermediate risk
3–4	High risk

metastasis ($P = 0.008$), presence of peritoneal dissemination ($P < 0.0001$), and elevation of the serum CRP level to greater than 1.0 mg/dL ($P < 0.0007$), were identified as independent prognostic factors (Table 3).

Risk Groups Based on the Regression Model

To be able to apply the indicated prognostic factors to clinical routine use, patients were stratified into 3 risk groups according to their number of the negative prognostic factors (Table 4): a low-risk group of 47 patients with 0 risk factors, an intermediate-risk group of 276 patients with 1 to 2 risk factors, and a high-risk group of 86 patients with 3 to 4 risk factors. The survival curves of these groups are shown in Figure 1. There were significant differences between survival time in the 3 groups (median survival time: low-risk group, 11.0 months; intermediate-risk group, 7.3 months; and high-risk group, 3.2 months; $P = 0.0001$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

Validation of the Prognostic Index

The prognostic index was applied to each of the 145 cases used for validation. The patient's characteristics were similar to those of the cases in the construction set (Table 1), but the proportion of patients with diabetes mellitus and the proportion of patients whose primary tumor was in the uncus or the head were lower in the validation set. In addition, median age was younger, the median leukocyte count was higher, and the LDH value was lower in the validation set than those in the construction set. Of the 145 patients in the validation set, 141 had died. The median survival time of the 145 patients was 4.8 months, and their 1-year survival rate was 12%. We calculated the prognostic index of the 145 patients and then stratified them into 3 risk groups as described previously and compared the distribution of survival times among the 3 risk groups. Figure 2 shows a comparison of the survival curves of the 3 risk groups. There were significant differences in survival time among the 3 groups (median survival time: low-risk group, 8.6 months; intermediate-risk group, 5.2 months; and high-risk group, 2.3 months; $P = 0.03$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

DISCUSSION

In this study, we attempted to identify prognostic factors in patients with metastatic PC who had received systemic chemotherapy, and 14 of the 24 potential prognostic factors assessed were identified as significant predictors of survival by the univariate analysis. However, only 4 factors, abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and elevated serum CRP level, were found to have independent prognostic value by the multivariate analysis.

Abdominal and/or back pain is one of the most common symptoms of PC patients. Previous studies have shown correlations between pancreatic tumor size, invasion of the anterior pancreatic capsule, and lymph node metastasis and the pain intensity of patients with operable tumors.[23,34] Several studies have also shown a significant impact of preoperative pain has on the outcome after resection.[34 36] However, the pain of patients with unresectable, more advanced PC may be attributable to invasion of the retroperitoneum or extrapancreatic nerve plexus

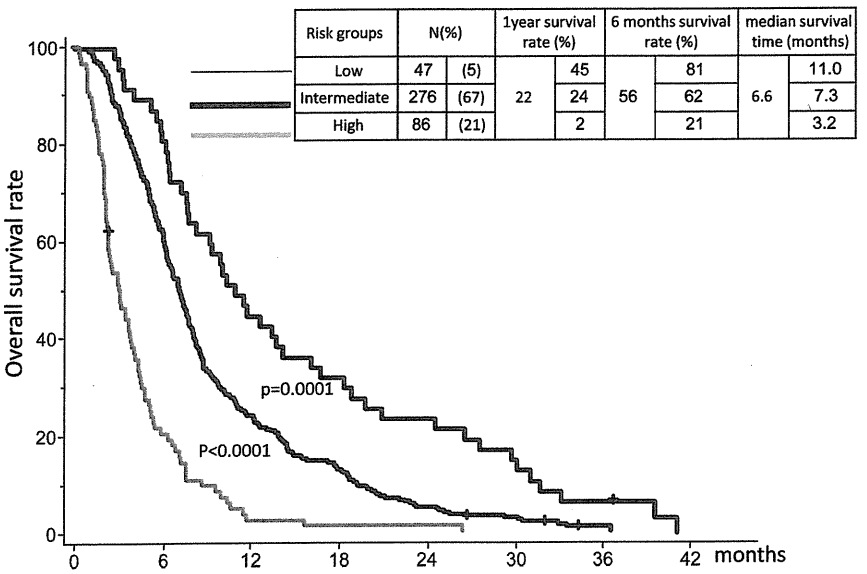
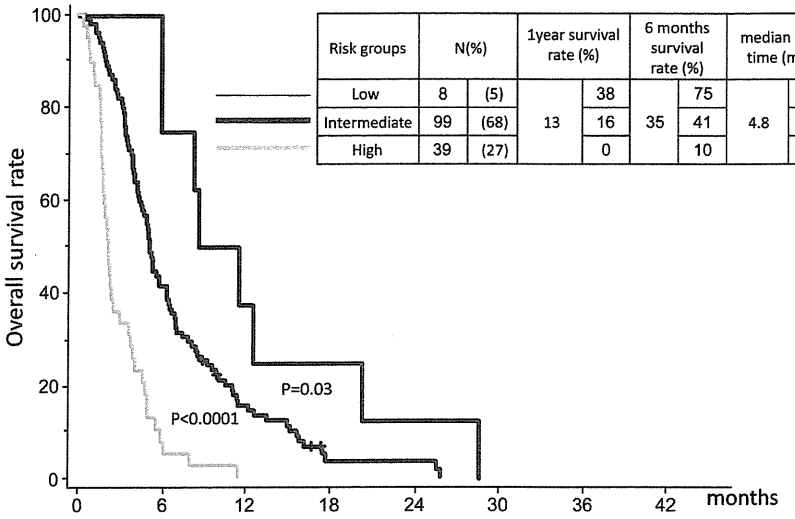


FIGURE 1. Comparison of the survival curves of patients who have received GEM-containing systemic chemotherapy and stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.0001$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.



Risk groups	N(%)		1year survival rate (%)		6 months survival rate (%)		median survival time (months)	
Low	8	(5)	13	38	35	75	4.8	8.6
Intermediate	99	(68)		16		41		5.2
High	39	(27)		0		10		2.3

FIGURE 2. Comparison of the survival curves of patients used for validation stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.03$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.

because such advanced tumors sometimes destroy nerves more extensively than resectable tumors.

Peritoneal dissemination[37,38] and liver metastasis[39 41] have long been considered to tend to result in a fatal clinical course. Patients with peritoneal dissemination exhibit the clinical manifestations of bowel obstruction, ascites, and abdominal pain. Such complications often cause malnutrition and general deterioration. Patients with liver metastasis often have jaundice or lapse into a hepatic coma. Moreover, the dose and the schedule of chemotherapy sometimes have to be modified for patients with peritoneal dissemination or liver dysfunction because the adverse effects of chemotherapy are more severe in such patients. A previous study found that peritoneal dissemination predicts limited the effectiveness of chemotherapy in advanced PC.[42]

An elevated CRP level[13,16] has been demonstrated to be of prognostic significance in patients with PC and a variety of other gastrointestinal neoplasms.[43 45] Proinflammatory cytokines, including interleukin 6, are key signals in promoting hepatic CRP production, and there is evidence that they play a role in the genesis of cancer-associated cachexia,[46 48] which shortens the survival time of patients with metastatic PC.

Although previous studies have shown that performance status is one of the most important prognostic factors in patients with advanced PC,[13,49,50] it was not identified as a significant predictor of survival in this study. One of the main reasons for not having identified it as a significant predictor may be that proportion of patients with a performance status of 2 to 3 was extremely small in this study, only 3%.

Many models for clinical outcome prediction have been described in the medical literature, but most never find their way into clinical practice. One reason for their failure to be adopted in clinical practice may be that they have not been validated by external data and therefore lack universality and credibility. To our knowledge, this is the first report of not only construction but also validation of a practical prognostic index for patients with metastatic PC.

Some of the factors assessed in this study were continuous variables, and continuous variables are often converted into categorical variables by grouping the values into 2 or more categories. However, there is also the risk of major bias when the choice of the cutoff value is data driven, and the use of different cutoff points across multiple studies hinders direct comparisons. Dichotomizing continuous variables, on the other hand, is a reasonable method of constructing simple and practical tools for routine clinical use. To achieve a balance between convenience and credibility, we applied the Cox regression model to continuous variables in the univariate analysis to select candidates for the multivariable analysis. We then identified objective cutoff values by ROC curve analysis for the candidates, divided continuous variables into 2 categories, and applied the multivariate analysis.

Because we used a data set of patients treated with a GEM-containing regimen to construct the prognostic index and a data set of patients treated with anticancer agents other than GEM to validate it, this prognostic index may be helpful in designing clinical trials of systemic chemotherapy even if the investigational regimen does not contain GEM.

In conclusion, the presence of abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and serum CRP elevation to 1.0 mg/dL or greater were identified as significant prognostic factors in patients with metastatic PC who had received systemic chemotherapy. Accurate prediction of survival may be achieved by applying a prognostic index incorporating these 4 factors. This index facilitates stratification of patients with metastatic PC into 3 risk groups. Our index is expected to be useful for selecting treatment strategies; patients with an extremely poor prognosis could be offered supportive care alone or more conservative treatment. Furthermore, it is also expected to be useful for designing future clinical trials for patients with metastatic PC.

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Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer

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Abstract. Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI) has become a standard regimen for advanced or recurrent colorectal cancer. Numerous studies have reported that long-term use of FOLFOX or FOLFIRI leads to better survival for these patients. Thus, control of the toxicity of these drugs may be crucial to prolonging survival. Fucoidan is one of the major sulfated polysaccharides of brown seaweeds and exhibits a wide range of biological activities. In the present study, we analyzed the effect of fucoidan on suppressing the toxicity of anti-cancer drugs. A total of 20 patients with unresectable advanced or recurrent colorectal cancer scheduled to undergo treatment with FOLFOX or FOLFIRI were randomly allocated into a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). Results showed that fucoidan regulated the occurrence of fatigue during chemotherapy. Chemotherapy with fucoidan was continued for a longer period than chemotherapy without fucoidan. Additionally, the survival of patients with fucoidan treatment was longer than that of patients without fucoidan, although the difference was not significant. Thus, fucoidan may enable the continuous administration of chemotherapeutic drugs for patients with unresectable advanced or recurrent colorectal cancer, and as a result, the prognosis of such patients is prolonged.

Introduction

To prolong the survival of patients with unresectable advanced or recurrent colorectal cancer, it is essential to continue effective chemotherapy for as long as possible. Since the introduction of oxaliplatin for use in Japan in April 2005, combination chemotherapy with oxaliplatin plus 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) has become the standard regimen for advanced or recurrent colorectal cancer, and a high response rate has been reported (1-3). However, FOLFOX and FOLFIRI are associated with severe toxicity, such as nausea, vomiting, stomatitis, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia and liver dysfunction. A number of patients discontinue these effective chemotherapies due to toxicity. Thus, the prognosis of patients with unresectable advanced or recurrent colorectal cancer remains low despite advances in chemotherapeutic drugs.

To reduce the toxicity of chemotherapeutic drugs, various types of drugs or dietary supplements have been introduced (4-6). Among these supplements, fucoidan has been reported to exhibit anti-inflammatory, antiviral and anti-tumor activities (7-9). Fucoidan is a sulfated polysaccharide found mainly in various species of brown seaweeds such as kombu, wakame, mozuku and hijiki. Subsequently, fucoidan has become the focus of substantial pharmaceutical research.

The present study investigated whether fucoidan reduces the toxicity of chemotherapeutic drugs in patients with unresectable advanced or recurrent colorectal cancer.

Materials and methods

Patients. Between April 2008 and June 2009, 20 patients were diagnosed with unresectable advanced or recurrent colorectal cancer and were scheduled to undergo FOLFOX or FOLFIRI chemotherapy at our hospital. The Eastern Cooperative Oncology Group performance status of these patients was 0 or 1, and they had adequate bone marrow (platelet count ≥100,000/l, white blood cell count ≥4,000/l, granulocyte count ≥1500/l, hemoglobin level of ≥10.0 mg/dl), renal (serum creatinine concentration ≤2.0 mg/dl), and hepatic (serum bilirubin level ≤2.0 mg/dl) functions. Adjuvant chemotherapy using 5-FU plus LV was administered to 9 of the 20 patients prior to enrollment in this study. The Ethics Committee of Tottori University approved treatment with fucoidan to reduce the toxicity of chemotherapeutic drugs in 2008 (approval no. 1223).

Informed consent was obtained from the 20 patients, who were randomly allocated to a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). The patients were followed up until July 2010. The patient details are shown in Table I.

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Key words: fucoidan, colorectal cancer, chemotherapy, fatigue

Table I. Patient characteristics.

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Age (mean ± SD, years)	71.3±7.5	69.6±8.8	0.762
Male/Female	6/4	7/3	0.639
ECOG			0.653
PS 0/1	5/5	4/6	
Tumor			0.653
Primary/Recurrent	4/6	5/5	
Primary tumor			0.639
Colon/Rectum	6/4	7/3	
Previous chemotherapy			0.653
Yes/No	4/6	5/5	
Site of disease			0.953
Liver	5	4	
Lung	2	2	
Pelvis	1	1	
Peritoneum	1	1	
Lymph node	1	1	
Primary tumor	0	1	

ECOG, The Eastern Cooperative Oncology Group; PS, performance status.

Table II. Major adverse events.[a]

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Leukocytopenia	1	0	0.305
Neutropenia	3	4	0.639
Anemia	2	1	0.531
Thrombocytopenia	0	2	0.136
Nausea	1	1	1.000
Diarrhea	1	2	0.531
Stomatitis	3	1	0.264
Fatigue	1	6	0.019
Peripheral neuropathy	3	5	0.361
Liver dysfunction	0	2	0.136

[a]Adverse events ≥2.

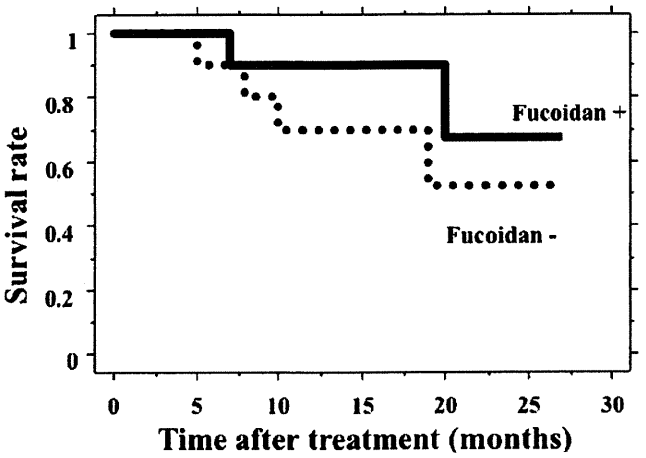

Figure 1. Survival curves of advanced or recurrent colorectal cancer patients. Solid line, survival curve of 10 patients who received fucoidan treatment. Dotted line, survival curve of 10 patients who did not receive fucoidan treatment. The difference was not significant (P=0.314).

Chemotherapy. A number of versions of FOLFOX therapy exist, of which modified FOLFOX6 (mFOLFOX6) allows for more convenient administration and has been adopted by various medical institutions in association with popularization of outpatient chemotherapy. Thus, mFOLFOX6 has been the first-line therapy for patients with unresectable advanced or recurrent colorectal cancer at our hospital (10). A 2-h intravenous infusion of oxaliplatin (85 mg/m^2) plus l-LV (200 mg/m^2) was followed by a bolus intravenous injection of 5-FU (400 mg/m^2), after which 5-FU (2,400 mg/m^2) was administered by continuous infusion for 46 h. However, 4 of the 20 patients requested FOLFIRI as first-line therapy. In the FOLFIRI regimen, on day 1, 180 mg/m^2 of irinotecan and 200 mg/m^2 of l-LV were administered as a 2-h infusion, prior to a 400 mg/m^2 5-FU intravenous bolus injection. Subsequently, 2,400 mg/m^2 of 5-FU was administered as a 46-h continuous infusion. The duration of one cycle of mFOLFOX6 was the same as that of FOLFIRI (2 weeks). Details of the chemotherapy regimens have been previously described (10).

Fucoidan treatment. Fucoidan is a sulfated polysaccharide that is extracted from brown seaweed, such as mozuku. In the present study, a high-molecular-weight product of fucoidan was used, which was derived from *Cladosiphon okamuranus* (Okinawamozuku) by Marine Products Kimuraya Co., Ltd. (Tottori, Japan). In the fucoidan group, each patient received 150 ml/day of liquid that contained 4.05 g fucoidan for 6 months from the initial day of chemotherapy.

Clinical assessment. All toxicities, with the exception of peripheral neuropathy, were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) (11). Peripheral neuropathy was graded according to the specific grading system (12). Hematological variables and clinical status were recorded every 2 weeks during the chemotherapy period. The drug dose level was reduced in the case of severe or persistent toxicity according to our protocol (10). In the case of persistent grade 3 toxicity or when grade 4 toxicity was recorded, chemotherapy was terminated.

Endpoints. The incidence and severity of adverse events were assessed as the primary endpoints, and patient survival, measured from the date of the first treatment until the patient succumbed to the disease, was assessed as the secondary endpoints.

Statistical analysis. The Chi-square test for independence, Fisher's exact probability test and the Mann-Whitney U test were used to compare patient characteristics, treatment status,

adverse events and the anti-tumor effect. The survival rates of the two groups were estimated by the Kaplan-Meier method, and the statistical differences between survival curves were examined by the log-rank test. $P<0.05$ was considered to be statistically significant.

Results

It was noted that fucoidan exhibited no side effects, such as allergic dermatitis. All 20 patients completed the 6 months of fucoidan therapy safely. Additionally, no patients succumbed due to chemotherapeutic toxicity. A total of 307 cycles of mFOLFOX6 or FOLFIRI were administered during the study, with a median of 15.4 cycles per patient (range 7-38). The average number of treatment cycles (19.9) in the fucoidan group was significantly greater than that in the control group (10.8 cycles, $P=0.016$).

The observed toxicities of the chemotherapeutic drugs are listed in Table II. No patients presented with severe toxicity (grade 4) in either group. The occurrences of diarrhea and neurotoxicity were not suppressed by fucoidan. Myelosuppression was found to be similar in the fucoidan and control groups. In contrast, general fatigue was detected in 60% of the control group, but was significantly suppressed to 10% in the fucoidan group (Table II).

Patients were followed up at our hospital. The median follow-up period of the 20 patients was 15 months (range 5-27). During the follow-up period, 6 patients (2 in the fucoidan group and 4 in the control group) succumbed due to colorectal cancer progression. The survival of the 10 patients receiving fucoidan treatment was longer than that of the 10 patients in the control group, but the difference was not significant ($P=0.314$, Fig. 1).

Discussion

Fucoidan is one of the major sulfated polysaccharides of brown seaweeds, and it has a wide range of biological activities. Choi *et al* (13) found that fucoidan protects gastric mucosa from inflammatory cytokine-mediated oxidative damage in rats. Hayashi *et al* (7) reported that fucoidan reduces CCl_4-induced acute and chronic liver failure with hepatic fibrosis. The anti-inflammatory activity of fucoidan was demonstrated in rats (14), and fucoidan conferred no toxicity in rats at high doses (15). Thus, fucoidan is anticipated to improve human health, and has been widely distributed as a foodstuff but not as a drug. However, the detailed mechanism of action of fucoidan remains to be verified, and its effects in humans have yet to be determined.

In the present study, we analyzed whether fucoidan protects patients from the toxicity of anti-cancer drugs. Nausea, vomiting, diarrhea, general fatigue and bone marrow suppression are well-known common adverse effects of anti-cancer drugs. Peripheral neuropathy is specific for oxaliplatin. We found that fucoidan suppressed the occurrence of general fatigue in colorectal cancer patients during chemotherapy. It has been demonstrated that fatigue reduces the individual resources of patients, affects their nutritional status, increases morbidity and can have a negative impact on the dose intensity of cancer therapy (16). Iop *et al* (16) reported that fatigue, which was graded using NCI CTC, was detected in almost 30% of patients receiving chemotherapy. In the present study, grade 2 and 3 fatigue was detected in 60% of colorectal cancer patients during chemotherapy. The use of antidepressants may also play a role in the treatment of fatigue, and a number of patients are administered chemical supplements of unproven efficacy. However, no published data exist to confirm this hypothesis. In our study, patients who received fucoidan were able to endure prolonged chemotherapy without fatigue. However, fucoidan did not have an impact on other adverse effects of anti-cancer drugs. The mechanisms that explain chemotherapy-induced fatigue remain to be determined, and no general treatment is currently available to alleviate the symptoms.

Fucoidan has also been found to play a significant role in tumor suppression (17-20). Yamasaki-Miyamoto *et al* (8) and Hyun *et al* (21) showed that fucoidan activates caspase-8 or extracellular signal-regulated kinase and induces apoptosis in tumor cells. These pro-apoptotic effects of fucoidan have not been detected in normal cells. However, no indisputable evidence exists that fucoidan prolongs the survival of cancer patients, even in animal models with human tumor implants. In the present study, although the number of patients was limited and the results were not statistically significant, the prognosis of patients with unresectable advanced or recurrent colorectal cancer was more favorable upon treatment with fucoidan than without. This may be explained by the fact that fucoidan prolonged the duration of the chemotherapy by suppressing the toxicity of the anti-cancer drugs or through an anti-cancer effect of fucoidan itself. Therefore, large controlled studies are required to evaluate the therapeutic effect of fucoidan for unresectable advanced or recurrent colorectal cancer.

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Review Article

Topoisomerase I Expression in Tumors as a Biological Marker for CPT-11 Chemosensitivity in Patients with Colorectal Cancer

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Abstract
Irinotecan (CPT-11) is used as a first- and second-line chemotherapy for advanced or recurrent colorectal cancer (CRC). However, only 20%–30% of patients show an objective response to CPT-11 and the drug has severe toxicities, such as delayed-onset diarrhea, neutropenia, nausea, and vomiting. It is important to select patients who will demonstrate sensitivity to CPT-11 treatment to avoid unnecessary drug toxicities and to introduce anticancer treatment benefits to CRC patients. DNA topoisomerase I (Topo I) is essential for vital cellular processes such as DNA replication, transcription, translation, recombination, and repair. This article reviews the possibility of assessing Topo I protein expression in tumors as a biological marker for CPT-11 treatment in CRC.

Key words Chemosensitivity · Colorectal cancer · DNA topoisomerase I · Immunohistochemistry

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide, and has undergone a rapid increase in incidence in Japan.[1] Advances in screening programs, surgical techniques, adjuvant chemotherapy, and surveillance programs have improved the 5-year survival of patients with CRC.[2] Moreover, recent advances in chemotherapeutic drugs have prolonged the survival of patients with unresectable advanced or recurrent CRC. Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan (CPT-11) plus 5-fluorouracil/leucovorin (FOLFIRI) has become the standard regimen for unresectable advanced or recurrent CRC, and high response rates have been reported.[3–6]

CPT-11 is one of the key drugs for CRC.[7,8] CTP-11, a semisynthetic derivative of camptothecin, is activated in vivo to form SN-38, which is a potent topoisomerase I inhibitor and is 300–20000 times more cytotoxic than CPT-11.[9] However, the efficacy of CPT-11 is strongly limited by the development of drug resistance. Although treatment of advanced CRC patients with CPT-11 as a single agent has shown response rates of approximately 30%, these rates can reach 50% when used in combination with other agents.[10,11] Moreover, this drug has severe toxicities, such as diarrhea, nausea, vomiting, and neutropenia. Therefore it is necessary to identify new molecular markers that can identify the subset of patients who are unlikely to respond in order to improve the response rate to CPT-11 and to avoid the harmful toxicities of CPT-11 chemotherapy for patients with CPT-11-resistant tumors.

DNA topoisomerase I (Topo I) belongs to the DNA topoisomerase multimember family, which is essential for DNA topology modulation. Topo I transiently cleaves one strand of DNA, thereby allowing relaxation of the supercoiled DNA. This process is important during cell replication, translation, recombination, and repair.[12] Western and Northern blotting analyses have shown the Topo I protein and mRNA levels to be more abundant in several human tumors than in normal tissue.[13–16] Topo I is also a target for anticancer drugs. Topo I-inhibiting drugs, such as camptothecin and its derivatives,[17] interfere with the function of Topo I by binding to its active site and preventing religation of the DNA strand.[18] Camptothecin inhibits Topo I by forming stable Topo I–DNA cleavage complexes, and is specifically cytotoxic toward cells in the S phase.[19] In vitro, tumor cells with high Topo I protein levels respond better to Topo I inhibitors.[20] Moreover, a decreased Topo I content in cells is a frequent cause of resistance to camptothecin derivatives.[21,22]

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This article evaluates whether Topo I protein expression in primary tumors can act as a biomarker for chemosensitivity to CPT-11 in patients with recurrent CRC by reviewing several earlier studies and discussing previous data.

Topo I Protein Expression in Tissue

The clinical significance of Topo I protein expression has been intensively investigated by immunostaining formalin-fixed and paraffin-embedded tissue. Topo I protein is mainly detected in the nuclei of cells. Normal tissue shows an increased Topo I expression in the germinal centers of the tonsils and in the mucosal lymphocytes of the colon, and Topo I positivity is also detected in the glandular epithelium of the colon.[23] Topo I-positive cells are detected in the basal cell layer of normal skin.[24] Bauman et al.[25] and Hafian et al.[26] reported that Topo I and Topo II proteins are detected in normal tissues containing proliferating cells, including normal skin. Consequently, there is a close correlation between Topo I protein expression and cell proliferation.

An increased Topo I protein expression is detected in from 30% to 100% of cancer cells in ovarian carcinomas,[23] testicular tumors,[27] renal cell carcinomas,[28] gastric carcinomas,[29] breast carcinomas,[30] and oral squamous cell carcinomas.[26] Topo I protein expression is not detected in normal colorectal mucosa, and is mainly located in the nuclei of cancer cells.[24] Furthermore, Topo I protein expression was detected in 45 of 104 (43.2%) patients with primary CRC.[24] Therefore, Topo I protein expression is detected in almost 50% of CRCs.[31,32]

Topo I Protein Expression and Clinicopathological Findings in CRC

Data both in vitro and in vivo demonstrate that malignant cells with high proliferative activity can have high Topo I protein expression levels. Therefore, high Topo I protein expression is thought to correlate with tumor progression and a poor patient survival in CRC. The incidence of detectable Topo I protein expression increases with tumor progression in human sarcomas.[33] Topo I protein is more frequently detected in Dukes' C CRC tumors than in Dukes' A and B tumors, and Topo I protein expression is correlated with poor patient survival.[24] However, analyses of the relationship between Topo I immunohistochemical findings and clinical and pathologic parameters (T and N stages and differentiation) in oral squamous cell carcinomas showed only differentiation to be correlated with the Topo I expression rate.[26] In addition, Staley et al.[34] reported no correlation between the Topo I expression and Dukes' stage in 29 patients with CRC. Recently, Boonsong et al.[31] reported that Topo I protein expression in 249 primary CRCs was not correlated with sex, Dukes' stage, differentiation grade, survival status, p53 status, or status of proliferating cell nuclear antigen. Therefore, the clinical significance of Topo I protein expression in tumors is still unknown. Furthermore, the prognostic importance of Topo I in CRC remains controversial.

Topo I Protein Expression in Tumors and Effectiveness of CPT-11 Chemotherapy

Only 20%–30% of patients with CRC show an objective response to CPT-11. Moreover, patients who do not respond experience the toxicities of the drug. Consequently, there is a great need for new molecular makers that are capable of identifying the subset of patients who are unlikely to respond to CPT-11. In vitro studies have shown that tumors with higher Topo I protein levels respond to Topo I inhibitors, but Topo I mRNA expression is not predictive of the antiproliferative effects of Topo I inhibitors.[35,36] The ATP-binding cassette transporters designated ABCG2 and carboxylesterases are correlated with tumor sensitivity to Topo I inhibitors.[37–40] In addition, many molecular markers are associated with the response to CPT-11.[41] However, these data were obtained from in vitro analyses, and the clinical effectiveness of these markers has not yet been established in CRC. Therefore, further experiments are required before such molecular markers can be used in clinical settings.

A previous study investigated 23 Dukes' C patients who died from CRC recurrence, and reported that 16 were treated with CPT-11 just after the detection of cancer recurrence. The treatment protocol of CPT-11-based chemotherapy for these patients was an oral dose of 300 mg/m^2 per day of 1-(2-tetrahydrofuryl)-5-fluorouracil/uracil (1:4; UFT; Taiho Pharmaceutical, Tokushima, Japan) administered on days 1–28, followed by a 1-week rest during each course (35 days). CPT-11 was administered intravenously over 90 min at 100 mg/m^2 on days 1 and 15. Twelve of these patients had Topo I-positive primary tumors and the remaining four patients had Topo I-negative tumors. The survival periods after starting CPT-11 chemotherapy ranged from 2 to 43 months. The 50% survival periods after starting CPT-11 chemotherapy were 12 months in the 12 patients with Topo I-positive primary tumors, and only 4 months in the four patients with Topo I-negative primary tumors (Fig. 1). Although the number of patients in this study was small, the difference was significant ($P = 0.041$).[24] These findings suggest that Topo I protein expression in primary tumors may thus be a good indicator for the response to CPT-11 chemotherapy.

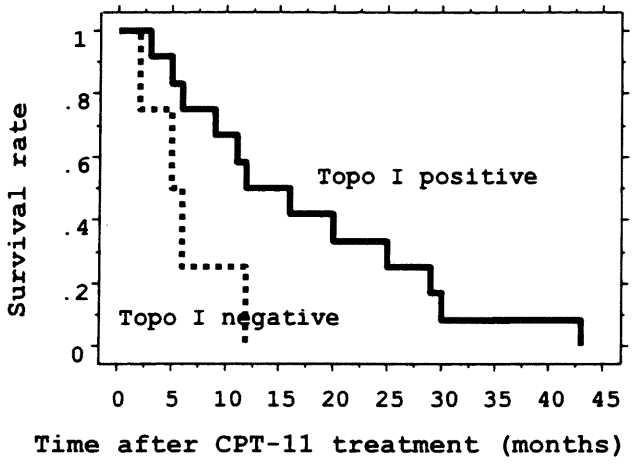

Fig. 1. Survival curves of 16 patients who were treated with irinotecan (*CPT-11*) just after the detection of colorectal cancer recurrence. The survival curve of the 12 patients with topoisomerase I (*Topo I*)-positive primary tumors (*solid line*) is significantly better than that of the four patients with Topo I-negative tumors (*dotted line*) ($P = 0.041$)

Topo I is a negative prognostic marker but at the same time a positive predictive marker in CPT-11 treatment in CRC. Topo I protein is detected mainly in proliferating cells and in tumors with high proliferative activity. The correlation between tumor Topo I expression and increased tumor progression was considered in CRC. Moreover, various tumors with high proliferative activity demonstrate high chemosensitivity.[42,43] Cells in S-, G2-, or M-phase of the cell cycle are more susceptible to applied chemotherapy. Therefore, the observation that Topo I is a negative prognostic marker is not contradicted by the fact that it is a positive predictive marker in CPT-11 treatment.

The Topo I protein levels in metastatic tumors from patients with CRC who were treated with 5-fluorouracil-based adjuvant chemotherapy are significantly increased in comparison with those in the primary tumors.[44,45] These findings may indicate that patients with recurrent CRC would benefit from Topo I targeting anticancer drug therapies. Dopeso et al.[46] reported that patients with absent or low levels of aprataxin in their tumors have better response rates and progression-free and overall survival rates than patients with moderate or high aprataxin levels among CRC patients treated with CPT-11. Aprataxin is a member of the histidine triad domain superfamily of nucleotide hydrolase and transferase, and participates in the repair of single- and double-stranded DNA breaks. Dopeso et al. emphasized that aprataxin will be a new molecular marker for a response to CPT-11 treatment. The sensitivity of tumors to Topo I inhibitors should therefore be extensively investigated to prolong the survival of patients with advanced or recurrent CRC and to prevent unnecessary harmful side effects of Topo I inhibitors.

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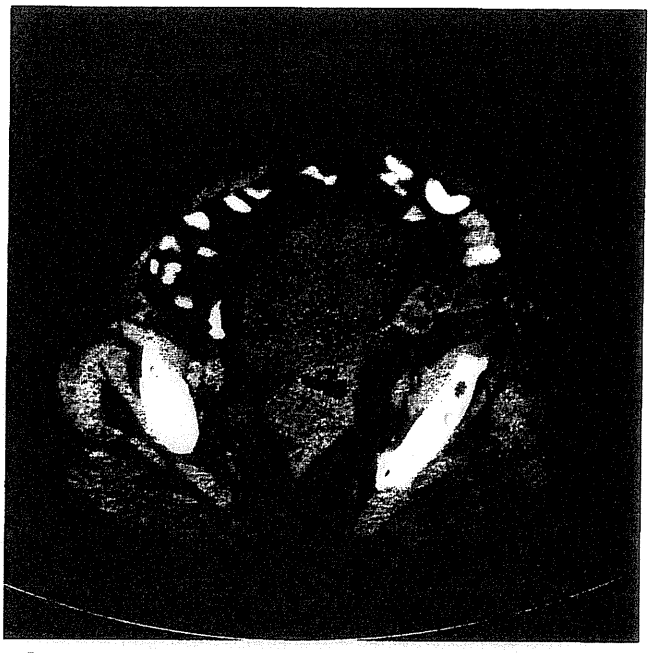

FIG. 1. An axial image of the mass with the abutting colon to the anatomic left.

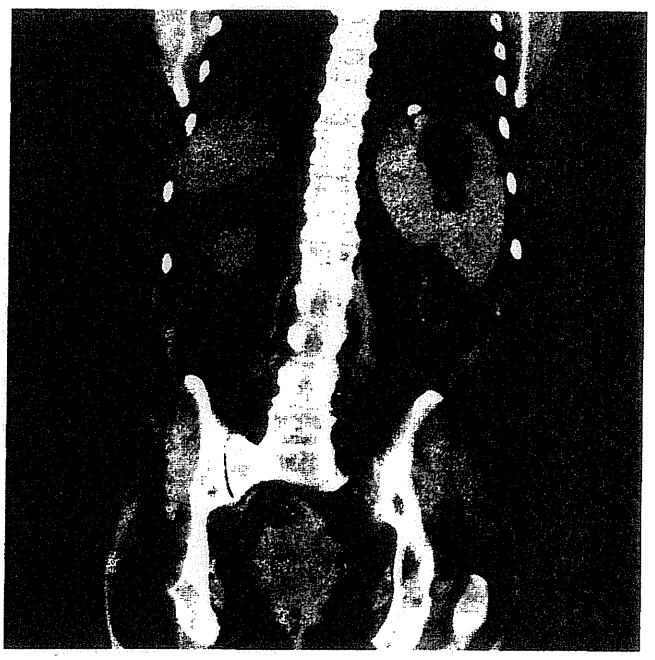

FIG. 2. A coronal image of the mass with similar relationship of the colon to the mass.

anterior mass was palpated on vaginal examination. Digital rectal examination was unremarkable. Colonoscopy revealed only a hyperplastic sigmoid polyp. A congenitally solitary kidney was hydronephrotic on computed tomography. An ostensible vaginal mass was suggested on cystoscopy. Radiologic biopsy was reported as adenocarcinoma consistent with colorectal origin. Computed tomography demonstrated that the pelvic mass was closely associated with the vagina but also involved the ureter and potentially the bladder (Figs. 1 and 2).

Inability to pass a ureteral stent because the mass obscured the ureteral orifice demanded a percutaneous nephrostomy. Given the involvement of the vagina, ureter, and bladder, a pelvic exenteration with urinary ileal conduit was performed. Grossly the tumor encased the ureter and invaded both the colon and vagina. Histologic examination revealed a poorly differentiated adenocarcinoma consistent with the prior biopsy. The postoperative course was uncomplicated.

This case of colonic adenocarcinoma arising in the vicinity of a previous pull-through procedure for an imperforate anus is rare. After surgical repair of this malformation, extraenteric mucosal rests are possible and unfortunately are not amenable to endoscopic surveillance. The patient's history remains paramount to guiding the investigation of related complaints. The exact operative details of this patient's original procedure are not known nor whether the anomaly was accompanied by a rectovestibular fistula.

In this case, the occult tumor presented at a late stage and created significant sequelae. Colonoscopy and digital rectal examination failed to explain the etiology of the patient's complaints. The only physical finding was a vaginal mass. This atypical presentation of colonic adenocarcinoma confirms the importance of understanding and thoroughly reviewing a patient's history.

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Outcome of Treatment of Liver Metastasis after Curative Surgery for Gastric Cancer

The efficacy of operative resection for liver metastases from colorectal cancer has been established. However,

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TABLE 1. *The Differences of Intervals Between Gastrectomy and Detection of Cancer Recurrence and Between Detection of Cancer Recurrence and the End of Follow-up According to the Types of Cancer Recurrence*

	No.	Average Interval Between Gastrectomy and Detection of Cancer Recurrence (months, mean ± SD)	Average Interval Between Detection of Cancer Recurrence and the End of Follow-up (months, mean ± SD)
Peritoneal	26	17.6 ± 13	7.6 ± 6.7[a]
Hepatic	18	20.4 ± 16.3	17.6 ± 14.8[b]
Lymph node	12	23.5 ± 19.4	13.5 ± 12.2[c]

a and b: $P = 0.004$; a and c: $P = 0.058$; b and c: $P = 0.437$.
SD, standard deviation.

the treatment of liver metastases from gastric cancer is controversial, because of the biologic aggressiveness of the disease. In addition, hepatic recurrence usually occurs in a combination of patterns, including peritoneal dissemination, lung metastases, and lymph node metastases. Only a few patients with liver metastases from gastric cancer are candidates for hepatic resection. Recent advancement of chemotherapeutic drugs has prolonged the survival of such patients with hepatic recurrence.[1] In this study, we retrospectively analyzed the outcomes of patients who developed liver metastases after curative surgery for gastric cancer to determine the outcomes of surgical intervention.

Between 1999 and 2008, 535 patients underwent curative (R0) gastrectomy for gastric adenocarcinoma at Tottori University Hospital. All patients were followed at our hospital until February of 2011. The type of cancer recurrence was determined by computed tomography and magnetic resonance imaging. Statistical analyses were performed using either the Mann-Whitney *U* test or the chi-squared test. All values with $P < 0.05$ were considered statistically significant.

A total 62 patients (11.6%, 48 male, 14 female; mean age, 68.7 years; range, 43 to 100 years) developed cancer recurrences. Peritoneal metastasis was found in 26 (4.9%), liver metastasis in 18 (3.4%), lymph node recurrence in 12 (2.2%), lung metastasis in three (0.6%), and bone metastasis in three (0.6%) patients. The mean interval between gastrectomy and detection of recurrence was similar for the different sites of cancer recurrence (peritoneal, hepatic, or lymph node recurrence). However, the prognosis of patients with hepatic or lymph node recurrence after detection of cancer recurrence was better than that of patients with peritoneal recurrence (Table 1).

Eighteen patients (14 male, 4 female; mean age, 70.7 years; range, 56 to 84 years) had recurrence in the liver. After gastrectomy, 10 patients (Stage II: 1 and III: 9) received adjuvant chemotherapy. Adjuvant chemotherapy did not prolong the time between gastrectomy and detection of hepatic metastasis (no adjuvant chemotherapy; n = 8; mean period, 28.4 months, adjuvant chemotherapy; n = 10; mean period, 19.4 months, $P = 0.328$). At the time of detection of liver metastasis, other types of metastases were found in four patients (peritoneal metastasis: 2 and lymph node metastasis: 2). After detection of liver metastasis, five patients refused additional treatment for cancer recurrence because of old age (n = 3) and poor performance status (n = 2). The remaining 13 patients were started on S-1-based chemotherapy.

Our criteria for hepatectomy in patients with hepatic recurrence from gastric cancer were: 1) age younger than 75 years; 2) good performance status (PS 0 to 1); 3) less than three metastatic tumors in the unilateral lobe; and 4) during S-1-based chemotherapy for 6 months, no new tumors appeared either inside or outside the liver. According to our criteria, three patients (mean age, 67 years) underwent hepatectomy after 6 months of S-1-based chemotherapy. One patient had three metastatic tumors in the right lobe and two patients had one metastatic tumor in the liver. The number and the size of metastatic liver tumors had not changed during S-1-based chemotherapy and the patients had no additional sites of cancer recurrence. Right hepatectomy was performed in the patient with three metastatic tumors, and partial hepatectomies were performed in two patients with a single metastatic tumor. Of the remaining 10 patients who did not have a hepatectomy, five were treated with only S-1 and 5 were treated with S-1 followed by another anticancer drugs. The mean survival time (MST) of five patients with best supportive care was 3.2 months and that of 10 patients treated with S-1-based chemotherapy was 18.7 months. However, no patient survived over 31 months. In contrast, of three patients who underwent hepatectomy after 6 months of S-1-based chemotherapy, two were alive 20 and 60 months after hepatectomy.

Recent advances in chemotherapeutic drugs have brought some hope for long-term survival of patients with hepatic metastases from gastric cancer. S-1 is a novel oral anticancer drug composed of tegafur (FT, a prodrug of 5-FU), gimestat (CDHP), and otastat potassium (Oxo) in a molar ratio of 1:0.4:1 and is based on the biochemical modulation of 5-FU. S-1 improves the tumor-selective toxicity of 5-FU by the modulatory actions of CDHP and Oxo.[2] A trial of S-1 plus cisplatin *versus* S-1 alone for first-line treatment of advanced gastric cancer (S-1 Plus cisplatin versus S-1 In RCT

In the Treatment for Stomach cancer [SPIRITS] trial) reported that the median overall survival was significantly longer in patients assigned to S-1 plus cisplatin (13 months) than in those assigned to S-1 alone (11 months).[3] From the result of the SPIRITS trial, S-1 plus cisplatin was recommended for the basic treatment of metastatic gastric cancer in Japan.

Our study indicated that S-1-based chemotherapy followed by hepatectomy prolonged survival time compared with S-1-based chemotherapy alone. Kakeji et al.[1] reported a hepatic resection rate of 17 to 38 per cent and the MST of patients was 12 to 34 months with a 5-year survival rate after hepatectomy of 18 to 42 per cent. A potentially curative hepatectomy may bring some hope of long-term survival for patients with hepatic metastasis. However, the reported survival rate after hepatectomy was rather unsatisfactory, because two thirds of the patients developed intrahepatic recurrence, and this high recurrence rate within 2 years of the surgery might suggest the presence of occult intrahepatic metastases even at the time of the hepatectomy. Thus, to avoid the possibility of intrahepatic recurrence or another type of recurrence after hepatectomy, we need to select the patients for hepatectomy. Thus, we started with S-1-based chemotherapy for patients with hepatic metastasis. During these chemotherapy periods (almost 6 months), patients who developed tumors in new regions or who showed enlargement of tumor size were excluded from hepatic resection.

We believe that surgical resection may bring some hope of long-term survival for selected patients with hepatic recurrence from gastric cancer.

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Indication of Emergency Operation and Intensive Care for Cardiopulmonary Arrest Related with Gastrointestinal Perforation

The survival rates of gastrointestinal perforation (GIP) have improved as the clinicopathological concept and practice guidelines for treating GIP, systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction syndrome have improved as well as organ-supporting systems.[1] However, we often encounter patients with GIP who have already fallen into septic shock or cardiopulmonary arrest (CPA). Patients with severe peritonitis with unstable circulatory dynamics just before the CPA in itself are difficult to save. Although we often hesitate to perform surgery for these patients, this choice means withdrawal and withholding, basically.

We made a retrospective study of cases diagnosed with GIP from all CPA cases on arrival and just after arrival. We made a diagnosis of GIP based on findings in the operation and the autopsy, intestinal contents aspirated by abdominal paracentesis, and image findings of intraperitoneal free air with free fluid. Patients showing intraperitoneal free air without free fluid were excluded, whose intraperitoneal free air was often accompanied by pneumothorax and mediastinal emphysema. We used all information collected from arrival at the hospital to discharge. In patients with CPA just after arrival, we dealt with the duration from contact with the patients to arrival at the hospital as 0 minutes and substituted the initial rhythm with the rhythm at the CPA confirmation in the hospital. We examined the indication of resuscitation for CPA and the indication of surgery using the patients' medical records. Statistical analysis was performed using a *t* test and chi-squared test.

In our city, we established a unique system for the prehospital transfer of patients with CPA, who are transferred to the nearest of the selected 11 hospitals (12 since 2007), which received all patients with CPA regardless of the etiology, possibility for resuscitation, and any other reason except the predecision of transfer to a designated hospital. The data concerning CPA of these 11 hospitals can be population-based data, which considered a transportation network.[2, 3]

Of 12 subjects (four gastric, one duodenal, one small intestinal, four colorectal, and two unknown), four could not achieve return of spontaneous circulation (ROSC) (group unresuscitatable, group UR). The other eight patients could successfully achieve ROSC, four of whom were also able to undergo emergency surgery and be saved (operable group, group O), whereas the other four

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REVIEW ARTICLE

Second-line chemotherapy for gastric cancer: a new issue lies ahead in global trials

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Abstract Chemotherapy for gastric cancer has been advancing fairly well. It has been indicated that not only advances in first-line chemotherapy but also those in second-line chemotherapy have contributed to the prolongation of overall survival. The Arbeitsgemeinschaft Internistische Onkologie (AIO) study supports the idea that second-line chemotherapy is appropriate in patients with a good general condition. Also, the Japan Clinical Oncology Group (JCOG) integral analysis suggests that advances have been made in second-line chemotherapy. However, most recently reported studies of second-line chemotherapy have been conducted as small-scale phase II or retrospective trials. No randomized control trial to establish standard treatment has been reported. Which regimen is the most appropriate as second-line therapy must be investigated in the future. Currently, molecularly targeted agents for gastric cancer are being developed and tested in global trials. As a new issue in global trials, second-line chemotherapy has been emphasized. In recent global trials, subset analysis showed regional differences in overall survival. This was possibly associated with the regional differences in second-line chemotherapy. When developing new molecularly targeted agents for first-line chemotherapy, we cannot ignore the result that the proportion of patients in whom treatment was switched to second-line chemotherapy was high in Asia. In planning a global trial, this new issue should be sufficiently discussed.

Keywords Gastric cancer · Second-line chemotherapy · Global trial · Molecularly targeted agent

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Introduction

Gastric cancer is frequent in Asia, South America, and Eastern Europe, accounting for more than 800,000 new cases per year worldwide, and it is the second most common cause of cancer death [1]. Because early detection strategies are rarely practiced, except in Japan and Korea, most patients will present with advanced-stage disease, and will therefore need palliative chemotherapy. Some chemotherapy regimens have been established as first-line therapy, and some progress has been made in the treatment of advanced-stage disease [2–12]. However, almost all patients with metastatic gastric cancer will develop progressive disease (PD) after first-line therapy. With the availability of several active chemotherapy drugs, many patients who retain a good performance status after the initial treatment remain good candidates for additional therapy.

However, most clinical studies of second-line chemotherapy have been conducted as phase II, small-scale trials. The data obtained are limited, and there is no standard second-line chemotherapy. In this review, differing from previous reviews of second-line chemotherapy [13, 14], I have clarified the significance of second-line chemotherapy based on the recently reported results of randomized control trials of first-line chemotherapy. On the other hand, I refer to the concept of second-line chemotherapy as a potentially confounding factor in recent global trials.

Evidence for second-line chemotherapy

Chemotherapy for advanced/recurrent gastric cancer has been advancing fairly well. As evidence, the median survival in recent randomized comparative studies involving