Table 2 Reported patient characteristics in the 67 clinical trials analyzed in the present study

Characteristic	Reported studies (%)	Reported year			Area of trial[a]		
		Before 2004 ($n = 36$)	After 2004 ($n = 31$)	P value[†]	Non-Asian ($n = 51$)	Asian ($n = 14$)	P value[†]
Age	67 (100)	36 (100)	31 (100)	ns	51 (100)	14 (100)	ns
Gender	66 (99)	35 (97)	31 (100)	ns	50 (98)	14 (100)	ns
PS	64 (96)	34 (94)	30 (97)	ns	48 (94)	14 (100)	ns
Measurable disease	46 (69)	21 (58)	25 (81)	0.05	35 (69)	9 (64)	ns
Metastatic site	43 (64)	22 (61)	21 (68)	ns	33 (65)	9 (64)	ns
Disease extension (local or metastatic)	38 (57)	19 (53)	19 (61)	ns	33 (65)	5 (36)	ns
Histology	30 (45)	12 (33)	18 (58)	0.04	20 (39)	9 (64)	ns
Location of primary tumor	26 (39)	8 (22)	18 (58)	≤0.01	24 (47)	1 (7)	≤0.01
Number of metastatic organs	25 (37)	5 (14)	20 (65)	≤0.01	18 (35)	5 (36)	ns
Disease status (advanced or recurrent)	18 (27)	5 (14)	13 (42)	ns	13 (25)	5 (36)	ns
Previous gastrectomy	46 (69)	21 (58)	25 (81)	0.05	32 (63)	12 (86)	ns
Previous adjuvant chemotherapy	16 (24)	0 (0)	16 (52)	≤0.01	6 (12)	9 (64)	≤0.01
Previous radiotherapy	11 (16)	3 (8)	8 (26)	ns	9 (17)	1 (7)	ns
Second-line chemotherapy	18 (27)	3 (8)	15 (48)	≤0.01	10 (20)	6 (43)	ns

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the χ^2 test or Fisher's exact test, with the level of significance set at $P < 0.05$ (underlined)

esophageal cancer. The frequency of reporting these characteristics appeared to be increasing in more recent trials, although most examined characteristics were reported in less than 60% of the trials (Table 2). Only primary tumor location was more frequently reported in non-Asian than Asian trials, and no other significant differences in reporting of disease characteristics were observed based on trial area.

The other reported patient characteristics were as follows: weight loss ($n = 12$; 18%); any symptoms (anorexia, dysphasia, etc., $n = 7$; 10%); body surface area ($n = 3$; 4%); ethnic groups ($n = 2$; 3%); hemoglobin level ($n = 4$; 6%); serum ALP level ($n = 3$; 4%); comorbidities ($n = 3$; 4%), and Royal Marsden hospital prognostic index ($n = 1$; 1%).

Previous treatment and second-line chemotherapy

An indication of the proportion of patients with previous gastrectomy was reported in 69% of trials, with the curability of gastrectomy (curative or palliative with residual disease) specified in approximately 50% of trials. Previous adjuvant chemotherapy and radiotherapy were infrequently reported (24 and 16% of trials, respectively). Second-line chemotherapy was also reported with low frequency (27% of trials), and was typically indicated in the text, rather than being included in patient characteristic tables. The reporting of previous treatment and second-line chemotherapies was found to be increasing in recent trials, although more than half did not include information related to second-line chemotherapy. In addition, Asian trials more commonly reported the use of adjuvant chemotherapy than non-Asian trials.

Patient characteristics of the combined trial population

The characteristics of the 12,656 AGC patients were calculated based on the reported values in each of the 67 clinical trials (Table 3). Recent trials included more patients with better PS (ECOG PS 0–1; 94 vs. 64%; $P < 0.01$) and less locally advanced disease (4 vs. 27%) than older trials. Asian trials included more patients with diffuse histology than non-Asian trials (53 vs. 34%; $P < 0.01$), while patients with liver metastasis (43 vs. 31%; $P = 0.01$) or locally advanced disease (15 vs. 3%; $P = 0.04$) were more common in non-Asian trials. Second-line chemotherapy was more commonly used in Asian and recent trials.

Stratification factors

Among the 67 trials, 40 (60%) used stratification factors (Table 4). The median number of factors was 3, with an observed range of 1–5. The most common stratification factor was PS, followed by institution and previous gastrectomy. More recent trials used one or more stratification factors than older trials (47 vs. 75%, $P = 0.03$, Table 4).

Table 3 Patient characteristics ($n = 12{,}656$) in AGC trials included in this analysis

Patient characteristic	Entire patient population (median)	Median per trial	Range	Reported year			Area of trial[a]		
				Before 2004 (median)	After 2004 (median)	*P* value[†]	Non-Asian (median)	Asian (median)	*P* value[†]
Median age (years)	–	59	52–72	58	59	ns	59	58	Ns
Male gender (%)	73	72	58–83	70	74	ns	72	69	ns
PS0–1 (%)	84	83	18–100	69	94	≤0.01	78	89	ns
PS2 or more (%)	16	17	0–82	31	6	≤0.01	22	11	ns
Diffuse histology (%)	42	38	1–66	44	34	ns	34	53	≤0.01
One metastatic organ (%)	33	30	9–51	26	32	ns	27	35	ns
Locally advanced disease (%)	15	14	0–43	27	4	≤0.01	15	3	0.04
Liver metastasis (%)	44	42	18–79	42	42	ns	43	31	0.02
Peritoneal metastasis (%)	23	24	3–62	23	29	ns	20	29	ns
With measurable disease (%)	88	99	33–100	96	100	ns	100	96	ns
Previous gastrectomy (%)	33	39	8–83	38	40	ns	41	33	ns
Previous adjuvant chemotherapy (%)	5	5	1–31	–	5	–	4	9	0.02
Previous radiotherapy (%)	1	1	0–3	2	1	ns	1	1	ns
Second-line chemotherapy (%)	40	41	14–83	18	40	≤0.01	36	57	0.01

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the Mann–Whitney test, with the level of significance set at $P < 0.05$ (underlined)

Table 4 Stratification factors in the 67 clinical trials analyzed in the present study

Stratification factor	*N* of studies (%)	Reported year			Area of trial[a]		
		Before 2004 (%)	After 2004 (%)	*P* value[†]	Non-Asian (%)	Asian (%)	*P* value[†]
No factor	27 (47)	19 (53)	8 (26)	0.03	22 (43)	5 (36)	ns
1 or 2 factors	12 (21)	5 (14)	7 (23)		7 (14)	4 (29)	
3 or more factors	28 (49)	12 (33)	16 (52)		22 (43)	5 (36)	
PS	24 (42)	9 (25)	15 (48)	ns	16 (31)	7 (50)	ns
Previous gastrectomy	18 (32)	9 (25)	9 (29)	ns	14 (27)	4 (29)	ns
Institution	18 (32)	5 (14)	7 (23)	0.35	16 (31)	2 (14)	ns
Measurable disease	12 (21)	6 (17)	6 (19)	ns	10 (20)	1 (7)	ns
Metastatic sites	8 (14)	2 (6)	6 (19)	0.08	8 (16)	0 (0)	ns
Disease extension	8 (14)	4 (11)	4 (13)	ns	7 (14)	1 (7)	ns
Age	6 (11)	5 (14)	1 (3)	ns	5 (10)	1 (7)	ns
Gender	5 (9)	5 (14)	0 (0)	0.03	5 (10)	0 (0)	ns
Adjuvant chemotherapy	5 (9)	1 (3)	4 (13)	ns	3 (6)	2 (14)	ns
Disease status	3 (5)	0 (0)	3 (10)	ns	0 (0)	2 (14)	≤0.01
Location of primary tumor	3 (5)	1 (3)	2 (6)	ns	2 (4)	0 (0)	ns

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the χ^2 test or Fisher's exact test, with the level of significance set at $P < 0.05$ (underlined)

Gender was more commonly used in older trials (14 vs. 0%). No significant difference of stratification factors was observed between Asian and non-Asian trials, other than the frequency of use of disease status (0 vs. 14%).

Discussion

To our knowledge, this represents the first study to review the reporting of patient characteristics in published

randomized trials for AGC. Our results showed considerable inconsistency in the reporting of patient characteristics and the use of stratification factors in clinical trials for AGC. A similar finding was reported by Sorbye et al. [16], who analyzed metastatic colorectal cancer (MCRC) clinical trials and advocated that an urgent need exists for an international consensus on the reporting of patient characteristics and stratification in MCRC trials. Our data also revealed several differences in patient characteristics between trials conducted before and after 2004, and between Asian and non-Asian trials. It is possible that these differences may have contributed to the observed heterogeneity in the survival outcomes of each trial.

Several prognostic factors have been identified for patients with AGC who have undergone chemotherapy [10–14]. As described in the "Introduction", the GASTRIC project confirmed the impact of ECOG PS, disease status, number of metastatic organs, location of metastasis, and prior surgery on the survival of AGC patients, as determined by individual patient data analysis of previous randomized studies [10]. Notably, this project, which may have included the largest AGC patient set to date, identified that PS1 and PS2 were significantly associated with poor survival, with hazard ratios (HRs) of death of 1.36 and 2.17, respectively [10]. In the GASTRIC analysis, although most trials included PS among the reported patient characteristics, a number of studies classified PS0 and PS1 separately, and several studies used KPS rather than the ECOG scale. In addition, local recurrence and metastatic disease were reported to be associated with worse outcomes than locally advanced disease [10]. In our present analysis, approximately 50% of trials reported disease extension (locally advanced or metastatic disease), and only 30% of trials indicated disease status (advanced or recurrent disease).

Although the GASTRIC analysis did not evaluate the importance of specific metastatic organs on outcomes, another large prognostic analysis, by Chau et al. [11, 12], reported the impact of liver and peritoneal metastasis on AGC patient survival. Affected metastatic organs were reported in 64% of the trials in our analysis, but the number of metastatic organs, which has significant impact on survival according to the GASTRIC analysis, was only reported with a frequency of 39%. Although histology was not identified as prognostic in the GASTRIC analysis, several recent trials suggest that an interaction exists between histology and drug response [6, 7, 17, 18]. For example, a subset analysis of the First-line Advanced Gastric Cancer Study (FLAGS) trial has indicated that the oral fluoropyrimidine S-1 appears to be superior to fluorouracil in the treatment of diffuse-type gastric cancer [6]. This finding is consistent with the results of a subset analysis of the Japan Clinical Oncology Group (JCOG) 9912 study that also indicated S-1 is better than fluorouracil in patients with diffuse-type AGC or gastric cancer associated with high dihydropyrimidine dehydrogenase (DPD) activity, which is more commonly associated with diffuse-type than intestinal-type tumors [17]. This result was not unexpected, because S-1 is a potent competitive inhibitor of DPD. In contrast to DPD, human epidermal growth factor receptor 2 (HER2)-positive AGC, for which the anti-HER2 agent trastuzumab is effective [7], is reported to be higher among intestinal-type tumors [18]. The prognostic factors and tumor characteristics identified in these studies should be reported in all clinical trials of AGC, as they are necessary to adequately interpret trial data and treatment outcomes.

Our analysis also revealed that the types of second-line chemotherapy and proportions of patients who received such treatment were not routinely reported in AGC trials. As several recent reports have suggested that second-line chemotherapy has a significant impact on OS [19–21], we propose that second-line therapies should be diligently reported in future clinical trials of first-line AGC treatment, because second-line chemotherapy might influence the OS as the primary endpoint, as suggested by our previous analysis [22].

Additionally, the numerous prognostic factors identified for AGC may be important for the stratification of patients with respect to risk and treatment arms in randomized trials. To adequately analyze treatment effects on clinical outcomes, efforts should be undertaken to maximally decrease imbalance of prognostic factors between treatment arms in a clinical trial [23]. Although there is no definite consensus on the optimal method for stratification, stratification is recommended for superiority trials with fewer than 400 patients [24] and for non-inferiority trials with any number of patients [25]. In our analysis, stratification was conducted in only 60% of the examined trials, and was performed with quite variable stratifying factors. Based only on the present analysis, it is difficult to suggest a standardization approach for stratification factors in AGC trials, and further analysis and discussion are necessary.

In recent years, a trend of increased median OS in AGC patients has been observed concurrent with the development of new chemotherapeutic agents [2, 4, 7, 26]. It is also possible that second-line chemotherapy may have contributed to the improvement in OS [19–21]; however, our crude comparison of trials conducted prior to and after 2004 also showed significant differences in PS and disease extension. These differences may have also contributed to the improved survival reported in more recent trials, as well as survival differences between Asian and non-Asian trials. The exact impact of chemotherapy and patient characteristics on survival would be best addressed in well-designed randomized studies and meta-analyses of individual patient data.

In conclusion, our analyses of published clinical trials for AGC revealed inconsistencies in the reporting of

patient characteristics and use of stratification factors. An international consensus on the reported characteristics and stratification in AGC trials is necessary to improve the analysis of future clinical trials.

Conflict of interest None.

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Chemotherapy for Patients With Advanced Gastric Cancer With Performance Status 2

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ABSTRACT

Methods: We retrospectively analyzed 657 patients with advanced gastric cancer who received first-line chemotherapy. Baseline patient characteristics and treatment results were compared between Eastern Cooperative Oncology Group performance status (PS) 0–1 and PS 2 patients.

Results: Prior to beginning first-line chemotherapy, 513, 112, and 32 patients were PS 0–1, PS 2, and PS 3–4, respectively. Patients with massive ascites (42% vs. 3%; $P < .001$) or inability to eat (39% vs. 4%; $P < .001$) were more likely to be PS 2 than PS 0–1. Significantly fewer PS 2 patients received first-line chemotherapy regimens containing oral agents (40% vs. 77%; $P < .001$) or combination chemotherapy (19% vs. 40%; $P < .001$) compared to PS 0–1 patients. Median survival time was significantly shorter in PS 2 patients (5.8 vs. 13.9 months; $P < .001$). Multivariate survival analysis revealed that use of oral agents was associated with a better prognosis in PS 0–1 patients (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.59–0.97, $P = .03$), while it was associated with poorer survival in PS 2 patients (HR 1.52, 95% CI 1.0–2.3, $P = .046$).

Conclusion: Advanced gastric cancer patients with PS 2 not only had a poorer prognosis but also differed in several baseline characteristics compared to PS 0–1 patients. These results indicate that additional clinical trials that specifically target gastric cancer patients with PS 2 may be required to evaluate optimal treatment regimens for this patient population.

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Performance status (PS) is an independent prognostic factor for survival in patients with advanced gastric cancer.[1,2] As a result of disease progression, patients with gastric cancer are subject to several debilitating complications, including anorexia, fatigue, and abdominal distension, that can lead to deterioration of general patient status. Overall, inclusion criteria for the majority of clinical trials have specified an Eastern Cooperative Oncology Group (ECOG) PS ≤ 2. According to multivariate survival analysis of three phase-III studies conducted between 1992 and 2001, PS 2 patients represented 22.8% of the patient population, and these patients experienced significantly poorer survival compared to patients with a more favorable PS.[2] However, because recent pivotal phase-III studies performed in Japan[3–5] and Western countries[6–8] included very few PS 2 patients (2% in three Japanese trials and 0%–10% in Western trials), standard treatment of PS 2 patients has not yet clearly been established. Furthermore, the characteristics of advanced gastric cancer patients with PS 2 have not yet been reported in detail.

To address this issue, we conducted a retrospective analysis comparing baseline characteristics and treatment results in advanced gastric cancer patients with PS 0–1 vs. PS 2.

PATIENTS AND METHODS

This study was a retrospective analysis of patients with advanced or recurrent gastric cancer who received chemotherapy. Principal inclusion criteria were the presence of histologically or cytologically proven, inoperable gastric cancer. Written informed consent was obtained from all patients prior to chemotherapy. Performance status was evaluated prior to initiation of first-line chemotherapy according to ECOG criteria.[9]

Between April 2001 and June 2008, 657 patients with gastric cancer underwent first-line chemotherapy at Aichi Cancer Center and Misawa City Hospital. Baseline characteristics and treatment results were compared between patients with PS 0–1 and PS 2. Patients with PS 3 or 4 were excluded from this analysis. The following baseline characteristics were assessed: age (<65 years or ≥65 years), gender, disease status (advanced or recurrent), previous gastrectomy (yes or no), previous adjuvant chemotherapy (yes or

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no), pathologic classification (diffuse or intestinal), metastasis to peritoneum (yes or no), metastasis to liver (yes or no), presence of massive ascites (yes or no), number of metastatic sites (one or multiple), and inability to eat (yes or no).

"Multiple metastatic sites" was defined as the presence of metastases in more than one organ. "Massive ascites" was defined as the presence of ascites from the pelvic cavity to the liver surface or upper abdominal cavity, or ascites that required drainage. "Inability to eat" was defined as requirement for daily intravenous fluids or hyperalimentation. Chemotherapeutic regimens were selected individually by physicians or within the context of a clinical trial. Dosing and scheduling of most chemotherapy regimens were performed as reported in the literature.[3–5,10–15]

First-line chemotherapeutic regimens were directly compared, with particular attention focused on oral vs. infusional drugs and monotherapy vs. combination chemotherapy regimens. Toxicities grade ≥ 3, according to the National Cancer Institute Common Toxicity Criteria version 3.0, were also compared between PS 0–1 and PS 2 patients.

Statistical Methods

Overall survival (OS) was estimated starting from the date of initial chemotherapy to the date of death or last follow-up visit using the Kaplan-Meier method. Time-to-treatment failure (TTF) was measured from the date of treatment initiation to the last day of first-line treatment. OS and TTF in PS 0–1 and PS 2 patients were compared using the log-rank test. Distribution of baseline characteristics was assessed by chi-square test or Fisher exact test, as appropriate.

To evaluate the effect of types of treatment (oral vs. infusional; combination therapy vs. monotherapy) on OS in PS 0–1 vs. PS 2 patients, univariate and multivariate Cox proportional hazards modeling was applied. Therefore, a measure of association in this study was the hazard ratio (HR) along with the 95% confidence interval (95% CI). Forward and backward stepwise methods were used for model building. Threshold *P* values for inclusion or exclusion in the model were defined as .10 and .20, respectively. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX, USA). All tests were two-sided, and *P* values less than .05 were considered statistically significant.

Table 1. Patient characteristics (PS 0–1 vs. PS 2)

Characteristics		PS 0–1 (n=513) n (%)	PS 2 (n=112) n (%)	*P* value
Median age (range)		63 (28–85)	64 (29–81)	.8
Gender	Male	353 (69)	63 (56)	.01
	Female	160 (31)	49 (44)	
Pathologic type	Intestinal	166 (32)	15 (13)	< .001
	Diffuse	347 (68)	97 (87)	
Disease status	Advanced	340 (66)	75 (67)	.9
	Recurrent	173 (34)	37 (33)	
Prior gastrectomy	Yes	283 (55)	42 (38)	< .001
	No	230 (45)	70 (62)	
Adjuvant chemotherapy	Yes	77 (15)	10 (9)	.08
	No	435 (85)	102 (91)	
Disease site	Peritoneum	240 (47)	83 (74)	< .001
	Ascites (massive)	17 (3)	47 (42)	< .001
	Liver	163 (32)	21 (19)	.02
	Multiple sites	228 (44)	72 (64)	< .001
Inability to eat	Yes	23 (4)	44 (39)	< .001

Table 2. First-line treatment in PS 0–1 vs. PS 2 patients

		PS 0–1 (n=513) n (%)	PS 2 (n=112) n (%)
First-line regimens	5-FU*-based†	277 (54)	66 (59)
	5-FU* + cisplatin	130 (25)	12 (12)
	5-FU* + taxane	22 (4)	5 (6)
	5-FU* + irinotecan	14 (3)	0 (0)
	Irinotecan ± cisplatin	33 (6)	2 (2)
	Taxane ± cisplatin	37 (7)	21 (20)
First-line agents	5-FU	444 (86)	83 (78)
	Cisplatin	171 (34)	17 (16)
	Taxane	59 (11)	26 (23)
	Irinotecan	47 (9)	2 (2)

* Including S-1 or capecitabine.
† Including 5-FU plus methotrexate.
Abbreviations: 5-FU = 5-fluorouracil

RESULTS

Patient Characteristics

Among the 657 patients, PS at initiation of first-line chemotherapy was as follows: PS 0, 172 patients (26.1%); PS 1, 341 patients (51.9%); PS 2, 112 patients (17.0%); and PS 3–4, 32 patients (4.9%). The characteristics of patients with PS 0–1 or PS 2 are shown in Table 1. A larger proportion of PS 2 patients had peritoneal dissemination, massive ascites, and/or multiple metastatic sites compared to PS 0–1 patients. A larger number of PS 2 patients suffered an "inability to eat" (39% vs. 4%; $P < .001$), primarily due to the presence of gastrointestinal stenosis/obstruction and/or massive ascites. In contrast, liver metastasis was less common in PS 2 patients than in PS 0–1 patients.

Treatment Results

Table 2 shows the results of first-line treatment in PS 0–1 and PS 2 patients. Significantly fewer PS 2 patients (n = 1, 0.9%) were registered in clinical trials compared

to PS 0–1 patients (n = 148, 29%; P < .001). Overall, first-line chemotherapy containing oral agents (S-1/capecitabine) was less frequently used in PS 2 patients (n = 45, 40%) than in PS 0–1 patients (n = 394, 77%; P < .001). Furthermore, fewer PS 2 patients received combination regimens as first-line chemotherapy (n = 22, 19%) than PS 0–1 patients (n = 210, 41%; P < .001).

With respect to chemotherapeutic agents, taxanes (paclitaxel or docetaxel) were more frequently used in PS 2 patients than in PS 0–1 patients. In contrast, cisplatin and irinotecan were less frequently given to PS 2 patients compared to PS 0–1 patients, with reduced doses used in most PS 2 patients. Median TTF for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (2.4 months vs. 4.8 months; P < .001; Figure 1). Significantly fewer PS 2 patients received second-line chemotherapy (n = 56, 50%) compared to PS 0–1 patients (n = 400, 78%; P < .001). In addition, significantly fewer PS 2 patients received third-line chemotherapy (n = 16, 14%) compared to PS 0–1 patients (n = 210, 41%; P < .001).

Toxicity

Grade 3/4 hematologic toxicity was more frequently observed in PS 2 patients compared to PS 0–1 patients (Table 3). Febrile neutropenia also occurred significantly more frequently in PS 2 patients (6.3% vs. 1.2%). The incidence of chemotherapy-related grade 3/4 diarrhea and stomatitis did not significantly differ between PS 0–1 and PS 2 patients. Anorexia and nausea/vomiting were more frequently observed in PS 2 patients, though in some cases it was difficult to determine whether anorexia and nausea/vomiting were related to treatment, as the majority of PS 2 patients experienced these symptoms prior to chemotherapy. The frequency of treatment withdrawal due to toxicity or treatment-related death did not significantly differ between PS 0–1 and PS 2 patients (Table 3).

Survival

At a median follow-up time of 38 months, OS of PS 0–1 patients was 13.9 months (95% CI 12.7–15.3) and that of PS 2 patients was 5.8 months (range 4.7–6.9 months; HR for death 3.5, 95% CI 2.7–4.5, P < .001; Figure 2).

Use of Oral Agents and Combination Chemotherapy in PS 0–1 and PS 2 Patients

Table 4 shows the results of univariate and multivariate analyses comparing types of treatment (use of oral vs. infusional agents; combination therapy vs. monotherapy) and survival in PS 0–1 and PS 2 patients. In PS 0–1 patients, use of oral agents was significantly associated with better prognosis (HR 0.76, 95% CI 0.59–0.97, P = .03), while it was associated with poorer survival in PS 2 patients (HR 1.52, 95% CI 1.0–2.3, P = .046) after adjustment of other baseline characteristics. The interaction between PS and oral agents was statistically significant (P = .02). Combination chemotherapy tended to be associated with a better prognosis in PS 0–1 patients, though this difference was not statistically significant.

DISCUSSION

In this study, we retrospectively compared several baseline characteristics and treatment results of PS 0–1 and PS 2 patients with advanced gastric cancer who underwent chemotherapy. To our knowledge, this is the first report to show several differences between PS 0–1

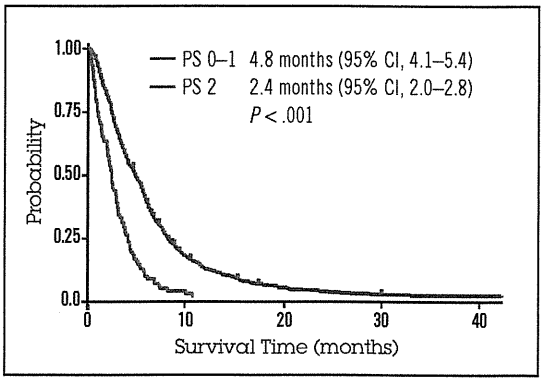

Figure 1. Kaplan-Meier survival curves of time to treatment failure (TTF). Median TTF for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (2.4 months vs. 4.8 months; P < .001).

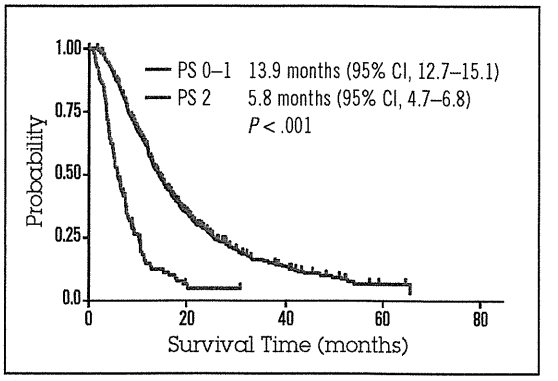

Figure 2. Kaplan-Meier survival curves of overall survival (OS). Median OS for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (5.8 months vs. 13.9 months; P < .001).

Table 3. Toxicity during first-line treatment in PS 0–1 vs. PS 2 patients

Adverse event (≥ grade 3)	PS 0–1 (%) (n=513)	PS 2 (%) (n=112)	*P* value
Leukopenia	5.7	17.8	< .001
Neutropenia	14.3	26.7	< .001
Febrile neutropenia	1.2	6.3	< .001
Anemia	5.8	25.0	< .001
Thrombocytopenia	0.4	4.5	< .001
Increased transaminases	2.3	7.1	< .001
Increased creatinine	0.4	1.8	NS
Anorexia	9.4	17.8	< .001
Nausea/vomiting	5.6	11.6	.02
Diarrhea	3.9	4.5	NS
Stomatitis	2.1	4.5	NS
Treatment withdrawal due to toxicity	5.6	6.3	NS
Treatment-related death	1.0	1.8	NS

Abbreviations: NS = not significant

Table 4. Use of oral agents and combination chemotherapy in PS 0–1 vs. PS 2 patients

Treatment		Univariate analysis			Multivariate analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
PS 0–1 (n=513)	Oral agents: Yes (n=394) vs. No (n=119)	0.75	0.59–0.94	.014	0.76	0.59–0.97	.03
	Combination CTx: Yes (n=210) vs. No (n=303)	1	0.82–1.2	.92	0.85	0.70–1.07	.19
PS 2 (n=112)	Oral agents: Yes (n=45) vs. No (n=67)	1.51	0.99–2.2	.051	1.52	1.0–2.3	.046
	Combination CTx: Yes (n=22) vs. No (n=90)	0.97	0.60–1.5	.91	1	0.62–1.7	.94

*Adjusted by age, gender, pathologic type, disease status, prior gastrectomy, adjuvant chemotherapy, peritoneal metastasis, liver metastasis, massive ascites, multiple metastatic sites, and inability to eat. *P* for interaction between PS and oral agents = .02.
Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval; CTx = chemotherapy

and PS 2 patients with gastric cancer in Japan. Our results demonstrate that PS 2 patients not only have a poorer prognosis compared with PS 0–1 patients but they also differ in several baseline characteristics.

Although the cause and type of PS deterioration may differ between individual advanced gastric cancer patients, the results of our study clearly showed that patients with a poor PS more frequently suffered inability to eat and massive ascites. These complications may specifically reflect the characteristics of Japanese gastric cancer patients, among whom pathologically diffuse-type disease and peritoneal metastasis are more common than in gastric cancer patients in Western countries.[2,6,7] As a result of these complications, administration of oral agents is difficult in many PS 2 patients and is therefore less commonly used. Recent clinical trials[3–5] have frequently excluded patients with inability to eat or massive ascites due to the increasing use of oral agents such as S-1 and capecitabine; this may explain the relatively low entry rate of PS 2 patients into clinical trials conducted at our institutions.

Additionally, our multivariate survival analysis revealed that use of oral agents was associated with poorer prognosis only in PS 2 patients (HR 0.76), while it is associated with better survival in PS 0–1 patients (HR 1.52). Although the cause of unfavorable results with oral agents in PS 2 patients is not known, it may be due in part to decreased absorption or motility in the gastrointestinal tract in patients with gastrointestinal stenosis or massive ascites, which is frequently observed in PS 2 patients in this analysis. Recent combined analysis of phase-III studies (REAL-2 and ML17032) showed that capecitabine tended to be associated with better survival than infusional 5-fluorouracil (5-FU) in PS 2 patients.[16] However, less than 20% of patients had peritoneal metastasis,[16,17] which is quite different from patients in this analysis (peritoneal carcinomatosis, 74%; massive ascites, 42%). Jeung et al reported the feasibility of S-1 monotherapy in patients with advanced gastric cancer with a poor PS.[18] However, their study also included a relatively small proportion of patients with peritoneal carcinomatosis (29%). It would seem, therefore, that a study that specifically targets patients with peritoneal metastases might be warranted.

The results of a phase-III study in Japan, which compared 5-FU vs. methotrexate plus 5-FU in patients with advanced gastric cancer with peritoneal metastasis, were recently reported (JCOG0106).[19] However few PS 2 patients (3.3%) were included in this study, because patients with massive ascites or gastrointestinal obstruction were excluded; thus, data in PS 2 patients are limited. Therefore, additional studies may be required to identify optimal regimens in PS 2 gastric cancer patients.

Since the chemotherapeutic regimens used for PS 2 patients in this analysis varied considerably, the optimal regimen for this patient population remains unclear. The incidence of treatment discontinuation due to toxicity or treatment-related death did not differ significantly between PS 0–1 and PS 2 patients, which indicates that systemic chemotherapy could be feasible and indeed warranted in PS 2 patients. Hematologic toxicity such as neutropenia, however, was significantly more common in PS 2 patients, despite a low rate of combination chemotherapy administration, suggesting that caution should be used when giving combination chemotherapy to PS 2 patients. Since current clinical trials frequently use combination chemotherapy regimens, including those containing standard doses of platinum agents, it might be necessary to exclude PS 2 patients from future trials that employ more toxic combination chemotherapy regimens.

Our study has several limitations. First, PS is not an absolute criterion for evaluating the general status of gastric cancer patients. However, no alternative criteria for classifying general status are currently available. Second, comorbidities and age were not considered. Both comorbidities and advanced age can contribute to PS deterioration and should be considered as a matter of course in the clinical decision-making process. We should develop more comprehensive criteria—including general status, nutrition status, age, and comorbidity—to make better informed decisions in the best interest of our patients. However, it should be noted that none of the patients in our analysis had poor PS due only to age or comorbidity.

In conclusion, advanced gastric cancer patients with PS 2 not only had a poorer prognosis but also differed in several baseline characteristics, including frequency of ascites and eating status, compared to PS 0–1 patients. These results suggest that clinical trials that specifically target gastric cancer patients with PS 2 may be required to evaluate optimal chemotherapeutic regimens for this patient population.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Prognostic Factors for Metastatic Colorectal Cancer Patients Undergoing Irinotecan-Based Second-Line Chemotherapy

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ABSTRACT

Background: No reports about factors that predict prognosis after second-line chemotherapy for metastatic colorectal cancer have been published.

Methods: We retrospectively analyzed 124 patients with metastatic colorectal cancer who received irinotecan-based second-line chemotherapy after first-line folinic acid/5-fluorouracil (5-FU)/oxaliplatin (FOLFOX) with or without bevacizumab.

Results: A multivariate Cox model revealed 5 prognostic factors for worse survival: ECOG performance status 2, pathologically poorly differentiated adenocarcinoma, peritoneal metastasis, progression-free survival of first-line FOLFOX < 6 months, and lactate dehydrogenase ≥ 400 IU/L. When patients were categorized into 3 risk groups—patients without any prognostic factors (low-risk, n = 55), patients with one prognostic factor (intermediate-risk, n = 32), and patients with 2 or more prognostic factors (high-risk, n = 37)—overall survival from initiation of second-line chemotherapy was 23.5, 14.6, and 5.5 months, respectively. The proportion of patients who were eligible to receive further chemotherapy after disease progression was significantly lower in the high-risk group (41%) than in the intermediate- (67%) and low-risk (95%) groups.

Conclusion: Several prognostic factors for survival after second-line therapy and probability of receiving third-line chemotherapy were identified. This risk classification system might be useful for determining which patients should receive cetuximab in the second-line setting rather than the third-line setting.

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Folinic acid/5-fluorouracil (5-FU)/oxaliplatin (FOLFOX) plus bevacizumab is the most widely used first-line chemotherapy regimen for metastatic colorectal cancer (MCRC).[1,2] After failure of FOLFOX, FOLFIRI [folinic acid/ (5-FU)/irinotecan] or irinotecan monotherapy is usually administered in the second-line setting.[3,4] The results of a large observational study have also suggested that continued use of bevacizumab during second-line therapy may provide additional benefit.[1]

Cetuximab, a recombinant, human-mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor (EGFR) has been shown to improve the prognosis of MCRC significantly compared to best supportive care alone in the third-line setting.[5] Furthermore, combining cetuximab with irinotecan results in a higher response rate than cetuximab alone, even in patients with irinotecan-refractory disease, suggesting that cetuximab may restore chemosensitivity in these patients.[6]

The EPIC trial was a large phase III study that compared irinotecan plus cetuximab to irinotecan monotherapy as second-line treatment in patients with MCRC following failure of oxaliplatin-based therapy.[7] Although the primary end point of improved survival was not achieved (10.7 vs 10.0 months, $p = .71$), patients in the combination arm experienced a superior response rate and progression-free survival (PFS). Approximately half of the patients in the irinotecan monotherapy arm received cetuximab after irinotecan failure, which may have contributed to the similar overall survival rates in the 2 arms. However, 35% of patients in the irinotecan group were unable to receive any third-line chemotherapy, most likely due to rapid tumor progression.[7] Thus, it was suggested that cetuximab with irinotecan may be better than irinotecan as second-line therapy for patients with rapidly progressing disease. So far, no reports about factors that predict the prognosis after second-line irinotecan or

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probability of receiving third-line therapy have been published. To address this issue, we conducted the following retrospective analysis of MCRC patients who received irinotecan-based chemotherapy as second-line treatment after first-line FOLFOX.

PATIENTS AND METHODS

This was a retrospective cohort study of MCRC patients who received irinotecan-based chemotherapy as second-line treatment after first-line FOLFOX. Irinotecan-based chemotherapy consisted of FOLFIRI (2-hr infusion of leucovorin isomers at 200 mg/m^2 followed by bolus 5-FU 400 mg/m^2 plus a 46-hr infusion of 5-FU 2,400 mg/m^2 every 2 weeks, with irinotecan 150 mg/m^2 as a 1.5-hr infusion on day 1) with or without bevacizumab (5 mg/m^2 every 2 weeks), irinotecan monotherapy (irinotecan 150 mg/m^2 every 2 weeks), or S-1 plus irinotecan (S-1 40 mg/m^2 twice daily for 14 consecutive days followed by a 2-week rest, with irinotecan 100 mg/m^2 every 2 weeks). Individual regimens were selected at the discretion the physicians or as called for in clinical trials.

Principal inclusion criteria were presence of histologically proven, inoperable colorectal cancer, age < 80 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, sufficient bone marrow function, and normal liver and renal function. Treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of first-line fluoropyrimidine and oxaliplatin treatment for metastatic disease was required. Prior bevacizumab was allowed. These criteria were very similar to those of the EPIC study. Written informed consent was obtained from all patients prior to chemotherapy.

Among patients with MCRC treated at our institution between October 2005 and December 2008, 124 patients who fulfilled the inclusion criteria were identified. Detailed patient characteristics prior to initiation of second-line chemotherapy were acquired from hospital patient records. Objective tumor response of first-line FOLFOX was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST).[8] PFS associated with first-line FOLFOX was measured from the beginning of treatment to the date of progression.

Statistical Methods

The primary end point of this study was evaluation of the association between several prognostic factors and overall survival, which was defined as the interval between the date of initiation of second-line treatment and the date of death or last follow-up using the Kaplan-Meier method. Progression-free survival was also measured from the beginning of second-line treatment to the date of disease progression.

To evaluate the prognostic factors associated with overall survival, univariate and multivariate Cox proportional hazards modeling was applied. The hazard ratio (HR) along with the 95% confidence interval (95% CI) was used as a measure of association in this study. Forward and backward stepwise methods were used for model building. Threshold p values for inclusion or exclusion in the model were defined as .10 and .20, respectively.

Factors included in the uni- and multivariate analyses were age (< 65 vs ≥ 65 years), gender (male vs female), ECOG PS (0–1 vs 2), peritoneal metastasis (yes vs no), liver metastasis (yes vs no), number of metastatic sites (1–2 vs ≥ 3), pathologic type (moderately or well-differentiated adenocarcinoma vs poorly differentiated adenocarcinoma), serum alkaline phosphatase (ALP) level (< 400 vs ≥ 400 IU/L), serum lactate dehydrogenase (LDH) level (< 400 vs ≥ 400 IU/L), serum carcinoembryonic antigen (CEA) level (< 500 vs ≥ 500 ng/mL), leukocyte count (< 8.0 × 10^9/L vs ≥ 8.0 × 10^9/L), response to first-line FOLFOX (responder vs nonresponder), and PFS associated with first-line FOLFOX (< 6 months vs ≥ 6 months). "Responders" were defined as patients who achieved a complete response or partial response, while "nonresponders" were patients with stable disease or progressive disease.

Distribution of subject characteristics was assessed by the chi-square test or the Fisher exact test, as appropriate. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX). All tests were 2-sided, and p values < .05 were considered to be statistically significant.

RESULTS

Detailed patient characteristics are shown in Table 1. All 124 patients experienced disease progression prior to second-line chemotherapy. Oxaliplatin was discontinued due to neuropathy or allergy prior to disease progression in 59 patients; most of these patients continued 5-FU/leucovorin with or without bevacizumab until disease progression. First-line FOLFOX resulted in a partial response in 54 patients (43.5%), stable disease in 47 patients (37.9%), and progressive disease in 23 patients (18.5%). Median PFS associated with first-line FOLFOX was 7.3 months (95% CI, 6.2–8.0).

Second-line chemotherapy was administered as follows: FOLFIRI, 71 patients; irinotecan, 39 patients; and S-1 plus irinotecan, 14 patients. Bevacizumab was also used in 21 patients. The median treatment duration of second-line chemotherapy was 3.8 months (95% CI, 3–4.8).

At the time of analysis, 74 (59.6%) patients had died, with a median follow-up of 24.1 months since initiation of second-line chemotherapy. Median overall survival for all patients was 14.6 months (95% CI, 10.8–18.8). Median PFS was 3.8 months (95% CI, 2.9–5.2).

Salvage Chemotherapy

Among the 124 patients, 115 patients experienced disease progression despite second-line irinotecan-based chemotherapy; 82 of these patients (71%) received salvage chemotherapy as follows: anti-EGFR antibody (including cetuximab and panitumumab; n = 33), mitomycin-C plus irinotecan (n = 11), FOLFOX reintroduction with bevacizumab (n = 15), hepatic arterial infusion chemotherapy mainly using 5-FU (n = 10), and other regimens (n = 13). *KRAS* status was evaluated in 40 patients; 25 of these patients were determined to have cancers with a wild-type *KRAS* genotype.

Survival Analyses and Probability of Receiving Salvage Chemotherapy

Tables 2 and 3 show the results of univariate and multivariate analyses of baseline and clinical characteristics as prognostic factors for survival, including objective response and PFS associated with first-line FOLFOX. According to a multivariate Cox model, 5 prognostic factors for worse survival were identified: PS 2, pathologically poorly differentiated adenocarcinoma, peritoneal metastasis, PFS associated with first-line FOLFOX < 6 months, and LDH ≥ 400 IU/L.

Table 1. Patient characteristics

Characteristic		Number of patients (N = 124)
Median age, years (range)		63 (23–79)
Gender	Male/female	74/50
Performance status	0–1/2	111/13
Pathology	Wel or mod/por	113/11
Peritoneal metastasis	Yes/no	26/98
Liver metastasis	Yes/no	69/55
Metastatic sites	1–2/> 3	99/25
First-line treatment	FOLFOX/FOLFOX+BV	107/17
Response to first-line FOLFOX	CR/PR/SD/PD	0/54/47/23
PFS of first-line FOLFOX	< 6 months/> 6 months	49/75
Cause of oxaliplatin discontinuation	Disease progression/other	65/59
Leukocyte count (/L)	$< 8\times10^9/\geq 8\times10^9$	110/14
ALP (IU/L)	< 400/≥ 400	70/54
LDH (IU/L)	< 400/≥ 400	98/26
CEA (ng/mL)	< 500/> 500	110/14

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; CR = complete response; LDH = lactate dehydrogenase; mod = moderately differentiated adenocarcinoma; PD = progressive disease; PFS = progression-free survival; por = poorly differentiated adenocarcinoma; PR = partial response; SD = stable disease; wel = well-differentiated adenocarcinoma.

A multivariate prognostic model was constructed by incorporating all 5 prognostic factors, and patients were categorized into 3 risk groups: patients without any prognostic factors (low-risk, n = 55), patients with 1 prognostic factor (intermediate-risk, n = 32), and patients with 2 or more prognostic factors (high-risk, n = 37). Overall survival from initiation of second-line chemotherapy was 23.5 months (95% CI, 18.7–not reached), 14.6 months (95% CI, 8.4–19.9), and 5.5 months (95% CI, 4.2–8.9), respectively (Figure 1).

Significant survival differences among the 3 risk groups were observed ($p < .001$). PFS of second-line chemotherapy of each risk groups was 6.1 months (95% CI, 4.1–8.5), 3.4 months (95% CI, 2.3–5.4), and 2.6 months (95% CI, 1.6–2.9), respectively (Figure 2), and significant differences were observed between each groups ($p < .001$). If we limited the patients who did not receive anti-EGFR antibody (n = 91), a similar difference in overall survival was observed in these 3 risk groups (median 18.8 months vs 14.1months vs 5.0 months, $p < .001$).

Salvage chemotherapy after disease progression was performed in 95% (46 of 48 progressed patients) of good-risk patients, 67% (21 of 31 progressed patients) of intermediate-risk patients, and 41% (15 of 36 progressed patients) of high-risk patients; all between-group differences were statistically significant ($p < .001$).

DISCUSSION

In this study, we identified 5 independent prognostic factors in patients with MCRC undergoing irinotecan-based second-line chemotherapy after first-line FOLFOX. Additionally, we defined 3 risk groups using these 5 prognostic factors that significantly differed in survival rate and probability of receiving further salvage chemotherapy. To the best of our knowledge, this is the first report to evaluate pretreatment clinical prognostic factors in MCRC patients undergoing second-line therapy. These results may be useful when selecting the appropriate treatment line for cetuximab.

Cetuximab appears to improve the prognosis of MCRC patients when used in the third-line setting compared to best supportive care alone, and irinotecan plus cetuximab has been shown to result in a higher response rate in patients with irinotecan-refractory MCRC (over half of whom also had oxaliplatin-refractory disease) compared to cetuximab alone.[5,6] In contrast, the combination of irinotecan plus cetuximab did not improve overall survival in the second-line setting following first-line oxaliplatin-based chemotherapy.[7]

Based on these results, it may be optimal to use cetuximab in the third-line setting due to its toxicity profile and ability to restore irinotecan responsiveness even after irinotecan failure. However, considering the efficacy of cetuximab in MCRC, opportunities to administer cetuximab to MCRC patients, particularly those with wild-type *KRAS* disease, should not be missed.[9–12]

Our risk classification results suggest that cetuximab is not required during second-line treatment in low-risk patients due to their favorable prognosis (almost as long as first-line treatment [> 20 months]) and higher probability of receiving salvage chemotherapy (> 90%). In contrast, it might be optimal to use cetuximab in the second-line setting for high-risk patients with wild-type *KRAS* disease, to ensure that the opportunity to use cetuximab is not lost.

Determination of the optimal treatment for patients with intermediate-risk disease is more challenging and should therefore be conducted on an individual basis. For example, as PS2 had a significantly higher HR compared to other prognostic factors, cetuximab may be appropriate in second-line treatment of PS2 patients without prognostic factors. Risk classification may also

Table 2. Univariate survival analysis

Characteristic	Cut-off	n	HR	95% CI	*p* value
Age (years)	< 65	50	0.85	0.53–1.36	.51
	≥ 65	74	ref		
Gender	Male	74	0.61	0.38–0.98	.04
	Female	50	ref		
Performance status	0–1	111	ref		
	2	13	4.2	2.3–7.6	< .001
Pathology	Well to mod	115	ref		
	Por	9	3.4	1.7–6.9	.001
Peritoneal metastasis	Yes	26	3.1	1.87–5.1	< .001
	No	98	ref		
Liver metastasis	Yes	69	1.37	0.86–2.1	.18
	No	55	ref		
Metastatic site	1 or 2	99	ref		
	≥ 3	25	1.94	1.12–3.36	.017
Response to FOLFOX	Responder	54	ref		
	Nonresponder	70	1.92	1.18–3.2	.008
Cause of oxaliplatin discontinuation	Progression	65	2.18	1.36–3.49	.001
	Other	59	ref		
PFS of first-line FOLFOX (months)	< 6 months	49	2.95	1.81–4.81	< .001
	≥ 6 months	75	ref		
Leukocyte count (/L)	$< 8\times10^9$	110	ref		
	$> 8\times10^9$	14	3.7	1.97–6.9	< .001
ALP (IU/L)	< 400	70	ref		
	≥ 400	54	1.81	1.13–2.9	.013
LDH (IU/L)	< 400	98	ref		
	≥ 400	26	2.78	1.61–4.8	< .001
CEA (ng/mL)	< 500	110	ref		
	≥ 500	14	2.36	1.26–4.1	.007

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; CI = confidence interval; CR = complete response; HR = hazard ratio; LDH = lactate dehydrogenase; mod = moderately differentiated adenocarcinoma; PD = progressive disease; PFS = progression-free survival; por = poorly differentiated adenocarcinoma; PR = partial response; ref = reference value; SD = stable disease; wel = well-differentiated adenocarcinoma.

Table 3. Multivariate survival analysis[1]

Factors	HR	*p* value	95% CI
Performance status 2	4.8	< .001	2.55–10.2
Pathologic por	3.50	.002	1.60–7.96
Peritoneal met	2.10	.009	1.20–3.68
LDH ≥ 400 (IU/L)	2.05	.019	1.13–3.74
PFS < 6 months	1.80	.040	1.08–3.01

[1]Adjusted by gender, liver metastasis, metastatic sites, response to FOLFOX, cause of oxaliplatin discontinuation, leukocyte count, ALP, and CEA.
Abbreviations: CI = confidence interval; HR = hazard ratio; LDH = lactate dehydrogenase; met = metastasis; PFS = progression-free survival; por = poorly differentiated adenocarcinoma.

be important for designing future clinical trials evaluating second-line treatment of MCRC and should be included as a stratifying factor considering the significantly different prognosis of each risk group.

This analysis had several methodologic limitations. First, it was a retrospective cohort design that evaluated the association between various prognostic factors and overall survival in patients who received several irinotecan-containing regimens (FOLFIRI, irinotecan, and S-1 plus irinotecan). However, the classification system used in this study has also proven to be similarly useful when patients are stratified by treatment regimen or bevacizumab use.

Second, the utility of salvage chemotherapy other than cetuximab or panitumumab is unknown, as no other treatment has been demonstrated to prolong the survival of patients with MCRC. However, the probability of receiving salvage chemotherapy in our study suggests the possibility that patients may have a chance to receive benefit from third-line chemotherapy, including anti-EGFR antibody therapy (in wild-type *KRAS* cases).

Third, *KRAS* status was not evaluated in all patients, since most of the patients initiated treatment before the introduction of cetuximab. As cetuximab should only be used in patients with wild-type *KRAS* disease, *KRAS* status should be evaluated in all patients prior to selection of third-line

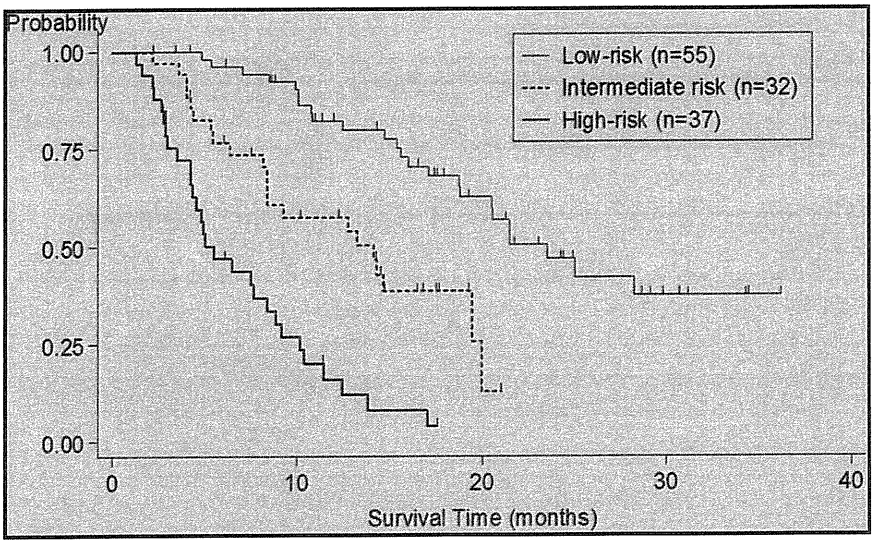

Figure 1. Overall survival according to risk group. Median overall survival from initiation of second-line chemotherapy was 23.5 months (95% CI, 18.7–not reached) in the low-risk group, 14.6 months (95% CI, 8.4–19.9) in the intermediate-risk group, and 5.5 months (95% CI, 4.2–8.9) in the high-risk group.

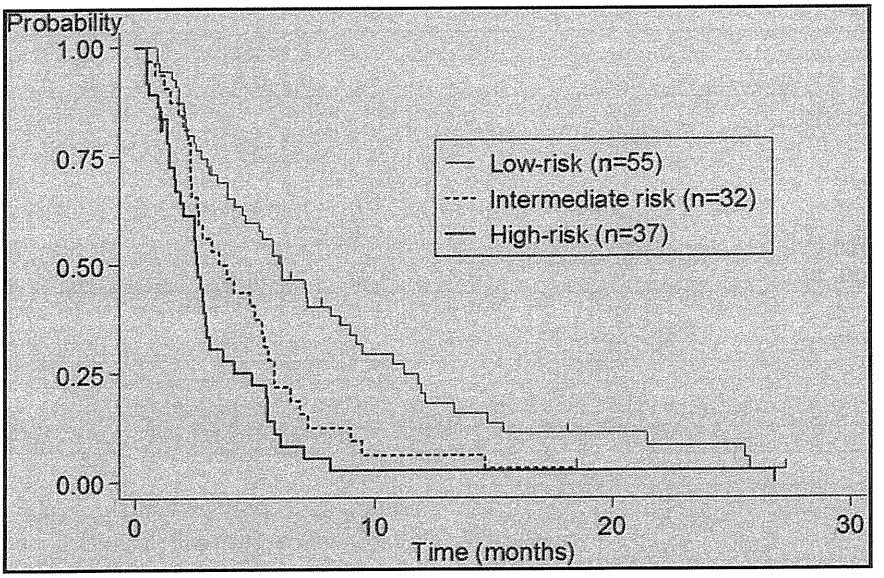

Figure 2. Progression free survival according to risk group. Median progression free survival from initiation of second-line chemotherapy was 6.1 months (95% CI, 4.1–8.5) in the low-risk group, 3.4 months (95% CI, 2.3–5.4) in the intermediate-risk group, and 2.6 months (95% CI, 1.6–2.9) in the high-risk group.

chemotherapy. Finally, the moderate sample size of this study necessitates confirmation of these results in a large cohort study, similar to the EPIC study.

In summary, several prognostic factors for survival after second-line therapy for MCRC and probability of receiving salvage chemotherapy were identified in this study. This risk classification system might be useful for determining which patients should receive cetuximab in the second-line setting rather than the third-line setting.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

—Note—

進行・再発大腸がん患者の mFOLFOX6 及び FOLFIRI 療法における悪心・嘔吐発現状況に関する後ろ向き調査

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Induced Nausea and Vomiting Induced by mFOLFOX6 and FOLFIRI with Advanced Colorectal Cancer: A Retrospective Survey

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Controlling of chemotherapy-induced nausea and vomiting (CINV) is very important for the continuation of chemotherapy, especially for outpatients. CINV can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. In this retrospective study, we investigated the incidence of CINV induced by mFOLFOX6 and FOLFIRI in 59 outpatients (32 males and 27 females) with advanced colorectal cancer to evaluate CINV severity using the Common Terminology Criteria for Adverse Events v.3.0. The incidence of nausea in the female group receiving FOLFIRI (grade 1: 66.7% and grade 2: 20.0%) was significantly higher than that in the male group (grade 1: 23.1% and grade 2: 7.7%, $p=0.0066$). The incidence of nausea in the younger (<63 years old) group receiving FOLFIRI (grade 1: 57.1% and grade 2: 28.6%) was significantly higher than that in the older (≧63 years old) group (grade 1: 35.7%, $p=0.0031$). Multivariable logistic regression analysis indicated that patients who were female or younger had a significantly higher incidence of nausea or vomiting than patients who were male or older, respectively, when treated with FOLFIRI. This suggests that gender (female) and age (younger) are factors predicting poor antiemetic control in outpatients receiving FOLFIRI, but not those treated with mFOLFOX6. Information on such predictive factors should be useful to promote the effectiveness of cancer chemotherapy.

Key words——antiemesis; chemotherapy-induced nausea and vomiting (CINV); FOLFIRI; mFOLFOX6; age; gender

緒　　言

がん化学療法の副作用の中で患者にとって最もつらい症状の1つである悪心・嘔吐に対する支持療法では，5-hydroxytryptamine-3 受容体拮抗剤 (5-HT_3) と dexamethasone (Dexa)，及び高度催吐性薬剤に対しては aprepitant を併用することが American Society of Clinical Oncology (ASCO) や National Comprehensive Cancer Network (NCCN) のガイドラインで推奨され，その発現リスク別の支持療法も示されている.[1,2] また最近，日本においても制吐薬適正使用ガイドライン[3]が出版されたが，かならずしもガイドラインに沿った支持療法が化学療法時に用いられているわけではないとの報告もあり，ガイドラインに基づいた制吐支持療法の実施が求められている.[4]

一方，外来で行われるがん化学療法は年々増加している．その背景には，副作用の少ない化学療法レジメンの開発や，支持療法剤の進歩により，外来でも安全に管理することが可能となった[5]こと，それにより患者の生活スタイルが維持されるようになったこと，さらには外来化学療法加算の創設が挙げられる．これらの利点を最大限に活かすためには，抗がん剤の投与時のみならず在宅時に発現する副作用

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についても，その発現状況を正確に把握するとともに，適切な支持療法の実施に努めることが重要である．また，悪心・嘔吐の発現リスクが高まる患者個別の因子として，女性あるいは若年者が高度催吐リスクに分類されているcisplatinで報告[6,7]されているが，中等度催吐リスクに分類されている薬剤については，同様な関連性を示す報告はない．

そこで今回，中等度催吐リスクに分類されている薬剤について悪心・嘔吐の発現リスクを把握し，適正な制吐支持療法を実施する目的で，特に進行・再発大腸がん患者において広く実施されているmFOLFOX6療法及びFOLFIRI療法に着目した．これらのレジメンはともに進行・再発大腸がんの一次治療及び二次治療で用いられ，同等の効果であると報告[8]されているが，副作用の特徴は異なっている．悪心・嘔吐の発現頻度は報告[8]されているが，患者個別の因子に関する報告はない．今回，これらのレジメンを実施した患者を対象に，診療記録を用いた後ろ向き調査にて検討を行ったところ，若干の知見を得たので報告する．

方　　法

1. 対象患者　愛知県がんセンター中央病院において，2009年6月25日から2010年5月25日までに外来化学療法室にて制吐支持療法として5-HT_3及びDexaの前投薬を含むmFOLFOX6療法又はFOLFIRI療法を施行された進行・再発大腸がん患者を対象とした．ただし，抗がん剤投与が初回の患者，オピオイドを併用していた患者は対象より除外した．本研究の実施に当たり，愛知県がんセンター倫理審査委員会の承認を得た（受付番号3-26）．

2. 調査方法　全対象症例の診療録（医師記録，看護記録，薬剤管理指導記録）及び処方・注射オーダリング情報より，年齢，性別，Performance Status (PS)，合併症，及び悪心・嘔吐の発現を調査した．悪心・嘔吐に関しては，Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v. 3.0) に基づき，前回の化学療法後から今回の来院時までの発現についてGrade評価された記録を抽出した．なお，調査期間中に調査日を6回設け，調査日直近に実施された化学療法について調査し，前回までの調査で対象とした患者は除外した．調査日の設定については，事前に対象患者の情報を得ることなく設定した．

3. 患者個別因子の検討　悪心・嘔吐の発現頻度と性別及び年齢との関連性の検討を，mFOLFOX6療法を施行した患者及びFOLFIRI療法を施行した患者とに分けて行った．2群比較にて発現頻度と性別及び年齢の関連性を検討した後，各因子の交絡による影響を除いた結果を得るため，ロジスティック解析を行った．なお，年齢の2群比較については，全体の中央値であった63歳を基準とし，63歳未満群及び63歳以上群の2群に分けて比較した．

4. 統計学的解析　Grade評価を含めた悪心・嘔吐の発現頻度の比較には，2群比較ではMann-Whitney *U*-testを用い，$p<0.05$の場合を有意とした．ロジスティック解析についてはエクセル統計2008（株式会社社会情報サービス）を用いて行い，$p<0.05$の場合を有意とした．

結　　果

1. 患者背景　患者背景をTable 1に示す．mFOLFOX6療法が施行された患者群とFOLFIRI療法が施行された患者群との間で患者背景に差は認められず，また特記すべき合併症もなかった．mFOLFOX6療法及びFOLFIRI療法のレジメンについて，Table 2に示した．

2. 悪心・嘔吐発現状況　mFOLFOX6療法が施行された患者群では，悪心の発現頻度はGrade 1が45.2% (14/31)，Grade 2が3.2% (1/31)であり，嘔吐の発現頻度はGrade 1が12.9% (4/31)，Grade 2が3.2% (1/31) であった．FOLFIRI療法が施行された患者群では，悪心の発現頻度はGrade 1が46.4% (13/28)，Grade 2が14.3% (4/28) であり，嘔吐の発現頻度はGrade 1が14.3% (4/28)，Grade 2が3.6% (1/28) であった．両群の間に違いは認められなかった [Mann-Whitney *U* test, $p=0.1972$ (悪心)，$p=0.8613$ (嘔吐)]．

制吐支持療法については，5-HT_3及びDexaの前投薬について薬剤又は投与量の違いが認められた．前投薬の5-HT_3は1例でazasetron 10 mg，それ以外ではgranisetron 3 mg，同じく前投薬のDexaは5例で16 mg，1例で12 mg，それ以外では8 mgであった．また，化学療法後にDexaが12例で投与されていた．

mFOLFOX6療法が施行された患者群では，化学

Table 1. Characteristics of Patients

	All	mFOLFOX6	FOLFIRI
Number of patients	59	31	28
Gender			
Male/Female	32/27	19/12	13/15
Age			
Median	63	64	63
Range	40–82	46–82	40–74
Performance status			
0/1/2	10/48/1	5/25/1	5/23/0
Number of prior chemotherapy			
1/2/3/4/5	11/23/14/5/6	8/9/9/2/3	3/14/5/3/3
Number of cycle			
Median	5	4	6
Range	2–33	2–11	2–33
Relative dose intensity			
Average	93.1	95.2	90.7
Range	60–100	65–100	60–100

Table 2. Chemotherapy Regimens

		Number of patients	
		Male	Female
mFOLFOX6	L-OHP 85 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, every 2 weeks	4	2
mFOLFOX6+BV	L-OHP 85 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, BV 5 or 10 mg/kg, every 2 weeks	15	10
FOLFIRI	CPT-11 150 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, every 2 weeks	2	1
FOLFIRI+BV	CPT-11 150 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, BV 5 or 10 mg/kg, every 2 weeks	11	14

BV: bevacizumab, CPT-11: irinotecan, L-OHP: oxaliplatin.

療法後のDexa投与ありの場合，Grade 1が60.0% (3/5)であり，化学療法後のDexa投与なしの場合，Grade 1が42.3% (11/26)，Grade 2が3.8% (1/26)であった．FOLFIRI療法が施行された患者群では，化学療法後のDexa投与ありの場合，Grade 1が14.3% (2/7)，Grade 2が14.3% (2/7)であり，化学療法後のDexa投与なしの場合，Grade 1が52.4% (11/21)，Grade 2が9.5% (2/21)であった．いずれにおいても化学療法後のDexa投与有無による有意な差は認められなかった [Mann-Whitney U test, $p>0.9999$ (mFOLFOX6), $p=0.7498$ (FOLFIRI)]．同様に嘔吐でも化学療法後のDexa投与有無による発現頻度の違いは認められなかった．

3. 悪心・嘔吐の発現頻度に及ぼす性別の影響

mFOLFOX6療法では男性と女性で有意な差は認められなかった (Table 3)．FOLFIRI療法では悪心の発現頻度について女性が，男性と比較して有意に高率であった (Table 3)．

4. 悪心・嘔吐の発現頻度に及ぼす年齢の影響

mFOLFOX6療法では63歳未満群と63歳以上群で有意な差は認められなかった (Table 3)．FOLFIRI療法では悪心・嘔吐の発現頻度について63歳未満群が63歳以上群と比較して有意に高率であった (Table 3)．

5. レジメン別悪心・嘔吐の発現に関連する因子の多変量解析 各レジメンにおける悪心・嘔吐の発現頻度と性別及び年齢との関連性についてロジスティック回帰分析を行い，性別と年齢の交絡を調整した結果を得た (Table 4)．FOLFIRI療法において，悪心については性別のオッズ比は17.69であ

り，女性での発現頻度が有意に高かった．嘔吐については性別のオッズ比は10.49であり，女性での発現頻度が高い傾向にあったが有意差は認められなかった．年齢ではオッズ比が0.85であり，若年者で発現頻度が有意に高かった．mFOLFOX6療法では性別，年齢による悪心・嘔吐発現頻度の有意差は認められなかった．

考　　察

今回，外来化学療法における制吐支持療法を用いたmFOLFOX6療法及びFOLFIRI療法における悪心の発現リスク因子について小規模ながら見い出すことができた．

Table 3. Effects of Gender and Age on Nausea (a) and Vomiting (b) Induced by mFOLFOX6 or FOLFIRI

(a) Nausea

		mFOLFOX6				FOLFIRI			
		G0	G1	G2	p value	G0	G1	G2	p value
Gender	Male	9	9	1	0.4885	9	3	1	*0.0066
	Female	7	5	0		2	10	3	
Age	<63	5	10	0	0.1685	2	8	4	*0.0031
	≧63	11	4	1		9	5	0	

(b) Vomiting

		mFOLFOX6				FOLFIRI			
		G0	G1	G2	p value	G0	G1	G2	p value
Gender	Male	16	2	1	>0.9999	12	1	0	0.1887
	Female	10	2	0		11	3	1	
Age	<63	12	3	0	0.6427	9	4	1	*0.0157
	≧63	14	1	1		14	0	0	

G0, G1, G2: Grade 0, Grade 1, Grade 2 (Common Terminology Criteria for Adverse Events version 3.0). Mann-Whitney U-test. *$p<0.05$.

FOLFIRI療法誘発性の悪心・嘔吐においては女性あるいは若年者で発現リスクが高まる傾向が見い出され，ASCOガイドラインや制吐剤適正使用ガイドラインに記載されている内容を支持するものであった．一方，mFOLFOX6誘発性悪心・嘔吐の発現リスク因子については，若年者で発現リスクが高まる傾向はあったが有意差は認められず，性別についてはFOLFIRIと同様な傾向は認められなかった．

mFOLFOX6療法とFOLFIRI療法の選択において，いずれも進行・再発大腸がんの一次及び二次治療として国際的ガイドラインで推奨されているが，本研究ではmFOLFOX6が一次治療に選択されている症例がほとんどであり，患者背景による選択の違いはなかった．また，先行化学療法での悪心・嘔吐の発現状況については，今回は後ろ向き調査であったため評価していないが，本研究では無作為に特定の日に治療を受けた患者を抽出して調査を行っているため結果に大きく影響することはないと考えられる．

制吐支持療法については5-HT_3及びDexaの前投薬を含む患者を対象としたが，5-HT_3及びDexaの前投薬について薬剤又は投与量の違いが認められ，また5-HT_3及びDexaの前投薬以外の制吐剤が併用されている症例もあった．前投薬の5-HT_3は1例でazasetron 10 mg，それ以外ではgranisetron 3 mgであったが，これらの薬剤の制吐効果は同等であると報告されている．[9] 前投薬のDexaが8 mgより多かった6例のうち5例，化学療法後にDexaが処方されていた12例のうち7例で悪心が発現していたが，年齢，性別，及びレジメンに偏りはなかった．このうち遅発性の悪心・嘔吐発現に影響すると考え

Table 4. Multivariable Logistic Regression Analysis

	Relative factor	Odds ratio	(95% Confidence Interval)	p value
1. mFOLFOX6				
Nausea	Gender (Male *vs.* Female)	0.64	(0.13–3.10)	0.58
	Age	0.91	(0.81–1.01)	0.09
Vomiting	Gender (Male *vs.* Female)	1.08	(0.15–7.76)	0.94
	Age	0.96	(0.85–1.08)	0.52
2. FOLFIRI				
Nausea	Gender (Male *vs.* Female)	17.69	(2.20–142.1)	0.007
	Age	0.91	(0.82–1.01)	0.09
Vomiting	Gender (Male *vs.* Female)	10.49	(0.39–284.7)	0.16
	Age	0.85	(0.74–0.99)	0.04

られる化学療法後のDexa投与有無による悪心・嘔吐の発現頻度を比較したところ，違いは認められなかった．さらに5-HT_3及びDexa以外の制吐剤について，59例中16例で処方がされていたが，服用状況については確認できなかった．16例の処方内容としては，メトクロプラミドやラモセトロンの内服，ドンペリドン坐薬，及び予測性嘔吐を抑制するといわれているベンゾジアゼピン系薬剤等であった．処方されていた患者のうち13例が悪心・嘔吐発現例であり，そのうち9例が女性，10例が63歳未満であった．よって，これらの制吐剤がリスクを軽減することによるリスク因子に対する影響があったとは考え難く，今回見い出されたリスク因子の結果には影響を及ぼしていないと考えられる．

mFOLFOX6とFOLFIRIは5-FUとlevofolinateの併用療法に，oxaliplatin（L-OHP）又はirinotecan（CPT-11）を組み合わせたレジメンである．L-OHPとCPT-11はASCOのガイドラインにて中等度催吐性薬剤に分類されており，これまでに報告された悪心・嘔吐発現頻度は同等である．[10-12] CPT-11の薬理作用として，アセチルコリンエステラーゼを阻害することが知られているが，嘔吐中枢にはセロトニン受容体だけではなく，アセチルコリン受容体も存在している．CPT-11により引き起こされる悪心・嘔吐では，抗がん剤による嘔吐中枢の直接刺激だけでなく，アセチルコリンによる刺激も関与している可能性が考えられ，この作用機序の違いが悪心のリスク因子の違いに影響を及ぼしているのかもしれない．また，これまでに女性あるいは若年者で悪心・嘔吐の発現リスクが高まる傾向にあると報告されているのは，高度催吐リスクに分類されているcisplatinである[6,7]が，同じプラチナ系抗がん剤であるL-OHPでは同様のリスク因子が見い出されなかった．このように，同じ催吐性のある抗がん剤でも，悪心・嘔吐発現因子が異なる可能性が示唆されたため，今後はこの点にも配慮した副作用調査を行ったうえで，それぞれの催吐リスクに応じた対策が必要であると考えられた．

今回の調査で悪心の発現頻度が高かったFOLFIRI投与中の女性あるいは若年者に対しては，制吐支持療法を強化して悪心発現の予防に努めることが重要であると思われる．ASCOのガイドラインでは，中等度催吐性抗がん剤投与時における制吐支持療法として，5-HT_3及びDexaの前投薬と，投与後のステロイド剤内服を推奨しており，[2] CPT-11により誘発される悪心に対して，ステロイド剤の3日間投与が有効であることも報告されている．[13] また，制吐剤適正使用ガイドラインでは，中等度催吐性抗がん剤使用時のオプションとして，carboplatin, ifosfamide, methotrexate，並びにCPT-11など使用時にはaprepitantの併用も推奨されているため，今後さらに詳細な検討をしていきたい．

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