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Impact of sex and histology on the therapeutic effects of fluoropyrimidines and oxaliplatin plus bevacizumab for patients with metastatic colorectal cancer in the SOFT trial

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Abstract: Mechanisms accounting for sex differences in the incidence of adverse events caused by fluoropyrimidine treatments, and histologic differences in efficacy are insufficiently understood. We determined differences between the sexes in terms of the safety of S-1 plus oxaliplatin (SOX)/bevacizumab-versus-l-leucovorin, 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX)/bevacizumab, and the impact of histology on their therapeutic effects, in 512 unresectable metastatic colorectal cancer patients from the SOFT phase III study. Nausea (OR: 2.88, $P < 0.001$) and vomiting (OR: 3.04, $P = 0.005$) occurred more frequently in females than males treated with SOX/bevacizumab, while nausea (OR: 2.12, $P = 0.006$), vomiting (OR: 3.26, $P = 0.004$), leukopenia (OR: 2.61, $P < 0.001$), neutropenia (OR: 2.92, $P < 0.001$), and alopecia (OR: 4.13, $P < 0.001$) were higher in females on FOLFOX/bevacizumab. Mean relative dose intensities (RDIs) of S-1 during all cycles of SOX/bevacizumab were significantly lower in females (73.9%) than males (81.5%) ($P < 0.001$), while RDIs of continuous infusion of 5-FU in the FOLFOX/bevacizumab regimen were 75.0% in females and 80.5% in males ($P = 0.005$). No significant differences in efficacy with regard to overall survival (OS) and progression-free survival (PFS) were identified between the sexes for either SOX/bevacizumab or FOLFOX/bevacizumab treatment. Patients with poorly-differentiated adenocarcinoma had significantly worse OS (HR: 2.72, 95% CI: 1.67-4.44, $P < 0.0001$) and PFS (HR: 1.89, 95% CI: 1.18-3.02, $P = 0.0079$) than patients with well- or moderately-differentiated adenocarcinoma. Female patients experienced more frequent and severe adverse reactions to SOX/bevacizumab and FOLFOX/bevacizumab and a worse prognosis for poorly-differentiated adenocarcinoma were confirmed in this phase III study. This warrants further translational research to identify the responsible mechanisms.

***Keywords*:** gender, fluorouracil, S-1, poorly differentiated adenocarcinoma, bevacizumab

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths worldwide (*1*). Fluoropyrimidines and their biochemical modulators have been key drugs used in strategies for treating patients with metastatic colorectal cancer for more than 6 decades. FOLFOX (leucovorin, 5-fluorouracil (5-FU), and oxaliplatin) or FOLFIRI (leucovorin, 5-FU, and irinotecan) plus bevacizumab have been widely used as first-line treatment options for metastatic colorectal cancer (*2,3*). The SOFT trial showed that oral S-1 and oxaliplatin

(SOX) plus bevacizumab was non-inferior to FOLFOX plus bevacizumab and the TRICOLORE (*4*) study showed that S-1 and irinotecan plus bevacizumab was non-inferior to FOLFOX or capecitabine/oxaliplatin (CapeOX) plus bevacizumab for progression-free survival (PFS), thereby establishing the therapeutic usefulness of this agent (*5-7*). S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-FU, with two modulators. The first of these, gimeracil, reversibly inhibits DPD, the primary metabolizing enzyme of 5-FU, and thus maintains higher 5-FU levels in the blood for a longer period of time. The second is oteracil potassium, which suppresses, and thereby decreases, the activity and toxicity of 5-FU for normal gastrointestinal tissue (*8*). In patients with compromised renal function, gimeracil clearance is decreased, leading to high concentrations of 5-FU in blood and an increased risk of 5-FU-related side effects (*9*). Previously, we found that the incidence of grade 3 or higher diarrhea in metastatic colorectal cancer patients in the SOFT trial who were treated with SOX and bevacizumab depended on renal function (*5*). Thus, the incidence of diarrhea in patients with a creatinine clearance (Ccr) of < 70 mL/min before treatment exceeded 20% and tended to be higher than in patients with a Ccr of ≥ 70 mL/min.

It had been previously established that female patients treated with fluoropyrimidines developed leukopenia, stomatitis, diarrhea, nausea, vomiting, and alopecia more often and more severely than males (*10-15*). It was suggested that poorer clearance of 5-FU, reduced activity of dihydropyrimidine dehydrogenase (DPD; the initial enzyme in the catabolism of 5-FU (*10,16*)), and polymorphism of DPD or thymidylate synthase (*13,17*) are possible causes of such sex-related differences in adverse events during fluoropyrimidine treatment. However, the fundamental cause of this perceived sex difference is not yet known. DPD expression and activity in human liver did not reveal any sex-related differences (*13*). Dose modification and the administration schedule of 5-FU, and changing optimal supportive therapies for female patients, are not usually considered and are not implemented in clinical practice. Sex differences in the toxicity of anti-cancer agents are not only observed for 5-FU but also cisplatin, doxorubicin, and other anti-cancer agents (*18*). Female patients had significantly higher rates of nausea and vomiting, but the cause of the sex discrepancy is also unknown (*19*). We need to investigate any sex differences in disease and biological response in comparison of males and females genetically and epigenetically.

Several reports have documented a poor prognosis for advanced resectable colorectal cancer with poorly-differentiated adenocarcinoma histology relative to well- or moderately-differentiated adenocarcinoma. However, whether this also applies to unresectable metastatic cancer during palliative chemotherapy was not known (*20,21*). Poorly-differentiated adenocarcinoma is closely associated with the presence of microsatellite instability (MSI) and is found more often in females. Microsatellite unstable poorly-differentiated adenocarcinoma (23%, 12/53), which is characterized as having a right colon predilection, larger size, and infrequent lymph node metastasis, has a better prognosis than microsatellite-stable poorly-differentiated adenocarcinoma (74%, 41/53) (*22,23*).

In the present study, we aimed to evaluate and compare the safety of the SOX plus bevacizumab and FOLFOX plus bevacizumab regimens in female and male patients with metastatic colorectal cancer and the impact on histological tumor type treatment efficacy.

Patients and Methods

Patients

The SOFT trial was a randomized, open-label, phase III study that compared the efficacy and safety of the SOX/bevacizumab and FOLFOX/bevacizumab regimens in patients with unresectable advanced or recurrent metastatic colorectal cancer (*5*). SOX/bevacizumab was confirmed to be non-inferior to FOLFOX/bevacizumab in 512 randomized patients. In the SOX/bevacizumab regimen, S-1 was given orally for the first 2 weeks of a 3-week cycle, oxaliplatin at a dose of 130 mg/m^2 and bevacizumab at 7.5 mg/kg infused on day 1. In the FOLFOX/bevacizumab regimen, patients received a 5 mg/kg intravenous infusion of bevacizumab and a simultaneous intravenous infusion of 85 mg/m^2 oxaliplatin, 200 mg/m^2 *l*-leucovorin, 400 mg/m^2 bolus fluorouracil, and 2,400 mg/m^2 infused fluorouracil (46 h) delivered with an infusion pump on day 1 to 2 of a 2-week cycle. A 5-hydroxytryptamine-3 (5-HT$_3$) receptor antagonist and dexamethasone were usually given to patients treated with either SOX or FOLFOX. The Ccr was estimated using the Cockcroft-Gault equation.

Statistical analysis

We did analyses of survival by modified intention to treat: we excluded individuals who underwent randomization but who were subsequently shown not to meet inclusion criteria. Patients who received at least one dose of the assigned study drugs were included in analyses of safety.

The incidence of adverse events during the first 8 weeks and then all periods was compared between the two regimens using Fisher's exact test and logistic regression for males and females separately. Multivariate analyses for toxicities were also carried out using a logistic regression model. Adverse events were assessed in accordance with the Common Terminology Criteria for Adverse Events version 3.0. Median OS and PFS were estimated using the Kaplan-Meier method. Statistical significance was considered to be $P < 0.05$.

Multivariate analyses by Cox proportional hazards model was used to estimate hazard ratios (HRs) of prognostic factors for OS and PFS. Treatment delivery was evaluated for females and males in both treatment groups.

Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Baseline characteristics of all patients enrolled in the SOFT study were similar in the two sexes and in the treatment groups, although the proportion of patients with liver metastases in the SOX/bevacizumab group was higher in females than males. The proportion of female patients treated with SOX/bevacizumab and FOLFOX/bevacizumab was 33% (83/250) and 37% (93/249), respectively, for primary analysis (Table 1).

Safety

The most common hematologic adverse events of grade 3 or higher were leukopenia in 21 (8%) of 249 patients given FOLFOX/bevacizumab *vs*. 6 (2%) of 250 given SOX/bevacizumab ($P = 0.0029$) and neutropenia in 84 (34%) *vs*. 22 (9%) ($P < 0.0001$). Grade 3 or higher diarrhea in 23 (9%) *vs*. 7 (3%) ($P = 0.0040$) were significantly more common in patients given SOX/bevacizumab than in those given FOLFOX6/bevacizumab. Adverse events are shown in Table 2 (Appendix). Female patients treated with SOX/bevacizumab developed nausea and vomiting significantly more frequently than males, while females treated with FOLFOX/bevacizumab exhibited more leukopenia, neutropenia, nausea, vomiting, and alopecia 8 weeks after the beginning of each treatment cycle and over the entire treatment period. The difference between the sexes in the incidence of nausea and vomiting after FOLFOX/bevacizumab was more marked in patients with Ccr > 70 mL/min. According to multivariate analysis, sex was an independent predictive factor for nausea and vomiting due to SOX/bevacizumab, and for leukopenia, neutropenia, nausea, vomiting, and alopecia due to FOLFOX/

Table 1. Baseline characteristics of male and female patients

Items	SOX/Bev (n = 250)					FOLFOX/Bev (n = 249)				P
	Male (n = 167)		Female (n = 83)			Male (n = 156)		Female (n = 93)		
	n	%	n	%	P	n	%	n	%	
Age										
< 70	120	71.9	67	80.7	0.164	116	74.4	69	74.2	0.164
≥ 70	47	28.1	16	19.3		40	25.6	24	25.8	
Primary lesion										
Colon	80	47.9	48	57.8	0.422	76	48.7	47	50.5	0.422
Rectosigmoid	30	18.0	14	16.9		21	13.5	19	20.4	
Rectum	55	32.9	20	24.1		59	37.8	27	29.0	
Others	2	1.2	1	1.2		0		0		
Differentiation assessed by histology										
Well or moderate	148	88.6	67	80.7	0.223	135	86.5	77	82.8	0.223
Poorly	6	3.6	5	6.0		4	2.6	6	6.5	
Other	13	7.8	11	13.3		17	10.9	10	10.8	
Adjuvant chemotherapy for colorectal cancer										
No	142	85.0	72	86.7	0.849	128	82.0	83	89.2	0.849
Yes	25	15.0	11	13.3		28	18.0	10	10.8	
Target lesion										
No	12	7.2	9	10.8	0.340	11	7.0	11	11.8	0.340
Yes	155	92.8	74	89.2		145	93.0	82	88.2	
Liver metastases										
No	45	26.9	38	45.8	0.004	53	34.0	34	36.6	0.004
Yes	122	73.1	45	54.2		103	66.0	59	63.4	
Lung metastases										
No	93	55.7	50	60.2	0.501	87	55.8	47	50.5	0.501
Yes	74	44.3	33	39.8		69	44.2	46	49.5	
Lymph node metastases										
No	123	73.7	66	79.5	0.350	119	76.3	67	72.0	0.350
Yes	44	26.3	17	20.5		37	23.7	26	28.0	
Other metastases										
No	135	80.8	53	63.9	0.005	136	87.2	70	75.3	0.005
Yes	32	19.2	30	36.1		20	12.8	23	24.7	
Metastatic organs										
1	73	43.7	38	45.8	0.788	83	53.2	44	47.3	0.788
≥ 2	94	56.3	45	54.2		73	46.8	49	52.7	

P: Fisher's exact test. Bev, bevacizumab; FOLFOX, 5-FU/*l*-leucovorin plus oxaliplatin; SOX, S-1 plus oxaliplatin.

bevacizumab at 8 weeks and over all cycles (Table 3, Appendix). Thrombocytopenia with SOX/bevacizumab and FOLFOX/bevacizumab was more frequent in patients with Ccr < 70 mL/min and lower body mass index (BMI) after 8 weeks. Thrombocytopenia after FOLFOX/bevacizumab also developed more often in patients ≥ 70 years of age.

The mean relative dose intensities (RDIs) of S-1 during all cycles of SOX/bevacizumab were significantly lower in females (73.9%) than males (81.5%) ($P < 0.001$), while the RDIs of continuous infusion of 5-FU in FOLFOX/bevacizumab were 75.0% in females and 80.5% in males ($P = 0.005$) (Table 4, Appendix). The RDIs of oxaliplatin were not significantly different between female and male patients treated with either SOX/bevacizumab or FOLFOX/bevacizumab.

Efficacy

No significant differences in efficacy with regard to OS and PFS were identified between the sexes. The worse prognostic factor was poorly differentiated adenocarcinoma for OS ($P < 0.0001$) and PFS ($P = 0.0079$) (Table 5 and Table 6 (Appendix), Figure 1).

Discussion

Nausea and vomiting due to treatment with SOX/bevacizumab, and leukopenia, neutropenia, nausea, vomiting and alopecia due to FOLFOX/bevacizumab were more frequent in female patients than males in multivariate analysis. Sex differences in response to fluoropyrimidines and irinotecan combination therapy were also reported in a recent randomized trial, PETACC-3. These findings document a statistically significant and clinically relevant greater risk of nonhematological and objectively measurable hematological adverse events in female patients (*24*).

Nausea and vomiting are the most common adverse reactions associated with chemotherapy that can significantly diminish patient quality of life. To mitigate this, the use of 5-HT_3 receptor antagonists and dexamethasone have been recommended by the guidelines from the Japanese Society of Clinical Oncology (JSCO), the American Society of Clinical Oncology (ASCO), and the Multinational Association of Supportive Care in Cancer / European Society for Medical Oncology (MASCC/ESMO) (*25-27*). A Japanese phase III randomized controlled trial, the SENRI trial, was conducted in > 400 colorectal cancer patients treated with oxaliplatin-based chemotherapy. This trial established that a combination of 5-HT_3 receptor antagonists, dexamethasone and aprepitant/fosaprepitant was superior to the combination of 5-HT_3 receptor antagonists and dexamethasone alone in controlling nausea and vomiting over the entire treatment period, especially in the late phase (*28*). Other recent Japanese phase III trials have documented a

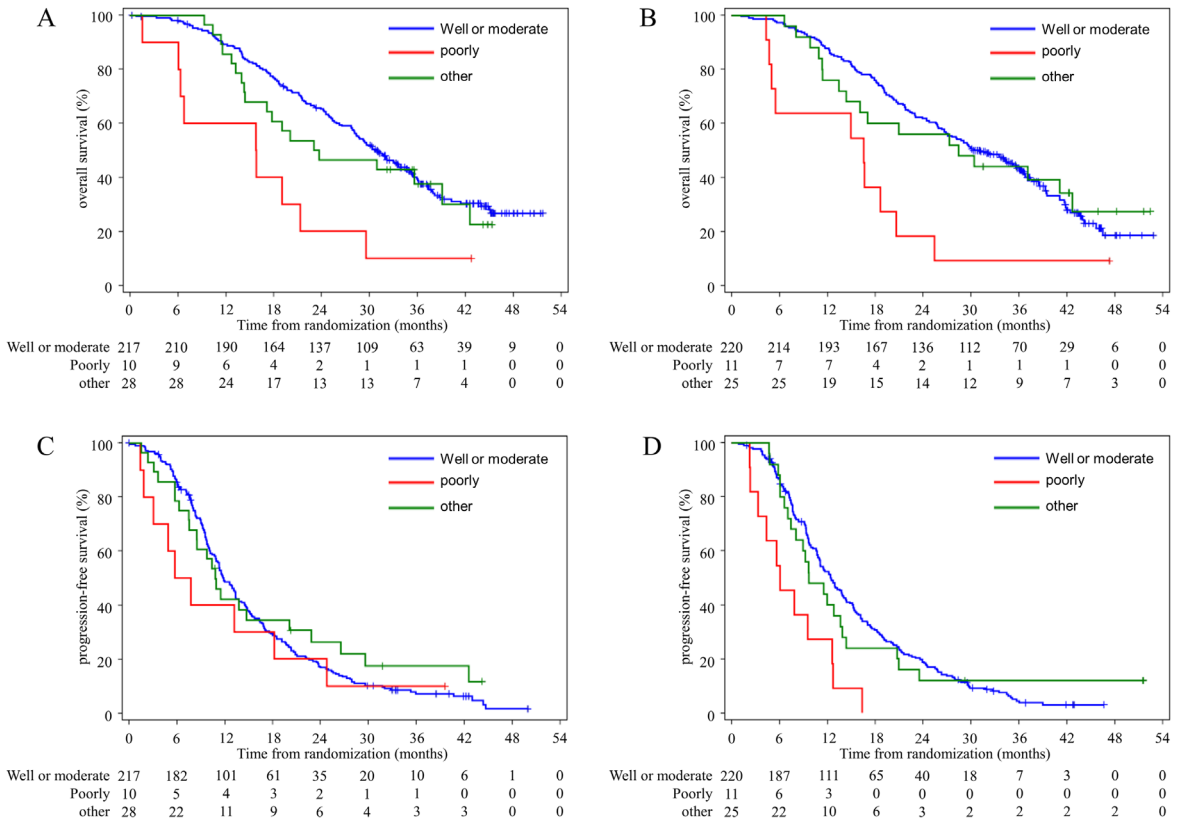

Figure 1. Kaplan-Meier estimates of overall survival according to histology of colorectal cancer treated with FOLFOX/Bev (A) or SOX/Bev (B) and progression-free survival with FOLFOX/Bev (C) and SOX/Bev (D) in the full dataset.

superior efficacy of dexamethasone on day 2 to 3, and olanzapine at a dose of 5 mg plus standard antiemetic therapy with 5-HT_3 receptor antagonists, aprepitant, and dexamethasone on day 1 (*29*). Female sex is a well-known risk factor for chemotherapy-induced nausea and vomiting, and we should therefore consider treatment options employing consecutive dexamethasone on day 2 to 3 and olanzapine for female patients receiving oxaliplatin-based regimens as is done for treatment with highly emetogenic chemotherapeutic agents (*25,30*).

Significantly more patients given FOLFOX/bevacizumab had grade 3 or higher leukopenia, neutropenia, and any grade of alopecia, than patients given SOX/bevacizumab, in a first analysis (*5*). In addition, females treated with FOLFOX/bevacizumab suffered leukopenia, neutropenia, and alopecia significantly more frequently than male patients. The proportions of patients with grade 3 or higher sensory neuropathy did not differ significantly between the groups. Ruzzo *et al.* recently reported that interactions of gene polymorphisms and sex on hematological toxicity of adjuvant therapy with FOLFOX or CapeOX were detected for MTHFR rs1801133 (*31*). In female patients, the ERCC1 rs11615 CC genotype worsened grade 3 or more neurological toxicity, as did XPD rs13181G, for example. Genomic effects have rarely been analyzed by sex, but such approaches may reveal sex differences in adverse events in the near future. Leukopenia and neutropenia occurred more often in patients ≥ 70 years of age, according to multivariate analysis. Decreased hematopoietic capacity and proliferation of monoclonal hematopoietic cells in the elderly may affect the higher incidence of leukopenia and neutropenia despite relatively mild SOX/bevacizumab effects on bone marrow suppression (*32*). Thrombocytopenia after SOX/bevacizumab was more frequent in patients with Ccr < 70 mL/min and lower BMI 8 weeks from the beginning of chemotherapy. Thrombocytopenia after FOLFOX/bevacizumab was also more common in patients with a lower Ccr, lower BMI, and aged ≥ 70 years. Cespedes Feliciano *et al.* reported that a higher proportion of patients in the lowest versus highest tertile of muscle mass experienced neutropenia (55% *vs.* 38%, $P = 0.008$) and thrombocytopenia (13% *vs.* 5%; $P = 0.02$) (*33*). Low muscle mass was associated with poor chemotherapy outcomes in that severe adverse events were more likely, either because patients with low muscle mass are over-dosed or because they are more frail or have an older functional age, conferring a higher risk of toxicity. However, no significant sex differences were observed in the incidence of subjective adverse reactions like stomatitis because patients could temporarily stop oral S-1 by themselves, depending on their symptoms, following their education in adequate self-administration routines. This is in contrast to infusions of 5-FU that patients cannot control themselves. The proportions of patients with grade 3 or greater diarrhea was significantly higher in the group given SOX/bevacizumab than in those given FOLFOX/bevacizumab, especially in patients with lower Ccr. On the other hand, there was no sex difference in the incidence of diarrhea.

A significantly more frequent incidence of nausea, vomiting, neutropenia, thrombocytopenia, and alopecia was seen with bolus 5-FU compared with its protracted venous infusion, similar to S-1 in terms of pharmacokinetics (*34,35*). 5-FU clearance is significantly lower in females than in males regardless of age and the dose given (*10*). Females receive supra-optimal doses compared with males (*36*) and higher plasma 5-FU concentrations are significantly related to more severe neutropenia and stomatitis (*37*). It would be difficult to explain the higher incidence of toxicities of 5-FU by rare DPYD variants. Only 3-5% of Caucasians have reduced DPD activity (*38-40*) and patients without a DPYD variant resulting in decreased or lack of function may still experience severe toxicity due to additional genetic, environmental, or other factors (*41,42*).

Although a significantly worse prognosis for poorly-differentiated adenocarcinoma was observed here, similar to previous reports (*20,21,43*), genomic analyses of somatic mutations or MSI were not carried out in the SOFT trial. Information on tumor location (right or left side) was also not recorded in this trial, other than whether the tumor was in the colon or rectum. Therefore, nothing can be said on this topic. Intensive anti-emetic therapy should be considered at least because of the higher incidence of nausea and vomiting in SOX/bevacizumab and FOLFOX/bevacizumab-treated female patients. It is difficult to argue for reducing the starting dose of SOX for female patients to compensate for the higher incidence of adverse events compared with males because severe toxicities are rarely induced by SOX. In conclusion, sex differences regarding adverse reactions during treatment with SOX/bevacizumab or FOLFOX/bevacizumab were confirmed in the SOFT study. This warrants further fundamental research to pursue the underlying cause.

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Conflict of interest

YY has received honoraria from Taiho, Chugai, Nipponkayaku, Japan. KM has received honoraria from Eli Lilly, Chugai, Takeda, Ono, Taiho, Sanofi, Bristol-Myers Squibb, and Bayer; and research funding from Parexel International, Merck Serono, Daiichi-Sankyo, Sumitomo-Dainippon Pharma, Shionogi, Pfizer, Mediscience Planning, and Solasia Pharma. HB has received honoraria from Taiho and Chugai; and research

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Table 2. Adverse events of any grade after 8 weeks of therapy and over the entire treatment period with S-1 plus oxaliplatin and bevacizumab or 5-FU/*l*-LV plus oxaliplatin and bevacizumab in patients stratified by creatinine clearance

	SOX/Bev (*n* = 250)							FOLFOX/Bev (*n* = 249)						
	Female (*n* = 83)		Male (*n* = 167)					Female (*n* = 93)		Male (*n* = 156)				
	n	%	*n*	%	Fisher *P*[(a)]	OR [95% CI]	*P*	*n*	%	*n*	%	Fisher *P*[(a)]	OR [95% CI]	*P*
8 weeks														
Leukopenia	30	36.1	47	28.1	0.244	1.45 [0.83-2.53]	0.198	63	67.7	70	44.9	<0.001	2.58 [1.51-4.41]	**<0.001**
CCr 70 mL/min >	9	50.0	12	40.0	0.558	1.50 [0.46-4.87]	0.500	22	75.9	13	44.8	0.031	3.87 [1.26-11.9]	**0.018**
70 mL/min≦	21	32.3	35	25.5	0.319	1.39 [0.73-2.65]	0.317	41	64.1	57	44.9	0.014	2.19 [1.18-4.07]	**0.013**
Neutropenia	26	31.3	50	29.9	0.884	1.07 [0.60-1.89]	0.823	61	65.6	63	40.4	<0.001	2.81 [1.65-4.80]	**<0.001**
CCr 70 mL/min >	10	55.6	10	33.3	0.147	2.50 [0.75-8.30]	0.135	18	62.1	11	37.9	0.114	2.68 [0.93-7.74]	**0.069**
70 mL/min≦	16	24.6	40	29.2	0.614	0.79 [0.40-1.55]	0.497	43	67.2	52	40.9	<0.001	2.95 [1.57-5.55]	**<0.001**
Thrombocytopenia	21	25.3	55	32.9	0.245	0.69 [0.38-1.25]	0.218	25	26.9	51	32.7	0.394	0.76 [0.43-1.34]	0.336
CCr 70 mL/min >	8	44.4	16	53.3	0.766	0.70 [0.22-2.27]	0.552	11	37.9	14	48.3	0.596	0.66 [0.23-1.86]	0.427
70 mL/min≦	13	20.0	39	28.5	0.230	0.63 [0.31-1.28]	0.201	14	21.9	37	29.1	0.305	0.68 [0.34-1.38]	0.286
Nausea	50	60.2	55	32.9	<0.001	3.09 [1.79-5.32]	**<0.001**	48	51.6	55	35.3	0.012	1.96 [1.16-3.30]	**0.012**
CCr 70 mL/min >	10	55.6	12	40.0	0.375	1.88 [0.58-6.12]	0.297	11	37.9	8	27.6	0.577	1.60 [0.53-4.85]	0.403
70 mL/min≦	40	61.5	43	31.4	<0.001	3.50 [1.89-6.48]	**<0.001**	37	57.8	47	37.0	0.009	2.33 [1.26-4.31]	**0.007**
Vomiting	19	22.9	14	8.4	0.003	3.24 [1.53-6.87]	**0.002**	18	19.4	11	7.1	0.007	3.16 [1.42-7.04]	**0.005**
CCr 70 mL/min >	7	38.9	4	13.3	0.074	4.14 [1.00-17.1]	**0.049**	5	17.2	1	3.4	0.194	5.83 [0.64-53.5]	0.119
70 mL/min≦	12	18.5	10	7.3	0.028	2.88 [1.17-7.06]	**0.021**	13	20.3	10	7.9	0.018	2.98 [1.23-7.25]	**0.016**
Diarrhea	31	37.3	56	33.5	0.575	1.18 [0.68-2.05]	0.551	27	29.0	29	18.6	0.061	1.79 [0.98-3.27]	0.058
CCr 70 mL/min >	12	66.7	15	50.0	0.369	2.00 [0.59-6.73]	0.263	9	31.0	5	17.2	0.358	2.16 [0.62-7.49]	0.225

	70 mL/min≦	19	29.2	41	29.9	1.000	0.97 [0.51-1.85]	0.920	18	28.1	24	18.9	0.195	1.68 [0.83-3.39]	0.148
Stomatitis		17	20.5	35	21.0	1.000	0.97 [0.51-1.86]	0.931	31	33.3	43	27.6	0.390	1.31 [0.75-2.29]	0.336
	CCr 70 mL/min >	4	22.2	3	10.0	0.400	2.57 [0.50-13.1]	0.256	9	31.0	12	41.4	0.585	0.64 [0.22-1.88]	0.414
	70 mL/min≦	13	20.0	32	23.4	0.718	0.82 [0.40-1.69]	0.593	22	34.4	31	24.4	0.172	1.62 [0.84-3.13]	0.148
Alopecia		3	3.6	1	0.6	0.108	6.23 [0.64-60.8]	0.116	28	30.1	14	9.0	<0.001	4.37 [2.16-8.85]	**<0.001**
	CCr 70 mL/min >	0	0	0	0	-	-	-	11	37.9	3	10.3	0.030	5.30 [1.29-21.7]	**0.021**
	70 mL/min≦	3	4.6	1	0.7	0.099	6.58 [0.67-64.5]	0.106	17	26.6	11	8.7	0.002	3.81 [1.66-8.75]	**0.002**
Sensory neuropathy		60	72.3	128	76.6	0.534	0.80 [0.44-1.45]	0.453	62	66.7	106	67.9	0.889	0.94 [0.55-1.63]	0.834
	CCr 70 mL/min >	14	77.8	22	73.3	1.000	1.27 [0.32-5.03]	0.731	20	69.0	18	62.1	0.783	1.36 [0.46-4.03]	0.581
	70 mL/min≦	46	70.8	106	77.4	0.383	0.71 [0.36-1.38]	0.311	42	65.6	88	69.3	0.625	0.85 [0.45-1.60]	0.263
All periods															
Leukopenia		49	59.0	96	57.5	0.892	1.07 [0.63-1.82]	0.815	76	81.7	99	63.5	0.003	2.57 [1.39-4.78]	0.003
	CCr 70 mL/min >	13	72.2	20	66.7	0.757	1.30 [0.36-4.68]	0.688	24	82.8	22	75.9	0.747	1.53 [0.42-5.52]	0.518
	70 mL/min≦	36	55.4	76	55.5	1.000	1.00 [0.55-1.80]	0.990	52	81.3	77	60.6	0.005	2.81 [1.37-5.79]	**0.005**
Neutropenia		50	60.2	98	58.7	0.892	1.07 [0.62-1.82]	0.814	76	81.7	104	66.7	0.013	2.24 [1.20-4.17]	**0.011**
	CCr 70 mL/min >	12	66.7	16	53.3	0.546	1.75 [0.52-5.89]	0.367	24	82.8	23	79.3	1.000	1.25 [0.34-4.68]	0.738
	70 mL/min≦	38	58.5	82	59.9	0.879	0.94 [0.52-1.72]	0.850	52	81.3	81	63.8	0.013	2.46 [1.19-5.08]	**0.015**
Thrombocytopenia		52	62.7	123	73.7	0.080	0.60 [0.34-1.05]	0.075	45	48.4	90	57.7	0.189	0.69 [0.41-1.15]	0.155
	CCr 70 mL/min >	12	66.7	23	76.7	0.513	0.61 [0.17-2.22]	0.452	16	55.2	21	72.4	0.274	0.47 [0.16-1.40]	0.175
	70 mL/min≦	40	61.5	100	73.0	0.106	0.59 [0.32-1.11]	0.101	29	45.3	69	54.3	0.284	0.70 [0.38-1.27]	0.240
Nausea		58	69.9	72	43.1	<0.001	3.06 [1.75-5.36]	**<0.001**	62	66.7	77	49.4	0.009	2.05 [1.20-3.50]	**0.008**
	CCr 70 mL/min >	12	66.7	14	46.7	0.237	2.29 [0.68-7.70]	0.182	16	55.2	13	44.8	0.600	1.52 [0.54-4.26]	0.432
	70 mL/min≦	46	70.8	58	42.3	<0.001	3.30 [1.75-6.21]	**<0.001**	46	71.9	64	50.4	0.005	2.52 [1.32-4.80]	**0.005**
Vomiting		28	33.7	23	13.8	<0.001	3.19 [1.69-6.00]	**<0.001**	29	31.2	21	13.5	0.001	2.91 [1.54-5.50]	**0.001**

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	CCr 70 mL/min >	8	44.4	5	16.7	0.049	4.00 [1.05-15.2]	**0.042**	10	34.5	3	10.3	0.056	4.56 [1.10-18.9]	**0.036**
	70 mL/min≦	20	30.8	18	13.1	0.004	2.94 [1.43-6.06]	**0.004**	19	29.7	18	14.2	0.019	2.56 [1.23-5.32]	**0.012**
Diarrhea		48	57.8	85	50.9	0.347	1.32 [0.78-2.25]	0.301	41	44.1	55	35.3	0.180	1.45 [0.86-2.45]	0.167
	CCr 70 mL/min >	14	77.8	16	53.3	0.127	3.06 [0.82-11.5]	0.097	13	44.8	10	34.5	0.592	1.54 [0.54-4.45]	0.422
	70 mL/min≦	34	52.3	69	50.4	0.881	1.08 [0.60-1.95]	0.797	28	43.8	45	35.4	0.274	1.42 [0.77-2.62]	0.265
Stomatitis		31	37.3	72	43.1	0.415	0.79 [0.46-1.35]	0.384	48	51.6	75	48.1	0.603	1.15 [0.69-1.93]	0.590
	CCr 70 mL/min >	5	27.8	8	26.7	1.000	1.06 [0.29-3.92]	0.933	13	44.8	16	55.2	0.600	0.66 [0.24-1.86]	0.432
	70 mL/min≦	26	40.0	64	46.7	0.449	0.76 [0.42-1.38]	0.370	35	54.7	59	46.5	0.289	1.39 [0.76-2.54]	0.284
Alopecia		6	7.2	9	5.4	0.579	1.37 [0.47-3.98]	0.565	36	38.7	25	16.0	<0.001	3.31 [1.82-6.02]	**<0.001**
	CCr 70 mL/min >	0	0	2	6.7	0.521	-	0.952	14	48.3	3	10.3	0.003	8.09 [2.00-32.8]	**0.003**
	70 mL/min≦	6	9.2	7	5.1	0.357	1.89 [0.61-5.86]	0.271	22	34.4	22	17.3	0.011	2.50 [1.25-4.99]	**0.009**
Sensory neuropathy		74	89.2	154	92.2	0.479	0.69 [0.28-1.70]	0.423	85	91.4	139	89.1	0.665	1.30 [0.54-3.14]	0.561
	CCr 70 mL/min >	16	88.9	26	86.7	1.000	1.23 [0.20-7.51]	0.822	27	93.1	27	93.1	1.000	1.00 [0.13-7.62]	1.000
	70 mL/min≦	58	89.2	128	93.4	0.403	0.58 [0.21-1.64]	0.306	58	90.6	112	88.2	0.807	1.30 [0.48-3.51]	0.612

[a] Fisher's exact test; comparing frequency of adverse events.

Bev, bevacizumab; CCr, creatinine clearance rate; FOLFOX, 5-FU/*l*-leucovorin plus oxaliplatin; OR, odds ratio; SOX, S-1 plus oxaliplatin; 95% CI, 95% confidence interval.

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Table 3. Multivariate analyses for adverse events after 8 weeks and all periods from the beginning of treatment with S-1 plus oxaliplatin with bevacizumab or 5-FU/*l*-LV plus oxaliplatin with bevacizumab

					Objective variables								
		Explanatory variables	Base category		Leukopenia	Neutropenia	Thrombo-cytopenia	Nausea	Vomiting	Diarrhea	Stomatitis	Alopecia	Sensory neuropathy
8 weeks	SOX/Bev	Sex	male	OR	1.54	1.15	0.62	2.88	3.04	1.18	0.95	5.94	0.72
		Female *vs.* male		95% CI	0.86-2.74	0.64-2.07	0.33-1.15	1.66-5.01	1.41-6.56	0.67-2.09	0.49-1.83	0.60-58.80	0.39-1.33
				P value	0.147	0.642	0.131	**< 0.001**	**0.005**	0.572	0.871	0.128	0.291
		CCr	70 mL/min >	OR	0.61	0.70	0.31	0.66	0.37	0.36	1.45	-	0.77
		70 mL/min ≦ *vs.* 70 mL/min >		95% CI	0.31-1.22	0.35-1.41	0.15-0.62	0.32-1.35	0.15-0.91	0.18-0.71	0.58-3.60	-	0.35-1.67
				P value	0.165	0.314	**0.001**	0.255	**0.031**	**0.003**	0.424	0.958	0.502
		BMI	median >	OR	0.96	1.01	1.93	1.24	1.37	0.79	1.00	2.55	1.57
		Median ≦ *vs.* median > per sex		95% CI	0.55-1.69	0.57-1.76	1.08-3.45	0.73-2.12	0.63-2.98	0.46-1.37	0.54-1.87	0.26-25.45	0.87-2.83
				P value	0.899	0.986	0.028	0.428	0.429	0.406	0.995	0.426	0.139
		Age	70 >	OR	1.92	2.36	1.25	0.49	0.82	1.14	0.61	-	0.56
		70 ≦ *vs.* 70 >		95% CI	1.02-3.61	1.26-4.42	0.65-2.41	0.25-0.95	0.32-2.08	0.60-2.16	0.27-1.37	-	0.29-1.09
				P value	**0.043**	**0.007**	0.497	**0.035**	0.670	0.686	0.226	0.954	0.09
	FOLFOX/Bev	Sex	male	OR	2.61	2.92	0.68	2.12	3.26	1.82	1.25	4.13	0.98
		Female *vs.* male		95% CI	1.51-4.51	1.69-5.02	0.38-1.24	1.24-3.64	1.45-7.35	0.99-3.36	0.71-2.20	2.02-8.43	0.56-1.71
				P value	**< 0.001**	**< 0.001**	0.212	**0.006**	**0.004**	0.055	0.437	**< 0.001**	0.945
		CCr	70 mL/min >	OR	0.89	1.21	0.46	1.72	1.63	0.96	0.62	0.70	1.06
		70mL/min ≦ *vs.* 70 mL/min >		95% CI	0.46-1.75	0.62-2.35	0.23-0.93	0.87-3.41	0.58-4.59	0.45-2.06	0.31-1.24	0.31-1.58	0.54-2.09

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				P value	0.739	0.580	**0.030**	0.121	0.355	0.914	0.176	0.391	0.868
		BMI	median >	OR	1.16	1.13	1.86	1.01	0.65	1.35	1.16	0.70	1.54
		Median ≦ *vs.*		95% CI	0.68-1.98	0.67-1.92	1.03-3.36	0.59-1.71	0.29-1.47	0.73-2.51	0.66-2.05	0.34-1.43	0.89-2.67
		median > per sex		*P* value	0.575	0.643	**0.039**	0.984	0.300	0.345	0.599	0.321	0.124
		Age	70 >	OR	1.65	1.17	2.04	0.77	1.07	1.20	0.78	0.94	1.23
		70 ≦ *vs.* 70 >		95% CI	0.88-3.09	0.63-2.18	1.08-3.83	0.41-1.45	0.41-2.80	0.59-2.44	0.40-1.52	0.41-2.17	0.64-2.37
				P value	0.120	0.614	**0.027**	0.426	0.897	0.621	0.466	0.888	0.531
all	SOX/Bev	Sex	male	OR	1.06	1.07	0.57	2.87	3.00	1.32	0.76	1.29	0.65
		female *vs*. male		95% CI	0.61-1.82	0.62-1.85	0.32-1.01	1.63-5.07	1.58-5.71	0.77-2.27	0.44-1.33	0.44-3.83	0.26-1.62
				P value	0.848	0.796	0.053	**< 0.001**	**< 0.001**	0.307	0.342	0.642	0.355
		CCr	70 mL/min >	OR	0.59	1.06	0.72	0.73	0.55	0.66	1.89	1.31	1.33
		70 mL/min ≦ *vs.*		95% CI	0.29-1.19	0.54-2.09	0.34-1.52	0.36-1.49	0.24-1.23	0.33-1.31	0.91-3.92	0.26-6.50	0.46-3.85
		70 mL/min >											
				P value	0.140	0.862	0.391	0.387	0.144	0.232	0.090	0.745	0.355
		BMI	median >	OR	1.11	0.94	1.25	1.20	0.99	0.88	1.55	2.06	1.18
		Median ≦ *vs.*		95% CI	0.66-1.86	0.56-1.56	0.72-2.18	0.71-2.03	0.51-1.89	0.53-1.47	0.92-2.61	0.67-6.32	0.48-2.89
		median > per sex											
				P value	0.693	0.800	0.429	0.507	0.964	0.626	0.098	0.205	0.724
		Age	70 >	OR	1.20	1.00	0.78	0.51	0.54	1.05	0.87	0.80	0.57
		70 ≦ *vs.* 70 >		95% CI	0.65-2.23	0.54-1.83	0.41-1.49	0.27-0.96	0.23-1.26	0.58-1.93	0.46-1.62	0.21-3.09	0.22-1.51
				P value	0.560	0.992	0.448	**0.036**	0.156	0.865	0.657	0.741	0.258
	FOLFOX/Bev	Sex	male	OR	2.55	2.23	0.66	2.16	2.92	1.45	1.15	3.29	1.21
		Female *vs.* male		95% CI	1.35-4.79	1.18-4.21	0.38-1.13	1.25-3.73	1.52-5.58	0.85-2.48	0.68-1.94	1.80-6.02	0.49-2.95
				P value	**0.004**	**0.014**	0.127	**0.006**	**0.001**	0.170	0.602	**< 0.001**	0.680

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	CCr	70 mL/min >	OR	0.76	0.64	0.60	1.45	0.77	0.84	0.86	0.96	0.54
	70mL/min ≦ *vs.* 70 mL/min >		95% CI	0.35-1.66	0.29-1.42	0.30-1.17	0.74-2.81	0.35-1.73	0.43-1.64	0.45-1.64	0.46-2.02	0.16-1.78
			P value	0.491	0.275	0.134	0.277	0.534	0.616	0.648	0.921	0.310
	BMI	median >	OR	1.03	1.39	1.73	0.77	1.24	1.34	1.24	0.92	0.87
	Median ≦ *vs.* median > per sex		95% CI	0.57-1.83	0.77-2.50	1.01-2.95	0.45-1.30	0.64-2.40	0.78-2.27	0.74-2.07	0.50-1.69	0.37-2.04
			P value	0.933	0.277	**0.045**	0.323	0.527	0.287	0.420	0.782	0.750
	Age	70 >	OR	2.08	1.78	2.24	0.61	0.51	0.75	0.77	1.30	0.60
	70 ≦ *vs.* 70 >		95% CI	0.99-4.35	0.85-3.74	1.18-4.24	0.33-1.12	0.22-1.20	0.40-1.41	0.42-1.41	0.64-2.63	0.23-1.53
			P value	0.052	0.127	**0.013**	0.112	0.122	0.367	0.397	0.464	0.280

The median BMI of female patients was 21.3 kg/m^2, and the BMI of males was 22.0 kg/m^2; -, not evaluable

Bev, bevacizumab; BMI, body mass index; CCr, creatinine clearance; CI, confidence interval; FOLFOX, 5-FU/*l*-leucovorin plus oxaliplatin; OR, odds ratio; SOX, S-1 plus oxaliplatin.

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Table 4. Total dose and relative dose intensity

		SOX/Bev (*n* = 250)				FOLFOX/Bev (*n* = 249)			
		Male (*n* = 167)	Female (*n* = 83)	*P*		Male (*n* = 156)	Female (*n* = 93)	*P*	
Bevacizumab	Median	90.6	85.7	0.166	a	83.3	83.4	0.466	a
	Range	0-100	0-100			0-100	36.7-100		
	Mean	85.2	81.6	0.134	b	78.9	79.4	0.832	b
	SD	16.3	20.4			19.1	14.6		
Oxaliplatin	Median	77.6	71.9	0.141	a	64.8	58.3	0.202	a
	Range	5.3-100	27.7-100			21.4-100	18.2-100		
	Mean	74.3	70.2	0.157	b	65.3	61.7	0.219	b
	SD	21.4	20.7			23.0	20.7		
l-leucovorin	Median					87.8	84.8	0.017	a
	Range					48.6-100	55.6-100		
	Mean					86.4	82.9	0.017	b
	SD					11.0	11.8		
5-FU, bolus	Median					82.8	70.0	0.001	a
	Range					36.8-100	34.8-100		
	Mean					77.8	69.9	< 0.001	b
	SD					17.6	17.7		
5-FU, ci	Median					84.1	74.9	0.005	a
	Range					44.4-100	41.7-100		
	Mean					80.5	75.0	0.005	b
	SD					14.9	15.0		
S-1	Median	82.2	76.0	0.003	a				
	Range	16.7-104.2	0-100						
	Mean	81.5	73.9	< 0.001	b				
	SD	14.9	19.9						

a: Wilcoxon rank sum test; b: *t* test.

ci, continuous infusion; FOLFOX/Bev, *l*-leucovorin, 5-fluorouracil, oxaliplatin, and bevacizumab; SOX/Bev, S-1, oxaliplatin, and bevacizumab.

Table 5. Prognostic factors for overall survival in patients treated with S-1 plus oxaliplatin with bevacizumab or 5-FU/*l*-LV plus oxaliplatin with bevacizumab

Variables		Base category	SOX/Bev			FOLOX/Bev			**All patients**		
			HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	Female *vs*. male	Male	0.97	0.69-1.35	0.84	1.25	0.90-1.73	0.17	1.12	0.89-1.41	0.32
Age	70 ≦ *vs.* 70 >	70 >	1.14	0.80-1.62	0.47	0.95	0.64-1.38	0.77	1.06	0.82-1.36	0.66
Primary lesion	Rectosigmoid *vs.* colon	Colon	0.78	0.50-1.20	0.26	0.86	0.54-1.38	0.54	0.84	0.61-1.15	0.26
	Rectum *vs.* colon	Colon	0.96	0.66-1.40	0.85	0.95	0.67-1.35	0.78	0.97	0.75-1.25	0.82
Histology	Poorly *vs.* well/ moderate	Well/ moderate	2.61	1.32-5.15	0.0056	2.41	1.12-5.17	0.024	2.72	1.67-4.44	< 0.0001
	Others *vs.* well/ moderate	Well/ moderate	0.90	0.52-1.53	0.70	1.25	0.75-2.04	0.39	1.07	0.74-1.53	0.72
Adjuvant chemotherapy	Yes *vs.* No	No	0.97	0.61-1.53	0.89	0.73	0.45-1.18	0.20	0.83	0.59-1.15	0.25
Target lesion	Yes *vs.* No	No	1.22	0.65-2.25	0.53	1.7	0.83-3.44	0.15	1.40	0.88-2.22	0.15
Liver metastases	Yes *vs.* No	No	1.12	0.69-1.80	0.63	1.46	0.88-2.38	0.14	1.27	0.90-1.78	0.16
Lung metastases	Yes *vs.* No	No	0.98	0.63-1.50	0.91	1.48	0.88-2.46	0.13	1.21	0.88-1.66	0.23
Lymph node metastases	Yes *vs.* No	No	1.25	0.76-2.06	0.38	1.41	0.89-2.20	0.14	1.33	0.95-1.84	0.092
Other metastases	Yes *vs.* No	No	1.29	0.79-2.09	0.31	1.32	0.78-2.223	0.30	1.26	0.89-1.77	0.18
Metastatic organs	2 ≦ *vs.* 1	1	0.90	0.52-1.55	0.72	0.98	0.54-1.75	0.94	0.96	0.65-1.39	0.82
Treatment	SOX/Bev *vs.* FOLFOX/Bev	FOLFOX/Bev	-	-	-	-	-	-	1.02	0.82-1.26	0.88

FOLFOX/Bev, *l*-leucovorin, 5-fluorouracil, oxaliplatin, and bevacizumab; HR, hazard ratio; SOX/Bev, S-1, oxaliplatin, and bevacizumab; 95% CI, 95% confidence interval.

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Table 6. Prognostic factors for progression-free survival in patients treated with S-1 plus oxaliplatin with bevacizumab or 5-FU/*l*-LV plus oxaliplatin with bevacizumab

Variables		Base category	SOX/Bev			FOLFOX/Bev			All patients		
			HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	Female *vs.* male	Male	0.90	0.68-1.20	0.49	1.09	0.82-1.44	0.56	0.97	0.79-1.18	0.72
Age	70 ≦ *vs.* 70 >	70 >	1.05	0.77-1.43	0.77	0.81	0.58-1.12	0.20	0.89	0.71-1.11	0.30
Primary lesion	Rectosigmoid *vs.* colon	Colon	0.85	0.58-1.24	0.40	0.94	0.63-1.38	0.74	0.89	0.68-1.16	0.40
	Rectum *vs.* colon	Colon	0.94	0.67-1.30	0.71	0.81	0.59-1.11	0.19	0.85	0.68-1.06	0.15
Histology	Poorly *vs.* well/ moderate	Well/ moderate	3.33	1.74-6.35	0.0003	1.30	0.63-2.68	0.48	1.89	1.18-3.02	0.0079
	Others *vs.* well/ moderate	Well/ moderate	1.07	0.66-1.71	0.78	0.87	0.55-1.37	0.55	0.91	0.65-1.25	0.55
Adjuvant chemotherapy	Yes *vs.* No	No	0.68	0.45-1.02	0.059	0.75	0.51-1.11	0.15	0.75	0.57-0.99	0.038
Target lesion	Yes *vs.* No	No	0.85	0.51-1.40	0.52	1.17	0.70-1.95	0.58	0.96	0.67-1.37	0.83
Liver metastases	Yes *vs.* No	No	1.05	0.69-1.59	0.81	0.97	0.62-1.50	0.88	1.03	0.77-1.39	0.82
Lung metastases	Yes *vs.* No	No	1.19	0.82-1.72	0.35	1.26	0.82-1.94	0.29	1.24	0.94-1.62	0.12
Lymph node metastases	Yes *vs.* No	No	1.00	0.63-1.58	0.99	0.87	0.58-1.32	0.52	0.98	0.73-1.30	0.87
Other metastases	Yes *vs.* No	No	0.99	0.64-1.52	0.95	1.02	0.64-1.63	0.92	1.04	0.76-1.42	0.80
Metastatic organs	2 ≦ *vs.* 1	1	1.08	0.67-1.74	0.74	0.99	0.61-1.60	0.96	1.00	0.72-1.37	0.98
Treatment	SOX/Bev *vs.* FOLFOX/Bev	FOLFOX/Bev	-	-	-	-	-	-	1.06	0.88-1.28	0.51

FOLFOX/Bev, *l*-leucovorin, 5-fluorouracil, oxaliplatin, and bevacizumab; HR, hazard ratio; SOX/Bev, S-1, oxaliplatin, and bevacizumab; 95% CI, 95% confidence interval.

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