Original Study

Impact of Sex on Chemotherapy Toxicity and Efficacy Among Patients With Metastatic Colorectal Cancer: Pooled Analysis of 5 Randomized Trials

Omar Abdel-Rahman[1,2]

Abstract

This pooled analysis from 5 clinical trials of metastatic colorectal cancer patients found no difference in overall or progression-free survival between female and male subjects. Female subjects had a higher rate of gastrointestinal and hematologic toxicities.

Purpose: To evaluate the impact of sex on toxicity and efficacy outcomes among patients with metastatic colorectal cancer receiving first-line 5-fluorouracil–based regimens. **Patients and Methods:** A pooled analysis of data sets from 5 clinical trials (NCT00115765, NCT00364013, NCT00272051, NCT00305188, NCT00384176) was performed. Kaplan-Meier analysis and log-rank testing were used to assess the differences in overall and progression-free survival between male and female subjects. Chi-square testing was used to examine the differences in the incidence of different toxicities between male and female subjects. Multivariate logistic regression analysis (adjusted for age, body mass index, Eastern Cooperative Oncology Group performance status, race, bevacizumab-containing treatment, and panitumumab-containing treatment) was further utilized to assess the impact of gender on different toxicities. Most of the patients were treated with FOLFOX (folinic acid, fluorouracil, and oxaliplatin)-based regimens. **Results:** A total of 3223 participants were included in the pooled cohort, among which were 1925 male and 1298 female subjects. Kaplan-Meier survival analysis and log-rank testing were utilized to compare overall and progression-free survival outcomes between male and female subjects. For both end points, there was no difference between male and female subjects ($P = .884$; $P = .647$, respectively). Comparing female to male subjects, female subjects were more likely to experience alopecia (20% vs. 8.6%; $P < .001$), all-grade diarrhea (60.3% vs. 56.7%; $P = .039$), all-grade nausea and vomiting (68.7% vs. 56.6%; $P < .001$), high-grade nausea and vomiting (7.1% vs. 4.5%; $P = .002$), all-grade anemia (19.6% vs. 14.2%; $P < .001$), all-grade neutropenia (51.1% vs. 36.6%; $P < .001$), and high-grade neutropenia (37.1% vs. 24.1%; $P < .001$). These differences were further confirmed in multivariate logistic regression analyses. **Conclusion:** Female subjects with metastatic colorectal cancer receiving first-line chemotherapy demonstrated higher rates of a number of toxicities (essentially hematologic and gastrointestinal in nature). Additional studies into the differential effect of systemic therapy on female versus male subjects are needed.

Clinical Colorectal Cancer, Vol. 18, No. 2, 110-5

Keywords: Adverse events, 5-FU, Female, Male, Survival

Introduction

Numerous prognostic models have been hypothesized to predict potential outcomes of patients with metastatic colorectal cancer.[1] Factors evaluated within these models include patient-related factors (like age and comorbidity), disease-related factors (like primary tumor site, biology, the extent of metastatic disease, and surrogate laboratory markers), and treatment-related factors.[2]

Sex has been shown as an important prognostic factor in a number of solid tumors.[3] Moreover, it has been hypothesized to be a potential

[1]Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2]Department of Oncology, University of Calgary, Tom Baker Cancer Centre, Calgary, Alberta, Canada

Submitted: Nov 28, 2018; Accepted: Dec 24, 2018; Epub: Dec 28, 2018

Address for correspondence: Omar Abdel-Rahman, MD, Department of Oncology, University of Calgary, Tom Baker Cancer Centre, Calgary, Alberta T2N4N1, Canada
E-mail contact: omar.abdelsalam@ahs.ca

1533-0028/$ - see frontmatter
https://doi.org/10.1016/j.clcc.2018.12.006

Table 1 Cohorts Included in Pooled Analysis

Study	Treatment Regimen	Start Date	Completion Date	Patients Contributing to Pooled Analysis, N (%)
NCT00115765 (PACCE)	• Experimental arm: chemotherapy and bevacizumab with panitumumab • Active comparator: chemotherapy and bevacizumab	June 2005	December 2009	842 (26.1)
NCT00364013 (PRIME)	• Experimental arm: panitumumab plus FOLFOX • Active comparator: FOLFOX alone	August 2006	March 2013	935 (29)
NCT00272051 (comparator arm only)[a]	• Active comparator: placebo plus FOLFOX chemotherapy	July 2002	May 2004	322 (10)
NCT00305188 (comparator arm only)[a]	• Active comparator: placebo plus FOLFOX chemotherapy	December 2005	October 2009	434 (13.5)
NCT00384176 (Horizon III) (comparator arm only)[a]	• Active comparator: bevacizumab plus FOLFOX	August 2006	August 2015	690 (21.4)

Abbreviation: FOLFOX = folinic acid, fluorouracil, and oxaliplatin.
[a]In these 3 studies, only comparator arms were included.

predictor of efficacy and toxicity of some anticancer treatments.[4,5] Previous studies evaluating the impact of sex on outcomes of colorectal cancer patients were primarily retrospective studies.[6,7] Thus, the results of these studies might be confounded by some missing variables that might have affected the outcomes. Moreover, most of these studies did not provide comment on the potential impact of sex on different chemotherapy-related toxicities. Thus, there is a need to study this variable in the context of prospectively collected data sets, with as few missing variables as possible and with an adequate analysis of both efficacy and toxicity outcomes.

A possible medium that fulfills the above requirements is the Project Data Sphere (PDS; https://www.projectdatasphere.org/projectdatasphere/html/home), which is an initiative by multiple stakeholders interested in data sharing of deidentified data sets of clinical trials. Through this portal, individual patient data of clinical trials evaluating metastatic colorectal cancer patients can be accessed and analyzed.

The findings of the current analysis should be highly informative to patients and practicing physicians alike because colorectal cancer is one of the leading causes of cancer mortality globally (http://gco.iarc.fr/)[8] and because of the widespread use of systemic treatment in the management of advanced stages of this disease.

The objective of the current study was to assess the impact of patient sex on the efficacy and toxicity outcomes of metastatic colorectal cancer treated with first-line systemic chemotherapy.

Patients and Methods

Data Sources

Sources of data for the current study included deidentified data sets of 5 randomized clinical trials (NCT00115765, NCT00364013, NCT00272051, NCT00305188, NCT00384176). All included patients were treated with 5-fluorouracil–based chemotherapy. The details of the treatment regimens used in each of the 5 trials are listed in Table 1. Additional methodologic details were clarified in the ClinicalTrials.gov records of each study. For 2 of the included studies (NCT00364013, NCT00115765), both control and experimental arms were available, and they were included in the final analysis. For the other 3 trials (NCT00305188, NCT00272051, NCT00384176), only data sets of the control arms were available in the PDS platform; they were included in the final analysis.

Primary results of the NCT00384176, NCT00364013, and NCT00115765 trials have been published.[9-11]

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the studies.

Data Collection

From each of the included data sets, the following information was collected: age at diagnosis, gender, race, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status (PS), number of sites with metastatic disease, primary tumor site, whether the systemic therapy regimens contains oxaliplatin, panitumumab, or bevacizumab, and preexisting diabetes mellitus or hypertension.

Toxicity was graded in each of the included data sets according to the Common Terminology Criteria for Adverse Events. High-grade toxicities were defined as toxicities grade 3 or higher. Incidence of the following toxicities was collected: diarrhea (all grade and high grade), stomatitis (all grade and high grade), nausea and vomiting (all grade and high grade), anemia (all grade and high grade), neutropenia (all grade and high grade), thrombocytopenia (all grade and high grade), febrile neutropenia, any cardiac adverse event, ischemia (all grade), arrhythmias (all grade), and alopecia (all grade). Peripheral neuropathy was also collected among patients receiving oxaliplatin-containing regimens. Serious adverse events (as reported in individual studies) and fatal adverse events were also collected.

Primary end points of the current analysis include overall survival (defined as the time from randomization till the death of any cause), progression-free survival (defined as the time from randomization till progression of the disease), and incidence of toxicities.

According to the available protocols of the included studies, all included patients had adequate liver, renal, and cardiac function at the time of randomization.

Table 2 Baseline Characteristics of 3223 Patients Included in Cohort

Parameter	Men (N = 1925)	Women (N = 1298)	P
Age (Years)			< .001
Mean (SD)	61.7 (10.6)	59.1 (11.5)	
Missing	0	0	
Race			.101
White	1760 (91.4%)	1165 (89.8%)	
Other	160 (8.3%)	132 (10.2%)	
Unknown	5 (0.3%)	1 (0.1%)	
Body Mass Index			< .001
Mean (SD)	26.6 (4.8)	25.8 (5.3)	
Missing	29	36	
ECOG PS			.026
0	1132 (58.8%)	716 (55.2%)	
1	744 (38.6%)	551 (42.4%)	
2	44 (2.3%)	22 (1.7%)	
Missing	5 (0.3%)	9 (0.7%)	
Primary Tumor Site			.023
Colon	1010 (52.5%)	716 (55.2%)	
Rectum	515 (26.8%)	292 (22.5%)	
Unknown	400 (20.8%)	290 (22.3%)	
No. of Organs With Distant Metastases			.322
1	571 (29.7%)	406 (31.3%)	
≥ 2	951 (49.3%)	601 (46.3%)	
Unknown	403 (21%)	291 (22.4%)	
Panitumumab-Containing Chemotherapy			.871
Yes	533 (27.7%)	356 (27.4%)	
No	1392 (72.3%)	942 (72.6%)	
Bevacizumab-Containing Chemotherapy			.017
Yes	907 (47.1%)	667 (51.4%)	
No	1018 (52.9%)	631 (48.6%)	
Oxaliplatin-Containing Chemotherapy			.260
Yes	1829 (95%)	1221 (94.1%)	
No	90 (4.7%)	75 (5.8%)	
Unknown	6 (0.3%)	2 (0.2%)	
Diabetes Mellitus			< .001
Yes	187 (9.7%)	80 (6.2%)	
No	1145 (62.7%)	876 (67.5%)	
Unknown	593 (30.8%)	342 (26.3)	
Hypertension			< .001
Yes	507 (26.3%)	310 (23.9%)	
No	825 (42.9%)	646 (49.8%)	
Unknown	593 (30.8%)	342 (26.3%)	

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; SD = standard deviation.

Statistical Analysis

The chi-square test was used to assess the potential differences in categorical baseline characteristics between male and female subjects included in the pooled data set. Likewise, ANOVA testing was used to examine the differences in continuous baseline characteristics between male and female subjects. The chi-square test was also used to examine the differences in the incidence of different toxicities between male and female subjects. The impact of sex on different toxicities was further clarified through multivariate logistic regression analysis (adjusted for age, body mass index, ECOG PS, race, bevacizumab-containing treatment, and panitumumab-containing treatment).

Kaplan-Meier analysis and log-rank testing were used to assess the differences in overall and progression-free survival between male and female subjects. SPSS 20.0 software (IBM, Armonk, NY) was used for all statistical procedures.

Results

Patient Characteristics

A total of 3223 participants were included in the pooled cohort, among which there were 1925 male and 1298 female subjects. Comparing female to male subjects in the pooled cohort, female subjects were more likely to have a younger age at presentation ($P <$ .001), lower body mass index ($P <$ .001), higher ECOG score ($P =$ .026), colon primary site ($P =$ .023), and bevacizumab-containing regimens ($P =$ .017). Female subjects were also less likely to have preexisting diabetes mellitus ($P <$ .001) or preexisting hypertension ($P <$ .001). There was no difference between male and female subjects with regards to race ($P =$ .101), number of organs with metastatic deposits ($P =$ .322), or receipt of oxaliplatin-containing ($P =$ .260) or panitumumab-containing ($P =$ .871) treatment regimens (Table 2).

Survival Outcomes According to Sex

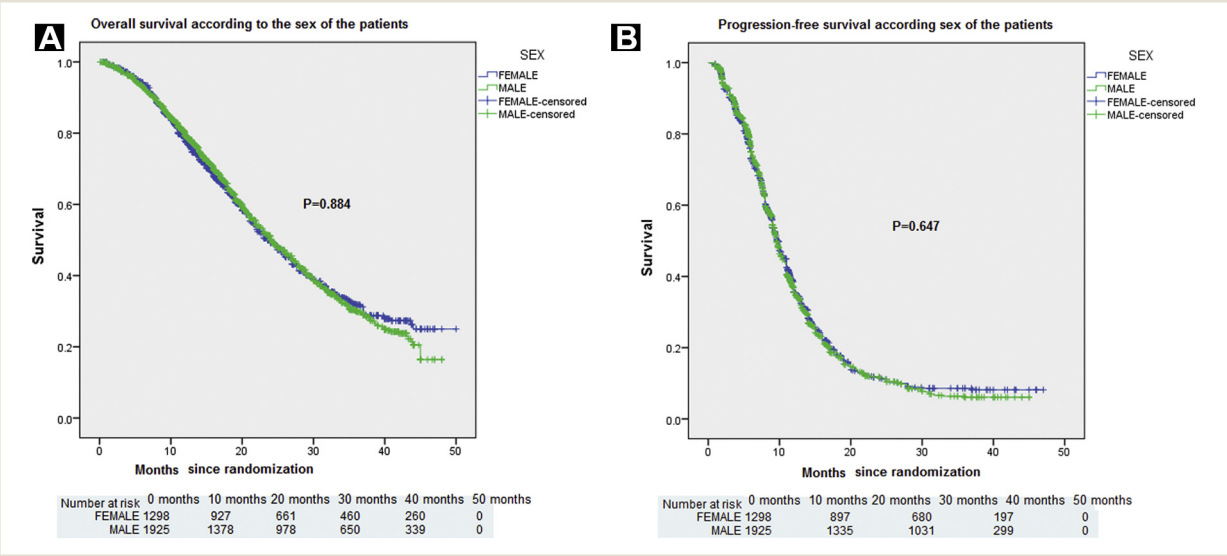
Kaplan-Meier survival analysis and log-rank testing were utilized to compare overall and progression-free survival outcomes between male and female subjects. For both end points, there was no difference between male and female subjects ($P =$ .884; $P =$ .647, respectively) (Figure 1).

Incidence of Different Toxicities According to Sex

Comparing female to male subjects, female subjects were more likely to experience alopecia (20% vs. 8.6%; $P <$ .001), all-grade diarrhea (60.3% vs. 56.7%; $P =$ .039), all-grade nausea and vomiting (68.7% vs. 56.6%; $P <$ .001), high-grade nausea and vomiting (7.1% vs. 4.5%; $P =$ .002), all-grade anemia (19.6% vs. 14.2%; $P <$ .001), all-grade neutropenia (51.1% vs. 36.6%; $P <$ .001), and high-grade neutropenia (37.1% vs. 24.1%; $P <$ .001). Female subjects also tended toward a higher incidence of all-grade stomatitis (26.3% vs. 23.3%; $P =$ .050).

There was no difference between female and male subjects with regards to serious adverse events (39.2% vs. 38.2%; $P =$ .575), fatal adverse events (4.5% vs. 5.9%; $P =$ .101), arrhythmias (5.2% vs. 4.5%; $P =$ .363), ischemic events (1.6% vs. 2.1%; $P =$ .299), peripheral neuropathy (50.5% vs. 51.2%; $P =$ .361), high-grade diarrhea (13.4% vs. 12.1%; $P =$ .275), high-grade stomatitis (1.8% vs. 2%; $P =$ .800), high-grade anemia (2.6% vs. 1.9%; $P =$ .152), all-grade thrombocytopenia (17.1% vs. 18.3%; $P =$ .369), high-grade thrombocytopenia (2.7% vs. 2.6%; $P =$ .863), or febrile neutropenia (2.2% vs. 2.9%; $P =$ .276) (Table 3).

Figure 1 Kaplan-Meier Curve for (A) Overall Survival and (B) Progression-Free Survival According to Patient Sex



Multivariate Logistic Regression Analysis for Impact of Sex on Toxicity

In order to further assess the impact of sex on toxicities, multivariate logistic regression analysis was conducted (Supplemental Tables 1-8 in the online version). It showed that female subjects were more likely to have all-grade diarrhea (odds ratio [OR] = 1.193; 95% confidence interval [CI], 1.029-1.384; $P = .019$), all-grade nausea and vomiting (OR = 1.655; 95% CI, 1.422-1.927; $P < .001$), high-grade nausea and vomiting (OR = 1.582; 95% CI, 1.161-2.156; $P = .004$), all-grade anemia (OR = 1.443; 95% CI, 1.187-1.754; $P < .001$), all-grade neutropenia (OR = 1.904; 95% CI, 1.641-2.210; $P < .001$), high-grade neutropenia (OR = 1.985; 95% CI, 1.690-2.330; $P < .001$), and all-grade alopecia (OR = 2.616; 95% CI, 2.111-3.242; $P < .001$). On the other hand, female subjects were not more likely to have all-grade stomatitis (OR = 1.165; 0.984-1.378; $P = .076$).

Discussion

The current study provides an assessment of the impact of sex on the outcomes of metastatic colorectal cancer in patients receiving first-line systemic therapy. Although survival outcomes did not differ according to sex, toxicity patterns were quite different between male and female subjects. Specifically, female subjects were more likely to experience alopecia, all-grade and high-grade nausea and vomiting, all-grade diarrhea, all-grade anemia, and all-grade and high-grade neutropenia.

A potential explanation for the differences in chemotherapy toxicity between female and male subjects might be related to the fact that sex is an important factor in determining interpatient variability in metabolism of chemotherapy.[12] Likewise, there is a recognizable difference in the sensitivity of different organs between male and female subjects.[13]

There are a number of limitations in the current analysis that need to be acknowledged, foremost of which is that the primary research question of the included studies did not deal with the impact of sex on outcomes of those metastatic colorectal cancer patients. Thus, the current analysis should be considered as a retrospective analysis of prospectively collected data sets. Second, some baseline information was missing in some of the included studies. However, this missing information is not expected to significantly affect the observed differences in toxicity between female and male subjects.

These limitations need to be assessed against the strengths of the current analysis: the reliance on a prospectively collected data set and the well-controlled nature of data collection, which make toxicity data more credible compared to other retrospective studies.

It must be remembered that patients selected for clinical trials are usually younger, have a better PS, and have minimal comorbidities. Thus, the incidence of some of the reported toxicities in the current analysis might be higher in a real-world setting with older age, worse PS, and more severe comorbidities.

The current results are in line with a previously presented pooled analysis at the European Society of Medical Oncology 2018 meeting. That analysis evaluated the impact of sex on chemotherapy efficacy and toxicity in esophagogastric cancer, and—similar to the current analysis—female subjects were more likely to experience a number of gastrointestinal toxicities.[14] The current study is also in line with a previously published study suggesting a higher risk of chemotherapy-induced nausea and vomiting among female versus male subjects.[15] This information should be taken into consideration when deciding on the proper antiemetic regimen for female subjects receiving systemic chemotherapy for metastatic colorectal cancer.

Most patients included in the current study received FOLFOX (folinic acid, fluorouracil, and oxaliplatin)-based regimens. Thus, the results of the current study might not be applicable to patients receiving other first-line regimens, such as those based on FOLFIRI (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin).

The current study is thought provoking and hypothesis generating for a number of additional research questions. Most notably, the biologic basis of the differential impact of chemotherapy on

Table 3 Incidence of Toxicities Between Men and Women

Parameter	Men, N (%)	Women, N (%)	*P*
Serious Adverse Events			.575
Yes	736 (38.2)	509 (39.2)	
No	1189 (61.8)	789 (60.8)	
Fatal Adverse Events			.101
Yes	113 (5.9)	59 (4.5)	
No	1812 (94.1)	1239 (95.5)	
Any Cardiac Adverse Events			.480
Yes	147 (7.6)	108 (8.3)	
No	1778 (92.4)	1190 (91.7)	
Arrhythmias			.363
Yes	86 (4.5)	67 (5.2)	
No	1839 (95.5)	1231 (94.8)	
Ischemic Events			.299
Yes	41 (2.1)	21 (1.6)	
No	1884 (79.4)	1277 (98.4)	
Alopecia			< .001
Yes	165 (8.6)	259 (20)	
No	1760 (91.4)	1039 (80)	
Peripheral Neuropathy[a]			.361
Yes	936 (51.2)	616 (50.5)	
No	893 (48.8)	605 (49.5)	
Diarrhea (All Grade)			.039
Yes	1091 (56.7)	783 (60.3)	
No	834 (43.3)	515 (39.7)	
Diarrhea (High Grade)			.275
Yes	233 (12.1)	174 (13.4)	
No	1692 (87.9)	1124 (86.6)	
Stomatitis (All Grade)			.050
Yes	449 (23.3)	342 (26.3)	
No	1476 (76.7)	956 (73.7)	
Stomatitis (High Grade)			.800
Yes	38 (2)	24 (1.8)	
No	1887 (98)	1274 (98.2)	
Nausea/Vomiting (All Grade)			< .001
Yes	1089 (56.6)	892 (68.7)	
No	836 (43.4)	406 (31.3)	
Nausea/Vomiting (High Grade)			.002
Yes	87 (4.5)	92 (7.1)	
No	1838 (95.5)	1206 (92.9)	
Anemia (All Grade)			< .001
Yes	274 (14.2)	254 (19.6)	
No	1651 (85.5)	1044 (80.4)	
Anemia (High Grade)			.152
Yes	36 (1.9)	34 (2.6)	
No	1889 (98.1)	1264 (97.4)	
Thrombocytopenia (All Grade)			.369
Yes	353 (18.3)	222 (17.1)	
No	1572 (81.7)	1076 (82.9)	
Thrombocytopenia (High Grade)			.863
Yes	50 (2.6)	35 (2.7)	
No	1875 (97.4)	1263 (97.3)	
Neutropenia (All Grade)			< .001
Yes	704 (36.6)	663 (51.1)	
No	1221 (63.4)	635 (48.9)	
Neutropenia (High Grade)			< .001
Yes	464 (24.1)	481 (37.1)	
No	1461 (75.9)	817 (62.9)	
Febrile Neutropenia			.276
Yes	55 (2.9)	29 (2.2)	
No	1870 (97.1)	1269 (97.8)	

[a]Only among patients receiving oxaliplatin.

female versus male subjects needs to be addressed. Moreover, it is important for practicing physicians to pay attention to these differences while counseling their female patients with metastatic colorectal cancer. It is important to clarify that some chemotherapy adverse effects might be higher in female compared to male subjects.

In conclusion, female subjects with metastatic colorectal cancer receiving first-line chemotherapy demonstrated higher rates of a number of toxicities (essentially hematologic and gastrointestinal in nature). Additional studies into the differential effect of systemic therapy on female versus male subjects are needed.

Clinical Practice Points

- A pooled analysis of data sets from 5 clinical trials (NCT00115765, NCT00364013, NCT00272051, NCT00305188, NCT00384176) was performed.
- Kaplan-Meier analysis and log-rank testing were used to assess the differences in overall and progression-free survival between male and female subjects. Chi-square testing was used to examine the differences in the incidence of different toxicities between male and female subjects.
- A total of 3223 participants were included in the pooled cohort, among which there were 1925 male and 1298 female subjects.
- Kaplan-Meier survival analysis and log-rank testing was utilized to compare overall and progression-free survival outcomes between male and female subjects. For both end points, there was no difference between male and female subjects ($P = .884$; $P = .647$, respectively).
- Comparing female to male subjects, female subjects were more likely to have alopecia (20% vs. 8.6%; $P < .001$), all-grade diarrhea

(60.3% vs. 56.7%; $P = .039$), all-grade nausea and vomiting (68.7% vs. 56.6%; $P < .001$), high-grade nausea and vomiting (7.1% vs. 4.5%; $P = .002$), all-grade anemia (19.6% vs. 14.2%; $P < .001$), all-grade neutropenia (51.1% vs. 36.6%; $P < .001$), and high-grade neutropenia (37.1% vs. 24.1%; $P < .001$).

Acknowledgments

This publication is based on research using information obtained from www.projectdatasphere.org, which is maintained by Project Data Sphere LLC. Neither Project Data Sphere LLC nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this publication.

Disclosure

The author stated that he has no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.12.006.

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Supplemental Data

Supplemental Table 1 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of All-Grade Diarrhea

Parameter	Odds Ratio (95% CI)	*P*
Age (years) (continuous)	1.014 (1.007-1.021)	< .001
ECOG PS		.511
0	Reference	
1	1.051 (0.906-1.218)	
Sex		.019
Male	Reference	
Female	1.193 (1.029-1.384)	
BMI (continuous)	1.022 (1.007-1.037)	.004
Race		.173
White	Reference	
Nonwhite	1.195 (0.925-1.544)	
Bevacizumab-Containing Treatment		< .001
Yes	Reference	
No	0.747 (0.645-0.866)	
Panitumumab-Containing Treatment		.001
Yes	Reference	
No	0.759 (0.645-0.892)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 2 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of All-Grade Stomatitis

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	0.996 (0.989-1.004)	.303
ECOG PS		.186
0	Reference	
1	0.891 (0.751-1.057)	
Sex		.076
Male	Reference	
Female	1.165 (0.984-1.378)	
BMI (continuous)	0.988 (0.972-1.004)	.146
Race		.003
White	Reference	
Nonwhite	0.619 (0.453-0.846)	
Bevacizumab-Containing Treatment		< .001
Yes	Reference	
No	0.661 (0.558-0.784)	
Panitumumab-Containing Treatment		< .001
Yes	Reference	
No	0.690 (0.578-0.825)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 3 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of All-Grade Nausea and Vomiting

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	0.987 (0.980-0.994)	< .001
ECOG PS		.662
0	Reference	
1	0.967 (0.832-1.124)	
Sex		< .001
Male	Reference	
Female	1.655 (1.422-1.927)	
BMI (continuous)	1.031 (1.015-1.047)	< .001
Race		.253
White	Reference	
Nonwhite	1.165 (0.897-1.515)	
Bevacizumab-Containing Treatment		.009
Yes	Reference	
No	0.819 (0.705-0.951)	
Panitumumab-Containing Treatment		.218
Yes	Reference	
No	1.107 (0.942-1.302)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 4 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of High-Grade Nausea and Vomiting

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	0.999 (0.985-1.013)	.882
ECOG PS		.019
0	Reference	
1	1.455 (1.064-1.989)	
Sex		.004
Male	Reference	
Female	1.582 (1.161-2.156)	
BMI (continuous)	1.008 (0.980-1.038)	.573
Race		.178
White	Reference	
Nonwhite	0.667 (0.370-1.203)	
Bevacizumab-Containing Treatment		.004
Yes	Reference	
No	0.620 (0.449-0.857)	
Panitumumab-Containing Treatment		< .001
Yes	Reference	
No	0.478 (0.350-0.654)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 5 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of All-Grade Anemia

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	1.007 (0.998-1.016)	.125
ECOG PS		.048
0	Reference	
1	1.220 (1.002-1.486)	
Sex		< .001
Male	Reference	
Female	1.443 (1.187-1.754)	
BMI (continuous)	0.984 (0.966-1.003)	.106
Race		.033
White	Reference	
Nonwhite	1.387 (1.027-1.873)	
Bevacizumab-Containing Treatment		< .001
Yes	Reference	
No	0.424 (0.345-0.521)	
Panitumumab-Containing Treatment		< .001
Yes	Reference	
No	0.521 (0.426-0.637)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 6 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of All-Grade Neutropenia

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	1.016 (1.009-1.023)	< .001
ECOG PS		.979
0	Reference	
1	1.002 (0.863-1.163)	
Sex		< .001
Male	Reference	
Female	1.904 (1.641-2.210)	
BMI (continuous)	0.982 (0.967-0.996)	.014
Race		.014
White	Reference	
Nonwhite	1.373 (1.067-1.768)	
Bevacizumab-Containing Treatment		< .001
Yes	Reference	
No	1.592 (1.370-1.849)	
Panitumumab-Containing Treatment		< .001
Yes	Reference	
No	0.693 (0.590-0.814)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 7 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of High-Grade Neutropenia

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	1.024 (1.016-1.031)	< .001
ECOG PS		.728
0	Reference	
1	0.972 (0.826-1.143)	
Sex		< .001
Male	Reference	
Female	1.985 (1.690-2.330)	
BMI (continuous)	0.957 (0.941-0.974)	< .001
Race		.219
White	Reference	
Nonwhite	1.188 (0.902-1.563)	
Bevacizumab-Containing Treatment		< .001
Yes	Reference	
No	1.533 (1.302-1.804)	
Panitumumab-Containing Treatment		< .001
Yes	Reference	
No	0.720 (0.606-0.855)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

Supplemental Table 8 Multivariate Logistic Regression Analysis for Factors Affecting Occurrence of All-Grade Alopecia

Parameter	Odds Ratio (95% CI)	*P*
Age (continuous)	0.998 (0.989-1.008)	.745
ECOG PS		.106
0	Reference	
1	0.834 (0.669-1.039)	
Sex		< .001
Male	Reference	
Female	2.616 (2.111-3.242)	
BMI (continuous)	0.999 (0.978-1.019)	.889
Race		.846
White	Reference	
Nonwhite	0.964 (0.669-1.389)	
Bevacizumab-Containing Treatment		.517
Yes	Reference	
No	0.931 (0.749-1.156)	
Panitumumab-Containing Treatment		.025
Yes	Reference	
No	0.772 (0.615-0.968)	

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.