# Effect of Body Mass Index on 5-FU-Based Chemotherapy Toxicity and Efficacy Among Patients With Metastatic Colorectal Cancer; A Pooled Analysis of 5 Randomized Trials

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## Abstract

**We conducted a pooled analysis of 5 clinical trials to assess the effect of baseline body mass index (BMI) on the toxicity and efficacy of systemic chemotherapy among patients with metastatic colorectal cancer (CRC). Lower BMI was associated with a higher risk of hematological toxicities (anemia and neutropenia) whereas higher BMI was associated with a higher risk of nausea, vomiting, and peripheral neuropathy, and seemed to be associated with better overall survival among patients with metastatic CRC.**

**Introduction:** We conducted this study to assess the effect of baseline body mass index (BMI) on the toxicity and efficacy of systemic chemotherapy among patients with metastatic colorectal cancer (CRC). **Patients and Methods:** This was a pooled analysis of 5 clinical trials (NCT00115765, NCT00364013, NCT00272051, NCT00305188, and NCT00384176), which were accessed from the Project Data Sphere (www.projectdatasphere.org) platform. Multivariable logistic regression analysis was used to assess the relationship between BMI and the probability of different toxicities. Kaplan–Meier survival estimates were used to assess the effect of BMI on overall and progression-free survival. Multivariable Cox regression analysis was additionally conducted to evaluate the effect of BMI on overall and progression-free survival. **Results:** A total of 3155 patients were included in the current analysis. Within multivariable logistic regression analysis, higher BMI was associated with higher probability of all-grade nausea and vomiting (odds ratio [OR], 1.025; 95% confidence interval [CI], 1.009-1.042; $P = .002$) and peripheral neuropathy (OR, 1.018; 95% CI, 1.001-1.034; $P = .036$; analysis restricted to oxaliplatin-treated patients). Lower BMI was associated with a higher probability of all-grade anemia (OR, 0.975; 95% CI, 0.956-0.995; $P = .015$), high-grade anemia (OR, 0.941; 95% CI, 0.890-0.994; $P = .030$), all-grade neutropenia (OR, 0.983; 95% CI, 0.968-0.999; $P = .034$), and high-grade neutropenia (OR, 0.962; 95% CI, 0.945-0.979; $P < .001$). Higher BMI also seemed to correlate with better overall survival in a multivariable Cox regression model (hazard ratio as a continuous variable: 0.977; 95% CI, 0.967-0.988; $P < .001$). **Conclusion:** Lower BMI was associated with a higher risk of hematological toxicities (anemia and neutropenia) whereas higher BMI might be associated with a higher risk of nausea, vomiting, and peripheral neuropathy. Higher BMI also seemed to be associated with better overall survival among patients with metastatic CRC.


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## Introduction

Numerous studies have examined a possible relationship between body mass index (BMI) and cancer incidence and mortality.[1,2] However, little is known about the potential effect of BMI on the toxicity of anticancer therapy in general, and 5-fluorouracil (5-FU)-based treatment of metastatic colorectal cancer (CRC) in particular.[3]

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To provide a robust, bias-free assessment of the potential relationship between BMI and toxicity of systemic therapy, such an assessment should be on the basis of a prospectively collected data set, which prospectively collects BMI data at the start of cancer therapy and then the incidence of difference toxicities.

More recently, the Project Data Sphere (PDS; www.projectdatasphere.org) platform has been launched, which provided a unique opportunity to access deidentified data sets of a number of landmark cancer clinical trials.[4] This provided an excellent chance to perform the previously described assessment about the relationship between BMI and toxicity of treatment of metastatic CRC. The

**Table 1** Baseline Characteristics of Included Patients in the Cohort (3155 Patients)

| Parameter | BMI <25 (1384 Patients) | BMI ≥25 (1771 Patients) | *P* |
|---|---|---|---|
| **Age** | | | <.001 |
| Mean (SD) | 59.6 (11.9) | 61.7 (10.2) | |
| Missing | 0 | 0 | |
| **Race** | | | .043 |
| Caucasian | 1235 (89.2) | 1624 (91.7) | |
| Others | 147 (10.6) | 143 (8.1) | |
| Unknown | 2 (0.1) | 4 (0.2) | |
| **Sex** | | | <.001 |
| Male | 757 (54.7) | 1137 (64.2) | |
| Female | 627 (45.3) | 634 (35.8) | |
| **ECOG** | | | .002 |
| 0 | 747 (54) | 1066 (60.2) | |
| 1 | 599 (43.3) | 672 (37.9) | |
| 2 | 36 (2.6) | 28 (1.6) | |
| Missing | 2 (0.1) | 5 (0.3) | |
| **Primary Tumor Site** | | | .007 |
| Colon | 743 (53.7) | 971 (54.8) | |
| Rectum | 328 (23.7) | 474 (26.8) | |
| Unknown | 313 (22.6) | 326 (18.4) | |
| **Number of Organs With Distant Metastases** | | | .001 |
| 1 | 378 (27.3) | 588 (33.2) | |
| ≥2 | 690 (49.9) | 856 (48.3) | |
| Unknown | 316 (22.8) | 327 (18.5) | |
| **Panitumumab-Containing Chemotherapy** | | | <.001 |
| Yes | 340 (24.6) | 548 (30.9) | |
| No | 1044 (75.4) | 1223 (69.1) | |
| **Bevacizumab-Containing Chemotherapy** | | | <.001 |
| Yes | 617 (44.6) | 901 (50.9) | |
| No | 767 (55.4) | 870 (49.1) | |
| **Oxaliplatin-Containing Chemotherapy** | | | .198 |
| Yes | 1319 (95.3) | 1664 (94.0) | |
| No | 61 (4.4) | 103 (5.8) | |
| Unknown | 4 (0.3) | 4 (0.2) | |
| **Diabetes Mellitus** | | | <.001 |
| Yes | 63 (4.6) | 199 (11.2) | |
| No | 887 (64.0) | 1072 (60.5) | |
| Unknown | 434 (31.4) | 500 (28.3) | |
| **Hypertension** | | | <.001 |
| Yes | 238 (17.2) | 556 (31.4) | |
| No | 712 (51.4) | 715 (40.3) | |
| Unknown | 434 (31.4) | 500 (28.3) | |

Data are presented as n (%) except where otherwise noted.
Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group.

**Table 2** Incidence of Toxicities According to BMI

| Parameter | BMI <25 (1384 Patients) | BMI ≥25 (1771 Patients) | *P* |
|---|---|---|---|
| **Serious Adverse Events** | | | .931 |
| Yes | 534 (38.6) | 686 (38.7) | |
| No | 850 (61.4) | 1085 (61.3) | |
| **Fatal Adverse Events** | | | .780 |
| Yes | 75 (5.4) | 92 (5.2) | |
| No | 1309 (94.6) | 1679 (95.5) | |
| **Any Cardiac Adverse Events** | | | .376 |
| Yes | 103 (7.4) | 147 (8.3) | |
| No | 1281 (92.6) | 1624 (91.7) | |
| **Arrhythmias** | | | .047 |
| Yes | 54 (3.9) | 96 (5.4) | |
| No | 1330 (96.1) | 1675 (94.6) | |
| **Ischemic Events** | | | .757 |
| Yes | 26 (1.9) | 36 (2) | |
| No | 1358 (98.1) | 1735 (98) | |
| **Alopecia** | | | .468 |
| Yes | 188 (13.6) | 225 (12.7) | |
| No | 1196 (86.4) | 1546 (87.3) | |
| **Peripheral Neuropathy**[a] | | | .042 |
| Yes | 7641 (48.6) | 871 (52.3) | |
| No | 678 (51.4) | 793 (47.7) | |
| **Diarrhea-All Grade** | | | .002 |
| Yes | 761 (55) | 1071 (60.5) | |
| No | 623 (45) | 700 (39.5) | |
| **Diarrhea-High Grade** | | | .429 |
| Yes | 169 (12.2) | 233 (13.2) | |
| No | 1215 (87.8) | 1538 (86.8) | |
| **Stomatitis-All Grade** | | | .767 |
| Yes | 340 (24.6) | 427 (24.1) | |
| No | 1044 (75.4) | 1344 (75.9) | |
| **Stomatitis-High Grade** | | | .409 |
| Yes | 24 (1.7) | 38 (2.1) | |
| No | 1360 (98.3) | 1733 (97.9) | |
| **Nausea/Vomiting-All Grade** | | | .027 |
| Yes | 818 (59.1) | 1115 (63) | |
| No | 566 (40.9) | 656 (37) | |
| **Nausea/Vomiting-High Grade** | | | .507 |
| Yes | 81 (5.9) | 94 (5.3) | |
| No | 1303 (94.1) | 1677 (94.7) | |
| **Anemia-All Grade** | | | .043 |
| Yes | 249 (18) | 271 (15.3) | |
| No | 1135 (82) | 1500 (84.7) | |
| **Anemia-High Grade** | | | .008 |
| Yes | 41 (3) | 28 (1.6) | |
| No | 1343 (97) | 1743 (98.4) | |
| **Thrombocytopenia-All Grade** | | | .514 |
| Yes | 240 (17.3) | 323 (18.2) | |
| No | 1144 (82.7) | 1448 (81.8) | |

**Table 2** Continued

| Parameter | BMI <25 (1384 Patients) | BMI ≥25 (1771 Patients) | *P* |
|---|---|---|---|
| **Thrombocytopenia-High Grade** | | | .371 |
| Yes | 32 (2.3) | 50 (2.8) | |
| No | 1352 (97.7) | 1721 (97.2) | |
| **Neutropenia-All Grade** | | | .024 |
| Yes | 619 (44.7) | 721 (40.7) | |
| No | 765 (55.3) | 1050 (59.3) | |
| **Neutropenia-High Grade** | | | <.001 |
| Yes | 461 (33.3) | 466 (26.3) | |
| No | 923 (66.7) | 1305 (73.7) | |
| **Febrile Neutropenia** | | | .927 |
| Yes | 36 (2.6) | 47 (2.7) | |
| No | 1348 (97.4) | 1724 (97.3) | |

Data are presented as n (%) except where otherwise noted.
Abbreviation: BMI = body mass index.
[a]Only among patients who received oxaliplatin.

current study was thus on the basis of a pooled analysis of the 5 clinical trials in the PDS platform that dealt with 5−FU-based treatment in the first-line treatment of metastatic CRC.

Understanding the interaction between BMI and outcomes of chemotherapy-treated metastatic CRC should provide physicians and patients alike with a more personalized assessment of the outcomes of cancer treatment.

### *Objective*

The objective of this study was to assess the effect of baseline BMI on the toxicity and efficacy of systemic chemotherapy among patients with metastatic CRC.

## Patients and Methods

### *Selection of the Study Cohort*

The study cohort comprised participants from 5 previously published randomized trials; (namely: NCT00115765, NCT00364013, NCT00272051, NCT00305188, and NCT00384176). These 5 trials evaluated different 5−FU-based regimens in the first-line treatment of metastatic CRC. Within the PDS platform, data sets from investigational and control arms were provided for 2 of these trials; whereas in the remaining 3 trials, only data sets from control arms were provided. Details about these trials are provided in Supplemental Table 1 in the online version. Primary findings of the trials NCT00384176, NCT00364013, and NCT00115765 are discussed elsewhere.[5-7]

A total of 3223 metastatic CRC patients were available from the data sets of the 5 trials. After excluding 65 patients with unknown BMI and 3 patients with BMI >50, a total of 3155 patients were finally included in the current analysis.

### *Ethical Approval*

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent was obtained from all participants included in the studies pooled in this analysis.

### *Data Collection*

Where available, the following data were collected from each of the included data sets: BMI (at time of study randomization), age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status, number of metastatic sites, primary tumor location, codiagnosis with hypertension and/or diabetes mellitus, cotreatment with oxaliplatin, bevacizumab, and/or panitumumab. Data about the following toxicities were also collected: arrhythmias, ischemic cardiac events, any cardiac adverse events, serious adverse events, fatal adverse events, diarrhea (all-grade and high-grade), nausea and vomiting (all-grade and high-grade), stomatitis (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, alopecia, and peripheral neuropathy.

Overall survival was defined in the current analysis as the time from study randomization until death from any cause. Patients who were alive at the end of the follow-up period were censored. Progression-free survival was defined as the time from study randomization until disease progression and/or death. Patients who were alive without progression at the end of follow-up period were censored. According to the available protocols of the primary studies, dosing was on the basis of actual body weight in all patients.

### *Statistical Analysis*

For the sake of descriptive statistics, patients were categorized into 2 BMI groups (<25 and ≥25). $\chi^2$ Testing was used to compare baseline categorical variables as well as different toxicities between the 2 groups of patients. Analysis of variance testing was used to compare continuous variables between both groups.

Multivariable logistic regression analysis was used to further assess the relationship between BMI and the probability of different toxicities. This analysis was adjusted for all the available baseline/treatment characteristics of the included patients (namely, age, sex, race, number of metastatic sites, primary tumor location, ECOG performance score, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment).

**Table 3** Multivariate Logistic Regression Analysis for the Effect of BMI on the Probability of Selected Toxicities[a]

| Selected Toxicity | Odds Ratio (95% CI) | *P* |
|---|---|---|
| Arrythmias | 1.016 (0.983-1.050) | .337 |
| All-Grade Diarrhea | 1.014 (0.998-1.030) | .080 |
| All-Grade Nausea And Vomiting | 1.025 (1.009-1.042) | .002 |
| All-Grade Anemia | 0.975 (0.956-0.995) | .015 |
| High-Grade Anemia | 0.941 (0.890-0.994) | .030 |
| All-Grade Neutropenia | 0.983 (0.968-0.999) | .034 |
| High-Grade Neutropenia | 0.962 (0.945-0.979) | <.001 |
| Peripheral Neuropathy[b] | 1.018 (1.001-1.034) | .036 |

For all analyses BMI was treated as a continuous variable.
Abbreviation: BMI = body mass index.
[a]Each of which was adjusted for age, sex, race, number of metastatic sites, primary tumor location, Eastern Cooperative Oncology Group performance status, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment.
[b]Only for patients who received oxaliplatin-based treatment.

Kaplan–Meier survival estimates/log-rank testing were used to assess the effect of BMI on overall and progression-free survival. Multivariable Cox regression analysis was additionally conducted to evaluate the effect of BMI on overall and progression-free survival. This was also adjusted for all available baseline/treatment characteristics as previously stated. For logistic and Cox regression models, BMI was analyzed as a continuous variable and as a categorical variable (<25 and ≥25).

SPSS statistics (version 20.0; IBM Corp) was used to conduct the statistical calculations.

## Results

### *Patients' Characteristics*

Among 3155 patients included in the current analysis, a total of 97 patients (3.1%) were underweight (BMI <18.5), 1287 patients (40.8%) had normal BMI (18.5 to <25), 1148 patients (36.4%) had overweight BMI (25 to <30), and 623 patients (19.7%) had obese BMI (≥30). Mean BMI in the overall cohort was 26.26 (SD, 4.97).

Comparing patients with BMI <25 versus those with BMI ≥25, patients with higher BMI were more likely to have older age ($P < .001$), male sex ($P < .001$), Caucasian race ($P = .043$), ECOG performance score of 0 ($P = .002$), lower number of metastatic sites ($P = .001$), higher probability of bevacizumab-containing ($P < .001$) and panitumumab-containing ($P < .001$) regimens and higher rates of hypertension ($P < .001$) and diabetes mellitus ($P < .001$) codiagnosis. There was, however, no difference in probability of oxaliplatin-based treatment ($P = .198$; Table 1). Mean follow-up duration for the entire cohort was 17.95 months (SD, 11.04).

### *Incidence of Toxicities According to BMI*

In a comparison of both groups of patients together, patients with higher BMI were more likely to experience cardiac arrhythmias ($P = .047$), peripheral neuropathy ($P = .042$; assessed only among oxaliplatin-treated patients), all-grade diarrhea ($P = .002$), and all-grade nausea/vomiting ($P = .027$). Patients with lower BMI were more likely to experience all-grade anemia ($P = .043$), high-grade anemia ($P = .008$), all-grade neutropenia ($P = .024$), and high-grade neutropenia ($P < .001$).

There was no difference, however, between both groups with regard to serious adverse events ($P = .931$), fatal adverse events ($P = .780$), any cardiac adverse event ($P = .376$), ischemic cardiac events ($P = .757$), alopecia ($P = .468$), high-grade diarrhea ($P = .429$), all-grade stomatitis ($P = .767$), high-grade stomatitis ($P = .409$), high-grade nausea and vomiting ($P = .507$), all-grade thrombocytopenia ($P = .514$), high-grade thrombocytopenia ($P = .371$), and febrile neutropenia ($P = .927$; Table 2).

Multivariable logistic regression analysis was then conducted to confirm the relationship between BMI (as a continuous variable) and selected toxicities (which were significant in $\chi^2$ testing). Higher BMI was associated with higher probability of all-grade nausea and vomiting (odds ratio [OR], 1.025; 95% confidence interval [CI], 1.009-1.042; $P = .002$) and peripheral neuropathy (OR, 1.018; 95% CI, 1.001-1.034; $P = .036$; analysis restricted to oxaliplatin-treated patients). Lower BMI was associated with a higher probability of all-grade anemia (OR, 0.975; 95% CI, 0.956-0.995; $P = .015$), high-grade anemia (OR, 0.941; 95% CI, 0.890-0.994; $P = .030$), all-grade neutropenia (OR, 0.983; 95% CI, 0.968-0.999; $P = .034$), and high-grade neutropenia (OR, 0.962; 95% CI, 0.945-0.979; $P < .001$; Table 3). BMI did not seem, however, to be independently associated with all-grade diarrhea (OR, 1.014; 95% CI, 0.998-1.030; $P = .080$).

The same analysis was repeated using BMI as a categorical variable with generally similar findings (see Supplemental Table 2 in the online version).

### *Survival Outcomes in Relationship to BMI*

Kaplan–Meier analysis was used to compare overall and progression-free survival according to BMI at the time of study randomization. Higher BMI was associated with better overall survival ($P = .001$; Figure 1A). Likewise, higher BMI was associated with better progression-free survival ($P = .003$; Figure 1B).

Moreover, higher BMI correlated with better overall and progression-free survival in multivariable Cox regression models (whether approached as a continuous variable or as a categorical variable). Hazard ratio for overall survival as a continuous variable was 0.977; 95% CI, 0.967-0.988; $P < .001$; hazard ratio for overall survival as a categorical variable was 0.854; 95% CI, 0.769-0.949; $P = .003$. Hazard ratio for progression-free survival as a continuous variable was 0.983; 95% CI, 0.974-0.993; $P < .001$; hazard ratio for progression-free survival as a categorical variable was 0.901; 95% CI, 0.824-0.985; $P = .022$ (Table 4). An additional analysis for the effect of BMI on overall and progression-free survival was conducted with the BMI classified into 4 categories (normal, overweight, underweight, and obese) and the results were generally consistent with the previous findings (hazard ratio for normal vs. obese BMI for overall survival: 1.219; 95% CI, 1.055-1.410; $P = .007$; hazard ratio for normal vs. obese BMI for progression-free survival: 1.200; 95% CI, 1.060-1.358; $P = .004$; Table 4).

## Discussion

In the current study we evaluated the effect of BMI on toxicity and efficacy of 5–FU-based treatment for metastatic CRC. It showed that lower BMI is associated with a higher risk of

**Figure 1** Kaplan–Meier Curve for (A) Overall Survival; (B) Progression-free Survival According to Patient Body Mass Index (BMI)

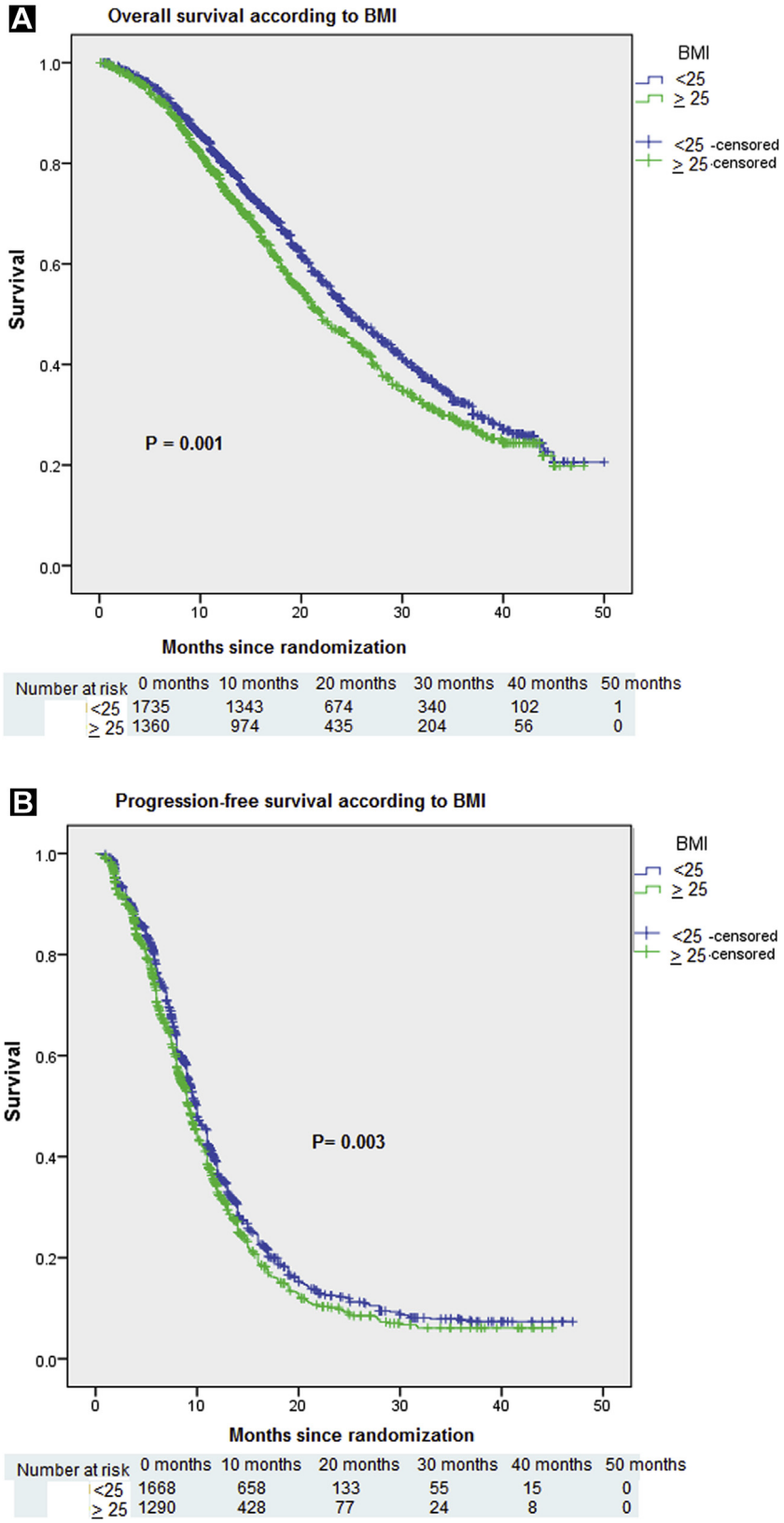

**Table 4** Multivariate Cox Regression Analysis for the Effect of BMI on Overall and Progression-Free Survival

| Parameter[a] | Hazard Ratio (95% CI) | *P* |
|---|---|---|
| **Overall Survival** | | |
| BMI (categorical variable) | | .003 |
| BMI <25 | Reference | |
| BMI ≥25 | 0.854 (0.769-0.949) | |
| BMI (categorical variable) | | |
| Obese (BMI >30) | Reference | |
| Normal (18.5 to <25) | 1.219 (1.055-1.410) | .007 |
| Overweight (25 to <30) | 1.082 (0.935-1.251) | .292 |
| Underweight (<18.5) | 1.464 (1.076-1.992) | .015 |
| BMI (continuous variable) | 0.977 (0.967-0.988) | <.001 |
| **Progression-Free Survival** | | |
| BMI (categorical variable) | | .022 |
| BMI <25 | Reference | |
| BMI ≥25 | 0.901 (0.824-0.985) | |
| BMI (categorical variable) | | |
| Obese (BMI >30) | Reference | |
| Normal (18.5 to <25) | 1.200 (1.060-1.358) | .004 |
| Overweight (25 to <30) | 1.139 (1.007-1.288) | .038 |
| Underweight (<18.5) | 1.391 (1.057-1.831) | .019 |
| BMI (continuous variable) | 0.983 (0.974-0.993) | <.001 |

[a]Each of these analyses was adjusted for age, sex, race, number of metastatic sites, primary tumor location, Eastern Cooperative Oncology Group performance status, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment.

hematological toxicities (anemia and neutropenia) whereas higher BMI might be associated with a higher risk of nausea, vomiting, and peripheral neuropathy. Higher BMI also seems to be associated with better overall and progression-free survival.

The current study is in line with a previously published secondary analysis of the Intergroup trial 0114 (a randomized trial of adjuvant chemoradiotherapy for patients with stage II/III rectal cancer). In that secondary analysis, obese patients were less likely to have Grade 3/4 neutropenia.[8] It is also in line with a previously published secondary analysis of a randomized trial of adjuvant chemotherapy in colon cancer (Intergroup Trial 0089), which has also shown a lower incidence of Grade 3/4 neutropenia among obese patients.[9] The current study is also in line with a previously published systematic review, which showed that obese patients experience generally lower hematological toxicities compared with nonobese patients when chemotherapy is dosed on the basis of actual body weight.[10] However, this systematic review incorporated 13 different cancer types with 21 different regimens of chemotherapy. The current study was thus needed to confirm the results of that analysis in the context of 5−FU-based chemotherapy for metastatic CRC.

The current study is also in line with previous studies suggesting a higher probability of oxaliplatin-induced neuropathy among obese patients.[11,12] This information will be useful in terms of counseling colon cancer patients about their personalized risk of toxicity.

The current study is also in line with a previously published pooled analysis from the Analysis and Research in Cancers of the Digestive System (ARCAD) database, which suggested that lower BMI is associated with a higher risk of progression and/or death among patients with metastatic CRC treated with first-line systemic therapy.[13] That pooled analysis, however, did not comment on the effect of BMI on observed toxicities among included patients.

It has to be remembered that among patients who receive adjuvant treatment for colon cancer, very obese patients, BMI ≥35 is associated with increased risk of colon cancer recurrence and death.[14] A possible link between lower BMI and higher rates of hematological toxicities as well as higher risks of progression and/or death among metastatic CRC patients might lie in cancer cachexia, which has been associated with diminished survival and poor performance status among cancer patients.[15]

The current study has a number of limitations that need to be addressed. First, despite the prospective nature of data collection in the current study, the primary question(s) of primary studies was not the effect of BMI on outcomes of treatment. Thus, the current study represents a retrospective analysis of this prospectively collected pooled data set. Second, some baseline clinicopathological information was missing in the current data set. That said, this missing information is not expected to radically change the primary conclusions of the current study with regard to efficacy or toxicity. Third, the generalizability of results from the current study (derived from a pooled clinical trial data set) to patients treated in the real-world setting might be an issue. Having said that, the distribution of adiposity in the current data set was quite similar to previously published studies that evaluated the distribution of adiposity in the general population of the United States.[16] Fourth, some of the evaluated toxicities in the current analysis were observed in a small number of patients. This might have prevented the demonstration of subtle differences in chemotherapy-related toxicities on the basis of BMI.

These limitations need to be weighed against the clear strengths of the current study; most importantly, the reliance on well conducted, prospective clinical trials as the basis of data collection which increases the credibility of the current analysis compared with previously published retrospective studies that tackled the same research question.

Findings from the current study suggest that overweight/obese patients do not have a generally higher rate of hematological or nonhematological toxicities. This provides additional support to the American Society of Clinical Oncology (ASCO) recommendations for the use of actual body weight (rather than adjusted body weight) in the calculation of chemotherapy doses for overweight and obese patients.[17]

## Conclusion

Lower BMI was associated with a higher risk of hematological toxicities (anemia and neutropenia) whereas higher BMI might be associated with a higher risk of nausea, vomiting, and peripheral neuropathy. Higher BMI also seemed to be associated with better overall and progression-free survival among patients with metastatic CRC.

### *Clinical Practice Points*

- A pooled analysis of 5 clinical trials to assess the effect of baseline BMI on the toxicity and efficacy of systemic chemotherapy among patients with metastatic CRC.

- Lower BMI was associated with a higher risk of hematological toxicities (anemia and neutropenia) whereas higher BMI was associated with a higher risk of nausea, vomiting, and peripheral neuropathy, and seemed to be associated with better overall survival among patients with metastatic CRC.
- Findings from the current study suggest that overweight/obese patients do not have a generally higher rate of hematological or nonhematological toxicities. This provides additional support to the ASCO recommendations for the use of actual body weight (rather than adjusted body weight) in the calculation of chemotherapy doses for overweight and obese patients.

## Acknowledgments

This study was on the basis of 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 Web site have contributed to, approved, or are in any way responsible for the contents of this publication.

## Disclosure

The author has stated no conflicts of interest exist.

## Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.07.005.

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**Supplemental Table 1** Description of Cohorts Included in the Current Analysis

| Study | Start Date | Completion Date | Treatment Regimen | Patients Within the Pooled Cohort, n (%) |
|---|---|---|---|---|
| NCT00115765 (PACCE) | June 2005 | December 2009 | Investigational arm: chemotherapy and bevacizumab and panitumumab<br>Control arm: chemotherapy and bevacizumab | 840 (26.6) |
| NCT00364013 (PRIME) | August 2006 | March 2013 | Investigational arm: FOLFOX and panitumumab<br>Control arm: FOLFOX alone | 934 (29.6) |
| NCT00272051[a] | July 2002 | May 2004 | Control arm: FOLFOX and placebo | 319 (10.1) |
| NCT00305188[a] | December 2005 | October 2009 | Control arm: FOLFOX and placebo | 423 (13.4) |
| NCT00384176 (Horizon III)[a] | August 2006 | August 2015 | Control arm: FOLFOX and bevacizumab | 639 (20.3) |

Abbreviations: FOLFOX = 5FU, Leucovorin and Oxaliplatin; PACCE = Panitumumab Advanced Colorectal Cancer Evaluation Study; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.
[a]In these 3 studies, only comparator arms were included.

**Supplemental Table 2** Multivariate Logistic Regression Analysis for the Effect of BMI (as a Categorical Variable) on the Probability of Selected Toxicities[a]

| Selected Toxicity | BMI | Odds Ratio (95% CI) | *P* |
|---|---|---|---|
| Arrythmias | <25<br>≥25 | Reference<br>1.292 (0.906-1.841) | .157 |
| All-Grade Diarrhea | <25<br>≥25 | Reference<br>1.144 (0.985-1.329) | .078 |
| All-Grade Nausea and Vomiting | <25<br>≥25 | Reference<br>1.200 (1.030-1.398) | .019 |
| All-Grade Anemia | <25<br>≥25 | Reference<br>0.706 (0.576-0.866) | .001 |
| High-Grade Anemia | <25<br>≥25 | Reference<br>0.648 (0.388-1.083) | .098 |
| All-Grade Neutropenia | <25<br>≥25 | Reference<br>0.907 (0.778-1.057) | .211 |
| High-Grade Neutropenia | <25<br>≥25 | Reference<br>0.760 (0.645-0.896) | .001 |
| Peripheral Neuropathy[b] | <25<br>≥25 | Reference<br>1.138 (0.971-1.333) | .111 |

Abbreviation: BMI = body mass index.
[a]Each of these analyses was adjusted for age, sex, race, number of metastatic sites, primary tumor location, Eastern Cooperative Oncology Group performance status, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment.
[b]Only for patients receiving oxaliplatin-based treatment.