Body Mass Index Is Prognostic in Metastatic Colorectal Cancer: Pooled Analysis of Patients From First-Line Clinical Trials in the ARCAD Database

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose

In recent retrospective analyses of early-stage colorectal cancer (CRC), low and high body mass index (BMI) scores were associated with worsened outcomes. Whether BMI is a prognostic or predictive factor in metastatic CRC (mCRC) is unclear.

Patients and Methods

Individual data from 21,149 patients enrolled onto 25 first-line mCRC trials during 1997 to 2012 were pooled. We assessed both prognostic and predictive effects of BMI on overall survival and progression-free survival, and we accounted for patient and tumor characteristics and therapy type (targeted v nontargeted).

Results

BMI was prognostic for overall survival ($P < .001$) and progression-free survival ($P < .001$), with an L-shaped pattern. That is, risk of progression and/or death was greatest for low BMI; risk decreased as BMI increased to approximately 28 kg/m², and then it plateaued. Relative to obese patients, patients with a BMI of 18.5 kg/m² had a 27% increased risk of having a PFS event (95% CI, 20% to 34%) and a 50% increased risk of death (95% CI, 43% to 56%). Low BMI was associated with poorer survival for men than women (interaction $P < .001$). BMI was not predictive of treatment effect.

Conclusion

Low BMI is associated with an increased risk of progression and death among the patients enrolled on the mCRC trials, with no increased risk for elevated BMI, in contrast to the adjuvant setting. Possible explanations include negative effects related to cancer cachexia in patients with low BMI, increased drug delivery or selection bias in patients with high BMI, and potential for an interaction between BMI and molecular signaling pathways.

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INTRODUCTION

Each year in the world, more than 1,350,000 people receive a diagnosis of colorectal cancer (CRC), and approximately 700,000 men and women die as a result of the disease.¹ Obesity is associated with an increased incidence of CRC,² and body mass index (BMI) at the time of diagnosis is an independent prognostic factor among patients with early-stage disease whose primary tumors were resected and who received adjuvant chemotherapy with curative intent.³⁻⁶ In a recent analysis based on 25,291 patients from the ACCENT (Adjuvant Colon Cancer End Points) database, patients with stage II or III

disease who were either underweight or obese had overall survival (OS), disease-free survival, and time to recurrence (TTR) results that were worse than those of patients with an intermediate BMI.⁴ In the ACCENT analysis, high BMI particularly affected outcomes of men, with greater reductions in OS, disease-free survival, and TTR caused by obesity compared with women. Men with low BMIs additionally exhibited greater decreases in TTR than women with low BMI. No predictive effect was observed with BMI on the response to fluorouracil-based treatment in the adjuvant-therapy setting.

Despite strong documentation of the effect of BMI on long-term prognoses in early-stage colon

cancer, whether similar effects are seen in patients with metastatic CRC (mCRC) is unclear. Furthermore, we lack an understanding of whether patient BMI is predictive of a differential response to traditional chemotherapeutic drugs versus biologic agents to treat mCRC. In both cases, the mechanisms by which obesity influences the prognosis of colon cancer and its treatment response are poorly understood. Simkens et al⁷ analyzed data from patients in the clinical trials CAIRO (capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer) for chemotherapy and CAIRO2 for chemotherapy plus targeted (T) therapy to look for an association between BMI and OS.⁷ Among the 796 patients on the CAIRO study, a higher BMI category corresponded to significantly longer OS, but no association was found in CAIRO2 (n = 730). Other mechanisms that relate BMI and outcomes in mCRC have been hypothesized. For example, insulin resistance, hyperinsulinemia, increased levels of *insulin-like growth factor*, elevated levels of steroid and peptide hormones, and inflammatory markers appear to play a role in the connection between obesity and outcome in patients with cancer.⁸

Here, we examine whether patient BMI is prognostic for primary outcomes in mCRC and whether BMI is predictive of the patient response to therapy. We conducted a pooled analysis of individual patient data from 21,149 persons enrolled on 25 recent, first-line clinical trials included in the ARCAD (Aide et Recherche en Cancérologie Digestive)⁹ database, in which both traditional chemotherapies and biologic agents were evaluated. In contrast to most previous investigations, our investigation treated BMI as a continuous variable rather than categorizing it according to pre-specified cut points. This allowed for a more detailed and visually intuitive representation of its effect.

PATIENTS AND METHODS

Database

The database created by the ARCAD Foundation contains patient-level data from more than 33,000 individuals enrolled on 39 international first-line and subsequent-line clinical trials for mCRC conducted from 1997 to the present.⁹ The focus of ARCAD is integration of high-quality data across similar trials with similar patient populations, with the goal of powering definitive evaluations of key trial and patient characteristics, such as end points and prognostic factors that will inform future trials and research endeavors. Since its inception, the ARCAD database has been used to evaluate progression-free survival (PFS) as a surrogate end point for OS¹⁰ and to demonstrate that patient age is a strong prognostic factor for OS and PFS; young patients have the highest risk.¹¹ In the present analysis, patients from first-line trials included in the ARCAD database with available baseline BMI—or, as an alternative, height and weight—and relevant outcome data were included in both prognostic and predictive analyses. Nonprimary variables with less than 30% missing data were imputed by means of multiple imputation,¹² for which the missing-at-random assumption was both statistically confirmed and practically assumed given that all factors were collected at baseline. The primary end points were OS, defined as time from random assignment to death as a result of any cause, and PFS, defined as the time from random assignment to the earlier occurrence of death or disease progression.

Descriptive Analyses

Patient characteristics were described, and differences in BMI distribution by other variables were tested by using *t* tests for two groups or an analysis of variance for more than two groups when the approximate normality of BMI could be reasonably assumed. Otherwise, Wilcoxon rank-sum and Kruskal-Wallis tests were performed, respectively.

BMI As Prognostic for Patient Outcomes

Cox proportional hazards models were used to build prognostic models for OS and PFS, and baseline BMI was a key covariate. All models were stratified by study-specific treatment arms and/or strategies to account for differential baseline hazard (risk) functions associated with individual treatments and studies and to allow estimation of purely prognostic effects of BMI. Although BMI is often treated as a categorical variable in statistical models, doing so forces the risk of outcomes—OS or PFS—to be completely flat within BMI categories and creates artificial discontinuities, or jumps, in risk from one category to the next that are often clinically difficult to interpret. As such, we chose to model BMI as a continuous variable and used restricted cubic splines to address possible nonlinearity of the BMI effect on the log relative hazard scale.¹³ First, the joint null hypotheses of no effect of BMI on outcomes and linearity of the BMI effect were tested in single variable models for OS and PFS, for which both $P < .05$ and the presence of a clinically meaningful or clinically nonlinear BMI-outcome relationship were deemed necessary to declare prognostic significance of BMI or significant nonlinearity of BMI, respectively. Clinical significance and nonlinearity were assessed visually with spline plots, which showed risk of progression or death as a continuous function of BMI on the relative hazard scale. When no significant nonlinearity was found, BMI was subsequently treated as a continuous variable in the standard linear fashion; otherwise, splines continued to be used to model BMI in multivariable models.

Next, multivariable Cox models stratified by treatment arm within study were used to test the prognostic effect of BMI on OS and PFS after adjustment for available patient characteristics, including baseline age, sex, Eastern Cooperative Oncology Group performance status (PS), colon versus rectal cancer, previous chemotherapy, number of metastatic sites, and presence versus absence of liver, lung, or lymph node metastases. At this stage, differential effects of BMI according to other patient variables were also considered by the inclusion of interaction effects in Cox models; both an interaction $P < .01$ and a clinically meaningful differentiation (eg, clinically different hazard ratios or hazard curves) were required to conclude significance.

BMI As Predictive of Therapeutic Benefit

The predictive effect of BMI on benefit from therapy type, T versus nontargeted (NT), was tested by means of the interaction of BMI and therapy type within the Cox proportional hazards models for OS and PFS. Each of these models was stratified by trial and reduced to the set of patients with concurrent random assignment to T versus NT treatments. In this case, BMI was considered predictive of benefit for a given therapeutic type if the interaction $P < .01$ and clinically meaningfully differential effects were found. Similar to the prognostic analyses, clinical significance in these predictive analyses was assessed visually by using spline plots of OS and PFS risk by therapy type as a function of BMI. Significant findings prompted subsequent model adjustments for other patient variables, as applicable.

Statistical Modeling Assumptions

Throughout all prognostic and predictive analyses, BMI was modeled as a continuous variable with a possibly nonlinear effect on OS and PFS. For each variable included in prognostic and predictive analyses, the assumption of proportional hazards was assessed by using the method of Therneau and Grambsch.¹⁴ When the proportional hazards assumption was violated, as indicated by both $P < .01$ and visually apparent nonproportionality (ie, of Kaplan-Meier survival curves and diagnostic plots for categorical factors and spline-based hazard plots at regular time intervals for continuous variables), we considered subsequent modeling by using time-dependent covariates.

Exploration of Dose Burden As Associated With BMI Effect

BMI is related to body-surface area, which, in turn, frequently determines the chemotherapy dosing strategy for individual patients. However, given the large number of multidrug regimens used throughout the 25 ARCAD trials and the general lack of specific dosing information provided for most trials, we were unable to formally incorporate a singularly defined dose effect in our main analyses. To explore this issue on a smaller scale where specific dosing information was available, we considered BMI and dose together within a single ARCAD trial (North Central Cancer Treatment Group

[NCCTG] N9741; $n = 1,340$).¹⁵ In this trial, a variable that represented dose burden was constructed by considering the maximum cumulative dose for each drug administered during cycle 1 among like-treated patients, which were defined as those patients randomly assigned to the same arm (taking protocol revisions into account) and treated with the same drugs in the same way (eg, bolus *v* infusional fluorouracil considered separately even if patients were randomly assigned to the same arm). Within groups of similar patients and per drug, each patient's percentage of the maximum drug received during cycle 1 was then averaged across drugs to yield an overall percentage of maximum dose-burden score for each patient within a group. The Spearman correlation between the resulting dose-burden variable and BMI was then computed across the patients from the N9741 trial, and dose burden was used as an adjustment variable in exploratory Cox proportional hazards models for BMI.

RESULTS

Descriptive Analyses

The first-line ARCAD trials used in the pooled analysis of BMI are listed in Table 1. In total, 21,149 patients from 25 trials with available BMI, PFS, and OS data were considered in the analyses. The median

OS was 17.9 months (95% CI, 17.7 to 18.2 months), whereas the median PFS was 8.8 months (95% CI, 8.02 to 8.18 months). Median length of follow-up among surviving patients was 18.9 months.

Descriptive statistics for the 21,149 patients analyzed are presented in Table 2. The mean BMI was 26.0 kg/m² (median, 25.4 kg/m²), and the interquartile range was 22.7 kg/m² to 28.6 kg/m². Overall, 3.1% of patients were classified as underweight (BMI < 18.5 kg/m²), 42.8% had weight within normal limits (BMI of 18.5 to < 25 kg/m²), 36.3% were overweight (BMI of 25 to < 30 kg/m²), and 17.8% were obese (BMI ≥ 30 kg/m²); however, BMI categorization was not imposed in statistical modeling. Worsened PS was associated with lower BMI (BMI_{PS0} = 26.4 kg/m²; BMI_{PS1} = 25.6 kg/m²; BMI_{PS2+} = 24.9 kg/m²; $P < .001$), and BMI was significantly higher in patients who had received previous chemotherapy than in chemotherapy-naïve patients (BMI_{prior} = 27.4 kg/m² and BMI_{no prior} = 25.6 kg/m²; $P < .001$). No clinical differences were observed in BMI distribution for patient age, number of metastasis sites, presence versus absence of liver, lung, or lymph node metastases, colon versus rectal cancer, or therapy type (T *v* NT).

Table 1. ARCAD Trials Used in Body Mass Index Analyses

Trial	Years Accrued	Frontline Treatment Arms	No. of Patients
AGITG (MAX)	2005-2007	Capecitabine <i>v</i> capecitabine + bevacizumab <i>v</i> capecitabine + bevacizumab + mitomycin	463
AIO22	2002-2004	Fluorouracil plus oxaliplatin <i>v</i> CAPOX	459
AVF2107g*	2000-2002	IFL <i>v</i> IFL + bevacizumab	915
AVF2192g*	2000-2002	FU <i>v</i> FU + bevacizumab	207
BICC-C*	2003-2004	mIFL ± bevacizumab <i>v</i> FOLFIRI ± bevacizumab <i>v</i> capIRI	532
C97-3	1997-1999	FOLFOX <i>v</i> FOLFIRI	219
CAIRO	2003-2004	Capecitabine <i>v</i> capIRI	767
CAIRO2	2005-2006	CAPOX + bevacizumab <i>v</i> CAPOX + bevacizumab + cetuximab	733
COIN*	2005-2008	FOLFOX <i>v</i> FOLFOX + cetuximab <i>v</i> intermittent FOLFOX	2,414
CRYSTAL*	2004-2005	FOLFIRI + cetuximab <i>v</i> FOLFIRI	1,204
FIRE II (CIOX)	2004-2006	XELOX + cetuximab <i>v</i> capIRI + cetuximab	177
FIRE III	2007-2012	FOLFIRI + bevacizumab <i>v</i> FOLFIRI + cetuximab	585
FOCUS	2000-2003	FU <i>v</i> FU + oxaliplatin <i>v</i> FU + irinotecan	2,085
FOCUS II	2004-2006	FU <i>v</i> FOLFOX <i>v</i> capecitabine <i>v</i> CAPOX	381
GONO	2001-2005	FOLFOXIRI <i>v</i> FOLFIRI	239
HORIZON II*	2006-2010	FOLFOX + CAPOX + cediranib <i>v</i> FOLFOX + CAPOX	1,070
HORIZON III	2006-2009	FOLFOX + cediranib <i>v</i> FOLFOX + bevacizumab	1,596
MACRO	2006-2008	XELOX + bevacizumab <i>v</i> bevacizumab	475
N016966*	2004-2005	FOLFOX + CAPOX + bevacizumab <i>v</i> FOLFOX + CAPOX	2,031
N9741	1999-2001	IFL <i>v</i> FOLFOX <i>v</i> irinotecan and oxaliplatin	1,340
OPTIMOX 2	2004-2006	mFOLFOX <i>v</i> mFOLFOX	200
OPUS*	2005-2006	FOLFOX <i>v</i> FOLFOX + cetuximab	340
PACCE (C249)	2005-2006	Chemotherapy + bevacizumab <i>v</i> chemotherapy + bevacizumab + panitumumab	1,052
PRIME (C203)*	2006-2008	FOLFOX <i>v</i> FOLFOX + panitumumab	1,179
TRIBE	2008-2011	FOLFIRI + bevacizumab <i>v</i> FOLFOXIRI + bevacizumab	495
Total†			21,149

Abbreviations: AGITG, Australasian gastrointestinal trials group; AIO, Arbeitsgemeinschaft Internistische Onkologie; ARCAD, Aide et Recherche en Cancérologie Digestive; AVF, anastomotic-vaginal fistula; BICC-C, breast cancer in city and country; CAIRO, capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer; capIRI, capecitabine and irinotecan; CAPOX, capecitabine and oxaliplatin; COIN, Combination Chemotherapy With or Without Cetuximab As First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer; CRYSTAL, Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer; FIRE III, FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First-Line Treatment of Colorectal Cancer; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, FOLFOX plus irinotecan; FU, fluorouracil; HORIZON II, Cediranib (AZD2171, RECENTIN) in Addition to Chemotherapy in Patients With Untreated Metastatic Colorectal Cancer; HORIZON III, First-Line Metastatic Colorectal Cancer Therapy in Combination With FOLFOX; GONO, Gruppo Oncologico Nord Ovest; IFL, irinotecan, leucovorin, and fluorouracil; m, modified; MACRO, maintenance in colorectal cancer; OPUS, Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer; PACCE, panitumumab advanced colorectal cancer evaluation; PRIME, Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; TRIBE, Combination Chemotherapy and Bevacizumab As First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer; XELOX, capecitabine plus oxaliplatin.

*Trials had concurrent target versus nontarget random assignment.

†Total represents ARCAD population.

Table 2. Postimputation Demographic and Disease Characteristics of Patients Used for the Aide et Recherche en Cancérologie Digestive Body Mass Index Analyses

Characteristic	Patients	
	No.	%
Body mass index		
Mean (SD)	26 (5)	
Median (IQR)	25 (23-29)	
Sex		
Male	13,061	62
Female	8,088	38
Performance status*		
0	11,291	53
1	9,000	43
2+	858	4
Age, years*		
Mean (SD)	61 (11)	
Median (IQR)	62 (55-69)	
Therapy type		
Nontarget	11,432	57
Target	9,717	43
Tumor location†		
Colon	14,734	70
Rectum	6,052	29
Both	363	2
Previous chemotherapy*		
Yes	4,427	21
No	16,722	79
No. of metastatic sites‡		
1	8,707	41
2+	12,442	59
Liver metastases‡		
Yes	16,483	78
No	4,666	22
Lung metastases‡		
Yes	7,916	37
No	13,233	63
Lymph node metastases‡		
Yes	8,455	40
No	12,694	60
Total	21,149	100

Abbreviations: IQR, interquartile range; SD, standard deviation.
 *Missing data imputation rate < 10%.
 †Missing data imputation rate from 20% to 30%.
 ‡Missing data imputation rate from 10% to 20%.

BMI As Prognostic for Patient Outcomes

BMI was prognostic for OS ($P < .001$) and PFS ($P < .001$) with an L-shaped pattern; that is, the risk was highest for patients with the lowest BMI, it decreased until a BMI of approximately 28 kg/m², and it remained similar for patients with higher BMI (Figs 1A and 1B). The BMI effect on each end point was significantly nonlinear on the log relative hazard scale (OS, $P < .001$; PFS, $P < .001$). Relative to obese patients, patients with a BMI of 18.5 kg/m² had a 50% increased risk of death (95% CI, 43% to 56%) and a 27% increased risk of progression or death (95% CI, 20% to 34%); greater risk is suggested for patients with a BMI less than 18.5 kg/m². BMI remained a significant prognostic indicator for both OS ($P < .001$) and PFS ($P < .001$) after adjustment for age; sex; PS; colon versus rectal cancer; number of metastatic sites; previous chemotherapy usage; and presence versus absence of liver, lung, and lymph node metastases. Low BMI was associated with

Fig 1. Risk of (A) death overall, (B) progression or death overall, and (C) death by sex on the relative hazard scale. Shaded regions indicate 95% confidence bands for risk of outcomes as a function of body mass index (BMI). HR, hazard ratio.

poorer OS for men than women, whereas high BMI was associated with improved OS for men versus women (interaction $P = .001$; Fig 1C). The same effect was not observed for PFS. The observed prognostic effect of BMI on OS and PFS did not differ significantly by age, PS, colon versus rectal cancer, previous chemotherapy exposure, number of metastatic sites, or presence versus absence of liver, lung, or lymph node metastases.

BMI As Predictive of Therapeutic Benefit

BMI was not predictive of response by treatment type; that is, the effect of BMI on OS and PFS did not differ according to treatment with T versus NT therapy. The proportional hazards assumption was statistically and/or visually satisfied for all prognostic and predictive models.

Trial N9741 Exploration of Dose Burden Associated With BMI Effect

The Spearman correlation between BMI and dose burden among patients enrolled onto the N9741 trial was 0.41, which indicated a moderate correlation. Univariable models for BMI, stratified by N9741 treatment arm, demonstrated a reduced level of significance from the pooled analysis of all 25 studies (PFS, $P = .009$; OS, $P = .02$), but a similar L shape of the BMI effect remained for each end point (Fig 2). Subsequent adjustment for dose burden in Cox models that already contained yielded BMI effects were no longer significantly prognostic.

DISCUSSION

The prognostic effect of BMI is beginning to be well understood in the setting of early-stage colon cancer, for which both underweight

Fig 2. Risk of (A) death and (B) progression on death as a function of body mass index (BMI) for patients enrolled onto the N9741 trial.

and obese patients have increased risk for progression or death. However, to date, the prognostic and predictive relationships between patient BMI and patient outcomes have remained poorly understood in the metastatic setting. Because of its size, breadth, and the quality of data collection inherent to clinical trials in general, the ARCAD multitrail database is well suited to provide a robust analysis of the influence of BMI on outcomes in mCRC. By pooling patient-level data from more than 21,000 individuals enrolled worldwide onto recent major randomized trials for front-line treatment, we have shown that BMI is prognostic for OS and PFS in this population, but with a shape of the risk curve across the BMI spectrum different than that observed in the adjuvant setting. Specifically, obese patients with stage II or III colon cancer were previously found to be at increased risk for disease recurrence or death; however, in the this study, obese patients with metastatic disease were not at increased risk. With a much larger sample than that previously analyzed by other groups, and including patients from CAIRO and CAIRO2, as previously reported by Simkens et al,⁷ we confirmed that patient outcomes are not worsened by high BMI and that this relationship is not differentiated by T versus NT agents. These findings lead to a greater understanding of the influence of BMI and obesity on long-term patient outcomes in a disease where obesity is already understood to be highly associated with prevalence.

Our analyses revealed a differential effect of BMI on OS between men and women. Although men with low BMIs had a greater risk of death than women with low BMIs, no sex-based differences were found among patients with moderate and higher BMIs, for whom the risk of death was much lower overall (interaction $P = .001$). It was previously shown that women with CRC have improved prognoses compared with men,^{16,17} and it has been hypothesized that estrogen is protective in the development and progression of colon cancer.¹⁷

The strongly negative prognostic relationship between low BMI and disease progression or death, together with the significant association between low BMI and poor PS, suggest that patients with advanced CRC and low BMI are likely cachectic. Cancer cachexia affects approximately 50% of patients with colon cancer, and across all tumor groups, cachexia is associated with a 20% mortality rate.¹⁸ Patients with tumors in the GI tract generally experience a large degree of weight loss, which in turn is associated with shorter survival times, worsened PS, and decreased response to chemotherapy,¹⁹ as observed in the present analysis. Furthermore, cachexia and associated weight loss have previously been identified as negative prognostic factors in patients with CRC.^{20,21} In 2009, Lieffers et al²² hypothesized that a viscerally driven cachexia syndrome in patients with CRC originates from an increase in mass of high-metabolic-rate tissues, such as the liver and spleen. Similarly, other authors have proposed that preexisting illness could result in unintended weight loss and higher mortality in patients with lower BMI as a possible methodologic explanation for the association between higher BMI and better outcome.^{23,24} It is also plausible that some patients with low BMI and poor PS are underdosed because of a fear of toxicity, whereas some patients with high BMI receive adjustments that are based on ideal rather than actual body weight. Although we were unable to consistently measure dosing effects or markers of cachexia across all 25 ARCAD trials, we believe that our finding of particularly poor prognosis for patients with low BMI and poor PS suggest that cachexia was likely a contributing factor.

Furthermore, this finding underscores the utility of low BMI as a prognostic marker.

Limitations of this research include restriction of the patient population to those deemed eligible and appropriate for participation in clinical trials. This may have made the percentage of patients with numerous comorbidities lower than that of the general population. Also, given the limited nature of clinical trial data, possible confounders related to socioeconomic and nutritional factors, or to the use of megestrol acetate, progestins, or corticosteroids, were not available for analysis. Also, as previously described, a singularly defined dose variable was not possible across studies, and a tentative analysis from the N9741 trial alone was performed. This dose-adjustment analysis was meant to be more suggestive than definitive, given the low relative sample size and limited generalizability compared with the analysis of all trials combined. However, the results stated herein suggest that future explorations of BMI as a prognostic factor should formally incorporate BMI- or weight-dependent dosing strategies into testing and modeling procedures, when feasible.

In conclusion, in this pooled analysis of 21,149 patients from first-line mCRC trials, BMI was prognostic for both OS and PFS; low but not high BMI was associated with increased risk of progression or death. The increased risk associated with low BMI is worse for men than women. Additional studies are warranted to investigate issues that include the possibility that molecular pathways are related to the impact of BMI on patient outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERM

insulin-like growth factor (IGF): proteins with sequences similar to that of insulin. IGFs trigger cellular responses similar to those of insulin, including mitogenesis. IGF-1, which is secreted by the liver, and IGF-2, which is secreted by the brain, kidney, pancreas, and muscle, function by means of cell surface receptors. See IGF-1R.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Body Mass Index Is Prognostic in Metastatic Colorectal Cancer: Pooled Analysis of Patients From First-Line Clinical Trials in the ARCAD Database

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