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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

How to Manage the Obese Patient With Cancer

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A B S T R A C T

Purpose

Obesity (body mass index [BMI] $\geq$ 30 kg/m^2) is common among patients with cancer. We reviewed management issues in the obese patient with cancer, focusing on how obesity influences treatment selection (including chemotherapy dosing), affects chemotherapy toxicity and surgical complications, and might be a treatment effect modifier.

Methods

The majority of evidence is drawn from observational studies and secondary analyses of trial data, typically analyzed in N × 3 BMI categories (normal weight, overweight, and obese) matrix structures. We propose a methodological framework for interpretation focusing on sample size and composition, nonlinearity, and unmeasured confounding.

Results

There is a common perception that obesity is associated with increased treatment-related toxicity. Accordingly, cytotoxic chemotherapy dose reduction is common in patients with elevated BMI. Contrary to this, there is some evidence that full dosing in obese patients does not result in increased toxicity. However, these data are from a limited number of regimens, and fail to fully capture cytotoxic drug pharmacodynamics and pharmacokinetic variability in obese patients. Among patients undergoing surgery, there is evidence that elevated BMI is associated with increased perioperative mortality and increased rates of infectious complications. A novel finding is that these relationships hold after surgery for malignancy, but not for benign indications. There are biologic plausibilities that obesity might be an effect modifier of treatment, but supporting evidence from clinical studies is inconsistent.

Conclusion

In line with the ASCO 2012 guidelines, chemotherapy dosing is probably best performed using actual body weight in obese patients. However, specific regimens known to be associated with increased toxicity in this group should be used with caution. There is no guidance on dose for obese patients treated with biologic agents. Currently, there are no specific recommendations for the surgical management of the obese patient with cancer.

J Clin Oncol 34:4284-4294. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Excess body weight, commonly expressed as elevated body mass index (BMI; overweight and obesity), is an established risk factor for several incident adult cancers.[1] The International Agency for Research on Cancer[2] lists 13 obesity-related cancers, which include esophageal adenocarcinoma; cancers of the gastric cardia, colorectum, liver, gallbladder, pancreas, postmenopausal breast, endometrium, ovary, kidney (renal cell), and thyroid; meningioma; and multiple myeloma. Thus, for many cancer types, the proportions of patients with obesity (BMI $\geq$ 30 kg/m^2) are

high. For example, the ranges (11% to near 50%) of the proportions of obese patients by some cancer types are endometrial, 39% to 47%; renal cell carcinoma, 42%; rectal, 18% to 37%; esophageal adenocarcinoma, 35%; GI and colon, 18% to 26%; ovarian, 12% to 15%; breast, 11% to 27%; and metastatic colorectal cancer, 12% (Data Supplement).

We review management issues in the obese patient with cancer, focusing on how obesity influences treatment selection (including chemotherapy dosing), affects chemotherapy toxicity and surgical complications, and might be a treatment effect modifier. We also include a number of specific miscellaneous aspects that are relevant to the

treatment of the obese patient with cancer, but are not covered elsewhere in this Special Issue.

METHODS

The majority of evidence is drawn from observational studies and secondary analyses of trial data, typically analyzed in N × 3 BMI categories (normal weight, overweight, and obese) matrix structures. We first propose a methodological framework to interpret this structure. Because of the wide scope of this review, a formal literature search of observational studies was deemed impracticable.

Sample Size and Composition

Case studies in the Data Supplement illustrate the following: small study size can result in both type 1 and type 2 statistical errors in relationships of proportions of interest (eg, complications) and BMI categories (for this reason, in this review, we have cited studies with greater than 1,000 participants, wherever possible); tabulations with greater than two rows of interest (eg, three histologic grades) can be difficult to interpret; and for the same effect size between obese versus normal-weight individuals, with an increasing size of the proportions of obese within a cohort, there is an increased likelihood of statistical significance.

Obesity and Outcomes As Nonlinear Relationships

Obesity is associated with increased risk of incident cancers[3] and may also be associated with poorer prognosis, especially in breast cancer (and

dealt with elsewhere in this Special Issue[4]). These relationships might be nonlinear. Similarly, there might be several types of nonlinear relationships between BMI and the event of interest closer to the treatment window, such as perioperative mortality. These are illustrated in Fig 1 and might include U-shaped curve; inverse J-shaped curve, as observed between BMI and 30-day mortality by Mullen et al[5] in their analysis of 2,258 patients who underwent major intraabdominal cancer surgery; a bimodal curve, as observed between BMI and in-hospital mortality after coronary artery bypass graft (CABG) surgery[6]; and a fourth relationship known as the obesity paradox.[7] The latter is the observation of an unexpected risk reduction in an outcome of interest (usually mortality, but could be peritreatment mortality) among individuals with elevated BMI (≥ 25 kg/m^2), in whom an increased risk is anticipated, compared with those of normal weight (18.5 to 25 kg/m^2).

Once the many types of nonlinear relationships are recognized, one can appreciate that simple BMI categorizations into normal weight, overweight, and obese might be misleading. For example, in scenario (C) in Figure 1, a patient with a BMI = 30 kg/m^2 might have a similarly low probability of a complication as a normal-weight patient, but this might hide the possibility that this complication is substantially increased in higher obese states.

Unmeasured Confounding

For cancer incidence (cohort) studies, there is usually a large array of variables (potential confounders), including smoking status, alcohol consumption, level of education, and socioeconomic status. Taking account of these potential confounders and effect modifiers is important. For example, stratification by smoking status is relevant in the interpretation of
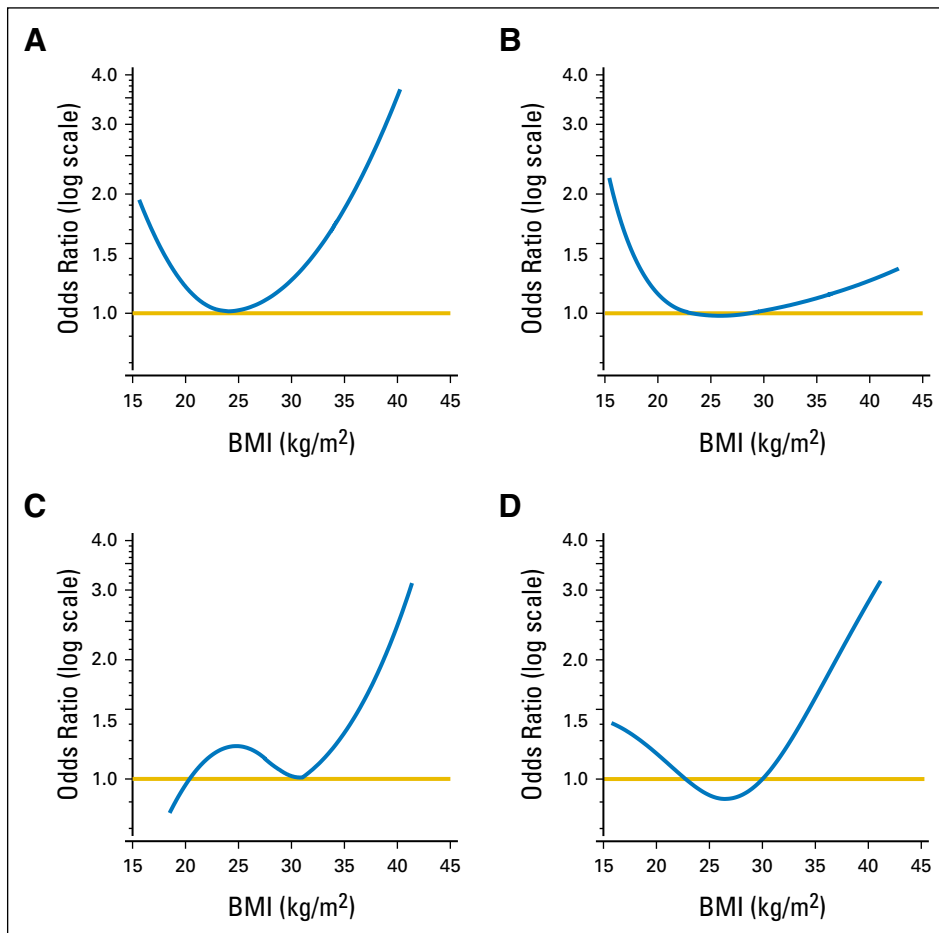

Fig 1. Schematic diagrams of various nonlinear patterns of relationships between body mass index (BMI) and odds ratio of outcome of interest (for example, perioperative mortality). (A) U-shaped; (B) inverse J-shaped; (C) bimodal curve; and (D) obesity paradox (the latter modified from Lennon et al[7]).

studies of obesity exposure and incident cancer risk,[8] because smokers have lower mean BMI values compared with those of never smokers. Unfortunately, data on smoking status are infrequently collected in oncology trials (ie, an unmeasured confounder), yet smoking might have major influence on early outcomes such as postoperative complications, peritreatment mortality, and toxicity.

RESULTS

Treatment Selection

Selection for specific treatment modalities. Studies have addressed the influence of obesity on the decision to offer certain types of cancer treatments, in specific settings. For example, a review of the National Comprehensive Cancer Network centers' breast cancer data (N = 9,527; stages I, II, and III; 1997 to 2007) showed that BMI had no effect on the decision to offer adjuvant chemotherapy.[9] Similarly, in rectal cancer, there appears to be no difference in the decision to perform an abdomino-perineal resection versus an anterior resection (a colostomy avoiding operation) between obese versus nonobese patients.[10]

In contrast, obesity negatively influences the decision for immediate breast reconstruction after mastectomy.[11] In 2007, van de Poll-Franse et al,[12] using broad modalities of treatments (surgery, radiotherapy, and chemotherapy) recorded in the Eindhoven Cancer Registry, concluded that patients with diabetes (an obesity-related condition) and cancer of the esophagus, colon, breast, or ovary were treated less aggressively (received fewer treatment modalities) compared with those without diabetes. However, this simplistic classification of aggressiveness of treatment is probably not applicable today because present-day management is both multimodal and across multiple phases.

Chemotherapy dosing. In contrast, once a decision is made to offer chemotherapy, there is a large volume of data showing that oncologists frequently reduce doses when prescribing in obese patients because of concerns about toxicity. This philosophy has been challenged for a long time.[13] Table 1 summarizes a number of studies evaluating chemotherapy dose reductions according to BMI categories in breast,[14,15] colorectal,[16,17] and ovarian[18,19] cancers. This tabulation illustrates that, even within trials, obesity is associated frequently with reduced chemotherapy intensity (ie, reduced frequency and/or failure to complete the prescribed regimen). For example, in an ovarian cancer trial, 66% of obese patients received suboptimal chemotherapy intensity compared with 30% for those of normal weight.[18]

What are the consequences of the fact that a high proportion of obese patients with cancer are treated by reduced doses? Among trials where participants received reduced doses of adjuvant chemotherapy, and where the adjuvant chemotherapy is known to improve survival, there is evidence in several cancer types (breast,[20-22] colorectal,[16,23] lung,[24] and lymphoma[21]) that survival advantages are lost and outcomes are similar to those of the untreated or control cohorts. Importantly, the implication of this is that the observed adverse prognosis associated with obesity in many cancer types (discussed in other reviews in the Special Issue[4]) may reflect confounding as a result of suboptimal chemotherapy dosing and reduced therapeutic effect relative to normal-weight patients with cancer,[25] rather than obesity per se.

Impact of Obesity on Treatment Complications

Chemotherapy toxicity. Hourdequin et al[26] recently reviewed and meta-analyzed data that evaluated toxic effects of chemotherapy dosing using actual body weight (ABW) in obese versus normal-weight patients with cancer. Against conventional expectations, the summary risk estimates initially suggested that obese patients experience less hematologic toxicity when dosed using ABW, and that among patients in trials where full chemotherapy doses were received, any grade 3/4 toxicities were fewer in obese versus normal-weight participants (summary odds ratio favoring obese patients, 0.75; 95% CI, 0.65 to 0.87). However, such conclusions rely heavily on colorectal trials investigating fluorouracil-based regimens, and other trials in breast cancer and lymphoma showed no effect.[26] More recent data from 3,023 patients with breast cancer, published after this meta-analysis, demonstrate an increase in severe toxicity in ABW-dosed obese patients given dose-intense anthracycline- and taxane-containing regimens.[27]

A further dimension is that BMI is a crude approximation of body adiposity and fails to fully capture cytotoxic drug pharmacodynamic and pharmacokinetic variability in obese patients. In the largest analysis to date (N = 1,206) of the effect of obesity on the pharmacokinetics of cytotoxic drugs, Sparreboom et al[28] showed drug-specific interactions between BMI and pharmacokinetic clearance, and sex-specific interactions for drugs such as doxorubicin.

There is a paucity of toxicity data on new biologic agents in obese patients with cancer. One recent review demonstrated increased cardiac toxicity associated with Herceptin administration in obese patients.[29] Traditionally, Herceptin has been dosed per kilogram when an intravenous route is used. However, in many countries (but not in the United States), the administration has been changed to subcutaneous delivery as a single standard 600-mg dose. Detailed pharmacokinetic data show that this alteration results in reduced exposure in obese patients, but the impact on toxicity and survival has yet to be assessed.[30]

In conclusion, data in large adjuvant trial databases should be analyzed to increase our understanding. The observation that fat distribution may have a greater effect on cytotoxic clearance than obesity per se, as well as the complexities of the influence of genetics on pharmacokinetics, suggests that detailed prospective studies of tailoring chemotherapy doses to the individual are required.[31,32]

Surgical complications and perioperative mortality. There is a common perception that obesity is associated with increased postsurgical morbidity and mortality, but there are caveats to this dictum. Table 2 lists studies evaluating relationships among elevated BMI, major complications, and perioperative mortality after nonbariatric, nonvascular general surgery. Many studies were cancer only[5,33-36] whereas others included benign and malignant indications,[37-39] which were included to demonstrate that there might be an effect modification by indication. The summary from this tabulation is that elevated BMI is associated with increased perioperative mortality and increased rates of infectious complications, but that there are inconsistent associations between elevated BMI categories and composite (eg, Clavien-Dindo III/IV) or total postsurgical complications. Relationships might be site specific. Thus, for example, for breast reconstruction after

Table 1. Studies Evaluating Chemotherapy Dose Reductions According to Body Mass Index Categories

Author and Country	Cancer Type	Study Name/Type	No. of Patients	Clinical Setting	Chemotherapy Regimens	Normal Weight	Overweight	Obese	Severely Obese	P
First cycle dose reduction (< 0.9 standard dose)										
Griggs et al 2005, United States[15]	Breast	Retrospective cohort study, Pittsburgh	9,672	Adjuvant	Doxorubicin hydrochloride and cyclophosphamide, between 1990 and 2001	9.0	11.0	20.0	37.0	< .001*
Dose reduction (not specified)										
Gennari et al 2016, Italy[14]	Breast	Phase III trial	1,066	Adjuvant	Standard chemotherapy with and without anthracyclines	3.0	3.0	8.0		.03*
Dose reduction (< 0.95 standard dose)										
Dignam et al 2006, United States[17]	Colon	NSABP C-04 and C-05	4,288	Adjuvant	Leucovorin-modulated fluorouracil (FU + LV); FU and levamisole (FU + LEV), or FU + LV + LEV	7.0		55.0	73.0	
Chambers et al 2012, United Kingdom[16]	Colorectal	FOCUS trial	2,057	Metastatic	A five-arm trial: scheduling two drugs: irinotecan and oxaliplatin	4.0	9.0	32.0		< .001
Chambers et al 2012, United Kingdom[16]	Colorectal	FOCUS2 trial	380	Metastatic	2 × 2 factorial trial of FOCUS chemotherapy for elderly and/or frail patients	12.0	21.0	60.0		< .001
Chambers et al 2012, United Kingdom[16]	Colorectal	COIN trial	2,344	Metastatic	Continuous FU + Ox (or OxCap) v intermittent FU + Ox (or OxCap)	4.0	16.0	54.0		< .001
Dose reduction (any course)										
Wright et al 2008, United States[19]	Ovarian	Gynecologic Oncology Group (GOG) protocol 158	387	Optimally cytoreduced (residual tumor < 1 cm after surgery)	Carboplatin based on an AUC of 7.5 and a GFR derived from the Jelliffe formula	34.0	14.8	21.1		.004
Relative dose intensity < 85%										
Au-Yeung et al 2014, Australia[18]	Ovarian	Australian Ovarian Cancer Study (AOCS)	333	Stage III/IV	Carboplatin AUC 5-6, dosed per Calvert formula, based on creatinine clearance calculated with the Cockcroft-Gault formula using measured body weight and serum creatinine.	39.0	39.0	67.0		< .001
Au-Yeung et al 2014, Australia[18]	Ovarian	Australian Ovarian Cancer Study (AOCS)	333	Stage III/IV	Paclitaxel 175 mg/m^2 based on measured height and weight, and BSA calculated using the Dubois formula.	50.0	54.0	48.0		.76

Abbreviations: AUC, area under the curve; BMI, body mass index; BSA, body surface area; FOCUS, fluoxetine or control under supervision; GFR, glomerular filtration rate; NSABP, National Surgical Adjuvant Breast and Bowel Project; Ox, oxaliplatin; OxCap; OxCap, oxaliplatin and capecitabine.
*Estimated from raw data in publication and using ptrendi for ordered proportions in STATA (College Station, TX).

Table 2. Overview of Studies Evaluating Relationships Among Elevated Body Mass Index, Major Complications, and Perioperative Mortality After Bariatric General Cancer Surgery

Author and Country	Design	No. of Patients	Main Procedures	Outcome	Outcomes (%)					P
					Nonobese	Overweight	Obese I	Obese II	Obese III	
Dindo et al 2003, Switzerland[38]	Prospective cohort	6,336	Excluded thoracic, vascular, and transplantation surgery	Major complications (Clavien-Dindo III/IV)	6.9		6.3	7.9 (Obese II/III)		GIII: .25*, GIV: .36*
				30-day mortality	1.0		1.0	0 (Obese II/III)		.12*
					Normal Weight	Overweight	Obese I	Obese II	Obese III	
Mullen et al 2008, United States[5]	ACS NSQIP database. Prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intraabdominal cancer surgery was performed in 14 university hospitals	2,258	Oesophagectomy (n = 29), gastrectomy (n = 223), hepatectomy (n = 554), pancreatectomy (n = 699), or low anterior resection/proctectomy (n = 753) (cancer indication not specified)	Major complications	14.4	15.3	16.5	18.2	15.2	.87
				Wound infections	10.0	12.5	16.5	13.1	19.0	.0084
				30-day mortality	2.0	2.1	0.84	0.73	3.8	.0018
					Normal Weight	Overweight	Obese I	Obese II	Obese III	
Gedaly et al 2009, United States[35]	ACS NSQIP database. Prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intraabdominal cancer surgery was performed in 14 university hospitals	1,029	Liver resections (cancer indication not specified).	Noninfectious major complications	6.1†	6.6†	9.1†	14.5†	19.4†	Not estimable
				Infectious complications	17.4†	17.4†	24.4†	26.1†	31.3†	Not estimable
				30-day mortality	Not specified					
					Normal Weight	Overweight	Obese I	Obese II	Obese III	
Mustain et al 2012, United States[39]	ACS NSQIP database. Prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intraabdominal cancer surgery was performed in 14 university hospitals		Laparoscopic colectomy (indication was malignancy in 40%)	Return to operating theater	3.7	4.4	4.4	4.7	4.9	.18
				Wound complications	7.1	8.7	10.8	12.4	18.6	<.01
				30-day mortality	0.9	0.9	0.5	0.9	0.5	.55
					Nonobese		Obese I	Obese II	Obese III	
Fischer et al 2013, United States[34]	ACS NSQIP database. Prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intraabdominal cancer surgery was performed in 14 university hospitals	15,937	Breast reconstructions	Wound complications	2.4		5.3	6.3	10.4	<.001
				Medical complications	1.2		2.6	2.3	3.6	<.001
				Wound infections	1.3		2.7	3.3	5.5	<.001
				Major surgical complications	7.1		10.6	13.6	14.9	<.001
				Graft and prosthesis loss	1.0		1.5	3.8	2.7	<.001
				Return to operating theater	6.2		9.1	10.8	11.6	<.001
					Normal Weight	Overweight	Obese			
Melis et al 2013, United States[36]	New York University Medical School	540	Oesophagectomy for adenocarcinoma	Any complication	41.9	48.9	48.7			.30
				Surgical-site infection	4.7	7.2	8.6			.40
				30-day mortality	1.3	1.5	2.7			.70

(continued on following page)

Table 2. Overview of Studies Evaluating Relationships Among Elevated Body Mass Index, Major Complications, and Perioperative Mortality After Bariatric General Cancer Surgery (continued)

Author and Country	Design	No. of Patients	Main Procedures	Outcome	Outcomes (%)			P
					Normal Weight	Overweight/Obese I	Obese II/III	
Althumairi et al 2016, United States[33]	ACS NSQIP database. Prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intraabdominal cancer surgery was performed in 14 university hospitals	8,999	Abdominoperineal resection for rectal cancer	Deep surgical-site infection	3.0	3.1	5.0	.040
					Normal Weight	Overweight	Obese	
STARSurg Collaborative 2016, United Kingdom[37]	Multicenter prospective cohort study across the United Kingdom and Republic of Ireland	7,965	Benign and malignant	Major complications (Clavien-Dindo III/IV)	12.1	12.0	10.2	.274
				Surgical-site infection	5.3	6.2	6.2	< .001
				30-day mortality	1.9	1.8	0.8	< .001
STARSurg Collaborative 2016, United Kingdom[37]	Multicenter prospective cohort study across the United Kingdom and Republic of Ireland	5,836	Benign	Major complications (Clavien-Dindo III/IV)	11.4‡	9.7‡	7.8‡	.513
				Surgical-site infection	5.1‡	5.8‡	5.0‡	.002
				30-day mortality	1.9‡	1.4‡	0.6‡	
STARSurg Collaborative 2016, United Kingdom[37]	Multicenter prospective cohort study across the United Kingdom and Republic of Ireland	2,129	Malignant	Major complications (Clavien-Dindo III/IV)	13.6‡	17.4‡	19.4‡	.016
				Surgical-site infection	5.8‡	7.2‡	11.1‡	.001
				30-day mortality	1.9‡	2.5‡	1.3‡	.242

Abbreviations: ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; BMI, body mass index.
*Comparison between patients with BMI < 30 kg/m² and ≥ 30 kg/m².
†Estimated from the odds ratio tables.
‡Data are directly from the STARSurg Collaborative investigators.[37]

mastectomy, obesity is likely to be an adverse factor for wound and infectious complications.[34,40]

What is interesting is the emerging evidence that the indication for surgery might be an effect modifier. This is clearly illustrated in the recently published STARSurgUK study,[37] where there were no effects of increased BMI on complications after surgery for benign disease (indeed, there was some evidence of an inverse relationship), but clear (positive) relationships between BMI and postsurgical complications in cases where the surgical indication was malignant disease. This is an important new observation that may explain previous inconsistencies in the literature. It could also reflect that surgeons are highly selective or even avoid operating on obese individuals for benign conditions (and even advocate weight loss before some surgeries for benign indications).

There are other observations worth mentioning. For patients undergoing abdominal laparoscopic surgery for intraabdominal malignancy, there is a recognized increased risk for open conversion with increasing BMI. For the Cleveland Clinic Colorectal Laparoscopic Conversion Score,[41] BMI is a key predictor; eg, for a team with 75 to 100–patient experience, the predicted conversion rate increases from 2.4% in subjects with a BMI < 22 kg/m^2 to 7.4% in subjects with a BMI > 28.5 kg/m^2 undergoing right hemicolectomy surgery. Obesity might have an impact on intermediate-term complications after abdominal cancer surgery, such as incisional and parastomal hernia development. The US Muscle and Adiposity Research Consortium[42] reported a rate of 21% incisional hernia formation (median time, 12 months), and that visceral obesity (quantified on routine computed tomography imaging) was a better predictor than BMI for this occurrence.

Obesity As a Treatment Effect Modifier

It is increasingly recognized that the response to specific cancer therapies differs significantly as a result of different tumor and patient characteristics. These characteristics are termed treatment effect modifiers or treatment predictive biomarkers, and are distinct from prognostic biomarkers.[43] Obesity is a potential predictive biomarker.

In the setting of aromatase inhibitors (AIs) as hormonal therapy for breast cancer, because obesity is associated with increased peripheral aromatase activity (the target for AIs), it is hypothesized that these agents might be less effective in overweight and obese women (addressed by Goodwin[44] and within sections of this Special Issue[45]). Secondary analyses of four randomized trials found inconsistent results[44] and concluded that the findings did not support the use of BMI as a treatment predictive biomarker of AIs (v tamoxifen) in the adjuvant setting in women with postmenopausal breast cancer.

There is some evidence that antiangiogenic agents, such as bevacizumab (dosed per kilogram of weight rather than body surface area), might be less effective in obese patients. Excess adiposity is associated with increased circulating levels of vascular endothelial growth factor,[46] a key regulator of tumor angiogenesis and the main target for bevacizumab antibody therapy; hence, there is a biologic plausibility that obesity might be a potential predictive biomarker in this setting. This has been tested in the settings of metastatic colorectal cancer[47,48]; metastatic renal cell carcinoma[49,50]; and advanced ovarian cancer[51] (listed in Table 3).

Several of these studies were retrospective, had small sample sizes, lacked controls of conventional treatment arms, and were underpowered to perform tests for interaction; not unexpectedly, the findings are inconsistent. Some studies support the notion that antiangiogenic agents are less effective in obese patients with metastatic colorectal[47] and advanced ovarian cancer[51]; the opposite is noted in metastatic renal cancer[49,50]; and no difference was seen in the largest analysis, which was a secondary analysis of two trials in metastatic colorectal cancer.[48] We conclude that currently, obesity is not a treatment predictive biomarker for antiangiogenic therapies in these cancers.

Miscellaneous Matters

There are a number of issues that require specific discussion regarding the obese patient with cancer, which are not covered elsewhere in this Special Issue.

Weight gain during chemotherapy. All discussion on this matter relates to women with breast cancer. Historically, women who received first-generation nonanthracycline-containing chemotherapy regimens received concomitant corticosteroid therapy, and this contributed substantially to weight gain. Weight gain continues to be seen in women on contemporary regimens of 4.5 to 6 months of anthracycline and taxane chemotherapy, but again, concomitant administration of corticosteroid may contribute. Examples of prospective studies from the United States,[52] Europe,[53] and Asia[54] report that 30% to 50% of women gain $> 5\%$ of body weight, with a mean weight change of 2 to 3 kg in the first year after diagnosis, although this is not reported in all cohorts.[55-58]

Greatest weight gain is observed among women who are premenopausal, have a healthy weight at diagnosis,[59] stop smoking after diagnosis,[60] or experience a chemotherapy-induced menopause.[58,61] Weight gains may be greater with cyclophosphamide, methotrexate, and fluorouracil compared with anthracycline (2.9 kg [5%] v 0.9 kg [1%]),[62] but this is not a consistent finding.[52,61,63] Weight is gained both during and after the chemotherapy period,[58,64] and has been shown to persist when measured at 3 years[52] and 6 years[65] after diagnosis.

What are the consequences of chemotherapy-related weight gain? Playdon et al[66] addressed this question in a meta-analysis of 23,832 cancer cases from seven cohorts and two chemotherapy trials. They reported that compared with women who maintained stable weight, those who experienced $\geq 10\%$ weight gains after diagnosis had increased overall mortality (hazard ratio [HR], 1.23; 95% CI, 1.09 to 1.39), and to a lesser extent increased breast cancer mortality (HR, 1.17; 95% CI, 1.00 to 1.38). But there was no association between weight gain and recurrence. However, the meta-analysis highlighted considerable between-study heterogeneity and on close scrutiny, most of the increased risk was within the first years after cancer diagnosis and driven by two studies,[67,68] raising concerns of reverse causality.

A recently reported pooled project analysis, from the WHEL, LACE, and NHS cohorts,[69] addressed the question of specificity of associations among 6,596 women with estrogen receptor–positive tumors, and in contrast to the Playdon review,[66] linked $\geq 10\%$ weight gain with increased risk of late recurrence, defined

Table 3. Summary of Treatment Response (generally median times to progression) in Patients With Colorectal, Renal, and Ovarian Cancers Treated by Antiangiogenic Therapies According to Categories of Adiposity

Author and Country	Cancer Type	No. of Patients	Study Design	Antiangiogenic Regimens	Antiangiogenic Therapy			Conventional Therapy			$P_{\text{interaction}}$
					Low VFA	High VFA	P_{between}	Low VFA	High VFA	P_{between}	
Guiu et al 2010, France[47]	Metastatic colorectal cancer	120	Retrospective	80 first-line bevacizumab-based treatment; 40 chemotherapy only*	14.0	9.0	.0008	10.0	6.0	.65	.022
					Underweight	Normal weight	Overweight	Obese			
Simkens et al 2011, Netherlands[48]	CAIRO2: Metastatic colorectal cancer	755	Secondary analysis trial data	First-line treatment with capecitabine, oxaliplatin, and bevacizumab with (arm B) or without (arm A) cetuximab	10.1	9.7		9.5		.528	
Simkens et al 2011, Netherlands[48]	CAIRO: Metastatic colorectal cancer	820	Secondary analysis trial data	Phase III trial of sequential v the combined use of capecitabine, irinotecan, and oxaliplatin†	4.4	6.2		7.0	7.2	.153	
					Low VFA	High VFA					
Ladoire et al 2011, France[49]	Metastatic renal cell carcinoma	64	Retrospective	Antiangiogenic agents (bevacizumab, sunitinib, or sorafenib)*	Approximately 4	Approximately 22	.0009				
					Low VFA	High VFA					
Steffens et al 2011, Germany[50]	Metastatic renal cell carcinoma	116	Retrospective	Antiangiogenic agents (sunitinib, sorafenib, axitinib, bevacizumab)[‡]	8.4	11.5	.005				
					Low SFA	High SFA					
Steffens et al 2011, Germany[50]	Metastatic renal cell carcinoma	116	Retrospective	Antiangiogenic agents (sunitinib, sorafenib, axitinib, bevacizumab)[‡]	8.4	10.5	.037				
					Low BMI§	High BMI§					
Slaughter et al 2014, United States[51]	Advanced ovarian	46	Retrospective	Twenty-one bevacizumab-based; 25 chemotherapy only†	24.7	9.8	.03	11.9	17.6	.19	
					Low BMI§	High BMI§		Low BMI§	High BMI§		

Abbreviations: BMI, body mass index; CAIRO, capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer; SFA, subcutaneous adipose fat; VFA, visceral adipose fat.
*Results shown as time to progression (months).
†Results shown as median progression-free survival (months).
‡Results shown as progression-free survival interval (months).
§Cutoff BMI: 28.6 kg/m² in bevacizumab group; 28.1 kg/m² in cytotoxic group.

as > 5 years after diagnosis (HR, 1.24; 95% CI, 1.00 to 1.53). However, this significant finding was isolated; no associations were seen for any weight gain and late all-cause mortality. Several randomized trials of lifestyle and weight control interventions in breast cancer survivors, with survival end points, are currently ongoing and covered elsewhere in this special issue.[70] However, for the most part, recruitment is after treatment and these studies are unlikely to directly address the chemotherapy-related weight gain conundrum.

Excess body weight, noncancer and cardiovascular mortalities. Noncancer deaths may be an issue both during and years after cancer treatment. The ASCO position statement[4,71] on obesity and cancer recognized that excess body weight might contribute to increased mortality through noncancer deaths, and that of these, approximately half are as a result of cardiovascular disease. However, only a small number of studies have directly addressed this relationship (Data Supplement). For breast cancer, the systematic review and meta-analysis from Chan et al[72] identified five studies that evaluated the association between BMI (determined < 12 months after diagnosis) and noncancer mortality. Compared with normal BMI, the HRs were increased for obesity (but not overweight), but these were not statistically significant. Similarly, the HRs of cardiovascular deaths were increased among obese women compared with those of normal weight (based on pooled data in the Chan meta-analysis[72] from two studies, where BMI was measured before cancer diagnosis), but these were not statistically significant. In the After Breast Cancer Pooling Project,[73] which was not included in the Chan meta-analysis,[72] women who were obese II and III before breast cancer diagnosis (compared with normal weight) were at increased risk of non-breast cancer deaths.

For colorectal cancer, Campbell et al[74] demonstrated a significantly increased risk of cardiovascular death with increasing prediagnosis (mean, 7 years) BMI (per 5 kg/m^2: HR, 1.28; 95% CI, 1.04 to 1.58), but not postdiagnosis (mean, 1.5 years) BMI (per 5 kg/m^2: HR, 1.06; 95% CI, 0.84 to 1.33). For endometrial cancer, Ward et al[75] used the SEER registries, and although they were unable to establish a link with BMI, approximately half of women with endometrial cancer are estimated to be obese.[76] They concluded that "cardiovascular disease is the leading cause of death among endometrial cancer patients and survivors."

Excess body weight and quality of life. There is a common perception that obesity among cancer survivors has negative consequences on quality of life (QoL).[59] The prevailing argument is that trials among cancer survivors generally demonstrate that lifestyle interventions that lead to weight reduction are associated with increased physical activity, improved QoL, and less fatigue.[71] However, these trials are short term and it remains unclear whether a long-term state of excess body weight per se is associated with reduced QoL in cancer survivors. A number of reviews have addressed this question: one study in multiple cancer types[77]; two studies in breast cancer survivors[78,79]; one meta-analysis of 10 studies in colorectal cancer[80]; one meta-analysis of five studies in prostate cancer[81]; one meta-analysis of four studies in endometrial cancer[82]; and one study in ovarian cancer survivors[83] (Data Supplement).

QoL measures were determined using a variety of different assessment tools and at varying times during survivorship, making direct comparisons difficult. Overall, there were consistent findings that obesity is associated with reduced physical function and reduced vitality, but there was no consistent association for mental health or cognitive function. In a recent review, Smits et al[82] recognized that sociodemographic factors and the presence of comorbidities are key determinants of QoL, but these are infrequently available in adjusted models in the cancer survivorship setting. Furthermore, and importantly, almost no study among cancer survivors included appropriately matched noncancer control subjects. One exception is the recently published data from the Long-Term Quality of Life Study in breast cancer survivors,[78] which reported decreased physical function on SF-36 surveys among obese survivors, but this was also observed among obese individuals without cancer.

PRACTICE RECOMMENDATIONS

ASCO Clinical Practice Guideline

The question of chemotherapy dosing in the obese patient was the subject of an ASCO 2012 clinical practice guideline.[84] The Panel[84] made six clear clinical recommendations regarding these questions, summarized in Table 4. The recommendations highlighted that ABW should be used for chemotherapy dosing, regardless of obesity status. Our updated review broadly agrees with these guidelines. However, specific regimens known to be associated with increased toxicity in this group should be used with caution, and this should be taken into account in initial dose selection.

As yet, there is no equivalent guidance for biologic agents (for example, Herceptin and bevacizumab). Currently, there are no specific recommendations for the surgical management of the obese patients with cancer.

Future Research

This review has highlighted that BMI is a crude measure of body adiposity and fails to capture cytotoxic drug pharmacodynamic

Table 4. Summaries of Key Recommendations From the ASCO Clinical Practice Guidelines on Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer[84]

Question	Summary Recommendations
1	ABW be used when selecting cytotoxic chemotherapy doses regardless of obesity status
2	Full weight–based chemotherapy doses (IV and oral) be used in the treatment of the obese patient with cancer, particularly when the goal of treatment is cure
3	Clinicians should follow the same guidelines for dose reduction, regardless of obesity status, for all patients, depending on the type and severity of toxicity, any comorbid conditions, and whether the treatment intention is cure or palliation
4	Consideration of fixed dosing only with select cytotoxic agents (eg, carboplatin, bleomycin, vincristine)
5	BSA be calculated using any of the standard formulae
6	To the sixth question, the Panel recommended "further research into the role of pharmacokinetic and pharmacogenetic information for guiding the dosing of IV and oral chemotherapeutic agents for adult patients with cancer who are obese."

Abbreviations: ABW, actual body weight; BSA, body surface area; IV, intravenously.

and pharmacokinetic variability in obese patients. There is a need to initiate studies to better assess body composition (for example, computed tomography– or magnetic resonance–derived anthropometric measures such as visceral and subcutaneous adipose tissue[85]; and dual-energy x-ray absorptiometry[86]) and early outcomes (such as complications and toxicity). Although BMI is the most common measure used to characterize body composition, it cannot distinguish lean mass from fat mass, determine sarcopenic obesity, or characterize body fat distribution. This relationship may differ for individuals with or without cancer, a strategy detailed elsewhere,[86] and is important to pursue to better define the management of the increasing proportion of obese patients with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

How to Manage the Obese Patient With Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Andrew G. Renehan
Honoraria: Janssen-Cilag, Merck Serono
Research Funding: Novo Nordisk

Michelle Harvie
No relationship to disclose

Ramsey I. Cutress
Other Relationship: A body composition analyzer (SECA mBCA 515) was provided to the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre in Nutrition by SECA more than 2 years ago.

Michael Leitzmann
No relationship to disclose

Tobias Pischon
No relationship to disclose

Sacha Howell
Consulting or Advisory Role: Novartis
Research Funding: Evgen Pharma Ltd
Travel, Accommodations, Expenses: Amgen

Anthony Howell
No relationship to disclose

Acknowledgment