How to manage the obese patient with cancer


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How to Manage the Obese Patient With Cancer

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ABSTRACT

Purpose

Obesity (body mass index [BMI] ≥ 30 kg/m²) 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.

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. The International Agency for Research on Cancer 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 ≥ 30 kg/m²) 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 $N \times 3$ 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 and may also be associated with poorer prognosis, especially in breast cancer (and dealt with elsewhere in this Special Issue). 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 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; and a fourth relationship known as the obesity paradox. 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 ($\geq 25 \text{ kg/m}^2$), 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 of 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

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**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).
studies of obesity exposure and incident cancer risk, 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, perioperative mortality, and toxicity.

Impact of Obesity on Treatment Complications

Chemotherapy toxicity. Hourdequin et al 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. 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.

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 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. 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.

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 genomics on pharmacokinetics, suggests that detailed prospective studies of tailoring chemotherapy doses to the individual are required.

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 only3,33–36 whereas others included benign and malignant indications, 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>
<thead>
<tr>
<th>Author and Country</th>
<th>Cancer Type</th>
<th>Study Name/Type</th>
<th>No. of Patients</th>
<th>Clinical Setting</th>
<th>Chemotherapy Regimens</th>
<th>Percentage</th>
<th>P</th>
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<tr>
<td><strong>First cycle dose reduction (≤ 0.9 standard dose)</strong></td>
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<td>Griggs et al 2005, United States</td>
<td>Breast</td>
<td>Retrospective cohort study, Pittsburgh</td>
<td>9,672</td>
<td>Adjuvant</td>
<td>Doxorubicin hydrochloride and cyclophosphamide, between 1990 and 2001</td>
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<td>Breast</td>
<td>Phase III trial</td>
<td>1,066</td>
<td>Adjuvant</td>
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<td><strong>Dose reduction (≤ 0.95 standard dose)</strong></td>
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<td>Colon</td>
<td>NSABP C-04 and C-05</td>
<td>4,288</td>
<td>Adjuvant</td>
<td>Leucovorin-modulated fluorouracil (FU + LV); FU and levamisole (FU + LEV), or FU + LV + LEV</td>
<td>7.0</td>
<td>55.0</td>
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<td>Chambers et al 2012, United Kingdom</td>
<td>Colorectal</td>
<td>FOCUS trial</td>
<td>2,057</td>
<td>Metastatic</td>
<td>A five-arm trial: scheduling two drugs; irinotecan and oxaliplatin</td>
<td>4.0</td>
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<td>Wright et al 2008, United States</td>
<td>Ovarian</td>
<td>Gynecologic Oncology Group (GOG) protocol 158</td>
<td>387</td>
<td>Optimal cytoreduction (residual tumor &lt; 1 cm after surgery)</td>
<td>Carboplatin based on an AUC of 7.5 and a GFR derived from the Jelliffe formula</td>
<td>34.0</td>
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<td><strong>Relative dose intensity &lt; 85%</strong></td>
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<tr>
<td>Au-Yeung et al 2014, Australia</td>
<td>Ovarian</td>
<td>Australian Ovarian Cancer Study (AOCIS)</td>
<td>333</td>
<td>Stage II/IV</td>
<td>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.</td>
<td>39.0</td>
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<td>Au-Yeung et al 2014, Australia</td>
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<td>Australian Ovarian Cancer Study (AOCIS)</td>
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<td>Stage II/IV</td>
<td>Paclitaxel 175 mg/m² based on measured height and weight, and BSA calculated using the Dubois formula.</td>
<td>50.0</td>
<td>54.0</td>
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</table>

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>
<thead>
<tr>
<th>Author and Country</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Main Procedures</th>
<th>Outcome</th>
<th>Outcomes (%)</th>
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<td>ACS NSQIP database. Prospective, multi-institutional, risk-adjusted cohort study of patients undergoing major intraabdominal cancer surgery was performed in 14 university hospitals</td>
<td>2,258</td>
<td>Oesophagectomy (n = 29), gastrectomy (n = 223), hepatectomy (n = 554), pancreatic resection (n = 699), or low anterior resection/proctectomy (n = 753) (cancer indication not specified)</td>
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<td>Wound infections</td>
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<td>1,029</td>
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<td>Infectious complications</td>
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<td>30-day mortality</td>
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<td>Laparoscopic colectomy (cancer indication was malignancy in 40%)</td>
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<td>Wound infections</td>
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<td>Major surgical complications</td>
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<td>Graft and prostheses loss</td>
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<td></td>
<td></td>
<td></td>
<td>Return to operating theater</td>
<td>6.2</td>
<td>9.1</td>
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<td>New York University Medical School</td>
<td>540</td>
<td>Oesophagectomy for adenocarcinoma</td>
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<td>Surgical-site infection</td>
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<td>30-day mortality</td>
<td>1.3</td>
<td>1.5</td>
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<th>No. of Patients</th>
<th>Main Procedures</th>
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<th>Normal Weight</th>
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<th>Obese II/III</th>
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<td>12.0</td>
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<td>6.2</td>
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<td>0.8</td>
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<td>Malignant</td>
<td>Major complications (Clavien-Dindo II/IV)</td>
<td>11.4†</td>
<td>9.7‡</td>
<td>7.8‡</td>
<td>.001</td>
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<td>Surgical-site infection</td>
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<td>Major complications (Clavien-Dindo II/IV)</td>
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<td>1.9†</td>
<td>2.5‡</td>
<td>1.3‡</td>
<td>.242</td>
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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.44,40

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,47 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,48 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/m² to 7.4% in subjects with a BMI > 28.5 kg/m² 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 Consortium49 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 Goodwin44 and within sections of this Special Issue45). Secondary analyses of four randomized trials found inconsistent results44 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 cancer47,48; metastatic renal cell carcinoma49,50; and advanced ovarian cancer51 (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 colorectal48 and advanced ovarian cancer49; the opposite is noted in metastatic renal cancer49,50; 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 Asia54 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,40 or experience a chemotherapy-induced menopause.58,61 Weight gains may be greater with cyclophosphamide, methotrexate, and fluorouracil compared with anthracyline (2.9 kg [5%] v 0.9 kg [1%]),62 but this is not a consistent finding.62,63,64 Weight is gained during and after the chemotherapy period,58,64 and has been shown to persist when measured at 3 years52 and 6 years65 after diagnosis.

What are the consequences of chemotherapy-related weight gain? Playdon et al56 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 ≥ 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, 1.09 to 1.39). 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 year 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 ≥ 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 Measures

<table>
<thead>
<tr>
<th>Author and Country</th>
<th>Cancer Type</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Antiangiogenic Regimens</th>
<th>Treatment Response</th>
<th>Conventional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antiangiogenic Therapy</td>
<td>Conventional Therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low VFA  High VFA</td>
<td>Low VFA  High VFA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$p_{between}$  $p_{interaction}$</td>
<td>$p_{between}$  $p_{interaction}$</td>
</tr>
<tr>
<td>Guiu et al 2010,</td>
<td>Metastatic colorectal cancer</td>
<td>120</td>
<td>Retrospective</td>
<td>80 first-line bevacizumab-based treatment; 40 chemotherapy only*</td>
<td>14.0  9.0</td>
<td>0.0008</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.0  6.0</td>
<td>0.65  0.22</td>
</tr>
<tr>
<td>Simkens et al 2011,</td>
<td>CAIRO: Metastatic colorectal cancer</td>
<td>755</td>
<td>Secondary analysis trial data</td>
<td>First-line treatment with capecitabine, oxaliplatin, and bevacizumab with (arm B) or without (arm A) cetuximab</td>
<td>10.1  9.7</td>
<td>0.528</td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Simkens et al 2011,</td>
<td>CAIRO2: Metastatic colorectal cancer</td>
<td>820</td>
<td>Secondary analysis trial data</td>
<td>Phase III trial of sequential v the combined use of capecitabine, irinotecan, and oxaliplatin†</td>
<td>4.4  6.2</td>
<td>0.153</td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladoire et al 2011,</td>
<td>Metastatic renal cell carcinoma</td>
<td>64</td>
<td>Retrospective</td>
<td>Antiangiogenic agents (bevacizumab, sunitinib, or sorafenib)*</td>
<td>Approximately 4</td>
<td>Approximately 22</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Steffens et al 2011,</td>
<td>Metastatic renal cell carcinoma</td>
<td>116</td>
<td>Retrospective</td>
<td>Antiangiogenic agents (sunitinib, sorafenib, axitinib, bevacizumab)†</td>
<td>8.4  11.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
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</tr>
<tr>
<td>Steffens et al 2011,</td>
<td>Metastatic renal cell carcinoma</td>
<td>116</td>
<td>Retrospective</td>
<td>Antiangiogenic agents (sunitinib, sorafenib, axitinib, bevacizumab)†</td>
<td>8.4  10.5</td>
<td>0.037</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slaughter et al 2014,</td>
<td>Advanced ovarian cancer</td>
<td>46</td>
<td>Retrospective</td>
<td>Twenty-one bevacizumab-based; 25 chemotherapy only†</td>
<td>24.7  9.8</td>
<td>0.03  11.9</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.6  0.19</td>
</tr>
</tbody>
</table>

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 statement4,57 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 al77 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-analysis72 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 al74 demonstrated a significantly increased risk of cardiovascular death with increasing prediagnosis (mean, 7 years) BMI (per 5 kg/m²: HR, 1.28; 95% CI, 1.04 to 1.58), but not postdiagnosis (mean, 1.5 years) BMI (per 5 kg/m²: HR, 1.06; 95% CI, 0.84 to 1.33). For endometrial cancer, Ward et al75 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).77 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 types77; two studies in breast cancer survivors78,79; one meta-analysis of 10 studies in colorectal cancer80; one meta-analysis of five studies in prostate cancer48; one meta-analysis of four studies in endometrial cancer82; and one study in ovarian cancer survivors83 (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 al82 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.

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Summary Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ABW be used when selecting cytotoxic chemotherapy doses regardless of obesity status</td>
</tr>
<tr>
<td>2</td>
<td>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</td>
</tr>
<tr>
<td>3</td>
<td>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</td>
</tr>
<tr>
<td>4</td>
<td>Consideration of fixed dosing only with select cytotoxic agents (eg, carboplatin, bleomycin, vincristine)</td>
</tr>
<tr>
<td>5</td>
<td>BSA be calculated using any of the standard formulae</td>
</tr>
<tr>
<td>6</td>
<td>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.”</td>
</tr>
</tbody>
</table>

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\(^3\); and dual-energy x-ray absorptiometry\(^4\)) 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, and is important to pursue to better define the management of the increasing proportion of obese patients with cancer.

**REFERENCES**


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

**AUTHOR CONTRIBUTIONS**

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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

Obesity in Patients With Cancer
70. Chlebowski RT, Reeves MM: Weight loss randomized intervention trials in women cancer survivors. Journal of Clinical Oncology Special Issue: Obesity and Cancer. In press
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How to Manage the Obese Patient With Cancer

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