

# Management of Cancer Cachexia: ASCO Guideline

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**PURPOSE** To provide evidence-based guidance on the clinical management of cancer cachexia in adult patients with advanced cancer.

**METHODS** A systematic review of the literature collected evidence regarding nutritional, pharmacologic, and other interventions, such as exercise, for cancer cachexia. PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and systematic reviews of RCTs published from 1966 through October 17, 2019. ASCO convened an Expert Panel to review the evidence and formulate recommendations.

**RESULTS** The review included 20 systematic reviews and 13 additional RCTs. Dietary counseling, with or without oral nutritional supplements, was reported to increase body weight in some trials, but evidence remains limited. Pharmacologic interventions associated with improvements in appetite and/or body weight include progesterone analogs and corticosteroids. The other evaluated interventions either had no benefit or insufficient evidence of benefit to draw conclusions on efficacy. Limitations of the evidence include high drop-out rates, consistent with advanced cancer, as well as variability across studies in outcomes of interest and methods for outcome assessment.

**RECOMMENDATIONS** Dietary counseling may be offered with the goals of providing patients and caregivers with advice for the management of cachexia. Enteral feeding tubes and parenteral nutrition should not be used routinely. In the absence of more robust evidence, no specific pharmacological intervention can be recommended as the standard of care; therefore, clinicians may choose not to prescribe medications specifically for the treatment of cancer cachexia. Nonetheless, when it is decided to trial a drug to improve appetite and/or improve weight gain, currently available pharmacologic interventions that may be used include progesterone analogs and short-term (weeks) corticosteroids.

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## INTRODUCTION

The purpose of this guideline is to provide evidence-based guidance on the optimal approach for the treatment of cachexia in patients with advanced cancer. Cachexia is a multifactorial syndrome characterized by loss of appetite, weight, and skeletal muscle,<sup>1</sup> leading to fatigue,<sup>2</sup> functional impairment,<sup>3</sup> increased treatment-related toxicity,<sup>4</sup> poor quality of life,<sup>5</sup> and reduced survival.<sup>4,6-11</sup> Across malignancies, cachexia is highly prevalent, impacting approximately half of patients with advanced cancer.<sup>12,13</sup> Assessment and management of cancer cachexia are major challenges for clinicians.

Definitions of cancer cachexia have changed over time. Early definitions focused on weight, physical

performance, and patient function. In 2008, members of the Society of Cachexia and Wasting Disorders published diagnostic criteria of non-cancer-specific cachexia, defined as 5% weight loss in the previous 6 months with at least three of five clinical symptoms: fatigue, anorexia, reduced muscle strength, reduced fat-free mass, and/or systemic signs of inflammation.<sup>14</sup> In 2009, the Italian research group SCRINIO defined cancer-specific cachexia as weight loss > 10% with symptoms of anorexia, early satiety, and fatigue.<sup>15</sup> Most recently, in 2011, an international Delphi consensus definition and classification of cancer cachexia was published, provisionally defining cancer cachexia as > 5% weight loss in the previous 6 months or 2%-5% weight loss with either a body mass index

### ASSOCIATED CONTENT

#### Appendix

#### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## THE BOTTOM LINE

### Management of Cancer Cachexia: ASCO Guideline

#### Guideline Questions

Among adult patients with advanced cancer and cachexia, do: (1) nutritional interventions, (2) pharmacologic interventions, and/or (3) other interventions improve clinical outcomes? In this syndrome, there is no single clinical variable widely regarded as the standard primary outcome; therefore, appetite, body weight, lean body mass, physical function, and quality of life were included as appropriate end points.

#### Target Population

Adult patients with advanced cancer and loss of appetite, body weight, and/or lean body mass (ie, skeletal muscle).

#### Target Audience

Clinicians who provide care to adult patients with cancer, as well as patients and caregivers.

#### Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature and expert opinion.

#### Recommendations

##### Nutritional Interventions

**Recommendation 1.1.** Clinicians may refer patients with advanced cancer and loss of appetite and/or body weight to a registered dietitian for assessment and counseling, with the goals of providing patients and caregivers with practical and safe advice for feeding; education regarding high-protein, high-calorie, nutrient-dense food; and advice against fad diets and other unproven or extreme diets (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 1.2.** Outside the context of a clinical trial, clinicians should not routinely offer enteral tube feeding or parenteral nutrition to manage cachexia in patients with advanced cancer. A short-term trial of parenteral nutrition may be offered to a very select group of patients, such as patients who have a reversible bowel obstruction, short bowel syndrome, or other issues contributing to malabsorption, but otherwise are reasonably fit. Discontinuation of previously initiated enteral or parenteral nutrition near the end of life is appropriate (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Information about additional nutritional interventions considered by the Expert Panel is provided in [Table 1](#).

##### Pharmacologic Interventions

**Recommendation 2.1.** Evidence remains insufficient to strongly endorse any pharmacologic agent to improve cancer cachexia outcomes; clinicians may choose not to offer medications for the treatment of cancer cachexia. There are currently no FDA-approved medications for the indication of cancer cachexia (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 2.2.** Clinicians may offer a short-term trial of a progesterone analog or a corticosteroid to patients experiencing loss of appetite and/or body weight. The choice of agent and duration of treatment depends on treatment goals and assessment of risk versus benefit (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Information about additional pharmacologic interventions considered by the Expert Panel is provided in [Table 1](#).

##### Other Interventions

**Recommendation 3.** Outside the context of a clinical trial, no recommendation can be made for other interventions, such as exercise, for the management of cancer cachexia.

##### Additional Resources

More information, including a supplement with additional tables, slide sets, and clinical tools and resources, is available at [www.asco.org/supportive-care-guidelines](http://www.asco.org/supportive-care-guidelines). The Methodology Manual (available at [www.asco.org/guidelines-methodology](http://www.asco.org/guidelines-methodology)) provides additional information about the methods used to develop this guideline. Patient information is available at [www.cancer.net](http://www.cancer.net)

**ASCO believes that clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.**

(BMI) of  $< 20 \text{ kg/m}^2$  or reduced muscle mass.<sup>16,17</sup> Subsequently, this group provided mortality-based diagnostic criteria for the severity of cancer-associated weight loss, with 5 grades (0-4) in a sample of 8,000 patients and a validation cohort of approximately 3,000 patients.<sup>11</sup>

According to the international consensus, cancer cachexia is a continuum that can be categorized into three phases: precachexia, cachexia, and refractory cachexia.<sup>16</sup> Not all patients with cancer progress through all stages of cachexia. The risk of progression depends on factors such as cancer type, stage, food intake, presence of systemic inflammation, inactivity, lack of response or complications to anticancer therapy, and/or sequela of surgery. In *precachexia*, patients have experienced only minimal weight loss (ie, 2%-5%), with early clinical and metabolic signs predictive of future weight loss such as anorexia, insulin resistance, inflammation, and hypogonadism. There are not, as yet, consensus diagnostic criteria for *precachexia*. While preemptive intervention has been suggested,<sup>16</sup> only small randomized controlled trials (RCTs) have focused on a *precachexia* population. The onset of *cachexia* has been described as a weight loss in excess of 5% over the preceding 6 months, or a BMI  $< 20 \text{ kg/m}^2$  with ongoing  $> 2\%$  weight loss, or depletion of muscle mass and  $> 2\%$  weight loss.<sup>11</sup> The definition of “ongoing” was not further defined in this report. *Refractory cachexia* has been conceptualized as a clinically resistant catabolic state characterized by poor performance status, progressive cancer, and a life expectancy  $< 3$  months; however, there are not yet consensus diagnostic criteria for refractory cachexia. Limitations of these definitions include the lack of inclusion of cancer stage and goal of treatment (ie, curative v palliative).

Multiple factors contribute to the complex pathophysiology of cancer cachexia; detailed reviews are found elsewhere.<sup>18-22</sup> Cancer profoundly alters the normal homeostatic control of energy balance. Reduced food intake is an important and, in some cases, predominant component of cancer-associated weight loss,<sup>20,22</sup> and this results, in part, from altered hypothalamic control of appetite and satiety.<sup>21</sup> Additionally, uncontrolled symptoms of cancer or its treatments (eg, pain, nausea, vomiting, depression, and dysgeusia) can be detrimental to food intake. Aberrant metabolism is also implicated in cancer cachexia, distinguishing it from simple malnutrition. The metabolic alterations may include neurohormonal dysregulation, elevated energy expenditure, and increased catabolism. Increased catabolic mediators are derived from tumor overexpression, and inflammation elicited by a cancer can generate catabolic proinflammatory cytokines and eicosanoids.<sup>18-20</sup>

The goal of identifying and treating cancer cachexia is to improve treatment tolerability, improve survival, and optimize the quality of life of patients with advanced cancer.

The aim of this review is to provide evidence-based recommendations for the treatment of cancer cachexia.

## GUIDELINE QUESTIONS

Among adult patients with advanced cancer and loss of appetite, body weight, and/or lean body mass, are outcomes such as weight, lean body mass, appetite, physical function, or quality of life improved by:

1. Nutritional interventions
2. Pharmacologic interventions
3. Other interventions (eg, exercise)?

## METHODS

### Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met in person and via webinars and corresponded through e-mail (Appendix Table A1, online only). Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were made available for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were considered while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. Ultimately, all ASCO guidelines are reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee (CPGC) prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of the literature and clinical experience. PubMed and the Cochrane Library were searched for RCTs or systematic reviews of RCTs published from 1966 through October 17, 2019. Search terms are provided in the Data Supplement. Articles were selected for inclusion in the systematic review based on the following criteria:

- Population: Adult patients with appetite loss, weight loss, and/or body composition changes associated with advanced cancer.
- Interventions: Dietary counseling, dietary supplements, enteral or parenteral nutrition, exercise, complementary or alternative therapies, pharmacologic agents, or multimodal approaches. Pharmacologic approaches of interest were appetite stimulants (cannabis and cannabinoids, corticosteroids, cyproheptadine, megestrol acetate), anabolic agents

(anamorelin, androgens, or selective androgen receptor modulators), cytokine inhibitors (hydrazine sulfate, thalidomide, tumor necrosis factor [TNF] inhibitors), and other (adenosine triphosphate, insulin, mirtazapine, melatonin, nonsteroidal anti-inflammatory agents [NSAIDs], and olanzapine).

- Sample size: A total of at least 20 patients.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; (3) published in a non-English language; or (4) addressed in an included systematic review.

The guideline recommendations were crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.<sup>23</sup> In addition, a guideline review regarding implementation was conducted. Based on the implementation review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep updated regarding new information related to this topic. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at [www.asco.org/guideline-methodology](http://www.asco.org/guideline-methodology)) provides additional information about the guideline update process. This is the most recent information as of October 17, 2019, the end date of the literature search for this Guideline.

### Guideline Disclaimer

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and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating clinician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating clinician in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

### Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker’s bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

## RESULTS

The literature review identified 1,374 potentially relevant citations. Of these, 144 were examined in detail; 36 met eligibility criteria and comprised the evidence base for the guideline recommendations. These publications consisted of 20 systematic reviews<sup>24-43</sup> and 13 additional RCTs (16 publications).<sup>44-59</sup> A summary of the literature search results is provided in the Data Supplement.

Primary outcomes varied across studies. Most studies provided information about body weight, but few provided information regarding lean body mass. Among the studies that reported on appetite or quality of life, measurement tools varied. Evidence tables are provided in the Data Supplement.

### Study Quality

Study quality was formally assessed for all included publications. The risk of bias was assessed as intermediate or high for a majority of included RCTs. Sample sizes tended to be small, and many studies reported high rates of patient dropout. These limitations are not unexpected in the patient population being studied; however, they complicate

interpretation of the results. Systematic reviews scored well in many quality domains. Meta-analyses were available for progesterone analogs, some aspects of diet, and anamorelin. Additional information regarding quality assessments is provided in the Data Supplement.

## RECOMMENDATIONS

A summary of recommendations is provided in Table 1. For recommended pharmacologic agents, Table 2 provides suggested dosing, risks and benefits, and cost estimates.

### CLINICAL QUESTION 1

Among adult patients with advanced cancer and loss of appetite, body weight, and/or lean body mass, are outcomes such as weight, lean body mass, appetite, physical function, or quality of life improved by **nutritional interventions**?

#### Recommendation 1.1

Clinicians may refer patients with advanced cancer and loss of appetite and/or body weight to a registered dietitian for assessment and counseling, with the goals of providing patients and caregivers with practical and safe advice for feeding; education regarding high-protein, high-calorie,

nutrient-dense food; and advice against fad diets and other unproven or extreme diets (Type of recommendation: informal consensus. Evidence quality: low; Strength of recommendation: moderate).

#### Recommendation 1.2

Outside the context of a clinical trial, clinicians should not routinely offer enteral tube feeding or parenteral nutrition to manage cachexia in patients with advanced cancer. A short-term trial of parenteral nutrition may be offered to a very select group of patients, such as patients who have a reversible bowel obstruction, short bowel syndrome, or other issues contributing to malabsorption, but otherwise are reasonably fit. Discontinuation of previously initiated enteral or parenteral nutrition near the end of life is appropriate (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

#### Literature Review and Analysis

**Dietary counseling.** Three systematic reviews evaluated dietary counseling, oral nutritional supplements, or a combination of these approaches. One key limitation in the evaluation of nutritional counseling interventions is the lack of a clear definition of what these interventions entail.

**TABLE 1.** Summary of Recommendations for the Treatment of Cancer Cachexia in Patients With Advanced Cancer

Intervention	Strength of Recommendation	Strength of the Evidence	Benefits <sup>a</sup>	Harms <sup>a</sup>
Nutritional interventions				
Dietary counseling <sup>25,26,37</sup>	Moderate in favor	Low	Moderate	Low
Parenteral or enteral nutrition (routine use) <sup>31,42</sup>	Moderate against	Low	Low	Moderate to high
Omega-3 fatty acids <sup>26,29,40</sup>	No recommendation	Low	Low	Low
Vitamins, minerals, and other dietary supplements <sup>38</sup>	No recommendation	Low	Low	Low
Pharmacologic interventions				
Progesterone analogs <sup>30,33,35,36,43</sup>	Moderate in favor	Intermediate	Moderate	Moderate
Corticosteroids <sup>43</sup>	Moderate in favor	Intermediate	Moderate	Moderate
Anamorelin <sup>24,32,68</sup>	No recommendation (not commercially available)	Intermediate	Moderate	Low
Olanzapine <sup>56</sup>	No recommendation	Low	Moderate	Low
Androgens <sup>36,43,59</sup>	No recommendation	Low	Moderate	Low
Thalidomide <sup>34,36</sup>	No recommendation	Low	Low	Low
NSAIDs <sup>39,41</sup>	No recommendation	Low	Low	Low
Cyproheptadine <sup>43</sup>	No recommendation	Low	None	Low
Cannabinoids <sup>36,43</sup>	Weak against	Low	None	Low
Melatonin <sup>36,43</sup>	Weak against	Low	None	Low
TNF inhibitors <sup>36,43</sup>	Moderate against	Intermediate	None	Moderate
Hydrazine sulfate <sup>43</sup>	Strong against	Intermediate	None	Moderate
Other interventions				
Exercise <sup>27</sup>	No recommendation	Low	Unknown	Unknown

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

<sup>a</sup>Categorization of benefits and harms was based on use of the intervention for cancer cachexia in the populations that were enrolled in randomized controlled trials.

**TABLE 2.** Pharmaceutical Options for Management of Cancer Cachexia

Drug	Suggested Dosing	Benefits	Risks	Cost per Month <sup>a</sup>
Megestrol acetate/ medroxyprogesterone	200-600 mg/d; liquid formulation may be less expensive and more bioavailable than tablets	Improved appetite, weight gain	Edema, thromboembolism, adrenal insufficiency	\$57.41 <sup>b</sup>
Corticosteroids	3-4 mg dexamethasone equivalent dose/d <sup>c</sup>	Improved appetite	Multiple common toxicities <sup>82</sup>	\$27.11

<sup>a</sup>Prices for orally administered drugs reimbursed through Medicare Part D were identified in the PlanFinder for a beneficiary living within ZIP code 10065 ([www.medicare.gov](http://www.medicare.gov)). We selected a Humana Premier Prescription Drug plan with the lowest cost for beneficiaries to identify the full cost of each drug. Drug costs may vary by plan and by pharmacy where a prescription is filled (eg, preferred or nonpreferred pharmacies). Note: drug prices are dynamic and the prices listed in the table may not reflect current prices.

<sup>b</sup>Cost is for megestrol acetate, 400 mg/d, given as 40 mg/ml suspension in 10-ml cups

<sup>c</sup>The original dose evaluated was 0.75 mg 4 times daily.<sup>67</sup> However, given the long biologic half-life, once-daily dosing is recommended.

A 2018 meta-analysis of nine RCTs did not restrict by nutritional status or stage of cancer, although a majority of included trials enrolled patients with advanced cancer. All patients were receiving chemo(radio)therapy. Overall, dietary counseling and/or oral nutritional supplements were associated with improved body weight (mean difference, 1.31 kg; 95% CI, 0.24 to 2.38).<sup>26</sup>

A 2014 systematic review focused on dietary counseling regarding weight loss and energy intake in patients with advanced cancer and cachexia.<sup>37</sup> Of the five studies included, three were RCTs. The content, duration, and effects of the oral nutrition interventions varied across studies, and the authors concluded “Based on the limited number of conducted studies, the inconsistent results, as well as the moderate quality of the included studies, it is not possible to conclude firmly on the effectiveness of nutritional interventions in advanced cancer and cachexia.”<sup>37</sup> (p219)

A 2012 meta-analysis of dietary advice, oral nutritional supplements, or the combination evaluated adults with cancer who were malnourished or at risk for malnutrition but did not restrict by cancer stage.<sup>25</sup> The results suggested that oral nutritional interventions do not affect mortality but may improve quality of life. Analyses of weight gain and energy intake indicated a high heterogeneity across studies; after excluding the studies that contributed to this heterogeneity, results for weight gain and energy intake were not statistically significant.

**Parenteral or nonvolitional enteral nutrition.** A 1990 meta-analysis of total parenteral nutrition (TPN) in patients receiving chemotherapy reported that TPN was associated with reduced survival and increased infectious complications.<sup>31</sup> The authors concluded, “Routine use of TPN in patients undergoing chemotherapy should be strongly discouraged.”<sup>31</sup> (p233) Noting the administration, dosing, and composition of parenteral nutrition has changed since 1990, a 2019 systematic review provided an updated evaluation focusing on patients with advanced cancer.<sup>42</sup> The review included observational studies as well as two RCTs,<sup>60,61</sup> both of which enrolled fewer patients than planned. One of the trials, published in 2019, evaluated

dietary counseling with or without home parenteral nutrition in 47 patients with incurable GI cancer.<sup>60</sup> An improvement in fat-free mass in the intervention arm was noted at week 12, but not at weeks 6, 18, or 24. The second trial, published in 2014, compared parenteral nutrition with intravenous fluid in 31 patients with terminal cancer.<sup>61</sup> Parenteral nutrition did not significantly improve overall survival. The overall level of evidence provided by the RCTs and observational studies was deemed “weak.”

Parenteral nutrition was also a component of a palliative care intervention evaluated in a 2004 RCT.<sup>54</sup> The study enrolled more than 300 patients with cancer who were losing weight. The intervention involved specialized nutritional support consisting of supplemental oral nutrition and home parenteral nutrition when intake declined to a pre-specified level. Patients in the control arm relied on spontaneous oral nutritional intake to meet energy needs. In the intent-to-treat analysis, the intervention resulted in higher caloric intake but did not improve body composition (per dual x-ray absorptiometry [DXA]) or survival.

**Long-chain omega-3 fatty acids (eicosapentaenoic and docosapentaenoic acids).** A 2011 systematic review evaluated omega-3 fatty acids in patients with advanced cancer and cachexia.<sup>40</sup> These fatty acids are derived from fatty marine fish and are provided in the form of fish oil concentrates containing both eicosapentaenoic (EPA) and docosapentaenoic acids, or these fatty acids in a purified form such as EPA ethyl ester. The review included three systematic reviews and nine RCTs, as well as non-randomized studies. The authors concluded that, within studies with higher methodological quality, there was no clear evidence that omega-3 fatty acids provided benefit. Adverse effects were reported in only a few studies and included mild abdominal discomfort, flatulence, nausea/vomiting, transient diarrhea/steatorrhea, fish aftertaste, or belching. No severe adverse effects were reported.

A 2015 meta-analysis evaluated 11 RCTs with a total of 1,367 patients with unresectable pancreatic cancer. The data suggested that the consumption of omega-3 fatty acids was safe and may improve weight, lean body mass, and survival.<sup>29</sup> Included RCTs were relatively small, and

there was moderate to high heterogeneity in the results across studies.

Most recently, in a 2018 meta-analysis,<sup>26</sup> 11 studies with a total of 1,350 patients were identified and reviewed. The primary aim of this evaluation was to determine whether oral nutritional interventions had an impact on a range of nutritional and clinical outcomes in patients undergoing chemo(radio)therapy. The authors concluded that the nutritional interventions had a positive effect on body weight. A subset analysis of four RCTs supported that omega-3 fatty acids improved body weight by approximately 2 kg.<sup>26</sup> The authors recommended future clinical trials to obtain additional data.

**Vitamins, minerals, and other dietary supplements.** A 2017 systematic review evaluated vitamins, minerals, and other dietary supplements for the treatment of cancer cachexia.<sup>38</sup> Interventions included magnesium; vitamin E in combination with omega-3 fatty acids; vitamin D; vitamin C; a combination of  $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB), arginine, and glutamine; and L-carnitine. Though some studies reported a benefit in outcomes such as lean body mass or BMI, the authors of the review concluded that evidence remains insufficient for a recommendation in favor of these interventions. No serious adverse effects were reported.

An additional RCT, also published in 2017, compared creatine with placebo in 263 evaluable patients with incurable cancer and cancer cachexia.<sup>52</sup> Creatine did not improve weight, appetite, quality of life, strength, body composition, or survival.

**Clinical Interpretation.** Although evidence remains limited regarding the role of counseling by registered dietitians in improving cachexia outcomes, such interventions may provide important support to patients and their caregivers. In addition to helping individuals with advanced cancer meet estimated energy and protein needs as much as practicable, referral to a registered dietitian may serve to protect patients against potentially harmful dietary supplement use, fad diets, and other unproven or extreme diets. It is reported that up to 48% of patients with cancer pursue, or are interested in, “fad” or popular diets, including ketogenic, vegan, alkaline, paleolithic, and macrobiotic diets.<sup>62</sup> A recent survey of 603 patients being treated at a US comprehensive cancer center found that 49% of individuals receiving any cancer treatment, 52% receiving chemotherapy, and 51% undergoing radiation therapy reported using dietary supplements during treatment.<sup>63</sup> Nearly one of five adults were using herbal supplements, which pose a potentially higher risk of adverse drug interactions with cancer therapies and other medications, compared with vitamins and minerals. Referral to a registered dietitian may help patients, already struggling with poor food intake, to avoid dietary plans and products that further worsen the clinical picture.

Despite the recommendation against the routine use of parenteral nutrition in patients with advanced cancer, there are specific situations in which a patient has a non-functioning alimentary tract but does not have other organ involvement with a cancer that portends a very poor prognosis. For example, a patient with a relatively indolent malignancy that causes multifocal bowel obstructions may benefit from a time-limited trial of home parenteral nutrition. However, even in select cases, the risks, benefits, and cost of parenteral nutrition should be discussed with the patient and caregivers. Comprehensive reviews regarding the use and safety of parenteral nutrition in patients with cancer are available elsewhere.<sup>64,65</sup> If a parenteral nutrition trial is initiated in an individual patient, it should be evaluated after a prospectively agreed upon fixed time period with a specific goal (eg, able to walk to the mailbox). Parenteral nutrition should be stopped if no significant benefit has occurred and when death appears imminent.

Finally, although the available data regarding the use of omega-3 fatty acids are not strong enough to make a recommendation for their use in all patients with cachexia, it is reasonable to use these fats as a source of calories in patients with cancer cachexia. Natural sources of omega-3 fats, such as salmon, are nutrient-dense foods and can be included in the diet as tolerated.

## CLINICAL QUESTION 2

Among adult patients with advanced cancer and loss of appetite, body weight, and/or lean body mass, are outcomes such as weight, lean body mass, appetite, physical function, or quality of life improved by **pharmacologic interventions**?

### Recommendation 2.1

Evidence remains insufficient to strongly endorse any pharmacologic agent to improve cancer cachexia outcomes; clinicians may choose not to offer medications for the treatment of cancer cachexia. There are currently no FDA-approved medications for the indication of cancer cachexia (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

### Recommendation 2.2

Clinicians may offer a short-term trial of a progesterone analog or a corticosteroid to patients experiencing loss of appetite and/or body weight. The choice of agent and duration of treatment depends on treatment goals and assessment of risk versus benefit (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

## Literature Review and Analysis

**Progesterone analogs.** Five systematic reviews assessed progesterone analogs for cachexia management,<sup>30,33,35,36,43</sup> and three of these reported meta-analyses.<sup>30,33,35</sup> The most recent meta-analysis, a 2013 Cochrane review, evaluated

patients with cachexia due to cancer, AIDS, or other underlying pathologies.<sup>35</sup> The review included 23 RCTs of patients with cancer (total of 3,428 patients). Among the patients with cancer, those in the megestrol acetate arm were more likely than those in the placebo arm to experience improvements in appetite (relative risk [RR], 2.57; 95% CI, 1.48 to 4.49), weight (RR, 1.55; 95% CI, 1.06 to 2.26), and quality of life (assessed by validated instruments or scales of functional scores; RR, 1.91; 95% CI, 1.02 to 3.59). Weight gain tended to be modest. Uncertainties remain about the optimal dose and duration of megestrol acetate, but higher doses were associated with greater improvement in weight than lower doses. Adverse events were not reported for the subgroup of patients with cancer, but overall, megestrol acetate was associated with increased risks of death (RR, 1.42; 95% CI, 1.04 to 1.94), thromboembolic events (RR, 1.84; 95% CI, 1.07 to 3.18), and edema (RR, 1.36; 95% CI, 1.07 to 1.72). Generally similar results were reported in an earlier, 2004 meta-analysis.<sup>33</sup>

The included systematic reviews also addressed trials comparing megestrol acetate to other active agents or combination regimens. A three-arm trial randomly assigned 496 adults with incurable cancer (other than breast, prostate, ovarian, or endometrial) and cancer anorexia/cachexia to megestrol acetate, dexamethasone, or fluoxymesterone.<sup>66</sup> Differences in weight gain across the 3 arms were not statistically significant. Megestrol acetate was more effective than fluoxymesterone for appetite improvement (5-item questionnaire). Megestrol acetate and dexamethasone produced similar appetite results, but different toxicities. Thirty-six percent of patients in the dexamethasone arm stopped the study medication because of toxicity or patient refusal, compared with 25% of patients in the megestrol acetate arm ( $P = .03$ ).

**Corticosteroids.** The initial trial reporting that a corticosteroid (dexamethasone) provided benefit in patients with advanced cancer-associated anorexia was published in 1974 by Moertel et al.<sup>67</sup> This placebo-controlled, double-blind study of 116 patients with advanced GI cancers demonstrated an improvement in appetite and sense of well-being. A 2005 systematic review included this trial and five additional placebo-controlled trials.<sup>43</sup> Improvements in appetite were reported among patients who received corticosteroids. Only two trials reported weight findings, with no significant improvement in the corticosteroid arms. The authors noted that optimal dose and duration of corticosteroid use remained unknown.

**Combination of olanzapine and megestrol acetate.** The addition of olanzapine to megestrol acetate was evaluated in a 2010 RCT of 80 patients with advanced lung or GI cancers.<sup>56</sup> Patients in the combination arm were more likely than patients in the megestrol acetate arm to experience a weight gain of  $\geq 5\%$  over 8 weeks (85% v 41%). No grade 3-4 toxicities were reported in this trial.

**Anamorelin.** Anamorelin—a ghrelin receptor agonist—is the most rigorously evaluated cancer cachexia agent to date. Briefly, anamorelin was evaluated in two meta-analyses in 2017, both of which reported improvements in body weight, lean body mass, and patient-reported quality of life.<sup>24,32</sup> The largest study included in these meta-analyses was an analysis of two phase III RCTs by Temel et al.<sup>68</sup> A total of 979 patients with advanced non-small-cell lung cancer and cachexia (defined as  $\geq 5\%$  weight loss within 6 months or BMI  $< 20$  kg/m<sup>2</sup>) were randomly assigned 2:1 to anamorelin 100 mg orally once daily or placebo. The dual primary end point was the median change in lean body mass (assessed by DXA) and handgrip strength over 12 weeks. Anamorelin increased lean body mass but did not improve handgrip strength. Similar findings were reported in a 12-week extension study<sup>69</sup> and a 2018 RCT conducted in 174 patients with advanced non-small-cell lung cancer.<sup>70</sup> Study findings were reviewed by the US Food and Drug Administration (FDA) but did not receive approval for treatment of cancer cachexia. Additionally, as of March 2020, anamorelin has not received approval for use by any other, national drug agency. Therefore, it was not included as a treatment option in the current recommendations.

**Cannabinoids.** Included systematic reviews<sup>36,43</sup> reported on three RCTs of cannabinoids. A 2018 trial randomly assigned 47 patients with advanced non-small-cell lung cancer and anorexia to 8 weeks of treatment with nabilone or placebo.<sup>71</sup> Study arms did not differ significantly with respect to appetite, weight change, or total energy intake. A 2006 trial of 243 patients with advanced cancer and weight loss of  $\geq 5\%$  within the previous 6 months evaluated three arms: (1) delta-9-tetrahydrocannabinol (THC) and cannabidiol, (2) THC alone, and (3) placebo.<sup>72</sup> The intended duration of treatment was 6 weeks. The trial was stopped early due to insufficient differences between arms. Another trial published in 2002 evaluated dronabinol, megestrol acetate, and the combination in 469 patients with incurable cancer excluding brain, breast, ovarian, or endometrial cancers.<sup>73</sup> Treatment was continued for as long as the patient appeared to be receiving clinical benefit. Dronabinol was less effective than megestrol acetate with respect to weight gain, appetite, and quality of life, the latter as being assessed by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT<sup>74</sup>) instrument. The combination of dronabinol and megestrol acetate was not more effective than megestrol acetate alone.

**Androgens or selective androgen receptor modulators.** Included systematic reviews reported on three RCTs of androgens or selective androgen receptor modulators.<sup>36,43</sup> The previously described three-arm trial of megestrol acetate, dexamethasone, or fluoxymesterone reported that megestrol acetate was more effective than fluoxymesterone for improving appetite.<sup>66</sup> Four weeks of weekly nandrolone decanoate was evaluated in a 1986 trial of 37 patients with

inoperable non–small-cell lung cancer treated with chemotherapy.<sup>75</sup> Patients in the nandrolone decanoate arm were less likely to lose weight than patients in the control arm (12% of patients v 25% of patients, respectively), but this difference was not statistically significant ( $P = .15$ ). In the third RCT, two different doses of enobosarm (an investigational selective androgen-receptor modulator) were compared with placebo in a phase II RCT.<sup>76</sup> Patients receiving enobosarm experienced greater increases in lean body mass than patients in the placebo arm ( $P < .05$  for the higher dose of enobosarm), but no follow-up phase III trials have been reported.

A more recent study evaluated weekly injections of testosterone enanthate. The double-blind, placebo-controlled, phase II trial enrolled 28 men and women.<sup>59</sup> Weight loss and decreases in lean body mass were significantly greater in the placebo group, and physical performance improved in the testosterone group.

**NSAIDs.** Two 2013 meta-analyses addressed NSAIDs for the treatment of cancer cachexia.<sup>39,41</sup> Each reported that NSAIDs were associated with improved outcomes such as body weight or quality of life in some studies but that evidence remains insufficient for a clear conclusion regarding the efficacy of NSAIDs for cachexia treatment. An additional RCT, published in 2018, randomly assigned 90 patients with GI cancer and weight loss to treatment with megestrol acetate with or without celecoxib.<sup>77</sup> The addition of celecoxib to megestrol acetate did not improve outcomes.

**Thalidomide.** A 2018 systematic review of pharmacologic management of cachexia<sup>36</sup> included two RCTs of thalidomide. A 2005 trial enrolled 50 patients with advanced pancreatic cancer and weight loss. At 4 weeks, patients in the thalidomide arm had gained an average of 0.37 kg, while patients in the placebo arm had lost an average of 2.21 kg. Adverse effects in the thalidomide arm included somnolence and constipation.<sup>78</sup> A 2012 RCT of thalidomide versus placebo was unable to draw clear conclusions.<sup>79</sup>

A 2012 Cochrane review also assessed thalidomide for the management of cancer cachexia, but a meta-analysis was not possible due to the small number and high heterogeneity of studies.<sup>34</sup> Based on a narrative review of these studies, the authors stated, “At present, there is insufficient evidence to refute or support the use of thalidomide for the management of cachexia in advanced cancer patients.”<sup>34</sup>(p2)

**Other pharmacologic agents.** Among other pharmacologic agents that have been evaluated, several lack benefit or currently have insufficient evidence of benefit. These include cyproheptadine, hydrazine sulfate, melatonin, TNF inhibitors, and insulin.<sup>36,43</sup> MAB-P1, a monoclonal antibody targeting interleukin 1 $\alpha$  that has shown promise in a placebo-controlled trial of patients with refractory

metastatic colorectal cancer and weight loss, remains investigational.<sup>51</sup>

**Clinical Interpretation.** Megestrol acetate improves appetite and body weight in patients with cancer cachexia. However, the type of weight gain associated with megestrol acetate use is primarily adipose tissue, rather than skeletal muscle.<sup>81</sup> Whether efficacy can be improved further by combining megestrol acetate with other agents remains uncertain. Toxicities of megestrol acetate include thromboembolic events, edema, and adrenal suppression. Similar findings have been observed with medroxyprogesterone acetate.

Corticosteroids also improve appetite, to a similar degree as seen with megestrol acetate. However, given the toxicities and decline in efficacy associated with long-term use of corticosteroids,<sup>82</sup> their role as an appetite stimulant often is limited to patients with a life expectancy of weeks to a couple months.

There is limited available information regarding olanzapine as an appetite stimulant in patients with cancer cachexia, and further evaluation is recommended to better understand its potential role. In addition to the published trial described previously,<sup>56</sup> a study presented at the 2019 Supportive Care in Oncology Symposium compared olanzapine with placebo in 30 patients.<sup>83</sup> The trial enrolled patients with nausea/vomiting associated with advanced cancer but who had not received recent chemotherapy or radiation. At baseline, all patients reported appetite scores of 1-2 for both study arms (on a scale of 0-10 points; 0 = poor and 10 = excellent). While the appetite scores were unchanged in the placebo group over the 1-week study period, scores improved to 6-8 in the patients receiving olanzapine ( $P < .001$ ).

Additional support for the potential utility of olanzapine for combatting cachexia come from data demonstrating considerable undesired weight gain in patients prescribed the drug for psychiatric reasons.<sup>84</sup> The current ASCO Expert Panel had considerable discussion as to whether to recommend olanzapine as a therapeutic option for patients with cancer cachexia. The final recommendation was not to recommend it at this time, given the paucity of clinical trials regarding this agent for this situation.

### CLINICAL QUESTION 3

Among adult patients with advanced cancer and loss of appetite, body weight, and/or lean body mass, are outcomes such as weight, lean body mass, appetite, physical function, or quality of life improved by **other interventions?**

#### Recommendation 3

Outside the context of a clinical trial, no recommendation can be made for other interventions, such as exercise, for the management of cancer cachexia.

**Literature review and analysis.** A 2014 Cochrane review of exercise for cancer cachexia identified no eligible trials,<sup>27</sup>

and no eligible trials were identified by the systematic review conducted for this guideline.

**Clinical interpretation.** Exercise is currently being evaluated as part of a multimodal intervention for cancer cachexia,<sup>85</sup> but at present, evidence remains insufficient for a recommendation.

### THE CANCER CACHEXIA SYMPTOM COMPLEX

Insufficient calorie and protein intake are common in patients with cancer cachexia.<sup>86</sup> Symptoms such as depression, dysgeusia, pain, excessive drowsiness, nausea, and constipation may contribute appreciably to poor intake. These nutrition impact symptoms are frequently encountered in patients with cachexia<sup>87</sup> and are associated with adverse outcomes such as weight loss and decreased survival.<sup>88</sup>

Retrospective studies suggest a clinical benefit when nutrition impact symptoms are treated. Half of patients with advanced cancer who were referred to a cachexia clinic reported between 2 and 4 nutrition impact symptoms, while 15% had  $\geq 5$ .<sup>87</sup> Appetite scores improved significantly between initial and follow-up visits, while about one-third of patients gained weight. Readily available pharmacological therapies for pain, chronic nausea, depression, and constipation were well tolerated and included metoclopramide, antidepressants, opioids, and laxatives. Nonpharmacological therapies, including dietary counseling and physical therapy, were provided in combination with medications when clinically indicated. In addition, minimizing sedating medications and avoiding polypharmacy appeared to be helpful in mitigating nutrition impact symptoms such as excessive drowsiness and fatigue.

Another retrospective analysis evaluated the impact of 17 symptoms on 635 patients with head and neck cancer referred to a cancer center.<sup>88</sup> Participants received all nutrition orally and were not using enteral tube feeding or parenteral nutrition. Individual symptoms significantly associated with reduced food intake included loss of appetite, difficulty chewing, dry mouth, thick saliva, and pain. Importantly, aggregate symptom burden was found to be an independent predictor of reduced intake, weight loss, and survival.<sup>88</sup>

### PATIENT, CAREGIVER, AND CLINICIAN COMMUNICATION

Optimally, communication regarding cachexia management will involve caregivers as well as the patient. Caregivers frequently experience high distress when witnessing the impact of cancer cachexia and may be more troubled than the patient by a symptom such as anorexia.<sup>89</sup> When patients do not eat well, caregivers may become frustrated and misinterpret their lack of eating as a failure of the caregivers to provide adequate care. This frustration may be compounded by family and cultural beliefs that align feeding with the demonstration of love and hope.<sup>90-93</sup>

An excellent discussion regarding feeding recommendations near the end of life has been published.<sup>94</sup> Key points to discuss with patients and their caregivers, related to interactions about nutrition, include the following:

1. Loss of appetite is common in patients with advanced cancer and may be the result of the cancer process itself.
2. Trying to force a patient to eat is usually counterproductive, potentially leading to increased nausea/vomiting.
3. In most patients with advanced cancer and cachexia, providing additional calories by feeding tubes and/or intravenously does not improve outcomes.
4. Trying to make a patient eat, when they have marked appetite loss, can lead to decreased social interactions and increased patient distress regarding interactions with caregivers (including stories of patients, in their dying days, pretending to be asleep when relatives visit, so that the relatives do not try to make them eat something).
5. For caregivers, it may be best to listen to and support the patient in a variety of other ways (such as giving the patient a massage or applying a lip moisturizer), instead of trying to talk them into eating more. Referral to a registered dietitian may provide patients and caregivers with additional opportunities to discuss concerns and challenges related to nutrition, appetite, and meal planning.

For recommendations and strategies to optimize general patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.<sup>95</sup>

### HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.<sup>96-98</sup> Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and clinicians should strive to deliver the highest level of cancer care to these vulnerable populations.

### COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through

deductibles and coinsurance.<sup>99,100</sup> Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.<sup>101,102</sup>

Discussion of cost can be an important part of shared decision making.<sup>103</sup> Clinicians should discuss with patients the use of less-expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.<sup>103</sup>

**Table 2** provides recommended dosing and estimated cost of megestrol acetate and dexamethasone. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.<sup>103</sup>

#### EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from December 2, 2019 through December 16, 2019. Response categories of “Agree as written,” “Agree with suggested modifications,” and “Disagree. See comments” were captured for every proposed recommendation with six written comments received. Five of the six respondents either agreed or agreed with slight modifications to the recommendations. One of the respondents disagreed with one of the recommendations. Prior to CPGC review, Expert Panel members reviewed the comments and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

The draft was submitted to two external reviewers with content expertise. Review comments were reviewed by the Expert Panel and integrated into the final manuscript before final approval by the CPGC.

#### GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness

of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *JCO Oncology Practice*.

#### LIMITATIONS AND FUTURE RESEARCH

To date, the primary limitations of cancer cachexia clinical research include the use of highly varied definitions, heterogeneous end points, and a lack of integrated biomarkers. The most recent international consensus guidelines<sup>16</sup> have described three stages of cancer cachexia and expanded the definition of cancer cachexia to include reduced muscle mass.<sup>6</sup> However, these most recent definitions do not capture the clinical impact of symptoms, decreased quality of life, and impaired physical activity. While, in the recent past, the FDA required a dual primary end point including lean body mass and physical function, the FDA now has adopted a composite end point that includes quality of life as a primary end point (ClinicalTrials.gov Identifier: [NCT03743064](https://clinicaltrials.gov/ct2/show/study/NCT03743064)).

Regarding lean body mass evaluation, data support the use of body composition analysis using computed tomography (CT) with practical and quantitative benefits over DXA.<sup>104</sup> Given that CT scans are, in many situations, an integral method of diagnosis and monitoring response to cancer-directed therapy, evaluating body composition captured on CT scans is becoming increasingly more feasible with automated technologies.<sup>105,106</sup> Routine body composition analysis also may allow clinicians to screen patients for early skeletal muscle loss, often occurring in patients without substantial weight loss.<sup>107-109</sup> Changes in body composition are associated with treatment, toxicity, quality of life, and survival.<sup>5,10,107,110-116</sup> However, limited data delineate how to incorporate body composition analysis in daily clinical work, and implementation research is needed in this context.

Future research could focus on a number of end points. First, assessment of changes in patient-reported outcomes (PROs), including symptoms and quality of life, are increasingly more prevalent in clinical practice. Prior studies support the integration of PROs into routine oncology care to improve patients' symptom management, quality of life, and, potentially, survival.<sup>117-119</sup> Thus, the evaluation of novel agents in the prevention and treatment of cancer cachexia should continue to use PROs as a primary end point.

A second opportunity for cancer cachexia research is the identification and validation of novel biomarkers. As the understanding of cancer pathophysiology improves, so too

should the understanding of cancer cachexia. In an approach paralleling cancer-directed treatment, evaluation of cancer cachexia biomarkers may allow identification of critical time points for potential intervention and effective markers for surveillance of cachexia-related characteristics, such as appetite.<sup>18,120</sup> Opportunities exist for collaboration among clinical and basic science researchers to identify and validate novel biomarkers in this setting.

Additionally, cancer cachexia, specifically sarcopenia, has a demonstrated relationship with treatment-related toxicity.<sup>4,10,121</sup> Researchers evaluating novel cancer treatments should recognize that changes in body composition may help predict dose-limiting toxicities. Incorporation of longitudinal body composition changes as a secondary end point across cancer trials, in addition to tumor response criteria, may promote early identification of patients at highest risk of treatment-related toxicity.

Increasingly, multiple clinical trials are evaluating novel pharmacologic agents for the treatment of cancer cachexia.<sup>122</sup> As the understanding of cancer, cachexia, biomarkers, and body composition changes continues to grow, optimal approaches for the treatment of cancer cachexia may involve single or combination strategies, including targeted pharmacologic agents, nutritional support, and exercise. Promising agents being evaluated for further study in this setting include anamorelin and olanzapine, discussed above. Mirtazapine has also been recognized clinically as an appetite enhancer. A phase II study across multiple cancer types suggested improvement in appetite and weight gain in approximately one-third of patients but lacked information regarding the impact of cancer treatment.<sup>123</sup> Further research with this drug is being developed. Along a similar line, reports of appetite enhancement by medical cannabis may prompt additional research.

Last, another area of future research interest might involve evaluating earlier nutritional interventions in patients with metastatic cancer. Patients who experience refractory

cachexia are relatively malnourished first, before they begin to experience the gross metabolic aberrations of cachexia. In one study,<sup>124</sup> 51% of 1,952 patients were prospectively screened for malnutrition at an initial oncology visit. Many of them had nutritional impairment; 9% were overtly malnourished and 43% were identified as being at risk for developing malnutrition. In the 6 months prior to patients' first oncology visit, 64% of the patients had reported weight loss. Given this, it is theoretically possible that identifying patients with early evidence of malnutrition (potentially through several means, such as CT body composition, a history of weight loss, and/or data obtained from a detailed diet history) might identify a group of patients who could benefit from earlier interventions related to nutrition. Such interventions might include dietitian-led nutritional and/or pharmacological interventions. Goals of such research could be to improve nutritional status through all phases of treatment, to help ensure that individuals with advanced cancer do not become as nutritionally depleted as they might have become without intervention. Ultimately, improving quality and/or quantity of life in this population may be possible.

#### ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at [www.asco.org/supportive-care-guidelines](http://www.asco.org/supportive-care-guidelines). Patient information is available at [www.cancer.net](http://www.cancer.net).

#### RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice<sup>125</sup> (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)
- Patient-Clinician Communication<sup>95</sup> (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)

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#### EDITOR'S NOTE

This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at [www.cancer.net](http://www.cancer.net), is available at [www.asco.org/supportive-care-guidelines](http://www.asco.org/supportive-care-guidelines).

## EQUAL CONTRIBUTION

E.J.R. and C.L.L. were Expert Panel co-chairs.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.20.00611>.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Management of Cancer Cachexia: ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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## APPENDIX

**TABLE A1.** Management of Cancer Cachexia Expert Panel Membership

<b>Name</b>	<b>Affiliation/Institution</b>	<b>Area of Expertise</b>
Eric J. Roeland, MD, co-chair	Massachusetts General Hospital Cancer Center, Boston, MA	GI oncology, palliative care, and symptom science
Charles L. Loprinzi, MD, co-chair	Mayo Clinic, Rochester, MN	Medical oncologist with research interest in symptom control
Vickie E. Baracos, PhD	University of Alberta, Edmonton, Alberta, Canada	Clinical and experimental cancer cachexia, cachexia pathophysiology, oncology nutrition, body composition
Eduardo Bruera, MD	MD Anderson Cancer Center, Houston, TX	Medical oncology, hospice and palliative medicine
Egidio del Fabbro, MD	Virginia Commonwealth University, Richmond, VA	Palliative care, with research interests in cancer-related fatigue and cachexia
Suzanne Dixon, MPH, MS, RD	Cambia Health Solutions, Portland, OR	Nutrition, epidemiology
Marie Fallon, MD	Edinburgh Oncology Centre, University of Edinburgh, UK	Palliative medicine, clinical studies and symptom control trials in supportive and palliative care
Jørn Herrstedt, MD, DMSci	Zealand University Hospital Roskilde and University of Copenhagen, Denmark	Gynecologic oncology, supportive care
Harold Lau, MD	University of Calgary, Calgary, Alberta, Canada	Radiation oncology, head and neck cancer, lung cancer
Mary Platek, PhD, MS, RD	Roswell Park Comprehensive Cancer Center and D'Youville College, Buffalo, NY	Nutrition, epidemiology
Hope S. Rugo, MD	University of California San Francisco, San Francisco, CA	Medical oncology, breast cancer, clinical trials
Hester H. Schnipper, LICSW, BCD, OSW-C	Beth Israel Deaconess Medical Center, Boston, MA	Oncology social work, cancer survivorship
Thomas J. Smith, MD	Johns Hopkins Medicine, Baltimore, MD	Medical oncology, hospice and palliative medicine
Winston Tan, MD	Mayo Clinic, Jacksonville, FL	Medical oncology, genitourinary cancer, cancer clinical trials and drug development
Kari Bohlke, ScD	American Society of Clinical Oncology, Alexandria, VA	ASCO practice guidelines staff (health research methods)