Japanese Journal of Gastroenterology and Hepatology

Review Article

ISSN 2435-1210 |Volume 6

# Review of Cancer - Related Cachexia: Definition, Physiopathology and Treatment

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Received: 11 May 2021
Accepted: 04 June 2021
Published: 11 June 2021



**Keywords:**

Cancer- related cachexia; Physiopathology cachexia; Refractory cancer cachexia; Megestrol acetate; Corticosteroids

**Citation:**

Rioja P. Review of Cancer - Related Cachexia: Definition, Physiopathology and Treatment. Japanese J Gstro Hepato. 2021; V6(15): 1-5

## 1. Abstract

The deterioration in nutrition status is frequently seen in cancer patients. Cancer- related Cachexia (CC) is a common multifactorial condition that highly impacts on survival and quality of life of cancer patients. CC has been categorized into three phases: pre-cachexia, cachexia and refractory cachexia. The risk of progression depends on several factors related to the type of cancer or clinical stage. The pathophysiology of CC involves more complex mechanisms than simply caloric deficiency. The process is mainly mediated by proinflammatory cytokines/neuroendocrine hormones, the alteration of the synthesis/degradation of the hepatic proteins and of the skeletal muscles as well as the lipolysis of the adipocytes. Nowadays, no effective medical intervention completely reverses cachexia; however, an adequate nutritional support remains a mainstay of cachexia therapy. In this review we outline the recent knowledge of mechanisms involved of CC, which will enable the understanding of pharmacologic interventions that have been developed to the present day improving quality of life and more importantly improving survival in cancer patients.

## 2. Introduction

Cancer - related cachexia (CC) is a life-threatening condition associated with several pathologies [1]. It was first described in 2006 as a complex syndrome that can be related to weight loss or pathological wasting of muscle or in combination with fat tissue. CC is multifactorial and its physiopathology leads to an imbalance between catabolism and anabolism independent of food intake [2]. CC has been recognized as a relevant adverse effect in cancer patients, with an incidence of up to 80% in advanced cancers, being considered as an unfavorable prognosis marker for survival [3, 4]. Multiple factors contribute to the complex physiopathology of CC, being the reduction of food intake a fundamental (and in some cases, predominant) component in the weight loss of these patients [5].

It is important to timely recognize the onset of cachexia in order to implement various interventions aimed at reducing or delaying its impact, since a specific intervention in one of the phases of cachexia (pre-cachexia, cachexia and refractory cachexia) can have a greater impact on survival and quality of life (QoL) [6].

## 3. Definition and Diagnostic Criteria

CC is defined as a multifactorial syndrome characterized by a continuous loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully resolved by conventional nutritional support and leads to progressive functional impairment [7]. The following criteria have been established for its recognition: weight loss greater than 5% in the last 6 months, body mass index (BMI) < 20, skeletal appendicular mass index consistent with sarcopenia (males < 7.26 kg/m2; females < 5.45 kg/m2), and any weight loss > 2% [8] (Table 1).

**Table 1:** Diagnostic criteria for cancer –related cachexia (CC)

| DIAGNOSTIC CRITERIA FOR CANCER- RELATED CACHEXIA | |
|---|---|
| 1 | Weight loss greater than 5% in the last 6 months. |
| 2 | Body Mass Index (BMI) < 20. |
| 3 | Skeletal appendicular mass index consistent with sarcopenia (males < 7.26 kg/m2; females < 5.45 kg/m2) and any weight loss >2 %. |

Source: Clinical practice guidelines on cancer cachexia in advanced cancer patients. Aachen, Department of Palliative Medicine/European Palliative Care Research Collaborative; 2010.

**Table 2:** Diagnostic criteria for the diagnosis of refractory cachexia

| DIAGNOSTIC CRITERIA FOR THE DIAGNOSIS OF REFRACTORY CACHEXIA | |
|---|---|
| 1 | Meet the definition criteria for cachexia. |
| 2 | Prognosis (life expectancy) < 3 months |
| 3 | Functional status (WHO scale) 3 or 4. |
| 4 | No response to anti-cancer therapy |
| 5 | Catabolism in progress at an increasing rate |
| 6 | Not suitable for artificial nutritional support. |

Source: Clinical practice guidelines on cancer cachexia in advanced cancer patients. Aachen, Department of Palliative Medicine/European Palliative Care Research Collaborative; 2010.

### 3.1. Phases of The CC

CC has been categorized into three phases: pre-cachexia, cachexia and refractory cachexia. The risk of progression depends on factors such as: the type of cancer, the clinical stage, food intake, the presence of systemic inflammation, inactivity, lack of response or complications of anti-cancer treatment, and/or the surgical sequelae [8].

- Pre-cachexia: Those who have experienced only minimal weight loss (between 2% and 5%), with early clinical and metabolic signs that predict future weight loss such as anorexia, insulin resistance, inflammation and hypogonadism.
- Cachexia: Weight loss of more than 5% in the previous 6 months, or BMI < 20 kg/m2 with continued weight loss greater than 2%, or muscle mass depletion and weight loss greater than 2%.
- Refractory cachexia: Defined as a clinically resistant catabolic state. According to the European Palliative Care Research Collaborative (EPCRC), the current diagnostic criteria for refractory cachexia are included in Table No. 2 (8)

## 4. Incidence

CC has a significant impact on the quality of life and prognosis of patients. It is responsible for an overall incidence of approximately 50% of cancer patients and accounts for up to 30% of cancer-related deaths [9]. Half of the patients with cancer lose body weight and a third lose more than 5% of their original body weight, which represents a diagnostic criterion for CC. It has been shown that the incidence of weight loss at the time of diagnosis varies according to the location of the tumor [10]. A study of more than 3,000 patients showed that the highest incidence of weight loss was observed among patients with solid tumors (e.g., gastric, pancreatic, lung, colorectal, head and neck) with 85% being in gastrointestinal tumors (gastric and pancreatic being the most prevalent) [10, 11].

## 5. Physiopathology

The physiopathology of Cancer Cachexia (CC) is characterized by a systemic inflammation, with a reduction in food intake and alterations in metabolism leading to loss of muscle mass and decrease in body weight. The mechanisms are complex and multifactorial, which generate alterations in food intake. The physiopathology is mainly mediated by: proinflammatory cytokines/neuroendocrine hormones, the alteration of the synthesis/degradation of the hepatic proteins and of the skeletal muscles as well as the lipolysis of the adipocytes [6].

The systemic inflammation that occurs in these patients helps to increase lipolysis in the adipose tissue and to increase muscle proteolysis. High levels of pro-inflammatory cytokines with tumor necrosis factor-alpha (TNF-α), IL-1 and IL-6 have been found [12]. There is also a decrease in anabolic pathways, including decreased levels of insulin growth factor type 1 (IGF-1) and testosterone, which are likely to worsen the decrease in muscle mass and strength, and increase fatigue, this being a characteristic symptom of CC [13-15].

In conclusion, it is known that there are multiple biological pathways involved in the physiopathology of CC: pro-cachectic signals from tumor cells, systemic inflammation in the host, and metabolic changes. Cytokines seem to play an important role; however, other mediators are involved and are still being studied.

## 6. Treatment

The evaluation of anorexia/cachexia should include: medical history of appetite and gastrointestinal symptoms, history of weight loss and body mass index (BMI), C-reactive protein (CRP) and functional status (ECOG or Karnofsky scale) [8]. The initial approach should be the reversal of weight and muscle mass loss. As a minimum goal, body weight should be maintained and further weight loss should be

prevented [8].

CC management is multimodal and includes: continuous assessment and monitoring, nutritional support, anti-inflammatory treatment, treatment of gastrointestinal symptoms and other causes of decreased oral intake, and evaluation of antineoplastic therapy options to reduce the catabolic burden of cancer [16, 17].

For treatment strategies in this review, we considered recommendations from current clinical practice guidelines: National Comprehensive Cancer Network (NCCN) [18]; American Society of Medical Oncology (ASCO) [19]; and the European Palliative Care Research Collaborative (EPCRC) [8], dividing interventions as follows: nutritional and pharmacological interventions.

## 7. Nutritional Interventions

Some studies have shown that nutritional interventions are not effective [20, 21]. A meta-analysis showed that nutritional interventions do not significantly affect weight or energy gain, but may improve some aspects of quality of life (QoL), including emotional status, dyspnea, and appetite [22]. Another meta-analysis (9 clinical trials) included patients with advanced cancer receiving chemotherapy or radiotherapy treatment and showed that nutritional consultation and/or nutritional supplements were associated with improved body weight (mean difference: 1.31 kg, 95% CI, 0.24 - 2.38) [23]. On the other hand, an additional systematic review (which included patients with advanced cancer and cachexia) concluded that, due to the limited number of studies, as well as the quality of evidence analyzed, it is not possible to conclude on the effectiveness of nutritional interventions in patients with advanced cancer and cachexia [24].

## 8. Pharmacological Interventions

For patients with life expectancies of months to weeks/weeks to days, appetite stimulants may be helpful (e.g., megestrol, dexamethasone, olanzapine) [25-29].

Combination therapy may provide better results for patients with CC. A randomized phase III study of cancer patients with anorexia/cachexia (n = 332) showed better results when they received combination therapy that included medroxyprogesterone, megestrol, eicosapentaenoic acid (EPA), L-carnitine supplements, and thalidomide vs. therapy with any of these agents in monotherapy [30]. Another phase III study (n = 104) with advanced gynecological cancers and cachexia also showed the benefit of combination therapy; patients who received megestrol + L-carnitine, celecoxib and antioxidants improved body mass, appetite and QoL [31].

The evidence for the use of cannabinoids (e.g. dronabinol - marijuana -, cannabis) in these patients is limited. A clinical trial did not demonstrate a benefit of this agent vs. placebo on appetite and QoL [32]. Another randomized trial comparing the use of megestrol acetate vs. dronabinol for the treatment of anorexia in patients with advanced cancer and revealed that megestrol was superior in promoting weight gain (75% vs. 49%) and appetite (11% vs. 3%) [33]. The cannabinoides can induce delirium in older patients, and the local regulation on its use in the country for this indication must be considered previously [19].

## 9. Megestrol and Progesterone Analogs

Megestrol acetate is a synthetic progestin, widely used as an appetite stimulant and associated with slight weight gain in patients with AIDS and anorexia/cachexia syndrome [34]. High doses of megestrol result in a greater increase in appetite in some patients with cancer and anorexia. However, the weight gain is due to an increase in fat mass rather than body mass. Megestrol has adverse events such as an increased risk of thromboembolic events and an inadequate response to chemotherapy [34]. Compared to placebo, megestrol acetate reduces the symptoms of anorexia/cachexia syndrome, with no effect on survival [26].

In an updated meta-analysis that included 23 randomized clinical trials (n = 3428), those patients with CC who were treated with megestrol had an improvement in appetite (RR: 2.57, 95% CI, 1.48 - 4.49), weight (RR: 1.55, 95% CI, 1.06 - 2.26), and QoL (assessed by functional scales or validated instruments) (RR: 1.91, 95% CI, 1.02 - 3.59) compared to the placebo group. The optimal dose and duration of use of megestrol acetate is not clear, but high doses are associated with improved weight gain compared to low doses. Overall results showed no difference for deaths in megestrol-treated participants (RR 1.26, 95% CI [0.70, 2.27] [25].

## 10. Corticosteroids

An initial study reported that dexamethasone provides benefit in patients with advanced gastrointestinal cancer and anorexia (n=116), providing an improvement in appetite and sense of well-being compared to placebo [35]. A systematic review included this initial study and five additional placebo studies. Appetite improvement was reported in patients receiving steroids (dexamethasone, prednisolone). Only two studies reported weight results with no significant improvement in the group using steroids. The authors concluded that the optimal dose and duration of steroids remains unknown [27].

## 11. Combination of Olanzapine and Megestrol

The addition of olanzapine to megestrol was evaluated in a clinical trial of patients with advanced lung or gastrointestinal cancer. Patients in the combination group had a weight gain ≥ 5% at 8 weeks (85% vs. 41%). No grade 3/4 toxicities were reported in this study [29].

## 12. Conclusions

Cancer Cachexia (CC) is a multifactorial and multisystem syndrome that cannot be reversed with conventional nutritional support, is frequent in the cancer patient and has been identified as an independent factor of poor survival. Multiple mechanisms are involved in its physiopathology.

CC has three phases (pre-cachexia, cachexia and refractory cachexia) and its severity is related to weight loss. Its clinical manifestations

include a variety of symptoms, which cause metabolic dysfunction and deterioration of the patient's QoL. The cardinal symptom is the consumptive syndrome.

Management of CC is multimodal; initial treatment should focus on reversing weight and muscle loss. In addition, it should include: relief of symptoms that may interfere with oral intake, nutritional support, management of gastrointestinal or other symptoms that decrease oral intake, and assessment of antineoplastic therapy (in order to reduce cancer catabolism). In refractory cachexia, assessment should focus on symptom management rather than improving nutritional status.

With respect to current drug treatment recommendations, at this time only corticosteroids, megestrol, and the use of multimodal therapy (combination of nutrition and drug therapy) have shown benefit in weight gain and improved QoL, with no impact on overall survival.

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