

Cachexia in oncology patients

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Cite this article as: Balcı BH, Yalçın S. Cachexia in oncology patients. *Intercont J Int Med.* 2026;4(1):22-25.

Received: 31.12.2025

Accepted: 25.02.2026

Published: 28.02.2026

ABSTRACT

Cancer-related cachexia is a complex metabolic syndrome characterized by involuntary weight loss, systemic inflammation, and a significant disruption of protein-energy homeostasis. It serves as a primary determinant of mortality and negatively impacts the efficacy of oncological treatments such as chemotherapy. The prevalence of cachexia ranges between 40% and 70%, with the highest incidence observed in pancreatic and gastrointestinal cancers. The pathophysiology is driven by pro-inflammatory cytokines secreted by tumors (e.g., TNF- α , IL-1, IL-6), which cause systemic catabolism, such as faster proteolysis in skeletal muscles and more lipolysis in adipose tissue. Furthermore, the syndrome involves the impairment of the central nervous system's homeostatic control over energy balance, leading to anorexia and high resting energy expenditure. Diagnosis is mainly based on keeping an eye on unintentional weight loss and body mass index (BMI), with a weight loss of 5% being a key sign of a bad prognosis. Effective management requires a multisystemic and multidisciplinary approach. This includes early nutritional interventions (oral, enteral, or parenteral), the use of appetite stimulants (orexigens), and tailored exercise programs to mitigate muscle atrophy. Additionally, comprehensive symptom management-addressing pain, nausea, and psychological distress-is essential for holistic care. As cachexia gets worse, it may not respond to standard treatments, which will lead to a decline that cannot be stopped. Given the increasing global incidence of cancer, there is a critical need for specialized teams and further research to develop effective, targeted treatment strategies for this challenging condition.

Keywords: Cancer, cachexia, inflammation, weight loss, oncology

INTRODUCTION

Cachexia is characterized by involuntary weight loss and loss of homeostatic control of protein-energy balance. Although it usually develops in association with malignancies, it can also occur in association with certain neurological and rheumatological diseases such as heart failure, renal pathologies, chronic obstructive pulmonary disease, and multiple sclerosis.^{1,2}

The disruption of protein-energy homeostasis in cachexia is very different from the easily reversible weight loss resulting from inadequate food intake. In cachexia, there is a combined picture of increased energy consumption, increased catabolism due to the underlying etiology, and the development of inflammation.³

Cachexia is considered one of the primary determinants of mortality in cancer patients. Studies have found that 80% of patients with stomach and pancreatic cancer, in particular, were cachectic at the time of death.⁴ In addition, there are publications indicating that cachexia negatively affects the response rate to chemotherapy.⁵ For this reason, cancer patients should be closely monitored for weight loss, and the development of cachexia should be prevented.

EPIDEMIOLOGY

Cancer incidence is increasing worldwide every day. Among the reasons for this are population growth and higher

diagnosis rates driven by advances in blood tests and imaging methods. Research indicates that the United States will detect approximately 2 million new cancer cases in 2023. In addition, over 600.000 cancer-related deaths were reported.⁶

Different prevalence rates have been identified for cachexia in cancer patients, generally ranging from 40% to 70%.⁷ This range is due to variations in the incidence of cachexia associated with different malignancies. In particular, the prevalence of cachexia is above 50% in gastrointestinal system, pancreatic, and head and neck cancers, while it is below 50% in prostate, lung, and hematological malignancies.⁸

PATHOPHYSIOLOGY

Advances in the pathophysiological mechanism of cachexia have mostly emerged in the recent past. The reason for this situation may be that cachexia often occurs in the final stages of malignant patients, and the use of invasive and metabolic tests in these patients is limited. Studies conducted recently have revealed that cachexia is a multi-organ syndrome; the brain, intestines, immune system, adipose tissue, muscle tissue, and numerous hormonal mechanisms are associated with cachexia, as summarized in [Figure 1](#).⁹

One of the key points in cancer-related cachexia is the disruption of central homeostatic control over energy balance. Decreased food intake is often a leading cause of weight loss.

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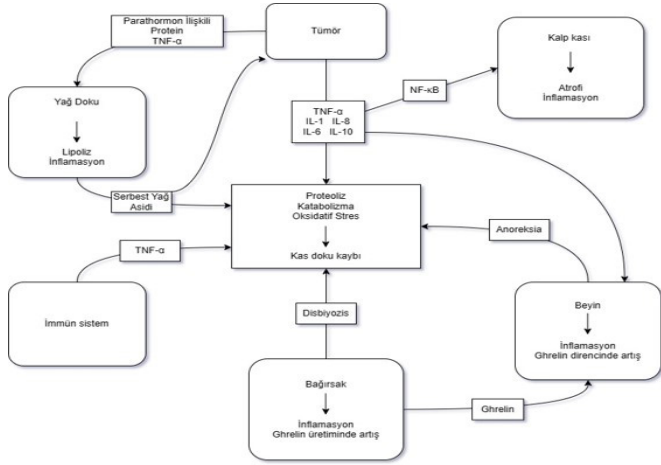


Figure 1. Molecular mechanism in cancer-related cachexia

However, the cause of weight loss is not solely due to an energy deficit resulting from reduced food intake. In these patients, high energy expenditure at rest creates an energy deficit, which can exceed 1200 kilocalories per day.¹⁰ Tumor cells often compete with other tissues for energy, fuels, and substrates. As a result of insufficient substrates and fuels reaching the tissues, increased lipolysis, increased gluconeogenesis, and protein breakdown occur.¹¹

Cytokines secreted by tumor cells are also considered an important cause of cancer-related cachexia. Tumor cells secrete various molecules that can cause catabolism in target tissues, such as proinflammatory cytokines, heat shock proteins, and eicosanoids, as summarized in Table. As a secondary response to these molecules, proteolysis, lipolysis, and even apoptosis may develop in target organs.¹²

Table. Cytokines secreted by tumor cells and the immune system in cancer cachexia

Tumor-related catabolic factors	Proinflammatory factors released as a result of tumor-immune system interactions
Activins	IL-1α IL-1β
Myostatin	IL-6 IL-11 IL-17
TGF-β	TNF-α
Serotonin	IFN-γ
Parathyroid hormone-related protein	GDF 15 (Growth Differentiation Factor 15)
Adrenomedullin	LIF (Leukemia Inhibitory Factor)
HSP 70-90	TWEAK (TNF-associated apoptosis trigger) TRAF 6 (TNF receptor-associated factor 6)
	Oncostatin M PGE2

TGF-β: Transforming growth factor beta, HSP: Henoch-Schönlein purpura, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, IFN: Interferon-gamma, PGE: Prostaglandin

In cancer-related cachexia, it has been established that the mediobasal hypothalamus is functionally impaired by peripheral inflammation, thereby impairing the activity of neurons regulating proteolysis, lipolysis, and appetite. This effect is thought to result specifically from IL-1B-dependent catabolism.¹³

Skeletal muscle atrophy observed in cancer cachexia occurs as a result of cytokines secreted by the tumor and surrounding stromal tissue and the pathways activated by the immune system in response. Generally, this activation leads to the destruction of myofibrillar proteins that provide contraction

function to skeletal muscles. This results in muscle atrophy and muscle weakness. On the other hand, growth factors such as TGF-B cause sarcomere dysfunction as a result of their calcium-mediated effect.¹⁴ The signaling pathways of cancer-mediated skeletal muscle atrophy are summarized in Figure 2.

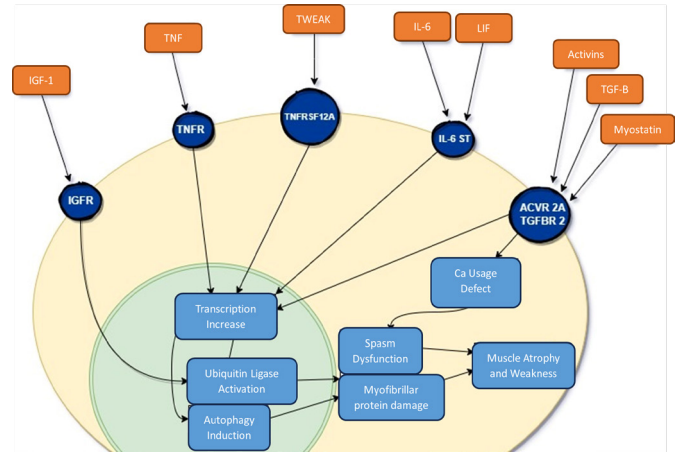


Figure 2. Signaling pathways of skeletal muscle atrophy in cancer cachexia

In addition to skeletal muscle loss, fat tissue loss is also a significant cause of cachexia in cancer patients. Studies have determined that fat tissue loss is due to lipolysis rather than apoptosis and that the rate of lipolysis in the body increases by approximately 50% in cachectic patients.¹⁵ Furthermore, biopsy evaluations of cachectic patients revealed that the lipolytic effect of catecholamines and natriuretic peptides in white adipose tissue is 2-3 times higher in cancer-related cachexia patients.¹⁶

DIAGNOSIS

Weight loss is usually the first noticeable sign of cachexia. Weight loss may even be the first sign of cancer, allowing patients to be diagnosed. After intentional weight loss has been ruled out in these patients, other alternative etiologies should be investigated.¹⁷

Weight loss is typically the first sign of cachexia and varies in each patient. Weight loss can be slow, rapid, intense, continuous, or intermittent. It must be monitored over time and compared to the patient's pre-cancer weight. The severity of weight loss can provide insight into the prognosis. A 5% weight loss is considered the first threshold for poor prognosis, and the risk of poor prognosis increases with greater weight loss.¹⁸

To grade cachexia, studies conducted internationally on more than 10.000 patients have resulted in a system based on body mass index (BMI) and weight loss that predicts prognosis.¹⁹ This classification is summarized in Figure 3.

Kilo Kaybı	Vücut Kitle İndeksi					VKI-Kilo Kaybı Derecesi	Ortalama Yaşam Süresi (Ay)
	28	25	22	20			
2.5	0	0	1	1	3	0	20.9
	1	2	2	2	3		
6	2	3	3	3	4	1	14.6
	3	3	3	4	4		
11	3	3	3	4	4	2	10.8
	3	3	3	4	4		
15	3	4	4	4	4	3	7.6
	3	4	4	4	4		
						4	4.3

Figure 3. Prognosis grading based on weight loss in patients with advanced cancer

Various studies have been conducted recently for the diagnosis of cancer cachexia. Although there is still no consensus on skeletal muscle loss, decreased food intake, metabolic changes, and catabolism measurement, it is predicted that these will be among the diagnostic methods in the future²⁰ Management: Cancer-related cachexia develops over time. Cachexia will develop in most patients with advanced lung, esophageal, stomach, colon, and liver cancer. It is essential to be aware of this, take early, systematic precautions, and not wait until it is completely obvious to intervene. The approach to cachexia should not be limited to oral nutritional solutions but should be multisystemic.²¹

There is no clear consensus on the point at which treatment for cachexia should begin. Some studies have used the concept of pre-cachexia to objectively define the threshold for early intervention. Although the term "pre-cachexia" is defined as weight loss of 2% or more, it is not a widely used concept today.²² Ensuring adequate nutrition is fundamental in cancer cachexia. First-line approaches recommend consulting a nutritionist to increase the quantity and quality of oral nutritional products. Providing adequate active nutritional support in patients experiencing rapid weight loss enhances their tolerance to the administered treatment, such as chemotherapy.²³ On the other hand, active nutritional support is often insufficient, especially in patients with advanced cancer. Compliance with oral nutritional solutions is generally low in these patients. In such cases, enteral or parenteral nutritional support should be administered without delay.²⁴ Appetite stimulants (orexigens) are available for patients with cachexia who have a poor appetite. Although the primary effect of these drugs is not to stimulate appetite, they have been shown to increase appetite in various settings and are considered appropriate for use in cachectic patients. Cannabinoids, corticosteroids, and progestogens generally have appetite-stimulating properties. However, these drugs also have side effects. Corticosteroids accelerate skeletal muscle atrophy, which is already present in cachectic patients. Progestogens also accelerate muscle atrophy and further increase the risk of thromboembolism, which is already high, especially in cancer patients.²⁵

In recent years, new agents that increase food intake have been investigated. In particular, growth hormone-releasing receptor type 1 agonists and melanocortin receptor 4 agonists, which act on the hypothalamus in the central nervous system, have been shown to increase appetite and are available for use in appropriate patients.^{26,27} In addition to nutritional recommendations, regular exercise is also recommended to prevent skeletal muscle loss in cachectic patients. Appropriate exercise programs should be planned for patients, taking into account the risk of falling, to the extent that it is safe for them.²⁸ In a study of patients undergoing chemotherapy, the group that performed aerobic exercise and resistance training showed improvements in muscle strength across the body.²⁹ Cachexia is not the only finding in cancer patients and always occurs alongside other findings. Accompanying symptoms vary depending on the patient's malignancy, the chemotherapy or other treatments they are receiving, and the toxicity of the treatment, and they can change rapidly, with new symptoms emerging. Studies have shown that clinicians fail to identify accompanying symptoms in approximately 50% of these patients.³⁰ It should be remembered that the management of accompanying symptoms is also part of

cachexia management. Certain symptoms, in particular, increase the severity of cachexia more than others. These include pain, nausea, vomiting, dysphagia, early satiety, oral and dental problems, swallowing difficulties, constipation, diarrhea, anxiety, depression, and insomnia.²⁵ All these symptoms should not be ignored; they should be carefully examined at every visit, and comprehensive symptomatic treatments should be planned. One important element of supportive care is the formation of a multidisciplinary team. Clinical studies have found that patients benefit more and have a better disease course in clinics where palliative care and oncology physicians work together.³¹

In addition to cachexia treatment, another important consideration is dose adjustment in patients receiving active systemic chemotherapy. The required chemotherapy dose may decrease as a result of weight loss and skeletal muscle loss; failure to reduce the dose may lead to toxicity.³² Studies have concluded that a multisystemic approach to cancer-related cachexia has a proportional distribution, as summarized in **Figure 4**.

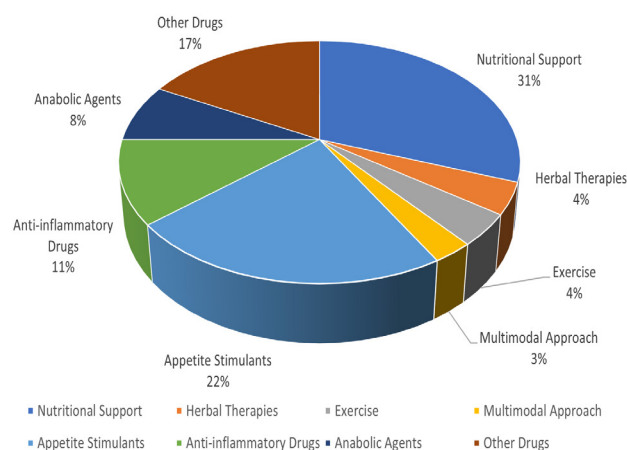


Figure 4. Proportional distribution of therapeutic approaches in cancer-related cachexia treatment

Cancer-related cachexia can become resistant to therapeutic treatments over time. This situation is usually caused by an underlying disease that does not respond to antineoplastic treatment. Patients experience increased weight loss and progressively worsening catabolism, and death becomes inevitable.³³

CONCLUSION

In cancer-related cachexia, many pathophysiological mechanisms remain unclear, and there is no consensus on most issues. Therefore, it is evident that more research is needed from all angles. The increasing incidence of cancer each year highlights the need to establish experienced teams that will closely monitor patients in order to develop specialized, effective treatment approaches for cancer cachexia.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

No financial support was received for the preparation or publication of this article.

Author Contributions

Concept: B.H.B., S.Y.; Design: B.H.B., S.Y.; Control: B.H.B., S.Y.; Data Collection and/or Processing: B.H.B., S.Y.; Analysis and/or Interpretation: B.H.B., S.Y.; Literature Review: B.H.B., S.Y.; Article Writing: B.H.B., S.Y.; Critical Review: All authors

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