

What is cancer anorexia-cachexia syndrome? A historical perspective

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ABSTRACT Cancer anorexia-cachexia syndrome (CACS) is a lethal but poorly defined involuntary wasting disorder. Loss of skeletal muscle and fat distinguishes it from starvation. Cachexia has been described as a clinical syndrome since ancient times, and the poor prognosis has long been acknowledged. In this article we have reviewed historical perspectives on cancer cachexia, and commented on modern definitions. In cancer cachexia, most historical descriptions included anorexia, wasting and a pale complexion. Other associated symptoms, such as fatigue, early satiety and taste changes, were inconsistently described. Newer descriptions have not significantly expanded the clinical picture. Today, there is still no consensus definition, hindering research on early diagnosis and effective therapy. The language descriptors used to characterise the syndrome are important. For example, the word ‘cachexia’ itself may mislead; perhaps cancer-related wasting syndrome is more accurate. Cancer anorexia-cachexia syndrome is a disorder associated with high morbidity and mortality, and deserves greater attention in both clinical and translational research.

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INTRODUCTION

Cachexia (Gr. *kakos*, ‘bad’; *hexis*, ‘habit’)... It is chiefly used in regard to chronic diseases, where the general nutrition is defective, and the blood in an unhealthy state. Thus cancerous cachexia indicates the peculiar impoverished state of the blood and general debility which are associated with the deposits of cancer in various parts of the body...

– *Chambers Encyclopaedia*, 1901¹

Syndrome: a group of signs and symptoms that occur together and characterize a particular abnormality.

– *The American Heritage Stedman’s Medical Dictionary*, 2002²

Cachexia is a major complication associated with various severe diseases, poor quality of life and short survival. Survival has increased in many common acute and chronic illnesses,³ so more interest has focused on their complications. Cachexia is an independent poor prognostic indicator in chronic disease,^{4,5} but often it does not elicit sufficient clinical or research attention.

Cancer anorexia-cachexia syndrome (CACS) is a poorly defined progressive wasting disorder. Loss of both skeletal muscle and fat distinguishes it from starvation (where lean body mass is preserved at first). The

prevalence is unknown. Most observers link it to the degree of weight loss, combined with anorexia. Some prevalence data are available for other symptoms that may constitute the syndrome: easy fatigue (69%), weakness (66%), anorexia (66%), lack of energy (61%), early satiety (51%), >10% involuntary weight loss (50%), taste changes (28%) and oedema (28%).⁶ A fatigue symptom cluster (i.e. easy fatigue, weakness and lack of energy) is closely aligned with an anorexia-cachexia cluster (i.e. anorexia, early satiety, taste changes and weight loss).⁷ Such clusters suggest a common pathophysiology and support the idea that fatigue/asthenia should be included in the definition of CACS.

Cancer anorexia-cachexia syndrome impacts upon prognosis but also on patients’ quality of life.⁵ Weight loss causes morbidity, alters body image, decreases performance status and increases the risk of therapy-related toxicities and mortality.⁴ Anorexia is defined as loss of appetite, especially when prolonged.⁸ In fact, it may consist of appetite loss, early satiety, a combination of both or altered food preferences.⁹ Anorexia may affect nutritional status, but also reduces the social pleasure of sharing a meal with loved ones. Once established, CACS cannot be reversed in cancer patients with available pharmacological or nutritional support techniques.¹⁰ This underlines the importance of early detection and prevention.

Cancer anorexia-cachexia syndrome incorporates a complex metabolic syndrome with abnormal carbohydrate, protein and lipid metabolism.⁵ Some progress has been made in understanding the multifactorial pathophysiology. Although incompletely understood, the cancer syndrome is likely to arise from imbalanced interactions between inflammatory cytokines, neuropeptides, hormones and tumour-derived products.⁵ The presence of cachexia among other chronic illnesses (often with inflammatory components) suggests a major role for cytokines as the common aetiologic pathway.¹¹ A precise understanding of the pathophysiology would elicit better therapeutic intervention and perhaps prevention.

What exactly is CACS? A literature search in oncology (but also of other chronic diseases associated with cachexia), nutrition, internal medicine and palliative medicine textbooks revealed no answer. This was not a systematic review but a comprehensive literature search with web-based searches of the key words 'cachexia' or 'wasting' in PubMed (from 1948 to present) and in 'books.google.com' (from 1800 to present), which allowed downloads of old textbooks and a search of their contents. The tables of contents and indexes of major textbooks in oncology, internal medicine (*Cecil textbook of medicine*), palliative medicine and nutrition were manually searched. Cancer anorexia-cachexia syndrome is not included in the *Dictionary of medical syndromes*¹² nor listed in *Jablonski's dictionary of syndromes and eponymic diseases*.¹³ This is not therefore a simple matter of a dictionary or text-book definition. In this article, we review historical perspectives on cachexia and comment on more recent definitions.

HISTORY

[Cachexia is] an ill-defined term used to include almost any depraved condition of the body in which nutrition everywhere is defective... It is generally applied to patients who exhibit at the same time progressive loss of weight, and change of complexion in the direction of sallowness or actual anaemia. The word is generally prefixed by a qualifying adjective, such as cancerous cachexia...

– Herbert French, *An index of differential diagnosis of main symptoms*, 1912¹⁴

Biblical descriptions of King David, more than 3,500 years ago, include the following: 'I forgot to eat my bread'; 'My knees are weak through fasting; and my flesh failed of fatness'; 'My strength failed... and my bones are consumed'; 'My bones wasted away through my anguished roaring all day long'; 'My bones cleave to my skin'; and 'I am feeble and depressed'. These descriptions suggest the presence of anorexia, cachexia, weakness, bone pain and depression,⁸ and that King David possibly suffered from cancer. Old age, anorexia, reduced activity from illness, social factors such as isolation and loneliness and

psychological factors such as depression, together with cancer, probably all contribute to CACS.⁸

Early reports by physicians on wasting in chronic illness were made on the island of Kos in ancient Greece. The term 'cachexia' is derived from the Greek words *kakós* (bad) and *hexis* (habit). The word 'anorexia' is from the Greek *a* and *orexis*, which together mean no appetite, i.e. loss of appetite.⁸

Hippocrates (c. 460–377 BC) linked hydropsy to cachexia:

The flesh is consumed and becomes water... the abdomen fills with water; the feet and legs swell, the shoulders, clavicles, chest and thighs melt away... This illness is fatal.¹⁵

Celsus (c. 25 BC–c. 50 AD) described categories of 'consumption':

And of this also there are several species. One of them occurs when the body is not nourished, and since something is naturally ever leaving it, while nothing succeeds in its place, a most extreme emaciation takes place; and unless an attempt is made to cure death ensues... There is a second species, which the Greeks call cachexia, where the condition of the body is bad; and on this account all the nutriment becomes putrid.¹⁶

Aretaeus of Cappadocia (first century AD), a famous Greek physician during the reign of the Roman emperor Nero, complemented the Hippocratic description of pulmonary tuberculosis and vividly portrayed consumption (also referred to as wasting away, phthisis, *tussis sicca*, syntexis, atrophica and cachexia):

For the sight is more to be trusted than every other sense... but also with regard to the appearance of the sick person. For if one of the people should see a man pale, weak, coughing, and emaciated, he rightly divines consumption... the nose is sharp, and slender, cheeks protruding and red; eyes hollow, glittering and bright; they are swollen and pale, or livid in countenance. The thin parts of the jaws rest upon the teeth resembling a smile, in other respects corpse-like. So also in all other respects they are slender without flesh; it is not only easy to tell the number of their ribs, but also to know where they terminate.¹⁶

Elizabeth I, Queen of England (1533–1603), described her own condition. Depression, altered body image, taste changes and anorexia plagued her last days:

When thou doste feeble creeping tyme at thye gate, these fooleries will please thee lesse; I am paste my relishe for such matters: thou seest my bodilie meate

TABLE I Further historical descriptions of cachexia

1906	'A yellow, waxy face, associated with anaemia, general debility, and more or less emaciation, are the characteristic signs of a condition which is spoken of as "cachectic" or a "cachexia"... it expresses very graphically a state which would otherwise require many words of description, and the recognition of which is often of diagnostic value... cancer cachexiae: debility, emaciation, anaemia, and a dirty yellowish-brown or brown-green complexion.' Butler GR. <i>The diagnostics of internal medicine</i> . 2nd ed. New York: D Appleton & Co; 1906.
1915	'There is however, nothing that is distinctive about cancerous cachexia. Any of the known changes and a similar picture may be produced by other diseases... The symptoms of the cachexia are gradual but progressive... The color of the patient is described as a straw pallor... The emaciation is a late symptom... The emaciation is due to disturbances of the gastro-intestinal tract, with the resulting loss of appetite, nausea...' Taylor HC. <i>Cancer: its study and prevention</i> . Philadelphia: Lea & Febiger; 1915.
1917	Definition – ... the bodily deterioration accompanied by subjective feelings of exhaustion met with in neoplasm (carcinoma, myoma), in Graves disease, in severe anemias, in chronic intoxications... and in long continued fevers of infectious origin. Symptoms – emaciation (loss of both fat and musculature); anemia; sallow tint, tendency to hemorrhagic diathesis (cachectic purpura), impairment of functions of digestive organs, cardiac weakness... Barker LF. <i>The clinical diagnosis of internal diseases</i> . New York: D Appleton & Co; 1917.

doth not suit me well; I have eaten but one ill tasted cake since yesternight.¹⁷

In subsequent centuries, cachexia was viewed as an inevitable, non-specific, serious complication of diseases such as tuberculosis or cancer, or of uncontrolled metabolic disorders, including diabetes mellitus or thyrotoxicosis.¹⁵ In Scotland, it was classified in the third group of diseases in William Cullen's *Synopsis nosologiae methodicae* of 1769 (diseases were divided into neuroses, fevers, cachexias and local disorders).¹⁸ Cachexia was reported in various conditions, for example anaemia of young women or chlorosis (*cachexia virginum*), myxoedema following thyroidectomy (*cachexia strumpriva*)⁵ and Simmond's disease due to panhypopituitarism (pituitary cachexia).^{12,18} In the nineteenth century, *cachexia Africana* was reported as a consequence of dirt or clay eating (pica) among slave populations of the Americas. Pica sufferers had stomach pains and difficulty breathing, followed by nausea, diarrhoea, depression and listlessness. Death followed in two to three months.¹⁹

In 1858 the English ophthalmologist John Zachariah Laurence described cancer cachexia. He believed it to be a poor prognostic predictor:

... exhausting sweats, derangement of the digestive organs, and a peculiar waxy tint of the countenance, form together the principal elements of the so-called 'cancerous cachexia'.²⁰

In the USA, William Osler described cachexia in cancer, tuberculosis, malaria and syphilis, lead poisoning and *cachexia strumpriva* in *The principles and practice of medicine*, published in 1901.²¹ He identified associated symptoms in cancer of the stomach (e.g. pain, dyspepsia, vomiting), and considered emaciation and anaemia integral to neoplastic cachexia:

Progressive emaciation is one of the most constant features... Loss in strength is usually proportionate to the loss in weight... Anemia is present in a large proportion... and with emaciation gives the picture of cachexia... Anorexia, loss of desire for food, is a frequent and valuable symptom, more constant perhaps than any other.²²

According to Osler's description, emaciation (defined as 'to waste away physically'²³) was part of cachexia, but emaciation alone did not define cachexia.

Subsequently, in 1913, Professor Rudolph Schmidt from Vienna added that adynamia seemed to be a feature of cancer cachexia:

There is a combination of general symptoms, namely, the trio: emaciation, adynamia and an unhealthy colour of the face... Occasionally those surrounding the patient have noticed the falling of the cheeks, prominence of the zygomatic arches, and the 'pointed' appearance... emaciation, this is, the loss of flesh and, later on, of muscle tissue... this symptom (adynamia) will appear earlier and more pronouncedly in asthenic constitutions and vice versa manifest itself late in stronger constitutions... Adynamia shows itself... not only in general fatigue but also in a lowering of circulatory force.²⁴

Schmidt suggested an association between wasting, adynamia, fatigue and low blood pressure. Autonomic nervous system dysfunction, recently reported in cancer,²⁵ could explain some of his observations.

Around the same time, in 1915, Howard Canning Taylor, the founder of the American Society for the Control of Cancer (known today as the American Cancer Society), wrote a book chapter about cancer cachexia:

Cachexia is the late constitutional manifestations of the malignant process. The general clinical picture is quite characteristic of cancer... there is however, nothing that is distinctive about cancerous cachexia... the term cachexia might be, and in fact is, sometimes

applied to the general condition seen in the terminal stage of various chronic exhausting diseases.²⁶

He recognised that the presence or absence of cachexia and time of its appearance varied with tumour type and location:

In general, there is less cachexia in sarcomata than in carcinomata... A carcinoma of an organ necessary for nutrition and life, such as the stomach, liver, etc., causes cachexia earlier than a similar growth in a less important organ, such as the uterus or breast.²⁶

In a discussion of the pathophysiology, Taylor stated:

The cause of the cachexia cannot be assigned to a single influence. By the ancient writers the cachexia of a malignant growth was looked upon as a separate disease and not as a result of the cancer... With our present beliefs, parts of which are based on theoretical knowledge and part on clinical experience, the causes of the cachexia can practically be arranged under two headings: (1) Absorption of decomposition products, toxins, etc., from primary tumor and its metastases, and (2) interference with the functions of the various organs.²⁶

He also described cachexia symptoms as progressive and variable:

The rapidity with which they develop is subject to wide variations... The change in color is due mostly to the diminution of the hemoglobin in the red blood cells. The emaciation is a late symptom, but is usually present before the termination of the disease... The emaciation is due to disturbances of the gastro-intestinal tract, with the resulting loss of appetite, nausea, vomiting, etc.²⁶

This is probably one of the most extensive descriptions of CACS in the twentieth century. This amazingly detailed description proved to be true in a study conducted in 1980. The effects of weight loss (>5% or >10% during the last six months) on prognosis were studied in a little more than 3,000 patients with cancer before they underwent chemotherapy.⁴ This study showed that breast cancer, non-lymphocytic leukaemia and sarcomas had the least weight loss. The difference in median survival was particularly remarkable between 0–5% weight loss versus >5% or >10% weight loss.

RECENT DEVELOPMENTS

Cachexia [cac- + Gr. hexis (habit) + -ia]: a profound and marked state of constitutional disorder; general ill health and malnutrition.

Cardiac c.: emaciation due to heart disease usually caused by a combination of increased caloric expenditure and decreased caloric intake or utilization.

C. Hypophysiopri'va: the train of symptoms resulting from total deprivation of function of the pituitary gland, including phthisis, loss of sexual function, atrophy of the pituitary target glands, bradycardia, hypothermia, apathy, and coma.

– *Dorland's illustrated medical dictionary, 2007*²⁷

In 1970 a multidisciplinary American Cancer Society conference discussed cancer-related anorexia and cachexia.²⁸ Definitions offered ranged from dictionary ones to more inclusive definitions. Anorexia was described as food intake insufficient to meet the metabolic needs of the tumour-bearing host.²⁸ For cachexia, the metabolic abnormalities encountered during the disease (such as systemic inflammation, insulin resistance, increased protein and lipids degradation) were suggested to be included in the definition. Attempts to further define cachexia in 1997 during a workshop held by the American Society for Nutritional Sciences, entitled 'Clinical trials for the treatment of secondary wasting and cachexia: selection of appropriate endpoints', highlighted the difficulties of such an endeavour.²⁹ The same year, Roubenoff and colleagues distinguished between cachexia and wasting:

We suggest that the term wasting be reserved for involuntary weight loss. In contrast, we propose that the term cachexia be used for involuntary loss of body cell mass or fat-free mass when this compartment is reduced with little or no weight loss. That is everyone with wasting has cachexia, but the opposite is not true.³⁰

There are problems with this definition, and the opposite in fact is true. Cachexia, as described since ancient times, is a purely clinical diagnosis in clearly emaciated patients. One look at a cachectic patient suffices to make a diagnosis. Wasting, on the other hand, can be overlooked in an otherwise obese patient where body cell mass is wasted. Body compartment measurement is needed in this case for diagnosis. To the contrary of the above definition, cachexia includes severe weight loss: everyone with cachexia is wasted, but the opposite is not true.

Another definition by MacDonald et al. in 2003 – 'a wasting syndrome involving loss of muscle and fat directly caused by tumor factors, or indirectly caused by an aberrant host response to tumor presence'³¹ – addressed mechanisms but did not define CACS as a clinical entity nor address its complexity.

Also in 2003, Ohnuma identified CACS as a syndrome with combined clinical and biochemical abnormalities. It was distinguished from starvation both by the wasted body compartment and by the limitation of nutrition's benefits in cachexia. However, weight loss was not characterised in this definition:

Cancer cachexia is a complex syndrome presenting anorexia, early satiety, wasting of muscle and adipose tissues, weight loss, fatigue, anemia, hyperlipidemia, systemic inflammatory response, and other metabolic abnormalities, usually seen in patients with advanced cancer... In addition, cancer cachexia results from altered metabolism rather than just an energy deficit, and it cannot be reversed by simple feeding.³²

A further analysis by Dahele and Fearon in 2004 is provocative and counterintuitive:

Cachexia is a syndrome and therefore does not have a specific definition. Patients are characterized by the presence of anorexia, early satiety, weight loss, weakness, anemia and edema. These features occur to a variable extent in different patients and may change in severity during the course of a patient's illness. The multifactorial origin of cachexia precludes a uniform pathophysiological definition.³³

A syndrome (i.e a group of symptoms or signs² that occur together and characterise a particular abnormality) does have characteristics, but this does not mean we cannot define it. How would you diagnose or even less manage any syndrome if there was not at least some definition? A clear and concise definition of any medical condition, whether a disease or a syndrome, is the basis of any sound clinical approach to assessment or management.

In 2008 Evans et al. again presented cachexia as a syndrome, distinguished from starvation and other secondary causes of wasting, with characteristic weight loss:

Cachexia is a complex metabolic syndrome... characterized by loss of muscle with or without loss of fat mass... Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated... Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity.³⁴

It is tempting to use weight loss as a clinical marker of CACS, especially as it has known prognostic value. One study compared various degrees of weight loss and their prognostic value, concluding that the value of weight loss as a prognostic factor in non-small cell lung cancer depends on its definition.³⁵ Weight loss definitions vary. A temporal component may also be important, since body weight even in healthy individuals can vary up to 5% within a six-month period.³⁶ Loss of $\geq 10\%$ of pre-illness weight in six months defines severe depletion in the ill.²⁰ Any definition of cachexia based only on degree of weight loss (i.e. without any temporal definition) may be insensitive to wasting dynamics.³⁷

Another modern approach used a three-factor profile in advanced pancreatic cancer.³⁸ This included weight loss ($\geq 10\%$), low food intake ($\leq 1,500$ kcal/d) and evidence of systemic inflammation (C-reactive protein ≥ 10 mg/L). The three-factor profile identified those with both poorer performance status and adverse prognosis. Weight loss alone was not an independent prognostic variable. These results may have been confounded by the universal weight loss and short survival in advanced pancreatic cancer. Body weight inaccuracies due to the common complications in pancreatic cancer of oedema and ascites might also skew outcomes. It was concluded that cancer cachexia was not synonymous just with weight loss.³⁸ Weight loss in other studies correlated with poor survival in different tumour types.

The use of biochemical markers is appealing. There is evidence to suggest cytokine involvement in cancer cachexia.¹¹ C-reactive protein (CRP) could be used as a proxy marker of pro-inflammatory cytokine activity, especially interleukin (IL)-6. Although some studies explored the value of CRP as a predictor of cachexia in cancer, available data to date are insufficient (few studies, small sample sizes) to recommend CRP to define cancer cachexia.

In a multicentre study of nutritional risk in 1,307 cancer patients, cachexia was classified based on degree of weight loss (precachexia if $< 10\%$ weight loss, cachexia when $\geq 10\%$ weight loss of usual body weight) and the presence or absence of one of the following symptoms: fatigue, anorexia and early satiety.³⁹ This was the first attempt to define cachexia by degree of severity and the absence/presence of associated symptoms. This approach is of particular interest as it could easily be applied in any oncology practice, with no expensive and/or invasive tests. It did not include any temporal definition of weight loss.

CONCLUSION

The clinical picture of malignant cachexia is as clear cut as that, for example, of old age... Clinical evidence warrants the conclusion that it is a genuine entity and that it is a generalised disease... Clinically however, the most deadly effects seem to be those produced on the cardiac and alimentary musculature...

The clinical picture – we are all only too familiar with the clinical picture of malignant cachexia, the unsmiling, wasted face, the somewhat sallow and occasionally anaemic complexion, the languid air, the flaccid dry skin, the complete lack of energy, the loss of appetite, the history of loss of weight, and not infrequently the infection of the mouth with thrush... Loss of appetite is one of the outstanding symptoms of malignant cachexia...

– Hugh Donovan, presidential address of the Royal Society of Medicine, 1953⁴⁰

This historical overview of cachexia reveals that it has been described as a medical entity since ancient times. Cachexia was recognised as a severe constitutional manifestation of many illnesses, not just cancer, and was a purely clinical diagnosis that physicians could give by inspection alone. It has always been distinguished from starvation, and reduced body weight, appetite loss and anaemia are an integral part of the definition in both old and newer descriptions. The inevitable outcome, death, has long been acknowledged. In cancer, most definitions described the pale complexion, the clear wasting and the anorexia. Other associated symptoms such as fatigue, although mentioned, have not been extensively and

consistently described. More recent descriptions have not significantly expanded the definition.

Although cachexia has been described since the early days of the practice of medicine, we have a limited understanding of the pathophysiology and best treatment. Modern techniques of metabolic and biochemical measurements seem likely to help us understand the physiological disruptions which underlie the historical clinical descriptions discussed in this article. Given the associated high morbidity and mortality, CACS should receive greater attention in clinical practice and research as a high-impact disorder.

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