

## PERSPECTIVE



## Translational Therapeutics

# Cancer cachexia: a nutritional or a systemic inflammatory syndrome?

Josh McGovern<sup>1</sup>✉, Ross D. Dolan<sup>1</sup>, Richard J. Skipworth<sup>2</sup>, Barry J. Laird<sup>2,3</sup> and Donald C. McMillan<sup>1</sup>

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Cancer cachexia has long been perceived as a nutritional syndrome. However, nutritional interventions have continued to be ineffective. With the recent recognition of the importance of systemic inflammation in the definition of this syndrome and treatment, has the time come to consider whether this syndrome is primarily a manifestation of systemic inflammation with the consequent implications for future treatment?

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## INTRODUCTION

Cancer cachexia is universally recognised to be associated with poor outcomes [1]. In the last decade, since the international consensus on the definition of cancer cachexia [2], there has been increasing research interest in the field. Indeed, a search of PubMed.gov using the term ‘cancer cachexia’, returns 216 published articles in 2011, compared with 457 articles published in 2020 [3].

The definition of cancer cachexia has evolved over this time, with the development of robust criteria for diagnosis [4]. Specifically, systemic inflammation has slowly moved to the forefront of the definition, diagnosis and treatment of cancer cachexia. While the basis of the systemic inflammatory response (SIR) in cancer patients is not clear, it is thought to be the non-specific host response to tumour hypoxia/necrosis and/or local tissue damage [5]. The host response to a noxious stimulus such as cancer include changes in neuroendocrine metabolism, haematopoietic changes and production of acute-phase proteins by the liver, such as C-reactive protein (CRP), which initiates and/or sustains the SIR [6]. Conversely, a drop in serum albumin is also observed with rising CRP [7]. Given that the SIR is a key component of the cancer cachexia, CRP and albumin have been combined in scores including the Glasgow Prognostic Score (GPS) and modified GPS (mGPS) to objectively define cachexia [5, 7].

The following article examines the trend of increased recognition of the importance of systemic inflammation in the definitions of cancer cachexia over time and diagnostic frameworks proposed. Furthermore, how the shift to viewing cancer cachexia as a SIR syndrome has and will inform on treatment and clinical trials [8].

## The role of inflammation in defining cachexia

To date, there have been numerous definitions of cancer cachexia proposed within the literature [9] (see Table 1). One of the first

arose in 2006, in the ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Arends and colleagues defined cancer cachexia as activation of “systemic pro-inflammatory processes in response to the tumour”, with “metabolic derangements include insulin resistance, increased lipolysis and high normal or increased lipid oxidation with loss of body fat, increased protein turnover with loss of muscle mass and an increase in production of acute-phase proteins” [10]. This definition was supported by the work of Fearon et al. who found that weight loss alone did not identify the full effect of cachexia on physical function and was not a prognostic variable. As such, they proposed a three-factor assessment (weight loss, reduced food intake and systemic inflammation), to identify patients at risk of adverse outcomes [11].

In 2008, the cachexia consensus conference defined cancer cachexia as “a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass”. Evans et al. also came to the conclusion that “the prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders)” and that “Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease” [12]. This proposed definition was supported by the Special Interest Group (SIG), part European Society for Clinical Nutrition and Metabolism (ESPEN). Furthermore, Muscaritoli et al. specifically noted that “inflammation does play a pivotal role in the pathogenesis of cachexia and its presence allows for cachexia identification” [13]. Given that systemic inflammation was a key component of the syndrome of cancer cachexia, scores including the Glasgow Prognostic Score (GPS, combination of CRP and albumin) were subsequently developed to objectively define cachexia [5, 7]. This led to Grey and co-workers terming this combination laboratory cachexia [14].

<sup>1</sup>Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK. <sup>2</sup>Institute of Cancer, University of Edinburgh, Edinburgh, UK. <sup>3</sup>St Columba's Hospice, Edinburgh, UK. ✉email: JoshMcGovern@glasgow.ac.uk

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**Table 1.** Proposed definitions and diagnostic criteria for cancer cachexia in chronological order.

	<b>Definition of cachexia</b>	<b>Diagnostic criteria</b>	<b>Comment</b>
Evans et al. [12]	A complex metabolic syndrome associated characterised by loss of muscle mass, frequently associated with anorexia, inflammation and insulin resistance.	Weight loss >5% in past 12 months and underlying chronic disease Or BMI < 20 kg/m <sup>2</sup> And Either three of the following criteria: abnormal biochemistry (serum CRP > 5 mg/L, serum albumin <3.2 g/dL or haemoglobin <12 g/dL), fatigue, anorexia, decreased muscle strength, lean tissue depletion.	Prognostic value not extensively validated but superior to similar Fearon criteria.
McMillan [7]	Activation of systemic pro-inflammatory processes in response to the tumour (innate immune response, acute-phase proteins) associated with the syndrome of cachexia.	Glasgow Prognostic Score. CRP ≤ 10 mg/l and albumin ≥35 g/l—no cachexia CRP ≤ 10 mg/l and albumin <35 g/l—malnourished CRP > 10 mg/l and albumin ≥35 g/l—pre-cachexia CRP > 10 mg/l and albumin <35 g/l—refractory cachexia	Prognostic value extensively validated.
Fearon et al. [2]	A multi-factorial syndrome characterised by loss of muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.	Weight loss >5% over past 6 months (in absence of simple starvation) Or BMI < 20 and any degree of weight loss >2% Or Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m <sup>2</sup> ; females <5.45 kg/m <sup>2</sup> ) and any degree of weight loss >2%	Forms the basis of the prognostic value of BMI/weight loss grade [24]. Not extensively validated.
Cederholm et al. [4]	Chronic disease-related malnutrition with inflammation.	One phenotypic criterion from involuntary weight loss, low BMI or low muscle mass And One aetiologic criterion from reduced food intake/ assimilation or inflammation/ disease burden	Forms the basis of the prognostic value of cachexia assessment. Not extensively tested or validated.

### Inflammation as a diagnostic criterion of cachexia

In the 2011 international consensus, Fearon and colleagues outlined the “agreed diagnostic criterion for cachexia as weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (body mass index [BMI] <20 kg/m<sup>2</sup>) or skeletal muscle mass (sarcopenia). An agreement was made that the cachexia syndrome can develop progressively through various stages—pre-cachexia to cachexia to refractory cachexia” [2]. They noted that although C-reactive protein (CRP), the prototypical marker of systemic inflammation, had prognostic value in these patients, cachexia could occur in the absence of systemic inflammation. These Fearon criteria have been taken into the BMI/weight loss grade framework that has been shown to have prognostic value [15] and to be associated with quality of life in patients with advanced cancer [16]. However, uncertainty remains around the existence of cancer cachexia in the absence of systemic inflammation, a recognised hallmark of cancer [17].

Where the Evans and the Fearon criteria have been prospectively compared, it was concluded that “This study presents a correlation with prognosis in favour of Evans et al.” definition as a tool for cachexia diagnosis. This means that weight loss and BMI decline are both key factors in patients with cancer leading to cachexia but less decisive as stated by Fearon et al. Instead, extra factors gain importance in order to predict survival, such as chronic inflammation, anaemia, protein depletion, reduced food intake, fatigue, decreased muscle strength and lean tissue depletion” [18]. This conclusion is in accord with subsequent attempts to define cachexia [19, 20] and in recent guidelines [21]. In particular, the Global Leadership Initiative on Malnutrition (GLIM) criteria proposed by Cederholm et al. in a consensus report defined cancer cachexia as chronic disease-related malnutrition with inflammation and the three phenotypic criteria identified were involuntary weight loss, low BMI, low muscle mass and the

tumour aetiologic criteria were reduced food intake or assimilation, and inflammation or disease burden [4]. Indeed, Laird et al., in ~2500 patients, proposed that the combination of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and mGPS effectively stratified quality of life and survival in patients with advanced cancer [22, 23]. More recently, Martin et al. reported, in a cohort of almost 5000 patients that weight loss is largely determined by dietary intake and systemic inflammation (as evidenced by CRP [24]). They concluded that “Modelling weight loss as the dependent variable is an approach that can help to identify clinical features and biomarkers associated with weight loss. Here, we identify criterion values for food intake impairment and CRP that may improve the diagnosis and classification of cancer-associated cachexia” [24]. With reference to the other GLIM phenotypic criteria, low muscle mass, a consistent association with the systemic inflammatory response has been reported [25] and interestingly tumour burden appears to be a less important aetiologic factor [26].

### The prognostic value of modulating the systemic inflammatory response in the treatment of cancer cachexia

The role of systemic inflammation in cancer cachexia is highlighted in the definition of Evans et al. and Cederholm et al. [4, 12]. Therefore, nutritional supplementation or therapeutic modification of skeletal muscle mass alone in patients with cancer, whom demonstrate signs of systemic inflammation may be futile [27]. This is consistent with the findings Merker and co-workers [28], who found that nutritional support was not effective in cancer and non-cancer patients with high-grade systemic inflammation (CRP >100 m/l), in a secondary analysis of a randomised clinical trial conducted across eight Swiss hospitals ( $n = 1950$  with a CRP measurement). Indeed, the significance of the systemic inflammatory response to outcomes in patients with cancer is well recognised [29–33], with McAllister and Weinberg noting

measures of the systemic inflammatory response (such as the GPS and neutrophil: lymphocyte ratio (NLR) “would seem to represent the tip of a far larger iceberg” [34].

The developments in the last decade now allow us to think differently about the syndrome of cancer cachexia. This was foretold by MacDonald nearly a decade ago “Particularly in the more aggressive tumour types (e.g. pancreas and lung), the future of patients with elevated mGPS scores (systemic inflammation) is so grim that they should be given pre-cachexia status and offered multimodal therapy which may delay the onset of cachexia and/or death [35]”. On this background, our approach to the management of cachexia has evolved [36]. Specifically, the rationale for multimodal therapy, such as that utilised in the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) studies [37, 38].

Despite advances in our understanding of the molecular and clinical pathogenesis of cachexia, the basis of the consistent association between weight loss, sarcopenia and the systemic inflammatory response (as evidenced by CRP) is not altogether clear. Inflammation is a recognised driver of the loss of skeletal muscle mass in patients with cancer [39, 40]. Specifically, an increased production of pro-inflammatory cytokines including the interleukins 1 and 6 [41, 42]. Furthermore, it has long been recognised that at a tissue and cellular level, that such pro-inflammatory cytokines have a profound impact on cellular and tissue metabolism and therefore provide a rational therapeutic target [43]. While the use of anti-inflammatory agents in cancer patients was once daunting [44], the experience of corticosteroids and anti-IL-6 agents inhibitors in other areas of routine clinical care of systemic inflammation [45], in cancer immunotherapy [46] and recently in COVID-19 [47] has informed how these agents might be efficaciously used. However, further study will be required to address how we down-regulate the systemic inflammatory response in patients with cancer.

## DISCUSSION

Over the last decade or so, systemic inflammation has progressively moved to the forefront of the definition and diagnosis of cancer cachexia. The work of Vanhoutte in carrying out a direct comparison between the Fearon and Evans criteria showed clearly the additional prognostic role of a number of criteria, in particular systemic inflammation. However, the more extensive Evans criteria made assessment more complex and therefore pre-cachectic patients and the opportunity for early intervention could be missed. Indeed, it is of interest that some of the Evans criteria such as anaemia and low muscle mass in cancer patients are now recognised to be associated with systemic inflammation and therefore these criteria may be simplified [25, 48].

More recently, the GLIM criteria have included systemic inflammation as an aetiological factor and introduced the concept that cachexia in patients with cancer is “disease-related malnutrition with inflammation. However, this concept may also miss the pre-cachectic patients and the opportunity for early intervention. Therefore, a more useful approach going forward may be that of MacDonald (2012) who proposed “Particularly in the more aggressive tumour types (e.g. pancreas and lung), the future of patients with elevated mGPS scores is so grim that they should be given pre-cachexia status and offered multimodal therapy which may delay the onset of cachexia and/or death [35].” In accord with the above perhaps a more useful interpretation of cancer cachexia is “disease-related inflammation with malnutrition” since this would emphasise the pre-cachectic state and the opportunity for early intervention.

From the above-detailed pathophysiology and criteria of cancer-related cachexia there are a number of potential implications for daily clinical practice. These include:

1. Monitoring on a routine clinical basis of markers of systemic inflammation such as the mGPS [19, 21]. This will identify patients at risk of cachexia although with no weight loss and good performance status [49, 50]. It may be in the future with the increased recognition of inflammation in the determination of nutritional status that there will be a more detailed assessment of the host inflammatory response including pro-inflammatory cytokines such as IL-1, TNF alpha and IL-6.
2. Treatment of patients with pre-cachexia/cachexia, together with standard oncological care, with a multimodal approach including anti-inflammatory medication, nutrition, exercise and symptom control [38]. However, further clinical work is required to determine the optimal modal treatment both individually and in combination. In particular, the use anti-inflammatory medications in patients with cancer is increasingly being examined. For example, Elwood and co-workers have recently reported that, in a systematic review and meta-analysis including ~250,000 patients, that there was a considerable body of evidence suggestive of about a 20% reduction in mortality in patients with cancer who take aspirin, and the benefit appears not to be restricted to one or a few cancers. They concluded that Aspirin deserves serious consideration as an adjuvant treatment for cancer [51].

## CONCLUSION

In summary, based on the present evidence, the role of systemic inflammation in cancer cachexia is exigent. Therefore, we feel the time has now come to consider cancer cachexia as primarily a SIR syndrome and herald a new era in the treatment of this life-shortening condition.

## DATA AVAILABILITY

Raw data will be made available on request to the senior author (DCM).

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## AUTHOR CONTRIBUTIONS

JM and DCM wrote the paper and analysed the data. RDD, RJS and BJL aided in conceptualisation, reviewing, and writing of the paper. DCM had primary responsibility for the final content.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The following review was conducted in accordance with the declaration of Helsinki. Ethical approval was not required for this study as this was a systematic review of published data.

## CONSENT TO PUBLISH

All authors consent to publication.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Josh McGovern.

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