

Cachexia in cancer: what is in the definition?

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ABSTRACT

Objective: This study aimed to provide evidence-based results on differences in overall survival (OS) rate to guide the diagnosis of cancer cachexia.

Design: Data collection and clinical assessment was performed every 3 months (5 visits): baseline data, muscle strength, nutritional and psychosocial status. 2 definitions on cachexia using different diagnostic criteria were applied for the same patient population. Fearon *et al*'s definition is based on weight loss, body mass index (BMI) and sarcopenia. Evans *et al* nuances the contribution of sarcopenia and attaches additional attention to abnormal biochemistry parameters, fatigue and anorexia. The mean OS rates were compared between patients with and without cachexia for both definitions.

Results: Based on the population of 167 patients who enrolled, 70% developed cachexia according to Fearon *et al*'s definition and 40% according to Evans *et al*'s definition. The OS in the cachectic population is 0.97 and 0.55 years, respectively. The difference in OS between patients with and without cachexia is more significant using the diagnostic criteria of Evans *et al*. The focus of Fearon *et al* on weight loss and sarcopenia over-rates the assignment of patients to the cachectic group and OS rates have less prognostic value.

Conclusion: 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.

Trial registration number: B300201112334.

INTRODUCTION

Cancer cachexia is a multifactorial syndrome with a dramatic impact on patient's quality of

Summary box

What is already known about this subject?

- Cachexia is a multifactorial syndrome with involuntary progressive weight loss as a result of reduction of skeletal muscle mass with or without depletion of adipose tissue.
- Cancer cachexia is characterised by systemic inflammation and metabolic changes leading to progressive functional impairment.
- Sarcopenia as an index for cancer cachexia is a matter of debate.
- There is a lack of consensus on a definition, diagnostic criteria and classification of cancer cachexia

What are the new findings?

- Evidence-based results showing a substantial difference in the prediction of overall survival comparing the diagnostic guidelines according to Fearon *et al*² with the diagnostic guidelines according to Evans *et al*.¹
- Putting the focus on weight loss and sarcopenia over-rates the assignment of the diagnosis of cachexia resulting in survival rates with less prognostic value.
- Additional factors gaining importance in the diagnosis of cancer cachexia are: chronic inflammation, anaemia, protein depletion, anorexia and fatigue.
- Extra humoral factors should be a new point of interest in the further exploration of cachexia parameters.

life associated with poor responses to antitumour therapy and decreased survival.^{1–5} The prevalence of cancer cachexia is high: it is estimated to affect 50–80% of patients with cancer and accounts for up to 20% of deaths due to cancer in 2014.³ The main clinical feature of cachexia is involuntary progressive weight loss as a result of reduction of skeletal

Summary box

How might it impact on clinical practice in the foreseeable future?

- ▶ Standardisation of the routine clinical practice for diagnosis of cancer cachexia would help in the identification of patients who are more at risk for the development of cachexia.
- ▶ In view of the current therapeutic approach, which targets the fundamental pathways involved in the pathogenesis of cancer cachexia, monitoring the humoral factors in daily practice would create the possibility to capture the diagnosis of cancer cachexia up close.

muscle mass (SMM) with or without depletion of adipose tissue. While starvation is also characterised by the same properties, it is not possible to reverse cachexia by means of conventional nutritional support.^{6 7} This is due to the complex underlying pathophysiology of cancer cachexia in response to the tumour–host interactions.

Many of the primary events driving cachexia are mediated by the central nervous system.^{8 9} The best known cachexia-mediating factors are cytokines (tumour necrosis factor α (TNF- α), interleukin 1 (IL-1), IL-6 and interferon- γ), neuropeptide-Y and hormones (insulin, glucagon and leptin). This means that cancer cachexia is characterised by systemic inflammation and metabolic changes resulting in a negative protein and energy balance. Cancer cachexia leads to progressive functional impairment. Although studies of molecular pathways involved in muscle wasting made progress in unravelling the complex biology of cachexia,^{10 11} there still remains a lack of consensus on the diagnostic criteria of cancer cachexia, which impedes any meaningful advancement in therapeutic clinical trials and clinical practice.

Many definitions of cachexia have been published.^{1 2 12–14} However, guidelines for diagnosis of cancer cachexia are just starting to appear. In a formal consensus process, expert groups discussed the key factors that guide clinical decision-making in the management of cachexia defined as the Fearon *et al* criteria² which were based on a generic definition proposed earlier by Evans *et al*¹ in 2008. This generic definition applies to all types of cachexia and includes, besides weight loss and low body mass index (BMI), at least three additional criteria from five other contributing factors such as decrease in muscle strength, fatigue, anorexia, low fat-free mass (FFM) and abnormal biochemistry (high C reactive protein (CRP), low albumin or low haemoglobin (Hb)). The key difference between Evans *et al* definition and Fearon *et al*'s definition is the emphasis on the loss of SMM (ie, sarcopenia), to which the latter definition attaches more importance. However, the annex of the factor sarcopenia has no proven added value and it remains undetermined to which extent sarcopenia is a useful index for cancer cachexia.¹⁵

Since in the literature, no evidence-based results are available to guide the diagnosis of cancer cachexia, the criteria to use remain arbitrary. Currently, in routine

clinical practice, cachexia is diagnosed by combining anthropometric measures (body weight and BMI), biological values (albumin, CRP), body composition (total body water (TBW) and FFM) and nutritional screening questionnaires.¹⁶

Objective

The objective of this study was to monitor the cachectic status of oncology patients according to Fearon *et al*'s and Evan's criteria (table 1) for 1 year and to compare the actual survival between patients with and without cachexia by means of the Fearon *et al*'s and Evan's criteria (table 1).^{1 2} This way, we could evaluate whether the two-factor profile of Fearon *et al* incorporating anthropometric values and sarcopenia might relate sufficiently to the patient's overall survival (OS) as compared with the incorporating criteria by Evans *et al*. In addition, the study evaluates the feasibility of additional methods (eg, bioelectrical impedance analysis (BIA)) in daily clinical practice in support of patients with cancer cachexia.

MATERIALS AND METHODS**Patient population**

Ambulatory patients with cancer of 18 years or more, with digestive, lung, breast or head/neck tumours, with WHO performance status of 0–2, without a pacemaker and who received previous therapy admitted to a standard care facility and provided signed informed consent were eligible for the study.

Recruitment took place in four Belgian medical centres between 2012 and 2013:¹ Universitair Ziekenhuis Antwerpen (UZA; Edegem),² AZ Maria Middelaers (Gent),³ Heilig Hart Ziekenhuis Lier (Lier),⁴ St Jozef Kliniek (Bornem). A total number of 167 patients started the study.

Investigational assessments and analysis

Baseline data (eg, demography, diagnosis and disease status), nutritional status, muscle strength and psychosocial status of the patients were assessed at five consecutive hospital visits with an (average) interval of 3 months.

Nutritional status

The nutritional status was assessed by means of the Nutritional Risk Screening score (NRS-score), Patient-Generated Subjective Global Assessment (PG-SGA) and bioelectric impedance analysis (BIA, Equilibre3, Belgium).¹⁷ The NRS-score and PG-SGA estimate the risk of malnutrition based on body weight, BMI and dietary intake. On the base of dietary intake, a member of the nutrition team estimated the individual protein need and energy need. BIA is used as a method to estimate the body composition by measuring individual resistance (RZ), reactance (XC) and phase angle (PA) to calculate TBW, FFM and SMM (for equations see online supplementary appendix 1).^{18 19}

Table 1 List of criteria for diagnosis of cachexia according to Evans *et al* and Fearon *et al* with translation to our study methods

Fearon <i>et al</i> 's criteria	Evans <i>et al</i> 's criteria	Translation in our study
Weight loss >5% in past 6 months without starvation	Weight loss >5% in past 12 months and underlying chronic disease	NRS, PG-SGA
And/or	Or	
Weight loss >2% and BMI<20	BMI<20	NRS, PG-SGA
And/or	And 3 out of next 5 criteria	
	Abnormal biochemistry	Standard blood test
	CRP>5 mg/L	Standard blood test
	Hb<12 g/dL	Standard blood test
	Albumin <3.2 g/d	EORTC tiredness: score ≥66.7
	Fatigue	EORTC appetite loss: score ≥3
	Anorexia	Hand grip strength (dynamometer)
	Decreased muscle strength	BIA
Weight loss >2% and sarcopenia	Lean tissue depletion	Male SMI<7.26 kg/m ² Female SMI<5.45 kg/m ²

BIA, bioelectric impedance analyses; BMI, body mass index (kg/m²); CRP, C reactive protein; Hb, hemoglobin; NRS, Nutritional Risk Screening; PG-SGA, Patient-Generated Subjective Global Assessment; SMI, Skeletal Muscle mass Index.

Muscle strength

The hand grip strength was measured as an indicator of the muscle strength of the upper extremities using a digital hand dynamometer on the dominant hand (Fysiomed, Saehan medical, country). Patients were instructed to stand upright holding the dynamometer on the side but not against their body. Patients were asked to perform three maximum force trials. The average attained value was used as the final score.

Psychosocial status

The psychosocial status of the patient was assessed by means of the EORTC Quality of Life Questionnaire C30 (EORTC QLQ-C30), which incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain and nausea/vomiting) and a Global Health Status/Quality of Life (QoL) scale.

Definitions of cachexia

The generic definition of cachexia (Evans *et al*) is based on the presence of weight loss of at least 5% during the past 6 months or BMI<20 kg/m², plus at least three criteria out of the list described in table 2. According to Fearon *et al* a patient could be diagnosed with cachexia based on one out of three weight loss definitions: weight loss of at least 5% during the past 6 months in the absence of simple starvation or weight loss of at least 2% together with either a BMI<20 kg/m² or sarcopenia. Table 1 indicates the details of all the criteria of both definitions and how these criteria were translated to our study.

Table 2 Descriptive characteristics of the cancer patient population included in the trial (average and SD)

	Total
Age (years)	63.96 (11.04)
Gender	
Female	55/167 (32.9%)
Male	112/167 (67.1%)
Primary location	
Breast	7/167 (4.2%)
GI tract	109/167 (65.3%)
Lung	32/167 (19.2%)
Head/neck	19/167 (11.4%)
Metastases	
No	54/167 (32.3%)
Yes	113/167 (67.7%)
Cancer stage	
I	21/167 (12.6%)
II	23/167 (7.2%)
III	21/167 (12.6%)
IV	111/167 (66.5%)
V	2/167 (1.2%)

GI, gastrointestinal.

Laboratory analysis

Following each visit, 10 mL of peripheral blood was collected in EDTA tubes. The tubes were instantly cooled on ice and centrifuged at 3000 rpm for 10 min at 4°C and aliquots were immediately stored at -20°C before transport (<1w) to the biobank of the UZA or stored immediately at -80°C, when available, until analysed at the biobank of the UZA. Standard laboratory tests for albumin, prealbumin, Hb and CRP were centrally performed at the Department of Clinical Biology, UZA.

Statistical analysis

All data were recorded using the commercial electronic data capturing system (Remecare, Remedus, Belgium). Categorical data are reported as number and percentages, continuous data as mean and SD, when normally distributed, or as median with lower and upper quartile if not. Normality has been checked by Shapiro-Wilk tests and QQ plots. If needed, a log transformation is used to improve normality. Differences between baseline characteristics of patients with and without cachexia were assessed by means of χ^2 test for categorical variables or unpaired t-test for continuous, normally distributed data (age). For the relation between the cachectic status of the patient and time-varying variables, linear mixed-effects models are used. By including a patient-specific intercept, correlations between measurements of the same patient are taken into account. Means and SEs based on the mixed-effects model are reported. p Values are corrected for multiple testing using the stepdown Bonferroni-Holm correction.

OS of the patients was studied with Kaplan-Meier curves and Cox regression where cachexia is treated as a time-dependent covariate. HRs and corresponding 95% CIs are reported. All analyses were performed with SAS V.9.4 or R V.3.1.1.

RESULTS

Diagnosis of cachexia

A total number of 176 patients of which 167 started their study visit. In 67.1% men, an average age of 64 years, the gastrointestinal tract was the predominant location of the primary tumour (65.3%) and the majority of the patient population had metastases (67.7%; table 2).

A consort diagram presents the number of patients, dropouts and deaths during the study (figure 1). A total of 176 patients were initially recruited of which 167 patients (95%) started their first study visit (consult 1). Fifty-four of the patients completed their five study visits (26%). During the study, 35 patients (21%) withdrew for variable reasons (too weak, end of treatment, etc), 25 entered palliative setting (15%) and 62 deaths (37%).

Patients were monitored for the cachectic status at every consult by inspecting all criteria listed by Fearon *et al* and Evans *et al* (table 3). About 70% of the population developed cachexia at some time during the five visits according to Fearon *et al*'s definition, while it was about 40% according to Evans *et al*'s definition. This difference was already visible from consult 1 onwards: 50% patients with cachexia (83/167) according to Fearon *et al* and 18% of the same patient group (30/167) according to Evans *et al*. The percentage of patients with cachexia according to Fearon *et al* was significantly higher for every time point as compared with Evans *et al* (an average of 57 ± 8 (%) patients with cachexia vs an average of 18 ± 7 (%) patients with cachexia).

The total patient population was evaluated for the presence of differences between the cachectic and the non-

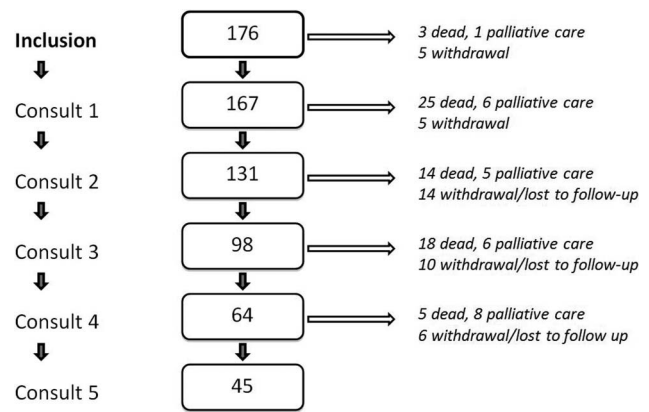


Figure 1 Consort diagram of the number of patients through the longitudinal follow-up of five consults with 3-month interval. Patients entering palliative care, patients withdrawing from the study or patients who died could not be taken into account at the following consult.

cachectic group based on the primary tumour location, the metastatic status, age and gender. The cachectic group contains patients who were diagnosed as cachectic at minimum one consult and the non-cachectic group contains patients who were never diagnosed as cachectic along the five consults. We could not demonstrate significant differences between patients with and without cachexia based on age, gender, primary location of the tumour or the absence or presence of metastases (table 4).

Survival rates

According to Fearon *et al*, the median OS in the cachectic population is 0.97 years, which is significantly shorter than 1.25 years for patients without cachexia (respectively 95% CI 0.83 to 1.29 and 1.02 to 1.63 with $p=0.00338$; figure 2A). Similarly, patients with cachexia diagnosed according to Evans *et al* have a shorter median OS rate of 0.55 years as compared with the median OS rate of 1.38 years of patients without cachexia (respectively 95% CI 0.40 to 1.14 and 1.25 to 1.63 with $p<0.0001$; figure 2B). The HR of patients with cachexia versus without cachexia according to the definition of Evans *et al* is 3.32 while for Fearon *et al* this HR is only 1.82. While both are significant (respectively $p<0.0001$ and $p=0.00338$), the effect size is larger by the definition of Evans *et al*. This difference in effect size cannot be formally tested since for both models the same patient population is used. Following correction for primary tumour location, metastatic status, age and gender, the difference between patient groups with and without cachexia diagnosis according to Fearon *et al* becomes more significant ($p=0.0055$ instead of $p=0.00338$) and the difference according to Evans *et al* remains highly significant ($p<0.0001$; figure 2A, B).

Effect of weight loss and sarcopenia

The effect of weight loss on the OS of patients with cachexia has been evaluated by regrouping the population

Table 3 For both definitions of cachexia, the number of patients meeting separate criteria are presented per consult

	Consult 1	Consult 2	Consult 3	Consult 4	Consult 5
Criteria definition by Fearon <i>et al</i>					
Weight loss >5% in the past 6 months	64	61	57	36	21
Weight loss >2% and BMI<20 and	15	7	10	6	4
Weight loss >2% and sarcopenia	50	19	25	10	16
Patients with cachexia	83 (49.7%)	69 (52.6%)	61 (62.2%)	44 (68.7%)	23 (51.1%)
Total patients	167	131	98	64	45
Criteria definition by Evans <i>et al</i>					
Weight loss of at least 5% in 6 months or BMI<20	71	69	62	40	22
+ At least 3 out of the next criteria					
Decreased muscle strength	41	30	27	14	6
Fatigue	42	26	21	17	5
Anorexia	48	26	27	19	4
Low fat-free mass index	70	43	35	25	18
Abnormal biochemistry					
CRP>5 mg/L or IL6>4 pg/mL	27	15	10	8	2
Anaemia	74	70	44	23	15
Low serum albumin	35	25	21	9	4
Patients with cachexia	30 (17.9%)	29 (22.1%)	23 (23.5%)	14 (21.9%)	3 (6.7%)
Not enough information	0	4	6	2	4
Total patients	167	131	98	64	45

The resulting number of patients diagnosed with cachexia are calculated for both definitions per consult (grey rows). The row 'Total patients' indicates the total number of patients of which cachectic status was monitored longitudinally. BMI, body mass index; CRP, C reactive protein; IL, interleukin.

Table 4 The total patient population was evaluated for the effect of four confounding factors (primary tumour location, metastatic status, age and gender) known to have an effect on general survival

	Patients without cachexia	Patients with cachexia	Comparison
(A) Overall definition by Fearon <i>et al</i>			
Primary location			p=0.1018
Head/neck/breast	9/26 (35%)	17/26 (65%)	
GI tract	27/109 (25%)	82/109 (75%)	
Lung	14/32 (44%)	18/32 (56%)	
Metastases			p=0.8094
No	15/54 (28%)	39/54 (72%)	
Yes	35/113 (31%)	78/113 (69%)	
Age (SD)	63.53 (10.99)	64.15 (11.1)	p=0.7255
Gender			p=0.2756
Female	20/55 (36%)	35/55 (64%)	
Male	30/112 (27%)	82/112 (73%)	
(B) Overall definition by Evans <i>et al</i>			
Primary location			p=0.4110
Head/neck/breast	18/26 (69%)	8/26 (31%)	
GI tract	62/109 (57%)	47/109 (43%)	
Lung	21/32 (66%)	11/32 (34%)	
Metastases			p=0.3363
No	36/54 (67%)	18/54 (33%)	
Yes	65/113 (57%)	48/113 (42%)	
Age (SD)	62.81 (11.11)	65.72 (10.77)	p=0.0695
Gender			p=0.1536
Female	38/55 (69%)	17/55 (31%)	
Male	63/112 (56%)	49/112 (44%)	

The presence of differences between the cachectic group and the non-cachectic group was evaluated for the definition of Fearon *et al* in A and for the definition of Evans *et al* in B. The cachectic group contains patients who were diagnosed as cachectic at minimum one consult and the non-cachectic group contains patients who were never diagnosed as cachectic along the five consults. All the effects of confounding factors are not significant. GI, gastrointestinal.

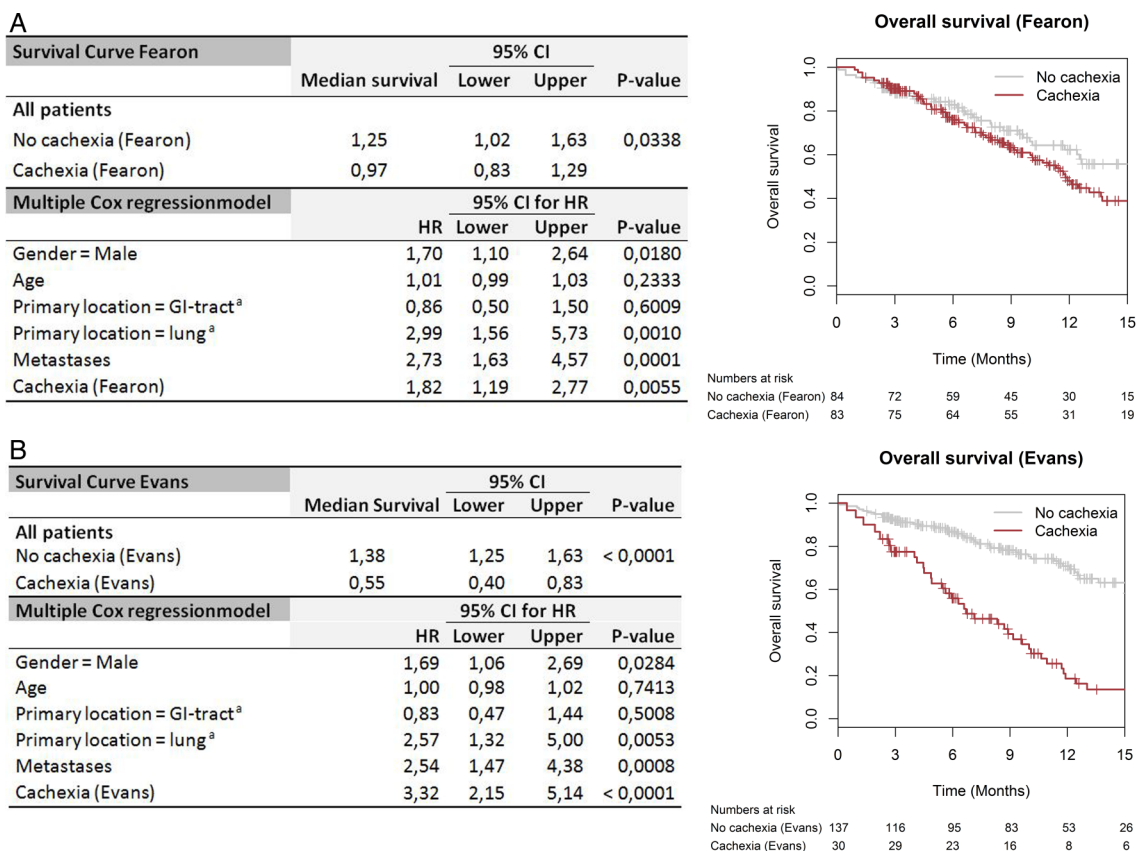


Figure 2 Kaplan-Meier estimation of the survival analysis and multiple Cox regression for all patients as separated in cachectic and non-cachectic; in 2A according to Fearon *et al* and in 2B according to Evans *et al*. ^aReference=primary location=other (breast/head/neck). ^bReference=no sarcopenia—no cachexia. GI, gastrointestinal.

into:¹ patients without weight loss and BMI>20 kg/m²,² patients with weight loss only, being patients with cachexia according to Fearon *et al* but no cachexia according to Evans *et al*,³ and patients selected by the definition of Evans *et al* (weight loss and three out of five criteria). There was no difference in OS between patients without weight loss and patients with only weight loss (p=0.519; figure 3A). However, there was a highly significant difference in OS between patients selected according the definition of Evans *et al* and patients with or without weight loss only (p<0.0001).

The influence of sarcopenia on the OS of patients when classified according to Fearon *et al*'s criteria has been evaluated by regrouping the population into:¹ no sarcopenia and no cachexia,² sarcopenia and no cachexia,³ no sarcopenia and cachexia and,⁴ sarcopenia and cachexia. There was no difference detected in OS between all patient groups (p=0.1358; figure 3B).

Cachexia markers

The diagnostic criteria included in the definition of Fearon *et al* being weight loss, BMI and skeletal muscle mass index (SMI) were all significantly decreased in the patients with cachexia (p<0.0001; table 5A). Similarly, there were significant differences for every diagnostic criteria defined by Evans *et al* (weight loss, BMI,

handgrip power, CRP, SMI, albumin) when comparing patients with and without cachexia diagnosed according to Evans *et al* (table 5B). For the patient with cachexia, the percentage of weight loss and CRP were both higher (p<0.0001), BMI, handgrip power, albumin and SMI were all lower (p<0.0001 for SMI p=0.0145). The group of patients with cachexia according to Fearon *et al* demonstrated significant reduction of handgrip power (p<0.0001), increased CRP (p=0.026) and unchanged albumin (p=0.066), being criteria included in the definition of Evans *et al*.

Our methods used for assessing nutritional status and muscle strength also provide extra parameters in addition to the criteria as defined by Fearon *et al* and Evans *et al*. Protein need and energy need used to estimate the risk of malnutrition from the NRS and PG-SGA were lower for patients of both cachectic groups. The BIA method used to measure the SMI also provides extra parameters related to the body composition. FFM and TBW were significantly lower (p<0.001) for patients of both cachectic groups. RZ was significantly higher (p<0.001) for patients of both cachectic groups. XC and PA were significantly lower for the patients of the cachectic group only in case the criteria of Evans *et al* were applied (table 5B; p=0.0145 and p<0.0001, respectively). XC, PA and prealbumin were unchanged in the

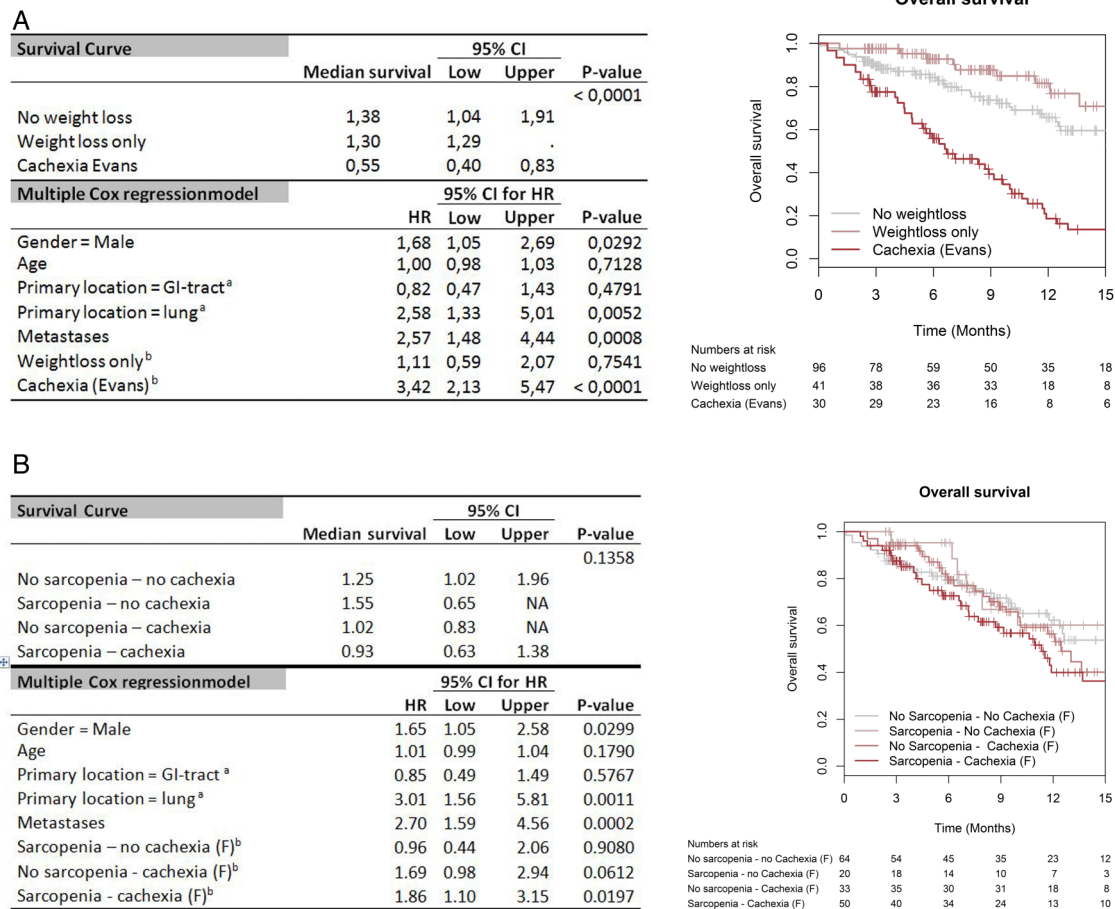


Figure 3 Kaplan-Meier estimation of the survival analysis and multiple Cox regression for all patients to evaluate the influence of weight loss in 3A and the influence of sarcopenia in 3B. ^aReference=primary location=other (breast/head/neck). ^bReference=no weight loss. GI, gastrointestinal.

cachectic group diagnosed according to Fearon *et al* ($p=0.392$, $p=0.066$ and $p=0.070$, respectively).

EORTC questionnaires used to estimate the fatigue and anorexia (being a criteria defined by Evans *et al*) also revealed a lower quality of life score for both cachectic groups ($p<0.0012$ and $p<0.0001$ for respectively patients with cachexia according to Fearon *et al* and Evans *et al*).

DISCUSSION

Cancer cachexia remains a challenging multifactorial syndrome with an important impact on the patient's quality of life and response to therapy. Despite many efforts to unravel the complex biology of cachexia, its diagnosis remains infrequently defined. Many definitions of cancer cachexia have been published so far but no consensus exists on which diagnostic criteria should be used in clinical decision-making or clinical trials. Estimation of cachexia among patients with cancer in daily practice is based on arbitrarily selected definitions.

For the first time, this pilot study in which patients were followed in a longitudinal way provides insights into the impact of OS rates comparing two different

definitions of cachexia for the same population with cancer. On the one hand we applied the criteria according to an international consensus reported by Fearon *et al*² with limited criteria but cancer specific and on the other hand the more generic cachexia definition according to Evans *et al*¹ based on the complex interplay between food intake and an abnormal metabolism.

OS rates: main findings comparing two definitions of cachexia

A total of 167 patients were included and longitudinally monitored for cachectic status for 1 year at five consecutive visits for nutritional status, muscle strength and psychosocial status. A significant shorter OS was observed for patients with cachexia regardless of the diagnostic criteria used as defined by Fearon *et al* or by Evans *et al*. This prediction of worse survival for the patients with cachexia remains even after correction for variables with a known effect on survival (gender, primary tumour location, metastatic disease).

However, the proportion of patients with cachexia varied considerably depending on the criteria used. Across all five visits, the number of patients with

Table 5 Parameters associated with the diagnosis of cachexia are demonstrated for cachectic patient groups according to the definition of Fearon *et al* (A) and for Evans *et al* (B)

Parameter (Fearon <i>et al</i> , Evans <i>et al</i>)	(A) Cachexia according to Fearon <i>et al</i>			(B) Cachexia according to Evans <i>et al</i>		
	Non-cachectic	Cachectic	Adjusted p value	Non-cachectic	Cachectic	Adjusted p value
Body weight	74.32 (1.04)	68.30 (1.04)	<0.0001	72.03 (1.04)	68.28 (1.12)	<0.0001
WLOSS (%/m)	0.22 (0.13)	-1.42 (0.11)	<0.0001	-0.36 (0.10)	-1.94 (0.20)	<0.0001
BMI	25.52 (0.30)	23.46 (0.30)	<0.0001	24.75 (0.30)	23.44 (0.33)	<0.0001
Power (handgrip)	32.75 (0.83)	30.45 (0.82)	<0.0001	32.22 (0.79)	29.09 (0.89)	<0.0001
SMI	8.88 (0.13)	8.23 (0.13)	<0.0001	8.61 (0.13)	8.30 (0.15)	0.0145
Albumin	3.61 (0.05)	3.47 (0.04)	0.0657	3.67 (0.04)	3.08 (0.06)	<0.0001
CRP (log)	0.34 (0.03)	0.44 (0.02)	0.0260	0.30 (0.02)	0.69 (0.03)	<0.0001
Parameters (extra)						
Energy need	1489.71 (13.50)	1423.56 (13.28)	<0.0001	1470.16 (12.65)	1406.26 (14.84)	<0.0001
Protein need	89.77 (1.28)	82.44 (1.26)	<0.0001	87.01 (1.25)	82.39 (1.41)	<0.0001
RZ	525.90 (7.10)	571.52 (6.93)	<0.0001	544.01 (6.74)	571.61 (8.38)	<0.0001
XC	48.18 (1.05)	50.03 (1.01)	0.3924	50.05 (0.91)	46.61 (1.26)	0.0145
PA	5.24 (0.09)	5.00 (0.08)	0.0657	5.25 (0.07)	4.67 (0.11)	<0.0001
FFM	55.53 (0.80)	51.77 (0.80)	<0.0001	53.93 (0.79)	52.18 (0.86)	0.0007
TBW	39.75 (0.62)	36.55 (0.62)	<0.0001	38.40 (0.62)	36.83 (0.68)	<0.0001
Quality of life	61.45 (1.65)	53.75 (1.53)	0.0012	61.04 (1.27)	44.04 (2.10)	<0.0001

Parameters as defined by Fearon *et al* and Evans *et al*: Body weight (kg), WLOSS (%/body mass), BMI (kg/m²), Power (handgrip), SMI (kg/m²), albumin (g/dl), CRP (log mg/L). Parameters additionally collected by the measurements: energy need (calories), protein need, RZ, XC, PA, FFM (kg/m²), TBW (%) and Quality of life (EORTC outcome score).

BMI, body mass index; CRP, C reactive protein; EORTC, European organisation for research and treatment of cancer; FFM, fat-free mass; PA, phase angle; RZ, resistance; SMI, skeletal muscle mass index; TBW, total body water; WLOSS, weight loss; XC, reactance.

cachexia according to Fearon *et al* is high as compared with the number of patients with cachexia according to Evans *et al* (data not shown).

The focus by Fearon *et al* is put on a minimum degree of body weight loss. Body weight loss is indeed a hallmark of cancer cachexia, but is not the only symptom. Despite this less rigorous definition, a small but significant difference in OS exists between the patients with and without cachexia (respectively median survival: 0.97 vs 1.25 years, $p=0.034$). We were however able to show that weight loss alone had no significant impact on the survival curve. Another important factor in the definition of Fearon *et al* is the absence or presence of sarcopenia. Our results illustrate this since the factor sarcopenia is not able to influence OS. Sarcopenia as an index for cachexia in patients with cancer was already a matter of debate we can only support this controversy.²⁰

Compared with Fearon *et al*, Evans *et al* also included weight loss but combined this with at least three of the following criteria: loss of muscle strength, anorexia, lean tissue depletion, distinct fatigue or abnormal biochemistry (decreased albumin, increased CRP or anaemia) to define cachexia. This definition focuses on the complex interplay between reduced food intake and abnormal metabolism and is therefore able to distinguish patients with cachexia from patients without cachexia by the survival rate (respectively median survival: 0.55 vs 1.38 years, $p<0.0001$). Also, where according to Fearon *et al* the presence of sarcopenia with weight loss can assign the diagnosis of cachexia to a patient, Evans *et al* criteria is stricter and sarcopenia is rather one of the

components of cachexia and defined as loss of muscle strength and loss of lean tissue.

In conclusion, Evans *et al* argue for the use of more criteria to diagnose cachexia and in accordance to our population-based results, its definition makes a better prediction of survival. Whereas the focus of Fearon *et al* on weight loss and sarcopenia over-rates the assignment of patients to the cachectic group and results in survival rates with less prognostic value. On the other hand, one must be aware that the use of Fearon *et al*'s criteria might diagnose cachexia in a much earlier state, thus making the patients with a lower risk a potential target for early intervention. Cachexia indeed represents a spectrum through which patients progress but at present there are no robust biomarkers to identify those patients with precachexia. Loss of SMM could also be age-related without any underlying disease. Therefore, a profiling system for cachexia needs to reflect the underlying metabolic complexity. Also strategies for treating cachexia focus on the underlying metabolic adaptations of increased protein degradation and not only on the measurement of the loss of weight or SMM. These elements are in favour of the use of the criteria of Evans *et al* in clinical practice where diagnostic criteria include abnormal biochemistry values such as CRP.

Cancer cachexia assessment in clinical practice

In this study, a quantitative correlation with patient prognosis is presented in favour of using the criteria of Evans

et al as a tool for the diagnosis of patients with cachexia. This means that weight loss and a decrease in BMI in patients with cancer are both key factors leading to cachexia (table 1) but less decisive as stated by Fearon *et al*. Instead, other factors need to be taken into consideration in order to be able to predict survival. Extra factors gaining importance according to Evans *et al* are chronic inflammation (CRP), anaemia (Hb), protein depletion (albumin), reduced food intake (anorexia), fatigue, decreased muscle strength and lean tissue depletion.¹

Results are based on a population of 167 enrolled patients. This number reflects a part of the total population seen in clinical practice during the duration of the study. However, according to the strong quantitative correlation between cachexia diagnosis and prognosis, the application of the criteria of Evans *et al*, is a good choice to use as prognosticator.

The first step in clinical practice should be to identify the patient for recognition of either malnutrition or starvation measuring nutritional risk (ie, NRS, PG-SGA, mini nutritional assessment (MNA), etc). Patients with cancer with weight loss >5% during the past 6 months or a BMI<20 have to be considered to be diagnosed with cachexia. However, cachexia is distinct from starvation, nutritional intervention should be implemented as soon as cancer is diagnosed to reduce nutritional status impairment and improve the general condition and quality of life. Keeping an optimised balance between energy waste and food intake will achieve further specific purposes such as a decrease of rate of complications and an amelioration of the response and tolerance of the patient to the oncological therapy.^{15–17} This study demonstrated the applicability in ambulatory setting of the NRS-score, being easy in use and accepted in European regions.

Evaluation of the presence of extra factors characterising cachexia in the definition of Evans *et al* can be performed through standard blood tests (CRP, Hb, albumin), EORTC QLQ-C30 (anorexia, fatigue) and analysis of body composition to quantify the SMM (muscle strength and lean tissue depletion). Cachexia is indeed characterised by loss of SMM but is not the same as sarcopenia.

BIA is a method commonly used to assess body composition by measuring individual RZ, XC and PA to calculate TBW, FFM and SMM. Only SMM is incorporated in both definitions whereas every single parameter resulting from the BIA measurement was demonstrated to be significantly different in the cachectic population according to Evans *et al*. Stratification according to Fearon *et al* could not demonstrate any XC or PA changes. Determination of body composition has not only added value to the diagnosis of sarcopenia but can be used as a predictor of chemotherapy toxicity and survival.^{21–23} Despite the fact that BIA might provide less information than imaging methods such as MRI and CT,²¹ its low cost and simplicity makes it clearly an opportunity to implement in clinical practice.¹⁸

Future directions: beyond the definition of Evans *et al*

Monitoring the nutritional health status of the patient with cancer using the criteria of Evans *et al*¹ is highly recommended and creates the opportunity to assign the diagnosis of cachexia to the patient. During the past few decades, we have witnessed a dramatic increase in the understanding of the underlying pathophysiology of cancer cachexia. Different cytokines, such as IL-6 and TNF- α , are responsible for protein breakdown in SMM and play an important role in the aetiology of cancer cachexia.^{3–4} Also several hormonal abnormalities related to ghrelin, leptin and adiponectin have been reported in the setting of cancer cachexia.²⁴ These hormones participate in body weight regulation by regulating food intake and energy homeostasis.^{25–27} Disturbance of aforementioned humoral factors is the most common cause of a variety of clinical symptoms of cancer cachexia.⁹ It was noticed that none of these elements, except for systemic inflammation (ie, high CRP), are incorporated into the criteria according to Evans *et al* and that it would be valuable to explore if adding humoral factors would mean a surplus in the diagnosis of cancer cachexia. Moreover, in view of the current therapeutic approach, which targets the fundamental pathways involved in the pathogenesis of cancer cachexia,^{28–29} monitoring the humoral factors in daily practice would create the possibility to capture the diagnosis of cancer cachexia up close.

CONCLUSION

While the clinical decision-making in the management of cachexia as reported by Fearon *et al* is based on a consensus process of expert groups in oncology, it was demonstrated in this study that applying these criteria results in an over-rating of the assignment of patients to the diagnosis of cachexia. From the results based on our population, one can conclude that neither the weight loss nor the presence of sarcopenia in oncology patients is decisive for diagnosing cachexia. Other key factors that guide the clinical decision-making must comprise the evaluation of the underlying mechanisms of cachexia. Understanding the causes of cachexia sheds light on the subsequent need for a multimodality approach to diagnosis and also treatment of cancer cachexia.

This means, next to specialised nutrition support based on monitoring anthropometric values (body weight and BMI), also biological values reflecting abnormal biochemistry and body composition measurements must be combined. This is reflected in the criteria applied by Evans *et al* and creates the opportunity to assign the diagnosis of cachexia to the patient more accurately in order to outline the treatment possibilities.

Therefore, we propose that oncology patients should be identified first for recognition of either malnutrition or starvation. To this end, the NRS seems to be more easily applicable and has gained acceptance in European regions. As NRS is already validated for

hospitalised patients at admission, further analysis in this study population could offer perspectives in validation for ambulant setting.

Second, standard blood tests should be evaluated for the presence of multiple factors characterising cachexia such as high CRP, low Hb or low albumin. Next to this the implementation of BIA in daily clinical practice is an opportunity to assess sarcopenia at low cost and to analyse additionally the total body composition as secondary elements having significant meaning for patients with cachexia. In future, the value of adding humoral factors the diagnosis of cancer should be explored more deeply.

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REFERENCES

- Evans WJ, Morley JE, Argilés J, *et al*. Cachexia: a new definition. *Clin Nutr* 2008;27:793–9.
- Fearon K, Strasser F, Anker SD, *et al*. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489–95.
- Argilés JM, Busquets S, Stemmler B, *et al*. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer* 2014;14:754–62.
- Bilir C, Engin H, Can M, *et al*. The prognostic role of inflammation and hormones in patients with metastatic cancer with cachexia. *Med Oncol* 2015;32:56.
- Fujiwara Y, Kobayashi T, Chayahara N, *et al*. Metabolomics evaluation of serum markers for cachexia and their intra-day variation in patients with advanced pancreatic cancer. *PLoS ONE* 2014;9:e113259.
- Grimble RF. Nutritional therapy for cancer cachexia. *Gut* 2003;52:1391–2.
- Gullett NP, Mazurak VC, Hebbard G, *et al*. Nutritional interventions for cancer-induced cachexia. *Curr Probl Cancer* 2011;35:58–90.
- Egerman MA, Glass DJ. Signaling pathways controlling skeletal muscle mass. *Crit Rev Biochem Mol Biol* 2014;49:59–68.
- Mendes MC, Pimentel GD, Costa FO, *et al*. Molecular and neuroendocrine mechanisms of cancer cachexia. *J Endocrinol* 2015;226:R29–43.
- Tisdale MJ. Biology of cachexia. *J Natl Cancer Inst* 1997;89:1763–73.
- Argilés JM, Busquets S, Stemmler B, *et al*. Cachexia and sarcopenia: mechanisms and potential targets for intervention. *Curr Opin Pharmacol* 2015;22:100–6.
- Blum D, Omlin A, Fearon K, *et al*. European Palliative Care Research Collaborative. Evolving classification systems for cancer cachexia: ready for clinical practice? *Support Care Cancer* 2010;18:273–9.
- Muscaritoli M, Anker SD, Argilés J, *et al*. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics”. *Clin Nutr* 2010;29:154–9.
- Argilés JM, Anker SD, Evans WJ, *et al*. Consensus on cachexia definitions. *J Am Med Dir Assoc* 2010;11:229–30.
- Rolland Y, van Kan G, Gillette-Guyonnet S, *et al*. Cachexia versus sarcopenia. *Curr Opin Clin Nutr Metab Care* 2011;14:15–21.
- Muscaritoli M, Molino A, Lucia S, *et al*. Cachexia: a preventable comorbidity of cancer. A T.A.R.G.E.T. approach. *Crit Rev Oncol Hematol* 2015;94:251–9.
- Kondrup J, Rasmussen HH, Hamberg O. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 2003;22:321–36.
- Sun SS, Chumlea WC, Heymsfield SB, *et al*. Development of bioelectrical impedance analysis prediction equations for body composition with the use of a multicomponent model for use in epidemiologic surveys. *Am J Clin Nutr* 2003;77:331–40.
- Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *JAGS* 2002;50:889–96.
- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, *et al*. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on Sarcopenia in older people. *Age Ageing* 2010;39:412–23.
- Jacquelin-Ravel N, Pichard C. Clinical nutrition, body composition and oncology: a critical literature review of the synergies. *Crit Rev Oncol Hematol* 2012;84:37–46.
- Paiva SI, Borges LR, Halpern-Silveira D, *et al*. Standardized phase angle from bioelectrical impedance analysis as prognostic factor for survival in patients with cancer. *Support Care Cancer* 2010;19:187–92.
- Prado CM, Baracos VE, McCargar LJ, *et al*. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine

- treatment. *Clin Cancer Res* 2009;15:2920–6.
24. Molino A, Formiconi A, Rossi Fanelli F, *et al.* Ghrelin: from discovery to cancer cachexia therapy. *Curr Opin Clin Nutr Metab Care* 2014;17:471–6.
 25. Mak RH, Cheung WW, Gertler A. Exploiting the therapeutic potential of leptin signaling in cachexia. *Curr Opin Support Palliat Care* 2014;8:352–7.
 26. Kim HJ, Kim HJ, Yun J, *et al.* Pathophysiological role of hormones and cytokines in cancer cachexia. *J Korean Med Sci* 2012;27:128–34.
 27. Wolf I, Sadetzki S, Kanety H, *et al.* Adiponectin, ghrelin, and leptin in cancer cachexia in breast and colon cancer patients. *Cancer* 2006;106:966–73.
 28. Kumar NB, Kazi A, Smith T, *et al.* Cancer cachexia: traditional therapies and novel molecular mechanism-based approaches to treatment. *Curr Treat Options Oncol* 2010;11:107–17.
 29. Madeddu C, Mantovani G, Gramignano G, *et al.* Advances in pharmacologic strategies for cancer cachexia. *Expert Opin Pharmacother* 2015;16:2163–77.