21. Gentleman RC, Carey VJ, Bates DM et al. Bioconductor: open software development for computational biology and bioinformatics. Genome Biol 2004; 5: R80.
22. Porzelius C, Binder H, Schumacher M. Parallelized prediction error estimation for evaluation of high-dimensional models. Bioinformatics 2009; 25: 827–829.
23. Yasrebi H. SurvJamda: an R package to predict patients' survival and risk assessment using joint analysis of microarray gene expression data. Bioinformatics 2011; 27: 1168–1169.
24. Schröder MS, Culhane AC, Quackenbush J et al. Survcomp: an R/Bioconductor package for performance assessment and comparison of survival models. Bioinformatics 2011; 27: 3206–3208.
25. Winter SC, Buffa FM, Silva P et al. Relation of a hypoxia metagene derived from head and neck cancer to prognosis of multiple cancers. Cancer Res 2007; 67: 3441–3449.
26. Eschrich SA, Pramana J, Zhang H et al. A gene expression model of intrinsic tumor radiosensitivity: prediction of response and prognosis after chemoradiation. Int J Radiat Oncol Biol Phys 2009; 75: 489–496.
27. Jung SH. Samples size calculation for microarray studies with survival endpoints. J Comput Sci Syst Biol 2013; 6: 177–181.
28. Slebos RJ, Yi Y, Ely K et al. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma. Clin Cancer Res 2006; 12: 701–709.
29. Resnick RM, Cornelissen MT, Wright DK et al. Detection and typing of human papillomavirus in archival cervical cancer specimens by DNA amplification with consensus primers. J Natl Cancer Inst 1990; 82: 1477–1484.
30. Yang X, Regan K, Huang Y et al. Single sample expression-anchored mechanisms predict survival in head and neck cancer. PLoS Comput Biol 2012; 8: e1002350.
31. Edén P, Ritz C, Rose C et al. "Good Old" clinical markers have similar power in breast cancer prognosis as microarray gene expression profilers. Eur J Cancer 2004; 40: 1837–1841.
32. Sorlie T, Tibshirani R, Parker J et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003; 100: 8418–8423.
33. Pramana J, Van den Brekel MW, van Velthuysen ML et al. Gene expression profiling to predict outcome after chemoradiation in head and neck cancer. Int J Radiat Oncol Biol Phys 2007; 69: 1544–1552.
34. Micheel CM, Nass SJ, Omenn GS, Editors; Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials; Board on Health Care Services; Board on Health Sciences Policy; Institute of Medicine; Evolution of translational OMICS: lessons learned and the path forward. (2012) The National Academies Press (Washington, D.C.)
35. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration. PLoS Med 2012; 9: e1001216.

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# Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model—a study based on data from an international multicentre project (EPCRC-CSA)

D. Blum[1,2*], G. B. Stene[1,2,3,†], T. S. Solheim[1,2], P. Fayers[1,4], M. J. Hjermstad[1,5], V. E. Baracos[6], K. Fearon[7], F. Strasser[1,8] & S. Kaasa[1,2], on behalf of Euro-Impact

*[1]European Palliative Care Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim; [2]Cancer Clinic, St Olavs Hospital, Trondheim University Hospital, Trondheim; [3]Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [4]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK; [5]Department of Oncology, Regional Centre for Excellence in Palliative Care, Oslo University Hospital, Ullevål, Oslo, Norway; [6]Department of Oncology, Division of Palliative Care Medicine, University of Alberta, Alberta, Canada; [7]Clinical and Surgical Sciences (Surgery), University of Edinburgh, Royal Infirmary, Edinburgh, UK; [8]Department of Internal Medicine and Palliative Center Cantonal Hospital, Oncological Palliative Medicine, Oncology, St Gallen, Switzerland*

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**Background:** Weight loss limits cancer therapy, quality of life and survival. Common diagnostic criteria and a framework for a classification system for cancer cachexia were recently agreed upon by international consensus. Specific assessment domains (stores, intake, catabolism and function) were proposed. The aim of this study is to validate this diagnostic criteria (two groups: model 1) and examine a four-group (model 2) classification system regarding these domains as well as survival.

*Correspondence to: David Blum, European Palliative Research Center, Department of Cancer Research and Molecular Medicine, NTNU, Faculty of Medicine, Trondheim N-7491, Norway. Tel: +47-728-26486; Fax: +47-728-26486; E-mail: david.blum@ntnu.no

†BD and SGB have contributed equally to this manuscript and are to be considered as joint first authors.

**Patients and methods:** Data from an international patient sample with advanced cancer ($N = 1070$) were analysed. In model 1, the diagnostic criteria for cancer cachexia [weight loss/body mass index (BMI)] were used. Model 2 classified patients into four groups 0-III, according to weight loss/BMI as a framework for cachexia stages. The cachexia domains, survival and sociodemographic/medical variables were compared across models.

**Results:** Eight hundred and sixty-one patients were included. Model 1 consisted of 399 cachectic and 462 non-cachectic patients. Cachectic patients had significantly higher levels of inflammation, lower nutritional intake and performance status and shorter survival. In model 2, differences were not consistent; appetite loss did not differ between group III and IV, and performance status not between group 0 and I. Survival was shorter in group II and III compared with other groups. By adding other cachexia domains to the model, survival differences were demonstrated.

**Conclusion:** The diagnostic criteria based on weight loss and BMI distinguish between cachectic and non-cachectic patients concerning all domains (intake, catabolism and function) and is associated with survival. In order to guide cachexia treatment a four-group classification model needs additional domains to discriminate between cachexia stages.

**Key words:** cancer, cachexia, classification, validation

## introduction

Cachexia affects 60%–80% of all advanced cancer patients [1], and its consequences are devastating as it decreases physical function and quality of life, and shortens survival [2]. Cancer cachexia is a complex condition that is not yet fully understood and there is no standard treatment available [3].

Traditionally, patients with a weight loss of more than 5% of pre-illness stable weight have been considered to have some degree of cachexia, but other cut-offs have also been used (e.g. >10%, 2%) [4]. A three-factor model incorporating weight loss (≥10%), low food intake (1500 kcal/day) and systemic inflammation (C-reactive protein ≥10 mg/l) was tested by Fearon et al. in 170 advanced cancer patients [5]. In this study, all three factors had to be applied in order to identify patients with both adverse function and shortened survival.

Recently, an international panel of cachexia experts initiated a formal consensus process to agree on a common definition and a framework for the development of a new classification system for cancer cachexia [6]. Weight loss, body mass index (BMI) and levels of muscle mass (sarcopenia) forms the basis of this consensus definition. Additionally, information about anorexia or reduced food intake, catabolic drive, muscle strength as well as physical, social and psychological function were proposed as important domains for a cancer cachexia classification system. It was furthermore agreed that cancer cachexia is to be considered a trajectory and can be classified into the stages, pre-cachexia, cachexia and refractory cachexia.

Staging of cancer cachexia is of importance in guiding treatment decisions and inclusions into clinical trials. Both ends of the cancer cachexia trajectory must be recognized. For instance treatments to prevent or delay the development of cancer cachexia should be initiated early in the trajectory, and thus a clear distinction of the pre-cachexia is needed. In refractory cachexia where the tumour is no longer responding to anticancer treatment and the life expectancy is short, the primary focus should be symptom management and general care according to end of life care guidelines.

These stages were not accurately defined and how these domains should be assessed and operationalized in a classification system remains unclear.

The overall aim of this study was to contribute to the development of a new classification system for cancer cachexia by examining two classification models based on information on weight loss and BMI: (i) a two-group model validating the diagnostic criteria and (ii) a four-group model as a preliminary framework for classifying cachexia into stages. The research questions asked were as follows:

- Is a four-group model better than a two-group model in terms of classifying patients into different stages of cachexia?
- How can factors representing the other key cancer cachexia domains (intake, catabolism and function) contribute to the classification?

## materials and methods

### patients and study design

Patients were recruited from an international multicentre study initiated by the European Palliative Care Research Collaborative (EPCRC) [7]. A cross-sectional data collection was conducted from October 2008 until December 2009 in palliative care in-and out-patient units, hospices and general oncology and medical wards in several European countries (Norway, UK, Austria, Germany, Switzerland, Italy, Canada and Australia). Patients were eligible if they were aged ≥18 years and had an incurable metastatic or locally advanced cancer diagnosis. Patients not able to complete assessments due to physical or cognitive impairment or language problems were excluded. The ethical authorities in all participating centres approved the study protocol, and all patients gave their written informed consent.

### data collection

Data were collected on touch-sensitive computers (HP Compaq TC4200 1200 tablet PCs made by Hewlett-Packard Development Company L.D.). Details on the lay-out and specifications for the computerized assessment have been presented by the EPCRC previously [8]. Data collection consisted of two parts: one to be completed by the study coordinators and the other part to be completed by the patients. A research assistant was available and provided help as necessary. All data were entered by tapping directly on the computer screen with an electronic pen.

### assessments

Demographic information (age, gender, CRP and date of death), cancer diagnosis (ICD-10), stage of disease (locally advanced versus metastatic), performance status [9] and current oncological treatment (chemotherapy

or not) was collected from the patients' medical records by the study coordinators.

Assessments of symptoms were performed using Edmonton Symptom Assessment System (ESAS) [10] which includes nine numerical ratings scales, scoring 0 (no problem) to 10 (worst possible problem), for the symptoms pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being and shortness of breath.

Information about stature (weight, height), weight loss last 6 months (in kg) and food intake past month (unchanged, changed or less than usual) was provided by the patients using questions from the Scored Patient-Generated Subjective Global Assessment (PG-SGA) [11].

### two-group classification model (model 1)

Patients were classified into two groups based on criteria from the international consensus [6]. Cachexia was weight loss >5% the past 6 months OR any degree of weight loss >2% the last 6 months + BMI <20 kg/m$^2$. Patients above or below these cut-offs were grouped as: cachexia and no cachexia.

### four-group classification model (model 2)

As a preliminary framework for the staging system for cancer cachexia proposed by the international consensus, a four-group model based on information about weight loss and BMI was used in this analysis. In this model, patients were classified into four weight loss groups (0–III) according to the following criteria:

'No cachexia (group 0)': weight change (± 1 kg) or weight gain
'Pre-cachexia (group I)': weight loss >1 kg, but <5%
'Cachexia (group II)': weight loss >5% the last 6 months, or weight loss >2% the last 6 month + BMI <20 kg/m$^2$
'Refractory cachexia (group III)': weight loss >15% last 6 months + BMI <23 kg/m$^2$ OR weight loss >20% last 6 months + BMI <27 kg/m$^2$.

To further explore the consensus framework definition of pre-cachexia, a weight loss model adding information from the cachexia domains catabolism (CRP < or >10) and intake (appetite ESAS >3) was tested in terms of survival (model 3).

### statistical analysis

Model 1 (two groups) was tested by group-wise comparison of cachectic versus non-cachectic patients with regards to items representing cachexia domains as well as a range of demographic and medical information. For continuous variables, an independent sample *t*-test was applied and a $\chi^2$ test for categorical variables. In model 2 (four groups), comparisons using a one-way analysis of variance (ANOVA), or a non-parametric equivalent (Kruskal–Wallis test). Ninety-five percent confidence intervals (95% CIs) and *P*-values are presented.

To explore the relationship between cachexia domains and classification model (model 2), candidate items that differed between the groups in the univariate analysis were entered into a multivariate logistic regression by forced entry, and the no cachexia group (group 0) acted as the reference group.

Univariate survival analysis was performed using the Kaplan–Meier method and Cox regression (log-rank tests) to compare survival curves for both models (model 1 and model 2) and for the pre-cachexia model (model 3). In this analysis, survival was defined as time between date of clinical assessment and death. Patients alive on 1 January 2011 were treated as censored.

## results

The EPCRC-CSA study included 1070 patients. Nineteen patients were excluded either because they withdrew consent ($n = 4$) or for technical failure ($n = 15$). Patients with missing data on body weight ($n = 86$) and survival ($n = 104$) were also excluded from the present study.

In total, 861 patients were subject to the final analyses. Mean age for all included patients was 62 years, 53% were males and the mean performance status was 71.7. BMI was 24.2 kg/m$^2$ and the average weight loss last six months was 3.9 kg. The most frequent diagnosis was cancer of the digestive organs (28%), followed by breast cancer (17%) and cancer of the respiratory organs (16%). The majority of patients suffered from metastatic disease and more than half of the patients were hospitalized (56%).

### two-group classification (model 1)

In model 1, 399 patients were classified as cachectic, while 462 patients were non-cachectic. The cachectic patients had a mean BMI 23.0 kg/m$^2$ and an average weight loss 9.8 kg, while the non-cachectic had a mean BMI of 25.3 kg/m$^2$ and an average weight gain 1.1 kg. A separate analysis for criteria WL >5% showed that by this criterion alone, 388 patients were classified as cachectic. Ninety-nine patients were classified as cachectic by the other diagnostic criteria WL >2% + BMI <20 kg/m$^2$. There was an overlap between these two criteria of 88 patients, leaving only 11 that were not classified by both.

Characteristics for the two groups in model 1 are shown in Table 1. In the cachectic patients, there were more males than females (59% versus 41%; $P < 0.01$). In cachectic patients, the most prevalent diagnosis was cancer of the digestive (30%) and respiratory (18%) organs. There were more in-patients among the cachectic patients (53% versus 47%, $P < 0.001$).

When comparing cachectic versus non-cachectic patients on items representative of the key cachexia domains, higher levels of CRP (44.8 versus 29.6 ml/g; $P < 0.001$) and appetite loss (3.9 versus 2.6; $P < 0.001$) and reduced food intake (58.6% versus 29.8%, $P < 0.001$) was observed for cachectic patients. Cachectic patients had lower scores on KPS than the non-cachectic patients (68.3 versus 74.5, $P < 0.001$).

### four-group classification (model 2)

As shown in Table 2, 147 patients were classified into pre-cachexia group (mean BMI 25.1 kg/m$^2$ and WL 2.4 kg), 305 into cachexia group (mean BMI 23.8 kg/m$^2$ and WL 7.9 kg) and 86 patients into refractory cachexia group (mean BMI 19.9 kg/m$^2$ and WL 16.8 kg). Three hundred twenty-three patients were classified into no cachexia group (mean BMI 25.4 kg/m$^2$ and weight gain of 2.8 kg).

Serum concentrations of CRP (catabolism domain) were similar in patients in the no cachexia and the pre-cachexia group (30.3 and 29.3 ml/g, respectively) and were significantly higher in the cachexia group (40.6 ml/g) and the refractory cachexia group (60.6 ml/g, $P < 0.001$).

The proportion of patients reporting a reduced food intake (eating less than usual) was significantly higher in pre-cachexia, cachexia and refractory cachexia groups (48%, 56% and 47%)

**Table 1.** Two-group classification model (model 1)

| Variables | Groups in model 1 | | | All patients in study |
|---|---|---|---|---|
| | No cachexia: no weight loss or low BMI | Cachexia: weight loss and low BMI | *P*-value* | |
| Number of patients | 462 | 399 | | 861 |
| Age, mean (95% CI), years | 62 (61–63) | 62 (61–63) | 0.850 | 62 (61–63) |
| Number of female within group (%) | 235 (59) | 166 (41) | 0.07 | 401 (47) |
| Performance status | | | | |
| Karnofsky score (KPS), mean (95% CI) | 74.5 (73.1–76.0) | 68.3 (66.7–70.0) | 0.001 | 71.7 (70.6–72.2) |
| Current medical situation, number (%) | | | | |
| In-patient | 226 (47) | 254 (53) | <0.001 | 480 (56) |
| Outpatient | 236 (62) | 145 (38) | <0.001 | 381 (44) |
| Diagnosis, number of yes within group (%) | | | | |
| Cancer of the head | 13 (48) | 14 (52) | | 27 (3) |
| Cancer of the digestive organs | 123 (51) | 119 (49) | | 242 (28) |
| Cancer of the respiratory organs | 65 (48) | 71 (52) | | 136 (16) |
| Malignant bone tumours | 3 (100) | 0 | | 3 (0) |
| Skin cancer including malignant melanoma | 18 (51) | 17 (49) | | 35 (4) |
| Malignant connective and soft tissue tumours | 17 (57) | 13 (43) | | 30 (4) |
| Breast cancer | 95 (65) | 51 (35) | | 146 (17) |
| Gynaecological cancer | 14 (64) | 8 (36) | | 22 (3) |
| Cancer of male genital organs | 46 (49) | 47 (51) | | 93 (11) |
| Urinary cancer | 25 (51) | 24 (49) | | 49 (6) |
| Tumours of the CNS | 11 (79) | 3 (21) | | 14 (2) |
| Malignant endocrine tumours | 1 (17) | 5 (83) | | 6 (1) |
| Secondary an ill-defined malignant tumours | 13 (59) | 9 (41) | | 22 (3) |
| Leukaemia and lymphomas | 17 (55) | 14 (45) | | 31 (4) |
| Multiple primary cancers | 1 (25) | (3 (75) | | 4 (1) |
| Current status of disease, number (%) | | | | |
| Advanced, non-metastatic | 74 (58) | 54 (42) | 0.500 | 128 (15) |
| Metastatic | 388 (53) | 345 (47) | 0.307 | 733 (85) |
| Current oncology treatment: number of yes within group (%) | | | | |
| Radiotherapy | 86 (47) | 98 (53) | 0.034 | 184 (21) |
| Chemotherapy | 247 (60) | 166 (40) | 0.001 | 413 (48) |
| Serum concentrations, mean (95% CI)[a] | | | | |
| CRP | 29.6 (24.1–35.2) | 44.8 (38.0–51.6) | 0.001 | 36.9 (32.5–41.3) |
| Haemoglobin | 12.1 (11.9–12.3) | 11.6 (11.4–11.8) | 0.001 | 11.9 (11.7–12.0) |
| Albumin | 38.0 (37.3–38.6) | 35.1 (34.4–35.7) | 0.001 | 36.7 (36.1–37.1) |
| Food intake, number of yes within group (%) | | | | |
| Unchanged | 275 (69) | 125 (31) | <0.001 | 400 (46) |
| More than usual | 58 (64) | 33 (36) | 0.089 | 91 (11) |
| Less than usual | 129 (35) | 241 (65) | <0.001 | 370 (43) |
| Symptoms, mean (95% CI) | | | | |
| Pain | 1.9 (1.7–2.1) | 2.4 (2.2–2.6) | 0.001 | 2.1 (2.0–2.3) |
| Fatigue | 3.3 (3.1–3.5) | 4.1 (3.8–4.3) | 0.001 | 3.6 (3.5–3.8) |
| Nausea | 0.9 (0.8–1.1) | 1.3 (1.1–1.6) | 0.004 | 1.1 (1.0–1.3) |
| Depression | 1.8 (1.6–2.0) | 2.0 (1.8–2.3) | 0.090 | 1.9 (1.7–2.1) |
| Anxiety | 2.0 (1.8–2.2) | 2.2 (1.9–2.4)) | 0.200 | 2.1 (1.9–2.2) |
| Drowsiness | 3.1 (2.9–3.3) | 3.6 (3.4–3.8) | 0.001 | 3.3 (3.2–3.5) |
| Appetite | 2.6 (2.3–2.8) | 3.9 (3.6–4.2) | 0.001 | 3.2 (3.0–3.4) |
| Feeling of well-being | 3.1 (2.9–3.3) | 3.7 (3.5–3.9) | 0.001 | 3.4 (3.2–3.5) |
| Shortness of breath | 1.8 (1.6–2.0) | 2.0 (1.8–2.3) | 0.200 | 1.9 (1.7–2.1) |

The table shows descriptive data on demographics, medical information and items representing key cachexia domains. Data are presented as means and 95% confidence intervals (95% CIs) for continuous variables and as frequencies (*n*) and proportions (%) for categorical variables.

[a]CRP ($n = 628$), haemoglobin($n = 737$), albumin ($n = 671$).

*In comparison to the two groups in the statistical analysis, an independent *t*-test was applied for continuous variables and for categorical variables, a $\chi^2$ test.

**Table 2.** Four-group classification model (model 2) based on weight loss and BMI

| Variables | No cachexia (Group 0) | Pre-cachexia (Group I) | Cachexia (Group II) | Refractory cachexia (Group III) | *P*-value* |
|---|---|---|---|---|---|
| Number of patients | 323 | 147 | 305 | 86 | |
| Age, mean (95% CI), years | 61 (59.3–62.1) | 64 (62.0–66.0) | 63 (61.5–64.0) | 60 (57.3–62.4) | 0.010 |
| Number of female within group (%) | 168 (52) | 70 (48) | 126 (41) | 37 (43) | 0.030 |
| Performance status | | | | | |
| Karnofsky score (KPS), mean (95% CI) | 74.7 (73.0–76.4) | 75.0 (72.6–77.4) | 68.2 (66.4–70.0) | 66.8 (63.4–70.2) | <0.001 |
| Current medical situation, number of yes within group (%) | | | | | |
| In-patient | 158 (33) | 78 (16) | 184 (38) | 60 (13) | <0.001 |
| Out-patient | 165 (43) | 69 (18) | 121 (32) | 26 (7) | <0.001 |
| Diagnosis, number of yes within group (%) | | | | | |
| Cancer of the head | 9 (33) | 4 (15) | 14 (52) | 0 | |
| Cancer of the digestive organs | 82 (34) | 41 (17) | 86 (36) | 33 (14) | |
| Cancer of the respiratory organs | 45 (33) | 19 (14) | 60 (44) | 12 (9) | |
| Malignant bone tumours | 2 (67) | 1 (33) | 0 | 0 | |
| Skin cancer including malignant melanoma | 13 (37) | 5 (14) | 13 (37) | 4 (11) | |
| Malignant connective and soft tissue tumours | 12 (40) | 5 (17) | 8 (27) | 5 (17) | |
| Breast cancer | 71 (49) | 27 (19) | 40 (27) | 8 (6) | |
| Gynaecological cancer | 11 (50) | 4 (18) | 3 (14) | 4 (18) | |
| Cancer of male genital organs | 32 (34) | 17 (18) | 37 (40) | 7 (8) | |
| Urinary cancer | 15 (31) | 11 (22) | 15 (31) | 8 (16) | |
| Tumours of the CNS | 7 (50) | 4 (29) | 2 (14) | 1 (7) | |
| Malignant endocrine tumours | 1 (17) | 0 | 4 (67) | 1 (17) | |
| Secondary an ill-defined malignant tumours | 10 (46) | 5 (28) | 6 (27) | 1 (5) | |
| Leukaemia and lymphomas | 12 (39) | 4 (13) | 14 (45) | 1 (3) | |
| Multiple primary cancers | 1 (25) | 0 | 2 (50) | 1 (25) | |
| Current status of disease, number of yes within group (%) | | | | | |
| Advanced, non-metastatic | 48 (38) | 25 (19) | 43 (34) | 12 (9) | <0.001 |
| Metastatic | 275 (37) | 122 (17) | 262 (36) | 74 (10) | <0.001 |
| Current oncology treatment, number of yes within group (%) | | | | | |
| Radiotherapy | 57 (31) | 34 (18) | 76 (41) | 17 (9) | 0.036 |
| Chemotherapy | 167 (40) | 79 (19) | 139 (34) | 28 (7) | 0.074 |
| Serum concentrations, mean (95% CI)[a] | | | | | |
| CRP | 30.3 (23.5–37.1) | 29.3 (21.2–37.3) | 40.6 (33.7–47.5) | 60.6 (2.9–78.4) | <0.001 |
| Haemoglobin | 12.1 (11.3–12.9) | 12.0 (11.7–12.3) | 11.7 (11.5–11.9) | 11.0 (10.6–11.5) | <0.001 |
| Albumin | 38.4 (37.6–39.2) | 37.6 (36.7–38.6) | 35.5 (34.8–36.2) | 32.9 (31.4–34.4) | <0.001 |
| Food intake, number of yes within group (%) | | | | | |
| Unchanged | 206 (52) | 68 (17) | 106 (26) | 20 (5) | <0.001 |
| More than usual | 48 (53) | 9 (10) | 27 (30) | 7 (8) | 0.010 |
| Less than usual | 69 (19) | 70 (19) | 172 (47) | 59 (16) | <0.001 |
| Symptoms, mean (95% CI) | | | | | |
| Pain | 2.1 (1.8–2.3) | 1.6 (1.3–1.9) | 2.4 (2.1–2.7) | 2.5 (2.0–3.0) | 0.003 |
| Fatigue | 3.2 (2.9–3.5) | 3.4 (3.1–3.8) | 3.9 (3.6–4.2) | 4.6 (4.1–5.2) | <0.001 |
| Nausea | 1.0 (0.8–1.2) | 0.8 (0.6–1.1) | 1.2 (1.0–1.5) | 1.6 (1.1–2.2) | 0.009 |
| Depression | 1.7 (1.5–1.9) | 1.9 (1.5–2.3) | 2.0 (1.8–2.3) | 2.0 (1.5–2.5) | 0.291 |
| Anxiety | 1.9 (1.7–2.1) | 2.1 (1.7–2.5) | 2.1 (1.8–2.4) | 2.3 (1.8–2.9) | 0.377 |
| Drowsiness | 3.0 (2.7–3.3) | 3.2 (2.8–3.6) | 3.6 (3.4–3.9) | 3.7 (3.2–4.3) | 0.006 |
| Appetite | 2.5 (2.2–2.8) | 2.9 (2.4–3.4) | 3.7 (3.3–4.0) | 4.6 (3.9–5.2) | <0.001 |
| Feeling of well-being | 3.1 (2.9–3.4) | 3.1 (2.7–3.5) | 3.7 (3.4–3.9) | 3.9 (3.4–3.5) | 0.003 |
| Shortness of breath | 1.7 (1.5–2.0) | 1.9 (1.6–2.3) | 2.1 (1.8–2.4) | 1.8 (1.3–2.3) | 0.325 |

The table shows descriptive data on demographics, medical information and items representing key cachexia domains. Data are presented as means and 95% confidence intervals (95% CIs) for continuous variables and as frequencies (*n*) and proportions (%) for categorical variables.

[a]CRP ($n = 628$), hemoglobin ($n = 737$), albumin ($n = 671$).

*In comparison to the four groups in the statistical analysis, an analysis of variance (ANOVA) was applied for continuous variables and for categorical variables, a Kruskal–Wallis test.

compared with the no-cachexia group (22%; $P < 0.001$). Compared with the no-cachexia group, mean scores on appetite loss were significantly higher in the pre-cachexia group (2.9), cachexia group 2 (3.9) and the refractory cachexia group (4.6, $P < 0.001$) than in the non-cachexia group.

The mean performance status (KPS) was significantly lower in the cachexia group (68.2) and the refractory cachexia group (66.8) compared with scores in the no-cachexia and the pre-cachexia group (75.0; $P < 0.001$).

Results from the multivariate logistic regression of candidate items are presented in the appendix. Food intake (eating less than usual) was a significant item for all cachexia groups. Appetite loss was a significant item in terms of classifying refractory cachexia ($P < 0.05$). CRP was not a significant item for the classification into any of the three cachexia groups but a tendency could be seen for the refractory cachexia group ($P < 0.065$).

### survival

The median overall survival for all patients was 207 days. In model 1, the median survival for patients classified as cachectic was shorter than for non-cachectic patients (139 versus 269 days; $P < 0.001$). There was no significant survival difference, between no cachexia and pre-cachexia (Figure 1).

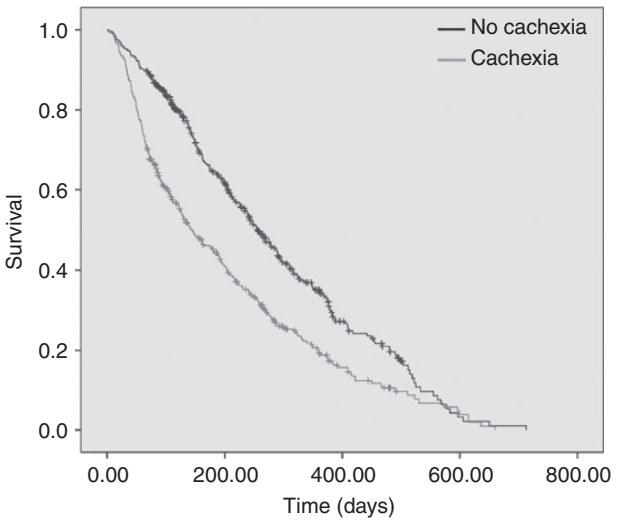
A definition of pre-cachexia in a model adding additional factors representing the cachexia domains (model 3) was tested. By adding CRP (>10 ml/g) and appetite loss (ESAS >3) to the <5% weight loss, the median survival was significantly shorter for patients with all three cachexia factors present compared with those with only 0%–5% weight loss (143 versus 377 days; $P < 0.001$).

## discussion

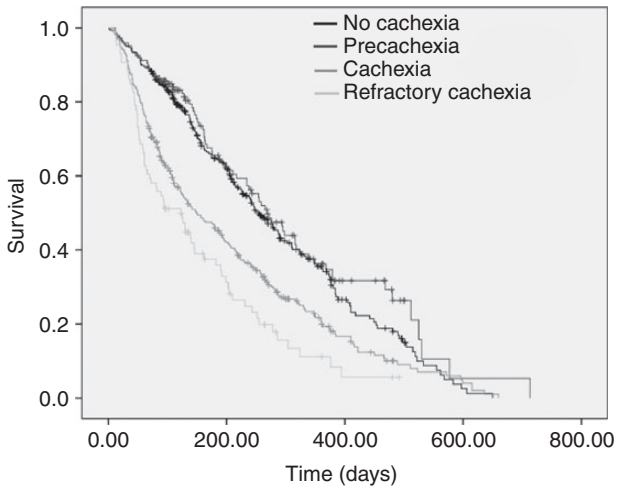
This study shows that patients with cachexia are clearly distinct from patients with no cachexia with regards to the key cachexia domains (stores, nutrition, catabolism and function) and survival (model 1). This underlines the legitimacy of the established diagnostic criteria for cancer cachexia based on weight loss/BMI. However using weight loss/BMI alone is not sufficient when classifying cancer cachexia from pre-cachexia to refractory cachexia (model 2).

In terms the cachexia characteristics, there appears to be little distinction between the no cachexia and pre-cachexia; this finding is also supported by the survival curves. Classification of pre-cachexia might be better based on additional items. A possible explanation for this is the inaccuracy of body weight measures and lack of information on sarcopenia. If only weight loss is taken into account, some patients suffering from slight muscle loss may be misclassified, because muscle loss can be masked due to fluid retention [12]. A measure of muscle loss by an objective method such as computed tomography, dual-energy X-ray, magnetic resonance imaging may be essential to specifically diagnose pre-cachexia but these methods have so far not been easily available in cancer clinics [13].

The refractory stage can be considered as cachexia with very poor prognosis, as it is the cancer disease that defines this stage. Unfortunately, there is no simple marker for tumour activity or




Overall 861; Number of censored = 281, survival (SE) 207d (10.6)
No cachexia: *n* = 462; dead 270; Survival (SE) 255d (14.5)
Cachexia: *n* = 399; dead 310; Survival (SE) 142f (14.1), *P < 0.001*
d = days




No cachexia: *n* = 323, dead = 194, survival (SE) = 255 (18.7)
Precachexia: *n* = 147, dead78, survival (SE) = 269d (24.0), *P = 0.204*
Cachexia: *n* = 305, dead = 239, survival (SE) = 150d (18.1), *P < 0.001*
Refractory: *n* = 86, dead = 69, survival (SE) = 123d (23.5), *P < 0.001*

**Figure 1.** Kaplan–Meyer survival plot for two-group (model 1) and four-group (model 2) classification models.

dynamics readily obtainable, which impedes an easily applicable classification in clinical practice.

Since the publication of the international consensus, two other proposals for classification of patients into cachexia stages have been made. The first, the Cachexia Score (CASCO) weights and sums five different factors: body weight and lean body mass loss; anorexia; inflammatory, immunological and metabolic disturbances; physical performance and quality of life [14]. A validation of the score is awaited. A barrier for the use in clinics may be the rarely available biochemical tests and missing cut-offs.

The clinical relevance of the consensus classification has been evaluated in 207 cancer patients by Vigano et al. [15]. In this

pilot study, patients were classified into the three stages by two independent researchers according to different combinations of clinical criteria and biological measurements. The final classification was mainly performed by subjective judgement, which is not easily replicated. Similar to the present study, pre-cachexia was not clearly distinctive but the other stages correlated with differences in patient-reported outcomes and survival. Both of these studies underline the importance of classification to guide treatment, but also the lack of simple indicators to classify patients into the stages. In clinical practice, it is important to have easily applicable measurements/assessments which allow bedside diagnostics.

A recent publication highlighted the association of cancer cachexia with symptoms, function, quality of life and survival in a cluster analysis. Prevalence of cachexia varied highly according to different definitions, which indicated once more the need for a classification with clear cut-offs [16].

### limitations

A main limitation is that there was no measurement of muscle mass available. In the nutrition domain, the simple answer of 'eating less than usual' was considered to be sufficiently precise to measure decreased nutritional intake, even though this PG-SGA question has not been validated for this comparison.

In the catabolism domain, CRP was used as the main item as it is the most robust biomarker for cachexia inflammation [4]. CRP is indeed a marker for systemic inflammation, but is neither specific for cancer, cachexia or for tumour activity as it can be influenced by other factors such as infections. Due to the inclusion criteria (computerized assessment), the population of the study is younger and fitter than the average cancer population.

### conclusion

In a large international cohort of advanced cancer patients, weight loss and BMI clearly distinguish between non-cachectic and cachectic patients both with regards to all the available domains proposed by the international consensus and with survival. Exploring the possibility to classify patients into four groups representing cachexia stages, using weight loss and BMI only, provides some indication of a possible distinct refractory cachexia group. The pre-cachexia stage might be better defined by additional factors representing the cachexia domain, for instance CRP and appetite loss. A clear definition of pre-cachexia is needed, especially because this group is the target of intervention trials. The next steps in the validation of a cachexia classification should quantify additional factors and investigate the role of muscle mass measurement.

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## disclosure

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## references

1. Baracos VE. Pitfalls in defining and quantifying cachexia. J Cachexia Sarcopenia Muscle 2011; 2: 71–73.
2. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle 2010; 1: 1–5.
3. Yavuzsen T, Davis MP, Walsh D et al. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol 2005; 23: 8500–8511.
4. Blum D, Omlin A, Baracos VE et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol 2011; 80: 114–144.
5. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006; 83: 1345–1350.
6. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12: 489–495.
7. Kaasa S, Loge JH, Fayers P et al. Symptom assessment in palliative care: a need for international collaboration. J Clin Oncol 2008; 26: 3867–3873.
8. Hjermstad MJ, Lie HC, Caraceni A et al. Computer-based symptom assessment is feasible in patients with advanced cancer: results from an International Multicenter Study, the EPCRC-CSA. J Pain Symptom Manage 2012; 44: 639–54.
9. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980; 45: 2220–2224.
10. Bruera E, Kuehn N, Miller MJ et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991; 7: 6–9.
11. Detsky AS, McLaughlin JR, Baker JP et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987; 11: 8–13.
12. Martin L, Birdsell L, Macdonald N et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013; 31: 1539–1547.
13. Strasser F. Diagnostic criteria of cachexia and their assessment: decreased muscle strength and fatigue. Curr Opin Clin Nutr Metab Care 2008; 11: 417–421.
14. Argiles JM, Lopez-Soriano FJ, Toledo M et al. The cachexia score (CASCO): a new tool for staging cachectic cancer patients. J Cachexia Sarcopenia Muscle 2011; 2: 87–93.
15. Vigano A, Del Fabbro E, Bruera E et al. The cachexia clinic: from staging to managing nutritional and functional problems in advanced cancer patients. Crit Rev Oncog 2012; 17: 293–304.
16. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer 2013; 21: 1569–77.

## appendix 1

**Table A1.** Logistic regression for the four-group model (model 2)

| Domains | Group I (pre-cachexia) B(SE) | $e^B$ | Group II (cachexia) B(SE) | $e^B$ | Group III (refractory cachexia) B(SE) | $e^B$ |
|---|---|---|---|---|---|---|
| Intercept | −1.33 (0.86) | | 0.87 (0.65) | | −2.16* (1.07) | |
| Catabolism | | | | | | |
| C-reactive protein mg/l | −0.16 (0.20) | 0.9 | 0.07 (0.17) | 1.1 | 0.48 (0.26) | 1.6 |
| Nutrition | | | | | | |
| Food intake: eating less than usual | 1.33** (0.46) | 3.8 | 1.15** (0.34) | 3.1 | 1.44* (0.59) | 4.2 |
| Nutition | | | | | | |
| ESAS appetite | −0.02 (0.05) | 1.0 | 0.07 (0.04) | 1.1 | 0.12* (0.06) | 1.1 |
| Function | | | | | | |
| ESAS fatigue | −0.01 (0.06) | 1.0 | 0.05 (0.05) | 1.1 | 0.12 (0.07) | 0.9 |
| ESAS feeling of well-being | −0.12 (0.07) | 0.9 | −0.05 (0.05) | 1.0 | −0.14 (0.08) | 1.0 |
| Function | | | | | | |
| Karnofsky Performance Status | 0.01 (0.01) | 1.0 | −0.02** (0.01) | 1.0 | −0.01 (0.01) | 1.0 |

[a]Group 0 (no cachexia) is the reference category.
*$P < 0.05$, **$P < 0.01$.

## appendix 2

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## collaborators

Van den Block Lieve[a], Meeussen Koen[a], Brearley Sarah[e], Caraceni Augusto[g], Cohen Joachim[a], Costantini Massimo[h], Francke Anneke[b], Harding Richard[c,d], Higginson Irene J[c,d], Kaasa Stein[f], Linden Karen[k], Miccinesi Guido[i], Onwuteaka-Philipsen Bregje[b], Pardon Koen[a], Pasman Roeline[b], Pautex Sophie[j], Payne Sheila[e], Deliens Luc[a,b]

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