Chapter 5

Cancer cachexia: identification by clinical assessment versus international consensus criteria

Anne van der Werf
Querijn N.E. van Bokhorst
Marian A.E. de van der Schueren
Henk M.W. Verheul
Jacqueline A.E. Langius

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Abstract

Background: Cancer cachexia is associated with poorer outcomes and is often diagnosed by the Fearon criteria. Oncologist clinically identify cachexia based on a patient’s presentation. The aim of this study was to evaluate agreement between these identification methods and to study associations with outcomes in patients with metastatic colorectal cancer.

Methods: Fearon criteria comprised weight loss >5% OR weight loss >2% with either BMI <20 kg/m² or sarcopenia (determined by CT-imaging). Clinical assessment by the oncologist was based on the patient’s clinical presentation. Agreement was tested with Kappa. Associations with treatment tolerance and progression free survival (PFS) were tested with logistic regressions and Cox proportional hazards, respectively.

Results: Of 69 patients, 52% was identified cachectic according to the Fearon criteria and 9% according to clinical assessment. Agreement between both methods was slight (Kappa 0.049, p=0.457). Clinically cachectic patients had a shorter PFS than clinically non-cachectic patients (HR 3.310, p=0.016). No other differences in outcomes were found between cachectic versus non-cachectic patients using both methods.

Conclusion: Agreement between cancer cachexia identification by clinical assessment versus Fearon criteria was slight. Further improvement is necessary to identify cachectic patients, who are at risk of poorer outcomes and may benefit from targeted cachexia interventions.

Keywords: Cachexia, cancer, criteria, clinical assessment, Fearon
Introduction

Cancer cachexia is a syndrome characterized by loss of skeletal muscle mass due to reduced food intake, systemic inflammation and metabolic changes\(^1\). It is associated with reduced quality of life, treatment tolerance and survival\(^2\)-\(^{11}\). Although its relevance has been shown, there is no agreement on the criteria defining cancer cachexia. Proposed definitions vary in criteria, some focus on weight loss and body composition, while others incorporate additional factors like energy intake, fatigue and inflammatory markers\(^1,12\)-\(^{14}\). When different diagnostic criteria are used within the same population, the prevalence of cachexia varies from 12-85\%\(^{13}\).

International consensus criteria that are often used in research were proposed by Fearon et al (2011). They defined cancer cachexia as unintentional weight loss >5% over the past 6 months OR a body mass index (BMI) <20 kg/m\(^2\) and any degree of weight loss >2% OR sarcopenia and any degree of weight loss >2\%\(^1\). A limitation of these criteria is that assessment of muscle mass is time consuming and not always feasible in routine clinical care.

In a survey among oncologists, 69\% of the oncologists identified themselves as the profession most likely to identify cancer cachexia\(^15\). Although clinical assessment of cachexia by the oncologist is not a validated method, it is known that oncologists consider weight loss, loss of appetite, muscle wasting, changes in physical appearance and extreme fatigue, among other criteria, as part of cancer cachexia\(^15\)-\(^{17}\). Taking this into account, a patient’s clinical presentation might provide an easily assessable indication to evaluate whether a patient is cachectic and has poorer prognosis. However, identifying cachexia by clinical assessment has never been compared to the Fearon et al cachexia criteria. Therefore, the aim of this study is to evaluate agreement between cancer cachexia identification according to clinical assessment and the Fearon et al criteria. Furthermore, the association of both methods with treatment tolerance and with progression free survival will be assessed.

Methods

Study design

This study is a sub-study of a randomized controlled trial (RCT) evaluating the effect of individualized nutritional counseling and physical activity on skeletal muscle mass during first-line chemotherapy in patients diagnosed with metastasized colorectal cancer (mCRC)\(^{18}\). Patients were eligible for study participation if they were diagnosed with mCRC, were scheduled for first-line chemotherapy with capecitabine monotherapy, capecitabine
and oxaliplatin (CAPOX) or infusional 5-fluorouracil and oxaliplatin (FOLFOX) and had a World Health Organization performance score of 0-2. After enrolment patients were randomised between intervention, comprising nutritional counselling and physical activity recommendation from the first cycle of chemotherapy, and usual care. Ethics approval for the study was obtained from the Medical Ethical Committee of the VU University Medical Center and the study was conducted according to the principles of the Declaration of Helsinki (64th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO, 1-3-2006). All patients gave informed consent prior to study inclusion.

For the current sub-study, baseline data including performance status, laboratory data and disease characteristics, were used, as well as chemotherapy data from the first 3-4 cycles to evaluate treatment tolerance and data from follow-up visits to evaluate progression free survival.

Cancer cachexia

Cachexia was diagnosed prior to first the cycle of chemotherapy using two methods: assessment based on the Fearon et al criteria and clinical assessment by the oncologist. Cachexia according to the Fearon et al\textsuperscript{1} was defined by:

- Weight loss >5\% over 6 months prior to baseline OR
- BMI <20 kg/m\textsuperscript{2} AND any degree of weight loss >2\% over 6 months prior to baseline OR
- Low muscle mass measured on a single CT-slice according to the cut-offs defined by Martin et al\textsuperscript{10} AND any degree of weight loss >2\% over 6 months prior to baseline.

Clinical assessment comprised the oncologists’ opinion based on the patient’s clinical presentation. The treating oncologist was asked whether the patient was considered being clinically cachectic (yes/no)? The oncologists were not further questioned on their motivation to consider a patient cachectic or not and they were not specifically asked to identify cachexia symptoms such as weight loss or fatigue, in order to not bias their opinion.

Body weight

Self-reported weight at baseline and 6 months prior to baseline was inquired by a research assistant. Weight was corrected for clothes or clothes and shoes (1.6 and 2.0 kg for men and 1.0 and 1.3 kg for women, respectively)\textsuperscript{19}.  

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Because the difference between hospital measured weight and self-reported weight in patients in which both values were available was negligible (n=63, mean difference 0.05 kg), the baseline hospital measured weight was used if baseline self-reported weight was missing (n=3).

Muscle mass
Skeletal muscle area (SMA, cm²) was analyzed by a trained researcher using a single CT slice at the level of the third lumbar vertebra. Skeletal muscles at this level were identified based on anatomical features and quantified using Hounsfield units with thresholds for skeletal muscle tissue from −29 to +150. The sum of the indicated muscle pixels was summed to compute SMA\(^{20,21}\). Scans were analyzed using SliceOmatic software V5.0 (Tomovision, Canada). SMA was adjusted for height\(^2\) resulting in skeletal muscle index (SMI, cm\(^2\)/m\(^2\)). Because the SMI cut-offs for sarcopenia used by Fearon et al in 2011 were based on an obese population (52.4 cm\(^2\)/m\(^2\) in men and 38.5 cm\(^2\)/m\(^2\) in women)\(^{11}\), more recently published cut-offs derived from a population of both non-obese and obese patients were used. These cut-off values were defined as an SMI below 43.0 cm\(^2\)/m\(^2\) in men with a BMI <25.0 kg/m\(^2\), 53.0 cm\(^2\)/m\(^2\) in men with a BMI ≥25.0 kg/m\(^2\) and 41.0 cm\(^2\)/m\(^2\) in women\(^{10}\).

A sensitivity analysis was done using the former cut-off values.

Treatment tolerance
Start dose of chemotherapy was compared to standard dose and reasons for a reduced start dose were recorded. Treatment tolerance was defined as relative dose intensity (RDI). This is a measure taking both the dose index (DI) and time index (TI) into account. The dose index was calculated by dividing the total delivered dose by the total standard dose. In case of a reduced start dose because of dihydropyrimidine dehydrogenase (DPD)-deficiency, this dose adapted to DPD activity was considered as 100% (standard dose). The time index was defined as the planned duration divided by the actual duration of the given cycles. The RDI (%) was calculated using the formula RDI = DI x TI x 100. For the treatment schedules consisting of multiple drugs, indices were calculated for each single drug and the mean value of these indexes was used in the analysis\(^{22,23}\). For CAPOX and capecitabine the first 3 cycles were analyzed and for FOLFOX the first 4 cycles were analyzed. When chemotherapy was stopped early because of toxicity/patient condition, the planned cycles were included in the analyses. When chemotherapy was stopped early because of patient preference (without medical indication),
only the given cycles were analyzed, with a minimum of 2 cycles. RDI was dichotomized into RDI ≤90% and RDI >90% for analyses.

**Progression free survival**

Progression free survival was defined as the time period between baseline (i.e. just before the start of first-line chemotherapy) and the date of disease progression or death. Disease progression was defined as radiological progression according to the Response Evaluation Criteria In Solid Tumors (RECIST) or clinical progression leading to discontinuation of first-line treatment\textsuperscript{24,25}. If patients had been recently included in the RCT and therefore had not had a follow-up visit, they were excluded for the progression free survival analyses. Overall survival was not evaluated because most patients had been included in the RCT in the recent 2 years and therefore follow-up time was limited.

**Statistics**

Differences in patient characteristics between non-cachectic and cachectic patients were analyzed using independent t-tests, χ²-tests and Mann-Whitney U tests where applicable. To assess agreement between both identification methods of cachexia, Cohen’s Kappa was used, which indicates measurement agreement (<0.00 poor agreement, 0.00–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement and 0.81–1.00 almost perfect agreement\textsuperscript{26}). The association between both cachexia assessments with RDI was studied using logistic regression with adjustment for treatment allocation within the RCT. Odds ratios were reported, including 95% confidence interval (95% CI) and p-value. This was done for all patients, including those with a reduced start dose, and separately only for patients starting with a standard treatment dose. To compare progression free survival between non-cachectic and cachectic patients, Kaplan-Meier curves were plotted and differences between the curves were tested with log-rank tests. Cox proportional hazards analyses were performed to test the associations between cachexia and progression free survival, adjusted for treatment allocation.

**Results**
From the 74 patients within the database, 69 had complete data to be included in the analysis of the agreement between the Fearon et al criteria and clinical assessment of cachexia. Follow-up data were available for 66 patients. From 4 of these patients, treatment tolerance could not be assessed (figure 1).

**Patients in database**
(n = 74)

Excluded
- No subjective cachexia assessment (n = 5)

**Inclusion Agreement between clinically and objectively diagnosed cancer cachexia**
(n = 69)

Excluded (n = 3)
- Chemotherapy never started/switch (n = 1)
- Lost to follow-up (switch hospital) (n = 1)
- No follow-up visit yet (n = 1)

**Follow-up data available**
(n = 66)

Excluded (n = 4)
- Chemotherapy stopped after 1st cycle, not for medical reasons (n = 3)
- First 3-4 cycles of chemotherapy not yet completed (n = 1)

**Inclusion Association of cancer cachexia with treatment tolerance**
(n = 62)

**Inclusion Association of cancer cachexia with progression free survival**
(n = 66)

**Figure 1** Study flowchart

*Population*
The mean age of the patients was 65 (±11) years old and 67% was male. Most patients had a performance status of 0 or 1. Mean BMI was 25.7 (±4.1) kg/m² and mean weight loss in the 6 months prior to baseline was 3.6 (±7.7) %.

An overview of all relevant baseline characteristics is shown in table 1.

| Table 1 Baseline characteristics for the total study population and for cachectic versus non-cachectic patients |
|------------------------------------|---------------------------------|-----------------|-----------------|------------------------------------|---------------------------------|-----------------|-----------------|
|                                    | Total (n=69)                    | Fearon et. al criteria (n=36) | Clinical assessment (n=63) |                                    |                                 |                         |
| Age (years)                        | 65 ± 11                         | 66 ± 11                      | 65 ± 11                      | 0.661                              | 69 ± 11                        | 66 ± 11                      | 0.444 |
| Gender male                        | 46 (67%)                        | 24 (67%)                     | 22 (67%)                     | 1.000                              | 4 (67%)                        | 42 (67%)                     | 1.000 |
| WHO performance score*             |                                 |                               |                               | 0.123                              |                                 |                         |
| 0                                  | 27 (40%)                        | 12 (33%)                     | 15 (47%)                     | 0 (0%)                             | 27 (44%)                       | 6 (100%)                     | 33 (53%) |
| 1                                  | 39 (57%)                        | 24 (67%)                     | 15 (47%)                     | 6 (100%)                           | 33 (53%)                       | 2 (3%)                       | 0.087 |
| 2                                  | 2 (3%)                          | 0 (0%)                       | 2 (6%)                       | 0 (0%)                             | 2 (3%)                         | 0.087 |
| Charlson comorbidity index         | 0 [0-1]                         | 0 [0-1]                      | 1 [0-1]                      | 0.278                              | 1 [0-1]                        | 0 [0-1]                      | 0.862 |
| C reactive protein (mg/L)          | 20 [7-106]                      | 36 [8-73]                    | 8 [3-35]                     | 0.007                              | 52 [20-80]                     | 15 [5-59]                    | 0.220 |
| Carcinoembryonic antigen (μg/L)    | 16 [5-61]                       | 47 [7-149]                   | 13 [7-72]                    | 0.216                              | 149 [10-1110]                  | 19 [7-80]                    | 0.112 |
| Body mass index (kg/m²)            | 25.7 ± 4.1                      | 24.7 ± 3.3                   | 26.7 ± 4.7                   | 0.042                              | 22.2 ± 3.7                     | 26.0 ± 4.0                   | 0.032 |
| Weight change recent 6 months (%)  | 3.6 ± 7.7                       | -9.1 ± 5.7                   | 2.4 ± 4.4                    | <0.001                             | -6.9 ± 8.3                     | -3.3 ± 7.7                   | 0.286 |
| Skeletal muscle index (cm²/m²)     |                                 |                               |                               |                                    |                                 |                         |
| Male                               | 45.7 ± 6.7                      | 45.2 ± 7.1                   | 46.1 ± 6.5                   | 0.656                              | 42.0 ± 6.5                     | 46.0 ± 6.7                   | 0.262 |
| Female                             | 39.1 ± 5.0                      | 38.5 ± 4.5                   | 39.7 ± 5.6                   | 0.574                              | 31.6 ± 2.0                     | 39.8 ± 4.6                   | 0.023 |
| Below sex-specific cut-off         | 55 (80%)                        | 29 (81%)                     | 26 (79%)                     | 0.855                              | 6 (100%)                       | 49 (78%)                     | 0.196 |
| Start treatment dose (%)           | 100 [100-100]                   | 100 [100-100]                | 100 [96-100]                 | 0.946                              | 100 [75-100]                   | 100 [100-100]                | 0.578 |
| Start treatment reduced dose       | 16 (24%)                        | 8 (22%)                      | 8 (24%)                      | 0.868                              | 2 (33%)                        | 14 (22%)                     | 0.738 |

Table 1 Continued
Cancer cachexia

In total 36 patients (52%) were cachectic based on the Fearon et al criteria. Of these patients, 22 (61%) fulfilled more than one of the Fearon et al criteria, mostly >5% weight loss in the previous 6 months and a SMI below the sex-specific cutoff combined with >2% weight loss (figure 2).

<table>
<thead>
<tr>
<th>QoL function scales</th>
<th>Total (n=69)</th>
<th>Fearon et. al criteria (n=69)</th>
<th>Clinical assessment (n=63)</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>83 [67-100]</td>
<td>73 [67-93]</td>
<td>93 [67-100]</td>
<td>0.066</td>
<td>60 [40-80]</td>
</tr>
<tr>
<td>Role functioning</td>
<td>67 [50-100]</td>
<td>67 [50-83]</td>
<td>83 [50-100]</td>
<td>0.112</td>
<td>50 [17-100]</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>83 [83-100]</td>
<td>73 [73-100]</td>
<td>83 [83-100]</td>
<td>0.816</td>
<td>92 [83-100]</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation, median [interquartile range] or number (%)

Abbreviations: WHO - world health organization; QoL - quality of life.

Missing data: WHO performance score n=1 (WHO 0-1 but not further specified), C reactive protein n=11, Carcinoembryonic antigen n=4, QoL function scales: physical n=5; role n=6; emotional n=7; cognitive n=4, QoL symptom scales/items: fatigue n=6, appetite loss n=4, perceived health n=4, perceived QoL n=4.

**Figure 2** Frequency of criteria for cachexia according to the Fearon et al criteria. In total 36 out of 69 patients fulfilled one or more of the Fearon et al criteria for cachexia.
Sensitivity analysis using the SMI cut-off values based on the original, obese population\textsuperscript{11} resulted in exactly the same population fulfilling the Fearon et al criteria. Six patients (9\%) were cachectic according to clinical assessment by the oncologist. Agreement between both methods was slight (table 2, Kappa 0.049, 95\% CI -0.079-0.176, p=0.457).

Cachectic patients according to Fearon et al had a significantly higher C reactive protein, lower BMI, a higher percentage of weight loss and lower perceived health and perceived quality of life compared to non-cachectic patients. Clinically cachectic patients had a lower BMI, a lower SMI (only significant in females) and lower quality of life scores for physical function, emotional functioning, perceived health and perceived quality of life.

**Table 2** Cancer cachexia – agreement between identification by clinical assessment versus international consensus criteria

<table>
<thead>
<tr>
<th></th>
<th>Cachectic according to clinical assessment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Cachectic according to Fearon et. al criteria</td>
<td>4</td>
<td>32</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>31</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>63</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

Kappa 0.049, 95\% CI -0.079–0.176, p=0.457

**Treatment tolerance**

Of the 62 patients of whom RDI could be assessed, 47 (76\%) started treatment with a reduced dose. Reasons for dose reduction of the first cycle were related to the patient’s condition (n=10), laboratory abnormalities (liver function or hemoglobin, n=3), comorbidity (enterocutaneous fistula n=1) and as part of a desensitization schedule (n=1). Start of treatment with a reduced dose was not related to cachexia according to the Fearon et al criteria nor to clinical assessment (table 1).

Median RDI was 96 [75-100] \% and 47\% of the patients (n=29) had a RDI ≤90\%. Of the patients who were cachectic according to the Fearon et al criteria (n=33), 48\% had a RDI ≤90\%, compared to 45\% of the non-cachectic patients (n=29). Of the clinically cachectic patients (n=5), 80\% had a RDI ≤90\%, which was 44\% in the clinically non-cachectic patients (n=57). There was no significant difference in the treatment tolerance between cachectic versus non-cachectic patients using either of the two methods (odds for RDI >90\%: Fearon et al criteria 0.917, 95\% CI 0.331-2.537, p=0.867; clinical assessment 0.201, 95\% CI 0.021-1.923, p=0.164). When only patients starting with a standard treatment dose (n=47) were analyzed, comparable results were found (odds for RDI >90\%: objective assessment 0.804, 95\% CI 0.224-2.886, p=0.738; clinical assessment 0.202, 95\% CI 0.016-2.520, p=0.214).
Progression free survival

In patients who had disease progression within the study period (n=52, 79%), median progression free survival was 220 [108-294] days. Median follow-up time of the censored patients (n=14, 21%) was 198 [137-298] days. Using the Fearon et al criteria, cachectic (n=34) versus non-cachectic (n=32) patients did not have different progression free survival curves (p=0.389, figure 3a) or hazard ratios for disease progression (HR 1.311, 95% CI 0.753-2.284, p=0.339). The progression free survival curve for patients who were clinically classified cachectic (n=6) was significantly different from patients not clinically cachectic (n=60) (p=0.023, figure 3b). Progression free survival was significantly shorter for patients who had been identified cachectic clinically (HR 3.310, 95% CI 1.252-8.748, p=0.016).

Discussion

The prevalence of cancer cachexia was 52% according to the Fearon et al criteria and 9% when identified by clinical assessment. Agreement between both methods was slight. Previous studies have reported proportions of cancer cachexia using different criteria as well. Using the Fearon et al criteria, the prevalence of cachexia was 55% in patients with stage IV colorectal cancer (n=75) \(^4\), which is in line with the prevalence found in the current study. Studies in other populations showed higher numbers: the prevalence was 85% in palliative care patients
In patients with various cancer types and stages \( (n=167) \) 70% developed cancer cachexia at some time during the study period of 1 year\(^{28} \). In these studies, cachexia prevalence was higher using the Fearon et al criteria compared to other criteria including C reactive protein, dietary intake, fatigue and/or muscle strength. Significant associations between cachexia according to the Fearon et al criteria with overall survival were found (HR 1.3\(^{13} \) till 1.8\(^{28} \)), however other cachexia criteria were more predictive for survival (HR 1.4\(^{13} \) till 3.3\(^{28} \)). While other studies indicated that cachexia according to the Fearon et al criteria was associated with overall survival, no association with progression free survival was found in the current study. This could be explained by the fact that most cachectic patients may be fit enough to complete first-line chemotherapy, while further-line treatment is hampered by cumulative toxicity and by a patient’s poor physical condition, resulting in shorter overall survival\(^{29} \). Cachexia identified by clinical assessment did show a significant association with progression free survival (HR 3.310, \( p=0.016 \)). A possible explanation for this might be the lower treatment tolerance to first-line treatment in these patients resulting into lower chemotherapy dose intensities (80% had a RDI ≤90%)\(^{30} \).

Moreover, the proportion of patients identified as clinically cachectic was low compared to cachexia prevalence according to the Fearon et al criteria, indicating that the oncologists only identified the patients with the worst clinical condition and the patients presenting with externally observable cachexia characteristics. This is supported by the fact that clinically cachectic patients had a lower BMI, lower physical functioning and lower quality of life scores. However, cachexia characteristics that are not externally observable may be missed. This may be the case for sarcopenic obesity, in which a low muscle mass is masked by obesity\(^{11,29,31} \). In this way clinical assessment may result in an underestimation of the cachexia prevalence. On the other hand, the cachexia prevalence may be overestimated using mortality-related cut-off values. In the current study, 68% of patients had a muscle mass below the sex-specific cut-off. The specific cut-offs defined by Martin et al correspond to the 10 and 50\(^{th} \) percentile in healthy men (BMI <25 kg/m\(^2\) and BMI ≥25 kg/m\(^2\), respectively) and 50\(^{th} \) percentile in healthy women\(^{32} \), indicating that the cut-offs by Martin et al are relatively high. As a consequence patients with a normal muscle mass may be considered as being sarcopenic, which is one of the Fearon et al criteria for cachexia.

In conclusion, there is a substantial difference in cancer cachexia prevalence when clinical assessment is compared to the cancer cachexia criteria defined by Fearon et al. In this study, clinical assessment of cancer cachexia was related to progression free survival but may underestimate cachexia prevalence. Further
improvement in cancer cachexia recognition is necessary to identify cachectic patients, who are at risk of poorer clinical outcomes and may benefit from targeted cachexia interventions.

**Conflict of interest**

The authors declare no relevant conflict of interest regarding the submitted work.

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References


