Comparing two Classifications of Cancer Cachexia and Their Association with Survival in Patients with Unresected Pancreatic Cancer

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ABSTRACT

Cancer cachexia is characterized by reduced weight and muscle mass, poor treatment tolerance and short survival. A universally accepted definition of this condition lacks. Two classifications have recently been proposed; the 3-factor classification requiring ≥two of three factors; weight loss ≥10%, food intake ≤1500 kcal/d, and C-reactive protein ≥10 mg/l, and the consensus classification defining cachexia by either weight loss >5% the past 6 months, or BMI <20 kg/m² or sarcopenia, both with ongoing weight loss >2%. Furthermore, cachexia may be considered a trajectory with pre-cachexia as the initial stage identified by weight loss ≤5%, anorexia and metabolic change. We examined the consistency between the two classifications, and their association with survival in a palliative cohort of pancreatic cancer patients. Patients with unresected pancreatic cancer were recruited. CT-images were used to determine sarcopenia. Height/weight/C-reactive protein and survival were extracted from medical records. Food intake was estimated from patients' self-report. Forty-five patients (25 males, median age 72 years, range 35-89) were included. The agreement for cachexia and non-cachexia was 78% across classifications. Overall survival was poorer in cachectic compared to non-cachectic patients (3-factor classification, P=0.0052; consensus classification, P=0.056; when pre-cachexia was included in the consensus classification, P=0.027). Both classifications showed a trend towards lower median survival (P<0.05) with the presence of cachexia. In conclusion, the two classifications showed good overall agreement in defining cachectic pancreatic cancer patients, and cachexia was associated with poorer survival according to both.

BACKGROUND

Cancer cachexia is a multi-factorial condition characterized by ongoing, involuntary loss of weight and muscle mass with or without the loss of fat mass, leading to impaired physical function, reduced quality of life (QoL) and survival and decreased effect of anticancer treatment (1). There is currently no effective treatment of cachexia. Neither pharmacological interventions nor nutritional support are able to fully reverse the loss of weight and muscle mass (1, 2). Because of the complex and multi-factorial origin of cachexia it is suggested that future treatment should be multimodal and include both anti-inflammatory treatment and nutritional support (1, 3, 4). In order to develop a multimodal treatment for cachexia there is a need to agree on a uniform definition of the condition (4).

The definition of cancer cachexia remains a matter of debate and several classification systems have been proposed (5-8). Fearon et al. (9) suggested a 3-factor classification, based on the presence of at least two of three factors: weight loss $\geq$ 10%, low food intake, and systemic inflammation, e.g. C-reactive protein (CRP) $\geq$ 10 mg/l. In 2011, an international consensus classification was suggested (1). To be categorized as cachectic based on the international consensus classification one of three criteria must be fulfilled: weight loss > 5% during the past 6 months; or low body mass index (BMI); < 20 kg/ m² and ongoing weight loss > 2%; or sarcopenia and ongoing weight loss > 2%. Notably, assessment of sarcopenia requires measurements of muscle mass, using e.g. either dual energy X-ray absortiometry scanning, bioelectrical impedance or computer tomography (CT)-imaging (10-12). The consensus classification suggested three stages of cachexia with clinical relevance, of which pre-cachexia is the initial stage. Pre-cachectic patients are considered responsive to interventions and it is therefore important to be able to identify these patients (13). However, the cut-off points of the pre-cachectic domains are not accurately defined by the international consensus (1). A study from 2012 investigated pre-cachexia in non-small-cell lung carcinoma

patients, (14) and used the following cut-offs for pre-cachexia: unintentional weight loss ≤ 5% during the previous 6 months, anorexia (the presence of: appetite <5cm (Visual Analogue Scale), energy intake of <84 kilojoules/kg body weight/day, or energy intake < 70% of total energy expenditure), and systemic inflammation, assayed as CRP ≥8 mg/l.

Wallengren et al. (15) recently compared three cachexia classifications (1, 6, 9) and their association with patient-reported outcomes, QoL and survival among 405 weight-losing patients with different tumor types (pancreatic-, colorectal-, biliary tract- and upper gastro-intestinal cancer). The prevalence of pre-cachexia was not evaluated. All three classifications were significantly associated with increased symptom burden and decreased survival. Importantly, the prevalence of cancer cachexia using the different classifications varied substantially, from 12 to 85%, indicating a need for further validation of the classification systems in more homogenous patient groups.

Cancer cachexia affects the majority of patients with advanced cancer. Patients with pancreatic cancer (PC) are suggested as a useful model for the study of cachexia as the majority of these patients present with advanced disease (16). They often report significant weight loss at the time of diagnosis and 5-year survival is less than 4% (17). To the best of our knowledge, no studies have compared the consistency of the 3-factor and the consensus classifications in defining cancer cachexia in a patient cohort with advanced PC and evaluated the prevalence of pre-cachexia in the same cohort. Thus, the primary aim of the present study was to determine the consistency in defining cachexia between the two classifications in an unselected cohort of unresected patients, i.e. those with either advanced PC or PC that could not be resected due to comorbidity. In addition we explored the possible associations of these classifications, including the classification of pre-cachexia with overall survival.

METHODS

Study Population

Patient data were retrieved from an interdepartmental database at Oslo University Hospital-Ullevål, including all patients referred to the hospital for solid or cystic pancreatic or peri-ampullary neoplasms. The clinical database contains prospective data on anamnestic, diagnostic and treatment-related issues as well as patients' self-reported symptoms collected once a month until death, and is approved by the Regional Ethical Committee for Medical and Health Research Ethics.

The present study focused on patients with unresected PC referred to the Palliative Care Unit from January 2008 to December 2011. Survival data were collected retrospectively. Eligibility criteria included a verified pancreatic adenocarinoma (histology/cytology/imaging), age $\geq$ 18 years, fluency in oral and written Norwegian, ability to complete questionnaires, provision of informed consent, and at least one available CT-scan of the abdomen for analyzes of muscle mass. All included patients received standard palliative care including chemotherapy and interventions aimed at relieving symptoms. This included pancreatic enzyme supplementation and oral nutritional supplements whenever indicated. Enteral tube feeding or parenteral feeding was not initiated.

Inclusion of Patients

Demographic data, survival data, clinical information on diagnosis, treatment and CT-scans, anamnestic data on food intake, height- and weight, and CRP values were obtained from the database or from the patients' medical records. Our initial search criteria identified 113 patients. There were 325 CT-scans available from this cohort (range 1–12 scans per patient), which had been conducted for diagnosis, staging, or follow-up. We wanted to reduce a potential bias due to change in the patient's condition between the CT scans. Thus, patients

were eligible if the CT scans were taken less than 30 days before or 10 days after diagnosis, which was defined as the date of histology (n=30), cytology (n=77), or CT-imaging (n=6). Reasons for exclusion were: missing CT-scans within the defined time span (n=47), CT scans that could not be analyzed due to technical problems (n=7), missing CRP values (n=6), or missing information about food intake, weight or height (n=8), thus yielding a final study sample of 45 patients.

Cachexia Assessment

Patients were classified as having cachexia using two definitions; 1) the 3-factor classification by Fearon et al. (9), incorporating the presence of at least two of three factors: weight loss $\geq$ 10%, low food intake ($\leq$ 1500 kcal/day), and systemic inflammation (CRP $\geq$ 10 mg/L) and 2) the 2011 expert panel consensus definition of screening and staging of cachexia using weight loss, BMI or low muscle mass (1). To be categorized as cachectic one of three criteria had to be fulfilled: weight loss > 5% during the past 6 months; or low BMI < 20 kg/ m² and ongoing weight loss > 2%; or sarcopenia and ongoing weight loss > 2%. Furthermore, non-cachectic patients with unintentional weight loss $\leq$5 % during the last 6 months, anorexia (food intake reported as less than usual by Subjective Global Assessment (SGA) (18)) and metabolic change (i.e. systemic inflammation with CRP $\geq$ 8 mg/l), were classified as pre-cachectic (1, 14).

Determination of BMI and Food Intake

Data on height and weight development (pre-illness weight, time of weight loss, and current weight) were collected from all patients by a self-report questionnaire and entered into the database. In addition, patients were asked to answer a question from the SGA

questionnaire, about food intake the past month compared to normal intake (18). The response alternatives to this question were 1 = *normal*, 2 = *more than usual*, or 3 = *less than usual*.

The percentage of weight loss was calculated as follows: (pre-illness weight - current weight) x 100/pre-illness weight. Patients were defined to have ongoing weight loss if they had lost > 2% weight at inclusion and reported additional weight loss at the second follow up. BMI was calculated from weight and height (kg/m²).

The 3-factor classification (9) includes reduced energy intake with ≤ 1500 kcal/d. However, adequately measuring dietary intake is time consuming and difficult in clinical practice and many studies extrapolate the amount of energy intake from self-reported intake (19). In the present study category 3; *less than usual* from the SGA questionnaire was defined as an indication of an energy intake of 1500 kcal/d or less, as used by others (20, 21).

CT Image Analysis

The CT scans were taken as a part of the diagnostic procedures and to evaluate therapy response in patients receiving chemotherapy (Fig. 1). Muscle tissues were analyzed with the software program Slice-O-Matic V4.3 (Tomovision, Montreal, Canada), which permitted specific tissue demarcation by using Hounsfield unit thresholds of –29 to 150 for skeletal muscles (22). Muscle tissue surface areas (cm²) were evaluated at the level of the third lumbar vertebra (L3) because tissue areas in this region are significantly related to whole-body muscle mass (23). A single trained observer analyzed all the CT images. The muscle index (muscle tissue surface area (cm²)/body height (m²)) was used to assess sarcopenia (1). The sex-specific cut-offs for sarcopenia determined by Prado et al. (55.4 cm²/m² for men and 38.9 cm²/m² for women) were used (24).

Biochemistry

The serum concentration of CRP determined with standard methodology as part of the routine diagnostic assessment was used as a proxy to assess systemic inflammation as required in the 3-factor classification (9).

Statistical Methods

The data were analyzed with PASW 18 (SPSS Inc., Chicago, Il, USA) and the software program GrafPad Prism (version 6, La Jolla, CA, USA). A comparison between the two classifications was done by a 2x2 contingency table and McNemars test. Weeks of survival was calculated from the date of diagnosis, and analyzed using Kaplan Meier curves and the log rank test. Comparisons of mortality before three months (12 weeks), when diagnosed with the two classifications, were analyzed with Fishers exact test. Significance was accepted for $P < 0.05$.

RESULTS

Of the 45 patients that were included, 56% were males and the median age was 71.7 years (35-89) (Table 1). Twenty-three patients had locally advanced cancer, 20 had metastatic disease, and two were not suitable for surgery because of comorbidity. The patients were treated at the discretion of the responsible physician. Thirty-one patients received chemotherapy (gemcitabine n=30; 5-fluorouracil/leucovorin n=1), three received radiation therapy (with or without concomitant chemotherapy), whereas nine patients did not receive antineoplastic treatment. Two patients were transferred to local hospitals for further follow-up and information about treatment not available. Of the 68 patients that were excluded from the analysis mainly due to lack of CT scans, 52% were males and the median age was 70.3 years (40-90). Median overall survival in this group was 39 weeks (range 3-159) and one patient was still alive at the time of data analysis.

Comparison of the two Cancer Cachexia Classifications

There was a high agreement (35/45; 78%) with respect to the classification of patients as cachectic or non-cachectic according to the two classification systems. The numbers of cachectic patients were 29 (64%) and 27 (60%) according to the 3-factor and the consensus classifications, respectively. In line with this, McNemars test failed to reject the null-hypothesis ($P = 0.75$) of a difference between the two classifications. With the consensus classification, 7 (15%) were classified as pre-cachectic, leaving a total of 11 (24%) patients to be classified as non-cachectic.

Fig. 2 shows the distribution of the criteria that were fulfilled according to the two classifications. With the 3-factor classification, nine patients (20%) fulfilled all three criteria with low food intake being most frequent. Sarcopenia was the most frequent criterion in the consensus classification.

Survival and Cancer Cachexia Classifications

Median overall survival for the included cohort (n = 45) was 37 weeks (range 2-176) and all patients were dead by the end of 2012. The Kaplan Meier curves in Fig. 3A show that the non-cachectic patients had significantly (P = 0.0052) longer survival than the cachectic patients, when grouped according to the 3-factor classification. The corresponding ratio of the median survival for the cachectic group (21 weeks) and the non-cachectic group (54 weeks), was 0.39 (95% CI 0.21 – 0.72), i.e. markedly significant. Correspondingly, Fig. 3B shows the survival curves for those grouped as cachectic according to the consensus classification and all other grouped as non-cachectic. Using this classification, the survival was not statistically significant (P = 0.056) longer in non-cachectic than cachectic patients, but nevertheless shorter in the cachectic group: 21 weeks versus 43 weeks, with the corresponding ratio being 0.49 (95% CI 0.27 – 0.89). When the non-cachectic group was divided into pre-cachectic and non-cachectic, the median survival times in the cachectic, pre-cachectic and non-cachectic groups were 21, 27 and 61 weeks, respectively (Fig. 3C). The corresponding ratio between the pre-cachectic and non-cachectic was 0.44 (95% CI 0.17-1.14), and the median survival was significantly higher (P = 0.027) in the cachectic vs non-cachectic group, with the corresponding ratio being 0.34 (95% CI 0.17-0.69).

A higher proportion of the patients who were considered cachectic according to the 3-factor classification died before 3 months, when compared to the non-cachectic patients (Fig. 4). This difference was, however, not statistically significant (OR 2.7, 95% CI 0.49 – 14). A similar non-significant finding was obtained when comparing 3-month survival among cachectic and pre- and non-cachectic patients according to the consensus classification (OR 3.4, 95% CI 0.62 – 18).

DISCUSSION

In order to develop a universally accepted classification system for cancer cachexia, there is a need for clinical validation of already proposed classifications. We have here compared the 3-factor (9) and the international consensus classifications (1) in patients with PC that could not be resected due to advanced disease. We found a strong overall agreement across the two classification systems in defining cachexia and non-cachexia. Overall and median overall survival were lower in patients defined as cachectic compared to non-cachectic, according to both classifications. With the consensus classification, 15% was classified as pre-cachectic. These patients had a shorter survival than non-cachectic and a longer survival than cachectic patients, although not statistically significant. Statistically significant differences were not found for 3-month survival with any of the classification systems.

The present study is among the first of its kind to make use of data that was taken as routine assessments in patients with advanced PC, and suggests that the variables included in the two classification systems indeed may represent a step in the strive for a uniform classification of cancer cachexia. Height and weight are simple measurements that should always be registered during the first patient encounter as part of nutritional screening. Preferably, weight development should be followed, which is unfortunately not always the case. The challenge in cachexia classification will be to obtain measures of energy intake or muscle mass as this is not part of the clinical routine today.

Wallengren et al.(15), recently compared three definitions of cancer cachexia including the 3-factor and the consensus classification. They found a wide variation in the prevalence of cancer cachexia in their population, ranging from 12% to 85%. With the 3-factor classification the prevalence of cachexia was 12% when all three factors were used to identify cachexia, and 45% when two factors were used. With the consensus classification they found

a cachexia prevalence of 85%. Thoresen et al (25) also found a lack of concordance between results obtained by the 3-factor and the consensus classification in their study of patients with advanced colorectal carcinoma. The discrepancy between our results and the ones reported by Wallengren et al (15) and Thoresen et al (25) may be explained by the heterogeneity of the study populations. We included a homogenous population with advanced PC, and did not find this large variation in prevalence of cachexia when comparing the two definitions. With both definitions the prevalence in our study was in line with Fearon et al. (9) i.e. 60% when using ≥ 2 of the three factors, who also studied PC patients with unresectable disease. This emphasizes the need for validating the classification systems in different patient populations.

Two recent studies have investigated the prevalence of pre-cachexia in patients with advanced cancer. Data from heterogeneous population of patients with incurable metastatic or locally advanced cancer diagnosis (13) indicated a prevalence of 14% while a prevalence of 23% was found in patients with non-small cell lung cancer (14). In the present study population, the prevalence of pre-cachexia was 15%, which was close to the finding by Blum et al. (13). The study included a relatively large group with cancer in the digestive organs, which may be comparable with our cohort. None of the two studies found a statistically significant difference in survival between pre-cachexia and non-cachexia (13, 14), as in our study, which may suggest that pre-cachectic patients have not yet developed a severe condition. In our study non-cachectic patients lived longer than the pre-cachectic patients (not significantly), which may indicate that the classification of pre-cachexia distinguished patients with a forthcoming cachexia in our population.

For patients with advanced PC the 3-factor classification might be suitable for detecting cachexia since it was developed in this group (9). However, a major challenge related to the clinical use of the 3-factor classification is the registration of food intake. Our data showed that food intake was the most frequently occurring criterion when using this

method to identify cachectic patients. However, there is a large uncertainty associated with this factor since we did not assess the actual intake but defined the SGA-score of 3; *less than usual* to indicate an energy intake ≤ 1500 kcal/d. The SGA tool has previously been used to estimate reduced food intake, stipulating *less than usual* to be about 1000-1500 kcal/d (20, 21). However, we do not know if this is applicable for our study population, and if not, we may have overestimated the prevalence of cachexia even if our findings were in line with Fearon et al (9). Nevertheless, in future studies food intake should be assessed since it is an important contributor to weight loss in cachexia (19). Usually food intake is assessed by the patient's own reports of overall intake. However, this is time-consuming and not always precise since it is difficult to estimate energy intake based on evaluations of portion size (26). A dietary record at home, as used by Wallengren et al. (15), may be more accurate, but it requires extensive respondent training and motivation and is difficult to use in clinical practice (26). It has been suggested that appetite, which is easier to assess, could replace registration of food intake (19, 26). Unfortunately, it does not seem to be a strong correlation between appetite and food intake in cachectic patients (27). Therefore, it is important to improve the methods for assessment of food intake that are easy to use.

Wallengren et al. (15) showed that CRP was significantly associated with adverse patient-related outcomes and survival. However, CRP concentrations fluctuate, and may be influenced by use of drugs like antibiotics and steroids. Moreover, CRP is not always included in the routine diagnostic assessment. Other measurements have been proposed. For example Evans et al. (6) included abnormal biochemistry (CRP > 5 mg/l, anemia (hemoglobin concentration < 12 g/dl) or low albumin concentration (< 3.2 g/dl) in the cachexia definition. A study done by Di Sebastiano et al. (28) showed that the presence of anemia at diagnosis significantly influenced the rate of skeletal muscle loss. The inclusion of anemia as a factor in

the classification of cancer cachexia may be questionable, since anemia often has a high prevalence in cancer patients owing to antineoplastic therapy (2).

Weight loss is common in advanced cancer and may reflect increased tumor activity, metabolic changes, or disease progression (29). It is difficult to determine the cut-off points and time span for the loss of weight (30). Taken together, this reduces the usefulness of weight loss in a cancer cachexia classification system. On the other hand, following weight development over time is feasible and should be part of routine clinical follow-up, as weight loss may indicate physical deterioration.

For people over 65 years the BMI threshold for undernutrition is ≤ 24 kg/m² (31). Thus the validity of the consensus classification which includes BMI may largely depend of the age of the patients. For our study group with a median age of 72 years, this may have led to an underestimation of the prevalence of cachexia. On the other hand the normal decrease in muscle mass from the age of 60 (32) may have led to an overestimation of prevalence. However, few, if any studies, have discussed the use of different BMI threshold values according to age when examining cachexia in adults.

Cancer cachexia represents a continuous spectrum (1, 4), with minimal weight loss characterizing pre-cachexia, systemic inflammation resulting in cachexia, and loss of body reserves resulting in refractory cachexia. In order to treat patients, there is a need to identify where in this trajectory the patients are. Early recognition and treatment are important, in order to reduce or postpone cachexia (3). To achieve this, and to improve the classification of cancer cachexia, we suggest that specific studies are launched with this as the major objective. Most definitions are usually validated in existing cohorts using data from studies that were planned for other purposes, such as our own and other (9, 32). One problem related to this is the variation in time span between the time of diagnosis and between the different assessments that are used as criteria for classifying cachexia. This is particularly important in

patients with rapidly progressing disease and may affect the results. For example, follow-up studies of muscle mass in PC patients (28, 32) had variations of +/- 60 days between diagnosis and the first CT-scan, which is why we decided to imply a narrower time span for the CT scans in the present study. This decision undoubtedly reduced our sample size. However, our sample is well-characterized and limited to PC patients that were not resected due to advanced disease or comorbidity. CT-scans were taken close to the time of diagnosis, which enabled us to capture the muscle mass at early stages of the disease. We also have a complete data set of the 45 patients with no missing values. The median survival times were almost identical in the included and excluded groups, 37 and 39 weeks respectively.

The main limitations of our study are the small sample size and the fact that there is still a longer than desired time span between the CT-scans and the assessment of some of the other measures (weight/height, CRP, food intake). Notably, other studies have longer time span between measurements (33) and many studies actually do not report on this at all (9, 15). Furthermore, due to the low number of patients we have not examined the various tumor stages or the therapeutic modes separately as such analyses would be invalid by too low statistical power.

In conclusion, there was good overall agreement regarding the classification of patients as cachectic or non-cachectic across the two classifications. There was also a consistent finding that cachexia and pre-cachexia are associated with poorer survival compared to non-cachexia. To move towards a universally accepted definition, prospective studies with specific subjective and objective outcome measures at fixed intervals are necessary, in larger, well-defined patient populations with data on nutritional intake.

AUTHOR CONTRIBUTION

Study conception: Ikdahl, Dajani, Hjermstad, Bye, Ulven. Data collection: Rao, Hjermstad, Bye, Dajani. Statistical analyses: Rao, Iversen Hjermstad, Bye. Manuscript drafting: Rao, Iversen, Ulven, Hjermstad, Bye. Repeated critical reviews and manuscript editing: All. All authors read and approved the final manuscript.

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FIGURE LEGENDS

Fig. 1. CT scans from female patients with (A; muscle index 35.2 cm^2/m^2, BMI 19.6 kg/m^2) or without (B; muscle index 40.5 cm^2/m^2, BMI 18.4 kg/m^2) sarcopenia. The scans show transverse sections at the level of the third lumbar vertebra with the ventral side at the top and the dorsal side at the bottom. The muscle mass is depicted in red.

Fig. 2. Distribution of the number of fulfilled criteria for cancer cachexia according to (A) the 3-factor classification and (B) the consensus classification (n=45). According to the consensus classification, no patients were defined as cachectic because of BMI < 20 kg/m^2 and ongoing weight loss $\geq$ 2%.

Fig. 3. Kaplan Meier survival curves of cachectic (red line) and non-cachectic patients (n=45) according to (A) the 3-factor classification (cachectic n=29), (B) the consensus classification (cachectic n=27), and (C) consensus classification including pre-cachectic patients (n=7, green line).

Fig. 4. Distribution of 3-month survival of the patients (n=45) when classified as cachectic or non-cachectic, according to either the 3-factor (cachectic n=29) or the consensus cancer cachexia classifications (cachectic n=27).